

JOÃO ANGELO FERRES BROGIN

**A contribution to the dynamics of epilepsy:
identification and control for seizure attenuation**

Ilha Solteira - SP
2023

JOÃO ANGELO FERRES BROGIN

**A contribution to the dynamics of epilepsy:
identification and control for seizure attenuation**

A thesis submitted to the School of Engineering of Ilha Solteira in partial fulfillment of the requirements for the degree of PhD in Mechanical Engineering.

Prof. Dr. Douglas Domingues Bueno
Advisor

Prof. Dr. Jean Faber Ferreira de Abreu
Co-advisor

Ilha Solteira - SP
2023

FICHA CATALOGRÁFICA
Desenvolvido pelo Serviço Técnico de Biblioteca e Documentação

B866c Brogin, João Angelo Ferres.
A contribution to the dynamics of epilepsy: identification and control for seizure attenuation / João Angelo Ferres Brogin. -- Ilha Solteira: [s.n.], 2023
238 f. : il.

Tese (doutorado) - Universidade Estadual Paulista. Faculdade de Engenharia de Ilha Solteira. Área de conhecimento: Mecânica dos Sólidos , 2023

Orientador: Douglas Domingues Bueno
Co-orientador: Jean Faber Ferreira de Abreu
Inclui bibliografia

1. Epilepsia. 2. Identificação de sistemas. 3. Atenuação de crises.


Amanda Sertori dos Santos
Bibliotecária - CRB/8-9061
Seção Técnica de Referência, Atendimento ao
Usuário e Documentação
Diretoria Técnica de Biblioteca e Documentação

CERTIFICADO DE APROVAÇÃO

TÍTULO DA TESE: A CONTRIBUTION TO THE DYNAMICS OF EPILEPSY: IDENTIFICATION AND CONTROL FOR SEIZURE ATTENUATION

AUTOR: JOÃO ANGELO FERRES BROGIN

ORIENTADOR: DOUGLAS DOMINGUES BUENO

COORDENADOR: JEAN FABER FERREIRA DE ABREU

Aprovado como parte das exigências para obtenção do Título de Doutor em Engenharia Mecânica, área: Mecânica dos Sólidos pela Comissão Examinadora:

Prof. Dr. DOUGLAS DOMINGUES BUENO (Participação Presencial)
Departamento de Matemática / Faculdade de Engenharia de Ilha Solteira



gov.br

Documento assinado digitalmente
MARCELA RODRIGUES MACHADO
Data: 08/01/2024 11:01:57-0300
Verifique em <https://validar.iti.gov.br>

Prof. Dr. JOAO ANTONIO PEREIRA (Participação Presencial)
Departamento de Engenharia Mecânica / Faculdade de Engenharia de Ilha Solteira - UNESP



gov.br

Documento assinado digitalmente
SARAH NEGREIROS DE CARVALHO LEITE
Data: 08/01/2024 10:40:05-0300
Verifique em <https://validar.iti.gov.br>

Profa. Dra. MARCELA RODRIGUES MACHADO (Participação Virtual)
Departamento de Engenharia Mecânica / Universidade de Brasília - UnB

Profa. Dra. SARAH NEGREIROS DE CARVALHO LEITE (Participação Virtual)
Departamento de Telecomunicações / Instituto Tecnológico de Aeronáutica - ITA

gov.br

Documento assinado digitalmente
RICARDO SUYAMA
Data: 26/12/2023 18:01:04-0300
Verifique em <https://validar.iti.gov.br>

Prof. Dr. RICARDO SUYAMA (Participação Virtual)
Centro de Engenharia, Modelagem e Ciências Sociais Aplicadas / Universidade F

Ilha Solteira, 19 de dezembro de 2023

ACKNOWLEDGEMENTS

Firstly, I would like to thank my parents, Maria and João, for having always done everything to provide my sisters and me with great educational background despite all financial issues. This accomplishment largely belongs to you.

I also thank my sisters, Fabiana and Juliana, for all the patience and affection they have always had for me. You have greatly contributed to my personal growth and supported me whenever necessary.

I thank my advisor, professor Douglas D. Bueno, for teaching me valuable lessons about work and life. Thank you for having always trusted that I was capable of achieving great results even when I myself was not confident. Thank you for teaching me how to build autonomy and critical thinking. Thank you for having always encouraged me to explore my creativeness. I would not have the knowledge and courage to pursue my goals if it was not for you. Thank you very much.

I thank my co-advisor, professor Jean Faber, for all the support and time dedicated to my work. Thank you for helping me to expand my horizons and make me look at research from a different perspective. Thank you for all the technical and philosophical discussions. Thank you for believing in my potential and teaching me how to take full advantage of my imagination as a researcher.

I thank professor Philippe Ryvlin and all his team for having greatly supported me in all aspects before, during and after my stay at the Centre hospitalier universitaire vaudois (CHUV), in Switzerland. This was a life-changing experience that helped me to grow professionally and personally.

A special thanks to all the employees and professors of the School of Engineering of Ilha Solteira (FEIS). Directly or indirectly, you have contributed to this accomplishment. To the Post-Graduate Program in Mechanical Engineering (PPGEM) as well, for all the opportunities I have had so far.

To the Coordination for the Improvement of Higher Education (CAPES) for the scholarship (Grant No. 88887.481049/2020-00) I have had throughout these years.

At last, I would like to thank all my friends for having always been by my side in good or bad times. This accomplishment belongs to you as well.

*“Rien dans la vie n’est à craindre, tout doit être compris.
C’est maintenant le moment de comprendre davantage, afin de craindre moins.”*

Marie Curie

RESUMO

A epilepsia é uma das desordens neurológicas mais comuns no mundo, afetando milhões de pessoas todo ano e apresentando implicações físicas, psicológicas e sociais que podem comprometer significativamente suas vidas. Atualmente, há tratamentos que auxiliam a mitigar a frequência e intensidade das crises, mas nenhum deles é plenamente eficaz, e os mecanismos precisos que as causam também não são totalmente compreendidos ainda. Isso tem motivado pesquisadores a abordar a epilepsia a partir de um ponto de vista teórico, resultando no desenvolvimento de modelos matemáticos computacionais capazes de elucidar a geração, sincronização e propagação de crises. O modelo Epileptor é um marco nessa área de pesquisa devido a suas características altamente representativas, implementação relativamente simples e aderência a observações experimentais. Similarmente, modelos baseados em dados também têm sido propostos na literatura para descrever as assinaturas temporais de registros eletrofisiológicos. Questões relevantes que surgem nesse contexto são como obter modelos dinâmicos a partir de dados reais para os quais um sistema de controle pode ser projetado e como definir a natureza das entradas de controle que podem levar à atenuação de crises em ambos os modelos, teórico e experimental. Nesse sentido, as principais contribuições desta tese são estratégias para definir as entradas de controle capazes de suprimir ou mitigar as crises descritas pelo Epileptor e sinais reais, baseadas no projeto de controladores, observadores e identificação de sistemas. Ambos são desenvolvidos computacionalmente, mas superando uma série de restrições numéricas, teóricas e práticas para obter uma abordagem final de controle com forte apelo prático e potencialmente útil a médicos como ferramenta auxiliar para uma melhor definição do formato, intensidade e frequência dos estímulos que devem ser aplicados para atenuar crises em terapias de estimulação elétrica. Os resultados demonstram que é possível reconstruir e atenuar os padrões epileptiformes em ambos os modelos a partir de sinais de controle específicos a cada nível de atividade cerebral, sendo também consistentes com resultados previamente catalogados na literatura.

Palavras-chave: epilepsia; identificação de sistemas; atenuação de crises.

ABSTRACT

Epilepsy is one of the most common neurological disorders worldwide, affecting millions of people every year and leading to physical, psychological and social implications that may significantly compromise their lives. There are treatments today that help to mitigate the frequency and intensity of seizures, but none is fully successful, and the precise mechanisms that trigger them are not yet completely understood either. This has motivated researchers to address epilepsy from a theoretical point of view, resulting in the development of mathematical computational models that provide insights into seizure generation, synchronization and propagation. The Epileptor model is a breakthrough in this field due to its highly representative features, relatively easy implementation and adherence with experimental observations. Similarly, data-driven models have also been presented in the literature to describe the temporal signatures of electrophysiological recordings. Relevant questions that arise in this context are how to obtain dynamic models from real data for which a control system can be designed and how to define the nature of the control inputs that achieve seizure attenuation in both theoretical and experimental models. In this sense, the main contributions of this thesis are strategies to define the control inputs able to suppress or mitigate the epileptiform activity described by the Epileptor and real signals, based on the design of controllers, state observers and system identification techniques. Both are developed computationally but overcoming a series of numerical, theoretical and practical restrictions to obtain a final control approach with a strong practical appeal that can be potentially used by physicians as an auxiliary tool to better define the shape, intensity and frequency of the input stimulus that must be applied to attenuate seizures in electrical stimulation therapies. The results show that it is possible to reconstruct and attenuate the epileptiform patterns of both models from control signals that are specific to each level of brain activity and consistent with previous studies in the literature.

Keywords: epilepsy; system identification; seizure attenuation.

LIST OF FIGURES

Figure 1 – General flowchart of the integration proposed in this thesis.	24
Figure 2 – Illustration of neurons generating an action potential.	28
Figure 3 – Illustration of how action potentials are related to EEGs.	30
Figure 4 – Example of spiking generation on the phase portrait of a dynamic system that simulates a neuron dynamics with two state variables. .	32
Figure 5 – Example of spiking generation on the time domain and its corresponding burster, revealed from two regular state variables a third control one.	33
Figure 6 – Examples of firing patterns simulated using the Izhikevich model. .	35
Figure 7 – Examples of firing patterns simulated using the Hindmarsh-Rose model.	36
Figure 8 – Relationship between the phase portraits and behavior in the time domain of the Hindmarsh-Rose model.	37
Figure 9 – Illustration of the 10-20 system for measuring EEGs.	38
Figure 10 – Epileptor's behavior in the time domain: $LFP(-x_1(t) + x_2(t))$ and state $z(t)$	44
Figure 11 – Analysis of the interspike intervals (IS) of the Epileptor model. . . .	44
Figure 12 – Representation of both subsystems in the time domain and in their phase portraits.	45
Figure 13 – Relationship between the phase portraits and behavior in the time domain of the Epileptor model.	46
Figure 14 – Concept of sector nonlinearity to reconstruct a nonlinear function. .	50
Figure 15 – Nonlinear functions of the Epileptor model for a specific time interval.	53
Figure 16 – Comparison of the system's output in both uncontrolled and controlled conditions.	56
Figure 17 – Euclidean norm for $(\mathbf{x}(t) - \mathbf{x}_h)$ over time.	58
Figure 18 – Control signals $F_{c(j)}$ ($j = 1, \dots, 6$) over time for $\mu = \alpha = 0$ (no constraints) to suppress Epileptor's seizure.	58
Figure 19 – State variables after switching the controller on.	59
Figure 20 – State variables after switching the controller on.	60
Figure 21 – Euclidean norm for $(\mathbf{x}(t) - \mathbf{x}_h)$ after adding the decay rate.	61

Figure 22 – Epileptor’s behavior in the time domain as $LFP = (-x_1(t) + x_2(t))$ and state $z(t)$, and all of its variables, categorized as measurable or unmeasurable.	66
Figure 23 – Performance of the fuzzy observer for an on-going seizure.	75
Figure 24 – Error dynamics for the fuzzy observer considering an-ongoing seizure.	76
Figure 25 – Performance of the fuzzy observer for the transition between inter-ictal and ictal states.	78
Figure 26 – Comparison between the bursters defined for the original Epileptor and the estimated ones using $\beta = 0$ and $\beta \neq 0$	79
Figure 27 – Flowchart for the proposed parameter estimation process.	84
Figure 28 – Visual illustration of the non-null values in $\delta \mathbf{D}_n$	86
Figure 29 – Visual illustration of the iteration process for a time window of an LFP.	88
Figure 30 – Main stages of the Nelder-Mead algorithm.	90
Figure 31 – Steps prior to the validation process for the parameter estimation approach using sequential time windows to estimate the unknown parameters of the target LFP.	92
Figure 32 – Box-plots for the set of 8 parameters estimated using different time windows (given in number of points) and $\delta = 0.25$	94
Figure 33 – Optimizations for the set of 8 parameters estimated using a 250-point time window, comparing the preictal and ictal states.	96
Figure 34 – Box-plots for the set of 8 parameters estimated comparing the interictal (II) and ictal (IC) states using a 250-point time window.	97
Figure 35 – Box-plots for the set of 8 parameters estimated using different uncertainty factors δ and a 250-point time window.	99
Figure 36 – Influence of noise addition on the process of parameter estimation in both regions, using a 250-point time window and $SNR = 70$ dB.	101
Figure 37 – Influence of noise addition on the process of parameter estimation using a 250-point time window and different SNR dB, combining both IC and II regions.	102
Figure 38 – Integration process considering the proposed parameter estimation technique and seizure suppression.	104
Figure 39 – Comparison between the reference LFP (W) and the one using the estimated parameters obtained from the optimization process proposed in this work (w), as well as the controller’s action, over time.	105

Figure 40 – Euclidean norms of the error dynamics considering all estimated states ($\ \mathbf{e}(t) \ $) and between the actual states and the seizure-free condition ($\ \mathbf{x}(t) - \mathbf{x}_h \ $).	106
Figure 41 – Action of the FTSM controller considering different sets of parameters.	108
Figure 42 – General flowchart with the 3 major stages of the proposed SI and control approach.	114
Figure 43 – Raw and filtered downsampled signals with their respective spectrograms.	116
Figure 44 – Reference II and PIS signals from SUB and their respective AR models obtained after order selection based on the AIC/BIC/MSE criteria.	120
Figure 45 – Model extensions calculated for the whole time series based on the AR models found using the first $N_{\min}$ samples.	121
Figure 46 – Discrete and continuous dynamic matrices obtained from the AR coefficients in state-space notation.	124
Figure 47 – Illustration of the time windows used (whose minimum size is $N_{\min}$) to obtain the AR models and to which the observers and controllers are applied, ranging from $m = 1, 2, \dots, M$	126
Figure 48 – Action of the observer and controller over time and behavior of the error dynamics and Euclidean norms.	132
Figure 49 – Action of the observer and non-hybrid controller over time analyzed in terms of the normalized Euclidean norm $\ \mathbf{x}(t) - \mathbf{x}_{ref} \ $ and frequency content over time (spectrograms).	133
Figure 50 – Action of the observer and hybrid controller over time analyzed in terms of the normalized Euclidean norm $\ \mathbf{x}(t) - \mathbf{x}_{ref} \ $ and frequency content over time (spectrograms).	135
Figure 51 – Effect of tuning α and B_{11} on the input response of the signal in the time domain.	136
Figure 52 – Comparison between the reference observed II and PIS signals and the uncontrolled/controlled ones using PSDs and PCA after activating the non-hybrid controller.	138
Figure 53 – Comparison between the reference observed II and PIS signals and the uncontrolled/controlled ones using PSDs and PCA after activating the hybrid controller.	139
Figure 54 – NAR model reconstruction considering an iEEG signal.	145

Figure 55 – Histograms obtained from the NAR coefficients after successive identifications over the iEEG signal.	146
Figure 56 – NAR identification considering the iEEG signal and concept of sector nonlinearity.	149
Figure 57 – Performance of both observer and controller for the reconstruction and attenuation of the iEEG signal.	150
Figure 58 – Analysis of patterns in both non-seizure and seizure conditions (time domain).	159
Figure 59 – Analysis of patterns in both non-seizure and seizure condition in the frequency domain for the first patient.	160
Figure 60 – Analysis of patterns in both non-seizure and seizure condition for different patients in the frequency domain.	161
Figure 61 – PCA considering the PSDs of all the patients and seizures.	162
Figure 62 – Analysis of convergence for the number of terms in the Fourier vector basis considering the real signals in Fig. 58.	166
Figure 63 – Truncated Fourier series compared to the real signals.	167
Figure 64 – Identification of dummy/candidate models based on the real recordings.	168
Figure 65 – Closed-loop model reconstruction using the real signals.	171
Figure 66 – Full closed-loop model reconstruction and reconstruction error. . . .	172
Figure 67 – Closed-loop model reconstructions for different decay rates.	173
Figure 68 – Seizure attenuation considering reconstructed models.	175
Figure 69 – Activation of the adaptive controller for attenuating the reconstructed signal.	177
Figure 70 – Adaptive gains and input stimulus applied for seizure attenuation. .	178
Figure 71 – Decay rate in function of maximum magnitude of input stimulus, adherence and attenuation level for the adaptive controller.	179
Figure 72 – Different approaches to limit the magnitude of the input stimulus considering adaptive gains.	180
Figure 73 – Activation of the fixed gain controller for attenuating the reconstructed signal.	181
Figure 74 – Activation of the fixed gain controller for seizure attenuation. . . .	182
Figure 75 – Input stimuli applied for attenuating the reconstructed signal considering fixed gains compared to adaptive ones.	183

Figure 76 – Decay rate in function of maximum magnitude of input stimulus, adherence and attenuation level for the fixed-gain controller.	184
Figure 77 – Different approaches to limit the magnitude of the input stimulus considering fixed gains.	185
Figure 78 – Power Spectral Density (PSD) of the input stimuli of both control strategies (adaptive and fixed gain).	186
Figure 79 – Offline integration of identification, reconstruction and attenuation: for color coding, please see Figs. 64 to 68.	189
Figure 80 – Integration of identification, reconstruction and attenuation for a practical (online) application: for color coding, please see Figs. 64 to 68.	190
Figure 81 – Phase portrait for the response of the mass-spring-damper system. .	220
Figure 82 – Response of the mass-spring-damper system in the time domain with the respective Lyapunov functions using varying α and β	221
Figure 83 – Response of the mass-spring-damper system in the time domain after noise addition using varying α and β	222
Figure 84 – Response of the mass-spring-damper system in the time domain and phase portrait using the following dynamic systems: $\mathbf{A}$ and $\mathbf{A}_{\beta 1}$. .	224
Figure 85 – Complementary results for the fuzzy observer considering α and β . .	227
Figure 86 – Autocorrelation function ρ considering the lags of the residuals obtained after estimation of the both AR models (for II and PIS, respectively) for the first time window: $m = 1$	229
Figure 87 – AR coefficients of the identified models for the II and PIS signals from SUB to design matrices $\mathbf{A}_m^{\{c\}}$, $m = 1, 2, \dots, M$ and the gains $\mathbf{L}_{II}$ and $\mathbf{G}_{II}$, or $\mathbf{L}_{PIS}$ and $\mathbf{G}_{PIS}$	230
Figure 88 – Performance of the controller when applied to signals coming from different hippocampal subfields: DG, CA2 and CA1.	231
Figure 89 – Signals used to design both gains $\mathbf{L}_{II}$ and $\mathbf{G}_{II}$ in the hybrid approach and the healthy reference $\mathbf{x}_h$	232
Figure 90 – Complementary results for all the remaining patients, considering adaptive MRCs.	237
Figure 91 – Complementary results for all the remaining patients, considering fixed-gain MRCs.	238

LIST OF TABLES

Table 1 –	Controller’s performance, in terms of LFP input, for different constraints on the input.	60
Table 2 –	Controller’s performance, in terms of LFP inputs, for different pairs of constraints on the input and output.	61
Table 3 –	Performance of the optimization approach, in terms of the relative mean squared error (RMSE), for different time windows, considering median values between the estimated ($\mathbf{S}^{\text{best}}$) and reference ($\mathbf{S}^{\text{ref}}$) parameters, and associated median final objective-function evaluations ($f^{\text{best}}(W, w)$).	95
Table 4 –	Performance of the optimization approach, in terms of the relative mean squared error (RMSE), for different uncertainty factors δ , considering median values between the estimated ($\mathbf{S}^{\text{best}}$) and reference ($\mathbf{S}^{\text{ref}}$) parameters, and associated median final objective-function evaluations ($f^{\text{best}}(W, w)$).	100
Table 5 –	Selected cases for the performance of the optimization approach, in terms of parameters, relative mean squared error (RMSE), for different levels of noise, considering median values between the estimated ($\mathbf{S}^{\text{best}}$) and reference ($\mathbf{S}^{\text{ref}}$) parameters, and their respective associated median final objective-function evaluations ($f^{\text{best}}(W, w)$).	103
Table 6 –	Coefficients for AR($k = 6$) models obtained for the SUB signal in the interictal (II) and periodic ictal spiking (PIS) conditions.	125
Table 7 –	P-values obtained from the post-hoc Dunn’s test considering the samples projected on the second principal component PC_2 , for both non-hybrid and hybrid controllers.	141
Table 8 –	Effect of the addition of lags to the NAR model considering the number of lags and the RRMSE.	146
Table 9 –	Performance of individual NAR models for selected patients and the general one.	147
Table 10 –	Notation adopted for the MRC approach, considering a generic $\mathbf{W}_{\{.\}}^{\{*\}}$	157
Table 11 –	Kruskal-Wallis and post hoc Dunn’s test applied to distinguish the non-seizure condition from the seizure one.	162

Table 12 – Comparison between the input stimuli from the adaptive and fixed-gain controllers when varying the decay.	183
Table 13 – Comparison between the parameters used in for seizure attenuation with other studies in the literature.	193

LIST OF ACRONYMS

AIC	Akaike Information Criterion
AR	Autoregressive (Model)
BIC	Bayesian Information Criterion
CA	Cornu Ammonis
CHUV	Centre hospitalier universitaire vaudois
CSS	Continuous-Time State-Space
DG	Dentate Gyrus
DMVT	Differential Mean Value Theorem
DSS	Discrete-Time State-Space
ECG	Electrocardiogram
ECoG	Electrocorticogram
EDA	Electrodermal Activity
EEG	Electroencephalogram
EMU	Epilepsy Monitoring Unit
ETHZ	Eidgenössische Technische Hochschule Zürich
FTS	Fuzzy Takagi-Sugeno
HT	Hilbert Transform
IC	Ictal
iEEG	Intracranial Electroencephalogram
II	Interictal
ISI	Interspike Interval
LFP	Local Field Potential
LMI	Linear Matrix Inequality
LSM	Least Squares Method
MRAC	Model Reference Adaptive Controller
MRC	Model Reference Controller
MSE	Mean Squared Error
NAR	Nonlinear Autoregressive (Model)
NM	Nelder-Mead
NMSE	Normalized Mean Squared Error
OMI	Operational Matrix of Integration
OP	Orthogonal Polynomials
PCA	Principal Component Analysis

PIS	Periodic Ictal Spiking
PPG	Photoplethysmography
PSD	Power Spectral Density
PSO	Particle Swarm Optimization
RMS	Root Mean Square
RMSE	Root Mean Squared Error
RRMSE	Relative Root Mean Squared Error
sEEG	Stereo Electroencephalogram
SI	System Identification
SpO2	Pulse Oximetry
SS	State-Space
SSE	Sum of Squared Errors
SUB	Subbiculum
SWEC	Sleep-Wake-Epilepsy Center
ZCH	Zürich

LIST OF SYMBOLS

f_s	Sampling frequency
I	Generic flow of electric current
p_i	Generic parameter of dynamic models
$x_i, i = 1, 2, 3$	Generic state variables
t	Continuous time
dt	Time step/sampling rate
(x_1, y_1)	First subsystem of the Epileptor model
(x_2, y_2)	Second subsystem of the Epileptor model
$z(t)$	Control variable of the Epileptor model
$u(t)$	Dummy variable of the Epileptor model
I_{rest1}, I_{rest2}	Flow of electric currents in the Epileptor model
x_0	Epileptogenicity of the Hindmarsh-Rose or Epileptor model
y_0	Constant of the Epileptor
c	Constant of the Epileptor
s	Variable of the Laplace transform
$\mathcal{L}(\ast)$	Laplace transform
$\mathbf{x}(t)$	Vector of states
$\hat{\mathbf{x}}(t)$	Vector of reconstructed states
$\mathbf{A}$	Dynamic matrix
$\mathbf{b}$	Constant vector
$\mathbf{y}(t)$	Vector of observable states
$\mathbf{C}$	Matrix of measurable states
$\mathbf{F}_c$	Stimulus vector
$\mathbf{x}_h$	Non-seizure reference vector
$\mathbf{B}$	Input matrix
$\mathbf{G}$	Gain of the controller
$\mathbf{u}(t)$	Input vector
$f_k(\mathbf{x}(t))$	Nonlinear function
M_{ij}	Fuzzy set
f_k^{min} and f_k^{min}	Maximum and minimum values of $f_k(\mathbf{x}(t))$
$g_k(\mathbf{x}(t))$	Membership function
g_k^{min} and g_k^{min}	Membership functions
$N_i(\mathbf{x}(t))$	Combination of membership functions

P	Stability matrix of the controller
X	Auxiliary variable for the stability matrix
G_x	Auxiliary variable for the gain of the controller
W	Generic matrix
T	Generic matrix
I	Identity matrix
x_{tc0}	Vector of initial conditions at the moment the controller is activated
L	Weighting matrix for the state observer
z	Full vector of states
f(z)	Full function of z
e(t)	Error associated to the state observer
a, b	Constants to represent upper and lower boundaries
E	Positioning vector
v_{ij}^k	Membership functions for the observer
ã_{ijk}	Upper and lower boundaries of v_{ij}^k
h_i	Combination of membership functions of the observer
P_{obs}	Stability matrix of the observer
M	Auxiliary variable for the gain of the observer
S	Vector of parameters
D	Disturbance matrix
S^{ref}	Vector of reference parameters
S_{dB}^{noise}	Level of noise
N	Noise variable
W	Reference LFP for the optimization
w	LFP for varying parameters
m	Number of windows
M	Maximum number of windows
x'	State vector of the differences equation
R	Matrix related to the continuous-time state space
Z	Matrix containing only zeros
J	Auxiliary matrix for identifying parameters
r	Input vector for the adaptive controller
Ḡ	Approximation of the gain of the controller
Q	Generic stability matrix

LIST OF GREEK LETTERS

τ	Generic time scale parameter for the Hindmarsh-Rose and Izhikevich models
$\omega_i, i = 1, 2$	Coupling functions of the Epileptor model
$\bar{\omega}_i, i = 1, 2$	Coupling functions of the Epileptor model inside the dynamic matrix
$\tau_i, i = 0, 1, 2$	Time scale parameters of the Epileptor model
γ	Constant of the Epileptor model
χ	Premisse variable
Δ_{Sc}	Schur complement
μ	Constant for the constraint on the input
α	Decay rate
Ψ	Linear subsystem of the observer
β	Parameter for enhancing the performance of the observer
Φ	Base of eigenvectors
δ	Uncertainty factor
φ	Pseudorandomly generated vector
ν	Normalization factor between W and w
ϵ	Stop criterion for the Nelder-Mead optimization
κ_{ref}	Reflection factor for the Nelder-Mead optimization
κ_{exp}	Expansion factor for the Nelder-Mead optimization
κ_{ctr}	Contraction factor for the Nelder-Mead optimization
κ_{shr}	Shrink factor for the Nelder-Mead optimization
ϕ	Coefficients of the autoregressive model
$\boldsymbol{\phi}$	Vector of coefficients of the autoregressive model
$\boldsymbol{\theta}$	Vector of delayed signals for the autoregressive model
ρ	Pearson linear correlation
ε	Error of the autoregressive model
ς_1	Scaling factor of the linear dynamic matrix
ς_2 and ς_3	Tuning factors for the control input
Υ	Nonlinear functions of the nonlinear autoregressive model
Ξ	Fourier vector base
Θ	Estimated parameters using orthogonal polynomials
λ	Generic eigenvalue
Λ	Matrix of eigenvalues
ϵ	Error between approximate and perfect gains of the adaptive controller
Γ	Gain matrix multiplied by the sign of its determinant

CONTENTS

1	INTRODUCTION	16
1.1	Objectives	20
1.2	Achieved contributions	20
1.3	Summary of the chapters	22
1.4	Strategies employed to develop this thesis	23
1.4.1	Theoretical data	24
1.4.2	Experimental data	25
2	FUNDAMENTALS OF ELECTROPHYSIOLOGY AND NEURAL DYNAMICS	27
2.1	Action potentials	27
2.2	From action potentials to EEGs	28
2.3	Intracranial EEG	30
2.4	Mathematical fundamentals of neural dynamics	31
2.4.1	Examples of spiking neuron models	33
2.5	10-20 System for signal acquisition	38
3	SEIZURE SUPPRESSION USING THE EPILEPTOR MODEL	39
3.1	The Epileptor	39
3.1.1	State-space representation	42
3.1.2	Epileptor's uncontrolled behavior	43
3.2	Applying the controller	46
3.2.1	Fuzzy Takagi-Sugeno modeling	48
3.2.2	Example of Fuzzy Takagi-Sugeno modeling	49
3.2.3	Stability analysis	51
3.2.4	The submodels for the Epileptor	52
3.2.5	Constraints on the input and output	54
3.2.6	Epileptor's controlled behavior	55
3.3	Contributions, limitations and conclusions	62
4	RECONSTRUCTING THE UNMEASURABLE VARIABLES OF THE EPILEPTOR MODEL	64
4.1	Measurable and unmeasurable variables	64
4.2	Fuzzy state observer	66

4.2.1	Differential Mean Value Theorem (DMVT)	68
4.2.2	Stability analysis of the error dynamics	70
4.3	Reducing the time necessary for stability to be achieved	71
4.3.1	Classic approach	71
4.3.2	Proposal of enhancement	72
4.4	Applying the observer	73
4.4.1	Observer for an on-going seizure	74
4.4.2	Observer for the transition between non-seizure and seizure	77
4.5	Contributions, limitations and conclusions	80
5	ESTIMATING THE PARAMETERS OF THE EPILEPTOR MODEL	82
5.1	Parameter estimation: overview	84
5.1.1	Pre-optimization	84
5.1.2	Optimization	87
5.1.3	Validation	90
5.2	Parameter estimation: application	92
5.2.1	Influence of the time window	93
5.2.2	Influence of interictal and ictal states	95
5.2.3	Influence of the uncertainty factor δ	98
5.2.4	Influence of noise addition $\mathcal{N}(t)$	100
5.3	Integrating parameter estimation and controllers for seizure suppression	103
5.3.1	Relevance to real seizure suppression	107
5.4	Contributions, limitations and conclusions	108
6	BLACK-BOX MODELING FOR RECONSTRUCTING AND ATTENUATING REAL SEIZURES	111
6.1	General methodology	113
6.2	Design stage	114
6.2.1	Signal processing and frequency analysis	115
6.2.2	AR model definition, order selection, fitting and extension	117
6.2.3	Discrete and continuous state-space definition (DSS/CSS)	122
6.2.4	Design of the observer	126
6.2.5	Design of the controller	128
6.2.6	Hybrid and non-hybrid observers and controllers	130
6.2.7	Remarks on the controller	130
6.3	Simulation stage	130

6.3.1	Applying the observer and controller	131
6.3.2	Non-hybrid controller	132
6.3.3	Hybrid controller	134
6.3.4	Input stimulus	134
6.4	Comparison stage	137
6.4.1	Power Spectral Density (PSD) and Principal Component Analysis (PCA)	137
6.5	Relevant aspects of non-hybrid and hybrid controllers	140
6.6	Assessing nonlinear models	143
6.6.1	NAR models	144
6.6.2	Statistical analysis	144
6.6.3	Analysis of general model	145
6.6.4	state-space conversion	147
6.6.5	Seizure reconstruction and attenuation	148
6.7	Contributions, limitations and conclusions	150
6.7.1	Remarks on the NAR model	153
7	GRAY-BOX MODELING FOR RECONSTRUCTING AND ATTENUATING REAL SEIZURES	155
7.1	General methodology	156
7.1.1	Definitions and notation	156
7.2	Signal processing and analysis	158
7.3	Identifying candidate models	162
7.3.1	Orthogonal Polynomials	163
7.3.2	Examples of candidate models	165
7.3.3	Remarks on the identification process	168
7.4	Signal reconstruction via closed-loop models	169
7.4.1	Reconstruction error	171
7.4.2	Influence of the decay rate	172
7.4.3	Remarks on the closed-loop reconstructed models	173
7.5	Signal attenuation via closed-loop models	174
7.5.1	Adaptive controller	176
7.5.2	Fixed-gain controller	179
7.5.3	Remarks on closed-loop attenuated seizure	186
7.6	Integration of identification, reconstruction and attenuation	187
7.7	Operational aspects for practical applications	189
7.8	Assessment of the controllers and comparison with existing results	192
7.9	Contributions, limitations and conclusions	194

8	Final Remarks	198
8.1	Main contributions	198
8.2	Future work	198
	REFERENCES	200
	APPENDIX A - MATHEMATICAL FORMULATION FOR THE PARAMETER β	213
	APPENDIX B - COMPLEMENTARY RESULTS FOR THE FUZZY OBSERVER	226
	APPENDIX C - COMPLEMENTARY RESULTS FOR THE BLACK- BOX MODELING	228
	APPENDIX D - MODEL REFERENCE ADAPTIVE CONTROLLER (MRAC)	233
	Remarks on the adaptive controller	235
	Complementary results for seizure attenuation	236

1 INTRODUCTION

Epilepsy affects millions of people worldwide every year (Iasemidis, 2003; Dua et al., 2006), some of which may even have complications that lead to unexpected death (Surges et al., 2009; Ryvlin; Nashef; Tomson, 2013). For the remaining patients who survive, there are several physical, psychological/psychiatric and social implications that reduce their quality of life, such as: headaches or migraines, mental confusion, depression and embarrassment (Fisher; Schachter, 2000). Consequently, this disorder is regarded as a very sensitive and relevant topic of research. It is usually associated to the progressive hypersynchrony of neural firing over time and loss of brain complexity, generated by endogeneous (genetic or developmental abnormalities, central nervous system infection, traumas, for example) or exogenous agents (external flickering stimuli) (Iasemidis, 2003; Zhu et al., 2010). However, the precise triggering mechanisms that cause a healthy brain to have a seizure are not sufficiently understood yet (Vezzani et al., 2011).

Different possible therapies that aim at seizure mitigation or control are available nowadays, ranging from pharmacological, surgical or electrical stimulation procedures, to specific types of diets, such as ketogenic ones (Iasemidis, 2003; Meira et al., 2019). Nonetheless, none of them is fully succesful: approximately 1/3 of patients with epilepsy are drug-resistant or may develop a tolerance to the conventional medicines (Iasemidis, 2003); undergoing surgery is a complex and risky procedure, and only carefully selected cases are suitable to it (Iasemidis, 2003); brain electrical or magnetic stimulation, in turn, either present moderate results or need further research (Iasemidis, 2003; Chen r; Nolan, 2016); ketogenic diets, albeit efficient in reducing neural excitability and seizures, tend to be impalatable or too restrictive, apart from side effects, which often causes patients to abandon them (Meira et al., 2019).

These are the main reasons that motivated researchers to address epilepsy from a more theoretical standpoint, using mathematical and physical tools. An important contribution in this sense is the development of dynamic models that can represent the main features of epileptiform activities (Jirsa et al., 2014; Chizhov et al., 2018). This was made possible thanks to previously well documented investigations about neuron spiking/bursting in the literature, some of which compared to real brain activities (Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003), and it is worth mentioning that such models have been increasingly well accepted in the scientific community (Wendling et al., 2016). One of them, called Epileptor, is a phenomenological dynamic model whose objective is to reproduce epileptic-like events on a scale (usually measured in μV or mV) that is similar to that ob-

served in local field potentials (LFP) (Jirsa et al., 2014), the activity that can be measured from the portion of electrical current that flows through the extracellular space of neurons. It has been consistent with a relatively wide range of types of seizures, mainly those from mice, and helped to explain experimental observations concerning, for instance, seizure onset and propagation (Jirsa et al., 2014; Jirsa et al., 2017).

The Epileptor model has been a breakthrough in the field of neurosciences for specific reasons: it was designed based on experimental models of mice but considering that epileptiform features are shared accross species, using well-established tools from nonlinear systems theory (Jirsa et al., 2014), which made it possible to represent well interictal (non-seizure) and ictal (on-going seizure) states, as well as transitions between them; it can generate spike and wave events and fast oscillations, common structures in real activities (Jirsa et al., 2014); its simulations have been consistent with experimental observations in terms of seizure onset and triggering effects (Jirsa et al., 2014); it is a relatively simple, general-purpose and easily addressable model.

Also, it has led to several follow-up studies: Houssaini et al. (2015) carried out a detailed bifurcation analysis using this model and verified the coexistence of different pathological brain activities and states under certain particular conditions; Zhang and Xiao (2018) studied the synchronization of Epileptor models under different coupling conditions; Proix et al. (2017) addressed the recruitment of brain regions during seizure propagation using a virtual brain modeling approach consisting of Epileptors; Jirsa et al. (2017) developed patient-specific personalized brain network models by fitting experimental data to the results obtained by coupling Epileptors.

Possible questions that arise are whether and how the dynamics described by the Epileptor can be controlled, as well as if the controlling effects can be extended to practical situations. Some of them have been partially answered: Nagaraj, Lamperski and Netoff (2017) investigated an approach of optimizing stimulation frequencies for controlling the seizures described by Epileptor based on a reinforcement learning algorithm. The authors evaluated their method adopting periodic pulses of one mili-second width and a reduced version of Epileptor. However, duration, frequency, shape and amplitude for this type of stimulus can be very different depending on the set of parameters used to define the dynamic model. This fact is endorsed by applications in clinical environments, in which a considerable variability is verified not only in terms of the shape of the stimuli (Velasco et al., 2001; Tellez-zenteno et al., 2006; Velasco et al., 2007; Rizzone et al., 2001), but also their regularity over time, presenting positive results being periodic or randomly spaced (Cota et al., 2009). Besides, because of the reduced model, which accounts for only two of the six states, the authors mention that finer state-space (SS) partitioning or the additional feature dimensions may enhance their results (Nagaraj; Lamperski; Netoff,

2017).

Approaches for designing controllers able to suppress the activity described by the full Epileptor lack in the literature. This type of solution may be interesting to provide the necessary conditions to study not only seizure propagation, as previously mentioned, but also seizure mitigation in virtual brain schemes (Proix et al., 2017), for example. Moreover, it may lead to a better definition of the inputs that must be applied to patients, considering electrical stimuli, so that seizure suppression is attained. The first goal of the present thesis is, thus, to design efficient controllers to drive Epileptor's activity out of a seizure, restoring it to a non-seizure condition. The tool adopted for doing so is fuzzy Takagi-Sugeno (FTS) modeling (Takagi; Sugeno, 1985; Tanaka; Wang, 2004), a sophisticated control approach based on Linear Matrix Inequalities (LMIs) that handles particularly well dynamic models with nonlinear functions (Tanaka; Wang, 2004), as the case of Epileptor.

In practice, for the controller to work, Epileptor's variables and parameters (i.e., its plant, or SS representation) must be known, which is only true for simulations, not practical situations. In this case, the present work also considers LMIs to design state observers (which have also proved to be efficient in different kinds of systems¹) in order to reconstruct the unmeasurable variables from Epileptor based only on its measurable activity in the time domain. As for the parameters of the system, a successive optimization approach is adopted (Nelder; Mead, 1965; Luersen; Le Riche, 2004) considering, as inputs, only the measurable activity as well. A full integration process can then be accomplished by adopting a state-feedback approach: measuring the output of the system, represented by Epileptor's electrical activity in the time domain, estimating its parameters to design the observer and reconstruct its unmeasurable variables, and designing controllers based on the same parameters for purposes of seizure suppression. Nevertheless, this can only be carried out in practical applications assuming that a plant is accurately obtained, i.e. if the Epileptor model is, indeed, representative of a real seizure. This can be assessed by analyzing its behavior over time compared to a real signal, which is also directly related to its SS representation.

In this thesis, the SS model is found by calculating successive optimizations as a parameter estimation approach considering simulated Epileptors with and without the addition of artificial noise. Although important and useful to validate the hypothesis of obtaining a representative SS notation that may lead to the design of observers and controllers, this might be too restrictive to certain types of signatures. In fact, even with the proposed integration process to overcome theoretical limitations, Epileptor does not capture all the dynamics present in all seizures and remains a rather abstract model.

¹See, for instance: Ichalal, Arioui and Mammar (2011), Ichalal et al. (2011), Ichalal et al. (2012), Hammoudi et al. (2014)

This is also addressed in this thesis by taking into account experimental data coming from different areas of the brain and levels of electrical activity.

Thus, to extend the applicability of the proposed approach to seizure signatures that are not accurately described by Epileptor, most notably those from real data, a different strategy must be applied: system identification (SI) techniques (Ljung, 1998; Noël; Kerschén, 2017). SI is a widely studied topic in some areas of knowledge, such as structure and control engineering (Ljung, 1998), in which the identification depends on the knowledge about the system: there exist, for example, white-box models, which rely on having prior knowledge and deterministic equations that represent it (Duun-henriksen et al., 2013); gray-box models, which rely on prior knowledge and some available data (Ljung, 1998; Duun-henriksen et al., 2013), which in this case is the electrophysiological recordings from brain activity; and black-box models, which only take the data into account, without any previous knowledge (Ljung, 1998; Duun-henriksen et al., 2013). As far as this thesis is concerned, black- and gray-box models are investigated, especially because there is not a full representative set of equations that can completely and accurately emulate the behavior of the whole brain – which would be considered a white-box model.

Studies involving linear or nonlinear autoregressive models (AR/NAR), typical black-box modeling tools, have been mostly proposed in the literature for seizure detection, prediction and synchronization (Franaszczuk; Bergey, 1999; Chisci et al., 2010; Yu et al., 2016; Ouyang et al., 2020; Attia; Moussaoui; Chahir, 2021), but approaches considering system identification have also been used to describe the so-called NAR fingerprints of patients (Schiff et al., 1995; Schiff; Victor; Canel, 1995). However, the latter ones do not provide a systematic procedure to characterize the AR equations in terms of dynamic models. If this is done, seizures can be described in state-space notation and used for purposes of control², which is precisely what is covered in this thesis, at the LFP level. Furthermore, as a gray-box modeling, an SI procedure is carried out based on orthogonal polynomials (Pacheco; Jr, 2002) to reconstruct the seizures measured at more global brain activities, such as the electroencephalogram (EEG) or intracranial EEG (iEEG), and then apply the controller to attenuate them, a concept that has not been proposed yet.

In summary, this thesis proposes a comprehensive approach for controlling seizures, whether generated by a theoretical parametric model or based on real electrophysiological recordings combined with system identification techniques. Numerical, theoretical and practical limitations are surpassed by using state observers, parameter estimation techniques, and artificial reconstruction/attenuation of signals. Since the inputs of the controller can be computed during its application, the main inference that can be made

²As a matter of fact, AR/NAR models are inherently convertible into state-space notations, which makes it possible to use them as plants for the design of controllers and observers (Durbin; Koopman, 2012; Fox, 2015).

is that their shape, intensity and frequency may be translatable into real stimuli that are able to attenuate the seizure represented by the signals. Such information can be used as an auxiliary tool to help physicians in the process of decision making when it comes to choosing the parameters in electrical stimulation therapies. Ultimately, the results obtained in this thesis are helpful and potentially applicable in hospital centers for seizure attenuation, thus representing a significant advance in the field of epilepsy.

1.1 Objectives

The general objective of this thesis is to develop a new comprehensive approach to attenuate the epileptic seizures described by parametric semi-physical models or electrophysiological responses (theoretical and real experimental data, respectively). The specific objectives are presented below:

1. to develop an FTS-LMI-based controller to suppress epileptic seizures described by the Epileptor model;
2. to design an FTS-LMI-based state observer to estimate the non-physical states of the Epileptor model based on its LFP;
3. to create an approach to estimate the parameters of the Epileptor model based on its LFP;
4. to adapt the same approach proposed in 1 to 3 to real electrophysiological recordings using black-box modeling such that seizure reconstruction and attenuation can be carried out artificially at the LFP level;
5. to apply the same strategy as in 4, but using gray-box modeling at more global brain activities, such as EEG and iEEG;
6. to provide a careful assessment of the practical use of active controllers for epileptic seizure suppression based on the findings and other articles from the literature. This includes how the shape, frequency and amplitude of the electrical input obtained from the simulations in this thesis can be used as auxiliary information in electrical stimulation therapies for real seizure suppression in clinical environments.

1.2 Achieved contributions

The main achieved contributions are listed below, each of which associated to its corresponding specific objective.

- **Specific Objective 1 (achieved):** the Fuzzy Takagi-Sugeno modeling was applied to design an LMI-based controller. The Epileptor model was previously written in the SS notation, and a robust strategy was defined to compute the input stimuli to suppress its seizures. The results can be found at (Brogin; Faber; Bueno, 2020a):

BROGIN, J. A. F., FABER, J., & BUENO, D. D. *An Efficient Approach to Define the Input Stimuli to Suppress Epileptic Seizures Described by the Epileptor Model*. **International Journal of Neural Systems**, v. 30, n. 11, p. 2050062, 2020. PMID: 32938259. Available from: <<https://doi.org/10.1142/S0129065720500628>>. *This article already has 11 citations (Google Scholar)*.

- **Specific Objective 2 (achieved):** the LMI-based approach was proposed to design a state observer based on the local field potential. Epileptor's states were accurately reconstructed, and the results were published can be found at (Brogin; Faber; Bueno, 2021):

BROGIN, J. A. F., FABER, J., & BUENO, D. D. *Burster Reconstruction Considering Unmeasurable Variables in the Epileptor Model*. **Neural Computation**, v. 33, n. 12, p. 3288-3333, 11 2021. ISSN 0899-7667. Available from: <<https://doi.org/10.1162/neco.2021.01443>>. *This article already has 3 citations (Google Scholar)*.

- **Specific Objective 3 (achieved):** a parameter estimation approach was developed and the integration with observers and controllers was successfully carried out. The results can be found at (Brogin; Faber; Bueno, 2022):

BROGIN, J. A. F., FABER, J., & BUENO, D. D. *Estimating the parameters of the epileptor model for epileptic seizure suppression*. **NeuroInformatics**, 20, 919-941, 2022. Available from: <<https://doi.org/10.1007/s12021-022-09583-6>>. *This article already has 2 citation (Google Scholar)*.

- **Specific Objective 4 (achieved):** AR models were used to identify the epileptiform signatures in the time domain of real LFPs as state-space representations; the seizures were artificially reconstructed and attenuated. A manuscript has been submitted to **PLoS One** and is currently under review. The results can be found as a preprint at (Brogin et al., 2023):

BROGIN, J. A. F., FABER, J., & BUENO, D. D. *Epileptic seizure suppression: a computational approach for identification and control using real data*. **bioRxiv**, Cold Spring Harbor Laboratory, 2023. Available from: <<https://www.biorxiv.org/content/early/2023/01/08/2023.01.08.522971>>. *This article already has 1 citation*.

Besides, an NAR model was identified based on common statistical features shared across patients. The results have been submitted and accepted for publication in the [IX Latin American Congress on Biomedical Engineering \(CLAIB 2022\)](#) and in the [International Federation for Medical and Biological Engineering \(IFMBE\) Proceedings](#). Although they have not been published yet, they can be found as a preprint at:

BROGIN, J. A. F., FABER, J., & BUENO, D. D. *A general NAR model for seizure identification across different patients*. [IX Latin American Congress on Biomedical Engineering \(CLAIB 2022\)](#), 2022. Available from: <[https://www.research gate.net/publication/363740393 _A_general_NAR_model_for_seizure_identification_across_different_patients](https://www.researchgate.net/publication/363740393_A_general_NAR_model_for_seizure_identification_across_different_patients)>.

As complementary results, a NAR model was combined with an FTS strategy to obtain a nonlinear model and attenuate seizures computationally, presented in the Workshop of the Post-Graduate Program in Mechanical Engineering (PPGEM) in 2022.

- **Specific Objective 5 (achieved):** orthogonal polynomials and closed-loop controllers were combined with model reference controllers to reconstruct and attenuate the seizures computationally. The results have been organized a new article to be submitted soon to an international journal.
- **Specific Objective 6:** a complete bibliographic revision has been continually carried out, and a thorough evaluation of the findings will be done before finishing this doctoral research, mainly for establishing the state of the art, current limitations and challenges, and opportunities for future researches.

1.3 Summary of the chapters

This thesis is organized in 8 chapters, each of which is briefly described below:

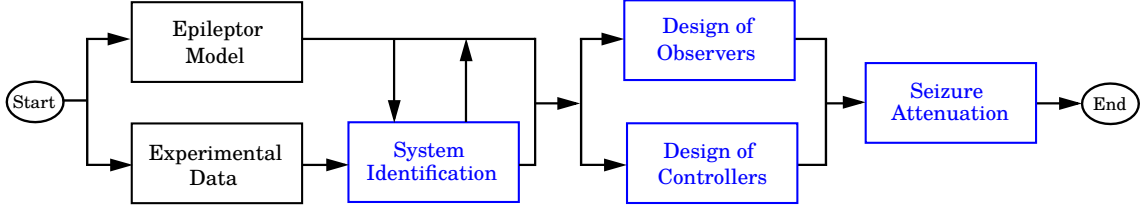
- **Chapter 1:** Presents an introduction containing the context and the motivation of this thesis, as well as its objectives, achieved and expected contributions;
- **Chapter 2:** Covers basic concepts of neural dynamics and electrophysiology. Since specific time signatures (at different scales) are analyzed in this work, this chapter is important to introduce the main types of signals that can be measured from brain tissues;

- **Chapter 3:** Introduces the Epileptor, the single closed-form dynamic model studied in this thesis, as well as the main control approach (FTS) for attenuating its seizures. The main constraints about the controller are discussed in detail;
- **Chapter 4:** Presents the FTS observer for estimating Epileptor's unmeasurable variables, thus eliminating the first theoretical constraint for the control approach;
- **Chapter 5:** Introduces the strategy of successive optimizations developed for the Epileptor to estimate its parameters over time, thus eliminating the second theoretical constraint for the control approach;
- **Chapter 6:** Extends the approach to time signatures that are not well represented by the Epileptor by applying linear and nonlinear autoregressive (AR/NAR) modeling to real electrophysiological activity at the LFP and iEEG level;
- **Chapter 7:** Presents an alternative to AR/NAR modeling by using model reference controllers (MRCs), thus eliminating theoretical constraints about this technique. The MRCs are applied to other types of signals, such as iEEG and EEG;
- **Chapter 8:** Summarizes the main findings of the thesis and indicates some directions for future work.

1.4 Strategies employed to develop this thesis

The methodology adopted for this thesis comprises two main strategies to evaluate different applications: the first one involving theoretical data and the second one based on experimental data obtained from real electrophysiological recordings. Regardless, the same approach holds for any of them, as shown in Fig. 1: the system identification stage is responsible for estimating the parameters of the Epileptor model or identifying full models based on the real data from experimental recordings; for the Epileptor, there is already a state-space notation with the estimated parameters, but for the identified models it is necessary to perform a double conversion: into discrete-time SS notation (Durbin; Koopman, 2012; Fox, 2015) and then into continuous-time SS (Shieh; Wang; Yates, 1980); the design of observers and controllers can be carried out based on both plants; closed-loop simulation results in the behavior of Epileptor in the time domain or reconstructs the real signals, which then are attenuated by the input stimulus.

Figure 1 – **General flowchart of the integration proposed in this thesis.** System identification provides either estimations of the parameters of the Epileptor model or full models based on the real data. After conversion into state-space notation, observers and controllers can be designed for seizure attenuation. It must be stressed that, although similar stages are applied to the data, only Epileptor can be readily implemented computationally, the other models are firstly identified from real data and then reconstructed artificially. The stages for which this thesis proposes a contribution are indicated in blue



Source: Own authorship.

1.4.1 Theoretical data

The theoretical data used in this thesis are generated by a mathematical dynamic model called the Epileptor. Basically, it consists of six coupled first-order differential equations, leading to six different states as well, which together are able to simulate the behavior of epileptiform activity. Only two of the states, related to LFPs, have a precise physical meaning, given in terms of difference of potential measurable in the time domain. Therefore, the seizure signature analyzed is the linear combination between these two states.

Since Epileptor is a canonical model, its typical behavior attempts to capture the main features found in time signatures of seizures from different species – such as mouse, rat, zebrafish and human – recorded in the time domain at the LFP level. Considering this, according to Jirsa et al. (2014), any experimental model system could be used to validate the model, but due to convenient experimental conditions, recordings were made *in vitro* from the hippocampus of mice, resulting in seizure-like events that, in general, contain sequences of tonic or tonic-clonic patterns (Jirsa et al., 2014). These recordings may exhibit changes of dynamics from seizure onset to offset such as variations of amplitude and frequency of discharge, characterizing transitions between silent to active (ictal) phases, called bursting, or vice-versa, leading to non-seizure (interictal) phases (Jirsa et al., 2014).

The same authors also mention that in total there are 4 most common transitions, or bifurcations, at seizure onset, and 4 other ones at seizure offset, of which 2 stand out for being prevalent in the recordings: saddle-node (onset) and homoclinic (offset) bifurcations, thus characterizing the so-called square wave burster. In this sense, the theoretical data provided by the Epileptor may be directly (but not strictly) related to

tonic-clonic patterns from field potentials of mice. This makes the model an interesting system of study for understanding this class of seizure, but given its generality the results obtained in this thesis can be extended to the epileptiform activity of other species as well. Further information about this model is found in Chapter 3.

1.4.2 Experimental data

The experimental data used in this thesis consist of three different datasets. Details for each of them are presented below:

- **First Dataset:** this set is only analyzed in Chapter 6 and its signals correspond to chemically induced epileptiform patterns recorded *in vitro* from the main microstructures found in the hippocampus: cornu ammonis, dentate gyrus and subiculum³, by using glass electrodes placed on slices of 12 human hippocampal specimens that were surgically resected from patients with pharmacoresistent temporal lobe epilepsy, leading to 35 time signatures acquired at a 10 kHz sampling frequency. This process was approved by the Ethics Committee of Universidade Federal de São Paulo (CAAE 47551015.1.0000.5505) with written informed consent from all the patients, and then recently published (Araújo et al., 2022). The study in this chapter was also approved by the Ethics Committee of Universidade Estadual Paulista “Júlio de Mesquita Filho” (CAAE 60470222.9.0000.5402), thus allowing for the use, analysis and sharing of the dataset, which is currently available on the platform Zenodo at: <https://doi.org/10.5281/zenodo.5039479>;
- **Second Dataset:** this dataset is only analyzed in Chapter 6 as a shorter complementary result to the approach applied to the first one. It is composed of the SWEC-ETHZ iEEG Database⁴, which is public and free of charge for research and education purposes, and can be found at the following address: <http://ieeg-swez.ethz.ch/>. A specific portion of it is chosen containing short-term intracranial electroencephalograms (iEEGs, recorded intracranially by strip, grid, and depth electrodes) of 100 seizures coming from 16 patients. The pre-ictal stage lasts up to the first three minutes of recording; the post-ictal stage, in turn, starts at the last three minutes of recording; at last, the ictal stage presents a variable number of time/samples (Burrello et al., 2019). All patients presented pharmaco-resistant epilepsies and were evaluated for surgery at the SWEC of the University Department of Neurology at the Inselspital Bern, after written informed consent was provided (Burrello et al., 2019). Each patient presents a varying number of seizures and electrodes, all of which digitally filtered between 0.5 and 150 Hz using a fourth-order Butterworth

³Further details about these structures can be found in Anand and Dhikav (2012).

⁴SWEC: Sleep-Wake-Epilepsy-Center; ETHZ: Eidgenössische Technische Hochschule Zürich.

filter prior to analysis, and stored with a 512 Hz sampling frequency (Burrello et al., 2019). In this work, the ictal condition is used to construct the models, whereas pre- and post-ictal conditions are neglected. The interictal condition, in turn, is only considered as a non-seizure reference for attenuation purposes;

- **Third Dataset:** this dataset is only used in Chapter 7 and is part of the multicenter prospective project led by Prof. Philippe Ryvlin, collaborator to this thesis, and coordinated by the Centre hospitalier universitaire vaudois (CHUV, Lausanne, Switzerland), currently involving 13 epilepsy centers in Switzerland and Europe. The main purpose of this project was to analyze biomarkers to establish a link between seizure severity and them. The data were collected at the Epilepsy Monitoring Unit (EMU) of the hospital and includes several types of signals (such as Pulse Oximetry (SpO2), skin temperature, Electrodermal Activity (EDA), Electrocardiogram (ECG), Photoplethysmography (PPG), and others) as well as video-EEG, which includes important information such as times of seizure onset/offset and type of seizure (local or generalized). Its use was approved by the Swiss National Science Foundation (SNF), number 320030_179240, protocol 2019-00437, for quantifying the severity of generalized tonic-clonic seizures (GTCS) with ambulatory connected devices (SEVERITY). For the analysis in this thesis, only the EEG data were included, because the main interest lies on the electrical brain activity. Besides, only the sub-dataset named SEVERITY-ZCH (Zurich) has been included due to its: 1) availability, since it was readily available for use in the platform of the Clinical Neuroscience Department of the CHUV; 2) flexibility, since it contains 11 seizures (each of which with a variable number of electrodes) from 13 different patients (for some, there are only annotations or complementary information, not biophysical signals), measured using a relatively low sampling frequency (256 Hz), representing a considerably large dataset but lightweight at the same time, which is a major advantage for computational purposes; 3) scale, since the signals recorded are either EEGs (10 patients) or iEEGs (3 patients), thus representing more global activities, and to which electrical stimulation for seizure attenuation can be associated aiming at future practical non-invasive (or less invasive). The use of this dataset was allowed inside the facilities of the CHUV and is thus not available on any online platform yet.

2 FUNDAMENTALS OF ELECTROPHYSIOLOGY AND NEURAL DYNAMICS

Brain activities are complex phenomena composed of a wide and rich range of patterns. They can be measured from different brain sites and layers at higher or lower time scales, which has direct implications on the type of signal and signature recorded by the electrodes. In this thesis, since several processing, analysis and control techniques are applied to simulated or real time series of such activities, it is relevant to introduce how they are generated and recorded, as well as their differences, which is precisely what is covered in this chapter.

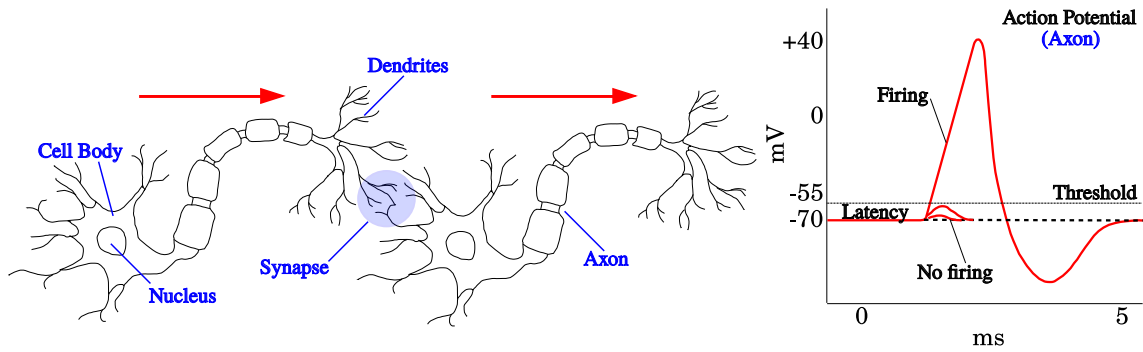
2.1 Action potentials

Neurons cannot only be analyzed from the point of view of biology as fundamental structures for processing information, they can also be understood from a more mathematical-physical standpoint as nonlinear systems with their intrinsic dynamics (Izhikevich, 2007). A neuron does not fire by itself, it receives inputs from other hundreds of neurons by connections between their dendrites or between a dendrite and the axon, called synapses (Izhikevich, 2007). These inputs induce transmembrane electrical currents that change its potential: the higher the current, the higher the potential. The potentials are amplified depending on both temporal and spatial synchronization: as any other type of oscillation, synchronized waves lead to constructive interferences whereas de-synchronized waves lead to destructive interferences. If the sum of potentials is strong enough to reach a specific level (inherent to neurons as well), known as firing threshold, there is an abrupt electrical discharge that flows through the axon of the neuron to the next one (Izhikevich, 2007). If the sum is not greater than the threshold, no firing occurs. In biological terms, this discharge characterizes an action potential; for convenience of nomenclature, it is considered a pre-synaptic potential. In mathematical terms, it qualifies neurons as excitable systems, operating near transitions (from latency, or rest state, to spiking or pulsing activity) called bifurcations (Izhikevich, 2000; Izhikevich, 2007).

This process is depicted in Fig. 2, where there is an illustration of two neurons connected by a synapse generating an action potential. Electrodes usually measure it in terms of difference of potential – in millivolts, at the neuron scale. Since such an activity is relatively fast (in the order of milliseconds), a high sampling frequency is necessary to record it. Upon signal acquisition in practice, an essential technical requirement must be met such that the potential is accurately measured: supposing the inherent frequency of

firing is $f_{s,\text{fire}}$, the minimum sampling frequency must be $2f_{s,\text{fire}}$ according to the Nyquist criterion (Shannon, 1984)¹. Another issue imposed in this case is the need of isolating a neuron, or a small group of neurons, from its surroundings, which can only be carried out considering invasive approaches (Graumann; Allison; Pfurtscheller, 2010). Therefore, although an action potential is the fundamental electrophysiological signature of the neuron, it is not the most commonly measured electrical activity. Furthermore, invasive procedures such as surgeries usually require the approval of an ethics committee before being performed, as well as the expertise of an interdisciplinary team during the operation, thus rendering signal acquisition even more complex.

Figure 2 – **Illustration of neurons generating an action potential.** A neuron is composed of four main parts: nucleus, cell body, dendrites and axons; connections between dendrites or a dendrite and axon are called synapses. The action potential is transmitted through the axon after the inherent threshold of the neuron is reached, leading to a single pulse in the time domain.



Source: Own authorship.

2.2 From action potentials to EEGs

As seen, the pre-synaptic (action) potential flows through the neurons. According to the same convenience of nomenclature, the post-synaptic potential is thus not related to the axon, but to the region of dendrite “trees” in between neurons, leading to the so-called Local Field Potentials (LFPs) (Graumann; Allison; Pfurtscheller, 2010). They also depend on both temporal and spatial synchronization of micropotentials that are summed up at the dendrites and arrive at the next cell body. In this sense, LFPs can also be seen as the electrical current that flows outside the neural cells (Graumann; Allison; Pfurtscheller, 2010). At this point, it becomes difficult to distinguish what portion of the potentials is from a single axon or from the dendrites. Besides, if an electrode is placed sufficiently

¹It is worth mentioning that, given that this criterion is theoretical, it assures only that the oscillatory phenomenon can be detected, not accurately reconstructed, which means that this value tends to be underestimated in practice.

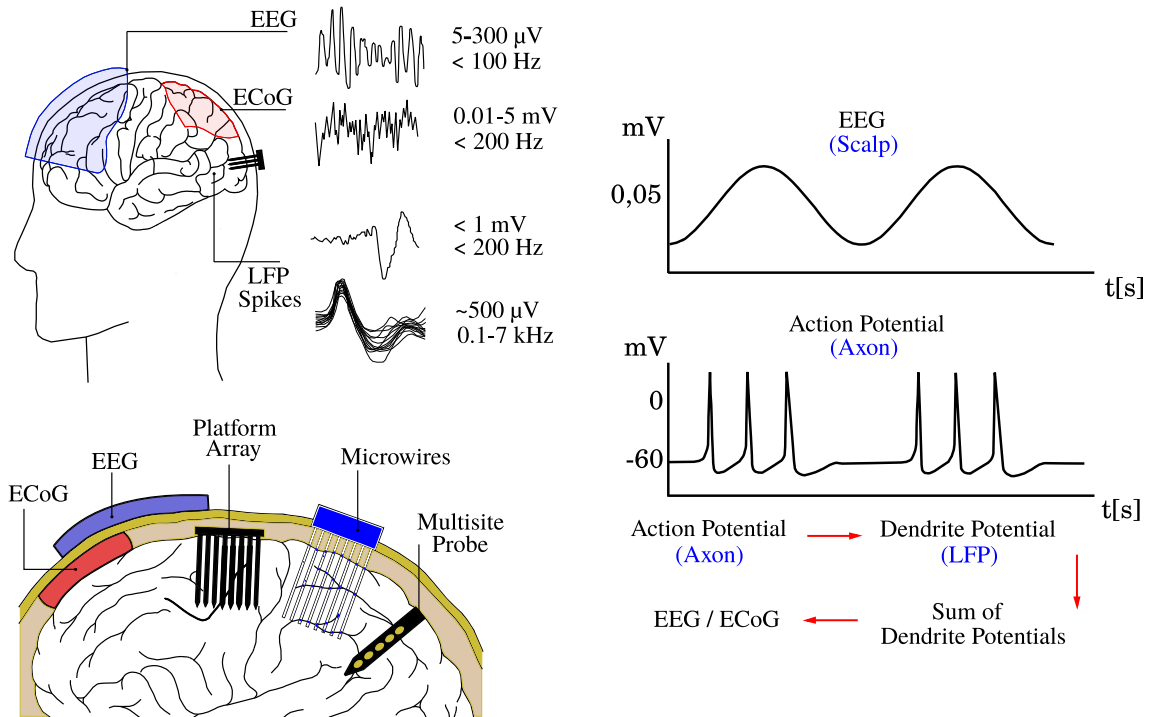
near the dendrites to measure the LFPs, it no longer records phenomena at $f_{s,\text{fire}}$, only at $f_{s,\text{LFP}} \leq f_{s,\text{fire}}$.

Depending on the intensity of the activity in which the neurons are engaged, the frequency and regularity of firing may increase or decrease (Graumann; Allison; Pfurtscheller, 2010), influencing directly the LFPs. Besides, firing is not necessarily continuous, it may be composed of intricate patterns including the formation of bursts, which basically are sequences of spikes followed by periods of latency again (Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003), or combinations of bursts, single spikes and latency (Araújo et al., 2022). If all of this activity is added together during synchronization and de-synchronization events of some neurons, the resulting wave probably looks like a complex combination of spikes/oscillations. Considering now a larger portion of brain tissue, the first LFPs give rise to more global activities: if they are measured on the surface of the cortex, they are called electrocorticograms (ECoG); if they are measured non-invasively (on the scalp of patients), they called electroencephalograms (EEG). For these cases, electrodes of sampling frequencies $f_{s,\text{ECoG}} \leq f_{s,\text{LFP}}$ and $f_{s,\text{EEG}} \leq f_{s,\text{ECoG}}$ are sufficient to record the differences of potential.

This happens because the placements of the electrodes is usually farther from the neurons that first emitted the firings, and thus they are both less intense (usually measured in microvolts, not millivolts anymore) and less sharp. At this point, the time signature does not look like a spike, but roughly like sines or cosines, which means that their time scale is relatively slower than that from action potentials and LFPs. In other words, the groups of neurons, layers of tissue and bones play the role of physical filters, and the appropriate electrodes to measure their electrical activity have a reduced sampling frequency (Graumann; Allison; Pfurtscheller, 2010). Illustrations of these potentials are depicted in Fig. 3 (Lago; Cester, 2017): measurements made at the neuron level (or small groups of neurons) have stronger potentials of high $f_{s,\text{fire}}$ and $f_{s,\text{LFP}}$; recordings made at the surface of the cortex have intermediate values of intensity and $f_{s,\text{ECoG}}$; at last, EEGs present the lowest intensity and $f_{s,\text{EEG}}$ ². It should be stressed that these characteristics are general and fluctuations always occur, as shown in the same figure.

²Recall that the higher the sampling rate, the lower the sampling frequency.

Figure 3 – **Illustration of how action potentials are related to EEGs.** They are essentially trains of spikes that, if synchronized, give rise to LFPs; if LFPs are in turn combined, ECoGs and EEGs are formed. Given that these latter activities are measured relatively far from individual neurons using electrodes of lower sampling frequency, the original spikes are attenuated by the layers of brain tissue, bones and skin, giving way to more global oscillations that look like sine waves in the time domain. Action potentials/LFPs can be measured using invasive devices such as platform arrays, microwires or multisite probes, whereas ECoGs and EEGs are usually measured by electrodes placed on the surface of the cortex and the scalp of patients, respectively.



Source: Own authorship.

2.3 Intracranial EEG

Although the nomenclature used for the types of electrophysiological activity is useful and usually indicates accurately the potentials that can be measured by the sensors or electrodes, it should be stressed that “EEG” can be regarded as an ensemble of LFPs, which in turn are composed of spikes. Consequently, it may be sometimes difficult to distinguish precisely when LFP is no longer an appropriate term to indicate an electric potential. Therefore, although EEG is typically a measurement made on the scalp (non-invasively), there seems to be adapted names using this terminology for some types of potentials in the literature, such as intracranial electroencephalograms (iEEG) and stereotactic EEG (sEEG), which are recorded invasively (Bourdillon et al., 2017; Parvizi; Kastner, 2018).

Unlike EEGs, iEEGs (as their name suggests) are recorded by electrodes implanted inside the brain, which makes an ECoG, for instance, a type of iEEG (Parvizi; Kastner, 2018), thus being able to measure populations of neurons (Parvizi; Kastner, 2018). Stereotactic EEGs, in turn, refer to potentials obtained by penetrating depth electrodes, positioned using stereotactic guidance, implanted through small burr holes in the skull (Herff; Krusienski; Kubben, 2020). These types of EEGs allow for the measurement of neural activity in deeper structures of the brain (Parvizi; Kastner, 2018; Herff; Krusienski; Kubben, 2020). In other words, for the sake of understanding, the following relation holds: both ECoG and sEEG are iEEGs (because they are measured invasively), but ECoG is usually obtained on the surface of the cortex, whereas sEEG uses a special technique for recording deeper layers of brain tissue.

These two techniques in particular have some advantages: they provide a high temporal resolution (Bourdillon et al., 2017; Parvizi; Kastner, 2018; Herff; Krusienski; Kubben, 2020) and can be efficiently used to identify the epileptogenic zone in the case of refractory epilepsy or medically intractable epilepsy, as well as other diseases such as Parkinson or even brain tumors (Herff; Krusienski; Kubben, 2020; Parvizi; Kastner, 2018). Along with LFPs and EEGs, they are of particular interest in this thesis because part of the dataset used to generate the results are based on iEEGs and sEEGs. The type of signal analyzed is always indicated when necessary in the next chapters. At last, this thesis does not deal with action potentials.

2.4 Mathematical fundamentals of neural dynamics

The nonlinear behavior of neurons and LFPs can be modeled using tools from the nonlinear systems theory (Izhikevich, 2000). This is particularly useful in this thesis since the Epileptor model, which simulates epileptic seizures at the LFP level, is designed based widely on these tools. Therefore, in this subsection a brief introduction is presented to how time signatures such as spikings are generated over time. Consider the following simple dynamic system composed of two state variables (Izhikevich, 2000):

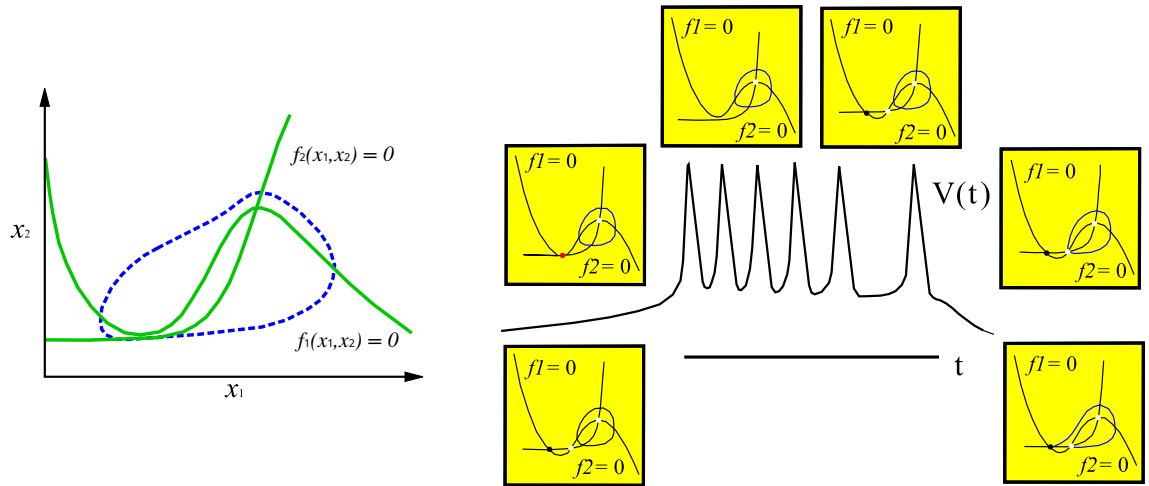
$$\begin{cases} \dot{x}_1 = \frac{1}{\tau} f_1(x_1, x_2) \\ \dot{x}_2 = f_2(x_1, x_2) \end{cases} \quad (1)$$

where τ is a time scale parameter and $f_i(x_1, x_2)$, $i = 1, 2$ are usually nonlinear functions that couple both states³. According to Izhikevich (2000), spiking formation can be generated from the relative motion of the nullclines ($f_i(x_1, x_2) = 0$, $i = 1, 2$) of both of these coupling functions on the phase portrait represented by (x_1, x_2) , as presented in Fig. 4.

³These functions are usually parabolic or cubic (Izhikevich, 2000).

Such motion depends on the choice of the coupling functions and, as the system evolves in the time domain, it presents a behavior that characterizes the so-called limit cycle (Izhikevich, 2000). In the case presented in the same figure, the choice of the functions leads to 3 equilibrium points (at which all the states are equal to zero). If this dynamic system is simulated, as the iterations proceed, the nullclines move closer to each other and two of the equilibrium points collapse, making the trajectory of the curves on the phase portrait enter the limit cycle; it only “escapes” from the cycle if the relative motion of the nullclines is such that the three equilibrium points can be formed again (which depends on the coupling functions as well).

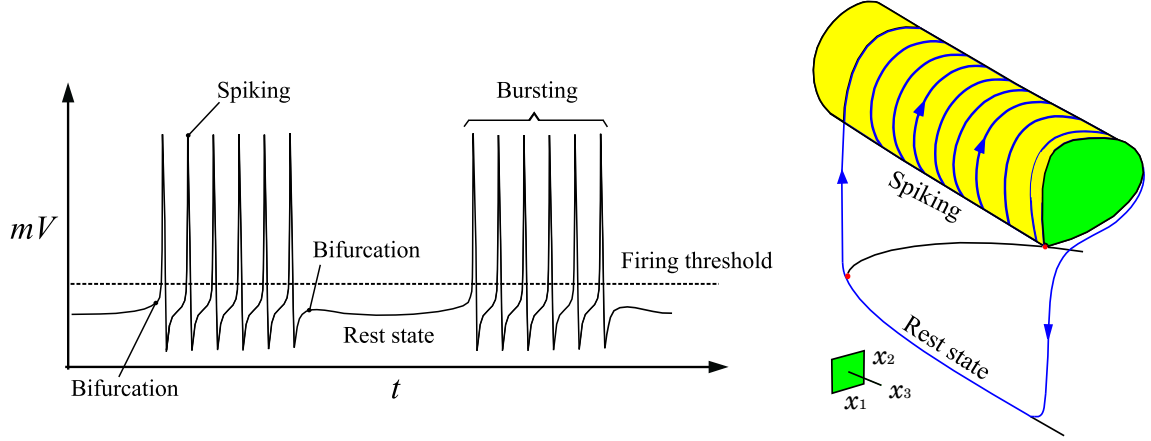
Figure 4 – **Example of spiking generation on the phase portrait of a dynamic system that simulates a neuron dynamics with two state variables.** The relative motion of the nullclines ($f_i(x_1, x_2) = 0$, $i = 1, 2$) of both of these coupling functions make one of the equilibrium points collapse and enter the limit cycle; moments later, the same motion makes the trajectory “escape” from the cycle.



Source: Adapted from Izhikevich (2000).

Although there are dynamic systems composed of only two state variables that are able to generate spikes based on transitions from rest states into limit cycles and then from the cycles back to the rest states (Izhikevich, 2003), most of them operate according to a third state called control variable (Slotine; Li et al., 1991). Such a variable is the main responsible for the transitions verified in the time domain (or, as seen in the previous sections, bifurcations). An example of a system with a control variable is presented in Fig. 5, with two regular states (x_1 and x_2) and a control one (x_3). Note that the two main behaviors switch over time, thus characterizing a bi-stable system composed of sequential spikes (known as bursts) and rest states. This is typical of neurons of ensemble of neurons, whose electrical activity can be action potentials or LFPs, as is the case for the Epileptor (Jirsa et al., 2014).

Figure 5 – **Example of spiking generation on the time domain and its corresponding burster, revealed from two regular state variables a third control one.** The first bifurcation leads to a sequence of spikes; a second bifurcation leads the system out of the limit cycle, ceasing the spikes; this behavior is repeated over time, characterizing the transitions from rest state into bursting and vice-versa.



Source: Adapted from Izhikevich (2000).

2.4.1 Examples of spiking neuron models

Two widely studied spiking neuron models are the Hindmarsh-Rose and Izhikevich models (Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003). For illustration purposes, the parameters of both models are generically represented by p_i in this subsection. The Izhikevich model is given by the following set of equations (Izhikevich, 2003):

$$\begin{cases} \dot{x}_1 = 0.04x_1^2 + 5x_1 - x_2 + I + 140 \\ \dot{x}_2 = \frac{1}{\tau}(p_1 - x_2) \end{cases} \quad (2)$$

subjected to: if $x_1 \geq 30$ mV, then $x_1 \leftarrow p_2$ and $x_2 \leftarrow x_2 + p_3$, where τ is the time scale of the recovery variable x_2 ; p_i , $i = 1, \dots, 3$ are the sensitivity of x_2 to threshold oscillations, the after-spike reset of the membrane potential x_1 , and the after-spike reset of x_2 , respectively; and I is the electrical current applied to the membrane of the neuron. The set of equations for the Hindmarsh-Rose model is (Hindmarsh; Rose; Huxley, 1984)⁴:

$$\begin{cases} \dot{x}_1 = x_2 - p_1x_1^3 + p_2x_1^2 - x_3 + I \\ \dot{x}_2 = p_3 - p_4x_1^2 - x_2 \\ \dot{x}_3 = \frac{1}{\tau}[p_5(x_1 - x_0) - x_3] \end{cases} \quad (3)$$

⁴This model is of particular interest in this thesis for illustration purposes because the Epileptor, the system used for obtaining theoretical data, is designed based partially on it (Jirsa et al., 2014).

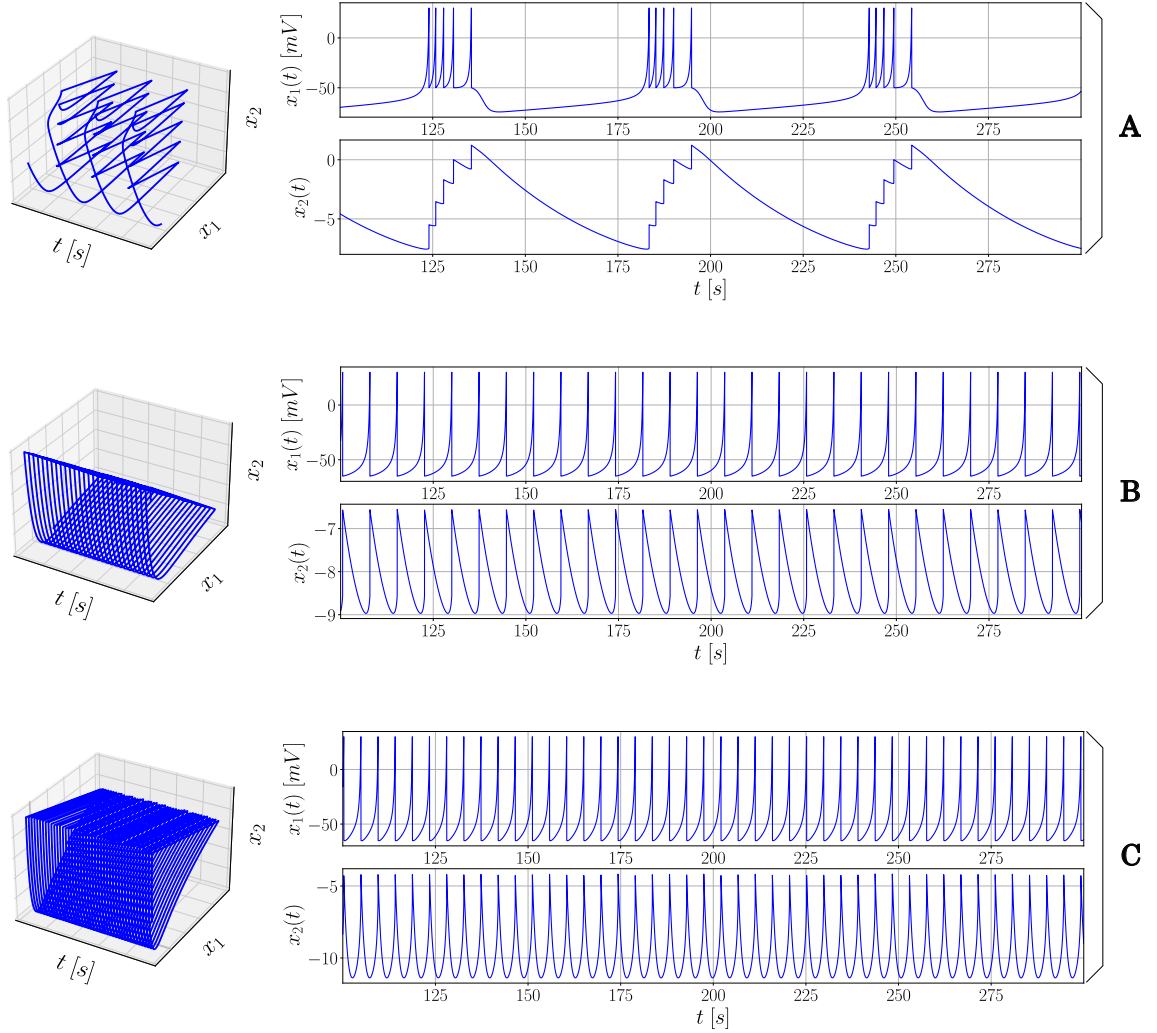
where, according to Hindmarsh, Rose and Huxley (1984) and Storace, Linaro and Lange (2008), τ is the time scale parameter; p_i , $i = 1, \dots, 4$ are usually (but not necessarily) fixed parameters, which model the nullclines in the phase portrait; p_5 is the so-called adaptation parameter; x_0 is the resting potential; x_i , $i = 1, \dots, 3$ are the state variables, related to the membrane potential, recovery variable and control variable, related to the efficiency of slow channels in exchanging ions, respectively; and I is the electrical current applied to the membrane of the neuron.

The first important difference between these models is that the Izhikevich model is only capable of reproducing the firing patterns because it presents a “jump” in the time domain, given by the resets of the membrane and recovery variables, whereas the Hindmarsh-Rose model presents transitions controlled by the third variable. Figure 6 depicts simulations of the Izhikevich model in two different modes (Izhikevich, 2003): chattering and fast spike, showing the richness in behavior it is able to emulate. Besides, changing the time scale parameter τ leads to more or less firing cycles: in the chattering mode, $\tau = 50$ yields few peaks distributed in the bursts and a fixed interval between them; in the fast spike mode, changing from $\tau = 10$ to $\tau = 1$ leads to more spikes per unit of time. At last, it is worth mentioning that the Izhikevich model does not present a characteristic burster because its set of equations contains only 2 state variables.

Figure 7 depicts simulations of the Hindmarsh-Rose model in two different modes (Hindmarsh; Rose; Huxley, 1984), similar to the ones from the Izhikevich model, showing the richness in behavior it is able to emulate. Besides, changing the time scale parameter τ leads again to more or less firing cycles: in the chattering-like mode, $\tau = 1000$ yields few peaks distributed in the bursts and a fixed interval between them; in the periodic spiking mode, changing from $\tau = 100$ to $\tau = 12.5$ leads to more spikes per unit of time. Close attention must be paid to the third variable x_3 , which controls, in the case of the chattering-like mode, when the system presents transitions from rest state to firing and vice-versa.

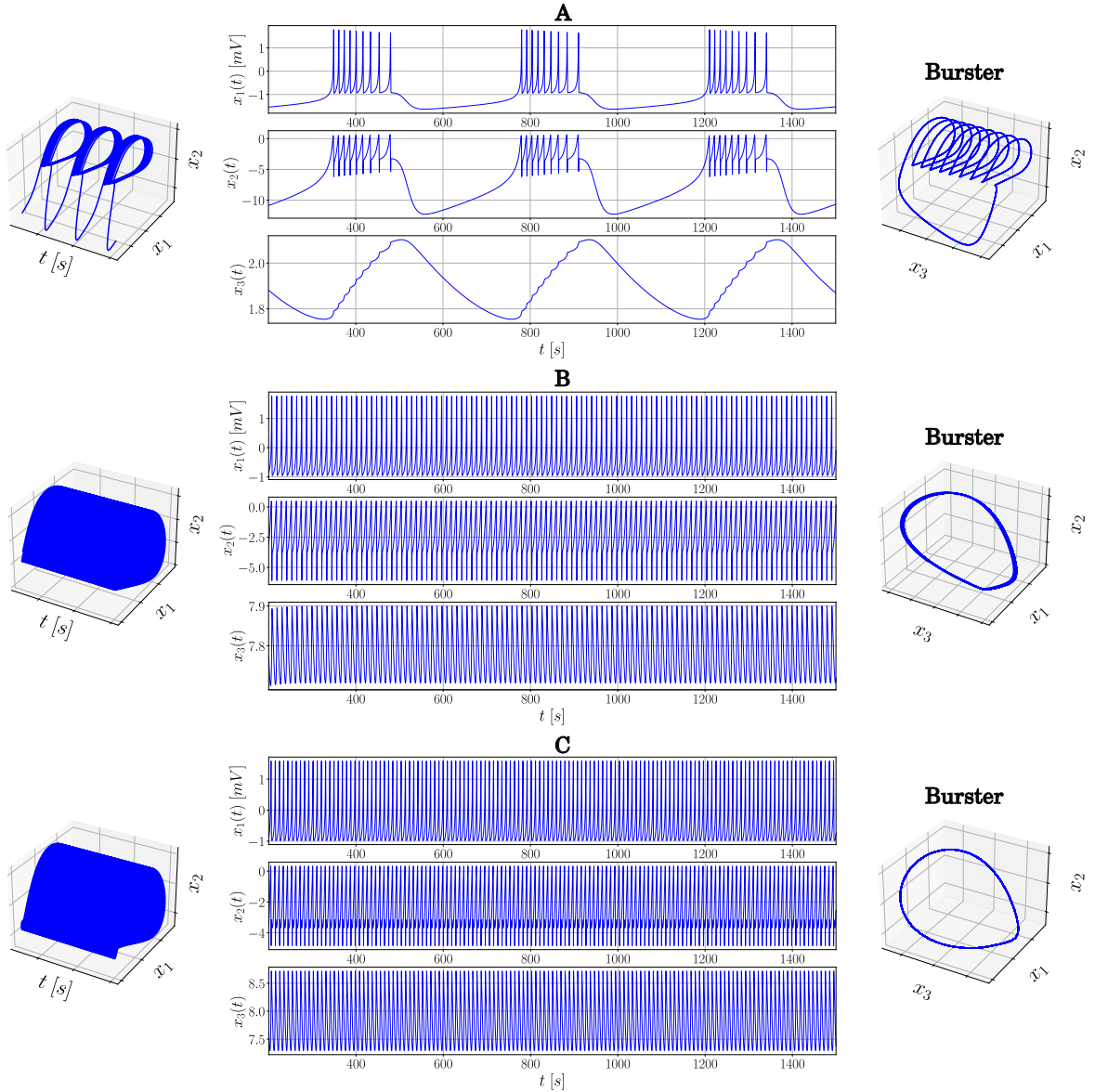
To provide a fuller understanding about spike generation, Fig. 8 shows the phase portraits of the Hindmarsh-Rose model related to their trajectories in the time domain at three different instants considering the chattering mode: during the rest state, when firing starts, and all the remaining spikes until they cease. Note that, since the model has three state variables, there are three equilibrium points as well, marked by the asterisks, which are located at the intersection of the nullclines. Besides, as the simulation proceeds the trajectory in the phase portrait leaves the first equilibrium point until it reaches the second one, right before entering the limit cycle – which is responsible for the spikes in the time domain. It remains stuck inside the cycle until firing ceases and then it goes back to the rest state.

Figure 6 – **Examples of firing patterns simulated using the Izhikevich model.** The first case (A) is simulated in the chattering mode using the following parameters: $\tau = 50$, $p_1 = 0.2$, $p_2 = -50$ and $p_3 = 2$; the second case (B) is simulated in the fast spiking mode using the following parameters: $\tau = 10$, $p_1 = 0.2$, $p_2 = -50$ and $p_3 = 2$; the third case (C) is simulated in the fast spiking mode using the following parameters: $\tau = 1$, $p_1 = 0.2$, $p_2 = -50$ and $p_3 = 2$. This illustrates part of the richness in behavior the Izhikevich model can simulate. Moreover, note how increasing the time scale τ leads to more spikes for the same time window.



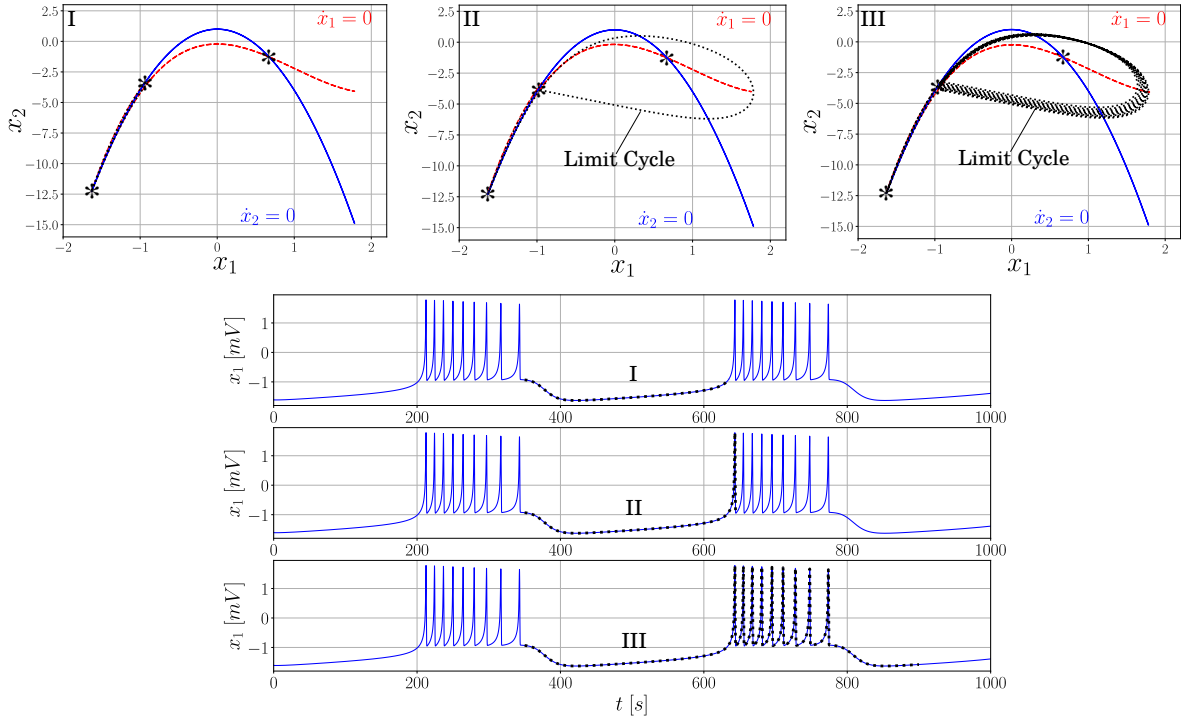
Source: Own authorship.

Figure 7 – **Examples of firing patterns simulated using the Hindmarsh-Rose model.** The first case (A) is simulated in a similar condition as the chattering mode using $\tau = 1000$; the second case (B) is simulated in a similar condition as the fast spiking mode using the following parameters: $\tau = 100$; the third case (C) is simulated in a similar condition as the fast spiking mode $\tau = 12.5$. For all simulations, the following parameters are used: $p_1 = 1$, $p_2 = 3$, $p_3 = 1$, $p_4 = 5$, $p_5 = 4$ and $x_0 = -1.6$. This illustrates part of the richness in behavior the Hindmarsh-Rose model can simulate. Moreover, note how increasing the time scale τ leads to more spikes for the same time window.



Source: Own authorship.

Figure 8 – **Relationship between the phase portraits and behavior in the time domain of the Hindmarsh-Rose model.** The chattering mode is used in the simulation again, leading to 3 equilibrium points, which are located at the intersection of the nullclines, according to Hindmarsh, Rose and Huxley (1984). In the phase portraits, the red dashed lines (---) indicate the first nullcline ($\dot{x}_1 = 0$); the solid blue lines (—) indicate the second nullcline ($\dot{x}_2 = 0$); the black dotted lines (...) indicate the trajectory. In the time domain, the solid blue lines (—) indicate the membrane potential and the black dotted lines (...) indicate the correspondence between the potential and the trajectory in the phase portraits.



Source: Own authorship.

The Epileptor, introduced in the next chapter, uses the standard Hindmarsh-Rose model to design the first ensemble of neurons, which corresponds to the fast oscillations in the time domain (Jirsa et al., 2014), whose time scale parameter plays the same role as the ones presented in this chapter⁵. In total, Epileptor presents 3 time scale parameters, two of which related to subsystems that generate a combined electrical activity, and the last one is linked to the control variable, as is the case for x_3 in the Hindmarsh-Rose model. Considering this, features of both models in the phase portrait are quite similar. Close attention must be paid to the parameter $x_0 = -1.6$ as well: this value is the same used for the Epileptor and is known as the degree of excitability of the system (epileptogenicity) (Jirsa et al., 2014). Varying the other parameters (such as I or p_i) also entails a wide range of firing patterns; however, a comprehensive sensitivity analysis is out of the scope

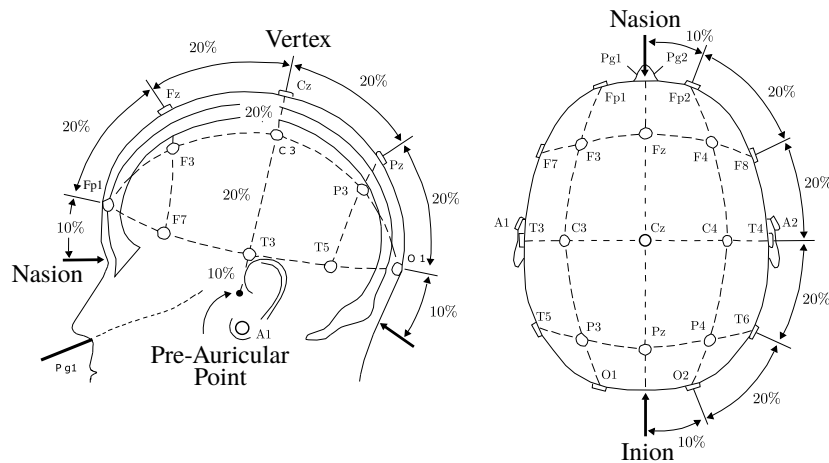
⁵To model the second subsystem, the excitable system shown by Roy, Ghosh and Jirsa (2011) was considered. For illustration purposes, only the Hindmarsh-Rose model was included in this thesis.

of this thesis. For a thorough investigation on these parameters and how they lead to bifurcations in both models, please see Storace, Linaro and Lange (2008), Nobukawa et al. (2015) and Saggio et al. (2020).

2.5 10-20 System for signal acquisition

Regardless of the level of brain activity of interest, it is important to place the electrodes at representative regions so that the resulting potential is properly recorded. To do so, there are standardized positioning systems that have been used for decades (Jasper, 1958) such as the 10-20 system, which is implemented considering electrodes placed at distance intervals of 10% and 20% from one another (Webster, 2006). Each electrode is labeled with a specific number and letter, according to their respective region. It should be stressed that this system is suitable for measuring EEGs since its positioning is on the scalp of patients. A more comprehensive description of the anatomy and function of such brain regions is out of the scope of this thesis; however, to provide enough information consistent with the that from the labels of the electrodes presented in this section, consider the following notation (Sepulveda et al., 2015): pre-frontal (Fp), frontal (F), central (C), auricular (A), parietal (P), occipital (O) and temporal (T). Close attention should be paid to the electrode Fp2, because it is the main one used in Chapter 7. Figure 9 presents an example of the 10-20 system placed according to 4 main points of the head: nasion, vertex, inion and pre-auricular point.

Figure 9 – **Relationship between the phase portraits and behavior in the time domain of the Hindmarsh-Rose model. Illustration of the 10-20 system for measuring EEGs.** Four main points are used as references: nasion, vertex, inion and pre-auricular point. The notation includes: pre-frontal (Fp), frontal (F), central (C), auricular (A), parietal (P), occipital (O) and temporal (T).



Source: Adapted from Sepulveda et al. (2015).

3 SEIZURE SUPPRESSION USING THE EPILEPTOR MODEL

This chapter introduces the dynamic model studied in this thesis for purposes of seizure suppression: the Epileptor. Firstly, the model is presented mathematically along with detailed explanations about the variables and parameters that describe its behavior. Then, the FTS approach is introduced as control technique for suppressing its seizures. The codes used in this chapter are available online on the platform GitHub at the following address: <https://github.com/GMSINT/Epilepsy-Dynamics-Control>.

3.1 The Epileptor

The Epileptor was designed as a phenomenological canonical model for describing epileptic seizures considering the hypothesis that invariant features related to epileptogenic activity are shared across species (Jirsa et al., 2014). To do so, tools and concepts from nonlinear dynamics were used, such as the notion of limit cycles, attractors and bifurcations. Essentially, after analyzing signals that represent epileptic activities in some species (human, mouse, rat and zebrafish), Jirsa et al. (2014) proposed a taxonomy of seizure-like events according to the bifurcations verified in them. Also, as an experimental model, the authors used signals obtained from hippocampi of mice, given in terms LFPs, which were placed in persistent epileptogenic conditions.

Based on the experiments carried out and a thorough statistical analysis, two major activities in time were identified for such LFPs (Jirsa et al., 2014): fast oscillations and spike (or spike and wave) events, which are usually (but not necessarily) coupled. As for the dynamic structures, the predominant features are as follows (Jirsa et al., 2014)¹: *i*) the intervals between spikes present a logarithmic scale as the seizure approaches its offset; *ii*) the onset of a seizure is characterized by an abrupt change in behavior, which entails fast oscillations and a baseline shift, and, thus, represents the bifurcation known as saddle-node; *iii*) at the seizure offset, another shift occurs back to the baseline, which, in conjunction with the interspike logarithmic scale, defines a homoclinic bifurcation. Naturally, there are other types of behavior present in epileptic seizures, which lead to different possible bifurcations²; however, the purpose of Epileptor is to account for the main behavior verified. To represent all of these features as a mathematical model, a set of first-order differential equations was proposed (Jirsa et al., 2014; Nagaraj; Lamperski;

¹These features can be seen in Fig. 10.

²For a thorough analysis and nomenclature, see Izhikevich (2000).

Netoff, 2017):

$$\begin{cases} \dot{x}_1 = y_1 - \omega_1(x_1, x_2) - z + I_{rest1} \\ \dot{y}_1 = \frac{1}{\tau_1}(y_0 - 5x_1^2 - y_1) \\ \dot{z} = \frac{1}{\tau_0}[4(x_1 - x_0) - z] \\ \dot{x}_2 = -y_2 + x_2 - x_2^3 + I_{rest2} + 0.002u(t) - 0.3(z - 3.5) \\ \dot{y}_2 = \frac{1}{\tau_2}[-y_2 + \omega_2(x_2)] \end{cases} \quad (4)$$

where:

$$u(t) = \int_{t_0}^t e^{-\gamma(t-\tau)} x_1(\tau) d\tau \quad (5)$$

$$\omega_1(x_1, x_2) = \begin{cases} x_1^3 - 3x_1^2, & x_1 < 0 \\ [x_2 - 0.6(z - 4)^2]x_1, & x_1 \geq 0 \end{cases} \quad (6)$$

$$\omega_2(x_2) = \begin{cases} 0, & x_2 < -0.25 \\ 6(x_2 + 0.25), & x_2 \geq -0.25 \end{cases} \quad (7)$$

Each of the variables and parameters in this model intends to represent a biophysical entity (Jirsa et al., 2014), as briefly explained below:

First subsystem: The variables (x_1, y_1) represent the first subsystem, which accounts for the fast oscillations. Therefore, this set evolves in a relatively faster time scale compared to the other variables. In practice, they may be linked to membrane potentials, and in this case represent LFPs, given in mV or μV .

Second subsystem: The variables (x_2, y_2) represent the second subsystem, responsible for the spike and wave events. Compared to the first subsystem, it evolves relatively slower in time, and is also given in terms of LFPs (mV or μV).

Permittivity: Variable z , in turn, is known as permittivity, a variable that evolves in the slowest time scale compared to the other variables. It is responsible for driving the whole system from the baseline condition into a state of constant epileptic activity, and vice-versa. Based on the nonlinear systems theory, it is a control parameter that triggers bifurcations (Slotine; Li et al., 1991). In biophysical terms, it may be related to extracellular processes that also evolve in a slow time scale during seizures, such as levels of ions, oxygen and energy metabolism (Jirsa et al., 2014).

Time scale parameter: τ is the time scale control parameter. Depending on its value, a specific number of oscillation may occur relatively faster or not. Thus, for the Epileptor model, the following relation holds: $\tau_1 < \tau_2 < \tau_0$.

Electric currents: I_{rest1} and I_{rest2} are associated to the flow of electric currents moving inward or outward the neural cells for the first and second subsystems, respectively.

Epileptogenicity: x_0 , in particular, represents a parameter defined as degree of epileptogenicity; that is, depending on its value, Epileptor presents a more regular (associated with brain baseline condition) or less regular condition (associated to a higher intensity of epileptic-like events).

Coupling functions: $\omega_1(x_1, x_2)$ and $\omega_2(x_2)$ are coupling functions. According to Jirsa et al. (2014), during most signals for seizure-like events in their experiments, fast discharges (first subsystem) are connected to the spike and wave events (second subsystem), and their activity is only present during the wave, and not the spike, or not present at all. This suggests a coupling between both activities, presented by aforementioned functions.

Associated constant values: at last, y_0 and γ are constant parameters associated to the model. The first of which was defined following the formulation of Hindmarsh, Rose and Huxley (1984); the second of which was added along with $u(t)$ by Jirsa et al. (2014). The term $u(t)$ can be rewritten as a differential equation, which is convenient to establish the state-space model used later on. To demonstrate that, consider it as follows (Jirsa et al., 2014):

$$\dot{u} = -\gamma(u - 0.1x_1) \quad (8)$$

In its homogeneous form:

$$\frac{du(t)}{dt} + \gamma u(t) - 0.1\gamma x_1 = 0 \quad (9)$$

By applying the Laplace transform, it becomes $\mathcal{L}\{u'\} + \gamma\mathcal{L}\{u\} = 0.1\gamma\mathcal{L}\{x_1\}$, which is also equivalent to $sU(s) - u(0) + \gamma U(s) = 0.1\gamma X_1(s)$. Considering initial conditions equal to zero:

$$U(s) = 0.1\gamma \frac{1}{s + \gamma} X_1(s) \quad (10)$$

At last, after defining the following new variables: $F(s) = 0.1\gamma/(s + \gamma)$ and $G(s) = X_1(s)$, it is possible to state, therefore, that $U(s) = F(s)G(s)$. Taking advantage of the fact that a convolution in time between two any functions $f(t)$ and $g(t)$ is:

$$(f * g)(t) = \int_0^t g(\tau) f(t - \tau) d\tau \quad (11)$$

whose Laplace Transform is $\mathcal{L}\{f * g\} = F(s)G(s)$, and considering that the individual Inverse Laplace Transforms of $F(s)$ and $G(s)$ are $\mathcal{L}\{F(s)\} = 0.1\gamma e^{-\gamma t}$ and $\mathcal{L}\{G(s)\} = x_1(t)$. By analogy, $u(t)$ can be represented by:

$$u(t) = 0.1\gamma \int_{t_0=0}^t e^{-\gamma(t-\tau)} x_1(\tau) d\tau \quad (12)$$

Hence, a convenient choice for γ – in this case, 0.02 (Jirsa et al., 2014) – may lead this equation to be represented in its original integral form.

3.1.1 State-space representation

The design of the controller is based on the Epileptor model written in its state-space representation, as usually done in FTS applications (Tanaka; Wang, 2004). It is thus convenient to rearrange it in matrix form as:

$$\begin{cases} \dot{\mathbf{x}}(t) = \mathbf{A}_{nl}\mathbf{x}(t) + \mathbf{b} \\ \mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) \end{cases} \quad (13)$$

where the dynamic matrix $\mathbf{A}_{nl}$ is nonlinear and state-dependent, and the affine term $\mathbf{b}$ are respectively given by

$$\mathbf{A}_{nl} = \begin{bmatrix} -\bar{\omega}_1(x_1, x_2) & 1 & -1 & 0 & 0 & 0 \\ -5x_1 & -1 & 0 & 0 & 0 & 0 \\ 4/\tau_0 & 0 & -1/\tau_0 & 0 & 0 & 0 \\ 0 & 0 & -0.3 & (1 - x_2^2) & -1 & 2 \\ 0 & 0 & 0 & \bar{\omega}_2(x_2)/\tau_2 & -1/\tau_2 & 0 \\ 0.1\gamma & 0 & 0 & 0 & 0 & -\gamma \end{bmatrix} \quad (14)$$

$$\mathbf{b} = \{I_{rest1} \quad y_0 \quad -4x_0/\tau_0 \quad 1.05 + I_{rest2} \quad c/\tau_2 \quad 0\}^T \quad (15)$$

and the state vector is defined as $\mathbf{x} = \{x_1 \quad y_1 \quad z \quad x_2 \quad y_2 \quad u\}^T$. Also:

$$\bar{\omega}_1(x_1, x_2) = \begin{cases} x_1^2 - 3x_1, & x_1 < 0 \\ x_2 - 0.6(z - 4)^2, & x_2 \geq 0 \end{cases} \quad (16)$$

$$\bar{\omega}_2(x_2) = \begin{cases} 0, & x_2 < -0.25 \\ 6, & x_2 \geq -0.25 \end{cases} \quad (17)$$

$$c = \begin{cases} 0, & x_2 < -0.25 \\ 1.5, & x_2 \geq -0.25 \end{cases} \quad (18)$$

Note that c implies that $\mathbf{b}$ is a vector with a piecewise linear function. Besides, as defined by Jirsa et al. (2014), $\tau_1 = 1$ for Epileptor's typical behavior, and it is omitted from the equations above. At last, $\mathbf{y}(t)$ is the vector of observable states, which is discussed in detail in the next chapter.

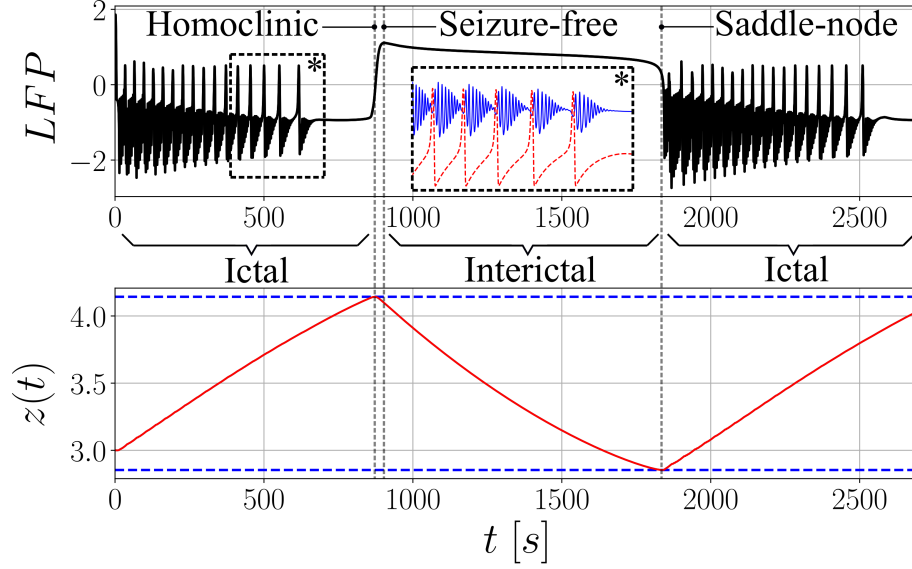
3.1.2 Epileptor's uncontrolled behavior

To illustrate Epileptor's typical behavior, the parameters used for the following simulation are the same as those previously defined by Jirsa et al. (2014), i.e.: $x_0 = -1.6$, $\tau_0 = 2857$, $\tau_1 = 1$, $\tau_2 = 10$, $\gamma = 0.01$, $I_{rest1} = 3.1$, $I_{rest2} = 0.45$, $y_0 = 1$; also, the initial conditions are: $x_1(0) = 0$, $y_1(0) = -5$, $z(0) = 3$, $x_2(0) = 0$, $y_2(0) = 0$ and $u(0) = 0$. It must be stressed that, for $x_0 = -1.6$ (among other values), Epileptor is subjected to a persistent epileptic condition (Jirsa et al., 2014). Although only this particular condition is presented, different configurations were exhaustively evaluated, and similar results were obtained from all numerical simulations. The computational codes were implemented in Python 3.7, which is free and open source, on the Spyder scientific environment, considering a fourth-order Runge-Kutta integrator with time step equal to $dt = 0.01$.

Figure 10 presents Epileptor's behavior in time, which can be obtained by a linear combination between both subsystems, thus representing an LFP (Jirsa et al., 2014): $-x_1(t) + x_2(t)$. The permissivity variable $z(t)$ is also plotted, and note that it is responsible for driving the system into and out of the seizures, depending whether specific extreme values (indicated by the peaks) are reached. The first of these values stands for the saddle-node bifurcation, after which the ictal period starts; the second one, in turn, is the homoclinic bifurcation, after which the ictal period ends, and the interictal period begins. A third event is highlighted, right after seizure offset. Such a point is particularly relevant because it represents the beginning of a seizure-free state, which is of our interest when designing the controller, defined as $\mathbf{x}_h$. Also, it is important to clarify that these types of results are known in the literature, and they are included in this section to demonstrate the uncontrolled system.

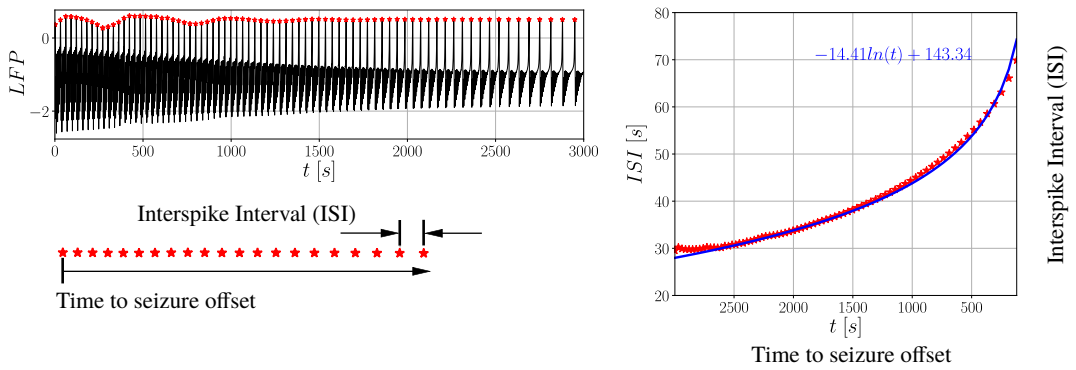
Figure 11 depicts the analysis of the interspike intervals (ISI) generated by Epileptor. As mentioned in the beginning of this chapter, one feature related to the hypothesis of the homoclinic bifurcation is that the ISIs exhibit a logarithmic scaling at seizure offset. For this figure, the same parameters previously used were kept, but the epileptogenicity was set to $x_0 = -0.8$ to obtain a longer ictal period for illustration purposes. As done by Jirsa et al. (2014), the time interval between each peak and seizure offset was measured so as to obtain a reversed time vector; then, curve fitting was applied to obtain the equation that best describes the samples. For this specific condition, $-14.14\ln(t) + 143.34$ provides a fairly good approximation to the ISIs of the simulation, thus endorsing the hypothesis.

Figure 10 – **Epileptor’s behavior in the time domain: LFP ($-x_1(t) + x_2(t)$) and state $z(t)$.** The ictal period begins right after the saddle-node bifurcation and ends at the homoclinic bifurcation, giving rise to the interictal period. This defines Epileptor as a bi-stable model (Jirsa et al., 2014). Details for the subsystems are also presented: $x_1(t)$ is indicated by the solid line (—), and $x_2(t)$ is indicated by the dashed line, (- -).



Source: Own authorship.

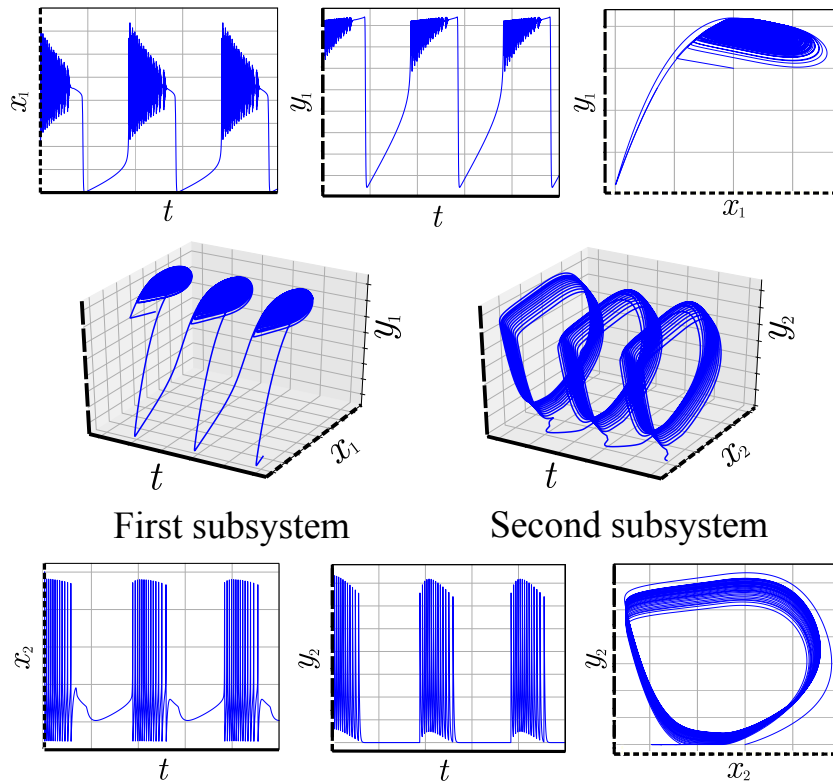
Figure 11 – **Analysis of the interspike intervals (ISI) of the Epileptor model.** The peaks (*) were identified using the “find_peaks” built-in function from the numpy library after setting a 0.23 threshold. The ISIs were measured as well as the time interval between each peak and seizure offset, organized in a reversed time vector; then curve fitting was applied to the samples. In this case, all parameters remain the same except the epileptogenicity, which is $x_0 = -0.8$, leading to the following logarithmic curve, indicated by the solid blue line (—): $-14.14\ln(t) + 143.34$.



Source: Own authorship.

Figure 12 presents the portraits for Epileptor’s subsystems. As $\tau_1 = 1$, the first subsystem evolves in a relatively faster time scale, and its phase portrait defines two main points: the first one to which the trajectory spirals in, thus representing its attractor and the ictal period, and the second one, out of the attractor, which represents a seizure-free condition (or the “healthy” condition). For the second subsystem, $\tau_2 = 10$, that is, it evolves in a slower time scale, and the seizure is represented by the finite number of cycles of its attractor, which remains open during all the ictal period; at last, the seizure-free point is located out of it. Both of these activities are synchronized, as seen in Fig. 10, due to the coupling functions defined in Eqs. 6 and 7; this leads to regular intervals between seizure and baseline behaviors over time.

Figure 12 – **Representation of both subsystems in the time domain and in their phase portraits.** Epileptor’s cyclic behavior can be better visualized in both of these domains; the time scale parameters define how many “loops” are formed during the ictal event. For the first subsystem, they spiral inwards the attractor; for the second subsystem, they remain open.

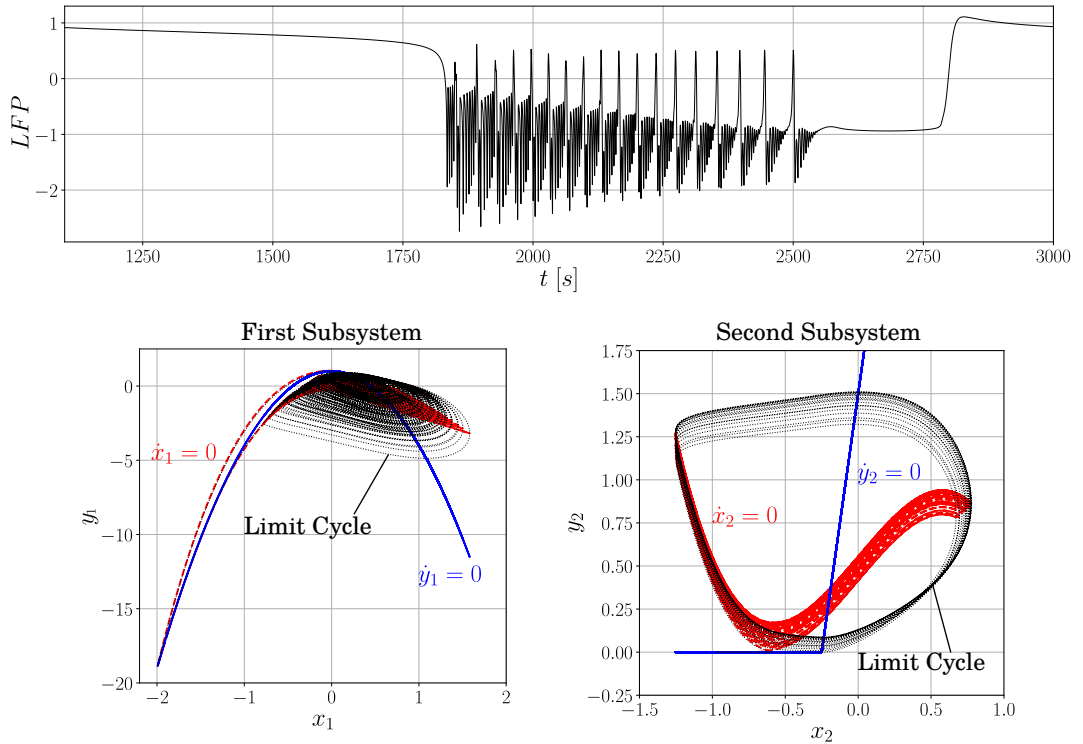


Source: Own authorship.

To better explore Epileptor’s features and its similarities to the Hindmarsh-Rose model, a full time window cell is plotted in Fig. 13, containing again its behavior in the time domain but showing its phase portraits and nullclines. For the first subsystem, the attractor has a similar shape to the one presented in Fig. 8, which is expected since Epileptor is designed based partially on the Hindmarsh-Rose model, as previously dis-

cussed. However, the cycles of the fast oscillations decrease in amplitude at each loop of the second limit cycle from the second subsystem, which is reflected on the phase portraits by the trajectories spiralling inwards the attractor. Note that this behavior is only possible due to the interaction between both nullclines $\dot{x}_1 = 0$ and $\dot{y}_1 = 0$: $\dot{x}_1 = 0$ is slightly modified at each cycle so that their intersection occurs at a different location. For the second subsystem, the cycles do not spiral into the center of the attractor, but they remain open. Nonetheless, their mean diameter decreases in size as the simulation proceeds, which is a consequence of the interaction of both nullclines $\dot{x}_2 = 0$ and $\dot{y}_2 = 0$ as well.

Figure 13 – **Relationship between the phase portraits and behavior in the time domain of the Epileptor model.** The different intersections of the nullclines generates differences in the loops of both limit cycles. In the phase portraits, the red dashed lines (---) indicate the first nullcline of the subsystems ($\dot{x}_1 = 0$ or $\dot{x}_2 = 0$); the solid blue lines (—) indicate the second nullcline of the subsystems ($\dot{y}_1 = 0$ or $\dot{y}_2 = 0$); the black dotted lines (...) indicate the trajectory. The whole time window shown for the Epileptor is used to generate the phase portraits.



Source: Own authorship.

3.2 Applying the controller

The epileptic seizure described by the Epileptor model can be suppressed by designing a feedback controller. It is assumed that six control signals $F_{u(k)}$, $k = 1, \dots, 6$, can be added to the system of equations, i.e., each one in Eq. (4) and Eq. (8). In this case, the vector of

control signals $\mathbf{F}_c = \{F_{c_1}, \dots, F_{c_6}\}^T$ can be considered to establish the closed loop system representation as follows:

$$\dot{\mathbf{x}}(t) = \mathbf{A}_n \mathbf{x}(t) + \mathbf{b} + \mathbf{F}_c(t) \quad (19)$$

The physical nature of these control signals is somewhat abstract for some variables, just as the physical meaning of the states that define the Epileptor model is not fully established in the literature (Jirsa et al., 2014). However, the focus herein is to introduce the methodology to compute these control signals efficiently for any configuration of Epileptor, i.e., for any individual for which the epileptic seizure is sufficiently described by this model.

The key to applying the active controller is to define a non-seizure (“healthy”) condition through the state vector $\mathbf{x}_h = \{x_{1h} \ y_{1h} \ z_h \ x_{2h} \ y_{2h} \ u_h\}^T$. Conceptually, this state vector represents any instantaneous condition before an epileptic seizure, and note that the practical definition of this healthy condition also depends on the complete understanding of the physical meaning of the states. The idea behind this strategy is based on the hypothesis that there are active control signals capable of acting locally in the patient’s brain during the epileptic seizure, continuously, until the baseline condition is reached. Hence, it is a feedback-based electrical stimulation procedure.

The proposal considers that the instantaneous state vector is known during the seizure event, while the controller is working. It is a neural feedback-based strategy, that is why it is necessary to identify a state space model for each individual. The system’s identification requires adjusting the parameters in the matrix $\mathbf{A}$ to get a representative behavior of the epileptic seizure, before designing the controller. Using the state vector $\mathbf{x}(t)$ the control signals are computed as:

$$\mathbf{F}_c(t) = -\mathbf{B}\mathbf{G}[\mathbf{x}(t) - \mathbf{x}_h] \quad (20)$$

where $\mathbf{B}$ is the the input matrix conveniently defined by

$$\mathbf{B} = \text{diag}(d_{x_1}, d_{y_1}, d_z, d_{x_2}, d_{y_2}, d_u) \quad (21)$$

where d_k is the k -th weighting factor in the range $]0, 1]$ used to limit the control signals differently among the states. These factors are adjusted once, when designing the controller. As well established for practical feedback-based control applications (Tanaka; Wang, 2004; Ichalal; Arioui; Mammari, 2011; Hammoudi et al., 2014), it is important to highlight that a state observer can be employed to estimate unmeasurable states from the measurable ones. However, the state-space observer design is not discussed in this chapter yet. Also, the performance of the controller is strongly dependent on the gain matrix $\mathbf{G}$, which is computed by applying the FTS-based approach introduced in the next subsection.

3.2.1 Fuzzy Takagi-Sugeno modeling

The strategy used to compute the gain of the controller is based on the FTS modeling (Takagi; Sugeno, 1985). It basically consists in rewriting the nonlinear dynamic model as a set of linear subsystems that represent the original dynamics. Essentially, two approaches can be employed for doing so: *i*) constructing local linear models and choosing the so-called membership functions to adequate the approximate fuzzy model to the original one; *ii*) carrying out an exact modeling based on specific well-defined membership functions (Tanaka; Wang, 2004). In this work, the second approach is applied due to specific reasons: an exact modeling avoids approximation errors; furthermore, a simple method for identifying the local models (also known as submodels) was proposed by Taniguchi et al. (2001). It is particularly helpful because a high number of submodels can be critical when designing this type of fuzzy-based controller since it considerably increases the number of variables to be found during the optimization process, as well as the computational cost.

The state-space model in Eq. (13) is rewritten neglecting the term $\mathbf{b}$: $\dot{x}_i(t) = \sum_{j=1}^N f_{ij}[\mathbf{x}(t)]x_j(t)$, where $f_{ij}[\mathbf{x}(t)] = f_k$ represents the k -th nonlinear function, N is the number of rows or columns, and $k = 1, \dots, N_{nl} \leq N^2$ is the total number of nonlinear functions. Although $\mathbf{b}$ is initially neglected to compute the gain, it is considered during the feedback loop. It was observed during the simulations that it affects the dynamics as a disturbance over time and it does not decrease substantially the controller's performance. According to the FTS modeling, the new system can be described by the following If-Then rule:

$$\text{Rule } i : \begin{cases} \text{If } \chi_1(t) \text{ is } M_{i1} \text{ and } \dots \text{ and } \chi_p(t) \text{ is } M_{ip} \\ \text{Then, } \dot{\mathbf{x}}(t) = \mathbf{A}_i \mathbf{x}(t), \quad i = 1, \dots, r \end{cases} \quad (22)$$

where M_{ij} is called a fuzzy set, r is the number of rules, and $\chi_1(t), \dots, \chi_p(t)$ are known as premise variables. These concepts can be understood according to fuzzy inference (Kalogirou, 2014): it is a method for mapping a given input to an output based on the substitution of an originally binary logic by a fuzzy one. In this sense, any statement is not simply true or false, but its truth becomes a matter of a degree. In mathematical terms, a fuzzy set is thus characterized by a function that measures the membership of a variable in the range $[0,1]$, or from 0 to 100% (zero to perfect chances of belonging to the fuzzy set). Premise variables are, in turn, functions of the state variables, external disturbances, and/or time, for example (Tanaka; Wang, 2004).

Each i -th matrix $\mathbf{A}_i$ defines the i -th submodel employed to describe the original nonlinear model. As presented herein, $\chi_i(t)$ are the reconstructed nonlinear functions present in the model, and the M_{ij} are fuzzy sets of combinations between maximum and mini-

imum values of the state variables contained in $\chi_i(t)$ that represent Epileptor. To identify the submodels, Taniguchi et al. (2001) proposed writing all f_k as linear combinations between their maximum ($f_k^{max} = \max[f_k(\mathbf{x})]$) and minimum ($f_k^{min} = \min[f_k(\mathbf{x})]$) values. Therefore, the nonlinear functions can be rewritten as follows:

$$f_k(\mathbf{x}) = [g_k^{min}(\mathbf{x})]f_k^{min} + [g_k^{max}(\mathbf{x})]f_k^{max} \quad (23)$$

where:

$$g_k^{min}(\mathbf{x}) = \frac{[f_k^{max} - f_k(\mathbf{x})]}{f_k^{max} - f_k^{min}} \quad (24)$$

$$g_k^{max}(\mathbf{x}) = 1 - g_k^{min}(\mathbf{x})$$

are the membership functions³ which must meet the following conditions: a) $g_k^{min}(\mathbf{x}) \geq 0$; b) $g_k^{max}(\mathbf{x}) \leq 1$; and c) $g_k^{min}(\mathbf{x}) + g_k^{max}(\mathbf{x}) = 1$. This last condition allows writing $f_k(\mathbf{x}) = \prod_{j=1, j \neq k}^{N_{nl}} \{g_j^{min}(\mathbf{x}) + g_j^{max}(\mathbf{x})\} f_k(\mathbf{x})$, or, alternatively,

$$f_k(\mathbf{x}) = \sum_{j=1}^{r_1} N_j(\mathbf{x}) f_k^{min} + \sum_{j=r_1+1}^{(2^{N_{nl}})} N_j(\mathbf{x}) f_k^{max} \quad (25)$$

where $r_1 = 2^{(N_{nl}-1)}$, and $N_j(\mathbf{x}) = \prod_{k=1}^{N_{nl}} g_k^{(\cdot)}(\mathbf{x})$, which, necessarily, must meet $\sum_{j=1}^{2^{N_{nl}}} N_j[\mathbf{x}] = 1$. The superscript $(\cdot)$ indicates a combination between the maximum and minimum values for the k -th nonlinear function $g_k^{(\cdot)}(\mathbf{x})$. After substituting each f_k according to Eq. 25 into the matrix $\mathbf{A}_{nl}$, the system in Eq. (19) is rewritten as

$$\dot{\mathbf{x}}(t) = \sum_{j=1}^{2^{N_{nl}}} N_j(\mathbf{x}) [(\mathbf{A}_j - \mathbf{B}\mathbf{G})\mathbf{x}(t) + \mathbf{B}\mathbf{G}\mathbf{x}_h + \mathbf{b}] \quad (26)$$

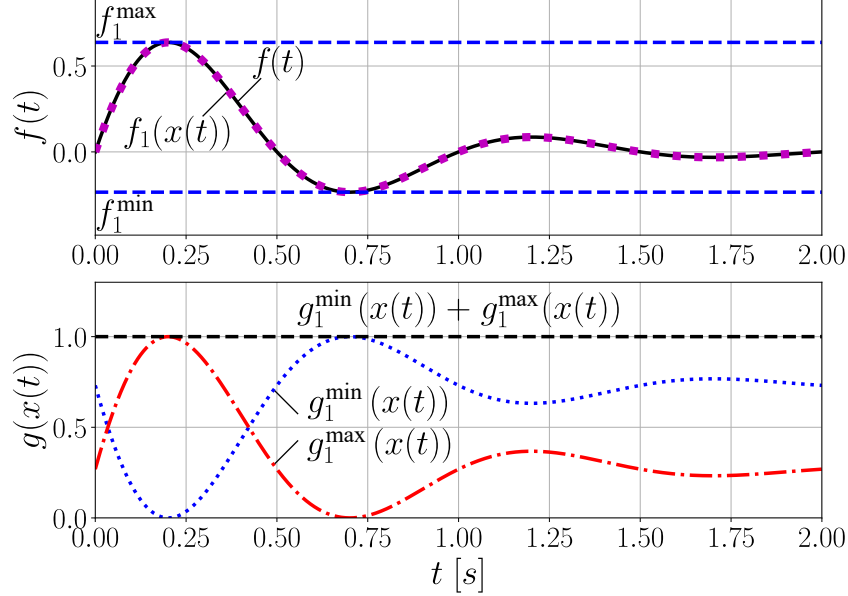
3.2.2 Example of Fuzzy Takagi-Sugeno modeling

For the sake of understanding, Fig. 14 presents an example of the exact reconstruction of a nonlinear function using the membership functions and linear submodels. In this case: $f(t) = e^{-2t} \sin(2\pi t)$, that is, $N_{nl} = 1$. The membership functions $g_1^{max}(x(t))$ and $g_1^{min}(x(t))$ weigh the maximum and minimum values of $f(t)$ (f_1^{max} and f_1^{min} , respectively) over time such that its exact representation is obtained as $f_1(x(t))$. Note that that it is always necessary to know such boundaries beforehand so that this approach can be correctly employed. For dynamic systems, which may have more than one nonlinear function, a process known as fuzzification can be applied (Tanaka; Wang, 2004).

³Note that membership functions can be understood as the mathematical representation of fuzzy sets.

Figure 14 – **Concept of sector nonlinearity to reconstruct a nonlinear function.**

The function $f_{\sin}(t) = e^{-2t}\sin(2\pi t)$ (—) is reconstructed using the exact solution (Tanaka; Wang, 2004; Taniguchi et al., 2001) based on the maximum and minimum values of $f_{\sin}(t)$, expressed by $f_1^{\max}$ and $f_1^{\min}$ (---), and the membership functions: $g_1^{\min}(x(t))$ (···) and $g_1^{\max}(x(t))$ (-.-). The reconstructed model is represented by $f_1(x(t))$ (■).



Source: Own authorship.

As an example, consider the following dynamic matrix containing $N_{nl} = 2$ nonlinear functions $\mathbf{A}_{nl} = \mathbf{A}_{nl}(f_1, f_2)$ of minimum and maximum values $f_k^{\{*\}}$, $k = 1, 2$, where $\{.\}$ is a minimum or maximum. By using Eq. 23, it follows that $f_1(\mathbf{x}) = [g_1^{\min}(\mathbf{x})]f_1^{\min} + [g_1^{\max}(\mathbf{x})]f_1^{\max}$ and $f_2(\mathbf{x}) = [g_2^{\min}(\mathbf{x})]f_2^{\min} + [g_2^{\max}(\mathbf{x})]f_2^{\max}$. Remember that $f_k(\mathbf{x}) = \prod_{j=1, j \neq k}^{N_{nl}} \{g_j^{\min}(\mathbf{x}), g_j^{\max}(\mathbf{x})\} f_k(\mathbf{x})$, $k = 1, 2$, which leads to the following system of equations:

$$\begin{cases} f_1(\mathbf{x}) = \underbrace{\{g_2^{\min}(\mathbf{x}) + g_2^{\max}(\mathbf{x})\}}_{=1} \{ [g_1^{\min}(\mathbf{x})]f_1^{\min} + [g_1^{\max}(\mathbf{x})]f_1^{\max} \} \\ f_2(\mathbf{x}) = \underbrace{\{g_1^{\min}(\mathbf{x}) + g_1^{\max}(\mathbf{x})\}}_{=1} \{ [g_2^{\min}(\mathbf{x})]f_2^{\min} + [g_2^{\max}(\mathbf{x})]f_2^{\max} \} \end{cases} \quad (27)$$

By expanding the terms and omitting “ $(\mathbf{x})$ ” for convenience of notation, it follows that:

$$\begin{cases} f_1(\mathbf{x}) = g_1^{\min} g_2^{\min} f_1^{\min} + g_1^{\min} g_2^{\max} f_1^{\min} + g_1^{\max} g_2^{\min} f_1^{\max} + g_1^{\max} g_2^{\max} f_1^{\max} \\ f_2(\mathbf{x}) = g_1^{\min} g_2^{\min} f_2^{\min} + g_1^{\max} g_2^{\min} f_2^{\min} + g_1^{\min} g_2^{\max} f_2^{\max} + g_1^{\max} g_2^{\max} f_2^{\max} \end{cases} \quad (28)$$

Note that a pattern begins to arise, for example: $g_1^{min} g_2^{max}$ are common to f_1^{min} and f_2^{max} , leading to a notation similar to that from Eq. 25:

$$\begin{cases} f_1(\mathbf{x}) = \underbrace{[g_1^{min} g_2^{min}]}_{N_1(\mathbf{x})} + \underbrace{[g_1^{min} g_2^{max}]}_{N_2(\mathbf{x})} f_1^{min} + \underbrace{[g_1^{max} g_2^{min}]}_{N_3(\mathbf{x})} + \underbrace{[g_1^{max} g_2^{max}]}_{N_4(\mathbf{x})} f_1^{max} \\ f_2(\mathbf{x}) = \underbrace{[g_1^{min} g_2^{min}]}_{N_1(\mathbf{x})} + \underbrace{[g_1^{max} g_2^{min}]}_{N_3(\mathbf{x})} f_2^{min} + \underbrace{[g_1^{min} g_2^{max}]}_{N_2(\mathbf{x})} + \underbrace{[g_1^{max} g_2^{max}]}_{N_4(\mathbf{x})} f_2^{max} \end{cases} \quad (29)$$

This allows performing the fuzzification procedure and defining the subsystems as:

$$\begin{aligned} \mathbf{A}_1 &= \mathbf{A}(f_1^{min}, f_2^{min}) \\ \mathbf{A}_2 &= \mathbf{A}(f_1^{min}, f_2^{max}) \\ \mathbf{A}_3 &= \mathbf{A}(f_1^{max}, f_2^{min}) \\ \mathbf{A}_4 &= \mathbf{A}(f_1^{max}, f_2^{max}) \end{aligned} \quad (30)$$

Consequently, the minimum and maximum values of both nonlinear functions replace them completely in the dynamic matrices, which become linear. It is also important to stress that each of these values is associated only to its specific subsystem. Considering this, the defuzzification procedure can be summarized in the following equation:

$$\mathbf{A}_{nl} = \sum_{j=1}^4 N_j(\mathbf{x}) \mathbf{A}_j \quad (31)$$

In the case that nonlinear functions are present in matrix $\mathbf{B}$ as well, a similar procedure is applied. Since a constant input matrix is adopted in this thesis, the system can be rearranged as the closed-loop state-space notation from Eq. 26.

3.2.3 Stability analysis

The problem stated above can be easily solved to determine $\mathbf{G}$ using Lyapunov Stability Theory if $\mathbf{b}$ is neglected and $\mathbf{x}_h = \mathbf{0}$. Note that the controller imposes $\mathbf{x} \rightarrow \mathbf{0}$ when it is designed, but considering the not null $\mathbf{x}_h$, the controller imposes $\mathbf{x} \rightarrow \mathbf{x}_h$, as desired for this case. The solution considers the Lyapunov function $V(\mathbf{x}) = \mathbf{x}^T \mathbf{P} \mathbf{x} > 0$, where $\mathbf{P}$ is a positive definite matrix (whose all eigenvalues are positive) (Slotine; Li et al., 1991). The derivative of $V(\mathbf{x})$ implies that $\dot{\mathbf{x}}^T \mathbf{P} \mathbf{x} + \mathbf{x}^T \mathbf{P} \dot{\mathbf{x}} < 0$, and by substituting Eq. (26) into it without considering $\mathbf{b}$ and $\mathbf{x}_h$, the following matrix inequality (MI) is obtained

$$\sum_{j=1}^{2^{N_{nl}}} N_j(\mathbf{x}) [(\mathbf{A}_j - \mathbf{B} \mathbf{G})^T \mathbf{P} + \mathbf{P} (\mathbf{A}_j - \mathbf{B} \mathbf{G})] < \mathbf{0} \quad (32)$$

The MI above can be conveniently rewritten by its equivalent form, which consists in writing an MI for each j -th submodel (Tanaka; Wang, 2004):

$$(\mathbf{A}_j - \mathbf{B}\mathbf{G})^T \mathbf{P} + \mathbf{P}(\mathbf{A}_j - \mathbf{B}\mathbf{G}) < \mathbf{0} \quad (33)$$

where $j = 1, \dots, 2^{N_{nl}}$. In addition, the following changes of variables are applied: $\mathbf{X} = \mathbf{P}^{-1}$ and $\mathbf{G}_x = \mathbf{G}\mathbf{X}$. Then, each j -th matrix inequality is rewritten as a linear matrix inequality (LMI), as follows (Boyd et al., 1994):

$$\mathbf{X}\mathbf{A}_j^T - \mathbf{G}_x\mathbf{B} + \mathbf{A}_j\mathbf{X} - \mathbf{B}\mathbf{G}_x < \mathbf{0} \quad (34)$$

The $2^{N_{nl}}$ LMIs must be simultaneously solved to compute the matrices $\mathbf{X}$ and $\mathbf{G}_x$. So, finally, the gain matrix is given by

$$\mathbf{G} = \mathbf{G}_x\mathbf{X}^{-1} \quad (35)$$

and using such a gain, the closed loop system is defined by $\dot{\mathbf{x}}(t) = (\mathbf{A} - \mathbf{B}\mathbf{G})\mathbf{x}(t) + \mathbf{B}\mathbf{G}\mathbf{x}_h + \mathbf{b}$. Note at this point that the control signals shown in Eq. (20) can be computed for each time instant if $\mathbf{x}(t)$ is available.

3.2.4 The submodels for the Epileptor

The implication of Eq. (26) is that the Epileptor model is described by 2^4 linear submodels. They are obtained by the combination of the minimum and maximum values of the nonlinear functions f_k , $k = 1, \dots, 4$. For instance: the premise variables z_i represent $f_k \in [f_k^{min}, f_k^{max}]$, where $k = 1, \dots, N_{nl} = 4$; if $f_1 = f_1^{max}$ and $f_2 = f_2^{max}$ and $f_3 = f_3^{max}$ and $f_4 = f_4^{max}$, $\mathbf{A}_1$ is obtained. The fuzzification procedure is applied, leading to⁴:

$$\begin{aligned} \mathbf{A}_1 &= \mathbf{A}(f_1^{max}, f_2^{max}, f_3^{max}, f_4^{max}) \\ \mathbf{A}_2 &= \mathbf{A}(f_1^{max}, f_2^{max}, f_3^{max}, f_4^{min}) \\ \mathbf{A}_3 &= \mathbf{A}(f_1^{max}, f_2^{max}, f_3^{min}, f_4^{max}) \\ &\vdots \\ \mathbf{A}_{14} &= \mathbf{A}(f_1^{min}, f_2^{min}, f_3^{max}, f_4^{min}) \\ \mathbf{A}_{15} &= \mathbf{A}(f_1^{min}, f_2^{min}, f_3^{min}, f_4^{max}) \\ \mathbf{A}_{16} &= \mathbf{A}(f_1^{min}, f_2^{min}, f_3^{min}, f_4^{min}) \end{aligned} \quad (36)$$

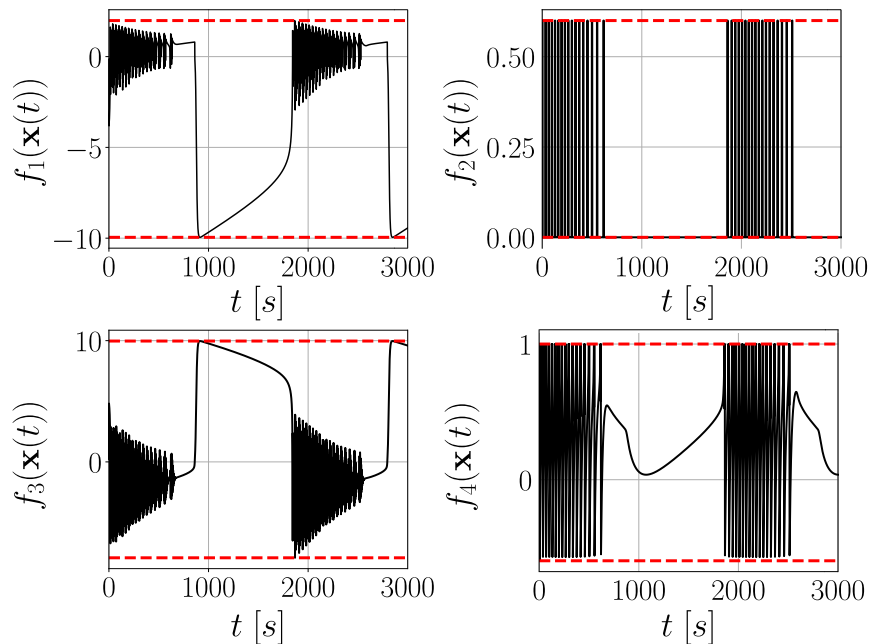
and the f_k functions, in the case of Epileptor, correspond to the elements a_{11} , a_{44} , a_{21} and a_{54} of the dynamic matrix $\mathbf{A}$ (Eq. 14), i.e., $f_1 = -\omega_1(x_1, x_2)$, $f_2 = \omega_2(x_2)/\tau_2$,

⁴Note again that each maximum or minimum value of the nonlinear functions replaces it completely in the linear submodel.

$f_3 = -5x_1$, and $f_4 = 1 - x_2^2$. For the sake of understanding, the second linear submodel, for instance, is composed of the maximum values of the first three nonlinear functions f_1^{max} , f_2^{max} , f_3^{max} , and the minimum value of the fourth nonlinear function f_4^{min} . To reconstruct exactly the original model based on this equation, the process of defuzzification is carried out, which leads directly to Eq. 26 with the 16 sub-models, where $N_1(\mathbf{x}) = g_1^{max}(\mathbf{x})g_2^{max}(\mathbf{x})g_3^{max}(\mathbf{x})g_4^{max}(\mathbf{x})$, and so forth, where $g_k^{(\cdot)}(\mathbf{x})$ are given by Eq. 24. It is important to consider these 16 sub-models to design the controller and ensure the sufficient condition to suppress the seizures

The active controller can be easily designed considering these four f_k nonlinear functions. In the first step, it is necessary to establish their boundaries (maximum and minimum values) for each particular individual. It can be done if the epileptic seizure is monitored for a representative period of time, such that the associated state-space model is appropriately identified – which is assumed as true in this chapter. After knowing the values of these nonlinear functions, a conservative strategy can be employed by increasing them. Although large ranges can conceptually decrease the LMI feasibility, on the other hand, it can assure the accuracy of the controller's performance. The ranges of each k -th nonlinear function are shown in Fig. 15, and they correspond to the time interval considered in the simulations used in Fig. 10.

Figure 15 – **Nonlinear functions of the Epileptor model for a specific time interval.** In total, there are four nonlinear functions inside the dynamic matrix: $f_1 = -\omega_1(x_1, x_2)$, $f_2 = \omega_2(x_2)/\tau_2$, $f_3 = -5x_1$, and $f_4 = 1 - x_2^2$. They are represented by the solid black lines (—) and their extreme values are represented by dashed red lines (- -).



Source: Own authorship.

3.2.5 Constraints on the input and output

Although not all states can be described by a precise biophysical entity, since Epileptor intends mainly to represent LFPs, the practical application of the feedback-based controller involves applying electrical stimuli to the brain proportionally to the states of the system. The general idea consists in using a sensor to obtain the states (measuring them in terms of electrical voltage⁵). Based on the state vector the control signals are computed using the gain matrix. These control inputs must be carefully monitored to assure the use of a limited and safe range of external electricity, which is important for the protection of the patient. Therefore, an additional condition must be considered before solving the LMI shown in Eq. (34), as discussed below.

Consider a generic matrix $\mathbf{H}$, which is formed, for convenience, by the matrices $\mathbf{A}$ and $\mathbf{B}$ (used to describe the closed loop Epileptor model), and a generic $\mathbf{T}$:

$$\mathbf{H} = \begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B}^T & \mathbf{T} \end{bmatrix} \quad (37)$$

These matrices can be of any convenient dimension as long as $\mathbf{H}$ is square. For illustration purposes, consider a square dynamic matrix of Epileptor's dimensions $\mathbf{A}_{(6 \times 6)}$. Then, the following matrices can be potentially used: $\mathbf{B}_{(6 \times j)}$ and $\mathbf{T}_{(j \times j)}$, where $j \in \mathbb{N}^*$. The Schur complement states that, if $\mathbf{A} = \mathbf{A}^T$ and $\det(\mathbf{H}) \neq 0$, then (Tanaka; Wang, 2004):

$$\begin{bmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{B}^T & \mathbf{T} \end{bmatrix} = \begin{bmatrix} \mathbf{I} & \mathbf{B}\mathbf{T}^{-1} \\ \mathbf{0} & \mathbf{I} \end{bmatrix} \begin{bmatrix} \Delta_{\text{Sc}} & \mathbf{0} \\ \mathbf{0} & \mathbf{T} \end{bmatrix} \begin{bmatrix} \mathbf{I} & \mathbf{0} \\ \mathbf{T}^{-1}\mathbf{B} & \mathbf{I} \end{bmatrix} > 0 \quad (38)$$

which is an LMI, where $\Delta_{\text{Sc}} = \mathbf{A} - \mathbf{B}\mathbf{T}^{-1}\mathbf{B}^T > 0$ is the Schur complement itself, and $\det(\mathbf{T}) \neq 0$. Thus, if it is possible to obtain an equation that is similar to Δ_{Sc} , then it is also possible to propose a new LMI, which is solvable. Particularly, in the context of constraints on the input, the LMIs are given in terms of the initial conditions of the system, according to the formulation in Tanaka and Wang (2004). Assume the vector of initial conditions at the moment when the controller is activated is known: $\mathbf{x}(t_{c0})$; the constraint on the input $|\mathbf{u}(t)| \leq \mu$, where μ is a predefined constant value, is reinforced at all times $t \geq t_{c0}$ if the following LMIs are hold true:

$$\begin{bmatrix} 1 & \mathbf{x}(t_{c0})^T \\ \mathbf{x}(t_{c0}) & \mathbf{X} \end{bmatrix} \geq 0, \quad \begin{bmatrix} \mathbf{X} & \mathbf{G}_x^T \\ \mathbf{G}_x & \mu^2 \mathbf{I} \end{bmatrix} \geq 0 \quad (39)$$

⁵Or, alternatively, measuring some of the states (or a combination of states, as the LFP, for example) and estimating the other ones using a state observer.

where $\mathbf{X} = \mathbf{P}^{-1}$ and $\mathbf{G}_x = \mathbf{G}\mathbf{X}$. Their Schur complement forms are as follows:

$$\mathbf{X} - \mathbf{x}(t_{c0})^T \mathbf{x}(t_{c0}) \geq 0, \quad \frac{1}{\mu^2} \mathbf{G}_x^T \mathbf{G}_x - \mathbf{X} \leq 0 \quad (40)$$

Note that this input limitation is an Euclidean norm (Tanaka; Wang, 2004). Besides, it is included for the model neglecting the vector $\mathbf{b}$, which makes the real maximum input level equal to $\mu_r = p_\mu \mu$. However, because $\mathbf{b}$ is defined by a piecewise constant function (and constant elements), it has been verified in the simulations that $p_\mu \leq 1$.

Consider now the open loop case for Eq. (33) (i.e., $\mathbf{G} \equiv \mathbf{0}$), and replace $\mathbf{A}$ by $\mathbf{A}_N = \mathbf{A} + \alpha \mathbf{I}$, where $\mathbf{I}$ is the identity matrix. It follows that $\mathbf{A}_N^T \mathbf{P} + \mathbf{P} \mathbf{A}_N < 0$, or, alternatively, $(\mathbf{A} + \alpha \mathbf{I})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha \mathbf{I}) < \mathbf{0}$. By expanding its terms, it is possible to verify that its structure corresponds to:

$$\mathbf{A}^T \mathbf{P} + \mathbf{P} \mathbf{A} + 2\alpha \mathbf{P} < 0 \quad (41)$$

Its solution is possible if matrix $\mathbf{P} = \mathbf{P}^T$ is positive definite (Slotine; Li et al., 1991)⁶. Thus, note that, the more positive its eigenvalues are, the more negative the inequality becomes, thus intensifying the stability effect by a factor of α , known as decay rate (Tanaka; Wang, 2004). The decay rate is associated to how fast the system responds to the inputs. The main idea is to add a specific condition for influencing the positiveness of the eigenvalues of $\mathbf{P}$. To include this parameter into the LMIs, Eq. 42 must hold (Tanaka; Wang, 2004):

$$\mathbf{X} \mathbf{A}_j^T - \mathbf{G}_x \mathbf{B}_j + \mathbf{A}_j \mathbf{X} - \mathbf{B}_j \mathbf{G}_x + 2\alpha \mathbf{X} < \mathbf{0} \quad (42)$$

where $j = 1, \dots, 2^{N_{nl}}$ and α is previously set upon criteria defined by the designer.

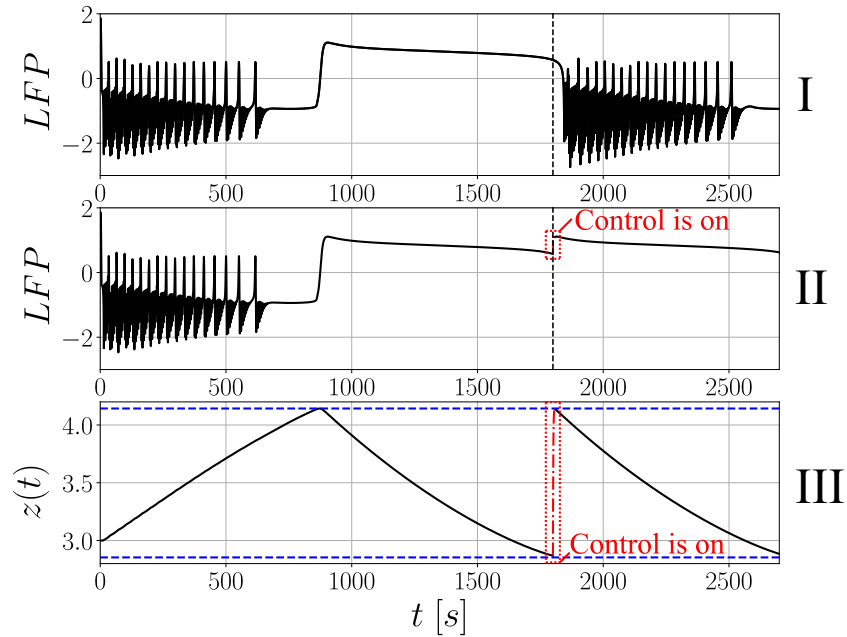
3.2.6 Epileptor's controlled behavior

To compute the gains of the controller, it is necessary to implement an optimization routine to handle all the LMIs together properly. Nowadays, there exist specific packages for this purpose such as PICOS (Sagnol; Stahlberg, 2012) (combined with CVXOPT) for Python, or YALMIP (Lofberg, 2004), for MATLAB. Since all the codes in this thesis were implemented in Python, PICOS is the package of choice for all the simulations. Epileptor's controlled behavior is implemented from scratch and simulated with the same parameters described for the uncontrolled one. The gain matrix is computed by preliminarily setting an input matrix through the scalar d_i , $i = 1, \dots, 6$ in Eq. (21). The definition of these values is empirical, if the analyst intends to consider different weighting factors for the states.

⁶It is worth mentioning that, while $\mathbf{P}$ must be positive definite to assure stability during the control design, matrix $\mathbf{A}$ must present negative eigenvalues for the system to be considered stable.

However, they do not affect substantially the controller's performance. For this chapter $\mathbf{B} = \text{diag}(1, 1, 0.05, 1, 1, 1)$ is used to limit the level of $z(t)$ during the controller's action to the same maximum level for this individual in a normal condition (i.e., the interictal period in Fig. 10). Nonetheless, for simplicity, $\mathbf{B}$ can be assumed as an identity matrix as well, if desired. Figure 16 shows a comparison between the uncontrolled (Fig. 16-I) and controlled (Fig. 16-II) LFP over time. Extreme values of $z(t)$ are considered as triggers to switch on the controller, that is, at the imminence of an epileptic seizure, when $z(t)$ is sufficiently close to its lower boundary (indicated by the lower dashed blue line in Fig. 16-III).

Figure 16 – **Comparison of the system's output in both uncontrolled and controlled conditions.** The LFP = $-x_1(t) + x_2(t)$ is uncontrolled (I) and then controlled (II) after closing the loop in the simulation for about 5 seconds. The levels of $z(t)$ (III) are indicated for when the controller is off by the solid black line (—) and on by the dashed red line (-.-). Its upper and lower limits are indicated by the dashed horizontal lines (- -).



Source: Own authorship.

It must be stressed that different criteria can also be used as triggers, such as alerts by automated detection and diagnosis algorithms. Deep convolutional neural networks have been used for automated seizure and neonatal seizures detection in electroencephalograms (EEGs), for example (Acharya et al., 2018; Ansari et al., 2019). Another promising technique is the Wavelet Transform (WT): it can capture well subtle changes in EEGs, which present a nonstationary nature (Yuan et al., 2018; Faust et al., 2015). Besides, it works for both denoising and feature extraction (Faust et al., 2015), and has been applied along with machine learning techniques for detecting interictal and ictal states (Li et al.,

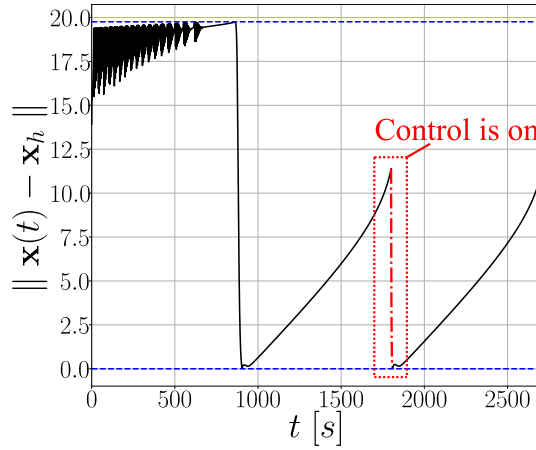
2018a), and even for nonconvulsive seizure detection, which are more difficult to identify (Sharma et al., 2014). Yuan, Zhou and Chen (2018) even proposed an interesting concept: seizure prediction horizon (SPH), defined as a time interval after a prediction alarm until the beginning of the seizure occurrence period (SOP). Therefore, such techniques are consistent with our approach and can be combined with it in possible practical applications considering LFPs. This description suggests that the individual must be continually monitored⁷ over time, and, when potential risks of a new seizure arise (or when it starts), the controller needs to be switched on. This concept is similar to that presented in Nagaraj, Lamperski and Netoff (2017), considering a reinforcement learning algorithm: according to the authors, their controller is constantly vigilant and must be activated when changes that may indicate a seizure arise.

It is important thereby to define a convenient trigger criterion to start the controller's action. Although $z(t)$ is potentially one of the best states to identify the imminence of this type of seizure, the measurement of the LFP is an interesting alternative due to its practical feasibility. In this case, the time history of this output can be monitored and a threshold can be used to trigger the controller. As well known in the literature, patients may present physical, psychiatric or subjective auras seconds or minutes before undergoing seizures (Chen r; Nolan, 2016; Spencer, 2015), which might also help during the process of control activation. Nonetheless, the concept of an automatic trigger is considered in this chapter.

Figure 17 shows the Euclidean norm over time for the vector $(\mathbf{x}(t) - \mathbf{x}_h)$ to demonstrate quantitatively the controller's performance. For $t < 700$ it is possible to see the effect of a first seizure (i.e., for when the controller is off). This norm increases after $t \approx 1000$ s, and the controller is switched on when $t = 1800$ s, and after ~ 5 seconds the state vector achieves the healthy condition (see the dotted line box). The controller's action over time can be better visualized in Figs. 18 and 19, in which the stimuli to each state and the convergence of states are shown. Approximately five seconds are enough to attain the zero baseline again (i.e. convergence) and, thus, suppress the epileptic seizure. The behavior of the inputs, in turn, is similar to an overdamped oscillation with no more than a cycle. These results indicate that the higher level of inputs is required when the controller is switched on, and it is important thereby to consider constraints on the input, as discussed later on in this chapter.

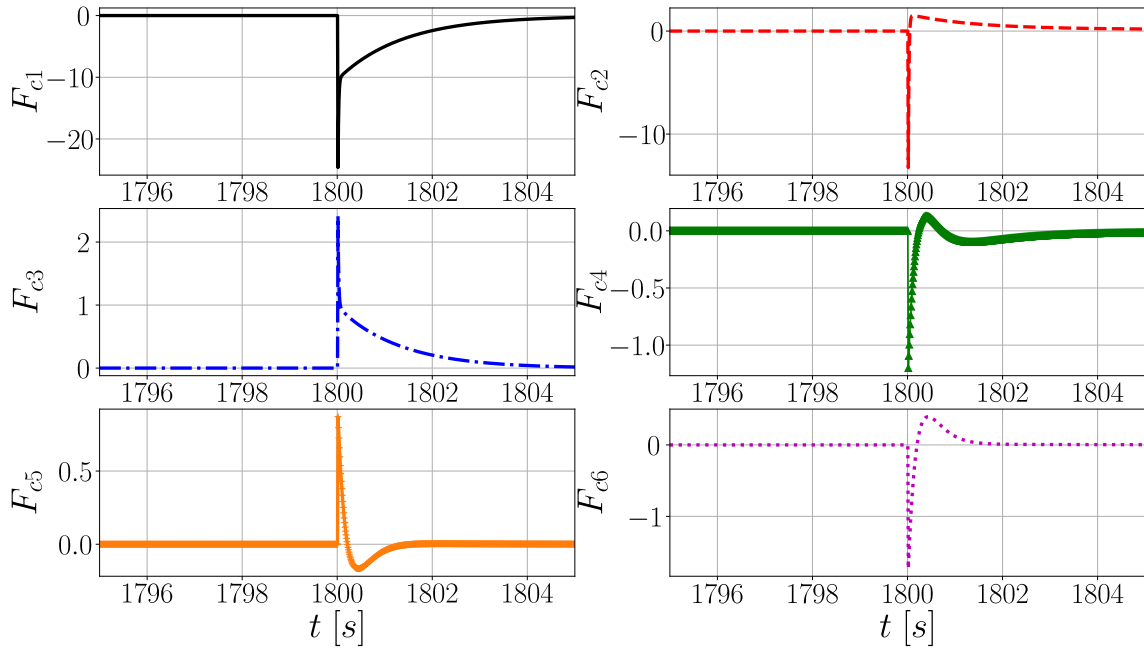
⁷As seen in Jirsa et al. (2014), the biological model used to design Epileptor was based on signals obtained from mice. The authors even carried out experiments (using hippocampi and the septum) to test some hypotheses related to the prediction capability of Epileptor. Further details on how LFPs can be monitored and acquire can be seen in the same reference.

Figure 17 – **Euclidean norm for $(\mathbf{x}(t) - \mathbf{x}_h)$ over time.** The controller is switched on just for a few seconds, indicated by the dotted box (...). Then, it is switched off, driving the system out of the seizure, thus returning to the non-seizure baseline close to the zero levels. The Euclidean norm is indicated by the solid black lines (—) and it measures the distance between the state variables and the seizure-free state; during the action of the controller, it is indicated by the red dash-dotted lines (-.-).



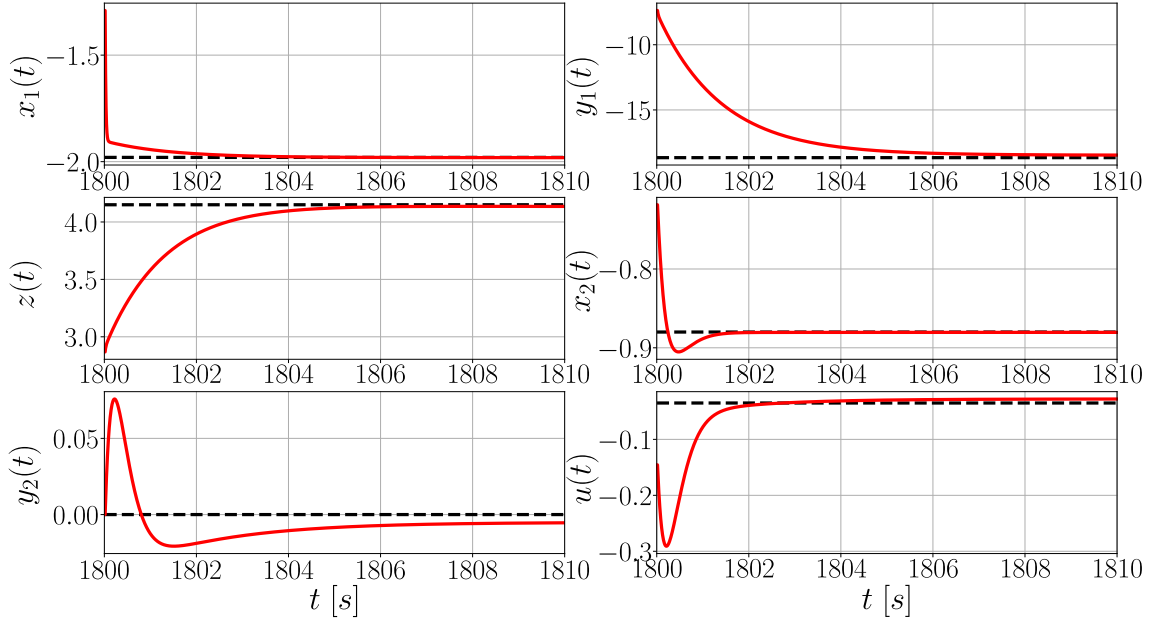
Source: Own authorship.

Figure 18 – **Control signals $F_{c(j)}$ ($j = 1, \dots, 6$) over time for $\mu = \alpha = 0$ (no constraints) to suppress Epileptor's seizure.** Seizure suppression is attained after approximately 5 seconds by stimuli that resemble overdamped oscillations of one cycle.



Source: Own authorship.

Figure 19 – **State variables after switching the controller on.** The solid red lines (—) represent the states converging to the target ones, indicated by the dashed black lines (---), thus demonstrating the efficiency of the controller. In this simulation, no constraints are applied to the input.



Source: Own authorship.

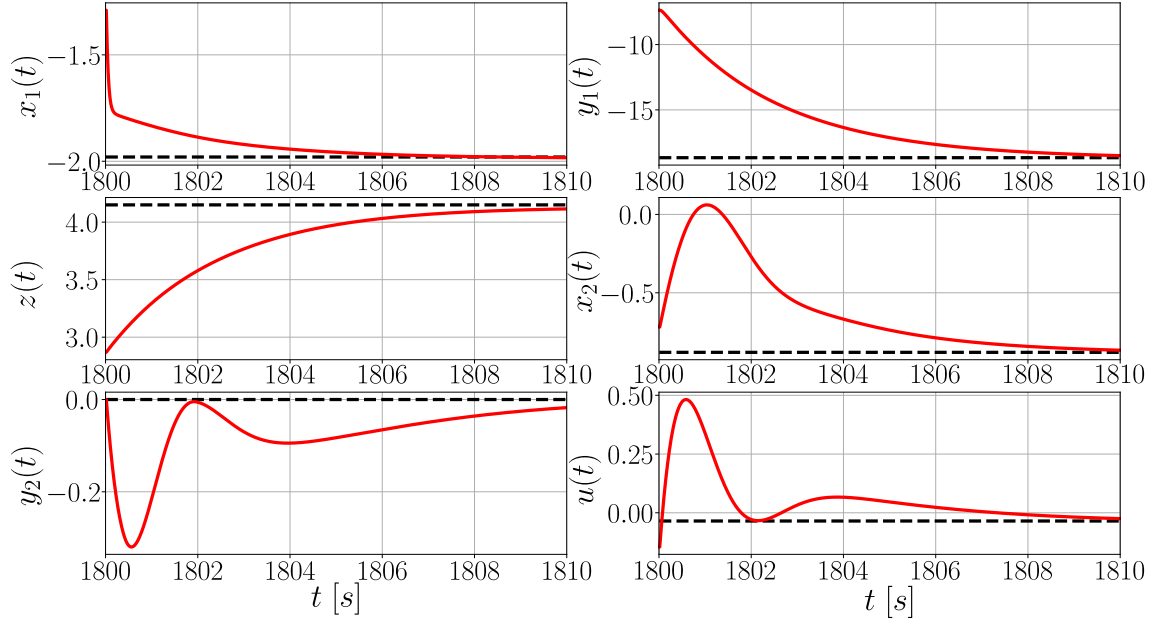
To illustrate a practical implementation of the controller, constraints on the input and output are evaluated. Table 1 shows the controller's performance for different values of μ , presenting the maximum level of each input, $F_{c(j)}^{max} = \max(|F_{c(j)}(t)|)$, and each respective time (t_c [s]) to achieve $\mathbf{x}_h$ after switching the controller on. Also, the maximum value for the ratio $z(t)/z_{max}$ is shown during the controller's action, where $z_{max} = 4.15$ (Fig. 10) for the present case. Since the choice of μ influences $\max(z(t)/z_{max})$ (referred to as z_{ratio}), this implies that μ must be chosen also considering z_{max} . If μ is too high, a seizure is suppressed, but $\max(z(t)) > z_{max}$. If μ is too low, in turn, a seizure is suppressed, but it takes longer until $\mathbf{x}(t) \cong \mathbf{x}_h$ (in case the controller is switched on for shorter than the specified value, $\max(z(t)/z_{max}) \ll 1$, which may suppress a seizure, but $\mathbf{x}(t)$ remains at surrounding seizure-free points other than $\mathbf{x}_h$ and the seizure-free condition lasts shorter). The respective inputs are omitted, but they are similar to those shown in Fig. 19. Fig. 20 shows that constraints on inputs can change the trajectory of the states until achieving the target $\mathbf{x}_h$. In particular, for $\mu = 30$ (and $\alpha = 0$) the main differences are observed for x_2 and y_2 (see Fig. 19 to compare them).

Table 1 – **Controller’s performance, in terms of LFP input, for different constraints on the input ($d_z = 0.05$).** For all cases, μ is applied such that z_{ratio} is kept close to the ideal unity and the inputs do not exceed the boundaries of the control variable $z(t)$.

μ	F_{c1}^{max}	F_{c2}^{max}	F_{c3}^{max}	F_{c4}^{max}	F_{c5}^{max}	F_{c6}^{max}	t_c [s]	z_{ratio}
–	24.63	13.25	2.41	1.20	0.87	1.73	~ 5	0.99
20	9.24	7.32	0.38	0.62	0.69	1.26	~ 50	0.98
30	10	2.64	0.57	1.42	1.27	2.56	~ 10	0.99

Source: Own authorship.

Figure 20 – **State variables after switching the controller on.** The solid red lines (—) represent the states converging to the target ones, indicated by the dashed black lines (- -), thus demonstrating the efficiency of the controller even when constraints on the input are applied. In this simulation, the parameter of the constraint on the input is: $\mu = 30$.

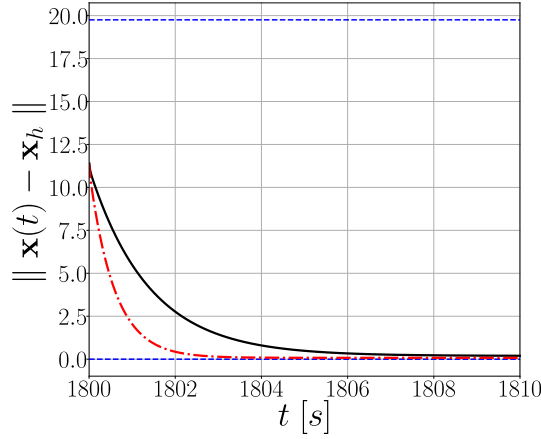


Source: Own authorship.

Figure 21 presents a comparison between the time the system takes to achieve the healthy condition if the controller’s design considers $\alpha = 0$ (no constraints on the output) and $\alpha = 1$. For both cases no constraints on the input are used ($\mu = 0$). Note that the controller exhibits a higher decay rate when the output constraint is taken into account. However, large values of α commonly require high levels of inputs, and due to this fact, the combination of both constraints can be used to define a more suitable solution. Table 2 shows the controller performance for two different pairs (μ, α) , and it is possible to note that, by tuning specific combinations of such parameters, similar values to those from Table 1 (where no decay rates were included) can be used to obtain relatively short t_c

and low amplitude input forces such that $\max(z(t)/z_{max}) < 1$.

Figure 21 – **Euclidean norm for $(\mathbf{x}(t) - \mathbf{x}_h)$ after adding the decay rate**. Note that α is a performance-enhancing parameter, leading to seizure suppression in a shorter period of time. The controller's performance is compared for when $\alpha = 0$ (no constraint on the output), indicated by the solid black line (—), and when $\alpha = 1$, indicated by the dash-dotted red line (-.-).



Source: Own authorship.

Table 2 – **Controller's performance, in terms of LFP inputs, for different pairs of constraints on the input and output ($d_z = 0.05$)**. Combinations of μ and α are used such that z_{ratio} is kept close to the ideal unity and the inputs do not exceed the boundaries of the control variable $z(t)$.

μ	α	F_{c1}^{max}	F_{c2}^{max}	F_{c3}^{max}	F_{c4}^{max}	F_{c5}^{max}	F_{c6}^{max}	t_c [s]	z_{ratio}
38	0.52	10.78	11.55	0.48	0.55	0.58	1.16	~ 5	0.99
35	0.48	10.75	12.41	0.44	0.53	0.52	1.05	~ 5	0.99

Source: Own authorship.

In possible practical applications, combinations of μ and α mean weaker or stronger constraints on the voltage amplitude necessary for suppressing seizures. It is thus reasonable to assume that moderate parameters are suitable for treating patients, since relatively low inputs are associated to longer times or suboptimal efficiency to suppress a seizure, whereas significantly high inputs may suppress a seizure in a shorter time (as seen in Table 3, for example) but compromise the health of brain tissues. The best trade-off between these parameters is not discussed in this chapter, but realistic values of some parameters used in electrical therapies for seizure attenuation are analyzed and compared to other results obtained in this thesis in Chapter 7.

3.3 Contributions, limitations and conclusions

Considering the results and discussion addressed in this chapter, the main contributions that can be highlighted are:

- the controller proposed in this chapter is able to efficiently suppress the epileptic seizures because its formulation is carried out considering a sufficient condition for stability;
- its design depends on solving a set of linear matrix inequalities, which computationally can adjust the values of α to obtain a feasible solution. This means that the intensity of the input can be amplified if necessary;
- it is also possible to limit the admissible intensity of input by the constraint on the output from μ . This is particularly useful in possible future applications of the controller in practice since an arbitrarily high input is not a realistic option for patients with epilepsy. This issue is addressed in more detail in Chapter 7;
- regarding the shapes of the control signals, the results show that overdamped inputs can suppress a seizure if they are computed proportional to the difference between the nonlinear dynamics described by the system's states during the seizure event and a reference healthy condition. It means that establishing a baseline reference for a seizure-free condition for the individual is an important step to define the input stimuli. Besides, these inputs are consistent with the shapes of the stimuli applied in real clinical environments for seizure suppression, essentially composed of pulses of periodic or non-periodic frequency (Velasco et al., 2001; Velasco et al., 2007; Rizzone et al., 2001; Cota et al., 2009).

For the proposed approach to work, the following hypotheses are implicitly assumed, thus imposing some limitations to the current results:

- the state vector is known for each time instant and it is possible to define $\mathbf{x}_h$. Nonetheless, it is known that some variables involved in the Epileptor dynamic model are not measurable in a real brain or do not have a precise biophysical meaning (Jirsa et al., 2014). Important effort has been made by researchers to link Epileptor's variables and parameters to the chemical and electrical characteristics of brain dynamics, but to improve the possibilities of using this relevant tool in real applications further developments and investigations are required.
- a set of parameters $\mathbb{S} = \{\tau_0, \tau_1, \tau_2, \gamma, x_0, y_0, I_{rest1}, I_{rest2}\}$ is known to define a representative Epileptor model (i.e., a model to describe a real epileptic seizure for an individual);

- the electrophysiological time signature can be accurately represented or at least approximated by the Epileptor, which probably does not hold true for all existing seizures.

To address the first hypothesis, the concept of fuzzy observers can be used, for example (Tanaka; Wang, 2004; Ichalal; Arioui; Mammar, 2011; Hammoudi et al., 2014). In this case, the LFPs can provide input information for the observer to estimate the remaining states. For the second hypothesis, as a typical control application, the online implementation of the proposed methodology requires previous identification and fitting (or parameter estimation) of the model that represents a patient. This topic is associated to model identification and is discussed in the next chapters.

This chapter introduced an approach to design a feedback controller to suppress epileptic seizures described by the Epileptor. This dynamic model represents the most recurring and relevant characteristics of this type of disorder. Although previous works discuss alternative methodologies to design controllers for suppressing epileptic seizures, they typically consider simpler models, compared to the Epileptor, which in turn limits their applicability to particular types of epilepsy. However, once that different types of epileptic conditions can be described by tuning the Epileptor's parameters, it is very convenient to use the general methodology developed in this work to write the nonlinear dynamics by a combination of linear local models using an exact solution. In addition, if an associated set of LMIs is feasible, the controller ensures a sufficient condition to suppress the undesired dynamics.

The methodology described herein allows one to simultaneously consider constraints on the input and output, which provides an interesting strategy for practical applications. Nonetheless, further investigations are required to improve the understanding about the Epileptor, particularly to link its dynamics to chemical and electrical activities measurable in real cases. On the other hand, once that modeling a controller that is capable of reducing the effects of epilepsy is addressable, more realistic applications can be envisioned, especially because the control law and state feedback indicate which variables must be targeted when designing a closed-loop controller in practice, and how the shapes of the input stimuli must be for a seizure-free state (that is, a “healthy” nonseizure condition) to be achieved again.

At last, if the parameters of the model are known, as in the present case, the FTS modeling can be applied to obtain control gains for seizure suppression. Furthermore, the proposed approach can be used as of now to study coupled Epileptors not only for seizure propagation (Proix et al., 2017), but also for seizure suppression.

4 RECONSTRUCTING THE UNMEASURABLE VARIABLES OF THE EPILEPTOR MODEL

Even if the epileptiform has been effectively suppressed using all Epileptor's variables, not all of them are of concrete nature or have a precise physical meaning (Jirsa et al., 2014); that is, they cannot be directly measured. Therefore, further work needs to be done to circumvent this problem and bring the application of controllers closer to realistic scenarios. In this sense, the concept of observability plays an important role: it is possible to estimate/reconstruct unmeasurable variables based on the output response of the system by designing a copy of the original dynamic set of equations, if its parameters are known (Tanaka; Wang, 2004).

Thus, a fuzzy Takagi-Sugeno observer (Tanaka; Wang, 2004) is developed in this chapter considering a specific formulation for its error dynamics that has presented effective results in the literature (Ichalal; Arioui; Mammar, 2011). Naturally, a fundamental assumption is made: the dynamic model is known, that is, all of its parameters are known. The problem of identifying them is discussed in the next chapter. Moreover, the objective of this chapter is twofold: designing the above-mentioned observer and enhancing its performance. As seen, the parameter known in the literature as decay rate (α) intensifies the action of controllers and observers by decreasing the time necessary for stability to be achieved (Tanaka; Wang, 2004; Ichalal; Arioui; Mammar, 2011). In this chapter, a novel approach using the parameter β is introduced, which outperforms the one with α alone and provides a smoother response when reconstructing the unmeasurable variables of the system. The codes used in this chapter are available online on the platform GitHub at the following address: <https://github.com/GMSINT/Epilepsy-Dynamics-Control>.

4.1 Measurable and unmeasurable variables

The role of observers is to reconstruct variables that cannot be directly measured in practice, based on the measurable ones. Therefore, a clear definition about what is considered as measurable or not needs to be stated. A comprehensive description of the variables and parameters associated to the Epileptor has already been introduced in the previous chapter, so a brief analysis is presented below to explain which variables (and why) have been considered as measurable:

- *First sub-system:* although this sub-system is described by LFPs, thus measured in mV or μV , only $x_1(t)$ can be recorded over time – thus, it is likely to be measured;

$y_1(t)$, in turn, is not measurable — rather, it plays the role of a higher-dimensional entity which helps unfold the attractor of this subsystem, thus revealing its dynamics (thus, it is unlikely to be measured);

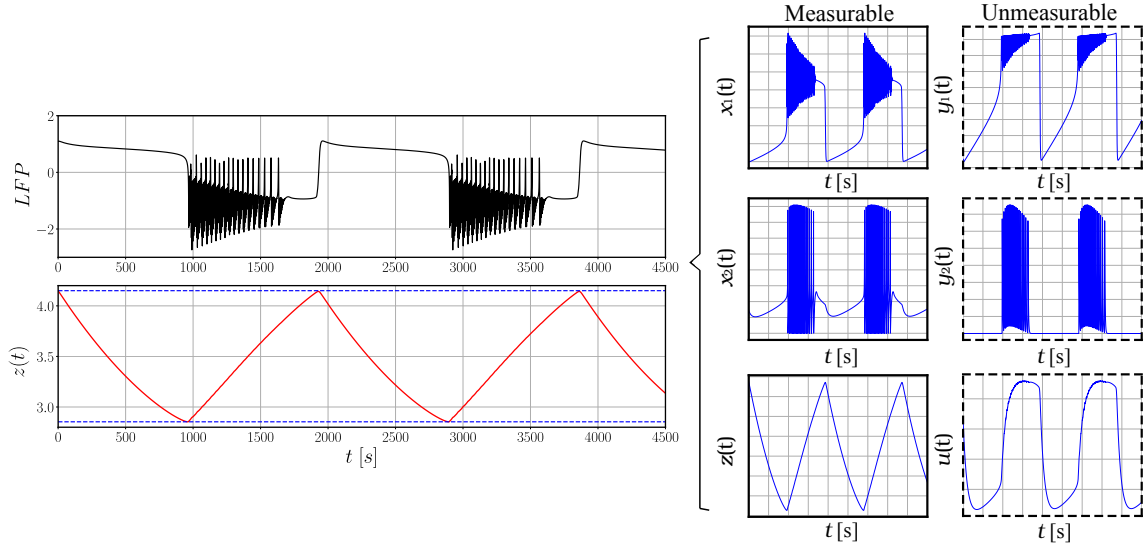
- *Second sub-system:* similarly, $x_2(t)$ is associated to neuron membrane potentials (mV or μ V) and is considered likely to be measurable, whereas $y_2(t)$ is responsible for revealing the attractor of the second sub-system, which makes it unlikely to be measured;
- *Permittivity:* $z(t)$ is the slowest time-evolving variable potentially associated to levels of ions, oxygen or energy metabolism (Jirsa et al., 2014). Given its possible but uncertain biophysical meaning, it is considered an entity that is unlikely to be measured;
- *Variable $u(t)$:* since $u(t)$ is a “dummy” variable that plays the role of a low-pass filter due to the time scale separation $1/\gamma = 100 \gg \tau_2$ (Jirsa et al., 2014), it is considered unlikely to be measured.

All of the other entities associated to the model are parameters of the system, not variables, which is why they have not been included. Therefore, for the definition of matrix $\mathbf{C}$ (that is, the information that can actually be recorded over time), there are only three candidate variables available in this case: $x_1(t)$, $x_2(t)$ and $z(t)$. Nevertheless, due to the inherent uncertainty of $z(t)$, matrix $\mathbf{C}$ is composed of $x_1(t)$ and $x_2(t)$:

$$\mathbf{C} = [-1 \quad 0 \quad 0 \quad 1 \quad 0 \quad 0] \quad (43)$$

Note that $\mathbf{C}$ is actually a vector. This can be explained by the fact that, as defined by the authors of Epileptor (Jirsa et al., 2014), the resulting LFPs in the time domain are formed by a coupling between both sub-systems, which is, in turn, defined as the following linear combination: $-x_1(t) + x_2(t)$. For the sake of understanding, Fig. 22 depicts Epileptor’s behavior in the domain time again, but now with all of its variables indicated, categorized as measurable (from the output) and unmeasurable.

Figure 22 – **Epileptor’s behavior in the time domain as $LFP = (-x_1(t) + x_2(t))$ and state $z(t)$, and all of its variables, categorized as measurable or unmeasurable.** Of all the six state variables that describe Epileptor’s behavior, only x_1 and x_2 are related to the membrane potential, measurable in the time domain as difference of potential. Although $z(t)$ is potentially measurable (Jirsa et al., 2014), it is considered unmeasurable in this thesis due to its inherent uncertainty.



Source: Own authorship.

4.2 Fuzzy state observer

By measuring the output of the system, given as electrical/voltage activity in LFPs, it is possible to access the “hidden” information in the brain and then reconstruct all of the states. Once they are available, this is useful for two main purposes: *i*) a fuller understanding of the brain dynamics is obtained – in particular, for the reconstruction of the attractors and bursters which characterize epileptic seizures as cyclic bi-stable phenomena (Jirsa et al., 2014); *ii*) control approaches for seizure suppression for Epileptor have been designed recently (Nagaraj; Lamperski; Netoff, 2017) (including the one from the previous chapter), but since state-feedback controllers rely on knowing all of the states, their applicability is restricted unless an observer is also designed. Based on this context, the design of the observer applied to Epileptor using the DMVT is presented in this section to tackle this specific problem.

State observers are, essentially, “copies” of the original system that are capable of measuring its output and estimating possible variables that, for different reasons (such as: abstract nature, physical constraints or limited resources), cannot be directly measured, which often occurs in practical applications (Tanaka; Wang, 2004). Considering the state-

space representation, a fuzzy observer is given by (Tanaka; Wang, 2004):

$$\begin{cases} \dot{\hat{\mathbf{x}}}(t) = \sum_{i=1}^{2^{N_{nl}}} \hat{N}_i(\hat{\mathbf{x}}(t)) \{ \mathbf{A}_i \hat{\mathbf{x}}(t) + \mathbf{B}_i \mathbf{u}(t) + \mathbf{L}_i [\mathbf{y}(t) - \hat{\mathbf{y}}(t)] \} \\ \hat{\mathbf{y}}(t) = \mathbf{C} \hat{\mathbf{x}}(t) \end{cases} \quad (44)$$

where $\mathbf{L} \in \Re^{n_y}$ is a weighting matrix for the observer. That is, once the output vector $\mathbf{y}$ from the original system is measurable, if it is compared to a known predefined copy of the system whose output is $\hat{\mathbf{y}}$, and weighted by matrices $\mathbf{L}_i$ of proper dimension, $\hat{\mathbf{y}} \rightarrow \mathbf{y}$, which implies that $\mathbf{L}_i [\mathbf{y}(t) - \hat{\mathbf{y}}] \rightarrow 0$, and the observer becomes an exact copy of the system, yielding recreated versions of the original variables as well. Note that, for this approach to work, the system and its parameters must be known.

Moreover, $\hat{\mathbf{x}}(t) \neq \mathbf{x}(t)$ (the estimated states are different from the actual states), as well as $\hat{N}_i(\hat{\mathbf{x}}(t)) \neq N_i(\hat{\mathbf{x}}(t))$, for the most general case (the weighting functions for the estimated states are different from the actual weighting functions too). The latter condition is particularly relevant in this chapter, because it indicates that the membership functions depend on the unmeasurable variables. Therefore, there are two main cases (Tanaka; Wang, 2004):

- $\hat{N}_i(\hat{\mathbf{x}}(t)) = N_i(\hat{\mathbf{x}}(t))$: the membership functions do not depend on the estimated states. That is, the nonlinear functions in $\mathbf{A}_{nl}$ do not depend on estimated variables/states;
- $\hat{N}_i(\hat{\mathbf{x}}(t)) \neq N_i(\hat{\mathbf{x}}(t))$: the membership functions depend on the estimated states. That is, the nonlinear functions in $\mathbf{A}_{nl}$ depend on estimated variables/states.

The case for the Epileptor model falls in the latter one¹. The estimation error for state observers, in turn, is defined as: $\mathbf{e}(t) = \mathbf{x}(t) - \hat{\mathbf{x}}(t)$. For linear models (that is, time-invariant systems), this equation can be written in its dynamic form after deriving it (Ogata, 2010): $\dot{\mathbf{e}}(t) = (\mathbf{A} - \mathbf{L}\mathbf{C})\mathbf{e}(t)$, where $\mathbf{A}$ is a constant matrix. However, Epileptor presents a non-constant dynamic matrix $\mathbf{A}_{nl}$. Therefore, the fuzzy observer can be strategically applied to cope with this issue, leading to the following expression (Ichalal; Arioui; Mammar, 2011):

$$\dot{\mathbf{e}}(t) = f(\mathbf{z}(t)) - f(\hat{\mathbf{z}}(t)) - \mathbf{L}\mathbf{C}\mathbf{e}(t) \quad (45)$$

For simplicity, single gain and output matrices $\mathbf{L}$ and $\mathbf{C}$ are considered (that is, $\mathbf{L}_i = \mathbf{L}$ and $\mathbf{C}_i = \mathbf{C}$, $i = 1, 2, \dots, 2^{N_{nl}}$). Also, $f(\mathbf{z}(t)) = f(\mathbf{x}(t), \mathbf{u}(t))$ and $f(\hat{\mathbf{z}}(t)) = f(\hat{\mathbf{x}}(t), \mathbf{u}(t))$,

¹Since Eq. 6 depends on $z(t)$, one of the nonlinear functions (and, thus, its membership function) contains a variable that is not considered as measurable. In other words: $\hat{N}_i(\hat{\mathbf{x}}(t)) \neq N_i(\hat{\mathbf{x}}(t))$ because of $z(t)$, which explains why it is necessary to apply the DMVT.

defined as (Ichalal; Arioui; Mammar, 2011):

$$f(\mathbf{z}(t)) = \sum_{i=1}^{2^{N_{nl}}} N_i(\mathbf{x}(t)) [\mathbf{A}_i \mathbf{x}(t) + \mathbf{B}_i \mathbf{u}(t)] \quad (46)$$

$$f(\hat{\mathbf{z}}(t)) = \sum_{i=1}^{2^{N_{nl}}} \hat{N}_i(\hat{\mathbf{x}}(t)) [\mathbf{A}_i \hat{\mathbf{x}}(t) + \mathbf{B}_i \mathbf{u}(t)] \quad (47)$$

As discussed by Tanaka and Wang (2004), if $\hat{N}_i(\hat{\mathbf{x}}(t)) = N_i(\hat{\mathbf{x}}(t))$, the stability analysis is straightforward. However, considering the worst case scenario where $\hat{N}_i(\hat{\mathbf{x}}(t)) \neq N_i(\hat{\mathbf{x}}(t))$ (which is the case for Epileptor, as mentioned above), the stability analysis of this kind of estimation error cannot be carried out using the traditional tools available for Takagi-Sugeno systems (Ichalal; Arioui; Mammar, 2011). Thus, a different approach must be employed to cope with the following term: $\vartheta = f(\mathbf{z}(t)) - f(\hat{\mathbf{z}}(t))$. In this thesis, the Differential Mean Value Theorem (DMVT) is chosen for this purpose. Its formulation extends the concept of linear sub-models to the error dynamics, whose stability is assured by using a Lyapunov function (Ichalal; Arioui; Mammar, 2011).

This approach has been chosen for specific reasons: it has presented fairly good results in terms of convergence and stability for continuous (Ichalal et al., 2011; Hammoudi et al., 2014; Hammoudi et al., 2015; Ichalal et al., 2018) and discrete-time systems (Ichalal et al., 2012), as well as common practical (Ichalal; Arioui; Mammar, 2011; Hammoudi et al., 2014; Hammoudi et al., 2015) or more abstract systems (Ichalal et al., 2012); at last, it is a relatively simple approach, in terms of implementation.

4.2.1 Differential Mean Value Theorem (DMVT)

The formulation using the DMVT in this work is based on the results obtained by Ichalal, Arioui and Mammar (2011). Considering all of the n entries of the nonlinear functions from $f(\mathbf{z}) : \mathbb{R}^n \rightarrow \mathbb{R}$, denoted as $f_i(\mathbf{z})$ (Ichalal; Arioui; Mammar, 2011):

$$f(\mathbf{z}) = [f_1(\mathbf{z}) \quad \cdots \quad f_n(\mathbf{z})]^T \quad (48)$$

where $f_i(\mathbf{z}) : \mathbb{R}^n \rightarrow \mathbb{R}$, $i = 1, \dots, n$. Let $a, b \in \mathbb{R}^n$. If $f_i(\mathbf{z})$ is differentiable on $[a, b]$, then there exists a constant vector $\mathbf{z}^i$, satisfying $\mathbf{z}^i \in]a, b[$, i.e., $\mathbf{z}_j^i \in]a_j, b_j[$, for $j = 1, \dots, n$, such that (Ichalal; Arioui; Mammar, 2011)

$$f_i(b) - f_i(a) = \frac{\partial f_i(\mathbf{z}^i)}{\partial \mathbf{z}} (b - a) \quad (49)$$

It follows that, in terms of vectors (Ichalal; Arioui; Mammar, 2011):

$$\underbrace{f(\mathbf{z}) - f(\hat{\mathbf{z}})}_{\vartheta} = \frac{\partial f_i(\mathbf{z}^i)}{\partial \mathbf{z}} (\mathbf{z} - \hat{\mathbf{z}}) \quad (50)$$

To expand this notation taking all nonlinear entries $f_i(\mathbf{z})$ ($i = 1, \dots, n$) into account, as well as all variables involved in the system z_j ($j = 1, \dots, n$), the following vector is defined (Ichalal; Arioui; Mammar, 2011):

$$\mathbf{E}_i = \begin{bmatrix} 0 & \cdots & 0 & 1 & 0 & \cdots & 0 \\ 1 & & i-1 & i & i+1 & & n \end{bmatrix}^T \quad (51)$$

Then, the function $f(\mathbf{z})$ can be expressed as a sum of all individual $f_i(\mathbf{z})$ and $\mathbf{E}_i$ (Ichalal; Arioui; Mammar, 2011):

$$f(\mathbf{z}) = \sum_{i=1}^n \mathbf{E}_i f_i(\mathbf{z}) \quad (52)$$

or, alternatively, for i and j (Ichalal; Arioui; Mammar, 2011):

$$\vartheta = \sum_{i=1}^n \sum_{j=1}^n \mathbf{E}_i \mathbf{E}_j^T \frac{\partial f_i(z^i)}{\partial z_j} \underbrace{(\mathbf{z} - \hat{\mathbf{z}})}_{\mathbf{e}(t)} \quad (53)$$

Thus, replacing the equation above into the error dynamics (see Eq. 45) leads to (Ichalal; Arioui; Mammar, 2011):

$$\dot{\mathbf{e}}(t) = \sum_{i=1}^n \sum_{j=1}^n \mathbf{E}_i \mathbf{E}_j^T \frac{\partial f_i(z^i)}{\partial z_j} \mathbf{e}(t) - \mathbf{L} \mathbf{C} \mathbf{e}(t) \quad (54)$$

Alternatively (Ichalal; Arioui; Mammar, 2011):

$$\dot{\mathbf{e}}(t) = \left[\sum_{i=1}^n \sum_{j=1}^n \mathbf{E}_i \mathbf{E}_j^T \frac{\partial f_i(z^i)}{\partial z_j} - \mathbf{L} \mathbf{C} \right] \mathbf{e}(t) \quad (55)$$

The concept of sector nonlinearity from TS systems, which is the main characteristic that allows rewriting nonlinear systems as linear sub-models, can be applied to model each of the derivatives present in the Jacobian, for $i = 1, \dots, n$ and $j = 1, \dots, n$, as (Ichalal; Arioui; Mammar, 2011):

$$a_{ij} \leq \frac{\partial f_i(z^i)}{\partial z_j} \leq b_{ij} \quad (56)$$

if, and only if, $\frac{\partial f_i(z^i)}{\partial z_j}$ is differentiable on each $[a_{ij}, b_{ij}]$, where a_{ij} and b_{ij} are individual maximum and minimum values for each i and j . Therefore, this term can be rewritten

as a linear combination between such extreme values (Ichalal; Arioui; Mammar, 2011):

$$\frac{\partial f_i(z^i)}{\partial z_j} = \sum_{k=1}^2 v_{ij}^k(z^i) \tilde{a}_{ijk} \quad (57)$$

where:

$$v_{ij}^1(z^i) = \frac{\frac{\partial f_i(z^i)}{\partial z_j} - a_{ij}}{b_{ij} - a_{ij}}, \quad v_{ij}^2(z^i) = 1 - v_{ij}^1(z^i) \quad (58)$$

which, necessarily, must meet the following requirements of convexity (Ichalal; Arioui; Mammar, 2011):

$$\sum_{k=1}^2 v_{ij}^k(z^i) = 1, \quad 0 \leq v_{ij}^k(z^i) \leq 1, \quad k = 1, 2 \quad (59)$$

After carrying out this expansion, the error dynamics becomes, then (Ichalal; Arioui; Mammar, 2011):

$$\dot{\mathbf{e}}(t) = \left[\sum_{i=1}^n \sum_{j=1}^n \sum_{k=1}^2 v_{ij}^k(z^i) \mathbf{E}_i \mathbf{E}_j^T \tilde{a}_{ijk} \frac{\partial f_i(z^i)}{\partial z_j} - \mathbf{LC} \right] \mathbf{e}(t) \quad (60)$$

Alternatively, for the sake of simplicity, new matrices $\mathbf{A}^*$ can be introduced (Ichalal; Arioui; Mammar, 2011):

$$\sum_{i=1}^n \sum_{j=1}^n \sum_{k=1}^2 v_{ij}^k(z^i) \mathbf{E}_i \mathbf{E}_j^T \tilde{a}_{ijk} = \sum_{i=1}^q h_i(\tilde{\mathbf{z}}) \mathbf{A}_i^* \quad (61)$$

where $q \leq 2^{n^2}$, which leads to (Ichalal; Arioui; Mammar, 2011):

$$\dot{\mathbf{e}}(t) = \sum_{i=1}^q h_i(\tilde{\mathbf{z}}) \Psi_i \mathbf{e}(t) \quad (62)$$

where $\Psi_i = \mathbf{A}_i^* - \mathbf{LC}$ is a linear subsystem.

4.2.2 Stability analysis of the error dynamics

To analyze the error dynamics in terms of convergence, Lyapunov theory can be used, which is a sufficient condition to assure stability. Consider the following quadratic Lyapunov function:

$$V(\mathbf{e}(t)) = \mathbf{e}(t)^T \mathbf{P}_{obs} \mathbf{e}(t) \quad (63)$$

where $\mathbf{P}_{obs} = \mathbf{P}_{obs}^T > 0$ (that is, $\mathbf{P}_{obs}$ is a positive-definite matrix, whose all eigenvalues are positive) (Slotine; Li et al., 1991), in this case, is the stability matrix for the error dynamics of the fuzzy observer. After deriving this equation and substituting Eq. 62 into

it (Ichalal; Arioui; Mammar, 2011):

$$\dot{V}(\mathbf{e}(t)) = \sum_{i=1}^q h_i(\tilde{\mathbf{z}}) \mathbf{e}(t)^T (\Psi_i^T \mathbf{P}_{obs} + \mathbf{P}_{obs} \Psi_i) \mathbf{e}(t) < \mathbf{0} \quad (64)$$

Alternatively, this sum can be converted into a set of Linear Matrix Inequalities (LMIs) (Boyd et al., 1994; Tanaka; Wang, 2004):

$$\mathbf{A}_i^{*T} \mathbf{P}_{obs} + \mathbf{A}_i^* \mathbf{P}_{obs} - \mathbf{M} \mathbf{C} - \mathbf{C}^T \mathbf{M}^T < \mathbf{0}, \quad i = 1, \dots, q \quad (65)$$

where $\mathbf{M} = \mathbf{P}_{obs} \mathbf{L}$. All of the q inequalities above must be solved simultaneously to compute $\mathbf{M}$. Therefore, if there exists a matrix $\mathbf{M}$, which implies that there also exist $\mathbf{P}_{obs}$ and $\mathbf{L}$, then the error dynamics converges towards zero, based on the Lyapunov criterion.

4.3 Reducing the time necessary for stability to be achieved

This section presents a methodology known in the literature for increasing the speed at which the error dynamics is reduced to its minimum value over time, based on the so-called decay rate (α), as previously introduced in this thesis. Besides, a novel approach using the parameter β is introduced, which outperforms the approach with α alone and provides a smoother response when reconstructing the unmeasurable variables of the system.

4.3.1 Classic approach

The decay rate is responsible for increasing the speed of convergence in control engineering problems (Tanaka; Wang, 2004). Essentially, it influences the positiveness of matrix $\mathbf{P}_{obs}$, contributing to making its eigenvalues even more positive, which enhances the performance of controllers/observers. Based on Eq. 65, for the specific case of the fuzzy observer, adding the decay rate α leads to (Tanaka; Wang, 2004; Ichalal; Arioui; Mammar, 2011):

$$(\mathbf{A}_i^* + \alpha \mathbf{I})^T \mathbf{P}_{obs} + (\mathbf{A}_i^* + \alpha \mathbf{I}) \mathbf{P}_{obs} - \mathbf{M} \mathbf{C} - \mathbf{C}^T \mathbf{M}^T < \mathbf{0}, \quad i = 1, \dots, q \quad (66)$$

According to (Ichalal; Arioui; Mammar, 2011), the performance of the fuzzy observer can be improved by pole assignment in an LMI region of the type $S = \{z \in \mathbb{C} | \text{Re}(z) < -\alpha, |z| < r\}$, defined as the intersection between the left plan $\text{Re}(z) < -\alpha$ and a disc with center $(0,0)$ and radius r . This region leads to the following LMIs:

$$(\mathbf{A}_i + \alpha \mathbf{I})^{*T} \mathbf{P}_{obs} + (\mathbf{A}_i + \alpha \mathbf{I}) \mathbf{P}_{obs} - \mathbf{M} \mathbf{C} - \mathbf{C}^T \mathbf{M}^T < \mathbf{0}, \quad i = 1, \dots, q \quad (67)$$

$$\begin{bmatrix} -r\mathbf{P}_{obs} & \mathbf{P}_{obs}\mathbf{A}_i^* - \mathbf{MC} \\ \mathbf{A}_i^{*T}\mathbf{P}_{obs} - \mathbf{C}^T\mathbf{M}^T & -r\mathbf{P}_{obs} \end{bmatrix} < \mathbf{0}, \quad i = 1, \dots, q \quad (68)$$

4.3.2 Proposal of enhancement

Additionally, with the purpose of smoothing and increasing the effect of α , a new parameter can be included to the set of equations, referred to as β :

$$(\mathbf{A}_i^* + \alpha\mathbf{I} + \beta\mathbf{1})^*T\mathbf{P}_{obs} + (\mathbf{A}_i^* + \alpha\mathbf{I} + \beta\mathbf{1})\mathbf{P}_{obs} - \mathbf{MC} - \mathbf{C}^T\mathbf{M}^T < \mathbf{0}, \quad i = 1, \dots, q \quad (69)$$

where $\mathbf{1}$ is an n -dimensional matrix containing only 1, and Eq. 68 remains the same. Essentially, it is also responsible for influencing the positiveness of $\mathbf{P}_{obs}$. However, the main difference compared to α is that it does not add eigenvalues directly to the system $\mathbf{A}$ in the Lyapunov LMIs; rather, this parameter acts as a performance enhancer in its own eigenvector base. Besides, $\beta\mathbf{1}$ can be seen as a matrix that increases the coupling among the states of the system by a factor β . Note that, once the constraint imposed by this LMI is satisfied, stability is assured according to the Lyapunov criterion.

For instance, consider the Lyapunov inequality (Eq. 65) without any additional inputs: $(\mathbf{A} + \alpha\mathbf{I})^T\mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I}) < \mathbf{0}$. It can be shown that multiplying both sides of this equation by the eigenvectors of matrices $\alpha\mathbf{I}$ and $\mathbf{A}$

$$\Phi_A^{-1}\Phi_{\alpha\mathbf{I}}^{-1}[(\mathbf{A} + \alpha\mathbf{I})^T\mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I})]\Phi_{\alpha\mathbf{I}}\Phi_A < \mathbf{0} \quad (70)$$

leads to:

$$(\Lambda_{\mathbf{A}} + \Lambda_{\alpha\mathbf{I}})^T\mathbf{P} + \mathbf{P}(\Lambda_{\mathbf{A}} + \Lambda_{\alpha\mathbf{I}}) < \mathbf{0} \quad (71)$$

Note that the matrices of eigenvalues $\Lambda_{\mathbf{A}}$ and $\Lambda_{\alpha\mathbf{I}}$ are, in fact, superposed. After including β : $(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})^T\mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1}) < \mathbf{0}$. A similar procedure can be applied to find that:

$$(\Lambda_{\mathbf{A}} + \Lambda_{\alpha\mathbf{I}} + \Phi_A^{-1}\beta\mathbf{1}\Phi_A)^T\mathbf{P} + \mathbf{P}(\Lambda_{\mathbf{A}} + \Lambda_{\alpha\mathbf{I}} + \Phi_A^{-1}\beta\mathbf{1}\Phi_A) < \mathbf{0} \quad (72)$$

That is, including β adds $\Lambda_{\mathbf{A}}$ and $\Lambda_{\alpha\mathbf{I}}$ to the projection of $\beta\mathbf{1}$ onto the base of eigenvectors of $\mathbf{A}$. Alternatively, using the base of eigenvectors of $\beta\mathbf{1}$,

$$(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha\mathbf{I}} + \Lambda_{\beta\mathbf{1}})^T\mathbf{P} + \mathbf{P}(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha\mathbf{I}} + \Lambda_{\beta\mathbf{1}}) < \mathbf{0} \quad (73)$$

which can be understood as: since the addition of eigenvalues of $\beta\mathbf{1}$ is not direct (as seen for $\alpha\mathbf{I}$), the addition of $\Lambda_{\alpha\mathbf{I}}$ and $\Lambda_{\beta\mathbf{1}}$ occurs on $\Phi_{\beta\mathbf{1}}$. Mathematically, it means that there is a linear transformation that, albeit abstract, drives the original system into a new convenient noncanonical base, where the speed at which stability is attained is increased.

Further details about this formulation can be found in Final Remarks.

4.4 Applying the observer

This section presents the results obtained for the fuzzy observer when applying the DMVT to Epileptor, based on its state-space representation. It must be stressed that the observer is designed for an identified model capable of representing the dynamics of the system. The process of obtaining this model and its parameters is not discussed in this chapter. According to the DMVT, each of the rows of the dynamic matrix $\mathbf{A}$, combined with the rows from the affine term $\mathbf{b}$, can be modeled as a different entry, as given by Eq. 48, thus representing the variables associated to the model:

$$f(\mathbf{z}) = \left\{ f_1(\mathbf{z}) \quad f_2(\mathbf{z}) \quad f_3(\mathbf{z}) \quad f_4(\mathbf{z}) \quad f_5(\mathbf{z}) \quad f_6(\mathbf{z}) \right\}^T = \left\{ x_1 \quad y_1 \quad z \quad x_2 \quad y_2 \quad u \right\}^T \quad (74)$$

These are, therefore, the entries used for designing the observer. Consider again the equations in state-space representation. Based on Eq. 55, the Jacobian can be defined as:

$$\frac{\partial f(\mathbf{z})}{\partial \mathbf{z}} = \begin{bmatrix} \frac{\partial f_1}{\partial z_1} & \cdots & \frac{\partial f_1}{\partial z_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial z_1} & \cdots & \frac{\partial f_n}{\partial z_n} \end{bmatrix} \quad (75)$$

where $n = 6$. For simplicity, only the following partial derivatives (all non-zero) are presented below:

$$\begin{aligned} \frac{\partial f_1}{\partial z_1} = \frac{\partial f_1}{\partial x_1} &= \begin{cases} -[x_1^2 - 3x_1], & x_1 < 0 \\ -[x_2 - 0.6(z - 4)^2], & x_1 \geq 0 \end{cases} \\ \frac{\partial f_1}{\partial z_3} = \frac{\partial f_1}{\partial z} &= 1.2x_1z - 4.8x_1 - 1 \\ \frac{\partial f_1}{\partial z_2} = \frac{\partial f_1}{\partial y_1} &= 1 & \frac{\partial f_1}{\partial z_4} = \frac{\partial f_1}{\partial x_2} &= -x_1 \\ \frac{\partial f_2}{\partial z_1} = \frac{\partial f_1}{\partial x_1} &= -10x_1/\tau_1 & \frac{\partial f_2}{\partial z_2} = \frac{\partial f_2}{\partial y_1} &= -1/\tau_1 \\ \frac{\partial f_3}{\partial z_1} = \frac{\partial f_3}{\partial x_1} &= 4/\tau_0 & \frac{\partial f_3}{\partial z_2} = \frac{\partial f_3}{\partial y_1} &= -1/\tau_0 \\ \frac{\partial f_4}{\partial z_3} = \frac{\partial f_4}{\partial z} &= -0.3 & \frac{\partial f_4}{\partial z_4} = \frac{\partial f_4}{\partial x_2} &= 1 - 3x_2^2 \\ \frac{\partial f_4}{\partial z_5} = \frac{\partial f_4}{\partial y_2} &= -1 & \frac{\partial f_4}{\partial z_6} = \frac{\partial f_4}{\partial u} &= 2 \\ \frac{\partial f_5}{\partial z_4} = \frac{\partial f_5}{\partial x_2} &= \begin{cases} 0, & x_2 < -0.25 \\ 1/\tau_2, & x_2 \geq -0.25 \end{cases} \\ \frac{\partial f_5}{\partial z_5} = \frac{\partial f_5}{\partial y_2} &= -1/\tau_2 \end{aligned} \quad (76)$$

There are, thus, 6 nonconstant values inside the Jacobian. According to Eq. 62, then, $q = 2^{(\sqrt{6})^2}$, which leads to 64 linear sub-models:

$$(\mathbf{A}_i^* + \alpha \mathbf{I} + \beta \mathbf{1})^{*T} \mathbf{P}_{obs} + (\mathbf{A}_i^* + \alpha \mathbf{I} + \beta \mathbf{1}) \mathbf{P}_{obs} - \mathbf{M}\mathbf{C} - \mathbf{C}^T \mathbf{M}^T < \mathbf{0}, \quad i = 1, \dots, 64 \quad (77)$$

$$\begin{bmatrix} -r \mathbf{P}_{obs} & \mathbf{P}_{obs} \mathbf{A}_i^* - \mathbf{M}\mathbf{C} \\ \mathbf{A}_i^{*T} \mathbf{P}_{obs} - \mathbf{C}^T \mathbf{M}^T & -r \mathbf{P}_{obs} \end{bmatrix} < \mathbf{0}, \quad i = 1, \dots, 64 \quad (78)$$

where the linear sub-systems are, in turn, given by:

$$\begin{aligned} \mathbf{A}_1 &= \mathbf{A}(\tilde{a}_{112}, \tilde{a}_{132}, \tilde{a}_{142}, \tilde{a}_{212}, \tilde{a}_{442}, \tilde{a}_{542}) \\ \mathbf{A}_2 &= \mathbf{A}(\tilde{a}_{112}, \tilde{a}_{132}, \tilde{a}_{142}, \tilde{a}_{212}, \tilde{a}_{442}, \tilde{a}_{541}) \\ \mathbf{A}_3 &= \mathbf{A}(\tilde{a}_{112}, \tilde{a}_{132}, \tilde{a}_{142}, \tilde{a}_{212}, \tilde{a}_{441}, \tilde{a}_{542}) \\ &\vdots \\ \mathbf{A}_{62} &= \mathbf{A}(\tilde{a}_{111}, \tilde{a}_{131}, \tilde{a}_{141}, \tilde{a}_{212}, \tilde{a}_{441}, \tilde{a}_{541}) \\ \mathbf{A}_{63} &= \mathbf{A}(\tilde{a}_{111}, \tilde{a}_{131}, \tilde{a}_{141}, \tilde{a}_{212}, \tilde{a}_{441}, \tilde{a}_{541}) \\ \mathbf{A}_{64} &= \mathbf{A}(\tilde{a}_{111}, \tilde{a}_{131}, \tilde{a}_{141}, \tilde{a}_{211}, \tilde{a}_{441}, \tilde{a}_{541}) \end{aligned} \quad (79)$$

For the sake of understanding, $\tilde{a}_{112}$ indicates, for example, the maximum value of $\frac{\partial f_1}{\partial z_1}$, whereas $\tilde{a}_{111}$ indicates its minimum value. Each matrix $\mathbf{A}$ is composed, thus, of all constant partial derivatives plus each combination of maximum and minimum values for the six nonconstant ones.

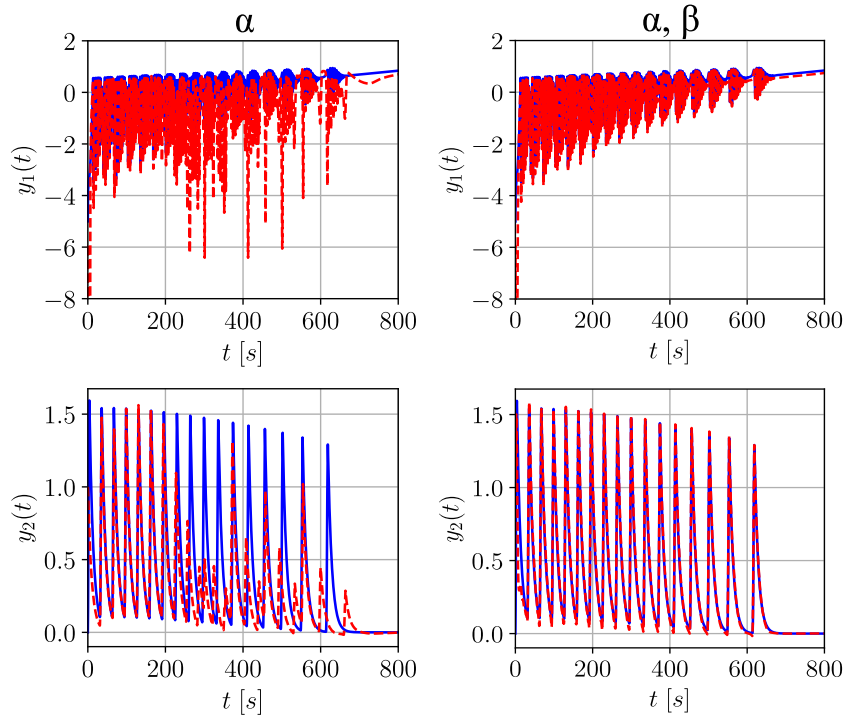
4.4.1 Observer for an on-going seizure

This section presents the results obtained for the fuzzy observer applied to Epileptor when the initial conditions are set to an on-going seizure, which implies that the convergence occurs during epileptiform activity. All of the computational codes were implemented in Python 3.7, which is free and open source, on the Spyder environment. Epileptor's responses in the time domain were obtained using a Fourth-Order Runge-Kutta numerical integrator with a time step of $dt = 0.01$. The gains of the observer, in turn, were computed using again PICOS (Sagnol; Stahlberg, 2012), combined with CVXOPT.

Figure 23 shows the results obtained for the fuzzy Takagi-Sugeno observer considering the following parameters: $\alpha = 1.10^{-6}$, $\beta = 0$, $r = 2$ (left column) and $\alpha = 1.10^{-6}$, $\beta = 0.2$, $r = 2$ (right column). For simplicity, only two of the variables considered unmeasurable were plotted; further results for all of them can be found in Final Remarks. The initial conditions for the simulation are the same as the ones originally defined for Epileptor (Jirsa et al., 2014), that is, they refer to an on-going seizure state. Also, the time window

was set to last until approximately the seizure offset. Note that, although there is a certain oscillating behavior after adding β (especially for variables $z(t)$ and $u(t)$ – Final Remarks), the convergence speed is increased, which is reflected on all the variables, leading to a better synchronization of both fast oscillations and spike events.

Figure 23 – **Performance of the fuzzy observer for an on-going seizure.** The observer is activated during the ictal event of the Epileptor model considering the addition α or α and β together, a combination que provides a smoother reconstruction. The solid blue line (—) indicates the actual states (initial conditions: $x_1(0) = 0$, $y_1(0) = -5$, $z(0) = 3$, $x_2(0) = 0$, $y_2(0) = 0$, $u(0) = 0$) and the red dashed line (- -) indicates the estimated states (initial conditions: $\hat{x}_1(0) = x_1(0) - 1$, $\hat{y}_1(0) = y_1(0) - 1$, $\hat{z}(0) = z(0) - 0.2$, $\hat{x}_2(0) = x_2(0) - 1$, $\hat{y}_2(0) = y_2(0) + 1$, $\hat{u}(0) = u(0) - 0.1$).



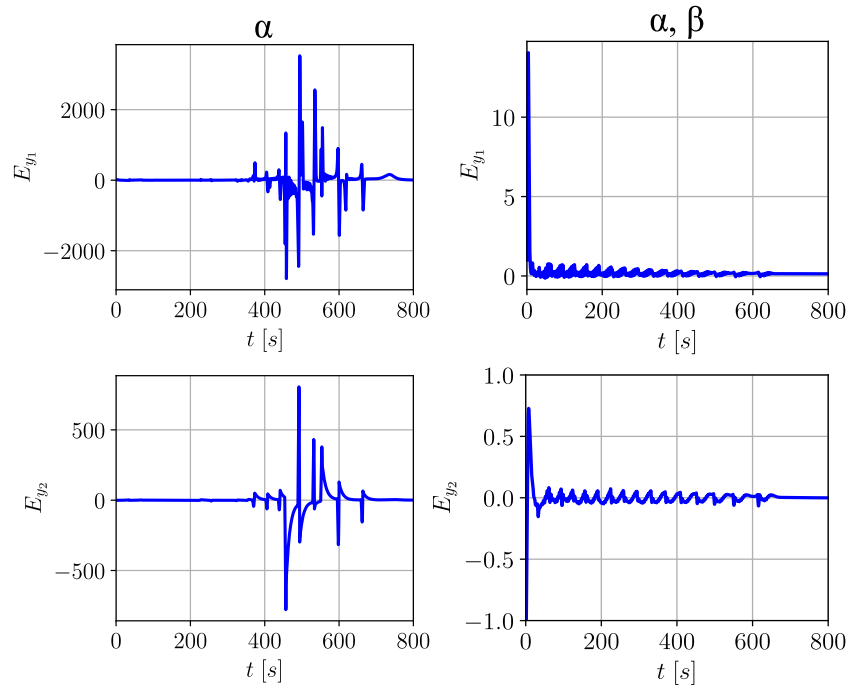
Source: Own authorship.

Figure 24 presents the error dynamics for both cases considering the same variables (more details can be found in Final Remarks). Without β , such a dynamics tends to become unstable and not follow a smooth behavior towards zero. This is due to the discontinuity observed in Fig. 23 for $y_1(t)$ and $y_2(t)$, for example, which is reflected on the magnitude of the error, assuming a considerably higher value compared to the curves including β . Furthermore, since Epileptor's subsystems are coupled, the discontinuities are passed on to the other variables ($z(t)$ and $u(t)$), but at lower amplitudes. In practice, this is not desired since it can severely compromise the observer's performance and lead to inconsistencies during the measurements. On the other hand, this effect is reduced after including β , since no discontinuities are visually recognizable: notice that the same

oscillating behavior is still present in the curves (as in Fig. 23), but the convergence is sped up while keeping a smoother behavior towards zero.

Figure 24 – **Error dynamics for the fuzzy observer considering an-ongoing seizure.**

Adding the parameter β along with α leads to a smoother performance when reconstructing the states during the ictal event of the Epileptor model, endorsing its efficiency in the application of the observer. The results without including the parameter β are in the left column and the ones after including it are in the right column.



Source: Own authorship.

A specific case to be considered is if only α is increased while setting $\beta = 0$, to verify whether α alone can attain the same quality of convergence. Nevertheless, it must be stressed that, after carrying out several simulations, depending on the values set for α , the gains for the observer may be too high for Epileptor, leading to numerical errors. Moreover, even when α is considerably higher (that is, regardless of its value), the addition of β enhances the results. An additional proof for this statement can be found in Final Remarks. Therefore, β is a good option when designing the observer², and combining it with α is essential to obtaining the best possible results.

The main advantage of this type of observer is that no previous recording of brain electrical activity is necessary. That is, in practical/clinical applications, as soon as a seizure arises, the observer is activated to measure such activity, which implies in fewer data points, thus considerably reducing the computational cost in terms of storage. This

²As seen in Final Remarks, this also holds for controllers.

strategy is particularly suitable if controllers are envisioned for seizure suppression: once the states are accurately measured and estimated during the beginning of a seizure (even if no previous information is available), control inputs may be sent to the epileptogenic locus via electrical stimuli, thus mitigating the effects of a seizure. Therefore, designing an observer for on-going seizures is useful for clinical applications, especially for seizure suppression purposes. A disadvantage, however, is that, as discussed in the next section, if no baseline behavior is recorded, relevant information related to the brain dynamics is missing.

It is well known in the literature that the use of nonlinear dynamics tools, especially limit cycles, attractors and bifurcations, is of great importance for understanding spiking formation and its triggering factors (Hindmarsh; Rose; Huxley, 1984; Morris; Lecar, 1981; Izhikevich, 2000). Besides, particularly for Epileptor, bifurcation analyses have verified the coexistence of different pathological behaviors and brain states (Houssaini et al., 2015). Such findings often make use of phase portraits, which essentially are helpful graphical tools that help better understand motion patterns and stability of dynamical systems without solving their nonlinear equations analytically (Slotine; Li et al., 1991). When the system is two-dimensional, the phase portrait is well defined, as discussed by (Slotine; Li et al., 1991). However, higher dimensional representations can also be obtained using, for example, the concept of phase space reconstruction by time delays (Hajiloo; Salarieh; Alasty, 2018). At last, combinations of these representations and control variables (Slotine; Li et al., 1991), which may lead to abrupt transitions as the case of Epileptor (Jirsa et al., 2014), generate the so-called bursters (Izhikevich, 2000), equally important structures.

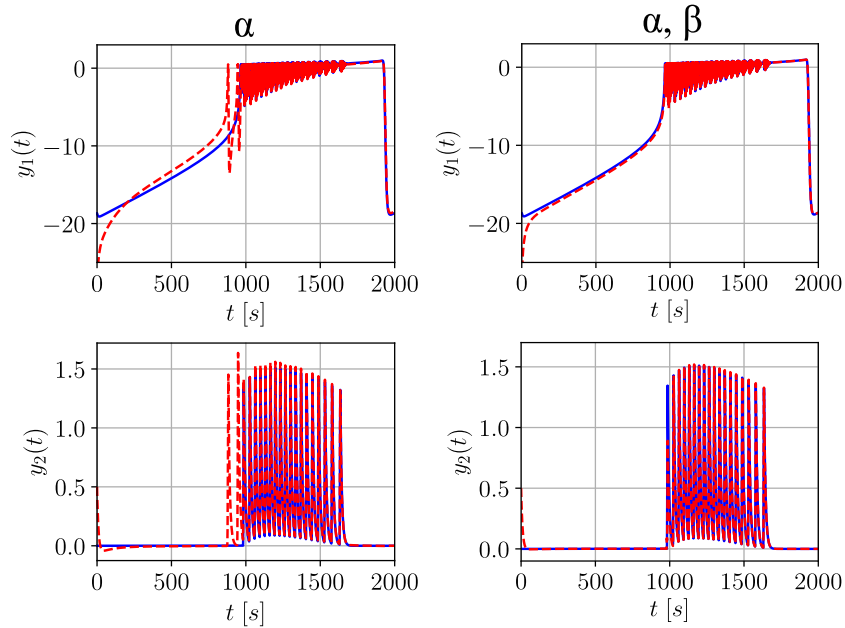
Thus, estimating and reconstructing phase spaces is key to accessing nonmeasurable (and usually abstract) activity, which nonetheless is useful to understand the complexity of brain behavior. Although on-going seizure signals represent well the main attractors of Epileptor (Jirsa et al., 2014), including baseline states provides a more comprehensive analysis, especially in terms of interictal and pre-ictal states, which are fundamental for seizure prediction and diagnosis (Faust et al., 2015; Li et al., 2018a; Sharma et al., 2014; Yuan et al., 2018; Acharya et al., 2018; Ansari et al., 2019). The next section presents, thereby, a variation of the fuzzy observer to account for baseline and pre-ictal states, as well as how Epileptor's bursters can be obtained from them.

4.4.2 Observer for the transition between non-seizure and seizure

Figure 25 presents the performance of the fuzzy observer considering the following parameters: $\alpha = 2 \cdot 10^{-6}$, $\beta = 0$, $r = 0.5$ (left column) and $\alpha = 2 \cdot 10^{-6}$, $\beta = 0.03$, $r = 0.5$ (right column). Only two of the unmeasurable variables were plotted; further results for

this condition can be found in Final Remarks. Note that, since the baseline does not include any oscillating or spiking behavior, lower values for some parameters are needed to attain a good convergence. Once again, the results after adding β are better compared to the ones without it, as seen in the previous section: the transition to the seizure is brought forward when $\beta = 0$, which significantly compromises the fitting between the spikes and fast oscillations, whereas the inclusion of $\beta \neq 0$ implies in a smoother and more adherent behavior.

Figure 25 – **Performance of the fuzzy observer for the transition between interictal and ictal states.** The observer is activated during the transition between interictal and ictal events of the Epileptor model considering the addition α or α and β together, a combination que provides a smoother reconstruction. The blue solid line (—) indicates the actual states (initial conditions: $x_1(0) = -1.98$, $y_1(0) = -18.66$, $z(0) = 4.15$, $x_2(0) = -0.88$, $y_2(0) = 0$, $u(0) = -0.035$) and the red dashed line (- -) indicates the estimated states (initial conditions: $\hat{x}_1(0) = x_1(0) - 2$, $\hat{y}_1(0) = y_1(0) - 8$, $\hat{z}(0) = z(0) - 0.2$, $\hat{x}_2(0) = x_2(0) - 2$, $\hat{y}_2(0) = y_2(0) + 0.5$, $\hat{u}(0) = u(0) - 0.4$).



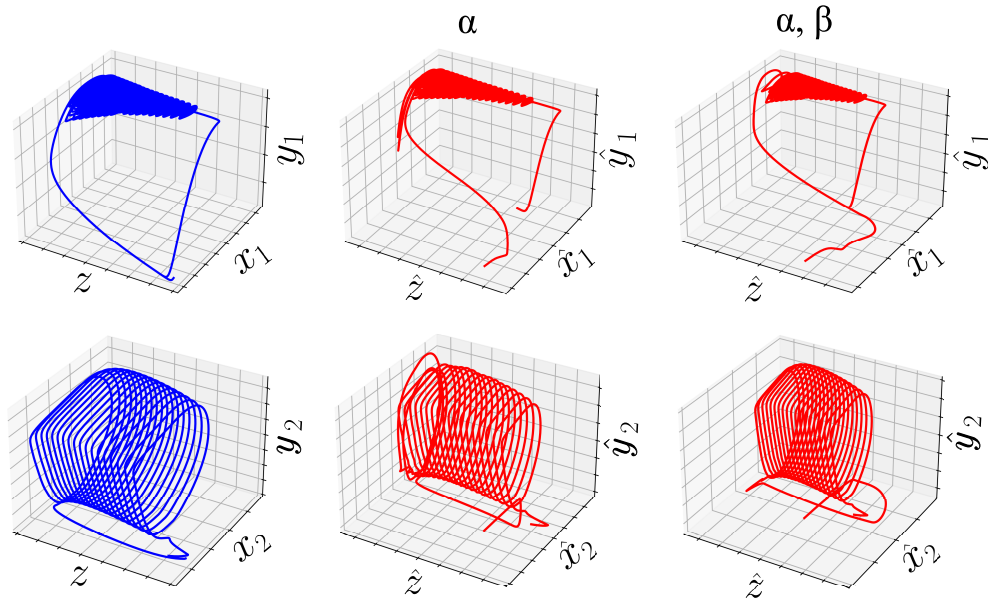
Source: Own authorship.

The main disadvantage of this type of observer is, as discussed previously, the need for constant monitoring of brain activity, which considerably increases the burden of computational storage. One of its advantages is, in turn, that it takes both conditions into account, healthy and epileptiform, thus accounting for the full bi-stable behavior that is inherently designed for Epileptor (Jirsa et al., 2014)³. To illustrate such bi-stable

³As seen in the same reference (Jirsa et al., 2014), this bi-stable behavior characterizes two bursters for Epileptor, one for the first subsystem, composed of fast oscillations, and the other one for the second subsystem, composed of spike and wave events.

characteristic and how the observer is able to recreate it, Fig. 26 is presented. Three situations are considered: *i*) Epileptor implemented without the fuzzy observer; *ii*) its implementation with the decay rate α , but $\beta = 0$; and *iii*) with both α and β . Note that, when β is added, the burster is as well defined as the original Epileptor behavior, clearly unveiling the cyclic behavior, whereas this trait is not as recognizable for when only α is taken into account.

Figure 26 – **Comparison between the bursters defined for the original Epileptor and the estimated ones using $\beta = 0$ and $\beta \neq 0$.** The bursters are composed of each subsystem of the Epileptor model, plotted using estimated variables with the application of the observer using α or α and β together, a combination that provides a smoother reconstruction, especially at the bifurcations, thus endorsing β as a performance-enhancing parameter. The burster obtained by simulating an Epileptor is in the first column, to the left; the reconstructed one using $\beta = 0$ is in the middle column; the reconstructed one using $\beta \neq 0$ is the last column, to the right.



Source: Own authorship.

Another advantage for this approach is that, once both behaviors are captured by the observer, interictal and pre-ictal states, which generally play an important role for understanding and predicting seizures, are identified as well. Nowadays, there exist several techniques involving machine learning algorithms applied to electroencephalogram signals (EEGs) which are able to detect seizures before they happen (that is, pre-ictal states) (Faust et al., 2015; Li et al., 2018a; Sharma et al., 2014; Yuan et al., 2018; Acharya et al., 2018; Ansari et al., 2019). Therefore, online integration between patients and fuzzy observers are of great interest in the fields of computational neuroscience, for understanding the complex dynamics of seizures and their bursters/attractors, or in clinical applications

involving seizure detection and suppression.

4.5 Contributions, limitations and conclusions

Considering the results and discussion addressed in this chapter, the main contributions are:

- considering the concept of DMVT, a fuzzy observer can be efficiently designed and, once it is applied, Epileptor's unmeasurable variables can be estimated based only on the measurable ones. Such variables yield relevant information related to the complex activity of the brain and, by design or due to their inherent uncertainty in terms of physical meaning, cannot be directly measured;
- this enables accessing the underlying information that occurs in neural systems (in this specific case, electrical activity that accounts for local field potentials). By doing so, two possible scenarios are envisioned in practice: clinical/therapeutic applications, where the fuzzy observers can be integrated with controllers, for seizure mitigation during on-going epileptiform activity; neuroscientific applications, where the study of the complex brain activities can be better understood by estimating and reconstructing the bursters that are associated to them;
- two variations of the fuzzy observer can be designed: *i*) for on-going seizures and *ii*) considering the transition between interictal and ictal states. For the first one, the observer is only switched on as soon as the epileptiform activity arises, which is advantageous especially because of the reduced burden in terms of computational storage, since no previous recording of brain activity is required. For the second one, in turn, although it might demand more computational cost, both healthy and epileptiform activities are taken into account, which is useful to possibly record and predict pre-ictal activities;
- the proposal of enhancement based on β is also introduced as an alternative for designing controllers or observers using Lyapunov theory. It significantly improves the response of the observer in terms of speed of convergence and smoothness, outperforming the traditional tools available nowadays.

However, for the proposed approach to work, some of hypotheses assumed in Subsection 3.3 still hold, that is: a set of parameters that define Epileptor's behavior must be known beforehand; only electrophysiological signatures that are accurately represented or approximated by the model can be considered candidates.

As a consequence of the contributions achieved so far, the integration of fuzzy observers and fuzzy controllers can be an interesting option to simultaneously estimate and reconstruct the unmeasurable variables of the model while using this full information to compute gains for the controllers to emit signals to suppress epileptic seizures online. Of course, to do so, the parameters of the Epileptor model must be known, which is hypothesized as true in this chapter, although this is not the case in practice. However, there are techniques in the literature that deal with this specific problem, that is, system identification or parameter estimation strategies that, once applied, result in the estimation of such parameters (Nowak, 2002; Noël; Kerschen, 2017). The complete integration between parameter estimation, observers and controllers is discussed in the next chapter.

5 ESTIMATING THE PARAMETERS OF THE EPILEPTOR MODEL

The approaches developed for designing the controller and the state observer are powerful tools that may lead to promising investigations on the use of active control techniques for epileptic seizure suppression. However, for practical applications, it is necessary to obtain a patient-specific or/and condition-specific Epileptor model, which represents each individual for whom an active controller is designed. To do so, a specific set of parameters must be found such that Epileptor's dynamics can be defined and represent features of realistic seizures¹. A recent work in the literature (Hashemi et al., 2020) partially addresses this problem by using Bayesian inference to estimate the epileptogenicity parameter (x_0 , which represents the degree of excitability of the system). The authors consider a reduced-order Epileptor, leading to a set of 2 equations (x_1 , the LFP for the first subsystem, and z , the control variable) and 3 parameters (I_{rest1} , τ_0 and x_0). In this chapter, a more comprehensive approach is proposed for estimating all of the 8 parameters in the full-order Epileptor, which can nonetheless be applied to the reduced-order one. Besides, this strategy is consistent with all the previous chapters involving state-feedback control/state observers, which are designed considering all of these parameters.

It is worth mentioning that there is a wide range of seizures with different dynamics. In fact, their categorization has been of particular interest in the fields of neuroscience, and there are articles in the literature which propose a taxonomy of seizures based on their types of bifurcations (Jirsa et al., 2014) or the so-called dynamotypes (Saggio et al., 2020). The latter one even discusses on how such dynamotypes evolve during patients' lifetime, display complex variations, as well as how often they may occur (individually or together). Furthermore, as mentioned above, variations of Epileptor exist today, such as the reduced-order model (Proix et al., 2017; Hashemi et al., 2020), or a model considering longer interictal periods (Proix et al., 2014). This chapter focuses on obtaining the set of parameters that was originally defined for Epileptor (Jirsa et al., 2014). Nevertheless, as long as any of these systems of equations can be converted into state-space notation, the proposed approach can be applied.

The approach chosen for this article is based on the Nelder-Mead (NM) optimiza-

¹In the context of system identification, this process is known as parameter estimation, which implies finding the parameters of a model that best describe the existing data (Ljung, 1998; Bos, 2007). In practical applications, this would consist of defining an Epileptor model whose parameters are estimated for a single patient or different Epileptors for the same patient, but adapting to each seizure. Once they are available, a controller can be designed based on such models with specific parameters.

tion algorithm, introduced by Nelder and Mead (1965). The application of heuristic algorithms, such as the NM or the Particle Swarm Optimization (PSO) (Poli; Kennedy; Blackwell, 2007), for example, have been widely used in the fields of engineering for purposes of parameter estimation (Neto et al., 2013; Hardt; Schraknepper; Bergs, 2021; Altan, 2020; Altan; Parlak, 2020). Besides, their use in biomedical engineering, especially in the context of epilepsy, is relatively common, involving, for instance, epileptic seizure prediction (Dollfuß et al., 2013; Kim et al., 2014; Hamad et al., 2018; Subasi; Kevric; Canbaz, 2019) or classification (Abuhasel; Ilyasu; Fatichah, 2015; Li et al., 2018b), based on the use of one of the algorithms alone or hybrid approaches. In fact, the NM algorithm has been even employed in an optimization problem concerning seizure propagation speed in the Epileptor model (Proix et al., 2018). However, applications for determining Epileptor's parameters in the time domain, mainly for seizure mitigation purposes, still lack in the literature.

In this chapter, the NM algorithm is not directly and simply applied; an efficient strategy to obtaining the state-space representation of the Epileptor model for an individual undergoing an epileptic seizure is introduced. The main idea is to measure the LFP during the epileptic seizure and use it as input to the algorithm. The strategy involves a pseudo-random matrix and a normalization criterion to apply the algorithm successively until the best set of parameters is attained to describe the input LFP through the Epileptor model.

Furthermore, since there is an inter-dependency between controller, observer, and parameter estimation, the latter one plays a crucial role when conceiving possible therapeutic strategies based on feedback control. In practice, once the parameters of the Epileptor model are properly identified, the gains of the controller and state observer can be accurately computed, as introduced in the previous chapters. Therefore, this chapter presents how an integration process between these three stages can be carried out as well.

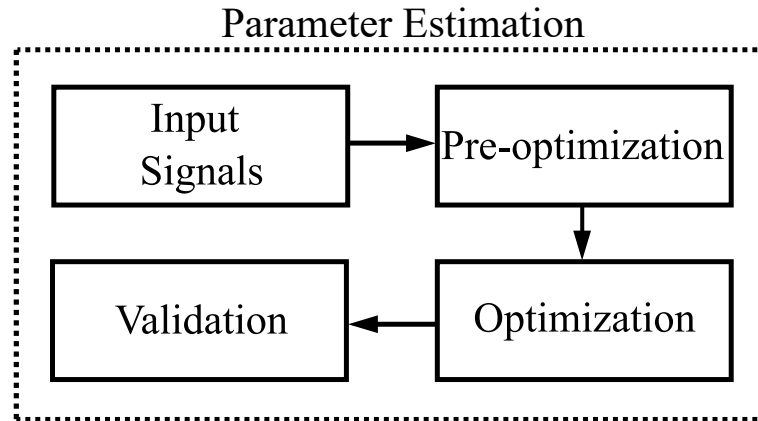
At last, although the Nelder-Mead algorithm involves a heuristic approach, which may lead to local minima or maxima², this problem is also addressed in this work by using a successive optimization approach in the time domain, combined with a statistical analysis and median values to assure that the estimated parameters converge towards the reference ones. Therefore, it is regarded herein as a simpler, more straightforward, and only output-dependent approach, among other advantages, as discussed in the next sections. For these specific reasons, it represents an attractive option with a strong practical appeal. The codes used in this chapter are available online on the platform GitHub at the following address: <https://github.com/GMSINT/Epilepsy-Dynamics-Control>.

²An interesting investigation on this topic is provided by Luersen and Le Riche (2004).

5.1 Parameter estimation: overview

The strategy proposed in this chapter consists of a process with four main stages: *i*) obtaining the input signals (i.e., the LFP), *ii*) pre-optimization, defining initial guesses for the parameters, *iii*) optimization for parameter estimation (modeled as a minimization problem), and *iv*) validation. The third stage characterizes the optimization itself, during which the unknown parameters of the model are estimated via an objective function based on the LFP. As for the last stage, a validation process is carried out considering several successive optimizations along the LFPs over time, whose median values tend to converge towards the target ones. Figure 27 depicts an illustration of the aforementioned parameter estimation process.

Figure 27 – **Flowchart for the proposed parameter estimation process.** It comprises four main stages: obtaining the input signals as references, pre-optimization used to define the initial guesses of the parameters, the optimization itself, and validation.



Source: Own authorship.

Note that for practical applications of epileptic seizure suppression, the identified state-space model is used for designing the controller and state observer, as introduced in the previous chapters. Moreover, the first stage, consisting of obtaining input signals, has already been previously presented and represents the LFPs in the time domain. It is thus not covered in the next subsections.

5.1.1 Pre-optimization

Based on the Epileptor model, the parameters considered correspond to every entity that likely has a biophysical meaning and is not a variable or a purely mathematical constant (e.g. c from Eq. 18), or influences significantly its behavior. Therefore, from the point of view of the system's dynamics, it is necessary to define 6 initial conditions

(for the 6 variables considered in state-space representation) and 8 parameters which, if changed, also change Epileptor's behavior. By doing so, the set of 8 parameters that characterize a local field potential can be expressed as $\mathbf{S}$:

$$\mathbf{S} = \{\tau_0, \tau_1, \tau_2, \gamma, x_0, y_0, I_{rest1}, I_{rest2}\}^T \quad (80)$$

or, using an equivalent notation, for simplicity, $\mathbf{S} = \{s^{(1)}, \dots, s^{(8)}\}^T$, where $s^{(1)} \equiv \tau_0$ and so forth until $s^{(8)} \equiv I_{rest2}$. Note that all of them must be known before using the Epileptor model. In practice, this means the set is patient-specific; that is, each individual presents their unique seizure signature, which, in turn, implies that estimating these parameters leads to the full description of their epileptiform activity, for a given time window recorded over time. Therefore, the pre-optimization stage concerns the definition of initial guesses for each of them. In this case, the set of parameters over the n optimizations can be described by

$$\mathbf{S}_n = (\mathbf{I} + \delta \mathbf{D}_n) \mathbf{S}^{\text{ref}} \quad (81)$$

where $\mathbf{I}$ 8×8 is an identity matrix, δ is an uncertainty factor, $\mathbf{D}_n$ is the disturbance matrix, which changes for each n -th iteration. Vector $\mathbf{S}^{\text{ref}}$ contains reference values, which in practice is unknown, but for the proposed approach it is taken as the target or desired parameters, to simulate a real scenario. At last, $\mathbf{S}_n$ is the input matrix for the n -th iteration. Note that, if no iterations are carried out, $n = 0$, and $\mathbf{S}_0 \equiv (\mathbf{I} + \delta \mathbf{D}_0) \mathbf{S}^{\text{ref}}$; therefore, the estimated vector is $\mathbf{S} \equiv \mathbf{S}_0$, and the disturbance $(\mathbf{I} + \delta \mathbf{D}_0) \neq \mathbf{0}$ is the highest possible. On the other hand, as the iterations proceed, $n \rightarrow N$, where N is the defined maximum number of iterations, the estimated vector is $\mathbf{S}_n \rightarrow \mathbf{S}^{\text{ref}}$. That is, $\mathbf{S} \equiv \mathbf{S}_{n=N}$ is sufficiently close to the reference $\mathbf{S}^{\text{ref}}$, and $\delta \mathbf{D}_N \cong \mathbf{0}$.

The reference vector $\mathbf{S}^{\text{ref}}$ can be arbitrarily defined. However, it is recommended to use values typically employed to describe representative epileptic seizures to improve the feasibility of the optimization process. In this sense, without loss of generality, the values used by Jirsa et al. (2014) are considered. The robust identification is achieved by conveniently computing the disturbance matrix $\mathbf{D}_n$ of each n -th iteration by the following equation

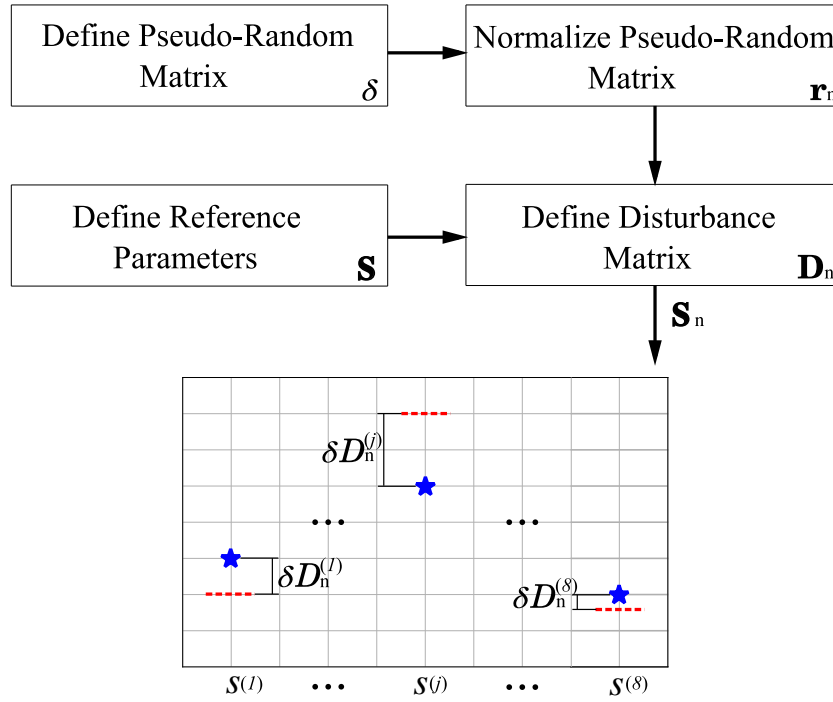
$$\mathbf{D}_n = \frac{\text{diag}(\boldsymbol{\varphi}_n)}{\max(|\boldsymbol{\varphi}_n|)} \quad (82)$$

where $\text{diag}(\boldsymbol{\varphi}_n)$ is a pseudorandomly-generated vector $\boldsymbol{\varphi}_n = \{r_1 \ r_2 \ r_3 \ r_4 \ r_5 \ r_6 \ r_7 \ r_8\}^T$ for the n -th iteration and $\max(|\boldsymbol{\varphi}_n|)$ is the highest value in $|\boldsymbol{\varphi}_n|^3$. The highest element r_j is obtained in a different position into the diagonal of the matrix $\mathbf{D}_n$. The disturbance factor

³Pseudorandom values can be obtained by drawing samples from a typical Gaussian distribution commonly used in signal processing applications as additive noise (Liu; Lin, 2013). In Python, this is done with the built-in function *random.normal* from the NumPy library.

δ is previously defined considering $\delta > 0$, such that $\delta = 1$ is the maximum percentage of variation admitted to the parameter in $\mathbf{S}_n$ in relation to the reference value in $\mathbf{S}^{\text{ref}}$. For example, if $\delta = 0.25$, $\delta\mathbf{D}_n$ includes 25% of variation in p_j (i.e., the j -th element into $\mathbf{S}_n$) in relation to its reference value defined in $\mathbf{S}^{\text{ref}}$. Figure 28 shows a schematic illustration of this approach, in which $D^{(j)}$ is the j -th element from the diagonal of $\mathbf{D}_n$. Note that $D^{(i)} < D^{(j)} \forall i \neq j$.

Figure 28 – **Visual illustration of the non-null values in $\delta\mathbf{D}_n$.** Initially, the uncertainty factor for the optimization is defined as δ , along with the pseudo-random matrix $\mathbf{r}_n$; then, this matrix is normalized by its maximum value, thus leading to the disturbance $\mathbf{D}_n$; at last, the initial guesses $\mathbf{S}_n$ are formed by the disturbance term and the previously defined reference values $\mathbf{S}$. Red dashed lines represent the reference values and $\star$ represents each value of s_j for the n -th iteration. The superscript j from each $\mathbf{D}_n$ indicates its j -th element, whereas n indicates the number of the iteration process during optimization. The same holds for $\mathbf{S}_n$. Source: Own authorship.



Source: Own authorship.

The process of estimating the actual parameters is also subjected to disturbances related to the presence of noise in experimental signals, which is usually associated to the output variables, i.e., the physical quantities that are measured in the time domain ($\mathbf{y}(t)$). Thus, along with the uncertainty factor, the influence of noise addition is also considered in this chapter as:

$$S_{dB}^{\text{noise}} = SNR_{dB} - S_{dB}^{\text{signal}} \quad (83)$$

where S_{dB}^{noise} stands for the power of the noise present in the output, $S_{dB}^{\text{signal}} \equiv LFP_{dB}^{\text{ref}}$ is the power associated to the measurable reference LFP, and SNR_{dB} is a pre-defined signal-to-noise ratio, given in decibels (dB). By applying the appropriate logarithm-linear conversion, the noise-corrupted output can be modeled in the time domain as:

$$LFP_{\text{noisy}}^{\text{ref}} = LFP^{\text{ref}} + \mathcal{N}(t) \quad (84)$$

where $\mathcal{N}(t) \sim (0, \sqrt{S^{\text{noise}}})$ is an artificially generated and normally distributed pseudorandom variable, known as additive white Gaussian noise (AWGN) (Liu; Lin, 2013), given in the same unities as the LFP.

5.1.2 Optimization

The optimization process is employed to get $\mathbf{S}_n \rightarrow \mathbf{S}$ from $\mathbf{S}^{\text{ref}}$. Each n -th iteration is evaluated by computing the function $f(W, w_n)$, where $W \equiv LFP^{\text{ref}}$, i.e., the target LFP. Similarly, w_n is the LFP obtained by integrating the Epileptor model in the time domain considering the parameters in $\mathbf{S}_n$, i.e., the n -th set of parameters. The function $f(W, w_n)$ is defined by

$$f(W, w_n) = \frac{1}{\nu} \left[\frac{1}{K} \sum_{k=1}^K (W(k) - w_n(k))^2 \right]^{1/2} \quad (85)$$

where $W(k)$ and $w_n(k)$ correspond respectively to the k -th value of W and w_n , $k = 1, \dots, K$, i.e., their discrete representation for computational purposes is considered, $\nu = |W^{\text{max}} - W^{\text{min}}|$ is a normalization factor and K is the number of time instants considered. Note that the target LFP is the reference local field potential to be described using the identified Epileptor model. In practical applications, it is a recording of epileptiform activity, whose parameters are unknown. The optimization procedure is defined as a minimization problem, as follows:

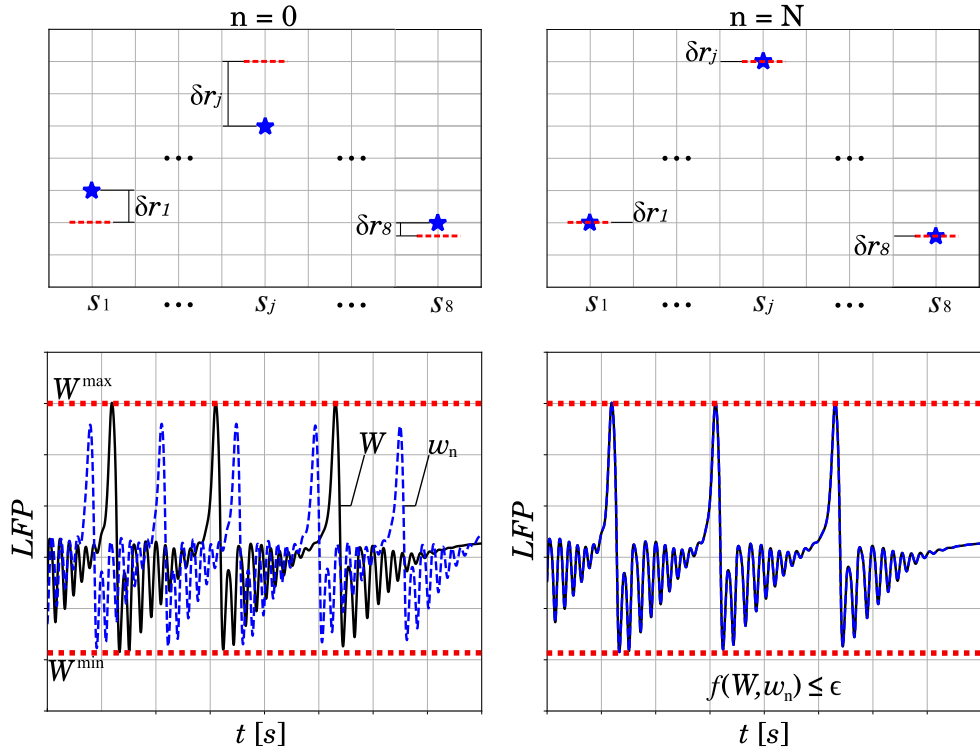
$$\min_{\mathbf{S}_n} [f(W, w_n)] \quad (86)$$

The strategy established in the optimization procedure is as follows: for each n -th iteration, a set of parameters $\mathbf{S}_n$ is evaluated; a computational simulation for the Epileptor model is then run for such a set; in case $f(W, w_n) = 0$, then $w_n \equiv W$, and the iteration process is stopped. Typically $f(W, w_n) = 0$ is not achieved, and the tolerance value ϵ and the maximum number of iterations N are predefined. Then, the following criterion is assessed: $f(W, w_n) \leq \epsilon$, which limits the number of iterations, as is the case in practice⁴.

⁴As stated by Luersen and Le Riche (2004), the number of analyses (in this case, optimizations) in real situations is usually restricted. Naturally, this fact is taken into account in this chapter by using a limited number of iterations and threshold, since computational applications are sometimes time-consuming and

Figure 29 shows an illustration of this iteration process.

Figure 29 – **Visual illustration of the iteration process for a time window of an LFP.** Initially, at $n = 0$, both target W and optimized w_n LFPs present different parameters, whose variation is defined by the uncertainty factor δ ; as the iterations proceed, this difference is minimized until a maximum number of iterations N or tolerance ϵ is achieved. The estimated parameters $\star$ tend to converge towards the desired references as the optimization proceeds, so that w_n matches W . Source: Own authorship.



Source: Own authorship.

The Nelder-Mead algorithm was chosen because it provides a good convergence speed (Neto et al., 2013), it is easily addressable, its implementation is relatively simple, and presents a low computational complexity (Neto et al., 2013), which makes it an interesting option, for which several successive optimizations are performed, as shown in next section. It has been used for different applications, such as the tuning of Kalman filters (Powell, 2002), or model parameters estimation (Neto et al., 2013; Hardt; Schraknepper; Bergs, 2021), for example. This algorithm was first established in 1965 (Nelder; Mead, 1965) and it is also known as Downhill Simplex Method (Neto et al., 2013). It is based on a heuristic approach, which may lead to local minima or maxima; however, this problem is addressed herein by adopting successive optimizations over time, as presented in the next subsection. Another important advantage is that it can be applied directly to Epileptor's

require a high processing. However, as seen in the next sections, the proposed approach provides a good strategy for estimating the parameters of the system with a strong practical appeal.

output, in the time domain, which thus requires no previous stages of signal processing or manipulation.

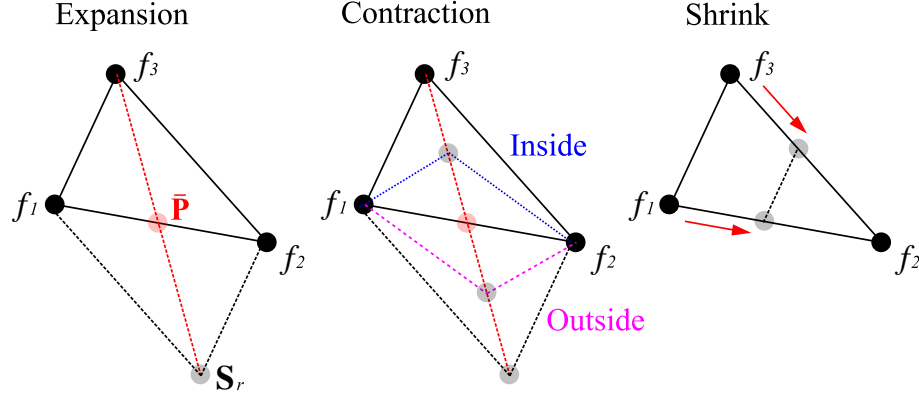
Consider that there are S parameters to be estimated; then, as seen in (Gao; Han, 2012), the Nelder-Mead algorithm involves a simplex of $S + 1$ points (or vertices) that attempts to find the best solution in the parameter space based on the objective function. Essentially, this is attained by five main operations: 1) sort, 2) reflection, 3) expansion, 4) contraction and 5) shrink, each of which is briefly explained below⁵.

1. **Sort:** the objective function $f(.) = f(W, w_n)$ is evaluated at each of the $S + 1$ vertices based on the initial guesses given in the pre-optimization stage, and these values are sorted in ascending order such that: $f_1 < f_2 < \dots < f_{S+1}$;
2. **Reflection:** calculate the vector of parameters $\mathbf{S}_r = \bar{\mathbf{S}} + \kappa_{ref}(\bar{\mathbf{S}} - \mathbf{S}_{S+1})$, where $\kappa_{ref} > 0$ is the reflection factor and $\bar{\mathbf{S}}$ is the centroid of the S best vertices. If $f(\mathbf{S}_1) \leq f(\mathbf{S}_r) < f(\mathbf{S}_S)$, replace $\mathbf{S}_{S+1}$ with $\mathbf{S}_r$;
3. **Expansion:** if $f(\mathbf{S}_r) < f(\mathbf{S}_1)$, then try $\mathbf{S}_e = \bar{\mathbf{S}} + \kappa_{exp}(\mathbf{S}_r - \bar{\mathbf{S}})$, where $\kappa_{exp} > 1$ is the expansion factor. If $f(\mathbf{S}_e) < f(\mathbf{S}_r)$, replace $\mathbf{S}_{S+1}$ with $\mathbf{S}_e$; otherwise, replace $\mathbf{S}_{S+1}$ with $\mathbf{S}_r$;
4. **Contraction:**
 - (a) Outside: if $f(\mathbf{S}_S) \leq f(\mathbf{S}_r) < f(\mathbf{S}_{S+1})$, calculate $\mathbf{S}_o = \bar{\mathbf{S}} + \kappa_{ctr}(\mathbf{S}_r - \bar{\mathbf{S}})$, where $\kappa_{ctr} < 1$. If $f(\mathbf{S}_o) \leq f(\mathbf{S}_r)$, then replace $\mathbf{S}_{S+1}$ with $\mathbf{S}_o$; otherwise, go to the shrink step;
 - (b) Inside: if $f(\mathbf{S}_r) \geq f(\mathbf{S}_{S+1})$, calculate $\mathbf{S}_i = \bar{\mathbf{S}} - \kappa_{ctr}(\mathbf{S}_r - \bar{\mathbf{S}})$. If $f(\mathbf{S}_i) < f(\mathbf{S}_{S+1})$, replace $\mathbf{S}_{S+1}$ with $\mathbf{S}_i$, otherwise go to the shrink step;
5. **Shrink:** if all else fails, then calculate $\mathbf{S}_s = \mathbf{S}_1 + \kappa_{shr}(\mathbf{S}_s - \mathbf{S}_1)$ for $2 \leq s \leq S + 1$, where $0 < \kappa_{shr} < 1$ is a shrink factor.

Figure 30 shows an illustration of the main stages of the Nelder-Mead algorithm to better understand this calculation flow. For representation purposes, the number of parameters was limited to $S = 2$, such that the Simplex method is formed by $S + 1 = 3$ vertices.

⁵This formulation, although applied to the notation developed in this work, is consistent with the one from Gao and Han (2012).

Figure 30 – **Main stages of the Nelder-Mead algorithm.** The objective function $f(.) = f(W, w_n)$ is evaluated at each of the simplex vertices based on the the initial guesses for the parameters to be estimated. Then, after consecutive expansion, contraction and shrink operations, the iteration process is stopped considering a tolerance value of maximum number of iterations.



Source: Own authorship.

5.1.3 Validation

The validation stage comprises repeating the optimization process considering M different time frames to define W . The idea is to evaluate an entire seizure, from preictal to postictal states, by cutting the signal in M parts. According to the number of points measured in the target LFP, it is possible to consider an overlap as usually done in signal processing techniques (Oppenheim et al., 1997). The M repetitions provide $\mathbf{S}^{(1)}, \dots, \mathbf{S}^{(M)}$ sets of parameters. The set used is the median resulting value of all optimizations, i.e.,

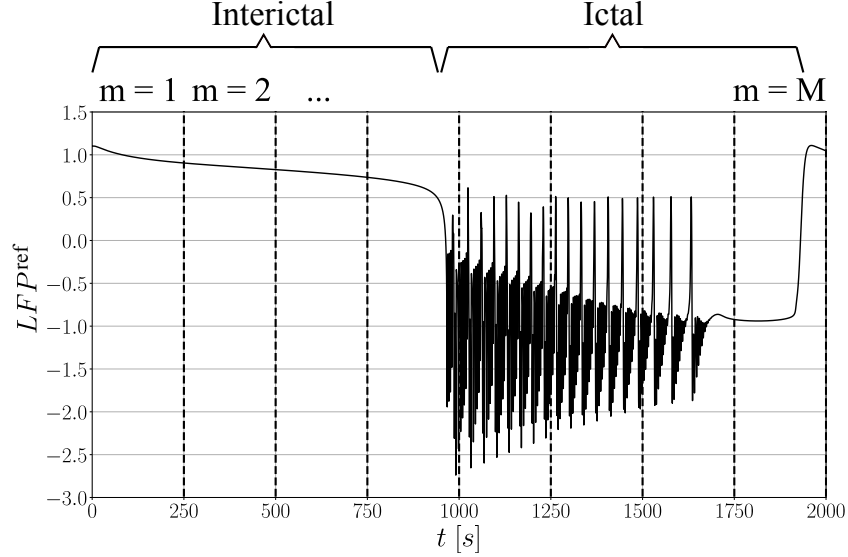
$$\mathbf{S} = \text{med}\{\mathbf{S}^{(1)}, \dots, \mathbf{S}^{(m)}, \dots, \mathbf{S}^{(M)}\} \quad (87)$$

Since $m = 1, \dots, M$, the estimated parameters are considered as random variables. As such, an intuitive choice to summarize them would be the mean, but if they are averaged using it, they risk being biased, assuming high values which do not reflect the real parameters (Soong, 2004), because the algorithm only aims at the best numerical solution. In this sense, medians are more stable and conservative as they are centered samples (Soong, 2004). Other advantages in doing so are summarized below:

- depending on the requirements of the optimization (in this case, the number of points, for example), it may take a relatively long time for the parameters to converge towards the desired ones. Therefore, shorter time windows enable to perform several shorter, faster evaluations, which leads to a finer resolution in function of the number of windows applied;
- since preictal, ictal and postictal signals have different characteristics, the best estimate for the parameters can be found individually, for each part, or as a whole, based on median values of multiple successive operations, whose number is defined based on the time window analyzed (as addressed in Subsection 5.2.1);
- by estimating the parameters according to pieces of the signals, it may be possible that they are dominated by the local dynamics, which implies that they do not fully reflect Epileptor's true general behavior, a problem commonly associated to overfitting (Hawkins, 2004). However, even if a set of parameters proves to be the best fit for a part of the LFP but not for another one, by using median values, all of the parameters yielded from the optimization can be analyzed as independent values and converge to the desired ones. For instance: in case $f_m(W, w_n) > \epsilon$, obtained if the number of iterations exceeds the predefined one or a global minimum that does not tend to zero is achieved for some m , it is possible that one or more of its $p^{(j)}$ diverge considerably from its reference value. Once many time windows are adopted, the overall median result tends to compensate for particular discrepancies like this, because it is supposed to tend towards the target values without being significantly affected by extreme values.

Based on the aforementioned reasoning, Subsection 5.2.1 is designed to specifically address this issue and find the best trade-off between number of time windows and accuracy. Figure 31 depicts an illustration of this approach, considering sequential time windows over time, based on a reference (i.e., the target) LFP. The frame chosen refers to the one with the minimum non-repeating cell for reproducing Epileptor's main stages: interictal and ictal. After the specified number of points, the same structure is obtained over and over, which characterizes the system's bi-stable behavior (Jirsa et al., 2014). Moreover, by considering such a frame, the transitions between states are also captured during the optimizations.

Figure 31 – **Steps prior to the validation process for the parameter estimation approach using sequential time windows to estimate the unknown parameters of the target LFP.** According to Eq. 87, each window m represents a full optimization process, as described in Section 5.1.2, leading to a set of parameters $\mathbf{S}^{(m)}$, $m = 1, 2, \dots, M$. The final set of parameters, considered the best representative one, is given by $\mathbf{S} = \text{med}\{\mathbf{S}^{(1)}, \dots, \mathbf{S}^{(m)}, \dots, \mathbf{S}^{(M)}\}$.



Source: Own authorship.

5.2 Parameter estimation: application

The proposed approach is evaluated considering a target LFP numerically obtained. An Epileptor model is defined considering the following reference parameters (Jirsa et al., 2014): $\mathbf{S}^{\text{ref}} = \{2857, 1, 10, 0.01, -1.6, 1, 3.1, 0.45\}^T$. An example of the vector of parameters before the iterations is $\mathbf{S} = \{2142.75, 1.1860, 12.6744, 0.0103, -1.3674, 1.0436, 2.5773, 0.4343\}^T$. In particular for this case, note that the main difference is verified for the parameter $\tau_0 = 2142.75$, which is 25% ($\delta = 0.25$) lower than its original value. However, different $\mathbf{S}^{\text{ref}}$ were investigated and similar results were obtained for $\mathbf{S}$. Values of $\epsilon = 10^{-6}$ and $K = 200000$ were set for the integration in the time domain using the fourth order Runge-Kutta algorithm, with $dt = 0.01$ s.

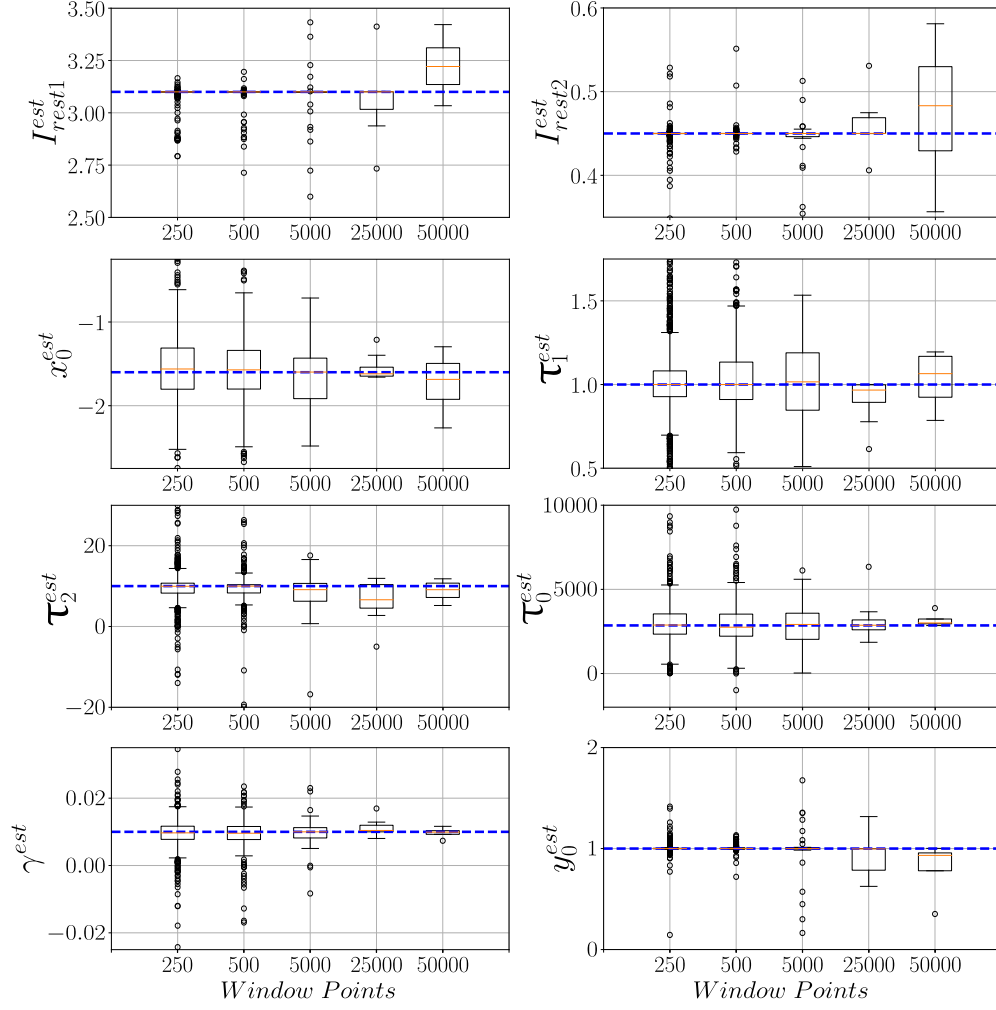
5.2.1 Influence of the time window

Figure 32 presents the results obtained for the proposed parameter estimation approach using successive optimizations, based on box plots, in which the center value is the median ($\mathbf{S}^{\text{best}}$). For I_{rest1} , I_{rest2} , τ_1 , τ_2 and y_0 , small time windows lead to a smaller region inside the box plot and less scattering around their respective medians, compared to those from longer time windows, which suggests that a finer time resolution is more appropriate in terms of parameter estimation in these cases. A reason for this behavior is that all of these parameters are related to variables that evolve in a faster time scale (as Epileptor’s subsystems, which define the epileptiform dynamic features). A more detailed analysis on this topic shall be covered in the next subsection.

For x_0 , since this parameter is linked to the intensity of a seizure (in terms of amplitude and duration), shorter time windows may benefit the overall performance of the optimizations, but longer ones may comprise the information of the whole ictal state better, which is a possible reason why an intermediate value (25000) seems to be the best result. For τ_0 , in turn, longer time windows seem to favor its estimation. This parameter is associated to both duration and interval between two consecutive seizures in Epileptor, and thus epochs that capture the global behavior of an LFP better seem to be more appropriate choices. At last, longer time windows also favor the estimation of γ . This parameter does not present a precise physical meaning, which makes it difficult to relate it to a specific behavior; however, it plays the role of a slow-pass filter in the model, and slower activities might be benefited from longer time windows. As a general result, considering that all parameters were fairly well estimated regardless of the time window, the values obtained for the parameters tend to approach those originally defined for Epileptor (Jirsa et al., 2014), and a finer time partitioning is beneficial for most cases.

Table 3, in turn, presents the relative mean squared errors (RMSE) between the estimated and actual parameters, as well as their median final objective-function evaluations (after $M = 800, 400, 40, 8$ and 4 optimizations, respectively, depending on the number of windows). Based on the function evaluation, it endorses the advantage of a relatively smaller time window to improve the estimation of the parameters. However, the RMSE does not necessarily reflect the same results. This may happen because $f^{\text{best}}(W, w)$ is obtained as a median final evaluation of all M windows, whereas RMSE is only related to the difference between a simulated reference signal and a new one obtained with the final set of parameters estimated (that is, it is not a median value). Nonetheless, the general behavior is that the finer the resolution (shorter time windows), the better the results are.

Figure 32 – **Box-plots for the set of 8 parameters estimated using different time windows (given in number of points) and $\delta = 0.25$.** The overall behavior is that reducing the size of the time windows enhances the results of the estimation, meaning that greater resolutions in the time domain may lead to higher accuracies. Blue dashed lines (- -) represent the reference values (Jirsa et al., 2014).



Source: Own authorship.

Table 3 – **Performance of the optimization approach, in terms of the relative mean squared error (RMSE), for different time windows, considering median values between the estimated (S^{best}) and reference (S^{ref}) parameters, and associated median final objective-function evaluations ($f^{\text{best}}(W, w)$).** Although a 5000-point window is an exception, the overall result is that the shorter the time window, the better the estimation.

Window (points)	250	500	5000	25000	50000
RMSE (%)	0.63	1.21	0.66	3.96	1.47
$f^{\text{best}}(W, w)$	$1.32 \cdot 10^{-6}$	$5.83 \cdot 10^{-6}$	$2.36 \cdot 10^{-4}$	$5.5 \cdot 10^{-2}$	$1.1 \cdot 10^{-1}$

Source: Own authorship.

This is possibly due to the pseudo-random characteristic of the initial guesses: since an unknown combination of them is set at the beginning of the process, slightly higher or lower values are likely to be obtained for the parameters; also, a set of parameters that best fits one time window is not necessarily the best choice for the remaining ones; however, the guesses tend to converge towards the correct values on average, as the number of available signal samples increases. Furthermore, note that, for this particular case, to obtain an RMSE lower than 1%, the threshold that relates the RMS of an LFP $f^{\text{best}}(W, w) \leq \epsilon$ must be such that $\epsilon = 10^{-6}$.

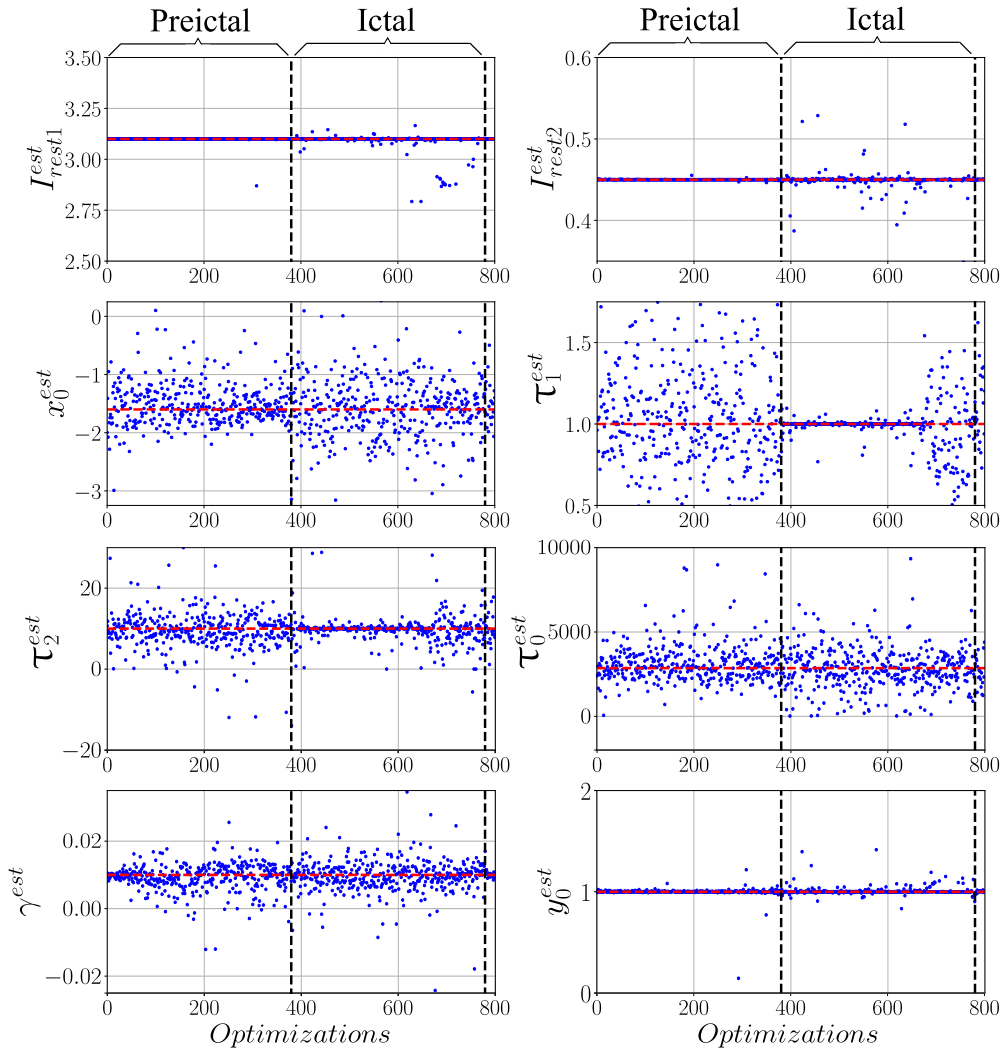
5.2.2 Influence of interictal and ictal states

In Fig. 33, the same parameters as in Fig. 32 are shown over the number of optimizations (alternatively, the number of time windows), but using a 250-point frame. For the parameters chosen, different characteristics are observed over the number of optimizations (which include information about the LFP over time). For $I_{\text{rest}1}$, the estimated values remain at an almost unchanged baseline, thus providing an accurate representation of its original magnitude. Such a parameter is only present in vector $\mathbf{b}$ in Epileptor's equations, which is decoupled from the dynamic matrix, which might be why it is relatively easier to be approximated (the same behavior occurred for $I_{\text{rest}2}$).

As for x_0 , two possible reasons may be associated with its behavior: it interacts with other parameters that must be estimated (as τ_0 , for example), which makes it difficult for the algorithm to yield a precise value throughout the whole signal; besides, it is associated with variable $z(t)$, which represents processes that evolve slowly in time. Note that, for τ_1 , the opposite behavior is obtained, probably because it is associated (and interacts) with fast-evolving variables and parameters, as x_1 and y_0 , respectively. Therefore, each of the parameters are better estimated according to their biophysical nature in terms of time scale. Furthermore, this endorses the fact that adopting successive optimizations,

including interictal and ictal states, is an interesting strategy, even if the resulting values must be averaged.

Figure 33 – **Optimizations for the set of 8 parameters estimated using a 250-point time window, comparing the preictal and ictal states.** The overall behavior is that parameters associated to a relatively faster time scale (such as τ_1 and τ_2) are better estimated in the ictal condition (faster activity), whereas parameters associated to a relatively slower time scale (such as τ_0) are better estimated in the interictal (baseline) condition. Constant parameters (such as I_{rest1} and I_{rest2}) are well estimated in both conditions, but slightly better in the interictal condition. Red dashed lines (--) represent the reference values. Vertical dashed lines represents transitions from interictal to ictal.

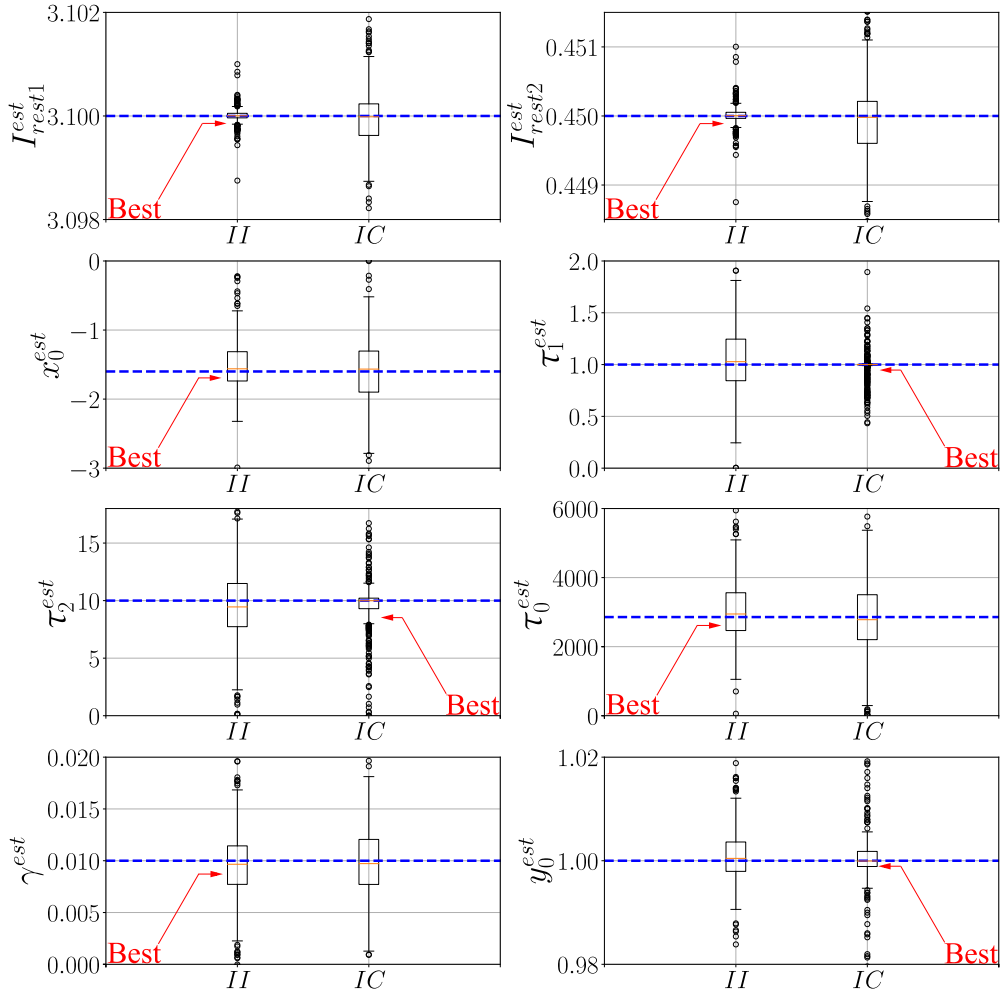


Source: Own authorship.

This result can be generalized, as seen in Fig. 34, where a comparison between the box plots in the interictal and ictal states is presented. For these cases, a 250-point frame is also adopted, such that the resulting box plot represents all optimizations carried out for the parameters (as seen in Fig. 33) in one of the aforementioned conditions. For τ_0

and x_0 , their best estimation is performed before a seizure occurs. The first one is a time scale parameter that, essentially, influences on the duration and interval between seizures. The second one, in turn, is known as epileptogenicity and influences on the intensity of a seizure, in terms of amplitude and duration. It interacts with τ_0 according to the state control variable z in the Epileptor model, which is a slow-evolving variable. This helps explain why their estimation is better in the interictal region, the period between two consecutive seizures.

Figure 34 – **Box-plots for the set of 8 parameters estimated comparing the interictal (II) and ictal (IC) states using a 250-point time window.** The box-plots generalize the behavior seen in Fig. 33: parameters associated to a faster time scale are better estimated in the ictal condition, whereas the ones associated to a slower time scale are better estimated in the interictal condition. Blue dashed lines (—) represent the reference values.



Source: Own authorship.

As for the parameters τ_1 and τ_2 , they are time scales that regulate the behavior of both subsystems that define the main features of an ongoing seizure: fast oscillations and

spike and wave events, described by x_1 and x_2 , respectively, which are both fast-evolving variables (the following relation always holds: $\tau_0 > \tau_2 > \tau_1$ (Jirsa et al., 2014)). Parameter y_0 , in turn, is a constant value associated to the first subsystem (x_1, y_1) in the Epileptor model. Since all of them are linked to events that take place in the ictal state, this suggests that they are likely to be more accurately estimated in this region.

Parameters I_{rest1} and I_{rest2} can be considered as particular cases: even though each of them is associated to one of the subsystems (which represent fast-evolving activities in the time domain), they were better estimated in the interictal region in the cases analyzed, not the ictal one. However, both are assumed as a constant flow of electric currents that flow inward or outward neural cells in the model (Jirsa et al., 2014), and thus they do not belong to the dynamic matrix, which might explain this finding. It should be stressed that the results for the ictal period are fairly good as well and do not significantly compromise their estimation.

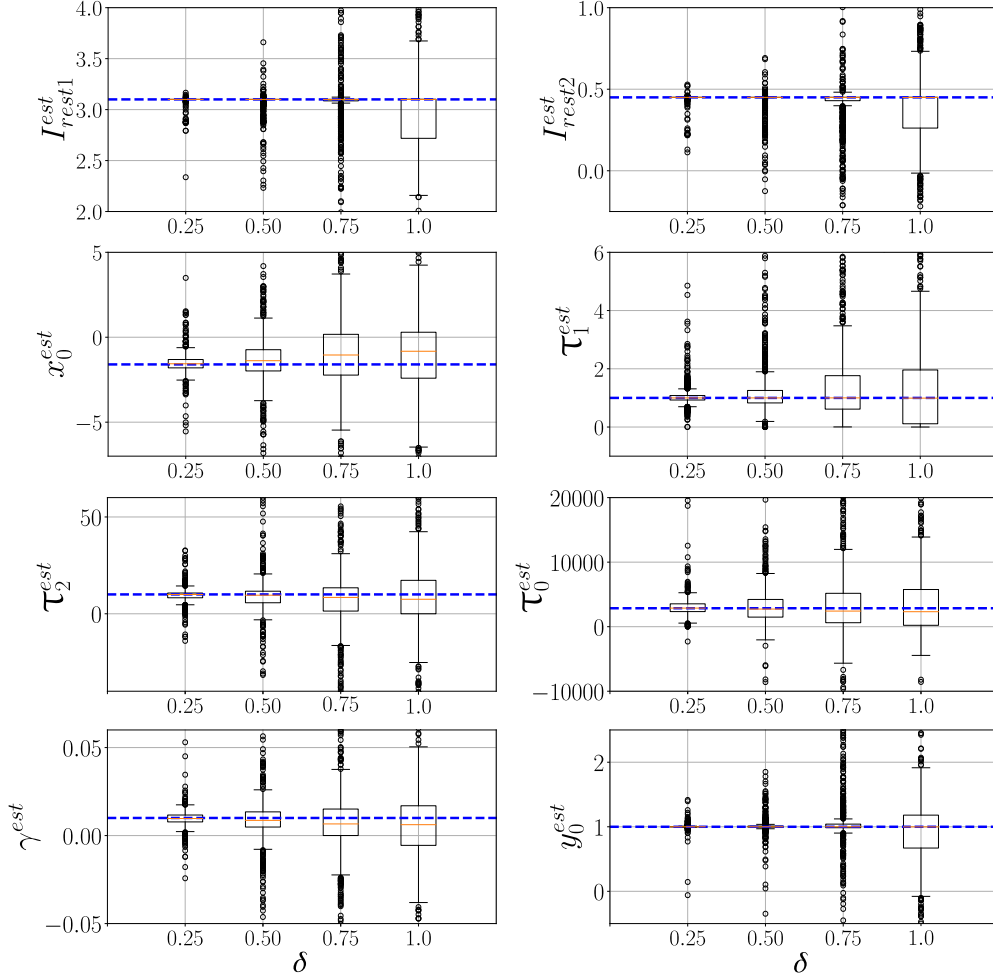
Finally, parameter γ , linked to the dummy variable $u(t)$, presented a slightly better result for the interictal state; however, since it is not directly related to any biophysical entity and works as a low-pass filter, it can be reasonably estimated in both regions.

As a general rule for deciding which periods of time during an LFP activity described by Epileptor should be measured for the best possible estimation of its parameters, that is, which parts of the signal over time are more likely to provide the right estimates, arrows pointing to the best box plot are indicated in Fig. 34. Essentially, the criterion used is not only how close the median values are to the reference ones, but the variation around them: low fluctuations imply in higher chances of estimating the correct values.

5.2.3 Influence of the uncertainty factor δ

Figure 35, in turn, depicts a comparison between the estimated parameters obtained for different uncertainty factors δ . The box plots were obtained using a 250-point frame and combining both interictal and ictal states. Note that, as the uncertainty (that is, the relative difference in magnitude between the estimated and actual values) increases, the parameters tend to move farther from the reference ones. This is particularly evidenced by some visual features: for low δ , the region inside the box plot is smaller, more concentrated around the medians, whereas the outliers are less spread around them as well; for high δ , in turn, the opposite behavior is seen, with larger regions inside the box plots and a higher scattering in terms of outliers. It is worth mentioning, however, that even for $\delta = 0.75$ and $\delta = 1.0$, the resulting medians are fairly close to the target values for most parameters analyzed.

Figure 35 – **Box-plots for the set of 8 parameters estimated using different uncertainty factors δ and a 250-point time window.** The overall behavior seen in the box-plots is that decreasing the value of the uncertainty factor leads to a better estimation. Blue dashed lines (- -) represent the reference values.



Source: Own authorship.

In practical terms, the prior lack of information about the initial guesses influences directly the final output; that is, the less information, the worse. Nonetheless, accurate predictions can be made based on the successive optimizations method. At last, Table 4 summarizes these results, showing that not only does the relative mean square error get higher with the uncertainty, but also that the final objective-function evaluation is farther from zero. In other words, the resulting value of the objective function, which expresses how close the estimated LFP is to the reference signal, diverges from zero as the uncertainty increases, which leads to a less precise estimation.

Table 4 – **Performance of the optimization approach, in terms of the relative mean squared error (RMSE), for different uncertainty factors δ , considering median values between the estimated (S^{best}) and reference (S^{ref}) parameters, and associated median final objective-function evaluations ($f^{\text{best}}(W, w)$).** The overall behavior is that decreasing the uncertainty factor leads to a better estimation since the difference between estimated w and reference W LFPs is smaller.

δ (%)	25	50	75	100
RMSE (%)	0.63	4.47	12.40	16.43
$f^{\text{best}}(W, w)$	$1.32 \cdot 10^{-6}$	$1.71 \cdot 10^{-5}$	$5.22 \cdot 10^{-4}$	$3.1 \cdot 10^{-3}$

Source: Own authorship.

5.2.4 Influence of noise addition $\mathcal{N}(t)$

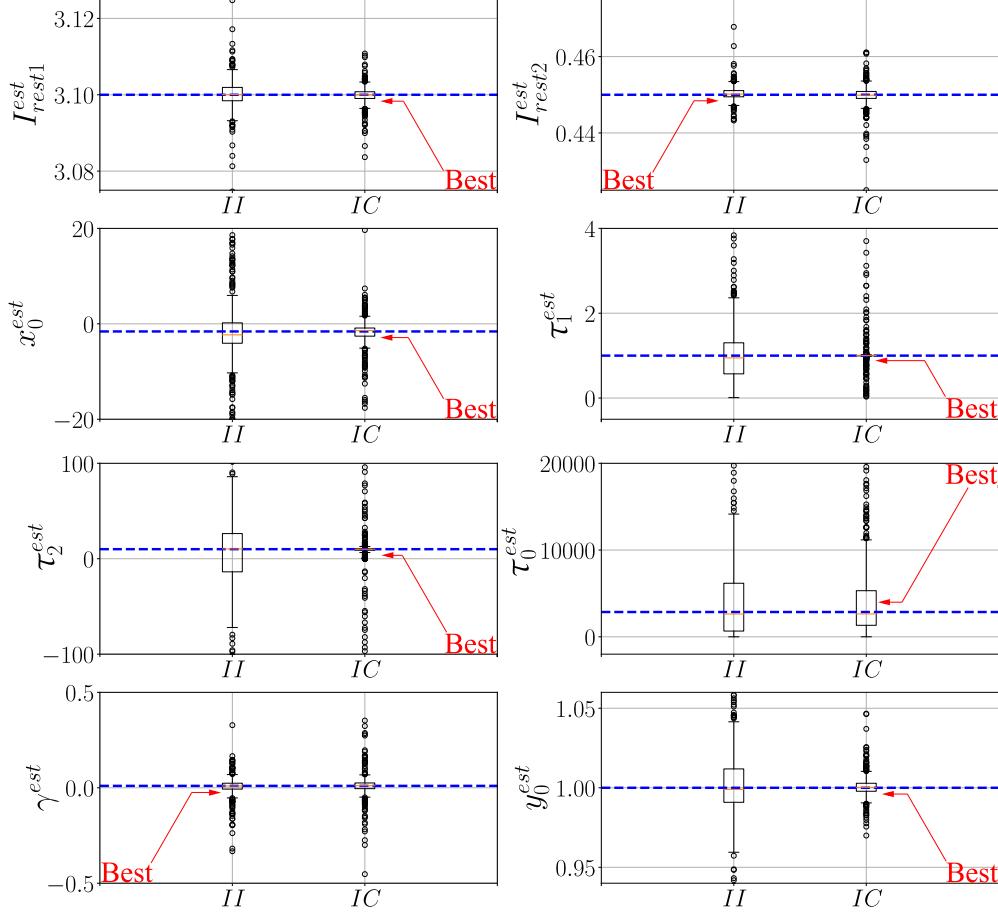
Figure 36 depicts the influence of noise addition when estimating the set of 8 parameters in both conditions, interictal and ictal. The box-plots are obtained considering a 250-point frame and $SNR_{dB} = 70$ dB. It is worth mentioning that other values of SNR (which shall be presented in this subsection) were tested and similar results were obtained. For τ_1 , τ_2 and y_0 , the same behavior from Fig. 34 is observed: since they are parameters related to the subsystems that define Epileptor’s main epileptiform features, they are better estimated in the ictal region. Parameter γ , in turn, is best estimated in II as before, and the same conclusions hold for this case as well.

For the remaining parameters, an interesting behavior occurs: especially for the ones related to slow-evolving variables, they are not better estimated in the interictal region. Note that τ_0 , x_0 and I_{rest1} ⁶ present a lower variation around the median values in IC. This may be explained due to the main features of each region in the time domain. Before the seizure onset (first bifurcation), the model essentially behaves as a positive DC trend, without any other strong dynamic structures, as spikes or fast oscillations. When noise is added to this part of the signal, it causes a progressive degradation of the baseline⁷, thus compromising the estimation process. During the ictal period, nonetheless, the main epileptiform structures take place and help the algorithm identify the correct parameters more easily. Despite this peculiarity, the estimations are fairly good in both regions.

⁶Although II is considered as the best region for I_{rest2} , note that there is not a clear visual distinction between II and IC, in terms of estimation.

⁷The effect of progressive degradation caused by noise is commonly found in applications involving brain signals, in which the source can be from eye movements, muscle artifacts or the environment, for example (Agarwal et al., 2017; Hussein et al., 2018).

Figure 36 – **Influence of noise addition on the process of parameter estimation in both regions, using a 250-point time window and $SNR = 70$ dB.** The overall behavior seen in the box-plots is that, even with the addition of noise, parameters related to faster time scales are still better estimated in the ictal condition, whereas the ones associated to a slower time scale are better estimated in the interictal condition. Blue dashed lines (—) represent the reference values. Red arrows and text 'Best' indicate the condition with the most accurate estimation.

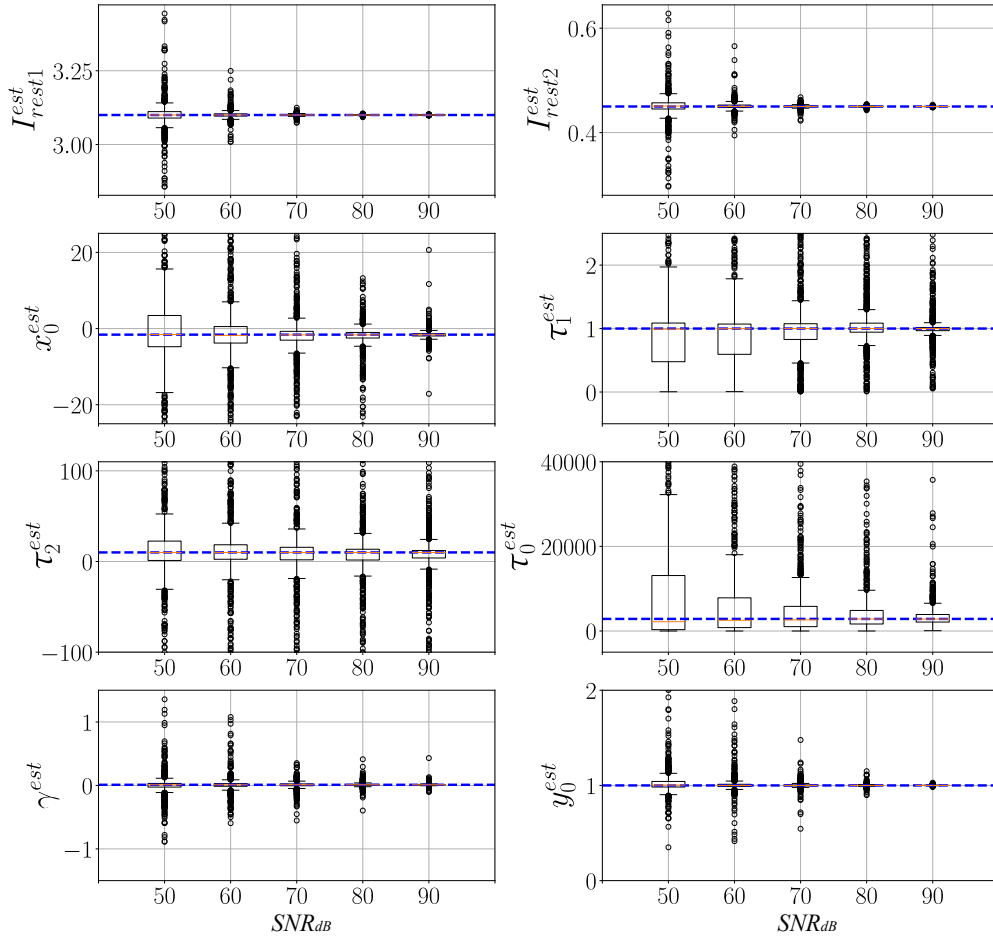


Source: Own authorship.

Finally, Fig. 37 shows the results for the parameter estimation process considering different moderate SNR_{dB} . The box-plots were obtained using a 250-point frame and combining both II and IC regions. Essentially, the overall behavior is that, as the power of the noise present in the LFP decreases, the process of parameter estimation is more accurately carried out. This can be particularly seen by the lower region inside the box-plots and fewer outliers as SNR_{dB} increases. A higher SNR implies in less signal degradation (Agarwal et al., 2017; Hussein et al., 2018), that is, the intensity of the measured activity, as the LFP in this case, is stronger (or overcomes) than that of the noise that corrupts the output, which thus helps the optimization algorithm find an appropriate solution more easily. Conversely, as the noise progressively kicks in, it corrupts the dynamic structures, thus compromising the estimation process. Nonetheless, for the cases analyzed in this

work, even relatively lower SNR yielded fairly good results, which is evidenced by the small distance from the reference values and the median ones.

Figure 37 – **Influence of noise addition on the process of parameter estimation using a 250-point time window and different SNR dB, combining both IC and II regions.** The overall behavior seen in the box-plots is that the higher the intensity of the noise added to the signals, the worse is the estimation, because the signal-to-noise ratio is compromised. Blue dashed lines (—) represent the reference values.



Source: Own authorship.

To obtain a more comprehensive and detailed analysis, especially considering the influence of noise (which is responsible for corrupting the quality of the reference signal and decreasing significantly the accuracy of the optimization process), different sets were tested having one of their parameters changed. In this case, the first set is the same as the one addressed in the previous sections; the second one, in turn, is the same set, except for x_0 ; the third one is again the same set, except for I_{rest1} . Table 5 presents the results for these selected cases based on a 250-point frame, $\delta = 0.25$, and three levels of noise.

For $f^{best}(W, w)$, it increases as the noise increases, moving farther from the ideal

value close to zero. However, the overall result is within 0.2 (or 20%), which is relatively low. A similar behavior occurs to the RMSE: in general, it becomes higher as the levels of noise increase, leading even to percentages that exceed 100%. This can be explained by the fact that it represents a pointwise comparison between the reference LFP and the reconstructed one. That is, the signals are not perfectly synchronized, especially due to τ_0 , which varies considerably and is responsible for the slow-evolving processes. Nonetheless, when analyzed individually, the estimated parameters are fairly close to their reference values, which explains why a low $f^{\text{best}}(W, w)$ is achieved, as previously mentioned. Therefore, the proposed parameter estimation approach is consistent across the different sets of parameters tested in the presence of noise.

Table 5 – **Selected cases for the performance of the optimization approach, in terms of parameters, relative mean squared error (RMSE), for different levels of noise, considering median values between the estimated (S^{best}) and reference (S^{ref}) parameters, and their respective associated median final objective-function evaluations ($f^{\text{best}}(W, w)$, whose notation is simplified for visual purposes).** Values obtained based on a 250-point frame, $\delta = 0.25$, and rounded up to the third significant figure. “Est.” stands for estimated values. The RMSE is significantly affected by the addition of noise, but the individual parameters present values still close to the reference ones.

1 st set	τ_0	τ_1	τ_2	γ	x_0	y_0	I_1	I_2	RMSE(%)	f^{best}
Reference	2857.000	1.000	10.000	0.010	-1.600	1.000	3.100	0.450	0.000	–
Est. (80 dB)	2843.117	1.000	9.952	0.009	-1.651	1.000	3.099	0.449	54.388	0.028
Est. (50 dB)	2201.157	0.991	9.991	0.011	-1.568	1.004	3.100	0.451	114.467	0.156
Est. (20 dB)	2451.317	0.972	8.637	0.008	-1.534	1.167	3.069	0.433	115.473	0.165
2 nd set	τ_0	τ_1	τ_2	γ	x_0	y_0	I_1	I_2	RMSE(%)	f^{best}
Reference	2857.000	1.000	10.000	0.010	-1.400	1.000	3.100	0.450	0.000	–
Est. (80 dB)	2823.374	0.999	9.983	0.009	-1.336	0.999	3.100	0.450	62.348	0.011
Est. (50 dB)	2428.167	0.999	9.877	0.009	-1.412	1.004	3.099	0.449	93.252	0.136
Est. (20 dB)	2691.772	0.978	8.983	0.007	-1.319	1.134	3.082	0.451	82.542	0.158
3 rd set	τ_0	τ_1	τ_2	γ	x_0	y_0	I_1	I_2	RMSE(%)	f^{best}
Reference	2857.000	1.000	10.000	0.010	-1.600	1.000	2.800	0.450	0.000	–
Est. (80 dB)	2840.615	1.000	10.011	0.009	-1.497	1.000	2.800	0.450	70.386	0.027
Est. (50 dB)	2607.437	1.001	9.989	0.009	-1.510	1.007	2.802	0.451	82.693	0.144
Est. (20 dB)	2607.133	1.008	9.749	0.006	-1.504	1.154	2.799	0.447	91.542	0.161

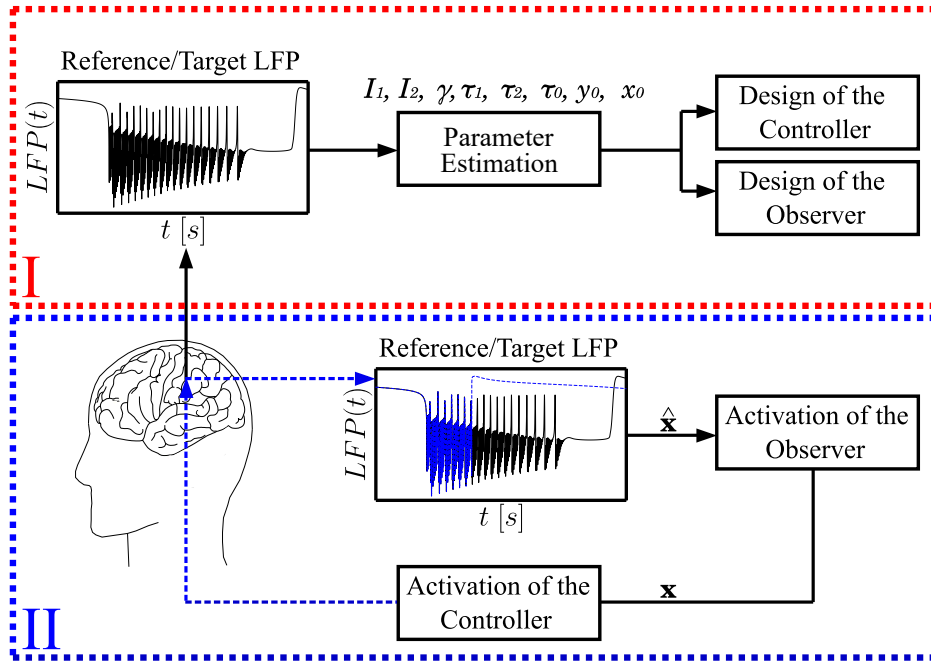
Source: Own authorship.

5.3 Integrating parameter estimation and controllers for seizure suppression

Figure 38 presents the integration of all the stages mentioned in this chapter. Two major steps are, thus, expected: an offline/preparation one (I), during which LFPs are acquired (or previously simulated), taken as reference or target signals, and used to design the observer and controller – therefore, note that there must be available data sets, which

represent well patients' specific seizure signatures, prior to this stage; and an online one (II), where the gains computed in (I) are already defined and used to reconstruct the unmeasurable variables, thus leading to the full definition of Epileptor's states, necessary to activate the controller – which, in turn, proceeds to deliver the inputs for seizure suppression.

Figure 38 – **Integration process considering the proposed parameter estimation technique and seizure suppression.** In the offline stage (I), previously acquired LFPs are used as reference signals to carry out the optimization process and obtain the best set of parameters $\mathbf{S}$, as seen in Fig. 31; these values are then used to design both observer and controller. In the online stage (II), the observer is activated to reconstruct Epileptor's actual states $\mathbf{x}$ based on the estimated ones $\hat{\mathbf{x}}$, and the controller uses the reconstructed states to deliver the input stimuli for seizure suppression.

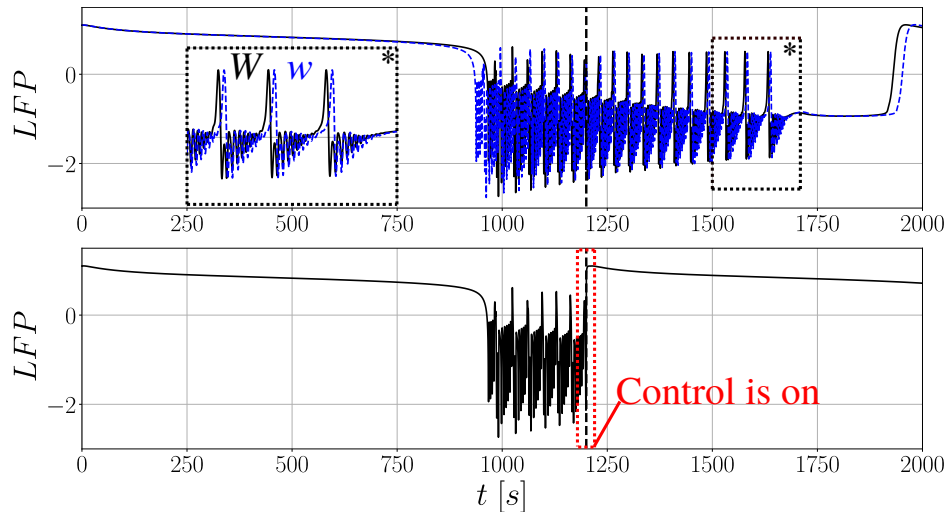


Source: Own authorship.

As illustrated in Fig. 38, after carrying out the parameter estimation methodology proposed in this chapter, the first requirement for applying observers and controllers is met: since both rely on knowing the initially unknown parameters before being designed, once these values are available, the necessary respective gains for reconstructing the Epileptor's model and driving it out of a seizure can be properly computed, as discussed in the previous chapters. Therefore, the following strategy for seizure suppression is adopted: the estimated parameters are directly used to design both controllers and observers; the gains obtained from the design are then used along with inputs to each of the states of the system, which characterizes the state feedback control approach. Note that the design is performed with estimated parameters, whereas the activation of both

observer and controller is for the system with the actual values of the parameters. It is expected thus that, albeit the set $\mathbf{S}^{\text{best}}$ is different from the real condition, it is sufficiently close to it so that seizure mitigation can be attained effectively. Figure 39 presents the aforementioned strategy, including the reference LFP (W) and the resulting one (w) after the successive optimization process, constructed with the estimated values using a 250-point time window and $\delta = 0.25$. Note that the curves present a good fit, and the only major visual difference is related to a horizontal stretch from both sides, leading to a positive delay over time. Nonetheless, such a discrepancy does not significantly compromise the controller's performance: as soon as it is activated, it can efficiently drive Epileptor out of a seizure, back to the healthy condition, expressed by the baseline at a higher LFP level.

Figure 39 – **Comparison between the reference LFP (W) and the one using the estimated parameters obtained from the optimization process proposed in this work (w), as well as the controller's action, over time.** The resulting LFP after simulating the Epileptor with estimated parameters is close to the reference one, only presenting a residual horizontal stretch. The controller is designed with these estimated parameters and is effective in suppressing an on-going seizure. Black solid lines (—) indicate the reference LFP; blue dashed lines (---) indicate the LFP with estimated parameters; the red dotted box (...) indicates that the controller, which is designed based on estimated states reconstructed by the observer, is activated at 1200 seconds and kept for 10 seconds.



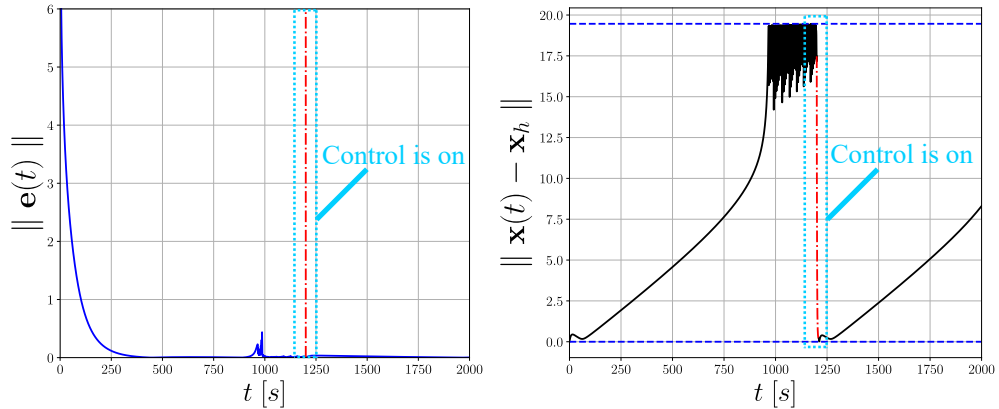
Source: Own authorship.

It is worth mentioning that, although the relative mean square error for this condition is around zero ($RMSE = 0.63\%$, from Table 3) and the difference between the expected output signal and the target one is slight, it can still be visually well identified. This suggests that the threshold ϵ must be as low as possible for an accurate estimation of Epileptor's parameters to be made. Due to this fact, close attention should be paid

to those whose variation affect significantly slow-evolving processes in the time domain and, thus, are directly related to driving Epileptor into and out of seizures: x_0 and τ_0 . Mathematically (Slotine; Li et al., 1991) and physically (Jirsa et al., 2014) speaking, $z(t)$ is a control variable, which explains this behavior, and since it presents both of these parameters linked together (as in Eq. 4), it might be difficult for the optimization to yield highly precise values. Nonetheless, these results highlight that both interictal and ictal states are relevant when applying parameter estimation approaches to the Epileptor model.

Furthermore, since both fuzzy observer's and controller's designs are carried out using estimated parameters, to assure that Epileptor's states are indeed properly reconstructed by the first one, as well as efficiently driven out of a seizure by the latter one, the Euclidean norm of the dynamic error ($\| \mathbf{e}(t) \|$) and the one associated to the actual states in relation to the healthy condition ($\| \mathbf{x}(t) - \mathbf{x}_h \|$) were calculated and presented in Fig. 40. The seizure-free condition $\mathbf{x}_h$ can be defined as the vector composed of the states that are immediately after the seizure offset (desired behavior), as seen in Chapter 3. Both norms are computed based on the results of Fig. 39. Note that, after approximately 1000s, $\| \mathbf{e}(t) \| \rightarrow 0$; also, right after the control input is activated (at 1200s, for 10s), $\| \mathbf{x}(t) - \mathbf{x}_h \| \rightarrow 0$. There is a small fluctuation on the error dynamics at the seizure onset (that is, when the behavior is more unstable); however, as seen, this does not significantly compromise the observer's performance, and the error tends to converge towards zero.

Figure 40 – **Euclidean norms of the error dynamics considering all estimated states ($\| \mathbf{e}(t) \|$) and between the actual states and the seizure-free condition ($\| \mathbf{x}(t) - \mathbf{x}_h \|$).** The observer is active during the whole simulation and when the states converge towards the desired ones, the controller is switched on, leading to the suppression of an on-going seizure. The controller is activated at 1200 s, as indicated by the red dash-dotted line, and lasts for 10 s, as indicated by the turquoise dotted boxes (...).



Source: Own authorship.

5.3.1 Relevance to real seizure suppression

The case analyzed in the previous section evidences the effectiveness of the controller when designed with parameters estimated at an $RMSE = 0.63\%$. In terms of real epileptiform activity, however, a stronger background activity is present along with other artifacts and noise. Although there exist techniques for dealing with artifact removal (Chen et al., 2016; Islam; Rastegarnia; Yang, 2016), as well as the classic techniques for signal processing and filtering (Oppenheim et al., 1997), it is reasonable to assume these activities are inevitably part of real signals, which requires that the FTSM approach works well under more adverse conditions too.

This issue is addressed in Fig. 41, where the action of the controller is simulated for different conditions of the Epileptor model (as in Table 5) and their respective Euclidean norms are calculated:

1. **First set:**

$$\begin{cases} \mathbf{S}^{\text{ref}} = \{2857, 1, 10, 0.01, -1.6, 1, 3.1, 0.45\}^T \\ \mathbf{S} = \{2629.268, 1.250, 8.804, 0.011, -1.965, 1.148, 3.819, 0.456\}^T \end{cases}$$

2. **Second set:**

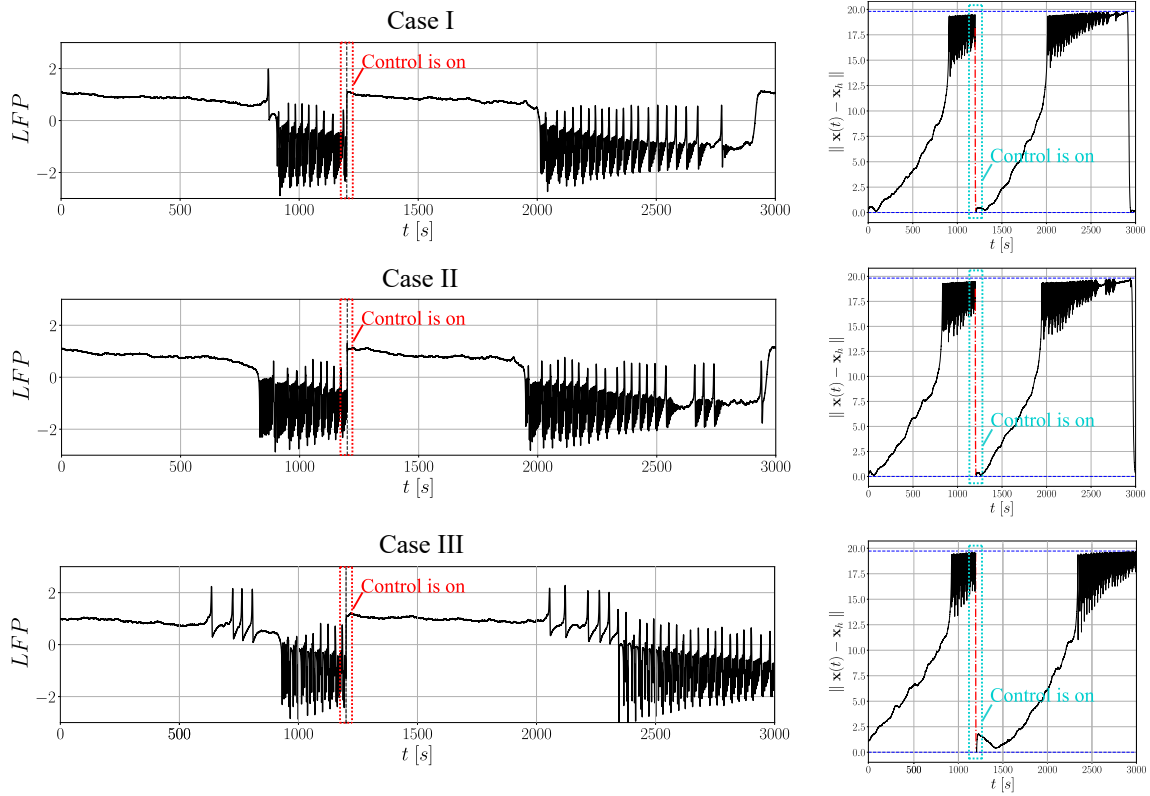
$$\begin{cases} \mathbf{S}^{\text{ref}} = \{2857, 1, 10, 0.01, -1.6, 1, 3.1, 0.45\}^T \\ \mathbf{S} = \{2629.268, 1.250, 8.804, 0.011, -1.965, 1.148, 3.819, 0.456\}^T \end{cases}$$

3. **Third set:**

$$\begin{cases} \mathbf{S}^{\text{ref}} = \{2857, 1, 10, 0.01, -1.6, 1, 2.8, 0.45\}^T \\ \mathbf{S} = \{3571.25, 0.997, 8.144, 0.001, -1.781, 0.997, 3.110, 0.356\}^T \end{cases}$$

For reference, $\mathbf{S}^{\text{ref}}$ is the set of reference values (simulated) and $\mathbf{S}$ is the set of values used to design the controller. To emphasize only seizure suppression, for simplicity, the set of parameters was manually set according to Eq. 81, and a fixed level of noise was also added to each simulation according to Eq. 84. Based on these cases, it can be seen that Epileptor is driven out of a seizure towards the seizure-free point. This implies that, even if no optimizations were carried out and the only different between estimated and actual parameters was related to the uncertainty δ , it would still be possible to design effective controllers.

Figure 41 – **Action of the FTSM controller considering different sets of parameters as in Table 5.** The uncertainty factor used to generate $\mathbf{S}^{\text{ref}}$ is $\delta = 0.25$. Designing the controller with estimated parameters and applying it to a reference LFP corrupted by relatively high levels of noise still leads to seizure suppression, thus endorsing the efficiency of the controller for this purpose. The level of noise is: 20dB . The control is activated at 1000 seconds, as indicated by the vertical dashed lines, and kept on for 10 seconds, indicated by the red dotted box.



Source: Own authorship.

5.4 Contributions, limitations and conclusions

Considering the results and discussion addressed in this chapter, the main contributions are: ’

- estimating the parameters of the Epileptor model based on a reference LFP with a good accuracy is possible by using the proposed successive optimization approach, leading to the reconstruction of the signal in the time domain;
- a comprehensive analysis about the influence of the time window, interictal and ictal conditions, uncertainty factor and addition of noise showed that, in general, parameters associated to a relatively faster time scale are better estimated in the ictal condition, whereas parameters that evolve at a slower time scale are better estimated in the interictal condition;

- it is possible to integrate parameter estimation with the previous approach for designing observers and controllers that aim at estimating Epileptor's states and providing input stimuli that suppress its seizures. For the latter one, since such a design relies on knowing the parameters that describe a seizure in the model, its application would be restricted without the contributions achieved in this chapter;
- this integration has also provided evidence that, once the initially unknown parameters that describe a seizure over time are available, that is, if the model is accurately identified as introduced in this work, they can be used to design the gains for both.

The limitations of the proposed approach are, in turn, presented as follows:

- although the necessary tools for designing controllers and observers for seizure suppression are already available, another relevant aspect on this matter is how the input stimulus can be delivered to the brain region undergoing a seizure. The state-space representation used in this chapter and the previous ones considers the full-order Epileptor with six states, but since the fairly abstract physical nature of the model prevents the real system from receiving multi-input stimuli, only one of them must be delivered, whose units are expressed in terms of electrical activity;
- the proposed approach assumes that an Epileptor model can accurately describe the dynamics of an experimental LFP that represents a seizure of interest, and the unknown parameters (as well as their variations) may be sufficiently well estimated by the proposed approach, which is not the case in all real scenarios due to the large variability of seizures;
- besides, real data usually contain noise, background activity and other artifacts that have not been accounted for in the proposed approach.

The proposed parameter estimation approach aims at the best possible outcome, which is supposed to provide an accurate approximation of the true parameters. Nonetheless, considering real applications where the number of iterations, time windows and processing is limited, finding the exact actual parameters that represent a seizure seems unrealistic, which makes it necessary to assume a variation around them. From this point of view, designing the controllers based on the uncertainty factor is an interesting strategy and demonstrates its purposes in terms of seizure suppression.

However, as stated in the limitations, it is necessary to define boundaries within which each parameter can vary (especially in the presence of noise, artifacts and background activity), which in clinical applications is not always possible. To circumvent this issue, articles addressing variations on the parameters in the literature (Houssaini et al., 2015;

Zhang; Xiao, 2018) may be useful for establishing references for the initial guesses, which is a major requirement for the optimization process to work properly and convergence to be achieved.

As for the issue of the absence of multi-input stimuli, underactuated control approaches can be applied (Spong, 1998; Reyhanoglu et al., 1999), in which the number of states used during control design and activation is not the same. This remains to be addressed in the next chapters, with a relatively different approach. Nevertheless, the current status of the controller for seizure suppression purposes allows applications in computational neuroscience as of today, along with the study of seizure propagation (Proix et al., 2017; Proix et al., 2018), for example.

At last, although the main restrictions regarding the applicability of the controller to the Epileptor have been removed or overcome (reconstruction of unmeasurable states and parameter estimation), no real electrophysiological signal has been analyzed so far. This is precisely what the next chapter covers.

6 BLACK-BOX MODELING FOR RECONSTRUCTING AND ATTENUATING REAL SEIZURES

From the physical point of view, epilepsy can be understood as a multivariable and multiparameter dynamic system, described as differential equations or state-space notation (Jirsa et al., 2014). The parameters in these equations intend to represent biophysical factors that, if modulated, may change its overall behavior (Jirsa et al., 2014; Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003). Computationally speaking, by setting them, it is possible to pre-define the response of the system and analyze several scenarios (i.e., how the response is influenced by different parameters). In practice, if one or more of these simulations match a specific signature of real brain activity (usually given in the time domain), this indicates that the set of parameters used for this case is consistent with the real activity. In system identification (SI) approaches (Ljung, 1998; Noël; Kerschen, 2017), this strategy is known as parameter estimation (Bos, 2007).

In the case of epileptiform activity, there are few SI applications involving dynamic models such as the Epileptor. As discussed in the previous chapter, a successive optimization approach was introduced to estimate all of its parameters, which is synergetic to the work developed by Hashemi et al. (2020). A fundamental limitation is that it considers only a reference output LFP related to seizures that are accurately represented by the model, not real experimental signals. Therefore, it is necessary to account for a wider range of signatures so that the results obtained in this thesis can be better validated. To do so, it is important to define which SI strategy to apply.

SI is a widely studied topic in some areas of knowledge, such as structure and control engineering (Ljung, 1998; Noël; Kerschen, 2017), where each case depends on the knowledge about the system. For example: there exist white-box models, which rely on having prior knowledge and deterministic equations that represent it (Duun-henriksen et al., 2013); gray-box models, which rely on prior knowledge and some available data (in this case, real signals from brain activity) (Ljung, 1998; Duun-henriksen et al., 2013); and black-box models, which only take the data into account, without any previous knowledge (Ljung, 1998; Duun-henriksen et al., 2013).

Articles involving linear or nonlinear autoregressive models (AR/NAR), typical black-box modeling tools, have been mostly proposed in the literature for seizure detection, prediction and synchronization (Franaszczuk; Bergey, 1999; Chisci et al., 2010; Yu et al., 2016; Ouyang et al., 2020; Attia; Moussaoui; Chahir, 2021), but approaches considering system identification have also been used to describe the so-called NAR fingerprints of

patients (Schiff et al., 1995; Schiff; Victor; Canel, 1995). However, the latter ones do not provide a systematic procedure to characterize the AR equations in terms of dynamic models. If this is done, seizures can be described in state-space notation and used for purposes of control, for example, as discussed in Chapter 3.

Considering this, the aim of this chapter is twofold: *i*) to propose an SI approach, which comprises the use of real brain activity (at the LFP level), recorded from human brain slices; *ii*) to provide a strategy for reconstructing real signals and applying control inputs to attenuate the epileptiform activity based on state-space plants. For the first one, AR models (Ljung, 1998; Durbin; Koopman, 2012; Fox, 2015) are used, making the identification process simpler, since they only take into account the output of the system, which is often the case in practice. For the second one, state-space (SS) models are obtained based on rearrangements of the AR equations (Durbin; Koopman, 2012) and converted into continuous-time models (Shieh; Wang; Yates, 1980; Åström; Wittenmark, 2013). Once the SS plants are available, they make it possible to design both observers and controllers.

Furthermore, the second objective is achieved considering two other different cases: the SS plant used to design both observer and controller is obtained from a signal undergoing epileptiform activity (named here as periodic ictal spiking – PIS) and the control inputs are applied to the same signal; the plant is obtained from a signal that represents interictal activity (named here as II) and applied to the PIS signal, which is taken as a hybrid controller in this work. The main purpose is to assess the possibility of designing observers and controllers without necessarily having access to seizure events, only the interictal ones. This is regarded as an interesting and important study in the sense that one does not need to rely on awaiting seizures to occur to be prepared for it. Although these events are cyclic (Jirsa et al., 2014; Fisher et al., 2014), they are often unpredictable (Kalitzin; Velis; Silva, 2010; Kalitzin et al., 2011), leading to interictal periods that are typically much longer than the ictal ones (Proix et al., 2014), so hybrid controllers may compensate for the possible lack of PIS activity recorded.

At last, as a synergetic approach to AR models, a smaller section including NAR models is also presented in this chapter. The main reasons for doing so are: *i*) NAR modeling is a generalization of its linear AR version; *ii*) the use of nonlinear regressors may compensate for local instability caused by stationarity issues, as discussed later on; *iii*) it allows writing the state-space notation in a similar way as the one of the Epileptor model, taking advantage of FTS modeling; *iv*) at last, it is not applied to LFPs anymore, but to iEEGs, thus extending the results to more global activities – which are usually easier to measure in practice. The nonlinear parameters are also explored to provide a single general model that share common features across patients, which is of particular

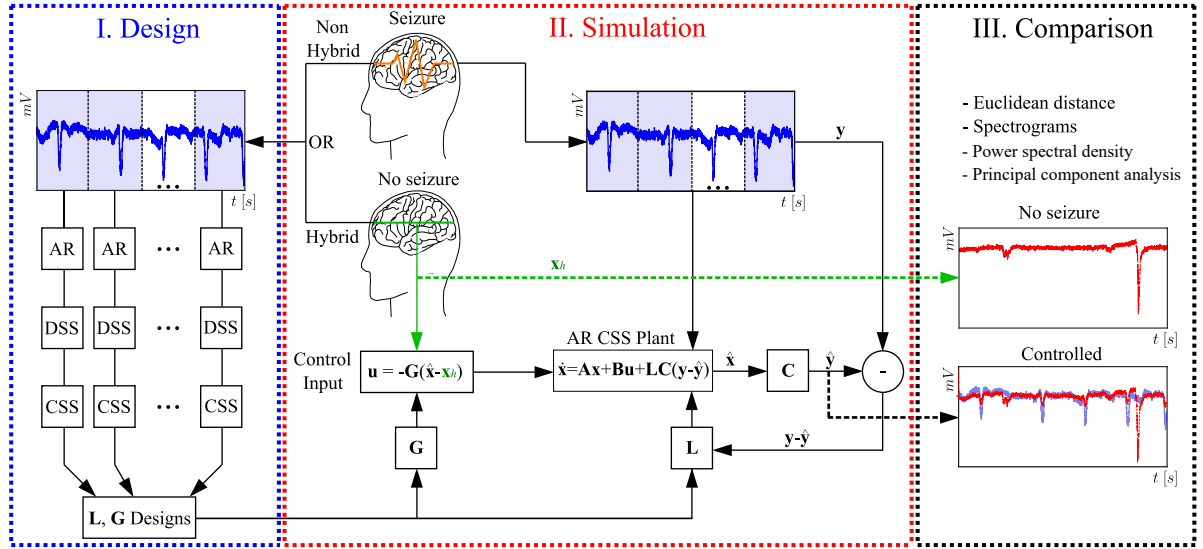
interest to provide controllers, for instance, that may work regardless of the patient or seizure. The codes used in this chapter are available online on the platform GitHub at the following address: <https://github.com/GMSINT/Epilepsy-Dynamics-Control>.

6.1 General methodology

The general methodology of this chapter comprises 3 major stages: 1) design, 2) simulation and 3) comparison. **Design** is composed of 10 main steps: *i*) obtaining raw signals, which are the brain activity directly measured during clinical procedures (either II or PIS); *ii*) signal processing, which in this case consists of filtering and downsampling; *iii*) frequency analysis; *iv*) AR model definition; *v*) AR model order selection and fitting; *vi*) model extension; *vii*) discrete-time state-space definition (DSS); *viii*) conversion to continuous-time state-space model (CSS); *ix*) design of the observer; *x*) design of the controller. **Simulation** has 2 other steps: *i*) applying the observer to reconstruct the real signal, which is a copy of the PIS/II activity; and *ii*) applying the controller to attenuate the epileptiform activity while driving the signal (i.e., brain region) to the II condition, where no seizure takes place. This stage is performed such that the estimated states are used as input variables for the controller. At last, **Comparison** comprises comparisons between the controlled signal (i.e., mitigated PIS driven back to II) and the original II one. For this purpose, the Euclidean norm, spectrograms/power spectral density (PSD), cross-correlations, principal component analysis (PCA) and appropriate statistical tests are considered. In this way, a comprehensive time-frequency analysis is carried out to assess the efficiency of the controller.

Figure 42 presents a flowchart with all the 3 major stages proposed in this work. Note the interdependency between observer and controller: as the first one recreates the real signal computationally, a control input is applied to the recreated artificial signal to verify whether its epileptiform activity can be mitigated. This integration approach is consistent with the one introduced in Chapter 5. It must be emphasized that the present approach is only carried out because there is no access to the true system. In real applications, a controller would not be applied to an artificial signal, but to a real brain region. It is thus expected that the simulations reflect real conditions sufficiently well to reproduce the results in clinical environments.

Figure 42 – **General flowchart with the 3 major stages of the proposed SI and control approach.** Design: PIS or II signals are obtained beforehand (thus defining the non-hybrid or hybrid approach) so that the AR modeling can be applied; several AR models are obtained from evenly-spaced time windows, whose size is defined during steps *iii* and *iv*; the models are rearranged into DSS and then converted to CSS; the same number of plants for designing the observers and controllers is used to generate single individual gains: $\mathbf{G}$ and $\mathbf{L}$, respectively (it is important thus to emphasize that: several models from one single lead to single gains). Simulation: II signals ($\mathbf{x}_h$) are taken as the reference behavior to which drive the system after the control is activated (i.e., no seizure condition); the real PIS activity is reconstructed based on the output matrix $\mathbf{C}$ (identifying the measurable state) and the relative difference between measured ($\mathbf{y}$) and estimated ($\hat{\mathbf{y}}$) states, weighed by the gain $\mathbf{L}$; with the gain of the observer $\mathbf{G}$, control inputs are applied to mitigate the PIS activity. Comparison: the controlled activity ($\hat{\mathbf{y}}$) is compared to the reference behavior ($\mathbf{x}_h$) using specific techniques: Euclidean distance, spectrograms and PSDs, normalized cross-correlation and PCA. Matrices $\mathbf{A}$ and $\mathbf{B}$ correspond to the identified CSS AR (which varies over time) plant and control input one (identifying the controlled states), properly defined in the next subsections.



Source: Own authorship.

6.2 Design stage

This section comprises the results from the first stage. For simplicity, some of the steps have been merged. Besides, for purposes of better explaining each of the steps, the analysis is carried out using only 2 signals, one from each condition: PIS and II. Nonetheless, other results considering more signals can be found in Final Remarks.

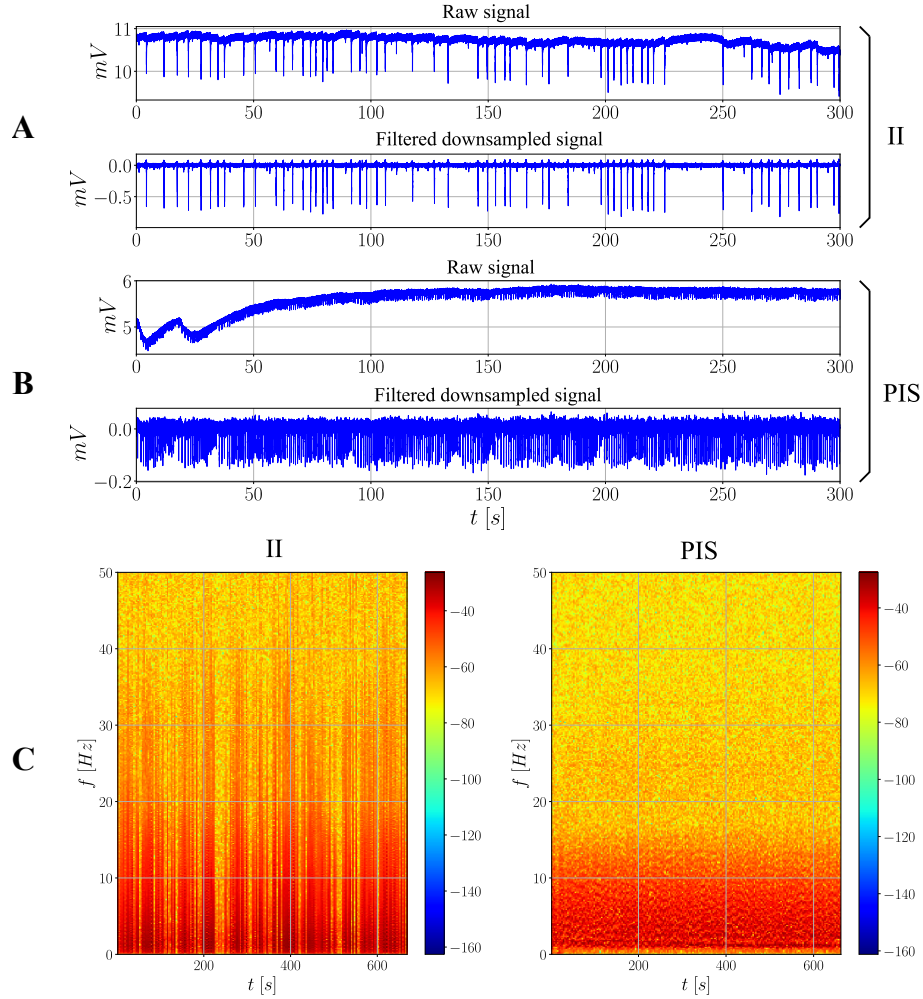
6.2.1 Signal processing and frequency analysis

The raw signals are properly filtered to remove any uncorrelated activity (i.e., shifting baseline, spurious harmonics), as carried out in (Araújo et al., 2022): Butterworth low-pass and high-pass filters were applied to limit the signals above 0.5 Hz and below 1 kHz, respectively; a notch-filter was also applied to remove the 50 Hz frequency and its 10 first harmonics. By filtering them, the resulting activity consists mainly of only epileptic spiking or bursting behavior over time. Then, a downsampling of factor 10 is applied (from 10 kHz to 1 kHz), which helps significantly to reduce the computational cost and time, without compromising its overall behavior.

Figure 43 presents examples of different signals obtained from the same hippocampal subfield (in this case, the subiculum – SUB) in two conditions: interictal (Fig. 43A) and ictal states (Fig. 43B). For the raw signals, there is a moving baseline over time, which is likely due to an external source of voltage that is not inherent to the spiking activity. This issue is addressed by implementing a high-pass filter, which in this case was at 0.5 Hz. This process is not only important to unveil the spikes and bursts, but also necessary so that the mean properties of the signal are better kept over time, which is a condition for the AR models to be properly estimated (Durbin; Koopman, 2012). Although the downsampling effect cannot be explicitly seen, a factor of 10 was applied to all signals, such that the sampling frequency becomes 1 kHz instead of the previously defined one, equal to 10 kHz.

The main difference between ictal (PIS) and interictal (II) spikings concerns the interspike intervals: while the PIS activity presents more regular evenly-spaced spikes, the spikes of the II activity are more irregular, switching from local bursts to isolated spikes over the whole signal. A previous statistical analysis and classification of the signals used in this chapter has been carried out (Araújo et al., 2022). Essentially, according to the authors, the patterns exhibited in PIS signals indicate a more deterministic activity and underlying mechanism, whereas II signals suggest a more complex/chaotic one. Further considerations on this matter are out of the scope of the present chapter, but some of these findings are important and shall be recovered in the next sections.

Figure 43 – **Raw and filtered downsampled signals with their respective spectrograms.** (A) and (B) contain examples of raw and filtered downsampled signals from SUB in the II and PIS conditions, respectively. For the filtering, a high-pass first-order filter is applied at 0.5 Hz. For the downsampling, a factor of 10 is applied in this case, which means that the initially 10 kHz-sampled series becomes a 1 kHz-sampled series. (C) presents the spectrograms for the same signals, both obtained after filtering and downsampling. A higher range of frequency is re-glected because it does not contain further strong frequency components.



Source: Own authorship.

By analyzing each signal in the frequency domain through its spectrograms, it is possible to find out which frequency components are more pronounced in the brain activity, and an appropriate time window can be selected based on them, covering a range from $f_{\min}$ to $f_{\max}$. Therefore, the minimum time window that must be used for the identification process is $T = t_{\min} = 1/f_{\min}$, leading to $N_{\min}$ samples. It must be stressed that this value is only the first reference. As shall be shown in the next steps, sufficiently long time windows are applied as a conservative approach.

Figure 43 also shows the spectrogram of both signals analyzed above, after filter-

ing and downsampling (Fig. 43C). There is an increase in terms of power over a wider frequency range for the interictal activity for the period of time in question, which is evidenced by the darker pixels, indicating that its activity is more complex, whereas a concentration in low-frequency bands is seen in the ictal activity, suggesting that periodicity and synchronization are indeed typical features of this condition (Araújo et al., 2022). Nevertheless, in terms of frequency components, their ranges remain relatively the same for both conditions, comprising approximately from ~ 0.5 Hz up to ~ 40 Hz. A higher range of frequency is not shown in the same figure because it does not contain strong components. As a conservative approach, it is assumed in this work that: $f_{\min} = 0.5$ Hz. Therefore, $t_{\min} = 2$ seconds, at least, to assure that all spectral activity is properly represented during the AR model definition, which leads to $N_{\min} = 2000$ points considering $f_s = 1000$ Hz, the sampling frequency for the downsampled series.

6.2.2 AR model definition, order selection, fitting and extension

AR models are equations whose current value depends on previous observations of a time series. They try to predict present states based on the time history. The classical AR model can be expressed as (Ljung, 1998):

$$\hat{y}(n) = \phi_0 - \sum_{i=1}^k \phi_i y(n-i) \quad (88)$$

where $n = 1, \dots, N$ indicates a discrete-time series, ϕ_i , $i = 1, \dots, k$, are coefficients that weigh each past observation $y(n-i)$, $i = 1, \dots, k$, of variable $\hat{y}(n)$, which in this case represents the output of the system (i.e., the electrophysiological recordings), and ϕ_0 is the mean value of the time series (or the intercept). Suppose the AR model can be rewritten as $\hat{\mathbf{y}}(n) = \boldsymbol{\theta}^T(n)\boldsymbol{\phi}$, where:

$$\boldsymbol{\phi} = [\phi_1 \ \phi_2 \ \dots \ \phi_{k-1} \ \phi_k]^T \quad (89)$$

$$\boldsymbol{\theta}(n) = [-y(n-1) \ -y(n-2) \ \dots \ -y(n-k+1) \ -y(n-k)]^T \quad (90)$$

the first step to calculating the vector of coefficients $\boldsymbol{\phi}$ is considering a minimization function $\min_{\boldsymbol{\phi}} f(\mathbf{y}, \hat{\mathbf{y}})$ based on the Least Squares Method (LSM) (Ljung, 1998):

$$f(\mathbf{y}, \hat{\mathbf{y}}) = \frac{1}{N} \sum_{n=1}^N [\mathbf{y}(n) - \hat{\mathbf{y}}(n)]^2 = \frac{1}{N} \sum_{n=1}^N [\mathbf{y}(n) - \boldsymbol{\theta}^T(n)\boldsymbol{\phi}]^2 \quad (91)$$

The vector of coefficients that minimizes this function is the one obtained when its derivative is zero:

$$\frac{d}{d\boldsymbol{\phi}} f(\mathbf{y}, \hat{\mathbf{y}}) = \frac{2}{N} \sum_{n=1}^N \boldsymbol{\theta}(n) [\mathbf{y}(n) - \boldsymbol{\theta}^T(n)\boldsymbol{\phi}] = 0 \quad (92)$$

This equation holds if $\sum_{n=1}^N \boldsymbol{\theta}(n) \mathbf{y}(n) = \sum_{n=1}^N \boldsymbol{\theta}(n) \boldsymbol{\theta}^T(n) \boldsymbol{\phi}$ or, alternatively:

$$\boldsymbol{\phi} = \left[\sum_{n=1}^N \boldsymbol{\theta}(n) \boldsymbol{\theta}^T(n) \right]^{-1} \sum_{n=1}^N \boldsymbol{\theta}(n) \mathbf{y}(n) \quad (93)$$

thus yielding the coefficients. In this chapter, one of the main assumptions is that the time series is stationary (Durbin; Koopman, 2012), despite local variations represented by the spikes. As shall be shown herein, with an appropriate number of AR coefficients, the epileptiform activity can be adequately reconstructed. In practice, no AR model is capable of fully describing the dynamics of a time series, because the number of coefficients is usually limited, and for certain time intervals there might be local non-stationary behaviors. Therefore, if the error considered during the modeling is taken into account, Eq 88 becomes:

$$\hat{y}(n) = \phi_0 - \sum_{i=1}^k \phi_i y(n-i) + \varepsilon_n \quad (94)$$

where ε_n is the error associated to the n discrete time. One possible way to evaluate model consistency is by calculating the autocorrelation function (ACF) of its residuals: (Fox, 2015):

$$\rho_i = \text{corr}(\varepsilon_n, \varepsilon_{n-i}) = \frac{\text{cov}(\varepsilon_n, \varepsilon_{n-i})}{\sqrt{\text{var}(\varepsilon_n) \text{var}(\varepsilon_{n-i})}} \quad (95)$$

where, for simplicity of notation, $\varepsilon_n = \varepsilon(n)$ and $\varepsilon_{n-i} = \varepsilon(n-i)$, $\text{cov}(\cdot)$ is the covariance operator, and $\text{var}(\cdot)$ is the variance operator. If ρ_i is relatively steady and close to zero for any $i > 0$, then ε_n can be assumed as a Gaussian error of the type $\mathcal{N} \sim (\mu, \sigma^2)$, where μ is a zero mean and σ^2 is a unity variance. If this proves to be true, then the AR model has captured the significant dynamics of the time series, and the residuals are merely random fluctuations.

Some criteria that are often used in the literature to define the order of an AR model are: the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Both attempt to obtain a good trade-off between the order k and the sum of squared errors $\text{SSE} = \sum_{i=1}^N [y(n) - \hat{y}(n)]^2$ between the resulting model and the original time series. Their equations can be defined, respectively, as (Durbin; Koopman, 2012; Fox, 2015; Gordon, 2015):

$$\text{AIC} = \ln\left(\frac{\text{SSE}}{N}\right)N + 2k \quad (96)$$

$$\text{BIC} = \ln\left(\frac{\text{SSE}}{N}\right)N + \ln(\text{SSE})k \quad (97)$$

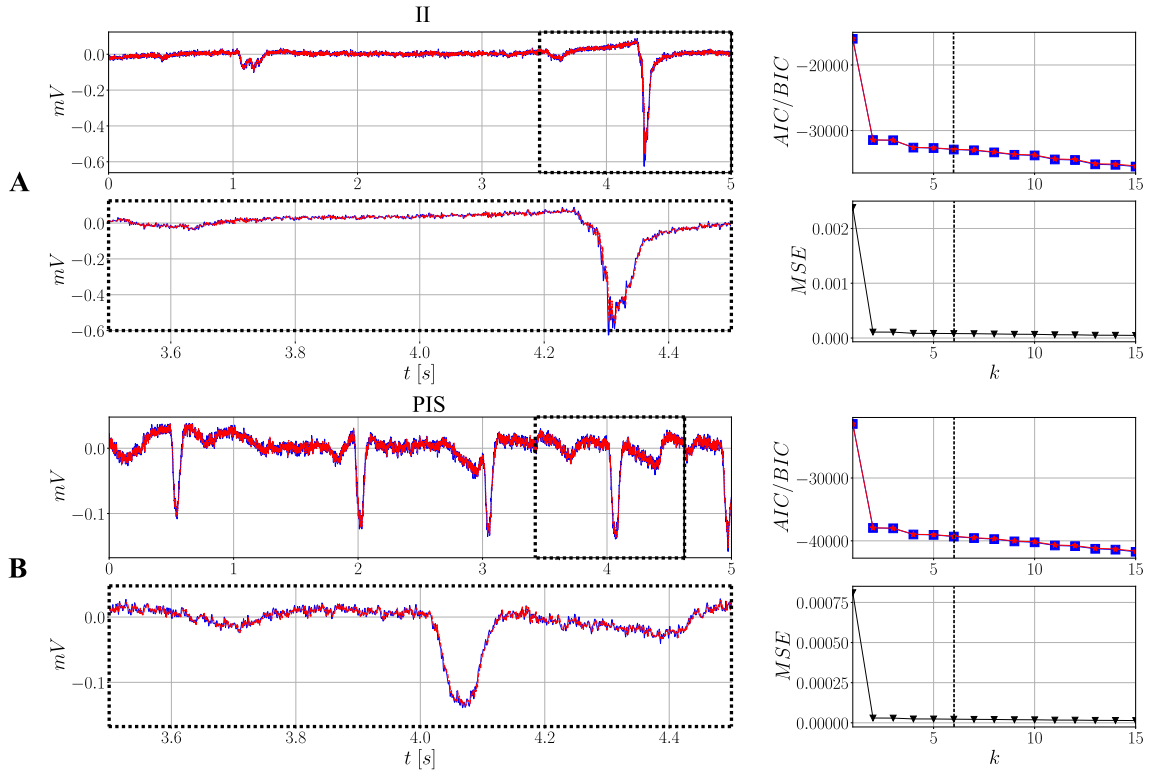
Based on these equations, when a minimum is found on the k vs AIC/BIC plane, it represents the best order for the model. Another possible way to assess order selection is

by the mean squared error (MSE), which is closely related to the previous ones. In this chapter, MSE is also tested to balance the order of the model and fix a limited error, and $N = N_{\min}$ is used as the minimum time window.

Since the definition of an AR model is closely linked to its fitting, which, in turn, is based on order selection, these steps are carried out together. To define the AR model, $N_{\min}$ comes in handy, because it has already been calculated as an adequate time resolution. As a conservative approach, this number of points is increased by a factor of 2.5 in this work, leading to $N_{\min} = 5000$. By doing so, it is also possible to comprise different features over a longer period of time, thus providing a source of heterogeneity to the model. Figure 44 presents the results for the k vs AIC, BIC or MSE criteria, considering the two previously studied signals, in the interictal (Fig. 44A) and ictal conditions (Fig. 44B). Note that, as the number of k increases, all of the measures for the criteria decrease. Additionally, the difference between previous and past values tends to become less and less abrupt, indicating that the $\text{AR}(k)$ coefficients of higher order have a weaker effect in improving significantly the quality of the model. At last, both criteria provide similar results, which is evidenced by the superposition of both curves.

From the same curves, $k = 6$ has been selected for specific reasons: *i*) as mentioned, the decrease after $k = 6$ is smoother, less steep; *ii*) for higher values of k , some coefficients for the interictal model may assume a magnitude such that $|\phi| > 1$, which theoretically is not adequate due to the stationarity assumption (Fox, 2015); *iii*) the main goal is to keep both models as simple as possible. It is worth mentioning that, for both conditions, the overall MSE is less than 0.05%, indicating a good representation of both spiking activities. Figure 44 also shows the models obtained for both conditions considering $k = 6$. Overall, the AR models capture well the dynamics involved in the signals, from steadier behaviors, as the fluctuations around the baselines close to zero, to the abrupt changes that arise as spikes occur. Further results concerning the autocorrelation functions of the residuals are presented in Final Remarks, where similar conclusions can be drawn. Furthermore, the six coefficients found are different between the conditions. This result is important because it provides evidence that relatively simple models, as autoregressive ones, might be an interesting option to describe and distinguish types of seizures, thus providing patient-specific models with their own features.

Figure 44 – **Reference II and PIS signals from SUB and their respective AR models obtained after order selection based on the AIC/BIC/MSE criteria.** Although the best order of the model is supposed to be at the global minimum on the k vs AIC/BIC plan, $k = 6$ is chosen to make the model as simple as possible; besides, after 6 there is a less steep reduction in the AIC/BIC values, as well as a stabilization of the MSE. **(A)** contains the results for the II case whereas **(B)** contains the results for the PIS case: blue solid lines (—) represent the reference II/PIS signals; red dashed lines (---) represent the respective fitted $AR(k = 6)$ models. Order selection: blue solid lines with square markers (—□—) indicate AIC curves; red solid lines with star markers (—★—) indicate BIC curves.

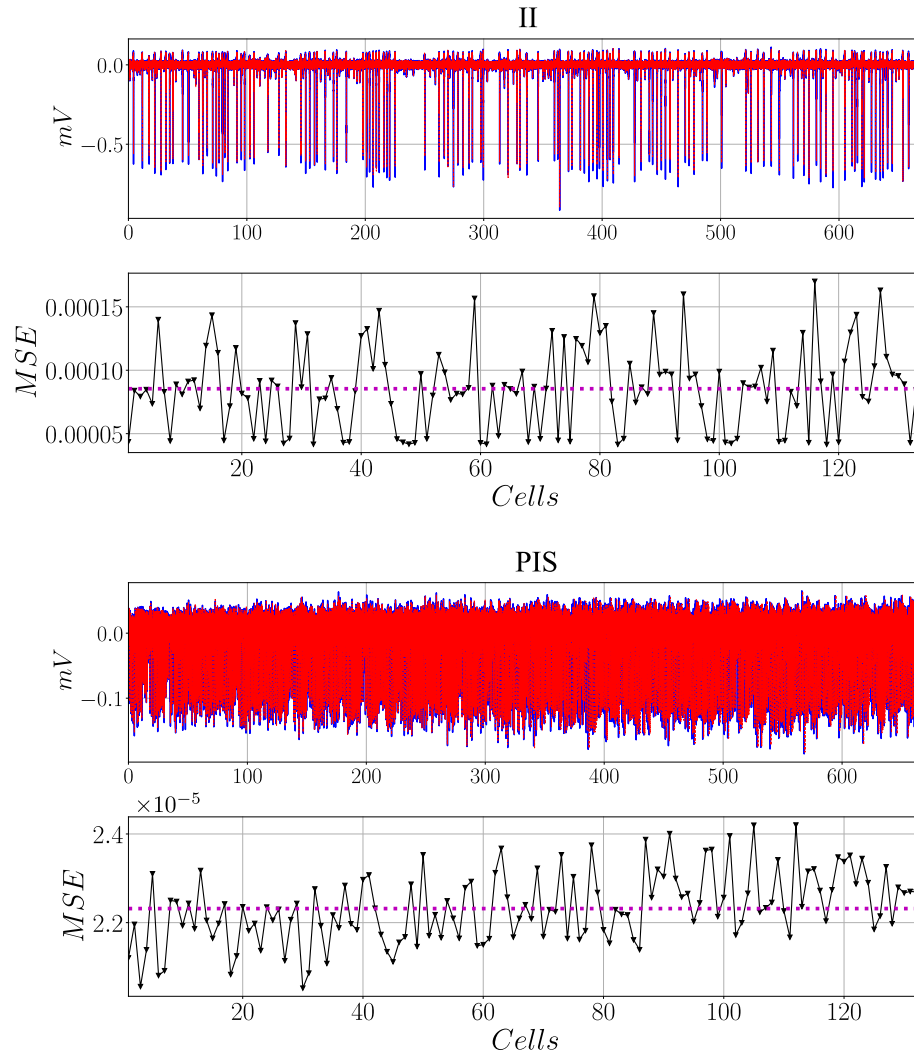


Source: Own authorship.

Concerning model extension, this step comprises extending $AR(k)$ model to more samples from the measured signal. That is, if $N_{\min}$ samples were used to fit it, $N > N_{\min}$ samples are now included. In practice, since it is not feasible to measure an infinite time of epileptiform activity, this strategy is useful to extend the fitted model to future time instants. Naturally, this extension involves errors; however, they do not significantly compromise the system identification approach in this chapter. Once the $AR(k)$ has been obtained considering $N_{\min}$, the same equations can be applied to the remaining samples of the whole time series ($N > N_{\min}$). Fig. 45 presents both AR models fitted to their respective signals (interictal and ictal), as well as their MSE over time. To obtain this error, equally spaced moving windows of size $N_{\min}$ were taken as references so that MSE could be calculated for each of them. The errors exhibit a quite regular behavior, whose

means are below 0.01%, the value that was previously found during order selection. This result is important especially envisioning more realistic practical situations, where storing an infinite number of samples is not feasible. Therefore, epochs of interictal or ictal signatures can be acquired to be used as templates for the AR models, and then used for the upcoming brain activities.

Figure 45 – **Model extensions calculated for the whole time series based on the AR models found using the first $N_{\min}$ samples.** The coefficients of the AR model are calculated for the first time window of $N_{\min}$ samples, then reapplied to the remaining ones, suggesting that there the pattern is maintained over the whole signal and extension can indeed be performed. Blue solid lines (—) indicate the filtered downsampled signals; red dashed lines (--) indicate the fitted models; magenta dotted lines (...) indicate the mean values of the MSE. Each cell contains $N_{\min}$ samples.



Source: Own authorship.

6.2.3 Discrete and continuous state-space definition (DSS/CSS)

Once the AR models are properly obtained, they can be converted into state-space notation according to the difference equation $\mathbf{x}_k'$ in function of the states $\mathbf{x}_k$ (which contains the dynamic matrix composed of the AR coefficients), and the measurable activity in the time domain, represented by $\mathbf{y}_k$ (Durbin; Koopman, 2012):

$$\underbrace{\begin{bmatrix} y_n \\ y_{n-1} \\ \vdots \\ y_{n-k+2} \\ y_{n-k+1} \end{bmatrix}}_{\mathbf{x}_k'} = \underbrace{\begin{bmatrix} \phi_0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}}_{\mathbf{b}} + \underbrace{\begin{bmatrix} \phi_1 & \phi_2 & \dots & \phi_{k-1} & \phi_k \\ 1 & 0 & \dots & 0 & 0 \\ 0 & 1 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}}_{\mathbf{A}^{\{d\}}} \underbrace{\begin{bmatrix} y_{n-1} \\ y_{n-2} \\ y_{n-3} \\ \vdots \\ y_{n-k} \end{bmatrix}}_{\mathbf{x}_k} + \underbrace{\begin{bmatrix} \varepsilon_1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}}_{\boldsymbol{\varepsilon}_k} \quad (98)$$

$$\mathbf{y}_k = \underbrace{\begin{bmatrix} 1 & 0 & 0 & \dots & 0 \end{bmatrix}}_{\mathbf{C}} \mathbf{x}_k \quad (99)$$

where $\mathbf{A}^{\{d\}}$ is the discrete SS model and $\mathbf{C}$ is the matrix corresponding to the measurable states in time – in this case, only the first one, y_n , can actually be measured, whereas the remaining ones are delayed states, thus not having a specific physical meaning. Since low-frequency components are filtered out, $\mathbf{b} = 0$. Besides, this AR modeling identifies the discrete plant and the error is evaluated a posteriori. In this sense, in practice $\boldsymbol{\varepsilon}_k = 0$ is adopted for design purposes.

The previous step presents the AR model in terms of a difference equation, which is a common practice for a one-step ahead prediction, for example (Ljung, 1998). Although digitized signals are finite and taken as an ensemble of samples, a more realistic approach is to consider a continuous-time model that accounts for all time instants, as usually done in engineering applications (Tanaka; Wang, 2004; Ogata, 2010). Besides, because the application proposed in this work requires observers and controllers, a numerical integration procedure is carried out in SS notation, which also justifies the need for a continuous-time plant. For this purpose, the formulation becomes (Shieh; Wang; Yates, 1980; Åström; Wittenmark, 2013):

$$\bar{\mathbf{A}}^{\{c\}} = 2f_s \left[\mathbf{R} + \frac{1}{3}\mathbf{R}^3 + \frac{1}{5}\mathbf{R}^5 + \dots + \frac{1}{p}\mathbf{R}^p \right] \quad (100)$$

where $\bar{\mathbf{A}}^{\{c\}}$ is the continuous-time model, $\mathbf{R} = (\mathbf{A}^{\{d\}} - \mathbf{I})(\mathbf{A}^{\{d\}} + \mathbf{I})^{-1}$ and $\mathbf{I}$ is an identity matrix of the same size as $\mathbf{A}^{\{d\}}$. By adopting the Direct Truncation Method (Shieh;

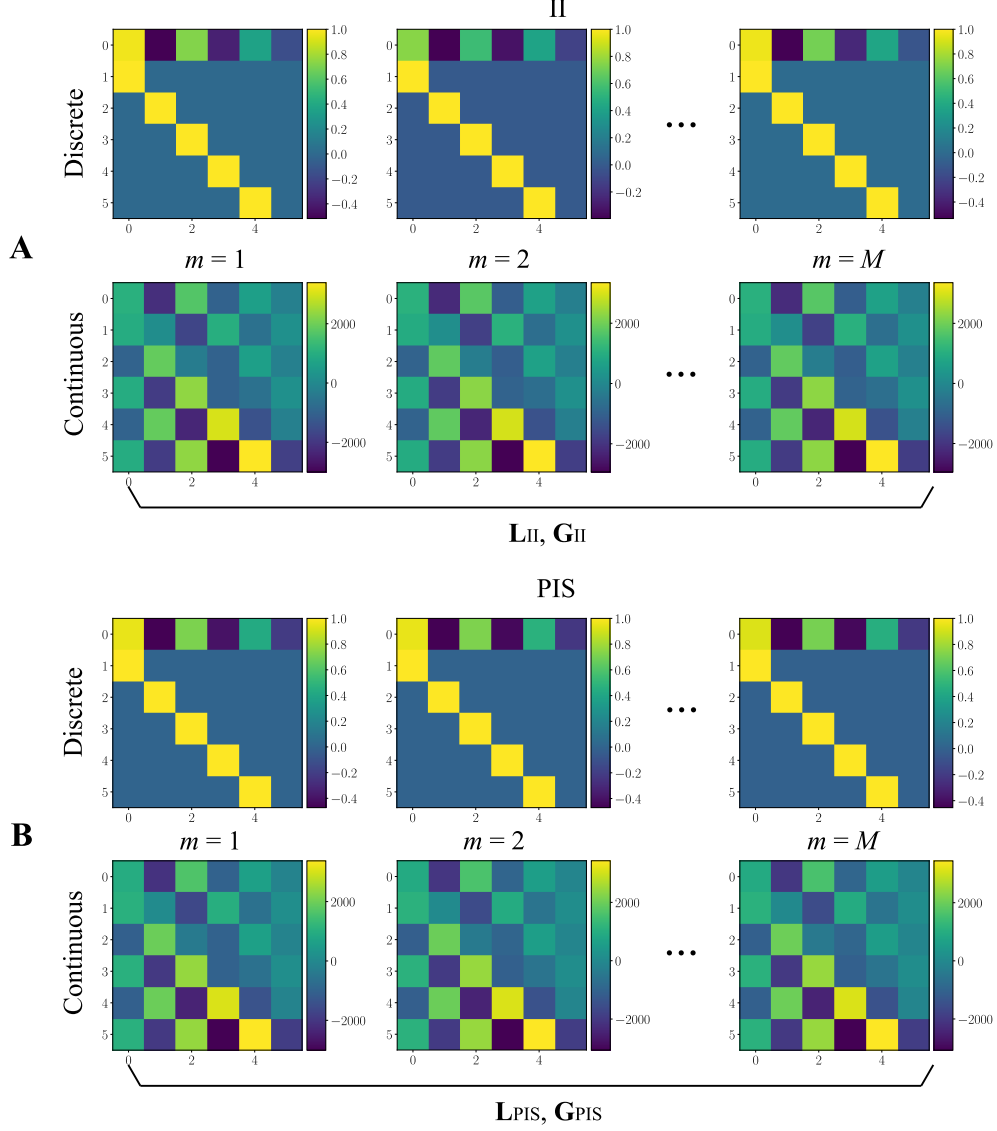
Wang; Yates, 1980), the continuous-time model can be approximated, for simplicity, by:

$$\bar{\mathbf{A}}^{\{c\}} \cong 2f_s(\mathbf{A}^{\{d\}} - \mathbf{I})(\mathbf{A}^{\{d\}} + \mathbf{I})^{-1} \quad (101)$$

Note that this model avoids terms of higher order, thus reducing the magnitude of the elements in the continuous-time matrix. It can be further adapted by considering a scaling factor such that $\mathbf{A}^{\{c\}} = \frac{1}{\varsigma_1} \bar{\mathbf{A}}^{\{c\}}$, where $\varsigma_1 \neq 0$. This is particularly interesting for some reasons: (1) local or quasi-non-stationary behavior of the signals leads to higher AR coefficients in the discrete model (Fox, 2015), which in turn is reflected on the continuous one; thus, scaling down the models is proposed in this chapter to mitigate this problem; (2) this problem is endorsed by the sampling frequency of the signals, which is considerably high even after downsampling (1 kHz) due to the time scale of neuron firing being relatively fast; (3) since the proposed approach focuses on AR models of low order, local fluctuations may not be captured by them, which means that the difference between the dynamics of the recording being read and the one reconstructed by the identified AR model may not be compensated for by the gains of the observer.

Figure 46 presents the matrices for the discrete-time models (Eq. 118), obtained directly from the AR coefficients, and the continuous-time models (Eq. 101), after the appropriate conversion. For illustration purposes, only the $m = 1, 2, M$ models are shown, i.e., the ones obtained from the two first time windows and the last one. Light colors indicate that the magnitude of the element inside a matrix increases positively, whereas cold colors indicate this magnitude increases negatively. All $m = 1, 2, \dots, M$ together in the continuous form are used to design the gains of both observer and controller for one of the proposed schemes: hybrid ($\mathbf{L}_{II}$ and $\mathbf{G}_{II}$, Fig. 46A) and non-hybrid ($\mathbf{L}_{PIS}$ and $\mathbf{G}_{PIS}$, Fig. 46B). In this way, single gains assure dynamic stability when applied to the whole signal. Note that their structure is quite similar to each other, regardless of the condition, mostly having magnitudes of the type $|\phi| < 1$ (for discrete models), which is desired in the case of AR modeling (Fox, 2015).

Figure 46 – **Discrete and continuous dynamic matrices obtained from the AR coefficients in state-space notation.** (A) and (B) represent $\mathbf{A}_m^{\{d\}}$ and $\mathbf{A}_m^{\{c\}}$, from Eqs. 98 and 100, respectively. The set of matrices $\mathbf{A}_m^{\{c\}}$, $m = 1, 2, \dots, M$, is used to compute single gains for the observer ($\mathbf{L}$) and controller ($\mathbf{G}$) in one of the two conditions (II or PIS). For illustration purposes, only the $m = 1, 2, M$ models are shown, i.e., the ones obtained from the two first time windows and the last one.



Source: Own authorship.

For clarity of understanding, Table 6 shows the AR coefficients for some of the aforementioned matrices. There are differences from the coefficients calculated in both conditions, which indicates that AR models can capture the dynamic transitions inherent to the real signals, which is reflected on their coefficients. This distinction is particularly evidenced by the fluctuation in the values between each condition, especially for II, where the first term (ϕ_1) is less stable across the windows presented (characterizing the irregular pattern of II compared to a more regular PIS activity (Araújo et al., 2022)). This

characteristic is specific to this type of modeling and has been used in pattern recognition approaches involving, for instance, structural health monitoring (Yao; Pakzad, 2012; Entezami; Shariatmadar, 2018; Yang; Lam, 2019; Yano et al., 2021) as well as analysis and validation of computational models in describing II and PIS activities (Araújo et al., 2022), since the AR coefficients are sensitive to changes in the signal dynamics (Entezami; Shariatmadar, 2018).

Table 6 – **Coefficients for AR($k = 6$) models obtained for the SUB signal in the interictal (II) and periodic ictal spiking (PIS) conditions.** Means are calculated considering all of the time windows ($m = 1, 2, 3, \dots, M$), not only the ones presented. Each line corresponds to the first line of the matrices (discrete case) from Fig. 46. The table is restricted for illustration purposes. For further results, please see Final Remarks.

Time Window (II)	ϕ_1	ϕ_2	ϕ_3
$m = 1$	0.96601012	-0.51796275	0.71708485
$m = 2$	0.74988617	-0.39621265	0.56154335
$m = M - 1$	0.66563797	-0.43145048	0.51627098
$m = M$	0.96324516	-0.53397719	0.67803996
Time Window (II)	ϕ_4	ϕ_5	ϕ_6
$m = 1$	-0.37918536	0.35394271	-0.15192228
$m = 2$	-0.32536739	0.41139278	-0.12343279
$m = M - 1$	-0.35454543	0.36084365	-0.17006476
$m = M$	-0.35530265	0.36815283	-0.13206332
Time Window (PIS)	ϕ_1	ϕ_2	ϕ_3
$m = 1$	0.94856822	-0.47273578	0.70742222
$m = 2$	0.95015544	-0.47088456	0.71662639
$m = M - 1$	0.88594754	-0.37282567	0.61554666
$m = M$	0.92252666	-0.45359902	0.69951633
Time Window (PIS)	ϕ_4	ϕ_5	ϕ_6
$m = 1$	-0.40025955	0.42473779	-0.21686942
$m = 2$	-0.43850637	0.46697371	-0.23336034
$m = M - 1$	-0.35305278	0.44163889	-0.22369959
$m = M$	-0.42437682	0.46004082	-0.21459317

In fact, the authors used the same signals present in this work, and by applying non-linear/nonparametric classification techniques, such as logistic regression and confidence intervals, fairly good classifications were obtained (Araújo et al., 2022). Moreover, within each condition, the coefficients are relatively bounded over the time windows (for further results, please see Final Remarks), which suggests that not only the patterns of II/PIS are sustained differently, but also that the coefficients do reflect this consistency.

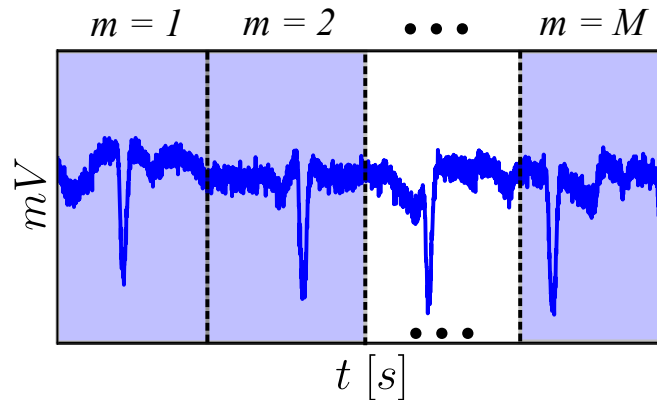
6.2.4 Design of the observer

Suppose that, for each of the $m = 1, 2, \dots, M$ time windows of size $N_{\min}$ presented in Fig. 47, there exists an identified plant: for $m = 1$, $\mathbf{A}_m^{\{c\}} = \mathbf{A}_1^{\{c\}}$ during the $N_{\min}$ first points; for $m = 2$, $\mathbf{A}_m^{\{c\}} = \mathbf{A}_2^{\{c\}}$ in the interval $]N_{\min}, 2N_{\min}]$, and so forth. Then, the local models in state-space notation become:

$$\begin{cases} \dot{\mathbf{x}}(t) = \mathbf{A}_m^{\{c\}} \mathbf{x}(t), & m = 1, 2, \dots, M \\ \mathbf{y}(t) = \mathbf{C} \mathbf{x}(t) \end{cases} \quad (102)$$

where $t = n/f_s$ represents the continuous time variable, such that $\mathbf{x}(n/f_s) \cong \mathbf{x}(t)$ (Shieh; Wang; Yates, 1980). This system can be understood as the mathematical representation of the real PIS/II signatures in time. However, controllers cannot be directly applied to it since the signals are only samples stored computationally, not dynamic systems. In other words, there is no access to the true system set of deterministic equations that describes the electrophysiological brain activity in hippocampal subfields or as a whole, only the signals that have been previously measured. To tackle this problem, the concept of observability needs to be applied.

Figure 47 – **Illustration of the time windows used (whose minimum size is $N_{\min}$) to obtain the AR models and to which the observers and controllers are applied, ranging from $m = 1, 2, \dots, M$.** For each time window, $\mathbf{A}_m^{\{c\}}$ is defined based on the state-space representation in continuous time and, as the observer/controller proceeds in time, models are then switched to adequately represent the window. The gains, however, are single for the whole signal: $\mathbf{G}$ and $\mathbf{L}$.



Source: Own authorship.

As previously discussed, although $\mathbf{C} = [1 \ 0 \ 0 \ \dots \ 0]^T$ is consistent with the fact that only the first state is measurable and the other ones are merely artificial states, for purposes of recreating the signal in time and applying a control input afterwards, it is neces-

sary to implement an observer such that the numerical integrator recreates its behavior artificially. For this purpose, a “copy” of the identified plant is required, represented by the following equation (Tanaka; Wang, 2004; Ogata, 2010):

$$\begin{cases} \hat{\mathbf{x}}(t) = \mathbf{A}_m^{\{c\}} \hat{\mathbf{x}}(t) + \mathbf{L}[\mathbf{y}(t) - \hat{\mathbf{y}}(t)], & m = 1, 2, \dots, M \\ \hat{\mathbf{y}}(t) = \mathbf{C} \hat{\mathbf{x}}(t) \end{cases} \quad (103)$$

During the numerical integration in the time domain, the matrix $\mathbf{L}$ weighs the relative difference between the output of the stored PIS signal $\mathbf{y}(t)$ and the estimated output $\hat{\mathbf{y}}(t)$ (which is in fact the recreated signal) such that, as $\hat{\mathbf{y}}(t) \rightarrow \mathbf{y}(t)$, $\mathbf{L}[\mathbf{y}(t) - \hat{\mathbf{y}}(t)] \rightarrow 0$, and the copy becomes an exact approximation of the actual output. In practice, $\mathbf{y}(t)$ is not a stored signal, but the real activity measured, for instance, by electrodes positioned on specific brain regions. To assess how accurate this approximation is, the error can be calculated by $\mathbf{e}(t) = \mathbf{x}(t) - \hat{\mathbf{x}}(t)$ (Tanaka; Wang, 2004; Ogata, 2010). By taking the derivative of this equation, the error dynamics becomes (Ogata, 2010):

$$\dot{\mathbf{e}}(t) = (\mathbf{A}_m^{\{c\}} - \mathbf{L}\mathbf{C})\mathbf{e}(t), \quad m = 1, 2, \dots, M \quad (104)$$

It is thus expected that $\dot{\mathbf{e}}(t) \rightarrow 0$ as $t \rightarrow mN_{\min}/f_s$, according to each $m = 1, 2, \dots, M$. Although the time windows switch over time, it is an interesting strategy to obtain a single $\mathbf{L}$ that is capable of observing the whole signal, i.e., one that is valid for all time windows. To do so, it is necessary that this gain be stable across all the identified plants $\mathbf{A}_m^{\{c\}}$. This issue is addressed in this chapter by taking advantage again of the concept of FTS Modeling (FTSM), which states that a nonlinear plant can be exactly reconstructed using linear submodels represented by the so-called Linear Matrix Inequalities (LMIs) (Tanaka; Wang, 2004). LMIs can be formulated considering the stability criterion by Luapunov theory (Slotine; Li et al., 1991) applied to the error dynamics:

$$V(\mathbf{e}(t)) = \mathbf{e}(t)^T \mathbf{P}_{\text{obs}} \mathbf{e}(t) > 0 \quad (105)$$

whose derivative is

$$\dot{V}(\mathbf{e}(t)) = \dot{\mathbf{e}}(t)^T \mathbf{P}_{\text{obs}} \mathbf{e}(t) + \mathbf{e}(t)^T \mathbf{P}_{\text{obs}} \dot{\mathbf{e}}(t) < 0 \quad (106)$$

By substituting Eq 104 into the derivative, it follows that:

$$\mathbf{e}(t)^T [(\mathbf{A}_m^{\{c\}T} - \mathbf{C}^T \mathbf{L}^T) \mathbf{P}_{\text{obs}} + \mathbf{P}_{\text{obs}} (\mathbf{A}_m^{\{c\}} - \mathbf{C} \mathbf{L})] \mathbf{e}(t) < 0, \quad m = 1, \dots, M \quad (107)$$

Since the norm of the error remains positive still convergence towards zero, the equation

above can be rewritten as

$$(\mathbf{A}_m^{\{c\}T} - \mathbf{C}^T \mathbf{L}^T) \mathbf{P}_{\text{obs}} + \mathbf{P}_{\text{obs}} (\mathbf{A}_m^{\{c\}} - \mathbf{C} \mathbf{L}) < 0, m = 1, \dots, M \quad (108)$$

Therefore, in the case of the observers, the LMIs are stated as the following optimization problem (Tanaka; Wang, 2004):

$$\mathbf{A}_m^{\{c\}T} \mathbf{P}_{\text{obs}} + \mathbf{P}_{\text{obs}} \mathbf{A}_m^{\{c\}} - \mathbf{M} \mathbf{C} - \mathbf{C}^T \mathbf{M}^T < \mathbf{0}, m = 1, \dots, M \quad (109)$$

where $\mathbf{L} = \mathbf{M} \mathbf{P}_{\text{obs}}^{-1}$ and $\mathbf{P}_{\text{obs}}$ is a positive-definite matrix (Slotine; Li et al., 1991). In this optimization problem, all of these inequalities are solved simultaneously to find $\mathbf{L}$ before the numerical integration in the domain. If there exists a solution, then there exists $\mathbf{M}$, thus also assuring the existence of $\mathbf{L}$. Once $\mathbf{L}$ is found, it is applied in the state-space equation from Eq. 103. These inequalities are formulated based on the Lyapunov theory, so solving them implies that there exist sufficient conditions that assure stability (Slotine; Li et al., 1991). An important difference is that, while FTSM assumes that nonlinear functions can be rewritten in terms of linear combinations between their maximum and minimum values (Tanaka; Wang, 2004), the present approach only considers the several linear models obtained from the CSS AR identified models. It is expected that if $\mathbf{L}$ exists, it can be applied to the whole signal observing it every m time window as the models switch over time. ‘

6.2.5 Design of the controller

Considering again the $m = 1, 2, \dots, M$ time windows observed and recreated by the responses of the observer, a control input can be applied to each of them according to the following equation, as carried out for the Epileptor model:

$$\begin{cases} \hat{\mathbf{x}}(t) = \mathbf{A}_m^{\{c\}} \hat{\mathbf{x}}(t) + \mathbf{L}[\mathbf{y}(t) - \hat{\mathbf{y}}(t)] + \mathbf{B} \mathbf{u}(t), & m = 1, 2, \dots, M \\ \hat{\mathbf{y}}(t) = \mathbf{C} \hat{\mathbf{x}}(t) \end{cases} \quad (110)$$

where $\mathbf{u}(t)$ is the input entry for control (which in this case represents an active electrical stimulus, in terms of volts) and $\mathbf{B}$ is the input matrix, whose elements can be set according to the design requirements or applications. The input $\mathbf{u}(t)$ has been proposed to be of the following form, as done for the Epileptor model as well:

$$\mathbf{u}(t) = -\mathbf{G}[\hat{\mathbf{x}}(t) - \mathbf{x}_h] = -\mathbf{G} \mathbf{x}(t) + \mathbf{G} \mathbf{x}_h \quad (111)$$

Note that it is actually composed of two superposed stimuli: the negative term attempts to attenuate the undesired dynamics while the positive term induces the desired one, based

on a predefined non-seizure behavior $\mathbf{x}_h$ and gains coming from the matrix $\mathbf{G}$. Thus, the system can be rewritten as:

$$\begin{cases} \hat{\mathbf{x}}(t) = \mathbf{A}_m^{\{c\}} \hat{\mathbf{x}}(t) + \mathbf{L}[\mathbf{y}(t) - \hat{\mathbf{y}}(t)] - \mathbf{B}\mathbf{G}[\hat{\mathbf{x}}(t) - \mathbf{x}_h], & m = 1, 2, \dots, M \\ \hat{\mathbf{y}}(t) = \mathbf{C}\hat{\mathbf{x}}(t) \end{cases} \quad (112)$$

If $\mathbf{x}_h = 0$, then the controller supposes the stability point is a zero baseline; otherwise, if $\mathbf{x}_h \neq 0$, it attempts to drive the current state to the desired condition while simultaneously mitigating the undesired epileptiform activity. Recall that $\mathbf{x}_h$ is taken as a reference signal in the II condition, with the first state being one of its samples at each time instant and the remaining ones equal to zero. To be consistent with the output matrix $\mathbf{C}$, it is considered as $\mathbf{B} = \text{diag}\{B_{11}, 0, 0, \dots, 0\}$, which means that the only target state (the one that actually receives an input) is the first one, whose magnitude can be conveniently adjusted.

Similarly, the design of the controller can also be carried out considering a single $\mathbf{G}$ for all of the $m = 1, 2, \dots, M$ time windows over time, thus assuring stability based on the Lyapunov criterion, but now considering the states, not the error dynamics: $V(\mathbf{e}(t)) = \mathbf{x}(t)^T \mathbf{P} \mathbf{x}(t) > 0$. By applying the same procedure described for the observer, the LMIs for the controller are (Tanaka; Wang, 2004):

$$\mathbf{A}_m^{\{c\}T} \mathbf{P} + \mathbf{P} \mathbf{A}_m^{\{c\}} - \mathbf{G}_x \mathbf{B} - \mathbf{B}^T \mathbf{G}_x^T < \mathbf{0}, \quad m = 1, \dots, M \quad (113)$$

where $\mathbf{G}_x = \mathbf{G} \mathbf{P}^{-1}$. Considering that the system of interest in this case where physical inputs are intended to be applied is a brain region, close attention must be paid to the intensity of the gain $\mathbf{G}$, so that it is properly delivered to suppress only the epileptiform activity with an acceptable input intensity. This can be carried out considering again the decay rate (Tanaka; Wang, 2004):

$$\mathbf{A}_m^{\{c\}T} \mathbf{P} + \mathbf{P} \mathbf{A}_m^{\{c\}} - \mathbf{G}_x \mathbf{B} - \mathbf{B}^T \mathbf{G}_x^T + 2\alpha \mathbf{P} < \mathbf{0}, \quad m = 1, \dots, M \quad (114)$$

In this chapter, a good trade-off between this parameter and $\mathbf{B}^1$ is analyzed. This set of inequalities, as well as the previous ones for the observer, can be simultaneously solved using specific optimization tools, such as YALMIP (Lofberg, 2004), for MATLAB, or PICOS (Sagnol; Stahlberg, 2012), for Python. Without loss of generality, the computational package adopted in this work is PICOS.

¹For purposes of design, matrix $\mathbf{B}$ can be any convenient matrix defined by the designer. The simplest one is the identity $\mathbf{B} = \mathbf{I}$, for example. However, to be consistent with the fact that only one state is measurable in this work, the application of the controller during numerical integration requires $\mathbf{B} = \text{diag}\{B_{11}, 0, 0, \dots, 0\}$. This approach is known as underactuation in the control engineering (Reyhanoglu et al., 1999).

6.2.6 Hybrid and non-hybrid observers and controllers

This chapter investigates the possibility of not only designing observers and controllers based on the epileptiform/PIS activity to suppress PIS activity, but also designing them using II activity and then applying them to attenuate PIS activities. This is regarded as an interesting study in the sense that one does not need to rely on awaiting seizures to occur to take action. The two types of designs carried out are: non-hybrid (design performed using PIS to suppress PIS) and hybrid (design performed using II to suppress PIS), respectively. Essentially, this implies that the internal dynamic structure of $\mathbf{A}_m^{\{c\}}$ changes according to the signal from which the AR models were obtained.

6.2.7 Remarks on the controller

The input can be adapted as (Bueno et al., 2014):

$$\mathbf{u}(t) = -\frac{1}{\varsigma_2}\mathbf{G}\mathbf{x}(t) + \frac{1}{\varsigma_3}\mathbf{G}\mathbf{x}_h \quad (115)$$

where $\varsigma_2, \varsigma_3 \neq 0$ are constants that are applied to tune its intensity. Therefore, during the time integration the controlling effect is given by:

$$\hat{\mathbf{x}}(t) = \frac{1}{\varsigma_1\varsigma_2\varsigma_3}\{[\varsigma_2\varsigma_3\bar{\mathbf{A}}_m^{\{c\}} - \varsigma_1\varsigma_3\mathbf{B}\mathbf{G}]\mathbf{x}(t) + \varsigma_1\varsigma_2\mathbf{B}\mathbf{G}\mathbf{x}_h\}, \quad m = 1, 2, \dots, M \quad (116)$$

In sum, the continuous-time models and control inputs are weighted over time normalized by the combined constants ς_i , $i = 1, 2, 3$. The simulations showed that this approach provides more flexibility for a finer tuning of the controller, especially considering the limited order of the AR model.

6.3 Simulation stage

This section comprises the results from the simulation of the action of the observer and controller proposed in this work. A fourth-order Runge-Kutta was applied as the numerical integrator, considering the time step equal to the one from the real signal (that is: $dt = 0.001$ s). This procedure is implemented on the Spyder platform, using Python 3.2, which is free and open-source.

6.3.1 Applying the observer and controller

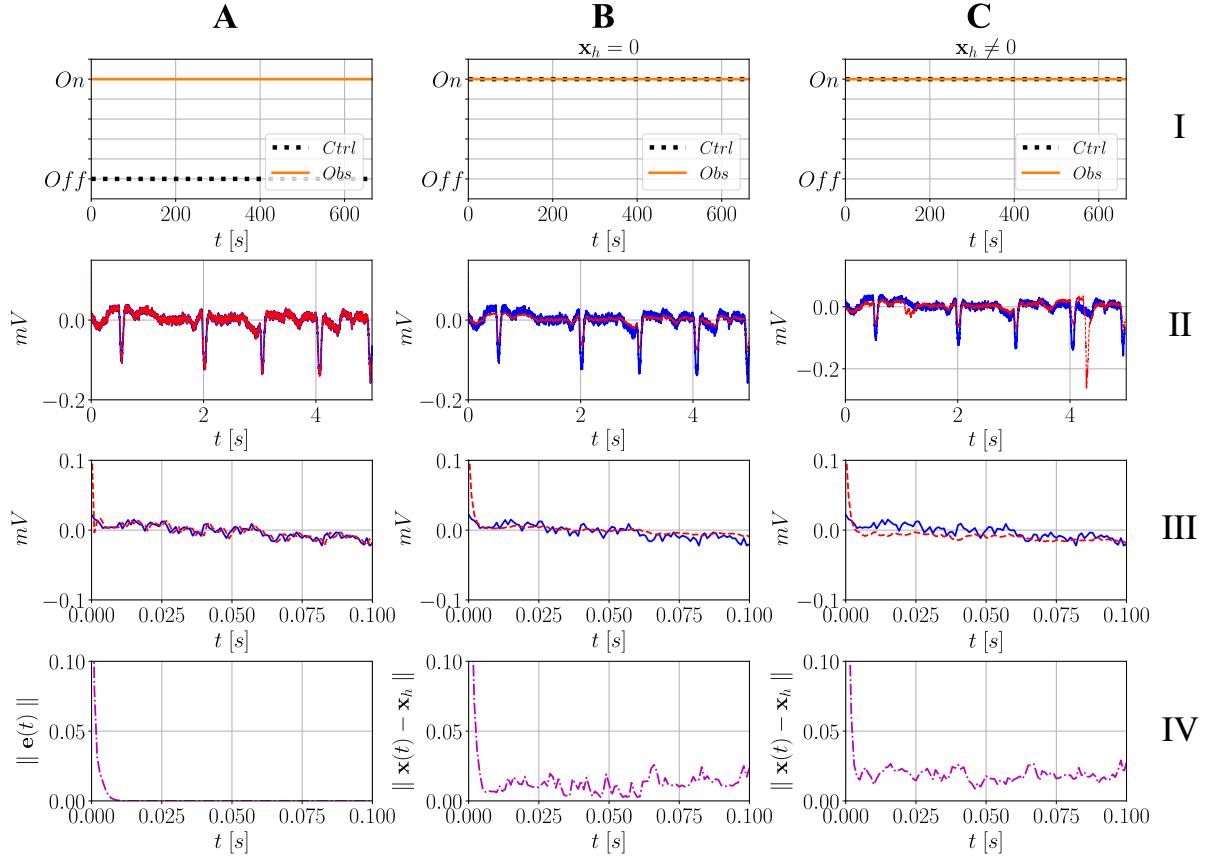
Figure 48 presents the results obtained after the application of both observer and controller. For the sake of understanding, it was divided into three parts showing the first 5 seconds of simulation (and a zoomed in pannel during the first 0.1s): for the first one (Fig. 48A), only the observer is activated while the controller is kept off. To verify the efficiency of the observer, the copy of the system is set with different initial conditions from the ones measured in the real system. It is expected that the gain $\mathbf{L}$ weighs the relative difference between states such that both time signatures converge. This is evidenced in the same by the fact that the error $\mathbf{e}(t) \rightarrow 0$ in a relative short time (first 0.1 seconds).

In this case, the numerical integrator reconstructs the stored signal computationally over time. In practice, however, the process of signal acquisition would be carried out from a real electrode, positioned on the brain region of interest. In other words, by designing a state observer, the real PIS/II activities can be reconstructed (or “observed”) artificially. It must be stressed that this process is different from simply recording the signals: if there were more states in vector $\hat{\mathbf{x}}(t)$, all of them would be recreated, regardless of their physical interpretation. Besides, this approach enables having an artificial dynamic model where control inputs can be applied.

Fig. 48B presents the case in which both observer and controller are activated from the beginning of the simulation, while setting $\mathbf{x}_h = 0$. This implies that the control attempts only to drive the system to a constant baseline around zero. Its action is efficient in attenuating the amplitudes of the spikes over time. Nonetheless, this is not the most realistic scenario, since it is desired not only to mitigate the PIS activity, but also drive the system back to the condition it was before a seizure started. Thus, the reference state must necessarily be of the type $\mathbf{x}_h \neq 0$, as presented in Fig. 48C. Note that not only are the amplitudes of the spikes mitigated (from the PIS activity), but the controller progressively delivers the reference input to bring the signal back to the II condition.

At last, considering the normalized Euclidean norms between the reference state $\mathbf{x}_h$ and actual states $\mathbf{x}(t)$, values fluctuate close to zero but do not reach this level in both applications of the controller. This is also expected, firstly because for $\mathbf{x}_h = 0$, the difference is calculated from the signal and zero, and since a complex activity is going on, a zero baseline is never achieved. Similarly, for $\mathbf{x}_h \neq 0$ the spikes are attenuated but not canceled, and since it is desired that $\mathbf{x} \rightarrow \mathbf{x}_h$, the progressive addition of the reference $\mathbf{x}_h$ to the controller makes it interact with the PIS activity reconstructed from the observer. The final result is not an exact version of the reference, but a close one. Therefore, it is expected that the controlled signal presents a similar behavior to the reference globally, not locally.

Figure 48 – **Action of the observer and controller over time and behavior of the error dynamics and Euclidean norms.** In (A), only the observer is activated while the controller is not. In (B), both are activated while setting $\mathbf{x}_h = 0$. In (C), both are activated while setting $\mathbf{x}_h \neq 0$. For the observer, $\mathbf{x}(0)$ (states of the real system) and $\hat{\mathbf{x}}(0)$ (states of the copy of the system) are set with different values and, as it progressively weighs the outputs $\hat{\mathbf{y}}$ and $\mathbf{y}$, the trajectories over time converge within a limited period of time. When $\mathbf{x}_h = 0$, the controller attenuates the epileptic spikes, but attempts to mitigate them towards zero. When $\mathbf{x}_h \neq 0$, in turn, it delivers an additional input to simultaneously attenuate these spikes while driving the system to the II condition. In this case $\mathbf{L}_{\text{PIS}}$ and $\mathbf{G}_{\text{PIS}}$ are used. Subfigures in columns II, III and IV are zoomed-in time windows of the beginning of the signals. Solid orange lines (—) indicate the activation of the observer; solid black dashed lines (--) indicate the activation of the controller; blue solid lines (—) indicate the measured signal; red dashed lines (--) indicate the reconstructed signal; magenta dash-dotted lines (— · —) indicate the error or Euclidean norm of each case.



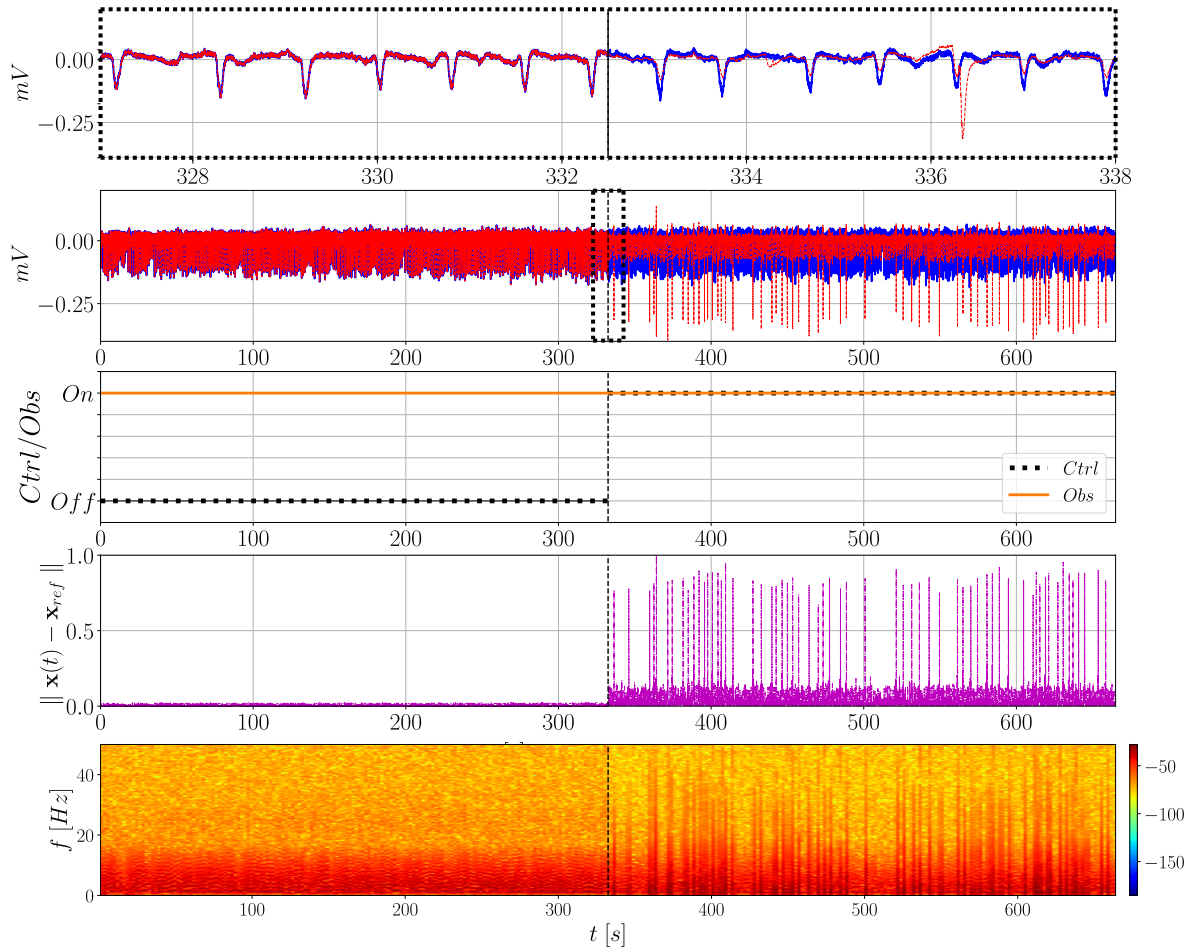
Source: Own authorship.

6.3.2 Non-hybrid controller

Figure 49 presents the action of both observer and controller, but now considering the whole signal from SUB. The observer remains activated all the time while the controller is only turned on at the middle of the signal (half of the entire time of simulation). In

the time domain, note that there is again a clear difference in the observed signal as soon as the controller is activated. The amplitude of the undesired activity (i.e., PIS) is significantly reduced and the controller keeps delivering the input signal to drive it back to the II condition ($\mathbf{x}_h$), which is indicated by the irregular spiking pattern of higher amplitude that arises.

Figure 49 – **Action of the observer and non-hybrid controller over time analyzed in terms of the normalized Euclidean norm $\|\mathbf{x}(t) - \mathbf{x}_{ref}\|$ and frequency content over time (spectrograms).** The overall effect is mitigation of the undesired peaks of the PIS activity and induction of the non-seizure dynamics to reestablish the II condition. The controller is activated at half of the entire time of the signal, whereas the observer remains on during all the time. In this case $\mathbf{L}_{PIS}$ and $\mathbf{G}_{PIS}$ are used. Before the controller is activated, $\mathbf{x}_{ref}$ is the PIS signal being observed; after it is activated, $\mathbf{x}_{ref}$ is the non-seizure II signal. Solid orange lines (—) indicate the activation of the observer; solid black dashed lines (—) indicate the activation of the controller; blue solid lines (—) indicate the measured signal; red dashed lines (—) indicate the reconstructed signal; magenta dash-dotted lines (—) indicate the Euclidean between measured and reconstructed/attenuated signal.



Source: Own authorship.

However, such a difference is not reflected on the Euclidean norm, as previously discussed, resulting in no significant improvement. By plotting the spectrogram it becomes clear that the uncontrolled signal has a similar frequency content pattern as the PIS signal, whereas the controlled one presents higher similarity with the II signal (Fig. 43). This is the global similar behavior expected when the controller is activated.

6.3.3 Hybrid controller

As part of the hybrid strategy also covered in this chapter, Fig. 50 presents similar results, but using $\mathbf{L}_{II}$ and $\mathbf{G}_{II}$, that is, both observer and controller are designed using a SUB signal in the II condition². When the controller is activated, the amplitude of the undesired activity is mitigated and the peaks of the reference signal can be seen standing out among the others, as previously. This indicates that the design can be carried out without the need of having epileptiform activity recorded, only the pre-ictal states. This is an interesting result aiming at practical applications, where seizures often occur spontaneously and unpredictably – which makes it difficult to measure them several times. For illustration purposes, the controller remained activated for half of the duration of the signal³.

6.3.4 Input stimulus

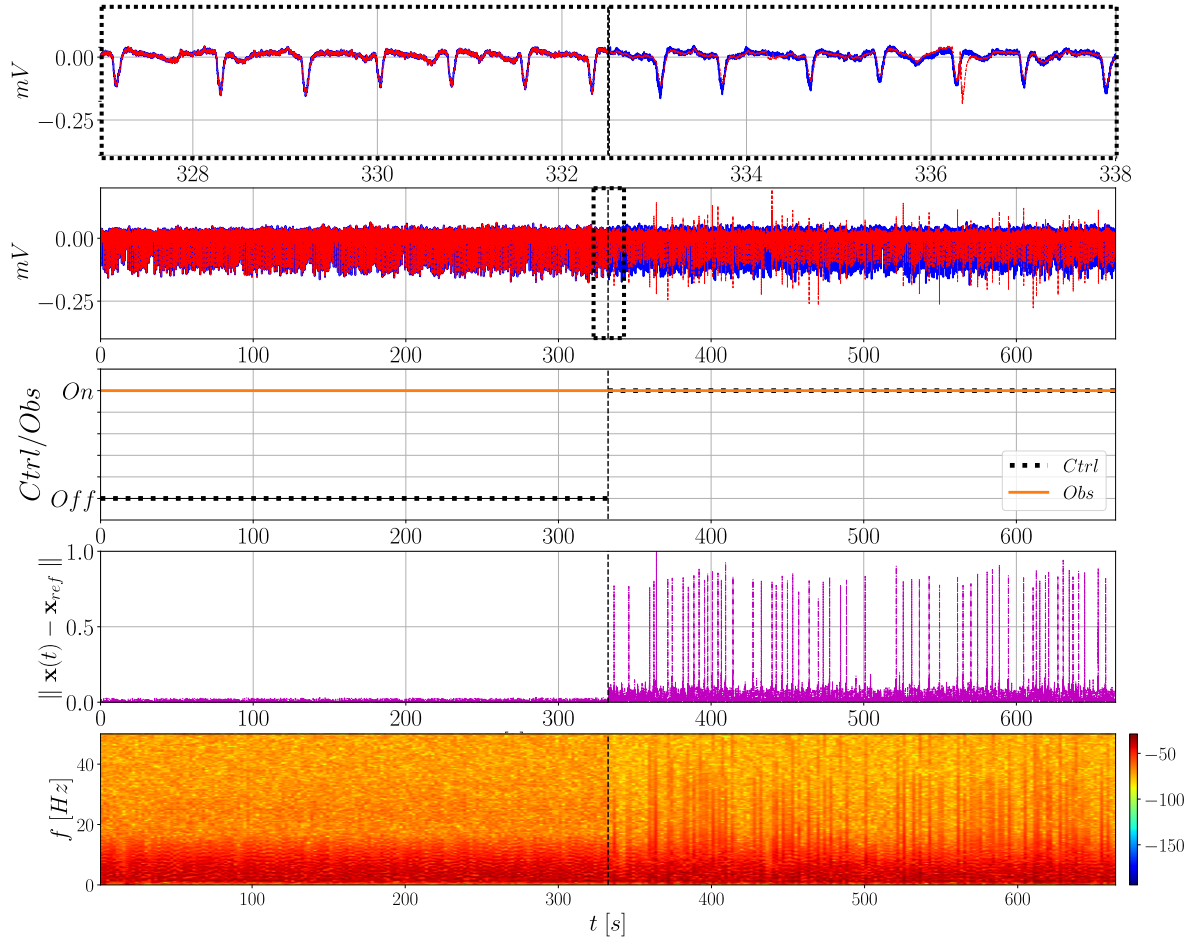
In practice, it is not expected to act for a long time since this might not be the ideal case considering that patients would have to wear devices from which the inputs are delivered, and also for economy reasons, because if the controller is activated for short periods time, not continuously, its lifespan is increased. Besides, its intensity must also be taken into account for the same reasons. In this sense, the amplitude of such inputs must be adequately tuned so as not to compromise the health of desired brain activities. Figure 51 presents the responses of the signals in time when the parameters of the controller (α and γ) are tuned to decrease the intensity of the input (for both hybrid and non-hybrid cases). For illustration purposes, only the first 20 seconds of activation (and zoomed in windows) are shown. For the non-hybrid controller (Fig. 51A), when the amplitude is limited it changes from its previous highest peak (based on the time window analyzed) at $\sim 1480\text{mV}$ to 740mV (in modulus), a reduction of 50%. Naturally, this implies that amplitudes of the undesired activity are not as efficiently mitigated as

²A different signal from $\mathbf{x}_h$ is used to match the amplitude of the epileptiform activity without significantly increasing the gains of the controller. Further details can be found in Final Remarks

³In approaches where the equations of the system are deterministic, such as the one applied to Epileptor, the control can be activated for a few seconds to suppress a seizure. In this chapter, only the signals are known, that is, the partial representation in time of a broader system, so control inputs that last longer must be applied to better visualize their effects. This is also discussed in detail in the next sections.

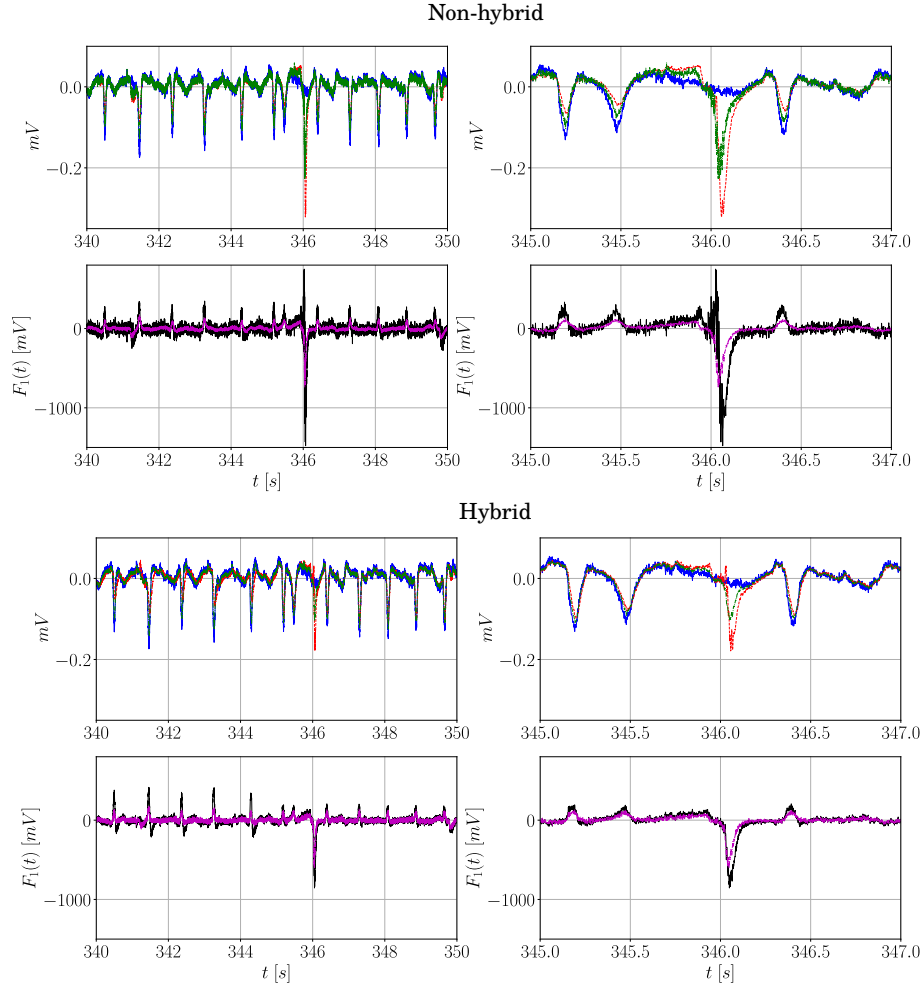
before, but a considerable attenuation can be seen, specially in the zoomed in epochs of the signal.

Figure 50 – **Action of the observer and hybrid controller over time analyzed in terms of the normalized Euclidean norm $\| \mathbf{x}(t) - \mathbf{x}_{ref} \|$ and frequency content over time (spectrograms).** The overall effect is mitigation of the undesired peaks of the PIS activity and induction of the non-seizure dynamics to reestablish the II condition. The controller is activated at half of the entire time of the signal, whereas the observer remains on during all the time. In this case $\mathbf{L}_{II}$ and $\mathbf{G}_{II}$ are used. Before the controller is activated, $\mathbf{x}_{ref}$ is the PIS signal being observed; after it is activated, $\mathbf{x}_{ref}$ is the non-seizure II signal. Solid orange lines (—) indicate the activation of the observer; solid black dashed lines (—) indicate the activation of the controller; blue solid lines (—) indicate the measured signal; red dashed lines (—) indicate the reconstructed signal; magenta dash-dotted lines (—) indicate the Euclidean between measured and reconstructed/attenuated signal.



Source: Own authorship.

Figure 51 – **Effect of tuning α and B_{11} on the input response of the signal in the time domain.** By tuning these parameters, the intensity of the input can be modulated so that an excessive amplitude is avoided. The attenuation effect is given by canceling out the peaks of the PIS activity while simultaneously introducing aperiodic peaks of the II activity. **(A)** contains results for the non-hybrid case, whereas **(B)** contains the results for the hybrid case: blue solid lines (—) represent the reference PIS signal (from SUB); red dashed lines (- -) represent the controlled signal before tuning the parameters; green dash-dotted lines (-.-) represent the controlled signal after tuning them. The input forces are indicated as: black solid lines (—) for the control input without tuning and magenta dash-dotted lines (-.-) for the same input after tuning. In this case $\mathbf{L}_{\text{PIS}}$ and $\mathbf{G}_{\text{PIS}}$ and $\mathbf{L}_{\text{II}}$ and $\mathbf{G}_{\text{II}}$ are used, respectively. The parameters before tuning are: $\alpha = 1680$, $1/\varsigma_2 = 1$ and $1/\varsigma_3 = 1.55$ (non-hybrid), and $\alpha = 810$, $1/\varsigma_2 = 1$ and $1/\varsigma_3 = 2$ (hybrid). The parameters after tuning are: $\alpha = 840$ and $1/\varsigma_2 = 1$ and $1/\varsigma_3 = 1.55$ (non-hybrid), and $\alpha = 675$ and $1/\varsigma_2 = 1$ and $1/\varsigma_3 = 1.5$ (hybrid). For all cases, $1/\varsigma_1 = 1/10$.



Source: Own authorship.

Concerning the shape of the control stimulus, two components can be distinguished: the first one acts in the opposite sense of the PIS activity, presenting spikes of inverse

magnitude; the second one, in turn, is responsible for delivering spikes of irregular time intervals (similar to the II activity). This finding is consistent with previous observations made in the literature, where continuous periodic stimulation/trains of pulses (Velasco et al., 2001; Tellez-zenteno et al., 2006; Velasco et al., 2007) or randomly-spaced ones (Cota et al., 2009) have been relatively efficient in suppressing seizures. Thus, an interesting investigation in practice would be the use of combined types of stimulation to verify their controlling effects in real epileptiform activity. As for the inputs of the hybrid controller (Fig. 51B), the main difference compared to the first one is that its amplitude decreases from $\sim 850\text{mV}$ to 595mV (a reduction of 30% in modulus). For both of them, a significant attenuation is observed nonetheless.

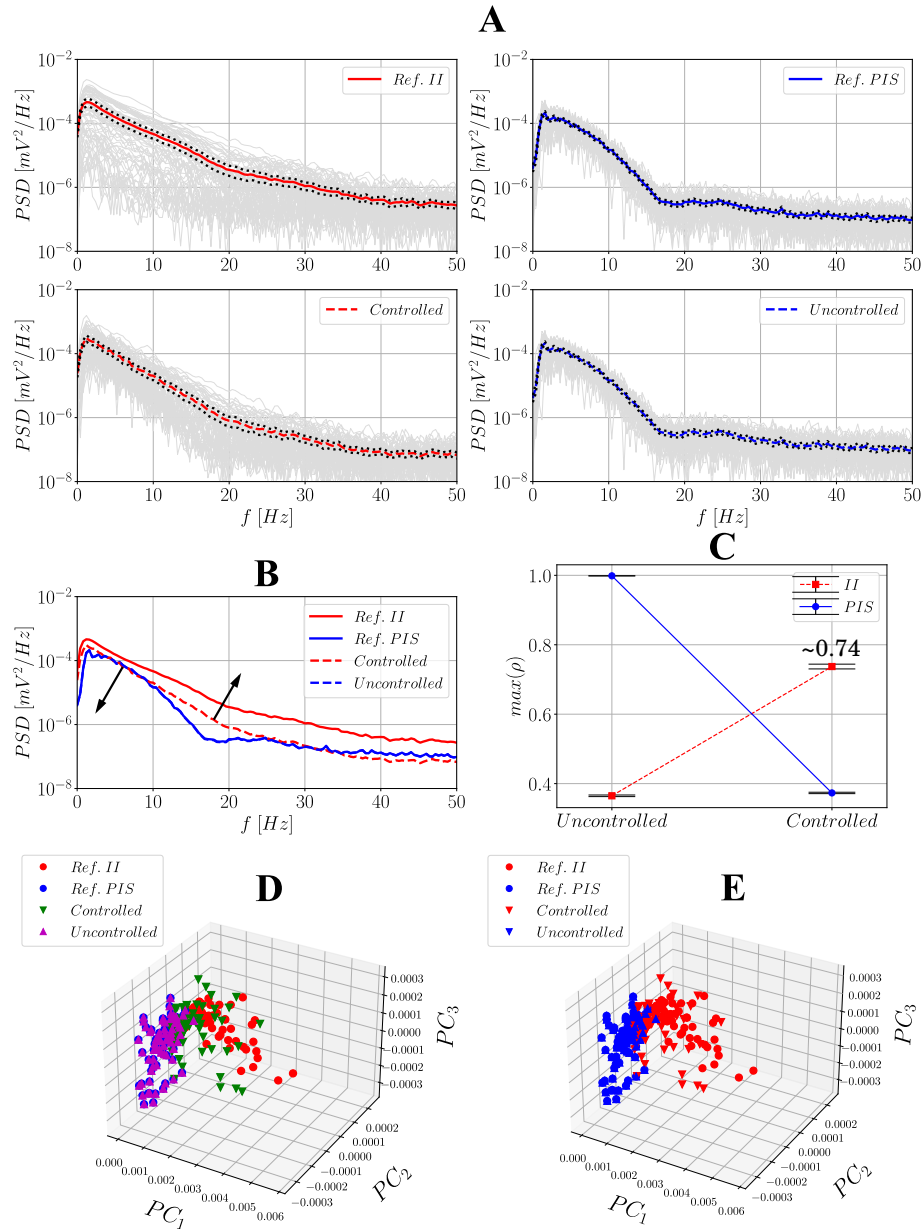
6.4 Comparison stage

To better assess the efficiency of the controller and endorse the previously presented results of Euclidean norm and spectrograms, this section presents results for the comparisons using PSDs, cross-correlations and PCA. For the sake of understanding: reference II represents the stored II signal ($\mathbf{x}_h$); reference PIS represents the stored PIS signal to be observed/controlled; the uncontrolled signal represents the observed PIS signal after activating the observer; the controlled one, in turn, represents the signal after activating the controller.

6.4.1 Power Spectral Density (PSD) and Principal Component Analysis (PCA)

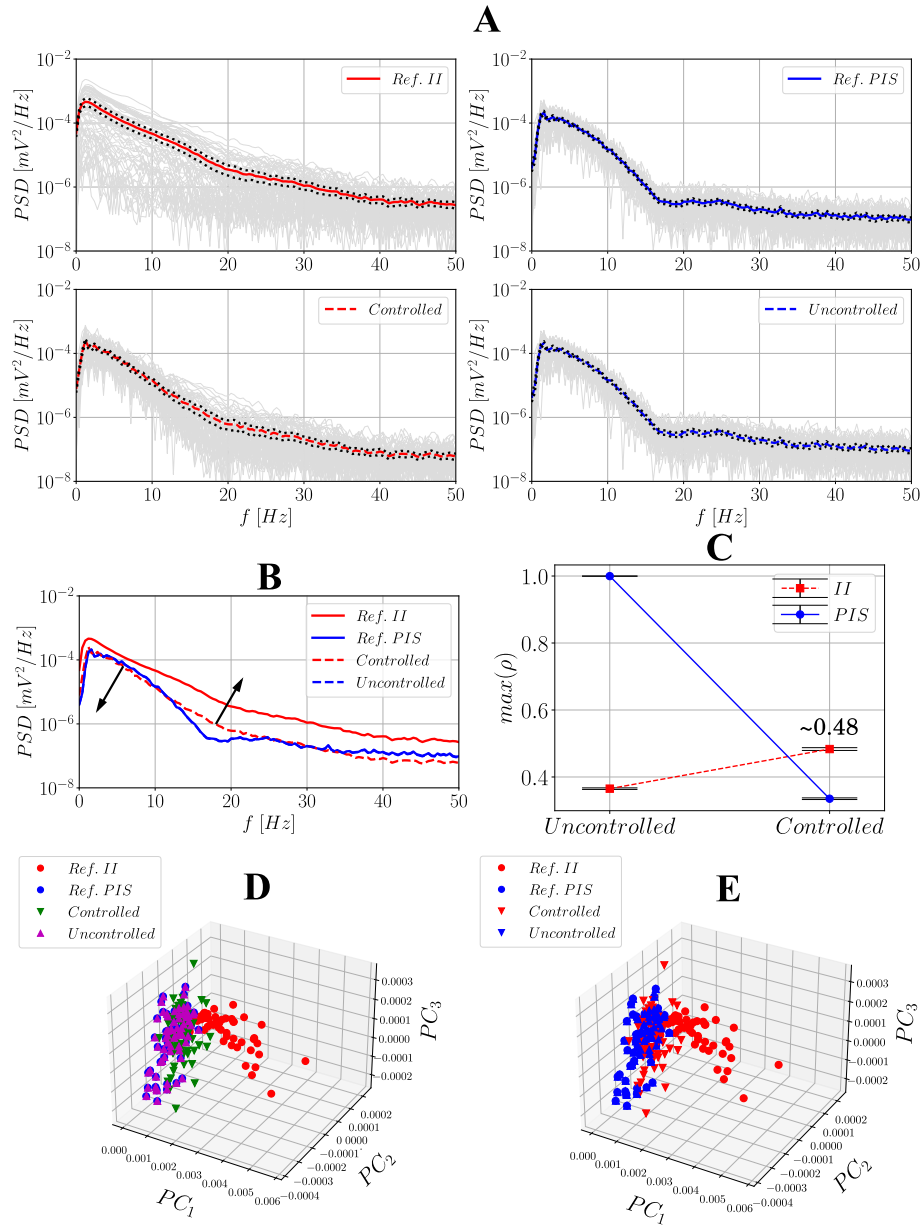
Figures 52 and 53 summarize all of these metrics for the non-hybrid and hybrid controllers, respectively. To generate the PSDs, several $N_{\min}$ -long windows were considered such that they are taken as random variables, which makes it possible to calculate mean PSDs with standard deviations and confidence intervals (Figs. 52A and 53A). By analyzing the means (Figs. 52B and 53B), two interesting patterns can be observed concerning the controlled signal compared to the uncontrolled one: there is a slight decrease in power up to ~ 10 Hz and an increase after this frequency, consistent with the fact that II represents more complex activities, thus covering a large frequency band, while PIS is a more deterministic periodic activity (Araújo et al., 2022). This suggests that upon activation of the controller, the signal tends to move towards the reference II and leave the PIS condition, regardless of the control strategy.

Figure 52 – **Comparison between the reference observed II and PIS signals and the uncontrolled/controlled ones using PSDs and PCA after activating the non-hybrid controller.** For reference: (A) contains the PSD results: gray solid lines (—) represent the PSDs obtained for each of the $N_{\min}$ -long windows; red solid lines (—) represent the mean PSD of the reference/observed II signal; red dashed lines (---) represent the mean PSD of the controlled signal; blue solid lines (—) represent the mean PSD of the PIS reference/observed signal; blue dashed lines (---) represent the mean PSD of the controlled signal; black dotted lines (...) represent the confidence intervals at a 95% level. (B) represents all the mean PSDs together for visual inspection; (C) contains the maximum cross-correlation values between the combinations reference II/PIS and uncontrolled/controlled signals using all of the $N_{\min}$ -long windows and their respective confidence intervals at a 95% level. (D) and (E) present the principal components of PCA highlighting the clusters individually and after considering II/controlled and PIS/uncontrolled groups.



Source: Own authorship.

Figure 53 – **Comparison between the reference observed II and PIS signals and the uncontrolled/controlled ones using PSDs and PCA after activating the hybrid controller.** For reference: (A) contains the PSD results: gray solid lines (—) represent the PSDs obtained for each of the $N_{\min}$ -long windows; red solid lines (—) represent the mean PSD of the reference/observed II signal; red dashed lines (---) represent the mean PSD of the controlled signal; blue solid lines (—) represent the mean PSD of the PIS reference/observed signal; blue dashed lines (---) represent the mean PSD of the controlled signal; black dotted lines (...) represent the confidence intervals at a 95% level. (B) represents all the mean PSDs together for visual inspection; (C) contains the maximum cross-correlation values between the combinations reference II/PIS and uncontrolled/controlled signals using all of the $N_{\min}$ -long windows and their respective confidence intervals at a 95% level. (D) and (E) present the principal components of PCA highlighting the clusters individually and after considering II/controlled and PIS/uncontrolled groups.



Source: Own authorship.

Figures 52C and 53C show the results for the analysis of maximum cross-correlation coefficients. Each of the $N_{\min}$ -long window was taken as a sample; then, uncontrolled and controlled signals were both compared to references II and PIS. As expected, PIS activities correlate better with uncontrolled ones, whereas II activities correlate better with controlled ones, which again evidences the effectiveness of the controller, but analyzed in the time domain – for this metric, the non-hybrid controller has a better performance, with ~ 0.74 vs ~ 0.48 . In the 3-dimensional principal component space, when each of the $N_{\min}$ -long PSD windows is projected four different clusters are revealed, corresponding to references II and PIS and uncontrolled/controlled signals.

When plotted together, regardless of the control strategy used, the samples from uncontrolled signals are spatially closer to PIS references, reference II is farther from the groups, and samples from controlled signals fall in between. When plotting only two categories (relating uncontrolled to PIS samples and controlled to II ones), the difference between these clusters becomes more pronounced. To assess statistical similarity between these four clusters, a bilateral Kruskal-Wallis test was carried out considering only the second principal component (PC_2), which proved to be the best one to distinguish them. This test yielded $H = 137.64$ and $p \lll 0.001$ for the non-hybrid controller and $H = 105.39$ and $p \lll 0.001$ for the hybrid one, thus indicating the samples are statistically different.

Next, the post-hoc Dunn's test was also performed to evaluate individual differences, whose results are summarized in Table 7. For the non-hybrid controller, this test can efficiently distinguish reference PIS from reference II and uncontrolled from controlled signals. Besides, it does not distinguish between reference PIS and the uncontrolled signal, and between reference II and the controlled signal at 95%, which endorses the effect of the controller in restoring the signal to the II condition. For the hybrid controller, as the non-hybrid one, the test distinguishes well between references PIS and II as well as controlled from PIS references, endorsing the effectiveness of the controller in attenuating PIS. However, it does not attest the similarity between controlled and reference II, demonstrating that its performance compared to the non-hybrid one is moderate.

6.5 Relevant aspects of non-hybrid and hybrid controllers

This chapter addresses a relevant challenge in the context of epileptic seizures, which is obtaining a data-based model that describes its signatures over time. System identification approaches involving epileptiform activity (or from interictal to ictal states) are not commonly found in the literature. An important implication of doing so is to provide models that are patient-specific or seizure-specific; that is, models that adept to each type of time signature or patient. From these models, observers and controllers can be designed for purposes of recreating the epileptiform dynamics and controlling it artificially.

Table 7 – **P-values obtained from the post-hoc Dunn’s test considering the samples projected on the second principal component PC_2 , for both non-hybrid and hybrid controllers.** The tests indicate similarity between controlled signals and II reference ones as well as uncontrolled signals and PIS reference ones for the non-hybrid controller, but only similarity between uncontrolled signals and PIS activity for the hybrid controller, suggesting its efficiency is moderate. The following notation is adopted: $p \lll 0.001$ if $p < 10^{-6}$.

Non-hybrid	Reference II	Reference PIS	Controlled	Uncontrolled
Reference II	1.0	$\lll 0.001$	0.197	$\lll 0.001$
Reference PIS	$\lll 0.001$	1.0	$\lll 0.001$	0.923
Controlled	0.197	$\lll 0.001$	1.0	$\lll 0.001$
Uncontrolled	$\lll 0.001$	0.923	$\lll 0.001$	1.0
Hybrid	Reference II	Reference PIS	Controlled	Uncontrolled
Reference II	1.0	$\lll 0.001$	$\lll 0.001$	$\lll 0.001$
Reference PIS	$\lll 0.001$	1.0	0.002	0.908
Controlled	$\lll 0.001$	0.002	1.0	$\ll 0.001$
Uncontrolled	$\lll 0.001$	0.908	$\ll 0.001$	1.0

From the time-frequency analysis, the total number of samples was reduced, which considerably relieves the computational burden without compromising the signals’ inherent dynamics. In addition, the main frequency components were identified and used as a reference from which to define the templates (several time windows over time) for the AR models with an appropriate fixed time length. This strategy enabled obtaining AR models of reduced order: in this work, $AR(k=6)$ provided a good trade-off between accuracy and complexity, resulting in low values of MSE and other relevant criteria, such as AIC and BIC. Naturally, as the order gets higher, models become increasingly closer to their reference signals. However, one of the main goals of the proposed approach is to make the models as simple as possible (specially envisioning the later stages of state-space representation), besides avoiding potential problems of overfitting. In this sense, the models can sufficiently approximate the inherent dynamics of periodic ictal activity (PIS) and interictal activity (II), distinguishing them according to the AR coefficients obtained, thus endorsing previous results using the same signals (Araújo et al., 2022).

For the model extension step, the $AR(6)$ model calculated from the first $N_{\min}$ samples was reapplied to the whole signal ($N > N_{\min}$), in both conditions (PIS and II). Since the evolution of the MSE over time was stable, this suggests that the identification from restricted time intervals can be used in other parts of the signal too, a fact that is also endorsed by the consistency of AR coefficients over time windows presented in Table 6 and Final Remarks. This result is particularly interesting because, in practice, obtaining arbitrarily long time signals of epileptiform activity, especially from humans, usually involves complex procedures, or recordings may not be readily available. Therefore, even

with reduced information about the time signatures, it is possible to infer about their remaining dynamics over time, which is also important for the next steps of designing observers and controllers.

When applying the state observer, it was verified that the dynamic error $\mathbf{e}(t) \rightarrow \mathbf{0}$ during the first instants of the simulation. This makes it possible to recreate the time signature over time accurately from stored signals, as the case of this work. This result is consistent with a previous study that reconstructed the unmeasurable activity of the Epileptor model based on its measurable activity. The main difference is that this time the reference signal is not dynamically simulated through the numerical integrator, but approximated based on observations of stored signals. In practice, it is expected that the observed signal is not a stored one, but brain activity measured in real time. As long as such activity can be properly recorded, the proposed approach can be applied.

As for the controllers, its activation could attenuate significantly the amplitude of the undesired activity, i.e., periodic ictal spiking (PIS), while simultaneously driving the system back to the interictal condition (II). To do so, it is required to record II events previously so as to provide a dataset from which to choose $\mathbf{x}_h$. This is an interesting result because, since seizures present a wide variety, the reference for each case and design is seizure/patient-specific as well. The design of hybrid controllers (state-space plant built using II signals applied to PIS signals) proved to be relatively effective, which means that it is still possible to design such a hybrid control in the absence of ictal events, a good advantage considering that seizures cannot be easily measured and often occur abruptly.

The metrics used to evaluate how close controlled signals are to their reference desired ones provided complementary results. The Euclidean norm could be reasonably applied during the first seconds of simulation to visualize the efficiency of the controller along with the dynamic error; however, for longer time windows, the norm did not prove to be the best measure for this purpose. In other words, the norm is an interesting tool to assess small-scale events, not global ones. On the other hand, both spectrograms and PSDs provided relevant information regarding the frequency content of signals: they revealed that PIS activities have higher power in lower frequency bands (~ 10 Hz) whereas II activities spread over the spectrum. Upon the activation of the controller, the controlled signal tends to recover a significant part of power lost in higher bands, which is also reflected on the similarity between both II and controlled signal's spectrograms.

Concerning the normalized cross-correlation, both controllers provided significant results in the sense that PIS activities correlate better with uncontrolled signals and II activities correlate better with controlled ones. This effect is, however, stronger for the non-hybrid controller. At last, PCA confirmed that both controllers yield easily separable clusters in the principal component space, and they can be distinguished statistically.

Control inputs could be tuned and constrained, which is essential in practical applications not to deliver unnecessarily strong stimuli to the brain region of interest. The shape of the input stimulus is also an important result in this work. As seen, previous approaches considering trains of pulses or continuous stimulation for purposes of seizure suppression are commonly found in the literature (Velasco et al., 2001; Tellez-zenteno et al., 2006; Velasco et al., 2007). Alternative approaches considering irregular time intervals for the simulation can also be found (Cota et al., 2009). This raises an important question on which type of simulation is the most effective. On the one hand, applying pulses of inverse magnitude to “cancel out” the spikes of PIS activities seems an acceptable premise, which may explain the similarity of the results obtained here with the first studies. On the other hand, the reasoning behind aperiodic stimulation lies on attempting to disengage the hypersynchronism and reverberating effects of neural networks (Cota et al., 2009), which is also promising considering epilepsy as a progressive hypersynchronization process (Iasemidis, 2003) and consistent with the definition of $\mathbf{x}_h$.

From a physical point of view, epilepsy can be interpreted as the progressive loss of complexity due to a hypersynchronized activity (Iasemidis, 2003; Araújo et al., 2022), so considering this context and the results obtained here for the control inputs, it may be inferred that periodic stimulation acts on reducing the on-going undesired PIS activity, whereas aperiodic stimulation ($\mathbf{x}(t) \rightarrow \mathbf{x}_h$) acts on progressively re-establishing the complexity of the brain region that had been oversynchronized. In this sense, combined types of stimuli remains an open topic for future investigation.

6.6 Assessing nonlinear models

AR modeling has already been used for seizure description and prediction and provided promising results. However, there is still a need for more general models which are not only suitable for describing individual activity from patients, but also general across subjects. In this sense, this section introduces an alternative approach to constructing nonlinear autoregressive models (NAR) that adhere to individual seizures and the ones coming from different patients. The main assumption in this case is that, although each epileptiform signature is unique to a subject, there are common features across patients, as also proposed by Jirsa et al. (2014). These features are in turn reflected by the magnitude of the NAR coefficients.

To extend the validity of the results obtained so far, not only is the approach adapted as a nonlinear model, it is also applied to iEEG signals, not LFPs anymore. Essentially, it consists of analyzing a public dataset (Burrello et al., 2019) and performing several consecutive regressions so as to obtain random variables for each of the NAR coefficients. The results show that it is possible to use median coefficients to build a model that

summarizes all the remaining seizures. This finding is useful in applications where a sufficiently large number of recordings is not available, as well as in the context of seizure prediction and attenuation using NAR modeling. For the signals analyzed in this section, a similar filtering as the one mentioned in the beginning of this chapter was carried out.

6.6.1 NAR models

NAR models can be defined in terms of linear and nonlinear contributions (Schiff et al., 1995; Schiff; Victor; Canel, 1995):

$$\hat{y}(n) = - \underbrace{\sum_{i=1}^r \phi_i y(n-i)}_{\text{Linear}} - \underbrace{\sum_{j=1}^r \sum_{k=1}^r \phi_{ij} y(n-j) y(n-k)}_{\text{Nonlinear}} + \dots + \phi_0 + \varepsilon_n \quad (117)$$

where $n = 1, \dots, N$ is a discrete-time series (i.e., the samples of the signal), ϕ_i , $i = 1, \dots, r$, are the coefficients of the model, $y(n-i)$, $i = 1, \dots, r$, are past observations of variable $\hat{y}(n)$, which is the output of the system. The first coefficient ϕ_0 is the mean value of the time series, and ε_n is the error associated to the n discrete-time instant. These coefficients, obtained by a similar LSM (Ljung, 1998) discussed in the beginning of this chapter, are sensitive to the inherent dynamics present in the signals (Entezami; Shariatmadar, 2018) and may indicate differences or similarities in behavior if they occur over time, which is why they are used in as features.

6.6.2 Statistical analysis

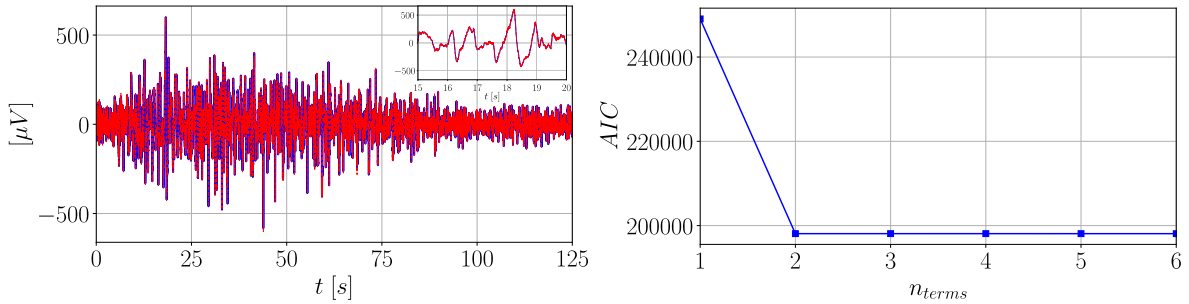
The number of available electrodes and seizures is not the same across the patients. For convenience, only the first seizure of each subject was selected, but including all of the channels. In this way, it is possible to assure a significantly high number of samples (a total of 1016 time windows from 16 patients) while accounting for representations of all patients at the same time. Histograms are used to depict the resulting distribution obtained after successive estimations of each coefficient. Medians are adopted to summarize the distributions, which implies that no assumptions regarding normality are made. To assess goodness of fit, two metrics are employed: the Pearson correlation and relative root mean squared error (RRMSE)⁴ between the signal and the model.

⁴The RRMSE is normalized by the difference between the maximum and minimum values of the time series in this work.

6.6.3 Analysis of general model

Figure 54 depicts an example of epileptiform signature and its reconstructed version. A second-order NAR model with six terms was considered. That is, the nonlinearity assumed is parabolic, and the number of terms resulting from the expansion of the polynomial $[\phi_i + \sum_{j=i}^r \phi_{ij}y(n-j)]y(n-i)$, $i = 1, 2$, is six. However, note that the AIC suggests that only the first two terms of the NAR model should be used, which implies that the effect of the nonlinearities in this case is not strong. This is endorsed by the resulting equation, where coefficients of the order 10^{-4} are related to the second-degree terms, whereas coefficients of the order 10^0 to 10^{-1} are associated to the first-degree terms.

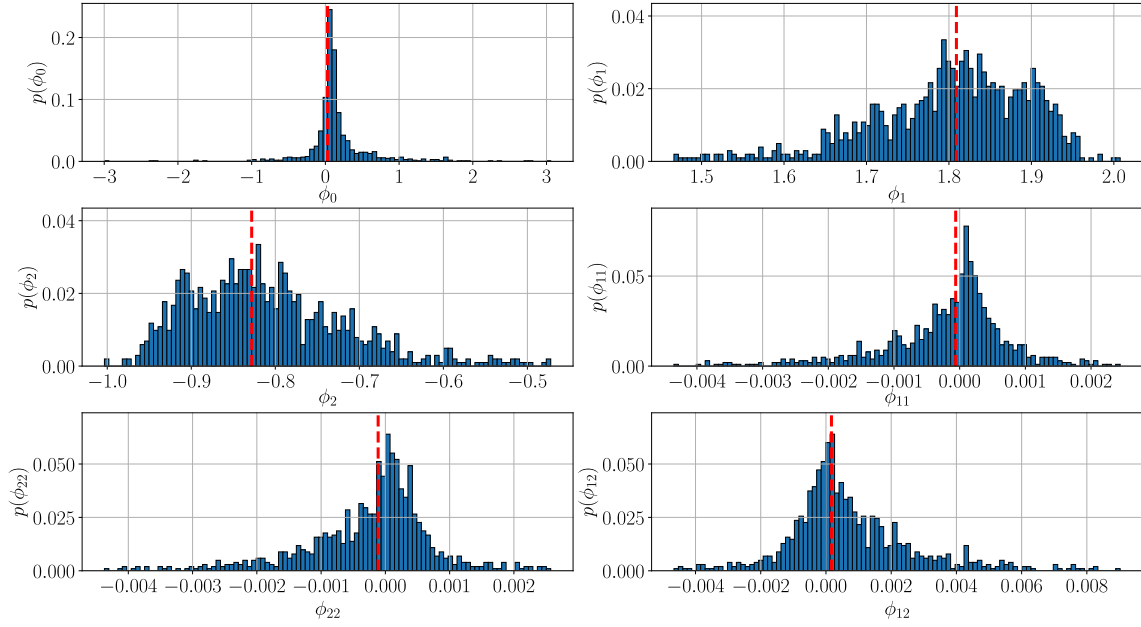
Figure 54 – **NAR model reconstruction considering an iEEG signal.** The seizure is measured invasively (iEEG) and can be accurately described by a second-order NAR model. The solid blue line (—) indicates the epileptiform activity obtained from the first seizure and first electrode of the first patient; the red dashed line (---) indicates the reconstructed 6 terms: $\hat{y}(n) = 0.0319 + 1.7363y(n-1) - 0.7404y(n-2) - 0.0005y(n-1)^2 - 0.0005y(n-2)^2 + 0.0009y(n-1)y(n-2)$; since only the first two are relatively high, this indicates an AR model would be sufficient for the same purpose. Blue solid lines with square markers (—■—) indicate the Akaike Information Criterion. Coefficients are rounded up to the 4th significant figure..



Source: Own authorship.

Figure 55 presents the histograms for the random variables of each ϕ_i . The distributions tend to be assymmetric, but there is a clear tendency of the values concentrating around their medians. This provides evidence of a common pattern across patients, represented by the NAR coefficients: a stable $\phi_0 \sim -0.03$ indicates that all iEEG have a similar mean value; besides, their linear components are well pronounced ($\phi_1 \sim 1.81$ and $\phi_2 \sim 0.83$) while the nonlinear ones ($\phi_{11} \sim -6.1 \cdot 10^{-5}$, $\phi_{22} \sim -1.13 \cdot 10^{-4}$ and $\phi_{12} \sim 1.68 \cdot 10^{-4}$) less strong.

Figure 55 – **Histograms obtained from the NAR coefficients after successive identifications over the iEEG signal.** Each box contains a random variable consisting of the NAR parameters identified over successive regressions, leading to the histograms, which in general present a region of concentration, thus suggesting a common pattern across the patients. The red dashed line (- -) indicates the median values of the parameters.



Source: Own authorship.

To better analyze how strong the influence of the nonlinearities in the model is, the first channel and seizure of the first patient was selected and new regressions were performed varying the number of lags to match the number of terms, i.e., $i = 1, \dots, 6$, so that the last resulting model is purely the traditional linear AR ($\sum_i^6 \phi_i y(n-i)$, $i = 1, \dots, 6$). Then, the RRMSE was calculated for all cases, resulting in Table 8. As seen, the error tends to decrease as the model becomes more linear, also suggesting that the addition of delays can provide a more refined description of the seizure. In other words, a precise identification of seizures required dependency on early stages of the electrophysiological activity. It is worth mentioning that the order of the polynomial has also been varied but no significant improvement was verified.

Table 8 – **Effect of the addition of lags to the NAR model considering the number of lags and the RRMSE.** As the number of lags increases, the RRMSE decreases, indicating a higher accuracy, but this effect is mild in general, since from 2 to 6 lags the decrease is about 0.25%.

Lags	2	3	4	5	6
RRMSE	0.3973%	0.3130%	0.2299%	0.1894%	0.1508%

Table 9 presents the Pearson correlation and RRMSE between the seizures and their reconstructed versions using individual NAR models and a general NAR model, composed of the median coefficients from Fig. 55. For all cases, both RRMSE and correlation are slightly higher for the model built using the medians, but they still remain at a considerably low level, indicating that the median model provides a sufficiently good description of all seizures analyzed.

Table 9 – **Performance of individual NAR models for selected patients and the general one: ρ_1 and ρ_2 correspond to the Pearson correlation for each of them, respectively. “P” stands for patient and “Sz” stands for seizure.** The mean is calculated using all patients. The RRMSE and correlation from the general model are close to the ones obtained from individual models, indicating the general model can represent well similarities across patients.

P/Sz	ρ_1	$RRMSE_1$	ρ_2	$RRMSE_2$
#01/#01	0.99892	0.3973%	0.99890	0.4197%
#02/#01	0.99896	0.4958%	0.99891	0.5188%
#15/#01	0.99719	0.6467%	0.99712	0.6557%
#16/#01	0.99511	0.9176%	0.99504	0.9250%
Mean	0.99789	0.5559%	0.99781	0.5839%

6.6.4 state-space conversion

Following the same approach proposed to the linear AR, the NAR models can be converted into state-space (SS) notation according to the difference equation $\mathbf{x}_r'$ in function of the states $\mathbf{x}_r$, and the measurable activity in the time domain, represented by $\mathbf{y}_r$ (Durbin; Koopman, 2012):

$$\underbrace{\begin{bmatrix} y_n \\ y_{n-1} \\ \vdots \\ y_{n-r+2} \\ y_{n-r+1} \end{bmatrix}}_{\mathbf{x}_r'} = \underbrace{\begin{bmatrix} \phi_0 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}}_{\mathbf{b}} + \underbrace{\begin{bmatrix} \Upsilon_1 & \Upsilon_2 & \dots & \Upsilon_{r-1} & \Upsilon_r \\ 1 & 0 & \dots & 0 & 0 \\ 0 & 1 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}}_{\mathbf{A}^{\{d\}}} \underbrace{\begin{bmatrix} y_{n-1} \\ y_{n-2} \\ y_{n-3} \\ \vdots \\ y_{n-r} \end{bmatrix}}_{\mathbf{x}_r} + \underbrace{\begin{bmatrix} \varepsilon_1 \\ 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}}_{\boldsymbol{\varepsilon}_r} \quad (118)$$

$$\mathbf{y}_r = \underbrace{\begin{bmatrix} 1 & 0 & 0 & \dots & 0 \end{bmatrix}}_{\mathbf{C}} \mathbf{x}_r \quad (119)$$

where $\mathbf{A}^{\{d\}}$ is the discrete SS model, $\mathbf{C}$ is the matrix corresponding to the measurable states in time, and each Φ_i is a nonlinear function of the type:

$$\Upsilon_i = \phi_i + \sum_{j=i}^r \phi_{ij}y(n-j) + \sum_{j=i}^r \phi_{ijj}y^2(n-j) + \frac{1}{2} \sum_{j=i}^r \sum_{k=i}^r \phi_{ijk}y(n-j)y(n-k) + P^q, \quad j \neq k \quad (120)$$

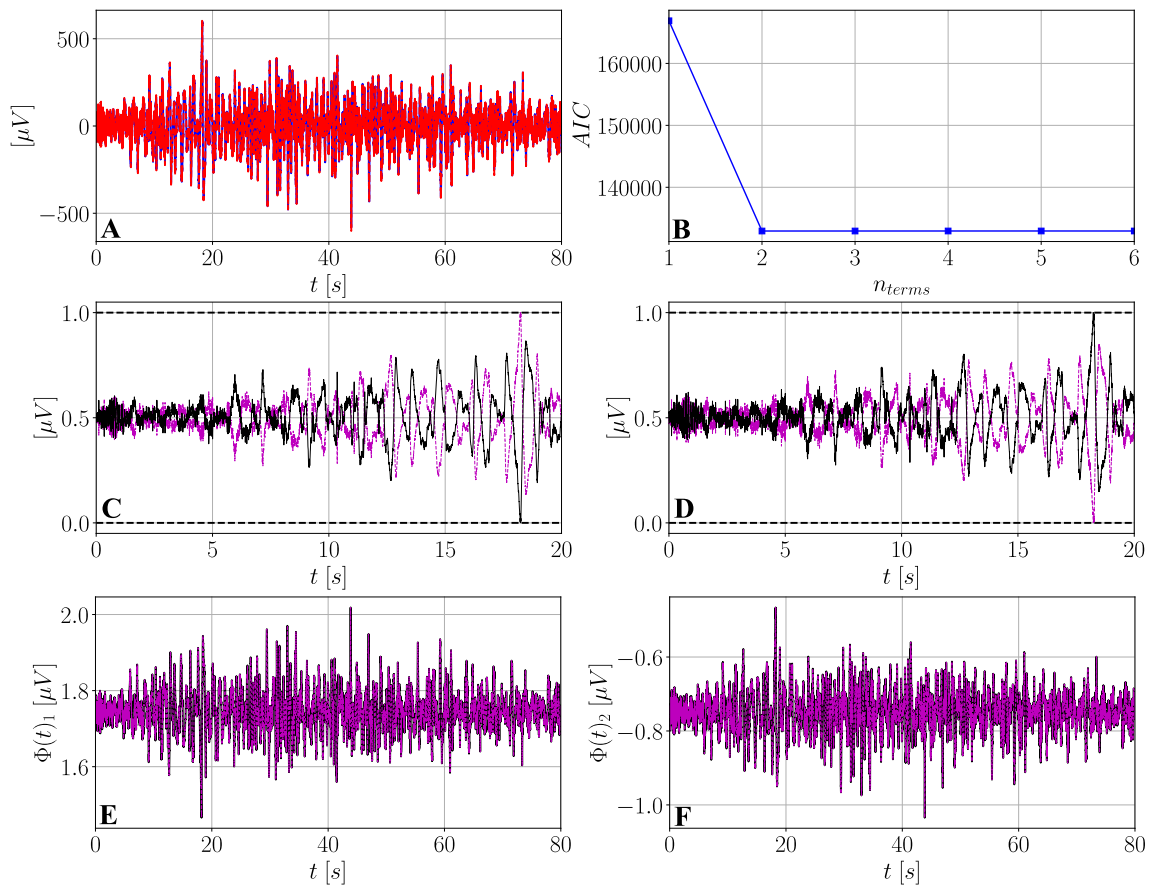
where P^q are polynomials of higher order q . For the sake of understanding, ϕ_1 indicates the coefficient of the linear regressor for the first delayed time series $y(n-1)$, ϕ_{11} is the coefficient of the nonlinear regressor for the first delayed time series $y(n-1)^2$, and so forth, all of them associated to the $y(n-i)$ delayed series. For applying observers and controllers, the formulation in continuous time is used again, as in Eq. 101 (Shieh; Wang; Yates, 1980). Since the dynamic matrix has nonlinear terms, the FTS modeling can be conveniently applied, as carried out in Chapter 3.

6.6.5 Seizure reconstruction and attenuation

Figure 56 presents the reconstructed NAR model based on the epileptiform signature (A) along with the AIC (B), membership functions (C and D) and reconstructed nonlinear functions (E and F). In the AIC plot, the terms do not correspond to the order of the NAR model, but the number of terms used for a specific order (in this case, $k=2$), after polynomial expansion. Therefore, for 6 terms and a 2nd-order model, the real signal can be accurately reconstructed.

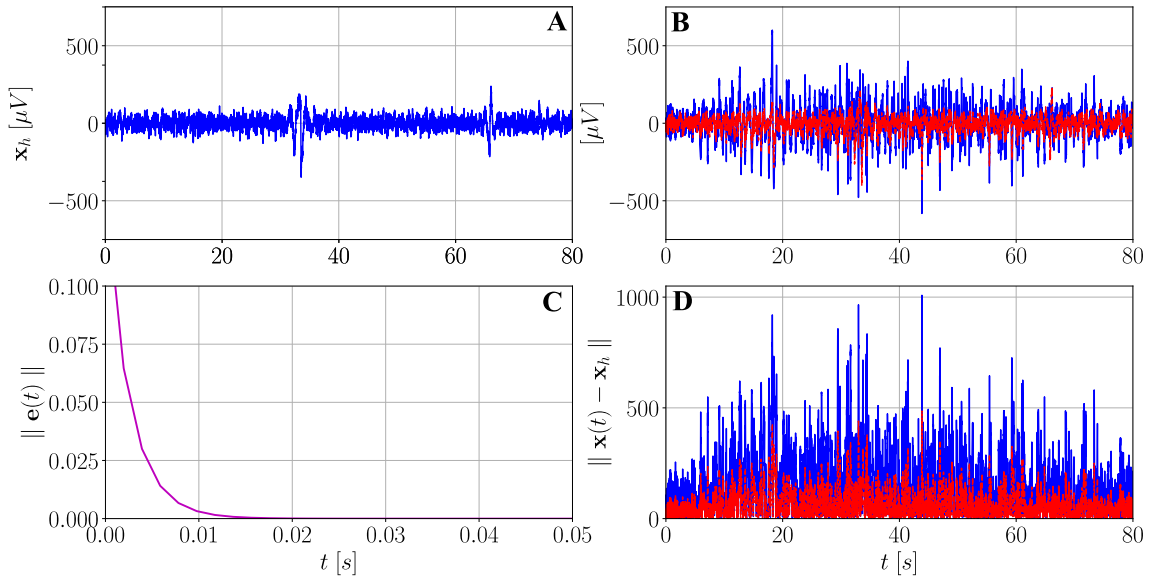
Figure 57, in turn, depicts the reference signal $\mathbf{x}_h$ (A) used for seizure attenuation (B), the convergence of the error dynamics of the observer towards zero (C), as well as the Euclidean norm between the controlled signal in time and the epileptiform iEEG (D). A significant reduction in amplitude can be seen after the activation of the controller, which demonstrates its effectiveness. However, $\mathbf{x}_h$ is not fully reestablished, indicating that it must be enhanced in future applications.

Figure 56 – **NAR identification considering the iEEG signal and concept of sector nonlinearity.** (A) contains model reconstruction with the solid blue line (—) representing the iEEG signal and the red dashed line (---) representing the reconstructed one; (B) contains the Akaike Criterion; (C) contains the membership functions g_1^{min} and g_1^{max} of the first nonlinear function (Υ_1), indicated by the solid black line (—) and solid magenta line (—), respectively; (D) contains the membership functions g_1^{min} and g_1^{max} of the second nonlinear function (Υ_2), indicated by the solid black line (—) and solid magenta line (—), respectively; (E) contains the first nonlinear function Υ_1 , indicated by the solid black line (—), and its recreated version, indicated by the solid magenta line (—); and (F) contains the second nonlinear function Υ_2 , indicated by the solid black line (—), and its recreated version, indicated by the solid magenta line (—).



Source: Own authorship.

Figure 57 – **Performance of both observer and controller for the reconstruction and attenuation of the iEEG signal.** In this case, the same approach done with the AR model is applied: the control input attempts to cancel out the undesired epileptiform activity while simultaneously inducing the non-seizure dynamics. **(A)** is the reference seizure-free signal $\mathbf{x}_h$; **(B)** contains the uncontrolled signal, indicated by the solid blue line (—), and the controlled one, indicated by the red dashed line (- -); **(C)** is the error dynamics over time; and **(D)** is the Euclidean norm between controlled and reference signals in the uncontrolled condition, indicated by the blue solid line (—), and controlled one, indicated by the red dashed line (- -).



Source: Own authorship.

6.7 Contributions, limitations and conclusions

Considering the results and discussion addressed in this chapter, the main contributions that can be highlighted are:

- **Advances in system identification and control of seizures:** the fact of providing a state-space representation that accurately describes epileptiform activity is a major step towards representing real brain activities. Previous dynamic models designed considering tools from nonlinear systems theory, such as Epileptor and Epileptor-2 (Jirsa et al., 2014; Chizhov et al., 2018), found important patterns/classifications in epileptic seizures, and experimental observations have been consistent with some predictions. However high their fidelity and representativeness may be, these models remain fairly abstract to a certain extent. In the present work, the proposed approach is different because it obtains a mathematical set of equations directly from real brain activity. Furthermore, rearranging them into

state-space notation enables the application of observers and controllers for seizure suppression purposes. It must also be considered that the signals used in this work were obtained from slices of the hippocampal tissues resected from human patients (Araújo et al., 2022). Therefore, controlling the activity of these signals is highly relevant in the context of epilepsy. A possible extension of this study is to analyze and build experimental set-ups where such brain tissues can be adequately stimulated and verify the outcomes. AR modeling and variations such as NAR usually work for any kind of time series, so this step can be carried out using animal tissue, not necessarily human, which considerably facilitates experimental verification.

- **Seizure suppression on different subfields:** by using observers and controllers, the signal studied in this work proved to be controllable in the sense that its spikings were attenuated while it was driven back to the reference II activity. Nonetheless, as seen in Final Remarks, different signals (from subfields of the hippocampus, such as DG, CA1-CA4 and SUB) were also tested in this work and similar results were obtained. This demonstrates the flexibility and robustness of the proposed control approach regardless of the region of interest. Considering this, future strategies focused on controlling seizures locally can be carried out (on a smaller scale, specific to each subfield). Moreover, it may also be possible to design controllers taking into account time signatures from several subfields at the same time, thus providing a more global suppression approach. These are interesting topics for future investigation.
- **Possible applications in seizure classification and prediction:** once the autoregressive models are available in practice, they can be used, for instance, to identify each type of seizure, or even for distinguishing ictal from interictal states. This is possible because their coefficients are sensitive to the inherent dynamics existing in real signals, and then will likely indicate a difference in behavior if it exists. Besides, given that the main characteristic of AR models is trying to foresee next states based on the time history, it is a predictor by design, a powerful and helpful feature to be taken into account. As a matter of fact, seizure prediction is a widely studied topic in neural engineering, but the methods employed for this purpose usually rely on machine learning (Sharma et al., 2014; Faust et al., 2015; Acharya et al., 2018; Yuan et al., 2018; Li et al., 2018a; Yuan et al., 2018; Ansari et al., 2019). Although regarded as a black-box method too, AR modeling for system identification in the context of seizure prediction still needs to be better explored, and may be an alternative to such algorithms.

The main limitations are, in turn:

- **The issue of stationarity and AR order:** considering that AR models are most suitable to stationary time series, the baseline shifts represented by the spikings from the real brain activities analyzed may influence their quality, which helps explain why the PIS activity is not completely attenuated: since the modeling consists of a regression of the signal onto itself, features of its inherent dynamics are expressed by the AR coefficients; if such a dynamics is not fully captured during the fitting process, the resulting state-space representation may not be accurate enough. Nevertheless, consistent representations of the real signals have been obtained at a relatively low order, which indicates that, although simple, AR models may be an alternative for system identification in the context of epilepsy. In this sense, alternative autoregressive techniques can be used to enhance the present results, such as ARMA, ARIMA or NARMA (Landau; Karimi, 1999; Jansson, 2003; Baldacchino; Anderson; Kadirkamanathan, 2013; Liu et al., 2017; Retes; Aguirre, 2019). In particular, the latter one is a nonlinear version of AR and might thus be appropriate to capture PIS/II dynamics efficiently.
- **The issue of noise and background activity:** another interesting issue that must be taken into account is the level of noise and background activity in the signals. The proposed approach was partially successful due to a certain level of noise: it grants the signals a more stochastic/stationary nature, thus compensating for local abrupt variations. However, it may also mask important dynamic structures that would otherwise be more evident and meaningful for the identification and design procedures. In this work, filters were mostly applied to remove low-frequency components, so a great part of the remaining dynamics contains seizure-unrelated activity. On the one hand, this is necessary envisioning realistic applications; on the other hand, this might render the observers/controllers less efficient. Besides, this work assumes that the existence of such low-frequency components is negligible, as previously carried out (Araújo et al., 2022), but they may actually lead to modifications in the future designs too.
- **The issue of controlling signals, not systems:** since this work considers a reconstruction of signals that were previously measured and stored, the present strategy is not based on a full system control approach. In other words, there is no access to a more comprehensive mathematical/dynamical model that represents epilepsy in detail, such as the Epileptor (Jirsa et al., 2014), for example. Rather, control inputs were applied to data-driven models that were observed in time, which makes the present approach signal-specific (or partially patient-specific), but not generalizable. In other words, the controller is effective in attenuating the epileptiform in signals (or, in the present context, regions of slices from hippocampal subfields), which are partial representations of a broader and intricate dynamics of the whole brain. For

this reason, while the controller is activated, it attenuates the undesired activity; as soon as it is deactivated, this effect cannot be visualized anymore. Therefore, the exact duration of a control input is yet to be determined in the case of real activity. This issue remains a challenge in the current literature, but considering the promising results obtained here, data-driven modeling may be a relevant resource in this direction.

6.7.1 Remarks on the NAR model

The use of NAR in this chapter attempted to address and overcome some specific restrictions verified in the application of the AR models: *i*) extend the approach to more global activities, such as iEEGs; *ii*) mitigate stationarity issues; *iii*) find a general model that is suitable to a set of patients. Since there seems to be a common pattern across all the patients, it is reasonable to assume that any processing or analysis made to one signal/patient may hold true for the remaining ones. In this sense, applications involving seizure prediction and attenuation using AR/NAR modeling may benefit from this contribution. For instance, a model obtained from one patient can be used as knowledge to design predictors to new patients for whom no signal is available yet, a similar approach to that of transfer learning (Taylor; Kacprzyk, 2009).

A parabolic nonlinearity has been assessed along with an order selection criterion (AIC), suggesting that the nonlinear regressors do not have a strong influence on enhancing the quality of the model. Besides, adding delays to the estimated model implies in a better goodness of fit, which indicates that the epileptiform activity is strongly state-dependent. This is consistent with the fact of seizures being assessed from the point of view of chaotic dynamics, which is sensitive to initial conditions (Iasemidis, 2003; Jirsa et al., 2014). Still, it is a good practice to use NAR models to generalize the approach to any type of signal and to mitigate stationarity issues (Fox, 2015).

AR/NAR modeling can be used in future work to build state space models (Durbin; Koopman, 2012) from which state observers and controllers can be designed and integrated to study seizure reconstruction and attenuation, respectively. The same concept of transfer learning can be adopted by identifying a model from one patient and using it to design controllers applied to other ones. Although there is an inherent fluctuation of the AR coefficients, which may lead to moderate outcomes, the general model proposed in this work is regarded as a helpful alternative for addressing seizures.

NAR models and FTS modeling can be applied together to accurately describe epileptiform activities over time considering a relatively low order. The performances of both observer and controller indicate that the signal can be reconstructed and attenuated arti-

ficially, thus simulating a real case scenario using electrodes on brain regions. This result is of particular interest as an alternative to mitigate the problem of stationarity verified in the AR models. However, further improvements are necessary so that the controlled signal fully attains the desired behavior, represented by the seizure-free condition.

In sum, this chapter proposed an efficient approach for attenuating the epileptiform activity of electrophysiological recordings considering the artificial reconstruction of the stored signals based on AR modeling and an integration between state observers and controllers. Several stages/steps of design, application and comparison are involved, thus characterizing a systematic and straightforward procedure that has not been reported elsewhere.

The results provided evidence that attenuating the undesired effects of real seizures can be computationally emulated, being efficient for different hippocampal subfields (DG, CA1, CA2, CA3, CA4 and SUB). Both non-hybrid and hybrid approaches can be used for this purpose: the first one provides stronger input stimuli to mitigate periodic ictal spikings while simultaneously driving the signal to the interictal-like behavior; the second one, despite causing slightly milder attenuation effects, is also able to generate effective outcomes. This endorses the possibility of designing controllers in the absence of sufficient PIS recordings, which is considered an advantage in this work given the inherent difficulty in acquiring signals with seizure events.

The shape of the control input seems consistent with previous approaches that adopt regular and irregular stimulation individually for seizure suppression. A major contribution in this sense found in this work is that they may be more effective if combined, applied as a superposed one consisting of periodic pulses of inverse magnitude (similar to the regular stimuli) and chaotically-behaved ones (closer to the irregular stimuli). These findings may be of great interest for real applications comprising the modeling and description of seizures (characterized by the AR models), and seizure mitigation and suppression.

7 GRAY-BOX MODELING FOR RECONSTRUCTING AND ATTENUATING REAL SEIZURES

Although promising results have been attained using the AR models to reconstruct and attenuate the real seizure, such models require time series to be stationary, which is usually not the case for epileptiform activities. This issue was partially addressed by the NAR models considering a polynomial nonlinearity, but according to the Akaike Criterion and regressors, the nonlinear coefficients do not provide a significant contribution/improvement to its accuracy. This suggests that the relatively higher sophistication of the NAR model may not be worth it. Besides, the hybrid concept (i.e., designing controllers from models in the non-seizure condition and applying them to mitigate seizure conditions) still lacks theoretical basis. At last, it would be interesting to extend even more the applicability of the proposed approach to other electroencephalograms (EEG), intracranial EEGs (iEEGs) or stereo-EEGs (sEEGs).

To overcome these obstacles, this chapter introduces a new approach using the concept of model reference controllers (MRC) (Goel; Kumar; Narayan, 2016) combined with system identification (SI) techniques (Ljung, 1998; Pacheco; Jr, 2002). The main idea lies on identifying models based on real signals, reconstruct them artificially and then attenuate specific oscillations associated to seizures. This process is purely computational, using previously stored signals. However, since it enables the visualization of brain patterns dynamically, it is expected that the results obtained artificially reflect those that would occur in actual patients. Besides, they provide information about how seizures could be mitigated in realistic scenarios. The approach proposed in this chapter is theoretically consistent and similar to the previous ones; however, the main differences are: it extends the concepts to global levels of electrical activity (mainly EEG); it does not require stationarity as an assumption; the use of MRC provides a more formal concept for the hybrid controllers; it is simpler than both AR and NAR, thus having a stronger practical appeal.

Therefore, this chapter has two main objectives: to formalize the concept of hybrid controllers that were previously introduced; to propose a new approach for attenuating seizures computationally but with a strong practical appeal. The MRC approach is applied to reconstruct and attenuate seizures artificially, which is considered a major advance in terms of simplicity, efficiency and practical appeal. To do so, three main hypotheses are adopted:

1. There is a characteristic signature for both conditions (non-seizure and seizure), for at least some cases. This means that patterns in the signals can be visualized in both time and frequency domains, such that they can be correctly distinguished and associated to each condition;
2. A closed-loop linear model represents well each of the measured activities (non-seizure and seizure). Neural systems are usually nonlinear and time-varying (Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003; Jirsa et al., 2014), so linear models are not sufficient to describe their behavior; however, with an appropriate choice of the parameters of the controller (such as gain and input stimulus), a closed-loop linear system is equivalent (i.e. it converges) to the real/measured activities;
3. The formulation in closed loop can be applied for seizure attenuation in open loop in real scenarios. In other words, the closed-loop strategy is carried out in this work for simulation purposes, but in realistic applications the controller should operate as a constant or alternate pulse emission with a monitoring system. This is discussed in detail in the next sections.

The codes used in this chapter are available online on the platform GitHub at the following address: <https://github.com/GMSINT/Epilepsy-Dynamics-Control>.

7.1 General methodology

The general methodology of this chapter comprises 4 major stages: *i*) signal processing and analysis, *ii*) identifying candidate models *iii*) signal reconstruction via closed-loop models; *iv*) signal attenuation via closed-loop models. **Signal processing and analysis** explains the filtering and time window selection procedures performed to each signal. **Identifying candidate models** presents the mathematical technique based on orthogonal polynomials to identify the main oscillating components of the signals to generate the so-called “candidate models” in this chapter. **Signal reconstruction via closed-loop models** applies artificial closed-loop controllers to reconstruct the time signatures. **Signal attenuation via closed-loop models** applies a second closed-loop to attenuate the seizures artificially as well.

7.1.1 Definitions and notation

This subsection comprises important definitions regarding the model used for seizure reconstruction and attenuation, as well as the notation adopted for the whole chapter.

First, consider the following generic linear time-invariant state-space model (Ogata, 2010):

$$\underbrace{\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t)}_{\text{Open loop}}, \quad \underbrace{\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t)}_{\text{Closed loop}} \quad (121)$$

where $\mathbf{x}(t) \in \mathbb{R}^{2n \times 1}$ is the vector of states, $\mathbf{A} \in \mathbb{R}^{2n \times 2n}$ is the dynamic matrix, $\mathbf{B} \in \mathbb{R}^{2n \times q}$ is the input matrix and $\mathbf{u}(t) \in \mathbb{R}^q$ is the input stimulus (the same as defined since the Epileptor model and black-box modeling):

$$\mathbf{u}(t) = -\mathbf{G}[\mathbf{x}(t) - \mathbf{x}_d(t)] = \underbrace{-\mathbf{G}\mathbf{x}(t)}_{\text{Attenuated}} + \underbrace{\mathbf{G}\mathbf{x}_d(t)}_{\text{Desired}} \quad (122)$$

composed of two terms that are responsible for attenuating the undesired activity to the zero level while inducing the desired dynamics, respectively. The difference between open loop and closed loop is highlighted due to its relevance in this chapter. As presented in this work later on, without the control input, only the candidate models are simulated, based on a previous identification procedure, thus none of the activities can be reconstructed. With the control input, the gains act on the states attempting to mitigate the epileptic patterns while following the trajectory defined by the real recorded activities, such that they can be artificially reconstructed. In this sense, the desired dynamics is precisely what represents the model reference, and all controllers proposed in this chapter are Model Reference Controllers (MRC)¹.

Considering this, it is convenient to define a notation to distinguish between recorded/stored signals from reconstructed ones. Table 10 presents the notation adopted throughout the text, where the subscripts refer to actual recorded or reconstructed activities, whereas the superscripts refer to different conditions (non-seizure and seizure, for example).

Table 10 – **Notation adopted for the MRC approach, considering a generic $\mathbf{W}_{\{.\}}^{\{*\}}$.**

Subscript	Notation	Meaning
$\{.\}$	$\{ \}$	Actual: recorded or stored
$\{.\}$	$\{m\}$	Reconstructed model
Superscript	Notation	Meaning
$\{*\}$	$\{h\}$	Non-seizure activity
$\{*\}$	$\{s\}$	Seizure activity
$\{*\}$	$\{ch\}$	Candidate for non-seizure
$\{*\}$	$\{cs\}$	Candidate for seizure
$\{*\}$	$\{sh\}$	Seizure to non-seizure
$\{*\}$	$\{ad\}$	Adaptive

Source: Own authorship.

¹Further information about MRC can be found in Final Remarks.

For the sake of understanding, consider the following examples: $\mathbf{x}^{\{h\}}$ is the vector of states of the real recorded activity in the non-seizure condition; $\mathbf{A}_m^{\{cs\}}$ is the candidate dynamic matrix for the model that represents the seizure condition. The curly braces of the subscripts and the reference to time ' (t) ' are intentionally omitted throughout the whole text for better readability.

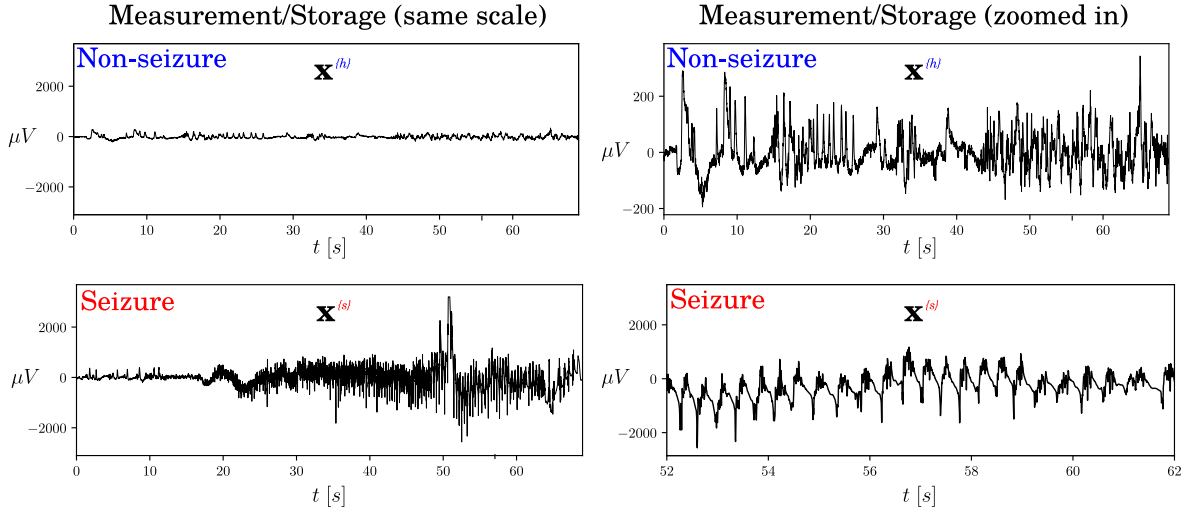
7.2 Signal processing and analysis

Before analysis, all signals were notch-filtered at 50 Hz and its harmonics to remove spurious components. No further filtering was carried so that all of the dynamic patterns present in the signals could be preserved, which is close to real situations where the only activity not taken into account is the spurious one. As they were already labeled, the times for seizure onset (t_{on}) and offset (t_{off}) were taken as references to define the time window for each patient, such that: $t_w = t_{off} - t_{on}$. The time instants that represent the non-seizure condition were shifted 3600 seconds in time: $t_h = t_{h,f} - t_{h,i}$, where $t_{h,i} = t_{on} - 3600$ and $t_{h,f} = t_{h,i} + t_w$. This procedure results in an equal number of points for both conditions and tracks the non-seizure behavior one hour back in time². The analysis presented in this section refer to the electrode Fp2, according to the international 10-20 system (Webster, 2006). This electrode was selected based on visual inspection because it provided a good visualization of the epileptiform patterns. However, complementary results, considering more patients, are provided in Final Remarks, to demonstrate the validity of the proposed approach. It should also be stressed that several tests/simulations were carried out and similar results were obtained.

According to the first hypothesis, there is a characteristic signature for both conditions (non-seizure and seizure), for at least some cases. Figure 58 presents epochs of real signals for each of them, acquired from one of the patients, electrode Fp2. Note that the amplitude of the seizure is approximately 10 times stronger than that of the non-seizure activity. Besides, the oscillating pattern is quite different in both conditions: while more erratic spikes with irregular intervals are present in the non-seizure condition, more regular spikes with an increasing and then decreasing amplitude are predominant in the seizure condition. Even at the EEG level, this is consistent with observations made in Chapter 6: this behavior indicates that, physically, the brain region under the seizure condition presents a higher level of synchronization between the neurons, which is thus reflected on the repetitive features over time. Besides, since a higher amount of energy is necessary to sustain the neurons spiking, their combined activity leads to higher amplitudes.

²Biomarkers for epileptic seizures may be traced for different periods of time. Due to a limited number of signals and recording time (as well as to reduce computational burden when processing them), one hour was the choice for this chapter.

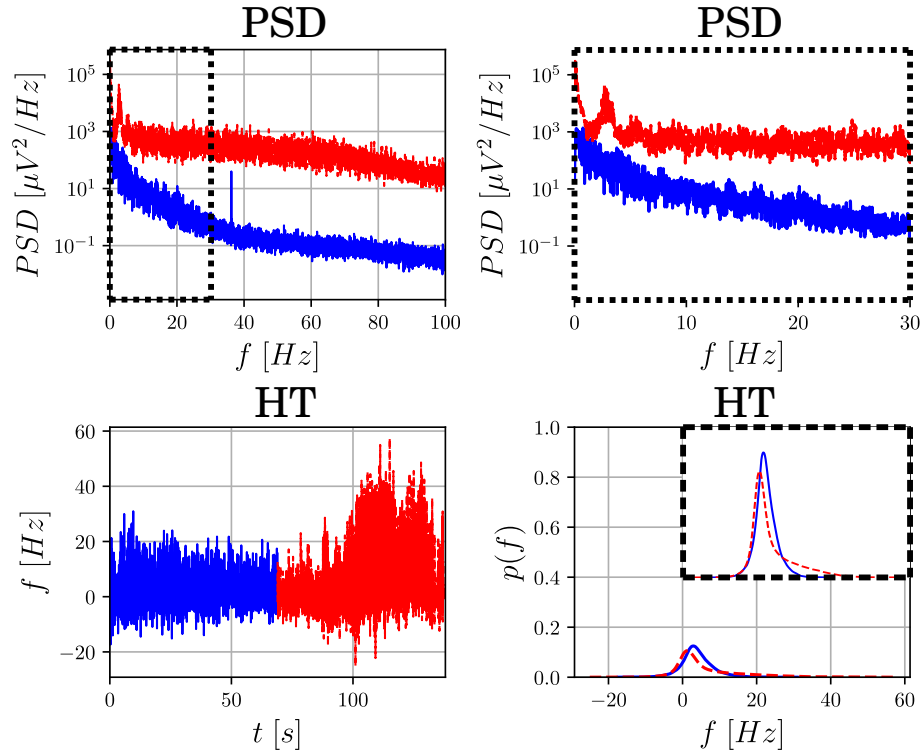
Figure 58 – **Analysis of patterns in both non-seizure and seizure conditions (time domain)**. Signals are presented on the same scale to the left to show the difference in amplitude that a seizure causes, and on zoomed-in versions to the right so that their respective patterns can be better visualized: non-seizure behavior presents more erratic spikes with irregular intervals; seizure behavior presents more regular spikes. The non-seizure signal is obtained approximately one hour before seizure onset, thus evidencing significant differences in amplitude and oscillating behavior.



Source: Own authorship.

The seizure activity seems to have dominant frequencies driving its behavior, whereas the non-seizure one does not. This can be visualized in Fig. 59 by the analysis in the frequency domain. To do so, all of the electrodes from the same patient are considered; successive Power Spectral Densities (PSD) and Hilbert Transforms (HT) are calculated for each electrode and a mean vector is obtained; the following results correspond, thus, to the mean behavior. The PSD shows two main effects of the seizure condition compared to the non-seizure one: there is an overall increase in power over the whole frequency range, characterized possibly by homeostasis imbalance and the oversynchronized neurons firing simultaneously (Iasemidis; Sackellares, 1996; Turrigiano; Nelson, 2000; Klausberger; Somogyi, 2008; Yizhar et al., 2011; Ziburkus; Cressman; Schiff, 2013; Araújo et al., 2022); a concentration of power around low frequencies ~ 2.5 Hz, which may be related to the high-amplitude oscillations seen in the time domain (Fig. 58). After applying the HT and obtaining the instantaneous frequencies over time, similar conclusions can be drawn: higher frequency bands seem to be recruited over time, and the concentration is reflected on its probability density function, since it is displaced to the left of the plot, compared to the non-seizure condition.

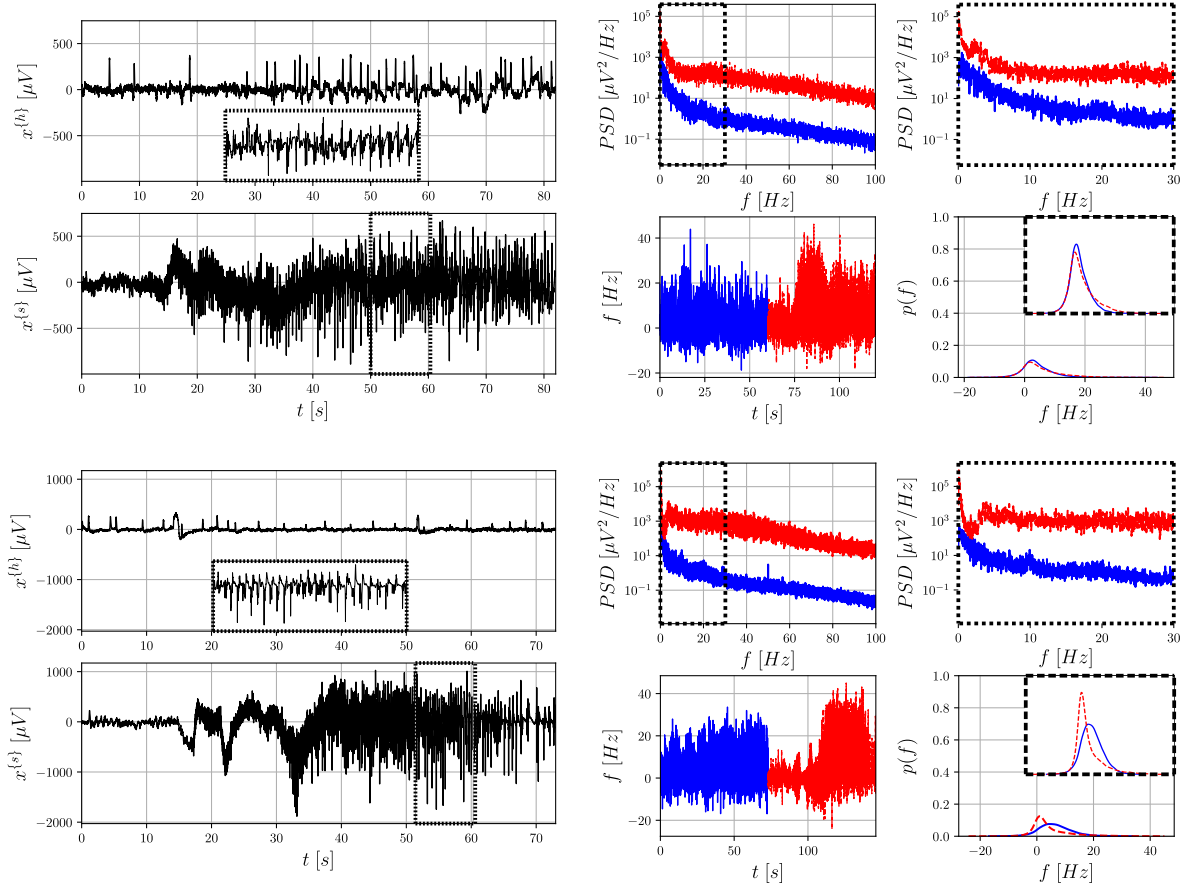
Figure 59 – **Analysis of patterns in both non-seizure and seizure condition in the frequency domain for the first patient.** The PSD shows a double effect: an overall increase in energy in all frequency bands, and a concentration of energy in bands of low frequency; this is endorsed by the HT and its representation in the estimated probability density function $p(f)$. The solid blue line (—) indicates the curves for the non-seizure condition; the red dashed line (---) indicates the curves for the seizure condition. PSDs are calculated using the following parameters: number of windows: 5; type of window: Hanning; overlap: 10%; averaging technique: mean; scaling: density.



Source: Own authorship.

As a complementary result, Fig. 60 presents the analysis in both time and frequency domains for different patients using the same electrode. Note that a similar behavior can be observed: the patterns in the time domain indicate that the non-seizure condition is more erratic and has irregular spaces between spikes, whereas the seizure condition has more frequency regular firings; besides, the amplitude of the seizure is considerably stronger than the one of the non-seizure. As for the frequency domain, there is again an increase in energy along with a spread over a wide band of frequencies. There is also a concentration of power in lower frequencies, although it is not as prominent as in the one from the first patient. These results show that seizures tend to have a relatively well defined time signature that can be identified in both domains, suggesting again that synchronized neuron spiking is a common factor that dictates epileptiform behavior.

Figure 60 – **Analysis of patterns in both non-seizure and seizure condition for different patients in the frequency domain.** Similar results using PSDs and HTs are found in other patients: spread in energy in all frequency bands and concentration on low-frequency ones. The solid black line (—) indicates the real recorded signals; the solid blue line (—) indicates the curves for the non-seizure condition; the red dashed line (---) indicates the curves for the seizure condition. PSDs are calculated using the following parameters: number of windows: 5; type of window: Hanning; overlap: 10%; averaging technique: mean; scaling: density. The patients used for these results are different from the one used in Figure 59.

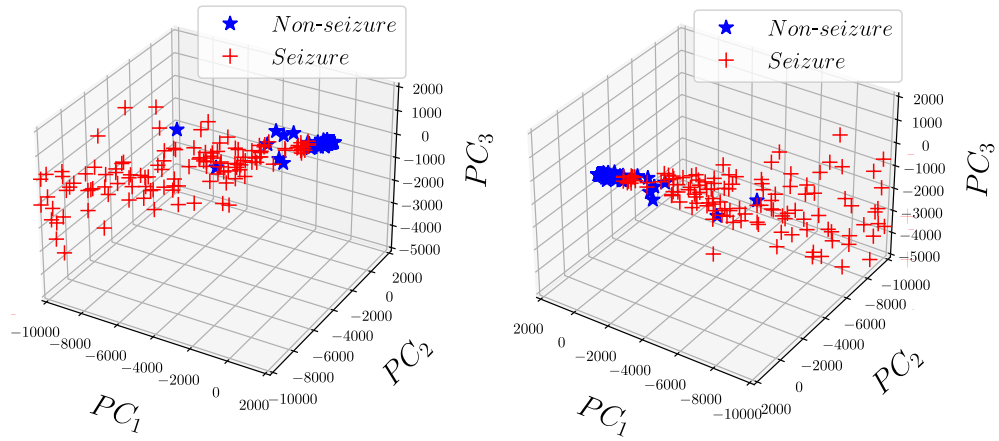


Source: Own authorship.

To assess if the pattern repeats for all of the signals and electrodes, the PCA of all the patients and seizures was carried out, considering the mean PSDs as features, as presented in Fig. 61. One of the patients had 5 seizures in approximately 4 hours, so the non-seizure condition associated to its signals was only one for all, not one for each seizure. To compensate for the reduced number of patients, the PSDs of all seizures were divided into smaller windows of 100 points each up to 1000 points. Note that there are two clusters of points, each of which corresponding to one of the conditions, non-seizure and seizure. Although they can be visually distinguished, there is a region of transition between them, thus requiring further evaluation. The Kruskal-Wallis test followed by post hoc Dunn's test are carried out and the results are available in Table 11. For all of

the Principal Components (PCs), both tests are statistically different one from the other, thus endorsing the fact that each condition has its own specific pattern and feature.

Figure 61 – **PCA considering the PSDs of all the patients and seizures.** Seizure and non-seizure clusters are formed, thus endorsing the hypothesis of these two conditions being spatially and statistically distinguishable. The blue asterisks (*) indicate the non-seizure condition; the red crosses (+) indicate the seizure condition. To better visualize the clusters, the same plot is presented twice, from different perspectives, and the axes have been limited to an acceptable range.



Source: Own authorship.

Table 11 – **Kruskal-Wallis and post hoc Dunn's test applied to distinguish the non-seizure condition from the seizure one.** The p-values indicate that, for all components, the two clusters are statistically different.

Component	H (KW value)	p-value (KW)	p-value (Dunn's test)
PC_1	231.88	$p \lll 0.01$	$p \lll 0.01$
PC_2	193.53	$p \lll 0.01$	$p \lll 0.01$
PC_3	152.35	$p \lll 0.01$	$p \lll 0.01$

Source: Own authorship.

7.3 Identifying candidate models

This section introduces the concept of orthogonal polynomials and how they can be applied to identify the (open-loop) candidate models. These are the same models that help to reconstruct the real activity after the loop is closed.

7.3.1 Orthogonal Polynomials

A set of real functions $\phi_k(t)$, $k = 1, 2, \dots$ is said to be orthogonal in the interval $[a, b]$ if:

$$\int_a^b f_i(t)f_j(t)dt = K \quad (123)$$

where $K \neq 0$ if $i = j$ and $K = 0$ if $i \neq j$. The same set is said to be orthonormal if it is the Kronecker delta. In this latter case, this implies that there exists a $\bar{f}(t) \geq 0$ such that $\Phi_k(t) = \sqrt{\bar{f}(t)}f_k(t)$, $k = 1, 2, 3, \dots$ and:

$$\int_a^b f_i(t)f_j(t)\bar{f}(t)dt = K \quad (124)$$

If a function $f(t)$ is continuous or at least partially continuous in $[a, b]$, it can be expanded in the series of orthogonal functions truncated up to a certain number of terms r :

$$f(t) \cong \sum_{i=1}^r c_i \Xi_i(t) \quad (125)$$

where c_i , $i = 1, 2, \dots, r$ are the coefficients of expansion. If the series converges to $f(t)$, Φ_j can be multiplied by both sides of the equation and integrated in $[a, b]$. The successive integration of the vectorial basis in the time domain $([0, t])$ has the following property:

$$\int_0^t \underbrace{\quad}_{n \text{ times}} \int_0^t \Xi_i(\tau) \cong \mathbf{H}_m^n \Xi_i \quad (126)$$

where $\Xi_i = [\Xi_0(t) \ \Xi_1(t) \ \dots \ \Xi_r(t)]^T \in \mathbb{R}^{r \times 1}$ is the vector composed of the truncated orthogonal series and $\mathbf{H}_m$ is the Operational Matrix of Integration (OMI) (Paraskevopoulos; Mouroutsos, 1985; Pacheco; Jr, 2002), which depends on the choice of the polynomial used and order r . In this thesis, the Fourier series was adopted due to its easy implementation and inherent sine/cosine behavior, which is usually associated to the brain dynamics (Graumann; Allison; Pfurtscheller, 2010; Brogin; Faber; Bueno, 2020b; Griffith et al., 2023):

$$\mathbf{H}_m = \begin{bmatrix} \frac{T}{2} & \mathbf{Z}_{1 \times s} & -\frac{T}{\pi} \tilde{\mathbf{e}}_s^T \\ \mathbf{Z}_{s \times 1} & \mathbf{Z}_{s \times s} & \frac{T}{2\pi} \tilde{\mathbf{I}}_{s \times s} \\ \frac{T}{2\pi} \tilde{\mathbf{e}}_s & -\frac{T}{2\pi} \tilde{\mathbf{I}}_{s \times s} & \mathbf{Z}_{s \times s} \end{bmatrix} \quad (127)$$

where T is the maximum time window considered, $\tilde{\mathbf{e}}_s = [1 \ 1/2 \ 1/3 \ \dots \ 1/s]^T \in \mathbb{R}^{1 \times s}$, $\tilde{\mathbf{I}}_{s \times s} = \text{diag}(\tilde{\mathbf{e}}_s) \in \mathbb{R}^{s \times s}$ and each $\mathbf{Z}$ of its respective dimension is a matrix containing only zeros. Now consider the following generic state-space notation for the reconstructed

models ($\{*\}$ can be any superscript):

$$\dot{\mathbf{x}}_m^{\{*\}} = \mathbf{A}_m^{\{*\}} \mathbf{x}_m^{\{*\}} + \mathbf{B}_m^{\{*\}} \mathbf{u}_m^{\{*\}}$$

where:

$$\mathbf{A}_m^{\{*\}} = \begin{bmatrix} \mathbf{Z} & \mathbf{I} \\ \mathbf{A}_1^{\{*\}} & \mathbf{A}_2^{\{*\}} \end{bmatrix}, \quad \mathbf{B}_m = \begin{bmatrix} \mathbf{Z} \\ \bar{\mathbf{M}}^{\{*\}-1} \end{bmatrix} \quad (128)$$

where $\mathbf{Z} \in \mathbb{R}^{n \times n}$ is a matrix containing only zeros, $\mathbf{I} \in \mathbb{R}^{n \times n}$ is the identity matrix, $\mathbf{A}_1^{\{*\}} = -\bar{\mathbf{M}}^{-1\{*\}} \mathbf{K}^{\{*\}}$ and $\mathbf{A}_2^{\{*\}} = -\bar{\mathbf{M}}^{-1\{*\}} \mathbf{C}^{\{*\}} \in \mathbb{R}^{n \times n}$, where $\bar{\mathbf{M}}^{\{*\}} \in \mathbb{R}^{n \times n}$ is the matrix of inertia, $\mathbf{K}^{\{*\}} \in \mathbb{R}^{n \times n}$ is the stiffness matrix, and $\mathbf{C}^{\{*\}} \in \mathbb{R}^{n \times n}$ is the damping matrix³ The dimension (or degrees of freedom) n must be selected previously, and is usually associated to the dynamic behavior of the system (Rao, 2001; Ogata, 2010). After integrating both sides in time:

$$\int_0^t \dot{\mathbf{x}}_m^{\{*\}} dt = \int_0^t \mathbf{A}_m^{\{*\}} \mathbf{x}_m^{\{*\}} dt + \int_0^t \mathbf{B}_m^{\{*\}} \mathbf{u}_m^{\{*\}} dt \quad (129)$$

$$\mathbf{x}_m^{\{*\}} - \mathbf{x}_m^{\prime\{*\}} = \mathbf{A}_m^{\{*\}} \int_0^t \mathbf{x}_m^{\{*\}} dt + \mathbf{B}_m^{\{*\}} \int_0^t \mathbf{u}_m^{\{*\}} dt \quad (130)$$

where $\mathbf{x}_m^{\prime\{*\}}$ is the vector of initial conditions. The Orthogonal Polynomial (OP) approach states that both response vector and input stimulus can be expanded in r number of terms considering a truncated polynomial series (Paraskevopoulos; Mouroutsos, 1985; Pacheco; Jr, 2002):

$$\mathbf{x}_m^{\{*\}} \cong \mathbf{X}_m^{\{*\}} \boldsymbol{\Xi}_m \quad (131)$$

$$\mathbf{u}_m^{\{*\}} \cong \mathbf{U}_m^{\{*\}} \boldsymbol{\Xi}_m \quad (132)$$

where $\mathbf{X}_m^{\{*\}}$ and $\mathbf{U}_m^{\{*\}}$ are the matrices of the coefficients after expansion, whose sizes are $(2n \times r)$. By replacing the terms into the state-space equation:

$$\mathbf{X}_m^{\{*\}} \boldsymbol{\Xi}_m - \mathbf{x}_m^{\prime\{*\}} \mathbf{e}_m \boldsymbol{\Xi}_m = \mathbf{A}_m^{\{*\}} \mathbf{X}_m^{\{*\}} \mathbf{H}_m \boldsymbol{\Xi}_m + \mathbf{B}_m^{\{*\}} \mathbf{U}_m^{\{*\}} \mathbf{H}_m \boldsymbol{\Xi}_m \quad (133)$$

where the following relations were applied: $\mathbf{e}_m = [1 \ 0 \ \dots \ 0]$, $\mathbf{e}_m \boldsymbol{\Xi}_m = 1$, $\mathbf{P}_m \boldsymbol{\Xi}_m = \int_0^t \boldsymbol{\Xi}_m(\tau) d\tau$ (Paraskevopoulos; Mouroutsos, 1985; Pacheco; Jr, 2002). After canceling out $\boldsymbol{\Xi}_m$ and rearranging the terms, the identified forced system is:

$$[\mathbf{A}_m^{\{*\}} \ \mathbf{B}_m^{\{*\}} \ \mathbf{x}_m^{\prime\{*\}} \mathbf{e}_m] \begin{bmatrix} \mathbf{X}_m^{\{*\}} \mathbf{H}_m \\ \mathbf{U}_m^{\{*\}} \mathbf{H}_m \\ \mathbf{e}_m^T \end{bmatrix} = \mathbf{X}_m^{\{*\}} \quad (134)$$

³There is a direct analogy between mass-spring-damper systems with resistor-capacitor-inductor ones. Although RCL systems are more consistent with the electrical activity of the brain, the MCK notation is kept in this text for easiness of interpretation.

For the identification of unforced (free) systems, in turn:

$$[\mathbf{A}_m^{\{*\}} \quad \mathbf{x}_m^{\prime\{*\}} \mathbf{e}_m] \begin{bmatrix} \mathbf{X}_m^{\{*\}} \mathbf{H}_m \\ \mathbf{e}_m^T \end{bmatrix} = \mathbf{X}_m^{\{*\}} \quad (135)$$

By performing the following change of variables $\boldsymbol{\Theta}_m^{\{*\}} = [\mathbf{A}_m^{\{*\}} \quad \mathbf{B}_m^{\{*\}} \quad \mathbf{x}_m^{\prime\{*\}} \quad \mathbf{e}_m]^T \in \mathbb{R}^{2n \times (2n+q+r)}$ and $\mathbf{J}_m^{\{*\}} = [\mathbf{X}_m^{\{*\}} \mathbf{P}_m \quad \mathbf{U}_m^{\{*\}} \mathbf{P}_m \quad \mathbf{e}_m^T]^T \in \mathbb{R}^{r \times (2n+q+1)}$, the vector of identified matrices $\boldsymbol{\Theta}_m^{\{*\}}$ can be expressed as:

$$\boldsymbol{\Theta}_m^{\{*\}} = (\mathbf{J}_m^{\{*\}} \mathbf{J}_m^{\{*\}T})^{-1} \mathbf{J}_m^{\{*\}} \mathbf{X}_m^{\{*\}T} \quad (136)$$

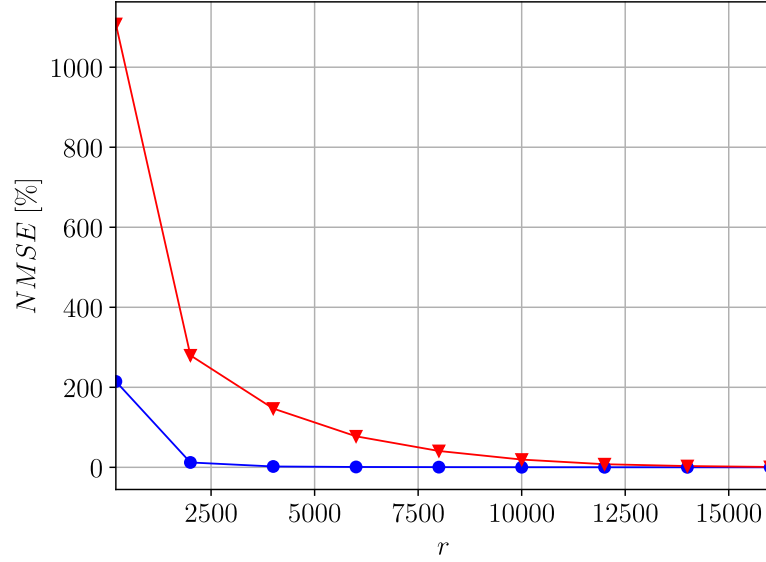
where $(\mathbf{J}_m^{\{*\}} \mathbf{J}_m^{\{*\}T})^{-1} \in \mathbb{R}^{(2n+q+1) \times (2n+q+1)}$ is non-singular. It must stressed that, in the present case, matrices $\mathbf{X}_m^{\{*\}}$ and $\mathbf{U}_m^{\{*\}}$ are obtained from the recorded activities $\mathbf{x}^{\{*\}}$ and $\mathbf{u}^{\{*\}}$ projected onto $\boldsymbol{\Phi}_m$, since they are the information available for the identification.

7.3.2 Examples of candidate models

Considering the features of both activities, it is desirable to have models of the type: $\dot{\mathbf{x}}^{\{h\}} = \mathbf{A}^{\{h\}} \mathbf{x}^{\{h\}}$, for the non-seizure condition, and $\dot{\mathbf{x}}^{\{s\}} = \mathbf{A}^{\{s\}} \mathbf{x}^{\{s\}}$, for the seizure condition. However, dynamic matrices that fully represent both behaviors are difficult to obtain, and even highly representative analytical models, such as the Epileptor (Jirsa et al., 2014), do not fully capture the richness of all dynamics found in seizures. Thus, an alternative solution is proposed in this chapter, considering candidate (or “dummy”) unforced models of the type: $\dot{\mathbf{x}}_m^{\{h\}} = \mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}}$ and $\dot{\mathbf{x}}_m^{\{s\}} = \mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}}$.

To find appropriate $\mathbf{A}_m^{\{ch\}}$ and $\mathbf{A}_m^{\{cs\}}$ for the recordings used in Fig. 58, a convergence analysis was carried out to find a reasonable r that provided a low error between $\mathbf{x}^{\{*\}}$ and $\mathbf{X}_m^{\{*\}} \boldsymbol{\Phi}_m$. Figure 62 presents an r vs $NMSE$ plot, where $NMSE$ is the mean squared error normalized by the difference between the maximum and minimum values of each signal. To achieve $NMSE \leq 1\%$, relatively high values of r are necessary: $r = 6001$ and $NMSE \cong 0.88\%$ for the non-seizure condition; $r = 16001$ and $NMSE \cong 0.95\%$ for the seizure condition. This is due to the richness and complexity of the signals analyzed, composed of several frequency components, which thus implies in more terms to reconstruct them.

Figure 62 – **Analysis of convergence for the number of terms in the Fourier vector basis considering the real signals in Figure 58.** For the non-seizure condition, it takes $r = 6001$ terms to obtain $NMSE < 1\%$, whereas it takes 16001 terms in the seizure condition to achieve that error, thus evidencing the complexity of the seizure signature. The blue line with dot markers (-●-) indicates values for the non-seizure condition; the red red with triangle markers (-▲-) represents values for the seizure condition.



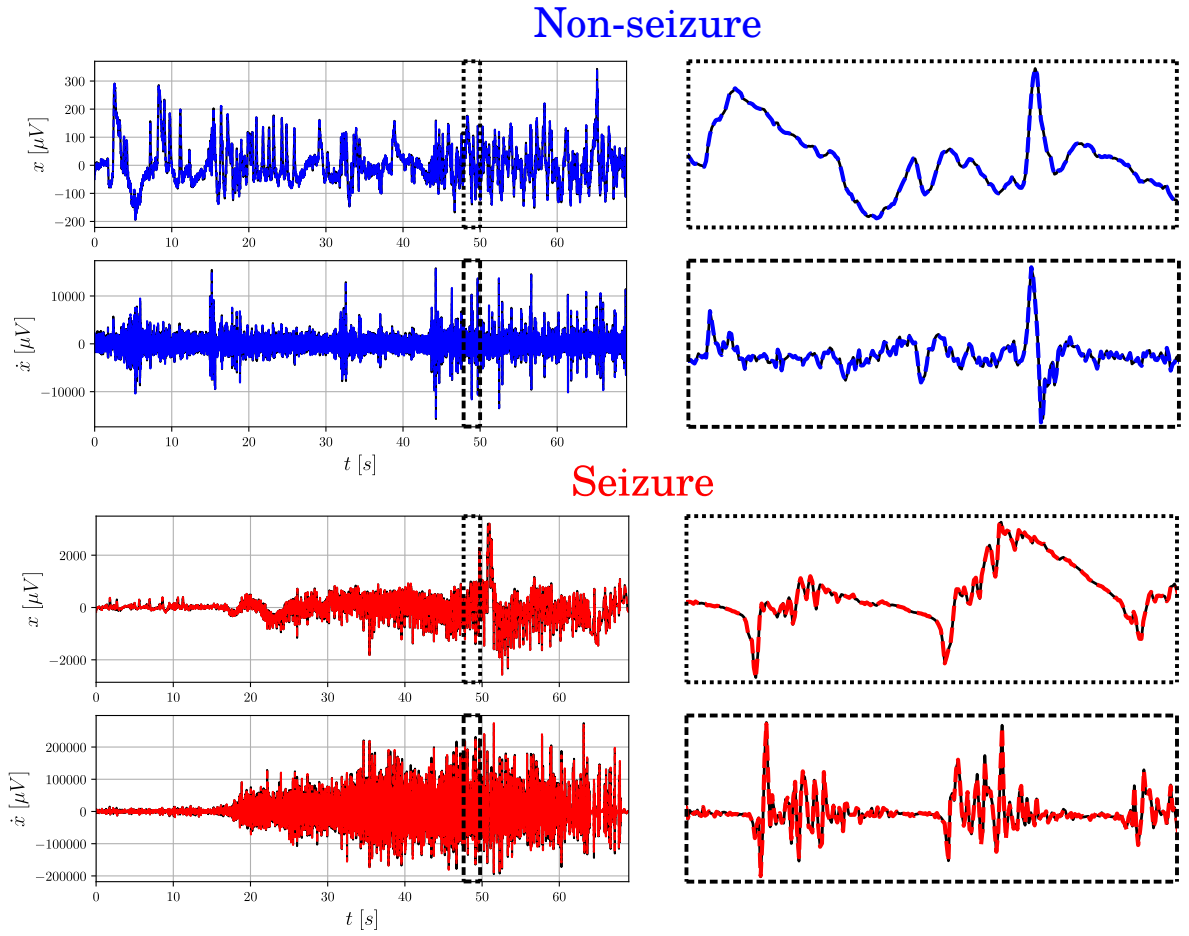
Source: Own authorship.

As an example, Fig. 63 presents both $\mathbf{x}^{\{*\}}$ and $\mathbf{X}_m^{\{*\}}\Phi_m$ in time using $r = 16001$ for both conditions. It must be stressed that these are only the truncated Fourier series composed of the coefficients of expansion (based on the real signals) and vector basis, not the closed-loop reconstructed ones. This number of terms is considered sufficient because both states (difference of potential and derivative) are well approximated. Besides the description provided for Figs. 58 and 59, it is also interesting to visualize the derivatives in the time domain of both signals: while the irregularity of the non-seizure condition is reflected on its derivative, presenting mostly a noisy-like baseline with short bursts of energy, the high increase in energy is even more evident in the seizure condition.

Figure 64, in turn, presents an illustration of the identification approach: dynamic matrices $\mathbf{A}_m^{\{h\}}$ and $\mathbf{A}_m^{\{s\}}$ are identified based on the states of the real recordings $\mathbf{x}^{\{h\}}$ and $\mathbf{x}^{\{s\}}$, respectively. For simplicity, only the equivalent responses are shown in the figure, not including any derivatives. Physically, the resulting oscillation is equivalent to the best approximation of a single degree-of-freedom mass-spring-damper system (or, by analogy, resistant-indutance-capacitance circuit) based on the Fourier basis considering $r = 16001$ terms. In other words, all information contained in the non-seizure and seizure signals is summarized as single predominant oscillatory systems, which are the candidate

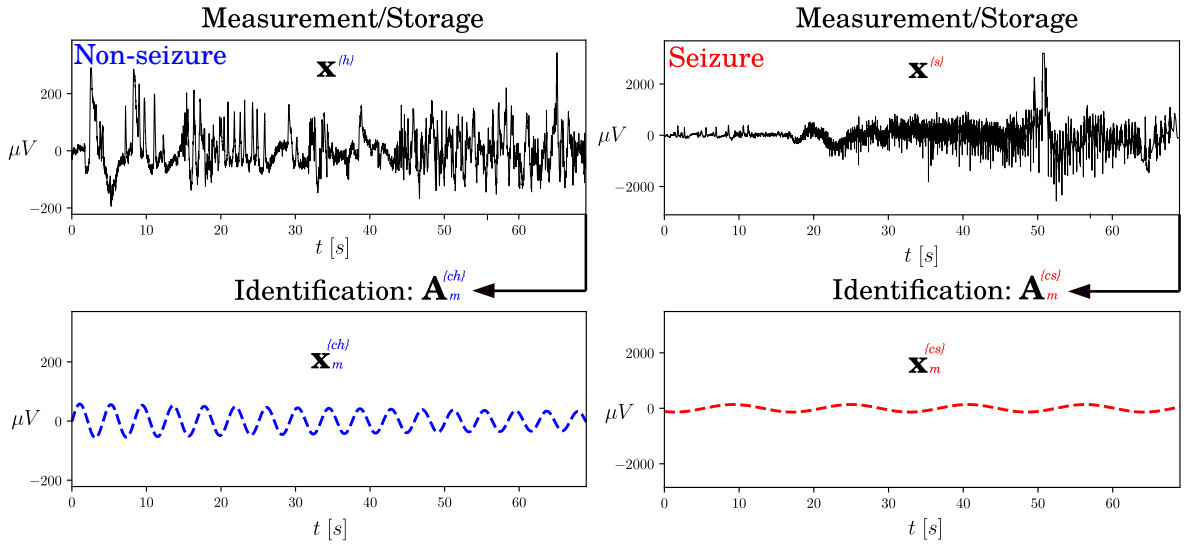
models. Simulations can then be run considering these identified dummy models, which are represented as $\mathbf{x}_m^{\{h\}}$ and $\mathbf{x}_m^{\{s\}}$, respectively.

Figure 63 – **Truncated Fourier series compared to the real signals.** The sines and cosines of the Fourier basis are capable of reconstructing fairly well the signals from Fig. 62, thus evidencing their suitability for this purpose. The solid black line (—) indicates the real signals; the blue dashed line (— —) indicates the series for the non-seizure conditions; the red dashed line (- -) indicates the series for the seizure condition. The truncated series for each one is composed of $\mathbf{X}_m^{\{*\}}\boldsymbol{\Xi}_m$, that is, the coefficients of expansion and vector basis. The number of terms for both conditions is $r = 16001$.



Source: Own authorship.

Figure 64 – **Identification of dummy/candidate models based on the real recordings.** The dynamic matrix $\mathbf{A}_m^{\{h\}}$ is identified based on the non-seizure condition $\mathbf{x}^{\{h\}}$; the dynamic matrix $\mathbf{A}_m^{\{s\}}$ is identified based on the seizure condition $\mathbf{x}^{\{s\}}$. Responses $\mathbf{x}_m^{\{h\}}$ and $\mathbf{x}_m^{\{s\}}$ in time can be generated by running simulations considering both matrices. Recall that the states $\mathbf{x}^{\{*\}}$ represent the real recording and its numerical derivative; $\mathbf{x}_m^{\{*\}}$, in turn, contains an equivalent response (shown in the figure) and its derivative (not shown in the figure). The solid black line (—) indicates the recorded signals; the blue dashed line (—) indicates the candidate states $\mathbf{x}_m^{\{h\}}$; the red dashed line (—) indicates the candidate states $\mathbf{x}_m^{\{s\}}$.



Source: Own authorship.

7.3.3 Remarks on the identification process

1. Nature of the stimulus input. Note that these matrices can only be identified based on previous knowledge about $\mathbf{u}^{\{*\}}$, i.e., if the input stimulus is known. Conversely, $\mathbf{u}^{\{*\}}$ can be estimated if the parameters from the pair $(\mathbf{A}_m^{\{*\}}, \mathbf{B}_m^{\{*\}})$ are known. In the case of the non-seizure and seizure activities, none of them is available. Besides, there is not a clear meaning of the possible mechanisms that play the role of a stimulus in generating a seizure (Vezzani et al., 2011). Therefore, an alternative strategy is adopted and the system is identified in the free condition: $\mathbf{u}^{\{*\}} = 0$, $\Theta_m^{\{*\}} = [\mathbf{A}_m^{\{*\}} \mathbf{x}_m^{\{*\}'} \mathbf{e}_m]$ and $\mathbf{J}_m^{\{*\}} = [\mathbf{X}_m^{\{*\}} \mathbf{P}_m \mathbf{e}_m^T]^T$ and only $\mathbf{A}_m^{\{*\}}$ is obtained (Final Remarks).

2. Representativeness of the dynamic matrix. The whole identification process assumes a linear time-invariant dynamic matrix $\mathbf{A}_m$, which is too simple of a model to fully capture the dynamics of a real brain activity. However, $\mathbf{A}_m$ is a system equivalent to the physical one, but not strictly a physical system. Besides, to compensate for this, not only is the approach applied in closed loop, but a pseudo-time-varying $\mathbf{A}_m(t)$ is proposed considering an update of this model over time based on a monitoring system, which is

discussed in the next sections.

3. Definition of the input matrix. Although the identification imposes a restriction on $\mathbf{A}_m$, it makes the choice of $\mathbf{B}_m$ more convenient because it is defined *a posteriori*. In this work, $\mathbf{B}_m^{\{*\}} = \mathbf{B} = [\mathbf{Z} \ \mathbf{I}]^T$ is adopted, regardless of $\{*\}$, and the input stimulus $\mathbf{u}_m$ is allowed to have a direct 1:1 relation when applied to the system for control purposes. It is tacitly assumed that $\mathbf{M} = \mathbf{I}$, and to compensate for this fact, the control gain is adjusted also *a posteriori*, which is discussed in the next sections.

4. Number of degrees of freedom. Since the brain activity is complex, one might argue that a high degree of freedom is necessary to represent it well. Nevertheless, it must be stressed that, as dummy/candidate models, the main interest lies on their behavior after closed-loop evaluation, and thus they do not need to be highly accurate in open loop. Based on this reasoning, $n = 1$ in this work, and although this is the simplest state-space model possible, it is also the most flexible one⁴, such that: $\mathbf{x}_m = [x_m \ \dot{x}]^T$. During the simulations, x_m is reconstructed based on the stored signal x , and $\dot{x}_m$ is reconstructed based on $\dot{x}$, which is the numerical derivative of x . In this sense, note that each $\mathbf{x}_m$ represents a single electrode and its numerical derivative, and it is also taken as an independent oscillating system.

7.4 Signal reconstruction via closed-loop models

According to the second hypothesis, a closed-loop linear model represents well each of the measured activities (non-seizure and seizures). Therefore, if the candidate model for the non-seizure condition is used to reconstruct the non-seizure activity in closed loop:

$$\dot{\mathbf{x}}_m^{\{ch\}} = \underbrace{\mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}} + \mathbf{B} \mathbf{u}_m^{\{ch\}}}_{\equiv \mathbf{A}_m^{\{h\}} \mathbf{x}_m^{\{h\}} \text{ (Closed loop)}}, \quad \text{and} \quad \mathbf{u}_m^{\{ch\}} = -\mathbf{G}_m^{\{h\}} [\mathbf{x}_m^{\{ch\}} - \mathbf{x}^{\{h\}}] \quad (137)$$

then the closed-loop candidate model behaves “as if” it were the real recorded one $\mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}} + \mathbf{B} \mathbf{u}_m^{\{ch\}} \equiv \mathbf{A}_m^{\{h\}} \mathbf{x}_m^{\{h\}}$. Note that, according to the notation of Eq. 122:

$$\mathbf{u}_m^{\{ch\}} = -\mathbf{G}_m^{\{h\}} \mathbf{x}_m^{\{ch\}} + \mathbf{G}_m^{\{h\}} \mathbf{x}^{\{h\}} \quad (138)$$

that is, the states from the candidate model $\mathbf{x}_m^{\{ch\}}$ are attenuated while the states of the non-seizure condition $\mathbf{x}^{\{h\}}$ are induced. This implies that $\dot{\mathbf{x}}_m^{\{ch\}}, \mathbf{x}_m^{\{ch\}} \rightarrow \dot{\mathbf{x}}^{\{h\}}, \mathbf{x}^{\{h\}}$. To compute the gain $\mathbf{G}_m^{\{h\}} \in \mathbb{R}^{1 \times 2n}$, the same candidate model $\mathbf{A}_m^{\{ch\}}$ is used in an optimization problem based on a positive-definite matrix $\mathbf{P}_m^{\{ch\}}$ which assures stability (Slotine; Li

⁴“Flexible” also means “controllable” in this work. Several degrees of freedom were tested and $n = 1$ has proved to be the best one in terms of controllability

et al., 1991; Tanaka; Wang, 2004).

If the candidate model for the seizure condition is used to reconstruct the seizure activity in closed loop, an analogous procedure is done:

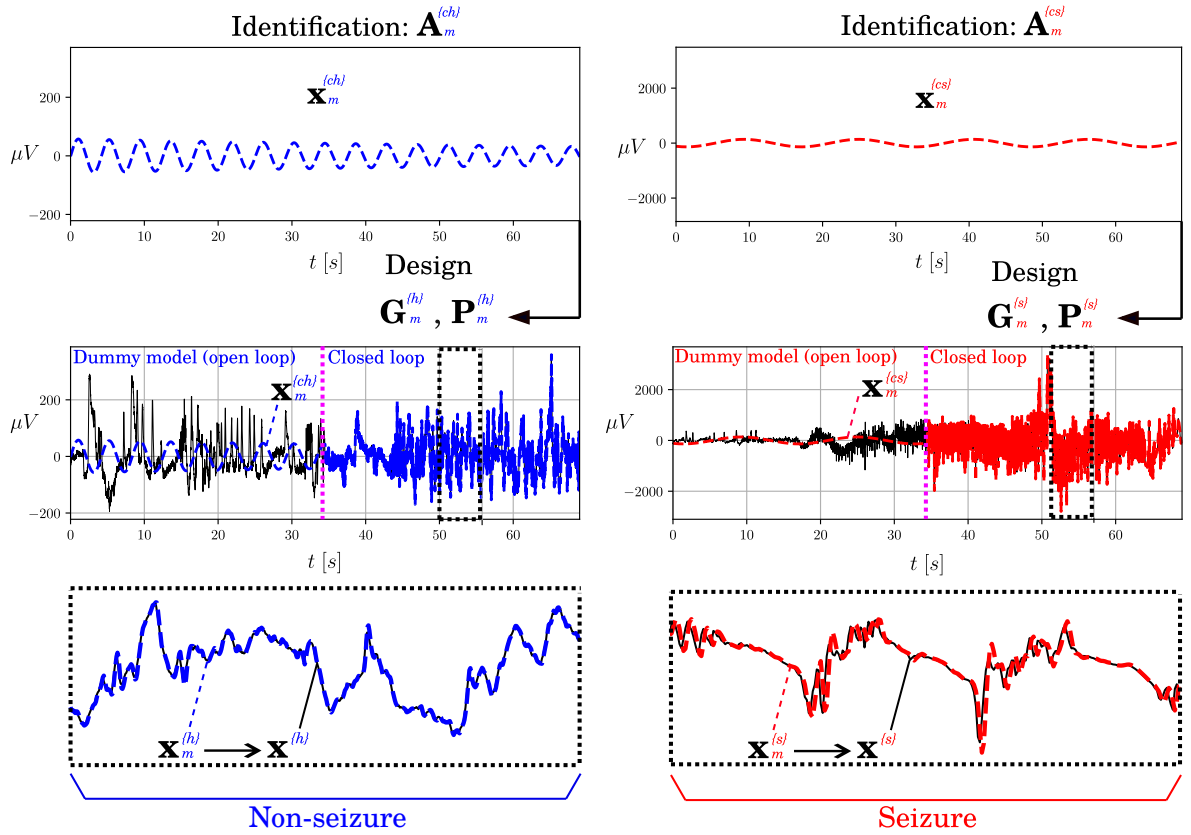
$$\begin{aligned} \dot{\mathbf{x}}_m^{\{cs\}} &= \overbrace{\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}}}^{\text{Open loop}}, \quad \text{and} \quad \mathbf{u}_m^{\{cs\}} = -\mathbf{G}_m^{\{s\}} [\mathbf{x}_m^{\{cs\}} - \mathbf{x}^{\{s\}}] \\ &\equiv \mathbf{A}_m^{\{s\}} \mathbf{x}_m^{\{s\}} \text{ (Closed loop)} \end{aligned} \quad (139)$$

then the closed-loop candidate model behaves “as if” it were the real recorded one $\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}} \equiv \mathbf{A}_m^{\{s\}} \mathbf{x}_m^{\{s\}}$. Note that, according to the notation of Eq. 122:

$$\mathbf{u}_m^{\{cs\}} = -\mathbf{G}_m^{\{s\}} \mathbf{x}_m^{\{cs\}} + \mathbf{G}_m^{\{s\}} \mathbf{x}^{\{s\}} \quad (140)$$

that is, the states from the candidate model $\mathbf{x}_m^{\{cs\}}$ are attenuated while the states of the seizure condition $\mathbf{x}^{\{s\}}$ are induced. This implies that $\dot{\mathbf{x}}_m^{\{cs\}}, \mathbf{x}_m^{\{cs\}} \rightarrow \dot{\mathbf{x}}^{\{s\}}, \mathbf{x}^{\{s\}}$. To compute the gain $\mathbf{G}_m^{\{s\}} \in \mathbb{R}^{1 \times 2n}$, the same candidate model $\mathbf{A}_m^{\{cs\}}$ is used in an optimization problem based on a different positive-definite matrix $\mathbf{P}_m^{\{cs\}}$ which assures stability (Slotine; Li et al., 1991; Tanaka; Wang, 2004). An illustration of the full procedure is depicted in Fig. 65. The gains are calculated during the optimization problem; before the activation of the controller, the simulated states are the candidate/dummy ones; after its activation, the states of the reconstructed models converge towards the desired ones from the real recordings. This reconstruction is completely artificial, in an attempt to “copy” the actual signal being recorded. This is only possible thanks to the candidate model, which plays the role of the best malleable substract possible (according to the identification by the Fourier basis) that adapts itself to the time signatures.

Figure 65 – **Closed-loop model reconstruction using the real signals.** Gains $\mathbf{G}_m^{\{h\}}$ and $\mathbf{G}_m^{\{s\}}$, as well as stability matrices $\mathbf{P}_m^{\{h\}}$ and $\mathbf{P}_m^{\{s\}}$, are computed based on the identified candidate models $\mathbf{A}_m^{\{ch\}}$ and $\mathbf{A}_m^{\{cs\}}$, respectively, in an optimization problem. Before the control is activated, $\mathbf{x}_m^{\{ch\}}$ and $\mathbf{x}_m^{\{cs\}}$ are the states of the dummy models; after its activation, the states of both reconstructed models converge towards the desired ones: $\mathbf{x}_m^{\{h\}} \rightarrow \mathbf{x}^{\{h\}}$ and $\mathbf{x}_m^{\{s\}} \rightarrow \mathbf{x}^{\{s\}}$. The solid black line (—) indicates the recorded signals; the blue dashed line (— —) indicates the reconstructed models of the non-seizure condition in open loop $\mathbf{x}_m^{\{ch\}}$ and closed loop $\mathbf{x}_m^{\{h\}}$; the red dashed line (— —) indicates the reconstructed models of the seizure condition in open loop $\mathbf{x}_m^{\{cs\}}$ and closed loop $\mathbf{x}_m^{\{s\}}$; the magenda dotted line (...) indicates the activation of the controller.



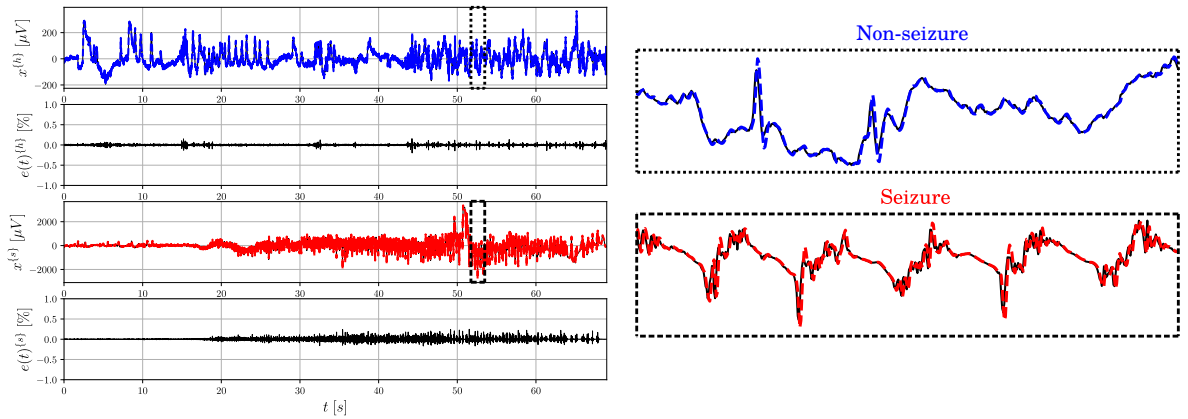
Source: Own authorship.

7.4.1 Reconstruction error

Figure 66 presents both non-seizure and seizure activities with their corresponding reconstructions – in this case, considering full closed-loop simulations over the whole time. With the values chosen for the decay rate, the minimum and maximum values for the normalized relative errors of both are, respectively: $e(t)^{\{h\}} = [1.03 \cdot 10^{-4}, 19.72]\%$, $e(t)^{\{s\}} = [5, 89 \cdot 10^{-7}, 24.65]\%$. Therefore, the proposed approach is not only more effective in reconstructing the non-seizure activity, but such a reconstruction depends on the magnitude of the decay rate: increasing this parameter means searching for solutions that

provide more intense gains for the closed-loop controllers (Tanaka; Wang, 2004); since the application of these controllers in this case corresponds to obtaining an approximated response of a desired reference signal, better approximations can only be attained at the expense of high-intensity gains. For now this does not pose any problem because the gains are not associated to attenuation, representing only abstract values. Nonetheless, since attenuation relies on an appropriate reconstruction, this issue is taken into account in this chapter and discussed in the next sections. At last, reconstructing the seizure activity leads to a higher error, indicating again the complexity of the signal, which is expected since its sine-cosine model has more terms and is, thus, more complex.

Figure 66 – **Full closed-loop model reconstruction and reconstruction error.** The errors are calculated over the whole time of simulation in closed-loop, and the results indicate that there is a higher error, or less efficiency, in reconstructing the seizure activity. The solid black line (—) indicates the recorded signals; the dashed blue line (—) indicates the reconstructed model of the non-seizure condition; the red dashed line (—) indicates the reconstructed models of the seizure condition. The decay rate used for the simulation is $\alpha^{\{h\}} = \alpha^{\{s\}} = 100$.



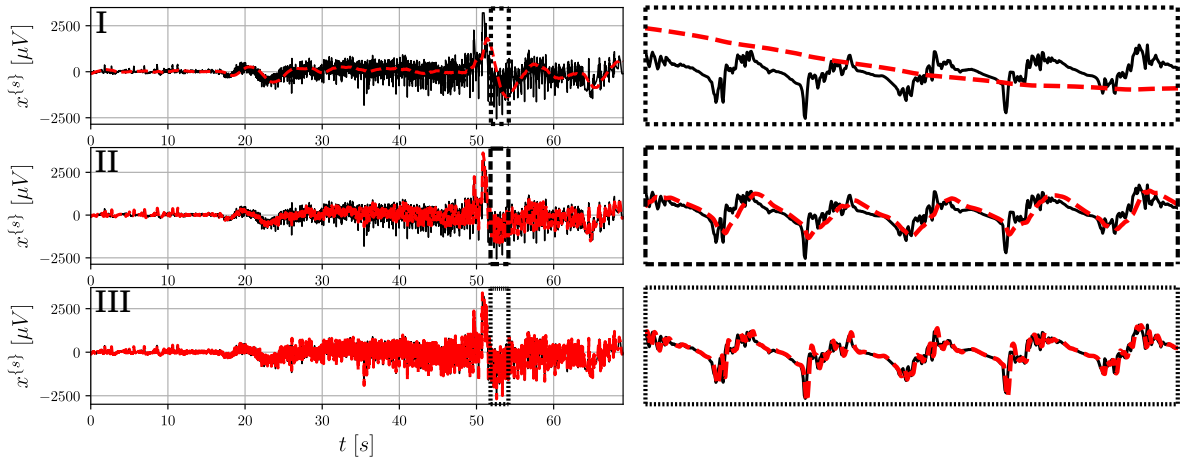
Source: Own authorship.

7.4.2 Influence of the decay rate

The simulations demonstrated that the higher the decay rate, the lower the error between reconstructed model and real signal, which is then related to the representativeness of the dynamics reconstructed. This effect is shown in more detail in Fig. 67, where other values for the decay rate are used. Recall that the non-seizure condition is always an artificial reconstruction, but since the seizure condition is also considered to represent a real epileptiform event that eventually suffers the influence of the controller, it is the only analyzed in the figure. In the first simulation (I), $\alpha^{\{s\}} = 0$ leads to the reconstruction of low-frequency components, which basically traces the silhouette of the seizure activity, capturing the transitions in amplitude and the highest peak. In the second simulation (II), $\alpha^{\{s\}} = 10$ leads to a refined reconstruction, capturing faster components as well, but

missing some small peaks. In the third simulation (III), $\alpha^{\{s\}} = 80$ provides an even better reconstruction, capturing slow or fast components, as well as small peaks. As discussed in the next section, the decay rate influences directly the effectiveness of the controllers proposed to attenuate the seizure.

Figure 67 – **Closed-loop model reconstructions for different decay rates.** As the decay rates increases, seizure reconstruction captures not only slow oscillations, but also high-frequency ones. The solid black line (—) indicates the recorded signals; the red dashed line (---) indicates the reconstructed models of the seizure condition. The decay rates used for the simulations are: (I) $\alpha^{\{s\}} = 0$, (II) $\alpha^{\{s\}} = 10$ and (III) $\alpha^{\{s\}} = 80$.



Source: Own authorship.

7.4.3 Remarks on the closed-loop reconstructed models

1. Gains of the input stimulus. Note that both $\mathbf{u}_m^{\{ch\}}$ and $\mathbf{u}_m^{\{cs\}}$ are artificial entries that are only applied computationally to assure that the reconstructed states converge towards the recorded/stored ones. Considering this, the magnitude of both gains $\mathbf{G}_m^{\{h\}}$ and $\mathbf{G}_m^{\{s\}}$ can be conveniently adjusted, even to relatively high levels.

2. Application of the stimulus. As mentioned in the previous section, $\mathbf{A}_m^{\{*\}}$ is a system equivalent to the physical one. Besides, given that $\mathbf{B} = [\mathbf{Z} \ \mathbf{I}]^T$ is defined *a posteriori*, to remove the effect of the inertia $\mathbf{M}$ over the input stimulus, the following adaptation is adopted:

$$\mathbf{u}_m^{\{*\}} = -\varsigma \mathbf{G}_m^{\{*\}} [\mathbf{x}_m^{\{*\}} - \mathbf{x}^{\{*\}}] \quad (141)$$

where $\varsigma = m$, since $\mathbf{M}_{1 \times 1} = m$, for a single degree-of-freedom system.

7.5 Signal attenuation via closed-loop models

Since the closed-loop model for the seizure condition now describes the dynamics of a seizure sufficiently well, it can be regarded “as if” it were a new single model ($\mathbf{A}_m^{\{s\}} \mathbf{x}_m^{\{s\}}$). If the closed-loop approach can also be used to simulate seizure attenuation by adding a second layer of control:

$$\dot{\mathbf{x}}_m^{\{cs\}} = \underbrace{\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}} + \mathbf{B} \mathbf{u}^{\{sh\}}}_{\equiv \mathbf{A}_m^{\{sh\}} \mathbf{x}_m^{\{sh\}} \text{ (2nd Closed loop)}}, \quad \text{and} \quad \mathbf{u}^{\{sh\}} = -\mathbf{G}^{\{ad\}} [\mathbf{x}^{\{s\}} - \mathbf{x}^{\{h\}}] \quad (142)$$

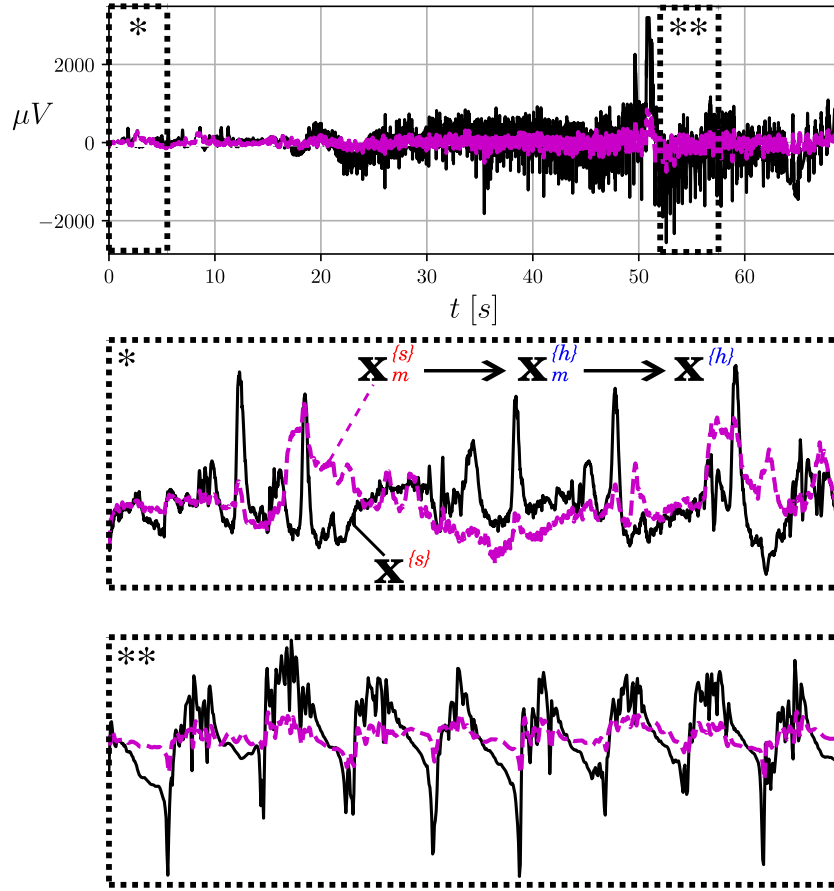
then the closed-loop candidate model behaves “as if” it were the real recorded one being attenuated: $\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}} + \mathbf{B} \mathbf{u}^{\{sh\}} \equiv \mathbf{A}_m^{\{sh\}} \mathbf{x}_m^{\{sh\}}$. Note that, according to the notation of Eq. 122:

$$\mathbf{u}^{\{sh\}} = -\mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}} \mathbf{x}^{\{h\}} \quad (143)$$

that is, the states from the seizure model are attenuated while the states of the non-seizure condition $\mathbf{x}^{\{h\}}$ are induced. This implies that $\dot{\mathbf{x}}_m^{\{s\}}, \mathbf{x}_m^{\{s\}} \rightarrow \dot{\mathbf{x}}_m^{\{h\}}, \mathbf{x}_m^{\{h\}}$, and $\dot{\mathbf{x}}_m^{\{h\}}, \mathbf{x}_m^{\{h\}} \rightarrow \dot{\mathbf{x}}_m^{\{h\}}, \mathbf{x}_m^{\{h\}}$, that is, the reconstructed states from the seizure condition are driven to the desired reconstructed non-seizure states, which, in turn, converge to the actual non-seizure states. The vectors $\mathbf{x}^{\{s\}}$ and $\mathbf{x}^{\{h\}}$ are used in the input stimulus because $\mathbf{x}_m^{\{s\}} \rightarrow \mathbf{x}^{\{s\}}$ and $\mathbf{x}_m^{\{h\}} \rightarrow \mathbf{x}^{\{h\}}$, as previously mentioned. Besides, as discussed in the next subsection, this stimulus is the one responsible for attenuating a seizure in a real scenario.

To compute the gains $\mathbf{G}_1^{\{ad\}}, \mathbf{G}_2^{\{ad\}} \in \mathbb{R}^{1 \times 2n}$, the concept of adaptive control is used (Goel; Kumar; Narayan, 2016), and a positive-definite $\mathbf{P}^{\{ad\}}$ (also found from an optimization problem) is combined with the information from the reconstructed states and error compared to the actual states to update $\mathbf{G}^{\{ad\}}$. For further details on the formulation to obtain the gains, please see Final Remarks. For the sake of understanding, Figure 68 presents a comparison between the recorded signal $\mathbf{x}^{\{s\}}$ and the closed-loop model that simulates seizure attenuation. The controller is active during the whole simulation, and note that not only is the amplitude considerably reduced, but the patterns are also changed.

Figure 68 – **Seizure attenuation considering reconstructed models.** The input used to reconstruct the seizure $\mathbf{Bu}_m^{\{cs\}}$ is counterbalanced by the input stimulus that attempts to attenuate it: $\mathbf{Bu}^{\{sh\}}$. This leads to two competing effects in the same simulation: seizure reconstruction and seizure attenuation. The controller is active during the whole simulation. Violet is chosen intentionally to represent a seizure being attenuated since it is an intermediate condition between seizure and non-seizure. The solid black line (—) indicates the recorded signal in the seizure condition $\mathbf{x}^{\{s\}}$; the violet dashed line (—) indicates the reconstructed seizure model being attenuated.



Source: Own authorship.

To evaluate seizure attenuation, the first parameter used is $\alpha^{\{s\}}$, defined as the decay rate to reconstruct the seizure model in relation to a real seizure. Essentially, since it is related to the speed of convergence in the control theory (Tanaka; Wang, 2004), it plays the role of an intensifier: the higher it is, the better the seizure is reconstructed, i.e., the closer to the behavior of the real seizure it becomes. The adherence, in turn, can be defined as:

$$\bar{\gamma}_{ad} = \{1 - \max[\text{abs}(e(t)^{\{s\}})]\} \times 100 \quad (144)$$

where $e(t)^{\{s\}}$ is the normalized relative error between the real and reconstructed seizure:

$$e(t)^{\{s\}} = \frac{x^{\{s\}} - x_m^{\{s\}}}{\max(x^{\{s\}}) - \min(x^{\{s\}})} \quad (145)$$

Note that, since this parameter is based on the maximum error, it can be regarded as the minimum adherence. This means that it is a conservative parameter, and for other parts of the signal, the model necessarily achieves higher similarities. As for the attenuation level ΔV , the following equation is applied:

$$\Delta V = \frac{1}{W} \sum_{i=1}^W \left[\frac{\Delta V_i^{\{s\}} - \Delta V_{m,i}^{\{s\}}}{\Delta V_i^{\{s\}}} \right] \times 100 \quad (146)$$

where:

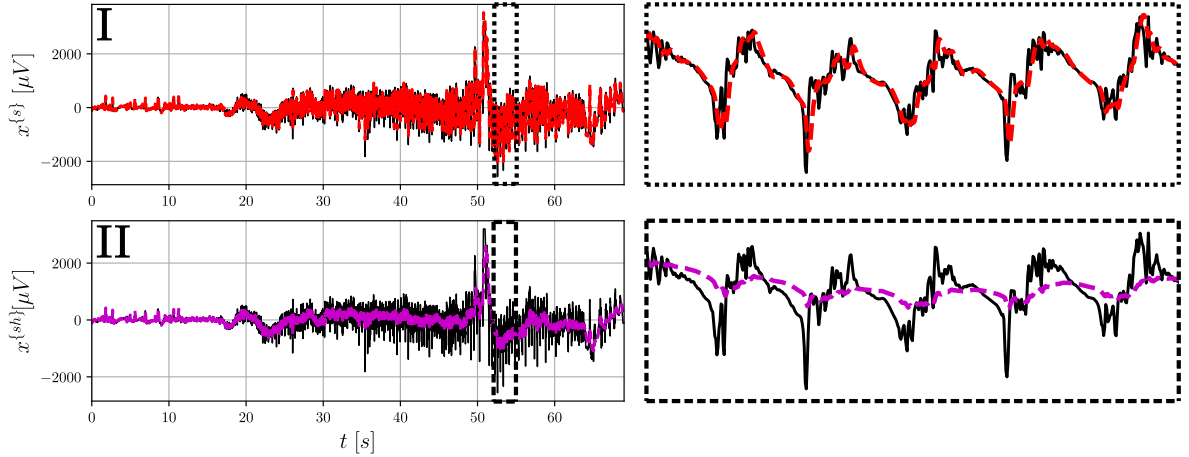
$$\Delta V_i^{\{s\}} = \frac{\text{RMS}(x_i^{\{s\}}) - \text{RMS}(x_i^{\{h\}})}{\text{RMS}(x_i^{\{h\}})}, \quad \Delta V_{m,i}^{\{s\}} = \frac{\text{RMS}(x_{m,i}^{\{s\}}) - \text{RMS}(x_i^{\{h\}})}{\text{RMS}(x_i^{\{h\}})} \quad (147)$$

where $\text{RMS}(x_i^{\{s\}})$ is the Root Mean Square (RMS) value of the i -th time window of the real seizure signal, $\text{RMS}(x_i^{\{h\}})$ is the RMS value of the corresponding i -th time window of the real non-seizure signal, $\text{RMS}(x_{m,i}^{\{h\}})$ is the RMS value of the corresponding i -th time window of the reconstructed seizure, and W is the number of time windows considered – which, for all cases, is $W = 10$. It should be stressed that this equation is proposed in the present form to remove the effect of the RMS value of the non-seizure signal compared to the one from the attenuated seizure. This is necessary because the controller does not only attenuate a seizure, but also attempts to drive it back to the non-seizure behavior.

7.5.1 Adaptive controller

Figure 69 presents the results for the adaptive controller, which is activated during the whole simulation. A decay rate of $\alpha^{\{s\}} = 25$ was chosen to reconstruct the seizure and $\alpha^{\{ad\}} = 10$ to attenuate it. For the pair of $(\alpha^{\{s\}}, \alpha^{\{ad\}})$, a significant reduction (more precisely, 30.85% of reduction, in terms of power of signal) can be seen both in terms of amplitude and oscillating behavior, which illustrates the efficiency of the controller. Physically, its application means emitting a combined electrical stimulus that attempts to mitigate the undesired seizure dynamics while inducing a non-seizure one at all time instants, whose intensity of amplitude is modulated by the adaptive gains. In this sense, both input and gains are adjustable, which is not the case for the next type of controller, presented in the next section.

Figure 69 – **Activation of the adaptive controller for attenuating the reconstructed signal.** The controller is activated during the whole simulation with two simultaneous inputs (as in Fig. 68) to reconstruct and attenuate a seizure based on adaptive gains. The solid black line (—) indicates the recorded signal; the red dashed line (—) indicates the reconstructed model of the seizure condition before attenuation (**I**); and the violet dashed line (—) indicates the reconstructed model after attenuation (**II**).. The decay rate used for the simulation is: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$.



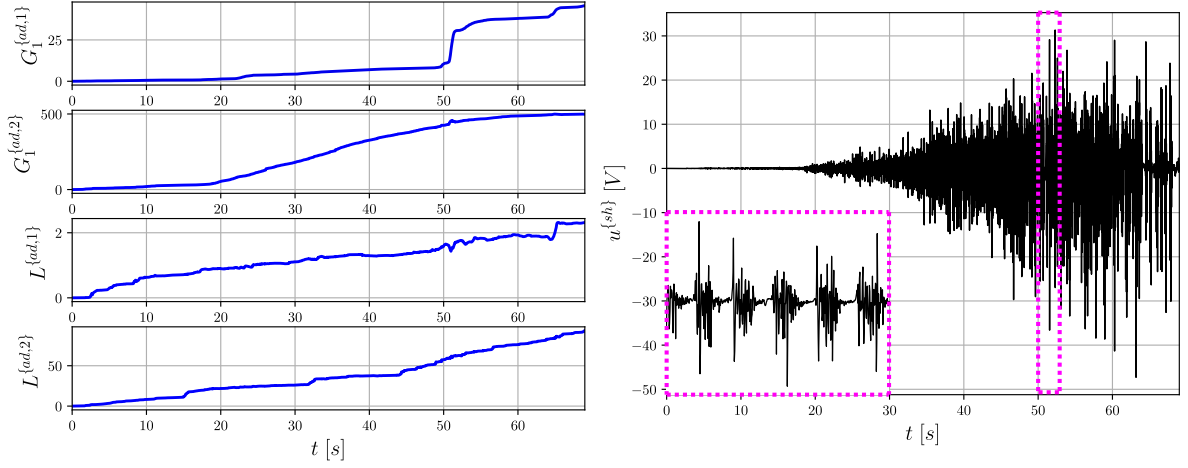
Source: Own authorship.

Figure 70, in turn, presents the adaptive gains and input stimulus necessary to attenuate the seizure. The gains $G_1^{\{ad,1\}}$, $G_1^{\{ad,2\}}$ and $L_1^{\{ad,1\}}$ tend to stabilize over time, especially after 50 seconds when the seizure begins to approach offset, whereas $G_1^{\{ad,2\}}$ presents a monotonically increasing behavior for the period of time considered. Since this latter gain is related to the state that represents the derivative of the real signal, it means that the controller has more difficulties in assimilating it and use it as an input to drive the seizure back to a non-seizure condition. However, this does not significantly compromise its efficiency. As for the input stimulus, it also tends to stabilize over time, especially after the highest amplitude right after 50 seconds. Its magnitude is bounded between $-47.28V$ and $31.34V$ and the shapes of the pulses resemble bursts.

Since there is a close dependency of the intensity of the input stimulus on $\alpha^{\{s\}}$, which also influences the attenuation level, this parameter is analyzed in more detail in Fig. 71. In general, as $\alpha^{\{s\}}$ increases, the minimum adherence of the reconstructed model in relation to the real seizure as well as the magnitude of input stimulus increase, but the level of attenuation decreases. This means that the better a seizure is described (as in Fig. 67), the more intensity in terms of input is necessary to attenuate it. Suppose $\alpha^{\{s\}} = 20$ is selected; then, the minimum adherence $\gamma = 55.13\%$ is obtained (i.e., the seizure is at least 55.13% correctly described by the model), and the attenuation level obtained is $\Delta V = 37.57\%$. Such information is relevant in practical terms when designing controllers

for real applications: by adjusting the level of tension applied, it is expected that 37.57% of the seizure is attenuated.

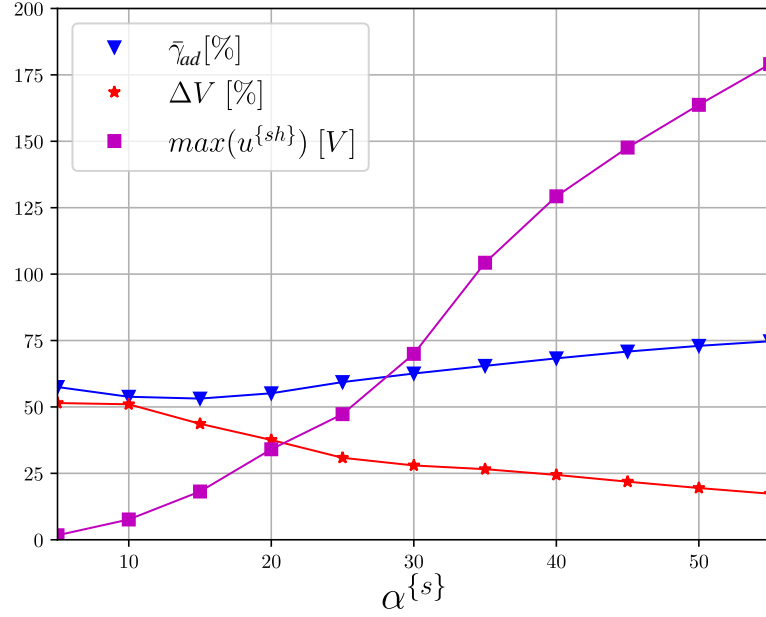
Figure 70 – **Adaptive gains and input stimulus applied for seizure attenuation.** The gains are dynamically adapted to each part of the signal, leading to different inputs of different amplitude that attenuate the seizure locally. The solid blue line (—) represents the adaptive gains and the solid black (—) represents the input stimulus. The decay rate used for the simulation is: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$.



Source: Own authorship.

High values of adherence result in unrealistic levels of voltage, and it is clear that the magnitude of $\|\mathbf{u}^{\{ad\}}\|$ should be constrained in some cases to avoid delivering an excessively high level of tension to the patient. In practice, besides adjusting $\alpha^{\{s\}}$, other approaches can be adopted to limit the maximum level of $\|\mathbf{u}^{\{ad\}}\|$, such as saturation (i.e., designing the controller with a specific $\alpha^{\{s\}}$ but limiting the level of input *a posteriori*) or switching the controller on and off successively. Simulations for all of these strategies are carried out and shown in Fig. 72. Compared to the full control, which has been previously introduced, a saturation level of 50% results in 18.92% of attenuation with 47.98V; when saturation is applied simultaneously with on-off switching (i.e., the controller is activated and deactivated several times), this results in 10.21% of attenuation with 37.53V. It is expected, thus, that the efficiency of the controller is decreased by modulating the way the stimulus is delivered; however, it is still possible to attenuate a seizure.

Figure 71 – **Decay rate in function of maximum magnitude of input stimulus, adherence and attenuation level for the adaptive controller.** As the maximum voltage allowed increases, the model adherence is improved, enhancing the percentage of signal attenuated. The blue line with triangle markers ($\text{--}\blacktriangle\text{--}$) indicates the adherence $\bar{\gamma}_{ad}$; the red line with asterisk markers ($\text{--}\star\text{--}$) indicates the level of attenuation; and magenta line with square markers ($\text{--}\blacksquare\text{--}$) indicates the maximum magnitude of the input stimulus. Only $\alpha^{\{s\}}$ varies from 5 to 55, in steps of 5, to reconstruct the seizure while $\alpha^{\{sh\}} = 10$ is fixed.

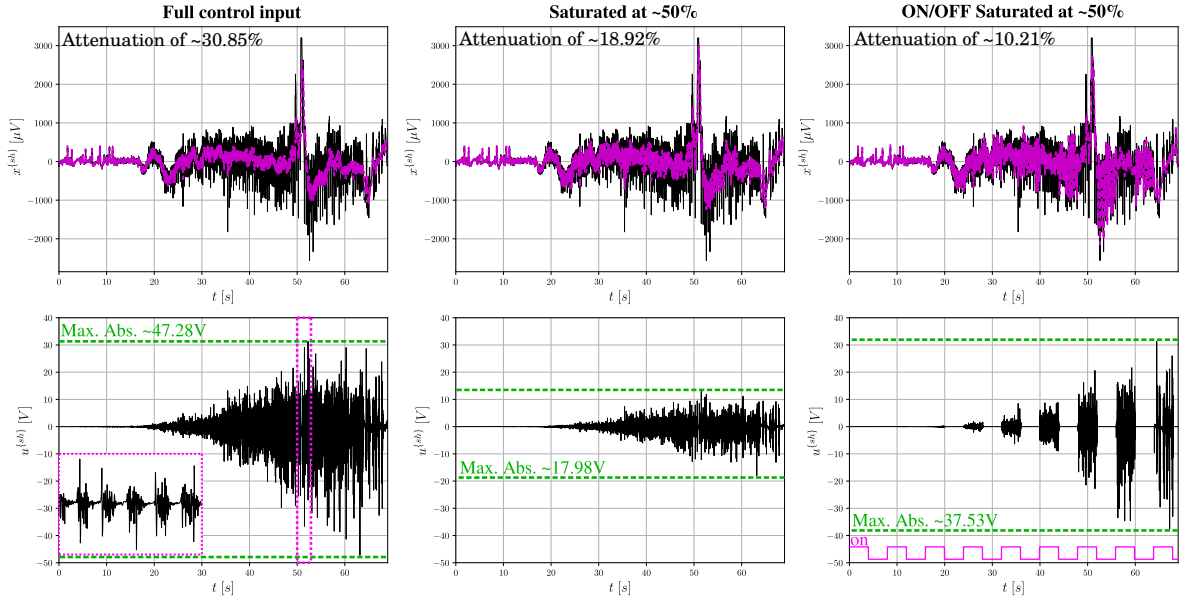


Source: Own authorship.

7.5.2 Fixed-gain controller

An alternative to the adaptive controller is also considered in this article, using a fixed gain for the whole simulation. For this purpose, instead of using an adaptive $\mathbf{G}^{\{ad\}}$, whose values change over time, $\mathbf{G}_m^{\{h\}}$ is adopted. Recall that this latter gain is applied to reconstruct the non-seizure condition, associated to an artificial input. This time, it is thus reused as the gain for seizure attenuation. The main reasoning behind this idea is that, if $\mathbf{G}_m^{\{h\}}$ can be used to reconstruct a non-seizure condition, it can also drive a seizure condition back to it. By doing so, the controller becomes even more simplified, which, on the one hand, may be less accurate but, on the other hand, makes its application simpler and practical.

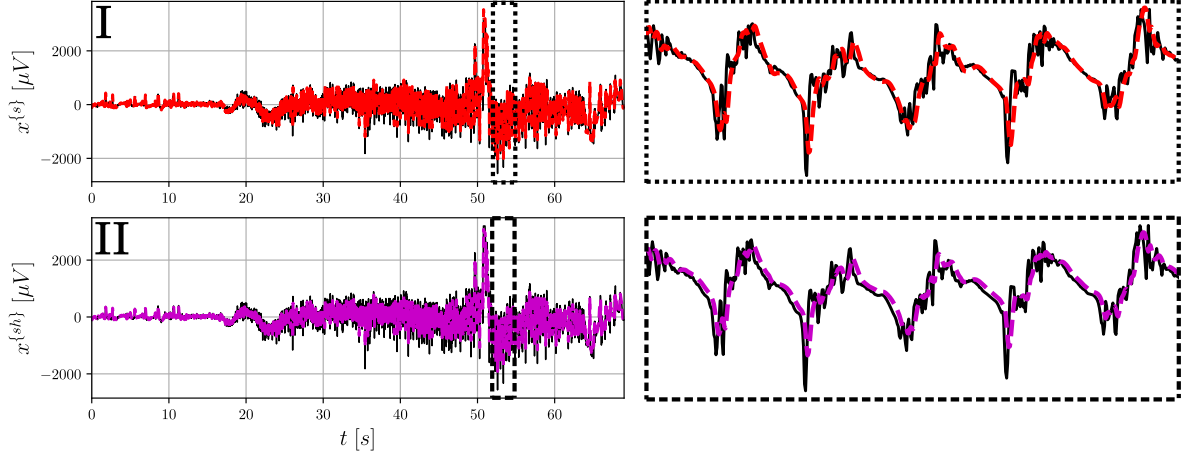
Figure 72 – **Different approaches to limit the magnitude of the input stimulus considering adaptive gains.** For the full control input, no saturation or modification is applied to the controller, which leads to the best attenuation of the cases presented; when saturation is applied, the performance is intermediate; at last, when both saturation and the on/off switching are applied, there is still attenuation, but it is considerably reduced. The black solid line (—) indicates the real seizure signals and their respective input stimulus; the violet dashed line (- -) indicates the attenuated signals; and green dashed line (- -) indicates the maximum absolute magnitude of the input stimulus. The parameters used for this simulation are: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$.



Source: Own authorship.

Figure 73 presents the results for the fixed gain controller, which is activated during the whole simulation. A decay rate of $\alpha^{\{s\}} = 25$ was chosen to reconstruct the seizure and $\alpha^{\{ad\}} = 10$ to attenuate it (the same parameters used for the adaptive controller). For the pair of $(\alpha^{\{s\}}, \alpha^{\{sh\}})$, a moderate reduction (more precisely, 17.39% of reduction, in terms of power of signal) can be seen specially in terms of amplitude. This implies that, for the same parameters, the fixed gain controller is less effective. Physically, its application also means emitting a combined electrical stimulus that attempts to mitigate the undesired seizure dynamics while inducing a non-seizure one at all time instants, whose intensity of amplitude is modulated by the fixed gain. In this sense, only the input is adjustable, not the gains.

Figure 73 – **Activation of the fixed gain controller for attenuating the reconstructed signal.** The controller is activated during the whole simulation with two simultaneous inputs (as in Fig. 68) to reconstruct and attenuate a seizure based on fixed gains. The black solid line (—) indicates the recorded signal; the red dashed line (- -) indicates the reconstructed model of the seizure condition before attenuation (**I**); and the violet dashed line (- -) indicates the reconstructed model after attenuation (**II**). The decay rate used for the simulation is: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$.

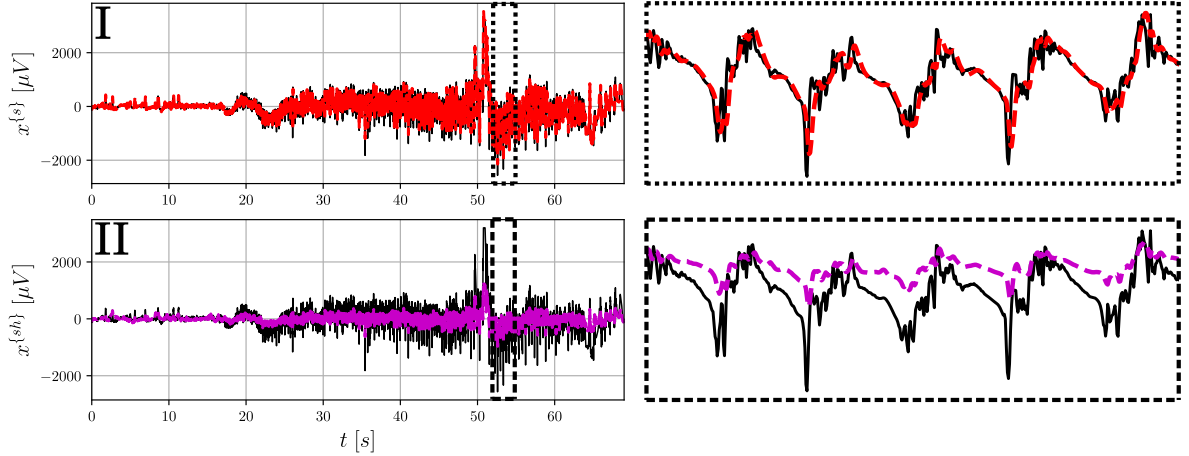


Source: Own authorship.

However, by increasing $\alpha^{\{ad\}} = 50$ for the same $\alpha^{\{s\}} = 25$, it follows that a higher reduction (more precisely, 87.18%⁵) is observed for the fixed gain controller compared to the adaptive one, as shown in Fig. 74. Physically, this means that the input is modulated so that its maximum amplitude allowed is higher. This is particularly relevant in terms of practical applications, because it might not be necessary to apply an adaptive approach for seizure attenuation purposes, especially considering its cumbersome formulation and implementation (for further details, please see Final Remarks).

⁵Visually, the adaptive controller may seem to provide a greater attenuation. However, the performance of the fixed gain controller is usually better especially due to the attenuation of the highest peak, just after 50 seconds. Besides, since the attenuation is based on a mean value of shorter time windows, the local RMS of the non-seizure reference also influences the final result.

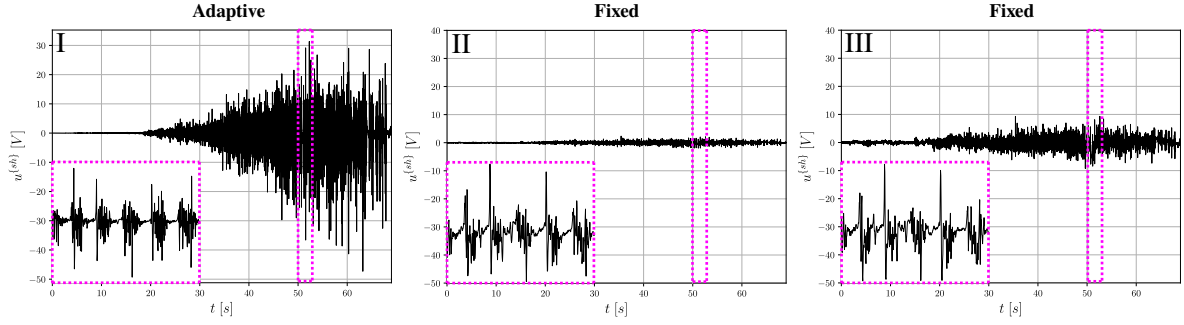
Figure 74 – **Activation of the fixed gain controller for seizure attenuation.** The controller is activated during the whole simulation with two simultaneous inputs to reconstruct and attenuate a seizure based on fixed gains. The increase in $\alpha^{\{sh\}}$ leads to an improvement in attenuation. (—) represents the recorded signal; (- -) represents the reconstructed model of the seizure condition before attenuation (I); and (- -) represents the reconstructed model after attenuation (II). The decay rate used for the simulation is: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 50$.



Source: Own authorship.

To analyze if its performance is indeed better, not only must the attenuation level be higher, but the intensity of the input stimulus must be lower. Figure 75 shows a comparison between the input stimuli from Fig. 69 (adaptive gain), and Figs. 73 and 74 (fixed gains), respectively. Therefore, the increase in $\alpha^{\{sh\}}$ for the fixed-gain controller results in a better performance because it provides a greater attenuation compared to the adaptive one at a considerably lower magnitude of input stimulus. These results are summarized in Table 12 for better interpretation and analysis. Moreover, the shape of the input changes slightly when the fixed-gain controller is applied: the stimulus presents a less burst-like behavior and tends to be a combination of small bursts and peaks. Regardless of the type of the controller, this result is particularly interesting because, similar to the blackbox application, it is consistent with previous studies that found periodic pulse stimulation to be effective against some seizures (Velasco et al., 2001; Tellez-zenteno et al., 2006; Velasco et al., 2007; Rizzone et al., 2001).

Figure 75 – **Input stimuli applied for attenuating the reconstructed signal considering fixed gains compared to adaptive ones.** The intensity of the fixed-gain input is relatively lower than the one from the adaptive input, but the shapes of both are quite similar, presenting peaks or small bursts during the whole signal. The decay rates used for the simulation are: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$ (I – adaptive); $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$ (II – fixed); $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 50$ (III – fixed).



Source: Own authorship.

Table 12 – **Comparison between the input stimuli from the adaptive and fixed-gain controllers when varying the decay.** Recall that: $\alpha^{\{s\}}$ is the decay rate for reconstruction, $\alpha^{\{sh\}}$ is the decay rate for attenuation, $u^{\{sh\}}$ is the input stimulus, and ΔV is the attenuation level. The fixed-gain controller achieves a higher attenuation with a relatively lower input. Besides, as $\alpha^{\{sh\}}$ increases, the attenuation is higher.

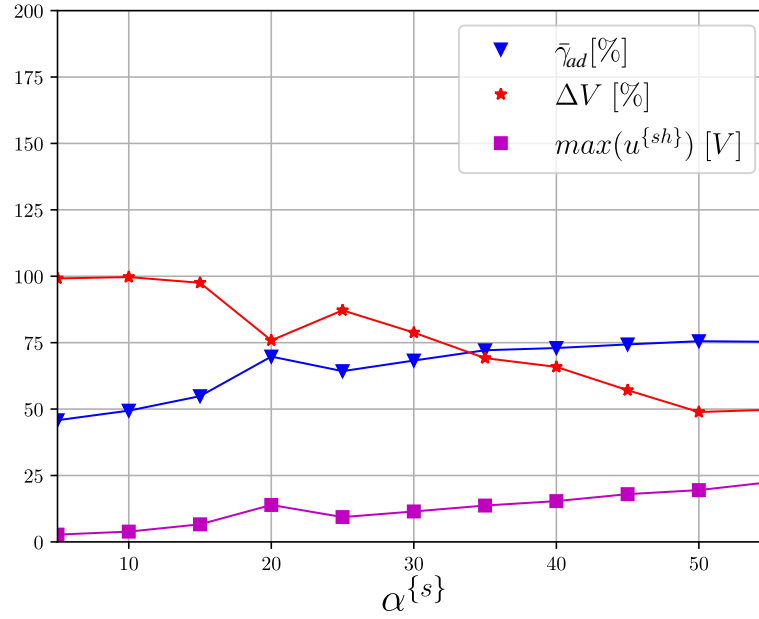
Controller	$\alpha^{\{s\}}$	$\alpha^{\{sh\}}$	$u^{\{sh\}} [V]$	$\Delta V [\%]$
Adaptive	25	10	$[-47.28, 31.34]$	30.85
Fixed-Gain	25	10	$[-1.93, 2.34]$	17.39
Fixed-Gain	25	50	$[-9.23, 9.34]$	87.18

Source: Own authorship.

Concerning the influence of the decay rate, in general Fig. 76 presents the same behavior seen in Fig. 71 occurs⁶: as $\alpha^{\{s\}}$ increases, the adherence of the reconstructed model in relation to the real seizure as well as the magnitude of input stimulus increase, but the level of attenuation decreases. The main difference is that relatively lower values of input are necessary to obtain similar adherence to the model at a considerably higher attenuation level.

⁶The scale is kept the same as before for purposes of comparison.

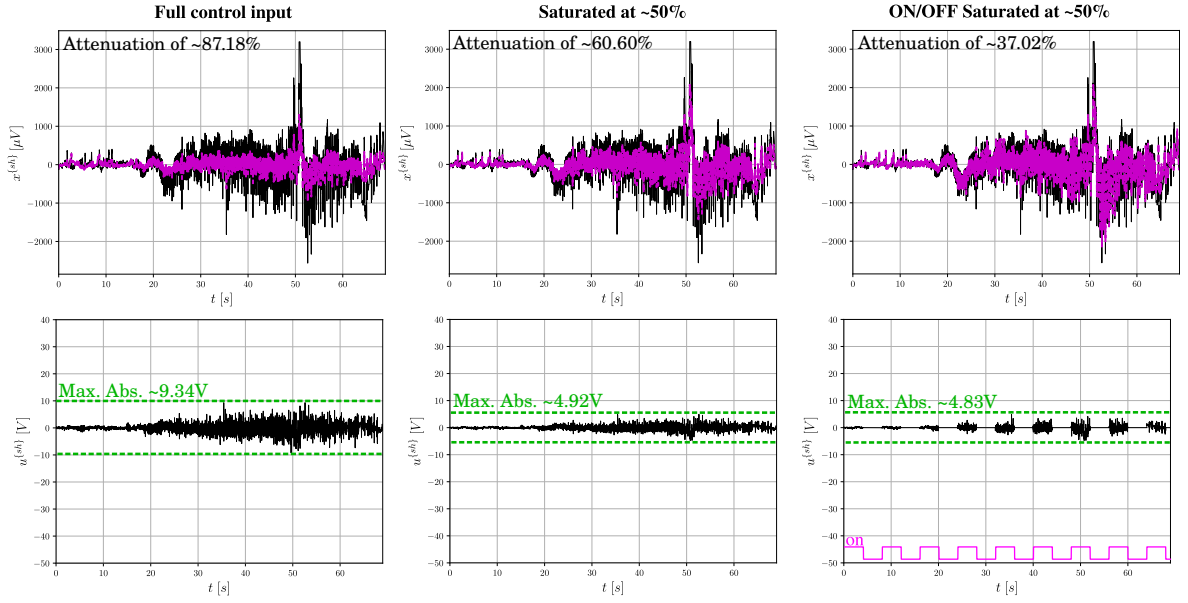
Figure 76 – **Decay rate in function of maximum magnitude of input stimulus, adherence and attenuation level for the fixed-gain controller.** Similar to the results from the adaptive controller, as the maximum voltage allowed increases, the model adherence is improved, enhancing the percentage of signal attenuated. The blue line with triangle markers ($\blacktriangle$) indicates the adherence $\bar{\gamma}_{ad}$; the red line with asterisk markers ($\star$) indicates the level of attenuation; and the magenta line with square markers ($\blacksquare$) indicates the maximum magnitude of the input stimulus. Only $\alpha^{\{s\}}$ varies from 5 to 55, in steps of 5, to reconstruct the seizure while $\alpha^{\{sh\}} = 50$ is fixed.



Source: Own authorship.

This implies that the fixed-gain control may be a more effective strategy in terms of seizure attenuation. Saturation and on-off switching can also be carried out, as presented in Fig. 77. Compared to the full control, a saturation level of 50% results in 60.60% of attenuation with 4.92 V of maximum input applied. When saturation is applied simultaneously with on-off switching, this results in 37.02% of attenuation with a maximum value for the input equal to 4.83 V. Note that, in this case, the combined switching strategy produced a slightly lower level of input, which nonetheless does not compensate for the low attenuation percentage achieved. However, any of the three strategies seems to be valid feasible options when dealing with these types of seizure.

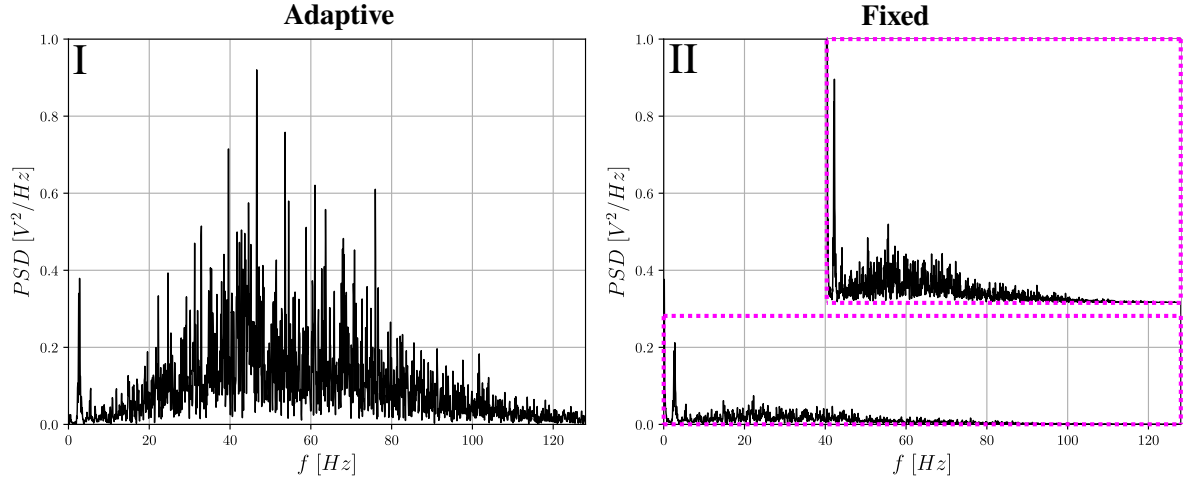
Figure 77 – **Different approaches to limit the magnitude of the input stimulus considering fixed gains.** For the full control input, no saturation or modification is applied to the controller, which leads to the best attenuation of the cases presented; when saturation is applied, the performance is intermediate; at last, when both saturation and the on/off switching are applied, there is still attenuation, but it is considerably reduced. The black solid line (—) indicates the real seizure signals and their respective input stimulus; the violet dashed line (---) indicates the attenuated signals; and green dashed line (---) indicates the maximum absolute magnitude of the input stimulus. The parameters used for this simulation are: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 50$.



Source: Own authorship.

At last, 78 presents a comparison between the input stimuli from the adaptive and fixed-gain strategies in the frequency domain, using Power Spectral Density (PSD). For both, there is a prominent frequency around 2.8 Hz and a relatively wide band with stronger power from 10 to 110 Hz, approximately. For the adaptive strategy, there is a concentration between 20 to 80 Hz; for the fixed-gain one, in turn, from 10 to 50 Hz. This means that coping with a seizure demands actuation in a wide range of frequencies, which is consistent since this disorder provides a generalized increase in energy over them. Although slow components can be identified, the stimulus cannot be narrowed down to a single band. Moreover, the adaptive strategy requires a broader band to attenuate a seizure, which may explain why it attenuates the seizure activity over all the signal. The fixed-gain one focuses on lower frequencies, which may also explain why it attenuates the highest peaks of activity, but not as much the other bands, compared to the adaptive one. Note that, in either case, the power associated to each frequency band is relatively small, up to $1V^2/Hz$. This also endorses the effectiveness of both controllers in terms of seizure attenuation at low power input.

Figure 78 – **Power Spectral Density (PSD) of the input stimuli of both control strategies (adaptive and fixed gain).** Both PSDs present a similar behavior: there is an increase followed by a decrease in energy over the frequency bands, with a steep concentration in low-frequency components. For the adaptive controller, the predominant band is 2–80 Hz, whereas for the fixed-gain one is 2–50 Hz. The parameters used for this simulation are: $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 10$ (I – adaptive); $\alpha^{\{s\}} = 25$ and $\alpha^{\{sh\}} = 50$ (II – fixed-gain). The parameters used for the PSD are: number of windows: 5; type of window: Hanning; overlap: 10%; averaging technique: mean; scaling: density.



Source: Own authorship.

7.5.3 Remarks on closed-loop attenuated seizure

1. Similarities between the input stimuli. Like $\mathbf{u}_m^{\{ch\}}$ and $\mathbf{u}_m^{\{cs\}}$, $\mathbf{u}^{\{sh\}}$ is used for purposes of simulation, and is the input stimulus that is introduced to attenuate a seizure computationally. In this sense, the following inputs:

$$\mathbf{Bu}_m^{\{cs\}} + \mathbf{Bu}^{\{sh\}}$$

represent the “dispute” between the model simulating a seizure while simultaneously attempting to counterbalance it with an attenuation input.

2. Differences between the input stimuli. Unlike $\mathbf{u}_m^{\{ch\}}$ and $\mathbf{u}_m^{\{cs\}}$, $\mathbf{u}^{\{sh\}}$ has a practical meaning, being the responsible for actually attenuating a real seizure. Its numerical values are equal to the voltage tension that should be delivered in a real situation or clinic environment. In other words, Eq. 142 represents a system “as if” it were in the seizure condition, but being attenuated by an external input (seizure to non-seizure condition):

$$\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{Bu}_m^{\{cs\}} + \mathbf{Bu}^{\{sh\}} \equiv \mathbf{A}_m^{\{s\}} \mathbf{x}_m^{\{s\}} + \mathbf{Bu}^{\{sh\}} \equiv \mathbf{A}_m^{\{sh\}} \mathbf{x}_m^{\{sh\}}$$

3. Use of adaptive gains. Gains of the type $\mathbf{G}^{\{ad\}}$ are used to attempt to compensate for the simplifications assumed in the proposed approach. Since the dynamics are reconstructed artificially based on simple candidate models, adaptive gains are reasonable choices. Nonetheless, as shall be shown in this article, $\mathbf{G}^{\{ad\}}$ can be replaced by the fixed gain $\mathbf{G}_m^{\{h\}}$. Therefore, even the gains for the actual control inputs can be computed based solely on the candidate models and adopted in practice.

4. Physical meaning of the input stimulus. According to the third hypothesis, the formulation in closed loop can be applied for seizure attenuation in open loop in real scenarios. Therefore, note that the second layer of control is precisely what represents the tension delivered to a patient, for example. Nonetheless, since the model is only representative of the brain activity being reconstructed, it does not fully capture the whole brain dynamics (as a comprehensive analytical model), and thus it cannot be associated to a real closed-loop scenario. On the other hand, it provides relevant information about the shape and magnitude of the input, and open loop stimulation (such as pulse emission, for example) becomes possible.

7.6 Integration of identification, reconstruction and attenuation

The main steps of seizure identification and their artificial reconstruction and attenuation are closely connected. For the sake of understanding, this section is thus dedicated to summarizing and better explaining how their integration is carried out offline. This is also particularly useful as a contrast to the next section, in which operational aspects for practical (online) applications are presented.

1. **Identification:** the first step concerns the identification of candidate models. This is done beforehand by having access to the datasets where signals that represent both non-seizure and seizure behavior are stored. Then, they are projected on the Fourier vector basis to estimate the coefficients of expansion. The OMI $\mathbf{H}_m$ is applied to estimate the dynamic matrices for the dummy models in both conditions: $\mathbf{A}_m^{\{ch\}}$ (non-seizure) and $\mathbf{A}_m^{\{cs\}}$ (seizure);
2. **Open-loop simulation:** with matrices $\mathbf{A}_m^{\{ch\}}$ and $\mathbf{A}_m^{\{cs\}}$, open-loop simulations can be carried out to visualize the behavior of the candidate models, respectively:

$$\dot{\mathbf{x}}_m^{\{ch\}} = \mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}}, \quad \dot{\mathbf{x}}_m^{\{cs\}} = \mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}}$$

3. **Closed-loop simulation for reconstruction:** if the input of both candidate models are included, closed-loop simulations result in the reconstructed models for

non-seizure and seizure conditions, respectively:

$$\dot{\mathbf{x}}_m^{\{ch\}} = \mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}} + \mathbf{B} \mathbf{u}_m^{\{ch\}}, \quad \dot{\mathbf{x}}_m^{\{cs\}} = \mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}}$$

Note that, although a single loop can be coded for the whole simulation, the two systems are independent.

4. **Closed-loop simulation for attenuation:** by considering superposition, a second layer of input stimulus is added to the seizure model:

$$\dot{\mathbf{x}}_m^{\{ch\}} = \mathbf{A}_m^{\{ch\}} \mathbf{x}_m^{\{ch\}} + \mathbf{B} \mathbf{u}_m^{\{ch\}}, \quad \dot{\mathbf{x}}_m^{\{cs\}} = \mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}} + \mathbf{B} \mathbf{u}^{\{sh\}}$$

Recall that: $\mathbf{u}^{\{sh\}} = -\mathbf{G}^{\{ad\}}[\mathbf{x}^{\{s\}} - \mathbf{x}^{\{h\}}]$. In practice, this means that the real seizure is attenuated considering a real stored non-seizure signal. For the simulations, however:

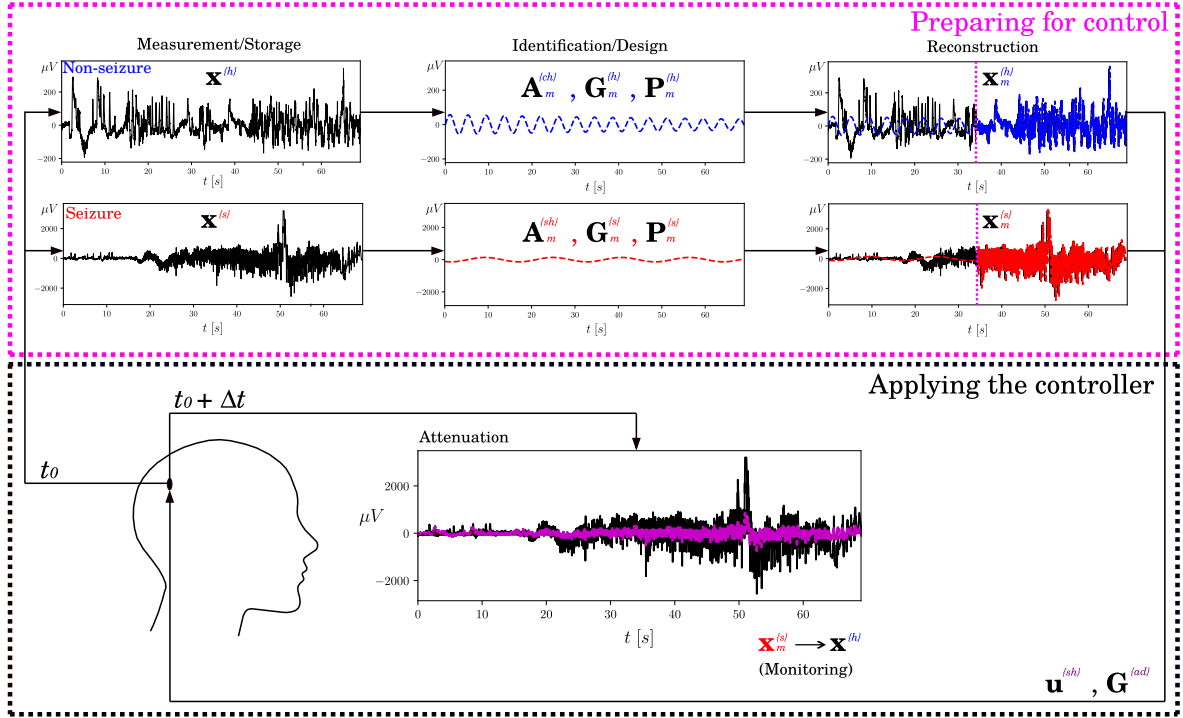
$$\mathbf{u}^{\{sh\}} = -\mathbf{G}^{\{ad\}}[\mathbf{x}_m^{\{cs\}} - \mathbf{x}_m^{\{ch\}}]$$

since $\mathbf{x}_m^{\{cs\}} \rightarrow \mathbf{x}^{\{s\}}$ and $\mathbf{x}_m^{\{ch\}} \rightarrow \mathbf{x}^{\{h\}}$. By doing so, the two systems become interconnected in the same simulation, such that seizure attenuation is achieved by a combination of both behaviors.

Figure 79 illustrates a flowchart of the proposed integration. The preparation for control corresponds to the three following steps: identification, closed-loop simulation and closed-loop simulation for reconstruction. All of them are previously carried out at t_0 , without connecting both systems. It should be stressed that this time instant is merely illustrative, not specific, and only intends to indicate that this stage precedes the next one.

Due to the importance of the application of the controller for attenuation purposes, a whole stage is dedicated to it. This stage corresponds to the following step: closed-loop simulation for attenuation. It is the only one carried out afterwards, at $t_0 + \Delta t$, thus connecting both of the systems. Here, Δt is again merely illustrative and can be any convenient time interval that is considered necessary to separate both stages. Furthermore, it also explicitly highlights that this procedure is not simultaneously carried out with the first one.

Figure 79 – **Offline integration of identification, reconstruction and attenuation:** for color coding, please see Figs. 64 to 68. Firstly, signals are acquired in both seizure and non-seizure conditions. For purposes of simulation, the orthogonal polynomials are applied to identify the dummy models, then the two systems are simulated individually in open loop (dummy models) and in closed loop to reconstruct the desired activity. For purposes of attenuation, a second layer of input is added afterwards, thus interconnecting them, leading to seizure attenuation.



Source: Own authorship.

7.7 Operational aspects for practical applications

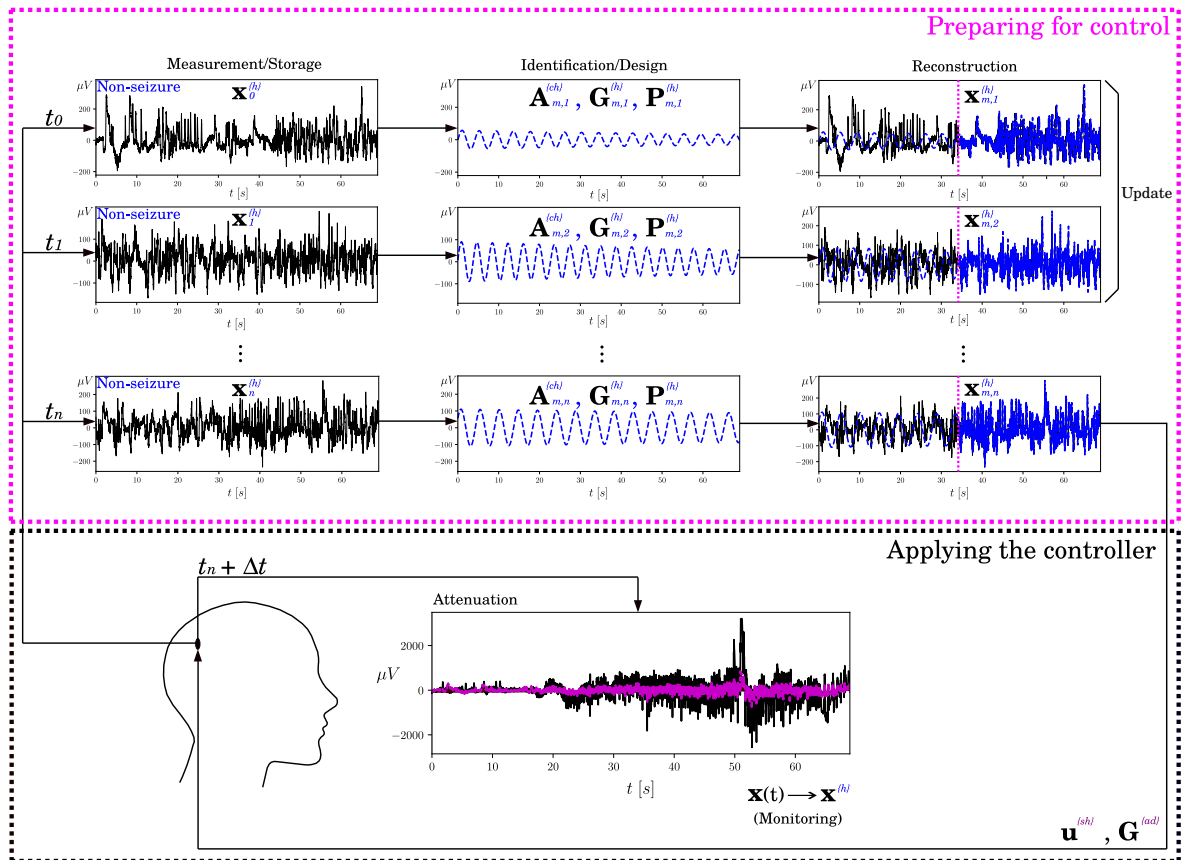
One of the main purposes of the proposed controller is to provide conditions for realistic applications in clinical environments. Figure 80 presents a flowchart illustrating how the integration of all of the steps (identification, open-loop simulation, closed-loop simulation for reconstruction and closed-loop simulation for attenuation) can be carried out in practice. Initially, a reference non-seizure activity is recorded and stored; the identification technique is applied at t_0 to find the first candidate model, being this time instant merely illustrative; once it is identified as $\mathbf{A}_{m,0}^{\{ch\}}$, the optimization algorithm computes the gain $\mathbf{G}_{m,0}^{\{h\}}$ and stability matrix $\mathbf{P}_{m,0}^{\{h\}}$; the signal can then be reconstructed to verify its adherence to the recorded activity; even after reconstruction, the reconstructed activity and parameters are associated with the time window obtained at t_0 , and this requires the model to be updated (at $t_1, t_2, \dots, t_n$) given that non-seizure/seizure behaviors are

time-varying in general.

Any time interval can be previously defined and applied between t_n and t_{n+1} . Since the electrical activity can be regarded as a continuous variable whose underlying system is probably time-varying, the current pseudo-time-varying approach attempts to compensate for this fact by updating the models based on successive time windows. Supposing a seizure can be detected, the most updated model can be used as a reference to attenuate it after Δt , which is again merely illustrative and is yet to be defined.

Figure 80 – **Integration of identification, reconstruction and attenuation for a practical (online) application: for color coding, please see Figs. 64 to 68.**

Non-seizure signals are acquired online by electrodes that monitor the patient. The identification procedure is carried out to obtain dummy models, simulated artificially in open loop, and then closed-loop simulation is applied to reconstruct the desired activity. The non-seizure reference is updated from time to time ($t_1, t_2, \dots, t_n$), resulting in the updated triplet $(\mathbf{A}_m^{\{ch\}}, \mathbf{P}_m^{\{h\}}, \mathbf{G}_m^{\{h\}})$, characterizing this approach as pseudovarying in time. Based on this triplet, such reconstruction yields the information needed to define the shape, amplitude and frequency of the electrical inputs necessary to attenuate the seizure, regardless of the type of controller chosen. Once this input is defined, stimuli are applied in open loop to the brain region of interest.



Source: Own authorship.

Some remarks should be made at this point to validate the proposed approach as a possible operational procedure in practice:

- seizure reconstruction is only required when simulating a seizure, otherwise it is not possible to study attenuation, computationally speaking. In a real application, the seizure model represents the actual on-going seizure itself, and the only stimulus applied is a real one ($\mathbf{u}^{\{sh\}}$);
- the first main hypothesis must hold to distinguish correctly between non-seizure and seizure behavior, such that the reference non-seizure behavior is only updated if the patient is not undergoing a seizure event. When and how to detect seizures is out of the scope of the present article, but there exist several algorithms in the literature that are capable of doing so (Alotaiby et al., 2014; Faust et al., 2015; Sándor; Maffione, 2016; Li et al., 2018a; Yuan et al., 2018; Fan; Chou, 2019; Ansari et al., 2019; Prasanna et al., 2021) and could also be readily integrated;
- the third hypothesis states that, in a real application, closed-loop stimulation cannot be carried out. This restriction is imposed because there is no access to the full representative epileptogenic model of the brain, only the signals. The attenuation achieved in the simulations reflect, thus, the input necessary to mitigate a seizure locally. This implies that only open-loop stimulation is feasible. To compensate for this, a monitoring strategy can be integrated to assess if $\mathbf{x}^{\{s\}} \rightarrow \mathbf{x}^{\{h\}}$: if true, decrease/saturate the intensity of the input stimulus; if false, keep the intensity;
- for the adaptive controller, $\mathbf{G}^{\{ad\}}$ is adapted over time based on the information obtained in $\mathbf{P}_{m,n}^{\{h\}}$ (Goel; Kumar; Narayan, 2016), which is the most updated reference in this case;
- for the fixed-gain controller, $\mathbf{G}_m^{\{h\}}$, computed based on the most updated time window, is used instead of $\mathbf{G}^{\{ad\}}$, as commonly done in control applications (Slotine; Li et al., 1991; Tanaka; Wang, 2004; Ogata, 2010);
- note that, regardless of the controller chosen, seizure attenuation relies on having a candidate model available, which provides information in terms of the triplet $(\mathbf{A}_m^{\{ch\}}, \mathbf{P}_m^{\{h\}}, \mathbf{G}_m^{\{h\}})$ used in the optimization problem (Boyd et al., 1994; Tanaka; Wang, 2004; Sagnol; Stahlberg, 2012);
- furthermore, although it might seem that the approach only takes the candidate model into account, the effectiveness of the controller relies on $\alpha^{\{h\}}$ as well (Tanaka; Wang, 2004), which directly influences the adherence of the closed-loop candidate model to the actual non-seizure condition. In this sense, the triplet $(\mathbf{A}_m^{\{ch\}}, \mathbf{P}_m^{\{h\}}, \mathbf{G}_m^{\{h\}})$

can only be used as reference parameters for real seizure attenuation because convergence towards the actual signals is assured, especially because of the decay rate $\alpha^{\{h\}}$;

- as a rule of thumb, the higher $\alpha^{\{h\}}$, the more efficient the attenuation. However, it must be stressed that this also implies a higher intensity of input stimulus. The practical trade-off is achieved by the need of saturating $\mathbf{u}^{\{sh\}}$ to avoid delivering an excessively high input according to medical specifications.

7.8 Assessment of the controllers and comparison with existing results

In terms of signal reconstruction, both non-seizure and seizure conditions can be artificially recreated. To do so, the proposed system identification technique (via orthogonal polynomials) must be applied to generate candidate models. In open-loop simulations, such models behave as spring-mass-damper systems (or resistor-capacitor-inductor circuits) of one degree of freedom. Although this kind of dynamics does not fully represent all the patterns existing in brain activities, it does capture their main oscillating frequencies, because the formulation in state-space notation takes into account the damped natural frequency of the system, its corresponding damping factor and amplitude of oscillation (Rao, 2001; Pacheco; Jr, 2002). It is unlikely that each electrode can be considered as an independent oscillator, as implicitly assumed, but this assumption does not significantly influence the final results of reconstructed states converging towards the desired activities (in closed loop). In other words, the simplicity of the identified models is justified to prioritize the closed-loop simulations. This renders the process of reconstructing signals relatively easy and almost model-independent, which is the major advantage. On the other hand, the main disadvantage is that the closed-loop model cannot be explicitly written mathematically in the same state-space notation, it can only be visualized dynamically over time.

The decay rate plays an important role in such a reconstruction: the higher it is, the higher the adherence (i.e., the lower the error) between the model and the real signal. This parameter usually dictates the intensity of the input stimulus necessary to achieve convergence (Tanaka; Wang, 2004), but in this case these are artificial entries for reconstruction purposes only. However, it does have a physical meaning for attenuation purposes: its numerical values correspond to the magnitude of the stimulus, measured in volts, that should be applied to a patient in real scenarios. In this case, close attention must be paid when designing the controller, which is why the decay rate has been associated to other parameters as well: adherence and maximum voltage. For both controllers, the general conclusion is that, the higher the adherence, the lower the attenuation level, and the higher the input stimulus must be.

In the limit, when the model converges perfectly to the real signal, arbitrarily high-voltage inputs must be applied to attenuate a seizure. This seems unrealistic, especially for preserving the physical health of patients. However, by considering the strategies adopted in this chapter, the results obtained are within reasonable boundaries commonly seen in the literature. Table 13 presents a summary of the parameters used in several studies for treating common brain disorders compared to the adaptive/fixed-gain ones (only the best trade-off between attenuation and intensity is shown). In terms of frequency, there is a similar 2-200 Hz (all studies) vs 2-80 Hz (this chapter); as for the voltage, 2-14V (all studies) vs 0-18V (this chapter). The results seem, thus, to be consistent with the parameters that have already been used in real applications, for different disorders (from epilepsy to obsessive compulsive disorder). There is only a slight difference between the adaptive controller (up to 18 V, if the saturated version is selected) and the maximum 14V.

Table 13 – **Comparison between the parameters used in for seizure attenuation with other studies in the literature.** The proposed fixed-gain and adaptive controllers, using the saturated (open loop) strategy, provide similar parameters as the ones already existing in the literature. Abbreviations: TS - Thalamic Stimulation (Schulze-bonhage, 2017); AH-DBS (Boex et al., 2011) - Amygdala-Hippocampal Deep Brain Stimulation; ANT/H-SS - Anterior Nucleus of the Thalamus and the Bippocampus Scheduled Stimulation (Jobst et al., 2010); CSCS - Chronic Subthreshold Cortical Stimulation (Lundstrom et al., 2016); CMTN - Centromedian Thalaci Nucleus (Fisher; Velasco, 2014); IC/NA - Internal Capsule and Nucleus Accumbens (Laere et al., 2006); ANT - Anterior Nucleus of Thalamus (Klinger; Mittal, 2016); CMT - Centromedian Nucleus of Thalamus (Klinger; Mittal, 2016); Bi-STN - Subthalamic Nucleus (Klinger; Mittal, 2016); P - Partial Seizure; G - Generalized Seizure; MYO - Myoclonic Seizure (Klinger; Mittal, 2016); SPS - Simple Partial Seizure; CPS - Complex Partial Seizure; STC; LG - Lennox-Gastaut Syndrome; AA - Atypical Absence Seizure; DIA - Dialeptic Seizure; CER - Cerebellum; MTLs - Mesial Temporal Lobe Seizure; SGTC - Secondly Generalized Seizure; GTCS - Generalized Tonic-Clonic Seizure; DRFS - Drug-Resistant Focal Seizure; MRS - Medication Refractory Seizure; OCT - Obsessive Compulsive Disorder; Bi - Bilateral.

Stimulation	Strategy Specified	Disorder	Frequency [Hz]	Voltage [V]
TS	Open Loop	Epilepsy (Unspecified)	145	5
AH-DBS	Continuous	MTLS	130	0–2
ANT/H-SS	Continuous/Intermittent	GTCS	130–200	0.1–5
CSCS	Continuous Pulsing	DRFS	2–100	1–6
CMTN-DBS	Cycles of Pulses	MRS	65	5
IC/NA-DBS	Cycles of Pulses	OCD	100–130	4–10.5
ANT-DBS	Cycles of Pulses	SPS/CPS/SGTC	100	1–10
Bi-CMT-DBS	Cycles of Pulses	LG (GTC)/AA/SGTC/CPS	60	4–6
Bi-STN/ANT-DBS	Cycles of Pulses	DIA/SGTC/TS	130	3–7
P, G, MYO-DBS	Unspecified	CER	10–200	10–14
All	–	–	2–200	0–14
Adaptive	Saturated (Open Loop)	GTCS	2–80	0–18
Fixed-Gain	Saturated (Open Loop)	GTCS	2–50	0–5

Source: Own authorship.

Considering that DBS, used in most of the studies presented, is an invasive approach, and that the signals used in the main text are at the EEG/iEEG level, the intensity of the input is approximately the same as if it were being applied in an invasive way. Besides, the proposed approach takes saturation into account as well, which in practice means that the voltage applied cannot exceed the one recommended by the physician. For example: the adaptive controller exceeds (up to 18V) in 4V the maximum observed voltage (up to 14V), so in practice saturation must be intensified to assure only 14V (or even less, if necessary) are applied. It can also be inferred that, inasmuch as the reconstruction of the model depends on the adherence, and the stimulus, in turn, attenuates only the reconstructed activity, attenuation always occurs. For low decay rates, the reconstructed activity preserves low-frequency patterns, whereas high decay rates lead to a better reconstruction of fast/high-frequency patterns. Therefore, there is always a trade-off between attenuation level and input, which nonetheless may help to mitigate a seizure.

Comparing the controllers, both adaptive and fixed-gain seem to provide positive results in terms of attenuation. For the first one, there is an overall reduction in amplitude along the whole signal, and the input stimulus presents a burst-like behavior. Of the three strategies applied, the most effective one was full control, then saturated control, then saturated combined with switching. The saturated one should be highlighted because of its relatively high attenuation level at a moderate magnitude of input. For the second one, in turn, the main advantage is the reduction in the highest peak of the seizure, which leads to high levels of attenuation, and the input stimulus has a peaky behavior. Of the three strategies applied, the most effective was full control, then saturated, then saturated with switching. This time, the lowest magnitude of input corresponds to the combined strategy, but it is considerably lower than the saturated one, for example, which provided a significant attenuation at low input levels.

At last, as also seen in Table 13, most strategies for attenuating their corresponding disorders represent cycles of pulses (on/off activation for different periods of time, for example), or open loop stimulation, approaches that are consistent with the one proposed in this article. Thus, in practice, as covered in Section 7.7, a possible realistic way of applying the controller is considering open loop along with a parallel monitoring system, which measures the current electrical activity: if it is indeed attenuating the seizure (based on reference pre-defined values), reduce/saturate the input; if not, keep the same input level.

7.9 Contributions, limitations and conclusions

Considering the results and discussion addressed in this chapter, the main contributions are:

- the concept of hybrid controllers, proposed in Chapter 6, can be better formalized with the current approach using MRC, since it provides two types of input: the first one to attenuate the undesired activity and the second one to “induce” a new dynamics based on a desired reference. This is made possible especially by adopting adaptive gains over time; in this sense, the controlling effects fit to the current local information of the signal and attempt to drive the state back to the desired reference. In other words, as long as there is a desired reference, all the responsibility “falls on” the adaptive gains, without the need of a formal seizure model;
- the fixed-gain controller has also proven to be an interesting option. It can be considered as a particular case of the adaptive one, in which all gains are the same. This renders the application even simpler, but still conceptually consistent;
- based on MRC, it is possible to design controllers considering only non-seizure epochs, which is a major advantage, especially because there are usually more recordings for this activity compared to seizure events;
- the proposed approach also allows for signal reconstruction, simulation and attenuation artificially, without requiring stationarity as an assumption, which makes it an interesting option in the context of brain activity, which is usually not stationary. Besides, it is the first time that a modeling composed of consecutive loops to simulate seizure attenuation is proposed;
- if MRC is applied in practice, no model for the seizure is required, only dummy models for the non-seizure condition. The adherence of such models to real activities is limited to certain frequency bands, but in closed-loop simulation convergence is indeed verified, which demonstrates the flexibility of the dummy models;
- the shape, frequency and amplitude of the stimuli that must be applied for seizure attenuation, at the EEG/iEEG level, has been better defined. The values obtained seem consistent with previously published articles in the literature, and explanations about their similarities and differences have been provided;
- considering the already existing approaches for seizure attenuation in practice, the results obtained in this paper provide complementary information to help physicians during electrical stimulation therapy. Therefore, the proposed controller has a relatively simple concept yet a strong practical appeal;
- two main ideas are used to compensate for the simplicity of the (linear time-invariant) models: (1) the reconstruction and attenuation of the activities in closed-loop simulation, for a specific time window; (2) the pseudo-time-varying strategy, which updates the reference window from time to time, thus accounting for a richer,

more general non-seizure reference. This is the first time such a strategy is proposed, which represents a major contribution in control theory as well;

- at last, it should be stressed again that, although the identification of seizure activities has been carried out in this work, it is only necessary for simulation purposes (otherwise attenuation could not be tested, for example). In practice, the integration of Fig. 80 should be applied such that: successive identifications are performed directly online (no previously stored signals are necessary) to assure an updated model is obtained; assuming a seizure can be detected, the controller designed using the non-seizure parameters is activated and monitored. Thus, this qualifies the proposed approach as almost model-independent and a major finding not seen elsewhere in the literature.

The main limitations, in turn, are presented as follows:

- the error between reconstructed models and real activities is not significant to the point of expressively compromising the effectiveness of the controller. However, even in closed-loop simulations, it is about 20%. The inaccuracy of the model in some parts of the signal may thus explain why slightly high voltage levels are obtained in some cases (around 18V for the adaptive controller compared to a maximum of 10-14V in practice);
- perhaps the main limitation of the study is the fact that only signals are reconstructed and attenuated. There is not a fully description of a region or the whole brain. On the one hand, this makes the approach flexible for dealing only with datasets; on the other hand, as mentioned before, only open-loop stimulation can be carried out in practice. This problem has been found and discussed in the previous chapter, so it is expected in a certain way; however, since the stimulus can always be saturated in practice, the information about shape, frequency and amplitude can still be used as long as it does not exceed the parameters defined by the physician;
- at last, although new information about the stimulus can be defined, the exact site, region and type of stimulation (DBS, vagus nerve stimulation, or other types that provide attenuation at a more global level) still need to be assessed and tested to determine the consistency between the proposed approach and the existing ones.

All the similarities between the proposed controllers and real approaches point to some conclusions:

- the reason why the frequency and voltage ranges applied in reality lead to positive results in terms of seizure mitigation might be related to the fact that seizures present

similar signatures across patients, which, in turn, require similar input parameters to be attenuated. This is consistent with the first hypothesis;

- to account for the individual signatures, which of course change from patient to patient, as well as their inherent variance and richness of behavior, not one frequency/voltage pair is required, but a set of frequencies and voltages;
- in any case, the variability of positive outcomes (attenuation level ΔV) depends on how intense and specific the input ($u^{\{sh\}}$) is to that signature. Such a specificity depends on a correct association between the stimulus and the target oscillating behavior to be attenuated. In other words, its effectiveness relies on a sufficiently good representation of the activity to be attenuated;
- the quality of such a representation can be related to the parameter γ , which provides a percentage of adherence between the real signal and the reconstructed activity. A good adherence is only achieved in closed-loop simulation. The second hypothesis is the main responsible for that;
- therefore, the triplet $(\Delta V, \gamma, u^{\{sh\}})$ determines the success of the open-loop electrical therapy in practice. The results obtained in this work, associated to the third hypothesis, are consistent with this fact;
- both controllers are feasible options, specially if applied with saturation and/or switching strategies to meet practical requirements, and provide relevant information in terms of the shape, magnitude and frequency of the stimulus input that must be applied for seizure attenuation. This information can be used by physicians as an auxiliary tool for electrical stimulation therapies.

The main implication of these findings is the possibility to propose an experimental setup in which on-going electrical therapies for treating epilepsy can take advantage of them. This investigation can occur in two stages: for the first one, it is required to collect signals from non-human patients to study their features and design the controllers; the resulting information associated to the parameters of the input should be tested and compared to other traditionally applied inputs based on the literature; for the second one, a similar procedure can be carried out, but considering human patients. To do so, other interesting parallel issues remain open for future research: to verify which of the existing stimulation techniques (DBS and vagus nerve stimulation, among others) are more suitable and representative for seizure attenuation in practice based on the study of EEG signals, as done in this work; to choose which strategy (continuous, intermittent, cycles of pulses) provides the best outcomes.

8 FINAL REMARKS

8.1 Main contributions

This thesis proposes a comprehensive approach to integrate system identification, parameter estimation, state reconstruction and attenuation in a dynamic model called Epileptor and data-driven models based on real electrophysiological recordings. The results comprise different levels of brain activity (from LFPs to EEGs), thus demonstrating that they can be generalized. The main outcomes of this research are:

- the possibility of improving the process of defining shape, frequency and amplitude of the electrical stimuli that must be applied for seizure attenuation. This may work as an auxiliary tool to physicians in hospital centers during electrical stimulation therapies in patients with epilepsy;
- a deeper understanding about the dynamics of epilepsy not only in terms of modeling but also considering concepts of the nonlinear systems theory. The results obtained in this thesis are consistent with those published in recent studies relating epileptic brains to bi-stable phenomena that undergo transitions, thus manifesting characteristics of deterministic and chaotic systems. In this sense, the proposed control approach plays the role of mitigating periodic deterministic patterns while simultaneously attempting to drive the brain region to a more chaotic non-seizure condition with aperiodic stimulation, as if it were restoring its complexity.

8.2 Future work

The main implication of the findings obtained in this thesis is the possibility to propose an experimental setup in which on-going electrical therapies for treating epilepsy can take advantage of them. This investigation can occur in two stages: 1) to collect signals from non-human patients to study their features and design the controllers; the resulting information associated to the parameters of the input should be tested and compared to other traditionally applied inputs based on the literature; 2) the same, but considering human patients. To do so, other parallel issues remain open for future research: to verify which of the existing stimulation techniques are more suitable and representative for seizure attenuation in practice based on the study of LFP/EEG signals; and to choose which strategy provides the best outcomes.

As a matter of fact, there is already an on-going research project at the post-doctorate level taking place at the Federal University of São Paulo (São José dos Campos campus) investigating the effects of different types of stimulation in attenuating the epileptiform patterns generated by slices of hippocampus in animal models: “Estimulação elétrica controlada em tempo real para supressão da atividade epileptiforme *in vitro* em fatias hipocâmpais de modelos animais”. The main goal is to evaluate the efficiency of the controller when electrical pulses are emitted considering spiking intervals that behave chaotically or stochastically, for example. The aforementioned research project is a direct consequence of one of the articles produced in this thesis, Brogin et al. (2023), and indirect consequence of the previously published ones that served as a theoretical basis for it. Besides, it is potentially helpful to shed light on practical stimulation strategies to attenuate epileptiform activities. Depending on the outcome, clinical tests in human patients can be included as well.

REFERENCES

- ABUHASEL, K. A.; ILIYASU, A. M.; FATICHAH, C. A hybrid particle swarm optimization and neural network with fuzzy membership function technique for epileptic seizure classification. **Journal of Advanced Computational Intelligence and Intelligent Informatics**, Tokyo, JP, v. 19, n. 3, p. 447–455, 2015.
- ACHARYA, U. R.; OH, S. L.; HAGIWARA, Y.; TAN, J. H.; ADELI, H. Deep convolutional neural network for the automated detection and diagnosis of seizure using EEG signals. **Computers in Biology and Medicine**, Amsterdam, NL, v. 100, p. 270–278, 2018. ISSN 0010-4825.
- AGARWAL, S.; RANI, A.; SINGH, V.; MITTAL, A. EEG signal enhancement using cascaded s-golay filter. **Biomedical Signal Processing and Control**, Amsterdam, NL, v. 36, p. 194–204, 2017. ISSN 1746-8094.
- ALOTAIBY, T. N.; ALSHEBEILI, S. A.; ALSHAWI, T.; AHMAD, I.; EL-SAMIE, F. E. A. EEG seizure detection and prediction algorithms: a survey. **EURASIP Journal on Advances in Signal Processing**, Springer, Heidelberg, DE, v. 2014, p. 1–21, 2014.
- ALTAN, A. Performance of metaheuristic optimization algorithms based on swarm intelligence in attitude and altitude control of unmanned aerial vehicle for path following. In: **2020 4th International Symposium on Multidisciplinary Studies and Innovative Technologies (ISMSIT)**. [S.l.: s.n.], 2020. p. 1–6.
- ALTAN, A.; PARLAK, A. Adaptive control of a 3d printer using whale optimization algorithm for bio-printing of artificial tissues and organs. In: **2020 Innovations in Intelligent Systems and Applications Conference (ASYU)**. [S.l.: s.n.], 2020. p. 1–5.
- ANAND, K. S.; DHIKAV, V. Hippocampus in health and disease: An overview. **Annals of Indian Academy of Neurology**, Wolters Kluwer–Medknow Publications, Mumbai, IN, v. 15, n. 4, p. 239, 2012.
- ANSARI, A. H.; CHERIAN, P. J.; CAICEDO, A.; NAULAERS, G.; VOS, M. D.; HUFFEL, S. V. Neonatal seizure detection using deep convolutional neural networks. **International Journal of Neural Systems**, Singapore, v. 29, n. 04, p. 1850011, 2019. PMID: 29747532.
- ARAÚJO, N. S.; REYES-GARCIA, S. Z.; BROGIN, J. A. F.; BUENO, D. D.; CAVALHEIRO, E. A.; SCORZA, C. A.; FABER, J. Chaotic and stochastic dynamics of epileptiform-like activities in sclerotic hippocampus resected from patients with pharmacoresistant epilepsy. **PLOS Computational Biology**, Public Library of Science, California, US, v. 18, n. 4, p. 1–31, 04 2022.

- ÅSTRÖM, K. J.; WITTENMARK, B. **Computer-controlled systems: theory and design**. [S.l.]: Courier Corporation, 2013.
- ATTIA, A.; MOUSSAOUI, A.; CHAHIR, Y. Epileptic seizures identification with autoregressive model and firefly optimization based classification. **Evolving Systems**, Springer, v. 12, n. 3, p. 827–836, 2021.
- BALDACCHINO, T.; ANDERSON, S. R.; KADIRKAMANATHAN, V. Computational system identification for bayesian NARMAX modelling. **Automatica**, Amsterdam, NL, v. 49, n. 9, p. 2641–2651, 2013. ISSN 0005-1098.
- BOEX, C.; SEECK, M.; VULLIEMOZ, S.; ROSSETTI, A. O.; STAEDLER, C.; SPINELLI, L.; PEGNA, A. J.; PRALONG, E.; VILLEMURE, J.-G.; FOLETTI, G.; POLLO, C. Chronic deep brain stimulation in mesial temporal lobe epilepsy. **Seizure**, Amsterdam, NL, v. 20, n. 6, p. 485–490, 2011. ISSN 1059-1311.
- BOS, A. Van den. **Parameter estimation for scientists and engineers**. [S.l.]: John Wiley & Sons, 2007.
- BOURDILLON, P.; RYVLIN, P.; ISNARD, J.; MONTAVONT, A.; CATENOIX, H.; MAUGUIÃRE, F.; RHEIMS, S.; OSTROWSKY-COSTE, K.; GUÃ©NOT, M. Stereotactic electroencephalography is a safe procedure, including for insular implantations. **World Neurosurgery**, Amsterdam, NL, v. 99, p. 353–361, 2017.
- BOYD, S.; GHAOUI, L. E.; FERON, E.; BALAKRISHNAN, V. **Linear matrix inequalities in system and control theory**. [S.l.]: SIAM, 1994.
- BROGIN, J. A. F.; FABER, J.; BUENO, D. D. An efficient approach to define the input stimuli to suppress epileptic seizures described by the Epileptor model. **International Journal of Neural Systems**, Singapore, v. 30, n. 11, p. 2050062, 2020. PMID: 32938259.
- BROGIN, J. A. F.; FABER, J.; BUENO, D. D. Enhanced use practices in SSVEP-based bcis using an analytical approach of canonical correlation analysis. **Biomedical Signal Processing and Control**, Amsterdam, NL, v. 55, p. 101644, 2020. ISSN 1746-8094.
- BROGIN, J. A. F.; FABER, J.; BUENO, D. D. Burster Reconstruction Considering Unmeasurable Variables in the Epileptor Model. **Neural Computation**, Cambridge, US, v. 33, n. 12, p. 3288–3333, 11 2021. ISSN 0899-7667.
- BROGIN, J. A. F.; FABER, J.; BUENO, D. D. Estimating the parameters of the Epileptor model for epileptic seizure suppression. **Neuroinformatics**, Springer, Heidelberg, DE, p. 1–23, 2022.
- BROGIN, J. A. F.; FABER, J.; REYES-GARCIA, S. Z.; CAVALHEIRO, E. A.; BUENO, D. D. Epileptic seizure suppression: a computational approach for identification and control using real data. **bioRxiv**, 2023.
- BUENO, D. D.; GOES, L. C. S.; GONÇALVES, P. J. P. et al. Control of limit cycle oscillation in a three degrees of freedom airfoil section using fuzzy takagi-sugeno modeling. **Shock and Vibration**, Hindawi, London, UK, v. 2014, 2014.

- BURRELLO, A.; CAVIGELLI, L.; SCHINDLER, K.; BENINI, L.; RAHIMI, A. Laelaps: An energy-efficient seizure detection algorithm from long-term human iEEG recordings without false alarms. In: **2019 Design, Automation & Test in Europe Conference & Exhibition (DATE)**. [S.l.: s.n.], 2019. p. 752–757.
- CHEN R, S. D. W. J.; NOLAN, S. Transcranial magnetic stimulation for the treatment of epilepsy. **Cochrane Database of Systematic Reviews**, John Wiley & Sons, Ltd, Hoboken, US, n. 8, 2016. ISSN 1465-1858.
- CHEN, X.; LIU, A.; CHIANG, J.; WANG, Z. J.; MCKEOWN, M. J.; WARD, R. K. Removing muscle artifacts from EEG data: Multichannel or single-channel techniques? **IEEE Sensors Journal**, New Jersey, US, v. 16, n. 7, p. 1986–1997, 2016.
- CHISCI, L.; MAVINO, A.; PERFERI, G.; SCIANDRONE, M.; ANILE, C.; COLICCHIO, G.; FUGGETTA, F. Real time epileptic seizure prediction using ar models and support vector machines. **IEEE Transactions on Biomedical Engineering**, IEEE, New Jersey, US, v. 57, n. 5, p. 1124–1132, 2010.
- CHIZHOV, A. V.; ZEFIROV, A. V.; AMAKHIN, D. V.; SMIRNOVA, E. Y.; ZAITSEV, A. V. Minimal model of interictal and ictal discharges “Epileptor-2”. **PLOS Computational Biology**, Public Library of Science, California, US, v. 14, n. 5, p. 1–25, 05 2018.
- COTA, V. R.; MEDEIROS, D. de C.; VILELA, M. R. S. da P.; DORETTO, M. C.; MORAES, M. F. D. Distinct patterns of electrical stimulation of the basolateral amygdala influence pentylenetetrazole seizure outcome. **Epilepsy & Behavior**, Amsterdam, NL, v. 14, n. 1, Supplement 1, p. 26–31, 2009. ISSN 1525-5050. International Symposium NEWroscience 2008.
- DOLLFUSS, P.; HARTMANN, M.; SKUPCH, A.; FÜRBASS, F.; KLUGE, T. Automatic optimization of parameters for seizure detection systems. In: **2013 35th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)**. [S.l.: s.n.], 2013. p. 1976–1979.
- DUA, T.; BOER, H. M. D.; PRILIPKO, L. L.; SAXENA, S. Epilepsy care in the world: Results of an ILAE/IBE/WHO global campaign against epilepsy survey. **Epilepsia**, Hoboken, US, v. 47, n. 7, p. 1225–1231, 2006.
- DURBIN, J.; KOOPMAN, S. J. **Time series analysis by state space methods**. [S.l.]: Oxford university press, 2012.
- DUUN-HENRIKSEN, A. K.; SCHMIDT, S.; RØGE, R. M.; MØLLER, J. B.; NØRGAARD, K.; JØRGENSEN, J. B.; MADSEN, H. Model identification using stochastic differential equation grey-box models in diabetes. **Journal of diabetes science and technology**, SAGE Publications, Thousand Oaks, US, v. 7, n. 2, p. 431–440, 2013.
- ENTEZAMI, A.; SHARIATMADAR, H. An unsupervised learning approach by novel damage indices in structural health monitoring for damage localization and quantification. **Structural Health Monitoring**, Thousand Oaks, US, v. 17, n. 2, p. 325–345, 2018.

- FAN, M.; CHOU, C.-A. Detecting abnormal pattern of epileptic seizures via temporal synchronization of EEG signals. **IEEE Transactions on Biomedical Engineering**, New Jersey, US, v. 66, n. 3, p. 601–608, 2019.
- FAUST, O.; ACHARYA, U. R.; ADELI, H.; ADELI, A. Wavelet-based EEG processing for computer-aided seizure detection and epilepsy diagnosis. **Seizure**, Amsterdam, NL, v. 26, p. 56–64, 2015. ISSN 1059-1311.
- FIGARI, M.; ALTOSOLE, M. Dynamic behaviour and stability of marine propulsion systems. **Proceedings of the Institution of Mechanical Engineers, Part M: Journal of Engineering for the Maritime Environment**, Thousand Oaks, US, v. 221, n. 4, p. 187–205, 2007.
- FISHER, R. S.; ACEVEDO, C.; ARZIMANOGLU, A.; BOGACZ, A.; CROSS, J. H.; ELGER, C. E.; JR, J. E.; FORSGREN, L.; FRENCH, J. A.; GLYNN, M.; HESDORFFER, D. C.; LEE, B.; MATHERN, G. W.; MOSHÉ, S. L.; PERUCCA, E.; SCHEFFER, I. E.; TOMSON, T.; WATANABE, M.; WIEBE, S. ILAE official report: A practical clinical definition of epilepsy. **Epilepsia**, Hoboken, US, v. 55, n. 4, p. 475–482, 2014.
- FISHER, R. S.; SCHACHTER, S. C. The postictal state: A neglected entity in the management of epilepsy. **Epilepsy & Behavior**, Amsterdam, NL, v. 1, n. 1, p. 52–59, 2000. ISSN 1525-5050.
- FISHER, R. S.; VELASCO, A. L. Electrical brain stimulation for epilepsy. **Nature Reviews Neurology**, London, UK, v. 10, n. 5, p. 261–270, 2014.
- FOX, J. **Applied regression analysis and generalized linear models**. [S.l.]: Sage Publications, 2015.
- FRANASZCZUK, P. J.; BERGEY, G. K. An autoregressive method for the measurement of synchronization of interictal and ictal EEG signals. **Biological cybernetics**, Springer, Berlin, DE, v. 81, n. 1, p. 3–9, 1999.
- GAO, F.; HAN, L. Implementing the Nelder-Mead simplex algorithm with adaptive parameters. **Computational Optimization and Applications**, Springer, [S.l.], v. 51, n. 1, p. 259–277, 2012.
- GOEL, A.; KUMAR, R.; NARAYAN, S. Design of mrac augmented with PID controller using genetic algorithm. In: **2016 IEEE 1st International Conference on Power Electronics, Intelligent Control and Energy Systems (ICPEICES)**. [S.l.: s.n.], 2016. p. 1–5.
- GORDON, R. A. **Regression analysis for the social sciences**. [S.l.]: Routledge, 2015.
- GRAIMANN, B.; ALLISON, B. Z.; PFURTSCHELLER, G. **Brain-computer interfaces: Revolutionizing human-computer interaction**. [S.l.]: Springer Science & Business Media, 2010.
- GRIFFITH, T. D.; GEHLOT, V. P.; BALAS, M. J.; HUBBARD, J. E. An adaptive

- unknown input approach to brain wave EEG estimation. **Biomedical Signal Processing and Control**, Amsterdam, NL, v. 79, p. 104083, 2023. ISSN 1746-8094.
- HAJILOO, R.; SALARIEH, H.; ALASTY, A. Chaos control in delayed phase space constructed by the Takens embedding theory. **Communications in Nonlinear Science and Numerical Simulation**, Amsterdam, NL, v. 54, p. 453–465, 2018. ISSN 1007-5704.
- HAMAD, A.; HOUSSEIN, E. H.; HASSANIEN, A. E.; FAHMY, A. A. Hybrid grasshopper optimization algorithm and support vector machines for automatic seizure detection in EEG signals. In: SPRINGER. **The International Conference on Advanced Machine Learning Technologies and Applications (AMLT2018)**. [S.l.], 2018. p. 82–91.
- HAMMOUDI, M. Y.; ALLAG, A.; BECHERIF, M.; BENBOUZID, M.; ALLOUI, H. Observer design for induction motor: an approach based on the mean value theorem. **Frontiers in Energy**, Springer, [S.l.], v. 8, n. 4, p. 426–433, 2014.
- HAMMOUDI, M. Y.; BENBOUZID, M. E. H.; RIZOUG, N.; ALLAG, A. New state observer based on takagi-sugeno fuzzy controller of induction motor. In: **2015 4th International Conference on Systems and Control (ICSC)**. [S.l.: s.n.], 2015. p. 145–150.
- HARDT, M.; SCHRAKNEPPER, D.; BERGS, T. Investigations on the application of the downhill-simplex-algorithm to the inverse determination of material model parameters for fe-machining simulations. **Simulation Modelling Practice and Theory**, v. 107, p. 102214, 2021. ISSN 1569-190X.
- HASHEMI, M.; VATTIKONDA, A.; SIP, V.; GUYE, M.; BARTOLOMEI, F.; WOODMAN, M.; JIRSA, V. The bayesian virtual epileptic patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. **NeuroImage**, Amsterdam, NL, v. 217, p. 116839, 2020. ISSN 1053-8119.
- HAWKINS, D. M. The problem of overfitting. **Journal of Chemical Information and Computer Sciences**, ACS Publications, [S.l.], v. 44, n. 1, p. 1–12, 2004.
- HERFF, C.; KRUSIENSKI, D. J.; KUBBEN, P. The potential of stereotactic-EEG for brain-computer interfaces: Current progress and future directions. **Frontiers in Neuroscience**, Lausanne, CH, v. 14, 2020. ISSN 1662-453X.
- HINDMARSH, J. L.; ROSE, R. M.; HUXLEY, A. F. A model of neuronal bursting using three coupled first order differential equations. **Proceedings of the Royal Society of London. Series B. Biological Sciences**, London, UK, v. 221, n. 1222, p. 87–102, 1984.
- HOUSSAINI, K. E.; IVANOV, A. I.; BERNARD, C.; JIRSA, V. K. Seizures, refractory status epilepticus, and depolarization block as endogenous brain activities. **Physical Review E**, College Park, US, v. 91, p. 010701, Jan 2015.
- HUSSEIN, R.; ELGENDI, M.; WANG, Z. J.; WARD, R. K. Robust detection of epileptic

- seizures based on l1-penalized robust regression of EEG signals. **Expert Systems with Applications**, Amsterdam, NL, v. 104, p. 153–167, 2018. ISSN 0957-4174.
- IASEMIDIS, L. Epileptic seizure prediction and control. **IEEE Transactions on Biomedical Engineering**, New Jersey, US, v. 50, n. 5, p. 549–558, 2003.
- IASEMIDIS, L. D.; SACKELLARES, J. C. Review: Chaos theory and epilepsy. **The Neuroscientist**, [S.l.], v. 2, n. 2, p. 118–126, 1996.
- ICHALAL, D.; ARIQUI, H.; MAMMAR, S. Observer design for two-wheeled vehicle: A takagi-sugeno approach with unmeasurable premise variables. In: **2011 19th Mediterranean Conference on Control Automation (MED)**. [S.l.: s.n.], 2011. p. 934–939.
- ICHALAL, D.; MARX, B.; MAMMAR, S.; MAQUIN, D.; RAGOT, J. Observer for Lipschitz nonlinear systems: Mean Value Theorem and sector nonlinearity transformation. In: **2012 IEEE International Symposium on Intelligent Control**. [S.l.: s.n.], 2012. p. 264–269.
- ICHALAL, D.; MARX, B.; MAMMAR, S.; MAQUIN, D.; RAGOT, J. How to cope with unmeasurable premise variables in takagi-sugeno observer design: Dynamic extension approach. **Engineering Applications of Artificial Intelligence**, Amsterdam, NL, v. 67, p. 430–435, 2018. ISSN 0952-1976.
- ICHALAL, D.; MARX, B.; MAQUIN, D.; RAGOT, J. On observer design for nonlinear takagi-sugeno systems with unmeasurable premise variable. In: **2011 International Symposium on Advanced Control of Industrial Processes (ADCONIP)**. [S.l.: s.n.], 2011. p. 353–358.
- ISLAM, M. K.; RASTEGARNIA, A.; YANG, Z. A wavelet-based artifact reduction from scalp EEG for epileptic seizure detection. **IEEE Journal of Biomedical and Health Informatics**, New Jersey, US, v. 20, n. 5, p. 1321–1332, 2016.
- IZHIKEVICH, E. Simple model of spiking neurons. **IEEE Transactions on Neural Networks**, New Jersey, US, v. 14, n. 6, p. 1569–1572, 2003.
- IZHIKEVICH, E. M. Neural excitability, spiking and bursting. **International Journal of Bifurcation and Chaos**, Singapore, v. 10, n. 06, p. 1171–1266, 2000.
- IZHIKEVICH, E. M. **Dynamical systems in neuroscience**. [S.l.]: MIT press, 2007.
- JANSSON, M. Subspace identification and arx modeling. **IFAC Proceedings Volumes**, v. 36, n. 16, p. 1585–1590, 2003. ISSN 1474-6670. 13th IFAC Symposium on System Identification (SYSID 2003), Rotterdam, The Netherlands, 27-29 August, 2003.
- JASPER, H. H. Ten-twenty electrode system of the international federation. **Electroencephalography and Clinical Neurophysiology**, Amsterdam, NL, v. 10, p. 371–375, 1958.
- JIRSA, V.; PROIX, T.; PERDIKIS, D.; WOODMAN, M.; WANG, H.; GONZALEZ-MARTINEZ, J.; BERNARD, C.; BÉNAR, C.; GUYE, M.; CHAUVEL, P.;

- BARTOLOMEI, F. The virtual epileptic patient: Individualized whole-brain models of epilepsy spread. **NeuroImage**, Amsterdam, NL, v. 145, p. 377–388, 2017. ISSN 1053-8119. Individual Subject Prediction.
- JIRSA, V. K.; STACEY, W. C.; QUILICHINI, P. P.; IVANOV, A. I.; BERNARD, C. On the nature of seizure dynamics. **Brain**, Oxford, UK, v. 137, n. 8, p. 2210–2230, 06 2014. ISSN 0006-8950.
- JOBST, B. C.; DARCEY, T. M.; THADANI, V. M.; ROBERTS, D. W. Brain stimulation for the treatment of epilepsy. **Epilepsia**, Hoboken, US, v. 51, n. s3, p. 88–92, 2010.
- KALITZIN, S.; KOPPERT, M.; PETKOV, G.; VELIS, D.; da Silva, F. L. Computational model prospective on the observation of proictal states in epileptic neuronal systems. **Epilepsy & Behavior**, Amsterdam, NL, v. 22, p. S102–S109, 2011. ISSN 1525-5050. The Future of Automated Seizure Detection and Prediction.
- KALITZIN, S. N.; VELIS, D. N.; SILVA, F. H. L. da. Stimulation-based anticipation and control of state transitions in the epileptic brain. **Epilepsy & Behavior**, Amsterdam, NL, v. 17, n. 3, p. 310–323, 2010. ISSN 1525-5050.
- KALOGIROU, S. A. Chapter 11 - designing and modeling solar energy systems. In: KALOGIROU, S. A. (Ed.). **Solar Energy Engineering (Second Edition)**. Second edition. Boston: Academic Press, 2014. p. 583–699. ISBN 978-0-12-397270-5.
- KIM, H.; BERNHARDT, B. C.; KULAGA-YOSKOVITZ, J.; CALDAIROU, B.; BERNASCONI, A.; BERNASCONI, N. Multivariate hippocampal subfield analysis of local mri intensity and volume: application to temporal lobe epilepsy. In: SPRINGER. **Medical Image Computing and Computer-Assisted Intervention–MICCAI 2014: 17th International Conference, Boston, MA, USA, September 14-18, 2014, Proceedings, Part II 17**. [S.l.], 2014. p. 170–178.
- KLAUSBERGER, T.; SOMOGYI, P. Neuronal diversity and temporal dynamics: The unity of hippocampal circuit operations. **Science**, Washington DC, US, v. 321, n. 5885, p. 53–57, 2008.
- KLINGER, N. V.; MITTAL, S. Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy. **Clinical Neurology and Neurosurgery**, v. 140, p. 11–25, 2016. ISSN 0303-8467.
- LAERE, K. V.; NUTTIN, B.; GABRIELS, L.; DUPONT, P.; RASMUSSEN, S.; GREENBERG, B. D.; COSYNS, P. Metabolic imaging of anterior capsular stimulation in refractory obsessive-compulsive disorder: a key role for the subgenual anterior cingulate and ventral striatum. **Journal of Nuclear Medicine**, Society of Nuclear Medicine, [S.l.], v. 47, n. 5, p. 740–747, 2006. ISSN 0161-5505.
- LAGO, N.; CESTER, A. Flexible and organic neural interfaces: a review. **Applied Sciences**, Basel, CH, v. 7, n. 12, 2017. ISSN 2076-3417.
- LANDAU, I.; KARIMI, A. A recursive algorithm for ARMAX model identification in closed loop. **IEEE Transactions on Automatic Control**, New Jersey, US, v. 44, n. 4,

p. 840–843, 1999.

LI, Y.; CUI, W.; LUO, M.; LI, K.; WANG, L. Epileptic seizure detection based on time-frequency images of EEG signals using gaussian mixture model and gray level co-occurrence matrix features. **International Journal of Neural Systems**, Singapore, v. 28, n. 07, p. 1850003, 2018. PMID: 29607682.

LI, Y.; WANG, X.-D.; LUO, M.-L.; LI, K.; YANG, X.-F.; GUO, Q. Epileptic seizure classification of EEGs using time-frequency analysis based multiscale radial basis functions. **IEEE Journal of Biomedical and Health Informatics**, New Jersey, US, v. 22, n. 2, p. 386–397, 2018.

LIU, H.; ZHU, L.; PAN, Z.; BAI, F.; LIU, Y.; LIU, Y.; PATEL, M.; FARANTATOS, E.; BHATT, N. ARMAX-based transfer function model identification using wide-area measurement for adaptive and coordinated damping control. **IEEE Transactions on Smart Grid**, New Jersey, US, v. 8, n. 3, p. 1105–1115, 2017.

LIU, W.; LIN, W. Additive white gaussian noise level estimation in svd domain for images. **IEEE Transactions on Image Processing**, New Jersey, US, v. 22, n. 3, p. 872–883, 2013.

LJUNG, L. **System identification: theory for the user**. [S.l.]: Prentice Hall-New Jersey, 1998.

LOFBERG, J. Yalmip : a toolbox for modeling and optimization in matlab. In: **2004 IEEE International Conference on Robotics and Automation (IEEE Cat. No.04CH37508)**. [S.l.: s.n.], 2004. p. 284–289.

LUERSEN, M. A.; Le Riche, R. Globalized Nelder-mead method for engineering optimization. **Computers & Structures**, Amsterdam, NL, v. 82, n. 23, p. 2251–2260, 2004. ISSN 0045-7949. Computational Structures Technology.

LUNDSTROM, B. N.; GOMPEL, J. V.; BRITTON, J.; NICKELS, K.; WETJEN, N.; WORRELL, G.; STEAD, M. Chronic Subthreshold Cortical Stimulation to Treat Focal Epilepsy. **JAMA Neurology**, Chicago, US, v. 73, n. 11, p. 1370–1372, 11 2016. ISSN 2168-6149.

MEIRA, I. D.; ROMÃO, T. T.; PRADO, H. J. Pires do; KRÜGER, L. T.; PIRES, M. E. P.; CONCEIÇÃO, P. O. da. Ketogenic diet and epilepsy: What we know so far. **Frontiers in Neuroscience**, Lausanne, CH, v. 13, p. 5, 2019. ISSN 1662-453X.

MORRIS, C.; LECAR, H. Voltage oscillations in the barnacle giant muscle fiber. **Biophysical journal**, Elsevier, Amsterdam, NL, v. 35, n. 1, p. 193–213, 1981.

NAGARAJ, V.; LAMPERSKI, A.; NETOFF, T. I. Seizure control in a computational model using a reinforcement learning stimulation paradigm. **International Journal of Neural Systems**, Singapore, v. 27, n. 07, p. 1750012, 2017. PMID: 28030999.

NELDER, J. A.; MEAD, R. A Simplex Method for Function Minimization. **The Computer Journal**, Oxford, UK, v. 7, n. 4, p. 308–313, 01 1965. ISSN 0010-4620.

- NETO, L. A.; ERASME, D.; GENAY, N.; CHANCLOU, P.; DENIEL, Q.; TRAORE, F.; ANFRAY, T.; HMADOU, R.; AUPETIT-BERTHELEMOT, C. Simple estimation of fiber dispersion and laser chirp parameters using the downhill simplex fitting algorithm. **Journal of Lightwave Technology**, v. 31, n. 2, p. 334–342, 2013.
- NOBUKAWA, S.; NISHIMURA, H.; YAMANISHI, T.; LIU, J.-Q. Analysis of chaotic resonance in Izhikevich neuron model. **PLOS ONE**, Public Library of Science, California, US, v. 10, n. 9, p. 1–22, 09 2015.
- NOËL, J.; KERSCHEN, G. Nonlinear system identification in structural dynamics: 10 more years of progress. **Mechanical Systems and Signal Processing**, Amsterdam, NL, v. 83, p. 2–35, 2017. ISSN 0888-3270.
- NOWAK, R. D. Nonlinear system identification. **Circuits, Systems and Signal Processing**, Springer, v. 21, p. 109–122, 2002.
- OGATA, K. **Modern control engineering fifth edition**. [S.l.: s.n.], 2010.
- OPPENHEIM, A. V.; WILLSKY, A. S.; NAWAB, S. H.; DING, J.-J. **Signals and systems**. [S.l.]: Prentice hall Upper Saddle River, NJ, 1997.
- OUYANG, C.-S.; YANG, R.-C.; CHIANG, C.-T.; WU, R.-C.; LIN, L.-C. EEG autoregressive modeling analysis: A diagnostic tool for patients with epilepsy without epileptiform discharges. **Clinical Neurophysiology**, Amsterdam, NL, v. 131, n. 8, p. 1902–1908, 2020. ISSN 1388-2457.
- PACHECO, R.; JR, V. S. Using orthogonal functions for identification and sensitivity analysis of mechanical systems. **Journal of Vibration and Control**, Thousand Oaks, US, v. 8, n. 7, p. 993–1021, 2002.
- PARASKEVOPOULOS, P. D. S. P. N.; MOUROUTSOS, S. G. The fourier series operational matrix of integration. **International Journal of Systems Science**, Taylor & Francis, Oxfordshire, UK, v. 16, n. 2, p. 171–176, 1985.
- PARVIZI, J.; KASTNER, S. Promises and limitations of human intracranial electroencephalography. **Nature Neuroscience**, Nature Publishing Group US New York, v. 21, n. 4, p. 474–483, 2018.
- POLI, R.; KENNEDY, J.; BLACKWELL, T. Particle swarm optimization: An overview. **Swarm intelligence**, [S.l.], v. 1, p. 33–57, 2007.
- POWELL, T. D. Automated tuning of an extended Kalman filter using the downhill simplex algorithm. **Journal of Guidance, Control, and Dynamics**, [S.l.], v. 25, n. 5, p. 901–908, 2002.
- PRASANNA, J.; SUBATHRA, M. S. P.; MOHAMMED, M. A.; DAMASEVICIUS, R.; SAIRAMYA, N. J.; GEORGE, S. T. Automated epileptic seizure detection in pediatric subjects of CHB-MIT EEG database-a survey. **Journal of Personalized Medicine**, [S.l.], v. 11, n. 10, 2021. ISSN 2075-4426.
- PROIX, T.; BARTOLOMEI, F.; CHAUVEL, P.; BERNARD, C.; JIRSA, V. K.

- Permittivity coupling across brain regions determines seizure recruitment in partial epilepsy. **Journal of Neuroscience**, Society for Neuroscience, Washington DC, US, v. 34, n. 45, p. 15009–15021, 2014. ISSN 0270-6474.
- PROIX, T.; BARTOLOMEI, F.; GUYE, M.; JIRSA, V. K. Individual brain structure and modelling predict seizure propagation. **Brain**, Oxford, UK, v. 140, n. 3, p. 641–654, 02 2017. ISSN 0006-8950.
- PROIX, T.; JIRSA, V. K.; BARTOLOMEI, F.; GUYE, M.; TRUCCOLO, W. Predicting the spatiotemporal diversity of seizure propagation and termination in human focal epilepsy. **Nature communications**, Nature Publishing Group UK London, v. 9, n. 1, p. 1088, 2018.
- RAO, S. S. **Mechanical vibrations**. [S.l.: s.n.], 2001.
- RETES, P. F. L.; AGUIRRE, L. A. NARMAX model identification using a randomised approach. **International Journal of Modelling, Identification and Control**, [S.l.], v. 31, n. 3, p. 205–216, 2019.
- REYHANOGLU, M.; SCHAFT, A. van der; MCCLAMROCH, N.; KOLMANOVSKY, I. Dynamics and control of a class of underactuated mechanical systems. **IEEE Transactions on Automatic Control**, New Jersey, US, v. 44, n. 9, p. 1663–1671, 1999.
- RIZZONE, M.; LANOTTE, M.; BERGAMASCO, B.; TAVELLA, A.; TORRE, E.; FACCANI, G.; MELCARNE, A.; LOPIANO, L. Deep brain stimulation of the subthalamic nucleus in parkinson's disease: effects of variation in stimulation parameters. **Journal of Neurology, Neurosurgery & Psychiatry**, BMJ Publishing Group Ltd, London, UK, v. 71, n. 2, p. 215–219, 2001. ISSN 0022-3050.
- ROY, D.; GHOSH, A.; JIRSA, V. K. Phase description of spiking neuron networks with global electric and synaptic coupling. **Physical Review E**, College Park, US, v. 83, p. 051909, May 2011.
- RYVLIN, P.; NASHEF, L.; TOMSON, T. Prevention of sudden unexpected death in epilepsy: A realistic goal? **Epilepsia**, Hoboken, US, v. 54, n. s2, p. 23–28, 2013.
- SAGGIO, M. L.; CRISP, D.; SCOTT, J. M.; KAROLY, P.; KUHLMANN, L.; NAKATANI, M.; MURAI, T.; DÄMPPELMANN, M.; SCHULZE-BONHAGE, A.; IKEDA, A.; COOK, M.; GLISKE, S. V.; LIN, J.; BERNARD, C.; JIRSA, V.; STACEY, W. C. A taxonomy of seizure dynamotypes. **eLife**, eLife Sciences Publications, Ltd, [S.l.], v. 9, p. e55632, jul 2020. ISSN 2050-084X.
- SAGNOL, G.; STAHLBERG, M. Picos documentation. **A python interface to conic optimization solvers. Release 0.1**, v. 1, 2012.
- SÁNDOR, Z.; MAFFIONE, N. The relative lyapunov indicators: Theory and application to dynamical astronomy. In: _____. **Chaos Detection and Predictability**. Berlin, Heidelberg: Springer Berlin Heidelberg, 2016. p. 183–220.
- SCHIFF, N. D.; VICTOR, J. D.; CANEL, A. Nonlinear autoregressive analysis of

- the 3/s ictal electroencephalogram: Implications for underlying dynamics. **Biological cybernetics**, Springer, Berlin, DE, v. 72, n. 6, p. 527–532, 1995.
- SCHIFF, N. D.; VICTOR, J. D.; CANEL, A.; LABAR, D. R. Characteristic nonlinearities of the 3/s ictal electroencephalogram identified by nonlinear autoregressive analysis. **Biological Cybernetics**, Springer, Berlin, DE, v. 72, p. 519–526, 1995.
- SCHULZE-BONHAGE, A. Brain stimulation as a neuromodulatory epilepsy therapy. **Seizure**, v. 44, p. 169–175, 2017. ISSN 1059-1311. 25th Anniversary Issue.
- SEPULVEDA, R.; MONTIEL, O.; DIAZ, G.; GUTIERREZ, D.; CASTILLO, O. Classification of encephalographic signals using artificial neural networks. **Computación y Sistemas**, [S.l.], v. 19, n. 1, p. 69–88, 2015.
- SHANNON, C. Communication in the presence of noise. **Proceedings of the IEEE**, New Jersey, US, v. 72, n. 9, p. 1192–1201, 1984.
- SHARMA, P.; KHAN, Y. U.; FAROOQ, O.; TRIPATHI, M.; ADELI, H. A wavelet-statistical features approach for nonconvulsive seizure detection. **Clinical EEG and Neuroscience**, [S.l.], v. 45, n. 4, p. 274–284, 2014.
- SHIEH, L.; WANG, H.; YATES, R. Discrete-continuous model conversion. **Applied Mathematical Modelling**, Amsterdam, NL, v. 4, n. 6, p. 449–455, 1980. ISSN 0307-904X.
- SLOTINE, J.-J. E.; LI, W. et al. **Applied nonlinear control**. [S.l.]: Prentice hall Englewood Cliffs, NJ, 1991.
- SOONG, T. T. **Fundamentals of probability and statistics for engineers**. [S.l.]: John Wiley & Sons, 2004.
- SPENCER, D. Auras are frequent in patients with generalized epilepsy: Auras in generalized epilepsy. **Epilepsy Currents**, Chicago, US, v. 15, n. 2, p. 75–77, 2015.
- SPONG, M. W. Underactuated mechanical systems. In: SICILIANO, B.; VALAVANIS, K. P. (Ed.). **Control Problems in Robotics and Automation**. Berlin, Heidelberg: Springer Berlin Heidelberg, 1998. p. 135–150. ISBN 978-3-540-40913-7.
- STORACE, M.; LINARO, D.; LANGE, E. de. The Hindmarsh-Rose neuron model: Bifurcation analysis and piecewise-linear approximations. **Chaos: An Interdisciplinary Journal of Nonlinear Science**, College Park, US, v. 18, n. 3, p. 033128, 09 2008. ISSN 1054-1500.
- SUBASI, A.; KEVRIC, J.; CANBAZ, M. A. Epileptic seizure detection using hybrid machine learning methods. **Neural Computing and Applications**, Springer, [S.l.], v. 31, p. 317–325, 2019.
- SURGES, R.; THIJS, R. D.; TAN, H. L.; SANDER, J. W. Sudden unexpected death in epilepsy: risk factors and potential pathomechanisms. **Nature Reviews Neurology**, London, UK, v. 5, n. 9, p. 492, 2009.
- TAKAGI, T.; SUGENO, M. Fuzzy identification of systems and its applications to

- modeling and control. **IEEE Transactions on Systems, Man, and Cybernetics**, New Jersey, US, SMC-15, n. 1, p. 116–132, 1985.
- TANAKA, K.; WANG, H. O. **Fuzzy control systems design and analysis: a linear matrix inequality approach**. [S.l.]: John Wiley & Sons, 2004.
- TANIGUCHI, T.; TANAKA, K.; OHTAKE, H.; WANG, H. Model construction, rule reduction, and robust compensation for generalized form of takagi-sugeno fuzzy systems. **IEEE Transactions on Fuzzy Systems**, New Jersey, US, v. 9, n. 4, p. 525–538, 2001.
- TAYLOR, M. E.; KACPRZYK, J. **Transfer in reinforcement learning domains**. [S.l.]: Springer, 2009.
- TELLEZ-ZENTENO, J. F.; MCLACHLAN, R. S.; PARRENT, A.; KUBU, C. S.; WIEBE, S. Hippocampal electrical stimulation in mesial temporal lobe epilepsy. **Neurology**, Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology, v. 66, n. 10, p. 1490–1494, 2006. ISSN 0028-3878.
- TURRIGIANO, G. G.; NELSON, S. B. Hebb and homeostasis in neuronal plasticity. **Current Opinion in Neurobiology**, v. 10, n. 3, p. 358–364, 2000. ISSN 0959-4388.
- VELASCO, A. L.; VELASCO, F.; VELASCO, M.; TREJO, D.; CASTRO, G.; CARRILLO-RUIZ, J. D. Electrical stimulation of the hippocampal epileptic foci for seizure control: A double-blind, long-term follow-up study. **Epilepsia**, Hoboken, US, v. 48, n. 10, p. 1895–1903, 2007.
- VELASCO, F.; VELASCO, M.; VELASCO, A. L.; MENEZ, D.; ROCHA, L. Electrical stimulation for epilepsy: stimulation of hippocampal foci. **Stereotactic and Functional Neurosurgery**, [S.l.], v. 77, n. 1-4, p. 223–227, 2001.
- VEZZANI, A.; FRENCH, J.; BARTFAI, T.; BARAM, T. Z. The role of inflammation in epilepsy. **Nature Reviews Neurology**, London, UK, v. 7, n. 1, p. 31, 2011.
- WEBSTER, J. G. **Encyclopedia of medical devices and instrumentation**. [S.l.]: United States of America, 2006.
- WENDLING, F.; BENQUET, P.; BARTOLOMEI, F.; JIRSA, V. Computational models of epileptiform activity. **Journal of Neuroscience Methods**, Amsterdam, NL, v. 260, p. 233–251, 2016. ISSN 0165-0270.
- YANG, J.-H.; LAM, H.-F. An innovative bayesian system identification method using autoregressive model. **Mechanical Systems and Signal Processing**, Amsterdam, NL, v. 133, p. 106289, 2019. ISSN 0888-3270.
- YANO, M. O.; VILLANI, L. G.; SILVA, S. da; FIGUEIREDO, E. Autoregressive model extrapolation using cubic splines for damage progression analysis. **Journal of the Brazilian Society of Mechanical Sciences and Engineering**, [S.l.], v. 43, n. 1, p. 19, 2021.
- YAO, R.; PAKZAD, S. N. Autoregressive statistical pattern recognition algorithms for damage detection in civil structures. **Mechanical Systems and Signal Processing**,

Amsterdam, NL, v. 31, p. 355–368, 2012. ISSN 0888-3270.

YIZHAR, O.; FENNO, L. E.; PRIGGE, M.; SCHNEIDER, F.; DAVIDSON, T. J.; O'SHEA, D. J.; SOHAL, V. S.; GOSHEN, I.; FINKELSTEIN, J.; PAZ, J. T. et al. Neocortical excitation/inhibition balance in information processing and social dysfunction. **Nature**, London, UK, v. 477, n. 7363, p. 171–178, 2011.

YU, P.-N.; NAIINI, S. A.; HECK, C. N.; LIU, C. Y.; SONG, D.; BERGER, T. W. A sparse Laguerre-Volterra autoregressive model for seizure prediction in temporal lobe epilepsy. In: **2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)**. [S.l.: s.n.], 2016. p. 1664–1667.

YUAN, Q.; ZHOU, W.; XU, F.; LENG, Y.; WEI, D. Epileptic EEG identification via lbp operators on wavelet coefficients. **International Journal of Neural Systems**, Singapore, v. 28, n. 08, p. 1850010, 2018. PMID: 29665725.

YUAN, S.; ZHOU, W.; CHEN, L. Epileptic seizure prediction using diffusion distance and bayesian linear discriminate analysis on intracranial EEG. **International Journal of Neural Systems**, Singapore, v. 28, n. 01, p. 1750043, 2018. PMID: 28950741.

ZHANG, H.; XIAO, P. Seizure dynamics of coupled oscillators with Epileptor field model. **International Journal of Bifurcation and Chaos**, Singapore, v. 28, n. 03, p. 1850041, 2018.

ZHU, D.; BIEGER, J.; MOLINA, G. G.; AARTS, R. M. A survey of stimulation methods used in SSVEP-based bcis. **Computational Intelligence and Neuroscience**, London, UK, v. 2010, 2010.

ZIBURKUS, J.; CRESSMAN, J. R.; SCHIFF, S. J. Seizures as imbalanced up states: excitatory and inhibitory conductances during seizure-like events. **Journal of Neurophysiology**, [S.l.], v. 109, n. 5, p. 1296–1306, 2013.

APPENDIX A - MATHEMATICAL FORMULATION FOR THE PARAMETER β

The classic definition of the decay rate is as follows:

$$\alpha \mathbf{I} = \begin{bmatrix} \alpha & 0 & \cdots & 0 \\ 0 & \alpha & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \alpha \end{bmatrix}$$

Its characteristic polynomial is given by $|\alpha \mathbf{I} - \lambda \mathbf{I}| = 0$. Alternatively:

$$\begin{vmatrix} (\alpha - \lambda) & 0 & \cdots & 0 \\ 0 & (\alpha - \lambda) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & (\alpha - \lambda) \end{vmatrix} = 0$$

Therefore, the eigenvalues λ_i , $i = 1, \dots, n$, where n is the dimension of the system, are all the same, given by the following equation:

$$(\alpha - \lambda)^n = 0$$

whose determinant, since it is a diagonal matrix, is always greater than zero. For the proposed matrix $\beta \mathbf{1}$, in turn:

$$\beta \mathbf{1} = \begin{bmatrix} \beta & \beta & \cdots & \beta \\ \beta & \beta & \cdots & \beta \\ \vdots & \vdots & \ddots & \vdots \\ \beta & \beta & \cdots & \beta \end{bmatrix}$$

Its characteristic polynomial can be obtained by induction. Consider two systems of dimension 2 and 3, respectively:

$$\beta \mathbf{1} = \begin{bmatrix} \beta & \beta \\ \beta & \beta \end{bmatrix}$$

$$\beta \mathbf{1} = \begin{bmatrix} \beta & \beta & \beta \\ \beta & \beta & \beta \\ \beta & \beta & \beta \end{bmatrix}$$

If $|\beta \mathbf{1} - \lambda \mathbf{I}| = 0$, the following polynomials are obtained:

$$p(\lambda) = (\beta - \lambda)^2 - \beta^2 = \lambda(\lambda - 2\beta)$$

$$p(\lambda) = (\beta - \lambda)^3 + 2\beta^3 - [3\beta^2(\beta - \lambda)] = \lambda^2(-\lambda + 3\beta)$$

Thus, the eigenvalues for $n = 2$ are $\lambda_1 = 0$ and $\lambda_2 = 2\beta$; the ones for $n = 3$, in turn, are: $\lambda_1 = 0$, $\lambda_2 = 0$ and $\lambda_3 = 3\beta$. A general equation for the characteristic polynomial can, thereby, be expressed by:

$$p(\lambda) = (-1\lambda)^n + n\beta(-1\lambda)^{n-1} = \lambda^{n-1}(\lambda - n\beta)$$

Since the rows of matrix $\beta \mathbf{1}$ are identical, its determinant is zero (thus implying in linear dependency among the rows and columns), which leads to the following relationship between eigenvalues:

$$\lambda_1 = \lambda_2 = \dots = \lambda_{n-1} = 0, \quad \lambda_n = n\beta$$

For the sake of understanding, the diagonal matrices of eigenvalues $\alpha \mathbf{I}$ and $\beta \mathbf{1}$ can be re-written as:

$$\Lambda_{\alpha \mathbf{I}} = \begin{bmatrix} \alpha & 0 & \cdots & 0 \\ 0 & \alpha & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \alpha \end{bmatrix}, \quad \Lambda_{\beta \mathbf{1}} = \begin{bmatrix} n\beta & 0 & \cdots & 0 \\ 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 0 \end{bmatrix}$$

Based on the superposition principle, the linear combination between the eigenvalues of both matrices, given by:

$$\alpha \mathbf{I} + \beta \mathbf{1} = \begin{bmatrix} (\alpha + \beta) & \beta & \cdots & \beta \\ \beta & (\alpha + \beta) & \cdots & \beta \\ \vdots & \vdots & \ddots & \vdots \\ \beta & \beta & \cdots & (\alpha + \beta) \end{bmatrix}$$

whose determinant is $|\alpha \mathbf{I} + \beta \mathbf{1}|$, presents the following matrix of eigenvalues:

$$\Lambda_{\alpha \mathbf{I} + \beta \mathbf{1}} = \begin{bmatrix} (\alpha + n\beta) & 0 & \cdots & 0 \\ 0 & \alpha & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & \alpha \end{bmatrix}$$

which can be, indeed, verified after calculating again the determinant for its characteristic polynomial. Note that:

- the introduction of matrix $\alpha\mathbf{I}$ leads to a single eigenvalue of multiplicity n ;
- the introduction of matrix $\beta\mathbf{1}$ leads to two different eigenvalues: 0, of multiplicity $n - 1$, and $n\beta$, of multiplicity 1;
- the introduction of matrix $\alpha\mathbf{I} + \beta\mathbf{1}$ leads to two different eigenvalues: α , of multiplicity $n - 1$, and $\alpha + n\beta$, of multiplicity 1;
- matrix $\alpha\mathbf{I} + \beta\mathbf{1}$ is a general case of all the other ones: if $\beta = 0$, the classical decay rate is obtained; if $\alpha = 0$, only the proposed matrix is obtained; at last, if $\alpha = \beta = 0$, no decay rate of any kind is applied.

This is particularly useful when applying such matrices to dynamic systems. For the classical Lyapunov inequality, it follows that:

$$\mathbf{A}^T \mathbf{P} + \mathbf{P} \mathbf{A} < \mathbf{0}$$

Note that, as the inequality is negative (that is, it is supposed to produce a negative definite matrix), the resulting positive eigenvalues of $\mathbf{P}$ imply, ultimately, in negative eigenvalues by the inequality, which assures stability. By introducing the decay rate in its classical form, the following equation is obtained:

$$(\mathbf{A} + \alpha\mathbf{I})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I}) < \mathbf{0}$$

The practical effect of the decay rate can be seen by rearranging the equation above:

$$\mathbf{A}^T \mathbf{P} + \mathbf{P} \mathbf{A} + 2\alpha\mathbf{P} < \mathbf{0}$$

That is, as the Lyapunov inequality is, by definition, negative, the addition of a positive term that must keep such inequality negative influences on the positiveness of matrix $\mathbf{P}$, thus forcing the system to look for solutions to the left of the real vs imaginary plane. Alternatively, using the proposed matrix:

$$(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1}) < \mathbf{0}$$

The main idea of applying this new equation is based on the qualitative characteristic of the eigenvalues of $\alpha\mathbf{I}$ compared to the ones from $\alpha\mathbf{I} + \beta\mathbf{1}$. Although both intend to produce an effect that speeds up the convergence to the equilibrium point, for the first case, the multiplicity n of the eigenvalues imply in a single value of λ (placed to the left of the imaginary plane, due to the Lyapunov inequality, but on the real axis); for the second one, the characteristics are the same, but there are two different values.

This peculiarity leads, in the first case, to an inflected stable node (Figari; Altosole, 2007); in the second one, to a stable node (Figari; Altosole, 2007). To better understand the relationship between the two decay rate matrices applied to the system, not only individually, we propose analyzing the problem from the eigenvector base point of view. For instance, matrices $\mathbf{A}$, $\alpha\mathbf{I}$ and $\beta\mathbf{1}$ can be re-written as:

$$\begin{aligned}\mathbf{A} &= \Phi_A \Lambda_A \Phi_A^{-1} \\ \alpha\mathbf{I} &= \Phi_{\alpha\mathbf{I}} \Lambda_{\alpha\mathbf{I}} \Phi_{\alpha\mathbf{I}}^{-1} \\ \beta\mathbf{1} &= \Phi_{\beta\mathbf{1}} \Lambda_{\beta\mathbf{1}} \Phi_{\beta\mathbf{1}}^{-1}\end{aligned}$$

Alternatively, it also holds that:

$$\begin{aligned}\Lambda_A &= \Phi_A^{-1} \mathbf{A} \Phi_A \\ \Lambda_{\alpha\mathbf{I}} &= \Phi_{\alpha\mathbf{I}}^{-1} \alpha\mathbf{I} \Phi_{\alpha\mathbf{I}} \\ \Lambda_{\beta\mathbf{1}} &= \Phi_{\beta\mathbf{1}}^{-1} \beta\mathbf{1} \Phi_{\beta\mathbf{1}}\end{aligned}$$

The first analysis herein focus on $\alpha\mathbf{I}$.

Base of Eigenvectors of $\alpha\mathbf{I}$

Considering the Lyapunov equation again, for $\alpha\mathbf{I}$:

$$\Phi_{\alpha\mathbf{I}}^{-1}[(\mathbf{A} + \alpha\mathbf{I})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I})] \Phi_{\alpha\mathbf{I}} < \mathbf{0}$$

which is the same as:

$$(\Phi_{\alpha\mathbf{I}}^{-1} \mathbf{A} \Phi_{\alpha\mathbf{I}} + \Phi_{\alpha\mathbf{I}}^{-1} \alpha\mathbf{I} \Phi_{\alpha\mathbf{I}})^T \mathbf{P} + \mathbf{P}(\Phi_{\alpha\mathbf{I}}^{-1} \mathbf{A} \Phi_{\alpha\mathbf{I}} + \Phi_{\alpha\mathbf{I}}^{-1} \alpha\mathbf{I} \Phi_{\alpha\mathbf{I}}) < \mathbf{0}$$

or, alternatively:

$$(\Phi_{\alpha\mathbf{I}}^{-1} \mathbf{A} \Phi_{\alpha\mathbf{I}} + \Lambda_{\alpha\mathbf{I}})^T \mathbf{P} + \mathbf{P}(\Phi_{\alpha\mathbf{I}}^{-1} \mathbf{A} \Phi_{\alpha\mathbf{I}} + \Lambda_{\alpha\mathbf{I}}) < \mathbf{0}$$

Since $\Phi_{\alpha\mathbf{I}}$ is a canonical base (all eigenvalues of the decay rate are α , which implies that $\Phi_{\alpha\mathbf{I}}^{-1} \mathbf{A} \Phi_{\alpha\mathbf{I}} = \mathbf{A}$), then:

$$(\mathbf{A} + \Lambda_{\alpha\mathbf{I}})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \Lambda_{\alpha\mathbf{I}}) < \mathbf{0}$$

By carrying out the same procedure for the base of eigenvectors of $\mathbf{A}$ the following

expression if obtained:

$$\Phi_A^{-1}[(\mathbf{A} + \Lambda_{\alpha\mathbf{I}})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \Lambda_{\alpha\mathbf{I}})]\Phi_A < \mathbf{0}$$

Since $\Lambda_{\alpha\mathbf{I}} = \alpha\mathbf{I}$, then $\Phi_A^{-1}\Lambda_{\alpha\mathbf{I}}\Phi_A = \Phi_A^{-1}(\alpha\mathbf{I})\Phi_A = \alpha\Phi_A^{-1}\mathbf{I}\Phi_A = \alpha\mathbf{I} = \Lambda_{\alpha\mathbf{I}}$. Therefore, for the stability analysis, it suffices that the Lyapunov inequality is defined as:

$$(\Lambda_A + \Lambda_{\alpha\mathbf{I}})^T \mathbf{P} + \mathbf{P}(\Lambda_A + \Lambda_{\alpha\mathbf{I}}) < \mathbf{0}$$

Note that eigenvalues of magnitude α are directly added to $\mathbf{A}$, whose base is the same as the one from the eigenvectors of $\alpha\mathbf{I}$. However, since including β does not lead to a canonical eigenvector base, its analysis is more difficult. Defining again the Lyapunov inequality:

$$\Phi_{\alpha\mathbf{I}}^{-1}[(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})]\Phi_{\alpha\mathbf{I}} < \mathbf{0}$$

By carrying out similar steps as previously done, a new equation is obtained, but it does not present only eigenvalues matrices:

$$(\Lambda_A + \Lambda_{\alpha\mathbf{I}} + \Phi_A^{-1}\beta\mathbf{1}\Phi_A)^T \mathbf{P} + \mathbf{P}(\Lambda_A + \Lambda_{\alpha\mathbf{I}} + \Phi_A^{-1}\beta\mathbf{1}\Phi_A) < \mathbf{0}$$

A possible interpretation for this result is that: adding β does not imply in a direct addition of eigenvalues to the system $\mathbf{A}$; rather, it adds the eigenvalues matrices Λ_A and $\Lambda_{\alpha\mathbf{I}}$ to the projection of $\beta\mathbf{1}$ onto the base of eigenvectors of $\mathbf{A}$. The resulting effect in this case is not given by the introduction of eigenvalues of $\beta\mathbf{1}$, but by its full matrix to the base of $\mathbf{A}$ (which defines the dynamics of the system in terms of oscillation and stability), weighed by a factor β for all states. It is expected that this weight, during the optimization process of the LMIs, provides a more balanced gain distribution among the states.

An alternate analysis of the same equation can lead to more concrete conclusions. Therefore, for purposes of comparison, the same formulation is carried out again, but applying the base of eigenvectors of $\beta\mathbf{1}$.

Base of Eigenvectors of $\beta\mathbf{1}$

Considering the Lyapunov inequality in terms of $\beta\mathbf{1}$, in turn:

$$\Phi_{\beta\mathbf{1}}^{-1}[(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})^T \mathbf{P} + \mathbf{P}(\mathbf{A} + \alpha\mathbf{I} + \beta\mathbf{1})]\Phi_{\beta\mathbf{1}} < \mathbf{0}$$

Once again, the following relation holds: $\Phi_{\beta\mathbf{1}}^{-1}(\alpha\mathbf{I})\Phi_{\beta\mathbf{1}} = \alpha\Phi_{\beta\mathbf{1}}^{-1}\mathbf{I}\Phi_{\beta\mathbf{1}} = \alpha\mathbf{I} = \Lambda_{\alpha\mathbf{I}}$. Thus,

it is possible to rearrange the equation above as:

$$(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha\mathbf{I}} + \Lambda_{\beta\mathbf{1}})^T\mathbf{P} + \mathbf{P}(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha\mathbf{I}} + \Lambda_{\beta\mathbf{1}}) < \mathbf{0}$$

Compared to Eq. A, this result can be interpreted as: since the addition of eigenvalues of $\beta\mathbf{1}$ does not occur directly (as it is the case for $\alpha\mathbf{I}$), due to its noncanonical base, the addition of eigenvalues of matrices $\Lambda_{\alpha\mathbf{I}}$ and $\Lambda_{\beta\mathbf{1}}$ occurs on the base of eigenvectors of $\beta\mathbf{1}$. Mathematically, although such a base is abstract, there exists a linear transformation that drives the original system $\mathbf{A}$ from the canonical base to the base $\Phi_{\beta\mathbf{1}}$, there, at last, a new addition of eigenvalues occurs. Both bases must assure stability. The main different consists, naturally, in the inclusion of eigenvalues $\lambda_1 = \lambda_2 = \dots = \lambda_{n-1} = 0$ and $\lambda_n = n\beta$ to the system, which enables a faster and smoother stability, as seen previously.

To check whether adding β is, indeed, more efficient than only α , the following LMI must, therefore, hold:

$$\mathbf{A}_{\beta\mathbf{1}} + \Lambda_{\alpha\mathbf{I}} + \Lambda_{\beta\mathbf{1}} > \mathbf{0}$$

where $\mathbf{A}_{\beta\mathbf{1}} = \Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}}$, and, again by induction for $n = 2, 3, 4, \dots$, $\Phi_{\beta\mathbf{1}}$ and $\Phi_{\beta\mathbf{1}}^{-1}$ can be defined as:

$$\Phi_{\beta\mathbf{1}} = \begin{bmatrix} -1 & -1 & \dots & -1 & -1 \\ 0 & 0 & \dots & 1 & 1 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 1 & \dots & 0 & 1 \\ 1 & 0 & \dots & 0 & 1 \end{bmatrix}$$

$$\Phi_{\beta\mathbf{1}}^{-1} = \begin{bmatrix} -\frac{1}{n} & -\frac{1}{n} & \dots & -\frac{1}{n} & \frac{(n-1)}{n} \\ -\frac{1}{n} & -\frac{1}{n} & \dots & \frac{(n-1)}{n} & -\frac{1}{n} \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ -\frac{1}{n} & \frac{(n-1)}{n} & \dots & -\frac{1}{n} & -\frac{1}{n} \\ \frac{1}{n} & \frac{1}{n} & \dots & \frac{1}{n} & \frac{1}{n} \end{bmatrix}$$

where n is the dimension of the system. Nonetheless, the behavior of the system $\mathbf{A}_{\beta\mathbf{1}}$ must be known yet, compared to the original one.

Practical Application

For simplicity and clarity of understanding, the system considered for the practical application is the classic mass-spring-damper, whose equation can be represented as:

$$m\ddot{x} + kx + c\dot{x} = u(t)$$

where m is the mass of the system, k is the stiffness of the spring, c is the damping coefficient, and $u(t)$ is an external input force. By rearranging such an equation into state-space representation, it follows that:

$$\begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ -\frac{k}{m} & -\frac{c}{m} \end{bmatrix} \begin{bmatrix} x \\ y \end{bmatrix} + \begin{bmatrix} 0 \\ \frac{1}{m} \end{bmatrix} u(t)$$

where $\dot{x} = y$ is the change of variables applied, with x being the linear displacement. For the control modeling, the linearization around the equilibrium point approach is used (which can be seen, in fact, directly from matrix $\mathbf{A}$ in Eq. A). The following parameters are, then, set: $m = 1kg$, $k = 1N/m$ e $c = 0Ns/m$. The latter one is zero for simplicity; that is, a simple oscillating behavior is expected to occur over the whole time window.

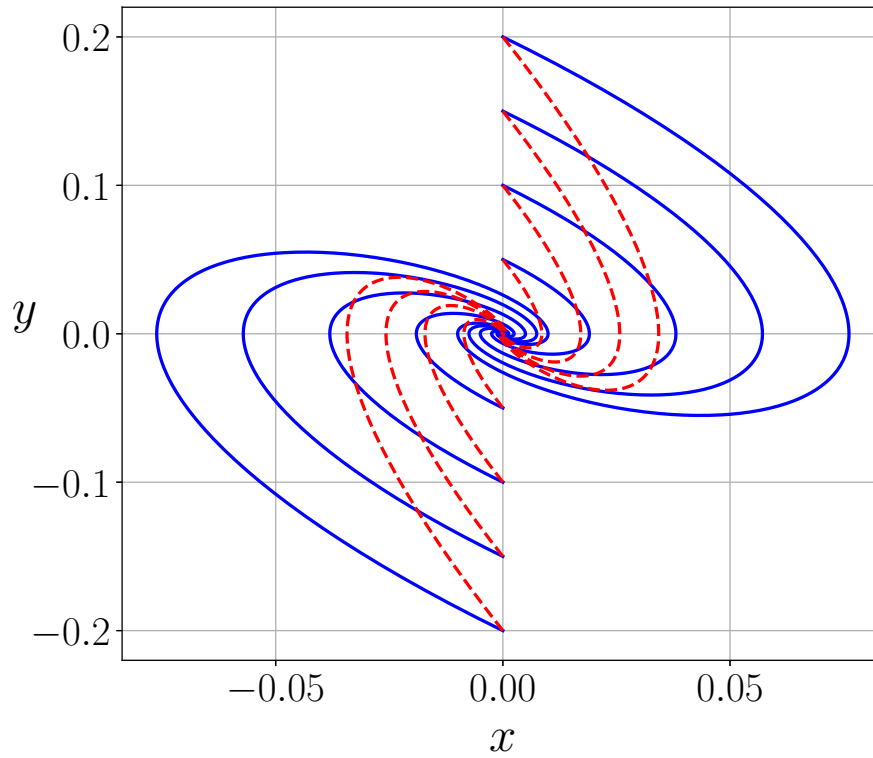
Figure 81 presents the phase portrait for the mass-spring system applying only α individually and, afterwards, along with β , considering the initial conditions as $x(0) = 0$ and $y(0)$, and then varying the latter one from -0.2 to 0.2 , with a step size of 0.05 . Note that, while both solutions reveal the stable nodes around the equilibrium point, the addition of β smooths out and speeds up the convergence of the system. In other words, the trajectory until the origin $(0,0)$ is shortened with β as the spiraling effect is reduced.

Figure 82a, in turn, presents particular cases among the ones above, in the time domain. Note that, while α itself speeds up the response of the system towards zero, adding β causes two effects: the curve gets smoother (that is, the oscillatory behavior is decreased) and the stability speed is increased. To check whether the Lyapunov constraint is met (that is, its derivative must be negative at all times greater than zero (Slotine; Li et al., 1991)), also note that including β leads, indeed, to a faster stabilization based on such criterion.

To endorse the efficiency of β (that is, to provide evidence that its effect cannot be obtained by only using α), consider a significantly higher decay rate for α . Figure 82b shows the results for this condition without and with β . Note that, even that the response is sped up with α , β provides, again, a smoother response such that the oscillating behavior below zero does not occur. Also, the convergence towards stability is slightly faster if compared to the case where $\beta = 0$.

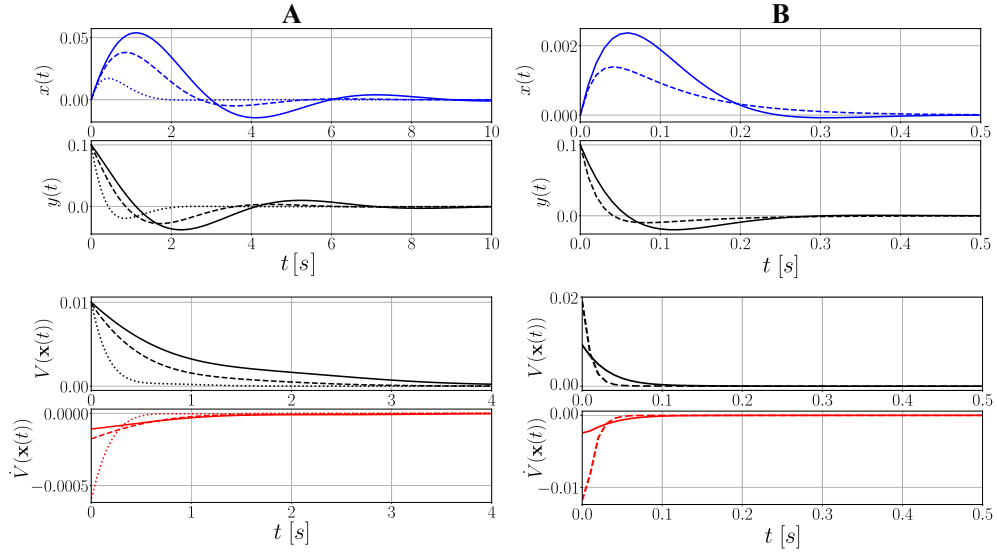
Figure 81 – **Phase portrait for the response of the mass-spring-damper system.**

The addition of β provides a faster smoother convergence towards the equilibrium point. The following parameters are used: $\alpha = 0.3$ and $\beta = 0$, indicated by the blue solid lines (—), and $\alpha = 0.3$ and $\beta = 1.0$, indicated by the red dashed lines (---).



Source: Own authorship.

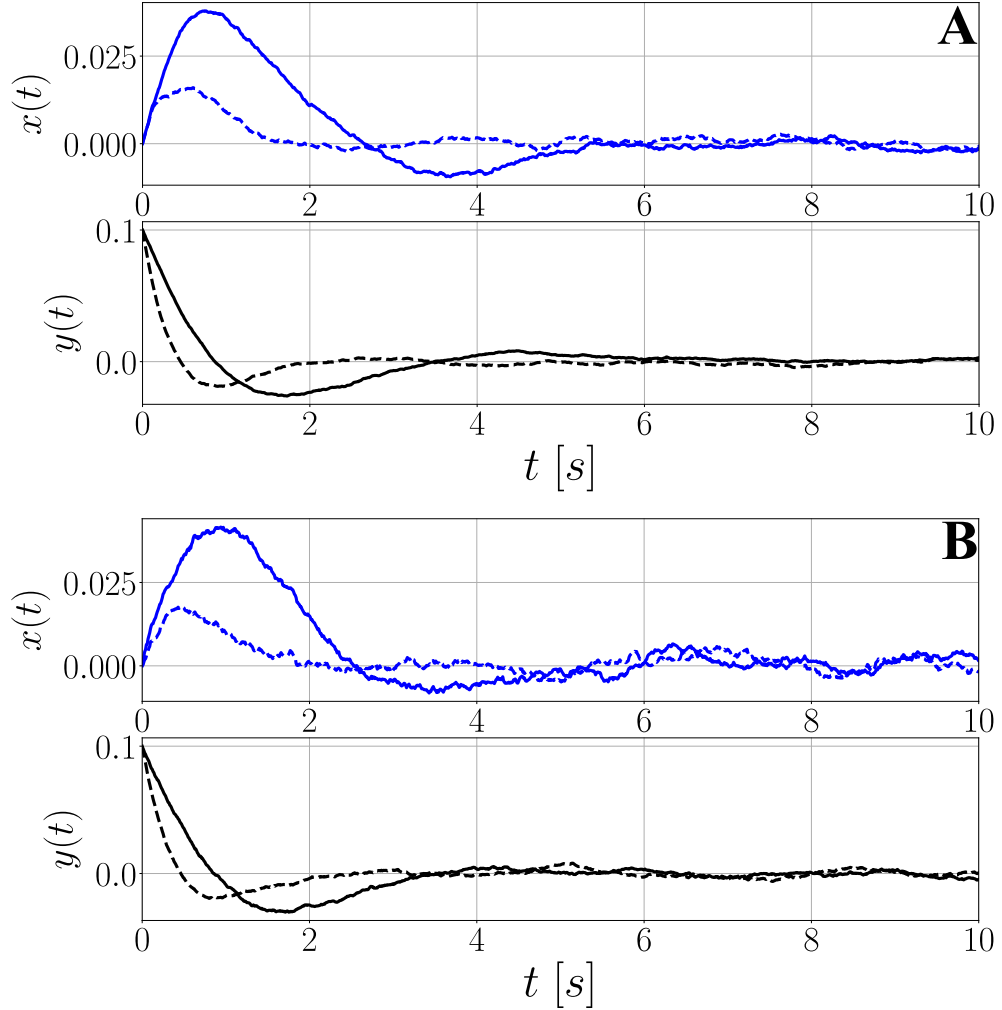
Figure 82 – **Response of the mass-spring-damper system in the time domain with the respective Lyapunov functions using varying α and β .** For both cases, the constraint of the Lyapunov function is met, being positive for all time instants and having its derivative negative for all time instants as well. a) Response of the mass-spring system in the time domain with the respective Lyapunov functions using the following parameters: $\alpha = 0$ and $\beta = 0$ (solid lines –), $\alpha = 0.3$ and $\beta = 0$ (dashed lines - -), and $\alpha = 0.3$ and $\beta = 1.0$ (dotted lines ...); b) response of the mass-spring system in the time domain with the respective Lyapunov functions using the following parameters: $\alpha = 10$ and $\beta = 0$ (solid lines –), and $\alpha = 10$ and $\beta = 1.0$ (dashed lines - -).



Source: Own authorship.

Figure 83, in turn, presents the response of the controlled system in the presence of noise. White noise was added to both state variables $x(t)$ and $y(t)$ considering the following relation: $x_n(t) = x(t) + t_n r(t)$, where $x_n(t)$ is the response of the system $x(t)$ after noise addition, expressed by $r(t)$, which represents elements from a gaussian distribution with zero mean and unity variance times the root mean square (RMS) value of $x(t)$, and t_n is an intensity factor. The same equation holds for $y(t)$. Note that, for the cases considered, the approach using the parameter β outperforms the one using only α , since the amplitudes of the states of the system remain at lower levels during the action of the controller.

Figure 83 – **Response of the mass-spring-damper system in the time domain after noise addition using varying α and β .** Adding noise does not significantly compromise the performance of the controller, which is still capable of driving the system to the equilibrium point effectively. The following parameters are used: a) $\alpha = 0.3$, $\beta = 0$ and $t_n = 0.5$, indicated by the solid lines (—), and $\alpha = 0.3$, $\beta = 1.0$ and $t_n = 0.5$, indicated by the dashed lines (---); b) $\alpha = 0.3$, $\beta = 0$ and $t_n = 1$, indicated by the solid lines (—), and $\alpha = 0.3$, $\beta = 1.0$ and $t_n = 1$, indicated by the dashed lines (---).



Source: Own authorship.

One caveat for applying this approach is that the use of both $\alpha \neq 0$ and $\beta \forall \mathbb{R}^+$ is mandatory, because:

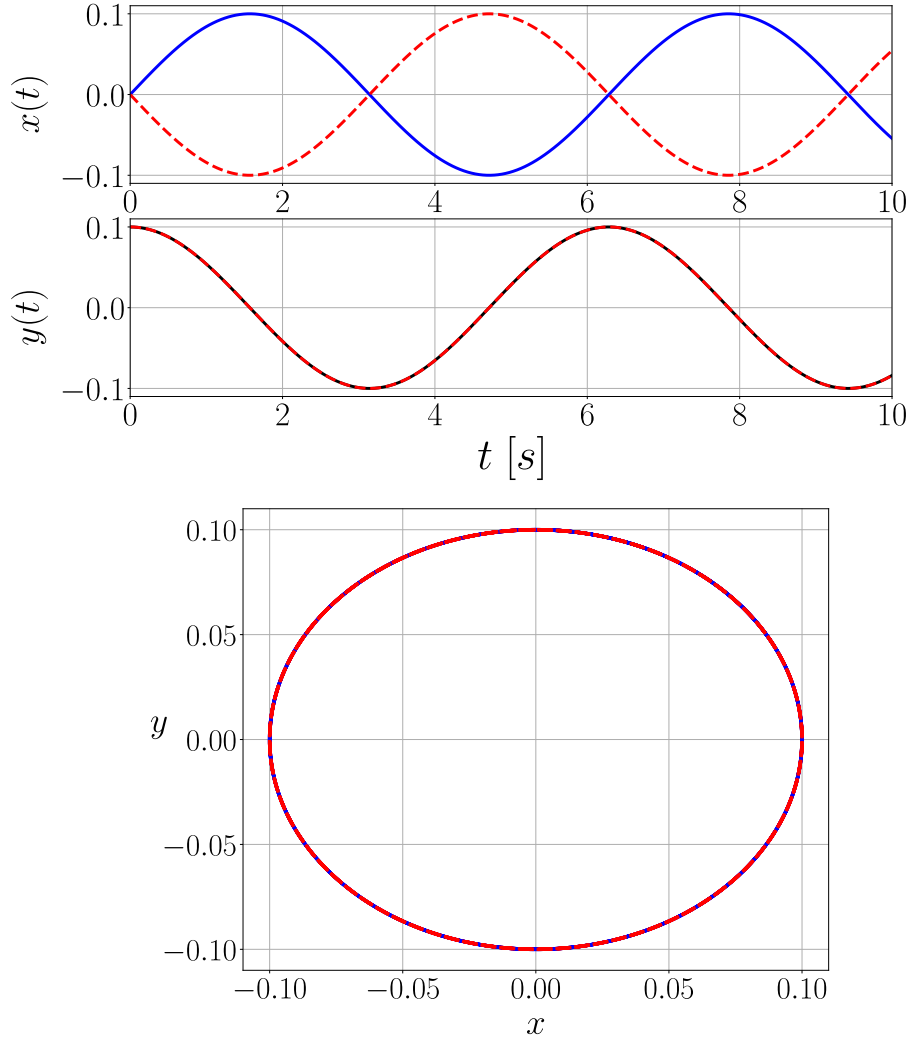
- if $\beta = 0$, the classical decay rate is defined, and no further gain is obtained;
- if $\alpha = 0$: $p(\lambda) = \lambda^{n-1}(\lambda - n\beta)$, which implies that $\lambda^{n-1} = 0$, which may lead to the addition of eigenvalues equal to zero, thus possibly causing a condition of marginal stability.

To analyze the effect of β in the dynamics of the system $\mathbf{A}$, consider Fig. 84, where the solutions for the system without any control input are presented for both $\mathbf{A}$ and $\mathbf{A}_{\beta\mathbf{1}}$ in the time domain and phase portrait. In this case, Eqs. A and A are as follows:

$$\Phi_{\beta\mathbf{1}} = \begin{bmatrix} -1 & 1 \\ 1 & 1 \end{bmatrix}$$

$$\Phi_{\beta\mathbf{1}}^{-1} = \begin{bmatrix} -0.5 & 0.5 \\ 0.5 & 0.5 \end{bmatrix}$$

Figure 84 – **Response of the mass-spring-damper system in the time domain and phase portrait using the following dynamic systems: $\mathbf{A}$ and $\mathbf{A}_{\beta\mathbf{1}}$.** The simulations show the similarity between both models in terms of frequency of oscillation, but opposed amplitude direction as the main difference. The following notation is used: solid lines (–) for $\mathbf{A}$ and dashed lines (– –) for $\mathbf{A}_{\beta\mathbf{1}}$.



Source: Own authorship.

Note that the transformation to the base of eigenvectors of $\beta\mathbf{1}$ implies that the inherent dynamics of the system is changed; in this case, since the oscillating behavior for the mass-spring system in its traditional form ($\mathbf{A}$) is controllable, in the base $\beta\mathbf{1}$, where its behavior presents the same attractor on the phase portrait, the system is also controllable. This fact is particularly relevant, because, according to Eq. A:

$$(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha}\mathbf{I} + \Lambda_{\beta\mathbf{1}})^T\mathbf{P} + \mathbf{P}(\Phi_{\beta\mathbf{1}}^{-1}\mathbf{A}\Phi_{\beta\mathbf{1}} + \Lambda_{\alpha}\mathbf{I} + \Lambda_{\beta\mathbf{1}}) < 0$$

the addition of eigenvalues occurs directly to matrix $\mathbf{A}_{\beta 1}$, which means that it should be, thus, controllable and susceptible to the decay rates for the parameter β to have a physical meaning. As for the eigenvalues of both conditions, they can be analyzed around the equilibrium point. For matrix $\mathbf{A}$:

$$\mathbf{A} = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}$$

whose eigenvalues are: $0 + 1j$ e $0 - 1j$; that is, a marginally stable system is obtained, as demonstrated by the attractor in Fig. 84. For $\mathbf{A}_{\beta 1}$, in turn:

$$\mathbf{A}_{\beta 1} = \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix}$$

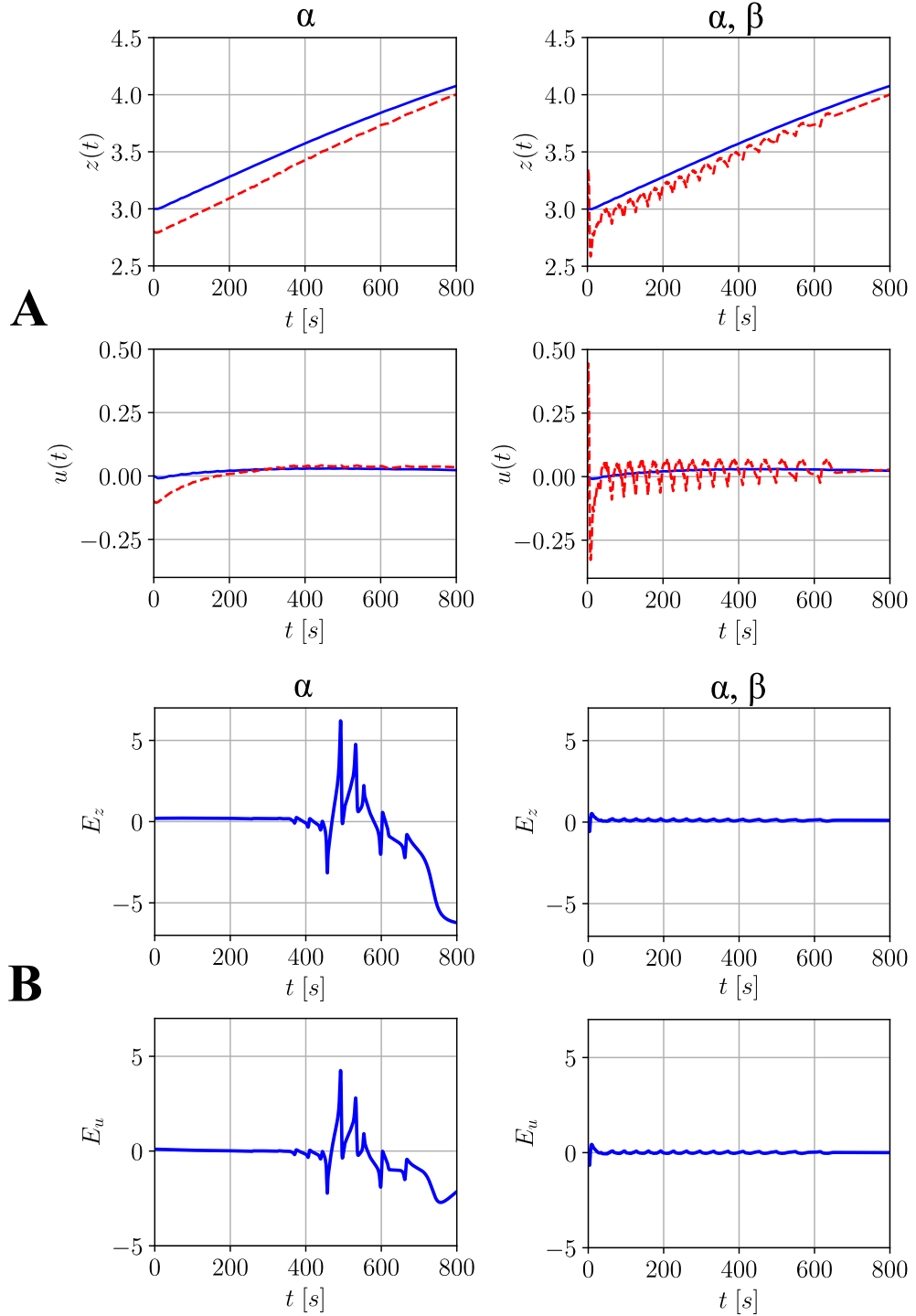
whose eigenvalues are $0 + 1j$ e $0 - 1j$ too. Note that the system, in this case, presents the same condition as the previous one in terms of stability. However, the change verified for $\mathbf{A}_{\beta 1}$ leads to a change in the direction of variable $x(t)$ in Fig. 84.

APPENDIX B - COMPLEMENTARY RESULTS FOR THE FUZZY OBSERVER

Figure 85 presents actual states for the remaining unmeasurable variables (obtained directly by the simulation) and their estimation computed by the fuzzy observer considering an on-going seizure, the error dynamics of each of them, and then considering the interictal period, respectively.

Figure 85 – **Complementary results for the fuzzy observer considering α and β .**

The remaining state variables of the Epileptor model are also efficiently reconstructed, especially with the addition of β , which leads to a smoother performance. A) Performance of the fuzzy observer: blue solid lines (—) indicate the actual states (initial conditions: $x_1(0) = 0$, $y_1(0) = -5$, $z(0) = 3$, $x_2(0) = 0$, $y_2(0) = 0$, $u(0) = 0$) and red dashed lines (---) indicate the estimated states (initial conditions: $\hat{x}_1(0) = x_1(0) - 1$, $\hat{y}_1(0) = y_1(0) - 1$, $\hat{z}(0) = z(0) - 0.2$, $\hat{x}_2(0) = x_2(0) - 1$, $\hat{y}_2(0) = y_2(0) + 1$, $\hat{u}(0) = u(0) - 0.1$). B) Error dynamics for the fuzzy observer without including the parameter β and after including it.

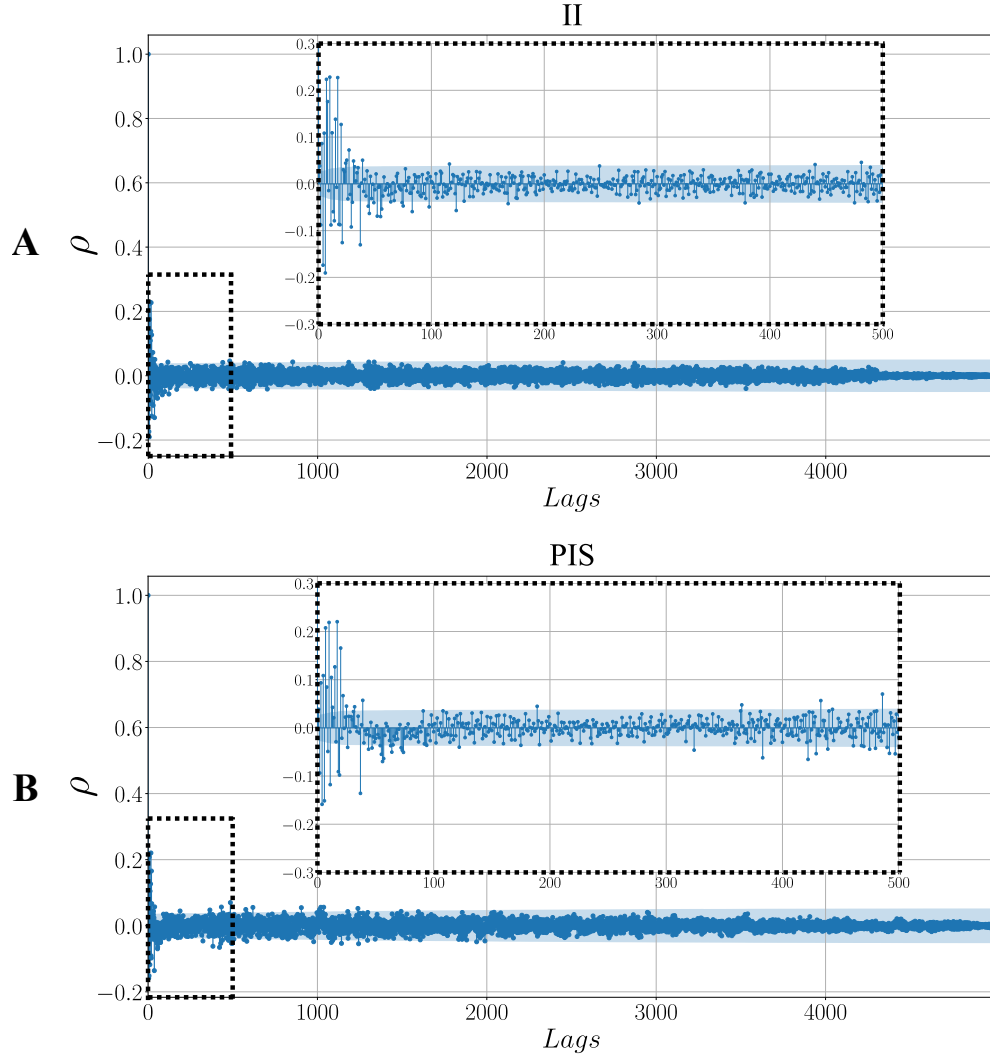


Source: Own authorship.

APPENDIX C - COMPLEMENTARY RESULTS FOR THE BLACK-BOX MODELING

Figure 86 depicts the autocorrelation function of the residuals of both AR models analyzed in the main body of the manuscript for the SUB signal (II and PIS, Figs. 86A and 86B, respectively). For both conditions, the same pattern can be observed: at the first lags, or time delays, the correlation values remain slightly higher than the confidence levels (at 95%); this indicates that these values of ρ are significant. As for the correlation for the next lags, they tend to decrease in magnitude and shrink into the confidence levels, which in turn indicates that they are not significant. This behavior is expected due to the relative simplicity of the model, which cannot fully capture all the dynamics involved in the real epileptiform activity. Nevertheless, since the values of ρ are low in general, the AR($k = 6$) models are taken as sufficiently good representations of the original signals.

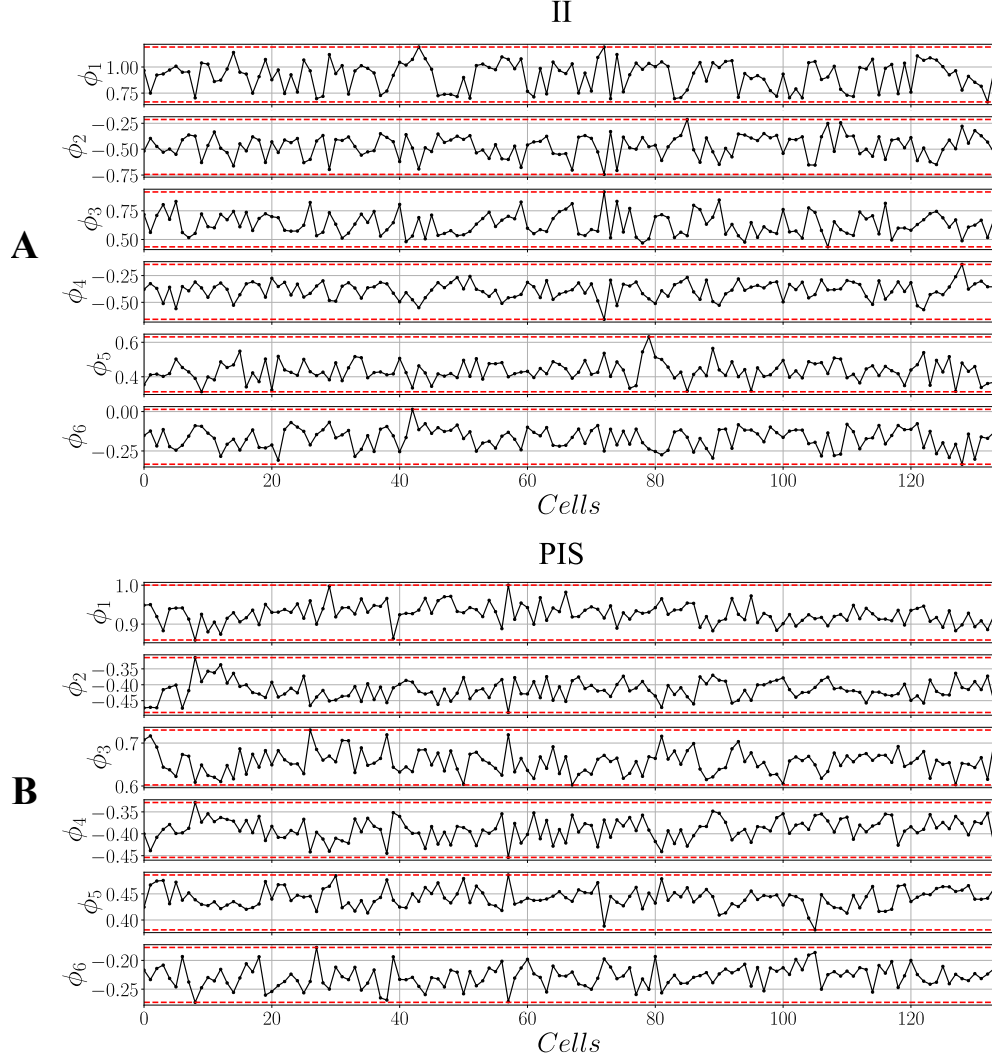
Figure 86 – Autocorrelation function ρ considering the lags of the residuals obtained after estimation of the both AR models (for II and PIS, respectively) for the first time window: $m = 1$. At the first lags, the correlation is slightly higher than the confidence levels at 95% significance, but they tend to decrease for the next lags, indicating that part of the dynamics of the signal was not well captured, which is also expected due to the simplicity of the model. The signal used in this case was from SUB, as in the main body of the manuscript.



Source: Own authorship.

Figure 87 presents the AR coefficients obtained for all of the discrete-time models $\mathbf{A}_m^{\{c\}}$, $m = 1, 2, \dots, M$ considering the II and PIS conditions (Figs. 87A and 87B), respectively. The coefficients vary over time but are enclosed within upper and lower limits.

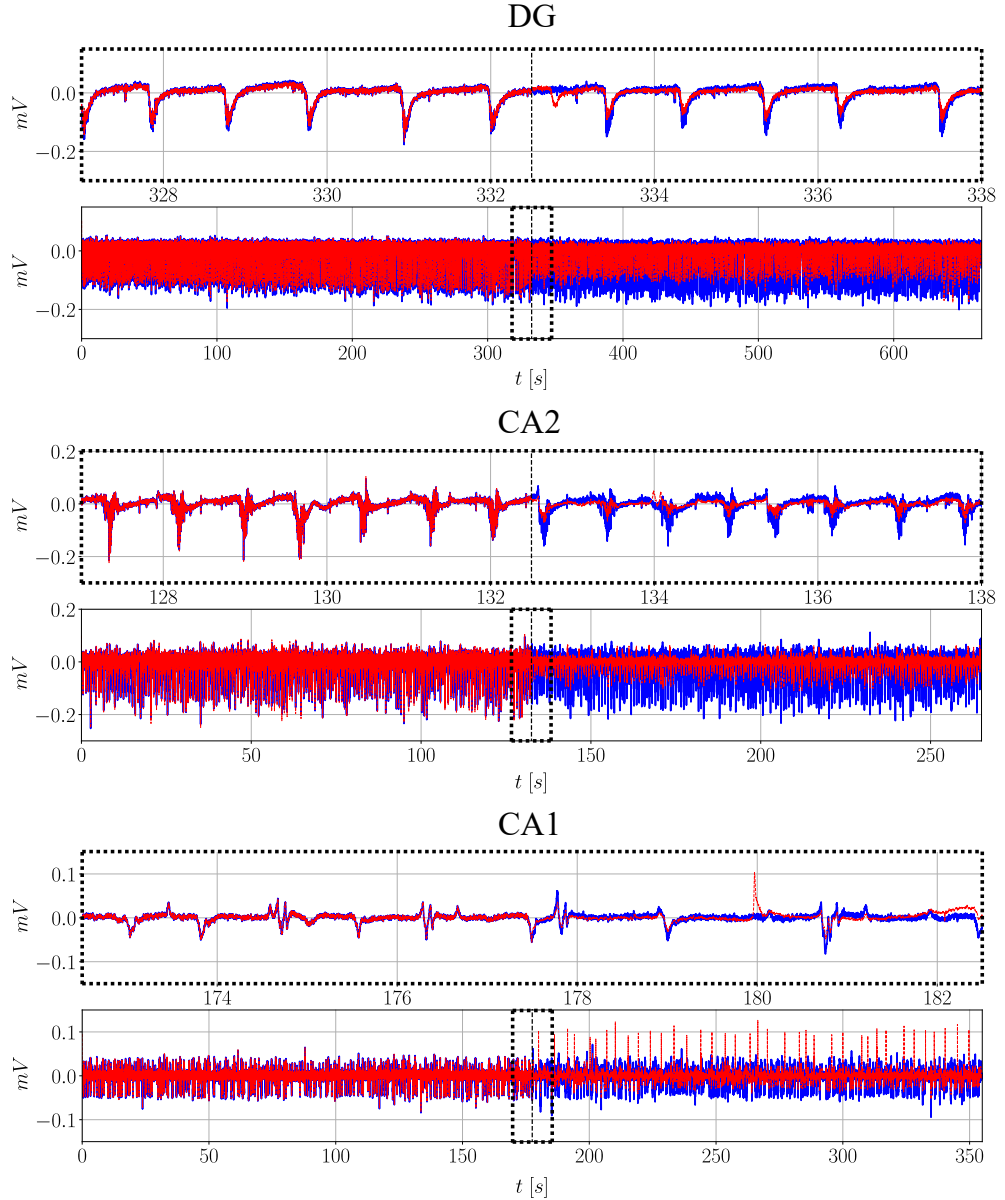
Figure 87 – **AR coefficients of the identified models for the II and PIS signals from SUB to design matrices $\mathbf{A}_m^{\{c\}}$, $m = 1, 2, \dots, M$ and the gains $\mathbf{L}_{\text{II}}$ and $\mathbf{G}_{\text{II}}$, or $\mathbf{L}_{\text{PIS}}$ and $\mathbf{G}_{\text{PIS}}$.** There is a fluctuation associated to the coefficients, but they remained bounded over time. The black solid line (—) indicates the AR coefficients; the red dashed line (—) indicates their upper and lower limits.



Source: Own authorship.

Figure 88 presents the results for the performance of the controller when applied to signals coming from different hippocampal subfields. In general, it is efficient in attenuating the PIS activities while driving the system back to the II condition. Even though attenuation occurs, poorer results are seen for CA1, where a high fluctuation around the baseline occurs, possibly due to stronger background/noise activity.

Figure 88 – **Performance of the controller when applied to signals coming from different hippocampal subfields: DG, CA2 and CA1.** The artificial reconstruction and attenuation of the signals from these subfields is fairly good as well, endorsing the efficiency of the proposed approach. The solid blue line (—) indicates the uncontrolled activity; the red dashed line (---) indicates the controlled activity. In this case $\mathbf{L}_{\text{PIS}}$ and $\mathbf{G}_{\text{PIS}}$ are used without any constraints on the input. The observers and controllers were designed according to the available dataset, so results for CA3 and CA4 could not be generated due to the lack of PIS activity available for them.

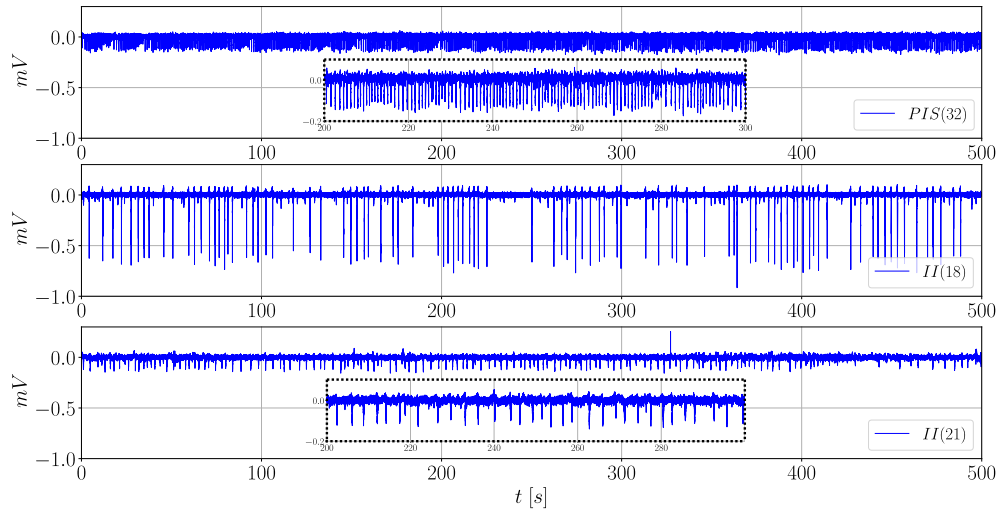


Source: Own authorship.

Figure 89 shows the signal (number 21 from SUB) used to design both gains $\mathbf{L}_{\text{II}}$ and $\mathbf{G}_{\text{II}}$ in the hybrid approach covered in the main text, whereas $\mathbf{x}_h$ (signal 18 from SUB) is the healthy reference signal to which drive the system. Note that the non-periodic

feature is present in both 18 and 21, thus characterizing the II events. However, signal 21 has lower amplitude and was chosen for the design to avoid significantly higher gains. This suggests that amplitude is just as important as the spiking pattern when designing controllers and observers.

Figure 89 – **Signals used to design both gains L_{II} and G_{II} in the hybrid approach and the healthy reference x_h .** The lower amplitude of signal 21 leads to a better performance, which means that this criterion should also be considered during the design of the controller. In this case, signal number 21 from SUB is used for the design, whereas signal number 18 is used as a reference to which drive the system.



Source: Own authorship.

APPENDIX D - MODEL REFERENCE ADAPTIVE CONTROLLER (MRAC)

According to the MRAC theory, there might be cases where the parameters of the reference model from which to design the controller do not match those from the real plant to be controlled (Goel; Kumar; Narayan, 2016). In this case, adaptive gains are proposed to compensate for this difference. In this paper, the main interest lies on attenuating a seizure without having its model/plant available, only an approximate model from the non-seizure condition, which is regarded as an analogous procedure. If both state-space models are fully available:

$$\dot{\mathbf{x}}^{\{h\}} = \mathbf{A}^{\{h\}}\mathbf{x}^{\{h\}} + \mathbf{B}^{\{h\}}\mathbf{r}_1, \quad \dot{\mathbf{x}}^{\{s\}} = \mathbf{A}^{\{s\}}\mathbf{x}^{\{s\}} + \mathbf{B}^{\{s\}}\mathbf{r}_2$$

then there exist exact gains $\mathbf{G}_1 \neq \mathbf{G}_2$ that attenuate a seizure, as follows (Goel; Kumar; Narayan, 2016):

$$\mathbf{r}_2 = -\mathbf{G}_1\mathbf{x}^{\{s\}} + \mathbf{G}_2\mathbf{r}_1$$

The attenuated seizure is, thus:

$$\dot{\mathbf{x}}^{\{s\}} = [\mathbf{A}^{\{s\}} - \mathbf{B}^{\{s\}}\mathbf{G}_1]\mathbf{x}^{\{s\}} + \mathbf{B}^{\{s\}}\mathbf{G}_2\mathbf{r}_1$$

For the adaptive control, it is tacitly assumed that, as an epileptogenic brain, the non-seizure condition can be triggered into the seizure condition and vice-versa (Hindmarsh; Rose; Huxley, 1984; Izhikevich, 2003; Jirsa et al., 2014; Araújo et al., 2022): $\mathbf{x}^{\{h\}} \rightarrow \mathbf{x}^{\{s\}}$ and $\mathbf{x}^{\{s\}} \rightarrow \mathbf{x}^{\{h\}}$, respectively. Although the two vectors of states are inherently different and take a mutually exclusive behavior in this thesis, they are part of a single epileptogenic brain. Thus, it is possible to state that the non-seizure condition can be written in terms of the seizure condition, and vice-versa. The responsibility for attenuating the seizure based on such reasoning falls solely on the adaptive gain. Therefore, considering that both activities come from the same system, by comparison:

$$[\mathbf{A}^{\{s\}} - \mathbf{B}^{\{s\}}\mathbf{G}_1] = \mathbf{A}^{\{h\}}$$

$$\mathbf{B}^{\{s\}}\mathbf{G}_2 = \mathbf{B}^{\{h\}}$$

However, perfect $\mathbf{G}_1$ and $\mathbf{G}_2$ are not available since the real plant has unknown parameters, only $\bar{\mathbf{G}}_1$ and $\bar{\mathbf{G}}_2$, which are approximations at best:

$$\mathbf{r}_2 = -\bar{\mathbf{G}}_1\mathbf{x}^{\{s\}} + \bar{\mathbf{G}}_2\mathbf{r}_1$$

To address this issue, by adding and subtracting the desired exact input $-\mathbf{G}_1\mathbf{x}^{\{s\}} - \mathbf{G}_2\mathbf{r}_1$ to the real plant, it follows that:

$$\dot{\mathbf{x}}^{\{s\}} = \mathbf{A}^{\{h\}}\mathbf{x}^{\{s\}} + \mathbf{B}^{\{h\}}\mathbf{r}_1 + \mathbf{B}^{\{s\}}[\mathbf{G}_1\mathbf{x}^{\{s\}} - \mathbf{G}_2\mathbf{r}_1 + \mathbf{r}_2]$$

By replacing the approximate $\mathbf{r}_2$:

$$\dot{\mathbf{x}}^{\{s\}} = \mathbf{A}^{\{h\}}\mathbf{x}^{\{s\}} + \mathbf{B}^{\{h\}}\mathbf{r}_1 + \mathbf{B}^{\{s\}}[-\mathbf{G}_1^{\{ad\}}\mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}}\mathbf{r}_1]$$

where the adaptive gains are defined as $\mathbf{G}_1^{\{ad\}} = \bar{\mathbf{G}}_1 - \mathbf{G}_1$ and $\mathbf{G}_2^{\{ad\}} = \bar{\mathbf{G}}_2 - \mathbf{G}_2$. Subtracting the non-seizure model, the error dynamics can be defined as:

$$\dot{\boldsymbol{\epsilon}} = \mathbf{A}^{\{h\}}\boldsymbol{\epsilon} + \mathbf{B}^{\{s\}}[-\mathbf{G}_1^{\{ad\}}\mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}}\mathbf{r}_1]$$

Given that $\mathbf{B}^{\{s\}}\mathbf{G}_2 = \mathbf{B}^{\{h\}}$:

$$\dot{\boldsymbol{\epsilon}} = \mathbf{A}^{\{h\}}\boldsymbol{\epsilon} + \mathbf{B}^{\{h\}}\mathbf{G}_2^{-1}[-\mathbf{G}_1^{\{ad\}}\mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}}\mathbf{r}_1]$$

consider the following Lyapunov function:

$$V(\boldsymbol{\epsilon}, \mathbf{G}_1, \mathbf{G}_2) = \boldsymbol{\epsilon}^T \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} + \text{tr}[\mathbf{G}_1^{\{ad\}T} \boldsymbol{\Gamma} \mathbf{G}_1^{\{ad\}} + \mathbf{G}_2^{\{ad\}T} \boldsymbol{\Gamma} \mathbf{G}_2^{\{ad\}}]$$

where $\boldsymbol{\Gamma}^{-1} = \mathbf{G}_2 \text{sgn}(g_2)$ and there exists a symmetric positive-definite $\mathbf{P}^{\{ad\}} > 0$ which satisfies the inequality:

$$\mathbf{A}^{\{h\}T} \mathbf{P}^{\{ad\}} + \mathbf{P}^{\{ad\}} \mathbf{A}^{\{h\}} = -\mathbf{Q}^{\{ad\}}$$

where there exists another symmetric positive-definite $\mathbf{Q}^{\{ad\}} > 0$. Therefore:

$$\begin{aligned} \dot{V}(\boldsymbol{\epsilon}, \mathbf{G}_1, \mathbf{G}_2) = & -\boldsymbol{\epsilon}^T \mathbf{Q}^{\{ad\}} \boldsymbol{\epsilon} + 2\boldsymbol{\epsilon}^T \mathbf{P}^{\{ad\}} \mathbf{B}^{\{h\}} \mathbf{G}_2^{-1} [-\mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}} \mathbf{r}_1] + \\ & + 2\text{tr}[\mathbf{G}_1^{\{ad\}T} \boldsymbol{\Gamma} \dot{\mathbf{G}}_1^{\{ad\}} + \mathbf{G}_2^{\{ad\}T} \boldsymbol{\Gamma} \dot{\mathbf{G}}_2^{\{ad\}}] \end{aligned}$$

Then:

$$\begin{aligned} \boldsymbol{\epsilon}^T \mathbf{P}^{\{ad\}} \mathbf{B}^{\{h\}} \mathbf{G}_2^{-1} \mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} &= \text{tr}[\mathbf{G}_1^{\{ad\}T} \boldsymbol{\Gamma} \mathbf{B}^{\{h\}T} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}^{\{s\}T}] \text{sgn}(g_2) \\ \boldsymbol{\epsilon}^T \mathbf{P}^{\{ad\}} \mathbf{B}^{\{h\}} \mathbf{G}_2^{-1} \mathbf{G}_2^{\{ad\}} \mathbf{r}_1 &= \text{tr}[\mathbf{G}_2^{\{ad\}T} \boldsymbol{\Gamma} \mathbf{B}^{\{h\}T} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{r}_1^T] \text{sgn}(g_2) \end{aligned}$$

At last, the adaptive gains are defined as:

$$\begin{aligned} \dot{\mathbf{G}}_1^{\{ad\}} &= \dot{\bar{\mathbf{G}}}_1 = \mathbf{B}^{\{h\}} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}^{\{s\}T} \text{sgn}(g_2) \\ \dot{\mathbf{G}}_2^{\{ad\}} &= \dot{\bar{\mathbf{G}}}_2 = -\mathbf{B}^{\{h\}} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{r}_1^T \text{sgn}(g_2) \end{aligned}$$

A necessary assumption of this approach is that, if $\text{sgn}(g_2) = 1$, then $\mathbf{G}_2 > 0$ (positive-definite); if $\text{sgn}(g_2) = -1$, then $\mathbf{G}_2 < 0$ (negative-definite). To compute the gains in this thesis, both $\text{sgn}(g_2) = 1$ and $\text{sgn}(g_2) = -1$ were tested and the one which provided stability was chosen.

Remarks on the adaptive controller

State-space representation and input stimulus. Since an actual plant of the seizure is not available, the input stimulus is added as follows in the seizure model after closing the loop of its respective candidate model:

$$\dot{\mathbf{x}}_m^{\{cs\}} = \underbrace{\mathbf{A}_m^{\{cs\}} \mathbf{x}_m^{\{cs\}} + \mathbf{B} \mathbf{u}_m^{\{cs\}}}_{\equiv \mathbf{A}_m^{\{s\}} \mathbf{x}_m^{\{s\}}} + \mathbf{B} \mathbf{r}_2$$

where $\mathbf{r}_2 = \mathbf{u}_m^{\{sh\}}$ in the notation used in the main text.

Reference model to design the controller. To design a stable $\mathbf{P}^{\{ad\}}$ as:

$$\mathbf{A}^{\{h\}T} \mathbf{P}^{\{ad\}} + \mathbf{P}^{\{ad\}} \mathbf{A}^{\{h\}} = -\mathbf{Q}^{\{ad\}}$$

the model $\mathbf{A}^{\{h\}}$ is used in open loop and the only possible $\mathbf{r}_1$ available comes from the candidate non-seizure model:

$$\mathbf{r}_1 = \mathbf{u}_m^{\{ch\}} = -\mathbf{G}_m^{\{h\}} \mathbf{x}_m^{\{ch\}} + \mathbf{G}_m^{\{h\}} \mathbf{x}^{\{h\}}$$

This implies that:

$$\mathbf{u}^{\{sh\}} = -\mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}} \{-\mathbf{G}_m^{\{h\}} [\mathbf{x}_m^{\{ch\}} + \mathbf{x}^{\{h\}}]\}$$

However, given that the activity to be attenuated is related to the following seizure model and input:

$$\mathbf{u}^{\{sh\}} = -\mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} + \mathbf{G}_2^{\{ad\}} \mathbf{x}^{\{h\}}$$

it follows that $\{-\mathbf{G}_m^{\{h\}} [\mathbf{x}_m^{\{ch\}} + \mathbf{x}^{\{h\}}]\} \neq \mathbf{x}^{\{h\}}$, and it is necessary to adapt the approach. By closing the loop of the candidate non-seizure model:

$$\dot{\mathbf{x}}_m^{\{h\}} = [\mathbf{A}_m^{\{h\}} - \mathbf{B}_m^{\{h\}} \mathbf{G}_m^{\{h\}}] \mathbf{x}_m^{\{h\}} + \mathbf{B}_m^{\{h\}} \mathbf{G}_m^{\{h\}} \mathbf{x}^{\{h\}}$$

then it is possible to consider a new:

$$\mathbf{r}_1 = \mathbf{G}_m^{\{h\}} \mathbf{x}^{\{h\}}$$

Replacing $\mathbf{r}_1$ again into $\mathbf{u}^{\{sh\}}$:

$$\mathbf{u}^{\{sh\}} = -\mathbf{G}_1^{\{ad\}} \mathbf{x}^{\{s\}} + \mathbf{L}^{\{ad\}} \mathbf{x}^{\{h\}}$$

where $\mathbf{L}^{\{ad\}} = \mathbf{G}_2^{\{ad\}} \mathbf{G}_m^{\{h\}}$. This leads to a direct relation between the desired condition $\mathbf{x}^{\{h\}}$ and the adaptive input stimulus. Besides, the controller is designed as (Tanaka; Wang, 2004):

$$\bar{\mathbf{P}}^{\{ad\}} \mathbf{A}_m^{\{h\}T} + \mathbf{A}_m^{\{h\}} \bar{\mathbf{P}}^{\{ad\}} - \bar{\mathbf{G}}_x^T \mathbf{B}^T - \mathbf{B} \bar{\mathbf{G}}_x < 0$$

where $\mathbf{B} = \mathbf{B}_m^{\{*\}} = [\mathbf{Z} \ \mathbf{I}]^T$, $\bar{\mathbf{P}}^{\{ad\}} = \mathbf{P}^{\{ad\}-1}$ and $\mathbf{G}_x = \bar{\mathbf{G}}_x \mathbf{P}^{\{ad\}}$. Note that only $\mathbf{P}^{\{ad\}}$ participates in the adaptive strategy, not $\mathbf{G}_x$, which is an auxiliary gain. This approach is consistent with the fact that the reference model for the controller is a closed-loop model. The last adaptation to be made concerns $\mathbf{L}^{\{ad\}}$: its dimension is commonly adopted to be (1×1) (Goel; Kumar; Narayan, 2016); however, the product $\mathbf{L}^{\{ad\}} = \mathbf{G}_2^{\{ad\}} \mathbf{G}_m^{\{h\}}$ requires dimensions of the type $(1 \times 2) = (1 \times 1)(1 \times 2)$ such that, when multiplied by $\mathbf{x}^{\{h\}}$, of dimension (2×1) , the same (1×1) is obtained for $\mathbf{u}^{\{sh\}}$ (considering a single degree of freedom). Therefore:

$$\begin{aligned} \dot{\mathbf{G}}_1^{\{ad\}} &= \mathbf{B} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}^{\{s\}T} \text{sgn}(g_2) \\ \dot{\mathbf{G}}_2^{\{ad\}} &= -\mathbf{B} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}^{\{h\}T} \text{sgn}(g_2) \end{aligned}$$

In practice, since $\mathbf{x}^{\{s\}}$ is the recorded signal which represents the activity to be attenuated and $\mathbf{x}_m^{\{h\}} \rightarrow \mathbf{x}^{\{h\}}$:

$$\begin{aligned} \dot{\mathbf{G}}_1^{\{ad\}} &= \mathbf{B} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}^{\{s\}T} \text{sgn}(g_2) \\ \dot{\mathbf{G}}_2^{\{ad\}} &= -\mathbf{B} \mathbf{P}^{\{ad\}} \boldsymbol{\epsilon} \mathbf{x}_m^{\{h\}T} \text{sgn}(g_2) \end{aligned}$$

Complementary results for seizure attenuation

To provide a more detailed assessment of the control approach, Figs. 90 and 91 present complementary results considering the adaptive or fixed-gain controllers, respectively, for all of the remaining patients (also using electrode Fp2). All of the signals correspond to EEGs, except for III, which is an intracranial EEG (iEEG). The strategy was selected so as to obtain a reasonably remarkable visual effect for illustration purposes. A decay rate of $\alpha^{\{s\}} = 50$ was adopted for all cases to have a better comparison with the main results. This is why seizure IV, for instance, is not as accurately described as the other ones. Increasing this value leads to a better reconstruction, but also stronger input values, as mentioned in the main text.

As for $\alpha^{\{ad\}}$, it was varied according to each case, such that the seizures could be efficiently attenuated at a moderate level of input stimulus and providing a reasonable visual effect. Note that, for all cases, reductions in the intensity of the peaks can be observed, providing reductions 12 to 45% using 20 to 25 V, approximately. Increasing the level of input implies in more effective attenuation. Although these voltage levels are slightly higher, lower ones can be adopted but at the cost of a less strong attenuation.

Figure 90 – **Complementary results for all the remaining patients, considering adaptive or fixed-gain MRCs.** For all cases, $\alpha^{\{s\}} = 50$ to have a better comparison with the main results, but $\alpha^{\{ad\}} = 40, 50, 20, 50, 50$ (from I through V, respectively), to adapt the intensity of gain of the controller. Reductions in the intensity of the peaks can be observed after applying both controllers at moderate input levels. Red dashed lines (- -) represent the reconstructed seizure; violet dashed lines (- -) represent the attenuated seizure.

