

Quantificação do Volume de Densidade Mamária a partir de Técnicas de Processamento de Imagens em Mamografias Digitais

ANA LUIZA MENEGATTI PAVAN

Tese apresentada ao Instituto de Biociências,
Universidade Estadual Paulista "Júlio de
Mesquita Filho", Campus de Botucatu para
obtenção do título de Doutor em
Farmacologia e Biotecnologia.

Orientadora: Prof.^a Associada Diana
Rodrigues de Pina

Coorientador: Prof. Dr. Antoine Vacavant

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“There is no chance, no destiny,
no fate, that can hinder or control
the firm resolve of a determined soul”

(Ella Wheller Wilcox)

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Resumo

Esta pesquisa teve como objetivo o desenvolvimento um novo algoritmo objetivo, confiável, reprodutível e de baixo custo para estimar com precisão o percentual do volume de DM (PDM) em mamografias digitais processadas, produzidas por sistema de radiologia computadorizada (CR). Para atingir esse objetivo três etapas foram adotadas: (i) Foi desenvolvido um algoritmo a ser utilizado como pré-processamento da imagem para realçar os tecidos presentes na região periférica da imagem mamográfica. Os resultados obtidos foram comparados com outras metodologias descritas na literatura, utilizando o valor médio dos pixels, *skweness*, *kurtosis* e por análise gradativa visual. Dentre os métodos avaliados a metodologia desenvolvida foi a que obteve os melhores resultados; (ii) Foi desenvolvido um algoritmo para segmentar a área do tecido fibroglandular da imagem mamográfica. A segmentação foi realizada através da otimização da técnica de *Fuzzy C-Means with Variable Compactness* (FCMVC). As imagens obtidas foram classificadas conforme a área de tecido fibroglandular e comparados com a avaliação do BI-RADS. O resultado dessa comparação apresenta 67,8% de classificação correta, com coeficiente de correlação de *Spearman* de $\rho = 0,618$, para $p < 0,001$. A estatística de Bland-Altman não mostrou diferenças significativas (viés de $-0,20 \pm 1,52$) entre os dois métodos. O coeficiente kappa de *Cohen* foi de 0,47, sugerindo uma concordância moderada; (iii) Finalmente foi utilizada a segmentação e quantificação resultante da aplicação do FCMVC. Nesse procedimento, utilizou-se a relação sinal-ruído diferencial para quantificar o volume de tecido fibroglandular. A partir desta medida, foi estimada a PDM em exames de mamografia. Os resultados obtidos foram comparados com dados obtidos por metodologia de quantificação utilizando exames de ressonância magnética (RM). A regressão linear dos

valores PDM por mamografia e RM foi de $R^2=0,821$. A diferença percentual média entre ambas modalidades foi de $3,39\pm 2,69\%$ e o coeficiente de *Pearson* foi de 0,91, indicando forte associação entre os métodos. A estatística de Bland-Altman não mostrou diferenças significativas entre os métodos. O novo algoritmo desenvolvido nesta pesquisa é objetivo, preciso e de baixo custo. Esse algoritmo pode auxiliar diretamente na prática clínica, na recomendação de rastreamento personalizado, em escolhas de estratégias preventivas para o tratamento de câncer de mama, de modo a avaliar a eficácia de drogas terapêuticas.

Abstract

The aim of this research was to develop of a new, reliable, reproducible and low cost algorithm to accurately estimate the percentage of breast density (PBD) in processed digital mammograms, produced by computerized radiology (CR) system. To achieve this goal, three steps were taken: (i) An image preprocessing algorithm was developed to enhance tissues present in the peripheral region of the mammographic image. The obtained results were compared with other methodologies described in the literature, using the mean value of the pixels, skewness, kurtosis and by visual gradient analysis. The methodology developed was the one that obtained the best results; (ii) An algorithm was developed to segment the area of the fibroglandular tissue in mammographic image. This segmentation was performed through the optimization of the Fuzzy C-Means with Variable Compactness (FCMVC) technique. The images obtained were classified according to the area of fibroglandular tissue and compared with the BI-RADS evaluation. The results of this comparison presented 67.8% of correct classification, with Spearman's correlation coefficient of $\rho = 0.618$, for $p < 0.001$. The Bland-Altman statistic did not show significant differences (bias of -0.20 ± 1.52) between the two methods. Cohen's kappa coefficient comparing the performance of the algorithm with the visual evaluation for the different BI-RADS scores was 0.47, suggesting a moderate but encouraging agreement; (iii) Finally, the segmentation and quantification resulting from the FCMVC application was used. In this procedure, the differential signal-to-noise ratio was used to quantify the volume of fibroglandular tissue. From this measure, PBD was estimated in mammography exams. The results obtained were compared with data obtained by quantification using magnetic resonance imaging (MRI). The linear regression of PDB values by mammography and MRI was of

$R^2 = 0.821$. The mean percentage difference between both modalities was $3.39 \pm 2.69\%$ and the Pearson coefficient was 0.91, showing the strong association between the methods. In addition, the Bland-Altman statistic did not show significant differences between mammography and MRI methods. The new algorithm developed in this research is objective, accurate and has low cost. This algorithm can directly aid in clinical practice, in the recommendation of personalized screening, in the choice of preventive strategies for the treatment of breast cancer, in order to evaluate the efficacy of therapeutic drugs.

Résumé

Cette recherche visait à développer un nouvel algorithme objectif, fiable, reproductible et peu coûteux, permettant d'estimer avec précision le pourcentage de volume du sein (PVS) dans les mammographies numériques analysées, issues d'un système de *computed radiography* (CR). Pour atteindre cet objectif, trois étapes ont été franchies :

(i) Un algorithme de prétraitement d'images a été développé pour améliorer les tissus présents dans la région périphérique de l'image mammographique. Les résultats obtenus ont été comparés à d'autres méthodologies décrites dans la littérature, en utilisant la valeur moyenne des pixels, le *kurtosis*, le *skewness* et la visibilité par analyse de gradient visuelle. La méthodologie développée est celle qui a obtenu les meilleurs résultats ;

(ii) Un algorithme a été développé pour segmenter la zone du tissu fibroglandulaire de l'image mammographique. Cette segmentation a été réalisée grâce à l'optimisation de la technique Fuzzy C-Means avec Compacité Variable (FCMVC). Les images obtenues ont été classées en fonction de la surface du tissu fibroglandulaire et comparées à l'évaluation BI-RADS. Les résultats de cette comparaison ont présenté 67,8% de la classification correcte, avec le coefficient de corrélation de *Spearman* de $\rho = 0,618$, pour $p < 0,001$. La statistique de Bland-Altman ne montre pas de différences significatives (biais de $-0,20 \pm 1,52$) entre les deux méthodes. Le coefficient kappa de *Cohen* comparant la performance de l'algorithme à l'évaluation visuelle des différents scores BI-RADS était de 0,47, ce qui suggère un accord modéré mais encourageant ;

(iii) Enfin, la segmentation et la quantification résultant de l'application FCMVC ont été utilisées. Dans cette procédure, le *Signal difference to Noise Ratio* a été utilisé pour quantifier le volume de tissu fibroglandulaire. À partir de cette mesure, le PVS a été estimé lors d'examens mammographiques. Les résultats obtenus ont été comparés aux

données obtenues par quantification par imagerie par résonance magnétique (IRM). La régression linéaire des valeurs du PVS par mammographie et IRM était de $R^2 = 0,821$. La différence moyenne en pourcentage entre les deux modalités était de $3,39 \pm 2,69\%$ et le coefficient de *Pearson* de 0,91, montrant la forte association entre les méthodes. De plus, la statistique de Bland-Altman ne montrait pas de différences significatives entre les méthodes de mammographie et d'IRM. Le nouvel algorithme développé dans cette recherche est objectif, précis et peu coûteux. Cet algorithme peut aider directement en pratique clinique, dans la recommandation d'un dépistage personnalisé, dans le choix de stratégies préventives pour le traitement du cancer du sein, afin d'évaluer l'efficacité des médicaments thérapeutiques.

Esta pesquisa foi desenvolvida no Laboratório de Física Aplicada ao Radiodiagnóstico (LAFAR), devidamente aprovada pelo Comitê de Ética em Pesquisa (CEP) sob protocolo: CAAE 50547315.8.0000.5411.

Os exames retrospectivos de mamografia e ressonância magnética utilizados neste estudo foram de pacientes do Hospital das Clínicas de Botucatu (HCB).

Lista de Figuras e Tabelas

Capítulo 1: Introdução

Figura 1. Esquema representando alguns dos métodos utilizados para avaliação da densidade mamária.	26
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Capítulo 3: Fundamentos Teóricos

Figura 2. Esquema ilustrativo da mama compreendendo a seção sagital da mama (Bontrager and Lampignano, 2014).	40
Figura 3. Exame de mamografia na incidência médio lateral oblíqua e crânio caudal ilustrando o aspecto dos tecidos presentes na mama (Sickles et al., 2013).	41
Figura 4. a) Relação entre a energia do feixe de raios X e o coeficiente de atenuação linear para os carcinoma dictal infiltrativo, tecido fibroglandular e tecido adiposo; b) Relação entre a energia do feixe de raios X e o contraste da imagem para um tumor de 5mm e uma calcificação de 0,2mm (Dance et al., 2014).	43
Figura 5. Ilustração do equipamento de mamografia e seus principais componentes (Dance et al., 2014).	44
Figura 6. Ilustração demonstrando a geometria do feixe de raios X. Em (a) a geometria permite que toda a mama seja imageada. Por outro lado, a geometria em (b) faz com que parte do tecido próximo à parede torácica não seja imageado (Dance et al., 2014).	45
Figura 7. Espectros de raios X provenientes de equipamentos de mamografia. a) comparação dos espectros para a combinação Mo/Mo e alterando a tensão aplicada ao tubo; b) Comparação dos espectros resultantes da combinação Mo/Mo (rosa) e Mo/Rh (verde); c) Comparação dos espectros quanto utilizadas as combinações Mo/Rh (verde)	

e Rh/Rh (laranja); d) Comparação dos espectros utilizando-se alvo/filtro de W/Rh (azul claro), W/Ag (azul escuro) e W/Al (preto).....	47
Figura 8.a) Mama sendo comprimida durante aquisição do exame mamográfico. Nota-se que a região periférica possui espessura variável; b) No exame de mamografia pode-se visualizar a diferença de intensidade da região periférica devido à superexposição.....	50
Figura 9. Demonstração da faixa de exposição (latitude do filme) ao qual o sistema tela-filme produz densidade ótica útil. A faixa útil para o sistema CR também é demonstrada(Bushberg, 2002).....	53
Figura 10. Processo de aquisição e formação a imagem usando sistema de radiologia computadorizada (Rowlands, 2002).....	55
Figura 11. Mamografias não processadas (a-d) e após o processamento em diferentes equipamentos (e-h) (Burton et al., 2016).....	57
Figura 12. Classificação da 5ª edição do BI-RADS com relação a glandularidade da mama. a) A mama é predominantemente adiposa, sendo possível visualizar pouco tecido fibroglandular; b) Existem áreas dispersas de densidade fibroglandular; c) a mama é heterogeneamente densa, o que pode obscurecer pequenas massas; d) a mama é extremamente densa, o que diminui a sensibilidade da mamografia (Sickles et al., 2013).	58
Figura 13. (A) Imagem contínua projetada em uma matriz de sensores. (B) Resultado da amostragem e quantização da imagem.	60
Figura 14. Exemplo de um processo de segmentação. a) Imagem original; b) Máscara representando tecidos adiposo e glandular; c) Imagem original após segmentação dos tecidos glandular (representando em amarelo e branco) e adiposo (representado em vermelho).....	62

Figura 15. Exemplo do processo de limiarização. (A) Imagem original. (B) Histograma da imagem original, ilustrando o valor de limiar de -500 unidades Hounsfield (HU). (C) Imagem limiarizada, representando as regiões de ar em preto, com valor de pixel igual a zero, e as regiões de tecido biológico em branco, com valor de pixel igual a um.	63
Figura 16. Exemplo da operação de abertura. (A) Imagem original. (B) Imagem após processo de erosão. (C) Imagem após processo de erosão seguido de dilatação, concluindo o processo de abertura.	65
Figura 17. Exemplo da operação de fechamento. (A) Imagem original. (B) Imagem após processo de dilatação. (C) Imagem após processo de dilatação seguido de erosão, concluindo o processo de fechamento.	65

Capítulo 4: Enhancement of breast periphery region in digital mammography

Figure 1. a) Rough estimation of compressed (white) and uncompressed (gray) breast area; b) Adipose tissue after segmentation of fibroglandular tissue by Otsu thresholding..	76
Figure 2. a) Distance map of adipose tissue; b) Intensity curve (black) and its fit (red) for the mean pixel values of adipose tissue..	76
Figure 3. a) Fit's derivate and the point (p) which the derivate is approximately zero; b) Accurately compressed (gray) and uncompressed (white) segmentation regions.....	77
Figure 4. a-c) Original images; Breast periphery correction by d-f) the proposed, g-i) Wang, et al. and j-l) He, et al. methods... ..	78
Figure 5 a-c) Example of images used to acquire histograms; d-f) Comparison of histograms between original image (black), proposed (red), Wang et al. (blue) and He et al. (green) methods.... ..	79

Table 1. Results of mean pixel value, skewness and kurtosis for the proposed, Wang and He methods.....	80
--	----

Capítulo 5: Fibroglandular Tissue Quantification in Mammography by Optimized Fuzzy C-Means with Variable Compactness

Figure 1. a) Filtered image; b) Equalized image; and c) Rough fibroglandular mask...	88
Figure 2. Bland–Altman plot for breast density assessment. The difference refers to the BI-RADS minus the algorithm assessment. The difference between BI-RADS and algorithm scores was compared with the average score between the radiologist and computational results. Dashed lines represents the interval of 2 standard deviations. The middle line represents bias of -0.20 ± 1.52	89
Figure 3. Mammogram assessed as category 3 by BI-RADS. a) Filtered mammography; b) Cluster1: adipose tissue; c) Cluster2: almost completely fibroglandular tissue; and d) Cluster3: fibroglandular tissue....	89
Table 1. Confusion matrix to compare breast groups using results from skewness versus BI-RADS density score....	89
Table 2. Confusion matrix for breast density using our algorithm versus BI-RADS density score.....	89

Capítulo 6: Estimate of breast density in mammography computed radiography systems

Figure 1. Flowchart showing the main image processing steps performed in the computational approach (FCVMC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio).....	100
--	-----

Figure 2. Reconstruction of 3D fibroglandular tissue distribution within the breast based on mammography. (a) Evaluated mammography. (b) 3D reconstruction..... 102

Figure 3. Schematic overview of the validation process. A total of 48 mammogram and magnetic resonance imaging (MRI) exams were used to estimate the percentage of breast density (PBD). The comparison between both methods was made using Pearson’s correlation, mean percentage difference, linear regression and Bland-Altman statistic. (MRI: Magnetic Resonance Imaging, CC: craniocaudal, FCVMC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio)..... 104

Figure 4. Percentage of breast density (PBD) versus Signal difference-to-noise ratio (SDNR) behavior for the mammography phantom using different radiographic techniques in routine and different thickness of compressed breasts. The dashed lines display the limits of 2 standard deviations of the data around the adjusted line shown by the solid line. The solid line represents the relation obtained (Equation 2).... 105

Figure 5. Percentage of breast density (PBD) quantification agreement of the proposed method (mammography), compared with the standard (Magnetic Resonance Imaging - MRI) for 48 patients. (a) Linear regression line was determined by $y=1.531x-4.189$, with $R^2=0.821$, demonstrating low dispersion between data. (b) Bland–Altman plot for both quantification methods. The difference refers to the reference standard minus the developed method. The central line corresponds to the mean value of deviations. The dashed lines indicate the interval of 2 standard deviations, indicating an adequate level of statistical agreement..... 106

Lista de Abreviaturas

AGV: Avaliação Gradativa Visual

BG: *Background*

BI-RADS: *Breast Imaging Reporting and Data System*

CR: Radiologia Computadorizada

DM: Densidade Mamária

FCM: *Fuzzy C-Means*

FCMVC: *Fuzzy C-Means with Variable Compactness*

FFDM: *Full-Field Digital Mammography*

IP: *Imaging Plate*

PDM: Porcentagem de Densidade Mamária

PMT: *Photomultiplies Tube*

PSP: *Photostimulable Phosphor*

RM: Ressonância Magnética

SNDR: *Signal difference to noise ratio*

STF: Sistema Tela-Filme

VDM: Volume de Densidade Mamária

Sumário

Capítulo 1	22
1. Introdução.....	23
Capítulo 2	35
2. Objetivos.....	36
Capítulo 3	38
3. Fundamentos Teóricos.....	39
3.1. Anatomia da mama.....	39
3.2. Formação da imagem em mamografia digital.....	41
3.3. BI-RADS	57
3.4. Processamento de Imagens digitais.....	59
3.5. Avaliação Gradativa Visual	68
3.6. Visão geral do estudo	69
Capítulo 4	71
4. <i>Enhancement of breast periphery region in digital mammography</i>	72
Capítulo 5	84
5. <i>Fibroglandular Tissue Quantification in Mammography by Optimized Fuzzy C-Means with Variable Compactness</i>	85
Capítulo 6	92
6. <i>Estimate of breast density in mammography computed radiography systems</i>	93

Capítulo 7	117
7. Conclusões.....	118
Capítulo 8	119
8. Perspectivas Futuras	120
Apêndice I.....	122
Referências Bibliográficas.....	134

Capítulo 1

1. Introdução

O câncer de mama é o câncer mais frequente entre as mulheres, impactando 2,1 milhões de pacientes a cada ano. O câncer de mama feminino causa o maior número de mortes relacionadas a doença. Em 2018, estima-se que 627.000 mulheres morreram de câncer de mama, isto é, aproximadamente 15% de todas as mortes por câncer entre as mulheres (WHO, 2018).

Em 2017, dados americanos estimaram cerca de 315 mil novos casos de câncer de mama, dos quais 40 mil mulheres morreram em decorrência da doença (ACS, 2017). Na Europa, o ano de 2018 estimou-se que cerca de 400 mil mulheres desenvolveram câncer de mama e 98 mil casos evoluíram para óbito (Carioli et al., 2017).

A estatística mundial apresenta um aumento na incidência do câncer de mama na maioria dos países. Entretanto, países altamente desenvolvidos mostram um declínio das taxas de mortalidade pelo câncer de mama. Este fato é reflexo da combinação de melhoria na detecção precoce, por meio de rastreamento populacional, e intervenções terapêuticas mais eficazes (INCA, 2018).

Para o Brasil, a estimativa para o biênio 2018-2019 é que ocorram 600 mil novos casos de câncer para cada ano. A estimativa mostra que o câncer de mama em mulheres e de próstata em homens serão os mais frequentes, atingindo 60 mil mulheres e 68 mil homens, respectivamente (INCA, 2018).

Vale ressaltar que, em países de baixa e média renda como o Brasil, o diagnóstico ocorre em estágios avançados do câncer de mama. Desta forma, há aumento da morbidade relacionada ao tratamento reduzindo a qualidade de vida e a sobrevida dos pacientes (INCA, 2018).

Sendo assim, o Brasil apresenta como uma das prioridades da política Nacional de Saúde o controle do câncer de mama. O Ministério da Saúde publicou o documento “Diretrizes para a Detecção Precoce do Câncer de Mama no Brasil” o qual recomenda a realização do rastreamento e diagnóstico precoce desta doença. Para mulheres na faixa etária de 50 a 69 anos as mamografias bienal nas projeções crânio-caudal e médio-lateral oblíqua são recomendadas como estratégia de rastreio (INCA, 2018).

A literatura apresenta muitos fatores associados à um aumento no risco de desenvolver câncer de mama, tais como idade, fatores endócrinos, histórico reprodutivo, fatores genéticos, densidade mamária, *etc* (Wang et al., 2013, Schousboe et al., 2011, Keller et al., 2012). A densidade mamária (DM) está relacionada com a quantidade de tecido fibroglandular da mama, o qual é radiopaco em um exame de mamografia (Wang et al., 2013, Schousboe et al., 2011, Keller et al., 2012). Áreas densas representam tecido fibroglandular, como estroma e epitélio, enquanto áreas não densas representam tecido predominantemente adiposo (Wang et al., 2013, Schousboe et al., 2011, Keller et al., 2012).

Em 1976, John N. Wolfe observou que altos níveis de DM estavam associados a um risco aumentado de câncer de mama e, desde então, a relação entre densidade e risco de câncer de mama tem sido extensivamente pesquisada (Wolfe, 1976, McCormack and dos Santos Silva, 2006, Lu et al., 2012, Freer, 2015, Kerlikowske et al., 2018).

Sabe-se que uma quantidade aumentada de DM dificulta a detecção de tumores em pacientes pré-sintomáticos (Mandelson et al., 2000). A literatura apresenta a relação entre o risco de câncer de mama em pacientes com elevada DM devido à diminuição na sensibilidade do exame mamográfico. Estes trabalhos concluem que o rastreamento em pacientes com grande DM indica um risco maior de não serem visualizados tumores e,

portanto, uma incidência artificialmente mais alta de câncer de mama (Byng et al., 1998, van Gils et al., 1998, Kolb et al., 2002, Checka et al., 2012). Entretanto, estudos recentes indicam que o aumento do risco de desenvolver câncer de mama não está associado apenas à diminuição da sensibilidade (McCormack and dos Santos Silva, 2006, Kerlikowske et al., 2018). A DM prediz o risco de câncer de mama até 10 anos antes do diagnóstico (Byrne et al., 1995, Boyd et al., 1995, Kerlikowske et al., 2018).

A DM é o fator de risco mais importante para o desenvolvimento de câncer de mama e pode ser reduzida pela terapia hormonal e dieta (Cuzick, 2008, Boyd et al., 1997). A literatura mostra que em mulheres com alto risco de câncer de mama tratadas com tamoxifeno há uma redução da densidade após a administração da droga. A diminuição da DM causa uma redução subsequente no risco de câncer. Desta forma, sugere-se que a quantificação da DM pode ser usada para selecionar indivíduos com elevado risco e que podem iniciar intervenções preventivas. Além disso, a quantificação da DM também pode ser utilizada para monitorar a eficácia de tais intervenções (Boyd et al., 2006). Portanto, espera-se que a redução de níveis particularmente altos de densidade, possa evitar uma proporção substancial de cânceres de mama (Assi et al., 2011).

A maioria dos fatores de risco para câncer de mama representa uma porcentagem muito pequena de casos. Tais fatores são idade, índice de massa corpórea, menopausa, uso de hormônios, fatores genéticos, histórico familiar (Assi et al., 2011, Wang et al., 2013, Schousboe et al., 2011, Keller et al., 2012). Boyd *et al.* reportaram que 16% de todos os cânceres de mama e 26% dos cânceres de mama em mulheres com menos de 56 anos foram devidos a DM maior que 50% (Boyd et al., 2007). Isto destaca o potencial do conhecimento da quantidade de DM na prevenção do câncer de mama.

A literatura apresenta estudos referentes a DM com diferentes objetivos: (i) desenvolvimento de métodos para medir a DM; (ii) a quantificação do efeito independente da densidade no risco de desenvolvimento de câncer de mama; (iii) a relação da densidade com outros fatores de risco para câncer de mama; (iv) a implicação da DM no rastreamento do câncer de mama; e (v) como a densidade pode ser alterada quando diversos tratamentos são aplicados ao paciente (Assi et al., 2011).

A Figura 1 apresenta uma panorâmica sobre metodologias apresentadas na literatura para a estimativa da PDM.. Esses métodos se enquadram em dois subtipos: qualitativos e quantitativos (Assi et al., 2011, Yaffe, 2008). As medidas qualitativas levam em consideração certas características que podem ser apreciadas em uma mamografia, como dutos e texturas proeminentes, bem como a quantidade visual da DM (Assi et al., 2011). Por outro lado, as medidas quantitativas consideram a medida objetiva da área e do volume da DM a partir de métodos computacionais (Assi et al., 2011, Wolfe, 1976, Sickles et al., 2013, van der Waal et al., 2015, Li et al., 2012).

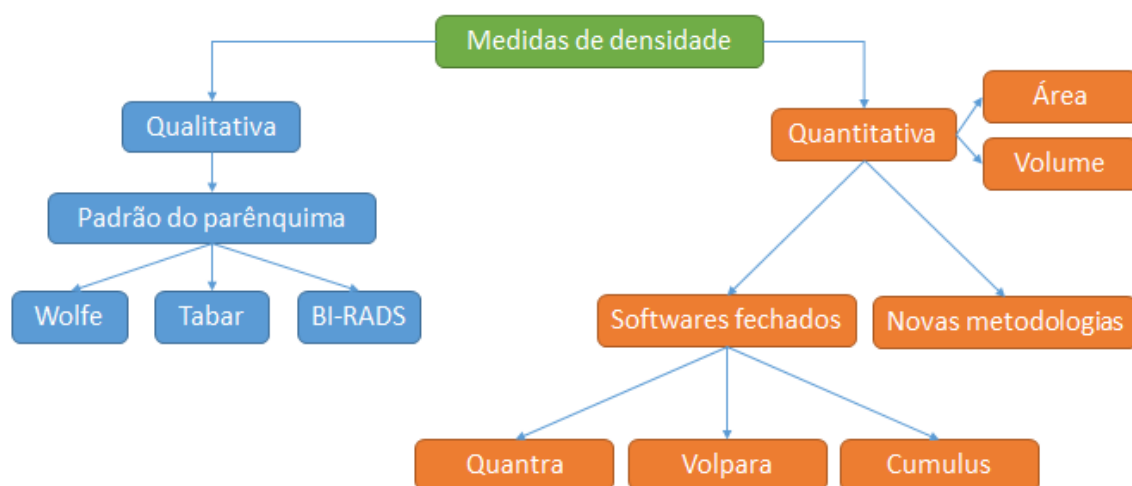


Figura 1. Esquema representando alguns dos métodos utilizados para avaliação da densidade mamária.

Duas metanálises abrangentes, realizadas com mais de uma década de intervalo, encontraram uma forte associação entre a DM e o risco de câncer de mama. Ambas observaram que as medidas quantitativas proporcionaram uma predição de risco superior às qualitativas (McCormack and dos Santos Silva, 2006, Warner et al., 1992). Aproximadamente 5% da população feminina tem mamas extremamente densas (porcentagem de área densa $\geq 75\%$). Estas mulheres apresentam um risco de quatro a seis vezes maior de desenvolvimento de câncer de mama em comparação àquelas com mamas adiposas ($<10\%$ de tecido denso) (McCormack and dos Santos Silva, 2006, Boyd et al., 2007, Cuzick, 2008). A densidade é, portanto, um importante preditor independente de risco de câncer de mama (Ursin et al., 2005, Boyd et al., 2009).

A metodologia de quantificação de DM mais antiga, a qual baseia-se nos padrões parenquimatosos, foi apresentada pela primeira vez por Wolfe em 1976 (Wolfe, 1976). Tanto Wolfe quanto Gram *et al.* (Gram et al., 1997) verificaram que, frequentemente, em mulheres de 35 anos com grande quantidade de DM, havia uma alteração de padrão mamário para uma categoria menos densa quando atingida a idade de 50 anos. Isso ocorre devido a substituição de tecido fibroglandular por tecido adiposo com o avanço da idade. Assim, para mulheres jovens, próximas da pré-menopausa, Wolfe e Gram *et al.* classificaram as mamas de acordo com a quantidade de DM observadas no exame de mamografia (Gram et al., 1997, Wolfe, 1976).

No entanto, ambas as categorias de classificação foram abandonadas e foram substituídas pelas classificações de composição da mama do *The American College of Radiology* denominado *Breast Imaging Reporting and Data System* (BI-RADS) (Sickles et al., 2013). O BI-RADS é uma classificação da imagem mamográfica avaliada visualmente. Neste sistema, um radiologista treinado visualiza a mamografia e realiza

um julgamento subjetivo sobre qual categoria a mamografia pertence (Assi et al., 2011, Sickles et al., 2013, Brandt et al., 2016, Winkler et al., 2015). Uma grande desvantagem desse método é a variabilidade intra e interavaliadores (van der Waal et al., 2015, Assi et al., 2011, Ciatto et al., 2005, Ooms et al., 2007, Redondo et al., 2012, Timmers et al., 2012).

Em uma mamografia, medidas quantitativas de densidade podem ser relativas ou absolutas. Quando a medida é relativa a quantidade de DM é expressa como uma porcentagem da área ou volume total da mama (por exemplo, área densa de 5%). Quando quantificada de forma absoluta, a área ou o volume de DM é medido baseando-se no número de pixels de tecido fibroglandular, em cm^2 ou cm^3 (por exemplo, área densa absoluta de $11,70 \text{ cm}^2$) (Assi et al., 2011).

Métodos assistidos por computador para quantificar a DM foram desenvolvidos para tornar o processo menos trabalhoso e reduzir a subjetividade (Assi et al., 2011, Yaffe, 2008, van der Waal et al., 2015). Além disso, estes métodos tem como objetivo permitir a extração de informações mais abrangentes, como por exemplo medidas contínuas de área total da mama, a área densa e área não densa (Assi et al., 2011, Yaffe, 2008). Sendo assim, muitos estudos têm sido realizados para o desenvolvimento de métodos computacionais quantitativos e objetivos (Winkler et al., 2015). Os métodos descritos na literatura recente para quantificar objetivamente a densidade mamográfica se enquadram em dois subtipos: área e volume.

Os métodos para quantificar a DM através da área são baseados no número de pixels densos na região que compreende a mama na imagem mamográfica (Assi et al., 2011). Dentro deste contexto, diferentes metodologias podem ser encontradas na literatura tais como a limiarização semi-automática interativa publicada por Byng *et al.*

(Byng et al., 1996); segmentação automática baseada no processamento de limiarização ótima de *Kittler* descrito por Sivaramakrishna *et al.* (Sivaramakrishna et al., 2001); e regressão multivariada *model-derived mathematical equation* (MATH) desenvolvida por Lu *et al* (2007) (Lu et al., 2007).

Dentre as metodologias citadas, a descrita por Byng *et al.* tem sido utilizada como método *Gold Standard*, sendo a mais amplamente empregada para estimar o risco de desenvolvimento de câncer de mama em pesquisas epidemiológicas (Lu et al., 2012, Assi et al., 2011, van der Waal et al., 2015). Esta metodologia deu origem ao software comercializado pelo nome Cumulus, (Sunnybrook Health Sciences Center, Toronto, Canadá). Neste software, o radiologista observa uma imagem de mamografia em um computador e segmenta a área de DM e a margem da mama utilizando-se limiarização interativa. De forma automática o software calcula o número de pixels obtendo-se a área da mama total e a área do tecido fibroglandular. Como resultado, o software retorna ao radiologista medidas da porcentagem de área densa (Byng et al., 1998, Heine et al., 2008, Yaffe, 2008). Entretanto, a aplicação desta metodologia permanece subjetiva uma vez que requer que o usuário insira manualmente alguns valores de limiar (Winkler et al., 2015, Keller et al., 2012, Assi et al., 2011, Yaffe, 2008, van der Waal et al., 2015). Vale enfatizar que as metodologias baseadas na área não levam em consideração a espessura do tecido denso, o qual tem sido observado ser uma medida mais "biologicamente relevante" (Yaffe, 2008, van der Waal et al., 2015).

Métodos que avaliam o volume de tecido denso em mamografias estão atualmente sendo desenvolvidos e espera-se que forneçam estimativas mais precisas da quantidade de DM (Assi et al., 2011). Sendo assim, tais métodos podem ser usados com maior confiabilidade como preditores do risco de câncer de mama (Aitken et al., 2010,

Jeffreys et al., 2008, Malkov et al., 2009, Pawluczyk et al., 2003, Kaufhold et al., 2002). Com o advento da mamografia digital, várias abordagens volumétricas totalmente automatizadas foram propostas (Aitken et al., 2010, Jeffreys et al., 2008, Malkov et al., 2009, Pawluczyk et al., 2003, Kaufhold et al., 2002).

Em 1996, Highnam *et al.* desenvolveu um modelo físico padrão para mamografia com sistema tela-filme (STF). A mamografia precisava ser digitalizada em um *scanner* dedicado. Usando os parâmetros de formação da imagem tais como tensão do tubo, espectro e tempo de exposição, os autores estimaram a DM com bons resultados (Highnam et al., 1996).

Ainda utilizando-se STF digitalizada, Pawluczyk *et al* (2003) apresentou um método para estimar o volume de densidade mamária (VDM) usando uma relação empírica entre o sinal medido na imagem mamográfica e o sinal medido ao adquirir uma imagem de um objeto simulador da mama (Pawluczyk et al., 2003). Este simulador da mama apresenta distintas composições mamárias com diferentes espessuras. Neste estudo, para estimar a VDM foi necessário conhecer os parâmetros de aquisição da imagem (tensão, corrente e tempo) assim como a espessura da mama comprimida (Pawluczyk et al., 2003).

Em 2006, Van Engeland *et al.* propuseram um modelo físico através de mamografia de sistema digital (FFDM – do inglês *full-field digital mammography*) utilizando-se uma relação entre valores do coeficiente de atenuação linear efetivo dos tecidos adiposo e denso e os valores de tensão, material do ânodo, filtração e espessura da mama comprimida (van Engeland et al., 2006).

Recentemente, Alonzo-Proulx *et al.* apresentaram um algoritmo para quantificação do VDM baseado na calibração inicial do sistema mamográfico digital a

partir de um fantoma. A calibração teve como objetivo relacionar o sinal da imagem com distintas espessuras e composições de fantasmas equivalentes a mama (Alonzo-Proulx et al., 2010b).

Em 2017, Holland *et al.* propuseram três formas de quantificar o VDM. A estimativa foi realizada levando-se em consideração valores de tecidos adiposo e fibroglandular como referência. Para cada uma das abordagens descritas, os valores de referência foram alterados. A estimativa realizada por mamografia digital foi comparada com exames de ressonância magnética (RM) resultando em boa concordância entre as modalidades (Holland et al., 2017).

De maneira geral, até então os métodos propostos para quantificar o VDM necessitam de informações específicas para realizar a estimativa, tais como a espessura da mama comprimida e dos parâmetros utilizados durante a aquisição da imagem (Winkler et al., 2015, Yaffe, 2008). Entretanto, em sistemas que utilizam a radiologia computadorizada (CR – do inglês *computed radiography*) tais parâmetros não são armazenados juntos com a imagem DICOM, impossibilitando a aplicação de tais metodologias nestes sistemas.

Além disso, outra limitação comum dos algoritmos que estimam o VDM é a utilização exclusiva de imagens no formato não processado (*raw image*) (Keller et al., 2012). Vale enfatizar que os sistemas mamográficos digitais produzem ambas as imagens processadas e não processadas (Vachon et al., 2013, Yaffe, 2008). Entretanto, devido ao grande tamanho para armazenamento magnético destas imagens, a imagem não processada é frequentemente excluída do sistema e apenas a imagem no formato processada permanece disponível (Vachon et al., 2013, Burton et al., 2016). Portanto, a aplicação de método que utiliza apenas as imagens não processadas torna-se limitado,

sendo de difícil aplicação em estudos retrospectivos epidemiológicos e multicêntricos (Keller et al., 2012).

Durante a aquisição da imagem mamográfica faz-se necessário a compressão dos tecidos mamários. Apesar da compressão minimizar a quantidade de tecidos sobrepostos, a imagem resultante é composta pela projeção da mama contendo porções variáveis de tecidos adiposo e glandular. Desta forma, os pixels da imagem não podem ser classificados como puramente adiposo ou glandular, mas sim como uma composição variável destes tecidos (Lu et al., 2012).

Modalidades de imagens tridimensionais, tais como tomografia computadorizada e RM, são alternativas para estimar o VDM uma vez que não há sobreposição de tecidos (van Engeland et al., 2006, Alonzo-Proulx et al., 2010b, Gubern-Merida et al., 2014, Wang et al., 2013, Schmachtenberg et al., 2015). Entretanto, estas modalidades são de alto custo e não são amplamente solicitadas na rotina de rastreamento. Vale ressaltar que apesar da mamografia ser uma imagem bidimensional e possuir reduzida sensibilidade para pacientes com mama densa, não existe até o momento nenhuma modalidade de imagem que a substitua (Winkler et al., 2015). Sendo assim, modalidades tridimensionais são frequentemente utilizadas como *Ground-truth* para validar metodologias desenvolvidas a partir de imagens mamográficas (van Engeland et al., 2006, Alonzo-Proulx et al., 2010b, Gubern-Merida et al., 2014, Wang et al., 2013, Schmachtenberg et al., 2015).

Esta pesquisa teve como objetivo o desenvolvimento um novo algoritmo objetivo, confiável e reprodutível, de baixo custo o qual leva em média 130 segundos para estimar com precisão o percentual do volume de DM (PDM) em mamografias digitais processadas. O algoritmo desenvolvido pode auxiliar diretamente na prática clínica, na

recomendação de rastreamento personalizado, em escolhas de estratégias preventivas para o tratamento de câncer de mama, de modo a avaliar a eficácia de drogas terapêuticas. Os resultados oriundos desta pesquisa vêm contribuir para a saúde da população e comunidade científica.

A seguir será descrito brevemente os Capítulos que compõem essa tese.

No Capítulo 2 serão apresentados os objetivos gerais e específicos desta pesquisa.

No Capítulo 3 serão apresentados os Fundamentos Teóricos, como subsídios para o leitor, abordando temas utilizados nesta pesquisa que varrem desde sistema de processamento, descrição de formação de imagem de equipamentos utilizados até composição mamária.

Nos Capítulos 4 e 5 estão anexadas as publicações, 2 artigos, correspondentes à dois objetivos desta pesquisa. O Capítulo 4 foi publicado no *Proceedings SPIE Medical Imaging* e apresenta uma metodologia desenvolvida para ser utilizada como pré-processamento da imagem para realçar os pixels presentes na região periférica da mama, melhorando a acurácia da estimativa da PDM. O Capítulo 5 foi publicado no *Innovation And Research In Biomedical Engineering – IRMB* e descreve a quantificação dos tecidos mamários associando-se de forma inédita técnicas de lógica *fuzzy* para segmentar e quantificar a área de tecido denso em imagens mamográficas. Ainda neste Capítulo, os resultados oriundos da segmentação e quantificação são divididos em quatro classes progressivas de quantidade de DM. Sendo assim, a estimativa da área de tecido fibroglandular foi comparada com a classificação através do sistema BI-RADS.

No Capítulo 6 está anexado o artigo final da tese, o qual está submetido para publicação na revista *Radiology*. Este Capítulo apresenta a quantificação do VDM. Para

isto, nesta etapa é utilizada a segmentação dos tecidos através da metodologia por *fuzzy* descrita no Capítulo 5. Após a segmentação, é aplicada a técnica de razão sinal-ruído diferencial de forma a estimar o VDM e calcular o PDM. Os resultados oriundos da metodologia apresentada neste Capítulo são validados a partir de exames de RM. A metodologia desenvolvida neste Capítulo apresenta uma nova abordagem e vem preencher uma lacuna da literatura: volumetria dos tecidos a partir de mamografias por sistema CR.

O Capítulo 7 discorre sobre as conclusões gerais provenientes desta pesquisa. Além disso, apresenta todos os trabalhos publicados durante o período de doutorado, como apresentado no Apêndice I.

O Capítulo 8 apresenta as perspectivas futuras com relação ao tema.

Capítulo 2

2. Objetivos

Esta pesquisa teve como objetivo o desenvolvimento de uma ferramenta computacional automática para quantificar a porcentagem do volume de densidade mamária (PDM) através de exames de mamografia por sistema CR. Este trabalho traz contribuições originais quanto à utilização de diferentes técnicas de processamento de imagem para o desenvolvimento de uma metodologia híbrida, totalmente automática, rápida e de fácil implementação. Os objetivos específicos estão descritos a seguir:

- Realce da região periférica da mama em exames de mamografia CR (Capítulo 4);
- Quantificação da área de tecido denso em mamografia e comparação com sistema BI-RADS (Capítulo 5);
- Quantificação da PDM em exames de mamografia (Capítulo 6);
- Quantificação da PDM em exames de RM, utilizado como *Ground truth* (Capítulo 6);
- Validação da ferramenta desenvolvida para estimativa de PDM, através da comparação dos resultados obtidos pelos dois métodos: mamografia e RM (Capítulo 6).

Face a estes objetivos específicos, almeja-se que a ferramenta desenvolvida possa ser utilizada em futuros estudos, na padronização das medidas de VDM em sistemas CR e FFDM permitindo a realização de estudos confiáveis para associação da quantidade de tecido denso e o risco de desenvolvimento de câncer de mama. A ferramenta desenvolvida também pode ajudar diretamente a prática clínica, auxiliando médicos na recomendação de rastreamento personalizado, para determinar se estratégias

preventivas devem ser iniciadas, para avaliar a eficácia de drogas terapêuticas e para estimar a dose glandular média resultante da realização do exame de mamografia.

Capítulo 3

3. Fundamentos Teóricos

Os assuntos tratados nesta seção serão brevemente revisados, de modo a introduzir subsídios necessários para a compreensão dos objetivos e metodologia realizada nesta pesquisa.

3.1. Anatomia da mama

As mamas são estruturas glandulares, localizadas na parede anterior do tórax, à frente dos músculos peitorais e serráteis anteriores, no intervalo entre a terceira e sétima costela, entre o bordo do esterno e linha axilar média (Bernardes, 2011). Apresenta grande variação entre as mulheres e também entre os diferentes períodos da vida (Seo et al., 2013). Em média, possui de 12 a 13 cm de largura, 10 a 11 cm de altura e de 5 a 6 cm de espessura (Bernardes, 2011).

A Figura 2 representa a arquitetura de uma mama, vista em uma seção sagital externamente, no centro da face convexa, anterior. Em sua estrutura, a mama apresenta o tecido glandular, o qual é composto por lóbulo, ductos excretor e lactífero e seio lactífero. O lóbulo propriamente dito é composto por ductos terminais e interlobulares e por ácinos. O tecido adiposo envolve todo o tecido glandular e apresenta duas partes: a primeira anterior, superficial, entre a glândula e a pele; e a segunda, posterior, profunda, denominada gordura retromamária, localizada entre a base da glândula e o músculo peitoral maior. O tecido fibroso ajuda a sustentar os lobos da mama, formando uma rede de tecido fibroso denominado ligamento de Cooper (Bernardes, 2011 , Drake et al., 2010).

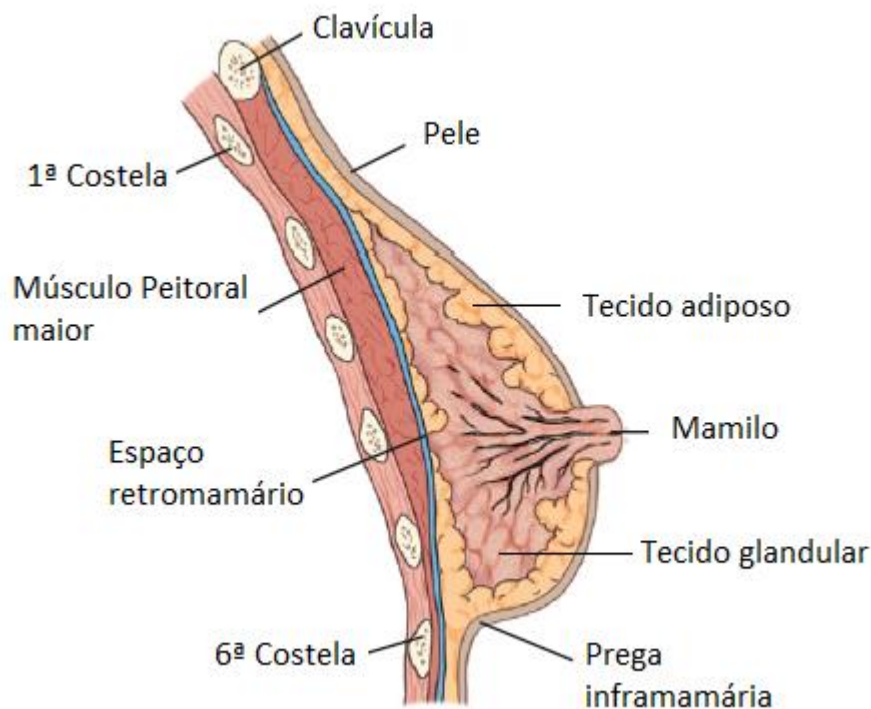


Figura 2. Esquema ilustrativo da mama compreendendo a seção sagital da mama (Bontrager and Lampignano, 2014).

Em um exame de mamografia o tecido adiposo da mama possui coeficiente de atenuação de radiação menor que os tecidos fibrolangulares. Desta forma, o tecido adiposo é representado na imagem de mamografia em tons mais enegrecidos. Os tecidos fibrosos e glandulares possuem coeficiente de atenuação muito próximos e por isso, são visualizados em um mesmo tom de cinza. É por este motivo que estes dois tecidos são descritos como tecido fibroglandular em um exame de mamografia (Bontrager and Lampignano, 2014, Drake et al., 2010, Paredes, 2007). A Figura 3 apresenta um exame de mamografia nas projeções médio lateral-oblíqua e crânio-caudal (Paredes, 2007), destacando-se o tecido fibroglandular, tecido adiposo, pele, músculo peitoral e o mamilo. Nestas imagens nota-se que o tecido fibroglandular fica imerso em meio ao tecido adiposo.

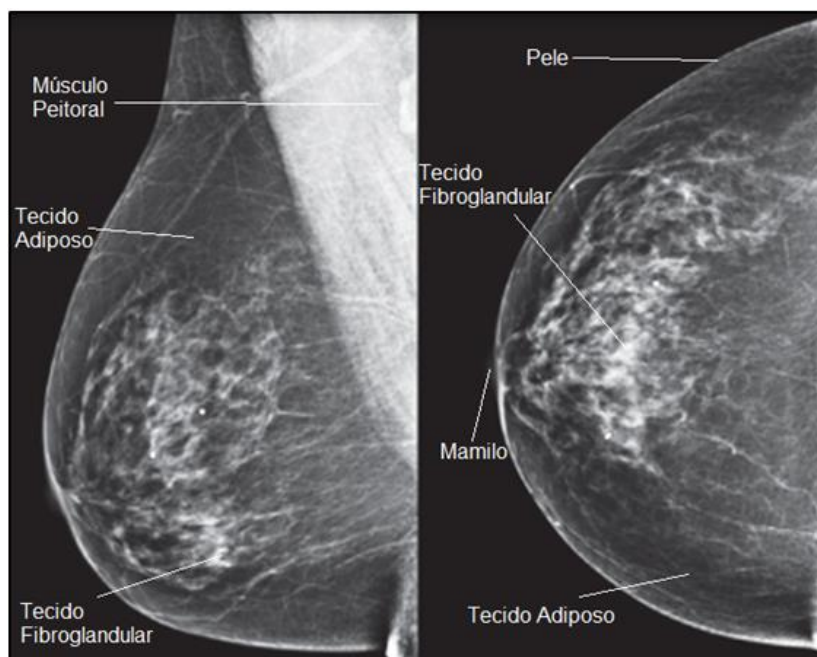


Figura 3. Exame de mamografia na incidência médio lateral oblíqua e crânio caudal ilustrando o aspecto dos tecidos presentes na mama (Sickles et al., 2013).

Neste estudo, serão quantificados os tecidos fibroglandular e adiposo de forma totalmente automática através de um algoritmo desenvolvido no software Matlab®. Para a quantificação dos tecidos através da mamografia foi necessário utilizar técnica para realçar a região periférica da mama na imagem, seguida de técnica de segmentação por lógica *Fuzzy* e, finalmente, aplicação da técnica de razão sinal-ruído diferencial para estimar a PDM.

3.2. Formação da imagem em mamografia digital

A mamografia é um procedimento radiográfico otimizado para a região anatômica da mama. Para muitas mulheres, a mamografia é altamente eficaz na detecção do câncer em estágios iniciais. Essa modalidade é utilizada para imagear mulheres sintomáticas e assintomáticas a partir de certa idade. O exame é normalmente

realizado a partir de duas projeções de cada uma das mamas: crânio-caudal e médio lateral-oblíqua. Apesar de ser utilizada principalmente para detecção de patologias da mama, a mamografia também é usada para avaliação pré-cirúrgica da região suspeita e também para guiar biópsias (Dance et al., 2014, Bushberg, 2002).

3.2.1. Equipamento de mamografia

O equipamento de mamografia possui muitas semelhanças com o equipamento de radiologia convencional. As características específicas de um equipamento de mamografia se dão pela anatomia específica da mama. Os principais tecidos mamários e patológicos possuem coeficiente de atenuação linear muito próximo. A Figura 4a mostra a relação da variação da energia em função do coeficiente de atenuação linear do tecido adiposo, tecido fibroglandular e carcinoma ductal infiltrativo. Na Figura 4b pode-se observar a influência da energia usada para produzir fótons de raios X e o contraste entre um tumor e calcificações. Desta forma, fica evidente que energias normalmente utilizadas em radiodiagnóstico (40 à 120 kVp) não devem ser aplicadas à mama. Tais energias diminuem o coeficiente de atenuação linear dos tecidos resultando em menor contraste dos mesmos na imagem (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

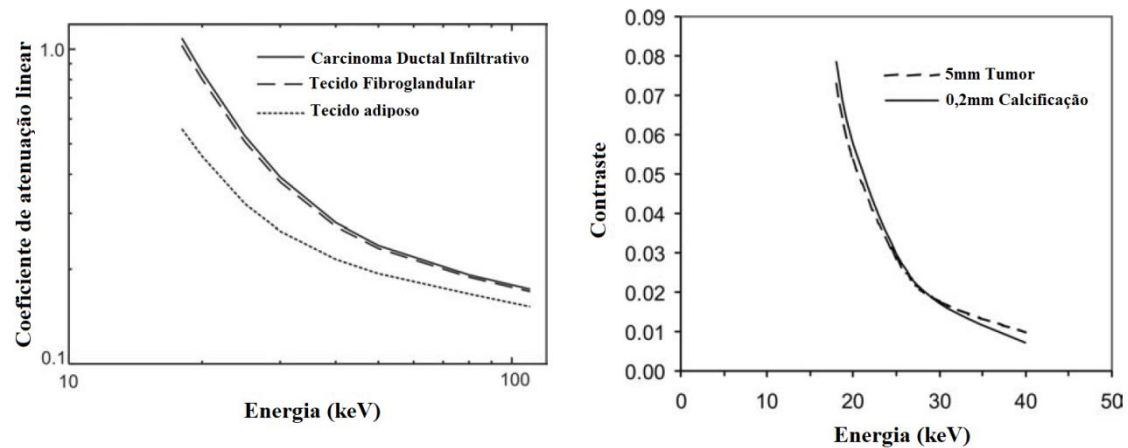


Figura 4. a) Relação entre a energia do feixe de raios X e o coeficiente de atenuação linear para os carcinoma dictal infiltrativo, tecido fibroglandular e tecido adiposo; b) Relação entre a energia do feixe de raios X e o contraste da imagem para um tumor de 5mm e uma calcificação de 0,2mm (Dance et al., 2014).

Desta forma, o contraste do exame de mamografia requer o uso de um espectro específico, o qual possa enfatizar as diferentes composições dos tecidos mamários. Sendo assim, a escolha da combinação ânodo/filtro deve ser exclusiva para mamografia. Além da energia específica, o equipamento de mamografia também deve possuir resolução para altas frequências de forma a exibir estruturas com aproximadamente 50 μm . Outra característica que distingue o equipamento é a utilização de uma bandeja de compressão a qual possui a função de diminuir a espessura total da mama (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

A Figura 5 ilustra um equipamento de mamografia e seus principais componentes: tubo de raios X, bandeja de compressão, suporte para apoio da mama, grade anti-espalhamento e detector de imagem. Durante a realização do exame, o equipamento deve ser rotacionado para que seja possível a aquisição de imagens em diferentes angulações. Sendo assim, o equipamento é desenvolvido de forma que o tubo

de raios X e o detector rotacionem juntos, mantendo sempre um ângulo de 90° entre ambos (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

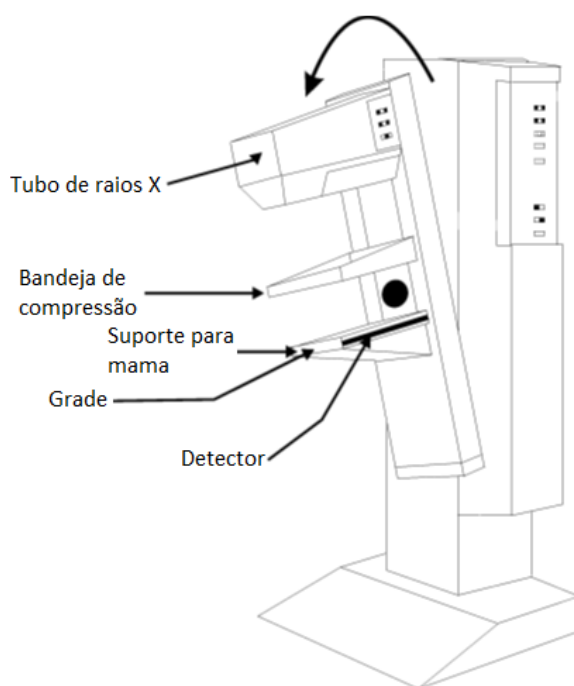


Figura 5. Ilustração do equipamento de mamografia e seus principais componentes (Dance et al., 2014).

A imagem mamográfica é adquirida quando os fótons de raios X atingem o detector. Entre a saída do tubo de raios X e o detector, os fótons de raios X passam um filtro, são colimados, atravessam a bandeja de compressão e a mama e, finalmente, passam pela grade e são detectados por um sistema tela-filme, placa de imagem ou detector digital (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

Diferentemente de equipamentos convencionais, os mamógrafos não possuem o feixe de raios X centralizado. A geometria do feixe no mamógrafo é específica para que os tecidos próximos a parede torácica do paciente também possam ser imageados. A Figura 6a apresenta a geometria do feixe, onde uma linha vertical do ponto focal da fonte de raios X passa tangente a parede torácica do paciente. Caso o feixe de raios X

estivesse posicionado ao centro, como em equipamentos convencionais, parte do tecido mamário não seria imageado (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002), como mostra a região em destaque da Figura 6b.

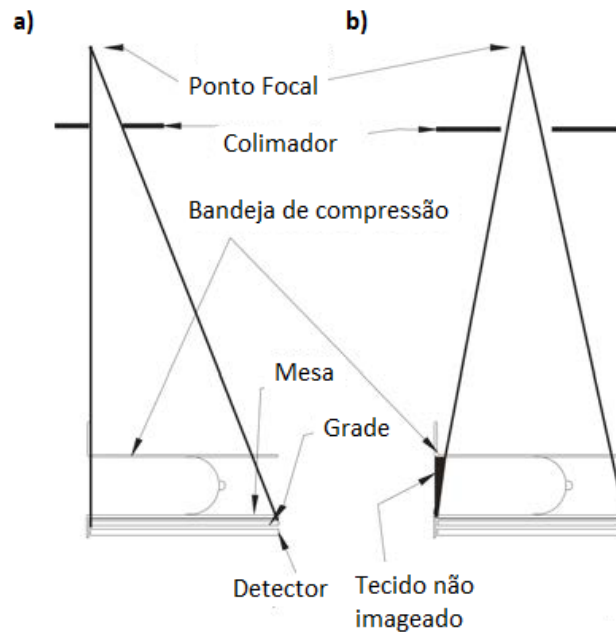


Figura 6. Ilustração demonstrando a geometria do feixe de raios X. Em (a) a geometria permite que toda a mama seja imageada. Por outro lado, a geometria em (b) faz com que parte do tecido próximo à parede torácica não seja imageado (Dance et al., 2014).

Nesta pesquisa, o equipamento de mamografia utilizado foi um Senographe 600T (Ge Healthcare, Milwaukee, WI) com sistema de radiologia computadorizada.

3.2.2. Tubo, filtros e espectro

Em equipamentos modernos de mamografia a fonte de energia é tipicamente do tipo alta frequência e fornece um potencial próximo do constante. O tubo de raios X possui ânodo giratório onde os elétrons são acelerados atingindo o alvo em um pequeno ângulo. O ponto focal grosso típico é 0,3mm e o fino é 0,1mm (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

O tubo de raios X é disposto de tal forma que o cátodo do tubo é adjacente à parede torácica do paciente. Desta forma, usa-se o efeito anódico à favor do contraste da imagem: a região mais espessa da mama (próxima à parede torácica) é exposta pela parte mais intensidade do feixe. Isto fornece uma imagem mais homogênea e uniforme (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

O espectro de raios X é resultado da escolha da tensão aplicada ao tubo, do material utilizado no alvo e no filtro. A otimização do espectro de raios X depende do sistema utilizado. Para o STF, o contraste da imagem possui forte dependência do gradiente do filme utilizado. Entretanto, em sistemas digitais a qualidade da imagem exibida é limitada pela relação sinal ruído da imagem. Desta forma, em STF a energia ótima a ser utilizada é entre 18 e 23 keV, dependendo da espessura e composição da mama. Neste caso, para uma mama típica, o espectro de raios X produzidos por alvos de molibdênio (Mo) e ródio (Rh) fornecem bom desempenho de imagem. Entretanto, em sistemas digitais onde o contraste da imagem pode ser controlado durante a visualização da imagem, energias maiores podem ser melhores. Por esta razão, alguns equipamentos modernos de mamografia digital são equipados com alvos de tungstênio (W) (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

Após serem gerados, os fótons de raios X atravessam um filtro de forma a remover seletivamente fótons de baixa e alta energias. Fótons com baixa energia são indesejados uma vez que não possuem energia o suficiente para atravessarem a mama do paciente e resultam em dose. Fótons de alta energia influenciam negativamente no contraste da imagem como já mencionado e mostrado através da Figura 4. Uma combinação típica de alvo/filtro é Mo/Mo, resultando em um espectro com fótons entre 17 e 20 keV. A Figura 7a mostra o espectro resultante da escolha Mo/Mo. O espectro em roxo foi

adquirido com 25 kV e o rosa com 28 kV. Nota-se que neste caso o aumento da tensão tem influência no número de fótons produzidos, mas não na energia média do feixe (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

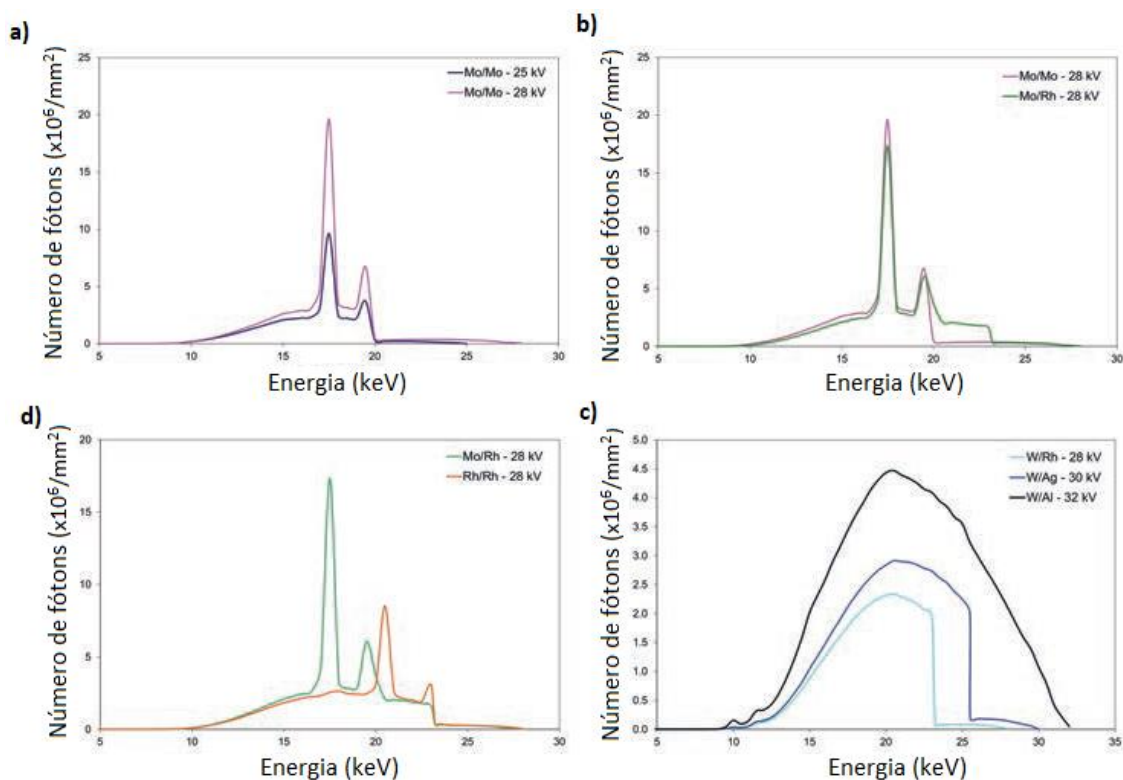


Figura 7. Espectros de raios X provenientes de equipamentos de mamografia. a) comparação dos espectros para a combinação Mo/Mo e alterando a tensão aplicada ao tubo; b) Comparação dos espectros resultantes da combinação Mo/Mo (rosa) e Mo/Rh (verde); c) Comparação dos espectros quanto utilizadas as combinações Mo/Rh (verde) e Rh/Rh (laranja); d) Comparação dos espectros utilizando-se alvo/filtro de W/Rh (azul claro), W/Ag (azul escuro) e W/Al (preto).

Apesar do espectro do Mo ser relativamente bem adequado para imagear mamas típicas, energias mais altas são desejadas para realizar o exame em mamas maiores e mais densas. Desta forma, o uso de material com maior número atômico no filtro pode ser utilizado. A combinação Mo/Rh permite que o feixe seja composto por fótons de maiores energias. A Figura 7b compara um espectro produzido pela mesma tensão e alvo, mas com diferentes filtros. O espectro em verde é mais penetrante, resultando em

menor dose quando comparado com o espectro em rosa (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

Outras combinações podem ser utilizadas com o objetivo de otimizar o espectro de raios X de forma a minimizar a dose no paciente. A Figura 7c compara o espectro de Mo/Rh com o espectro Rh/Rh. Este último possui energia média maior, sendo mais penetrante. Recentemente, os novos equipamentos possuem alvo composto por tungstênio (W) e diferentes filtros, aumentando ainda mais a energia do feixe, como mostra a Figura 7d (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

Neste estudo o equipamento de mamografia utilizado possui gerador trifásico de 12 pulsos e combinação ânodo/filtro de Mo/Mo.

3.2.3. *Compressão*

A compressão da mama durante a aquisição da imagem é de extrema importância. Ao comprimir a mama, os tecidos dentro da mesma se espalham resultando em uma menor sobreposição de estruturas e melhor visualização das mesmas. Além disso, a radiação espalhada é um dos principais fatores para degradar o contraste da imagem. A utilização da compressão diminui a espessura da mama e como resultado há diminuição da radiação espalhada. Vale salientar, que a compressão também diminui a distância entre os tecidos e o detector, aumentando consideravelmente a nitidez geométrica das estruturas. A compressão da mama também permite redução da dose, uma vez que diminui a probabilidade de interação dos fótons com os tecidos. Finalmente, a compressão é importante para reduzir a possibilidade de movimentação do paciente evitando que artefatos sejam produzidos (Dance et al., 2014, Bushberg, 2002, Hendee and Ritenour, 2002).

Um grande número de trabalhos publicados na literatura para a estimativa do VDM utilizam a informação da espessura da mama comprimida. Entretanto, em equipamentos CR (utilizado neste trabalho) esta medida não está disponível na informação DICOM. Desta forma, neste estudo foi desenvolvida uma metodologia para estimar o VDM sem a necessidade de conhecer a espessura da mama comprimida.

3.2.4. Aspectos radiológicos da mama decorrente da compressão

A região periférica da mama possui espessura diferente da espessura da mama comprimida e, desta forma, torna a estimativa do VDM mais desafiadora (Chen et al., 2016, Alonzo-Proulx et al., 2010b). Durante a aquisição da imagem mamográfica, a mama é comprimida e parte da mesma perde contato com a bandeja de compressão (Holland et al., 2017, Alonzo-Proulx et al., 2010a). Como resultado, a imagem mamográfica possui uma região periférica que possui espessura variável, como mostra a Figura 8a. Devido a esta diferença de espessura, o há uma superexposição na região periférica, como mostra a Figura 8**Erro! Fonte de referência não encontrada.**b, onde a região periférica possui tons de cinza mais próximos do preto. As diferenças na intensidade dos pixels na região periférica são, portanto, fortemente influenciadas pela espessura da mama (Chen et al., 2016, van Engeland et al., 2006).

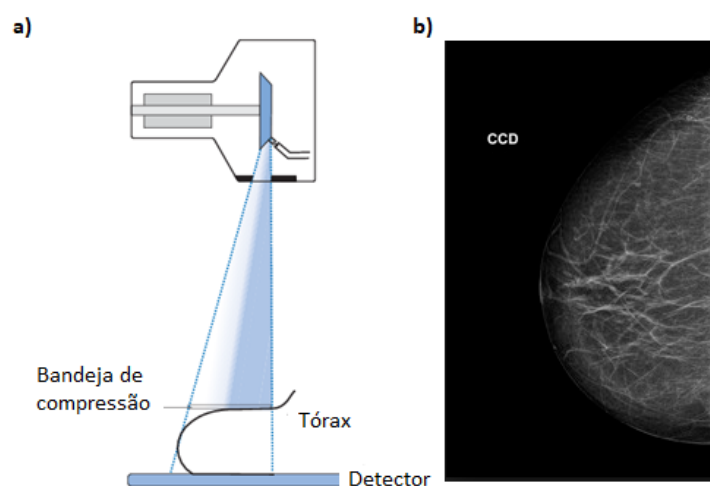


Figura 8.a) Mama sendo comprimida durante aquisição do exame mamográfico. Nota-se que a região periférica possui espessura variável; b) No exame de mamografia pode-se visualizar a diferença de intensidade da região periférica devido à superexposição.

Para que a quantificação do VDM seja realizada de forma confiável, faz-se necessário o conhecimento acurado da espessura de tecido denso em cada pixel que compõe a imagem mamográfica (Chen et al., 2016, Holland et al., 2017, Yaffe, 2008). Entretanto, os métodos volumétricos são altamente sensíveis à espessura da mama (Yaffe, 2008, Alonzo-Proulx et al., 2010a, van Engeland et al., 2006).

Desta forma, procedimentos para corrigir a não-uniformidade da espessura dos tecidos na região periférica são necessários para estimar acuradamente o VDM (Wang et al., 2003). Técnicas de pré-processamento devem ser usadas em imagens mamográficas para realçar a visibilidade da área periférica e melhorar a distribuição da intensidade de pixels (He et al., 2015).

Estudos mostram o desenvolvimento de algoritmos para identificar a região periférica na mamografia e para corrigir a superexposição desta região (Wang et al., 2003, Alonzo-Proulx et al., 2010a, Tortajada et al., 2014, Snoeren and Karssemeijer,

2004). Na literatura esta metodologia tem sido denominada “equalização da espessura” ou “realce da periferia” (Snoeren and Karssemeijer, 2004).

Os diferentes métodos que realizam a correção da espessura da região periférica variam na determinação da área na qual será implementada a correção e no fator de correção a ser utilizado. Com relação a área, os algoritmos podem ser aplicados em toda a imagem (Wang et al., 2003, Bick et al., 1996, Byng et al., 1997) ou somente em uma região determinada por um algoritmo de segmentação (He et al., 2015, Tortajada et al., 2014, Snoeren and Karssemeijer, 2004).

A metodologia descrita por Wang *et al.* cria uma curva de realce gerando valores de correção para cada pixel, o qual é adicionado no valor do pixel original. Nesta abordagem é aplicado um fator de correção na área da mama inteira e não apenas na região periférica. Como resultado, para mamas pouco densas há um bom realce. Entretanto, em mamas densas as regiões que possuem grande quantidade de tecido fibroglandular chegam ao valor máximo do pixel, gerando artefatos (He et al., 2015, Tortajada et al., 2014). Além disso, os pixels próximos da parede torácica que não sofrem influência da variação de espessura e, portanto, não deveriam ser corrigidos, também são alterados. Como consequência, este método pode superestimar o valor do VDM não sendo apropriado para ser utilizado em mamografias com grande quantidade de tecido fibroglandular.

Na metodologia descrita por Tortajada *et al.*, a correção da espessura da mama é iterativamente aplicada em uma região previamente segmentada. Este método segmenta a periferia da mama e calcula o fator de correção baseado nos valores de pixel vizinhos à região periférica. Esta abordagem gera bons resultados em mamas adiposas e mamas com áreas dispersas de densidade fibroglandular. Entretanto, mamas com tecido denso

localizado próximo da região periférica podem superestimar o fator de correção nas primeiras iterações. Vale salientar que a região periférica da mama é predominantemente adiposa (Karssemeijer, 1998) e, desta forma, esta metodologia pode superestimar o valor de correção causando erro na estimativa do VDM.

Neste estudo, o primeiro passo para a estimativa acurada do VDM será o realce da periferia da mama. Para isto, uma nova metodologia foi desenvolvida onde o fator de correção é aplicado apenas na região superexposta da mama.

3.2.5. *Radiologia Computadorizada*

Radiologia Computadorizada (CR- do inglês *Computed Radiography*) é um termo comercialmente utilizado para o sistema de detecção o qual utiliza fósforos fotoestimuláveis (PSP- do inglês *Photostimulable Phosphor*).

A aceitação da CR nos centros de diagnóstico por imagem se deve a sua ampla faixa dinâmica, sua natureza digital e fácil portabilidade do mesmo (Rowlands, 2002). Sua ampla faixa dinâmica é a principal vantagem em relação ao STF. Observando-se a Figura 9, pode-se notar que a faixa de exposição útil da CR é maior quando comparada ao sistema convencional, possibilitando uma maior utilização de imagens superexpostas e subexpostas para um diagnóstico médico seguro.

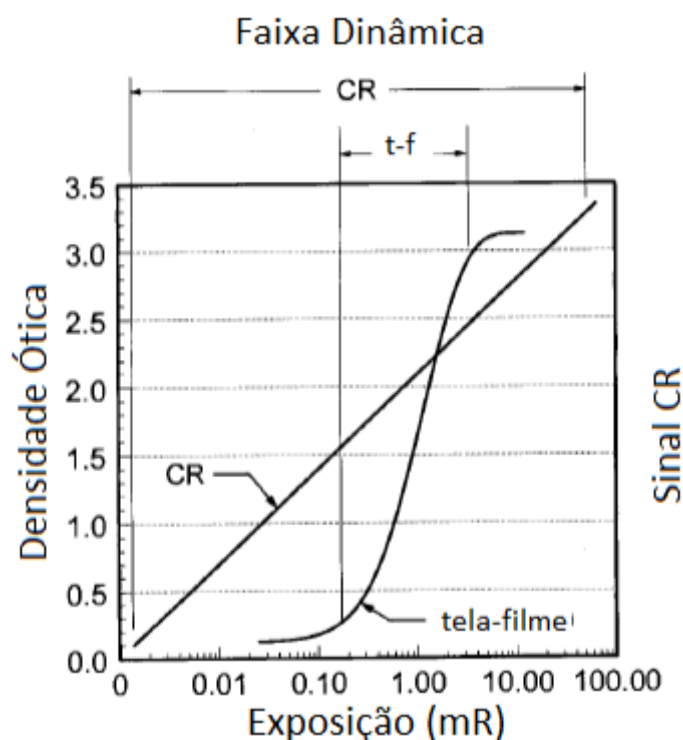


Figura 9. Demonstração da faixa de exposição (latitude do filme) ao qual o sistema tela-filme produz densidade ótica útil. A faixa útil para o sistema CR também é demonstrada (Bushberg, 2002).

Embora a tecnologia CR seja capaz de produzir imagens com tons de cinza adequados mesmo quando utilizados altos e baixos níveis de exposição, os esforços de garantia de qualidade ainda devem estar presentes para garantir níveis de exposição tão baixos quanto razoavelmente exequíveis (Bushberg, 2002, Davidson and Sim, 2008).

Na aquisição de imagens com tecnologia CR utilizam-se detectores baseados no princípio de luminescência fotoestimulada (Rowlands, 2002). O PSP armazena a energia dos raios X absorvendo-a em “armadilhas” na estrutura cristalina (Seibert et al., 2006). Esta energia armazenada constitui a imagem latente. Ao longo do tempo, a imagem latente desaparece espontaneamente pelo processo de fosforescência. O material PSP pode armazenar uma imagem latente por um longo período onde, em geral, após 8 horas de irradiação ainda contém 75% da informação (Rowlands, 2002).

Se houver estímulo com luz de comprimento de onda adequado, o processo de luminescência fotoestimulada (PSL- do inglês *Photostimulated Luminescence*) pode liberar uma parte da energia armadilhada imediatamente. Por este motivo, as placas PSP são também chamadas de *storage phosphor* ou *imaging plates* (IP). A luz emitida constitui o sinal para a criação da imagem digital (Rowlands, 2002, Seibert et al., 2006).

A energia depositada na IP faz os elétrons locais serem elevados do nível de energia de equilíbrio (estado fundamental) para uma armadilha metaestável conhecida como "centroF". Esta é a imagem latente não observável, onde o número de elétrons armadilhados é proporcional ao número de fótons de raios X incidentes sobre a IP (Seibert et al., 2006).

As técnicas de aquisição de imagem são similares à aquisição do sistema convencional. A Figura 10a demonstra a exposição, onde os raios X são transmitidos através da mama do paciente e absorvidos pela IP (Rowlands, 2002, Seibert et al., 2006). Na CR, a IP é levada para uma leitora onde vários processos ocorrem para transformar a imagem latente da placa em uma imagem digitalizada. A Figura 10b exemplifica o processo de leitura da imagem latente, que se inicia ao colocar o cassete na unidade leitora de CR, onde a placa de imagem é removida mecanicamente de seu interior. Esta é transladada através de um mecanismo de movimentação e varrida por um feixe de laser com comprimento de onda adequado (Rowlands, 2002). Os elétrons armadilhados na PI são estimulados pela energia do laser, e uma fração significativa retorna ao nível mais baixo de energia dentro do fósforo, com um lançamento simultâneo da PSL de maior energia.

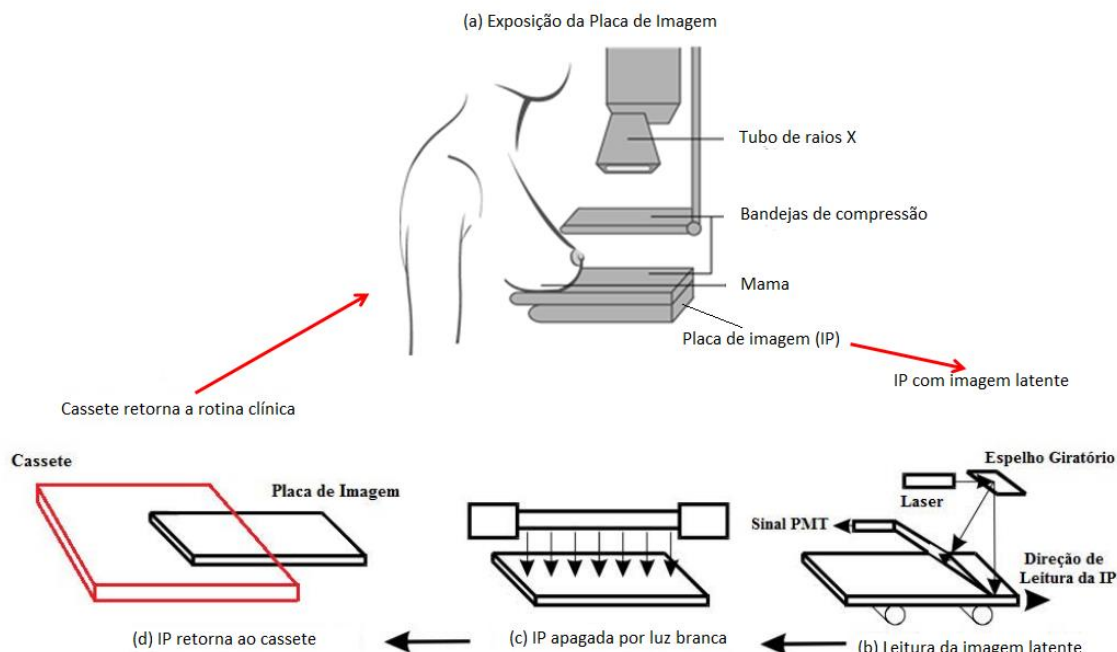


Figura 10. Processo de aquisição e formação a imagem usando sistema de radiologia computadorizada (Rowlands, 2002).

A intensidade da PSL, proporcional ao número de elétrons liberados, é opticamente filtrada a partir da luz laser. Esta é capturada por um conjunto de guia de luz próximo à IP, o qual atinge um tubo fotomultiplicador (PMT- do inglês *Photomultiplier Tube*), sendo produzido um sinal elétrico (Rowlands, 2002, Seibert et al., 2006). A IP é transladada ao longo de seu sentido de leitura na direção vertical, através de cilindros de translação; enquanto o laser percorre a placa na direção horizontal, com auxílio do espelho giratório. Este processo é realizado de modo que toda a imagem latente seja lida. Os sinais elétricos provenientes da PMT são digitalizados e armazenados (Rowlands, 2002). Esta digitalização utiliza um conversor analógico-digital, produzindo um número digital correspondente a um local específico da imagem radiográfica. Isto é determinado pela sincronização do feixe de laser e da localização da IP (Seibert et al., 2006).

A Figura 10c representa a IP sendo apagada através da exposição da mesma a uma luz intensa para que a energia residual armadilhada seja emitida. Finalmente a IP retorna ao cassete e está pronta para ser utilizada novamente, como mostra Figura 10d.

A imagem digitalizada é então processada para realçar a anatomia da mama. Desta forma, duas imagens são produzidas: uma imagem não processada (*raw*) e uma imagem processada. A imagem não processada (*raw*) é adquirida baseada no sinal incidente no detector, o qual é normalmente proporcional à transmissão dos raios X através da mama (Yaffe, 2008). As Figura 11a-d mostram mamografias não processadas. A imagem processada é a imagem final a qual será utilizada pelo radiologista para avaliação clínica, como aprensetadas nas Figura 11e-h. Esta imagem é proveniente do processamento da imagem *raw* por operações lineares ou não lineares. Os algoritmos que realizam este processamento realçam detalhes na anatomia imageada para que seja possível realizar um diagnóstico médico mais preciso. Entretanto, tais algoritmos são de propriedade particular e muitos estão sob patente hoje em dia (Yaffe, 2008).

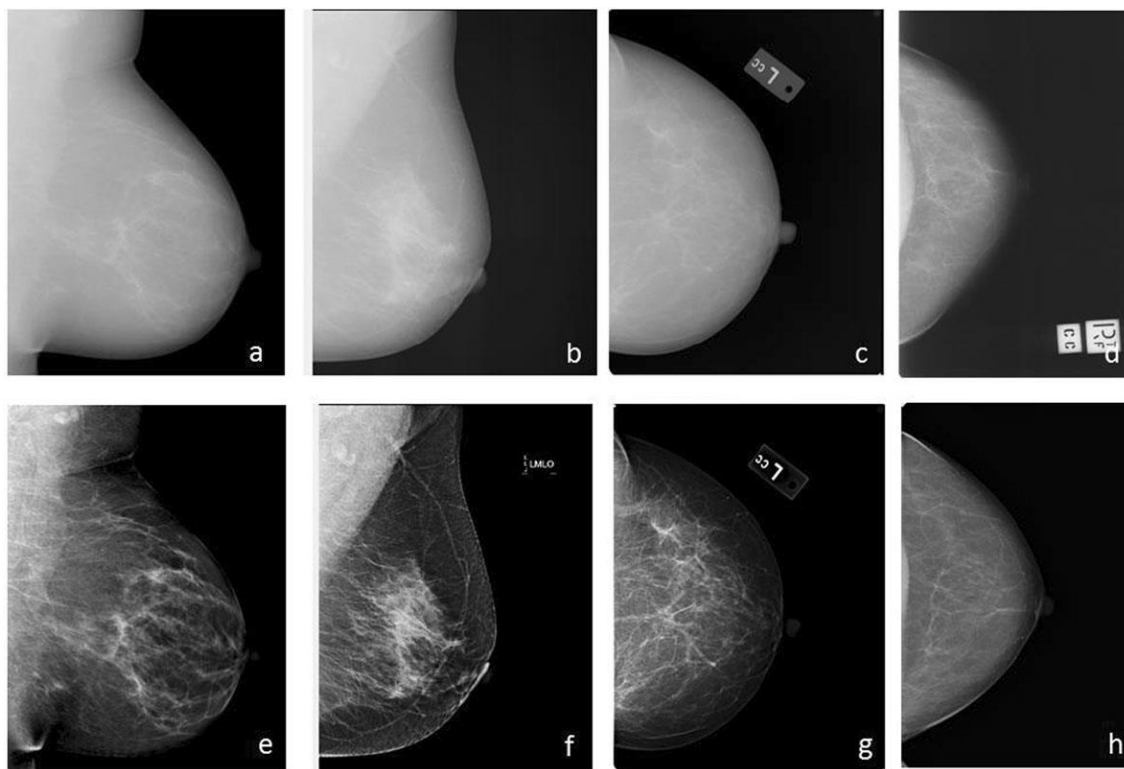


Figura 11. Mamografias não processadas (a-d) e após o processamento em diferentes equipamentos (e-h) (Burton et al., 2016)

Após o processamento, a imagem está pronta para ser utilizada no diagnóstico médico. Esta pode ser impressa ou mesmo arquivada, podendo ser visualizada em qualquer ponto de acesso do sistema computacional da instituição (Rowlands, 2002).

Neste estudo, o sistema CR empregado é da Agfa modelo CR85-X. Exames de mamografia de 48 pacientes foram utilizados para estimar o VDM em imagens processadas.

3.3. BI-RADS

Breast Imaging Reporting and Data System (BI-RADS) é comumente utilizada na prática clínica para relatar de forma qualitativa a densidade mamográfica (Nicholson

et al., 2006). Este método é utilizado de maneira a padronizar a terminologia da avaliação de mamografia (Orel et al., 1999). A 4ª edição do BI-RADS é definida em quatro categorias de composição mamária: predominantemente adiposa (menor que 25% de tecido glandular), parcialmente adiposa (entre 26 a 50% de tecido glandular), padrão denso e heterogêneo (entre 51 a 75% de tecido glandular) e muito denso (mais que 76% de tecido glandular) (Nicholson et al., 2006).

Em sua 5ª edição, o BI-RADS classifica a composição das mamas da seguinte maneira: (a) mamas predominantemente adiposas; (b) mamas com áreas dispersas de densidade fibroglandular; (c) mamas heterogeneamente densas, o que pode obscurecer pequenas massas; (d) a mama é extremamente densa, o que diminui a sensibilidade da mamografia (Sickles et al., 2013). Exemplos desta classificação podem ser observados na Figura 12.

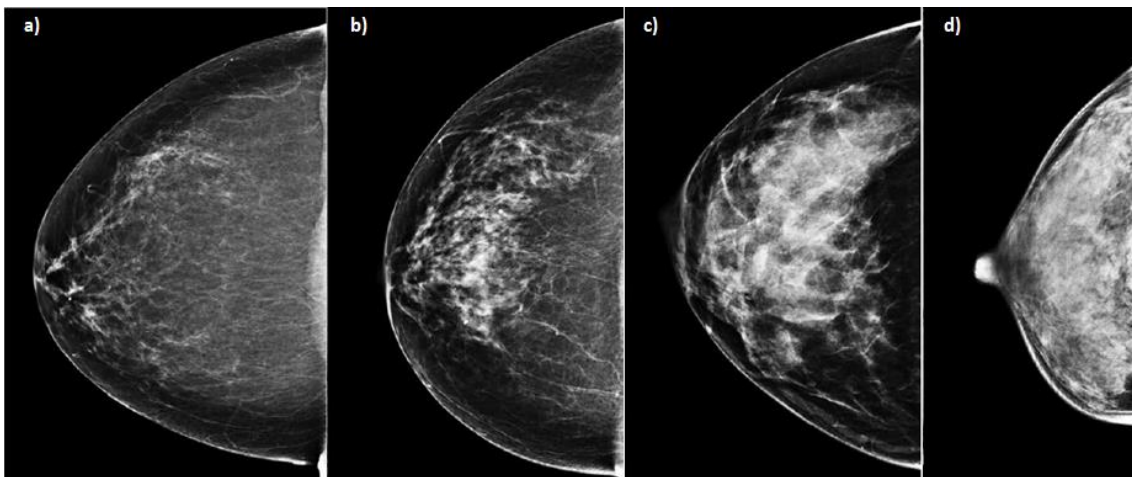


Figura 12. Classificação da 5ª edição do BI-RADS com relação a glandularidade da mama. a) A mama é predominantemente adiposa, sendo possível visualizar pouco tecido fibroglandular; b) Existem áreas dispersas de densidade fibroglandular; c) a mama é heterogeneamente densa, o que pode obscurecer pequenas massas; d) a mama é extremamente densa, o que diminui a sensibilidade da mamografia (Sickles et al., 2013).

Estudos mostram que o BI-RADS possui grande potencial para ser usado como modelo de avaliação do risco de desenvolver câncer de mama (Nicholson et al., 2006). Entretanto, esta forma qualitativa mostra-se muito variável intra e inter-observador (Seo et al., 2013).

Neste estudo, os valores de quantificação da área de tecido fibroglandular obtidos através da quantificação pela mamografia serão comparados ao método de classificação qualitativo BI-RADS 4ª edição associado a cada exame de mamografia, como descrito no Capítulo 5.

3.4. Processamento de Imagens digitais

Uma imagem pode ser definida como uma função bidimensional, $f(x,y)$, em que x e y são coordenadas espaciais (plano), e o valor de f em qualquer par de coordenadas (x,y) é chamado de intensidade ou nível de cinza da imagem neste ponto. Quando x e y e os valores de intensidade de f são quantidades finitas e discretas, temos uma imagem digital. Neste caso, cada elemento da imagem é chamado de pixel (Gonzalez and Woods, 2008, Bovik, 2005).

Para a geração de imagens digitais a partir de dados capturados por sensores (dados reais), é necessária a conversão de dados contínuos que foram capturados para o formato digital (Gonzalez and Woods, 2008). Para converter uma imagem contínua ao formato digital, tem-se que fazer a amostragem da função em ambas as coordenadas e na amplitude. A digitalização dos valores de coordenada é chamado de amostragem, enquanto a digitalização dos valores de amplitude é chamada de quantização (Gonzalez and Woods, 2008, Bovik, 2005).

Na prática, o método de amostragem é determinado pelo arranjo de sensores utilizados para gerar a imagem. Quando uma matriz de sensores é utilizada para a aquisição da imagem, como ilustra a Figura 13, a qualidade da imagem digital é claramente determinada, em grande parte, pelo número de amostras e de níveis discretos de intensidade utilizados na amostragem e quantização (Gonzalez and Woods, 2008).

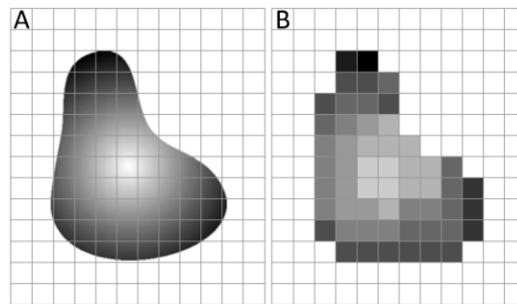


Figura 13. (A) Imagem contínua projetada em uma matriz de sensores. (B) Resultado da amostragem e quantização da imagem.

O campo de processamento de imagens digitais se refere a manipulação de uma imagem por um computador de modo que a saída do processo seja uma imagem com diferentes características, de acordo com a necessidade do usuário (Gonzalez and Woods, 2008). Portanto, o termo processamento de imagens é geralmente aplicado aos métodos que recebem uma imagem como entrada e geram uma imagem modificada (realçando características), medidas (analisando regiões de interesse) ou classificações (auxiliando a percepção visual humana) como saída (Zarinbal and Zarandi, 2014).

Desta forma, os métodos de processamento de imagem têm por objetivo melhorar a aparência visual de uma imagem ou converter a imagem em uma forma mais adequada para uma análise por humanos ou máquinas. No entanto, não há um método padrão para as propostas de processamento de imagem, necessitando, portanto, de uma combinação

de técnicas para cada objetivo desejado e cada tipo de imagem a se trabalhar (Zarinbal and Zarandi, 2014).

A segmentação de imagens desempenha um papel importante em processamento de imagens (Lin et al., 2006), a qual compreende um processo de separação entre objetos e o fundo. Desta forma, a segmentação divide a imagem em diferentes regiões, de modo que cada região seja homogênea em relação a alguma propriedade, tal como o valor do pixel ou textura (Roerdink and Meijster, 2000, Khokher et al., 2012). Um exemplo de deste processo é apresentado na Figura 14, onde a imagem inicial (Figura 14a) é segmentada em três grupos (Figura 14b). Cada um dos grupos possui uma quantidade de tecido fibroglandular, sendo que o primeiro possui 0% e é representado pela cor vermelha na Figura 14c. Os outros dois grupos são compostos por 50% e 100% de tecido fibroglandular e estão representados pelas cores amarelo e branca na Figura 14c, respectivamente.

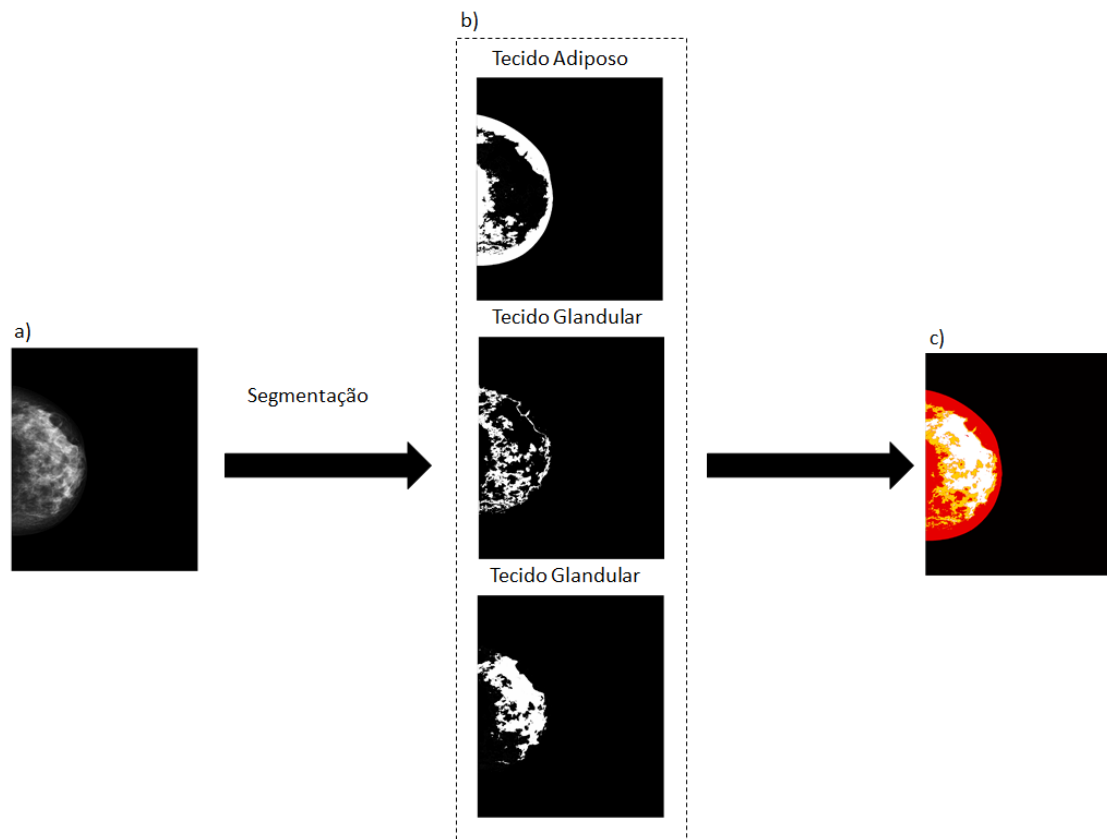


Figura 14. Exemplo de um processo de segmentação. a) Imagem original; b) Máscara representando tecidos adiposo e glandular; c) Imagem original após segmentação dos tecidos glandular (representando em amarelo e branco) e adiposo (representado em vermelho).

3.4.1. Limiarização

Em virtude de suas propriedades intuitivas, a simplicidade de implementação e a velocidade computacional, a limiarização de imagens tem uma posição central nas aplicações de processamento de imagem, principalmente em abordagens de segmentação. Este processo consiste em separar as intensidades de cinza de uma imagem. Determina-se um valor de intensidade de cinza, chamado de limiar, que separa as partes da imagem de acordo com os valores dos pixels. Desta forma, qualquer pixel com valor maior que o limiar é chamado de ponto do objeto. Em contrapartida, qualquer pixel com valor menor que o limiar é chamado de ponto de fundo. Isto pode ser exemplificado na Equação 1 (Gonzalez and Woods, 2008, Bovik, 2005):

$$g(x,y) = \begin{cases} 1 & \text{se } f(x,y) > \text{limiar} \\ 0 & \text{se } f(x,y) < \text{limiar} \end{cases} \quad (1)$$

Onde $g(x,y)$ representa os pixels da imagem limiarizada e $f(x,y)$ representa os pixels da imagem original. A Figura 15 apresenta um exemplo de um processo de limiarização, a fim de separar as regiões de ar e de tecidos biológicos. A Figura 15a ilustra uma imagem de um corte tomográfico. A Figura 15b mostra o histograma desta imagem e o valor de limiar utilizado no processo. Após o processo de limiarização, a imagem final (Figura 15c) representa as regiões de ar em preto, com valor de pixel igual a zero, e as regiões de tecido biológico em branco, com valor de pixel igual a um.

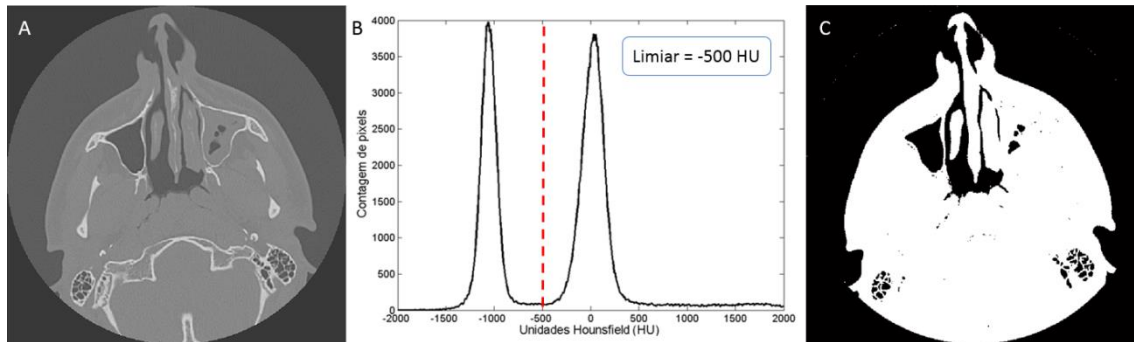


Figura 15. Exemplo do processo de limiarização. (A) Imagem original. (B) Histograma da imagem original, ilustrando o valor de limiar de -500 unidades Hounsfield (HU). (C) Imagem limiarizada, representando as regiões de ar em preto, com valor de pixel igual a zero, e as regiões de tecido biológico em branco, com valor de pixel igual a um.

Quando as distribuições de intensidades dos pixels do fundo e dos objetos são suficientemente diferentes, é possível utilizar um único limiar aplicável a toda a imagem, sendo denominado como limiar global. No entanto, em alguns casos específicos é necessário utilizar uma limiarização variável, onde o valor do limiar muda ao longo da imagem. O uso destes limiares depende do tipo de imagem a se trabalhar e da região a ser segmentada (Gonzalez and Woods, 2008).

Neste estudo foram utilizadas técnicas de limiarização em diferentes etapas do algoritmo, a fim de segmentar diferentes tecidos biológicos. Para isto, diferentes valores de limiar foram estabelecidos, a fim de se obter limiares globais para cada segmentação desejada.

3.4.2. Operadores Morfológicos

A morfologia matemática corresponde a um amplo conjunto de operações de processamento de imagens baseadas em formatos (Gonzalez and Woods, 2008, Haralick et al., 1987, Vincent, 1989, Maragos, 1996). Operadores morfológicos aplicam um elemento estruturante à uma imagem de entrada, criando uma imagem de saída do mesmo tamanho (Haralick et al., 1987, Gonzalez and Woods, 2008). Numa operação morfológica, o valor de cada pixel na imagem de saída é baseada numa comparação entre o pixel correspondente na imagem de entrada com os seus vizinhos. Ao escolher o tamanho e formato da vizinhança, é possível construir uma operação morfológica que é sensível às formas específicas na imagem de entrada (Haralick et al., 1987, Bai, 2013).

Os operadores morfológicos mais básicos são a dilatação e erosão. Dilatação acrescenta pixels para os limites dos objetos em uma imagem, enquanto a erosão remove pixels nos limites do objeto. A regra utilizada para processar os pixels define a operação como uma dilatação ou uma erosão (Haralick et al., 1987, Gonzalez and Woods, 2008, Vincent, 1989).

Com a combinação destes operadores, tem-se a operação conhecida como abertura, a qual geralmente suaviza o contorno de um objeto, rompe os istmos e elimina as saliências finais, como exemplificado na Figura 16.

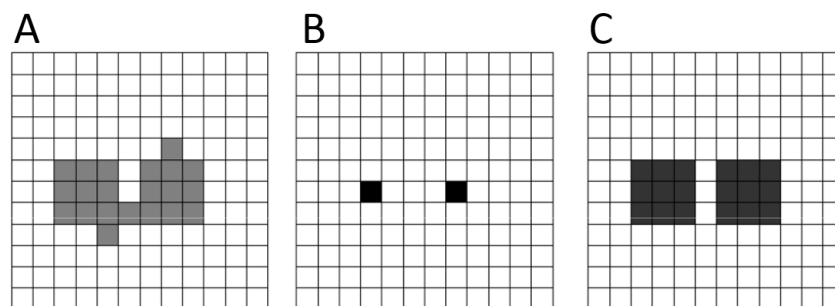


Figura 16. Exemplo da operação de abertura. (A) Imagem original. (B) Imagem após processo de erosão. (C) Imagem após processo de erosão seguido de dilatação, concluindo o processo de abertura.

A operação de fechamento também tende a suavizar contorno, mas, ao contrário da abertura, geralmente funde as descontinuidades estreitas, elimina pequenos buracos e preenche as lacunas em um contorno. Isto pode ser visualizado na Figura 17.

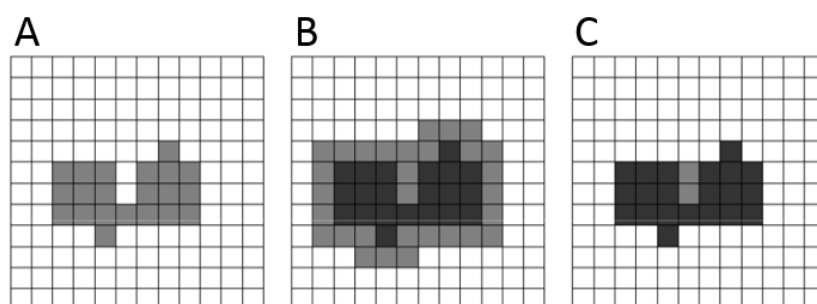


Figura 17. Exemplo da operação de fechamento. (A) Imagem original. (B) Imagem após processo de dilatação. (C) Imagem após processo de dilatação seguido de erosão, concluindo o processo de fechamento.

Neste estudo, operadores morfológicos foram utilizados na remoção de pequenas áreas erroneamente segmentadas, bem como no preenchimento de descontinuidades presentes nas estruturas avaliadas.

3.4.3. Segmentação por Fuzzy

Fuzzy C-means (FCM) clustering é uma técnica que tem sido aplicada com sucesso na segmentação de imagens (Chuang et al., 2006). Uma imagem pode ser

representada por vários grupos de característica (Chuang et al., 2006). O algoritmo FCM classifica a imagem através de agrupamentos de pixels, os quais possuem dados semelhantes, em um espaço (Chuang et al., 2006). Tal método de agrupamento permite que um único pixel pertença a mais de um grupo de características (Kannan et al., 2011). Esta aglomeração é realizada por minimização iterativa de uma função, como mostra a Equação 2 (Kannan et al., 2011, Chuang et al., 2006, Kang et al., 2009), a qual é dependente da distância entre os pixels e os centros dos grupos de características.

$$J_m = \sum_{i=1}^N \sum_{j=1}^C \mu_{ij}^m \|x_i - c_j\|^2, 1 \leq m < \infty \quad (2)$$

Onde m é qualquer número real maior que 1, μ_{ij} é o grau de pertinência de x_i no grupo j , x_i é o i -ésimo dado mensurado na dimensão d , c_j é o centro da dimensão d do grupo, e $\|\cdot\|$ é qualquer norma que expressa a similaridade entre quaisquer dados medidos e o centro. Partição *fuzzy* é realizada através de uma otimização iterativa da função mostrada acima, com a atualização da função de pertinência μ_{ij} e os centros dos grupos c_j , dados pela Equação 3 (Kannan et al., 2011, Chuang et al., 2006, Kang et al., 2009):

$$\mu_{ij} = \frac{1}{\sum_{k=1}^C \left(\frac{\|x_i - c_j\|}{\|x_i - c_k\|} \right)^{\frac{2}{m-1}}}, \quad \text{e} \quad c_j = \frac{\sum_{i=1}^N \mu_{ij}^m \cdot x_i}{\sum_{i=1}^N \mu_{ij}^m} \quad (3)$$

Esta iteração vai parar quando $\max_{ij} \left| \mu_{ij}^{(k+1)} - \mu_{ij}^{(k)} \right| < \varepsilon$, onde ε é o critério de parada entre 0 e 1, e k são os passos da iteração. Este procedimento converge para um mínimo local ou um ponto de sela de J_m (Kannan et al., 2011).

Este estudo utilizou um método baseado no FCM para segmentar os tecidos presentes na mama através de imagens de mamografia por sistema CR. Conforme a literatura mostra, este é um método amplamente utilizado para segmentação de imagens

médicas (Kang et al., 2009, Nie et al., 2008, Ahmed et al., 2002, Keller et al., 2012). No caso de imagens mamográficas, alguns estudos têm utilizado técnicas de limiarização e gradiente, porém resultam em classificação errônea de alguns pixels, fazendo da técnica FCM um método decididamente apropriado para segmentação (Wirth et al., 2004).

3.4.4. Estimativa de volume por SDNR

A SDNR (do inglês, *Signal difference to Noise Ratio*) é definida como a capacidade de detecção de um objeto com relação a um fundo (BG- do inglês *background*) (Bernhardt et al., 2006). Esta técnica é utilizada para descrever a magnitude relativa de informações úteis e o ruído que prejudica a detecção desta diferença (Wu et al., 2013). A SDNR é definida como a razão entre a diferença do sinal médio de um objeto de interesse (u_{obj}) e o BG (u_{BG}), e o desvio padrão do ruído no BG (σ_{BG}) como mostra Equação 4 (Wu et al., 2013, Bernhardt et al., 2006, Bloomquist et al., 2011):

$$SDNR = \frac{u_{obj} - u_{BG}}{\sigma_{BG}} \quad (4)$$

Esta definição tem a vantagem de ser independente das rotinas de processamento de imagens lineares, tal como a mudança da janela de contraste (Bernhardt et al., 2006, Kruger, 2000). O parâmetro SDNR tem sido utilizado para comparar e avaliar a capacidade de discriminar diferentes tecidos (Kruger, 2000). A literatura mostra que a medida de SDNR já foi usada com sucesso para estimar o volume de estruturas anatômicas em imagens bidimensionais (Giacomini et al., 2015).

No presente trabalho, o SDNR foi medido nas imagens de mamografia de pacientes e de fantoma, de modo a diferenciar o tecido fibroglandular e tecido adiposo,

sendo este último utilizado como BG. A partir de relação dos valores obtidos no fantoma, foi estimada a espessura dos tecidos em questão, permitindo, portanto, quantificar o volume de DM no exame. Esta metodologia permitiu estimar a PDM na mamografia e está descrita com detalhes no Capítulo 6.

3.5. Avaliação Gradativa Visual

Alguns métodos vêm sendo utilizados para avaliar se o sistema de imagem radiográfica ou a técnica utilizada produzem imagens com qualidade, dada uma dose específica. Um deles é o método de Avaliação Gradativa Visual (AGV) (Tingberg et al., 2005), o qual consiste na classificação gradativa visual pelo observador de estruturas importantes para um diagnóstico médico seguro. Desta forma, o observador tem liberdade para declarar sua opinião sobre a qualidade da imagem. Tal avaliação pode ser realizada de modo absoluta ou relativa.

Na escala absoluta o observador classifica a visibilidade de uma dada estrutura sem comparar a imagem com uma de referência. Frequentemente consiste de uma escala de quatro a cinco passos, a qual varia de “muito bom” até “muito ruim” (Bath and Mansson, 2007).

Na escala relativa da AGV o observador compara a imagem a ser classificada com uma imagem de referência, previamente determinada. Neste caso o observador confere um *score* declarando a visibilidade relativa da estrutura. Normalmente consiste de uma escala de cinco passos, o qual varia de “muito pior” até “muito melhor” (Tingberg et al., 2005, Bath and Mansson, 2007, Sund et al., 2004).

No método de AGV um observador avalia vários critérios pré-estabelecidos na imagem, onde cada critério recebe um *score*. A fim de se reduzir uma avaliação tendenciosa de um único radiologista, o método de AGV permite que mais de um radiologista classifique os mesmos critérios da imagem. Desta forma, a partir da Equação 5, um único *score* é atribuído à imagem em questão (Tingberg et al., 2005, Bath and Mansson, 2007, Sund et al., 2004, Precht et al., 2013).

$$AGV = \frac{\sum_{O,C} S_{O,C}}{N_O N_C} \quad (5)$$

Onde:

$S_{O,C}$ é o score individual para o observador O, e o critério de imagem C;

N_O é o número total de observadores e

N_C é o número total de critérios na imagem (Precht et al., 2013).

Nesta pesquisa, um dos passos do algoritmo é realçar a imagem mamográfica, como descrito no Capítulo 4. A AGV foi utilizada para comparar a imagem original de mamografia e a imagem realçada pelo método desenvolvido.

3.6. Visão geral do estudo

Com o objetivo de estimar a PDM em mamografias por sistema CR, este estudo foi realizado em diferentes etapas:

- 1) Realce da região periférica da imagem mamográfica – Descrito no Capítulo 4;
- 2) Quantificação da área de tecido fibroglandular e a comparação com o sistema BI-RADS 4ª edição – Descrito no Capítulo 5;

3) Quantificação da PDM e validação com quantificação dos tecidos a partir de exames de ressonância magnética (*ground-truth*) – Descrito no Capítulo 5;

Capítulo 4

4. *Enhancement of breast periphery region in digital mammography*

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Enhancement of breast periphery region in digital mammography

Ana Luiza Menegatti Pavan, Antoine Vacavant, Andre Petean Trindade, Caio Cesar Quini, Diana Rodrigues de Pina

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SPIE.

Event: SPIE Medical Imaging, 2018, Houston, Texas, United States

Enhancement of Breast Periphery Region in Digital Mammography

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ABSTRACT

Volumetric breast density has been shown to be one of the strongest risk factor for breast cancer diagnosis. This metric can be estimated using digital mammograms. During mammography acquisition, breast is compressed and part of it loses contact with the paddle, resulting in an uncompressed region in periphery with thickness variation. Therefore, reliable density estimation in the breast periphery region is a problem, which affects the accuracy of volumetric breast density measurement. The aim of this study was to enhance breast periphery to solve the problem of thickness variation. Herein, we present an automatic algorithm to correct breast periphery thickness without changing pixel value from internal breast region. The correction pixel values from periphery was based on mean values over iso-distance lines from the breast skin-line using only adipose tissue information. The algorithm detects automatically the periphery region where thickness should be corrected. A correction factor was applied in breast periphery image to enhance the region. We also compare our contribution with two other algorithms from state-of-the-art, and we show its accuracy by means of different quality measures. Experienced radiologists subjectively evaluated resulting images from the three methods in relation to original mammogram. The mean pixel value, skewness and kurtosis from histogram of the three methods were used as comparison metric. As a result, the methodology presented herein showed to be a good approach to be performed before calculating volumetric breast density.

Keywords: Mammography, peripheral enhancement, thickness correction, image processing

1. INTRODUCTION

Estimation of volumetric breast density (VBD) has been widely discussed in the recent literature [1-7]. Fibroglandular tissue in the breast is represented as radiographically dense tissue on a mammogram [8-10]. VBD has been shown to be one of the strongest risk factors for breast cancer diagnosis [4, 8, 9], which is being used to personalize preventive and screening strategies for women [4, 11, 12]. Women with high breast density have increased risk of developing breast cancer in twofold to sixfold compared to women with low breast density [5, 8, 13, 14].

Digital mammography introduction has made feasible to develop automated volumetric methods [5, 15, 16]. To do so, accurate knowledge of tissue thickness at each pixel in mammogram is necessary [5, 7, 16]. However, volumetric methods are highly sensitive to the breast thickness [16-18]. This is particularly difficult to estimate at the breast periphery [5, 19]. During mammography acquisition, breast is compressed and part of it loses contact with the paddle [7, 17], resulting in an uncompressed region in periphery with thickness variation. Differences in pixel intensities in periphery are therefore governed principally by breast thickness [5, 18].

Procedures to correct the non-uniform tissue thickness in mammograms are necessary to accurately estimate VBD [13]. Pre-processing techniques should be used in mammograms to enhance peripheral areas visibility and improve intensity distribution [20]. Studies show the development of algorithms to identify the peripheral region on mammogram and to correct overexposed area [13, 17, 21, 22]. In the literature this approach has been called as thickness equalization or peripheral enhancement [22].

The different methods realizing breast thickness periphery correction may vary in the determination of the correction area and in the used correction factor. Regarding area, algorithms can be either applied to the whole image [13, 23, 24] or just to a region determined by a segmentation algorithm [20-22].

In the first case, as Wang *et al.* method [13], the fitted enhancement curve defines the necessary correction value for each pixel, which is added to the original pixel value to create the processed image. Such an approach applies the thickness correction to the entire breast. It works well with a homogeneous fatty and dense breast but localized artefacts can be seen when a breast exhibits large density variations across the mammogram [20, 21]. As a consequence, these methods may be unappropriated to be used before the VBD measurement. This fact is due to the pixel values of entire breast are altered, even where there is no overexposed problem, which influences in three-dimensional information.

In the second case, as Tortajada *et al.* [21] method, the breast thickness correction is iteratively applied in a region determined by a segmentation algorithm. These methods segment the breast periphery and calculate the correction factor based on periphery neighborhood. The approach works well with adipose and scattered fibroglandular breasts. However, breast with large dense regions near the periphery neighborhood may overestimate the correction factor in first iterations. Since breast periphery is a predominantly adipose region [25], correction factor overestimation may cause a bias in future VBD estimation.

In this study, we present an algorithm that corrects intensities variations in breast periphery using digital mammograms. The aim herein is to implement a new hybrid methodology, which could be used independent of breast size, breast composition and mammographic view. In Section B, we present the developed algorithm. We also compare, in Section C, the results from corrected and uncorrected images with other methodologies of literature.

2. METHODOLOGY

2.1 Dataset

The present study was developed with ethical approval from the authors' institutions under protocol number 50547315.8.0000.5411.

Women aged 18 years or older undergoing screening mammography between 2013 and 2015 at Botucatu Medical School were included. For a woman who has been included in the study, she must have had no previous history of breast cancer or breast surgery, and had a BI-RADS assessment of either 1 or 2 (negative or benign finding, respectively). Only mammography of one side, left or right, was used for each patient in craniocaudal (CC) view, allowing assessment of different breast compositions. Third mammograms were evaluated.

The computed radiography (CR) mammography system used was a Senographe 600T (GE Healthcare, Milwaukee, WI) with a CR-85X image digitizer (Agfa-Gevaert Group, Mortsel, BE). An Agfa image plate (18 × 24 cm²) with a pixel pitch of 50 µm was employed. A Mo/Mo anode/filter combination was used for all X-ray exposures. Processed images were used, since raw data is often not achieved in clinical practice [20].

2.2 Developed Algorithm

The proposed algorithm has been developed in Matlab software to enhance breast periphery region in a mammogram. The algorithm is a fully automatic hybrid method, which uses different image processing techniques. It is based on mean values over iso-distance lines from the breast skin-line. Detailed process is explained in the following subsections.

Preprocessing

In the first stage, a median filter is applied in the mammogram to reduce image noise and to allow good breast edge detection. Then, the mammogram is segmented into the breast area and the background by thresholding, resulting in a mask with the region of interest.

Adipose Tissue Otsu Thresholding

To acquire an image with only adipose tissue, the fibroglandular tissue intensity level is removed from breast area by Otsu thresholding process [26]. To define the Otsu threshold, only the compressed breast area is employed, in order to avoid bias segmentation of pixels from periphery region. Therefore, the breast mask is eroded to estimate the compressed area, as highlighted in white in Fig. 1a. We apply Otsu thresholding technique in the estimated compressed area to define a threshold value [8]. This value is then used to segment fibroglandular tissue in complete breast region, resulting in an image with only adipose tissue area. At this stage, the segmentation of dense tissue is roughly estimated, as shown in Fig. 1b.

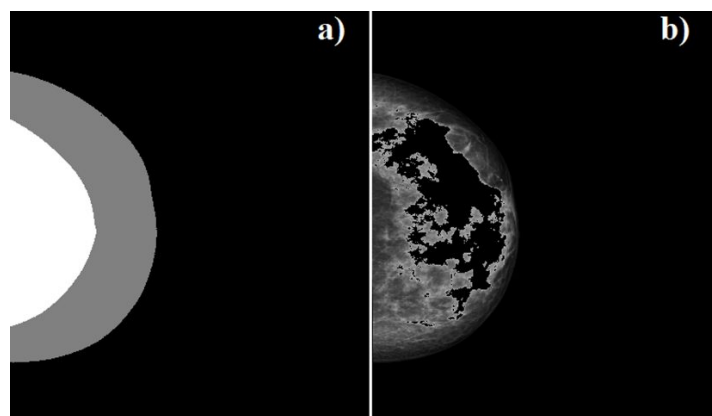


Figure 1. a) Rough estimation of compressed (white) and uncompressed (gray) breast area; b) Adipose tissue after segmentation of fibroglandular tissue by Otsu thresholding.

Distance Mapping

Using the adipose tissue area estimated before, a distance map is generated by calculating the shortest distance from each pixel to the skin-line. Each pixel from adipose tissue area is labeled with its minimum Euclidean distance to the skin-line, as shown in Fig. 2a. Through the distance map, an intensity curve is created based on the average intensity level values that are within the same distances (d) to the skin-line. Therefore, the curve is an approximation of the mean intensity values from pure adipose tissue in relation of d . Fig. 2b shows the intensity curve and its two-term exponential model fit ($M(d)$).

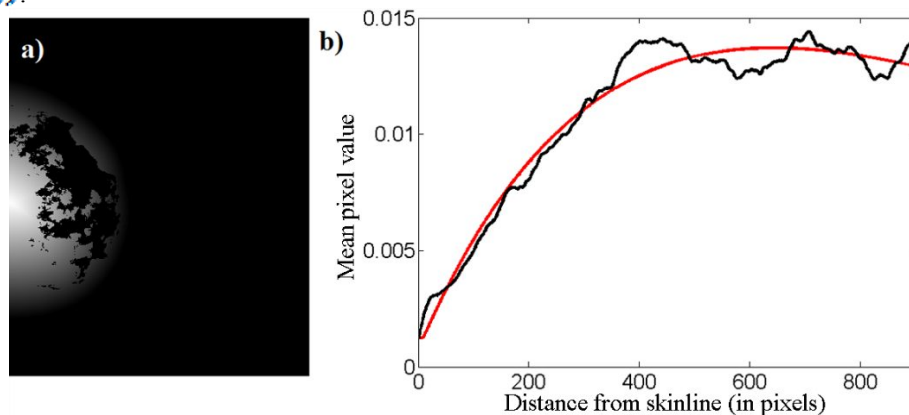


Figure 2. a) Distance map of adipose tissue; b) Intensity curve (black) and its fit (red) for the mean pixel values of adipose tissue.

Identifying Periphery Region

The exponential fit $M(d)$ for adipose tissue area shows that the pixel value from periphery region strongly varies in relation with the distance from skin-line. On the other hand, compressed region has almost constant thickness and,

therefore, intensity values vary slowly. To identify the distance from the skin-line that separates compressed to uncompressed areas, the algorithm calculates the fit's derivate. By the analysis of derivate, the optimum position, which defines the limit between both areas, is defined as the first point in which the derivate is less than 0.1, representing the beginning of a constant value in the fit. Fig. 3a shows the derivate and the selected point (p). Fig. 3b shows an example of segmentation with gray and white areas indicating the compressed and uncompressed regions respectively.

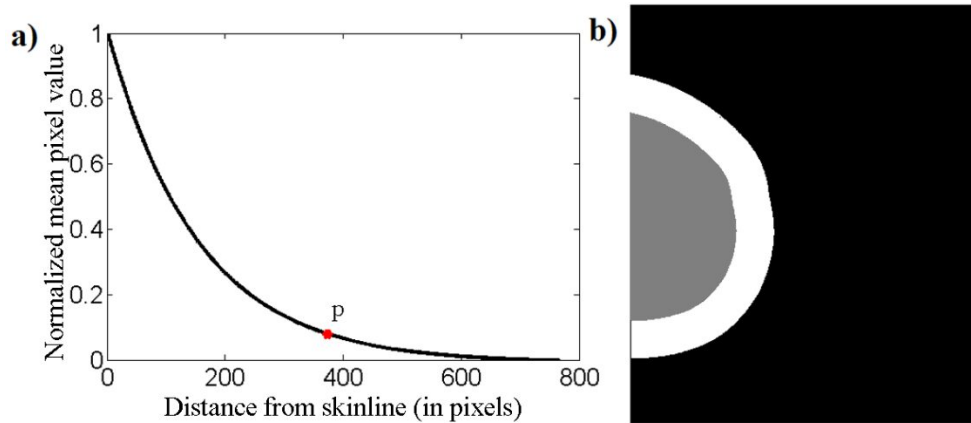


Figure 3. a) Fit's derivate and the point (p) which the derivate is approximately zero; b) Accurately compressed (gray) and uncompressed (white) segmentation regions.

Correction Factor

The periphery area is corrected by using a correction factor. For each distance d within the breast area, a thickness correction factor (CF) was calculated as in:

$$CF(d) = \frac{M_{max}}{M(d)} \quad (1)$$

where M_{max} is the maximal value from $M(d)$.

The CF is then multiplied by each pixel value from the periphery region, allowing enhancement of the area.

Comparison with Other Methods

For the same dataset, periphery enhancement is corrected using our method and compared with the ones proposed by Wang *et al.* [13] and He *et al.* [20], which used screen-film and full field digital mammography, respectively. Therefore, methods were adapted for CR mammograms. For He's method only breast periphery separation and intensity ratio propagation steps were used since our dataset is composed with only CC view. The histogram for images before and after enhancement were evaluated using the three methodologies. Skewness, kurtosis and mean pixel values were also used to compare methods. The values are presented as median and interquartile range. Since all data are nonparametric, we perform paired Wilcoxon signed-rank test to compare the different methods.

A relative visual grading analysis (VGA) was made by three experienced radiologists to compare image quality after periphery correction between the methodologies described in this paper and original mammogram. Radiologists gave a score for each corrected image varying from +2 to -2 to describe image quality in relation to periphery visualization [27, 28]. Positive score means an improvement in image quality, highlighting periphery visualization. Zero score represents that the correction did not change the periphery visualization relative to the original image, preserving original image quality. A negative score means a reduction of image quality when compared with original mammogram. In this case,

even with better visualization of breast periphery, a global analysis of image quality, reveals to be worse than original one. A resulting score was achieved by summing all scores and dividing by the number of observers (radiologists) and the number of assessed images for each observer [27, 28]. For the purpose of this work, radiologists were not allowed to window image contrast.

3. RESULTS

Fig. 4 shows comparison between original (without periphery enhancement- Fig. 4a-c) and enhanced images by the proposed (Fig. 4d-f), Wang, *et al.* (Fig. 4g-i) and He, *et al.* (Fig. 4j-l) methods, respectively. Images are represented for the same window width and center contrast adjustments.

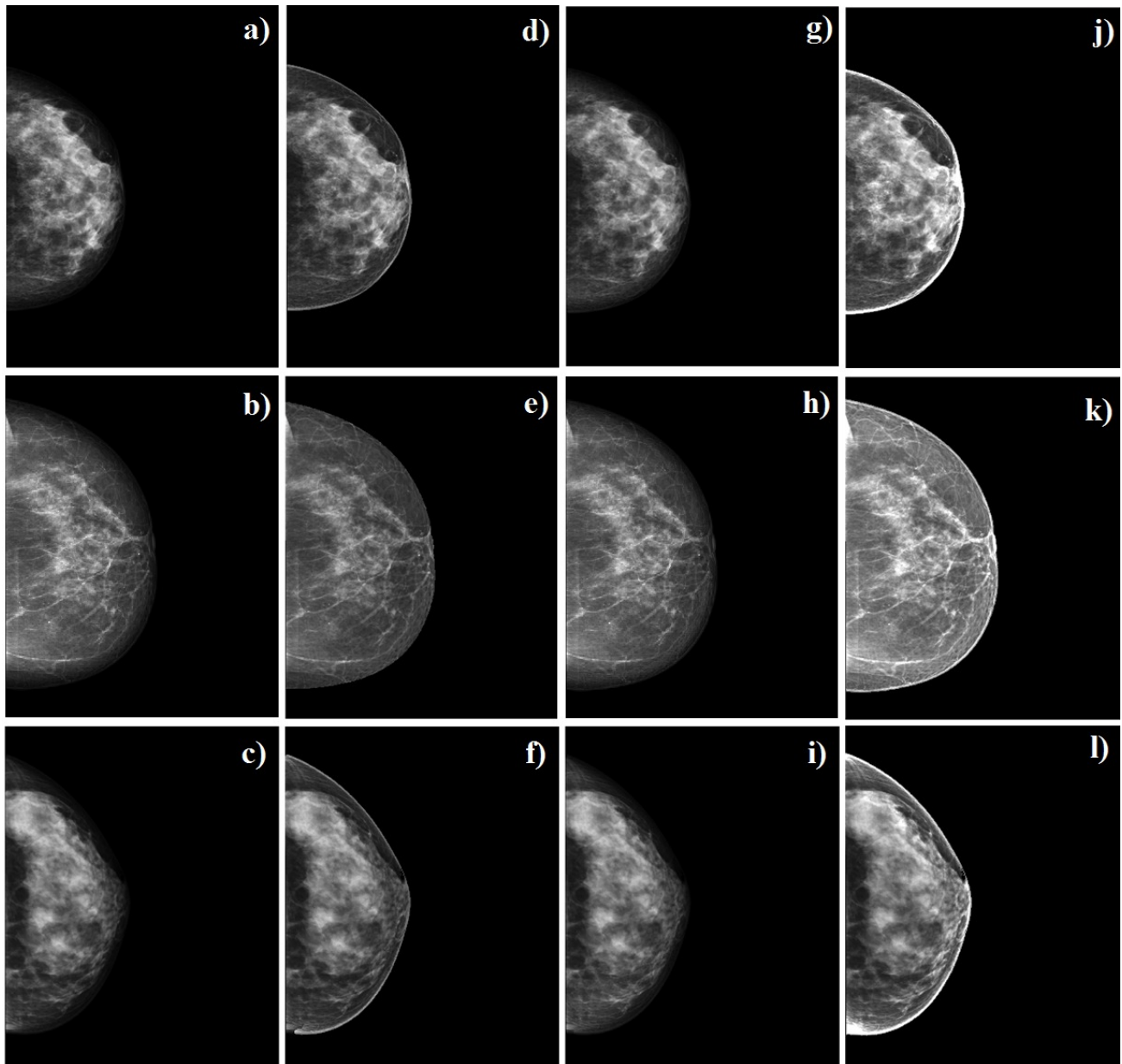


Figure 4. a-c) Original images; Breast periphery correction by d-f) the proposed, g-i) Wang, *et al.* and j-l) He, *et al.* methods.

Fig. 5 shows examples of histograms from images of Fig. 4. In Fig. 5 d-f histograms for original mammogram (Fig. 4a-c) are represented by black line, for the proposed (Fig. 4d-f) are represented by red line, Wang *et al.* (Fig. 4g-i) are represented by blue line and He *et al.* (Fig. 4j-l) are represented by green line.

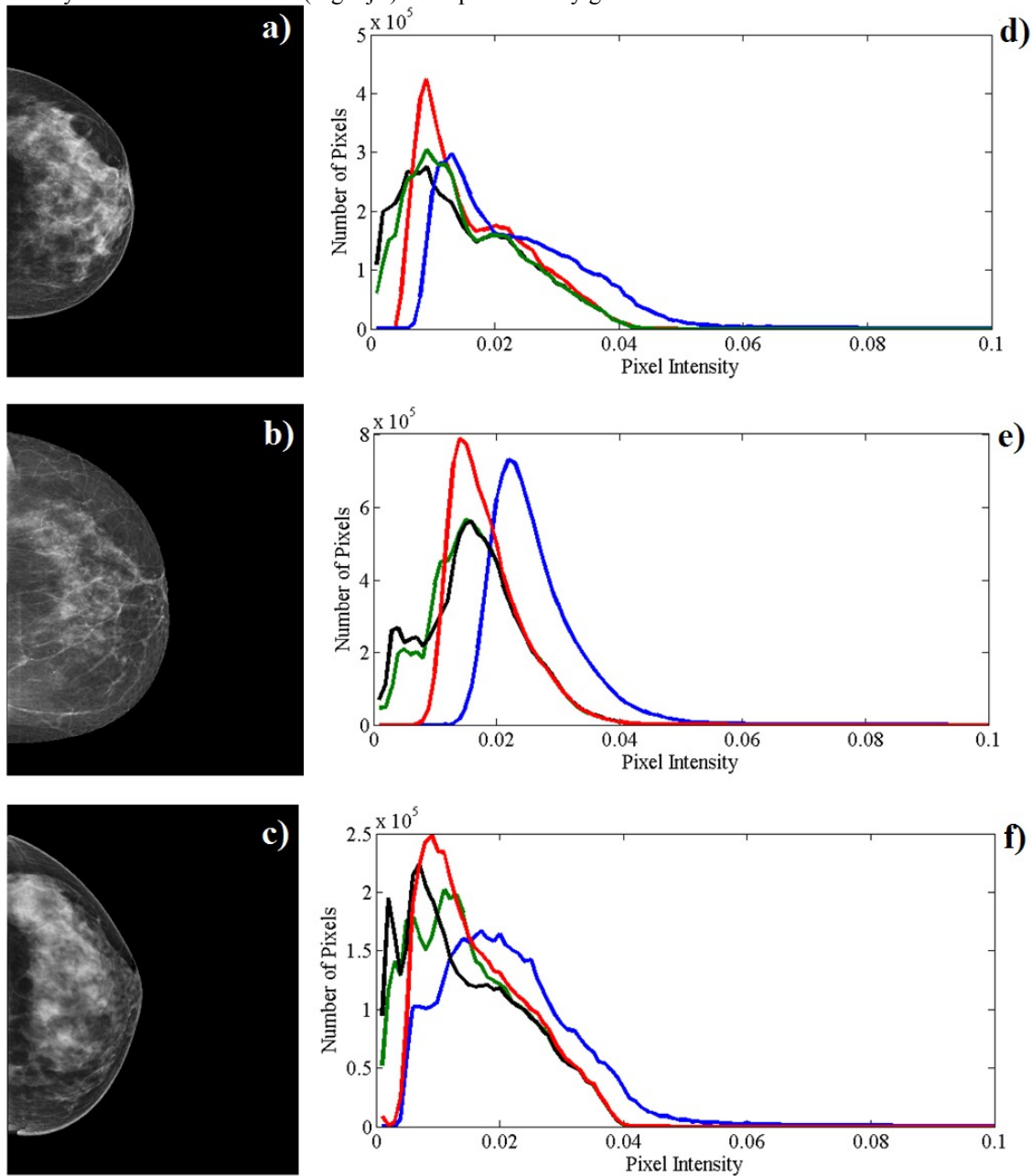


Figure 5. a-c) Example of images used to acquire histograms; d-f) Comparison of histograms between original image (black), proposed (red), Wang *et al.* (blue) and He *et al.* (green) methods.

Table 1 shows comparison between methods in relation of mean pixel value, skewness and kurtosis for 30 assessed mammograms. Different letters indicate statistical difference ($p < 0.05$).

Table 1. Results of mean pixel value, skewness and kurtosis for the proposed, Wang and He methods.

	Original	Proposed Method	Wang	He
Mean pixel value ($\times 10^{-3}$)	15.67 (14.88 – 16.68) ^a	16.86 (16.23 – 18.15) ^b	24.02 (23.11 – 29.98) ^c	16.02 (15.22 – 17.03) ^d
Skewness	0.92 (0.41 – 1.30) ^a	1.41 (1.05 – 1.79) ^b	1.55 (1.11 – 1.78) ^b	0.99 (0.51 – 1.50) ^a
Kurtosis	2.80 (2.12 – 3.86) ^a	3.85 (2.83 – 5.02) ^b	4.04 (3.03 – 4.82) ^b	2.69 (1.98 – 4.76) ^a

As a result of radiologists visual assessment, the final VGA score was +1.5, -0.3 and +0.7 for our, Wang and He methodologies respectively. All images had better visualization of periphery area when compared with original mammogram

4. DISCUSSION

We have developed a methodology for digital mammogram thickness periphery correction to be used in future work of VDB estimation. Our automatic approach combines different image processing techniques, such as morphological operators, thresholding and distance mapping, to define a valid correction factor. The correction factor is used to enhance breast periphery without changing pixel value of the compressed breast region.

Fig. 4 shows an example of original and enhanced images, which are realized by the proposed, Wang and He methods. By radiologists visual assessment all images had better visualization of periphery area when compared with original mammogram. Subjective examination of processed images by the proposed method (Fig. 4d-f) reveals a good enhanced image presentation with structural information remaining unaltered by the correction algorithms, resulting in a VGA score near to the maximum value. This is due to correction factor is applied only in breast periphery. Using the method of He *et al.* to compare with original mammograms, radiologists describe moderated improvement of peripheral area. Although images corrected by this method were slightly better, the correction factor was not sufficient to correct all periphery area resulting in a VGA score of 0.7. This can be seen in Fig. 4g-i, since periphery area presents a gradient, resulting in lower correction near skin-line. In fibroglandular breasts cases, it is possible to notice intensity overestimation of pixels located close to frontier between compressed and uncompressed areas. By analyses of Fig. 4j-l, it can be seen that periphery is corrected. Nevertheless, radiologists reported a degradation of image contrast in area near to chest wall since pixels from compressed area were also multiplied by the correction factor resulting in higher intensity values. Therefore, although the periphery was better visualized in corrected image using Wang method, image quality from breast compressed area was worse, resulting in a negative VGA score of -0.3.

Fig. 5 shows examples of histograms for evaluated images in Fig. 4, for original image and after periphery enhancement realized by the three methods. Comparing the histogram from proposed method with the original, we may notice that the profile of histograms has almost the same shape for high pixel values. Histogram from proposed method is condensed to a smaller range of intensity values. This is due to pixels from periphery breast region (i.e. overexposed) that have been gathered to a central part of histogram after correction. Therefore, overexposed pixels are reallocated obtaining a more adipose homogeneous intensity distribution. Furthermore, the maximum pixel value of histogram was maintained. The histogram's shape from processed image by He method is also quite similar to the original. However, there are still low intensity pixels, which were not correctly corrected. This occurs due to the used correction factor losing power each iteration and, therefore, pixels near skin-line are multiplied by a low correction factor. Blue lines of Fig. 5 shows that the entire histograms are displaced to the right when using the Wang correction method. This modifies both the shape and the maximum pixel value of histogram.

Table I shows that the phenomenon illustrated in Fig. 5 is maintained in all assessed images. For the mean pixel value, all methods are statically different. However, for the proposed and He methods, the mean pixel value has a proximate value from the original (around 7% and 2% greater than the original value, respectively) because only periphery area is corrected. Wang method has a higher mean value (around 50% greater than the original value), due to its use of a correction factor in the entire breast region, not only in the periphery area.

Analyzing skewness and kurtosis values, the Table I shows that proposed and Wang methods are significantly different from original value. However, no differences were found between them. He method showed no differences when compared with original image.

The skewness measures how asymmetric the histogram is, 0 being a totally symmetric distribution [21]. Negative or positive values for slope indicate histograms that are inclined to the left or to the right, respectively. The presented skewness values agree with observed behavior in Fig. 5. For proposed and Wang methods, the median skewness is greater than the original value, which is due to the histogram of the processed image to be slightly skewed to the right. For the Wang method, the median skewness is higher, since all pixels in the image are corrected, inclining the histogram on the right.

The kurtosis measures how wide the peak is. Positive or negative kurtosis indicates a "heavy-tailed" or "light-tailed" distribution, respectively [21]. The presented kurtosis values from Table I also agree with observed behavior in Fig. 5. For proposed and Wang methods, the median kurtosis is greater than the original value, which is due to the histogram of the processed image to present a greater number of pixels in a smaller range of intensity values, i.e. a wide peak.

Skewness and kurtosis using He method are similar to the original image, because of pixels near to skin-line were not efficiency enhanced resulting in subtle changes in histogram.

Although the proposed method presents some advantages over the ones in literature, the aim of the work was to compare it with widely used methods, since no ground truth is available. We have shown that the proposed method is accurate and robust to automatically perform the enhancement of periphery breast region. The method presented herein fits enhancement curve based exclusively on adipose tissue of distance map, since the adipose tissue in compressed region is basically homogeneous and variations in the pixel values of periphery are governed by the breast thickness [5]. The fit is used to calculate the correction factor, which is applied in each pixel of uncompressed region. Then, the method is effective even on very dense breasts. Furthermore, the use of distance map allows to speed-up the correction of periphery breast region, since the use of it makes possible to deal with all pixels at the same distance at the same time [21].

5. CONCLUSION

As a conclusion, the methodology presented herein may be used independent of breast size, breast composition and mammographic view. Therefore, the proposed method shows to be a good approach to be performed before calculating VBD, since it does not change the pixel values of the interior breast region.

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REFERENCES

- [1] Alonzo-Proulx, O., Jong, R. A., and Yaffe, M. J., "Volumetric breast density characteristics as determined from digital mammograms," *Phys Med Biol*, 57(22), 7443-57 (2012).
- [2] Wang, J., Azziz, A., Fan, B. *et al.*, "Agreement of mammographic measures of volumetric breast density to MRI," *PLoS One*, 8(12), e81653 (2013).
- [3] Gubern-Merida, A., Kallenberg, M., Platel, B. *et al.*, "Volumetric breast density estimation from full-field digital mammograms: a validation study," *PLoS One*, 9(1), e85952 (2014).

- [4] Eng, A., Gallant, Z., Shepherd, J. *et al.*, "Digital mammographic density and breast cancer risk: a case-control study of six alternative density assessment methods," *Breast Cancer Res*, 16(5), 439 (2014).
- [5] Chen, X., Moschidis, E., Taylor, C. *et al.*, [Improving Mammographic Density Estimation in the Breast Periphery.] Springer International Publishing, Malmö Live, Malmö, Sweden(2016).
- [6] Keller, B. M., Nathan, D. L., Wang, Y. *et al.*, "Estimation of breast percent density in raw and processed full field digital mammography images via adaptive fuzzy c-means clustering and support vector machine segmentation," *Med Phys*, 39(8), 4903-17 (2012).
- [7] Holland, K., Gubern-Merida, A., Mann, R. M. *et al.*, "Optimization of volumetric breast density estimation in digital mammograms," *Phys Med Biol*, 62(9), 3779-3797 (2017).
- [8] Kallenberg, M. G., Lokate, M., van Gils, C. H. *et al.*, "Automatic breast density segmentation: an integration of different approaches," *Phys Med Biol*, 56(9), 2715-29 (2011).
- [9] Assi, V., Warwick, J., Cuzick, J. *et al.*, "Clinical and epidemiological issues in mammographic density," *Nat Rev Clin Oncol*, 9(1), 33-40 (2011).
- [10] Winkler, N. S., Raza, S., Mackesy, M. *et al.*, "Breast density: clinical implications and assessment methods," *Radiographics*, 35(2), 316-24 (2015).
- [11] Schousboe, J. T., Kerlikowske, K., Loh, A. *et al.*, "Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness," *Ann Intern Med*, 155(1), 10-20 (2011).
- [12] Checka, C. M., Chun, J. E., Schnabel, F. R. *et al.*, "The relationship of mammographic density and age: implications for breast cancer screening," *AJR Am J Roentgenol*, 198(3), W292-5 (2012).
- [13] Wang, X. H., Good, W. F., Chapman, B. E. *et al.*, "Automated assessment of the composition of breast tissue revealed on tissue-thickness-corrected mammography," *AJR Am J Roentgenol*, 180(1), 257-62 (2003).
- [14] Li, J., Szekely, L., Eriksson, L. *et al.*, "High-throughput mammographic-density measurement: a tool for risk prediction of breast cancer," *Breast Cancer Res*, 14(4), R114 (2012).
- [15] Kallenberg, M. G., van Gils, C. H., Lokate, M. *et al.*, "Effect of compression paddle tilt correction on volumetric breast density estimation," *Phys Med Biol*, 57(16), 5155-68 (2012).
- [16] Yaffe, M. J., "Mammographic density. Measurement of mammographic density," *Breast Cancer Res*, 10(3), 209 (2008).
- [17] Alonzo-Proulx, O., Mainprize, J. G., Packard, N. J. *et al.*, [Development of a Peripheral Thickness Estimation Method for Volumetric Breast Density Measurements in Mammography Using a 3D Finite Element Breast Model] Springer, Berlin, Heidelberg, Catalonia, Spain(2010).
- [18] van Engeland, S., Snoeren, P. R., Huisman, H. *et al.*, "Volumetric breast density estimation from full-field digital mammograms," *IEEE Trans Med Imaging*, 25(3), 273-82 (2006).
- [19] Alonzo-Proulx, O., Packard, N., Boone, J. M. *et al.*, "Validation of a method for measuring the volumetric breast density from digital mammograms," *Phys Med Biol*, 55(11), 3027-44 (2010).
- [20] He, W., Hogg, P., Juetten, A. *et al.*, "Breast image pre-processing for mammographic tissue segmentation," *Comput Biol Med*, 67, 61-73 (2015).
- [21] Tortajada, M., Oliver, A., Marti, R. *et al.*, "Breast peripheral area correction in digital mammograms," *Comput Biol Med*, 50, 32-40 (2014).
- [22] Snoeren, P., and Karssemeijer, N., "Thickness correction of mammographic images by means of a global parameter model of the compressed breast," *IEEE Trans Med Imaging*, 23(7), 799-806 (2004).
- [23] Bick, U., Giger, M. L., Schmidt, R. A. *et al.*, "Density correction of peripheral breast tissue on digital mammograms," *Radiographics*, 16(6), 1403-11 (1996).
- [24] Byng, J. W., Critten, J. P., and Yaffe, M. J., "Thickness-equalization processing for mammographic images," *Radiology*, 203(2), 564-8 (1997).
- [25] Karssemeijer, N., "Automated classification of parenchymal patterns in mammograms," *Phys Med Biol*, 43(2), 365-78 (1998).
- [26] Otsu, N., "A Threshold Selection Method from Gray-Level Histograms," *IEEE Transactions on Systems, Man, and Cybernetics*, 9(1), 62-66 (1979).
- [27] Precht, H., Tingberg, A., Waaler, D. *et al.*, "New Developed DR Detector Performs Radiographs of Hand, Pelvic and Premature Chest Anatomies at a Lower Radiation Dose and/or a Higher Image Quality," *J Digit Imaging*, (2013).

- [28] Sund, P., Bath, M., Kheddache, S. *et al.*, "Comparison of visual grading analysis and determination of detective quantum efficiency for evaluating system performance in digital chest radiography," *Eur Radiol*, 14(1), 48-58 (2004).

Capítulo 5

***5. Fibroglandular Tissue Quantification in Mammography by
Optimized Fuzzy C-Means with Variable Compactness***

Fibroglandular Tissue Quantification in Mammography by Optimized Fuzzy C-Means with Variable Compactness

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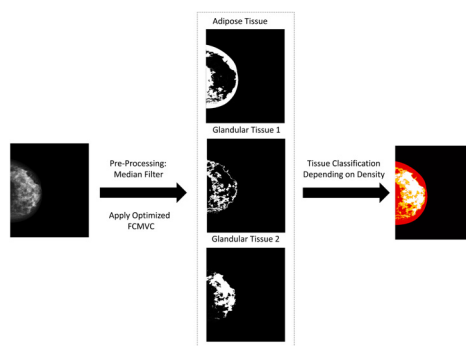
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Graphical abstract



Abstract

Background: Mammography is a worldwide image modality used to diagnose breast cancer, even for asymptomatic women. Due to its large availability, mammograms can be used to measure breast density and to predict cancer development.

Methods: We developed a methodology to estimate breast density using post-processed digital mammogram. Our automatic approach utilizes an optimized Fuzzy C-Means with variable compactness algorithm to classify and quantify fibroglandular tissue in mammograms.

Results: Fibroglandular tissue percentage estimation by our method has been compared with BI-RADS assessment from radiologist and achieved 67.8% of correct classification, with Spearman's correlation coefficient of $\rho = 0.618$, for $p < 0.001$. Furthermore, a Bland–Altman statistics showed no significant differences (bias of -0.20 ± 1.52) between both methods, indicating that the assessment widely used in clinical routine is consistent with the results generated by the algorithms. Cohen's kappa coefficient comparing the performance of the algorithm with the visual assessment for the different BI-RADS scores was 0.47 suggesting a moderate agreement.

Conclusion: Then, our methodology showed to be robust and accurate when compared with visual assessment. Furthermore, our methodology is fully automatic and reproducible, avoiding inter and intra observers variation, which has a potential to be implemented in clinical routine.

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1. Introduction

Breast cancer risk in women may be estimated from her age, history of breast biopsy, family history of breast cancer and breast density on an initial mammogram [1]. Studies have reported that women with increased mammographic density have a four- to six-fold increase in their risk of developing breast cancer [2,3].

In clinical routine, radiologists perform subjective visual assessments based on Breast Imaging Reporting and Data Systems (BI-RADS) density classification [2,3]. This is an important task to follow up patients under prevention therapy. However, BI-RADS density categories have limitations [4]. It has been suggested that subjective assessment of mammographic density shows variable intra- and inter-observer agreement [4, 5]. Furthermore, BI-RADS categories are too coarse to monitor breast density changes in individual women [4]. For this reason, tasks such as selection of women who may benefit from supplemental screening exams and prediction of breast cancer risk, may be challenging with only subjective density assessment [3,6,7].

Therefore, developing quantitative methods of measuring breast density has become a relevant approach, which is less dependent on the observer [3,8]. Fully automatic methods for breast density (BD) measurements have been proposed to accurately quantify mammographic density [3,4,8,9]. The standard method to estimate BD in scientific research is the Cumulus software, which is an area-based approach [7,10]. However, these methods presents problems with accuracy and reproducibility [11]. In addition, these techniques have some limitations, such as dependence on the parameters of image formation, the need of a small calibration object to be imaged in each mammogram, and compressed breast thickness value [9,12,13]. Furthermore, most of these semi-automated methods necessitate an experience user to define a threshold stage, which is time-consuming [5,14] and implies in measurement variability [7].

Area-based and volumetric methods in literature are often applied in raw images. However, most medical centers achieve only the post-processed images for clinical purposes. Therefore, development of methodology to estimate BD in post-processed mammogram would be beneficial both in terms of direct clinical application and retrospective research-related studies [15,16].

An alternative modality for estimating content of tissues involves Magnetic Resonance Imaging (MRI). MRI has the potential to quantify fibroglandular tissue with a much higher degree of accuracy and precision than mammography [2,17] and, therefore, has been used to estimate BD. But MRI is costly, requires intravenous contrast agent administration, has a risk for contrast agent reactions, and is not well tolerated by all patients [6].

Breast is compressed during mammography exam, producing a projection image, which contains a variable combination of fibroglandular and adipose tissues. In general, pixels are neither pure fibroglandular nor pure adipose tissues [2]. Fuzzy C-Means (FCM) approach allows pixels to belong to multi-

ple clusters with reasonable degree of membership grades [18]. Fuzzy C-Means with Variable Compactness (FCMVC) is an extended version of this algorithm, which improves pixel classification, when compared with popular FCM approach. Therefore, fibroglandular and adipose tissue may be classified with greater accuracy.

The aim of this work is to use an optimized FCMVC [19] algorithm to estimate the percentage of BD using digital mammography. The methodology, presented in Section 2, is applied in post-processed mammograms. Section 3 is dedicated to compare the BD results from the proposed algorithm with BI-RADS system, and shows its accuracy and reproducibility.

2. Materials and methods

2.1. Dataset

The present study was developed with ethical approval from the authors' institutions under protocol number 50547315.8. 0000.5411.

Women aged 18 years or older undergoing screening mammography between 2013 and 2015 at Botucatu Medical School were included. For a woman who has been included in the study, she must have had no previous history of breast cancer or breast surgery, and had a BI-RADS assessment of either 1 or 2 (negative or benign finding, respectively). Only mammography of one side, left or right, was used for each patient in craniocaudal view, allowing assessment of different breast compositions. A total of 30 mammograms were evaluated.

The mammography system used was a Senographe 600T (GE Healthcare, Milwaukee, WI) with a CR-85X image digitizer (Agfa-Gevaert Group, Mortsels, BE). An Agfa image plate ($18 \times 24 \text{ cm}^2$ or $24 \times 30 \text{ cm}^2$) with a pixel pitch of $50 \mu\text{m}$ was employed. A Mo/Mo anode/filter combination was used for all X-ray exposures. Processed images were used, since raw data is often not achieved in clinical practice [16].

For each evaluated mammography, an experienced radiologist rated breast density according to the qualitative BI-RADS density category (4th edition): category 1 implies breast tissue that is less than 25% glandular; category 2, breast tissue that is approximately 25–50% glandular; category 3, breast tissue that is approximately 51–75% glandular; and category 4, breast tissue that is more than 75% glandular.

2.2. Developed algorithm

The proposed algorithm has been developed in Matlab software to estimate fibroglandular breast tissue percentage. The algorithm is a fully automatic hybrid method, which uses different image processing techniques. It is based on FCMVC [19, 20]. Detailed process is explained in the following subsections.

2.2.1. Preprocessing

In the first stage, the mammogram is segmented into the breast area by thresholding based on the gray-level intensity histogram, as literature employs [15], resulting in a mask with

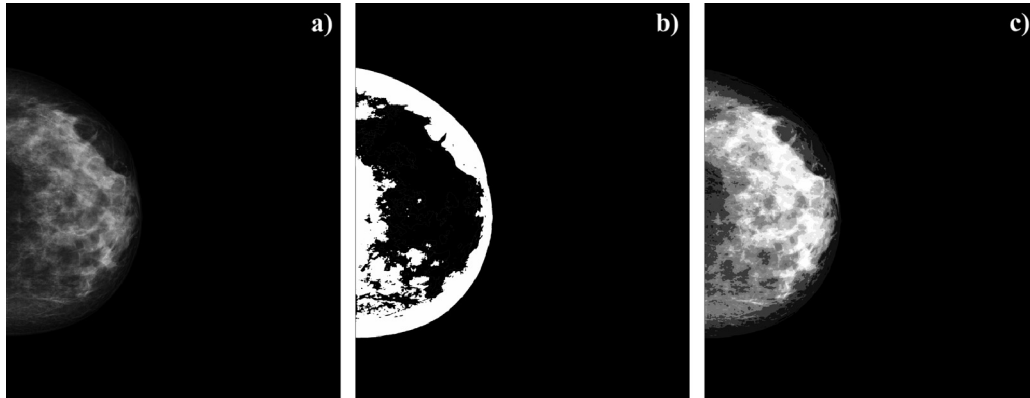


Fig. 1. a) Filtered image; b) Equalized image; and c) Rough fibroglandular mask.

the region of interest. A median filter is then applied in the breast area to reduce image noise.

2.2.2. Optimizing fuzzy C-means with variable compactness

FCMVC approach is based on FCM algorithm, which is an unsupervised clustering algorithm [19,20]. The advantage of FCMVC is that any cluster definition is improved by classifying pixels with a parameter called *compactness* (p_i). FCMVC is formulated as the minimization of the following objective function with respect to the fuzzy membership functions, the centroids and parameter p_i :

$$J_{FCMVC} = \sum_{j=1}^n \sum_{i=1}^c \hat{\mu}_{ij} (x_j - v_i)^{2p_i}$$

where n is the number of pixels which are classified into c clusters, $\mu_{ij} \in [0, 1]$ is the fuzzy membership of the input pixel x_i and v_i is the i th centroid associated to each cluster. Minimization of J_{FCMVC} gives the membership functions as:

$$\mu_{ij} = \frac{(x_j - v_i)^{-2p_i}}{\sum_{i=1}^c (x_j - v_i)^{-2p_i}}$$

For the implementation of FCMVC algorithm, it is necessary to introduce values for *compactness* and initial centroids. To do so, we optimize the algorithm by using information from equalized image, as described below.

The parameter p_i is a measure of compactness of a cluster, which should be large for small classes and small for large classes [19,20]. Therefore, for mammographic image, it is necessary to use different compactness values depending on breast type. As an example, adipose breasts has low amount of fibroglandular pixels representing a small group. Thus, in this example, adipose and fibroglandular clusters should have small and large compactness values, respectively. An exhaustive search was performed to estimate p_i , such that pixel classification generated could segment fibroglandular and adipose tissue efficiently.

For the purpose of the current study, the algorithm pre-classifies mammograms combining the two top and bottom BI-RADS category as “dense” and “fat” groups.

The classification is based on skewness values from equalized histogram image. “Fat” group has greater skewness values than “dense” group. Then, a threshold was established to automatically differentiate breast groups. Thus, a different compactness value is applied for each breast group.

In FCMVC, the energy function is minimized if high membership values are assigned to observations close to centroids and low membership values to observations far away from centroids. In each iteration, the centroid values are updated to achieve pixel classification. However, the choice of initial centroid value is important to reduce bias classification, to minimize number of iterations, time and computational cost.

In this work, initial centroid values are estimated for each image. This step is represented in Fig. 1. The segmentation of dense tissue is roughly estimated by a thresholding process in the equalized image (Fig. 1b), resulting in a fibroglandular mask (Fig. 1c). This mask is employed in the filtered image (Fig. 1a) to have the mean pixel intensities values. The mean adipose pixel values are computed with the remaining pixels. These values are then used to estimate the initial centroids in FCMVC.

2.2.3. Applying fuzzy C-means with variable compactness

FCMVC is applied in filtered mammography image to segment tissues in three different clusters, using the centroids and compactness parameters achieved before.

Defuzzification process was made by alpha-cut technique, using 0.95 as thresholding value. According to breast groups, classified in Section 2.2.2, each cluster represents different tissues. For “fat” breast group, clusters 1 and 2 represent pixels from adipose tissue; and cluster 3, fibroglandular tissue. On the other hand, for “dense” breast group, cluster 1 represents adipose tissue, while clusters 2 and 3 correspond to fibroglandular tissue.

As tissues are represented by different clusters in each mammogram groups (“fat” and “dense”), a different weight is given to clusters to calculate the percentage of fibroglandular tissue.

As a result, algorithm estimates the fibroglandular tissue percentage (FTP) in mammograms. FTP was computed by dividing the fibroglandular tissue area by total breast area.

Table 1
Confusion matrix to compare breast groups using results from skewness versus BI-RADS density score.

BI-RADS	Algorithm		
		Fat	Dense
BI-RADS	Fat	16	1
	Dense	4	9
		20	10
		30	

Table 2
Confusion matrix for breast density using our algorithm versus BI-RADS density score.

BI-RADS	Algorithm				
		1	2	3	4
BI-RADS	1	1	3	0	0
	2	0	12	1	0
	3	0	1	7	0
	4	0	3	2	0
		1	19	10	0
		30			

3. Results

From BI-RADS assessment made by the radiologist 4 mammograms were classified as category 1, 13 as category 2, 8 as category 3 and 5 as category 4, totalizing 30 mammograms.

As a result of using skewness to previously separate breasts into “fat” and “dense” groups, we obtained 83.3% of correct classification. At-test, comparing skewness values, shows significant difference ($p < 0.05$) between the “dense” and “fat” breast groups. Table 1 shows the confusion matrix to compare breast groups classified using results from skewness versus BI-RADS density score given by the radiologist. Cohen’s kappa coefficient comparing breast groups was 0.65 suggesting good agreement.

The estimated FTP by our method was compared with the assessment made by radiologist using BIRADS system, for each evaluated image, and achieved a 67.8% rate of correct classification.

Agreement between the BI-RADS density category and estimated FTP by the proposed method were determined with the Spearman’s correlation coefficient. This results showed a highly significant positive correlation with visual assessment, with Spearman’s correlation coefficient of $\rho = 0.618$, for $p < 0.001$. Table 2 shows the confusion matrix for BD using results from our algorithm versus BI-RADS density score given by the radiologist. Furthermore, Cohen’s kappa coefficient comparing the performances of the algorithm with the visual assessment for the different BI-RADS scores was 0.47 suggesting a moderate agreement.

In addition, Bland–Altman statistics were used to evaluate agreement between both assessments, to quantify the amount and direction of bias, and to determine the upper and lower limits of agreement (bias ± 1.96 of the difference). Fig. 2 shows the Bland–Altman plot of the score difference between FTP estimated by our method and the radiologist evaluations.

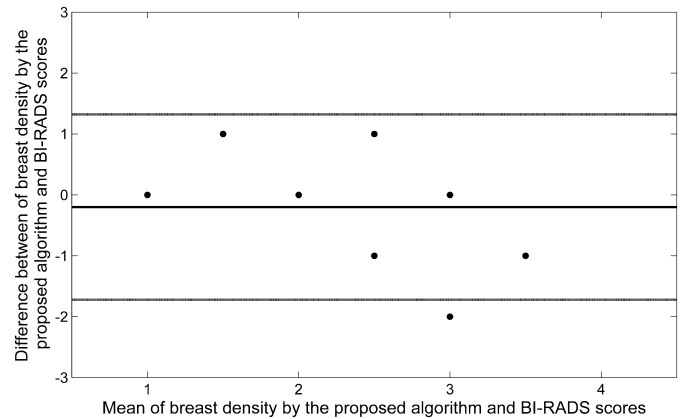


Fig. 2. Bland–Altman plot for breast density assessment. The difference refers to the BI-RADS minus the algorithm assessment. The difference between BI-RADS and algorithm scores was compared with the average score between the radiologist and computational results. Dashed lines represents the interval of 2 standard deviations. The middle line represents bias of -0.20 ± 1.52 .

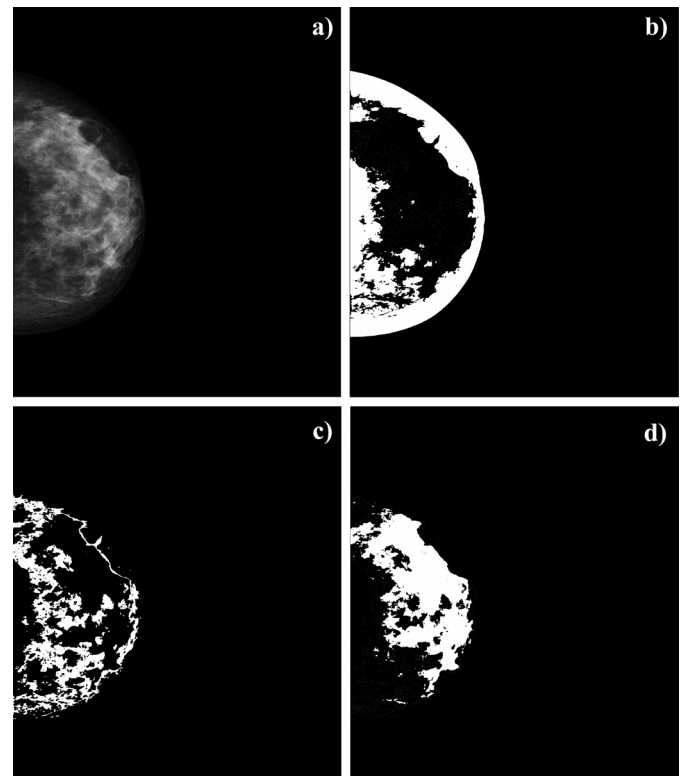


Fig. 3. Mammogram assessed as category 3 by BI-RADS. a) Filtered mammography; b) Cluster 1: adipose tissue; c) Cluster 2: almost completely fibroglandular tissue; and d) Cluster 3: fibroglandular tissue.

An example of FCMVC as a tool to segment tissues is showed in Fig. 3 for a “dense” breast group. Fig. 3a shows a mammogram classified as category 3 by radiologist BI-RADS evaluation. Figs. 3b–d illustrate membership function for the three clusters. In this example, Fig. 3b shows an adipose cluster while Figs. 3c–d shows fibroglandular clusters.

4. Discussion

We developed a methodology to estimate BD based on post-processed digital mammogram. Our automatic approach utilizes an optimized FCMVC algorithm to classify and quantify fibroglandular tissue in mammograms. FTP estimation by our method was compared with BI-RADS assessment from radiologist.

In relation with the results of breast groups pre-classification, skewness values could be used with high accuracy to significantly differentiate breast as “fat” and “dense”. As mammographic images has high resolution, statistics may reliably be performed in histogram analysis [15], such as skewness measurement. This classification was important to establish compactness and initial centroid values. Therefore, compactness values could be correctly assigned for each breast group. Furthermore, initial centroids values resulted in a few iteration in FCMVC, showing their good estimations. The dispended time by radiologists to make BI-RADS assessment may vary in the clinical practice according to radiologist experience, breast composition, and others [21]. The developed method showed be fast and easy to run, which implied in a short computational time (~ 130 s per exam in a mammogram with approximately 4700×5600 pixels).

Comparing the proposed method with BI-RADS, results suggest that this computational procedure offers a reliable, objective, and precise method that can be used to supplement visual grading, thereby providing a more advanced method for assessing BD in mammograms. Different from BI-RADS assessment, algorithm results presented no score equal to 4, as shows Fig. 2. Literature shows that when subjective visual evaluation is used, radiologists tend to give the maximum value [7]. Quantitative methods to evaluate breast density tend to underestimate values when compared to BI-RADS and MRI assessment [3,4,7], and our results corroborate with this.

From the statistical analyses comparing both methods, there was a positive association between FTP and the BI-RADS density scale. The rate of correct classification and Spearman's correlation coefficient found in this work represents a good association and low dispersion between methods. Results from confusion matrix and Cohen's kappa coefficient comparing the performances of the algorithm with the visual assessment for the different BI-RADS suggests a moderate agreement. The Bland–Altman analysis showed no significant differences (bias of -0.20 ± 1.52) between both methods, indicating that the assessment widely used in clinical routine is consistent with the results generated by the algorithms. These differences were sufficiently small to have the same confidence level for the results for both methods.

Fig. 3 shows an example of original and the three clusters used in our method. Visual examination of the clusters (Figs. 3b–d) revealed good segmentation of tissues.

One of the limitations of our study is that our approach is based in projected area, since it does not take the thickness of dense tissue into account. Dense volume is expected to be a more ‘biologically relevant’ measure and to be a better predictor of breast cancer risk [3,7,22]. However, no volumetric

method for mammography has been used as standard method yet [23]. Furthermore, differences in breast positioning, compression, and technical parameters have also been suggested as factors that could influence the apparent volumetric density of a mammogram [6,14]. Other limitation is that only one radiologist evaluated mammograms accordingly with BI-RADS and, therefore, intra and inter variability could not be assessed. Furthermore, future works should be done to evaluate the performance of our methodology using different mammography systems with different imaging parameters.

Automatic BD measurements would be easier to implement in screening programs due to the tendency to be less time-consuming and labor-intensive than visual assessment with BI-RADS breast density [7]. Objective BD measurements is important to develop breast cancer risk models and may be used in the development of personalized screening protocols [3]. The methodology presented herein, is free from variability inter- and intra-observer. In conclusion, our study shows that it is feasible to obtain automatic measurements of BD from digital mammograms.

This encouraging result invites us to improve our algorithm. We expect that it will have the capability to segment breast tissue objectively and accurately, avoiding subjective assessment by BI-RADS.

Conflict of interest statement

The authors declare that there is no conflict of interest for this study.

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References

- [1] Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med* 2011;155:10–20.
- [2] Lu LJ, Nishino TK, Johnson RF, Nayeem F, Brunder DG, Ju H, et al. Comparison of breast tissue measurements using magnetic resonance imaging, digital mammography and a mathematical algorithm. *Phys Med Biol* 2012;57:6903–27.
- [3] Gubern-Merida A, Kallenberg M, Platel B, Mann RM, Marti R, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms: a validation study. *PLoS ONE* 2014;9:e85952.
- [4] Wang J, Azziz A, Fan B, Malkov S, Klifa C, Newitt D, et al. Agreement of mammographic measures of volumetric breast density to MRI. *PLoS ONE* 2013;8:e81653.
- [5] Seo JM, Ko ES, Han BK, Ko EY, Shin JH, Hahn SY. Automated volumetric breast density estimation: a comparison with visual assessment. *Clin Radiol* 2013;68:690–5.
- [6] Freer PE. Mammographic breast density: impact on breast cancer risk and implications for screening. *Radiographics* 2015;35:302–15.
- [7] van der Waal D, den Heeten GJ, Pijnappel RM, Schuur KH, Timmers JM, Verbeek AL, et al. Comparing visually assessed BI-RADS breast density

- and automated volumetric breast density software: a cross-sectional study in a breast cancer screening setting. *PLoS ONE* 2015;10:e0136667.
- [8] van Engeland S, Snoeren PR, Huisman H, Boetes C, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms. *IEEE Trans Med Imaging* 2006;25:273–82.
 - [9] Alonzo-Proulx O, Jong RA, Yaffe MJ. Volumetric breast density characteristics as determined from digital mammograms. *Phys Med Biol* 2012;57:7443–57.
 - [10] Kallenberg MG, Lokate M, van Gils CH, Karssemeijer N. Automatic breast density segmentation: an integration of different approaches. *Phys Med Biol* 2011;56:2715–29.
 - [11] Malkov S, Mahmoudzadeh AP, Kerlikowske K, Shepherd J. Automated volumetric breast density derived by statistical model approach. In: *Breast imaging*, vol. 8539. 2014. p. 257–64.
 - [12] Highnam RP, Brady JM. *Mammographic image analysis (computational imaging and vision)*. Dordrecht: Kluwer Academic Publishers; 1999.
 - [13] Pawluczyk O, Augustine BJ, Yaffe MJ, Rico D, Yang J, Mawdsley GE, et al. A volumetric method for estimation of breast density on digitized screen-film mammograms. *Med Phys* 2003;30:352–64.
 - [14] Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA. Reliability of automated breast density measurements. *Radiology* 2015;275:366–76.
 - [15] Keller BM, Nathan DL, Wang Y, Zheng Y, Gee JC, Conant EF, et al. Estimation of breast percent density in raw and processed full field digital mammography images via adaptive fuzzy c-means clustering and support vector machine segmentation. *Med Phys* 2012;39:4903–17.
 - [16] He W, Hogg P, Juette A, Denton ER, Zwiggelaar R. Breast image pre-processing for mammographic tissue segmentation. *Comput Biol Med* 2015;67:61–73.
 - [17] Klifa C, Carballido-Gamio J, Wilmes L, Laprie A, Shepherd J, Gibbs J, et al. Magnetic resonance imaging for secondary assessment of breast density in a high-risk cohort. *Magn Reson Imaging* 2010;28:8–15.
 - [18] Kannan SR, Ramathilagam S, Devi R, Sathya A. Robust kernel FCM in segmentation of breast medical images. *Expert Syst Appl* 2011;38:4382–9.
 - [19] Vacavant A, Ali A-R, Grand-Brochier M, Albouy-Kissi Aei, Alfidja A, Chabrot P, et al. Smoothed shock filtered defuzzification with Zernike moments for liver tumor extraction in MR images. In: *International conference on image processing theory, tools and applications, IPTA*; 2015.
 - [20] Roy S, Agarwal H, Carass A, Bai Y, Pham DL, Prince JL. Fuzzy C-means with variable compactness. *Proc IEEE Int Symp Biomed Imaging* 2008;4541030:452.
 - [21] Ciatto S, Houssami N, Apruzzese A, Bassetti E, Brancato B, Carozzi F, et al. Categorizing breast mammographic density: intra- and interobserver reproducibility of BI-RADS density categories. *Breast* 2005;14:269–75.
 - [22] Morrish OW, Tucker L, Black R, Willsher P, Duffy SW, Gilbert FJ. Mammographic breast density: comparison of methods for quantitative evaluation. *Radiology* 2015;275:356–65.
 - [23] Tagliafico A, Tagliafico G, Astengo D, Airaldi S, Calabrese M, Housami N. Comparative estimation of percentage breast tissue density for digital mammography, digital breast tomosynthesis, and magnetic resonance imaging. *Breast Cancer Res Treat* 2013;138:311–7.

Capítulo 6

6. Estimate of breast density in mammography computed radiography systems

The logo for the journal Radiology, featuring the word "Radiology" in a blue serif font, enclosed within a thin black rectangular border.

Estimate of breast density in mammography computed radiography systems

Journal:	<i>Radiology</i>
Manuscript ID	Draft
Manuscript Type:	Original Research
Manuscript Categorization Terms:	Adults < 1. SUBJECT MATTER, Phantom Studies < 1. SUBJECT MATTER, Mammography < 2. MODALITIES/TECHNIQUES, Breast < 4. AREAS/SYSTEMS, Computer Applications-General (Informatics) < 6. TOPICS

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Manuscripts

ABBREVIATED TITLE PAGE (BLINDED) AND MANUSCRIPT

Estimate of breast density in mammography computed radiography systems

Manuscript Type: Original Research

Summary statement: A new methodology applied to mammograms was developed and validated to estimate Percentage of Breast Density (PBD) in computed radiography systems. Comparison between estimated PBD in mammograms and Magnetic Resonance Imaging showed that the methodology described here in has the potential to be used in clinical routine avoiding inter and intra variability.

Implications to patient care:

- 1) Automated breast density measurements are objective and are free of observer variability. Literature describes methodologies to be used in digital systems but not in computed systems.
- 2) The development of an automatic percentage of breast density in computed radiography systems may be used in places where digital systems are not available.
- 3) Dense breast tissue is indicated as one of the strongest independent risk factors to predict breast cancer development

Keywords: Mammography, Computed Radiography, Breast Density, Signal difference-to-noise ratio, Magnetic Resonance Imaging.

List of abbreviations:

PBD: Percentage of breast density

MRI: Magnetic resonance imaging

SDNR: Signal difference-to-noise ratio

FCMVC: Fuzzy C-means with variable compactness

CR: Computed Radiography

CC: Craniocaudal

BD: Breast density

VBD: Volumetric breast density

DR: Digital radiography

Abstract

Purpose: To develop a new methodology to estimate the percent of breast density (PBD) using computed radiography (CR) mammographic systems and validate it with magnetic resonance imaging (MRI).

Materials and Methods: In this retrospective study, 48 CR mammograms and MRI exams were evaluated. Mammography and MRI exams were selected if performed less than two months apart. Breast density in CR mammography was assessed by the developed methodology in three different steps: (i) enhancement of breast periphery image, (ii) segmentation of fibroglandular and adipose tissues by Fuzzy C-Means with Variable Compactness and (iii) estimate of PBD by Signal difference-to-noise ratio. Validation of the described method was made using MRI exams, used as ground-truth. Statistical linear regressions and mean percentage differences were measured based on data from both methods for the same patient. The error measurement was made according to Bland and Altman. Pearson correlation coefficient was calculated among the results obtained between both methods.

Results: The Bland–Altman statistical analyses showed no significant differences between the two quantification methods. The linear regression line had a correlation coefficient of $R^2=0.821$. Mean percentage difference between both methods was $3.39\pm2.69\%$. Pearson’s correlation coefficients acquired was 0.91. These results showed a strong association between the PBD using CR mammography methodology and the results obtained by direct MRI analysis.

Conclusion: Automated technique developed for measuring breast density showed a good correlation with ground-truth. The developed tool may be used in CR and digital radiography mammography systems using processed images to estimate PBD.

Introduction

Several factors are associated to the increased risk of developing breast cancer, such as age, endocrine factors, reproductive history, behavioral, environmental factors and genetic (1-3). Recently, dense breast tissue was indicated as one of the strongest independent risk factors to predict breast cancer development (1, 3-8). Women with increased breast density (BD) are 4 to 6 times more likely to develop cancer (5, 9).

BD can only be used for evaluation or risk-stratified screening when it is assessed objectively and reproducible (4, 10). Much effort has been devoted to the development of computer-based quantitative and objective methods of BD measurement (11). Methods for objective mammographic density measurement are divided into two subtypes: area and volume.

A thresholding approach developed by Byng *et al* (1996) (12) has become the gold standard method for determining BD area and is widely used for estimating breast cancer risk in epidemiologic research (4, 10, 13). Literature shows different methodologies to estimate volumetric breast density (VBD) in digital radiography (DR) systems. In general, most of the volumetric methods rely on knowing breast thickness at compression and/or image acquisition parameters and/or the necessity to image a small object in every mammogram (11, 14-17). Also, another common limitation of VBD algorithms presented in the literature is the use of only raw image data (3). Many DR mammography systems produce images in both raw and processed representations (18, 19). Due to the size of images and storage considerations, raw data is often deleted and only the processed format is available (20). Therefore, the application of methods requiring raw mammograms is sometimes impracticable (3).

The aim of this study was to develop an objective, reliable and reproducible computational tool to automatically estimate the percentage of BD (PBD) in CR mammography systems based on Fuzzy C-Means with Variable Compactness (FCMVC) and Signal difference-to-noise ratio (SDNR). Validation of developed tool was made comparing PBD values from CR mammograms with MRI for the same patients, which is considered as ground-truth. Results

showed strong agreement between methodologies. The presented methodology may be used in CR and DR mammography where only processed images are available.

Methodology

Mammography and Magnetic Resonance Image selection

This retrospective study was developed with ethical approval from the authors’ institutions and national review panels (protocol CAAE 50547315.8.0000.5411). The data sets were chosen randomly for women with mammography and MRI exams performed less than two months apart. Women aged 18 years or older undergoing screening mammography between 2013 and 2015 in our institution were included. Only women with no previous history of breast cancer or breast surgery, with a BI-RADS assessment of either 1 or 2 (negative or benign finding, respectively) were included. Mammography of one side, left or right, was used for each patient in craniocaudal (CC) view, allowing assessment of different breast compositions. A total of 48 pairs of CR mammograms and MRI examinations were evaluated.

The CR mammography system used was a Senographe 600T (GE Healthcare, Milwaukee, WI) with a CR-85X image digitizer (Agfa-Gevaert Group, Mortsel, BE). All exposures were performed with Mo/Mo anode/filter combination with automatic exposure control and an Agfa image plate (18 × 24 cm² or 24 × 30 cm²) with a pixel pitch of 50 μm. Mammograms were used in the processed form.

The MRI examinations were performed on a 3-T Siemens Magnetom Verio scanner (Siemens Healthcare, Erlangen, Germany), with dedicated breast coil (CP Breast Array, Siemens, Erlangen, Germany). A pre-contrast T1-weighted MRI without fat saturation sequence was used.

Breast density quantification in mammograms

In this study, it was developed a computational approach in Matlab software to automatically quantify the breast density in mammograms through a hybrid methodology. After application of a median filter to reduce image noise, breast periphery area was enhanced to correct pixel intensity. Then, segmentation of tissues (fibroglandular and adipose) was performed based on FCMVC. Finally, an estimate of PBD was acquired using the SDNR. The proposed approach steps are described in the flowchart in Figure 1.

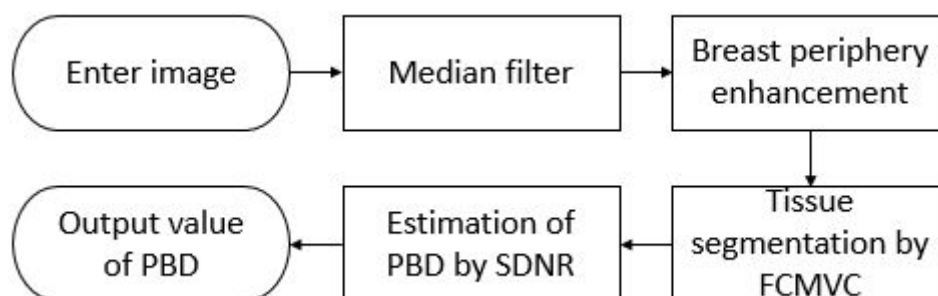


Figure 1. Flowchart showing the main image processing steps performed in the computational approach (FCVMC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio).

Signal difference-to-noise ratio study in a phantom

Exposure factors, breast thickness, breast composition and image post-processing has influence in pixel intensity. In DR mammography systems, it is possible to know exposure factors and breast thickness in DICOM information. This information is used in existing software to facilitate estimation of PBD (21-26). In CR systems such parameters are not recorded in DICOM information and it makes a challenge the estimation of PBD.

To address this limitation, in this study was acquired a calibration curve combining different exposure factors and breast thickness. Images acquired using a CIRS Tissue-Equivalent

Phantom for Mammography, model 011A (Computerized Imaging Reference Systems, Inc. Norfolk, VA) were analyzed to create the calibration curve. This step-wedge phantom mimics radiographic properties of a real breast. Each step simulates different breast compositions: 100%, 70%, 50%, 30% and 0% of fibroglandular tissue.

The phantom was imaged using different exposure factors combinations commonly used in clinical routine (kVp ranging from 26 to 31 and mAs from 80 to 400). Different thicknesses of breasts were simulated, ranging from 4.5 cm to 7.5 cm, inserting acrylic slabs of 1 cm of thick above the phantom.

SDNR for each step was calculated within the phantom as given in Equation 1 (27), where A is the average pixel intensity for fibroglandular steps, and B and C are the average pixel intensity and standard deviation of the adipose step (0% of fibroglandualr tissue), respectively.

$$SDNR = \frac{|A - B|}{C} \tag{1}$$

This analysis was applied in 17 acquired phantom images to determine the relation between PBD and SDNR. For this, PBD values were plotted against corresponding SDNRs and a curve adjustment was made.

Breast density estimation

PBD is defined as the ratio of dense tissue in relation to the total breast. The necessary tissue compression produces projected breast images that often contain a variable mix of glandular and fatty tissues, *i.e.* pixels are neither pure glandular nor pure adipose tissue (13). The first steps to estimate PBD was to correct breast periphery and segment breast tissues as adipose and fibroglandular. Supplemental Material describes those fundamental steps.

After application of FCMVC, the amount of fibroglandular and adipose tissue within each pixel was estimated through SDNR. The reference value B and its standard deviation C

were calculated using mean pixel values for pixels assigned as adipose. Pixels assigned as fibroglandular were used as A for SDNR calculation. The SDNR was calculated for each pixel.

Based on the SDNR for each fibroglandular pixel and the relation obtained from the phantom study, the PBD was directly determined. For this, SDNR value from each fibroglandular pixel was multiplied by the acquired curve calibration, resulting in the PBD value for the studied pixel PBD_{pixel} . Dividing the sum of each PBD_{pixel} by the total pixel of breast gives an estimate of the PBD for the entire exam.

The final information given to the observer is the PBD and an illustration of 3D fibroglandular tissue distribution within mammography, as shown in Figure 2. Using the SDNR values from the mammography (Figure 2a) the 3D reconstruction was realized by attributing different colors depending on the quantity of estimated PBD, as illustrated in Figure 2b. Lighter colors indicate a high percentage of breast density.

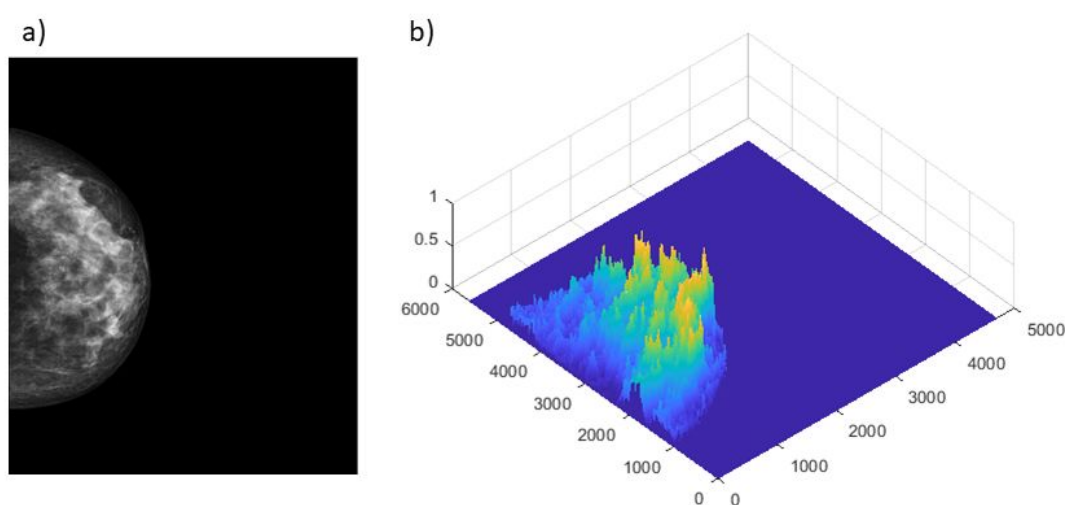


Figure 2. Reconstruction of 3D fibroglandular tissue distribution within the breast based on mammography. (a) Evaluated mammography. (b) 3D reconstruction

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6 *Validation by Magnetic Resonance Image*
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8 The PBD results achieved by a methodology developed in this study were validated
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10 measuring PBD in MRI exams.
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13 The validation of the PBD proposed herein was achieved by applying the methodology
14 proposed by Li *et al.* in the MRI scan to correct intensity inhomogeneity in the image (28).
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16 Then, an experienced radiologist, with 15 years of experience, manually segmented the entire
17 breast area. After that, each voxel was assigned as fibroglandular or adipose tissues by an
18 automatic thresholding technique (24). The radiologist reviewed all slices to ensure the accuracy
19 of the segmentation of fibroglandular tissue. Finally, the PBD for MRI was calculated dividing
20 the amount of fibroglandular tissue by the total amount of tissues, by a straightforward process.
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32 *Result analyses*
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34 To evaluate the accuracy of the mammography’s quantification, the results of 48 PBD
35 were compared with MRI direct quantification method, which was used as ground-truth.
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39 Figure 3 shows the validation process used in this study. Statistical linear regressions
40 and mean percentage differences were measured based on data from both methods for the same
41 patient. The error measurement was made according to Bland and Altman. Pearson correlation
42 coefficient was calculated among the results obtained between both methods. Statistical analysis
43 was processed in Matlab software R2014a.
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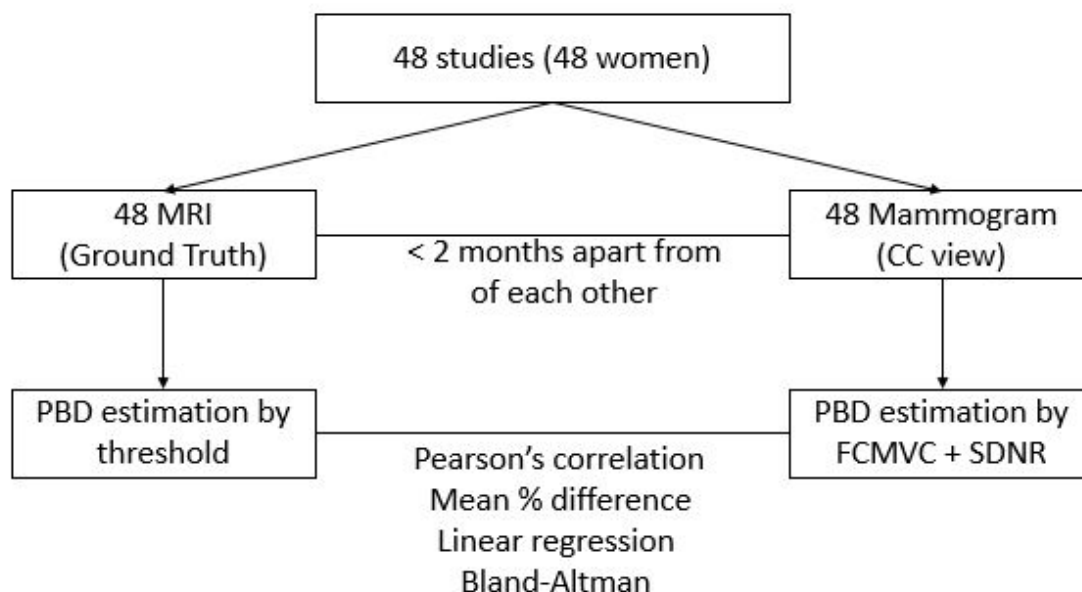


Figure 3. Schematic overview of the validation process. A total of 48 mammogram and magnetic resonance imaging (MRI) exams were used to estimate the percentage of breast density (PBD). The comparison between both methods was made using Pearson's correlation, mean percentage difference, linear regression and Bland-Altman statistic. (MRI: Magnetic Resonance Imaging, CC: craniocaudal, FCMVC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio)

Results

The obtained relation between PBD and SDNR from the analysis of the phantom is plotted in Figure 4, with linear adjustment. The regression for the adjustment of the curve has $R^2=0.94$ with 95% prediction intervals. The two dashed lines show the limits of two standard deviations of the data around the adjusted line shown by the solid line. The estimate PBD for each pixel (PBD_{pixel}) was calculated by using the linear adjustment, given by Equation 2.

$$PBD_{pixel} = 5.262 * SdNR + 4.289 \quad (2)$$

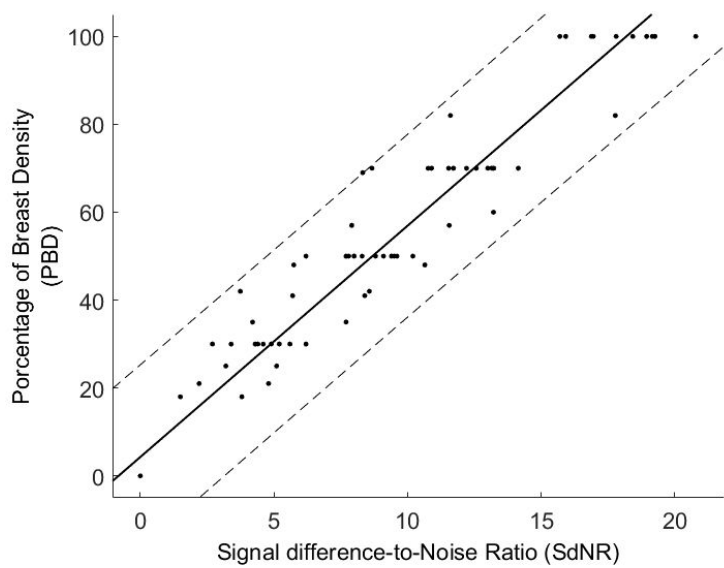


Figure 4. Percentage of breast density (PBD) versus Signal difference-to-noise ratio (SDNR) behavior for the mammography phantom using different radiographic techniques in routine and different thickness of compressed breasts. The dashed lines display the limits of 2 standard deviations of the data around the adjusted line shown by the solid line. The solid line represents the relation obtained (Equation 2).

The developed PBD quantification method in mammograms and the ground-truth measurement based on MRI were compared. The mean percentage difference between both methods is $3.39 \pm 2.69\%$. Pearson’s correlation coefficients acquired is 0.91. The linear regression line between them (Figure 5a) is $y = 1.531x - 4.189$, with a correlation coefficient of $R^2=0.821$. The statistical Bland–Altman plot is shown in Figure 5b for the difference and average between the two methods.

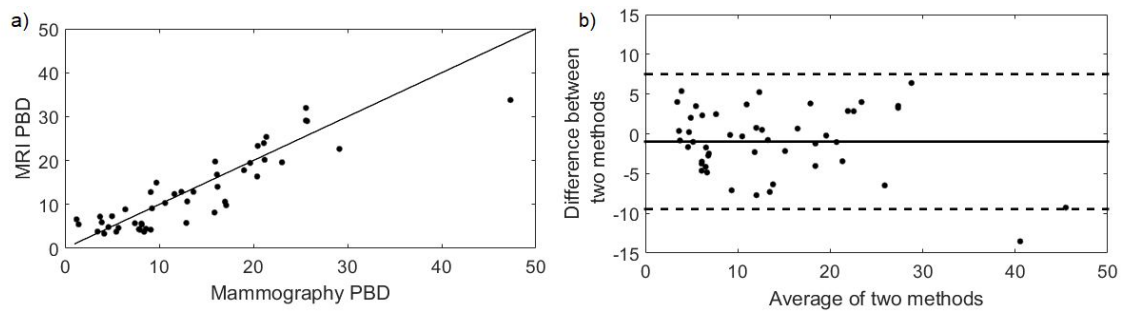


Figure 5. Percentage of breast density (PBD) quantification agreement of the proposed method (mammography), compared with the standard (Magnetic Resonance Imaging - MRI) for 48 patients. (a) Linear regression line was determined by $y=1.531x-4.189$, with $R^2=0.821$, demonstrating low dispersion between data. (b) Bland–Altman plot for both quantification methods. The difference refers to the reference standard minus the developed method. The central line corresponds to the mean value of deviations. The dashed lines indicate the interval of 2 standard deviations, indicating an adequate level of statistical agreement.

Discussion

In this work, we have proposed an objective, reliable and reproducible method to estimate the PBD in CR mammography exams. We proposed an approach based on enhancement of breast periphery, followed by tissues segmentation through FCMVC and estimate of PBD by SDNR. Results of estimate PBD in mammography were compared measuring breast tissues in MRI exams. Low difference between mammogram and MRI measurement was observed.

The behavior of SDNR vs. PBD studied in the phantom allowed the use of the acquired relation to estimate PBD in mammography exams from patients resulting in a calibration curve. Fluctuations of points around the adjusted curve occur mainly due to variations in some elements of analysis, such as the different thickness of compressed breast and the use of different mammographic techniques. Despite this diversified nature of data, the regression for the adjustment of the curve had $R^2=0.94$ with 95% prediction intervals, showing high

association and low dispersion between variables. Therefore, the phantom analysis provides a high level of confidence for the PBD versus SDNR relation to determine the total PBD directly from SDNRs in mammography exams.

From the statistical analysis for the comparison between both developed and MRI quantification methods, the linear regression showed a strong association and low dispersion between variables, with a correlation coefficient of $R^2=0.821$. The mean percentage difference between the present PBD evaluation and MRI quantifications was approximately $3.39\pm2.69\%$ and can be attributed to the influence of superimposed tissues (adipose and fibroglandular) (13) in the determination of SDNRs in mammographic images and the approximations incorporated into the adjustment and average values assumed by the method. Pearson's correlation coefficients acquired was 0.91, reassuring strong association between compared methods. The Bland–Altman analysis showed no significant differences ($P=0.98\%$) between both quantification methods. The limits of agreement at a 95% confidence interval were -9.46% and 7.50%. These differences were sufficiently small to have the same confidence level for the results for both quantification methods. Despite these differences, an analysis of original mammogram and 3D reconstruction showed visual agreement.

Literature shows different methodologies to estimate BD based on area or volume using DR mammography systems. Gubern-Merida *et al.* compared a commercial software (Volpara) to estimate breast density in full-field digital mammograms with MRI exams. In this study, they estimated volumetric breast density and fibroglandular tissue volume. The Pearson coefficient for volumetric breast density and fibroglandular tissue volume was 0.93 and 0.85, respectively. In the linear regression analysis, both measurements results were 0.84 (24). Wang *et al.* studied the agreement between three approaches to estimate BD: single energy X-ray absorptiometry, Quantra and Volpara. As a result of the comparison between approaches and volumetric MRI, the linear regression of percentage of fibroglandular tissue was 0.78, 0.51 and 0.73 for single energy X-ray absorptiometry, Quantra and Volpara (1), respectively. Holland *et al.* developed a methodology to optimize volumetric breast density estimation in full-field digital mammograms

and compared their results with MRI. Different approaches were tested and the best results acquired for percent of density achieved a Pearson's correlation coefficients of 0.9 (29).

Despite the limitations of a CR system (such as resolution, noise and linearity) results presented by developed tool shows that our methodology is in accordance with literature when compared with full-field digital mammograms (1, 24, 29). It is important to note that raw data is often deleted and only the processed format is available in DR systems (20). The advantage of our methodology is that it may be applicable in processed DR mammograms. Furthermore, our study is significant in developing countries where CR is the predominant available system. A limitation of our study is that the calibration of the system is necessary with the step-wedge phantom. However, after the calibration is made, the methodology may be applied to any CR and DR system. Another limitation is that this methodology was not tested yet in women with breast implants.

As a conclusion, results showed small difference between the developed methodology for CR systems and MRI measurements. It showed to be efficient and applicable for the PBD estimate in clinics and hospitals where CR or DR systems are used. The tool may be used for research proposes and in clinical routine to help physicians in diagnosis decisions. Furthermore, it is less time-consuming (~130s per exam) and labor-intensive than the rather intra and inter-variable visual assessment with BI-RADS breast density.

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References

1. Wang J, Azziz A, Fan B, et al. Agreement of mammographic measures of volumetric breast density to MRI. *PLoS One*. 2013;8(12):e81653.

2. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med*. 2011;155(1):10-20.

3. Keller BM, Nathan DL, Wang Y, et al. Estimation of breast percent density in raw and processed full field digital mammography images via adaptive fuzzy c-means clustering and support vector machine segmentation. *Med Phys*. 2012;39(8):4903-17.

4. van der Waal D, den Heeten GJ, Pijnappel RM, et al. Comparing Visually Assessed BI-RADS Breast Density and Automated Volumetric Breast Density Software: A Cross-Sectional Study in a Breast Cancer Screening Setting. *PLoS One*. 2015;10(9):e0136667.

5. Tagliafico A, Tagliafico G, Tosto S, et al. Mammographic density estimation: comparison among BI-RADS categories, a semi-automated software and a fully automated one. *Breast*. 2009;18(1):35-40.

6. Kerlikowske K, Scott CG, Mahmoudzadeh AP, et al. Automated and Clinical Breast Imaging Reporting and Data System Density Measures Predict Risk for Screen-Detected and Interval Cancers: A Case-Control Study. *Ann Intern Med*. 2018;168(11):757-65.

7. Brandt KR, Scott CG, Ma L, et al. Comparison of Clinical and Automated Breast Density Measurements: Implications for Risk Prediction and Supplemental Screening. *Radiology*. 2016;279(3):710-9.

8. Freer PE. Mammographic breast density: impact on breast cancer risk and implications for screening. *Radiographics*. 2015;35(2):302-15.

9. Raghavendra A, Sinha AK, Le-Petross HT, et al. Mammographic breast density is associated with the development of contralateral breast cancer. *Cancer*. 2017.

10. Assi V, Warwick J, Cuzick J, Duffy SW. Clinical and epidemiological issues in mammographic density. *Nature reviews Clinical oncology*. 2011;9(1):33-40.

11. Winkler NS, Raza S, Mackesy M, Birdwell RL. Breast density: clinical implications and assessment methods. *Radiographics*. 2015;35(2):316-24.

12. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. Automated analysis of mammographic densities. *Phys Med Biol*. 1996;41(5):909-23.

13. Lu LJ, Nishino TK, Johnson RF, et al. Comparison of breast tissue measurements using magnetic resonance imaging, digital mammography and a mathematical algorithm. *Phys Med Biol*. 2012;57(21):6903-27.

14. Yaffe MJ. Mammographic density. Measurement of mammographic density. *Breast Cancer Res*. 2008;10(3):209.

15. Highnam R, Brady M, Shepstone B. A representation for mammographic image processing. *Med Image Anal.* 1996;1(1):1-18.
16. Pawluczyk O, Augustine BJ, Yaffe MJ, et al. A volumetric method for estimation of breast density on digitized screen-film mammograms. *Med Phys.* 2003;30(3):352-64.
17. Morrish OW, Tucker L, Black R, Willsher P, Duffy SW, Gilbert FJ. Mammographic breast density: comparison of methods for quantitative evaluation. *Radiology.* 2015;275(2):356-65.
18. Burton A, Byrnes G, Stone J, et al. Mammographic density assessed on paired raw and processed digital images and on paired screen-film and digital images across three mammography systems. *Breast Cancer Research.* 2016;18(1):130.
19. Vachon CM, Fowler EE, Tiffenberg G, et al. Comparison of percent density from raw and processed full-field digital mammography data. *Breast Cancer Res.* 2013;15(1):R1.
20. Ganesan K, Acharya UR, Chua KC, Min LC, Abraham KT. Pectoral muscle segmentation: a review. *Comput Methods Programs Biomed.* 2013;110(1):48-57.
21. Alonzo-Proulx O, Packard N, Boone JM, et al. Validation of a method for measuring the volumetric breast density from digital mammograms. *Phys Med Biol.* 2010;55(11):3027-44.
22. Alonzo-Proulx O, Jong RA, Yaffe MJ. Volumetric breast density characteristics as determined from digital mammograms. *Phys Med Biol.* 2012;57(22):7443-57.
23. Geeraert N, Klausz R, Cockmartin L, Muller S, Bosmans H, Bloch I. Comparison of volumetric breast density estimations from mammography and thorax CT. *Physics in Medicine & Biology.* 2014;59(15):4391.
24. Gubern-Merida A, Kallenberg M, Platel B, Mann RM, Marti R, Karssemeijer N. Volumetric breast density estimation from full-field digital mammograms: a validation study. *PLoS One.* 2014;9(1):e85952.
25. Schmachtenberg C, Hammann-Kloss S, Bick U, Engelken F. Intraindividual Comparison of Two Methods of Volumetric Breast Composition Assessment. *Academic Radiology.* 2015;22(4):447-52.
26. Alonzo-Proulx O, Mawdsley GE, Patrie JT, Yaffe MJ, Harvey JA. Reliability of automated breast density measurements. *Radiology.* 2015;275(2):366-76.
27. Bloomquist A, Bosmans H, Burch A, et al. IAEA Human Health Series No.17: Quality Assurance Programme for Digital Mammography. Vienna, Austria: International Atomic Energy Agency, 2011.
28. Wolfe JN, Saftlas AF, Salane M. Mammographic parenchymal patterns and quantitative evaluation of mammographic densities: a case-control study. *AJR Am J Roentgenol.* 1987;148(6):1087-92.
29. Holland K, Gubern-Merida A, Mann R, Karssemeijer N. Optimization of volumetric breast density estimation in digital mammograms. *Phys Med Biol.* 2017.

Figure Legends

Figure 2. Flowchart showing the main image processing steps performed in the computational approach (FCVMC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio).

Figure 2. Reconstruction of 3D fibroglandular tissue distribution within the breast based on mammography. (a) Evaluated mammography. (b) 3D reconstruction of fibroglandular tissue. Lighter colors indicate a high percentage of breast density.

Figure 3. Schematic overview of the validation process. A total of 48 mammogram and magnetic resonance imaging (MRI) exams were used to estimate the percentage of breast density (PBD). The comparison between both methods was made using Pearson’s correlation, mean percentage difference, linear regression and Bland-Altman statistic. (MRI: Magnetic Resonance Imaging, CC: craniocaudal, FCVMC: Fuzzy C-Means with Variable Compactness, PBD: Percentage of Breast Density, SNDR: Signal difference-to-noise ratio)

Figure 4. Percentage of breast density (PBD) versus Signal difference-to-noise ratio (SDNR) behavior for the mammography phantom using different radiographic techniques in routine and different thickness of compressed breasts. The dashed lines display the limits of 2 standard deviations of the data around the adjusted line shown by the solid line. The solid line represents the relation obtained (Equation 2).

Figure 5. Percentage of breast density (PBD) quantification agreement of the proposed method (mammography), compared with the standard (Magnetic Resonance Imaging - MRI) for 48 patients. (a) Linear regression line was determined by $y=1.531x-4.189$, with $R^2=0.821$, demonstrating low dispersion between data. (b) Bland–Altman plot for both quantification methods. The difference refers to the reference standard minus the developed method. The central line corresponds to the mean value of deviations. The dashed lines indicate the interval of 2 standard deviations, indicating an adequate level of statistical agreement.

Supplemental Material

The first steps to estimate the percent of breast density (PBD) was the enhancement of breast periphery followed by segmentation of fibroglandular and adipose tissues by Fuzzy C-Means with Variable Compactness. The following sections explain those steps.

Periphery correction

In this study, PBD was estimated using pixel intensity information. Due to breast anatomy, breast peripheral area (uncompressed area) has different thickness when compared with internal breast (compressed area) thickness in mammograms. The first step was to apply a median filter to reduce noise. Then, it was applied a breast peripheral enhancement to adjust pixel intensity differences, using the methodology described in (1). Figure 1a shows an example of the original exam, after median filtering (Figure 1b) and after application of breast periphery enhancement (Figure 1c).

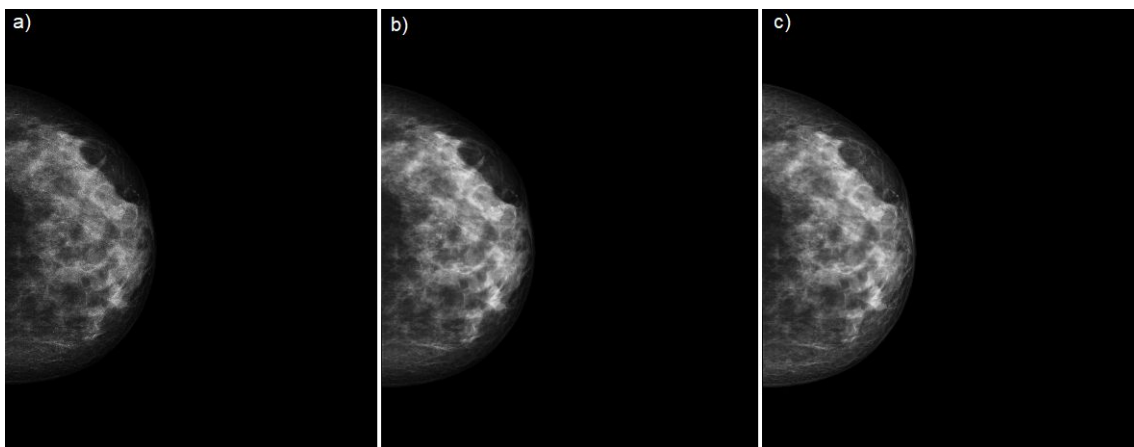


Figure 1. Example of original image (a), noise reduction after median filter application (b), and after breast periphery enhancement (c).

Tissue segmentation by Fuzzy C-Means with Variable Compactness

After breast periphery enhancement, breast tissues were segmented using FCMVC tool.

FCMVC approach is based on Fuzzy C-Means algorithm, which is an unsupervised clustering algorithm (2-4). FCMVC is formulated as the minimization of the following objective function concerning the fuzzy membership functions, the centroids and a parameter called compactness - p_i (2-4), as shown in Equation 1:

$$J_{FCMVC} = \sum_{j=1}^n \sum_{i=1}^c \hat{\mu}_{ij} (x_j - v_i)^{2p_i} \quad (1)$$

where n is the number of pixels which are classified into c clusters, $\mu_{ij} \in [0,1]$ is the fuzzy membership of the input pixel x_i and v_i is the i^{th} centroid associated to each cluster.

Minimization of J_{FCMVC} gives the membership functions as shown in Equation 2 (2, 3):

$$\mu_{ij} = \frac{(x_j - v_i)^{-2p_i}}{\sum_{i=1}^c (x_j - v_i)^{-2p_i}} \quad (2)$$

Prior to the FCMVC segmentation, the algorithm pre-classified roughly mammograms in two different breast groups: dense breasts ($Dens_g$) and adipose breasts ($Adip_g$) (4). This information was important in the following steps. The FCMVC was implemented using a methodology to segment tissues in three different clusters, where cluster 1 was adipose tissue, cluster 3 was fibroglandular tissue, and cluster 2 depended on the pre-classification of breast group, as described in (4).

According to the pre-classification of breast groups, each cluster represents different tissues. For $Adip_g$, clusters 1 and 2 represented pixels from adipose tissue; and cluster 3, fibroglandular tissue. On the other hand, for $Dens_g$, cluster 1 represented adipose tissue, while clusters 2 and 3 corresponded to fibroglandular tissue. Figure 2 shows an example of mammogram classified as $Dens_g$ (Figure 3a) and $Adip_g$ (Figure 2e) after breast periphery correction. In the case of $Dens_g$, cluster 1 (Figure 2b) was assigned as containing adipose pixels and clusters 2 and 3 as fibroglandular pixels (Figure 2c and 2d respectively). For $Adip_g$ group, clusters 1 and 2 were assigned as adipose pixels (Figure 2f and 2g respectively) and cluster 3 as fibroglandular (Figure 2h). This differentiation was necessary because different breast density patterns require different approaches (5).

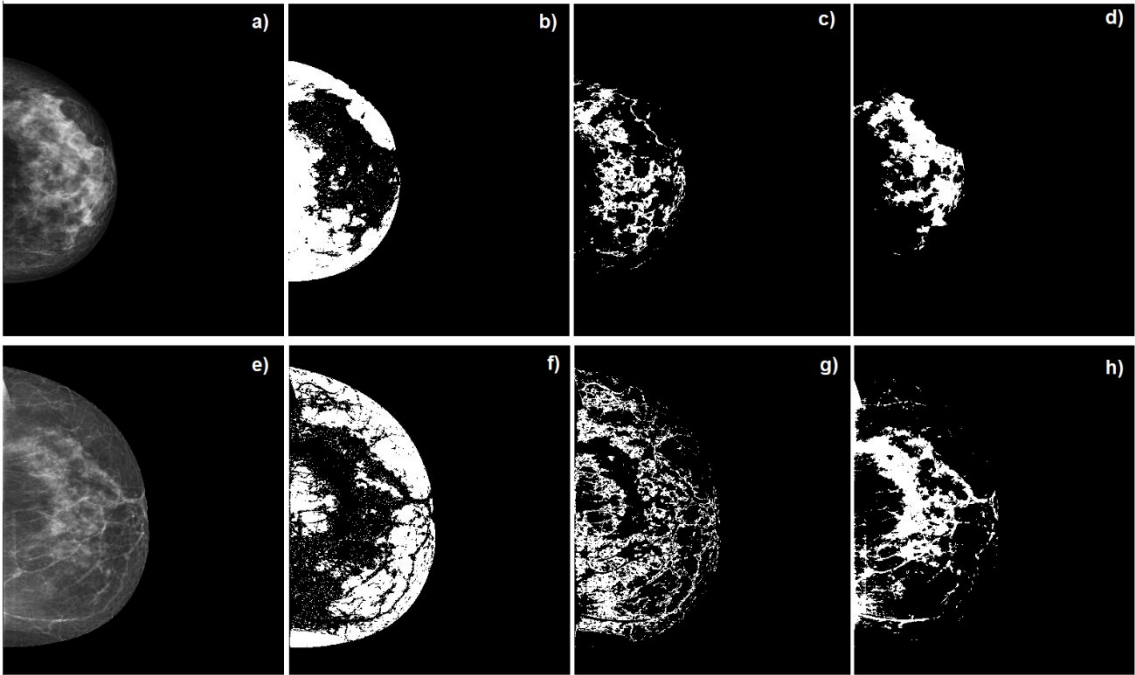


Figure 2. Example of mammograms for different groups: a) dense ($Dens_g$ and e) adipose ($Adip_g$). For dense group (a), cluster 1 (b) is assigned as containing adipose pixels and clusters 2 (c) and 3 (d) as fibroglandular pixels. For adipose group (e), clusters 1 (f) and 2 (g) are assigned as containing adipose pixels and cluster 3 (h) as fibroglandular pixels.

References of Supplemental Material

1. Pavan ALM, Vacavant A, Trindade AP, Quini CC, Pina DRd. Enhancement of breast periphery region in digital mammography. SPIE Medical Imaging: SPIE, 2018; p. 10.
2. Roy S, Agarwal H, Carass A, Bai Y, Pham DL, Prince JL. Fuzzy C-Means with Variable Compactness. Proceedings IEEE International Symposium on Biomedical Imaging. 2008;4541030:452.
3. Vacavant A, Ali A-R, Grand-Brochier M, et al. Smoothed Shock Filtered Defuzzification with Zernike Moments for Liver Tumor Extraction in MR Images.

1
2
3 International Conference on Image Processing Theory, Tools and Applications (IPTA). Orléans
4
5 - France: IEEE, 2015.
6
7

8 4. Pavan ALM, Vacavant A, Trindade AP, de Pina DR. Fibroglandular Tissue
9
10 Quantification in Mammography by Optimized Fuzzy C-Means with Variable Compactness.
11
12 IRBM. 2017;38(4):228-33.
13
14

15 5. Holland K, Gubern-Merida A, Mann R, Karssemeijer N. Optimization of volumetric
16
17 breast density estimation in digital mammograms. Phys Med Biol. 2017.
18
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Capítulo 7

7. Conclusões

As ferramentas desenvolvidas para obtenção da quantificação dos tecidos presentes na mama baseada em exames de mamografia conta com contribuições originais quanto à utilização de técnicas de processamento de imagem (limiarização, operadores morfológicos, FCMVC, SDNR) para o desenvolvimento de uma metodologia híbrida, totalmente automática, mostrando-se ainda:

- **Confiável, robusta, precisa e de baixo custo:** Apresentou forte correlação entre a quantificação e a avaliação subjetiva por sistema BI-RADS. Além disso, apresentou também grande concordância da quantificação da PDM com os valores resultantes do exame de RM;
- **Rápida:** Aproximadamente 130 segundos para avaliação;
- **Reprodutível:** Não apresenta variabilidade inter e intra observador;
- **De fácil manuseio:** Sendo automática, não necessita de grande experiência do usuário;
- **De baixa complexidade:** Pode ser utilizada em computadores convencionais.

Além dos resultados apresentados nesta tese, durante o período de doutorado a autora participou de outros projetos desenvolvidos pelo grupo na qual essa pesquisa foi desenvolvida (LAFAR-Laboratório de Física Aplicada ao Radiodiagnóstico). Estes são apresentados no Apêndice I.

Capítulo 8

8. Perspectivas Futuras

Como perspectivas para trabalhos futuros, almeja-se a aplicação da metodologia na rotina clínica. Desta forma, será possível padronizar medidas de VDM em sistemas CR e FFDM permitindo a realização de estudos confiáveis para associação da quantidade de tecido denso e o risco de desenvolvimento de câncer de mama

Além disso, esta metodologia, quando aplicada na rotina, pode auxiliar médicos na recomendação de rastreamento personalizado, determinar se estratégias preventivas devem ser iniciadas e avaliar a eficácia de drogas terapêuticas.

Outro objetivo futuro é, a partir da estimativa do VDM, calcular de forma acurada a dose glandular mamária e fornecer um cartão de dose para o paciente. Através desta medida, será possível realizar estudos associando-se o risco de desenvolvimento de câncer de mama proveniente da dose de radiação do exame mamográfico.

Vale ressaltar que nesta pesquisa parte dos resultados foram comparados ao BI-RADS 4^a edição. No momento da aquisição do bando de dados utilizados, o HCFMB utilizava esta versão. Entretanto, atualmente já são realizados com o BI-RADS 5^a edição. Sendo assim, seria de grande valia a utilização desta metodologia e comparação com esta nova edição.

Ainda, a aplicação desta metodologia em sistemas DR em imagens processadas vem a contribuir com a estimativa da PDM em exames retrospectivos. Além disso, pode-se ajustar o algoritmo e alimentá-lo com informações (não existentes no sistema CR: tensão, corrente, espessura da mama) resultando em uma melhor precisão na estimativa.

Vale enfatizar, que a metodologia empregada para segmentação dos tecidos, FCMVC, pode ser aplicada para quaisquer outras estruturas que se deseja segmentar e

quantificar. Esta abordagem é muito versátil podendo ser aplicada em diferentes modalidades de imagem, como TC, RM, US, tomossíntese da mama, *etc.*

Apêndice I



Technical Notes

Quality and dose optimization in hand computed radiography



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ABSTRACT

The objective of the present study was to optimize a radiographic technique for hand examinations using a computed radiography (CR) system and demonstrate the potential for dose reductions compared with clinically established technique. An exposure index was generated from the optimized technique to guide operators when imaging hands. Homogeneous and anthropomorphic phantoms that simulated a patient's hand were imaged using a CR system at various tube voltages and current settings (40–55 kVp, 1.25–2.8 mAs), including those used in clinical routines (50 kVp, 2.0 mAs) to obtain an optimized chart. The homogeneous phantom was used to assess objective parameters that are associated with image quality, including the signal difference-to-noise ratio (SdNR), which is used to define a figure of merit (FOM) in the optimization process. The anthropomorphic phantom was used to subjectively evaluate image quality using Visual Grading Analysis (VGA) that was performed by three experienced radiologists. The technique that had the best VGA score and highest FOM was considered the gold standard (GS) in the present study. Image quality, dose and the exposure index that are currently used in the clinical routine for hand examinations in our institution were compared with the GS technique. The effective dose reduction was 67.0%. Good image quality was obtained for both techniques, although the exposure indices were 1.60 and 2.39 for the GS and clinical routine, respectively.

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Introduction

Many disease processes are manifested in the small bones of the hands, wrists, and associated soft tissues [1,2]. Several diagnostic decisions depend on detecting the details and image contrast of interfaces in the hand and wrist. The early detection, diagnosis, and continuous evaluation of disease states are essential for successful treatment [1,2]. Radiography is the first choice for the evaluation of diseases of the hands, and other image techniques are rarely used to establish diagnosis and treatment. Therefore, the image quality of X-ray examinations is essential.

Homogeneous phantoms are widely used in image quality optimization to determine the optimal technique and establish

protocols for clinical routines while ensuring maximal image quality with as low as reasonably achievable (ALARA) doses [3,4]. Such phantoms are constructed of tissue-equivalent materials to simulate the absorption and scatter of the X-ray beam in the body. These phantoms are generally made with polymethyl methacrylate (acrylic) and aluminum. Numerous homogeneous phantoms have been constructed for different anatomical regions, such as the chest, abdomen, lumbar spine, skull, and extremities [3–5].

With technical advances from analog to digital systems, techniques that have been traditionally considered optimum for analog systems may no longer be considered optimal for digital systems [6,7]. Operators base their choice of technique on trial and error because digital radiography can be manipulated in the display of the image to obtain the desired contrast [8].

Ideally, the objective optimization of digital radiographs is based on the signal difference-to-noise ratio (SdNR) [6]. A digital image with a high SdNR may provide inherently superior image quality compared with a lower SdNR [6]. Measurements of the SdNR are usually performed in a test object, such as a homogeneous phantom, in which the pixel value of a contrast object (signal) is compared with its surrounding area (background). However, the SdNR is of

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Quantification of Pulmonary Inflammatory Processes Using Chest Radiography: Tuberculosis as the Motivating Application

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Abstract: The purpose of this work was to develop a quantitative method for evaluating the pulmonary inflammatory process (PIP) through the computational analysis of chest radiography exams in posteroanterior (PA) and lateral views. The quantification procedure was applied to patients with tuberculosis (TB) as the motivating application.

A study of high-resolution computed tomography (HRCT) examinations of patients with TB was developed to establish a relation between the inflammatory process and the signal difference-to-noise ratio (SDNR) measured in the PA projection. A phantom essay was used to validate this relation, which was implemented using an algorithm that is able to estimate the volume of the inflammatory region based solely on SDNR values in the chest radiographs of patients.

The PIP volumes that were quantified for 30 patients with TB were used for comparisons with direct HRCT analysis for the same patient. The Bland–Altman statistical analyses showed no significant differences between the 2 quantification methods. The linear regression line had a correlation coefficient of $R^2 = 0.97$ and $P < 0.001$, showing a strong association between the volume that was determined by our evaluation method and the results obtained by direct HRCT scan analysis.

Since the diagnosis and follow-up of patients with TB is commonly performed using X-rays exams, the method developed herein can be considered an adequate tool for quantifying the PIP with a lower patient radiation dose and lower institutional cost. Although we used patients with TB for the application of the method, this method may be used for other pulmonary diseases characterized by a PIP.

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Abbreviations: CR = computed radiography, CT = computed tomography, HRCT = high-resolution computed tomography, MFLIP = mean fractional length of inflammatory processes, PA

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= posteroanterior, PIP = pulmonary inflammatory process, PVC = polyvinyl chloride, ROI = region of interest, SDNR = signal difference-to-noise ratio, TB = tuberculosis, WHO = World Health Organization.

INTRODUCTION

Pulmonary diseases, including tuberculosis (TB) infection, cause an unacceptably large number of deaths, even given that most are preventable if people can access healthcare for proper diagnosis and treatment.^{1,2} The launch of a new international strategy for TB care and control by the World Health Organization (WHO) in the mid-1990s allowed the development of new diagnostic and treatment methods.^{1,2} While new treatments for TB are being developed, tools that are used to monitor the efficacy of TB treatments and quantify the disease remain limited and antiquated in both preclinical and clinical settings.³

Tuberculosis and others pulmonary diseases involve inflammation of the lung parenchyma, resulting in ongoing fibrotic scar formation of the pulmonary interstitium and alveoli.^{4,5} Chest radiography and sputum bacilloscopy are the primary tools for medical examination and the routine diagnosis of TB, even in well-equipped medical centers where skin testing is available.^{6,7} Physicians generally make decisions on TB cases mainly based on radiologic findings, combined with demographic and clinical data.^{6,8} High-resolution computed tomography (HRCT) can be useful when chest radiographs are inconclusive or complications of TB are suspected.⁹ However, this method results in higher radiation doses for the patients (ie, 2 orders of magnitude higher than radiographic examinations) and is associated with extremely high costs to the institution compared with chest radiography.^{10–12} Moreover, in many cases the chest radiography is the only imaging examination in the diagnosis and follow-up of the patient.^{6,8}

The quantification of TB by radiologists is commonly done on visual and subjective examination. An objective quantification tool is greatly important for the reliable and accurate assessment of TB's pulmonary inflammatory process (PIP).³ Reliable assessment helps physicians with follow-up of the patient's disease.³ The preliminary TB diagnosis is normally realized through chest radiography. However, the objective quantification of pulmonary diseases has been developed with HRCT scans^{3,4,13–15} because of its higher resolution.¹⁶

The purpose of this work was to develop an objective method for PIP quantification using chest radiography. The viability of the quantification of PIP based on radiography is demonstrated, with a lower radiation dose and cost, without the loss of a secure medical diagnosis or treatment follow-up. Furthermore, this method allows assess objectively patients which have only X-rays exams.

RESEARCH ARTICLE

Homogeneous Canine Chest Phantom Construction: A Tool for Image Quality Optimization

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Abstract

Digital radiographic imaging is increasing in veterinary practice. The use of radiation demands responsibility to maintain high image quality. Low doses are necessary because workers are requested to restrain the animal. Optimizing digital systems is necessary to avoid unnecessary exposure, causing the phenomenon known as *dose creep*. Homogeneous phantoms are widely used to optimize image quality and dose. We developed an automatic computational methodology to classify and quantify tissues (i.e., lung tissue, adipose tissue, muscle tissue, and bone) in canine chest computed tomography exams. The thickness of each tissue was converted to simulator materials (i.e., Lucite, aluminum, and air). Dogs were separated into groups of 20 animals each according to weight. Mean weights were 6.5 ± 2.0 kg, 15.0 ± 5.0 kg, 32.0 ± 5.5 kg, and 50.0 ± 12.0 kg, for the small, medium, large, and giant groups, respectively. The one-way analysis of variance revealed significant differences in all simulator material thicknesses ($p < 0.05$) quantified between groups. As a result, four phantoms were constructed for dorsoventral and lateral views. In conclusion, the present methodology allows the development of phantoms of the canine chest and possibly other body regions and/or animals. The proposed phantom is a practical tool that may be employed in future work to optimize veterinary X-ray procedures.

Introduction

The use of radiation in veterinary medicine demands responsibility to maintain rigid radiation safety standards and practice. Workers are often requested to restrain animals during the procedure to avoid movement artifacts and maintain image quality [1, 2]. Therefore, the exposure of workers have to be minimized considering the radiation protection principles because of

Paracoccidioidomycosis: level of pulmonary sequelae in high resolution computed tomography images from patients of two endemic regions of Brazil

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Background: The purpose of the present study was to evaluate differences in lung damage in patients with paracoccidioidomycosis (PCM) in two endemic regions of Brazil (Botucatu, SP, in the southeastern region and Campo Grande, MS, in the west central region).

Methods: The study sought to objectively quantify fibrosis and emphysema treated patients using high-resolution computed tomography (HRCT) that was performed according to an established and validated computational method. The analysis was based on clinical data that were associated with objective quantifications of pulmonary sequelae. We performed a retrospective analysis of HRCT exams from 32 successfully treated patients with the chronic form of PCM. The two groups had similar characteristics with regard to age, symptom duration, smoking history, and titers on a diagnostic serologic test.

Results: The statistical analysis revealed more severe cases and a higher percentage of emphysema in the Campo Grande group. The mean percentages of emphysema were 40.2% and 13.6% in the Campo Grande and Botucatu groups, respectively. The percentage of fibrosis was significantly higher in the Botucatu group (11.3%) than in the Campo Grande group (2.3%).

Conclusions: The present results may reflect differences in cryptic species of *P. brasiliensis* in these two geographic regions of Brazil. Further studies should be done to clarify the differences observed herein. Such findings may help unveil differences among cryptic species in terms of the pulmonary consequences that are caused by this disease, which would be highly beneficial to PCM patients.

Keywords: Cryptic species; emphysema; fibrosis; paracoccidioidomycosis (PCM); quantification; tissue

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Introduction

Paracoccidioidomycosis (PCM) is a systemic mycosis geographically restricted to Central and South America (1-4) and is endemic to populations who live in rural areas (1,5,6).

The majority of the PCM cases (around 80%) are reported in Brazil (7,8), which is the first one cause of death among systemic mycoses disease in the country (1,9). Different distribution in endemic areas and the difficult to notify the

ABDOMEN–PELVIS COMPUTED TOMOGRAPHY PROTOCOL OPTIMIZATION: AN IMAGE QUALITY AND DOSE ASSESSMENT

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Computed tomography (CT) has a high level of sensitivity and specificity for the diagnosis and follow-up of pathologies of the abdomen–pelvis region. Some features, such as automatic tube current modulation (ATCM), permits the acquisition of quality images with low radiation doses. This study evaluated the image quality and radiation dose of abdomen–pelvis CT protocols with ATCM technique. Were performed five CT protocols using 16-slice and 64-slice scanners, an anthropomorphic phantom for dosimetric measurements, an analytical phantom and retrospective examinations for image quality analysis. Were found significant reduction in effective dose. The highest absorbed doses were found in the stomach and spleen (56.1 and 47.2 mGy, respectively). Objective parameters as noise, low contrast and spatial resolution did not significantly differ between the protocols ($p > 0.05$). All protocols received the range of ‘Optimum/Acceptable’ in patient’s image quality analysis. This methodology can be reproduced in any clinical routine to optimize CT protocols.

INTRODUCTION

Computed tomography (CT) has a high level of sensitivity and specificity and is widely used for the diagnosis and follow-up of pathologies of the abdomen–pelvis region^(1, 2). It is highly sensitive for the diagnosis of ureteric calculus, appendicitis, bone metastases, and bowel and mesenteric injuries, with sensitivities of 92, 100, 71–100 and 82%, respectively⁽¹⁾. In 2008 and 2014, respectively, the French Speaking Society of Medical Emergencies and European Association of Urology recommended CT as the first-line imaging modality to investigate suspected cases of renal colic⁽²⁾. In the follow-up cases of ovarian cancer and nearly all pancreatic diseases, CT is considered the gold-standard imaging modality^(3, 4).

The possibility of acquiring a large number of images in a short scanning time substantially has increased the number of CT exams that are performed in clinical routines. This has consequently increased the radiation doses that are received by patient populations, which has become a public health concern^(4, 5). Published data indicate that 70% of the radiation doses that are received by patients who undergo medical

imaging is attributable to CT examinations^(1, 6). Furthermore, 31% of the annual radiation doses that are received from different imaging modalities is attributable to abdomen–pelvis CT exams⁽⁴⁾. This creates a concern about the high radiation doses that are received by patients, especially pediatric patients, and the well-known association between the risk of cancer and radiation exposure^(5, 7, 8).

Based on the ALARA principle (As Low As Reasonably Achievable), radiology examinations must achieve a balance between radiation doses and image quality, with the continual goal of reducing the doses that are received by patients^(2, 9). With advances in CT scanners, some features (e.g. automatic tube current modulation [ATCM]) permit the acquisition of high-quality images with low radiation doses⁽¹⁰⁾. ATCM automatically adjusts the tube current (mA) during each gantry rotation according to the patient’s size and attenuation body area^(1, 3) to achieve a specific degree of image quality⁽¹¹⁾, which reduces radiation exposure compared with fixed tube current techniques^(1, 10). Previous studies found that ~60% of the radiation dose can be reduced with ATCM^(1, 2, 12, 13).



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ORIGINAL ARTICLE

Radiographic predictors determined with an objective assessment tool for neonatal patients with necrotizing enterocolitis[☆]

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KEYWORDS

Necrotizing enterocolitis;
Abdominal radiography;
Image processing;
Texture analyses,
wavelet

Abstract

Objectives: The objective of this study was to develop and validate a computational tool to assist radiological decisions on necrotizing enterocolitis.

Methodology: Patients that exhibited clinical signs and radiographic evidence of Bell's stage 2 or higher were included in the study, resulting in 64 exams. The tool was used to classify localized bowel wall thickening and intestinal pneumatosis using full-width at half-maximum measurements and texture analyses based on wavelet energy decomposition. Radiological findings of suspicious bowel wall thickening and intestinal pneumatosis loops were confirmed by both patient surgery and histopathological analysis. Two experienced radiologists selected an involved bowel and a normal bowel in the same radiography. The full-width at half-maximum and wavelet-based texture feature were then calculated and compared using the Mann-Whitney U test. Specificity, sensibility, positive and negative predictive values were calculated.

Results: The full-width at half-maximum results were significantly different between normal and distended loops (median of 10.30 and 15.13, respectively). Horizontal, vertical, and diagonal wavelet energy measurements were evaluated at eight levels of decomposition. Levels 7 and 8 in the horizontal direction presented significant differences. For level 7, median was 0.034 and 0.088 for normal and intestinal pneumatosis groups, respectively, and for level 8 median was 0.19 and 0.34, respectively.

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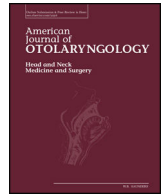
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Cochlear implants: Insertion assessment by computed tomography[☆]

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ABSTRACT

Background and objectives: Imaging exams play a key role in cochlear implants with regard to both planning implantation before surgery and quality control after surgery. The ability to visualize the three-dimensional location of implanted electrodes is useful in clinical routines for assessing patient outcome. The aim of this study was to evaluate linear and angular insertion depth measurements of cochlear implants based on conventional computed tomography.

Methods: Tools for linear and angular measurements of cochlear implants were used in computed tomography exams. The tools realized the insertion measurements in an image reconstruction of the CIs, based on image processing techniques. We comprehensively characterized two cochlear implant models while obviating possible changes that can be caused by different cochlea sizes by using the same human temporal bones to evaluate the implant models.

Results: The tools used herein were able to differentiate the insertion measurements between two cochlear implant models widely used in clinical practice. We observed significant differences between both insertion measurements because of their different design and construction characteristics ($p = 0.004$ and 0.003 for linear and angular measurements, respectively; t -test). The presented methodology showed to be a good tool to calculate insertion depth measurements, since it is easy to perform, produces high-resolution images, and is able to depict all the landmarks, thus enabling measurement of the angular and linear insertion depth of the most apical electrode contacts.

Conclusion: The present study demonstrates practical and useful tools for evaluating cochlear implant electrodes in clinical practice. Further studies should measure preoperative and postoperative benefits in terms of speech recognition and evaluate the preservation of residual hearing in the implanted ear. Such studies can also determine correlations between surgical factors, electrode positions, and performance. In addition to refined surgical techniques, the precise evaluation of cochlear length and correct choice of cochlear implant characteristics can play an important role in postoperative outcomes.

1. Introduction

Cochlear implants (CIs) functionally restore hearing in individuals with profound hearing impairment [1–4]. An array of electrodes is introduced into the cochlea, and electrical pulses are applied across the array to stimulate residual populations of dendritic and spiral ganglion nerve bodies. Most individuals are able to obtain 40–80% correct postoperative word recognition with their CI compared with zero or only modest scores preoperatively [5]. Although the implantation

procedure is safe and reliable, complications occur in approximately 16% of patients [6]. Following cochlear implantation, there is the possibility that residual hearing can be lost because of the surgical procedure itself or progression of the underlying pathology [7,8]. A greater focus has been placed on minimizing insertion trauma and preserving preexisting hearing [9,10]. For electroacoustic stimulation to be the most effective, the patient's residual hearing should be preserved during CI surgery [4,7,10–12]. Thus, selecting the optimal insertion depth should be patient-specific and based on the corresponding

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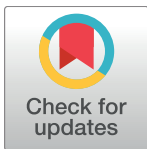
RESEARCH ARTICLE

Computed tomography-based volumetric tool for standardized measurement of the maxillary sinus

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files. Algorithm is available in the protocols.io ([dx.doi.org/10.17504/protocols.io.ig7cbzn](https://doi.org/10.17504/protocols.io.ig7cbzn)) and in the GitHub website (<https://github.com/dianapina/Maxillary-Sinus-Quantification>).

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Abstract

Volume measurements of maxillary sinus may be useful to identify diseases affecting paranasal sinuses. However, literature shows a lack of consensus in studies measuring the volume. This may be attributable to different computed tomography data acquisition techniques, segmentation methods, focuses of investigation, among other reasons. Furthermore, methods for volumetrically quantifying the maxillary sinus are commonly manual or semiautomated, which require substantial user expertise and are time-consuming. The purpose of the present study was to develop an automated tool for quantifying the total and air-free volume of the maxillary sinus based on computed tomography images. The quantification tool seeks to standardize maxillary sinus volume measurements, thus allowing better comparisons and determinations of factors that influence maxillary sinus size. The automated tool utilized image processing techniques (watershed, threshold, and morphological operators). The maxillary sinus volume was quantified in 30 patients. To evaluate the accuracy of the automated tool, the results were compared with manual segmentation that was performed by an experienced radiologist using a standard procedure. The mean percent differences between the automated and manual methods were $7.19\% \pm 5.83\%$ and $6.93\% \pm 4.29\%$ for total and air-free maxillary sinus volume, respectively. Linear regression and Bland-Altman statistics showed good agreement and low dispersion between both methods. The present automated tool for maxillary sinus volume assessment was rapid, reliable, robust, accurate, and reproducible and may be applied in clinical practice. The tool may be used to standardize measurements of maxillary volume. Such standardization is extremely important for allowing comparisons between studies, providing a better understanding of the role of the maxillary sinus, and determining the factors that influence maxillary sinus size under normal and pathological conditions.

Automatic Identification and Extraction of Pectoral Muscle in Digital Mammography

Ana L. M. Pavan, Antoine Vacavant, Allan F. F. Alves,
Andre P. Trindade, and Diana R. de Pina

Abstract

Mammography is a worldwide image modality used to diagnose breast cancer and can be used to measure breast density (BD). In clinical routine, radiologist perform image evaluations through BIRADS assessment. However, this method has inter and intraindividual variability. An automatic method to measure BD could relieve radiologist's workload by providing a first aid opinion. However, pectoral muscle (PM) is a high density tissue, with the same imaging characteristics as fibroglandular tissues, which makes its automatic detection a challenging task. The aim of this work is to develop an automatic algorithm to segment and extract PM in digital mammograms. A hybrid methodology has been developed using Hough transform, to find the edge of the PM, and active contour, to segment PM muscle. Seed of active contour is applied automatically in the edge of PM found by Hough transform. An experienced radiologist manually performed the PM segmentation. Manual and automatic methods were compared using the Jaccard index and Bland-Altman statistics. The comparison between methods presented a Jaccard similarity coefficient greater than 90% for all analyzed images. The Bland-Altman statistics compared the segmented PM area and showed agreement between both methods within 95% confidence interval. The method proved to be accurate and robust, segmenting rapid and free of intra and inter-observer variability.

Keywords

Mammography • Pectoral muscle • Hough transform and active contour

1 Introduction

Mammography is a worldwide image modality used to diagnose breast cancer, even in asymptomatic women. Due to its large availability, mammograms can be used to measure breast density and to predict cancer development [1]. Women with increased mammographic density have a four-to sixfold increase in their risk of developing breast cancer [1, 2]. In clinical routine, radiologist perform image evaluations through BIRADS (Breast Imaging Reporting and Data System) assessment. However, this subjective method shows variable intra-and inter-observer agreement [3, 4].

Furthermore, BIRADS categories are too rough to follow breast evolution in individual women [3]. For this reason, tasks such as selection of women who may benefit from supplemental screening exams and prediction of breast cancer risk, may be challenging with only subjective density assessment [2, 5]. Therefore, studies have been made to accurately quantify mammographic breast density. An automatic objective method to measure breast density could relieve radiologist's workload by providing a first aid opinion. Semi-automated and automated algorithms have been developed to achieve objective breast density measurements [2, 3, 5–8].

Algorithms are applied in digital mammograms in crano-caudal (CC) and medio-lateral oblique (MLO) views. However, pectoral muscle (PM) is a high density tissue, with similar image characteristics as fibroglandular tissues [9]. Furthermore, patient positioning during mammograms acquisition may cause variations in texture, size, position, intensity and shape of PM [10]. It is consequently hard to automatically quantify mammographic breast density. The

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U-CatchHCC: An Accurate HCC Detector in Hepatic DCE-MRI Sequences Based on an U-Net Framework

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Abstract. This paper presents a novel framework devoted to the detection of HCC (Hepato-Cellular Carcinoma) within hepatic DCE-MRI (Dynamic Contrast-Enhanced MRI) sequences, by a deep learning approach. In clinical routine, radiologists usually consider different phases during contrast injection (before injection; arterial phase; portal phase for instance) for HCC diagnosis. By employing a U-Net architecture, we are able to identify such tumors with a very high accuracy (98.5% of classification rate at best) for a small cohort of patients, which should be confirmed in future works by considering larger groups. We also show in this paper the influence of patch size for this machine learning process, and the positive impact of employing all phases available in DCE-MRI sequences, compared to use only one.

1 Context and Motivation

Liver cancer is the second leading cause of death by cancer worldwide with more than 700,000 deaths in 2012 according to the World Health Organization (WHO) [16]. This cancer is particularly aggressive and its mortality rate is still increasing since the 90s in the World. Hepatocellular Carcinoma (HCC) is the most common liver cancer (90%), and the WHO estimated the number of new cases per year at 704,000 in the World in 2012. HCC occurs in liver cirrhosis at 80%, and due to a late diagnosis, the 5-years overall survival is of about 10%. HCC nodules are hypervascularized and their growth can be unifocal (as a single mass) or multifocal (several nodules). Patients suffering from HCC are 30–50,

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A Parallel Framework for HCC Detection in DCE-MRI Sequences with Wavelet-Based Description and SVM classification

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ABSTRACT

In this article, we propose a complete framework devoted to detect liver HCC (Hepato-Cellular Carcinoma) tumors within DCE-MRI (Dynamic Contrast Enhanced-MRI) sequences. Our system employs different phases of these hepatic image sequences (depending on time after contrast agent injection) to describe local patches with wavelet-based descriptors. By using a SVM (Support Vector Machine)-based classification, we are able to distinguish healthy patches from pathological ones. Moreover, thanks to a parallel image processing strategy, we are able to reduce significantly the running time so that our system may be utilized as a computer aided diagnosis tool in the future. Our experiments show that our contribution is an accurate system for HCC detection, with a small cohort of patients, but representing a high volume of image data to be processed. This work encourages us to conduct deeper researches for detecting complex HCC cases for larger patients cohorts.

CCS CONCEPTS

•Computing methodologies → Support vector machines; Image processing; •Applied computing → Health care information systems;

KEYWORDS

Medical image analysis, machine learning, DCE-MRI, liver, HCC, tumor detection, parallelization, wavelet image description

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1 INTRODUCTION

Liver cancer is the second leading cause of cancer-related death worldwide: 746,000 deaths in 2012 according to the World Health Organization (WHO), this cancer is particularly aggressive and its mortality rate is still increasing since 1990s, as reveal statistics gathered from various countries (in the World and in Europe) [26].

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Referências Bibliográficas

- ACS 2017. American Cancer Society. *Cancer Facts & Figures 2017*. Atlanta: American Cancer Society.
- AHMED, M. N., YAMANY, S. M., MOHAMED, N., FARAG, A. A. & MORIARTY, T. 2002. A modified fuzzy C-means algorithm for bias field estimation and segmentation of MRI data. *Ieee Transactions on Medical Imaging*, 21, 193-199.
- AITKEN, Z., MCCORMACK, V. A., HIGHNAM, R. P., MARTIN, L., GUNASEKARA, A., MELNICHOUK, O., MAWDSLEY, G., PERESSOTTI, C., YAFFE, M., BOYD, N. F. & DOS SANTOS SILVA, I. 2010. Screen-film mammographic density and breast cancer risk: a comparison of the volumetric standard mammogram form and the interactive threshold measurement methods. *Cancer Epidemiol Biomarkers Prev*, 19, 418-28.
- ALONZO-PROULX, O., MAINPRIZE, J. G., PACKARD, N. J., BOONE, J. M., AL-MAYAH, A., BROCK, K. & YAFFE, M. J. Development of a Peripheral Thickness Estimation Method for Volumetric Breast Density Measurements in Mammography Using a 3D Finite Element Breast Model. In: MARTÍ J., O. A., FREIXENET J., MARTÍ R. , ed. International Workshop on Digital Mammography, 2010a Catalonia, Spain. Springer, Berlin, Heidelberg, 467–473.
- ALONZO-PROULX, O., PACKARD, N., BOONE, J. M., AL-MAYAH, A., BROCK, K. K., SHEN, S. Z. & YAFFE, M. J. 2010b. Validation of a method for measuring the volumetric breast density from digital mammograms. *Phys Med Biol*, 55, 3027-44.
- ASSI, V., WARWICK, J., CUZICK, J. & DUFFY, S. W. 2011. Clinical and epidemiological issues in mammographic density. *Nat Rev Clin Oncol*, 9, 33-40.
- BAI, X. 2013. Morphological image fusion using the extracted image regions and details based on multi-scale top-hat transform and toggle contrast operator. *Digital Signal Processing*, 23, 542-554.
- BATH, M. & MANSSON, L. G. 2007. Visual grading characteristics (VGC) analysis: a non-parametric rank-invariant statistical method for image quality evaluation. *Br J Radiol*, 80, 169-76.
- BERNARDES, A. 2011 *Manual de ginecologia*, Lisboa, Permanyer Portugal.

- BERNHARDT, P., MERTELMEIER, T. & HOHEISEL, M. 2006. X-ray spectrum optimization of full-field digital mammography: simulation and phantom study. *Med Phys*, 33, 4337-49.
- BICK, U., GIGER, M. L., SCHMIDT, R. A., NISHIKAWA, R. M. & DOI, K. 1996. Density correction of peripheral breast tissue on digital mammograms. *Radiographics*, 16, 1403-11.
- BLOOMQUIST, A., BOSMANS, H., BURCH, A., CHEVALIER, M., DAROS, K., GENNARO, G., HEGGIE, J., JONG, R., MAWDSLEY, G., MCLEAN, I. D., MORA, P., PONGNAPANG, N., RAJAPAKSHE, R., REHANI, M., RICKARD, M., YAFFE, M. & YOUNG, K. (eds.) 2011. *Quality Assurance Programme for Digital Radiography*, Vienna.
- BONTRAGER, K. L. & LAMPIGNANO, J. P. 2014. *Textbook of Radiographic Positioning and Related Anatomy*, St. Louis, Elsevier/Mosby.
- BOVIK, A. C. 2005. *Handbook of image and video processing*, Amsterdam ; Boston, MA, Elsevier Academic Press.
- BOYD, N., MARTIN, L., GUNASEKARA, A., MELNICHOUK, O., MAUDSLEY, G., PERESSOTTI, C., YAFFE, M. & MINKIN, S. 2009. Mammographic density and breast cancer risk: evaluation of a novel method of measuring breast tissue volumes. *Cancer Epidemiol Biomarkers Prev*, 18, 1754-62.
- BOYD, N. F., BYNG, J. W., JONG, R. A., FISHELL, E. K., LITTLE, L. E., MILLER, A. B., LOCKWOOD, G. A., TRITCHLER, D. L. & YAFFE, M. J. 1995. Quantitative classification of mammographic densities and breast cancer risk: results from the Canadian National Breast Screening Study. *J Natl Cancer Inst*, 87, 670-5.
- BOYD, N. F., GREENBERG, C., LOCKWOOD, G., LITTLE, L., MARTIN, L., TRITCHLER, D., BYNG, J. & YAFFE, M. 1997. Effects at Two Years of a Low-Fat, High-Carbohydrate Diet on Radiologic Features of the Breast: Results From a Randomized Trial. *JNCI: Journal of the National Cancer Institute*, 89, 488-496.
- BOYD, N. F., GUO, H., MARTIN, L. J., SUN, L., STONE, J., FISHELL, E., JONG, R. A., HISLOP, G., CHIARELLI, A., MINKIN, S. & YAFFE, M. J. 2007. Mammographic Density and the Risk and Detection of Breast Cancer. *New England Journal of Medicine*, 356, 227-236.

- BOYD, N. F., MARTIN, L. J., SUN, L., GUO, H., CHIARELLI, A., HISLOP, G., YAFFE, M. & MINKIN, S. 2006. Body size, mammographic density, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*, 15, 2086-92.
- BRANDT, K. R., SCOTT, C. G., MA, L., MAHMOUDZADEH, A. P., JENSEN, M. R., WHALEY, D. H., WU, F. F., MALKOV, S., HRUSKA, C. B., NORMAN, A. D., HEINE, J., SHEPHERD, J., PANKRATZ, V. S., KERLIKOWSKE, K. & VACHON, C. M. 2016. Comparison of Clinical and Automated Breast Density Measurements: Implications for Risk Prediction and Supplemental Screening. *Radiology*, 279, 710-9.
- BURTON, A., BYRNES, G., STONE, J., TAMIMI, R. M., HEINE, J., VACHON, C., OZMEN, V., PEREIRA, A., GARMENDIA, M. L., SCOTT, C., HIPWELL, J. H., DICKENS, C., SCHUZ, J., ARIBAL, M. E., BERTRAND, K., KWONG, A., GILES, G. G., HOPPER, J., PEREZ GOMEZ, B., POLLAN, M., TEO, S. H., MARIAPUN, S., TAIB, N. A., LAJOUS, M., LOPEZ-RIDUARA, R., RICE, M., ROMIEU, I., FLUGELMAN, A. A., URSIN, G., QURESHI, S., MA, H., LEE, E., SIROUS, R., SIROUS, M., LEE, J. W., KIM, J., SALEM, D., KAMAL, R., HARTMAN, M., MIAO, H., CHIA, K. S., NAGATA, C., VINAYAK, S., NDUMIA, R., VAN GILS, C. H., WANDERS, J. O., PEPLONSKA, B., BUKOWSKA, A., ALLEN, S., VINNICOMBE, S., MOSS, S., CHIARELLI, A. M., LINTON, L., MASKARINEC, G., YAFFE, M. J., BOYD, N. F., DOS-SANTOS-SILVA, I. & MCCORMACK, V. A. 2016. Mammographic density assessed on paired raw and processed digital images and on paired screen-film and digital images across three mammography systems. *Breast Cancer Res*, 18, 130.
- BUSHBERG, J. T. 2002. *The essential physics of medical imaging*, Philadelphia, Lippincott Williams & Wilkins.
- BYNG, J. W., BOYD, N. F., FISHELL, E., JONG, R. A. & YAFFE, M. J. 1996. Automated analysis of mammographic densities. *Phys Med Biol*, 41, 909-23.
- BYNG, J. W., CRITTEN, J. P. & YAFFE, M. J. 1997. Thickness-equalization processing for mammographic images. *Radiology*, 203, 564-8.
- BYNG, J. W., YAFFE, M. J., JONG, R. A., SHUMAK, R. S., LOCKWOOD, G. A., TRITCHLER, D. L. & BOYD, N. F. 1998. Analysis of mammographic density

- and breast cancer risk from digitized mammograms. *Radiographics*, 18, 1587-98.
- BYRNE, C., SCHAIRER, C., WOLFE, J., PAREKH, N., SALANE, M., BRINTON, L. A., HOOVER, R. & HAILE, R. 1995. Mammographic features and breast cancer risk: effects with time, age, and menopause status. *J Natl Cancer Inst*, 87, 1622-9.
- CARIOLI, G., MALVEZZI, M., RODRIGUEZ, T., BERTUCCIO, P., NEGRI, E. & LA VECCHIA, C. 2017. Trends and predictions to 2020 in breast cancer mortality in Europe. *Breast*, 36, 89-95.
- CHECKA, C. M., CHUN, J. E., SCHNABEL, F. R., LEE, J. & TOTH, H. 2012. The relationship of mammographic density and age: implications for breast cancer screening. *AJR Am J Roentgenol*, 198, W292-5.
- CHEN, X., MOSCHIDIS, E., TAYLOR, C. & ASTLEY, S. Improving Mammographic Density Estimation in the Breast Periphery. In: TINGBERG, A., LÅNG, K. & TIMBERG, P., eds. International Workshop on Digital Mammography, 2016 Malmö Live, Malmö, Sweden. Springer International Publishing, 469-477.
- CHUANG, K. S., TZENG, H. L., CHEN, S., WU, J. & CHEN, T. J. 2006. Fuzzy c-means clustering with spatial information for image segmentation. *Comput Med Imaging Graph*, 30, 9-15.
- CIATTO, S., HOUSSAMI, N., APRUZZESE, A., BASSETTI, E., BRANCATO, B., CAROZZI, F., CATARZI, S., LAMBERINI, M. P., MARCELLI, G., PELLIZZONI, R., PESCE, B., RISSO, G., RUSSO, F. & SCORSOLINI, A. 2005. Categorizing breast mammographic density: intra- and interobserver reproducibility of BI-RADS density categories. *Breast*, 14, 269-75.
- CUZICK, J. 2008. Assessing risk for breast cancer. *Breast Cancer Res*, 10 Suppl 4, S13.
- DANCE, D., CHRISTOFIDES, S., MAIDMENT, A., MCLEAN, I. & NG, K. 2014. *Diagnostic Radiology Physics: A Handbook for Teachers and Students*, International Atomic Energy Agency.
- DAVIDSON, R. & SIM, J. 2008. Computed Radiography and Dosimetry: Some Practical Tips for Dose Optimization Procedures. *Journal of Medical Imaging and Radiation Science*, 39, 109-114.
- DRAKE, R. L., VOGL, A. W. & MITCHELL, A. W. M. 2010. *Gray's Anatomia para Estudantes*, Rio de Janeiro, Elsevier.

- FREER, P. E. 2015. Mammographic breast density: impact on breast cancer risk and implications for screening. *Radiographics*, 35, 302-15.
- GIACOMINI, G., MIRANDA, J. R., PAVAN, A. L., DUARTE, S. B., RIBEIRO, S. M., PEREIRA, P. C., ALVES, A. F., DE OLIVEIRA, M. & PINA, D. R. 2015. Quantification of Pulmonary Inflammatory Processes Using Chest Radiography: Tuberculosis as the Motivating Application. *Medicine (Baltimore)*, 94, e1044.
- GONZALEZ, R. C. & WOODS, R. E. 2008. *Digital image processing*, Upper Saddle River, NJ, Pearson/Prentice Hall.
- GRAM, I. T., FUNKHOUSER, E. & TABAR, L. 1997. The Tabar classification of mammographic parenchymal patterns. *Eur J Radiol*, 24, 131-6.
- GUBERN-MERIDA, A., KALLENBERG, M., PLATEL, B., MANN, R. M., MARTI, R. & KARSSEMEIJER, N. 2014. Volumetric breast density estimation from full-field digital mammograms: a validation study. *PLoS One*, 9, e85952.
- HARALICK, R. M., STERNBERG, S. R. & ZHUANG, X. 1987. Image analysis using mathematical morphology. *IEEE Trans Pattern Anal Mach Intell*, 9, 532-50.
- HE, W., HOGG, P., JUETTE, A., DENTON, E. R. & ZWIGGELAAR, R. 2015. Breast image pre-processing for mammographic tissue segmentation. *Comput Biol Med*, 67, 61-73.
- HEINE, J. J., CARSTON, M. J., SCOTT, C. G., BRANDT, K. R., WU, F. F., PANKRATZ, V. S., SELLERS, T. A. & VACHON, C. M. 2008. An automated approach for estimation of breast density. *Cancer Epidemiol Biomarkers Prev*, 17, 3090-7.
- HENDEE, W. R. & RITENOUR, E. R. 2002. *Medical Imaging Physics*, Wiley-Liss.
- HIGHNAM, R., BRADY, M. & SHEPSTONE, B. 1996. A representation for mammographic image processing. *Med Image Anal*, 1, 1-18.
- HOLLAND, K., GUBERN-MERIDA, A., MANN, R. & KARSSEMEIJER, N. 2017. Optimization of volumetric breast density estimation in digital mammograms. *Phys Med Biol*.
- INCA, I. N. D. C. 2018. *Estimativa 2018: Incidência de Câncer no Brasil*.
- JEFFREYS, M., WARREN, R., HIGHNAM, R. & DAVEY SMITH, G. 2008. Breast cancer risk factors and a novel measure of volumetric breast density: cross-sectional study. *Br J Cancer*, 98, 210-6.

- KANG, J. Y., MIN, L. Q., LUAN, Q. X., LI, X. & LIU, J. Z. 2009. Novel modified fuzzy c-means algorithm with applications. *Digital Signal Processing*, 19, 309-319.
- KANNAN, S. R., RAMATHILAGAM, S., DEVI, R. & SATHYA, A. 2011. Robust kernel FCM in segmentation of breast medical images. *Expert Systems with Applications*, 38, 4382-4389.
- KARSSEMEIJER, N. 1998. Automated classification of parenchymal patterns in mammograms. *Phys Med Biol*, 43, 365-78.
- KAUFHOLD, J., THOMAS, J. A., EBERHARD, J. W., GALBO, C. E. & TROTTER, D. E. 2002. A calibration approach to glandular tissue composition estimation in digital mammography. *Med Phys*, 29, 1867-80.
- KELLER, B. M., NATHAN, D. L., WANG, Y., ZHENG, Y., GEE, J. C., CONANT, E. F. & KONTOS, D. 2012. Estimation of breast percent density in raw and processed full field digital mammography images via adaptive fuzzy c-means clustering and support vector machine segmentation. *Med Phys*, 39, 4903-17.
- KERLIKOWSKE, K., SCOTT, C. G., MAHMOUDZADEH, A. P., MA, L., WINHAM, S., JENSEN, M. R., WU, F. F., MALKOV, S., PANKRATZ, V. S., CUMMINGS, S. R., SHEPHERD, J. A., BRANDT, K. R., MIGLIORETTI, D. L. & VACHON, C. M. 2018. Automated and Clinical Breast Imaging Reporting and Data System Density Measures Predict Risk for Screen-Detected and Interval Cancers: A Case-Control Study. *Ann Intern Med*, 168, 757-765.
- KHOKHER, M. R., GHAFOR, A. & SIDDIQUI, A. M. 2012. Image segmentation using multilevel graph cuts and graph development using fuzzy rule-based system. *IET Image Process*, 7, 201-211.
- KOLB, T. M., LICHY, J. & NEWHOUSE, J. H. 2002. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology*, 225, 165-75.
- KRUGER, R. Analysis and Comparison of the Signal Difference to Noise Ratio (SDNR), Signal Difference (SD), and the Signal to Noise Ratio (SDR): Evaluating the Suitability of the SD and SDNR as MRI Quality Control Parameters. 22nd Annual EMBS International Conference, 2000 Chicago. Proceedings of 22nd Annual EMBS International Conference.

- LI, J., SZEKELY, L., ERIKSSON, L., HEDDSON, B., SUNDBOM, A., CZENE, K., HALL, P. & HUMPHREYS, K. 2012. High-throughput mammographic-density measurement: a tool for risk prediction of breast cancer. *Breast Cancer Res*, 14, R114.
- LIN, Y. C., TSAI, Y. P., HUNG, Y. P. & SHIH, Z. C. 2006. Comparison Between Immersion-Based and Toboggan-Based Watershed Image Segmentation. *IEEE Trans on Image Processing*, 15, 632-641.
- LU, L. J., NISHINO, T. K., JOHNSON, R. F., NAYEEM, F., BRUNDER, D. G., JU, H., LEONARD, M. H., GRADY, J. J. & KHAMAPIRAD, T. 2012. Comparison of breast tissue measurements using magnetic resonance imaging, digital mammography and a mathematical algorithm. *Phys Med Biol*, 57, 6903-27.
- LU, L. J., NISHINO, T. K., KHAMAPIRAD, T., GRADY, J. J., LEONARD, M. H., JR. & BRUNDER, D. G. 2007. Computing mammographic density from a multiple regression model constructed with image-acquisition parameters from a full-field digital mammographic unit. *Phys Med Biol*, 52, 4905-21.
- MALKOV, S., WANG, J., KERLIKOWSKE, K., CUMMINGS, S. R. & SHEPHERD, J. A. 2009. Single x-ray absorptiometry method for the quantitative mammographic measure of fibroglandular tissue volume. *Med Phys*, 36, 5525-36.
- MANDELSON, M. T., OESTREICHER, N., PORTER, P. L., WHITE, D., FINDER, C. A., TAPLIN, S. H. & WHITE, E. 2000. Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst*, 92, 1081-7.
- MARAGOS, P. 1996. Differential morphology and image processing. *IEEE Trans Image Process*, 5, 922-37.
- MCCORMACK, V. A. & DOS SANTOS SILVA, I. 2006. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. *Cancer Epidemiol Biomarkers Prev*, 15, 1159-69.
- NICHOLSON, B. T., LORUSSO, A. P., SMOLKIN, M., BOVBJERG, V. E., PETRONI, G. R. & HARVEY, J. A. 2006. Accuracy of assigned BI-RADS breast density category definitions. *Acad Radiol*, 13, 1143-9.
- NIE, K., CHEN, J. H., CHAN, S., CHAU, M. K. I., YU, H. J., BAHRI, S., TSENG, T., NALCIOGLU, O. & SU, M. Y. 2008. Development of a quantitative method for

- analysis of breast density based on three-dimensional breast MRI. *Medical Physics*, 35, 5253-5262.
- OOMS, E. A., ZONDERLAND, H. M., EIJKEMANS, M. J., KRIEGE, M., MAHDAVIAN DELAVARY, B., BURGER, C. W. & ANSINK, A. C. 2007. Mammography: interobserver variability in breast density assessment. *Breast*, 16, 568-76.
- OREL, S. G., KAY, N., REYNOLDS, C. & SULLIVAN, D. C. 1999. BI-RADS categorization as a predictor of malignancy. *Radiology*, 211, 845-50.
- PAREDES, E. S. D. 2007. *Atlas of Mammography*, Virginia, Lippincott Williams & Wilkins.
- PAWLUCZYK, O., AUGUSTINE, B. J., YAFFE, M. J., RICO, D., YANG, J., MAWDSLEY, G. E. & BOYD, N. F. 2003. A volumetric method for estimation of breast density on digitized screen-film mammograms. *Med Phys*, 30, 352-64.
- PRECHT, H., TINGBERG, A., WAALER, D. & OUTZEN, C. B. 2013. New Developed DR Detector Performs Radiographs of Hand, Pelvic and Premature Chest Anatomies at a Lower Radiation Dose and/or a Higher Image Quality. *J Digit Imaging*.
- REDONDO, A., COMAS, M., MACIA, F., FERRER, F., MURTA-NASCIMENTO, C., MARISTANY, M. T., MOLINS, E., SALA, M. & CASTELLS, X. 2012. Inter- and intraradiologist variability in the BI-RADS assessment and breast density categories for screening mammograms. *Br J Radiol*, 85, 1465-70.
- ROERDINK, J. B. T. M. & MEIJSTER, A. 2000. The Watershed transform: Definitions, algorithms and parallelization strategies. *Fundamenta Informaticae*, 41, 187-228.
- ROWLANDS, J. A. 2002. The Physics of Computed Radiology. *Physics in Medicine and Biology*, 47, 123-166.
- SCHMACHTENBERG, C., HAMMANN-KLOSS, S., BICK, U. & ENGELKEN, F. 2015. Intraindividual comparison of two methods of volumetric breast composition assessment. *Acad Radiol*, 22, 447-52.
- SCHOUSBOE, J. T., KERLIKOWSKE, K., LOH, A. & CUMMINGS, S. R. 2011. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med*, 155, 10-20.

- SEIBERT, J. A., BOGUCKI, T. M., CIONA, T. & AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE. 2006. *Acceptance Testing and Quality Control of Photostimulable storage Phosphor Imaging Systems* San Diego, California, USA, SPIE.
- SEO, J. M., KO, E. S., HAN, B. K., KO, E. Y., SHIN, J. H. & HAHN, S. Y. 2013. Automated volumetric breast density estimation: a comparison with visual assessment. *Clin Radiol*, 68, 690-5.
- SICKLES, E. A., D'ORSI, C. J., BASSETT, L. W. & AL., E. 2013. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. *American College of Radiology*.
- SIVARAMAKRISHNA, R., OBUCHOWSKI, N. A., CHILCOTE, W. A. & POWELL, K. A. 2001. Automatic segmentation of mammographic density. *Acad Radiol*, 8, 250-6.
- SNOEREN, P. R. & KARSSEMEIJER, N. 2004. Thickness correction of mammographic images by means of a global parameter model of the compressed breast. *IEEE Trans Med Imaging*, 23, 799-806.
- SUND, P., BATH, M., KHEDDACHE, S. & MANSSON, L. G. 2004. Comparison of visual grading analysis and determination of detective quantum efficiency for evaluating system performance in digital chest radiography. *Eur Radiol*, 14, 48-58.
- TIMMERS, J. M., VAN DOORNE-NAGTEGAAL, H. J., VERBEEK, A. L., DEN HEETEN, G. J. & BROEDERS, M. J. 2012. A dedicated BI-RADS training programme: effect on the inter-observer variation among screening radiologists. *Eur J Radiol*, 81, 2184-8.
- TINGBERG, A., BATH, M., HAKANSSON, M., MEDIN, J., BESJAKOV, J., SANDBORG, M., ALM-CARLSSON, G., MATTSSON, S. & MANSSON, L. G. 2005. Evaluation of image quality of lumbar spine images: a comparison between FFE and VGA. *Radiat Prot Dosimetry*, 114, 53-61.
- TORTAJADA, M., OLIVER, A., MARTI, R., GANAU, S., TORTAJADA, L., SENTIS, M., FREIXENET, J. & ZWIGGELAAR, R. 2014. Breast peripheral area correction in digital mammograms. *Comput Biol Med*, 50, 32-40.

- URSIN, G., HOVANESSIAN-LARSEN, L., PARISKY, Y. R., PIKE, M. C. & WU, A. H. 2005. Greatly increased occurrence of breast cancers in areas of mammographically dense tissue. *Breast Cancer Res*, 7, R605-8.
- VACHON, C. M., FOWLER, E. E., TIFFENBERG, G., SCOTT, C. G., PANKRATZ, V. S., SELLERS, T. A. & HEINE, J. J. 2013. Comparison of percent density from raw and processed full-field digital mammography data. *Breast Cancer Res*, 15, R1.
- VAN DER WAAL, D., DEN HEETEN, G. J., PIJNAPPEL, R. M., SCHUUR, K. H., TIMMERS, J. M., VERBEEK, A. L. & BROEDERS, M. J. 2015. Comparing Visually Assessed BI-RADS Breast Density and Automated Volumetric Breast Density Software: A Cross-Sectional Study in a Breast Cancer Screening Setting. *PLoS One*, 10, e0136667.
- VAN ENGELAND, S., SNOEREN, P. R., HUISMAN, H., BOETES, C. & KARSSEMEIJER, N. 2006. Volumetric breast density estimation from full-field digital mammograms. *IEEE Trans Med Imaging*, 25, 273-82.
- VAN GILS, C. H., OTTEN, J. D., VERBEEK, A. L. & HENDRIKS, J. H. 1998. Mammographic breast density and risk of breast cancer: masking bias or causality? *Eur J Epidemiol*, 14, 315-20.
- VINCENT, L. 1989. Graphs and Mathematical Morphology. *Signal Processing*, 16, 365-388.
- WANG, J., AZZIZ, A., FAN, B., MALKOV, S., KLIFA, C., NEWITT, D., YITTA, S., HYLTON, N., KERLIKOWSKE, K. & SHEPHERD, J. A. 2013. Agreement of mammographic measures of volumetric breast density to MRI. *PLoS One*, 8, e81653.
- WANG, X. H., GOOD, W. F., CHAPMAN, B. E., CHANG, Y. H., POLLER, W. R., CHANG, T. S. & HARDESTY, L. A. 2003. Automated assessment of the composition of breast tissue revealed on tissue-thickness-corrected mammography. *AJR Am J Roentgenol*, 180, 257-62.
- WARNER, E., LOCKWOOD, G., TRITCHLER, D. & BOYD, N. F. 1992. The risk of breast cancer associated with mammographic parenchymal patterns: a meta-analysis of the published literature to examine the effect of method of classification. *Cancer Detect Prev*, 16, 67-72.

- WHO, W. H. O. 2018. <https://www.who.int/cancer/prevention/diagnosis-screening/breast-cancer/en/> [Online]. [Accessed 09/01 2019].
- WINKLER, N. S., RAZA, S., MACKESY, M. & BIRDWELL, R. L. 2015. Breast density: clinical implications and assessment methods. *Radiographics*, 35, 316-24.
- WIRTH, M. A., LYON, J. & NIKITENKO, D. 2004. A fuzzy approach to segmenting the breast region in mammograms. *Nafips 2004: Annual Meeting of the North American Fuzzy Information Processing Society, Vols 1 and 2*, 474-479.
- WOLFE, J. N. 1976. Breast Patterns as an Index of Risk for Developing Breast-Cancer. *American Journal of Roentgenology*, 126, 1130-1139.
- WU, G., MAINPRIZE, J. G. & YAFFE, M. J. 2013. Characterization of a constrained paired-view technique in iterative reconstruction for breast tomosynthesis. *Med Phys*, 40, 101901.
- YAFFE, M. J. 2008. Mammographic density. Measurement of mammographic density. *Breast Cancer Res*, 10, 209.
- ZARINBAL, M. & ZARANDI, M. H. F. 2014. Type-2 fuzzy image enhancement: Fuzzy rule based approach. *Journal of Intelligent & Fuzzy Systems*, 26, 2291-2301.