Nonlinear dynamics of within-host parasite competition

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To My

Daughter and Wife

Abstract

In this thesis we study the population biology of host-parasite systems, with a systematic view of the effects produced by multiple infections of different parasites on a same host population. This situation is akin to multiple species competing for a shared resource. As parasites compete for a host, several outcomes at the population level can appear. If both parasites cannot jointly infect the same host, then the fittest parasite eliminates the other. When confection is possible, the pattern changes, and coexistence of both parasites becomes possible. Finally, if a parasite can displace the other within the host, the so-called intraguild effect, the outcome will strongly be dependent on the income rate of new hosts, which is determined by environmental factors. We studied this system through a mathematical model which is broad enough to encompass these situations. We proceed by steps: first we framed a simple mathematical model for a single parasite/host case and as we progress to other cases, our mathematical model includes new terms and finally it is shaped into a complete model. Our methods are twofold. We study analytically the stability of the disease-free state, which allows us to give conditions for the ability of the parasites to invade a disease-free/non-infected population. On the other hand, we resort to numerical methods to study the long-term behavior of the system, which in all cases tends to a fixed point. The main focus is to know which parasite prevails or if they are able to coexist, and determine the conditions that regulate this outcome . Through bifurcation diagrams we analyzed the importance of the richness of the environment, defined by the rate of production of new hosts. We found that the long-term states depend crucially on this rate. Our main original contribution is related to the study of the intraguild effect. Depending of the host income rate we can have four different states, which are a disease free state, a competitive exclusion state, a coexistence state and finally, and quite newly, a competitive switching state where the intraguild effect is the dominant feature to shape the long-run outcome of the system. Competitive switching is important mainly in rich environments and our results suggest that experimental research on intraguild effect in host-parasite system would benefit from comparing a system under several different host input rates.

Resumo

Nesta tese estudamos a biologia de populações de sistemas hospedeiro-parasita, com especial atenção para os efeitos produzidos por múltiplas infecções de diferentes parasitas numa dada população de hospedeiros. Tal situação se assemelha a múlpiplas espécies competindo por um mesmo recurso. Com os parasitas competindo por hospedeiros, diversos resultados no nível populacional podem ocorrer. Se ambos parasitas não puderem infectar um hospedeiro conjuntamente, então o parasita mais apto elimina o menos apto. Quando co-infecções são possíveis, o padrão muda e a coexistência pode ser estabelecida. Finalmente, se um parasita pode deslocar o outro, o assim chamado *efeito intraguilda*, o resultado dependerá fortemente da taxa de geração de novos hospedeiros, a qual é determinada por fatores ambientais. Nós estudamos este sistema por meio de um modelo matemático suficientemente abrangente para dar conta destas situações. Procedemos passo-a-passo: começamos com um modelo matemático simples para o caso de um parasita e um hospedeiro. Ao progredirmos para outros casos nosso modelo matemático passa a incluir novos termos até chegarmos num modelo completo. Há dois métodos de análise envolvidos. Estudamos analiticamente a estabilidade do estado livre de infecções, o que nos permite dar condições sobre a capacidade dos parasitas de invadir uma população não infectada/parasitada. Por outro lado, usamos métodos numéricos para estudar o comportamento para grandes tempos, que em todos os casos tende a um ponto fixo. O foco é saber qual parasita prevelacerá ou se haverá coexistência, além de determinar as condições que regulam o resultado da interação. Através de diagramas de bifurcação analisamos a importância da riqueza de recursos do ambiente, relacionada à taxa de produção de novos hospedeiros. Encontramos que os estados assimptóticos dependem fortemente desta taxa. Nossa principal contribuição original é o estudo do efeito intraguilda. Dependendo da taxa de recrutamento de novos hospedeiros podemos ter quatro casos, que são o estado livre de infecções, um estado com exclusão por competição, um estado de coexistência e finalmente, um fato novo, um estado com resultado de exclusão competitiva trocada quando o efeito intraguilda é o fator dominante a determinar a dinâmica de longos tempos. Tal exclusão trocada é importante sobretudo em ambientes enriquecidos de recursos e nosso

resultados sugerem que pesquisa experimental sobre efeitos intraguilda em sistemas hospedeiro-parasita teriam muito a ganhar ao comparar o comportamento do sistema sob diferentes condições de enriquecimento ambiental.

Contents

Acknowledgments

The woods are lovely, dark, and deep,
But I have promises to keep,
And miles to go before I sleep,
And miles to go before I sleep.
Robert Frost

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1 Introduction

Preamble

This thesis concerns the mathematical description of some specific situations involving interactions of hosts and parasites. Before we begin to undertake this enterprise we will give an introduction to the biology of parasitism. The reader should be aware that we use in the term "parasitism" in a broad sense. In some sub-disciplines, as in entomology, parasitism is associated with insects that parasite either eggs or larvae of other species. Here we adhere to the definition of parasite given in the *Princeton Guide to Ecology*, [1] :"A parasite is an organism that obtains its nutrients from one or a very few host individuals". This includes also pathogens - parasites that gives rise to a disease - and we will use the term *infection* for the state of a host that has been parasitized, and a host population not parasitized will be called *disease-free*. In this context we can speak of host-parasite systems as referring to insect parasitism, a pathogen that invades a body, a virus that infects a cell, amog others.

1.1 Introduction

Parasitism is an ancient behavior that prevails in records as old as several million years (400 million years). Parasitism is non-mutual relationship between the organisms of different species where one organism, the parasite, benefits at the expense of the other, the host. The very first observance is the gastropod molluscus parasitized crinoids in the Devonian (419-359 millions of years ago) period

[2]. Almost half of the know species on the earth evolved through parasitic life cycle [3, 4, 5, 6]. The word parasite originates from greek word $\pi\alpha\rho\alpha\sigma\imath\tau o\zeta$ (parasitos), meaning, "the one who eats at the table of someone else". The parasites are defined as the organisms which grows by exploiting the hosts for resources necessary for their survival e.g. food, water, heat, habitat, reproduction and transmission[7]. Parasites covers microscopic virus(20-300nm) to large worms like cestoda (tape-worms) whose length may be up to 10m and even more. Some parasites exhibit a complex and more specialized life cycle. For example, feather mites, a type of parasites which are specialized for life on a particular feather type and feather position. It feeds on the oily secretions and cellular detritus. Another type of parasites, which are commonly referred as generalists feeds from all type of hosts. For example, mosquitoes which feed on the blood of any large organism. The life cycle of parasites involves various critical mechanisms, hence it becomes necessary to understand the dynamics of parasites life cycle in order to manage them to understand their population dynamics which are of ecological and epidemiological importance. Based on the behavior, parasites can be classified in to three types as micro-parasite, macro parasite and parasitoid.

1.2 Micro-parasite

Micro-parasites are small sized parasites like virus, bacteria or protozoa. They, as an individual or as a group, infect a host and multiply rapidly within hosts and are commonly associated with the concept of infectious agent in the case where the host is a large animal or humans. When the micro-parasites increase in number inside a host, the disease symptoms begins to show up . We call this stage as infected stage. At this stage, the infection is transmitted to an uninfected host either by direct contagion (as in influenza, sexually transmitted diseases, smallpox, tuberculosis) or by a vector (as in malaria, dengue, yellow fever), or still through abiotic carriers (as in cholera, which is water-borne, or anthrax, which is soil-borne). The best example of a vector are mosquitoes which are blood sucking animals that transmit the parasites to a new host while feeding on it. In order to understand the disease and the dynamics of the disease, there are many models developed so far. Some models requires large set of data's to be analyzed and to understand the properties of the disease. One of the widely studied infectious disease is measles[8], which is an infectious disease that prevails among children's. The dynamics of this disease is very complex in nature due to the very fact that the children infected by measles are prone to spread this disease in schools. So the working duration (time) of the school will become the prior factor. In fact connecting data to theory is far from obvious in most cases, even for a simple disease, as influenza.

1.3 Macro-parasite

Macro-parasites are larger parasites are visible to the naked-eye. The life history of a macro-parasite is usually complex, as it has to transmit itself through many host species it encounters during its entire life cycle. But this transmission depends on the circumstances that prevails around. Macro-parasites can be either external (like mites and fleas) to internal (like helminths). In case of internal parasites, when there is an increase of the parasite population within the host, the virulence increases [1]. So, the number of within host parasites is considered to be a burden. The increase in the level of burden is determined by how frequent the macro-parasites contacts the outside parasites. As an example, let us look the complex life cycle of one species, say *Schistosoma mansoni*. *S.mansoni* is a parasitic worm whose length will be around 10mm-30mm. This is commonly found in mesenteric veins of the gut causing intestinal schistosomiasis. Adult worms breeds, the eggs are laid in small blood vessels. These eggs are responsible for blood vessel rupturing, through these blood vessels, they spread to different cells. Some of these eggs comes out of human body through excretions The eggs which come to the environment, hatch in fresh waters and attains free swimming stage called *miracidia*. The *miracidia* is capable of surviving 24 hours in the fresh water. Within this 24 hours, the miracidia manages to penetrate a snail tissue (of the *biomphalaria* genus). Then it enters its second stage of development. This stage is called *Sporocyst*. The *Sporocyst* reproduces its offspring, which then migrates to the snail's digestive gland. Inside the digestive gland it develops to a new stage called *cercariae*. The *cercariae* then comes out of the snail through its excretion and *Schistosoma mansoni* undergoes the second free swimming stage of its life cycle. Using the small backward pointing spine, these parasites enters human body via the exposed skin. Then, in some weeks, it reaches lungs and then to liver. In the liver, it pairs with existing worms and matures, initiating a new cycle [10]. To construct a mathematical model for an infectious disease as mentioned above becomes a difficult task owing to the variety of factors involved in. For example, the growth of parasites depends on the following facts: (i) virulence increases with burden and time because, as the number of eggs increases, the mobility decreases which eventually decreases the chance of spreading of parasites; (ii) the transmission rate depends on the snail population. The population of snail depends on its predator efficiency and the abundance of fresh water, which relays on annual rainfall. One has to take all these factors into consideration to construct an efficient predictive model. So, it is unlikely that any general pattern will emerge that holds true in most environments and for most host-parasite system of this type despite the accuracy of any individual model.

[1] **Definition of virulence:** "Virulence is an emergent property of host parasite interactions that causes from host exploitation. From an evolutionary perspective virulence is the extent of parasite-induced reduction of fitness. Although this definition encompasses effects on both fecundity and mortality, attention is given predominantly to mortality, "[9].

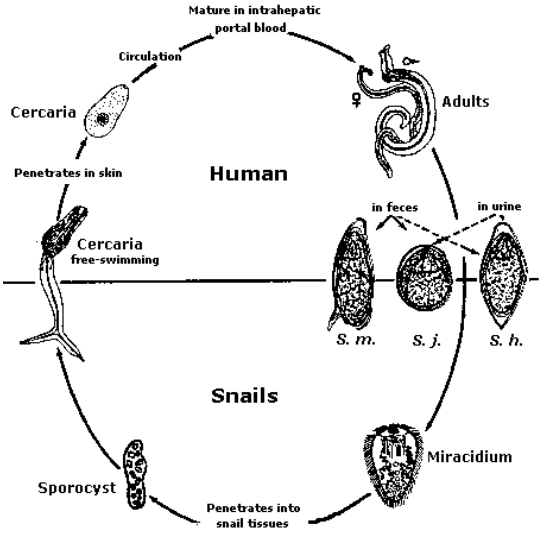

Figure 1.1: Example of macro-Parasite life cycle[10]

1.4 Parasitoid

Insects are species of the sub-kingdom of animals, called Metazoa. More than 10% of metazoan species are parasitoids[12]. Parasitoids are, like parasites, animals that feed on a host, but unlike parasites, they ultimately kill the host. Based on their reproductive cycle, these parasitoids are classified into different types. (i) The female parasitoid finds its host (usually larvae of the host), then lays either a single egg or a batch of them on/in the host. There are two types of egg laying behavior: (i) idiobiont is a kind of parasitoid that kills or paralyzes the host and oviposit on it. (ii) koinobiont is another kind of parasitoid that oviposit directly on host or into the host, and uses the resources of the host for its own growth. Here the host becomes the living nursery and larder for the parasitoid. The grown offspring comes out of the host by killing it. Depending on the egg laying strategies parasitoids are classified as, (i) solitary parasitoids which lay only one egg on the host. In this parasitoids the competition for nutrients is much smaller; (ii) gregarious parasitoids which lay more than one egg on the host. This kind of parasitoids spend a shorter time in search of suitable host,[1, 13]. Parasitoids are present in many families of insects. Parasitic wasps are a good example of the amount of specialized evolution that may be found among parasitoids. Many have developed disproportionately long ovipositors[2]. *Rhyssa persuasoria*, for instance, can grow an ovipositor up to 40mm to lay its eggs on the larva of horntails or wood-wasps which lie deep inside trees. The spider-hunting wasps of

[2] "Ovipositor is the specialized structure in many adult female parasitoids that allows them to lay an egg on or in a host", [1].

Figure 1.2: Parasitoid

the (*Pompilidae*) family have specialized to parasite spiders: members of the genus *Pepsis*, more commonly known as *Tarantula Hawks*, common in South America, reach up to 80mm allowing them to it seeks out the huge *Mygalomorph* (bird-eating) spiders, enter their burrow and begin a struggle, which can last for up to an hour, and is usually ending when the wasp stings and paralyzes the spiders head and jaws. The parasitoid then lays its eggs before leaving and sealing the burrow containing her offspring and their food source [11].

1.5 Significance of host parasite system

Parasitism is very widespread phenomenon. All known kinds of living organisms/species are susceptible to parasitism. This nature prevails from bacterial(attacked by virus) to giant whales. Many parasites breeds on/in the host. As in the previously discussed examples, the life histories of parasites and their hosts read as a catalogue of the bizarre and unlikely and are a subject on their own. The understanding of host-parasite interaction is therefore an important step in beginning to comprehend the working of the biosphere. How we use, monitor and regulate parasites can also have a large bearing on the quality and longevity of human life.

1.5.1 Biological control

Realizing the adverse effect of crop sprays, farmers and agro-industry more and more frequently shift to use parasites as crop pest control. To utilize parasites for controlling crop pests, we have to understand the dynamics of parasites. There are lots of evidence for the limiting effects of parasites on their hosts. Here the hosts are the crop pests. Injudicious use of insecticides that kill more natural enemies (parasites) than pests may result in host resurgence, suggesting that they were

previously maintained at low densities by the natural enemies [12]. One striking situation occurred in the British wheat fields in1994, [14]. May and June had been particularly cold, strongly depleting the population of aphids (insects popularly known as plant lice), but also driving their natural enemies (parasitoids, mainly) almost to local extinction. During July and August, the temperature increased, and the aphid population grew unchecked resulting in four fold increase in aphid population, with huge economic impact.

In 1960, most agricultural pests were controlled with the aid of insecticides. Usage of insecticides, however, decreases the potential crop production. Between 1950-1985, in U.S, the usage of pesticides had increased 10 fold and the loss in crops was found to increase from 7% to 13%. It is also important to note that some of the pests can perhaps never be controlled by insecticides. For example, the Colorando potato beetle *Leptinotursa decemlineata* has become, by unintentional selective breeding, resistant to all registered pesticides. As an alternative, integrated pest management(IPM) was suggested. Farmers preferred parasites to control the host species rather than using predators to control their prey due to specificity of host-parasite relationship. The success of IPM became evident to the world through cassava(*Manihot esculenta*) pest control, which is a stable food crop for about 200 million Africans. In 1970-1980, Africa suffered almost 80% crop loss because of the outbreak of mealybug(*Phenacoccus manihiot*) pest. IPM based on a natural parasitoid *Apoanagyrus lopezi* (a parasitoid wasp, originally from South America) , was used to control the pest, which became under control in this region resulting in 200 million USD savings. This has rather obvious influence for human populations that rely heavily on cassava, [15, 16].

1.5.2 Infectious diseases

Every year, millions of people are dying due to macro-parasite or virus and bacteria infection. In 2010, nearly 219 millions of documented cases of malaria were reported [17]. As another example, approximately 158000 persons died of measles in 2011 [18]. Parasites infecting mankind abound, a single and rather unfortunate burden. Human can be host to fleas(*Pulex irritans*), crab lice (*Pthirus pubis*), body lice(*Pediculus humanus humanus*), head lice(*Pediculus humanus capitis*), human bot flies(*Dermatobia hominis*) as well as an assortment of flukes, helminths, protozoans, bacteria, fungi and viruses. The diseases prevail not only in least developed countries , but also in rich countries like USA and Europe which witnesses,for instance, epidemic influenza, childhood disease outbreaks(measles) and spread of AIDS. Although medical and public health progress in the 20th century has reduced enormously the number of deaths due to infection disease, influenza is still in the leading causes of death in USA. In low income countries, malaria is also present in this list [19]. To eradicate or, at least, control these diseases, the basic understanding of disease pattern, its dynamics and its interaction are necessary.

1.6 Within-host parasite interaction

Having shown a broad view of the host-parasite interaction and its importance for agriculture and epidemiology, we now begin to introduce the particular aspects that will be the focus of this thesis. We will mainly be interested in the case where one host can be infected by more than one parasite. This gives rise to the study as within-host parasite interactions

To understand the ecological properties of within-host parasite interactions, we need to understand the interaction between the parasites with the host and between them. Let us first see what types of interactions exist and how they are differentiated from other characteristics. Host opposes the growth of parasite within it and creates unfavorable condition for the growth of parasites. In this circumstances, we need to study how the parasite grows inside the host, how the changes in host affects the parasites. The interaction between many species in a biological system depends on limited resources and space occupation. This interaction may be positive or negative. Depending on the resources, individual requirement, mechanism of interaction, within-host parasite interaction is classified into competition, predation/parasitism and mutualism. By understanding the resources and the mechanism that a parasite require to undergo in a host, we can build expectations on whether competition between different parasites is likely or not, and use this knowledge to develop control strategies.

1.7 Competition

Most of the species or organisms interact in competitive form. Here, competition is considered as an interaction between two populations that requires the use of a shared resource. Resources range from biological requirements (food) to physical space (nesting). Resource can also concern less tangible concepts such as enemy free space [20, 21, 22, 23]. When the availability of resource is very limited, the species compete strongly with each other causing a negative effect of one population on the other population. Competitive interaction may arise within species or between species. If the competition arises between the same species or organism, it is called intra-specific competition. If the competition arises between different kinds of species, then it is called inter-specific competition. This rule applies for within-host system and their importance has been confirmed by field data and laboratory data [24, 25, 26]. There are three types of competition mechanisms: are exploitation, interference and apparent competition.

1.7.1 Exploitative competition

Resource competition between two population need not necessarily be direct. When one population uses the available resources for its growth, the depletion of

resources degrades the growth of the other population leading to smaller survivorship. Slowly, one population excludes the other. A good example for exploitative competition is illustrated by the study of freshwater diatoms *Asterionella Formosa* and *Synedra ulna* in [27]. The common resources for both the species is silicate, which is used to construct their cell walls. When we feed silicate constantly in this system, both the species grow steadily and saturate. On the other hand, if limited silicate resource is available in the system, *S.ulna* utilizes more silicate leading to the extinction of *A. Formosa* population. The same scenario may prevail in within-host system, because the growth of parasite also depends on availability of resources. This property is evident in parasitic intestinal worms of three-spined sticklebacks [28]. The common resource is gut epithelium space. Two kinds of worms namely *P.Filicollis* and *N. Rutili* competes for gut epithelium space. *P.Filicollis* attaches itself to the upper part of the gut and begins to grow in number whereas *N. Rutili* attaches to the lower part of the gut and grows. They both commonly utilizes the resource for their growth. In this competition, the major populated species excludes the minor population.

1.7.2 Interference competition

Sometimes two species may compete directly. This type of competition is known as interference competition. This competition happens when one species gets hold of majority of resources by actively interfering with other species. The mechanism of this competition may be mechanical or chemical. Observation of organism behavior that would implicate direct interaction between organism is necessary to ascertain this mechanism of competition. Classic example for interference competition is Connell's barnacle study [29]. This example is about the physical displacement of scottish barnacle. There exists two kinds of species, *Chthamalus stellatus* and *Balanus balanoides*. They live along sea-shore line. *C.stellatus* were found to live in higher inter-tidal zone and balanus lives in lower inter-tidal zone. Young *C.stellatus* sometimes settles in lower zone but dies before they reach their adulthood. The reason behind this premature death is that *B.balanoides* physically removes, crushes or smothers *C. stellatus.* This reaffirmed that *B.balanoides* was indeed having direct physical competition for development space and was able to out compete *C.stellatus* in the lower regions of the intertidal zone. An example for within-host system is chemical production of antibiotics or chemical warfare mechanisms. Production of chemicals that manipulate the growth and survivorship of others is called allelopathy. This characteristics was observed in plants [30] and is also observed in within-host bacterial dynamics. *Streptococcus pneumonia* and *Staphylococcus aureus* are two bacterias that colonizes the respiratory tract of a human hosts [31]. Hydrogen peroxide compound produced by *S.pneumonia* lyses the other bacterial on the SOS pathway [32]. In counteract, *S.aureus* while traveling along SOS pathway produces lethal lysis. By doing so, *S.Pnuemoniae* is able to proliferate to higher densities as more resources will be at that pop-

ulations disposal. Direct measurement of these hydrogen peroxide compounds provides evidence that this competition is facilitated by interference. There are lot more examples for within-host interference competition like bacteriocin produced by bacteria to kill closely related bacteria that competes for resources [33]. Bacteriocin usage may be one of the most common mechanism for within-host competition between bacteria [34].

1.7.3 Apparent competition

This type of competition is less tangible than the direct exploitation of resources or interference between competitors. Apparent competition happens when the population of a competitor of a particular species decreases due to predation (or some other reasons), eventually resulting in increase in population of other species. This is traditionally thought to occur via competition for "enemy-free space" [20, 22, 23] or other indirect benefits. A classical example where apparent competition has been characterized is a shoreline ecosystem [35] in Southern California. This case encompasses two groups of preys and three predators. The first group of preys contains three species of mobile *gastropods* and second group of prey contains two species of *sessile bivalves*. Shared predators are a set of invertebrates[3]. Presence of either prey group was inversely correlated to the other, but there was no evidence of a shared food source (exploitation) or direct exclusion (interference). *S.bivalves* lives in abundance at places where the hiding spots are abundant and predation is very low. In these places, *gastropods* were found in least quantities. Similarly, *gastropods* live in places where predation is high. In these places, *S.bivalves* lives in least quantities. When *S.bivalves* were added in the places with high predation, a striking increase in predators was observed. When *gastropods* were added in the areas with low predation, the death rate of *S.bivalves* were found to increase. The increase in the population of one species causes a negative impact on the other kind of species, generating competition for space with reduced predator numbers. Within-host ecology throws light in understanding the apparent competition in many aspects. The parasites interact through host biological response such as the immune system. This seems to be very important in intra-specific competition studies, as parasite strains will likely have similar biology that is recognizable to the immune system. An example for immune mediated apparent competition is that of the infectious agent of rodent malaria, *Plasmodium chabaudi* [36]. This study reveals that the virulent and avirulent clones infect both immuno-deficient and immuno-competent mice host. In mixed type infection, inside imuno-competent mice host, avirulent clone density is lesser than virulent clone density . But, in immuno-deficient mice hosts, the avirulent clone density and virulent clone densities are almost equal. All other

[3]In popular language, gastropods are snail species, sessile bivalves are mollusk species. The predators, in this case, are particular species of lobsters, octopus and whelks

things being equal, as these were genetically equivalent mice(competence was induced by the reintroduction of T cells), the avirulent clone suffered from immune mediated apparent competition in the presence of more virulent counterparts.

1.8 Predation

Predation phenomena are a very a different interaction. This happens when one species/organism uses the other as its resource. Evidence for these interactions will be rather explicit, when predator or parasite gains from the loss of associated prey or host. In the context of this thesis the competition interaction happens within host but the predation-like interaction happens between two different within-host organisms. A well established example for this category is one virus being parasitized by other viruses. Under this circumstance, the replication machinery of adenovirus and adeno-associated virus are co-opted within a host cell [37, 38]. We will not extend the discussion in this topic further, as our concern in the following chapter falls on competitive interactions.

1.9 Mutualism

The interaction between two organisms does not always warrants a negative effect of one on the other. Sometimes the interacting organisms benefits out of the interaction. Such a phenomena is known as mutualism. Example for mutualism is lichens that grows on the trees and the variety of pollinator species and their associated plants. Mutualism also exists in within-host parasites and symbionts. There are two types of mutualistic interactions in within-host system. They are symbiont-host interaction and the interaction between different parasites living in the host. It is important to establish this distinction as the different interactions result in different ecological mechanisms and selection pressures. Example: *Bacillus bacteria, Bacillus thuringiensis* and *Bacillus cereus* which colonize the gut of the Diamondback moth [39, 40]. Antibiotic producing strains of either *B.thuringiensis* or *B.cereus* are shown to result in synergistic growth of non-antibiotic producing strains in the moth's gut as compared to growth in the absence of the antibiotic producing bacteria. This occurs both within each species and between them. These results are supported by findings and the idea is that these antibiotics reduce the abundance of host commensal gut bacteria, enabling invasion by the *Bacillus genus*. Again, as the case of predation, we will not go further into this topic, as it is not our main concern.

1.10 History of modelling parasite dynamics

To understand the dynamics of a disease, the primary task becomes predicting the life and time-development of the species involved within. Prediction may be simple and qualitative or complex and quantitative. It is usually too costly (both monetarily and in terms of the environment or population) to experiment the methodology in real time, and a mathematical models become important. In 1760, Daniel Bernoulli first constructed a quantitative model for smallpox disease and studied its dynamics. Following this, in 1798, Thomas Malthus constructed a mathematical model for human population growth. In 19th century, little progress in this line of thought ideas occurred and only in 20th century firm mathematical techniques were applied to these leads of biological problems.

1.10.1 Lotka-Volterra model

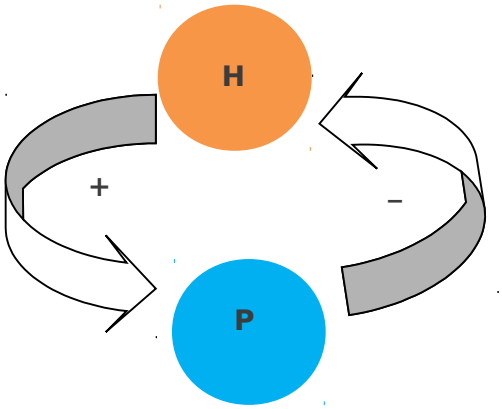

Figure 1.3: Block diagram for host-parasite interaction

The earliest examples of ecological modeling for more than one species dynamics was the predator-prey system [41, 42], which is characterized by a predator specialized in a certain prey (being dependent on it) and a prey that would grow unchecked in absence of predators. The Lotka-Volterra model takes the form of two coupled ordinary differential equations, and so can only possess fixed points and cycles. The model assumes continuous reproduction and constant mortality of both the predators and prey throughout the year, so it is more suitable for modeling tropical ecosystems. The Lotka-Volterra model is by far the most simple set of equations that can be used to predict the behavior of two species, and yet it is still a highly used. Let H indicate the host and P indicates the parasite, which correspond to prey and predator in the host-parasite case. The dynamical

equation is thus,

$$\frac{dH}{dt} = \gamma H - \lambda PH \tag{1.1a}$$

$$\frac{dP}{dt} = a\lambda PH - dP \tag{1.1b}$$

Here, γ is the biotic potential, the rate of increase of the host in the absence of parasitism, λ is related to the success rate of parasite at finding and laying an egg in the host, d is the death rate of parasite and a is the number of offspring produced and that survive to maturity form in the infected host. This is an example for a single host species with one specialized parasite, that is it exclusively feeds on this host. The dynamics are simple oscillations about a fixed point, the fixed point has neutral stability. This means there are an infinite set of neutral orbits, so the population keeps returning back to their initial values as they perform the oscillations. This however is not a very realistic point, as a limit cycle behavior is usually expected in natural systems [43]. Another unrealistic feature of the model is the manner in which both hosts and parasites always survive, they can recover from extremely low densities, usually soaring to large numbers before crashing again. To overcome these problems one usually generalizes the Lotka-Volterra model by introducing more realistic biological factor. The first, and most obvious one, is to introduce a carrying capacity for the prey, that is, an intra-specific competition term. Another change is to modify the interaction term taking into account predators saturation and finite handling time for prey consumption. This leads to the Rosenzweig-MacArthur model[44] which reads

$$\frac{dH}{dt} = \gamma H\left[1 - \frac{H}{k}\right] - \frac{\lambda PH}{1 + hH} \tag{1.2a}$$

$$\frac{dP}{dt} = \frac{\alpha\lambda PH}{1 + hH} - dP \tag{1.2b}$$

Here we have two more constants h and k related to the above mentioned mechanisms.. This model exhibits different dynamical regimes depending on the relations between the constants. There is a fixed point domain in parameter space and a limit cycle region.

1.10.2 Nicholson-Bailey models

In the year 1935, Nicholson and Bailey proposed a simple model equation for host and parasitoids [45] with non-overlapping generations, time becoming a discrete variable (indexing generations). Let h be the density of unparasitized host, then the number of uninfected hosts encountered by a parasitoid whilst searching an area ds is equal to hds, so if all these are infected, $-dh = hds$, hence $h = h_0 e^{-s}$. They first considered the breeding of host, which is increased by the factor F, then

they considered the breeding of parasitoids. Each mature parasitoid identifies its host in the given area a, lays a single egg on the host and dies. These eggs then successfully mature to adulthood. This situation is best explained with standard Nicholson-Bailey equation as,

$$H_{t+1} = FH_t e^{-aP_t} \tag{1.3a}$$
$$P_{t+1} = FH_t \left(1 - e^{-aP_t}\right) \tag{1.3b}$$

Though this model was framed purely on theoretical arguments, latter it is modified by including realistic factors like larger brood sizes, a constant inefficiency in searching and early parasitoid mortality. In 1969, Hassell included the logistic host growth in this model , Varley included the interference effect between the parasites and the factor that decreases the searching efficiency due to increase in parasite density [46]. In 1972, Royama included two factors to this model, they are the handling time for laying egg and the factor that limits the number of eggs a parasitoid could lay [47]. In 1978, May included the aggregated distribution of attacks per host, corresponding to some hosts being easier to detect and so suffering more parasitism [48]. In 1990, Hassell and Pacala introduced the heterogeneity in the model [49]. Nicholson-Bailey model which has undergone major modifications, cannot explain many biological phenomena, but it produces an extraordinary agreement between the theoretical and laboratory results of certain host parasite interaction when generations of host and parasites can be well-defined. Growing fluctuations are seen in both populations with either the parasites or the hosts (quickly followed by the parasites) being driven to extinction.

1.10.3 Structured disease model

When we try to frame a model for a disease caused by bacteria or virus, the actual number of infecting pathogens would not be an adequate variable. So in this case we resort to a different framework adapted to epidemiological studies. It will be worthy to classify the host population based on burden of parasites and previous history of the parasites. Let us give an example of a simple model of this kind. We consider the population structured in four classes. They are S, E, I and R.

S stands for number of susceptible. In this susceptible class, the host is uninfected by the disease or has no resistance. When the host comes in contact with infectious individual, the probability of infection is taken as $\mathscr{T}$. Hosts are born into the susceptible group if it is assumed that there is no vertical transmission.

E refers to exposed class. In this category, the host in already infected, but the infectious agent doesn't find enough time to multiply within host body. So the host of this category cannot spread the disease to susceptible host.

I denotes Infectious class. The host of this class is highly infected by virus and the host can transmit the disease to another individual susceptible host.

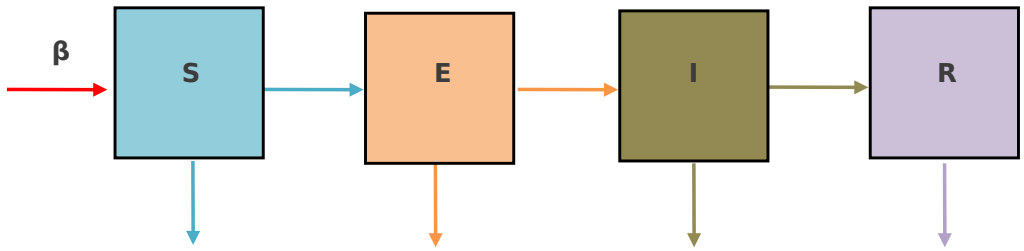

Figure 1.4: Block diagram for SEIR model

R represents removed class. Hosts in this class are immune to the disease.

Once a host attains exposed class E, after a definite time, it will move on to I class. Say for example, measles disease. Its latent period in exposed class is 6 to 9 days, then it moves on to infectious class in the next 4 to 5 days. Then it moves to immune (removed) class [8]. The structured disease model considers that the host population is high, this condition eventually ignores the stochastic fluctuations. Also it takes the population as highly mixed, so all the individuals are in contact with each other on a regular basis. Under this consideration, by law of mass-action, a set of ordinary differential equation is constructed. The population homogeneity assumption is otherwise called as mean field theory approach. The equations in this case are

$$\frac{dS}{dt} = \beta\left(S+E+I+R\right) - \mathscr{T}SI - mS \tag{1.4a}$$

$$\frac{dE}{dt} = \mathscr{T}SI - \left(m+\mathscr{D}_1\right)E - aE \tag{1.4b}$$

$$\frac{dI}{dt} = aE - \left(m+\mathscr{D}_2\right)I - gI \tag{1.4c}$$

$$\frac{dR}{dt} = gI - mR \tag{1.4d}$$

Here β is the birth rate, $\mathscr{T}$ is the transmission rate, m is the mortality rate, $\mathscr{D}$ is the death rate due to infection, $\frac{1}{a}$ is the latent period and $\frac{1}{g}$ is the infectious period. The above equation has four variables and seven parameters and exploring the parameters space we can exploit different patterns of the infections disease dynamics. This equation exhibits many qualitative interesting behavior like fixed points, limit cycles, chaotic attractors and repellers [50].

In order to understand more detailed information and most realistic phenomena, one has to subdivide the host population. For example, as in measles disease, to understand a more realistic situation, age classes are included in population along with the four equations. The reason to include the age classes is that the disease spreads mostly in schools from the infected children to the other children's

and the population grows as an immune adult. Schenzle, in 1984 used this technique and subdivided the population into 21 groups, ie., one for each year up to the age group of 1 to 20 and one for above 20 years [51]. In this type of highly structured model, a larger number of parameters gets involved in the equation, making analytics almost impossible. But the major credit for simple models, even sometimes it predicting the disease very accurately, is to shed light on the main mechanisms that generate patterns of epidemics. From now on, the majority of models used will be simple and very general, often called "generic" models. These have the advantage of containing all the main features common to the type of system being studied and yet are hopefully simple enough to allow some examination and analysis of the behavior. Although the results cannot be compared numerically to real data in most cases they can be compared qualitatively, in the words of Lorenz, they are "predictions of the second kind."[52]

1.11 Thesis outlook

In this thesis we will focus on a particular situation, which is that of the competition of parasites for a host. The host dynamics itself will not be our main concern, as we will always consider that a certain rate of hosts inflows the system due to external sources. If this inflow is low we say that the environment's productivity is poor, or just that the environment is poor. On the contrary, if we inflow is high we say the environment is rich.

We will proceed step by step, first considering a single host/parasite pair, then a two-parasite/one-host triple which splits into several different cases: single infections case (the host can be infected only once), double infections case, the existence or not of free-living states of the parasites and finally, in the context of double infections, the intraguild effect, where one parasite can displace the other within the host at a certain rate.

As the quality of the environment is an important factor, we will study these cases along a gradient of environmental richness. This will be particularly important with respect to the intraguild effect.

To obtain our results we use standard methods. First, we resort to stability of the disease free equilibrium, which will tell us if the host population can be invaded by the parasites. Secondly, we numerically integrate our equations and look for the long-term regime, having thus access of the outcome of the competitive interactions. This will be best framed by bifurcation analysis.

2 Within-host two parasites competition

2.1 Introduction

In this chapter, we discuss the importance of within-host parasite models and their development, particularly we will study a model of two parasites competing within a host.

2.2 Within-host single parasite dynamics

Initially, the dynamics of parasite population within-hosts was studied only from an epidemiological point of view. Anderson and May [53, 54] studied the population biology of directly transmitted macro-parasites. Taking this as a general framework, Grenfell in the year 1988 [55] constructed a new model for the parasite population for within-host single parasite system. In his model, he divided the parasite population into two groups: adult parasites, A , that prevails within the host population H and the free living transmission stage L. This model considers a fixed host population and is described by the following equations:

$$\frac{dL}{dt} = \lambda - (\rho + \beta H)L \tag{2.1a}$$

$$\frac{dA}{dt} = \beta HL - \mu A \tag{2.1b}$$

here ρ is the death rate of free living state, μ is the death rate of parasitic state, β is the effective transmission rate per host, λ is the effective reproductive rate

per adult parasite, which has the form

$$\lambda = \lambda_0 \left[1 - \frac{A}{HA_0}\right]. \tag{2.2}$$

This equation for λ limits the growth rate of the parasite population through density dependence which is controlled by the A_0. λ_0 is the maximum reproductive rate per head.

We can easily calculate the fixed points of Eq.(2.1a-b) by setting the left hand sides of the equations to zero, implying

$$\begin{aligned} \lambda - (\rho + \beta H)L &= 0 && \text{(2.3a)} \\ \beta HL - \mu A &= 0. && \text{(2.3b)} \end{aligned}$$

The fixed point (L^*, A^*) has the form

$$\begin{aligned} L^* &= \frac{\mu}{\beta H} A^* && \text{(2.4a)} \\ A^* &= \frac{\lambda_0}{\left(\frac{\rho}{\mu H} + \mu + \frac{\lambda_0}{HA_0}\right)}. && \text{(2.4b)} \end{aligned}$$

This fixed point is always stable, as the Jacobian matrix corresponding to Eq.(2.3a-b), given by

$$\mathscr{J} = \begin{bmatrix} -(\rho + \beta H) & \frac{-\lambda_0}{HA_0} \\ \beta H & -\mu, \end{bmatrix} \tag{2.5}$$

has $tr(\mathscr{J}) < 0$ and $Det(\mathscr{J} > 0)$, hence both the eigenvalues are negative. If both the eigenvalues are negative then the system is always stable.

In the above system, the host population is left unaccounted. When we include the host population in our system, it results in two groups, uninfected host population and infected host population. S. Bonhoeffer et al. [56] in 1996 included host population in the dynamics and constructed a model for within-host micro-parasite dynamics with a free living stage. The model is as follows

$$\begin{aligned} \frac{dX}{dt} &= \Phi(X, Y, F) && \text{(2.6a)} \\ \frac{dY}{dt} &= \kappa XF - \mu Y && \text{(2.6b)} \\ \frac{dF}{dt} &= pY - cF. && \text{(2.6c)} \end{aligned}$$

Here X is the density of uninfected (susceptible) hosts, Y is the density of infected hosts and F is the density of free transmission stages. X, Y, F are functions of time. $\Phi(X, Y, F)$ is the general functional form of the rate of change of uninfected host population. κ is the rate of infection of host by the free living parasites which

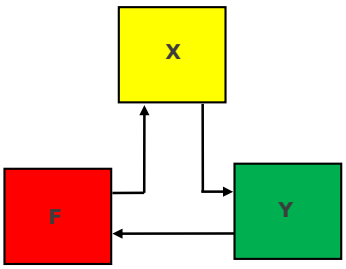

Figure 2.1: Block diagram for One Parasite, Single infection

is supposed to the only way a host gets infected. μ is the natural death rate plus the infective agent induced death rate of hosts (virulence or disease induced mortality) of infected host. Here p is the production rate of free living parasites from infected host. c is natural removal rate of free living parasites.

The basic reproductive number is defined as the average number of secondary infections caused by a single infected host in an entirely susceptible host population. In the next chapter we will show how to calculate it in general. For now we just state the results. The basic reproductive number of our present model is

$$\mathscr{R}_0 = \frac{p\kappa}{c\mu} X^* \tag{2.7}$$

X^* in the above equation represents the equilibrium density of uninfected hosts in the absence of parasite ($Y = F = 0$). When $\mathscr{R}_0 > 1$, the condition becomes favorable for the parasites to invade and spread in the uninfected hosts. On the other hand, if $\mathscr{R}_0 < 1$, the condition becomes unfavorable for the parasites to invade and spread in the uninfected hosts.

Example

The model which we have discussed above not only explains the within-host parasite dynamics, but also explains several infectious disease dynamics [57]. More specifically, these model helps to understand the HIV infectious disease [58, 59]. Here T are the uninfected host/target cells, V are the free virions, T_i are the infected host/target cells. The model which has the form of Eq.(2.6a-c) is as

follows

$$\frac{dT}{dt} = \lambda - dT - \kappa TV \tag{2.8a}$$
$$\frac{dT_i}{dt} = \kappa TV - \mu T_i \tag{2.8b}$$
$$\frac{dV}{dt} = pT_i - cV \tag{2.8c}$$

Here λ is the production rate of uninfected cells and d is its death rate. According to free virus particle mass-action law, the uninfected cell is infected at the rate κ and the infected cell produces free virus at the rate p, the natural loss rate in virus is denoted by c. The coefficient μ gives the rate at which the infected cells die.

The basic reproductive ratio, $\mathscr{R}_0$, is the expected number of virions that one virion gives rise to in an uninfected cell population, where $T = \frac{\lambda}{d}$. One virion gives rise to κT infected cells in a time $\frac{1}{c}$. Each of these infected cells gives rise to p virions in a time $\frac{1}{\mu}$. This gives the reproductive ratio to be

$$\mathscr{R}_0 = \frac{\lambda p \kappa}{d \mu c}. \tag{2.9}$$

Which is an agreement with Eq.(2.7).

In the next subsection we will show that, if $\mathscr{R}_0 < 1$ the uninfected state is globally stable and if $\mathscr{R}_0 > 1$, the infected state is globally stable. From the above expression we can already deduce an interesting conclusion. Note the $\mathscr{R}_0$ decreases with μ. The mortality rate of infected hosts (μ) has two contributions: natural death rate and disease induced death rate. So if the infection is too virulent, it will not successfully invade the uninfected population. This is also true in a more general setting: very virulent diseases do not become epidemic.

2.2.1 Stability analysis

Setting the left hand sides of the model equations (2.8a-2.8c) to zero and solving for each variable gives the steady states of the system: the disease free steady state ($T = \frac{\lambda}{d}, T_i = 0, V = 0$) and the endemic steady state $(T, T_i, V) = (T^*, T_i^*, V^*)$ where

$$T^* = \frac{\mu c}{\kappa p} = \frac{T_0}{\mathscr{R}_0} \tag{2.10a}$$
$$T_i^* = \frac{\lambda}{\mu} - \frac{cd}{\kappa p} = \frac{dc}{\kappa p}(\mathscr{R}_0 - 1) \tag{2.10b}$$
$$V^* = \frac{p\lambda}{\mu c} - \frac{d}{\kappa} = \frac{d}{\kappa}(\mathscr{R}_0 - 1) \tag{2.10c}$$

where $T_0 = \frac{\lambda}{d}$ is the value of T in the disease free steady state ($T_i = V = 0$). The stability of the steady states is determined by the Jacobian of the system

$$\mathcal{J} = \begin{bmatrix} -(d + \kappa V^*) & 0 & -\kappa T^* \\ \kappa V^* & -\mu & \kappa T^* \\ 0 & p & -c \end{bmatrix} \tag{2.11}$$

evaluated at the steady state. The characteristic polynomial is obtained by setting the determinant of $(\mathcal{J} - \alpha I) = 0$, the roots of which are the eigenvalues of the system (2.11). If the real parts of each eigenvalue are negative the steady state is stable, otherwise it is unstable. This can be determined using Descartes rule of signs which states that if the terms of a single-variable polynomial with real coefficients are ordered by descending variable exponent, then the number of positive roots of the polynomial is either equal to the number of sign differences between consecutive nonzero coefficients, or is less than it by a multiple of 2. Therefore there are no positive roots if all of the coefficients are either all positive or all negative, meaning the steady state is stable.

The characteristic polynomial of the disease free steady state is

$$(\alpha + d)\left[(\alpha + \mu)(\alpha + c) - \frac{\kappa\lambda p}{d}\right] = 0. \tag{2.12}$$

This has negative roots, if and only if $\mathscr{R}_0 < 1$, so that in this case the disease free state is stable.

The characteristic polynomial of the endemic steady state is

$$\alpha^3 + (\mu + c + d\mathscr{R}_0)\alpha^2 + (\mu + c)d\mathscr{R}_0\alpha + \mu cd(\mathscr{R}_0 - 1) = 0. \tag{2.13}$$

This has negative roots, if and only if $\mathscr{R}_0 > 1$, which means that the endemic state becomes stable.

We note that we have here an "exchange of stability": when the disease free stable state becomes unstable, the endemic one becomes stable.

2.3 Within-host two parasites dynamics

In this section, we discuss the competition between two parasites to invade the same host [56]. In this model, each host is invaded only by one parasite, so that there is no intra-host competition but a competition for the host by the parasites. The model is an immediate generalization of Eq.(2.6a-c) and reads

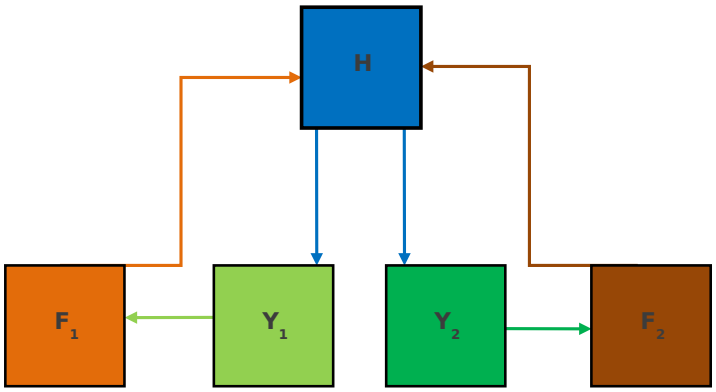

Figure 2.2: Block diagram for Two Parasites, Single infection

$$\frac{dX}{dt} = \Phi(X, Y_1, Y_2, F_1, F_2) \tag{2.14a}$$
$$\frac{dY_1}{dt} = \kappa_1 X F_1 - \mu_1 Y_1 \tag{2.14b}$$
$$\frac{dY_2}{dt} = \kappa_2 X F_2 - \mu_2 Y_2 \tag{2.14c}$$
$$\frac{dF_1}{dt} = p_1 Y_1 - c_1 F_1 \tag{2.14d}$$
$$\frac{dF_2}{dt} = p_2 Y_2 - c_2 F_2 \tag{2.14e}$$

Here, X is the number of uninfected host, $\Phi(X, Y_1, Y_2, F_1, F_2)$ is the general function for the rate of change of the host population, Y_1 and Y_2 are the infective states, produced by two different parasites F_1 and F_2 respectively. The rate at which the infection happens is given by κ_1 and κ_2, μ_1 and μ_2 are the corresponding death rate created by the parasites, p_1 and p_2 are the production rate of the parasites present outside the host. Here, c_1 and c_2 are the natural death rate of free living parasites. As there are no co-infected states, the two infectious agents indeed compete for hosts. As in the general theory of competition for resources, only one of the competitors will subsist in the system on the long run. The broad view is the following: the condition for parasite 1 to invade the disease-free equilibrium, in absence of parasite 2, is

$$\mathscr{R}_0|_1 = \frac{X_0 \kappa_1 p_1}{c_1 \mu_1} > 1 \quad , \tag{2.15}$$

and, symmetrically, the condition for parasite 2 to invade the disease-free equilibrium is

$$\mathscr{R}_0|_2 = \frac{X_0 \kappa_2 p_2}{c_2 \mu_2} > 1 \quad . \tag{2.16}$$

If any of the $\mathscr{R}_0|_i$ is smaller than one, it will be absent of the system. The question that arises is to know what happens in the case when both $\mathscr{R}_0|_1$ and $\mathscr{R}_0|_2$ are greater than one. To answer this question one has to consider the stability of the endemic state with parasite 1 to perturbations introducing parasite 2. If parasite 2 can invade this state, and vice-versa (parasite 1 can invade the endemic state with parasite 2) both parasites can coexist. Otherwise, only one of them subsists. For this specific case, no coexistence can be found and the parasite with greater $\mathscr{R}_0$ will eliminate its competitor [56].

If the parameters used in this system are independent on each other, then the death rate induced by parasites decreases $\mathscr{R}_0$. On the other hand, the infection rate of parasites and the birth rate of parasites from infected host increases $\mathscr{R}_0$. Generally, there are different opinions about the independence or not of these parameters. One group of researchers says that, [60, 61, 62, 63, 64] there is a positive correlation between the parasite detrimental effect on host (μ) and the production rate of parasites (p). Also, they state that there is a trade-off between virulence and parasite transmission. However a different group [65, 66] questions the existence of this trade-off. These question is not settled at this moment.

2.4 Within-host two parasites and multiple infection with no free living stage

In this section, we discuss the dynamics of a populations of hosts infected multiple times by two parasites. Even though we call it multiple times, we restrict our discussion to two times for simplicity and actual relevance. Due to multiple infection, there will be a huge change in the epidemiological process.

The colonizing of parasites in the host initiates pathological effects (virulence) on host that interferes with the transmission to new host. So, the dynamics of within-host solely depends on two fundamental aspects of infection and disease: virulence and transmission. Under this scenario, it was proposed that when a host is co-infected by different parasites, the host population favors the parasite population that produces higher virulence[67, 68]. But many experimental and theoretical studies disagree with this point. The studies confirm that the co-infection favors least virulence strain[69].

Though the proliferation of a parasite inside a host depends on several interacting factors, [70, 71, 72], we now concentrate on one aspect, "The dynamical changes the system undergoes due to co-infection". Here, we considered that the host favors the parasite population with low virulence.

To understand the epidemiological dynamics of a host which is being infected multiple times by multiple parasites, we study a model of classical susceptible-infected(SI) type. In this model, the parasites cannot transmit vertically and they will never recover from infection i.e., the infection is permanent. This model may resemble Van Baalen and Sabelis model, [73], but it has its own differences. The primary difference is that this model explicitly accounts the order of arrival of parasites within the host. In this model, we introduced two parameters, the susceptibility of uninfected host (σ_s) and susceptibility of infected host to the disease (σ_I). When $\sigma_I = 0$, the infected host becomes immune to co-infection. In this circumstance, our model behaves like SI model with single infection. On the other hand, when σ_I is very large, all the singly infected hosts become doubly infected. In this situation, our system contains only the uninfected and co infected host population.

This model was first considered in [74] and contains three different populations, which are: uninfected hosts, singly infected hosts and doubly infected hosts. The schematic representation of our model is given in figure 2.3. In this case, we do not consider a free living stage of the parasites, we will do so in the generalization considered in the next chapter.

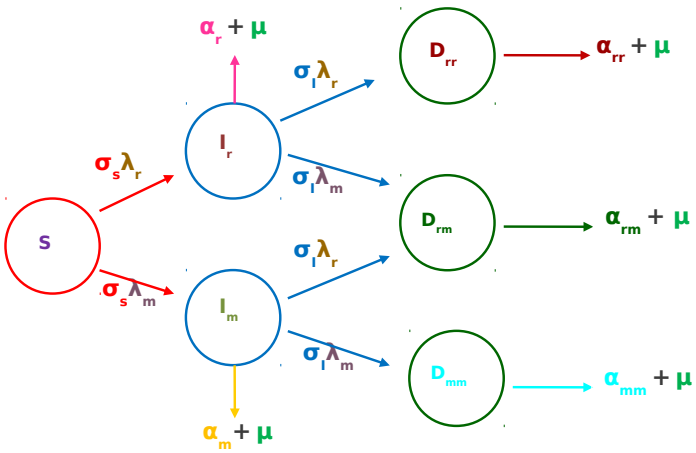

Figure 2.3: Block diagram for Co-infection(Multiple Infection)

The complete mathematical model is given below and follows the same ratio-

nale as in the previous cases. The model reads

$$\frac{dS}{dt} = \rho(S, I_w, I_m, D_{ww}, D_{wm}, D_{mm}) - \sigma_s(\lambda_w + \lambda_m)S - \mu S \quad (2.17a)$$
$$\frac{dI_w}{dt} = \sigma_s\lambda_w S - \sigma_I(\lambda_w + \lambda_m)I_w - (\mu + \alpha_w)I_w \quad (2.17b)$$
$$\frac{dI_m}{dt} = \sigma_s\lambda_m S - \sigma_I(\lambda_w + \lambda_m)I_m - (\mu + \alpha_m)I_m \quad (2.17c)$$
$$\frac{dD_{ww}}{dt} = \sigma_I\lambda_w I_w - (\mu + \alpha_{ww})D_{wW} \quad (2.17d)$$
$$\frac{dD_{mm}}{dt} = \sigma_I\lambda_m I_m - (\mu + \alpha_{mm})D_{mm} \quad (2.17e)$$
$$\frac{dD_{wm}}{dt} = \sigma_I\lambda_m I_w + \sigma_I\lambda_w I_m - (\mu + \alpha_{wm})D_{wm} \quad (2.17f)$$

S are the uninfected hosts, which can become infected by the parasite i at the rate of λ_i. Where

$$\lambda_w = \beta_w I_w + \beta_{wm} D_{wm} + 2\beta_{ww} D_{ww} \quad (2.18a)$$
$$\lambda_m = \beta_m I_m + \beta_{mw} D_{wm} + 2\beta_{mm} D_{mm}. \quad (2.18b)$$

Contrary for the case of Eq.(2.14), we have already partially fixed the form of the rate of change of the uninfected hosts . Here β_{ij} is the transmission rate of parasite i in a host co-infected by parasites i and j. First the host is singly infected and then it is doubly infected. i in our model refers to m and w. I_w and I_m are singly infected hosts. Similarly D_{mm}, D_{wm} and D_{ww} are doubly infected hosts. ρ is the input of uninfected host/susceptible. σ_s refers the susceptibility to primary infection, μ is the natural death rate of uninfected host and infected host. α_j is the disease induced mortality where $j = m, w, ww, mm, wm$.

One can calculate the fitness of micro-parasites from the basic reproduction ratio $\mathscr{R}_0$ i.e., the number of new infections caused by an infected host in a susceptible population. This condition cannot be used as such in our present model because another parasite invades the dominating parasite population. There occurs a complication due to the presence of different transmission routes, one route is due to the infecting healthy hosts and the other is through the presence of already infected host. This kind of problem can be solved easily by shifting the level of propagule that is just released by the host, [73]. Propagule is a form of parasites that colonizes new hosts. A more general expression can be formulated for the number of new propagules that a single propagule will engender. This value is given as $\mathscr{R}_0$. For a parasite, if $\mathscr{R}_0 > 1$, it will survive in the host population and when $\mathscr{R}_0 < 1$, the parasites disappears.

It is very difficult to analyse this model completely, so we formulated certain plausible assumptions and analyzed the suitable condition for the parasites to invade the hosts.

The density of the doubly infected host is assumed to be very low, so that we can neglect it. Hence, I_w and D_{ww} stays in their equilibrium state and are neglected. Now the reproduction ratio $\mathscr{R}_0$ is given as,

$$\mathscr{R}_0 = \frac{\beta_m + \frac{\beta_{wm}\sigma_I\lambda_w}{(\mu+\alpha_{wm})}}{\mu + \alpha_m + \sigma_I\lambda_w}\sigma_s S^* + \frac{\beta_{wm}}{\mu + \alpha_{wm}}\sigma_I I_w^*. \tag{2.19}$$

Here, S^* and I_w^* refers to uninfected host and infected host equilibrium densities. The above equations contains two sub-cases: (i) When the double infection parameter $\sigma_I = 0$, the equation becomes,

$$\mathscr{R}_0 = \frac{\beta_m}{\mu + \alpha_m}\sigma_s S^*. \tag{2.20}$$

This is the expression for basic reproductive ratio of host which is singly infected. (ii) When we assume that the host is doubly infected once it gets singly infected,

$$\mathscr{R}_0 = \frac{\beta_{wm}}{\alpha_{wm}} I_w^*. \tag{2.21}$$

Here $S^* = 0$, then the value of $\mathscr{R}_0$ depends on parasite transmission and the host mortality rate. From the above discussion, we understand that the outcome of $\mathscr{R}_0$ depends both on single and double infection parameters and the disturbance produced by parasites on host population.

2.4.1 Numerical analysis

Figure 2.4 is plotted for the solution of equation (2.17a-f). The values of the parameters used in these equations are given in table-2.1. As we are dealing with co-infection, both the parasites may subsist in the hosts indefinitely. Since the double infection rate σ_I is greater than the single infection rate σ_s, the double infected host population is at higher levels.

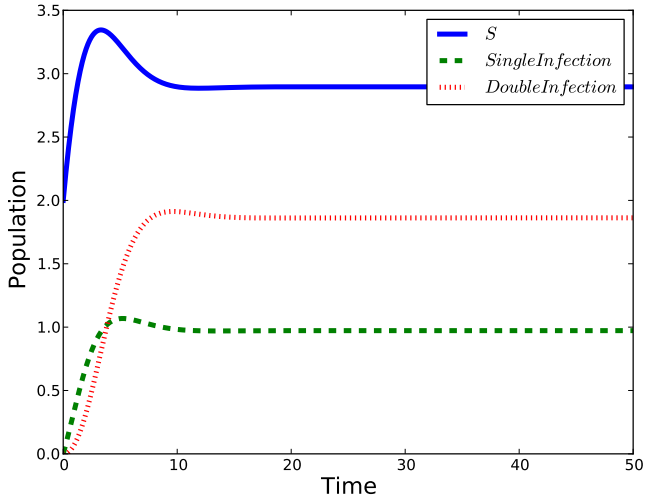

Figure 2.4: Population dynamics for within-host two parasites competition with co-infection. Both parasites coexist

Table 2.1: Model Parameter Values

Case	Symbol	Values
1	ρ	1.5
2	μ	0.1
3	σ_s	0.1
4	σ_I	0.25
5	α_w	0.1
6	α_{ww}	0.4
7	α_{mm}	0.4
8	α_{wm}	0.4
9	β_w	0.45
10	β_{wm}	0.45
11	β_{ww}	0.45
12	β_m	0.4
13	β_{mw}	0.5
14	β_{mm}	0.5

In this figure 2.5, we have taken the double infection parameter σ_I along the x-axis, host equilibrium populations (uninfected, single infected, double infected) along y-axis. When $\sigma_I = 0$, the population is composed of uninfected hosts and singly infected hosts. As σ_I increases, the double infected equilibrium population increases,. Finally , when σ_I is very large, the total population consists of uninfected and doubly infected hosts alone. As it becomes apparent from the

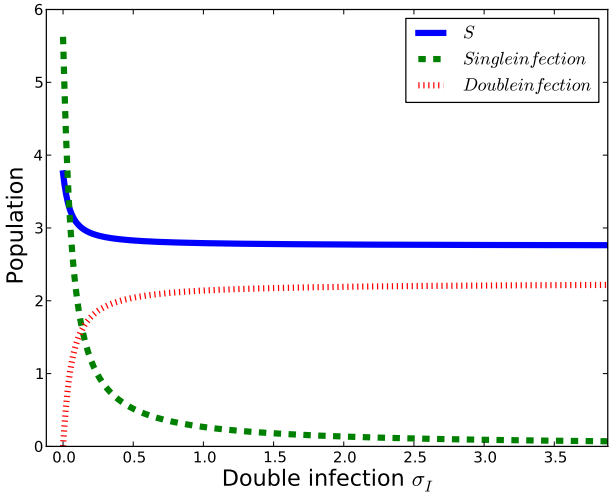

Figure 2.5: Equilibrium states along a Double Infection rate gradient : Single infection gets eliminated

Table 2.2: Parameter Values

Case	Symbol	Values
1	ρ	1.5
2	μ	0.1
3	σ_s	0.1
4	α_w	0.1
5	α_{ww}	0.4
6	α_{mm}	0.4
7	α_{wm}	0.4
8	β_w	0.45
9	β_{wm}	0.45
10	β_{ww}	0.45
11	β_m	0.4
12	β_{mw}	0.5
13	β_{mm}	0.5

results, the fact that two infectious agents can co-infect a host promotes their coexistence. In this sense, competition is released. The parameters values used in the numerical integration are given below in table(2.2).

2.5 Conclusion

In this chapter, we discussed the factors that determine the reproduction rate of within-host parasites. In particular, we discussed the competition between two parasites to infect a host. First we showed that if there is no co-infection, in a system with one host, two-parasites with free-living states, there occurs the competitive exclusion of one parasite in favor of the other, the one with highest basic reproductive number remaining in the system. We further went on to consider a system where co-infection is possible, but with no free-living states. It turns out that co-infections promotes coexistence and we do not have competitive exclusion anymore. It is thus a natural step to be taken to consider the effects of the existence of a free-living states of the parasites in this last case. We do so in the next chapter, but before we will outline a method of calculating the basic reproductive number.

3

Next generation matrix method for within-host parasite competition

3.1 Introduction

In this chapter, we discuss the calculation of the basic reproduction number and its impact on understanding of the dynamics of within-host parasite system. The flow of this chapter is: we first give a historical perspective on the development on calculating $\mathscr{R}_0$ then we discuss the method of calculating $\mathscr{R}_0$ using the next generation matrix method(NGM). We apply this method to the case of two parasites coinfecting a host and having free living stages.

3.2 Early developments of $\mathscr{R}_0$

Though $\mathscr{R}_0$ has some profound influence in epidemiology, in its early stage, it was used in mainly demography and ecology. For example, this parameter is used to calculate the number of offspring's produced by a female parasite in its lifetime, without using the name as basic reproductive ratio.

3.2.1 Progress of $\mathscr{R}_0$ in demography

In the year 1886, Richard Böckh, [75], published the 1879 demography data of Berlin city. In that article , he specified the fertility table as an appendix, in which he calculated the age dependent fertility and the *per capita* number of off-springs per woman. He estimated the number of birth of off-springs including

male and female babies as 2172 in Berlin city. This work was much criticized initially. Later on, he used the correct sex ratio for the estimation and got the value as 1.06 for the *per capita* birth rate. This value is now named as $\mathscr{R}_0$. In 1932, Kuczynski [76], student of Richard Böckh, recalculated Richard's work for the period 1891-1895. Many independent proposals emerged in the intermediate years from Richards estimation to Kuczynski's estimation. As an example, Knibbs (1917)[77] is one such remarkable work, in which he called the fertility as crude fertility or corrected fertility. The work of Alfred Lotka (1880-1949) is another remarkable one. In the year 1925, Alfred Lotka [78, 41] published four consecutive papers on demography, out of these, the paper published in the year 1911 along with F.R. Sharpe [79] has an explicit mathematical expression on age dependent birth rate and he proposed that a fixed age distribution is stable. Taking r as the *per capita growth rate* of the population, Lotka&Sharpe obtained a condition for the population to persists as:

$$r > 0 \Rightarrow \int_0^\infty b(a)p(a)da > 1 \tag{3.1}$$

Here, $b(a)$ is the average birth rate of an individual at an age 'a'. p is the survival probability. From the above integration, Lotka concluded that the growth of population and the spreading of disease are very similar from a mathematical point of view.

3.2.2 Advancement of $\mathscr{R}_0$ in epidemiological way

Epidemiologically, $\mathscr{R}_0$ refers to the number of individuals infected by a single infectious individual, during his/her entire infectious period, in a population which is entirely susceptible [80] . In terms of in-host dynamics, $\mathscr{R}_0$ refers to the number of newly infected cells produced by one infected cell during its lifetime, assuming all other cells are susceptible [81]. Like demography, epidemiologists did many independent research on $\mathscr{R}_0$. Among them, important contribution is from Enko [82, 83], who explained the threshold phenomenon in childhood infectious disease and Ronald Ross, 1902 Nobel Laureate, who in 1898 disproved the concept that malaria spreads by air and he clearly proved that malaria spreads through mosquitoes. He did extensive work on mathematical modeling of malarial spreading mosquitoes and the ways to control it. As an outcome of this research Ross derived the critical threshold value for malaria epidemics. Inspired by Ross works, McKendrick tried to find the critical density for the population of infectious agents to sustain in an competitive environment. In 1927, McKendrick [84] along with Kermack, successfully derived the formula for critical density, in the context of an age dependent infections given by,

$$N_c = \frac{1}{A} \quad \text{where} \quad A = \int_0^\infty \phi_t B_t dt \tag{3.2}$$

Here ϕ_t is the infective population at age t, B_t is the probability of having a newly infected individual. George Macdonald [85] in 1952 named it as basic reproduction rate. Deitz, in 1975 gave a clear definition for the basic reproduction rate and he gave the notation $\mathscr{R}_0$ for the basic reproduction rate.

After defining $\mathscr{R}_0$ clearly, the research was focused on controlling the infectious disease agent through an epidemiological model. Robert May and Roy Anderson have contributed much for the epidemiological modeling to control diseases. The papers published in Nature by these authors in the year 1979 [86, 64] revolutionized the research on population biology of infectious diseases. Following this, another paper published in science in the year 1982 [87] explained the uniqueness of $\mathscr{R}_0$ in this field. These works paved way for more research works on infectious diseases.

3.3 Calculation of $\mathscr{R}_0$ using next generation matrix

From 1982, works on utilizing $\mathscr{R}_0$ in applied point of view have increased many folds, and the main focus was laid on using the available real data on population dynamics. Diekmann et al. (1990) [88] developed a method to find $\mathscr{R}_0$ for one kind of population. Dietz (1993)[83] developed a method to calculate $\mathscr{R}_0$ for all kinds of populations.

Since we use Diekmann's methodology for our calculation, let us study Diekmenn et al. $\mathscr{R}_0$ calculation in detail. He formulated a linear positive operator called *Next generation operator* which connects the infected individuals and its generation maps. Here generation is the one obtained from Demography, with a slight modification in its definition. Instead of interpreting generations as being born, here it is taken as becoming infected. Let us now see how to express the next generation operator in matrix notation [89]. Our model consists of n compartments, bearing m infected proportion. Let $\overline{x} = x_i$, $i = 1, 2, 3, \ldots\ldots, n$, be the number or proportion of individuals in the i^{th} compartment. Similarly, $\mathcal{F}_i(\overline{x})$ is the infection rate in the i^{th} compartment.

Let $\mathcal{V}_i^+(\overline{x})$ represent the transfer rate of individuals to the i^{th} compartment, $\mathcal{V}_i^-(\overline{x})$ represents the outflow rate of individuals from i^{th} compartment and define:

$$\mathcal{V}_i = \mathcal{V}_i^-(\overline{x}) - \mathcal{V}_i^+(\overline{x}).$$

The difference between $\mathcal{F}_i(\overline{x})$ and $\mathcal{V}_i(\overline{x})$ gives the rate change of x_i. The crucial point which we have to notice here is that $\mathcal{F}_i$ should include only infections that are newly arising, but does not include terms which describe the transfer of infectious individuals from one infected compartment to another. Using these rules, the next generation matrix (operator) $\mathcal{F}\mathcal{V}^{-1}$ is written as,

$$\mathcal{F} = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right] \quad \text{and} \quad \mathcal{V} = \left[\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}\right]; i, j = 1, 2, \cdots m,$$

where x_0 is a disease-free equilibrium point. The stability of this fixed point is related to the dominant eigenvalue of the NGM. If it is smaller than one, the fixed point is stable, otherwise it is unstable. Usually the square of the dominant eigenvalue is called $\mathscr{R}_0$.[1] The matrix elements in $\mathcal{FV}^{-1}$ are the product of rate of new infection produced in x_i due to the visit of infected individuals in x_j and the average time duration that an individual spends in one visit to compartment j.

3.4 Within-host, two parasites, co-infection and free living stage

In this section, we study a mathematical model for within-host, two parasites with multiple infection and free-living stages. This model makes a difference from the model we discussed previously (Eq.(2.17a-f)). It includes free living stage of parasites explicitly. It was first proposed in [90] in the context of the study of HIV dynamics, where the second parasite corresponds to a mutant virus.The present model consists of two parasites b and p. The population of uninfected hosts is denoted by l. The singly infected host by parasite b is represented as l_b. As we consider co-infection, the doubly infected host by the same parasite b twice is represented by l_{bb}. If the host is singly infected by p, it is denoted as l_p and the co-infection is denoted as l_{pp}. The single infection rate of parasite b is taken as λ_1 and the double infection rate of b is ϵ_2. Similarly, the double infection rate of p is ϵ_4.

As the cross infection is allowed in this case, the host infected by both parasites b and p is denoted as l_{bp}. Corresponding infection rates of parasite p and parasite b are denoted as ϵ_1 and ϵ_3 respectively. Also, the production rate of free living parasite b from the cross infected hosts is represented as γ and that of doubly infected host is represented as γ_b. In the same way, the production rate of free living parasite p from the cross infected hosts is represented as λ_2 and that of doubly infected hosts is represented as γ_p. Let μ be the natural death rate of uninfected hosts. We have taken ϕ_1, ϕ_2, ϕ_3 and ϕ_4 as the disease induced mortality rate of single, double and cross-infected hosts respectively. Let ϕ_5 and ϕ_6 is the natural removal rate of parasite b and parasite p respectively. Our model then

[1] In the scientific literature on the subject, some authors define $\mathscr{R}_0$ as the square of the dominant eigenvalue, others call the eigenvalue itself $\mathscr{R}_0$.

reads:

$$\begin{aligned}
\frac{dl}{d\tau} &= w - \mu l - lb - lp, && (3.3a)\\
\frac{dl_b}{d\tau} &= \lambda_1 lb - \epsilon_1 l_b p - \epsilon_2 l_b b - l_b, && (3.3b)\\
\frac{dl_p}{d\tau} &= lp - \epsilon_3 l_p b - \epsilon_4 l_p p - \phi_1 l_p, && (3.3c)\\
\frac{dl_{bb}}{d\tau} &= \epsilon_2 l_b b - \phi_2 l_{bb}, && (3.3d)\\
\frac{dl_{pp}}{d\tau} &= \epsilon_4 l_p p - \phi_3 l_{pp}, && (3.3e)\\
\frac{dl_{bp}}{d\tau} &= \epsilon_1 l_b p + \epsilon_3 l_p b - \phi_4 l_{bp}, && (3.3f)\\
\frac{db}{d\tau} &= l_b + \gamma l_{bp} + \gamma_b l_{bb} - \phi_5 b, && (3.3g)\\
\frac{dp}{d\tau} &= l_p + \lambda_2 l_{bp} + \gamma_p l_{pp} - \phi_6 p. && (3.3h)
\end{aligned}$$

Compared to equation (2.17) we have, besides a change in notation, two more equations for the free living states of the parasites.

3.5 NGM for doubly infected within-host parasite system

The transmission matrix $\mathcal{F}$ is:

$$\mathcal{F} = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & \lambda_1 l^* & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & l^* \\
\epsilon_2 b^* & 0 & 0 & 0 & 0 & \epsilon_2 l_b^* & 0 \\
0 & \epsilon_4 p^* & 0 & 0 & 0 & 0 & \epsilon_4 l_p^* \\
\epsilon_1 p^* & \epsilon_2 b^* & 0 & 0 & 0 & \epsilon_3 l_p^* & \epsilon_1 l_b^* \\
1 & 0 & \gamma_b & 0 & \gamma & 0 & 0 \\
0 & 1 & 0 & \gamma_p & \lambda_2 & 0 & 0
\end{bmatrix} \qquad (3.4)$$

The transition matrix $\mathcal{V}$ is:

$$\mathcal{V} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \phi_1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \phi_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \phi_3 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \phi_4 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \phi_5 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & \phi_6
\end{bmatrix} \qquad (3.5)$$

The inverse of transition matrix is:

$$\mathcal{V}^{-1} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\phi_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\phi_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\phi_4} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\phi_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\phi_6} \end{bmatrix} \tag{3.6}$$

The NGM operator $\mathcal{F}\mathcal{V}^{-1}$ is:

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\lambda_1 l^*}{\phi_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{l^*}{\phi_6} \\ \epsilon_1 b^* & 0 & 0 & 0 & 0 & \frac{\epsilon_2 l_b^*}{\phi_5} & 0 \\ 0 & \frac{\epsilon_4 p^*}{\phi_1} & 0 & 0 & 0 & 0 & \frac{\epsilon_4 l_p^*}{\phi_6} \\ \epsilon_1 p^* & \frac{\epsilon_3 b^*}{\phi_1} & 0 & 0 & 0 & \frac{\epsilon_3 l_p^*}{\phi_5} & \frac{\epsilon_1 l_b^*}{\phi_6} \\ 1 & 0 & \frac{\gamma_b}{\phi_2} & 0 & \frac{\gamma}{\phi_4} & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & \frac{\gamma_p}{\phi_3} & \frac{\lambda_2}{\phi_4} & 0 & 0 \end{bmatrix} \tag{3.7}$$

3.5.1 $\mathscr{R}_0$ for the model with two parasites without co-infection

The dominant eigenvalue for the infectious state equilibrium is difficult to find. Since the infectious state is given by a higher order polynomial equation, one cannot solve it explicitly. By analyzing its sub-cases, we can understand some of its properties. When we consider our system as singly infected, matrix (3.7) becomes:

$$\mathcal{F}\mathcal{V}^{-1}_{singleinfection} = \begin{bmatrix} 0 & 0 & \frac{\lambda_1 l^*}{\phi_5} & 0 \\ 0 & 0 & 0 & \frac{l^*}{\phi_6} \\ 1 & 0 & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & 0 \end{bmatrix} \tag{3.8}$$

We have to find the eigenvalues for the above matrix (3.8). The square of the dominant eigenvalues gives the reproduction number of the system. Using the NGM operator, we now calculate the $\mathscr{R}_0$ value for the uninfected equilibrium points.

Disease free equilibrium

The disease free equilibrium points are given as $l^* = \frac{w}{\mu}, l_b^* = 0, l_p^* = 0, b^* = 0, p^* = 0$. On substituting these values in the above matrix (3.8), we calculate the characteristic polynomial as:

$$\alpha^4 - \frac{w}{\mu}\left[\frac{\lambda_1}{\phi_5} + \frac{1}{\phi_1\phi_6}\right]\alpha^2 + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6} = 0. \tag{3.9}$$

The above equation is a fourth order polynomial equation, which gives four solutions, of which only two solutions are positive. The square of these two eigenvalues gives corresponding $\mathscr{R}_0$,

$$\mathscr{R}_0^1 = \frac{w\lambda_1}{\mu\phi_5} \quad ; \quad \mathscr{R}_0^2 = \frac{w}{\mu\phi_1\phi_6}. \tag{3.10}$$

Depending on the values of $\mathscr{R}_0^1$ and $\mathscr{R}_0^2$, the endurance of parasite(p) and parasite(b) in the host population is decided. When $\mathscr{R}_0^1 > \mathscr{R}_0^2$, $\frac{\lambda_1}{\phi_5} > \frac{1}{\phi_1\phi_6}$. Here λ_1 is the single infection class growth rate of parasite b, and should also satisfy the conditions $\lambda_1 > 1$, $\lambda_1 > \phi_5$ and at the same time $\phi_5 < \phi_1\phi_6$ ie., the removal rate of parasite b should be less than parasite p. Under this circumstance, parasite b excludes parasite p from the competition. On contrary ($\mathscr{R}_0^1 < \mathscr{R}_0^2$), when the condition changes to $\frac{\lambda_1}{\phi_5} < \frac{1}{\phi_1\phi_6}$, parasite p eliminates parasite b from the competition. This matches the results obtained in the previous chapter.

3.5.2 $\mathscr{R}_0$ for cross-infection

Here, we consider the case of cross infection by both parasites b and p in the same host. This is a kind of reduced co-infective case, as we will consider $l_{bb} = l_{pp} = 0$ but not l_{bp}. So, our matrix.(3.7) now becomes,

$$\mathcal{FV}^{-1}_{crossinfection} = \begin{bmatrix} 0 & 0 & 0 & \frac{\lambda_1 l^*}{\phi_5} & 0 \\ 0 & 0 & 0 & 0 & \frac{l^*}{\phi_6} \\ \epsilon_1 p^* & \frac{\epsilon_3 b^*}{\phi_1} & 0 & \frac{\epsilon_3 l_p^*}{\phi_5} & \frac{\epsilon_1 l_b^*}{\phi_6} \\ 1 & 0 & \frac{\gamma}{\phi_4} & 0 & 0 \\ 0 & \frac{1}{\phi_1} & \frac{\lambda_2}{\phi_4} & 0 & 0 \end{bmatrix} \tag{3.11}$$

Disease free equilibrium

We substituted the disease free equilibrium points $l^* = \frac{w}{\mu}$, $l_b^* = 0$, $l_p^* = 0$, $l_{bp}^* = 0$, $b^* = 0$ and $p^* = 0$ in the cross infection NGM operator matrix and obtained the characteristic equation as,

$$\alpha^5 - \frac{w}{\mu}\left[\frac{\lambda_1}{\phi_5} + \frac{1}{\phi_1\phi_6}\right]\alpha^3 + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6}\alpha = 0. \tag{3.12}$$

On simplifying this equation, we get one eigenvalue as zero. So, the above equation becomes,

$$\alpha^4 - \frac{w}{\mu}\left[\frac{\lambda_1}{\phi_5} + \frac{1}{\phi_1\phi_6}\right]\alpha^2 + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6} = 0. \tag{3.13}$$

Solving this fourth order polynomial equation, we get the same expression as above (3.10). Since we discussed these in the previous section, the steps involved is quite evident.

Coexistence

As cross-infection is a kind of specific co-infection, we could wonder if coexistence of the parasites is possible, assuming that each of them can invade the disease-free equilibrium. However, to investigate this analytically we would have to study the mutual invasibility of parasites 1 and 2, a problem which would amount to fifth order polynomial. Given this, it is simpler to numerically explore the system. In Fig.(3.1) we give the analogue of Fig.(2.5), wherefrom it is clear that coexistence is present. Further, in Fig.(3.2) we give a bifurcation diagram on the dependence of the equilibrium states of l, b, p along a gradient of increasing recruitment rate. Upon increasing w we go through three different patterns: no infection, single infection, double-infection.

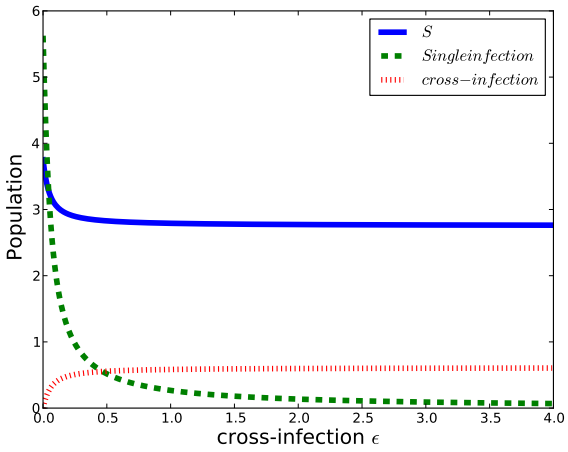

Figure 3.1: Equilibrium states along a cross-infection rate gradient.

The parameter values of the above figure 3.1 and figure 3.2 are given in the tables 3.1 and 3.2

Table 3.1: Parameters values of figure 3.1

Symbol	Values
λ_1	1.1
ϕ_1	0.9
ϕ_4	0.85
ϕ_5	0.85
ϕ_6	0.95
μ	0.5
w	2.5
γ	0.35
λ_2	0.35

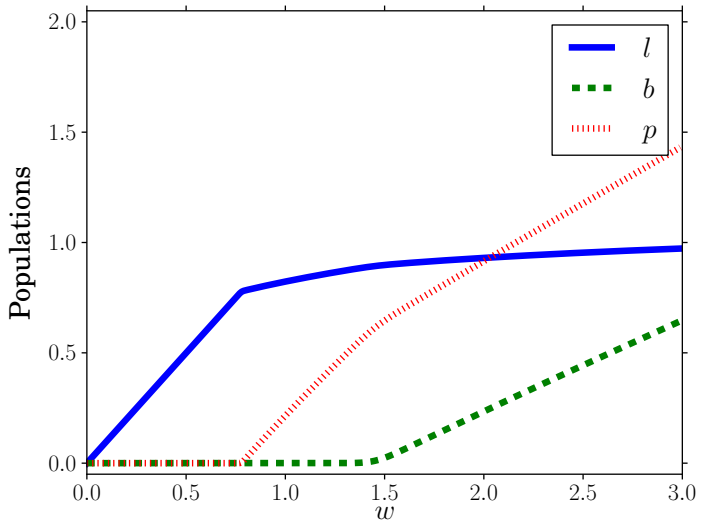

Figure 3.2: Equilibrium states along a recruitment gradient : as we increase w we from a disease-free equilibrium to a one-parasite equilibrium and then to a coexistence equilibrium

Table 3.2: Parameters values of figure 3.2

Symbol	Values
λ_1	1.1
ϕ_1	0.9
ϕ_4	0.85
ϕ_5	0.85
ϕ_6	0.95
μ	0.5
ϵ_1	0.6
ϵ_3	0.6
γ	0.35
λ_2	0.35

3.5.3 $\mathscr{R}_0$ for co-infection

In this subsection we discuss the complete model that includes, within-host, two parasites, single and co-infection cases.

Disease free equilibrium state

When we substitute the disease free equilibrium points ($l = \frac{w}{\mu}, l_b = 0, l_{bb} = 0, l_{pp} = 0, l_{bp} = 0, b = 0, p = 0$), in matrix (3.7) we get,

$$\mathcal{FV}^{-1}_{diseasefree} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\lambda_1 w}{\mu\phi_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{w}{\mu\phi_6} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & \frac{\gamma_b}{\phi_2} & 0 & \frac{\gamma}{\phi_4} & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & \frac{\gamma_p}{\phi_3} & \frac{\lambda_2}{\phi_4} & 0 & 0 \end{bmatrix} \tag{3.14}$$

the resultant characteristic equation is,

$$\alpha^7 - \frac{w}{\mu}\left[\frac{\lambda_1}{\phi_5} + \frac{1}{\phi_1\phi_6}\right]\alpha^5 + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6}\alpha^3 = 0. \tag{3.15}$$

Solving this equation, first we get three eigenvalues zero then the polynomial becomes fourth order polynomial. As discussed in previous section (3.10), the solution of this polynomial equation gives $\mathscr{R}_0$,

$$\mathscr{R}_0^1 = \frac{w\lambda_1}{\mu\phi_5} \quad ; \quad \mathscr{R}_0^2 = \frac{w}{\mu\phi_1\phi_6}. \tag{3.16}$$

Coexistence

Analysis of coexistence patterns should again go through numerical simulations as analytics is too involved. The patterns that emerge are analogous to the ones in the previous subsection and we will not display them here. In the next chapter, a generalized model will be studied and the plots corresponding to the case of co-infection with free living states will be a special case. There is no real change in the patterns of coexistence between the cross-infection and the co-infections cases.

3.6 Conclusion

In this chapter we have considered a model which extends the model discussed in the previous chapter by including free-living states of the parasites. Analysis becomes more involved, but we could show that the coexistence states found in Chapter 2 do continue to exist, although the quantitative aspects of the coexistence equilibrium change.

4

Within-host parasite competition with ecological effect

4.1 Introduction

In chapter 2 we studied within-host, two parasites (without free living stage) infections. Competitive exclusion occurs if no co-infections are allowed. When co-infection was included the two parasites were found to possibly coexist. In chapter 3 we extended the result to the case where the parasites also exist in free-living states. In this chapter, we discuss the change in dynamics which occurs if the consider a further effect, one that is known by intraguild effect (IG). This effect is a displacement effect. It occurs when one of the parasites can displace the other in a co-infected state. To go back to the setting of the previous chapter, we can have the displacement, for instance, of l_{bp} to l_{bb} if b is able to displace p. We can as well have l_{bp} becoming l_{pp}.

The reason behind the inclusion of IG effect in our model is because of the fact that the IG effect highly influences the outcome of parasite competition. This is an experimental fact, and we will set-out to formulate a model to understand it. For instance, Antonino et al. ,[91], observed that the IG effect on two parasitoids whose hosts are eggs and experimentally confirmed the change in the competition outcome of these parasitoids due to the IG effect. In this experiment the parasitoids are *Trissolcus basalis* and *Ooencyrtus telenomicida* and the host is southern green stink bug *Nezara Viridula*(egg). He experimentally observed the single, sequential (one by one) and simultaneous infection of these parasitoids on the host. His experiments shows that mortality of *Nezara Viridula*

eggs was higher in sequential and simultaneous infections compared to single infection. Of these two parasitoids, *O.telenomicida* is superior competitor at larvae level and *T. basalis* is superior in finding host. The IG interaction occurs when *O.telenomica* acts as a hyperparasitoid, interacting with *T.basalis* not only via competition but also via tropic interaction (ie IG interaction). In a nutshell, in this two parasitoids and host interaction, when we consider only the competition among them, the result is competitive exclusion and when we include IG effect, the two parasitoids are found to coexist. In the same paper, Antonino et al.[91] expressed that laboratory conditions vary from field conditions. So it is not easy to infer exact results from the former to field populations.

Hence, we have taken the task of understanding these experimental observations by constructing a mathematical model. Following section elaborates our mathematical model and analysis. We analytically calculated $\mathscr{R}_0$ using NGM operator. We then numerically simulated the model to understand the dynamics involved.

4.2 Mathematical model

The model which we have considered here is a well mixed model consisting of host and parasite populations. In our system, recruitment rate of host is taken as constant. The parasites invade and grow inside hosts and upon reaching a complete adulthood, kill the host. We consider a free living parasite i.e., the parasite that lives in an environment outside the host. It lives in the environment, until it gets a suitable host for its breeding. Our model consists of one host which can be multiply infected by two parasites. There exists no cross immunity between these parasites so both the parasites can infect the host any number of times. For simplicity, we restrict the number of infections as two. By sequential infection method the two parasites infect the host. Since parasite(b) and parasite (p) infects host twice and there is no cross immunity, the host undergoes five infected stages or classes in our system. A distinguished feature in the model that we will present is that it admits a so called IG effect- *the effect in which parasite b can replace p from host in co-infected states* is taken into account. The mathematical model

for our system is given below:

$$\begin{aligned}
\frac{d\mathscr{L}}{dt} &= \mathfrak{W} - \mu\mathscr{L} - \alpha_1\mathscr{L}B - \alpha_2\mathscr{L}P, && (4.1a)\\
\frac{d\mathscr{L}_B}{dt} &= \alpha_1\mathscr{L}B - \beta_1\mathscr{L}_BP - \beta_2\mathscr{L}_BB - \delta_1\mathscr{L}_B, && (4.1b)\\
\frac{d\mathscr{L}_P}{dt} &= \alpha_2\mathscr{L}P - \beta_3\mathscr{L}_PB - \beta_4\mathscr{L}_PP - \delta_2\mathscr{L}_P, && (4.1c)\\
\frac{d\mathscr{L}_{BB}}{dt} &= \beta_2\mathscr{L}_BB + \chi_1L_{BP}B - \delta_3\mathscr{L}_{BB}, && (4.1d)\\
\frac{d\mathscr{L}_{PP}}{dt} &= \beta_4\mathscr{L}_PP + \chi_2L_{BP}P - \delta_4\mathscr{L}_{PP}, && (4.1e)\\
\frac{d\mathscr{L}_{BP}}{dt} &= \beta_1\mathscr{L}_BP + \beta_3\mathscr{L}_PB - \chi_1L_{BP}B - \chi_2L_{BP}P - \delta_5\mathscr{L}_{BP}, && (4.1f)\\
\frac{dB}{dt} &= \gamma_1\mathscr{L}_B + \gamma_2\mathscr{L}_{BP} + \gamma_3\mathscr{L}_{BB} - \delta_6B, && (4.1g)\\
\frac{dP}{dt} &= \gamma_4\mathscr{L}_P + \gamma_5\mathscr{L}_{BP} + \gamma_6\mathscr{L}_{PP} - \delta_7P. && (4.1h)
\end{aligned}$$

The above equation involves many parameters and it becomes difficult to study the dynamics of within-host parasites interactions. So we convert these equation to its non-dimensional form to study its dynamics more clearly. The non-dimensional equations are as follows

$$\begin{aligned}
\frac{dl}{d\tau} &= w - \mu l - lb - lp, && (4.2a)\\
\frac{dl_b}{d\tau} &= \lambda_1 lb - \epsilon_1 l_b p - \epsilon_2 l_b b - l_b, && (4.2b)\\
\frac{dl_p}{d\tau} &= lp - \epsilon_3 l_p b - \epsilon_4 l_p p - \phi_1 l_p, && (4.2c)\\
\frac{dl_{bb}}{d\tau} &= \epsilon_2 l_b b + \xi_1 l_{bp} b - \phi_2 l_{bb}, && (4.2d)\\
\frac{dl_{pp}}{d\tau} &= \psi l_p p + \xi_2 l_{bp} p - \phi_3 l_{pp}, && (4.2e)\\
\frac{dl_{bp}}{d\tau} &= \zeta_1 l_b p + \zeta_2 l_p b - \xi_1 l_{bp} b - \xi_2 l_{bp} p - \phi_4 l_{bp}, && (4.2f)\\
\frac{db}{d\tau} &= l_b + \gamma l_{bp} + \gamma_b l_{bb} - \phi_5 b, && (4.2g)\\
\frac{dp}{d\tau} &= l_p + \lambda_2 l_{bp} + \gamma_p l_{pp} - \phi_6 p. && (4.2h)
\end{aligned}$$

Where the non-dimensional parameters are

$$
\begin{aligned}
w &= \frac{\alpha_2\gamma_4}{\delta_1^3}\mathfrak{W}; \quad l = \frac{\alpha_2\gamma_4}{\delta_1^2}L; \quad l_b = \frac{\alpha_1\gamma_1}{\delta_1^2}L_B; \quad l_p = \frac{\alpha_2\gamma_4}{\delta_1^2}L_P; \quad l_{bb} = \frac{\alpha_1\gamma_1}{\delta_1^2}L_{BB} \\
l_{pp} &= \frac{\alpha_2\gamma_1}{\delta_1^2}L_{PP}; \quad l_{bp} = \frac{\alpha_1\gamma_1}{\delta_1^2}L_{BP}; \quad b = \frac{\alpha_1}{\delta_1}B; \quad p = \frac{\alpha_2}{\delta_1}P; \quad \tau = \delta_1 t; \quad \mu = \frac{\mu}{\delta_1} \\
\zeta_1 &= \frac{\beta_1}{\gamma\alpha_1}; \quad \zeta_2 = \frac{\epsilon_3\gamma_1}{\gamma_4\alpha_1}; \quad \lambda_1 = \frac{\alpha_1\gamma_1}{\gamma_4\alpha_2}; \quad \lambda_2 = \frac{\alpha_2\gamma_6}{\gamma_1\alpha_1}; \quad \psi = \frac{\epsilon_4}{\gamma}; \quad \xi_1 = \frac{\chi_1}{\alpha_1} \\
\xi_2 &= \frac{\chi_2}{\alpha_2}; \quad \gamma_b = \frac{\gamma_2}{\gamma_1}; \quad \gamma_p = \frac{\gamma_5}{\gamma_4}; \quad \gamma = \frac{\gamma_3}{\gamma_1}; \quad \epsilon_1 = \frac{\beta_1}{\alpha_2}; \quad \epsilon_2 = \frac{\beta_2}{\alpha_1}; \quad \epsilon_3 = \frac{\beta_3}{\alpha_1} \\
\epsilon_4 &= \frac{\beta_4}{\alpha_2}; \quad \phi_1 = \frac{\delta_2}{\delta_1}; \quad \phi_2 = \frac{\delta_3}{\delta_1}; \quad \phi_3 = \frac{\delta_4}{\delta_1}; \quad \phi_4 = \frac{\delta_5}{\delta_1}; \quad \phi_5 = \frac{\delta_6}{\delta_1}; \quad \phi_6 = \frac{\delta_7}{\delta_1}.
\end{aligned}
$$

The description of symbol given in table 4.1.

Table 4.1: Notation Description

Case	Symbol	Description
1	w	Uninfected host recruitment rate
2	μ	Natural death rate of uninfected host
3	λ_1	Single infection rate of parasite b
4	ϵ_1	Cross-infection rate of parasite p
5	ϵ_2	Double infection rate of parasite b
6	ϵ_3	Cross-infection rate of parasite b
7	ϵ_4	Double infection rate of parasite p
8	ψ	Growth rate of doubly infected host
9	ζ_1, ζ_2	Growth rate of cross-infected host
10	ξ_1	Intraguild strength of parasite b
11	ξ_2	Intraguild strength of parasite p
12	γ_b	Growth rate of parasite b from doubly infected host
13	γ_p	Growth rate of parasite p from doubly infected host
14	γ	Growth rate of parasite b from cross-infected host
15	λ_2	Growth rate of parasite p from cross-infected host
16	ϕ_1	Mortality rate of singly infected host
17	ϕ_2	Mortality rate of doubly infected host
18	ϕ_3	Mortality rate of doubly infected host
19	ϕ_4	Mortality rate of cross-infected host
20	ϕ_5	Natural removal rate of parasite b
21	ϕ_6	Natural removal rate of parasite p

4.3 Analytical analysis

Eqn (4.2a-h) cannot be solved explicitly and it is difficult to analyse the full model in its original form. So we prefer to analyze the sub-cases first and with those results, we can analyze the full model numerically in a better way.

4.3.1 Within-host single parasite

In this subsection, we have taken the subcase of Eq. (4.2a-h) as one parasite (b), multiple infection (two times) ie., parasite b can infect host l two times. Let us consider that the parasite b infect the uninfected host l at the rate of λ_1. The natural death rate of uninfected host is μ. Now, parasite b infects the singly infected host l_b at the rate of ϵ_2 . γ_b is the production rate of parasite b from doubly infected host l_{bb}. ϕ_5 is the natural removal rate of parasite b. Here single infected host mortality rate is equal to one. ϕ_2 is the mortality rate of doubly infected host l_{bb}.

$$\frac{dl}{d\tau} = w - \mu l - lb, \tag{4.3a}$$

$$\frac{dl_b}{d\tau} = \lambda_1 lb - \epsilon_2 l_b b - l_b, \tag{4.3b}$$

$$\frac{dl_{bb}}{d\tau} = \epsilon_2 l_b b - \phi_2 l_{bb}, \tag{4.3c}$$

$$\frac{db}{d\tau} = l_b + \gamma_b l_{bb} - \phi_5 b. \tag{4.3d}$$

Transmission matrix ($\mathcal{F}$) for the above eqns. (4.3a-4.3d) is

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & \lambda_1 l^* \\ \epsilon_2 b^* & 0 & \epsilon_2 l_b^* \\ 1 & \gamma_b & 0 \end{bmatrix} \tag{4.4}$$

Transition matrix ($\mathcal{V}$) for the above set of equations(4.3a-4.3d) is

$$\mathcal{V} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \phi_2 & 0 \\ 0 & 0 & \phi_5 \end{bmatrix} \tag{4.5}$$

The inverse transition matrix ($\mathcal{V}$) is

$$\mathcal{V}^{-1} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{1}{\phi_2} & 0 \\ 0 & 0 & \frac{1}{\phi_5} \end{bmatrix} \tag{4.6}$$

We can obtain a NGM operator by multiplying the matrix (4.4) and (4.6)

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} 0 & 0 & \frac{\lambda_1 l^*}{\phi_5} \\ \epsilon_1 b^* & 0 & \frac{\epsilon_2 l_b^*}{\phi_5} \\ 1 & \frac{\gamma_b}{\phi_2} & 0 \end{bmatrix} \tag{4.7}$$

The square of the dominant eigenvalue of the above matrix (4.7) at the disease-free equilibrium gives the corresponding $\mathscr{R}_0$.

Disease free equilibrium

Let us find the dominant eigenvalue of the above matrix (4.7) for disease free equilibrium state $l^* = \frac{w}{\mu}, l_b^* = 0, l_{bb}^* = 0$ and $b^* = 0$. The characteristic polynomial which we got by substituting the disease free equilibrium points in the NGM matrix(4.7) is given as,

$$\alpha^3 - \left(\frac{w\lambda_1}{\mu\phi_5}\right)\alpha = 0 \tag{4.8}$$

Solving this equation gives three eigenvalues $0, -\sqrt{\frac{w\lambda_1}{\mu\phi_5}}$ and $\sqrt{\frac{w\lambda_1}{\mu\phi_5}}$. The square of the dominant eigenvalue gives the as,

$$\mathscr{R}_0 = \frac{w\lambda_1}{\mu\phi_5}. \tag{4.9}$$

The parameters w, λ_1, μ and ϕ_5 are all real and positive. The parasite population b persist in the system if $\mathscr{R}_0$ is greater than 1 ($\mathscr{R}_0 > 1$). $\mathscr{R}_0 > 1$ only when $w\lambda_1 > \mu\phi_5$. This corresponds to the instability of the disease-free equilibrium, and to the invasion of the parasite into this equilibrium.

4.3.2 Within-host, two parasites, co-infection with intraguild effect

In order to construct NGM operator for equation(4.2a-h), we should first construct the transmission matrix ($\mathcal{F}$) and then the transition matrix($\mathcal{V}$).
The transmission matrix($\mathcal{F}$) is given as,

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \lambda_1 l^* & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & l^* \\ \epsilon_2 b^* & 0 & \xi_1 b^* & 0 & 0 & \epsilon_2 l_b^* + \xi_1 l_{bp}^* & 0 \\ 0 & \psi p^* & 0 & \xi_2 p^* & 0 & 0 & \psi l_p^* + \xi_2 l_{bp}^* \\ \zeta_1 p^* & \zeta_2 b^* & 0 & 0 & 0 & \zeta_2 l_p^* & \zeta_1 l_b^* \\ 1 & 0 & \gamma_b & 0 & \gamma & 0 & 0 \\ 0 & 1 & 0 & \gamma_p & \lambda_2 & 0 & 0 \end{bmatrix} \tag{4.10}$$

The transition matrix $\mathcal{V}$ is

$$\mathcal{V} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \phi_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \phi_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \phi_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \phi_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \phi_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \phi_6 \end{bmatrix} \tag{4.11}$$

The Inverse of transtion$\mathcal{V}$ matrix is

$$\mathcal{V}^{-1} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\phi_2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\phi_3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\phi_4} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\phi_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{\phi_6} \end{bmatrix} \tag{4.12}$$

Multiplying matrix (4.12) and (4.14) gives $\mathcal{F}\mathcal{V}^{-1}$ a NGM operator as,

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\lambda_1 l^*}{\phi_5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{l^*}{\phi_6} \\ \epsilon_2 b^* & 0 & \frac{\xi_1 b^*}{\phi_2} & 0 & 0 & \frac{\epsilon_2 l_b^* + \xi_1 l_{bp}^*}{\phi_5} & 0 \\ 0 & \frac{\psi p^*}{\phi_1} & 0 & \frac{\xi_2 p^*}{\phi_3} & 0 & 0 & \frac{\psi l_p^* + \xi_2 l_{bp}^*}{\phi_6} \\ \zeta_1 p^* & \frac{\zeta_2 b^*}{\phi_1} & 0 & 0 & 0 & \frac{\zeta_2 l_p^*}{\phi_5} & \frac{\zeta_1 l_b^*}{\phi_6} \\ 1 & 0 & \frac{\gamma_b}{\phi_2} & 0 & \frac{\gamma}{\phi_4} & 0 & 0 \\ 0 & \frac{1}{\phi_1} & 0 & \frac{\gamma_p}{\phi_3} & \frac{\lambda_2}{\phi_4} & 0 & 0 \end{bmatrix} \tag{4.13}$$

Disease free equilibrium

On substituting the disease free equilibrium points in NGM operator matrix(4.15), we get the characteristic polynomial equation as

$$\alpha^7 - \alpha^5 \left(\frac{w\lambda_1}{\mu\phi_5} + \frac{w}{\mu\phi_1\phi_6} \right) + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6}\alpha^3 = 0. \tag{4.14}$$

Neglecting zero eigenvalue reduces the above 7^{th} order polynomial equation to 4^{th} order polynomial equation,

$$\alpha^4 - \alpha^2 \left(\frac{w\lambda_1}{\mu\phi_5} + \frac{w}{\mu\phi_1\phi_6} \right) + \frac{w^2\lambda_1}{\mu^2\phi_1\phi_5\phi_6} = 0. \tag{4.15}$$

Solving this equation gives four eigenvalues as $\pm\sqrt{\frac{w\lambda_1}{\mu\phi_5}}$ and $\pm\sqrt{\frac{w}{\mu\phi_1\phi_6}}$. Let us take square of the dominant eigenvalue to calculate $\mathscr{R}_0$

$$\mathscr{R}_0^1 = \frac{w\lambda_1}{\mu\phi_5} \tag{4.16a}$$

$$\mathscr{R}_0^2 = \frac{w}{\mu\phi_1\phi_6} \tag{4.16b}$$

In our system, the condition for the persistence of the population of parasite b and parasite p is that both $\mathscr{R}_0^1$ and $\mathscr{R}_0^2$ should be greater than one.

This means

$$\frac{w\lambda_1}{\mu\phi_5} > 1; \qquad \frac{w}{\mu\phi_1\phi_6} > 1. \tag{4.17}$$

Only when the above condition is satisfied, both the parasites populations persists.

Coexistence patterns

As in the previous chapters, once the invasibility condition for parasites 1 and 2 are satisfied, the question is to know the endemic states, that is, the long-term equilibrium. This problem has to be tackled numerically and we will do so in the next section, studying the possible different cases. At the end this will give a clear view of the change of coexistence patterns introduced by the IG effect.

4.4 Numerical analysis

As our model equation (4.2a-h) is a coupled nonlinear ordinary differential equation, finding explicit solution is nearly impossible. Though we can analytically get some information about our system by taking certain assumptions, the complete dynamics of the system cannot be clearly understood analytically. With the aid of numerical techniques, we can have a better understanding of the dynamics of our model.

4.4.1 Low food/recruitment of uninfected host

We consider the birth rate of uninfected host as constant. So, the first and foremost condition is that, when the birth rate of host is too low, the possibility of the parasites b and parasite p to find, invade and reproduce in the host is lower and both may be excluded from our system. From this graph it is quite clear

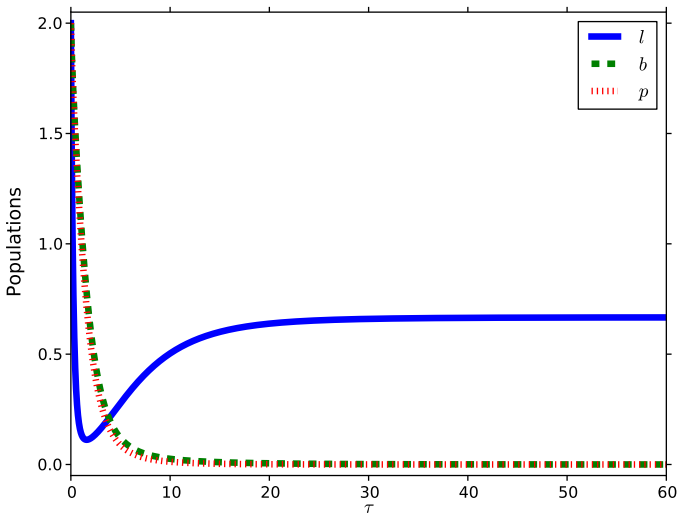

Figure 4.1: Population dynamics for Low recruitment/food of uninfected host (w) parasites do not persist in the Low recruitment/food. Parameters are shown in table 4.2.

that the population of both the parasites cannot persist in our system when the recruitment of uninfected host is low. This is shown in figure 4.1. The populations mentioned in y-axis in figure 4.1 are the equilibrium state populations and this notation has been followed for all the graph from now on. Equation (4.2a-h) is used for this numerical simulation. The values of the parameters used for simulation is listed in the table 4.2.

Table 4.2: Parameters values of figure 4.1

Symbol	Values
λ_1	1.1
ϕ_1	1.2
ϕ_2	0.85
ϕ_3	0.85
ϕ_4	0.85
ϕ_5	0.85
ϕ_6	0.95
w	0.75
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35
ξ_1	0.75
ξ_2	2.5

4.4.2 High recruitment/food of host

In this subsection, we discuss the competition outcome of both parasites in our model Eqn. (4.2a-h) when the recruitment rate of uninfected host (w) is high.

Single infection

In this subcase, we have taken two parasites and single infection condition. Single infection means that a parasite finds an uninfected host and infects only once. And the host which is already infected will not be infected by either the same or another parasite. Equation (4.2a-h) is used for numerical simulation with suitable assumption, the assumption are $\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \xi_1, \xi_2, \zeta_1, \zeta_2, \gamma, \gamma_b, \gamma_p, \lambda_2, \phi_2, \phi_3, \phi_4$ and ψ equal to zero. The important parameter in our simulation is ϕ_5 the natural removal rate of parasite b and ϕ_6, the natural removal rate of parasite p. As we consider the single infection only, let us take ϕ_1 as the disease induced mortality rate of parasite p. We have chosen a fixed value for the single infection rate λ_1 of parasite b. Here single infection rate of parasite p is equal to one. For simulation of figure 4.2(a) and 4.2(b), we used the same value of the uninfected

host recruitment rate w and natural death rate of uninfected host μ.

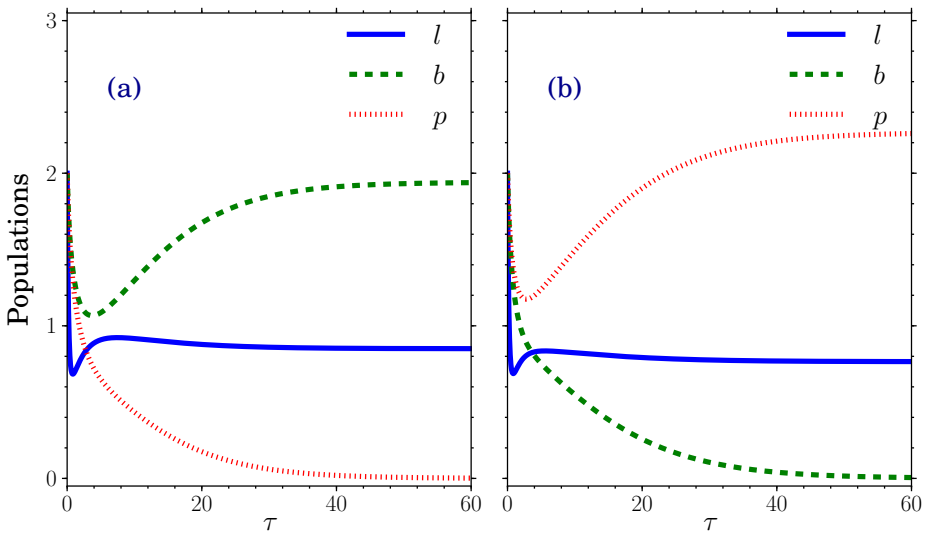

Figure 4.2: Population dynamics for high recruitment/food of host. Figure a) parasite p is eliminated ($\phi_5 < \phi_6$). Figure b) parasite b is eliminated ($\phi_6 < \phi_5$)

Consider figure 4.2a, here the natural removal rate of parasite b (ϕ_5) is taken to be less than the natural removal rate of parasite p (ϕ_6). Also, we considered the disease induced mortality (ϕ_1) rate of parasite p infected host greater than one. In our model disease induced mortality rate of parasite b infected host equal to one. Under this circumstance, parasite b eliminates parasite p. As the parasite p has high value for natural removal rate ϕ_6, compared to natural removal rate ϕ_5 of parasite b, the parasite p gets only less number of uninfected host l, subsequently decrease its reproduction rate. So as the system progress, the population of parasite p is excluded in due course of time. The parameters used for this simulation is given in table 4.3.

In figure 4.2b, we have taken $\phi_5 > \phi_6$, $\phi_1 < 1$ and $\lambda_1 < 1$. All the parametric values used in figure 4.2b is given in table 4.4. We considered the infection rate λ_1 of parasite b is less than that of parasite p and the natural removal rate ϕ_5 of parasite b is greater than that of parasite p (ϕ_6). Under this condition now parasite p eliminates parasite b.

To conclude, from the single infection subcase it is clear that in a model with one host, two parasites and single infection, coexistence of both parasite is impossible and the parasite competition outcome will always be competitive exclusion.

The parameters values of the above figure 4.2 are given in the two tables

Table 4.3: Parameters values of figure 4.2a

λ_1	1.1
ϕ_1	1.2
ϕ_5	0.85
ϕ_6	0.95
w	2.5
μ	0.5

Table 4.4: Parameters values of figure 4.2b

λ_1	0.9
ϕ_1	0.9
ϕ_5	0.95
ϕ_6	0.85
w	2.5
μ	0.5

Co-infection

In this subcase, we discuss within-host, two parasites, with multiple infection (two times). When the host is multiply infected, we look for the change in dynamics of parasite competition due to this multiple infection. The outcome of this parasites competition is given in figure 4.3. In the figure, the populations mentioned in Y-axis are the equilibrium state population. Equation (4.2a-h) is used for numerical simulation provided ξ_1, ξ_2 equal to zero.

The parameters of single infection rate (λ_1), uninfected host recruitment rate (w), natural death rate of uninfected host (μ), the cross infection parameters ζ_1, ζ_2, ϵ_1 and ϵ_3 of parasite b and parasite p respectively given in table 4.5 and table 4.6. The production rate of parasite b from cross-infected host γ and doubly infected host γ_b are fixed. Similarly, the production rate of parasite p from cross infection (λ_2) and doubly infected host (γ_p) are fixed. Here we fixed the values for all parameters arbitrarily.

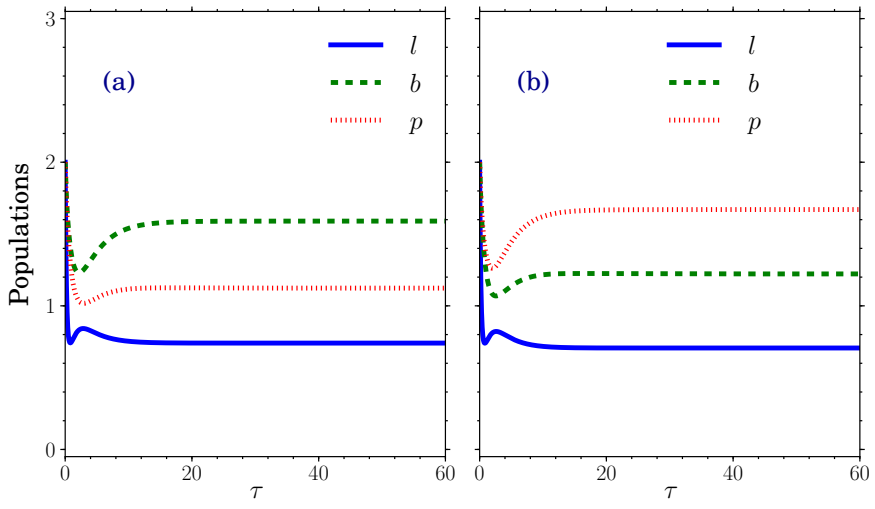

Figure 4.3: Population dynamics for high recruitment/food of host with co-infection. Figure a) both the parasites coexist. Figure b) both the parasites coexist

For plotting figure 4.3a, we have taken $\phi_5 < \phi_6$, $\phi_1 > 1$, $\epsilon_2 > \epsilon_4$ and $\phi_2 < \phi_3$. As we allowed the multiple infection(co-infection), both the parasites were found to coexists indefinitely.

For plotting figure 4.3b, we have taken $\phi_5 > \phi_6$, $\phi_1 < 1$, $\epsilon_2 < \epsilon_4$ and $\phi_2 > \phi_3$. As we allowed the multiple infection(co-infection), in this condition also both the parasites were found to coexists indefinitely.

From the co-infection subcase, we understand that two parasites in within-host interaction, when co-infection effect is added, can coexist indefinitely. The parameters values of the above figure 4.3 are given in the two tables

Table 4.5: Parameters values of figure 4.3a

λ_1	1.1
ϕ_1	1.2
ϕ_2	0.75
ϕ_3	0.85
ϕ_4	0.65
ϕ_5	0.85
ϕ_6	0.95
w	2.5
μ	0.5
ϵ_1	0.6
ϵ_2	0.55
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35

Table 4.6: Parameters values of figure 4.3b

λ_1	0.9
ϕ_1	0.9
ϕ_2	0.85
ϕ_3	0.75
ϕ_4	0.85
ϕ_5	0.95
ϕ_6	0.85
w	2.5
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.55
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35

Co-infection and intraguild effect

In the above discussed case, we considered co-infection alone and found that both the parasites coexists indefinitely. In this section, along with co-infection, we include IG effect in our system. Equation (4.2a-h) is used for numerical simulation. Let the IG parameters of the parasite b and parasite p be ξ_1 and ξ_2 respectively. In this section, we discuss the dynamical changes the system undergoes and the changes the parasites proves due to inclusion of IG effect. In single infection case, the natural removal rate ϕ_5 of parasite b is less than the natural removal rate ϕ_6 of the parasite p ($\phi_5 < \phi_6$). When the host is singly

infected l_p host mortality rate is $\phi_1 > 1$, then the parasite p is eliminated from the system.

At this stage, when we include the IG effect, and the condition that $\xi_1 < \xi_2$, competition switching arises and the parasite b is eliminated from the system instead of parasite p. This is illustrated in the figure 4.4a. Whenever the IG parameter of p exceeds that of b, the parasite b is displaced by parasite p from the host and consequently the parasite b is unable to find a host. Since parasite b is displaced from the host, subsequently reproduction rate of parasite b decreases. On the other hand, the reproduction rate of parasite p increases on account of freely available host and at one stage, parasite b is completely eliminated from the system.

When the natural removal rate ϕ_5 of the parasite b is greater than the natural removal rate ϕ_6 of parasite p, and when the infected host mortality rate is less than 1 ($\phi_1 < 1$), parasite b is eliminated by parasite p. When we include the IG effect in the system ($\xi_1 > \xi_2$), the system is found to have a different exclusion pattern, parasite p being now eliminated in favor of parasite b. Following figure 4.4b explains these results. The values of the parameter used for simulation figure(4.4) is listed in the table 4.7, 4.8 respectively.

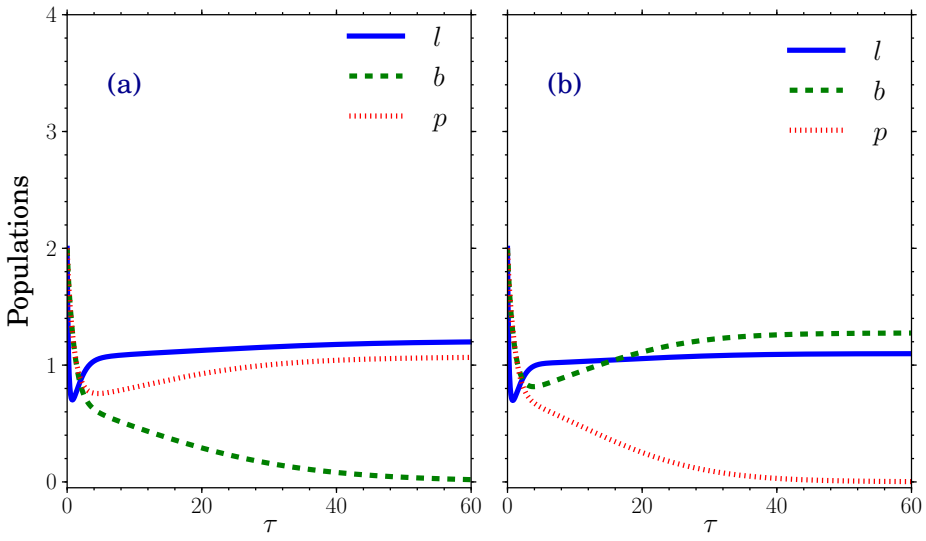

Figure 4.4: Population dynamics for high recruitment/food of uninfected host (w) with co-infection and IG effect. Figure a) parasites b eliminated. Figure b) parasites p eliminated.

The parameters values of the above figure 4.4 are given in the two tables

Table 4.7: Parameters values of figure 4.4a

λ_1	1.1
ϕ_1	1.2
ϕ_2	0.85
ϕ_3	0.85
ϕ_4	0.85
ϕ_5	0.85
ϕ_6	0.95
w	2.5
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35
ξ_1	0.75
ξ_2	2.5

Table 4.8: Parameters values of figure 4.4b

λ_1	0.9
ϕ_1	0.9
ϕ_2	0.85
ϕ_3	0.85
ϕ_4	0.85
ϕ_5	0.95
ϕ_6	0.85
w	2.5
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35
ξ_1	2.5
ξ_2	0.75

4.5 Bifurcation analysis

In our model equation (4.2a-h), the recruitment rate of uninfected host w is the most important parameter. This is because, when the value of w goes below certain threshold value, both the parasites were unable to persist in the population. In this section, we analyze the qualitative changes that the system undergoes when we increase the w parameter.

4.5.1 Single infection

Let us consider that one parasite can infect the host only once or in other words, an infected host cannot be infected again by other parasite. There exists cross immunity between two parasites. For bifurcation analysis we used equation (4.2a-h) with suitable assumption, the assumption are $\epsilon_1, \epsilon_2, \epsilon_3, \epsilon_4, \xi_1, \xi_2, \zeta_1, \zeta_2, \gamma, \gamma_b, \gamma_p, \lambda_2$, ϕ_2, ϕ_3, ϕ_4 and ψ equal to zero. Under this consideration, the dynamics of our parasites depends greatly on the parasite removal rate ϕ_5 and ϕ_6 and the death rate of single infected host. When $\phi_5 < \phi_6$ and $\phi_1 > 1$, parasite b eliminates parasite p from the competition. This is shown in the figure 4.5a. On the other hand, when $\phi_5 > \phi_6$ and $\phi_1 < 1$, parasite p eliminates parasite b from the competition.

It is illustrated in the figure 4.5b. The parameters used in the figure 4.5a and 4.5b are given in the table 4.9 and 4.10 respectively.

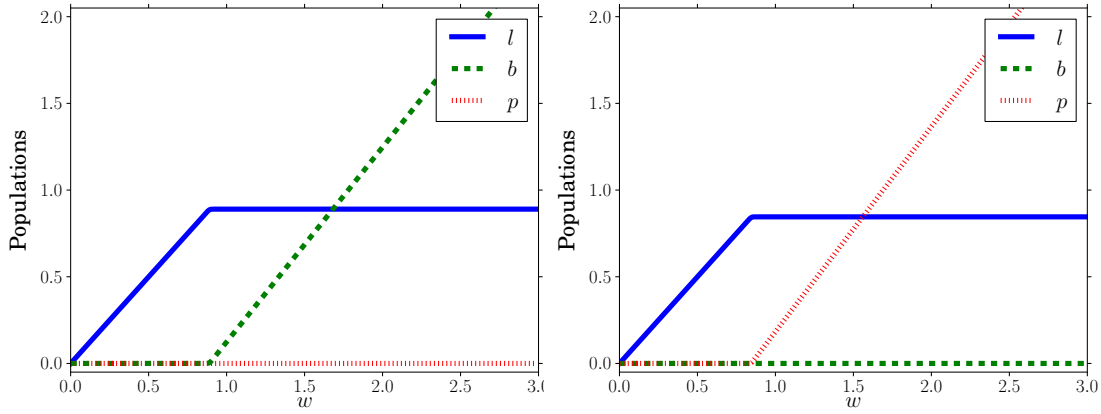

Figure 4.5: Equilibrium states along a recruitment/food of uninfected host (w) gradient : a) Parasites p eliminated and b) Parasites b eliminated.

The parameters values of the above figure 4.5a are given in the two tables

Table 4.9: Parameters values of figure 4.5a

λ_1	1.1
ϕ_1	1.2
ϕ_5	0.85
ϕ_6	0.95
μ	0.5

Table 4.10: Parameters values of figure 4.5b

λ_1	0.9
ϕ_1	0.9
ϕ_5	0.95
ϕ_6	0.85
μ	0.5

4.5.2 Co-infection

In this subcase, we consider two parasites, within-host under co-infection (multiple infection) condition. We analyze the qualitative response of the above said system for various values of the recruitment rate w. This bifurcation analysis we used equation (4.2a-h) on condition that ξ_1, ξ_2 are equal to zero. The qualitative behavior of the system is given in figure 4.6. The parameters used while plotting figure 4.6a and figure 4.6b are tabulated in table 4.11 and table 4.12 respectively. Some of the parameters remain fixed through all calculations. Those parameters are the natural death rate of uninfected host μ, the production rate of parasite from infected host under single infection, cross-infection and double infection are taken as $1, \gamma$ and γ_b respectively. Similarly, the production of parasite p from

single infection, cross-infection and double infection are taken as 1, λ_2 and γ_p respectively.

Let us first consider figure 4.6a, in this plot, the recruitment rate of uninfected host w is taken along x-axis and steady state population is taken along y-axis. We used the following conditions while plotting figure 4.6a. The conditions are $\phi_5 < \phi_6$, $\phi_1 > 1$, $\phi_2 < \phi_3$ and $\epsilon_2 > \epsilon_4$.From this graph it is evident that the co-infection phenomenon facilitates the residence of both the parasites inside the same host. So both the parasites population persists in the system. We can see from the graph that the population of parasite b grows for smaller values of w than p. The reason behind this faster growth is due to lower values of ϕ_2 and natural removal rate ϕ_5 of parasite b than that of parasite p. This factors favours the growth of parasite b.

Figure 4.6b, is similar to figure 4.6a, interchanging b and p. In this bifurcation plot, the condition adopted are, $\phi_5 > \phi_6$, $\phi_1 < 1$, $\phi_2 > \phi_3$ and $\epsilon_2 < \epsilon_4$. The same considerations as in the case apply.

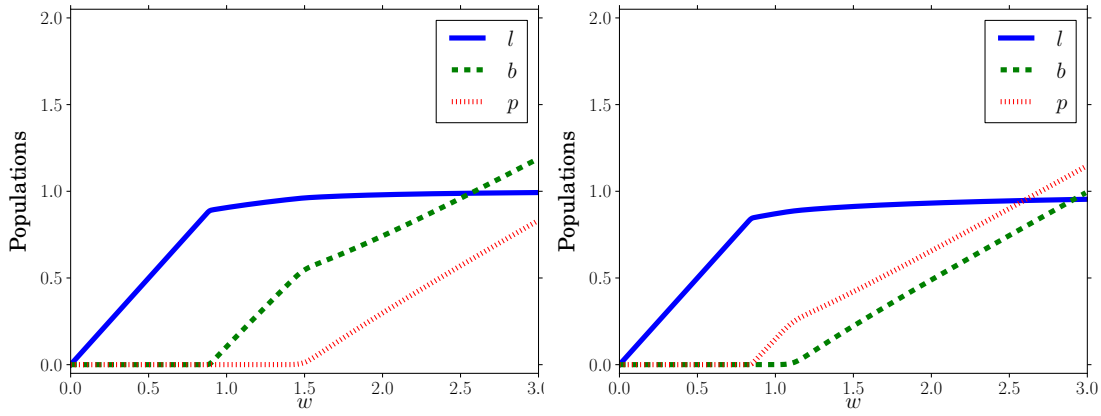

Figure 4.6: Equilibrium states along a recruitment/food of uninfected host (w) gradient with co-infection : a) Both the parasites coexist and b) Both the parasites coexist.

Table 4.11: Parameters values of figure 4.6a

λ_1	1.1
ϕ_1	1.2
ϕ_2	0.75
ϕ_3	0.85
ϕ_4	0.65
ϕ_5	0.85
ϕ_6	0.95
μ	0.5
ϵ_1	0.6
ϵ_2	0.55
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35

Table 4.12: Parameters values of figure 4.6b

λ_1	0.9
ϕ_1	0.9
ϕ_2	0.85
ϕ_3	0.75
ϕ_4	0.85
ϕ_5	0.95
ϕ_6	0.85
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.55
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35

4.5.3 Co-infection and intraguild effect

We now include the IG effect along with co-infection in within-host, two parasites system and discuss the qualitative changes the system undergoes with the change in recruitment rate w.The qualitative behavior of this system is portrayed in figure 4.7. For this bifurcation analysis we used equation (4.2a-h). The parametric values used for plotting figure 4.7a and figure 4.7b are given in the table 4.13 and table 4.14 respectively.

Consider figure 4.7a. The parameters that can alter the dynamics with respect to the previous subsection are ξ_1 and ξ_2. Here ξ_1 is the IG parameter for parasite b and ξ_2 is the IG parameter for parasite p. Depending on the strength of ξ_1 and ξ_2, the outcome of the competition may change. In figure 4.7a, we have taken the IG strength of parasite(b) ξ_1 to be less than the IG strength of parasite(p) ξ_2, i.e $\xi_1 < \xi_2$. Also, $\phi_5 < \phi_6$ and $\phi_1 > 1$. Beyond a threshold value of w, the population of parasite b begins to increases gradually and reaches a maximum level at a particular value of w. Just before the population of parasite b reaches the maximum value, parasite p begins its growth. Once the population of parasite p gains its increasing mode, the population of parasite b begins to decline. At a particular value of w, the population of parasite p attains a maximum value and the parasite b is eliminated completely from the competition. On contrary, if $\xi_1 = 0$, $\xi_2 = 0$ and if there is no multiple infection, then parasite b would eliminate parasite p from the competition. This is shown in figure 4.5a. When we

include multiple infection and IG effect in our system, we can observe competitive switching in our system.

Let us discuss Figure 4.7a more closely. It comprises of four different regions. Initially, when the value of w is less than the threshold value ($w \approx 0.9$), both parasites are unable to invade the uninfected host population and hence no growth for the parasites populations occurs. As w increases and crosses the threshold value, the parasite b begins to invade the host and continues to grow up to certain value of $w(w \approx 0.9 - 1.5)$. In this parametric region, only the parasite b subsists. This region corresponds to a competitive exclusion state. As the value of w increases further, the threshold value for parasite p is reached and hence favors the invasion and growth of parasite p within the host. The growth of parasite p is found to retard the growth of parasite b. In this parametric region($w \approx 1.5-2.25$), both parasites coexists. With further increase in the value of w, we observed a competition switching state - the phenomena in which one parasite population eliminates the other parasite population completely from the system. Here, in our system, we found that parasite p excludes parasite b from the competition and hence the population of parasite b goes to zero.

Figure 4.7b gives a symmetric case with respect to Figure 4.7a. The conditions taken for plotting figure 4.7b are $\xi_1 > \xi_2$, $\phi_5 > \phi_6$, $\phi_1 < 1$ and the IG strength of parasite p greater than IG strength of parasite b. Essentially the same coexistence and exclusion patterns appear, interchanging b and p.

The phenomena of competitive switching is explained as follows: When $\phi_5 < \phi_6$ and $\phi_1 > 1$, parasite b becomes superior competitor than parasite p. In this stage, when IG effect is included $\xi_1 < \xi_2$, parasite p becomes superior competitor than parasite b inside the host. So the parasite p displaces parasite b from the host. As parasite b is eliminated from the host, it could not reproduce and at the same time, the parasite p continues to grow inside the host. At one stage parasite p eliminates parasite b. When the conditions are reversed, the outcome also gets reversed.

The parameters values of the above figure 4.7 are given in the two tables

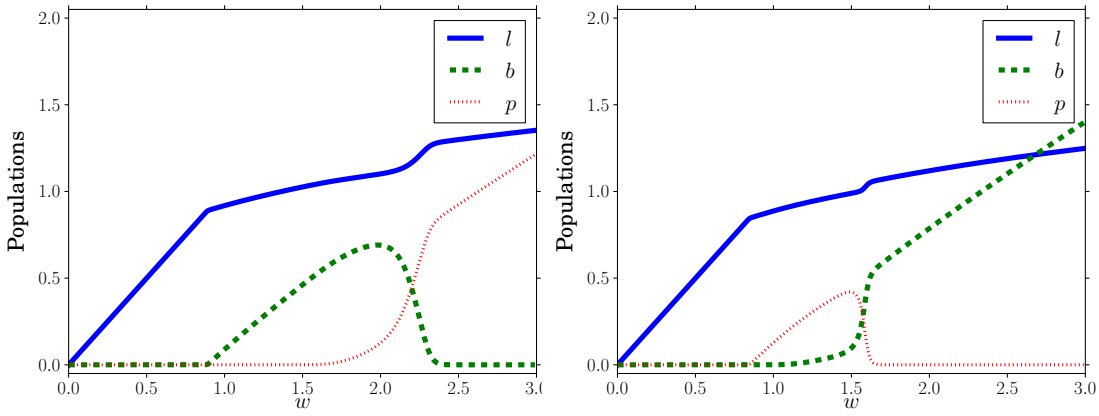

Figure 4.7: Equilibrium states along a recruitment/food of uninfected host (w) gradient with co-infection and IG effect : a) parasites b eliminated and b) parasites p eliminated.

Table 4.13: Parameters values of figure 4.7a

λ_1	1.1
ϕ_1	1.2
ϕ_2	0.85
ϕ_3	0.85
ϕ_4	0.85
ϕ_5	0.85
ϕ_6	0.95
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35
ξ_1	0.75
ξ_2	2.5

Table 4.14: Parameters values of figure 4.7b

λ_1	0.9
ϕ_1	0.9
ϕ_2	0.85
ϕ_3	0.85
ϕ_4	0.85
ϕ_5	0.95
ϕ_6	0.85
μ	0.5
ϵ_1	0.6
ϵ_2	0.5
ϵ_3	0.6
ϵ_4	0.5
ζ_1	0.25
ζ_2	0.25
γ	0.35
γ_b	0.45
γ_p	0.45
λ_2	0.35
ξ_1	2.5
ξ_2	0.75

4.6 Conclusion

In this chapter we have introduced a new mathematical model that generalizes the models discussed previously by taking into account the IG effect. We studied this

model step by step, introducing effect after effect, making, therefore, also sense of the results obtained before. Given the number of ODEs that define our model, we could only study analytically the stability of the disease-free equilibrium.

Our main contribution is the study of the importance of the IG effect. We observed many interesting behavior in the qualitative analysis of our system when it was included. The best way to grasp the IG effects is to look at bifurcation diagrams with respect to the recruitment parameter w. We find four different patterns of exclusion or coexistence. First, when the value of w is less than threshold value, both the parasite cannot invade the host as the condition for the invasion is unfavorable. Second, when w crosses threshold value, the condition for the invasion of parasites becomes favorable. The question of which parasite invades the host first is primarily decided by other parameters, not connected to the IG effect. We call this as competitive exclusion state. Third, when w increases further, both the parasite are found to subsist simultaneously. We call this stage as coexistence state. Finally, when the value of w further increase , then one out of two parasites is completely excluded from the system and we call this state as competitive switching state. The outcome of competitive switching state is found to solely depend on the IG parameter. It is therefore apparent that the IG effect becomes important in the high recruitment regime, being negligible in the low recruitment regime. This suggests that future experiments on the IG effect should be performed in a rich food environment.

5

Conclusions

The object of this thesis is the dynamics of parasites that interact competitively and antagonistically for and within hosts. The situation where multiple parasites compete for hosts is widespread in nature. In an ecological setting it is at the basis of population biology and the study of the communities constituted by these populations. A most well-know result is that of competitive exclusion, where the best competitor for a shared resource always excludes the other, coexistence being only possible when a diversity of resources is available.

In this work we took a different view of competition and antagonistic interactions in general. We considered the so-called "within-host" dynamics. Instead of different species competing for resources, we have parasites that develop inside hosts. The presence of more than one parasite creates competition for the hosts. This may refer to several biologically different situations. For instance, to go back to the example of Chapter 4, parasites may be parasitoids (parasites that ultimately kill the host) that feed on a host from inside. In the case of Chapter 4, the parasitoids were small (1mm) wasps and hosts were eggs of the southern green stink bug, a common pest of soybean plantations, [93]. On the other hand, the same multiple parasite competition for hosts can be found in disease dynamics, where co-infections from several pathogens are not rare, as is well illustrated by the yellow fever and dengue co-infection dynamics,[94]. and that of Tuberculosis and HIV, which is one of the most widespread case, [95]. Finally, at the level of viral dynamics, a similar situation occurs. Indeed, many viruses have high mutation rates, a mutant being effectively another "species" competing with the previous one. This is the case for many diseases and hinders the development of

efficient vaccines for a series of cases. Most prominently, HIV virus escapes the action of the immune system by creating mutants, [96].

Our approach in this thesis has been based on the fundamental equations of epidemiology applied to the situation described above. We have proceeded by a step-by-step methodology, building simple models first, and then including new elements.

The first segment of our work was elaborated in chapter 2. We started with a mathematical model for a single parasite/host case. By analyzing the dynamics, we observed that the prime condition for the disease-free equilibrium state to become stable is given by $\mathscr{R}_0 < 1$, where $\mathscr{R}_0$ is the basic reproductive number, a quantity that is central to epidemiological studies. When $\mathscr{R}_0 > 1$, then the infected state becomes stable. Next, we considered two parasites competing for the hosts but still restricted the infection to be single, i.e., the host can be infected only once by any one out of two different parasites. An important result that was obtained is that the invasibility of the host population by parasites depends on the relation between the basic reproductive numbers of each parasite. The parasite with higher $\mathscr{R}_0$ outcompetes the other. No coexistence is possible on the long-run.

An important step in the construction of the main model was to drop the condition that a host can only be single infected. When we allow the host to be double infected (referred also as co-infected) the coexistence of both parasites becomes possible. No qualitative changes occur when we consider that parasites may also have a free-living state. This coexistence mechanism is widely known in the ecological setting, but less well established at the viral dynamics case. Recent work, [90], on HIV viral dynamics suggest that co-infection plays an important role. In this case, the competing parasites are the HIV wild virus and the HIV variant known as escape variant, as in is not recognized by the immune system. It has been argued that the existence of co-infected cells prevent the total replacement of the wild variant in favor of the escape variant. The consequences of this for treatment proposals are still under scrutiny but the point is certainly important: drugs acting on one single strain may favor the other strain, opening a niche for its development. Effective treatment has to target both strains, making knowledge of the mechanisms that promote coexistence of fundamental value.

After developing the machinery of NGM, we set out to propose a model that encompasses the previous one by adding a new effect. The intraguild effect reflects the possibility that a parasite displaces the other in a co-infected state. The long-term dynamics is highly dependent on the environmental richness (recruitment rate of hosts), denoted by w. We found that four different long-term equilibria can be present,: (i) below of a threshold value for w both the parasite cannot invade the uninfected host; (ii) above the threshold value, and up to certain second threshold value of w, we have a competitive exclusion state; (iii) when we further increase the value of w, we go to a coexistence state; (iv) and finally, above a new threshold value of w, a competitive switching can occur, depending on the values that gauge the intraguild effect (ξ_1 and ξ_2). The interesting situation is

as follows: suppose parasite 1 is competitively superior to parasite 2, being able to outcompete it in the low recruitment regime. Now consider that parasite 2 is able to displace parasite 1 in the co-infected state. Our result is that parasite 2 will prevail in the high recruitment regime.

The result on competitive switching can be understood in more intuitive way. In the low recruitment regime (poor environment) competition for hosts is the main mechanism shaping exclusion patterns, as hosts are rare. Therefore, competitive fitness is a great advantage. On the contrary, in the high recruitment regime, hosts abound and competition becomes less important. In this case, it is the intraguild effect that dominates the long-term dynamics. This is analogous to results on intraguild predation obtained theoretically in [97] and studied in [98] with microcosmos experiments with mites. These results refer more directly to the case where one of the competitors is able to feed on the other, therefore the name *predation*. In our case the intraguild effect is a dislocation effect, the dislocated competitor not being actually consumed. However, the analogy holds: in both cases we have a strong dependence on environmental richness, with for possible outcomes for the competition for long times.

Our results show that the outcome of experiments in systems with co-infection depends largely on the recruitment rate of hosts. This is a situation that has largely been overlooked in many cases. At the level of parasitoid/host interactions, where the intraguild effect is best established, it would be of great interest to investigate the outcome of competition experiments along a recruitment rate gradient and is potentially useful to address pest control by parasitoids in agricultural areas.

On a more speculative basis, intraguild effects at the viral level should be investigated in view of addressing the problem of strain replacement, [99, 100]. Strain replacement (or serotype replacement) is just the substitution of a certain strain of a virus by another. From the public health point of view this can be either a problem - when the new strain is more virulent, as might the case with the re-emergence of new strain of Tuberculosis, [101, 102] , and with the different serotypes of dengue, citepesteva - or a benefit, if one can use controlled strain replacement to exclude a virulent strain and replace it by a less virulent, [104]. It has been a matter of debate why replacement takes place and which mechanisms are responsible for it. As it follows from our results, intraguild effects could be one of such mechanisms, or at least should be taken into account in studies on the subject.

The model that we have built has a a large number of parameters. This could constitute a problem, as the dynamical behavior is dependent on a too large set of unknown parameter values. This parameters can only be fixed if we are interested in a specific system, for which experimental work has been done. This, however, is not frequently what happens. Therefore, in order to get insight into the results implied by the model, we resort to different strategy. We look for patterns. And we fix a large set of parameters and we look for the consequences

on the long-term equilibrium states when a certain specific parameter, related to a biological process is changed. We have adopted this procedure to study the effects of intraguild replacement processes in the two-parasites/one-host system. The same order of ideas can be applied to different aspects of the same system. Such would be the case of the study of sequential infections. One example of such a case is when a host can only be initially infected by one parasite, but once it is infected, it is prone to be co-infected by another parasite. This is a curious case in which a parasite competes with another parasite, but at the same time, facilitates invasion through co-infection. Studying the patterns that emerge in such situation is one of the prospective subjects for future studies.

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