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Biomathematics of *Chlamydia*
PhD Thesis

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Abstract

Chlamydia trachomatis (*C. trachomatis*) related sexually transmitted infections are a major global public health concern. *C. trachomatis* afflict millions of men, women, and children worldwide and frequently result in serious medical diseases. In this thesis, mathematical modeling is applied in order to comprehend the dynamics of *Chlamydia* pathogens within host, their interactions with the immune systems, behavior in the presence of other pathogens, transmission dynamics in a human population, and the efficacy of control measures.

The thesis begins with a brief introduction of the bacteria *Chlamydia* in Chapter 1. In Chapter 2, we give a brief detail of the mathematical modeling of infectious diseases, and its specific application to study the pathogen.

In Chapter 3, a linear delay differential compartmental model is developed, and its special application is shown for a laboratory experiment conducted to study the intracellular development cycle of *Chlamydia*. The delay accounts for the time spent by bacteria in their various forms and for the time taken to go through the replication cycle. The mathematical model tracks the number of *Chlamydia* infected cells at each stage of the cell division cycle. Moreover, the formula for the final size of each compartment is derived. With initial conditions taken from the experiment, the model is fitted to results from the laboratory data. This simple linear model is capable of reflecting the outcomes of the laboratory experiment.

In Chapter 4, at a population level, a novel mathematical model is introduced to study the dynamics of the co-infection between *C. trachomatis*, and herpes simplex virus (HSV). The concept of the model is based on the observation that in an individual simultaneously infected with both pathogens, the presence of HSV will make the *Chlamydia* persistent. In its persistent phase, *Chlamydia* is not replicating and is non-infectious. Important threshold parameters are obtained for the persistence of both infections. We prove global stability results for the disease-free and the boundary equilibria by applying the theory of asymptotically autonomous systems. Further, the model is calibrated to disease parameters to determine the population prevalence of both diseases and compare it with epidemiological findings.

In Chapter 5, a compartmental maturity structured model is developed to investigate an optimal control problem for the treatment of chronic *Chlamydia* infection. The model takes into account the interaction of the pathogens with the immune system and its effects on the formation of persistent *Chlamydia* particles. As the

system takes the form of a mixed ODE-PDE system, the results of the conventional form of Pontryagin's maximal principle for ordinary differential equations are not suitable. For our purpose, we construct an optimal control problem for a general maturity compartmental model, and hence it consists of ordinary and partial differential equations, moreover, the boundary conditions are also nonlinear. For a fixed control, we verify the existence, uniqueness, and boundedness of the solutions. The system is numerically simulated for a variety of cost functions in order to calculate the optimal treatment for curing *Chlamyida* infection. We believe that since our findings were validated for a general model with maturity structure, they may be applied to any specific compartmental model that is compatible with the established system.

Contents

1 Introduction

Sexually transmitted infections (STIs) are persistently accountable for causing health crises of epic proportions. Millions of men, women, and infants are globally affected by STIs which can often lead to severe medical conditions including long-term disability and death, additionally instigating psychological repercussions [1]. The World Health Organization (WHO) in 2012 estimated the loss of 100 million disability-adjusted life years (DALYs) as a consequence of STIs. The WHO also reported alarming statistics of 340 million annual cases of curable STIs occurring worldwide. *Chlamydia trachomatis* (*C. trachomatis*) is the most common notifiable STI caused due to bacteria and is among the most significant contributors to disease burden due to STIs. A report on the global incidence and prevalence of selected curable STIs in the year 2008 reported 105.7 million cases of *C. trachomatis* [1]. The Centers for Disease Control and Prevention (CDC) reports that there are 4 million new instances of *C. trachomatis* infections in the United States each year. Moreover, it is overtly distressing that young people between 15-24 are primarily affected, marking up to 50% of new STIs occurring each year. Among the *C.trachomatis* infection report received by CDC, 74% cases were recorded to occur in persons aged 15–24 [2]. A more recent study conducted in 2018 made a similar assertion, 2.6 million incident *Chlamydia* infections occurred in the age group 15-24 representing 66.5% of the total cases [3]. The European Centre for Disease Prevention and Control (ECDC), recently reported that the highest notification rates were among women aged 15-24 years (1305 cases per 100,000 population) and men aged 15-29 years (672 cases per 100,000 population) [4]. In Hungary, the notification rate for *Chlamydia* in men was 141 cases per 100,000 population, while in women, it was 173 cases per 100,000 population. This relatively high male-to-female ratio in Hungary was noted, especially when compared to other European countries with lower notification rates [4]. These statistics represent a startling fact about the epidemic stature that STIs have reached worldwide.

1.1 Epidemiological Background

Chlamydia is a genus of pathogenic gram-negative bacteria which are obligate intracellular parasites. It is responsible for causing epizootic outbreaks in mammals, potentially targeting domesticated poultry, cattle, pigs, sheep, and horses, as well as feral birds and human beings [5]. The bacterial family *Chlamydiaceae* is in-

clusive of several disease-causing pathogens in humans including, *C. pneumoniae*, *C. psittaci*, and *C. trachomatis* whereas *C. muridarum*, *C. suis* are animal pathogens, infecting mice and swine respectively [6]. Among the species, *C.trachomatis* typically affects humans and is reportedly the most common STI worldwide. It causes diseases in humans by infecting the genital tract and ocular epithelium [7]. *C. trachomatis* infections primarily do not show any symptoms, and consequently are left undetected and untreated. With the rate of asymptomatic *Chlamydia* infection ranging between 70-75% in women and 40% in men, it is frequently attributed as the 'silent epidemic' [8–10]. Untreated *Chlamydia* infections are capable of establishing latency which may lead to long-lasting chronic infections, further increasing the risk of acquiring and transmitting other infectious diseases, such as HIV [11]. Untreated *Chlamydia* infection can manifest in serious sequelae in both men and women. It leads to more serious complications in women as they develop health issues such as chronic pelvic pain, tubal factor infertility (TFI), pelvic inflammatory disease (PID), and ectopic pregnancy, which is often life-threatening [12].

C. trachomatis is classified into two biovars, the trachoma biovar and the Lymphogranuloma Venereum (LGV) biovar, which are further separated into several serovars based on cell surface antigens. There are four LGV-causing serovars which are designated as serovars L1, L2, L3, and L2b, serovars A-C cause trachoma, the leading source of preventable blindness worldwide. It is estimated that serovars A-C infects approximately 162 million people with ocular infection while rendering 6 million people with total blindness [6]. Although Trachoma still prevails in some countries, it has been mostly eradicated from the rest of the world [13]. *C. trachomatis* serovars D-K causes urethritis or cervicitis and represents the world's most prevalent bacterial STD agent. A very high percentage (85-90%) of *Chlamydia* infections are chronic and asymptomatic which facilitates the bacteria to establish long-term inflammation and tissue scarring of the genital tract. The silent attribute of infections due to *Chlamydia* eventually results in more damage sustained by the host and is the principal reason for the excessive burden of the disease.

1.2 Biological Background

1.2.1 Life Cycle of *Chlamydia*

Chlamydia's unique biphasic intracellular developmental cycle differs from other bacterial parasites (Fig. 1.1). They manifest in two morphologically distinct forms

within the host: the elementary bodies (EBs) and the reticulate bodies (RBs). The EBs are the extracellularly viable, but metabolically inert forms, responsible for spreading the infection by attaching and invading susceptible epithelial human cells. RBs are metabolically active non-infectious forms that can replicate inside human cells. The life cycle of *Chlamydia* is initiated when the EBs attach themselves to the surface of the host epithelial cell; followed by the internalization into an intracytoplasmatic parasitophorous vacuole called inclusion, whereby they undergo morphological changes and differentiate into the replicative form RBs. The RBs then multiply by undergoing repeated cycles of binary fission (200-500 fold [11]). Matured RBs then differentiate back to EBs and are eventually released at the end of the cycle with the lysis of the infected host cell [14].

1.2.2 Persistence in *Chlamydia*

As it stands, the fact that *Chlamydia*'s developmental forms exclusively alternate between EB and RB has been oversimplified. *Chlamydia* can enter a non-infectious yet viable stage known as persistence, when under stress, despite being efficiently treatable. Persistence in *Chlamydia* is a reversible phase that is characterized by an anomalous development cycle where the bacteria is capable of establishing latent infections and can persist asymptomatically in many individuals [15]. Unresolved *Chlamydia* infections leading to the persistence of the bacteria are believed to be a principal reason behind recurrent *Chlamydia* diseases.

Weiss observed in 1950 that exposure to the antibiotic penicillin caused *C. muridarum* and *C.felis* to exhibit an expanded, aberrant shape [16]. According to Hurst et al., [17], Tamura and Manire [18], and Matsumoto and Manire [19], *C. trachomatis* LGV and *C. psittaci*, which were at the time known as lymphogranuloma and meningopneumonitis viruses respectively, both experienced similar outcomes.

The mechanism that induces *Chlamydia* into persistence is still obscure, however, laboratory experiments have substantiated their occurrence in vivo, even prevailing for several years [6]. Persistence induction offers a crucial experimental tool for examining these fascinating creatures in the absence of a tractable genetic system. Several studies have concluded the existence of numerous factors that can trigger the manifestation of *C. trachomatis* into the persistent phase, such as exposure to unfavorable physiological conditions, presence of growth inhibitors such as IFN-γ, iron deficiency, nutrient deprivation, or treatment with some antibiotics [20]. However, this process is reversed once the growth inhibitors or other hindrances are removed, and the persistent *C. trachomatis* differentiates back into it's infectious forms [20–22]. To date, the IFN-γ induced persistence has been

best specified and is characterized by the induction of *Chlamydia* persistence by allowing tryptophan inadequacy, an essential amino acid that is required for the natural development of *Chlamydia* [23].

Various additional experiments (recently summarized in [24, 25]) have extensively demonstrated that growing *Chlamydiae* can detour from the productive developmental cycle when they encounter particular stimuli. With regard to *Chlamydia*, persistence is referred to as a developmental stage in which the *Chlamydiae* are alive but not contagious. This usage can be a little perplexing because most microbiologists use the word ”persistence” to describe an infection that lasts a long time inside of a host. *Chlamydial* metabolism slows down during persistence and RB division and differentiation into EB stop. This lowers the production of infectious particles and promotes aberrant RB (AB) development.

Persistence seems to be a technique by which *Chlamydiae* can ”ride out” adverse circumstances and sustain a protracted infection within a host cell. It is significant to emphasize that persistent *Chlamydiae*, which are alive but not contagious, have mostly been researched in culture. The in vivo findings demonstrate that *Chlamydiae* persist, these investigations do not, however, provide solid evidence that the *Chlamydiae* persist in a modified form [24, 25].

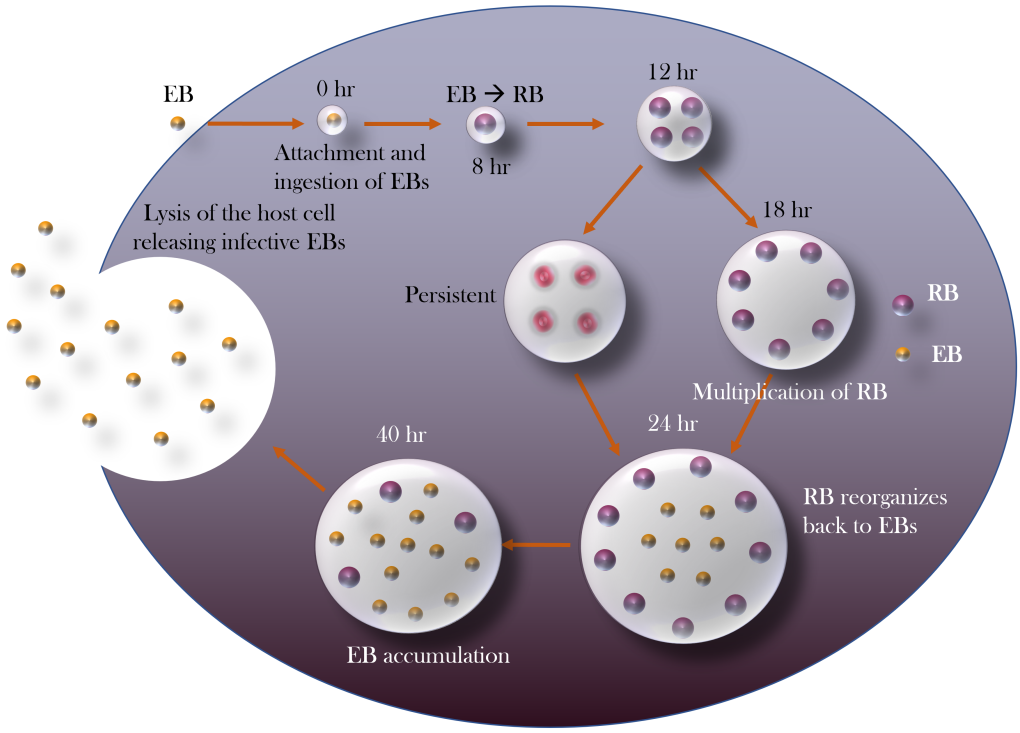


Figure 1.1: Graphical representation of the *Chlamydia* development cycle in the presence of persistence. Arrows indicate the transition from one stage to another.

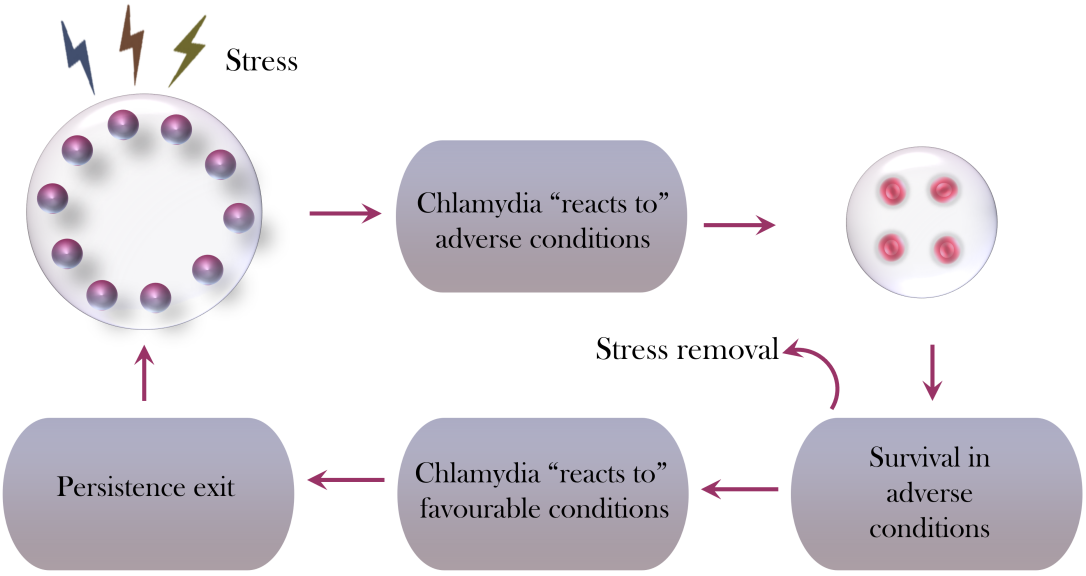


Figure 1.2: The persistence phenomenon.

1.2.3 Therapy and Therapeutic Failure

Despite the fact that *Chlamydia* infections do not contribute to mortality and are easily treatable, its pervasiveness and a high proportion of people who are asymptomatically infected represent a threat to general health. *Chlamydia* infection can be efficiently treated and cured with antibiotics if effectively diagnosed. The most common treatment regimen is a single 1g oral dose of azithromycin or 7 days of doxycycline [26]. The effects of these antimicrobial agents are purely bacteriostatic, meaning they can only inhibit the growth of bacteria [27]. Depending on the choice of drug administered, the success of treatment may vary from 90% to 100% [28]. Regardless of these high recovery rates, there are reports of recurrent, exacerbating infections. Survey has determined that the rates of persistent or recurrent infection range from 5% to 38% in adolescents and young women treated for *Chlamydia* infection [29].

Recurrent *Chlamydia* infection of the genital tract is a frequent and well-known condition. The etiology behind such a common occurrence of repeat infection appears to be a composite of several aspects including antimicrobial resistance, misdiagnosis, treatment non-adherence, repeat exposure to infection, frequent screening, and limited immune system protection [26, 30].

Regardless of a few published case studies ([30–33]) pointing to resistance as the root of clinical therapeutic pitfalls, the hypothesis surrounding *C. trachomatis* be-

ing able to develop antimicrobial resistance has received no significant study. ”Homotypic resistance” for *C. suis* strains against tetracycline have been observed in pigs [34], nevertheless, there are no examples of antibiotic resistance originating in human-pathogenic *chlamydiae* [35]. It is significant to note that there are extreme challenges to studying antibiotic resistance among *Chlamydia* species, including lack of a consistent *in vitro* test, and deficiency in comprehension of the connection between outcomes of existing clinical results following therapy and *in vitro* studies [36]. Current evidence suggests it seems improbable that antimicrobial resistance poses any threat to the resolution of *Chlamydial* infection. It is considered advantageous that incidences of *C. trachomatis* resistance is uncommon where in this age, antimicrobial resistance has become an issue of increasing concern [36].

According to an *in vitro* research conducted to evaluate the effect of β- lactam antibiotics on *Chlamydia* persistence, all penicillins studied caused the production of ABs with *Chlamydia*'s infectivity reduced by 95% [37]. In comparison, persistent *Chlamydial* are more resistant to azithromycin (AZM) in culture than normally developing organisms [38, 39], whereas *C. trachomatis* exposure to IFN-γ increases resistance to doxycycline treatment [40]. Samples from treated individuals have shown to have persistent *Chlamydial* forms [33], additionally, antimicrobial resistance has grown among persistent *Chlamydiae* in culture [39–41]. Consequently, some researchers have suggested that persistent *Chlamydiae* may exacerbate chronic diseases by eluding antibiotic treatment.

The high frequency of recurring infection rates may also be influenced by *Chlamydia* testing and treatment. As *Chlamydia* is primarily asymptomatic, regular screening of priority populations is seen as a crucial public health control strategy. However, the possible drawbacks of a ”screen and treat” strategy are still up for debate. It was suggested that increased rates of reinfection might be caused by the early removal of pathogens from genital tissue following antibiotic treatment, which might have a negative impact on the growth of naturally acquired protective immunity. Results from a murine model with early antibiotic administration demonstrate that, despite being extremely successful in removing *chlamydiae* from genital tissue and averting upper genital tract infection, mediation with doxycycline severely reduces the growth of protective immunity [42]. It remains challenging to answer this question in a natural infection. A study reported spontaneous resolution of *Chlamydia* infection in women who had not received antibiotic treatment, on the basis of which they concluded that host defense mechanisms may mediate *Chlamydial* clearance [43]. If outcomes from the animal model are an appropriate

prediction of what happens in humans, there is a greater risk of reinfection or recurrent *Chlamydial* infection in women who receive early treatment in the course of the infection [42, 44]. To sum up, it is abundantly evident that it would be beneficial to understand the cause behind such a common occurrence of recurrent *C. trachomatis* infection.

There is presently no vaccine for *Chlamydia*, and the solely available treatment is antibiotics, however, considering the high rate of reinfection, there is a growing demand to provide a vaccine. Large-scale field studies in Saudi Arabia, Taiwan, The Gambia, India, and Ethiopia were conducted in the 1960s to assess the effectiveness of *C. trachomatis* vaccines against ocular infection. These studies concluded that whole organism vaccines could promote short-term immunity to ocular infection and lower the incidence of inflammatory trachoma. At the time, extensive research on non-human primates revealed that vaccination could cause inflammatory illness to worsen when challenged later, however, the evidence pointing towards the same conclusion in humans is questionable [45].

Vast research for non *C. trachomatis* vaccine has been carried out with animal models and has had greater success. The majority of these studies for vaccination trials were conducted using mouse models as hosts, the earliest of which was developed to specifically target *C. muridarum* [46], that shares the majority of the genes with the human strains of *C. trachomatis* [47]. These trials indicate that whole cell antigenic targets trigger an effective response, shielding from illness and decreasing shedding rates. There are a number of noteworthy distinctions between *C. trachomatis* and *C. muridarum* that may have an impact on the immunobiology of infection, regardless, these models appear to be helpful for examining *C. trachomatis* immunity [22, 48].

So far, only two *Chlamydial* vaccines, targeting *C. felis* in cats and *C. abortus* in sheep have been marketed, of which *C. felis* was ultimately discontinued in 1992, as it seemed to lose some of its potency [49]. A methodical research program is being dedicated to the development of *C. pecorum* for koalas. The earliest immunization trial on koalas evaluated the neutralizing ability of plasma against *C. pecorum*, consequently offering an alternative to the use of antibiotics and/or a three-dose vaccination schedule which was standard for earlier vaccine trials [50].

Replicating mouse vaccine trial results in other host species, particularly non-human primates, is one of the most challenging components of *chlamydia* vaccine research. There have been efforts in recent years to reproduce murine model trial

outcomes in non-human primates, the earliest of which used whole cell antigenic targets, and documented little to no post-challenge protection [51–53]. The mouse models provide great insight into the challenges involved in developing an efficacious vaccine that will provide protection against infection and disease sequelae. Although live vaccines and Major Outer Membrane Protein (MOMP)-based vaccines have had some success, these outcomes have not been replicated in non-human primate models, probably due to variations in *chlamydial* species genetics and host immunity responses. Nevertheless, recent vaccine trials using the whole cell antigen method have shown encouraging outcomes [54, 55].

A recent study concluded that the majority (85%) of vaccine studies have been conducted in substitute hosts and have mostly focused on creating vaccines for humans [46]. According to the survey, despite more than 70 years of research, assisted with considerable technological breakthroughs, and increased understanding of the target species, no transparent method of vaccine administration has been established.

2 Mathematical Modeling of Infectious Diseases

2.1 Historical Background

The history of communicable diseases, although very ruthless, has been a significant part of humanity. Since the beginning of time, epidemics have invaded populations, frequently killing a large number of people before vanishing, possibly reoccurring years later, and probably becoming less severe as populations build up some immunity. Examples include the ”Spanish” flu Pandemic of 1918–19, which resulted in more than 50,000,000 deaths globally [56], and the annual influenza seasonal epidemics, which can result in an average of up to 389,000 fatalities globally [57]. The outbreak of the novel coronavirus, first emerging in late 2019 quickly spread worldwide, leading to a significant global health crisis with far-reaching social, economic, and public health impacts. The disease referred to as COVID-19 (coronavirus disease), is a viral respiratory illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is proclaimed the deadliest kind since the 1918 H1N1 influenza pandemic [58].

In the fourteenth century, beginning in 1346, the Black Deaths (perhaps the bubonic plague) moved from Asia to Europe in numerous waves, killing up to one-third of the continent’s population by 1350 [59]. For more than 300 years, the illness recurred frequently in different regions of Europe, most memorably as the Great Plague of London in 1665–1666. Then it began to progressively leave Europe.

There are other illnesses that are endemic (constantly prevalent) in some communities and result in a lot of fatalities. Particularly prevalent in underdeveloped nations with subpar healthcare services. Measles, lung infections, diarrhea, and other conditions that are easily treatable and not regarded as dangerous in the Western world cause millions of deaths each year. Many regions of the world are plagued by endemic illnesses such as malaria, typhus, cholera, schistosomiasis, and sleeping sickness. The work of John Graunt (1620–1674), published in his book ”Natural and Political Observations Made upon the Bills of Mortality” in 1662, marked the beginning of the analysis of data related to infectious diseases [60]. The Bills of Mortality were weekly lists of the fatalities that occurred in the parishes of London. The data used by Graunt came from the records, which were started in

1592 and kept up to date starting in 1603. He provided the first approach to a theory of competing risks by analyzing the numerous causes of death and outlining a mechanism for calculating the relative chances of passing away from various illnesses.

The earliest application of mathematics to study infectious diseases can be traced back to the 18th century. During the period when smallpox was still rampant, treatment and eradication of the disease was a subject of grave importance. Although it was believed that immunity could be achieved through vaccination against smallpox, with particles from its lesion, it was highly controversial because of the potential threat and fatality linked with it. It was a matter of dispute whether the benefits of mass inoculation counterbalanced the associated risk. In 1760, Daniel Bernoulli, one of the most renowned scientists of the time, in his attempt to boost global immunization against smallpox, conducted a mathematical investigation of the fatality caused due to smallpox, with variolation and without. His approach to the issue of competing hazards resulted in the 1760 publishing of a concise summary [61]. This was followed by a more exhaustive analysis which he presented to the Royal Academy of Science in Paris the same year and subsequently published in 1766 [62]. Bernoulli through his evaluation justified the claim that the merits of variolation far surpassed the dangers of the disease and mortality caused due to it. His studies provide a comprehensive understanding of the historically significant disease of smallpox.

The contribution by John Snow, a medical professional from England who pioneered the creation of anesthesia and medical hygiene, is quite significant and is thought to have been the beginning of the science of epidemiology. Based on research into the temporal and geographic distribution of cholera cases during the London outbreak of 1855, he successfully located the Broad Street water pump as the infection source [63]. William Budd was successful in gaining a comparable comprehension of the typhoid epidemic in 1873 [64].

Regardless of Bernoulli's established account, a substantial length of time would pass before the vast application of mathematical modeling in the scope of infectious diseases. The works of P. D. En'ko and Ronald Ross are considered critical in the advancement of this field. En'ko is recognized for his contribution to the theoretical analysis of the measles epidemic [65]. In 1889, he developed a discrete-time model which he successfully correlated with the real measles epidemic in educational institutions of St. Petersburg, which he surveyed in an enclosed environment. His work is the basis of the famous 'Reed-Frost models' proposed by Lowell Reed and Wade Hampton Frost. Although the mathematical model was

published only later in 1950, it was presented by Frost in a lecture in 1928. Ronald Ross, a British medical doctor, one of the greatest in the field, is distinguished for his remarkable contribution in the understanding of malaria disease through mathematical modeling. His pioneering works laid the foundation for quantitative analysis of the transmission of mosquito-borne diseases and their epidemiology. Ross's contribution to engineering the groundwork that laid the foundation for the conceptual awareness of infection dynamics earns him high regard as a historical figure. Additionally, Ross is also credited for introducing a significant notion in epidemiology (a similar concept to the reproduction number, $\mathscr{R}_0$). Along with identifying anopheles mosquitoes as vectors responsible for transmitting malaria, his analysis of the mathematical model showed that malaria could be eliminated so long as the number of humans per mosquito was beneath a certain "threshold" value [66]. Ross's original work which consists of two separate mathematical models greatly influenced a generation of successors in the field including George Macdonald, which led to the development of the Ross-Macdonald theory of mosquito-borne disease transmission [67, 68]. With the "threshold" concept already existing in epidemiology, Macdonald also later established its link with demographics and the approach to the formulation of reproduction number (using the expression z_0).

Ross's earliest models gave rise to several other modified versions including the Ross-Waite-Lotka Model [69], the Ross-Lotka Model [70], the Sharpe-Lotka Model [71]. A detailed analysis of the historical evolution inclusive of more recent advancements can be found in [72]. Ross remains significant not only for his key role in exploring mosquito-borne disease transmission but also for his fundamental part in the scientific developments in the field of mathematical studies of infectious diseases.

Ross's other major impact in the field would be his association with Anderson Gray McKendrick, a Scottish military physician, who pioneered the use of compartmental modeling in the mathematical study of infectious diseases. McKendrick widely acknowledges Ross for his work in epidemiology. The year 1927 is regarded as a benchmark for the mathematical modeling of infectious diseases with the introduction of the famous Susceptible-Infected-Recovered (SIR) model by Anderson Gray McKendrick and William Ogilvy Kermack [73]. The model which segregates a population into different compartments describes the movement of individuals through successive compartments by considering progression rates of various stages of infection. The model assumes that an individual attains lifelong immunity upon recovery from an infection. Adhering to Ross' footsteps, Kermack and McKendrick

went on to broaden the theory of ”threshold” in communicable diseases by extending the SIR model and presenting through subsequent publications [74, 75]. The 1905 Mumbai plague epidemic is such a case study considered by them.

Roy Anderson and Robert May in their much-esteemed book titled ”Infectious Diseases of Humans”, further developed the SIR model and applied it to analyze the spread of communicable diseases such as measles, malaria, river blindness, schistosomiasis, sleeping sickness, and AIDS. Their distinctive work is aimed at providing a comprehensive characterization for reviewing public health strategies toward the annihilation or control of infectious diseases. This book stands out for its demonstration of the far-reaching potential of mathematical modeling in the field of epidemiology [76]. The due credit for finally adopting the expression ”basic reproduction rate” (resuming Macdonald's terminology), along with the notation $\mathscr{R}_0$ instead of z_0 (representation is due to Lotka [77]) goes to Anderson and May [78], as well as associating $\mathscr{R}_0$ to the following definition:

> **” Basic Reproduction Number, Epidemiological Definition. The number of secondary infections resulting from a single primary infection into an otherwise susceptible population.”**

Furthermore, Anderson and May proposed and analyzed the Susceptible-Infected-Susceptible (SIS) form of compartmentalizing an infectious disease. This simplified version of the SIR model yielded high suitability for the formulation of STIs, and its application has been far-reaching in recent years.

These mathematical models have been utilized extensively in order to gain insight into the dynamics of infectious diseases, as a tool for analyzing epidemic risk, for devising vaccination strategies, to study the effect of biodiversity on a disease spread, and many more. $\mathscr{R}_0$ can be used as a forecasting tool to measure and prevent epidemic outbreaks, using the well-established fact that vaccination of a population fraction larger than $1 - 1/\mathscr{R}_0$ will establish herd immunity leading the disease to eventually die out.

2.2 Compartmental Modeling at an In-host Level: Understanding the Infection

Compartmental modeling is a very efficient modeling technique in mathematics and has been extensively applied to demonstrate the evolution of biological systems over time. Its applicability is largely reflected in structures that can be separated into compartments that display certain distinctive features. The flow of

the particles along successive compartments is specified by probable input and output factors that closely reflect the changes occurring in the system [79]. The particles flowing through compartments can be various biological entities, such as populations of cells, bacteria, viruses, other organisms, human populations, birds, or animals. They are capable of reproducing and performing other biological functions. Detailed discussions of multi-compartmental models used as mathematical descriptions of biological systems can be found in various books on mathematical models [79–81].

The SIR epidemic model introduced by Kermack and McKendrick is a major landmark that popularized the use of compartmental modeling for the dynamic representation of communicable diseases. In a simplified version of the original Kermack-McKendrick equation, the model divides the population into susceptibles (S), infectives (I), and recovered (R). The dynamics of the disease transmission are then defined by the following system of ordinary differential equations (ODEs)

$$\begin{aligned}\frac{dS}{dt} &= -\beta SI,\\ \frac{dI}{dt} &= \beta SI - \gamma I,\\ \frac{dR}{dt} &= \gamma I,\end{aligned}$$

where β is the transmission rate and denotes the efficiency of the disease process, and γ is the rate of recovery for infected individuals. This elementary approach forms the premise for mathematical modeling of important infectious diseases and many variations have been considered to study infection dynamics by partitioning the population contingent upon disease status.

The SIR model is conveniently designed to model the spread of infection within a population of human beings separated into healthy and infected individuals, but an equal concept can be applied to describe the dynamics of infection within a host. Various important aspects of infection can be studied and understood using such tools, as has been proven with the research carried out in the domain of viral infections, most notably for the human immunodeficiency virus (HIV) [82–85]. The far-reaching insight that is gained through the analysis described in the aforementioned works, including establishing and quantifying the interconnection between infection parameters validate the relevance of mathematical models in the characterization of such dynamics.

ODEs have been predominantly used to describe the basic equations used to

model in-host dynamics as the time taken for movement of particles between compartments is considered negligible [86, 87]. However, as specified in several literatures, for most biological systems, the transit time for particle movement cannot be taken as zero [88–93]. A relevant example of such a structure is one where compartments are linked with each other by pipes. The time required for the flow of materials along the pipes may be associated with, for e.g. the dimension of these pipes, and hence are significant. Such pipe-compartment models are application specific and can be found in abundance in bio-mathematical literature [94, 95]. In such models, the delay caused by the length of pipes is mathematically described by differential equations with retarded arguments [88, 96, 97]. For classical compartmental models, the system of ODEs takes on explicit forms relative to the biological and physical phenomenon [86]. Accordingly, for the mathematical characterization of systems with time delay, delay differential equations of the specific structure are taken into account [93].

2.3 In-host Level Modeling of *Chlamydia*

Mathematical modeling has the potential to significantly advance numerous fields of *Chlamydia* research. Dynamical equations can be applied as a guiding framework for investigating a variety of *Chlamydia* infections and pathology-related issues. Owing to the unique life cycle displayed by the bacterium *Chlamydia*, which is significantly alike to the life process of viruses, 'viral dynamics' equations have been conveniently applied to study its dynamics at an in-host level. The similar life cycle *Chlamydia* (explained in Chapter 1, Section 1.2.1, Fig. 1.1) shares with viruses assure successful application of viral dynamics equations to *Chlamydia*. Relatively simple to more advanced models have been incorporated for within-host *Chlamydia* infection and calibrated to experimental data to gain meaningful insights about immunity, including crucial information about the development of vaccines. However, regardless of the critical insights in-host viral dynamics modeling can provide in the area of research in virus dynamics, its application to *Chlamydia* has been minuscule. With the valuable information that mathematical modeling as a tool has provided for other STDs such as HIV, gonorrhea, or Herpes Simplex Virus, it is unquestionable that dynamical study can uncover previously unexplored insight into the intricate process of *Chlamydia* growth cycle.

A fundamental component of in-host modeling comprises of in-depth investigation of the intricate *Chlamydia* growth process that involves the inclusion of EBs into epithelial cells, the replication of RBs, and their transition back to EBs. Such a study was first attempted by Wilson in [11], where a viral dynamics model consist-

ing of a mixed ODE-PDE system was considered in order to predict the possible effects of increasing the efficacy of the Th1 immune response. However, considering that the system of equations takes the form of PDE to represent change over both time and replication stages, are substantially more complex compared to usual viral dynamics equations. Several other extensions have been considered to the mathematical description in order to better facilitate predictions about *Chlamydial* pathogenesis. By considering the populations of *Chlamydia* particles, susceptible mucosal epithelial cells, and *Chlamydia*-infected epithelial at certain times, Wilson models the interactive processes of the ”species” involved. These mathematical within-host modeling of *Chlamydia* considered by Wilson using viral dynamics equations are summarized in [11]. Wilson and McElwain in [98], models the effects of humoral immunity against neutralizing *Chlamydia* by tracking the antibody and host cell receptor aggregation over *Chlamydial* EB surfaces. Another paper by Wilson correctly predicted the reduction in pathology following the reduction in inclusion-forming unit (IFU) levels using a mathematical model that connected pathology to the area under the IFU time course curve (experiment performed and achieved in guinea pigs by use of a chlamydiaphage) [99]. Another model was formulated to facilitate the hypothesis that attachment of RBs to the inclusion membrane is modulated via a type III secretion (TTS) system, and the loss of these projections aids the translation of RBs back to EBs, subsequently leading to detachment from the inclusion membrane [100].

Burns et al. using a delay differential equations model estimated the parameters related to the intracellular developmental cycle of *C. trachomatis* [101]. Sharomi et al. consider a multistage model for the intracellular growth of *Chlamydia*, with and without the effect of humoral and cell-mediated immune responses. The mathematical model considered takes the form of ODEs, with the variables denoting separate compartments for various stages of cell infection [102].

Other significant mentions on in-host modeling of *Chlamydia* are works of Mallet et al. Their approach involves developing a spatial dynamical model using a cellular automata model [103], a PDE model [104], and a combination of both [105]. The shortcomings of the models are associated with the challenges of procuring data from in vivo cell infections that are spatially explicit. It has been suggested that image processing techniques (e.g., [106]) may come to be advantageous in this view.

Wan and Enciso developed a two-form deterministic model for the population of EBs and RBs, formulated as a constraint maximization problem that optimizes the number of EBs at the end of the development cycle [107]. The model is built on the

Darwinian theory of natural selection and hypothesizes that boosting the number of EB after the host cell lysis would be the feedback by the bacteria against odds from species competition. Enciso et al. and Lee et al. considered an identical problem in a stochastic context [108, 109].

One of the most recent applications of compartmental modeling was to investigate the effects of various treatment combinations for chronic genital *Chlamydial* infections within-host. Pontryagin's Maximum Principle is used to find the drug-treatment combination that defines the optimal control strategy. Their numerical findings suggest that a combination therapy consisting of antibiotics that has a bacteriostatic effect, supplemented with tryptophan that will assist in reversing persistent *Chlamydial* particles is the best way for stopping the progression of a persistent *Chlamydial* infection, and ultimate clearance [8].

2.4 Population Level Modeling of *Chlamydia*

As in the case of in-host modeling, the application of mathematics to study the population transmission dynamics of *Chlamydia* is less than significant compared to other STDs. Owing to its asymptomatic nature, intervention strategies for *Chlamydia* are centered mostly on screening for symptoms of infection prevalent in young, sexually active women, with variable emphasis to screen women for reinfection. Consequently, a major portion of articles related to population-level *Chlamydia* modeling is affiliated with studies of screening.

An important highlight in this regard is the Stochastic Network model adopted in the works of Kretzschmar et el. in order to study the spread of gonorrhea and genital infection with *C.trachomatis* [110]. Three of their earlier articles designed to study the epidemic spread of STDs discuss in detail the model approaches [111–113]. The individual-based model considers an age-structured heterosexual population and assumes that individuals can have both steady and casual partnerships, but there is a core group with sexually more active members. Individuals in this core group have particularly more sexual partners compared to the non-core group and can have a single steady partner simultaneously with other casual relationships. The authors examine the effectiveness of various prevention strategies such as contract tracing, screening, and the use of condoms. The results obtained via a Monte Carlo simulation conclude that contact tracing is a very effective measure of prevention, whereas screening of women in the age class 15-24 years resulted in a more successful application when combined with the treatment of symptomatic infection. Moreover, regular use of condoms can highly

reduce the prevalence of STDs. However, the comparison showed that screening as a prevention strategy was more effective in case of reducing the prevalence of gonorrhea than *Chlamydia*.

With the high frequency of reinfection cases in *Chlamydia*, it forms an integral part of the investigation and is considered a major part of research activities related to *Chlamydia* infection. The arrested immunity hypothesis has been closely associated with reinfection cases and is suggested to be a key component of the *Chlamydia* transmission dynamics [114]. The hypothesis suggests that the normal development of protective immunity is subjugated as a result of rapid treatment with antibiotics. This phenomenon first came to prominence after a control strategy was adopted to curb *C.trachomatis* infection in British Columbia, Canada. The program had an unusual outcome where it was observed that *Chlamydia* cases dropped from 216 to 104 per 100,000 population in 1991-1997, but subsequently increased to exceed previously recorded case counts [115]. Evidence shows that the rate of reinfection in women is decreased following the natural resolution of infection in the interim of a positive *Chlamydia* screening test and treatment [116]. Brunham et al. considers a dynamic mathematical model for *C.trachomatis* transmission that incorporates multiple reinfections throughout an individual's sexually active life. The study outcome corroborates with the hypothesis that antimicrobial based treatment of *Chlamydia* infection may paradoxically increase population susceptibility, further suggesting the importance of the development of an effective vaccine in order to halt the spread of *C.trachomatis* infection [115].

Vickers et el. makes use of the deterministic compartmental model to test the speculation that early treatment hinders the feedback from the immune response, which further escalates susceptibility as the population is reintroduced into the same system of sexual risk connections. The mathematical model formulated in the framework of susceptible-infected-treated-removed-susceptible (or SITRS) was calibrated to fit the historic trend of notification data for Saskatchewan, Canada [117]. The outcome of the investigation was however inconclusive concerning the assumption that arrested immunity could influence epidemiological trends.

Regan et al. make use of an ODE compartmental model to investigate *Chlamydia* transmission dynamics in a heterosexual population in Australia. The model assumes that treatment is administered upon positive detection through screening. Individuals in the age group of 20–24 years old are found to be the most effective target group. The study predicts a rapid reduction in cases of *Chlamydia* infection in 10 years with systematic annual screening, with a larger than 50% achieved within the 4 years if 40% of people undergo screening annually in the

target group. Sensitivity analysis also highlights key biological and behavioral parameters strongly associated with *Chlamydia* transmission [118].

Mathematical modeling had also been applied for estimating the significance of vaccine efficacy on disease prevalence. de la Maza and de la Maza consider a computer model formed in the mathematical framework of a Markov model to study discrete-time systems. They conducted simulations to analyze the impact of vaccine efficacious on the population for periods of 10, 20, and 40 years with vaccine efficacies ranging between 50% to 100%. Their simulation determines that by vaccinating 10 years olds for 11 steady years with an 'optimal vaccine' that is 100% efficacious for a duration of 40 years, a reduction in the prevalence of disease for the entire population could be achieved. A similar outcome could be achieved with 15 years of continuous vaccination with a vaccine that is 50% efficacious for 10 years [119].

The model developed by Brunham et el. to study potential causes for *Chlamydia* re-emergence was also used to investigate the effects of the vaccine. The model outcome predicts the imperative presence of an effective vaccine to prevent *Chlamydia* prevalence at a population level in the absence of careful planning to reconstruct the sexual network. Their simulation showed that it is possible to achieve total eradication of *Chlamydia* following extensive vaccination where 80% of the population are vaccinated with 100% efficacious vaccine [115].

One modeling study examined the important aspects of *Chlamydia* vaccines by taking into account measurable biological phenomena that are critical for designing vaccines, in addition to potential vaccine outcomes for the population. The individual-based model developed by Gray et al. was used to test the effect of vaccines with varying levels of efficacious at a population level, at the same time taking into account the progression of infection at an individual level. The model keeps track of the bacterial load in each individual and their ensuing infectiousness, with the vaccine aimed at decreasing *Chlamydia* load in infected individuals and increasing the "critical load" in susceptible individuals, the threshold value required to successfully infect a susceptible individual. The model predicts that a fully adequate vaccine could hypothetically eradicate *Chlamydia* epidemic in 20 years given that young people are vaccinated at the onset of their sexual debut [120].

An in-depth analysis of *Chlamydia* models for screening programs has been carried out by contrasting different transmission models. Their research demonstrates that a screening program's impact increases with a prolonged asymp-

tomatic period. Moreover, there is an indication of the possibility to reduce transmission in the wider population with a periodic and targeted screening of a particular segment of the population. The results from the sensitivity analysis demonstrate how disease-specific factors can significantly affect a screening program's effectiveness [121, 122].

J. Viana et al. present a composite discrete-event (DES) and system dynamics (SD) simulation approach to investigate how the operational level choices made in the hospital outpatient department are impacted (and are impacted by) *Chlamydia* on a community level [123].

Much more recently, an ODE model was used to evaluate the effects of *Chlamydia* vaccines, where Pontryagin's Maximum Principle was applied to find the best prevention and treatment measures for *Chlamydia* infection [124].

Although the application of mathematical modeling is considered in infancy, available research articles have proven that mathematical modeling can be very helpful at different levels, in improving our understanding of the pathogen. A search in the database for mathematical modeling of *Chlamydia*, both at an in-host and at a population level will bring many more results for scientific articles based on *Chlamydia* than has been currently cited, which is an indication to the fact that mathematical modeling has been successfully applied to study *Chlamydia* dynamics.

3 Delay Linear Chains in Mathematical Biology: An Insight into the Intracellular *Chlamydia* Infection

3.1 Introduction

There is a long history of the application of ODEs and partial differential equations (PDEs) to model diversified systems including biological, ecological, physical, and chemical systems. Although these mathematical models have been inordinately helpful in getting meaningful insights into such complex processes, it is indisputable that a model that incorporates some of its past history would give a more realistic reflection of the system. The reason is that many natural as well as artificial systems have time delays that must be taken into account. A model that has an initial dependence on its past is called functional differential equations (FDEs) or delay differential equations (DDEs) [125]. The use of DDEs gives us many advantages over the models that use larger systems of ODEs and PDEs to overcome the pitfalls associated with simpler systems. While expanding simple ode or pde systems into models that involve more equations can help us in more accurate representations of the behavior of the phenomenon under study, we are at a disadvantage of having to deal with multiple parameters, the significance of which cannot often be determined qualitatively.

A classic example of a differential equation with time delay is the delayed logistic equation, where the lag time emphasizes the indirect adverse impacts high population density can have on the environment by influencing birth rates later in life due to delay in growth and maturity [126]. The mathematical modeling of forest regeneration after harvest is another example of a natural system that involves time delay, as it is apparent that a forest after disturbance, will require a minimum of 20 years to arrive at any level of maturity. Consequently, in accordance with the system under consideration, the delays may represent latency period, gestation time, transition delay, or can simply account for the time taken to execute complex processes. The simplest differential equation with a dependence on it's past

history is of the form:

$$x'(t) = f(x(t), x(t-r)),$$

where $r > 0$ is the delay. For compartmental systems, the structure of the differential equations is specific to the biological and physical aspects. The model variables are assigned to compartments to express the number of particles that behave homogeneously. The transition from one compartment to another takes place when the particles undergo some physical or biological transformation or change their spatial location [127]. In our case, we construct a model with a finite number of compartments where the rates of inflow and outflow are governed by physical and biological mechanisms.

We develop a linear system of delay differential equations that is applicable to the mathematical representation of some compartmental models in biology and ecology. This model is suitable for studying ecological phenomena such as seasonal bird migration, which describes the movement of the bird population during a full cycle of migration. An example of biological application is to study stem cell maturation. It also is largely applicable for modeling the evolution of disease-causing pathogens such as viruses or bacteria.

3.2 The Model Description

Consider a delayed linear chain as shown in Fig. 3.1, illustrating particles moving through a number of successive compartments before reaching a final stage. The multiplicative rates represent growth between the compartments. All the compartments have inflow and outflow terms except the first and the last: the first compartment has only outflow and the last compartment has only inflow. Time delay signifies the time needed to complete the transition of particles between successive compartments.

Let the number of particles in the ith compartment at time t be $y_i(t)$ ($i = 0, 1, \ldots, n$).

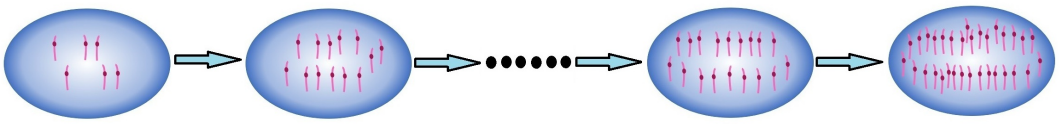


Figure 3.1: Schematic diagram of a linear chain.

The rate at which the particles are moving out of the ith compartment is denoted by a_i for $i = 0, 1, \ldots, n-1$ and b_{i-1} is the rate at which the particles are entering the

ith compartment for $i = 1, 2, \ldots, n$. Also, we assume that the particles are arriving with a time delay τ_{i-1} into the ith compartment for $i = 1, 2, \ldots, n$. We describe such a process by a system of delay differential equations as follows:

$$\begin{aligned} y_0'(t) &= -a_0 y_0(t), \\ y_i'(t) &= b_{i-1} y_{i-1}(t - \tau_{i-1}) - a_i y_i(t), \qquad i = 1, 2, \ldots, n-1, \\ y_n'(t) &= b_{n-1} y_{n-1}(t - \tau_{n-1}), \end{aligned} \tag{3.1}$$

where $a_i > 0$, $b_i > 0$ and $\tau_i \geq 0$ for all i. The natural phase space for our system is $C([-\tau, 0], \mathbb{R}^{n+1})$, where $\tau = \max\{\tau_0, \ldots, \tau_{n-1}\}$. Initial conditions for this system are given by

$$y_i(\theta) = \varphi_i(\theta) \text{ for } \theta \in [-\tau, 0], i = 0, \ldots, n \tag{3.2}$$

where $\varphi := (\varphi_0, \ldots, \varphi_n) \in C([-\tau, 0], \mathbb{R}_+^{n+1})$.

It is well known that the initial value problem (3.1)-(3.2) is well posed. Non-negativity of the initial data is a natural requirement for the biological systems we consider, and from the non-negativity of the rates it follows that solutions remain non-negative for all future time.

For the biological problems we consider later, it is paramount to predict the eventual state of the system. This is addressed in the following proposition, giving an explicit expression for the limit of each compartment.

Proposition 3.2.1. *Solutions of problem (3.1) has the following limits:*

$$\lim_{t\to\infty} y_i(t) = 0 \text{ for } i = 0, 1, 2, \ldots, n-1$$

and

$$\begin{aligned} \lim_{t\to\infty} y_n(t) = {} & \frac{b_0 \ldots b_{n-1}}{a_0 \ldots a_{n-1}} \varphi_0(0) + \frac{b_1 \ldots b_{n-1}}{a_1 \ldots a_{n-1}} \varphi_1(0) + \cdots + \frac{b_{n-1}}{a_{n-1}} \varphi_{n-1}(0) \\ & + \varphi_n(0) + \frac{b_0 \ldots b_{n-1}}{a_1 \ldots a_{n-1}} \int_{-\tau_0}^{0} \varphi_0(s) ds + \frac{b_1 \ldots b_{n-1}}{a_2 \ldots a_{n-1}} \int_{-\tau_1}^{0} \varphi_1(s) ds \\ & + \cdots + \frac{b_{n-2} b_{n-1}}{a_{n-1}} \int_{-\tau_{n-2}}^{0} \varphi_{n-2}(s) ds + b_{n-1} \int_{-\tau_{n-1}}^{0} \varphi_{n-1}(s) ds. \end{aligned}$$

Proof. Solving the first equation gives us $y_0(t) = \varphi_0(0) e^{-a_0 t}$. Thus, $\lim_{t\to\infty} y_0(t) = 0$. Next, we assume that $\lim_{t\to\infty} y_k(t) = 0$ for some k. Since for $k+1$ we have $y_{k+1}'(t) = b_k y_k(t - \tau_k) - a_{k+1} y_{k+1}(t)$, the assumption that $\lim_{t\to\infty} y_k(t) = 0$ implies $\lim_{t\to\infty} y_{k+1}(t) = 0$. By induction, we find that for $i = 0, 1, \ldots, n-1$, each compartment has limit zero.

Now, for $k = 0, 1, \ldots, n$, we define $I_k := \int_0^\infty y_k(t)dt$ and $J_k := \int_{-\tau_k}^0 \varphi_k(s)ds$. Integrating the first equation from zero to infinity, since $\lim_{t\to\infty} y_0(t) = 0$, we have,

$$-a_0 I_0 = \int_0^\infty -a_0 y_0(t)dt = \int_0^\infty y_0'(t)dt = -y_0(0) = -\varphi_0(0).$$

Hence, $I_0 = \frac{1}{a_0}\varphi_0(0)$.

Integrating the kth equation of the system (3.1) from zero to infinity for $k = 1, \ldots, n-1$, and using $\lim_{t\to\infty} y_k(t) = 0$, we have

$$\begin{aligned}
-y_k(0) &= \int_0^\infty [b_{k-1}y_{k-1}(t-\tau_{k-1}) - a_k y_k(t)]dt \\
&= b_{k-1}\left[\int_{-\tau_{k-1}}^0 \varphi_{k-1}(s)ds + \int_0^\infty y_{k-1}(s)ds\right] - a_k\int_0^\infty y_k(t)dt \\
&= b_{k-1}J_{k-1} + b_{k-1}I_{k-1} - a_k I_k.
\end{aligned}$$

Rearranging the terms, for I_k we find the recursive relation

$$I_k = \frac{b_{k-1}}{a_k}I_{k-1} + \frac{b_{k-1}}{a_k}J_{k-1} + \frac{1}{a_k}\varphi_k(0) \quad \text{for } k = 1, 2, \ldots, n-1.$$

Substituting $k = 1$ in the above relation, we have,

$$\begin{aligned}
I_1 &= \frac{b_0}{a_1}I_0 + \frac{b_0}{a_1}J_0 + \frac{1}{a_1}\varphi_1(0) \\
&= \frac{b_0}{a_0 a_1}\varphi_0(0) + \frac{b_0}{a_1}\int_{-\tau_0}^0 \varphi_0(s)ds + \frac{1}{a_1}\varphi_1(0).
\end{aligned}$$

Iteratively, from the above relation, substituting $k = n-1$, we have,

$$\begin{aligned}
I_{n-1} = &\frac{b_0\ldots b_{n-2}}{a_0\ldots a_{n-1}}\varphi_0(0) + \frac{b_1\ldots b_{n-2}}{a_1\ldots a_{n-1}}\varphi_1(0) + \cdots + \frac{1}{a_{n-1}}\varphi_{n-1}(0) \\
&+ \frac{b_0\ldots b_{n-2}}{a_1\ldots a_{n-1}}\int_{-\tau_0}^0 \varphi_0(s)ds + \frac{b_1\ldots b_{n-2}}{a_2\ldots a_{n-1}}\int_{-\tau_1}^0 \varphi_1(s)ds + \ldots \\
&+ \frac{b_{n-2}}{a_{n-1}}\int_{-\tau_{n-2}}^0 \varphi_{n-2}(s)ds.
\end{aligned}$$

Finally, integrating the last equation of the system (3.1) from zero to infinity, we

have

$$\begin{aligned}\lim_{t\to\infty} y_n(t) &= \int_0^\infty b_{n-1}y_{n-1}(t-\tau_{n-1})dt + y_n(0)\\ &= b_{n-1}\left[\int_{-\tau_{n-1}}^0 \varphi_{n-1}(s)ds + \int_0^\infty y_{n-1}(s)ds\right] + \varphi_n(0)\\ &= b_{n-1}J_{n-1} + b_{n-1}I_{n-1} + \varphi_n(0).\end{aligned}$$

Substituting the value of I_{n-1} and replacing J_{n-1} by the integral, we have the limit as

$$\begin{aligned}\lim_{t\to\infty} y_n(t) = \frac{b_0\dots b_{n-1}}{a_0\dots a_{n-1}}\varphi_0(0) + \frac{b_1\dots b_{n-1}}{a_1\dots a_{n-1}}\varphi_1(0) + \dots + \frac{b_{n-1}}{a_{n-1}}\varphi_{n-1}(0)\\ + \varphi_n(0) + \frac{b_0\dots b_{n-1}}{a_1\dots a_{n-1}}\int_{-\tau_0}^0 \varphi_0(s)ds + \frac{b_1\dots b_{n-1}}{a_2\dots a_{n-1}}\int_{-\tau_1}^0 \varphi_1(s)ds\\ + \dots + \frac{b_{n-2}b_{n-1}}{a_{n-1}}\int_{-\tau_{n-2}}^0 \varphi_{n-2}(s)ds + b_{n-1}\int_{-\tau_{n-1}}^0 \varphi_{n-1}(s)ds.\end{aligned}$$

□

3.3 Mathematical Formulation of the Intracelluler *Chlamydia* Development Cycle

In this section, we construct a mathematical model for a laboratory experiment conducted to investigate the intracellular growth of *Chlamydia* bacteria [128]. The intracellular development of *Chlamydia* is governed by a very distinct life cycle, the mechanism of which has been explained in Chapter 1, Section 1.2.1, Fig. 1.1. However, in the absence of the persistent form, it alternates between EB and RB forms (Figure 3.2). The life cycle starts with the EBs attaching and infecting the susceptible cells. The EBs then transform into RBs, which replicate by undergoing repeated cycles of binary fission within an intracytoplasmatic parasitophorous vacuole called inclusion. After the secondary transformation of the RBs back to EBs, the host cell lyses releasing a large number of new EBs that infect neighboring cells [14].

Microbiological investigation of the intracellular development of *Chlamydia* is an extensive field of research [129]. Recently, a number of dynamic models of disease transmission as well as intracellular growth have been developed [130]. Here, we present a model for a laboratory experiment of *Chlamydia* infecting hu-

man cells [128].

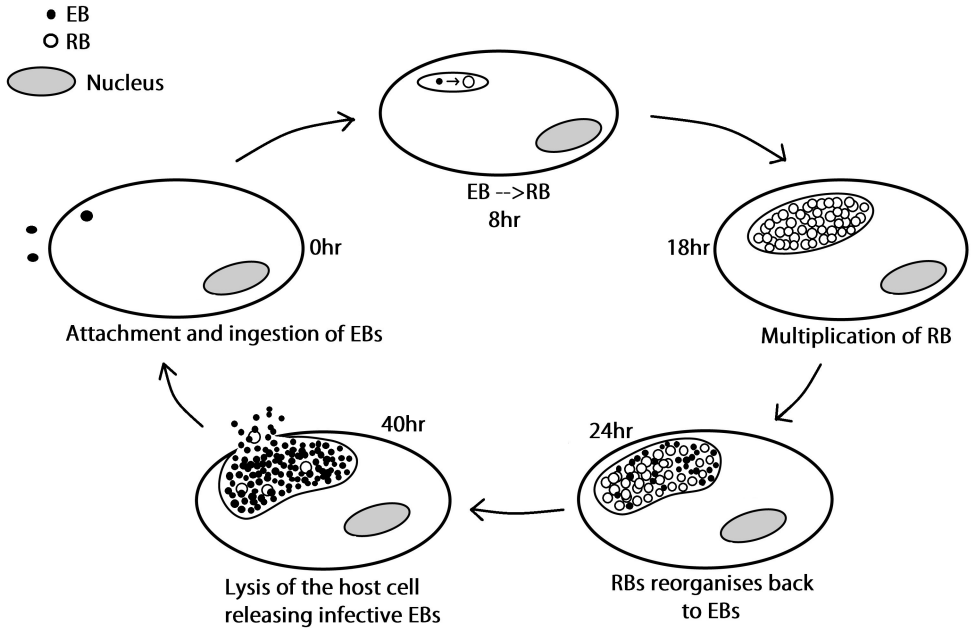


Figure 3.2: Graphical representation of the *Chlamydia* development cycle in the absence of the persistent phase

The basic model for the intracellular development of the *Chlamydia* cells in vivo is formulated as follows. Let $y_0(t)$ denote the number EBs outside human cells at time t, $y_1(t)$ denotes the EBs attached to the human cells at time t. Upon infection of the healthy human cells, the intracellular EBs transform into RBs upon which the RBs undergo repeated cycles of division. Hence, we will denote by $y_2(t)$ EBs that have transformed to RBs, and $y_i(t)$ will denote the number of RBs after the ith cycle of replication for $i = 3, 4, \ldots, n-1$. The RBs then reorganize back to the EBs, following which the host cell lyses releasing the newly formed EBs. The $y_n(t)$ will denote the number of RBs converting back to EBs. We impose time delays to account for the time needed for transforming between RBs and EBs, as well as for completing cell division.

Furthermore, the rate at which the EBs enter human cells is denoted by a_0. EBs are assumed to differentiate to RBs at a rate a_1 inside the human cells. Parameter a_{i-1} is the rate at which the RBs enter the ith cycle of replication for $i = 3, 4, \ldots, n-1$, and the RBs will convert back to the EBs with the rate a_{n-1}.

According to these assumptions and interactions, the population dynamics of EBs

and RBs can be described in mathematical terms as follows:

$$\begin{aligned}
y_0'(t) &= -a_0 y_0(t), \\
y_1'(t) &= a_0 y_0(t-\tau_0) - a_1 y_1(t), \\
y_2'(t) &= a_1 y_1(t-\tau_1) - a_2 y_2(t), \\
y_i'(t) &= 2a_{i-1} y_{i-1}(t-\tau_{i-1}) - a_i y_i(t), \qquad i = 3, 4, .., n-1 \\
y_n'(t) &= a_{n-1} y_{n-1}(t-\tau_{n-1}).
\end{aligned} \tag{3.3}$$

In consistency with the laboratory experiment [128], we have the initial conditions

$$\begin{aligned}
&y_0(0) = 100, \\
&y_0(t) = 0, \qquad \text{for } t < 0, \\
&y_i(t) = 0, \qquad \text{for } t \leqslant 0, \quad \text{where} \quad i = 1, 2, \ldots, n.
\end{aligned} \tag{3.4}$$

As in the previous two cases, we can have equations for the number of cells undergoing transformation or differentiation, but since the equations decouple from the rest, we ignore them in this case too.

Proposition 3.3.1. *The compartments of the system* (3.3) *with initial condition* (3.4) *have the following limits:*

$$\lim_{t\to\infty} y_i(t) = 0 \text{ for } i = 0, 1, \ldots, n-1$$

and

$$\lim_{t\to\infty} y_n(t) = 100 \times 2^{n-3}.$$

Proof. The system of equations (3.3) is a special case of the system (3.1) with $a_i = b_i$ for $i = 0, 1$, $b_j = 2a_j$ for $i = 1, 2, \ldots, n-2$, and $a_{n-1} = b_{n-1}$, with $\tau_0 = 0$ and initial conditions $y_0(0) = 100$, $y_0(t) = 0$ for $t < 0$ and $y_i(0) = 0$ for $t \leq 0$, $i = 1, 2, \ldots, n$. Making these substitutions in Proposition 2.1, we have that

$$\begin{aligned}
\lim_{t\to\infty} y_n(t) &= \frac{a_0 a_1 2a_2 \ldots 2a_{n-2} a_{n-1}}{a_0 a_1 a_2 \ldots a_{n-1}} 100 \\
&= 100 \times 2^{n-3}
\end{aligned}$$

and

$$\lim_{t\to\infty} y_i(t) = 0 \text{ for } i = 0, 1, \ldots, n-1.$$

□

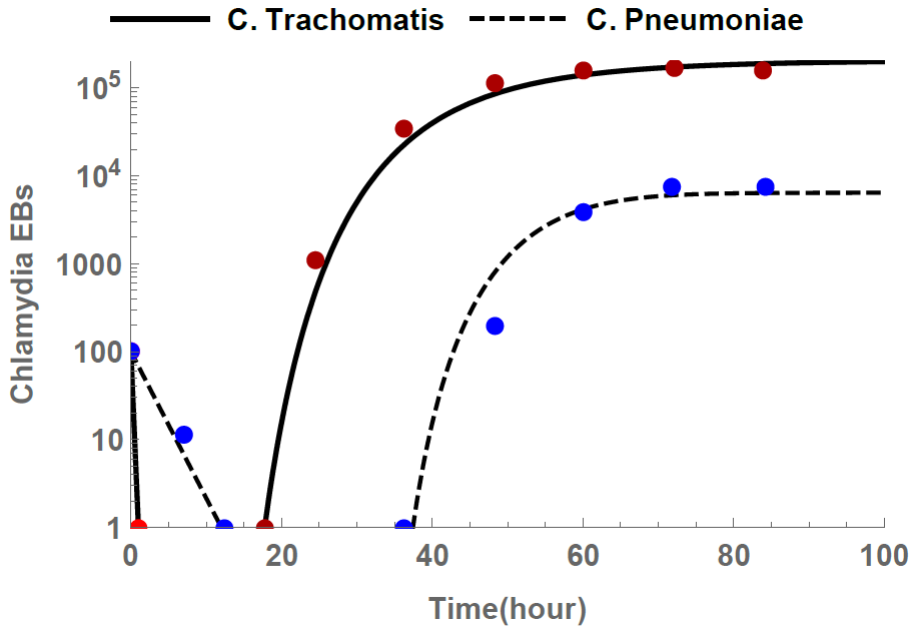


Figure 3.3: Model-based curves after parameter fitting. The colored dots are taken from laboratory measurements. It shows the growth cycle of two different strains of *Chlamydia* bacteria, the fast-replicating *C. trachomatis* and slow-replicating *C. pneumoniae* as reflected in the figure.

The result of the proposition simply states that there are $n-3$ replication cycles. However, the model can accurately reproduce the empirical findings of the laboratory experiments, in particular, it can predict the number of EBs at any given time. Figure 3.3 shows that, after fitting our model parameters, we could generate time curves that match the laboratory measurements [128]. The fitting was done in Mathematica using the least square method, the codes for which can be found in the supplementary file available in our public GitHub repository [131]. As the plotting is done on a logarithmic scale, for the purpose of fitting we take the logarithm of the solution and fit the solution to the logarithm of the data values with respect to the parameters.

4 A Mathematical Model of Herpes and *Chlamydia* Co-Infection In Humans

4.1 Introduction

Simultaneous infection of pathogens is a very common occurrence and is highly prevalent in nature [132, 133]. The co-infection may involve pathogens belonging to different species like viruses, bacteria, protozoa, fungal parasites, helminths, etc. There are several instances involving the human immunodeficiency virus (HIV) (for example, co-infection of HIV with TB [134], or Hepatitis B [135], or Hepatitis C [136], or malaria [137]). Other co-infections may occur with numerous strains or serotypes of the same organism [138] (for example, co-infection with multiple strains of influenza [139], or HIV [140]).

The interaction between the co-infecting pathogens may greatly influence the dynamics of the infection, as compared to the infection involving a single pathogen. Depending on the interaction between the coexisting pathogens which may be direct or via the human host's immune system or other resources, it may have significant effects on the consequences of the infection. The most frequently reported outcome of mixed infection is enhanced pathogen abundance and worsened host health conditions [133]. Further, co-infections have been directly identified with increasing morbidity and mortality rates [141]. Co-infection involving HIV is the most typical example of such an instance, the presence of which increases the possibility of consecutive infections by causing immunosuppression [142]. However, there are a number of simultaneous infection cases where the presence of a pathogen during an ongoing infection inhibits the growth of the other [133]. Co-infection involving two or more strains of influenza is among the best-known examples of such an event; infection with one strain imparts cross-immunity against other strains, a phenomenon also referred to as concomitant immunity [143]. The co-infection occurring between *C. trachomatis* bacteria and HSV, where the presence of active HSV has been indicated to induce *C.trachomatis* into a state where it is non-infectious[144–147] is an instance of such a co-infection.

Experimental studies have demonstrated the occurrence of *C. trachomatis* and

herpes simplex virus type 2 (HSV-2) co-infections *in vivo*, and data from cell culture indicate certain types of HSV such as HSV-2 and HHV6 as inducers of *chlamydial* persistence. The occurrence of co-infection between the two pathogens in humans has been well documented in many literatures [148–151]. Serologic investigations have indicated that there is a high probability of HSV-2 infected individuals being *C. trachomatis* infected as well [152]. Furthermore, direct examination of cervical biopsy specimens by PCR has implied the occurrence of *C. trachomatis*, HSV, and Human Papilloma Virus simultaneously in comparatively 10% of women [148].

Herpes Simplex Virus Types 1 and 2 (HSV-1 and HSV-2) are two members of the viral family, *Herpesviridae* and are the most significant human pathogens. HSV-2 is the major cause of genital herpes and is predominantly sexually transmitted. HSV-1 primarily causes oral infections; however, it contributes to a sizeable proportion of genital HSV infections [153]. According to estimates on a yearly basis, $200,000 - 500,000$ cases of primary genital HSV occur which is an indication of that, the alarming burden of viral STIs [145]. HSV has the ability to establish latent infection in the neurons of the ganglia and the autonomic nervous system. Once latency has been established, the virus persists and cannot be destroyed. A number of internal as well as external stimuli such as psychological or physical stress, or immune suppression can induce the virus to recover its active phase [154]. A unique biological characteristic exhibited by both *C. trachomatis* and HSV is their capability to establish latent infections, are frequently attributed as hidden epidemics [155, 156].

In vitro model investigations of HSV-2/*C. trachomatis* co-infections have indicated that the presence of HSV-2 alters the *Chlamydia* development. The number of cells infected with chlamydiae was also less accounted for when HeLa cells were co-infected with HSV-2/*C. trachomatis* serovar D [157]. Findings from a tissue culture model of HSV-2 and *C. trachomatis* have documented a decreased production of infectious chlamydial progeny indicating that viral co-infection can induce persistence into developing chlamydiae [145]. A number of mechanisms have been stated that might be responsible for inducing *C. trachomatis* persistence, such as HSV-2-induced cell death resulting in the termination of *chlamydial* developmental cycle, [145] or amino acid starvation of the *C. trachomatis* due to the competing presence of HSV-2, which is a well investigated inducer of *chlamydial* persistence [158]. Another *in vitro* experiment has demonstrated that the developmental cycle of C. trachomatis is interfered with when co-infected with human herpes virus 6 (HHV6). It was established that the presence of HHV6 causes im-

balanced oxidative stress, inducing a fully reversible persistence in *C. trachomatis*, influencing its infectivity substantially. Similar experiments showed that co-infection with HSV 1 also induces chlamydial persistence by a similar mechanism. However, contrary to the persistence caused by antibiotics, once the virus is removed from the culture, the bacteria is able to retain its productive developmental cycle, recovering from the virus-induced persistence [159].

Mathematical models studying such mixed infections can greatly reflect the dynamics of co-infections and can be found in abundance in literature. K. Okosun et al. [160], in their article consider cholera-schistosomiasis co-infection, analyzing the local asymptotic stability of the disease free equilibrium (DFE) for the sub-models and the full model, also showing the existence of endemic equilibrium and investigating the possibility of bifurcation. In addition, an optimal control problem is formulated. A Chikungunya-dengue co-infection model is considered by Musa et al. [161], where the local asymptotic stability of the DFE is shown for the sub-models and the full model, and numerical analysis is performed to exhibit the phenomenon of backward bifurcation for the sub-models. There are numerous mathematical articles studying the dynamics of HIV-TB co-infection, [162–166]. In [162], the TB and HIV sub-models are locally analyzed, the DFE of the entire system is shown to be globally asymptotically stable (GAS), and a co-infection equilibrium point is shown to exist only under some restrictions on the parameters. Gakkhar et al. [163] in their HIV and TB co-infection model studies global analysis of the disease-free, HIV-free, and TB-free equilibrium points using Lyapunov stability theorem under certain conditions on the reproduction numbers. Further, the endemic equilibrium point is shown to be unstable whenever it exists. Naresh et al. [164] consider a non-linear model for HIV-TB co-infection where they study the local asymptotic stability of the disease-free, HIV-free, and TB-free equilibrium points, the endemic equilibrium point is shown to be global asymptotic stability whenever it exists under some assumptions using Lyapunov theory. Pinto et al. [165] considers the integer order and the fractional order of the HIV-TB co-infection model where they study the stability of the DFE for the integer order model along with some bifurcation diagram illustrations, and simulate the fractional order model numerically. Bhunu et al. [166] considers HIV/AIDS-TB co-infection models with and without treatment. The TB-only model is shown to exhibit backward bifurcation and the glocal asymptotic stability of the DFE in the HIV/AIDS-only model is analyzed. Further, the HIV/AIDS-TB co-infection model is shown to have a LAS disease free equilibrium.

The aforementioned papers study co-infection of a synergistic nature, implying

that being infected with type one enhances the susceptibility to type two, along with the possibility that the two co-infecting pathogens are simultaneously transmitted. However, to our knowledge, no mathematical model has been developed to study *Chlamydia*-HSV co-infection. Moreover, the co-infection considered in this article is unique pertaining to its uncooperative attribute; the emergence of one hindrance to the growth of the other.

The structure of this Chapter is organized as follows: In the second section, a non-linear mathematical model is proposed to describe the *C. trachomatis*-HSV co-infection in a population. In Sections 3 and 4 respectively, the *C. trachomatis* and HSV subsystems are studied, where we compute equilibrium points and analyze their stability. Building on these results, we investigate the co-infection system in Section 5. In Section 6, we consider a limiting system of the original co-infection model, analyze its dynamics, and determine the conditions for the existence of an endemic equilibrium. Then we extend the results on the limiting system to the original system. In Section 7, we show under which conditions will both diseases persist in the population. Section 8 contains numerical simulations to illustrate the analytical results. In Section 9, we calibrate the model, estimate the prevalence of both diseases in the population, and compare it with epidemiological observations. The Chapter is concluded with a discussion in the last section.

4.2 Model Formulation

A six-dimensional deterministic non-linear mathematical model is proposed in this section to analyze the transmission dynamics of *C. trachomatis* and herpes co-infection in human beings. Let $N(t)$ denote the total number of population at time t. The human population is subdivided into six compartments. $S(t)$ denotes the class of population susceptible to both diseases, the bacteria *C. trachomatis* $C(t)$, and herpes virus $H(t)$. The class of population infected with *C. trachomatis* but having latent herpes is denoted by $I_{LC}(t)$, while $I_{HP}(t)$ will denote the number of populations with active herpes but having persistent *C. trachomatis*. $L(t)$ is the class of population with latent herpes. Hence

$$N(t) = S(t) + C(t) + H(t) + I_{LC}(t) + I_{HP}(t) + L(t). \tag{4.1}$$

In order to formulate the model, the following assumptions have been made:

A 1. *C. trachomatis infection may occur upon the susceptibles acquiring it by effectively coming in contact with an infected and infective individual from either*

the class of $C(t)$ or $I_{LC}(t)$ at the rate β.

A 2. *Susceptibles acquire HSV infection due to effective contact with individuals from class $H(t)$ or $I_{HP}(t)$ at the rate $\hat{\beta}$.*

A 3. *Susceptible individuals cannot acquire C. trachomatis and HSV simultaneously, which means, they cannot move directly into the co-infection classes, $I_{LC}(t)$ or $I_{HP}(t)$.*

A 4. *Co-infection of C. trachomatis-HSV may occur when C. trachomatis ($C(t)$) infected individuals get infected with HSV, or HSV ($H(t)$) infected individuals get infected with C. trachomatis, in both cases, effectively putting C. trachomatis bacteria into it's persistent phase (I_{HP}).*

A 5. *The class of active C. trachomatis-latent HSV (I_{LC}) co-infected population is generated as a consequence of individuals from the class of latent HSV ($L(t)$) acquiring C. trachomatis.*

A 6. *In the case of the class of co-infected populations, the transition between the classes I_{LC} and I_{HP} occurs when the active herpes goes to latency at the rate ρ rendering C. trachomatis it's persistent phase, or when the latent herpes retains its active status at the rate σ, putting C. trachomatis into persistency.*

A 7. *C. trachomatis infected individuals will recover upon antibiotic treatment at a rate r and move back to $S(t)$, whereas, the individuals from the class I_{LC} will be added to the class of latent herpes $L(t)$ upon recovery from C. trachomatis.*

A 8. *The movement between the classes $H(t)$ and $L(t)$ occurs as HSV infected individuals go into latency or individuals with latent HSV relapse to their active phases, at the rates ρ and σ respectively.*

A 9. *Finally, for simplicity, we have the following assumption for the total population $N(t)$,*

$$N(t) = S(t) + C(t) + H(t) + I_{LC}(t) + I_{HP}(t) + L(t) = Constant.$$

Accordingly, we denote by μ the recruitment rate of newly sexually active susceptible individuals into the class of susceptibles (S), and μ is the rate of demographic turnover for our population. We normalize the constant population to unity $(N = 1)$. It is important to note here that with this normalization, the bilinear incidence βSI is mathematically equivalent to the standard incidence $\beta SI/N$ for constant population size.

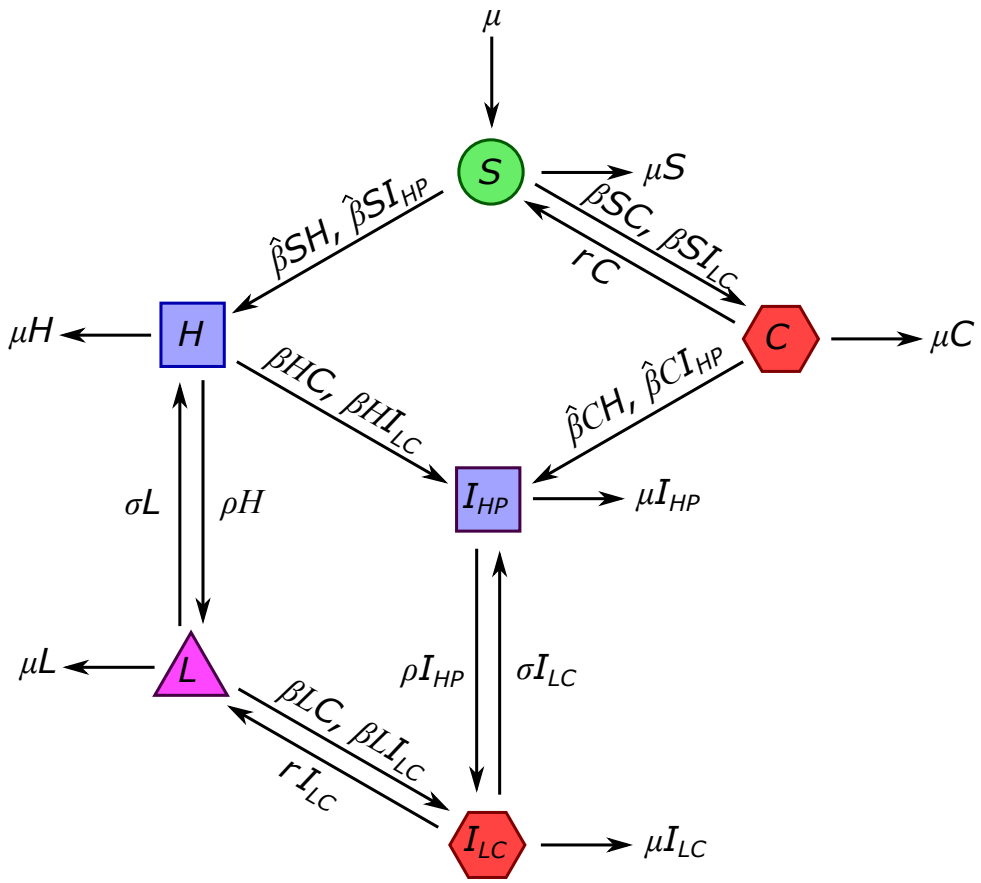


Figure 4.1: Schematic diagram for the *C. trachomatis*-HSV co-infection model.

From these assumptions, the description of variables and parameters given in Table 4.1 and the above-mentioned facts, the mathematical model can be formulated with the help of the schematic diagram given in Figure 4.1. In summary, the co-infection model consists of the following system of nonlinear ordinary differential equations:

$$\begin{aligned}
S' &= \mu - \beta SC - \hat{\beta} SH - \beta SI_{LC} - \hat{\beta} SI_{HP} - \mu S + rC,\\
C' &= \beta SC + \beta SI_{LC} - \hat{\beta} CH - \hat{\beta} CI_{HP} - rC - \mu C,\\
H' &= \hat{\beta} SH + \hat{\beta} SI_{HP} - \beta HC - \beta HI_{LC} - \rho H + \sigma L - \mu H,\\
I'_{LC} &= \rho I_{HP} + \beta LC + \beta LI_{LC} - r_c I_{LC} - \mu I_{LC} - \sigma I_{LC},\\
I'_{HP} &= \hat{\beta} CH + \beta HC + \hat{\beta} CI_{HP} + \beta HI_{LC} - \rho I_{HP} - \mu I_{HP} + \sigma I_{LC},\\
L' &= \rho H + r_c I_{LC} - \sigma L - \beta LC - \beta LI_{LC} - \mu L,
\end{aligned} \tag{4.2}$$

where $'$ denotes time-derivative, with non-negative initial conditions

$$P_0 = (S(0), C(0), H(0), I_{LC}(0), I_{HP}(0), L(0)) \in \mathbb{D}, \tag{4.3}$$

where

$$\mathbb{D} = \{(S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{R}^6_+ \mid S + C + H + I_{LC} + I_{HP} + L = 1\} \tag{4.4}$$

is the natural state space, and is clearly positive invariant to the system (4.2).

Parameters	Descriptions
β	transmission rate for *C. trachomatis*
$\hat{\beta}$	transmission rate for HSV
ρ	rate at which active HSV goes into latency
σ	rate at which latent HSV is activated
μ	natural death rate
r	recovery rate for *C. trachomatis*

Table 4.1: Parameters and their Descriptions

4.3 The *Chlamydia* Subsystem

We consider the HSV free subspace defined by

$$\mathbb{D}_C = \{(S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{D} \mid S + C = 1\},$$

which is clearly invariant. The dynamics in this space is governed by the following system of equations,

$$\begin{aligned} S' &= \mu - \beta SC - \mu S + rC, \\ C' &= \beta SC - rC - \mu C. \end{aligned} \tag{4.5}$$

4.3.1 Equilibria, Basic Reproduction Number and Global Stability

The equilibria of the *Chlamydia* subsystem are easily obtained by solving the algebraic system of equations

$$\begin{aligned} 0 &= \mu - \beta SC - \mu S + rC, \\ 0 &= \beta SC - rC - \mu C, \end{aligned}$$

resulting in the two possible equilibria

$$E_0 = (S_0, C_0) = (1, 0), \qquad E_C = (S_C, C_C) = \left(\frac{r+\mu}{\beta}, \frac{\beta - r - \mu}{\beta}\right), \tag{4.6}$$

where E_0 is the *Chlamydia*-free equilibrium point. It is clear that the components of the *Chlamydia* present equilibrium point, E_c, are positive only when $\beta-(r-\mu) > 0$, i.e when $\beta/(r+\mu) > 1$, where

$$\mathscr{R}_C = \frac{\beta}{r+\mu} \tag{4.7}$$

is the basic reproduction number for *Chlamydia* infection. Putting $S = 1 - C$ into the equation (4.5), we have

$$C' = (\beta - r - \mu)C\left(1 - \frac{\beta}{\beta - r - \mu}C\right).$$

This is the logistic equation for C, with carrying capacity $\beta/(\beta-r-\mu)$, when $\beta > r+\mu$. Hence, we can apply the standard results for a logistic equation: when the basic reproduction number $\mathscr{R}_C > 1$, then the equilibrium E_C is globally asymptotically stable, and when $\mathscr{R}_C \leq 1$, then the equilibrium E_0 is globally asymptotically stable.

4.4 The HSV Subsystem

We consider the *Chlamydia* free subspace defined by

$$\mathbb{D}_H = \{(S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{D} \mid S + H + L = 1\},$$

which is clearly invariant. The dynamics in this space is governed by the following system of equations

$$\begin{aligned} S' &= \mu - \hat{\beta}SH - \mu S, \\ H' &= \hat{\beta}SH - \rho H + \sigma L - \mu H, \\ L' &= \rho H - \sigma L - \mu L. \end{aligned} \tag{4.8}$$

4.4.1 Equilibria, Basic Reproduction Number and Global Stability

Some algebraic calculations show that there are two possible equilibria. The HSV free equilibrium point is given by

$$E_* = (S_*, H_*, L_*) = (1, 0, 0),$$

and the HSV present equilibrium point is given by

$$E_H = (S_H, H_H, L_H) = \left(\frac{\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)}, \frac{\mu}{\hat{\beta}} \left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1 \right), \right.$$
$$\left. \frac{\mu\rho}{\hat{\beta}(\mu+\sigma)} \left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1 \right) \right). \tag{4.9}$$

Following the next generation matrix approach established in [167, 168], we compute analytically the basic reproduction number $\mathscr{R}_H$ of (4.8). The infected compartments are H and L. Linearizing at the equilibrium E_*, the transmission and transition matrices F_1 and V_1 are

$$F_1 = \begin{bmatrix} \hat{\beta} & 0 \\ 0 & 0 \end{bmatrix}, \quad V_1 = \begin{bmatrix} \mu+\rho & -\sigma \\ -\rho & \mu+\sigma \end{bmatrix},$$

giving

$$F_1 V_1^{-1} = \begin{bmatrix} \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} & \frac{\hat{\beta}\sigma}{\mu(\mu+\rho+\sigma)} \\ 0 & 0 \end{bmatrix}.$$

Thus, we have the reproduction number as $\varrho(F_1 V_1^{-1})$, where ϱ represents the spectral radius, given by the formula

$$\mathscr{R}_H = \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)}. \tag{4.10}$$

It is clear that all the components of $E_H > 0$ i.e., the HSV present equilibrium point exists *iff* $\left(\mathscr{R}_H = \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} \right) > 1$.

In the following section, we prove the global asymptotic stability of the two equilibria corresponding to two cases of the reproduction number being smaller or larger than one using Lyapunov theory.

Theorem 4.4.1. *If $\mathscr{R}_H \leq 1$, then the disease free steady state E_* is globally asymptotically stable in $\mathbb{D}_H$.*

Proof. The system of equations (4.8) is mathematically equivalent to the model considered in [169], while their biological interpretations are different. Analogous to Theorem 1 in [169], we can define $V : \mathbb{D}_H \to \mathbb{R}_+$ by

$$V(S, H, L) = \frac{\mu+\sigma}{2S_*}(S - S_*)^2 + (\mu+\sigma)H + \sigma L. \tag{4.11}$$

It is clear that at E_*, the function $V(S, H, L)$ reaches its global minimum in $\mathbb{D}_H$.

The derivative of (4.11) with respect to t along solution curves of (4.8) is given by,

$$\begin{aligned}
V'(S,H,L) &= \frac{\mu+\sigma}{S_*}(S-S_*)\frac{dS}{dt} + (\mu+\sigma)\frac{dH}{dt} + \sigma\frac{dL}{dt} \\
&= \frac{\mu+\sigma}{S_*}(S-S_*)(\mu - \hat{\beta}SH - \mu S) \\
&+ (\mu+\sigma)(\hat{\beta}SH - (\rho+\mu)H + \sigma L) + \sigma(\rho H - (\sigma+\mu)L) \\
&= \frac{\mu+\sigma}{S_*}(S-S_*)(\mu S_* - \hat{\beta}SH - \mu S) + (\mu+\sigma)\hat{\beta}SH \\
&- \mu(\rho+\mu+\sigma)H. \\
&= -\frac{\mu+\sigma}{S_*}\mu(S-S_*)^2 - \frac{\mu+\sigma}{S_*}\hat{\beta}SH(S-S_*) + (\mu+\sigma)\hat{\beta}SH \\
&- \mu(\rho+\mu+\sigma)H.
\end{aligned}$$

Making use of the expression

$$\hat{\beta}SH\frac{S-S_*}{S_*} = \hat{\beta}H\frac{(S-S_*)^2}{S_*} + \hat{\beta}H(S-S_*),$$

we obtain

$$\begin{aligned}
V'(S,H,L) &= -\frac{\mu+\sigma}{S_*}(\mu+\hat{\beta}H)(S-S_*)^2 \\
&+ \mu(\rho+\mu+\sigma)H\left(\frac{\hat{\beta}S_*(\mu+\sigma)}{\mu(\rho+\mu+\sigma)} - 1\right) \\
&= -\frac{\mu+\sigma}{S_*}(\mu+\hat{\beta}H)(S-S_*)^2 - \mu(\rho+\mu+\sigma)H(1-\mathscr{R}_2).
\end{aligned}$$

Therefore, when $\mathscr{R}_H \leq 1$, $V'(S,H,L) \leq 0$ for all $(S,H,L) \in \mathbb{D}_H$, and that $V'(S_*,0,0) = 0$. Hence V is a Lyapunov function, and the steady state E_* is globally asymptotically stable in $\mathbb{D}_H$. □

Theorem 4.4.2. *If $\mathscr{R}_H > 1$, then the endemic equilibrium E_H is globally asymptotically stable in the interior of $\mathbb{D}_H$.*

Proof. Similarly as in the previous theorem, now following Theorem 2 of [169], we define $J : \{(S,H,L) \in \mathbb{D}_H \mid S,H,L > 0\} \to \mathbb{R}_+$ by

$$\begin{aligned}
J(S,H,L) &= \frac{(S-S_H)^2}{2S_H} + (H - H_H - H_H \ln\frac{H}{H_H}) \\
&+ \frac{\sigma L_H}{\rho H_H}(L - L_H - L_H \ln\frac{L}{L_H}).
\end{aligned} \tag{4.12}$$

This function is continuously differentiable and bounded from below. Since (S_h, H_h, L_h)

is an endemic equilibrium point of the system (4.8), we have

$$\mu = \hat{\beta} S_h H_h + \mu S_h, \quad (\rho + \mu) = \hat{\beta} S_h + \frac{\sigma L_h}{H_h}, \quad (\sigma + \mu) = \frac{\rho H_h}{L_h}. \tag{4.13}$$

Computing the derivative of (4.12) along the solutions of system (4.8), we obtain

$$\begin{aligned} J'(S,H,L) &= \frac{S - S_h}{S_h}\frac{dS}{dt} + \frac{H - H_h}{H}\frac{dH}{dt} + \frac{\sigma L_h}{\rho H_h}(1 - \frac{L_h}{L})\frac{dL}{dt} \\ &= \frac{S - S_h}{S_h}(\mu - \hat{\beta} SH - \mu S) + (H - H_h)(\hat{\beta} S - \rho - \mu + \frac{\sigma L}{H}) \\ &+ \frac{\sigma L_h}{\rho H_h}(1 - \frac{L_h}{L})(\rho H - (\sigma + \mu)L). \end{aligned}$$

Using the relation (4.13), we obtain,

$$\begin{aligned} J'(S,H,L) = \frac{S - S_h}{S_h}(\mu(S - S_h) + \hat{\beta}(SH - S_h H_h)) + (H - H_h)\big(\hat{\beta}(S - S_h) \\ + \sigma(\frac{L}{H_h} - \frac{L_h}{H})\big) + \frac{\sigma L_h}{\rho H_h}(1 - \frac{L_h}{L})(\rho H - \sigma H_h \frac{L_h}{L}). \end{aligned}$$

Since $SH - S_h H_h = S_h(H - H_h) + H(S - S_h)$. Thus,

$$\begin{aligned} J'(S,H,L) &= -\frac{S - S_h}{S_h}(\mu(S - S_h) + \hat{\beta}(S_h(H - H_h) + H(S - S_h))) \\ &+ \hat{\beta}(H - H_h)(S - S_h) + \sigma L_h(\frac{L}{L_h} - \frac{H}{H_h} - \frac{H_h L}{H L_h} + 1) \\ &+ \sigma L_h(\frac{H}{H_h} - \frac{L}{L_h} - \frac{L_h H}{L H_h} + 1) \\ &= -(\mu + \hat{\beta} H)\frac{(S - S_h)^2}{S_h} + \sigma L_h(2 - \frac{H_h L}{H L_h} - \frac{H L_h}{H_h L}) \\ &= -(\mu + \hat{\beta} H)\frac{(S - S_h)^2}{S_h} - \sigma L_h \left[\sqrt{\frac{H_h L}{H L_h}} - \sqrt{\frac{H L_h}{H_h L}}\right]^2. \end{aligned}$$

Therefore, $J'(S,H,L) \leq 0$ whenever J is defined, and $J'(S,H,L) = 0$ holds when $S = S_H$ and $HL_H = H_H L$. It is easy to see that the set $\{(S,H,L) \in \mathbb{D}_H | S,H,L > 0$ and $J'(S,H,L) = 0\}$ contains only the endemic equilibrium E_H. Hence, by the LaSalle's invariance principle [170], the steady state E_H is globally asymptotically stable in the interior of $\mathbb{D}_H$. □

Note that the global asymptotic stability of E_H can be easily extended to the set $\mathbb{D}_H \setminus \{E_*\}$.

4.5 Mathematical Analysis of the Co-infection Model

4.5.1 Equilibria, Reproduction Numbers

System (4.2) may have 4 different equilibrium points. We denote the disease free equilibrium point by $\mathcal{E}_S$ which always exists, and corresponds to the situation where all the infected compartments equal to 0, thus given by

$$\mathcal{E}_S = (S, C, H, I_{LC}, I_{HP}, L) = (1, 0, 0, 0, 0, 0). \tag{4.14}$$

The second equilibrium point denoted by $\mathcal{E}_C$ corresponds to the situation where only *Chlamydia* infection is present and is given by

$$\mathcal{E}_C = (S = S_C, C = C_C, H = 0, I_{LC} = 0, I_{HP} = 0, L = 0), \tag{4.15}$$

where S_C, C_C are as in (4.6). The third equilibrium denoted by $\mathcal{E}_H$ corresponds to the situation where only HSV infection is present and is given by

$$\mathcal{E}_H = (S = S_H, C = 0, H = H_H, I_{LC} = 0, I_{HP} = 0, L = L_H), \tag{4.16}$$

where S_H, H_H, L_H are as in (4.9). There is a possibility of existence of a fourth equilibrium point which is the endemic equilibrium point, when all compartments are positive. We denote this equilibrium point by $\mathcal{E}_{CH}$, and the conditions for it's existence will be discussed later.

Various reproduction numbers can be calculated by introducing a single *Chlamydia* (infected and infectious) individual or a single HSV (infected and infectious) individual into a completely susceptible population ($\mathcal{E}_S$). The infected compartments are C, H, I_{HP}, I_{LC} and L. Using the next generation matrix approach, let us introduce the notations F_2 and V_2 for the transmission and transition matrices. Linearizing at the equilibrium $\mathcal{E}_S$, we have

$$F_2 = \begin{bmatrix} \beta & 0 & \beta & 0 & 0 \\ 0 & \hat{\beta} & 0 & \hat{\beta} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \qquad V_2 = \begin{bmatrix} r+\mu & 0 & 0 & 0 & 0 \\ 0 & \mu+\rho & 0 & 0 & -\sigma \\ 0 & 0 & r+\mu+\sigma & -\rho & 0 \\ 0 & 0 & -\sigma & \mu+\rho & 0 \\ 0 & -\rho & -r & 0 & \mu+\sigma \end{bmatrix}.$$

We obtain the expression for the basic reproduction number of the co-infection

model as

$$\mathscr{R}_0 = \hat{\varrho}(F_2 V_2^{-1}) = \max\{\mathscr{R}_C, \mathscr{R}_H\},$$

where

$$\mathscr{R}_C = \frac{\beta}{r+\mu} \text{ and } \mathscr{R}_H = \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)},$$

are the reproduction numbers for *chlamydia* and herpes respectively, and are consistent with the reproduction numbers obtained in the respective subsystems. It is obvious that the equilibrium points $\mathcal{E}_C$ and $\mathcal{E}_H$ exist if and only if $\mathscr{R}_C > 1$ and $\mathscr{R}_H > 1$ respectively.

The next reproduction number is obtained by calculating the expected number of secondary infections caused by the introduction of a H-individual into a population existing in the equilibrium $\mathcal{E}_C$. In this situation, the infected compartments are H, I_{HP}, I_{LC} and L. By introducing the notations F_3 and V_3 for the transmission and transition matrices, and linearizing at the equilibrium $\mathcal{E}_C$, we have

$$F_3 = \begin{bmatrix} \frac{\hat{\beta}(r+\mu)}{\beta} & 0 & \frac{\hat{\beta}(r+\mu)}{\beta} & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\hat{\beta}(\beta-r-\mu)}{\beta} & 0 & \frac{\hat{\beta}(\beta-r-\mu)}{\beta} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$V_3 = \begin{bmatrix} \beta - r + \rho & 0 & 0 & -\sigma \\ 0 & r+\mu+\sigma & 0 & r-\beta+\mu \\ r-\beta+\mu & -\sigma & \mu+\rho & 0 \\ -\rho & -r & 0 & \beta-r+\sigma \end{bmatrix}.$$

We obtain the spectral radius as $\hat{\varrho}(F_3 V_3^{-1}) = \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)}$. Thus, we obtain exactly the same reproduction number $\mathscr{R}_H$ as the transmission rate from H-individuals is the same for the S and C compartments.

To calculate the last reproduction number, we introduce a C-individual into a population existing at the equilibrium $\mathcal{E}_H$, and follow the next generation matrix approach. Splitting the system into vectors $\mathcal{X} = \big(C, I_{LC}, I_{HP}\big)$, composed of infectious compartments, and $\mathcal{Y} = \big(S, H, L\big)$, composed of non-infectious compartments (with respect to chlamydia), the system can be expressed as

$$\begin{aligned} \mathcal{X}_i' &= \mathcal{F}_i(\mathcal{X}, \mathcal{Y}) - \mathcal{V}_i(\mathcal{X}, \mathcal{Y}), \qquad i = 1, 2, 3, \\ \mathcal{Y}_j' &= g_j(\mathcal{X}, \mathcal{Y}), \qquad\qquad\quad j = 1, 2, 3, \end{aligned}$$

where $\mathcal{F}_i$ represents the new infections due to *Chlamydia* and $\mathcal{V}_i$ contains the

transitions between infected compartments, and are given as follows:

$$\mathcal{F}_i = \begin{bmatrix} \beta SC + \beta SI_{LC} \\ \beta LC + \beta LI_{LC} \\ \beta HC + \beta HI_{LC} \end{bmatrix} \tag{4.17}$$

and

$$\mathcal{V}_i = \begin{bmatrix} \hat{\beta}CH + \hat{\beta}CI_{HP} + rC + \mu C \\ -\rho I_{HP} + rI_{LC} + \mu I_{LC} + \sigma I_{LC} \\ -\hat{\beta}CH - \hat{\beta}CI_{HP} + \rho I_{HP} + \mu I_{HP} - \sigma I_{LC} \end{bmatrix}. \tag{4.18}$$

By means of linearization at the HSV free equilibrium $\mathcal{E}_H$, we obtain the equation

$$\mathcal{X}' = A\mathcal{X}$$

where A is the Jacobian matrix. Next, we take the decomposition

$$A = F_4 - V_4,$$

where

$$(F_4)_{i,j} = \left[\frac{\partial \mathcal{F}_i}{\partial \mathcal{X}_j}(\mathcal{E}_H)\right], \qquad (V_4)_{i,j} = \left[\frac{\partial \mathcal{V}_i}{\partial \mathcal{X}_j}(\mathcal{E}_H)\right].$$

In the present scenario, the non-negative matrices of transmission terms corresponding to the new infections generated due to *Chlamydia*, and the remaining transfer terms respectively take the form

$$F_4 = \begin{bmatrix} \frac{\beta\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)} & \frac{\beta\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)} & 0 \\ \frac{\beta\rho\mu}{\hat{\beta}(\mu+\sigma)}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right) & \frac{\beta\rho\mu}{\hat{\beta}(\mu+\sigma)}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right) & 0 \\ \frac{\beta\mu}{\hat{\beta}}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right) & \frac{\beta\mu}{\hat{\beta}}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right) & 0 \end{bmatrix}$$

and

$$V_4 = \begin{bmatrix} r + \frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} & 0 & 0 \\ 0 & r+\mu+\sigma & -\rho \\ \mu - \frac{\hat{\beta}(\mu+\sigma)}{\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)}} & -\sigma & \mu+\rho \end{bmatrix}.$$

The reproduction number associated with the equilibrium point $\mathcal{E}_H$, denoted by

$\mathscr{R}_{CH}$, is given by $\hat{\varrho}(F_4V_4^{-1})$, where $\hat{\varrho}$ is the spectral radius, and is obtained as

$$\mathscr{R}_{CH} = \frac{\Delta_{11}}{\Delta_{12}}, \tag{4.19}$$

where

$$\begin{aligned}\Delta_{11} = [&\beta(\mu^5 + 3\mu^4(\rho+\sigma) + \hat{\beta}^2\rho\sigma(\rho+\sigma) + \hat{\beta}^2\rho\mu(\rho+3\sigma) + r(\rho+\sigma+\mu)\\ &\times(\mu^4 + 2\hat{\beta}\rho\mu + \mu^2(\rho+\sigma) + \hat{\beta}\rho(\rho+\sigma)) + \mu^3(-\hat{\beta}\rho + 3(\rho+\sigma)^2) + \mu^2\\ &\times(2\hat{\beta}^2\rho - \hat{\beta}\rho(\rho+\sigma) + (\rho+\sigma)^2))],\end{aligned}$$

and

$$\Delta_{12} = \big[\hat{\beta}(\rho+\sigma+\mu)((r+\mu)(\rho+\mu)+\sigma\mu)(\hat{\beta}(\sigma+\mu) + r(\rho+\sigma+\mu))\big].$$

The details of the algebraic calculations leading to Δ_{11} and Δ_{12} can be found in the supplementary file available in our public GitHub repository, Section 5.1 of [171].

4.5.2 Relation between $\mathscr{R}_C$ and $\mathscr{R}_{CH}$

In this section, we establish the relation between the two reproduction numbers associated with *Chlamydia* $\mathscr{R}_C$ and $\mathscr{R}_{CH}$, calculated at the equilibrium points $\mathcal{E}_S$ and $\mathcal{E}_H$ respectively.

Lemma 4.5.1. *Whenever $\mathscr{R}_{CH}$ is defined (i.e. if $\mathscr{R}_H > 1$), then $\mathscr{R}_{CH} < \mathscr{R}_C$.*

Proof. We begin with the assumption that the herpes reproduction number $\mathscr{R}_H$ is greater than 1, which implies that

$$\hat{\beta}(\mu+\sigma) - \mu(\mu+\rho+\sigma) > 0.$$

$$\begin{aligned}\text{We set } \theta = &-\mu(\hat{\beta}(\mu^2 + 2\mu\sigma + \sigma(\rho+\sigma)) + \mu(\mu+\rho+\sigma)^2 + r^2(\mu+\rho+\sigma)\\ &+ r(\hat{\beta}(\mu+\sigma) + 2\mu^2 + 3\mu\times(\rho+\sigma) + (\rho+\sigma)^2)).\end{aligned}$$

It is clear that $\theta < 0$ for positive parameter values. Hence for $\mathscr{R}_H > 1$,

$$\Big(\hat{\beta}(\mu+\sigma) - \mu(\mu+\rho+\sigma)\Big)\,\theta < 0.$$

With some algebraic manipulation, the left hand side of the above inequality turns out to be $(r+\mu)\Delta_{11} - \beta\Delta_{12}$, where Δ_{11} and Δ_{12} are the numerators and denomi-

nators of $\mathscr{R}_{CH}$ respectively. Hence,

$$\frac{\Delta_{11}}{\Delta_{12}} - \frac{\beta}{r+\mu} < 0,$$

which implies that $\mathscr{R}_{CH} - \mathscr{R}_C < 0$. We can therefore conclude that $\mathscr{R}_{CH} < \mathscr{R}_C$ whenever $\mathscr{R}_H > 1$. The algebraic calculations carried out using Wolfram Mathematica are available in our public GitHub repository, Section 5.2 of the notebook [171].

□

This means that for *Chlamydia* it is more difficult to invade a population where HSV is established than a population without HSV.

4.5.3 Local Asymptotic Stability of the Disease Free Equilibrium $\mathcal{E}_S$

Theorem 4.5.2. *The equilibrium $\mathcal{E}_S$ is locally asymptotically stable if $\mathscr{R}_C < 1$ and $\mathscr{R}_H < 1$ and unstable if $\mathscr{R}_C > 1$ or $\mathscr{R}_H > 1$.*

Proof. We compute the eigenvalues of the Jacobian of the linearized equation around the equilibrium $\mathcal{E}_S$:

$$\begin{aligned}
\lambda_1 &= -\mu, \\
\lambda_2 &= \beta - r - \mu, \\
\lambda_{3,4} &= \frac{1}{2}\big(\hat{\beta} - 2\mu - \rho - \sigma \pm \sqrt{(\rho-\hat{\beta})^2 + 2\rho\sigma + 2\hat{\beta}\sigma + \sigma^2}\big), \\
\lambda_{5,6} &= \frac{1}{2}\big(-r - 2\mu - \rho - \sigma \pm \sqrt{(\rho-r)^2 + 2\rho\sigma + 2r\sigma + \sigma^2}\big).
\end{aligned}$$

Clearly, λ_1 is negative, and λ_2 is negative for $\mathscr{R}_C < 1$. As for conjugate pairs of eigenvalues λ_3 and λ_4, since all the parameters are positive the terms under the square roots are non-negative and hence both the eigenvalues are reals. Their product is obtained as $\mu(\mu+\rho+\sigma) - \hat{\beta}(\mu+\sigma)$ which is greater then zero, as from $\mathscr{R}_H < 1$ we have $\mu(\mu+\rho+\sigma) > \hat{\beta}(\mu+\sigma)$. Moreover, their sum is $\hat{\beta} - 2\mu + \rho + \sigma$ which is always negative for $\mathscr{R}_H < 1$. From this, it follows that λ_3 and λ_4 are always negative for $\mathscr{R}_H < 1$. Similarly, it can be shown that $\lambda_5 < 0$ and $\lambda_6 < 0$. Hence, all the eigenvalues are negative if $\mathscr{R}_C < 1$ and $\mathscr{R}_H < 1$ and the disease free steady state $\mathcal{E}_S$ is locally asymptotically stable. □

4.5.4 Local Asymptotic Stability of the *Chlamydia* Present Equilibrium $\mathcal{E}_C$

Theorem 4.5.3. *Let $\mathscr{R}_C > 1$. The equilibrium point $\mathcal{E}_C$ for the model system (4.2) is locally asymptotically stable if $\mathscr{R}_H < 1$ and unstable if $\mathscr{R}_H > 1$.*

Proof. The eigenvalues of the Jacobian of the linearized equation around the equilibrium $\mathcal{E}_S$ are given by

$$\begin{aligned}
\lambda_1 &= -\mu,\\
\lambda_2 &= \beta - r - \mu,\\
\lambda_{3,4} &= \frac{1}{2}\big(\hat{\beta} - 2\mu - \rho - \sigma \pm \sqrt{(\rho-\hat{\beta})^2 + 2\rho\sigma + 2\hat{\beta}\sigma + \sigma^2}\big),\\
\lambda_{5,6} &= \frac{1}{2}\big(r - 2\beta - \rho - \sigma \pm \sqrt{(\rho-r)^2 + 2\rho\sigma + 2r\sigma + \sigma^2}\big).
\end{aligned}$$

Clearly, λ_1 is negative, and λ_2 is negative for $\mathscr{R}_C > 1$. Also, since all the parameters are positive, the terms under the square roots for eigenvalues λ_5 and λ_6 are non-negative. Hence, they are both reals. The sum of the conjugate pair of eigenvalues λ_5 and λ_6 is $(\beta - r)(\beta + \sigma) + \beta\rho$ which is greater then zero, as from $\mathscr{R}_C > 1$ we have $\beta > r + \mu$. Moreover, their sum is $2(r - 2\beta - \rho - \sigma)$ which is always negative for $\mathscr{R}_C > 1$. From this, it follows that λ_5 and λ_6 are always negative for $\mathscr{R}_C > 1$. Also, λ_3 and λ_4 are the same as the corresponding eigenvalues in the previous section, and have been shown to be negative for $\mathscr{R}_H < 1$. Hence, all the eigenvalues are negative if $\mathscr{R}_C > 1$ and $\mathscr{R}_H < 1$. Thus, the equilibrium point $\mathcal{E}_C$ is locally asymptotically stable in this case. □

4.5.5 Global Asymptotic Stability of the Disease Free Equilibrium ($\mathcal{E}_S$) and the *Chlamydia* Present Equilibrium ($\mathcal{E}_C$)

Theorem 4.5.4. *Assume that $\mathscr{R}_H \leq 1$. If $\mathscr{R}_C \leq 1$, then the equilibrium point $\mathcal{E}_S$ is globally asymptotically stable, and if $\mathscr{R}_C > 1$, then $\mathcal{E}_C$ is globally asymptotically stable .*

Proof. Consider the auxiliary function $q_1 : \mathbb{D} \to \mathbb{R}_+$,

$$q_1 = \frac{\sigma(L + I_{LC}) + (\mu + \sigma)(H + I_{HP})}{\mu(\mu + \rho + \sigma)}, \tag{4.20}$$

which is continuously differentiable, and bounded from below. The derivative of (4.20) with respect to t along solution curves of (4.2) is given by,

$$\begin{aligned} q_1' &= \frac{(I_{LC}' + L')\sigma + (H' + I_{HP}')(\mu + \sigma)}{\mu(\mu + \rho + \sigma)} \\ &= (H + I_{HP}) \left[-1 + (C + S) \frac{\hat{\beta}(\mu + \sigma)}{\mu(\mu + \rho + \sigma)} \right] \\ &= (H + I_{HP}) \left[(C + S)\mathscr{R}_H - 1 \right]. \end{aligned}$$

The following two cases arise corresponding to the initial point P_0.

The first case is when $P_0 \notin \mathbb{D}_C$. In this case, since $\mathscr{R}_H \leq 1$, and $S + C \leq 1$, we have $q_1' \leq 0$, thus LaSalle's Invariance Principle implies

$$\omega(P_0) \subseteq \{(S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{D} \mid q_1' = 0\} = \{(S, C, 0, I_{LC}, 0, L) \in \mathbb{D}\}.$$

Inside $\omega(P_0)$, the dynamics is described by the following system,

$$\begin{aligned} S' &= \mu - \beta SC - \beta S I_{LC} - \mu S + rC, \\ C' &= \beta SC + \beta S I_{LC} - rC - \mu C, \\ I_{LC}' &= \beta LC + \beta L I_{LC} - r I_{LC} - \mu I_{LC} - \sigma I_{LC}, \\ L' &= r I_{LC} - \sigma L - \beta LC - \beta L I_{LC} - \mu L. \end{aligned}$$

For this system, we have $(I_{LC}(t) + L(t))' = -(\mu + \sigma)(I_{LC} + L)$. Applying LaSalle's Invariance Principle once more, we obtain

$$\omega(P_0) \subseteq \Omega := \{(S, C, 0, 0, 0, 0) \in \mathbb{R}_+^6 \mid S + C = 1\}. \tag{4.21}$$

The other case is when $P_0 \in \mathbb{D}_C$. In this case, due to the invariant property of $\mathbb{D}_C$, the omega limit set of the initial point P_0 will be as in (4.21). Thus, in either case, the omega limit set is described by (4.21). Now, there are two cases with respect to the reproduction number for *Chlamydia*, $\mathscr{R}_C$.

Let us consider the case $\mathscr{R}_C \leq 1$. The only whole trajectory inside ω in this case is the set containing only the disease free equilibrium $\mathcal{E}_S$. By the properties of the ω-limit sets, $\omega(P_0) = \{\mathcal{E}_S\}$, the solutions converge to $\mathcal{E}_S$, since P_0 is arbitrary. Since we know that $\mathcal{E}_S$ is LAS when $\mathscr{R}_C < 1$, the convergence implies that $\mathcal{E}_S$ is globally asymptotically stable.

Secondly, consider the case $\mathscr{R}_C > 1$. Inside ω, the dynamics is described by the *Chlamydia* subsystem, let us denote this dynamical system by Θ. The first

two equations for $S(t)$ and $C(t)$ of the system (4.2) can be considered as a non-autonomous system of differential equations that generate the non-autonomous dynamical system Φ. Since $H(t), I_{LC}(t), I_{HP}(t), L(t) \to 0$ as $t \to \infty$, Φ is asymptotically equivalent to Θ. As $\mathbb{D}$ is a compact invariant set, the forward orbits are pre-compact. Let $e_1 = \mathcal{E}_S$, $e_2 = \mathcal{E}_C$ and $X_1 = W^S_\Phi(e_1)$, the invariant set containing the disease free equilibrium $\mathcal{E}_S$. Let $X_2 = \mathbb{D} \setminus X_1$. X_1 is closed by definition and X_2 is open in $\mathbb{D}$. Solutions starting in X_1 will converge to e_1 as this is the only equilibrium point. For $\mathscr{R}_C > 1$, $\mathcal{E}_C$ is GAS in Θ, hence solutions starting in X_2 will converge to e_2. e_1 is GAS for restriction of Θ to X_1. X_2 is invariant, hence every ϕ orbit starting in X_2 will converge to e_2 and cannot converge to e_1. Hence, e_1 is a weak repeller. Thus every pre-compact forward ϕ orbit starting in X_2 converges to e_2. Hence, all the conditions of Theorem 2.5 of [172] are satisfied. Hence, applying the theorem, if $P_0 \in X_1$, then the solution starting from P_0 converges to $\mathcal{E}_S$, else it converges to $\mathcal{E}_C$. Since we know that $\mathcal{E}_C$ is LAS when $\mathscr{R}_C > 1$, the convergence implies that the $\mathcal{E}_C$ is globally asymptotically stable. □

4.5.6 Local Asymptotic Stability of the Herpes Present Equilibrium point $\mathcal{E}_H$

In this section, using Theorem 2 of van den Driessche & Watmough (2002), [168], we establish the local asymptotic stability of the equilibrium point $\mathcal{E}_H$.

Theorem 4.5.5. *The equilibrium point $\mathcal{E}_H$ for the model system (4.2) is locally asymptotically stable if $\mathscr{R}_{CH} < 1$ and unstable if $\mathscr{R}_{CH} > 1$.*

Proof. We consider the case when the system is existing at the herpes present equilibrium point $\mathcal{E}_H$. It is presumed that the new infection terms are only related to the infections caused by *Chlamydia*. Clearly, the assumptions (A1)-(A4) of Theorem 2, [168] are obviously satisfied, we verify condition (A5) in the following part.

Setting the new infection terms of the system (4.2) to zero, i.e setting $\mathcal{F}_i$ in (4.17) to zero, we obtain the Jacobian calculated at $\mathcal{E}_H$. Denoting

$$\zeta = \mu(\mathscr{R}_H - 1),$$

the matrix is obtained as follows:

$$\begin{bmatrix} -\mu-\zeta & r-\frac{\beta}{\mathscr{R}_H} & -\frac{\hat{\beta}}{\mathscr{R}_H} & -\frac{\beta}{\mathscr{R}_H} & -\frac{\hat{\beta}}{\mathscr{R}_H} & 0 \\ 0 & -r-\mu-\zeta & 0 & 0 & 0 & 0 \\ \zeta & -\zeta & -\mu+\zeta-\rho & -\frac{\beta\zeta}{\hat{\beta}} & \frac{\hat{\beta}}{\mathscr{R}_H} & \sigma \\ 0 & \zeta & 0 & \sigma & -\mu-\rho & 0 \\ 0 & 0 & 0 & -r-\mu-\sigma & \rho & 0 \\ 0 & -\frac{\beta\rho\zeta}{\hat{\beta}(\mu+\sigma)} & \rho & r-\frac{\beta\rho\zeta}{\hat{\beta}(\mu+\sigma)} & 0 & -\mu-\sigma \end{bmatrix}.$$

The eigenvalues corresponding to this Jacobian matrix are as follows:

$$\lambda_1 = -\mu, \qquad \lambda_2 = -r - \mathscr{R}_H, \qquad \lambda_3 = \frac{1}{2}(-q_1 - \sqrt{q_2}),$$
$$\lambda_4 = \frac{1}{2}(-q_1 + \sqrt{q_2}), \qquad \lambda_5 = -\frac{q_3 + \sqrt{q_4}}{2D}, \qquad \lambda_6 = -\frac{q_3 - \sqrt{q_4}}{2D},$$

where

$$\begin{aligned} q_1 &= r + 2\mu + \rho + \sigma, \\ q_2 &= (\rho - r)^2 + 2\rho\sigma + 2(r+\sigma)\sigma + \sigma^2, \\ q_3 &= \hat{\beta}(\mu+\sigma)^2 + \sigma(\mu+\rho+\sigma)^2, \\ q_4 &= \hat{\beta}^2(\mu+\sigma)^4 - 2\hat{\beta}(\mu+\sigma)^2(2\mu+\sigma)(\mu+\rho+\sigma)^2 \\ &\quad +(\mu+\rho+\sigma)^3(4\mu^3 + 8\mu^2\sigma + (5\mu+\rho)\sigma^2 + \sigma^3), \end{aligned}$$

and $D = (\mu+\sigma)(\mu+\rho+\sigma)$. All the parameters are positive, and clearly $\lambda_1 < 0$ and $\lambda_2 < 0$. For the conjugate pair of eigenvalues λ_3 and λ_4, the term under the square root is positive, hence both are reals. Their product is given by $(r+\mu)(\mu+\rho)+\mu\sigma$, which is positive, and their sum is $-r-2\mu-\rho-\sigma$, which is negative implying that both eigenvalues are negative. As for λ_5 and λ_6, by taking the difference of the squares of the first resp. the second term of the nominator, we obtain $4(\mu+\sigma)^2(\mu+\rho+\sigma)^2(\hat{\beta}(\mu+\sigma)-\mu(\mu+\rho+\sigma))$ which is greater then zero, as from $\mathscr{R}_H > 1$, we have $\hat{\beta}(\mu+\sigma)-\mu(\mu+\rho+\sigma)$. From this follows that λ_5 and λ_6 always have negative real parts for $\mathscr{R}_H > 1$. Thus, we can conclude that the equilibrium point $\mathcal{E}_H$ is LAS when the reproduction number $\mathscr{R}_{CH} < 1$. □

4.6 The Limiting System

Introducing $x = S + C$, $y = H + I_{HP}$ and $z = L + I_{LC}$, the system (4.2) reduces to

$$\begin{aligned} x' &= \mu - \hat{\beta}xy - \mu x, \\ y' &= \hat{\beta}xy - \rho y + \sigma z - \mu y, \\ z' &= \rho y - \sigma z - \mu z. \end{aligned} \tag{4.22}$$

The system (4.22) is completely analogous to the HSV subsystem given by the system (4.8). The two equilibria are given by,

$$\hat{E} = (\hat{x}, \hat{y}, \hat{z}) = E_*, \quad \text{and} \quad E^* = (x^*, y^*, z^*) = E_H. \tag{4.23}$$

Here E_* and E_H correspond to the disease free equilibrium and the herpes equilibrium respectively and are obtained from equation (4.9). Henceforth, all our analysis is subject to the condition that the reproduction number for herpes $\mathscr{R}_H$ given by (4.10) is larger than 1. From the analysis of the HSV subsystem (Section 4.4), it is clear that if $\mathscr{R}_H \leq 1$, then the equilibrium $\hat{E}$ is GAS. On the other hand, as $t \to \infty$, since the total population is 1, $x \to x^*$, $y \to y^*$, and $z \to z^*$ when $\mathscr{R}_H > 1$. Thus, we have the convergence

$$S + C \to x^*, \qquad H + I_{HP} \to y^*, \qquad L + I_{LC} \to 1 - x^* - y^*. \tag{4.24}$$

The system of equations C, I_{LC} and I_{HP} can be considered as a non-autonomous system of differential equations, where the non-autonomous terms $S(t), H(t), L(t)$ are generated by solutions of the dynamical system (4.2). As we have the convergence (4.24), this system is asymptotically autonomous with the following equalities,

$$S = x^* - C, \qquad H = y^* - I_{HP}, \qquad L = 1 - x^* - y^* - I_{LC}. \tag{4.25}$$

Consequently, the limiting system has the form

$$\begin{aligned} C' &= \beta(x^* - C)C + \beta(x^* - C)I_{LC} - \hat{\beta}y^*C - rC - \mu C, \\ I'_{LC} &= \rho I_{HP} + \beta(1 - x^* - y^*)C + \beta(1 - x^* - y^*)I_{LC} - \beta I_{LC}C - \beta I_{LC}^2 \\ &\quad - rI_{LC} - \mu I_{LC} - \sigma I_{LC}, \\ I'_{HP} &= \hat{\beta}y^*C + \beta(y^* - I_{HP})C + \beta(y^* - I_{HP})I_{LC} + \sigma I_{LC} - \rho I_{HP} - \mu I_{HP}, \end{aligned} \tag{4.26}$$

with phase space

$$\mathbb{D}_L = \{(C, I_{LC}, I_{HP}) \in \mathbb{R}^3_+ \mid C \leq x^*,\ I_{LC} \leq y^*,\ I_{HP} \leq 1 - x^* - y^*\}. \tag{4.27}$$

4.6.1 The Basic Reproduction Number in the Limiting Case

For the limiting system (4.26), the zero equilibrium point $\mathcal{E}_0 = (0, 0, 0)$ is equivalent to the original system (4.2) being at the herpes equilibrium and there's no *Chlamydia* infection in the system. In this section, we calculate the reproduction number, $\mathscr{R}_L$, as the expected number of secondary cases caused by introducing a single *Chlamydia* infected individual into the system, assuming that the system is at the herpes equilibrium, which is $\mathcal{E}_0 = (0, 0, 0)$ for the limiting case. For that purpose, we first establish the system (4.26) in the form of

$$\boldsymbol{I}' = \tilde{\mathcal{F}}(\boldsymbol{I}) - \tilde{\mathcal{V}}(\boldsymbol{I}), \qquad \text{where} \qquad \boldsymbol{I} = (C, I_{LC}, I_{HP})^T.$$

Here, $\tilde{\mathcal{F}} = (\tilde{\mathcal{F}}_1, \tilde{\mathcal{F}}_2, \tilde{\mathcal{F}}_3)$ represents the new infections due to *C. trachomatis*, while $\tilde{\mathcal{V}} = (\tilde{\mathcal{V}}_1, \tilde{\mathcal{V}}_2, \tilde{\mathcal{V}}_3,)$ contains the transitions between infected compartments. We linearize (4.26) at the zero equilibrium $\mathcal{E}_0 = (0, 0, 0)$ to obtain the equation

$$\boldsymbol{I}' = \tilde{A}\boldsymbol{I},$$

where $\tilde{A}$ is the Jacobian matrix. Next, we take the decomposition $\tilde{A} = \tilde{F} - \tilde{V}$, where

$$\tilde{F} = \left[\frac{\partial \tilde{\mathcal{F}}_i}{\partial I_j}(\mathcal{E}_0)\right], \qquad \tilde{V} = \left[\frac{\partial \tilde{\mathcal{V}}_i}{\partial I_j}(\mathcal{E}_0)\right].$$

For the limiting system (4.26), we have

$$\tilde{F} = \begin{pmatrix} \beta x^* & \beta x^* & 0 \\ \beta & \beta & 0 \\ \beta y^* & \beta y^* & 0 \end{pmatrix}$$

and

$$\tilde{V} = \begin{pmatrix} r + \hat{\beta} y^* + \mu & 0 & 0 \\ \beta x^* + \beta y^* & r + \beta x^* + \beta y^* + \mu + \sigma & -\rho \\ -\hat{\beta} y^* & -\sigma & \mu + \rho \end{pmatrix}.$$

The dominant eigenvalue of $\tilde{F}\tilde{V}^{-1}$ is,

$$\begin{aligned}\hat{\varrho}(\tilde{F}\tilde{V}^{-1}) = \big[&(r+\hat{\beta}y^*+\mu)((r+\beta(x^*+y^*)+\mu)(\mu+\rho)+\mu\sigma)\big]\\ &/\big[\beta(r(1+x^*)\mu)+\hat{\beta}y^*\mu+r(1+x^*+y^*)\rho+\hat{\beta}y^{*2}\rho\\ &+y^*(\hat{\beta}+\hat{\beta}x^*+\mu)\rho+(1+x^*)\mu(\mu+\rho+x^*\mu\sigma)\big].\end{aligned}$$

At the equilibrium $\mathcal{E}_0 = (0,0,0)$, we have $S = x^*, H = y^*, L = 1-x^*-y^*$. Substituting

$$x^* = \frac{\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)}, \text{ and } y^* = \frac{\mu}{\hat{\beta}}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)}-1\right), \tag{4.28}$$

from (4.9), we have

$$\mathscr{R}_L = \hat{\varrho}(\tilde{F}\tilde{V}^{-1}) = \frac{\Delta_{21}}{\Delta_{22}}, \tag{4.29}$$

where

$$\begin{aligned}\Delta_{21} = \beta\big((\mu+\sigma)\big(\hat{\beta}^2(\mu+\sigma)\big(\mu^2+\mu(3\rho+\sigma)+\rho(\rho+2\sigma)\big)+\hat{\beta}\mu\rho^2(\mu+\rho\\ +\sigma)+\mu^2(\mu+\rho+\sigma)^3\big)+r_C(\mu+\rho+\sigma)\big(\hat{\beta}(\mu+\sigma)\big(\mu^2+\mu(3\rho+\sigma)+\rho\\ \times(\rho+2\sigma)\big)+\mu\big(\mu^3+2\mu^2(\rho+\sigma)+\mu\big(2\rho^2+2\rho\sigma+\sigma^2\big)+\rho^2(\rho+\sigma)\big)\big)\big),\end{aligned}$$

and

$$\begin{aligned}\Delta_{22} = (\hat{\beta}(\mu+\sigma)+r(\mu+\rho+\sigma))\big(\beta(\mu+\rho)\big(\hat{\beta}(\mu+\sigma)^2+\mu\rho(\mu+\rho+\sigma)\big)\\ +\hat{\beta}\mu(\mu+\sigma)(\mu+\rho+\sigma)^2+\hat{\beta}r(\mu+\rho)(\mu+\sigma)(\mu+\rho+\sigma)\big).\end{aligned}$$

4.6.2 Relation between the Reproduction Numbers $\mathscr{R}_L$ and $\mathscr{R}_{CH}$

In this section, we establish that relation between the reproduction numbers associated with *Chlamydia*, $\mathscr{R}_{CH}$ and $\mathscr{R}_L$, obtained by introducing a *Chlamydia* infected individual into a population existing in a herpes equilibrium, with respect to the original system (4.2), and the limiting system (4.26).

Lemma 4.6.1. *The reproduction numbers $\mathscr{R}_L$ and $\mathscr{R}_{CH}$ share the same threshold, that is they are both smaller than one, or both larger than one.*

Proof. By subtracting 1 from both the reproduction numbers we have the following

equalities:

$$\begin{aligned}\mathscr{R}_L - 1 &= \frac{\Delta_{11}}{\Delta_{12}} - 1 = \frac{\Delta_{11} - \Delta_{12}}{\Delta_{12}},\\ \mathscr{R}_{CH} - 1 &= \frac{\Delta_{21}}{\Delta_{22}} - 1 = \frac{\Delta_{21} - \Delta_{22}}{\Delta_{22}}.\end{aligned} \tag{4.30}$$

From the expressions of the two reproduction numbers, $\mathscr{R}_L$ and $\mathscr{R}_{CH}$ obtained earlier, it is clear that the denominators Δ_{12}, Δ_{22} are positive for positive parameters. By dividing the numerators of the two expressions in (4.19), we obtain

$$\frac{\Delta_{11} - \Delta_{12}}{\Delta_{21} - \Delta_{22}} = \mu + \sigma > 0.$$

Hence, we can conclude that the two reproduction numbers $\mathscr{R}_L$ and $\mathscr{R}_{CH}$ will have the same threshold. The algebraic calculations can be found in the Wolfram Mathematica notebook available in our public GitHub repository, Section 6 of [171]. □

4.6.3 Local Asymptotic Stability of the Equilibrium Point $\mathcal{E}_0$

Using Theorem 2 of van den Driessche & Watmough (2002), [168], the following result is established.

Theorem 4.6.2. *The equilibrium point $\mathcal{E}_0$, of the system (4.26) is locally asymptotically stable if $\mathscr{R}_L < 1$, and unstable if $\mathscr{R}_L > 1$.*

Proof. The assumptions (A1)-(A4) of Theorem 2, [168] are clearly satisfied. we only have to verify condition (A5). Using the substitution (4.28), the Jacobian $D\boldsymbol{I}(\mathcal{E}_0)$ at the equilibrium $\mathcal{E}_0 = (0, 0, 0)$, and is given by the matrix:

$$\begin{pmatrix} -r - \mathscr{R}_H & 0 & 0 \\ \frac{-\beta}{\hat{\beta}}\big(\frac{\mu\sigma}{\mu+\sigma} + \mathscr{R}_H\big) & -r - \mu - \sigma + \beta\big(-1 - \frac{\rho}{\hat{\beta}(\mu+\sigma)}(\mu - \mathscr{R}_H\big) & \rho \\ \mu + \mathscr{R}_H & \sigma & -\mu - \rho \end{pmatrix},$$

where $\mathscr{R}_H$ is the reproduction number for herpes given earlier. We obtain three eigenvalues corresponding to the matrix $D\boldsymbol{I}(\mathcal{E}_0)$. The first eigenvalue is $-\mu - \mathscr{R}_H$ which is negative for positive parameters. We denote the other two eigenvalues as follows:

$$\lambda_1 = z_1 + \sqrt{z_2} \qquad \text{and} \qquad \lambda_2 = z_1 - \sqrt{z_3}.$$

For the case when the terms under the square roots are negative, the eigenvalues will have imaginary parts. The real part for each eigenvalue is given by

$$z_1 = -\beta\hat{\beta}(\mu+\sigma)^2 - 2\beta\mu\rho(\mu+\rho+\sigma),$$

which is negative. In the other case, the sum and the product are obtained as follows:

$$\begin{aligned}
\lambda_1 + \lambda_2 &= -2\beta\hat{\beta}(\mu+\sigma)^2 - 2\beta\mu\rho(\mu+\rho+\sigma) \\
&\quad - 2\hat{\beta}(\mu+\sigma)(\mu+\rho+\sigma)(r+2\mu+\rho+\sigma), \\
\lambda_1 \times \lambda_2 &= 4\hat{\beta}(\mu+\sigma)(\mu+\rho+\sigma)\big(r\hat{\beta}(\mu+\rho)(\mu+\sigma)(\mu+\rho+\sigma) \\
&\quad + \hat{\beta}\mu(\mu+\sigma)(\mu+\rho+\sigma)^2 + \beta(\mu+\rho)(\hat{\beta}(\mu+\sigma)^2 + \mu\rho(\mu+\rho+\sigma))\big).
\end{aligned}$$

It is clear that the sum is always negative and the product is positive, implying that the two eigenvalues are negative for positive parameters. Thus, we conclude that the equilibrium $\mathcal{E}_0 = (0,0,0)$ is LAS for $\mathscr{R}_L < 1$, and unstable for $\mathscr{R}_L > 1$. □

4.6.4 Global Asymptotic Stability of the Equilibrium Point $\mathcal{E}_0$

Theorem 4.6.3. *The equilibrium point $\mathcal{E}_0$, of the system (4.26) is globally asymptotically stable whenever $\mathscr{R}_L < 1$ and unstable if $\mathscr{R}_L > 1$.*

Proof. The system of equations in (4.26) can be expressed in the following manner

$$\begin{pmatrix} \frac{dc(t)}{dt} \\ \frac{dI_{LC}(t)}{dt} \\ \frac{dI_{HP}(t)}{dt} \end{pmatrix} = (\tilde{F} - \tilde{V} - \mathbf{S}) \begin{pmatrix} C(t) \\ I_{LC}(t) \\ I_{HP}(t) \end{pmatrix},$$

where the matrices $\tilde{F}$ and $\tilde{V}$ are as defined above, and S is a non negative matrix given by

$$\mathbf{S} = \begin{pmatrix} \beta C & \beta C & 0 \\ \beta I_{LC} & \beta I_{LC} & 0 \\ \beta I_{HP} & \beta I_{HP} & 0 \end{pmatrix}.$$

Thus,

$$\begin{pmatrix} \frac{dC(t)}{dt} \\ \frac{dI_{LC}(t)}{dt} \\ \frac{dI_{HP}(t)}{dt} \end{pmatrix} \leq (\tilde{F} - \tilde{V}) \begin{pmatrix} C(t) \\ I_{LC}(t) \\ I_{HP}(t) \end{pmatrix}. \tag{4.31}$$

From the local stability result given in (4.6.2), it follows that, if $\mathscr{R}_L < 1$, then $\hat{\varrho}(\tilde{F}\tilde{V}^{-1}) < 1$, which is equivalent to $\tilde{F} - \tilde{V}$ having all its eigenvalues in the left-half plane [168]. It follows that the linearized differential inequality system (4.31) is stable whenever $\mathscr{R}_L < 1$. Consequently, $(C(t), I_{LC}(t), I_{HP}(t)) \to (0, 0, 0)$ as $t \to \infty$ for this linear ODE system. Thus, using a standard comparison theorem [173, P. 31], $(C(t), I_{LC}(t), I_{HP}(t)) \to (0, 0, 0)$ as well for the nonlinear system (4.26) implying that the disease free equilibrium $\mathcal{E}_0$ is GAS in $\mathbb{D}_L$ whenever $\mathscr{R}_L < 1$. □

4.6.5 The Endemic Equilibrium Point

The endemic equilibrium point $\mathcal{E}^* = (C^*, I^*_{LC}, I^*_{HP})$ is obtained by setting the right hand sides in Eq. (4.26) to zero. Its existence is established in the next lemma.

Lemma 4.6.4. *If $\mathscr{R}_L > 1$, then the limiting system* (4.26) *has a positive endemic equilibrium point.*

Proof. At endemic equilibrium point $\mathcal{E}^*$, the system (4.26) becomes

$$\beta(x^* - C^*)C^* + \beta(x^* - C^*)I^*_{LC} - (\hat{\beta}y^* + r + \mu)C^* = 0 \tag{4.32}$$

$$\rho I^*_{HP} + \beta(1 - x^* - y^*)(C^* + I^*_{LC}) - \beta I^*_{LC}(C^* + I^*_{LC}) - (r + \mu + \sigma)I^*_{LC} = 0, \tag{4.33}$$

$$(\hat{\beta}y^* + \beta(y^* - I^*_{HP}))C^* + (\sigma + \beta(y^* - I^*_{HP}))I^*_{LC} - (\rho + \mu)I^*_{HP} = 0. \tag{4.34}$$

From equations (4.32) and (4.33), we obtain the following implicit solutions to the respective compartments,

$$I^*_{LC} = -\frac{C^*(r + \beta C - \beta x^* + \hat{\beta}y^* + \mu)}{\beta(C^* - x^*)},$$

$$I^*_{HP} = \frac{\beta I^{*2}_{LC} + \beta C^*(-1 + x^* + y^*) + I^*_{LC}(r + \mu + \sigma\beta(C^* - 1 + x^* + y^*))}{\rho},$$

where C^* is the solution of the following equation:

$$f(C^*) = \frac{C^*}{(C^* - x)^3\beta\rho}\left(f_1 C^{*4} + f_2 C^{*3} + f_3 C^{*2} + f_4 C^*\right) = 0,$$

and $f : [0, x^*) \to \mathbb{R}$ is a continuous function with f_1, f_2, f_3, f_4 given as follows:

$$
\begin{aligned}
f_1 &= \beta(r + \hat{\beta}y^*)(\hat{\beta}y^* - \sigma),\\
f_2 &= \big(y^{*3}\hat{\beta}^2(\beta - \hat{\beta}) + r^2(\beta(y^* - 1) - \hat{\beta}y^* + \sigma) + \hat{\beta}y^{*2}(\beta\hat{\beta}((2x^{*2} - 1)\\
&\quad + \mu) + \hat{\beta}(-\mu + \rho + \sigma)) + \beta\mu(\rho + \sigma x^*) + r(2\hat{\beta}y^2(\beta - \hat{\beta})\\
&\quad + \beta y^*(2\hat{\beta}(x^* - 1) + \mu) + \mu\sigma + \hat{\beta}y^*(-\mu + \rho + 2\sigma) + \beta(-\mu + \rho - 2x^*\sigma))\\
&\quad + \hat{\beta}y^*(\mu(\rho + \sigma) - \beta(\mu + \mu x^* - \rho + 2x^*\sigma)))\big),\\
f_3 &= x^*\big(r^3 + \beta\hat{\beta}^2y^{*3} + r^2(\beta(y^* - 1) + 2\hat{\beta}y^* + 2\mu - \rho + \sigma)\\
&\quad + \hat{\beta}^2y^{*2}(\beta(x^* - 1) + 2\mu + \rho + \sigma) - y^*(\beta\mu^2 - 2\hat{\beta}\mu^2 - 2\beta\hat{\beta}\rho\\
&\quad + \beta\hat{\beta}x^*(2\mu + \sigma)) + r(\hat{\beta}y^{*2}(2\beta + \hat{\beta}) + \mu^2 + 2\beta\rho - 2\mu\rho - \beta\sigma x^*\\
&\quad + \hat{\beta}y^*(-2\beta + \beta x^* + 4\mu + 2\sigma)) + \mu(-\mu(\rho + \sigma) + \beta(\mu + 2\rho + 2\sigma x^*)))\big),\\
f_4 &= x^{*2}\big(\beta\hat{\beta}\mu y^{*2} + r^2(\mu + \rho) + \beta y^*\big(\hat{\beta}\mu(x^* - 1) + \mu^2 - \hat{\beta}\rho\big)\\
&\quad + \hat{\beta}\mu y^*(\mu + \rho + \sigma) + \mu^2(\mu + \rho + \sigma) - \beta\mu(\mu + \rho + \sigma x^*)\\
&\quad + r\big(\beta\mu(y^* - 1) - \beta\rho + \hat{\beta}y^*(\mu + \rho) + \mu(2\mu + 2\rho + \sigma)\big)\big),
\end{aligned}
$$

for $C^* \in [0, x^*)$. We have $f(0) = 0$ and $\lim\limits_{C^* \to x^{*-}} f(C^*) = -\infty$. The derivative of $f(C^*)$ at 0 is given by

$$
\begin{aligned}
f'(0) = -\big[&(\mu + \sigma)\big(\beta\hat{\beta}\mu^2\rho + \hat{\beta}r^2(\mu + \rho + \sigma)^2 - \beta\mu^2(\mu + \rho + \sigma)^3\\
&+ \hat{\beta}^2(\mu + \sigma)(\mu^3 + 2\mu^2(\rho + \sigma) - \beta\rho(\rho + \sigma) + \mu(-2\beta\rho + (\rho + \sigma)^2))\\
&+ r(\mu + \rho + \sigma)(\hat{\beta}^2(\mu + \rho)(\mu + \sigma) - \beta\mu^2(\mu + \rho + \sigma)\\
&+ \hat{\beta}^2(\mu^3 + 2\mu^2(\rho + \sigma) - \beta\rho(\rho + \sigma) + \mu(-2\beta\rho + (\rho + \sigma)^2))))\big]\\
&/\big[\beta\mu\rho(\mu + \rho + \sigma)^3\big].
\end{aligned}
$$

Now,

$$
\begin{aligned}
\frac{f'(0)}{(\mathscr{R}_H - 1)(\mathscr{R}_L - 1)} = \big[&(\mathscr{R}_H + r_C)\big(r\hat{\beta}(\mu + \rho)(\mu + \sigma)(\mu + \rho + \sigma)\\
&+ \hat{\beta}\mu(\mu + \sigma)(\mu + \rho + \sigma)^2 + \beta(\mu + \rho)(\hat{\beta}(\mu + \sigma)^2\\
&+ \mu\rho(\mu + \rho + \sigma))\big)\big]/\big[\beta\mu\rho(\mathscr{R}_H - 1)\big]
\end{aligned}
$$

Hence if both the reproduction numbers $\mathscr{R}_H$ and $\mathscr{R}_L$ are greater than 1, then $f'(0) > 0$. Thus, there exists an $\epsilon > 0$ such that $f(C^*) > 0$ if $0 < C^* < \epsilon$. By continuity of f, there exists $\hat{C} \in (\epsilon, x^*)$ such that $f(\hat{C}) = 0$. Hence, we can conclude that the model in (4.33) will always have an endemic equilibrium point whenever $\mathscr{R}_L > 1$. For the algebraic calculations, refer to the Wolfram Mathematica notebook available in our public GitHub repository, Section 6 of [171]. □

Lemma 4.6.5. *The region*

$$\bar{\mathbb{D}}_L := \{(S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{D} \mid S + C = x^*,\ H + I_{HP} = y^*\}, \tag{4.35}$$

is invariant with respect to the system (4.2) defined in the phase space $\mathbb{D}$ given by (4.4).

Proof. From the original co-infection system (4.2), adding the equations for S and C, we have

$$\begin{aligned}(S+C)' &= \mu - \hat{\beta}(S+C)(H+I_{HP}) - \mu(S+C)\\ &= \mu - \hat{\beta}x^*y^* - \mu x^*.\end{aligned}$$

From (4.28), we substitute the values of x^* and y^* to obtain

$$(S+C)' = \mu - \frac{\hat{\beta}}{\mathscr{R}_H}\frac{\mu}{\hat{\beta}}(\mathscr{R}_H - 1) - \frac{\mu}{\mathscr{R}_H} = 0.$$

Similarly, adding the equations for H and I_{HP}, we have

$$\begin{aligned}(H+I_{HP})' &= \hat{\beta}(S+C)(H+I_{HP}) - \rho(H+I_{HP}) + \sigma(L+I_{LC}) - \mu(H+I_{HP})\\ &= \hat{\beta}x^*y^* - \rho y^* + \sigma(1-x^*-y^*) - \mu y^*.\end{aligned}$$

Substituting the values of x^* and y^*, and simplifying, we have

$$(H+I_{HP})' = \frac{\mu+\sigma}{\mathscr{R}_H} - \frac{(\rho+\sigma+\mu)\mu}{\hat{\beta}} = (\mu+\sigma)\left(\frac{1}{\mathscr{R}_H} - \frac{1}{\mathscr{R}_H}\right) = 0.$$

Thus, we have shown that $\bar{\mathbb{D}}_L$ is invariant with respect to the original co-infection system defined in the phase space $\mathbb{D}$. However, the space $\bar{\mathbb{D}}_L$ is analogous to $\mathbb{D}_L$ where the limiting system (4.26) is defined. □

Theorem 4.6.6. *The equilibrium point $\mathcal{E}_H$ for the model system (4.2) is globally asymptotically stable if $\mathscr{R}_{CH} < 1$ and unstable if $\mathscr{R}_{CH} > 1$. In the latter case, a co-existing equilibrium $\mathcal{E}_{CH}$ exists.*

Proof. The global stability of the zero equilibrium in the limiting system (4.26) implies that the herpes equilibrium of the full system (4.2), $\mathcal{E}_H$, attracts the whole subspace $\mathbb{D}_L$ (since on $\mathbb{D}_L$ the two systems coincide). Since solutions of the original system converge to $\mathbb{D}_L$, the ω-limit set of any solution of the original system intersects the basin of attraction of the zero equilibrium of the limiting system,

hence by the theory of asymptotically autonomous systems (see Thieme [172]), the herpes equilibrium $\mathcal{E}_H$ is GAS in the original system (4.2), whenever zero is GAS in the limiting system (4.26), i.e. when $\mathscr{R}_L > 1$ (Theorem 4.6.3), equivalently $\mathscr{R}_{CH} > 1$ with respect to the system (4.2). Moreover, $\mathcal{E}_H$ is unstable if the zero is unstable in the limiting system (4.26), i.e. $\mathscr{R}_L < 1$ (Theorem 4.6.3), equivalently $\mathscr{R}_{CH} < 1$ with respect to the original co-infection system (4.2).

If $\mathscr{R}_{CH} > 1$, then $\mathscr{R}_L > 1$ as well (see Lemma 4.6.4), thus $\mathcal{E}_0$ in the limiting system is unstable (Theorem 4.6.2). Consequently, $\mathcal{E}_H$ is unstable in the invariant domain $\mathbb{D}_L$ for the original system, hence it is unstable in system (4.2). By Lemma 4.6.5, there exists an endemic equilibrium point in the limiting system (4.26), which is, since $\mathbb{D}_L$ is invariant, corresponds to a co-existing equilibrium point within $\mathbb{D}_L$ of the system (4.2). □

4.7 Persistence of both Diseases

In the previous sections, we proved that if $\mathscr{R}_H \leq 1$ and $\mathscr{R}_C \leq 1$, then both diseases die out (since $\mathcal{E}_S$ is globally asymptotically stable by Theorem 5.4). If $\mathscr{R}_H \leq 1$ and $\mathscr{R}_C > 1$, then herpes dies out but chlamydia persists in the population (since $\mathcal{E}_C$ is GAS by Theorem 5.4). Furthermore, Theorem 6.6 states that if $\mathscr{R}_H > 1$ and $\mathscr{R}_{CH} \leq 1$, then herpes persists but *Chlamydia* is eradicated (since $\mathcal{E}_H$ is GAS). Then the remaining case is $\mathscr{R}_H > 1$ and $\mathscr{R}_{CH} > 1$: then we know that the coexistence equilibrium exists, and below we will show that in this case, both diseases will remain in the population.

To prove our persistence results, we use some definitions and results from [174].

Definition 4.7.1. *Let X be a nonempty set and $\varrho : X \to \mathbb{R}_+$. A semiflow $\Phi : \mathbb{R}_+ \times X \to X$ is called uniformly weakly ϱ-persistent, if there exists some $\epsilon > 0$ such that*

$$\liminf_{t\to\infty} \varrho(\Phi(t,\chi)) > \epsilon \quad \textit{for all} \quad \chi \in X, \varrho(\chi) > 0.$$

Φ is called uniformly (strongly) ϱ-persistent if there exists some $\epsilon > 0$ such that

$$\liminf_{t\to\infty} \varrho(\Phi(t,\chi)) > \epsilon \quad \textit{for all} \quad \chi \in X, \varrho(\chi) > 0.$$

A set $M \subset X$ is called weakly ϱ-repelling if there is no $\chi \in X$ such that $\varrho(\chi) > 0$ and $\Phi(t,\chi) \to M$ as $t \to \infty$.

System (4.2) generates a continuous flow on the feasible state space $\mathbb{D}$.

Theorem 4.7.2. *If $\mathscr{R}_H > 1$ and $\mathscr{R}_{CH} > 1$, then both diseases as well as the susceptible population are uniformly persistent.*

Proof. (i) $S(t)$ is uniformly persistent.

We use the method of fluctuation to prove the persistence of $S(t)$ (see e.g. Appendix A of [174]). We denote by S_∞ the limit inferior of $S(t)(t \to \infty)$. Using the fluctuation lemma it follows that there exists a sequence $t_k \to \infty$ such that $S(t_k) \to S_\infty$ and $S'(t_k) \to 0$ as $k \to \infty$. We apply this for the equation for $S(t)$:

$$S'(t_k) + \big(\beta C(t_k) + \hat{\beta} H(t_k) + \beta I_{LC}(t_k) + \hat{\beta} I_{HP}(t_k) + \mu\big) S(t_k) = \mu + rC(t_k),$$

and using $0 \leq C(t_k), H(t_k), I_{LC}(t_k), I_{HP}(t_k) \leq 1$ we obtain

$$(2\beta + 2\hat{\beta} + \mu) S_\infty \geq \mu$$

$$\text{i.e.} \quad S_\infty \geq \frac{\mu}{2\beta + 2\hat{\beta} + \mu} > 0.$$

(ii) Chlamydia persistence.

For the sake of simplicity, for the state of the system, we use the notation $\chi = (S, C, H, I_{LC}, I_{HP}, L) \in \mathbb{D}$. Let $\varrho_c = C + I_{LC} + I_{HP}$ be our persistence function, and consider the corresponding extinction space, which is

$$\mathbb{D}_H = \{\chi \in \mathbb{D} : \varrho_c(\chi) = 0\} = \{(S, 0, H, 0, 0, L) \in \mathbb{R}^6_+ : S + H + L = 1\}.$$

Clearly $\mathbb{D}_H$ is invariant. Following [174, Chapter 8], we examine the set $\Omega := \cup_{\chi \in \mathbb{D}_H} \omega(\chi)$. On the extinction space, the system coincides with the HSV subsystem (4.8), with solutions converging to one the two equilibria, corresponding to $\mathcal{E}_S$ and $\mathcal{E}_H$. Thus, $\Omega = \{\mathcal{E}_S, \mathcal{E}_H\}$. We let $M_1 = \{\mathcal{E}_S\}$ and $M_2 = \{\mathcal{E}_H\}$. Then $\Omega \subset M_1 \cup M_2$ and $\{M_1, M_2\}$ acyclic and M_1 and M_2 are invariant, isolated, and compact. We have to show that M_1 and M_2 are both weakly repelling.

Let us suppose that M_1 is not weakly ϱ_c-repelling, i.e. there exists a solution such that

$$\lim_{t \to \infty} (S(t), C(t), H(t), I_{LC}(t), I_{HP}(t), L(t)) = \mathcal{E}_S = (1, 0, 0, 0, 0, 0)$$

and

$$\varrho_c(\chi) > 0.$$

Then either $C(0) > 0$, or $I_{LC}(0) > 0$, or $I_{HP}(0) > 0$. In the latter case, from the

I_{LC} equation we conclude $I_{LC}(t) > 0$ for $t > 0$. This implies, using the C equation, $C(t) > 0$ as well. In any case, we have $C(t) > 0$ for $t > 0$.

For any $\epsilon > 0$, for sufficiently large t, $S(t) > (1-\epsilon), H(t) < \epsilon, I_{LC}(t) < \epsilon, I_{HP}(t) < \epsilon$ and $L(t) < \epsilon$ hold and we can give the following estimation for $C'(t)$:

$$\begin{aligned} C'(t) &= C(t)(\beta S(t) - \hat{\beta} H(t) - \hat{\beta} I_{HP}(t) - r - \mu) + \beta S(t) I_{LC}(t) \\ &> C(t)(\beta - \beta\epsilon - \hat{\beta}\epsilon - \hat{\beta}\epsilon - r - \mu) + \beta(1-\epsilon)\epsilon. \end{aligned} \tag{4.36}$$

But $\mathscr{R}_C > 1$ means $\beta > r+\mu$, so if ϵ is small enough then $(\beta - \beta\epsilon - \hat{\beta}\epsilon - \hat{\beta}\epsilon - r - \mu) > 0$ contradicting $C(t) \to 0$. Using the previous argument, we can conclude that if $\varrho_c(\chi) > 0$, then the solution cannot converge to $(1,0,0,0,0,0)$, and M_1 is weakly ϱ_c-repelling. To show the repelling property of M_2, assume that there exists a solution such that

$$\begin{aligned} \lim_{t\to\infty} (S(t), C(t), H(t), I_{LC}(t), I_{HP}(t), L(t)) = \Bigg(& \frac{\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)}, 0, \\ & \frac{\mu}{\hat{\beta}}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right), 0, 0, \frac{\mu\sigma}{\hat{\beta}(\mu+\sigma)}\left(\frac{\hat{\beta}(\mu+\sigma)}{\mu(\mu+\rho+\sigma)} - 1\right)\Bigg) \end{aligned}$$

and $\varrho_c > 0$. The Jacobian corresponding to the equations C, I_{LC}, and I_{HP} of the system (4.2) calculated at the equilibrium M_2 is given by

$$J_{\mathcal{E}_H} = \begin{bmatrix} r - \frac{\hat{\beta}(\mu+\sigma)}{(\mu+\rho+\sigma)} - \frac{\beta\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)} & \frac{\beta\mu(\mu+\rho+\sigma)}{\hat{\beta}(\mu+\sigma)} & 0 \\ \beta\rho\left(\frac{-\mu}{\hat{\beta}(\mu+\sigma)} + \frac{1}{(\mu+\rho+\sigma)}\right) & r - \mu - \sigma + \beta\rho\left(\frac{-\mu}{\hat{\beta}(\mu+\sigma)} + \frac{1}{(\mu+\rho+\sigma)}\right) & \rho \\ \frac{(\beta+\hat{\beta})(\hat{\beta}(\mu+\sigma)-\mu(\mu+\rho+\sigma))}{\hat{\beta}(\mu+\rho+\sigma)} & \frac{-\beta\mu}{\hat{\beta}} + \sigma + \frac{\beta(\mu+\sigma)}{(\mu+\rho+\sigma)} & -\mu-\rho \end{bmatrix}.$$

The characteristic polynomial of the above Jacobian is of the form

$$P(\lambda^*) = -\lambda^{*3} + \alpha_1\lambda^{*2} + \alpha_2\lambda^* + \alpha_3,$$

where $\alpha_3 > 0$ for $\mathscr{R}_{CH} > 1$ (see the details of the algebraic calculations in the supplementary file, Section 7 of [171]). Thus, in this case we have $P(0) > 0$ and $\lim_{\lambda^*\to\infty} P(\lambda^*) = -\infty$, and there exists $\hat{\lambda} > 0$ such that $P(\hat{\lambda}) = 0$. Hence, we can conclude that there exists a positive eigenvalue, whenever $\mathscr{R}_{CH} > 1$. One can check that the matrix $J_{\mathcal{E}_H}$ is quasi-positive, and also irreducible, so there is a positive left eigenvector v of $J_{\mathcal{E}_H}$. Now choose this eigenvector to define our $\varrho_v = v_1 C + v_2 I_{LC} + v_3 I_{HP}$, with $v_1 > 0, v_2 > 0, v_3 > 0$ being the components of v. Clearly, if $\varrho_c > 0$ for some solution then $\varrho_v > 0$ as well. This way we have, with

the notation $\chi_v(t) = (C(t), I_{LC}(t), I_{HP}(t))$,

$$\begin{aligned}\frac{d}{dt}\varrho_v(\chi_v(t)) &= v^T\chi_v'(t) = v^T J_{\mathcal{E}_S}\chi_v(t) + o(\|\chi_v(t)\|^2)\\ &= v^T\hat{\lambda}\chi_v(t) + o(\|\chi_v(t)\|^2) = \hat{\lambda}\varrho_v(\chi_v(t)) + o(\|\chi_v(t)\|^2) > 0\end{aligned}$$

for small $\|\chi_v(t)\|$, which contradicts that the solution converges to $\mathcal{E}_H$ (since that implies $\chi_v(t) \to 0$ and $\varrho_v(t) \to 0$ as well).

We established the weak persistence of ϱ_c.

(iii) Herpes persistence. Consider now $\varrho_h(\chi) = H + I_{LC} + I_{HP} + L$. The corresponding extinction space is

$$\mathbb{D}_C = \{\chi \in \mathbb{D} : \varrho_w(\chi) = 0\} = \{(S, C, 0, 0, 0, 0) \in \mathbb{R}^6_+ : S + C = 1\}.$$

Clearly $\mathbb{D}_C$ is invariant. Substituting $S(t) = 1 - C(t)$, on the extinction space our system takes the form

$$C'(t) = \beta(1 - C(t))C(t) - rC(t) - \mu C(t).$$

The two equilibria for $\mathscr{R}_C > 1$ are 0 and $(\beta - r - \mu)/\beta$, corresponding to $\mathcal{E}_S$ and $\mathcal{E}_C$. Similarly as in case (ii), consider the set $\Omega := \cup_{\chi\in\mathbb{D}_C}\omega(\chi)$, which is in this case $\Omega = \{\mathcal{E}_S, \mathcal{E}_C\}$. We let $M_1 = \{\mathcal{E}_S\}$ and $M_2 = \{\mathcal{E}_C\}$. Then $\Omega \subset M_1 \cup M_2$ and $\{M_1, M_2\}$ acyclic and M_1 and M_2 are invariant, isolated, and compact. We have to show that M_1 and M_2 are both weakly repelling, with respect to ϱ_h.

First, we show the repelling property of M_1. Let us assume that

$$\lim_{t\to\infty}(S(t), C(t), H(t), I_{LC}(t), I_{HP}(t), L(t)) = (1, 0, 0, 0, 0, 0),$$

and $\varrho_h(\chi(t)) > 0$ for all t. Let J denote the Jacobian corresponding to the equations H, I_{LC}, I_{HP} and L of the system (4.2) calculated at $\mathcal{E}_S$ which is given by

$$J_{\mathcal{E}_S} = \begin{bmatrix}\hat{\beta} - \mu - \rho & 0 & \hat{\beta} & 0\\ 0 & -r - \mu - \sigma & \rho & 0\\ 0 & \sigma & -\mu - \rho & 0\\ \rho & r & 0 & -\mu - \sigma\end{bmatrix}.$$

The largest eigenvalue of the Jacobian $J_{\mathcal{E}_S}$ is given by

$$\lambda = \frac{1}{2}(\hat{\beta} - 2\mu - \rho - \sigma) + \sqrt{(\rho - \hat{\beta})^2 + 2\rho\sigma + 2\hat{\beta}\sigma + \sigma^2}.$$

We have $\lambda > 0$ for $\mathscr{R}_H > 1$. A left eigenvector corresponding to the eigenvalue λ is given by

$$w = \begin{bmatrix} 1 \\ \frac{1}{2\rho}\left(\rho - \hat{\beta} - \sigma + \sqrt{(\rho-\hat{\beta})^2 + 2\rho\sigma + 2\hat{\beta}\sigma + \sigma^2}\right) \\ 1 \\ \frac{1}{2\sigma}\left(\rho - \hat{\beta} - \sigma + \sqrt{(\rho-\hat{\beta})^2 + 2\rho\sigma + 2\hat{\beta}\sigma + \sigma^2}\right) \end{bmatrix} \in \mathbb{R}^4.$$

All the components of w are positive for $\mathscr{R}_H > 1$. Let us consider $\varrho_w(\chi) = w^T\chi_w$, where $\chi_w = (H, I_{LC}, I_{HP}, L)^T$.

Then $\varrho_w(\chi(t)) > 0$ for all t and $\varrho_w(\chi(t)) \to 0$ as $t \to \infty$. For sufficiently large t, we can make the following estimation for the derivative of $\varrho_w(\chi(t))$:

$$\begin{aligned} \frac{d}{dt}\varrho_w(\chi(t)) &= w^T\chi_w'(t) = w^T J_{\mathcal{E}_S}\chi_w(t) + o(\|\chi_w(t)\|^2) \\ &= w^T\lambda\chi_w(t) + o(\|\chi_w(t)\|^2) = \lambda\varrho_w(\chi(t)) + o(\|\chi_w(t)\|^2) > 0, \end{aligned}$$

whenever $\|\chi_w(t)\|$ is small enough. Hence, for large t, ϱ_w is increasing which is a contradiction to the assumption that $\varrho_w(\chi(t)) \to 0$ as $t \to \infty$.

Next, we suppose that M_2 is not weakly ϱ_h-repelling, i.e. there exists a solution such that

$$\lim_{t\to\infty}(S(t), C(t), H(t), I_{LC}(t), I_{HP}(t), L(t)) = \left(\frac{r+\mu}{\beta}, 1 - \frac{r+\mu}{\beta}, 0, 0, 0, 0\right).$$

and $\varrho_h(\chi) > 0$. With an analogous argument, we can calculate the Jacobian at $\mathcal{E}_C$ along with the positive eigenvalue and positive eigenvector z explicitly to construct a function ϱ_z analogously and prove that the assumption $\varrho_h(\chi(t)) \to 0$ as $t \to \infty$ leads to a contradiction. The calculations are omitted here but can be found in Section 7 of our public GitHub repository [171].

Thus, uniform weak persistence is shown for both persistence functions, ϱ_c, ϱ_h. Since the phase space $\mathbb{D}$ is compact, the existence of a compact global attractor follows. Consequently, all conditions of [174, Theorem 4.5] hold, and thus we obtain uniform strong persistence in both cases. Since the persistence functions were given as a sum of all infected individuals by chlamydia and by herpes, respectively, we proved that both diseases will remain in the population. □

4.8 Numerical Results

The system (4.2) is numerically simulated for various sets of parameters. The stability of the disease free equilibrium point $\mathcal{E}_S$ is shown in Figure 4.2, where both the reproduction numbers $\mathscr{R}_C$ and $\mathscr{R}_H$ are less than 1, and the parameter values are as follows:

$$\beta = 0.054, \hat{\beta} = 0.0086, \rho = 0.05, \sigma = 0.01, \mu = 0.0154, r = 0.145.$$

The reproduction number in this case is obtained as $\mathscr{R}_C = 0.05$ and $\mathscr{R}_H = 0.18$. Figure 4.3 illustrates the existence of an endemic equilibrium for the set of parameter values,

$$\beta = 0.34, \hat{\beta} = 0.11, \rho = 0.3, \sigma = 0.12, \mu = 0.0154, r = 0.145,$$

where all the state variables are positive, and all the reproduction numbers greater than 1 and are given as $\mathscr{R}_C = 2.14$, $\mathscr{R}_H = 2.22$ and $\mathscr{R}_{CH} = 2.08$.

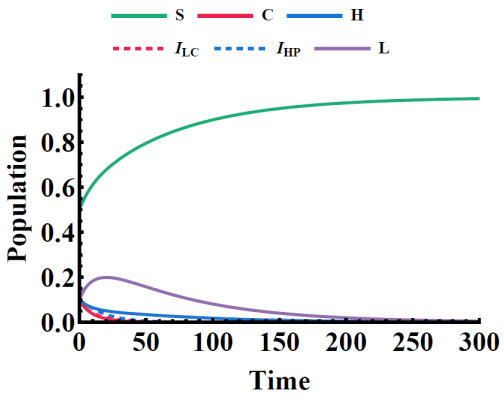


Figure 4.2: stability of $\mathcal{E}_S$ in the case where $\mathscr{R}_C < 1$, and $\mathscr{R}_H < 1$.

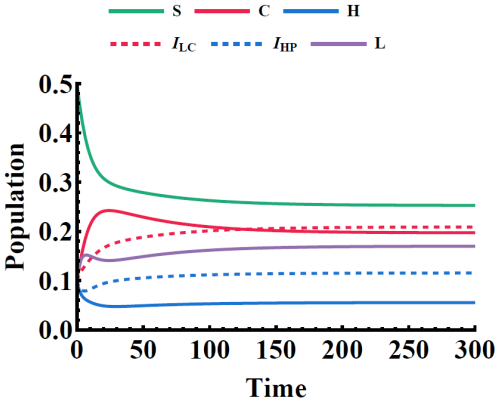


Figure 4.3: Existence of $\mathcal{E}_{CH}$ when $\mathscr{R}_C > 1$, $\mathscr{R}_H > 1$, and $\mathscr{R}_{CH} > 1$

Similarly, the stability of $\mathcal{E}_C$ is demonstrated in Figure 4.4 where $\mathscr{R}_C > 1$ and $\mathscr{R}_H < 1$. $\mathcal{E}_S$ exists but is unstable and the equilibrium points $\mathcal{E}_H$ and $\mathcal{E}_{CH}$ doesn't exist. The corresponding parameter values are as follows:

$$\beta = 0.34, \hat{\beta} = 0.01, \rho = 0.3, \sigma = 0.12, \mu = 0.0154, r = 0.145.$$

The reproduction numbers in this setting are obtained as $\mathscr{R}_C = 2.148$ and $\mathscr{R}_H = 0.2$. The stability of $\mathcal{E}_H$ is demonstrated in Figure 4.5 where the reproduction number $\mathscr{R}_H$ is greater than 1, but $\mathscr{R}_{CH}$ is less than 1. In this case, $\mathcal{E}_S$ and $\mathcal{E}_C$ exists but

are unstable, $\mathcal{E}_{CH}$ doesn't exists. The parameter values are as follows:

$$\beta = 0.163, \hat{\beta} = 0.11, \rho = 0.3, \sigma = 0.12, \mu = 0.0154, r = 0.145.$$

The reproduction numbers are obtained as $\mathcal{R}_C = 1.03$, $\mathcal{R}_H = 2.22$ and $\mathcal{R}_{CH} = 0.9$. It is to be noted that this situation is synonymous with $\mathcal{R}_C < 1$, as the presence of *Chlamydia*, doesn't affect the transmission of herpes in the population.

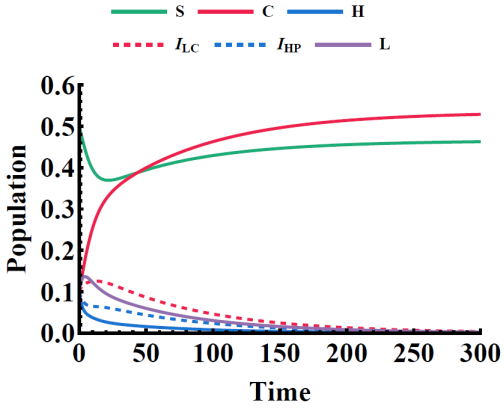


Figure 4.4: Stability of $\mathcal{E}_C$ in the case where $\mathcal{R}_C > 1$, and $\mathcal{R}_H < 1$.

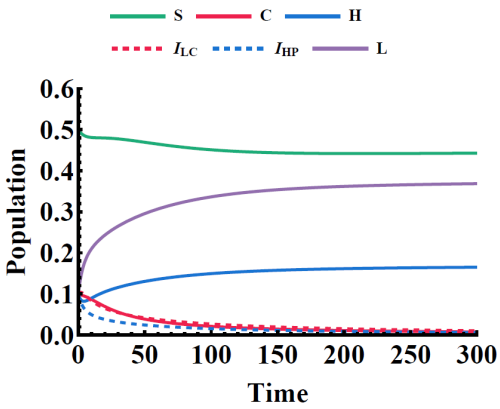


Figure 4.5: Stability of $\mathcal{E}_H$ in the case where $\mathcal{R}_H > 1$, and $\mathcal{R}_{CH} < 1$.

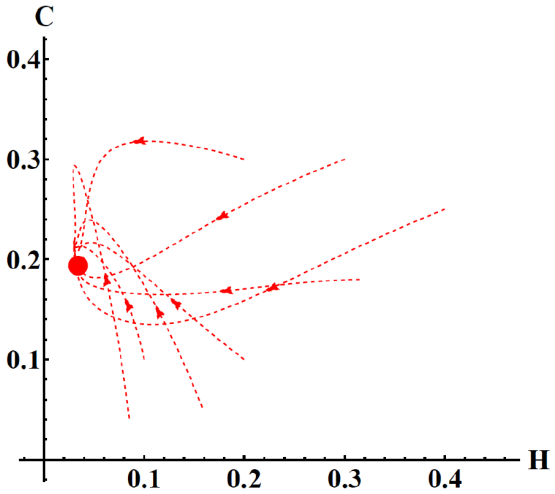


Figure 4.6: Figure illustrating existence of a co-infection equilibrium $\mathcal{E}_{CH}$ when $\mathcal{R}_C = 2.14861$, $\mathcal{R}_H = 1.9699$, and $\mathcal{R}_{CH} = 2.02736$. The figure is a projection of the solution curves on the $C - H$ plane and shows the convergence of solutions to the co-infection equilibrium starting from different initial points. Numerical values of the state variables at the equilibrium point are obtained to be $S = 0.399268, C = 0.193693, H = 0.0339702, I_{HP} = 0.0833719, I_{LC} = 0.0471582$, and $L = 0.0786341$. The numerical values of the eigenvalues are $-0.262134 + 0.i, -0.162314 + 0.i, -0.0732374 + 0.00898703i, -0.0732374 - 0.00898703i, -0.0157534 + 0.0188849i, -0.0157534 - 0.0188849i$. Clearly, all eigenvalues have negative real parts.

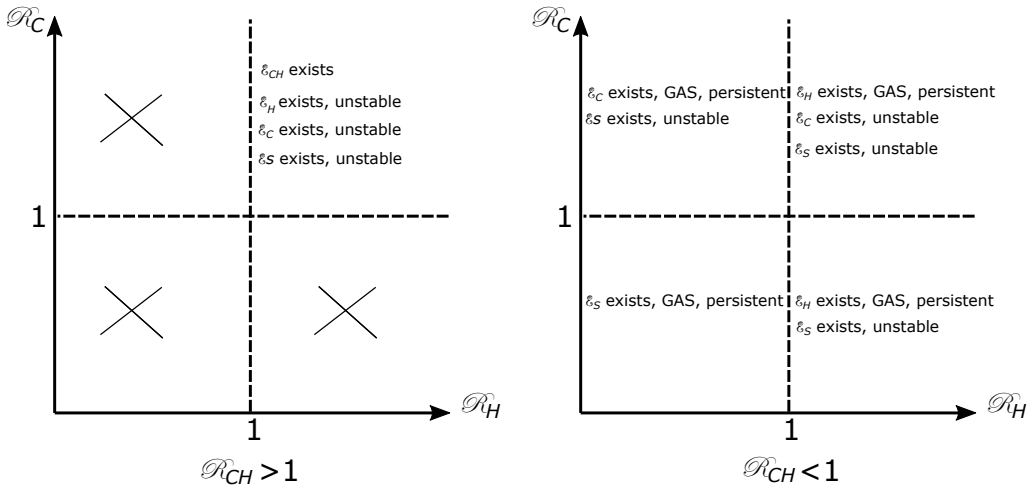


Figure 4.7: Existence and stability diagram of equilibrium points depending on $\mathscr{R}_C$, $\mathscr{R}_H$ and $\mathscr{R}_{CH}$. The global dynamics is fully described whenever $\mathscr{R}_{CH} < 1$. Cross-marks denote combinations of reproduction numbers that are not possible.

4.9 Parametrization and Prevalence Estimations

In the above simulations, the parameter values have been chosen so as to facilitate the realization of all possible scenarios as depicted in Figure 4.7, corresponding to the three reproduction numbers. A more exhaustive analysis was performed to obtain more robust parameters that have been also used in other similar studies. We would like to draw attention to the fact that for disease parameters related to *Chlamydia*, there are serious shortcomings and there are simply rough approximations. It is uncertain how likely it is to contract *C.trachomatis* in sexual contact. It is believed that though the transmission probabilities per contact are lower, the duration of infectiousness lasts longer than it does for other STDs such as gonorrhea [175]. Taking into account the large infrequency surrounding parameter values, several models have considered the impact of screening strategies in reducing *C.trachomatis* prevalence. A study based on a national survey carried out in the Netherlands estimated the transmission rate for *C.trachomatis* as depending on the type of connection, sexual contact frequency, and transmission likelihood per sexual contact [110]. However, a significantly varied pattern of the dynamics of sexual partnerships can result from differing presumptions about the individual's sexual behavior in different models. An SEIRS model used to analyze the effect of screening deduced the value of 'infection rate' β to be between 1.3 and 3.9 per person per year by adapting disease-specific parameters within the previously utilized range. Their data analysis indicated that the trend of infection is mainly represented by a natural clearance rate of 0.84 per year [121]. A

deterministic compartmental model constructed to qualitatively analyze the interrelationships between HIV and HSV-2 gives the range of baseline reactivation rate of latent HSV-2 to be 0.339 - 0.436, and the baseline rate of acute HSV-2 becoming latent as 2.083 - 2.678 [176]. With disease-specific parameter values obtained as above, we have $\rho = 2.083$, $\sigma = 0.436$, $r = 0.07$, and $\mu = 0.00128$ (the time unit is months). We then perform numerical simulations to adjust the transmission rates in our model, in order to obtain the same baseline reproduction number for both diseases. The base value for the reproduction number of HSV is calculated to be 1.79 [177], whereas it is estimated to be 1.07 for *C.trachomatis* [121]. With the disease-specific parameter values above, for these reproduction numbers, we obtain the transmission rates as $\beta = 0.0763$, and $\hat{\beta} = 0.0132$, moreover $\mathscr{R}_{CH} = 1.06$ follows.

	HSV present (22.661%)	HSV Absent
Active *Chlamydia*	10.629%	13.791%
Persistent *Chlamydia*	0.529%	0.161%
Total	11%	14%

Table 4.2: Frequency of *C.trachomatis* in the presence or absence of HSV

We estimated the disease prevalence obtained via the model simulation (Table 4.2) and, the results obtained had high correspondence with the disease prevalence in the incarcerated population [178]. The model simulation showed 22.621% HSV prevalence as compared to 22.4% obtained in the article, whereas the model predicted 10.103% prevalence for *C. trachomatis* against (1.02% - 6.7%) according to the paper. It is important to note that a relatively high percentage of *C. trachomatis* are asymptomatic in nature. It is observed that approximately 70% of infections with C. trachomatis run an asymptomatic course that remains undetected. The difference in the estimation for the *C. trachomatis* can be justified by this fact [179]. We also calculated the fraction of persistently *C. trachomatis* infected population in the presence of HSV and found it is around 5% of the *C. trachomatis* population. A study carried out to examine the use-efficacy of various drug therapies for preventing *C. trachomatis* persistence or recurrence infection in women recorded (9/165) cases of Persistent/Recurrent *C. trachomatis* cases which is approximately 5.455% [180]. The model predicts that when HSV is prevalent in the population, there is a slightly lower prevalence of *C. trachomatis* than it would be otherwise, but among the infected, a higher percentage of individuals have persistent *C. trachomatis* infection (0.529 %) compared to when HSV is absent (0.161%). With the given parameter values and the reproduction numbers, the second column of the disease prevalence table (Table 4.2) corresponds to the scenario depicted in the first quadrant of the bifurcation diagram

(4.7) with $\mathscr{R}_{CH} > 1$. This is the situation where both the disease are prevalent in the population, and there exists an endemic equilibrium. On the other hand, if the reproduction number of HSV is reduced below 1, then HSV is no longer prevalent, as depicted in the third column of the disease prevalence table (Table 4.2). The dynamics of the population is then shifted to the second quadrant of the bifurcation diagram (4.7). In this case, $\mathscr{R}_{CH} > 1$ is no longer accountable, and only *C. trachomatis* is prevalent in the population.

4.10 Discussion

In this Chapter, we have established and analyzed a six-compartment model describing *C. trachomatis*-HSV co-infection. The model introduced describes a novel approach to defining infection dynamics owing to the one-of-a-kind relationship between two cohabiting pathogens. The occurrence of co-infection has been observed to be more common, however the interrelationship between *C. trachomatis* and HSV gives us this unique opportunity to mathematically study a new dynamic model. We derive important threshold parameters that determine the conditions under which *C. trachomatis* can remain either active in the population or in a persistent phase in infected individuals.

The analysis of the *C. trachomatis* and HSV subsystems (when only one of the diseases is present) show that when the respective basic reproduction numbers are less than 1, then the disease free equilibrium points are globally asymptotically stable, and unstable when greater than 1. The endemic equilibrium points in both cases exist provided the reproduction numbers are greater than 1, and are globally asymptotically stable.

To understand the dynamics of the full co-infection system, when both pathogens are in circulation, we identify two new reproduction numbers, in addition to the *C. trachomatis* and HSV reproduction numbers calculated at the disease free equilibrium. These new threshold parameters determine whether a disease can invade a population where the other disease is already established. The reproduction number of HSV calculated at the *C. trachomatis*-endemic steady state is precisely the reproduction number calculated at the disease free equilibrium, indicating that the spread of HSV is not influenced by the presence of *C. trachomatis* in the system. On the other hand, the *C. trachomatis* reproduction number calculated at the HSV-endemic steady state is smaller than the basic reproduction number of *C. trachomatis* at the disease free equilibrium, meaning that for *chlamydia* it is more difficult to invade a population that has HSV.

”Persistence” in association with *Chlamydia* signifies a long term interrelation between the bacterium and their living host. Studies conducted in *in vitro* settings mostly constitute the current knowledge regarding *Chlamydia* persistence, and although such experiments have provided conclusive information, are accompanied by their own limitations. Substantial evidence has been obtained via animal experiments and epidemiological studies [181]. Experiments performed on mice to study *Chlamydia* quiescence have shown that immunosuppressive therapy can reactivate chronic *Chlamydia* infection, or can induce recurrence of unculturable chlamydial infections in mice [182–185]. Results from these studies demonstrated that persistent *Chlamydiae* were reactivated upon cortisone therapy that was administered after clearance of a culture-positive infection. Another study concluded that Persistent *Chlamydia*, also termed as aberrant RB were formed in *C. muridarum* infected mice after treatment with amoxicillin [186]. *In vitro* experiments have corroborated that penicillin or high interferon concentrations treatment of *Chlamydia* in culture inhibits binary fission and leads to the formation of abnormal RBs [19, 187, 188]. Persistent *Chlamydia* forms have also been closely associated with insensitivity towards antibiotics than normally developing organisms and are a significant cause of treatment failures. In this form, *Chlamydia* remains indiscernible by cell culture and may promote chronic *Chlamydia* infections in a sub-clinical manner [27]. Studies indicate that chronic *Chlamydial* infections due to persistence or recurrent infection are also linked with more hazardous health conditions [189]. It is yet unknown whether aberrant *Chlamydial* RBs exist *in vivo* and, if so, whether they contribute to persistent inflammation, fibrosis, and scarring. This is despite the fact that all persistence-inducing circumstances are capable of being there.

The divergence of *Chlamydia* from its normal growth is seemingly a stress-induced response and the presence of numerous diversified factors in actual cases of *Chlamydia* may further give rise to complications that can interrupt normal biological processes. In our current study, we have emphasized the appearance of abnormally growing *Chlamydiae* as a consequence of HSV-induced physiological trauma. We hypothesize that the process of persistent *Chlamydial* formation is reversed upon the HSV reneging its active form. Under the current setting, we have defined situations corresponding to disease parameters under which *Chlamydia* can either prevail in the population remain epidemiologically insignificant, or can co-exist with HSV.

We characterized the situation when the emergence of HSV can drive *Chlamydiae* into extinction in a population. The most interesting, and probably most realistic

case is when all reproduction numbers are greater than one and both pathogens remain in circulation. Then, it is an important public health issue to assess the impact of HSV on the overall disease burden caused by *Chlamydia* in the population, given that while the presence of HSV reduces *Chlamydia* transmission in the population, the composition of cases shifted towards a higher fraction of individuals having persistent *Chlamydia* infection.

It poses a fascinating case study, to compare and contrast the relative threats the two situations represent for public health. It remains to be factually concluded that the presence of active herpes can induce persistence in *Chlamydiae* in a natural infection. If evidence of such a phenomenon could be documented in *in vivo*, such discoveries could have profound implications in the epidemiological trend, along with significant influence in the medical treatment of *Chlamydiae* infection. Although conclusions obtained from animal studies are suggestive of the likely occurrence of *in vivo Chlamydia* persistence [186], there are many obscurities surrounding the characterization of persistence in human *Chlamydial* infection. Furthermore, there exists no conventional method for the detection of *Chlamydial* persistence and requires much more invasive sampling than in case of acute *Chlamydial* infection [190]. Active *Chlamydia* or reactivation of persistence *Chlamydia* while on one hand can facilitate transmission and/or aggravate infection, it might increase antibiotic vulnerability. It is nevertheless a key medical research question if patients with *Chlamydial* persistence experience worse outcomes than individuals who do not. This current study helped to shed light on some intriguing topics about the circumstances surrounding co-infection of *Chlamydia* and HSV, furthermore, it has elevated the significance of the central query pertaining to the potential effects of *chlamydial* persistence.

5 Optimal Control for Maturity-Structured Systems with an Application to *Chlamydia* Treatment

5.1 Introduction

Experimental studies have demonstrated that the role of Th1 CD4 T cell-mediated immune response is of primary importance in protective immunity, and is predominant in host defense against *Chlamydial* infection [191, 192]. Humoral immunity (anti-*Chlamydia* antibodies), although is able to neutralize infection in vitro, and plays a significant role in the secondary memory response, however, may not be substantial during initial infection [193]. The antibodies produced via humoral immunity help in the attachment blocking of the *Chlamydia* particles, but once the infection is established, the cell-mediated immune response becomes critical for the removal of *Chlamydia* [11]. Among the different cell types essential for immunity against *C. trachomatis*, the CD$4+$ and CD$8+$ T lymphocytes play a significant role, particularly through their secretion of interferon-γ (IFN-γ) [191]. IFN-γ has been known to restrict *Chlamydia* infection, and high levels of IFN-γ can completely inhibit intracellular replication of *Chlamydia* [194].

Currently, there is no vaccine available for *Chlamydia* yet. The development of an effective vaccine is considered of primary importance and has been much invested in by WHO. However, *Chlamydia* infection can be efficiently treated and cured with antibiotics if effectively diagnosed. The most common treatment regimen is a single 1g oral dose of azithromycin or 7 days of doxycycline [26]. The effects of these antimicrobial agents are purely bacteriostatic, meaning they can only inhibit the growth of bacteria [27].

While larger cost is a concern for single-dose therapy which is estimated to be four to twelve times more expensive than multi-dose therapy, the multi-dose regimen on the other hand is associated with non-compliance of drug therapy. As a result, there are significant trade-offs between public and private prevention programs'

use-effectiveness of various regimens, which depends on both efficacy and compliance [180]. Moreover, it has been suggested that antibiotic therapy may not be as effective for chronic conditions. The inhibitory effects of IFN-γ on bacterial development are mediated by the inducement of indoleamine 2,3-dioxygenase (IDO), an enzyme implicated in L-tryptophan metabolism. L-tryptophan is an essential amino acid required for the biosynthesis of proteins, which humans derive solely from food nourishment [195]. IDO-mediated tryptophan deprivation appears to be the main innate immunological mechanism limiting *C. trachomatis* development in human cells [196]. IDO stimulates the process of reducing the concentration of L-tryptophan intracellular pools, a mechanism that leads to the formation of persistent *Chlamydia* due to starvation of the necessary amino acids [40, 158]. The organism then transforms into an abnormal nondividing persistent form in response to limited cellular tryptophan concentrations [158], which can be extremely effectively reactivated, leading to the bacteria resuming its normal life cycle once the persistence-inducing stimulus is removed [188]. Recently, there has been an expanding attraction in research regarding therapeutically targeting the catalyzing agents such as IDO1, IDO2, and tryptophan-2,3-dioxygenase (TDO), that has been sparked by the association of imbalances in tryptophan metabolism with disorders including cancer and neurodegenerative disease [195]. The absence of regulatory mechanisms that maintain immunological homeostasis is directly connected with allergic diseases, unresolved infections, and inflammation [197]. *In vitro* experiments conducted to study the mechanism involved in the process of persistent *Chlamydia* formation due to IFN-γ and its reversal, have shown that the addition of 1-levo-methyl tryptophan (1-L-MT) (at times referred to as levo-1-methyl tryptophan (L-1MT)) can defer IFN-γ stimulated tryptophan depletion, causing hindrance to the production of persistent *Chlamydia*. They further concluded that L-1MT considerably increased doxycycline's effectiveness in eradicating persistent *C.trachomatis* forms [198]. Laboratory studies have shown that commercially produced L-1MT can adequately supply tryptophan, counterbalancing its deficit mediated by IDO. Additionally, they demonstrate that 1-L-MT can restore IDO's immunoregulatory actions [199]. These pieces of evidence are highly suggestive of the fact that a therapy that is a combination of tryptophan and antibiotic can promote a better and more successful treatment for persistent chronic *Chlamydia* infections.

We have developed a compartmental maturity structured in-host model for intracellular development of *Chlamydia* taking into account its interactions with the immune system based on an earlier model developed by Wilson et al. [11], at the same time extending the model from several points of view. The basic model

describing the intracellular development cycle of *Chlamydia* is constructed as follows. $C(t)$ denotes the concentration of extracellular *Chlamydia* EBs in the system; $I_1(t)$, the concentration of host cells infected with *Chlamydia* particles; $I_2(t)$, the concentration of infected cells with *Chlamydia* EBs transforming to RBs; $P(t)$, the concentration of cells infected with persistent *Chlamydia*; $A(t)$, the concentration of IFN-γ cells produced by the cell-mediated immune response (assumed to be produced at a rate proportional to the number of newly infected epithelial cells $I_1(t)$ [102]).

We denote by $\rho(r,t)$ the concentration of host cells at time t that entirely contain replicating RBs, at the stage of maturity $r \in [r_1, r_2]$ over the replicating phase. $i(r,t)$ denotes the concentration of host cells that contain RBs converting to EBs structured with respect to the maturity level r, where $r \in [r_2, r_3]$. The parameter r denotes an age parameter tracking the maturity of the infected cell through the process, which can be associated with the maturity of the *Chlamydia* development in its internal inclusion. For the sake of simplicity, we rescale the maturity structured compartments such that $r \in [0,1]$. For $r > 0$, $\rho(r,t)$ consists entirely of host cells that include replicating RBs, whereas $\rho(0,t)$ comprises host cells that consist entirely of EBs that have transformed into RBs and are at the initial stage of replication. For the i compartment, when $r > 0$, $i(r,t)$ consists entirely of host cells that contain RBs transforming back to EBs, whereas $i(0,t)$ comprises host cells that consist of RBs that are at the final stage of replication. The rates of transition, k_ρ, of replicating RBs, and k_i, of RBs converting to EBs, throughout the replicating phase are positive L^1-function of r. Let T_ρ be the duration of the replication, and T_i be the duration for transformation from RBs to EBs. Based on the known description of the lytic cycle, $T_\rho = 6$ hours and $T_i = 16$ hours. Then $\int_0^1 \frac{1}{k_\rho(s)} ds = 6$. Assuming that k_ρ is a constant function, it implies that $k_\rho = 1/6$. similarly, we have $\int_0^1 \frac{1}{k_i(s)} ds = 16$, which implies $k_i = 1/16$, when k_i is a constant function.

The development of a mathematical model to investigate the optimal control for persistent *Chlamydia* infection in the presence of cell-mediated immune response derives its motivation from an earlier model presented by Akinlotan et al. [8]. We apply Pontryagin's maximum principle to determine the conditions for the most effective control to minimize systemic costs of the treatments/drugs, simultaneously minimizing the concentrations of extracellular EBs, infected host cells, and persistently infected cells present at treatment cessation. For effective control of the disease and to ensure optimum clearance, a treatment/control measure that reduces the number of *Chlamydia* infected cells with IFN-γ-induced persistent within, and also limits the production of infectious EBs is advocated. Persistent *Chlamydia*

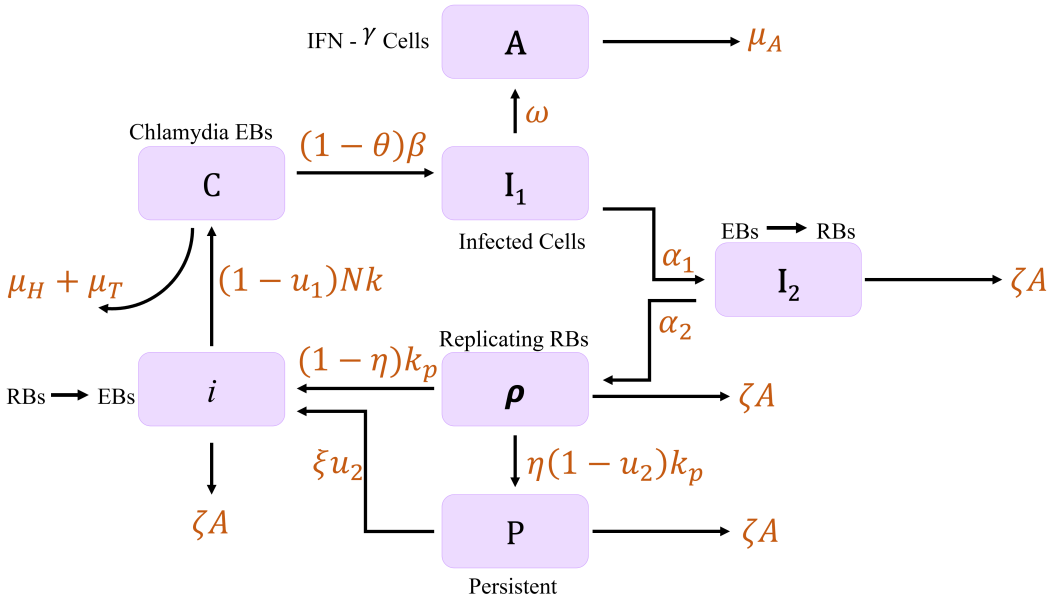


Figure 5.1: Schematic diagram for the *C. trachomatis* intracellular growth model with control.

can be reactivated with tryptophan replenishment which would further facilitate clearance by antimicrobial agents and the immune system. Levo-1-methyl tryptophan (L-1MT) supplement can inhibit the IFN-γ-induced persistent in *Chlamydia* whilst also reducing its resistance to antibiotic treatment, in addition, it also reduces the number of infectious EBs released upon the lysis of the infected cell.

The time-dependent control variable $u_1(t)$ is considered in order to reflect the effect of antibiotic treatment such as azithromycin and doxycycline. The bacteriostatic activity of antibodies inhibits the intracellular growth of *Chlamydia* by preventing their protein synthesis, consequently facilitating the reduction in the number of *Chlamydia* EBs produced at the end of the lytic cycle. $u_2(t)$ is a measure of the tryptophan-L-1MT concentration that prevents the formation of persistent *Chlamydia* formed due to IFN-γ cells and at the same time, aids in the persistent *Chlamydia* retaining its active form by reversing the process.

Using these definitions and assumptions, we construct the system of equations describing a maturity structure for *Chlamydia* with control, along with the boundary

Parameters	Descriptions	Values
N	Average number of EBs released upon bursting	$200 - 500$ [11]
β	Rate of attachment of *Chlamydia* particles into healthy epithelial cells	$2\,h^{-1}$ [11]
μ_H	Humoral immunity induced death rate of extracellular EBs	$0.08\,h^{-1}$ [11]
μ_T	Tryptophan-induced reduction in EB production	$0.04\,h^{-1}$ [8]
ω	Production rate of IFN-γ cells	$0.001\,h^{-1}$ [102]
μ_A	Natural death rate of IFN-γ cells	$0.1\,h^{-1}$ [102]
δ	Natural death rate of P	$0.1\,h^{-1}$
α_1	Rate of progression from I_1 to I_2	$0.125\,h^{-1}$ [11]
α_2	Rate of progression from I_2 to the beginning of ρ	$0.1\,h^{-1}$ [11]
η	Fraction of IFN-γ induced persistence	$0 \leqslant \eta \leqslant 1$
θ	Effect of attachment blocking due to humoral immune response	$0 \leqslant \theta \leqslant 1$
ζ	Rate of disintegration of *Chlamydia* infected cells by IFN-γ cell	$[0.05, 5]\,h^{-1}$ [102]
m_1	Maximum dosage of control $u_1(t)$	0.9 [8]
m_2	Maximum dosage of control $u_2(t)$	0.9 [8]
ξ	Rate at which Tryp. reverses persistence	$0.6\,h^{-1}$ [8]
T_ρ	Length of maturation of ρ	$10\,h$[11]
T_i	Length of maturation of i	$32\,h$[11]

Table 5.1: Parameters and their Descriptions

conditions as follows:

$$
\begin{aligned}
\dot{C}(t) &= (1-u_1(t))Nk_i(1)i(1,t) - \beta C(t) - \mu_C C(t),\\
\dot{A}(t) &= \omega I_1(t) - \mu_A A(t),\\
\dot{I}_1(t) &= (1-\theta)\beta C(t) - \alpha_1 I_1(t),\\
\dot{I}_2(t) &= \alpha_1 I_1(t) - \alpha_2 I_2(t) - \zeta A(t) I_2(t),\\
\rho(0,t) &= \alpha_2 I_2(t),\\
\frac{\partial \rho(r,t)}{\partial t} &= -\frac{\partial\left(k_\rho(r)\rho(r,t)\right)}{\partial r} - \zeta A(t)\rho(r,t),\\
\dot{P}(t) &= (1-u_2(t))\eta k_\rho(1)\rho(1,t) - \xi u_2(t)P(t) - \delta P(t),\\
i(0,t) &= (1-\eta)k_\rho(1)\rho(1,t) + \xi u_2(t)P(t),\\
\frac{\partial i(r,t)}{\partial t} &= -\frac{\partial\left(k_i(r)i(r,t)\right)}{\partial r} - \zeta A(t) i(r,t),
\end{aligned}
\tag{5A}
$$

where $r \in [0,1]$, $t \in [0,T]$. At the end of the maturity cycle, each infected cell releases N *Chlamydia* particles upon cell lysis. The death rate of the free extracellular *Chlamydia* particles is denoted by $\mu_C = \mu_H + \mu_T$, where μ_H denotes the action of the humoral immunity, and μ_T is the removal rate due to effect of the tryptophan-L-1MT cocktail. It is to be noted that $\mu_T > 0$ only if $u_2 > 0$, thereby facilitating the abatement of EB production upon lysis. The rate of production of IFN-γ cells ($A(t)$) is denoted by ω and μ_A denotes the rate at which they disintegrate.

The constant rates of progression through various stages of the development cycle are given by α_i's, $(i = 1, 2)$. The parameter $\theta \in [0, 1]$ indicates the effect of blocking *Chlamydia* attachment to the host cells due to antibodies, where $\theta = 1$ indicates complete blockage. The rate of clearance of infected cells due to cell-mediated immune response is denoted by ζ. The fraction of infected cells induced into persistence from $\rho(1)$ due to IFN-γ cells is indicated by $\eta \in [0, 1]$, whereas δ denotes their natural death rate. The rate of reversal of the persistent intracellular *Chlamydia* due to tryptophan supplement is denoted by ξ.

Initially, we assume that there is a small inoculum of EBs, of concentration $C_0 > 0$ introduced into the system at time $t = 0$. It is also assumed that there are no cells infected with *Chlamydia*. Hence, the initial conditions are

$$\begin{aligned} C(0) &= C_0, \\ A(0) &= 0, I_1(0) = I_2(0) = I_3(0) = P(0) = I_4(0) = 0, \\ \rho(r, 0) &= i(r, 0) = 0. \end{aligned} \tag{5B}$$

The results of the standard form of Pontryagin's maximal principle for ODEs are not suitable for the system we consider, hence in the following section, we construct an optimal control problem for a general maturity compartmental model.

5.2 Formulation of the Optimal Control Problem

Optimal control problem also referred to as dynamic optimization is a very efficient mathematical tool applied in a wide variety of natural and applied sciences. It has tremendous application in mathematical models of epidemic diseases, as such dynamical systems may involve elements or variables that can be externally controlled [200]. As such, the optimal control problem has been used to estimate optimal therapeutic intervention strategies for many epidemic models [201–204]. The theory for optimal control problems for age-structured systems finds its significance in its applicability in diverse fields of sciences such as harvesting [205], birth control of population [206], vaccination strategies [207], and in a wide range of investment economic and technology adoption models [208–210], COVID-19 [211]. More general age-structured models have been considered in [212–216], with applications in harvesting and population dynamics [214], capital accumulation and epidemics [215] etc. We consider a fairly general mixed system described by a continuous maturity structure.

Throughout this chapter, we assume that $T > 0$, $m, n, p \in \mathbb{N}$ are constants, and

U is a nonempty, compact subset of $\mathbb{R}^p$. Our aim is to minimize the function $J : L^1([0,T],U) \to \mathbb{R}$,

$$\begin{aligned} J(u) =& F\left(x(T), \int_0^1 W_F(r)y(r,T)dr, u(T)\right) \\ &+ \int_0^T G\left(t, x(t), \int_0^1 W_G(r,t)y(r,t)dr, u(t)\right) dt \end{aligned} \tag{5.1}$$

such that (x,y) is the (weak) solution of the system

$$\dot{x}(t) = f\left(t, x(t), \int_0^1 W_f(r,t)y(r,t)dr, y(1,t), u(t)\right), \tag{5.2}$$

$$y(0,t) = g\left(t, x(t), \int_0^1 W_g(r,t)y(r,t)dr, y(1,t), u(t)\right), \tag{5.3}$$

$$\frac{\partial y(r,t)}{\partial t} = -\frac{\partial (K(r)y(r,t))}{\partial r} + h\left(r,t,x(t), y(r,t), \int_0^1 W_h(s,r,t)y(s,t)ds, u(t)\right), \tag{5.4}$$

with initial condition

$$x(0) = x_0, \qquad x_0 \in \mathbb{R}^m \tag{5.5}$$

$$y(r,0) = y_0(r), \qquad y_0(r) \in \mathbb{R}^n, \quad 0 \le r \le 1. \tag{5.6}$$

Here, $x_i(t)$ denotes the number of individuals in the ith compartment which appear without maturity structure, $i = 1, \ldots, m$, $y_j(r,t)$ denotes the density of the population in the jth compartment with individuals at maturity $r \in [0,1]$ at time $t \in [0,T]$, $j = 1, \ldots, n$. The term $W_G(r,t)$ captures the time-varying importance or weight of cost associated with a particular variable or state $y(r,t)$ in this case. This time-dependent weighting allows one to model situations where certain aspects of the system become more or less important over time. We assume that the following hypotheses hold.

(H1) The weight functions are matrix-valued L^∞-functions, i.e.,

$$\begin{aligned} &W_F \in L^\infty([0,1], \mathbb{R}^{d_F \times n}), && W_G \in L^\infty([0,1]\times[0,T], \mathbb{R}^{d_G \times n}), \\ &W_f \in L^\infty([0,1]\times[0,T], \mathbb{R}^{d_f \times n}), && W_g \in L^\infty([0,1]\times[0,T], \mathbb{R}^{d_g \times n}), \\ &W_h \in L^\infty([0,1]^2\times[0,T], \mathbb{R}^{d_h \times n}), \end{aligned}$$

and the dimensions $d_F, d_G, d_f, d_g, d_h \in \mathbb{N}$ are fixed.

(H2) The functions

$$\begin{aligned}
F &: [0,\infty)^m \times \mathbb{R}^{d_F} \times U \to \mathbb{R},\\
G &: [0,T] \times [0,\infty)^m \times \mathbb{R}^{d_G} \times U \to \mathbb{R},\\
f &: [0,T] \times [0,\infty)^m \times \mathbb{R}^{d_f} \times [0,\infty)^n \times U \to \mathbb{R}^m,\\
g &: [0,T] \times [0,\infty)^m \times \mathbb{R}^{d_g} \times [0,\infty)^n \times U \to \mathbb{R}^n,\\
h &: [0,1] \times [0,T] \times [0,\infty)^m \times [0,\infty)^n \times \mathbb{R}^{d_h} \times U \to \mathbb{R}^n
\end{aligned}$$

are continuous, F and G continuously differentiable in their last three arguments, f, g, and h are continuously differentiable in their last four arguments.

(H3) The matrix-valued function K is diagonal with positive, bounded, continuous maturity rates on its diagonal, i.e.,

$$K = \mathsf{diag}(k_1, \dots k_n),$$

where $k_1, \dots, k_n \in C([0,1], [k_*, k^*])$, $0 < k_* \leq k^* < \infty$.

(H4) The initial values are

$$\begin{aligned}
x_0 &\in [0,\infty)^m,\\
y_0 &\in L^1([0,1], [0,\infty)^n).
\end{aligned}$$

The problem is formulated using L^1 spaces, but it can be modified to arbitrary L^q spaces for $q \in [1,\infty]$. Moreover, the systems introduced in [203, 213–216] can be considered as special cases of the system (5.1)–(5.6) introduced here.

There are several contributions to finding optimal control models in Banach spaces [217–220]. However, due to the complex nature of the model and the non-linearity of the boundary condition (5.3), the optimal control results obtained in the cited papers are not applicable.

In the following section, we prove the existence of a unique nonnegative solution of system (5.2)–(5.6) for a given control under further hypotheses. Section 5.4 contains the Pontryagin maximum principle for optimal control of the maturity structured model (5.1)–(5.6).

5.3 Existence and Uniqueness for a Given Control

In the sequel, the abbreviations

$$\begin{aligned}
\widetilde{F}(T) &= F\left(x(T), \int_0^1 W_F(r)y(r,T)dr, u(T)\right),\\
\widetilde{G}(t) &= G\left(t, x(t), \int_0^1 W_G(r,t)y(r,t)dr, u(t)\right),\\
\widetilde{f}(t) &= f\left(t, x(t), \int_0^1 W_f(r,t)y(r,t)dr, y(1,t), u(t)\right),\\
\widetilde{g}(t) &= g\left(t, x(t), \int_0^1 W_g(r,t)y(r,t)dr, y(1,t), u(t)\right),\\
\widetilde{h}(r,t) &= h\left(r, t, x(t), y(r,t), \int_0^1 W_h(s,r,t)y(s,t)ds, u(t)\right),
\end{aligned}$$

are used, for $r \in [0,1]$, $t \in [0,T]$.

We call $L^1([0,T],U)$ the set of admissible controls. The vector spaces $\mathbb{R}^l$, $l \in \mathbb{N}$ are endowed with the 1-norm defined by

$$|x|_1 = \sum_{i=1}^{l} |x_i|, \quad x \in \mathbb{R}^l.$$

The system (5.2)–(5.6) is considered on the phase space

$$X = \mathbb{R}^m \times L^1([0,1],\mathbb{R}^n)$$

with norm

$$\|(x,y)\|_X = |x|_1 + \|y\|_{L^1} = |x|_1 + \int_0^1 |y(r)|_1 dr = \sum_{i=1}^{m} |x_i| + \int_0^1 \sum_{j=1}^{n} |y_j(r)| dr.$$

The choice of the phase space X is natural as the norm defined above describes the total number of entities in the system. Next, we define the space containing the solutions of system (5.2)–(5.6) as

$$\begin{aligned}
W = \Big\{ &(x,y) \in L^1([0,T],X) : \ \dot{x} \in L^1([0,T],\mathbb{R}^m),\\
&\frac{\partial y}{\partial t} + \frac{\partial (Ky)}{\partial r} \in L^1([0,1]\times[0,T],\mathbb{R}^n) \Big\}.
\end{aligned}$$

Note that $L^1([0,T],X) \cong L^1([0,T],\mathbb{R}^m) \times L^1([0,1]\times[0,T],\mathbb{R}^n)$, and we write $y(t)(r) =$

$y(r,t)$ if $(x,y) \in L^1([0,T],X)$, $r \in [0,1]$, $t \in [0,T]$.

For a given control $u \in L^1([0,T],U)$, pair $(x,y) \in W$ is called a weak solution [213] of system (5.2)–(5.6) if and only if

$$\begin{aligned}
&\int_0^T \Bigg(\left\langle \dot{x}(t) - \widetilde{f}(t), \lambda(t) \right\rangle + \langle K(0)(y(0,t) - \widetilde{g}(t)), \mu(0,t) \rangle \\
&+ \int_0^1 \left\langle \frac{\partial y(r,t)}{\partial t} + \frac{\partial (K(r)y(r,t))}{\partial r} - \widetilde{h}(r,t), \mu(r,t) \right\rangle dr \Bigg) dt \\
&+ \langle x(0) - x_0, \lambda(0) \rangle + \int_0^1 \langle y(r,0) - y_0(r), \mu(r,0) \rangle \, dr \\
&= 0
\end{aligned} \tag{5.7}$$

for all $\lambda \in L^\infty([0,T],\mathbb{R}^m)$, $\mu \in L^\infty([0,1] \times [0,T],\mathbb{R}^n)$, where $\langle \cdot, \cdot \rangle$ denotes the euclidean inner product. In this paper, solutions are only considered in this weak sense, so we neglect the attributive "weak".

Proposition 5.3.1. *Assume that* (H1)–(H4) *holds and* $u \in L^1([0,T],U)$*. The system of equations* (5.2)–(5.6) *can be written as*

$$x(t) = x_0 + \int_0^t \widetilde{f}(\theta) d\theta, \tag{5.8}$$

$$y_j(r,t) = \frac{k_j(0)}{k_j(r)} \widetilde{g}_j \left(t - \int_0^1 \frac{1}{k_j(s)} ds \right) + \frac{1}{k_j(r)} \int_0^1 \widetilde{h}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds, \tag{5.9}$$

if $t - \int_0^1 \frac{1}{k_j(s)} ds \geq 0$*, and*

$$y_j(r,t) = \frac{k_j(\widetilde{r}_j(r,t))}{k_j(r)} y_0\left(\widetilde{r}_j(r,t)\right) + \frac{1}{k_j(r)} \int_{\widetilde{r}_j(r,t)}^r \widetilde{h}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds \tag{5.10}$$

where

$$t - \int_{\widetilde{r}_j(r,t)}^r \frac{1}{k_j(s)} ds = 0, \tag{5.11}$$

if $t - \int_0^1 \frac{1}{k_j(s)} ds < 0$*,* $r \in [0,1]$*,* $t \in [0,T]$*,* $j = 1, \ldots, n$*. If a pair of functions* $(x,y) \in L^1([0,T],X)$ *satisfy* (5.8)–(5.11) *then it is a solution of system* (5.2)–(5.6)*.*

Proof. (5.8) follows from a simple integration. (5.4) can be written coordinatewise as

$$\frac{\partial y_j(r,t)}{\partial t} = -\frac{\partial (k_j(r)\, y_j(r,t))}{\partial r} + \widetilde{h}_j(r,t), \quad j = 1, \ldots, n. \tag{5.12}$$

As $k_j(r) > 0$ for all $r \in [0,1]$, (5.12) can be transformed to

$$\frac{1}{k_j(r)}\frac{\partial y_j(r,t)}{\partial t} + \frac{\partial y_j(r,t)}{\partial r} = -k_j'(r)\frac{y_j(r,t)}{k_j(r)} + \frac{\widetilde{h}_j(r,t)}{k_j(r)}. \tag{5.13}$$

We apply the method of characteristics, our aim is to find a curve parametrized by $t = t_j(r)$ where (5.13) can be reduced to the following system of ordinary differential equations.

$$\begin{cases} \dfrac{dt(r)}{dr} = \dfrac{1}{k_j(r)}, \\ \dfrac{d}{dr}y_j(r,t(r)) = -k_j'(r)\dfrac{y_j(r,t(r))}{k_j(r)} + \dfrac{\widetilde{h}_j(r,t(r))}{k_j(r)}. \end{cases}$$

Integrating these equations from some $r_0 \in [0,r)$ to r, we get

$$t = t(r_0) + \int_{r_0}^{r} \frac{1}{k_j(s)} ds \tag{5.14}$$

and

$$y_j(r,t(r)) = \frac{k_j(r_0)}{k_j(r)} y_j(r_0,t(r_0)) + \frac{1}{k_j(r)} \int_{r_0}^{r} \widetilde{h}_j(s,t(s))\, ds \tag{5.15}$$

Expressing $t(r_0)$ from (5.14) and substituting it into (5.15), we obtain

$$\begin{aligned} y_j(r,t) = {} & \frac{k_j(r_0)}{k_j(r)} y_j\left(r_0, t - \int_{r_0}^{r} \frac{1}{k_j(s)} ds\right) \\ & + \frac{1}{k_j(r)} \int_{r_0}^{r} \widetilde{h}_j\left(s, t - \int_{s}^{r} \frac{1}{k_j(\sigma)} d\sigma\right) ds. \end{aligned}$$

There are two cases depending on the sign of $t_0 = t - \int_0^1 \frac{1}{k_j(s)} ds$:

- If $t_0 \geq 0$ then

$$\begin{aligned} y_j(r,t) = {} & \frac{k_j(0)}{k_j(r)} y_j\left(0, t - \int_{0}^{1} \frac{1}{k_j(s)} ds\right) \\ & + \frac{1}{k_j(r)} \int_{0}^{1} \widetilde{h}_j\left(s, t - \int_{s}^{r} \frac{1}{k_j(\sigma)} d\sigma\right) ds. \end{aligned}$$

  Using equation (5.3), this can be written as

$$y_j(r,t) = \frac{k_j(0)}{k_j(r)} g\left(t - \int_{0}^{1} \frac{1}{k_j(s)} ds\right) + \frac{1}{k_j(r)} \int_{0}^{1} \widetilde{h}_j\left(s, t - \int_{s}^{r} \frac{1}{k_j(\sigma)} d\sigma\right) ds.$$

- If $t_0 < 0$ then let $\widetilde{r}_j(r,t) \in [0,r)$ be the unique solution of (5.11), and we have

$$y_j(r,t) = \frac{k_j(\widetilde{r}_j(r,t))}{k_j(r)} y_0\left(\widetilde{r}_j(r,t)\right) + \frac{1}{k_j(r)} \int_{\widetilde{r}_j(r,t)}^{r} \widetilde{h}_j\left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma\right) ds.$$

Summarizing these cases, we obtain (5.9)–(5.11). By a straightforward calculation, one can see that a solution (x,y) of (5.8)–(5.11) is in W and satisfies (5.7) as well. Hence, the proof is complete. □

Proposition 5.3.2. *Assume that* (H1)–(H4) *hold,* (x,y) *is a solution of system* (5.2)–(5.6) *for some* $u \in L^1([0,T],U)$ *and the following hypothesis holds as well.*

(H5) *There exist integrable functions*

$$a_i : [0,T] \times \mathbb{R}^m \times \mathbb{R}^{d_f} \times \mathbb{R}^n \times U \to [0,\infty),$$
$$b_j : [0,1] \times [0,T] \times \mathbb{R}^m \times \mathbb{R}^n \times \mathbb{R}^{d_h} \times U \to [0,\infty)$$

such that

$$\widetilde{f}_i(t,x,z,y,u) \geq -a_i(t,x,z,y,u)x_i,$$
$$\widetilde{g}_j(t,x,z,y,u) \geq 0,$$
$$\widetilde{h}_j(r,t,x,y,z,u) \geq -b_j(r,t,x,y,z,u)y_j$$

hold for all $x \in [0,\infty)^m$, $y \in [0,\infty)^n$, $z \in \mathbb{R}$, $r \in [0,1]$, $t \in [0,T]$, $i = 1,\ldots,m$, $j = 1,\ldots,n$.

Then the solution is nonnegative, i.e. $x_i(t) \geq 0$ *and* $y_j(r,t) \geq 0$ *for all* $r \in [0,1]$, $t \in [0,T]$, $i = 1,\ldots,m$, $j = 1,\ldots n$.

Proof. By Proposition 5.3.1 and (H5),

$$x_i(t) \geq (x_0)_i - \int_0^t \widetilde{a}_i(\theta) x_i(\theta) d\theta,$$

for $t \in [0,T]$, $i = 1,\ldots,m$, where

$$\widetilde{a}_i(t) = a_i\left(t, x(t), \int_0^1 W_f(r,t) y(r,t) dr, y(1,t), u(t)\right).$$

Applying Grönwall's inequality we conclude

$$x_i(t) \geq (x_0)_i \exp\left(-\int_0^t \widetilde{a}_i(\theta) d\theta\right) \geq 0, \quad t \in [0,T].$$

A similar argument applies for y along the characteristic curves. In the case when $t - \int_0^1 \frac{1}{k_j(s)} ds \geq 0$, we have

$$\begin{aligned} y_j(r,t) &\geq \frac{k_j(0)}{k_j(r)} \widetilde{g}_j(t_0) - \frac{1}{k_j(r)} \int_0^1 \widetilde{b}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) y_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds \\ &\geq \frac{k_j(0)}{k^*} \widetilde{g}_j(t_0) - \frac{1}{k_*} \int_0^1 \widetilde{b}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) y_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds \end{aligned}$$

for $r \in [0,1]$, $t \in [0,T]$, $j = 1, \dots n$, where

$$\widetilde{b}_j(r,t) = b_j \left(r, t, x(t), y(r,t), \int_0^1 W_h(s,r,t) y(s,t) ds, u(t) \right).$$

By Grönwall's inequality,

$$y_j(r,t) \geq \frac{k_j(0)}{k^*} \widetilde{g}_j(t_0) \exp \left(-\frac{1}{k_*} \int_0^1 \widetilde{b}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds \right) \geq 0.$$

In the other case, when $t - \int_0^1 \frac{1}{k_j(s)} ds < 0$, we obtain

$$\begin{aligned} y_j(r,t) \geq & \frac{k_j(\widetilde{r}_j(r,t))}{k^*} y_0 \left(\widetilde{r}_j(r,t) \right) \\ & - \frac{1}{k_*} \int_{\widetilde{r}_j(r,t)}^r \widetilde{b}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) y_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds, \end{aligned}$$

and analogously,

$$y_j(r,t) \geq \frac{k_j(0)}{k^*} y_0(\widetilde{r}_j(r,t)) \exp \left(-\frac{1}{k_*} \int_{\widetilde{r}_j(r,t)}^r \widetilde{b}_j \left(s, t - \int_s^r \frac{1}{k_j(\sigma)} d\sigma \right) ds \right) \geq 0$$

for $r \in [0,1]$, $t \in [0,T]$. □

Proposition 5.3.3. *If (H3) holds, the function $\widetilde{r}_j$ defined by* (5.11) *for $r \in [0,1]$, $t \in [0,t]$, $t - \int_0^1 \frac{1}{k_j(s)} ds < 0$ is continuously differentiable with*

$$\frac{\partial \widetilde{r}_j(r,t)}{\partial r} = \frac{k_j(\widetilde{r}_j(r,t))}{k_j(r)} \in \left[\frac{k_*}{k^*}, \frac{k^*}{k_*} \right], \qquad \frac{\partial \widetilde{r}_j(r,t)}{\partial t} = -k_j(\widetilde{r}_j(r,t)) \in [-k^*, -k_*]. \tag{5.16}$$

Proof. By the implicit function theorem, differentiating (5.11), we obtain

$$-\frac{1}{k_j(r)} + \frac{1}{k_j(\widetilde{r}_j(r,t))} \frac{\partial \widetilde{r}_j(r,t)}{\partial r} = 0, \qquad 1 + \frac{1}{k_j(\widetilde{r}_j(r,t))} \frac{\partial \widetilde{r}_j(r,t)}{\partial t} = 0,$$

implying the statement. □

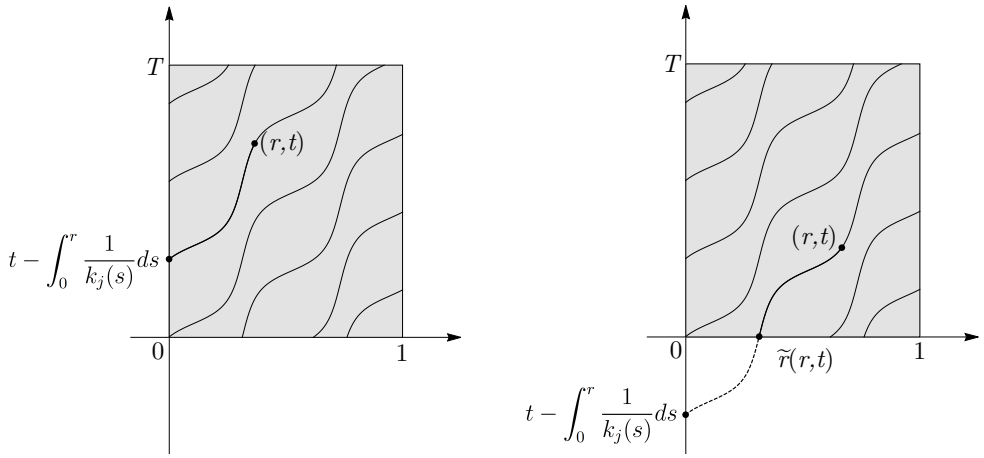


Figure 5.2: The two cases in the definition of y_j and the characteristic curves if $k_j(r) = 1.25 + \sin(5r)$, $r \in [0,1]$, $1 = 3$, $T = 3.5$.

Proposition 5.3.4. *Assume that* (H1)–(H5) *and the following hypothesis hold.*

(H6) g *is linearly bounded with its second, third, and fourth arguments, i.e. there exists* $L \geq 0$ *such that*

$$|g(t,x,z,y,u)|_1 \leq L(|x|_1 + |z|_1 + |y|_1)$$

for all $t \in [0,T]$, $x \in \mathbb{R}^m$, $y \in \mathbb{R}^n$, $z \in \mathbb{R}^{d_g}$, $u \in U$.

(H7) h *is nonpositive, i.e.* $h_j(r,t,x,y,z,u) \leq 0$ *for all* $r \in [0,1]$, $t \in [0,T]$, $x \in \mathbb{R}^m$, $y \in \mathbb{R}^n$, $z \in \mathbb{R}^{d_h}$, $u \in U$, $j = 1,\ldots,n$.

(H8) *There exist nonnegative constants* a *and* b, *such that if* (x,y) *is a solution of system* (5.2)–(5.6) *for some* $u \in L^1([0,T],U)$ *then*

$$\frac{d}{dt}\|(x(t),y(\cdot,t))\|_X \leq a\|(x(t),y(\cdot,t))\|_X + b|y(1,t)|_1$$

Then there exist positive constants B_1, B_2, B_3, B_4 *such that a solution* (x,y) *is bounded by*

$$\|(x(t),y(\cdot,t))\|_X \leq B_1\|(x_0,y_0)\|_X e^{B_2 t} \quad \textit{and} \tag{5.17}$$

$$\int_0^t |y(1,\theta)|d\theta \leq B_3 \int_0^t \|(x(\theta),y(\cdot,\theta))\|_X d\theta + B_4\|y_0\|_{L^1}, \tag{5.18}$$

for $t \in [0,T]$.

Proof. By Proposition 5.3.2, the solution is nonnegative, we can neglect the absolute value signs during the calculations. For $t \in [0, 1/k^*]$, the characteristic curve through $(1, t)$ crosses $[0, 1] \times \{0\}$, then, by (5.9), (5.16), and (H7),

$$\begin{aligned}
\int_0^t |y(1,\theta)|_1 d\theta &= \int_0^t \sum_{j=1}^n y_j(1,\theta) d\theta \\
&\leq \frac{k^*}{k_*} \int_0^t \sum_{j=1}^n (y_0)_j(\widetilde{r}_j(1,\theta)) d\theta \\
&\leq \frac{k^*}{k_*^2} \int_0^1 \sum_{j=1}^n (y_0)_j(r) dr \\
&= \frac{k^*}{k_*^2} \int_0^1 |y_0(r)|_1 \, dr \\
&\leq \frac{k^*}{k_*^2} \|y_0\|_{L^1}.
\end{aligned}$$

(H6) implies that there exists a $\widetilde{L}$ such that

$$\widetilde{g}(t) \leq \widetilde{L} \left(\|(x(t), y(\cdot, t))\|_X + |y(1,t)|_1 \right)$$

For $N \in \mathbb{N}$, $t \in [NR/k^*, (N+1)1/k^*]$, the characteristic curve through $(1, t)$ does not cross $\{0\} \times [NR/k^*, (N+1)1/k^*]$, then

$$\begin{aligned}
\int_0^t |y(1,\theta)|_1 d\theta &\leq \frac{k^*}{k_*} \int_0^{N\frac{1}{k^*}} |\widetilde{g}(\theta)|_1 \, d\theta + \frac{k^*}{k_*^2} \int_0^1 |y_0(r)|_1 \, dr \\
&\leq \frac{k^*}{k_*} \widetilde{L} \int_0^{N\frac{1}{k^*}} \left(\|(x(\theta), y(\cdot, \theta))\|_X + |y(1,\theta)|_1 \right) d\theta + \frac{k^*}{k_*^2} \|y_0\|_{L^1}.
\end{aligned}$$

By recursion,

$$\begin{aligned}
\int_0^t |y(1,\theta)|_1 d\theta &\leq \sum_{M=1}^N \left(\frac{k^*}{k_*} \widetilde{L} \right)^M \int_0^{M\frac{1}{k^*}} \|(x(\theta), y(\cdot, \theta))\|_X d\theta \\
&\quad + \sum_{M=1}^N \left(\frac{k^*}{k_*} \widetilde{L} \right)^M \frac{k^*}{k_*^2} \|y_0\|_{L^1} \\
&\leq B_3 \int_0^t \|(x(\theta), y(\cdot, \theta))\|_X d\theta + B_4 \|y_0\|_{L^1}
\end{aligned}$$

for some positive constants B_3, B_4. Hence, by (H8),

$$\|(x(t), y(\cdot, t))\|_X \leq \|(x_0, y_0)\|_X + \int_0^t \left(a \|(x(\theta), y(\cdot, \theta))\|_X + b|y(1,\theta)|_1 + c \right) d\theta$$

$$\leq B_1\|(x_0,y_0)\|_X + B_2\int_0^t \|(x(\theta),y(\cdot,\theta))\|_X d\theta$$

for some positive constants B_1, B_2. Applying Grönwall's inequality, we conclude the statement. □

Theorem 5.3.5. *Assume that the hypotheses (H1)–(H5), (H7), (H8) and the following ones hold.*

(H6') g *is linear, i.e. there exist bounded functions* $\alpha : [0,T]\times U \to \mathbb{R}^{n\times m}$, $\beta : [0,T]\times U \to \mathbb{R}^{n\times d_g}$, $\gamma : [0,T]\times U \to \mathbb{R}^{n\times n}$ *such that*

$$g\left(t,x,\int_0^1 W_g(r,t),y(r)dr,y(1),u\right) = \alpha(t,u)x + \beta(t,u)\int_0^1 W_g(r,t)y(r)dr + \gamma(t,u)y(1)$$

for all $t\in[0,T]$, $u\in U$, $(x,y)\in X$.

(H9) $f(t,0,0,0,u)=0$, $h(r,t,0,0,0,u)=0$ *for all* $r\in[0,1]$, $t\in[0,T]$, $u\in U$.

Then for a fixed control $u\in L^1([0,T],U)$, *there exists a nonnegative, unique solution* (x,y) *for system* (5.2)–(5.6).

Proof. Fix $u\in L^1([0,T],U)$, and define

$$A(t): D(A(t))\to X,\quad (A(t)(x,y))_1 = 0,\quad (A(t)(x,y))_2(r) = -\frac{\partial(K(r)y(r,t))}{\partial r}$$

with domain

$$D(A(t)) = \left\{(x,y)\in X,\ y(0) = \alpha(t,u)x + \beta(t,u)\int_0^1 W_g(r,t)y(r)dr + \gamma(t,u)y(1)\right\},$$

$$\varphi : [0,T]\times X\to X,\quad \varphi(t,z)_1 = \widetilde{f}(t),\quad \varphi(t,z)(r)_2 = \widetilde{h}(r,t)$$

Then, denoting $z(t) = (x(t), y(\cdot,t))$, $z_0 = (x_0,y_0)$ we can write system (5.2)–(5.6) in the following inhomogeneous abstract equation

$$\dot{z}(t) = A(t)z(t) + \varphi(t,z) \tag{5.19}$$

with initial value

$$z(0) = z_0. \tag{5.20}$$

In order to prove the existence and uniqueness of the solution of system (5.19)–

(5.20), we consider the homogeneous equation

$$\dot{z}(t) = A(t)z(t) \tag{5.21}$$

with initial condition (5.20). Using the original notation, this system can be written as

$$\dot{x}(t) = 0 \tag{5.22}$$

$$\frac{\partial y(r,t)}{\partial t} = -\frac{\partial (K(r)y(r,t))}{\partial r} \tag{5.23}$$

with (5.5)–(5.6). The solution of this system has x-component $x(t) = x_0$, $t \in [0,T]$. For finding the y-component, we consider the Banach space

$$Y = \{y \in L^1([0,T_1],\mathbb{R}^n), y(\cdot,0) = y_0\}$$

with L^1-norm, where $T_1 \in (0, \max\{T, 1/k^*\})$ is a constant to be determined later.

Let $P : Y \to Y$, $P(y) = \widetilde{y}$, where

$$\widetilde{y}_j(r,t) = \frac{k_j(0)}{k_j(r)} \overline{g}_j \left(t - \int_0^1 \frac{1}{k_j(s)} ds \right)$$

if $t - \int_0^1 \frac{1}{k_j(s)} ds \geq 0$,

$$\widetilde{y}_j(r,t) = \frac{k_j(\widetilde{r}_j(r,t))}{k_j(r)} y_0\left(\widetilde{r}_j(r,t)\right)$$

where $\widetilde{r}_j(r,t)$ is defined by (5.11) if $t - \int_0^1 \frac{1}{k_j(s)} ds < 0$, $r \in [0,1]$, $t \in [0,T]$, $j = 1,\ldots,n$.
Furthermore

$$\overline{g}_j \left(t - \int_0^1 \frac{1}{k_j(s)} ds \right) = g\left(t, x(t), \int_0^1 W_g(r,t) y(r,t) dr, \overline{y}(t), u(t) \right),$$

where

$$\overline{y}(t) = \frac{k_j(\widetilde{r}_j(1,t))}{k_j(1)} y_0\left(\widetilde{r}_j(1,t)\right).$$

Since

$$\left\| \widetilde{y}^1 - \widetilde{y}^2 \right\|_{L^1} = \int_0^{T_1} \sum_{j=1}^{n} \int_0^1 \left| \widetilde{y}_j^1(r,t) - \widetilde{y}_j^2(r,t) \right| dr\, dt$$

$$
\begin{aligned}
&= \int_0^{T_1} \sum_{j=1}^{n} \int_0^1 \frac{k_j(0)}{k_j(r)} \left| \overline{g}_j^1 \left(t - \int_0^1 \frac{1}{k_j(s)} ds \right) - \overline{g}_j^2 \left(t - \int_0^1 \frac{1}{k_j(s)} ds \right) \right|_1 dr\, dt \\
&\leq \frac{k^*}{k_*^2} \int_0^{T_1} \sum_{j=1}^{n} \int_0^t \left| \overline{g}_j^1(\theta) - \overline{g}_j^2(\theta) \right|_1 d\theta\, dt \\
&= \frac{k^*}{k_*^2} \int_0^{T_1} \int_0^t \left| \overline{g}_j(\theta) - \overline{g}_j(\theta) \right|_1 d\theta\, dt \\
&\leq C \int_0^{T_1} \int_0^t \left\| y^1(\cdot, \theta) - y^2(\cdot, \theta) \right\|_{L^1} d\theta\, dt \\
&\leq C \frac{T_1^2}{2} \left\| y^1 - y^2 \right\|_{L^1}
\end{aligned}
$$

for some positive constant C, P is a strict contraction if we choose $T_1 \in (0, \sqrt{2/C})$. Then by the Banach Fixed Point Theorem, it has a unique fixed point, that is the unique solution of system (5.22), (5.23), (5.5), (5.6), and $z = (x, y)$ is the unique solution of system (5.21),(5.20). Using method of steps with step length T_1, the solution can be extended uniquely to $[0, T]$, that is, system (5.21), (5.20) is well-posed.

Define the constant

$$D = B_1 \|(x_0, y_0)\|_X e^{B_2 T}$$

and the set

$$V = \{(x, y) \in L^1([0, T], X) : \|(x(t), y(t))\|_X \leq D,\ t \in [0, T]\}.$$

Since (H6') implies (H6), by Proposition 5.3.4, the possible solutions $z = (x, y)$ of system (5.19), (5.20) have values in the bounded set V. Restricting the problem to V, $\varphi(t, \cdot)|_V$ is uniformly Lipschitz continuous, and by (H9), $\varphi(t, 0) = 0$ for all $t \in [0, T]$. Applying [221, Proposition 2], system (5.19), (5.20) has a unique solution, that is nonnegative by Proposition 5.3.2. □

5.4 Optimal Control

We state the Pontryagin principle for the system (5.1)–(5.6):

Theorem 5.4.1. *If $u^* \in L^1([0,T],U)$ is an optimum of the control problem* (5.1)–(5.6) *with solution $(x^*,y^*) \in W$, then there exist a pair $(\lambda,\mu) \in L^\infty([0,T],\mathbb{R}^m) \times L^\infty([0,1]\times[0,T],\mathbb{R}^n)$ satisfying*

$$\begin{aligned}
\dot\lambda(t) &= -D_2\widetilde{G}^T(t) - D_2\widetilde{f}^T(t)\lambda(t) - D_2\widetilde{g}^T(t)K(0)\mu(0,t) \\
&\quad - \int_0^1 D_3\widetilde{h}^T(r,t)\mu(r,t)dr, \\
K(1)\mu(1,t) &= D_4\widetilde{f}^T(t)\lambda(t) + D_4\widetilde{g}^T(t)K(0)\mu(0,t), \\
\frac{\partial\mu(r,t)}{\partial t} &= -K(r)\frac{\partial\mu(r,t)}{\partial r} - W_G^T(r,t)D_3\widetilde{G}^T(t) - W_f^T(r,t)D_3\widetilde{f}^T(t)\lambda(t), \\
&\quad - W_g^T(r,t)D_3\widetilde{g}^T(t)K(0)\mu(0,t) - D_4\widetilde{h}^T(r,t)\mu(r,t) \\
&\quad - \int_0^1 W_h^T(r,s,t)D_5\widetilde{h}^T(r,t)\mu(s,t)ds, \\
\lambda(T) &= D_1\widetilde{F}^T(T), \\
\mu(r,T) &= W_F^T(r)D_2\widetilde{F}^T(T).
\end{aligned} \tag{5.24}$$

for almost every $r \in [0,1]$, $t \in [0,T]$, i.e., the corresponding integral equations hold. In this case, u^* minimizes the Hamiltonian

$$\begin{aligned}
&H(t,x(t),y(r,t),u(t),\lambda(t),\mu(r,t)) \\
&= \widetilde{G}(t) + \left\langle \widetilde{f}(t),\lambda(t)\right\rangle + \langle K(0)\widetilde{g}(t),\mu(0,t)\rangle + \int_0^1 \left\langle \widetilde{h}(r,t),\mu(r,t)\right\rangle dr
\end{aligned}$$

for almost every $t \in [0,T]$, i.e.

$$\begin{aligned}
&H(t,x^*(t),y^*(r,t),u^*(t),\lambda(t),\mu(r,t)) \\
&= \min_{u\in U} H(t,x^*(t),y^*(r,t),u,\lambda(t),\mu(r,t))
\end{aligned} \tag{5.25}$$

for almost every $t \in [0,T]$.

Note that by D_i we denote the partial derivative of the function without tilde with respect to the ith variable, $i = 1,2,3,4,5$, for example

$$D_4\widetilde{f}(t) = D_4 f\left(t,x(t),\int_0^1 W_f(r,t)y(r,t)dr,y(1,t),u(t)\right).$$

Proof. Assume that u^* is an optimum of the control problem (5.1)–(5.6) with so-

lution (x^*, y^*). The Lagrangian of the constraint optimization problem to be minimized is

$$\begin{aligned} L(x,y,u,\lambda,\mu) = \widetilde{F}(t) + \int_0^T \Bigg(& \widetilde{G}(t) - \left\langle \dot{x}(t) - \widetilde{f}(t), \lambda(t) \right\rangle \\ & - \langle K(0)(y(0,t) - \widetilde{g}(t)), \mu(0,t) \rangle \\ & - \int_0^1 \left\langle \frac{\partial y(r,t)}{\partial t} + \frac{\partial (K(r)y(r,t))}{\partial r} - \widetilde{h}(r,t), \mu(r,t) \right\rangle dr \Bigg) dt \\ & - \langle \lambda(0), x(0) - x_0 \rangle - \int_0^1 \langle y(r,0) - y_0(r), \mu(r,0) \rangle \, dr. \end{aligned}$$

To find the adjoint system, we solve the equation

$$D_{(x,y,u)} L(x,y,u,\lambda,\mu) = 0$$

by applying this Fréchet derivative to arbitrary functions $\overline{x} \in L^1([0,T], \mathbb{R}^m), \overline{y} \in L^1([0,1] \times [0,T], \mathbb{R}^n), \overline{u} \in L^1([0,T], U)$. Denote

$$x^\varepsilon = x^* + \varepsilon \overline{x}, \qquad y^\varepsilon = y^* + \varepsilon \overline{y}, \qquad u^\varepsilon = u^* + \varepsilon \overline{u}.$$

Then obviously

$$\overline{x} = \frac{d}{d\varepsilon} x^\varepsilon \big|_{\varepsilon=0}, \qquad \overline{y} = \frac{d}{d\varepsilon} y^\varepsilon \big|_{\varepsilon=0}, \qquad \overline{u} = \frac{d}{d\varepsilon} u^\varepsilon \big|_{\varepsilon=0}.$$

We introduce the abbreviations

$$\begin{aligned} \widetilde{F}^\varepsilon(T) &= F\left(x^\varepsilon(T), \int_0^1 W_F(r) y^\varepsilon(r,T) dr, u^\varepsilon(T) \right), \\ \widetilde{G}^\varepsilon(t) &= G\left(t, x^\varepsilon(t), \int_0^1 W_G(r,t) y^\varepsilon(r,t) dr, u^\varepsilon(t) \right), \\ \widetilde{f}^\varepsilon(t) &= f\left(t, x^\varepsilon(t), \int_0^1 W_f(r,t) y^\varepsilon(r,t) dr, y^\varepsilon(1,t), u^\varepsilon(t) \right), \\ \widetilde{g}^\varepsilon(t) &= g\left(t, x^\varepsilon(t), \int_0^1 W_g(r,t) y^\varepsilon(r,t) dr, y^\varepsilon(1,t), u^\varepsilon(t) \right), \\ \widetilde{h}^\varepsilon(r,t) &= h\left(t, r, x^\varepsilon(t), y^\varepsilon(r,t), \int_0^1 W_h(s,r,t) y^\varepsilon(s,t) u^\varepsilon(t) \right). \end{aligned}$$

Then the derivative is given by

$$D_{(x,y,u)} L(x,y,u,\lambda,\mu)(\overline{x},\overline{y},\overline{u}) = \frac{d}{d\varepsilon} L(x^\varepsilon, y^\varepsilon, u^\varepsilon, \lambda, \mu) \big|_{\varepsilon=0} = I_1 + I_2 + I_3 + I_4 + I_5 + I_6,$$

where

$$
\begin{aligned}
I_1 &= \frac{d}{d\varepsilon}\left(\widetilde{F}^{\varepsilon}(T) + \int_0^T \widetilde{G}^{\varepsilon}(t)dt\right)\Big|_{\varepsilon=0} \\
&= D_1\widetilde{F}(T)\overline{x}(T) + D_2\widetilde{F}(T)\int_0^1 W_F(r)\overline{y}(r,T)dr + D_3\widetilde{F}(T)\overline{u}(T) \\
&+ \int_0^T \left(D_2\widetilde{G}(t)\overline{x}(t) + D_3\widetilde{G}(t)\int_0^1 W_G(r,t)\overline{y}(r,t)dr + D_4\widetilde{G}(t)\overline{u}(t)\right)dt \\
&= \left\langle \overline{x}(T), D_1\widetilde{F}^T(T)\right\rangle + \int_0^1 \left\langle \overline{y}(r,T), W_F^T(r)D_2\widetilde{F}^T(T)\right\rangle dr + D_3\widetilde{F}(T)\overline{u}(T) \\
&+ \int_0^T \left(\left\langle \overline{x}(t), D_2\widetilde{G}^T(t)\right\rangle + \int_0^1 \left\langle \overline{y}(r,t), W_G^T(r,t)D_3\widetilde{G}^T(t)\right\rangle dr + D_4\widetilde{G}(t)\overline{u}(t)\right)dt, \\
I_2 &= \frac{d}{d\varepsilon}\left(-\langle x^{\varepsilon}(0) - x_0, \lambda(0)\rangle - \int_0^T \langle \dot{x}^{\varepsilon}(t), \lambda(t)\rangle\, dt\right)\Big|_{\varepsilon=0} \\
&= \frac{d}{d\varepsilon}\left(\langle x_0, \lambda(0)\rangle - \langle x^{\varepsilon}(T), \lambda(T)\rangle + \int_0^T \left\langle x^{\varepsilon}(t), \dot{\lambda}(t)\right\rangle dt\right)\Big|_{\varepsilon=0} \\
&= \langle \overline{x}(T), -\lambda(T)\rangle + \int_0^T \left\langle \overline{x}(t), \dot{\lambda}(t)\right\rangle dt, \\
I_3 &= \frac{d}{d\varepsilon}\int_0^T \left\langle \widetilde{f}^{\varepsilon}(t), \lambda(t)\right\rangle dt\Big|_{\varepsilon=0} \\
&= \int_0^T \left(\left\langle D_2\widetilde{f}(t)\overline{x}(t), \lambda(t)\right\rangle + \left\langle D_3\widetilde{f}(t)\int_0^1 W_f(r,t)\overline{y}(r,t)dr, \lambda(t)\right\rangle\right. \\
&+ \left\langle D_4\widetilde{f}(t)\overline{y}(1,t), \lambda(t)\right\rangle + \left\langle D_5\widetilde{f}(t)\overline{u}(t), \lambda(t)\right\rangle\Big)dt \\
&= \int_0^T \left(\left\langle \overline{x}(t), D_2\widetilde{f}^T(t)\lambda(t)\right\rangle + \int_0^1 \left\langle \overline{y}(r,t), W_f^T(r,t)D_3\widetilde{f}^T(t)\lambda(t)\right\rangle dr\right. \\
&+ \left\langle \overline{y}(1,t), D_4\widetilde{f}^T(t)\lambda(t)\right\rangle + \left\langle D_5\widetilde{f}(t)\overline{u}(t), \lambda(t)\right\rangle\Big)dt, \\
I_4 &= \frac{d}{d\varepsilon}\int_0^T \Big(-\langle K(0)\left(y^{\varepsilon}(0,t) - \widetilde{g}^{\varepsilon}(t)\right), \mu(0,t)\rangle \\
&- \int_0^1 \left\langle \frac{\partial(K(r)y^{\varepsilon}(r,t))}{\partial r}, \mu(r,t)\right\rangle dr\Big)dt\Big|_{\varepsilon=0} \\
&= \frac{d}{d\varepsilon}\int_0^T \Big(\langle K(0)\widetilde{g}^{\varepsilon}(t), \mu(0,t)\rangle - \langle K(1)y^{\varepsilon}(1,t), \mu(1,t)\rangle \\
&+ \int_0^1 \left\langle K(r)y^{\varepsilon}(r,t), \frac{\partial\mu(r,t)}{\partial r}\right\rangle dr\Big)dt\Big|_{\varepsilon=0} \\
&= \int_0^T \Big(\left\langle \overline{x}(t), D_2\widetilde{g}^T(t)K(0)\mu(0,t)\right\rangle + \int_0^1 \langle \overline{y}(r,t), W_g^T(r,t)D_3\widetilde{g}^T(t)K(0)\mu(0,t)\rangle dr \\
&+ \left\langle \overline{y}(1,t), D_4\widetilde{g}^T(t)K(0)\mu(0,t)\right\rangle + \langle K(0)D_5\widetilde{g}(t)\overline{u}(t), \mu(0,t)\rangle \\
&+ \langle \overline{y}(1,t), -K(1)\mu(1,t)\rangle + \int_0^1 \left\langle \overline{y}(r,t), K(r)\frac{\partial\mu(r,t)}{\partial r}\right\rangle dr\Big)dt,
\end{aligned}
$$

$$
\begin{aligned}
I_5 &= \frac{d}{d\varepsilon}\left(-\int_0^1 \langle y^\varepsilon(r,0)-y_0(r),\mu(r,0)\rangle\,dr - \int_0^T\int_0^1 \left\langle \frac{\partial y^\varepsilon(r,t)}{\partial t},\mu(r,t)\right\rangle dr\,dt\right)\Big|_{\varepsilon=0}\\
&= \frac{d}{d\varepsilon}\int_0^1\left(-\langle y^\varepsilon(r,0)-y_0(r),\mu(r,0)\rangle - \int_0^T\left\langle \frac{\partial y^\varepsilon(r,t)}{\partial t},\mu(r,t)\right\rangle dt\right)dr\Big|_{\varepsilon=0}\\
&= \int_0^1\left(\langle \overline{y}(r,T),-\mu(r,T)\rangle + \int_0^T\left\langle \overline{y}(r,t),\frac{\partial\mu(r,t)}{\partial t}\right\rangle dt\right)dr,
\end{aligned}
$$

$$
\begin{aligned}
I_6 &= \frac{d}{d\varepsilon}\int_0^T\int_0^1 \left\langle \widetilde{h}^\varepsilon(r,t),\mu(r,t)\right\rangle dr\,dt\Big|_{\varepsilon=0}\\
&= \int_0^T\int_0^1\Bigg(\left\langle D_3\widetilde{h}(r,t)\overline{x}(t),\mu(r,t)\right\rangle + \left\langle D_4\widetilde{h}(r,t)\overline{y}(r,t),\mu(r,t)\right\rangle\\
&+ \left\langle D_5\widetilde{h}(r,t)\int_0^1 W_h(s,r,t)\overline{y}(s,t)ds,\mu(r,t)\right\rangle + \left\langle D_6\widetilde{h}(r,t)\overline{u}(t),\mu(r,t)\right\rangle\Bigg)dr\,dt\\
&= \int_0^T\Bigg(\left\langle \overline{x}(t),\int_0^1 D_3\widetilde{h}^T(r,t)\mu(r,t)dr\right\rangle + \int_0^1\Bigg(\left\langle \overline{y}(r,t),D_4\widetilde{h}^T(r,t)\mu(r,t)\right.\\
&+ \left.\int_0^1 W_h^T(r,s,t)D_5\widetilde{h}^T(r,t)\mu(s,t)ds\right\rangle + \left\langle D_6\widetilde{h}(r,t)\overline{u}(t),\mu(r,t)\right\rangle\Bigg)dr\Bigg)dt.
\end{aligned}
$$

Collecting the terms with $\overline{x}(t)$, $\overline{y}(1,t)$, $\overline{y}(r,t)$, $\overline{x}(T)$, $\overline{y}(r,T)$, $\overline{u}(T)$ and $\overline{u}(t)$, the following is obtained

$$
\begin{aligned}
&\frac{d}{d\varepsilon}L(x^\varepsilon,y^\varepsilon,u^\varepsilon,\lambda,\mu)\big|_{\varepsilon=0} = \int_0^T\Bigg(\Bigg\langle \overline{x}(t),D_2\widetilde{G}^T(t)+\dot{\lambda}(t)+D_2\widetilde{f}^T(t)\lambda(t)\\
&+ D_2\widetilde{g}^T(t)K(0)\mu(0,t)+\int_0^1 D_3\widetilde{h}^T(r,t)\mu(r,t)dr\Bigg\rangle + \Bigg\langle \overline{y}(1,t),D_4\widetilde{f}^T(t)\lambda(t)\\
&+ D_4\widetilde{g}^T(t)K(0)\mu(0,t)-K(1)\mu(1,t)\Bigg\rangle + \int_0^1\Bigg\langle \overline{y}(r,t),W_G^T(r,t)D_3\widetilde{G}(t)\\
&+ W_f^T(r,t)D_3\widetilde{f}^T(t)\lambda(t)+W_g^T(r,t)D_3\widetilde{g}^T(t)K(0)\mu(0,t)+K(r)\frac{\partial\mu(r,t)}{\partial r}+\frac{\partial\mu(r,t)}{\partial t}\\
&+ D_4\widetilde{h}^T(r,t)\mu(r,t)+\int_0^1 W_h^T(r,s,t)D_5\widetilde{h}^T(r,t)\mu(s,t)ds\Bigg\rangle dr\Bigg)dt\\
&+ \left\langle \overline{x}(T),D_1\widetilde{F}^T(t)-\lambda(T)\right\rangle + \int_0^1\left\langle \overline{y}(r,T),W_F^T(r)D_2\widetilde{F}(T)-\mu(r,T)\right\rangle dr\\
&+ D_3\widetilde{F}(T)\overline{u}(T)+\int_0^T\Bigg(D_4\widetilde{G}(t)\overline{u}(t)+\left\langle D_5\widetilde{f}(t)\overline{u}(t),\lambda(t)\right\rangle + \langle K(0)D_5\widetilde{g}(t)\overline{u}(t),\mu(0,t)\rangle\\
&+ \int_0^1\left\langle D_6\widetilde{h}(r,t)\overline{u}(t),\mu(r,t)\right\rangle dr\Bigg)dt.
\end{aligned}
$$

Since the derivative of the Lagrangian with respect to ε must be zero for all triplets $(\overline{x},\overline{y},\overline{u})$, we obtain the adjoint system and the condition

$$D_3\widetilde{F}(T)\overline{u}(T) + \int_0^T \Big(D_4\widetilde{G}(t)\overline{u}(t) + \Big\langle D_5\widetilde{f}(t)\overline{u}(t), \lambda(t) \Big\rangle + \langle K(0) D_5\widetilde{g}(t)\overline{u}(t), \mu(0,t)\rangle + \int_0^1 \Big\langle D_6\widetilde{h}(r,t)\overline{u}(t), \mu(r,t) \Big\rangle \, dr \Big) dt = 0.$$

This is the Fréchet derivative of $\widetilde{F}(t) + \int_0^T \widetilde{H}(t)dt$ with respect to u, applied to $\overline{u}$. Hence we obtain (5.25), the theorem holds. □

The results obtained above are applicable to any maturity structured model that is compatible with the general system we consider. In the next section, we apply the results obtained in the previous section for obtaining the optimal treatment strategy for *Chlamydia* infection. In our paper, another application can be found that has been applied to a system describing stem cell maturation, where we aim to obtain the optimal conditions for achieving the desired level of matured stem cells in the system.

5.5 Optimal Treatment of *Chlamydia*

We recall our set of differential equations which is given by

$$\begin{aligned}
\dot{C}(t) &= (1-u_1(t))Nki(1,t) - \beta C(t) - \mu_C C(t),\\
\dot{A}(t) &= \omega I_1(t) - \mu_A A(t),\\
\dot{I}_1(t) &= (1-\theta)\beta C(t) - \alpha_1 I_1(t),\\
\dot{I}_2(t) &= \alpha_1 I_1(t) - \alpha_2 I_2(t) - \zeta A(t) I_2(t),\\
\rho(0,t) &= \alpha_2 I_2(t),\\
\frac{\partial \rho(r,t)}{\partial t} &= -\frac{\partial\left(k_\rho(r)\rho(r,t)\right)}{\partial r} - \zeta A(t)\rho(r,t),\\
\dot{P}(t) &= (1-u_2(t))\eta k_\rho(1)\rho(1,t) - \xi u_2(t)P(t) - \delta P(t),\\
i(0,t) &= (1-\eta)k_\rho(1)\rho(1,t) + \xi u_2(t)P(t),\\
\frac{\partial i(r,t)}{\partial t} &= -\frac{\partial\left(k_i(r)i(r,t)\right)}{\partial r} - \zeta A(t) i(r,t),
\end{aligned} \tag{5A}$$

with initial conditions

$$C(0) = C_0, A(0) = 0, I_1(0) = I_2(0) = I_3(0) = P(0) = I_4(0) = 0, \rho(r,0) = i(r,0) = 0. \tag{5B}$$

We consider an optimal control problem with the objective function given by

$$\begin{aligned} J(u) &= W_1C^2(T) + W_2I_1^2(T) + W_3I_2^2(T) + W_4P_2^2(T) \\ &+ \left(\int_0^1 (W_5(r)\rho(r,T) + W_6(r)i(r,T))dr\right)^2 \\ &+ \int_0^T \Big(W_7C^2(t) + W_8I_1^2(t) + W_9I_2^2(t) + W_{10}P_2^2(t) \\ &+ \left(\int_0^1 (W_{11}(r)\rho(r,t) + W_{12}(r)i(r,t))dr\right)^2 + W_{13}u_1^2(t) + W_{14}u_2^2(t)\Big)dt. \end{aligned} \tag{5C}$$

In vector form, the system (5A)–(5C) can be written in the form (5.1)–(5.6) with

$$x = (C, A, I_1, I_2, P)^T, \quad y = (\rho, i)^T.$$

The control $u = (u_1, u_2)^T \in L^1([0,T], U)$, where $U = [0, m_1] \times [0, m_2]$ and $m_1, m_2 \in (0, 1]$. As the system (5A) does not contain integral terms, we have $W_F = 0$, $W_f = 0$, $W_g = 0$, $W_h = 0$. The weights $W_i, i = 1, 2, 3, \ldots 14$, are scale-related factors that balance the trade-offs between the systemic treatment, the removal of the infection, and the significance of the fourteen components of the cost functional.

In correspondence with the general system (5.1)–(5.6), the following functions are obtained,

$$\begin{aligned} \widetilde{F}(T) &= W_1C^2(T) + W_2I_1^2(T) + W_3I_2^2(T) + W_4P_2^2(T) \\ &+ \left(\int_0^1 (W_5(r)\rho(r,T) + W_6(r)i(r,T))dr\right)^2, \end{aligned}$$

$$\begin{aligned} \widetilde{G}(t) &= W_7C^2(t) + W_8I_1^2(t) + W_9I_2^2(t) + W_{10}P_2^2(t) \\ &+ \left(\int_0^1 (W_{11}(r)\rho(r,t) + W_{12}(r)i(r,t))dr\right)^2 + W_{13}u_1^2(t) + W_{14}u_2^2(t), \end{aligned}$$

$$\widetilde{f}(t) = \begin{pmatrix} (1-u_1(t))Nki(1,t) - \beta C(t) - \mu_C C(t) \\ \omega I_1(t) - \mu_A A(t) \\ (1-\theta)\beta C(t) - \alpha_1 I_1(t) \\ \alpha_1 I_1(t) - \alpha_2 I_2(t) - \zeta A(t) I_2(t) \\ (1-u_2(t))\eta k_\rho(1)\rho(1,t) - \xi u_2(t) P(t) - \delta P(t) \end{pmatrix},$$

$$\widetilde{g}(t) = \begin{pmatrix} \alpha_2 I_2(t) \\ (1-\eta)k_\rho(1)\rho(1,t) + \xi u_2(t)P(t) \end{pmatrix},$$

$$\widetilde{h}(r,t) = \begin{pmatrix} -\zeta A(t)\rho(r,t) \\ -\zeta A(t)i(r,t) \end{pmatrix}, \qquad K(r) = \begin{pmatrix} k_\rho(r) & 0 \\ 0 & k_i(r) \end{pmatrix}.$$

Hypotheses (H1)–(H6'), (H7), (H9) clearly hold, (H8) is verified by

$$\begin{aligned}
&\dot{C} + \dot{A} + \dot{I}_1 + \dot{I}_2 + \dot{P} + \int_0^1 \left(\frac{\partial \rho(r,t)}{\partial t} + \frac{\partial i(r,t)}{\partial t} \right) dr \\
&= \dot{C} + \dot{A} + \dot{I}_1 + \dot{I}_2 + \dot{P} \\
&+ \int_0^1 \left(-\frac{\partial (k_\rho(r)\rho(r,t))}{\partial r} - \zeta A \rho(r,t) - \frac{\partial (k_i(r) i(r,t))}{\partial r} - \zeta A i(r,t) \right) dr \\
&= \dot{C} + \dot{A} + \dot{I}_1 + \dot{I}_2 + \dot{P} - k_\rho(1)\rho(1,t) + k_\rho(0)\rho(0,t) \\
&- k_i(1) i(1,t) + k_i(0) i(0,t) - \zeta A \int_0^1 (\rho(r,t) + i(r,t)) dr \\
&= Nk(1-u_1) i(1,t) - \theta\beta C - \mu_C C + \omega I_1 - \alpha_2 I_2 \\
&- \mu_A A - \zeta A I_2 + (1-u_2)\eta k_\rho(1)\rho(1,t) - \xi u_2 P - \delta P - k_\rho(1)\rho(1,t) + k_\rho(0)\alpha_2 I_2 \\
&- k_i(1) i(1,t) + k_i(0)((1-\eta)k_\rho(1)\rho(1,t) + \xi u_2 P) - \zeta A \int_0^1 (\rho(r,t) + i(r,t)) dr \\
&\leq Nki(1,t) + \omega I_1 + \eta k_\rho(1)\rho(1,t) + k_\rho(0)\alpha_2 I_2 + k_i(0)(k_\rho(1)\rho(1,t) + \xi u_2 P).
\end{aligned}$$

Hence, by Theorem 5.3.5, system (5A)–(5B) has a solution for any control $(u_1, u_2) \in L^1([0,T], U)$. We introduce the following adjoint variables

$$\lambda = (\lambda_C, \lambda_A, \lambda_{I_1}, \lambda_{I_2}, \lambda_P)^T,$$

$$\mu = (\mu_\rho, \mu_i)^T.$$

By Theorem 5.4.1, if the control is optimal then the following adjoint system holds:

$$\begin{aligned}
\dot{\lambda}_C &= -2W_7 C + (\beta + \mu_c)\lambda_C - (1-\theta)\beta\lambda_{I_1}, \\
\dot{\lambda}_A &= \mu_A \lambda_A + \zeta I_2 \lambda_{I_2} + \zeta \int_0^1 (\rho(r,t)\mu_\rho(r,t) + i(r,t)\mu_i(r,t)) dr, \\
\dot{\lambda}_{I_1} &= -2W_8 I_1 - \omega\lambda_A + \alpha_1\lambda_{I_1} - \alpha_1\lambda_{I_2}, \\
\dot{\lambda}_{I_2} &= -2W_9 I_2 + (\alpha_2 + \zeta A)\lambda_{I_2} - \alpha_2 k_\rho(0)\mu_\rho(0,t), \\
\dot{\lambda}_P &= -2W_{10} + (\xi u_2 + \delta)\lambda_P - \xi u_2 k_i(0)\mu_i(0,t)
\end{aligned} \tag{5.26}$$

with boundary conditions

$$\begin{aligned}\mu_\rho(1,t) &= (1-u_2)\eta\lambda_P + (1-\eta)k_\rho(0)\mu_i(0,t),\\ \mu_i(1,t) &= \frac{(1-u_1)Nk}{k_i(1)}\lambda_C,\end{aligned} \tag{5.27}$$

partial differential equations

$$\begin{aligned}\frac{\partial\mu_\rho(r,t)}{\partial t} &= -k_\rho(r)\frac{\partial\mu_\rho(r,t)}{\partial r} - 2\int_0^1 (W_{11}(r)\rho(r,t) + W_{12}(r)i(r,t))dr\, W_{11}\\ &\quad + \zeta A\mu_\rho(r,t),\\ \frac{\partial\mu_i(r,t)}{\partial t} &= -k_i(r)\frac{\partial\mu_i(r,t)}{\partial r} - 2\int_0^1 (W_{11}(r)\rho(r,t) + W_{12}(r)i(r,t))dr\, W_{12}\\ &\quad + \zeta A\mu_i(r,t),\end{aligned} \tag{5.28}$$

and the transversality conditions given by

$$\begin{aligned}\lambda_C(T) &= 2W_1C(T),\\ \lambda_A(T) &= 0,\\ \lambda_{I_1}(T) &= 2W_2I_1(T),\\ \lambda_{I_2}(T) &= 2W_3I_2(T),\\ \lambda_P(T) &= 2W_4P(T),\\ \mu_\rho(r,T) &= 2\int_0^1 (W_5(r)\rho(r,T) + W_6(r)i(r,T))dr\, W_5(r),\\ \mu_i(r,T) &= 2\int_0^1 (W_5(r)\rho(r,T) + W_6(r)i(r,T))dr\, W_6(r).\end{aligned} \tag{5.29}$$

As u minimizes the Hamiltonian

$$\begin{aligned}&H(t,C,A,I_1,I_2,P,\rho,i,u_1,u_2,\lambda_C,\lambda_A,\lambda_{I_1},\lambda_{I_2},\lambda_P,\mu_\rho,\mu_i)\\ &= W_7C^2W_8I_1^2 + W_9I_2^2 + W_{10}P_2^2 + \left(\int_0^1 (W_{11}\rho + W_{12}i)dr\right)^2 + W_{13}u_1^2 + W_{14}u_2^2\\ &+ \lambda_C((1-u_1)Nki(1,t) - \beta C - \mu_C C) + \lambda_A(\omega I_1 - \mu_A A) + \lambda_{I_1}((1-\theta)\beta C - \alpha_1 I_1)\\ &+ \lambda_{I_2}(\alpha_1 I_1 - \alpha_2 I_2 - \zeta A I_2) + \lambda_P((1-u_2)\eta k_\rho(0)\rho(1,t) - \xi u_2 P - \delta P)\\ &+ k_\rho(0)\alpha_2 I_2\mu_\rho(0,t) + k_i(0)((1-\eta)k_\rho(1)\rho(1,t) + \xi u_2 P)\mu_i(0,t)\\ &- \zeta A\int_0^1 (\rho\mu_\rho + i\mu_i)dr\end{aligned}$$

for all $t \in [0,T]$, we compute its partial derivatives as follows

$$\frac{\partial H}{\partial u_1} = 2W_{13}u_1 - \lambda_C Nki(1,t),$$
$$\frac{\partial H}{\partial u_2} = 2W_{14}u_2 - \lambda_P \eta k_\rho(0)\rho(1,t) - \xi P\lambda_P + \xi P k_i(0)\mu_i(0,t),$$

and obtain the optimal control as

$$u_l(t) = \min\{\max\{d_l(t), 0\}, m_l\}, \quad t \in [0,T],\ l = 1,2,$$

where

$$d_1(t) = \frac{\lambda_C(t)Nki(1,t)}{2W_{13}},$$
$$d_2(t) = \frac{\lambda_P(t)\eta k_\rho(0)\rho(1,t) + \xi P(t)\lambda_P(t) - \xi P(t)k_i(0)\mu_i(0,t)}{2W_{14}}.$$

5.6 Numerical Results

In this section, we present graphical illustrations of the model system (5A) corresponding to different scenarios. We demonstrate the numerical results for the dynamics of intracellular bacterial growth with and without any therapy. For this purpose, the system of equations (5A) is solved in the absence of any control until time zero which is equivalent to the system with $u_1 = u_2 = 0$. The analysis shows that the infection will persist in the absence of any therapeutic intervention, in spite of the fact that the presence of the cell-mediated immune response triggers an antimicrobial response. The simulation shows that each of the variables remains at the endemic equilibrium. The objective is to obtain an optimal treatment for *chlamydia* where the host is suffering from chronic *chlamydia* infection, whereby the bacterial population has reached chronic equilibrium. The *chlamydia* steady state is obtained by setting the right-hand side of the system of equations (5A) to zero by allowing $u_1 \equiv u_2 \equiv 0$ that is in the absence of any control.

5.6.1 Optimal control

The optimal control strategy is numerically approximated by the forward-backward sweep method (FBSM) [200, 222]: Starting with an initial guess, we integrate the state equations (5A) forward in time (using Euler scheme for the state variables corresponding to ODEs and the method of finite differences for those described by PDEs) with initial condition (5B). Using the current approximating solution of the state equations, the adjoint system (5.26)–(5.28) is integrated backward in time by means of the transversality conditions (5.29). The guess for the optimal

control is obtained as the minimum of the Hamiltonian for every $t \in [0, T]$. By repeated iteration of the process, the optimal solution is attained as the limit of the approximating solutions. The simulation is subject to various combinations of the weight parameters $W_i, i = 1, 2, 3, \ldots 14$, and the initial condition is considered to be the equilibrium solutions of the system excluding the treatment.

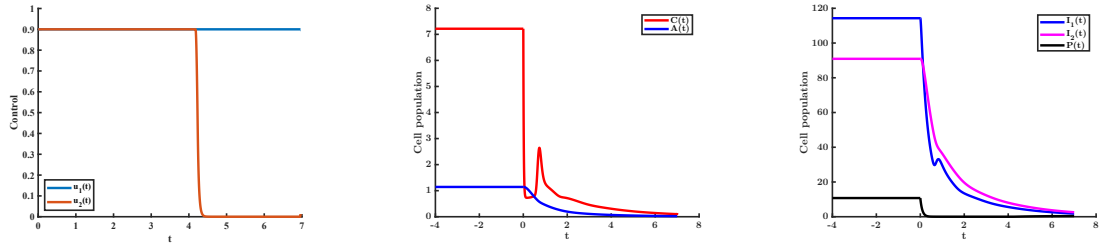
This control strategy is to examine the application of the recommended treatment as a combination of tryptophan supplement, L-1MT, and the bacteriostatic agent. A supplementary cocktail of tryptophan and L-1MT is hypothesized to act as an immunomodulating agent thereby facilitating the abatement in the number of EBs produced upon lysis of infected epithelial cells [8]. The system (5A) is solved by utilizing both the controls u_1 and u_2 to optimize the objective functional J defined as in (5C), for different $W_i, i = 1, 2, 3, \ldots 14$. The optimal control for this particular treatment regimen suggests that the population of active *Chlamydia* particles, as well as persistently infected cells, are eliminated at the end of the period of therapy.

We look for the outcome that optimizes the usage of both the treatment types u_1, which acts as a bacteriostatic agent on *chlamydia*, and u_2 which stands for tryptophan-L-1MT supplement, with respect to two distinctive scenarios: (i) when the effect of the intermediate weights $W_i, i = 7, 8, 9, 10, 11, 12$ are accounted for, and; (ii) when they are neglected. In both cases, we use identical values for weights W_i, for $i = 1, 2, \ldots 6$, which are values indicating the relative importance of extracellular EBs and infected epithelial cells at the end of the treatment period T, as well as identical values for weights W_{13}, and W_{14}, which are values indicating the relative costs for the antibiotic therapy, and the tryptophan and L-1MT cocktail respectively.

	W_1	W_2	W_3	W_4	W_5	W_6	W_7	W_8	W_9	W_{10}	W_{11}	W_{12}	W_{13}	W_{14}
(a)	10	10	10	10	10	10	1	1	1	1	1	1	10	5
(b)	10	10	10	10	10	10	0	0	0	0	0	0	10	5

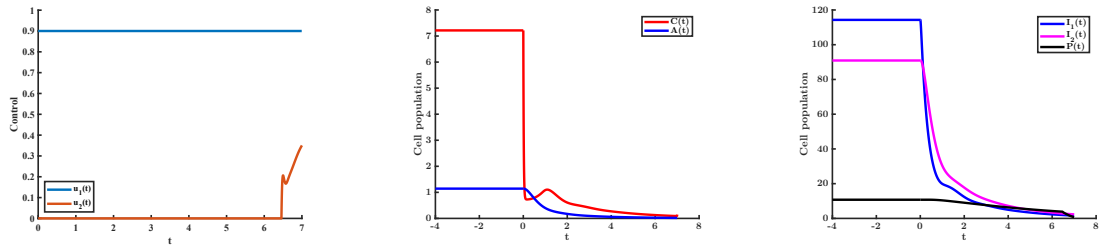
Table 5.2: Table of weights

In the initial scenario, we have allocated specific values to weights denoted as W_i, where i ranges from 7 to 12, to represent the relative significance of extracellular EBs and infected epithelial cells throughout the duration of the treatment period. These weight values have been set uniformly at 1 to maintain consistency and standardize their respective importance. Furthermore, in this context, the weight values designated for W_{13} and W_{14} have been assigned 10 and 5, respectively. As depicted in Fig. 5.3b, Fig. 5.3c, and Fig. 5.5, in this case, with the values of the weights as indicated in Table 5.2 (a), the optimal control problem predicts that



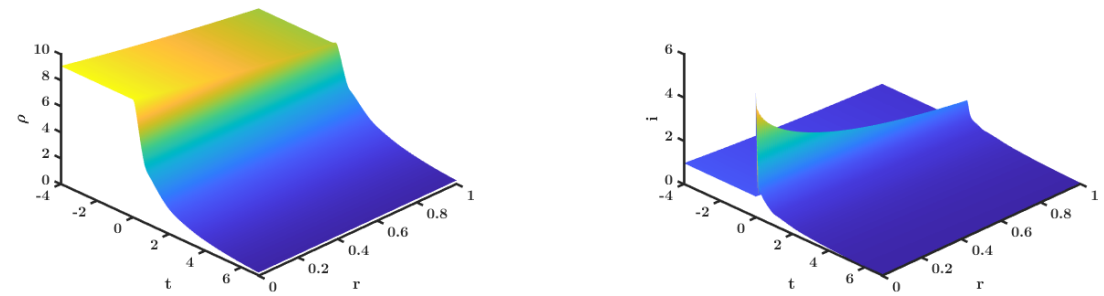
(a) (b) (c)

Figure 5.3: Numerical simulation for the control problem with the bacteriostatic agent and tryptophan-L-1MT supplementation for weights corresponding to Table 5.2 (a): (a) solution sketch for controls $u_1(t)$ and $u_2(t)$; (b) time course plot of state variables $C(t)$, and $A(t)$; and (c) time course plot of state variables $I_1(t)$, $I_2(t)$, and $P(t)$.



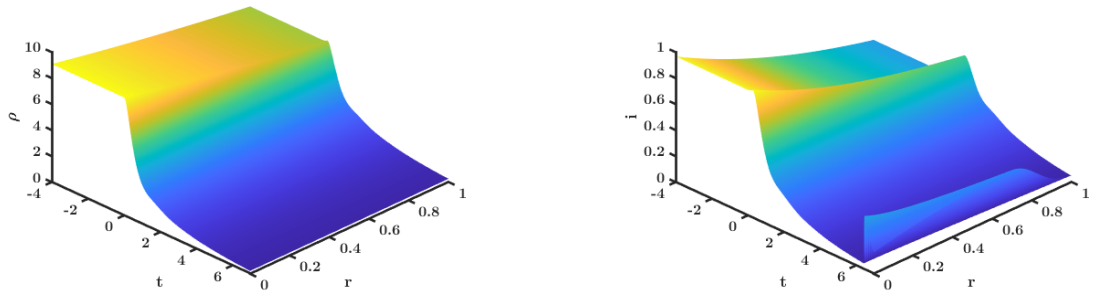
(a) (b) (c)

Figure 5.4: Numerical simulation for the control problem with the bacteriostatic agent and tryptophan-L-1MT supplementation for weights corresponding to Table 5.2 (b): (b) solution sketch for controls $u_1(t)$ and $u_2(t)$; (b) time course plot of state variables $C(t)$, and $A(t)$; and (c) time course plot of state variables $I_1(t)$, $I_2(t)$, and $P(t)$.



(a) (b)

Figure 5.5: Numerical simulation for the control problem with a bacteriostatic agent and tryptophan-L-1MT supplementation for weights corresponding to Table 5.2 (a): (a) time course plot of state variable $\rho(r,t)$; and (b) time course plot of state variable $i(r,t)$.



(a) (b)

Figure 5.6: Numerical simulation for the control problem with bacteriostatic agent and tryptophan-L-1MT supplementation for weights corresponding to Table 5.2 (b): (a) time course plot of state variable $\rho(r,t)$; and (b) time course plot of state variable $i(r,t)$.

when tryptophan supplements and bacteriostatic drugs are used in conjunction for treatment, the chronic *Chlamydial* infection will be eradicated. According to our simulations, as detailed in Fig. 5.3a, the optimal control strategy advises maintaining the maximum concentration of the bacteriostatic agent, denoted as $u_1(t)$, throughout the entire treatment period. Likewise, for the tryptophan and L-1MT cocktail, referred to as $u_2(t)$, the optimal approach entails continuous administration, with the only exception being the discontinuation of $u_2(t)$ a few days prior to the conclusion of the treatment. This strategy is deemed effective in achieving the desired outcome. Next, we investigate the scenario in which the weights W_i, for $i = 7, 2, \ldots 12$ are all null, and the remaining weights have the previous values. In this case, with the values of the weights as indicated in Table 5.2 (b), the optimal control predicts, as shown in Fig. 5.4b, Fig. 5.4c, and Fig. 5.6, by primarily administering the bacteriostatic agent $u_1(t)$, and maintaining minimum concentration of tryptophan and L-1MT cocktail, *Chlamydial* elimination can be achieved. As depicted in Figure Fig. 5.4a, the optimal control strategy indicates that treatment should be administered using the highest concentration of u_1 for the entire duration of the treatment period, with some concentration of tryptophan and L-1MT cocktail administered before the end of therapy. In both cases, persistent *Chlamydia* have been successfully cleared from the system. In both cases, the commencement of the treatment period is $t = 0$, and it is seen that, before the initiation of the therapy, the disease remains at the chronic condition, which is the equilibrium point of the system.

The primary distinction between the two control types lies in their effect on the per-

sistent *Chlamydial* load within the system throughout the course of therapy. In the initial scenario, as illustrated in (Fig. 5.3c), it is evident that the control measures effectively and promptly eliminate the persistent *Chlamydia* from the system. In the second scenario, when the weights W_i for $i = 7, 2, \ldots, 12$ are not factored into consideration, the model forecasts a prolonged duration for the treatment to effectively eradicate the persistent *Chlamydial* particles from the system. This is visually represented in Figure (Fig. 5.4c).

5.7 Discussion

Optimal control theory is a phenomenal mathematical tool for investigating control policies. It has found its application in many dynamical systems, as well as numerous other systems, especially for exploring control measures in maintaining disease transmission. The application of control theory in epidemiology is undeniable and is enforced by the primary goal of health authorities and policymakers, which is to curtail the spread of various infectious illnesses. Numerous disease models with control have been presented in the scientific community, from general disease models to models describing specific infections [223–228].

In this chapter, we have constructed an optimal control problem for a general compartmental model, where some of the compartments are maturity structured. Hence, it is a mixed system of ordinary and partial differential equations, moreover, the boundary conditions are also nonlinear. Subject to certain assumptions, for a fixed control, we verify the existence, uniqueness, and boundedness of the solutions. A suitable objective function is formulated, and results for the presence of ideal control variables that minimize the objective function are determined. For the given system, we make use of Pontryagin's principle, which is a necessary condition for the optimality of the control. The Hamiltonian function, the adjoint variables, and the corresponding differential equations along with transversality conditions are derived. In the proof, we consider the task as a constraint optimization problem, define the Lagrangian functional, and derive the condition for its Fréchet derivative to be zero. As our results are proven for a general model with a maturity structure, we believe that they can be applied to any particular compartmental model that is compatible with the system we have defined.

We then apply the results obtained to the particular problem involving *C. trachomatis* infection introduced at the beginning of the chapter. We checked that our hypotheses hold, and derived the adjoint equations, the Hamiltonian, and the formula of the control for that particular system.

STIs are consistently responsible for causing massive health catastrophes. According to estimates, in the year 2010, treatable STIs stood responsible for the loss of nearly 11 million disability-adjusted life years [229]. *C. trachomatis* remains the most common STI and accounts for high global economic cost and morbidity.

It is a well-known fact that viral STIs are constantly evolving and pose severe challenges to virologists and medical health professionals. However, today, it has been established that not only viruses, but bacteria as well, in a manner of incorporating genetic factors, metamorphosis, or adaptations, have likely been evolving [230]. As such, mathematical models are quite handy in helping us better understand their dynamics. Infectious disease models that are defined by age structure and cell-to-cell transmission are remarkable ways to describe the dynamics of within-host infection processes. The application of structured models has seen many applications, particularly for studying the disease progression for viruses [231, 232]. Nevertheless, such models have been utilized to study the evolution of bacterial populations and can be found in literature [230].

We have considered a maturity structured model, earlier developed by Wilson et al. [11], and investigate the optimal treatment of chronic *C. trachomatis* infection. The chronic condition of the patient is subject to the presence of IFN-γ mediated persistent *Chlamydia* particles. The optimal control problem is formulated in the presence of two distinct types of therapies, a bacteriostatic agent, the effect of which is denoted by u_1, and tryptophan analogs acting as effective competitors that counteract and block *Chlamydial* persistence due to IFN-γ cells.

Chlamydial persistence refers to a long-term relationship between the bacteria and its living host. In this form, the bacteria do not manifest clinically and may remain undetectable for a long period of time, ultimately developing chronic health problems. For *C. trachomatis* treatment with bacteriostatic agents alone, the ultimate clearance also depends not only on the efficacy of the antibiotic but also on the host's ability to eradicate the residual bacteria in the system. The production of persistent forms of *Chlamydia* has also emerged as a potential issue with bacteriostatic drug treatment of *Chlamydia* infections. In addition to being more resistant to antibiotics than typically developing organisms, persistent *Chlamydia* forms have also been strongly linked to treatment failures [27]. According to studies, *Chlamydia* can survive after therapy in a form, the presence of which cell culture or immunoassay may fail to detect [233, 234]. The transformation of the RBs into persistent bodies, although indefinite, in the presence of growth obstacles in the form of IFN-γ, its reactivation into the infectious EB forms is immediate once the tryptophan level retains its balance [40].

The optimal control problem formulated here predicts total clearance of *Chlamydia* particles from the system with respect to both scenarios, as depicted in Fig. 5.3b, Fig. 5.3c, and Fig. 5.5, and Fig. 5.4b, Fig. 5.4c, and Fig. 5.6. Nonetheless, as previously mentioned, the second treatment protocol, while ultimately successful in eradicating the infection by the conclusion of the therapy, does require a comparatively extended period to completely eliminate the persistent chlamydia from the system. This phenomenon can have a very significant impact on the health of the infected host. As previously elaborated in the preceding Chapter (4), the deviation of *Chlamydia* from its typical growth pattern appears to be a response triggered by stress, and in real-world cases of *Chlamydia* infection, the presence of numerous diverse factors can potentially lead to complications that disrupt normal biological processes. Research findings suggest that chronic *Chlamydial* infections, arising from either persistence or recurrent infections, are associated with a heightened risk of more severe and deleterious health conditions [189]. In conclusion, we advocate the first type of control, which gives emphasis to the intermediate weights, which are in some way connected to the health status of the patient being treated during the course of therapy.

Summary

In this thesis, we contribute to the study of *Chlamydia* infection, by means of applying compartmental modeling to obtain a thorough understanding of the bacterial infection *C. trachomatis* at an in-host level and at a population level. At a fundamental level, a mathematical model using a delay differential equation is formulated to gain insight into the dynamics of infection within host. These observations can be invaluable in understanding the unique development cycle of the bacterium. Furthermore, they can prove to be useful in building treatments. Secondly, we model *C. trachomatis* dynamics in a population by considering its interaction with another pathogen, Herpes Simplex Virus (HSV) within-host and, investigating the impact their peculiar association can have in a population of human beings. Lastly, we develop a compartmental maturity structured in-host model for the *C. trachomatis* growth cycle and apply Pontryagin's maximum principle to identify the optimal conditions to reduce the systemic expenses of the treatments and medications, at the same time reducing the quantities of extracellular *Chlamydia* particles, and chronically infected cells.

The first two Chapters are introductory to the *chlamydiae* bacteria. We provide a concise description of the pathogen's biotic attributes, describing its very peculiar development cycle, evolution, and epidemiology. A brief history of the application of mathematical modeling to study infectious diseases in general and its particular application in studying *chlamydia* is provided.

In Chapter 3, a mathematical model for a laboratory experiment that describes the growth of the intracellularly growing bacteria is constructed. The system of delay differential equation tracks the number of cells infected with *chlamydiae* at each in-host level. The delay is introduced to account for the time taken for the pathogen to move through successive compartments, which corresponds to various stages of the bacteria. The state variables in the basic *in vitro* model are considered to account for the following developmental stages:

Stage 1: Attachment and incorporation of an EB to the host epithelial cell's surface;
Stage 2: EBs differentiate into RB forms within the infected epithelial cell;
Stage 3: RBs divide by undergoing repeated cycles of binary fission within the infected epithelial cell;
Stage 4: Matured RBs differentiate back to EBs within the infected epithelial cell;

Stage 5: Infected epithelial cells undergo cell lyses to produce more EB particles.

This model though very simple can very well mirror the dynamics of the in-host developing bacteria. An explicit formula for the final size of the system, i.e. the number of infected cells, and the total number of EBs generated at the end of the development cycle is derived. This model can, in particular, anticipate the amount of EBs at any given time and accurately duplicate the empirical results of the laboratory trials.

In Chapter 4, the dynamics of the co-infection between *C. trachomatis*, and HSV is developed. The model takes into account the establishment of persistent *Chlamydia* infection in the presence of HSV, allowing susceptible individuals to be dually infected with both pathogens. However, in the case of the presence of active herpes, *Chlamydia* is driven into persistence. First off, we consider the sub-system, which is when only one of the diseases is present in the population. We explore the global dynamics and determine important threshold values for disease prevalence. The analysis of the co-infection model shows that the presence of *Chlamydia* is inconsequential for the disease dynamics of HSV, and its pervasiveness or extinction is entirely dependent on the reproduction number of HSV. Conversely, it is shown that *Chlamydia* is not invariably capable of invading an HSV-endemic population, and its capacity to spread is subject to a new threshold parameter. Further, when all reproduction numbers are greater than one, a co-infection steady state is shown to exist. Calibrating the model to determine the population prevalence of both diseases and their comparison with epidemiological findings indicate that this scenario is perhaps the most plausible. It is also particularly the most intriguing case, as when both infections are in circulation and all reproduction numbers are greater than one, then a higher percentage of *Chlamydia* infected individual is driven to being persistently infected. This means HSV reduces *Chlamydia* transmission in the population, but the distribution of cases has changed to include a greater percentage of people with persistent *Chlamydia* infection.

In Chapter 5, an optimal control problem for a general compartmental model, where some of the compartments exhibit maturity structure is constructed. Consequently, we have a mixed system of partial differential equations and ordinary differential equations with nonlinear boundary conditions. For a fixed control, we establish the existence, uniqueness, and boundedness of solutions. The Pontryagin principle, which states that the control must always minimize a Hamiltonian function, additionally requiring the adjoint variables to satisfy differential equations with transversality conditions, has also been demonstrated for the system. The fundamental aim is to apply the results for *Chlamydia* infection.

In the second part of Chapter 5, an optimal control problem for a maturity-structured model is considered for within-host *Chlamydia* infection. The age-structured model, or more precisely the maturity-structured model as it explores the maturity of the infected cells is considered, taking into account the role of the immune response. The effects of two types of immune systems are taken into consideration: the humoral immune response (antibody-mediated feedback) plays a dominant role in preventing the onset of infection; the cell-mediated immune response (activity of cytotoxic T cells or macrophages) is crucial for the removal of infection once pathogens have moved passed initial protection and have successfully established infection within the epithelial cells. Our goal is to identify the best treatment/drug combination that will reduce the systemic cost of the treatment, at the same time reducing extracellular *Chlamydia*, infected epithelial host cells, and more critically, curtail the development of *Chlamydia* persistence/alter persistent *Chlamydia* into its normal form. *Chlamydia* in its persistent form does not manifest clinically and may go lengthy periods of time undetected before establishing chronic health issues. Hence, a control measure that helps the prevention of persistent *Chlamydia* development is favorable. Our approach is to consider two types of treatments: (1) a bacteriostatic agent that inhibits the growth of bacteria, and (2) tryptophan and levo-1-methyl tryptophan supplement that has the ability to reverse *Chlamydial* persistence, and also reacts by reducing the production of infectious forms of the bacteria. The results of the first section are then applied to obtain the optimal control strategy, which is then numerically solved.

The optimal control problem numerically solved is conditional to two different scenarios: (1) In the first scenario, during the days encompassed by the ongoing therapy, we place particular emphasis on the significance of the infected compartments and the extracellular EBs. Consequently, the weights assigned to represent their relative importance are positive. In this case, the weights W_i for $i = 7, 2, \ldots, 12$ hold positive values, and (2) In the second scenario, the weights W_i for $i = 7, 2, \ldots, 12$ are disregarded. A significant distinction between the two cases lies in the fact that although the treatment regimens recommended by both scenarios are capable of eliminating the infection, it is evident that the process takes a comparatively longer duration to completely clear persistent *Chlamydia* from the system when the weights W_i for $i = 7, 2, \ldots, 12$ are omitted from consideration. This could have a critical impact on the health of the infected host. We, therefore, would like to highlight the importance of considering the status of the infection during the process of treatment.

Summary in Hungarian

A disszertációban a *Chlamydia* fertőzést tanulmányozzuk matematikai modellek segítségével. A dolgozat az 1. fejezetben a *Chlamydia* baktérium és az általa okozott betegség rövid leírásával kezdődik. A 2. fejezetben bemutatjuk a fertőző betegségek matematikai modellezését, és annak konkrét alkalmazását az adott kórokozóra. A 3. fejezetben egy lineáris késleltetett differenciálegyenletek rendszerével kifejezett kompartmentális modellt dolgozunk ki a *Chlamydia* intracelluláris fejlődési ciklusának tanulmányozására. A modell a fertőzött sejtek számát írja le a sejtosztódási ciklus minden egyes szakaszában. Ezen túlmenően az egyes kompartmentek végső méretére vonatkozó képletet is levezetjük. A megoldást a laboratóriumi adatokból származó eredményekre illesztjük, és megmutatjuk hogy ez az egyszerű lineáris modell nagyon jól tükrözi a laboratóriumi kísérlet eredményeit. A 4. fejezetben egy új matematikai modellt mutatunk be a *C. trachomatis*, és a HSV (humán herpeszvírus) közötti együttes fertőzés dinamikájának tanulmányozására az emberben. A modell feltételezi, hogy egy olyan egyénben, aki egyidejűleg mindkét kórokozóval fertőzött, a HSV jelenléte a *Chlamydiá*t perzisztenssé teszi. A perzisztens fázisban a *Chlamydia* nem szaporodik és nem fertőz. Ljapunov-függvények, és az aszimptotikusan autonóm rendszerek elméletének alkalmazásával globális stabilitási eredményeket bizonyítunk a betegségmentes és az endemikus egyensúlyokra. Továbbá a modellt kalibráljuk a betegség paramétereire, hogy meghatározzuk mindkét betegség populációs előfordulását, és összehasonlítsuk azt a járványtani eredményekkel. Az 5. fejezetben egy parciális differenciálegyenletes modellt dolgozunk ki a krónikus *Chlamydia*-fertőzés kombinált terápiájának optimalizálására. A Pontryagin-féle maximum-elv segítségével meghatározunk egy olyan kezelési protokollt, ami minimalizálja a felhasznált gyógyszerek és a krónikusan fertőzött sejtek mennyiségét.

Publications

The dissertation is based on the following three articles, the first two of which are published, and the third one is a manuscript:

1. B Das, G Röst, Delay Linear Chains in Mathematical Biology: Migratory Birds, Stem Cell Maturation, and Intracellular Chlamydia Infection, *Trends in Biomathematics: Modeling Cells, Flows, Epidemics, and the Environment* (ed. R. Mondaini), pp. 71–80, Springer (2020)
2. B Das, G Röst, Dynamics of herpes and chlamydia co-infection in a population, *Discrete and Continuous Dynamical Systems-B* 28 (8) (2023) 4366–4398.
3. B Das, István Balázs, G Röst, Optimal control for maturity-structured systems with an application to *Chlamydia* treatment.

Other Publications

1. Barua, Saumen and Das, Bornali and Dénes, Attila, A compartmental model for COVID-19 to assess effects of non-pharmaceutical interventions with emphasis on contact-based quarantine, *Studia Universitatis Babes-Bolyai, Mathematica* 68 (3) (2023) 679-697.

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