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Drug Resistance in Infectious Diseases

Modeling, Analysis and Simulation

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To my dear family

Tặng cả nhà thương yêu

Summary

Drug resistance in infectious diseases is a significant global concern. This work aims to quantitatively study drug resistance in infectious diseases by way of mathematical modeling, analysis and simulations. Within the thesis, we present two new models of drug resistance in infectious diseases.

This thesis contains several contributions:

1. The background: We give an overview of the state of the art in mathematical modeling of drug resistance, covering more than a hundred papers including several surveys.

2. The modeling process: We contribute to the development of the mathematical models that describe the dynamics of vector-borne diseases by new models for both non-structured and structured populations.

3. The theory: We contribute to the mathematical theory of integro-partial differential equations by expanding the method of characteristics to treat a system with different characteristics in multi-dimensional space. This provides a strong background for numerical studies.

4. The numerics: We suggest methods and algorithms to investigate the models. For the non-structured model, we do parameter estimation and simulation with a data set taken from Burkina Faso, Africa. For the structured population model, we propose a constructive algorithm and discuss potential data to investigate the model numerically.

5. The application: We consider different quantitative settings and policies. With a good data set, the simulations can deliver important results to improve treatment toward drug resistance control, especially for vector-borne diseases. The models also suggest the necessity of further experimental work to reach a more precise understanding.

With all of these contributions, we bridge theory and practice to discover suitable strategies for reducing drug resistance and controlling infectious diseases.

Zusammenfassung

Resistenzen bei Infektionskrankheiten stellen ein großes gesundheitliches Problem in der ganzen Welt dar. Das Ziel dieser Arbeit ist eine quantitative Untersuchung von Resistenzen bei Infektionskrankheiten durch mathematische Modellierung, Analyse und Simulation. Im Rahmen unserer Arbeit präsentieren wir zwei neue Modelle von Resistenzen bei Infektionskrankheiten.

Diese Arbeit enthält mehrere Beiträge:

1. Der Hintergrund: Wir geben einen Überblick über den Stand der mathematischen Modellierung von Resistenzen.

2. Die Modellierung: Durch zwei neue Modelle für nicht-strukturierte und strukturierte Populationen tragen wir zur Entwicklung der mathematischen Modelle bei, die die Dynamik von vektorübertragenen Krankheiten beschreiben.

3. Die Theorie: Wir tragen zur mathematischen Theorie der Integro-Differentialgleichungen bei, durch Erweiterung der Methode der Charakteristiken, um ein System mit unterschiedlichen Charakteristiken in multi-dimensionalem Raum zu behandeln. Dies bietet eine solide Grundlage für numerische Untersuchungen.

4. Die Numerik: Wir empfehlen geeignete Methoden und Algorithmen, um die Modelle zu untersuchen. Für das nicht-strukturierte Modell präsentieren wir eine Parameterschätzung und Simulation mit einem Datensatz aus Burkina Faso, Afrika. Für das strukturierte Modell schlagen wir einen konstruktiven Algorithmus vor und diskutieren über mögliche Daten, um das Modell numerisch zu untersuchen.

5. Die Anwendung: Wir betrachten verschiedene quantitative Situationen und Richtlinien. Mit einem guten Datensatz können die Simulationen wichtige Ergebnisse liefern, die die Behandlung von Resistenz, vor allem bei vektorübertragenen Krankheiten, verbessern. Die Modelle verweisen auch auf die Notwendigkeit weiterer experimenteller Arbeiten, um ein genaueres Verständnis zu erreichen.

Mit all diesen Beiträgen bauen wir eine wichtige Brücke von der Theorie zur Praxis, um geeignete Strategien zur Verminderung von Resistenz und zur Kontrolle von Infektionskrankheiten herauszufinden.

Acknowledgements

Writing this part is not easy for me. There are so many people who have supported me both professionally and personally over the last few years.

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*

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Contents

List of Figures

List of Tables

Introduction

This chapter introduces our research. In it, we delineate our motivation, specify the aims and describe the contents of the thesis.

0.1 Motivation

Infectious diseases are also known as communicable diseases, contagious diseases and transmissible diseases. They are often caused by pathogens, living inside host bodies. They can be transmitted directly to other susceptible hosts or indirectly via intermediate hosts.

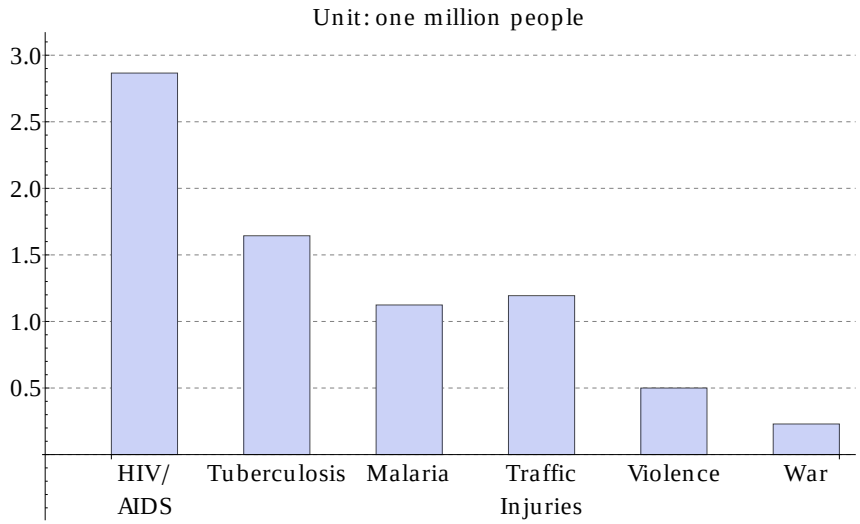

Figure 1: Deaths by causes in World Health Organization (WHO) regions, 2002 [107].

As indicated in figure 1, infectious diseases induce more deaths every year than war, violence, traffic injuries or any other reasons. They also damage people's

health and their ability to live healthy lives. In public health a common measure for this loss is the disability-adjusted life year (DALY). One DALY is equal to the loss of one healthy year of life [107]. A concrete comparison concerning DALYs are expressed in table 1 in regard to some of the most common diseases and injuries.

Table 1: Burden of diseases in DALYs by causes in WHO Regions, approximations for 2001, [107].

Diseases	DALYs (thousand)	Percentage(%)
Transmittable conditions	**615 737**	**42.0**
HIV/AIDS	88 429	6.0
STDs excluding HIV	12 404	0.8
Diarrheal diseases	62 451	4.3
Childhood diseases	48 268	3.3
Meningitis	6 420	0.4
Malaria	42 280	2.9
Respiratory infections	94 037	6.4
Maternal conditions	30 943	2.1
Perinatal conditions	98 422	6.7
Other	132 043	9.1
Not transmittable conditions	**672 865**	**45.8**
Neuropsychiatric disorders	191 260	13.0
Cardiovascular diseases	144 471	9.8
Other	337 134	23.0
Injuries	**178 656**	**12.2**
Road traffic accidents	37 719	2.6
Self-inflicted	19 923	1.4
War	8 309	0.6
Other	112 705	7.6

The discovery of antimicrobials signaled a strong weapon against infectious diseases. However, over the last several decades, antimicrobials and similar drugs have been losing their ability to fight infections. Recently the World Health Organization has emphasized the dangers of antimicrobial resistance. If these resistant strains are spread over the world, we would lose the main solutions to treat patients.

In the following we show three different reports about multi-resistance in HIV-AIDS, tuberculosis and malaria, see detail in figures 2, 3 and 4.

More than twenty laboratories accredited by WHO reported about HIV drug resistance. These laboratories are located in America, Europe, Africa, Asia and Australia. From 2006 to 2010 WHO also conducted about 102 surveys on HIV

drug resistance in 52 countries. The data suggested to pay attention to some common causes, such as adherence and loss of treatment follow-up.

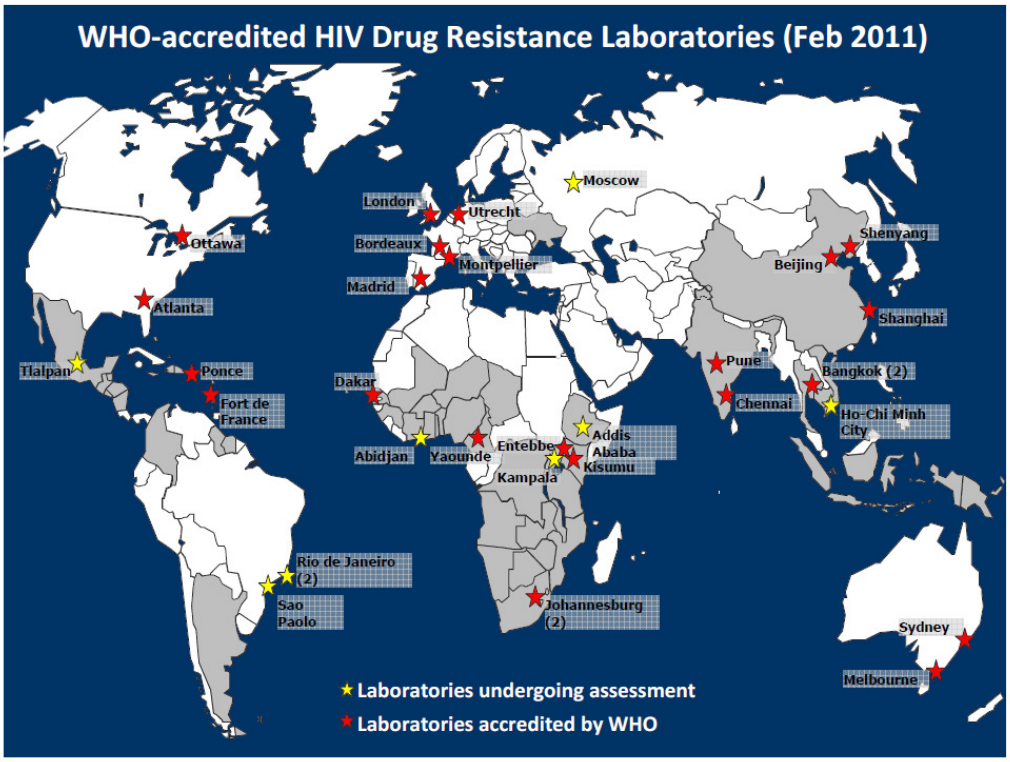

Figure 2: Network of HIV drug resistance laboratories (2011), [100].

In a study published in the Bulletin of the World Health Organization 2007 [14], Bloendal discussed multidrug-resistance in tuberculosis. Figure 3 indicates that the previously treated patients were more likely to develop multidrug-resistant tuberculosis compared to those who had not received treatment before.

Figure 4 concerns malaria in South East Asia. This is one of the central regions of anti-malarial resistance. Some agents, which used to be the first line of treatment in the past, like Chloroquine or Sulfa-doxine pyrimethamine, now have almost no effect in some parts of Vietnam, Cambodia, Philippines, Laos and China. The newly discovered antimalarials of the Artemisinin group also had 40% resistance in Vietnam. The resistance levels vary a lot from region to region, see figure 4.

We have now discussed several significant reasons to study drug resistance. We are going to give some contributions within our project.

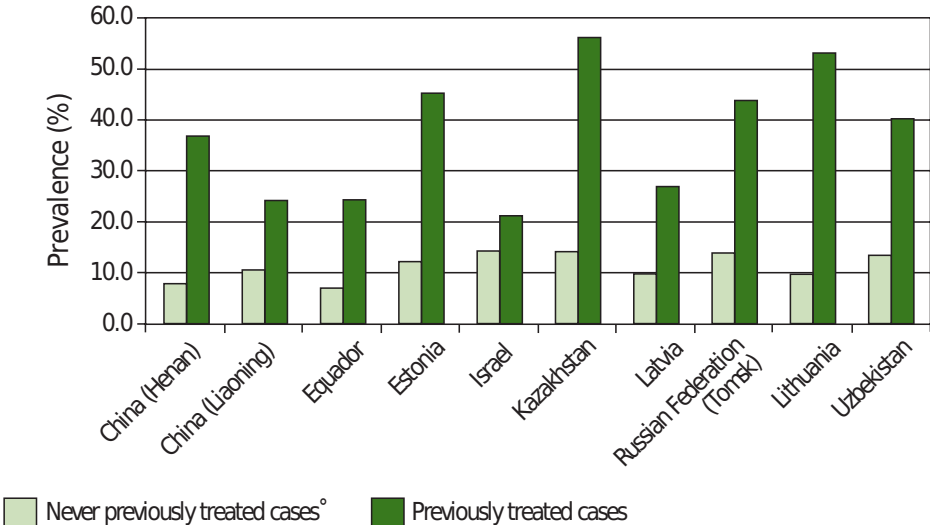

Figure 3: Prevalence of multi drug-resistant tuberculosis (2007), [14].

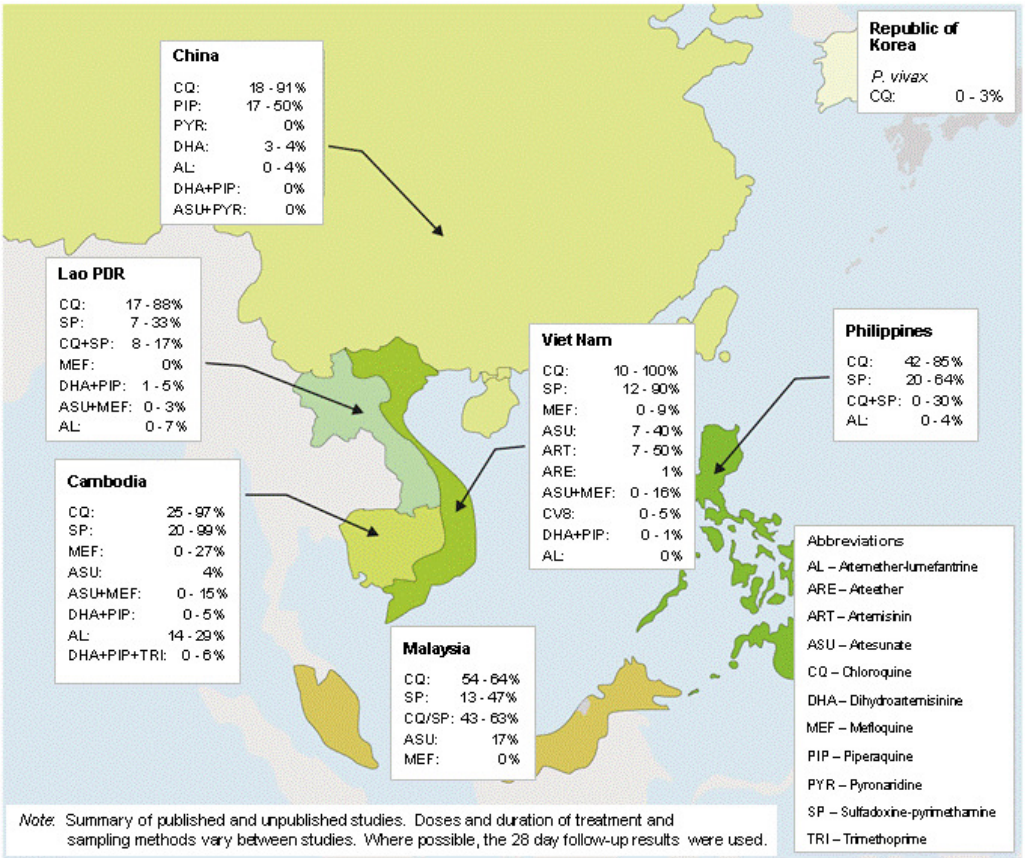

Figure 4: Drug-resistance in Malaria, South East Asia [102].

0.2 Aims of our research

Despite the fact that many scientists have been studying drug resistance and searching for practical solutions against it, the results so far are very limited. Mathematicians have started to pay attention to the topic in recent decades. However, it is difficult to get all biology-related phenomena in the form of precise mathematical formulas.

Taking into account that there are many diseases and each of them has various medical regiments, it is not possible to include all of them in one general model. Moreover, when categorizing infectious diseases into two groups, the group of single-host diseases and the multi-host diseases, the latter case is often omitted from studies. In some sense, single-host diseases (such as HIV and tuberculosis), are a little bit less complicated for modeling. We will come back to this point later.

In our study, we have wanted to address the complex case of multi-host diseases. The objectives of the project are as follows:

1. to describe the dynamics of vector-borne diseases, focusing on malaria, through new mathematical models,

2. to investigate the model system analytically,

3. to study the models numerically,

4. to consider different settings in order to find out suitable strategies to reduce drug resistance, control the diseases and to suggest which experimental works need to be done to provide a more precise understanding.

0.3 Description of the contents and our contributions

This dissertation is organized in four main chapters. In each chapter, our contributions are stated concisely in italics.

Chapter 1. We would like to reserve chapter 1 to:

- *Summarize the necessary medical background,*

- *Summarize the state of the art: mathematical models concerning drug resistance.*

This chapter starts by explaining the biological and medical background and reviews shortly some existing epidemic models of drug resistance. We recall most of the relevant concepts and focus on one of the most common vector-borne diseases, malaria. The established epidemic models which take drug resistance into account are classified in different groups: HIV-AIDS, tuberculosis, malaria, other diseases.

In each group we divide the models into deterministic and stochastic forms if necessary.

Chapter 2. In this chapter, we present our new model of drug resistance in vector-borne diseases. It is described by a system of ordinary differential equations. Here we work on:

- *Modeling: compartment population dynamics with drug treatment,*

- *Analysis: proving the existence of local and global solutions, uniqueness and positivity,*

- *Numerical study: posing and solving the parameter estimation problem and numerical simulation.*

This chapter presents a new model described by a system of ordinary differential equations. The first part is modeling, which contains the network system, the formulas of the dynamical system in differential equations and the detailed explanation of every component appearing in the model. The following two parts study the model analytically and numerically. We prove here the existence of solutions locally and globally. The uniqueness and positivity of the solution are included. We also describe in detail the problem of parameter estimation and numerical simulation. Using VPLAN - a software package developed in Interdisciplinary Center for Scientific Computing (IWR) Heidelberg, we estimate the unknown parameters and obtain an agreement with the data from Burkina Faso, Africa. Numerical simulations with different model settings are performed leading to useful medical interpretations which we discuss in detail in the last part of this chapter.

Chapter 3. In chapter 3, we explore a new challenge with structured population:

- *Modeling: general structured population dynamics of vector-borne diseases,*

- *Analysis: transforming the system to a new form by expanding the method of characteristics for system of equations, proving the existence, uniqueness and positivity of the solution for unknown boundary problem,*

- *Numerical approach: proposing a constructive method for doing numerical simulation,*

This chapter presents general structured population dynamics in an integral partial differential equation system. The first part describes and explains the new network system and the model formula. We extend here the mathematical theory using more than one characteristic. The boundary conditions for integral partial differential equations are carefully modeled with inspiration from the canonical birth law. After transforming the system to integral form, the existence and uniqueness of the solution are obtained by using the Banach fixed point theorem with the help of a newly defined norm. Since the model is new and complicated, software for complete simulation has not yet become available. However,

we present an approach for numerical studies. The complete numerical simulation for such a system can be a new interesting project.

Chapter 4. This chapter provides:

- *Summary of the results,*

- *Discussion of the perspectives of further study.*

This chapter summarizes the results and states our remarks on the perspectives. We discuss some open questions of possible directions we could not include in the study because of time limitations.

Chapter 1

Medical background and literature review

In this chapter we present the medical background of drug resistance in infectious diseases and a short review of some existing models in epidemiology to see what is currently the state of the art.

1.1 Medical background

To be ready for modeling, we first need to understand the fundamental background of infectious diseases, their transmission and the concept of drug resistance. Afterwards we present some facts on malaria - the most common vector-borne disease.

1.1.1 Infectious diseases and drug treatments

Infection is the invasion of one organism by another (usually smaller) organism. The invasion agents are often called parasites while the other organisms are their hosts. Most infections are harmless or even good for the host. However, some pathogenic infectious agents bring harm to their hosts and cause some severe diseases [83]. In general, any organism can be the host, such as animals or plants. In our context, the hosts are normally humans.

A disease that can be transmitted or spread from one host to another is called an infectious disease.

As suggested by their name, infectious diseases often come with some pathogens. Infectious diseases are a heavy burden not only because they harm their hosts but also because of their transmittable property. Infection happens when some specific types of contacts take place between infected individuals and uninfected individ-

uals. In humans these contacts can happen in many ways, e.g. by air, by food, by blood, by skin contact or by using the same equipments. In addition, some other organisms can also be involved in the transmission as intermediate hosts.

Provided below is a table that summarizes several types of infectious agents (reproduced from [83]).

Table 1.1: Different types of infectious agents.

Agent Types	**Characteristics**	**Examples (diseases)**
Micro-parasite		
Virus	Small, simple, usually can replicate only inside the living cells of organisms	HIV, measles, mumps, rubella, smallpox, severe acute respiratory syndrome (SARS), influenza
Bacteria	Larger, more complex than viruses- many are able to grow independently but some require a cell host	Mycobacterium tuberculosis, Bordetella pertussis (whooping cough), Salmonella typhi (typhoid fever)
Protozoa	Larger single-celled organism, more complex than bacteria - many are able to grow independently but some require a cell host	Plasmodium falciparum (malaria), Entamoeba histolytica (dysentery), trypanosoma brucei & Trypanosoma cruzi (African & American sleeping sickness), Giardia lamblia (Giardiasis)
Macro-parasite		
Worms	Large (1mm to 10m), multicellular organisms	Schistosoma mansoni (schistosomiasis)
Arthropods	Insects, lice, ticks and their relatives	Ixodes spp (ticks)

From looking at the history, we have learnt that until the beginning of the twentieth century, there was hardly an effective medication to treat infectious diseases. Even today under poor health care conditions, infectious diseases continue to be among the major causes of deaths.

In 1928, Penicillin, the first usable antibiotic agent was discovered. Although according to rumors, antibiotic-like materials were observed before, the credit was given to Alexander Fleming, a Scottish biologist and pharmacologist. The discovery launched a completely new era in human medicine [97]. Penicillin saved an incredible number of lives during World War II.

Since then there have been a lot of efforts to search for antimicrobial agents. Based on the fundamental difference between bacterium and human cells, scientists were able to find many new antibacterial compounds, such as Cefalexin, Erythromycin, Amoxicillin, Streptomycin, etc. However, some other microorganisms, such as viruses, usually live inside living host cells, therefore making it harder to fight them. So far only few antiviral or anti-fungal agents have been made available. Recent news from Lincoln Laboratory, Massachusetts Institute of Technology, report that a team has been working on a "Broad-Spectrum Antiviral Therapeutic" and obtained some promising results in trials on mice [71]. The new drug name is DRACO - a short form of Double-stranded RNA (dsRNA) Activated Caspase Oligomerizer, see figure 1.1. The group would like to test more on other animals and then later on humans.

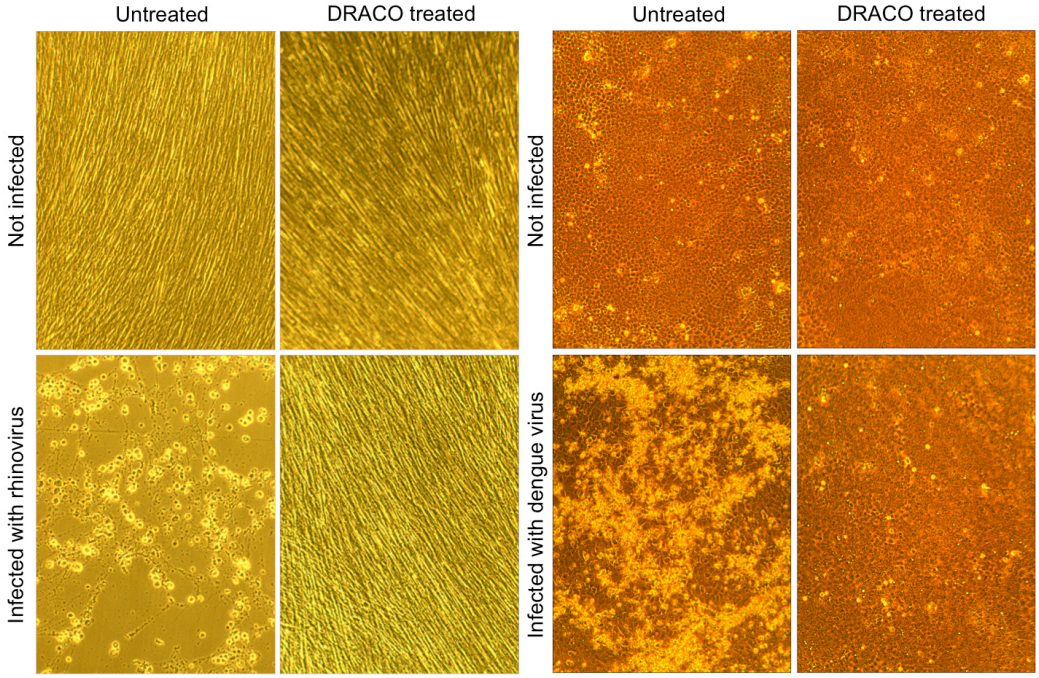

Figure 1.1: DRACO successfully treats virally infected cells and has no toxicity on healthy cells - trials on mice [108]. Notice how the patterns of the healthy cells stay the same while the patterns of the infected cells change to healthy patterns after treatments.

1.1.2 What is drug resistance?

Here we would like to discuss the term "drug resistance" and where it often appears. From the beginning drug resistance has been mentioned [19] as

"the ability of a parasite strain to survive and multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject".

This definition refers only to the persistence of parasites after treatment, which is why later it is carefully modified so that the drugs at least

"gain access to the parasite or the infected cells for the duration of the time necessary for its normal action" [19].

This particular definition was originally about malaria but it sufficiently met the requirement to be generalized to other diseases. In addition, Medical Subject Headings suggested that drug resistance should be differentiated from drug tolerance, which is the progressive diminution of the susceptibility of a human or animal to the effects of a drug due to long continued administration [96].

Theoretically, a resistance problem can happen to any drug. However, antimicrobial agents are the most common group which encounters this issue. Why do they have much higher potential to encounter this issue compared to other medicines? The answer relates to microorganisms - the typical pathogens of infectious diseases.

We know that medicines like insulin and anti-hypertensives have been in use for centuries. They interact directly with human cells so the good or harm is shown only in the particular patient under treatment. The medicines should have the same effect worldwide and likely keep their effects in the future [97].

On the other hand, antimicrobial agents are not supposed to harm the patient at all or no more than a certain permissible limit. They mainly attack the microorganisms. The sensitive parasites can be cleared, but the resistant strains are likely to remain. Because microorganisms usually multiply very fast and have opportunities to continue their life-cycles in other hosts, they can spread throughout the community. As a consequence antimicrobial agents lose their effects in future generations.

Overall, antimicrobial drugs are the most common group facing the resistance problem. That is the reason why the term "drug resistance" is often used synonymously with "antimicrobial resistance".

Remark. In some places we meet also "bacteria resistance", "fly resistance", "resistant bacteria" or "resistant mosquitoes" or "resistant cell" (in cancer chemotherapy), etc. In most of the cases, drug treatments are involved and these terms actually all imply "drug resistance".

Since there are numerous types of organisms that cause infectious diseases in humans and animals, a number of drugs have been used in hospitals and communities. Resistance is also rapidly increasing in all environments. In this tough battle, we can point out some of the most active leading agents, as in table 1.2.

Table 1.2: Leading resistant agents, reported by WHO [106].

Species/Genus	**Diseases**	**Common symptoms**
Bacteria community		
Escherichia coli	Diarrheal diseases, peritonitis	Diarrhea, abdominal pain
Myco-bacterium TB	Tuberculosis	Chest pain, blood cough
Neisseria gonorrhea	Gonorrhea	Vaginal discharge
Salmonella Typhi	Typhoid fever	Fever, sweat, gastroenteritis
Staphylococcus aureus	Pneumonia, meningitis	Cough, chest pain, fever; headache, neck stiffness
Streptococcus pneumonia	Pneumonia, Sinusitis	Cough, chest pain, fever; headache, facial pain
Bacteria- hospitals		
Acinetobacter baumannii	Pneumonia	Cough, chest pain, fever
Enterococcus faecalis	Infective endocarditis (heart)	Fever (unknown origin), malaise, fatigue, weight loss
Bacteria- Zoonotic		
Campylobacter species	Campylobacteriosis	Bloody diarrhea or dysentery, cramps, fever and pain
Salmonella species	Typhoid or paratyphoid fever	Fever, sweat, gastroenteritis, malaise;
Fungi		
Candida albicans	Candidiasis	Redness, itching, discomfort
Parasites		
Leishmania species	Leishmaniasis	Fever, sweat, weakness, weight loss, anemia
Plasmodium species	Malaria	Fever, shivering, joint pain, vomiting, anemia
Trypanosoma species	Sleeping sickness	Fever, headache, joint pain, fatigue, sleep disruption
Viruses		
Herpes simplex virus	Herpes simplex	Watery blisters (skin), mucous membranes (mouth, lips, genital)
Human immunodeficiency virus (HIV)	Acquired immune deficiency syndrome (AIDS)	Immune deficiency, fever, night sweat, swollen gland, chill, weight loss.

1.1.3 Our focus: malaria and antimalarial drug treatment

There are two main groups of infectious diseases: the first group, such as HIV/AIDS, tuberculosis, can be transmitted directly from one person to another and the second group, such as malaria, dengue hemorrhagic fever, is transmitted mainly via some intermediate hosts. From the perspective of infectious diseases, vectors are the transmitters of disease-causing organisms that carry the pathogens from one host to another [101]. That is why a disease belonging to the second group is called a vector-borne disease.

In most of the cases vectors are usually arthropods. However, technically vectors can have big size, such as cat, dog, cow, fox or raccoon, etc. Some of the well-known vector-borne diseases are shown in table 1.3.

Table 1.3: Some well-known vector-borne diseases.

Diseases	**Vectors**	**Remarks**
American Trypanosomiasis, (Chagas diseases)	Triatomine Bugs	Common in Latin America, can be transmitted in several ways, e.g. via blood transfusion.
Dengue	Aedes mosquitoes	Could turn into the life-threatening dengue hemorrhagic fever or dengue shock syndrome.
Hemorrhagic fever with renal syndrome and Hantavirus pulmonary syndrome	Rodents (e.g. Peromyscus maniculatus)	Cause by Hantavirus, prevalence in Korean, China, Russia, Argentina, Chile, Brazil, the United States, Canada, Panama and some parts of Europe.
Lyme diseases	Ticks (e.g Ixodes genus)	Mostly appears in Northern Hemisphere temperate regions.
Lymphocytic choriomeningitis	Rodents (e.g. Mus musculus)	Infections have been reported in Europe, America, Australia and Japan.
Malaria	Anopheles mosquitoes	The most deadly vector-borne disease, prevalence in tropical climate, e.g. Africa, South Asia, South America.
Typhus Fever (not typhoid fever)	Arthropod vectors (e.g. human body lice)	Typhus mostly occurs in Central and South America, Africa, northern China, and certain regions of the Himalayas.

Figure 1.2 is about all deaths from vector-borne diseases in WHO subregions. Since most of the vectors, such as flies or ticks, often appear in tropical climate, these regions seem to be at more risk compared to other regions. In a lot of African countries, many people were lost due to vector-borne diseases.

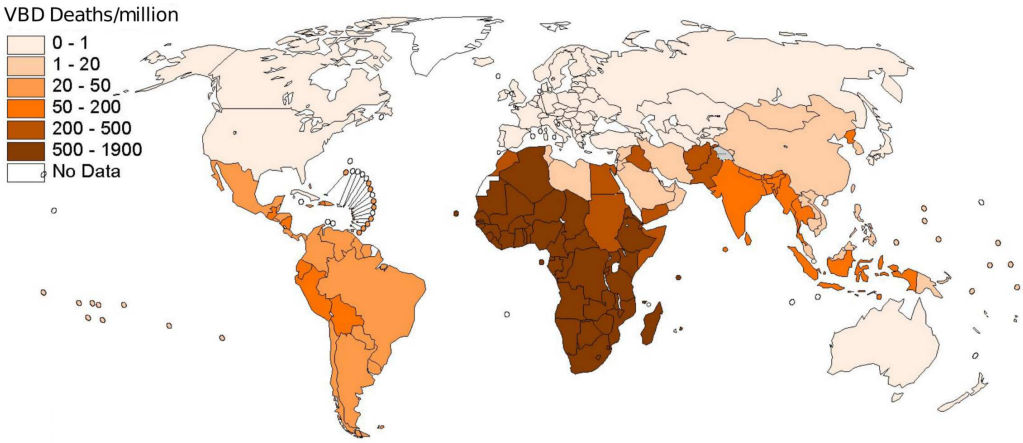

Figure 1.2: Deaths from vector-borne diseases, 2004 [109].

Among vector-borne diseases, the most deadly is malaria. It kills millions of people yearly (appropriately 781 000 people in 2009 [110]). Despite many efforts of World Health Organization as well as malaria-endemic countries to reduce mosquitoes and protect humans, malaria appears to be one of the most dangerous diseases for children, especially those under five years old. At this age children do not have their own strong immunity against malaria.

In the past, most of the malaria patients had to suffer without any treatment. They often did not know what kind of disease they had encountered and mixed it up with common fever. The earliest evidence of parasites was found in mosquitoes preserved in amber from the Paleogene period - around 100 million years old [105]. In addition, research on pre-dynastic mummified remains shows that around 42% of ancient Egypt carried Plasmodium falciparum malaria, as indicated in figure 1.3. A lot of famous people were lost due to malaria, e.g. Alexander the Great (Macedonia, 323 BC), Otto II - the King of the Germans and Emperor of Rome (983), Pope Leo X (1521), King Mongkut of Thailand (1868).

The life cycle of malaria consists of two parts: one inside human hosts and one inside mosquito hosts. Both are shown in figure 1.5.

Although it is believed that the extract of some herbs have been used to treat "deadly fever" in Asia a long time ago, the first synthetic medications for malaria were reported in the twentieth century. Starting from the discoveries of Quinine, Chloroquine, many other compounds were found, e.g. Amodiaquine, Sulfadoxine,

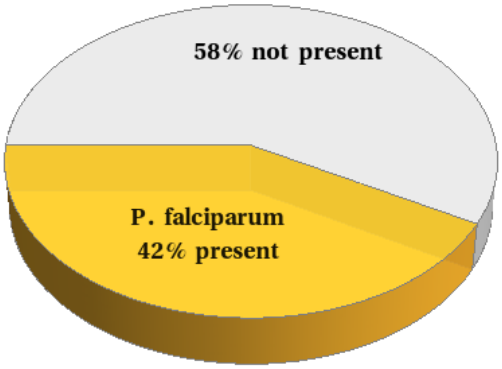

Figure 1.3: Percentage of P. falciparum malaria in ancient Egypt: investigation on pre-dynastic mummified remains [63].

Figure 1.4: Insect was trapped in amber, [105].

Mefloquine, Artemisinin, see more at figure 1.6. At the beginning most of the drugs were really effective. The fact that they rapidly lost their effects causes a serious headache for many scientists and doctors. One of the challenges is that malaria comes together with Anopheles mosquitoes and parasites. The four main types of parasites are Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale and Plasmodium malariae. Their organisms are much more complex compared to pathogens with single-cell or sub-cellular structure, such as bacteria, archaea, viruses, etc. This also partly explains why there are only few mathematical models concerning drug treatment of malaria.

What may influence drug resistance?

- In most of the diseases, it takes a long time to find out which factors may characterize and reduce drug efficiency. Usually there are many individuals of the pathogen population which already have “resistant” mechanisms. They are naturally not eliminated by drugs. When infected people take medicine, it reduces the number of sensitive parasites and makes a good environment for resistance to grow.

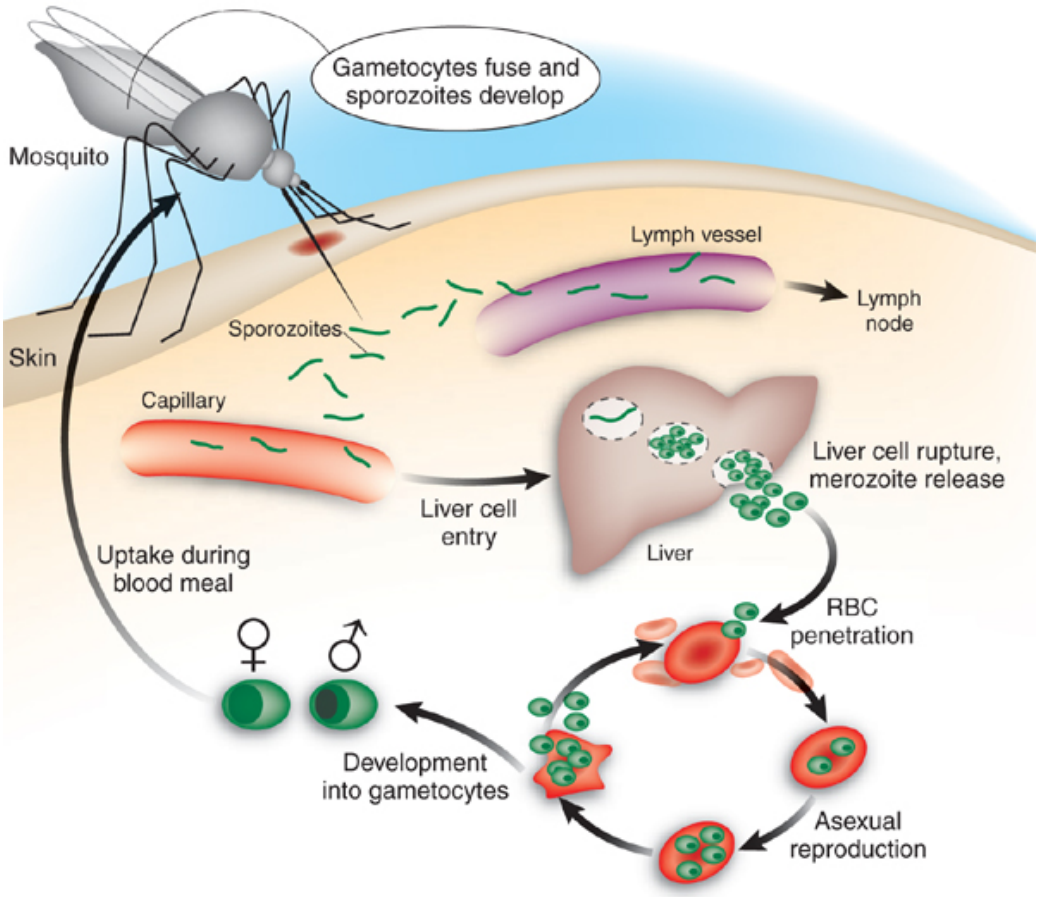

Figure 1.5: The life cycle of malaria, one of the three most prevalent infectious diseases and the most deadly vector-borne disease [103].

- In malaria the parasite organisms are very complex. They would either mutate or adapt variously. Due to natural selection they have a better chance of survival and maintain their best genetic system. Therefore, their new generations are "fitter" in a drug environment.

- Another important cause of drug resistance is that malaria is more widespread in tropical places, such as Africa, where it is difficult to have a global policy to treat all patients properly.

At the moment a majority of doctors believe that only Artemisinin-based combination therapies can provide some hope for clearing malaria in patients. However, there is more and more evidence that parasites also resist to them.

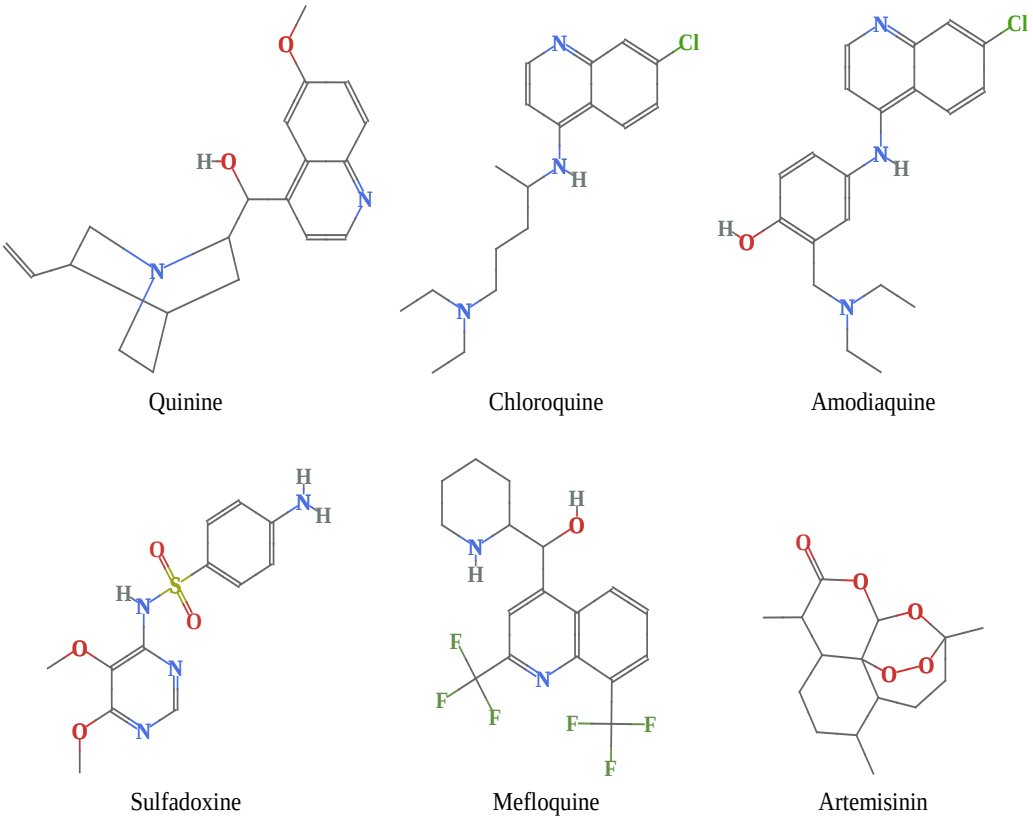

Figure 1.6: Chemical structures of several antimalarial drugs.

1.2 Existing mathematical models of drug resistance

There is a great amount of research on drug resistance in general. We are going to address here the recent works related to *quantitative mathematical models*. They are selected mainly from MathSciNet and have connection with many different diseases. To make it easy to follow we have divided all of them into four groups: the first one concerning HIV- AIDS, the second concerning tuberculosis, the third for malaria, the fourth about cancer and the fifth about other diseases. We are sure that there are a lot of other relevant papers, which are not listed in mathematics but in other fields, e.g. epidemics. We will discuss those works elsewhere.

We also have to state that we are not going to represent the mathematical formulas in this short chapter, but we do our best to select and show some important model frameworks. We believe that through these selected models, the readers can get an overview of the modeling landscape so far. Since modeling in drug resistance is a fairly recent emerging field, it is not our main aim to make

evaluations or statements on the quality and the importance of the models we are going to review. By seeing how much other scientists are interested in the modeling approach, readers certainly see important and popular models.

1.2.1 HIV- AIDS

To date most of the mathematical models concerning HIV-AIDS are deterministic. Since HIV is small and very simple, it can multiply very fast. The virus population has often been studied and considered as a large population. This reason helps to lessen the stochastic effects.

Deterministic models about HIV- AIDS drug resistance

To begin with, we have a look at the short review written by Heffernan and Wahl [49]. Here the authors included not only mathematical papers but also those that came from related resources, such as epidemiology, immunology, etc. They focused on two parts: adherence and structured treatment interruption. Adherence was described through three papers of Wahl and Nowak (2000), Phillips et al. (2001), Huang et al. (2003) [84, 69, 52]. Structured treatment interruption was described through five papers of Kirschner and Webb (1996), Dorman et al. (2000), Bonhoeffer et al. (2000), Wodarz (2001), Walensky et al. (2002) [59, 30, 18, 88, 85].

Most of the models were given in quite detail. Mathematical parts are not too complex, such as standard pharmacokinetics in exponential decay, ordinary differential equations, pattern study, so it is recommended for interested readers. Besides that, Heffernan and Wahl also discussed the models' drawbacks, including their own model. Those drawbacks were, for example, neglecting cross-resistance between mutations, assuming that all the drug-resistant strains have the same infectivity (in Wahl and Nowak); neglecting effects of the latently infected cells, assuming that only one mutation can occur at a time (in Phillips et al.); neglecting immune response (in Kirschner and Webb, Dorman et al.); assuming that the early-stage mutants were less fit than the wild-type virus, even when drugs are present (Dorman et al.), etc. The authors suggested that more research should be done in both adherence and structured treatment interruption. Their effects on the drug-resistant mutants are still very challenging for both theoreticians and clinicians.

Not included in the above review, Smith and Wahl used impulsive differential equations to describe the dynamics of T cell populations and viruses in different drug behavior [77]. It was assumed that wild-type strain was controlled by both intermediate and high drug concentrations, while a mutant strain was controlled only by high drug concentrations. Using the classical analysis to study the equilib-

ria and their stability, the authors claimed it was a good approach to capture the effect of three relatively different drug concentrations (low, intermediate, high). However, some disadvantages remained, such as: the drug effects must be instantaneous; each and every dose must be taken properly. Unlike the previous works, the relationship between drug resistance and adherence was not included.

Another recent review was written by Rong, Feng and Perelson in 2008 [72]. In fact, these three authors are among productive researchers of the field. Mainly the works by them and their collaborators were presented. Apart from the part that introduced general models describing virus and cell dynamics, the authors paid attention to some specific models related to drug resistance. They considered several problems, such as dominance of a wild-type strain in the absence of therapy; development of a resistant strain when antiretroviral (ARV) drugs were used; eradication of both strains; occurrence of resistance when a small number of drug doses were missed and cases when more doses were missed.

Targeting drug resistance, Rong et al. had a pretreatment two-strain model with a wild-type (sensitive) strain and a resistant strain in the form of ordinary differential equations. The effect of antiretroviral therapy was included by additional parameters. In analysis, drug efficacies (of reverse transcriptase inhibitors and protease inhibitors) were first assumed to be constant for both strains. Later, the authors found it was necessary to include time-varying drug efficacy and effect of adherence patterns. Following the models, a standard analysis (e.g. concerning the steady states and stability) was presented. Some of their numerical results are shown in three figures 1.7, 1.8, 1.9. They related to lots of the common quantities in the authors' models.

The upper panel of figure 1.7 contains the relation between reproductive ratio and the sensitive strain while assuming drug efficacy on resistant strain is different in (a) and (b). The lower panel is the relation of virus steady states and reproductive ratios. The authors claimed that the wild-type virus could be completely suppressed even when the reproductive ratio R_s is greater than 1. The resistant virus would die out only when reproductive ratio was smaller than 1, and remained at a very low level when reproductive ratio was larger than 1.21 - this was not clearly shown in the figure due to the magnitude of the vertical axis [72]!

In figure 1.8 and 1.9, the number of uninfected cells, wild-type viruses, resistant viruses and total viruses were presented under two conditions: perfect adherence and imperfect adherence. Drug resistance emerged in the second condition much faster than the first one. In the latter case, missing every other dose or missing more doses did not change so much the total viruses. According to the authors, when missing more doses, the wild-type viruses continued to survive while the resistant viruses stayed low due to not enough selecting force.

In the same paper, the authors also discussed the persistence of HIV. There were several factors which are not easily included in deterministic models, e.g.

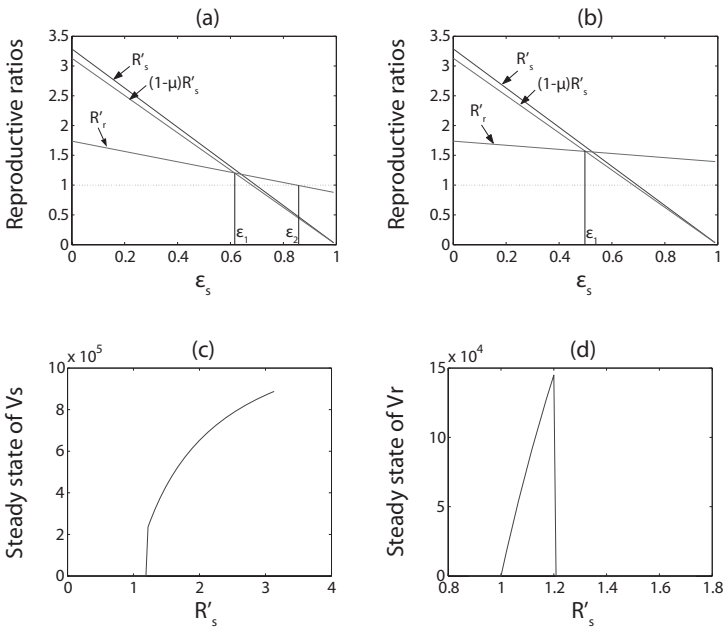

Figure 1.7: The upper panel: the reproductive ratio of each strain as a function of the drug efficacy ϵ_s for the wild-type strain, (a) $\epsilon_r = 0.5\epsilon_s$, (b) $\epsilon_r = 0.2\epsilon_s$. The lower panel: the steady states of the wild-type and resistant strains as the function of reproductive ratios [72].

poor drug penetration in specific sites, activation of latently infected cells. These reasons would make the problem of HIV eradication very difficult.

After interpreting the results, Rong et al. realized that there were several serious model drawbacks, e.g. "the patterns of adherence" were not very realistic; spatial heterogeneity (different drug concentration in different parts of the body) was not yet taken into account, etc.

Apart from the above works, there were only few other deterministic models, which shared the same model types as well as analytical and numerical patterns, such as in [61, 74]. There is a lot of room for model improvement.

Stochastic models about HIV- AIDS drug resistance

Unlike deterministic models, stochastic models about HIV- AIDS drug resistance are scattered. To our knowledge, none of them really drew a great amount of attention from the community. In the nineties Tan derived a stochastic model for drug resistance in AIDS chemotherapy, extended the work by Longini et al.

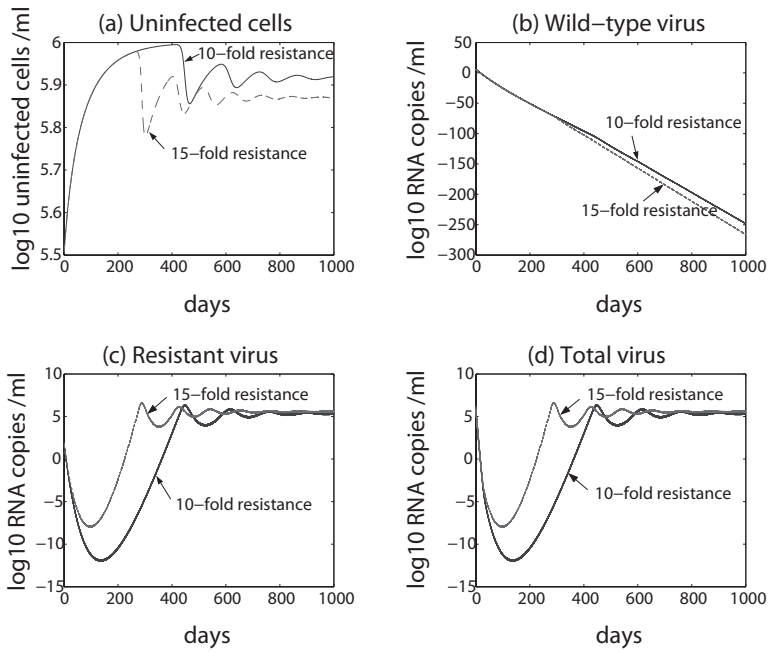

Figure 1.8: The dynamics of uninfected cells, wild-type viruses, resistant viruses and total viruses with perfect adherence [72].

and himself, see [80] and the references therein. By using a probability generated function, the HIV incubation distribution and its moments were studied under treatment of antiviral drugs. Later, in a book of Tan and Wu [81], Liang et al. used "Bayesian approach for assessing drug resistance in HIV infection using viral load"; Zhou and Dorman used "a branching process" to model HIV drug resistance. Close to the latter, Healy and DeGruttola mentioned two possible extensions to the two works of Albert (1962), Foulkes and DeGruttola (2003) in their paper "Hidden Markov models for settings with interval-censored transition times and uncertain time origin: application to HIV genetic analyses" [47]. They continued to use Markov models in two other papers [48, 51]. Here statistical method was adopted to study viral genetic states. Eriksson et al. [32] also used a statistical procedure (method of Pyrosequencing) to estimate viral population.

1.2.2 Tuberculosis

There were a lot of mathematical models describing tuberculosis, but only few of them concerning drug resistance. They were often deterministic although some stochastic models, such as Markov chain models, were also used in general cases. Two leading experts in this field, Castillo-Chavez and Song, contributed a review

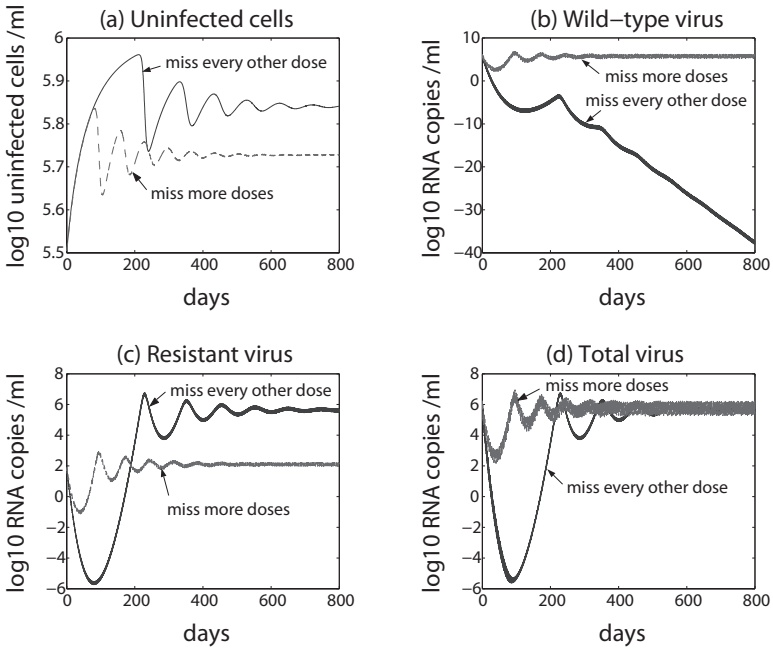

Figure 1.9: The dynamics of uninfected cells, wild-type viruses, resistant viruses and total viruses with imperfect adherence [72].

on "dynamical models of tuberculosis and their applications" [22]. They discussed the history, models with demography, cell-based models and few others (see references therein) shortly. The main part mentioned the intrinsic mechanics of transmission and control strategies.

In transmission model several authors developed ordinary differential equation models with drug-sensitive and drug-resistant strains, such as Blower et al. in [16], Castillo-Chavez and Feng in [21, 6]. Feng et al. also combined models for both multiple strains and variable latent period. Here the authors included the age of the infection with drug sensitive strain [34]. Details are presented in figure 1.10. Using analysis and numerical simulation, the authors answered their main question concerning the effects of variable periods of latency on the transmission dynamics of tuberculosis. They concluded that the arbitrary distributed latent stage did not yield very different qualitative dynamics compared to their works before [21, 35].

Concerning control strategies, the review of Castillo-Chavez and Song recalled vaccination, treatment of latent period, etc. There was no direct study on how to reduce drug resistance. A few other papers later also studied tuberculosis in dynamical consideration [42, 27] using the approach mentioned in the above

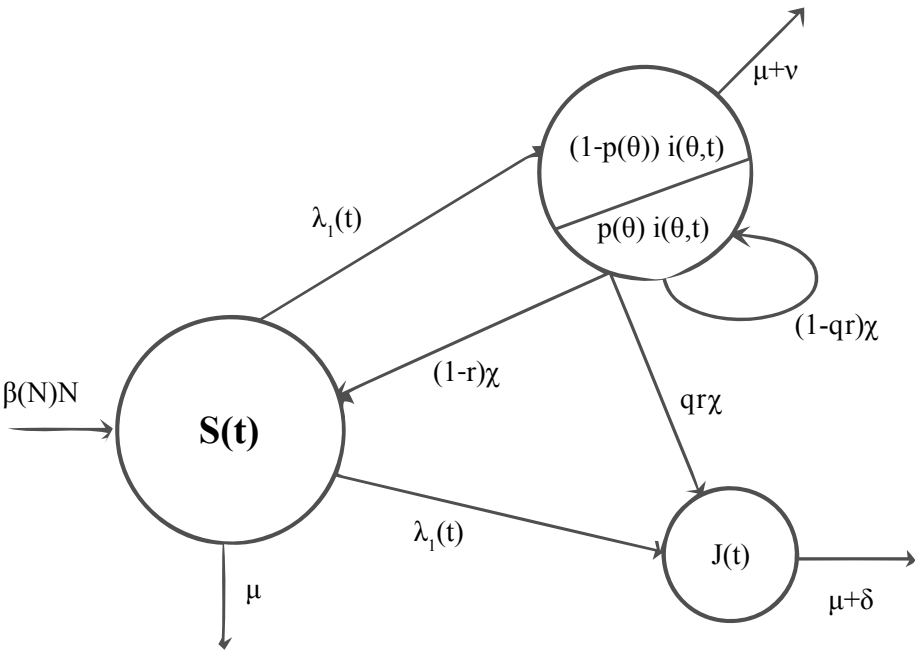

Figure 1.10: Model network of tuberculosis from Feng et al. 2002. The authors denoted $S(t)$ as the number of susceptibles at time t, $i(\theta, t)$ as the infection-age density of infected individuals with the drug-sensitive strain at time t and $J(t)$ as the number of infected individuals with a drug-resistant strain at time t [34].

review. The problem of drug resistance in tuberculosis is still a challenging open field for further investigation.

1.2.3 Malaria

In the previously mentioned diseases, the patients often go to hospital and obtain certain treatments from clinicians. Treatment policies are well-defined and followed. In addition, there is only interaction between parasites and one direct host. Much worse situations apply to malaria and several other vector-borne diseases. They often appear in countries where the health care systems are quite weak. Patients may not have access to any treatment or receive inappropriate treatments. Lack of proper health care systems causes mixing up the symptoms of malaria with those of other illnesses, especially common fever. Malaria usually involves parasites and two hosts. Due to the involvement of non-human hosts, mostly flies or insects, the dynamics of the whole system become difficult to predict and highly environment-dependent. Parasites causing malaria, like Plasmodium falciparum, have complex cell structures which enable them to survive in many tough environ-

ments. In addition to a quantitative study of malaria, model validation requires a large collection of data. In practice data collection is often quite imprecise and very expensive.

So far there have been only a few mathematical models which included drug resistance in malaria. Readers, who are not interested in complex analysis but rather in model simulation or numerical methods, can find their ways in the reviews of Schapira et al., Watkins et al., Hastings et al., Artavanis-Tsakonas et al., White [73, 86, 46, 7, 87], etc. They covered several classical models in epidemiology, making them easily accessible to experimentalists and field workers. For readers who are interested in more analytical works, there are some scattered works in this field, such as Aneke (2002), Feng et al. (2004), Bacaër and Sokhna (2005), Esteva et al. (2009) [4, 36, 8, 33].

In short, most of the authors chose differential equations to describe the population dynamics. Aneke included an ordinary differential equation model of human hosts and vectors, then later divided hosts into those that "only carry sensitive parasites" and those that "carry resistant parasites". Feng et al. also modeled the same classes, but divided humans into two groups corresponding to two genotypes of the sickle-cell gene (AS, AA). Bacaër and Sokhna created a model with spatial diffusion for similar quantities (five compartments for humans, three compartments for mosquitoes). Esteva et al. had four compartments for humans, three compartments for mosquitoes in an ordinary differential equation system. Most of the authors used classical theory of differential equations to study the existence of the equilibria and their stability, provided numerical simulation to visualize and support analytical parts. Beside the theoretical results, so far the data for model calibration and validation is still a big question without an appropriate answer.

In conclusion, there are many phenomena blocking successful models in malaria, particularly in antimalarial drug resistance. The few existing models really encouraged fellows to contribute further studies to improve the situation.

1.2.4 Cancer

Among all mathematical papers concerning drug resistance, more than one third studies cancer. Although cancer is not an infectious disease, we would like to mention it briefly here. In cancer tumor cells play the role that microorganism do in general infectious diseases. They can change, adapt or mutate to escape from the presence of drugs. The few first records of quantitative models in drug resistance concerning cancer treatment date back to the end of the seventies and the beginning of the eighties. It is no surprise that they are mostly initiated by related studies, both quantitative and non-quantitative concerning medical treatment. We are going to have a quick look through most of them.

We would like to mention first a work by Clairambault [25]. He wrote a synoptic

review on "Modelling physiological and pharmacological control on cell proliferation to optimise cancer treatments". Having background both in mathematics and medicine, he answered positively the question how mathematics could help to cure cancer. In the first part of this review, one can find a nice summary about biological basics of cancer. The author stated that among all treatment therapies, (e.g. surgery, radiotherapy, immunotherapy) drugs were the main weapons for fighting cancer. However, there were toxic side effects on healthy cells, drug resistance in tumor cells and genetic difference from each individual when processing drug treatment, etc. With more than a general interest in modeling tumor cell proliferation, Clairambault was really concerned with drug modeling and anticancer treatment optimization. The author mentioned drug resistance as a difficult issue in cancer treatment and to prevent this was a big question for scientists and clinicians. Based on the available literature, he pointed out two different ways of describing the evolution of cell populations including resistance: the classical way used ordinary differential equations theory with equilibrium, stability and bifurcation; the recent way looked more complex, e.g. adaptive dynamics, structured populations. The latter was initiated in theoretical settings but remained in development. In contrast to the beginning of the review, the last part did not present detailed information. Clairambault's review was also a bit biased on differential equation models.

Numerous studies remind us that there are several model types in cancer treatment. It can be deterministic or stochastic, continuous or discrete, structured or non-structured, spatial or non-spatial, etc. For convenience we also classify all models by two groups: deterministic and stochastic. In the following we recall some stochastic models first, then turn to deterministic models.

Stochastic models of cancer treatment

Goldie and Coldman were credited by a lot of authors as the pioneers who worked on cancer treatment models. Goldie and Coldman both worked in cancer research and they contributed a lot of studies in medical treatment. In their few early papers the existence of drug sensitive and resistant strains was mentioned. They were among the few first people who began to use quantitative theory to study cancer development, especially in drug resistance. In 1979, they developed a model to study drug sensitivity and the mutation rate of tumors [39]. This model showed that the probability of resistant phenotype increased with mutation. The result of this paper was cited in several later studies as one of the first few attempts to model drug resistance in cancer treatment [68, 90, 70]. In 1998, they wrote the book "Drug resistance in cancer: mechanisms and models" [40]. The book contained a lot of works by Goldie, Coldman and their collaborators. It included mechanism of stem cells and tumor growth, molecular aspects of drug resistance and some quantitative models about random mutation. It was an accessible book,

especially for oncologists. However, some mathematicians might find this as a minimized version of mathematical modeling in cancer chemotherapy.

Based on the concepts of Goldie, Coldman, MacKillop et al. [39, 41, 62], Hiep built a model of mutant growth in tumor cells [31]. The author mainly focused on mutation dynamic since he believed that mutation was highly connected to the drug resistance mechanism. A joint probability function was used to describe the relation between stem cell and mutant cell tumor sizes. Hiep showed that his result was in good agreement with some other studies [62, 41] despite the fact that different approaches were employed.

Not far from the direction of Goldie and Coldman, Tan and Brown developed a non-homogeneous stochastic model for drug resistance in chemotherapy with immunity [79]. The probability distribution of the number of resistant tumor cells, the expected value and the cumulants of the number of resistant tumor cells were of interest. The authors did some simple numerical simulations and showed that immuno-stimulation plays a great role in determining the above quantities.

As a further probabilistic approach, Birkhead and Gregory proposed a discrete model for drug resistance [13]. We redraw their diagram in figure 1.11 since this was and still remains common for a number of cancer treatments.

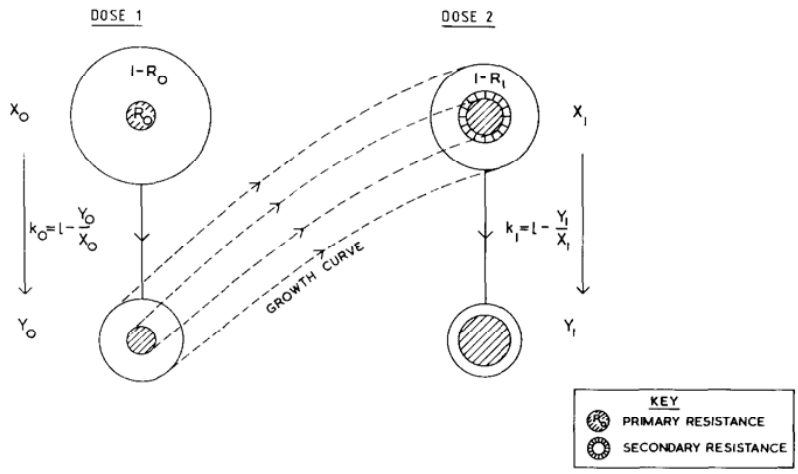

Figure 1.11: Model diagram from Birkhead and Gregory, [13].

In this paper the fractional tumor reduction of drug dose and the tumor size in single-agent therapy as well as multi-agents were investigated. However, the lack of precise measurements and adequate knowledge could limit the potential applications. Later, Birkhead also developed a model to study the probability that there is a certain number of mutant and normal cells at a time point. He used the theory of partial differential equations to find the probability generating

function.

At around the same time in the eighties another direction to address the drug resistance issue was suggested by Gyori, Michelson and Leith as an extension of the ordinary differential equation system from Jansson- Revesz [55, 43, 65]. A stochastic term was added to the system. The authors briefly discussed analysis and compared their numerical simulation to experimental data from Leith and his collaborators.

In 2000 Coldman and Murray continued their probabilistic models with optimal control on treatment regimens [26]. They compared their model prediction to data in clinical breast cancer. In 2004, Gaffney [37] developed the model from Goldie and Coldman a bit further and included cell cycle effects or age structures. This was close to what Chiorino et al. had published before [23]. Gaffney also compared his numerical simulation with the one of the model from Goldie and Coldman.

In another approach, Harnevo and Agur used the branching process theory to study the dynamics of gene amplification. Kimmel et al. also investigated the continuous branching walk models in [56]. This motivated Kimmel, Swierniak, Polanski, Smieja in further works [58, 78]. There they transformed the model to infinite system of linear (bilinear) differential equations. From this, they considered the optimal problem and solved it classically by a gradient method. A review of this thread, mainly the works by Kimmel, Swierniak and their collaborators, can be found in [57].

Deterministic models of cancer treatment

Compared to the stochastic direction, developed earlier in the end of the seventies, eighties and nineties, the deterministic direction has been active more recently, at least concerning models on drug resistance.

Jackson et al. developed a model based on the model of tumor growth from Byrne and Chaplain [20]. The model described the reduction in volume of a vascular tumor in response to chemotherapy. It consisted of a partial differential equation system, expressing the interaction between drug concentration and tumor cell density. They began with radially symmetric coordinates, and later relaxed this assumption partially [54, 53]. The authors did some numerical simulations to demonstrate how the resistant cell population influenced other quantities, such as tumor evolution, curing duration, etc. Despite several attempts, the model analysis still required a lot of simplified conditions. In 2003, motivated by Dordal et al. (1995) [29], Jackson generalized the model to investigate the mechanism of Doxorubicin in tumor model. This model aimed to find a dosage strategy for tumor reduction and parameters which were sensitive to resistant tumors. The author studied this model numerically, so it was less theoretical than his two previous

works. Later, using the Banach fixed point theorem, Zhou proved theoretically that a similar model had a unique global classical solution, [91].

In another context, Banasiak and his co-workers [10], [11] studied a system of infinite linear ordinary differential equations. In which they modeled neoplastic cells with different drug resistance levels. This was a simplified alternative to structured population models.

1.2.5 Other diseases

Other models discussed drug resistance in schistosomiasis, influenza, etc., primarily in relation to antibiotics or antimicrobials. Most of the authors posed their models in similar forms to what we have seen above. The preferences were dynamical systems, differential equations, probability functions and Markov chains, etc. Many works focused only on mutation, which, the authors argued, was the main origin of drug resistance. Some others focused on understanding how drugs had been administrated and studied the development of immunity under different treatment policies. Some focused on the transmission of infection and/or the spread of diseases spatially.

There are two main ways that have been adopted to include the effect of drugs on patients and community:

- Direct way: drug was mentioned as one independent quantity, can be in specific name or type, drug concentration, number of doses, patterns of treatment or adherence, etc.

- Indirect way: drugs were modeled in other quantities, such as immunity boosting, recovery rate, different effects on sensitive and resistance strains.

After examining drug resistance models, we see that neither the quantity nor the quality have been comparable to other fields. Scientists, especially mathematicians, have only recently begun to consider drug resistance. In this critical time when many of our drugs are losing their therapeutic effects, we need to spend more effort on gaining insight into the related mechanisms and into designing effective control strategies.

Chapter 2

Population dynamics with drug treatment

In this chapter, we present a network of all population compartments, formulate the dynamical system and study this analytically and numerically.

2.1 Modeling of population dynamics with drug treatment

We divide the modeling process into three sub-sections: the first one introduces the model network, the second presents the model formulation and the third summarizes the system, all the model parameters and their meanings.

2.1.1 Network of compartments

We would like to model dynamics of pathogen, vector and human populations. We consider two hosts: number of humans denoted by H_1 and number of vectors denoted by H_2. The number of pathogens within the human hosts are denoted by P. Like in the classical case, there are three compartments for human hosts which we call susceptible H_{1s}, infected H_{1i}, recovered H_{1r}. We have two compartments for vector hosts H_{2s}, H_{2i} - susceptible and infected. Since drugs are employed, there are two compartments for pathogens, sensitive and resistant P_n, P_r, respectively. All transmissions among the seven groups are indicated in figure 2.1.

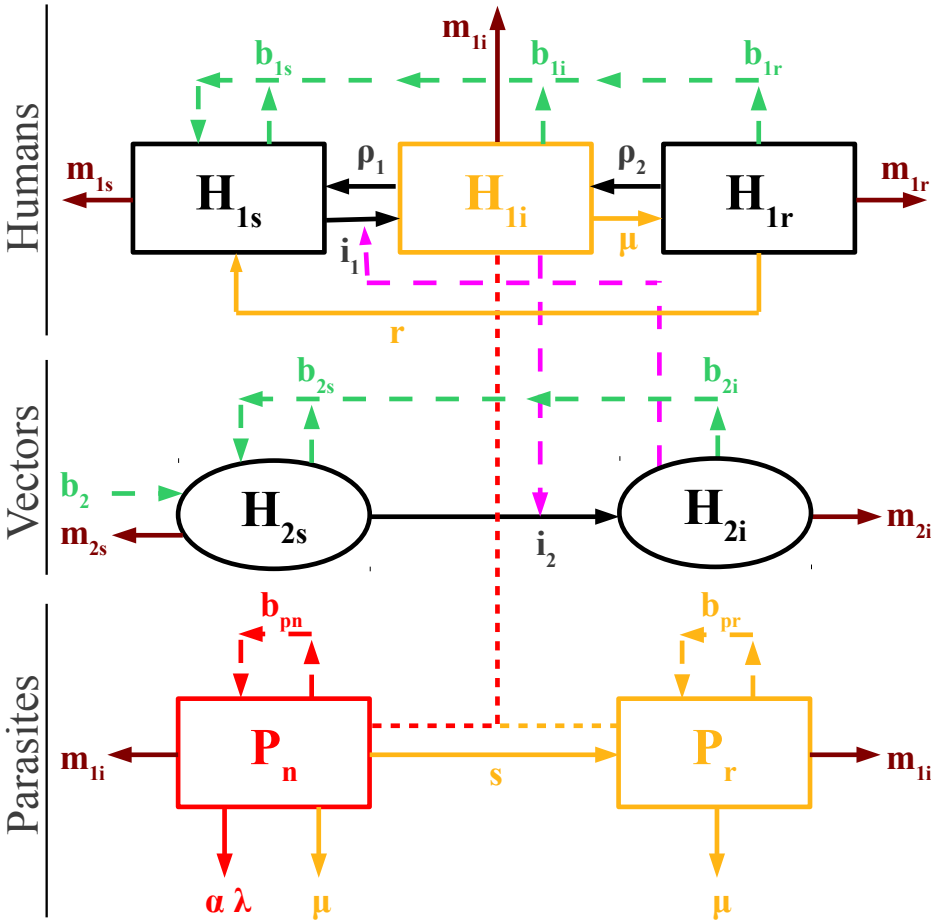

Figure 2.1: Network for the population dynamics with drug treatment.

2.1.2 Model formulation

Now we give an overview of the modeled processes, as schematically indicated in figure 2.1. Since our focus is drug treatment for humans, the model does not include some interference applying on vectors directly. We include the influence of drugs on the host population and the subsequent effect on vector and pathogen populations.

Susceptible human population H_{1s}

In vector-borne diseases, human hosts become infected mainly after coming in contact with vectors. Most of the new infants are susceptible. Like other epidemic models, we use common notations for the natural birth rates of susceptible,

infected, recovered human classes b_{1s}, b_{1i}, b_{1r}. Also, mortality rate of H_{1s} is denoted by m_{1s}, infection rate by i_1, re-susceptibility rate from infected class H_{1i} by ρ_1 (individuals from infected class H_{1i} could come back to susceptible class again if they had a very small amount of parasites) and from recovered class H_{1r} by r (individuals from recovered class H_{1r} after a certain time would come back to susceptible class H_{1s}). Values of m_{1s}, i_1, ρ_1 are given before the computation. The value of r is unknown and it can be found after fitting the data. The dynamic equation of the susceptible human population is the following:

$$\begin{aligned} \dot{H_{1s}} = \quad & b_{1s}(t,u)H_{1s} + b_{1i}(t,u)H_{1i} + b_{1r}(t,u)H_{1r} - m_{1s}(t,u)H_{1s} \\ & -i_1(t,u)\frac{H_{2i}}{H_{2s}+H_{2i}}H_{1s} + \rho_1(t,u)H_{1i} + r(t,u)H_{1r} \\ \text{where} \quad & u(t) := (H_{1s}(t), H_{1i}(t), H_{1r}(t), H_{2s}(t), H_{2i}(t), P_n(t), P_r(t)). \end{aligned} \tag{2.1}$$

Notice that the infection term depends on $\dfrac{H_{2i}}{H_{2i}+H_{2s}}$, which implies that vectors have to compete with each other to get successful contact to humans (e.g., obtain a blood meal in case of malaria). This is a quite usual situation in Africa, where the tropical climate is suitable for vector (mosquitoes) development. Although only infected (female) Anopheles can transmit malaria, they still have to compete with other uninfected (also female) Anopheles to get blood meals. On the other hand, the size of the mosquito population induces a corresponding protection force from human side.

Concerning additional details for parameter r, we are aware that different drugs have different half-lives. They partly remain inside human bodies after treatment and provide the same protection as immunity. Medically, we consider five times of drug half-life equal to wash-out time. When drug is washed out and immunity is no longer active, the person returns to the susceptible class. This process is modeled by formula $r = k_r r_0$, where $r_0 = [\max(T,d)]^{-1}$, T is natural immune duration, d is drug wash-out duration; k_r is a scalar factor subject to estimation. After fitting, we use this formula for simulation, with the controllable parameter d.

Infected human population H_{1i}

After susceptible individuals get infected, they go to the infected class. Here are some possibilities that they may move out of this class: they can go back to susceptible class if there is too little amount of parasites; they can recover after treatment or they might die. The natural and disease-induced mortality rate is denoted by m_{1i} with value based on literature [89], and the recovery rate μ is an unknown parameter. In addition, depending on the diseases some recovered

people from H_{1r} may fall back to infection again with rate ρ_2.

$$\begin{aligned} \dot{H_{1i}} = \quad & i_1(t,u)\frac{H_{2i}}{H_{2s}+H_{2i}}H_{1s} - \rho_1(t,u)H_{1i} - \mu(t,u)H_{1i} \\ & +\rho_2(t,u)H_{1r} - m_{1i}(t,u)H_{1i}. \end{aligned} \tag{2.2}$$

Moreover, we foresee that the recovery rate μ depends on the individual immunity, the employed medical treatment and the way how the drug is administrated. We are going to take the data from Cissé in Burkina Faso, a poor village. We should notice that most of the local population does not have access to any treatment easily. With support from a common project between Heidelberg researchers and local people, classical Chloroquine regimen was given to all patients and showed good effect. That is why in simulation we can assume that drugs start with a good efficacy. We then can concentrate on how treatment is administrated. It is a reasonable assumption that when one patient takes the full dose as recommended, all his/her sensitive pathogens are killed at rate λ. The proportion of people that follows proper treatment is expressed by α.

In general, most of the patients carry both sensitive and resistant parasites. Drug treatment strengthens the immunity and shortens the recovery process. In the other word, it helps to increase the recovery rate. We combine immune and treatment effects in formula

$$\mu = k_\beta \lambda \beta \alpha + \beta(1-\alpha),$$

where β is the rate of parasites which are eliminated by natural host immunity without treatment, $k_\beta\lambda$ is the factor which expresses how drugs strengthen the immunity in treated patients. The value of k_β is subject to estimation.

Recovered human population H_{1r}

All recovered individuals from H_{1i} go to the recovered class H_{1r}. For a certain while they have protection due to the retained drug and natural immunity. Depending on different diseases they can or can not be reinfected again. With malaria, especially in highly endemic areas without medical supplies, some recovered patients with very little protection could get new infection almost instantly (ρ_2). In the setting where most patients are treated, the majority of recovered individuals have noticeable protection. However, they can lose their immunity and return to susceptible class (r). The process can be fast or slow depending on drug wash-out duration and individual health. We have already explained the detail of r in the section of susceptible human population H_{1s}. We also call m_{1r} mortality rate of recovered class H_{1r}, the value of m_{1r} is given in table 2.2.

$$\dot{H_{1r}} = \mu(t,u)H_{1i} - \rho_2(t,u)H_{1r} - r(t,u)H_{1r} - m_{1r}(t,u)H_{1r}. \tag{2.3}$$

Susceptible vector population H_{2s}

This compartment is similar to the susceptible human compartment. However, since parasites do not influence vectors in the same way as humans, there is no recovery or re-susceptibility effect.

Let b_{2s}, b_{2i} be the unknown birth-rates of susceptible and infected vectors. In addition, eggs from vectors (mosquitoes) are supposed to be able to hibernate over unfavorable time spans and hatch to become new vectors when the season provides better conditions. This process has an effect close to immigration and emigration, modeled by parameter b_2. Vectors become infected on contacting infected humans in class H_{1i}, this is modeled by rate i_2. All of these four parameters are subject to estimation. Mortality rate of vectors m_{2s} is taken as in [89].

$$\begin{aligned} \dot{H_{2s}} = \quad & b_{2s}(t,u)H_{2s} + b_{2i}(t,u)H_{2i} + b_2(t,u) \\ & -i_2(t,u)\frac{H_{1i}}{H_{1s}+H_{1i}+H_{1r}}H_{2s} - m_{2s}(t,u)H_{2s}. \end{aligned} \tag{2.4}$$

Infected vector population H_{2i}

All infected vectors from susceptible class H_{2s} go to class H_{2i}. Since the life-cycle of vectors is not so long, in most cases either parasites are transmitted to human or they stay in vectors' abdomen until they die. The mortality rate of vectors is denoted by m_{2i}, its value is given in table 2.2.

$$\dot{H_{2i}} = i_2(t,u)\frac{H_{1i}}{H_{1s}+H_{1i}+H_{1r}}H_{2s} - m_{2i}(t,u)H_{2i}. \tag{2.5}$$

Non-resistant parasite population P_n

Now we pay attention to parasite population in humans. They are supposed to be inside the infected human class H_{1i} so naturally depend on H_{1i}. Since this dependence is likely reduced when the number of infected humans becomes large, we use Michaelis– Menten relation, involving $\frac{H_{1i}}{C+H_{1i}}$. We also assume that parasite population growth follows the logistic rule governed by rate b_{pn}, b_{pr} and some maximal capacity K.

Unlike the hosts, parasites usually clone themselves, so in some sense there is no "death". It practically applies for malaria parasites in humans, they only multiply asexually inside human red blood cells. On the other hand, all parasites inside the infected hosts also die out due to the mortality of these hosts.

Since drugs are present, there is the proportion α of the infected human population H_{1i}, who received full drug treatment. Together with immunity, drugs can

eliminate pathogens with rate $(\mu + \alpha\lambda)$, λ presents the rate in which (sensitive) parasites are eliminated by drug.

Also due to drug presence, some sensitive pathogens need to change themselves to be able to increase their chances of survival, such as by mutation or adaptation. This makes a certain ratio of sensitive pathogens become resistant, the process is occurring with rate

$$s = s_0 + k_d \frac{\alpha \min(d, d_0)}{\lambda}.$$

The rate s_0 describes the mutation and the part $k_d \alpha \min(d, d_0)/\lambda$ describes the adaption rate. We assume that the adaption rate is directly increased in the same time with the proportion α of treatment and drug wash-out duration d, but inversely proportional to the efficacy λ of the given treatment. There is also a parameter d_0, an upper threshold of drug wash out duration d, which implies that above a certain limit parasite adaptation rate would not increase considerably but rather stay the same. Factor k_d is an unknown subject to estimation.

$$\begin{aligned} \dot{P}_n = \; & b_{pn}(t,u) \frac{H_{1i}}{C + H_{1i}} \left(1 - \frac{P_n + P_r}{K}\right) P_n - m_{1i}(t,u) P_n \\ & -(\mu(t,u) + \alpha(t,u)\lambda(t)) P_n - s(t,u) P_n. \end{aligned} \tag{2.6}$$

Resistant parasite population P_r

As we discussed before, the resistant parasite population P_r grows with the rate b_{pr}. Resistant parasites decrease only due to the death of the host H_{1i} or is eliminated by host immunity. Since resistant parasite population is fitter in drug presence, it gains some new ones from sensitive population sP_n.

$$\begin{aligned} \dot{P}_r = \; & b_{pr}(t,u) \frac{H_{1i}}{C + H_{1i}} \left(1 - \frac{P_n + P_r}{K}\right) P_r - m_{1i}(t,u) P_r \\ & -\mu(t,u) P_r + s(t,u) P_n. \end{aligned} \tag{2.7}$$

2.1.3 Full model system and parameters

Now we put together all equations (2.1), (2.2), (2.3), (2.4), (2.5), (2.6) and (2.7). For convenience we re-write

$$u = (u_1, u_2, u_3, u_4, u_5, u_6, u_7) = (H_{1s}, H_{1i}, H_{1r}, H_{2s}, H_{2i}, P_n, P_r)$$

and re-denote some factor functions accordingly. The general system is:

$$\dot{u} = A(t,u)u + B(t,u).$$

In this chapter, we would restrict ourselves to the case where all functions (the details in table 2.1) depend only on the independent variable t. We obtain a

system that is connected to our network in figure 2.1:

$$
\begin{aligned}
\dot{u_1}(t) = \;& b_{1s}(t)u_1(t) + b_{1i}(t)u_2(t) + b_{1r}(t)u_3(t) - m_{1s}(t)u_1(t) \\
& -i_1(t)\frac{u_5(t)}{u_4(t)+u_5(t)}u_1(t) + \rho_1(t)u_2(t) + r(t)u_3(t), \\
\\
\dot{u_2}(t) = \;& i_1(t)\frac{u_5(t)}{u_4(t)+u_5(t)}u_1(t) - \rho_1(t)u_2(t) - \mu(t)u_2(t) \\
& +\rho_2(t,u)u_3(t) - m_{1i}(t)u_2(t), \\
\\
\dot{u_3}(t) = \;& \mu(t)u_2(t) - \rho_2(t,u)u_3(t) - r(t)u_3(t) - m_{1r}(t)u_3(t), \\
\\
\dot{u_4}(t) = \;& b_{2s}(t)u_4(t) + b_{2i}(t)u_5(t) + b_2(t) \\
& -i_2(t)\frac{u_2(t)}{u_1(t)+u_2(t)+u_3(t)}u_4(t) - m_{2s}(t)u_4(t), \\
\\
\dot{u_5}(t) = \;& i_2(t)\frac{u_2(t)}{u_1(t)+u_2(t)+u_3(t)}u_4(t) - m_{2i}(t)u_5(t), \\
\\
\dot{u_6}(t) = \;& b_{pn}(t)\frac{u_2(t)}{C+u_2(t)}\left(1-\frac{u_6(t)+u_7(t)}{K}\right)u_6(t) - m_{1i}(t)u_6(t) \\
& -(\mu(t)+\alpha(t)\lambda(t))u_6(t) - s(t)u_6(t), \\
\\
\dot{u_7}(t) = \;& b_{pr}(t)\frac{u_2(t)}{C+u_2(t)}\left(1-\frac{u_6(t)+u_7(t)}{K}\right)u_7(t) - m_{1i}(t)u_7(t) \\
& -\mu(t)u_7(t) + s(t)u_6(t)
\end{aligned}
\tag{2.8}
$$

where

$$
\begin{aligned}
r &= k_r r_0 = k_r \max^{-1}(T,d), \\
\mu &= k_\beta \lambda\beta\alpha + \beta(1-\alpha), \\
s &= s_0 + k_d \alpha\lambda^{-1}\min(d,d_0).
\end{aligned}
$$

All initial conditions are given:

$$(u_1, u_2, \ldots, u_7)(t^0) = (u_1^0, u_2^0, \ldots, u_7^0) \geq 0,$$

especially the susceptible classes u_1^0, u_4^0 are positive and at least one infected class should be positive. Without loss of generality, we assume the initial number of infected vectors u_5^0 is positive.

This is a non-linear differential equation system. The system is designed for vector-borne diseases. Compared to the already established models concerning drug resistance of vector-borne diseases, such as in [4, 33], we add two new compartments of parasites. They are sensitive and resistant parasites corresponding to the given treatment. The treatment can take effect on infected human hosts, sensitive parasites and indirectly on resistant parasites inside the infected humans.

Details about all model parameters and their biological meanings are presented in table 2.1. We order them according to the places where they appeared in equation system (2.8).

Table 2.1: All factors and their biological meaning

Factors	Biological meaning
$b_{1s}(t)$	birth rate of susceptible humans H_{1s}
$b_{1i}(t)$	birth rate of infected humans H_{1i}
$b_{1r}(t)$	birth rate of recovered humans H_{1r}
$i_1(t)$	infection rate of susceptible humans H_{1s}
$\rho_1(t)$	re-susceptibility rate from infected group H_{1i}
$r(t) = k_r(t)\max^{-1}(T, d)$	re-susceptibility rate of humans H_{1r}
T	natural immune duration in humans H_{1r}
d	drug wash-out duration
$k_r(t)$	unknown factor, appeared in r
$m_{1s}(t)$	mortality rate of susceptible humans H_{1s}
$\mu(t) = k_\beta(t)\lambda\beta(t)\alpha$ $+ \beta(t)(1-\alpha)$	the recovery rate of patients with treatment
α	proportion of full treatment
$\beta(t)$	rate of parasites eliminated by immunity
λ	elimination rate of sensitive parasites (by drug)
$k_\beta(t)$	unknown factor describing treatment effect
$\rho_2(t)$	re-infection rate from recovered group H_{1r}
$m_{1i}(t)$	mortality rate of infected humans H_{1i}
$m_{1r}(t)$	mortality rate of recovered humans H_{1r}
$b_{2s}(t)$	birth rate of susceptible vectors H_{2s}
$b_{2i}(t)$	birth rate of infected vectors H_{2i}
$b_2(t)$	hibernated eggs contributing to H_{2s}
$i_2(t)$	infection rate of susceptible vectors H_{2s}
$m_{2s}(t)$	mortality rate of susceptible vectors H_{2s}
$m_{2i}(t)$	mortality rate of infected vectors H_{2i}
$b_{pn}(t)$	relative birth rate of sensitive parasites P_n
C	constant in the Michaelis- Menten formula
K	parasite-holding capacity of human hosts
$s(t) = s_0(t)$ $+ k_d(t)\alpha\lambda^{-1}\min(d, d_0)$	selection force of resistance in drug presence
$s_0(t)$	parasite mutation rate (become resistant)
d_0	effective threshold of drug-wash-out duration
$k_d(t)$	unknown factor, appeared in s
$b_{pr}(t)$	relative birth rate of resistant parasites P_r

2.2 Analytical study

In this section, we study the existence, uniqueness, boundedness and positivity of solutions of system (2.8). We first consider the local case, then later the global case.

We shorten the right hand side of system (2.8) by $f(t, u(t))$ and have a Cauchy problem:

$$\begin{aligned} \dot{u}(t) = &\quad f(t, u(t)), \quad t \in [t^0, \infty), u_i(t) \text{ have values in } \mathbb{R}, \\ u(t^0) = &\quad u^0, \qquad\quad \text{where } u_1^0, u_4^0, u_5^0 > 0 \text{ and all other } u_i^0 \geq 0. \end{aligned} \tag{2.9}$$

We have the classical theorem on the existence and uniqueness of solution: If f is continuous in (t, u) in a neighborhood of (t^0, u^0) and Lipschitz continuous in u, then there exists a unique solution of (2.9), defined in a neighborhood of t^0. In this study, we would like to look at the existence of solutions not only in a neighborhood of t^0 but also in $[t^0, \infty)$.

Remark. For the whole section, if there is no further notice, one solution u would be called "*positive*" if three components u_1, u_4 and u_5 are strictly positive, the other components are non-negative.

We need the following assumption:
Assumption $\mathcal{A}$
All the factor functions in table 2.1 are continuous, positive and bounded for all $t \in [t^0, \infty)$.

2.2.1 A local solution

First of all, we would like to prove the local existence in a neighborhood of initial time t^0.

Proposition 2.1. *Under assumption $\mathcal{A}$, we have the following statements:*
(i) there exists a local solution of system (2.9) in a neighborhood of t^0, which is a closed interval in $[t^0, \infty)$,
(ii) the solution is "positive" on its defined domain,
(iii) the solution is unique.

Proof. Let b be any arbitrary function. For the rest of this chapter, we use the common notations for supremum and infimum:

$$\overline{b} = \sup_t b(t), \quad \underline{b} = \inf_t b(t).$$

Also, for any given x, $N(x)$ is a neighborhood of x. In our case, $N(x)$ is always connected set.

(i) Since $u_1^0, u_4^0 > 0$, there are neighborhoods $N(u_1^0), N(u_4^0)$ such that for all $u_1 \in N(u_1^0)$ then $u_1 > \frac{u_1^0}{2}$, all $u_4 \in N(u_4^0)$ then $u_4 > \frac{u_4^0}{2}$.

Since $u_2^0, u_3^0 \geq 0$, there are neighborhoods $N(u_2^0), N(u_3^0)$ such that for all $u_2 \in N(u_2^0)$ and $u_3 \in N(u_3^0)$ then $u_2 > \max(\frac{-C}{2}, \frac{-u_1^0}{4})$ and $u_3 > \frac{-u_1^0}{4}$.

Since $u_5^0 > 0$, there are neighborhoods $N(u_5^0)$ such that for all $u_5 \in N(u_5^0)$ then $u_5 > \frac{u_5^0}{2}$.

Take some small enough neighborhoods $N(u_6^0), N(u_7^0)$ and

$$N(u^0) = N(u_1^0) \times N(u_2^0) \times \cdots \times N(u_7^0).$$

For all $u \in N(u^0)$ then:

$$u_1 + u_2 + u_3 > \frac{u_1^0}{2} + \frac{-u_1^0}{4} + \frac{-u_1^0}{4} = 0,$$

$$u_4 + u_5 > \frac{u_4^0}{2} + \frac{u_5^0}{2} > 0,$$

$$C + u_2 > C + \frac{-C}{2} > 0.$$

From assumption $\mathcal{A}$, we know K is also positive. Combine all the conditions with the formula of f, we derive that f is continuous on a small neighborhood $N(t^0, u^0)$ of (t^0, u^0).

So $f \in C(N(t^0, u^0), \mathbb{R}^7)$. Since all spaces are finite dimensional Banach spaces, using Cauchy-Peano theorem, there exists (not yet unique) a local solution of system (2.9) on a small enough neighborhood $N^0(t^0)$. In case $N^0(t^0)$ is not a closed interval we can shorten this to obtain a closed one. E.g., if $N^0(t^0) = [t^0, t^f)$, then we choose $\overline{t^f}$ such that $t^0 < \overline{t^f} < t^f$ and $[t^0, \overline{t^f}]$ is a closed neighborhood. We can denote it by the similar notation $N(t^0)$. Its compactness is used in the proof of part (iii).

(ii) Now we look at the positivity of the solution on the neighborhood $N(t^0)$.

Since u is a solution of (2.9) on $N(t^0)$, we have all u_i are continuous, differentiable on $N(t^0)$. For $i = 1, 4$ and $i = 5$ we know that $u_1(t), u_4(t), u_5(t)$ are strictly positive on $N(t^0)$, so we mainly need to take care of $u_i(t)$ where $i = 2, 3, 6, 7$.

Now we focus on the local solution defined on $N(t^0)$. We set

$$I^+ = \{t \in N(t^0) \mid u_i(t) \geq 0 \ \forall i = 2, 3, 6, 7\}.$$

We are going to verify that

$$I^+ = N(t^0).$$

Firstly, using the initial conditions, $I^+ \neq \emptyset$ because $t^0 \in I^+$.

Secondly, I^+ is closed because all functions $u_i(t)$ are continuous. Indeed, if there is a series of t^j such that $u_i(t^j) \geq 0$ for all $i = 2, 3, 6, 7$ then $u_i(\lim_{j\to\infty} t^j) \geq 0$. So $\lim_{j\to\infty} t^j \in I^+$.

Thirdly, I^+ is open in $N(t^0)$. To verify this, we assume that we have a $t^1 \in I^+$, we are going to prove that there exists a neighborhood $N(t^1) \subset N(t^0)$ such that for all $t \in N(t^1)$: $t \in I^+$.

Using the fact $t^1 \in I^+$ and assumption $\mathcal{A}$ - all the factor functions are positive, continuous - we get:

$$\begin{aligned} \dot{u_2}(t^1) &= i_1(t^1)\frac{u_5(t^1)}{u_5(t^1)+u_4(t^1)}u_1(t^1) - \rho_1(t^1)u_2(t^1) \\ &-\mu(t^1)u_2(t^1) + \rho_2(t^1)u_3(t^1) - m_{1i}(t^1)u_2(t^1) \\ &> -\delta(t^1)u_2(t^1), \end{aligned}$$

where $\delta(t) = \rho_1(t) + \mu(t) + m_{1i}(t)$.
Using assumption $\mathcal{A}$, $\rho_1(t)$, $\mu(t)$ and $m_{1i}(t)$ are positive bounded, so $\delta(t)$ is positive bounded, too.

Using the continuity of all unknowns $u_i, i = 1, \ldots, 7$ on $N(t^0)$, we can say there exists a neighborhood $N(t^1) \subset N(t^0)$ such that for all $t \in N(t^1)$:

$$\dot{u_2}(t) \geq -\delta(t)u_2(t).$$

Keeping the same initial condition, the solution $u_2(t)$ is always larger than or equal to the solution of the equation:

$$\dot{w}(t) = -\delta(t)w(t).$$

Therefore, with nonnegative initial condition $u_2^0 \geq 0$, we obtain $u_2(t) \geq 0$ on $N(t^1)$.

Similarly, we can prove that $u_i \geq 0$ for $i = 3, 6, 7$. With different i, the neighborhoods $N(t^1)$ can be different. We take the intersection of all neighborhoods, which still satisfies as a neighborhood of t^1. We now can re-denote this new intersection by $N(t^1)$. We have $N(t^1) \subset I^+$. So I^+ is open.

Due to the fact that $N(t^0)$ is connected space; I^+ is both closed and open in $N(t^0)$ and not empty, we have $I^+ = N(t^0)$. The part (ii) is proved.

(iii) We already have the existence and the positivity of the local solution, now we are going to prove that on $N(t^0, u^0)$, $f(t, u)$ satisfies the Lipschitz continuous condition with respect to u, so that the local solution is unique. Here we use the compactness of $N(t^0, u^0)$. Since the solution is continuous on $N(t^0, u^0)$, which is compact, all of their components are bounded.

We look at the first right hand side of system (2.9) (represented by f_1) and the first unknown u_1 on domain $N(t^0)$:

$$\begin{aligned}
&\left\|f_1(t,u_1^1,u_2,\dots,u_7)-f_1(t,u_1^2,u_2,\dots,u_7)\right\| \\
&=\left\|(b_{1s}(t)-m_{1s}(t))(u_1^1-u_1^2)-i_1(t)\frac{u_5}{u_5+u_4}(u_1^1-u_1^2)\right\| \\
&\le \left\|\overline{b_{1s}}-\underline{m_{1s}}\right\|\left\|u_1^1-u_1^2\right\|+\overline{i_1}\left\|u_1^1-u_1^2\right\| \ \text{(since } u_4>0 \text{ and } u_5\ge 0) \\
&\le (\overline{b_{1s}}+\underline{m_{1s}}+\overline{i_1})\left\|u_1^1-u_1^2\right\|.
\end{aligned}$$

So, f_1 is Lipschitz continuous with respect to u_1. Similarly, f_1 is also Lipschitz continuous with respect to u_2, u_3. Now we consider u_4:

$$\begin{aligned}
&\left\|f_1(t,u_1,u_2,u_3,u_4^1,u_5,u_6,u_7)-f_1(t,u_1,u_2,u_3,u_4^2,u_5,u_6,u_7)\right\| \\
&=\left\|-i_1(t)u_1\left(\frac{u_5}{u_5+u_4^1}-\frac{u_5}{u_5+u_4^2}\right)\right\| \\
&\le \overline{i_1}\left\|u_1\right\|\left\|\frac{u_5}{(u_5+u_4^1)(u_5+u_4^2)}\right\|\left\|u_4^1-u_4^2\right\| \\
&\le L\left\|u_4^1-u_4^2\right\| \qquad (0<L<\infty \text{ since } u_i \text{ is bounded, “positive” on } N(t^0)).
\end{aligned}$$

So we can verify that f_1 is Lipschitz on $N(t^0)$ for all the unknowns u_i, $i = 1,2,\dots,7$. The same procedure can apply for f_i, $i = 2,\dots,7$ and we obtain that f is Lipschitz function. The right hand side of system (2.9) satisfy the condition of the existence and uniqueness equation on $N(t^0)$, that's why system (2.9) has a unique solution on $N(t^0)$, this solution is “positive” (as we stated above). □

2.2.2 A global solution

Before the main theorem, we are going to prove a lemma on the boundedness of the existing solution.

Lemma 2.2. *Under assumption $\mathcal{A}$, the solution of system (2.9), whenever it exists, is exponentially bounded. As a consequence, the solution is always bounded in finite time.*

Proof. We estimate the derivative of the first unknown, using assumption $\mathcal{A}$ and the result of proposition 2.1 above. Notice that the solution is positive on the defined domain (u_1 and u_4 is strictly positive, the other components are nonnegative).

$$\begin{aligned}
\dot{u_1} &= b_{1s}u_1+b_{1i}u_2+b_{1r}u_3-m_{1s}u_1-i_1\frac{u_5}{u_5+u_4}u_1+\rho_1u_2+ru_3 \\
&\le \overline{b_{1s}}u_1+(\overline{b_{1i}}+\overline{\rho_1})u_2+(\overline{b_{1r}}+\overline{r})u_3.
\end{aligned}$$

Since all factors are bounded, their supremum and infimum values are also bounded. Similar to this, the derivatives of other u_i can also be estimated by linear right hand sides.

According to proposition 7.8 in [2], the solution of system (2.9) is exponentially bounded. Using the positivity of the solution in the previous section 2.1, we have the solution bounded in finite time by positive values (all lower bounds and upper bounds are non-negative, especially three components u_1, u_4, u_5 are bounded by positive values). □

Now we are going to prove the main theorem concerning a global solution.

Theorem 2.3. *Assume that all factors satisfy assumption $\mathcal{A}$ as before, system (2.9) has a unique solution defined on $[t^0, \infty)$. This solution is positive, exponentially bounded.*

Proof. At first, we would like to comment that the positive condition of all factors is actually not mathematically essential, they just come from the biological meaning.

We already proved that there exists a unique local solution in a neighborhood $N(t^0)$. From the part where the solution exists, it stays positive, bounded. Taking $t^1 \in N(t^0)$ and $t^1 > t^0$, using the same argument from proposition 2.1, we can prove that the function f is also Lipschitz in a neighborhood $N(t^1)$ of t^1, so the solution can be extended on $N(t^1)$.

Assume that the solution can be extend to $[t^0, a)$ but not yet $[t^0, a]$. If a is finite then we define $u(a) = \lim\limits_{t \to a} u(t)$. Due to the continuity of $\dot{u}(t)$ and function $f(t, u(t))$, we have:

$$\dot{u}(a) = \lim_{t \to a} \dot{u}(t) = \lim_{t \to a} f(t, u(t)) = f(a, u(a)).$$

So the solution can be extended to a. We can also say, the solution exists up to a. Now we consider:

$$\overline{a} := \sup_{\forall t} t \quad \text{(for all } t \text{ belonging to the domain of the solution).}$$

If $\overline{a} < \infty$ then $\overline{a}$ is finite. Using the same argument as before we obtain that $\overline{a}$ belongs to the defined domain of the existing solution of (2.9). Note that from lemma 2.2, in finite time every component of the solution is bounded by the constant "positive" value. That means, at the point $\overline{a}$, the values of function u_i are "positive" and satisfy the conditions as in the proof of the proposition 2.1. Because of this, we can continue to apply the proposition 2.1, extend the solution over a small neighborhood $N(\overline{a})$. Denote δ as the radius of this neighborhood ($\delta > 0$). The solution is now also defined at $\overline{a} + \frac{\delta}{2} > \overline{a}$, this contradicts with the fact that $\overline{a}$ is the supremum of all the t in the domain of the solution.

We have proven that $\overline{a} = +\infty$. By virtue of proposition 2.1, we obtain that system (2.9) has a unique positive global solution. Using lemma 2.2, this solution is exponentially bounded. □

2.2.3 Remarks

Assumption $\mathcal{A}$ for all factors is natural. Note that in most of the biological systems, the resources are often limited. The growth function could have high positive values from the beginning, but eventually have to decrease when the population size becomes large. When we consider infinite time, this kind of function is usually bounded. On the other side, mortality function is obviously bounded.

System (2.8) is just the original form of (2.9), so all results of (2.9) are also valid for (2.8). That means, under assumption $\mathcal{A}$, system (2.8) has a global unique solution.

In addition, we would like to mention that the analysis will stay the same if some quotient terms in the system (2.8) change. For example, if the term $H_{2i}/(H_{2s} + H_{2i})$ becomes $H_{2i}/(H_{1s} + H_{1i} + H_{1r})$ then our analysis will still be valid.

Before moving to the numerical part, we would like to comment that our model is designed to study the dynamics on finite time. This period can be quite long as far as there is no big sudden "jump" in the surrounding environment. For instance, we approximate the birth rates of humans by functions which depend only on time, does not depend on the number of the compartments themselves. In finite time, this approximation is appropriate and gives advantages, particularly in the parameter estimation and numerical simulation problems. It is necessary to reduce the complexity. Otherwise, we likely end up with time consuming computation without gaining much further details.

Considering infinite time, this assumption can be revised to meet a new situation. For example, the natural resource is often limited over time, so growth rate of susceptible humans should reduce to 0 or negative when the total number of humans becomes quite large. Readers who are interested in this kind of situation may see more information at [5, 82]. Below we switch to a concrete situation and study this numerically.

2.3 Numerical study

For numerical study, we use finite intervals. For short time periods, parameters related to human hosts do not change very much. That is why we are going to specify some factors, in order to reduce the complexity of the problem.

In this section we present data extraction, all known and unknown parameters, establish a parameter estimation problem and a simulation problem. Using the software package VPLAN [50, 60], we solve the two problems. The results are presented in detail.

2.3.1 Data extraction

Observation data is mainly extracted from [89], in Burkina Faso. We need the following assumptions:

- The study focused on children and all observations were generalized for the whole town.

- In the period of study, most of the clinical malaria cases were treated so most of the infected people recover after treatment. Whole population was only slightly decreased due to malaria.

- Given a certain drug, all parasites are either sensitive or resistant.

In addition, we assume some appropriate observation errors (based on the information in [89]) which are normally distributed.

2.3.2 Parameter values

Before simulation in the case of malaria in Burkina Faso, we have to specify all parameters to meet the specific situation. We present all parameters in two tables: the first one for known parameters and the second for unknown parameters. Our time unit is five days.

After several discussions with experts in epidemiology, also based on the data from literature, we take some factors as constant over the year of study (2004): birth rate and mortality rate of human classes, mortality rate of vectors (mosquitoes), etc. We also take into account the properties of the drugs that were given (mainly Chloroquine) and its efficacy. We then obtain a list of the known parameters as given in table 2.2. Infection rate i_1 is a piecewise linear function as in figure 2.2.

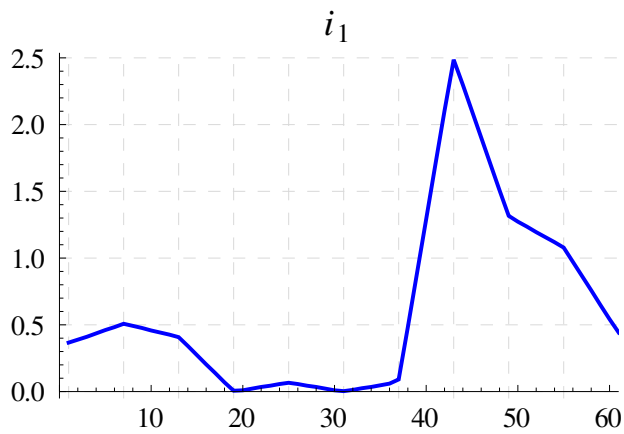

Figure 2.2: Approximated function of human infection rate i_1, based on [89] and information about the proportion of infected human class. The horizontal axis is the time and one unit is 5 days.

In table 2.3 we present all unknown parameters. We plan to estimate them by

Table 2.2: All known parameters

Parameter	Value(unit)	References
b_{1s}	0.00063(time^{-1})	[89]
b_{1i}	0.0005(time^{-1})	[89]
b_{1r}	0.00063(time^{-1})	[89]
ρ_1	0(time^{-1})	assumed (Cissé)
T	12(time)	[92]
d	40(time)	[15]
m_{1s}	0.000285(time^{-1})	[104]
α	0.9(dimensionless)	[89]
β	0.025(time^{-1})	[67]
λ	0.7 (time^{-1})	assumed, based on [89]
ρ_2	0(time^{-1})	assumed (Cissé)
m_{1i}	0.000613(time^{-1})	[89, 104]
m_{1r}	0.000285(time^{-1})	[104]
m_{2s}	0.75(time^{-1})	[89]
m_{2i}	0.75(time^{-1})	[89]
C	5 (dimensionless)	based on data size
K	25×10^6(dimensionless)	[89], scaled $1/10^{10}$
s_0	7×10^{-7}(time^{-1})	[46]
d_0	73 (time)	[15]

piecewise functions, each interval corresponds to one month. We state also some constraints needed to analyze estimation results.

Table 2.3: All unknown parameters for estimation

Parameter	Unit	Remark
k_r	dimensionless	$k_r \geq 0$
k_β	time	$k_\beta \geq 0$
b_{2s}	time^{-1}	$b_{2s} \geq 0$
b_{2i}	time^{-1}	$b_{2i} \geq 0$
b_2	dimensionless	$b_2 \geq 0$
i_2	time^{-1}	$i_2 \geq 0$
b_{pn}	time^{-1}	$b_{pn} \geq 0$
b_{pr}	time^{-1}	$b_{pr} \geq 0$
k_d	time^{-3}	$k_d \geq 0$

2.3.3 Setup of parameter estimation and simulation problems

In this part, we recall some classical problems concerning parameter estimation in differential equations and specify our problems to be solved later. Interested readers can refer to [17] and references therein for related information.

For the rest of this section, without further notice, all variables are elements in $\mathbb{R}^n$. As we see before, we have established a population dynamics in the form of a differential equation system (2.8). Generalizing the system, we denote time by t, state variables by $u(t)$, unknown parameters by p, control parameters by q, control functions by $v(t)$, the right hand side of system (2.8) by f, the equality constraints by g. Notice that g is often present due to initial or boundary values. We have a problem:

$$\begin{aligned} \dot{u}(t) = &\quad f(t, u(t), p, q, v(t)), \quad t \in [t^0, t^f], \\ 0 = &\quad g(u(t^0), u(t^f), p, q). \end{aligned} \tag{2.10}$$

For all parameter estimation problems, we need data. It is assumed that experiments $i, i = 1, \ldots, N$ have been carried out at the given times $t^j, j = 1, \ldots, M$, yielding the measurements η_{ij}. On the other hand, measurement errors are ε_{ij} and the "true" model response corresponding to these measurements are b_{ij}:

$$\eta_{ij} = b_{ij}(t^j, u(t^j), p) + \varepsilon_{ij}.$$

Parameter p is found by minimizing the deviation between data and model response. Due to statistical reasons, some weights σ_{ij}^{-1} can be introduced, see detail in [17]. In addition, if we have prior knowledge about some approximate value p_0 of parameter p then we can add a regularization term $\delta(p - p_0)^2$ to the objective function. Vector δ has the same dimension as vector p and all components δ^l are nonnegative.

Summing up, a general parameter estimation problem can be formulated as:

$$\begin{aligned} \min_{(u,p)} \quad & \left[\sum_{i,j} \left(\frac{\eta_{ij} - b_{ij}(t^j, u(t^j), p)}{\sigma_{ij}} \right)^2 + \sum_l \delta^l (p^l - p_0^l)^2 \right], \\ \text{s.t. } (u, p) \quad & \text{solves equation (2.10).} \end{aligned} \tag{2.11}$$

In our case, we have one experiment ($i = 1$) with all observation data η_j about the state variables $u(t^j)$ and the weights σ_j. The unknown parameters are given in table 2.3

$$p = (k_r, k_\beta, b_{2s}, b_{2i}, b_2, i_2, b_{pn}, b_{pr}, k_d).$$

The initial values for the state variables, which are implied by g, are given at $t = t^0$. In the parameter estimation problem, all the control factors are given, we are interested in finding p.

After parameter estimation, values for the parameters are determined. Now we can consider the simulation. Unlike before, the control parameters q play the key roles. They are the proportion of full treatment α, the drug wash-out duration d and the treatment efficacy λ. For each simulation, there is a fixed set of values. With different values of control parameters, we need to solve the differential equation (2.8) to compute the simulation.

2.3.4 Software package VPLAN

For both parameter estimation and simulation, we use VPLAN (Versuchplanung), see [60] and references therein. VPLAN is a software package developed at the Interdisciplinary Center for Scientific Computing (IWR), University of Heidelberg. VPLAN works well with models in the form of ordinary differential equations or differential algebraic equations. The four main features of VPLAN are Integration, Simulation, Parameter Estimation and Optimal Experimental Design. VPLAN uses the Gauss-Newton method for fitting data. Multiple shooting method is also integrated to improve the numerical stability.

In order to run properly, VPLAN requires problem description, experiment description, model description and (optional) measurement data. They are mainly defined by using Fortran 77 and ini files. The diagrams of the essential files are shown in figure 2.3, 2.4. In figure 2.5, there is a screen shot of VPLAN main problem description file. Further information concerning how to install and work with VPLAN is provided on its wiki page and in [12, 50, 60].

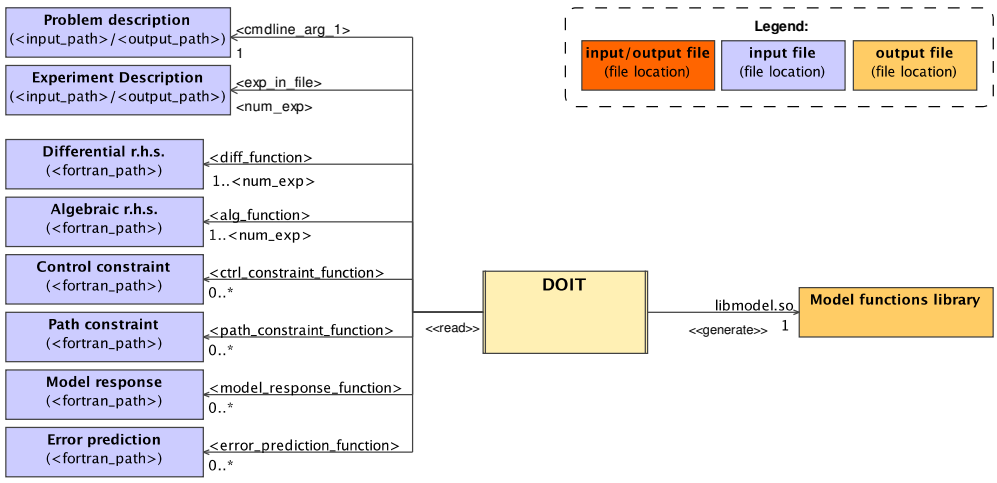

Figure 2.3: DOIT (a VPLAN command) and its related files. DOIT reads problem description and all experiment files referenced there. Form that DOIT creates a model function library, which is needed in all other actions in VPLAN [50].

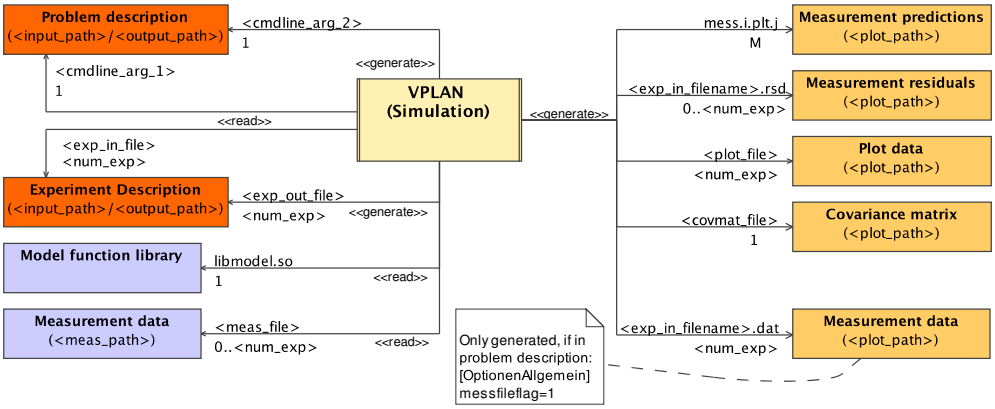

Figure 2.4: Input and output files involved in VPLAN simulation. VPLAN reads problem description, all referenced experiment files and model function library. After successful run, the measurement prediction files and plot files are generated. The available data can be used to compute the measurement residual, this is optional in simulation but absolutely required in parameter estimation [50].

2.3.5 Result of parameter estimation

In this part we are going to present the estimation results. As mentioned before, to minimize the residual, we take into account all parameters in the form of piecewise constant functions. We divide the domain into an appropriate number of intervals and find parameter values in each interval. To be more specific, we solve problem (2.11) in the first interval, then pass the last state variable values as the initial values of the next intervals. This assures the continuity of the solutions. The results of p in all intervals form piecewise constant functions, see figure 2.7.

In addition, we use multiple shooting [17] and maximize the usage of data information to deliver a good fit, see figure 2.6. Since parasite populations are very large compared to the host populations, we scale them by $1/10^{10}$.

As we can see in figure 2.6, all the predicted populations (green curves) are in agreement with data (red points) from Cissé, Burkina Faso. The different scales between hosts and parasites were taken into account by using a weighted least squares function. Due to technical reasons, in some place we use small regularization factors (see the problem setup 2.3.3). As we see, the overall residual is very low.

For clear visibility, we show only half of the data points. The study was carried out from the end of 2003 to the end of 2004. Since data at the beginning and closing periods were not very good, we only take the part from middle of January to November 2004, around 300 days or 60 units of time. There are

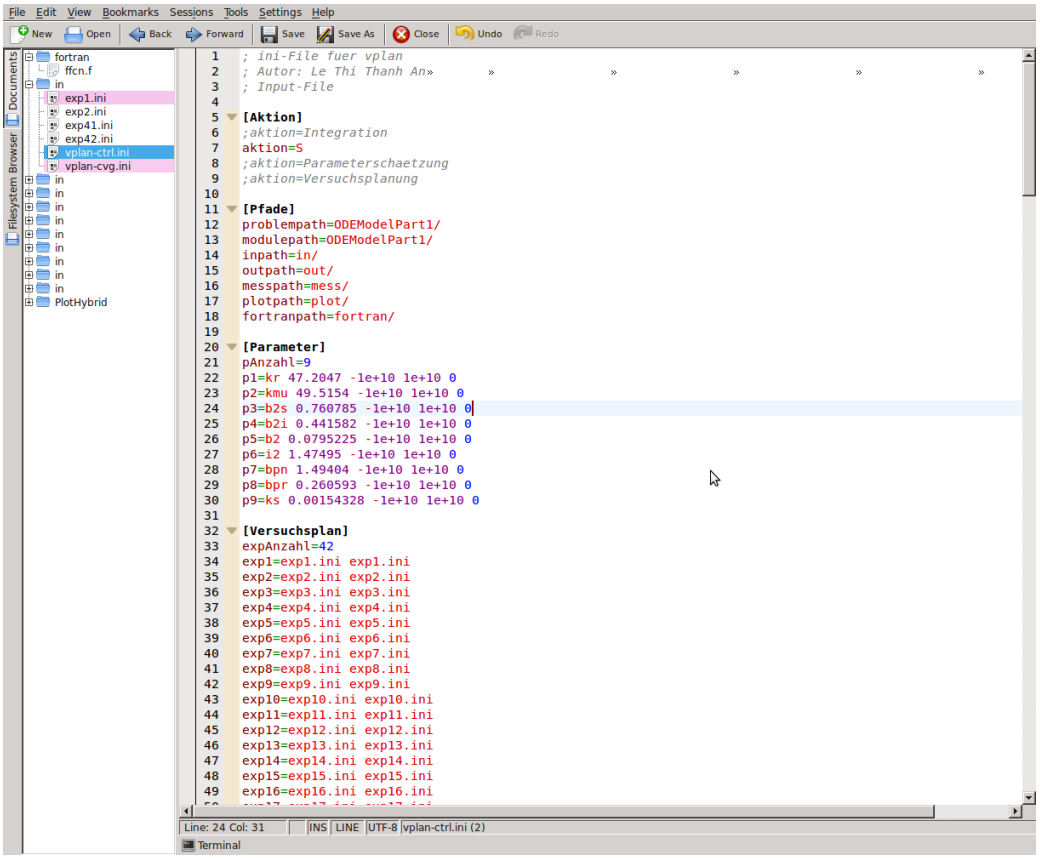

Figure 2.5: A screen shot of VPLAN problem description file.

peaks in the number of mosquitoes and parasites around August since the season becomes more suitable for vector development. Notice that the eggs can survive through dry season and hatch in rainy season to become larvae, pupae and then mosquitoes.

All the parameters are presented in figure 2.7. It shows that most of the parameters are not constant during the year, they vary a lot due to seasonal conditions, host environments, interactions among different populations.

As expected, the rainy season creates the peaks of mosquito growth rates, see figure 2.7. There are many more susceptible mosquitoes available compared to dry season. Through the contact with infected humans, they also become infected by parasites. Due to the weather condition, mosquitoes are much more active than in dry months. With Human Land Capture method, volunteers caught many more mosquitoes in rainy months compared to just a few in the other months [89].

In the same time, the value of k_r has a big drop, indicating that there are almost no recovered people that come back to susceptible class. In malaria, no

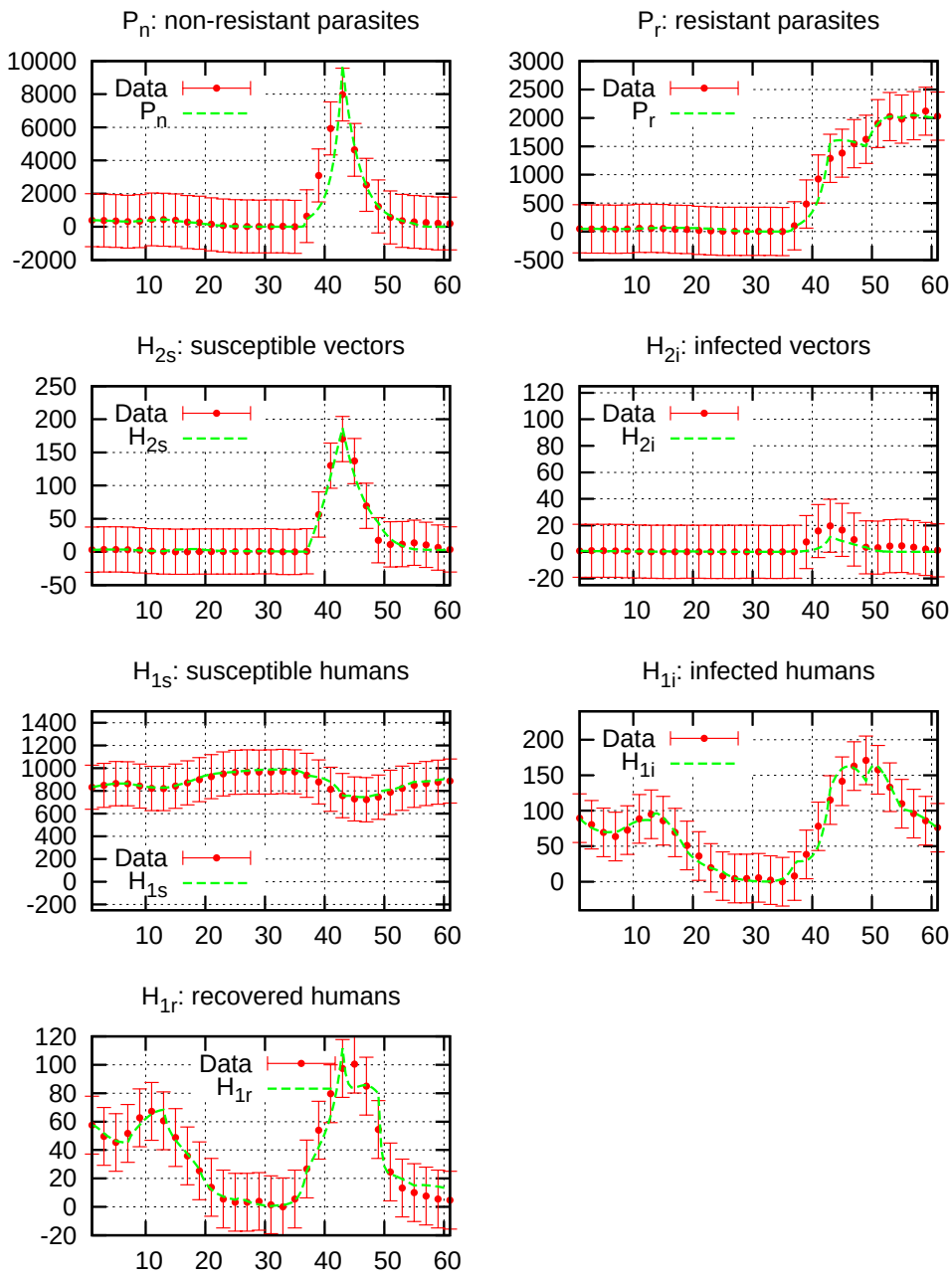

Figure 2.6: The observed and predicted populations. Data from middle of January to November 2004, [89]. For clear visibility, we show only half of the data points. These data (red points) are plotted together with their error bars. Time unit is 5 days.

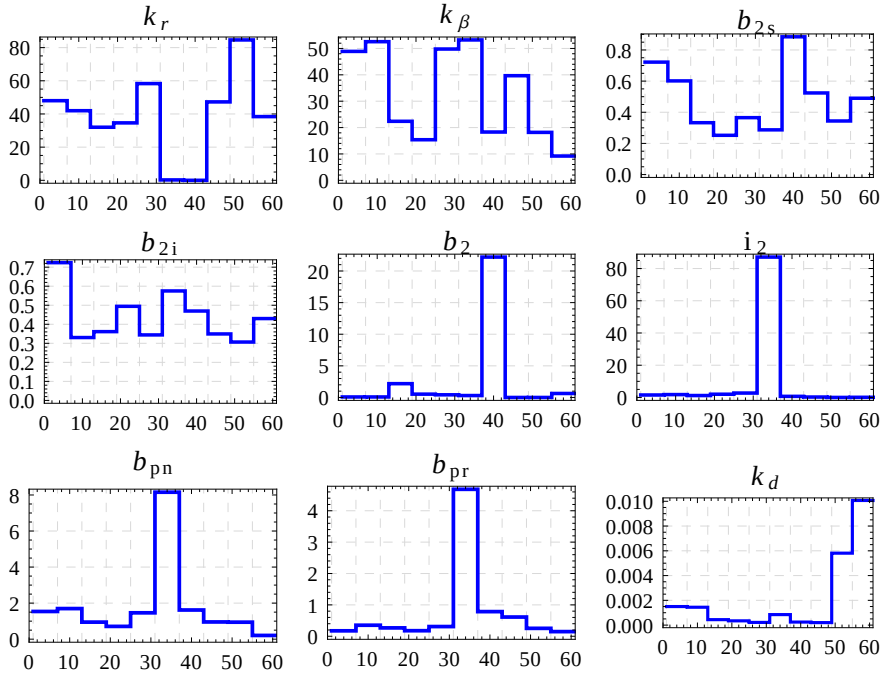

Figure 2.7: The fitted parameters. The horizontal axes are time axes, unit 5 days.

recovery or complete clearance is expected in a short period of time. Here we should mention one common weak point of the malarial data - patients with low parasite densities sometime are not detected and can be considered healthy. In fact, the parasite density develops slowly and symptoms appear in patients after few weeks or much later than the exposure to mosquitoes. Similar to this, the peak of selection force of resistance also comes later than the intensive treatment period, this is expressed in the last parameter k_d in figure 2.7.

2.3.6 Result of simulation with controllable parameters

In this section, using the set of fitted parameters, we simulate the model (2.8). Here we can control the proportion of full treatment α, the drug regimen corresponding to drug wash-out duration d and the treatment efficacy λ. Values of (α, d, λ) are varied within certain ranges. We also use VPLAN to compute the simulations.

Proportion of infected human class with full treatment

In this part α is our control parameter. This is the proportion of infected human class with full treatment. In this case, two drugs are chosen, Chloroquine (CQ) with wash-out duration $d = 40.0$ and Sulfadoxine-pyrimethamine (SP) with $d = 6.0$. Their results turn out to be quite similar. By virtue of the treatment, the sensitive parasite population is changed much faster than the resistant one.

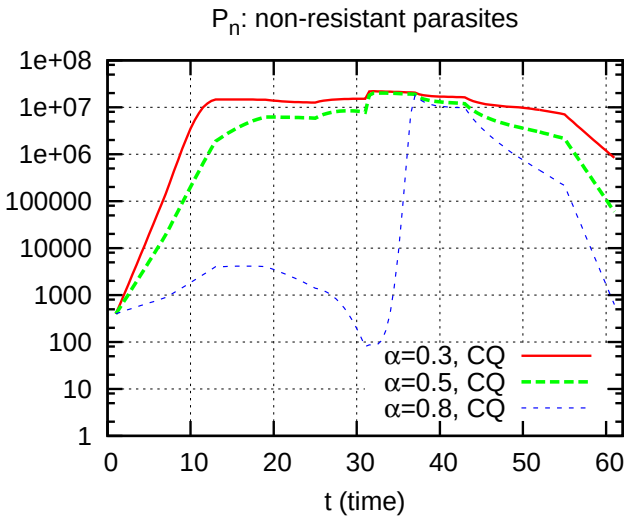

Figure 2.8: Simulations of sensitive parasite populations for different proportions of treatments. Increasing α leads to rapid decrease in sensitive parasite population to both treatments. Time unit is 5 days.

Simulation in figure 2.8 shows that the proportion of infected humans receiving full medical treatment is very critical in disease control. More important, the figure indicates that *at least a certain proportion* of the population needs to be treated properly in order to avoid deadly clinical malaria in the case of very high density of parasites. Recall that we have shown parasite populations with scale $1/10^{10}$ and Cissé is only a small town with around one thousand habitants. We can calculate the average density of parasites in each patient accordingly.

Beside that, different levels of treatment strongly influence the fitness between sensitive and resistant parasite populations. As we see in figure 2.9, full treatments give resistant parasites a chance to better compete with sensitive parasites to invade the environment.

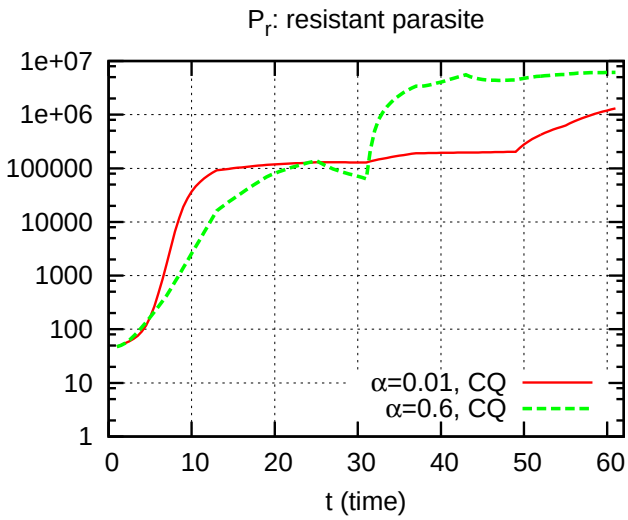

Figure 2.9: Simulations of resistant parasite population for different proportions of treatment. High proportion of full treatment makes resistant parasite population increase faster than low proportion of treatment. The green line represents 60% full treatment with Chloroquine while the red line represents only 1% Chloroquine full treatment. Time unit is 5 days.

Drug regimens with different half-lives

Using drug regimens with different half-life time would affect the picture of sensitive and resistant parasite populations. This affects the initial ratios of sensitive and resistant populations and also the number of parasites which become adapted to the drug environment. In Burkina Faso we do not have any data about different drug usages and how parasites would resist to certain treatment. It is necessary to run virtual simulations with different possible values of parameters d. For clear comparison, we use (artificially) the same initial values for the seven populations and keep the same treatment efficacy in all simulations. Assuming that all drug regimens have the same efficacy $\lambda = 0.7(\text{time}^{-1})$ and that 80% of infected human receiving full treatment $\alpha = 0.8$, different therapies lead to noticeable changes in the resistant parasite population, see figure 2.10.

According to our simulation, for long treatment periods using drugs with shorter half-life gives better performance. However, in the first period of treatment, the difference is not much due to the fact that a large proportion of parasites is sensitive to drugs. That is why in this period it does not matter which type of antimalarial drugs are used. The effect shows later, see the fast increase starting from $t = 30$ in figure 2.10.

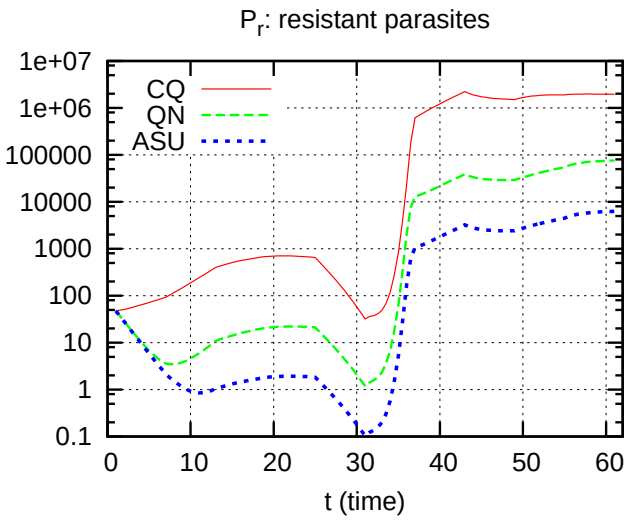

Figure 2.10: Simulations of resistant parasites for different drug half-lives. Switching between different therapies leads to noticeable changes in the number of resistant parasites. Simulations are done for Artesunate (ASU), Quinine (QN), Chloroquine (CQ) with approximated wash-out durations $d_{ASU} = 0.04$, $d_{QN} = 0.5$, $d_{CQ} = 40.0$, based on their half-lives given in [15].

We also simulate the case when first Chloroquine is used and afterward switched to Artesunate in the last three months of study. As expected, the resistant population was reduced considerably fast, this provides a good alternative treatments.

Different treatment policies: Combined control of α and d

Taking the setting as in countries like Burkina Faso, we have similar high efficacy for most of the antimalarial drugs. We simulate here the case when we combine the two mentioned controls, the proportion of full treatment α and the drug type expressed by d. Shortly speaking, we have combined advantages. We can keep both the sensitive and resistant parasite populations under control. The resistant parasite population is relatively small, as we see with Artesunate treatment in the lower panel of figure 2.11. On the upper panel, combined control leads to noticeable change in the infected human population.

Extended setting: Different efficacies of drug treatments

In this part we consider the case in which all the infected people can afford their necessary medication or the health care systems are good enough to cover all

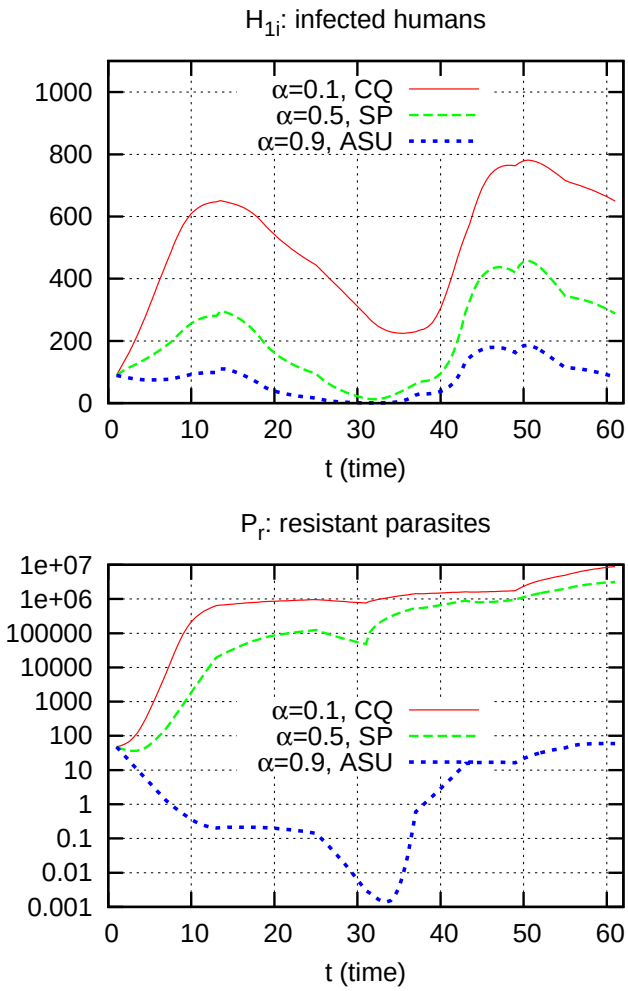

Figure 2.11: Simulations of resistant parasites and infected humans with different drug treatment policies. Time unit is 5 days.

the cost. So all patients can be treated and $\alpha = 1.0$. The treatment efficacy λ and drug d are our control parameters. Simulations are done for Chloroquine (CQ), Sulfadioxine-pyrimethamine (SP), Mefloquine (MQ), Artesunate (ASU). The treatment efficacies are close to the values of antimalarial drugs taken from Asia, especially Vietnam. They are based on a report by WHO in [102]. Note that in the Burkina Faso setting, most of the antimalarial medication would have similarly high efficacy - since most of the people living in the rural regions have had no access to them before.

Figure 2.12 using logarithmic scale, lets us easily see that there are big differences between Chloroquine, Sulfadioxine-pyrimethamine, Mefloquine and Artesunate. In the first three drugs, parasite resistance levels in the last period are very high. In contrast, with Artesunate or the similar Artemisinin Combination Therapy, the regimens are still effective, they keep parasite resistance low.

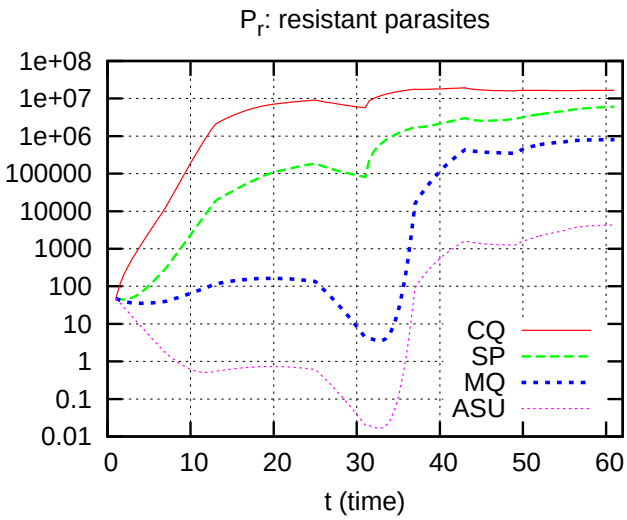

Figure 2.12: Simulations of resistant parasites for different treatment efficacies. Simulations are done for Chloroquine (CQ), Sulfadioxine-pyrimethamine (SP), Mefloquine (MQ), Artesunate (ASU) with the values of λ being $0.2, 0.4, 0.6, 0.6$ respectively. The wash-out duration d of all drugs is based on [15]: $d_{ASU} = 0.04$, $d_{QN} = 0.5$, $d_{MQ} = 16.0$, $d_{CQ} = 40.0$. The time unit is 5 days.

2.4 Concluding remarks

We discuss the simulation results and summarize this chapter.

2.4.1 Interpretation of the simulation results

The simulations which have been done with the fitted model lead to the following interpretations.

- From our result, we have found that the use of medication accelerates resistance in parasite populations. However, we need it to avoid the high (sensitive) parasite density in infected humans, so as, to keep the average density in human blood below N parasites per volume unit. Our model can serve as the base for the control problems, providing an optimal strategy of treatment. We can optimize the proportion (or number) of patients who need to be treated properly to prevent an outbreak of drug resistance.

- In case of malaria, our model simulations suggest that parasite mutation and drug adaptation both play key roles in resistance. Quantitatively, the simulation shows that: when drugs with long half-lives are employed, drug adaptation is dominant. Adaptation is weaker in drugs with shorter half-lives. So the shorter

the drug's half-life is, the fewer resistant parasites develop.

- During the initial treatment periods, our simulations show that different drug treatments create similar outcomes. It is explained by the fact that very few people have access to treatment in Burkina Faso. Most of the drugs are too expensive for many people in this region, especially in Cissé, where our data comes from. That is why in Burkina Faso or similar regions in Africa, treatment can start with any drugs and later switch to a new therapy when the resistant pathogens to the old drugs become dominant. This shows clearly that despite the type of medication they are first given, the parasites develop resistance to it and only become weaker if the type of medication is changed.

- We have also considered different regions with different drug usage. In Asia, antimalarial drugs are sold openly, and any persons can buy them without prescriptions from doctors. Most patients have been treated more than once. We observe in our simulations that the drug therapies and their efficacies strongly influence the success of treatment.

By using a quantitative model, we can simulate multiple scenarios in advance. Depending on preferred criteria, such as keeping the total parasite density below certain threshold or reducing the resistant parasite population, clinicians should be able to choose what they believe to be suitable therapies. In general, the model's results are valid not only for malaria but also for other infectious diseases with similar biological compositions.

2.4.2 Remarks on the chapter

To summarize, in this chapter we have developed a model describing the population dynamics arising in vector-borne diseases. In comparison to the other mathematical models [4, 33], our model has two new compartments for parasite populations and it includes parameters describing drug treatment.

We have studied the dynamics analytically and numerically.

By way of analysis, we have been able to prove the existence, uniqueness and positivity of the solution. This is necessary for all numerical steps. In other words, it is an essential condition before one can begin to compute numerical simulations.

By way of numerical study, we have solved parameter estimation and simulation problems. We have obtained fitted parameters and an agreement with the data in Burkina Faso. We have also simulated the fitted model with controllable parameters. Using the VPLAN package, we have been able to solve the systems and to see the influence of drug treatment not only on parasites but also on the host populations.

Chapter 3

Structured population dynamics of vector-borne diseases including drug treatment

In chapter 2, we have studied the population dynamics without structures among the different populations. All micro-organism populations and macro-organism populations appear in the system of equations equally. This model has the form of ordinary differential equations, so clearly we can use some available methods to study them analytically. The numerical parameter estimation and simulations give us a lot of knowledge which we can bring to clinical practice. However, the model has a certain limit in application. For parameter estimation and numerical simulation, there is a high cost when we want to obtain high precision data. For some quantities, we have to accept relatively low precision - such as for parasite populations. A common alternative, one may study models of the parasite population in an individual person, but one loses the global meaning.

This chapter proposes a new model to balance the issues. We are going to model structured population dynamics, where parasites appear in two structured variables (sensitive parasite and resistant parasite densities). This type of model is supposed to "bridge the gap between the individual and the population level" (Metz and Diekmann, [64]). The model is a system of integro-partial differential equations. It is naturally more complex, but this motivates us to explore some new methodology.

In order to understand structured population dynamics, we have to go back at least to the age structured model of McKendrick 1926, Bailey 1931 [66, 9]. In 1967, Sinko and Streifer included a size structure variable in their model [76, 44].

According to Sinko and Streifer, despite the fact that the age structured model had been created in the form of an integro-differential equation system quite early (Bailey 1931), this system had not been solved until the sixties. Sinko's thesis [75] mostly focused on the existence of solutions for the structured model in partial differential form. Since then, several authors have studied similar types of the model, but most of the results were limited to a single structured population.

In this chapter, we are going to model the system of hosts and vectors, with structured variables on the densities of sensitive and resistant parasites. These quantities are very crucial for drug treatment. For the mathematical model, it is essential to analyze the existence of solutions and uniqueness. The results can be used to develop numerical algorithms for simulation. With the rapid development of modern technologies, especially for life sciences, there is strong evidence that we can obtain the necessary data for model comparison at an affordable cost. More details are given in the numerical section.

In the first section we present all the steps necessary to build a new mathematical model of structured population dynamics. We start by setting up a network of all related populations and formulating a dynamical system with an explanation of every component of the model. In the second section we investigate the model analytically. Based on this investigation, the third section offers an approach to numerical simulation. In the final section, we discuss the practical meaning of the structured model and summarize the content of the chapter.

3.1 Modeling of structured population dynamics with drug treatment

3.1.1 Network of human and vector compartments

We consider here two groups: humans and vectors. There are two compartments for human hosts which we call uninfected S, infected I. Two compartments for vectors are uninfected U and infected (real vectors) V. Compared to the previous studies of vector-borne diseases [4, 36, 8, 33], we divide human hosts into two compartments with structured infected class I. This knowledge provides a strong background to investigate different treatment policies. It also brings out the need to study the same structure in the infected vector class. Hence, we consider infected humans and vectors which carry sensitive parasites and resistant parasites. These two groups of parasites show different behavior under medical treatments. We are going to express them by two separated structured variables in our model, x and y, representing sensitive and resistant parasite densities. The population dynamics with all transmissions among four compartments are described in figure 3.1.

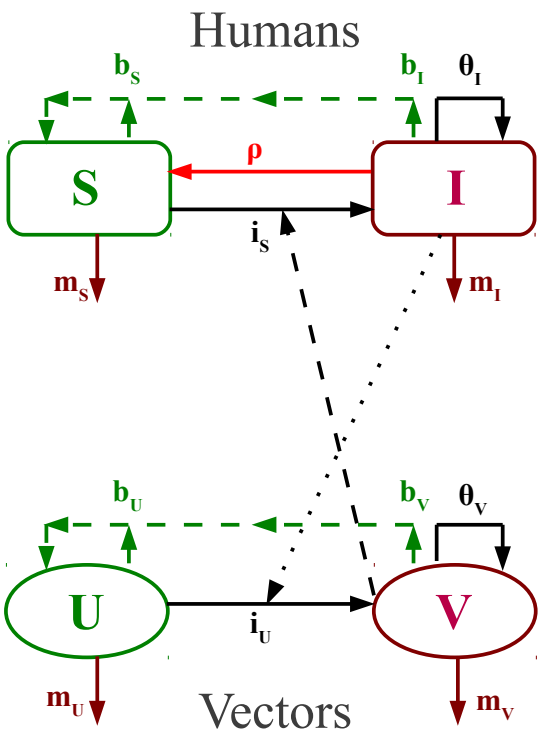

Figure 3.1: Network for the transportation among all the compartments: humans and vectors.

Based on the network of transmissions, we are going to give an overview of the parameters and the related phenomena. Because this model is aimed at population dynamics, we can expect some of the arguments from the previous model to be still valid.

As we know already, in vector-borne diseases, most of the offspring are susceptible. We denote the natural growth rates of S, I, U, V by b_S, b_I, b_U, b_V; the mortality rates (including the cause by diseases) by m_S, m_I, m_U, m_V; currently we neglect immigration and emigration. The infection rates of S, U are expressed through i_S, i_U.

In addition to above, we take into account the influence of drug treatment on the pathogen population and how its effect appears directly on the host population. While immunity is assumed to be able to handle all types of parasites, each drug regimen only influences those pathogens which are sensitive to them. We also know that immunity develops very slowly compared to parasite invasion and multiplication. As usual, both immunity and drug fight together against the

parasites in infected people. Their combined effects are expressed by ρ.

With or without treatment, the sensitive and resistant strains always multiply inside hosts, so bring the patients from one level of parasites to another level. In the presence of drugs, the sensitive strain can be killed but the resistant strain survives. Some mutations, which give advantage to sensitive parasites, are selected and grow even in drug presence. The sensitive parasites can also adapt to the new environment and become resistant. All these processes lead to movements inside infected classes I, V, which are denoted by θ_I, θ_V.

3.1.2 Dynamical system

Now we present the model formulation in connection with the above network. Since our focus is population dynamics with drug treatment on humans, we use three variables:

- for the dynamics, time variable is denoted by $t \in \mathbb{R}_+ = [0, +\infty)$,

- for a given treatment, sensitive and resistant parasite densities in a host or vector are respectively denoted by x, y; $(x, y) \in \mathbb{R}_+^2$.

As in our figure 3.1, (S, I, U, V) are the host and vector compartments. In the mathematical model, (S, I, U, V) are four unknown functions. In principle, two unknowns I, V depend on (t, x, y) - because the corresponding compartments carry parasites. Two compartments S, U do not carry parasites, so they only depend on t. We are going to formulate the dynamics of all four populations.

Change in uninfected human population S

The uninfected human population includes all humans who do not carry parasites. This compartment increases due to recruitment of new-born children (usually susceptible), which is expressed by birth-functions b_S, b_I. The population decreases by natural mortality rate m_S. Some part of this compartment moves to the second compartment after exposure to infected vectors. Due to different environments and the interaction between all compartments, there is an operator $\mathbb{P}_S$, which represents the movement from uninfected class S to infected class I. This operator can depend on all unknowns (S, I, U, V). We are going to talk about the specific form of $\mathbb{P}_S$ right below. In addition, uninfected population S also receives a number of recovered individuals from I class, therefore we have:

$$\begin{aligned}\frac{dS(t)}{dt} &= b_S(t)S(t) + \int_{\mathbb{R}_+^2} b_I(t,x,y)I(t,x,y)dxdy - m_S(t)S(t) \\ &\quad - \int_{\mathbb{R}_+^2} \mathbb{P}_S(S,I,U,V)(t,x,y)dxdy + \int_{\mathbb{R}_+^2} \rho(t,x,y)I(t,x,y)dxdy.\end{aligned} \tag{3.1}$$

Now we look at the form of $\mathbb{P}_S$. In general, the vector population is noticeably large. There is certainly some force from the human side to protect themselves from infection. The vectors, e.g. mosquitoes in malaria, can not easily have successful contacts to humans. In general, the protection force is often directly proportional to the total population of vectors. The total population includes infected and uninfected vectors, because they both want to have contact to humans. This situation commonly happens in tropical diseases, that is why we take $\mathbb{P}_S$ as the following:

$$\mathbb{P}_S(S,I,U,V)(t,x,y) = S(t)\frac{\displaystyle\int_{\mathbb{R}_+^2} i_S(t,x,y,\overline{x},\overline{y})V(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + U(t) + \displaystyle\int_{\mathbb{R}_+^2} V(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}$$

where $K_{vec} > 0$ is a weight value, related to the vector population. Technically, when the vector population is noticeably large (much more than K_{vec}), this induces almost no influence on the quotient value. On the other hand, this excludes the case when the total number of the vector population is quite small, which is usually not common.

Change in infectious human population I

We are going to take into account the total change in the infected human population I. On the left hand side, functions g_I, h_I represent growth rates of the population due to internal processes regulating the two structured variables x and y.

As we discussed before, $\mathbb{P}_S$ represents the movement from uninfected class S to infected class I. Following network 3.1, θ_I represents the exchange among different infection levels inside the compartment I, m_I is the mortality rate of the infected population and ρ is the treatment effect together with immunity.

$$\begin{aligned}
&\frac{\partial I(t,x,y)}{\partial t} + \frac{\partial}{\partial x}(g_I(t,x,y)I(t,x,y)) + \frac{\partial}{\partial y}(h_I(t,x,y)I(t,x,y)) \\
&= \mathbb{P}_S(S,I,U,V)(t,x,y) + \int_{\mathbb{R}_+^2} \theta_I(t,\overline{x},\overline{y},x,y)I(t,\overline{x},\overline{y})d\overline{x}d\overline{y} \\
&-m_I(t,x,y)I(t,x,y) - \rho(t,x,y)I(t,x,y).
\end{aligned} \tag{3.2}$$

Now we come to the two compartments of vectors: the uninfected and the infected populations.

Change in uninfected vector population U

The uninfected vector population has a similar dynamics as the uninfected human population.

Mosquito's offspring have no parasite. This is described through birth rates b_U and b_V. The natural death rate is m_U.

Uninfected vectors get infected when they come into contact with infected humans, in this case, anyone in I class. Similar to uninfected humans, the number of uninfected vectors U that become infected is expressed by way of an operator $\mathbb{P}_U(S, I, U, V)$. The value of operator $\mathbb{P}_U(S, I, U, V)$ is specified at a particular point (t, x, y) as follows:

$$\mathbb{P}_U(S, I, U, V)(t, x, y) = U(t) \frac{\displaystyle\int_{\mathbb{R}_+^2} i_U(t, x, y, \overline{x}, \overline{y}) I(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}{K_{hum} + S(t) + \displaystyle\int_{\mathbb{R}_+^2} I(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}$$

where $K_{hum} > 0$ is a weight value, related to the human population. The dynamics of the uninfected vector population U is:

$$\begin{aligned} \frac{dU(t)}{dt} &= b_U(t)U(t) + \int_{\mathbb{R}_+^2} b_V(t, x, y)V(t, x, y)dxdy \\ &\quad - m_U(t)U(t) - \int_{\mathbb{R}_+^2} \mathbb{P}_U(S, I, U, V)(t, x, y)dxdy. \end{aligned} \tag{3.3}$$

Change in infected vector population V

This compartment shares the same mechanism as the infected human compartment.

On the left hand side there are two functions g_V and h_V, having the same meaning as two functions g_I and h_I in the dynamics of the infected human population.

After obtaining a blood meal from individuals o infected human population I, the uninfected vectors usually get infected with parasites. This is expressed by operator $\mathbb{P}_U(S, I, U, V)$, whose form is given above.

By the natural multiplication of parasites, the infected vectors change the level of parasites inside themselves, and often keep the parasites all the rest of their lives. Within compartment V, this changing process is expressed by θ_V. There is also a

natural death, expressed by the rate m_V:

$$\begin{aligned}\frac{\partial V(t,x,y)}{\partial t} &+ \frac{\partial}{\partial x}(g_V(t,x,y)V(t,x,y)) + \frac{\partial}{\partial y}(h_V(t,x,y)V(t,x,y)) \\ &= \mathbb{P}_U(S,I,U,V)(t,x,y) \\ &+ \int_{\mathbb{R}^2_+} \theta_V(t,\overline{x},\overline{y},x,y)V(t,\overline{x},\overline{y})d\overline{x}d\overline{y} - m_V(t,x,y)V(t,x,y).\end{aligned} \tag{3.4}$$

3.1.3 Boundary conditions and the full model

So far we have not mentioned the boundary conditions yet. Now we look for these conditions on the boundary of $\mathbb{R}^3_+ = [0,\infty) \times [0,\infty) \times [0,\infty)$.

Boundary conditions

For two uninfected compartments S and U, we only need to give initial values at $t = 0$. Notice that we are modeling vector-borne diseases, so these two compartments are supposed to be positive:

$$S(0) = S^* > 0, \quad U(0) = U^* > 0.$$

For two infected compartments I and V, the situation is more complex. First, at $t = 0$, we have initial conditions:

$$I(0,x,y) = I^*(x,y), \quad V(0,x,y) = V^*(x,y).$$

We need $I^*(x,y) \geq 0$, $V^*(x,y) \geq 0$ and satisfy:

$$0 \leq \int_{\mathbb{R}^2_+} I^*(x,y)dxdy < \infty, \quad 0 \leq \int_{\mathbb{R}^2_+} V^*(x,y)dxdy < \infty.$$

Second, we consider the part where $t \neq 0$. Under the influence of immunity and medical treatment, both sensitive parasite density x and resistant parasite density y can be reduced to 0. Let $\bar{t} \leq t$ and

$\alpha_I(\bar{t},\eta,t,y)$ denotes the rate at which $I(\bar{t},0,\eta)$ changes to $I(t,0,y)$,
$\beta_I(\bar{t},\xi,\eta,t,y)$ denotes the rate at which $I(\bar{t},\xi,\eta)$ changes to $I(t,0,y)$,
$\zeta_I(t,y)$ denotes the out-going rate of $I(t,0,y)$,
$\alpha_V(\bar{t},\eta,t,y)$ denotes the rate at which $V(\bar{t},0,\eta)$ changes to $V(t,0,y)$,
$\beta_V(\bar{t},\xi,\eta,t,y)$ denotes the rate at which $V(\bar{t},\xi,\eta)$ changes to $V(t,0,y)$*and*
$\zeta_V(t,y)$ denotes the out-going rate of $V(t,0,y)$.

We obtain:

$$I(t,0,y) = I(0,0,y) + \int_0^t \int_{\mathbb{R}_+} \alpha_I(\bar{t},\eta,t,y) I(\bar{t},0,\eta) d\eta d\bar{t}$$
$$+ \int_0^t \int_{\mathbb{R}_+^2} \beta_I(\bar{t},\xi,\eta,t,y) I(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \zeta_I(\bar{t},y) I(\bar{t},0,y) d\bar{t},$$

$$V(t,0,y) = V(0,0,y) + \int_0^t \int_{\mathbb{R}_+} \alpha_V(\bar{t},\eta,t,y) V(\bar{t},0,\eta) d\eta d\bar{t}$$
$$+ \int_0^t \int_{\mathbb{R}_+^2} \beta_V(\bar{t},\xi,\eta,t,y) V(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \zeta_V(\bar{t},y) V(\bar{t},0,y) d\bar{t}.$$

Similarly, patients carrying resistant parasites $y > 0$ can be reduced and become patients with $y = 0$, so we have the following condition at $y = 0$:

$$I(t,x,0) = I(0,x,0) + \int_0^t \int_{\mathbb{R}_+} \gamma_I(\bar{t},\xi,t,x) I(\bar{t},\xi,0) d\xi d\bar{t}$$
$$+ \int_0^t \int_{\mathbb{R}_+^2} \delta_I(\bar{t},\xi,\eta,t,x) I(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \nu_I(\bar{t},x) I(\bar{t},x,0) d\bar{t},$$

$$V(t,x,0) = V(0,x,0) + \int_0^t \int_{\mathbb{R}_+} \gamma_V(\bar{t},\xi,t,x) V(\bar{t},\xi,0) d\xi d\bar{t}$$
$$+ \int_0^t \int_{\mathbb{R}_+^2} \delta_V(\bar{t},\xi,\eta,t,x) V(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \nu_V(\bar{t},x) V(\bar{t},x,0) d\bar{t}$$

where

$\gamma_I(\bar{t},\xi,t,x)$ denotes the rate of $I(\bar{t},\xi,0)$ becoming $I(t,x,0)$,
$\delta_I(\bar{t},\xi,\eta,t,x)$ denotes the rate of $I(\bar{t},\xi,\eta)$ becoming $I(t,x,0)$,
$\nu_I(t,x)$ denotes the out-going rate of $I(t,x,0)$,
$\gamma_V(\bar{t},\xi,t,x)$ denotes the rate of $V(\bar{t},\xi,0)$ becoming $V(t,x,0)$,
$\delta_V(\bar{t},\xi,\eta,t,x)$ denotes the rate of $V(\bar{t},\xi,\eta)$ becoming $V(t,x,0)$,
$\nu_V(t,x)$ denotes the out-going rate of $V(t,x,0)$.

The full dynamical model

Putting together equations (3.1), (3.2), (3.3), (3.4) in section 3.1.2 and all the boundary conditions above, we have a complete system of non-linear integro-partial differential equations. For convenience, we now introduce a new practical form of this model. We write

$$u_1 = I, u_2 = V, u_3 = S, u_4 = U$$

and

$$u = (u_1, u_2, u_3, u_4).$$

The indexes of all factors are also changed accordingly. The operators $\mathbb{P}_S$ and $\mathbb{P}_U$ are replaced by their explicit formulas. The original system has the practical form given in (3.5).

$$
\begin{aligned}
&\frac{\partial}{\partial t}u_1(t,x,y) + \frac{\partial}{\partial x}(g_1 u_1(t,x,y)) + \frac{\partial}{\partial y}(h_1 u_1(t,x,y)) \\
&= u_3(t)\frac{\int_{\mathbb{R}^2_+} i_3(t,x,y,\overline{x},\overline{y})u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + u_4(t) + \int_{\mathbb{R}^2_+} u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}} \\
&+ \int_{\mathbb{R}^2_+} \theta_1(t,\overline{x},\overline{y},x,y)u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y} \\
&-\rho(t,x,y)u_1(t,x,y) - m_1(t,x,y)u_1(t,x,y), \\
&\frac{\partial}{\partial t}u_2(t,x,y) + \frac{\partial}{\partial x}(g_2 u_2(t,x,y)) + \frac{\partial}{\partial y}(h_2 u_2(t,x,y)) \\
&= u_4(t)\frac{\int_{\mathbb{R}^2_+} i_4(t,x,y,\overline{x},\overline{y})u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{hum} + u_3(t) + \int_{\mathbb{R}^2_+} u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}} \\
&+ \int_{\mathbb{R}^2_+} \theta_2(t,\overline{x},\overline{y},x,y)u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y} - m_2(t,x,y)u_2(t,x,y), \\
&\frac{d}{dt}u_3(t) = b_3(t)u_3(t) + \int_{\mathbb{R}^2_+} b_1(t,x,y)u_1(t,x,y)dxdy - m_3(t)u_3(t) \\
&- \int_{\mathbb{R}^2_+} u_3(t)\frac{\int_{\mathbb{R}^2_+} i_3(t,x,y,\overline{x},\overline{y})u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + u_4(t) + \int_{\mathbb{R}^2_+} u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}dxdy \\
&+ \int_{\mathbb{R}^2_+} \rho(t,x,y)u_1(t,x,y)dxdy, \\
&\frac{d}{dt}u_4(t) = b_4(t)u_4(t) + \int_{\mathbb{R}^2_+} b_2(t,x,y)u_2(t,x,y)dxdy \\
&-m_4(t)u_4(t) - \int_{\mathbb{R}^2_+} u_4(t)\frac{\int_{\mathbb{R}^2_+} i_4(t,x,y,\overline{x},\overline{y})u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{hum} + u_3(t) + \int_{\mathbb{R}^2_+} u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}dxdy
\end{aligned}
\tag{3.5}
$$

where

$$g_1 = g_I, h_1 = h_I, i_3 = i_S, \theta_1 = \theta_I, m_1 = m_I,$$

$$g_2 = g_V, h_2 = h_V, i_4 = i_U, \theta_2 = \theta_V, m_2 = m_V,$$

$$b_3 = b_S, b_1 = b_I, m_3 = m_S,$$

$$b_4 = b_U, b_2 = b_V, m_4 = m_U.$$

The initial values (also their conditions) and the boundary equations are

rewritten as the following:

$$
\begin{aligned}
&u_1(0,x,y) = u_1^*(x,y) \geq 0, \quad 0 \leq \int_{\mathbb{R}_+^2} u_1^*(x,y)dxdy < \infty,\\
&u_1(t,0,y) = u_1^*(0,y) + \int_0^t \int_{\mathbb{R}_+} \alpha_1(\bar{t},\eta,t,y)u_1(\bar{t},0,\eta)d\eta d\bar{t}\\
&\quad + \int_0^t \int_{\mathbb{R}_+^2} \beta_1(\bar{t},\xi,\eta,t,y)u_1(\bar{t},\xi,\eta)d\xi d\eta d\bar{t} - \int_0^t \zeta_1(\bar{t},y)u_1(\bar{t},0,y)d\bar{t},\\
&u_1(t,x,0) = u_1^*(x,0) + \int_0^t \int_{\mathbb{R}_+} \gamma_1(\bar{t},\xi,t,x)u_1(\bar{t},\xi,0)d\xi d\bar{t}\\
&\quad + \int_0^t \int_{\mathbb{R}_+^2} \delta_1(\bar{t},\xi,\eta,t,x)u_1(\bar{t},\xi,\eta)d\xi d\eta d\bar{t} - \int_0^t \nu_1(\bar{t},x)u_1(\bar{t},x,0)d\bar{t}\\
&u_2(0,x,y) = u_2^*(x,y) \geq 0, \quad 0 \leq \int_{\mathbb{R}_+^2} u_2^*(x,y)dxdy < \infty,\\
&u_2(t,0,y) = u_2^*(0,y) + \int_0^t \int_{\mathbb{R}_+} \alpha_2(\bar{t},\eta,t,y)u_2(\bar{t},0,\eta)d\eta d\bar{t}\\
&\quad + \int_0^t \int_{\mathbb{R}_+^2} \beta_2(\bar{t},\xi,\eta,t,y)u_2(\bar{t},\xi,\eta)d\xi d\eta d\bar{t} - \int_0^t \zeta_2(\bar{t},y)u_2(\bar{t},0,y)d\bar{t},\\
&u_2(t,x,0) = u_2^*(x,0) + \int_0^t \int_{\mathbb{R}_+} \gamma_2(\bar{t},\xi,t,x)u_2(\bar{t},\xi,0)d\xi d\bar{t}\\
&\quad + \int_0^t \int_{\mathbb{R}_+^2} \delta_2(\bar{t},\xi,\eta,t,x)u_2(\bar{t},\xi,\eta)d\xi d\eta d\bar{t} - \int_0^t \nu_2(\bar{t},x)u_2(\bar{t},x,0)d\bar{t},\\
&\quad u_3(0) = u_3^* > 0,\\
&\quad u_4(0) = u_4^* > 0.
\end{aligned}
\tag{3.6}
$$

Remark on the model system

In system (3.5), functions $g_{(.)}(t,x,y), h_{(.)}(t,x,y)$ are the growth rates of the populations due to internal processes regulating the two structured variables x and y at time t. For technical reason, we are going to consider only the system where functions $g_{(.)}, h_{(.)}$ are positive constants, denoted by g_1, h_1, g_2, h_2 respectively.

In different settings we can have further forms of operators $\mathbb{P}_{(.)}$. They are required to be well-defined. Following the biological meaning, they should map a nonnegative function in function space to a nonnegative one and map function $u \equiv 0$ to 0. If we denote by f the operator of the right hand side of system (3.5), we should be able to obtain $f(0) \equiv 0$. We also notice that there are several improper integrals over $\mathbb{R}_+$ and $\mathbb{R}_+^2$ in the model, they should converge in an appropriate space.

Compared to the previous model already established in chapter 2, we have two new variables of parasite densities, representing sensitive and resistant parasites. The structured population of humans and vectors enable us to obtain more detail on all infected individuals. This is essential for a drug treatment strategy. The

established model brings our attention to develop a method to study the system of integro-partial differential equations.

3.2 Analytical study

To study our model system (3.5), we first need to set up a normed function space. In the second subsection we bring the system to a simpler form by using method of characteristics. In the third subsection we prove that the transformed system has a unique solution when initial boundary conditions are given. In the fourth subsection we study the mapping of the initial boundary values to the solution, this mapping is Lipschitz. Using this result, the fifth subsection is devoted to deriving unknown boundary conditions. Combining all of them, in the last section we show that the transformed system (as well as the original system) has a unique "positive" solution. The interconnection between all the subsections is going to be explained in detail right after the second subsection, in order to help to understand the flow of proofs.

3.2.1 Function space

We begin to set up a function space, which is appropriate for the problem.

Let $\mathbb{R}_+ = [0, \infty)$ and

$$L^{1,\infty}(\mathbb{R}_+^2) = \{w|\ w \in L^1(\mathbb{R}_+^2), w \in BC^0(\mathbb{R}_+^2)\}$$

with a norm:

$$\|.\|_{1,\infty} = \|.\|_1 + \|.\|_\infty .$$

Let $u_1, u_2 \in C^0([0,\infty), L^{1,\infty}(\mathbb{R}_+^2))$ and $u_3, u_4 \in C^0([0,\infty))$. Furthermore, for $\lambda \in (0,\infty)$ (λ will be chosen later), we consider:

$$\begin{aligned} \sup_{t\in\mathbb{R}_+} (e^{-\lambda t} \|u_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}) &< \infty \quad (j = 1,2), \\ \sup_{t\in\mathbb{R}_+} (e^{-\lambda t} |u_j(t)|) &< \infty \quad (j = 3,4). \end{aligned}$$

We denote the space of functions $u = (u_1, u_2, u_3, u_4)$ by X and define a norm $\|.\|_\lambda$ as follows:

$$\begin{aligned} \|u_j\|_\lambda &:= \sup_{t\in\mathbb{R}_+} (e^{-\lambda t} \|u_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}) \quad (j = 1,2), \\ \|u_j\|_\lambda &:= \sup_{t\in\mathbb{R}_+} (e^{-\lambda t} |u_j(t)|) \quad (j = 3,4), \\ \|u\|_\lambda &:= \max_{1\le j\le 4} \|u_j\|_\lambda . \end{aligned}$$

Remark 3.1. Given a $\lambda \in (0, \infty)$, $\|.\|_\lambda$ is a well-defined norm, and $(X, \|.\|_\lambda)$ or X_λ is a Banach space.

Throughout all sections, we need an assumption on all factor functions.
Assumption $\mathcal{A}$.

(i) All factor functions b_j, m_j, ρ are continuous, nonnegative and bounded.
(ii) Let k be any of the factors i_j, θ_j, α_j, β_j, γ_j, δ_j, ($j = 1, 2$ or $j = 3, 4$). We assume that for all their variables ($z = (z_1, z_2) \in D_{z_1} \times D_{z_2}$):

$$k(z_1, z_2) \in BC^0_+(D_{z_1}, L^1(D_{z_2})), \quad k(z_1, z_2) \in BC^0_+(D_{z_2}, L^1(D_{z_1})).$$

(iii) The derivatives of factor functions $\alpha_j, \beta_j, \gamma_j, \delta_j$ ($j = 1, 2$) in the boundary equations are nonnegative with respect to variable t.
(iv) Four factor functions ζ_j, ν_j ($j = 1, 2$) are bounded and differentiable over their respective domains.

3.2.2 Transformation of the equations using the method of characteristics

In order to simplify system (3.5), we are going to transform the variables in each equation. In principle, we keep the original form of the equations corresponding to u_3, u_4. We mainly need to transform those two equations which include all the partial derivatives of the unknown functions.

We consider the equation with the partial derivatives of u_j ($j = 1, 2$). Using the method of characteristics, we want to find a parameterization $t(s_j, r_j)$, $x(s_j, r_j)$, $y(s_j, r_j)$ such that:

$$\begin{aligned}
&\frac{\partial}{\partial t} u_j(t, x, y) + \frac{\partial}{\partial x}(g_j u_j(t, x, y)) + \frac{\partial}{\partial y}(h_j u_j(t, x, y)) \\
&\quad = \frac{\partial}{\partial s_j} u_j(t(s_j, r_j), x(s_j, r_j), y(s_j, r_j)), \\
&r_j \text{ is independent of } s_j, (r_j \in \partial\mathbb{R}^3_+, \text{ the boundary of } \mathbb{R}^3_+).
\end{aligned}$$

According to the chain rule,

$$\frac{\partial}{\partial s_j} u_j(t, x, y) = \frac{\partial u_j}{\partial t}\frac{\partial t}{\partial s_j} + \frac{\partial u_j}{\partial x}\frac{\partial x}{\partial s_j} + \frac{\partial u_j}{\partial y}\frac{\partial y}{\partial s_j},$$

that is why we choose $t(s_j, r_j), x(s_j, r_j), y(s_j, r_j)$ to satisfy:

$$\begin{aligned}
\frac{\partial t}{\partial s_j} &= 1, \\
\frac{\partial x}{\partial s_j} &= g_j, \\
\frac{\partial y}{\partial s_j} &= h_j, \\
r_j &= (t|_{s_j=0}, x|_{s_j=0}, y|_{s_j=0}) \in \partial\mathbb{R}^3_+.
\end{aligned} \tag{3.7}$$

We have two new coordinate systems, denoted by (s_j, r_j) $(j = 1, 2)$.

We denote $\varphi_j (j = 1, 2)$ as the transformations which bring the original coordinate to the coordinates (s_j, r_j). We need to look at the detailed formula of φ_j. The parameterization of (t, x, y) in the first equation is described in system (3.7), so the characteristic curves are parallel to a vector with coordinates $(1, g_1, h_1)$. The solution of (3.7) depends on initial value $r_1 \in \partial\mathbb{R}^3_+$. To be more precise, we have to divide $\mathbb{R}^3_+$ into three sub-domains which correspond to three surfaces of the boundary of $\mathbb{R}^3_+$.

In our case, the common boundaries of these domains are three surfaces. They are shown in figure 3.2, distinguished by rectangle, circle and triangle patterns.

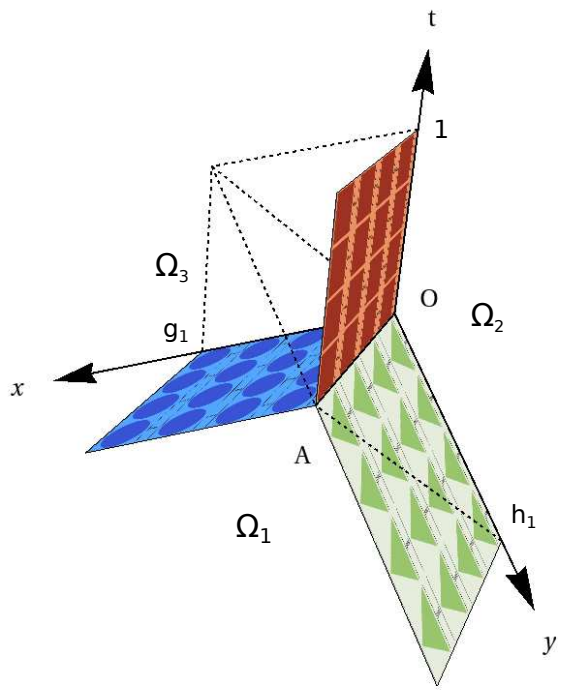

Figure 3.2: Three sub-domains divided by characteristic curves. The first one, Ω_1, contains the characteristic curves cutting the positive quadrant of Oxy, the second one, Ω_2, contains the characteristic curves cutting Oty, the third one, Ω_3, contains the characteristic curves cutting Otx.

The three domains are described by $\Omega_j(g_1, h_1)$, $(j = 1, 2, 3)$:

$$\begin{aligned}\Omega_1(g_1, h_1) =& \{(t, x, y) |\ t \geq 0, x \geq 0, y \geq 0;\\ & \exists r_1 = (0, x_1, y_1) \in \partial\mathbb{R}^3_+ \colon \frac{t-0}{1} = \frac{x - x_1}{g_1} = \frac{y - y_1}{h_1}\},\end{aligned}$$

$$\begin{aligned}
\Omega_2(g_1,h_1) =& \{(t,x,y)|\ t>0, x\geq 0, y\geq 0;\\
&\exists r_1=(t_1,0,y_1)\in\partial\mathbb{R}^3_+\colon \frac{t-t_1}{1}=\frac{x-0}{g_1}=\frac{y-y_1}{h_1}\},\\
\Omega_3(g_1,h_1) =& \{(t,x,y)|\ t>0, x\geq 0, y\geq 0;\\
&\exists r_1=(t_1,x_1,0)\in\partial\mathbb{R}^3_+\colon \frac{t-t_1}{1}=\frac{x-x_1}{g_1}=\frac{y-0}{h_1}\}.
\end{aligned}$$

To specify $\Omega_j(g_1,h_1)(j=1,2,3)$, we first compute the equation of the blue circle plane P_1 generated by $\overrightarrow{OA}$ and axis Ox, the green triangle plane P_2 generated by $\overrightarrow{OA}$ and axis Oy, the red square plane P_3 generated by $\overrightarrow{OA}$ and axis Ot. Equations of $P_j, j=1,2,3$ are given by:

$$\begin{aligned}
(P_1):&\quad h_1t-y=0,\\
(P_2):&\quad -g_1t+x=0,\\
(P_3):&\quad h_1x-g_1y=0.
\end{aligned}\tag{3.8}$$

From this we obtain:

$$\begin{aligned}
\Omega_1(g_1,h_1) =& \{(t,x,y)|\ 0\leq t, h_1t\leq y, \frac{g_1y}{h_1}\leq x\}\cup\\
&\cup\{(t,x,y)|\ 0\leq t, g_1t\leq x, \frac{h_1}{g_1}x\leq y\},\\
\Omega_2(g_1,h_1) =& \{(t,x,y)|\ 0<t, 0<y\leq h_1t, 0\leq x\leq \frac{g_1}{h_1}y\}\cup\\
&\cup\{(t,x,y)|\ 0<t, h_1t\leq y, 0\leq x\leq g_1t\},\\
\Omega_3(g_1,h_1) =& \{(t,x,y)|\ 0<t, 0<x\leq g_1t, 0\leq y\leq \frac{h_1}{g_1}x\}\cup\\
&\cup\{(t,x,y)|\ 0<t, g_1t\leq x, 0\leq y\leq h_1t\}.
\end{aligned}$$

Now we can define φ_1 as follows:
On $\Omega_1(g_1,h_1)$: $(t,x,y)=\varphi_1(s_1,r_1),(s_1,r_1)=(s_1,(0,x_1,y_1))$ such that:

$$\begin{aligned}
t =& \quad \varphi_1^{(1)}(s_1,(0,x_1,y_1)) = \quad s_1,\\
x =& \quad \varphi_1^{(2)}(s_1,(0,x_1,y_1)) = \quad x_1+g_1s_1,\\
y =& \quad \varphi_1^{(3)}(s_1,(0,x_1,y_1)) = \quad y_1+h_1s_1.
\end{aligned}\tag{3.9}$$

On $\Omega_2(g_1,h_1)$: $(t,x,y)=\varphi_1(s_1,r_1),(s_1,r_1)=(s_1,(t_1,0,y_1))$ such that:

$$\begin{aligned}
t =& \quad \varphi_1^{(1)}(s_1,(t_1,0,y_1)) = \quad t_1+s_1,\\
x =& \quad \varphi_1^{(2)}(s_1,(t_1,0,y_1)) = \quad g_1s_1,\\
y =& \quad \varphi_1^{(3)}(s_1,(t_1,0,y_1)) = \quad y_1+h_1s_1.
\end{aligned}\tag{3.10}$$

On $\Omega_3(g_1,h_1)$: $(t,x,y)=\varphi_1(s_1,r_1),(s_1,r_1)=(s_1,(t_1,x_1,0))$ such that:

$$\begin{aligned}
t =& \quad \varphi_1^{(1)}(s_1,(t_1,x_1,0)) = \quad t_1+s_1,\\
x =& \quad \varphi_1^{(2)}(s_1,(t_1,x_1,0)) = \quad x_1+g_1s_1,\\
y =& \quad \varphi_1^{(3)}(s_1,(t_1,x_1,0)) = \quad h_1s_1.
\end{aligned}\tag{3.11}$$

Notice that the three domains are disjointed (except on their common boundaries) and the map definitions on the same boundary are identical. For example, on the boundary plane P_2 ($g_1 t = x$), given (t, x, y) then we obtain the same (s_1, r_1) using formula (3.9) or formula (3.10).

In the same manner we obtain three domains $\Omega_1(g_2, h_2)$, $\Omega_2(g_2, h_2)$, $\Omega_3(g_2, h_2)$ and the map φ_2. Note that $\Omega_j(.)$ is just the notation, not a function. In detail: On $\Omega_1(g_2, h_2)$: $(t, x, y) = \varphi_2(s_2, r_2), (s_2, r_2) = (s_2, (0, x_2, y_2))$ such that:

$$\begin{aligned} t = &\quad \varphi_2^{(1)}(s_2, (0, x_2, y_2)) = \quad s_2, \\ x = &\quad \varphi_2^{(2)}(s_2, (0, x_2, y_2)) = \quad x_2 + g_2 s_2, \\ y = &\quad \varphi_2^{(3)}(s_2, (0, x_2, y_2)) = \quad y_2 + h_2 s_2. \end{aligned} \tag{3.12}$$

On $\Omega_2(g_2, h_2)$: $(t, x, y) = \varphi_2(s_2, r_2), (s_2, r_2) = (s_2, (t_2, 0, y_2))$ such that:

$$\begin{aligned} t = &\quad \varphi_2^{(1)}(s_2, (t_2, 0, y_2)) = \quad t_2 + s_2, \\ x = &\quad \varphi_2^{(2)}(s_2, (t_2, 0, y_2)) = \quad g_2 s_2, \\ y = &\quad \varphi_2^{(3)}(s_2, (t_2, 0, y_2)) = \quad y_2 + h_2 s_2. \end{aligned} \tag{3.13}$$

On $\Omega_3(g_2, h_2)$: $(t, x, y) = \varphi_2(s_2, r_2), (s_2, r_2) = (s_2, (t_2, x_2, 0))$ such that:

$$\begin{aligned} t = &\quad \varphi_2^{(1)}(s_2, (t_2, x_2, 0)) = \quad t_2 + s_2, \\ x = &\quad \varphi_2^{(2)}(s_2, (t_2, x_2, 0)) = \quad x_2 + g_2 s_2, \\ y = &\quad \varphi_2^{(3)}(s_2, (t_2, x_2, 0)) = \quad h_2 s_2. \end{aligned} \tag{3.14}$$

In the following we prove that the map φ_1 (similarly for φ_2) is bijective by using the Jacobian matrix. The Jacobian determinant of transformation φ_1 on $\Omega_1(g_1, h_1)$ is given as:

$$J\varphi_1|_{\Omega_1(g_1,h_1)} = \begin{vmatrix} \frac{\partial t}{\partial s_1} & \frac{\partial t}{\partial x_1} & \frac{\partial t}{\partial y_1} \\ \frac{\partial x}{\partial s_1} & \frac{\partial x}{\partial x_1} & \frac{\partial x}{\partial y_1} \\ \frac{\partial y}{\partial s_1} & \frac{\partial y}{\partial x_1} & \frac{\partial y}{\partial y_1} \end{vmatrix}_{\Omega_1(g_1,h_1)} = \begin{vmatrix} 1 & 0 & 0 \\ g_1 & 1 & 0 \\ h_1 & 0 & 1 \end{vmatrix} = 1,$$

The Jacobian determinant of transformation φ_1 on $\Omega_2(g_1, h_1)$ is:

$$J\varphi_1|_{\Omega_2(g_1,h_1)} = \begin{vmatrix} \frac{\partial t}{\partial s_1} & \frac{\partial t}{\partial t_1} & \frac{\partial t}{\partial y_1} \\ \frac{\partial x}{\partial s_1} & \frac{\partial x}{\partial t_1} & \frac{\partial x}{\partial y_1} \\ \frac{\partial y}{\partial s_1} & \frac{\partial y}{\partial t_1} & \frac{\partial y}{\partial y_1} \end{vmatrix}_{\Omega_2(g_1,h_1)} = \begin{vmatrix} 1 & 1 & 0 \\ g_1 & 0 & 0 \\ h_1 & 0 & 1 \end{vmatrix} = -g_1.$$

The Jacobian determinant of transformation φ_1 on $\Omega_3(g_1, h_1)$ is:

$$J\varphi_1|_{\Omega_3(g_1,h_1)} = \begin{vmatrix} \frac{\partial t}{\partial s_1} & \frac{\partial t}{\partial t_1} & \frac{\partial t}{\partial x_1} \\ \frac{\partial x}{\partial s_1} & \frac{\partial x}{\partial t_1} & \frac{\partial x}{\partial x_1} \\ \frac{\partial y}{\partial s_1} & \frac{\partial y}{\partial t_1} & \frac{\partial y}{\partial x_1} \end{vmatrix}_{\Omega_3(g_1,h_1)} = \begin{vmatrix} 1 & 1 & 0 \\ g_1 & 0 & 1 \\ h_1 & 0 & 0 \end{vmatrix} = h_1.$$

Similarly, we have transformation φ_2 also with three different corresponding subdomains and three corresponding Jacobian determinants. Assuming that for all $j, g_j > 0, h_j > 0$, then all Jacobian determinants are different from 0. That means, there always exists uniquely a φ_j^{-1} $(j = 1, 2)$ so that

$$(s_j, r_j) = \varphi_j^{-1}(t, x, y).$$

Moreover, for both $j = 1$ and $j = 2$, we obtain the following domains of (s_j, r_j) corresponding to $\Omega_1, \Omega_2, \Omega_3$:

$$\begin{aligned} \varphi_j^{-1}(\Omega_1(g_j, h_j)) &= [0, \infty) \times \{(0, x, y)| \quad x, y \geq 0\}, \\ \varphi_j^{-1}(\Omega_2(g_j, h_j)) &= [0, \infty) \times \{(t, 0, y)| \quad t, y \geq 0\}, \\ \varphi_j^{-1}(\Omega_3(g_j, h_j)) &= [0, \infty) \times \{(t, x, 0)| \quad t, x \geq 0\}. \end{aligned}$$

Recall that we denote $f = (f_1, f_2, f_3, f_4)$ as the vector operator of the right hand side of system (3.5). We write system (3.5) in the differential form:

$$\begin{aligned} \frac{\partial}{\partial s_1} u_1 \circ \varphi_1(s_1, r_1) &= f_1 u \circ \varphi_1(s_1, r_1) \\ \frac{\partial}{\partial s_2} u_2 \circ \varphi_2(s_2, r_2) &= f_2 u \circ \varphi_2(s_2, r_2) \\ \frac{d}{dt} u_3(t) &= f_3 u(t) \\ \frac{d}{dt} u_4(t) &= f_4 u(t) \end{aligned} \tag{3.15}$$

where

$$\varphi_1(s_1, r_1) = \varphi_2(s_2, r_2) = (t, x, y)$$

and

$$\begin{aligned} f_1 u(t, x, y) = u_3(t) & \frac{\int_{\mathbb{R}_+^2} i_3(t, x, y, \overline{x}, \overline{y}) u_2(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}{K_{vec} + u_4(t) + \int_{\mathbb{R}_+^2} u_2(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}} \\ & + \int_{\mathbb{R}_+^2} \theta_1(t, \overline{x}, \overline{y}, x, y) u_1(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y} \\ & - \rho(t, x, y) u_1(t, x, y) - m_1(t, x, y) u_1(t, x, y), \end{aligned}$$

$$f_2u(t,x,y) = u_4(t)\frac{\int_{\mathbb{R}_+^2} i_4(t,x,y,\overline{x},\overline{y})u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{hum}+u_3(t)+\int_{\mathbb{R}_+^2} u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}$$
$$+\int_{\mathbb{R}_+^2} \theta_2(t,\overline{x},\overline{y},x,y)u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y} - m_2(t,x,y)u_2(t,x,y),$$

$$f_3u(t) = b_3(t)u_3(t) + \int_{\mathbb{R}_+^2} b_1(t,x,y)u_1(t,x,y)dxdy$$
$$-m_3(t)u_3(t) - \int_{\mathbb{R}_+^2} u_3(t)\frac{\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec}+u_4(t)+\int_{\mathbb{R}_+^2} u_2(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}dxdy$$
$$+\int_{\mathbb{R}_+^2} \rho(t,x,y)u_1(t,x,y)dxdy,$$

$$f_4u(t) = b_4(t)u_4(t) + \int_{\mathbb{R}_+^2} b_2(t,x,y)u_2(t,x,y)dxdy$$
$$-m_4(t)u_4(t) - \int_{\mathbb{R}_+^2} u_4(t)\frac{\int_{\mathbb{R}_+^2} i_4(t,x,y,\overline{x},\overline{y})u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{hum}+u_3(t)+\int_{\mathbb{R}_+^2} u_1(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}dxdy.$$

We have two different transformations. To write the transformations flexibly, sometimes we use the notations φ_j and φ_j^{-1}, sometimes (if possible) we can use directly the notations (t,x,y) and (s_j,r_j) as functions.

If (t,x,y) are given then $(s_j,r_j)(j=1,2)$ are uniquely determined. Given (s_j,r_j) $(j=1,2)$ with one j then we can also determine (t,x,y) and the other (s_j,r_j) $(j=2,1)$. After integration of system (3.15) with the corresponding variables s_1, s_2 and t, we obtain the following result:

Proposition 3.2. *Let $g_j,h_j>0$ for $j=1,2$, we have:*
(i) system (3.5) can be transformed to either the differential form (3.15) with the initial boundary conditions (3.6) or the integral form as the following:

$$\begin{aligned} u_1\circ\varphi_1(s_1,r_1) &= u_1\circ\varphi_1(0,r_1) + \int_0^{s_1(t,x,y)} f_1u\circ\varphi_1(s_1,r_1)ds,\\ u_2\circ\varphi_2(s_2,r_2) &= u_2\circ\varphi_2(0,r_2) + \int_0^{s_2(t,x,y)} f_2u\circ\varphi_2(s_2,r_2)ds,\\ u_3(t) &= u_3(0) + \int_0^t f_3u(\tau)d\tau,\\ u_4(t) &= u_4(0) + \int_0^t f_4u(\tau))d\tau. \end{aligned} \tag{3.16}$$

where φ_1, φ_2 are defined explicitly in equations (3.9, 3.10, 3.11), (3.12, 3.13, 3.14).
(ii) The transformation from system (3.5,3.6) to system (3.15,3.6) or system (3.16) is bijective.

Remark 3.3. Compared to the other problems of the Volterra type, we have several difficulties. They include:

- there are implicit boundary equations, given by several equations containing the unknowns,

- there are several nonlinear operators f_j $(j = 1, 2, 3, 4)$,

- the operators f_j $(j = 1, 2, 3, 4)$ contain integrals over $\mathbb{R}^2_+$,

- there are two additional transformations φ_j $(j = 1, 2)$ on variables (s, r_j).

As stated before, we would like to discuss our coming work-flow. To treat the unknown boundary conditions, we look at figure 3.3. Remember that we have

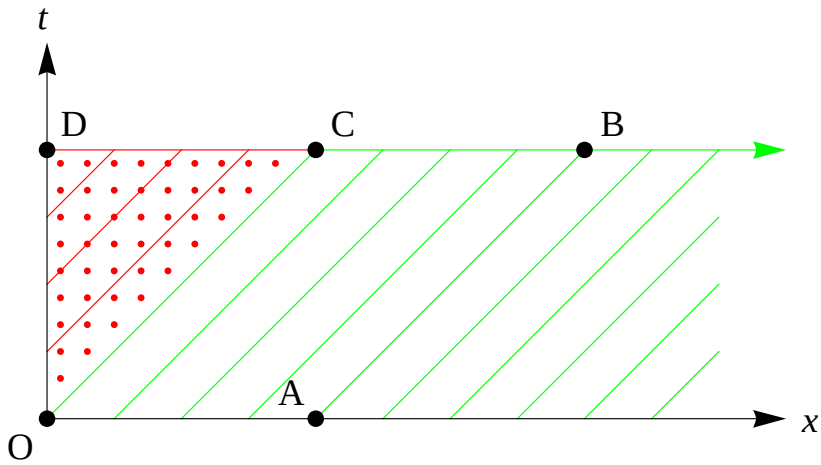

Figure 3.3: Method to solve the unknown boundary problem. We simplify the two variables (x, y) by x. When $t = 0$ we have the known initial conditions, which shows on Ox. When $x = 0$ we have the unknown boundary condition, which shows on OD. We need to compute value on OD.

used the method of characteristics and have obtained system (3.16). The idea in this figure is:

- If we know the right hand side of system (3.16), for any given initial value at point A we can compute the value from A to B. Knowing all initial values $(t = 0)$ allows us to compute the green striped region.

- Only with initial values we can not compute the red dotted part OCD. If the values on the boundary OD are also given $(x = 0)$, then we can fill this red dotted region.

- If we know all information inside the infinite strip xODB (combination of green striped and red dotted regions), then we can compute the values on boundary

OD by using the boundary equations.

We are going to use the Banach fixed point theorem to solve this problem. We have to reformulate the problem as a fixed point problem and choose a proper function space such that the conditions of the Banach theorem are fulfilled. In this process, we need to study the properties of the operators f_j $(j = 1, 2, 3, 4)$ and the transformations φ_j $(j = 1, 2)$. In other words, we are going to deal with all the difficulties mentioned in remark 3.3.

Our plan includes four steps:

1. We assume that the initial boundary values are given, then prove that system (3.16) has a unique solution. This solution is positive, as long as the initial boundary values are positive.

2. The mapping from the initial boundary values to this solution is Lipschitz.

3. Considering the equations of the boundaries, we represent the unknowns in the right hand sides by functionals of the corresponding boundaries. Using the Banach theorem we can find the boundary values explicitly.

4. Substitute the boundary values to system (3.16) to obtain its solution. This solution is unique, positive.

All these steps are performed in the following four theorems.

3.2.3 System with given initial boundary values

In this subsection we deal with the first step, which has the longest proof. We are going to show that there exists a solution for system (3.16) with given positive initial boundary values. Moreover, the solution is unique, positive. The results are stated below:

Theorem 3.4. *Assuming that the initial boundary conditions of $u_j, j = 1, 2, 3, 4$ and assumption $\mathcal{A}$ are given. We have the following:*
(i) There is a λ such that on X_λ system (3.16)

$$\begin{aligned}
u_1 \circ \varphi_1(s_1, r_1) &= u_1 \circ \varphi_1(0, r_1) + \int_0^{s_1(t,x,y)} f_1 u \circ \varphi_1(s_1, r_1) ds, \\
u_2 \circ \varphi_2(s_2, r_2) &= u_2 \circ \varphi_2(0, r_2) + \int_0^{s_2(t,x,y)} f_2 u \circ \varphi_2(s_2, r_2) ds, \\
u_3(t) &= u_3(0) + \int_0^t f_3 u(\tau) d\tau, \\
u_4(t) &= u_4(0) + \int_0^t f_4 u(\tau)) d\tau.
\end{aligned}$$

has a unique solution u.
(ii) The solution is positive if the initial boundary values are positive.

To prove this theorem we also need the Banach fixed point theorem. We need to carry out this proof in several lemmas. To focus on the main results, we present at first all the lemmas. If all the lemmas are valid then we can derive theorem 3.4. Afterward the proofs for all the lemmas are presented sequentially.

Shortly speaking, to be able to treat system (3.16), we first need to treat some "cut-off" operator of the right hand side. This operator is Lipschitz. Choosing a suitable λ, the cut-off system has a unique solution. We then prove that the cut-off is actually inactive. So we can have the unique positive solution for the original system. All details are given below.

Since the initial boundary values are given, we know all

$$u_j \circ \varphi_j(0, r_j) = u_j^0(r_j) \ (r_j \in \partial\mathbb{R}^3_+, j = 1, 2) \text{ and } u_j(0) = u_j^0 \ (j = 3, 4).$$

We consider an operator $K = (K_1, \ldots, K_4)$ corresponding to the system. For $j = 1, 2$:

$$K_j u(t, x, y) = \int_0^{s_j(t,x,y)} f_j(u) \circ (\varphi_j(s, r_j(t, x, y)))ds + u_j^0(r_j(t, x, y))$$

and for $j = 3, 4$

$$K_j u(t) = \int_0^t f_j(u)(\tau)d\tau + u_j^0.$$

The operator contains unbounded functions, therefore we consider an operator f^M (corresponding K^M), which is similar to the original one.
Let $M > 0$. we define an operator $[.]_0^M$:

$$[u_j(t)]_0^M := \begin{cases} u_j(t) & \text{if } u_j(t) \in [0, M], \\ 0 & \text{if } u_j(t) < 0, \\ M & \text{if } u_j(t) > M \end{cases}$$

Similarly, $[.]_0$ means only cut from below 0 and $[.]^M$ means only cut from above M. We consider operator $f^M = (f_1^M, f_2^M, f_3^M, f_4^M)$ as follows:

$$\begin{aligned} f_1^M(t, x, y) := {} & [u_3]_0^M(t) \frac{\int_{\mathbb{R}^2_+} i_3(t, x, y, \overline{x}, \overline{y})[u_2]_0(t, \overline{x}, \overline{y})d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}^2_+} [u_2]_0(t, \overline{x}, \overline{y})d\overline{x}d\overline{y}} \\ & + \int_{\mathbb{R}^2_+} \theta_1(t, \overline{x}, \overline{y}, x, y)u_1(t, \overline{x}, \overline{y})d\overline{x}d\overline{y} \\ & -\rho(t, x, y)u_1(t, x, y) - m_1(t, x, y)u_1(t, x, y), \end{aligned}$$

$$\begin{aligned} f_2^M u(t, x, y) := {} & [u_4]_0^M(t) \frac{\int_{\mathbb{R}^2_+} i_4(t, x, y, \overline{x}, \overline{y})[u_1]_0(t, \overline{x}, \overline{y})d\overline{x}d\overline{y}}{K_{hum} + [u_3]_0(t) + \int_{\mathbb{R}^2_+} [u_1]_0(t, \overline{x}, \overline{y})d\overline{x}d\overline{y}} \\ & + \int_{\mathbb{R}^2_+} \theta_2(t, \overline{x}, \overline{y}, x, y)u_2(t, \overline{x}, \overline{y})d\overline{x}d\overline{y} - m_2(t, x, y)u_2(t, x, y), \end{aligned}$$

$$
\begin{aligned}
f_3^M u(t) &:= b_3(t)u_3(t) + \int_{\mathbb{R}_+^2} b_1(t,x,y)u_1(t,x,y)dxdy - m_3(t)u_3(t) \\
&- \int_{\mathbb{R}_+^2} [u_3]_0^M(t) \frac{\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}_+^2} [u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}} dxdy \\
&+ \int_{\mathbb{R}_+^2} \rho(t,x,y)u_1(t,x,y)dxdy,
\end{aligned}
$$

$$
\begin{aligned}
f_4^M u(t) &:= b_4(t)u_4(t) + \int_{\mathbb{R}_+^2} b_2(t,x,y)u_2(t,x,y)dxdy - m_4(t)u_4(t) \\
&- \int_{\mathbb{R}_+^2} [u_4]_0^M(t) \frac{\int_{\mathbb{R}_+^2} i_4(t,x,y,\overline{x},\overline{y})[u_1]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{hum} + [u_3]_0(t) + \int_{\mathbb{R}_+^2} [u_1]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}} dxdy.
\end{aligned}
$$

To be compatible with norm $\|.\|_\lambda$ on X_λ, for any given $t \in [0,\infty)$ and $u \in X$ we also need a $L^{1,\infty}$-norm:

$$
\|u(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} := \max_{j=1,2}\{\|u_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}, |u_3(t)|, |u_4(t)|\}.
$$

We first have the following lemma:

Lemma 3.5. *f^M is Lipschitz with norm $\|.\|_{L^{1,\infty}(\mathbb{R}_+^2)}$. That means, for $j \in \{1,2,3,4\}$, $\forall u,v \in X$, for any given $t \in [0,\infty)$ there is a constant $l > 0$ (l does not depend on t) such that:*

$$
\left\|(f_j^M u - f_j^M v)(t,.)\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq l \ \|(u-v)(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}.
$$

To work with operator K^M, beside the knowledge of operator f^M we also need to look at transformations φ_j $(j = 1,2)$. It is necessary to know their Jacobian determinants and the new domains. We state here a lemma which provides us with the necessary results to proceed with the next steps.

Lemma 3.6. *Let $(\overline{t},\overline{x},\overline{y}) = \varphi_1(s, r_1(t,x,y))$ over the three domains Ω_j $(j = 1,2,3)$ of (t,x,y). We have:*
(i) On all three sub-domains:

$$
d\overline{t}d\overline{x}d\overline{y} = dsdxdy.
$$

(ii) The new domains of $(\overline{t},\overline{x},\overline{y})$ can be computed according to (t,x,y). In detail:
- when $(t,x,y) \in \Omega_1$:

$$
\overline{t} \in [0,t], \overline{x} \in [x - g_1 t, x], \overline{y} \in [y - h_1 t, y],
$$

- when $(t,x,y) \in \Omega_2$:

$$
\overline{t} \in [t - \frac{x}{g_1}, t], \overline{x} \in [0,x], \overline{y} \in [y - \frac{h_1}{g_1}x, y],
$$

- *when* $(t, x, y) \in \Omega_3$*:*

$$\overline{t} \in [t - \frac{y}{h_1}, t], \overline{x} \in [x - \frac{g_1}{h_1} y, x], \overline{y} \in [0, y].$$

Remark 3.7. Similar results hold for the transformation φ_2.

We now have enough information to treat operator K^M.

Lemma 3.8. *For any given* $M > 0$*:*
There is a $\lambda > 0$ *such that* K^M *is a contraction map with norm* $\|.\|_\lambda$*. With this* λ*, the equation*

$$u = K^M u$$

with given initial boundary conditions has a unique solution.

The next consideration concerns the positiveness of the solution. Taking into account the meaning of each variable, our definition of positiveness is: if $u_1, u_2 \geq 0$ and $u_3, u_4 > 0$ then we call the solution $u = (u_1, u_2, u_3, u_4)$ "positive". This comes from the fact that the infected populations (humans and vectors) should be nonnegative and the susceptible populations should be positive.

Lemma 3.9. *As far as the initial boundary conditions are positive, the solution in lemma 3.8 is positive.*

To complete the proof of theorem 3.4, we just need to show that the cut-off M is "inactive". Concerning this we have the following lemma.

Lemma 3.10. *Given an interval* $[0, T]$ *with* T *being arbitrarily large.*
The values of $u_3(t)$ *and* $u_4(t)$ *are bounded by a value* $\overline{u}$ *which only depends on* T*, not on* M*.*

So given any T arbitrarily large, we can always choose $M > \overline{u}(T)$. The solution is unique, so the cut-off M is inactive.

Proof of theorem 3.4

It is clear that all lemmas 3.5, 3.6, 3.8, 3.9, 3.10 create a work-flow to solve system (3.16)

$$u = Ku.$$

Proof. First, we cut operator f to f^M. Lemma 3.5 proves the Lipschitz property of operator f^M. Lemma 3.6 studies transformations φ_1, φ_2. These two provide the information to deal with operator K^M in lemma 3.8. Following this lemma,

operator K^M is a contraction map with an appropriate λ. So using the Banach fixed point theorem, the equation

$$u = K^M u$$

possesses a unique solution.

In lemma 3.9, we prove that this solution is positive, so we are free from the cut-off below of f^M. In lemma 3.10, we continue to prove that the cut-off above is also "inactive". For any arbitrary large time, we can always choose $M > 0$ large enough such that

$$f^M \equiv f.$$

Since the initial boundary values are given, we obtain

$$K^M \equiv K.$$

In this way, K is also a contraction map and the original equation

$$u = Ku$$

has a unique positive solution. Theorem 3.4 is proved. □

Remark 3.11. The Lipschitz property of f is also useful for the next section to prove that the mapping of the boundary values to the solution is Lipschitz.

Our task now is to prove all the lemmas.

Proof of lemma 3.5

In lemma 3.5, we need to prove that f^M is Lipschitz with norm $\|.\|_{L^{1,\infty}}$. Since f^M has four components, it is enough if we can prove that each component f_j^M $(j = 1, 2, 3, 4)$ is Lipschitz. Maximum of four Lipschitz constants is the Lipschitz constant of f^M.

Proof. We are going to consider the Lipschitz property of f_1^M, for other f_j^M $(j = 2, 3, 4)$ would be similar. We need to compare $\left\|f_1^M u - f_1^M v\right\|_{L^{1,\infty}}$ to $\|u - v\|_{L^{1,\infty}}$.

By looking at all their components, we have:

$$\begin{aligned}
&\left\|f_1^M u(t,.) - f_1^M v(t,.)\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&\leq \|(\rho(t,.) + m_1(t,.))(u_1(t,.) - v_1(t,.))\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&+\left\|\int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},.)(u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y}))d\overline{x}d\overline{y}\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&+\left\|([u_3]_0^M(t) - [v_3]_0^M(t))\frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}_+^2}[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&+\left\|[v_3]_0^M(t)(\frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}_+^2}[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}\right. \\
&\qquad\left. -\frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec} + [v_4]_0(t) + \int_{\mathbb{R}_+^2}[v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}})\right\|_{L^{1,\infty}(\mathbb{R}_+^2)}.
\end{aligned}$$

We are going to estimate each term separately. The first term is linear, so it can be estimated directly:

$$\begin{aligned}
&\|(\rho(t,.) + m_1(t,.))(u_1(t,.) - v_1(t,.))\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
\leq\ & l_1(t)\,\|u_1(t,.) - v_1(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
\leq\ & \overline{l_1}\,\|u(t,.) - v(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}
\end{aligned}$$

where $l_1(t) = \sup\limits_{(x,y)} |\rho(t,x,y) + m_1(t,x,y)|$
and $\overline{l_1} = \sup\limits_{t\in\mathbb{R}_+} l_1(t) < \infty$, due to assumption $\mathcal{A}$.
The second term is

$$\left\|\int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},.)(u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y}))d\overline{x}d\overline{y}\right\|_{L^{1,\infty}(\mathbb{R}_+^2)}.$$

We estimate the two norms separately:

$$\begin{aligned}
&\left\|\int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},.)(u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y}))d\overline{x}d\overline{y}\right\|_{L^{\infty}(\mathbb{R}_+^2)} \\
&+\left\|\int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},.)(u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y}))d\overline{x}d\overline{y}\right\|_{L^{1}(\mathbb{R}_+^2)} \\
&\leq \sup_{(x,y)\in\mathbb{R}_+^2}\left|\int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},x,y)(u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y}))d\overline{x}d\overline{y}\right| \\
&+\int_{\mathbb{R}_+^2}\int_{\mathbb{R}_+^2} |\theta_1(t,\overline{x},\overline{y},x,y)|\ \ |u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y})|\,d\overline{x}d\overline{y}dxdy
\end{aligned}$$

$$
\begin{aligned}
&\leq \sup_{(x,y)\in\mathbb{R}_+^2} \left| \int_{\mathbb{R}_+^2} \theta_1(t,\overline{x},\overline{y},x,y) d\overline{x}d\overline{y} \right| \|u_1(t,.) - v_1(t,.)\|_{L^\infty(\mathbb{R}_+^2)} \\
&+ \int_{\mathbb{R}_+^2} \Big(\int_{\mathbb{R}_+^2} |\theta_1(t,\overline{x},\overline{y},x,y)| dxdy \Big) |u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y})| \, d\overline{x}d\overline{y} \\
&\leq \sup_{(x,y)\in\mathbb{R}_+^2} \|\theta_1(t,.,x,y)\|_{L^1(\mathbb{R}_+^2)} \|u_1(t,.) - v_1(t,.)\|_{L^\infty(\mathbb{R}_+^2)} \\
&+ \sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2} \|\theta_1(t,\overline{x},\overline{y},.)\|_{L^1(\mathbb{R}_+^2)} \int_{\mathbb{R}_+^2} |u_1(t,\overline{x},\overline{y}) - v_1(t,\overline{x},\overline{y})| d\overline{x}d\overline{y} \\
&\leq l_2(t) \|u_1(t,.) - v_1(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&\leq \overline{l_2} \|u(t,.) - v(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}
\end{aligned}
$$

where
$l_2(t) = \sup_{(x,y)} \|\theta_1(t,.,x,y)\|_{L^1(\mathbb{R}_+^2)} + \sup_{(\overline{x},\overline{y})} \|\theta_1(t,\overline{x},\overline{y},.)\|_{L^1(\mathbb{R}_+^2)}$,
$\overline{l_2} = \sup_{t\in\mathbb{R}_+} l_2(t)$ bounded by positive values due to assumption $\mathcal{A}$.

The third term is

$$
\left\| ([u_3]_0^M(t) - [v_3]_0^M(t)) \frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y}) d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}_+^2} [u_2]_0(t,\overline{x},\overline{y}) d\overline{x}d\overline{y}} \right\|_{L^{1,\infty}(\mathbb{R}_+^2)}.
$$

Since $([u_3]_0^M(t) - [v_3]_0^M(t))$ is easy to estimate, we focus on the complex quotient part. Using the same estimation as in the second term, we have:

$$
\left\| \int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y}) d\overline{x}d\overline{y} \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq l_3(t) \|[u_2]_0(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}
$$

where $l_3(t) = \sup_{(x,y)} \|i_3(t,.,x,y)\|_{L^1(\mathbb{R}_+^2)} + \sup_{(\overline{x},\overline{y})} \|i_3(t,\overline{x},\overline{y},.)\|_{L^1(\mathbb{R}_+^2)} < \infty$.
Substitute this into the third term:

$$
\begin{aligned}
&|[u_3]_0^M(t) - [v_3]_0^M(t)| \left\| \frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y}) d\overline{x}d\overline{y}}{K_{vec} + [u_4]_0(t) + \int_{\mathbb{R}_+^2} [u_2]_0(t,\overline{x},\overline{y}) d\overline{x}d\overline{y}} \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
&\leq |[u_3]_0^M(t) - [v_3]_0^M(t)| \frac{l_3(t) \|[u_2]_0(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}}{K_{vec} + [u_4]_0(t) + \|[u_2]_0(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}} \\
&\leq l_3(t)|u_3(t) - v_3(t)| \\
&\leq \overline{l_3} \|u(t,.) - v(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}
\end{aligned}
$$

where $\overline{l_3} = \sup_{t\in\mathbb{R}_+} l_3(t)$ is bounded by a positive value due to assumption $\mathcal{A}$.

The last term is:

$$\left\| [v_3]_0^M(t)\Big(\frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec}+[u_4]_0(t)+\int_{\mathbb{R}_+^2}[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}} - \frac{\int_{\mathbb{R}_+^2} i_3(t,.,\overline{x},\overline{y})[v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}{K_{vec}+[v_4]_0(t)+\int_{\mathbb{R}_+^2}[v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}\Big)\right\|_{L^{1,\infty}(\mathbb{R}_+^2)}.$$

Since $[v_3]_0^M(t)$ is bounded, we mainly need to take care of the difference. Re-write

$$g(u) = \frac{p(u)}{q(u)}$$

where

$$p(u)(t,x,y) := \int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y},$$

$$q(u)(t) := K_{vec} + [u_4]_0^M(t) + \int_{\mathbb{R}_+^2}[u_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}.$$

Define $w_\tau = v + (u-v)\tau$ then the difference in the last term is

$$g(u) - g(v) = \int_0^1 \frac{d}{d\tau} g(w_\tau)d\tau.$$

Now we calculate the derivative of $g(w_\tau)$ with respect to variable τ. We begin with the derivatives of $p(w_\tau)$ and $q(w_\tau)$:

$$\begin{aligned}
\frac{d}{d\tau}p(w_\tau) =& \frac{d}{d\tau}\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[v_2+(u_2-v_2)\tau]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y} \\
=& \int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}; \\
\frac{d}{d\tau}q(w_\tau) =& \frac{d}{d\tau}\Bigg(K_{vec} + [v_4+(u_4-v_4)\tau]_0(t) \\
&+ \int_{\mathbb{R}_+^2}[v_2+(u_2-v_2)\tau]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}\Bigg) \\
=& [u_4-v_4]_0(t) + \int_{\mathbb{R}_+^2}[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}.
\end{aligned}$$

Using the quotient rule, we can calculate the derivative of $g(w_\tau)$:

$$\begin{aligned}
\frac{d}{d\tau}g(w_\tau) =& \frac{d}{d\tau}\left(\frac{p(w_\tau)}{q(w_\tau)}\right) \\
=& \frac{p_\tau(w_\tau)}{q(w_\tau)} - \frac{q_\tau(w_\tau)}{q(w_\tau)}\frac{p(w_\tau)}{q(w_\tau)}
\end{aligned}$$

$$\leq K_{vec}^{-1}\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}$$
$$+K_{vec}^{-1}\left([u_4-v_4]_0(t)+\int_{\mathbb{R}_+^2}[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}\right)\frac{p(w_\tau)}{q(w_\tau)}.$$

Now we look at the $L^{1,\infty}$-norm of $(g(u)-g(v))$. Using the result we have obtained above, we can estimate the L^1-norm and the L^∞-norm. We are going to treat them separately.

$$\begin{aligned}
&\|g(u)-g(v)\|_{L^1(\mathbb{R}_+^2)} = \left\|\int_0^1 \frac{d}{d\tau}g(w_\tau)d\tau\right\|_{L^1(\mathbb{R}_+^2)}\\
&\leq \int_{\mathbb{R}_+^2}\int_0^1 K_{vec}^{-1}\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}d\tau dxdy\\
&+\int_{\mathbb{R}_+^2}\int_0^1 K_{vec}^{-1}\Big([u_4-v_4]_0(t)+\int_{\mathbb{R}_+^2}[u_2-v_2]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}\Big)\frac{p(w_\tau)}{q(w_\tau)}d\tau dxdy\\
&\leq K_{vec}^{-1}\int_{\mathbb{R}_+^2}\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[u_2-v_2]_0(t,\overline{x},\overline{y})dxdyd\overline{x}d\overline{y}\\
&+2K_{vec}^{-1}\|(u-v)(t,.)\|_{L^1(\mathbb{R}_+^2)}\\
&\times\int_0^1 \frac{\int_{\mathbb{R}_+^2}\int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})[v_2+(u_2-v_2)\tau]_0(t,\overline{x},\overline{y})dxdyd\overline{x}d\overline{y}}{K_{vec}+[v_4+(u_4-v_4)\tau]_0(t)+\int_{\mathbb{R}_+^2}[v_2+(u_2-v_2)\tau]_0(t,\overline{x},\overline{y})d\overline{x}d\overline{y}}d\tau\\
&\leq K_{vec}^{-1}\sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2}\|i_3(t,.,\overline{x},\overline{y})\|_{L^1(\mathbb{R}_+^2)}\|(u_2-v_2)(t,.)\|_{L^1(\mathbb{R}_+^2)}\\
&+2K_{vec}^{-1}\|(u-v)(t,.)\|_{L^1(\mathbb{R}_+^2)}\\
&\times\int_0^1 \frac{\sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2}\|i_3(t,.,\overline{x},\overline{y})\|_{L^1(\mathbb{R}_+^2)}\|[v_2+(u_2-v_2)\tau]_0(t,.)\|_{L^1(\mathbb{R}_+^2)}}{K_{vec}+[v_4+(u_4-v_4)\tau]_0(t)+\|[v_2+(u_2-v_2)\tau]_0(t,.)\|_{L^1(\mathbb{R}_+^2)}}d\tau\\
&\leq K_{vec}^{-1}\sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2}\|i_3(t,.,\overline{x},\overline{y})\|_{L^1(\mathbb{R}_+^2)}\|(u_2-v_2)(t,.)\|_{L^1(\mathbb{R}_+^2)}\\
&+2K_{vec}^{-1}\|(u-v)(t,.)\|_{L^1(\mathbb{R}_+^2)}\sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2}\|i_3(t,.,\overline{x},\overline{y})\|_{L^1(\mathbb{R}_+^2)}\\
&\leq \overline{l_4^1}\|(u-v)(t,.)\|_{L^1(\mathbb{R}_+^2)}
\end{aligned}$$

where $\overline{l_4^1}=3K_{vec}^{-1}\sup_{(t,\overline{x},\overline{y})\in\mathbb{R}_+^3}\|i_3(t,.,\overline{x},\overline{y})\|_{L^1(\mathbb{R}_+^2)}>0$. Similar to this, we can estimate the L^∞-norm:

$$\|g(u)-g(v)\|_{L^\infty(\mathbb{R}_+^2)} = \left\|\int_0^1 \frac{d}{d\tau}g(w_\tau)d\tau\right\|_{L^\infty(\mathbb{R}_+^2)} \leq \overline{l_4^2}\|(u-v)(t,.)\|_{L^\infty(\mathbb{R}_+^2)}$$

where $\overline{l_4^2}>0$.
Combining the two norms, we obtain:

$$\begin{aligned}
\left\|[v_3]_0^M(t)(g(u)-g(v))\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} &\leq M\|g(u)-g(v))\|_{L^{1,\infty}(\mathbb{R}_+^2)}\\
&\leq M\overline{l_4}\|(u-v)(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)}
\end{aligned}$$

where $\overline{l_4} = \max\{\overline{l_4^1}, \overline{l_4^2}\}$.

Due to assumption $\mathcal{A}$, all $\overline{l_4^j}$ $(j = 1, 2, 3, 4)$ are positive values. The last term of operator f_1^M is smaller than $\overline{l_4}\,\|u(t,.) - v(t,.)\|_{L^{1,\infty}}$. Summing up all the estimations of the four terms, we obtain that f_1^M is Lipschitz with norm $\|.\|_{L^{1,\infty}}$.

Similar procedures are applied for f_j^M $(j = 2, 3, 4)$. So operator f^M is Lipschitz with norm $\|.\|_{L^{1,\infty}}$. For later use, we denote the Lipschitz constant by l. Lemma 3.5 is proved. □

Proof of lemma 3.6

Now we prove lemma 3.6, concerning transformation φ_1, the result for φ_2 is similar.

Proof. Given (t, x, y) in each domain Ω_j $(j = 1, 2, 3)$, based on the formula of φ_1 given before, we can calculate:

$$(s_1, r_1) = (s_1(t, x, y), r_1(t, x, y)) = \varphi_1^{-1}(t, x, y).$$

Knowing $r_1(t, x, y)$, given arbitrary $s \in [0, s_1(t, x, y)]$, we can compute

$$(\overline{t}, \overline{x}, \overline{y}) = \varphi_1(s, r_1(t, x, y))$$

and obtain:

$$\begin{aligned}
&\forall (t, x, y) \in \Omega_1(g_1, h_1) : \\
&(\overline{t}, \overline{x}, \overline{y}) = \varphi_1(s, (0, x - g_1 t, y - h_1 t)) = (s, x - g_1 t + g_1 s, y - h_1 t + h_1 s), \\
&\forall (t, x, y) \in \Omega_2(g_1, h_1) : \\
&(\overline{t}, \overline{x}, \overline{y}) = \varphi_1(s, (t - \frac{x}{g_1}, 0, y - \frac{h_1}{g_1} x)) = (s + t - \frac{x}{g_1}, g_1 s, y - \frac{h_1}{g_1} x + h_1 s), \\
&\forall (t, x, y) \in \Omega_3(g_1, h_1) : \\
&(\overline{t}, \overline{x}, \overline{y}) = \varphi_1(s, (t - \frac{y}{h_1}, x - \frac{g_1}{h_1} y, 0)) = (s + t - \frac{y}{h_1}, x - \frac{g_1}{h_1} y + g_1 s, h_1 s).
\end{aligned}$$

By standard calculation, we have

$$d\overline{t} d\overline{x} d\overline{y} = ds dx dy$$

since the absolute values of the corresponding Jacobian determinants are always equal to 1 over three domains. So (i) is proved.

Using the formulas of $(\overline{t}, \overline{x}, \overline{y})$ above, we also obtain part (ii) directly. □

The result for φ_2 is analog of the one for φ_1. We denote the new domains of $(\overline{t}, \overline{x}, \overline{y})$ after applying φ_1, φ_2 by $\overline{\Omega}(g_1, h_1)$ and $\overline{\Omega}(g_2, h_2)$.

Proof of lemma 3.8

With the results of the two lemmas above, we can prove lemma 3.8 concerning operator K^M.

Proof. Given $u, v \in X$, we are going to look at $K_j^M u - K_j^M v$ $(j = 1, 2, 3, 4)$ with $L^{1,\infty}$-norm, then λ-norm. Since the initial boundary values are given, we subtract them and they vanish. We then just need knowledge of f_j^M and two transformations φ_1, φ_2. First we look at the L^1-norm, then the L^∞-norm of $K_j^M u - K_j^M v$. The L^1-norm is:

$$\begin{aligned}
& \int_{\mathbb{R}_+^2} \Big| \int_0^{s_1(t,x,y)} (f_1^M u - f_1^M v) \circ \varphi_1(s, r_1(t,x,y)) ds \Big| dxdy \\
\leq & \int_{\mathbb{R}_+^3} \left| \chi_{s\in[0,s_1(t,x,y)]} (f_1^M u - f_1^M v) \circ \varphi_1(s, r_1(t,x,y)) \right| dsdxdy \\
\leq & \int_{\mathbb{R}_+^3} \left| \chi_{(\bar{t},\overline{x},\overline{y})\in\overline{\Omega}(g_1,h_1)} (f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y}) \right| d\bar{t}d\overline{x}d\overline{y}
\end{aligned}$$

where $\chi(.)$ is a characteristic function, which is equal to 1 on the defined set and equal to 0 on the rest of the domain. Using the explicit form of domain $\overline{\Omega_j}(h_1, g_1)$ $(j = 1, 2, 3)$, on $\overline{\Omega}(h_1, g_1) = \cup\overline{\Omega_j}(h_1, g_1)$ we have $0 \leq \bar{t} \leq t$, and $\overline{x} \leq 0$, $\overline{y} \leq 0$. So:

$$\begin{aligned}
& \int_{\mathbb{R}_+^3} \left| \chi_{(\bar{t},\overline{x},\overline{y})\in\overline{\Omega}(g_1,h_1)} (f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y}) \right| d\bar{t}d\overline{x}d\overline{y} \\
\leq & \int_0^t \int_{\mathbb{R}_+^2} \left| (f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y}) \right| d\bar{t}d\overline{x}d\overline{y} \\
= & \int_0^t \left\| (f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y}) \right\|_{L^1(\mathbb{R}_+^2)} d\bar{t}.
\end{aligned}$$

Now we continue with the L^∞-norm:

$$\begin{aligned}
& \sup_{(x,y)\in\mathbb{R}_+^2} \Big| \int_0^{s_1(t,x,y)} (f_1^M u - f_1^M v) \circ \varphi_1(s, r_1(t,x,y)) ds \Big| \\
\leq & \sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2} \int_0^t |(f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y})| d\bar{t} \\
\leq & \int_0^t \sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2} |(f_1^M u - f_1^M v)(\bar{t},\overline{x},\overline{y})| d\bar{t} \\
\leq & \int_0^t \left\| f_1^M u - f_1^M v \right\|_{L^\infty(\mathbb{R}_+^2)} d\bar{t}.
\end{aligned}$$

Summing up the two norms above, combined with the fact that f_1^M is Lipschitz

(lemma 3.5), we obtain:

$$\begin{aligned}
& \left\| \int_0^{s_1(t,x,y)} (f_1^M u - f_1^M v) \circ \varphi_1(s, r_1(t,x,y)) ds \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\
\leq & \int_0^t \left\| f_1^M u(\bar{t},.) - f_1^M v(\bar{t},.) \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} d\bar{t} \\
\leq & \int_0^t l \ \left\| (u(\bar{t},.) - v(\bar{t},.)) \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} d\bar{t}.
\end{aligned}$$

Now we use the weight λ:

$$\begin{aligned}
& \left\| K_1^M u - K_1^M v \right\|_\lambda \\
\leq & \sup_{t \in \mathbb{R}_+} \{ e^{-\lambda t} \int_0^t l \ \left\| (u(\bar{t},.) - v(\bar{t},.)) \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} d\bar{t} \} \\
= & \sup_{t \in \mathbb{R}_+} l \ \{ e^{-\lambda t} \int_0^t \left\| (u(\bar{t},.) - v(\bar{t},.)) \right\|_{L^{1,\infty}(\mathbb{R}_+^2)} e^{-\lambda \bar{t}} e^{\lambda \bar{t}} d\bar{t} \} \\
\leq & \sup_{t \in \mathbb{R}_+} l \ \{ e^{-\lambda t} \int_0^t \left\| (u(.,.) - v(.,.)) \right\|_\lambda \ e^{\lambda \bar{t}} d\bar{t} \} \\
= & \ l \ \left\| u - v \right\|_\lambda \sup_{t \in \mathbb{R}_+} \{ e^{-\lambda t} \int_0^t e^{\lambda \bar{t}} d\bar{t} \} \\
\leq & \ \frac{l \ \left\| u - v \right\|_\lambda}{\lambda}.
\end{aligned}$$

So if we choose $\lambda > l$ then $k = l/\lambda < 1$ and K_1^M satisfies:

$$\left\| K_1^M u - K_1^M v \right\|_\lambda \leq k \left\| u - v \right\|_\lambda .$$

We should also notice that when $u = 0$ then $f^M = 0$ and given any $u \in X$ we have $K_1^M u \in X$. So the equation $K_1^M u = u$ has a unique solution by the Banach fixed point theorem. □

Proof of lemma 3.9

We already have a solution, now we prove lemma 3.9 to guarantee that it is "positive": $u_1(t,x,y) \geq 0$, $u_2(t,x,y) \geq 0$, $u_3(t) > 0$, $u_4(t) > 0$.

Proof. We have a unique solution with operator K^M. If we can now prove that the obtained solution is actually "positive", that means the cut-off below by 0 is inactive for all u_j $(j = 1,2,3,4)$. For this, we use the differential form of the equation, which is given in (3.15), with corresponding cut-off operators as we have

in K^M. Using the transformations φ_1 and φ_2 we have the following:

$$\begin{aligned}
&\frac{\partial}{\partial s_1} u_1 \circ \varphi_1(s_1, r_1) = f_1(u) \circ \varphi_1(s_1, r_1) \\
&\quad \geq -(\rho \circ \varphi_1(s_1, r_1) + m_1 \circ \varphi_1(s_1, r_1))\ u_1 \circ \varphi_1(s_1, r_1) \\
&\frac{\partial}{\partial s_2} u_2 \circ \varphi_2(s_2, r_2) = f_2(u) \circ \varphi_2(s_2, r_2) \\
&\quad \geq m_2 \circ \varphi_2(s_2, r_2)\ u_2 \circ \varphi_2(s_2, r_2) \\
&\frac{d}{dt} u_3(t) = f_3(u)(t) \\
&\quad \geq -\Big(m_3(t) + \int_{\mathbb{R}^2_+} \frac{\int_{\mathbb{R}^2_+} i_3(t, x, y, \overline{x}, \overline{y}) u_2(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}{K_{vec} + u_4(t) + \int_{\mathbb{R}^2_+} u_2(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}\Big) u_3(t) \\
&\frac{d}{dt} u_4(t) = f_4(u)(t) \\
&\quad \geq -\Big(m_4(t) + \int_{\mathbb{R}^2_+} \frac{\int_{\mathbb{R}^2_+} i_4(t, x, y, \overline{x}, \overline{y}) u_1(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}{K_{hum} + u_3(t) + \int_{\mathbb{R}^2_+} u_1(t, \overline{x}, \overline{y}) d\overline{x} d\overline{y}}\Big) u_4(t).
\end{aligned}$$

Using standard arguments, we obtain that all functions u_j $(j = 1, 2, 3, 4)$ can not decrease faster than exponential decay. Given an arbitrary large time T and "positive" initial boundary values, the values of all functions stay "positive". □

Remark 3.12. The "cut-off" below 0 of $u_3(t)$, $u_4(t)$ and also $u_1(t, x, y)$, $u_2(t, x, y)$ are naturally inactive.

Proof of lemma 3.10

To complete the proof of theorem 3.4, we need to show that the cut-off above M of $u_3(t)$, $u_4(t)$ is also inactive or $f^M \equiv f$. This is the task in lemma 3.10.

Proof. In this proof we denote

$$\overline{u_j}(t) = \int_{\mathbb{R}^2_+} u_j(t, x, y) dx dy \quad (j = 1, 2).$$

We are going to consider a system involving $\overline{u_1}(t)$ and $u_3(t)$, then later a system involving $\overline{u_2}(t)$ and $u_4(t)$. We compare them with linear differential systems of order 1 in order to obtain their upper bounds.

Using the result of lemma 3.9, saying that the solution of the system is positive,

we can estimate:

$$
\begin{aligned}
&\frac{d}{dt}\overline{u_1}(t) = \int_{\mathbb{R}_+^2} \partial_t u_1(t,x,y)dxdy \\
&= -\int_{\mathbb{R}_+^2} (\partial_x(g_1 u_1(t,x,y)) + \partial_y(h_1 u_1(t,x,y)))dxdy + \int_{\mathbb{R}_+^2} f_1 u(t,x,y)dxdy \\
&\leq \int_{\mathbb{R}_+} (g_1 u_1(t,0,y)dy + h_1 u_1(t,x,0)dx) \\
&\quad + u_3(t) \sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} i_3(t,x,y,\overline{x},\overline{y})dxdy \frac{\overline{u_2}(t)}{K_{vec} + u_4(t) + \overline{u_2}(t)} \\
&\quad + \sup_{(\overline{x},\overline{y})\in\mathbb{R}_+^2} \int_{\mathbb{R}_+^2} \theta_1(t,x,y,\overline{x},\overline{y})dxdy\ \overline{u_1}(t) \\
&\leq c_1(t) + c_2(t)u_3(t) + c_3(t)\overline{u_1}(t), \\
&\frac{d}{dt}u_3(t) \leq (b_3(t) - m_3(t))u_3(t) + \sup_{(x,y)\in\mathbb{R}_+^2} (b_1(t,x,y) + \rho(t,x,y))\overline{u_1}(t) \\
&= c_4(t)u_3(t) + c_5(t)\overline{u_1}(t).
\end{aligned}
$$

We consider the system with two unknowns $\overline{u_1}(t), u_3(t)$ on the interval $[0,T]$. Since it can be compared with a linear system which has a unique solution in exponential growth, for any $T > 0$ the solution $(\overline{u_1}(t), u_3(t))$ (which already exists) is bounded by a constant C. C only depends on T, not M.

Similarly, we obtain the same result for $\overline{u_2}(t), u_4(t)$. Combining them, for any given $T > 0$, we can always choose $M > C(T)$, so

$$\sup_{t\in[0,T]} u_j(t) < M, (j = 3, 4).$$

So operator $[.]^M$ becomes inactive. Since we can let $T \to \infty$, lemma 3.10 is proved. □

By this proof, we have completed all the lemmas which support theorem 3.4. So system (3.16) with given initial boundary values has a unique positive solution.

3.2.4 Mapping from the boundary values to the solution

We have shown that if the initial boundary values are given then the system has a solution. Now we study the mapping from the boundary values to the solution. Using the results of the last subsection, from now on we always consider $t \in [0,T]$ ($T > 0$ is arbitrary large) and write $\Omega_{(.)}$ by $[\Omega_{(.)}]$. In this consideration, we can identify f^M by f. That means, f also has the Lipschitz property like f^M, with respect to $L^{1,\infty}$-norm.

Denote $\mathbb{A}$ for $\{0\} \times \mathbb{R}_+$, $\mathbb{R}_+ \times \{0\}$ and

$$L^{1,\infty}(\mathbb{A}) = \{w|\ w \in L^1(\mathbb{A}), w \in BC^0(\mathbb{A})\}$$

with a norm:

$$\|w(.,.)\|_{L^{1,\infty}([0,t]\times\mathbb{A})} = \|w(.,.)\|_{L^1([0,t]\times\mathbb{A})} + \|w(.,.)\|_{L^\infty([0,t]\times\mathbb{A})}\, ds.$$

We denote the boundary (not initial) function by $u^0(t,a)$, which is defined on $[0,T] \times \mathbb{A}$. Let $r = (t,a) \in [0,T] \times \mathbb{A}$ and

$$u_1^0(t,a), u_2^0(t,a) \in C^0([0,T), L^{1,\infty}(\mathbb{A})).$$

We have the following theorem.

Theorem 3.13. *The mapping from the boundary values to the solution is Lipschitz with respect to $L^{1,\infty}$-norm. More precisely, we are going to prove that for $j = 1,2$ and $u_j^0(t,a)$, $v_j^0(t,a)$ given, there is a $l_0 > 0$, such that for all $t \in [0,T]$:*

$$\|\tilde{u}(t,.) - \tilde{v}(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq l_0(t) \left\|\tilde{u}^0(.,.) - \tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}$$

where $\tilde{u} = (u_1, u_2), \tilde{u}^0 = (u_1^0, u_2^0)$ and

$$\|\tilde{u}(t,.)\|_{L^{1,\infty}([\mathbb{R}_+^2)} := \max_{j=1,2} \|u_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)},$$

$$\left\|\tilde{u}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} := \max_{j=1,2} \left\|u_j^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}.$$

Remark. Since there is only one solution corresponding to the fixed initial values, so

$$\|u(t,.) - v(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} = \|\tilde{u}(t,.) - \tilde{v}(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)},$$

Proof. We are mainly interested in the mapping of boundary functions to the solution, so we do not need the initial part which corresponds to $[\Omega_1(g_j,h_j)]$. We only focus on $[\Omega_2(g_j,h_j)]$ and $[\Omega_3(g_j,h_j)]$. Given (t,x,y) in these domains, we can determine uniquely $(s_j,r_j) = \varphi_j^{-1}(t,x,y)$ for $j = 1,2$:

$$(s_j,r_j) = \begin{cases} \left(\frac{x}{g_j}, \left(t - \frac{x}{g_j}, 0, y - h_j\frac{x}{g_j}\right)\right) & \forall (t,x,y) \in \Omega_2(g_j,h_j), \\ \left(\frac{y}{h_j}, \left(t - \frac{y}{h_j}, x - g_j\frac{y}{h_j}, 0\right)\right) & \forall (t,x,y) \in \Omega_3(g_j,h_j). \end{cases}$$

We then have for $j = 1,2$:

$$u_j(t,x,y) = u_j^0(r_j(t,x,y)) + \int_0^{s_j(t,x,y)} f_j u \circ \varphi_j(s, r_j(t,x,y))ds,$$

$$v_j(t,x,y) = v_j^0(r_j(t,x,y)) + \int_0^{s_j(t,x,y)} f_j v \circ \varphi_j(s, r_j(t,x,y))ds.$$

We can estimate $L^{1,\infty}$-norm for $j = 1, 2$:

$$\begin{aligned}\|u_j(t,.) - v_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq & \left\|u_j^0(r_j(t,.)) - v_j^0(r_j(t,.))\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \\ & + \left\|\int_0^{s_j(t,.)} (f_j u - f_j v) \circ \varphi_j(s, r_j(t,.))ds\right\|_{L^{1,\infty}(\mathbb{R}_+^2)}.\end{aligned}$$

According to the proof of lemmas 3.5 and 3.6, we have:

$$\left\|\int_0^{s_j(t,.)} (f_j u - f_j v) \circ \varphi_j(s, r_j(t,.))ds\right\|_{L^{1,\infty}} \leq \int_0^t l \ \left\|u(\bar{t},.) - v(\bar{t},.)\right\|_{L^{1,\infty}} d\bar{t}.$$

Since u, v are solutions corresponding to the same initial condition (only boundary conditions are different), so $u_j(t) \equiv v_j(t), (j = 3, 4)$. Hence:

$$\left\|\int_0^{s_j(t,.)} (f_j u - f_j v) \circ \varphi_j(s, r_j(t,.))ds\right\|_{L^{1,\infty}} \leq \int_0^t l \ \left\|\tilde{u}(\bar{t},.) - \tilde{v}(\bar{t},.)\right\|_{L^{1,\infty}} d\bar{t}.$$

In addition, we have an inequality (its proof is going to be given in an additional lemma below):

$$\left\|u_j^0(r_j(t,.)) - v_j^0(r_j(t,.))\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq c_0 \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \tag{3.17}$$

Combining $j = 1$ and $j = 2$:

$$\begin{aligned}\|\tilde{u}(t,.) - \tilde{v}(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq & \ c_0 \left\|\tilde{u}^0(.,.) - \tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \\ & + \int_0^t l \ \left\|\tilde{u}(\bar{t},.) - \tilde{v}(\bar{t},.)\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} d\bar{t}.\end{aligned}$$

Using Gronwall's lemma (note that $\left\|\tilde{u}^0(.,.) - \tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}$ is nondecreasing with respect to t), we obtain:

$$\|\tilde{u}(t,.) - \tilde{v}(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq c_0 \left\|\tilde{u}^0(.,.) - \tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} e^{lt}.$$

Choosing $l_0(t) = c_0 e^{lt}$ then

$$\|\tilde{u}(t,.) - \tilde{v}(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq l_0(t) \left\|\tilde{u}^0(.,.) - \tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}.$$

The theorem is proved. □

Here we would like to complete the proof of the inequality (3.17) stated in theorem 3.13.

Lemma 3.14. *Given $(t,x,y) \in [0,T] \times \mathbb{R}_+^2$ and u_j^0, v_j^0 $(j = 1,2)$ as boundary functions. There is a constant $c_0 > 0$ such that:*

$$\left\|u_j^0(r_j(t,.)) - v_j^0(r_j(t,.))\right\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq c_0 \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}$$

where $r_j(t,x,y)$ is determined by way of φ_j.

Proof. We are going to consider the L^1-norm and the L^∞-norm.

Notice that the initial part of the left hand side is formally included, but it does not contribute anything, since $u_j^0(0,x_j,y_j) \equiv v_j^0(0,x_j,y_j)$ for all (x_j,y_j). It just helps to clarify the variable change in $\|u_j^0(r_j(t,.))\|_{L^{1,\infty}(\mathbb{R}_+^2)}$.

For $(x,y) \in \mathbb{R}_+^2$, we are going to fix some $t \in [0,T]$ and use the definition of φ_j to calculate the domain of r_j and the differential $dxdy$. Recall figure 3.2: when the value of t below the blue circle and green triangle planes, then $(t,x,y) \in [\Omega_1]$, otherwise $(t,x,y) \in [\Omega_2] \cup [\Omega_3]$.

- The set of (x,y) corresponding to $[\Omega_1]$ is the positive quadrant Oxy. Fix a value of t such that $(t,x,y) \in [\Omega_1(g_j,h_j)]$ then

$$r_j(t,x,y) = (0,x_j,y_j) = (0, x - g_j t, y - h_j t), dxdy = dx_j dy_j$$

and the domain of r_j is:

$$[\overline{\Omega_1}(g_j,h_j)] = \{0\} \times \mathbb{R}_+^2.$$

- The orthogonal projection images of $[\Omega_2]$ and $[\Omega_3]$ on Oxy also cover the positive quadrant Oxy. Fix a value of t such that $(t,x,y) \in [\Omega_2(g_j,h_j)]$ then

$$r_j(t,x,y) = (t_j,0,y_j) = \big(t - \frac{x}{g_j}, 0, y - h_j\frac{x}{g_j}\big), dxdy = g_j dt_j dy_j$$

and the domain of r_j is:

$$[\overline{\Omega_2}(g_j,h_j)] = [0,t] \times \{0\} \times \mathbb{R}_+.$$

Fix a value of t such that $(t,x,y) \in [\Omega_3(g_j,h_j)]$ then

$$r_j(t,x,y) = (t_j,x_j,0) = \big(t - \frac{y}{h_j}, x - g_j\frac{y}{h_j}, 0\big), dxdy = h_j dt_j dx_j$$

and the domain of r_j is:

$$[\overline{\Omega_3}(g_j,h_j)] = [0,t] \times \mathbb{R}_+ \times \{0\}.$$

So there are two value classes for t, leading to two possible domains of r_j. If the value of t is below the two planes $t = \frac{x}{g_j}$ and $t = \frac{y}{h_j}$ then domain of r_j is $[\overline{\Omega_1}(g_j,h_j)] = \{0\} \times \mathbb{R}_+^2$, otherwise it is

$$[\overline{\Omega_2}(g_j,h_j)] \cup [\overline{\Omega_3}(g_j,h_j)] = [0,t] \times \mathbb{A}.$$

We have

$$\begin{aligned}
&\left\|u_j^0(r_j(t,.))\right\|_{L^1(\mathbb{R}_+^2)} = \int_{\mathbb{R}_+^2} \left|u_j^0(r_j(t,x,y))\right| dxdy \\
&= \left[\begin{array}{l} \displaystyle\int_{\mathbb{R}_+^2} \left|u_j^0(0,x_j,y_j)\right| dx_j dy_j \quad (\text{if } t < \frac{x}{g_j} \text{ and } t < \frac{y}{h_j}), \\ \displaystyle g_j \int_{[0,t]\times\mathbb{R}_+} \left|u_j^0(t_j,0,y_j)\right| dt_j dy_j + h_j \int_{[0,t]\times\mathbb{R}_+} \left|u_j^0(t_j,x_j,0)\right| dt_j dx_j \end{array}\right.
\end{aligned}$$

and

$$\begin{aligned}
&\left\|u_j^0(r_j(t,.))\right\|_{L^\infty(\mathbb{R}_+^2)} = \sup_{(x,y)\in\mathbb{R}_+^2} \left|u_j^0(r_j(t,x,y))\right| \\
&= \left[\begin{array}{ll} \displaystyle\sup_{(x_j,y_j)\in\mathbb{R}_+^2} \left|u_j^0(0,x_j,y_j)\right| & (\text{if } t < \frac{x}{g_j} \text{ and } t < \frac{y}{h_j}), \\ \displaystyle\sup_{(t_j,a_j)\in[0,t]\times\mathbb{A}} \left|u_j^0(t_j,a_j))\right| & \text{otherwise.} \end{array}\right.
\end{aligned}$$

Similarly, we have the transformation for L^1-norm and L^∞-norm of $v_j^0(r_j(t,.))$. Since the initial condition is given $u_j^0(0,x_j,y_j) \equiv v_j^0(0,x_j,y_j)$, we obtain:

$$\begin{aligned}
&\left\|u_j^0(r_j(t,.)) - v_j^0(r_j(t,.))\right\|_{L^1(\mathbb{R}_+^2)} \\
&\leq g_j \int_{[0,t]\times\mathbb{R}_+} \left|u_j^0(t_j,0,y_j) - v_j^0(t_j,0,y_j)\right| dt_j dy_j \\
&+ h_j \int_{[0,t]\times\mathbb{R}_+} \left|u_j^0(t_j,x_j,0) - v_j^0(t_j,x_j,0)\right| dt_j dx_j \\
&\leq c_j \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^1([0,t]\times\mathbb{A})}
\end{aligned}$$

where $c_j = \max\{g_j, h_j\}$ for $j = 1, 2$ and

$$\left\|u_j^0(r_j(t,.)) - v_j^0(r_j(t,.))\right\|_{L^\infty(\mathbb{R}_+^2)} \leq \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^\infty([0,t]\times\mathbb{A})}$$

Taking $c_0 = \max\{c_1, c_2, 1\}$ and summing up the two norms above we obtain the claim in this lemma. □

3.2.5 Solving the unknown boundary equations

In this subsection, we only look at u_j where $j = 1, 2$. For the unknown boundary equations, we have a system of boundary values $u_j(t, 0, y)$ and $u_j(t, x, 0)$ $(j = 1, 2)$:

$$\begin{aligned} u_j(t,0,y) &= u_j^*(0,y) + \int_0^t \int_{\mathbb{R}_+} \alpha_j(\bar{t},\eta,t,y) u_j(\bar{t},0,\eta) d\eta d\bar{t} \\ &+ \int_0^t \int_{\mathbb{R}_+^2} \beta_j(\bar{t},\xi,\eta,t,y) u_j(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \zeta_j(\bar{t},y) u_j(\bar{t},0,y) d\bar{t}, \\ u_j(t,x,0) &= u_j^*(x,0) + \int_0^t \int_{\mathbb{R}_+} \gamma_j(\bar{t},\xi,t,x) u_j(\bar{t},\xi,0) d\xi d\bar{t} \\ &+ \int_0^t \int_{\mathbb{R}_+^2} \delta_j(\bar{t},\xi,\eta,t,x) u_j(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \nu_j(\bar{t},x) u_j(\bar{t},x,0) d\bar{t}. \end{aligned} \tag{3.18}$$

It is clear that we need to compute values of u_j on the boundary. We have denoted

$$\mathbb{A} = (\{0\} \times \mathbb{R}_+) \cup (\mathbb{R}_+ \times \{0\}).$$

Or more precisely, $\mathbb{A}$ is just a short notation for either $\{0\} \times \mathbb{R}_+$ or $\mathbb{R}_+ \times \{0\}$ so that the points $(t, 0, y)$, $(t, x, 0)$ can be written by (t, a). In the right hand side we re-denote all the factor functions by

$$\iota_j = (\alpha_j, \gamma_j), \kappa_j = (\beta_j, \delta_j), \sigma_j = (\zeta_j, \nu_j).$$

We consider all functions

$$u_1^0(t,a), u_2^0(t,a) \in C^0\big([0,T], L^1(\mathbb{A}) \cap BC^0(\mathbb{A})\big)$$

such that for any given $\lambda > 0$:

$$\sup_{t\in[0,T]} \{e^{-\lambda t} \left\|u_j^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})}\} < \infty.$$

Our λ-norm is defined as follows:

$$\begin{aligned} \left\|u_j^0(.,.)\right\|_\lambda &:= \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \left\|u_j^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \right\}, \\ \left\|\tilde{u}^0(.,.)\right\|_\lambda &:= \max_{j=1,2} \left\|u_j^0(.,.)\right\|_\lambda \end{aligned}$$

where $\tilde{u}^0(t,a) = (u_1^0(t,a), u_2^0(t,a))$.
Remark. The space of all functions $\tilde{u}^0$ with λ-norm is a Banach space. We are going to prove the following theorem.

Theorem 3.15. *Given functions u_j $(j = 1, 2)$ as in system (3.16). We have the following:*

(i) There is a suitable λ such that the equation system

$$\begin{aligned} u_j^0(t,a) &= u_j^*(a) + \int_0^t \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},t,a) u_j^0(\bar{t},\bar{a}) d\bar{a} d\bar{t} \qquad (j=1,2) \\ &+ \int_0^t \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,t,a) u_j(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \sigma_j(\bar{t},a) u_j^0(\bar{t},a) d\bar{t} \end{aligned} \tag{3.19}$$

has a unique solution.
(ii) The solution is nonnegative as long as the initial values are nonnegative.

Proof. Since initial value $u^*(a) = (u_1^*(a), u_2^*(a))$ is known, we can put it to the center of the considered ball. For $j = 1, 2$, let

$$\begin{aligned} \mathbb{T}_j \tilde{u}^0(t,a) &:= u_j^*(a) + \int_0^t \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},t,a) u_j^0(\bar{t},\bar{a}) d\bar{a} d\bar{t} \\ &+ \int_0^t \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,,t,a) u_j(\bar{t},\xi,\eta) d\xi d\eta d\bar{t} - \int_0^t \sigma_j(\bar{t},a) u_j^0(\bar{t},a) d\bar{t} \end{aligned}$$

For part (i) we need to prove that there exists a λ such that operator $\mathbb{T}$ is a contraction map. Given $\tilde{u}^0$ and $\tilde{v}^0$, we have:

$$\begin{aligned} \left\|(\mathbb{T}_j \tilde{u}^0 - \mathbb{T}_j \tilde{v}^0)(.,.)\right\|_\lambda &\leq \left\| \int_0^{(.)} \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},.,.)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a})) d\bar{a} d\bar{t} \right\|_\lambda \\ &+ \left\| \int_0^{(.)} \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,.,.)(u_j(\bar{t},\xi,\eta) - v_j(\bar{t},\xi,\eta)) d\xi d\eta d\bar{t} \right\|_\lambda \\ &+ \left\| \int_0^{(.)} \sigma_j(\bar{t},.)(u_j(\bar{t},.) - v_j(\bar{t},.)) d\bar{t} \right\|_\lambda . \end{aligned}$$

At first, we take care of the L_1-norm of the first term:

$$\begin{aligned} &\left\| \int_0^{(.)} \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},.,.)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a})) d\bar{a} d\bar{t} \right\|_{L^1([0,t]\times\mathbb{A})} \\ &= \int_0^t \int_{\mathbb{A}} \left| \int_0^\tau \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},\tau,a)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a})) d\bar{a} d\bar{t} \right| da d\tau \\ &\leq \int_0^t \int_0^\tau \int_{\mathbb{A}} \Big(\int_{\mathbb{A}} \left|\iota_j(\bar{t},\bar{a},\tau,a)\right| da \Big) \left|u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a})\right| d\bar{a} d\bar{t} d\tau \\ &\leq \int_0^t \sup_{(\bar{t},\bar{a})\in[0,\tau]\times\mathbb{A}} \left\|\iota_j(\bar{t},\bar{a},\tau,.)\right\|_{L^1(\mathbb{A})} \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^1([0,\tau]\times\mathbb{A})} d\tau \\ &\leq l_5^j \int_0^t \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^1([0,\tau]\times\mathbb{A})} d\tau \end{aligned}$$

where

$$l_5^j = \sup_{\forall(\bar{t},\bar{a},\tau)} \left\|\iota_j(\bar{t},\bar{a},\tau,.)\right\|_{L^1(\mathbb{A})} < \infty.$$

Second, the L^∞-norm of the first term is:

$$\begin{aligned}
&\left\| \int_0^{(.)} \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},.,.)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a}))d\bar{a}d\bar{t} \right\|_{L^\infty([0,t]\times\mathbb{A})} \\
&= \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \left| \int_0^\tau \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},\tau,a)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a}))d\bar{a}d\bar{t} \right| \\
&\leq \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \int_0^\tau \left(\int_{\mathbb{A}} \left|\iota_j(\bar{t},\bar{a},\tau,a)\right| d\bar{a} \right) \sup_{\bar{a}\in\mathbb{A}} \left|u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a})\right| d\bar{t} \\
&\leq \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \int_0^\tau \left\|\iota_j(\bar{t},.,\tau,a)\right\|_{L^1(\mathbb{A})} \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^\infty([0,\bar{t}]\times\mathbb{A})} d\bar{t} \\
&\leq \sup_{\forall(\bar{t},\tau,a)} \left\|\iota_j(\bar{t},.,\tau,a)\right\|_{L^1(\mathbb{A})} \sup_{\tau\in[0,t]} \int_0^\tau \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^\infty([0,\bar{t}]\times\mathbb{A})} d\bar{t} \\
&\leq l_6^j \int_0^t \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^\infty([0,\bar{t}]\times\mathbb{A})} d\bar{t}
\end{aligned}$$

where

$$l_6^j = \sup_{\forall(\bar{t},\tau,a)} \left\|\iota_j(\bar{t},.,\tau,a)\right\|_{L^1(\mathbb{A})} < \infty.$$

Taking $l_7^j = \max\{l_5^j, l_6^j\}$ and summing up two parts of the first term, we obtain:

$$\begin{aligned}
&\left\| \int_0^{(.)} \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},.,.)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a}))d\bar{a}d\bar{t} \right\|_\lambda \\
&= \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \left\| \int_0^{(.)} \int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},.,.)(u_j^0(\bar{t},\bar{a}) - v_j^0(\bar{t},\bar{a}))d\bar{a}d\bar{t} \right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \right\} \\
&\leq \sup_{t\in[0,T]} \left\{ e^{-\lambda t} l_7^j \int_0^t \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} d\bar{t} \right\} \\
&= l_7^j \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \int_0^t \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} e^{-\lambda\bar{t}} e^{\lambda\bar{t}} d\bar{t} \right\} \\
&\leq l_7^j \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_\lambda \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \int_0^t e^{\lambda\bar{t}} d\bar{t} \right\} \\
&\leq \frac{l_7^j}{\lambda} \left\|u_j^0(.,.) - v_j^0(.,.)\right\|_\lambda .
\end{aligned}$$

In the next step, we consider the second term. From theorem 3.13, we know that the mapping from the initial boundary value $\tilde{u}^0$, to the solution $\tilde{u}$ is Lipschitz with a constant depending on time t:

$$\|u_j(t,.)\|_{L^{1,\infty}(\mathbb{R}_+^2)} \leq c_0 e^{lt} \left\|\tilde{u}^0(.,.)\right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \quad (j = 1, 2).$$

From this, we are able to estimate the L^1-norm and L^∞-norm of the second term

in the two following estimates:

$$
\begin{aligned}
&\left\| \int_0^{(.)} \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,.,.)(u_j(\bar{t},\xi,\eta)-v_j(\bar{t},\xi,\eta))d\xi d\eta d\bar{t} \right\|_{L^1([0,t]\times\mathbb{A})} \\
&= \int_0^t \int_{\mathbb{A}} \left| \int_0^\tau \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,\tau,a)\ (u_j(\bar{t},\xi,\eta)-v_j(\bar{t},\xi,\eta))d\xi d\eta d\bar{t} \right| da d\tau \\
&\leq \int_0^t \int_0^\tau \int_{\mathbb{R}_+^2} \left(\int_{\mathbb{A}} \left|\kappa_j(\bar{t},\xi,\eta,\tau,a)\right| da \right) \left|u_j(\bar{t},\xi,\eta)-v_j(\bar{t},\xi,\eta)\right| d\xi d\eta d\bar{t} d\tau \\
&\leq \int_0^t \int_0^\tau \sup_{\forall(\bar{t},\xi,\eta,\tau)} \left\|\kappa_j(\bar{t},\xi,\eta,\tau,.)\right\|_{L^1(\mathbb{A})} \left\|u_j(\bar{t},.)-v_j(\bar{t},.)\right\|_{L^1(\mathbb{R}_+^2)} d\bar{t} d\tau \\
&\leq \int_0^t \int_0^\tau l_8^j \left\|u_j(\bar{t},.)-v_j(\bar{t},.)\right\|_{L^1(\mathbb{R}_+^2)} d\bar{t} d\tau \\
&\leq l_8^j \int_0^t \int_0^\tau c_0 e^{l\bar{t}} \left\|\tilde{u}^0(.,.)-\tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} d\bar{t} d\tau \quad \text{(theorem 3.13)} \\
&\leq c_0 l_8^j \int_0^t \left(\left\|\tilde{u}^0(.,.)-\tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,\tau]\times\mathbb{A})} \int_0^\tau e^{l\bar{t}} d\bar{t} \right) d\tau \\
&\leq \frac{c_0 l_8^j}{l} \int_0^t \left\|\tilde{u}^0(.,.)-\tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,\tau]\times\mathbb{A})} e^{l\tau} d\tau
\end{aligned}
$$

where

$$
l_8^j = \sup_{\forall(\bar{t},\xi,\eta,\tau)} \left\|\kappa_j(\bar{t},\xi,\eta,\tau,.)\right\|_{L^1(\mathbb{A})} < \infty.
$$

$$
\begin{aligned}
&\left\| \int_0^{(.)} \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,.,.)(u_j(\bar{t},\xi,\eta)-v_j(\bar{t},\xi,\eta))d\xi d\eta d\bar{t} \right\|_{L^\infty([0,t]\times\mathbb{A})} \\
&= \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \left| \int_0^\tau \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,\tau,a)\ (u_j(\bar{t},\xi,\eta)-v_j(\bar{t},\xi,\eta))d\xi d\eta d\bar{t} \right| \\
&\leq \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \int_0^\tau \left(\int_{\mathbb{R}_+^2} \left|\kappa_j(\bar{t},\xi,\eta,\tau,a)\right| d\xi d\eta \right) \left\|u_j(\bar{t},.)-v_j(\bar{t},.)\right\|_{L^\infty(\mathbb{R}_+^2)} d\bar{t} \\
&\leq \sup_{(\tau,a)\in[0,t]\times\mathbb{A}} \int_0^\tau \left\|\kappa_j(\bar{t},.,\tau,a)\right\|_{L^1(\mathbb{R}_+^2)} \left\|u_j(\bar{t},.)-v_j(\bar{t},.)\right\|_{L^\infty(\mathbb{R}_+^2)} d\bar{t} \\
&\leq l_9^j \sup_{\tau\in[0,t]} \int_0^\tau \left\|u_j(\bar{t},.)-v_j(\bar{t},.)\right\|_{L^\infty(\mathbb{R}_+^2)} d\bar{t} \\
&\leq l_9^j \sup_{\tau\in[0,t]} \int_0^\tau c_0 e^{l\bar{t}} \left\|\tilde{u}^0(.,.)-\tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} d\bar{t} \quad \text{(theorem 3.13)} \\
&\leq c_0 l_9^j \int_0^t \left\|\tilde{u}^0(.,.)-\tilde{v}^0(.,.)\right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} e^{l\bar{t}} d\bar{t}
\end{aligned}
$$

where

$$
l_9^j = \sup_{\forall(\bar{t},\tau,a)} \left\|\kappa_j(\bar{t},.,\tau,a)\right\|_{L^1(\mathbb{R}_+^2)} < \infty.
$$

Taking $l_{10}^j = \frac{c_0 l_8^j}{l} + c_0 l_9^j$, we can sum up the two estimates above and obtain the

estimate for λ-norm:

$$\begin{aligned}
&\left\| \int_0^{(.)} \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,.,.)(u_j(\bar{t},\xi,\eta) - v_j(\bar{t},\xi,\eta)) d\xi d\eta d\bar{t} \right\|_\lambda \\
&= \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \left\| \int_0^{(.)} \int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,.,.)(u_j(\bar{t},\xi,\eta) \right.\right. \\
&\qquad\qquad \left.\left. -v_j(\bar{t},\xi,\eta)) d\xi d\eta d\bar{t} \right\|_{L^{1,\infty}([0,t]\times\mathbb{A})} \right\} \\
&\leq \sup_{t\in[0,T]} \left\{ e^{-\lambda t} l_{10}^j \int_0^t \left\| \tilde{u}^0(.,.) - \tilde{v}^0(.,.) \right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} e^{l\bar{t}} d\bar{t} \right\} \\
&= l_{10}^j \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \int_0^t \left\| \tilde{u}^0(.,.) - \tilde{v}^0(.,.) \right\|_{L^{1,\infty}([0,\bar{t}]\times\mathbb{A})} e^{-\lambda\bar{t}} e^{\lambda\bar{t}} e^{l\bar{t}} d\bar{t} \right\} \\
&\leq l_{10}^j \left\| \tilde{u}^0(.,.) - \tilde{v}^0(.,.) \right\|_\lambda \sup_{t\in[0,T]} \left\{ e^{-\lambda t} \int_0^t e^{(\lambda+l)\bar{t}} d\bar{t} \right\} \\
&\leq \frac{l_{10}^j e^{lT}}{\lambda + l} \left\| \tilde{u}^0(.,.) - \tilde{v}^0(.,.) \right\|_\lambda .
\end{aligned}$$

The last component of $\left\|(\mathbb{T}_j\tilde{u}^0 - \mathbb{T}_j\tilde{v}^0)(.,.)\right\|_\lambda$ is a linear term and factor function σ_j is bounded (due to assumption $\mathcal{A}$) by:

$$l_{11}^j := \sup_{t,a} |\sigma_j(t,a)| < \infty.$$

Using the λ-norm with a similar procedure, we have:

$$\left\| \int_0^t \sigma_j(\bar{t},a)(u_j^0(\bar{t},a) - v_j^0(\bar{t},a)) d\bar{t} \right\|_\lambda \leq \frac{l_{11}^j}{\lambda}.$$

Together with the estimates for the first term and the second term, we can sum up all the three terms and get:

$$\left\|\mathbb{T}_j\tilde{u}^0(.,.) - \mathbb{T}_j\tilde{v}^0(.,.)\right\|_\lambda \leq \left(\frac{l_7^j}{\lambda} + \frac{l_{10}^j e^{lT}}{\lambda + l} + \frac{l_{11}^j}{\lambda} \right) \left\| \tilde{u}^0(.,.) - \tilde{v}^0(.,.) \right\|_\lambda$$

Choosing $\lambda > 0$ large enough, we have

$$\max_{j=1,2} \left(\frac{l_7^j}{\lambda} + \frac{l_{10}^j e^{lT}}{\lambda + l} + \frac{l_{11}^j}{\lambda} \right) < 1.$$

So $\mathbb{T}$ is a contraction map. Part (i) is proved.

In the next part, we would like to show the positivity in (ii). We first differentiate the unknown boundary system with respect to variable t. Considering the equivalent differential system with given initial values at $t = 0$, we can study

the positivity of its solution. Since the integral system and the differential system have the same unique solution, they have the same properties.

$$\begin{aligned}
&\frac{\partial}{\partial t}u_j^0(t,a) = \frac{\partial}{\partial t}\int_0^t\int_{\mathbb{A}} \iota_j(\bar{t},\bar{a},t,a)u_j^0(\bar{t},\bar{a})d\bar{a}d\bar{t}\\
&+\frac{\partial}{\partial t}\int_0^t\int_{\mathbb{R}_+^2} \kappa_j(\bar{t},\xi,\eta,t,a)u_j(\bar{t},\xi,\eta)d\xi d\eta d\bar{t} - \frac{\partial}{\partial t}\int_0^t \sigma_j(\bar{t},a)u_j^0(\bar{t},a)d\bar{t}\\
&= \int_0^t\int_{\mathbb{A}} \frac{\partial}{\partial t}\iota_j(\bar{t},\bar{a},t,a)u_j^0(\bar{t},\bar{a})d\bar{a}d\bar{t} + \int_{\mathbb{A}} \iota_j(t,\bar{a},t,a)u_j^0(t,\bar{a})d\bar{a}\\
&+\int_0^t\int_{\mathbb{R}_+^2} \frac{\partial}{\partial t}\kappa_j(\bar{t},\xi,\eta,t,a)u_j(\bar{t},\xi,\eta)d\xi d\eta d\bar{t}\\
&+\int_{\mathbb{R}_+^2} \kappa_j(t,\xi,\eta,t,a)u_j(t,\xi,\eta)d\xi d\eta - \sigma_j(t,a)u_j^0(t,a)
\end{aligned} \tag{3.20}$$

Using cut-off operator $[.]_0$ defined above, we consider the system:

$$\begin{aligned}
&\frac{\partial}{\partial t}u_j^0(t,a) = -\sigma_j(t,a)u_j^0(t,a)\\
&+\int_0^t\int_{\mathbb{A}} \frac{\partial}{\partial t}\iota_j(\bar{t},\bar{a},t,a)[u_j^0]_0(\bar{t},\bar{a})d\bar{a}d\bar{t} + \int_{\mathbb{A}} \iota_j(t,\bar{a},t,a)[u_j^0]_0(t,\bar{a})d\bar{a}\\
&+\int_0^t\int_{\mathbb{R}_+^2} \frac{\partial}{\partial t}\kappa_j(\bar{t},\xi,\eta,t,a)[u_j]_0(\bar{t},\xi,\eta)d\xi d\eta d\bar{t}\\
&+\int_{\mathbb{R}_+^2} \kappa_j(t,\xi,\eta,t,a)[u_j]_0(t,\xi,\eta)d\xi d\eta
\end{aligned} \tag{3.21}$$

Using assumption $\mathcal{A}$, factor functions ι_j, κ_j and their derivatives with respect to t are nonnegative, so from the equation above:

$$\frac{\partial}{\partial t}u_j^0(t,a) \geq -\sigma_j(t,a)u_j^0(t,a).$$

With initial value $u_j^*(a) \geq 0$ for $j = 1, 2$, we obtain that the solution of system (3.21) is nonnegative.

In theorem 3.4, we have proved that if the given boundary values u_j^0 and the initial value u_j^* are nonnegative then the solution u of system (3.16) is also nonnegative. So in equation (3.21), we can identify

$$[u_j^0]_0 \equiv u_j^0, [u_j]_0 \equiv u_j \quad (j = 1, 2).$$

The solution of equation (3.20) has the same property as equation (3.21). So equation (3.20) as well as integral equation (3.19) both have a unique nonnegative solution. The proof of theorem 3.15 is complete. □

3.2.6 Solution of the original system

Combining the results obtained up to now, we see that we can choose λ large enough such that both theorems 3.4 and 3.15 are valid.

Now we come back to the systems (3.16) and (3.5) with unknown boundary conditions. Remember that we always have assumption $\mathcal{A}$.

Theorem 3.16. *Given assumption $\mathcal{A}$, we have the following:*
(i) There exists a λ such that system (3.16) with unknown boundary conditions has a unique solution.
(ii) The solution is positive if the initial values are positive (more precisely, $u_1, u_2 \geq 0$ and $u_3, u_4 > 0$).

Proof. (i) Taking λ large enough such that theorems 3.4 and 3.15 are valid. Then:

- The system of unknown boundary (3.19) is solvable and gives explicit boundary conditions.

- Substitute these boundary conditions into system (3.16) then we have the solution for original unknown u.

(ii) The uniqueness and the positiveness of the solution are induced from the corresponding properties in the two theorems 3.4 and 3.15. □

Remark. Coming back from system (3.16) to system (3.5), we use the two bijective transformations φ_j $(j = 1, 2)$. So with the same assumption in $\mathcal{A}$, all the results for system (3.16) are also valid for the original system (3.5). System (3.5) with its initial boundary conditions also has a unique positive solution.

3.3 Numerical approach

To the best of our knowledge, systems of integro-partial differential equations which are similar to the one in this paper have not been treated numerically so far. Most of the literature focused on a simpler case where only a single unknown structured variable was considered, as in the survey by Abia et al. [1]. Some authors included the second unknown without structured variables, such as the Lotka-Volterra model with age-structured prey population and non-structured predator population.

3.3.1 Iteration method

Based on the theory we have just established above, we can derive an algorithm to find the numerical solution of system (3.16). This opens a possibility to solve system (3.5).

The iteration method, based on theorem 3.16, is leading to an approximation of the solution. However, other possible approaches have to be investigated and

evaluated. In sketching the steps of this iteration, we may assume that the kernels have compact support.

Step 1. Specify the initial time t^0 (often as 0), the final time t^{end} and the initial values of $u_1(0,x,y)$, $u_2(0,x,y)$, $u_3(0)$, $u_4(0)$. Calculate the transformations φ_1, φ_2, $\varphi_1^{-1}, \varphi_2^{-1}$. Specify a small enough $\varepsilon > 0$ as a stopping condition.

Step 2. Give a starting function $u_j^0(t,a)$ (where $j = 1,2$, $t \in [0,T]$ and $a \in \mathbb{A}$). By iteration with stopping condition defined by ε, we can compute the solution at $(t,x,y) \in [0,T] \times \mathbb{R}_+^2$ as the fixed point of the system:

$$\begin{aligned}
u_1 \circ \varphi_1(s_1,r_1) = &\quad u_1 \circ \varphi_1(0,r_1) + \int_0^{s_1(t,x,y)} f_1 u \circ \varphi_1(s_1,r_1) ds, \\
u_2 \circ \varphi_2(s_2,r_2) = &\quad u_2 \circ \varphi_2(0,r_2) + \int_0^{s_2(t,x,y)} f_2 u \circ \varphi_2(s_2,r_2) ds, \\
u_3(t) = &\quad u_3(0) + \int_0^t f_3 u(\tau) d\tau, \\
u_4(t) = &\quad u_4(0) + \int_0^t f_4 u(\tau)) d\tau.
\end{aligned}$$

Step 3. We can then compute the boundary values from equation (3.19) for $j = 1,2$:

$$\begin{aligned}
&u_j^0(t,a) = u_j^*(a) + \int_0^t \int_{\mathbb{A}} \iota_j(t,a,s,\overline{a}) u_j^0(s,\overline{a}) d\overline{a} ds \\
&+ \int_0^t \int_{\mathbb{R}_+^2} \kappa_j(t,a,s,\xi,\eta) u_j(s,\xi,\eta) d\xi d\eta ds - \int_0^t \sigma_j(s,a) u_j^0(s,a) ds
\end{aligned}$$

Step 4. Compute the distance d between the new boundary function and the one before. If $d > \varepsilon$ then take the newly obtained boundary functions to step 2 to continue the iteration process.

Step 5. The iteration runs until $d \leq \varepsilon$. We obtain the boundary values as the fixed point of the loop. The solution is finally computed using these explicit boundary values.

This algorithm is constructed directly from the analysis. We have proved that there is a converging solution for the continuous problem. However, in numerical solution we have a discrete system, so consistency and stability should be considered. We are also aware of other methods, such as Galerkin or Finite Difference which have been employed to solve a single equation of a structured population. The study of the convergence would be very essential topic.

3.3.2 Data for the model quantities

For the validation of the mathematical model, we need some field data. The question is whether we can obtain this data with medium amount of cost and

time. In the following we are going to address this question.

In malaria, we know that there are some common methods to detect drug resistance, such as in vivo, in vitro, animal model studies, and molecular characterization [15]. One of the main differences between these methods is the information resolution. In vivo, treated patients are monitored over time for "either failure to clear parasites or for reappearance of parasites" [98] while the molecular characterization method zooms in on genetic markers of resistant parasites in blood samples. For our model, it is necessary to distinguish and quantify the amount of sensitive and resistant parasites, this is the reason why we are interested in high resolution methods. In the following we draw the readers' attention to the molecular characterization, which often involves blood samples of humans or animals.

Concerning the molecular characterization method, there are two important parts. Both of them involve intensive laboratorial works.

- In the first part, scientists have to identify genes and molecular markers which confer resistance of given drugs (e.g. antimalarial). A lot of genes have been found so far, some of them cause multi-drug resistance, see table 3.1.

- In the second part, molecular techniques, such as the polymerase chain reaction (PCR) or gene sequencing are used to check the presence of the identified markers in blood samples [98].

For the last few decades many experts have been paying attention to this field. Although there is still a long way to go, many valuable results have been achieved.

For identification of parasite genes that are linked with antimalarial drug resistance, there was a work by Anderson et al [3] which referred to more than two hundred related papers. In this work, the authors collected linkage analysis of drug resistance traits in Plasmodium falciparum and Plasmodium chabaudi (the two prevalent parasites causing malaria in man and mouse, respectively) for many antimalarial drugs, such as Chloroquine, Sulfadoxine, Amodiaquine, Quinine, Trimethoprim, Triamterene, Mefloquine, Artemisinin, etc. Most of them were described in detail, including their markers, their quantitative trait loci regions, their corresponding genes as well as the gene positions on the parasite chromosomes, see table 3.1.

Concerning the molecular techniques to identify specific markers on genomes, especially for malaria parasite genomes, we should emphasize some key information as follows:

- In the late 1970's, two DNA sequencing techniques for considerably long DNA molecules were invented. One is the Maxam–Gilbert method and the other one is the Sanger method. The Sanger method, based on "dideoxy" chain-termination, has several advantages and rapidly became the method of choice [95].

Table 3.1: Linkage analysis of drug resistance traits in Plasmodium [3]. *Classic LM: Classic Linkage Mapping; LGS: Linkage Group Selection; AFLP: Amplified fragment length polymorphism; Chr.: Chromosome; DHMS: Dihydroergotamine methanesulfonate; Pc: Plasmodium chabaudi; Pf: Plasmodium falciparum; QTL: Quantitative trait loci region; Pyroseq: Pyrosequence.*

Trait	Sp.	Notes	Markers	QTL	Gene
Classic LM					
Chloroquine	Pf	Dd2 x HB3 cross, 16 progeny	85 RFLPs	400 kb, 90 genes	
Chloroquine	Pf	Dd2 x HB3 cross, 35 progeny	Micro-satellites	40 kb, 9 genes	pfcrt
Sulfadoxine	Pf	Dd2 x HB3 cross, 16 progeny	Micro-satellites		Chr.8,
Endogenous folate utilization	Pf	Dd2 x HB3 cross, 22 progeny	Micro-satellites	49 kb	Chr.4, possibly dhfr
Amodiaquine	Pf	Dd2 x HB3 cross, 35 progeny	Micro-satellites		pfmdr1
Monosesethyl-amodiaquine	Pf	7G8 x GB4 cross, 32 progeny			
Quinine	Pf	Dd2 x HB3 cross, 35 progeny	Micro-satellites		Chr.13, pfnhe-1
Transcription phenotypes	Pf	Dd2 x HB3 cross, 35 progeny	Micro-satellites		
DHMS	Pf	7G8 x GB4 cross, 32 progeny	Micro-satellites	150 kb, 34 genes	pfmdr1
Trimethoprim	Pf	7G8 x GB4 cross, 32 progeny	Micro-satellites	59 kb, 10 genes	dhfr
Triamterene	Pf	7G8 x GB4 cross, 32 progeny	Micro-satellites	59 kb, 10 genes	dhfr
Chloroquine	Pc	AS(3CQ) x AJ, 20 progeny	46 RFLPs	250 kb, 50 genes	Chr.11 locus
Mefloquine	Pc	AS(15MF/3) x AJ, 16 progeny	46 RFLPs		Chr.4,
Sulfadoxine/ pyrimethamine	Pc	AS(50S/P) x AJ	31 RFLPs		Chr.7 &chr.13
LGS					
Artemisinin	Pc		Pyroseq		pcubp1
Chloroquine	Pc		Pyroseq		Chr.11
Mefloquine	Pc		Pyroseq		Chr.4

- Typically, the automated Sanger reaction is only accurate for sequences up to 700-800 base-pairs in length. However, it is possible to obtain full sequences of larger genes and also whole genomes, using step-wise methods such as the Primer Walking and the Shotgun sequencing [95].

- The high demand for low-cost sequencing has driven the development of high-throughput sequencing technologies [45, 24]. Among them are Lynx Therapeutics' Massively Parallel Signature Sequencing (MPSS), Polony sequencing, 454 pyrosequencing, Illumina sequencing, SOLiD sequencing, Ion semiconductor sequencing, etc. Table 3.2 provides some details about three popular methods.

Table 3.2: Some available sequencing methods [38].

	Ion Torrent 318	Illumina HiSeq 2000- v3	SOLiD- 5500xl (4hq)
Sequencing method	Synthesis	Synthesis	Ligation
Amplification method	Emulsion PCR	Bridge PCR	Emulsion PCR
Mb per run	>1000	$\leq$ 600 000	155 100
Time per run	2 hours	10 days	8 days
Read length	>100 bp	100 + 100 (bp)	75 + 35 (bp)
Cost per run	$ 925 USD	$ 23 470 USD	$ 10 503 USD
Cost per Mb	$ 0.93 USD	$ $\geq$ 0.04 USD	$ $<$ 0.07 USD

- During the last ten years, the cost of DNA sequencing has been rapidly decreasing, as shown in figure 3.4. The current technology restriction-site associated DNA sequencing can provide high resolution population genomic data at reasonable cost [28, 99].

- The Plasmodium genome is about 23 Mb (Mega base pairs) [3]. With the help of genetic markers, only about 1-2 Mb contain the identified genes of interest, see table 3.1. The cost for sequencing these parts is about 0.06$ and takes approximately a few seconds on average (Illumina, table 3.2).

With an approximate calculation, we can see that the sequencing of all parasites in malaria blood samples is now in reach [93]. With the current global efforts toward exploring the "Code of Life", we strongly believe that the data concerning our model quantities can be attained at a medium cost.

3.3.3 The inverse problem of parameter determination

We have shown that it is now possible to obtain the necessary data for our model quantities. Now we would like to discuss the model parameters. They are the

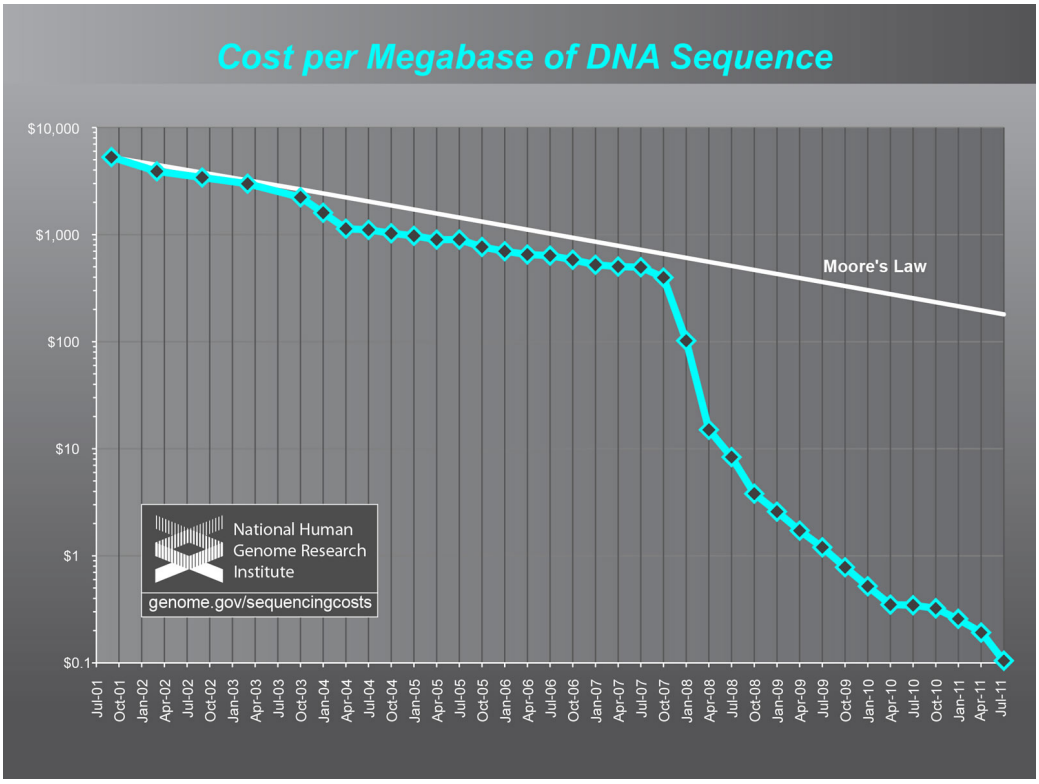

Figure 3.4: Cost per Megabase of DNA Sequence from July 2001 to July 2011 [94].

function factors, the integral kernels which appear in the equation system (3.15).

Usually, some parameters can be found directly from careful clinical observations or laboratorial experiments. The rest, such as some parameters in the form of integral kernels, we can find by way of parameter estimations. Here mathematics and computer science can help. Assuming a suitable data set is given, there is a possibility to estimate some unknown parameters in the model. The setup of parameter estimation is similar to the corresponding part in chapter 2. The unknown parameters are found by minimizing the deviation between data and model responses. Some available approaches, e.g. the Gauss Newton method can be considered.

The inverse problem of parameter determination is one of the important, challenging problems to connect the model to practice. It is crucial that our established model and analytical study provide a background and a strong motivation toward several interesting problems.

3.4 Concluding remarks

3.4.1 The practical meaning of the structured model

Beyond the theoretical contribution, it is very essential that the model has a practical meaning. During the study, we have shown evidence that

1. we can obtain data concerning the model quantities (e.g. malaria) at a medium cost.

2. we can consider the parameter estimation problem and make numerical simulations with the structured model to predict different scenarios.

As we have discussed in the section above, with current technologies it is possible that we can obtain a complete data set. It is also likely that the laboratorial and experimental costs rapidly decrease. If we gain enough information from the data set, we have a chance to determine the parameters and validate the concrete model. This model then can be used to simulate many different scenarios in advance and deliver critical results to improve drug treatment policies.

3.4.2 Remark on the chapter

So far we have built a structured model to describe the population dynamics in vector-borne diseases and studied this analytically.

Compared to the established model in chapter 2, the structured population of humans and vectors contains more detailed information of all infected individuals. We introduce the two new variables of sensitive and resistant parasite densities. The system appears in the form of integro-partial differential equations with implicit boundary conditions. This demands for a new method for analytical and numerical studies.

Within the chapter, we have developed the transformations to change the system to an integral equation system. Motivated by the fixed point theorem, we have reformulated the problem to solve the difficulties coming from the unknown boundaries. By constructing an appropriate function space, we have proved the existence and the uniqueness of the boundary conditions. With these boundary values, we have found a unique solution for the original problem. We have also proved that the solution is positive as long as the initial values are positive.

Moreover, our analysis provides a strong background for performing numerical simulations. Together with the potential data concerning model quantities, the model can be used for parameter estimation as well as can deliver simulation results to help in designing drug treatment policies. The software development and implementation for the validation of the theoretical model and for numerical simulations are very inspiring topics for future studies.

Chapter 4

Results and perspectives

In this chapter we summarize the results and discuss some open questions for the future.

4.1 Results

This dissertation has contributed to several fields concerning the topic of drug resistance. We state these contributions concisely in the following.

1. The background: We have summarized the medical background which is related to the diseases, the micro-organism and the difficult issues in medical treatment. Covering more than a hundred mathematical papers including several surveys, we have given the state-of-the-art of drug resistance models. This has included the model types, the study methods and the linked interpretations.

2. The modeling process: We have developed two models describing the population dynamics of vector borne diseases. The first one is a non-structured population model in the form of ordinary differential equations and the second one is a structured population model in the form of integro-partial differential equations. In comparison to established models in the past they are both new models offering unique approaches to the subject. They take into account more phenomena, especially the drug treatment and drug resistance problems. These newly created models are the bases with which to obtain theoretical and numerical results as well as to open clinical applications. They also serve as a basis for further studies, such as the investigation of optimal control problems.

3. The theory: Modeling vector-borne diseases has been long considered a difficult task because it involves a second host. This is also shown quantitatively in our mathematical problems. We had a lot of challenges when dealing with analysis parts of the models. Overcoming all that, we have analyzed the two

models systematically. Especially through the structured population model, we contribute to the mathematical theory of integro-partial differential equations by treating a system with different characteristics in multi-dimensional space. The results provide an opportunity for solving a lot of similar-type systems that have not been solved so far.

4. The numerics: In addition to the analysis, we have concerned ourselves with numerical studies. We have performed parameter estimation and simulation for the non-structured model. The data set was taken from Burkina Faso, Africa. We have proposed an algorithm and discussed the potential data to investigate the structured population model numerically. A software for doing numerical simulations of this model is becoming much more within reach.

5. The application: We are able to deliver several practical applications by way of our models, particularly through the simulations of the first model. Along with the data set, the model simulations give important results with which to improve treatment policies toward drug resistance control, especially for malaria and other vector-borne diseases.

4.2 Perspectives: open questions

Of course, drug resistance is a big topic. There are some problems which are open for further studies.

Concerning the non-structured population model, there are optimal strategy problems, which we have not considered formally. To work with this, we would need more related data. For example, to optimize the drug regimen, we would need precise data concerning drug efficacies, their own mechanism and the interaction between different drugs. We would like to mention here that the used software, VPLAN, also supports Optimal Experimental Design.

Concerning the structured population model, we have not analyzed all classes of the model. Several coefficients and also the boundary conditions can be generalized to cover more cases. The method which we developed here can be used to study these generalized problems. Mathematically, our transformations can be extended to larger classes of equation systems, covering any finite number of variables and unknowns. Based on our analysis, a software for solving the equation system could be developed and implemented. Theoretical works show that the iterations should converge to a global solution. However, the study of convergence speed and also comparisons to different possible methods would provide valuable information.

Concerning the application of the models, we need to search for clinical data to be able to estimate the model quantities. We would like to point out that our modeling process and theoretical works open a great channel for cooperation be-

tween theoreticians and clinicians. Clinicians can provide material such as data, problems for modeling. Theoreticians can provide models and tools for quantitative investigations. Provided suitable experimental data, parameters can be determined, and the simulations of the model can run in computers to produce concrete predictions of clinical quantities of interest. Optimal control methods can then be used to deliver better strategies for practical treatment.

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