

SPONTANEOUS CHANGES OF HUMAN BEHAVIORS AND INTERVENTION
STRATEGIES: HUMAN AND ANIMAL DISEASES

by

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B.S., Tianjin University, 2010

AN ABSTRACT OF A DISSERTATION

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Abstract

The topic of infectious disease epidemics has recently attracted substantial attentions in research communities and it has been shown that the changes of human behaviors have significant impacts on the dynamics of disease transmission. However, the study and understanding of human reactions into spread of infectious disease are still in the very beginning phase and how human behaviors change during the spread of infectious disease has not been systematically investigated. Moreover, the study of human behaviors includes not only various enforced measures by public authorities such as school closure, quarantine, vaccination, etc, but also the spontaneous self-protective actions which are triggered by risk perception and fear of diseases. Hence, the goal of this research is to study the impacts of human behaviors to the epidemic from these two perspectives: spontaneous behavioral changes and public intervention strategies.

For the sake of studying spontaneous changes of human behaviors, this research first time applied evolutionary spatial game into the study of human reactions to the spread of infectious disease. This method integrated contact structures and epidemics information into the individuals' decision processes, by adding two different types of information into the payoff functions: the local information and global information. The new method would not only advance the field of game theory, but also the field of epidemiology. In addition, this method was also applied to a classic compartmental dynamic system which is a widely used model for studying the disease transmission. With extensive numerical studies, the results first proved the consistency of two models for the sake of validating the effectiveness of the spatial evolutionary game. Then the impacts of changes of human behaviors to the dynamics of disease transmission and how information impacts human behaviors were discussed temporally and spatially.

In addition to the spontaneous behavioral changes, the corresponding intervention strategies by policy-makers played the key role in process of mitigating the spread of infectious disease. For the purpose of minimizing the total lost, including the social costs and number of infected individuals, the intervention strategies should be optimized. Sensitivity analysis, stability analysis, bifurcation analysis, and optimal control methods are possible tools to understand the effects of different combination of intervention strategies or even find an appropriate policy to mitigate the disease transmission. One zoonotic disease, named Zoonotic Visceral Leishmaniasis (ZVL), was studied by adopting different methods and assumptions. Particularly, a special case, backward bifurcation, was discussed for the transmission of ZVL.

Last but not least, the methodology and modeling framework used in this dissertation can be expanded to other disease situations and intervention applications, and have a broad impact to the research area related to mathematical modeling, epidemiology, decision-making processes, and industrial engineering. The further studies can combine the changes of human behaviors and intervention strategies by policy-makers so as to seek an optimal information dissemination to minimize the social costs and the number of infected individuals. If successful, this research should aid policy-makers by improving communication between them and the public, by directing educational efforts, and by predicting public response to infectious diseases and new risk management strategies (regulations, vaccination, quarantine, etc.).

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Chapter 1 - Research Summary

1.1 Introduction and background

The infectious disease is a continuous threat to the human communities. In 1918, the influenza pandemic, called Spanish influenza, infected around “500 million people across the world and killed 50 to 100 millions of them” (1). Between November 2002 and July 2003, an infectious disease called severe acute respiratory syndrome, abbreviated as SARS, outbreak in China. It resulted in 775 deaths worldwide from the WHO report. In 2009, the second influenza pandemic involving H1N1 after 1918 appeared and more than 14,000 people dead because of this disease based on WHO report. Besides these new diseases showing up in the world, human beings are still suffering from some other infectious diseases, such as measles, HIV, malaria, etc.

Human behaviors, as one of the most important factors which impact the dynamics of disease transmission, play a key role on mitigating and controlling the epidemic. However, the study and understanding of human reactions to the spread of infectious diseases are still in the very beginning phase and how human behaviors change during the spread of infectious disease has not been systematically investigated(2). Moreover, the study of human behaviors includes not only various enforced measures by public authorities such as school closure, quarantine, vaccination, etc, but also the spontaneous self-protective actions which are triggered by risk perception and fear of diseases.

When an infectious disease spreads out into human communities, individuals may alter their behaviors to protect themselves from becoming infected. Such changes include improvement of personal hygiene, taking antiviral medicine, voluntary social distancing, voluntary vaccination, and other protective measures. As an example, the outbreak of the SARS epidemic in 2003 caused many people to change their behaviors by taking several preventative measures (3,4).

On the other hand, the appropriate response from the public health authorities is essential to mitigate the spread of infectious diseases. However, the corresponding control strategies are not always known or the optimal policies are very difficult to quantify from the known facts or experiments for some diseases, especially those resulting in high mortality or huge loss on economics. One example is the Visceral Leishmaniasis (VL), which is a protozoan disease caused by parasites of the genus *Leishmania* and transmitted through the bite of infected sandflies. The current annual estimate of VL mortality is more than 50000 (5), an assumed underestimation because not all cases are reported and VL is often undiagnosed or unrecognized. However, quantitative conditions that are required to control or eradicate VL transmission have not been provided and there are no mathematical methods proposed to quantitatively calculate optimal control strategies for VL transmission.

Hence, understanding the impacts of human behaviors to the dynamics of disease transmission and seeking the appropriated control strategies are two significant tasks to help policy-makers mitigate or control the spread of infectious diseases, which direct the needs of new models and methodologies in future public disease research.

1.2 Research objectives

Several studies have been conducted in order to understand how these spontaneous behavioral changes help mitigate the spread of infection. Funk reviewed the recent work on the influence of human behavior on the spread of infectious diseases, including using game theory to study the human response to epidemics (2). Reluga constructed a differential game to study the benefit of social distancing behaviors (6). Another differential model showing that changes to human behaviors significantly impact the spread of epidemics was proposed by Poletti, Ajelli, and Merler (7). To model the spontaneous changes of human behaviors, the susceptible individuals

were assumed to adopt two mutually exclusive behaviors, “normal” and “altered”, based on the perceived risk of infection. Regula, Bauch, and Galvani, in an epidemiological game examining voluntary vaccination, claimed disease eradication is hard to achieve by voluntary vaccination in a homogeneous population (8). All three models considered only the cases in a well-mixed population and failed to address the importance of contact structure over a heterogeneous population. On the other hand, studies focusing on a heterogeneous and spatially structured population can be shown to be more realistic and flexible successful when a social contact network is incorporated into the model (9-11). Hence, models that combines both a spatially contact structure and spontaneous behavior changes are could be a more suitable way to improve the existing models, and hence this is one the main objectives of this research. In addition, adoption of intervention strategies to different infectious diseases were studied under different scenarios. For different scenarios, the corresponding optimal strategies were taken into consideration. For demonstrating the effectiveness of this approach, one case study is chosen in this research to discuss the appropriate intervention strategies in epidemic.

The motivation of this research was inspired by the evidences and discussion above. This research is aimed to develop new models and analytical methodologies to study the impacts of human behaviors in epidemic, which includes two main research tasks as follows:

1. **Understanding spontaneous changes of human behaviors:** Adopt game theory to study the decision making process for changes of human behaviors. Develop temporal and spatial analytical models to simulate the changes of human behaviors by integrating the game theory into spatial contact structure. During this task, specific tasks are as follows:

- Study the risk perception of individuals to the information about infectious disease
 - Develop a novel spatial evolutionary game for decision making of individuals based on their risk perception
 - Identify key factors which impacts human decisions.
 - Evaluate the effects of human behavioral changes to the dynamics of disease transmission temporally and spatially.
2. **Seeking appropriate intervention strategies:** Build mathematical models for VL transmissions. Conduct a variety of analyses to seek the feasible or optimal control strategies and provide recommendations on control strategy combinations for the different scenarios. During this tasks, specific methods are used as follows:
- Develop mathematical models for VL disease
 - Identify key factors for transmission of VL through sensitivity analysis.
 - Study models' behaviors at equilibrium points through stability and bifurcation analysis
 - Discuss the appropriate intervention strategies and seek optimal control strategies if possible.

1.3 Proposed methodologies

To understand the spontaneous changes of human behaviors, a key concept is emphasized—the balance of benefits and costs from such changes. With the assumption of rationality and self-interest, people make decisions according to the information they acquire about a disease. Hence, information dissemination and individuals' perception about the prevalence of infectious disease play crucial roles in the tradeoff between benefits and costs. In this research, a new methodology,

which combines the information transmission, contact networks, and changes of human behaviors with the dynamics of an epidemic is demonstrated. The methodology uses a spatial evolutionary game to model human behavior change and its impacts on the transmission process of infectious disease. One advantage of adopting a spatial evolutionary game is the “spatial decision” The spatial game take the location information into consideration when individuals balance their costs and benefits, i.e. individuals in different locations may choose different strategies based on their local and global situations. The other advantage of adopting a spatial evolutionary game is the convenience for studying the impacts of local information and global information related to behavior change. The assumption on the impact of local information transmission is different from the impact of global information transmission and each individual will make behavior change decisions based on these two different pieces of information. Sensitivity analysis and numerical simulation are then carried out to study what are the key parameters that can significantly impact of human behaviors. This methodology is also applied to classic dynamic systems, which is widely used in the study of epidemiology. This application to dynamic system not only validate the correctness of the methodology, but also further discusses the impact of information dissemination to human decisions. A detailed description of the mathematical models is presented in Chapter 3 and Chapter 4.

For the sake of understanding the intervention strategies, a collaborative research with researchers in the Department of Entomology at Kansas State University is conducted for transmission of VL. This study is focusing on the Visceral Leishmaniasis (VL) transmission. The VL is a vector-borne disease caused by protozoan flagellates of the genus *Leishmania*, is transmitted by sand flies. Except malaria, VL is the second-largest parasitic killer, responsible for an estimated 500,000 infections and 51,000 deaths annually worldwide. Mathematical models

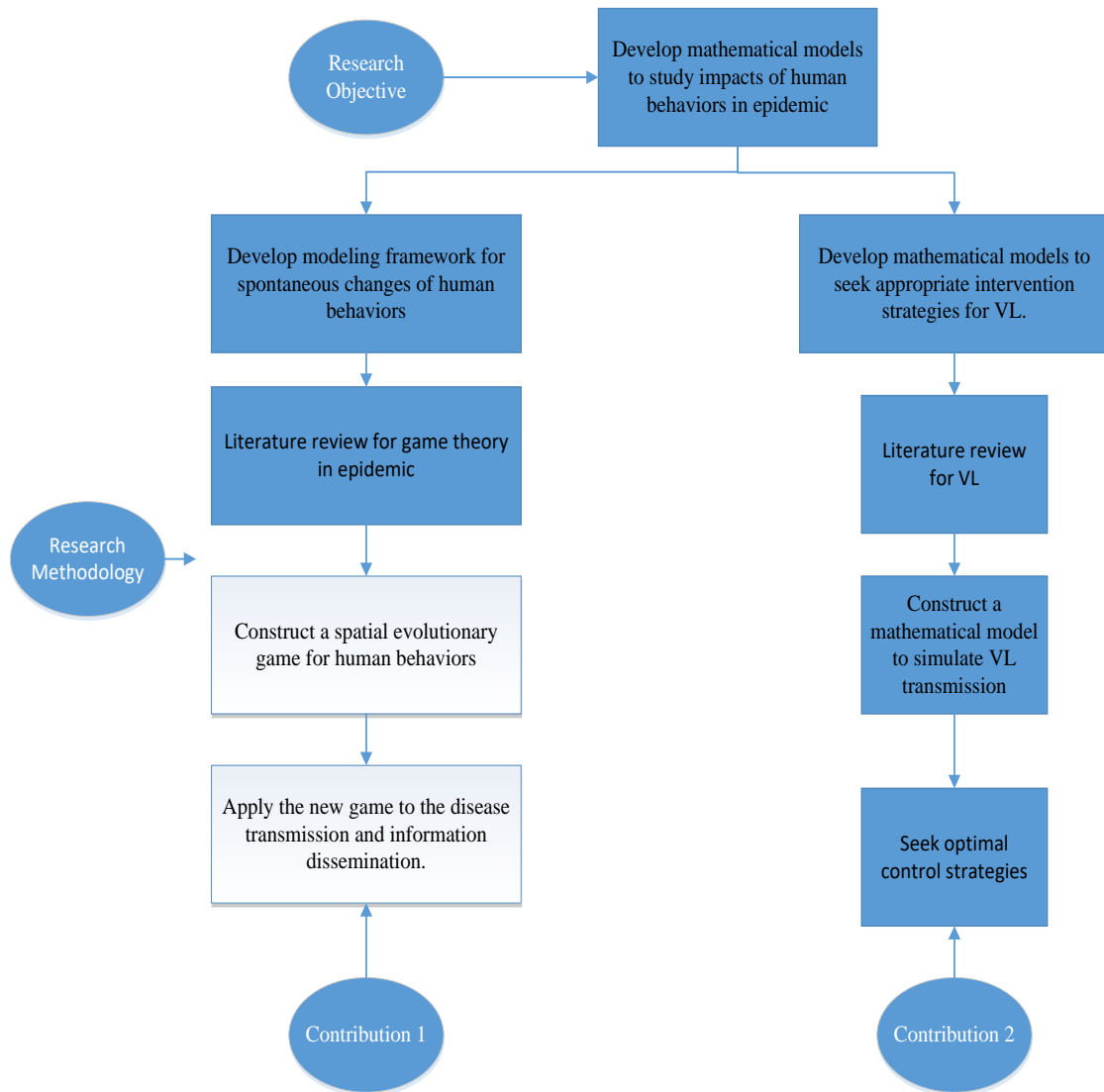
proposed for VL have included the impact of dogs versus wild canids in disease dissemination and models developed to assist in control approaches. However, quantitative conditions that are required to control or eradicate VL transmission are not provided and there are no mathematical methods proposed to quantitatively calculate optimal control strategies for VL transmission. The research objective of this work was to model VL disease transmission system (specifically Zoonotic VL), perform bifurcation analysis to discuss control conditions, and calculate optimal control strategies. Three time-dependent control strategies involving dog populations, sand fly population, and humans are mainly discussed. Another strategy sometimes used in attempts to control zoonotic VL transmission, dog culling, is also evaluated. A detailed description of the mathematical models and analyses is presented in Chapter 5.

1.4 Research map

This research plans to provide scientific and effective mathematical models for studying the impacts of human behaviors to the spread of infectious disease. Both of spontaneous changes of human behaviors and those changes by enforced measurements due to the intervention strategies are taken into consideration and this research should aid policy-makers by improving communication between them and the public, by directing educational efforts, and by predicting public response to infectious diseases and new risk management strategies.

Figure 1.1 shows a research map that describes the research objective, research methodologies, and potential research contributions.

Figure 1.1 Research map



1.5 Outlines

The rest of dissertation is organized into five chapters: 1) Literature Review: for the study of spontaneous changes of human behaviors, the application of game theory to the epidemiology are reviewed and the basic spatial evolutionary game is introduced. For the study of intervention strategies, the optimal control theory in dynamic system and its application to infectious disease are discussed. 2) Modeling Infection Spread and Behavioral Change Using Spatial Games: for the first time, the new spatial evolutionary game to spontaneous changes of human behaviors is

developed and main numerical results are discussed. 3) Temporal and Spatial Analysis for Human Behaviors in Epidemic: The spatial evolutionary game built in Chapter 2 is applied to a dynamic system for validating the effectiveness of implementing the new game. More impacts of information dissemination are discussed temporally and spatially. 4) Zoonotic Visceral Leishmaniasis Transmission: Modeling, Backward Bifurcation, and Optimal Control: mathematical model is developed for better understanding the transmission of VL and seeking the optimal control strategies. 5) Conclusions, Contributions, and Future Works: the main conclusions and contributions are summarized and the potential future works are discussed.

Chapter 2 - Literature Review

2.1 Game theory for human behaviors in epidemic

2.1.1 Introduction

Infectious diseases continue to pose a threat to human society. In order to control the spread of infectious diseases and mitigate their impact, various strategies may be implemented such as pharmaceutical interventions (i.e. vaccine and antivirals) and non-pharmaceutical interventions (i.e. quarantine, isolation, social distancing, and school closure) (12). In addition, effective control of an epidemic outbreak requires rapid logistics operation. Allocation and transportation of medical supplies and human resources are of critical importance since rapid responses may contain the spread of infectious disease under control (13). Recently, self-initiated human behaviors (i.e. voluntary vaccination, voluntary quarantine, or public avoidance), as important factors that affect the spread of infectious disease, have attracted increasing attentions (2). Understanding the impact of human behaviors on the spread of disease can not only be a key to improving control efforts, but also can guide policy-maker to determine necessary intervention strategies. Regardless of whether human behavior is spontaneous or regulated; individuals' decisions do not merely depend on themselves, but also on others' choices. Thus, game theory, as a study of conflict and cooperation between intelligent rational decision-makers, plays an important role in the control of the spread of infectious diseases.

Game theory is a commonly used approach for modeling competing behaviors of interacting decision-makers. It has been applied to a variety of fields, including economics, politics, resource allocation and networking, biology, artificial intelligence, philosophy, and so on. In recent decades, game theory has also been used in epidemiology, especially involving epidemic

problems related to human behaviors. A variety of topics are covered, such as vaccination, social distancing, preparedness for disasters (including epidemics), and so on.

Here, we aim to systematically review the applications of game theory to epidemic control. The literature classification is based on intervention/prevention strategies. There are a total of four categories taken into consideration: vaccination, antivirals/antibiotics, social distancing, and logistic operations. More specifically, vaccination and antivirals/antibiotics correspond to reduce the intensity of the infection, social distancing corresponds to the reduction of contact rates (sometimes social distancing also includes the reduction of intensity of the infection in general models which do not specify certain type of strategies), and logistic operations correspond to resource allocations and preparedness for pandemics. We do not combine vaccination and antivirals/antibiotics into one category since effects of vaccination and usage of drugs are quite different and there are substantial papers focusing on vaccination instead of usage of antivirals/antibiotics. Considering the vast amount of literature, only human disease is considered in this paper. All other diseases are excluded.

This section is organized as follows: basic concept of game theory and Nash Equilibrium are introduced in Section 2.1.2. Section 2.1.3 illustrates the classification of game theory in epidemiology with applications, and Section 2.1.4 is a summary with further discussion.

2.1.2 Game theory and Nash equilibrium

Individuals have to make decisions regarding a variety of prevention strategies during epidemics such as vaccination, usage of antiviral/antibiotic drugs, avoidance of public places, etc. Not all of these decisions are made depending on individuals themselves, but also determined by others' choices. Game theory, as a commonly used tool to study conflicts among decision-makers, is an appropriate approach to study human behaviors during the epidemic.

In a classic game, there are three elementary components: players, strategies, and payoffs. Each player has the complete information about the game and rationally (but non-cooperatively) chooses the strategy which could maximize his/her own payoff. As such, players make the best decisions for themselves after a game; however, the outcome is not necessarily optimal for the entire system. One of the most famous games is the one called “prisoner’s dilemma”, which describes a scenario in which two prisoners could either betray the other by testifying the other’s crime or remain silent. The payoff matrix is shown below:

Table 2.1 Payoff Matrix for Prisoner’s Dilemma

	Cooperate	Betray
Cooperate	R, R	S, T
Betray	T, S	P, P

In Table 2.1, the relationship among R , S , T , and P is $T > R > P > S$. In this case, both prisoners always choose to betray the other. By using this strategy they both maximize their own payoff regardless of what choice the other makes. Hence, in the end the payoff for both of them is P . However, it is apparent that prisoners can gain some payoff if both of them choose to cooperate with the other one since R is greater than P . From this point of view, one could argue that the self-interest behavior sometimes is not the best choice for individuals.

In game theory, if no players can gain any payoff by changing only their own strategies, we called it “Nash Equilibrium”. The outcome “betray – betray” in the prisoner’s dilemma is the Nash Equilibrium since the prisoner will lose payoff if he only changes his own strategy. The Nash Equilibrium concept is commonly used to analyze a game and study the interaction among decision-makers. However, the Nash Equilibrium in the classic game cannot explain the cooperation phenomena which could optimize the entire system’s payoff due to the self-interest behaviors of players.

In reality, sometimes individuals will cooperate with others, leading to an optimization for all players. To explain this phenomenon, one extension of the classic game is that individuals have a chance to change their strategies based on a rule, called “revision protocol”, if they play the game repeatedly. For instance, individuals could imitate others’ strategies based on the previous game’s outcome. As such, individuals do not have to play the game rationally, but instead, they are able to test how well their strategies are. This style of game is referenced as “evolutionary game” which is originally studied in biology. Many variations of the revision protocol could be applied to the evolutionary game and, in turn, the outcome of game could be shifted to the global optimal solution with different degrees. Particularly, if the contact network is taken into consideration for revision protocol, the game is called spatial game.

In epidemiology, game theory can be adopted to explain a variety of self-interest behaviors during the epidemic, for instance, free riders in vaccination problem. When a large number of people in a population are immune to a certain type of infectious disease, the spread of this disease will be stopped or slowed down and people who do not have immunity to this disease are protected indirectly by others. This phenomenon is called “herd immunity” and people who are not immune to the disease are called “free riders”. In this case, game theory becomes an appropriate method to analyze human behaviors for voluntary vaccination problems. More details of vaccination problems and other applications of game theory in epidemiology are discussed in the next section.

2.1.3 Classification of game theory in epidemiology

The application of game theory in epidemiology is categorized as four parts: vaccination, antivirals/antibiotics, social distancing, and logistic operations. The distribution of article references within the mentioned four categories is shown in Table 2.2.

Table 2.2 Distribution of paper in literature

Category	Number of papers
Vaccination	23
Antivirals/antibiotics	4
Social distancing	8
Logistics operations	2

In Table 2.2, it is obvious that game theory is most commonly linked to a vaccination topic. Very few papers discuss usage of drugs and logistics operations using game theory. For antivirals/antibiotics, one reason is that it is very difficult to evaluate the effect of usage of drugs; on the other hand, some models integrate usage of antivirals/antibiotics into social distancing which do not focus on the study of usage of drugs itself. For logistics operations, very few topics are related to competing behaviors among individuals so that game theory is not a proper approach in most cases. However, there are still a few applications when considering the competition among organizations or countries.

2.1.3.1 Vaccination

Vaccination is referenced as “the most effective approach to preventing transmission of vaccine-preventable diseases, such as seasonal influenza and influenza-alike epidemics, as well as reducing morbidity and mortality” (14). However, to date, smallpox is the only human disease that has been entirely eliminated because of the use of vaccination (15). “Herd immunity” and vaccine scares is part of reasons for the resiliency of vaccine-preventable diseases and extensive efforts have been contributed to studying interplay between disease transmission, vaccine coverage, and human behaviors by integrating game theory into a traditional epidemiological models (2,8,14,16-35). The main topics of this review could be classified into three parts: self-interest vs group-interest in a homogeneous population, self-interest vs group-interest in a heterogeneous population, and others.

Self-interest vs group-interest in a homogeneous population

A basic vaccination game was developed by Bauch et al (17) to study the smallpox vaccination which integrated game theory into the epidemic modelling. Based on the model, the author concluded that the global optimality could be achieved only by voluntary vaccination. The simple version of a vaccination game in (17) is shown below:

Considering a population with N individuals, all of them are players in the game. There are two strategies available to them: vaccination and non-vaccination. The risk associated to the vaccination is denoted by r and the risk of infection is denoted by π_θ whose value is related to θ which represents the fraction of the population that is vaccinated. The player who chooses vaccination get payoff $-r$ while the player who chooses non-vaccination gets payoff $-\pi_\theta$. Hence, the expected payoff for individuals who choose strategy P is

$$E(P, \theta) = -rP - \pi_\theta(1 - P) \quad (2.1)$$

In epidemiology, the basic reproduction number R_0 , which is defined as the secondary attack rate when an infectious individual invades into an entire susceptible population, is a critical indicator. When R_0 is smaller than 1, the spread of infectious disease could be controlled; while the infectious disease will spread out if R_0 is larger than 1.

By coupling game theory into epidemical model, the vaccination coverage levels in Nash Equilibrium P^* and optimal solution P_{crit} could be solved respectively and the results are shown below:

$$P^* = 1 - \frac{1}{R_0(1-r)} \quad (2.2)$$

$$P_{crit} = 1 - \frac{1}{R_0} \quad (2.3)$$

where $0 < r < 1$. As such, the vaccination coverage level in Nash Equilibrium is unlikely to reach the level in optimal solution. A similar conclusion was also drawn in model (21), which considered self-interested people in a voluntary vaccination problem using a vaccination game.

Many variations are studied based on the above vaccination game, including include imitation/learning behaviors in well-mixed population (8,22) and in complex networks (19,20,34), incentives offered (18), and altruism (23).

Vardavas et al (18) used computational modelling to determine whether the vaccination coverage level, which is necessary for preventing influenza epidemics, can be reached when offering incentives to individuals. In their work, they proposed that “the severe epidemics will not be prevented if vaccination is voluntary and no incentives are offered”. In contrast, Reluga (8) claimed that “optimal individual behavior can vary between universal vaccination and no vaccination, depending on the relative costs and benefits to individuals”. Self-interested behaviors can lead to oscillations in vaccination coverage levels over time.

People’s behavior and decisions are often influenced by many external factors, such as the opinions of friends and families, rumors, fear, information from news, radio, report, and so on. Instead of choosing static strategies, dynamic behaviors are studied when the imitation or learning behaviors are taken into consideration. Considering learning behaviors, Bauch (22) developed a game dynamic model and assumed “people adopt strategies according to an imitation dynamic, and subsequently base vaccination decisions on disease prevalence and perceived risks of vaccines and disease”. Instead of obtaining a stable state, oscillations in vaccination coverage levels are more possible when people dynamically change their strategies based on the disease prevalence and others’ behaviors. More recently, the dynamics of vaccination behaviors are studied in more complex network. Particularly in (20), two different game rules lead to very different outcomes. The results from memory-based model, which means individuals choose strategies based on past experience, and from risk-evaluation model, which means individuals choose strategies based on the prevalence, are opposite when we consider different costs of vaccination.

In game theory, a basic assumption is that individuals interplay with others according to self-interest and always want to maximize their own payoffs. However, it may not be always true in reality. Shim et al (23) conducted a survey to test how altruism affected individuals' decisions in vaccination problem. They claimed that "that altruism plays an important role in vaccination decisions". A game-based epidemiological model was developed for influenza vaccination and it turned out that the Nash Equilibrium moved towards the optimal solution when the altruism was taken into consideration.

Self-interest vs group-interest in heterogeneous population

The population is considered to be heterogeneous, when its individuals are divided into a finite number of distinct population groups, where each group may have distinct perceptions about vaccine and risks' evaluation. According to the specific disease, the group could be classified by age and gender. For example, transmission of influenza indicate that elderly individuals face the highest mortality risk, but children contribute most to disease transmission. In this case, elderly individuals face the higher disease risks than adults and should be protected through vaccination of adults.

In (24,31), Cojcaru et al analyzed the dynamics of the vaccinating behavior in a population consisting of two distinct social groups, a "vaccine-inclined majority group" and a "vaccine-averse minority group". It turned out that the vaccine coverage level in this heterogeneous population is higher than the corresponding homogeneous population. In addition, it is possible that there is a high vaccination rate for majority group and a low vaccination rate for minority group under certain conditions.

As the previous discussion, the elderly has the highest risk of influenza mortality. The Centers for Disease Control follow the principles of voluntary vaccination and vaccinate the

elderly with higher priority. However, preferentially vaccinating children may be more efficient to reduce the influenza transmission. Galvani et al (25) parameterized a game-theoretic model of influenza vaccination according to “a questionnaire data on actual perceptions of influenza and its vaccine”. Their results proposed that it is possible to align Nash Equilibrium with global optimal solution. Another age-structured model is constructed by Shim et al (26). Their results claimed that priorities of vaccination for different age groups are different compared Nash Equilibrium and optimal solution. To imitate the real world transmission of influenza, a game theory experiment was conducted by Chapman et al (27). The results of this experiment are consistent with the general conclusion which self-interested players lead to Nash Equilibrium and global-interested players lead to optimal solution.

Instead of grouping population by age, a disease which could be transmitted from a mother to a fetus results in gender-specific vaccination.

For example, rubella is a highly contagious childhood disease and rubella can result in severe congenital defects if transmitted from a mother to a fetus. Shim et al (28) developed a game theoretic epidemiological model for rubella transmission and vaccination. Their results showed that high vaccination coverage levels for both of males and females are required for optimal solutions, while Nash Equilibrium indicated that demands for vaccines among males and females are 0% and 100%, respectively.

When a heterogeneous population is taken into consideration, the general conclusion -- self-interest optimal coverage is lower than group-interest optimal coverage -- may not be always true. The typical relationship was reversed. In (29), where an age-depend game-theory epidemic model was applied to the USA and Israel for chickenpox.

Others

Although most of research focuses on Nash vaccination and global optimal vaccination, game theory is also applied to other topics in vaccination. Barrett (30) developed a model which combined epidemiology, economics, and game theory to study the global disease eradication, showing that “even epidemiology favors eradication, but a global disease eradication program may fail for institutional reasons”. Wu et al (32) took the imperfect vaccine into account. The results in their study showed that the number of effectively vaccinated individuals increased when the effectiveness of vaccination increased and therefore contain the epidemic spread. The results suggested that the impact of the epidemic can be better mitigated if vaccination effectiveness was increased. Another topic was discussed in (33) which focused on the incentives’ effect in influenza vaccination policy. Results suggested that “the optimal incentives should be greater when less contagious seasonal strains of influenza are involved and greater for the nonelderly population rather than the elderly”. Moreover, a phenomenon known as the “wait and see” vaccinating behavior during 2009 H1N1 pandemic was studied in (35). Many individuals prefer to “wait and see” until further information was available instead of choosing vaccination in the beginning. The delay-vaccinators either are protected by early vaccinators due to herd immunity or get vaccination after the safety of vaccine tested by early vaccinators. This adaptive behavior lead to “the timing of the epidemic peak to be strongly conserved”.

Summary

Vaccination problem is most commonly studied by using game theory in epidemiology. In vaccination game, all individuals in the population are players. Strategies are vaccination or non-vaccination. Payoff functions and revision protocols could be different but the basic concept for payoff function is utility function (cost function) and for revision protocols are memory-based or risk evaluation. Most of research focus on the comparison of Nash Equilibrium and global optimal

solution. In general, the vaccination coverage level is lower in Nash Equilibrium than that in optimal solution. However, the conclusion may vary under different extensions and assumptions. Adaptive behaviors such as imitation, risk evaluation, wait and see, etc, may shift the Nash Equilibrium towards the optimal solution. When it comes to different groups of individuals, the typical conclusion could be reversed. In sum, voluntary vaccination program is very difficult to eradicate the infectious disease but better solutions could be obtained if individuals are motivated or instructed correctly.

2.1.3.2 Antivirals/Antibiotics

Only four papers are selected in the topic of antivirals/ antibiotics. The concept of application of game theory are also quite different among different authors. In the usage of drugs games, all individuals in the population are players and their strategies include drug-acceptance and drug-refusal. Payoff functions are defined in different ways in different papers, including cost function (36), life expectancy (37), and lengths of infected period in terms of drug-resistance (38,39).

In (36), Shim et al studied antiviral intervention during an influenza pandemic through evaluating optimal coverage level for antiviral drug use, from both of individual and the population sides, which is similar to the method of studying vaccination game. Their results showed that the self-interest driven demand for antiviral drugs during a pandemic would be much lowered than the optimal solution. The cost of drugs plays a key role when individuals make decisions. And therefore, it is almost impossible to control infectious disease through only usage of drugs if no incentives are offered. A similar conclusion was drawn by van Boven et al. (37) when considering the costs of treatment.

Another two papers focused on the use of antibiotic drugs. Overuse of antibiotic drugs may lead to an increase of the number of drug-resistance strains which make a “tragedy of commons” while antibiotics could protect individuals from infectious diseases. The conflict of self-interest use and global-interest use could be analyzed by game theory. In (38), Porco et al developed a simple transmission model which study the development and spread of drug resistant organisms. According to their results, “antibiotic use may indeed lead to a tragedy of the commons, in which individual incentives lead to antibiotic use rates that are too high to yield the best community outcome”. A similar result was obtained in (39) when Gao et al proposed a simple two-disease epidemic model, where there is only one drug-sensitives strain for first disease, while there are both drug-sensitive and drug-resistant strains for second disease.

2.1.3.3 Social distancing

Social distancing is the prevention strategy by reducing daily contact rates to other individuals. It includes school closure, isolation, public avoidance, and so on. Sometimes social distancing also includes the behavior which reduces the intensity of infection. In literature, some models are developed in a general way, which fail to specify the certain type of human behaviors. All of these human behaviors are considered as social distancing. In social distancing game, all individuals in the population are players, and their strategies include normal behaviors (which is not changed at all during the epidemic) and altered behaviors (individuals protect themselves through changing their behaviors, including reduction of intensity of contacts and reduction of contact rate to others.) Change of human behaviors could be extended into different levels but we refer to “altered behaviors” to represent individuals who change their behaviors to protect themselves. The payoff function is an utility function or cost function since individuals have to

pay extra costs if they would like to protect themselves but they have less risks than normal individuals.

People are sometimes reluctant to pay the costs for social distancing, which will impact the effectiveness as a control measure. A differential game was used by Reluga (6) to study the impacts of social distancing by calculating the equilibrium behaviors based on different cost-functions. Their results showed that individuals can have benefits through social distancing but only social distancing cannot stop the spread of infectious disease. In (40,41), Chen adopted different players' responses to study the equilibrium of the public avoidance game. The results showed that, "in some cases, the Nash equilibrium could also be the social optimum but for other cases, Nash equilibrium is typically not socially optimal in the public avoidance game. "

In (7), two mutually exclusive behaviors "normal" and "altered" are incorporated into SIR models to study the spontaneous changes of human behaviors. The altered individuals have a reduced infection rate, which could be achieved by social distancing, vaccination, or antivirals. Game theory is applied to the process by which individuals choose to be normal or altered. A similar concept is adopted in (42) which also takes the spatial structure into consideration.

An interesting topic about contact tracing, defined as "the identification of individuals who have come into contact with an infectious case and may be infected", is studied by Sippl-Swezey (43). A small group of individuals are investigated and a mathematical model with game theory was proposed to study conflicts of interests considering the perceived costs of disclosure. The results showed that the optimal decision is to choose not disclose to others if the costs are taken into consideration. However, if all individuals disclose all contacts, it turns out the alignment of individual and group optimality.

2.1.3.4 Logistic operations

Very few models are studied for the application of game theory in the topic of logistics operation in epidemiology. A systematic review about epidemics control and logistics operations is written by Dasaklis (13). However, only two papers are related to game theory, one for the allocation of influenza vaccines (44) and the other one for stockpile of medical supplies for hospitals before a disaster (45). In logistics operation game, the players are not individuals, but hospitals, health organizations, countries, etc. Strategies and payoff functions varied in different scenarios. Both of studies focus on comparing decentralized model and centralized model, which corresponds to the self-interest solution and optimal solution.

2.1.4 Summary and discussion

From the selected literature, game theory has been applied to most topics that are related to mitigation strategies in epidemiology. Most of efforts are focused on the vaccination program, which is the most effective approach for vaccine-preventable infectious diseases. In order to solve the game in epidemiology, researchers mainly compare the Nash Equilibrium and optimal solution. Different assumptions lead to different conclusions and sometimes Nash Equilibrium could be shifted to the optimal solution. In addition, the impacts of game to the spread of infectious disease are also studied. Through changing the value of parameters in payoff functions or revision protocols, the solution could be shifted to the optimal solution.

Despite the fact that game theory has been successfully applied to epidemiology, the application of game theory still remains a promising research area. We believe that there is a great opportunity for future research efforts. More precisely, future research directions may include:

- Incomplete information for individuals: most of research in game theory assumes that people have complete information and estimates the risk based on the correct information. However, lacking information may lead people to make wrong decisions.

- Media broadcast: information dissemination mainly depends on mass media. Thus, media plays an essential role in the game. Involving media into the game portion could impact human behaviors, so that may indirectly impact the spread of infectious disease.
- Involve policy-makers: most of game theory in epidemiology studies the change of human behaviors and how to align Nash equilibrium to global-optimum. However, policy-makers, who is a very crucial player in the game, could be involved in the epidemic game.
- Incentives of individuals: there are a few articles mentioning the incentives of individuals. To motivate individuals to be global-interested, different motivation programs could be played by policy-makers.
- Development of harmonized approaches: Most models only consider one strategy or one topic. More harmonized models could be developed, such as combining pharmaceutical interventions with non-pharmaceutical ones, or human behaviors with logistic operation plans.
- Spatial Game: most of game theories do not consider the contact network which has a significant impact on both of spread of infectious disease and individuals' decisions.
- Analysis of models: after we compare the Nash Equilibrium and optimal solution, the corresponding policy should be studied so that Nash Equilibrium could be shifted to optimal solution. The effectiveness of these policies should be studied as well.

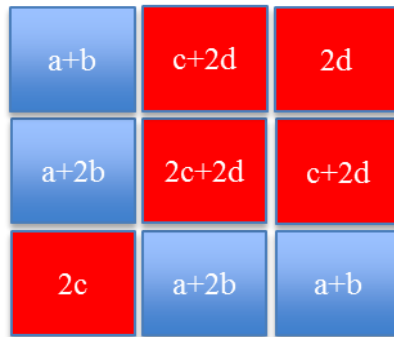
2.2 Spatial evolutionary game

The spatial evolutionary game is a combination of classic game theory and cellular automaton, representing strategies, players, payoff function, structure of population, and an updating rule. It is first introduced to study the local cooperation phenomena in prisoner dilemma by Nowak and May (46). This methodology can analyze various structures of populations using a regular lattice (47), scale-free networks (48), and real social networks (49). Evolutionary games

on graphs are reviewed by Szabo and Fath (49). This concept requires an updating policy based on the payoff function with different updating schemes such as synchronous or asynchronous updates. Several common updating schemes are reviewed by Newth (50) and update rules are summarized by Roca, Cuesta, and Sanchez (51).

A simple example of spatial evolutionary game in lattice is shown below for the purpose of introduction. Assume two types of players play a game, and two strategies are available to each player. The payoff matrix is shown in Table 2.3. Players could choose either strategy A or strategy B and payoff value could be a , b , c , or d correspondingly according to players' strategies. Figure 2.1 describes the location of each player. The contact pattern in this game is von Neumann neighborhood (four nearest neighborhood). The player would play the game with all neighbors and the summation of payoff value in the game against each neighbor is the final payoff value for each player. The result is shown in Figure 2.1.

Figure 2.1 Spatial evolutionary game example



After each turn, players could reconsider their own strategies based on their own payoff values and other players' payoff values. In addition, players update their strategies synchronously or asynchronously.

Table 2.3 Payoff Matrix

	A	B
A	a	b
B	c	d

2.3 Optimal control for intervention strategies

2.3.1 Introduction

For a given system, an optimal control problem is to find a control strategy which reaches a certain optimality criterion. Specifically, a set of differential equations are given to describe the trajectory of the control variables which minimize the objective function. The optimal control can be calculated by Pontryagin's maximum principle or solving the Hamilton–Jacobi–Bellman equation. In this section, the basic definition of optimal control problem and Pontryagin's maximum principle are introduced based on the book by Evans L.C.(52).

Given an ordinary differential equation(ODE) with the form below:

$$\begin{cases} \dot{x}(t) = f(x(t)) & (t > 0) \\ x(0) = x^0 \end{cases} \quad (2.4)$$

Assume the initial point $x^0 \in R^n$ and the function $f: R^n \rightarrow R^n$, our goal is to study the dynamical evolution of the state of the system, which is the curve $x: [0, \infty) \rightarrow R^n$.

If f also depends on control parameter $u(\cdot)$ where $u(t) \in R^m$, the equation in 2.4 is rewritten as:

$$\begin{cases} \dot{x}(t) = f(x(t), u(t)) & (t > 0) \\ x(0) = x^0 \end{cases} \quad (2.5)$$

Suppose the initial time be 0 and the final time be t_f , the objective function (or payoff function) can be described as:

$$S(u(\cdot)) = \varphi(x(t_f)) + \int_0^{t_f} F(x(t), u(t))dt, \quad (2.6)$$

where $\varphi: R^n \rightarrow R$ and $F: R^n \times U \rightarrow R$ are given.

The aim of optimal control is to find a control $u^*(\cdot)$, which maximizes (or minimizes) objective function $S(u(\cdot))$, i.e.

$$S(u^*(\cdot)) \geq S(u(\cdot)) \quad (2.7)$$

To derive the solution of $u^*(\cdot)$, the optimal control can be solved using Pontryagin's maximum principle. Suppose Hamiltonian function is

$$H(x, \lambda, u) = f(x, u) * \lambda + F(x, u) \quad (2.8)$$

where $x, \lambda \in R^n, u \in U, u^*(\cdot)$ is the optimal control, λ and $x^*(\cdot)$ is the corresponding trajectory.

Also, for $0 \leq t \leq t_f$ a function $\lambda^*: [0, t_f] \rightarrow R^n$ satisfies

$$\dot{x}^*(t) = \nabla_{\lambda} H(x^*(t), \lambda^*(t), u^*(t)), \quad (2.9)$$

$$\dot{\lambda}^*(t) = -\nabla_x H(x^*(t), \lambda^*(t), u^*(t)), \quad (2.10)$$

and

$$H(x^*(t), \lambda^*(t), u^*(t)) = \max(H(x^*(t), \lambda^*(t), u(t))). \quad (2.11)$$

In addition, the terminal condition is

$$\dot{\lambda}^*(t_f) = \nabla \varphi(x(t_f)), \quad (2.12)$$

2.3.2 Application of optimal control for dynamic models

The optimal control methods have been used widely to study infectious diseases and the corresponding optimal intervention strategies when the dynamic models are considered. However, the methods introduced in section 2.3.1 may not work for non-dynamic systems (such as statistical model), which requires other numerical methods to solve the optimal control problems. Those methods are out of the scope and are not included in this section.

Lashari (53) developed a simple mathematical model to seek the cost effective control strategies for the general vector borne disease. The SIR model was adopted to represent the compartments of hosts and the SI model was used to describe the vector population. An iterative method, called the semi-implicit finite difference method, was present to find the numerical

solution of the control problem. A similar model representing the optimal control of a vector borne disease with horizontal transmission was also discussed by Lashari in 2012 (54).

Jung (55) studied the optimal control of treatments for a two-strain tuberculosis using a system of six ordinary differential equations. The objective functional not only minimized the number of latent and infectious drug-resistant tuberculosis but also minimized the cost of control treatments. In 2009, treatment and prevention from Malaria was discussed by Blayneh (56). The objective of optimal control was minimizing the implementing costs. Numerical results showed that prevention and treatment strategies lowered the number of exposed individuals and infected individuals. Blayneh (57) also developed a more complicated dynamic system with 9 differential equations to study the transmission of West Nile Virus in 2010. Using an iterative method, the optimality system coupled with two control strategies were solved numerically by Runge-Kutta method of order four. The results showed that mosquito-reduction strategies were more effective than personal protection. In 2009, Zaman (58) discussed the optimal treatment of an SIR model with time delay. Particularly, the optimal control strategies were solved for the transmission of Ebola virus.

In addition, the optimal control problems are also adopted in cellular level disease modeling, such as HIV. An ODE system was used to study the interplay between human immune system and HIV(59). In this study, chemotherapy was introduced in an early treatment setting and the corresponding optimal chemotherapy strategy was solved based on a combination of maximizing benefit from T cell counts and minimizing total costs of chemotherapy. Later on, Culshaw (60) studied the same optimal treatment problem by maximizing the benefit from levels of healthy CD4+ cells and immune response cells instead of only T cell counts as well as minimizing the cost of chemotherapy. The ODEs were also used to study the interaction between

HIV and T-cells by Joshi (61) in 2002, and an interactive method was adopted to solve the optimal control strategies with two drug treatments.

Chapter 3 - Modeling Infection Spread and Behavioral Change

Using Spatial Games

Chapter 3 is based on the paper “Modeling Infection Spread and Behavioral Change Using Spatial Games” to be published in the journal Health Systems, 2015, 4(1): 41-53.

Abstract

This chapter presents a methodology that combines information transmission, contact networks, and changes of human behaviors in modeling the dynamics of infectious diseases. The methodology presented is based on a spatial evolutionary game with additional information representing human behavior. This approach is used to model the transmission process of infectious disease, which emphasizes the human response and information transmission in a social context. It combines the advantages of evolutionary game theory with modeling the spontaneous changes of human behaviors based on the balance of benefits and costs. The model assumes rational participants who use information acquired to make individual decisions. This novel modeling approach shows the global spread of infection considering the individualized behavior.

3.1 Introduction

When an infectious disease spreads out into human communities, individuals may alter their behaviors to protect themselves from becoming infected. Such changes include improvement of personal hygiene, taking antiviral medicine, voluntary social distancing, voluntary vaccination, and other protective measures. As an example, the outbreak of the SARS epidemic in 2003 caused many people to change their behaviors by taking several preventative measures (3,4).

Several studies have been conducted in order to understand how these spontaneous behavioral changes help mitigate the spread of infection. Funk reviewed the recent work on the influence of human behavior on the spread of infectious diseases, including using game theory to study the human response to epidemics (2). Reluga constructed a differential game to study the benefit of social distancing behaviors (6). Another differential model showing that changes to human behaviors significantly impact the spread of epidemics was proposed by Poletti, Ajelli, and Merler (7). To model the spontaneous changes of human behaviors, the susceptible individuals were assumed to adopt two mutually exclusive behaviors, “normal” and “altered”, based on the perceived risk of infection. Regula, Bauch, and Galvani, in an epidemiological game examining voluntary vaccination, claimed disease eradication is hard to achieve by voluntary vaccination in a homogeneous population (8). All three models only considered the case in a well-mixed population and failed to indicate the importance of contact structure. However, a heterogeneous and spatially structured population can be more successful when a social contact network is incorporated into the model (9-11). Hence, the combination of the impact of a spatially contact structure and the impact of spontaneous behavior changes is believed to be an appropriate way to improve the existing models.

Based on these works about spontaneous changes of human behaviors, a key concept is emphasized—the balance of benefits and costs from such changes. With the assumption of rationality and self-interest, people make decisions according to the information they acquire about a disease. Hence, information transmission and individuals’ perception about the prevalence of infectious disease play crucial roles in the tradeoff between benefits and costs. To evaluate individuals’ assessments of prevalence of infectious diseases based on the information acquired, Chen (63) introduced a social sampling method. It allows participants to make assessments based

on partial information, instead of full information assumed by other models. However, this method assumes there is no centralized dissemination of information regarding the prevalence of the disease. Funk et al. studied the effect of local information transmission in a social network on epidemic outbreaks (64). The model was based on the author's hypothesis that changes of human behavior affected by the information transmission network can restrict the spread of infectious diseases. Kiss developed a model considering sexually transmitted infections based on the information transmission (65). It illustrated how an active host population and the transmission of information triggered by the disease can eradicate or minimize infection levels.

Over the course of the epidemic, the spread patterns of the disease could be very different between the rural and metropolitan areas due to the population density and contact structure variations between different areas. In addition, human behaviors changes within a largely heterogeneous population group during the course of the epidemic could sway the disease's reproduction ratio (R_0) over time, instead of the commonly assumed constant R_0 for the underlying disease suggested in majority the existing literatures. The changes of the human behaviors or self-mitigation activities many times are by and large driven by the current information individual obtain either by the media, propaganda, or other individuals within their community. The model presented in this article attempt to include these significant factors in our model using a straight forward spatial game structure. We assume the un-infected population can make free will behavior changes, such as social distancing, self-quarantining, vaccination, taking preventive medicine, self-protection devices, etc. to reduce his or her chances to get infected. However, these behavior changes come with associated "costs," including expenses, loss of income opportunities, costs of inconveniences, etc. Each individual could also possess different perceptions for the information

related to the ongoing epidemic and decided to either do nothing or take on different actions to reduce his or her chances to acquire the disease.

In this paper, we demonstrate a methodology that combines the information transmission, contact networks, and changes of human behaviors with the dynamics of an epidemic. The methodology uses a spatial evolutionary game to model human behavior change and its impacts on the transmission process of infectious disease. One advantage of adopting a spatial evolutionary game is the “spatial decision” The spatial game take the location information into consideration when individuals balance their costs and benefits, i.e. individuals in different locations may choose different strategies based on their local and global situations. The other advantage of adopting a spatial evolutionary game is the convenience for studying the impacts of local information and global information. We assumed the impact of local information transmission is different from the impact of global information transmission. Hence, it is convenient to collect local information as well as global information from which individuals base their decisions in a spatially structured population.

The spatial evolutionary game is a combination of classic game theory and cellular automaton, representing strategies, players, payoff function, structure of population, and an updating rule. This methodology can analyze various structures of populations using a regular lattice (46), scale-free networks (47), and real social networks (48). This concept requires an updating policy based on the payoff function with different updating schemes such as synchronous or asynchronous updates. Several common updating schemes are reviewed by Newth (50) and update rules are summarized by Roca, Cuesta, Sanchez (51).

This paper first presents in Section 3.2 a conceptual model which relates the spatial game using information transmission to the spread of epidemics. Then a mathematical model is

constructed in Section 3.3, and a small example and sensitivity analysis is shown in Section 3.4. In Section 3.5, we demonstrate the calculations of the reproductive ratio (R_0). A brief summary is presented in Section 3.6.

3.2 Conceptual Model

The basic idea of changing human behavior based on information dissemination is described in Figure 3.1. When the first infected individual is discovered in a community, the infectious disease starts spreading in the local neighborhood. At the same time, information about the disease such as transmission patterns, infection rate, prevalence populations and locations, mortality, and other relative information is spread through word-of-mouth or informal networks, reports on newspaper, radio, and TV or online. People make decisions after acquiring this information. Some might take protective measures to prevent being infected. Therefore, these human behavior changes impact the spread of underlying infectious diseases.

To model the process of changes of human behaviors, a spatial game is applied to the epidemic. Combining a spatial game and the epidemic is done by integrating the transmission process into the spatial game. The basic transmission process can be illustrated by employing the classic compartmental SIR model which represents susceptible, infected, and recovered individuals, as shown in Figure 3.2.

Figure 3.1 Conceptual model

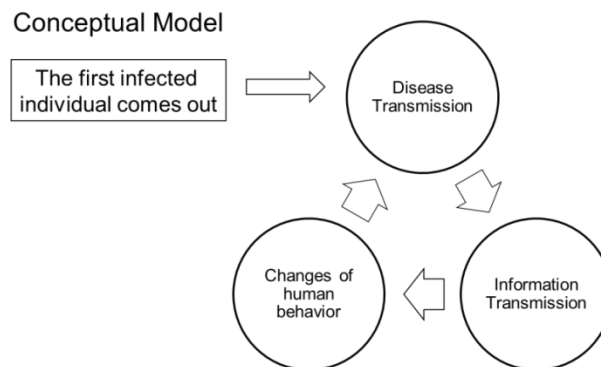
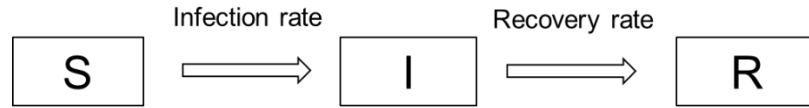


Figure 3.2 SIR model



A popular approach to present the SIR system dynamics model is using a system of ordinary differential equations (66):

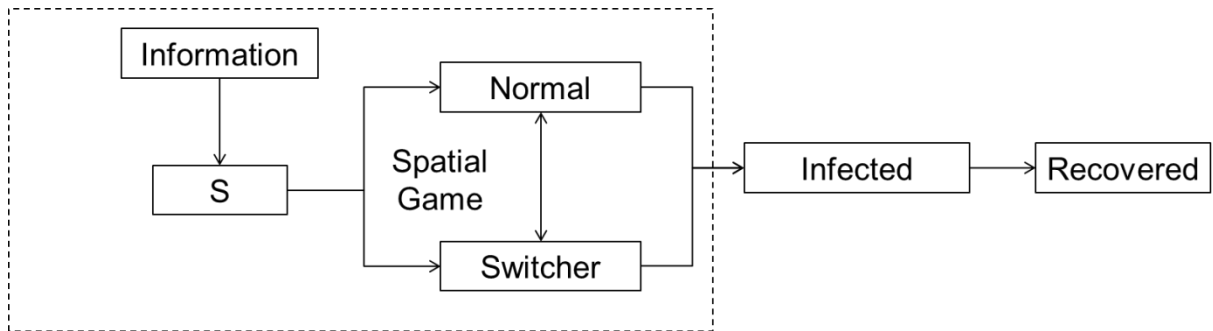
$$\frac{dS}{dt} = -\frac{1}{N}\beta SI$$

$$\frac{dI}{dt} = \frac{1}{N}\beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

Given human behavior when individuals acquire information about infectious diseases corresponding to the ongoing epidemic, a susceptible individual can adopt one of two different strategies: normal or switch. Normal strategy means the individual decided to maintain the status quo and do nothing to prevent the possible infections and such individuals here are called normal individuals. The name “normal” is based on the “status quo bias” individual facing when making decision making. The switch strategy means an individual will make an effort to protect him or herself and such individual is called a switcher. The same concept is also defined as normal and altered populations (7). This process is shown in Figure 3.3, and then a mathematical model is constructed according to this concept.

Figure 3.3 SIR model with spatial game



3.3 Mathematical Model

3.3.1 Notations

To explain the whole process clearly, a list of notations is shown in this section. The population is assumed to be distributed in an m by n lattice and each location is indicated by (i, j) , where $i = 1, 2, \dots, m$ and $j = 1, 2, \dots, n$, are shown in Table 3.1.

Table 3.1 Parameters in the model

Parameters	Interpretation
m	number of rows in the lattice for population distribution
n	number of columns in the lattice for population distribution
(i, j)	location at the i th row and j th column in the lattice

The total four compartments in this model are normal individuals, switchers, infected individuals, and recovered individuals, all listed in Table 3.2.

Table 3.2 Notation for compartments

Parameters	Interpretation
$NORMAL(i, j)$	number of <i>normal individuals</i> in location (i, j)
$S(i, j)$	number of <i>switchers</i> in location (i, j)
$I(i, j)$	number of <i>infected individuals</i> in location (i, j)
$R(i, j)$	number of <i>recovered individuals</i> in location (i, j)
$NORMAL^t(i, j)$	number of <i>normal individuals</i> in location (i, j) at time t in Eq. (3.11)
$S^t(i, j)$	number of <i>switchers</i> in location (i, j) at time t in Eq. (3.12)
$I^t(i, j)$	number of <i>infected individuals</i> in location (i, j) at time t in Eq. (3.13)
$R^t(i, j)$	number of <i>recovered individuals</i> in location (i, j) at time t in Eq. (3.14)

Some additional notations for the distribution of population are used to denote the total number of individuals and population distribution in local and global perspectives, as shown in Table 3.3.

Table 3.3 Additional notations for population distribution

Parameters	Interpretation
$N(i, j)$	total number of individuals in location (i, j)
$S_l(i, j)$	portion of $N(i, j)$ who are <i>switchers</i> in the neighborhood of location (i, j) in Eq. (3.17)
$I_l(i, j)$	portion of $N(i, j)$ who are infected individuals in the neighborhood of location (i, j) in Eq. (3.15)
S_g	portion of individuals who are <i>switchers</i> in the population in Eq. (3.18)
I_g	portion of individuals who are infected individuals in the population in Eq. (3.16)

For the spatial game, several notations are defined and further discussed in the next section.

A brief description for these notations is shown in Table 3.4.

Table 3.4 Additional notations for population distribution

Parameters	Interpretation
$F_n(i, j)$	payoff value for <i>normal individuals</i> in location (i, j) in Eq. (3.1)
$F_s(i, j)$	payoff value for <i>switchers</i> in location (i, j) in Eq. (3.2)
$G(\cdot)$	function for the estimated risk for <i>normal individuals</i> in local perspective in Eq. (3.3)
$H(\cdot)$	function for the estimated risk for <i>normal individuals</i> in global perspective in Eq. (3.4)
$g(\cdot)$	function for <i>switchers</i> externality in local perspective in Eq. (3.5)
$h(\cdot)$	function for <i>switchers</i> externality in global perspective in Eq. (3.6)
k_c	average cost of switching strategy in Eq. (3.2)
λ	associated risk reduction due to the <i>switch</i> strategy in Eq. (3.2)
m_1	multiplier of local prevalence status in Eq. (3.3)
m_2	multiplier of global prevalence status in Eq. (3.4)
c_1	multiplier of local externality from <i>switchers</i> in Eq. (3.5)
c_2	multiplier of global externality from <i>switchers</i> in Eq. (3.6)
$P_{ij}(n \rightarrow s)$	probability of an individual switching from strategy <i>normal</i> to strategy <i>switch</i> in location (i, j) in Eq. (3.7)
θ	intensity of selection, i.e. rationality of the decision maker in Eq. (3.7)

For the disease transmission process, infection rate, recovery rate, number of effective contacts, and the associated parameter are shown in Table 3.5.

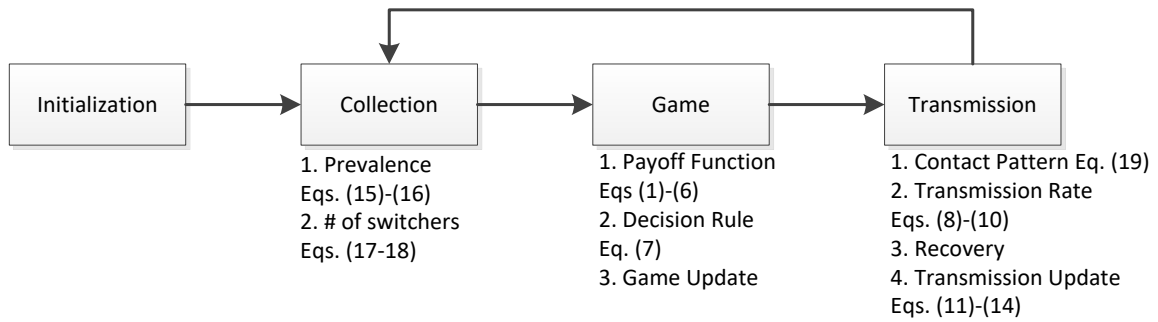
Table 3.5 Notations for transmission of infectious diseases

Parameters	Interpretation
$P_{trans_n}(i, j)$	transmission rate for <i>normal individuals</i> in location (i, j) in Eq. (3.8)
$P_{trans_s}(i, j)$	transmission rate for <i>switchers</i> in location (i, j) in Eq. (3.9)
$C_I(i, j)$	total number of effective contacts with infected individuals for <i>normal individuals</i> in location (i, j) in Eq. (3.10)
$C_{ij}(s, t)$	number of effective contacts with infected individuals in neighborhood location (s, t) for <i>normal individuals</i> in location (i, j) in Eq. (3.10)
$N_{ij}(s, t)$	total number of effective contacts in neighborhood location (s, t) for <i>normal individuals</i> in location (i, j) in Eq. (3.19)
β	infection rate per contact between <i>normal individuals</i> and <i>infected individuals</i> in Eqs. (3.8) and (3.9)
γ_1	contact reduction rate for <i>switchers</i> in Eq. (3.19)
γ_2	infection reduction rate for <i>switchers</i> in Eq. (3.9)
n_1	average number of contacts to individuals in a neighborhood grid(s) except its own grid for a <i>normal individual</i> in Eq. (3.19)
n_2	average number of contacts to individuals in the same grid for a <i>normal individual</i> in Eq. (3.19)
μ	Average recovery rate in Eqs. (3.25) and (3.26)

3.3.2 Detail Processes of the Model

The mathematical model describing the transmission of an epidemic consists of four steps as shown in Figure 3.4. In these four steps, there is a loop among the last three steps. The first step goes through the initialization process. Then a loop goes through the collection process, game process, transmission process, and then back to collection process. All details of each process will be discussed in the following subsection.

Figure 3.4 Process of spatial game in epidemics



3.3.2.1 Initialization

At the beginning, the various population distributions are initialized, including normal individuals, switchers, infected individuals, and recovered individuals. No recovered and switchers populations are generated in the first iteration, and it is assumed only one individual is infected initially.

3.3.2.2 Collection

Human responses to an infectious disease depend on many factors such as prevalence of the disease, mortality rate, means of transmission, and others. In this simple model, two major factors –the prevalence and the amount of switchers –are considered. The prevalence factor represents the potential risk of being exposed to the infectious disease, and the number of switchers determines the benefit of switching. Throughout this chapter, we assume that individuals have the complete information, i.e. individuals clearly know how many people are infected and the number of switchers. Moreover, two types of information are represented in our model: local and global information, each with different impacts on the spatial game. Thus, four types of information are considered in the model: local prevalence, global prevalence, local number of switchers, and global number of switchers.

3.3.2.3 Game

As illustrated in Figure 3.4, the Game step is divided into three main procedures as the main part of the spatial game, including payoff function, decision rule, and game update. The details are discussed in the following four subsections.

Payoff Function

It is assumed that individuals will adopt the switching strategy if the risk of the infectious disease is high enough. Judgment of threat or risk for each individual is mainly based on two aspects: the percentage of population infected in their local neighborhoods (local prevalence status) and the percentage of infection in the global environment (global prevalence status). The information of local and global prevalence status can be practically obtained through television, newspaper, radio, etc.

With the current information, individuals could decide to change their strategies spontaneously based on the benefit and cost, which includes their judgment about potential risk and the cost associated with the protective behaviors, which are modeled as the payoff function. In addition, switchers could create externality, which means that normal individuals could also benefit from switchers' efforts, since the aggregate effects of switching beyond reducing one's own potential risk of infection is also reducing the overall transmission or the spread of the disease (6).

From this point of view, payoff functions for normal individuals or switchers are defined as follows:

$$F_n(i, j) = -G(I_l(i, j))g(S_l(i, j)) - H(I_g)h(S_g) \quad (3.1)$$

$$F_s(i, j) = -k_c + \lambda F_n(i, j) \quad (3.2)$$

where

$$G(I_l(i, j)) = m_1 I_l(i, j) \quad (3.3)$$

$$H(I_g) = m_2 I_g \quad (3.4)$$

$$g(S_l(i, j)) = \frac{1}{1+c_1 S_l(i, j)} \quad (3.5)$$

$$h(S_g) = \frac{1}{1+c_2 S_g} \quad (3.6)$$

Given a contact network, $I_l(i, j)$ represents the portion of $N(i, j)$ who are infected individuals in the neighborhood of location (i, j) , I_g represents the portion of individuals who are infected in the entire population, $S_l(i, j)$ represents the portion of $N(i, j)$ who are *switchers* in the neighborhood of location (i, j) , and S_g represents the portion of individuals who are *switchers* in the whole population.

Equations (3.1) and (3.2) define payoff functions for *normal individuals*, $F_n(i, j)$, and *switchers*, $F_s(i, j)$, in location (i, j) , respectively. *Normal individuals* pay nothing for protective behavior since they do not spend any additional efforts for protection. *Switchers*, however, pay a cost for preventive efforts. In Eq. (3.2), the parameter, k_c , is denoting the cost of such *switching* strategy. Parameter λ is the associated risk reduction due to the *switch* strategy.

Functions $G(\cdot)$ and $H(\cdot)$ in Eq. (3.1), which are defined in Eqs. (3.3) and (3.4), denote the estimated risk for *normal individuals*, which is calculated by local and global prevalence status as discussed above. It is hard to require *normal individuals* to make accurate estimates of the risk; however, the prevalence status (e.g., knowledge on the percentage of population that got infected based on public information) could be an important reference for them. In this paper, the estimate for the risk and conversion from the risk to the payoff value, based on the real prevalence status, is modeled by a simple linear relationship. Specifically, m_1 denotes a multiplier of local prevalence status (local information) and m_2 denotes a multiplier of global prevalence status (global information). These two parameters are defined to help translate the prevalence status to the payoff value.

Functions $g(\cdot)$ and $h(\cdot)$ in Eq. (3.1), which are defined in Eqs. (3.5) and (3.6), denote the externality of *switchers* for local and global environments. As discussed above, *switchers* create local and global externality (potential benefits) for the entire population, not just for themselves. Therefore, the more *switchers* in the location, the safer the place is. In Eqs (3.5) and (3.6), c_1 denotes the multiplier of “switch strategy” for local externality and c_2 denotes the multiplier of "switch strategy" for global externality.

Decision rule

In every iteration of the game, each susceptible individual makes a decision between being a *normal individual* or being a *switcher* through balancing the benefits and costs. Individuals will change their strategies with a probability according to the payoff. The probability function of switching in location (i, j) is shown as

$$P_{ij}(n \rightarrow s) = \frac{1}{1 + e^{-\theta(F_s(i,j) - F_n(i,j))}} \quad (3.7)$$

This update rule is also referred to as the *Fermi rule*, which is used widely in the literature (67,68), based on the Fermi distribution function. In Eq. (7), $P_{ij}(n \rightarrow s)$ denotes the probability of an individual switching from strategy *normal* to strategy *switch* in location (i, j) when comparing the differences in payoffs between $F_s(i, j)$ and $F_n(i, j)$. The parameter θ represents the intensity of selection on the differences between both payoff functions, $F_s(i, j)$ and $F_n(i, j)$, which models the rationality of the decision maker. If payoffs of the different strategies are the same, i.e., $F_s(i, j) - F_n(i, j) \rightarrow 0$, individuals would choose either strategy with equal chance. If, the parameter θ itself equals zero, individuals will also choose either strategy with the probability of 50%, and in this case, the individual is making random choices with equal chance. When parameter θ approaches infinity, players will definitely choose the strategy with the higher payoff.

Similarly, we could also define the probability function of switching from *switchers* to *normal individuals* in location (i, j) as $P_{ij}(s \rightarrow n)$. Hence, the transmission matrix in spatial game between *switchers* and *normal individuals* is shown below:

$$\begin{array}{cc} & \begin{array}{cc} \text{Normal} & S \end{array} \\ \begin{array}{c} \text{Normal} \\ S \end{array} & \begin{bmatrix} 1 - P_{ij}(n \rightarrow s) & P_{ij}(n \rightarrow s) \\ P_{ij}(s \rightarrow n) & 1 - P_{ij}(s \rightarrow n) \end{bmatrix} \end{array}$$

In general, the switching processes for *normal individuals* and *switchers* are independent. However, in our model we assume

$$P_{ij}(s \rightarrow n) = \frac{1}{1 + e^{-\theta(F_n(i,j) - F_s(i,j))}}$$

so that we have $P_{ij}(n \rightarrow s) + P_{ij}(s \rightarrow n) = 1$. The transmission matrix can be written as

$$\begin{array}{cc} & \begin{array}{cc} \text{Normal} & S \end{array} \\ \begin{array}{c} \text{Normal} \\ S \end{array} & \begin{bmatrix} 1 - P_{ij}(n \rightarrow s) & P_{ij}(n \rightarrow s) \\ 1 - P_{ij}(n \rightarrow s) & P_{ij}(n \rightarrow s) \end{bmatrix} \end{array}$$

Game update

After evaluating the payoffs, each susceptible individual at each spatial location update their strategies according to probability defined in Eq. (3.7). Each update period is referred to as one turn, whose length can be predefined by the users. In our test model presented in Section 4, the update period is assumed to be one day.

The number of normal individuals and switchers in the susceptible population is recalculated at each spatial location as individuals update their strategies. Hence, initial values of the matrices, and the normal and switchers' distributions, are updated after each iteration.

3.3.2.4 Transmission

In this article, transmission of the disease follows conventional transmission processes defined in the standard SIR model (Figure 3.2). The details are given below.

Contact Pattern

The contact pattern is an important factor which affects the dynamics of an epidemic. Most researchers rely on a presumed contact pattern with little or no empirical basis. In Mossong et al. (69), the authors provide the first large-scale quantitative approach to contact patterns relevant to how infectious diseases are transmitted. Theoretically, any type of contact pattern can be applied to the model (70). In this paper, a very simple contact pattern based on the Poisson counting process is assumed as described in Section 3.4. This contact pattern is used to analyze the characteristic of the model and the sensitivity of each parameter in the model. In the future, a more complicated and realistic contact pattern will be considered to extend this model.

Transmission rate

The transmission process is based on the simple SIR model. In this paper, different transmission rates and contact rates are defined for *normal individuals* and *switchers*, respectively. For *switchers*, there is a reduction in transmission rate due to the change of behaviors, such as social distancing. The probability function for transmission of the underlying disease in one specific location, say (i, j) , is defined as follows:

$$P_{trans_n}(i, j) = 1 - (1 - \beta)^{C_I(i, j)} \quad (3.8)$$

$$P_{trans_s}(i, j) = 1 - (1 - \gamma_2 \beta)^{C_I(i, j)} \quad (3.9)$$

$$C_I(i, j) = \sum_{(s, t) \in neighborhood} C_{ij}(s, t) \quad (3.10)$$

where γ_2 is the infection rate reduction for *switchers*, $C_I(i, j)$ denotes the total number of contacts with infected individuals in its own location and in its neighborhood for an individual in location (i, j) , and $C_{ij}(s, t)$ denotes the number of contacts with infected individuals in its neighborhood location (s, t) for an individual in location (i, j) , and β denotes the transition rate between infected and susceptible individuals.

Recovery

Infected individuals usually stay infected over a period of time depending on the underlining disease, and recover from the disease on a certain day with a specific probability. The recovery probability distribution can be defined according to the specific disease.

Transmission update

Define $NORMAL^t(i, j)$ to be the number of *normal* individuals in location (i, j) at time t , $S^t(i, j)$ to be the number of *switchers* in location (i, j) at time t , $I^t(i, j)$ to be the number of infected individuals in location (i, j) at time t , and $R^t(i, j)$ to be the number of recovered individuals in location (i, j) at time t . After the transmission process, each location updates its properties as follows:

$$NORMAL^{t+1}(i, j) = (NORMAL^t(i, j) + S^t(i, j)) * (1 - P(n \rightarrow s)) - \Delta(NORMAL^t(i, j)) \quad (3.11)$$

$$S^{t+1}(i, j) = (NORMAL^t(i, j) + S^t(i, j)) * P(n \rightarrow s) - \Delta(S^t(i, j)) \quad (3.12)$$

$$I^{t+1}(i, j) = I^t(i, j) + \Delta(NORMAL^t(i, j)) + \Delta(S^t(i, j)) - \Omega(I^t(i, j)) \quad (3.13)$$

$$R^{t+1}(i, j) = R^t(i, j) + \Omega(I^t(i, j)) \quad (3.14)$$

where $\Delta(NORMAL^t(i, j))$ and $\Delta(S^t(i, j))$ denote the number of individuals infected at time t , from *normal individuals* and *switchers*, respectively. $\Omega(I^t(i, j))$ denotes the number of infected individuals recovered at time t . $I^t(i, j)$, in (3.13) represents, at time t , the infected population in location (i, j) and $R^t(i, j)$, in (3.14) represents, at time t , the recovered population in location (i, j) .

3.4 Test bed

In this section, a small example is constructed to analyze the characteristics of this model. Consider a small region with m by n locations in a regular lattice where $m=5$ and $n=5$, and 100

individuals who live in each location. Initialize the population as follows: $N(i, j)$ denotes the number of individuals in location (i, j) , $I(i, j)$ denotes the number of infected individuals in the location (i, j) , $S(i, j)$ denotes the number of *switchers* in the location (i, j) , $NORMAL(i, j)$ denotes the number of *normal* individuals in location (i, j) , and $R(i, j)$ denotes the number of recovered individuals in the location (i, j) . On the first day, one infected person exists in the focal site and all other individuals are *normal* individuals.

The contact pattern is based on the *Moore neighborhood* (46), which means individuals will contact others only in the adjacent eight locations and in their own location. Hence the number of $I_l(i, j)$, I_g , $S_l(i, j)$, and S_g in Eq. (3.1) can be calculated in Eqs. (3.15-3.18).

$$I_l(i, j) = \frac{\sum_{k=\max(i-1,1)}^{\min(i+1,m)} \sum_{l=\max(j-1,1)}^{\min(j+1,n)} I(k, l)}{\sum_{k=\max(i-1,1)}^{\min(i+1,m)} \sum_{l=\max(j-1,1)}^{\min(j+1,n)} N(k, l)} \quad (3.15)$$

$$I_g = \frac{\sum_{k=1}^m \sum_{l=1}^n I(k, l)}{\sum_{k=1}^m \sum_{l=1}^n N(k, l)} \quad (3.16)$$

$$S_l(i, j) = \frac{\sum_{k=\max(i-1,1)}^{\min(i+1,m)} \sum_{l=\max(j-1,1)}^{\min(j+1,n)} S(k, l)}{\sum_{k=\max(i-1,1)}^{\min(i+1,m)} \sum_{l=\max(j-1,1)}^{\min(j+1,n)} N(k, l)} \quad (3.17)$$

$$S_g = \frac{\sum_{k=1}^m \sum_{l=1}^n S(k, l)}{\sum_{k=1}^m \sum_{l=1}^n N(k, l)} \quad (3.18)$$

In this model, assume the number of interactions for each individual follows the Poisson distribution and most contacts happen for individuals in the same site. Three parameters are defined to determine the interaction patterns, which are γ_1 , n_1 , and n_2 . Parameter γ_1 denotes the decreasing rate of interactions, which means the *switchers* will contact fewer individuals than *normal* individuals do; n_1 and n_2 denote the average number of contacts to individuals in a neighborhood grid(s) and to those in the same grid for a *normal* individual, respectively. $N_{ij}(s, t)$ denotes the number of contacts in location (s, t) for an individual in location (i, j) . Hence, the probabilities that an individual has k contacts with his/her neighborhood locality/community

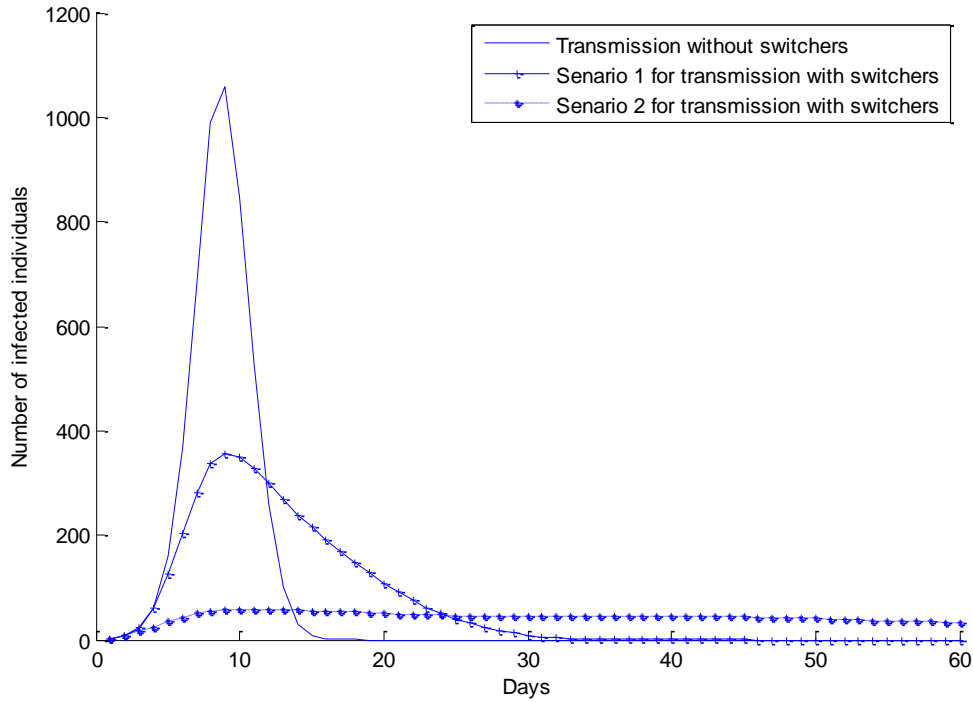
and home locality/community are modeled using Poisson distributions, and their definitions are given in Eq. (3.19), respectively:

$$P(N_{ij}(s, t) = k) = \begin{cases} \frac{e^{-\gamma_1 n_1} (\gamma_1 n_1)^k}{k!}, k = 0, 1, 2 \dots & s = i - 1, i, i + 1 \quad t = j - 1, j, j + 1 \quad (s, t) \neq (i, j) \\ \frac{e^{-\gamma_1 n_2} (\gamma_1 n_2)^k}{k!}, k = 0, 1, 2 \dots & (s, t) = (i, j) \end{cases} \quad (3.19)$$

where $0 \leq \gamma_1 \leq 1$ for *switchers* and $\gamma_1 = 1$ for *normal* individuals. Equation (19) denotes the two cases in which contacts happen in the neighborhood locality and in the home locality. Hence, the number of individuals in the neighborhood who create contacts has a Poisson distribution with the average n_1 for *normal* individuals and the average $\gamma_1 n_1$ for *switchers*. Similarly, the number of individuals in the same cell subpopulation has a Poisson distribution with average n_2 for the *normal* individuals and average $\gamma_1 n_2$ for *switchers*.

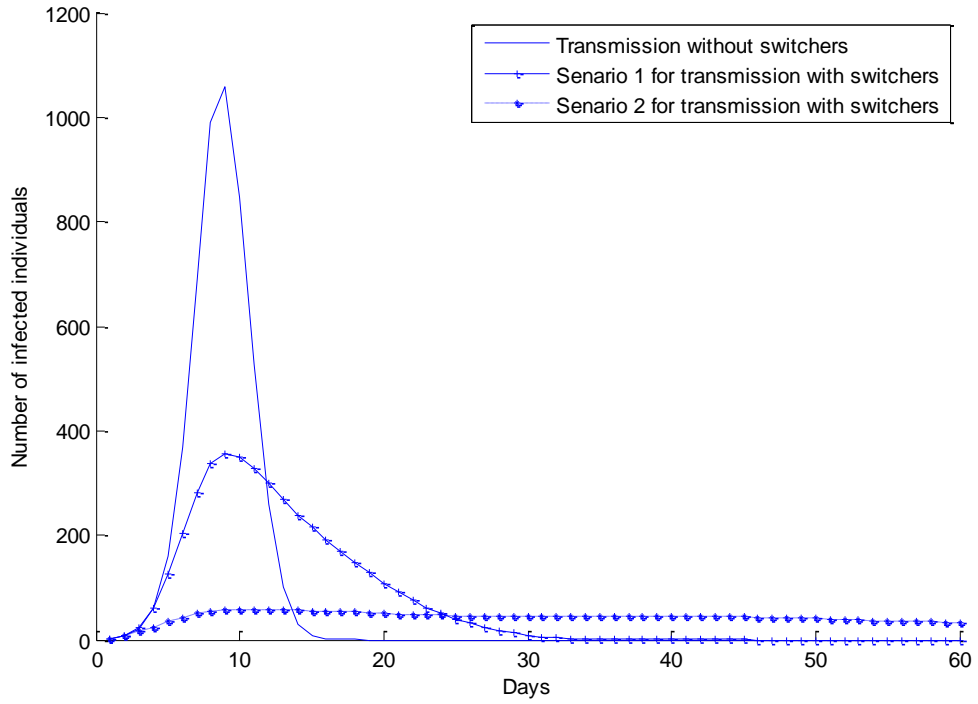
The parameters for scenario 1 with *switchers* are initialized as follows: $k_c=3$, $\lambda=0.5$, $m_1=100$, $m_2=10$, $c_1=1$, $c_2=1$, $\theta=1$, $\gamma_1=0.5$, and $\gamma_2=0.5$. The transmission rate per effective contact with an infected person is defined as, $\beta=0.2$. The recovery probability distribution is fixed and defined as [0.3, 0.4, 0.2, 0.1]. Infected individuals will recover from the disease at the end of the first infected day with the probability 0.3, at the end of the second infected day with probability 0.4, at the end of the third infected day with probability 0.2, and at the end of the fourth infected day with probability 0.1. The contact pattern is defined as $n_1=0.5$, and $n_2=8$ (on average an individual contacts half of the individual in its neighborhoods and eight individuals in his or her own location per day). The model is simulated for a period of 60 days and it runs 100 times. In addition, there are two more scenarios: scenario 2 with *switchers* and scenario without *switchers*. In scenario 2 with *switchers*, values of four parameters are changed: $m_1=500$, $m_2=100$, $\gamma_1 = 0.25$ and $\gamma_2=0.25$. The simulation result is shown in Figure 3.5.

Figure 3.5 Total number of infected individuals on each day



In the scenario without *switchers*, the spread only lasts less than 20 days but leads to 2469 individuals being infected. In the scenario 1 with *switchers*, a total of 2115 individuals are infected, which is less than the previous case. The epidemic lasts around 30 days and close to 84% of individuals is infected in this episode. Around the 9th day, the epidemic is at its peak and there are nearly 360 individuals on infected status that day, compared to the nearly 1057 infected individuals at the peak with no switching. Obviously, disease transmission is delayed effectively due to the switching strategy. Considering higher awareness to information and stronger preventive measures through increasing values of m_1 and m_2 and decreasing values of γ_1 and γ_2 , the epidemic is contained effectively in scenario 2. The number of infected individuals keeps less than 50 on each day and decreases gradually.

Figure 3.6 Change of number of individuals on each compartment over time



The number of *normal individuals*, *switchers*, infected individuals and recovered individuals on each day in scenario 1 are also shown in Figure 3.6. As the number of infected

Figure 3.7 Change of portion of normal individuals and switchers

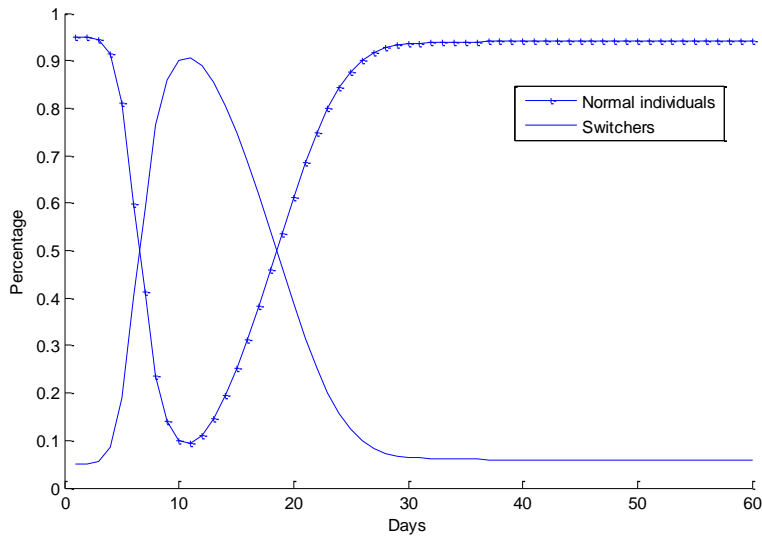
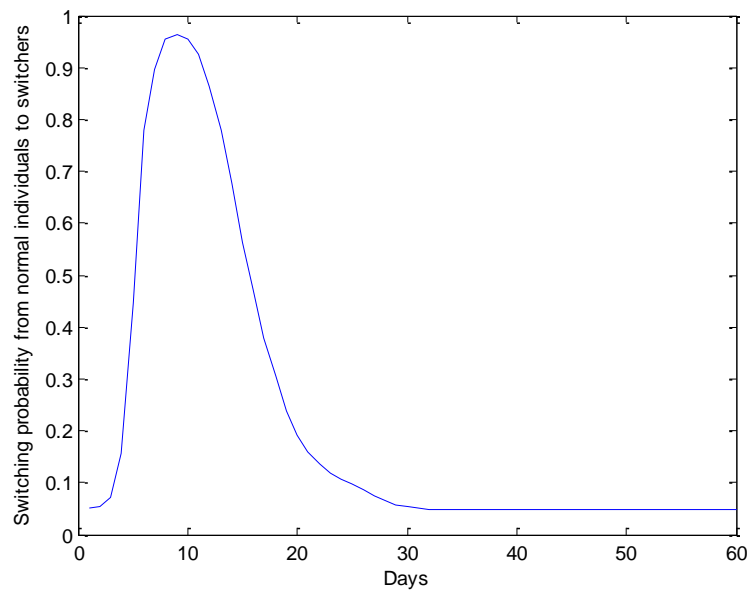


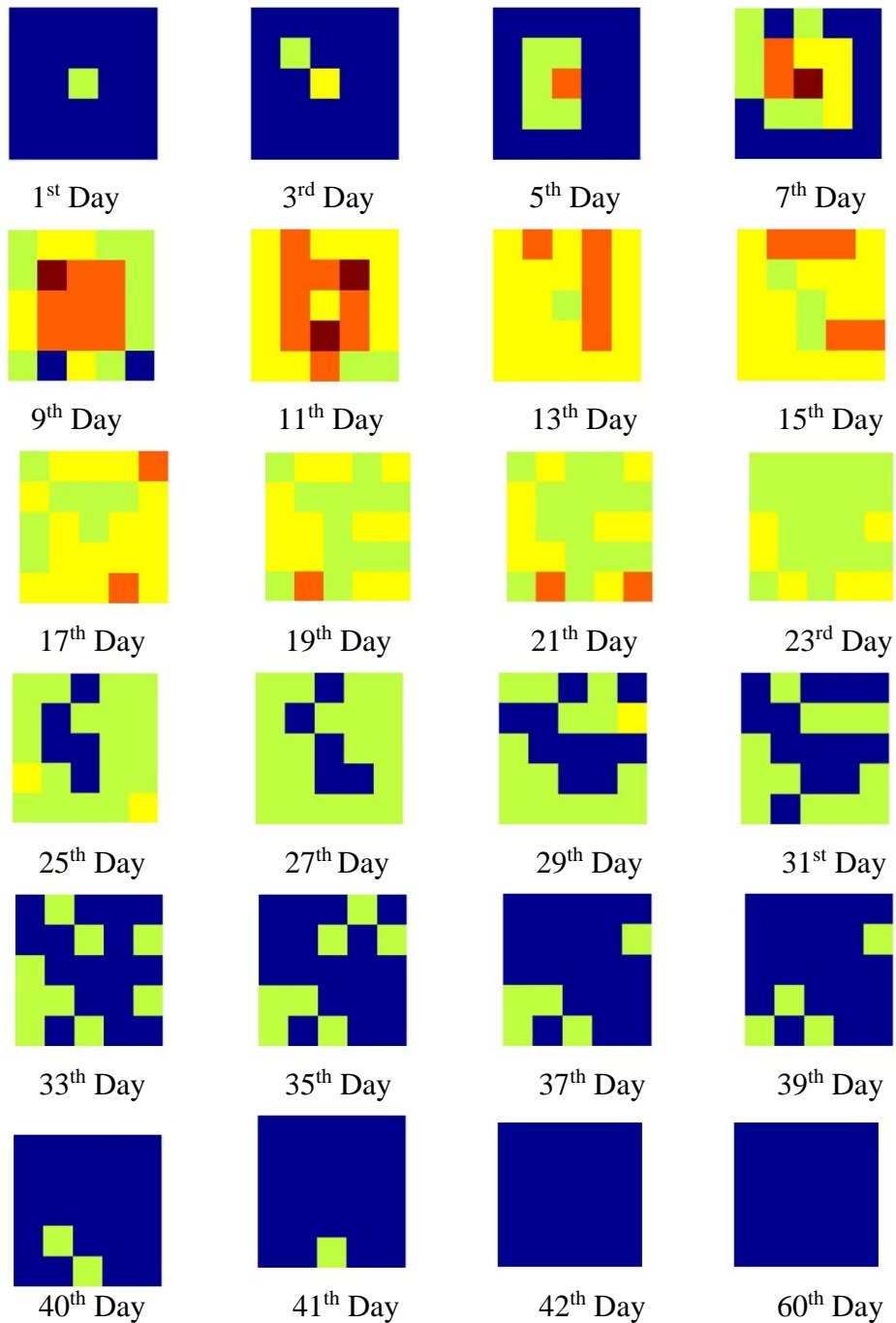
Figure 3.8 Switching probability from normal individuals to switchers in location (3,3)



population increases, *normal individuals* obtain the information about the infectious disease and some of them will become *switchers*, so the number of *switchers* also increases. After most of infected individuals recover, *switchers* will become back to *normal individuals*. Hence, there are nearly not any *switchers* eventually. The portion of susceptible individuals on each day who are *normal individuals* and *switchers* respectively is shown in Figure 3.7 and the switching probabilities i.e., $P_{ij}(s \rightarrow n)$ at location (3,3) over time is shown in Figure 3.8.

The evolutionary process of transmission of the infectious disease in the scenario 1 with switchers is shown in Figure 3.9.

Figure 3.9 The evolutionary process of transmission of the infectious disease for 60 days



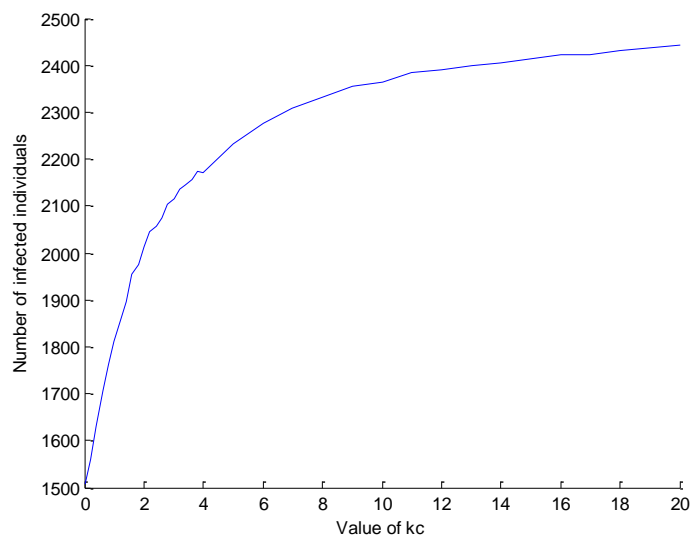
(There are no infected individuals in the blue locations; there are less than five infected individuals in the green locations; there are less than 10 infected individuals in the yellow locations; there are less than 15 infected individuals in the orange locations; and there are more than 15 infected individuals in the red locations.)

3.5 Parameters Analysis

3.5.1 Sensitivity analysis

There are a total of nine system parameters in this model, k_c , λ , m_1 , m_2 , c_1 , c_2 , θ , γ_1 , and γ_2 , respectively. The definitions of these parameters are summarized in Tables 4 and 5. To verify the influence of these parameters on the dynamic process of the epidemic, the sensitivity analysis will be made for each parameter. However, the goal of the game part is to provide a criterion concerning when individuals prefer to keep themselves from epidemics. Hence, the absolute value of payoff is meaningless and only relative value which is payoff for *normal individuals* over payoff for *switchers* is important. From this point of view, the relative value of the parameter is emphasized in the sensitivity analysis. For example, if m_1 is 100 and m_2 is 10, this indicates the effect of m_1 is 10 times that of m_2 . Other values can also be set for m_1 and m_2 , but values of other parameters are required to change correspondingly.

Figure 3.10 Change of k_c



3.5.1.1 Impacts on the cost of switch strategy (k_c)

The parameter k_c evaluates the cost of choosing a strategy switch (e.g., undertaking the social distancing) for a susceptible individual. Considering k_c , ranging from 0.0 to 20.0, the changes of total infected individuals are shown in Figure 3.10.

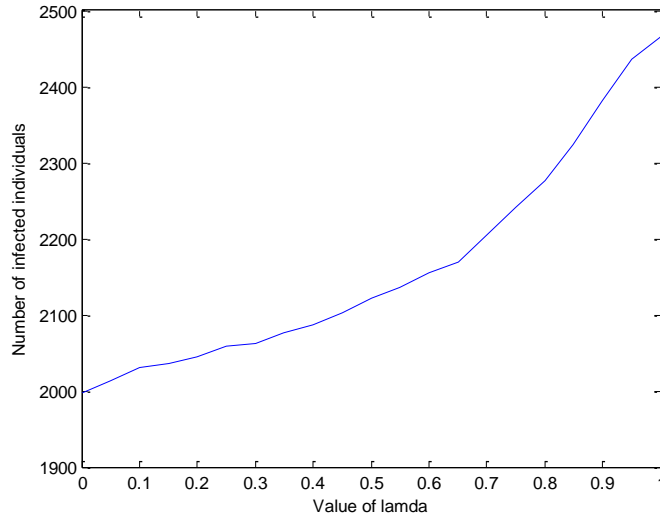
When the value of k_c (i.e., the costs undertaking the switch strategy) increases, fewer susceptible individuals will choose the switch strategy so that more individuals are exposed to the risk of infection. In the real world, the value of k_c represents the associated cost if a person chooses to avoid contacting others, for example, the loss of business or other opportunity incomes, purchasing costs for self-protection or isolation equipment, or voluntary vaccination and so on. Hence, when the value of k_c is big enough, very few susceptible individuals will choose the switching strategy so that almost all individuals are infected and the result is very similar to the scenario without *switchers*.

3.5.1.2 Impacts of the associated risk reduction due to the switch strategy (λ)

The parameter λ in Eq. (3.2), ranging from 0 to 1 denotes individuals' estimated benefits from the switch strategy (in terms of prevention of the disease). If $\lambda = 0$, individuals will evaluate that *switchers* absolutely avoid infection from infected individuals. However, if $\lambda = 1$, the switch strategy does not help individuals prevent getting the disease at all. The simulated result over the possible range is shown in Figure 3.11.

The trend of this Figure 3.11 is straightforward and self-explanatory. An increasing number of individuals are being infected as the estimate effectiveness of switch strategy (λ) becomes worse, which leads to very small portion of individuals choosing the switch strategy. A larger population of *normal* individuals means more individuals are exposed to the risk, so more individuals are infected.

Figure 3.11 Total infected population based on different values of λ



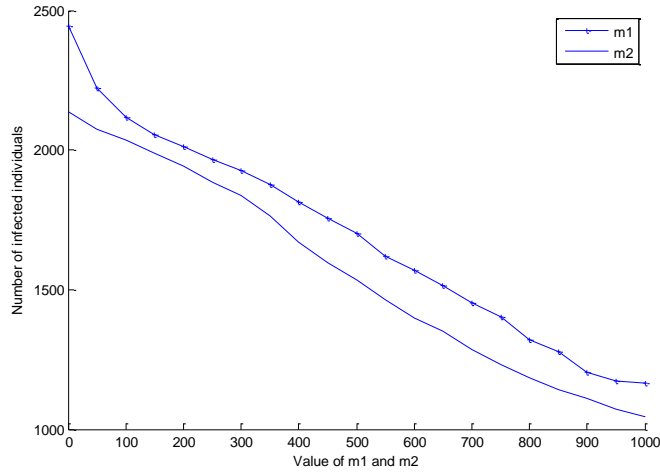
3.5.1.3 Changes of multipliers of local and global prevalence status m_1 and m_2

In the spatial game section, m_1 and m_2 are extremely significant parameters in the proposed model, which determine the subjective estimation of risks from susceptible individuals via either local or global information or knowledge. The main information sources of estimate of disease can be either from local status or global situations. In this paper, local status is defined as more important than the global situation since local information is much closer to individuals than is global. Although the estimate is the same for *normal individuals* and *switchers*, the function of parameter k_c will be weakened when m_1 and m_2 are big numbers. The influence of m_1 and m_2 are set to be similar in our test model since the size of the simulated region is small. Figure 3.12 depicts the simulated results when m_1 and m_2 ranges from 0 to 1000.

The total number of infected individuals decreases as m_1 (local risk perceptions) or m_2 (global risk perceptions) increase. When m_1 is small, individuals will have an underestimate about the risk of infection and most of individuals will be *normal individuals*. When m_1 becomes

significantly large, the influence of k_c can be ignored and almost all susceptible individuals chose the switch strategy. The effects for m_2 is similar to m_1 .

Figure 3.12 Change m_1 and m_2



3.5.1.4 Changes of estimated externality parameters c_1 and c_2

In Eqs. (3.5) and (3.6), parameters c_1 and c_2 denote the estimated externality of *switchers* for both *normal* individuals and *switchers*, respectively. They frequently represent the estimate of risk reductions to infectious disease due to *switchers*. Similarly, the effectiveness of c_1 and c_2 are fairly similar if the simulated region is too small. However, the local impact is assumed to be stronger than the global impact (m_1 is 10 times of m_2), c_2 which denotes the global externality of *switchers* has little influence to the switching rate. Figure 13 depicts simulated results based on c_1 and c_2 being changed from 0 to 10.

It is obvious from Figure 3.13 that as the value of c_1 increases, the total number of infected individuals also increases. The basic reason is the over-estimate to the externality from *switchers*. Large values of c_1 will result in larger payoff for *normal individuals* (Eq. (3.5)). Intrinsically, there will be fewer susceptible individuals choosing the switch strategy and more individuals will be

exposed to the infectious disease, which will eventually lead to a more-infected population. The effects of c_2 are relatively less significant than that of the c_1 , which mean the externality of the *normal* population is much more dominant comparing to the externality of the *switchers*.

Figure 3.13 Total infected population based on different values of c_1 and c_2

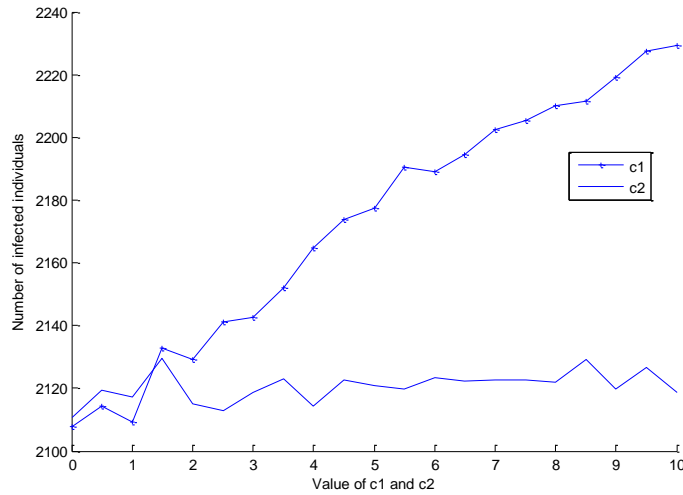
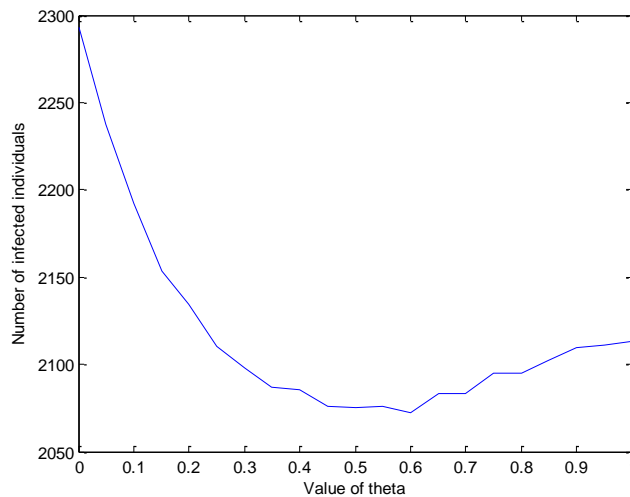


Figure 3.14 Change in selection intensity parameter θ



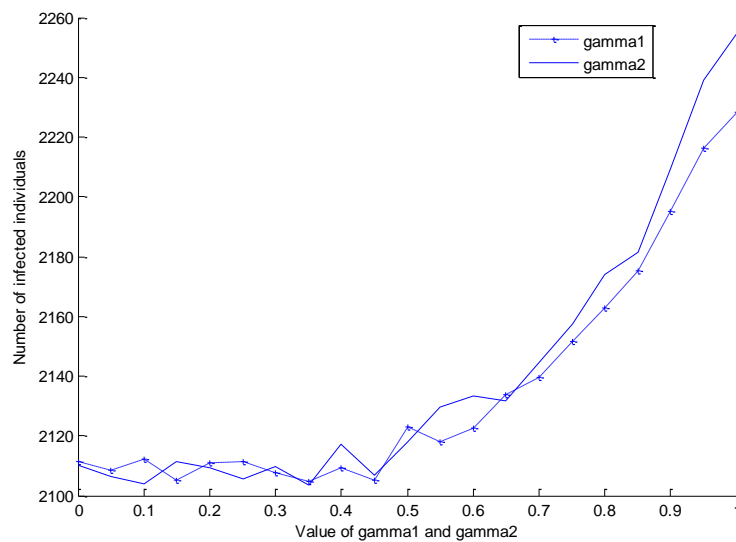
3.5.1.5 Change of intensity of selection θ

The parameter θ in Eq. (3.7) denotes the intensity of selection, which shows the extent of rationality (or irrationality) in human behaviors. If θ is equal to 0, the game is useless and

individuals will choose either strategy randomly since the choice of strategy ignores the difference in their corresponding payoffs. A large value of θ means strong intensity of selection and the decision of individuals' strategies are vastly contingent upon the difference in payoffs. Figure 14 shows the influences of different values of θ .

3.5.1.6 Changes of parameters related to the decreasing rate of interactions for switchers

Figure 3.15 Total infected population based on different values of γ_1 and γ_2



In Eqs. (3.19) and (3.9), γ_1 and γ_2 are two essential parameters which determine the real effectiveness of the switch strategy. If either of them is equal to zero, the *switcher* will definitely avoid infection from the infected person. In the real world, γ_2 will be zero when the individual is vaccinated effectively and could be treated as a recovered individual. If the *switcher* does not contact any other individuals, γ_1 will be zero and obviously the *switcher* is not infected. Result of changing γ_1 and γ_2 are shown in Figure 3.15.

Low value of γ_1 and γ_2 could effectively prevent individuals from infectious disease. Many are still being infected because most individuals do not choose the *switch* strategy, according to the spatial game rule.

3.5.2 Calculating R_0

The basic ratio R_0 is defined as “the average number of secondary cases arising from an average primary case in an entirely susceptible population” (71). In the deterministic SIR model, R_0 could be calculated as the ratio of transmission rate over the recovery rate. In the stochastic SIR model on a contacting network, the basic reproductive ratio can be estimated as \hat{R}_0 by (64,72,73):

$$\hat{R}_0 = TD_k \quad (3.20)$$

$$D_k = \bar{k} - 1 + Var(k)/\bar{k} \quad (3.21)$$

where T is the probability of infection per contact, D_k represents the effective number of contacts for each individual in the network, and \bar{k} denotes the average contacts for each individual. The basic reproductive number \hat{R}_0 defines a threshold similar to R_0 .

Here, *normal individuals* and *switchers* have different values of T and D_k . At any time t on location (i, j) , give us

$$\hat{R}_0^t(i, j) = p_n^t(i, j) * T_n^t(i, j) * D_{Kn} + p_s^t(i, j) * T_s^t(i, j) * D_{Ks} \quad (3.22)$$

$$p_n^t(i, j) = NORMAL^t(i, j)/(NORMAL^t(i, j) + S^t(i, j)) \quad (3.23)$$

$$p_s^t(i, j) = 1 - p_n^t(i, j) \quad (3.24)$$

$$T_n^t(i, j) = \beta/(\beta + \mu) \quad (3.25)$$

$$T_s^t(i, j) = \gamma_2\beta/(\gamma_2\beta + \mu) \quad (3.26)$$

$$D_{Kn} = \bar{k} - 1 + Var(k)/\bar{k} \quad (3.27)$$

$$D_{Ks} = \gamma_1\bar{k} - 1 + Var(\gamma_1k)/\gamma_1\bar{k} \quad (3.28)$$

where $p_n^t(i, j)$ represents the proportions of the susceptible population who did not practice social distancing on location (i, j) . A simple linear relationship between $\hat{R}_0^t(i, j)$ and $p_n^t(i, j)$: as the portion of *normal* individuals increases, a larger outbreak of the infectious disease will happen with a larger possibility. We use $R_n^t(i, j)$ to represent the basic reproductive ratio when there are

no *switchers* on location (i, j) . Similarly, $R_s^t(i, j)$ denotes the basic reproductive rate when all susceptible individuals are *switchers* on location (i, j) . To prevent the disease from spreading globally, the condition $\hat{R}_0(i, j) < 1$ should be satisfied, which implies

$$p_n^t(i, j) < (1 - R_s^t(i, j)) / (R_n^t(i, j) - R_s^t(i, j)) \quad (3.29)$$

$$R_n^t(i, j) = T_n^t(i, j) * D_{Kn} \quad (3.30)$$

$$R_s^t(i, j) = T_s^t(i, j) * D_{Ks} \quad (3.31)$$

$R_n^t(i, j)$ and $R_s^t(i, j)$ are defined in a similar way to $\hat{R}_0^t(i, j)$, but for the population in which all susceptible individuals are *normal individuals* and *switchers*, respectively.

From the spatial game update Eq. (3.7), we have

$$p_n^t(i, j) = \frac{1}{1 + \exp(-\theta((1-\lambda)F_n^t(i, j) + k_c))} \quad (3.32)$$

If $R_n^t(i, j) < 1$, $\hat{R}_0^t(i, j)$ will be less than 1 even without any *switchers*. If $R_s^t(i, j) > 1$, the infectious disease will spread out globally with only self-protective strategies when we do not consider any other forces such as some public policies and measures taken to control the epidemic. In this case, *switchers* could only slow down the transmission of infectious disease and reduce the number of infected individuals, but could not eliminate the epidemics. If $R_n^t(i, j) > 1$ and $R_s^t(i, j) < 1$, $p_n^t(i, j)$ from Eq. (32) can be plugged into the Eq. (29), solve the inequality for $F_n^t(i, j)$, we have

$$F_n^t(i, j) < \frac{-\theta k_c - \ln((R_n^t(i, j) - 1) / (1 - R_s^t(i, j)))}{\theta(1-\lambda)} = F_{critical} \quad (3.33)$$

$F_{critical}$ is the threshold from which the infectious disease will be controlled due to the *switchers'* impacts. When $F_n^t(i, j) < F_{critical}$, the infectious disease cannot spread out; otherwise *switchers* who changed their behaviors because of information dissemination cannot eradicate the epidemics.

If we assume the local information is much more effective than global information, we have

$$S_l(i, j) > \frac{1}{c_1} \left(\frac{-m_1 I_l(i, j)}{\frac{m_2 I_g}{1+c_2 S_g} + F_{critical}} - 1 \right) \approx \frac{1}{c_1} \left(\frac{-m_1 I_l(i, j)}{F_{critical}} - 1 \right) \quad (3.34)$$

If this simple inequality is satisfied, $\hat{R}_0(i, j)$ will be less than 1 which means that individuals' self-protective behaviors could eliminate the transmission of infectious disease.

3.5.3 Discussion

One key point behind this model is to study the incentives that motivate individuals to become *switchers* and how *switchers* effectively avoid getting infected by potential epidemics. Based on a sensitivity analysis of the model, most of the parameters have significant impacts on the disease-spreading processes; however, some are difficult to manage and control. For example, the parameters k_c , and θ can vary significantly from one individual to another with different occupations, different education level, different ethnical cultures, etc. Hence, parameters which are relatively easy to control will be the focus of the study. Parameters γ_1 and γ_2 in Eqs. (3.19) and (3.9) are good examples. More powerful antibiotic medicines, immunization, broadcast or education of prevention methods by the federal and local governments could effectively reduce the values of γ_1 and γ_2 , since *switchers* who adopted these strategies could have better resistances to the disease. This is one way to make *switchers* better protected. On the other side, government should lead susceptible individuals to recognize epidemic situations correctly and give them sufficient incentives to become *switchers*. Two other important factors are the speculative prevalence of the infectious disease (individual's perception of the prevalence of disease) by each individual, as the parameters m_1 and m_2 denoted in Eqs. (3.3) and (3.4). It is hard to collect complete and real-time disease-spreading information on all *normal* individuals. Two main

information sources are local information and more global information such as mass media (TV, radio, internet, social media and newspapers). Underestimating impact or spread of the disease could lead to a worsening situation. In such cases, increasing the dissemination of information will develop awareness of the infection risk to susceptible individuals and may convince them to protect themselves.

Although it is always better to prevent infectious disease from spreading, there is the possibility of vast unnecessary spending to promote protective measurements. A criterion generally used to evaluate the risk of an infectious disease is R_0 , which our model found that it can be different in different locations and is changed over time, representing the changes of human behaviors. Effective dissemination of information related to the infectious disease can control the proportion of *switchers* based on the assumption in our model. Hence, different information transmission strategies can be used by the government based on the value of R_0 at that time. If R_0 is smaller than one, no further information about the disease is necessary to be released to the public.

3.6 Summary

In this paper, a general spatial game model was presented to model the dynamics of transmission of an infectious disease, considering spontaneous changes of human behavior based on information acquired related to the disease. The model includes the consideration of information synthesis, individual decision making based on the tradeoffs between the benefits and costs of changing his or her behavior, information evaluation based on both local and global information with a heterogeneous population distribution. Without the loss of generality, a classical SIR model is assumed to be the underlying infectious disease behavior. A simple example was used to illustrate the characteristics of the model and to analyze how each of the modeling

parameters impacts the results. Most of the modeling parameters have significant impacts toward the underlying epidemic and we found some of them are very difficult to control. We believed that an overestimate of impacts of the infectious disease always helps to control the epidemic but sometimes at a prohibitively high and unnecessary cost. Hence, an effective strategy of information dissemination can be used to balance the benefits and costs, and the value of R_0 is an important criterion to determine the best information dissemination strategy for the government. Interestingly, the results from our computational experiments have shown that the disease's reproduction rate R_0 changes throughout the course of the epidemic and it varies from location to location due to the different population structure at different spatiality.

In addition, there are still some limitations in our model. First, a very simple contact pattern is given. In our model, individuals only contact their neighbors in the Moore neighborhood. However, long-distance travel and other type of contacts are not considered. Second, complete information assumption is not realistic. In reality, information about the infectious disease is not accurate and different individuals have different judgments. So a more complex rule to calculate individuals' estimates is required. Third, only SIR model is considered in the paper, additional efforts are still needed to incorporate the more complicated models such as SIRS model, SEIR model, and lethal rate of diseases into the spatial game.

Chapter 4 - Information Dissemination and Human Behaviors in Epidemics

Chapter 4 is based on the manuscript “Information Dissemination and Human Behaviors in Epidemics” submitted to plos one.

Abstract

Individuals experiencing an epidemic may change their behaviors to prevent themselves from infection by balancing the benefits and costs based on the information about the infectious disease. This study incorporated two types of information, local information, which impacts local human contacts, and global information, which impacts people’s travel behaviors, into a spatial evolutionary game to determine individuals’ decisions. This paper constructs a new behavior-switching-based susceptible-infected-recovered (SIR) model using a spatial evolutionary game to study the impact of human behaviors and information dissemination to the spread of infectious disease. This model was evaluated and analyzed using numerical simulations for the population in State of Kansas. Particularly, individuals’ perception to the risk based on the local information were deeply discussed, which could help us better understand the human behaviors and improve communication between policy makers and the public.

4.1 Introduction

The influence of human behaviors on infectious disease transmission has been a focused area of study for recent decade. Individuals often change their behaviors to prevent infection, including improving personal hygiene, taking antiviral medicine, implementing voluntary social

distancing, receiving voluntary vaccination, and other protective measures (4). These voluntary behaviors are referred to as spontaneous changes of human behaviors.

Funk (2) reviewed recent work on the influence of human behavior on the spread of infectious diseases. The rationality of self-protective behaviors based on information about infectious diseases has caused increased application of game theory to epidemiology (74-81). However, the literature only applies game theory to the mixed homogeneous population without considering the contact pattern. Hence, a study for the combined impacts of a spatially contact structure and spontaneous behavior changes using game theory would significantly improve existing models.

In addition, information transmission about the spread of infectious disease and individuals' perception to risk must be considered in order to study human behaviors. Chen (63) introduces a social sampling method to evaluate individuals' assessments of infectious disease prevalence based on acquired information. The model in (65) considers sexually transmitted infections, accounting for information transmission and individuals' responses to the infectious disease and showing that information transmission can reduce the prevalence of the infection.

A study described in (82) recently investigated a methodology that combines information dissemination, contact networks, and human behavior changes in order to model the dynamics of infectious diseases. A spatial evolutionary game was adopted to study the impact of human behavior changes on the dynamics of disease transmission. Human responses were determined by the spatial evolutionary game, based on the balance of benefits and costs evaluated from the information related to infectious disease, such as prevalence, severity, etc. Two types of susceptible individuals were considered: normal individuals and switchers. Switchers are typically more conservative than normal individuals and tend to protect themselves and reduce risks. All

susceptible individuals collected information about the infectious diseases (particularly indicating the number of infected individuals and the number of switcher) locally and globally and then made decisions based on that information. The impact of information to individuals' decisions (choose to be normals or switchers) referred to as the payoff in the spatial evolutionary game. Individuals could change their minds or stay on their current status (normal or switcher) based on their own and their neighbors' payoff values. Hence, the contact structures among individuals also played a key role in the spatial evolutionary game since these contact structures heavily impact the payoff values which explicitly determined individuals' decisions.

The spatial evolutionary game model in (82) successfully describes impacts of changes of human behaviors and information dissemination to the spread of infectious diseases, however, it is an unstructured system which is not easy to use analytical methods to analyze the system. In this paper, we applied it into a classical dynamic system which is commonly adopted to study epidemics and prove consistency between two models. To clarify the differences of these two models, the spatial evolutionary game model is named as (SEGM) and the modified dynamic model developed in this paper is named as (MDM). In addition, a new concept related to the impact of local information dissemination is introduced and discussed in this paper.

Section 4.1 of this paper includes a brief introduction, and Section 4.2 presents construction of a mathematical model to study the dynamic transmission of infectious disease using a spatial evolutionary game. Equilibrium analysis is shown in Section 4.3, and Section 4.4 demonstrates a numerical simulation and a comparison of simulation results using SEGM and MDM. The long-distance scenario is also introduced. A brief summary and discussion is presented in Section 4.5.

4.2 Mathematical Model

The basic assumptions in this paper, which are identical to the assumptions in (82), are briefly reviewed in this section, and the new modified dynamic model (MDM) is presented as one of the major objectives of this article. This model considers three main aspects of the an epidemic, including disease transmission, information dissemination, and change of human behaviors. Each of them is discussed in subsections 4.2.1, 4.2.2, and 4.2.3, respectively. Section 4.2.4 introduces the spatial evolutionary game, and MDM model is constructed in Section 4.2.5 and extended in Section 4.2.6.

4.2.1 Process description

Ordinary differential equations (ODEs) are commonly used to model disease transmission. One of the most classic models is

$$\frac{dS}{dt} = -\frac{1}{N}\beta SI \quad (4.1)$$

$$\frac{dI}{dt} = -\frac{1}{N}\beta SI - \gamma I \quad (4.2)$$

$$\frac{dR}{dt} = \gamma I \quad (4.3)$$

where S represents the number of susceptible individuals, I represents the number of infected individuals, R represents the number of recovered individuals, and N represents the number of individuals in the population. The model above is the classic susceptible-infected-recovered (SIR) model without demography (71).

4.2.2 Information Transmission

Increasing development of transportation and communication technologies has increased the spreading rate of infectious disease and the transmission of disease information. Individuals can acquire the information about the disease and current epidemics through a myriad of mediums,

including news broadcasts on television or radio, internet, face-to-face communication, or education about prevention from infectious disease. The acquired amount and accuracy of information consequently impact how individuals react to disease transmission and influence their decisions during an epidemic outbreak. Chen (63) studied how the quality of information affects the transmission of infectious disease.

In this paper, we assume individuals are well informed, meaning that individuals always acquire complete and correct information (no rumor spread among individuals) in all locations. In addition, information about the infectious disease is characterized as local information and global information. Local information, defined as information about the disease in neighborhoods within a certain distance from an individual's location, locally impacts individuals' contacts. Global information, defined as information about disease transmission in all locations, impacts individuals' decisions and travel behaviors. Both local and global information are considered within individuals' decision-making processes.

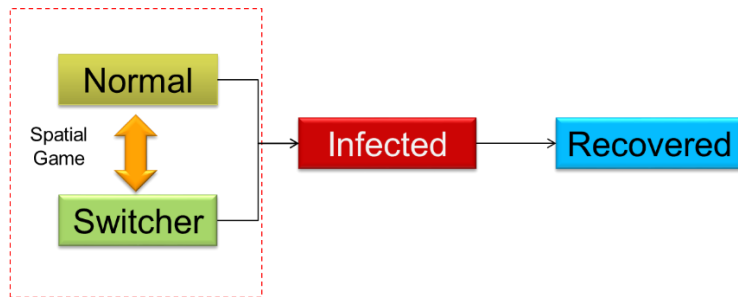
4.2.3 Change of Human Behaviors

Based on infectious disease information, some individuals may take protective measures to prevent infection and others may not, thereby revealing two distinct types of susceptible population: normal individuals and switchers. Normal individuals believe very little chance exists for their infection, so they do not attempt to change their behaviors to keep themselves from getting infected. Switchers, however, estimate the risk and assume a high probability of infection so they change their behaviors (such as taking antibiotic medicine, wearing face mask, avoiding crowded places, etc.) to attempt to avoid infection. Although switchers can be categorized according to the extent of their changes in behaviors, we assumed all switchers to be identical for this study, and

we did not consider multiple levels of switchers to retain model simplicity. We modified the classic SIR model to our MDM model, as shown in Figure 4.1.

In order to reduce exposure to disease, switchers commonly use the strategy of social distancing, which includes reducing the number of contacts, such as avoiding crowded places, limiting friend contacts, or avoiding school or work. Social distancing also includes reducing the intensity of contacts, such as receiving vaccination if applicable, taking antiviral medicine, or wearing face masks. However, because any of these actions require increased cost (monetary cost, loss of incomes, or leading to inconvenience to their lives, etc.) for switchers, individuals must balance their costs and benefits during the decision-making process. Moreover, individuals may routinely change their minds based on daily updates of new epidemic information. Considering change of contacts pattern and evolutionary decision process, the spatial evolutionary game was applied to the model Figure 4.1.

Figure 4.1 SIR model



4.2.4 Spatial Evolutionary Game

The spatial evolutionary game combines both classic game theory and cellular automaton, in representing strategies, players, payoff function, structure of population, and an updating rule. Nowak and May (83) first introduced the spatial evolutionary game in order to study the local cooperation phenomena for a classic problem, called “prisoner dilemma”. This methodology analyzes various structures of populations using a regular lattice (47), scale-free networks (48),

and real social networks (49). Szabo and Fath (49) reviewed evolutionary games on graphs. In addition, the spatial evolutionary game requires an updating policy based on the payoff function with updating schemes such as synchronous or asynchronous updates. Newth (50) reviewed several common updating schemes, and Roca, Cuesta, and Sanchez (51) summarized update rules.

An example of classical spatial evolutionary game in lattice is introduced in (84), and a simplified example is shown as follows. Assume two types of players play a game, and two strategies are available to each player. The payoff matrix is shown in Figure 4.2. Players choose strategy A or strategy B, and payoff value could be a, b, c, or d corresponding to players' strategies. Figure 4.3 describes the location of each player. The contact pattern in this game is von Neumann neighborhood (four nearest neighborhood). A player would play the game with all neighbors, and the summation of payoff value in the game against each neighbor is the final payoff value for each player. The result is shown in Figure 4.3.

Figure 4.2 Payoff Matrix

	A	B
A	a	b
B	c	d

After each turn, players could reconsider their strategies based on their payoff values as well as other players' payoff values. In addition, players update their strategies synchronously or asynchronously.

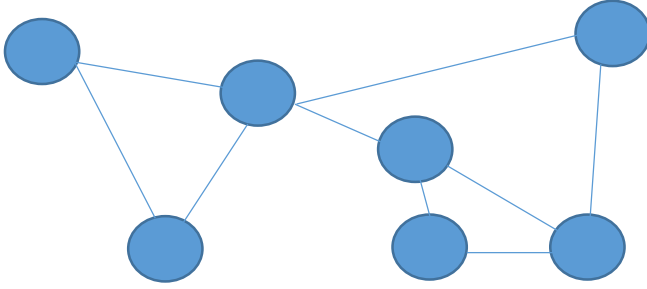
Figure 4.3 Spatial Evolutionary Game Example

$a+b$	$c+2d$	$2d$
$a+2b$	$2c+2d$	$c+2d$
$2c$	$a+2b$	$a+b$

4.2.5 MDM model

This section extends the classic SIR ODEs model of Eqs. (4.1) – (4.3) to a local commute model with the spatial evolutionary game based on a local contact network, which is called modified dynamic model, in short, MDM. Individuals may work in another location besides their home or visit neighboring businesses or families daily. Frequent commuting behaviors are included in the local commute model. Considering population heterogeneities, the classic model could be modified to involve spatial structure. For example, as illustrated in Figure 4, the network could be adopted to present different locations, and an index x could be used to indicate the specific location in the map. Each location contains a population with four possible types of individuals: normal, switchers, infected, and recovered individuals. Individuals could interact with others in the same location or in connected neighborhood locations, and the contact rate depends on the distance between two locations. For example, individuals in location 2 could interact with individuals in locations 1, 2, 3, 4, or 7 with probabilities depending on distances between two locations.

Figure 4.4 Network with Metapopulation



The modified SIR model built on the network (such as the one in Figure 4) for the disease transmission process is

$$\frac{dS_n}{dt}(x) = -\beta_n S_n(x) \lambda_n(x) - (1 - \rho(x)) S_n(x) + \rho(x) S_a(x) \quad (4.4)$$

$$\frac{dS_a}{dt}(x) = -\beta_a S_a(x) \lambda_a(x) + (1 - \rho(x)) S_n(x) - \rho(x) S_a(x) \quad (4.5)$$

$$\frac{dI}{dt}(x) = \beta_n S_n(x) \lambda_n(x) + \beta_a S_a(x) \lambda_a(x) - \gamma I(x) \quad (4.6)$$

$$\frac{dR}{dt}(x) = \gamma I(x) \quad (4.7)$$

where

$$\lambda_n(x) = \sum_{y \in local} I(y) K_n(x - y) / N(y) \quad (4.8)$$

$$\lambda_a(x) = \sum_{y \in local} I(y) K_a(x - y) / N(y) \quad (4.9)$$

and

$S_n(x)$ Number of normal individuals at location x ,

$S_a(x)$ Number of switchers at location x ,

$\rho(x)$ Percentage of normal individuals to total susceptible individuals at location x

$K_n(x - y)$ Contact probability function for normal between location x and location y ,

$K_a(x - y)$ Contact probability function for switchers between location x and location y ,

$I(x)$ Number of infected individuals at location x ,

$R(x)$ Number of recovered individuals at location x ,

$N(\mathbf{y})$ Total number of individuals at location \mathbf{y} ,

β_n Infection rate of individuals adopting normal behavior,

β_a Infection rate of individuals adopting switcher behavior,

γ Recovery rate

Eqs. (4.4) and (4.5) use two infection rates, β_n and β_a , for normal individuals and switchers, respectively, where assuming $\beta_a < \beta_n$. The contact rates, $\lambda_n(\mathbf{x})$ and $\lambda_a(\mathbf{x})$ are for normal individuals and switchers in location \mathbf{x} , respectively, and they are calculated in Eqs. (4.8) and (4.9), where $K_n(\bullet)$ and $K_a(\bullet)$ are kernel functions that represent the possibilities that one individual may contact others in a certain location (i.e. same location or neighboring location). Individuals could interact with others in the same location or other locations with different possibilities. depending on the distance between two locations and the number of infected individuals in the location where susceptible individuals visit.

Considering individuals' decision-making processes, the payoff functions, $F_n(\mathbf{x})$ and $F_a(\mathbf{x})$ in Eqs. (4.10) – (4.11), for the normal individuals and switchers, respectively, are defined similarly to (82):

$$F_n(\mathbf{x}) = -\frac{\frac{m_1 \sum_{y_l \in local} I(y_l)}{\sum_{y_l \in local} N(y_l)}}{1 + \frac{c_1 \sum_{y_l \in local} S_a(y_l)}{\sum_{y_l \in local} (S_a(y_l) + S_n(y_l))}} - \frac{\frac{m_2 \sum_{y_g \in global} I(y_g)}{\sum_{y_g \in global} N(y_g)}}{1 + \frac{c_2 \sum_{y_g \in local} S_a(y_g)}{\sum_{y_g \in local} (S_a(y_g) + S_n(y_g))}} \quad (4.10)$$

$$F_a(\mathbf{x}) = -k_c + \alpha F_n(\mathbf{x}) \quad (4.11)$$

And the percentage for an individual to switch his/her behaviors are defined as and logistic function based on the difference between the normal individuals and switchers,

$$\rho(\mathbf{x}) = \frac{1}{1 + e^{-\theta(F_n(\mathbf{x}) - F_a(\mathbf{x}))}} \quad (4.12)$$

where

k_c Fixed cost for social distancing behavior,

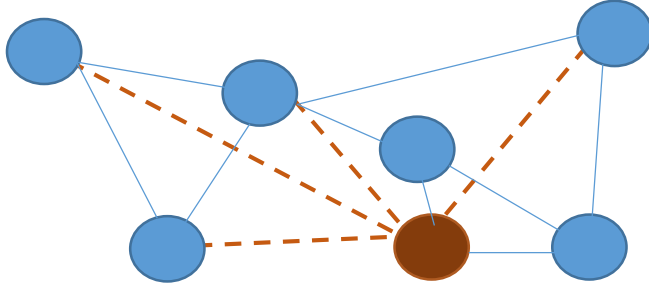
- m_1 Parameter related to estimated risk based on local prevalence,
- m_2 Parameter related to estimated risk based on global prevalence,
- c_1 Parameter related to estimated risk based on local switchers,
- c_2 Parameter related to estimated risk based on global switchers,
- $0 \leq \alpha \leq 1$ Parameter related to discount of estimated risk by switcher,
- θ Parameter related to switch rate of normal individuals based on the difference of payoff

Local and global information of prevalence (proportion of the number of infected individuals to the total population) and the number of switchers were considered as they relate to susceptible individuals' decisions. In Eqs. (4.10) and (4.11), we assumed that risks could be a negative value; therefore, payoff values for both normal individuals and switchers are always non-positive. However, switchers incurred an additional cost, k_c , for the preventive measure, on the other hand the switcher's risk for infection is consequently less than that for normal individuals, as denoted by discount parameter $0 \leq \alpha \leq 1$ in Eq. (4.11). The difference of payoff values between normal individuals and switchers determines the percentage of normal individuals in Eq. (4.12).

4.2.6 MDM with Long-Distance Travel Model

Beside local commuting behaviors, individuals may also travel to large cities or tourist resorts for shopping, vacations, business, or social engagements, causing those locations to become network centers that connect to various distant locations. Individuals may only visit the center monthly, quarterly, or yearly instead of daily. As illustrated in Fig. 4.4, if location 5 represents a center node, then the corresponding modified network is shown in Figure 4.5. The dashed lines represent contacts resulting from long-distance travels. Considering such long distance travels, the system of Eqs. (4.4) – (4.12) remains the same, but kernel functions $K_n(\bullet)$ and $K_a(\bullet)$ correspondingly change based on the probability of contacts for long-distance travels.

Figure 4.5 Network for Long-Distance Travels



If infection cases occur in the center node, switchers may cancel their travels for their own safety, depending on the number of cases in their destinations. The probability of travel cancellations for switchers based on the number of cases is defined as

$$p_c = \ln\left(\frac{e^{I(x)+d}}{I(x)+d}\right), \quad (4.13)$$

where e is the natural logarithm, $I(x)$ is the number of infectious individuals at location x (destination), and d is a constant that determines the increasing rate of cancellation. Switchers who cancel travels are assumed to stay in their location and contacts with others their current location since they will not contact with individuals in their planned destination for travel. The value of p_c impacts kernel function $K_a(\bullet)$ since the contact probability distribution changes due to travel cancellations. For example, if switchers in location 3 have probability distributions of 10%, 10%, 75%, and 5% to contacts in locations 1, 2, 3, and 5, respectively, and half the switchers cancel their travel plans, then the modified probability distribution is 10%, 10%, 77.5%, and 2.5%, respectively.

4.3 Equilibrium Analysis

Using The system of Eqs. (4.4)–(4.13) admits the disease-free equilibrium (DFE) $(S_n; S_a; I; R) = (S_n^*; S_a^*; 0; 0)$ for each location x with the fixed ratio of normal individuals and switchers, thereby satisfying

$$\frac{S_n^*(x)}{S_n^*(x)+S_a^*(x)} = 1/(1 + e^{-\theta k_c}) \quad (4.14)$$

$$S_n^*(x) + S_a^*(x) = N(x) \quad (4.15)$$

The solution of $S_n^*(x)$ and $S_a^*(x)$ yields

$$S_n^*(x) = N(x)e^{\theta k_c}/(1 + e^{\theta k_c}) \quad (4.16)$$

$$S_a^*(x) = N(x)/(1 + e^{\theta k_c}) \quad (4.17)$$

In the epidemiology, R_0 is one significant indicator to evaluate the force of infection of the infectious disease, and it is defined as “the average number of secondary cases arising from an average primary case in an entirely susceptible population” (71). When R_0 is less than 1, the DFE is stable, meaning that the spread of infectious disease could be controlled. When R_0 is larger than 1, however, the DFE is unstable. One homogeneous population without any contact structure contained

$$R_0 = \frac{\beta_n S_n^* + \beta_a S_a^*}{\gamma N} \quad (4.18)$$

Considering spatial structure and one infected individuals in location \mathbf{x} , Eq. (4.18) can be rewritten as

$$R_0 = \frac{\beta_n \sum_{y \in neighbor} S_n^*(y) K_n(x-y) + \beta_a \sum_{y \in neighbor} S_a^*(y) K_a(x-y)}{\gamma N(x)} \quad (4.19)$$

where R_0 is related to the initial location, contact probabilities, and the population in each location, meaning that R_0 is not fixed in this model. Usually the largest one calculated for all counties is adopted as the real R_0 . The calculation of R_0 in Eq. (4.19) is consistent with R_0 in Eq. (4.18) when the spatial contact structure is removed. For simplicity, Eq. (4.19) can be rewritten as

$$R_0 = \frac{R_n e^{\theta k_c}}{1 + e^{\theta k_c}} + \frac{R_a}{1 + e^{\theta k_c}} \quad (4.20)$$

where R_n is the value of R_0 for the population in which all susceptible individuals are normal individuals, and R_a is the value of R_0 for the population in which all susceptible individuals are

switchers. If R_a is greater than 1, the infectious disease will outbreak even when all susceptible individuals are switchers. If R_n is less than 1, the infectious disease can be controlled even when all susceptible individuals are normal individuals. Therefore, the spread of infectious disease may be stopped by a change in human behavior only when $R_a < 1 < R_n$.

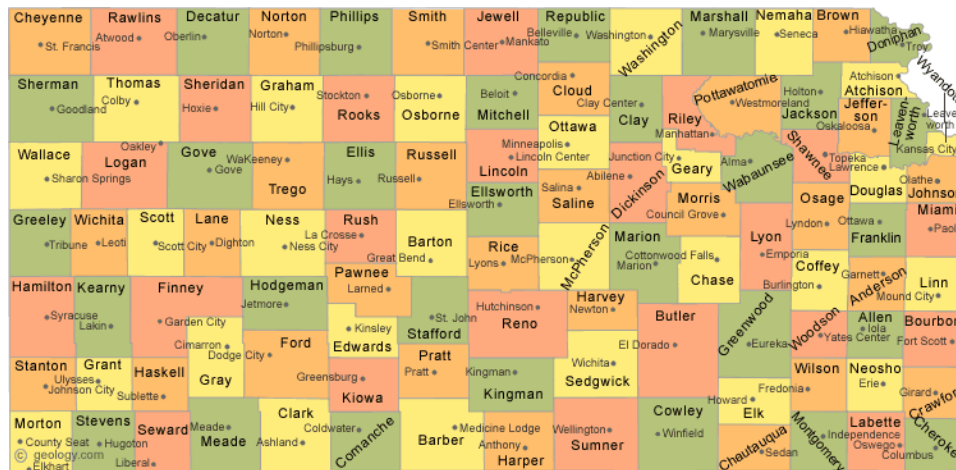
Birth rate and death rate were not included in this model, so no endemic equilibrium existed in the system of Eqs. (4.4)–(4.13). The system would stabilize until all infected individuals were recovered.

4.4 Numerical study

4.4.1 Model comparison

This section included numerical simulations for SEGM model in (82) and MDM model using a county map of the state of Kansas with county-level population in order to compare the SEGM model to the MDM model. The map was shown in Figure 4.6 (*Source: this map is from <http://geology.com/county-map/kansas.shtml>). Population distribution was collected from the U.S. Census Bureau (Census 2010 Redistricting Data (Public Law 94-171) Summary File).

Figure 4.6 County Map of Kansas



SEGM model and MDM model were compared using the following three settings: deterministic commuting contacts, stochastic commuting contacts, and long-distance travel. Although the contact pattern significantly affected dynamics of an epidemic, most researchers relied on a presumed contact pattern with little or no empirical basis. Theoretically, any type of contact pattern could be applied to the model. Only local contacts were allowed in the first two contact patterns, meaning that individuals could only contact others in the same county or in a neighboring county. In the third contact pattern we assumed that individuals would travel to some cities which are not their neighborhood for business or recreation. Testing the three contact patterns proved that results from the MDM model are consistent with results in SEGM model.

For all the simulation runs, the first infected individual was located in the northwest corner county of Cheyenne. Results in six counties were tested for comparison, including Cheyenne (source), Thomas (neighbor of Cheyenne – subgraph a), Ness (two counties away from Cheyenne – subgraphs b and c), Riley (far away from source in the north – subgraph d), Sedgwick (county with second largest population in Kansas – subgraph e), and Johnson (county with the largest population in Kansas – subgraph f) in Figures 7, 8, 9, 12, 17, and 18. Parameters were initialized as follows: $\alpha = 0.5, k_c = 1, \theta = 1, \gamma = 0.294, m_1 = 100, m_2 = 10, n_1 = 100, n_2 = 10$. The following subsections present spatial-temporal comparisons to prove the consistency of simulation results for two models.

4.4.1.1 Deterministic Commuting Contacts

In this section, we assume that individuals contact a fixed number of people each day, denoted as n_2 . The number of contacts for normal individuals and switchers differs, and parameter γ_2 denotes the discount rate of contacts for switchers. Similarly, protective behaviors could reduce the infection rate for switchers; parameter γ_1 denotes the corresponding discount rate. β represents

the infection rate per contact between infected individuals and susceptible individuals. All parameters used in models should be consistent in order to compare two models. The parameter relationships between two models are

$$\beta_n = -n_2 \ln(1 - \beta) \quad (4.21)$$

$$\beta_a = -\gamma_2 n_2 \ln(1 - \gamma_1 \beta) \quad (4.22)$$

where n_2 , β , γ_1 , and γ_2 were parameters also used in (82). All other parameters are identical for two models.

According to comparison results in Figure 4.7, the number of infected individuals in each county was consistent in two models, spatially and temporally. Wherever the county locates does not impact the consistency of results from two models and the plots show that two curves are almost overlap for all tested six counties. In addition, the further from the source of the infectious disease, the later the infection occurred.

4.4.1.2 Stochastic Commuting Contacts

All assumptions in this subsection are identical to assumptions in Section 4.4.1.1 with the exception of the number of contacts on each day. Instead of using a fixed number of contacts, let the number of contacts N_c on each day follow the Poisson distribution according to the contact assumption in (82):

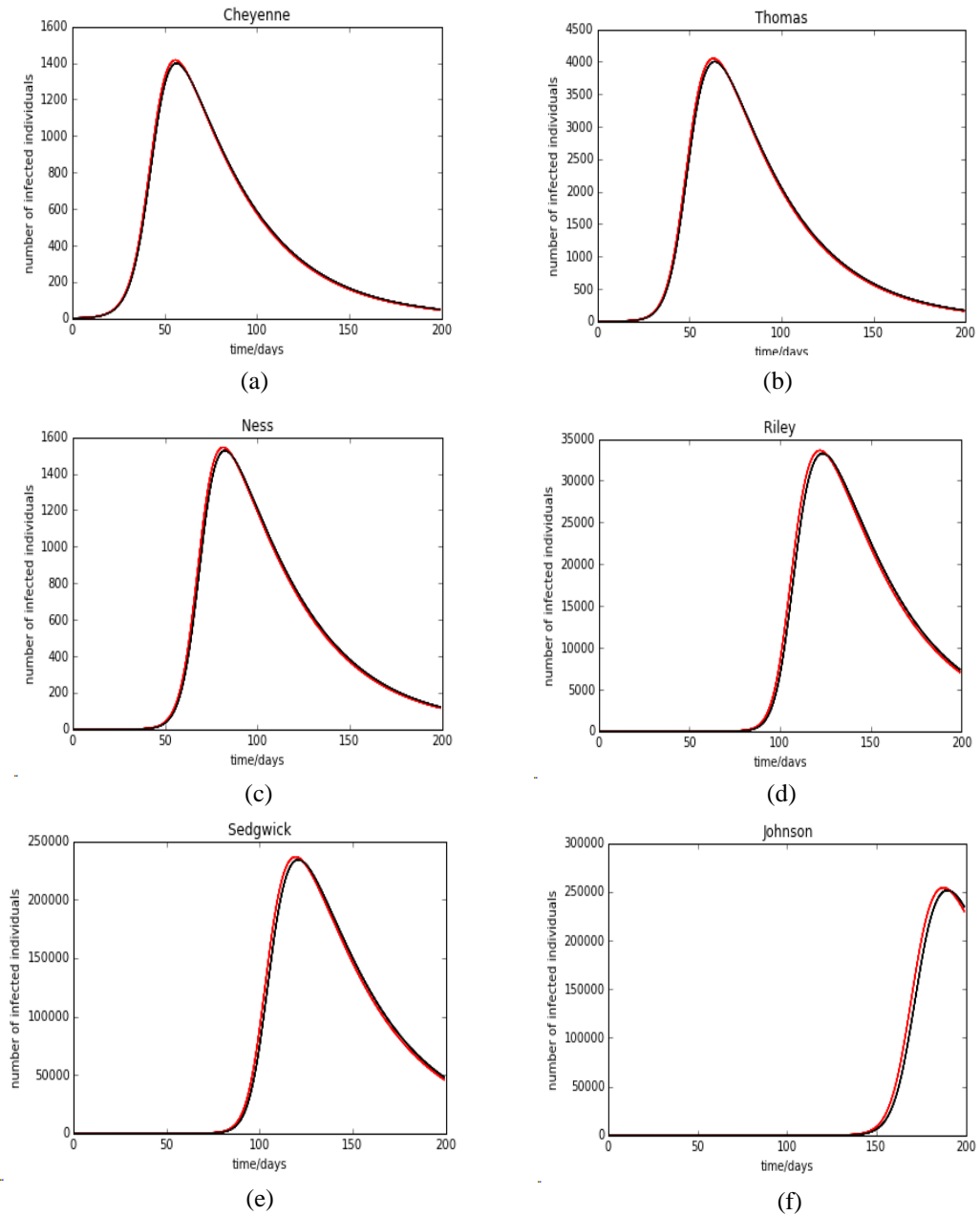
$$P(N_c = k) = \frac{e^{-\gamma_1 n_2} (\gamma_1 n_2)^k}{k!} \quad (4.23)$$

Parameters β_n and β_a in MDM model were consequently changed to be

$$\beta_n = -N_c \ln(1 - \beta) \quad (4.24)$$

$$\beta_a = -\gamma_2 N_c \ln(1 - \gamma_1 \beta) \quad (4.25)$$

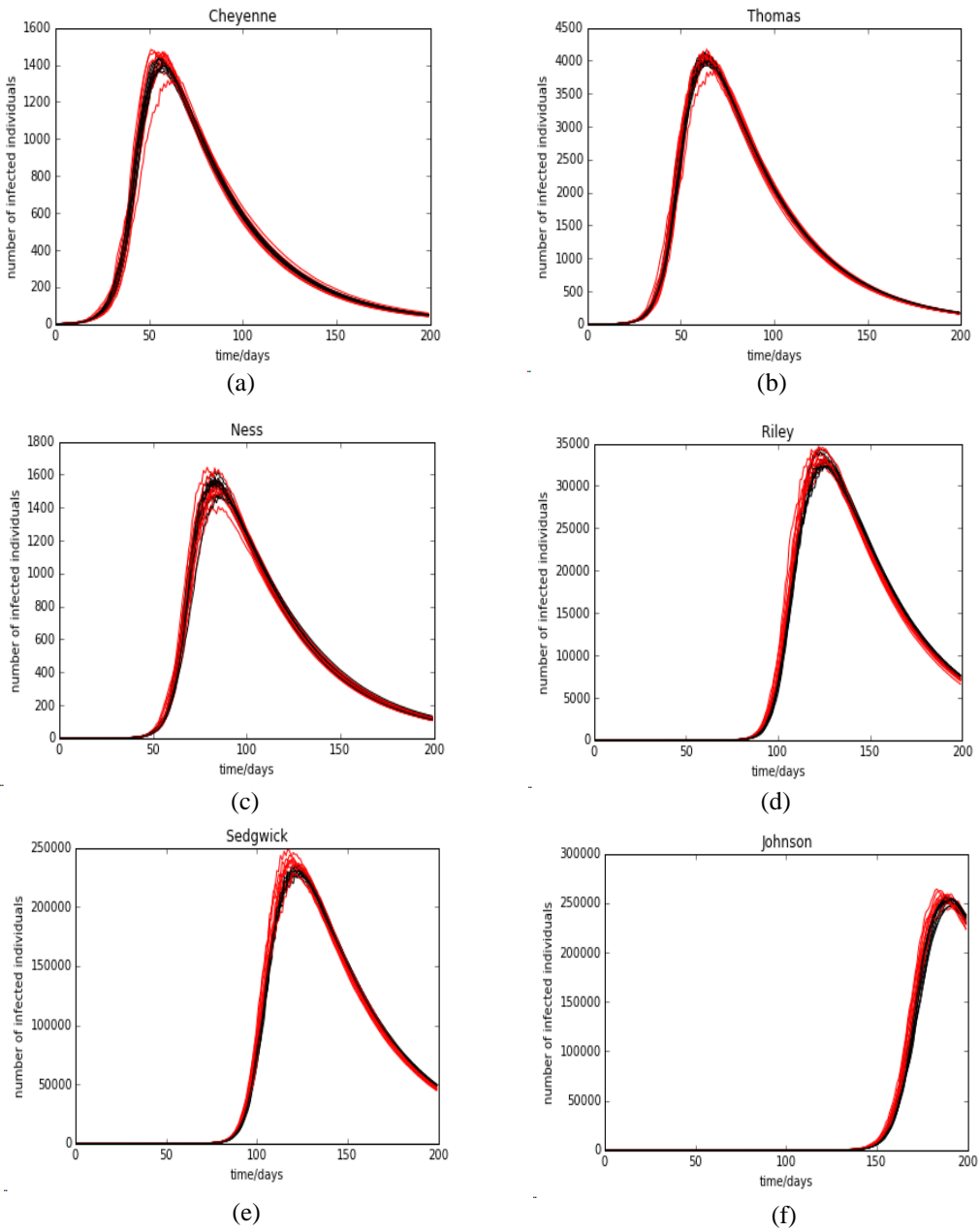
Figure 4.7 Model Comparison under Deterministic Contacts



(Red line is the plot of SEGM model; black line is the plot of MDM model.)

Ten replications were run for each model, and results are presented in Figure 4.8. The red curve represents results for SEGM model; the black curve represents results for MDM model. Results from both models were similar, as evidenced by overlapping of most of the curves.

Figure 4.8 Model Comparison under Stochastic Contacts



(Red line is the plot of SEGM model; black line is the plot of MDM model.)

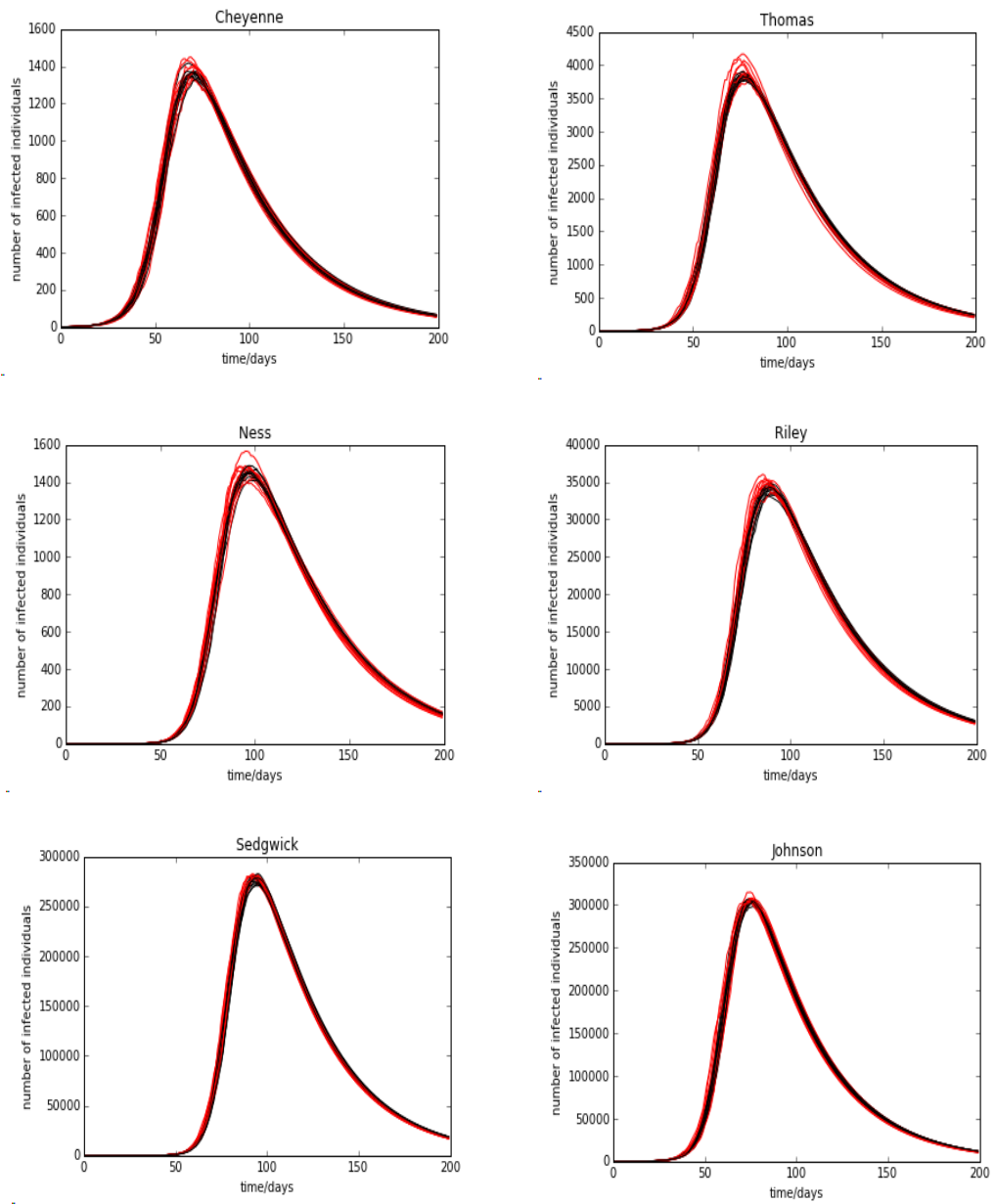
4.4.1.3 Long-Distance Travel

Sedgwick and Johnson Counties, the two counties with most population in Kansas, were selected as network centers in our long-distance contact model. People in all other counties were assumed to travel to these counties for shopping or business.

Stochastic contacts remained in this simulation, and 10 replications were run for each model. Results from the two models were similar. In addition, the spread of infectious disease was faster than the spread shown in the local contacts pattern, as shown in Figures 4.9e and 4.9f (compared to Figures 4.8e, 4.8f, 4.7e, and 4.7f). Infectious disease typically is more readily transmitted to large cities when long-distance travel is involved in the model.

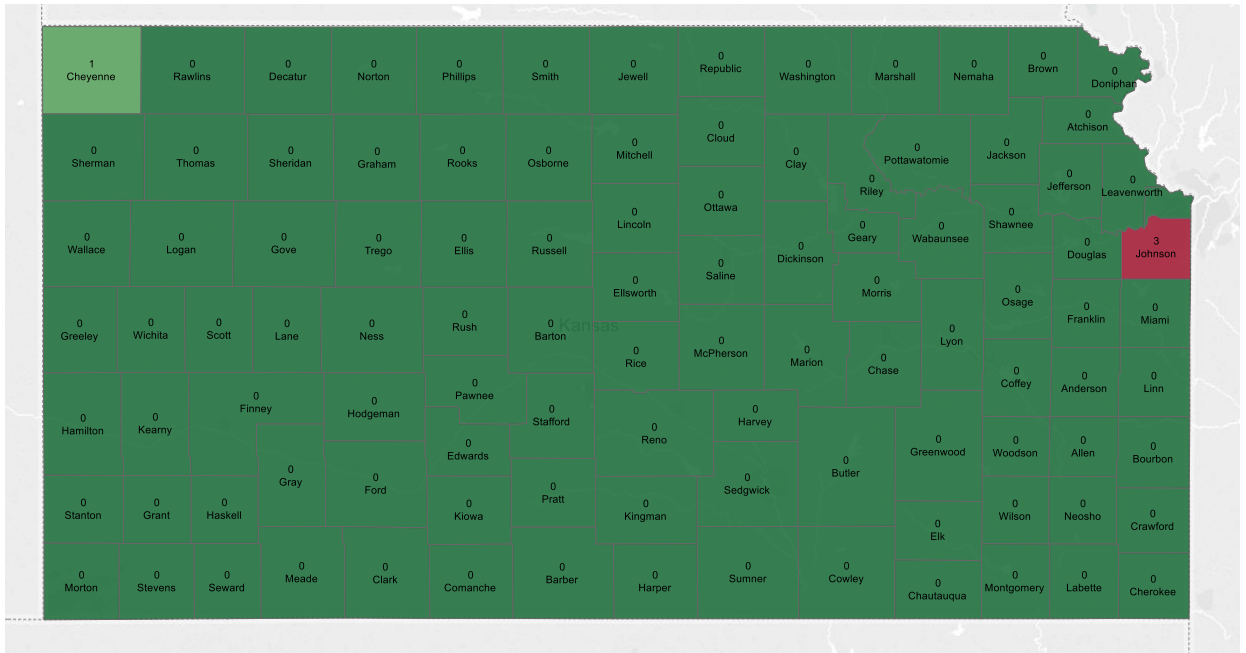
Due to the high volume of transportation and large populations within Sedgwick and Johnson Counties, infectious diseases are rapidly transmitted to areas surrounding those network centers. Peak time for the number of infected individuals in Johnson County is approximately 100 days earlier compared to that in the model without long distance travel. Fig. 4.10 shows the number of infected individuals in each county on the third simulation day. Cheyenne County showed one infected case as the source location of infectious disease, but Johnson County indicated three cases. Because the spread of infectious disease is extremely fast in Johnson County due to large population, avoidance of long-distance travel to network center may be a crucial strategy for decreasing the spread of infectious disease.

Figure 4.9 Model Comparison under Long-Distance Travel



(Red line is the plot of SEGM model; black line is the plot of MDM model.)

Figure 4.10 Numbers of Infected Individuals in Each County in Kansas



4.4.2 Impacts of Changes of Human Behaviors

This section included discussion of the impacts to disease transmission dynamics due to changes of human behaviors temporally and spatially on state and county scales, respectively. Long-distance travel was involved, and commute contacts are assumed to be deterministic.

Figure 4.11 Numbers of Infected Individuals in Kansas

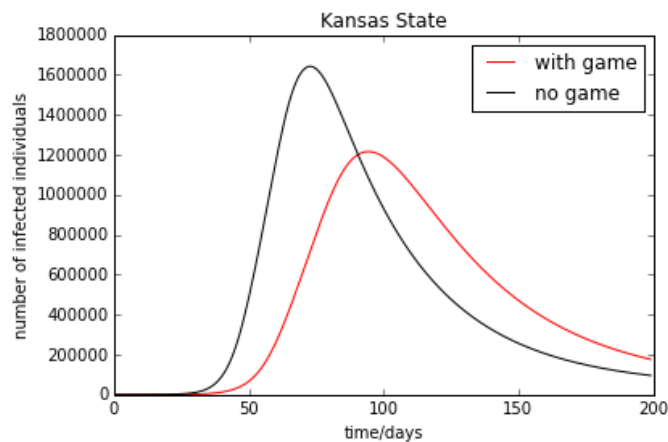
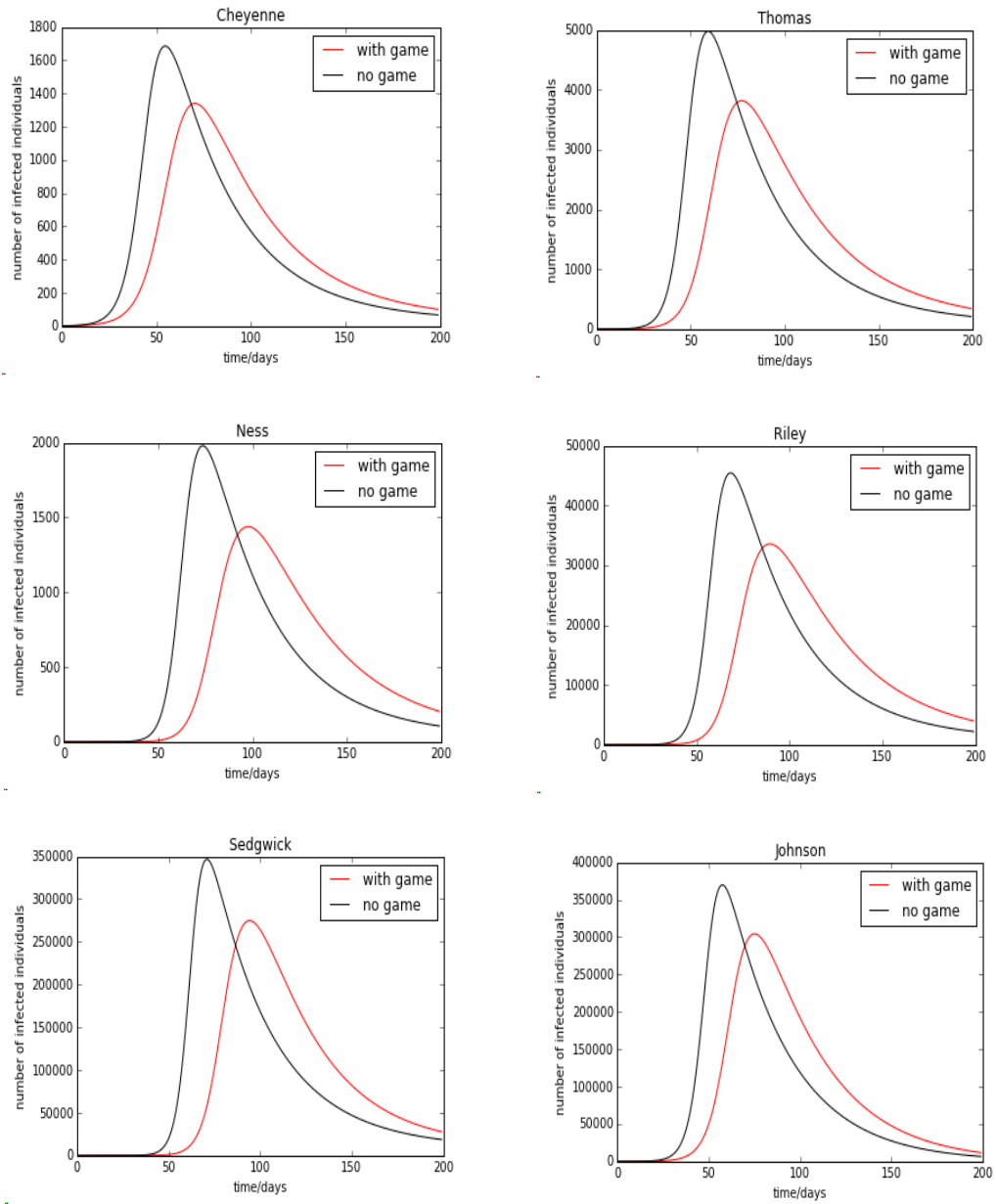


Figure 4.12 Numbers of Infected Individuals in Various Counties in Kansas



Comparisons of the number of total infected individuals in the entire state of Kansas and in various counties in Kansas are shown in Figures 4.11 and 4.12, respectively.

In Figures 4.11 and 4.12, the black line (“no game”) indicates no changes of human behaviors in epidemics; the red line (“with game”) indicates that changes of human behaviors were considered. On a statewide scale, human behaviors significantly impacted the dynamics of disease

transmission, lowering the total number of infected individuals and delaying the peak time of epidemics. On a county scale, identical impact patterns were obtained for all counties in Kansas, implying that the distance between the studied county and the source county for patient 0 did not affect the impacts of human behaviors to the spread of infectious diseases, so does the distance between small counties and network centers due to our homogeneous assumption of risk estimates for each county. Individuals' perspectives of the infectious disease based on prevalence were scaled by parameters m_1 and m_2 in Eq. (4.10), indicating local information and global information, respectively. Global information impacts were assumed to be identical for all individuals, but local information impacts potentially varied in different. The following section discussed the impact of local information (parameter m_l) in details.

4.4.3 Impacts of Risk Estimates Based on Local Information

As mentioned in Section 4.2, individuals' perspectives of an infectious disease based on local information may differ by location. As a multiplier of local prevalence in Eq. (4.10), parameter m_1 essentially bridges the local information and risk estimates by individuals. Individuals' behaviors are determined by the game update rule, which is calculated by the differences of payoff values for normal and switchers, while the payoff value is primarily impacted by the product of m_1 and local prevalence, as explained in (82). Therefore, local information is translated to payoff by m_1 to motivate individuals to choose either normal or alternatives, thereby implicitly affecting the dynamics of the epidemic. In addition, the value of m_1 could be changed due to intervention strategies. Public health education, policies of vaccination, and quarantine measures could also alter an individual's risk estimate of the infectious disease, leading to changes in m_1 . Consequently, impacts of m_1 must be studied further in order to understand human behaviors in epidemics. Analyses for m_1 are discussed in the following subsections.

4.4.3.1 Sensitivity Analysis for m_1

A sensitivity analysis is conducted in this section in order to understand the impact of m_1 on the dynamics of disease transmission. The range of m_1 was set from 0 to 5000, and the step size was set at 500.

Figure 4.13 Numbers of Infected Individuals with an Altered Value of m_1

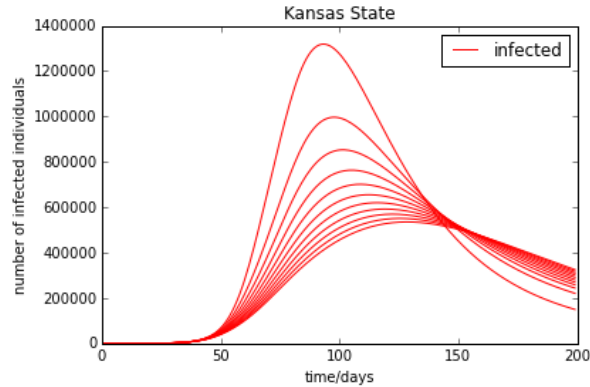
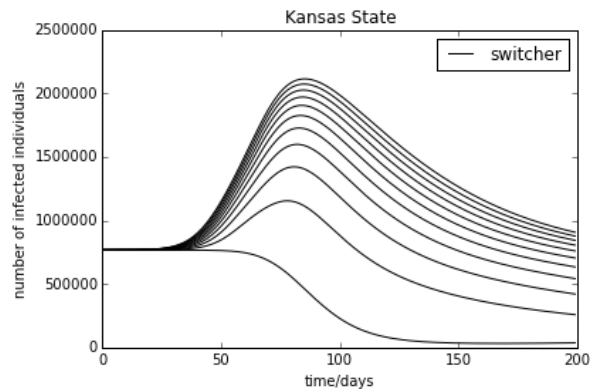


Figure 4.14 Numbers of Switchers with an Altered Value of m_1



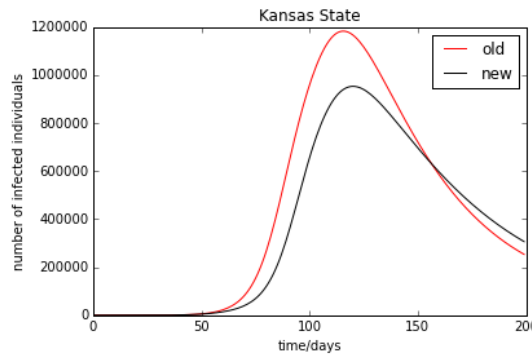
As shown in Figure 4.13, the peak of number of infected individuals in Kansas decreased as the value of m_1 increased from 0 to 5000. The higher the value of m_1 was, the more risk individuals estimated, proving that individuals were more self-protective if m_1 become larger, consequently decreasing the numbers of infected individuals, as shown in Figure 4.13. Similarly,

as shown in Figure 4.14, an increasing value of m_1 led to an increasing number of switchers throughout the state of Kansas. An identical pattern of changes also occurred in all counties.

4.4.3.2 Stochastic Commuting Contacts

In this section, the assumption of m_1 in Eq. (4.10) is changed to be heterogeneous in order to indicate that the value of m_1 could vary by location. Because network centers were the most severe areas of epidemics in Kansas, they were assigned a higher value of m_1 than other areas, allowing individuals in network centers to have more motivations to choose protective behaviors. Results demonstrated how this strategy impacted the dynamics of disease transmission and verified whether or not infectious disease could be mitigated when epidemics were controlled only in network centers.

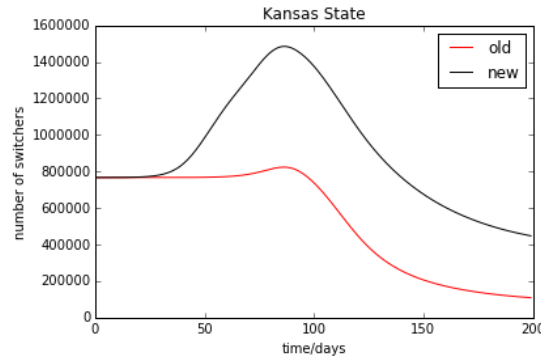
Figure 4.15 Comparison of Numbers of Infected Individuals in Kansas with Altered m_1 for network centers



Figs. 15 and 16 illustrate changes in the number of infected individuals and the number of switchers in Kansas under MDM model and denotes the model with various values of m_1 in network centers, respectively. The “old” curve represents the MDM model, and the “new” curve denotes the model with various values of m_1 in network centers. Significantly high numbers of switchers were evident throughout the state of Kansas due to the high value of m_1 in metropolitan areas, resulting in fewer infected individuals and a delayed peak time. However, as shown in Figs.

17 and 18, the network center (in subgraphs (e) and (f)) had significantly fewer infected individuals because of the increased number of switchers, but other counties in Kansas were not significantly impacted. The “new” curves and the “old” curves did not differ significantly in the counties of Cheyenne, Thomas, Ness, and Riley; therefore, increasing changing human behaviors in network centers could reduce the overall numbers of infected individuals, however, cannot impact the dynamics of disease transmission in other areas.

Figure 4.16 Comparison of Numbers of Switchers in Kansas with Altered m_1 for network centers



The epidemic could be mitigated further with a high value of m_1 for all areas, as shown in Figure 19 (“all high” curve). The number of infected individuals can be significantly decreased when individuals choose protective behaviors in all counties in Kansas. However, with consideration of social costs, control of spread of infectious disease changes to an optimization problem that requires effective control of disease transmission and minimization of total costs. This topic exceeds the scope in this paper, but it will be studied in our future study.

Figure 4.17 Comparison of Numbers of Infected Individuals in Various Counties with Altered m_1 for Network Centers

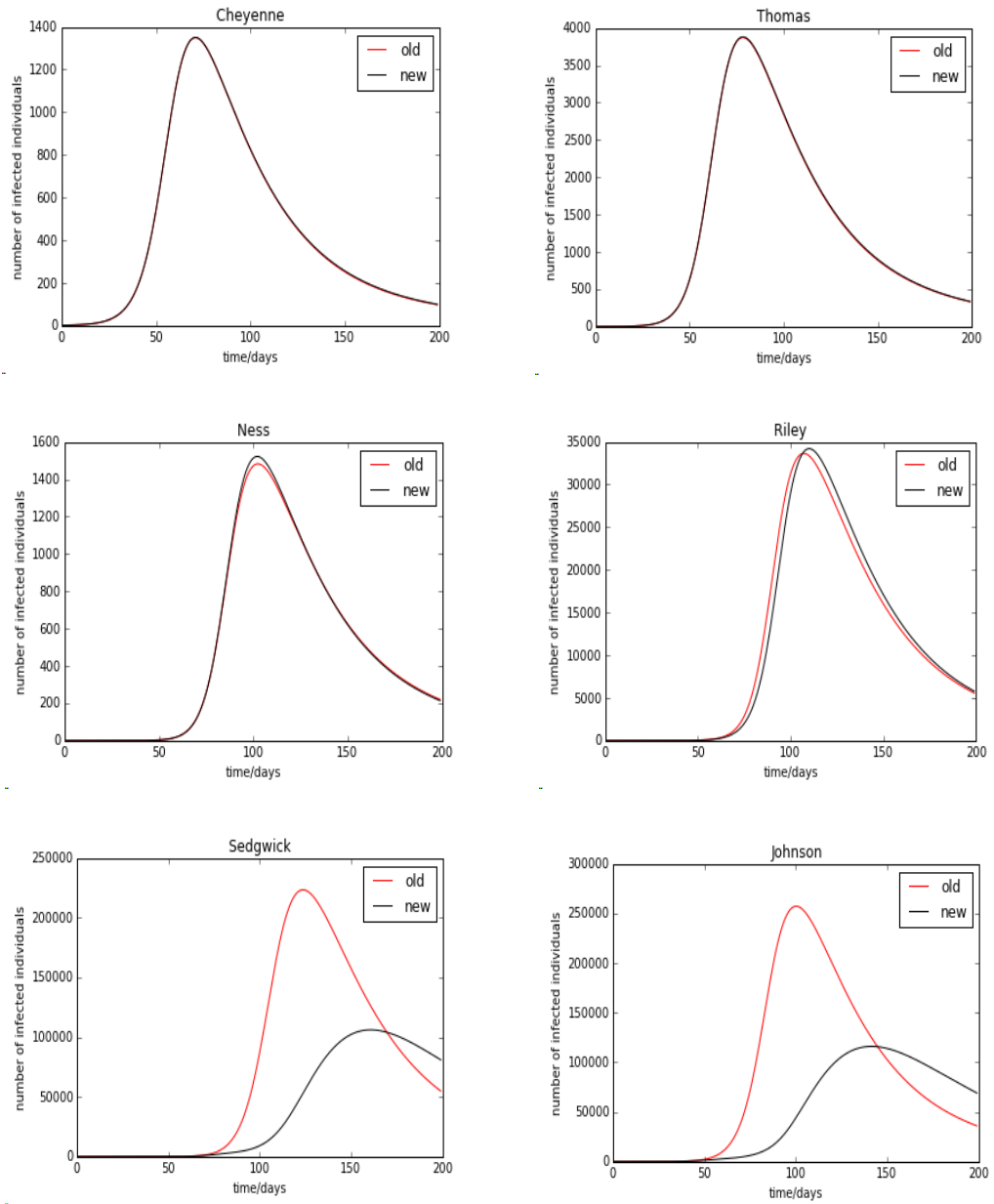


Figure 4.18 Comparison of Numbers of Switchers in Various Counties with Altered m_1 for Network Centers

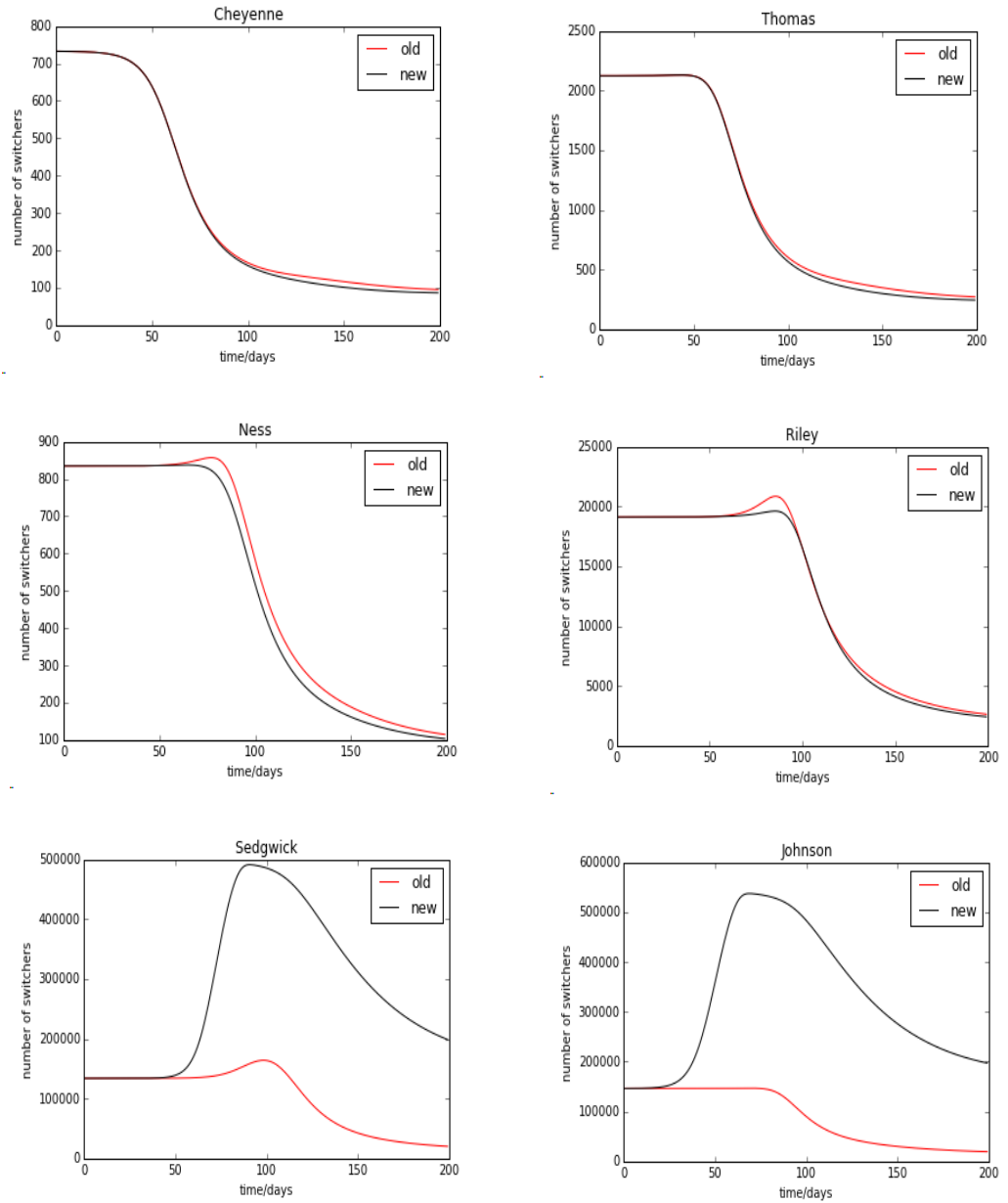
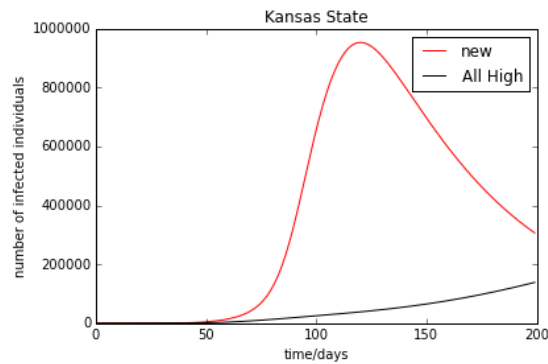


Figure 4.19 Numbers of Infected Individuals with High Values of m_1



4.4.3.3 Impacts of memory for individuals' risk estimates

Impacts of local information to individuals may not only vary by locations as described in Section 4.4.3.2, but also vary by individuals and time in a heterogeneous population. In particular, basic perceptions and cognitions researchers have shown that “biased media coverage, misleading personal experiences, and the anxieties generated by life’s gambles cause risks to be misjudged (sometimes overestimated and sometimes underestimated), and judgments of fact to be held with unwarranted confidence” (85). The perception of risk to the infectious disease does not stay to the same extent all the time. Individuals are affected by both of their memories on prior information as well as the new information. For instance, after a slow exponential increase of changes of human behaviors in the beginning of 2009 H1N1 pandemic in Italy, there is a sudden and sharp increase of growth rate occurred in the next month due to the new cases reported (7). On the other hand, a quick drop in the attention to protect themselves from an infectious disease frequently occurs when the epidemic is over the peak or people are getting used to the disease prevalence reports by the media (86). Hence, it is our belief that individuals’ decisions are impacted by their prior knowledge and the number of newly infected individuals. The memory mechanism was also assumed for protective behaviors in several other existing literatures (7,87,88). In this section, we attempt to model the memory mechanism via a stochastic differential equation of a Itô drift-diffusion process

with a drifting factor and a random walk (89). Itô drift-diffusion process is commonly used in mathematical finance to model stock price and the first time to be recognized to illustrate the changes of individuals' perception to risks in epidemic. The drifting factor could represent the average change rate of individuals' perception to the risk based on the prior knowledge and new information, and the random walk could represent the diversity of individuals. Hence, the dynamics of m_1 is defined as a Itô drift-diffusion process with a drift factor $\mu_t(x)$ and the uncertainty factor $\sigma(x)$ as follows:

$$\frac{dm_1(x)}{m_1(x)} = \mu_t(x)dt + \sigma(x)dZ_t \quad (4.26)$$

where $Z = \{Z_t : t \in [0, \infty)\}$ is standard Brownian motion with mean of 0 and standard deviation of 1.

Individuals were kept updated for the new information and gradually forgot the prior knowledge. Hence, the information cumulating and memory fading effects were necessary to be applied to the study of average perception of risks to the infectious disease $\mu_t(x)$ at time t and location x . The variation term $\sigma(x)$ represents a heterogeneous risk estimate in different locales as well as various individuals' risk perception to the underlying epidemic in a diverse population. The information cumulating process was modelled by a hill equation, which could provide a reasonable boundary for the change rate of individuals' perception between 0 and 1. Hill equation is extensively used in biochemistry and pharmacology and we believe that the behavior of hill equation can properly describe the changes of individuals' perception to the risk. The memory fading process was modelled as a negative exponential function with argument infection prevalence. As prevalence increases, the fading effects were assumed to be weaker since large prevalence could increase individuals' risk estimates. According to the cumulating information assumption and memory fading assumption, calculation of $\mu_t(x)$ was shown as follows:

$$\mu_t(x) = H(L_t(x), n) - \varepsilon \quad (4.27)$$

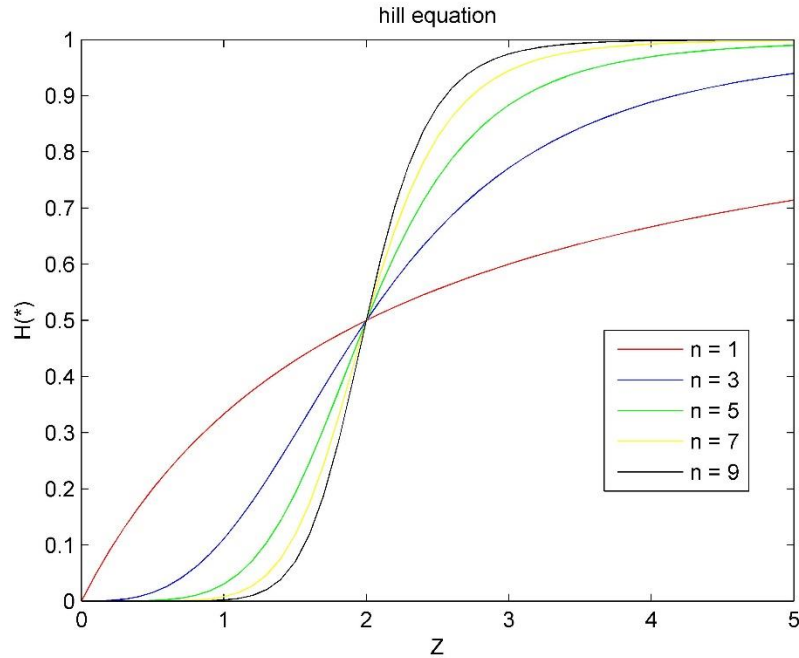
Where

$$L_t(x) = -\sum_{y_l \in local} \left(\frac{dS_n}{dt}(y_l) + \frac{dS_a}{dt}(y_l) \right) \quad (4.28)$$

$$H(L_t(x), n) = \frac{(L_t(x))^n}{(K)^n + (L_t(x))^n} \quad (4.29)$$

Where $L_t(x)$ represents the newly infected population in location x at time t , ε is a constant which acts as a negative exponential in Eq. (4.26) and K is the equilibrium constant and n is the hill coefficient in hill equation.

Figure 4.20 Hill Equation



When the hill coefficient n is greater than 1, the $H(*)$ is monotone increasing with $L_t(x)$ and the lower bound and upper bound are 0 and 1, respectively. What's more, it increases very slowly in the beginning which means the first few new cases of infection have small impact on individuals' decision, while the impacts are amplified as more and more individual are infected. After a quick increasing period, the increase of impacts of information slows down since most of

individuals already recognize the severity of the disease transmission. An example of plots of general hill equations with different n is shown in Figure 4.20. In this example, the equilibrium constant is set to be 2 and Z represents the variable $L_t(x)$ in Eq (4.29).

Figure 4.21 Altered m_I

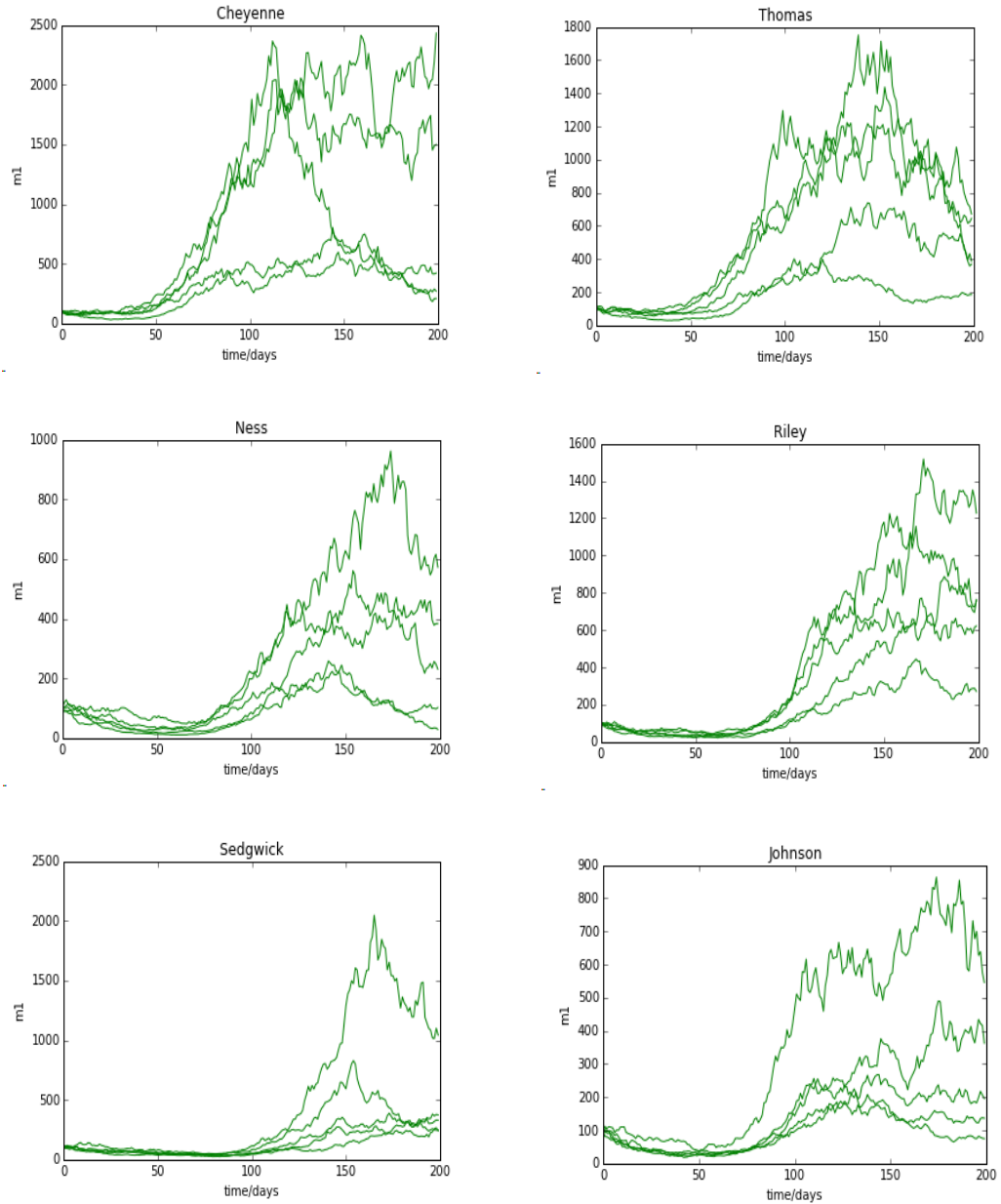
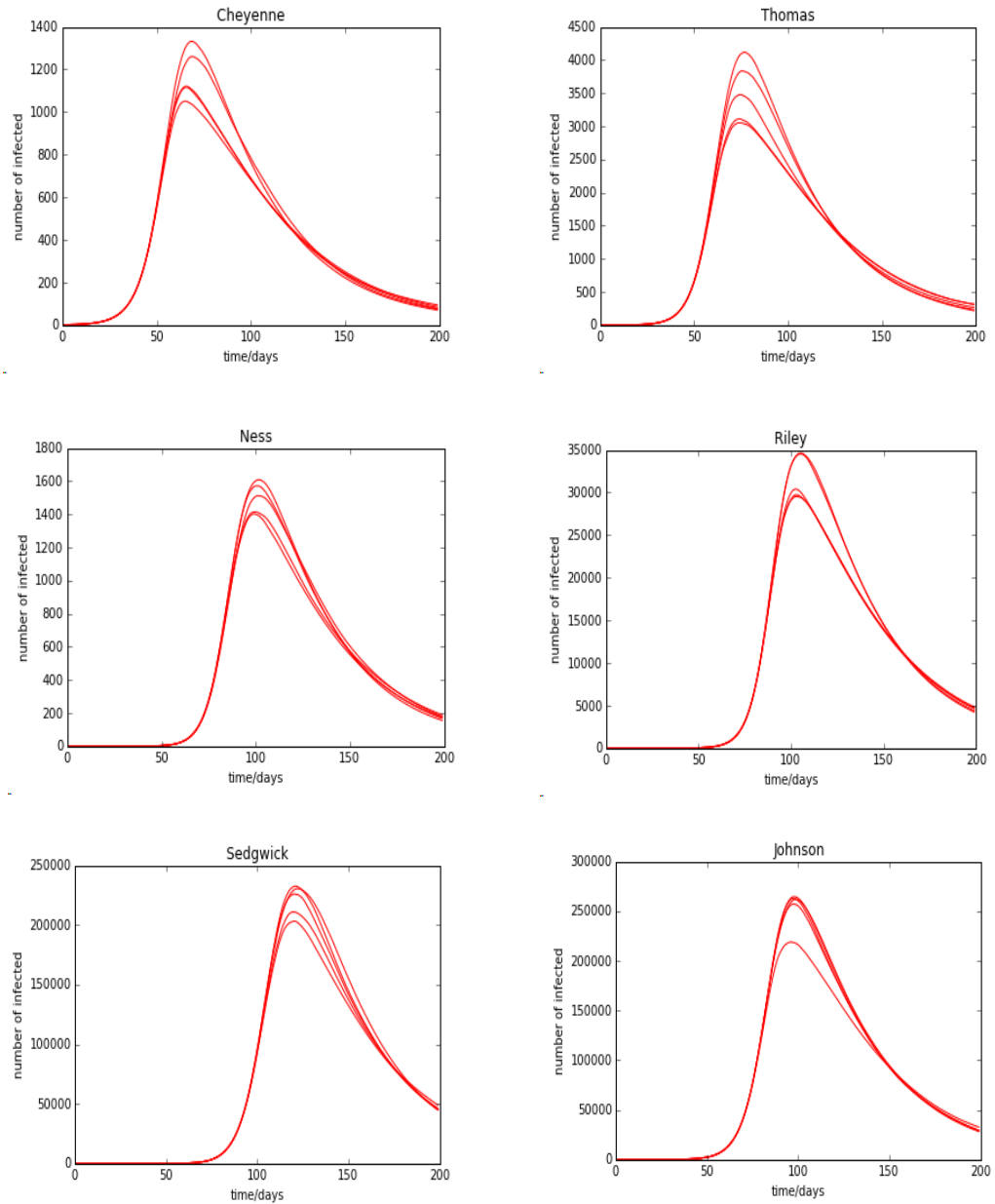


Figure 4.22 Changes in the Numbers of Infected Individuals



One numerical simulation was conducted to study the impacts of m_I on the dynamics of disease transmission based on the memory mechanism. We assumed that $\sigma^2(x) = 0.2$, and we ran five replications. The changes of m_I and the numbers of infected individuals by county are shown in Figure 4.21 and Figure 4.22, respectively. Overall, the value of m_I slightly decreased in the beginning and then exponentially increased due to the increasing number of infected individuals.

Moreover, there is a time delay between the increase of m_I and the increase of infected individuals since some individuals would choose “wait and see” (35) and not all individuals changed their behaviors immediately. Susceptible individuals gradually recognized the severity of infection so that perception to the risk increased as more and more individuals were infected. In addition, the average number of infected individuals in Figure 4.22 was slightly lower than those in Figure 4.17 (red line), since the increased value of m_I could only impact individuals’ decision (i.e. more susceptible individuals choose switchers), not explicitly mitigating the spread of infectious disease.

4.5 Discussion

Spontaneous changes of human behaviors during an epidemic has recently attracted increasing research attention for the recent decade. Assessment of whether benefits of protective actions outweigh the corresponding costs after estimating the payoff according to information and infectious disease risk perception significantly impacts the determination of appropriate behaviors for individuals. Game theory, a commonly used tool to study conflicts and cooperation between decision makers, provides a mathematical framework to discuss individuals’ decision-making processes. A spatial evolutionary game specifically combines spatial association between individuals’ contacts and disease information and temporal impacts of information to the dynamics of human decisions, thereby increasing understanding of the impacts of heterogeneous population and human behaviors on disease transmission dynamics.

This paper applied the spatial evolutionary game used in (82) to a classic dynamic system for the spread of infectious disease. The classic compartmental SIR model has been widely used for epidemic study, including changes in human behaviors due to the spread of infectious diseases. The numerical simulation first proved the consistency of two models, thereby validating the effectiveness of the spatial evolutionary game. Then the impacts of changes of human behaviors

on the dynamics of disease transmission and how information impacts human behaviors were discussed using the numerical simulation. Results showed that protective behaviors decrease the numbers of infected individuals and delay the peak time of infection. Increased numbers of switchers and preemptive actions can more effectively mitigate disease transmission; however, changes in human behavior requires a high social cost (such as avoidance of crowded places leading to absent in school, workplace, or other public places). An appropriate response to the epidemic and wise selection of corresponding intervention strategies is our ultimate goal to prevent infectious diseases. Therefore, individuals' perceptions of risks based on available information were discussed under various assumptions. Heterogeneous responses to an epidemic showed maximum reasonableness since individuals have unique cognitions based on personalized memories and understandings of new information. Itô drift-diffusion process was formulated according to this assumption, and the drift factor was defined as a memory mechanism which included two parts: cumulating information and memory fading. Hill equation and negative exponential function were used to describe the cumulating information process and memory fading process, respectively.

In this paper, MDM model was only studied through numerical simulation. In order to fully understand the behavior of dynamic system, stability analysis and bifurcation analysis should be conducted later. In addition, further studies should combine changes in human behaviors and intervention strategies to identify optimal information dissemination in order to minimize social costs and the numbers of infected individuals. Stability analysis and optimization in epidemic were studied for different infectious diseases, such as Visceral Leishmaniasis (90,91). In addition, optimal control strategies for prevention of infectious disease transmission should be studied considering changes of human behaviors coupled with intervention strategies. In order to increase

understanding of the variation of individuals' responses to infectious disease, a small scale of population, including individualized behaviors, should be taken into consideration for modeling human behaviors. Correspondingly, intervention strategies should be temporally and spatially characterized. As such, an agent-based model, which was used to simulate other diseases, such as Sepsis (92,93), could be used as a tool to study the complex system with interactions among changes of human behaviors, disease transmission, and intervention strategies (public policy). If successful, this research should improve communication between policy makers and the public by directing educational efforts and predicting public response to infectious diseases and new risk management strategies (regulations, vaccination, quarantine, etc.).

Chapter 5 - Zoonotic Visceral Leishmaniasis Transmission: Modeling, Backward Bifurcation, and Optimal Control

Chapter 5 is based on the paper “Zoonotic Visceral Leishmaniasis Transmission: Modeling, Backward Bifurcation, and Optimal Control” published in *Journal of Mathematical Biology* (2016), doi:10.1007/s00285-016-0999-z.

Abstract

Visceral Leishmaniasis (VL), a vector-borne disease caused by protozoan flagellates of the genus *Leishmania*, is transmitted by sand flies. After malaria, VL is the second-largest parasitic killer, responsible for an estimated 500,000 infections and 51,000 deaths annually worldwide. Mathematical models proposed for VL have included the impact of dogs versus wild canids in disease dissemination and models developed to assist in control approaches. However, quantitative conditions that are required to control or eradicate VL transmission are not provided and there are no mathematical methods proposed to quantitatively calculate optimal control strategies for VL transmission. The research objective of this work was to model VL disease transmission system (specifically Zoonotic VL), perform bifurcation analysis to discuss control conditions, and calculate optimal control strategies. Three time-dependent control strategies involving dog populations, sand fly population, and humans are mainly discussed. Another strategy sometimes used in attempts to control zoonotic VL transmission, dog culling, is also evaluated in this paper.

Keywords

Visceral Leishmaniasis, Zoonotic Disease Transmission, Backward Bifurcation, Optimal Control

5.1 Introduction

Visceral Leishmaniasis (VL) is a protozoan disease caused by parasites of the genus *Leishmania* and transmitted through the bite of infected sand flies. After malaria, VL is the second-largest parasitic killer in the world, occurring in 65 countries with a majority (90%) of cases in poor rural and suburban areas of Bangladesh, India, Nepal, Sudan, Ethiopia, and Brazil. The current annual estimate of VL mortality is more than 50,000 (5), an assumed underestimation because not all cases are reported and VL is often undiagnosed or unrecognized. VL has become one of the most prevalent public health concerns because of its high morbid mortality. It is generally characterized by an acute stage with generalized symptoms, including fever, cachexia, hepatomegaly, splenomegaly, and pancytopenia.

VL can be classified into Zoonotic Visceral Leishmaniasis (ZVL) and Anthroponotic Visceral Leishmaniasis (AVL). ZVL is caused by *Leishmania infantum* transmitted by the bite of an infected sand fly from sylvatic animal reservoir (such as wild canids and rodents, or domestic, such as the domestic dog) to humans. ZVL is widely distributed from the Mediterranean Basin, parts of the Middle East and North Africa, and the Americas. Since the early 2000s, an outbreak of ZVL also has been identified in American Foxhounds in the United States (94). In contrast, AVL can be transmitted directly from humans to humans by the bite of an infected sand fly (95). AVL is found primarily in India (Bihar State) and other parts of the Indian Subcontinent (96), and in Sudan and South Sudan and caused by *Leishmania donovani* (97). Once a person is infected, the parasite migrates to internal organs such as the liver, spleen (hence "visceral"), and bone marrow. Lack of treatment almost always results in death of the host.

Several mathematical models have been constructed to describe VL transmission. Stauch (96) modeled the spread of VL in the Indian Subcontinent by modified SEIR model in terms of

AVL characteristics and extended it to a ZVL model with animal reservoirs. Vector-related intervention was recommended in combination with treatment-related intervention in order to control VL transmission. Ribas (98) used a mathematical model adapted from one proposed by Burattini (99) to assess interaction between humans, sand flies, and dogs. The risk of requiring the infection R was calculated and optimal control strategy was estimated based on the formula of calculating R . It provided a combination of two ways to control ZVL transmission instead of culling seropositive dogs: insecticide-impregnate collar and vector control. However, they fail to provide a quantitative condition to control or eradicate VL transmission and did not propose mathematical methods to quantitatively calculate optimal control strategies.

In this paper, a mathematical model was developed to describe the ZVL transmission process in Brazil using a modified SEIR model, particularly focused on the reservoir (dogs) because of the crucial role played by these animals in disease transmission. Castillo-Chavez (100) suggested that the zoonotic disease model may exhibit backward bifurcation, in which local asymptotically stable disease free equilibrium (DFE) coexists with a locally-asymptotically stable endemic equilibrium when $R_0 < 1$. Using the reasonable range for each parameter in our mathematical model, a backward bifurcation analysis was performed, resulting in the conclusion that backward bifurcation may exhibit in ZVL transmission. In this case, the condition $R_0 < 1$ may lead to an endemic equilibrium instead of DFE. Therefore, $R_0 < 1$, the classical requirement for the control of infectious disease spread, although necessary, is no longer sufficient for ZVL elimination. Another significant parameter, R_c , was calculated, thereby demonstrating that it coexists in two equilibrium, disease-free equilibrium and endemic equilibrium, when $R_c < R_0 < 1$. In addition, optimal control was discussed to give support in decision for controlling disease transmission. A general mathematical method was used to analyze optimal control strategies and

numerical analysis was described to illustrate implementation of this method. Based on numerical results, optimal control strategies are discussed.

The structure of this paper is as follows: Section 5.2 details a new mathematical model for ZVL transmission; Section 5.3 demonstrates the phenomenon of backward bifurcation existing in the model; Section 5.4 calculates optimal control strategies based on Pontryagin's maximum principle and discusses impacts to disease control with various control costs and effectiveness of control strategies; Section 5.5 concludes the paper and suggests future work.

5.2 Mathematical Model

In this section, a basic model for ZVL transmission dynamics among dogs-sand flies-humans system is constructed. Parameters used in the model are listed in Table 5.1.

ZVL is transmitted by female sand flies, with *Lutzomyia longipalpis* being the primary vector in the Americas. In this paper, we use the word "sand flies", primarily indicating *L. longipalpis* and other species of sand flies which are not ZVL vectors are not considered. Dogs serve as the primary reservoir host for the transmission of parasites to humans (dead-end hosts for ZVL (101)), and dogs are the principal risk factor for human infections with ZVL in endemic areas (102,103). A system diagram of ZVL transmission among dogs, sand flies, and humans is shown in Figure 6.1 in which populations for the three systems are assumed to be homogenous. In addition, the recovered dog may be changed back to infectious dogs if they are removed from treatment (dotted line from R_d to I_d in Figure 5.1). However, this process is not shown in our model and we assumed that all recovered dogs are always under treatment. For humans, recovered humans are not necessarily immune and may be re-infected, but there is now evidence that some level of immunity can be achieved. In this paper, we assume recovered individuals either obtain the immunity or prevent themselves from getting infected. In addition, the VL cannot be

transmitted from human to human, sand flies or dogs, so this assumption will not affect the spread of the VL. Moreover, absent from the parameters is the potential replacement of culled dogs with young

Table 5.1 Parameters in the model

Parameters	Interpretation
λ_d	Recruitment rate of susceptible dogs
λ_f	Recruitment rate of susceptible sand flies
λ_h	Recruitment rate of susceptible humans
$1/\mu_d$	Average lifespan of dogs
$1/\mu_f$	Average lifespan of sand flies
$1/\mu_h$	Average lifespan of humans
b_{fd}	Average biting rate per infected sand fly to dogs
b_{fh}	Average biting rate per infected sand fly to humans
β_{fd}	Transmission probability from an infected sand fly to a susceptible dog
β_{df}	Transmission probability from an infected dog to a susceptible sand fly
β_{fh}	Transmission probability from an infected sand fly to a susceptible human
d_d	VL-induced death rate of dogs (including culled dogs)
d_f	VL-induced death rate for sand flies
d_l	VL-induced death rate of humans
d_H	Death rate of hospitalized humans
m_f	Migration rate of sand flies
$1/\tau_d$	Incubation period in dogs
$1/\tau_f$	Incubation period in sand flies
$1/\tau_h$	Incubation period in humans
δ_h	Hospitalization rate of humans
r_d	Recovery rate of infected dogs

r_I

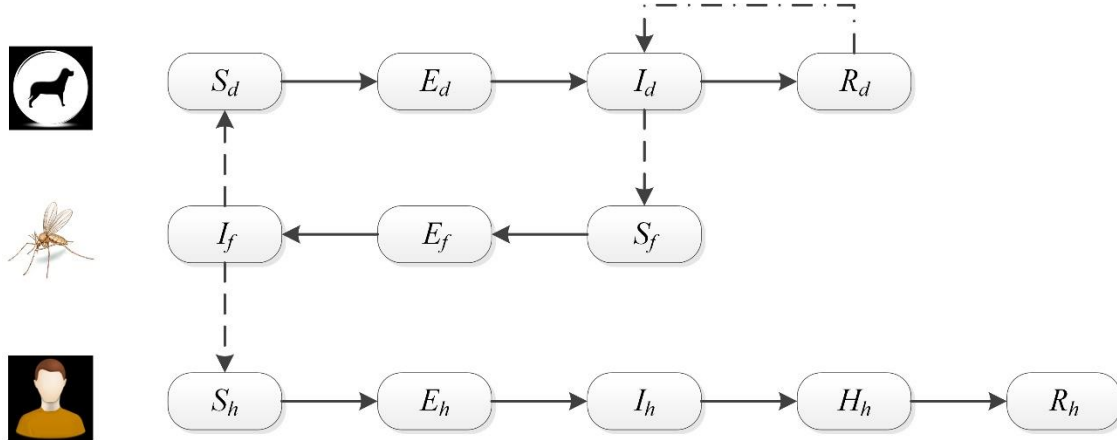
Natural recovery rate of infected humans

 r_H

Recovery rate of hospitalized humans

animals, which is frequently adopted in many endemic areas, but are very hard to ascertain for the purpose of generality of the model.

Figure 5.1 System diagram of ZVL transmission model



In the above system, dogs were classified into four compartments: susceptible dogs (S_d), exposed/infected (but not infectious) dogs (E_d), infectious dogs (I_d), and recovered dogs (R_d). Susceptible dogs could be transferred to exposed dogs, exposed/infected dogs could be transferred to infectious dogs, and infectious dogs could recover and become recovered dogs. Similarly, sand flies were distributed among susceptible sand flies (S_f), exposed/infected sand flies (E_f), and infectious sand flies (I_f). A modified SEIR model for human system is defined as susceptible humans (S_h), exposed (during incubation period) humans (E_h), infected humans (I_h), hospitalized humans (H_h), and recovered humans (R_h). The mathematical model for three sub-systems is shown below.

5.2.1 Dog population

$$\frac{dS_d}{dt} = \lambda_d - \frac{b_{fd}\beta_{fd}I_f S_d}{N_d} - \mu_d S_d \quad (5.1)$$

$$\frac{dE_d}{dt} = \frac{b_{fd}\beta_{fd}I_f S_d}{N_d} - \tau_d E_d - \mu_d E_d \quad (5.2)$$

$$\frac{dI_d}{dt} = \tau_d E_d - r_d I_d - d_d I_d - \mu_d I_d \quad (5.3)$$

$$\frac{dR_d}{dt} = r_d I_d - \mu_d R_d \quad (5.4)$$

where S_d denotes the number of susceptible dogs, E_d denotes the number of exposed/infected dogs, I_d denotes the number of infectious dogs, R_d denotes the number of recovered dogs, and N_d denotes the total number of dogs.

The above model is a classic SEIR model. In equation (5.1), a constant birth rate λ_d was used for susceptible dogs, the amount of $b_{fd}\beta_{fd}I_f S_d/N_d$ susceptible dogs were moved from compartment S_d (susceptible population) to E_d (exposed/infected population) due to ZVL transmission where S_d/N_d denotes the contact rate between susceptible dogs and sand flies, and $\mu_d S_d$ susceptible dogs were removed because of natural death. Similarly, in equation (5.2) $\tau_d E_d$ exposed/infected dogs (from compartment E_d) became infectious dogs (into compartment I_d) and $\mu_d E_d$ exposed dogs were removed due to natural death. In equation (5.3), a portion of $r_d I_d$ infectious dogs recovered and converted to R_d , but $d_d I_d$ more infectious dogs died due to the disease or culling strategy, in addition to $\mu_d I_d$ natural deaths. Recovered dogs remained under treatment and were assumed to not be reinfected and $\mu_d R_d$ ones were removed because of natural death. In addition, E_d could be seropositive but not culled or dead due to the disease (This was assumed as these animals are, at least in theory, infected but not yet tested).

5.2.2 Sand fly population

$$\frac{dS_f}{dt} = \lambda_f - \frac{b_{fd}\beta_{df}I_d S_f}{N_d} - m_f S_f - \mu_f S_f \quad (5.5)$$

$$\frac{dE_f}{dt} = \frac{b_{fd}\beta_{df}I_d S_f}{N_d} - \tau_f E_f - m_f E_f - \mu_f E_f \quad (5.6)$$

$$\frac{dI_f}{dt} = \tau_f E_f - d_f I_f - m_f I_f - \mu_f I_f \quad (5.7)$$

where S_f denotes the number of susceptible sand flies, E_f denotes the number of exposed/infected sand flies, I_f denotes the number of infectious sand flies.

The above model is a SEI model similar to the system in Section 5.2.1 but without the recovered stage. With a constant birth rate λ_f for susceptible sand flies, $b_{fd}\beta_{df}I_d S_f/N_d$ susceptible sand flies moved from compartment S_f (susceptible) to E_f (exposed/infected) due to ZVL transmission via contacts between infectious dogs and susceptible sand flies, and $\mu_f S_f$ susceptible sand flies were eliminated because of natural death. The portion of $\tau_f E_f$ exposed sand flies became infectious sand flies, and $\mu_f E_f$ exposed sand flies are expired due to natural death. In equation (5.7), the portion of $d_f I_f$ more infectious sand flies expired due to the disease, in addition to $\mu_f I_f$ natural deaths. Infectious sand flies cannot recover from the disease. Moreover, $m_f(S_f + E_f + I_f)$ sand flies were assumed to emigrate from the system.

5.2.3 Sand fly population

$$\frac{dS_h}{dt} = \lambda_h - \frac{b_{fh}\beta_{fh}I_f S_h}{N_h} - \mu_h S_h \quad (5.8)$$

$$\frac{dE_h}{dt} = \frac{b_{fh}\beta_{fh}I_f S_h}{N_h} - \tau_h E_h - \mu_h E_h \quad (5.9)$$

$$\frac{dI_h}{dt} = \tau_h E_h - \delta_h I_h - d_I I_h - r_I I_h - \mu_h I_h \quad (5.10)$$

$$\frac{dH_h}{dt} = \delta_h I_h - d_H H_h - r_H H_h - \mu_h H_h \quad (5.11)$$

$$\frac{dR_h}{dt} = r_H H_h + r_I I_h - \mu_h R_h \quad (5.12)$$

where S_h denotes the number of susceptible individuals, E_h denotes the number of exposed individuals, I_h denotes the number of infected individuals, H_h denotes the number of hospitalized

individuals, and R_h denotes the number of recovered individuals, and N_h denotes the total number of humans.

The above model is a modified SEIR model with compartment H_h , which represents the number of individuals who are taken to the hospital by family and/or health authorities with regards to infected and symptomatic people. A constant birth rate λ_h exists for susceptible individuals. In Eq. (5.8), the amount of $b_{fh}\beta_{fh}I_fS_h/N_h$ susceptible individuals moved from compartment S_h to E_h due to ZVL transmission, and μ_hS_h susceptible individuals were removed because of natural death. For exposed individuals in Eq. (5.9), τ_hE_h became infected individuals, and μ_hE_h exposed individuals were removed due to natural death. In Eq. (5.10), δ_hI_h infected individuals are taken to the hospital and move to compartment H_h and $d_I I_h$ of them died due to the disease before they went to the hospital. We assume few infected individuals, $r_I I_h$, recovered and moved to recovered individuals. For hospitalized individuals in Eq. (5.11), $r_H H_h$ recovered and converted to recovered individuals and $d_H H_h$ expires because of disease. In Eq. (5.12), recovered individuals could not be reinfected so that only $\mu_h R_h$ are removed due to natural death.

5.2.4 Well-posedness of the solutions

Considering the physical meaning of ZVL transmissions, only nonnegative initial conditions are used and negative solutions are not allowed. All parameters in the system are nonnegative as well. In this section, we prove that all solutions in Eqs (5.1) - (5.12) are nonnegative if initial conditions are nonnegative and they are bounded.

Proof: According to Theorem 2.1 in (104) which is

"Assume that whenever $\phi \in D$ satisfies $\phi \geq 0, \phi_i(0) = 0$ for some i and $t \in R$, then $f_i(t, \phi) \geq 0$. If $\phi \in D$ satisfies $\phi \geq 0$ and $t_0 \in R$, then $f_i(t, \phi) \geq 0$."

It is easy to test that all of our equations satisfy the conditions in the above theorem so that we know $S_d(t) \geq 0, E_d(t) \geq 0, I_d(t) \geq 0, R_d(t) \geq 0, S_f(t) \geq 0, E_f(t) \geq 0, I_f(t) \geq 0, S_h(t) \geq 0, E_h(t) \geq 0, I_h(t) \geq 0, H_h(t) \geq 0$, and $R_h(t) \geq 0$, if $S_d(0) \geq 0, E_d(0) \geq 0, I_d(0) \geq 0, R_d(0) \geq 0, S_f(0) \geq 0, E_f(0) \geq 0, I_f(0) \geq 0, S_h(0) \geq 0, E_h(0) \geq 0, I_h(0) \geq 0, H_h(0) \geq 0$, and $R_h(0) \geq 0$.

Based on Eqs (5.1) - (5.12), we have

$$\frac{dN_d}{dt} = \lambda_d - d_d I_d - \mu_d N_d \quad (5.13)$$

$$\frac{dN_f}{dt} = \lambda_f - m_f N_f - d_f I_f - \mu_f N_f \quad (5.14)$$

$$\frac{dN_h}{dt} = \lambda_h - d_I I_h - d_H H_h - \mu_h N_h \quad (5.15)$$

where $N_d = S_d + E_d + I_d + R_d, N_f = S_f + E_f + I_f, N_h = S_h + E_h + I_h + H_h + R_h$. When $t \rightarrow \infty$, we have $N_d < \lambda_d/\mu_d, N_f < \lambda_f/(m_f + \mu_f), N_h < \lambda_h/\mu_h$ since $d_d, I_d, d_f, I_f, d_I, I_h, d_H, H_h \geq 0$. Hence, N_d, N_f , and N_h are bounded. Then $S_d, E_d, I_d, R_d, S_f, E_f, I_f, S_h, E_h, I_h, H_h$, and R_h are bounded since they are all nonnegative.

5.2.5 Calculation of R_0

The basic ratio R_0 is defined as “the average number of secondary cases arising from an average primary case in an entirely susceptible population” (71). This ratio can be solved based on disease free equilibrium (DFE).

The entire system (Eqs. (5.1)-(5.12)) has a DFE given by

$$E_0 = (S_d^*, E_d^*, I_d^*, R_d^*, S_f^*, E_f^*, I_f^*, S_h^*, E_h^*, I_h^*, H_h^*, R_h^*) = \left(\frac{\lambda_d}{\mu_d}, 0, 0, 0, \frac{\lambda_f}{\mu_f + m_f}, 0, 0, \frac{\lambda_h}{\mu_h}, 0, 0, 0, 0 \right). \quad (5.16)$$

Linear stability of E_0 can be established using the next generation operator method (105).

Matrices F (for the rate of appearance of new infections) and V (for the rate of transfer of individuals) are given, respectively, by:

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{b_{fd}\beta_{fd}S_d^*}{N_d^*} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{b_{fd}\beta_{df}S_f^*}{N_d^*} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{b_{fh}\beta_{fh}S_h^*}{N_h^*} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad (5.17)$$

$$V = \begin{bmatrix} k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\tau_d & k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -r_d & \mu_d & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\tau_f & k_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\tau_h & k_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\delta_h & k_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -r_I & -r_H & \mu_h \end{bmatrix} \quad (5.18)$$

Where $k_1 = \tau_d + \mu_d$, $k_2 = r_d + d_d + u_d$, $k_4 = \tau_f + m_f + \mu_f$, $k_5 = d_f + m_f + \mu_f$, $k_6 = \tau_h + \mu_h$, $k_7 = \delta_h + d_I + r_I + \mu_h$, $k_8 = d_H + r_H + \mu_h$, $N_d^* = S_d^*$ and $N_h^* = S_h^*$.

Therefore, the basic reproduction number, denoted by R_0 , is given by

$$R_0 = \rho(FV^{-1}) = \frac{b_{fd} \sqrt{k_1 k_2 k_4 k_5 \beta_{fd} \beta_{df} \tau_d \tau_f S_d^* S_f^*}}{k_1 k_2 k_4 k_5 N_d^*}. \quad (5.19)$$

where ρ is the spectral radius (dominant eigenvalue in magnitude or maximum of the absolute values of eigenvalues of the matrix). The threshold quantity R_0 , the basic reproduction number of the disease, represents the average number of secondary cases that one infected case can generate if introduced into a completely susceptible population. Hence, using Theorem 2 of (105), we

established the following result: disease free equilibrium, E_0 , of the system (Eqs. (5.1) - (5.12)), is locally asymptotically stable (LAS) if $R_0 < 1$ and unstable if $R_0 > 1$.

In general, when R_0 is less than 1, a small influx of infected sand flies into the community does not lead to large outbreaks, and the disease is eliminated in the end (since DFE is LAS). However, as we demonstrate in Section 5.3, the disease may persist even when $R_0 < 1$.

5.3 Backward Bifurcation

5.3.1 Backward bifurcation

In (100), the conjecture was made that the zoonotic disease model may exhibit backward bifurcation. In order to find endemic equilibria of the system (equilibrium in which at least one of the infected components is non-zero), the following steps was taken.

$E_1 = (S_d^{**}, E_d^{**}, I_d^{**}, R_d^{**}, S_f^{**}, E_f^{**}, I_f^{**}, S_h^{**}, E_h^{**}, I_h^{**}, H_h^{**}, R_h^{**})$ represents any arbitrary endemic equilibrium of the model. Let $\theta_d^{**} = \frac{b_{fd}\beta_{fd}I_f^{**}}{N_d^{**}}$, $\theta_f^{**} = \frac{b_{fd}\beta_{df}I_d^{**}}{N_d^{**}}$, $\theta_h^{**} = \frac{b_{fh}\beta_{fh}I_f^{**}}{N_h^{**}}$, where $N_d^{**} = S_d^{**} + E_d^{**} + I_d^{**} + R_d^{**}$, $N_h^{**} = S_h^{**} + E_h^{**} + I_h^{**} + H_h^{**} + R_h^{**}$.

Solving the equations at steady state gives

$$S_d^{**} = \frac{\lambda_d}{\theta_d^{**} + \mu_d} \quad (5.20)$$

$$E_d^{**} = \frac{\theta_d^{**}\lambda_d}{k_1(\theta_d^{**} + \mu_d)} \quad (5.21)$$

$$I_d^{**} = \frac{\theta_d^{**}\tau_d\lambda_d}{k_1k_2(\theta_d^{**} + \mu_d)} \quad (5.22)$$

$$R_d^{**} = \frac{\theta_d^{**}\tau_d\lambda_d r_d}{k_1k_2\mu_d(\theta_d^{**} + \mu_d)} \quad (5.23)$$

$$S_f^{**} = \frac{\lambda_f}{\theta_f^{**} + k_3} \quad (5.24)$$

$$E_f^{**} = \frac{\theta_f^{**} \lambda_f}{k_4(\theta_f^{**} + k_3)} \quad (5.25)$$

$$I_f^{**} = \frac{\theta_f^{**} \lambda_f \tau_f}{k_4 k_5 (\theta_f^{**} + k_3)} \quad (5.26)$$

$$S_h^{**} = \frac{\lambda_h}{\theta_h^{**} + \mu_h} \quad (5.27)$$

$$E_h^{**} = \frac{\theta_h^{**} \lambda_h}{k_6(\theta_h^{**} + \mu_h)} \quad (5.28)$$

$$I_h^{**} = \frac{\theta_h^{**} \lambda_h \tau_h}{k_6 k_7 (\theta_h^{**} + \mu_h)} \quad (5.29)$$

$$H_h^{**} = \frac{\theta_h^{**} \lambda_h \tau_h \delta_h}{k_6 k_7 k_8 (\theta_h^{**} + \mu_h)} \quad (5.30)$$

$$R_h^{**} = \frac{\theta_h^{**} \lambda_h \tau_h (\delta_h r_H + r_I k_8)}{k_6 k_7 k_8 \mu_h (\theta_h^{**} + \mu_h)} \quad (5.31)$$

Substituting Eqs. (5.20) - (5.31) in θ_d^{**} and θ_f^{**} and simplifying after algebraic manipulations respectively gives

$$\theta_d^{**} = \frac{b_{fd} \beta_{fd} \tau_f \lambda_f k_1 k_2 \mu_d \theta_f^{**} (\theta_d^{**} + \mu_d)}{(\theta_f^{**} + k_3) k_4 k_5 [k_2 \mu_d \lambda_d (k_1 + \theta_d^{**}) + \tau_d \lambda_d \theta_d^{**} (\mu_d + r_d)]} \quad (5.32)$$

$$\theta_f^{**} = \frac{b_{fd} \beta_{df} \tau_d \mu_d \theta_d^{**}}{k_2 \mu_d (k_1 + \theta_d^{**}) + \tau_d \theta_d^{**} (\mu_d + r_d)} \quad (5.33)$$

Substitution of (5.33) in (5.32) shows that non-zero equilibria of the model satisfies the following quadratic (in terms of θ_d^{**})

$$a_0 (\theta_d^{**})^2 + b_0 (\theta_d^{**}) + c_0 = 0 \quad (5.34)$$

where $a_0 = k_4 k_5 \lambda_d [k_2 b_{fd} \beta_{df} \tau_d \mu_d^2 + k_2^2 k_3 \mu_d^2 + b_{fd} \beta_{df} \tau_d^2 \mu_d (\mu_d + r_d) + 2k_2 k_3 \mu_d \tau_d (\mu_d + r_d) + k_3 \tau_d^2 (\mu_d + r_d)^2]$, $b_0 = k_1 k_2 k_4 k_5 \mu_d \lambda_d [b_{fd} \beta_{df} \tau_d \mu_d + 2k_2 k_3 \mu_d + 2k_3 \tau_d (\mu_d + r_d) - k_1 k_2 k_3 R_0^2]$, $c_0 = k_1^2 k_2^2 k_3 k_4 k_5 \mu_d^2 \lambda_d (1 - R_0^2)$.

The quadratic equation can be analyzed for the possibility of multiple endemic equilibriums (57). We achieved positive equilibrium of the system by solving for θ_d^{**} from the

quadratic equation (5.34) and substituting the results (positive value of θ_d^{**}) into expressions in Eqs. (5.20) - (5.31). From above formula, the coefficient a_0 of (5.34) is always positive and c_0 is positive (negative) if R_0 is less than (greater than) one, respectively. Therefore, the following result is established:

Theorem 1: The system has:

- i. a unique endemic equilibrium exist if $c_0 < 0$;
- ii. a unique endemic equilibrium exist if $b_0 < 0$, and $c_0 = 0$ or $b_0^2 - 4a_0c_0 = 0$;
- iii. two endemic equilibriums exist if $c_0 > 0$, $b_0 < 0$, and $b_0^2 - 4a_0c_0 > 0$;
- iv. no endemic equilibrium exist otherwise.

This method, also used in a Dengue model (105), is a general way to evaluate the system. Theorem 1 (Case i) clearly demonstrates that the model has a unique endemic equilibrium when $R_0 > 1$. Case (iii) indicates the possibility of backward bifurcation in which local asymptotically stable DFE co-exists with a locally-asymptotically stable endemic equilibrium when $R_0 < 1$. In this case, we possibly reach an endemic equilibrium instead of DFE even when $R_0 < 1$, depending on how many infections occur in the population at the beginning. A critical value of R_0 , denoted by R_c , is given by setting $b_0^2 - 4a_0c_0 = 0$. Considering the physical meaning of each parameter, we could numerically test that only one solution of R_c is possible among four roots of the equation. To simplify the notation, let $b_1 = k_1k_2k_4k_5\mu_d\lambda_d$, $b_2 = b_{fd}\beta_{df}\tau_d\mu_d + 2k_2k_3\mu_d + 2k_3\tau_d(\mu_d + r_d)$, $b_3 = k_1k_2k_3$, $c_1 = k_1^2k_2^2k_3k_4k_5\mu_d^2\lambda_d$, we have:

$$R_c = \sqrt{\frac{-B_0 + \sqrt{B_0^2 - 4A_0C_0}}{2A_0}} \quad (5.35)$$

where $A_0 = b_1^2b_3^2$, $B_0 = 4a_0c_1 - 2b_1^2b_2b_3$, $C_0 = b_1^2b_2^2 - 4a_0c_1$.

R_c is critical because no endemics equilibrium exists when $R_0 < R_c$. To successfully control the spread of ZVL, the reproduction number should be brought below R_c . Condition $R_0 < 1$ is not sufficient for a complete control of the spread of ZVL described; therefore, backward bifurcation would occur for values of R_0 such that $R_c < R_0 < 1$.

Before analyzing the conditions of backward bifurcation, we presented numerical solutions for a given range of each parameter using Mathematica. For example, we simulated the model with a set of parameters that satisfies the condition of Case (iii) which also satisfies the reasonable range for each parameter.

The values applied are $\lambda_d = 25$, $\lambda_f = 65$, $\lambda_h = 25$, $\mu_d = 0.0014$, $\mu_f = 0.022$, $\mu_h = 8.3e - 5$, $b_{fd} = 0.1$, $b_{fh} = 0.1$, $\beta_{fd} = 0.5$, $\beta_{df} = 0.7$, $\beta_{fh} = 0.5$, $d_d = 0.017$, $d_f = 0$, $d_I = 0.0067$, $d_H = 0.0003$, $m_f = 0.0001$, $\tau_d = 0.1$, $\tau_f = 0.167$, $\tau_h = 0.0167$, $\delta_h = 0.8$, $r_d = 0.005$, $r_I = 0.12$, and $r_H = 0.95$ (57,96). With this set of parameters, $R_c = 0.968 < 1$ and $R_0 = 0.985 < 1$ (so that, $R_c < R_0 < 1$). The infectious dog population versus R_0 with the associated bifurcation diagram is depicted in Figure 6.2. In Region A, disease free equilibrium is locally asymptotically stable which indicates that the disease cannot spread out and the status would change back to disease free equilibrium if we have a few infected individuals in the beginning, while in Region B, one disease-persistent equilibrium is stable (little perturbation could not change the equilibrium status) and the other is unstable (little perturbation could change the status of the system and change to another equilibrium status, i.e. disease free equilibrium), thereby showing the coexistence of two stable equilibria when $R_c < R_0 < 1$ and confirming that the system exhibits backward bifurcation. Disease-persistent equilibrium is stable in Region C. Results shown in Figure 5.2 are summarized in Table 5.2.

To analyze the relationship between R_c and all possible parameters involved, we decide to focus on the parameters that are likely amenable to control and possibly represent the reality in the field (dogs, sand flies, and humans). In optimal control section, reduction of infection rate to dogs and humans, and use of insecticide against sand flies are considered. Hence, β_{fd} , β_{fh} , and μ_f are studied in order to figure out their impacts on R_0 and R_c .

Figure 5.2 Bifurcation diagram of the system

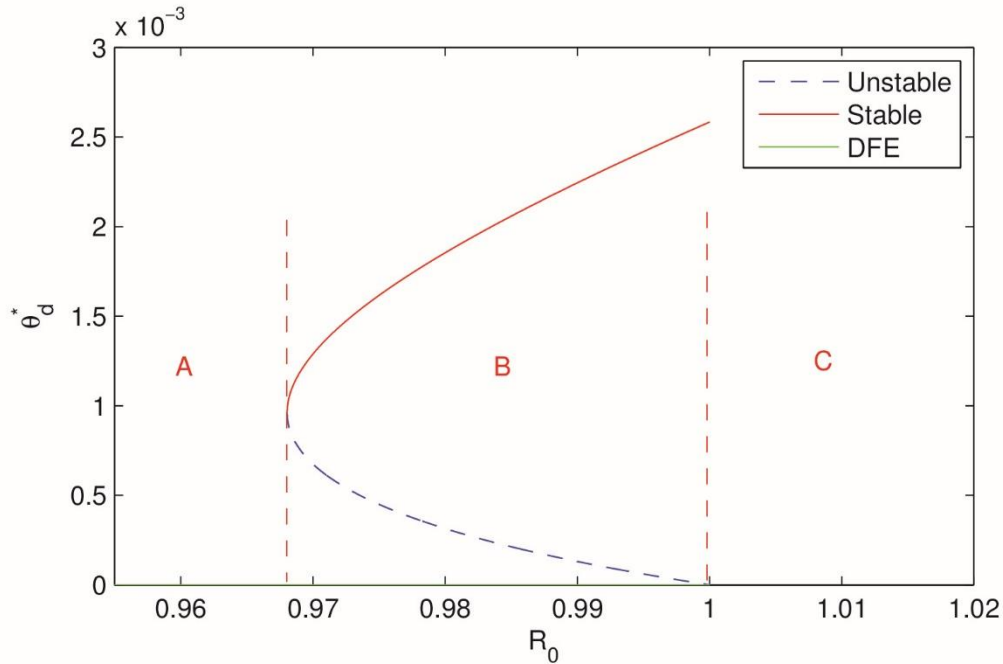


Table 5.2 Summary of backward bifurcation shown in Figure 5.2

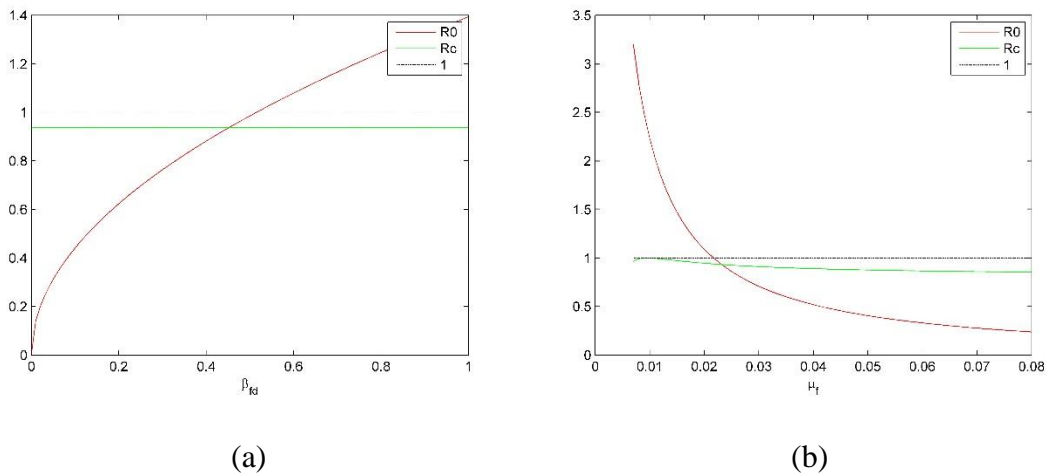
Region	R_0	Type of steady states	Stability of steady state
A	< 0.968	DFE	Stable
B	$0.968 \sim 1$	A DFE and two endemic equilibria	The DFE and one endemic equilibrium are stable while the other endemic equilibrium is unstable
C	> 1	A DFE and one endemic equilibrium	The DFE is unstable while the endemic equilibrium is stable

The value of R_c is not dependent on the parameter β_{fd} while the value of R_0 increases as β_{fd} increases. And therefore, we could find a range (shown in Fig. 5.3(a)) which satisfies the condition $R_c < R_0 < 1$ if we could change the infection rate to dogs.

It is surprising that neither of R_0 and R_c are dependent on the parameter β_{fh} , implying that the infection rate to humans does not affect the value of R_0 and R_c . Hence, humans do not contribute to the spread of disease since dogs and sand flies are not infected by humans. Although controlling the infection rate to humans will not impact the stability of disease free equilibrium, it is still very important when we discuss the optimal control strategies since reduction of the number of infected humans is one of our objectives. The optimal control strategies will be discussed in the next section.

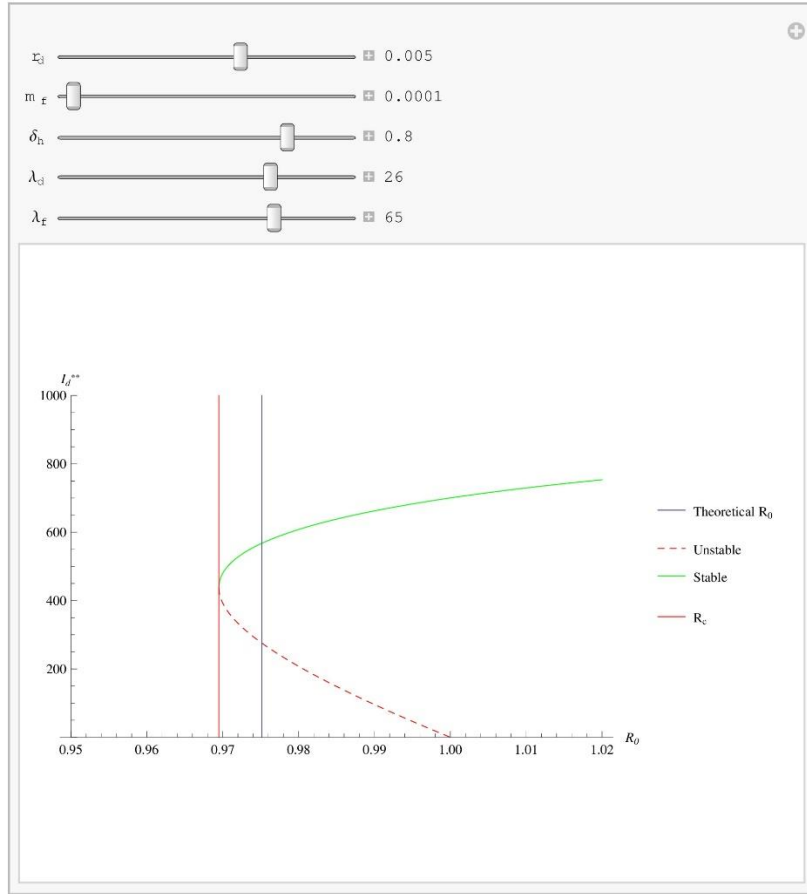
For the last parameter μ_f , it can affect the values of both of R_0 and R_c . The relationship between R_0 and μ_f and between R_c and μ_f is shown in figure 5.3(b). There is only a narrow range which satisfies the condition $R_c < R_0 < 1$. However, the value of R_0 is very sensitive to the value of μ_f , which shows that use of insecticide against sand flies is a good strategy if the insecticide is effective towards increasing the mortality rate of sand flies.

Figure 5.3 Impacts of parameters on backward bifurcation



A more general simulation is modeled using Mathematica which allow us to adjust the values of several model parameters and observe the simulation results in a dynamic fashion. Figure 5.4 shows a screenshot of this dynamical model which illustrates backward bifurcation for ZVL. I_d^{**} represents the number of infectious dogs at the endemic equilibrium point. The green curve represents a stable endemic equilibrium and the red dot curve represents an unstable endemic equilibrium. The intersection between two curves is a critical threshold R_c for backward bifurcation (which is represented using a red line in Figure 5.4). When $R_0 < R_c$, we only have one disease free equilibrium. When $R_c < R_0 < 1$, we have three equilibria: one stable disease free equilibrium, one unstable endemic equilibrium, and one stable endemic equilibrium. It turns out that if we have an endemic equilibrium in which the number of infectious dogs is in the range of the green line, we cannot control the spread of ZVL even if $R_0 < 1$. In the Figure 5.2, R_0 is calculated in terms of given parameters and it is in the range between R_c and 1. In this case, it is possible that we cannot control the spread of ZVL if we already have a certain number of infectious dogs.

Figure 5.4 General simulation with various parameter values



Analysis and simulation result established the following result: the model constructed in Section 5.2 underwent backward bifurcation when Case (iii) of Theorem 1 holds and $R_c < R_0 < 1$.

5.3.2 Stability of the endemic equilibrium

To discuss the stability of the endemic equilibrium, we need to determine the eigenvalues of the Jacobian matrix evaluated at the endemic equilibrium (106,107). Considering the complexity of the system, the calculation of eigenvalues is meaningful. However, we are interested in the stability of endemic equilibrium around $R_0 = 1$. And therefore, the centre manifold theory is considered.

$$\text{Let } \phi = \beta_{fd} \text{ as the bifurcation parameter, when } R_0 = 1, \text{ we have } \phi = \frac{k_1 k_2 k_4 k_5 \lambda_d (\mu_f + m_f)}{\mu_d \lambda_f b_{fd}^2 \beta_{df} \tau_d \tau_f}.$$

The Jacobian matrix of the dogs-sand flies-humans system at DFE when $\phi = \beta_{fd}$, is given

below:

$$J = \begin{bmatrix} -\mu_d & 0 & 0 & 0 & 0 & -b_{fd}\phi & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_1 & 0 & 0 & 0 & b_{fd}\phi & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \tau_d & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & r_d & -\mu_d & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\frac{b_{fd}\beta_{df}S_f^*}{N_d^*} & 0 & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{b_{fd}\beta_{df}S_f^*}{N_d^*} & 0 & 0 & -k_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \tau_f & -k_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_{fh}\beta_{fh} & -\mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & b_{fh}\beta_{fh} & 0 & -k_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_h & -k_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \delta_h & -k_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & r_I & r_H & -\mu_h \end{bmatrix} \quad (5.36)$$

We use Mathematica to calculate the eigenvalue of the Jacobian $J(\phi)$ and note that there is a simple zero eigenvalue. Hence, the centre manifold theory can be used to analyze the dynamics of the dogs-sand flies-humans system.

Let $\omega = (\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}, \omega_{11}, \omega_{12})^T$ be the right eigenvector associated with zero eigenvalue, we have

$$\omega_1 = -\frac{\lambda_d k_1 k_2 k_3 k_4 \omega_6}{\beta_{df} b_{fd} \lambda_f \mu_d^2 \tau_d} \quad (5.37)$$

$$\omega_2 = -\frac{\lambda_d k_2 k_3 k_4 \omega_6}{\beta_{df} b_{fd} \lambda_f \mu_d \tau_d} \quad (5.38)$$

$$\omega_3 = -\frac{\lambda_d k_3 k_4 \omega_6}{\beta_{df} b_{fd} \lambda_f \mu_d} \quad (5.39)$$

$$\omega_4 = \frac{\lambda_d r_d k_3 k_4 \omega_6}{\beta_{df} b_{fd} \lambda_f \mu_d^2} \quad (5.40)$$

$$\omega_5 = -\frac{k_4 \omega_6}{k_3} \quad (5.41)$$

$$\omega_6 = \omega_6 \quad (5.42)$$

$$\omega_7 = -\frac{\tau_f \omega_6}{k_5} \quad (5.43)$$

$$\omega_8 = -\frac{\beta_{fh} b_{fh} \tau_f \omega_6}{k_5 \mu_h} \quad (5.44)$$

$$\omega_9 = \frac{\beta_{fh} b_{fh} \tau_f \omega_6}{k_5 k_6} \quad (5.45)$$

$$\omega_{10} = \frac{\beta_{fh} b_{fh} \tau_f \tau_h \omega_6}{k_5 k_6 k_7} \quad (5.46)$$

$$\omega_{11} = \frac{\beta_{fh} b_{fh} \delta_h \tau_f \tau_h \omega_6}{k_5 k_6 k_7 k_8} \quad (5.47)$$

$$\omega_{12} = \frac{\beta_{fh} b_{fh} (\delta_h r_H + d_H r_I + \mu_h r_I + r_H r_I) \tau_f \tau_h \omega_6}{\mu_h k_5 k_6 k_7 k_8} \quad (5.48)$$

Similarly, the corresponding left eigenvector $v = (v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12})^T$

, where $v_1 = 0$, $v_2 = v_2$, $v_3 = \frac{k_1 v_2}{\tau_d}$, $v_4 = v_5 = 0$, $v_6 = \frac{\lambda_d k_1 k_2 k_3 v_2}{\beta_{df} b_{fd} \lambda_f \mu_d \tau_d}$, $v_7 = \frac{\lambda_d k_1 k_2 k_3 k_4 v_2}{\beta_{df} b_{fd} \lambda_f \mu_d \tau_d \tau_f}$, $v_8 = v_9 = v_{10} =$

$v_{11} = v_{12} = 0$.

To simplify the notation, let $S_d = x_1$, $E_d = x_2$, $I_d = x_3$, $R_d = x_4$, $S_f = x_5$, $E_f = x_6$, $I_f = x_7$, $S_h = x_8$,

$E_h = x_9$, $I_h = x_{10}$, $H_h = x_{11}$, and $R_h = x_{12}$. In addition, assume $\frac{dS_d}{dt} = f_1$, $\frac{dE_d}{dt} = f_2$, $\frac{dI_d}{dt} = f_3$, $\frac{dR_d}{dt} = f_4$,

$\frac{dS_f}{dt} = f_5$, $\frac{dE_f}{dt} = f_6$, $\frac{dI_f}{dt} = f_7$, $\frac{dS_h}{dt} = f_8$, $\frac{dE_h}{dt} = f_9$, $\frac{dI_h}{dt} = f_{10}$, $\frac{dH_h}{dt} = f_{11}$, $\frac{dR_h}{dt} = f_{12}$.

Let

$$a = \frac{1}{2} \sum_{i,j,k=1}^n v_i \omega_j \omega_k \frac{\partial^2 f_i}{\partial x_j \partial \beta_{fd}} (E_0, 0) \quad (5.49)$$

$$b = \sum_{i,j=1}^n v_i \omega_j \frac{\partial^2 f_i}{\partial x_j \partial \beta_{fd}} (E_0, 0) \quad (5.50)$$

If $b \neq 0$, the value of a (either positive or negative) determines the nature of the endemic equilibria near the $R_0 = 1$. In our system, we know $v_1 = v_4 = v_5 = v_8 = v_9 = v_{10} = v_{11} = v_{12} = 0$, so we only need to consider v_2 , v_3 , v_6 , and v_7 . In addition, the second derivative of f_3 , and f_7 are equal to 0, so

$$a = \frac{1}{2} (v_2 \sum_{j,k=1}^n \omega_j \omega_k \frac{\partial^2 f_2}{\partial x_j \partial x_k} (E_0, 0) + v_6 \sum_{j,k=1}^n \omega_j \omega_k \frac{\partial^2 f_6}{\partial x_j \partial x_k} (E_0, 0)) \quad (5.51)$$

$$b = v_2 \sum_{j=1}^n \omega_j \frac{\partial^2 f_2}{\partial x_j \partial \beta_{fd}} (E_0, 0) \quad (5.52)$$

Solve a and b , we have $a = -m_{11}\phi + m_{22}$, $b = v_2\omega_7 b_{fd} \neq 0$, where

$$m_{11} = v_2\omega_7(\omega_2 + \omega_3 + \omega_4)b_{fd}\mu_d/\lambda_d \quad (5.53)$$

$$m_{22} = \frac{v_6\omega_3 b_{fd}\beta_{df}\mu_d}{\lambda_d} (\omega_5 - \frac{\lambda_f\mu_d\omega_1\omega_2\omega_3\omega_4}{\lambda_d(\mu_f+m_f)}) \quad (5.54)$$

Based on the theorem in (108), if $\phi > \frac{m_{22}}{m_{11}}$, then $a < 0$ and the system undergoes a forward bifurcation and there are locally asymptotically stable endemic equilibria near DFE for $R_0 > 1$; while if $\phi < \frac{m_{22}}{m_{11}}$, the system has a backward bifurcation and there are unstable endemic equilibrium near DFE for $R_0 < 1$.

The epidemiological significance of backward bifurcation is that the classical requirement of $R_0 < 1$, although necessary, is no longer sufficient for disease elimination. In such a scenario, disease elimination depends on initial sizes of sub-populations (state variables) of the model. In other words, backward bifurcation in the ZVL transmission model suggests feasibility of controlling ZVL when $R_0 < 1$ could be dependent on initial sizes of the sub-population of the model. Therefore, methods for disease control must be improved.

5.4 Optimal Control

In this section, we extend the model in Section 5.2 to include density-dependent mortality rates in sand fly populations and recruitment rate in each susceptible population.

Define the density-dependent mortality rate for sand flies $\mu_f = \mu_1 + \mu_2 N_f$, where μ_1 is the density-independent death rate in the sand fly population, μ_2 is proportionality constant and N_f is the total number of sand flies. Similarly, we replaced previous recruitment rates to density-

dependent recruitment rate by $\lambda_d \rightarrow \lambda_d + \rho N_d$, $\lambda_f \rightarrow \lambda_f N_f$, and $\lambda_h \rightarrow \lambda_h + \gamma_h N_h$, where ρ and γ_h are proportionality constants showing the impact of density on recruitment rates.

In the dog population, the associated force of infection was reduced by a factor of $(1 - u_1(t))$, where $u_1(t)$ measures the level of successful prevention measures (vaccine protection). From the literature review, canine leishmaniasis (known as CanV or CanVL) was considered one of a few parasitic diseases likely to be controllable by vaccination (109,110). The strategy of culling dogs carries ethic and humanitarian issues, and it is not included as part of the three time-dependent control strategies in our studies but the model can easily address this issue by varying parameter d_d in the model (i.e., Eq.(5.3) in Section 5.2.1).

In the sand fly population, control strategy $u_2(t)$ represented the level of insecticide used for sand fly control administered at sand fly breeding sites. Consequently, the reproduction rate of the sand fly population was reduced by a factor of $(1 - u_2(t))$. The assumption was made that the mortality rate of sand fly increases at a rate proportional to $u_2(t)$, where $r_0 > 0$ is a rate constant.

In the human population, the associated force of infection was reduced by a factor of $(1 - u_3(t))$, where $u_3(t)$ measures the level of successful prevention (personal protection) efforts. Therefore, $u_3(t)$ indicates the use of alternative preventive measures to minimize or eliminate sand fly-human contacts.

Accounting for the above assumptions and extensions, the extended ZVL model with control strategy terms was constructed:

$$\frac{dS_d}{dt} = \lambda_d + \rho N_d - \frac{b_{fd}\beta_{fd}I_f S_d(1-u_1(t))}{N_d} - \mu_d S_d \quad (5.55)$$

$$\frac{dE_d}{dt} = \frac{b_{fd}\beta_{fd}I_f S_d(1-u_1(t))}{N_d} - \tau_d E_d - \mu_d E_d \quad (5.56)$$

$$\frac{dI_d}{dt} = \tau_d E_d - r_d I_d - d_d I_d - \mu_d I_d \quad (5.57)$$

$$\frac{dR_d}{dt} = r_d I_d - \mu_d R_d \quad (5.58)$$

$$\frac{dS_f}{dt} = \lambda_f N_f (1 - u_2(t)) - \frac{b_{fd} \beta_{df} I_d S_f}{N_d} - m_f S_f - (\mu_1 + \mu_2 N_f) S_f - r_0 u_2(t) S_f \quad (5.59)$$

$$\frac{dE_f}{dt} = \frac{b_{fd} \beta_{df} I_d S_f}{N_d} - \tau_f E_f - m_f E_f - (\mu_1 + \mu_2 N_f) E_f - r_0 u_2(t) E_f \quad (5.60)$$

$$\frac{dI_f}{dt} = \tau_f E_f - d_f I_f - m_f I_f - (\mu_1 + \mu_2 N_f) I_f - r_0 u_2(t) I_f \quad (5.61)$$

$$\frac{dS_h}{dt} = \lambda_h + \gamma_h N_h - \frac{b_{fh} \beta_{fh} I_f S_h (1 - u_3(t))}{N_h} - u_h S_h \quad (5.62)$$

$$\frac{dE_h}{dt} = \frac{b_{fh} \beta_{fh} I_f S_h (1 - u_3(t))}{N_h} - \tau_h E_h - u_h E_h \quad (5.63)$$

$$\frac{dI_h}{dt} = \tau_h E_h - \delta_h I_h - d_I I_h - r_I I_h - u_h I_h \quad (5.64)$$

$$\frac{dH_h}{dt} = \delta_h I_h - d_H H_h - r_H H_h - u_h H_h \quad (5.65)$$

$$\frac{dR_h}{dt} = r_H H_h + r_I I_h - u_h R_h \quad (5.66)$$

Moreover, the rate of change of the total populations of dogs, sand flies, and humans is respectively given by

$$\frac{dN_d}{dt} = \lambda_d + \rho N_d - d_d I_d - \mu_d N_d \quad (5.67)$$

$$\frac{dN_f}{dt} = N_f [\lambda_f (1 - u_2(t)) - m_f - (\mu_1 + \mu_2 N_f) - r_0 u_2(t)] - d_f I_f \quad (5.68)$$

$$\frac{dN_h}{dt} = \lambda_h + \gamma_h N_h - d_I I_h - d_H H_h - \mu_h N_h \quad (5.69)$$

According to the extended model above, an optimal control problem with the objective function is formulated by

$$J(u_1, u_2, u_3) = \int_0^T (A_1 E_h(t) + A_2 I_h(t) + A_3 N_f(t) + B_1 u_1^2(t) + B_2 u_2^2(t) + B_3 u_3^2(t)) dt \quad (5.70)$$

The objective is to minimize exposed and infected human populations, the total number of sand flies, and the cost of implementing the strategy. In Eq. (5.70), $A_1, A_2,$ and A_3 represent weight constants of the exposed, infected human and the total number of sand flies. In addition, $B_1, B_2,$

and B_3 are weight constants for dogs' prevention from disease, sand flies control, and human protection, respectively and $B_1u_1^2(t)$, $B_2u_2^2(t)$, and $B_3u_3^2(t)$ describe the costs associated with dogs' prevention, sand flies control, and human protection, respectively. These costs result from various sources. For example, cost associated with the first strategy primarily originates from the use of vaccination, cost associated with the second strategy primarily originates from the insecticide application, and cost associated with the third strategy originates from public health education to human populations, and testing equipment investments. We assumed that the costs are proportional to the square of the corresponding control function. Our goal was to determine optimal control functions (u_1^*, u_2^*, u_3^*) such that

$$J(u_1^*, u_2^*, u_3^*) = \min(J(u_1, u_2, u_3) | (u_1, u_2, u_3) \in \Gamma) \quad (5.71)$$

Subject to the extended system, where $\Gamma = \{(u_1, u_2, u_3) | u_i(t) \text{ is Lebesgue measurable on } [0, T], 0 \leq u_i(t) \leq 1, i = 1, 2, 3\}$ is the control set. The existence of an optimal control for the extended system would be proved and the optimality system would be derived.

5.4.1 Existence of an optimal control

Theorem 2: Consider the objective function J given by Eq. (5.70) with $(u_1, u_2, u_3) \in \Gamma$ subject to the constraint state system (Eqs. (5.55) - (5.66)). There exists $(u_1^*, u_2^*, u_3^*) \in \Gamma$ such that $J(u_1^*, u_2^*, u_3^*) = \min(J(u_1, u_2, u_3) | (u_1, u_2, u_3) \in \Gamma)$.

Proof: The integrand of the objective function given by Eq. (5.70) is convex on the closed, convex control set Γ . Conditions for the existence of optimal control are satisfied because the model is linear in the control variables and bounded by a linear system in the state variables (111).

5.4.2 Optimality system

Pontryagin's maximum principle (112) can be used for necessary conditions for an optimal control problem; the principle converts the problem into a problem of maximizing Hamilton H , with respect to u_1, u_2, u_3 :

$$H = A_1 E_h(t) + A_2 I_h(t) + A_3 N_f(t) + B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2 + \sum_{i=1}^{12} \lambda_i f_i \quad (5.72)$$

where f_i is the right-hand side of the differential equation of i -th state variable. Application of Pontryagin's Maximum Principle and the optimal control theory achieved the following theorem:

Theorem 3 Given an optimal control $u^* = (u_1^*, u_2^*, u_3^*)$ and corresponding state solutions $S_d, E_d, I_d, R_d, S_f, E_f, I_f, S_h, E_h, I_h, H_h$, and R_h of the corresponding state system, there adjoint functions, λ_i , exist for $i=1, 2, \dots, 12$, satisfying

$$\begin{aligned} \lambda_1' = & -\beta_{df} b_{fd} I_d \lambda_5 S_f / N_d^2 + \beta_{df} b_{fd} I_d \lambda_6 S_f / N_d^2 - \lambda_1 (-\mu_d + \rho + \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2 - \beta_{fd} b_{fd} I_f (1-u_1) / N_d) \\ & - \lambda_2 (\beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2 + \beta_{fd} b_{fd} I_f (1-u_1) / N_d) \end{aligned} \quad (5.73)$$

$$\begin{aligned} \lambda_2' = & -\beta_{df} b_{fd} I_d \lambda_5 S_f / N_d^2 + \beta_{df} b_{fd} I_d \lambda_6 S_f / N_d^2 - \lambda_1 (\rho + \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2) \\ & - \lambda_2 (-\mu_d - \tau_d - \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2) - \lambda_3 \tau_d \end{aligned} \quad (5.74)$$

$$\begin{aligned} \lambda_3' = & -\lambda_3 (-d_d - \mu_d - r_d) - \lambda_4 r_d - \lambda_5 (\beta_{df} b_{fd} I_d S_f / N_d^2 - \beta_{df} b_{fd} S_f / N_d) \\ & - \lambda_6 (-\beta_{df} b_{fd} I_d S_f / N_d^2 + \beta_{df} b_{fd} S_f / N_d) - \lambda_1 (\rho + \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2) \\ & + \lambda_2 \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2 \end{aligned} \quad (5.75)$$

$$\begin{aligned} \lambda_4' = & \lambda_4 \mu_d - \lambda_5 \beta_{df} b_{fd} I_d S_f / N_d^2 + \lambda_6 \beta_{df} b_{fd} I_d S_f / N_d^2 - \lambda_1 (\rho + \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2) \\ & + \lambda_2 \beta_{fd} b_{fd} I_f S_d (1-u_1) / N_d^2 \end{aligned} \quad (5.76)$$

$$\begin{aligned} \lambda_5' = & -A_3 + \lambda_7 \mu_2 I_f - \lambda_6 (-\mu_2 E_f + \beta_{df} b_{fd} I_d / N_d) \\ & - \lambda_5 (m_f - \mu_1 - \beta_{df} b_{fd} I_d / N_d - \mu_2 S_f - \mu_2 N_f + \lambda_f (1-u_2) - r_0 u_2) \end{aligned} \quad (5.77)$$

$$\lambda_6' = -A_3 - \lambda_7 (\mu_2 I_f + \tau_f) - \lambda_5 (-\mu_2 S_f + \lambda_f (1-u_2)) - \lambda_6 (m_f - \mu_1 - \mu_2 E_f - \mu_2 N_f - \tau_f - r_0 u_2) \quad (5.78)$$

$$\begin{aligned} \lambda_7' = & -A_3 + \lambda_6 \mu_2 E_f + \lambda_1 \beta_{fd} b_{fd} S_d (1-u_1) / N_d - \lambda_2 \beta_{fd} b_{fd} S_d (1-u_1) / N_d - \lambda_5 (\mu_2 S_f + \lambda_f (1-u_2)) \\ & - \lambda_7 (-d_f - m_f - \mu_1 - \mu_2 I_f - \mu_2 N_f - r_0 u_2) + \lambda_8 \beta_{fh} b_{fh} S_h (1-u_3) / N_h - \lambda_9 \beta_{fh} b_{fh} S_h (1-u_3) / N_h \end{aligned} \quad (5.79)$$

$$\begin{aligned}\lambda_8' &= -\lambda_8(\gamma_h - \mu_h + \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2 - \beta_{fh}b_{fh}I_f(1-u_3)/N_h) \\ &\quad -\lambda_9(-\beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2 + \beta_{fh}b_{fh}I_f(1-u_3)/N_h)\end{aligned}\quad (5.80)$$

$$\lambda_9' = -A_1 - \lambda_{10}\tau_h - \lambda_9(-\tau_h - \mu_h - \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2) - \lambda_8(\gamma_h + \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2) \quad (5.81)$$

$$\begin{aligned}\lambda_{10}' &= -A_2 - \lambda_{11}\delta_h - \lambda_{10}(-\delta_h - d_I - \mu_h - r_I) - \lambda_{12}r_I - \lambda_8(\gamma_h + \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2) \\ &\quad + \lambda_9\beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2\end{aligned}\quad (5.82)$$

$$\lambda_{11}' = -\lambda_{11}(-d_H - \mu_h - r_H) - \lambda_{12}r_H - \lambda_8(\gamma_h + \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2) + \lambda_9\beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2 \quad (5.83)$$

$$\lambda_{12}' = \lambda_{12}\mu_h - \lambda_8(\gamma_h + \beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2) + \lambda_9\beta_{fh}b_{fh}I_fS_h(1-u_3)/N_h^2 \quad (5.84)$$

The terminal conditions are

$$\lambda_i(T) = 0 \quad \text{for } i=1,2,\dots,12 \quad (5.85)$$

Moreover, optimal control u_1^*, u_2^*, u_3^* are given by

$$u_1^* = \max \left\{ 0, \min \left\{ 1, \frac{(\lambda_2 - \lambda_1)\beta_{fd}b_{fd}I_fS_d}{2B_1N_d} \right\} \right\} \quad (5.86)$$

$$u_2^* = \max \left\{ 0, \min \left\{ 1, \frac{\lambda_5\lambda_fN_f + r_0(\lambda_5S_f + \lambda_6E_f + \lambda_7I_f)}{2B_2} \right\} \right\} \quad (5.87)$$

$$u_3^* = \max \left\{ 0, \min \left\{ 1, \frac{(\lambda_9 - \lambda_8)\beta_{fh}b_{fh}I_fS_h}{2B_3N_h} \right\} \right\} \quad (5.88)$$

Proof:

Adjoint equations and transversality conditions can be obtained using Pontryagin's

Maximum Principle such that

$$\lambda_1' = -\frac{\partial H}{\partial S_d}, \lambda_1(T) = 0; \lambda_2' = -\frac{\partial H}{\partial E_d}, \lambda_2(T) = 0; \dots, \lambda_{12}' = -\frac{\partial H}{\partial R_h}, \lambda_{12}(T) = 0.$$

The optimal control u_1^*, u_2^*, u_3^* can be solved from the optimality conditions,

$$\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0, \quad \frac{\partial H}{\partial u_3} = 0.$$

5.4.3 Numerical results

We numerically calculated optimal control strategies based on the iterative method used in (57). Given initial state conditions without controls, we solved the state differential Eqs. (5.55) - (5.66) forward in time using the fourth order Runge-Kutta method. According to results of state values and the given final value in Eq. (5.85), we solved adjoint values in Eqs. (5.73) - (5.84) backward in time, using the fourth order Runge-Kutta method. Both updates of state values and adjoint values were utilized to calculate optimal control strategies in Eqs. (5.86) - (5.88). This process was repeated until a steady state was achieved. This algorithm is given below.

Step 1:

Initialize state variables:

$$S_d(0), E_d(0), I_d(0), R_d(0), S_f(0), E_f(0), I_f(0), S_h(0), E_h(0), I_h(0), H_h(0), R_h(0)$$

Initialize optimal control strategies:

$$u_1, u_2, u_3$$

Step 2:

Given small value $\varepsilon_1, \varepsilon_2, \varepsilon_3$ and final time value T:

While change of state values $> \varepsilon_1$, or change of adjoint values $> \varepsilon_2$, or change of controls $> \varepsilon_3$:

- I. Solve state values forward in time from 0 to T based on Eqs (5.55) - (5.66), using the fourth order of Runge-Kutta.

- II. Solve adjoint values backward in time from T to 0 based on Eqs (5.73) – (5.84), using the fourth order of Runge-Kutta.
- III. Solve control strategies u_1, u_2, u_3 using Eqs (5.86) – (5.88).

Step 3:

Find optimal control strategies:

$$u_1^* = u_1, u_2^* = u_2, u_3^* = u_3$$

The fourth order of Runge-Kutta method adopted here is given below.

$$\frac{dy}{dt} = f(y, t)$$

$$y_{i+1} = y_i + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4)h$$

where

$$k_1 = f(y_i, t_i)$$

$$k_2 = f\left(y_i + \frac{1}{2}k_1h, t_i + \frac{1}{2}h\right)$$

$$k_3 = f\left(y_i + \frac{1}{2}k_2h, t_i + \frac{1}{2}h\right)$$

$$k_4 = f(y_i + k_3h, t_i + h)$$

h is step size, given by $h = t_{i+1} - t_i$.

Table 5.3 Parameter values in numerical analysis

Parameter	Values
λ_d	0.02
λ_f	0.05
λ_h	0.05

$1/\mu_d$	700
$1/\mu_h$	12000
b_{fd}	0.1
b_{fh}	0.1
β_{fd}	0.5
β_{df}	0.7
β_{fh}	0.5
d_d	0.01
d_f	0
d_l	0.0067
d_H	3e-4
m_f	1e-4
$1/\tau_d$	10
$1/\tau_f$	6
$1/\tau_h$	60
δ_h	0.8
r_d	0.01
r_l	0.12
r_H	0.95
ρ	1e-3
μ_1	0.02
μ_2	5e-6
r_0	0.2
γ_h	2.85e-3

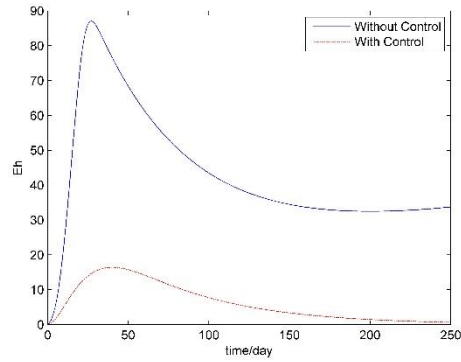
Parameter used in this section is defined in Table 5.3. The initialization of dogs, sand flies, and human population is given by $S_d(0)=100$, $S_f(0)=10000$, $S_h(0)=100$, $I_f(0)=10$, and $I_d(0)=5$. We proposed that control effectiveness could not be 100% effective for each control; then we reduced the upper bound of each control to observe the impact of control. The upper bounds of each control strategy u_1 , u_2 , and u_3 , were considered as 60%, 50%, and 60%, respectively.

Figure 5.5 describes scenarios for state variables E_h , I_h , and I_f for the case which $A_1=1$, $A_2=1$, $A_3=1e-5$, $B_1=1$, $B_2=1$, and $B_3=1$, meaning the reduction of exposed human, infected human, and number of sand flies are equally important and the cost of three control strategies are similar. Optimal control strategies are shown in Figure 5.6.

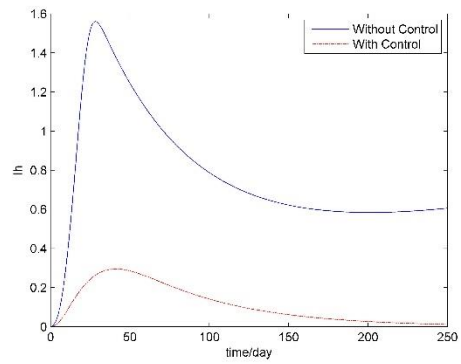
From the result in Figure 5.5, the number of exposed humans, infected humans, and infected sand flies were effectively controlled by the corresponding control strategies. However, the cost of each control did not have to be equal. When $B_1=10$, $B_2=1$, and $B_3=3$, meaning the dogs prevention measurement costs more, the control strategies are changed correspondingly. Figure 5.7 illustrates control strategies u_1 , u_2 , and u_3 in this scenario.

As the increase of the cost of u_1 , the optimal strategies are changed. The strategy for dog disease preventions was adopted much less than the previous scenario, shown in Figure 5.7(a). It is reasonable because increased costs lead to decreased use in order to minimize our objective function. Use of u_2 and u_3 also decreases after around 100 days. From Fig. 5.8(a) and 5.8(b), the number of exposed humans and infected humans both increase slightly due to the lower use of three strategies, while the number of sand flies keeps the same which is shown in Fig. 5.8(c). Hence,

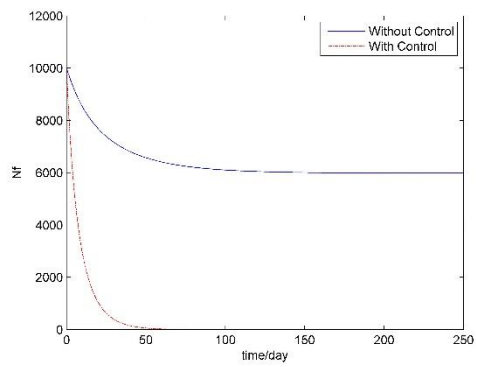
Figure 5.5 Simulation with controls $A_1=1, A_2=1, A_3=1e-5, B_1=1, B_2=1,$ and $B_3=1$



(a)

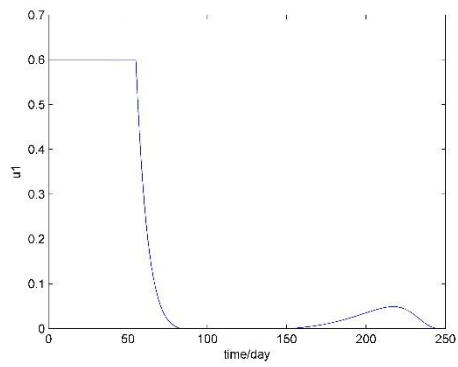


(b)

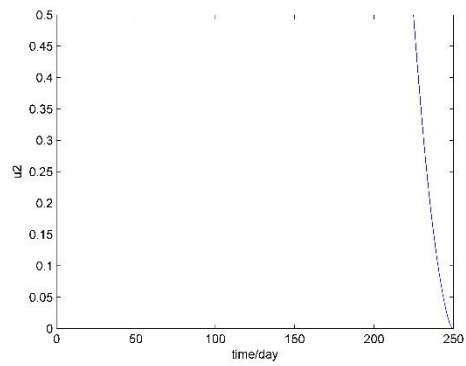


(c)

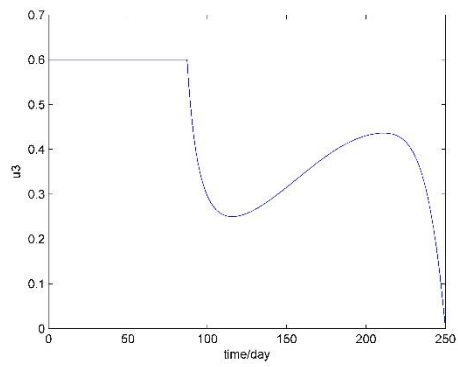
Figure 5.6 Control strategies with $A_1=1, A_2=1, A_3=1e-5, B_1=1, B_2=1,$ and $B_3=1$



(a)

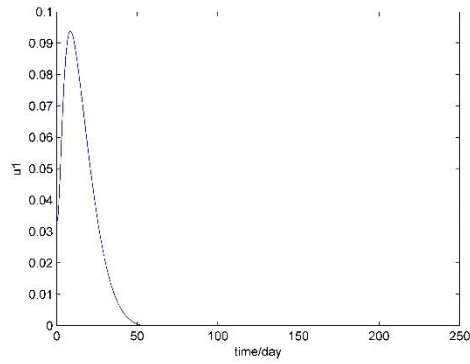


(b)

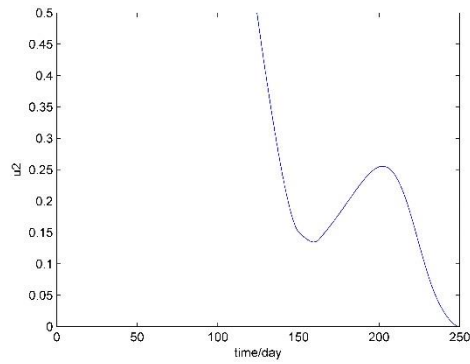


(c)

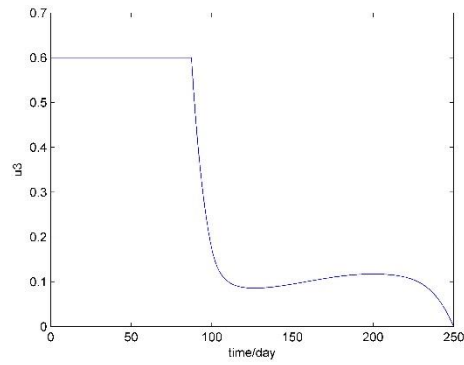
Figure 5.7 Control strategies with $A_1=1, A_2=1, A_3=1e-5, B_1=100, B_2=1,$ and $B_3=1$



(a)



(b)

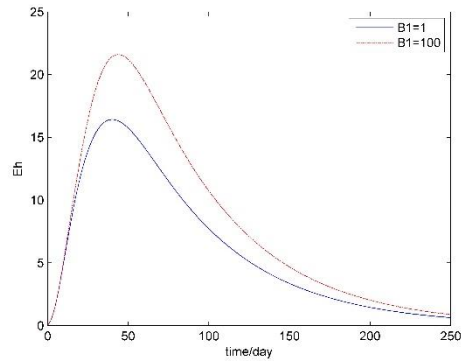


(c)

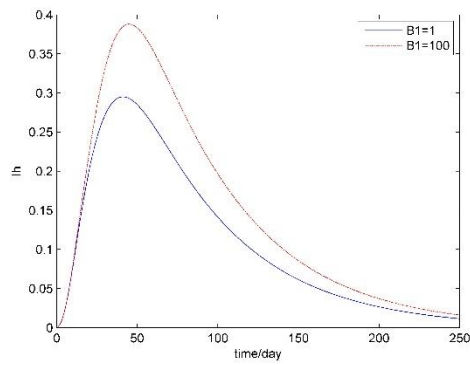
the change of the cost of implementing first strategy impacts controlling the number of exposed humans and infected humans but the number of sand flies.

Similarly, the impacts of u_2 and u_3 are evaluated through changing the cost of each strategy, which is shown in Figures 5.9 to 5.12. Compared to the first strategy, the second strategy has the similar impact to the system, as shown in Figure 5.9 and Figure 5.10. The use of u_2 decreases when

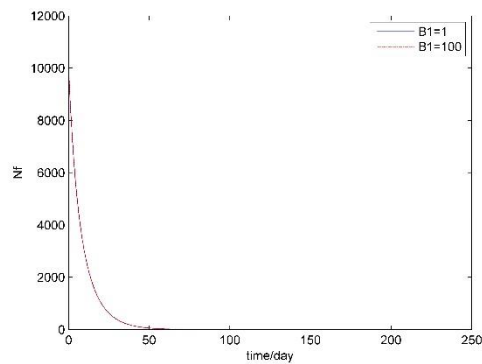
Figure 5.8 Simulation with $A_1=1, A_2=1, A_3=1e-5, B_2=1,$ and $B_3=1$



(a)

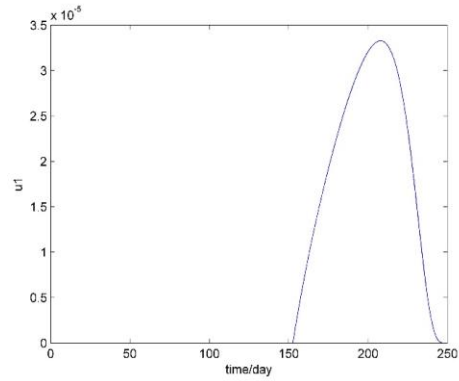


(b)

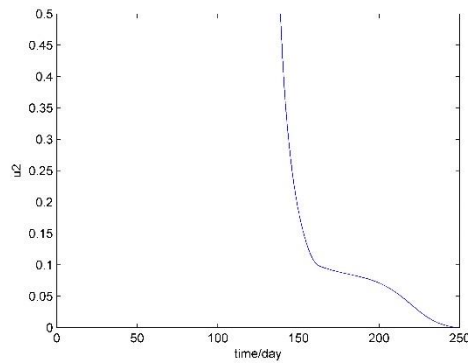


(c)

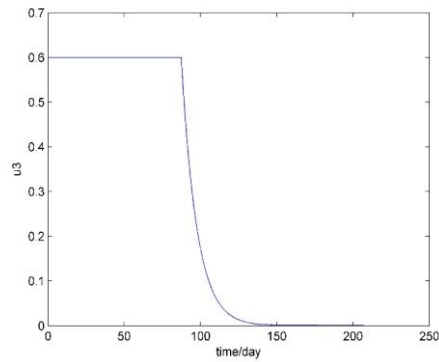
Figure 5.9 Control strategies with $A_1=1, A_2=1, A_3=1e-5, B_1=1, B_2=100,$ and $B_3=1$



(a)



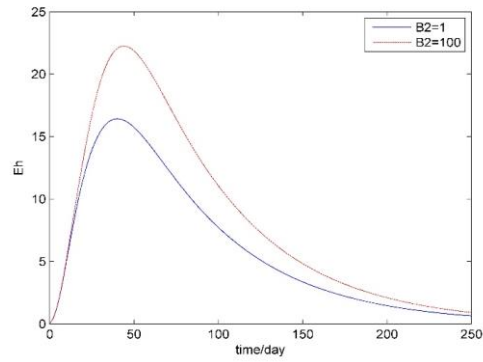
(b)



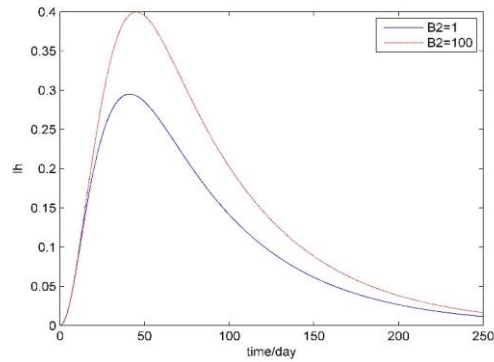
(c)

its cost changes from 1 to 100. Meanwhile, the use of u_1 and u_3 also decrease. As a response, the number of exposed humans and infected humans increase and the number of sand flies remains the same.

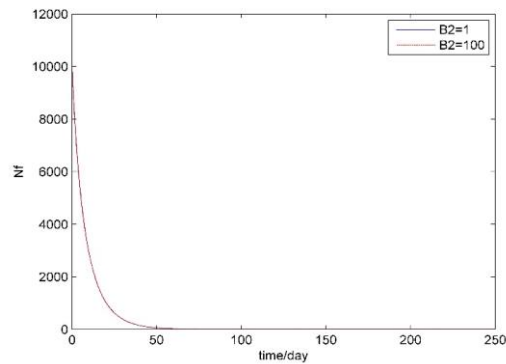
Figure 5.10 Simulation with $A_1=1, A_2=1, A_3=1e-5, B_1=1,$ and $B_3=1$



(a)



(b)

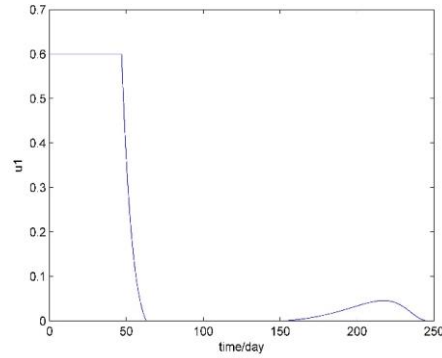


(c)

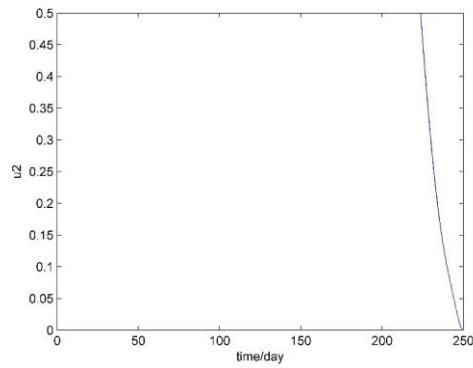
In Fig. 5.11 and Fig. 5.12, it shows the impact of changing the cost of the third strategy. As the cost increase from 1 to 100, the use of u_3 is reduced, while the use of u_1 and u_2 keep the

same. As a result, it leads to more exposed humans and infected humans and the number of sand flies remain the same.

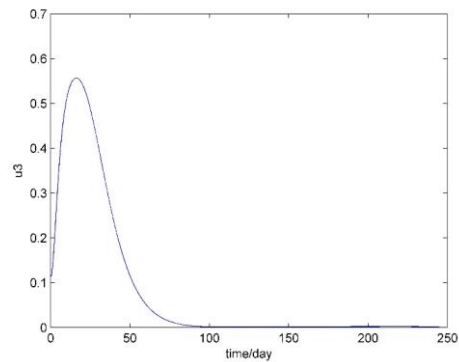
Figure 5.11 Control strategies with $A_1=1, A_2=1, A_3=1e-5, B_1=1, B_2=1,$ and $B_3=100$



(a)

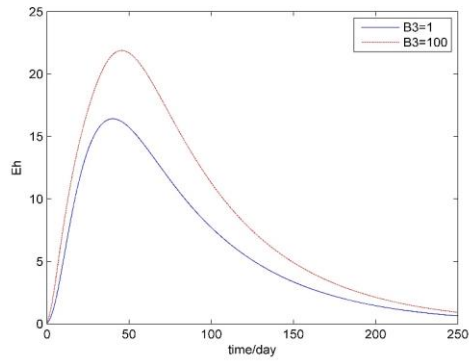


(b)

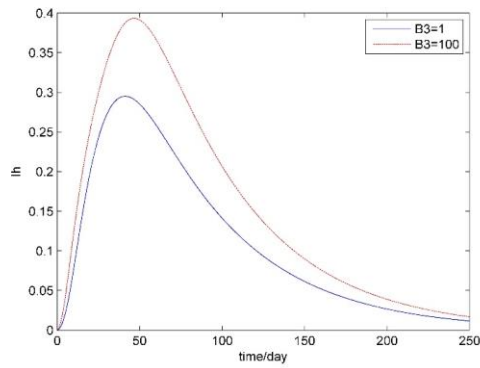


(c)

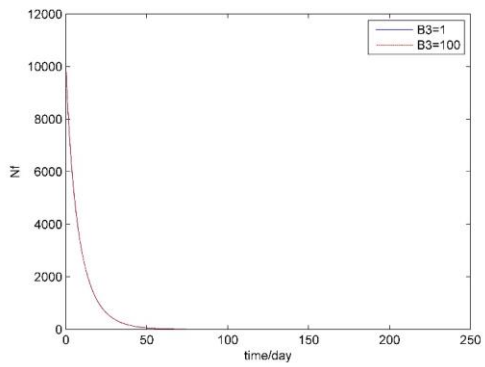
Figure 5.12 Simulation with $A_1=1, A_2=1, A_3=1e-5, B_1=1,$ and $B_2=1$



(a)



(b)

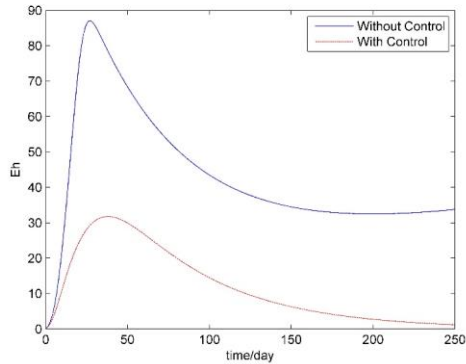


(c)

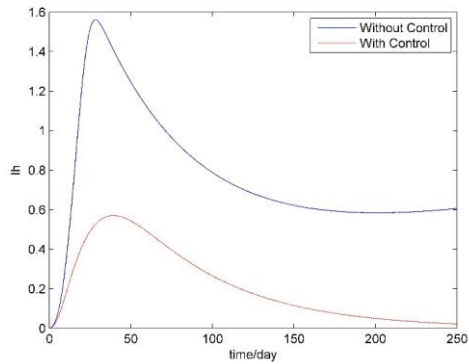
In sum, the overall use of the corresponding strategy decreases leading to the increased number of exposed and possibly infected humans, as the estimated cost for disease prevention in dogs, sand flies, and humans increase. Further, our simulation (presented in Figures 5.8, 5.10, and

5.12) indicate that the number of sand flies does not change significantly as the cost of the control strategies increase, whereas the number of exposed and infected humans increase. This indicates that the number of sand flies has a greater impact for minimizing our objective function. To control

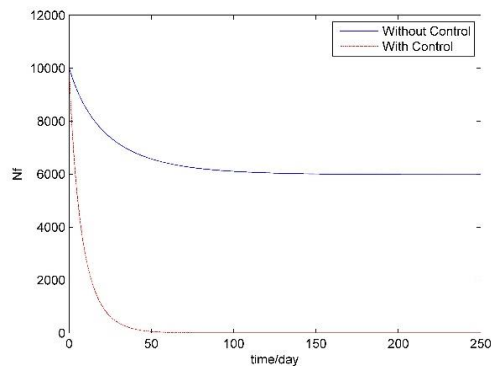
Figure 5.13 Simulation with upper bound of control $u_3 = 0.1$



(a)

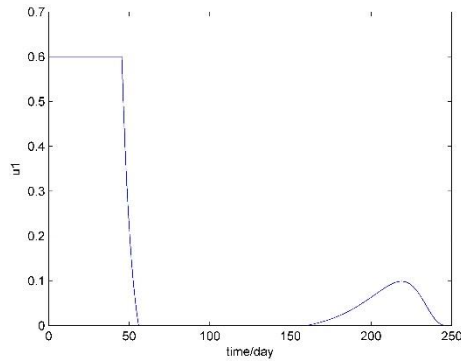


(b)

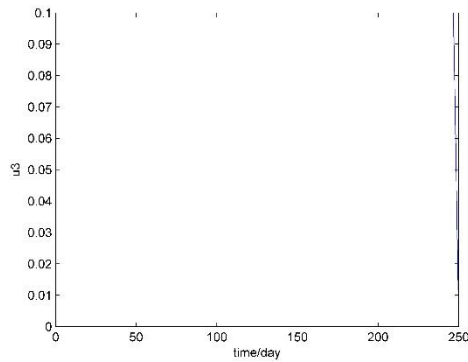


(c)

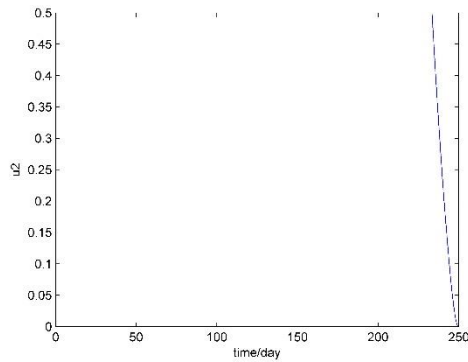
Figure 5.14 Control strategies with upper bound of control $u_3 = 0.1$



(a)



(b)



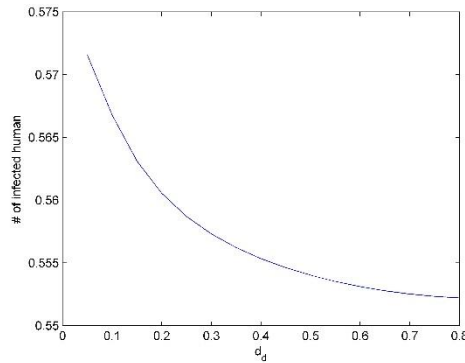
(c)

the number of sand flies, the use of u_2 (i.e., insecticide used to control sand flies) has to remain at high level. This is supported by our simulations of (unchanged) insecticide use for the first 150 days even if the cost of insecticides increases from 1 to 100 (Figures 5.7, 5.9, 5.11). Taken together,

our results indicate that controlling the number of sand flies is the most effective and recommended methodology to control ZVL transmission.

In addition, change of effectiveness of control strategies impacts the dynamics of the entire system from Eq. (5.55) to Eq. (5.66). Let upper bound of $u_3 = 0.1$, meaning that the effectiveness of human prevention from disease is extremely low. The number of exposed human, infected human, and infected sand flies are depicted in Figure 5.13. Compared to Figure 5.5, an increasing number of exposed and infected human populations is evident in Figure 5.13 due to the lessened control strategy effectiveness of prevention measurement for humans. In Figure 5.14, the use of each control strategy is shown and there is no big difference for the use of the first strategy and the second strategy.

Figure 5.15 Sensitivity analysis of culling dog strategy



Based on the above analyses, it is shown that control of ZVL transmission using the three strategies (u_1, u_2, u_3) is doable. In addition to the above strategies, culling dogs is often adopted as a control strategy for ZVL. Although culling dogs has been used, its efficacy has frequently been questioned. Our analysis of the parameter d_d , (in Eq. (5.57)) especially when the other three approaches are not available, clearly show culling to be ineffective (Figure 5.15), regardless of the culling rate.

5.5 Conclusion

Here, a three-system mathematical model for ZVL transmission with dogs, sand flies, and humans, was developed using a modified SEIR model. Backward bifurcation analysis suggested that $R_0 < 1$ is not a sufficient condition to control the spread of disease in this model, and both disease-free equilibrium and endemic equilibrium can coexist under certain conditions. Therefore, the condition $R_0 < R_c$ is required in order to control or eradicate the disease. A specific mathematical method to calculate optimal control strategies was given in this paper. Pontryagin's maximum principle, previously used to identify optimal control strategies against West Nile (57) or other vector-borne diseases (53), was also used here to determine possible optimal control strategies for ZVL. The results obtained for optimal control were highly dependent on the cost of each strategy and the effectiveness of each control strategy. Interestingly, our results (optimal system analysis) suggest that as the estimated cost for disease prevention increases, the overall use of the corresponding strategy or strategies decreases leading to the increased number of exposed and possibly infected humans. Further, our simulation (presented in Figures 5.8, 5.10, and 5.12) indicate that the number of sand flies does not change significantly as the cost of the control strategies increase, whereas the number of exposed and infected humans increase. This indicates that the number of sand flies has a greater impact for minimizing our objective function. To control the number of sand flies, the use of u_2 (i.e., insecticide used to control sand flies) has to remain at high level. This is supported by our simulations of (unchanged) insecticide use for the first 150 days even if the cost of insecticides increases from 1 to 100 (Figures 5.7, 5.9, 5.11). Taken together, our results indicate that controlling the number of sand flies is the most effective and recommended methodology to control ZVL transmission. Culling dogs is not an effective strategy to control the disease transmission. Although the simulation result shows ZVL may be controlled effectively

adopting the corresponding control strategies, the parameter $A_1, A_2, A_3, B_1, B_2, B_3$ used in the objective function are quite subjective. Therefore, further studies will focus on validation of the model in terms of real data and on actual control costs and effectiveness in various scenarios, especially for different endemic areas of ZVL.

Chapter 6 - Conclusions, Contributions, and Future Works

6.1 Conclusions

Human behaviors, as one of the most important factors which impact the dynamics of disease transmission, play a key role on mitigating and controlling the epidemic. In this dissertation, two types of human behaviors, spontaneous changes of human behaviors and enforce measure by public authority (intervention strategy), are studied in order to quantify their impacts to the infectious disease transmission and seek the optimal control strategies. The developed methodologies can be applied to human diseases (such as H1N1, SARS) as well as animal diseases (such as Visceral Leishmaniasis). Analytical and numerical simulation results are derived to help us better understand the disease transmission dynamics and recommend the corresponding control strategies.

Main conclusions drawn from this dissertation are:

1. Spontaneous changes of human behaviors could be quantified using a spatial evolutionary game with information dissemination. Specifically, individuals acquire information relating the infectious disease (such as prevalence) from mass media or their social contacts, and then decide if they need to take actions to protect themselves. Hence, the spatial evolutionary game well represented the process from information to risk reception by individuals, then to decision making, finally to behaviors' changes.
2. It has a higher possibility for individuals in endemic areas to take preventive measures, i.e. there are more switchers in the area where more individuals are infected. Hence, local information has more impact on human behaviors and disease transmission.

3. Local information is translated to payoff by m_1 to motivate individuals to choose either normal or alternatives, thereby implicitly affecting the dynamics of the epidemic. Sensitivity analysis showed that m_1 was sensitive to the system and an increasing value of m_1 led to an increasing number of switchers. Considering heterogeneity of m_1 in different counties, similar impact patterns were derived for each county. Even for long distance model, changes of m_1 in network centers cannot impact the disease transmission in other counties.
4. To demonstrate the heterogeneity of individuals in the same location (which is assumed to be homogeneous population in each county), a Itô drift-diffusion process with a drifting factor and a random walk was considered to study the risk reception. Memory mechanism represents the dynamic of the estimated average risk reception for individuals and the variance represents the deviation of risk reception from average value due to the differences of individuals in the same location.
5. Numerical simulations for SEGM model in (82) and MDM model using a county map of the state of Kansas with county-level population were conducted to compare the SEGM model to the MDM model. Our results showed that the results from two models are consistent which validated SEGM model.
6. Spontaneous changes of human behaviors can help mitigate the spread of infectious diseases, i.e. more switchers lead to less infected individuals. However, more switchers also lead to more social costs (cost to convince individuals to choose switcher, cost for switchers to protect themselves, etc.). The optimal control strategies are needed to be addressed.

7. Backward bifurcation phenomenon was proved for the transmission of ZVL, i.e. the disease free equilibrium and endemic equilibrium coexists when R_0 is smaller than 1. Hence, the condition $R_0 < 1$ cannot guarantee that we could eliminate ZVL. The similar scenario may occur for other zoonotic disease and the ODE system considering contact structure.
8. The optimal control theory was applied to study the intervention strategies for the mitigation of transmission of ZVL. Our results indicate that controlling the number of sand flies is the most effective and recommended methodology to control ZVL transmission. Culling dogs is not an effective strategy to control the disease transmission.

6.2 Contributions

Major contributions of this dissertation to the area of computational modeling, decision making on human behaviors, and epidemiology are listed as follows:

1. For the first time, this research developed a new spatial evolutionary game to study the changes of human behaviors in epidemics. This methodology successfully demonstrates how individuals change their behaviors from acquiring information, to risk perception, then to decision making, and finally to behaviors' changes. It is also the first time, for my best knowledge, to apply the spatial evolutionary game to epidemiological areas.
2. This research developed new mathematical models to study spontaneous changes of human behaviors temporally and spatially. Particularly, impact of local information and global information to human behaviors are distinguished and a

detailed discussion about impact of local information is emphasized in this research since the local information is assumed to be more crucial than global information.

3. For the first time, the Ito drift-diffusion process is used to study the accumulated risk perception which the average risk assessment is estimated by the memory mechanism and the heterogeneity of individuals is represented by random walk process.
4. This research demonstrates the backward bifurcation existing in the transmission of ZVL when certain conditions are satisfied. Stability analysis and bifurcation analysis are performed to help understand the dynamics of the spread of ZVL.
5. This study, for the first time, applied optimal control method to seek the most cost-effective control strategies to mitigate the ZVL transmission. The optimal control strategies were derived and efforts on controlling the number of sandflies are recommended.

6.3 Future Works

Major future works to the area of decision making on human behaviors, and mitigation of infectious diseases are listed as follows:

1. In order to fully understand the behavior of dynamic system, analytical study, such as stability analysis and bifurcation analysis, should be conducted later.
2. Further studies should combine changes in human behaviors and intervention strategies to identify optimal information dissemination in order to minimize social costs and the numbers of infected individuals.
3. In order to increase understanding of the variation of individuals' responses to infectious disease, a small scale of population, including individualized behaviors,

should be taken into consideration for modeling human behaviors. Correspondingly, intervention strategies should be temporally and spatially characterized. As such, an agent-based model could be used as a tool to study the complex system with interactions among changes of human behaviors, disease transmission, and intervention strategies (public policy).

4. For ZVL transmission, further studies will focus on validation of the model in terms of real data and on actual control costs and effectiveness in various scenarios, especially for different endemic areas.

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