Dynamics of coupled human and natural systems in epidemiology and ecology

by

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Many natural systems exist in a state of two-way coupling with human systems, where changes in the human system create changes in the natural system, which in turn create changes in the human system once again. The study of dynamics of such coupled human-and-natural systems is a growing area of research. For instance, in the case of influenza antiviral drug use during a pandemic, widespread use of antiviral drugs is a main contributor to the evolution of drug-resistant strains, and recent studies show that influenza viruses can acquire drug resistance without incurring a fitness penalty that reduces their transmission rate. This phenomenon illustrates a coupled human-and-natural system since an influenza pandemic causes a human population to respond with antiviral drug use, which in turn changes influenza epidemiology. It also creates the possibility of strategic (game theoretical) interactions between humans making decisions about antiviral drug use strategies.

On the other hand, the dynamics of endangered ecosystems can also illustrate a coupled human-and-natural dynamic, where processes such as agricultural expansion, migration and urbanization, road construction, mining and industry can endanger rare ecosystems, which in turn can stimulate human populations to enact conservation measures. Stochastic effects are important for evaluating the likelihood of extinction of a rare ecosystem,
but stochasticity has been little studied in the context of extinction in coupled human-and-
natural systems. This dissertation develops and analyzes a 2-player game theoretical model
of influenza antiviral drug use, with both (i) 2 strategies with payoffs based on a fixed ma-
trix and (ii) a continuous strategy set with payoffs determined by a stochastic differential
equation model of influenza transmission and drug resistance. It also develops and ana-
lyzes (iii) a stochastic differential equation model to explore extinction and conservation
opinion dynamics in a coupled forest-human system. The influenza models predict a coor-
dination game between the two jurisdictions, where both players either choose a socially
optimal low antiviral drug treatment rate or a suboptimal high treatment rate. This predic-
tion of two co-existing Nash equilibria is robust to the mutation rate and the effectiveness
of the drug in preventing transmission, but it is sensitive to the volume of travel between
the two jurisdictions. In the coupled human-forest model, we predict a new mechanism
that we call stochasticity-induced persistence, whereby an increase in stochasticity under
certain conditions can actually make the natural population more likely to persist, instead
of going extinct due to stochastic fade-out. All three models show how coupled human-
and-natural systems can have novel dynamics that are not predicted when the human and
natural systems are studied in isolation from one another.
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Chapter 1

Introduction

1.1 Preliminaries

Influenza (the “flu”) is an infectious respiratory disease caused by viruses. Influenza can be mild to severe and sometimes it may lead to death. Influenza epidemics are responsible for killing about 250,000 to 500,000 annually worldwide [1]. Even though influenza viruses may develop resistance to medication, antiviral drugs are often a crucial aspect of medical treatment. Therefore, reduction of influenza cases and optimization of its treatment strategies are major public health goals.

Deforestation represents a different but still significant kind of threat. Deforestation in tropical regions is often due to agricultural expansion, migration and urbanization, road construction, mining and industry [2]. Deforestation has threatened the persistence of a large number of endangered species by reducing their natural habitat, as well as threat-
ening rare forest ecosystems [3, 4]. On the other hand, when forest cover falls to sufficiently low levels, there are many examples where the human response has been a growth in conservationist opinion in the population, resulting in protection of rare species and rare ecosystems.

The cases of influenza and deforestation are more closely related than they may at first appear. In the case of influenza and other infectious diseases, we wish to eradicate a particular species (namely, the pathogen). However in the case of deforestation, we may wish to halt deforestation in order to conserve a particular species or even an entire endangered ecosystem. In either case, an understanding of dynamics near the eradication threshold is very relevant, as is understanding the role of human behaviour in accelerating or preventing the elimination of the species.

Both influenza transmission and the dynamics of endangered ecosystems have been studied through mathematical models. Epidemic models describe the propagation of communicable diseases like influenza in a population, in much the same way as ecological dynamics describe the propagation of a natural population. In a related vein, a mathematical tool called game theory helps us to model individual behaviour and shows us how behavioural responses can result from strategic interactions between people. This thesis develops two models to explore antiviral drug resistance evolution during an influenza pandemic and how it is determined by strategic interactions between human decision-makers. Also, this thesis describes the interaction effect between natural and human systems, including strategic interactions between humans, and how together they can determine the
long-term persistence of an endangered forest ecosystem.

I begin with a review of epidemiological modeling, which includes the ubiquitous compartmental SIR model. I then discuss game theory as a tool of behavioural modeling. Within this framework, the Prisoner’s Dilemma and the Coordination Game are discussed as models of social dilemmas, where there is a conflict between societal and individual desires. I finish the introduction with a discussion of human-environment systems, which combine aspects of all of these modeling tools. I note that the terms ‘human-environment system’, ‘human-and-natural system’, and ‘socio-ecological system’ are closely related to one another (with socio-ecological systems arguably representing a special case of human-environment systems, which in turn represent a special case of human-and-natural systems) and I will use them interchangeably throughout this thesis.

1.2 Compartmental models

Epidemiology is a tool of interpretation about disease that handles biological inferences derived from observations of disease-related phenomena in a population group [5]. It helps us to study the distribution and determinants of health-related states or events in stated group of people. The application of this study is to limit the health related problem in different age groups. What is notable about the definition of epidemiology is that it includes both a description of the content of the discipline and the aim or application for which epidemiological investigations are carried out. Two well known tools for mathematically
representing the dynamics of epidemics of infectious diseases are compartmental models and stochastic models.

Compartmental models are deterministic and often used to describe transfer of material in biological systems. A compartmental model consists of a finite number of homogeneous and well-mixed compartments. In epidemiology, these compartments stratify the total population into three different health states: susceptible denoted by $S(t)$ (persons who are vulnerable to the disease or who can be easily infected by the disease), infected denoted by $I(t)$ (persons who already have the disease), and a recovered denoted by $R(t)$ (persons who have recovered from the disease) [6]. These compartments often interact on the basis of particular assumptions on which the compartmental models are built. These models are often analyzed by using ordinary differential equations (ODEs) in which case they are termed ‘deterministic compartmental models’ (often shortened to ‘compartmental models’), but if the transitions between compartments are stochastic, they are termed ‘stochastic compartmental models’. There are various epidemic compartmental models, such as Susceptible-Infective (SI) model, Susceptible-Infective-Susceptible (SIS) model, Susceptible-Infective-Removed (SIR) model, Susceptible-Exposed-Infective-Removed (SEIR) model, and etc.

1.2.1 SIR model

This model was developed by Kermack and McKendrick [7] and a special case of their original integro-differential equation model is given by the set of differential equations as
follows [7, 8]:

\[
\frac{dS}{dt} = -\beta S(t)I(t) \quad (1.1)
\]
\[
\frac{dI}{dt} = \beta S(t)I(t) - \gamma I(t) \quad (1.2)
\]
\[
\frac{dR}{dt} = \gamma I(t) \quad (1.3)
\]

where \(\beta\) is the infection rate and \(\gamma\) is the recovery rate of the infected individuals.

It is assumed that the total population \(N = S(t) + I(t) + R(t)\) is fixed where \(S(t)\), \(I(t)\), and \(R(t)\) denote the susceptible, infected, and recovered individuals respectively. As before, it is also assumed that the susceptible becomes infected when they come in contact with an infected individual.

Figure 1.1: Scheme of the basic SIR model. Circles represent compartments, and arrows indicate flux between the compartments.

1.2.2 Basic reproduction number

The basic reproduction number, \(R_0\), is defined as the expected number of secondary infections produced by a single infection in a completely susceptible population [9]. This basic reproduction number is affected by several factors including the duration of infectivity, the infectiousness of the organism, and the number of susceptible people with whom
the infected patient comes in contact. For simple homogeneous models, we may define $R_0$ as [10],

$$R_0 = C \times P \times D \tag{1.4}$$

Where, $C$ is the number of contacts the infectious person makes per unit time, $P$ is the probability of transmission per contact with the infectious person, and $D$ is the duration that the infected person is infectious.

$R_0$ forms a threshold that is widely studied in infectious disease modeling. If $R_0 < 1$, the infection will die out eventually if the disease is at low levels, but if $R_0 > 1$, the infection is able to spread in a population. Generally, the greater the value of $R_0$, the harder it is to control the disease.

### 1.3 Stochastic epidemic models

The output of the deterministic model is fully determined by the parameter values and initial conditions [11]. The basic SIR model discussed above is an example of deterministic model. On the other hand, due to the possession of inherent randomness, stochastic models lead to different outputs for each simulation with the same set of parameter values and initial conditions [11]. A stochastic model is conceived in terms of a stochastic process. Mathematically, a stochastic process is a collection of random variables $(X_t(s)/t \in T, s \in S)$, where $T$ is the index set and $S$ is a sample space [12]. The index set usually represents time, such as $T \in [0, \infty)$, and can be discrete or continuous. Also, the study of stochastic
process is based on the probability theory. There are some stochastic modeling processes, such as, a discrete time Markov Chain (DTMC), a continuous time Markov Chain (CTMC), a stochastic differential equations (SDE) model, and etc.

In a small population, stochastic processes are expected to play a significant role in epidemic dynamics, especially when the number of infected hosts is low and epidemic fade-out is likely to happen [13]. This can lead to local elimination of an infection. Similarly, stochastic events are very relevant to the emergence of mutant strains with different properties. Mutation is inherently probabilistic and therefore if mutations are rare, a stochastic model is often the most appropriate model to use. Mutation can confer properties such as resistance to antiviral drugs. This is a common occurrence in influenza, which is the topic of our next subsection.

1.4 Influenza: transmission, epidemiology, and antiviral drug resistance

Influenza is an infectious disease caused by influenza viruses. There are three types of influenza viruses: A, B, and C. Influenza A viruses can infect humans, birds, pigs, horses and other animals, but wild birds are the natural hosts for these viruses. Influenza A viruses can cause pandemics. Influenza B viruses are usually found only in humans and generally are associated with less severe epidemics than influenza A viruses [14]. Influenza C viruses cause mild illness in humans and are not a significant concern for human health. Influenza
virus may be transmitted among human beings in various ways, such as direct contact with
infectious individual, by contact with contaminated objects, by inhalation of virus-laden
aerosols, etc. [15].

Influenza symptoms can be mild to severe and include high fever, cough, headache,
muscle and joint pain, sore throat, and runny nose [16]. Most people recover within a week
without medical treatment. However, influenza can cause severe illness or death especially
in people who are at high risk. The people who are categorized as highest risk are children
younger than age 2 years, adults aged 65 years or older, pregnant women, and people of
any age with certain medical conditions, such as chronic heart, lung, kidney, liver, blood or
metabolic diseases.

Antiviral resistance means that a virus has evolved in such a way that the antiviral drug
is less effective in treating or preventing illnesses. The genetic makeup of the virus may
change in a way that results in the virus becoming resistant to one or more of the antiviral
drugs used to treat or prevent influenza. If vaccines are not immediately available during
an influenza pandemic, antiviral drugs are one of the most effective ways to reduce the
health burden of infections [17]. However, abundant use of antiviral drug is one of the
factors to develop resistance. For instance, 18% prevalence of resistance to oseltamivir
has been observed among treated children in Japan [18]. Drug resistance is arguably less
problematic when mutants are less transmissible than original strain, since the original
strain can outcompete the mutants. Indeed, acquiring a mutation often results in tradeoffs,
such that a mutant strain that acquires drug resistance also suffers a fitness penalty (e.g., a
reduced transmission rate) [19].

A number of mathematical models (primarily ordinary differential equation models) have explored the potential impact of the emergence of drug resistant influenza and its spread during an outbreak [20, 21, 22]. These studies have provided useful insights into the emergence and spread of drug-resistant influenza. For instance, these models predict that the final size of a pandemic can be restricted by applying an adaptive antiviral strategy with properly timed increases in drug usage, and that chemoprophylaxis of susceptible individuals is one of the best ways to reduce the force of infection of an epidemic and keep the emergence of drug resistant viruses low [23]. A recent publication [24] presents a stochastic model of influenza transmission. However, these models focus on dynamics in a single population and do not consider strategic interactions between individuals or institutions during an influenza pandemic. In contrast, models like Ref. [25] capture the strategic interaction between vaccinating individuals and free-riders in a single population, but are not focussed specifically on influenza antiviral drug use strategies, and also consider a single population.

These and other mathematical models have been used to determine optimal antiviral drug use strategies that minimize the emergence and/or spread of antiviral drug resistant strains in a single population. When the evolution of drug resistance fails to cause a reduced transmission rate, a careful policy of restricting antiviral drug use to limit the emergence of resistant strains may not be helpful to a population that is connected to other populations through the travel: the focal population practicing limited antiviral drug usage remains
susceptible to importing the drug-resistant strain from other populations that practice high rates of antiviral drug use. Without a fitness penalty, the drug-resistant strain can spread freely in both populations, even though only one population generated the mutant strain. Thus, there are conditions under which decisions about antiviral drug use in one population can affect other populations. One of the motivations for the models I develop in this thesis is to model such situations where jurisdictions making decisions about influenza antiviral drug use during an influenza pandemic interact strategically with one another, due to the potential for generating drug-resistance mutants that can travel from one jurisdiction to another. Interactions between players such as jurisdictions can be explored using game theory and similar approaches, which is the topic of the next section.

1.5 Game theory

Game theory deals with situations in which decision-makers interact with one another, and the outcome depends not just on his/her own decisions but on the decisions made by others [26]. In other words, game theory is a systematic study of strategic interactions among decision-makers. A decision-maker chooses the best action according to his/her preferences, among all the actions available to him/her. Some examples of games are the Prisoner’s Dilemma, the Stag Hunt game, and Matching Pennies.
1.5.1 Prisoner’s Dilemma

Prisoner’s Dilemma is one of the most well-known games of game theory. Two suspects of a criminal gang are arrested and imprisoned. There is ample evidence to imprison them of a minor offense, but not enough to convict either of them of the major crime unless one of them confess. The detective offers each the chance to confess. If they both confess, each will be sentenced to three years in prison. If only one of them confesses, he will go free while the other will receive a sentence of four years. If neither confesses, they will receive minimum sentence of one year in prison [26]. This scenario can be written in a generalized form of a matrix as follows:

\[
\begin{array}{c|cc}
\text{Player 1} & \text{Cooperate} & \text{Defect} \\
\hline
\text{Cooperate} & (R, R) & (S, T) \\
\text{Defect} & (T, S) & (P, P) \\
\end{array}
\]

Figure 1.2: Payoff matrix for Prisoner’s Dilemma where the first element in a ordered pair represents the payoffs for player 1 and the second one is for player 2. For a Prisoner’s Dilemma game, the condition \( T > R > P > S \) and \( R > (T + S)/2 \) must hold where \( T, R, P \) and \( S \) are the entries in a ordered pair in the form of payoffs.

1.5.2 Coordination games

Coordination games are a class of games with multiple pure strategy Nash equilibria [26]. A coordination game occurs whenever the utility of two or more players is maximized by playing the same strategy as one another. There are many settings in which coordination games arise. For example, the Battle of the Sexes and the Stag Hunt game.
The Stag Hunt game describes a situation in which two hunters decide to hunt for stag or hare. Each hunter alone could be sure of bagging a hare, but both hunters are needed to corner the stag, which is the preferred game [26]. If only one hunts stag, that person is left empty handed. It is an unbalanced coordination game because there is a low-payoff equilibrium in which both hunt hare and a high-payoff equilibrium in which both hunt stag. The player who is trying for low-payoff doesn’t get penalized at all. The payoffs of stag hunt game are shown in the following diagram.

<table>
<thead>
<tr>
<th>Hunter 1</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hunt Stag</td>
<td>Hunt Hare</td>
</tr>
<tr>
<td>Hunt Stag</td>
<td>(4, 4)</td>
<td>(0, 3)</td>
</tr>
<tr>
<td>Hunt Hare</td>
<td>(3, 0)</td>
<td>(3, 3)</td>
</tr>
</tbody>
</table>

Figure 1.3: Payoff matrix for the stag hunt game.

1.5.3 Nash equilibrium

A Nash equilibrium is a steady state of a system that involves several interacting players in which no player can improve their payoff by changing his/her strategy, if other players’ strategies remain unchanged. Mathematically, a Nash equilibrium is an action profile $a^*$ with the property that no player $i$ can do better by choosing an action different from $a_i^*$, given that every other player $j$ adheres to $a_j^*$ [26]. A strategy $a_i^*$ is a strict Nash equilibrium for player $i$ if we have $u_i(a_i^*, a_j) > u_i(a_{-i}, a_j)$ for every other player $i$ strategy $a_{-i}$ and for every possible strategy $a_j$ adopted by player $j$.

In game theory, populations are often assumed to persist at Nash equilibria. However,
Nash equilibria are not necessarily stable. In particular, stability of a Nash equilibrium requires the assumption that only one player at a time can change their strategy. In situations where players can coordinate strategy changes, or where play is repeated, a Nash equilibrium may become unstable. Moreover, in a finite population, a strict Nash equilibrium may become non-strict and therefore admit neutral decay paths. A Nash equilibrium that a population evolves to from elsewhere in strategy space is called a convergently stable Nash equilibrium.

1.6 Forest ecosystems and dynamics of populations near extinction

Forest resources are one of the most valuable natural resources provided to human beings on which they depend highly and use abundantly [27]. Forests yield different products, such as timber, fuel, charcoal, and also contribute water purification and climate stabilization [28]. Human activities have exerted great pressure on forest cover which eventually cause rapid quick deforestation and a deficit of ecosystem services [29].

A forest ecosystem can be defined as an area fully dominated by trees and other plants. Forests consist not only of trees but they also provide shelter for many species including endangered plants and animals. At the same time, forests also accumulate carbon dioxide, protect soils and ensure natural biodiversity. To a first approximation, forest growth can be modelled in the same way as the dynamics of a single population, using a logistic growth
model that first appeared in [30]:

\[
\frac{dF}{dt} = RF(1 - F/K)
\]

where \( F \) is the amount of forest cover in a region, \( R \) is the net expansion rate, and \( K \) is the carrying capacity (maximum amount of forest in a region). Verhulst originally developed this model in the 19th century in order to study human population growth, although the model seems to have found its major expression in theoretical ecology. However, more sophisticated models are also possible, and complex agent-based models are often a favoured way to describe forest growth dynamics [31, 32].

Real ecosystems are heterogeneous and often distributed across multiple patches. In such cases, metapopulation models have been used to describe the dynamics of the entire population, including how mobile individuals move between patches [33]. In a metapopulation model, the population abundance of patch \( j \) is given by a model, and the rules for movement between patches are also described. For instance, the model

\[
\frac{dN_j}{dt} = R_j N_j (1 - N_j/K_j) + \alpha_{j-1,j} N_{j-1} + \alpha_{j+1,j} N_{j+1} - \alpha_{j,j-1} N_j - \alpha_{j,j+1} N_j
\]

describes a metapopulation consisting of a linear array of patches (such as in an archipelago). Such a population might consist of a bird species, for instance. The dynamics of the population size of patch \( N_j \) are given by a Verhulst model including patch-specific parameter values for the growth rate \( R_j \) and carrying capacity \( K_j \). The term \( \alpha_{j-1,j} N_{j-1} \) represents the
rate at which individuals move from patch $j - 1$ to patch $j$ and is the product of the number of individuals $N_{j-1}$ on patch $j - 1$, and the per capita rate $\alpha_{j-1,j}$ at which individuals move from patch $j - 1$ to patch $j$. The other four migration terms are similarly defined.

Metapopulations exhibit qualitatively distinct dynamics compared to single population models, including rescue effects, whereby complete extirpation on one patch can be averted by migration from other patches with robust population sizes [34]. Similarly, the cessation of habitat destruction does not immediately halt species extinctions but rather a species may go extinct many years later despite the fact that habitat destruction has stopped due to legacy effects, hence the term ‘extinction debt’ [35].

Stochastic processes are closely tied to extinction events. As mentioned in the earlier subsection on infectious diseases, an infection can stochastically fade-out during periods when numbers of cases are particularly low [13]. The same process of stochastic fade-out is relevant to ecological populations, where a species can go extinct due to random events when its numbers are very low. This has been the subject of intensive research in theoretical ecology [36].

Theoretical ecological models often assume that human influence is fixed and does not respond to changes in ecological states. This is a good approximation for systems where human influence does not change much over time, or when short timescales are considered. However, in many cases these assumptions do not hold. Land-cover changes have significant effect on environmental features which includes quality of water, land, and ecosystem process [37]. Moreover, land cover changes are driven strongly by human
16

behaviour: declining worldwide forest cover is an important socio-ecological challenge because of high influence of human decision-making on the preservation of forest cover [37, 38, 39]. In many such scenarios, it is necessary to treat human systems and natural systems as coupled to one another, and to model the dynamics of the human system as well. These coupled systems are described in more detail in the following subsection.

1.7 Coupled human and natural systems

A coupled human-and-natural system (CHANS) consists of a human system that influences a natural system, which in turn influences the human system (and in which the human and natural systems have their own characteristic dynamics) [40]. This is conceptualized in Figure 1.4. CHANS are often studied with the aid of theoretical models in which separate models for the human and natural systems are coupled together and analyzed, although other approaches are also adopted. As already discussed, CHANS can be considered as a concept inclusive of human-environment systems and socio-ecological systems, which are more narrowly focussed on environmental systems and social effects in ecological systems respectively.

The interactions between forest dynamics and human social and harvesting processes are often considered to exemplify a human-environment system [41]. For instance, landowners’ decisions whether to deforest or conserve the forest on their property plays is an important example of a human-environment system. Deforestation is mostly studied with
Figure 1.4: Schematic representation of a coupled human-and-natural system (CHANS).

land-use models, where the state of the land can be in one of several mutually exclusive categories, such as Forested or Deforested. In this way, they are highly analogous to compartmental epidemic models. A recent study [42] augments an existing land-use model with further mechanisms concerning landowner decision-making to examine the impact of governance on forest cover in a region. This study assumes that transitions between forested and deforested states occur with certain probabilities per unit time. The parameter $\mu$ is the transition probability from the deforested to the forested state (recovery) and $r(t)$ is the transition probability from forested to deforested state (deforestation) in year $t$ (Figure 1.5). The deforestation rate $r(t)$ is determined by a landowner decision process that depends on the current abundance of forests, and the current strategies being adopted by other landowners. Other studies have used similar approaches. For instance, Ref. [38] developed a model for forest use incorporating social learning to investigate if social learning is effective enough to enhance landowners’ decisions which eventually help to make effective forest management.
Human-environment interactions can play a vital role in the persistence of forest ecosystems and thereby in protecting the habitats of endangered species [43]. Human-environment systems are widely studied, especially in geography [44]. Most broadly, the coupled human-environment system perspective studies the common interactions of human socio-economic impacts on natural sub-systems such as atmospheric, biological, etc., of the planet [45]. Systems that are more narrowly focussed on specific ecological systems and their human interactions (socio-ecological systems) are also studied [46], but arguably the importance of socio-ecological dynamics remains relatively under-studied, based on a comparison of the number of papers published in socio-ecological systems versus ecological systems.

Figure 1.5: Schematic representation a land use model of transitions between forested and deforested states.

Agent-based models are widely used in CHANS [47]. Agent-based models have the advantage of enabling high levels of detail to be incorporated into the model, thereby enabling them to capture real-world heterogeneities. However, they have the disadvantages of being harder to analyze and harder to validate than simpler models. In contrast, simpler models such as low-dimensional systems of differential equations are easier to analyze and test against data, but may exclude important heterogeneities. As a result, simpler and more complicated models complement each other in the study of CHANS. However, most
CHANS models to date are agent-based models, suggesting that simpler models are being under-utilized in the field. Several differential equation models [48, 49] explored human-environment interactions and its importance behind the stability of the forest land.

Disease transmission dynamics are controlled by the epidemiological traits of the disease and the hidden structure of topology, and social framework which is governed by individual choices [50]. Therefore, disease systems also strongly exemplify CHANS, where they are sometimes referred to as socio-epidemiological systems or coupled behaviour-disease systems. A component of infection control involves understanding the complicated two-way interactions between human behavioural and social systems and disease transmission dynamics. Coupled behavior-disease models describe CHANS dynamics where infection spread influences human behaviour and risk perception, which in turn influences infection spread through adoption of vaccines, contact precautions, and other measures. For example, a coupled behaviour-disease model where influenza is transmitted through a contact network and individuals make vaccinating decisions based on perceived risks and benefits has shown how myopic human decision-making can result in highly erratic vaccinating behaviour [51]. Other research shows how coupled behaviour-disease interactions can cause the uptake of one type of control measure, such as social distancing, to partially undermine the uptake of another intervention, such as vaccinating [52].
1.8 Rationale and objectives of the thesis

Stochasticity is important to both ecological and epidemiological systems, not only because of mechanisms like stochastic fade-out which can eliminate a dangerous infectious disease, as well as endangered species [36, 53], but also because of potentially constructive effects [54]. Earlier models of human-and-natural dynamics in forests and other natural ecological systems [48, 49] used deterministic models to explore human impact on forest cover, but do not include stochastic factors. Agent-based models are often stochastic in nature, but stochastic effects *per se* cannot be studied because it is difficult to subtract stochasticity from an agent-based model due to its inherently discrete nature. Therefore these previous approaches may have limited application for understanding the impact of stochasticity on both human related activities and forest cover in coupled human-and-natural systems. As already noted, noise is generally related to a destructive effect in ecological systems, as an operator of large-amplitude fluctuations around stable states. In other cases, noise is also known for its constructive character and may also enhance biodiversity [55]. In either case, stochasticity in CHANS and in particular the impact of stochasticity on the time-to-extinction of a rare ecosystem in ecological CHANS or the probabilistic emergence of antiviral drug resistant influenza mutants in epidemiological CHANS have been studied relatively little in the literature. My first motivation of this thesis was to address this knowledge gap.

Secondly, the contrast between epidemiological CHANS and ecological CHANS is striking, in that for epidemiological CHANS the socially optimal solution that benefits
humans the most is usually to eradicate a given species (the pathogen), while for an eco-
logical CHANS the socially optimal solution that benefits humans the most is to preserve a
given species (the endangered species). The second motivation of my thesis was to explore
whether socially suboptimal outcomes can occur in both epidemiological CHANS and eco-
logical CHANS, despite the fact that the end goal is very different in the two systems. This
can provide some gauge of whether socially suboptimal behaviour is robust across different
types of CHANS. Addressing this problem was the second and more important motivation
for my thesis research.

1.8.1 Objectives

My objective was to compare and contrast model dynamics in ecological versus epi-
demiological CHANS in order to identify whether socially suboptimal outcomes were pos-
sible in both systems, when they might occur, and how the outcomes are influenced by
the presence or absence of stochasticity. I accomplished this by modelling the nonlinear
interactions between human and natural systems, in the specific context of influenza ant-
tiviral drug use during influenza pandemics, and for extinction events in a socio-ecological
system. The thesis is broken down in three separate papers; each with their own separate
sub-objectives which are as follows.

1. Strategic interactions in antiviral drug use during an influenza pandemic

(Chapter 2)
The objective of this chapter is to develop a 2-player, 2-strategy game theoretical model and analyze how two health jurisdictions choose antiviral drug use strategies in a situation where the drug resistant strain can emerge and travel between the jurisdictions.

2. Emergence and spread of drug resistant influenza: A two-population game theoretical model (Chapter 3)

The objective of this chapter is to develop a mechanistic, stochastic disease transmission model to study the strategic interaction between two populations, still in the context of a 2-player game theoretical model, but with a continuous strategy space and including a stochastic model of influenza transmission and antiviral drug resistance evolution.

3. Stochasticity-induced persistence of an endangered population in a coupled socioecological model (Chapter 4)

The objective of this chapter is to develop a stochastic differential equation model and analyze how does the time to extinction of a rare forest species depend on human actions, such as social learning rate, the maximal forest harvesting rate, injunctive social norms, and forest dynamics.

Chapters 2 and 3 have been published in *PLOS Currents Outbreaks* and *Infectious Disease Modeling*, respectively. Chapter 4 is in preparation for submission. Full bibliographic details appear in chapter headings. Jnawali led the background research, model development, model analysis and simulation, and writing of each paper. Co-authors provided
feedback, suggestions, and edits to model code and paper writing.
Chapter 2

Strategic interactions in antiviral drug use during an influenza pandemic


Abstract

Background: The evolution of antiviral drug resistance during influenza pandemics has created widespread concern. Use of antiviral drugs is a main contributor to the evolution of drug-resistant strains. Moreover, there are recent examples of influenza viruses acquiring drug resistance seemingly without incurring a fitness penalty that reduces their transmis-
sion rate. This creates the possibility of strategic (game theoretical) interaction between jurisdictions making decisions about use of antiviral drug stockpiles.

**Methods:** We developed and analyzed a 2-player 2-strategy game theoretical model. Each ‘player (an authority in a health jurisdiction) can choose to treat with antiviral drugs at a low rate or a high rate. High treatment rates are more likely to cause emergence of a drug-resistant strain, and once a drug-resistant strain has evolved, it can spread between the two jurisdictions. We determine the Nash equilibria of the game.

**Results:** We show that there is a coordination game between the jurisdictions, where both players choose a low treatment rate, or both choosing a high treatment rate, is the only stable outcomes. The socially optimal outcome occurs if both players cooperate by choosing a low treatment rate, thereby avoiding generating drug-resistant mutants. However, such cooperation may fail to materialize if the jurisdictions are closely connected through travel; if the drug-resistant mutant is tolerated (not seen as undesirable); or if the antiviral drug has partial efficacy against transmission of the drug-resistant strain.

**Conclusions:** Inter-jurisdictional cooperation could be essential during a severe influenza pandemic, but we know little about how jurisdictions will interact in a scenario where highly pathogenic, drug-resistant mutant strains are able to transmit as effectively as non-resistant strains. Therefore, strategic multi-population interactions during influenza pandemics should be further studied.

**Keywords:** Game theory, Influenza model, Antiviral drugs, Drug resistance, Fitness penalty, Antiviral stockpiles, Influenza epidemiology, H1N1, H7N9
2.1 Background

The 1918-1919 H1N1 influenza pandemic was a deadly event, killing an estimated 50-100 million people worldwide [56]. Subsequent pandemics occurred in 1957 and 1968, and the World Health Organization confirmed the beginning of another pandemic on June 11, 2009 [57, 58]. Vaccines were not available until the middle of the 2009 pandemic in many populations, and the problem of limited vaccine availability may occur in future pandemics until vaccine production technologies change. Thus, at the start of a pandemic, antiviral drugs may be the only available pharmaceutical intervention. Therefore, the frequent emergence of drug-resistant viruses has raised serious concerns.

Acquiring a mutation often entails tradeoffs, such that a strain that acquires drug resistance also suffers a fitness penalty (e.g., a reduced transmission rate). There is a rich literature on the implications of tradeoffs for pathogen strain structure and transmission dynamics [19, 59]. In the context of influenza subtype H1N1, the H274Y mutation weakens binding of the drug oseltamivir to viral neuraminidase (NA) enzyme, by reducing the amount of NA that is available at the cell surface [60]. However, this also has the effect of reducing the fitness of the virus, since NA is necessary for the virus to be released from the host cell. As a result, acquisition of the H274Y mutation without any secondary compensatory mutations can reduce the evolutionary fitness of the virus [60]. Drug resistance is less problematic when mutants are less transmissible than original strain (for instance, as a result of a fitness penalty), since the mutants can be outcompeted by the original strain in community-level transmission. Indeed, most early oseltamivir-resistant strains appeared to
have reduced transmissibility and infectivity, compared to their non-resistant progenitors [61].

However, more recently, influenza A (H1N1)pdm09 viruses have been increasingly capable of acquiring the H275Y mutation that confers oseltamivir-resistance, without suffering a fitness penalty, thanks to secondary mutations [60, 62]. In the 2007-2008 influenza season in Europe, oseltamivir-resistant influenza A (H1N1) with the H275Y mutation emerged and was observed to spread widely even in absence of widespread antiviral drug usage, suggesting that the mutants competed well with the resistant strains already in circulation [60, 63]. Drug resistance due to oseltamivir usage also emerged more quickly than in pre-pandemic strains [18, 61, 63]. Additionally, it appears that influenza A (H7N9) viruses are also capable of acquiring oseltamivir resistance without suffering a fitness penalty [64]. (However these viruses have not yet evolved the ability to transmit from person-to-person in a sustainable way [65, 66].)

The emergence of oseltamivir-resistant influenza viruses that are as transmissible as their non-resistant progenitors has implications for how jurisdictions decide upon antiviral drug strategies during a pandemic. Mathematical models have been used to determine optimal antiviral drug use strategies that minimize the emergence and/or spread of antiviral drug resistant strains in a single jurisdiction [20, 21, 22, 24]. When drug resistance confers a fitness penalty, single-jurisdiction approaches are adequate, since the less transmissible mutant will be outcompeted by the original strain in another jurisdiction that has chosen to practice limited antiviral drug use. However, when evolution of drug resistance fails to
cause a reduced transmission rate, a careful policy of restricting antiviral drug use to limit
the emergence of resistant strains may not be helpful to a jurisdiction that is connected to
another jurisdiction through travel: the jurisdiction practicing limited antiviral drug usage
remains susceptible to importing the drug-resistant strain from the other jurisdiction prac-
ticing high rates of antiviral drug use. Without a fitness penalty, the drug-resistant strain can
spread freely in both jurisdictions, even though only one jurisdiction generated the mutant
strain.

If the socially optimal approach is to restrict treatment only to the severest infections
and thereby avoid or limit the emergence of drug resistance, then two jurisdictions may
cooperate with one another by both using antiviral drugs at a low rate. However, if one
jurisdiction is treating at a high rate and thereby generating many drug-resistant mutants,
then there is little incentive for the other jurisdiction to continue treating at a low rate, if
importation of the resistant strain from the other jurisdiction seems likely. Instead, the
jurisdiction may want to treat at a high rate as well, in which case both jurisdictions end
up adopting the socially suboptimal strategy of using antiviral drugs at a high rate. This
strategic aspect of antiviral drug use policy between health jurisdictions has not yet received
much attention in the public health literature, to our knowledge.

Game theory is the formal study of decision-making where several players must make
choices that potentially affect the payoffs of the other players. A Nash equilibrium is a state
where no player can increase his or her payoff by unilaterally switching to a different stra-
tegy. More specifically, suppose that player \(i\) choosing strategy \(a_i\) gets a payoff \(u_i(a_i, a_j)\)
when the other player $j$ chooses strategy $a_j$. A strategy $a_i^*$ is a strict Nash equilibrium for player $i$ if we have $u_i(a_i^*, a_j) > u_i(a_{-i}, a_j)$ for every other player $i$ strategy $a_{-i} \neq a_i^*$ and for every possible strategy $a_j$ adopted by player $j$ [26]. Hence, there is no incentive for any player to change their strategy and we generally expect that rational players will choose Nash equilibrium strategies (convergence issues aside). In this paper we will only consider conditions for strict Nash equilibria, although we will refer simply to Nash equilibria throughout for brevity. The application of classical game theory to individual human behaviour has been criticized for its assumption that each player ‘rationally maximizes his or her own payoff without considering the impact of their decisions on the well-being of other players. In real populations, social processes may make this assumption untenable [67]. However, it may be a better description of how countries, regions, or municipalities interact with one another in a severe pandemic.

Some previous multi-population models have also incorporated human behaviour [68, 69]. These are based on compartmental epidemiological models, and focus on paediatric infectious disease. Other models explore the effect of individual adaptive decision-making on the epidemiology of infectious diseases [70, 71], or address the emergence and control measures of antiviral drug resistance in a single population [20, 24], but do not consider strategic interactions between multiple populations. Models of strategic inter-jurisdictional antiviral drug usage during an influenza pandemic appear to be rare, although approaches have been developed for other types of infectious diseases [68, 72].

In this Background section we have provided intuition for why antiviral drug use deci-
sions may create strategic interactions when drug resistance fails to confer a fitness penalty. In the remainder of this paper we develop and analyze a formal game theoretical model of how two health jurisdictions choose antiviral drug use strategies in a situation where the drug resistant strain can travel between the jurisdictions. This allows us to gain insight regarding: when such strategic interactions are likely to become important, what form the strategic interactions will take place, and when such interactions are more likely to result in socially suboptimal (i.e. non-Pareto optimal) outcomes. Our objective was to illustrate the wide range of possible outcomes that may occur in such situations, and to show how the outcomes may depend on epidemiological, geographical, and perceptual factors. Our objective was not to generate quantitatively correct predictions about strategic interactions in specific, real-world populations for specific influenza strains. In such cases, where models are intended to serve didactic purposes rather than predictive purposes, a simpler model is often preferable to a complicated model [73]. Hence, we opt to use simple game theoretical model based on fixed payoff matrices, rather than a more sophisticated dynamic evolutionary game theoretical model combined with a disease transmission model. Although this creates some limitations in terms of model interpretation, it also enables us to more easily discuss and classify different possible strategic outcomes under different circumstances.
2.2 Methods

We developed a symmetric 2-player, 2-strategy game where payoffs are derived from \textit{a posteriori} epidemiological and antiviral drug assumptions. Each player is an authority making decisions that affect their health jurisdiction and can choose to either treat at a low rate $L$, which we interpret to mean using antiviral drugs only for the severest infections, or to treat at a high rate $H$, which we interpret to mean using antiviral drugs for both severe and non-severe infections, and possibly also for prophylaxis. The payoffs depend on the final epidemic size, which is a parameter. Consider a given focal player for which we are determining payoffs based on epidemic outcomes in their focal jurisdiction, depending partly on what the other player in charge of the other jurisdiction does. We let $R(x, y)$ denote the epidemic final size (the number of recovered individuals at the end of the epidemic) of the regular strain in the focal jurisdiction,

\[
R(x, y) = \begin{cases} 
\kappa, & x = y = L \\
\eta, & x = L, y = H \\
\delta, & x = H 
\end{cases}
\]

(2.1)

where $x$ is the treatment level in the focal jurisdiction, $y$ is the treatment level in the other jurisdiction, $\kappa$ is the final size of the regular strain if both players treat at a low rate, $\eta$ is the final size if the focal player treats at a low rate and the other treats at a high rate, and $\delta$ is the final size if the focal player treats at a high rate.

The final size $\delta$ when the focal player treats at a high rate does not depend on the strategy
of the other player because we assume that only a small proportion of individuals travel between the jurisdictions, hence case imports from the other players jurisdiction are only a small part of the total incidence of infection in the focal jurisdiction. We expect $\delta < \kappa$, since a player that treats at a high rate will reduce the transmission of the regular strain, and hence will have a smaller final epidemic size of the regular strain. We expect $\delta < \eta$ for the same reasons. Generally, we expect $\eta < \kappa$, since the other player treating at a high rate instead of a low rate will create some small incremental benefit for the focal jurisdiction, by reducing the number of case imports of the regular strain. However, this effect is small if travel is small, such as for populations connected primarily through airplane travel, and so one could equally well assume $\kappa = \eta$ for simplicity, when travel is infrequent. In summary, $\delta < \eta \leq \kappa$, which simplifies to $\delta < \eta = \kappa$ by our assumption.

Similarly, we let $R_m(x, y)$ denote the epidemic final size of the drug-resistant strain in the focal jurisdiction, where $R_m(x, y)$ is given by

$$R_m(x, y) = \begin{cases} 
0, & x = y = L \\
\gamma, & x = L, y = H \\
\beta, & x = H 
\end{cases} \tag{2.2}$$

where $x$ and $y$ denote treatment levels for the focal player and the other player respectively, $\beta$ is the final size of the drug-resistant strain if the focal player treats at a high rate, and $\gamma$ is the final size of the drug-resistant strain if the focal player treats at a low rate and the other player treats at a high rate.
We assume that there is no emergence of drug-resistant influenza virus if both jurisdictions treat at a low rate, hence $R_{ir}(L, L) = 0$. If the focal jurisdiction treats at a high rate, then drug-resistant mutants are created, and the final epidemic size of the drug-resistant strain is $\beta$. Again $\beta$ does not depend on the strategy of the other player, since the focal player is already creating a large number of drug-resistant mutants through liberal use of antiviral drugs, and a few more case imports will not contribute much to the final size of the drug resistant strain. However, if the focal player treats at a low rate and the other player treats at a high rate, then the focal jurisdiction experiences a non-trivial final size of the drug-resistant strain, denoted $\gamma$. $\gamma$ is affected by the degree of isolation between the jurisdictions. The greater the isolation (i.e. the fewer travels between jurisdictions), the less the mutant strain emerging from a high treatment jurisdiction impacts a low treatment jurisdiction.

One possibility is that $\beta > \gamma$, because a high number of mutants are generated in jurisdiction 1 due to the high treatment level. This is more likely to occur when the jurisdictions are more isolated. Conversely, we may have that $\beta < \gamma$, especially when the jurisdictions are closer together: the focal jurisdiction experiences an inflow of drug-resistant strains from the other jurisdiction, and the mutants can spread effectively in the focal jurisdiction once they have become established. However, because the focal jurisdiction is not using antiviral drugs (which are assumed to have partial efficacy against the drug-resistant strains) at a high rate, the final size of the mutant strain is very large. The relationship between $\beta$ and $\gamma$ thus depends on the exact nature of travel connections, how much less effective the
drug is in controlling the drug resistant strain, and how transmissible the resistant strain is compared to the regular strain. We explore these two cases.

The payoff $P$ of a focal player that adopts treatment rate $x$ when the other player treats at the rate $y$ is

$$P(x, y) = M - \alpha R(x, y) - (1 - \alpha) R_m(x, y)$$  \hspace{1cm} (2.3)

where $M$ is a constant representing health payoff in absence of a pandemic (we can set $M = 0$ without loss of generality) and $\alpha$ is the weighting factor that determines control priorities. In a focal jurisdiction that treats at rate $x$ while the other jurisdiction treats at rate $y$, $R$ and $R_m$ are the final sizes of recovered individuals from the regular and mutant strains, respectively. We generally assume $\alpha < 0.5$, meaning that the jurisdictions consider a case of mutant strain influenza to be more undesirable than a case of regular strain influenza.

We furthermore assume $P(H) \equiv P(H, H) = P(H, L)$ where $P(H)$ is the payoff of a focal player playing $H$. The rationale for this assumption is that when case imports of the regular strain are rare, the final size of the regular strain in a jurisdiction is determined primarily by the actions of the player controlling that jurisdiction. (The case where $P(H, H) \neq P(H, L)$ is briefly described in the Discussion section.) By assuming $P(H, H) = P(H, L)$ (i.e., if a player treats at high level, its payoff is independent of the other players strategy), the payoffs for the three possible outcomes for equation (2.1) and
equation (2.2) are:

\[
P(L, L) = M - (1 - \alpha)R_m(L, L) - \alpha R(L, L)
= M - \alpha \kappa
\]

\[
P(L, H) = M - (1 - \alpha)\gamma - \alpha \eta
\]

\[
P(H) = M - (1 - \alpha)\beta - \alpha \delta
\]  

(2.4)

The payoff matrix of this game appears in Figure 2.1. Although the relationships between the three entries of the payoff matrix depend on the assumed values \(\beta, \gamma, \kappa, \eta, \delta,\) and \(\alpha,\) we generally expect that \(P(L, L) > P(H, H) = P(H, L) > P(L, H)\) for an undesirable drug-resistant strain (see discussion at beginning of methods). Thus, if both jurisdictions treat at a low level, they both have a high payoff. If both jurisdictions treat at high levels, both have medium payoffs. In the case where one has a high treatment level and the other a low treatment level, the high treatment level jurisdiction has a medium payoff and the low treatment level jurisdiction a low payoff.

2.2.1 Baseline parameters

We set parameter values according to published epidemiological literature whenever possible, allowing us to specify plausible values for \(\kappa, \eta, \delta\) (Table 2.1) that also satisfied the inequalities described in Methods section [74, 75]. The other parameters \(\beta, \gamma,\) and \(\alpha\) were varied during our analysis.
Table 2.1: Parameters, values, and descriptions: $R$ and $R_m$ are the final sizes of the regular and mutant strains in focal jurisdiction.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\kappa$</td>
<td>Final size of regular strain, $R$, in focal jurisdiction if both players treat at low rate</td>
<td>0.25</td>
<td>[74]</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Final size of regular strain, $R$, in focal jurisdiction if focal player treats at low rate and other player treats at high rate</td>
<td>0.24</td>
<td>[74], Assumption</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Final size of regular strain, $R$, in focal jurisdiction if focal player treats at high rate</td>
<td>0.10</td>
<td>[75]</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Final size of mutant strain, $R_m$, in focal jurisdiction if focal player treats at high rate</td>
<td>Between $0.1 - 0.2$</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Final size of mutant strain, $R_m$, in focal jurisdiction if focal player treats at low rate and other player treats at high rate</td>
<td>Between $0.1 - 0.2$</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Weighting parameter that controls how undesirable the mutant strain is</td>
<td>Between $0 - 0.5$</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

2.3 Results

2.3.1 Conditions for multiple versus single Nash Equilibria

Coordination games are a class of games with multiple pure strategy Nash equilibria [26]. The players can choose one Nash equilibrium or the other Nash equilibrium depending on process that may lead them naturally to one or the other. A coordination game can be yielded by a payoff matrix which we use here, with the likely relationships between $P(L, L), P(L, H), P(H, L), \text{ and } P(H, H)$ described in the Methods section (Figure 2.1).

If both players adopt high treatment levels ($H$) then they both will have medium payoffs, $P(H, H) \equiv m$; if both players have low treatment levels ($L$) and thereby avoid generating drug-resistant mutants, then both players will have high payoffs, $P(L, L) \equiv h$; if focal player has low treatment rate and other player has high treatment rate then focal player will have low payoff, $P(L, H) \equiv l$ (since focal player treated at a low rate to avoid generating
mutant strains, but was infected by mutant strains anyway due to the high treatment rate of other player and other player has medium payoff, \( P(H, L) \equiv m \). We assume \( h > m > l \), so the game has exactly two Nash equilibria at \((H, H)\) and \((L, L)\). Thus, it is an unbalanced coordination game where the players could adopt either \((H, H)\) or \((L, L)\) depending on how they coordinate their actions. We note that very different (non-coordination) games may emerge if \( h > m > l \) does not hold.

\[
\begin{bmatrix}
  m & m \\
  l & h
\end{bmatrix} = \begin{bmatrix}
  P(H, H) & P(H, L) \\
  P(L, H) & P(L, L)
\end{bmatrix} = \begin{bmatrix}
  M - (1 - \alpha)\beta - \alpha\delta & M - (1 - \alpha)\beta - \alpha\delta \\
  M - (1 - \alpha)\gamma - \alpha\eta & M - \alpha\kappa
\end{bmatrix}
\]

Figure 2.1: **The payoff matrix for the focal player:** The focal players strategies are to treat at a high rate (‘\(H\)’, row 1), or at a low rate (‘\(L\)’, row 2) while the other players strategy is also to treat at a high rate (‘\(H\)’, column 1) or a low rate (‘\(L\)’, column 2). Parameters \( l, m \) and \( h \) represent low, medium, and high payoffs respectively. \( P(x, y) \) is the payoff to the focal player when the focal player plays \( x \) and the other player plays \( y \). Other parameter values are defined in the Methods and Results sections.

According to this argument, the focal point in this game (i.e. the Nash equilibrium that we expect the players to adopt) is at \((L, L)\) which both jurisdiction tend to choose in the absence of communication. There is a natural tendency to choose the \((L, L)\) strategy, not only because of higher payoffs but also because of the likely temporal development of the pandemic. Initially, the number of infections will be low and hence the players might start out playing an “\(L\)” strategy to begin with. If that is the case, they would simply stay at \((L, L)\) as the pandemic unfolds. However, if \( \alpha \) is very small, such as might occur due to a mutant that is perceived as particularly severe, the players may ‘panic’ and converge to the \((H, H)\) strategy.
However, a closer investigation of the dependence of strategic outcomes on the epidemiological parameters $\beta$, $\gamma$, $\kappa$, $\eta$, $\delta$, and $\alpha$ reveal a more subtle picture with a greater range of possible outcomes than this approximate argument can provide (see Table 2.2 for summary). It can be shown (A.1) that a coordination game emerges if

$$
\kappa < \frac{(1 - \alpha)\beta}{\alpha} + \delta < \frac{(1 - \alpha)\gamma}{\alpha} + \eta
$$

(2.5)

Since $\kappa > \delta$, the leftmost inequality in inequality (2.5) is dependent upon the magnitude of $(1 - \alpha)\frac{\beta}{\alpha}$, which is decreasing in $\alpha$. Therefore, the leftmost inequality may be satisfied when the mutant strain is sufficiently undesirable (i.e., $\alpha$ is sufficiently small). Regarding the rightmost inequality in inequality (2.5), $\eta > \delta$, yet the relationship between $\beta$ and $\gamma$ is dependent upon the degree of connectedness of the jurisdictions. When the jurisdictions are highly connected, we have $\gamma > \beta$ and thus the rightmost inequality is trivially satisfied. However, more isolated jurisdictions with $\beta > \gamma$ satisfy the rightmost inequality for sufficiently high $\alpha$. In summary, coordination games exist when mutant strains are sufficiently undesirable, and also when jurisdictions are sufficiently connected. However, for isolated jurisdictions, inequality (2.5) might also be satisfied by an intermediate value of $\alpha$.

It can be shown (A.2) that a single Nash equilibrium at $(L, L)$ occurs when

$$
\kappa < \frac{(1 - \alpha)\gamma}{\alpha} + \eta < \frac{(1 - \alpha)\beta}{\alpha} + \delta
$$

(2.6)

Since we assume that $\kappa = \eta$, the left hand inequality in (2.6) is trivially satisfied. However,
the right hand inequality depends upon the relation of $\beta$ and $\gamma$. Opposite to the coordination game case, the right hand inequality is never satisfied when the jurisdictions are highly connected, since $\eta > \delta$ and $\gamma > \beta$. However, if the jurisdictions are isolated such that $\beta > \gamma$, then the inequality may still be satisfied if the mutant strain is sufficiently undesirable.

The condition for $(H, H)$ to be a Nash equilibrium (A.3) is:

\[
\left( \frac{\beta}{\beta + \kappa - \delta} \right) < \alpha < \left( \frac{\gamma}{\gamma + \kappa - \eta} \right)
\]

(2.7)

In general, this equation is satisfied when $\beta$ is sufficiently small and $\gamma$ is sufficiently large, corresponding to the situation where the jurisdictions are closely connected. Also, it requires that $\alpha$ takes on an intermediate value, which encourages players to use more antiviral drugs since the mutant strain is less undesirable. We furthermore note that the rightmost inequality is satisfied if $\kappa < \eta$ (which cannot occur under our assumptions), and if $\kappa \geq \eta$, it can be satisfied when $\alpha$ is sufficiently small and when $\gamma$ is sufficiently large.

It is also possible that $(L, H), (H, L)$ occurs as a Nash equilibrium (A.4), when:

\[
\alpha \left( \frac{\eta - \delta}{1 - \alpha} \right) + \gamma < \beta < \alpha \left( \frac{\kappa - \delta}{1 - \alpha} \right)
\]

(2.8)

In this case, it can be shown that

\[
P(L, H) - P(H, L) > \alpha(\eta - \delta) + \alpha(\delta - \eta) = 0
\]
Hence, the player treating at a low level is free-riding on the benefits provided by the player treating at a high level. At these parameter values, the player adopting $H$ provides benefits to the player adopting $L$ by reducing case imports of infections to their jurisdiction. In practice, this could occur if one player first moves from a lower to a higher treatment rate early during the pandemic, due to the relation $P(H, L) > P(L, L)$. However, once that player has switched to high treatment, the fact that $P(L, H) > P(H, H)$ means that the player who is slower to switch strategies has no incentive to also switch to high treatment rates. Hence, the Nash equilibrium is $(L, H), (H, L)$. However, since $\kappa \approx \eta$ and $\gamma > 0$ are reasonable assumptions, meaning that the leftmost term in inequality (2.8) will generally exceed the rightmost term and thus violate the inequality, we expect this outcome to be rare.

Finally, this game admits a mixed strategy Nash equilibrium which is found using the Bishop-Cannings theorem [76]. A mixed strategy is one in which a player plays his available pure strategies with a given probability. If $p$ is the probability of opponent playing $H$ then it can be shown (A.5) that the mixed Nash Equilibrium $p^*$ is

\[
(p^*, 1 - p^*) = \left(\frac{\alpha(\delta - \kappa - \beta) + \beta}{\alpha(\eta - \kappa - \gamma) + \gamma}, \frac{\alpha(\eta + \beta - \gamma - \delta) + \gamma - \beta}{\alpha(\eta - \kappa - \gamma) + \gamma}\right)
\]  

Parameter planes showing how these equilibrium states depend on model parameters are useful for better understanding these results. For a given value of the final size of the mutant strain if a player treats at a high rate ($\beta$), a less undesirable mutant strain (higher
\( \alpha \) shifts the outcome from a single Nash equilibrium at \((L, L)\) to two Nash equilibria at \((H, H)\) and \((L, L)\) (Figure 2.2). This occurs because a less ‘scary’ or dangerous mutant strain reduces the incentive to maintain low treatment levels. If the final size of the mutant strain for a player treating at a low rate while the other player is treating at a high rate \((\gamma)\) is higher, there is a similar effect of turning \((H, H)\) into a second Nash equilibrium: increasing \(\gamma\) increases the strength of externalities, since the other player treating at a higher rate has a larger impact on the focal player treating at a lower rate. An increase in \(\gamma\) may occur due to stronger travel connections between the two jurisdictions, for instance. Finally, we observe from Figure 2 that decreasing \(\beta\), the final size of the mutant strain for a player treating at a high rate, also causes \((H, H)\) to become a second Nash equilibria. This occurs because a reduced final size of the mutant strain under high treatment rates incentivizes high treatment rates, since it corresponds to the (often unrealistic) situation where widespread use of the drug significantly reduces the final size of the drug-resistance strain.

Table 2.2: Conditions for different equilibria.

<table>
<thead>
<tr>
<th>Description</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordination Game</td>
<td>( \kappa &lt; \frac{(1-\alpha)\gamma}{\alpha} + \delta &lt; \frac{(1-\alpha)\gamma}{\alpha} + \eta )</td>
</tr>
<tr>
<td>Nash Equilibrium at ((L, L))</td>
<td>( \kappa &lt; \frac{(1-\alpha)\gamma}{\alpha} + \eta &lt; \frac{(1-\alpha)\beta}{\alpha} + \delta )</td>
</tr>
<tr>
<td>Nash Equilibrium at ((H, H))</td>
<td>( \frac{\beta}{\beta+\kappa-\delta} &lt; \alpha &lt; \frac{\gamma}{\gamma+\kappa-\eta} )</td>
</tr>
<tr>
<td>Nash Equilibrium at ((L, H)), ((H, L))</td>
<td>( \alpha \left( \frac{\eta-\delta}{1-\alpha} \right) + \gamma &lt; \beta &lt; \alpha \left( \frac{\kappa-\delta}{1-\alpha} \right) )</td>
</tr>
<tr>
<td>Mixed Nash Equilibrium</td>
<td>( \frac{\alpha(\delta-\kappa-\beta)+\beta}{\alpha(\eta-\kappa-\gamma)+\gamma} &lt; \alpha \left( \frac{\kappa-\delta}{1-\alpha} \right) + \gamma &lt; \alpha \left( \frac{\kappa-\gamma}{\eta+\kappa-\gamma} \right) )</td>
</tr>
</tbody>
</table>

Parameter planes of \(\beta\) versus \(\gamma\) for various values of \(\alpha\) show a wider range of possible outcomes, especially when \(\alpha\) is larger (Figure 2.3). Here we again observe that low values
Figure 2.2: $\alpha - \gamma$ parameter plane: The $\alpha - \gamma$ parameter plane divided into regions containing one or two Nash Equilibria for various $\beta$ values. The region above each line contains two Nash Equilibria at $(L, L)$ and $(H, H)$ while the region below each line contains single Nash equilibria at $(L, L)$.

of $\beta$ (an unrealistic region of parameter space corresponding to a low final size of mutant infections under high treatment rates) or high values of $\gamma$ (corresponding to stronger externalities due to closer travel connections) correspond to a region of parameter space where both $(H, H)$ and $(L, L)$ are Nash equilibria. In contrast, when $\beta$ is large and/or $\gamma$ is small, $(L, L)$ is the only Nash equilibrium. Moreover, as $\alpha$ increases, corresponding to a less undesirable mutant strain, the region where $(H, H)$ is the sole Nash equilibrium appears and begins to expand. This occurs because when $\alpha$ is larger, generating mutants is less of a concern and hence higher treatment rates are acceptable. As $\alpha$ increases, a region with two Nash equilibrium $(L, H)$ and $(H, L)$ also appears, but it occupies a very small region of the parameter space (see also Figure 2.4, which shows a blown-up version of Figure 2.3f). Our model does not account for time spent in transit, such as time spent in an airplane, or
commuting via public transit or automobile. This might have an impact on our results if jurisdictions are connected by plane travel and symptom screening stations are set up at airport arrival terminals. However, it would not have an impact for jurisdictions connected primarily through public transit or automobile, for which screening is impractical.

Figure 2.3: $\beta - \gamma$ parameter plane: The $\beta - \gamma$ parameter plane divided into various regions depending on number and type of Nash equilibrium they contain, for $\alpha=0.01$ (a), 0.1 (b), 0.2 (c), 0.3 (d), 0.4 (e) and 0.5 (f). Nash equilibria are indicated by $(H, H)$, etc.

In summary, the best scenario for an outcome of $(L, L)$ where both players adopt low treatment levels occurs when: the jurisdictions are not strongly connected through travel (low $\gamma$), high levels of treatment would result in a high final size of infections by mutant strains (high $\beta$), and/or the mutant strain is highly undesirable (low $\alpha$). Most importantly, jurisdictions with close travel ties (low $\gamma$) and with the potential for mutants that do not respond to the antiviral drug (large $\beta$) are more subject to outcomes such as $(H, H)$ due to externalities, and if $\alpha$ is also small, then outcomes could be socially suboptimal (i.e.
Figure 2.4: $\beta - \gamma$ parameter plane: The $\beta - \gamma$ parameter plane divided into various regions depending on number and type of Nash equilibrium they contain, for $\alpha = 0.5$. Nash equilibria are indicated by $(H, H)$, etc. This figure is equivalent to Figure 3f.

non-Pareto optimal) since both jurisdictions end up treating at high rate due to strategic considerations.

### 2.3.2 Stackelberg Equilibria

The temporal development of events that occur during a real influenza pandemic could change the strategic nature of antiviral usage. For instance, the pandemic strain would first emerge in a single jurisdiction that might have to make decisions about antiviral usage before other jurisdictions that are presently virus-free.

The concept of a Stackelberg equilibrium is useful under these circumstances of a sequential game [77]. In a Stackelberg equilibrium, one player acts as a leader and the other as a follower. The leader adopts a strategy, taking into account the followers optimal response
strategy. It differs from the Nash equilibrium in which players act simultaneously. We will denote focal jurisdiction as the leader, where the pandemic starts, and other jurisdiction as the follower.

Under conditions where \((L, L)\) or \((H, H)\) are the only Nash Equilibria in the case of simultaneous play, then sequential play does not alter the predictions of our analysis. However, for the conditions that lead to a coordination game in the simultaneous case \((P(L, L) > P(H) > P(L, H))\) the outcome of sequential play differs from the simultane-
uous case. Sequential play permits the leader to direct the outcome to the \((L, L)\) equilibrium, since the leader can surmise that the follower will choose \(H\) if it chooses \(H\), and \(L\) if it chooses \(L\). Thus, the leader will choose \(L\), since \(P(L, L) > P(H)\).

Under conditions where we have the equilibria \((L, H)\) and \((H, L)\) in the simultaneous case, sequential play benefits the leader. If the leader chooses \(L\), then the follower will choose \(H\). And, if the leader chooses \(H\), then the follower will choose \(L\). Thus, we arrive at one of the two Nash Equilibria. Since \(P(L, H) > P(H)\), the leader will choose \(L\), and thus force the follower to take the lesser payoff, \(H\). Therefore, sequential play benefits the leader.

### 2.4 Discussion

Here we developed a two-player game of strategic interactions in antiviral usage during an influenza pandemic. The model highlights the possibility for externalities to develop, if a drug resistant influenza strain is as transmissible as the non-resistant variety. Under such circumstances, it is possible for a socially suboptimal Nash equilibrium to develop where both players use antiviral influenza drugs at a high rate, when the socially optimal behaviour is actually for both players to treat at a low rate. This occurs because players may opt to treat at a high rate, knowing that drug-resistant mutants will emerge and be imported to their jurisdiction anyway, due to high antiviral drug usage in the other jurisdictions. In this scenario, there is a Nash equilibrium at \((L, L)\) where both jurisdictions treat at a low rate,
and a socially suboptimal equilibrium at \((H, H)\) where both jurisdictions treat at a high rate. We found that such a scenario is more likely when the two jurisdictions are closely connected through travel (\(\gamma\) is high), since travel connections increase the chances of case importations. A higher travel volume increases the chance that a mutant strain is imported from the other jurisdiction, and therefore increases the likelihood that the jurisdiction will increase its treatment rate in anticipation of receiving mutant strains from the other jurisdiction. Similarly, socially suboptimal Nash equilibria such as \((H, H)\) or coordination games also occur when the mutant strain is tolerated (\(\alpha\) is high). This causes the players to be less concerned about generated drug-resistant strains and therefore more likely to choose \(H\). Finally, a socially suboptimal Nash equilibrium could occur if the antiviral drug is effective in reducing the final size of the drug resistant strain (\(\beta\) is low). However, antiviral drugs seem to have little influence on the final size of drug-resistant influenza strains [78] and so a situation where \(\beta\) is low may not occur in reality. In summary, a socially suboptimal outcome where two Nash equilibria are possible and player choose the one corresponding to a higher treatment rate occurs if the jurisdictions are closely connected through travel; if the drug-resistant mutant is tolerated (not seen as undesirable); or if the antiviral drug has partial efficacy against the drug-resistant strain.

In the Stackelberg model, in which players play sequentially, we found that conditions for both players to use antiviral drugs at a low rate were weaker (easier to satisfy). Such cases in which the Stackelberg model applies are: when the emergence of a disease is observed in a single jurisdiction, or when the disease is observed in both jurisdictions, but
one jurisdiction is able to react faster.

Our model considers an implied stochastic setting where players incur a probability to generate a mutant strain if they treat with antiviral drugs at a high rate. Because of this, when the volume of travel between the populations is sufficiently low, the main impact that a jurisdiction might have on other jurisdictions is if they treat with antiviral drugs at a very high rate, while other jurisdictions treat at a low rate. In that case, the jurisdictions treating at a low rate may receive case imports of mutant strains from the jurisdiction treating at a high rate \((P(L, H) \neq P(L, L))\), despite their attempts to treat at a low rate to avoid the emergence of antiviral drug resistance. On the other hand, a jurisdiction treating at a high rate is already generating mutant strains and is therefore little affected by other jurisdictions in this respect \((P(H, H) = P(H, L))\). Naturally, differing assumptions about travel volume or the impact of antiviral drugs on the epidemiology of the drug-resistant strain could change the predictions. Thus, future work could explore this effect through a stochastic, two-patch model.

Like other models, this model has some limitations. Perhaps most importantly, we derive payoffs from a posteriori epidemiological and antiviral drug assumptions. This was intentional, since our objective was to illustrate that the outcomes of strategic interactions in antiviral drug usage between jurisdictions during an influenza pandemic could vary widely depending on epidemiological \((\beta)\), geographical \((\gamma)\), and perception of the severity of the mutant strain compared to the resistant strain \((\alpha)\). However, the drawback of using a posteriori assumptions is that it is difficult to quantify the exact likelihood of various outcomes,
or even to quantify the outcomes themselves. For instance, we do not know what value of $\alpha$ real health authorities might adopt. Similarly, although we interpret $(H, H)$ to represent a socially suboptimal outcome where both jurisdictions engage in excessive antiviral drug use, we would need to better quantify the relationship between treatment levels and outcomes (for instance, by using a mechanistic model and/or using real cost estimates) in order to firmly establish this. A further limitation is that we did not capture stochastic events, which are important in the context of drug resistance evolution since mutation events are stochastic. We also assumed that jurisdictions can control stockpiles of drugs and that they may quickly and accurately dispense them during a pandemic. Additionally, this model is not based on an infectious disease transmission model, and thus we could not study any temporal dynamics.

Similarly, predictions might change if the Stackelberg model were changed to a multiple turn game where we alternate between the jurisdictions, giving them the option to increase their treatment levels. Under conditions where $P(L, L) < P(H) < P(L, H)$, both jurisdictions wish for the other to treat at a high level while they treat at a low level. In a repeated game this could result in a so-called Mexican standoff where neither side wishes to treat. However, this leads to the worst case scenario for both jurisdictions, $(L, L)$, because of the assumption $P(L, L) < P(H) < P(L, H)$.

The quantities $P(H, H)$ and $P(H, L)$ are in fact only approximately equal when case imports are not too high. Our assumption that $P(H, H) = P(H, L)$ may break under the various circumstances. For instance, we could achieve $P(H, H) > P(H, L)$ if the
use of the high antiviral treatment level in the other jurisdiction significantly decreases the number of cases that are imported from to the focal jurisdiction, and increases the focal players payoff (relative to the case where the other player uses the low treatment level). Alternatively, $P(H, H) < P(H, L)$ could happen if the use of the high treatment level at the other jurisdiction significantly increases the risk of a drug resistant strain arising, and being imported into the focal jurisdiction, and that the spread of such a strain is very costly to the focal jurisdiction. We speculate that these conditions are more likely to arise when the travel rates between the two jurisdictions are very high. It can be shown that we have a coordination game under these circumstances when $P(L, L) > P(H, L)$ and $P(H, H) > P(L, H)$. However, we leave a full exploration of the case $P(H, H) \neq P(H, L)$ to future work.

Other model limitations include lack of heterogeneity in the patient population and patient health status in particular, and the lack of including other drivers of behaviour. For instance, some individuals may have risk factors for severe infection, such as co-infection with HIV or advanced age. Such patients would merit a higher priority for antiviral drug treatment, and the moral imperative to provide treatment for those individuals could modify strategic considerations. To some extent, heterogeneity in patient health status is implicitly accounted for in our model: we allow for a low treatment strategy, but not a zero treatment strategy, because we assume that some individuals will always be treated. However, our assumption that the low treatment strategy will not produce antiviral drug resistance may not apply under all circumstances. Moreover, there may be other consequences of pop-
ulation heterogeneities for strategic interactions that we have not foreseen. It is difficult to know whether such heterogeneities would strengthen or weaken strategic interactions \textit{a priori}, therefore further research on this topic is needed. Strategic considerations could also be modified by political or economic factors. Political decisions receive input from factors other than strategic considerations, and likewise economic factors could be a strong determinant of antiviral drug use strategies. For instance, many countries simply cannot afford to practice prophylaxis or widespread treatment with antiviral drugs. Similarly, social cohesion could influence decisions and prevent a “rational” Nash equilibrium from materializing, either in favour of higher antiviral drug use, or lower antiviral drug use [79].

A model with multiple jurisdictions and connected by complex network could also result in very different predictions than our simple two jurisdiction model. Finally, we note that when antiviral drug resistance can emerge \textit{de novo}- independently of antiviral drug use- the nature of strategic interactions could change significantly, which has implications for predicted outcomes.

We leave it to future work using more realistic models to refine some of the results of our simple model, and determine more precisely the likelihood that strategic factors could become important, and what the corresponding outcomes would be. For now, this initial model shows that strategic interactions could potentially play a role in antiviral drug use decisions, and it calls for further research with more detailed and empirically motivated models.
2.5 Conclusion

The model shows how a wide range of outcomes are possible depending on epidemiological, geographical, and perceptual factors in the populations. Externalities caused by travel connections when drug-resistant mutants do not suffer a reduced transmission have the potential to lead both jurisdictions to socially suboptimal states of excessive antiviral drug use. Strategic interactions between jurisdictions during an influenza pandemic should be further studied.

List of abbreviations

$L$: treat at a low rate

$H$: treat at a high rate

$l$: low payoff

$m$: medium payoff

$h$: high payoff

$WHO$: World Health Organization

$HIV$: Human Immunodeficiency Virus
Chapter 3

Emergence and spread of drug resistant influenza: A two-population game theoretical model


Abstract

Background: The potential for emergence of antiviral drug resistance during influenza pandemics has raised great concern for public health. Widespread use of antiviral drugs is
a significant factor in producing resistant strains. Recent studies show that some influenza viruses may gain antiviral drug resistance without a fitness penalty. This creates the possibility of strategic interaction between populations considering antiviral drug use strategies.

**Methods:** To explain why, we develop and analyze a classical 2-player game theoretical model where each player chooses from a range of possible rates of antiviral drug use, and payoffs are derived as a function of final size of epidemic with the regular and mutant strain. Final sizes are derived from a stochastic compartmental epidemic model that captures transmission within each population and between populations, and the stochastic emergence of antiviral drug resistance. High treatment levels not only increase the spread of the resistant strain in the subject population but also affect the other population by increasing the density of the resistant strain infectious individuals due to travel between populations.

**Results:** We found two Nash equilibria where both populations treat at a high rate, or both treat at a low rate. Hence the game theoretical analysis predicts that populations will not choose different treatment strategies than other populations, under these assumptions. The populations may choose to cooperate by maintaining a low treatment rate that does not increase the incidence of mutant strain infections or cause case importations to the other population. Alternatively, if one population is treating at a high rate, this will generate a large number of mutant infections that spread to the other population, in turn incentivizing that population to also treat at a high rate. The prediction of two separate Nash equilibria is robust to the mutation rate and the effectiveness of the drug in preventing transmission, but it is sensitive to the volume of travel between the two populations.
Conclusions: Model-based evaluations of antiviral influenza drug use during a pandemic usually consider populations in isolation from one another, but our results show that strategic interactions could strongly influence a population’s choice of antiviral drug use policy. Furthermore, the high treatment rate Nash equilibrium has the potential to become socially suboptimal (i.e. non-Pareto optimal) under model assumptions that might apply under other conditions. Because of the need for players to coordinate their actions, we conclude that communication and coordination between jurisdictions during influenza pandemics is a priority, especially for influenza strains that do not evolve a fitness penalty under antiviral drug resistance.

Keywords: game theory, stochastic compartmental model, antiviral drugs, drug resistance, H1N1, fitness penalty

List of abbreviations:

$L$: treat at a low rate

$H$: treat at a high rate

$NE$: Nash equilibria

$ODE$: Ordinary differential equation

3.1 Introduction

Case importation is the primary means by which horizontally transmitted infectious diseases of humans can move between populations. For instance, the 2009 pandemic in-
fluenza A (pH1N1) viral strain originated in Mexico, but quickly spread to other countries through international travel [80]. pH1N1 spread as much in six weeks as other influenza strains spread in six months [81]. After an imported case of pH1N1 was identified in Germany on 27 April, 2009 (only a month after the virus was identified in Mexico City) the global transmission of pH1N1 appeared to be on the horizon [82].

If vaccines are not immediately available during an influenza pandemic, antiviral drugs are one of the most effective ways to reduce the health burden of infections [17]. There are four types of antiviral drugs available to treat influenza: oseltamivir, zanamivir, amantadine and rimantadine [83]. However, some factors delay the onset of treatment, and emergence and transmission of antiviral drug viruses may reduce the efficacy of treatment [84]. \( M_2 \) inhibitors such as amantadine and rimantadine work only against influenza A. In contrast, neuraminidase inhibitors such as zanamivir and oseltamivir are effective against both influenza A and influenza B [85]. Neuraminidase inhibitors block the function of the viral neuraminidase protein enzyme that prevents the discharge of viruses from the infected host cell and precludes new host cells from getting infected. The development of oseltamivir resistance is minimal if it is used at recommended doses for treatment [61]. However, high rates of resistance are possible: 18% prevalence of resistance to oseltamivir has been observed among treated children in Japan [18]. Also, in 2008, a high level of emergence and spread of oseltamivir resistance viruses was observed in Europe [63].

A number of mathematical models (primarily, ordinary differential equation models) have explored the potential impact of the emergence of drug resistant influenza and its
spread during an outbreak [20, 21, 22]. This research has provided useful insights into the emergence and spread of drug-resistant influenza. These models predict that the final size of a pandemic can be reduced by applying an adaptive antiviral strategy with properly timed increases in drug usage, and that chemoprophylaxis of susceptible individuals is one of the best ways to reduce the force of infection of an epidemic and keep the emergence of drug resistant viruses low [23]. A recent study [24] presents a stochastic model of influenza. A stochastic model is a tool for assessing the impact of noise on a dynamical systems’ trajectories, and generates probability distributions of possible outcomes by allowing random variation in one or more inputs over time. The importance of recognizing stochasticity relates to the fact that some characteristics of the spread of infectious diseases can depend on random events. In a small population especially, stochasticity is expected to play a significant role in epidemic dynamics, especially when the number of infected hosts is low and epidemic fade-out is likely to happen [13].

Most previous models on the emergence of antiviral drug resistance focus on dynamics in a single population in isolation from other populations, however, there are conditions under which decisions about antiviral drug use in one population can affect other populations, which calls for the use of tools like game theory. Game theory is the study of decision-making where players make choices that affect the outcomes (payoffs) for other players–the formalization of strategic interactions in a group [26]. The Prisoner’s Dilemma, for instance, is a two player game in which each player can choose between two strategies, either cooperate or defect. Each player earns a high payoff $r$ when both cooperate, but
if only one of them cooperates, the one who defects will gain a very high payoff \( t \) while the cooperator will get a very low payoff \( s \). If both defect, both receive moderate payoff \( u \) (where \( t > r > u > s \)). It can be shown that both players would be better off if they cooperated (since \( r > u \)) but what actually happens is that both players, if thinking strategically, will defect (since \( t > r \)). As a result, a situation where both players defect is the Nash equilibrium—the expected outcome of the game. This game captures the clash between individually optimal versus socially optimal actions.

In the case of antiviral drug use during a pandemic, there may be strategic aspects of antiviral drug use decisions of multiple populations connected through travel. For instance, consider two populations connected through travel, where a decision-maker in each population must decide how antiviral drugs will be distributed in their population. Under certain epidemiological circumstances, it may make sense for the two populations to cooperate (in the sense of the Prisoner’s Dilemma) with one another by both treating their infected individuals at a low level and thereby avoiding emergence of drug resistance. However, one population may defect by adopting a higher treatment level, thereby increasing the chance that a drug resistant strain is created and spread to the other population. The incentive for this strategy is the reduction in the final size of the epidemic. However, defection is available to both populations, and thus both have the incentive to defect by treating at a high level. If a drug resistant influenza strain is as transmissible as the non-resistant strain (i.e., no fitness penalty), then it is possible for a socially suboptimal Nash equilibrium to develop where both players use antiviral influenza drugs at a high rate, when the socially
optimal behaviour is actually for both players to treat at a low rate. Because the evolution of antiviral drug resistance without a fitness penalty has been observed [60, 62], this is a possibility that should be explored in mathematical models.

Most previous game theoretical analyses in epidemiology have looked at vaccinating decisions or social distancing decisions [86, 87, 88], although strategic, multi-population aspects of antiviral drug use during a pandemic has explored this interaction in a limited setting in Ref. [89]. This previous research assumes a 2-player, 2-strategy game where each player can only adopt one of two strategies: low treatment rate or high treatment rate. The payoffs of the model were fixed parameters representing final epidemic sizes for the four strategy combinations. This research showed how to formalize strategic interactions in antiviral drug use, and explored some of the possible consequences. For instance, conditions for two Nash equilibria were determined (i.e., both Defect-Defect and Cooperate-Cooperate are Nash equilibria), and it was also found that travel connections had a great impact on possible strategic outcomes such as defection or cooperation. However, the previous analysis was limited because of three simplifying assumptions: it did not use a disease transmission model to determine the final epidemic sizes and therefore the payoffs; players were limited to choosing between two discrete levels of antiviral drug use; and the approach did not capture stochasticity in disease transmission. As a result of the first and third limitations in particular, the existence of two Nash equilibria as might occur in a coordination game could not be deduced with as much confidence as would be permitted by a mechanistic stochastic model of disease transmission and emergence of antiviral drug
resistance.

Here, we relax these three simplifying assumptions of the previous research by developing a mechanistic, stochastic disease transmission model to study this strategic interaction, still in the context of a 2-player game theoretical model. The players—decision-makers in the two populations who limit antiviral drug supply and therefore determine usage levels—may pick from a set of strategies; the strategies chosen by each player determine the payoffs. The set of strategies that each population may choose from are the treatment rate of infectious persons. For each treatment rate there is a payoff as a function of the final size of the epidemic in that population. A population can treat their citizens once they get infected. However, a population cannot treat infectious people from the other population, and thus is susceptible to imported infections. Further, a very high treatment level will reduce the final size of the regular strain, but will increase the chances that a mutant strain is created and possibly spread to the other population as well. This dynamic is thus similar to the Prisoner’s Dilemma. In the next section we describe the Model structure.

3.2 Material and methods

3.2.1 Model Structure

We developed a discrete time Markov model of influenza transmission, antiviral drug use, and antiviral drug resistance evolution in two well-mixed populations connected through travel. Individuals may be treated with antiviral drugs, or not treated. They may also be
either infected with the regular drug sensitive strain, or with the mutant drug resistance
strain. The population consists of susceptible (S), infected, and recovered individuals (R).
Infected individual are categorized into infected with the regular strain and untreated (I),
infected with regular strain and treated ($I^t$), infected with the mutant strain and untreated
($I_m$), and infected with mutant strain and treated ($I^t_m$). A diagram of these interactions is
depicted in Figure 3.1.

The daily, one-step transition probabilities in the Markov model are:

$$P(S, I) = 1 - (1 - p\frac{I}{N})(1 - p\phi\frac{I^t}{N}) \quad (3.1)$$

$$P(S, I_m) = 1 - (1 - p\frac{I_m}{N})(1 - p\phi\frac{I^t_m}{N}) \quad (3.2)$$

$$P(I, R) = r \quad (3.3)$$

$$P(I^t, R) = r^t \quad (3.4)$$

$$P(I_m, R_m) = r_m \quad (3.5)$$

$$P(I^t_m, R_m) = r^t_m \quad (3.6)$$

$$P(I, I^t) = \mu \quad (3.7)$$

$$P(I_m, I^t_m) = \mu \quad (3.8)$$

$$P(I, I_m) = \rho \quad (3.9)$$

$$P(I_m, I) = \rho' \quad (3.10)$$

$$P(I^t, I^t_m) = \omega \quad (3.11)$$

$$P(I^t_m, I^t) = \omega' \quad (3.12)$$
where $P(S, I)$ is the transition probability from the susceptible compartment ($S$) to the

infected by the normal strain compartment ($I$); $P(S, I_m)$ is the transition probability from
the susceptible compartment ($S$) to the infected by the mutant strain compartment ($I_m$), and
similar meanings apply for the other transitions, $\phi$ is the relative transmissibility of treated
infected individuals, and $p$ is the probability that a susceptible-infected contact results in a
new infection. All other parameters concerning disease natural history in infected persons
are summarized in Table 3.1, and we explain each of the processes described by the above

Figure 3.1: Diagramatic Illustration of the Model: (a) Compartmental model of disease
transmission. The population is partitioned into three classes: Susceptible (S), Infectious
(I), and Recovered (R). There are four compartments for infected individuals $I, I_m, I^t, I^t_m$
and two for recovered individuals $R$ and $R_m$. (b) This diagram shows how the people of
different populations go from one compartment to another.
equations in the following subsections. Parameter values were set according to available literature whenever possible, or calibrated to available empirical targets. We assumed five initially infected individuals ($I(0) = 5$) unless otherwise noted.

Table 3.1: Variables and Parameters, values and descriptions: We use the following parameter values as our base case for model simulations.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I$</td>
<td>Infected untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$I'$</td>
<td>Infected treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$I_m$</td>
<td>Infected untreated with mutant strain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$I_{tm}$</td>
<td>Infected treated with mutant strain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$</td>
<td>Transmission between $S$ and $I$</td>
<td>0.335/day</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$p$</td>
<td>Transmission between $S$ and $I_m$</td>
<td>0.335/day</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$\phi$</td>
<td>Relative transmissibility of treated infected individual</td>
<td>0.25 − 1</td>
<td>[24]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Probability of treatment</td>
<td>0 − 0.5/day</td>
<td>Assumption</td>
</tr>
<tr>
<td>$\rho$</td>
<td>Probability of mutation from $I$ to $I_m$</td>
<td>$10^{-6}$/day</td>
<td>[24]</td>
</tr>
<tr>
<td>$\rho'$</td>
<td>Probability of mutation from $I_m$ to $I$</td>
<td>$10^{-6}$/day</td>
<td>[24]</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Probability of mutation from $I'$ to $I_{tm}$</td>
<td>0.04/day</td>
<td>[24]</td>
</tr>
<tr>
<td>$\omega'$</td>
<td>Probability of mutation from $I_{tm}$ to $I'$</td>
<td>0/day</td>
<td>[24]</td>
</tr>
<tr>
<td>$r$</td>
<td>Probability of recovery from $I$ to $R$</td>
<td>0.25/day</td>
<td>[21]</td>
</tr>
<tr>
<td>$r'$</td>
<td>Probability of recovery from $I'$ to $R$</td>
<td>0.5/day</td>
<td>[21]</td>
</tr>
<tr>
<td>$r_m$</td>
<td>Probability of recovery from $I_m$ to $R_m$</td>
<td>0.25/day</td>
<td>[21]</td>
</tr>
<tr>
<td>$r_{tm}$</td>
<td>Probability of recovery from $I_{tm}$ to $R_m$</td>
<td>0.375/day</td>
<td>[21]</td>
</tr>
<tr>
<td>$\tau$</td>
<td>Rate of infected people move from one population to another</td>
<td>0.01/day</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

### 3.2.2 Transmission Probability and Case Importation

We assume that susceptible individuals can be infected by either the regular strain or the mutant strain with the same rate of transmission, $p$, following the observation that drug resistant influenza strains can often spread without a fitness penalty [60, 62]. Influenza has a high person-to-person transmission rate. $\phi$ is the relative transmissibility of treated infected individual. We used the final size of the epidemic as 21% [90] to calibrate the value.
of \( p \) by varying \( p \) from 0 to 1 across multiple model realizations and choosing the value of \( p \) that minimized the difference \( |\frac{R_{\infty}}{N} - 0.21| \). We repeated this grid sweep procedure until \( p \) was determined through error minimization down to three decimal places.

### 3.2.3 Antiviral Drug Treatment

Once an individual becomes infected they may be treated with some probability. The probability of treatment per unit time, \( \mu \), is the same for the regular and mutant strains. We assume \( \mu \in [0, 0.5] \) per day, ranging from no treatment at all to a relatively rapid treatment rate of 50\% of infected cases moving into drug treatment per day (\( \mu = 0.05/\text{day} \)).

### 3.2.4 Natural Disease History / Recovery

In untreated individuals, resistance to the drug is gained with probability \( \rho = 10^{-6} \) per day and lost at the same rate [24]. We assume that treatment carries a small probability of generating a drug-resistant mutant strain. In treated individuals, resistance is gained with probability \( \omega = 0.04 \) per day and lost at \( \omega' \) (we will take \( \omega' = 0 \) for our analysis) [24]. We note the probability that antiviral drug treatment causes emergence of a drug-resistant influenza strain varies widely across subtypes, and in some cases it can even emerge de novo. Hence, our model is restricted to an influenza strain where de novo emergence of drug resistance is rare, and treatment carries a very low but non-negligible probability of causing evolution of drug resistance. There are two compartments \( R \) and \( R_m \) for recovered individuals after getting infected by the regular strain and the mutant strain respectively.
The probability of recovery from infected untreated to recovered is $r$, which is the same as the probability of recovery from infected untreated with mutant strain to recovered, $r_m$. Moreover, the probability of recovery from infected treated to recovered is $r^t$, and the probability of recovery from infected treated with mutant strain to recovered is $r^t_m$. We assume the inequality $r_m = r < r^t_m < r^t$ holds true [21]. Once an individual recovers, s/he will no longer be susceptible.

### 3.2.5 Demographic Processes

We ignored the birth and death rate throughout the whole epidemic, since the timescale of birth and death is very slow compared to the timescale of an epidemic. We let both populations have an equal number of 100,000 individuals. Air travel has greatly accelerated the spread of influenza and other diseases transmitted by person-to-person contact. As an example, populations with a higher volume of airline travel to and from Mexico experienced earlier outbreaks of pandemic H1N1 2009 [91]. Therefore we assume that infectious individuals can transmit to susceptible individuals living in the same locale, or to susceptible individuals in another population by traveling at a per capita rate $\tau$. Infected persons can also travel, since many individuals infected with influenza can be either pre-symptomatic or asymptomatic, we assumed that $\tau$ is the same for both populations (i.e. traveling rate from population 1 to population 2 and vice-versa).
3.2.6 A Two population Game

The strategic interaction between the two populations was formulated as a classical two-player game where each player is characterized by a strategy set and payoff functions describing the payoff for a given strategy, contingent on what strategy the other player chose. Using these assumptions and the transmission model, the Nash Equilibrium was then determined through numerical simulation of the Markov model.

Game Description

The players of the game are two populations, population 1 and population 2, who choose a treatment rate (per capita probability $\mu$ of treatment per unit time) for their members (or rather, we posit a central authority that recommends a policy of antiviral drug use and possibly also limits the supply of antiviral drugs accordingly). The populations may choose a treatment rate, $0 \leq \mu \leq 0.5$/day. We constrain $\mu \leq 0.5$ under the assumption that the process of visiting a physician, obtaining a diagnosis of influenza, and initiating treatment with antiviral drugs takes time, and therefore a treatment rate of more than 50% of currently infected persons per day would be unrealistic. The “currency” of the game is the final size of the epidemic of regular or mutant strains, measured by the number of individuals in the Recovered compartment at the end of the epidemic. The payoff, $P_i$, of population $i$ that adopts treatment rate, $\mu_i$, is

$$P_i(\mu_i, \mu_j) = -\alpha F_i^r(\mu_i, \mu_j) - (1 - \alpha) F_i^m(\mu_i, \mu_j)$$  \hspace{1cm} (3.13)
where $F_r^i$ and $F_m^i$ are the final epidemic size—the number of individuals recovered from infection during the outbreak—for the regular and mutant strains respectively, when population $i$ treats at the rate $\mu_i$ and $j$ at the rate $\mu_j$. $\alpha$ is the weighting factor which is used to control and balance the priorities of preventing infection by both strains. We constrain $\alpha < 0.5$ under the assumption that the mutant strain is less desirable than the regular strain, either on account of being drug-resistant or perhaps also on account of being more virulent. We note that the payoff function is negative, because maximizing payoff for a currency such as this is the same as minimizing harmful health impacts. Alternatively, one could formulate the currency in terms of some health-quality units such as quality-adjusted life-years (QALY), and subtract the QALY impacts of infection from a baseline QALY representing average remaining quality-adjusted life-years of a typical individual [92]. However, this would amount to the same expression as equation (3.13).

**Nash Equilibrium**

If each player has chosen a strategy and no player can improve his or her payoff by changing strategies while the other players keep theirs unchanged, then the current set of strategy choices constitute a Nash equilibrium, which game theorists assume to be the strategy most likely to be adopted by all players. Here we seek to identify the Nash equilibrium antiviral drug treatment rate. Since our game is a two-player symmetric game (assuming both players have the same initial conditions of infected individuals) with continuous strategy set $0 \leq \mu \leq 0.5$, a strategy $\mu^*$ is defined as a strict Nash equilibrium if and only if
for any alternative strategy $\mu \neq \mu^*$, such that a higher payoff cannot be achieved by switching strategies to $\mu \neq \mu^*$. The same equation applies to population 2.

**Algorithm for determining Nash Equilibrium**

To find the Nash equilibrium for the game, we use a Cournot model of best response functions. A player’s best response is the strategy that produces the greatest output for him/her given that what other players are doing. A curve which joins all these points is the best response curve. A pair of solution sets to such curves is a Nash equilibrium which is the point of intersection of the curves for each player [93]. For each value of $\mu_2$ from 0 to 0.5, we identify $\mu_1^*(\mu_2)$ that maximizes $P_1(\mu_1, \mu_2)$. The curve composed of these $\mu_1^*(\mu_2)$’s is the best response curve of population 1 against population 2’s decision of $\mu_2$. Similarly, for all values of $\mu_1$ from 0 to 0.5, we find $\mu_2^*(\mu_1)$ that maximizes $P_2(\mu_2, \mu_1)$. The curve of $\mu_2^*(\mu_1)$’s is the best response curve of population 2 against population 1’s decision of $\mu_1$. The Nash equilibrium is the intersection of these two best response curves.

We ran 10,000 simulations and averaged the payoff across all 10,000 simulations at each value of $\mu_1$ and $\mu_2$ tested, in order to find the best response for population 2 for each treatment rate for population 1. In addition, we found 100 such points for 100 different treatment rates for population 1 to produce the best response curve for population 2. Similarly, we repeat the process to find the best response for population 1 for each treatment rate.
for population 2. Moreover, we ran 5000 simulations for the output of other results (plots).
Initially, we introduced 5 infected people in population 1 and observed closely how disease spread into population 2 in 400 days. Some parameters such as $\mu, \omega, \tau,$ and $\phi$ are varied to uncover the impact of these parameters on disease transmission and Nash equilibria.

3.3 Results

3.3.1 Epidemic dynamics

On average, for the parameter values in Table 3.1, the epidemic curves are fairly similar in the two populations although the epidemics start and end somewhat earlier in population 1 (Figure 3.2a) than population 2 (Figure 3.2b), on account of the infection being introduced first in population 1. The final size in population 1 for the regular strain is higher than in population 2, whereas the final size for the mutant strain in population 2 is higher than population 1. The epidemic peak for the regular strain is much higher than for the mutant strain in the population 1, where the epidemic began. These dynamics occur because both regular and mutant strains compete for the same pool of susceptible hosts, and recovery from one type of strain confers immunity to the other type of strain, the regular strain spreads quite rapidly before the mutant strain arises in population 1, and individuals in population 2 experience case importations of both types of strains from population 1. Additional time series show how the epidemic unfolds for different treatment rates, $\mu$, and
mutation rates, $\omega$ in population 1 (Figures 3.3 and 3.4). When treatment is zero, $\mu = 0$, we observed an epidemic with no mutants, as expected. For $\mu = 0.1$, we observe a greatly reduced epidemic of the regular strain, compared to the no treatment case, but we also observe a sizeable epidemic of the mutant strain. Larger treatment rates, such as $\mu = 0.2$ and $\mu = 0.3$, result in further reductions in the percentage of regular and mutant strain
Figure 3.3: **Time Series Plots:** This plot is produced for different treatment rates, $\mu$ and $\omega$. The solid black line represents the regular strain and the dashed grey line represents the mutant strain.

We also explore the average final size for regular and mutant strains as a function of the treatment rate, in population 1 (Figure 3.5). The final size curve is produced for the total number of infected in 350 days in population 1. The curve shows that if the treatment rate increases then the total number of infected with the regular strain decreases gradually and goes to zero before the treatment rate reaches 0.25. On the other hand, the final size of the mutant strain increases, peaks at $\mu = 0.12$, and then declines when treatment levels are
Figure 3.4: **Time Series Plots:** This plot is produced for different treatment rates, $\mu$ and $\omega$. The solid black line represents the regular strain and the dashed grey line represents the mutant strain.

increased further. This occurs because infections with the mutant strain can not move to the compartment of individuals treated with the regular strain, since $\omega' = 0$. Supplementary Figure S1 shows the average total population of infected with both strains in population 1 with the standard deviation above and below. It shows that the deviation decreases if the treatment level increases.
Figure 3.5: **Final Size Plot:** The total number of people got infected in population 1 in 350 days for different treatment rates if $\phi = 0.85$. The solid black line represents the regular strain and the dashed grey line represents the mutant strain. See supplementary figure S1 for error bars.

### 3.3.2 Baseline scenario

Figure 3.6 depicts the best response curves for our baseline scenario (Table 3.1 parameter values). A player’s strategy that produces the most favorable payoff if the other player’s strategy is known is called a best response. The best response curve is composed of these values for the full range of possible opponent strategies. A Nash equilibrium (NE) occurs at the intersections of the best response curves of the players, since these represent points where each player cannot improve their payoff by changing strategies unilaterally. One curve is the best response of population 2 vs. population 1 and the other is the best response of population 1 vs population 2.

Here we have two Nash equilibria at $(\mu_1, \mu_2) = (0.0255, 0.0345)$ (both treat at a low rate) and $(\mu_1, \mu_2) = (0.5, 0.5)$ (both treat at a high rate). A strategy where both populations treat at a very high rate is a Nash equilibrium, since very high treatment rates can signifi-
Figure 3.6: Best Response Curve produced for various treatment rates for population 1 and population 2.

cantly reduce the final sizes of both regular and mutant strains (Figures 3.3-3.5). However, a strategy where population 1 treats at a very high rate while population 2 treats at a low rate (or vice versa) is not a NE, since population 2 will receive case imports of the mutant strain from population 1 but will not be using antiviral drugs to reduce infections. A strategy where both populations treat at a low rate is a NE because when $\alpha < 0.5$, it is worthwhile to restrict treatment only to the severest infections and thereby avoid or limit the emergence of drug resistance, and if the other population cooperates by doing the same, then emergence of antiviral drug resistance will be avoided.

3.3.3 Impact of travel rate ($\tau$), mutation rate ($\omega$), and relative transmissibility ($\phi$)

We explored how the low-treatment and high-treatment NE depend on model parameter values in a series of sensitivity analyses for the travel rate ($\tau$), mutation rate ($\omega$) and relative
Figure 3.7: High and low Nash equilibrium curve for population 1 and population 2 produced for different $\tau$ (a), $\omega$ (b), and $\phi$ (c). The solid black line represents the $\mu_1$ and the grey dash line represents $\mu_2$.

transmissibility ($\phi$).

In figure 3.7(a), we plot the NE versus $\tau$. As $\tau$ increases, the low-treatment and high-
treatment NE begin to converge toward one another, mostly on account of an increase in the treatment rate for the low treatment NE. The convergence occurs because when treatment rates are higher, case importations constitute a higher proportion of a population’s payoff function. However, the number of case importations is not under a player’s control—it is determined entirely by the strategy adopted by the other population. Therefore, for the lower treatment NE, as the travel rate increases, the number of case imports from the other player also increases for a given treatment rate, and a player shifts their own optimal treatment rate upwards since they are experiencing case imports of drug-resistant mutants anyway. As the travel rate increases to very high levels, the two populations increasingly resemble a single, homogeneously mixing population. In the limit of a single (isolated) population with a single decision-maker, there would only be a single equilibrium treatment rate that corresponds to an optimization of equation 3.13. The differences between the treatment rates of each population at the high treatment NE as well as the low treatment NE is due to the asymmetry in the initial conditions of the populations—the infection is initiated only in population 1.

Figure 3.7(b) displays the NE vs \( \omega \), which shows how mutation rate affects the NE. For higher \( \omega \), the risk of generating mutants is greater, causing a decrease in payoff if mutants are generated. In contrast to the response to increasing \( \tau \), the response to increasing \( \omega \) is that both high and low NE move toward lower treatment rates, while the relative difference in treatment between low and high treatment NE is roughly conserved. This occurs because when mutation rates are high, players are less willing to risk generating mutations (all else
being equal) and so the NE treatment rate declines. Interestingly, the spread between low and high NE is relatively constant as ω increases, so the presence of the social dilemma is not sensitive to the value of the mutation rate, at least for the parameter values we explored.

Finally, figure 3.7(c) depicts the NE for various values of the relative transmissibility of treated individuals, φ. We observe that the treatment level at both low and high treatment NE is higher for higher φ. This occurs because if treatment is less effective in preventing transmission, there will be a higher final size of both mutant and regular strains, and hence players will wish to increase their treatment rate in an attempt to reduce the final size and prevent more cases. However, this result is also interesting and unanticipated, since higher treatment rates will also generate a higher probability of mutation to antiviral drug resistance. The optimal outcome depends on the tension between the objectives of decreasing the final size through more antiviral drug usage, versus preventing the evolution of antiviral drug resistance through less antiviral drug usage. As for ω, the spread between treatment rates at low and high NE is not significantly affected by changes in φ.

In summary, the existence of low- and high-treatment Nash equilibria is sensitive to the travel rate, but not the mutation rate or the relative transmissibility of treated individuals.

### 3.4 Discussion

Here we developed and investigated the predictions of a game theoretical model where two populations choose from a continuum of antiviral drug treatment rates, μ₁ and μ₂, and
where each population must weigh the undesirable possibility of generating drug-resistant mutants through treatment and/or receiving case imports of the drug-resistant mutant from the other population, despite a conservative approach. The model was a stochastic, mechanistic simulation model that incorporated empirical estimates for parameter values and each population’s choice was determined according to game theory.

We identified two Nash Equilibria, one corresponding to both populations adopting a high treatment rate and one corresponding to both populations adopting a low treatment rate. Notably a mixture where one population adopts a high treatment rate and the other adopts a low treatment rate cannot occur, according to the predictions of a Nash equilibria. They tend to both adopt high rates, or both low rates, because of the influence of the other player. Therefore this analysis shows that strategic interactions can strongly influence what treatment rate strategy a population may decide to adopt, in populations open to travel. The populations may choose to maintain a low treatment rate that does not increase the incidence of mutant strain infections or to create more resistant cases by choosing a higher treatment level.

Interestingly, because the final size for both mutant strain and regular strain are so small under the high treatment NE, the high treatment NE cannot be interpreted as a socially suboptimal Nash equilibrium, as was suggested in our previous game theoretical analysis that did not use a transmission model [89]. However, this result depends on the assumption that the antiviral drug reduces transmission of both regular and mutant strains to an equal extent. Under other conditions, it is known that abundant use of antiviral drugs can result
in widespread transmission of the drug resistant strain, and a nontrivial final epidemic size of the resistant strain[78]. Under model assumptions where transmission of the resistant strain is less affected by antiviral drugs than transmission of the regular strain, the high treatment NE may therefore be socially suboptimal (i.e., non-Pareto optimal). This is a topic for future research. We also note that this work establishes the existence of two Nash equilibria more strongly than our previous research [89], because it is based on a mechanistic model for infection transmission and drug resistance evolution, rather than imposing fixed parameter values representing the final size and the risk of generate mutants through antiviral drug usage, for which we must then guess as to how they respond to changing treatment levels.

There are several limitations of our model, which future studies should aim to relax. For instance, in this model we only considered the first wave of an epidemic. Thus, we ignored the possibility of other waves (although our model is capable of exhibiting subsequent waves). Moreover, we only considered two populations, although in real-world pandemics, a large number of interconnected populations of differing sizes are making decisions about antiviral drug treatment. Future work could develop $N$-population models. Finally, we neglected social processes and the internal decision-making structure of each population, whereas future work could divide each population into decision-makers and influenza patients.

We used a stochastic model since all model realizations–including ones where the infection went extinct due to stochastic effects before causing a large outbreak–were used
to compute payoff functions. Stochastic fade-out is an important feature of real outbreaks especially in their early stages, and in our model the emergence of an initially rare drug resistant mutant is a stochastic process that also hinges upon the adopted level of antiviral drug usage. Deterministic models are less suited to this situation since they cannot be used to predict extinction probabilities. However, it would also be worthwhile to explore whether using an ordinary differential equation (ODE) model instead would be fruitful in circumstances where stochastic effects are not important, since ODEs are easier to analyze and thus can generate more insight.

3.5 Conclusions

We conclude that, because influenza can evolve resistance without a fitness penalty, strategic multi-population interaction should be further studied. Furthermore, because of the potential for socially suboptimal outcomes in situations where fitness penalties do not arise and for parameter values permitting higher rates of mutant transmission at high rates of antiviral drug treatment, this work suggests the need for better inter-jurisdictional coordination in the event of future influenza pandemics.
Chapter 4

Stochasticity-induced persistence of an endangered population in a coupled socioecological model


Abstract

Stochasticiy is often associated with negative consequences for population dynamics since a population may die out due to random chance during periods when population size is very low (stochastic fade-out). Here we develop a socio-ecological model based on stochastic
differential equations that includes natural expansion and harvesting of a forest system, and
dynamics of conservation opinions, social norms and social learning in a human popula-
tion. Our objective was to identify mechanisms that influence long-term persistence of the
forest ecosystem in the presence of noise. We found that most of the model parameters
had a significant influence on the time-to-extinction of the forest ecosystem. Increasing the
social learning rate and the net benefits of conservation significantly increased the time to
extinction, for instance. Most interestingly, we found parameter regimes where increasing
the stochasticity in the system actually increased the time-to-extinction, instead of caus-
ing stochastic fade-out. Such “stochasticity-induced persistence” occurs when stochastic
dynamics in the social system generates benefits in the forest system. We conclude that
studying relatively simple socio-ecological models has the benefit of facilitating charac-
terization of dynamical states and thereby enabling us to formulate new hypothesis about
mechanisms that could be operating in socio-ecological systems.

Keywords: human-and-natural system, stochastic fade-out, endangered species, stochastic
model, socio-ecological system, extinction, human-environment system

4.1 Introduction

Human behavior and disease dynamics have a mutual relationship in the disease trans-
mission system. Such as, consciousness in a population regarding disease and its preven-
tive measures may come after the start of an epidemic. Similarly, in a socio-ecological
system, human activities affect the environmental system and *vice-versa*. Hence, a coupled behaviour-disease system in an example of coupled socio-ecological system. We study the dynamics of socio-ecological system in Chapter 4.

Socio-ecological interactions play a dominant role in the fate of many forest ecosystems and the endangered species that make them their habitat. The main causes of deforestation in tropical regions include agricultural expansion, migration and urbanization, road construction, mining and industry [2]. For seven years after 1990, approximately 4.4 to 7.2 million hectares of humid tropical forest were destroyed each year [94]. Southeast Asia, for instance, is deemed to be a biodiversity hotspot because it provides shelter for a large number of endemic species that are threatened or endangered due to the loss of 70% of initial habitat area [95]. Approximately 50% of mangrove fields have vanished in the last 35 years and such mangrove extinction has greatly affected the shelter or feeding sites of fish [96]. Land use changes have other effects besides reducing biodiversity such as causing nitrogen accumulation and rising carbon dioxide levels, and changes in epidemiological patterns and disease vector allocations over time [28, 97].

However, forests provide numerous ecosystem services not only just with respect to timber products but also with respect to water purification (forest ecosystems promote soil types that provide natural filtration and vegetation types that minimize soil erosion and sediment runoff), climate stabilization, biodiversity, medicine, esthetics, and traditional values [27, 98, 99, 100]. As a result, public opinion has often reacted to declining forests with a demand to conserve natural forest cover, resulting in a subsequent stabilization and/or
increase in forest cover and thus completing a coupled human-environment feedback loop between forest dynamics and opinion dynamics. Although such relationships are complicated by other factors such as science communication, agro-economics, and special interest groups [101], this basic dynamic has been observed in various populations over the past two centuries [102, 103, 104, 105, 106, 107]. As well, it continues in the modern era with growing efforts by countries to conserve their natural forests and biodiversity hotspots [108].

A number of mathematical models have been developed to study coupled socio-ecological dynamics (which we will take to be synonymous with human-environment dynamics). These models use deterministic differential equations to model dynamics of human decision-making and land use dynamics [48, 109] or other resource dynamics [46, 110]. Other coupled HES models are stochastic models such as Markov models, stochastic differential equations, or agent-based models, wherein randomness partly governs the time evolution of a state variable. Such models have focused on how social learning affects landowners decision about forest land use [38] and how early warning signals of regime shifts in coupled HESs can emerge in stochastic systems [49], among other questions [111].

Random perturbations (i.e. noise, stochasticity) can play a crucial role in the formation and framework of environments [112]. Stochastic fluctuations are commonly considered to play a potentially damaging role in species dynamics. The persistence of a species may depend on the randomness of variables and hence stochasticity may strongly influence the extinction time of the species, especially if number of rare species is low and species extinction...
tion is likely to happen. Hence, a stochastic model will often predict fade-out of a species due to chance events when species numbers are very low, while the equivalent deterministic model will incorrectly predict continued persistence. This effect of such ‘stochastic fade-out’, or ‘stochastic extinction’, has been explored in a number of systems, including plant systems [36, 53]. However, other research explores how noise can play a constructive role in the dynamical system on account of multi-species interactions [54]. Ecosystems, much like species, can be endangered and subject to the risk of collapse [113].

The topic of stochastic extinction and the conditions under which it happens has been relatively little studied in the context of coupled socio-ecological systems. Here we developed a stochastic differential equation model to study potential mechanisms governing how the time to extinction of a rare forest ecosystem depends on human opinion dynamics and natural forest dynamics as governed by social learning, harvesting rates, conservation value of forest, natural growth rate of the forest species, and injunctive social norms. We identify changes to system parameters that are conducive to more rapid stochastic extinction. We also uncover some surprises, including that increasing levels of stochasticity can actually promote forest species persistence under certain circumstances due to the coupled nature of the socio-ecological system. This contrasts with the expectation that increasing levels of stochasticity should tend to make species extinction more likely due to stochastic fade-out. The model and methods are described in the next section, followed by Results, and Discussion and Conclusions.
4.2 Material and Methods

We build on a previous deterministic model of human-environment dynamics in a forest-grassland ecosystem mosaic where recruitment of forests is driven by a nonlinear function of forest cover [48]. We simplify this model by assuming a constant recruitment rate instead, since our focus is not on forest-grassland mosaics in particular. We let \( x \) denote the proportion of the general population adopting a forest conservationist opinion, while the remaining proportion \( 1 - x \) are non-conservationists. The resulting model consists of two ordinary differential equations (ODEs) which are [49]:

\[
\frac{dx}{dt} = \kappa x (1 - x) [c - F + \delta(2x - 1)] \tag{4.1}
\]

\[
\frac{dF}{dt} = RF (1 - F) - h(1 - x)F \tag{4.2}
\]

where \( F \) is the proportion of forest cover (\( F = 1 \) representing the maximal natural range of the forest in a given region), \( R \) is the natural expansion rate of the forest, \( h \) is the maximal forest harvesting rate, \( \delta \) is strength of injunctive social norms, and \( c \) is the net benefit of conservationism. Our goal was to explore theoretical mechanisms that could apply in real populations, rather than to create a highly realistic model of a specific population. Hence, a simple model helps us to better understand the basic features of such systems more clearly than a complex model with many parameters does.

When forest is rare \( F \approx 0 \) and if social norms are neglected, the net benefit of conservationism supports an increase in the proportion of conservationists in the population. In
contrast, if $F$ is large, the net benefits of conservationism are outweighed by the abundance of forests, making them less of a conservation priority. Social norms act to move $x$ to 0 or 1 since they represent the homogenizing effects of peer pressure. Forest grows logistically in the model but can be harvested, and harvesting is maximal when population support for conservationism is lowest (when $x$ is small).

The stability analysis for the deterministic case was conducted in a previous paper [49]. According to [49], this model has six steady states at $(x^*, F^*) = (0, 0), (0, 1 - \frac{h}{R}), (1, 0), (1, 1), (\frac{\delta-c}{2\delta}, 0)$, and $(1 + R(\frac{1-c-\delta}{2R\delta-h}), 1 + h(\frac{1-c-\delta}{2R\delta-h}))$. Local stability analysis shows that the steady state $(0, 0)$ is locally asymptotically stable if $\frac{\delta}{c} > 1$ and $\frac{h}{R} > 1; (0, 1 - \frac{h}{R})$ is locally asymptotically stable if $\frac{h}{R} < 1 + \delta - c < 1$ or $\frac{h}{R} < 1 < 1 + \delta - c; (1, 1)$ is also locally asymptotically stable if $c + \delta > 1$; and the other three steady states are unstable.

**Table 4.1: Baseline parameter values and descriptions:** We use the following parameter values as our baseline values in model simulations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
<td>Proportion of population supporting conservationism</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>$F$</td>
<td>Proportion of forest cover</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Parameter</td>
<td>Description</td>
<td>Value/Range</td>
<td>Reference</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Social learning rate</td>
<td>0.17/ year</td>
<td>[114]</td>
</tr>
<tr>
<td>$R$</td>
<td>Natural expansion rate of forest ecosystem</td>
<td>0.06/year</td>
<td>[114]</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Strength of injunctive social norms</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>$h$</td>
<td>Maximal forest harvesting rate</td>
<td>0.18/year</td>
<td>[114]</td>
</tr>
<tr>
<td>$c$</td>
<td>Net benefit of conservationism</td>
<td>0.35</td>
<td>[114]</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Noise</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

Deterministic models capture the average dynamics and provide the same result each time the model is simulated. However, as noted above, to study stochastic extinction it is often advantageous to use a stochastic model [115]. Following other recent work on
stochastic modelling of human-environment interactions in forests [49], we turn these two deterministic differential equations into stochastic differential equations (SDEs). The SDE version of the model consists of the original deterministic terms plus a noise term:

\[ dx = \kappa x(1 - x)[c - F + \delta(2x - 1)] \ast dt + \sigma_x(x_t) \ast dW_1 \]  
\[ dF = [RF(1 - F) - h(1 - x)F] \ast dt + \sigma_F(F_t) \ast dW_2 \]  

(4.3)  
(4.4)

where \( \sigma_x(x_t) \) and \( \sigma_F(F_t) \) are functions that govern the magnitude of noise. Here, we adopt the functional forms \( \sigma_x(x_t) \equiv \sigma_x x_t \) and \( \sigma_F(F_t) \equiv \sigma_F F_t \), where \( \sigma_x \) and \( \sigma_F \) (the diffusion coefficients) are constant parameters. Moreover, we will assume \( \sigma_x = \sigma_F = \sigma = 0.06 \) as the baseline value of the noise coefficient for simplicity. \( W_1 \) and \( W_2 \) are Wiener processes which are vectors of stochastic process [115].

Our assumption for the noise term is intended to represent the impact of environmental stochasticity in both subsystems. For instance, many environmental sources of perturbations (e.g. droughts in a forest system, or mass media in a social system) impact the whole population, imposing a fixed per capita risk of disturbance on each individual. The size of such fluctuations at the population level should therefore scale as the per capita risk times the population size of the system at the time, hence our assumption that the coefficients of the Wiener process are \( \sigma_x \) and \( \sigma_F \).

We employed the SDE Toolbox Matlab package to solve the SDE model, which uses the Milstein method to solve stochastic differential equations, integrating an N-dimensional
system of stochastic differential equations with N-dimensional diagonal noise from time $t_0$ to $t_{\text{max}}$, where the interval $[t_0, t_{\text{max}}]$ is partitioned into $N$ equal sub-intervals [116].

All baseline parameters, values and descriptions are summarized in Table 4.1. When possible, parameter values were taken from the previous literature on modelling socio-ecological forest systems. We choose baseline parameter values to represent a scenario where forest cover $F$ and conservationist opinion $x$ persist in the interior of the phase space. Parameters such as $\kappa, R, \delta, h,$ and $c$ were varied to better uncover their individual impact on the model dynamics.

### 4.3 Results

We simulated the model to determine outcomes including: (1) time series of model variables and (2) time to extinction for the forest ecosystem. We studied how these outcomes depended on model parameters. Time to extinction was defined as the time between the starting time and the time at which the forest variable $F$ first goes close to zero in the SDE model. For example, we set a tolerance level as $10^{-6}$ and recorded time to extinction as the time at which the forest cover is reduced to this level. For sensitivity analyses, one parameter was varied while other parameters were held at their baseline values, unless otherwise specified. For initial conditions we choose $F(0) = 0.9$ and $x(0) = 0.1$ unless otherwise specified, corresponding to a population with initially abundant forest and therefore initially rare conservationist opinion. Also, some parameter variations were tested in
combination to see their combined effect on time to extinction.

### 4.3.1 Dynamical Regimes

Figure 4.1 depicts dynamics of $F$ and $x$ for typical stochastic realizations of the model in various dynamical regimes (parameter sets). Figure 4.1a shows how the forest recovers after an initial collapse, at the baseline parameter values. Forest cover starts high but declines rapidly due to lack of support for conservationism in the population. However, the eventual collapse of the forest stimulates a surge of conservationism. This in turn eventually results in the recovery of the forest ecosystem, although it takes centuries to recover. (Assisted recovery, in contrast to the natural recovery we assume, might happen faster. Also, the time of recovery varies across stochastic realizations.) In the longer term, forest cover and conservationism persist in the interior of the phase space (Figure 4.1a).

The state of zero forest cover and no conservationism, $(0, 0)$, is stable if conservationism is initially sufficiently abundant, if social norms prevail over net conservation benefits of forest and if the harvesting rate dominates the natural succession rate, as illustrated in Figure 4.1b. In contrast, if the harvesting rate is dominated by the natural expansion rate, then forest can grow and persist even in the absence of conservationism, hence the state $(0, 1 - \frac{h}{R})$ corresponding to non-zero forest cover and no conservationism can be stable (Figure 4.1c). The state of full conservationism and full forest cover, $(1, 1)$, is stable when conservationism is initially sufficiently abundant and when $c + \delta > 1$, such that the sum of net benefits of conservationism and strength of social norms are sufficiently high; in this
Figure 4.1: Time series plots of $F$ (red) and $x$ (black) (a) at baseline parameter values (Table 4.1) showing solutions that remain in the interior of phase space, (b) for convergence to $(0, 0)$, (c) for convergence to $(0, 1 - \frac{h}{R})$, (d) for convergence to $(1, 1)$, (e) at baseline values but with $\sigma = 0.07$, and (f) at baseline values but with $\sigma = 0.001$. Other parameter values were $\delta = 0.6$ in subpanel 4.1b; $h = 0.1$/year and $R = 0.2$/year in subpanel 4.1c; $c = 0.6$ and $\delta = 0.8$ in subpanel 4.1d; all other parameter values were set to baseline values (Table 4.1).

regime, both forest cover and conservationism linger near $(1, 1)$ (Figure 4.1d).

At other parameter values we observe how forest cover and conservationism surge in large and long-lasting waves, neither approaching an equilibrium nor going extinct (Figure 4.1e). Forest cover surges lag conservationism surges. At the beginning of this time series, the forest ecosystem comes close to extinction when $F$ drops close to zero at $t \approx 100$, but a surge in conservationism prevents this from happening. This time series corresponds to
a choice of $\sigma = 0.07$ for the noise parameter. When we perform the same simulation, but with $\sigma = 0.001$ (Figure 4.1f), we observe very different dynamics. Both forest cover and conservationism converge to zero and go extinct, despite the fact that noise is lower in this case than it was in Figure 4.1e. We refer to this effect as stochasticity-induced persistence, and we will develop it more in some of the following subsections.

### 4.3.2 Predicted dynamics under changes in single parameters

In this subsection we explore how the time to extinction depends on changes in model parameters (univariate sensitivity analysis). The time to extinction was defined as the time between the start of the simulation and the time at which forest cover goes to zero. In all simulations we assumed the initial conditions $x = 0.1$ and $F = 0.9$. This represents a typical starting situation for a society in which forests are initially abundant and therefore conservationism is not yet a priority. We changed one parameter at a time while the other parameters were held constant at the baseline parameter values (Table 4.1). Simulations were run for a total simulated time of 1000 years. If the forest was not extinct at the end of 1000 years, the time to extinction was recorded as 1000 years, although in reality the forest cover would typically exist beyond this simulated time horizon if conditions continued to be favourable.

We observe that the time to extinction increases as $\kappa$ (the rate of social learning; Figure 4.2a). This makes biological sense because increasing the social learning rate will lead to a more rapid shift to conservationism in the human population, when declining forest cover
Figure 4.2: Time to extinction versus (a) social learning rate $\kappa$, (b) natural expansion rate of forest ecosystem $R$, (c) strength of injunctive social norms $\delta$, (d) maximal forest harvesting rate $h$, (e) net benefit of conservationism $c$, and (f) noise ($\sigma$). Circles denote mean time to extinction over 10,000 stochastic simulations, and error bars denote two standard deviations over the 10,000 stochastic realizations. All parameters were held at baseline values (Table 4.1) except for those being varied in the horizontal axis.

creates favourable conditions to stimulate conservationism. Similarly, we observe that time to extinction also increases with increasing $R$, the forest expansion rate (Figure 4.2b) and $c$, the net benefits of conservationism (Figure 4.2e). If the forests can expand more quickly, then they are less likely to go extinct. Also, if conservationism has higher net benefits over costs, it will also take longer for extinction to occur.

In contrast, we observe a decrease in the time to extinction as the maximal human har-
vesting rate $h$ increases (Figure 4.2d). The decrease is particularly rapid for lower harvesting rates, but plateaus for higher harvesting rates. This occurs because at higher harvesting rates, conservationism is stimulated and thus slows—but does not prevent—the extinction of the forest at these parameter values. There is also a decrease in the time to extinction for increasing strength of social norms, $\delta$ (Figure 4.2c). Because the initial conditions place conservationism at low levels, $x(0) = 0.1$, strong social norms will act to keep the population at low values of $x$, which accelerates forest extinction. We emphasize, however, that for higher starting values of $x$, social norms will act in the opposite direction, to maintain $x$ at high values regardless of forest cover dynamics.

The dependence of time to extinction on the noise parameter $\sigma$, contains surprises, however. As the level of noise increases, the theory of stochastic fadeout suggests that we should make extinction of forest cover (or even conservationism) more likely during the initial decline in forest cover, as seen in Figure 4.1a at the baseline parameter values). Instead, what we observe as noise is increased is that the time to extinction initially increases and becomes highly variable (Figure 4.1f). The time to extinction peaks at $\sigma = 0.05$, and thereafter begins to decline. During the decline phase, noise is accelerating collapse through stochastic fade-out. But when noise is still small, the addition of further noise acts to increase the time to extinction because of stochasticity-induced persistence.

The subpanels of Figure 4.2 show the average and standard deviation of many stochastic realizations. By plotting histograms that show the frequency distribution of time to extinction across different realizations, we can gain a better understanding of this effect (Figure
Figure 4.3: Frequency distribution histogram of time to extinction recorded across 500 simulations for (a) $\sigma = 0.01$, (b) $\sigma = 0.03$, (c) $\sigma = 0.05$, (d) $\sigma = 0.07$, (e) $\sigma = 0.09$, and (f) $\sigma = 0.11$. All other parameter values were set to baseline values (Table 1).

4.3. We observe that when noise is very low $\sigma = 0.01, 0.03$ or very high $\sigma = 0.11$, time to extinction is approximated by a normal distribution (Figure 4.3a, b, f). However, for intermediate noise levels ($\sigma = 0.05, 0.07, 0.09$) the distribution appears bimodal (Figure 4.3c, d, e). In particular, the histograms show a large peak at low time to extinction, corresponding to rapid stochastic fade-out, as well as infrequent outliers with very long time to extinction ($> 500$ years) that drive up the average time to extinction. In this regime, most simulations fall in a region of low time to extinction (as suggested by the stochastic fade-out hypothesis), but a few simulations fall in a region of very high time to extinction, thereby raising the average time to extinction and producing the results of Figure 4.2f. In these outliers, we observe dynamics similar to Figure 4.1e, where noise occasionally acts to conserve forest
by a chance increase in conservationism during the decline phase, which is timed just right in order to prevent forest extinction during the initial nadir in forest cover.

Figure 4.4: Time to extinction verses (a) maximal forest harvesting rate \( h \), (b) strength of injunctive social norms \( \delta \), (c) net benefit of conservationism \( c \), and (d) \( \sigma \) for three different values of \( \kappa \) if \( x = 0.1 \).

In this section we vary two parameters at a time to understand the effects of their combined variation. For instance, we re-generated Figure 4.2 for \( h, \delta, c \) and \( \sigma \) at several different values of \( \kappa \): 0.05/yr, 0.15/yr and 0.25/yr (Figure 4.4). We found that increasing \( \kappa \) above the baseline value continues to significantly increase the time to extinction across variation in \( h, \delta, c \) and \( \sigma \), with the important exception of when \( h \) is larger and no impact in changing \( \kappa \) is seen (Figure 4.4a). This suggests that when the maximal harvesting rate \( h \) is significant (\( h \gtrsim 0.1 \)), increasing the social learning rate \( \kappa \) will not contribute significantly to preserving forests. Also, stochasticity-assisted persistence observed in Figure 4.2 also
Figure 4.5: Time to extinction verses (a) maximal forest harvesting rate $h$, (b) strength of injunctive social norms $\delta$, (c) net benefit of conservationism $c$, and (d) $\sigma$ for three different values of $\kappa$ if $x = 0.9$. 

occurs at other values of $\kappa$ (Figure 4.4d).

Re-generating Figure 4.2 again for $h$, $\delta$, $c$ and $\sigma$ at several different values of $\kappa$: 0.05/yr, 0.15/yr and 0.25/yr, but this time also increasing the initial proportion of conservationists from $x(0) = 0.1$ to $x(0) = 0.9$ also has some significant effects (Figure 4.5). For instance, it dramatically increases the time to extinction, since forest cover does not experience the initial nadir that has a high likelihood of destroying it (compared Figure 4.5 to Figure 4.4 and note the difference in the vertical axis scale). For instance, the time to extinction as a function of $h$ when $\kappa = 0.25$ (Figure 4.4), is more than 400 years but it is nearly 700 years if $x = 0.9$ (Figure 4.5). Increasing the rate of social learning $\kappa$ has the same effects as observed when $x(0) = 0.1$, including lack of any impact for $h \gtrsim 0.2$, but this time also a very significant impact when $\delta$ is small. Surprisingly, when $x(0) = 0.9$, the time to extinction declines monotonically with increasing levels of noise, since the forest is not
Figure 4.6: Mean time to extinction across 10,000 stochastic realizations as a function of (a, b) maximal harvesting rate $h$ and social learning rate $\kappa$, and (c,d) noise level $\sigma$ and social norm strength $\delta$. Red corresponds to longer time to extinction and blue corresponds to shorter time to extinction. Subpanels (b) and (d) are the 2D views of subpanels (a) and (c) respectively. Other parameter values were set to baseline values (Table 1).

threatened by the initial nadir in forest cover and therefore stochasticity-assisted persistence does not operate (Figure 4.5).

We also generated a parameter plane showing how the time to extinction (height/colour
of plot) depends upon two-way variation in the parameters for maximal harvesting rate $h$ and social learning rate $\kappa$ (Figure 4.6a,b), as well as in social norms $\delta$ and noise $\sigma$ (Figure 4.6c,d). In these plots, a higher peak (or equivalently, red color) corresponds to a longer time to extinction. We found that the time to extinction is higher with smaller $h$ and bigger $\kappa$ (Figure 4.6a, b). When $h > 0.15$/year, the effect of changing $h$ is much stronger than the effect of $\kappa$, by an order of magnitude. But when $h = 0.15$/year (which is more biologically realistic), increasing $\kappa$ will still have beneficial effects. In contrast, changes in both $\delta$ and $\sigma$ have impacts on the time to extinction, but the time to extinction is very rapid unless both $\delta < 0.2$ and $\sigma < 0.1$ (Figure 4.6c, d). The effects of stochasticity-induced persistence are visible in the dark red region for $\sigma < 0.05$ and $\delta < 0.15$, suggesting that stochasticity-induced persistence requires that social norms not be too strong. This makes biological sense because stochasticity-induced persistence requires that the population respond to changing forest cover more strongly than to social norms that simply force the population to the majority opinion.

### 4.4 Discussion and Conclusions

Here we analyzed a stochastic socio-ecological model in order to show the complex dynamics of socio-ecological systems in the presence of random perturbations, and how time to extinction of a forest ecosystem depends on socio-ecological parameters such as the social learning rate ($\kappa$), natural expansion rate of forest ($R$), human harvesting rate of forest
(h), relative ratio of net benefit of conservationism (c), and strength of injunctive social norms (δ). We found that the model exhibits a wide range of possible dynamics, including low forest cover and low conservationism, high forest cover and high conservationism, high forest cover and low conservationism, and intermediate levels of forest cover and conservationism with nontrivial dynamics in the interior of phase space.

We found that most of the model parameters had a significant influence on the time to extinction, including parameters under some measure of human control such as the social learning rate κ, which could be increased through social media utilization, and the net benefits of conservationism c, which could be increased through public awareness programs, tax breaks or similar incentives. We also found a surprising dependence on the level of noise, σ. The influence of noise on dynamical systems has been analyzed by a number of stochastic models in recent years [117, 118]. Noise is often associated with a destructive effect, as an operator of chaotic fluctuations around the stable states and the cause of stochastic fade-out near an elimination threshold. However, noise is also known for its constructive character and may also enhance biodiversity [55]. We have also found that increasing the noise parameter can cause stochastic fadeout, but only when the noise levels are large. When they are smaller, increasing the noise can assist in the persistence of forest through an effect we called stochasticity-induced persistence. Noise in this case provides an unanticipated mechanism that sustains a species instead destroying it through stochastic fade-out. The effect is sensitive to the initial prevalence of conservationism and the strength of social norms.
There are several limitations of our model, and we leave them as our future work. For instance, in this model we only considered the time to extinction (forest cover reaches near zero) for the first time. Thus, we ignored the possibility of forest re-introduction, such as might happen under assisted recovery or even natural recovery, if a sufficient number of the species could be reassembled in a regeneration program (although we note that assisted regeneration programs often miss the mark and regeneration to a native state can be hard to accomplish for various reasons [119]). We assumed the same noise coefficient $\sigma$ in both the human and natural systems, but differing levels of noise in the two systems would change the strength of stochasticity-induced persistence. Developing individual-based metapopulation models may also enhance our understanding and predictions of population responses to conservation value of forest and preservation of biological diversity. Stochastic effects in socio-ecological systems is currently under-researched and has promise to yield both interesting new dynamical mechanisms as well as generating insights of practical importance.

In chapter 4, we only considered the time to extinction (forest cover reaches near zero) for the first time. Our future work aim to consider possibility of forest re-introduction, such as might happen under assisted recovery or even natural recovery, if a sufficient number of the species could be reassembled in a regeneration program.
Chapter 5

Discussion

5.1 Conclusions

The objective of this thesis was to compare and contrast model dynamics in ecological versus epidemiological CHANS in order to identify whether socially suboptimal outcomes were possible in both systems, when they might occur, and how the outcomes are influenced by the presence or absence of stochasticity. Chapters 2 and 3 concerned a natural system corresponding to a circulating infectious disease with dynamics either implicitly represented (Chapter 2) or explicitly represented by a stochastic model (Chapter 3). Human behaviour and its coupling to the natural system was represented using game theory. Chapter 4 concerned a natural system corresponding to a growing ecosystem explicitly represented by a stochastic model, and human behaviour was represented using an evolutionary game theoretical model. The results show that socially suboptimal outcomes are
common in both types of systems, despite the fact that socially optimal end goals are often different in ecological versus epidemiological CHANS.

From Chapters 2 and 3 we learned that socially suboptimal outcomes could occur where both populations treat at a high rate than they should and thereby generate harmful drug-resistant mutants, due to human behaviour and human strategic interactions. Likewise, human behaviour and strategic interactions also cause forest extinction in the model of Chapter 4 across a broad range of parameter values, despite the benefits of forest biodiversity and ecosystem services for human populations. In chapters 2 and 3, if both populations cooperated by limiting their treatment rates, they could achieve the optimal Nash equilibrium. However, resistant mutants may proliferate and the socially suboptimal Nash equilibrium may prevail if cooperation cannot be sustained (which may occur due to a variety of mechanisms such as myopic selfishness, or ignorance). Similarly, in chapter 4, socially optimal situations may fail to develop if individuals have the wrong priorities or do not respond quickly enough to changing forest cover. The result of this failure is forest cover collapse.

Model parameters and the interpretation of changing the parameter values across the two types of study systems can be compared. For example, increasing the value of $\alpha$ in chapter 3 means that the mutant is perceived to be less undesirable, and the population tolerates it. Therefore, increasing $\alpha$ causes the socially suboptimal outcome $(H, H)$ to become a Nash equilibrium for a wide range of parameter values. In the same way, reducing the conservation value of the forest ecosystem, $c$, means that the inherent value of having
a healthy forest cover is perceived as less to the population and therefore is analogous to increasing $\alpha$. In this case, it was observed how decreasing $c$ can lead to reduction or even elimination of forest cover, which is the socially suboptimal outcome in this scenario. Therefore, increasing $\alpha$ and decreasing $c$ have similar effects across these two different CHANS.

Stochasticity was found to play a major role in both ecological CHANS and epidemiological CHANS. In the epidemiological CHANS of chapters 2 and 3, stochasticity always had the undesirable effect of generating drug-resistant mutants through rare mutation events. These rare, stochastic events were modelled implicitly in chapter 2, and explicitly in chapter 3, using a stochastic transmission model. In the ecological CHANS of chapter 4, stochasticity often had a destruction impact as well. However, the destructive impact occurred not because stochastic effects were creating a new undesirable species as in chapters 2 and 3, but rather because stochastic effects were causing fade-out of the endangered ecosystem.

The models also illustrate how models of coupled human-and-natural dynamics can predict effects that do not occur in human systems or natural systems in isolation from one another. For instance, the effect of stochasticity-induced persistence—where stochastic effects can in some parameter regimes result in persistence of a population—occurred on account of the coupled nature of the system and would not be observed in a corresponding model with fixed human behaviour, where the ecosystem would simply be driven extinct by ever-rising harvesting intensities. Similarly, without a fear of generating antiviral
drug-resistance and/or in the lack of strategic interactions, jurisdictions will always simply
maximize their antiviral drug use, eliminating the possibility of a coordination game in the
epidemiological CHANS we studied.

5.2 Future work

Many avenues are available to expand the approaches of this thesis in future work, and
can address some of the limitations of the models in chapters 2-4.

In Chapter 2, we assumed that $P(H, H) = P(H, L)$. Our future studies aim to explore
what happens if $P(H, H) > P(H, L)$ or $P(H, H) < P(H, L)$. Our model predictions
may change if $P(H, H) > P(H, L)$ and this could happen if the use of the high antivi-
ral treatment level at other jurisdiction significantly decreases the number of cases that are
imported from the other jurisdiction to the focal jurisdiction, and increases the focal juris-
diction’s payoff (relative to when the other jurisdiction uses the low treatment level). Also,$P(H, H) < P(H, L)$ could occur if the use of the high treatment level in the other jurisdic-
tion significantly increases the risk of a drug resistant strain arising and being imported
into focal jurisdiction, and the spread of such a strain is very costly to focal jurisdiction.

Along other lines, future work could include strategic interactions between more than 2
jurisdictions, since in a real-world influenza pandemic, any given jurisdiction is likely to be
connected through travel to much more than just one other jurisdiction. However, higher-
dimensional systems such as multi-players games are inherently more difficult to analyze
because of the increased dimensionality of the system. For instance, a most common problem will likely to face is the different travel rate of an individual between the populations because the travel rate depends on the distance and spatial configuration of the landscape and hence affects the homogeneous disease transmission dynamics between the populations.

In Chapter 3, we only considered the first wave of a pandemic. Multiple waves of transmission during a pandemic may represent a major public health challenge and could also generate different dynamics, since antiviral drug treatment then resembles more strongly an iterated game where players alternate playing their strategies in multiple stages over the course of some time period. Other avenues for further research includes incorporation of the social processes that determine the jurisdictions’ strategy decisions. For instance, the impact of opinion dynamics in the susceptible population on the decision-making of the public health authorities could be modelled. Finally, additional population heterogeneity (e.g., demography, geography) could be included and would make sense in a model of multiple pandemic waves, where each wave spreads through one sub-population such as the elderly or young children. The possible challenges we might face includes phenomena like delayed susceptibility, where some individuals who were not susceptible to the virus during the first wave are susceptible to the mutant arising in the second wave. The model of chapter 3 could also be extended by a multi-population model.

In chapter 4, we only considered the time to extinction (the time when forest cover reaches zero). Future work aim could consider possibility of forest re-introduction, such
as might happen under assisted recovery or even natural recovery, if a sufficient number
of the species could be reassembled in a regeneration program. The same SDE model
with an extended program which captures various extinction dynamics could be used. Also
in chapter 4, we assumed the same noise coefficient, $\sigma$, for both the human and natural
systems. Our prospective goal is to investigate differing levels of noise in the two systems.
We expect this would change the strength of stochasticity-induced persistence. Analyzing
this model would require a more exhaustive exploration of parameter space, but could
be done relatively straightforwardly. Chapter 4 could also be extended by distinguishing
between opinion spread in the general population, and opinion spread among decision-
makers and land-owners. Expanding the model in this way carries the same challenges of
increasing dimensionality and therefore greater difficulty in analyzing the model. Another
promising avenue of future research is closer integration of socio-ecological forest-opinion
models with longitudinal data on forest cover and human opinions as measured through
surveys and online social media.

In summary, the research described in this thesis demonstrates the value of modelling
the dynamics of ecological and epidemiological CHANS. Future research will be likely
to address many of the limitations of the existing models and generate new insights, and
therefore further research in developing and contrasting mathematical models of ecological
and epidemiological CHANS should be undertaken.
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Appendix A

Appendix for chapter 2

A.1 Condition for coordination game

The conditions for a coordination game follow immediately from the structure of the payoff matrix (see first paragraph of results, and Ref.[26])

\[ P(L, L) > P(H) > P(L, H) \]

Then we have,

\[ M - \alpha \kappa > M - (1 - \alpha) \beta - \alpha \delta > M - (1 - \alpha) \gamma - \alpha \eta \]

\[ \alpha \kappa < (1 - \alpha) \beta + \alpha \delta < (1 - \alpha) \gamma + \alpha \eta \]

\[ \kappa < \frac{(1 - \alpha) \beta}{\alpha} + \delta < \frac{(1 - \alpha) \gamma}{\alpha} + \eta \]
A.2 Condition for a single Nash Equilibria at \((L, L)\)

We will have single Nash Equilibria at \((L, L)\) if,

\[
P(L, L) > P(L, H) > P(H)
\]

Then we have,

\[
M - \alpha \kappa > M - (1 - \alpha) \gamma - \alpha \eta > M - (1 - \alpha) \beta - \alpha \delta \\
\kappa < \frac{(1 - \alpha) \gamma}{\alpha} + \eta < \frac{(1 - \alpha) \beta}{\alpha} + \delta
\]

A.3 Condition for a single Nash Equilibria at \((H, H)\)

We will have single Nash Equilibria at \((H, H)\) if,

\[
P(H) > P(L, L) > P(L, H)
\]

Then we have,

\[
M - (1 - \alpha) \beta - \alpha \delta > M - \alpha \kappa > M - (1 - \alpha) \gamma - \alpha \eta \\
\frac{\beta}{\beta + \kappa - \delta} < \alpha < \frac{\gamma}{\gamma + \kappa - \eta}
\]
A.4 Condition for Nash Equilibria at \((L, H), (H, L)\)

We will have Nash Equilibria at \((L, H), (H, L)\) if,

\[
P(L, H) > P(H) > P(L, L)
\]

Then we have,

\[
M - (1 - \alpha)\gamma - \alpha\eta > M - (1 - \alpha)\beta - \alpha\delta > M - \alpha\kappa
\]

\[
\alpha \left( \frac{\eta - \delta}{1 - \alpha} \right) + \gamma < \beta < \alpha \left( \frac{\kappa - \delta}{1 - \alpha} \right)
\]

A.5 Mixed Nash Equilibria

We derive the mixed Nash equilibria using Bishop-Cannings theorem [76]. Now if \(p\) is the probability of opponent playing \(H\) then the expected payoff is

\[
E(H) = p(M - (1 - \alpha)\beta - \alpha\delta) + (1 - p)(M - (1 - \alpha)\beta - \alpha\delta)
\]

\[
= M - (1 - \alpha)\beta - \alpha\delta
\]

\[
E(L) = p(M - (1 - \alpha)\gamma - \alpha\eta) + (1 - p)(M - \alpha\kappa)
\]

\[
E(H) = E(L)
\]

\[
M - (1 - \alpha)\beta - \alpha\delta = p(M - (1 - \alpha)\gamma - \alpha\eta) + (1 - p)(M - \alpha\kappa)
\]

\[
p = \frac{\alpha(\delta - \kappa - \beta) + \beta}{\alpha(\eta - \kappa - \gamma) + \gamma}
\]
Hence, the mixed Nash Equilibrium:

$$\left( \frac{\alpha(\delta - \kappa - \beta) + \beta}{\alpha(\eta - \kappa - \gamma) + \gamma}, \frac{\alpha(\eta + \beta - \gamma - \delta) + \gamma - \beta}{\alpha(\eta - \kappa - \gamma) + \gamma} \right)$$ (A.1)
Appendix B

Supplementary figure for chapter 3

Figure S1: Final Size with Standard Deviation. The solid line represents for the regular strain and the dashed line is for the mutant.
Appendix C

Codes for simulation results

We provide prototypes of codes that were developed to obtain simulation results presented in this thesis.

C.1 Codes for chapter 2

C.1.1 Plotting $\alpha - \gamma$ parameter plane Figure 2.2

Other graphs in this figure were produced varying parameter values of the same code.

%Beta=.4
alpha=[0,.1,.2,.3,.4,.5];
gamma=[.4,.384,.365,.34,.306,.26];
plot(alpha,gamma,'black', 'linewidth', 3)
axis square
C.1.2 Plotting $\beta - \gamma$ parameter plane Figure 2.3

Other graphs in this figure were produced varying parameter values of the same code.

%alpha=0.01;
beta=[0,.04,.08,.1,.14,.18,.22,.24,.28,.3];
gamma=beta-0.0014;
figure;
subplot(2,3,1)
plot(beta,gamma,'black', 'linewidth', 2)
axis square
ylim([0 .3])
xlim([0 .3])
title('(a)', 'FontSize',15)
xlabel('\beta', 'FontSize',15)
ylabel(‘\gamma’, ’FontSize’,15, ’rotation’, 0)
set(gca,’FontSize’,15)
text(.06,.25,’\fontsize{15}(L, L),(H, H)’)
text(.13, .05,’\fontsize{15}(L, L)’)
hold on
line([.001,.001],ylim, ’linewidth’, 2, ’Color’,’k’)
hold on

C.2 Code for chapter 3

C.2.1 Plotting epidemic curve in Figure 3.2

clear all
clc
tic

varname={'S_1','I_1','I_{1,m}','I^t_1','I^t{1,m}','R_1','R_{1,m}',
'S_2', 'I_2','Im_2','It_2','Itm_2','R_2','R_{2,m}'};

% parameters
rhol=.000001; rho2=.000001; % mutation probabilites
rhop1=.000001; rhop2=.000001; % mutation probabilites
mu1=.2; mu2=.2;

r1=.25; r2=.25;
rt1=.5; rt2=.5;
rm1=.25; rm2=.25;
rtm1=1.5*.25; rtm2=1.5*.25;
omega1=.04; omega2=.04;
omegap1=0; omegap2=0;
p01=.335; p02=.335;
pml=.335; pm2=.335;
phi=.85;

m12=.01; m21=.01;

%S Initial values
S1=99995; S2=100000;
I1=5; I2=0;
Im1=0; Im2=0;
It1=0; It2=0;
Itm1=0; Itm2=0;
R1=0; R2=0;
Rm1=0; Rm2=0;

X1=zeros(7,7);
X1(2, 3) = rho1;
X1(2, 4) = mu1;
X1(2, 6) = r1;
X1(3, 2) = rhop1;
X1(3, 5) = mu1;
X1(3, 7) = rm1;
X1(4, 5) = omegal;
X1(4, 6) = rt1;
X1(5, 4) = omegap1;
X1(5, 7) = rtm1;
for i = 2:7
    X1(i, i) = 1 - sum(X1(i, :));
end

X2 = zeros(7, 7);
X2(2, 3) = rho2;
X2(2, 4) = mu2;
X2(2, 6) = r2;
X2(3, 2) = rhop2;
X2(3, 5) = mu2;
X2(3, 7) = rm2;
X2(4,5)=omega2;
X2(4,6)=rt2;
X2(5,4)=omegap2;
X2(5,7)=rtm2;
for i=2:7
    X2(i,i)=1-sum(X2(i,:));
end
% finish X2
T=400; % number of days
n=1000; % number of simulation runs
SIM=zeros(14,T,n); % number of individuals in a matrix 12xT stored for each one of the n simulation runs
for sim=1:n
    v=zeros(14,T); % number of individuals for every day
    v(:,1)=[S1;I1;Im1;It1;Itm1;R1;Rm1;S2;I2;Im2;It2;Itm2;R2;Rm2];
    for t=2:T;
        N1=sum(v(1:7,t-1));
        X1(1,2)=1-(1-p01*v(2,t-1)/N1)*(1-p01*phi*v(4,t-1)/N1);
        X1(1,3)=1-(1-pm1*v(3,t-1)/N1)*(1-pm1*phi*v(5,t-1)/N1);
        X1(1,1)=1-(X1(1,2)+X1(1,3));
    end
N2 = sum(v(8:14,t-1));

X2(1, 2) = 1 - (1 - p02 * v(9, t-1) / N2) * (1 - p02 * phi * v(11, t-1) / N2);
X2(1, 3) = 1 - (1 - pm2 * v(10, t-1) / N2) * (1 - pm2 * phi * v(12, t-1) / N2);
X2(1, 1) = 1 - (X2(1, 2) + X2(1, 3));

X = [(1 - m21) * X1, m21 * X2; m12 * X1, (1 - m12) * X2];

temp = mnrnd(v(:, t-1), X);
v(:, t) = sum(temp, 1)';

end

SIM(:, :, sim) = v;
end
MSIM = mean(SIM, 3);

figure(1)
plot(100 * (MSIM(2, :) + MSIM(4, :)) / N1, 'DisplayName', 'Infected',
     'color', 'b')
figure(gcf)
hold on
plot(100*(MSIM(3,:)+MSIM(5,:))/N1,'DisplayName','Infected mutated',
    'color','r')
figure(gcf)
axis square
xlabel('Day')
ylabel('Percentage')
hold off
legend('show');
hold off
figure(2)
plot(100*(MSIM(9,:)+MSIM(11,:))/N2,'DisplayName','Infected',
    'color','b')
figure(gcf)
hold on
plot(100*(MSIM(10,:)+MSIM(12,:))/N2,'DisplayName','Infected mutated',
    'color','r')
figure(gcf)
axis square
xlabel('Day')
C.2.2 Plotting time series in Figure 3.3 and Figure 3.4

Function m-file:

function [Y, avenum_mutations, increg, incmut] = onecountsim(n, T, p01, pm1, mu1, rho1, rhop1, omegai, omegap1)

% parameters
r1 = .25;
rm1 = .25;
rt1 = .5;
rtm1 = 1.5 * .25;
phi = .85;

% Initial values
S1 = 99995;
I1 = 5;
Im1 = 0;
It1 = 0;
Itm1=0;
R1=0;
Rm1=0;
% begin X1
X1=zeros(7,7);
X1(2,3)=rho1;
X1(2,4)=mu1;
X1(2,6)=r1;
X1(3,2)=rhop1;
X1(3,5)=mu1;
X1(3,7)=rm1;
X1(4,5)=omega1;
X1(4,6)=rt1;
X1(5,4)=omegap1;
X1(5,7)=rtn1;
for i=2:7
    X1(i,i)=1-sum(X1(i,:));
end
% finish X1

%T=400; % number of days
%n=1000; % number of simulation runs
SIM=zeros(7,T,n);
vnum_mutations=zeros(n,1);
for sim=1:n
    v=zeros(7,T); % number of individuals for every day
    v(:,1)=[S1;I1;Im1;It1;Itm1;R1;Rm1];
    num_mutations=0;
    for t=2:T;
        N1=sum(v(:,t-1));
        X1(1,2)=1-(1-p0l*v(2,t-1)/N1)*(1-p0l*phi*v(4,t-1)/N1);
        X1(1,3)=1-(1-pml*v(3,t-1)/N1)*(1-pml*phi*v(5,t-1)/N1);
        X1(1,1)=1-(X1(1,2)+X1(1,3));
        temp=mnrnd(v(:,t-1),X1);
        num_mutations = num_mutations + temp(2,3) + temp(4,5);
        v(:,t)=sum(temp,1)';
    end
    vnum_mutations(sim)=num_mutations;
    SIM(:,:,sim)=v;
end
Y=mean(SIM,3);
avenum_mutations=mean(vnum_mutations);

**Script m-file:**

w=[0 .001 .004 .008 .01 .02 .04 .06];
mu1=[0 .1 .2 .3];
for i=1:length(w)
    for j=1:length(mu1)
        [Y,num_mutations]=onecountsim(1000,400,.335,.335,mu1(j),0,0,w(i),0);
        Y=Y*100/100000;
        h=plot((Y(2,:)+Y(4,:)/100000)*100,'black','linewidth',3)
        axis square
        hold on
        plot((Y(3,:)+Y(5,:)/100000)*100,'--black','linewidth',3)
        axis square
        xlabel('Days', 'FontSize',48)
        ylabel('Percentage', 'FontSize',48)
        set(gca,'FontSize',48)
        hold off
file1=sprintf('fig_w%d_mu%d.fig',i,j);
file2=sprintf('fig_w%d_mu%d.pdf',i,j);
saveas(h,file1);
saveas(h,file2);
end
end

Script m-file for final size and final size with standard deviation:

mu=linspace(0,.25,30);
FS=zeros(length(mu),2);
sdFS=zeros(length(mu),2);
for i=1:length(mu)
    [Y,sdY,avenum_mutations,increg,incmut]=onecountsimsim(1000,350,.335,.335,mu(i),.000001,.000001,.04,0);
    sdY=sdY*100/sum(Y(:,end));
    Y=Y*100/sum(Y(:,end));
    FS(i,:)=[Y(6,end) Y(7,end)];
    sdFS(i,:)=[sdY(6,end) sdY(7,end)];
errorbar(mu,FS(:,1),-1*sdFS(:,1),sdFS(:,1), 'color','b');
axis square
hold on
errorbar(mu,FS(:,2),-1*sdFS(:,2),sdFS(:,2), 'color','r');
xlabel('mu');
ylabel('Final size');

C.2.3 Codes for best response curve

File: main.f95

! File: main.f95
!!The main function, where you declare global variables, and other functions
program main
    implicit none
    interface

!Parameters to be used. Global variables
function kamal()!

Kamal function declaration

real, parameter :: beta = 0.335, beta2 = 0.335,
phi = 0.8, tau = 0.01
real, parameter :: rho = 0.000001, rhop = 0.000001
real, parameter :: w = 0.04, wp = 0.0, r = 0.25,
rt = 0.5, rm = 0.25, rtm = 0.375
real :: eta1, eta2
integer :: S1, S2, I1, I2, It1, It2, Im1, Im2, Itm1,
Itm2, R1, R2,
Rm1, Rm2, Rt1, Rt2, Rtm1, Rtm2, N1, N2, n, TotalR1,
TotalR2, itemp
real :: trS1(2), trS2(2), trIt1(3), trIt2(3),
trItm1(3), trItm2(3)
real :: trI1(4), trI2(4), trIm1(4), trIm2(4)
in integer, allocatable :: seed(:)
in integer size, TotalRm1, TotalRm2
integer :: shS1(2), shS2(2), shIt1(3), shIt2(3),
shItm1(3)
in integer :: shItm2(3), shI1(4), shI2(4), shIm1(4),
shIm2(4), kamal(4)
character(LEN=100) :: option1, option2, arg
end function kamal

end interface

integer, dimension(4) :: results

results = kamal() !Run Kamal function

end program main

function kamal()

!Declare other functions used by Kamal function

implicit none

interface

function FtrS(aI, aIt, aIm, aItm, aN, abeta, abeta2, aphi)
real, dimension(2) :: FtrS, A
real :: aI, aIt, aIm, aItm, aN, abeta, abeta2, aphi
end function FtrS

function mnrnd2(mnX, mnSize, mnA)
integer :: mnX, mnSize, i, j, clock, n
real :: mnA(mnSize), temp
real, dimension(mnSize) :: cumProb
integer, dimension(mnSize) :: mnrnd2, mnOut
integer, dimension(:), allocatable :: seed

end function mnrnd2

end interface

!Define variables and parameters
real, parameter :: beta = 0.335, beta2 = 0.335, phi = 0.8,
tau = 0.01
real, parameter :: rho = 0.000001, rhop = 0.000001
real, parameter :: w = 0.04, wp = 0.0, r = 0.25, rt = 0.5,
rm = 0.25,
rtm = 0.375
real :: eta1, eta2
integer :: S1, S2, I1, I2, It1, It2, Im1, Im2, Itm1, Itm2,
R1, R2,
Rm1, Rm2, Rt1, Rt2, Rtm1, Rtm2, N1, N2, n, TotalR1
integer :: nI, nIm, i, TotalR2, TotalRm1, TotalRm2, Size,"itemp
real :: trS1(2), trS2(2), trIt1(3), trIt2(3), trItm1(3),
trItm2(3)
real :: trI1(4), trI2(4), trIm1(4), trIm2(4)
integer :: shS1(2), shS2(2), shIt1(3), shIt2(3), shItm1(3)
integer :: shItm2(3), shI1(4), shI2(4), shIm1(4), shIm2(4), kamal(4)
character(LEN=100) :: option1, option2, arg

N = IARGC()
CALL GETARG(1, option1)
CALL GETARG(2, option2)
CALL GETARG(3, arg)
read (arg,*) eta1
CALL GETARG(4, arg)
read (arg,*) itemp
write(*,*) option1, option2

eta2=REAL(itemp)
eta2 = eta2/200.0
WRITE(*,*) eta2, itemp
!Define parameters
N1 = 100000
N2 = 100000
$S_1 = 99995$

$S_2 = 100000$

$I_1 = 5$

$I_2 = 0$

$It_1 = 0$

$It_2 = 0$

$Im_1 = 0$

$Im_2 = 0$

$Itm_1 = 0$

$Itm_2 = 0$

$R_1 = 0$

$R_2 = 0$

$Rm_1 = 0$

$Rm_2 = 0$

$Rt_1 = 0$

$Rt_2 = 0$

$Rtm_1 = 0$

$Rtm_2 = 0$

$TotalR_1 = 0$

$TotalR_2 = 0$

$n = 1$
nI = 0
nIm = 0

shS1 = 0
shS2 = 0
shI1 = 0
shI2 = 0
shIt1 = 0
shIt2 = 0
shIm1 = 0
shIm2 = 0
shItm1 = 0
shItm2 = 0

!Set probabilities of transition
trIt1 = (/ rt, w, tau /)
trIt2 = (/ rt, w, tau /)
trItm1 = (/ rtm, wp, tau /)
trItm2 = (/ rtm, wp, tau /)
trI1 = (/ r, etal, rho, tau /)
trI2 = (/ r, eta2, rho, tau /)
trIm1 = (/ rm, eta1, rhop, tau /)
trIm2 = (/ rm, eta2, rhop, tau /)

!open file(s) to write
  open(1, file=option1, status = 'unknown')
  open(2, file=option2, status = 'unknown')

do n = 1, 500

!FtrS determines the transition array for the susceptibles (since this is dynamic).
trS1 = FtrS(real(I1), real(It1), real(Im1),
        real(Itm1), real(N1),
        beta, beta2, phi)
trS2 = FtrS(real(I2), real(It2), real(Im2),
        real(Itm2), real(N2),
        beta, beta2, phi)
!write (*,*) trS1

!First element is the number of individuals in a bin. The second is the number of pathways. The third element is the
transition array. mnrdn2 takes this information and determines how many individuals leave the bin and which paths they take.

\[
\begin{align*}
\text{shS1} &= \text{mnrnd2}(S1, \text{size(trS1)}, \text{trS1}) \\
\text{shS2} &= \text{mnrnd2}(S2, \text{size(trS2)}, \text{trS2}) \\
\text{shIt1} &= \text{mnrnd2}(It1, \text{size(trIt1)}, \text{trIt1}) \\
\text{shIt2} &= \text{mnrnd2}(It2, \text{size(trIt2)}, \text{trIt2}) \\
\text{shItm1} &= \text{mnrnd2}(Itm1, \text{size(trItm1)}, \text{trItm1}) \\
\text{shItm2} &= \text{mnrnd2}(Itm2, \text{size(trItm2)}, \text{trItm2}) \\
\text{shI1} &= \text{mnrnd2}(I1, \text{size(trI1)}, \text{trI1}) \\
\text{shI2} &= \text{mnrnd2}(I2, \text{size(trI2)}, \text{trI2}) \\
\text{shIm1} &= \text{mnrnd2}(Im1, \text{size(trIm1)}, \text{trIm1}) \\
\text{shIm2} &= \text{mnrnd2}(Im2, \text{size(trIm2)}, \text{trIm2})
\end{align*}
\]

transition individuals according to random numbers generated by mnrnd2

\[
\begin{align*}
S1 &= S1 - \text{sum(shS1)} \\
S2 &= S2 - \text{sum(shS2)} \\
I1 &= I1 - \text{sum(shI1)} + \text{shS1(1)} + \text{shIm1(3)} + \\
\end{align*}
\]
\[ shI2(4) \]

\[ I2 = I2 - \text{sum}(shI2) + shS2(1) + shIm2(3) + \]
\[ shI1(4) \]

\[ Im1 = Im1 - \text{sum}(shIm1) + shS1(2) + shI1(3) + \]
\[ shIm2(3) \]

\[ Im2 = Im2 - \text{sum}(shIm2) + shS2(2) + shI2(3) + \]
\[ shIm1(3) \]

\[ It1 = It1 - \text{sum}(shIt1) + shI1(2) + shItm1(2) + \]
\[ shIt2(3) \]

\[ It2 = It2 - \text{sum}(shIt2) + shI2(2) + shItm2(2) + \]
\[ shIt1(3) \]

\[ Itm1 = Itm1 - \text{sum}(shItm1) + shI1(2) + shIm1(2) + \]
\[ shItm2(3) \]

\[ Itm2 = Itm2 - \text{sum}(shItm2) + shI2(2) + shIm2(2) + \]
\[ shItm1(3) \]

\[ R1 = R1 + shI1(1) \]

\[ Rm1 = Rm1 + shIm1(1) \]

\[ R2 = R2 + shI2(1) \]

\[ Rm2 = Rm2 + shIm2(1) \]

\[ Rt1 = Rt1 + shIt1(1) \]

\[ Rt2 = Rt2 + shIt2(1) \]
Rtm1 = Rtm1 + shItm1(1)
Rtm2 = Rtm2 + shItm2(1)

TotalR1 = R1 + Rt1
TotalRm1 = Rm1 + Rtm1
TotalR2 = R2 + Rt2
TotalRm2 = Rm2 + Rtm2

!Output numbers to file
write(1, "(I3, A, I6, A, I5, A, I5, A, I5, A, I5)")
n, ',', S1, ',',
', I1, ',', Im1, ',', TotalR1, ',', TotalRm1
n, ',', S2, ',
', I2, ',', Im2, ',', TotalR2, ',', TotalRm2
end do
!end do
close(1)
close(2)
kamal = (/ R1, Rm1, Rt1, Rtm1 /)!Return values to main
end function kamal
!!Calculates transition from Susceptible to Infectious and Infectious Mutant

function FtrS(aI, aIt, aIm, aItm, aN, abeta, abeta2, aphi)
  real, dimension(2) :: A, FtrS
  real :: aI, aIt, aIm, aItm, aN, abeta, abeta2, aphi
  A(1) = 1.0 - (1.0 - abeta * aI/aN)*(1.0 - abeta * aphi * aIt/aN)
  A(2) = 1.0 - (1.0 - abeta2 * aIm/aN)*(1.0 - abeta2 * aphi * aItm/aN)
  FtrS = A
end function FtrS

!Random number generator according to multinomial distribution

function mnrnd2(mnX, mnSize, mnA)!Random number generator
  implicit none
  integer :: mnX, mnSize, i, j, n
  real :: mnA(mnSize), temp
  real, dimension(mnSize) :: cumProb
  integer, dimension(mnSize) :: mnrnd2, mnOut
  integer, dimension(:), allocatable :: seed
mnOut = 0
i = 1
j = 1
temp = 0.00
call random_seed(size = n)
allocate(seed(n))
seed = TIME()+mnX
call random_seed(put = seed)

do i=1,mnSize
    if (i .EQ. 1) then
        cumProb(i) = mnA(i)
    else
        cumProb(i) = cumProb(i-1) + mnA(i)
    end if
end do

do i=1, mnX
    CALL RANDOM_NUMBER(temp)
    !write(2, "(10f10.6)") temp
!write(2, *("(A)")*,`

do j = 1, mnSize
    if (temp .LT. cumProb(j)) then
        mnOut(j) = mnOut(j) + 1
        exit
    end if
end do

mnrnd2 = mnOut
end function mnrnd2

launch code.sh

#!/bin/bash
eta1=0.015
gfortran -o infection new_main.f95
for ((eta2=0;eta2<=100;eta2+=1)); do
    for ((N=0;N<=99;N+=1)); do
        logname1="country1_$eta1-$eta2-$N.dat"
        logname2="country2_$eta1-$eta2-$N.dat"
./infection $logname1 $logname2 $eta1 $eta2
done
filename1="country1_$eta1-$eta2"
filename2="country2_$eta1-$eta2"

python2.7 data_averager_file.py $filename1
python2.7 data_averager_file.py $filename2
done

data average file.py

#!/bin/python
from contextlib import contextmanager
from itertools import imap, izip
from glob import iglob
from math import sqrt
from sys import exit

import sys

@contextmanager

def multi_file_manager(files, mode='rt'):
    files = [open(file, mode) for file in files]
    yield files
for file in files:
    file.close()

# generator function to read and yield each value from a file
def read_values(file):
    for line in file:
        for value in imap(int, line.split(',')): # might only need 'int' here
            yield value

# enumerate multiple (equal length) iterables at the same time
def multi Enumerate(start, *iterables):
    return ((n,) + t for n, t in enumerate(izip(*iterables), start)) # returns gen expr

temp = len(sys.argv)

with multi_file_manager(iglob(str(sys.argv[1]) + "*.dat")) as files:
    num_files = len(files)
    if num_files < 1:
        print 'no *.dat files found to process'
exit(1)

# determine number of rows and cols from first file

temp = []
for line in files[0]:
    temp.append(line.split(','))

num_rows = len(temp)
num_cols = len(temp[0])
files[0].seek(0)  # rewind first file
print '{} files, each {} rows x {} cols
'.format(num_files, num_rows, num_cols)
del temp  # no longer needed

means = []  # reset
sigmas = []  # standard deviations

generators = [read_values(file) for file in files]
for j in xrange(num_rows):  # main loop
    for i in xrange(num_cols):
        values = map(next, generators)  # next cell value from each file
mean = float(sum(values)) / num_files
means.append(mean)
means_diff_sq = imap(lambda value: (value-mean)**2, values)
sigma = sqrt(sum(means_diff_sq) / num_files)
sigmas.append(sigma)

print 'average (and standard deviation) of values:
with open('average_+'+sys.argv[1]+'.dat', 'wt') as averages:
    for i,mean,sigma in multi_enumerate(0, means, sigmas):
        print '{} ({})'.format(mean, sigma),
        averages.write('{}'.format(mean))
        if i % num_cols != num_cols-1:
            averages.write(',') # delimiter between values on
        else:
            print # newline
            averages.write('
')

payoff.py

#!/usr/bin/python

et1 = 0.015
eta2 = 0.015
alpha = 0.09 ##change alpha for different results
R1 = []
Rm1 = []
R2 = []
Rm2 = []
payoff_max =[]
## Open writable files one for the payoff of the
model for the best response
curve, another to show all the payoffs from the
simulations
payoffFile = open("payoff_model_alpha_"+str(alpha)
+.dat", "w")
allPayoffFile = open("all_payoffs_alpha_"+str(alpha)
+.dat", "w")

#Find payoff for Country1
for i in range(101):
    payoff = []
    eta2 = i
    eta2s = "%d" % eta2
for j in range(101):
    etal = j/50.0
    etals = "%.2f" % etal
    files = open("average_country1_" + str(etal) + "-" + str(eta2s) + ".dat", "r")
    linelst = files.readlines()
    files.close()
    linelst[0].splitlines()
    lastline = linelst[-1]
    lastline = lastline.split(','),
    R1.append(float(lastline[4]))
    Rm1.append(float(lastline[5]))
    temp = (-alpha*float(lastline[4]) - (1-alpha) *float(lastline[5]))
    payoff.append(temp)
    allPayoffFile.write(eta1s + ',' + eta2s + ',' + str(temp) + ',' + str(R1[-1]) + ',' + str(Rm1[-1]) + '\n')
    #Write payoff
    temp = max(payoff)
indtemp = payoff.index(max(payoff))

etas = str(indtemp/50.0)

print etas +', ' + eta2s + ', ' + str(temp)

payoffFile.write(etas +', ' + eta2s + ', ' + str(temp) + '\n')

##Write maximum payoff

##Payoff for Country2

for i in range(101):
    payoff = []
    eta1 = i/50.0
    etals = "%.2f" % eta1
    for j in range(101):
        eta2 = j
        eta2s = "%d" % eta2
        files = open("average_country2_' + str(etas) + " "+ str(eta2s) + ".dat", "r")
        linelst = files.readlines()
        files.close()
        linelst[0].splitlines()
#print linelst
lastline = linelst[-1]
lastline = lastline.split(',,')
#print lastline
R2.append(float(lastline[4]))
Rm2.append(float(lastline[5]))
temp = (-alpha*float(lastline[4]) - (1-alpha)*float(lastline[5]))
payoff.append(temp)
allPayoffFile.write(eta1s + ', ' + eta2s + ', ' + str(temp) + ', ' + str(R2[-1]) + ', ' + str(Rm2[-1]) + '"
) #write payoff

temp = max(payoff)
indtemp = payoff.index(max(payoff))
eta2 = str(indtemp/50.0)
print etals + ', ' + eta2s + ', ' + str(temp)
payoffFile.write(etas + ', ' + etas + ', ' + str(temp) + '"
)  #write Maximum payoff
C.3 Code for chapter 4

Other graphs in this chapter were produced varying parameter values of the same code.

function [mins_found t_Fzero t_Fzero_average t_Fzero_std] = 
forestSolver_VariableP3()

% Defined Parameters
iterations = 10000;
tmax = 1000;
K = 0.17;
delta = 0.2;
R = 0.06;
h = 0.18;
c = 0.35;
noisex = 0.06;
noisef = 0.06;

% Average time, X, F for all iterations

time_avg = 0;
% X_avg = 0;
%F_avg = 0;
% Parameter to vary = var
var_min = 0.1;
var_max = 0.8;
var_divisions = 15;
vari = 0; % variable index to store values into array

for var = var_min: (var_max-var_min)/var_divisions : var_max
    var
    vari = vari + 1;
    mins_found(vari) = 0;

% Set the parameter to be varied to var
delta = var;
%h = var;
%K = var;
%c = var;
%R = var;
%noisex = var;
for i = 1 : iterations

    % Runs SDE solver
    [t y] = sde_function(tmax, K, c, delta, R, h, noisex, noisef);

    % Determine the where the 'lowest' F is (i.e. which time step)
    Ftolerance = 0.000001;
    k = 0;

    % Create Time series plots for each individual runs
    fig1 = figure;
    hold on;
    h1 = plot(t, y(:,2), 'color', 'red', 'LineWidth', 2);
    hold on
    h1 = plot(t, y(:,1), 'color', 'black', 'LineWidth', 2);
    xlabel('Time (Years)', 'FontSize',36);
while 1  
    k = k + 1;  
    if (k > tmax)  
        t_Fzero(vari, i) = -1;  
        break;  
    end  
    if ( abs( y(k,2) < Ftolerance) )  
        mins_found(vari) = mins_found(vari) + 1;  
        t_Fzero(vari, i) = t(k);  
        break;  
    end  
end
end
% Clean matrix to eliminate -1, does it row by row
m = 0;
clear temp_matrix;
for l = 1:iterations
    if (t_Fzero(vari, l) ~= -1)
        m = m + 1;
        temp_matrix(m) = t_Fzero(vari, l);
    end
end
t_Fzero_average(vari) = mean(temp_matrix);
t_Fzero_std(vari) = std(temp_matrix);
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
% Create and Save Plot
fig1 = figure;
hold on;
%h1 = errorbar(c_text(:,1), c_text(:,2), c_text(:, 3),
    'o', 'color', 'black',
    'LineWidth', 2);
%plot(c_text(:,1), c_text(:,2), 'o', 'color', 'black',

function [t y] = sde_function(tmax, k, c, delta, R, h, noisex, noisef)

    model = @(t,z) [ k*z(1)*(1-z(1))* (c-z(2)+delta*
\[ (2z(1) - 1) \];
\[
    Rz(2)*(1-z(2)) - h*(1-z(1))\times z(2) \];

\[ dt = 1; \]
\[ t = 0:dt:tmax; \]
\[ g = @(t, z) [\text{noisex}; \text{noisef}] \times z; \]
\[ y0 = [0.1, 0.9]; \]
\[ ops = sdeset('NonNegative', 'yes'); \]
\[ y = sde_milstein(model, g, t, y0, ops); \]
\[ end \]