Mathematical modeling of infectious diseases can help public health officials to make decisions related to the mitigation of epidemic outbreaks. However, over or under estimations of the morbidity of any infectious disease can be problematic. Therefore, public health officials can always make use of better models to study the potential implication of their decisions and strategies prior to their implementation. Previous work focuses on the mechanisms underlying the different epidemic waves observed in Mexico during the novel swine origin influenza H1N1 pandemic of 2009 and showed extensions of classical models in epidemiology by adding temporal variations in different parameters that are likely to change during the time course of an epidemic, such as, the influence of media, social distancing, school closures, and how vaccination policies may affect different aspects of the dynamics of an epidemic. This current work further examines the influence of different factors considering the randomness of events by adding stochastic processes to meta-population models. I present three different approaches to compare different stochastic methods by considering discrete and continuous time. For the continuous time stochastic modeling approach I consider the continuous-time Markov chain process using forward Kolmogorov equations, for the discrete time stochastic modeling I consider stochastic differential equations using Wiener's increment and Poisson point increments, and also I consider the discrete-time Markov chain process. These first two stochastic modeling approaches will be presented in a one city and two city epidemic models using, as a base, our deterministic model. The last one will be discussed briefly on a one city SIS and SIR-type model.
“There are people out there who tell you, you can’t. What you’ve got to do is turn around and say: watch me.” -Unknown

This dissertation is dedicated to my family the Cruzes and the Apontes; but more importantly to my mom Luz N. Aponte-Cruz, my dad Angel L. Cruz-Aponte, my sister Margie Cruz-Aponte, her husband Carmelo Lebrón-Gonzales, and to my sidekick Emmanuel Jesús Morales-Butler.

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Chapter 1

INTRODUCTION

Mathematical modeling of infectious diseases can help public health officials to make decisions related to the mitigation of epidemic outbreaks. However, over or under estimation of the morbidity of any infectious disease can be problematic. Therefore, public health officials can always make use of better models to study the implication of their decisions and strategies prior to their implementation. Better models also need realistic measure of parameters that can help mathematical models fit real case scenarios.

The most used models in epidemiology are based on the SIR (Susceptible-Infected-Recovered) compartment epidemic models developed in 1927 by Kermack and McKendrick [85, 84]. They considered a fixed population with only three compartments or disjoint categories: susceptible is used to represent the number of individuals not yet infected with the disease at time $t$, infected is used to represent individuals who have been infected and are capable of spreading the disease to those in the susceptible category, and recovered is the compartment used for those individuals who have recovered from the disease. When it comes to modeling communicable disease, such as influenza, a simple model can capture qualitative behavior and can generate short-term dynamics use to make quantitative predictions [26]. The work of Brauer [27, 26, 25] has focused on the study and analysis of compartmental models starting from the simple model and adjusting the compartments according to the behavior of the particular disease modeled. For example, for influenza an incubation period is necessary before an individual is considered infected, hence an SEIR (Susceptible-Exposed-Infected-Recovered) model is more appropriate. Now epidemiologists focus on complex models to adjust to real life situations, not only to generalize the
spread of disease but also to include behavioral aspects of a disease and mechanisms that affect the time course of a given epidemic.

Complex models are difficult to analyze mathematically and are computationally expensive, but they are necessary to studied the possible scenarios that can lessen the catastrophic effects of a disease spread in the population. Many works have been published that include metapopulation models [128, 81, 16, 86]. Rvachev’s (1985) work was the first attempt to apply the method at a global scale modeling the spread of influenza from city to city around the world during the 1968-1969 A/H3N2 (Hong Kong Flu) pandemic. The work of Julien Arino and colleagues focused on metapopulation models (see [16, 86, 13, 17, 15, 14]). In his early work Arino started with the analysis of a proposed model for the spread of a disease among cities [16, 17, 15] and his latest work with colleagues studies a model for global spread of disease by air transportation addressing the global spread of the A/H1N1 2009 pandemic [86]. The purpose of their analysis was to show how travelers would disseminate the A/H1N1 disease worldwide during the initial wave of this pandemic. They concluded that quantitative analysis of worldwide air-traffic patterns can help cities and countries around the world to anticipate their risks of importing global infectious diseases. For example, diseases are easily transmitted among children of the same age in school, hence it is important for us to consider as landmarks school closures implemented by the government and also academic year periods.

In one specific case of México, historically the spread of diseases does not occur uniformly. Instead, it travels with a north-south direction across the center of the country in an area that is referred to as the *influenza corridor* [4]. The difference between previous work and the work presented in this dissertation is that previous approaches were global considering air transportation and this present work is local considering only México where the transportation is mainly terrestrial. It is also important to address the work of Hyman and LaForce [81] since they model the spread of influenza between cities of the United States
and the model in our previous work [76] is based on their modeling approach, modified for the constraints of México and the 2009 pandemic.

My work focused on the mechanisms underlying the different epidemic waves observed in México during the novel swine origin influenza H1N1 pandemic of 2009 [76]. This work showed extensions of classical models in epidemiology by adding temporal variations in different parameters that are likely to change during the time course of an epidemic such as the influence of media, social distancing, school closures, and how vaccination policies may affect different aspects of the dynamics of an epidemic, in particular, the infection rate. The dynamics emerging from the combination of modulations in the infection rate and changes in the flow of individuals between regions due to transportation were studied through computational simulations. The idea is to further study the influence of different factors considering the randomness of events by adding stochastic processes to meta-population models. The different modeling formulations presented here will be first studied and analyzed for a single population, then a two city population model to later be generalized or applied on a meta-population context. For simulation purposes I will use parameter values of the swine origin influenza H1N1 pandemic of 2009. The models will be presented starting from a simple SIS model and the complexity will be increased to arrive to a stochastic scheme for the multi-regional SEUCR model. I present three different approaches to compare different stochastic methods by considering discrete and continuous time. I present three stochastic approaches that are the main ones discussed in the literature: discrete-time Markov chain (DTMC) models, continuous-time Markov chain (CTMC) models, and stochastic differential equation (SDE) models. These three stochastic modeling approaches will be presented in a one and two cities epidemic model whenever possible.

This dissertation presents a meta-population model which started as a simple compartmental model and evolved into a complex model including transportation across the different states in México. Now I am going to focus on the analysis of this complex model and
will include a stochastic approach to it. This introductory chapter (Chapter 1) presents an overview of the thesis and literature review of relevant papers that are used throughout the thesis. The second chapter presents our deterministic model and results from our first publication on the 2009 A/H1N1 epidemic outbreak in México. This supports the view that the three epidemic “waves” are the result of the synergistic interactions of three factors: regional movement patterns of Mexicans, the impact and effectiveness of dramatic social distancing measures imposed during the first outbreak, and the summer release of school children followed by their subsequent return to classes in the fall. The three “waves” cannot be explained by the transportation patterns alone but only through the combination of transport patterns and changes in contact rates due to the use of explicit or scheduled social distancing measures. The research identifies possible vaccination schemes that account for the school calendar and whose effectiveness are enhanced by social distancing measures. The limited impact of the late arrival of the vaccine is also analyzed. The third chapter presents a SIR-like model that explicitly takes into account vaccine supply and the number of vaccines administered per day and places data-informed limits on these parameters. This model would be refer to as a non-proportional model of vaccination and I compare it to the proportional scheme typically found in the literature. The fourth chapter focuses on different stochastic models. I present three stochastic approaches that are the main ones discussed in the literature: discrete-time Markov chain (DTMC) models, continuous-time Markov chain (CTMC) models, and stochastic differential equation (SDE) models. For the discrete time stochastic modeling I am considering the discrete time Markov chain (DTMC), for the stochastic differential equation (SDE) models I am using Wiener’s increment and Poisson point increments where time and population size are discrete, and for the continuous time stochastic modeling approach I will consider the CTMC using forward Kolmogorov equations where time is continuous and population size is discrete, I also consider the stochastic differential equation where it resembles a diffusion process using
Brownian motion increments where time is discrete and population size is continuous. Our main goal is to compare these three methods and discuss which ones are more appropriate or more accurate when comparing to the deterministic approach. The idea behind adding stochasticity to a model is to better understand the uncertainty of the randomness of events that can occur in any epidemic outbreak. The fifth chapter will discuss in more depth the differences among the distinct stochastic methods worked on Chapter 4 and conclusions and final remarks pertinent to all chapters presented in the thesis.
Chapter 2

DETERMINISTIC MODEL

2.1 General metapopulation SEUCR model and the 2009 A-H1N1 pandemic

The model presented in this chapter was constructed to explore the role of social distancing, school closures, transportation patterns, and vaccination policies on the time course of the 2009 A-H1N1 México’s epidemic [76]. An extension of the Kermac and McKendrick (1927) model [84] is constructed following the general framework originally proposed by Rvachev and Longini [128]. Our modeling framework resembles the modeling approach of Arino and van den Driessche [16], Hyman and LaForce [81]. Arino and van den Driessche published analytical results on a n-city model that describes the propagation of a disease in a population of individuals that travels among the cities and where the mobility component is represented as a directed graph. In this work they also provide an explicit formula for the basic reproduction number that I use for my model. Hyman and LaForce created a model of the spread of influenza among cities in the United States I use their modeling approach to construct my meta-population model for influenza AH1N1 described in this chapter.

A schematic of the relationships between the classes are shown in Figure 2.1 and the value of the parameters used for simulation purposes are described in Table 2.2.

For all our models I will use the following definition of classes present in Table 2.1.

México is divided into thirty-one States and DF (Distrito Federal); México City is contained in DF. These thirty-two regions are regarded as nodes in a star-shaped, weighted graph with all nodes connected to DF, but not directly connected to each other. The regions are indexed 0,1,...,31, with DF indexed by the number 0. Infected individuals are assumed
Figure 2.1: Compartment Diagram for city $k$ in the SEUCR model.

Table 2.1: Epidemiological Classes of SEUCR model of Figure 2.1.

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<td>$S$</td>
<td>Unprotected population</td>
<td>Individuals at risk of becoming infected by influenza</td>
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<tr>
<td>$E$</td>
<td>Latent or Exposed population</td>
<td>Individuals are in the period between acquiring the disease and becoming sick</td>
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<tr>
<td>$C$</td>
<td>Confirmed Infected population</td>
<td>Individuals who got tested and are confirmed to have A/H1N1</td>
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<td>$U$</td>
<td>Unconfirmed Infected population</td>
<td>Asymptomatic individuals, or people that did not get tested</td>
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<tr>
<td>$R$</td>
<td>Recovered population</td>
<td>Individuals that recover from influenza</td>
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to go through a latent period of 2 days before becoming infectious. Once infected, the recovery time was assumed to be between 5 and 9 days [49], [111]. Disease deaths are also included in the model. Infectious individuals are further divided into confirmed and unconfirmed cases. The unconfirmed cases include individuals who had symptoms of influenza but did not seek medical care, and also those who had an asymptomatic infection [10]. It is
assumed that the traveling plans of an infectious individual were not affected by symptoms and traveling did not change an individual epidemiological state. Individuals are assumed to infect others during this incubation period, at a lower rate than the infectious individuals. Also, recovered individuals gain permanent immunity against the novel A-H1N1pdm influenza virus [133, 12].

It is assumed that the net daily flow of people through DF is zero, with about half a million people coming into or out of México City every day. The contribution of each region to the daily flow through DF is determined as follows: let $F$, $q_{ij}$ and $N_i$ denote, respectively, the number of people that go through DF every day, the relative contribution of a city and the population size of the $i^{th}$ region. It is important to note that $q_{ij}$ represent the total daily flow of traffic from city $i$ to city $j$ and vice-versa (since it is assumed that our transportation matrix is symmetric. Assuming that our transportation matrix containing the $q_{ij}$ values, is symmetric which guarantees that the population in each city will remain constant since the same amount of people that go out of one city come back. This type of matrix can be use when assuming that an epidemic is not too long (the duration is less than a year). The flux between States given by transportation can be written with the aid of a time-dependent symmetrical matrix, $Q(t) = (Q_{ij})$ with entries defined as:

$$Q_{ij} = \begin{cases} 
q_{ij}(t)/N_i & \text{if } i = 0 \\
0 & \text{otherwise}
\end{cases} \quad (2.1)$$

$$Q_k = Q_{k0} - \sum_{i=1}^{M} \{Q_{0i} : i = 1, ..., M, i \neq k\} \quad (2.2)$$

Here, for $0 < i, j \leq M = 31$; $Q_{ij}(t)$ represents the proportion of the population from region $i$ that travels to region $j$ per day, where $q_{ij}$ measures the relative contribution to the flow of people in and out of Mexico City (D.F.). The term $Q_k$ denotes the proportion of people traveling from region $k$ to DF minus the proportion of people returning to region $k$. 

8
The population of each region is divided into disjoint subgroups based on the individuals epidemiological states: $S, E, C, U, R$ as described in table 2.1 indexed by region. The system of equations describing the time-dependent change in region $k$ is defined as follows:

\begin{align*}
\dot{S}_k &= (Q_k - \lambda_k) S_k + \sum_{i \neq k} Q_{i1} S_i \\
\dot{E}_k &= (Q_k - \alpha) E_k + \sum_{i \neq k} Q_{i1} E_i + \lambda_k S_k \\
\dot{C}_k &= (Q_k - \sigma_k - \delta_C) C_k + \sum_{i \neq k} Q_{i1} C_i + \alpha p E_k \\
\dot{U}_k &= (Q_k - \sigma_k - \delta_U) U_k + \sum_{i \neq k} Q_{i1} U_i + \alpha (1 - p) E_k \\
\dot{R}_k &= Q_k R_k + \sum_{i \neq k} Q_{i1} R_i + \sigma_k C_k + \sigma_k U_k
\end{align*}

where $\lambda_k = \beta \frac{C_k + U_k + \mu E_k}{N_k}$ for $k = 0, 1, \ldots, 31$ and the term $Q$'s denote the proportion of people traveling from region $k$ to the node.

### 2.1.1 Analysis

To start the mathematical analysis of the deterministic model, I consider the methods presented in Sattenspiel and Simon 1988 [130] and apply it to my metapopulation model. In this article a model of disease transmission is analyzed that considers heterogeneous mixing among population clusters or regions where each subpopulation is further divided in two. One division represent the part of the population that travels and the other represents the part of the population that do not interact with others (they interact only within the subpopulation cluster). Sattenspiel and Simon present 7 steps to analyze the system and I intend to implement them in a similar way. They are:

1. Demonstrate that the model has a constant population size to reduce the number of equations.

2. Show that the natural domain of the system of equations is invariant under the system by defining a compact domain $B$ in which the solutions stay.
3. Show \( \hat{N} = (S_1, \ldots, S_k, E_1, \ldots, E_k, C_1, \ldots, C_k, U_1, \ldots, U_k) \)

\( = (N_1, N_2, \ldots, N_k, 0, \ldots, 0, 0, \ldots, 0, 0) \) is always an equilibrium; this is the case where everyone is susceptible.

4. Show that there is a threshold level of the parameter values for which \( \hat{N} \) is a globally asymptotically stable equilibrium for \( B \) for all parameters below this threshold.

5. When the group sizes determined by the parameters are above the threshold level, show \( \hat{N} \) is unstable. All orbits which start inside \( B \) will tend away from \( \hat{N} \).

6. Demonstrate that when \( \hat{N} \) becomes unstable, a unique new “endemic” equilibrium appears in the interior of \( B \).

7. Find upper and lower bounds on the thresholds to define a persistence or extinction of the disease in the population.

The authors define a mobility matrix and called it a forward stochastic migration matrix where they claim that the contact matrix is defined as “the probability of two individuals from different neighborhoods coming into contact” [130] but they do not elaborate further on how the stochasticity plays a role in this matrix. They intend to analyze the model and claim that by doing so they can evaluate the effects of the heterogeneity in the contact patterns to define conditions for disease persistence by linking the migration matrices to these conditions. Here I develop the first three steps of my model analysis based on [130] as stated above, the rest will be analyzed further.

**First I need to show that the model has a constant population size.**

For the purpose of the analysis of the model let’s assume that I have:

- \( \delta_U = \delta_C = 0 \): I will assume that the death rate is 0 since I have no birth rate and in previous simulations the death rate has been set to \( 10^{-6} \).
• The number of cites is denoted by $\omega$.

• Recall that: $F$, $q_{ij}$, and $N_i$ denote, respectively, the number of people that go through DF the node city of our transportation network) every day, the relative contribution of a city to the total daily flow through DF, and the population size of the $i^{th}$ region. Also, $Q_{ij}(t)$ represents the proportion of the population from region $i$ that travels to region $j$ per day as described above (see Eq. 2.1 and 2.2).

With these two assumptions, I now show that the model has constant population size. By definition $N = \sum_{k=0}^{\omega} N_k$ is the total population, where $\omega$ is the number of cities and $N_k = S_k + E_k + C_k + U_k + R_k$. For constant population size I need to show that $\dot{N} = 0$. Starting with $N_k = \dot{S}_k + \dot{E}_k + \dot{C}_k + \dot{U}_k + \dot{R}_k$ I end up with the transportation dynamic left as

$$\dot{N}_k = Q_k N_k + \sum_{i \neq k} Q_{i0} N_i,$$  

(2.8)

as defined in Eq. 2.1 I have

$$Q_{i0} = \frac{FN_i}{N} \frac{1}{N_i} = \frac{F}{N},$$  

(2.9)

Substituting this expression into Eq. 2.2 yields

$$Q_k = Q_{k0} - \sum_{i \neq k} Q_{i0}$$  

(2.10)

$$= Q_{k0} - \sum_{i \neq k} F = \frac{FN_k}{N} \frac{1}{N_k} - \frac{1}{N} \sum_{i \neq k} F$$

$$= \frac{F}{N} (1 - \omega).$$

Hence, substitution of the previous results into Eq. 2.8 gives

$$\dot{N}_k = \frac{F}{N} (1 - \omega) N_k + \frac{F}{N} \sum_{i \neq k} N_i$$  

(2.11)

$$= \frac{F}{N} [(1 - \omega) N_k + (N - N_k)]$$

$$= \frac{F}{N} [N - \omega N_k].$$
It follows that

\[ \dot{N} = \sum_{k=1}^{\omega} \frac{F}{N} [N - \omega N_k] \]

\[ = \sum_{k=1}^{\omega} F - \frac{F \omega}{N} \sum_{k=1}^{\omega} N_k \]

\[ = \omega F - \frac{F \omega}{N} N = 0 \]

which shows that the population is constant (under the above assumptions) and I can disregard \( \dot{R}_k \) from the system.

Second, I need to show that the natural domain of the system is invariant.

I want \( S_k \geq 0, E_k \geq 0, C_k \geq 0, U_k \geq 0 \). The constraints can be summarized on the SECU state space by letting the domain be:

\[ B = \{ (S_0, S_1, \ldots, S_k, E_0, \ldots, E_k, C_0, \ldots, C_k, U_0, \ldots, U_k) : 0 \leq S_k, 0 \leq E_k, 0 \leq C_k, 0 \leq U_k, S_i + E_i + C_i + U_i \leq N_i; \forall i = 0 \ldots k \} \]

The compact convex set \( B \) is bounded by the \( 5n \) hyperplanes \( S_k = 0, E_k = 0, C_k = 0, U_k = 0, N_i = S_i + E_i + C_i + U_i \). I have

\[ S_k = 0 \Rightarrow \dot{S}_k = \sum_{i \neq k} Q_{i1} S_i > 0 \Rightarrow \text{moving into } B \]

\[ E_k = 0 \Rightarrow \dot{E}_k = \sum_{i \neq k} Q_{i1} E_i + \lambda_k S_k > 0 \Rightarrow \text{moving into } B \]

\[ C_k = 0 \Rightarrow \dot{C}_k = \sum_{i \neq k} Q_{i1} C_i + \alpha p E_k > 0 \Rightarrow \text{moving into } B \]

\[ U_k = 0 \Rightarrow \dot{U}_k = \sum_{i \neq k} Q_{i1} U_i + \alpha (1 - p) E_k > 0 \Rightarrow \text{moving into } B \]

thus, the natural domain of the system is invariant. \( \square \)
Third, $\hat{N} = (N_1, N_2, ..., N_k, 0, ..., 0, 0, ..., 0, 0, ..., 0)$ is always an equilibrium.

This is always the case since I assume that $\dot{S}_k = \hat{N}_k$ i.e., everyone is susceptible at the start of the epidemic.

$$
\dot{S}_k = (Q_k - \lambda_k)N_k + \sum_{i \neq k} Q_{i1}N_i \quad (2.13)
$$

$$
\dot{E}_k = \lambda_kN_k \quad (2.14)
$$

$$
\dot{C}_k = 0, \dot{U}_k = 0 \quad (2.15)
$$

2.2 Basic Reproductive Number

Much of the metapopulation work that had been done in the past has upper or lower bounds to the basic reproduction amount; see, for example, Arino in his paper Disease in Metapopulations [13] that extensively studied metapopulation models using patches. He states that the expression for $\mathcal{R}_0$ is complicated when considering a metapopulation model and he chose to define bounds for the term to take into consideration all classes and all cities as: $\min_{k=1..n} \mathcal{R}^k_0 \leq \mathcal{R}_0 \leq \max_{k=1..n} \mathcal{R}^k_0$ for $n$ cities where $k$ is the index of one city. To get a better understanding of the parameters that comprise $\mathcal{R}_0$, I first examine the combination of cases from one to two cities and one ($I$) to two ($C, U$) infectivity classes and then try to generalize this.

One city, two infectivity classes:

$$
\dot{S} = -\beta S \frac{\gamma C + U + \mu E}{N} \quad (2.16)
$$

$$
\dot{E} = \beta S \frac{\gamma C + U + \mu E}{N} - \alpha E \quad (2.17)
$$

$$
\dot{C} = \alpha pE - (\sigma + \delta)C \quad (2.18)
$$

$$
\dot{U} = \alpha (1 - p)E - (\sigma + \delta)U \quad (2.19)
$$

$$
\dot{R} = \sigma (C + U) \quad (2.20)
$$
\[ R_0 = \frac{\beta \alpha [\gamma p + (1 - p)] + \beta \mu (\sigma + \delta)}{\alpha (\sigma + \delta)} \]  \hspace{1cm} (2.21)

Two cities, two infectivity classes:

\[ \dot{S}_1 = -q_{12} S_1 - \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} + q_{21} S_2 \]  \hspace{1cm} (2.22)

\[ \dot{E}_1 = -q_{12} E_1 + \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} - \alpha E_1 + q_{21} E_2 \]  \hspace{1cm} (2.23)

\[ \dot{C}_1 = -q_{12} C_1 + \alpha p E_1 - (\sigma + \delta) C_1 + q_{21} C_2 \]  \hspace{1cm} (2.24)

\[ \dot{U}_1 = -q_{12} U_1 + \alpha (1 - p) E_1 - (\sigma + \delta) U_1 + q_{21} U_2 \]  \hspace{1cm} (2.25)

\[ \dot{R}_1 = -q_{12} R_1 + \sigma (C_1 + U_1) + q_{21} R_2 \]  \hspace{1cm} (2.26)

\[ \dot{S}_2 = -q_{21} S_2 - \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} S_1 \]  \hspace{1cm} (2.27)

\[ \dot{E}_2 = -q_{21} E_2 + \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} E_1 \]  \hspace{1cm} (2.28)

\[ \dot{C}_2 = -q_{21} C_2 + \alpha p E_2 - (\sigma + \delta) C_2 + q_{12} C_1 \]  \hspace{1cm} (2.29)

\[ \dot{U}_2 = -q_{21} U_2 + \alpha (1 - p) E_2 - (\sigma + \delta) U_2 + q_{12} U_1 \]  \hspace{1cm} (2.30)

\[ \dot{R}_2 = -q_{21} R_2 + \sigma (C_2 + U_2) + q_{12} R_1 \]  \hspace{1cm} (2.31)

\[ R_0 = \frac{\beta \alpha [\gamma p + (1 - p)] + \beta \mu (\sigma + \delta) + \beta \mu (q_{12} + q_{21})}{(\alpha + [q_{21} + q_{12}]) ([\sigma + \delta] + [q_{21} + q_{12}])} \]  \hspace{1cm} (2.32)

The general formula for an \( n \)-city metapopulation model with two infectious classes would be:

\[ R_0 = \frac{\beta \alpha [\gamma p + (1 - p)] + \beta \mu (\sigma + \delta) + \beta \mu \left( \sum_{j=0}^{n} \sum_{i=0}^{n} q_{ij} \right)}{\left( \alpha + \sum_{j=0}^{n} \sum_{i=0}^{n} q_{ij} \right) \left( \sigma + \delta + \sum_{j=0}^{n} \sum_{i=0}^{n} q_{ij} \right)} \]  \hspace{1cm} (2.33)

where \( n \) represent the total number of cities been considered, \( i \) is a particular city. But in practice when using values and doing simulations, using (2.33) gives an underestimation of
the real $\mathcal{R}_0$. Hence, as established by Julian Arino and Pauline van den Driessche on [16] if all the parameters are fixed for all the cities the total $\mathcal{R}_0$ of our system would be bounded by the maximum and minimum values of the individual $\mathcal{R}_0$ of the cities. If all the parameters are fixed for all the cities then the $\mathcal{R}_0$ would be the typical computation of a single city outbreak in accordance with the model used (i.e. if it is an SIR, SEIR or SEUCR). If the parameters vary from city to city then the bounds would look like $\min\limits_{k=1\ldots n} \mathcal{R}_0^k \leq \mathcal{R}_0 \leq \max\limits_{k=1\ldots n} \mathcal{R}_0^k$ for $n$ cities.

2.3 Multiple outbreaks for the same pandemic: Local transportation and social distancing explain the different “waves” of A-H1N1pdm cases observed in Mexico during 2009

We live in a highly interconnected world where individuals move between cities, states, countries, and continents in a matter of hours. Several studies have looked at the role of movement of individuals or transportation patterns on the recurrence of influenza epidemic outbreaks [81]. The first efforts to connect epidemic patterns explicitly to train-transportation flows where conducted by [20, 128], and most recently by [81], and [86]. The transmission and evolution of the influenza virus is influenced by local and global individual patterns of movement, massive demographic growth, and the diversity and availability of domestic and wild animal populations, a key reservoir of genetic variability [135, 29]. Unfortunately, despite the severity of single epidemic outbreaks and the availability of the earlier work of Kermack and McKendrick [84] most of the theoretical work on influenza has been driven by concerns over its long-term dynamics and/or A-subtype specific co-evolutionary dynamics [33, 34, 11, 120]. Further, the role of behavior in epidemic outbreaks has been explored in rather limiting settings [77, 27, 57, 70]. The impact of “social-distancing” and information on disease dynamics have gained relevance and importance during the last few years; a reinvigorated research direction by the impact of this 2009
A/H1N1 influenza pandemic [134, 143, 10, 22, 107]. Fortunately, theoretical extensions of the single outbreak models [84] have been carried out by various researchers, most notably F. Brauer [25]. In fact, a detailed account on recent advances in modeling influenza outbreaks can be found in [28].

![Map of Mexico showing the influenza corridor](image)

**Figure 2.2:** Initial influenza outbreak and the historical influenza corridor. A/H1N1 epidemic outbreak in México by region 2009. The Mexican States that contributed with more than half of the total cases during the initial spread of A/H1N1 up to June 4, 2009 are shown in dark gray (see Fig. 2.4). The remaining States (light gray) were the main contributors to secondary outbreaks later in the year. The red dots mark states in the historical influenza corridor (Acuña-Soto, personal communication, see also [6] and Figs. 2.3).

The study of the dynamics of influenza outbreaks in México must account for México’s unique characteristics. México is a highly centralized country in which the massive transportation of individuals occurs predominantly by land with México City as the main hub for most traffic (air transportation inclusive). México City has four “Central Bus Terminals”, connected by a subway system that moves 5 million people per day. In addition, there are 80 thousand taxicabs generating about 780 thousand rides daily [101] and a public city bus system with 11 main lines that moves approximately eight million users per day [100]. Influenza does not seem to follow uniform transmission patterns along México. In fact, it seems to “primarily” travel through what [4] has coined as Mexico’s influenza corridor.
(Fig. 2.2 red dots). This corridor extends from south to north along central México and is bounded by two mountain ranges, the West and East Sierra Madres. This geographical distinction seems to be supported by recent preliminary analysis of historical data of upper respiratory illnesses in México. The origins of “the” corridor are not entirely clear but the abundance of some metals and other minerals, and the historical patterns of commercial activity may constitute some of the underlying factors [88]. In fact, there is a large overlap between the States in “the” corridor (Fig. 2.2 red dots) and the States that collectively reported more than half of the cases of pandemic influenza A-H1N1 (A-H1N1pdm) during the first wave up to June 4, 2009 (about 12 weeks, Fig. 2.2 dark gray).

Confirmed cases of A-H1N1pdm in México.

Figure 2.3: A-H1N1pdm epidemic outbreak in México during 2009. Daily confirmed cases by RT-PCR reported by Mexican authorities [136]. January 1, 2009 is considered as day 1 and the last day was approximately December 25, 2009. From [136]. Social distancing and school closures were imposed in April 29, 2009. The official summer school closure occurs at the end of June and mid December, and fall classes start around Sept. 1.

The A-H1N1 pandemic of 2009 in México was characterized by three “waves” of morbidity and mortality (Fig. 2.3). For comparison, past pandemics have been characterized by the occurrence of multiple “waves” over short time periods [84, 43]. However, the size of the individual contributions from different geographical regions within México to these
“waves” is not uniform (Fig. 2.4A,B). These “waves” took shape during the year as data aggregated over time. What are the drivers of these epidemic “waves”? One possibility is that non-uniform aggregation of the data is due to delays in transmission that, in turn, were caused by social distancing measures, movement of people, and population density. Can these “waves” be explicitly tied in to transportation patterns, behavioral changes, and the regular school calendar schedule in México?

The influence of México City as a hub on the spatio-temporal patterns of spread of A-H1N1pdm cases during 2009 (Fig. 2.3) is investigated by assuming that the different Mexican States and the DF form a star-shaped graph with vertices representing the flow to or from DF. To do so, I combine official case data from the Mexican health authorities (Figs. 2.3 and 2.4A,B) and empirically estimate flows from observations collected at toll gates located at the different entry points to DF, taking into consideration a set of dates from 2009 hypothesized as important for the introduction of delays in the propagation of A-H1N1pdm in México. Scenarios that result in multiple epidemic “waves” due to the synergistic interactions between transportation flow patterns and changes in the contact rates between individuals are identified. It is observed that both of these factors induce delays in the evolution of influenza dynamics that cause the data to aggregate nonuniformly across different regions in México, displaying patterns consistent with the existing data shown in Figs. 2.3 and 2.4.

The rest of this chapter is organized as follows: A qualitative analysis of the main events related to the A-H1N1pdm epidemic in México is made first, followed by a description of the model. Simulations where the influence of transport flow, social distancing, and school closures on the time course of the epidemic are presented first, followed by simulations of the effects of vaccination with different arrival times during the year. We finish this chapter with a discussion and final remarks.
2.3.1 Qualitative analysis of the A-H1N1pdm epidemic in México during 2009

Three different reports of the number of A-H1N1pdm cases confirmed by real time polymerase chain reaction (RT-PCR) in México, ordered by the States, are shown in Fig. 2.4 A. The difference between the three reports is collected in Fig. 2.4 B. The data in these figures (Fig. 2.4 A-B) support the view that the first outbreak affected mostly States shown on the left portion of panel A (e.g. Distrito Federal, San Luis Potosí, etc. indicated by the line corresponding to June 4, 2009); the States in the right portion of the graph (e.g. Sinaloa, Coahuila, etc., in later reports), reported significant numbers of confirmed cases during the summer; while States like Baja California or Sonora did not experienced an outbreak until the fall. The majority of the States that contributed the most A-H1N1pdm cases during the initial phase of the outbreak have been identified as members of México’s influenza corridor (Fig. 2.2).

The first official case of novel swine-origin influenza disease was identified in Oaxaca [59, 150]. The diseased was a diabetic woman originally identified as a probable SARS case around March 5, 2009; she died of atypical pneumonia a few days later. A small outbreak of influenza-like illness was also reported in the town of La Gloria, Veracruz, between March 10 and April 6, 2009. About one fourth of the local population was affected but there were no hospitalizations [98, 136]. The first confirmation that a novel strain of type A influenza was circulating in México and affecting primarily a young population [41] was made in April 23, 2009 by the National Microbiology Laboratory in Canada. The report was based on two apparently unrelated cases, the woman from Oaxaca and a five year old child from La Gloria. An epidemiological alert was issued by The National Committee on Epidemiological Surveillance in México on April 16. On April 17, the United States Center for Disease Control started reporting cases of a new A-H1N1pdm strain. On April 18, the media spread the outbreak news while an ongoing alert on severe pneumonia cases
Figure 2.4: A-H1N1pdm epidemic outbreak in México by region 2009. A. Confirmed cases of A-H1N1pdm by State. Three different reports of confirmed cases dated June 4 and September 5, 2009, and January 4, 2010. Collection of States contributed differently to the reported total number of cases (aggregated three wave data) during the 2009-2010 pandemic. B. Difference between the reports shown in A.

had just been set in México City. On April 22, a large number of severe pneumonia cases were reported in México City, San Luis Potosí, and Oaxaca.
In response to the epidemiological alert, the government of México City implemented a series of social distancing measures that included school closures, closure of public spaces, and the cancellation of public events. The rest of the Mexican States implemented the same policy within days. School closures started on April 27 while non-essential economic activities were suspended on April 30. Schools reopened after May 10 and the population slowly resumed their normal activities as the summer arrived. By the time that social distancing measures were relaxed, the behavior of people was notably modified. For instance, many individuals in México were still wearing masks in public a year after the first A-H1N1pdm outbreak of 2009 was declared and hand sanitizers became part of the common office supplies.

Classes for kindergarten, elementary, middle, and high school typically end at around June 30 or earlier, marking the official start of the summer in México. Children resume school activities at the beginning of September and do not have another long break until mid December. These times during the year are regarded in this work as important landmarks for the time course of the epidemic and are modeled explicitly. The specific assumption made here is that infection rates decreased in México as a result of enforced social distancing measures, and as a consequence of the impact of school closures on contact rates \cite{103,148}. For instance, there were three surges in the reported cases of A-H1N1pdm in México during 2009, with peaks dated around April 30, July 1, and September 25 respectively (Fig.\ref{fig:2.3}). The first peak is in line with the implementation of social distancing measures and school closures by the Mexican authorities; the second occurred soon after schools for pre-college education closed for the summer; while the third took place during the fall of 2009. The rising phase of the third wave began about the time when schools returned to classes in the fall.
2.3.2 Vaccination during the pandemic.

The General Director of the World Health Organization communicated her decision to raise the A-H1N1pdm pandemic alert from phase 4 to phase 5 on April 29, 2009 [39]. It became clear soon after her announcement that the potential supply of vaccines was, at best, to be no more than 900 million [54]; that is, perhaps enough to cover 10-15% of the current world population [154]. The proportional distribution of vaccines would mean that each country would have vaccinations for about 10%-15% of its population. The number of vaccines that each country secured was in fact determined by the abundance or lack of financial resources. Massive vaccination against the novel A-H1N1pdm virus started in Canada, U.S., Northern Europe and other wealthy nations around the end of September of 2009; additional countries began to administer their share over the last months of the year. The first 650 thousand vaccines from an estimated 30 million vaccines, arrived in México on November 23, 2009 [95]. However, by the beginning of January 2010, the Secretariat of Health in México had approximately 13 million vaccines in hand, of which only 1.5 million had been administered to the general population [143]. Similar scenarios were repeated in other developing countries.

2.3.3 Modeling

Models are used to theoretically investigate the role of transportation flow and the impact of public health interventions (modulations of the infection rate of influenza) on the time course of an epidemic outbreak. The role of social distancing, school closures, transportation patterns, and vaccination policies on the time course of México’s epidemic is explored next. An extension of the [84] model is constructed following the general framework originally proposed by [128]. Our modeling framework resembles the modeling approach of [16], [81], and [84].
As stated previously, México is divided into thirty-one States and DF; México City is contained in DF. These thirty-two regions are regarded as nodes in a star-shaped, weighted graph with all nodes connected to DF, but not directly connected to each other. In the rest of this chapter the Mexican States will also be referred to as regions to facilitate the description. The regions are indexed 0,1,...,31, with DF (México City) index by the number 0. Regions are regarded as strongly and weakly connected to DF according to the data from Fig. 2.4A,B. More specifically, regions were ordered by their contribution to the initial total cases reported by June 4, 2009. Those regions with contributions larger than the median contribution up to June 4, 2009 are assumed to be strongly connected to DF. The rest of the Mexican States form the weakly connected group.

The infection rate is assumed to change as a function of social distancing measures, behavioral changes induced by the epidemiological alert, and school closures. The rates of infection and recovery periods are assumed depend on the region [16] while the interactions between individuals within a given region are assumed to be homogeneous. Populations in the so called influenza corridor are assumed to be more susceptible to the disease (possibly driven by higher contact rates); they are also assumed to recover 2 days later than in the rest of the México [88]. The results of our analysis are not sensitive to these last assumptions. That is, small variations on the values of these parameters do not change the general results presented here.

Infected individuals are assumed to go through an incubation period of 2 days before becoming infectious. Once infected, the recovery time was assumed to be between 5 and 9 days. Disease deaths are also included in the model. Infectious individuals are further divided into confirmed and unconfirmed cases. The unconfirmed cases include individuals who had symptoms of influenza but did not seek medical care, and also those who had an asymptomatic infection [10]. It is assumed that the traveling plans of an infectious individual were not affected by symptoms. Individuals are assumed to infect others during this
incubation period, at a lower rate than the infectious individuals. Also, recovered individuals gain permanent immunity against the novel A-H1N1pdm influenza virus \cite{133,12}. It is also assumed that there is a limited vaccine stockpile (see \cite{14}). People belonging to the susceptible, incubating, infected but unconfirmed, and recovered groups are eligible for vaccination. Daily vaccination rates are not assumed to be proportional to the populations receiving vaccinations. Instead it is assumed that only a maximum number of vaccines can be administered each day (constraints of the infrastructure) thus allowing a possible saturation in the demand for vaccines.

During the spring, summer, and winter breaks, the contribution to the total flow of people in and out of México City is assumed to be nearly the same for the strongly and weakly connected States. The strongly connected populations contribute more to the total flow of people in and out of México City the rest of the year. Note, for instance, that during the initial outbreak DF is followed by the strongly, and then the weakly connected regions, as ordered by their relative contribution to the first wave of the epidemic (report of June 4, Fig. 2.4). It is assumed that the net daily flow of people through DF is zero, with about half a million people coming into or out of México City every day.

The contribution of each region to the daily flow through DF is determined as follows: let $F$, $q$, and $N_i$ denote, respectively, the number of people that go through DF every day, the relative contribution of the strongly connected group to the total daily flow through DF, and the population size of the $i^{th}$ region. The daily contribution of the $i^{th}$ strongly connected region and the $k^{th}$ weakly connected region are written, respectively, as

$$q_i(t) = F \cdot \frac{q(t) \cdot N_i}{\sum \{N_j : j \in J_s\}}, \quad q_k(t) = F \cdot \frac{(1 - q(t)) \cdot N_k}{\sum \{N_j : j \in J_w\}}.$$  \hspace{1cm} (2.34) 

where $J_s$ and $J_w$ are index sets for the strongly and weakly connected regions, respectively. During the school breaks $q = 1/2$, and $q \gg (1 - q)$ during the rest of the year.
The flux between States given by transportation can be written with the aid of a time-dependent symmetrical matrix, \( Q(t) = (Q_{ij}) \) with entries defined as
\[
Q_{ij} = \begin{cases} 
  q_{ij}(t)/N_i & \text{if } i = 0 \\
  0 & \text{otherwise}
\end{cases}
\]
for \(0 < i, j \leq M = 31\). Here, \(Q_{ij}(t)\) represents the proportion of the population from region \(i\) that travels to region \(j\) per day.

The population of each region is divided into disjoint subgroups based on the individuals epidemiological states: \(S, E, C, U, R,\) and \(V\) represent, \(susceptibles, incubating, infected and confirmed, infected but not confirmed, recovered,\) and \(vaccinated\), respectively. A schematic of the relationships between the classes are as shown in Fig. 2.5.

![Figure 2.5: Schematic of the flow between compartments in each \(k^{th}\) state/city within Mexico.](image)

Each of the classes \(S, E, C, U, R,\) and \(V\) is indexed by region. The infection rate for region \(k\), \(\beta_k\), represents the mean infection probability per contact where \(\lambda_k(t)\) being
\[
\lambda_k(t) = g(t) \frac{\beta_k}{N_k} (C_k + U_k + \mu E_k)
\] (2.35)
where the parameter $\mu E$ takes values between 0 and 1 modeling a decrease in the infectivity of individuals who are within the incubation period. The contact rate is \textit{modulated} by a function $g(t)$ to capture \textit{social distancing and school closures} at specific dates during the year. The modulation of the infection rate was defined using a combination of sigmoid functions of the form

$$g(t) = \sum \{S(t; t_i, m) : i\}, \quad (2.36)$$

where

$$S(t; t_i, m) = A + \frac{B - A}{1 + \exp[m(t - t_i)]}, \quad (2.37)$$

with $0 < A < B < 1$. The time point at which the sigmoid reaches a value of $0.5(B - A)$ is $t_i$. The selected times $t_i$ are used as anchor points for the sigmoids, at or slightly after dates when social distancing or school closures occur. The rate at which the sigmoid function changes is controlled by $m$, that is $S$ is decreasing when $m > 0$ and increasing when $m < 0$.

For instance, a sharp downward sigmoid with $m = 10$ is used to represent a sudden drop in the contact rate as it happens when schools close or open, or if social distancing policies are imposed by the government. In contrast, a slowly increasing sigmoid with $m = 0.5$ is used to represent a slow recovery in the contact rate after social distancing was imposed.

The \textit{start of the epidemic} outbreak is modeled by inserting incubating individuals in the initially seeded regions are Oaxaca (in the south Pacific) and Veracruz (in the Gulf of México). These two regions are important ports of entry of tourists and goods from the Pacific and Atlantic, respectively, and were also the two regions where the first official cases of A-H1N1pdm were reported.

The \textit{vaccines} are assumed to be distributed on a daily basis with the system being able to deliver a maximum number of vaccines per day. The stockpiles are distributed as proportions of a total stockpile depending on policy. The number of vaccines in the initial
Table 2.2: Parameters for the A-H1N1pdm metapopulation SEUCR model, \((2.39) - (2.43)\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value/Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha^{-1})</td>
<td>incubation period</td>
<td>2 days</td>
<td>[106]</td>
</tr>
<tr>
<td>(\sigma_k^{-1})</td>
<td>recovery period for State (k)</td>
<td>7 days</td>
<td>[49],[111]</td>
</tr>
<tr>
<td>(\mu_I)</td>
<td>reduction factor for infectivity during incubation</td>
<td>0.5</td>
<td>Estimated, [110]</td>
</tr>
<tr>
<td>(\beta_k)</td>
<td>mean infection probability per contact for State (k)</td>
<td>0.95</td>
<td>Estimated, [111]</td>
</tr>
<tr>
<td>(\delta_x)</td>
<td>influenza-induced death rate for (x = {C, U})</td>
<td>(10^{-6})</td>
<td>Estimated, [111]</td>
</tr>
<tr>
<td>(p)</td>
<td>probability of confirmed case</td>
<td>([0.1, 0.3])</td>
<td>Estimated</td>
</tr>
<tr>
<td>(\hat{\nu})</td>
<td>maximum vaccines per day</td>
<td>([1, 160] \times 10^3/\text{day})</td>
<td>Estimated from Media [95, 54]</td>
</tr>
<tr>
<td>(F)</td>
<td>Thousands of people traveling to/from DF per day</td>
<td>([500, 1000] \times 10^3/\text{day})</td>
<td>México City government [1]</td>
</tr>
</tbody>
</table>

stock pile, \(\nu\) is adjusted to calculate the initial stockpile for each \(k^{th}\) State

\[
\nu_k = \nu \cdot w_i, \text{ for } i = 0,\ldots,31. \tag{2.38}
\]

The weights \(w_i\) are determined by setting a “vaccination policy”, which are proportionally distributed according to the relative population size in each region.

That is, \(w_i = \frac{N_i}{\sum_{\{N_k: k=0,\ldots,31\}}}\). The number of vaccines used per day, per class, within the \(k^{th}\) population, are denoted by \(\nu_{S_k}, \nu_{E_k}, \nu_{U_k}, \nu_{R_k}\) and calculated as follows: Given a maximum number of vaccines per day \(\hat{\nu}\), the number of vaccines that can be used each day
in the population $k$ is $\hat{v}_k = \frac{v_k N_k}{\sum_{i=0}^{31} N_i}$. Therefore, the number of vaccines that can be used in each class within a single region $k$ is a proportion of $\hat{v}_k$ determined by the number of individuals in that city, and the percentage of individuals in each class of that city. For instance, for the class $X$ in city $k$, the maximum number of vaccines available, $v_{Xk}$, is less than or equal to $\frac{\hat{v}_k X_k}{\sum_{i=0}^{31} X_i}$, for $X \in \{S, E, U, R\}$. The available number of vaccines for each region was calculated by subtracting $\sum \{\hat{v}_k : k = 0, ..., 31\}$ from the number of remaining vaccines for the region at each point in time considered in a simulation. At each point in time, the numerical implementation includes conditions that guarantee that the number of vaccinated people in a compartment does not exceed the number of people in the compartment. That is, at each point in time, $v_{Xk} < N_{Xk}$, for $X \in \{S, E, U, R\}$.

Equations. Having defined rates, transportation, and vaccination as above (Eqs. (2.34)-(2.38)), the system of equations describing the time-dependent change in region $k$ is

\begin{align*}
\dot{S}_k &= (Q_k - \lambda_k) S_k + \sum_{i \neq k} Q_{k1} S_i - \varepsilon(t) - v_S \quad (2.39) \\
\dot{E}_k &= (Q_k - \alpha) E_k + \sum_{i \neq k} Q_{i1} E_i + \lambda_k S_k + \varepsilon(t) - v_E \quad (2.40) \\
\dot{C}_k &= (Q_k - \sigma_k - \delta_C) C_k + \sum_{i \neq k} Q_{i1} C_i + \alpha p E_k \quad (2.41) \\
\dot{U}_k &= (Q_k - \sigma_k - \delta_U) U_k + \sum_{i \neq k} Q_{i1} U_i + \alpha (1-p) E_k - v_U \quad (2.42) \\
\dot{R}_k &= Q_k R_k + \sum_{i \neq k} Q_{i1} R_i + \lambda_k C_k + \sigma_k U_k - v_R \quad (2.43) \\
\dot{V}_k &= Q_k V_k + \sum_{i \neq k} Q_{i1} V_i + v_S + v_k + v_U + v_R \quad (2.44) \\
\dot{w}_k &= - (v_S + v_E + v_U + v_R) \quad (2.45) \\
\dot{D}_k &= \delta_C C_k + \delta_U U_k \quad (2.46)
\end{align*}

with variables $w_k$ and $D_k$ representing, respectively, the available vaccine stockpile and disease-induced deaths for the $k^{th}$ region. All population numbers are in thousands of individuals; the time is in days with $t_0$ equal to January 1st, 2009. The term

$Q_k = Q_{k0} - \sum \{Q_{0i} : i = 1, ..., M, i \neq k\}$ \quad (2.47)
denotes the proportion of people traveling from region $k$ to DF minus the proportion of people returning to region $k$.

2.4 Results

![Graph showing infected percentage over time]

**Figure 2.6:** Start of the pandemic. Data fit for the beginning of the first wave of the pandemic. The original data from confirmed cases (black curve) and the modeled curves (green curve) were normalized by total infectious cases, and the infection rate and incubation recovery periods ($\beta$ and $r_{infect} = \alpha$, respectively) were adjusted to fit the initial outbreak before the first peak. The resulting parameters are such that $\beta/\alpha \approx 1.9$. Day 73 corresponds to March 14. Day 117 corresponds to April 29.

2.4.1 Parameter estimation and start of the first outbreak

A reduced version of model (2.34)-(2.46) assuming no vaccination ($\nu = 0$) and no deaths was used to estimate parameters that best fit the curve of confirmed cases before
April 29, 2009. For this initial parameter estimation, it was assumed that there were no unconfirmed cases \((p = 0)\), and that the infection rate and total infectious period (incubation + infection recovery periods) of the system \((2.35)-(2.46)\) were assumed to be the same for all States. This yields the “aggregated” dynamics that would be generated by a single population model [16]. To do so, the simulated total of infective (incubating, confirmed, and unconfirmed, respectively, \(I, C\) and \(U\), for all regions) and the data for the first wave were normalized by their peaks so that both had a maximum of 1. The data examined does not let us test whether or not some populations in México were more susceptible to the novel A-H1N1pdm virus. However, the historical evidence on the patterns of respiratory disease support this assumption of same infection rate and total infectious period in all states[4]. Systematic variation of the incubation period and infectivity was performed to fit the slope of initial outbreak to the data up to the first of the three major epidemic peaks (Fig. 2.3 and also Fig. 2.6). The starting point of the epidemic was then shifted to find the time at which the initial increasing phase of the outbreak in the simulations overlapped with the initial phase of the normalized data. The death rate was carefully chosen to match the order of magnitude reported in official data (\(\sim 100s\) of people, not shown). From this initial estimation, our simulations suggest that the start of the epidemic occurred approximately between days 73 and 75, which correspond to March 15-17, 2009.

After fitting the model to the first outbreak, regional variations in the parameters were introduced by adding uniformly distributed random numbers between -0.1 and 0.1 to \(\beta_k\) and \(\sigma_k\) for each \(k \in \{0,\ldots,31\}\). The system \((2.34)-(2.46)\) was used to investigate the effects of transportation (weak/strong connections to DF), social distancing, and school closures on the development of the epidemic. As with the initial parameter estimation, it was assumed that there was no vaccination \((v=0, \text{Sec. } 2.4.2)\).

Simulations that include regional variations in the parameters (not shown) yield starting dates for the epidemic that are consistent with the initial estimations obtained assuming
homogeneity in the parameters. In particular, simulations in which the recovery period \( \sigma_k \) was 1 day longer in the influenza corridor and 1 day shorter out of the corridor (not shown) yield qualitatively similar average values for the mean infection probability per contact, \( \beta_k \). The overall results presented here are not significantly affected by the parameter variations mentioned above\[76\].

2.4.2 Influence of transport, social distancing and school closure on the time course of the epidemic

Transportation as a delay mechanism to generate multiple outbreaks.

The spread of A-H1N1pdm cases was not uniform across México. That is, not all States were hit by the epidemic at the same time, or with the same force (Fig. 2.4A-B, June 4 and September 4 reports, black and orange curves).

To test if land transport could be responsible for the delay observed in the epidemic outbreaks reported in the different Mexican States, simulations with the system \((2.34)-(2.46)\) were conducted assuming different contributions of the strongly and weakly connected States \(q\) and \(1 - q\), respectively) to the total daily flow from and to México City (Fig. 2.7). To do so, the number of confirmed cases was analyzed by region and the local spread of A-H1N1pdm during the first outbreak (Fig. 2.4, June 4 report) was considered explicitly in the derivation of the transportation matrix of the model (Eq. (2.35)). Figure 2.7 shows the total of infected people at each point in time (the sum of incubating \(I\), confirmed \(C\), and unconfirmed \(U\)) from the strongly and weakly connected States, respectively, in solid and dashed black lines. The total of infected people in the whole country is illustrated by a solid, thicker gray line. For all simulations presented here, it was assumed that the epidemic started in Veracruz and Oaxaca. Note the general aspects of the results presented in this section can be obtained assuming other starting states.
Figure 2.7: Influence of transportation on the time course of the epidemic from (2.39) - (2.43). The curves represent the total of infected people including the incubating ($I$), confirmed ($C$), and unconfirmed ($U$) groups. The solid and dashed curves are, respectively, the infected people in strongly and weakly connected populations to D.F. The dotted line is the epidemic curve in Veracruz and Oaxaca. The thicker gray line is the total of infected people. 

A. Simulation in which strongly and weakly connected populations contribute nearly the same ($q=0.5$) to the total traffic through México City. 

B and C. Simulations in which, respectively, 9 of every 10 ($q=0.9$, B), and 999 of every 1000 ($q=0.999$, C)) individuals traveling to and from D.F. come from a strongly connected region. Other parameters: $p=0.1$, $F=500$. 
A case in which all Mexican States contribute to the flow into and out of DF nearly proportionally to their population size \((q = 0.5)\) is shown in Fig. 2.7A. The small delay between the strongly and weakly connected is mainly due to the small difference between the contributions of strongly and weakly connected States and to a less extent, from the modest levels of heterogeneity coming from infection rates and recovery periods (assumed for the different populations). If the traffic weight \(q\) for the Mexican States in the strongly connected subset is increased (i.e., it is assumed that strongly connected populations contribute more than they would according to their proportion in the total population), the delays between the peaks become larger. Fig. 2.7B shows the case in which 9 out of 10 individuals come from the strongly connected States. Fig. 2.7C shows simulations in which 999 out of every 1000 individuals traveling through México City come from the strongly connected states. In general, the delay is an increasing function of \(q\). However, for the delay in the weakly connected regions to be similar to the delay of the secondary “wave” observed in the epidemic, the contribution of the weakly connected states to the total traffic has to be negligible \((q > 0.9999, \text{ not shown})\). The case in which only one in every 100 individuals traveling in and out of DF comes from one of the weakly connected states \((q = 0.99)\) is unrealistic but the delays in the total curve appear for \(q > 0.99\). Therefore, I conclude that transportation may contribute to create a delay between peaks of confirmed cases for different states, but the connectivity between DF and the 31 Mexican States alone does not fully explain the different peaks delayed by several weeks shown in the data curve of total cases.

**Social distancing and school closures.**

The first two local maxima in the epidemic curves shown in Fig. 2.3 occurred at times in which it is fair to assume that the contact rates suddenly decreased. In the first case, the peak is reached at, or soon after the Mexican government imposed social distancing
measures and school closures. In the second case the peak is reached around June 30, which marks the end of the school year. Similarly, the first two local minima occur at times in which contact rates among the population increase after a period of reduction. The first local minimum occurs at the end of May after the social distancing measures imposed by the Mexican government were relaxed and the population resumed normal activity; social distancing measures lasted for approximately 2 weeks, after which the population slowly resumed their normal activities. The second local minimum occurs near the end of August when the school year begins.

Remarkably, many of the States located within the historical influenza corridor that were hit by A-H1N1pdm during the first "wave", continued to be affected during the summer, but some seemed to be less affected than the weakly connected states during the summer, a trend that continued in some but not all States throughout the fall (see Fig. 2.4A,B). The epidemic, viewed from a whole-country perspective seemed to become milder during the summer and resumed to have a much larger peak and width at the end of the summer, which marks the end of the school break.

To test the possibility that social distancing and school closure had an impact on the epidemic, and more specifically, whether these two factors contributed to the generation of the second and third outbreaks, it is assumed that the changes in contact described in previous paragraphs are captured via the time-dependent modulation of the infection rates in each state, $\lambda_k$, $k = 0, \ldots, 31$. To introduce a time-dependent modulation in agreement with the dates at which government policies were implemented and with the school calendar, we combined sigmoid functions (Eq. (2.37)) to decrease and increase the rate of infection $\lambda_k$, at specific points in time (see also Fig. 2.8A). The measures implemented by the Mexican government during the last days of April 2009 (before day 120) were captured by modulating the contact rate with a decreasing sigmoid with very steep amplitude. The end of the social distancing policy and subsequent return to normal activity was represented by an
increasing sigmoid with a slower slope compared to that of the implementation of government policies. The final value of this second, increasing sigmoid function was such that the infection rate could be lower than the initial infection rate. The lower value is justified by the fact that behavioral changes occurred during the days and months following the start of the epidemic. Similar constructions were used to model the end of classes at the end of June (around day 180) and the reopening of schools in September (before day 240). The resulting modulating function for the infection rate, \( g(t) \), was varied by changing the slopes and final values for each of the sigmoid functions. The last value of this modulation function reflects long-term behavioral changes that occurred during the beginning of the epidemic Fig. 2.8A.

As illustrated in Fig. 2.8B1-B3, the government policies implemented at the end of April do explain the decrease of the epidemic outbreak observed in the data for the first wave. Further, the second “wave” can be generated by several combinations of the slope and inflection time of the sigmoid used to resume of activity in May (after day 120). Furthermore, our simulations suggest that the second “wave” is the result of a rebound in the epidemic in which the susceptibles from the weakly connected States played a significant role. Our simulations suggest that second “wave” was also cut short by the reduction in contacts at the end of the school year. The start of classes for the fall in Mexico is typically around September 1. The third “wave” of the A-H1N1pdm in México starting around then. For this reason, the mechanism of suppression and recovery of the infection rates described in the last paragraphs was used again, in this case with sharp slopes representing the sudden changes in transmission that may occur during closure and reopening of schools. Taken together, these results suggest that the implementation of measures that decrease the contact rates in combination with the school calendar, as it was the case in México, can have a significant mitigating effect on the spread of the influenza.
Figure 2.8: Social distancing and school closures can create multiple outbreaks. A. The different graphs show different modulations of the infection rate after behavioral changes occurred. B1-B3. Different time courses for the percentage of A-H1N1pdm cases. Panels B1, B2, and B3 correspond, respectively, to the curves g1-g3. The thick curves are the sum of all infected individuals. The strongly and weakly connected populations are shown in solid and dashed black lines, respectively. The values of the mean infection rate after behavioral changes have occurred is noted in the right upper corner of each plot and correspond to the curves g1-g3 shown in panel A. The slope of the modulation function g(t) after the relaxation of social distancing measures was 0.3. Other parameters: t₀=78 for Oaxaca and Veracruz as starting States. Other parameters as in previous figures.

The patterns shown by the strongly and weakly connected States in the different scenarios shown in Fig. 2.8B1-B3 also reflect nontrivial aspects of the epidemic. For instance, if the infection rate recovers to a small proportion of what it was originally (Fig. 2.8A, line labeled “g1”, g(t) ≈ 0.5, t > 300), infections would occur at a very low rate after the government intervention. In this case, the model predicts that there would be only two large “waves” during the year with one outbreak of small amplitude during the summer, and a third “wave” occurring after a long delay (Fig. 2.8B1, thick gray line). In cases like these, the strongly connected populations would experience the bulk of the epidemic
first (black, solid lines), followed by the weakly connected populations during the second “wave” (black, dashed lines).

As the recovery in the infection rate increases after the social distancing is relaxed, a second “wave” starts to emerge during the summer (Fig. 2.8B2), followed by a third wave that still occurs in the fall/winter ($0.3 < g(t) < 0.8, t > 300$). The contribution from the weakly connected States to the second “wave” is always more prominent than the contribution from the strongly connected States. Both strongly and weakly connected States contribute during the third “wave” of the fall/winter. However, the third “wave” starts first in the weakly connected States, followed by growth in the strongly connected States. If the final infection rate is large enough, the third “wave” starts at the strongly connected States (not shown). This occurs in part because during the second “wave” the weakly connected States are affected the most. That is, the (still large) susceptible population in the weak states is the driver for the second “wave”. If the infection rate recovers almost fully (Fig. 2.8B3, $g(t) \approx 0.9, t > 300$), the second “wave” increases in size until the third “wave” does not occur anymore. Not surprisingly, if there are enough susceptibles after a decrease in contact that caused a decay in the epidemic curve, and there are no further interventions (e.g., vaccination), there will be a rebound “wave” whose size depends on the size of the first outbreak.

The number of secondary outbreaks is highly dependent on the size of the first “wave”, and the timing and impact of subsequent interventions. In particular, the size of secondary and later “waves” depends on the similarity between infection rates before and after each decrease in the incidence curves. In the context of the above simulations, if the behavioral changes just mentioned result in a reduction of the infection rate of approximately 35% or more, then the rebound “wave” can take several months to occur (Fig. 2.8B1). In contrast, if the reduction is less than 35% a significant rebound “wave” can take as little as 2 months to occur (Fig. 2.8B2). If the decrease in infection rates is about 10% or less the pool
of susceptibles is almost completely depleted during the second (rebound) “wave”, thus eliminating the possibility of a third “wave” (e.g. Fig. 2.8B3).

2.4.3 Time course of epidemic by State.

Now the simulations of the dynamics of the epidemic by State using parameters that resulted in three “waves” with a qualitatively similar time course shown in the data (Figs. 2.3 and 2.8B2) are described. For instance, the second “wave” is milder and wider than the first one, and starts shortly before the summer. Also, the third “wave” is the strongest and occurs during the fall. An example of the temporal profile of the epidemic by State is shown in Fig. 2.9.

Local transportation patterns and changes in contacts during the epidemic as determined by social distancing measures and school closures are sufficient to generate specific aspects displayed by the data, including the delays between outbreaks in different populations (compare to Fig. 2.4). Importantly, these factors do not generate the patterns observed in the data when only transportation or behavior-dependent contact rates are considered in isolation. Fig. 2.9 clearly illustrates that the “waves” result from nonuniform aggregation of cases originated in the different Mexican States at different times during the year. Importantly, the change in the transportation patterns during the summer break underlies the contribution of the pool of susceptibles in the weakly connected states to the second outbreak. In a similar way, the change in the transportation pattern prior to the return to classes in the fall favors the contribution of the susceptibles in the strongly connected populations to the third outbreak. It is during this third outbreak that most States experience an outbreak without interruptions. Importantly, these simulations also highlight the possible risk of a more prominent rebound “wave” of influenza after social-distancing or school closure interventions if no further vaccination or other protective measures are implemented.
Figure 2.9: Percentage of cases by State assuming the first cases were in Oaxaca and Veracruz. The States have been ordered with respect to their population size.
In the next section, the vaccination stockpile, \( \nu \), is assumed to be nonzero and the arrival date of the vaccines is systematically varied to study the effects of introducing vaccination at different points in time during the epidemic (Sec. 2.4.4). The idea is that in the event that a very contagious virus emerges, interventions as the one made by the Mexican government could help avoid saturating the demand for resources destined to help the population when the initial outbreak and the next school closure are distant in time (at least 4 weeks). Further, a mitigation strategy to further constrain the spread of influenza through vaccination during the school break is conceivable by taking into account the dynamics shown in Figs. 2.8 and 2.9.

2.4.4 Role of vaccination

The simulations in Fig. 2.8 suggest that social distancing and school closures had a delaying effect on the transmission of the 2009 pandemic influenza virus, thus creating a window of opportunity to implement preventive measures such as vaccination. Therefore, I decided to examine the role that vaccination could have had in mitigating the last “intervention-free” outbreak.

Since it was clear from the beginning of the pandemic that supplies would be short for most of the countries in the world, simulations using the system (2.34)-(2.46) and assuming a limited number of vaccines are available are conducted. In this respect, the Mexican government announced that they would have a stockpile of nearly 30 million vaccines [136]. However, only a small fraction of the planned stockpile became available in November of 2009 (3% of 30 million). By mid January, only approximately 1.5 million had been distributed among the population [136].

To carry out the simulations, vaccination was introduced at different dates after the social distancing measures and school closures implemented by the Mexican government in April were suspended. The parameters for the simulations were the same as in Fig. 2.8B2.
Figure 2.10: Democratic vaccination for different arrival times. Vaccination of a maximum of 100,000 individuals per day from a stockpile of 30 million. A-D. Time course of the epidemic assuming starting vaccination times at days 200, 250, 300, and 350, corresponding, respectively, to July 18, Sept 5, Oct 25, and Dec 15. Vertical axis, percentage of the population. Parameters same as in Fig. 2.8.

and Fig. 2.9 with a stockpile of 30 million vaccines and a maximum of 100,000 vaccines administered per day. For the simulations shown in Fig. 2.10, vaccinations were distributed throughout the different States in México according to their population size. That is, vaccination was not assumed to be proportional to the populations that received the vaccines as typically assumed in previous models (e.g., [139]). Simulations were carried out assuming that every person, except those who had been confirmed as SOIV-AH1N1 cases, received

41
the vaccine. Vaccines were assumed to be distributed among the population as soon as they arrived.

The effects, starting vaccination on July 18, Sept 5, Oct 25, and Dec 15, are shown in Fig. 2.10. These simulations suggest that if vaccination started at least in September, the impact on the epidemic outbreak would have been minimal (compare panels A and D in Fig. 2.10). On the other hand, if vaccination is introduced before November, the effects on the incidence curves are more drastic and become noticeable on or before September 5, at the beginning of the fall scholar term. An estimate of the effect of introducing vaccination at different times was calculated by dividing the integrals of the incidence curves for each of the arrival times by the integral of the incidence curve when no vaccination was introduced (not shown). The maximum decrease obtained with the stock pile and maximum number of vaccines that produced Fig. 2.10A was approximately 15% for the simulations performed here.

In conclusion, the early arrival and application of vaccines could have had a noticeable but not too strong mitigating effect on the spread of the disease; even for stockpiles with as many vaccines as 30 percent the total population; a quantity that corresponds to the total of availability of vaccines originally announced by the Mexican government [92]. Further, our simulations indicate that the administration of the vaccines would have resulted in a significant waste after November since no visible effects on the size or time course of the epidemic curve could be observed in this case.

2.5 Discussion

The simulations presented here explain the existence of multiple “waves” in the data in terms of the combined effects of transportation patterns and behavioral changes. The behavioral changes are captured by considering the reductions in contact from social distancing measures implemented by the Mexican government, motivated by fear, or due to
the school calendar. As expected, local transportation without a decrease in the infection rates (social distancing) results in single epidemic outbreaks; recall that the pattern of traffic is described by a star-shaped graph with two sets of populations contributing differently to the daily flow through the “center” node (i.e. the hub). The macroscopic patterns displayed by the regional and whole-country data may thus be a consequence of the differences in flow between the strongly and weakly connected states, and the drops in contact rates. From a macroscopic (whole-country) perspective, the model shows three “waves” when transportation and modulation of contact rates are combined (Fig. 2.8). However, when examined in detail, the “waves” result from the aggregation cases occurring non-uniformly with respect to location and time (Fig. 2.9). In addition, the multiple “waves” do not occur because of differences in the recovery time or susceptibility to infection due to geographical factors. These results provide strong support to the hypothesis that a combined effect of local transportation, social distancing, and school closures can produce multiple macroscopic (whole-country) “waves” for the same epidemic, as observed in México during 2009 (Fig. 2.3).

2.5.1 Effects of behavioral modulation and intervention

Our simulations unravel different possible scenarios in which influenza epidemics can occur for qualitatively similar time dependent changes in the infection rate (Fig. 2.8). Remarkably, the two U-shaped modulations in the infection rate used here did not always result in three large “waves”. The “waves” in the cases considered here occur because the implementation of social distancing and school closure measures pause, but not stop, the spread of the disease. The novel A-H1N1pdm considered here is non-seasonal, so there are, a priori, no reasons to believe that the epidemic was mitigated by changes in temperature or weather at large. Our simulations show that the number of rebound “waves” depends on the number and steepness of U-shaped modulations in the infection rates but also on the
final value of the contact-modulating function $g$. As a rule of thumb, a significant rebound in an epidemic outbreak can be observed after an intervention if, aside from the timing the intervention before the epidemic peak, contact between individuals is decreased and then allowed to increase to similar, if not smaller values relative to the original infection rate. This result highlights the importance of quantifying behavioral changes and the speed at which these changes occur during an epidemic outbreak [30]. Therefore, it would be beneficial for future epidemics to obtain data that helps estimate the dynamics of contact.

The social distancing measures implemented in Mexico were very strict, much stricter than would have been imposed in other countries, and the behavioral changes (hand washing, use of masks in cold days or crowded places, television and newspaper adds, jokes, etc.) were still present during the summer of 2010 (personal observations of one of my collaborators). To the best of our knowledge, I interpret the first local maximum in the simulated epidemics as the result of reduced contact. I believe that the fall "wave" was actually reached in what can be think of as an outbreak free of intervention. The epidemic does not hit all the States during the first two “waves”, but both weak and strongly connected States are affected during the third wave. This pattern is consistent with the data globally and locally (by State), but it is worth to remark that it is highly dependent on the behavioral modulation captured included in the infection rate. For instance, there would have been no third wave during the year if the behavioral changes in the population were short-lasting ($g$ with a final value close to one and a fast positive slope after a decrease).

Government intervention during the initial stages of an epidemic outbreak can help to mitigate the spread of the infection. Governments can use this strategy to initially mitigate the spread of influenza while resources become available. The price to pay for the initial mitigation may be an increased likelihood of a second, or even a third more prominent outbreak. A disturbing possibility is that if the necessary resources are not available when the full outbreak occurs, the consequences can be significant depending on the severity
of the disease. In addition to the possible financial implications of a sudden reduction in the contact rates via the implementation of social distancing policies, an additional burden on the health care system could result from untimely interventions or interventions not followed by appropriate mitigation strategies. Therefore, mild virulence of the 2009 pandemic should be regarded as a luck factor that may not be present in future pandemics.

2.5.2 Global dynamics emerged from local interactions

The separation of States into strongly and weakly connected based on the initial report of the epidemic was partially consistent with historical evidence about a corridor of epidemic transmission [4]. Remarkably, assuming this initial division in the contribution to the flow through the central node in our model (DF) also resulted in local dynamical patterns of spread during the year that are consistent with the data separated by State (Fig. 2.8 and 2.9). Note that those States affected during the initial outbreak “wave” that were not in “the” influenza corridor belong to a subset of populations in México that have close commercial, touristic, and other interactions with México City. For instance, the State of Veracruz is the largest contributor of import/export goods to México and does not belong to States in “the” corridor. The simulated epidemics in those States are in reasonable agreement with the existing data, suggesting that the classification of States into weak and strong is an important factor in addition to the centralized traffic assumed in the transportation rates.

In Mexico, the social distancing measures were broad enough to affect the whole population. If the age profile of the traveling population was similar to the age profile of the population as a whole, the effect of age on travel would probably be of little importance. With less stringent distancing measures, school closures could have an effect, as the part of the population most involved in disease transmission is formed by students, and thus might have a larger effect than a homogeneous mixing model would indicate. Therefore, the question of whether school closures translated into a real decrease in contacts, as was
probably the case in Mexico, or whether they translate into more time at day care centers or the mall, as might have been the effect in the US or Canada could be asked. In fact, it could be the case that, in addition to the changes in transportation, there was an increase in contact during the summer breaks. However, based on the model, such an increase would have happened mostly in the weakly connected States. In addition, the model was built assuming that people within each State would randomly mix. For these reasons, I conclude that the school closures did have an impact on the time course of the epidemic, but this impact was indirect, as the flow of transportation changed, and with it, the availability of susceptibles. Age structure was significant for H1N1, and its effects have been documented elsewhere in the case of single populations [109]. The effects of including age structure in the model presented here would be helpful to study questions related to how data might be aggregated over time in different parts of the population, and in particular, to tackle questions related to the direct or indirect role played by the school closure on the transmission dynamics.

2.5.3 Timing the administration of a limited vaccine stockpile

The simulations presented in Figs. 2.8 and 2.9 suggest that the school closures due to the calendar can be used as reference time points to implement prevention strategies in anticipation of secondary epidemic outbreak. For instance, depending on the initial rate of change of the incidence in the outbreak, if the starting point is too far from the date of the next school break, it might be worth having a short lasting intervention like that implemented by the Mexican authorities. Such interventions might be costly from a financial perspective, but may prevent a challenge to the health care system that could be catastrophic. Importantly, as suggested by our simulations, such interventions will also cause rebound “waves”. As a consequence, the interventions aimed to decrease contacts among the population should be thought of as a delay mechanism that should be followed
by prevention strategies such as vaccination; delaying the spread also prevents people from acquiring immunity. The timing of the prevention strategies should be in sync with the times of the major school closures (summer, winter, and possibly spring breaks) and could be improved if coordinated with ongoing surveillance [44].

Our simulations corroborate in a quantitative way a prediction rooted in common sense: if the available vaccines are given to the population before the (third) epidemic “wave”, the number of infected people will decrease dramatically, and by extension, less vaccines will be wasted. Our model can be very useful in the sense that possible scenarios can be planned if data is used together with the model to produce short-term predictions. For instance, our simulations suggest that the best time to vaccinate people in the case of México would have been during the summer. As a general rule of thumb, these results can be generalized as: “vaccination campaigns are more effective during school breaks”. The reason, as suggested by our simulations and by existing data [103], is that the school breaks can be assumed to slow down epidemics of influenza (and similar viral diseases); on the flip side, the return to classes accelerates the spread of influenza. In fact, past studies have suggested that mass immunization of school children before vacation breaks would be an appropriate strategy for reducing the spread of influenza within communities [69, 71, 153, 152]. There are several reasons for targeting this group. First, school children are an easy group to reach and offer an excellent opportunity for mass immunization. School-based immunization programs or health fairs would preclude the need for a visit to a physician’s office to receive the vaccine. Furthermore, children and schools are the major pathways that spread influenza to families and neighborhoods.

Importantly, with the current infrastructure to make vaccines, the vaccination strategy suggested here can only be conceived assuming a morbidity of the novel virus comparable to that of seasonal influenza. This strategy can be combined with ongoing surveillance [44] and generalized for its utilization in Latin America and other places where local transporta-
tion is similar to México. It is important to note here that the vaccine was not available in time to have much effect for the A-H1N1pdm epidemic, even with measures that postponed later waves. This will continue to be an important general feature of pandemics, unless ways to develop vaccines faster are found.

2.5.4 Fitting procedure, emergent properties, and modeling vaccination

The parameter ranges used in the simulations were obtained by fitting the rate of change in simulations to the data. Since the confirmed cases present in the data are just a proportion of the actual cases, the fitting was done by first scaling the simulations and the data to have a common maximum and only the rate of change during the initial upstroke of the epidemic was considered. Errors resulting from this estimation procedure could be carried into our simulations and possibly bias our interpretation of the results. Two factors are reassuring in this respect. First, the parameters obtained in the fitting process were not disproportionate or in disagreement with estimations of the contact probabilities made by other groups \[80, 47, 30, 14\]. Second, based only on the fitting to the initial outbreak dynamics, I obtain qualitatively similar time courses for epidemics of the whole-country and also State by State.

México is a country with many different environments, which in principle could affect the predisposition of the population to different immunological insults \[89, 90\] (see also \[7, 141\]). In particular, the recent trend of urbanization and aging of the Mexican population could be increasing the vulnerability to acute infectious respiratory diseases \[4\]. However, as noted before, the differences in the recovery time and infection rate by State were not enough to produce drastically different scenarios. In addition, the qualitative observations of the study presented in this article depend more on the modulation of the infection rates by behavioral changes than on the specific rates of infection or recovery. For these reasons, I
am confident that our parameter estimation is within acceptable ranges, and that our results are not the consequence of making unrealistic assumptions.

Progress on the way vaccination is modeled is presented here and expanded on Chapter 3. In this work a vaccination scheme in which not there only was a limit for the total number of vaccines available, but also, one that allowed saturation in the daily demand for vaccines is implemented. To do so, the number of people that can be vaccinated per day was calculated by first setting up a policy for the distribution of the stockpile by State, and with respect to that distribution policy, a maximum number of vaccines per State per day was calculated. The actual number of vaccines given per day was either the maximum per day, or less depending on how many people were present in each State, and each class. This scheme is very different in comparison to the typical assumption that a proportion of the population gets vaccinated at any point in time [139, 110, 111].

2.5.5 Future directions and concerns raised by simulations

The results obtained in this work could have been obtained with a simpler model only containing three classes, namely, unprotected, infected, and recovered. However, since the difference in computational cost between a simpler model and the one used here was hardly noticeable using the code and the laptop computers described in Methods, I decided to numerically solve Eqs. (2.34)-(2.46) which allow the extension into a model that enables the calculation of wasted vaccines and tackle other important issues.

For instance, there is a big problem with influenza data since many, perhaps most, cases are mild enough not to be recorded or noticed. Therefore, a significant fraction of disease transmission comes from people that are asymptomatic in this sense. The presence of a population of asymptomatic or unconfirmed cases has been documented to be non-negligible [10], and it is believed to be close to 80% or 90% of the infected people [60].
The second and the third “waves” observed during 2009 could be explained by drifts or shifts. Our model does not include the possibility of relapse, or that a different virus(es) indistinguishable with the current methods from the original one for which the recovered population would not be completely immune. Drifts or shifts could explain part of the second and the third “waves” observed during 2009. This is a direction that requires more exploration. A priori, based on an intuition fixed by the simulations presented here and on the observations made about the different contributions to the number of confirmed cases by the different States, our interpretation is that the multiple “waves” resulted mostly from the combined dynamics of local transport and changes in contact rates. In other words, the magnitude of the incidence curves may change if different immunities are taken into account, but not the general trends related to the number of waves and their timing with respect to the events that change the probability of contact between individuals. The proportional distribution scheme used here can be modified to accommodate rules or policies not necessarily based on the size of the local populations. For instance, the distribution of vaccines in this model can be defined so that it reflects different levels of geographical isolation, or other differences due to the political and economical constraints (say, due to the existence of “guerrilla” in some areas of the country, budget for cities as opposed to whole States, etc.).

The effectiveness, supply, and capability of distribution of vaccines are aspects that have not been addressed in this work. Parameters that capture these features are hard to estimate for several reasons. There have been some problems with some of the stockpiles of the vaccination for the novel A-H1N1pdm virus. For instance, the week of November 16, the pharmaceutical company GlaxoSmithKline asked the Canadian authorities to recall a stockpile of about 176 thousand vaccines of the same kind that were supposed to arrive to México [95]. The reason for the recall in 6 of the 13 Canadian provinces and territories was suspected to cause more adverse reactions than normally expected (1 in 20 thousand).
In consequence, there are many uncertainties about the supply of the vaccination and at this point it is hard to estimate the effectiveness of the vaccines against a new virus \[51\]. In addition, there have been several reports about antiviral resistance in some patients to oseltamivir (Tamiflu) \[79, 105, 96\]. Regardless of the issues discussed above, the uncertainty about the novel A-H1N1pdm outbreak seem to have been resolved in the sense that the epidemic did not have devastating effects in terms of mortality and the infection seems to be mild in comparison to other influenza types and subtypes \[63, 117\]. These studies and others aimed to understand the transmission dynamics of highly virulent diseases like smallpox \[35\] are extremely important to assess the risk of threats like the deliberate release of biological agents among others.

### 2.5.6 Final remarks

Our results support the notion that the massive governmental intervention measures at the beginning of April did mitigate the spread of influenza but as a result exhausted the supply of susceptibles. In fact, the first two “waves” were interrupted by social distancing policies, the closing of schools in the summer, and altered by delays in transportation “effectiveness”. The only intervention measures during that third “wave” came from the vaccination of a relatively small group of people that started at the end of November. In other words, México’s transportation structure and the non-uniform flow of individuals over this network contributed significantly to the generation of three outbreaks; the third significantly larger (and over a longer time span) than the first two. The third outbreak of infection (Fig. 2.3) can therefore be thought of as the result of a fully operational network. The synergistic interactions between transport flow and modulation of the infection rate by social-distancing and school closures seem enough to cause the number of A-H1N1pdm cases to aggregate differently for the different States, thereby forming multiple peaks of different sizes (Fig. 2.3).
To summarize, social distancing and school closures have a delaying effect in the spread of the epidemic. However, the model suggests that an unprotected population is likely to suffer from a secondary or even a third harder epidemic outbreak in comparison to the initial wave if no further mitigation strategies are embraced. Governments can use a strategy based on this knowledge about the possible delays induced in an epidemic outbreak strategy to initially mitigate the spread of influenza while resources become available, but an alarming alternative is that if the resources are not available when the full outbreak occurs, the consequences can be significant depending on the severity of the disease. The A-H1N1pdm virus that caused the 2009 pandemic has been mild in terms of infection and mortality. As reports about transmission and recombination of different influenza viruses increase, and in view of the recent pandemic, which was caused by a novel form of the virus having portions of avian, porcine, and human A type influenza viruses, it may be worthwhile to destine more resources to increase the capacity of mass production of vaccines and treatment in preparation for a possibly more severe influenza epidemic in the future.
Chapter 3

MITIGATING EFFECTS OF VACCINATION ON INFLUENZA OUTBREAKS GIVEN CONSTRAINTS IN STOCKPILE SIZE AND DAILY ADMINISTRATION CAPACITY

Influenza viruses continue to be a major cause of hospitalizations and deaths worldwide due to annual seasonal epidemics [42, 127, 132, 131, 137, 147] and less-frequently occurring, but potentially more severe, pandemics [115, 132, 131, 138, 158]. Vaccination is one of the best tools health professionals have to prevent or mitigate influenza outbreaks [158, 159]. Each year, vaccines are developed based on predictions about which influenza strains are likely to be circulating [126, 158], and distributed prior to and during the influenza season. When there is good correspondence between the vaccine strains and the circulating strains, vaccination programs are highly effective in decreasing influenza-related hospitalizations and deaths, particularly in high-risk groups such as the elderly and children [68, 108, 124]. Vaccination prior to the first outbreak of a pandemic is usually not possible, due both to the unexpected nature of these outbreaks and the novelty of the viral strain responsible [115, 138, 158]. However, many influenza pandemics are characterized by multiple waves separated by months or years, which can allow time for vaccination development and administration in an attempt to mitigate subsequent outbreaks [56, 66, 93, 102, 162]. Unfortunately, resources are limited and many countries already struggle with insufficient doses of vaccines, as well as shortages in medical supplies, facilities, and workers to administer vaccines [55, 112, 114]. Resource limitations are likely to be even greater, and more widespread, in the case of a pandemic [55, 87, 114, 138, 163]. Even in the case of adequate resources, administration capacity is still limited; medical staff and facilities can only give a maximum number of vaccines per day [2, 36, 40, 118, 119, 151], and that number may be small relative to the size of the population under consideration.
Understanding how vaccination resources can affect the size and dynamics of influenza outbreaks is crucial to outbreak preparedness [158]. Yet, many modeling studies examining the effectiveness of vaccination in mitigating outbreaks are based on questionable assumptions about supply and administration of vaccines. First, the assumed vaccine stockpiles are often very large relative to the size, and sometimes the location, of the considered population [64, 97, 110, 164]. Second, previous studies modeling vaccination during a pandemic assume that vaccines are administered only to susceptible individuals [31, 44, 45, 58, 61, 91, 110]. This is problematic for several reasons. For one, medical professionals are rarely able to determine an individual’s epidemiological status (i.e., susceptible, infected, recovered) prior to vaccination. Laboratory testing of individuals seeking vaccination is not required, nor recommended, for general use or clinical decision-making [37]. Also, individuals may not be aware of their own epidemiological status, either because they are asymptomatic or are unsure that an illness they recently experienced was due to the virus in question. Therefore, the only individuals who are likely not to seek or receive vaccination are those who are infected and symptomatic, and it is possible that many individuals with existing immunity get vaccinated. Considering only the susceptible population may underestimate the overall number of vaccines used, including those that are potentially wasted, during a vaccination campaign [121]. Finally, the administration of vaccines is usually modeled by specifying that a proportion of the population is vaccinated per day [14, 31, 44, 45, 53, 58, 61, 64, 65, 67, 91, 97, 110, 125, 145, 164]. Such proportions may represent a very small or large number in comparison to the number of vaccines that can reasonably be administered on a daily basis. Although fixed-rate vaccination models exist (e.g., [24]), the formulations of which we are aware are not based on daily administration constraints. In practice, vaccination clinics are planned and run based on the number of people that can be vaccinated per day, given the availability and capacity of equipped facilities and medical professionals [2, 36, 40, 118, 119, 151]. The concern is that modeling
based on the assumptions discussed above may lead to inaccurate conclusions about the effects of vaccination programs on the size or progression of influenza outbreaks.

We developed an epidemiological model to investigate the spread of influenza that incorporates realistic constraints on vaccine supply and administration capacity. Our model allows the simulation of specific limits on the total number of vaccines available, the number that can be administered per day to a single population, the relative supply to different epidemiological classes, and the effects of the timing and duration of vaccination campaigns. Wherever possible, the values of these parameters were based on real and simulated data (see Table 3.1) from sources such as the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the Macroepidemiology of Influenza Vaccination (MIV) Study Group, and a variety of international researchers studying vaccine supply and administration. The vaccination parameters in our model can also easily be adjusted by public health officials or communities looking to examine the mitigating effects of vaccination given their specific supply and administration constraints.

We refer to our model as the non-proportional model of vaccination, since the administration of vaccines is limited by a daily maximum number rather than a proportion of the population, and compare the results to those obtained when vaccination is implemented using a proportional scheme. The results show that though the proportional and non-proportional models predict similar epidemics for a few different vaccination scenarios, there are regimes under which important differences in the dynamics of the two models are observed. Specifically, given particular combinations of vaccination campaign duration and daily supply limit, the proportional model predicts epidemics with larger final sizes and earlier peak times than those predicted by the non-proportional model. In addition, the proportional model predicts epidemics that last days less than in the non-proportional model. We argue that the non-proportional model provides more accurate information about the vaccine stockpiles and human resources needed to deal with real influenza outbreaks. Fur-
thermore, our model can be used by government and medical officials to create customized pandemic preparedness plans based on the resources available to their specific communities.

3.1 Methods

3.1.1 Assumptions of the model

We developed an SIR-like epidemiological model to study the spread of influenza [84] (for a review of these models see [46]). The model describes the dynamics of susceptible (S), infected (I), recovered (R), vaccinated (V), and deceased due to infection (D) populations. In turn, the infected individuals are divided into two groups, infected confirmed (IC) and infected unconfirmed (IU). The confirmed group represents those individuals who test positive for influenza in a medical facility, while the unconfirmed group includes either asymptomatic individuals, or those whose symptoms are not severe enough to seek treatment and therefore never get tested.

Infections are assumed to be caused by an outbreak of a single influenza viral strain (e.g., pandemic H1N1 of 2009 [5, 52, 94]). A small number of individuals become infected at a time \( t = t_0 \), referred to herein as the initial outbreak (e.g., the first H1N1 cases in the town of La Gloria in Veracruz, Mexico). For simplicity, all individuals in S are assumed to have an equal susceptibility to infection; age-related susceptibility and prior immune history are not considered. Individuals become infected through homogeneous mixing, at a rate proportional to the number of contacts between infected and susceptibles. Since several studies have shown a relationship between the degree of symptoms and the extent of viral shedding [32, 48, 62], we included a parameter, \( \alpha \), to simulate potentially reduced infectiousness of those in population IU. For most simulations \( \alpha = 0.5 \), but using different values of \( \alpha \) did not significantly change the results (data not shown).
Table 3.1: Parameters used in simulations for Non-Proportional Vaccination equations (3.1) - (3.7) in Chapter 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$</td>
<td>probability of being confirmed</td>
<td>0.2 or 0.65</td>
<td>low probability [60, 104], high probability [32]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>relative infectiousness of unconfirmed class</td>
<td>0.5</td>
<td>based on reduced viral shedding [32, 48, 62]</td>
</tr>
<tr>
<td>$t_a$</td>
<td>start of vaccination campaign (day)</td>
<td>20, 50, or 80</td>
<td>set to occur 10, 40, or 70 days after $t_0$</td>
</tr>
<tr>
<td>$t_b$</td>
<td>end of vaccination campaign (day)</td>
<td>Variable</td>
<td>depends on campaign start and duration</td>
</tr>
<tr>
<td>$t_d$</td>
<td>depletion of vaccine stockpile (day)</td>
<td>Variable</td>
<td>depends on stockpile size; see $\bar{v}$</td>
</tr>
<tr>
<td>$t_0$</td>
<td>starting point of the epidemic (day)</td>
<td>10</td>
<td>arbitrary</td>
</tr>
<tr>
<td>$b$</td>
<td>mean probability of infection per contact</td>
<td>0.476 or 0.346</td>
<td>adjusted as function of $p$ so $R_0=2.0$; see seasonal/pandemic $R_0$ values [42, 149]</td>
</tr>
<tr>
<td>$c$</td>
<td>rate of recovery (1/days)</td>
<td>1/7</td>
<td>based on symptoms, viral shedding, cytokine levels [32, 49, 73]</td>
</tr>
<tr>
<td>$N$</td>
<td>total population size</td>
<td>$10^8$</td>
<td>e.g. Mexico, Phillipines [142, 156]</td>
</tr>
<tr>
<td>$\bar{v}$</td>
<td>vaccine stockpile size</td>
<td>$30 \times 10^6$</td>
<td>based on 30% coverage; see vaccine production/distribution data [74, 112, 113]</td>
</tr>
<tr>
<td>$\bar{v}_D$</td>
<td>maximum number of vaccines per day</td>
<td>$10^5 - 10^7$</td>
<td>based on vaccination clinic modeling and clinic data [2, 36, 40, 118, 119, 151]</td>
</tr>
<tr>
<td>$k$</td>
<td>proportion of eligible vaccinated per day</td>
<td>0.001 - 0.1</td>
<td>see models using proportions in this range [44]</td>
</tr>
<tr>
<td></td>
<td>(0.1-10 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta$</td>
<td>infection-related death rate (1/days)</td>
<td>$10^{-6}$</td>
<td>based on U.S. viral surveillance data [140]</td>
</tr>
</tbody>
</table>
The majority of infected individuals recover at a rate $c$, which corresponds to a recovery period of 7 days based on data describing the progression of symptoms, viral shedding, and cytokine levels in influenza challenge studies [32, 49, 73]. Once recovered, individuals are assumed to have complete immunity against the virus that does not wane with time. Complete immunity, along with the fact that births are not included in the model, means that there is no continuing supply of susceptibles. Those who recover and were confirmed are represented by the population $R_C$, while those who recover but were unconfirmed are represented by $R_U$. A small number of people do not recover, however, and instead die as a result of infection, at a rate $\delta$. The occurrence of deaths in the unconfirmed population is not meant to indicate that individuals may die without ever showing symptoms, but rather that some individuals may die before seeking medical attention and officially being classified as infected with influenza. This is particularly applicable to developing countries where many people may not have access to timely medical care. The rate of disease-related death, $\delta$, is set low in our simulations to reflect a negligible death rate, but this parameter can be adjusted to simulate epidemics with higher mortality rates. For quantification purposes, a threshold of $n$ individuals serves to find the start and end times of an epidemic. For the simulations presented herein, $n=10^4$ (0.01% of the total population of $10^8$ people).

3.1.2 Assumptions about vaccination

In addition to acquiring immunity to the virus through infection, individuals can gain protection through vaccination. As previously explained, it is unrealistic to assume that only susceptibles will seek and receive vaccination during an epidemic. Therefore, in our model vaccines are distributed to the populations $S$, $I_U$, and $R_C$. Individuals from $I_U$ and $R_C$ are meant to represent those who become infected, but seek vaccination either because they are (were) unaware of their illness due to a lack of symptoms, or because the specific viral strain causing previously-experienced symptoms was not identified. As in recovered
populations, vaccinated individuals are assumed to have total protection against the virus that does not wane. Vaccines that go to individuals in populations $I_U$ and $R_C$ are considered wasted, since immunity was already acquired through infection. We use the variable $V_U$ to keep track of vaccinated individuals from $I_U$, and $V_{SC}$ to track those vaccinated from populations $S$ and $I_C$. Importantly, those vaccinated while belonging to the population $I_U$ continue to be infectious, and recover or die at the same rates as those who did not receive the vaccine.

The vaccine stockpile, $\bar{v}$, is limited. For most of the simulations shown here, it is assumed that $\bar{v}$ corresponds to a maximal coverage of 30% of the total population, a level of supply supported by vaccine production and distribution data for industrialized nations such as the U.S. [74, 112, 113]. The administration of vaccines starts at some time $t = t_a$ and effectively ends in one of two ways: (1) the vaccination campaign ends after some prescribed duration at time $t_b$, or (2) the stockpile is depleted at time $t_d$.

3.1.3 Model

The dynamics of the model are defined by a system of non-autonomous ordinary differential equations of the form

$$
\dot{S} = -\lambda(S, I(t)) - v_S(t) \tag{3.1}
$$

$$
\dot{I}_C = p\lambda(S, I(t)) - (c + \delta)I_C \tag{3.2}
$$

$$
\dot{I}_U = (1 - p)\lambda(S, I(t)) - (c + \delta)I_U - v_U(t) \tag{3.3}
$$

$$
\dot{V}_U = v_U(t) - (c + \delta)V_U \tag{3.4}
$$

$$
\dot{R}_C = cI_C - v_R(t) \tag{3.5}
$$

$$
\dot{R}_U = c(I_U + V_U) \tag{3.6}
$$

$$
\dot{V}_{SC} = v_S(t) + v_R(t) \tag{3.7}
$$

$$
\dot{D} = \delta(I_C + I_U + V_U) \tag{3.8}
$$
so the infected, recovered, and vaccinated populations are given by

\[ I = I_C + I_U + V_U, \quad R = R_C + R_U, \quad V = V_U + V_{SC}, \quad (3.9) \]

where \( p \) is the probability of being infected and confirmed, \( c \) is the rate of recovery of infected individuals (1/recovery time), \( \delta \) is the infection-related death rate, \( b \) represents the mean probability of infection per contact. The incidence or new infections per unit time are

\[ \lambda(S, I, t) = b \frac{S}{N} [I_C + \alpha(I_U + V_U)], \quad (3.10) \]

The functions \( v_S(t) \), \( v_U(t) \), and \( v_R(t) \) represent, respectively, expressions for the vaccines given each day to individuals from the \( S \), \( I_U \), and \( R_C \) populations, and will be defined in detail in the following section. The total number of vaccines administered per day is then

\[ v_D(t) = v_S(t) + v_U(t) + v_R(t). \quad (3.11) \]

Two extra (redundant) variables, \( W \) and \( F \), are introduced in the simulations to quantify, respectively, the wasted vaccines (those given to \( I_U \) and \( R_C \)) and the cumulative number of infected individuals (the sum of all new infections) as a function of time:

\[ \dot{W} = v_U + v_R \quad (3.12) \]
\[ \dot{F} = \lambda(S, I, t) \quad (3.13) \]

### 3.1.4 Proportional and non-proportional vaccination

The strategy adopted in most existing models of vaccination is to choose some constant, \( k \), such that the number of people vaccinated per day is \( kx \), where \( x \) is the vaccinable population [14, 31, 44, 45, 58, 61, 64, 65, 67, 91, 97, 110, 125, 145, 164]. As discussed earlier, many of these models also assume that vaccines are only administered to susceptible individuals, thereby setting the number of vaccinated people per day equal to \( kS \).
refer to this scheme as the proportional model of vaccination. However, such a proportion may represent a very small or large number of people compared to the number of overall vaccines available and the number that can reasonably be administered in one day. As mention earlier, we instead propose modeling vaccination by placing a limit on the number of daily vaccines before they are distributed between the epidemiological populations. We refer to the scheme presented herein as the non-proportional model of vaccination because the administration of vaccines depends on a daily limit, rather than on a proportion of the population.

Non-proportional vaccination rates

At each time step during the simulations, it is checked that there were enough vaccines in stock \((V(t) < \bar{v})\). If this condition is satisfied, the maximum number of vaccines per day, \(\bar{v}_D\), is split according to the relative sizes of the different populations eligible for vaccination. To do so, we define the weights

\[
\begin{align*}
    w_S(t) &= \frac{S(t)}{M(t)}, \\
    w_U(t) &= \frac{I_U(t)}{M(t)}, \\
    w_R(t) &= \frac{R_C(t)}{M(t)},
\end{align*}
\]

where \(M(t) = S(t) + I_U(t) + R_C(t)\) is the total number of people eligible for vaccination at time \(t\). \(M\) is thus a decreasing function of \(t\) satisfying \(M(t) \leq N\). The maximum number of
vaccines per day that each population can receive is

\[ \bar{v}_S(t) = \bar{v}_D w_S(t), \quad \bar{v}_U(t) = \bar{v}_D w_U(t), \quad \bar{v}_R(t) = \bar{v}_D w_R(t). \]  \tag{3.15}

Note that if either \( S \), \( I_U \), or \( R_C \) are zero, their corresponding weight would also be 0, and the maximum number of vaccines allocated for that population would be 0 as well.

Depending on the starting day of vaccination, \( t_a \), and on the maximum number of vaccines, \( \bar{v}_D \), it is possible that some days there will be fewer individuals in a given epidemiological population than \( \bar{v}_x(t) \), the maximum number of vaccines available for that population. In other words, the vaccinable population could become negative if for \( x \in \{ S, I_U, R_C \} \), \( x(t) < \bar{v}_x(t) \). To ensure that \( x \) never becomes negative due to the removal of vaccinated individuals, we assess whether each of these populations has enough people to be vaccinated at each step of the simulation. First, we calculate the vaccination-independent change in \( x \) at time \( t \):

\[ f(x,t) = \begin{cases} 
-\lambda(S,I,t) & x = S, \\
(1-p)\lambda(S,I,t) - (c + \delta)I_U & x = I_U, \\
cI_C & x = R_C.
\end{cases} \]  \tag{3.16}

We use \( f \) to estimate \( \hat{x} \), the size of \( x(t+h) \) where \( h \) is the maximum time step of the solver \[19\], and calculate the number of administered vaccines, \( v_x(t) \), based on this estimate. To ensure the non-negativity of \( x(t) \), the number of vaccinated people removed from \( x \) cannot be larger than \( \hat{x} \). In other words, the condition \( v_x(t) \leq \hat{x} \), must be satisfied so that \( x(t) \geq 0 \) for all \( t \). The number of vaccines administered per day to population \( x \) is then either:

\[ v_x(t) = \begin{cases} 
\bar{v}_x(t) & \hat{x} > \bar{v}_x(t), \\
\hat{x} & \hat{x} \leq \bar{v}_x(t).
\end{cases} \]  \tag{3.17}

Note that when \( \hat{x} \leq \bar{v}_x(t) \), if the estimated size of the population is zero, then there will be no vaccines given to that population. More formally, the number of vaccines adminis-
tered to population $x$ is defined as:

$$v_x(t) = \max \left( \min (\bar{v}_x(t), \hat{x}), 0 \right), \quad x \in \{S, I_U, R_C\}. \quad (3.18)$$

Eq. (3.18) results in non-negative values of $x(t)$ for all $t$ for all $x \in \{S, I_U, R_C\}$ if the time step is small enough. As a rule of thumb, the maximum time step should be $10^{-3}$ or smaller.

It follows from Eqs. (3.15) and (3.18) that $v_D(t) \leq \bar{v}_D$ for all $t$. Note that saturation ($v_D = \bar{v}_D$) cannot always be assumed because at some point there may not be enough individuals eligible for vaccination. This implies that there will be vaccines available for at least $\bar{v}/\bar{v}_D$ days.

### 3.1.5 Rationale of comparison between proportional and non-proportional vaccination

For simplicity, consider an interval of time in which a population of size $x$ contains no infected individuals, and assume all individuals are eligible for vaccination. If vaccines are supplied at the limit of capacity, the daily number of vaccines is a constant, namely, $\bar{v}_D$.

In this case, the time course of $x$ is described by a decreasing linear function of the form $x(t) = x_0 - \bar{v}_D t$ (Fig. 3.2, solid line; Fig. 3.4, solid line in right column.) For comparison, let $k = \bar{v}_D/x_0$ where $x_0$ is the initial size of the vaccinable population, and assume proportional vaccination ($\dot{x} = -kx$). The decay in this case will be exponential at a rate $k$ (Fig. 3.2, dashed line; Fig. 3.4, dashed line in right column). The difference in the time courses of these two decays, in particular the slower decay in the proportional model, may play an important role in shaping the mitigating effects of vaccination on a developing epidemic.
Figure 3.2: Proportional and non-proportional decay of the vaccinable population. Proportional decay (dashed line) is given by $x(t) = x_0e^{-kt}$, for $k=0.1$. Non-proportional decay (solid line) is given by $x(t) = x_0 - \bar{v}_D t$, where $\bar{v}_D = kx_0$.

Figure 3.3: Vaccination stockpile distribution scheme. I start with a given stockpile per country that will be distributed per city and then distribute by medical personal daily for a given period of time.

3.2 Results

3.2.1 Mitigating effects of vaccination in the proportional and non-proportional models

Initially, to compare the proportional and non-proportional models of vaccination, we conducted simulations in which the vaccination campaign lasted 30 days. This duration can be thought of as defined by constraints in medical personnel and other factors affecting the administration of vaccines (e.g., pharmaceutical company distribution schedules, operation
Figure 3.4: Effects of vaccination in the proportional and non-proportional models for different campaign starts. The proportional model is represented by dashed black lines and the non-proportional model by solid black lines. The graphs in the left column (a, c, e) show the proportion of infected people as a function of time. The graphs in the right column (b, d, f) show the proportion of the population vaccinated, and those still eligible for vaccination (vaccinable), over time. The initial population size is $10^8$ people. Infected individuals are inserted into the susceptible population on day 10 ($t_0=10$; solid vertical gray line). The vaccination campaign is initiated on day 20 (a, b), 50 (c, d), or 80 (e, f), and lasts 28 days. Start ($t_a$) and stop ($t_b$) times of the campaign are indicated by dashed vertical lines. Vaccination occurs at a rate of 1% of the eligible population per day (proportional; $k=0.01$), or at a maximum of $10^6$ vaccines per day (non-proportional, $\bar{v}_D = 10^6$).

of health care facilities, governmental budgets, etc.). Assuming a stockpile equivalent to 30% of the total population, the distribution rate in the proportional model is set to 1% of the vaccinable population per day ($k=0.01$). Equivalently, the maximum daily administration in the non-proportional model is then $10^6$ vaccines ($\bar{v}_D = 10^6$). Fig. 3.4 shows the infected, vaccinated, and vaccinables as functions of time for vaccination campaigns.
starting at three different times relative to the initial outbreak ($t_0=10$): (1) 10 days after $t_0$ ($t_a=20$), so that the entire campaign occurs well before the epidemic starts (Fig. 3.4 a, b), (2) 40 days after $t_0$ ($t_a=50$), so the campaign ends shortly before the start of the epidemic (Fig. 3.4 c, d); and (3) 70 days after $t_0$ ($t_a=80$), in which case the campaign is ongoing as the epidemic begins (Fig. 3.4 e, f). These campaign start times correspond to real-world scenarios. Early vaccination, as in campaign (1), is possible if a vaccine is already available and outbreaks are anticipated, as might be the case with seasonal influenza or with additional epidemic waves caused by a previously identified viral strain. Vaccination following detection of an outbreak, but before epidemic levels are reached (2), is again possible if a vaccine is available and efficient disease surveillance systems are present. However, if the surveillance system is not able to identify small outbreaks, or a vaccine is not immediately available, vaccination may not be implemented until after the epidemic starts (3).

The dynamics shown in Fig. 3.4 reveal a number of similarities and differences between the proportional and non-proportional models of vaccination, which in turn depend on interactions between the start time and duration of the vaccination campaign, and the limitations on daily administration. During the early stages of vaccination, the rate of increase in the proportion of vaccinated individuals in the population is equivalent in the two models, as is the rate of decrease in the proportion of vaccinable people (Fig. 3.4 b, d, f). As time proceeds, however, the rate of vaccination in the proportional model slows down, while the rate in the non-proportional model holds fairly steady. Due to the duration of the campaign and the daily rate of administration, the campaign ends before the stockpile is depleted, and the proportional model does not have time to ‘catch up’ to the non-proportional model. Therefore, by the end of the campaign, a larger proportion of the population has been vaccinated in the non-proportional model. This increased vaccination coverage causes the epidemic in the non-proportional model to develop more slowly, increasing its duration,
but ultimately resulting in a smaller and later peak in comparison to the proportional model (Fig. 3.4a, c, e).

The differences between the two models, with respect to the time course and severity of the epidemics, are largest when vaccination begins around the time of the initial outbreak \(t_0\) and ends well before the epidemic hits (Fig. 3.4a). As described previously, these differences are directly attributable to the increased number of vaccines administered in the non-proportional, relative to the proportional, model (Fig. 3.4b). If vaccination occurs early, then the majority of those vaccinated are from population \(S\), and therefore an increased level of coverage in the non-proportional model has a measurable effect on the epidemic development and size. Instead, if vaccination begins 40 days after \(t_0\) and the campaign ends shortly before the epidemic starts, the differences between the epidemics produced by the two models, especially with respect to the time course, are smaller (Fig. 3.4c). Again, the proportion of people vaccinated in the non-proportional model is larger than in the proportional (Fig. 3.4d). However, since vaccination begins some time after the initial introduction of infected individuals into the susceptible population, some of the additional vaccinated individuals in the non-proportional model are from populations \(I_U\) and \(R_C\). In other words, the increased coverage in the non-proportional model has less of a mitigating effect when vaccination starts later because fewer of the vaccinated people are susceptibles. Finally, if vaccination begins 70 days after \(t_0\) and is ongoing as the epidemic starts, the number of vaccinated individuals from populations \(I_U\) and \(R_C\) is now even greater, essentially diluting the effect of the increased coverage in the non-proportional model (Fig. 3.4f) further. Therefore, the models produce epidemics which are very similar in their time course, and differ primarily in their peak size (Fig. 3.4e).

We also compared the proportional and non-proportional models when the same total number of vaccines was administered in each. This was accomplished by setting the campaign duration and daily administration limits such that all the vaccines in the stockpile
were used. In this way, the same level of coverage is achieved, though the proportional model always takes longer to reach this level due to slowing of the administration rate over time. As long as vaccination occurs early, before the number of infections increases substantially, the additional time needed for the proportional model to administer the whole stockpile has a minimal effect on the final coverage in the susceptible population. Thus, the epidemics produced by the two models are nearly identical (Fig. 3.5). However, if vaccination does not begin until after the epidemic is underway, the increasing number of infections over time starts to affect the level of coverage achieved in $S$. The slower rate of administration in the proportional model results in an increased number of susceptibles at certain times during the epidemic, relative to the non-proportional model. This increased susceptibility results in a slightly faster epidemic development than is seen in the non-proportional model (Fig. 3.5 e), and occurs despite the fact that the final number of vaccines administered is the same for both models.

Additional simulations revealed similar results for several combinations of campaign duration and daily administration limit (see subsequent section for more details). In general, if the campaign ends before the vaccine stockpile is depleted, more vaccines are always administered in the non-proportional model, and the epidemics produced by the two models are different with respect to timing and severity. Instead, if the same total number of vaccines is administered in each model, the epidemics do not differ unless vaccination begins very late.

3.2.2 Comparison of the models for variable daily administration and campaign duration

To further explore in both models the effects of changing the timing of the vaccination campaign, we systematically varied $t_a$ under three different scenarios of daily administration capacity and campaign duration. These three scenarios can be thought of as ranging from ‘conservative’ to ‘aggressive’ in terms of the number of vaccines administered within
Figure 3.5: Comparison of the proportional and non-proportional models when the stockpile is depleted. The proportional model is represented by dashed black lines and the non-proportional model by solid black lines. The graphs in the left column (a, c, e) show the proportion of infected people as a function of time. The graphs in the right column (b, d, f) show the proportion of the population vaccinated, and those still eligible for vaccination (vaccinable), over time. The initial population size is 10^8 people. Infected individuals are inserted into the susceptible population on day 10 (t_0=10; solid vertical gray line). The vaccination campaign is initiated on day 20 (a, b), 50 (c, d), or 80 (e, f), and lasts 40 days such that all the vaccines are used in both models. Start (t_a) and stop (t_b) times of the campaign are indicated by dashed vertical lines. Vaccination occurs at a rate of 1% of the eligible population per day (proportional; k=0.01), or at a maximum of 10^6 vaccines per day (non-proportional, \( \bar{v}_D = 10^6 \)).

a given time period, and are as follows: (1) a 56 day campaign vaccinating 0.1% (proportional) or a maximum of 10^5 vaccines (non-proportional) per day; (2) a 28 day campaign vaccinating 1% or a maximum of 10^6 vaccines per day; (3) a 3 day campaign vaccinating 10% or a maximum of 10^7 vaccines per day. For each of these combinations of campaign duration and daily administration limit, the non-proportional model administers a larger
total number of vaccines than the proportional model. The data obtained from these simulations were used to calculate the final size, peak size, time to peak, and epidemic duration as a function of the difference between $t_a$ and $t_0$.

The conservative campaign (1) results in no detectable differences between the proportional and non-proportional models on any quantified measure (Fig. 3.6a1-a4). Under this low level of daily administration, the decay in the vaccinable population is very slow in both models and there is not time for the decay rates to diverge before the campaign ends. The level of vaccination coverage in both models is therefore the same and in turn, the number of susceptible people that get infected over time is very similar. In addition, because so few people are vaccinated overall, the mitigating effects of vaccination are minimal and each measure varies little as a function of the timing of the vaccination campaign ($t_a - t_0$). Late vaccination start times caused the peak and final size to increase, and the peak time and epidemic duration to decrease, but only marginally.

Though the models behave similarly when examined under the conservative vaccination regime, the moderate regime (2), equivalent to the campaign used for the simulations in Fig. 3.4, reveals important differences between the models on all four measures (Fig. 3.6b1-b4). For early vaccination starts, final and peak sizes are smaller, while peak times and epidemic durations are larger, in the non-proportional than the proportional model. As discussed previously, these differences result from the higher level of vaccine coverage achieved in the non-proportional, relative to the proportional, model. With later vaccination starts, due to the increasing number of vaccinated individuals from populations $I_U$ and $R_C$, the differences between the models decrease until the models converge on most measures. Interestingly, with respect to epidemic duration, the two models not only converge, but reverse their respective relationship: epidemic durations are slightly smaller in the non-proportional model for very late vaccination start times (Fig. 3.6b4).
Figure 3.6: Effects of vaccination in the two models for different administration rates and campaign durations. Epidemic measures are shown for proportional (open circles) and non-proportional (filled dots) models. Final size, peak size, peak time, and epidemic duration are plotted as a function of the difference between the vaccination start time ($t_a$) and the onset of the initial outbreak ($t_0$; solid gray line). The vaccination campaign durations and daily administration rates are as follows: (1) 56 day campaign with $k=0.001$ (proportional) or $\bar{\nu}_D = 10^5$ (non-proportional) (a1-a4), (2) 28 day campaign with $k=0.01$ or $\bar{\nu}_D = 10^6$ (b1-b4), and (3) 3 day campaign with $k=0.1$ or $\bar{\nu}_D = 10^7$ (c1-c4).
For the aggressive campaign (3), the proportional and non-proportional models also differ with respect to the time course and severity of epidemics (Fig. 3.6c1-c4). The differences are the same as those seen under the moderate vaccination regime, namely smaller final and peak sizes, and larger peak times and epidemic durations, in the non-proportional model. The same relationship is also observed between the magnitude of these differences and the timing of the vaccination campaign relative to the initial outbreak. Later vaccination start times result in a convergence of the proportional and non-proportional models on all measures.

We also performed these same simulations for different combinations of campaign duration and daily administration limit. The vaccination scenarios are as follows: (1) a 300 day campaign vaccinating 0.1% (proportional) or a maximum of $10^5$ vaccines (non-proportional) per day; (2) a 35 day campaign vaccinating 1% or a maximum of $10^6$ vaccines per day; (3) a 5 day campaign vaccinating 10% or a maximum of $10^7$ vaccines per day. Under these conditions, the vaccine stockpile is depleted before the end of the campaign, resulting in the same number of vaccines being administered in each model. The epidemics produced by the two models are thus not measurably different, as previously explained, except for the latest vaccination start times under the moderate regime (Fig. 3.7).

3.2.3 Effects of non-proportional vaccination for different levels of population coverage

Finally, we investigated the mitigating effects of vaccination in the non-proportional model when different target levels of total population coverage are met at different times relative to the initial outbreak. All simulations shown previously assume a maximum of 30% population coverage due to the size of the stockpile ($\bar{\nu}=30 \times 10^6$). To simulate vaccination campaigns with higher levels of coverage, we increased $\bar{\nu}$ to a size equivalent to 20, 40, 60, or 80% of the population. In addition, since the effective coverage in the susceptible population could be altered if a large number of vaccines go to infected unconfirmed
individuals, we performed the same simulations for $p = 0.2$ or $p = 0.65$ (the value used in all previous simulations). In other words, unconfirmed cases represent either 80% or 35% of total infections, respectively. The probability of infection per contact is adjusted so that the basic reproductive number ($R_0$) is the same in both simulations. Fig. 3.8 shows the proportion infected over time when 20% (a, e, i), 40% (b, f, j), 60% (c, g, k), or 80% (d, h, l) of the population is vaccinated with a maximum of $10^6$ vaccines per day. The vaccination campaign starts 10 (Fig. 3.8 left column), 40 (middle column), or 70 days (right column) after the initial outbreak at day $t_0=10$. Vaccination ends when the target level of coverage is achieved i.e., the higher the coverage, the longer the campaign.

The results show that even if 20% of the population is vaccinated, there is still a sizeable epidemic (Fig. 3.8a, e, i). Furthermore, starting vaccination earlier does not dramatically decrease the number of infections, though it does delay the start of the epidemic. At 40% coverage, the number of infections is highly dependent on when the vaccination campaign begins (Fig. 3.8b, f, j). When vaccination starts only 10 days after the epidemic starts, it successfully prevents an epidemic from occurring (Fig. 3.8b). A start time of 30 days later does not prevent a small number of late-occurring infections, but is still a highly effective mitigation strategy (Fig. 3.8f). A full-blown epidemic does occur if vaccination starts as late as 70 days after the initial outbreak, but the peak size is smaller than that observed with only 20% coverage (Fig. 3.8). At 60% coverage the results of vaccination are similar, though even more effective (Fig. 3.8c, g, k). Starting vaccination 10 or 40 days after the starting point of the epidemic completely quells the outbreak (Fig. 3.8c, g), while beginning 70 days later does not prevent a small, but short, epidemic from occurring (Fig. 3.8k). Increasing coverage from 60% to 80% does not confer much additional benefit with respect to either arrival, size, or time course of the epidemic (Fig. 3.8d, h, l), but does result in a larger number of wasted vaccines (Fig. 3.9).
The results are similar for the two values of $p$ for all simulations, regardless of the level of coverage or the vaccination start time. In other words, increasing the proportion of unconfirmed cases does not alter the mitigating effects of vaccination. Decreasing the value of $p$, and thereby increasing the number of vaccines going to population $I_U$, increases the number of wasted vaccines only slightly (Fig. 3.9). Thus, for the parameter choices made here, the majority of wasted vaccines go to population $R_C$, and changing the number going to $I_U$ does not significantly change the level of coverage in $S$.

3.3 Discussion

Epidemiological models can be vital tools for government and medical professionals who need to understand the spread of diseases and the effects of mitigating strategies, such as vaccination, to form public policies that will help reduce the burden of disease [158, 161]. These models are only useful, however, if they generate accurate predictions and the tools they provide can be applied to real situations. We argue that many epidemiological models examining the mitigating effects of vaccination incorporate a number of unrealistic assumptions. These include: (1) large vaccine stockpiles, (2) vaccination of only the susceptible class, and (3) the administration of vaccines based on a proportion of the population, without taking into account daily administration constraints. We constructed a model designed to incorporate more realistic assumptions about the supply and distribution of vaccines.

3.3.1 Vaccine stockpile size

We placed a conservative, but reasonable, limit on the total number of vaccines available at $30 \times 10^6$; enough to cover 30% of the population. A stockpile covering this percentage of the population is in agreement with seasonal influenza vaccine production and distribution for resource-rich countries, such as the U.S. [74, 112, 113]. From 2000 to 2009, the number
of seasonal vaccines produced annually for use in the U.S. did not exceed 140.6 million (~46% of the total population of 307 million) [156, 142], and in most years was far less at an average of 99.7 million (~32%) [74]. Even Canada, with the largest per capita annual influenza vaccine distribution of all countries surveyed, distributed only enough vaccines as of 2003 to cover ~34% of their population [112]. For many other countries in the world, annual vaccine supplies are nowhere near enough to cover 30% of their population, primarily due to the lack of vaccine production capabilities and the resources needed to buy vaccines from producing countries [55, 112, 114, 163]. As of 2003, over 60% of the total influenza vaccines distributed annually went to countries comprising only 12% of the world population, leaving 88% of the world facing potential vaccine shortages [55, 112].

In 2009, the emergence of a novel influenza A (H1N1) strain [5, 52, 94] tested the world’s ability to rapidly develop and distribute large numbers of vaccines to combat an ongoing pandemic [3, 116]. Though vaccine development was quick and successful, production levels fell far short of initial estimates [116], and even developed countries struggled to secure sufficient vaccines to cover their populations before subsequent waves hit [94, 99, 123]. By the time the fall wave peaked in the U.S. in mid October, only ~10 million vaccines were available [123]: Canada had distributed less than 6 million vaccines [122] when their second wave peaked just a few weeks later [75, 99]. It wasn’t until mid December 2009 that the number of vaccines available in the U.S. reached levels high enough to cover 30% of the population [123]. Canada had enough vaccines by the first week of December to cover a larger percentage of their population (~67%) [122], but were subsequently accused of wasting resources as most vaccines arrived too late to have an effect during the peak periods of influenza activity [99, 129]. For developing nations the situation was much worse [76, 94, 116]. For example, the Mexican government indicated in June of 2009 that they would have 30 million H1N1 vaccines (enough to cover ~30% of the population) [76, 59, 146]. Yet, three waves of infection had already hit by the time...
the first 650 thousand vaccines arrived in late November [76]. By December 1, 2009 the
global production of H1N1 vaccines had reached 534 million, enough to cover only ~8%
of the world population [116]. Many developing countries did not have any vaccines until
January 2010 [116].

The production and distribution of seasonal and pandemic vaccines show that stockpiles
assumed in many models are in excess of what is usually available. Some studies modeling
vaccination in simulated U.S. populations have considered upper limits of 300-400 million
vaccines (100%+ coverage) [64, 110]; levels more than double the U.S. annual production
[74] and close to the global production of seasonal influenza vaccines [116, 113, 160].
Other models looking at vaccination during a pandemic have assumed population coverage
levels as high as 70-90% [31, 58, 61, 72, 97, 164], levels not achieved by many wealthy
nations during the most recent pandemic, and currently out of reach for most developing
nations [55, 112, 114, 163].

In 2004, the WHO published two separate reports on guidelines for vaccine use dur-
ing a pandemic [158] and pandemic preparedness in countries with limited resources [157].
In both reports, they remarked on the usefulness of mathematical models for examining
different pandemic scenarios and the effectiveness of strategies, such as vaccination, in
mitigating outbreaks [158, 157]. However, they lamented that, “...no scenarios appropriate
to developing countries are readily available” (see [158], pg. 5), a sentiment echoed by
others [114]. In 2005, a model of a developing country in Southeast Asia, Thailand, was
used to examine vaccination strategies in the context of an avian influenza epidemic [97].
To realistically model factors such as age and household-size distributions, and population
mixing, they relied on census data from the Thai government and social network studies of
Thai communities. Yet, they assumed that vaccination coverage in the population of 500
thousand people was 50-70%, equivalent to a total of 250 - 350 thousand vaccines [97].
Between 2000 and 2003, a total of 64 - 253 thousand vaccines were distributed to the entire
WHO-defined region of Southeast Asia with a population of over 1.5 million [55, 112]. Specifically in Thailand, between 1997 and 2003 the number of vaccines distributed per capita was \( \sim 1 \) per 1000 people (0.1\% coverage) [55, 112]. Thus, the crucial detail of setting a limit on the vaccine stockpile that was realistic for Thailand was neglected in the model.

Though many of the parameters in our model listed in Table 3.1, including vaccine stockpile, were set to values observed mostly for developed countries, the model is easily adjusted to apply to developing countries. The size of the stockpile, \( \bar{v} \), can be set to correspond to very low levels of population coverage. In these cases, we would expect to see that vaccination campaigns would have less of a mitigating effect, resulting in larger epidemics with earlier time to peak than the simulations shown here. However, it should be noted that the general results regarding the comparison between the proportional and non-proportional models still hold for a wide range of stockpile sizes.

The vaccine stockpile can also be increased to model the effects of increasing population coverage, as done for the simulations in Fig. 3.8. As expected, we find that increasing the percentage of the population protected by vaccination decreases the size and duration, and delays the arrival, of the epidemic. At only 40\% coverage the epidemic can be completely prevented, if vaccination begins early enough. Even vaccination beginning around the start of the epidemic can help significantly to control the number of infections. However, if vaccination cannot begin sooner than this time, it is important to note that increasing coverage from 60\% to 80\% in our simulations does not further decrease the size or duration of the epidemic. Therefore, continuing campaigns during an epidemic until 80\% of the population is vaccinated may result in a large number of vaccines being wasted in return for little benefit (Fig. 3.9).
3.3.2 Vaccination of multiple epidemiological populations

In our model, not only susceptible individuals, but also unconfirmed infected and confirmed recovered people, are eligible for vaccination. There is little documentation about the actual number of unconfirmed and recovered people who do get vaccinated. However, in the context of the 2009 H1N1 vaccination campaigns, the CDC recommended that those who had influenza-like symptoms (i.e., recovered) should still get vaccinated, if medically indicated, due to uncertainty about which specific viral strain caused the illness [38]. In addition, they stated that even in those cases when infection by 2009 H1N1 had been confirmed by laboratory testing, it was an individual’s choice as to whether to receive vaccination. Thus, recovered people, even those who were previously symptomatic and confirmed, can seek and receive vaccination. In this respect, the eligible population in our model is reasonable.

Expanding vaccine administration to include the unconfirmed population, in particular, also allowed us to examine the role that a high rate of asymptomatic cases might play in the context of vaccination efforts [121]. This is particularly relevant for 2009 H1N1, which was reported by some as characterized by a large proportion of asymptomatic cases [60]. However, in our simulations, decreasing the probability of being confirmed, $p$, from 0.65 to 0.20 does not alter the mitigating effects of vaccination (Fig. 3.8). The majority of wasted vaccines in our model go to the confirmed recovered population (Fig. 3.9) so that the number of vaccines going to the unconfirmed class does not significantly change the level of coverage in the susceptible population. Larger effects may be seen when the vaccine stockpile is severely limited, as could be the case for developing countries.
3.3.3 Limited number of vaccines administered per day

The key observation prompting the development of the model presented here was that most existing models of vaccination of which we are aware distribute vaccines based on a proportion of the eligible population \[14, 31, 44, 45, 53, 58, 61, 64, 65, 67, 91, 97, 110, 125, 145, 164\]. Considering that vaccination clinics operate with a finite number of medical professionals for a finite number of hours, however, it is clear that distribution happens in practice based on the number of vaccines that can be administered per day \[2, 36, 40, 118, 119, 151\]. Pandemic preparedness plans devised by county health departments often calculate the necessary length of vaccination campaigns using a formula based on daily administration capacity (e.g., see \[118\]). Therefore, we model vaccination by placing a limit on the number of daily vaccines (non-proportional model).

Initially, to compare the proportional and non-proportional models of vaccination we assumed that the daily limit was \(10^6\) vaccines (a value corresponding to 1% of the population). A number of resources discuss the administration capabilities needed to distribute specific numbers of vaccines\[2, 36, 40, 118, 119, 151\]. For example, a model by Aaby et al. \[2\] predicted that 316 people could be vaccinated per hour with the aid of 18 nurses. Thus, one clinic operating for 8 hours could vaccinate 2,528 people per day. To reach a daily administration of \(10^6\) vaccines would therefore require more than 395 clinics and more than 7,110 nurses (or other capable medical professionals). Similarly, estimates from the CDC are that a single vaccinator at a station can administer 30 vaccines per hour. With 16 hours of operation and 4-8 stations, one clinic could administer 1,900-5,000 vaccines per day. At this rate, it would require 200-526 clinics and 1,600-8,416 vaccinators to distribute \(10^6\) vaccines per day. Data from actual vaccination clinics reveal a similar story. In 2004, a mass vaccination clinic in Maryland administered vaccines to more than 3,000 people in a single day with a workforce of 36 nurses, and 38 additional staff. Thus, to reach
10^6 vaccines per day would have required more than 333 clinics, nearly 12,000 nurses, and over 12,654 additional workers. Based on all these estimates, if instead a daily rate of 10^7 vaccines (10% of the population) is desired, the clinics and staff needed would increase to the thousands and hundreds of thousands, respectively. For these reasons, we set 10^7 (10%) as the upper limit of daily administration.

In some nations, where the medical resources are sufficient and the infrastructure is present, high daily rates of vaccine administration may be possible. Even so, mass vaccination campaigns often require extensive planning and agency cooperation to carry out [40, 118, 119, 123], and are not intended to be sustained for long periods of time. In addition, long campaigns at high rates of daily administration would require very large vaccine stockpiles. Therefore, we limited high daily administration (10^7 or 10%) campaigns to a small number of days (≤5). For many developing nations with minimal resources, however, daily vaccine administration capacity is much more limited [114]. To model the mitigating effects of vaccination in these nations the daily administration limit, \( \bar{v}_D \), is easily lowered in the model to reflect the medical facilities, workforce, and other resources available.

### 3.3.4 Comparison of models in context of total vaccines administered

We predicted, based on the solutions of the equations representing the proportional and non-proportional models, that the different decays in the vaccinable population (Fig. 3.2), would lead to distinct epidemic dynamics. This prediction was confirmed under several vaccination scenarios in which the campaign duration and daily administration limit were such that vaccination ended before the stockpile was depleted (Fig. 3.4 and Fig. 3.6). Under such conditions, the non-proportional model always administers a larger total number of vaccines, which results in smaller and later, but sometimes longer, epidemics than in the proportional model. This is true for both moderate and high levels of daily vaccine administration, and is more pronounced the sooner vaccination starts after the initial outbreak.
If instead vaccination continues until the stockpile is depleted, the same total number of vaccines are administered in each model, and the epidemics produced are very similar in time course and severity (Fig. 3.5 Fig. 3.7). The only differences between the two models in these cases are seen under the moderate regime when vaccination starts after the epidemic hits. Then, the slower rate of vaccine administration in the proportional model means that there is a small increase in the susceptibility of the population during the epidemic, which results in a slightly faster and more severe epidemic than in the non-proportional model. In contrast, at low daily rates of administration, the models do not differ much on any measure, regardless of whether the same total number of vaccines in administered. This occurs because so few people are vaccinated per day that the proportional and non-proportional decays in the vaccinable population do not have time to diverge. Thus, the models achieve the same level of vaccine coverage even if the stockpile is not depleted.

3.3.5 Difference in epidemic duration

One of the largest differences between the two models when different total numbers of vaccines are administered is the epidemic duration. This stems from the increased coverage of the population in the non-proportional model, which allows the epidemic to develop more slowly, but can also cause it to last tens of days longer than predicted by the proportional model. Interestingly, a similar effect was found in an agent-based model of influenza (for a review of these types of models see [21]). Hartvigsen et al. [72] showed that for certain schemes of connectivity between the agents (individuals), increasing vaccination coverage from 0% through ~30% increased the epidemic duration; an effect that occurred due to slowing of the epidemic development. Having the benefit of a smaller, delayed peak could therefore come at a cost, since it could result in a sustained burden on the healthcare system. Models that make more accurate predictions about the length of epidemics will allow health care professionals and medical facilities to prepare accordingly.
3.4 Conclusions

We developed a model to explore the mitigating effects of vaccination on influenza outbreaks. We argue that our model constitutes a theoretical improvement over existing models, with advantages that include data-informed parameter choices, vaccination of multiple epidemiological classes, a reasonable vaccine stockpile, limits on the number of vaccines administered per day, and ways to estimate wasted resources. In particular, the non-proportional vaccine administration implemented in our model may provide more accurate predictions of the mitigating effects of vaccination than proportional models, particularly when moderate or high levels of daily administration are considered. In addition, supply and daily administration capacity can be adjusted to study vaccination strategies in developing nations with limited resources. Government and medical officials can also use the tools provided here to create influenza preparedness plans for specific communities based on their available resources.
Figure 3.7: Effects of vaccination for administration rates and campaign durations resulting in stockpile depletion. Epidemic measures are shown for proportional (open circles) and non-proportional (filled dots) models. Final size, peak size, peak time, and epidemic duration are plotted as a function of the difference between the vaccination start time ($t_a$) and the onset of the initial outbreak ($t_0$; solid gray line). The vaccination campaign durations and daily administration rates are as follows: (1) 300 day campaign with $k=0.001$ (proportional) or $\bar{\nu}_D = 10^5$ (non-proportional) (a1-a4), (2) 40 day campaign with $k=0.01$ or $\bar{\nu}_D = 10^6$ (b1-b4), and (3) 5 day campaign with $k=0.1$ or $\bar{\nu}_D = 10^7$ (c1-c4).
Figure 3.8: Effects of vaccination in the non-proportional model given different levels of population coverage. Simulations were performed using the non-proportional model of vaccination with $\bar{v}_D=10^6$. Inserting infected individual(s) into the susceptible population at $t_0=10$ (gray solid vertical lines). The proportion of people infected over time is plotted for vaccination start times, $t_a=20$ (a-d), $t_a=50$ (e-h), and $t_a=80$ (i-l). Start times are indicated with dashed lines in each panel. The target level of vaccination coverage in the total population varies between 20% and 80%, as indicated. Dotted lines mark the end of the vaccination campaign when the target coverage level is reached. The probability of being confirmed, $p$, is set at either 0.20 (thick gray lines) or 0.65 (thin black lines), and $b$ adjusted accordingly such that $R_0=2.0$ for all simulations. Note that the gray and black lines overlap. The inset in panel (i) illustrates the change in the epidemic dynamics at the time vaccination ends.
Figure 3.9: Wasted vaccines for different population coverage levels, vaccination start times, and proportion of unconfirmed cases. Simulations were performed using the non-proportional model of vaccination with $\bar{\nu}_D=10^6$. Inserting infected individual(s) into the susceptible population at $t_0=10$ (gray solid vertical lines). The proportion of vaccines wasted over time is plotted for vaccination start times, $t_a=20$ (a-d), $t_a=50$ (e-h), and $t_a=80$ (i-l). Start times are indicated with dashed lines in each panel. The target level of vaccination coverage in the total population varies between 20% and 80%, as indicated. Dotted lines mark the end of the vaccination campaign when the target coverage level is reached. The probability of being confirmed, $p$, is set at either 0.20 (thick gray lines) or 0.65 (thin black lines), and $b$ adjusted accordingly such that $R_0=2.0$ for all simulations.
On Chapter 2 I use a metapopulation deterministic model to study the different mechanisms that shaped the multiple outbreaks of the AH1N1 pandemic that occurred in Mexico in 2009 and to assess the different factors that shape similar outbreaks. The factors that were studied in this chapter include; social distancing measures imposed by the government authorities, academic calendar (since kids and students are the main spreaders of diseases) and the possibility of the distribution of an effective vaccine. For Chapter 3 I study further the use of vaccination on a SIR-type model for a single outbreak to establish a novel method implementing realistically the distribution of vaccines by taking into account limitations on stockpile and human resources. In this Chapter 4 we use stochastic modeling to expand our work. The purpose of stochastic models is to estimate the probability of outcomes within a wide range of random trials to predict or estimate the expected value of a possible outbreak. The motivation for this work is to incorporate stochasticity to the multi-city metapopulation deterministic model in order to add more realistic outcomes of simulations that can be adapted to different scenarios.

Stochastic modeling has been extensively studied by Linda Allen (see [9]) and her book discuss different methods of stochastic processes, the main ones being discrete-time Markov chain (DTMC) models, continuous-time Markov chain (CTMC) models, and stochastic differential equation (SDE) models. As briefly discussed in a paper from E. Allen et al. [8] they compare those three methods using a birth-death process model that included demographic and environmental variability. They state that the main difference between the models rely on their continuous or discrete approach. In the case of DTMC time and population size are discrete, for CTMC time is continuous and population size is discrete and for
the case of SDE both time and population size are continuous as in the case of deterministic models. In this dissertation work I will compare deterministic against DTMC, CTMC and SDE. Markov chains are appropriate to use with epidemiological processes because the main property of a stochastic Markov chains is that the next step in time depends solely on the current state and not on how we got there. In epidemiology for example the amount of susceptible individuals that will get infected in the next time step depend on the number of infected individual in the previous step that successfully transmit the disease. Daley and Gani had also studied stochastic modeling [50] and state that discrete time stochastic models can be used in the modeling of disease spreading when the infectious period is short in comparison with the latent period specifically in populations that are small, with a discrete time period as small as the unit of time used. They also state that whenever the size of the population in question is large people should consider using deterministic models.

In order to understand the difference between considering time and/or space continuous versus discrete let’s describe some examples presented in [9]. When we have a falling object (like a ball) we can measure the position of the object at a certain time. In that case we will have a measurement of time and distance in this case both are discrete. In the case that we have a birth process in a population we consider that the time is continuous and the amount of births are discrete. If we consider the density of a species of plant per year we have discrete time and continuous space, the density of the plants grows continuously over time. Finally, when thinking of population density in a time period we have time and space continuous. In that sense it is important to consider continuous Markov chains in our modeling approaches since we are dealing with population dynamics and, as a memoryless process (i.e., the next step only depends on the past), we are dealing with continuous time
Table 4.1: Transition Rates of the SDE Process for the SIS one-city model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S \rightarrow S + 1$</td>
<td>$\alpha I$</td>
<td>$P(S_{t+\Delta t} = s + 1</td>
</tr>
<tr>
<td>$S \rightarrow S - 1$</td>
<td>$\beta \frac{SI}{N}$</td>
<td>$P(S_{t+\Delta t} = s - 1</td>
</tr>
<tr>
<td>$I \rightarrow I + 1$</td>
<td>$\beta \frac{SI}{N}$</td>
<td>$P(I_{t+\Delta t} = i + 1</td>
</tr>
<tr>
<td>$I \rightarrow I - 1$</td>
<td>$\alpha I$</td>
<td>$P(I_{t+\Delta t} = i - 1</td>
</tr>
</tbody>
</table>

and discrete population to specifically consider the amount of infected individuals at a certain point that can potentially spread a disease further.

4.1 Stochastic Differential Equations (SDE)

Using, as a base, classical deterministic models with one or two cities I will construct a stochastic model using a Markov Chain process with discrete time. First we need to identify the transition rates of our system. These transition rates take into consideration the movement of individuals among the compartments. In our stochastic model we are assuming that the parameters are exponentially distributed and the events follow an homogeneous Poisson process with discrete time. In Table 4.1 we show the transition stage table, the rate of the stage and the conditional probability rate for the stochastic process.

4.1.1 One-city model: SIS

In order to get a better understanding of this method let’s consider a simple case using one-city and one infectivity class i.e., a classical SIS model.

\[
\begin{align*}
\dot{S} &= -\beta \frac{SI}{N} + \alpha I \quad (4.1) \\
\dot{I} &= \beta \frac{SI}{N} - \alpha I. \quad (4.2)
\end{align*}
\]
In this case since time is discrete, \( o(\Delta t) \) again denotes a function depending on the time increment with \( \lim_{t \to 0} \frac{o(t)}{t} = 0 \). It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations \( \Delta Z_i \) for \( i = 1, 2 \).

\[
\Delta S = \left( -\beta S \frac{I}{N} + \alpha I \right) \Delta t - \Delta Z_1 + \Delta Z_2 \quad (4.3)
\]

\[
\Delta I = \left( \beta S \frac{I}{N} - \alpha I \right) \Delta t + \Delta Z_1 - \Delta Z_2. \quad (4.4)
\]

The differences of Poisson increments factors can be described as follows for their respective equations:

Eq. (4.3): \( -\Delta Z_1 + \Delta Z_2 \) denotes the transition of an unprotected individual to become infected (\( \Delta Z_1 \)), or an infected individual to recover and become susceptible again (\( \Delta Z_2 \)).

Eq. (4.4): \( \Delta Z_1 - \Delta Z_2 \) denotes the transition of a new infected individuals coming from the unprotected class, (\( \Delta Z_1 \)) or an infected individuals to become susceptible again (\( \Delta Z_2 \)).

**Table 4.2:** Transition Rates using Weiner’s Increments for the SDE Process for an SIS one-city model.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>( G = \sqrt{\text{Transition Rate}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta W_1 = \sqrt{\Delta t} \ r_1 )</td>
<td>( G_1 = \sqrt{\frac{\beta S(t)I(t)}{N}} )</td>
</tr>
<tr>
<td>( \Delta W_2 = \sqrt{\Delta t} \ r_2 )</td>
<td>( G_2 = \sqrt{\alpha I(t)} )</td>
</tr>
</tbody>
</table>
Table 4.3: Transition Rates of the SDE Process for an SIS two cities where \( \lambda_i = \beta S_i \frac{I_i}{N_i} \) (\( i = 1, 2 \)).

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_1 \rightarrow S_1 + 1 )</td>
<td>( \alpha I_1 + q_{21} S_2 )</td>
<td>( P((S_1)_{t+\Delta t} = s_1 + 1</td>
</tr>
<tr>
<td>( S_1 \rightarrow S_1 - 1 )</td>
<td>( \lambda_1 + q_{12} S_1 )</td>
<td>( P((S_1)_{t+\Delta t} = s_1 - 1</td>
</tr>
<tr>
<td>( I_1 \rightarrow I_1 + 1 )</td>
<td>( \lambda_1 + q_{21} I_2 )</td>
<td>( P((I_1)_{t+\Delta t} = i_1 + 1</td>
</tr>
<tr>
<td>( I_1 \rightarrow I_1 - 1 )</td>
<td>( (q_{12} + \alpha) I_1 )</td>
<td>( P((I_1)_{t+\Delta t} = i_1 - 1</td>
</tr>
<tr>
<td>( S_2 \rightarrow S_2 + 1 )</td>
<td>( \alpha I_2 + q_{12} S_1 )</td>
<td>( P((S_2)_{t+\Delta t} = s_2 + 1</td>
</tr>
<tr>
<td>( S_2 \rightarrow S_2 - 1 )</td>
<td>( \lambda_2 + q_{21} S_2 )</td>
<td>( P((S_2)_{t+\Delta t} = s_2 - 1</td>
</tr>
<tr>
<td>( I_2 \rightarrow I_2 + 1 )</td>
<td>( \lambda_2 + q_{12} I_1 )</td>
<td>( P((I_2)_{t+\Delta t} = i_2 + 1</td>
</tr>
<tr>
<td>( I_2 \rightarrow I_2 - 1 )</td>
<td>( (q_{21} + \alpha) I_2 )</td>
<td>( P((I_2)_{t+\Delta t} = i_2 - 1</td>
</tr>
</tbody>
</table>

### 4.1.2 Two cities model: SIS

We now consider two populations each in a different region and each governed by (4.1) - (4.2) and allow for movement between the same type of class in the other region:

\[
\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1}{N_1} + \alpha I_1 - q_{12} S_1 + q_{21} S_2 \\
\dot{I}_1 &= \beta S_1 \frac{I_1}{N_1} - \alpha I_1 - q_{12} I_1 + q_{21} I_2 \\
\dot{S}_2 &= -\beta S_2 \frac{I_2}{N_2} + \alpha I_2 + q_{12} S_1 - q_{21} S_2 \\
\dot{I}_2 &= \beta S_2 \frac{I_2}{N_2} - \alpha I_2 + q_{12} I_1 - q_{21} I_2
\end{align*}
\]

In this case since time is discrete \( o(\Delta t) \) denotes a function depending on the time increment with \( \lim_{t \to 0} \frac{o(t)}{t} = 0 \).

It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations \( \Delta Z_i \) for \( i = 1, \ldots, 8 \).
\[
\Delta S_1 = \left( -\beta S_1 \frac{I_1}{N_1} + \alpha I_1 - q_{12} S_1 + q_{21} S_2 \right) \Delta t - \Delta Z_1 + \Delta Z_2 - \Delta Z_5 + \Delta Z_6 \quad (4.9)
\]
\[
\Delta I_1 = \left( \beta S_1 \frac{I_1}{N_1} - \alpha I_1 - q_{12} I_1 + q_{21} I_2 \right) \Delta t + \Delta Z_1 - \Delta Z_2 - \Delta Z_7 + \Delta Z_8 \quad (4.10)
\]
\[
\Delta S_2 = \left( -\beta S_2 \frac{I_2}{N_2} + \alpha I_2 + q_{12} S_1 - q_{21} S_2 \right) \Delta t - \Delta Z_3 + \Delta Z_4 + \Delta Z_5 - \Delta Z_6 \quad (4.11)
\]
\[
\Delta I_2 = \left( \beta S_2 \frac{I_2}{N_2} - \alpha I_2 + q_{12} I_1 - q_{21} I_2 \right) \Delta t + \Delta Z_3 - \Delta Z_4 + \Delta Z_7 - \Delta Z_8 \quad (4.12)
\]

The differences of Poisson increments factors can be described as follows for their respective equations:

**Eq. (4.9):** \(-\Delta Z_1 + \Delta Z_2 - \Delta Z_5 + \Delta Z_6\) denotes the transition of an unprotected individual to become infected (\(\Delta Z_1\)), or an infected individual to recover and become susceptible again (\(\Delta Z_2\)), or a susceptible individual from city 1 traveling to city 2 (\(\Delta Z_5\)), or a susceptible individual from city 2 traveling to city 1 (\(\Delta Z_6\)).

**Eq. (4.10):** \(\Delta Z_1 - \Delta Z_2 - \Delta Z_7 + \Delta Z_8\) denotes the transition of a new infected individuals coming from the unprotected class, (\(\Delta Z_1\)) or an infected individuals to become susceptible again (\(\Delta Z_2\)), or an infected individual from city 1 traveling to city 2 (\(\Delta Z_7\)), or an infected individual from city 2 traveling to city 1 (\(\Delta Z_8\)).

**Eq. (4.11):** \(-\Delta Z_3 + \Delta Z_4 + \Delta Z_5 - \Delta Z_6\) denotes the transition of an unprotected individual to become infected (\(\Delta Z_3\)), or an infected individual to recover and become susceptible again (\(\Delta Z_4\)), or a susceptible individual from city 1 traveling to city 2 (\(\Delta Z_5\)), or a susceptible individual from city 2 traveling to city 1 (\(\Delta Z_6\)).

**Eq. (4.12):** \(\Delta Z_3 - \Delta Z_4 + \Delta Z_7 - \Delta Z_8\) denotes the transition of a new infected individuals coming from the unprotected class, (\(\Delta Z_3\)) or an infected individuals to become sus-
ceptible again ($\Delta Z_4$), or an infected individual from city 1 traveling to city 2 ($\Delta Z_7$), or an infected individual from city 2 traveling to city 1 ($\Delta Z_8$).

In order to simulate our SDE we need to use the Wiener’s increments and the diffusion approximation of the Markov chain step that depend on the random variables. The Wiener process $W_t$ follows three conditions: $W_0 = 0$, $W_t$ is mostly continuous and $W_t$ has normally distributed independent increments with mean 0 and variance $\Delta t$. The Wiener’s increments can be seen as martingales with $W_0 = 0$ and quadratic variation $[W_t, W_t] = t$. Let $r_i$ for $i = 1, ..., 8$ be randomly normal distributed variables i.e., $r_i \approx N(0, 1)$ then we define the following Weiner’s Increments and corresponding Transition Rate in Table 4.3.

**Table 4.4:** Transition Rates using Weiner’s Increments for the SDE Process for an SIS two cities model.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>G = $\sqrt{\text{Transition Rate}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta W_1 = \sqrt{\Delta t} r_1$</td>
<td>$G_1 = \sqrt{\beta S_1 I_1 N_1}$</td>
</tr>
<tr>
<td>$\Delta W_2 = \sqrt{\Delta t} r_2$</td>
<td>$G_2 = \sqrt{\alpha I_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_3 = \sqrt{\Delta t} r_3$</td>
<td>$G_3 = \sqrt{\beta S_2 I_2 N_2}$</td>
</tr>
<tr>
<td>$\Delta W_4 = \sqrt{\Delta t} r_4$</td>
<td>$G_4 = \sqrt{\alpha I_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_5 = \sqrt{\Delta t} r_5$</td>
<td>$G_5 = \sqrt{q_{12} S_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_6 = \sqrt{\Delta t} r_6$</td>
<td>$G_6 = \sqrt{q_{21} S_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_7 = \sqrt{\Delta t} r_7$</td>
<td>$G_7 = \sqrt{q_{12} I_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_8 = \sqrt{\Delta t} r_8$</td>
<td>$G_8 = \sqrt{q_{21} I_2(t)}$</td>
</tr>
</tbody>
</table>

### 4.1.3 Two cities model: SEUCR

We again consider our system with two cities but now consider two infectivity classes and a latent class:
\[
\begin{align*}
\dot{S}_1 &= -q_{12}S_1 - \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} + q_{21}S_2 \quad (4.13) \\
\dot{E}_1 &= -q_{12}E_1 + \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} - \alpha E_1 + q_{21}E_2 \quad (4.14) \\
\dot{C}_1 &= -q_{12}C_1 + \alpha p E_1 - (\sigma + \delta)C_1 + q_{21}C_2 \quad (4.15) \\
\dot{U}_1 &= -q_{12}U_1 + \alpha (1-p)E_1 - (\sigma + \delta)U_1 + q_{21}U_2 \quad (4.16) \\
\dot{R}_1 &= -q_{12}R_1 + \sigma (C_1 + U_1) + q_{21}R_2 \quad (4.17) \\
\dot{S}_2 &= -q_{21}S_2 - \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12}S_1 \quad (4.18) \\
\dot{E}_2 &= -q_{21}E_2 + \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12}E_1 \quad (4.19) \\
\dot{C}_2 &= -q_{21}C_2 + \alpha p E_2 - (\sigma + \delta)C_2 + q_{12}C_1 \quad (4.20) \\
\dot{U}_2 &= -q_{21}U_2 + \alpha (1-p)E_2 - (\sigma + \delta)U_2 + q_{12}U_1 \quad (4.21) \\
\dot{R}_2 &= -q_{21}R_2 + \sigma (C_2 + U_2) + q_{12}R_1 \quad (4.22)
\end{align*}
\]

As was done in the \(k^{th}\) city model, we simplify the notation in Table 4.5 by defining
\(\lambda_1 = \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1}\) and \(\lambda_2 = \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2}\). In the following table we indicate the different transition stages and the conditional transition rates as defined in the SDE where the time and population size are discrete. In this case since time is discrete \(o(\Delta t)\) denotes a function depending on the time increment with \(\lim_{t \to 0} \frac{o(t)}{t} = 0\) as we have seen before.

It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations \(\Delta Z_i\) for \(i = 1, \ldots, 20\).
Table 4.5: Transition Rates of the SDE Process for an SECUR two cities model with disease induced death. We define $\lambda_1 = \beta S_1 \frac{K_1 + U_1 + \mu E_1}{N_1}$ and $\lambda_2 = \beta S_2 \frac{K_2 + U_2 + \mu E_2}{N_2}$.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1 \rightarrow S_1 + 1$</td>
<td>$q_{21}S_2$</td>
<td>$P((S_1)_{t+\Delta t} = s_1 + 1</td>
</tr>
<tr>
<td>$S_1 \rightarrow S_1 - 1$</td>
<td>$q_{12}S_1 + \lambda_1$</td>
<td>$P((S_1)_{t+\Delta t} = s_1 - 1</td>
</tr>
<tr>
<td>$E_1 \rightarrow E_1 + 1$</td>
<td>$q_{21}E_2 + \lambda_1$</td>
<td>$P((E_1)_{t+\Delta t} = e_1 + 1</td>
</tr>
<tr>
<td>$E_1 \rightarrow E_1 - 1$</td>
<td>$(q_{12} + \alpha)E_1$</td>
<td>$P((E_1)_{t+\Delta t} = e_1 - 1</td>
</tr>
<tr>
<td>$C_1 \rightarrow C_1 + 1$</td>
<td>$q_{21}C_2 + p\alpha E_1$</td>
<td>$P((C_1)_{t+\Delta t} = c_1 + 1</td>
</tr>
<tr>
<td>$C_1 \rightarrow C_1 - 1$</td>
<td>$q_{12}C_1 + (\sigma + \delta)C_1$</td>
<td>$P((C_1)_{t+\Delta t} = c_1 - 1</td>
</tr>
<tr>
<td>$U_1 \rightarrow U_1 + 1$</td>
<td>$q_{21}U_2 + \alpha(1 - p)E_1$</td>
<td>$P((U_1)_{t+\Delta t} = u_1 + 1</td>
</tr>
<tr>
<td>$U_1 \rightarrow U_1 - 1$</td>
<td>$q_{12}U_1 + (\sigma + \delta)U_1$</td>
<td>$P((U_1)_{t+\Delta t} = u_1 - 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 + 1$</td>
<td>$\sigma(U_1 + U_1) + q_{21}R_2$</td>
<td>$P((R_1)_{t+\Delta t} = r_1 + 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 - 1$</td>
<td>$q_{12}R_1$</td>
<td>$P((R_1)_{t+\Delta t} = r_1 - 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 + 1$</td>
<td>$q_{21}S_1$</td>
<td>$P((S_2)_{t+\Delta t} = s_2 + 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 - 1$</td>
<td>$q_{21}S_2 + \lambda_2$</td>
<td>$P((S_2)_{t+\Delta t} = s_2 - 1</td>
</tr>
<tr>
<td>$E_2 \rightarrow E_2 + 1$</td>
<td>$q_{21}E_1 + \lambda_2$</td>
<td>$P((E_2)_{t+\Delta t} = e_2 + 1</td>
</tr>
<tr>
<td>$E_2 \rightarrow E_2 - 1$</td>
<td>$(q_{21} + \alpha)E_2$</td>
<td>$P((E_2)_{t+\Delta t} = e_2 - 1</td>
</tr>
<tr>
<td>$C_2 \rightarrow C_2 + 1$</td>
<td>$q_{21}C_1 + p\alpha E_2$</td>
<td>$P((C_2)_{t+\Delta t} = c_2 + 1</td>
</tr>
<tr>
<td>$C_2 \rightarrow C_2 - 1$</td>
<td>$q_{21}C_2 + (\sigma + \delta)C_2$</td>
<td>$P((C_2)_{t+\Delta t} = c_2 - 1</td>
</tr>
<tr>
<td>$U_2 \rightarrow U_2 + 1$</td>
<td>$q_{21}U_1 + \alpha(1 - p)E_2$</td>
<td>$P((U_2)_{t+\Delta t} = u_2 + 1</td>
</tr>
<tr>
<td>$U_2 \rightarrow U_2 - 1$</td>
<td>$q_{21}U_2 + (\sigma + \delta)U_2$</td>
<td>$P((U_2)_{t+\Delta t} = u_2 - 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 + 1$</td>
<td>$\sigma(U_2 + U_2) + q_{12}R_1$</td>
<td>$P((R_2)_{t+\Delta t} = r_2 + 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 - 1$</td>
<td>$q_{21}R_2$</td>
<td>$P((R_2)_{t+\Delta t} = r_2 - 1</td>
</tr>
</tbody>
</table>
\[ \Delta S_1 = (q_{21}S_2 - q_{12}S_1 - \lambda_1) \Delta t - \Delta Z_1 - \Delta Z_{11} + \Delta Z_{12} \quad (4.23) \]

\[ \Delta E_1 = (q_{21}E_2 + \lambda_1 - (q_{12} + \alpha)E_1) \Delta t + \Delta Z_1 - \Delta Z_2 - \Delta Z_3 + \Delta Z_{13} + \Delta Z_{14} \quad (4.24) \]

\[ \Delta C_1 = (q_{21}C_2 + p\alpha E_1 - q_{12}C_1 - (\sigma + \delta)C_1) \Delta t + \Delta Z_2 - \Delta Z_4 - \Delta Z_{15} + \Delta Z_{16} \quad (4.25) \]

\[ \Delta U_1 = (q_{21}U_2 + \alpha(1 - p)E_1 - q_{12}U_1 - (\sigma - \delta)U_1) \Delta t + \Delta Z_3 - \Delta Z_5 - \Delta Z_{17} \quad (4.26) \]

\[ + \Delta Z_{18} \]

\[ \Delta R_1 = (\sigma(C_1 + U_1) + q_{21}R_2 - q_{12}R_1) \Delta t + \Delta Z_4 + \Delta Z_5 + \Delta Z_{19} + \Delta Z_{20} \quad (4.27) \]

\[ \Delta S_2 = (q_{12}S_1 - q_{21}S_2 - \lambda_2) \Delta t - \Delta Z_6 + \Delta Z_{11} - \Delta Z_{12} \quad (4.28) \]

\[ \Delta E_2 = (q_{12}E_1 + \lambda_2 - (q_{21} + \alpha)E_2) \Delta t + \Delta Z_6 - \Delta Z_7 - \Delta Z_8 + \Delta Z_{13} - \Delta Z_{14} \quad (4.29) \]

\[ \Delta C_2 = (q_{12}C_1 + p\alpha E_2 - q_{21}C_2 - (\sigma + \delta)C_2) \Delta t + \Delta Z_7 - \Delta Z_9 + \Delta Z_{15} - \Delta Z_{16} \quad (4.30) \]

\[ \Delta U_2 = (q_{12}U_1 + \alpha(1 - p)E_2 - q_{21}U_2 - (\sigma - \delta)U_2) \Delta t + \Delta Z_8 - \Delta Z_{10} + \Delta Z_{17} \quad (4.31) \]

\[ - \Delta Z_{18} \]

\[ \Delta R_2 = (\sigma(C_2 + U_2) + q_{12}R_1 - q_{21}R_2) \Delta t + \Delta Z_9 + \Delta Z_{10} + \Delta Z_{19} - \Delta Z_{20} \quad (4.32) \]

The differences of Poisson increments factors can be described as follows for their respective equations:

**Eq. (4.23):** \(-\Delta Z_1 - \Delta Z_{11} + \Delta Z_{12}\) denotes the transition of an unprotected individual from city 1 to become a latent individual \((\Delta Z_1)\), or a susceptible individual traveling to the next city \((\Delta Z_{11})\), or a susceptible individual from city 2 traveling to city 1 \((\Delta Z_{12})\).

**Eq. (4.24):** \(\Delta Z_1 - \Delta Z_2 - \Delta Z_3 - \Delta Z_{13} + \Delta Z_{14}\) denotes the transition of latent individuals from city 1 coming from the unprotected class \((\Delta Z_1)\), or becoming confirmed \((\Delta Z_2)\),
or unconfirmed ($\Delta Z_3$), infected individuals or latent individuals traveling among each city ($\Delta Z_{13}$ and $\Delta Z_{14}$).

**Eq. (4.25):** $\Delta Z_2 - \Delta Z_4 - \Delta Z_{15} + \Delta Z_{16}$ denotes the transition of a confirmed individual from city 1 coming from the latent class ($\Delta Z_2$), or recovering ($\Delta Z_4$), or confirmed individuals traveling among each city ($\Delta Z_{15}$ and $\Delta Z_{16}$).

**Eq. (4.27):** $\Delta Z_3 - \Delta Z_5 - \Delta Z_{17} + \Delta Z_{18}$ denotes the transition of an unconfirmed individual from city 1 coming from the latent class ($\Delta Z_3$), or recovering ($\Delta Z_5$), or unconfirmed individuals traveling among each city ($\Delta Z_{17}$ and $\Delta Z_{18}$).

**Eq. (4.27):** $\Delta Z_4 + \Delta Z_5 - \Delta Z_{19} + \Delta Z_{20}$ denotes the transition of a recovered individual from city 1 coming from the confirmed ($\Delta Z_4$), or unconfirmed class ($\Delta Z_5$), or recovered individuals traveling among each city ($\Delta Z_{19}$ and $\Delta Z_{20}$).

**Eq. (4.28):** $\Delta Z_6 + \Delta Z_{11} - \Delta Z_{12}$ denotes the transition of an unprotected individual from city 2 to become a latent individual ($\Delta Z_6$), or a susceptible individual traveling among each city ($\Delta Z_{11}$ and $\Delta Z_{12}$).

**Eq. (4.29):** $\Delta Z_6 - \Delta Z_7 - \Delta Z_{13} - \Delta Z_{14}$ denotes the transition of latent individuals from city 2 coming from the unprotected class ($\Delta Z_6$), or becoming confirmed ($\Delta Z_7$), or unconfirmed ($\Delta Z_8$), infected individuals or latent individuals traveling among each city ($\Delta Z_{13}$ and $\Delta Z_{14}$).

**Eq. (4.30):** $\Delta Z_7 - \Delta Z_9 + \Delta Z_{15} - \Delta Z_{16}$ denotes the transition of a confirmed individual from city 2 coming from the latent class ($\Delta Z_7$), or recovering ($\Delta Z_9$), or confirmed individuals traveling among each city ($\Delta Z_{15}$ and $\Delta Z_{16}$).
Eq. (4.32): $\Delta Z_8 - \Delta Z_{10} + \Delta Z_{17} - \Delta Z_{18}$ denotes the transition of an unconfirmed individual from city 1 coming from the latent class ($\Delta Z_8$), or recovering ($\Delta Z_{10}$), or unconfirmed individuals traveling among each city ($\Delta Z_{17}$ and $\Delta Z_{18}$).

Eq. (4.32): $\Delta Z_9 + \Delta Z_{10} + \Delta Z_{19} - \Delta Z_{20}$ denotes the transition of an unconfirmed ($\Delta Z_9$), or confirmed ($\Delta Z_{10}$), individual to the recovery class or recovered individuals traveling among each city ($\Delta Z_{19}$ and $\Delta Z_{20}$).

In order to simulate our SDE we need to use the Wiener’s increments and the diffusion approximation of the Markov chain step that depend on the random variables just as we did for the 2-city SIS model. The Wiener process $W_t$ follows three conditions: $W_0 = 0$, $W_t$ is mostly continuous and $W_t$ has normally distributed independent increments with mean $0$ and variance $\Delta t$. The Wiener’s increments can be again seen as martingales with $W_0 = 0$ and quadratic variation $[W_t, W_t] = t$. Let $r_i$ for $i = 1, \ldots, 20$ be randomly normal distributed variables i.e. $r_i \approx N(0,1)$ then we define the following Weiner’s Increments and corresponding Transition Rate Table 4.6

4.2 Simulations for SDE

For the stochastic model I am using as a base the deterministic equations represented as the dotted functions in the following system. As stated previously we use the Poisson increments defined as $\Delta Z_i = G_i \Delta W_i$ to be the Brownian motion increments for the stochastic model normally distributed with mean $0$ and variance $G_i^2$. Since the process we are defining is memoryless and only depends on the previous step we define the system in term of the time elapsed by the $\Delta t$ increments as:
Table 4.6: Transition Rates using Weiner’s Increments for the SDE Process for an SECUR two cities model with disease induced death. We define $\lambda_1 = \beta S_1 \frac{C_1 + U_1 + \mu E_1}{N_1}$ and $\lambda_2 = \beta S_2 \frac{C_2 + U_2 + \mu E_2}{N_2}$.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>$G = \sqrt{\text{Transition Rate}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta W_1 = \sqrt{\Delta t} r_1$</td>
<td>$G_1 = \sqrt{\lambda_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_2 = \sqrt{\Delta t} r_2$</td>
<td>$G_2 = \sqrt{\alpha p E_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_3 = \sqrt{\Delta t} r_3$</td>
<td>$G_3 = \sqrt{\alpha (1 - p) E_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_4 = \sqrt{\Delta t} r_4$</td>
<td>$G_4 = \sqrt{\sigma C_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_5 = \sqrt{\Delta t} r_5$</td>
<td>$G_5 = \sqrt{\sigma U_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_6 = \sqrt{\Delta t} r_6$</td>
<td>$G_6 = \sqrt{\lambda_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_7 = \sqrt{\Delta t} r_7$</td>
<td>$G_7 = \sqrt{\alpha p E_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_8 = \sqrt{\Delta t} r_8$</td>
<td>$G_8 = \sqrt{\alpha (1 - p) E_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_9 = \sqrt{\Delta t} r_9$</td>
<td>$G_9 = \sqrt{\sigma C_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{10} = \sqrt{\Delta t} r_{10}$</td>
<td>$G_{10} = \sqrt{\sigma U_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{11} = \sqrt{\Delta t} r_{11}$</td>
<td>$G_{11} = \sqrt{q_{12} S_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{12} = \sqrt{\Delta t} r_{12}$</td>
<td>$G_{12} = \sqrt{q_{21} S_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{13} = \sqrt{\Delta t} r_{13}$</td>
<td>$G_{13} = \sqrt{q_{12} E_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{14} = \sqrt{\Delta t} r_{14}$</td>
<td>$G_{14} = \sqrt{q_{21} E_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{15} = \sqrt{\Delta t} r_{15}$</td>
<td>$G_{15} = \sqrt{q_{12} C_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{16} = \sqrt{\Delta t} r_{16}$</td>
<td>$G_{16} = \sqrt{q_{21} C_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{17} = \sqrt{\Delta t} r_{17}$</td>
<td>$G_{17} = \sqrt{q_{12} U_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{18} = \sqrt{\Delta t} r_{18}$</td>
<td>$G_{18} = \sqrt{q_{21} U_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{19} = \sqrt{\Delta t} r_{19}$</td>
<td>$G_{19} = \sqrt{q_{12} R_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{20} = \sqrt{\Delta t} r_{20}$</td>
<td>$G_{20} = \sqrt{q_{21} R_2(t)}$</td>
</tr>
</tbody>
</table>
\begin{align*}
S_1(t + 1) &= S_1(t) + \dot{S}_1(t)\Delta t - G_1\Delta W_1 - G_{11}\Delta W_{11} + G_{12}\Delta W_{12} \quad (4.33) \\
E_1(t + 1) &= E_1(t) + \dot{E}_1(t)\Delta t + G_1\Delta W_1 - G_2\Delta W_2 - G_3\Delta W_3 - G_{13}\Delta W_{13} \quad (4.34) \\
&\quad + G_{14}\Delta W_{14} \\
C_1(t + 1) &= C_1(t) + \dot{C}_1(t)\Delta t + G_2\Delta W_2 - G_4\Delta W_4 - G_{15}\Delta W_{15} + G_{16}\Delta W_{16} \quad (4.35) \\
U_1(t + 1) &= U_1(t) + U_1(t)\Delta t + G_3\Delta W_3 - G_5\Delta W_5 - G_{17}\Delta W_{17} + G_{18}\Delta W_{18} \quad (4.36) \\
R_1(t + 1) &= R_1(t) + \dot{R}_1(t)\Delta t + G_4\Delta W_4 + G_5\Delta W_5 - G_{19}\Delta W_{19} + G_{20}\Delta W_{20} \quad (4.37) \\
S_2(t + 1) &= S_2(t) + \dot{S}_2(t)\Delta t - G_6\Delta W_6 + G_{11}\Delta W_{11} - G_{12}\Delta W_{12} \quad (4.38) \\
E_2(t + 1) &= E_2(t) + \dot{E}_2(t)\Delta t + G_6\Delta W_6 - G_7\Delta W_7 - G_8\Delta W_8 + G_{13}\Delta W_{13} \quad (4.39) \\
&\quad - G_{14}\Delta W_{14} \\
C_2(t + 1) &= C_2(t) + \dot{C}_2(t)\Delta t + G_7\Delta W_7 - G_9\Delta W_9 + G_{15}\Delta W_{15} - G_{16}\Delta W_{16} \quad (4.40) \\
U_2(t + 1) &= U_2(t) + U_2(t)\Delta t + G_8\Delta W_8 - G_{10}\Delta W_{10} + G_{17}\Delta W_{17} - G_{18}\Delta W_{18} \quad (4.41) \\
R_2(t + 1) &= R_2(t) + \dot{R}_2(t)\Delta t + G_9\Delta W_9 + G_{10}\Delta W_{10} + G_{19}\Delta W_{19} - G_{20}\Delta W_{20} \quad (4.42)
\end{align*}

4.2.1 Simulations for the Stochastic Differential Equation (SDE):

The following graphs are simulations of the Stochastic Differential Equation (SDE). On Figures 4.1, 4.2 and 4.3 as an illustration we show the total cumulative case, the cumulative cases for city 1 and city 2 respectively of the two-city SEUCR model and their respective box plots and histograms of the final size after $t_f = 50$ days. We are using a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic ($t_0 = 0$) and a basic reproductive number $\mathcal{R}_0 = 2$ using 1000 trials with a time step of $dt = 0.01$. On Figures 4.4, 4.5 and 4.6 we use the same parameters as described above with the exception of adding 10 infected individuals at the beginning of the epidemic.
Figure 4.1: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the total cumulative cases for an SEUCR two cities model with a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic ($t_0 = 0$) and a basic reproductive number $R_0 = 2$ using 1000 trials with a time step of $dt = 0.01$ and for a final time of $t_f = 50$ days. The star in the boxplot represents the final size of the deterministic model.

Figure 4.2: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases in city 1 for an SEUCR two cities model with a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic ($t_0 = 0$) and a basic reproductive number $R_0 = 2$ using 1000 trials with a time step of $dt = 0.01$ and for a final time of $t_f = 50$ days. The star in the boxplot represents the final size of the deterministic model.
Figure 4.3: Cumulative cases (right) and boxplot and histogram (left) of the distribution of the cumulative cases in city 2 for an SEUCR two cities model with a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic ($t_0 = 0$) and a basic reproductive number $\mathcal{R}_0 = 2$ using 1000 trials with a time step of $dt = 0.01$ and for a final time of $t_f = 50$ days. The star in the boxplot represents the final size of the deterministic model.

Figure 4.4: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the total cumulative cases for an SEUCR two cities model with a population of $N = 100$ with an initial condition of 10 infected individual at the beginning of the epidemic ($t_0 = 0$) and a basic reproductive number $\mathcal{R}_0 = 2$ using 1000 trials with a time step of $dt = 0.01$ and for a final time of $t_f = 50$ days.
Figure 4.5: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases in city 1 for an SEUCR two cities model with a population of \( N = 100 \) with an initial condition of 10 infected individual at the beginning of the epidemic \( (t_0 = 0) \) and a basic reproductive number \( R_0 = 2 \) using 1000 trials with a time step of \( dt = 0.01 \) and for a final time of \( t_f = 50 \) days. The star in the boxplot represents the final size of the deterministic model.

Figure 4.6: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases in city 2 for an SEUCR two cities model with a population of \( N = 100 \) with an initial condition of 10 infected individual at the beginning of the epidemic \( (t_0 = 0) \) and a basic reproductive number \( R_0 = 2 \) using 1000 trials with a time step of \( dt = 0.01 \) and for a final time of \( t_f = 50 \) days. The star in the boxplot represents the final size of the deterministic model.
4.3 Continuous Time Markov Chains (CTMC)

In the case of continuous time Markov processes we assume that time is continuous and the population is discrete. For this approach we are using forward Kolmogorov equations as used in [23]. As we stated earlier continuous time Markov processes assume continuous time and discrete space. CTMC as well as DTMC are the type of models that are most used in biological applications[9] and the links between this two stochastic models and the deterministic type can be determined. Hence, we are using the derivation of the forward Kolmogorov equation to establish the connection between the stochastic and discrete model and for this we are presenting a one-city example to go through the process and we worked out the two cities, two epidemic classes model.

4.3.1 Simple example: SIS one-city model

In order to get a better understanding of this method let’s consider a simple case using one-city and one infectivity class i.e., a classical SIS model.

\[
\dot{S} = -\beta S \frac{I}{N} + \alpha I \quad (4.43)
\]

\[
\dot{I} = \beta S \frac{I}{N} - \alpha I \quad (4.44)
\]

By using the following transition variables for \( S \rightarrow i \), and \( I \rightarrow j \) Let’s define the transition stages and rates as follow: The forward Kolmogorov Equation for the above transition rates is:

\[
P'_{i,j}(t) = \beta \frac{(i+1)j}{N} P_{i+1,j}(t) + \beta \frac{i(j-1)}{N} P_{i,j-1}(t) + \alpha (j+1) P_{i,j+1}(t) \quad (4.45)
\]

\[+ \alpha j P_{i-1,j}(t) - 2 \left( \beta \frac{ij}{N} + \alpha j \right) P_{i,j}(t) \]

Note that we use the opposite sign of the transition rate Table D.1 in the Kolmogorov Equations since the idea is that the current stage will always be \( i, j \) hence to get to that
**Table 4.7**: Transition Rates for the CTMC Stochastic Process for an SIS one-city model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i \to i+1)</td>
<td>(\alpha j)</td>
</tr>
<tr>
<td>(i \to i-1)</td>
<td>(\beta_{ij}^{i}N)</td>
</tr>
<tr>
<td>(j \to j+1)</td>
<td>(\beta_{ij}^{j}N)</td>
</tr>
<tr>
<td>(j \to j-1)</td>
<td>(\alpha j)</td>
</tr>
</tbody>
</table>

**Figure 4.7**: Flow chart of the transition stages and rates for the SIS one-city model.

stage we come from either an \(i-1, j; i+1, j; i, j-1\) or \(i, j+1\) stage as it can be seen in the flow chart of the transition stages and rates (D.1). where the probability generating function (p.g.f) is \(\frac{\partial \phi}{\partial t}\).

\[
\phi(r,s) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} P_{i,j}(t)r^i s^j
\]

\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} P'_{i,j}(t)r^i s^j.
\]

Hence,
\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \beta (i + 1) \frac{j}{N} P_{i+1,j}(t) r^i s^j + \beta \frac{(j - 1)}{N} P_{i,j-1}(t) r^i s^j
\]

\[+ \alpha (j + 1) P_{i,j+1}(t) r^i s^j + \alpha j P_{i-1,j}(t) r^i s^j - 2 \left( \beta \frac{i}{N} + \alpha j \right) P_{i,j}(t) r^i s^j \quad (4.48)\]

In order to simplify this equation to have a clean form to get the partial derivatives with respect to \(r\) and \(s\) we need to re-index to get \(P_{ij}\) forms and substitute with partial derivatives.

I am going to demonstrate this step by step:

**First:** For the term \(\sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \beta (i + 1) \frac{j}{N} P_{i+1,j}(t) r^i s^j\) we can substitute \(u = i + 1\) to get

\[
\sum_{u=1}^{\infty} \sum_{j=0}^{\infty} \beta u \frac{j}{N} P_{u,j}(t) r^{u-1} s^j
\]

Since when \(u = 0\) the term inside the summation is still zero we can add that term without problem and we can disregard \(u = 1\) in the summation so we have:

\[
\sum_{u=0}^{\infty} \sum_{j=0}^{\infty} \beta u \frac{j}{N} P_{u,j}(t) r^{u-1} s^j = \sum_{u=0}^{\infty} \sum_{j=0}^{\infty} \beta \frac{u j}{N} P_{u,j}(t) r^{u-1} s^{j-1}
\]

\[
= \frac{\beta s}{N} \sum_{u=0}^{\infty} \sum_{j=0}^{\infty} u j P_{u,j}(t) r^{u-1} s^{j-1}
\]

\[
= \frac{\beta s}{N} \frac{\partial^2 \phi}{\partial r \partial s}
\]

**Second:** For the next term \(\sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \beta i \frac{(j - 1)}{N} P_{i,j-1}(t) r^i s^j\) we can substitute \(u = j - 1\) to get

\[
\sum_{i=0}^{\infty} \sum_{u=-1}^{\infty} \beta i \frac{u}{N} P_{i,u}(t) r^i s^{u+1}
\]

Since we are dealing with probability generating function the random variables need to be non-negative, hence \(P_{-1,j}(t) = 0\) and we can disregard the \(u = -1\) in the summation so we have:

105
\[
\beta \frac{rs^2}{N} \sum_{i=0}^{\infty} \sum_{u=0}^{\infty} iuP_{i,u}(t) r^{i-1} s^{u-1} = \beta \frac{rs^2}{N} \frac{\partial^2 \phi}{\partial r \partial s}
\]

**Third:** For the next terms we follow a similar process: For \(\sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \alpha(j+1)P_{i,j+1}(t) r^i s^j\) we get the expression \(\alpha \frac{\partial \phi}{\partial s}\). Also for \(\sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \alpha jP_{i-1,j}(t) r^i s^j\) we get the expression \(\alpha rs \frac{\partial \phi}{\partial r}\). For the last term \(\sum_{i=0}^{\infty} \sum_{j=0}^{\infty} (2\beta i + 2\alpha j)P_{i,j}(t) r^i s^j\) we get \(2\beta \frac{rs^2}{N} \frac{\partial^2 \phi}{\partial r \partial s} + 2\alpha s \frac{\partial \phi}{\partial s}\).

**Fourth:** We put everything together and get:

\[
\frac{\partial \phi}{\partial t} = \alpha rs \frac{\partial \phi}{\partial r} + (\alpha - 2\alpha s) \frac{\partial \phi}{\partial s} + \left[\beta \frac{s}{N} + \beta \frac{rs^2}{N} - 2\beta \frac{rs}{N}\right] \frac{\partial^2 \phi}{\partial r \partial s}
\]  \quad (4.49)

**Fifth:** Now we take the partial derivative of equation (4.49) with respect to each of the variables:

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) = \alpha s \frac{\partial \phi}{\partial s} + \left[\beta \frac{s^2}{N} - 2\beta \frac{s}{N}\right] \frac{\partial^2 \phi}{\partial r \partial s}
\]  \quad (4.50)

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) = (\alpha r - 2\alpha) \frac{\partial \phi}{\partial s} + [\alpha rs + \alpha - 2\alpha s] \frac{\partial^2 \phi}{\partial s^2}
\]  \quad (4.51)

**Sixth:** Evaluation of the partial derivatives equations (4.50) and (4.51) at \(r = s = 1\) (since we are interested in the expected values) in each case gives back the deterministic SIS model since the expected values of the variables are related to the deterministic SIS model since the expected values of the variables are related to the deterministic...
quantities:

\[ E[S] = \left. \frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=1} = \left. \frac{\partial^2 \phi}{N \partial r \partial s} \right|_{r=s=1} = \alpha \frac{\partial \phi}{\partial s} - \beta \frac{\partial^2 \phi}{N \partial r \partial s} \quad (4.52) \]

\[ E[I] = \left. \frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=1} = \left. \frac{\beta \partial^2 \phi}{N \partial r \partial s} - \alpha \frac{\partial \phi}{\partial s} \right|_{r=s=1} \quad (4.53) \]

For a clear view of the relationship, the expected value of a stochastic random variable in this approach is defined as the partial derivative with respect to the variable in question evaluated at one like we do below.

**Seventh:** In terms of seeing the connection we can interchange \( \frac{\partial \phi}{\partial r} \) with \( S \), \( \frac{\partial \phi}{\partial s} \) with \( I \) as follows:

\[ E[S] = \left. \frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=1} = \alpha \frac{\partial \phi}{\partial s} - \beta \frac{\partial^2 \phi}{N \partial r \partial s} = \alpha I - \frac{\beta IS}{N} \quad (4.54) \]

\[ E[I] = \left. \frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=1} = \beta \frac{\partial^2 \phi}{N \partial r \partial s} - \alpha \frac{\partial \phi}{\partial s} = \frac{\beta IS}{N} - \alpha I \quad (4.55) \]

Hence, using this method we can mathematically follow the connection between the deterministic model and the CTMC stochastic model.

4.3.2 Two-city model: SIS

Now let consider a two-city SIS model

\[ \dot{S}_1 = -\beta S_1 \frac{I_1}{N_1} + \alpha I_1 - q_{12} S_1 + q_{21} S_2 \quad (4.56) \]

\[ \dot{I}_1 = \beta S_1 \frac{I_1}{N_1} - \alpha I_1 - q_{12} I_1 - q_{21} I_2 \quad (4.57) \]

\[ \dot{S}_2 = -\beta S_2 \frac{I_2}{N_2} + \alpha I_2 + q_{12} S_1 - q_{21} S_2 \quad (4.58) \]

\[ \dot{I}_2 = \beta S_2 \frac{I_2}{N_2} - \alpha I_2 + q_{12} I_1 - q_{21} I_2 \quad (4.59) \]
By using the following transition variables for \( S_1 \rightarrow i \), \( I_1 \rightarrow j \), \( S_2 \rightarrow k \) and \( I_2 \rightarrow h \). Let’s define the transition stages and rates as in Table 4.8.

The forward Kolmogorov Equation for the above transition rates is:

\[
P'_{i,j,k,h}(t) = (\alpha j + q_{21}k) P_{i-1,j,k,h}(t) + \left[ \frac{\beta (i+1) j}{N_1} + q_{12}(i+1) \right] P_{i+1,j,k,h}(t) \\
+ (\alpha + q_{12})(j-1) P_{i,j-1,k,h}(t) + \left[ \frac{\beta i(j+1)}{N_1} + q_{21}h \right] P_{i,j+1,k,h}(t) \\
+ \left[ \frac{\beta (k-1)h}{N_2} + q_{21}(k-1) \right] P_{i,j,k-1,h}(t) + (\alpha h + q_{12}i) P_{i,j,k+1,h}(t) \\
+ (\alpha + q_{21})(h-1) P_{i,j,k,h-1}(t) + \left[ \frac{\beta k(h+1)}{N_2} + q_{12}j \right] P_{i,j,k,h+1}(t) \\
- 2 \left[ (\alpha + q_{12}) j + q_{21}k + \frac{\beta i j}{N_1} + q_{12}i + (q_{21} + \alpha)h + \frac{\beta k h}{N_2} \right] P_{i,j,k,h}(t)
\]
Table 4.8: Transition Rates for the CTMC Stochastic Process for an SIS two cities model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i \rightarrow i + 1$</td>
<td>$\alpha j + q_{21}k$</td>
</tr>
<tr>
<td>$i \rightarrow i - 1$</td>
<td>$\frac{\beta_{ij}}{N_i} + q_{12}i$</td>
</tr>
<tr>
<td>$j \rightarrow j + 1$</td>
<td>$\frac{\beta_{ij}}{N_i} + q_{21}h$</td>
</tr>
<tr>
<td>$j \rightarrow j - 1$</td>
<td>$(\alpha + q_{12})j$</td>
</tr>
<tr>
<td>$k \rightarrow k + 1$</td>
<td>$\alpha h + q_{12}i$</td>
</tr>
<tr>
<td>$k \rightarrow k - 1$</td>
<td>$\frac{\beta_{kh}}{N_2} + q_{21}k$</td>
</tr>
<tr>
<td>$h \rightarrow h + 1$</td>
<td>$\frac{\beta_{kh}}{N_2} + q_{12}j$</td>
</tr>
<tr>
<td>$h \rightarrow h - 1$</td>
<td>$(\alpha + q_{21})h$</td>
</tr>
</tbody>
</table>

where the p.g.f is $\frac{\partial \phi}{\partial t}$:

$$
\phi(r, s, w, v) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} P_{i,j,k,h}(t)r^i s^j w^k v^h
$$

(4.61)

$$
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} P'_{i,j,k,h}(t)r^i s^j w^k v^h.
$$

(4.62)
Hence,

\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \left( \alpha j + q_{21} k \right) P_{i-1,j,k,h}(t) r^i s^j w^k v^h
\]

(4.63)

\[
\left[ \frac{\beta (i+1) j}{N_1} + q_{12} (i+1) \right] P_{i+1,j,k,h}(t) r^i s^j w^k v^h
\]

\[
+ (\alpha + q_{12})(j-1)P_{i,j-1,k,h}(t) r^i s^j w^k v^h
\]

\[
+ \left[ \frac{\beta i (j+1)}{N_1} + q_{21} h \right] P_{i,j+1,k,h}(t) r^i s^j w^k v^h
\]

\[
+ \left[ \frac{\beta (k-1) h}{N_2} + q_{21} (k-1) \right] P_{i,j,k-1,h}(t) r^i s^j w^k v^h
\]

\[
+ (\alpha h + q_{12} i) P_{i,j,k+1,h}(t) r^i s^j w^k v^h
\]

\[
+ (\alpha + q_{21})(h-1)P_{i,j,k,h-1}(t) r^i s^j w^k v^h
\]

\[
+ \left[ \frac{\beta k (h+1)}{N_2} + q_{12} j \right] P_{i,j,k,h+1}(t) r^i s^j w^k v^h
\]

\[
- 2 \left[ (\alpha + q_{12}) j + q_{21} k + \frac{\beta i j}{N_1} \right] P_{i,j,k,h}(t) r^i s^j w^k v^h
\]

\[
- 2 \left[ q_{12} i (q_{21} + \alpha) h + \frac{\beta k h}{N_2} \right] P_{i,j,k,h}(t) r^i s^j w^k v^h.
\]

After a lot of re-indexing and simplifications it gives the following equation:

\[
\frac{\partial \phi}{\partial r} = [q_{12}(1 + rw - 2r)] \frac{\partial \phi}{\partial r} + [q_{21}(1 + rw - 2w)] \frac{\partial \phi}{\partial w}
\]

(4.64)

\[
+ [\alpha(1 + rs - 2s) + q_{12}(1 + sv - 2s)] \frac{\partial \phi}{\partial s}
\]

\[
+ [\alpha(1 + wv - 2v) + q_{21}(1 + sv - 2v)] \frac{\partial \phi}{\partial v}
\]

\[
+ \left[ \frac{\beta}{N_1} (s + rs^2 - 2rs) \right] \frac{\partial^2 \phi}{\partial r \partial s} + \left[ \frac{\beta}{N_2} (v + wv^2 - 2wv) \right] \frac{\partial^2 \phi}{\partial w \partial v}.
\]

After taking the partial derivative with respect to each of the variables:
\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) = q_{12}(1 + rw - 2r) \frac{\partial^2 \phi}{\partial r^2} + q_{12}(w - 2) \frac{\partial \phi}{\partial r} + \alpha s \frac{\partial \phi}{\partial s} + q_{21} w \frac{\partial \phi}{\partial w} \tag{4.65}
\]

\[
+ \left[ \frac{\beta}{N_1} (s^2 - 2s) \right] \frac{\partial^2 \phi}{\partial r \partial s} + \left[ \frac{\beta}{N_1} (s + rs^2 - 2rs) \right] \frac{\partial^3 \phi}{\partial r^2 \partial s}.
\]

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) = [\alpha(1 + rs - 2s) + q_{12}(1 + sv - 2s)] \frac{\partial^2 \phi}{\partial s^2} + \alpha(r - 2) \frac{\partial \phi}{\partial s} \tag{4.66}
\]

\[
+ q_{12}(v - 2) \frac{\partial \phi}{\partial s} + q_{21} v \frac{\partial \phi}{\partial v} + \left[ \frac{\beta}{N_1} (1 + 2rs - 2r) \right] \frac{\partial^2 \phi}{\partial r \partial s}
\]

\[
+ \left[ \frac{\beta}{N_1} (s + rs^2 - 2rs) \right] \frac{\partial^3 \phi}{\partial r \partial s^2}.
\]

\[
\frac{\partial}{\partial w} \left( \frac{\partial \phi}{\partial t} \right) = q_{21}(1 + rw - 2w) \frac{\partial^2 \phi}{\partial w^2} + q_{21}(r - 2) \frac{\partial \phi}{\partial w} + q_{12} r \frac{\partial \phi}{\partial r} + \alpha v \frac{\partial \phi}{\partial v} \tag{4.67}
\]

\[
+ \left[ \frac{\beta}{N_2} (v^2 - 2v) \right] \frac{\partial^2 \phi}{\partial w \partial v} + \left[ \frac{\beta}{N_2} (v + wv^2 - 2wv) \right] \frac{\partial^3 \phi}{\partial w^2 \partial v}
\]

\[
\frac{\partial}{\partial v} \left( \frac{\partial \phi}{\partial t} \right) = [\alpha(1 + wv - 2v) + q_{21}(1 + sv - 2v)] \frac{\partial^2 \phi}{\partial v^2} + \alpha(w - 2) \frac{\partial \phi}{\partial v} \tag{4.68}
\]

\[
+ q_{21}(s - 2) \frac{\partial \phi}{\partial s} + q_{12} s \frac{\partial \phi}{\partial s} + \left[ \frac{\beta}{N_2} (v + wv^2 - 2wv) \right] \frac{\partial^3 \phi}{\partial w \partial v^2}
\]

\[
+ \left[ \frac{\beta}{N_2} (1 + 2wv - 2w) \right] \frac{\partial^2 \phi}{\partial w \partial v}.
\]

Evaluation of the partial derivatives at \( r = s = w = v = 1 \) in each case gives back the deterministic SIS two cities model since the expected values of the variables are related to the deterministic quantities. In terms of seeing the connection we can in a sense by interchanging \( \frac{\partial \phi}{\partial r} \) with \( S_1 \), \( \frac{\partial \phi}{\partial s} \) with \( I_1 \), \( \frac{\partial \phi}{\partial w} \) with \( S_2 \), and \( \frac{\partial \phi}{\partial v} \) with \( I_2 \).
\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=w=v=1} = q_{12} \frac{\partial \phi}{\partial r} + \alpha \frac{\partial \phi}{\partial s} + q_{21} \frac{\partial \phi}{\partial w} - \frac{\beta}{N_1} \frac{\partial^2 \phi}{\partial r \partial s} \quad (4.69)
\]

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=w=v=1} = -[\alpha + q_{12}] \frac{\partial \phi}{\partial s} + q_{21} \frac{\partial \phi}{\partial v} + \frac{\beta}{N_1} \frac{\partial^2 \phi}{\partial r \partial s} \quad (4.70)
\]

\[
\frac{\partial}{\partial w} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=w=v=1} = -q_{21} \frac{\partial \phi}{\partial w} + q_{12} \frac{\partial \phi}{\partial r} + \alpha \frac{\partial \phi}{\partial v} + \frac{\beta}{N_2} \frac{\partial^2 \phi}{\partial w \partial v} \quad (4.71)
\]

\[
\frac{\partial}{\partial v} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=w=v=1} = -[\alpha + q_{21}] \frac{\partial \phi}{\partial v} + \frac{\beta}{N_2} \frac{\partial^2 \phi}{\partial w \partial v} \quad (4.72)
\]

Where \( E[S_1] = \left. \frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=w=v=1} \) and similarly for \( E[I_1], E[S_2] \) and \( E[I_2] \).

4.3.3 Two cities model: SEUCR

For the two cities - two infected classes we have:

\[
\dot{S}_1 = -q_{12} S_1 - \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} + q_{21} S_2 \quad (4.73)
\]

\[
\dot{E}_1 = -q_{12} E_1 + \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} - \alpha E_1 + q_{21} E_2 \quad (4.74)
\]

\[
\dot{U}_1 = -q_{12} U_1 + \alpha (1 - p) E_1 - (\sigma + \delta) U_1 + q_{21} U_2 \quad (4.75)
\]

\[
\dot{C}_1 = -q_{12} C_1 + \alpha p E_1 - (\sigma + \delta) C_1 + q_{21} C_2 \quad (4.76)
\]

\[
\dot{R}_1 = -q_{12} R_1 + \sigma (C_1 + U_1) + q_{21} R_2 \quad (4.77)
\]

\[
\dot{S}_2 = -q_{21} S_2 - \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} S_1 \quad (4.78)
\]

\[
\dot{E}_2 = -q_{21} E_2 + \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} E_1 \quad (4.79)
\]

\[
\dot{U}_2 = -q_{21} U_2 + \alpha (1 - p) E_2 - (\sigma + \delta) U_2 + q_{12} U_1 \quad (4.80)
\]

\[
\dot{C}_2 = -q_{21} C_2 + \alpha p E_2 - (\sigma + \delta) C_2 + q_{12} C_1 \quad (4.81)
\]

\[
\dot{R}_2 = -q_{21} R_2 + \sigma (C_2 + U_2) + q_{12} R_1. \quad (4.82)
\]

We use the following transition variables:
$S_1 \rightarrow i, E_1 \rightarrow j, C_1 \rightarrow k, U_1 \rightarrow h, R_1 \rightarrow m, S_2 \rightarrow b, E_2 \rightarrow e, C_2 \rightarrow d, U_2 \rightarrow u,$ and $R_2 \rightarrow o$.

Then we define the transition stages and rates in Table 4.9, where
\[ \lambda_1 = \beta \frac{i^k + h + m_j}{N_1} \] and
\[ \lambda_2 = \beta b \frac{y^d + u + \mu e}{N_1} : \]

**Table 4.9:** Transition Rates for the CTMC stochastic process for an SECUR two cities model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i \rightarrow i+1$</td>
<td>$q_{21} b$</td>
<td>$b \rightarrow b+1$</td>
<td>$q_{12} i$</td>
</tr>
<tr>
<td>$i \rightarrow i-1$</td>
<td>$q_{12} i + \lambda_1$</td>
<td>$b \rightarrow b-1$</td>
<td>$q_{21} b + \lambda_2$</td>
</tr>
<tr>
<td>$j \rightarrow j+1$</td>
<td>$q_{21} e + \lambda_1$</td>
<td>$e \rightarrow e+1$</td>
<td>$q_{12} j + \lambda_2$</td>
</tr>
<tr>
<td>$j \rightarrow j-1$</td>
<td>$(q_{12} + \alpha) j$</td>
<td>$e \rightarrow e-1$</td>
<td>$(q_{21} + \alpha) e$</td>
</tr>
<tr>
<td>$k \rightarrow k+1$</td>
<td>$q_{21} d + p\alpha j$</td>
<td>$d \rightarrow d+1$</td>
<td>$q_{12} k + p\alpha e$</td>
</tr>
<tr>
<td>$k \rightarrow k-1$</td>
<td>$(q_{12} + \sigma + \delta) k$</td>
<td>$d \rightarrow d-1$</td>
<td>$(q_{21} + \sigma + \delta) d$</td>
</tr>
<tr>
<td>$h \rightarrow h+1$</td>
<td>$q_{21} u + \alpha (1-p) j$</td>
<td>$u \rightarrow u+1$</td>
<td>$q_{12} h + \alpha (1-p) e$</td>
</tr>
<tr>
<td>$h \rightarrow h-1$</td>
<td>$(q_{12} + \sigma + \delta) h$</td>
<td>$u \rightarrow u-1$</td>
<td>$(q_{21} + \sigma + \delta) u$</td>
</tr>
<tr>
<td>$m \rightarrow m+1$</td>
<td>$\sigma (k+h) + q_{21} o$</td>
<td>$o \rightarrow o+1$</td>
<td>$\sigma (d+u) + q_{21} m$</td>
</tr>
<tr>
<td>$m \rightarrow m-1$</td>
<td>$q_{12} m$</td>
<td>$o \rightarrow o-1$</td>
<td>$q_{21} o$</td>
</tr>
</tbody>
</table>

In order to save space for notation let $\vec{\omega} = (r, s, x, y, z, a, b, n, g, f, v)$ and define $P_{\vec{\omega}} = P_{i,j,k,h,m,b,e,d,u,o}$ with $P_{\vec{\omega}(i-1)} = P_{i-1,j,k,h,m,b,e,d,u,o}$ to indicate the index that has a change.

After all this notation redefinitions for the two city, two infectivity classes model we get
the following Kolmogorov equation:

\[
P'_\phi = q_{21} b P_{\phi(i-1)}(t) + \left[q_{12}(i+1) + \beta(i+1) \frac{\gamma k + h + \mu j}{N_1}\right] P_{\phi(i+1)}(t) + q_{21} e + \beta i \frac{\gamma k + h + \mu (j-1)}{N_1} \right] P_{\phi(j-1)}(t) + (q_{12} + \alpha)(j+1) P_{\phi(j+1)}(t)
\]

\[
+ [q_{21} d + p \alpha j] P_{\phi(k-1)}(t) + [q_{12} + \sigma - \delta] (k+1) P_{\phi(k+1)}(t)
\]

\[
+ [q_{21} u + \alpha(1-p) j] P_{\phi(h-1)}(t) + [q_{12} + \sigma + \delta] (h+1) P_{\phi(h+1)}(t)
\]

\[
+ [\sigma(k+h) + q_{21} o] P_{\phi(m-1)}(t) + q_{12} (m+1) P_{\phi(m+1)}(t)
\]

\[
+ q_{12} i P_{\phi(b-1)}(t) + \left[q_{21}(b+1) + \beta(b+1) \frac{\gamma d + u + \mu e}{N_2}\right] P_{\phi(b+1)}(t)
\]

\[
+ [q_{12} j + \beta b \frac{\gamma d + u + \mu (e-1)}{N_2}] P_{\phi(e-1)}(t) + (q_{21} + \alpha)(e+1) P_{\phi(e+1)}(t)
\]

\[
+ [q_{12} k + p \alpha e] P_{\phi(d-1)}(t) + [q_{21} + \sigma - \delta] (d+1) P_{\phi(d+1)}(t)
\]

\[
+ [q_{12} h + \alpha(1-p)e] P_{\phi(u-1)}(t) + [q_{21} + \sigma + \delta] (u+1) P_{\phi(u+1)}(t)
\]

\[
- \left(q_{21} b - \left[q_{12} i + \beta i \frac{\gamma k + h + \mu j}{N_1}\right] - \left[q_{21} e - \beta i \frac{\gamma k + h + \mu j}{N_1}\right]\right) P_{\phi(t)}
\]

\[
- ((q_{12} + \alpha) j - [q_{21} d + p \alpha j] - [q_{12} + \sigma - \delta] k - [q_{21} u - \alpha(1-p) j]) P_{\phi(t)}
\]

\[
+ [q_{12} + \sigma + \delta] h P_{\phi(t)} - ((\sigma(k+h) + q_{21} o) - q_{12} m - q_{12} i) P_{\phi(t)}
\]

\[
+ \left(q_{21} b + \beta b \frac{\gamma d + u + \mu e}{N_2}\right) + \left[q_{12} j - \beta b \frac{\gamma d + u + \mu e}{N_2}\right] P_{\phi(t)}
\]

\[
- ((q_{21} + \alpha) e - [q_{12} k + p \alpha e] - [q_{21} + \sigma - \delta] d - [q_{12} h - \alpha(1-p)e]) P_{\phi(t)}
\]

\[
- ((q_{21} + \sigma + \delta) u - [\sigma(d+u) + q_{12} m] + sq_{21} o) P_{\phi(t)}
\]

where the p.g.f is \(\frac{\partial \phi}{\partial t}\)

\[
\phi(r,s,p,q,t) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \sum_{m=0}^{\infty} \sum_{b=0}^{\infty} \sum_{e=0}^{\infty} \sum_{d=0}^{\infty} \sum_{u=0}^{\infty} \sum_{o=0}^{\infty} \sum_{p'=0}^{\infty} \sum_{n'=0}^{\infty} \sum_{g'=0}^{\infty} \sum_{f'=0}^{\infty} \sum_{v'=0}^{\infty} P_{\phi}(t) r^i s^j x^k y^h z^m a^b n^e g^d f^u v^o (4.84)
\]

\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \sum_{m=0}^{\infty} \sum_{b=0}^{\infty} \sum_{e=0}^{\infty} \sum_{d=0}^{\infty} \sum_{u=0}^{\infty} \sum_{o=0}^{\infty} \sum_{p'=0}^{\infty} \sum_{n'=0}^{\infty} \sum_{g'=0}^{\infty} \sum_{f'=0}^{\infty} \sum_{v'=0}^{\infty} P_{\phi}'(t) r^i s^j x^k y^h z^m a^b n^e g^d f^u v^o (4.85)
\]

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After substitution of the derivative we get the following equation for the probability generating function:

\[
\frac{\partial \phi}{\partial t} = q_{21}(1 + ar - 2a) \frac{\partial \phi}{\partial a} + (q_{21}(1 + gx - 2g) + \sigma(1 + gv) + \delta) - 2\sigma g \frac{\partial \phi}{\partial g} \tag{4.86}
\]

\[+ q_{12}(1 + ar - 2r) \frac{\partial \phi}{\partial r} + (q_{12}(1 + xg - 2x) + \sigma(1 + zx) + \delta - (2\sigma + \delta)x) \frac{\partial \phi}{\partial x}
+ q_{12}(1 + vz - 2z) \frac{\partial \phi}{\partial z} + (q_{21}(1 + fy - 2f) + \sigma(1 + vf) + \delta - (2\sigma + \delta)f) \frac{\partial \phi}{\partial f}
+ (q_{21}(1 + zv - 2v) \frac{\partial \phi}{\partial v} + (q_{12}(1 + yf - 2y) + \sigma(1 + vy) + \delta - (2\sigma + \delta)y) \frac{\partial \phi}{\partial y}
+ (\alpha s(p(x - 1) + (1 - p)(y - 1) + q_{12}n - 1) - 2q_{12}s + q_{12} + \alpha) \frac{\partial \phi}{\partial s} - \delta g \frac{\partial \phi}{\partial g}
+ (\alpha s(p(g - 1) + (1 - p)(f - 1) + q_{21}s - 1) - 2q_{21}s + q_{21} + \alpha) \frac{\partial \phi}{\partial n}
+ \frac{\beta y x}{N_1} (1 + sr - 2r) \frac{\partial^2 \phi}{\partial r \partial x} + \frac{\beta y v}{N_1} (1 + sr - 2r) \frac{\partial^2 \phi}{\partial r \partial y} + \frac{\beta y s}{N_1} (1 + sr - 2r) \frac{\partial^2 \phi}{\partial r \partial s}
+ \frac{\beta y r}{N_2} (1 + na - 2a) \frac{\partial^2 \phi}{\partial a \partial d} + \frac{\beta f y}{N_2} (1 + na - 2a) \frac{\partial^2 \phi}{\partial d \partial f}
+ \frac{\beta y n}{N_2} (1 + na - 2a) \frac{\partial^2 \phi}{\partial d \partial n}
\]

After taking the partial derivatives we get the following system of equations:

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_i = -q_{12} \frac{\partial \phi}{\partial r} - \frac{\beta}{N_1} \left[ \gamma \frac{\partial^2 \phi}{\partial r \partial x} + \frac{\partial^2 \phi}{\partial r \partial y} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right] - \frac{q_{21}}{N_1} \frac{\partial \phi}{\partial a} \tag{4.87}
\]

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_i = -q_{12} \frac{\partial \phi}{\partial s} + \frac{\beta}{N_1} \left[ \gamma \frac{\partial^2 \phi}{\partial r \partial x} + \frac{\partial^2 \phi}{\partial r \partial y} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right] + \alpha \frac{\partial \phi}{\partial s} \tag{4.88}
\]

\[+ q_{21} \frac{\partial \phi}{\partial n}
\]

\[
\frac{\partial}{\partial x} \left( \frac{\partial \phi}{\partial r} \right) \bigg|_i = -q_{12} \frac{\partial \phi}{\partial x} + p \alpha \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial x} + q_{21} \frac{\partial \phi}{\partial g} \tag{4.89}
\]

\[
\frac{\partial}{\partial y} \left( \frac{\partial \phi}{\partial r} \right) \bigg|_i = -q_{12} \frac{\partial \phi}{\partial y} + (1 - p) \alpha \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial y} + q_{21} \frac{\partial \phi}{\partial f} \tag{4.90}
\]

\[
\frac{\partial}{\partial z} \left( \frac{\partial \phi}{\partial r} \right) \bigg|_i = -q_{12} \frac{\partial \phi}{\partial z} + \sigma \left( \frac{\partial \phi}{\partial x} + \frac{\partial \phi}{\partial y} \right) + q_{21} \frac{\partial \phi}{\partial v} \tag{4.91}
\]
\[\frac{\partial}{\partial a} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\vec{1}} = -q_{21} \frac{\partial \phi}{\partial a} - \frac{\beta}{N_2} \left[ \gamma \frac{\partial^2 \phi}{\partial a \partial g} + \frac{\partial^2 \phi}{\partial a \partial f} + \mu \frac{\partial^2 \phi}{\partial a \partial n} \right] + q_{12} \frac{\partial \phi}{\partial r} \] (4.92)

\[\frac{\partial}{\partial n} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\vec{1}} = -q_{21} \frac{\partial \phi}{\partial n} + \frac{\beta}{N_2} \left[ \gamma \frac{\partial^2 \phi}{\partial a \partial g} + \frac{\partial^2 \phi}{\partial a \partial f} + \mu \frac{\partial^2 \phi}{\partial a \partial n} \right] + \alpha \frac{\partial \phi}{\partial n} \] (4.93)

\[\frac{\partial}{\partial g} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\vec{1}} = -q_{21} \frac{\partial \phi}{\partial g} + p \alpha \frac{\partial \phi}{\partial n} - (\sigma + \delta) \frac{\partial \phi}{\partial g} + q_{12} \frac{\partial \phi}{\partial x} \] (4.94)

\[\frac{\partial}{\partial f} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\vec{1}} = -q_{21} \frac{\partial \phi}{\partial f} + (1 - p) \alpha \frac{\partial \phi}{\partial n} - (\sigma + \delta) \frac{\partial \phi}{\partial y} + q_{12} \frac{\partial \phi}{\partial y} \] (4.95)

\[\frac{\partial}{\partial v} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\vec{1}} = -q_{21} \frac{\partial \phi}{\partial v} + \sigma \left( \frac{\partial \phi}{\partial g} + \frac{\partial \phi}{\partial f} \right) + q_{12} \frac{\partial \phi}{\partial z} \] (4.96)

where \( \vec{1} = (r = 1, s = 1, x = 1, y = 1, z = 1, a = 1, b = 1, n = 1, g = 1, f = 1, v = 1) \). In the literature [23] they say that migrations terms will not give you the exact deterministic system with the forward Kolmogorov equations back but in our case we did get the system back since our system is closed and the migrations terms are transportation where people go back and forward to their respective cities i.e., there is not a real immigration or emigration process (in which individuals leave or enter the system).

### 4.4 Simulations and results for the Continuous Time Markov Chain:

For the simulations shown below, I ran 1000 trials of the CTMC. The CTMC, as described earlier, assumes continuous time and discrete population size (in each epidemiological class). In this sense we have a bivariate Markov chain for an SIS model and a multivariate Markov Chain for the rest of the models as we add more epidemiological classes. Since the time increments in this method are continuous random variables, in order to compute the mean of all the trials a linear interpolation is needed (see Appendix E for an overview on interpolation methods). In this case I use as a base time vector the same vector I used to compute the solution of the deterministic model using the ode45 solver in
Matlab. Hence, the time vector use for all simulations after the interpolation is applied is the same.

From the simulations presented on Figs. 4.9 - 4.19 on this chapter as well as the Figs. D.2 - D.6 in Appendix D we use a total population of 100 individuals, for a time step of $dt = 0.01$ and parameters comparable to the ones in Table 2.2 and whenever needed I adjust the infectious rate $\beta$ to the appropriate value of $R_0$ I needed. For the two cities epidemic model simulations shown in Figs. 4.11 - 4.19 we use the parameters as defined in Table 2.2. However, for the single city outbreak shown in Figs. D.5 and D.6 I redefine $\beta$ to have an $R_0 = 2$ that can be comparable to the simulations for the two cities models (since for these one is $R_0 = 1.01$ overall with the $R_0 \approx 2$ per city). For the simulations of the SEUCR model it can be observed that as more compartments are added to the system of equations the CTMC approximates the deterministic one more closely overall. Individually we can observe that although the CTMC simulations do not seem to agree with the deterministic one when we take the mean of the 1000 trials, the over and under estimations of the simulations made the overall approximation to be close to the deterministic one when we look more closely at the final size distribution and as it is shown in the boxplot graphs.

In general there are lots of factors that contribute to the mean of the stochastic trials to approach the deterministic simulation. These factors are the initial conditions, the population size, the time step and the amount of trials you run. It is observable that although it has been shown mathematically using the Kolmogorov equations that the deterministic model is the expected value of the stochastic models at least using CTMC, simulation wise it varies depending on the factors listed above. While running different cases (for an example I will use the SIS one city model) it seems that when the initial infected population size, the $R_0$ and the population size is large using at least 1000 trials the deterministic model and the mean of the stochastic simulations are fairly close as we can see on Figs. 4.22 in comparison with Figs. 4.20 and 4.21 Just as shown analytically with the Kolmogorov
Figure 4.9: Infected individuals for and SIS one-city model with a population of \( N = 100 \) and a basic reproductive number \( R_0 = 2 \).

Figure 4.10: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for and SIS one-city model with a population of \( N = 100 \) and a basic reproductive number \( R_0 = 2 \). The start in the boxplot represents the final size of the deterministic model.

equations, the deterministic model is in fact the expected value of the CTMC model in that sense its been noticed that when we have enough trials in any random variable scenario the mean of the trials will converge to the expected value \( [155] \).
Figure 4.11: City 1 exposed individuals for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$.

Figure 4.12: City 1 infected individuals (Confirmed (left) and Unconfirmed (right)) for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$. 
Figure 4.13: City 2 exposed individuals for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $R_0 = 1.01$.

Figure 4.14: City 2 infected individuals (Confirmed (left) and Unconfirmed (right)) for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $R_0 = 1.01$. 

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Figure 4.15: Total Exposed individuals for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$.

Figure 4.16: Total Infected individuals (Confirmed (left) and Unconfirmed (right)) for an SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$. 
Figure 4.17: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for city 1 on the SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$.

Figure 4.18: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for city 2 on the SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$. The star in the boxplot represents the final size of the deterministic model.
Figure 4.19: Total cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases on the SEUCR two cities model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 1.01$.

Figure 4.20: Endemic cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for an SIS one city model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 2$ using 1000 trials. The star in the boxplot represents the final size of the deterministic model.
Figure 4.21: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for an SIS one city model with a population of $N = 10000$ and a basic reproductive number $R_0 = 2$ using 1000 trials. The star in the boxplot represents the final size of the deterministic model.

Figure 4.22: Endemic cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for an SIS one city model with a population of $N = 1000$ and a basic reproductive number $R_0 = 15$ using 1000 trials with an initial condition of $I_0 = 10$. The star in the boxplot represents the final size of the deterministic model.
4.5 Discrete Time Markov Chain (DTMC)

As noted before we define a Markov Chain as a process where the current state (in this case the state of the population) depends only on the past state. This means, that for example, the amount of population at each epidemiological state at time \( t + 1 \) only depends on the population at time \( t \). In the case of the DTMC process the time is discrete as well as the population size at each time step [83, 9]. As discussed in the literature for a DTMC we are using a bivariate Markov chain process because two random variables are used in the process. In this case the random variables are the compartments in our model, hence depending on the complexity of our model a multivariate process might be used, for example, in the case of an SEUCR model. In order to explore the DTMC methodology I use simulations of an SIS and SIR one-city model (see Appendix A).

4.5.1 Simulations for the DTMC SIS and SIR one-city model:

The following simulations illustrate the variability of the simulations compared to the deterministic model when we vary the population size and the time step. We can see that the simulations get better as the time step becomes smaller. For this reason, this method is not well suited for metapopulation modeling because the accuracy of the method depends on the time step of the iterations and not so much on the parameters or population size. Although my personal observations lead me to think that the time step should depend on the population size e.g., \( dt = 1/N \) it is hard to tell. We can observe in the tables that for both cases (SIS and SIR) the simulations agree better as the time step is smaller for any population size. In this case we use \( N = 100, 1000 \) and 10000 and time steps varying between \( dt = 0.01, 0.001 \) and 0.0001. In order to work with metapopulation models we cannot have constraints on population size or guess which time step will work for a particular region due to its population size. In that sense we think that the DTMC Stochastic method is not
suitable for this particular problem. Hence, the DTMC stochastic method is not a suitable method for a metapopulation model where the population from city to city can be of different size magnitudes making it computationally slow if the time step is extremely small and this can make the approximation to the deterministic model not as accurate as desired.
Table 4.10: DTMC Simulation for a one-city SIS model

<table>
<thead>
<tr>
<th>N</th>
<th>dt</th>
<th>Time</th>
<th>Population Size (Infected Individuals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.01</td>
<td>0</td>
<td>Stochastic Average, Deterministic</td>
</tr>
<tr>
<td></td>
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<td>10</td>
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<td>60</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>0.001</td>
<td>0</td>
<td>Stochastic Average, Deterministic</td>
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<tr>
<td></td>
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<td>10</td>
<td></td>
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<td></td>
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<td>60</td>
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<tr>
<td>10000</td>
<td>0.0001</td>
<td>0</td>
<td>Stochastic Average, Deterministic</td>
</tr>
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<td>60</td>
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</tr>
</tbody>
</table>

Discrete Time Markov Chain SIS Model
Table 4.11: DTMC Simulation for a one-city SIR model

<table>
<thead>
<tr>
<th>N</th>
<th>dt</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.01</td>
<td><img src="image1" alt="DTMC Simulation" /></td>
<td><img src="image2" alt="DTMC Simulation" /></td>
<td><img src="image3" alt="DTMC Simulation" /></td>
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<tr>
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<td>0.001</td>
<td><img src="image4" alt="DTMC Simulation" /></td>
<td><img src="image5" alt="DTMC Simulation" /></td>
<td><img src="image6" alt="DTMC Simulation" /></td>
</tr>
<tr>
<td>10000</td>
<td>0.0001</td>
<td><img src="image7" alt="DTMC Simulation" /></td>
<td><img src="image8" alt="DTMC Simulation" /></td>
<td><img src="image9" alt="DTMC Simulation" /></td>
</tr>
</tbody>
</table>
DISCUSSION ON THE COMPARISON OF THE STOCHASTIC MODELS

In order to start assessing the difference between the SDE and the CTMC stochastic approaches we are computing the norm against the deterministic model. For comparison purposes I am using a one city SIR model in Tables 5.1 - 5.4, Figures 5.1 - 5.3 and a two cities SEUCR model for Tables 5.6 and 5.7 and Figures 5.4 and 5.5.

For the tables in this chapter we take the average of 1000 stochastic simulations for the CTMC and the SDE models and take the average and graph both of them along with the deterministic model. For the SDE all the trials use the same time step and it can be averaged normally but for the CTMC the time vector is constructed in each trial using random variables hence for each one of the 1000 trials the time vectors are not the same. In order to take the average of the CTMC trials I use a linear interpolation method (described in Appendix E). For the tables I use the difference of the stochastic average versus the deterministic and computed three different norms (1-Norm, 2-Norm-2 and $\infty$-Norm) where $||x||_\infty \leq ||x||_2 \leq ||x||_1$.

Let $x$ be a vector in $\mathbb{R}^n$ then the norms are defined as follow:

- 1-Norm is the sum of the absolute values of the vector defined as $||x||_1 = \sum_{i=1}^{n} |x_i|$

- 2-Norm is the Euclidean length is defined as $||x||_2 = \left( \sum_{i=1}^{n} |x_i|^2 \right)^{\frac{1}{2}}$

- $\infty$-Norm is the maximum of the absolute value of the elements $||x||_\infty = \max_{i=1...n} |x_i|$
**Table 5.1:** Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the one city simple SIR model with $N = 100$, $R_0 = 2$, step size of $dt = 0.01$ and final time of $t_f = 80$ days.

<table>
<thead>
<tr>
<th></th>
<th>CTMC $x_0 = 1$</th>
<th>CTMC $x_0 = 10$</th>
<th>SDE $x_0 = 1$</th>
<th>SDE $x_0 = 10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Norm</td>
<td>2.1441e+03</td>
<td>1.3455e+03</td>
<td>1.6930e+03</td>
<td>1.2149e+03</td>
</tr>
<tr>
<td>2-Norm</td>
<td>119.1847</td>
<td>57.9679</td>
<td>84.1484</td>
<td>51.2807</td>
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<tr>
<td>$\infty$-Norm</td>
<td>9.8533</td>
<td>3.7366</td>
<td>6.9303</td>
<td>3.1495</td>
</tr>
</tbody>
</table>

**Table 5.2:** Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the one city simple SIR model with $N = 100$, $R_0 = 4$, step size of $dt = 0.01$ and final time of $t_f = 80$ days.

<table>
<thead>
<tr>
<th></th>
<th>CTMC $x_0 = 1$</th>
<th>CTMC $x_0 = 10$</th>
<th>SDE $x_0 = 1$</th>
<th>SDE $x_0 = 10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Norm</td>
<td>1.0008e+03</td>
<td>408.0560</td>
<td>954.8643</td>
<td>399.1073</td>
</tr>
<tr>
<td>2-Norm</td>
<td>61.4594</td>
<td>20.9032</td>
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<td>18.9517</td>
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<tr>
<td>$\infty$-Norm</td>
<td>6.9377</td>
<td>2.2941</td>
<td>6.4136</td>
<td>1.8819</td>
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**Table 5.3:** Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the one city simple SIR model with $N = 1000$, $R_0 = 2$, step size of $dt = 0.01$ and final time of $t_f = 150$ days.

<table>
<thead>
<tr>
<th></th>
<th>CTMC $x_0 = 1$</th>
<th>CTMC $x_0 = 10$</th>
<th>CTMC $x_0 = 100$</th>
<th>SDE $x_0 = 1$</th>
<th>SDE $x_0 = 10$</th>
<th>SDE $x_0 = 100$</th>
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<tr>
<td>1-Norm</td>
<td>2.4800e+04</td>
<td>1.4831e+04</td>
<td>2.8497e+03</td>
<td>1.8716e+04</td>
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<td>2.7946e+03</td>
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<tr>
<td>2-Norm</td>
<td>956.9915</td>
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<td>$\infty$-Norm</td>
<td>68.7402</td>
<td>39.4852</td>
<td>5.6857</td>
<td>61.6305</td>
<td>33.7072</td>
<td>8.8509</td>
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**Table 5.4:** Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the one city simple SIR model with $N = 10000$, $R_0 = 2$, step size of $dt = 0.01$ and final time of $t_f = 150$ days.

<table>
<thead>
<tr>
<th></th>
<th>CTMC $x_0 = 1$</th>
<th>CTMC $x_0 = 10$</th>
<th>CTMC $x_0 = 100$</th>
<th>SDE $x_0 = 1$</th>
<th>SDE $x_0 = 10$</th>
<th>SDE $x_0 = 100$</th>
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</thead>
<tbody>
<tr>
<td>1-Norm</td>
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<td>1.0709e+05</td>
<td>8.2378e+03</td>
<td>1.5837e+05</td>
<td>1.0582e+05</td>
<td>2.2227e+04</td>
</tr>
<tr>
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<td>7.0074e+03</td>
<td>4.7529e+03</td>
<td>326.3591</td>
<td>6.3639e+03</td>
<td>5.0196e+03</td>
<td>991.7575</td>
</tr>
<tr>
<td>$\infty$-Norm</td>
<td>490.4866</td>
<td>335.7597</td>
<td>24.3297</td>
<td>438.0458</td>
<td>355.1881</td>
<td>71.2750</td>
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</tbody>
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Table 5.5: Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the one city simple SIR model with $N = 10000$, $R_0 = 10$, step size of $dt = 0.01$ and final time of $t_f = 150$ days.

<table>
<thead>
<tr>
<th></th>
<th>$x_0 = 1$</th>
<th>$x_0 = 10$</th>
<th>$x_0 = 100$</th>
<th>$x_0 = 1$</th>
<th>$x_0 = 10$</th>
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<tbody>
<tr>
<td>CTMC</td>
<td></td>
<td></td>
<td></td>
<td>SDE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Norm</td>
<td>3.7522e+04</td>
<td>5.7597e+03</td>
<td>593.1980</td>
<td>1.246e+04</td>
<td>2.6009e+04</td>
<td>1.3007e+04</td>
</tr>
<tr>
<td>2-Norm</td>
<td>5.2681e+03</td>
<td>846.5423</td>
<td>64.1283</td>
<td>8.3362e+03</td>
<td>3.9101e+03</td>
<td>2.0384e+03</td>
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<tr>
<td>$\infty$-Norm</td>
<td>1.1091e+03</td>
<td>195.6629</td>
<td>14.2275</td>
<td>$\infty$-Norm</td>
<td>1.6958e+03</td>
<td>879.0797</td>
</tr>
</tbody>
</table>

Table 5.6: Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the SEUCR two cities model with $N = 1000$, $R_0 = 2$ with initial condition $x_0 = 1$, step size of $dt = 0.01$ and final time of $t_f = 150$ days.

<table>
<thead>
<tr>
<th>$x_0 = 1$</th>
<th>City 1 SDE</th>
<th>City 2 SDE</th>
<th>Total SDE</th>
<th>City 1 CTMC</th>
<th>City 2 CTMC</th>
<th>Total CTMC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SDE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Norm</td>
<td>3.4472e+05</td>
<td>4.8521e+05</td>
<td>8.2992e+05</td>
<td>6.4745e+04</td>
<td>1.2648e+05</td>
<td>1.8862e+05</td>
</tr>
<tr>
<td>2-Norm</td>
<td>4.0863e+03</td>
<td>6.4048e+03</td>
<td>1.0468e+04</td>
<td>968.8600</td>
<td>1.6743e+03</td>
<td>2.6346e+03</td>
</tr>
<tr>
<td>$\infty$-Norm</td>
<td>98.5880</td>
<td>160.8380</td>
<td>258.9462</td>
<td>$\infty$-Norm</td>
<td>24.6471</td>
<td>41.4211</td>
</tr>
</tbody>
</table>

Table 5.7: Different norms comparing the difference between the deterministic model vs. the CTMC and the SDE for the SEUCR two cities model with $N = 1000$, $R_0 = 2$ with initial condition $x_0 = 10$, step size of $dt = 0.01$ and final time of $t_f = 150$ days.

<table>
<thead>
<tr>
<th>$x_0 = 10$</th>
<th>City 1 SDE</th>
<th>City 2 SDE</th>
<th>Total SDE</th>
<th>City 1 CTMC</th>
<th>City 2 CTMC</th>
<th>Total CTMC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SDE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-Norm</td>
<td>1.5774e+05</td>
<td>1.5026e+05</td>
<td>3.0800e+05</td>
<td>3.6171e+04</td>
<td>3.7762e+04</td>
<td>7.1769e+04</td>
</tr>
<tr>
<td>2-Norm</td>
<td>1.5270e+03</td>
<td>1.5439e+03</td>
<td>3.0602e+03</td>
<td>462.3504</td>
<td>608.7945</td>
<td>1.0254e+03</td>
</tr>
<tr>
<td>$\infty$-Norm</td>
<td>24.4845</td>
<td>25.0668</td>
<td>49.5513</td>
<td>$\infty$-Norm</td>
<td>10.5396</td>
<td>16.3866</td>
</tr>
</tbody>
</table>
Figure 5.1: Cumulative cases for an SIR one city model with a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic and a basic reproductive number $R_0 = 2$ (top panel), $R_0 = 4$ (middle panel) and $R_0 = 10$ (bottom panel) using 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 80$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.2: Cumulative cases for an SIR one city model with a population of $N = 10000$ with an initial condition of 1 (top panel), 10 (middle panel) and 100 (bottom panel) infected individuals at the beginning of the epidemic and a basic reproductive number $\mathcal{R}_0 = 2$ using 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 150$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.3: Cumulative cases for an SIR one city model with a population of $N = 100$ with an initial condition of 10 infected individual at the beginning of the epidemic and a basic reproductive number $R_0 = 2$ (top panel), $R_0 = 4$ (middle top panel) and $R_0 = 10$ (bottom panel) using 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 80$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.4: Cumulative cases for an SEUCR two cities model with a population of $N = 1000$ with an initial condition of 1 infected individual at the beginning of the epidemic in city 2 (where size of the cities are: $N_2 = \frac{N}{4}$ and $N_1 = N - N_1$) and a basic reproductive number $R_0 = 2$ using 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 150$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.5: Cumulative cases for an SEUCR two cities model with a population of $N = 1000$ with an initial condition of 10 infected individual at the beginning of the epidemic in city 2 (where size of the cities are: $N_2 = \frac{N}{2}$ and $N_1 = N - N_2$) and a basic reproductive number $R_0 = 2$ using 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 150$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Overall we can conclude that the norms decrease as the initial condition (i.e., the number of infected individuals at the beginning of the epidemic) increases for both the CTMC and the SDE stochastic methods. The general pattern is that the norms of the SDE stochastic method are lower than the norms for CTMC for the cumulative cases it is not the case when the population size reaches 10,000 in that case the CTMC has lower norm values. Hence, I can only conclude that there are many factors that affect the outcome such as the value of the $\mathcal{R}_0$, the population size and the initial conditions (the number of infected individuals at the beginning of the epidemic), the latter is the one that mostly affect the approximation since as the initial condition increases, less replicas of the stochastic runs die out early and many of them end out to end of the time period established.

**Final Remarks**

To study the effect of adding small or large noise to the stochastic simulations I study the changes on the behavior of the stochastic and deterministic models when the infectious rate $\alpha$ varies. Recall that here $\alpha$ is the rate of exposed individuals that become infectious and that a fraction $p$ (in this case $p = 0.3$ [60, 104]) are confirmed cases while the rest are unconfirmed. It is noted that in Cai et al. the difference between my SDE model and theirs is that I use a classical mass action force for the flow between susceptible and exposed individuals and they use a different approach where infected individuals play a role in the force of infection i.e., a frequency-dependent transmission of the form $\frac{\beta SI}{S+I}$ where $\beta$ is the proportionality constant.

I present figures illustrating the deterministic model, CTMC stochastic model and the SDE stochastic model. They show the infected and cumulative cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with distinct values of $\alpha = 0.2, 0.4, 0.6, 0.8, 1.0$ and $10.0$ for Figures 5.6, 5.7, 5.8, 5.9, 5.10 and 5.11 respectively. All this figures use a basic reproductive number $\mathcal{R}_0 = 2$ for 1000 trials, step size of $dt =$
0.01 and final time of $t_f = 200$ days. Overall as the infection rate $\alpha$ increases the peak of the epidemic occurs earlier for all the different models. For the SDE model when the value of $\alpha$ increases (hence increasing the noise) the model disagrees with the deterministic model more while the CTMC model stay in a similar disagreement independently of the value of $\alpha$. When the value of $R_0$ is large (around 10) or the initial condition is high ($x_0 = 10$) the value of $\alpha$ does not alter the outcome and all models agree (simulations not shown). There are many parameter value combinations that can be worked out but is beyond the scope of this work to explore all possible scenarios that can affect the outcome of the different models presented in this dissertation.

**Figure 5.6:** Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 0.2$ and a basic reproductive number $R_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
**Figure 5.7:** Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 0.4$ and a basic reproductive number $R_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.

**Figure 5.8:** Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 0.6$ and a basic reproductive number $R_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.9: Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 0.8$ and a basic reproductive number $\mathbb{R}_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.

Figure 5.10: Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 1.0$ and a basic reproductive number $\mathbb{R}_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.
Figure 5.11: Infected (top) and cumulative (bottom) cases for an SEUCR one city model with a population of $N = 1000$, initial condition $x_0 = 1$, with $\alpha = 10.0$ and a basic reproductive number $\mathcal{R}_0 = 2$ for 1000 trials, step size of $dt = 0.01$ and final time of $t_f = 200$ days. The blue line represents the deterministic model, the red line the CTMC stochastic model and the black line is the SDE stochastic model.

As a final note we address the probability of extinction in relation to chapter [4] since the main focus of this work was to simulate and work out the different stochastic methods to compare and contrast them in order to see which one gives a better agreement or which one was easier to implement in terms of constructing a stochastic metapopulation model in the long run. In order to work out the time to extinction for the CTMC method one could use Laplace transformations (see [18]) using a continuous random variable. Artalejo et al. [18] define $L_{ij}$ as the time to extinction of the epidemic given the current population state at time $t$ with $i$ infected individuals and $j$ susceptibles. This random variable is the absorption time; then they define the following probabilities and expected values to be

$$\phi_{ij}(s) = \mathbb{E} \left[ e^{-sL_{ij}} \right], \text{Re}(s) \geq 0 \quad (5.1)$$

$$M^k_{ij} = \mathbb{E} \left[ L_{ij}^k \right], k \geq 0 \quad (5.2)$$
I could apply formulas 5.2 and 5.2 to determine the $\phi_{ij}(s)$ and the moments $M^k_{ij}$ for each of the models I have here using the methods in [18] if we wanted to analytically calculate the time to extinction but it will be done later on in a future extension of the work on this chapter.
Chapter 6

CONCLUSION

The contents of this dissertation work are in metapopulation models and we now summarize the conclusions of the various chapters within this context. For the metapopulation deterministic model presented on the second chapter it can be stated that this work supports the view that the three epidemic “waves” are the result of the synergistic interactions of three main factors: social distancing, academic calendar and connectivity of cities represented in terms of the dynamics of transportation interactions. In particular; we saw the key roles of regional movement patterns of Mexicans, the impact and effectiveness of dramatic social distancing measures imposed during the first outbreak, and the summer release of school children followed by their subsequent return to classes in the fall. The three “waves” cannot be explained by the transportation patterns alone but only through the combination of transport patterns and changes in contact rates due to the use of explicit or scheduled social distancing measures. The research identifies possible vaccination schemes that account for the school calendar and whose effectiveness are enhanced by social distancing measures. The limited impact of the late arrival of the vaccine is also analyzed.

Our results support the notion that the massive governmental intervention measures at the beginning of April did mitigate the spread of influenza but as a result exhausted the supply of the susceptible population. In fact, the first two waves were interrupted by social distancing policies, the closing of schools in the summer, and altered by delays in transportation effectiveness. The only intervention measures during that third wave came from the vaccination of a relatively small group of people that started at the end of November. In other words, México’s transportation structure and the non-uniform flow of individuals over this network contributed significantly to the generation of three outbreaks; the third
significantly larger (and over a longer time span) than the first two. The third outbreak of infection (Fig. 2.3) can therefore be thought of as the result of a fully operational network. The synergistic interactions between transport flow and modulation of the infection rate by social-distancing and school closures seem enough to cause the number of A-H1N1pdm cases to aggregate differently for the different States, thereby forming multiple peaks of different sizes (Fig. 2.3).

To summarize, social distancing and school closures have a delaying effect in the spread of the epidemic. However, the model suggests that an unprotected population is likely to suffer from a secondary or even a third harder epidemic outbreak in comparison to the initial wave if no further mitigation strategies are embraced. Governments can use a strategy based on this knowledge about the possible delays induced in an epidemic outbreak strategy to initially mitigate the spread of influenza while resources become available, but an alarming alternative is that if the resources are not available when the full outbreak occurs, the consequences can be significant depending on the severity of the disease. The A-H1N1pdm virus that caused the 2009 pandemic has been mild in terms of infection and mortality. As reports about transmission and recombination of different influenza viruses increase, and in view of the recent pandemic, which was caused by a novel form of the virus having portions of avian, porcine, and human A type influenza viruses, it may be worthwhile to destine more resources to increase the capacity of mass production of vaccines and treatment in preparation for a possibly more severe influenza epidemic in the future.

From Chapter 3, it can be predicted, based on the numerical solutions of the equations representing the proportional and non-proportional vaccination models, that the different decays in the vaccinable population (Fig. 3.2) would lead to distinct epidemic dynamics. This prediction was confirmed under several vaccination scenarios in which the campaign duration and daily administration limit were such that vaccination ended before the stock-
pall was depleted (Fig. 3.4 and Fig. 3.6). Under such conditions, the non-proportional model always administers a larger total number of vaccines, which results in smaller and later, but sometimes longer, epidemics than in the proportional model. This is true for both moderate and high levels of daily vaccine administration, and is more pronounced the sooner vaccination starts after the initial outbreak.

If instead vaccination continues until the stockpile is depleted, the same total number of vaccines are administered in each model, and the epidemics produced are very similar in time course and severity (Fig. 3.5, Fig. 3.7). The only differences between the two models in these cases are seen under the moderate regime when vaccination starts after the epidemic hits. Then, the slower rate of vaccine administration in the proportional model means that there is a small increase in the susceptibility of the population during the epidemic, which results in a slightly faster and more severe epidemic than in the non-proportional model. In contrast, at low daily rates of administration, the models do not differ much on any measure, regardless of whether the same total number of vaccines is administered. This occurs because so few people are vaccinated per day that the proportional and non-proportional decays in the vaccinable population do not have time to diverge. Thus, the models achieve the same level of vaccine coverage even if the stockpile is not depleted.

One of the largest differences between the two models when different total numbers of vaccines are administered is the epidemic duration. This stems from the increased coverage of the population in the non-proportional model, which allows the epidemic to develop more slowly, but can also cause it to last tens of days longer than predicted by the proportional model. Having the benefit of a smaller, delayed peak could therefore come at a cost, since it could result in a sustained burden on the healthcare system. Models that make more accurate predictions about the length of epidemics will allow health care professionals and medical facilities to prepare accordingly.
The model in Chapter 3 constitutes a theoretical improvement over existing models, with advantages that include data-informed parameter choices, vaccination of multiple epidemiological classes, a reasonable vaccine stockpile, limits on the number of vaccines administered per day, and ways to estimate wasted resources. In particular, the non-proportional vaccine administration implemented in our model may provide more accurate predictions of the mitigating effects of vaccination than proportional models, particularly when moderate or high levels of daily administration are considered. In addition, supply and daily administration capacity can be adjusted to study vaccination strategies in developing nations with limited resources. Government and medical officials can also use the tools provided here to create influenza preparedness plans for specific communities based on their available resources.

For the last project on this dissertation work on stochastic models (Chapters 4 and 5) overall I established that the discrete time Markov chain (DTMC) process can not be reliable since the dependence on the time step increments make it computationally slow and there is no way to determine the appropriate time step size needed without first observing output from the numerical simulations. In that sense, in a metapopulation model there is a lot of variability on the population of particular cities (for example, the capital usually has a larger population that the rest of the cities as is the case of Mexico where the state of Campeche (at least in 2009) has a population size of 754,730 habitants in comparison with 22,728,411 that live in the capital (14,007,495.0 in Estado de Mexico and 8,720,916.0 in the Distrito Federal).

The main result from the continuous time Markov chain implementation that I presented here is the fact that mathematically it has been shown that the expected value of the forward Kolmogorov equations implementation of the stochastic equations is in fact the deterministic system of ordinary differential equations. The only thing that is not always consistent is that the numerical implementation does not quite show this fact as we can see
in Figure 5.1. In this figure we show the cumulative cases for an SIR one city model with a population of $N = 100$ with an initial condition of 1 infected individual at the beginning of the epidemic and different basic reproductive number $\mathcal{R}_0 = 2, 4, 10$ using 1000 trials. In the case when $\mathcal{R}_0 = 2$ (left top panel) the CTMC (red line) as well as the SDE stochastic model (black line) is not consistent with the deterministic solution (blue line) as it was shown mathematically.

As stated before; in the case of DTMC time and population size are discrete, for CTMC time is continuous and population size is discrete, and for the case of SDE both time and population size are continuous as in the case of deterministic models. Hence, it can be hypothesized that the SDE model would be a better approximation but it’s not always the case. There are a lot of factors that affect the approximation of the stochastic models, such as an increase the number of trials run, the value of the parameters used, the $\mathcal{R}_0$, the population size, and more importantly the initial conditions i.e., the number of infected individuals at the beginning of the epidemic. These factors are problematic since the variability of those values can be infinite. It has been established in the literature that stochastic processes approximation resemble more the deterministic models as the population size increases but its not always the case. For instance in Figure 5.4 we can observe that the approximation for the total population seems accurate but when looking at the individual cases for city 1 and city 2 the approximation for the first city is slightly off. This figure present the cumulative cases for an SEUCR two cities model with a population of $N = 1000$ with an initial condition of 1 infected individual at the beginning of the epidemic in city 2, where the size of the cities are: $N_2 = \frac{N}{4}$ and $N_1 = N - N_1$ and a basic reproductive number of $\mathcal{R}_0 = 2$ using 1000 trials. Hence, the key to having a better fit to the deterministic may be to have a large initial condition due to the stochastic trials being able to survive longer when there are more infected individuals at the beginning of an epidemic.
Hence, while this dissertation answered some important questions for metapopulation models this last chapter raises many questions regarding how to establish a regime of parameter values, initial conditions and different factors such as population size and number of trials that need to be explored in order to quantify the variability of the accuracy of this methods in comparison with the deterministic model that has been used for decades.
REFERENCES


[113] Oliver Wyman Group and Program for Appropriate Technology in Health. Influenza vaccine strategies for broad global access, key findings and project methodology, 2007.


APPENDIX A

DETERMINISTIC MODELS
In this appendix, we present the compartment diagrams and corresponding differential equations models for the SIS model, increasing in complexity through the SEUCR model. Only the SIS and SEUCR models were presented in Chapter 2.

A.1 One city model: SIS

![SIS Compartment Diagram]

Figure A.1: Compartment Diagram of an SIS one city model.

\[
\begin{align*}
\dot{S} & = -\beta \frac{SI}{N} + \alpha I \\
\dot{I} & = \beta \frac{SI}{N} - \alpha I \\
\end{align*}
\]  

(A.1)  

(A.2)

A.2 One city model: SIR with demographics

![SIR Compartment Diagram with Vital Dynamics and Death]

Figure A.2: Compartment SIR diagram with vital dynamics (\(\mu\)) and decease induce death (\(\delta\)) for one city.

\[
\begin{align*}
\dot{S} & = -\beta \frac{SI}{N} + \mu N - \mu S \\
\dot{I} & = \beta \frac{SI}{N} - (\sigma + \mu + \delta)I \\
\dot{R} & = \sigma I - \mu R \\
\end{align*}
\]  

(A.3)  

(A.4)  

(A.5)
Figure A.3: Compartment SEIR diagram with decease induce death ($\delta$) for one city.

A.3 One city model: SEIR

\[
\begin{align*}
\dot{S} &= -\beta S \frac{I + \mu E}{N} \\
\dot{E} &= \beta S \frac{I + \mu E}{N} - \alpha E \\
\dot{I} &= \alpha E - (\sigma + \delta)I \\
\dot{R} &= \sigma I 
\end{align*}
\] (A.6) (A.7) (A.8) (A.9)

A.4 One city model: SEUCR

Figure A.4: Compartment SEUCR diagram with decease induce death ($\delta$) for one city.
\[
\begin{align*}
\dot{S} &= -\beta S \frac{\gamma C + U + \mu E}{N} \quad \text{(A.10)} \\
\dot{E} &= \beta S \frac{\gamma C + U + \mu E}{N} - \alpha E \quad \text{(A.11)} \\
\dot{U} &= \alpha (1 - p) E - (\sigma + \delta) U \quad \text{(A.12)} \\
\dot{C} &= \alpha p E - (\sigma + \delta) C \quad \text{(A.13)} \\
\dot{R} &= \sigma (C + U) \quad \text{(A.14)}
\end{align*}
\]

A.5 Two cities model: SIS

Figure A.5: Compartment SIS diagram for two cities.

\[
\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1}{N_1} + \alpha I_1 - q_{12} S_1 + q_{21} S_2 \quad \text{(A.15)} \\
\dot{I}_1 &= \beta S_1 \frac{I_1}{N_1} - \alpha I_1 - q_{12} I_1 + q_{21} I_2 \quad \text{(A.16)} \\
\dot{S}_2 &= -\beta S_2 \frac{I_2}{N_2} + \alpha I_2 + q_{12} S_1 - q_{21} S_2 \quad \text{(A.17)} \\
\dot{I}_2 &= \beta S_2 \frac{I_2}{N_2} - \alpha I_2 + q_{12} I_1 - q_{21} I_2 \quad \text{(A.18)}
\end{align*}
\]
Figure A.6: Compartment SIR diagram with vital dynamics ($\mu$) and decease induce death ($\delta$) for two cities.

A.6 Two cities model: SIR

\[
\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1}{N_1} + \mu N_1 - \mu S_1 - q_{12} S_1 + q_{21} S_2 \quad (A.19) \\
\dot{I}_1 &= \beta S_1 \frac{I_1}{N_1} - (\sigma + \mu + \delta)I_1 - q_{12} I_1 + q_{21} I_2 \quad (A.20) \\
\dot{R}_1 &= \sigma I_1 - \mu R_1 - q_{12} R_1 + q_{21} R_2 \quad (A.21) \\
\dot{S}_2 &= -\beta S_2 \frac{I_2}{N_2} + \mu N_2 - \mu S_2 + q_{12} S_1 - q_{21} S_2 \quad (A.22) \\
\dot{I}_2 &= \beta S_2 \frac{I_2}{N_2} - (\sigma + \mu + \delta)I_2 + q_{12} I_1 - q_{21} I_2 \quad (A.23) \\
\dot{R}_2 &= \sigma I_2 - \mu R_2 + q_{12} R_1 - q_{21} R_2 \quad (A.24)
\end{align*}
\]
Figure A.7: Compartment SEIR diagram with decease induce death ($\delta$) for two cities.

A.7 Two cities model: SEIR

\[
\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1 + \mu E_1}{N_1} - q_{12} S_1 + q_{21} S_2 \quad \text{(A.25)} \\
\dot{E}_1 &= \beta S_1 \frac{I_1 + \mu E_1}{N_1} - \alpha E_1 - q_{12} E_1 + q_{21} E_2 \quad \text{(A.26)} \\
\dot{I}_1 &= \alpha E_1 - (\sigma + \delta) I_1 - q_{12} I_1 + q_{21} I_2 \quad \text{(A.27)} \\
\dot{R}_1 &= \sigma I_1 - q_{12} R_1 + q_{21} R_2 \quad \text{(A.28)} \\
\dot{S}_2 &= -\beta S_2 \frac{I_2 + \mu E_2}{N_2} - q_{12} S_1 - q_{21} S_2 \quad \text{(A.29)} \\
\dot{E}_2 &= \beta S_2 \frac{I_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} E_1 - q_{21} E_2 \quad \text{(A.30)} \\
\dot{I}_2 &= \alpha E_2 - (\sigma + \delta) I_2 + q_{12} I_1 - q_{21} I_2 \quad \text{(A.31)} \\
\dot{R}_2 &= \sigma I_2 + q_{12} R_1 - q_{21} R_2 \quad \text{(A.32)}
\end{align*}
\]
Figure A.8: Compartment SEUCR diagram of two interacting cities with decease induce death ($\delta$). In this case both cities has their own compartmental flow diagram and the arrows between the cities represent the transportation flow. Since transportation is instantaneous it does not alter the epidemiological class of an individual.
A.8 Two cities model: SEUCR

\begin{align*}
\dot{S}_1 &= -q_{12}S_1 - \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} + q_{21}S_2 \quad \text{(A.33)} \\
\dot{E}_1 &= -q_{12}E_1 + \beta S_1 \frac{\gamma C_1 + U_1 + \mu E_1}{N_1} - \alpha E_1 + q_{21}E_2 \quad \text{(A.34)} \\
\dot{U}_1 &= -q_{12}U_1 + \alpha (1 - p)E_1 - (\sigma + \delta)U_1 + q_{21}U_2 \quad \text{(A.35)} \\
\dot{C}_1 &= -q_{12}C_1 + \alpha p E_1 - (\sigma + \delta)C_1 + q_{21}C_2 \quad \text{(A.36)} \\
\dot{R}_1 &= -q_{12}R_1 + \sigma (C_1 + U_1) + q_{21}R_2 \quad \text{(A.37)} \\
\dot{S}_2 &= -q_{21}S_2 - \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} + q_{12}S_1 \quad \text{(A.38)} \\
\dot{E}_2 &= -q_{21}E_2 + \beta S_2 \frac{\gamma C_2 + U_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12}E_1 \quad \text{(A.39)} \\
\dot{U}_2 &= -q_{21}U_2 + \alpha (1 - p)E_2 - (\sigma + \delta)U_2 + q_{12}U_1 \quad \text{(A.40)} \\
\dot{C}_2 &= -q_{21}C_2 + \alpha p E_2 - (\sigma + \delta)C_2 + q_{12}C_1 \quad \text{(A.41)} \\
\dot{R}_2 &= -q_{21}R_2 + \sigma (C_2 + U_2) + q_{12}R_1 \quad \text{(A.42)}
\end{align*}
APPENDIX B

AN EXAMPLE OF THE REPRODUCTIVE NUMBER ON METAPOPULATION MODELS VIA THE SECOND GENERATION OPERATOR
I will present a simple model with transportation among \( k \) cities and discuss how to formulate the basic reproductive number and the effective reproductive number via the Second Generation Operator [144] proposed by van den Driessche and Watmough, in 2002 and highly cited by mathematical epidemiologists. Let’s begin with the definition of the different classes of our model, the diagram and the system of equations following a description of the parameters used. This approach was used in Chapter 2 to obtain equation (2.21, 2.32 and 2.33).

B.1 Definition of Classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( S_k )</td>
<td>Susceptible population in city ( k )</td>
<td>Individuals at risk of becoming infected by a disease</td>
</tr>
<tr>
<td>( L_k )</td>
<td>Latent population in city ( k )</td>
<td>Period between the initiation of a disease and the detection of the disease on an exposed individual</td>
</tr>
<tr>
<td>( I_k )</td>
<td>Infected population in city ( k )</td>
<td>Symptomatic individual that present symptoms of an infection</td>
</tr>
<tr>
<td>( R_k )</td>
<td>Recovered population in city ( k )</td>
<td>Individual that recover from an illness</td>
</tr>
<tr>
<td>( T_k )</td>
<td>Treated population in city ( k )</td>
<td>Individual that has presented symptoms and is been treated with antivirals</td>
</tr>
<tr>
<td>( D_k )</td>
<td>Deceased counter</td>
<td>Mortality cases due to the illness</td>
</tr>
</tbody>
</table>

B.2 System of Equations

\[
\begin{align*}
\dot{S}_k &= \left( -\beta \frac{\mu [L_k + T_k] + I_k}{N_k} \right) S_k + \sum_{i=1}^{4} q_{i0} S_i - \sum_{i=1}^{4} q_{i0} S_i \quad \text{(B.1)} \\
\dot{L}_k &= \left( \beta \frac{\mu [L_k + T_k] + I_k}{N_k} \right) S_k + \beta \frac{\mu R_k L_k}{N_k} - \left( \alpha + \sum_{i=1}^{4} q_{i0} \right) L_k + \sum_{i=1}^{4} q_{i0} L_i \quad \text{(B.2)} \\
\dot{I}_k &= \alpha p_L L_k - \left( \sigma + \delta_T + \phi + \sum_{i=1}^{4} q_{i0} \right) I_k + \sum_{i=1}^{4} q_{i0} I_i \quad \text{(B.3)} \\
\dot{R}_k &= \alpha (1 - p_L) L_k + \psi T_k - \beta \frac{\mu R_k L_k}{N_k} - \sigma I_k - R_k \sum_{i=1}^{4} q_{i0} + \sum_{i=1}^{4} q_{i0} R_i \quad \text{(B.4)} \\
\dot{T}_k &= \phi I_k - \left( \psi + \delta_T + \sum_{i=1}^{4} q_{i0} \right) T_k + \sum_{i=1}^{4} q_{i0} T_i \quad \text{(B.5)} \\
\dot{D}_k &= \delta_T I_k + \delta_T T_k \quad \text{(B.6)}
\end{align*}
\]
Here, $\alpha$ is the infectious rate (transition from $L_k$ to $I_k$), $\mu$ is the reduction factor of infectivity of latent and treated individuals, $\beta$ is the mean infection rate, $\delta_L$ and $\delta_T$ are the disease-induced death rates for the infected and the treated sub-populations, $\sigma$ is the recovery rate for infected individuals, $p_L$ is the probability of getting infectious in the latent class, $\psi$ is the recovery rate for the treated group, $\phi$ is the rate at which infected individuals are treated, and $q_{ij}$ is the per-capita rate at which the population from city $i$ travels to city $j$ per day. All of the above parameters can be assumed to be time-dependent. The matrix $\{q_{ij}\}$ is not necessarily symmetrical, since traveling is assumed to change in time to reflect vacation periods.

The rates at which people travel from one city to another are written in a transition matrix of the form

$$ q = \begin{pmatrix} 0 & q_{01} & q_{02} & q_{03} & q_{04} \\ q_{10} & 0 & 0 & 0 & 0 \\ q_{20} & 0 & 0 & 0 & 0 \\ q_{30} & 0 & 0 & 0 & 0 \\ q_{40} & 0 & 0 & 0 & 0 \end{pmatrix} \quad (B.7) $$

with

$$ q_{ij} = \begin{cases} \frac{m_i}{N_i} & i = 0 \\ \frac{m_i}{N_j} & i > 0 \end{cases} \quad (B.8) $$

Here, $N_i$, $i = 0, \ldots, N_r$, is the number of individuals from the $i$th population, $N_r$ is the number of regions, $m_i, i = 1, \ldots, N_r$ is the number of people that travel between the node, and the $i$th population per day, at time $t$. In principle, $q_{ij}(t)$ can be regarded as constant during off-vacation periods and increase/decrease by a certain percentage $\eta$ during traveling time ($\tau_v$) at the start/end of the vacation periods. The $m_i$'s for $i = 1, \ldots, N_r$ denote the number of people traveling from/to the node city to the population $i$ per day, and $N_i$ is the total population in the $i$th city.

$$ \eta = \begin{cases} (0,1) & \text{if } \tau_{v_{\text{start}}} \leq t \leq \tau_{v_{\text{end}}} \\ 0 & \text{otherwise} \end{cases} \quad (B.3) $$

In this section we discuss the computations to obtain the basic reproductive number $R_0$ and the effective reproductive number $R_e$.

**B.4 Basic Reproductive Number**

The basic reproductive number ($R_0$) is the number of secondary cases a single infectious individual generates during the period of infectivity on a completely susceptible population. We assume that the entire population is susceptible $S_k \approx N_k$, also the epidemic has not started yet, hence $R_k = 0$ and the individuals that can potentially carry on the infection in our models are the latent ($L_k$), infectious ($I_k$), and treated individuals ($T_k$). To compute the $R_0$ we use the second generation operator. Let the vector $F$ be the rate of new infections
flowing to the latent compartment and the vector \( V \) to be the rate of transfer of individuals out of the compartment that are able to transmit the disease \( L_k, I_k \) and \( T_k \). Then using our system of equations we define

\[
F = \begin{bmatrix}
\beta \frac{\mu L_k + T_k}{N_k} S_k \\
0 \\
0
\end{bmatrix}
\quad \text{and} \quad
V = \begin{bmatrix}
\left( \alpha + \sum_{i \neq k} q_{0i} \right) L_k \\
\left( \sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i} \right) I_k - p \alpha L_k \\
\left( \psi + \delta_T + \sum_{i \neq k} q_{0i} \right) T_k - \phi I_k
\end{bmatrix}
\]

to simplify our calculations let's define \( \mathcal{A} = \alpha + \sum_{i \neq k} q_{0i} \), \( \mathcal{O} = \sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i} \), and \( \mathcal{W} = \psi + \delta_T + \sum_{i \neq k} q_{0i} \). In order to compute \( \mathcal{R}_0 \) let the gradient of \( F \) be defined as \( \mathcal{F} = \left[ \frac{\partial F}{\partial L_k}, \frac{\partial F}{\partial I_k}, \frac{\partial F}{\partial T_k} \right] \) and let the gradient of \( V \) be define as \( \mathcal{V} = \left[ \frac{\partial V}{\partial L_k}, \frac{\partial V}{\partial I_k}, \frac{\partial V}{\partial T_k} \right] \) then we get:

\[
\mathcal{F} = \begin{bmatrix}
\mu \beta \\
0 \\
0
\end{bmatrix}
\quad \text{and} \quad
\mathcal{V} = \begin{bmatrix}
\mathcal{A} & 0 & 0 \\
-p \alpha & \mathcal{O} & 0 \\
0 & -\phi & \mathcal{W}
\end{bmatrix}
\]

Then \( \mathcal{R}_0 \) is the spectral radius of the second generation operator \( \rho(\mathcal{F} \mathcal{V}^{-1}) \) also known as the dominant eigenvalue of the matrix \( \mathcal{F} \mathcal{V}^{-1} \). Hence,

\[
\mathcal{F} \mathcal{V}^{-1} = \begin{bmatrix}
\mu \beta & \beta & \mu \beta \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix}
\begin{bmatrix}
\frac{1}{\mathcal{A}} & 0 & 0 \\
-p \alpha & \frac{1}{\mathcal{O}} & 0 \\
\phi p \alpha & \phi & \frac{1}{\mathcal{W}}
\end{bmatrix}
\]

\[
= \begin{bmatrix}
\mu \beta \frac{1}{\mathcal{A}} + \beta p \alpha & \mu \beta \frac{\phi p \alpha}{\mathcal{O} \mathcal{W}} & \beta + \mu \beta \frac{\phi}{\mathcal{W}} & \mu \beta \frac{1}{\mathcal{W}} \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}
\]
Then the dominant eigenvalue of $FV^{-1}$ is $ho(FV^{-1}) = \frac{\mu \beta}{\alpha + \sum_{i \neq k} q_{0i}} + \frac{\beta p \alpha}{(\alpha + \sum_{i \neq k} q_{0i})(\sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i})} + \frac{\mu \beta \phi p \alpha}{(\alpha + \sum_{i \neq k} q_{0i})(\sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i})(\psi + \delta_T + \sum_{i \neq k} q_{0i})}$ which means that the basic reproductive number is:

\[ R_0 = \frac{\mu \beta}{\alpha + \sum_{i \neq k} q_{0i}} + \frac{\beta p \alpha}{(\alpha + \sum_{i \neq k} q_{0i})(\sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i})} + \frac{\mu \beta \phi p \alpha}{(\alpha + \sum_{i \neq k} q_{0i})(\sigma + \delta_I + \phi + \sum_{i \neq k} q_{0i})(\psi + \delta_T + \sum_{i \neq k} q_{0i})} \]

$R_0$ consist of three parts separated by addition: the life span of the infectivity of an latent individual, the life span of an infectivity of an infected individual, and the life span of the infectivity of a treated individual respectively. Since we are working on a multicity model we define $R_{0k}$ to be the basic reproductive number for each individual city and define the whole system $R_0$ to be the maximum of all of them i.e., $R_0 = \max_k (R_{0k})$

### B.5 Effective Reproductive Number

In order to quantify the transmissibility of an ongoing epidemic we explore the concept of the effective reproductive number. The effective reproductive number ($R_e$) quantifies the number of secondary cases a single infectious individual generates during the period of infectivity when the population is not entirely susceptible. Hence the $R_e$ takes into consideration the reduced susceptibility of the population. With a similar approach as the last section we are computing the $R_e$. The effective reproductive number $R_e$ is defined as $R_e = \frac{S(t)}{N(t)} R_0$. Where $\frac{S(t)}{N(t)}$ quantifies the proportion of the population that is susceptible at time $t$. 

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Table C.1: Transition Rates of the SDE Process for the SIR one city model with vital dynamics and \((\delta)\) disease induced death.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S \rightarrow S + 1)</td>
<td>(\mu N)</td>
<td>(P(S_{t+\Delta t} = s + 1</td>
</tr>
<tr>
<td>(S \rightarrow S - 1)</td>
<td>(\beta \frac{N}{N} + \mu S)</td>
<td>(P(S_{t+\Delta t} = s - 1</td>
</tr>
<tr>
<td>(I \rightarrow I + 1)</td>
<td>(\beta \frac{N}{N})</td>
<td>(P(I_{t+\Delta t} = i + 1</td>
</tr>
<tr>
<td>(I \rightarrow I - 1)</td>
<td>((\sigma + \mu + \delta)I)</td>
<td>(P(I_{t+\Delta t} = i - 1</td>
</tr>
<tr>
<td>(R \rightarrow R + 1)</td>
<td>(\mu R)</td>
<td>(P(R_{t+\Delta t} = r + 1</td>
</tr>
<tr>
<td>(R \rightarrow R - 1)</td>
<td>(\mu R)</td>
<td>(P(R_{t+\Delta t} = r - 1</td>
</tr>
</tbody>
</table>

C.1 One city model: SIR with vital dynamics and decease induced death

In Appendix C, we present the SDE approach for the SIR models through the SEIR models. The 1-city SIS and the SEUCR 2-city models are presented in section 4.1 on Chapter 4. Let’s consider a simple case using one city and one infectivity class i.e., a classical SIR model.

\[
\dot{S} = -\beta S \frac{I}{N} + \mu N - \mu S \quad \text{(C.1)}
\]
\[
\dot{I} = \beta S \frac{I}{N} - (\sigma + \mu + \delta)I \quad \text{(C.2)}
\]
\[
\dot{R} = \sigma I - \mu R \quad \text{(C.3)}
\]

In this case since time is discrete \(o(\Delta t)\) denotes a function depending on the time increment with \(\lim_{\Delta t \to 0} \frac{o(\Delta t)}{\Delta t} = 0\). It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations \(\Delta Z_i\) for \(i = 1, ..., 7\).

\[
\Delta S = \left( -\beta S \frac{I}{N} + \mu N - \mu S \right) \Delta t - \Delta Z_1 - \Delta Z_2 + \Delta Z_3 \quad \text{(C.4)}
\]
\[
\Delta I = \left( \beta S \frac{I}{N} - (\sigma + \mu + \delta)I \right) \Delta t + \Delta Z_2 - \Delta Z_4 - \Delta Z_5 - \Delta Z_6 \quad \text{(C.5)}
\]
\[
\Delta R = (\sigma I - \mu R) \Delta t + \Delta Z_4 - \Delta Z_7 \quad \text{(C.6)}
\]

The differences of Poisson increments factors can be described as follows for their respective equations:

**Eq. (C.4):** \(-\Delta Z_1 - \Delta Z_2 + \Delta Z_3\) denotes the death of a susceptible individual (\(\Delta Z_1\)), the transition of an unprotected individual to become infected (\(\Delta Z_2\)), or the birth of a newborn and susceptible individual (\(\Delta Z_3\)).
\[ \Delta Z_2 - \Delta Z_4 - \Delta Z_5 - \Delta Z_6 \] denotes the transition of a new infected individuals coming from the unprotected class (\( \Delta Z_2 \)), or an infected individuals recovering (\( \Delta Z_4 \)), or the death of an infected individual due to natural causes (\( \Delta Z_5 \)), or the death of an infected individual due to the disease (\( \Delta Z_6 \)).

\[ \Delta Z_4 - \Delta Z_7 \] denotes the transition of a new infected individuals that recovers (\( \Delta Z_4 \)), or the death of a recovered individual (\( \Delta Z_7 \)).

**Table C.2:** Transition Rates using Weiner’s Increments for the SDE Process for the SIR one city model with vital dynamics and (\( \delta \)) disease induced death.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>( G = \sqrt{\text{Transition Rate}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta W_1 = \sqrt{\Delta t} r_1 )</td>
<td>( G_1 = \sqrt{\mu N} )</td>
</tr>
<tr>
<td>( \Delta W_2 = \sqrt{\Delta t} r_2 )</td>
<td>( G_2 = \sqrt{\frac{\beta S(t)I(t)}{N}} )</td>
</tr>
<tr>
<td>( \Delta W_3 = \sqrt{\Delta t} r_3 )</td>
<td>( G_3 = \sqrt{\mu S(t)} )</td>
</tr>
<tr>
<td>( \Delta W_4 = \sqrt{\Delta t} r_4 )</td>
<td>( G_4 = \sqrt{\sigma I(t)} )</td>
</tr>
<tr>
<td>( \Delta W_5 = \sqrt{\Delta t} r_5 )</td>
<td>( G_5 = \sqrt{\mu I(t)} )</td>
</tr>
<tr>
<td>( \Delta W_6 = \sqrt{\Delta t} r_6 )</td>
<td>( G_6 = \sqrt{\delta I(t)} )</td>
</tr>
<tr>
<td>( \Delta W_7 = \sqrt{\Delta t} r_7 )</td>
<td>( G_7 = \sqrt{\mu R} )</td>
</tr>
</tbody>
</table>

**C.2 One city model: SEIR**

\[
\begin{align*}
\dot{S} &= -\beta S \frac{I + \mu E}{N} \quad (C.7) \\
\dot{E} &= \beta S \frac{I + \mu E}{N} - \alpha E \quad (C.8) \\
\dot{I} &= \alpha E - (\sigma + \delta) I \quad (C.9) \\
\dot{R} &= \sigma I \quad (C.10)
\end{align*}
\]

In this case since time is discrete \( o(\Delta t) \) denotes a function depending on the time increment with \( \lim_{t \to 0} \frac{o(t)}{t} = 0 \). It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations \( \Delta Z_i \) for \( i = 1, \ldots, 4 \).

\[
\begin{align*}
\Delta S &= \left( -\beta S(t) \frac{I(t) + \mu E(t)}{N} \right) \Delta t - \Delta Z_1 \quad (C.11) \\
\Delta E &= \left( \beta S(t) \frac{I(t) + \mu E(t)}{N} - \alpha E \right) \Delta t + \Delta Z_1 - \Delta Z_2 \quad (C.12) \\
\Delta I &= (\alpha E - (\sigma + \delta) I) \Delta t + \Delta Z_2 - \Delta Z_3 - \Delta Z_4 \quad (C.13) \\
\Delta R &= (\sigma I) \Delta t + \Delta Z_3 \quad (C.14)
\end{align*}
\]
Table C.3: Transition Rates of the SDE Process for the SEIR one city model with vital dynamics and (δ) disease induced death.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>S → S − 1</td>
<td>βS(St + μE)N</td>
<td>P(S_{t+Δt} = s - 1</td>
</tr>
<tr>
<td>E → E + 1</td>
<td>βS(St + μE)N</td>
<td>P(E_{t+Δt} = e + 1</td>
</tr>
<tr>
<td>E → E − 1</td>
<td>αE</td>
<td>P(E_{t+Δt} = e - 1</td>
</tr>
<tr>
<td>I → I + 1</td>
<td>αE</td>
<td>P(I_{t+Δt} = i + 1</td>
</tr>
<tr>
<td>I → I − 1</td>
<td>(σ + δ)I</td>
<td>P(I_{t+Δt} = i - 1</td>
</tr>
<tr>
<td>R → R + 1</td>
<td>σI</td>
<td>P(R_{t+Δt} = r + 1</td>
</tr>
</tbody>
</table>

The differences of Poisson increments factors can be described as follows for their respective equations:

Eq. (C.11): −ΔZ₁ denotes the transition of an unprotected individual to become exposed and incubating the disease (ΔZ₁).

Eq. (C.12): ΔZ₁ − ΔZ₂ denotes the transition of an exposed individual coming from the susceptible class (ΔZ₁), or an exposed individual to become infected (ΔZ₂).

Eq. (C.13): ΔZ₂ − ΔZ₃ − ΔZ₄ denotes the transition of an exposed individual to become infected (ΔZ₂), or an infected individual to recover (ΔZ₃), or an infected individual death due to infection (ΔZ₄).

Eq. (C.14): ΔZ₃ denotes the transition of an infected individuals that recovers (ΔZ₃).

Table C.4: Transition Rates using Weiner’s Increments for the SDE Process for the SEIR one city model with (δ) disease induced death.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>G = √Transition Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆W₁ = √Δt r₁</td>
<td>G₁ = √βS(t)I(t)+μE(t)</td>
</tr>
<tr>
<td>∆W₂ = √Δt r₂</td>
<td>G₂ = √αE(t)</td>
</tr>
<tr>
<td>∆W₃ = √Δt r₃</td>
<td>G₃ = √σI(t)</td>
</tr>
<tr>
<td>∆W₄ = √Δt r₄</td>
<td>G₄ = √δI(t)</td>
</tr>
</tbody>
</table>
Table C.5: Transition Rates of the SDE Process for the SECUR one city model with vital dynamics and $(\delta)$ disease induced death.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S \rightarrow S - 1$</td>
<td>$\beta S \frac{\gamma C + U + \mu E}{N}$</td>
<td>$P(S_{t+\Delta t} = s-1</td>
</tr>
<tr>
<td>$E \rightarrow E + 1$</td>
<td>$\alpha E$</td>
<td>$P(E_{t+\Delta t} = e+1</td>
</tr>
<tr>
<td>$E \rightarrow E - 1$</td>
<td>$\alpha p E$</td>
<td>$P(E_{t+\Delta t} = e-1</td>
</tr>
<tr>
<td>$C \rightarrow C + 1$</td>
<td>$\alpha C$</td>
<td>$P(C_{t+\Delta t} = c+1</td>
</tr>
<tr>
<td>$C \rightarrow C - 1$</td>
<td>$(\sigma + \delta) C$</td>
<td>$P(C_{t+\Delta t} = c-1</td>
</tr>
<tr>
<td>$U \rightarrow U + 1$</td>
<td>$\alpha(1-p) E$</td>
<td>$P(U_{t+\Delta t} = u+1</td>
</tr>
<tr>
<td>$U \rightarrow U - 1$</td>
<td>$(\sigma + \delta) U$</td>
<td>$P(U_{t+\Delta t} = u-1</td>
</tr>
<tr>
<td>$R \rightarrow R + 1$</td>
<td>$\sigma(C+U)$</td>
<td>$P(R_{t+\Delta t} = r+1</td>
</tr>
</tbody>
</table>

C.3 One city model: SEUCR

\[
\dot{S} = -\beta S \frac{\gamma C + U + \mu E}{N} \tag{C.15}
\]
\[
\dot{E} = \beta S \frac{\gamma C + U + \mu E}{N} - \alpha E \tag{C.16}
\]
\[
\dot{C} = \alpha p E - (\sigma + \delta) C \tag{C.17}
\]
\[
\dot{U} = \alpha(1-p) E - (\sigma + \delta) U \tag{C.18}
\]
\[
\dot{R} = \sigma(C+U) \tag{C.19}
\]

In this case since time is discrete $o(\Delta t)$ denotes a function depending on the time increment with $\lim_{t \to 0} \frac{o(t)}{t} = 0$. It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations $\Delta Z_i$ for $i = 1, \ldots, 7$.

\[
\Delta S = \left( -\beta S \frac{\gamma C + U + \mu E}{N} \right) \Delta t - \Delta Z_1 \tag{C.20}
\]
\[
\Delta E = \left( \beta S \frac{\gamma C + U + \mu E}{N} - \alpha E \right) \Delta t + \Delta Z_1 - \Delta Z_2 - \Delta Z_3 \tag{C.21}
\]
\[
\Delta C = (\alpha p E - (\sigma + \delta) C) \Delta t + \Delta Z_2 - \Delta Z_4 - \Delta Z_5 \tag{C.22}
\]
\[
\Delta U = (\alpha(1-p) E - (\sigma + \delta) U) \Delta t + \Delta Z_3 - \Delta Z_6 - \Delta Z_7 \tag{C.23}
\]
\[
\Delta R = (\sigma(C+U)) \Delta t + \Delta Z_4 + \Delta Z_6 \tag{C.24}
\]

The differences of Poisson increments factors can be described as follows for their respective equations:
Eq. (C.20): \(-\Delta Z_1\) denotes the transition of an unprotected individual to become exposed and incubating the disease (\(\Delta Z_1\)).

Eq. (C.21): \(\Delta Z_1 - \Delta Z_2 - \Delta Z_3\) denotes the transition of an exposed individual coming from the susceptible class (\(\Delta Z_1\)), or an exposed individual to become a confirmed infected individual (\(\Delta Z_2\)), or an exposed individual to become an unconfirmed infected individual (\(\Delta Z_3\)).

Eq. (C.22): \(\Delta Z_2 - \Delta Z_4 - \Delta Z_5\) denotes the transition of an exposed individual to become a confirmed infected individual (\(\Delta Z_2\)), or a confirmed infected individual to recover (\(\Delta Z_4\)), or a confirmed infected individual dying due to infection (\(\Delta Z_5\)).

Eq. (C.23): \(\Delta Z_3 - \Delta Z_6 - \Delta Z_7\) denotes the transition of an exposed individual to become an unconfirmed infected individual (\(\Delta Z_3\)), or an unconfirmed infected individual to recover (\(\Delta Z_6\)), or an unconfirmed infected individual dying due to infection (\(\Delta Z_7\)).

Eq. (C.24): \(\Delta Z_4 + \Delta Z_6\) denotes the transition of a confirmed infected individuals to recover (\(\Delta Z_4\)), or an unconfirmed infected individual to recover (\(\Delta Z_6\)).

Table C.6: Transition Rates using Weiner’s Increments for the SDE Process for the SECUR one city model with disease induced death (\(\delta\)).

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>G = (\sqrt{\text{Transition Rate}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta W_1 = \sqrt{\Delta t} \ r_1)</td>
<td>(G_1 = \sqrt{\beta S(t) \frac{r_c(t) + \mu E(t)}{N}})</td>
</tr>
<tr>
<td>(\Delta W_2 = \sqrt{\Delta t} \ r_2)</td>
<td>(G_2 = \sqrt{\alpha p E(t)})</td>
</tr>
<tr>
<td>(\Delta W_3 = \sqrt{\Delta t} \ r_3)</td>
<td>(G_3 = \sqrt{\alpha (1 - p) E(t)})</td>
</tr>
<tr>
<td>(\Delta W_4 = \sqrt{\Delta t} \ r_4)</td>
<td>(G_4 = \sqrt{\sigma C(t)})</td>
</tr>
<tr>
<td>(\Delta W_5 = \sqrt{\Delta t} \ r_5)</td>
<td>(G_5 = \sqrt{\delta C(t)})</td>
</tr>
<tr>
<td>(\Delta W_6 = \sqrt{\Delta t} \ r_6)</td>
<td>(G_6 = \sqrt{\sigma U(t)})</td>
</tr>
<tr>
<td>(\Delta W_7 = \sqrt{\Delta t} \ r_7)</td>
<td>(G_7 = \sqrt{\delta U(t)})</td>
</tr>
</tbody>
</table>
Table C.7: Transition Rates of the SDE Process for an SIR two cities model with vital dynamics and disease induced death. We define $\lambda_1(t) = \beta S_1 \frac{I_1}{N_1}$ and $\lambda_2(t) = \beta S_2 \frac{I_2}{N_2}$.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1 \rightarrow S_1 + 1$</td>
<td>$\mu N_1 + q_{21} S_2$</td>
<td>$P((S_1)_{l+\Delta t} = s_1 + 1</td>
</tr>
<tr>
<td>$S_1 \rightarrow S_1 - 1$</td>
<td>$\lambda_1 + (\mu + q_{12}) S_1$</td>
<td>$P((S_1)_{l+\Delta t} = s_1 - 1</td>
</tr>
<tr>
<td>$I_1 \rightarrow I_1 + 1$</td>
<td>$q_{21} I_2 + \lambda_1$</td>
<td>$P((I_1)_{l+\Delta t} = i_1 + 1</td>
</tr>
<tr>
<td>$I_1 \rightarrow I_1 - 1$</td>
<td>$(\sigma + \mu + \delta + q_{12}) I_1$</td>
<td>$P((I_1)_{l+\Delta t} = i_1 - 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 + 1$</td>
<td>$\sigma I_1 + q_{21} R_2$</td>
<td>$P((R_1)_{l+\Delta t} = r_1 + 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 - 1$</td>
<td>$\mu R_1 + q_{12} R_1$</td>
<td>$P((R_1)_{l+\Delta t} = r_1 - 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 + 1$</td>
<td>$\mu N_2 + q_{12} S_2$</td>
<td>$P((S_2)_{l+\Delta t} = s_2 + 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 - 1$</td>
<td>$\lambda_2 + (\mu + q_{21}) S_2$</td>
<td>$P((S_2)_{l+\Delta t} = s_2 - 1</td>
</tr>
<tr>
<td>$I_2 \rightarrow I_2 + 1$</td>
<td>$q_{12} I_1 + \lambda_2$</td>
<td>$P((I_2)_{l+\Delta t} = i_2 + 1</td>
</tr>
<tr>
<td>$I_2 \rightarrow I_2 - 1$</td>
<td>$(\sigma + \mu + \delta + q_{12}) I_2$</td>
<td>$P((I_2)_{l+\Delta t} = i_2 - 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 + 1$</td>
<td>$\sigma I_2 + q_{12} R_1$</td>
<td>$P((R_2)_{l+\Delta t} = r_2 + 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 - 1$</td>
<td>$\mu R_2 + q_{21} R_2$</td>
<td>$P((R_2)_{l+\Delta t} = r_2 - 1</td>
</tr>
</tbody>
</table>

C.4 Two cities model: SIR

\[
\begin{align*}
S_1' &= -\beta S_1 \frac{I_1}{N_1} + \mu N_1 - \mu S_1 - q_{12} S_1 + q_{21} S_2 \tag{C.25} \\
I_1' &= \beta S_1 \frac{I_1}{N_1} - (\sigma + \mu + \delta) I_1 - q_{12} I_1 + q_{21} I_2 \tag{C.26} \\
R_1' &= \sigma I_1 - \mu R_1 - q_{12} R_1 + q_{21} R_2 \tag{C.27} \\
S_2' &= -\beta S_2 \frac{I_2}{N_2} + \mu N_2 - \mu S_2 + q_{12} S_1 - q_{21} S_2 \tag{C.28} \\
I_2' &= \beta S_2 \frac{I_2}{N_2} - (\sigma + \mu + \delta) I_2 + q_{12} I_1 - q_{21} I_2 \tag{C.29} \\
R_2' &= \sigma I_2 - \mu R_2 + q_{12} R_1 - q_{21} R_2 \tag{C.30} 
\end{align*}
\]

In the following table we indicate the different transition stages and the conditional transition rates as defined in the DCTM where the time and population size are discrete.

In this case since time is discrete $o(\Delta t)$ denotes a function depending on the time increment with $\lim_{t \to 0} \frac{o(t)}{t} = 0$.

It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations $\Delta Z_i$ for $i = 1, \ldots, 20$. 

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\( \Delta S_1 = \left( -\beta S_1 \frac{I_1}{N_1} + \mu N_1 - \mu S_1 - q_{12} S_1 + q_{21} S_2 \right) \Delta t - \Delta Z_1 + \Delta Z_2 - \Delta Z_3 \quad (C.31) \)

\( \Delta I_1 = \left( \beta S_1 \frac{I_1}{N_1} - (\sigma + \mu + \delta + q_{12}) I_1 + q_{21} I_2 \right) \Delta t + \Delta Z_1 - \Delta Z_6 - \Delta Z_7 \quad (C.32) \)

\( \Delta R_1 = (\sigma I_1 - \mu R_1 - q_{12} R_1 + q_{21} R_2) \Delta t + \Delta Z_6 - \Delta Z_{11} - \Delta Z_{12} + \Delta Z_{13} \quad (C.33) \)

\( \Delta S_2 = \left( -\beta S_2 \frac{I_2}{N_2} + \mu N_2 - \mu S_2 - q_{12} S_1 - q_{21} S_2 \right) \Delta t - \Delta Z_{14} + \Delta Z_{15} \quad (C.34) \)

\( \Delta I_2 = \left( \beta S_2 \frac{I_2}{N_2} - (\sigma + \mu + \delta + q_{21}) I_2 + q_{12} I_1 \right) \Delta t + \Delta Z_{14} - \Delta Z_{17} - \Delta Z_{18} \quad (C.35) \)

\( \Delta R_2 = (\sigma I_2 - \mu R_2 + q_{12} R_1 - q_{21} R_2) \Delta t + \Delta Z_{17} - \Delta Z_{20} + \Delta Z_{12} - \Delta Z_{13} \quad (C.36) \)

The differences of Poisson increments factors can be described as follows for their respective equations:

**Eq. (C.31):** \( -\Delta Z_1 + \Delta Z_2 - \Delta Z_3 - \Delta Z_4 + \Delta Z_5 \) denotes the transition of an unprotected individual to become infected (\( \Delta Z_1 \)), or the birth of a newborn and susceptible individual (\( \Delta Z_2 \)), or the death of a susceptible individual (\( \Delta Z_3 \)), or a susceptible individual from city 1 traveling to city 2 (\( \Delta Z_4 \)), or a susceptible individual from city 1 (\( \Delta Z_5 \)).

**Eq. (C.32):** \( \Delta Z_1 - \Delta Z_6 - \Delta Z_7 - \Delta Z_8 - \Delta Z_9 + \Delta Z_{10} \) denotes the transition of a new infected individuals coming from the unprotected class (\( \Delta Z_2 \)), or an infected individuals recovering (\( \Delta Z_4 \)), or the death of an infected individual due to natural causes (\( \Delta Z_5 \)), or the death of an infected individual due to the disease (\( \Delta Z_6 \)).

**Eq. (C.33):** \( \Delta Z_6 - \Delta Z_{11} - \Delta Z_{12} + \Delta Z_{13} \) denotes the transition of a new infected individuals that recovers (\( \Delta Z_4 \)), or the death of a recovered individual (\( \Delta Z_7 \)).

**Eq. (C.34):** \( \Delta Z_{14} + \Delta Z_{15} - \Delta Z_{16} - \Delta Z_4 - \Delta Z_5 \) denotes the death of a susceptible individual (\( \Delta Z_1 \)), the transition of an unprotected individual to become infected (\( \Delta Z_2 \)), or the birth of a newborn and susceptible individual (\( \Delta Z_3 \)).

**Eq. (C.35):** \( \Delta Z_{14} - \Delta Z_{17} - \Delta Z_{18} - \Delta Z_{19} + \Delta Z_9 - \Delta Z_{10} \) denotes the transition of a new infected individuals coming from the unprotected class (\( \Delta Z_2 \)), or an infected individuals recovering (\( \Delta Z_4 \)), or the death of an infected individual due to natural causes (\( \Delta Z_5 \)), or the death of an infected individual due to the disease (\( \Delta Z_6 \)).

**Eq. (C.36):** \( \Delta Z_{17} - \Delta Z_{20} + \Delta Z_{12} - \Delta Z_{13} \) denotes the transition of a new infected individuals that recovers (\( \Delta Z_4 \)), or the death of a recovered individual (\( \Delta Z_7 \)).
In order to simulate our Stochastic Differential Equations we need to use the Wiener’s increments and the diffusion approximation of the Markov chain step that depend on the random variables. The Wiener process \( W_t \) follows three conditions: \( W_0 = 0 \), \( W_t \) is mostly continuous and \( W_t \) has normally distributed independent increments with mean 0 and variance \( \Delta t \). The Wiener’s increments can be seen as martingales with \( W_0 = 0 \) and quadratic variation \( [W_t, W_t] = t \). Let \( r_i \) for \( i = 1, \ldots, 20 \) be randomly normal distributed variables i.e. \( r_i \approx N(0,1) \) then we define the following Weiner’s Increments and corresponding Transition Rate in Table C.8.

**Table C.8:** Transition Rates using Weiner’s Increments for the SDE Process for an SIR two cities model with vital dynamics and disease induced death. We define \( \lambda_1(t) = \beta S_1(t) \frac{I_1(t)}{N_1} \) and \( \lambda_2(t) = \beta S_2(t) \frac{I_2(t)}{N_2} \).

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>( G = \sqrt{\text{Transition Rate}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta W_1 = \sqrt{\Delta t} r_1 )</td>
<td>( G_1 = \sqrt{\mu N_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_2 = \sqrt{\Delta t} r_2 )</td>
<td>( G_2 = \sqrt{\lambda_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_3 = \sqrt{\Delta t} r_3 )</td>
<td>( G_3 = \sqrt{\mu S_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_4 = \sqrt{\Delta t} r_4 )</td>
<td>( G_4 = \sqrt{\sigma I_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_5 = \sqrt{\Delta t} r_5 )</td>
<td>( G_5 = \sqrt{\mu I_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_6 = \sqrt{\Delta t} r_6 )</td>
<td>( G_6 = \sqrt{\delta I_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_7 = \sqrt{\Delta t} r_7 )</td>
<td>( G_7 = \sqrt{\mu R_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_8 = \sqrt{\Delta t} r_8 )</td>
<td>( G_8 = \sqrt{\mu N_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_9 = \sqrt{\Delta t} r_9 )</td>
<td>( G_9 = \sqrt{\lambda_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{10} = \sqrt{\Delta t} r_{10} )</td>
<td>( G_{10} = \sqrt{\mu S_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{11} = \sqrt{\Delta t} r_{11} )</td>
<td>( G_{11} = \sqrt{\sigma I_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{12} = \sqrt{\Delta t} r_{12} )</td>
<td>( G_{12} = \sqrt{\mu I_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{13} = \sqrt{\Delta t} r_{13} )</td>
<td>( G_{13} = \sqrt{\delta I_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{14} = \sqrt{\Delta t} r_{14} )</td>
<td>( G_{14} = \sqrt{\mu R_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{15} = \sqrt{\Delta t} r_{15} )</td>
<td>( G_{15} = \sqrt{q_{12}S_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{16} = \sqrt{\Delta t} r_{16} )</td>
<td>( G_{16} = \sqrt{q_{21}S_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{17} = \sqrt{\Delta t} r_{17} )</td>
<td>( G_{17} = \sqrt{q_{21}I_2(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{18} = \sqrt{\Delta t} r_{18} )</td>
<td>( G_{18} = \sqrt{q_{12}I_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{19} = \sqrt{\Delta t} r_{19} )</td>
<td>( G_{19} = \sqrt{q_{12}R_1(t)} )</td>
</tr>
<tr>
<td>( \Delta W_{20} = \sqrt{\Delta t} r_{20} )</td>
<td>( G_{20} = \sqrt{q_{21}R_2(t)} )</td>
</tr>
</tbody>
</table>
Table C.9: Transition Rates of the SDE Process for an SEIR two cities model with vital dynamics and disease induced death. We define $\lambda_1(t) = \beta S_1 \frac{I_1 + \mu E_1}{N_1}$ and $\lambda_2(t) = \beta S_2 \frac{I_2 + \mu E_2}{N_2}$.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
<th>Conditional Transition Rates of Stochastic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_1 \rightarrow S_1 + 1$</td>
<td>$q_{21} S_2$</td>
<td>$P((S_1)_{t+\Delta t} = s_1 + 1</td>
</tr>
<tr>
<td>$S_1 \rightarrow S_1 - 1$</td>
<td>$\lambda_1 + q_{12} S_1$</td>
<td>$P((S_1)_{t+\Delta t} = s_1 - 1</td>
</tr>
<tr>
<td>$E_1 \rightarrow E_1 + 1$</td>
<td>$q_{21} E_2 + \lambda_1$</td>
<td>$P((E_1)_{t+\Delta t} = e_1 + 1</td>
</tr>
<tr>
<td>$E_1 \rightarrow E_1 - 1$</td>
<td>$(\alpha + q_{12}) E_1$</td>
<td>$P((E_1)_{t+\Delta t} = e_1 - 1</td>
</tr>
<tr>
<td>$I_1 \rightarrow I_1 + 1$</td>
<td>$q_{21} I_2 + \alpha E_1$</td>
<td>$P((I_1)_{t+\Delta t} = i_1 + 1</td>
</tr>
<tr>
<td>$I_1 \rightarrow I_1 - 1$</td>
<td>$(\sigma + \delta + q_{12}) I_1$</td>
<td>$P((I_1)_{t+\Delta t} = i_1 - 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 + 1$</td>
<td>$\sigma I_1 + q_{21} R_2$</td>
<td>$P((R_1)_{t+\Delta t} = r_1 + 1</td>
</tr>
<tr>
<td>$R_1 \rightarrow R_1 - 1$</td>
<td>$q_{12} R_1$</td>
<td>$P((R_1)_{t+\Delta t} = r_1 - 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 + 1$</td>
<td>$q_{21} S_1$</td>
<td>$P((S_2)_{t+\Delta t} = s_2 + 1</td>
</tr>
<tr>
<td>$S_2 \rightarrow S_2 - 1$</td>
<td>$\lambda_2 + q_{12} S_2$</td>
<td>$P((S_2)_{t+\Delta t} = s_2 - 1</td>
</tr>
<tr>
<td>$E_2 \rightarrow E_2 + 1$</td>
<td>$q_{21} E_1 + \lambda_2 E_2$</td>
<td>$P((E_2)_{t+\Delta t} = e_2 + 1</td>
</tr>
<tr>
<td>$E_2 \rightarrow E_2 - 1$</td>
<td>$(\alpha + q_{12}) E_2$</td>
<td>$P((E_2)_{t+\Delta t} = e_2 - 1</td>
</tr>
<tr>
<td>$I_2 \rightarrow I_2 + 1$</td>
<td>$q_{21} I_1 + \alpha E_2$</td>
<td>$P((I_2)_{t+\Delta t} = i_2 + 1</td>
</tr>
<tr>
<td>$I_2 \rightarrow I_2 - 1$</td>
<td>$(\sigma + \delta + q_{12}) I_2$</td>
<td>$P((I_2)_{t+\Delta t} = i_2 - 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 + 1$</td>
<td>$\sigma I_2 + q_{12} R_1$</td>
<td>$P((R_2)_{t+\Delta t} = r_2 + 1</td>
</tr>
<tr>
<td>$R_2 \rightarrow R_2 - 1$</td>
<td>$q_{21} R_2$</td>
<td>$P((R_2)_{t+\Delta t} = r_2 - 1</td>
</tr>
</tbody>
</table>

C.5 Two cities model: SEIR

\[
\begin{align*}
S_1 &= -\beta S_1 \frac{I_1 + \mu E_1}{N_1} - q_{12} S_1 + q_{21} S_2 \quad \text{(C.37)} \\
E_1 &= \beta S_1 \frac{I_1 + \mu E_1}{N_1} - \alpha E_1 - q_{12} E_1 + q_{21} E_2 \quad \text{(C.38)} \\
I_1 &= \alpha E_1 - (\sigma + \delta) I_1 - q_{12} I_1 + q_{21} I_2 \quad \text{(C.39)} \\
R_1 &= \sigma I_1 - q_{12} R_1 + q_{21} R_2 \quad \text{(C.40)} \\
S_2 &= -\beta S_2 \frac{I_2 + \mu E_2}{N_2} - q_{12} S_1 - q_{21} S_2 \quad \text{(C.41)} \\
E_2 &= \beta S_2 \frac{I_2 + \mu E_2}{N_2} - \alpha E_2 - q_{12} E_1 - q_{21} E_2 \quad \text{(C.42)} \\
I_2 &= \alpha E_2 - (\sigma + \delta) I_2 - q_{12} I_1 - q_{21} I_2 \quad \text{(C.43)} \\
R_2 &= \sigma I_2 + q_{12} R_1 - q_{21} R_2 \quad \text{(C.44)}
\end{align*}
\]

In Table C.9 we indicate the different transition stages and the conditional transition rates as defined in the DCTM where the time and population size are discrete.

In this case since time is discrete $o(\Delta t)$ denotes a function depending on the time increment with $\lim_{\Delta t \to 0} \frac{o(t)}{t} = 0$.

It resembles the deterministic model but with the incorporation of the randomness added by the addition of the Poisson Increment fluctuations $\Delta Z_i$ for $i = 1, \ldots, 20$.  

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\[ \Delta S_1 = \left( -\beta S_1 \frac{I_1 + \mu E_1}{N_1} - q_{12} S_1 + q_{21} S_2 \right) \Delta t - \Delta Z_1 - \Delta Z_9 + \Delta Z_{10} \]  
(C.45)

\[ \Delta E_1 = \left( \beta S_1 \frac{I_1 + \mu E_1}{N_1} - \alpha E_1 - q_{12} E_1 + q_{21} E_2 \right) \Delta t + \Delta Z_1 - \Delta Z_2 - \Delta Z_{11} \]  
(C.46)

\[ \Delta I_1 = (\alpha E_1 - (\sigma + \delta + q_{12}) I_1 + q_{21} I_2) \Delta t + \Delta Z_2 - \Delta Z_3 - \Delta Z_4 - \Delta Z_{13} \]  
(C.47)

\[ \Delta R_1 = (\sigma I_1 - q_{12} R_1 + q_{21} R_2) \Delta t + \Delta Z_3 - \Delta Z_{15} + \Delta Z_{16} \]  
(C.48)

\[ \Delta S_2 = \left( -\beta S_2 \frac{I_2 + \mu E_2}{N_2} + q_{12} S_1 - q_{21} S_2 \right) \Delta t - \Delta Z_5 + \Delta Z_9 - \Delta Z_{10} \]  
(C.49)

\[ \Delta E_2 = \left( \beta S_2 \frac{I_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} E_1 - q_{21} E_2 \right) \Delta t + \Delta Z_5 - \Delta Z_6 + \Delta Z_{11} \]  
(C.50)

\[ \Delta I_2 = (\alpha E_2 - (\sigma + \delta + q_{21}) I_2 + q_{12} I_1) \Delta t + \Delta Z_6 - \Delta Z_7 - \Delta Z_8 + \Delta Z_{13} \]  
(C.51)

\[ \Delta R_2 = (\sigma I_2 - q_{12} R_1 - q_{21} R_2) \Delta t + \Delta Z_7 + \Delta Z_{15} - \Delta Z_{16} \]  
(C.52)

The differences of Poisson increments factors can be described as follows for their respective equations:

Eq. (C.45): \(-\Delta Z_1 - \Delta Z_9 + \Delta Z_{10}\) denotes the transition of an unprotected individual to become exposed and incubating the disease (\(\Delta Z_1\)), or susceptible individuals traveling among each city (\(\Delta Z_9, \Delta Z_{10}\)).

Eq. (C.46): \(\Delta Z_1 - \Delta Z_2 - \Delta Z_{11} + \Delta Z_{12}\) denotes the transition of an exposed individual coming from the susceptible class (\(\Delta Z_1\)), or an exposed individual to become infected (\(\Delta Z_2\)), or exposed individuals traveling among each city (\(\Delta Z_{11}, \Delta Z_{12}\)).

Eq. (C.47): \(\Delta Z_2 - \Delta Z_3 - \Delta Z_4 - \Delta Z_{13} + \Delta Z_{14}\) denotes the transition of an exposed individual to become infected (\(\Delta Z_2\)), or an infected individual to recover, (\(\Delta Z_3\)), or an infected individual death due to infection (\(\Delta Z_4\)), or infected individuals traveling among each city (\(\Delta Z_{13}, \Delta Z_{14}\)).

Eq. (C.48): \(\Delta Z_3 - \Delta Z_{15} + \Delta Z_{16}\) denotes the transition of an infected individuals that recovers (\(\Delta Z_3\)), or recovered individuals traveling among each city (\(\Delta Z_{15}, \Delta Z_{16}\)).

Eq. (C.49): \(-\Delta Z_5 + \Delta Z_9 - \Delta Z_{10}\) denotes the transition of an unprotected individual to become exposed and incubating the disease (\(\Delta Z_5\)), or susceptible individuals traveling among each city (\(\Delta Z_9, \Delta Z_{10}\)).

Eq. (C.51): \(\Delta Z_5 - \Delta Z_6 + \Delta Z_{11} - \Delta Z_{12}\) denotes the transition of an exposed individual coming from the susceptible class (\(\Delta Z_5\)), or exposed individuals traveling among each city (\(\Delta Z_{11}, \Delta Z_{12}\)).
Wiener's increments and corresponding Transition Rates in Table C.10.

Table C.10: Transition Rates using Weiner’s Increments for the SDE Process for an SEIR two cities model with disease induced death. We define $\lambda_1(t) = \beta S_1 \frac{I_1 + \mu E_1}{N_1}$ and $\lambda_2(t) = \beta S_2 \frac{I_2 + \mu E_2}{N_2}$.

<table>
<thead>
<tr>
<th>Weiner’s Increments</th>
<th>G = $\sqrt{\text{Transition Rate}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta W_1 = \sqrt{\Delta t} r_1$</td>
<td>$G_1 = \sqrt{\lambda_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_2 = \sqrt{\Delta t} r_2$</td>
<td>$G_2 = \sqrt{\alpha E_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_3 = \sqrt{\Delta t} r_3$</td>
<td>$G_3 = \sqrt{\sigma I_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_4 = \sqrt{\Delta t} r_4$</td>
<td>$G_4 = \sqrt{\delta I_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_5 = \sqrt{\Delta t} r_5$</td>
<td>$G_5 = \sqrt{\lambda_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_6 = \sqrt{\Delta t} r_6$</td>
<td>$G_6 = \sqrt{\alpha E_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_7 = \sqrt{\Delta t} r_7$</td>
<td>$G_7 = \sqrt{\sigma I_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_8 = \sqrt{\Delta t} r_8$</td>
<td>$G_8 = \sqrt{\delta I_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_9 = \sqrt{\Delta t} r_9$</td>
<td>$G_9 = \sqrt{q_{12}S_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{10} = \sqrt{\Delta t} r_{10}$</td>
<td>$G_{10} = \sqrt{q_{21}S_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{11} = \sqrt{\Delta t} r_{11}$</td>
<td>$G_{11} = \sqrt{q_{12}E_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{12} = \sqrt{\Delta t} r_{12}$</td>
<td>$G_{12} = \sqrt{q_{21}E_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{13} = \sqrt{\Delta t} r_{13}$</td>
<td>$G_{13} = \sqrt{q_{12}I_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{14} = \sqrt{\Delta t} r_{14}$</td>
<td>$G_{14} = \sqrt{q_{21}I_2(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{15} = \sqrt{\Delta t} r_{15}$</td>
<td>$G_{15} = \sqrt{q_{12}R_1(t)}$</td>
</tr>
<tr>
<td>$\Delta W_{16} = \sqrt{\Delta t} r_{16}$</td>
<td>$G_{16} = \sqrt{q_{21}R_2(t)}$</td>
</tr>
</tbody>
</table>
APPENDIX D

MORE ON CONTINUOUS TIME MARKOV CHAIN AND KOLMOGOROV EQUATIONS
In Appendix D, we present the CTMC approach for the SIR one-city model through the 2-city SEIR models. The SIS and the 2-city SEUCR were presented in section 4.3 of Chapter 4.

D.1 One city model: SIR with demographics

Now, let’s consider a simple case using one city and one infectivity class i.e., a classical SIR model.

\[
\dot{S} = -\beta \frac{SI}{N} + \mu N - \mu S \quad (D.1)
\]

\[
\dot{I} = \beta \frac{SI}{N} - (\sigma + \mu + \delta) I \quad (D.2)
\]

\[
\dot{R} = \sigma I - \mu R \quad (D.3)
\]

By using the following transition variables for \( S \rightarrow i, I \rightarrow j, \) and \( R \rightarrow k. \) Let’s define the transition stages and rates in Table D.1:

**Table D.1: Transition Rates for the CTMC Process for an SIR one city model with vital dynamics.** Notice that in the \( i \rightarrow i + 1 \) transition we change \( N \) to \( i + j + k. \) This step is necessary for the further derivation of the Kolmogorov Equation.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>( i \rightarrow i + 1 )</td>
<td>( \mu N = \mu (i + j + k) )</td>
</tr>
<tr>
<td>( i \rightarrow i - 1 )</td>
<td>( \beta \frac{ij}{N} + \mu i )</td>
</tr>
<tr>
<td>( j \rightarrow j + 1 )</td>
<td>( \beta \frac{ij}{N} )</td>
</tr>
<tr>
<td>( j \rightarrow j - 1 )</td>
<td>( (\sigma + \mu + \delta) j )</td>
</tr>
<tr>
<td>( k \rightarrow k + 1 )</td>
<td>( \sigma j )</td>
</tr>
<tr>
<td>( k \rightarrow k - 1 )</td>
<td>( \mu k )</td>
</tr>
</tbody>
</table>

The forward Kolmogorov Equation for the above transition rates is:

\[
P'_{i,j,k}(t) = \mu((i - 1) + j + k)P_{i-1,j,k}(t) + \left[ \beta \frac{(i+1)j}{N} + \mu i \right]P_{i+1,j,k}(t) + \beta \frac{i(j-1)}{N}P_{i-1,j-1,k}(t) + [\sigma + \mu + \delta] (j + 1)P_{i,j+1,k}(t) + \mu(k + 1)P_{i,j,k+1}(t) + \sigma j P_{i,j,k-1}(t) - \left( 2\beta \frac{ij}{N} + 2\sigma j + 2\mu(i + j + k) + \delta j \right) P_{i,j,k}(t) \quad (D.4)
\]

where the probability generating function (p.g.f) is \( \frac{\partial \phi}{\partial t} \): \n
\[
\phi(r,s,p) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} P_{i,j,k}(t)r^i s^j p^k \quad (D.5)
\]

\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} P'_{i,j,k}(t)r^i s^j p^k \quad (D.6)
\]
Hence,

$$\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \mu ((i - 1) + j + k) P_{i-1,j,k}(t) r^i s^j p^k + \sigma j P_{i,j,k-1}(t) r^i s^j p^k$$  \hspace{1cm} (D.7)

$$\quad + \left[ \beta \frac{(i + 1) j}{N} + \mu (i + 1) \right] P_{i+1,j,k}(t) r^i s^j p^k + \beta \frac{(j - 1)}{N} P_{i,j-1,k}(t) r^i s^j p^k$$

$$\quad + \left[ \sigma + \mu + \delta \right] (j + 1) P_{i,j+1,k}(t) r^i s^j p^k + \mu (k + 1) P_{i,j,k+1}(t) r^i s^j p^k$$

$$\quad - \left( 2 \beta \frac{j}{N} + 2 \sigma j + 2 \mu (i + j + k) + \delta j \right) P_{i,j,k}(t) r^i s^j p^k$$

After a lot of re-indexing and simplifications it gives the following equation:

$$\frac{\partial \phi}{\partial t} = \left[ \mu \left( r^2 - 2r \right) \right] \frac{\partial \phi}{\partial r} + \left[ s (\mu r + \sigma p - 2 \mu - 2 \sigma - \delta) + \sigma + \mu + \delta \right] \frac{\partial \phi}{\partial s}$$  \hspace{1cm} (D.8)

$$\quad + \left[ \mu (rp - 2p) \right] \frac{\partial \phi}{\partial p} + \frac{\beta s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^2 \phi}{\partial r \partial s}$$
After taking the partial derivative with respect to each of the variables:

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) = 2\mu [r - 1] \frac{\partial \phi}{\partial r} + \mu \left[ r^2 + 1 - 2r \right] \frac{\partial^2 \phi}{\partial r^2} + \mu s \frac{\partial \phi}{\partial s} + \mu p \frac{\partial \phi}{\partial p} \quad (D.9)
\]

\[
+ \frac{\beta_s s}{N} \left[ s - 2 \right] \frac{\partial^2 \phi}{\partial r \partial s} + \frac{\beta_s s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r^2 \partial s}
\]

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) = [\mu (r - 2) + \sigma (p - 2) - \delta] \frac{\partial \phi}{\partial s} + \frac{\beta}{N} \left[ 1 + 2rs - 2r \right] \frac{\partial^2 \phi}{\partial r \partial s} \quad (D.10)
\]

\[
+ [\mu (rs + 1 - 2s) + \sigma (1 + sp - 2s) + \delta (1 - s)] \frac{\partial^2 \phi}{\partial s^2} + \frac{\beta s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r \partial s^2}
\]

\[
\frac{\partial}{\partial p} \left( \frac{\partial \phi}{\partial t} \right) = \sigma s \frac{\partial \phi}{\partial s} + \mu [r - 2] \frac{\partial \phi}{\partial p} + \mu [rp + 1 - 2p] \frac{\partial^2 \phi}{\partial p^2} \quad (D.11)
\]

Evaluation of the partial derivatives at \( r = s = p = 1 \) in each case gives back the deterministic SIR model since the expected values of the variables are related to the deterministic quantities. In terms of seeing the connection we can in a sense interchange \( \frac{\partial \phi}{\partial r} \) with \( S \), \( \frac{\partial \phi}{\partial s} \) with \( I \) and \( \frac{\partial \phi}{\partial p} \) with \( R \).

\[
\left. \frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=p=1} = \mu \frac{\partial \phi}{\partial s} + \mu \frac{\partial \phi}{\partial p} - \beta \frac{\partial^2 \phi}{\partial r \partial s} \quad (D.12)
\]

\[
\left. \frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=p=1} = \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial s} - (\mu + \sigma + \delta) \frac{\partial \phi}{\partial s} \quad (D.13)
\]

\[
\left. \frac{\partial}{\partial p} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=p=1} = \sigma \frac{\partial \phi}{\partial s} - \mu \frac{\partial \phi}{\partial p} \quad (D.14)
\]

Note that for equation (D.12) we need to add \( \mu \frac{\partial \phi}{\partial r} - \mu \frac{\partial \phi}{\partial r} = 0 \) to get:

\[
\left. \frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \right|_{r=s=p=1} = \mu \frac{\partial \phi}{\partial s} + \mu \frac{\partial \phi}{\partial p} - \beta \frac{\partial^2 \phi}{\partial r \partial s} = \mu \left[ \frac{\partial \phi}{\partial r} + \frac{\partial \phi}{\partial s} + \frac{\partial \phi}{\partial p} \right] - \mu \frac{\partial \phi}{\partial r} + \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial s}
\]
After substitution of the partial derivatives with the compartment variables we get:

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=p=1} = \mu \left[ \frac{\partial \phi}{\partial r} + \frac{\partial \phi}{\partial s} + \frac{\partial \phi}{\partial p} \right] - \mu \frac{\partial \phi}{\partial r} + \frac{\beta}{N} \frac{\partial^2 \phi}{\partial rs} \\
= \mu [S + I + R] - \mu S + \frac{\beta}{N} SI \\
\dot{S} = \mu N - \mu S + \frac{\beta}{N} SI
\]

Hence, we have that equation (D.15) it's exactly the same as our deterministic model equation (D.1).

\textbf{D.1.1 Simulations}

\textbf{Figure D.2:} Infected individuals for and SIR one city model with a population of \( N = 100 \) and a basic reproductive number \( R_0 = 2 \).

\textbf{D.2 One city model: SEIR}

Now, let's consider a simple case using one city and one infectivity class i.e., a classical SEIR model.

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Figure D.3: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for an SIR one city model with a population of \( N = 100 \) and a basic reproductive number \( R_0 = 2 \). The star in the boxplot represents the final size of the deterministic model.

\[
\begin{align*}
\dot{S} &= -\beta S \frac{I + \mu E}{N} & \text{(D.15)} \\
\dot{E} &= \beta S \frac{I + \mu E}{N} - \alpha E & \text{(D.16)} \\
\dot{I} &= \alpha E - (\sigma + \delta) I & \text{(D.17)} \\
\dot{R} &= \sigma I & \text{(D.18)}
\end{align*}
\]

By using the following transition variables for \( S \rightarrow i, E \rightarrow j, I \rightarrow k \) and \( R \rightarrow h \). Let’s define the transition stages and rates in Table D.2.

Table D.2: Transition Rates for the CTMC Process for an SEIR one city model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>( i \rightarrow i + 1 )</td>
<td>0</td>
</tr>
<tr>
<td>( i \rightarrow i - 1 )</td>
<td>( \beta \frac{I + \mu E}{N} )</td>
</tr>
<tr>
<td>( j \rightarrow j + 1 )</td>
<td>( \beta \frac{I + \mu E}{N} )</td>
</tr>
<tr>
<td>( j \rightarrow j - 1 )</td>
<td>( \alpha j )</td>
</tr>
<tr>
<td>( k \rightarrow k + 1 )</td>
<td>( (\sigma + \delta) k )</td>
</tr>
<tr>
<td>( k \rightarrow k - 1 )</td>
<td>( \alpha j )</td>
</tr>
<tr>
<td>( h \rightarrow h + 1 )</td>
<td>0</td>
</tr>
<tr>
<td>( h \rightarrow h - 1 )</td>
<td>( \sigma k )</td>
</tr>
</tbody>
</table>
Figure D.4: Flow chart of the transition stages and rates for the one city SECUR metapopulation model. See Table D.2

The forward Kolmogorov Equation for the above transition rates is:

\[ P'_{i,j,k,h}(t) = \beta(i+1) \frac{k + \mu j}{N} P_{i+1,j,k,h}(t) + \beta i \frac{k + \mu (j-1)}{N} P_{i,j-1,k,h}(t) \]

\[ + \alpha(j+1) P_{i,j+1,k,h}(t) + (\sigma + \delta)(k+1) P_{i,j,k+1,h}(t) \]

\[ + \alpha j P_{i,j,k-1,h}(t) + \sigma k P_{i,j,k,h+1}(t) \]

\[ - \left( 2\beta i \frac{k + \mu j}{N} + 2\alpha j + 2\sigma k + \delta k \right) P_{i,j,k,h}(t) \] (D.19)

where the probability generating function (p.g.f) is \( \frac{\partial \phi}{\partial t} \):

\[ \phi(r,s,p,q,t) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} P_{i,j,k,h}(t) r^i s^j p^k q^h \] (D.20)

\[ \frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} P'_{i,j,k,h}(t) r^i s^j p^k q^h \] (D.21)
Hence,
\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \beta(i+1) \frac{k+\mu j}{N} P_{i+1,j,k,h}(t) r^i s^j p^k q^h
\]
\[
+ \beta i \frac{k+\mu (j-1)}{N} P_{i,j-1,k,h}(t) r^i s^j p^k q^h
\]
\[
+ \alpha (j+1) P_{i,j+1,k,h}(t) r^i s^j p^k q^h
\]
\[
+ (\sigma + \delta) (k+1) P_{i,j,k+1,h}(t) r^i s^j p^k q^h
\]
\[
+ \alpha j P_{i,j,k-1,h}(t) r^i s^j p^k q^h + \sigma k P_{i,j,k,h+1}(t) r^i s^j p^k q^h
\]
\[
- \left( 2\beta (i+1) \frac{k+\mu j}{N} + 2\alpha j \right) P_{i,j,k,h}(t) r^i s^j p^k q^h
\]
\[
- (2\sigma k + \delta k) P_{i,j,k,h}(t) r^i s^j p^k q^h
\]
(D.22)

After a lot of re-indexing and simplifications it gives the following equation:
\[
\frac{\partial \phi}{\partial t} = (p + rs p - 2rp) \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial p} + (1 + rs - 2r) s \frac{\beta \mu}{N} \frac{\partial^3 \phi}{\partial r \partial p \partial s} + (1 + ps - 2s) \alpha \frac{\partial \phi}{\partial s} + (\sigma + \delta + \sigma p q - 2\sigma p - \delta p) \frac{\partial \phi}{\partial p}
\]
(D.23)

After taking the partial derivative with respect to each of the variables:
\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) = (1 + rs - 2r) p \frac{\beta}{N} \frac{\partial^3 \phi}{\partial r^2 \partial p} + (1 + rs - 2r) s \frac{\beta \mu}{N} \frac{\partial^3 \phi}{\partial r^2 \partial s}
\]
\[
+ (s - 2) p \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial p} + (s - 2) s \frac{\beta \mu}{N} \frac{\partial^2 \phi}{\partial r \partial s}
\]
(D.24)

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) = (1 + rs - 2r) s \frac{\beta \mu}{N} \frac{\partial^3 \phi}{\partial r \partial s^2} + (1 + 2rs - 2r) \frac{\beta \mu}{N} \frac{\partial^2 \phi}{\partial r \partial s}
\]
\[
+ rp \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial p} + (1 + ps - 2s) \alpha \frac{\partial^2 \phi}{\partial s^2} + (p - 2) \alpha \frac{\partial \phi}{\partial s}
\]
(D.25)

\[
\frac{\partial}{\partial p} \left( \frac{\partial \phi}{\partial t} \right) = (1 + rs - 2rp) p \frac{\beta}{N} \frac{\partial^3 \phi}{\partial r \partial p^2} + (1 + rs - 2r) \frac{\beta}{N} \frac{\partial^2 \phi}{\partial r \partial p}
\]
\[
+ (\sigma + \delta + \sigma p q - 2\sigma p - \delta p) \alpha \frac{\partial \phi}{\partial p^2}
\]
\[
+ (\sigma q - 2\sigma - \delta) \frac{\partial \phi}{\partial p} + s \alpha \frac{\partial \phi}{\partial s}
\]
(D.26)

\[
\frac{\partial}{\partial q} \left( \frac{\partial \phi}{\partial t} \right) = \sigma p \frac{\partial \phi}{\partial p}
\]
(D.27)

Evaluation of the partial derivatives at \( r = s = p = q = 1 \) in each case gives back the deterministic SEIR model since the expected values of the variables are related to the deterministic quantities. For a clear view of the relationship, the expected value of a stochastic
random variable in this approach is defined as the partial derivative with respect to the variable in question evaluated at one like we do below.

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=p=q=1} = -\frac{\beta}{N} \left( \frac{\partial^2 \phi}{\partial r \partial p} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right)
\]  
(D.28)

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=p=q=1} = \frac{\beta}{N} \left( \frac{\partial^2 \phi}{\partial r \partial p} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right) - \alpha \frac{\partial \phi}{\partial s}
\]  
(D.29)

\[
\frac{\partial}{\partial p} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=p=q=1} = \alpha \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial p}
\]  
(D.30)

\[
\frac{\partial}{\partial q} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=p=q=1} = \sigma \frac{\partial \phi}{\partial p}.
\]  
(D.31)

In terms of seeing the connection we can in a sense interchange \(\frac{\partial \phi}{\partial r}\) with \(S\), \(\frac{\partial \phi}{\partial s}\) with \(E\) and so on.

### D.2.1 Simulations

![Continuous Time Markov Chain SEIR Model](image)

**Figure D.5:** Infected individuals for and SEIR one city model with a population of \(N = 100\) and a basic reproductive number \(R_0 = 2\).
Figure D.6: Cumulative cases (left) and boxplot and histogram (right) of the distribution of the cumulative cases for an SEIR one city model with a population of $N = 100$ and a basic reproductive number $\mathcal{R}_0 = 2$. The star in the boxplot represents the final size of the deterministic model.

### D.3 One city model: SEUCR

Now, let’s consider a simple case using one city and one infectivity class i.e., a classical SECUR model.

\[
\dot{S} = -\beta S \frac{\gamma C + U + \mu E}{N} \\
\dot{E} = \beta S \frac{\gamma C + U + \mu E}{N} - \alpha E \\
\dot{U} = \alpha (1 - p)E - (\sigma + \delta)U \\
\dot{C} = \alpha p E - (\sigma + \delta)C \\
\dot{R} = \sigma (C + U)
\]

By using the following transition variables for $S \rightarrow i, E \rightarrow j, C \rightarrow k, U \rightarrow h$ and $R \rightarrow d$. Let’s define the transition stages and rates in Table D.3.

The forward Kolmogorov Equation for the above transition rates is:

\[
P'_{i,j,k,h,d}(t) = \beta (i+1) \frac{\gamma k + h + \mu j}{N} P_{i+1,j,k,h,d}(t) + \alpha (j+1)P_{i,j+1,k,h,d}(t) \\
+ \beta i \frac{\gamma k + h + \mu (j-1)}{N} P_{i,j-1,k,h,d}(t) + \alpha p j P_{i,j,k-1,h,d}(t) \\
+ (\sigma + \delta)(k+1)P_{i,j,k+1,h,d}(t) + \alpha (1-p) j P_{i,j,k,h-1,d}(t) \\
+ (\sigma + \delta)(h+1)P_{i,j,k,h+1,d}(t) + \sigma (k+h) P_{i,j,k,h,d-1}(t) \\
- \left[ 2\beta i \frac{\gamma k + h + \mu j}{N} + 2\alpha j + 2\sigma (k+h) + \delta (k+h) \right] P_{i,j,k,h,d}(t)
\]
Table D.3: Transition Rates for the CTMC Process for an SEUCR one city model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i \to i + 1$</td>
<td>0</td>
</tr>
<tr>
<td>$i \to i - 1$</td>
<td>$\beta i \frac{\gamma k + h + \mu j}{N}$</td>
</tr>
<tr>
<td>$j \to j + 1$</td>
<td>$\beta i \frac{\gamma k + h + \mu j}{N}$</td>
</tr>
<tr>
<td>$j \to j - 1$</td>
<td>$\alpha j$</td>
</tr>
<tr>
<td>$k \to k + 1$</td>
<td>$\alpha p j$</td>
</tr>
<tr>
<td>$h \to h + 1$</td>
<td>$(\sigma + \delta) k$</td>
</tr>
<tr>
<td>$h \to h - 1$</td>
<td>$\alpha (1 - p) j$</td>
</tr>
<tr>
<td>$d \to d + 1$</td>
<td>$\sigma (k + h)$</td>
</tr>
<tr>
<td>$d \to d - 1$</td>
<td>0</td>
</tr>
</tbody>
</table>

where the probability generating function (p.g.f) is $\frac{\partial \phi}{\partial t}$:

$$\phi(r, s, g, m, n) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \sum_{d=0}^{\infty} P_{i,j,k,h,d}(t) r^i s^j g^k m^h n^d$$  \hspace{1cm} (D.38)

$$\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \sum_{d=0}^{\infty} P'_{i,j,k,h,d}(t) r^i s^j g^k m^h n^d$$  \hspace{1cm} (D.39)

Hence,

$$\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{h=0}^{\infty} \sum_{d=0}^{\infty} \beta (i + 1) \frac{\gamma k + h + \mu j}{N} P_{i+1,j,k,h,d}(t) r^i s^j g^k m^h n^d$$  \hspace{1cm} (D.40)

$$+ \beta i \frac{\gamma k + h + \mu j}{N} P_{i,j,k,h,d-1}(t) r^i s^j g^k m^h n^d$$

$$+ \alpha (j + 1) P_{i,j+1,k,h,d}(t) r^i s^j g^k m^h n^d$$

$$+ \alpha p j P_{i,j,k-1,h,d}(t) r^i s^j g^k m^h n^d$$

$$+ (\sigma + \delta) (k + 1) P_{i,j,k+1,h,d}(t) r^i s^j g^k m^h n^d$$

$$+ \alpha (1 - p) j P_{i,j,k,h-1,d}(t) r^i s^j g^k m^h n^d$$

$$+ (\sigma + \delta) (h + 1) P_{i,j,k,h+1,d}(t) r^i s^j g^k m^h n^d$$

$$+ \sigma (k + h) P_{i,j,k,h,d-1}(t) r^i s^j g^k m^h n^d$$

$$- \left[ 2\beta i \frac{\gamma k + h + \mu j}{N} + 2\alpha j \right] P_{i,j,k,h,d}(t) r^i s^j g^k m^h n^d$$

$$- (2\sigma + \delta) (k + h) P_{i,j,k,h,d}(t) r^i s^j g^k m^h n^d$$

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After a lot of re-indexing and simplifications it gives the following equation:

\[
\frac{\partial \phi}{\partial t} = \frac{\beta \gamma g}{N} \left[ 1 + rs - 2r \right] \frac{\partial^2 \phi}{\partial r \partial g} + \frac{\beta m}{N} \left[ 1 + rs - 2r \right] \frac{\partial^2 \phi}{\partial r \partial m} + \frac{\beta \mu s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^2 \phi}{\partial r \partial s} + \alpha \left[ 1 + psg + (1 - p)ms - 2s\alpha \right] \frac{\partial \phi}{\partial s} + \left[ \sigma + \delta + \sigma ng - 2\sigma g - \delta g \right] \frac{\partial \phi}{\partial g} + \left[ \sigma + \delta + \sigma nm - 2\sigma m - \delta m \right] \frac{\partial \phi}{\partial m}
\]  

(D.41)

After taking the partial derivative with respect to each of the variables:

\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) = \frac{\beta \gamma g}{N} \left[ s - 2 \right] \frac{\partial^2 \phi}{\partial r \partial g} + \frac{\beta \gamma g}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r^2 \partial g} + \frac{\beta m}{N} \left[ s - 2 \right] \frac{\partial^2 \phi}{\partial r \partial m} + \frac{\beta m}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r^2 \partial m} + \frac{\beta \mu s}{N} \left[ s - 2 \right] \frac{\partial^2 \phi}{\partial r \partial s} + \frac{\beta \mu s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r^2 \partial s} + \beta \mu s \left[ 1 + rs - 2r \right] \frac{\partial^2 \phi}{\partial r^2 \partial s} + \alpha \left[ p g + (1 - p) m - 2 \right] \frac{\partial \phi}{\partial s} + \alpha \left[ 1 + p s g + (1 - p) m - 2 \right] \frac{\partial^2 \phi}{\partial s^2}
\]  

(D.42)

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) = \frac{\beta \gamma g}{N} \frac{\partial^2 \phi}{\partial r \partial g} + \frac{\beta \gamma m}{N} \frac{\partial^2 \phi}{\partial r \partial m} + \frac{\beta \mu s}{N} \left[ 1 + rs - 2r \right] \frac{\partial^3 \phi}{\partial r^2 \partial s} + \alpha \left[ p g + (1 - p) m - 2 \right] \frac{\partial \phi}{\partial s} + \alpha \left[ 1 + p s g + (1 - p) m - 2 \right] \frac{\partial^2 \phi}{\partial s^2}
\]  

(D.43)

\[
\frac{\partial}{\partial g} \left( \frac{\partial \phi}{\partial t} \right) = \alpha p \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial g}
\]  

(D.44)

\[
\frac{\partial}{\partial m} \left( \frac{\partial \phi}{\partial t} \right) = \alpha (1 - p) \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial m}
\]  

(D.45)

\[
\frac{\partial}{\partial n} \left( \frac{\partial \phi}{\partial t} \right) = \sigma \left[ g \frac{\partial \phi}{\partial g} + m \frac{\partial \phi}{\partial m} \right]
\]  

(D.46)

Evaluation of the partial derivatives at \( r = s = g = m = n = 1 \) in each case gives back the deterministic SEUCR model since the expected values of the variables are related to the deterministic quantities. In terms of seeing the connection we can in a sense interchange \( \frac{\partial \phi}{\partial t} \) with \( S \), \( \frac{\partial \phi}{\partial s} \) with \( E \), \( \frac{\partial \phi}{\partial g} \) with \( C \), \( \frac{\partial \phi}{\partial m} \) with \( U \) and \( \frac{\partial \phi}{\partial n} \) with \( R \).
\[
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=g=m=n=1} = -\frac{\beta}{N} \left[ \frac{\gamma}{\partial r \partial g} \frac{\partial^2 \phi}{\partial r \partial m} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right] \quad \text{(D.47)}
\]

\[
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=g=m=n=1} = \frac{\beta}{N} \left[ \frac{\gamma}{\partial r \partial g} \frac{\partial^2 \phi}{\partial r \partial m} + \mu \frac{\partial^2 \phi}{\partial r \partial s} \right] - \alpha \frac{\partial \phi}{\partial s} \quad \text{(D.48)}
\]

\[
\frac{\partial}{\partial g} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=g=m=n=1} = \alpha p \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial g} \quad \text{(D.49)}
\]

\[
\frac{\partial}{\partial m} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=g=m=n=1} = \alpha (1 - p) \frac{\partial \phi}{\partial s} - (\sigma + \delta) \frac{\partial \phi}{\partial m} \quad \text{(D.50)}
\]

\[
\frac{\partial}{\partial n} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{r=s=g=m=n=1} = \sigma \left( \frac{\partial \phi}{\partial g} + \frac{\partial \phi}{\partial m} \right) \quad \text{(D.51)}
\]

### D.3.1 Simulations

![Graphs showing simulations](image)

**Figure D.7:** Infected individuals for and SEUCR one city model with a population of \( N = 100 \) and a basic reproductive number \( R_0 = 2 \).
D.4 Two cities model: SIR with demographics

Now let consider a two cities SIR model with demographics

\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1}{N_1} + \mu N_1 - \mu S_1 - q_{12} S_1 + q_{21} S_2 \\
\dot{I}_1 &= \beta S_1 \frac{I_1}{N_1} - (\sigma + \mu + \delta) I_1 - q_{12} I_1 + q_{21} I_2 \\
\dot{R}_1 &= \sigma I_1 - \mu R_1 - q_{12} R_1 + q_{21} R_2 \\
\dot{S}_2 &= -\beta S_2 \frac{I_2}{N_2} + \mu N_2 - \mu S_2 + q_{12} S_1 - q_{21} S_2 \\
\dot{I}_2 &= \beta S_2 \frac{I_2}{N_2} - (\sigma + \mu + \delta) I_2 + q_{12} I_1 - q_{21} I_2 \\
\dot{R}_2 &= \sigma I_2 - \mu R_2 + q_{12} R_1 - q_{21} R_2
\end{align*}

By using the following transition variables for \( S_1 \to i, I_1 \to j, R_1 \to k, S_2 \to m, I_2 \to n \) and \( R_2 \to a \). Let’s define the transition stages and rates in Table D.4.

In order to save space for notation let \( \bar{\omega} = (i, j, k, m, n, a) \) and define \( P_{\bar{\omega}} = P_{i,j,k,m,n,a} \) with \( P_{\bar{\omega}(i-1)} = P_{i-1, j, k, m, n, a} \) to indicate the index that has a change. Hence, the forward Kolmogorov Equation for the above transition rates is:
Table D.4: Transition Rates for the CTMC Process for an SIR two cities model with demography.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i \to i+1$</td>
<td>$\mu N_1 + q_{21}m$</td>
</tr>
<tr>
<td>$i \to i-1$</td>
<td>$\frac{\beta i}{N_1} + (\mu + q_{12})i$</td>
</tr>
<tr>
<td>$j \to j+1$</td>
<td>$\frac{\beta j}{N_2} + q_{21}n$</td>
</tr>
<tr>
<td>$j \to j-1$</td>
<td>$(\sigma + \mu + \delta + q_{12})j$</td>
</tr>
<tr>
<td>$k \to k+1$</td>
<td>$\sigma j + q_{21}a$</td>
</tr>
<tr>
<td>$k \to k-1$</td>
<td>$(\mu + q_{12})k$</td>
</tr>
<tr>
<td>$m \to m+1$</td>
<td>$\mu N_2 + q_{12}i$</td>
</tr>
<tr>
<td>$m \to m-1$</td>
<td>$\frac{\beta mn}{N_2} + (\mu + q_{21})m$</td>
</tr>
<tr>
<td>$n \to n+1$</td>
<td>$\frac{\beta mn}{N_2} + q_{12}j$</td>
</tr>
<tr>
<td>$n \to n-1$</td>
<td>$(\sigma + \mu + \delta + q_{21})n$</td>
</tr>
<tr>
<td>$a \to a+1$</td>
<td>$\sigma n + q_{12}k$</td>
</tr>
<tr>
<td>$a \to a-1$</td>
<td>$(\mu + q_{21})a$</td>
</tr>
</tbody>
</table>

\[
P'_\tilde{\omega}(t) = (\mu N_1 + q_{21}m)P_{\tilde{\omega}(i-1)}(t) + \left[ \frac{\beta i(j-1)}{N_1} + q_{21}n \right] P_{\tilde{\omega}(j-1)}(t) + \left[ \frac{\beta (i+1)j}{N_1} + (\mu + q_{12})(i+1) \right] P_{\tilde{\omega}(i+1)}(t) + (\sigma j + q_{21}a)P_{\tilde{\omega}(k-1)}(t) + (\sigma + \mu + \delta + q_{12})(j+1)P_{\tilde{\omega}(j+1)}(t) + (\mu + q_{12})(k+1)P_{\tilde{\omega}(k+1)}(t) + (\mu N_2 + q_{12}i)P_{\tilde{\omega}(m-1)}(t) + \left[ \frac{\beta (m+1)n}{N_2} + (\mu + q_{21})(m+1) \right] P_{\tilde{\omega}(m+1)}(t) + (\sigma n + q_{12}k)P_{\tilde{\omega}(a-1)}(t) + (\mu + q_{21})(a+1)P_{\tilde{\omega}(a+1)}(t) - \delta(j+n)P_{\tilde{\omega}}(t) - 2\left[ \mu(N_1 + N_2) + q_{21}(m + n + a) + \frac{\beta ij}{N_1} + \sigma(n + j) \right] P_{\tilde{\omega}}(t) - 2\left[ q_{12}(i + j + k) + \frac{\beta mn}{N_2} \right] P_{\tilde{\omega}}(t) \tag{D.58}
\]

Where the probability generating function (p.g.f) is $\frac{\partial \phi}{\partial t}$.

\[
\phi(r,s,w,v,x,y) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \sum_{a=0}^{\infty} P_{i,j,k,m,n,a}(t) r^i s^j w^k v^m x^n y^a \tag{D.59}
\]

\[
\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \sum_{a=0}^{\infty} P'_{i,j,k,m,n,a}(t) r^i s^j w^k v^m x^n y^a \tag{D.60}
\]
After a lot of computations, taking the partial derivative with respect to each of the variables and evaluation of the partial derivatives at \( r = s = w = v = x = y = 1 \) in each case we get the deterministic SIR two cities model with demography. The expected values of the variables are related to the deterministic quantities. In terms of seeing the connection we can in a sense interchange \( \frac{\partial \phi}{\partial r} \) with \( S_1 \), \( \frac{\partial \phi}{\partial s} \) with \( I_1 \), \( \frac{\partial \phi}{\partial w} \) with \( R_1 \), \( \frac{\partial \phi}{\partial v} \) with \( S_2 \), \( \frac{\partial \phi}{\partial x} \) with \( I_2 \), and \( \frac{\partial \phi}{\partial y} \) with \( R_2 \).

\[
\begin{align*}
\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = - \beta \frac{\partial^2 \phi}{N_1 \partial r \partial s} + \mu N_1 - (\mu + q_{12}) \frac{\partial \phi}{\partial r} + q_{21} \frac{\partial \phi}{\partial v} \quad (D.61) \\
\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = \frac{\beta}{N_1} \frac{\partial^2 \phi}{\partial r \partial s} - (\sigma + \mu + \delta + q_{12}) \frac{\partial \phi}{\partial s} + q_{21} \frac{\partial \phi}{\partial x} \quad (D.62) \\
\frac{\partial}{\partial w} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = \sigma \frac{\partial \phi}{\partial s} - (\mu + q_{12}) \frac{\partial \phi}{\partial w} + q_{21} \frac{\partial \phi}{\partial y} \quad (D.63) \\
\frac{\partial}{\partial v} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = - \beta \frac{\partial^2 \phi}{N_2 \partial v \partial x} + \mu N_2 - (\mu + q_{21}) \frac{\partial \phi}{\partial v} + q_{12} \frac{\partial \phi}{\partial r} \quad (D.64) \\
\frac{\partial}{\partial x} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = \frac{\beta}{N_2} \frac{\partial^2 \phi}{\partial v \partial x} - (\sigma + \mu + \delta) \frac{\partial \phi}{\partial x} + q_{12} \frac{\partial \phi}{\partial s} - q_{21} \frac{\partial \phi}{\partial x} \quad (D.65) \\
\frac{\partial}{\partial y} \left( \frac{\partial \phi}{\partial t} \right) &\quad \bigg|_{\hat{\omega} = 1} = \sigma \frac{\partial \phi}{\partial x} - (\mu + q_{21}) \frac{\partial \phi}{\partial y} + q_{12} \frac{\partial \phi}{\partial w} \quad (D.66)
\end{align*}
\]

D.5 Two cities model: SEIR

Now let consider a two cities SEIR model:

\[
\begin{align*}
\dot{S}_1 &= -\beta S_1 \frac{I_1 + \mu E_1}{N_1} - q_{12} S_1 + q_{21} S_2 \quad (D.67) \\
\dot{E}_1 &= \beta S_1 \frac{I_1 + \mu E_1}{N_1} - \alpha E_1 - q_{12} E_1 + q_{21} E_2 \quad (D.68) \\
\dot{I}_1 &= \alpha E_1 - (\sigma + \delta) I_1 - q_{12} I_1 + q_{21} I_2 \quad (D.69) \\
\dot{R}_1 &= \sigma I_1 - q_{12} R_1 + q_{21} R_2 \quad (D.70) \\
\dot{S}_2 &= -\beta S_2 \frac{I_2 + \mu E_2}{N_2} - q_{12} S_1 + q_{21} S_2 \quad (D.71) \\
\dot{E}_2 &= \beta S_2 \frac{I_2 + \mu E_2}{N_2} - \alpha E_2 + q_{12} E_1 - q_{21} E_2 \quad (D.72) \\
\dot{I}_2 &= \alpha E_2 - (\sigma + \delta) I_2 + q_{12} I_1 - q_{21} I_2 \quad (D.73) \\
\dot{R}_2 &= \sigma I_2 + q_{12} R_1 - q_{21} R_2 \quad (D.74)
\end{align*}
\]

By using the following transition variables for \( S_1 \rightarrow i, E_1 \rightarrow j, I_1 \rightarrow k, R_1 \rightarrow m, S_2 \rightarrow n, E_2 \rightarrow a, I_2 \rightarrow b \) and \( R_2 \rightarrow c \). Let’s define the transition stages and rates as in Table D.5.
Table D.5: Transition Rates for the CTMC Process for an SEIR two cities model.

<table>
<thead>
<tr>
<th>Transition Stage</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$i \rightarrow i + 1$</td>
<td>$q_{21}n$</td>
</tr>
<tr>
<td>$i \rightarrow i - 1$</td>
<td>$\frac{\beta_i(k+\mu j)}{N_i} + q_{12}i$</td>
</tr>
<tr>
<td>$j \rightarrow j + 1$</td>
<td>$\frac{\beta_i(k+\mu j)}{N_i} + q_{21}a$</td>
</tr>
<tr>
<td>$j \rightarrow j - 1$</td>
<td>$(\alpha + q_{12})j$</td>
</tr>
<tr>
<td>$k \rightarrow k + 1$</td>
<td>$\alpha j + q_{21}b$</td>
</tr>
<tr>
<td>$k \rightarrow k - 1$</td>
<td>$(\sigma + \delta + q_{12})k$</td>
</tr>
<tr>
<td>$m \rightarrow m + 1$</td>
<td>$\sigma k + q_{21}c$</td>
</tr>
<tr>
<td>$m \rightarrow m - 1$</td>
<td>$q_{12}m$</td>
</tr>
<tr>
<td>$n \rightarrow n + 1$</td>
<td>$q_{12}i$</td>
</tr>
<tr>
<td>$n \rightarrow n - 1$</td>
<td>$\beta n(b+\mu a) + q_{21}n$</td>
</tr>
<tr>
<td>$a \rightarrow a + 1$</td>
<td>$\beta n(b+\mu a) + q_{21}j$</td>
</tr>
<tr>
<td>$a \rightarrow a - 1$</td>
<td>$(\alpha + q_{21})a$</td>
</tr>
<tr>
<td>$b \rightarrow b + 1$</td>
<td>$\alpha a + q_{12}k$</td>
</tr>
<tr>
<td>$b \rightarrow b - 1$</td>
<td>$(\sigma + \delta + q_{12})b$</td>
</tr>
<tr>
<td>$c \rightarrow c + 1$</td>
<td>$\sigma b + q_{12}m$</td>
</tr>
<tr>
<td>$c \rightarrow c - 1$</td>
<td>$q_{21}c$</td>
</tr>
</tbody>
</table>

In order to save space for notation let $\tilde{\omega} = (i, j, k, m, n, a, b, c)$ and define $P_{\tilde{\omega}} = P_{i,j,k,m,n,a,b,c}$ with $P_{\tilde{\omega}(i-1)} = P_{i-1,j,k,m,n,a,b,c}$ to indicate the index that has a change. Hence, the forward Kolmogorov Equation for the above transition rates is:

$$P'_{\tilde{\omega}}(t) = q_{21}n P_{\tilde{\omega}(i-1)}(t) + \left[ \frac{\beta_i(k+\mu j)}{N_i} + q_{12}(i+1) \right] P_{\tilde{\omega}(i+1)}(t)$$

$$+ \left[ \frac{\beta_i(k+\mu (j-1))}{N_i} + q_{21}a \right] P_{\tilde{\omega}(j-1)}(t) + (\sigma + \delta + q_{12})(k+1)P_{\tilde{\omega}(k+1)}(t)$$

$$+ (\alpha j + q_{12}b)P_{\tilde{\omega}(k-1)}(t) + q_{12}(m+1)P_{\tilde{\omega}(m+1)}(t)$$

$$+ (\sigma + q_{12})P_{\tilde{\omega}(m-1)}(t) + \left[ \frac{\beta(n+1)(b+\mu a)}{N_2} + q_{21}(n+1) \right] P_{\tilde{\omega}(n+1)}(t)$$

$$+ (\alpha + q_{21})(j+1)P_{\tilde{\omega}(j+1)}(t) + (\alpha + q_{21})(a+1)P_{\tilde{\omega}(a+1)}(t) + q_{12}P_{\tilde{\omega}(a+1)}(t)$$

$$+ \left[ \frac{\beta n(b+\mu (a-1))}{N_2} + q_{12}j \right] P_{\tilde{\omega}(a-1)}(t) + (\sigma + \delta + q_{21})(b+1)P_{\tilde{\omega}(b+1)}(t)$$

$$+ (\alpha a + q_{12}k)P_{\tilde{\omega}(b-1)}(t) + q_{21}(c+1)P_{\tilde{\omega}(c+1)}(t)$$

$$+ (\sigma b + q_{12}m)P_{\tilde{\omega}(c-1)}(t) - \delta(k+b) - 2(\sigma(k+b) + \alpha(j+a))P_{\tilde{\omega}}(t)$$

$$- 2 \left[ q_{21}(n+a+b+c) + q_{12}(i+j+k+m) + \frac{\beta n(b+\mu a)}{N_2} + \frac{\beta_i(k+\mu j)}{N_1} \right] P_{\tilde{\omega}}(t)$$

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where the probability generating function (p.g.f) is $\frac{\partial \phi}{\partial t}$:

$$\phi(r, s, w, v, x, y, u, z) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \sum_{a=0}^{\infty} \sum_{b=0}^{\infty} \sum_{c=0}^{\infty} P_{\omega}(t) r^i s^j w^k v^m x^n y^a u^b z^c \tag{D.76}$$

$$\frac{\partial \phi}{\partial t} = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \sum_{a=0}^{\infty} \sum_{b=0}^{\infty} \sum_{c=0}^{\infty} P'_{\omega}(t) r^i s^j w^k v^m x^n y^a u^b z^c \tag{D.77}$$

After a lot of computations, taking the partial derivative with respect to each of the variables and evaluation of the partial derivatives at $r = s = w = v = x = y = u = z = 1$ in each case we get the deterministic SIR two cities model with demography. The expected values of the variables are related to the deterministic quantities. In terms of seeing the connection we can in a sense interchange $\frac{\partial \phi}{\partial r}$ with $S_1$, $\frac{\partial \phi}{\partial s}$ with $E_1$, $\frac{\partial \phi}{\partial w}$ with $I_1$, $\frac{\partial \phi}{\partial v}$, with $R_1$, $\frac{\partial \phi}{\partial x}$ with $S_2$, $\frac{\partial \phi}{\partial y}$ with $E_2$, $\frac{\partial \phi}{\partial u}$ with $I_2$, and $\frac{\partial \phi}{\partial z}$ with $R_2$.

$$\frac{\partial}{\partial r} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = -\frac{\beta}{N_1} \frac{\partial^2 \phi}{\partial r^2} - \frac{\beta \mu}{N_1} \frac{\partial^2 \phi}{\partial r \partial s} - q_{12} \frac{\partial \phi}{\partial r} + q_{21} \frac{\partial \phi}{\partial x} \tag{D.78}$$

$$\frac{\partial}{\partial s} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = \frac{\beta}{N_1} \frac{\partial^2 \phi}{\partial r^2} + \frac{\beta \mu}{N_1} \frac{\partial^2 \phi}{\partial r \partial s} - (\alpha + q_{12}) \frac{\partial \phi}{\partial s} + q_{21} \frac{\partial \phi}{\partial y} \tag{D.79}$$

$$\frac{\partial}{\partial w} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = \alpha \frac{\partial \phi}{\partial s} - (\sigma + q_{12} + \delta) \frac{\partial \phi}{\partial w} + q_{21} \frac{\partial \phi}{\partial u} \tag{D.80}$$

$$\frac{\partial}{\partial v} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = \sigma \frac{\partial \phi}{\partial w} - q_{12} \frac{\partial \phi}{\partial v} + q_{21} \frac{\partial \phi}{\partial z} \tag{D.81}$$

$$\frac{\partial}{\partial x} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = q_{12} \frac{\partial \phi}{\partial r} - \frac{\beta}{N_2} \frac{\partial^2 \phi}{\partial x \partial r} - \frac{\beta \mu}{N_2} \frac{\partial^2 \phi}{\partial x \partial u} - q_{21} \frac{\partial \phi}{\partial x} \tag{D.82}$$

$$\frac{\partial}{\partial y} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = q_{12} \frac{\partial \phi}{\partial s} - (\alpha + q_{21}) \frac{\partial \phi}{\partial y} + \frac{\beta}{N_2} \frac{\partial^2 \phi}{\partial x \partial u} + \frac{\beta \mu}{N_2} \frac{\partial^2 \phi}{\partial x \partial y} \tag{D.83}$$

$$\frac{\partial}{\partial u} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = q_{12} \frac{\partial \phi}{\partial w} + \alpha \frac{\partial \phi}{\partial u} - (\delta + q_{21}) \frac{\partial \phi}{\partial u} \tag{D.84}$$

$$\frac{\partial}{\partial z} \left( \frac{\partial \phi}{\partial t} \right) \bigg|_{\omega=1} = \sigma \frac{\partial \phi}{\partial u} - q_{21} \frac{\partial \phi}{\partial z} + q_{12} \frac{\partial \phi}{\partial v} \tag{D.85}$$
APPENDIX E

INTERPOLATION
Figure E.1: This graphs shows a sample of point (labeled data in circles) of the function \( \sin(x) \) (fine line labeled real) and how the three interpolation methods \( pchip \) (dashed line with diamonds), \( spline \) (dashed line with crosses) and \( interp1 \) (dashed line with squares) model the data set. Here we use 6 points.

In order to compare the stochastic models with the deterministic we need to pair point wise the events by aligning the time steps specially for the CTMC where the time is a continuous random variable. To do so we use interpolation; as a random fact interpolation was invented in WW2 as a method to construct templates for airplanes by the British aircraft industry using wooden strips or splines (See http://en.wikipedia.org/wiki/Spline_(mathematics)). There are three main types of interpolation algorithms in Matlab: piecewise cubic Hermite interpolating polynomial (\( pchip \)), cubic spline data interpolation (\( spline \)) and linear interpolation \( interp1 \). The \( pchip \) uses a piecewise polynomial form of a shape-preserving piecewise cubic Hermite interpolant, the \( spline \) uses a cubic polynomial form and \( interp1 \) uses linear methods to approximate the shape of the data by connecting each point with a linear function. The two graphs below Fig. E.1 and Fig. E.2 show the three methods using as an example \( \sin(x) \) one with a few point than the other. We can see that the \( pchip \) method gets as close to the data points as it could since is shape preserving while the spline curves and look more similar to the graph of \( \sin(x) \). In this sense it is preferable to use \( pchip \) over \( interp1 \) or \( spline \) to preserve the shape of the data. But in our case since the data points are discrete with no polynomial shape the linear interpolation approach is more appropriate. Recall that here we are not looking to find a function for the data but simply want to align the points time wise to be able to compare different stochastic methods.
Figure E.2: This graph shows a sample of points (labeled data in circles) of the function $\sin(x)$ (fine line labeled real) and how the three interpolation methods *pch* (dashed line with diamonds), *spline* (dashed line with crosses) and *interp1* (dashed line with squares) model the data set. Here we use 11 points.
APPENDIX F

DATA ACQUISITION AND NUMERICAL SIMULATIONS.
All data presented in Chapter 2 from the publication [76] was obtained from the weekly reports of the Mexican Health Secretariat [136], recorded in spreadsheets using Open Office 2.3, and processed using Python 2.5 in MacBook notebooks running on OS X or in a Lenovo T400 laptop running Python2.6 under Ubuntu 9.10 with an Intel(R) Core(TM)2 Duo CPU T9600 at 2.8 GHz. All simulations were performed using the python module scipy [82]. Figures were produced with the python module matplotlib [78]. All numerical solutions of the model in Chapter 3 were obtained using Python 2.6 in a Lenovo T400 laptop with an Intel(R) Core(TM)2 Duo CPU T9600 at 2.8 GHz running Linux Kubuntu version 11. Simulations were performed using the solver odeint contained in the Python module scipy.integrate [82], which uses lsoda from the Fortran library odepack. The solver uses Adams method for nonstiff problems, and a method based on backward differentiation formulas for stiff problems. Figures were produced with the Python module matplotlib [78]. The rest of the simulations (parts of Chapter 2 and all of Chapter 4) were created using a MacBook notebook running on OS X using Matlab R2013a (8.1.0.604). Code used for simulations in all chapters of this dissertation is available upon request.