Investigating Stochastic Influences on Coinfection Dynamics of Respiratory Viruses: A Modeling Study

PROJECT REPORT

BE3001: Stochastic Modeling in Biology

Original Authors: Lubna Pinky, Gilberto Gonzalez-Parra and Hana M. Dobrovolny

Review Author: Atharva Sawant

Course Instructor: Dr. Monika Sharma

Course TA: Akhil Pratap

December 10, 2023

Acknowledgement

I sincerely thank Dr. Monika Sharma for her invaluable guidance during the Stochastic Modeling in Biology course. Her profound expertise enriched my understanding of stochastic modeling principles, crucial in the successful completion of my final project. Special appreciation to Akhil Pratap, whose scholarly contributions profoundly influenced my academic growth. His responsiveness, clarity in explanations, and commitment to an academically rigorous environment were integral to my educational experience.

I express gratitude to the original authors of *"Effect of stochasticity on coinfection dynamics of respiratory viruses"* – Lubna Pinky, Gilberto Gonzalez-Parra, and Hana M. Dobrovolny. Their seminal work laid the foundation for my project. The development of my final project was enriched by the knowledge gained, allowing me to apply rigorous stochastic modeling principles to explore respiratory virus coinfections, deepening my understanding and enhancing practical analytical skills.

To both Dr. Monika Sharma and Akhil Pratap, your commitment to scholarly pursuits has been inspirational. The acquired knowledge and analytical skills, coupled with your mentorship, profoundly influence my future endeavors in stochastic modeling and biology.

I extend profound gratitude for your support and dedication to fostering academic excellence.

Contents

1 Abstract

In this open-access study, the impact of respiratory viral coinfections on illness severity is explored through the lens of a continuous-time Markov chain (CTMC) model. Given that up to 40% of hospitalized influenza-like illness cases involve multiple viral infections, the research aims to elucidate whether such coinfections result in increased severity. Traditional mathematical models employing ordinary differential equations (ODE) might oversimplify dynamics due to the stochastic nature of viral replication. Stochastic simulations, revealing extinction probabilities in single virus infections, underscore the challenge of observing predicted coinfection dynamics in reality. The newly formulated CTMC model, building on a previous ODE-based coinfection model, employs the Gillespie method for stochastic simulation. Contrary to ODE predictions, the study demonstrates that stochasticity, especially in early infection stages, can lead to a slower-growing virus out-competing a faster-growing counterpart with similar initial growth rates. The research contributes insights into the probabilistic outcomes of respiratory viral coinfections, highlighting the importance of stochastic modeling for a more accurate understanding of infection dynamics and potential implications for illness severity.

2 Introduction

The advancement of molecular diagnostic techniques has brought about a transformative era in the analysis of respiratory tract specimens, particularly among patients presenting with influenza-like illness (ILI). This technological progression has revealed a complex landscape of multiple viruses coexisting within a single host [1–2] and emphasized the intricate nature of viral coinfections. Approximately 40% of individuals requiring hospitalization for ILI find themselves entangled in coinfections involving various pathogens, including influenza A virus (IAV), influenza B virus (IBV), respiratory syncytial virus (RSV), human rhinovirus (hRV), adenovirus (AdV), human enterovirus (hEV), human metapneumovirus (hMPV), coronavirus (CoV), parainfluenza virus (PIV), human bocavirus (hBoV), and numerous others [3–4]. As the complexities of coinfections unfold, understanding their implications on disease outcomes becomes an increasingly evident challenge. The trajectories of diseases following coinfections exhibit a spectrum of outcomes, ranging from heightened severity to mitigated or unaltered seriousness when compared with single-virus infections [5–6]. The elusive dynamics governing virus-virus and virus-host interactions within this complex environment are further compounded by diverse factors. The order of inoculation, inter-exposure time, initial inoculum size, combinations of viruses, the number of coinfecting viruses, and the host's immune state collectively contribute to the intricate combinatorial problem posed by coinfections [7, 8].

In addressing this substantial challenge, mathematical modeling emerges as an essential tool, offering a systematic approach to comprehend the complexities inherent in viral coinfections. While mathematical modeling has made significant progress in elucidating the intricacies of single virus

infections at the cellular level [9–10], a notable gap remains in the modeling of viral coinfections. Early research in this field predominantly leaned on deterministic approaches, effectively capturing the average behavior of coinfection kinetics [11–12]. However, the deterministic modeling framework, while instrumental in providing comprehensive insights, falls short in capturing the nuanced and stochastic nature of viral coinfections. The complexities arising from diverse interactions, temporal dynamics, and the inherent variability in host responses necessitate a shift towards more sophisticated modeling frameworks. The deterministic methods, having served as valuable foundations, now indicate an evolution towards stochastic models capable of accommodating the intrinsic variability and unpredictability inherent in coinfection dynamics.

Paving the way forward involves the integration of stochastic elements into mathematical models, promising to bridge the existing gap in our understanding of viral coinfections. This transformative shift enables a more nuanced exploration of the intricate dynamics shaping coinfection outcomes. As the research landscape evolves, the exploration of stochastic modeling in the context of viral coinfections holds the promise of unveiling novel insights that surpass the constraints of deterministic models. The evolving field of mathematical modeling, particularly within the domain of viral coinfections, becomes not only a significant beacon of scientific inquiry but also a crucial tool in deciphering the enigmatic interplay between multiple viruses within a host.

3 Literature Review

Pinky and Dobrovolny's seminal work [13] stands as a pivotal contribution to the field of viral coinfections, introducing a two-virus deterministic coinfection model with a primary focus on the observed viral interference in IAV-RSV coinfections [14]. This groundbreaking model served as the cornerstone for subsequent investigations that sought to expand its applicability and delve into the complexities of coinfection dynamics. Subsequent explorations by researchers aimed to extend the model's scope, with particular attention to the impact of resource availability on coinfection outcomes [15, 16]. These efforts reflect a concerted attempt to decipher the multifaceted factors influencing coinfection dynamics beyond the direct interactions between viruses. Despite these advancements, the majority of research within the domain of viral coinfections has been predominantly grounded in deterministic modeling paradigms. Limited attention has been accorded to stochastic models, which encapsulate the inherent variability and unpredictability of biological systems more comprehensively.

Dobrovolny et al. [17] and Deecke et al. [18], in their exploration of stochastic models, contributed valuable insights by investigating two strains of the same virus. However, their focus on a singular virus strain imposes limitations on the broader understanding of viral coinfections involving distinct pathogens. The need for a more expansive exploration of stochastic simulations within the broader context of viral coinfections becomes apparent. The transition from deterministic to stochastic

modeling represents a crucial shift in approach, providing a more nuanced lens through which to examine the intricacies of coinfection dynamics. This transition holds the promise of offering a more comprehensive understanding of the impact of stochastic effects, particularly in the early stages of the infection process. By embracing stochastic elements, researchers can delve into the inherent variability of biological systems and gain insights into how seemingly random events contribute to the overall dynamics of coinfections.

Stochastic simulations, a foundational element of this study, play a crucial role in revealing extinction probabilities and clarifying the intricate interactions between viruses and host cells. While stochastic modeling has been primarily applied to single virus infections [19–20], its extension to the intricate realm of viral coinfections is a novel and ambitious undertaking. Extinction probabilities, a feature elusive to deterministic models, assume a central position in stochastic modeling, particularly in the context of coinfections [21]. At the center of our study is the analytical derivation of the extinction coefficient, employing a multi-type branching method. This method, previously underutilized in the domain of viral coinfections, holds the potential to reveal unique insights into the impact of stochasticity on coinfection outcomes. The emphasis on the extinction probability, a vital parameter shaping coinfection dynamics, distinguishes our study by addressing a critical aspect often overlooked in deterministic models.

Our focus on stochastic simulations, coupled with the analytical derivation of the extinction coefficient, not only contributes to filling the existing gap in stochastic modeling of viral coinfections but also propels the broader understanding of how stochasticity shapes infection dynamics. The incorporation of stochastic elements provides a more realistic representation of viral coinfections, uncovering insights that remain unnoticed within deterministic models. Furthermore, our analytical approach enhances the understanding of extinction probabilities, shedding light on potential scenarios that may deviate from predictions made by deterministic models.

4 Methodology

Our methodology combines a Continuous-Time Markov Chain (CTMC) model with a Stochastic Simulation Algorithm (SSA) to comprehensively investigate viral coinfection dynamics [1]. This approach serves as a bridge between deterministic models and the intricate, stochastic nature of viral interactions within a host. The CTMC model establishes a probabilistic framework, capturing the stochastic aspects of early infection processes [13], while the SSA enables efficient simulations for large-scale models. This integrated approach goes beyond conventional deterministic models, providing fresh insights into the impact of stochasticity on coinfection dynamics [14].

Description	Transition	Propensity
Infection by V_1	$T \to T-1, E_1 \to E_1+1$	$\beta_1 T V_1$
Infection by V_2	$T \to T-1, E_2 \to E_2+1$	$\beta_2 T V_2$
Infection to infectious	$E_1 \to E_1-1, l_1 \Rightarrow I_1+1$	$k_1 E_1$
Infection to infectious	$E_2 \to E_2-1, l_2 \to I_2+1$	$k_2 E_2$
Death of I_1	$I_1 \to I_1-1$	$\delta_1 l_1$
Death of I_2	$I_2 \to I_2-1$	$\delta_2 I_2$
Production of V_1	$V_1 \to V_1+1$	$p_1 l_1$
Production of V_2	$V_2 \to V_2+1$	$p_2 l_2$
Decay of V_1	$V_1 \to V_1-1$	$c_1 V_1$
Decay of V_1	$V_2 \to V_2-1$	$c_2 V_2$

Table 1: State Transitions and Propensities for the CTMC Coinfection Model

4.1 Continuous-Time Marko Chain (CTMC) Model

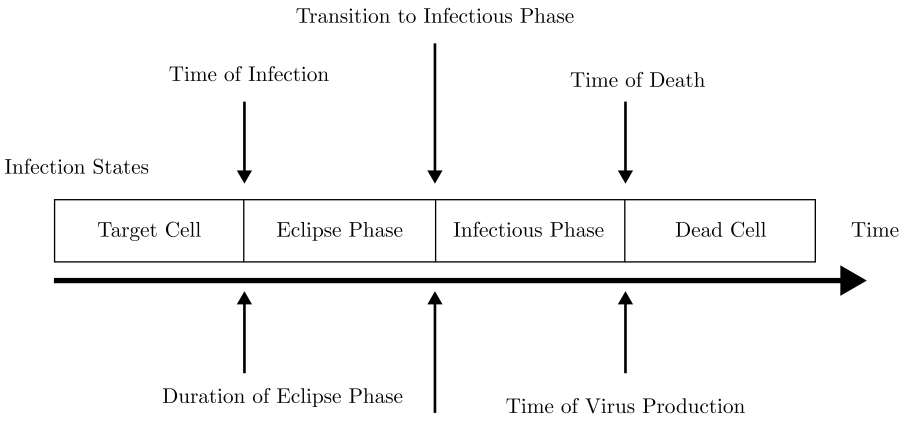

Figure 1: Stochastic States and their Transitions during Coinfection

Our Continuous-Time Markov Chain (CTMC) model serves as a probabilistic counterpart to the deterministic ODE models, offering a nuanced exploration of the stochastic effects within the early stages of viral coinfection processes [13]. This time-homogeneous CTMC model focuses on the dynamics of two competing viruses, introducing variability in each viral replication event. The model is constructed with discrete states forming the state space Ω, denoted as $\vec{m} = (n_T, n_{E_1}, n_{I_1}, n_{V_1}, n_{E_2}, n_{I_2}, n_{V_2})$. Here, each vector element represents the integer numbers of target cells, eclipse cells, infected cells, and virions for our test viruses—virus 1 and 2, respectively.

The model, illustrated in Figure 1, follows ten transitions with specific propensities, outlined in Table 1. The transitions capture critical events in the viral life cycle, from infection of target cells to the production and clearance of virions. Each transition is associated with a propensity, representing the rate at which the corresponding event occurs.

In detail, the model starts with the infection of target cells (T) by viruses (V_1 and V_2) at rates $\beta_1 T V_1$ and $\beta_2 T V_2$, respectively. Infected cells (E_1 and E_2) transition to infectious phases (I_1 and

I_2) at rates k_1E_1 and k_2E_2 after specific eclipse durations. Infected cells subsequently contribute to the production of virions (V_1 and V_2) at rates p_1l_1 and p_2l_2 over their respective lifespans. The model also accounts for the death of infected cells (I_1 and I_2) at rates δ_1l_1 and δ_2I_2 and the decay of virions (V_1 and V_2) at rates c_1V_1 and c_2V_2.

Importantly, the CTMC model assumes a time-homogeneous, discrete state space, aligning with the stochastic nature of biological systems at the microscopic level. This modeling framework is chosen considering the inherent stochasticity in chemical reactions involved in viral replication processes, where each reaction's probability is assumed to depend on the density of reactants. The states and transitions in the CTMC model allow for a detailed exploration of the intricate dynamics of coinfections involving two virus types. By capturing the variability in each viral replication event and considering discrete states, the model aims to provide a realistic representation of the complex interplay between multiple viruses within a host. It is essential to note that, in our model assumption, we have disregarded virus particle loss due to absorption into cells due to its negligible impact compared to free virus particles produced. Furthermore, specific immune interactions are not considered in this model, focusing primarily on the fundamental viral dynamics within the host.

The convergence of stochastic representations to differential equations, especially when the number of particles is sufficiently large, underscores the validity of the CTMC model in approximating the intricate dynamics of viral coinfections. This convergence is rooted in the assumption that the probability of a reaction depends on the density of reactants, extending to the broader context of viral replication processes.

4.2 Stochastic Simulation Algorithm

The Stochastic Simulation Algorithm (SSA) constitutes a vital component of our methodology, providing an efficient means to simulate the dynamics of viral coinfections within a host. Gillespie's direct method [22], widely adopted for solving trajectories of time-homogeneous Continuous-Time Markov Chain (CTMC) models, forms the basis for our SSA. However, the direct method's linear scaling with the initial number of target cells becomes impractical for realistic numbers, e.g., on the order of 1×10^8 cells [20]. To address this challenge, Gillespie tau-leap algorithms have gained prominence, offering increased simulation efficiency with a minimal accuracy trade-off.

In the tau-leap method, a small time interval is selected, and the number of times each transition occurs within this interval is drawn from a Poisson distribution. The mean of this distribution is equal to the expected number of transitions during the interval. The time step is fixed, but it should be sufficiently small to maintain an approximately constant transition rate during the interval. For our CTMC model's numerical implementation, we adopt the Gillespie tau-leaping method with a time step set to 10^{-3} day.

Parameter	Value $^{\alpha}$	Units
β	3.2×10^{-5}	cell $^{-1}$ $\left(\text{TCID}_{50}/\text{mL}^{-1}\ \text{d}^{-1}\right.$
k	4.6	d^{-1}
δ	5.2	d^{-1}
p	4.6×10^{-2}	$\text{TCID}_{50}/\text{mLd}^{-1}$
c	5.2	d^{-1}
T_0	4.0×10^{8}	cell
V_0	7.5×10^{-2}	$\text{TCID}_{50}/\text{mL}$
α	1×10^{2}	-

Table 2: Parameter Values for the CTMC Coinfection Model

The transitions involved in the stochastic process, accompanied by their rates, are summarized in Table 1. This comprehensive table outlines the key transitions governing the viral coinfection dynamics, providing a clear reference for understanding the intricate stochastic processes involved. To ensure accuracy and relevance, parameter values for numerical simulations are sourced from existing literature [9] and detailed in Table 2. These values include infection and transition rates, initial cell counts, and viral load concentrations. Viral load, conventionally measured in units such as TCID_{50} /mL or PFU/mL, is converted into the number of infectious virus particles using a conversion factor, denoted as α.

The parameter values cover critical aspects such as the infection rate (β), eclipse to infectious transition rate (k), death rate of infected cells (δ), production rate of virions (p), clearance rate of virions (c), initial target cell count (T_0), initial viral load concentration (V_0), and the conversion factor (α). Our choice of $\alpha = 1 \times 10^2$ aligns with previous estimates, allowing for the conversion of viral concentration measurements into the number of infectious virus particles. This conversion factor provides consistency with established methodologies, ensuring the meaningful integration of experimental data into our stochastic simulations.

4.3 Data Collection

The adopted methodology for data collection follows a systematic process aimed at gathering relevant information on viral coinfection dynamics. The review and extraction of data are conducted thoroughly from prevailing research papers, scholarly articles, and databases, emphasizing studies utilizing mathematical models to elucidate coinfection dynamics. Primary data sources encompass peer-reviewed journals within the domains of virology, immunology, and mathematical modeling, ensuring the reliability and scientific rigor of the acquired information.

Priority is given to research papers delving into coinfections involving various pathogens, including IAV, influenza B virus (IBV), respiratory syncytial virus (RSV), human rhinovirus (hRV), adenovirus (AdV), human enterovirus (hEV), human metapneumovirus (hMPV), coronavirus (CoV),

parainfluenza virus (PIV), human bocavirus (hBoV), and others. The selection of studies encompasses diverse host conditions, spanning distinct immune states, initial inoculum sizes, and inter-exposure times, thereby ensuring a comprehensive understanding of the factors influencing coinfection dynamics.

Quantitative data relevant to infection rates, transition rates, death rates of infected cells, production rates of virions, and clearance rates of virions are systematically extracted from chosen studies. However, in cases where specific data is not available, synthetic data is generated, ensuring that the model is tested under a variety of conditions. The synthetic data is carefully designed to mimic real-world scenarios and encompasses variations in infection parameters, immune responses, and initial conditions. This comprehensive approach ensures robustness in the analysis, accounting for diverse situations that may be encountered in viral coinfections.

4.4 Ethical Considerations

The fundamental consideration of ethical guidelines underscores the research process, particularly in handling sensitive data and employing mathematical models with implications for public health understanding. Adherence to established ethical norms ensures the strict utilization of collected data for scientific purposes, with a commitment to anonymization to uphold the confidentiality and privacy of individuals involved in the original studies. The research, grounded in mathematical modeling, extends ethical considerations to the responsible and transparent utilization of these models. Explicit acknowledgment of model limitations is communicated transparently in the research findings, prioritizing accuracy in model representation while exercising caution to avoid unjustified implications. Furthermore, the research aligns with ethical standards regarding proper citation and attribution. Due credit is extended to the original authors, acknowledging their contributions to the foundational knowledge of viral coinfection dynamics. This approach not only upholds academic integrity but also fosters a collaborative and ethical research environment.

5 Mathematical and Data Analysis

To further investigate the influence of stochasticity, this project explores the intricate dynamics of viral coinfections through a comprehensive mathematical and analytical model. The model incorporates stochastic elements and addresses crucial factors such as identical and divergent growth rates between viruses. While conventional ordinary differential equation (Deterministic ODE) models provide valuable insights into average behaviors, the incorporation of stochasticity is imperative for a detailed understanding of real-world biological processes. The employed model systematically examines stochastic extinction dynamics during the initial phases of infection, particularly in scenarios where the number of target cells is constrained. By utilizing a mathematical model derived from a multi-type branching process and continuous-time Markov chain (CTMC), and employing

an analytical model that utilizes the Gillespie algorithm with Tau-leaping, this study presents a comprehensive framework capturing the interplay among eclipse cells, infected cells, and virions for two distinct viruses. The resulting extinction probability ($\xi(\vec{m})$) emerges as a pivotal metric, quantifying the likelihood of complete elimination of both viruses and their infected cells from the host. This model's analytical insights complement traditional deterministic ODE approaches, providing a more realistic depiction of viral coinfection dynamics and offering insights on the impact of stochastic events on overall infection outcomes.

5.1 Model Assumptions

The foundation of our mathematical model relies on fundamental assumptions that establish a structured framework for delving into the complexities of viral coinfection dynamics. These key assumptions serve as the cornerstone for our stochastic model, elucidating the specific conditions under which the model operates.

At the initial phase of infection, we contemplate a scenario wherein the number of target cells is constrained, allowing us to treat these cells as a constant ($T \approx T_0$). This assumption plays a pivotal role in decoupling states, resulting in the independence of stochastic events. Consequently, the continuous-time Markov chain (CTMC) model undergoes a transformation into a multi-type branching process, capturing the intricate dynamics involving eclipse cells (E_1, E_2), infected cells (I_1, I_2), and virions (V_1, V_2) for two distinct viruses. The incorporation of the constant number of target cells leads to the expression of a reduced model through a series of reaction pathways, each distinguished by specific transition rates ($\beta_1, \beta_2, k_1, k_2, p_1, p_2, \delta_1, \delta_2, c_1, c_2$).

The emergence of the extinction probability ($\xi(\vec{m})$) as a focal point in our model becomes apparent, representing the likelihood of the complete elimination of both viruses and their infected cells from the host. The intricate interplay of transition vectors and probabilities is methodically presented, culminating in an algebraic expression for $\xi(\vec{m})$. This comprehensive understanding enriches our insight into the stochastic extinction dynamics inherent in viral coinfections.

5.2 Model Parameters, Equations, and Dynamics

At the core of our stochastic model lies a continuous-time Markov chain (CTMC) representing the dynamics of viral coinfections. The system encompasses various states, including eclipse cells (E_1, E_2), infected cells (I_1, I_2), and virions (V_1, V_2) for two distinct viruses. To facilitate the derivation, we initially consider a scenario with a constant number of target cells ($T \approx T_0$) at the onset of infection. The extinction process hinges on the probabilities associated with state transitions. Transition rates ($\beta_1, \beta_2, k_1, k_2, p_1, p_2, \delta_1, \delta_2, c_1, c_2$) govern the movement between different states, capturing the intricate dynamics of viral coinfections. These transition rates, coupled with the assumption of a constant number of target cells, pave the way for a set of reaction pathways defining the

system's evolution.

Furthermore, the extinction coefficient (ξ) serves as a quantitative measure of the likelihood of complete elimination of both viruses and their infected cells from the host. Its derivation involves a systematic exploration of the underlying mathematical principles and equations. Now employing a master equation, we derive a system of ordinary differential equations (Deterministic ODEs) describing the temporal evolution of the probability mass function. The final step involves obtaining an explicit expression for the extinction coefficient (ξ). This parameter encapsulates the probability of complete viral and infected cell elimination. The intricate interplay of transition probabilities, generating functions, and moments culminates in a concise mathematical expression, providing a quantitative measure of the likelihood of extinction in the context of viral coinfections.

5.2.1 Model Dynamics

The mathematical foundation of our study lies in a system of ordinary differential equations (Deterministic ODEs) capturing the intricate dynamics of viral coinfections. These equations serve as the backbone of our analytical framework, providing a quantitative representation of the interactions between viruses, infected cells, and the host environment. The model considers the populations of target cells (T), eclipse cells (E_1, E_2), infected cells (I_1, I_2), and free virions (V_1, V_2) for two distinct viruses. The dynamics of these populations are governed by a set of coupled Deterministic ODEs, incorporating key parameters that influence the rates of infection, replication, and clearance.

$$\frac{dT}{dt} = -\beta_1 V_1 T - \beta_2 V_2 T \tag{1}$$
$$\frac{dE_1}{dt} = \beta_1 V_1 T - k_1 E_1 - p_1 E_1 \tag{2}$$
$$\frac{dI_1}{dt} = k_1 E_1 - \delta_1 I_1 - c_1 I_1 \tag{3}$$
$$\frac{dV_1}{dt} = p_1 E_1 - c_1 V_1 \tag{4}$$
$$\frac{dE_2}{dt} = \beta_2 V_2 T - k_2 E_2 - p_2 E_2 \tag{5}$$
$$\frac{dI_2}{dt} = k_2 E_2 - \delta_2 I_2 - c_2 I_2 \tag{6}$$
$$\frac{dV_2}{dt} = p_2 E_2 - c_2 V_2 \tag{7}$$

5.2.2 Model Parameters

The model incorporates key parameters ($\beta_1, \beta_2, k_1, k_2, p_1, p_2, \delta_1, \delta_2, c_1, c_2$) representing infection rates, eclipse cell transition rates, infected cell death rates, and virion clearance rates for each virus. These parameters govern the transitions between different states, influencing the overall dynamics of the

system. To facilitate a clear understanding of our mathematical model, we present a systematic compilation of all parameters involved in the study. These parameters govern the dynamics of viral coinfections and play a crucial role in shaping the outcomes of the model.

Infection Parameters

- β_1: Infection rate for Virus 1, representing the probability of a susceptible target cell becoming infected by Virus 1 per unit time.
- β_2: Infection rate for Virus 2, analogous to β_1 but for Virus 2.

Transition Rates

- k_1, k_2: Transition rates from eclipse cells to infected cells for Virus 1 and Virus 2, respectively.
- p_1, p_2: Transition rates from eclipse cells to free virions for Virus 1 and Virus 2, respectively.

Death Rates

- δ_1, δ_2: Death rates of infected cells for Virus 1 and Virus 2, respectively.
- c_1, c_2: Clearance rates of free virions for Virus 1 and Virus 2, respectively.

These parameters collectively define the intricate interactions within our model, capturing the essential elements of viral coinfection dynamics. The systematic presentation ensures clarity and consistency, laying the foundation for a detailed exploration of the model's behavior under various conditions.

The transition from the mathematical foundations of our model to the analysis phase is marked by the robust framework provided by the mathematical model. Serving as a strong foundation, the model opens the door to a deeper understanding of coinfection dynamics, particularly those that persist. The subsequent analysis delves into the impact of stochasticity, revealing valuable insights into the intricacies of coinfection dynamics that endure. The goal is to explore the influence of randomness on the predicted dynamics, with a specific focus on scenarios where both viruses manage to persist.

5.2.3 Stochastic Dynamics of Identical Viruses

In contrast to the deterministic predictions of the Ordinary Differential Equation (ODE) model, where the virus with a higher growth rate consistently out-competes the slower-growing virus, stochastic simulations introduce an element of unpredictability. The inherent randomness in birth and death processes during the initial infection may lead to virus extinction, even in a population undergoing exponential growth [23]. Yan et al. [20] reported that the invasion of viral infection is dependent on the initial viral dose and growth rate of each virus. Here, we are interested in knowing how the coinfection dynamics change with a change in the growth rates of each virus.

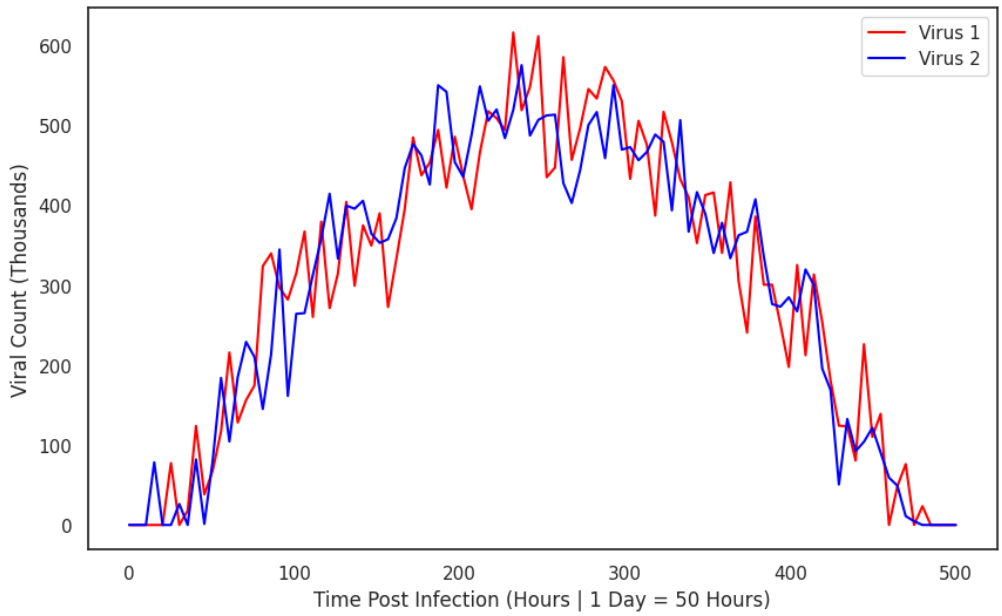

Figure 2: (Simulation 01 out of 100) Stochastic Trajectories for Viruses with the same Growth Rates. (All initial conditions and parameters are kept equal)

To examine the dynamics of coinfection with identical viruses, we maintain uniform initial conditions and transition rates for both viruses. The resulting stochastic trajectories of viral load over time are depicted in Figure 2. Notably, among the simulations, both viruses exhibit peaks above the detection threshold over time. Detailed analysis reveals that virus 1 and virus 2 undergo extinction 5 and 6 times (Fig. 3.), respectively, out of 100 repeated simulations. This insight emphasizes that, despite identical conditions, stochasticity introduces variability in coinfection outcomes.

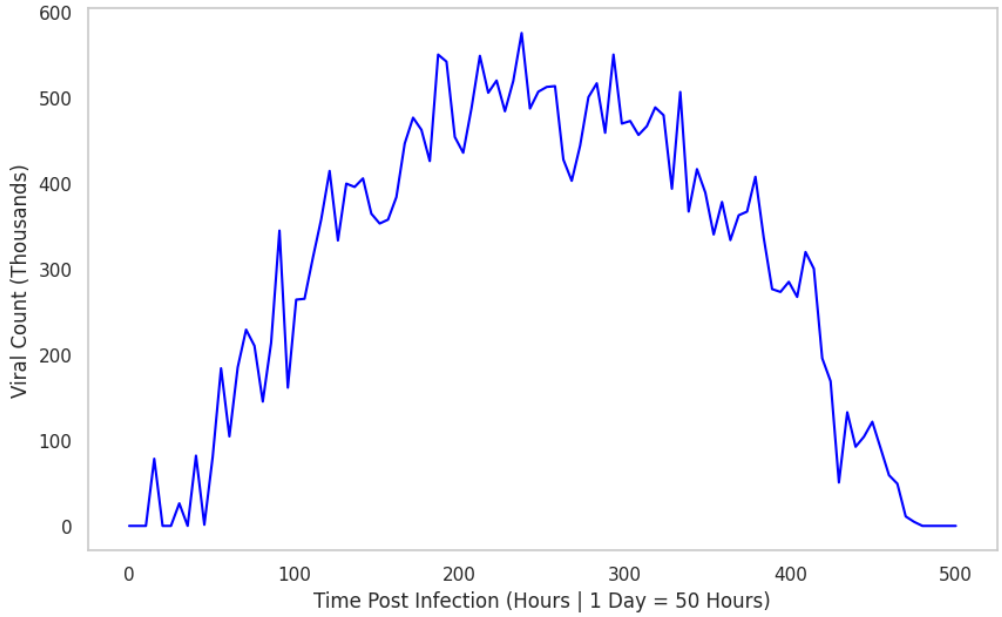

Figure 3: (Simulation 77 out of 100) Stochastic Trajectories for Viruses with the same Growth Rates. (All initial conditions and parameters are kept equal)

In contrast to the deterministic ODE model's prediction of identical time courses for both viruses under equal parameters, the stochastic model demonstrates a nuanced reality. Despite identical growth rates, certain realizations of the stochastic model lead to the out-competition of one virus over the other. In particular, Virus 2 achieves a higher peak, while Virus 1 surpasses it 7 times. So, while a particular realization of the model will have a clear dominant virus, on average, the viruses are equivalent, in agreement with the deterministic ODE model. To characterize the viral time course, we calculate the peak viral load, time of peak for each virus, as well as the duration of coinfection Fig. 4. The median time of peak for Virus 1 is found to be 1.14 ± 0.35 days, and for Virus 2, it is 1.37 ± 0.45 days. From the distributions Fig. 4, we see that even if the viruses behave differently for a particular model realization, on average, they tend to behave identically. Finally, the distribution of coinfection duration is given in (Fig. 3), where the median coinfection duration is found to be 5.760 ± 0.04 days. Despite fluctuations in the time course of each virus, the coinfection duration does not vary much.

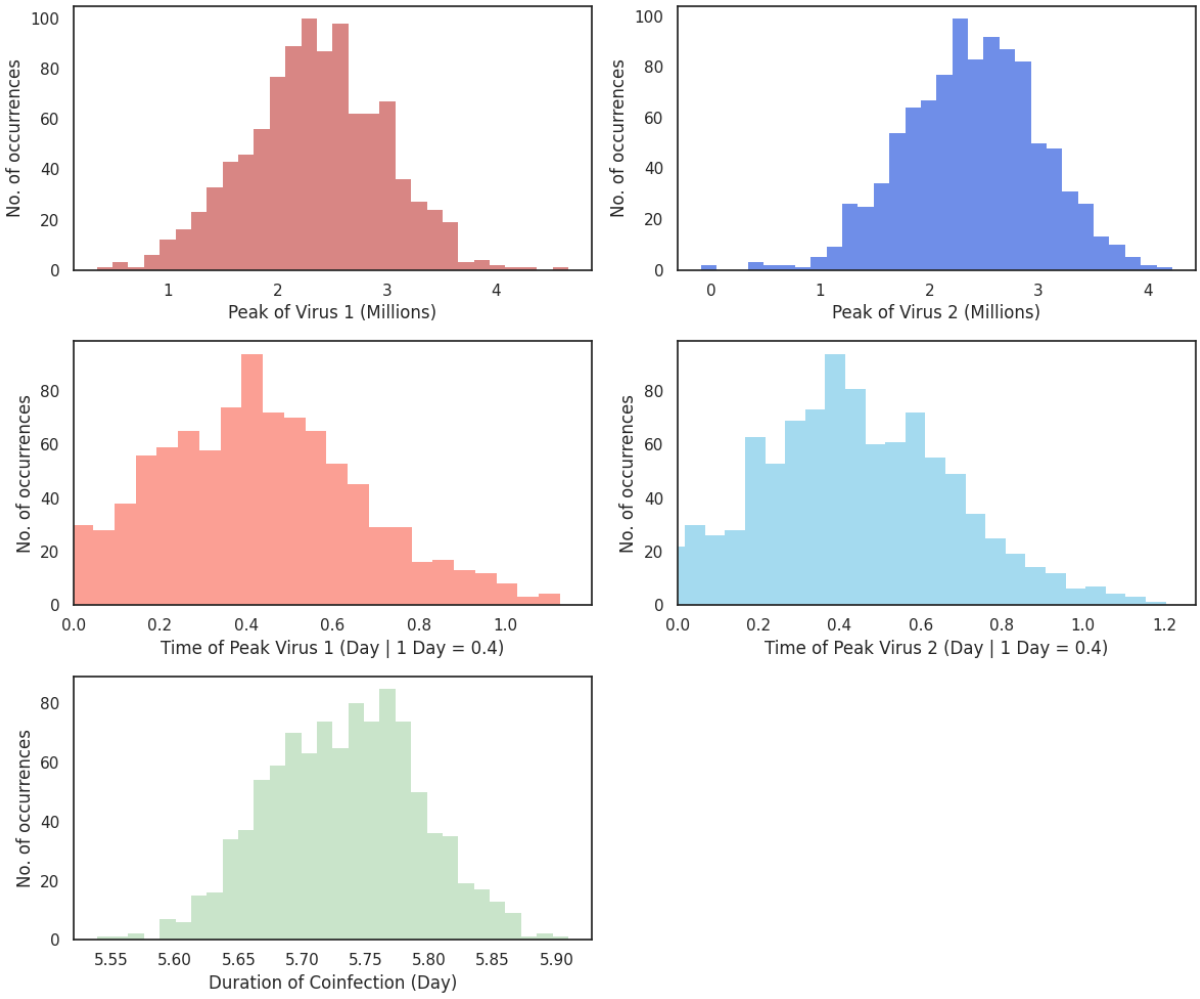

Figure 4: Stochastic Dynamics of Identical Viruses. Distribution of Time of Peak (Top Row), Peak Viral Load (Middle Row) for Virus 1 (Left Column) and Virus 2 (Right Column) and Duration of Coinfection (Bottom Row)

5.2.4 Stochastic Dynamics of Different Viruses

We explored the stochastic dynamics of coinfections involving identical viruses. Now, we extend our investigation to scenarios where the growth rates of the viruses differ. The objective is to understand how variations in growth rates influence stochastic infections, acknowledging that growth rates play a crucial role in determining the stronger competitor among the viruses.

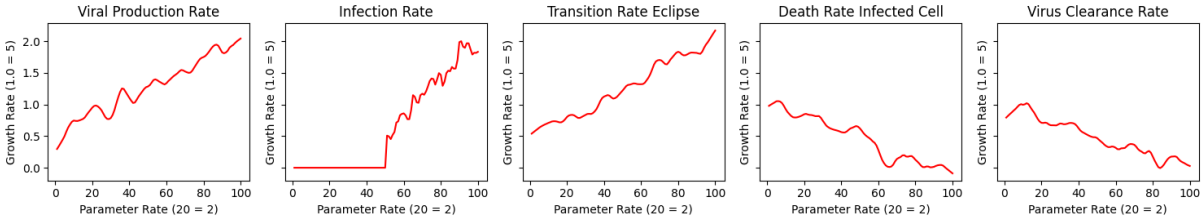

Figure 5: Variation of Growth Rate with respect to Model Parameters

Given that the growth rate is not a direct parameter in the model, we refer to the expression derived by Smith et al. [24] to quantify how the growth rate depends on different model parameters Fig. 5. Notably, the growth rate exhibits an approximately linear dependence with some discrepancies on the virus production rate, p. To systematically vary the growth rate, we define the relative viral production rate, $r = \frac{p_1}{p_2}$, and proceed to alter p for one virus while keeping the other constant.

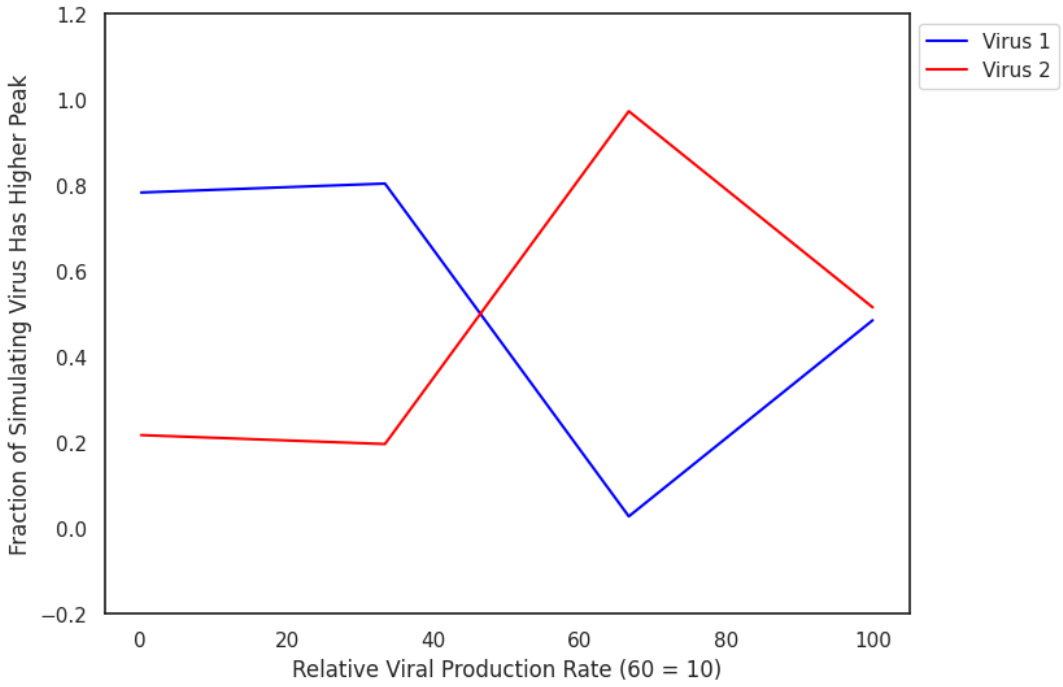

Figure 6: Number of Times One Virus has a Higher Peak Viral Titer than the Other Virus. Growth Rate is varied by varying the Relative Viral Production Rate, $r = \frac{p_1}{p_2}$

We initiate the investigation by introducing variation in the growth rate of Virus 1 while keeping the growth rate of Virus 2 constant for a range of $r = 1 \times 10^{-1} \times 10^{2}$. We record the number of

times, out of 04 simulated infections, a particular virus achieves a higher peak viral titer than the other. The results, depicted in (Fig. 6, reveal a significant impact on the probability of having a higher peak viral load as the production rate increases. Even with a less than 2-fold change in viral production, the probability of having the higher peak viral titer reaches 90%. This emphasizes the sensitivity of infection dynamics to early stochastic events, altering the infection time course.

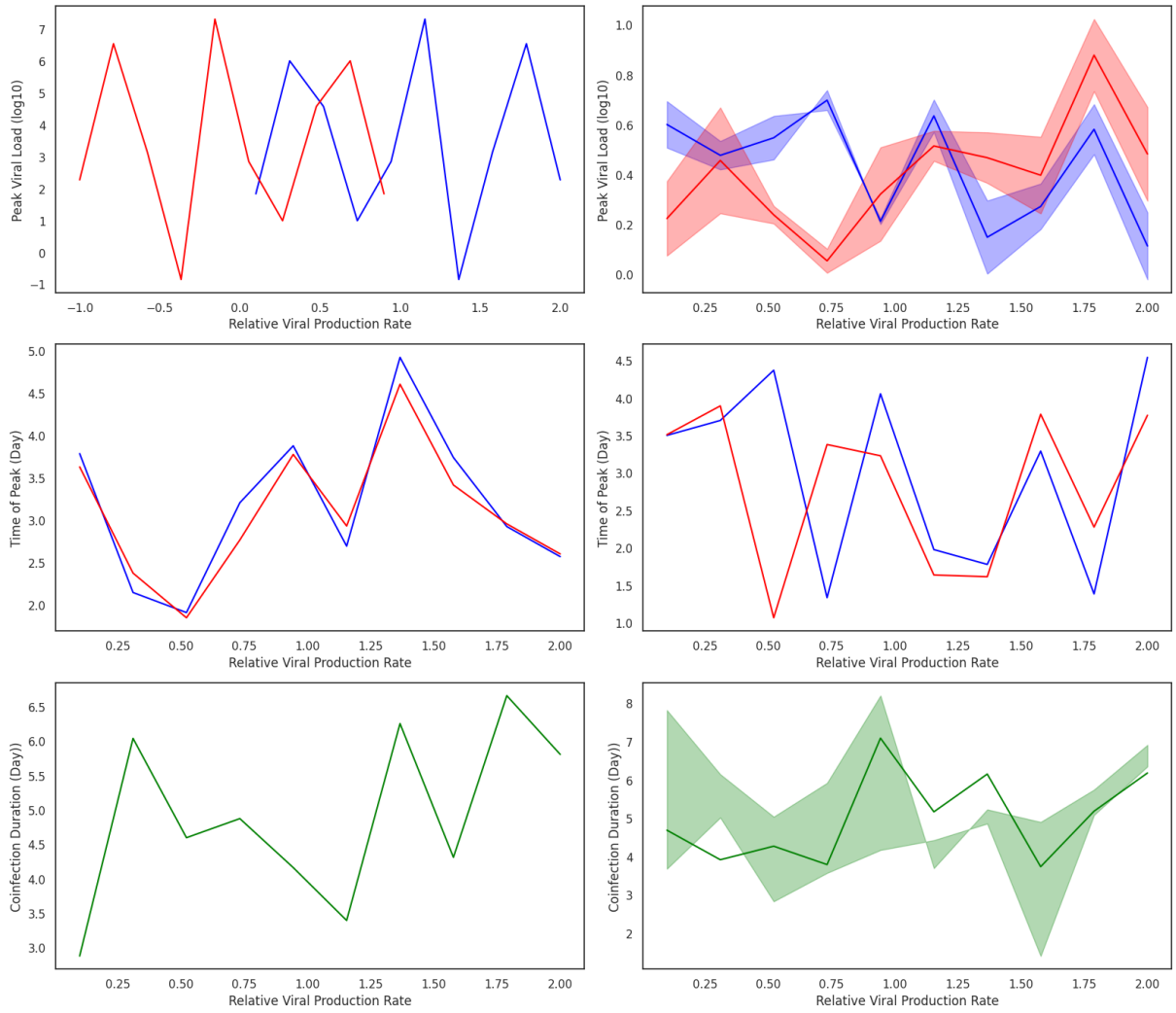

Figure 7: Comparison of the Deterministic ODE and the CTMC model infection dynamics. Variation in Peak Viral Load (Top Row), Time of Viral Peak (Center Row), and Duration of Coinfection (Bottom Row) as a function of Relative Viral Production in the Deterministic ODE model (Left Column) and in the stochastic model (Right Column). Also for every plot, 2.0 = 100 (X-Axis)

(Fig. 7 provides a comparative analysis of coinfection dynamics predicted by deterministic ODE and CTMC models. In the deterministic ODE model, a sharp transition occurs, with the faster-growing virus consistently dominating. However, the CTMC model allows for a more intricate transition, enabling the slower-growing virus to dominate infection dynamics. Stochastic variability in peak viral loads for both viruses overlaps over a broad range of relative viral production rates, indicating

potential similarity in peak viral loads despite growth rate differences. Examining the time of viral peak reveals differences between the ODE and CTMC models. While the deterministic ODE model shows similar peak times for both viruses when the relative viral production rate is greater than 100, the CTMC model exhibits a variability. Stochasticity in the CTMC model can moderate the effect of increased production rate, allowing both viruses to exhibit similar peak times. Finally, we compare the predicted duration of coinfection for both models. Coinfections last for about a week in either model, with the longest durations observed when the viruses have similar growth rates. This aligns with the expectation that the faster-growing virus out-competes the slower-growing virus, leading to shorter infections for the latter.

An aspect not captured by deterministic ODE models is the extinction of the infection. (Fig. 8 illustrates the probability of virus extinction, defined as the fraction of times when one virus does not grow above the virus detection limit (100 virus particles). The probability of both viruses growing to detectable levels is highest when relative viral production rates are similar. However, as the relative production rates differ (about 10–100 fold), there is a high probability that one virus becomes extinct. Notably, the probability of extinction approaches close to 100% more quickly for lower relative production rates than for higher relative rates. This comprehensive analysis highlights the intricate interplay between growth rates, stochastic events, and infection outcomes, providing valuable insights into the dynamics of coinfections involving viruses with varying competitive advantages.

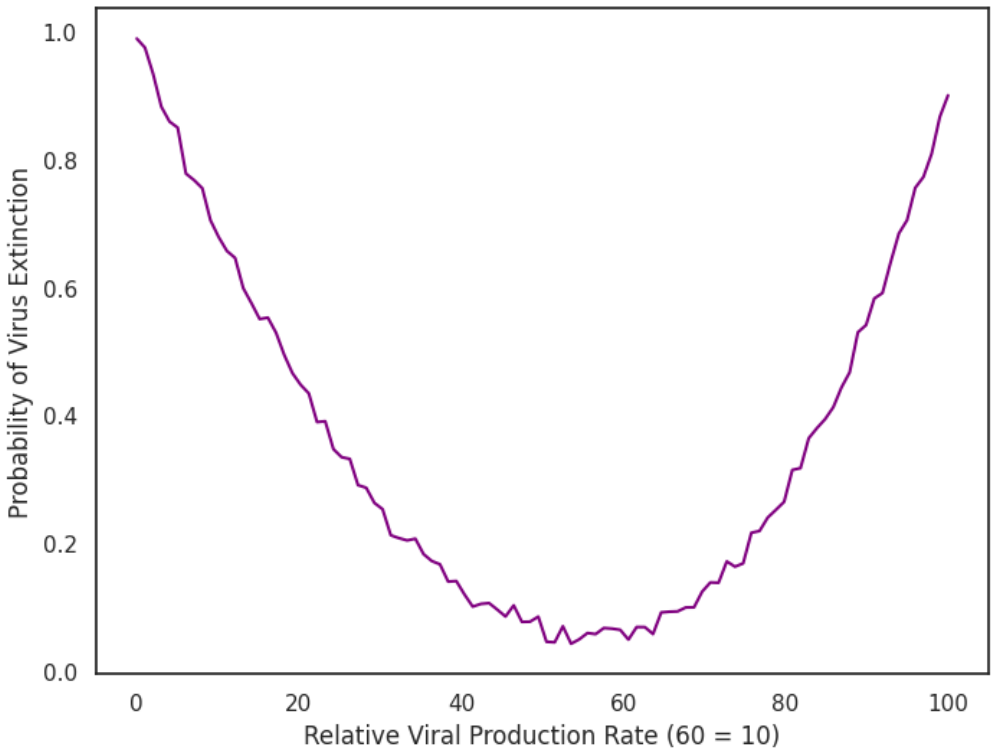

Figure 8: Probability of Virus Extinction with respect to varying Relative Production Rate. Extinction Probability is simulated for the case when the coinfection is initiated with a single copy of each virus.

6 Discussion

The conventional approach to modeling coinfections has primarily been deterministic, as seen in various studies [11, 15, 25]. However, deterministic ordinary differential equation (ODE) models, commonly used in these deterministic studies, fall short in capturing the intricate dynamics of very early infection stages, where stochastic effects may play a pivotal role. Our exploration into stochastic modeling has revealed crucial insights, demonstrating how stochastic effects can significantly alter the time course of infection dynamics, providing nuances beyond the capabilities of deterministic ODE models [13]. The deterministic ODE coinfection model [13] faced challenges in distinguishing between two identical or similar viruses, predicting identical time courses. The deterministic nature of the ODE model failed to consider the stochastic variability inherent in real-world infections. In contrast, our stochastic model, through simulations, highlights the significant impact of stochasticity, demonstrating that even two identical viruses can exhibit distinct time courses. Approximately 11% of infections initiated with two viruses result in infections with only one detectable virus, underscoring the unpredictability introduced by stochastic events.

In the context of different growth rates, the deterministic ODE model adheres to a straightforward rule: the virus with the higher growth rate dominates, yielding a higher peak viral titer. However, the continuous-time Markov chain (CTMC) model introduces complexity by allowing a slower-growing virus to gain a competitive advantage due to early stochastic effects. This competitive edge persists throughout the infection, challenging the deterministic dominance rule proposed by the deterministic ODE model. The deterministic ODE coinfection model's simplistic rule — favoring the virus with a higher growth rate — oversimplifies the complex dynamics observed in real-world coinfections. For instance, the application of the deterministic ODE model to respiratory viruses suggested that parainfluenza virus (PIV) replication should be substantially reduced during coinfection [13]. Nevertheless, the actual detection rate of PIV in coinfections ranges from 30% to 80% [26, 27–28], indicating the role of stochasticity. The stochastic model, accounting for variability, provides a more realistic understanding of coinfection dynamics

Stochasticity also poses challenges to strategies employing viral interference as a potential mechanism for treating or preventing infections. Approaches like using defective interfering particles (DIPs) may not be completely reliable, as our results suggest a non-zero probability that the slower-growing virus rises to a higher peak than the faster-growing virus, even with a significant difference in growth rates. While our stochastic coinfection model provides valuable insights, it is not without limitations. It does not encompass all biological processes during infection, and more complex deterministic ODE models with features like cell regeneration and superinfection have been proposed. Future work could involve developing stochastic versions of these models to explore how stochasticity affects behaviors such as chronic coinfections. Moreover, incorporating an explicit immune response and realistic delays for intracellular replication could further refine the model's accuracy.

One noteworthy limitation of our study is the reliance on synthetic data. Although synthetic data is valuable for initial model testing and development, it may not fully represent the complexity and variability observed in real-world scenarios. Future studies should aim to validate the model with empirical data to enhance its applicability and reliability in understanding actual coinfection dynamics.

7 Conclusion

In the domain of infection modeling, ordinary differential equation (ODE) models offer a comprehensive perspective on possible dynamical behaviors. However, our investigation highlights the crucial role of stochasticity in shaping the distinct outcomes of individual infections. This becomes especially relevant when examining interactions between viruses during coinfection, where early stochastic events can significantly influence disease outcomes. Our stochastic models reveal that stochastic effects can drive one or both viruses to extinction before the infection has a chance to establish itself. This introduces a level of unpredictability that is not adequately captured by deterministic ODE models. Contrary to deterministic predictions, our models demonstrate instances where a less fit virus can out-compete a more fit virus during coinfection. This emphasizes the importance of considering stochastic elements, as they can lead to unexpected infection dynamics.

The intricate dynamics observed in coinfections highlight the need for a more detailed approach that accounts for the inherent variability in real-world scenarios. While deterministic models provide valuable insights into average behaviors, stochastic models offer a more realistic depiction of infection dynamics, particularly during the initial phases where stochasticity plays a pivotal role. In conclusion, our study emphasizes the significance of stochasticity in infection dynamics and its potential impact on coinfections. The unpredictability introduced by stochastic events challenges the assumptions made by deterministic models, urging the inclusion of stochastic components for a comprehensive understanding of viral coinfection dynamics.

8 References

1. Goto, H., Ihira, H., Morishita, K., Tsuchiya, M., Ohta, K., Yumine, N., Tsurudome, M., & Nishio, M. (2016). Enhanced growth of influenza A virus by coinfection with human parainfluenza virus type 2. Medical microbiology and immunology, 205(3), 209–218. https://doi.org/10.1007/s00430-015-0441-y

2. Anderson, T. P., Werno, A. M., Barratt, K., Mahagamasekera, P., Murdoch, D. R., & Jennings, L. C. (2013). Comparison of four multiplex PCR assays for the detection of viral pathogens in respiratory specimens. Journal of virological methods, 191(2), 118–121. https://doi.org/10.1016/j.jviromet.2013.04.005

3. Kenmoe, S., Tchendjou, P., Vernet, M. A., Moyo-Tetang, S., Mossus, T., Njankouo-Ripa, M., Kenne, A., Penlap Beng, V., Vabret, A., & Njouom, R. (2016). Viral etiology of severe acute respiratory infections in hospitalized children in Cameroon, 2011-2013. Influenza and other respiratory viruses, 10(5), 386–393. https://doi.org/10.1111/irv.12391

4. Achten, N. B., Wu, P., Bont, L., Blanken, M. O., Gebretsadik, T., Chappell, J. D., Wang, L., Yu, C., Larkin, E. K., Carroll, K. N., Anderson, L. J., Moore, M. L., Sloan, C. D., & Hartert, T. V. (2017). Interference Between Respiratory Syncytial Virus and Human Rhinovirus Infection in Infancy. The Journal of infectious diseases, 215(7), 1102–1106. https://doi.org/10.1093/infdis/jix031

5. Goka, E. A., Vallely, P. J., Mutton, K. J., & Klapper, P. E. (2015). Single, dual and multiple respiratory virus infections and risk of hospitalization and mortality. Epidemiology and infection, 143(1), 37–47. https://doi.org/10.1017/S0950268814000302

6. Rotzén-Östlund, M., Eriksson, M., Tiveljung Lindell, A., Allander, T., Zweygberg Wirgart, B., & Grillner, L. (2014). Children with multiple viral respiratory infections are older than those with single viruses. Acta paediatrica (Oslo, Norway : 1992), 103(1), 100–104. https://doi.org/10.1111/apa.12440

7. Smith A. M. (2018). Host-pathogen kinetics during influenza infection and coinfection: insights from predictive modeling. Immunological reviews, 285(1), 97–112. https://doi.org/10.1111/imr.12692

8. Kumar, N., Sharma, S., Barua, S., Tripathi, B. N., & Rouse, B. T. (2018). Virological and Immunological Outcomes of Coinfections. Clinical microbiology reviews, 31(4), e00111-17. https://doi.org/10.1128/CMR.00111-17

9. Baccam, P., Beauchemin, C., Macken, C. A., Hayden, F. G., & Perelson, A. S. (2006). Kinetics of influenza A virus infection in humans. Journal of virology, 80(15), 7590–7599. https://doi.org/10.1128/JVI.01623-05

10. González-Parra, G., & Dobrovolny, H. M. (2015). Assessing Uncertainty in A2 Respiratory Syncytial Virus Viral Dynamics. Computational and mathematical methods in medicine, 2015, 567589. https://doi.org/10.1155/2015/567589

11. Pinilla, L. T., Holder, B. P., Abed, Y., Boivin, G., & Beauchemin, C. A. (2012). The H275Y neuraminidase mutation of the pandemic A/H1N1 influenza virus lengthens the eclipse phase and reduces viral output of infected cells, potentially compromising fitness in ferrets. Journal of virology, 86(19), 10651–10660. https://doi.org/10.1128/JVI.07244-11

12. Simeonov, I., Gong, X., Kim, O., Poss, M., Chiaromonte, F., & Fricks, J. (2010). Exploratory Spatial Analysis of in vitro Respiratory Syncytial Virus Co-infections. Viruses, 2(12), 2782–2802. https://doi.org/10.3390/v2122782

13. Pinky, L., & Dobrovolny, H. M. (2016). Coinfections of the Respiratory Tract: Viral Competition for Resources. PloS one, 11(5), e0155589. https://doi.org/10.1371/journal.pone.0155589

14. Shinjoh, M., Omoe, K., Saito, N., Matsuo, N., & Nerome, K. (2000). In vitro growth profiles of respiratory syncytial virus in the presence of influenza virus. Acta virologica, 44(2), 91–97.

15. Pinky, L., & Dobrovolny, H. M. (2017). The impact of cell regeneration on the dynamics of viral coinfection. Chaos (Woodbury, N.Y.), 27(6), 063109. https://doi.org/10.1063/1.4985276

16. Pinky, L., González-Parra, G., & Dobrovolny, H. M. (2019). Superinfection and cell regeneration can lead to chronic viral coinfections. Journal of theoretical biology, 466, 24–38. https://doi.org/10.1016/j.jtbi.2019.01.011

17. Dobrovolny, H. M., & Beauchemin, C. A. A. (2017). Modelling the emergence of influenza drug resistance: The roles of surface proteins, the immune response and antiviral mechanisms. PloS one, 12(7), e0180582. https://doi.org/10.1371/journal.pone.0180582

18. Deecke, L., & Dobrovolny, H. M. (2018). Intermittent treatment of severe influenza. Journal of theoretical biology, 442, 129–138. https://doi.org/10.1016/j.jtbi.2018.01.012

19. Pearson, J. E., Krapivsky, P., & Perelson, A. S. (2011). Stochastic theory of early viral infection: continuous versus burst production of virions. PLoS computational biology, 7(2), e1001058. https://doi.org/10.1371/journal.pcbi.1001058

20. Yan, A. W., Cao, P., & McCaw, J. M. (2016). On the extinction probability in models of within-host infection: the role of latency and immunity. Journal of mathematical biology, 73(4), 787–813. https://doi.org/10.1007/s00285-015-0961-5

21. Hartfield, M., & Alizon, S. (2015). Within-Host stochastic emergence dynamics of Immune-Escape mutants. PLOS Computational Biology, 11(3), e1004149. https://doi.org/10.1371/journal.pcbi.1004149

22. Gillespie, D. T. (1977). Exact stochastic simulation of coupled chemical reactions. The Journal of Physical Chemistry, 81(25), 2340–2361. https://doi.org/10.1021/j100540a008

23. Allen, L. J., & van den Driessche, P. (2013). Relations between deterministic and stochastic thresholds for disease extinction in continuous- and discrete-time infectious disease models. Mathematical biosciences, 243(1), 99–108. https://doi.org/10.1016/j.mbs.2013.02.006

24. Smith, A. M., Adler, F. R., & Perelson, A. S. (2010). An accurate two-phase approximate solution to an acute viral infection model. Journal of mathematical biology, 60(5), 711–726. https://doi.org/10.1007/s00285-009-0281-8

25. Petrie, S. M., Butler, J., Barr, I. G., McVernon, J., Hurt, A. C., & McCaw, J. M. (2015). Quantifying relative within-host replication fitness in influenza virus competition experiments. Journal of theoretical biology, 382, 259–271. https://doi.org/10.1016/j.jtbi.2015.07.003

26. Zhang, G., Hu, Y., Wang, H., Zhang, L., Bao, Y., & Zhou, X. (2012). High incidence of multiple viral infections identified in upper respiratory tract infected children under three years of age in Shanghai, China. PloS one, 7(9), e44568. https://doi.org/10.1371/journal.pone.0044568

27. Cai, X. Y., Wang, Q., Lin, G. Y., Cai, Z. W., Lin, C. X., Chen, P. Z., Zhou, X. H., Xie, J. C., & Lu, X. D. (2014). Respiratory virus infections among children in South China. Journal of medical virology, 86(7), 1249–1255. https://doi.org/10.1002/jmv.23931

28. Brand, H. K., de Groot, R., Galama, J. M., Brouwer, M. L., Teuwen, K., Hermans, P. W., Melchers, W. J., & Warris, A. (2012). Infection with multiple viruses is not associated with increased disease severity in children with bronchiolitis. Pediatric pulmonology, 47(4), 393–400. https://doi.org/10.1002/ppul.21552

9 Appendix

Additional Files: https://github.com/sawantatharva/BE3001_Final-Project_A-Modeling-Study (A GitHub repository consisting of all the code used for data analysis, written in Python using NumPy, Pandas, Matplotlib, and Seaborn.