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AMATH/BIOL 382: Computational Modelling of Cellular Systems

Prof. B. Ingalls

Final Project Report

Mathematical Modelling of SARS-CoV-2 In-Host Viral Dynamics and Its Potential Antiviral Treatments

Richard (Zhifei) Dong 20775623

Yolanda (Anqianyi) Tu 20775380

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We had learnt a lot from this project and had a lot of fun doing it. System biology is truly powerful and exciting, and we are looking forward to experiencing more of it should we have the opportunity in the future.

Abstract

The COVID-19 pandemic caused by the SARS-CoV-2 virus presents an unprecedented challenge for the global health care system. As an effort to end this pandemic through the discovery of SARS-CoV-2 antiviral drug targets, the in-host dynamic of SARS-CoV-2 is simulated and analyzed using system biology and differential equation models. Once the validity of the models is confirmed, several potential target sites for the antiviral drugs are investigated and simulated by incorporating their interactions into the models. It is found that a hypothetical antiviral drug can effectively combat SARS-CoV-2 by activating the interferon production in the innate immune response, suggesting a potential path for COVID-19 drug development.

Keywords: mathematical modelling; SARS-CoV-2; system biology; viral dynamics; antiviral drug

1. Introduction

Since the end of 2019, the COVID-19 pandemic caused by the SARS-CoV-2 virus has infected over 480 million people and killed over 6 million people around the globe as of April 5th, 2022 [1]. The SARS-CoV-2 virus is a novel mRNA coronavirus that can infect the respiratory tracts of individuals and cause symptoms such as cough, fever, breathing difficulties, and shortness of breath. In severe cases, the infection can lead to pneumonia and acute respiratory syndromes, which may even progress to death if no proper supportive care is provided [2, 3]. Given the huge impacts that the ongoing pandemic has brought to the global health care and financial systems, the world desperately needs a solution to lift those burdens by ending the pandemic as soon as possible.

To develop such a solution, one must understand the molecular mechanisms of the in-host viral dynamics of SARS-CoV-2 so that potential treatment targets can be identified. The SARS-CoV-2 virus, like many other viruses, replicate and reproduce through the viral replication cycle (**Figure 1**) once it enters the host [4]. The virus first enters the host cells through a process known as attachment and entry, where the receptor-binding domain of the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 receptor of human epithelial cell. This triggers the entry of the virus into the cells, where it can then translate its replicase gene from its RNA genome using the host cell's machinery. This gene product is then used to further produce more viral RNA materials and protein products through the replication and transcription process. Once the transcription and translation processes are finished, all the important viral structural proteins are sent to the endoplasmic reticulum for assembly, and viral RNA genomes are inserted into the assembled structural proteins to produce the complete virions. Those virions are then transported to the cell surface and released via exocytosis, where they are now able to infect more cells through the same cycle again [5].

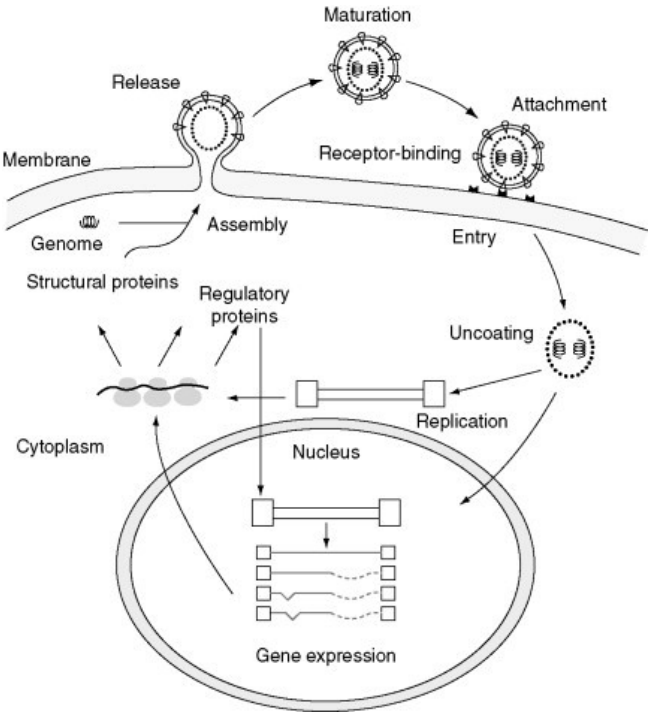

Figure 1: A schematic diagram of viral replication cycle. Reproduced from ref. [4] with permission from Elsevier.

With the viral replication processes in mind, one can start to develop a mathematical model to describe the interaction between a variety of molecular entities. Thanks to the advancement in computer simulation software, this mathematical description of complex biological systems, known as system biology, has gained much attention in the field of drug design. Studies have shown that system biology can effectively facilitate the development of novel drugs by simulating the complex interactions between the drug and different molecular species in order to find the most effective and safest target for ligand binding [6]. As a result, in this report, we aim to utilize the power of system biology to implement some established models in order to model the in-host viral dynamic of SARS-CoV-2. We then aim to extend the model to include several hypothesized antiviral drugs in order to determine the site with the best antiviral effect. We hope that the finding of this report can provide researchers with insights into the potential drug targets for the treatment of COVID-19 so that the world can end this pandemic as soon as possible.

2. Methods and Assumptions

The simple target cell model and the target cell model with innate immune responses for general viruses are reproduced from the work by Zitzmann and Kaderal [7]. These general models are then coupled with the modelling parameters of SARS-CoV-2 from the work by Li et al. and the parameters of the Influenza A virus in the work by Baccam et al. to simulate the viral dynamic of SARS-CoV-2 [8, 9]. The modelling parameters for Influenza A virus are used since some parameters are not provided in the work by Li et al. as the SARS-CoV-2 virus is fairly novel and some key parameters in the more complex target cell model with innate immune responses are missing. Since both viruses are respiratory viruses with similar life cycles, it is assumed that their immune responses will be similar and share similar modelling parameters. Those parameters are then fitted into the models by Zitzmann and Kaderal, and their analysis of the models through computer simulations is reproduced in R using the deSolve package, but with actual parameters for SARS-CoV-2 instead of a range of general parameters as in the paper. The result of the simulations is then analyzed in a biological context and compared with actual data obtained from COVID-19 patients to verify the validity of the models.

The models are then extended to include a variety of hypothesized antiviral drugs based on the results from local relative sensitivity analyses of the steady state concentrations. Simulations are then run with a variety of drug parameters and the effects of different drugs are compared.

There are three major assumptions of the models. Firstly, it is assumed that all species in the models, including cells, viruses, and signalling molecules, are evenly distributed in space. This allows the use of mass actions to describe those processes whenever appropriate. Secondly, it is assumed that the infection is initiated with the introduction of the virus into the respiratory tract at the initial viral load of V_0. Lastly, it is assumed that the dynamic of the system does not change throughout the model. This means that the cell does not modify its own behaviour (such as the rate of production and degradation) throughout the infection process, and every change is stimulated by an external source.

Some representitive R code for the simulations of the reimplemented and extended models can be found in **Appendix A**.

3. Mathematical Modelling for SARS-CoV-2 In-Host Dynamics

3.1 Simple Target Cell Model

Model Construction

Based on the assumptions outlined in *Section 2*, Zitzmann and Kaderal first proposed a simple target cell model that contains three species: the uninfected and healthy target cells (T), the infected virus-producing cells (I), and the virus (V). In this model, viruses can infect the uninfected target cells to produce infected virus-producing cells in order to make more viruses. The schematic network of this model is illustrated in **Figure 2**.

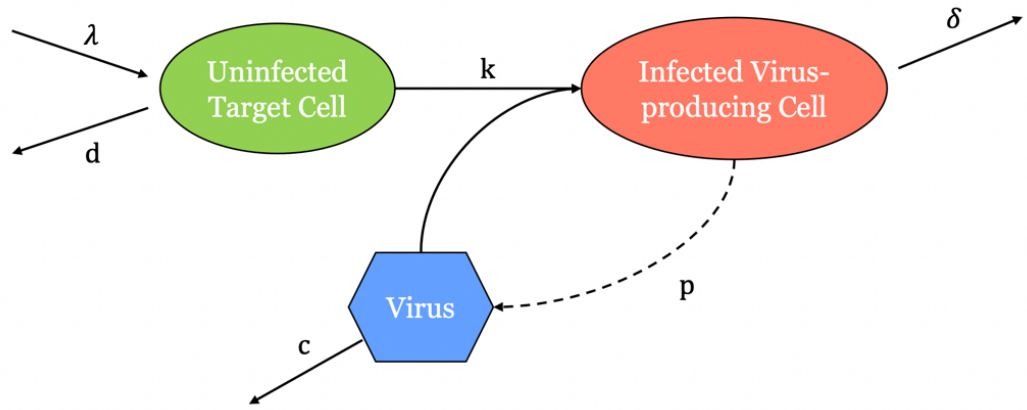

Figure 2: The schematic network of the simple target cell model.

In this model, the patient continuously produces healthy cells at a constant rate λ, and the healthy cells naturally die through first-order mass action with a rate constant of d. When a target healthy cell is infected by the virus at rate of k, it becomes an infected and virus-producing cell and dies naturally through first-order mass action with a rate constant of δ. The virus is produced by the infected cells through first-order mass action with a rate constant of p and naturally degrades at a first-order rate of c [7]. This system is formulated by the set of ordinary differential equations in **equation set (1)**:

$$\frac{dT}{dt} = \lambda - dT - kVT$$

$$\frac{dI}{dt} = kVT - \delta I \quad (1)$$

$$\frac{dV}{dt} = pI - cV$$

Model Simulation and Analysis

From the simulations in R, it is evident that initially, the concentration of healthy cells exhibits a sharp drop while the concentration of infected cells rises rapidly (**Figure 3a**) from the rapid infection of the virus onto the healthy cells. By zooming in and examining the dynamics of the virus, it is noticed that after an initial drop in the viral load, the viral load starts to increase rapidly as the concentration of infected cells starts to rise and start to produce new viruses (**Figure 3b**). The peak of viral load is located at approximately day 15, then it falls back with a long period of low concentration but it is never eliminated completely without the presence of any additional immune responses. This incomplete elimination allows the viral concentration to bounce back once the healthy cell concentrations start to increase, resulting in the re-activation of the virus (**Figure 4a)** and re-decline of the healthy cells (**Figure 4b**) down the road. This process is known as recurrence and has been observed in many COVID-19 patients [10]. Combining this result with finding from the study by He et al., where the researchers suggested that COVID-19 recurrence is more frequent in immune-suppressive patients, it is possible that the known cases of the reactivation of the viruses in recovered COVID-19 patients are a result of the weak immunities [11].

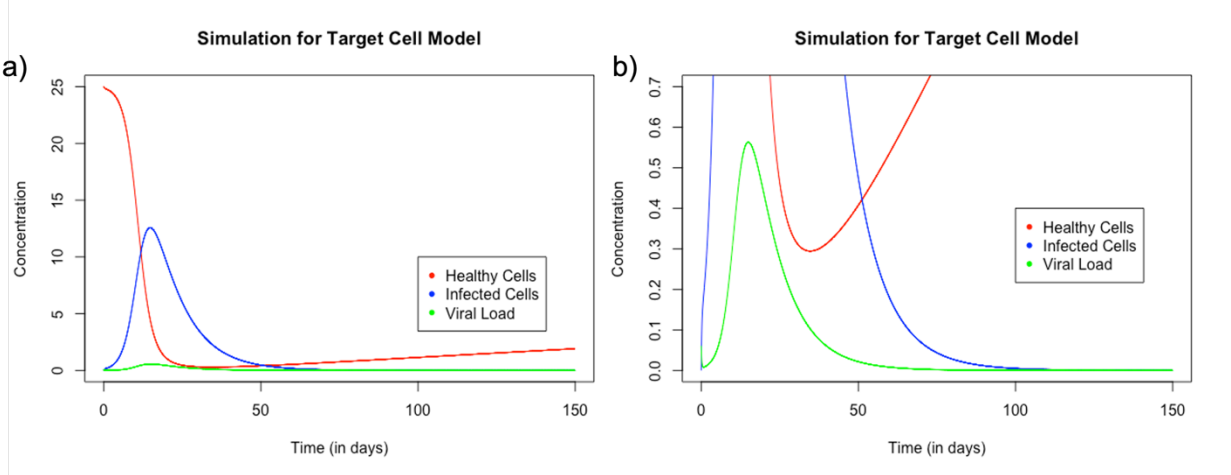

Figure 3: Simulation results for the simple target cell model in R for a period of 150 days since the start of the infection. The range of the concentration levels of the plots are from 0 to 25 in a) and 0 to 0.7 in b) to show the dynamics of cells and viruses at two different scales. Model parameters are d = 0.001 day^{-1}, k = 0.55 day^{-1} concentration unit^{-1}, δ = 0.11 day^{-1}, p = 0.24 day^{-1}, c = 5.36 day^{-1}, and λ = 0.0169 day^{-1} concentration unit^{1}. The initial concentrations (in arbitrary units) for the healthy cells, infected cells, and virus are 25, 0, and 0.061, respectively. The model is reproduced using the model from ref. [7] and the parameters values from ref. [8].

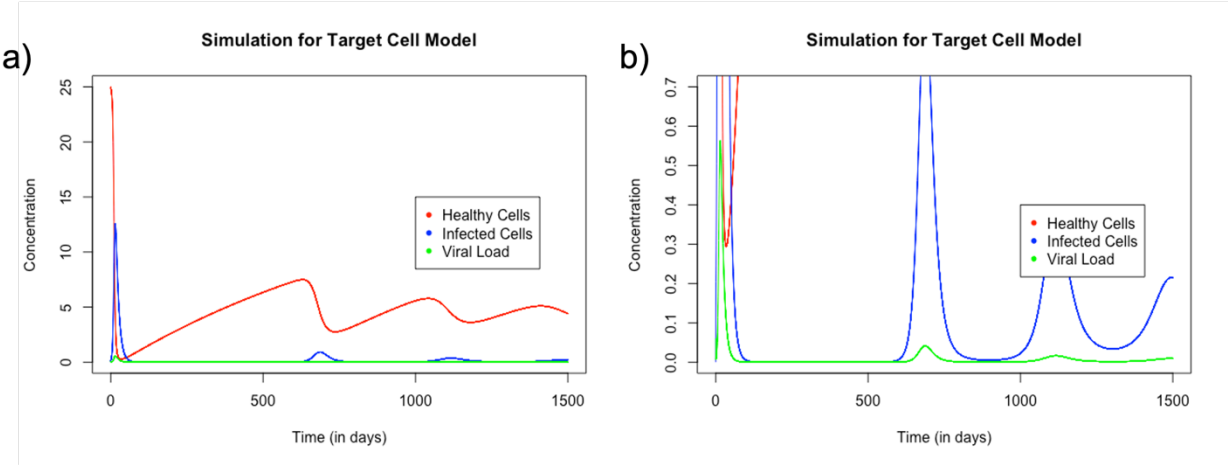

Figure 4: Simulation results for the simple target cell model in R for a period of 1500 days since the start of the infection. The range of the concentration levels of the plots are from 0 to 25 in a) and 0 to 0.7 in b) to show the dynamics of cells and viruses at two different scales. The modelling parameters are the same as in **Figure 3**.

Desimmie et al. conducted a review to determine the viral load as a function of time from data in actual COVID-19 patients (**Figure 5**) [12]. When compareing their findings with the modelling results, it is found that the overall pattern of viral load from the simulation is similar to the dynamic in actual COVID-19 patients, where a peak of viral load is found at around day 10 then is followed by a long period of low concentration based on the PCR test. It is noticed that the time of peaks is slightly different in the two cases (at day 10 and day 15 in actual data and simulation, respectively). This difference is hypothesized to be caused by the other biological processes and/or immune responses in the actual cellular environment other than the three species modelled above.

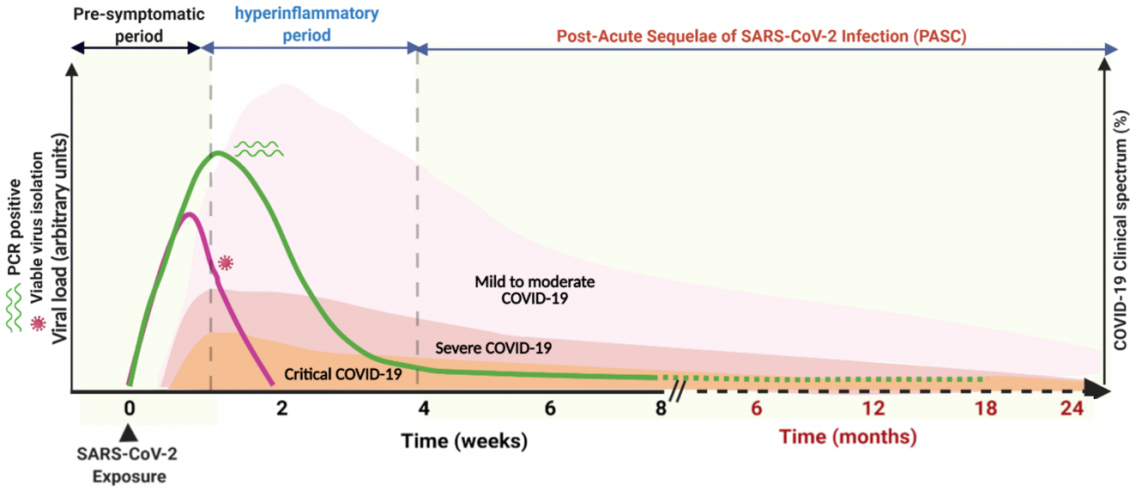

Figure 5: Viral load in actual cases of COVID-19 patients. Reproduced from ref. [12] with permission from MDPI.

3.2 Target Cell Model with Innate Immune Response

Innate Immune Response (IIR) and Interferon

In reality, there are far more biological species involved in the interaction between the virus and the host. Through evolution, human beings have evolved a complex immune system to protect themselves from a variety of pathogenies. When the threat of viruses is detected, the innate immune response (IIR) is firstly activated to provide the first line defense and prevent viral invasions or replications. Once a novel virus (such as the SARS-CoV-2 virus) is present within the body, specific viral components, such as viral RNA, DNA, or intermediate products, can activate the pattern recognition receptors

(PRRs). This activation stimulates the production of type I interferons, which acts on the cells to induce an antiviral state in order to inhibit the synthesis and translation of viral RNA and the exocytosis of virions [13-15].

Model Construction

Zitzmann and Kaderal then extended the simple target cell model from *Section 3.1* [7]. The extended target cell model with IIR consists of similar species: the healthy cells, the virus, and the infected cells. However, there are two distinct types of infected cells in this extended model. When the virus first infects the cell, it turns the cell into an infected yet not virus-producing cell (I_1). This infected cell is capable of producing more viral components through RNA synthesis and translation but not secreting any virions via exocytosis. At a certain rate, the I_1 species can become the infected and virus-producing cells (I_2), where they will be able to secret virions into the extracellular space. In addition, the model introduces another new species: interferon (N). The production of interferon is stimulated by the presence of I_2. Upon production, the interferon works by reducing the rate of I_1 becoming I_2 (hence inhibiting replication and translation), as well as by reducing the rate of production of virus from I_2 (hence inhibiting the viral secretion) [7]. This model is illustrated with a schematic network diagram shown in **Figure 6**.

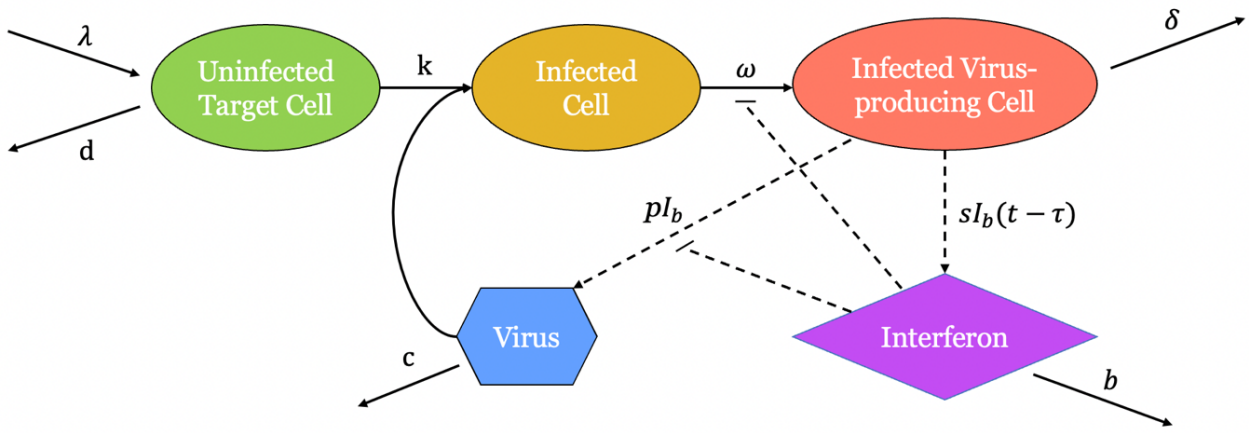

Figure 6: The schematic network diagram of the target cell model with IIR.

From this network, the interferon is produced at a rate constant of *s*, which is activated by the presence of I_2. There is a time delay (τ) between the stimulation from I_2 and the production of interferon, thus represented by $I_b(t-\tau)$. In addition, the interferon inhibits the viral RNA replication and translation processes in I_1 cells, characterized by the rate ω that I_1 turns into I_2, by dividing the rate with $1+\varepsilon_\omega F$, where ε_ω is the effectiveness of interferon inhibition on the viral replication. Similarly, interferon also acts to inhibit virus production in I_2 cells, by dividing the rate of production of virus, p, with $1+\varepsilon_p F$, where ε_p is the effectiveness of interferon inhibition on viral production. The rest of the parameters are identical to the parameters used in **equation set (1)**. This system is formulated by the set of ordinary differential equations in **equation set (2)**:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT - kVT \\
\frac{dI_1}{dt} &= kVT - \frac{\omega}{1+\varepsilon_\omega F} I_1 \\
\frac{dI_2}{dt} &= \frac{\omega}{1+\varepsilon_\omega F} I_1 - \delta I_2 \\
\frac{dV}{dt} &= \frac{p}{1+\varepsilon_p F} I_2 - cV \\
\frac{dF}{dt} &= sI_2(t-\tau) - bF
\end{aligned} \tag{2}$$

Model Simulation and Analysis

Based on the model simulation in R, the dynamic behaves similarly to the model in *Section 3.1*, but with several distinct differences. Firstly, the healthy cell concentration decreases at a much slower rate in this model (**Figure 7a**), suggesting that the interferon-induced antiviral state can successfully limit the healthy cell infection. This is because with the interferon, virus synthesis and secretion are significantly limited, as the peak of the viral load is not nearly as high as it is in the previous model (**Figure 7b**). However, a peak of viral load is still observed, due to the fact that it takes time for the interferon production to start.

Furthermore, the reactivation of the virus, represented by the oscillatory behaviour, is eliminated in this model (**Figure 8a** and **Figure 8b**), as the presence of interferons successfully limits the production of virions after the first peak and keeps its concentration always at a low level. It is also evident that the peak of the viral load is at around day 12 this time, instead of day 15 in the simpler model. This peak time resembles the dynamic by Desimmie et al. regarding the viral load in actual COVID-19 patients more, due to that the interferon limits the time of maximal growth for the virus.

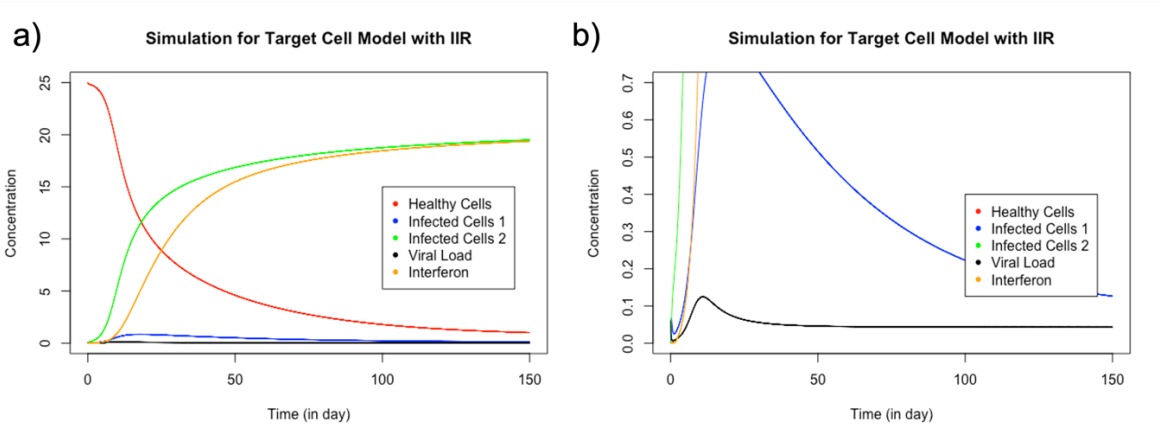

Figure 7: Simulation results for the target cell model with IIR in R for a period of 150 days since the start of the infection. The range of the concentration levels of the plots are from 0 to 25 in a) and 0 to 0.7 in b) to show the dynamics of cells and viruses at two different scales. The parameter values are the same as the ones used to generate **Figure 3**, with the following new parameter values: b = 0.1 day^{-1}, ω = 4 day^{-1}, ε_p = 1, ε_ω = 1, s = 0.1 day^{-1}, and τ = 1 day^{1}. The initial concentrations (in arbitrary units) for the healthy cells, infected cells 1, infected cells 2, virus, and interferon are 25, 0, 0, 0.061, and 0, respectively. The model is reproduced using the model from ref. [7] and the parameters values from ref. [8, 9].

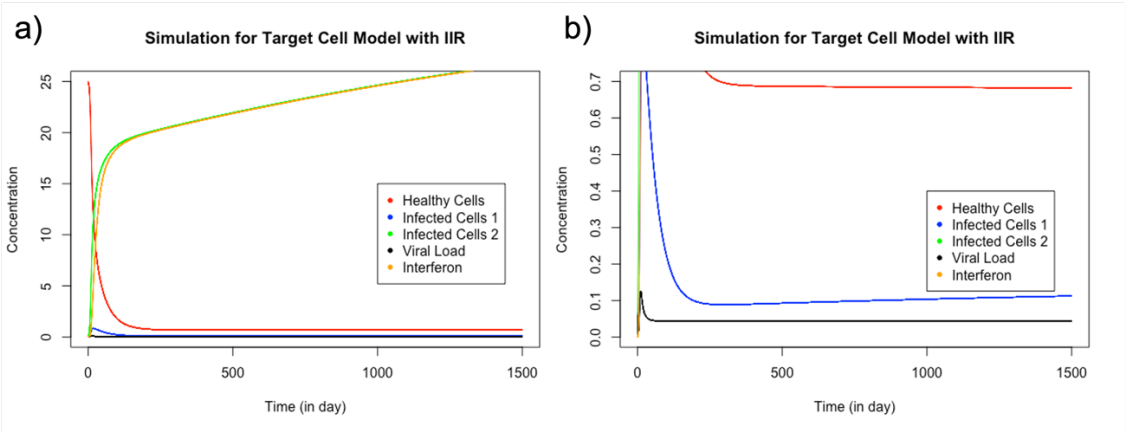

Figure 8: Simulation results for the simple target cell model in R for a period of 1500 days since the start of the infection. The range of the concentration levels of the plots are from 0 to 25 in a) and 0 to 0.7 in b) to show the dynamics of cells and viruses at two different scales. The modelling parameters are the same as in **Figure 7**.

4. Model Extension: Mechanisms for Effective Antiviral Drugs

4.1 Motivation

Since the beginning of the pandemic, SARS-CoV-2 has been vastly studied by researchers around the globe. Currently, there is already a variety of published literature on the modelling of SARS-CoV-2 molecular dynamics (such as metabolic models [16, 17] and viral replication dynamic models [8, 18]) and COVID-19 disease progression (such as clinical outcome models [19], infection risk models [20], and forecasting models [21, 22]).

Despite this large number of research, few have attempted to utilize the viral in-host dynamic models of SARS-CoV-2 to determine the best target site for the treatment of COVID-19. The lack of this information significantly hinders the ability to develop antiviral drugs for COVID-19 as a means to end the pandemic. Therefore, in this section, different antiviral drugs with different mechanisms of action are hypothesized and simulated through the use of the model with IIR to determine the best potential drug target to treat COVID-19.

4.2 Local Relative Sensitivity Analysis

The goal of the local relative sensitivity analysis is to determine the most sensitive parameters for the drug to act on in order to achieve the desired results. Two analyses are conducted for all the parameters in the model with IIR to determine the sites to be acted by the potential antiviral drug for COVID-19. One focuses on the sensitivity of parameters to healthy cell steady state concentration, and the other one focuses on the viral load steady state concentration. Here, a higher healthy cell steady state concentration or a lower viral load steady state concentration is expected with the application of a potential drug. Steady state concentrations are used because the IIR only acts to prevent the viral infection instead of regenerating healthy cells or completely eliminating the virus. Therefore, the more healthy cells and fewer viruses remain at the end of the IIR, the easier that the body can utilize other resources to recover from the infection. The values used for the computation of both local relative sensitivity analyses can be found in **Appendix B**.

Local Relative Sensitivity Analysis on Healthy Cell Steady State Concentration

The results of the local relative sensitivity analysis for all parameters are illustrated using a clustered column chart (**Figure 9**). The higher the column is, the higher effectiveness that the increase in the corresponding parameter would result in the increasing of the steady state concentration of healthy cells. It is evident that increasing the parameter values of c (the virus death rate), s (the interferon production rate), and ε_p (the inhibition of virus production) has relatively strong effects than other parameters. On the opposite side, decreasing the parameter values of k (the infectivity), p (the virus production rate), and b (the interferon decay rate) can also strongly increase the healthy cell steady state concentration.

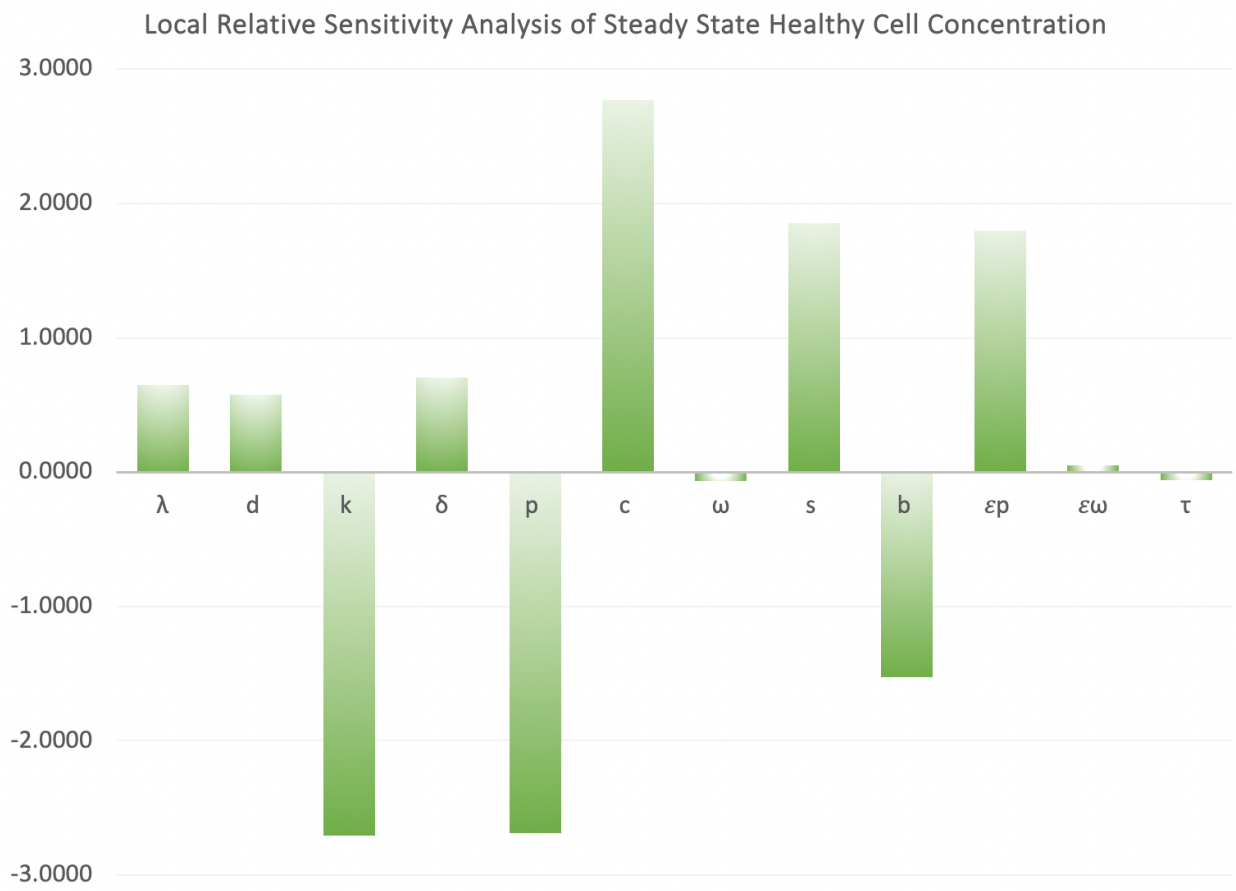

Figure 9: Results for the local relative sensitivity analysis of steady state healthy cell concentration from the target cell model with IIR with the initial parameters from the ones used in **Figure 7**.

Local Relative Sensitivity Analysis on Viral Load Steady State

In this case, a decrease in steady state viral load is necessary with the application of a potential drug. From the result of the analysis (**Figure 10**), lowering the parameter values of p (the virus production rate) and b (interferon decay rate) demonstrates a strong decrease in steady state viral load. On the other hand, increasing in c (the virus death rate), s (the interferon production rate), and ε_p (the inhibition of viral production) also decreases the steady state viral load.

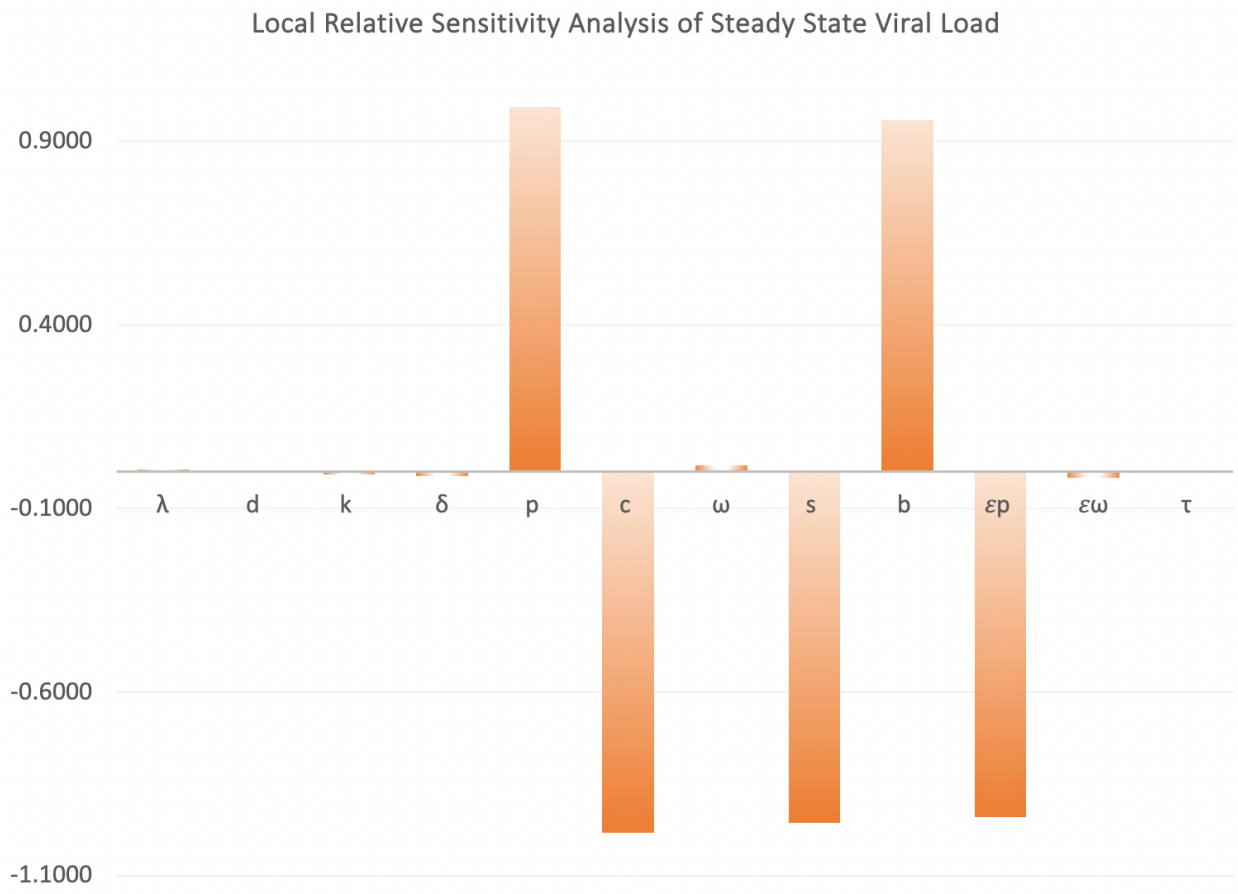

Figure 10: Results for the local relative sensitivity analysis of steady state viral load from the target cell model with IIR with the initial parameters from the ones used in **Figure 7**.

4.3 Proposed Drug Mechanisms

The results of the two sensitivity analyses are mostly consistent with each other, which suggests that the best drug can both increase healthy cell concentration and viral load simultaneously. In addition, not all those highly effective parameters are targetable by an external drug due to biological limitations. As an example, antiviral drugs usually do not destroy the viruses as viruses are considered to be obligate intracellular pathogens and therefore are hard to be targeted directly [23]. With everything being considered, three different parameters for three different species (healthy cells, interferons, and viruses) are selected from the model to be targeted by the hypothesized drugs:

1. Drug X inhibits the infection of the healthy cells by reducing k;
2. Drug Y stimulates the production of interferon by indirectly increasing s; and
3. Drug Z inhibits the production of the viral particles by decreasing p.

4.4 Investigation of the Effectiveness of Drugs

In the following models, it is assumed that the drug is administrated starting at day 0 at a constant rate m (a zeroth-order production of the drug), and the drug decays naturally within the body according to the first-order reaction with a rate constant n. The drug then acts to change the dynamic through the parameter K.

Antiviral Effects of The Three Drugs

Drug X works by inhibiting the infectivity of the virus onto the healthy cells. As a result, an inhibition of $1 + \frac{X}{K_X}$ is introduced to the rate constant k, where K_X is the dissociation constant of the binding of X. A larger K_X means the binding is less efficient. This dynamic is formulated in **equation set (3)**:

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT - \frac{kVT}{1+\frac{X}{K_X}} \\
\frac{dI_1}{dt} &= \frac{kVT}{1+\frac{X}{K_X}} - \frac{\omega}{1+\varepsilon_\omega F} I_1 \\
\frac{dI_2}{dt} &= \frac{\omega}{1+\varepsilon_\omega F} I_1 - \delta I_2 \\
\frac{dV}{dt} &= \frac{p}{1+\varepsilon_p F} I_2 - cV \\
\frac{dF}{dt} &= sI_2(t-\tau) - bF \\
\frac{dX}{dt} &= m_X - n_X X
\end{aligned} \tag{3}$$

Drug Y stimulates the production of interferon. Instead of changing s, the natural rate of production of interferon, a simpler way for the drug to work is through the activation of interferon production. This is done through an additional first-order production of interferon through the rate constant K_Y in the presence of Drug Y. A larger K_Y means that the drug is more effective. This dynamic is captured in **equation set (4)**.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT - kVT \\
\frac{dI_1}{dt} &= kVT - \frac{\omega}{1+\varepsilon_\omega F} I_1 \\
\frac{dI_2}{dt} &= \frac{\omega}{1+\varepsilon_\omega F} I_1 - \delta I_2 \\
\frac{dV}{dt} &= \frac{p}{1+\varepsilon_p F} I_2 - cV \\
\frac{dF}{dt} &= sI_2(t-\tau) - bF + K_Y Y \\
\frac{dY}{dt} &= m_Y - n_Y Y
\end{aligned} \tag{4}$$

Drug Z inhibits the production of virions by I_2. This is done through the inhibition onto the rate constant p with $1 + \frac{Z}{K_Z}$, where K_Z is the dissociation constant for the drug binding. The complete model is shown in **equation set (5)**.

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT - kVT \\
\frac{dI_1}{dt} &= kVT - \frac{\omega}{1+\varepsilon_\omega F} I_1 \\
\frac{dI_2}{dt} &= \frac{\omega}{1+\varepsilon_\omega F} I_1 - \delta I_2 \\
\frac{dV}{dt} &= \frac{\frac{p}{1+\varepsilon_p F} I_2}{1+\frac{Z}{K_Z}} - cV \\
\frac{dF}{dt} &= sI_2(t-\tau) - bF \\
\frac{dZ}{dt} &= m_Z - n_Z Z
\end{aligned} \tag{5}$$

Comparison of the Antiviral Effects

To test the robustness of the simulation results, a variety of *K* values (from 0.5 to 3.0) are selected to demonstrate the different outcomes based on how strong the drugs can interact. From the simulation results, it is evident that Drug X (**Figure 11a**) and Drug Z (**Figure 11c**) perform similarly in the delay of healthy cell decay and result in similar steady state concentrations of healthy cells. However, Drug Z performs better in lowering the steady state viral load (**Figure 11f**) as well as the peak of viral load for a range of *K* values than Drug X does (**Figure 11d**). Therefore, the effect of Drug Z is more significant than that of Drug X.

Drug Y outperformed both Drug X and Drug Z by a large margin, as it significantly slows down the decay of healthy cells and results in a much larger steady state concentration (**Figure 11b**) as well as significantly limits the virus production (**Figure 11e**). This is happening because the drug stimulates the production of interferon at an earlier time than its natural production time, therefore allowing the antiviral states to be induced earlier to protect more cells and prevent more viral replications.

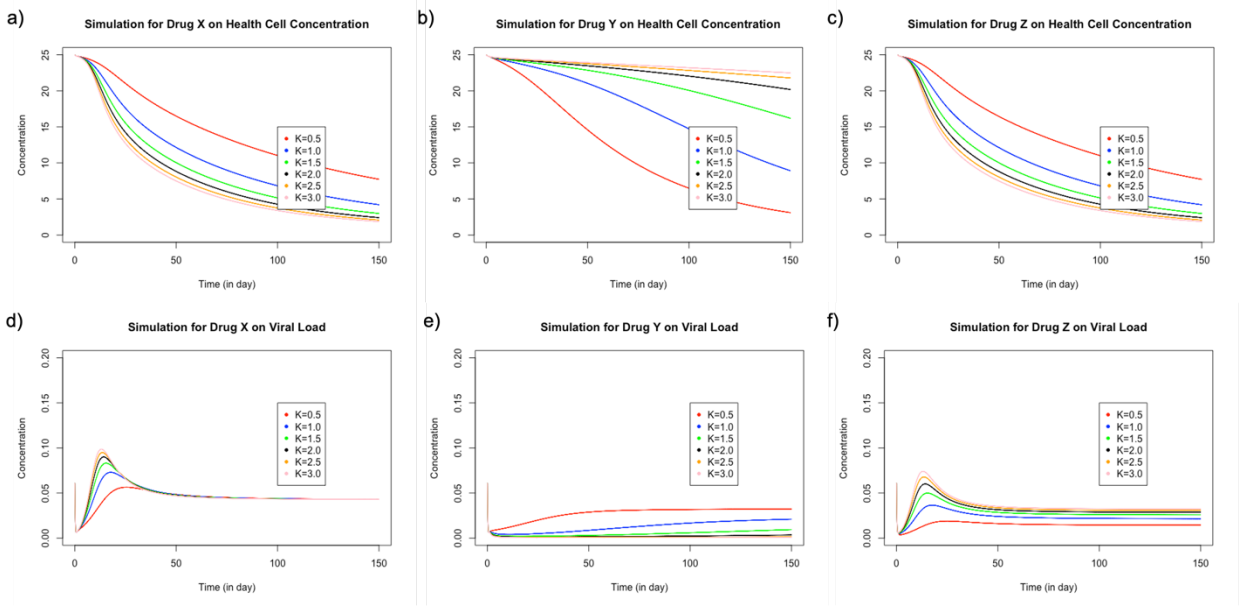

Figure 11: Simulation results for the effect of Drug X, Drug Y, and Drug Z. The effect of a vaireity of *K* values for Drug X, Drug Y, and Drug Z on healthy cell concentrations are shown in a), b), and c), respectively. The effects for Drug X, Drug Y, and Drug Z on viral load are shown in d), e), and f), respectively. Modelling parameters are the same as used in **Figure 7**, with m = 1 day^{-1} concentration unit^{1} and n = 1 day^{-1} for all three drugs.

Additional Biological Considerations for Antiviral Drug Design

It seems like the drug promoting the production of interferon works the best in lowering the viral load and maintaining healthy cell concentration than the other two drugs. However, it is necessary to consider the side effects of the overproduction of interferon in actual human body. As discussed in *Section 3*, interferon is one of the cytokine proteins that recruits other inflammatory factors, such as Tumor Necrosis Factor (TNF) and Interleukin-1 (IL-1), which exacerbates the inflammatory responses and further recruits circulating macrophages and neutrophils. As a result of this additional inflammatory responses, some studies suggested that the overproduction of interferon in COVID-19 patients can lead to more severe conditions and even mortality [24, 25]. As a result, Drug Y might cause more severe damages to patients due to the overactivated immune response, and more experiments should be conducted to unravel the relationship between interferons and disease severity before the development of this type of drug.

5. Conclusion and Future Perspectives

In this report, the host viral dynamic of SARS-CoV-2 is modelled using the simple target cell model and the target cell model with IIR from the work by Zitzmann and Kaderal. With the help from the model parameters by Li et al. and Baccam et al., both models show a consistent pattern of the viral dynamic in the host. When compared the modelling results with the viral load data from actual COVID-19 patients, the model with IIR resembles the observed viral load dynamic more closely. The model is then extended to include several hypothesized antiviral drugs to treat COVID-19. It is found that the drug that acts to activate interferon production is the most effective in combating COVID-19; however, the development of this kind of drug should be done cautiously as there might be some side effects with the overactivated immune responses. As a result, future researchers should develop a more sophisticated model to incorporate more interactions and responses of the immune system in order to better model the dynamic mathematically. In addition, more wet-lab experiments should also be conducted to explain the relationship between interferon and the severity of COVID-19. It is hoped that the results obtained in this report can provide some guidance and insights for future researchers to develop more effective COVID-19 treatments so that this global pandemic can be ended as soon as possible.

Appendix A: Simulation Code in R

The code in R used for generating **Figure 3** is shown below:

```
library(deSolve)

#parameter assignment - Values from the work by Li et al.
d = 0.001 # rate of death of uninfected cells
k = 0.55 # virus infect uninfected cells at rate k
delta = 0.11 # infected cell death rate
p = 0.24 # rate of production of virus from infected cells
c = 5.36  # death rate of virus
lambda = 0.0169  #rate of production of uninfected cells
Io = 0 #initial value of infected cells
Co = 25 #initial value of healthy cells
Vo = 0.061 #initial value of viral load

model1 <- function (t, x, params) {
  C <- x[1] #target cell
  I <- x[2] #infected cell
  V <- x[3] #viral load

  dCdt = lambda - d*C - k*V*C
  dIdt = k*V*C - delta * I
  dVdt = p*I-c*V

  dxdt <- c(dCdt, dIdt, dVdt)
  list(dxdt)
}

times <- seq(from=0, to=150, by=0.01) #time stamps

x_initial <- c(C=Co, I=Io, V=Vo) #initial values

#generate the data point
out <- as.data.frame(ode(func = model1, y=x_initial, parms = parms, times = t
imes))

# Plot for Figure 3a
plot(out$C~out$time, type = "l", col = "red", xlab = "Time (in days)", ylab =
 "Concentration", main = "Simulation for Target Cell Model", ylim = c(0,25))
points(out$I~out$time, type = "l", col = "blue")
points(out$V~out$time, type = "l", col = "green")
legend(100,10,legend = c("Healthy Cells", "Infected Cells", "Viral Load"), co
l = c("red", "blue", "green"), pch=20)

# Plot for Figure 3b
plot(out$C~out$time, type = "l", col = "red", xlab = "Time (in days)", ylab =
```

```
 "Concentration", main = "Simulation for Target Cell Model", ylim = c(0,0.7))
points(out$I~out$time, type = "l", col = "blue")
points(out$V~out$time, type = "l", col = "green")
legend(100,0.4,legend = c("Healthy Cells", "Infected Cells", "Viral Load"), c
ol = c("red", "blue", "green"), pch=20)
```

The code in R used for generating **Figure 8** is shown below:

```
library(deSolve)

#parameter assignment - Values from the work by Li et al. and Baccam et al.
d = 0.001 # rate of death of uninfected cells
k = 0.55 # virus infect uninfected cells at rate k
delta = 0.11 # infected cell death rate
p = 0.24 # rate of production of virus from infected cells
c = 5.36  # death rate of virus
lambda = 0.0169  #rate of production of uninfected cells
Io = 0 #initial value of infected cells
Co = 25 - Io #initial value of healthy cells
Vo = 0.061 #initial value of viral load
omiga = 4 #transition rate between I1 and I2
s = 0.1 #rate of secretion of IFN
b = 0.1 #rate of degradation of IFN
ep = 1 #effectiveness of blocking production of virus
ew = 1 #effectiveness of IFN blocking transition
tau = 1 #time delay before the IFN production kicks in

derivs <- function(t, y, parms) {
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4] - omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - k*y[1]*y[4] - d*y[1]
    dIadt = k*y[1]*y[4] - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = p/(1+ep*y[5])*y[3]-c*y[4]
    dNdt = s*lag[3] - b*y[5]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt))
}

times <- seq(from=0, to=150, by=0.01) #time stamps
```

```
yinit <- c(Co,0,0,Vo,0) #initial values

#generate the data point
yout <- dede(y = yinit, times = times, func = derivs, parms = NULL)

# Plot for Figure 5a
plot(yout[,2]~yout[,1], type = "l", col = "red", xlab = "Time (in day)", ylab
 = "Concentration", main = "Simulation for Target Cell Model with IIR", ylim
= c(0,25))
points(yout[,3]~yout[,1], type = "l", col = "blue")
points(yout[,4]~yout[,1], type = "l", col = "green")
points(yout[,5]~yout[,1], type = "l", col = "black")
points(yout[,6]~yout[,1], type = "l", col = "orange")
legend(100,15,c("Healthy Cells", "Infected Cells 1", "Infected Cells 2", "Vir
al Load", "Interferon"), col = c("red", "blue", "green", "black", "orange"),
pch=20)

# Plot for Figure 5b
plot(yout[,2]~yout[,1], type = "l", col = "red", xlab = "Time (in day)", ylab
 = "Concentration", main = "Simulation for Target Cell Model with IIR", ylim
= c(0,0.7))
points(yout[,3]~yout[,1], type = "l", col = "blue")
points(yout[,4]~yout[,1], type = "l", col = "green")
points(yout[,5]~yout[,1], type = "l", col = "black")
points(yout[,6]~yout[,1], type = "l", col = "orange")
legend(100,0.4,c("Healthy Cells", "Infected Cells 1", "Infected Cells 2", "Vi
ral Load", "Interferon"), col = c("red", "blue", "green", "black", "orange"),
 pch=20)
```

The code used for generating **Figure 11c** and **Figure 11f** is shown below:

```
library(deSolve)

#parameter assignment - Values from the work by Li et al. and Baccam et al.
d = 0.001 # rate of death of uninfected cells
k = 0.55 # virus infect uninfected cells at rate k
delta = 0.11 # infected cell death rate
p = 0.24 # rate of production of virus from infected cells
c = 5.36  # death rate of virus
lambda = 0.0169  #rate of production of uninfected cells
Io = 0 #initial value of infected cells
Co = 25 - Io #initial value of healthy cells
Vo = 0.061 #initial value of viral load
omiga = 4 #transition rate between I1 and I2
s = 0.1 #rate of secretion of IFN
b = 0.1 #rate of degradation of IFN
ep = 1 #effectiveness of blocking production of virus
ew = 1 #effectiveness of IFN blocking transition
```

```
tau = 1 #time delay before the IFN production kicks in
n = 1
m = 1

derivs1 <- function(t, y, parms) {
  K = 0.5
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}

derivs2 <- function(t, y, parms) {
  K = 1
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}
```

```
derivs3 <- function(t, y, parms) {
  K = 1.5
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}

derivs4 <- function(t, y, parms) {
  K = 2.0
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}

derivs5 <- function(t, y, parms) {
  K = 2.5
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
```

```
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}

derivs6 <- function(t, y, parms) {
  K = 3
  if (t < tau) {
    dCdt <- lambda - k*y[1]*y[4] - d*y[1] #uninfected cell
    dIadt <- k*y[1]*y[4]-omiga*y[2] #infected but not virus producing cells
    dIbdt <- omiga*y[2] - delta *y[3] #infected and virus producing cells
    dVdt <- p*y[3] - c*y[4] #viral load
    dNdt <- 0 #interferon produced by I2
    dXdt <- m - n*y[6]
  }
  else { #C=y[1],Ia=y[2],Ib=y[3],V=y[4],N=y[5]
    lag <- lagvalue(t - tau)

    dCdt = lambda - (k*y[1]*y[4]) - d*y[1]
    dIadt = (k*y[1]*y[4]) - (omiga/(1+ew*y[5]))*y[2]
    dIbdt = (omiga/(1+ew*y[5]))*y[2] - delta*y[2]
    dVdt = (p/(1+ep*y[5])*y[3])/(1+y[6]/K)-c*y[4]
    dNdt = s*lag[3] - b*y[5]
    dXdt = m - n*y[6]
  }
  list(c(dCdt, dIadt, dIbdt, dVdt, dNdt, dXdt))
}

times <- seq(from=0, to=150, by=0.01) #time stamps

yinit <- c(Co,0,0,Vo,0,0) #initial values

#generate the data point
yout1 <- dede(y = yinit, times = times, func = derivs1, parms = NULL)
yout2 <- dede(y = yinit, times = times, func = derivs2, parms = NULL)
yout3 <- dede(y = yinit, times = times, func = derivs3, parms = NULL)
```

```
yout4 <- dede(y = yinit, times = times, func = derivs4, parms = NULL)
yout5 <- dede(y = yinit, times = times, func = derivs5, parms = NULL)
yout6 <- dede(y = yinit, times = times, func = derivs6, parms = NULL)

# Plot for Figure 11c
plot(yout1[,2]~yout1[,1], type = "l", col = "red", xlab = "Time (in day)", yl
ab = "Concentration", main = "Simulation for Drug Z on Health Cell Concentrat
ion", ylim = c(0,25))
points(yout2[,2]~yout2[,1], type = "l", col = "blue")
points(yout3[,2]~yout3[,1], type = "l", col = "green")
points(yout4[,2]~yout4[,1], type = "l", col = "black")
points(yout5[,2]~yout5[,1], type = "l", col = "orange")
points(yout6[,2]~yout6[,1], type = "l", col = "pink")
legend(100,15,c("K=0.5", "K=1.0", "K=1.5", "K=2.0", "K=2.5","K=3.0"), col = c
("red", "blue", "green", "black", "orange","pink"), pch=20)

# Plot for Figure 11f
plot(yout1[,5]~yout1[,1], type = "l", col = "red", xlab = "Time (in day)", yl
ab = "Concentration", main = "Simulation for Drug Z on Viral Load", ylim = c
(0,0.2))
points(yout2[,5]~yout2[,1], type = "l", col = "blue")
points(yout3[,5]~yout3[,1], type = "l", col = "green")
points(yout4[,5]~yout4[,1], type = "l", col = "black")
points(yout5[,5]~yout5[,1], type = "l", col = "orange")
points(yout6[,5]~yout6[,1], type = "l", col = "pink")
legend(100,0.15,c("K=0.5", "K=1.0", "K=1.5", "K=2.0", "K=2.5","K=3.0"), col =
 c("red", "blue", "green", "black", "orange","pink"), pch=20)
```

Appendix B: Data for Local Sensitivity Analysis

Originial steady state concentration for healthy cells: 1.008975 in arbitrary concentration units.

Originial steady state concentration for viral load: 0.04287572 in arbitrary concentration units.

Originial parameter values:
d = 0.001 day^{-1}, k = 0.55 day^{-1} concentration unit^{-1}, δ = 0.11 day^{-1}, p = 0.24 day^{-1}, c = 5.36 day^{-1}, λ = 0.0169 day^{-1} concentration unit^{1}, b = 0.1 day^{-1}, ω = 4 day^{-1}, ε_p = 1, ε_ω = 1, s = 0.1 day^{-1}, and τ = 1 day^{1}.

Parameter	**Changed Parameter**	**New steady state [Healthy Cell]**	**New steady state [Virus]**
λ	Original * 1.01	1.015532	0.04287793
d	Original * 1.01	1.014811	0.04287744
k	Original * 1.01	0.9816995	0.04287267
δ	Original * 1.01	1.016062	0.04287035
p	Original * 1.01	0.9818793	0.04330143
c	Original * 1.01	1.036905	0.04245432
ω	Original * 1.01	1.008330	0.04288319
s	Original * 1.01	1.027640	0.04246586
b	Original * 1.01	0.9935970	0.04328569
ε_p	Original * 1.01	1.027137	0.04247274
ε_ω	Original * 1.01	1.009468	0.04286874
τ	Original * 1.01	1.008371	0.04287612

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