Dynamic Modeling of SARS-CoV-2 in Lung Tissues

[Redacted]

Introduction

Coronaviruses belong to the subfamily Coronavirinae in the family Coronaviridae of the order Nidovirales and can cause respiratory, digestive, and nervous system diseases in humans and many other animals. (Yang et al.) In 2002 and 2012, respectively, two highly pathogenic coronaviruses with zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), emerged in humans and caused fatal respiratory illness, making emerging coronaviruses a new public health concern in the twenty-first century1. (Hu et al.) In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly transmissible and pathogenic coronavirus emerged and has caused a pandemic of acute respiratory disease, which threatens human health and the public safety.

Mathematical and computational modeling are powerful tools for describing and analyzing infection dynamics in relation to many processes that lead to observed disease phenotypes. Many epidemiological mathematical models have been proposed to predict the spread of the disease, and evaluate the control measures in outbreak management. While researching the impact of the virus on the macro scale is important, it is also vital to have mathematical models at the in-host level that could be used to understand the virus reproduction mechanism and cell-virus interaction. Such model can be used to assess pharmacological therapy for the treatment of COVID-19. For a virus to infect a living organism, it must invade its cells, multiply and continue to infect other hosts. Consequently, the rate of change of cells and viruses is highly related to each other. In our project, an Ordinary Differential Equation (ODE) model is implemented to describe the in vivo environment during infection. Three objects virus, susceptible cell, and infected cell are included in the model. Each object has its own behavior that can influence the in vivo environment. Additionally, we used agent-based models to simulate the spatial structure of the respiratory system at which SARS-CoV-2 attacks. These models will be discussed in detail in the following sections.

The General Goal of this research is to analyze various problems related to virus-cell dynamics by developing algorithms based on modern programming techniques and to develop multiple computational models to simulate the dynamics of virus infection in human tissue like lungs. It is hoped that from the perspective of mathematical modeling, our model could be used to abstractly construct a process of virus dynamics in various biological conditions (under the influence of different external forces: medicine, the human body's immunity, etc.), which can be applied as a tool for medical research and drug development.

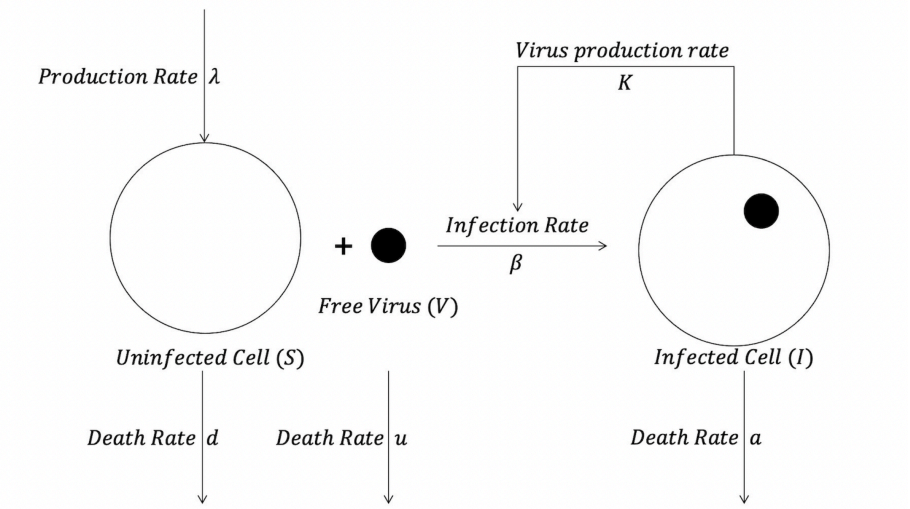
Background Information

Since the outbreak of COVID-19, many epidemiological models were established to understand and handle the COVID-19 pandemic, but only a few of them were focusing on the virus-cell interaction in the host, which can help the development of potential antivirals to tackle the infection. (Abuin et al.) Our research focuses on the SARS-CoV-2 dynamics in the host. The use of mathematical and computational modeling will provide a more intuitive way for people to understand the infection process. Computational and mathematical modeling has gradually been added to the toolbox of exploring virus dynamics due to the ability to better parse the non-linear interactions that characterize these dynamics. The models can help us understand cell-virus interaction, simulate the infection process of SARS-CoV-2 in human lung tissue, and compare different medications' impact on the virus. By tuning the model parameters, we can easily simulate virus dynamics under different situations. In our research, we intend to use three different models to explore the dynamics of SARS-CoV-2: Ordinary differential equations (hereafter abbreviated as ODE), 2D-Spatial Models, and 3D-Spatial Models. The ODE model we use is based on the model in "Complex Spatial Dynamics of Oncolytic Viruses In Vitro: Mathematical and Experimental Approaches" (Wodarz et al.) We use ODE to describe the basic interaction between virus, infected cells, and susceptible cells. One of the assumptions of the ODE model is that the cells and virus are mixed perfectly with each other so that for each virus there will be an

equal chance of infecting other susceptible cells. (Wodarz et al.) However, such a model is unrealistic given that SARS-CoV-2 infects people's respiratory systems which are solid and have a certain spatial structure. One way of modeling the spatial structure is to construct a recombinant virus and grow it on human cells in a dish. (Wodarz et al.) This method is both time-consuming and challenging. To include spatial structure in our model, we will be using an agent-based model to study the stochasticity of the virus infection process. Cells would be simulated as a block or a cube in 2D and 3D space respectively. Since the virus is far smaller than normal cells, we will not include the virus in our models. Instead, infected cells will be able to infect the susceptible cells nearby. The preliminary model will be shown in the Timeline and Methods section.

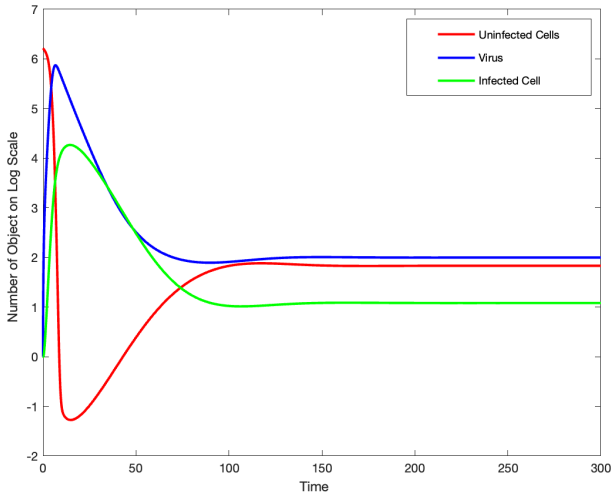
Timeline and Methods

Ordinary Differential Equation Model May 2 – May 22



$$\frac{dS}{dt} = \lambda - dS - \beta SV$$
$$\frac{dI}{dt} = \beta SV - aI$$
$$\frac{dV}{dt} = KI - uV$$

The first model is a basic infection ODEs model. This model only includes uninfected cells (S), free virus (V), and infected cells (I). In the previous studies, this model is used in the research of different kinds of virus. In our study, the plan is to use this model to figure out the spread of SARS-CoV-2 virus in human body. In research, MATLAB will be used to draw graphs showing of the spread of virus and find the equilibrium situation of SARS-CoV-2 virus in the lung tissue. This model is given by the equations above.

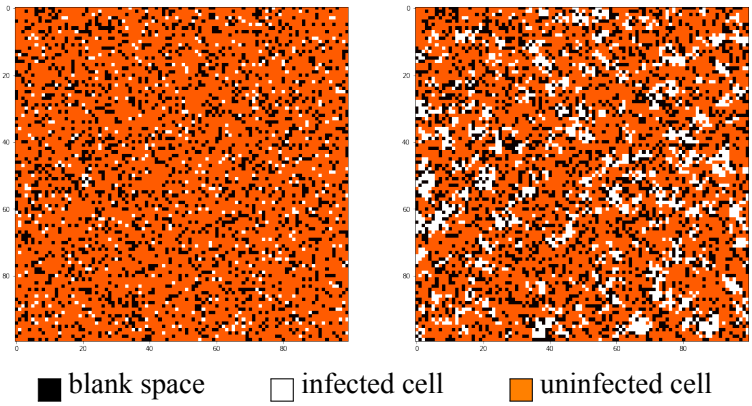


In those ODE equations, uninfected cells (S) are produced at rate λ and die at rate d per unit of uninfected cells (S). Also, in this model, uninfected cells are assumed to be infected by SARS-CoV-2 virus and change into infected cells (I) at rate βSV. We also assume the infected cells to die at rate a and produce new virus

at rate K per unit of infected cell. SARS-CoV-2 is assumed to be die at rate u per virus.

2D Spatial Model May 23 – June 23

The introduction of the spatial model aims at simulating how viruses spread in human cells with relatively fixed locations like lung cells. Considering the fact that the volume of the virus is negligibly small compared to lung cells, we will only take into account three objects which are uninfected cells, infected cells, and empty space in this model.



In the concept of stochastic processes, we think of these three objects as states and assign value to each of them as 0, 1, and 2. To set up the initial setting, we will build up a 2D array and use the initial probability parameter to randomly generate infected cells from all uninfected cells. The control and adjustment of such parameters can be used to simulate many different degrees of infection. In order to minimize the bias caused by the fact that computers can only execute orders in sequence, while every cells and virus are always varying simultaneously in human bodies, for each step, we will randomly pick one element in 2D array to determine its state change.

3D Spatial Model June 23 – July 23

Next, we will explore more on the 3D space model. Compared with 2D, the 3D model will be closer to the real composition of lung cells. We are convinced that the 3D model will give us a better simulation that will result in more convincing results. We are planning to use such a model to make many significant test. For example, run the model for many iterations to investigate the temporal trajectories, their averages, and their variation.

Effect of Medication July 24 – Sep 24

One important application of our model mentioned above is to test the effect of different medicine. The medicine that we are going to test is some western medicine that have been widely used over the world such as Paxlovid and Molnupiravir. We will focus on the treatment with Paxlovid and Molnupiravir, which have both received Emergency Use Authorization (EUA) in the United States by the FDA. We are going to employ the result and data from ”Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis”, which has already discussed a lot on the broad-spectrum antiviral activity of molnupiravir based on two-step mutagenesis mechanism probably. (Kabinger at al.) We may also need to model the immune function to see how B cell and T cell response react to different medications and try to combine this immune function model with the previous medication effect model together to see the effect of medication that act on people with different immune condition.

Responsibility

The group has made a clear division of research responsibilities for each person.
Member responsibilities are as follows:
[Redacted]: Responsible for designing computational modeling and data investigation and analysis and

also for diagram drawing using python and Matlab.

[Redacted]: Responsible for programming, developing and maintaining Python code. Optimize the system architecture of the model, and use programming to achieve modeling and planning.

[Redacted]: Data collection, literature review, research on related knowledge of biology and virology.

[Redacted]: Responsible for Matlab programming, using mathematical knowledge such as differential equation to build algorithm code.

[Redacted]: Responsible for the collection and organization of literature and research resources, assisting in data integration.

[Redacted]: Optimize the visualization of research results, assist in Matlab programming, literature collection, and data research.

References and Works Cited

Abuin, Pablo, et al. "Characterization of SARS-CoV-2 dynamics in the host." Annual reviews in control 50 (2020): 457-468

Hu, B., Guo, H., Zhou, P. et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 19, 141–154 (2021). https://doi.org/10.1038/s41579-020-00459-7

Kabinger, F., Stiller, C., Schmitzová, J. et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol 28, 740–746 (2021). https://doi.org/10.1038/s41594-021-00651-0

Wodarz, Dominik, et al. "Complex spatial dynamics of oncolytic viruses in vitro: mathematical and experimental approaches." PLoS computational biology 8.6 (2012): e1002547

Yang, Y., Xiao, Z., Ye, K. et al. SARS-CoV-2: characteristics and current advances in research. Virol J 17, 117 (2020). https://doi.org/10.1186/s12985-020-01369-z

Proposed Budget

Quantity	Item Description	Unit Price	Total Price
1	Textbooks for Math Modelling	$70	$70
1	Textbooks for Basic Biology	$75	$75
1	Relevant Data Purchase	$75	$75
1	Printing	$50	$50
1	Rental for High End Running Platform	$200	$200

TOTAL: $470