Imperial College London
Department of Earth Science and Engineering
M.Sc in Applied Computational Science and Engineering

Independent Research Project
Project Plan

Modeling of in-host viral dynamics using differential equations for estimating uncertainty applied to a classroom

by
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Github repository: https://github.com/acse-2020/acse2020-acse9-projectplan-acse-yl5520

Introduction

Wuhan, China first reported a newly discovered and highly infectious pneumonia in late December 2019 (Hui, D.S. et al., 2020). This disease and the causative virus is named coronavirus disease (COVID-19) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respectively by the World Health Organization (2020). COVID-19 is lethal once the hosts' lung is critically damaged by lymphocytopenia and hyperactive inflammatory response (Stebbing, J. et al., 2020). Xu, Z. et al. (2020) spotted the hyperactive inflammatory response is related to the centralization of lymphocytes - cells part of the immune system - to the patient's lung, and this causes the consequent pulmonary injury.

The hyperactive inflammatory response together with the lymphocytopenia - a phenomenon of abnormally low amount of lymphocytes in the blood - suggested SARS-CoV-2 could be targeting more than one type of cells (Wang, S. et al., 2020). They built and fitted a mathematical model with collected patient data, to simulate the interaction between the virus and cells within a host. Then by changing some parameters they introduced to the model to evaluate some therapeutic interventions for COVID-19.

This project uses a similar idea from Wang, S. et al., modifies and builds another mathematical model from the one they created, to simulate the amount of virus shed by an individual, and to also simulate how the shed virus interacts with others in the same classroom. The parameters in this model are also going to be varied, for evaluating the effect of different transmission control measures - covering with face mask and vaccination.

Literature Review

In 2013, Perelson, Alan S. and Ribeiro, Ruy M. (2013) used a simple viral dynamic model to simulate the HIV infection within individuals. They were interested on three values: 1. Uninfected target cells (T); 2. Infected cells (I); and 3. Free virus (V). The model is expressed as a system of ordinary differential equation (ODE) w.r.t time. This model is then used as the basis with modification in 2020 by Wang, S. et al (2020).

Wang and his team introduced one more value to the model according to their findings: the secondary target cells (T_2), and distinguished the primary target cells as T_1 (I and V remains the same meaning).

$$\frac{dT_1}{dt} = -\beta V T_1, \qquad \frac{dT_2}{dt} = \lambda - \beta V T_2$$

The alveolar type II cells T_1 (the primarily targeted cells by SARS-CoV-2 in lungs) and the lymphocytes T_2 gets infected by the infection rate β per day; while there are λ lymphocytes recruited to the infected site every day.

$$\frac{dI}{dt} = \beta V\left(T_1 + T_2\right) - \left[\delta(t) + \omega T_2\right] I, \qquad \delta(t) = \begin{cases} \delta_I, t < \mu \\ \delta_I e^{\sigma(t-\mu)}, t \geq \mu \end{cases}$$

The infected T_1 and T_2 becomes infected cells I, which is being cleared by both innate and adaptive immune system. Wang and his team assumed the innate immune system kills infected cells proportionally to the amount of lymphocytes (ωT_2); and used a function of time to express the killing rate of adaptive immune system, where μ is its activation day, σ indicates how fast the effectiveness increases and δ_I is the base killing rate.

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

Finally, Wang and his team let the equation on V remains unchanged where p represents the production rate of virus from infected cells, and c is the clearance rate of the virus.

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Wang and his team fitted the patients data collected in Germany, Korea, China and data from rhesus macaques to get the values of parameters in the model, and they found the immune respond in the lower respiratory tract (LRT) is much larger than in the upper respiratory tract (URT). This finding is also agreed by Mason, R.J. (2020).

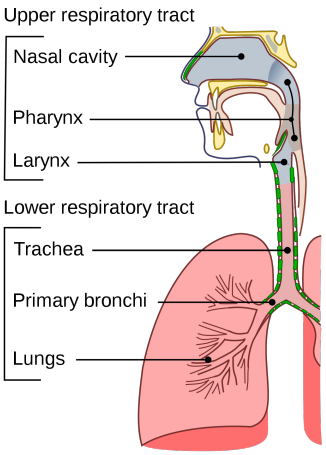

Illustration of URT and LRT (Wikipedia, 2021)

Mason divided the infection process of SARS-CoV-2 into three phrases based on the potential target cells at different stages, and concluded about 80% of COVID-19 patients are restricted to stage 2 with moderate symptom. The first stage is the first few days after inhaling the virus, and the proposed target cells at this stage are ciliated cells; second stage corresponding to the infection from URT to LRT which trigger the adaptive immune system, the proposed target cells are epithelial cells; the third stage indicates the virus is present in the alveoli and targeting the alveolar type II cells, the primary target cells used in Wang and his team's model.

In Wang's paper, the initial value of T_1 is also set according to the number of alveolar type II cells in human even when fitting model to the data in URT. This could be problematic according to Mason, alveolar type II cells are not the target cell of SARS-CoV-2 in URT. However, based on the parameters fitted from the model and the division proposed by Mason, URT and LRT emerges different behaviors in COVID-19.

After collecting 79 studies related to the duration of SARS-CoV-2 shedding and getting a 95% confidence interval of expectation value, Cevik, M. et al (2021) suggests separately modeling the URT and LRT is essential on simulating the viral shedding more accurately. From Cevik's calculations, the URT sheds SARS-CoV-2 for 17.0 days and the LRT sheds for 14.6 days. In Mason's division of the SARS-CoV-2 infection process, this is the time different between stage 1 and 2. Cevik also found the maxima of viral load in URT appear in the first week of symptom onset, this is also verified by the data used in Wang's model.

Description of Problem and Objectives

Modeling the within-host viral dynamic with intra-host interaction is intricate even the model create by Wang and his team already reflects each set of patient data well. The relation between the viral load in an individual and its effects to the surrounding people is obscure and could be affected by lots of factors: the air dynamic of this surrounding, the distance between each pair of individuals, the physical protection on each individual, also the different between each immune system. Considering the length of the given period of time, this project aims to build a simple model with convincing accuracy that focus more on the last two aspects: physical protection and discrepancy of immune system.

Therefore, the first objective of this project is to develop a model which can give an estimation of the amount of viral shed, based on an individual's viral load. The papers from last section advice on using both URT and LRT value to calculate the viral shed, so the new model is expecting to combine two of Wang's model in one, and a modification to the two viral load equations (URT and LRT) as inhaling term and/or exhaling term. This model could be verified by using the URT and LRT plots generated by Wang's model.

After verifying the new model, each parameter will be selected from a different Gaussian distribution for simulating the reality, e.g. group of vaccinated people would have higher mean on the virus clearance rate c, higher mean on the infected cells base death rate δ_I, etc.; group of masked people would have a lower mean on the coefficient which modulates the inhaling term in the developed model. This uncertainty quantification uses the developed model to justify the effectiveness of the health precautions suggested and conducted by governments all around the world. On the other hand, the results from these precautions could also verify the reliability of the developed model.

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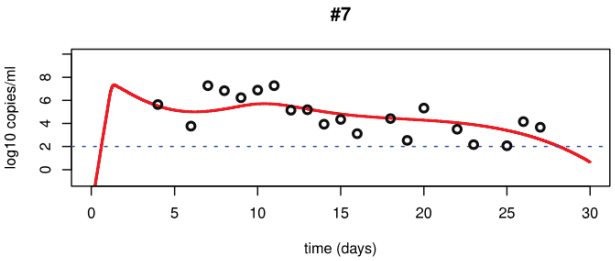
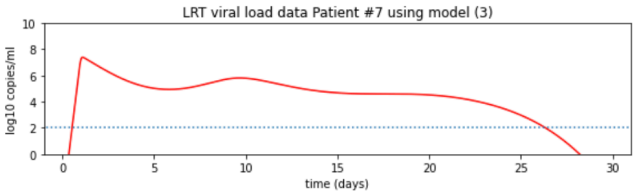
Progress to Date and Future Plan

A Fortran library is provided to speed up some computation steps in this project or to serve as a starting point. Two subroutines in this library are closely related to this project, (1) a forward Euler solver to the ODE in the model created by Wang and his team; (2) a generic linear solver with cells in grid, which can be used to aggregate different instances of the same model and solved all instances simultaneously. Both subroutines are verified with the plots in Wang's paper.



Plot (line) from Wang's model with actual data (dots)
$\beta = 1\times10^{-6}; \lambda = 10^4; \delta_I = 2; \sigma = 0.11; \mu = 9; \omega = 4.5\times10^{-4};$
$p = 1.1\times10^5; c = 209; V(0) = 10^{-3}; T_1(0) = 6\times10^4; T_2(0) = I(0) = 0$
(Wang, S. et al., 2020)

Using the parameter values given by Wang and his team for patient #7, here is the comparison between Wang's plot and the plot from the Fortran subroutine (1). The shape of both plots is similar enough to conclude the subroutine (1) has correctly implemented Wang and his team's model. The values provided by Wang has been approximated and thus lead to the minor disparity in the plot of subroutine (1) - viral load drops below 0 before day 30 while it is above 0 in the original plot.

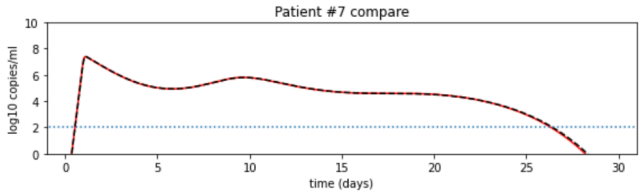


Plot from subroutine (1) with the same parameters

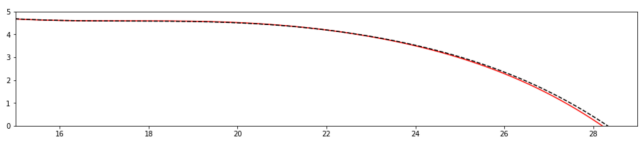
Wang's model is then being transformed to a linear combination, for verifying the subroutine (2). The plot from subroutine (2) is then compared against the plot from subroutine (1) using the same parameter values.

$$\begin{bmatrix} T_1^{n+1} \\ T_2^{n+1} \\ I^{n+1} \\ V^{n+1} \end{bmatrix} = \begin{bmatrix} T_1^{n} \\ T_2^{n} \\ I^{n} \\ V^{n} \end{bmatrix} + dt \left(\begin{bmatrix} 0 \\ \lambda \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} -\beta V^n & 0 & 0 & 0 \\ 0 & -\beta V^n & 0 & 0 \\ \beta V^n & \beta V^n & -\delta(t) - \omega T_2^n & 0 \\ 0 & 0 & p & -c \end{bmatrix} \begin{bmatrix} T_1^{n} \\ T_2^{n} \\ I^{n} \\ V^{n} \end{bmatrix} \right)$$

The subroutine (2) is designed to discretize a given 3D space and then solve each linear system under consideration of advection and diffusion. In this verification, the speed of advection and diffusion is set to zero, and the individual is placed in the central cell of a $3 \times 3 \times 3$ cube since this subroutine takes boundary into consideration.



Plot from both subroutines; (1 - red line; 2 - black dash)



The minor disparity near day 28

Again, there is a minor disparity between the plots from both subroutines, for this particular case (magnified in the bottom image). Because of the complexity of the Fortran library source code and the lack of documentation, it was unable to identify the reason which causes this mismatch. However, from the comparison shown in the top image, subroutine (2) is verified to be correct since it matches subroutine (1) almost perfectly.

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According to the objectives of this project, here is the provisional plan:

1. Expanding the model created by Wang and his team for modeling both URT and LRT simultaneously; and connect the URT and LRT part by a/some term(s) in the dV/dt equation.
2. Restricting the $V_{LRT}(0)$ to 0, then try to find a coefficient for the connecting term, which will make the model to reproduce a highly similar plot as in Wang's paper.
3. Collecting more parameter values (e.g., β, p, etc.), then calculate the corresponding mean and standard deviation by treating them as Gaussian distribution.
4. Using the Gaussian distribution acquired to quantify the uncertainty, and evaluate the effectiveness of some health precautions under different situation (e.g., the precautions are being strictly followed, half of the people in the classroom do not follow the precautions, etc.)

Following is a table recoding all the meetings about this project until the day of submission of this plan.

Date, duration	Meeting summary
June 1st, 60 minutes	Weekly supervision meeting
June 8th, 60 minutes	Weekly supervision meeting
June 9th, 60 minutes	Fortran library support
June 10th, 30 minutes	Discussion of project progress
June 15th, 60 minutes	Weekly supervision meeting
June 18th, 10 minutes	Fortran library support
June 22nd, 60 minutes	Weekly supervision meeting
June 24th, 30 minutes	Discussion of project progress

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Reference

Cevik, M. et al. (2021) SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *The Lancet Microbe*. 2(1), e13-e22.

Hui, D.S. et al. (2020) The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *International Journal of Infectious Diseases*. 91 (2020), 264-266.

Mason, R.J. (2020) Pathogenesis of COVID-19 from a cell biology perspective. *European Respiratory Journal*. 55(4), 2000607.

Perelson, A.S., Ribeiro, R.M. (2013) Modeling the within-host dynamics of HIV infection.*BMC Biology*. 11(1), 96.

Stebbing, J. et al. (2020) COVID-19: combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases*. 20(4), 400-402.

Wang, S. et al. (2020) Modeling the viral dynamics of SARS-CoV-2 infection. *Mathematical Biosciences*. 328(2020), 108438.

Wikipedia. (2021) *Upper respiratory tract infection*. Available from: https://en.wikipedia.org/wiki/Upper_respiratory_tract_infection.

World Health Organization. (2020) *Naming the coronavirus disease (COVID-19) and the virus that causes it*. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

Xu, Z. et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*. 8(4), 420-422.

Bibliography

Chan, J. et al. (2020) Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerging Microbes & Infections*. 9(1), 221-236.

Guan, W.J. et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *New England Journal of Medicine*. 382(18), 1708-1720.

Li, W. et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coro- navirus. *Nature*. 426(6965), 450-454.

Pan, Y. et al. (2020) Viral load of SARS-CoV-2 in clinical samples. *The Lancet Infectious Diseases*. 20(4), 411-412.

Ruan, Q. et al. (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Medicine*. 46(5), 846-848.

Wölfel, R. et al. (2020) Virological assessment of hospitalized patients with COVID-2019. *Nature*. 581(7809), 465-469.

Yang, X. et al. (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *The Lancet Respiratory Medicine*. 8(5), 475-481.

Zhou, P. et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*. 579(7798), 270-273.