Cell lysis analysis for respiratory viruses through simulation modeling

L Cuesta-Herrera¹, L Pastenes², F Córdova-Lepe¹, A D Arencibia³, and H A Torres-Mantilla⁴

¹ Departamento de Matemática, Física y Estadística, Universidad Católica del Maule, Talca, Chile
² Departamento de Biología y Química, Universidad Católica del Maule, Talca, Chile
³ Facultad de Ciencias Agrarias y Forestales, Universidad Católica del Maule, Talca, Chile
⁴ Facultad de Ciencias Exactas, Naturales y Agropecuarias, Universidad de Santander, Bucaramanga, Colombia

E-mail: ledyz.cuesta@alu.ucm.cl

Abstract. An ordinary system of differential equations leading to a simulation model is propose as methodological approach to analysis the incidence of infectious-contagious diseases, in this case using SARS-CoV-2 virus as pathogenic model. The dynamics of the model are drive by the interaction between susceptible cells contemplating respiratory epithelial cells and viral infection mediated by two types of lysis response. To perform the simulations, values of some variables and parameters were selected from referenced sources, considering that previous reports suggested that the viral load in the lower respiratory tract might reach its peak in the second week after the beginning of disease symptoms. The scenarios described in the simulations evidence the performance of the cell lysis response from susceptible cells that have been infected. The recommend model shows that an excess response from both the original virus and the mutated virus leads to an increase in the approximate time to control viral infection within the organism.

1. Introduction

Mathematical models of virus dynamics have used different mathematical tools and approaches, depending on the topics under investigation and the biological complexity considered. However, most models are based on ordinary differential equations (ODEs) [1,2]. The basic model of viral dynamics must contain certain features of the disease dynamics in the host, e.g., the cells that the virus infects, the existence of the virus in the host, the time scale of infection in the host, and the life cycle of the virus [3].

Viruses make copies of themselves in a process called replication in which the new copies sometimes have small changes. These changes are called “mutations”. A virus that has undergone one or more mutations is a “variant” of the original virus [4–6]. In these cases, a virus can replicate by division/proliferation and through infection of susceptible cells. Some mutations can lead to changes in the characteristics of a virus, such as alterations in transmission or severity. The frequency of mutations varies between different types of viruses. For example, the SARS-CoV-2 virus, which causes Covid-19, tends to mutate more slowly than others, such as HIV or influenza viruses [4–7].
The study of virus replication dynamics has generated important insights into several human infections, for example, severe acute respiratory syndrome (SARS) [8–11] novel influenza strains [12, 13] and West Nile virus [14]. Mathematical models have been developed to understand the dynamics of viral infections at the cellular level [1], playing an important role in different studies and allowing the estimation of critical replication parameters to obtain a better understanding of viral evolution, interactions between viruses and the immune system, the response of viral infections to antiviral drug therapy, among others [15]. It is worth noting that within the different studies of mathematical modeling at the cellular level, most of them fall into the category of the limited target cell model with some variations [1].

For the case of SARS-CoV-2 infection, the most widely used version includes: (1) uninfected susceptible target cells, which in this case are the epithelial cells located in the respiratory tract that constitute the epithelium of the nasal, tracheal, bronchial and alveolar mucosa, (2) virus-infected cells, where the virus reproduces and is subsequently released if cell lysis occurs [3, 16–18]. Viral infectious diseases are a global health concern, which have had a great impact on morbidity and mortality, with multiple studies relating to the projections of the behavior of epidemics having been known for centuries [19].

Viral epidemics represent a socioeconomic burden that generates short- and long-term costs for the diagnosis and treatment of the disease, as well as a loss of productivity due to work absenteeism. These outbreaks and their socioeconomic costs underline the need for precise analysis of virus-host interactions, which would help to understand disease mechanisms and develop therapeutic interventions [20], as demonstrated by Covid-19 [21, 22].

Therefore, the purpose of this work is to present a baseline model that explains the dynamics of the spread of viral infection between susceptible cells located in the respiratory tract versus the cell lysis response. Since the model does not explicitly incorporate the effect functions of immune responses, it is called “target cell limitation” [3].

2. Mathematical modeling

To carry out the mathematical approach, two different responses were assume within the cell population affected by the secretion of viral particles through a susceptible-exposed-infected (SEI) framework. It is important to highlight that the proposed approach of this study takes into account a partial competition between the two types of cell lysis responses involved in the process, because a first cell lysis response facilitates the activation of a second response that secretes mutated viral particles. Simplistically, we assume that viral particles with and without mutation can infect susceptible cells, taking into account that the former are more likely to spread the infection.

A graphical representation of the dynamics of the model is illustrated in Figure 1 where the dynamics of susceptible cells, (S), prior to contact with the free viral particles, subsequently come into contact with virions allowing their entry through their cellular receptors thus having the cells infected, (I). The mathematical model is given by the differential equation system, Equation (1), where we can imagine a set of susceptible cells undergoing cell turnover dependent on their rate of generation (g) and death (d_s) the latter resulting from apoptosis that begins after the completion of their life cycle [1–3, 15, 17, 20, 23].

Once the genetic material of the virus, which in this case will be an obligate intracellular pathogen, enters the susceptible cells, it initiates the viral RNA replication process generating copies of messenger RNA (mRNA) that serve as templates for the generation of viral proteins that will be used in the formation of new viral particles (virions) [24, 25]. These proteins, together with viral RNA replicas, are assembled and released from the infected cell which the Equation (1) corresponds to the variables R_L and R_m.

The probability of susceptible cell infection per cell in lysis response with unmutated virus is β_L and with mutated virus is β_m. Infected cells I can undergo cell death by apoptosis or give
rise transition rate $\sigma$ from infected cell to cell in lysis response with a probability $\rho$ of being cell lysis response unmutated and $1 - \rho$ for a mutated cell lysis response. For the compartments corresponding to the cell lysis response leading to the release of unmutated $R_L$ or mutated $R_m$ virus, different rates of cell lysis, $d_{RL}$ and $d_{Rm}$, different rates of lysing cell death, $d_{RL}$ and $d_{Rm}$, and different probabilities of infection of susceptible cells, $\beta_L$ and $\beta_m$, can be considered.

The cell lysis rate leads to the release of a high number of viral particles after cell destruction, whereas the death rates lead to immune-mediated cell clearance without virus release. The parameters involved in the dynamic interaction between susceptible cells and the cell lysis response are assumed in Table 1.

$$
\begin{align*}
S'(t) &= g - (\beta_L \kappa_L R_L + \beta_m \kappa_m R_m)S - d_s S, \\
I'(t) &= (\beta_L \kappa_L R_L + \beta_m \kappa_m R_m)S - (d_I + \sigma)I, \\
R'_L(t) &= \rho \sigma I - (d_{RL} + \kappa_L)R_L, \\
R'_m(t) &= \sigma (1 - \rho)I - (d_{Rm} + \kappa_m)R_m.
\end{align*}
$$

(1)

Figure 1. Conceptual model of the dynamics of interaction between susceptible cells of the respiratory epithelium and the lysis response of infected cells.

Table 1. Definition of variables and parameters of the dynamics of interaction between susceptible cells and the lysis response.

| Variables / Parameters | Description |
|------------------------|-------------|
| $S$                    | Susceptible cells |
| $I$                    | Infected cells |
| $R_L$                  | Cells in lysis response with unmutated virus |
| $R_m$                  | Cells in lysis response with mutated virus |
| $\beta_L$              | Probability of susceptible cell infection per cell in lysis response with unmutated virus |
| $\beta_m$              | Probability of susceptible cell infection per cell in lysis response with mutated virus |
| $\kappa_L$             | Lysis rate of cell with unmutated virus |
| $\kappa_m$             | Lysis rate of cell with mutated virus |
| $\sigma$               | Transition rate from infected cell to cell in lysis response |
| $\rho$                 | Proportion of the infected cells enter in lysis response with unmutated virus |
| $g$                    | Generation rate of susceptible cells. |
| $d_s$                  | Susceptible cells death rate |
| $d_I$                  | Infected cells death rate |
| $d_{RL}$               | Death rate of Cells in lysis response with unmutated virus |
| $d_{Rm}$               | Death rate of Cells in lysis response with mutated virus |
3. Results and discussion

By means of simulations, the state variables, susceptible cells $S$ (blue line), infected cells $I$ (red line), cell lysis response unmutated $R_L$ (yellow line) and mutated cell lysis response $R_m$ (green line) are represented in Figure 2.

To show the dynamics of the Equation (1), parameters were taken from secondary sources for SARS-CoV-2 [16–18,23–26], taking into account that some studies suggest that viral load in the lower respiratory tract may peak on the same day or a few days after symptom onset and is usually undetectable around the second week [26]. Despite the detection of viral particles in specimens from some individuals several weeks after symptom onset, these virions are usually not present beyond 8-14 days [27–32]. In addition, different studies including those mentioned above, demonstrated that viral samples testing negative for SARS-CoV-2 are found around day 20, more than half of the samples recorded on each of these days were below the detection limit, representing the decline in viral load after symptom onset [23,33,34].

Therefore, with the baseline parameters, we can extend the model to account for a more infectious variant, using hypothetical scenarios of the emergence of a mutated strain. It should be noted that if there are no susceptible and infected cells because the latter eventually die, the virus cannot replicate, which would lead to a decrease in viral load. Thus, in a case without an adequate immune response, or without effective therapeutic intervention, a progressive cell death of host cells in the respiratory tract may occur, losing the viral replication machinery in this model.

Figure 2 shows the spread of infection susceptible cells, $S = 1 \times 10^6$, are generated at a rate $g = 3 \times 10^4$ [day$^{-1}$] and decrease at a rate $d_s = 0.03$ [day$^{-1}$], which corresponds to the rate of cell death in all compartments, where $d = d_s \times S + d_I \times I + d_{R_L} \times R_L + d_{R_m} \times R_m$, with $d = g$. The difference in dynamics observed in Figure 2 is explained because the mutation involves lysis rates, lysis cell death rates and infection probabilities of susceptible cells. The reduction in susceptible cells is observed as the compartment of infected cells increases. The infection rate of cells depends on the lysis response of previously infected cells. Thus, in the absence of mutation the infection rate depends on $\kappa_L = 0.75$, whereas in the presence of mutation the contribution $\kappa_m = 0.8$ is added.

Figure 2. Dynamics of the system with the cell propagation of a viral infection with two possible lysis responses depending on the presence or absence of mutated virus. The values $\rho$ parameters are (a) $\rho = 1$; (b) $\rho = 0.75$; (c) $\rho = 0.5$; (d) $\rho = 0.1$. 

4
According to the above, infected cells go into transition rate from infected cell to cell in lysis response at a $\sigma = 2.4$ rate; a $\rho$ proportion of the infected cells enter a cell lysis response with an unmutated virus, while the remaining cells will go into a cell lysis response with a mutated virus. Infected cells decrease at a rate $d_I$ [day$^{-1}$] as a consequence of viral effects to biochemical and molecular changes caused during the viral replication cycle. Also, the probability of susceptible cell infection per cell in lysis response with the unmutated virus is $\beta_L = 10 \times 10^{-6}$ and with mutated virus $\beta_m = 20 \times 10^{-6}$.

When comparing the curves represented in Figure 2 of infected cells according to the values of $\rho$, it is shown that the lower the value of the mutated lysis response, the higher the maximum infected cell count and the earlier the day to reach it. Thus we went from a maximum infected cell count of approximately $2.736 \times 10^5$ cells at day 3 in Figure 2(a), to having $3.831 \times 10^5$ cells at day 1.91 as shown in Figure 2(d).

Likewise, a decrease is shown in the minimum number of susceptible cells reached and the number of days it takes to present, going from approximately $1.111 \times 10^4$ cells on day 4.4 in Figure 2(a), to around $4.088 \times 10^3$ on day 2.7 in Figure 2(d). A similar process is evident for Figures 2(c) and 2(d), noting that the proportion of the infected cells enter in the lysis response with and without mutation in Figure 2(c) is the same, thus the curves that represent tend to overlap.

4. Conclusions
It is shown that through mathematical modeling and simulation, different variations can be extrapolated by including new variables and parameters within the differential equations system. In this sense, the model proposed in this work has adjustable parameters, which makes it possible to study various contexts to interpretation for the uncertainty of the lysis response. The scenarios described in the simulations show the behavior of the cell lysis responses of susceptible cells that have been infected, this being an indicator of the intensity of the viral infection within the organism. Additionally, the model shows that an excessive response of lysis of the non-mutated virus, or of the mutation of the virus, leads to an increase in the approximate time to control the viral infection within the organism.

References
[1] Perelson A S 2002 Modelling viral and immune system dynamics Nature Reviews Immunology 2(1) 28
[2] Nowak M, May R M 2000 Virus Dynamics: Mathematical Principles of Immunology and Virology (United Kingdom: Oxford University Press)
[3] Ciupe S M, Heffernan J M 2017 In-host modeling Infectious Disease Modelling 2(2) 188
[4] Cuevas J M, Domingo-Calap P; Sanjuán R 2012 The fitness effects of synonymous mutations in DNA and RNA viruses Molecular Biology and Evolution 29(1) 17
[5] Chan J M, Carlson G, Rahaban R 2013 Topology of viral evolution Proceedings of the National Academy of Sciences ed Levine A J (New Jersey: Institute for Advanced Study)
[6] De Maio N, Walker C R, Turakhiya Y, Lanfear R, Corbett-Detig R, Goldman N 2021 Mutation rates and selection on synonymous mutations in SARS-CoV-2 Genome Biology and Evolution 13(5) evab087:1
[7] Drummond A J, Nicholls G K, Rodrigo A G, Solomon W 2002 Estimating mutation parameters, population history and genealogy simultaneously from temporally spaced sequence data Genetics 161(3) 1307
[8] Hernandez-Mejia G, Hernandez-Vargas E A 2020 When is SARS-CoV-2 in your shopping list? Mathematical Biosciences 328 108434
[9] Ferretti L, et al. 2020 Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing Science 368(6491) 1
[10] Linka K, Rahman P, Goriely A, Kuhl E 2020 Is it safe to lift COVID-19 travel bans? The newfoundland story Computational Mechanics 66(5) 1081
[11] Matrajt L, Leung T 2020 Evaluating the effectiveness of social distancing interventions to delay or flatten the epidemic curve of coronavirus disease Emerging Infectious Diseases 26(8) 1740
[12] Mccombs A, Kadell C 2020 A model-based evaluation of the efficacy of COVID-19 social distancing, testing and hospital triage policies PLoS Computational Biology 16(10) e1008388:1
[13] Lin Q, Zhao S, Gao D, Lou Y, Yang S, Musa S S, Wang M H, Cai Y, Wang W, Yang L, He D 2020 A conceptual model for the coronavirus disease 2019 (COVID-19) outbreak in Wuhan, China with individual reaction and governmental action International Journal of Infectious Diseases 93 211
[14] Ansumali S, Kaushal S, Kumar A, Prakash MK, Vidyasagar M 2020 Modelling a pandemic with asymptomatic patients, impact of lockdown and herd immunity, with applications to SARS-CoV-2 Annual Reviews in Control 50 432
[15] Wodarz D, Chan C N, Trinité B, Komarova N L, Levy D N 2014 On the laws of virus spread through cell populations Journal of Virology 88(22) 13240
[16] Wang S, Pan Y, Wang Q, Miao H, Brown A N, Rong L 2020 Modeling the viral dynamics of SARS-CoV-2 infection Mathematical Biosciences 328 108438
[17] Hernández-Vargas E A, Velasco-Hernandez J X 2020 In-host mathematical modelling of COVID-19 in humans Annual Reviews in Control 50 448
[18] Blanco-Rodríguez R, Du X, Hernández-Vargas E 2021 Computational simulations to dissect the cell immune response dynamics for severe and critical cases of SARS-CoV-2 infection Computer Methods and Programs in Biomedicine 211 106412
[19] Fresnadillo Martínez M J, García-Sánchez E, García-Merino E, del Rey A M, García-Sánchez J E 2013 Modelización matemática de la propagación de enfermedades infecciosas: de dónde venimos y hacia dónde vamos Revista Española de Quimioterapia 26(2) 81
[20] Zitzmann C, Kaderali L 2018 Mathematical analysis of viral replication dynamics and antiviral treatment strategies: from basic models to age-based multi-scale modeling Frontiers in Microbiology 9 1546
[21] Hui D S, I Azhar E, Madani T A, Ntoumi F, Kock R, Dar O, Zumla A 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 91 264
[22] Andrades-Grassi J E, Cuesta-Herrera L, Bianchi-Pérez G, Grassi H C, López-Hernández J Y, Torres-Martilla H 2021 Spatial analysis of risk of morbidity and mortality by COVID-19 in Europe and the Mediterranean in the year 2020 Cuadernos Geográficos 60(1) 279
[23] Almocera A E S, Quiroz G, Hernández-Vargas E A 2021 Stability analysis in Covid-19 within-host model with immune response Communications in Nonlinear Science and Numerical Simulation 95 105584
[24] Tyrrell D A, Myint S H 1996 Medical Microbiology: Coronaviruses (Galveston: University of Texas Medical Branch at Galveston)
[25] Cano F, Gajardo M, Freundlich M 2020 Eje renina angiotensina, enzima convertidora de angiotensina 2 y coronavirus Revista Chilena de Pediatría 91(3) 330
[26] Walsh K A, et al. 2020 SARS-CoV-2 detection, viral load and infectivity over the course of an infection Journal of Infection 81 357
[27] Wölfel R, et al. 2020 Virological assessment of hospitalized patients with COVID-2019 Nature 581 465
[28] Laferl H, et al. 2021 An approach to lifting self-isolation for health care workers with prolonged shedding of SARS-CoV-2 RNA Infection 49(1) 95
[29] Singanayagam A, et al. 2020 Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19; England, January to May 2020 Eurosurveillance 25(32) 2001483
[30] Sohn Y, et al. 2020 Assessing viral shedding and Infectivity of asymptomatic or mildly symptomatic patients with COVID-19 in a later phase Journal of Clinical Medicine 9(9) 2924
[31] Rhee C, Kanjilal S, Baker M, Klompas M 2020 Duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectivity: when is it safe to discontinue isolation? Clinical Infectious Diseases 72(8) 1467
[32] To K KW, et al. 2020 Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study The Lancet Infectious Diseases 20(5) 565
[33] Van Kampen J, et al. 2021 Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (Covid-19) Nature Communications 12(1) 267
[34] Kim M C, Cui C, Shin K R, Bae J Y, Kweon O J, Lee M K, Choi S H, Jung S Y, Park M S, Chung J W 2021 Duration of culturable SARS-CoV-2 in hospitalized patients with Covid-19 The New England Journal of Medicine 384(7) 671