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MODELING AND SIMULATION OF THE SARS-COV-2 LUNG INFECTION AND IMMUNE RESPONSE WITH CELL-DEVS

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ABSTRACT

Understanding why patients' viral loads vary dramatically across individuals is a critical challenge in addressing respiratory infections, especially the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The spatial-temporal dynamics of viral infection in the respiratory system and the immune system's response remain difficult to study. Using modelling and simulation (M&S) techniques may address this problem. In this paper, we present a novel modelling approach using the Cell-DEVS formalism (a combination of Cellular Automata and DEVS), to simulate the spatial-temporal dynamics of viral spread in the lungs. Using a two-dimensional cellular space that mimics a lung, the proposed approach focuses also on the immune system response, viral infection spread, state of lung epithelial tissue damage, and immune cells' state. We demonstrate the pertinence of our proposal on three different scenarios representing three types of patients. Qualitative evaluation by expert biologists confirms that the produced simulations match the observations made on patients.

1 INTRODUCTION

Respiratory viral infections (RVIs) are infections of parts of the body involved in breathing, such as the sinuses, throat, airways, or lungs. These infections are the leading cause of disease and mortality (Troy and Bosco 2016). They have always been a subject of major interest in various disciplines, but their importance has increased in recent years. With the Coronavirus Disease 2019 (Covid-19) pandemic, we have seen how an RVI can have a devastating impact on human health, economy, and society as a whole.

RVIs are studied in many disciplines, including medicine, virology, epidemiology, molecular biology, and computer science. These disciplines work together to understand the nature of RVIs, how they spread, and how they can be prevented or treated. However, the mechanisms that determine why some individuals suffer from severe illness whilst others do are not well understood (Troy and Bosco 2016).

Mathematical and computational modeling, along with simulation techniques, play a crucial role in understanding and combating respiratory viral infections (RVIs) such as Covid-19. These tools contribute to the design of efficient strategies for controlling the pandemic, predicting the effectiveness of antiviral treatments, studying infection dynamics, and comprehending viral transmission mechanisms. By modeling the intricate behaviors of viruses, their interactions with host cells, and the immune response, simulation

tools provide valuable insights, particularly from a spatio-temporal perspective, aiding in the advancement of RVI research and intervention strategies (Bernhauerová et al. 2021).

SARS-CoV-2 primarily targets the epithelium in the respiratory tracts as well as other cells within organs such as the lungs, heart, and vasculature (Ashraf et al. 2021). The immune system plays a crucial role in combating this viral infection by recognizing the virus through pattern recognition receptors and initiating the release of inflammatory molecules that facilitate viral elimination. Enhancing our understanding of the mechanisms underlying SARS-CoV-2 propagation in the respiratory system and the immune response can contribute to the development of targeted therapeutic interventions to mitigate the adverse effects of respiratory viral infections.

Thus, there is an urgent need for understanding the (i) SARS-CoV-2 replication and its interaction with host cells, and (ii) how it spreads in the different tissues and cellular hosts. We already addressed the first challenge in our previous works (Ayadi et al. 2021) by developing a DEVS-based approach for modeling and simulation of the SARS-CoV-2 life cycle, from entry to release, and studying its behavior at each stage of its replication process. While this paper will focus on the second objective.

In this study, we introduce a novel modeling approach utilizing the Cell-DEVS formalism (Ameghino et al. 2001), which combines Cellular Automata and DEVS, to simulate the spatial-temporal dynamics of viral spread in the lungs. The model incorporates the immune system response, viral infection spread, lung epithelial tissue damage, and immune cell activation within a two-dimensional cellular space representing a small lung. Implemented using the CD++ toolkit, a tool built to implement DEVS and Cell- DEVS models (Wainer 2022), the Cell-DEVS model leverages a specification language to define cell behavior, including computing functions and delays, as well as the coupled model's configuration and initial conditions. Through three distinct scenarios representing different patient types, namely weak immune system with low viral load, strong immune system with low viral load, and strong immune system with high viral load, we demonstrate the relevance of our simulation approach. These case studies shed light on the significant variability in viral loads observed among SARS-CoV-2 patients and showcase the potential of our model to address crucial questions related to infection dynamics.

2 BACKGROUND AND RELATED WORKS

2.1 Background

As depicted by Figure 1, the SARS-CoV-2 virus hijacks the respiratory system through the angiotensin-converting enzyme 2 (ACE2) receptors on the surface of the pulmonary alveolar epithelium (transition 1 in Figure 1) and causes pulmonary infections that result in Covid-19 (Diamond and Kanneganti 2022). At that time, the state of the epithelial lung cell moved from a healthy, uninfected cell to an infected one (transition 2). It then enters the epithelial cell and releases its RNA genome, which is used to produce viral proteins and replicate the viral genome (Ayadi et al. 2021). The new viral proteins and genomes are assembled into new virus particles, which are then released from the host cell (transitions 4a and 4b) until it is cleared (transition 6) and can infect other cells and starts their spread in the epithelial tissue (transition 5) (Ayadi et al. 2021). Throughout this life cycle, the virus can be transmitted between individuals through respiratory droplets or contact with contaminated surfaces (Kumar et al. 2020).

When the immune system detects SARS-CoV-2 particles, it launches an immune response to fight the virus. The innate immune system is the first line of defense (transitions 2a and 3a). Immune cells forming the innate immune system such as macrophages, dendritic cells, and natural killer cells are activated (transitions 2a and 3a) (Moses et al. 2021) and then release cytokines, small proteins that are secreted by immune cells, in response to the viral infection. They have the capacity to recognize the virus and trigger a response to neutralize it. Cytokines play a key role in regulating the immune response and act as messengers to signal other immune cells to respond to the threat. Thus, they recruit innate and adaptive immune cells, such as macrophages, dendritic cells, T cells, B cells, and NK cells, leading to a self-amplifying inflammatory cascade in a positive feedback loop manner (transition 8). For example, B-cells produce antibodies that

bind to the virus and prevent it from infecting cells, while T-cells can recognize and kill infected cells, which helps to prevent the virus from spreading (transitions 9 and 10). For the sake of simplicity, in this study, we will not address the different types of immune cells, and the different pro-inflammatory molecules secreted by these cells. We will only talk about immune cells and cytokines.

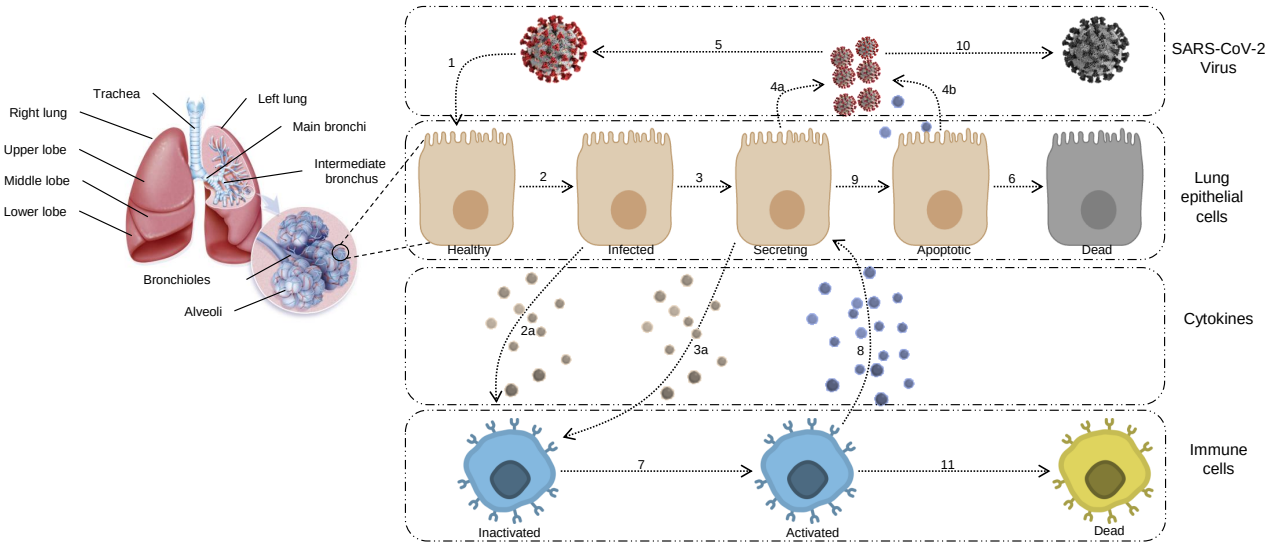

Figure 1: Anatomy of the respiratory system and the interactions among of epithelial lung cells, immune cells, virus and cytokines (inspired from (Moses et al. 2021)).

2.2 Related works

While there are many simulation models developed at an epidemiological level for analyzing the transmission of SARS-CoV-2 among populations, there are too few models at within-host level addressing the SARS-CoV-2 spread in cells, and the immune system response (Hernandez-Vargas and Velasco-Hernandez 2020).

Most prior work uses mathematical models to represent within-host virus dynamics. Chowdhury et al. (2022) analyze the interaction between SARS-CoV-2 and the immune system by considering the role of natural killer cells and T-cell. Li et al. (2020) develop a viral dynamic model to analyze the SARS-CoV-2 kinetics in host cells, using the chest radiograph score (Au-Yong et al. 2022). Carruthers et al. (2022) propose a within-host model, describing viral dynamics in the upper respiratory tract of individuals. Nath et al. (2021) develop a model, focusing on the properties of the model, such as non-negativity of solutions. Other mathematical models (Davies et al. 2020; Ferretti et al. 2020; Kyrychko et al. 2020) focused on the viral spread and involved pharmacological interventions to reduce the infection.

These models are useful for studying the duration of the incubation period (Nath et al. 2021) and the impact of therapeutics given at different times (Mahesh et al. 2022; Chatterjee et al. 2022). However, they have limited ability to fully account for dynamics in the large and complex structure of the lung (Sadria and Layton 2021; Quirouette et al. 2020), as they did not consider the scalable and spatial-temporal effects of viral spread and immune response in determining the time course of viral load within patients. Additionally, the non-spatiotemporal aspect of these models assume that the distribution of the modelled quantities are uniformly distributed in space and time (Sego et al. 2020), an assumption that might not be realistic in solid tissues, where viruses and host immune cells are not usually distributed homogeneously.

Other agent-based model have been proposed to address this spatio-temporal aspect. (Moses et al. 2021) develop the SIMCoV tool that replicates the viral growth dynamics observed in patients and shows how spatially dispersed infections can lead to increased viral loads in a 2D layer of epithelial cells. Sego

et al. (2020) propose a very useful open-source platform for multiscale spatio-temporal simulation of an epithelial tissue, viral infection, cellular immune response, tissue damage, and the impact of treatments.

To address the spread of, and response to, the SARS-CoV-2 viral infection, we start by developing a Discrete-Event Modelling and Simulation-based approach for modeling and simulation of the SARS-CoV-2 life cycle, from entry to release, and study its behavior at each stage of its replication process. The proposed model benefits from the advantages of formalism as its rigorous formal definition, and its support for modular composition. However, it does not consider the spatio-temporal effects of the viral infection in an epithelial tissue, and cellular immune response. In this paper, we extend these works to consider the spatial-temporal dynamics of viral spread in the lungs using the Cell-DEVS formalism.

3 PROPOSED CELL-DEVS SIMULATION MODELLING

The choice of a Cell-DEVS simulation model for simulating the dynamic behavior of the SARS-CoV-2 is justified by its advantages over other simulation models. By discretizing time and events, the proposed model captures the stochastic nature of viral replication, immune responses, and cell state changes, offering a more realistic representation of the complex dynamics of virus-host interactions. Furthermore, the cellular automata framework allows for the explicit modeling of spatial aspects within lung tissue, facilitating the understanding of the viral local behaviors, its spatial propagation, and tissue damage. In contrast to continuous mathematical models like differential equations, the discrete-event simulation model better captures the discrete nature of viral infections and incorporates various biological factors and events occurring at different time scales. This choice ensures a comprehensive analysis of COVID virus progression, integrating detailed spatial and temporal dynamics to provide valuable insights that could complement other simulation approaches. The proposed Cell-DEVS simulation model uses a series of interlinked multi-layer models that draw upon the biological background presented in section 2.1. It includes epithelial cell status, immune cell status, as well as cytokine and virus concentrations, all of which are intricately connected for understanding the SARS-CoV-2 lung infection and immune response. Such model allows visualizing the propagation of the virus within lung tissue, the damage to epithelial cells, and the corresponding reaction of the immune system to this viral infection.

In our multiscale model, cells are divided into two broad groups, epithelial and immune cells. Each one has its proper characteristics and how it interacts with the other components of the model. The specific interactions (resp. biological processes) of these cells are also defined for each one to describe its function, depending on its state. Epithelial cells can have one of four types healthy, infected, virus-releasing and dead. While immune cells can be inactivated or activated. For each cell's state, an identifier is associated. Both cells change according to their inputs, which arise from specific components of the model. Depending on the type of input, a specific biological process will occur. These biological processes are defined in the model and ensure the passage of cells from their initial states to another specific state. When cells (epithelial or immune) or viruses are dead, they are inactive.

As well, a particular cell function (corresponding to a biological process) was defined for each epithelial cell. These cell functions, corresponding to the transitions 2, 3, 6, and 9 in Figure 1 define the cells' state. To define the viral entry, we define a function that assigns the epithelial cell with a probability of engrossing viral particles from the total concentration of SARS-CoV-2 viral particles present in the extracellular environment, according to the number of ACE2 receptors in the epithelial cell surface and the connection between them. The viral particles absorbed by the cells are subtracted from the extracellular environment. Once infected, the epithelial cells stop absorbing viral particles. The viral replication described by transition 3 is defined by a simple generic formula including a viral replication parameter. Internal viral replication processes such as cell's metabolism, number of ribosomes cell's metabolism, ... were not considered in this study. The viral secreting biological function corresponding to transition 9 was also defined by a simple formula, producing viral particles in the extracellular environment. The secreted virions are added to the total amount of viral particles in the cells' extracellular environment. The duration of the incubation phase (time between virus entry and release of virions) of an epithelial-infected single-cell was also defined. A formula was also defined

to perform both virally-induced apoptosis of a secretory cell due to the number of intracellular viral particles and the cell death due to oxidizing cytotoxicity due to the concentration of cytokines (transition 6). We also consider that a part of the secreted viral particles are damaged by the immune responses and therefore become inactivated in dead state (transition 10). The rule of virus spread can be written in CD++ as follows:

```
{~virus := $vi; ~virus_movement := $vim;}//Output
{ $vim := if(round($vi*0.8) &gt; 0, round($vi*0.8), 0);
$vir :=round(((1,0,0)~virus_movement + (-1,0,0)~virus_movement

+ (0,1,0)~virus_movement + (0,-1,0)~virus_movement)/4);
$vi := max(0,$vi + round((0,0,1)~virion/4 - $vi*(0,0,1)~uptake_rate) - $vim +
$vir);}//Postcondition
250//Delay
```

The total number of immune cells is constant. These cells are by default inactivated. Their activation depends on the amount of absorbed cytokines. Once triggered by cytokines (transition 2a and 3a), they move to the activated cells and secrete in turn cytokines (transition 8). After a long cytokine secretion, they become dead and are no longer active (transition 11). The propagation cytokines rule can be written in CD++ as follows:

```
{~cytokine_secreting := $cs; ~cytokine_movement := $cm;}//Output
{ $cm := if( round($cs*0.9) &gt; 0, round($cs*0.9), 0);
$cr:=round(((1,0,0)~cytokine_movement+(-1,0,0)~cytokine_movement
(0,1,0)~cytokine_movement + (0,-1,0)~cytokine_movement)/4);
$cs := $cs + round((0,0,-1)~immune_signal +((0,0,1)~immune_signal ))*0.7*1000 -
$cm + $cr - $cs*((0,0,1)~uptake_rate + if((0,0,-1)~state &gt; 0,0.1,0));
}//Postcondition
250//Delay
```

Table 1 presents the values of the baseline parameter set for the proposed model. The source code of the proposed models and instructions on how to run them are provided in our publicly available repository.

Table 1: Main parameter values.

Parameter	**Value**	**Description**
Dimension of epithelial tissue	50 x 50	A 2D cellular space that mimics a lung, with 50 by 50 cells.
Virion released	1-100	Number of virions secreted by an epithelial cell.
Cytokines secreted by infected cells	1	Concentration of cytokines secreted by infected/secretory cells.
Cytokines secreted by immune cell	1.2	Concentration of cytokines secreted by activated immune cells.
Virus attached to ACE2 receptor	20%	Percentage of virus that ACE2 receptors in the epithelial cell surface.
Virus moves spread	80%	Migration rate of viruses within the epithelial tissue.
Virus absorbed by cells	10%	Percentage of viruses will enter the epithelial cells.
Cytokine attached to cell's surface	10%	Percentage of cytokines that hijack infected cells.
Cytokine moves to neighbor's cell	90%	Percentage of the cytokine transport among cells.
Cytokines absorbed by cells	10%	Percentage of cytokines attached to secreted/infected cells.
Virion release time	20 hours	Duration of viral secretion of secretory cells.
Anti-virus time	8 hours	Duration of epithelial cells in the non-secresecreting state.
Cytokine release time	8 hours	Duration of cytokines secretion of immune cells.
Immune cell activation time	10 hours	Duration of an immune cell in active state.

4 CASE STUDIES

4.1 Simulation Scenarios

To demonstrate the versatility of our simulation model, we conducted experiments across different case studies representing various categories of patients. For sake of space, we present here three specific types of patients, the selection was made in collaboration with biological experts to showcase the diversity of outcomes within different immune system states. These three scenarios are suitable for observing the spatial-temporal dynamics of viral propagation in the respiratory system and the immune system's response to the viral infection in three categories of patients, as follows:

1. *Patients with a weak immune system and exposed to low viral loads*:
   In the first scenario, we simulate patients with a weak immune system and low viral loads. Due to the compromised immune response, minimizing the concentration of cytokines is crucial. This scenario promotes accelerated viral spread and replication within the lung tissue, leading to a higher number of infected epithelial cells and increased release of virions. The infection initiates from a single epithelial cell, allowing the virus to propagate rapidly and cause extensive tissue damage, ultimately resulting in the destruction of all cells within the lung tissue.
2. *Patients with a strong immune system and exposed to low viral loads*:
   This scenario concerns patients with a strong immune system and low viral loads. In contrast to the first scenario, a significant quantity of cytokines will be produced by the immune cells. These cytokines will aim to bind to the infected epithelial cells, leading to their elimination and hindering viral replication and diffusion. The infection will originate from a single epithelial cell, resulting in a slow and sparse viral spread. As a consequence, minimal damage is expected to occur to the epithelial cells in this scenario.
3. *Patients with a strong immune system and exposed to high viral loads*:
   The last scenario involves patients with a strong immune system and high viral loads. In contrast to the previous scenarios, the virus infects eighteen cells scattered in the epithelial tissue at the onset. To impede viral replication and clustering, the immune cells in this scenario secrete a high concentration of cytokines. Consequently, the simulation of this scenario is anticipated to show a gradual viral spread with low density, despite the initial high viral exposure. The resulting damage is expected to be minimal, similar to that observed in the second scenario.

4.2 Simulation results

4.2.1 Scenario 1

The simulation of the SARS-CoV-2 viral infection progression in an epithelial tissue of size 50 x 50 cells starting from a single infected cell, corresponding to the scenario 1, is shown in Figure 2. In the initial stages, a single infected epithelial cell releases extracellular viruses and contaminates neighboring cells, triggering the activation of immune cells and the rapid release of cytokines. The virus spreads to adjacent cells, leading to virus-induced death of epithelial cells and immune cell activation. After 1500 minutes, the infection expands to the superior lobes of both lungs, accompanied by high cytokine concentration. By 3000 minutes, the viral infection extends to the middle lobe, with a notable concentration of the virus attributed to secretory epithelial cells. After 4500 minutes, most epithelial cells in the inferior lobes have died or are infected, while the virus has spread throughout the lung tissue mainly in the inferior lobes. Cytokines are shifting from upper to lower lobes. By 6000 minutes, all epithelial cells have died except for one immune cell. The virus has spread throughout the lung tissue at a low concentration, with cytokines still concentrated in the lower lobes. A video of this simulation can be viewed at link.

Furthermore, a Python script was developed to obtain the results of the simulation for each of the analyzed features, such as the state and number of epithelial cells, number of activated immune cells, concentration of cytokines, and viral load. The results are saved in a log file at the end of the scenario

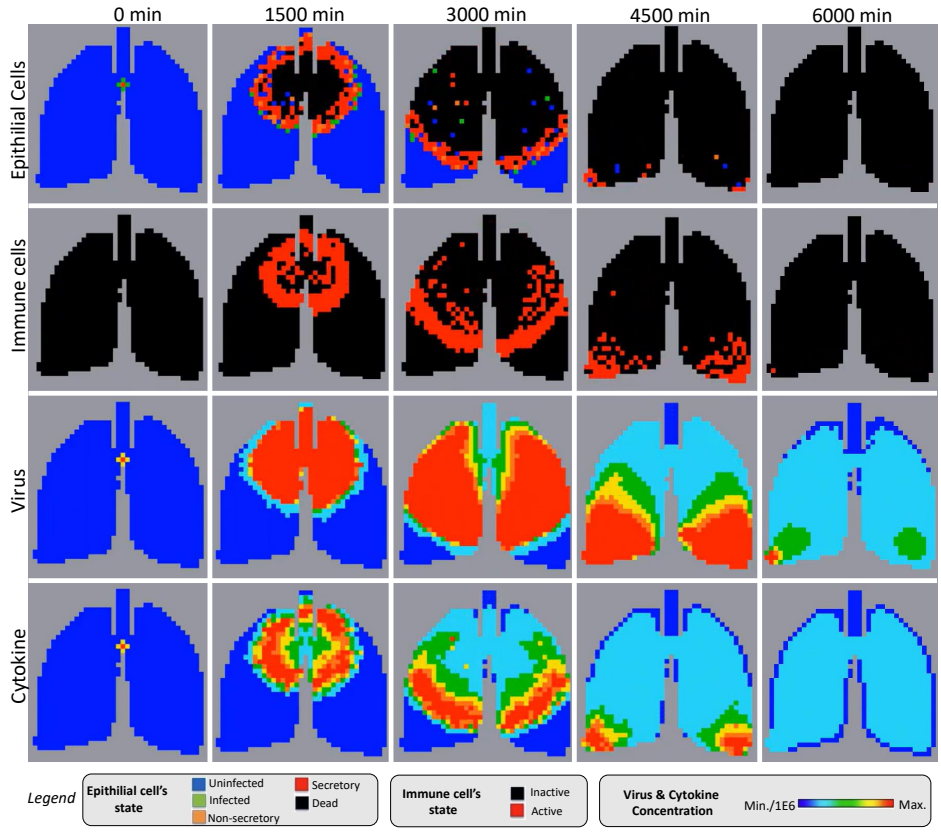

Figure 2: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 1.

simulation, and an evolving curve is generated, such as in Figure 3. Figure 3.A presents the number of healthy or uninfected (blue), infected (orange), secreting or virus-releasing (green), non-secreting (red) and dead (purple) epithelial cells over the simulation time in minutes. As depicted in the figure 3, it can be observed that after approximately 6000 minutes, all the epithelial cells transitioned from an uninfected state to dead. During the time frame of 2000–3000 minutes, the epithelial cells were most heavily infected with the virus. By observing the two lines representing the number of cells in secreting and non-secreting states, it becomes clear that the majority of infected cells are incapable of resisting the virus and generating virions for export. Figure 3.B displays the activation of immune cells over the simulation time in minutes. The graph shows a rapid increase in the number of activated cells from the onset of the infection, reaching a peak at around 2200 minutes, followed by a gradual decrease until the number of activated cells becomes null. The activation of immune cells is directly proportional to the number of infected cells and the viral concentration, indicating that they are the first cells to sense the danger signals from the infected epithelial cells or the presence of the infectious agent. Furthermore, the cytokine quantification curve shown in Figure 3.C can be explained by the activation of immune cells. The curve closely resembles the activation curve shown in Figure 3.B, with a slight shift. This activation leads to the release of cytokines into the extracellular environment, which can recruit circulating cells, eliminate the pathogen, and repair the lesion. Figure 3.D shows the evolution of the viral load concentration during the simulation time. We note that the curve of the viral load exhibit a remarkable similarity with the curve of the cytokine concentration, with a slight difference. Although they are not directly related, this similarity can be explained by their homologous relationship with epithelial cells in the secreting state. The viral load in the extracellular environment depends on the number of epithelial cells in the secreting state, while the extracellular cytokine concentration is dependent on the number of cells in the infected, secreting, and non-secreting states. Since most infected

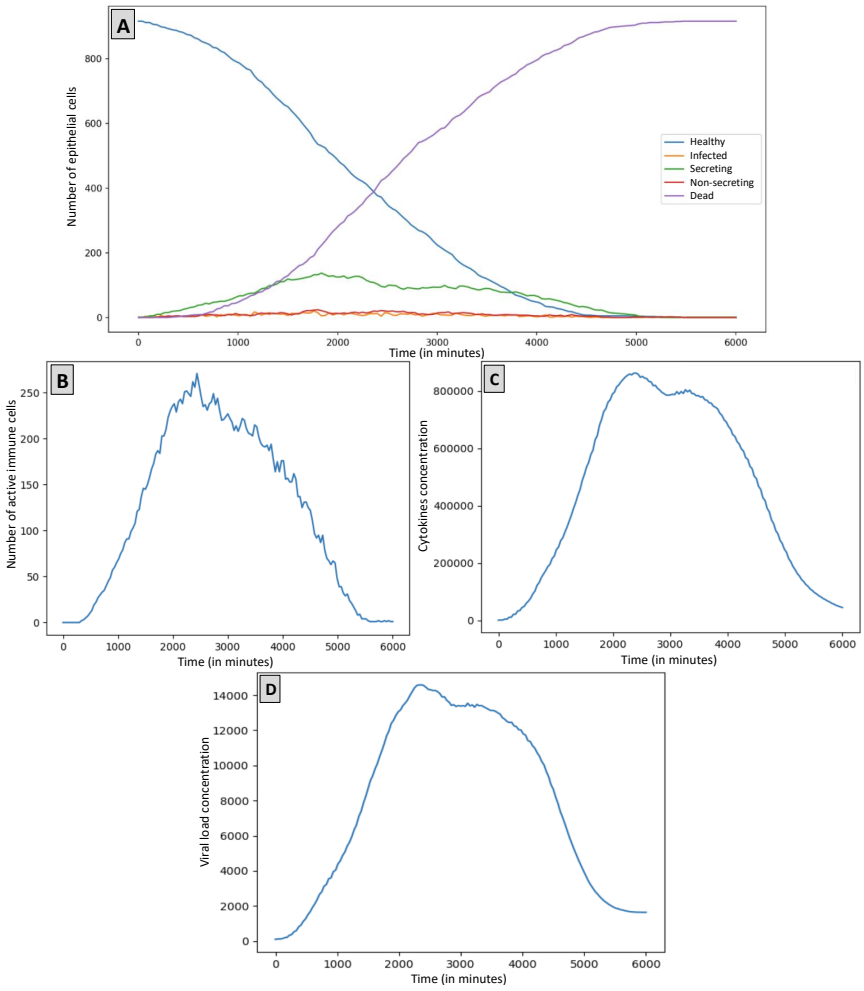

Figure 3: Simulation time series corresponding to the scenario 1.

cells quickly switch to the secreting state, it can be inferred that the number of cytokines largely depends on the number of epithelial cells in the secreting state.

4.2.2 Scenario 2

Figure 4 depicts the simulation of SARS-CoV-2 viral infection progression in a 50 x 50 epithelial tissue, focusing on scenario 2. A single infected epithelial cell releases extracellular viruses, which infect neighboring cells. Activation of immune cells results in the rapid release of cytokines. At 1500 minutes, the virus spreads to the main bronchi, accompanied by deceased surrounding epithelial cells. By 3000 minutes, viral spread remains limited, with reduced immune cell activation and cytokine concentration. At 4500 minutes, the initially infected region near the main bronchi dies off, leaving the rest of the lung tissue healthy and uninfected. The viral load is minimal, and cytokine concentration continues to decrease. A video of this simulation can be viewed at link.

For sake of space, we do not include the temporal series figure corresponding to Scenario 2, but you can access it at this link. By analyzing the Figure A (here), it appears that the number of epithelial cells that died during the first stage of the infection remained relatively stable at around 1000 cells throughout the simulation. The reason for this can be observed from Figure B (here), which displays the number of activated immune cells throughout the simulation. The number of activated immune cells increases rapidly

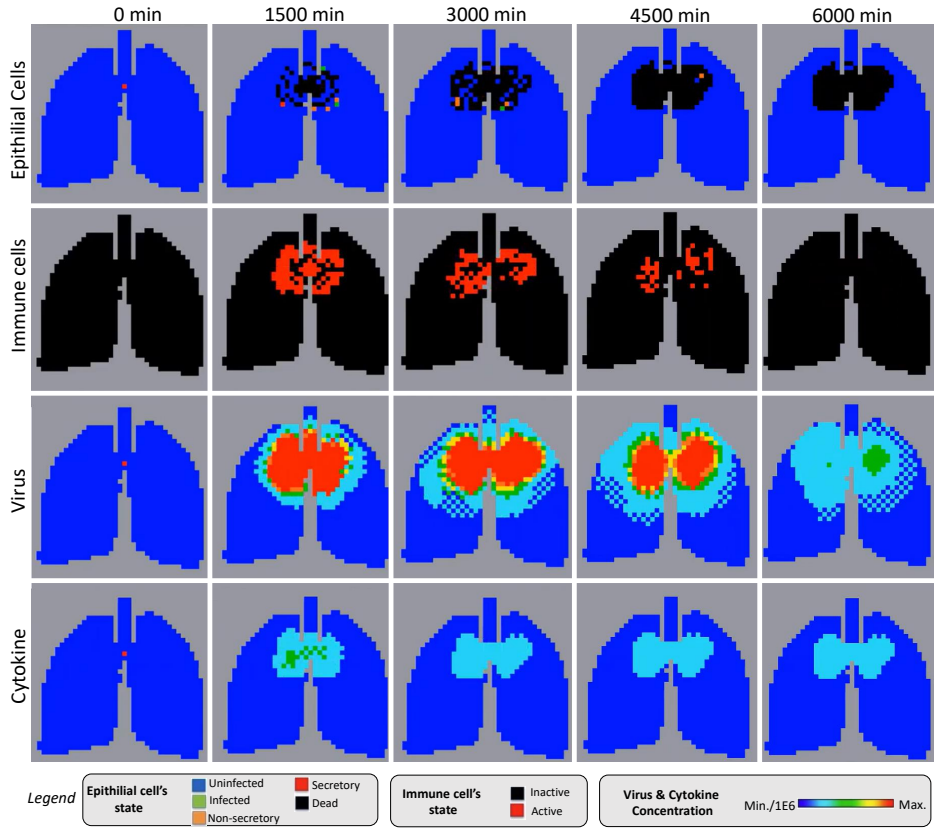

Figure 4: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 2.

from the start of the infection until around 2200 minutes, at which point it reaches its peak. After that, the number of activated cells remains stable but slightly elevated until 4000 minutes, when it begins to decline gradually until there are no more active immune cells at the end of the simulation. Compared to scenario 1, the curve in Figure C (here) depicts a notably high concentration of cytokines, which significantly inhibited the viral infection and mitigated the damage to the epithelial tissue. This effect is also evident in the viral load curve (Figure D, here), which displays an initial peak followed by a sharp decline, possibly due to the high cytokine concentration.

4.2.3 Scenario 3

Figure 5 presents the simulation of the SARS-CoV-2 viral infection progression in an epithelial tissue of size 50 x 50 cells starting from a single infected cell, corresponding to the scenario 3. For this scenario, we selected patients with a robust immune system, but they were exposed to a high viral load at the beginning. The simulation in Figure 5 demonstrates the progression of SARS-CoV-2 viral infection in an epithelial tissue of size 50 x 50 cells, focusing on the scenario with multiple initial infected cells. After an incubation period, infected cells release viruses, leading to a secretory state. Virions spread to neighboring cells, prompting a significant release of cytokines. Around 1500 minutes, the virus reaches the main bronchi, causing the death of surrounding epithelial cells. At 3000 minutes, the infection plateaus, with a slightly higher viral load but similar to that observed at 1500 minutes. The distribution of activated immune cells aligns with the deceased epithelial cells, particularly near the main bronchus. By 4500 minutes, the majority of the bronchial epithelial cells affected by the virus had died, leaving the remaining lung tissue healthy and virus-free. The number of activated immune cells decreased gradually as cytokine distribution decreased, and the viral load continued to decrease. At the end of the simulation, the viral infection ceased to spread

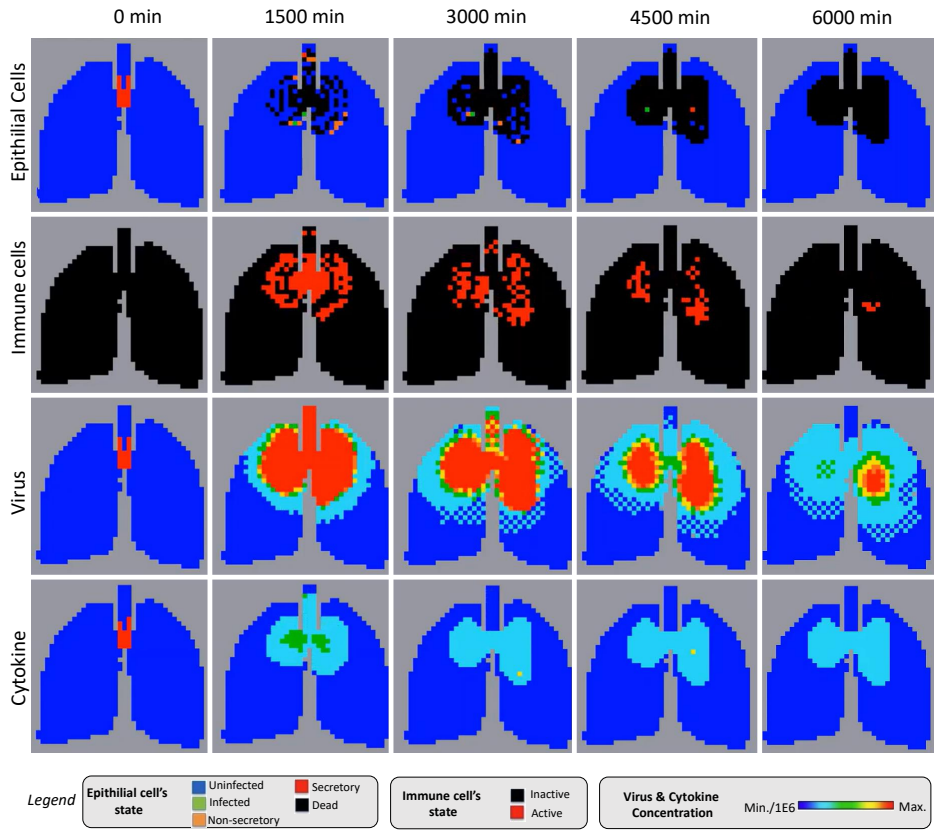

Figure 5: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 3.

entirely, with the damage to the epithelial cells being restricted to the infected region, resulting in most of the epithelial cells dying. There were no further activated immune cells, and the viral load dwindled until it was almost nonexistent, while the cytokine concentration continued to drop rapidly. A video of this simulation can be viewed at this link.

Due to space limitations, we are unable to include the temporal series figure for Scenario 3 in this paper. However, you can access it at the provided link link. In terms of the state of epithelial cells (Figure A, here), Scenario 3 exhibits similarities to Scenario 2, with a slightly higher number of infected cells. However, the number of dead cells is three times greater than in Scenario 2. In Figure B (here), the number of immune cells rapidly increases until around 1900 minutes, reaching a peak and then stabilizing at a slightly higher plateau compared to Scenario 2. The concentration of cytokines gradually decreases starting at 5700 minutes. Similar to Scenario 2, Figure C (here) demonstrates a significant concentration of cytokines that effectively inhibits viral infection and reduces damage to the epithelial tissue. This effect is also reflected in the viral load curve (Figure D, here), which shows an initial peak followed by a sharp decline, potentially due to the high cytokine concentration.

5 CONCLUSION AND FUTURE WORK

In this paper, we present a Cell-DEVS model to simulate the spread of SARS-CoV-2 in lung epithelial cells. This model integrates different biological components including viral replication, immune system response to the viral infection through the immune cells and their secreted cytokine molecules, and cellular epithelial tissue damage in both time and space. While this simulation model did not employ real parameters, it could allow biologists to observe the spread of the virus in lung tissue, the destruction of epithelial cells, and the body's response to the virus. The proposed simulation model could hold great potential for helping

virologists, biologists and clinical researchers in making more informed decisions. Virologists and biologists can leverage the model to gain deeper insights into the intricate dynamics of viral load and its impact on lung tissue at different stages of infection. By manipulating various parameters within the simulation, such as viral replication rates or immune response strength, researchers can explore hypothetical scenarios, enabling them to study the effects of potential treatment strategies or viral mutations. Additionally, ICU doctors can benefit from the model's ability to predict patient-specific outcomes by integrating individualized and real clinical data. They can use the simulation results to evaluate the effectiveness of different ventilation strategies to maximize patient recovery while minimizing complications. Overall, this proposed model could offer a valuable tool for these professionals, enabling them to make decisions.

While our simulation model serves as a valuable tool for studying the dynamics of lung infection caused by SARS-CoV-2, its current usage is primarily for demonstration and research purposes. It provides insights into viral dynamics and aids in the development and evaluation of potential treatment strategies, but it does not have real-time monitoring capabilities or the ability to act on the lung infection evolution of actual patients. It does not serve as a reference tool for clinicians, as it has not been validated on real data. It should be regarded as an approximation tool developed in collaboration with expert biologists, who have qualitatively validated its plausibility. It is important to note that the model does not possess the necessary validation or regulatory approvals for clinical use.

As mentioned earlier, we already worked on the modeling of the SARS-CoV-2 life cycle, from entry to release, and study its behavior at each replication process stage (Ayadi et al. 2021). A future perspective would be to explicitly incorporate these works within the proposed simulation model to quantify the different molecules produced at each stage according to the spatio-temporal evolution of the virus. Furthermore, extending our model to include treatments would be useful to study their impact on the viral progression.

CODE AVAILABILITY

The source code of these proposed simulations and the instructions on how to run them are provided in our publicly available repository at https://github.com/AliAyadi/SARS-COV-2_LUNG_INFECTION.

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REFERENCES

Ameghino, J., A. Troccoli, and G. Wainer. 2001. "Models of Complex Physical Systems Using Cell-DEVS". In *Proceedings. 34th Annual Simulation Symposium*, 266–273: Institute of Electrical and Electronics Engineers, Inc.

Ashraf, U. M., A. A. Abokor, J. M. Edwards, E. W. Waigi, R. S. Royfman, S. A.-M. Hasan, K. B. Smedlund, A. M. G. Hardy, R. Chakravarti, and L. G. Koch. 2021. "SARS-CoV-2, ACE2 Expression, and Systemic Organ Invasion". *Physiological Genomics* 53(2):51–60.

Au-Yong, I., Y. Higashi, E. Giannotti, A. Fogarty, J. R. Morling, M. Grainge, A. Race, I. Juurlink, M. Simmonds, S. Briggs et al. 2022. "Chest Radiograph Scoring Alone or Combined With Other Risk Scores for Predicting Outcomes in COVID-19". *Radiology* 302(2):460–469.

Ayadi, A., C. Frydman, W. Laddada, L. F. Soualmia, C. Zanni-Merk, E. Grellet, and I. Imbert. 2021. "Combining DEVS and Semantic Technologies for Modeling the SARS-CoV-2 Replication Machinery". In *2021 Annual Modeling and Simulation Conference (ANNSIM)*, 1–12: Institute of Electrical and Electronics Engineers, Inc.

Bernhauerová, V., B. Lisowski, V. V. Rezelj, and M. Vignuzzi. 2021. "Mathematical Modelling of SARS-CoV-2 Infection of Human and Animal Host Cells Reveals Differences in the Infection Rates and Delays in Viral Particle Production by Infected Cells". *Journal of Theoretical Biology* 531:110895.

Carruthers, J., J. Xu, T. J. R. Finnie, and I. Hall. 2022. "A Within-Host Model of SARS-CoV-2 Infection". *medRxiv*:2022–04.

Chatterjee, A. N., F. A. Basir, D. Biswas, and T. Abraha. 2022. "Global Dynamics of SARS-CoV-2 Infection with Antibody Response and the Impact of Impulsive Drug Therapy". *Vaccines* 10(11):1846.

Chowdhury, S., J. Chowdhury, S. F. Ahmed, P. Agarwal, I. A. Badruddin, S. Kamangar et al. 2022. "Mathematical Modelling of COVID-19 Disease Dynamics: Interaction Between Immune System and SARS-CoV-2 Within Host". *AIMS Mathematics* 7(2):2618–2633.

Davies, N. G., A. J. Kucharski, R. M. Eggo, A. Gimma, W. J. Edmunds, T. Jombart, K. O'Reilly, A. Endo, J. Hellewell, E. S. Nightingale et al. 2020. "Effects of Non-Pharmaceutical Interventions on COVID-19 Cases, Deaths, and Demand for Hospital Services in the UK: a Modelling Study". *The Lancet Public Health* 5(7):e375–e385.

Diamond, M. S., and T.-D. Kanneganti. 2022. "Innate Immunity: the First Line of Defense Against SARS-CoV-2". *Nature Immunology* 23(2):165–176.

Ferretti, L., C. Wymant, M. Kendall, L. Zhao, A. Nurtay, L. Abeler-Dörner, M. Parker, D. Bonsall, and C. Fraser. 2020. "Quantifying SARS-CoV-2 Transmission Suggests Epidemic Control With Digital Contact Tracing". *Science* 368(6491):eabb6936.

Hernandez-Vargas, E. A., and J. X. Velasco-Hernandez. 2020. "In-Host Mathematical Modelling of COVID-19 in Humans". *Annual Reviews in Control* 50:448–456.

Kumar, S., R. Nyodu, V. K. Maurya, and S. K. Saxena. 2020. "Host Immune Response and Immunobiology of Human SARS-CoV-2 Infection". *Coronavirus Disease 2019 (COVID-19) Epidemiology, Pathogenesis, Diagnosis, and Therapeutics*:43–53.

Kyrychko, Y. N., K. B. Blyuss, and I. Brovchenko. 2020. "Mathematical Modelling of the Dynamics and Containment of COVID-19 in Ukraine". *Scientific Reports* 10(1):1–11.

Li, C., J. Xu, J. Liu, and Y. Zhou. 2020. "The Within-Host Viral Kinetics of SARS-CoV-2". *bioRxiv*:2020–02.

Mahesh, N., N. Singh, and P. Talukdar. 2022. "A Mathematical Model for Understanding Nanoparticle Biodistribution After Intratumoral Injection in Cancer Tumors". *Journal of Drug Delivery Science and Technology* 68:103048.

Moses, M. E., S. Hofmeyr, J. L. Cannon, A. Andrews, R. Gridley, M. Hinga, K. Leyba, A. Pribisova, V. Surjadidjaja, H. Tasnim et al. 2021. "Spatially Distributed Infection Increases Viral Load in a Computational Model of SARS-CoV-2 Lung Infection". *PLoS Computational Biology* 17(12):e1009735.

Nath, B. J., K. Dehingia, V. N. Mishra, Y.-M. Chu, and H. K. Sarmah. 2021. "Mathematical Analysis of a Within-Host Model of SARS-CoV-2". *Advances in Difference Equations* 2021(1):1–11.

Quirouette, C., N. P. Younis, M. B. Reddy, and C. A. Beauchemin. 2020. "A Mathematical Model Describing the Localization and Spread of Influenza A Virus Infection Within the Human Respiratory Tract". *PLoS Computational Biology* 16(4):e1007705.

Sadria, M., and A. T. Layton. 2021. "Modeling Within-Host SARS-CoV-2 Infection Dynamics and Potential Treatments". *Viruses* 13(6):1141.

Sego, T., J. O. Aponte-Serrano, J. Ferrari Gianlupi, S. R. Heaps, K. Breithaupt, L. Brusch, J. Crawshaw, J. M. Osborne, E. M. Quardokus, R. K. Plemper et al. 2020. "A Modular Framework for Multiscale, Multicellular, Spatiotemporal Modeling of Acute Primary Viral Infection and Immune Response in Epithelial Tissues and its Application to Drug Therapy Timing and Effectiveness". *PLoS Computational Biology* 16(12):e1008451.

Troy, N. M., and A. Bosco. 2016. "Respiratory Viral Infections and Host Responses; Insights from Genomics". *Respiratory Research* 17(1):1–12.

Wainer, G. A. 2022. "Advanced Cell-DEVS Modeling Applications: a Legacy of Norbert Giambiasi". *Simulation* 98(6):465–491.

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