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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 not are not well understood (Troy and Bosco 2016).

Thus, mathematical and computational modelling and simulation of RVIs is an important research area that can address this issue by helping design efficient strategies to understanding RVIs and control the Covid-19 pandemic. Simulation tools are used to predict the efficiency of antiviral treatments, design strategies

for the prevention and control of epidemics, study infection dynamics, and understand the mechanisms of transmission of viral diseases (Bernhauerová et al. 2021). In particular, these tools allow modelling the complex behaviors of viruses and their interactions with host cells and the immune response to the infection, especially from a spatio-temporal perspective.

SARS-CoV-2 primarily infects the epithelium in both the upper and lower respiratory tracts of humans (Ashraf et al. 2021) and other types of cells of those in the organs including the lungs, heart, and vasculature (Ashraf et al. 2021). The initial defense against this viral infection is provided by the immune system, which detects the virus through pattern recognition receptors and triggers the release of targeted inflammatory molecules that aid in eliminating the virus. Gaining a deeper understanding of the mechanisms behind SARS-CoV-2 propagation in the respiratory system and the immune response to the virus can aid in the development of specific and effective therapeutic strategies to reduce the negative impact of these RVIs.

Thus, there is an urgent need for understanding on 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 study its behavior at each stage of its replication process. While, this paper will focus on the second objective.

In this study, we present a novel modelling approach using the Cell-DEVS formalism (Ameghino et al. 2001) (a combination of Cellular Automata and DEVS), to model and simulate the spatial-temporal dynamics of viral spread in the lungs. Using a two-dimensional cellular space that mimics a small lung, the proposed approach focuses also on the immune system response to fight the viral infections, the viral infection spread, and the state of lung epithelial tissue damage, and the activation of immune cells. We demonstrate the pertinence of the proposed simulation approach on three different scenarios representing three types of patients, those with a weak immune system and a low viral load, those with a strong immune system and a low viral load, and those with a strong immune system and a high viral load. Through these case studies, we demonstrated that the proposed simulation model can help answer a significant question in SARS-CoV-2 infection, which is the reason behind the significant variation in viral loads among patients.

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 (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 its 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.

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 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.

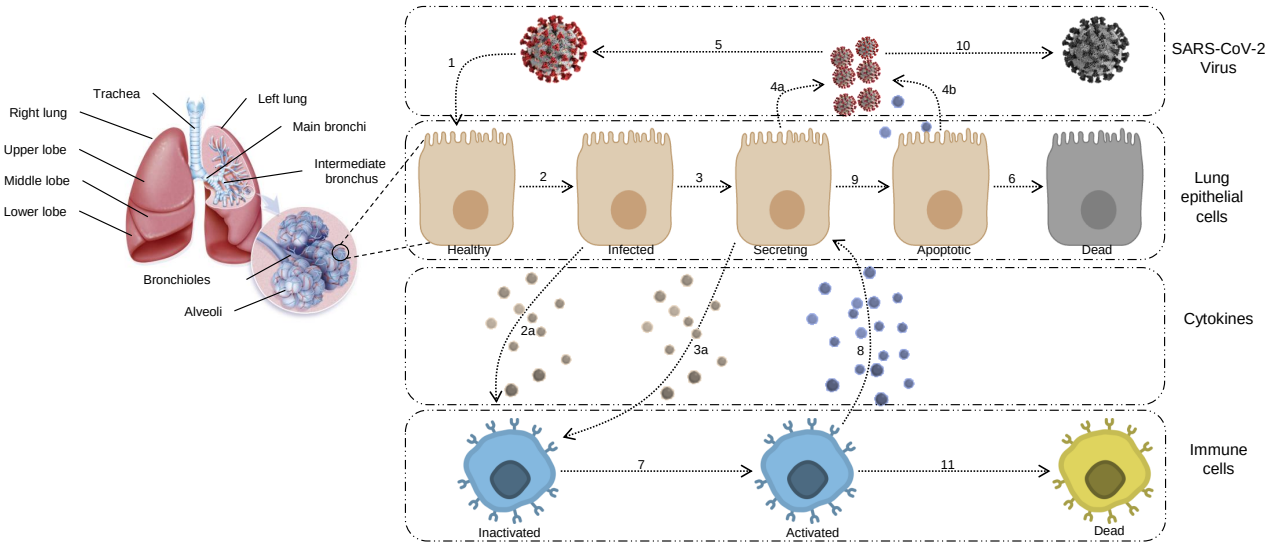

Figure 1: Anatomy of the respiratory system and the interactions among of epithelial lung cells, immune cells, virus and cytokines (inspired from (Moses et al. 2021)).

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, Chowdhury, Ahmed, Agarwal, Badruddin, Kamangar, 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, Xu, Liu, and Zhou (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, Xu, Finnie, and Hall (2022) propose a within-host model, describing viral dynamics in the upper respiratory tract of individuals. Nath, Dehingia, Mishra, Chu, and Sarmah (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. (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 proposed Cell-DEVS simulation model utilizes a series of interlinked multi-layer models that draw upon the biological background presented in section 2.1. The proposed multiscale model 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 biologists to visualize 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 were 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 were 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 immune cell 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

We apply our proposed simulation model in three different scenarios 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*:
   The first scenario we want to simulate refers to a category of patients having a weak immune system and exposed to low viral loads. Given the weakened state of the immune system in this scenario, it's important to keep the concentration of cytokines low, the molecules that immune cells secrete to fight the virus spread. This will likely facilitate faster spread and replication of the virus within lung cell tissue, resulting in a higher number of infected epithelial cells that are more likely to release virions. We will ensure that the virus infects only a single initial cell in the epithelial

tissue. In this scenario, it's anticipated that the virus will rapidly propagate within the lung tissue and cause extensive damage, ultimately resulting in the destruction of all cells within the tissue.

2. *Patients with a strong immune system and exposed to low viral loads*:
   This scenario refers to a category of patients having a strong immune system and exposed to low viral loads. Unlike the first scenario, a considerable amount of cytokines will be secreted by the immune cells. These molecules will endeavor to bind to the infected epithelial cells, causing their demise and thereby impeding viral proliferation and diffusion. We will ensure that the virus infects only a single initial cell in the epithelial tissue. In this scenario, it's anticipated that the virus will spread at a sluggish pace and with low density, resulting in minimal damage to the epithelial cells.
3. *Patients with a strong immune system and exposed to high viral loads*:
   The last scenario corresponds to a category of patients having a strong immune system and exposed to high viral loads. Unlike the previous scenarios, the virus will initially infect eighteen cells disseminated in the epithelial tissue. In this scenario, the immune cells will secrete a high concentration of cytokines to halt the proliferation and clustering of infected cells, once again in an effort to decelerate viral multiplication and spread. The simulation of this scenario is expected to demonstrate a slow viral spread with low density, despite a relatively high initial viral exposure. The resulting damage should be minor and likely comparable 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. At the outset, a single epithelial cell is infected, while all immune cells remain inactive and a substantial amount of extracellular virus is present on the surface of the infected cell. After a viral incubation period, the first infected epithelial cell starts releasing viruses into the extracellular environment, which explains its secretory cell status in red. These virions will in turn contaminate the neighboring cells (in green). At the same time, the first infected epithelial cell activates some immune cells, which begins to swiftly release cytokines into the surrounding extracellular environment. We also observe a notable viral concentration at the point of contact with the infected cell (red) and its subsequent spread to adjacent cells (yellow), prompting a significant production of cytokines to impede viral propagation in the initially infected cells. After 1500 minutes, the virus rapidly spread to neighboring cells, causing virus-induced death of epithelial cells and activation of immune cells around the infected site. Cytokine concentration was high around the infected cell population, and the virus propagated to the superior lobes of both lungs. After 3000 minutes, the viral infection had spread to the middle lobe, with a high 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 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

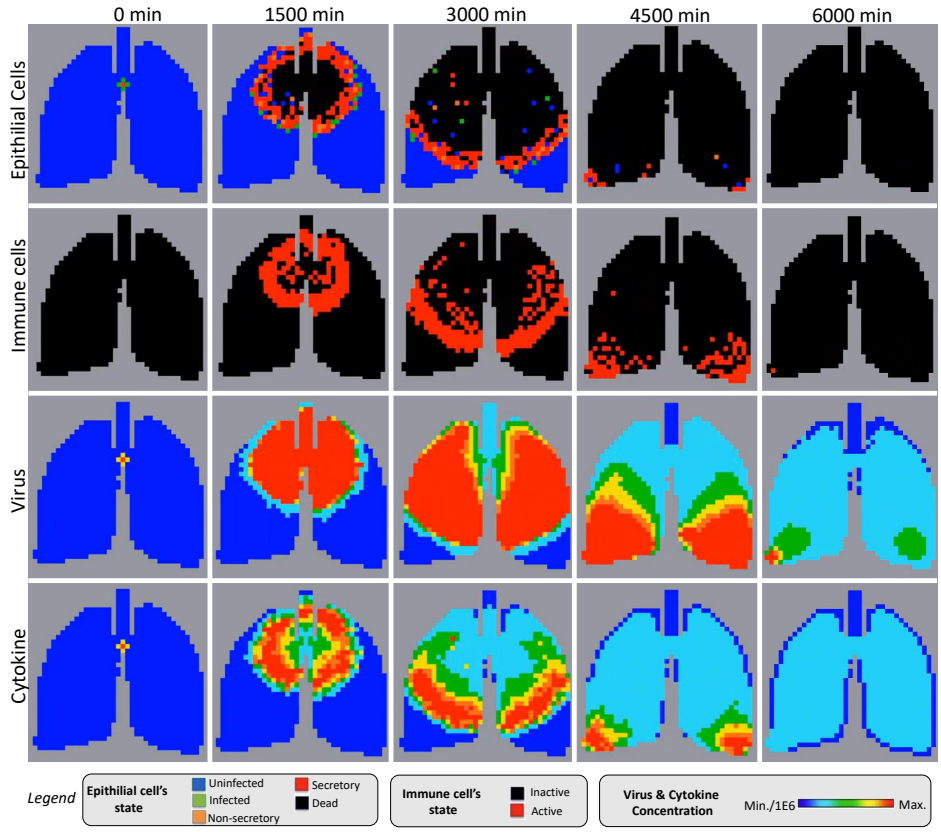

Figure 2: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 1.

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 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 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 2. As in scenario

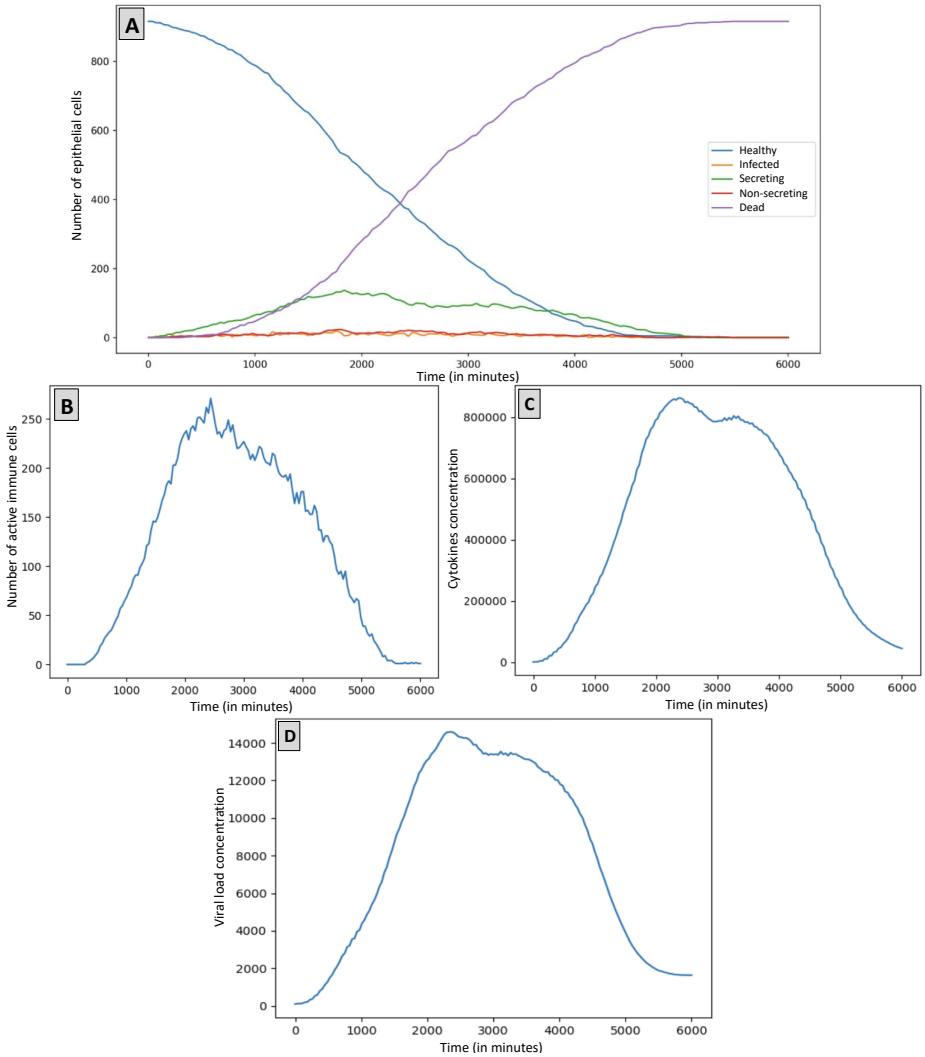

Figure 3: Simulation time series corresponding to the scenario 1.

1, a single epithelial cell is infected, while all immune cells remain inactive and a substantial amount of extracellular virus is present on the surface of the infected cell. Once the viral incubation period is over, the initial infected epithelial cell begins to release viruses into the extracellular environment. These virions stats infect the neighboring cells. Simultaneously, the initial infected epithelial cell triggers the activation of immune cells, leading to the rapid release of cytokines into the adjacent extracellular environment. At 1500 minutes, the virus spreads to the main bronchi, albeit with low density. The epithelial cells surrounding the main bronchi are deceased, with only one epithelial cell in a secretory state and a few in a non-secretory state. At 3000 minutes, there appears to be no further spread of the viruses, with low density and similar distribution pattern as observed 1500 minutes ago. The number of immune cells in the activated state has reduced and spread out horizontally, possibly due to the decrease in cytokine distribution and its horizontal spread. By 4500 minutes, the region of the epithelial tissue surrounding the main bronchi, which was initially highly infected, has died completely. The remaining epithelial tissue is in a healthy and uninfected state. Following a peak, there is a gradual decrease in the number of activated immune cells as well as the concentration of cytokines. The viral load remains low and unchanged. At the end, virus-induced cellular damage has ceased, leaving the epithelial cells around the main bronchi, where the viral infection started, dead. The rest of the lung tissue remains healthy and uninfected. There are no more activated immune cells

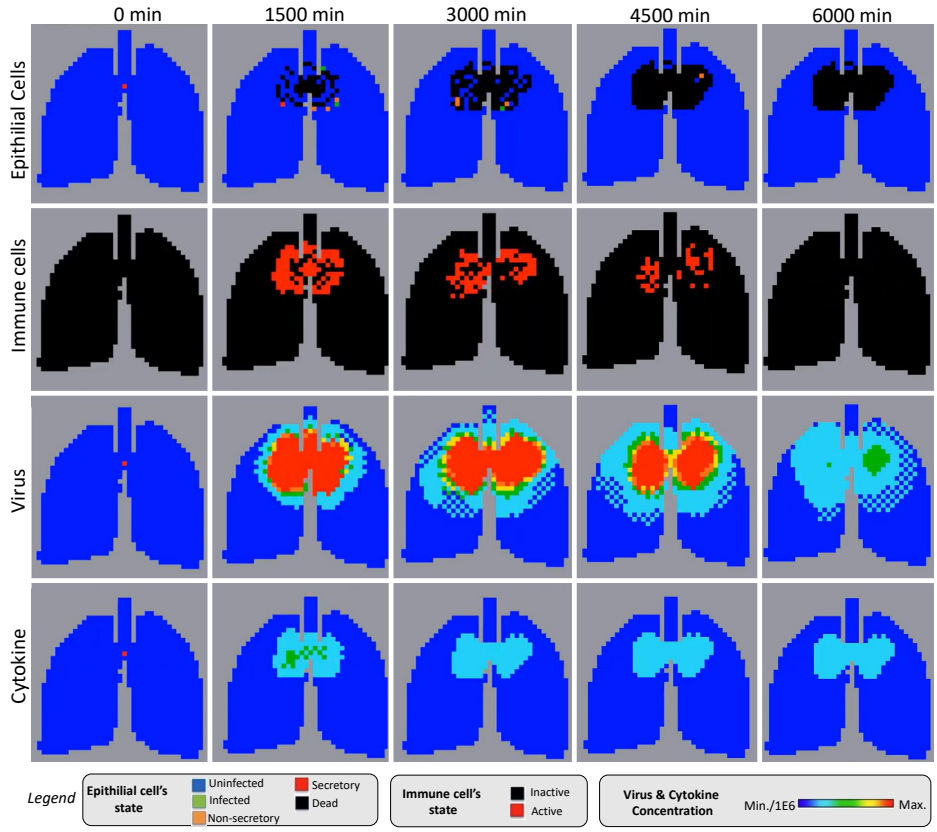

Figure 4: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 2.

since the infection has stopped spreading. The viral load is at its minimum, and the cytokine concentration continues to decrease significantly. 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 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. At the beginning of the simulation, multiple epithelial cells become infected, while all immune cells remain inactive, and a significant amount of extracellular virus is present on the surface of the infected cells. Following a viral incubation period, the first infected epithelial cells start to release viruses

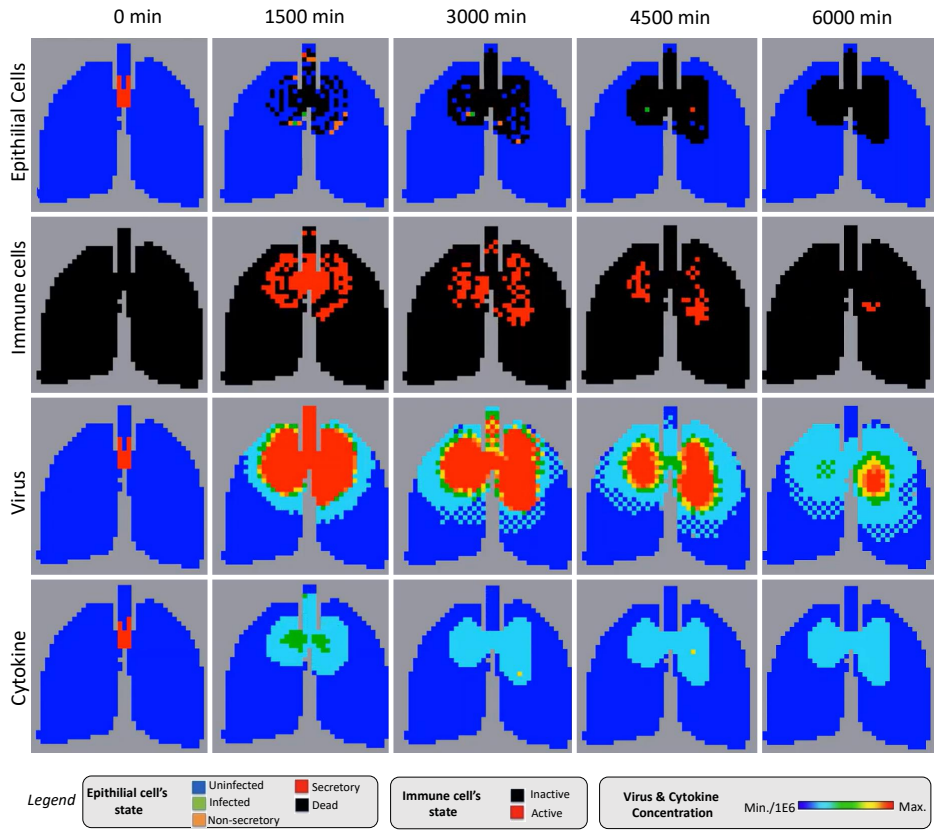

Figure 5: Simulation of the viral infection spread in an epithelial tissue corresponding to the scenario 3.

into their surrounding environment, leading to the presence of several cells in a red secretory state. The numerous secreted virions will, in turn, infect neighboring cells. Concurrently, the first infected epithelial cells activate several immune cells, which rapidly release high levels of cytokines into the surrounding extracellular environment. Furthermore, we observe a high viral concentration at the point of contact with the infected cell, followed by its spread to adjacent cells, resulting in a high production of cytokines to prevent the virus from spreading into the initially infected cells. After approximately 1500 minutes, the virus had spread to the main bronchi, with a high concentration. The surrounding epithelial cells were entirely dead, with only one epithelial cell in a secretory state and a few in a non-secretory state. The activated immune cells' distribution was similar to that of the dead epithelial cells, but with a higher density. This distribution could be attributed to the main bronchus's high density. At 3000 minutes, it appears that the viral infection has reached a plateau and is no longer spreading. Although the viral load is slightly higher compared to scenario 2, it remains similar to the viral load at 1500 minutes. 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 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.

As well, for sake of space, we do not include the temporal series figure corresponding to Scenario 3, but you can access it at this link. The state of the epithelial cells (Figure A, here) is similar to that of the second scenario, with only 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 increased sharply from the initial time to 900 minutes and reached its peak at around 1900 minutes. After that, the curve stabilized at a slightly higher plateau compared to scenario 2. At 5700 minutes, the concentration of cytokines began to gradually decrease. This phenomenon can be explained by the fact that the activation of an immune cell is proportional to the number of cytokines present on its surface. As similar to scenario 2, the curve of the cytokines concentration (Figure C, here) shows a concentration of cytokines, which significantly inhibited the viral infection and reduced 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.

5 CONCLUSION AND FUTURE WORK

In this paper, we introduce and implement a Cell-DEVS model to simulate the spread of the SARS-CoV-2 in lung epithelial cells. To study the SARS-CoV-2 viral infection dynamics, the proposed simulation 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. We showed the simulation results of different implementations of SARS-CoV-2 viral propagation in epithelial tissue through different scenarios: (i) with a weakened immune system and low penetration (i.e. the virus spreads rapidly inside the lung tissue and destroys all its cells), (ii) with a strong immune system and a regular penetration (i.e. the virus spreads slowly with low density and the damage to the epithelial cells is minimal), and (iii) with a strong immune system and significant viral penetration (i.e. the virus propagates rapidly with a very limited destruction of the epithelial cells). While this simulation model did not employ real parameters, it allows biologists to observe the spread of the virus in lung tissue, the destruction of epithelial cells, and the body's response to the virus.

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. Moreover, in this study, we only consider the immune response as a global response involving cytokines. However, other responses exist such as phagocytosis producing inflammatory mediators, or elimination of a virus by T cells. Thus, a more advanced and detailed improvement of our approach will probably be necessary to address the complex interaction between the different types of immune cells. Furthermore, extending our model to include treatments would be very useful to study their impact on the progression of the virus.

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