ON THE INTEGRATION OF TWO MODELS OF THE IMMUNE SYSTEM

Bárbara de Melo Quintela, Alexandre B. Pigozzo, Rodrigo W. dos Santos and Marcelo Lobosco

Computational Modelling, Federal University of Juiz de Fora, http://www.ufjf.br/mmc/

Abstract. The development of mathematical models of the immune response allows a better understanding of the multifaceted mechanisms of this defense system. The main purpose of this work is to establish a general meta-modeling scheme for coupling distinct models of different scales and aspects of the immune system. As an example, we propose a new model where the local tissue inflammation processes are simulated with Partial Differential Equations (PDEs) whereas a system of Ordinary Differential Equations (ODEs) is used as a model for the systemic response. The simulation of different scenarios allows the analysis of the dynamics of different immune cells in the presence of a bacteria. The proposed meta-model demonstrated to be a very promising technique to couple different models of the immune system. The software SI3D is available under request.

1 INTRODUCTION

Systems biology is an emerging inter-disciplinary area of science that advocates a distinct perspective on the study of biological phenomena, particularly focusing on understanding a system's structure and its dynamics (Kitano, 2002). The systems biology approach often involves the use of mathematical and computational techniques in the development of mechanistic models that describes complex interactions in biological systems.

One complex biological system that can benefit from the systems biology approach is the immune system (IS). The IS is composed by a large number of cells, molecules, tissues and organs that form a complex network that interact with each other in order to protect the body against pathogenic agents (Sompayrac, 2008). The IS of vertebrates is composed by three layers of defense: a) the physical barriers; b) innate IS and c) the adaptive IS.

The physical barriers are composed by the skin and mucous membranes that form a shield against the pathogenic agents. If this shield is crossed by pathogens, they encounter cells and molecules of the innate IS, such as proteins of the complement system and macrophages, that immediately develop a response to them. Macrophages phagocyte the pathogens and produce proteins called cytokines that signal other innate cells that their help is needed. Some of this innate cells such as the dendritic cells act like antigen presenting cells (APCs), activating the third layer of defense, the cells of the adaptive IS. B and T cells are examples of such cells. These cells can adapt to deal with almost any invader. B cells in its plasma form secrete antibodies. Antibodies bind to pathogens, which makes them more susceptible to the phagocytosis (in a process called opsonization). Three main types of T cells exist: a) killer T cells, b) helper T cells and c) regulatory T cells. Helper T (Th2) cells produce citokines and activate B cells; killer T cells induce infected cells to commit suicide, in a process called apoptosis; and regulatory T cells control other T cells, although it still is unclear how this process is done (Sompayrac, 2008).

A large number of works have proposed models to describe the IS (Gatton and Cheng, 2004; Lundegaard et al., 2007; Kesmir and De Boer, 1999; Carneiro et al., 1996; Perelson et al., 1998; Chao et al., 2004; Warrender, 2004). The vast majority of these works focus on developing models of the adaptive IS. Computational models of the adaptive IS are very often developed using pure mathematical tools, such as ordinary differential equations (ODEs), to describe the behavior of its components and their relationships, although other tools, such as System Dynamics (Knop et al., 2012), Cellular Automata (Zorzenon dos Santos and Coutinho, 2001; Sloot et al., 2002; Bezzi, 2001), Agent-based Systems (Stefania et al., 2005; Baldazzi et al., 2006; Grilo et al., 2001) and complex adaptive systems (Tay and Jhavar, 2005), are also used.

Although the innate IS is responsible for activating the adaptive one, very few works focus on modeling the innate IS (Su et al., 2009; Pigozzo et al., 2011). A previous work presented a mechanistic computational model of the innate immune response to a general pathogen (Pigozzo et al., 2011). This pathogen is represented by lipopolysaccharide (LPS) that is present in the outer membrane of Gram-negative bacteria. The model represents the behavior of the main defense cells, such as macrophages, and molecules, such as pro-inflammatory cytokines (TNF-α and IL-8) and anti-inflammatory cytokines (IL-10). A set of Partial Differential Equations (PDEs) was used to reproduce important phenomena such as the temporal order of cells arriving at the local of infection, the production of pro-inflammation and anti-inflammation cytokines and the chemotaxis phenomenon. The model has been extended a) to allow the use of a three-dimensional domain in order to better represent the site of infection and b) to use parallel programming techniques to guarantee a reasonable simulation time (Rocha et al., 2012).

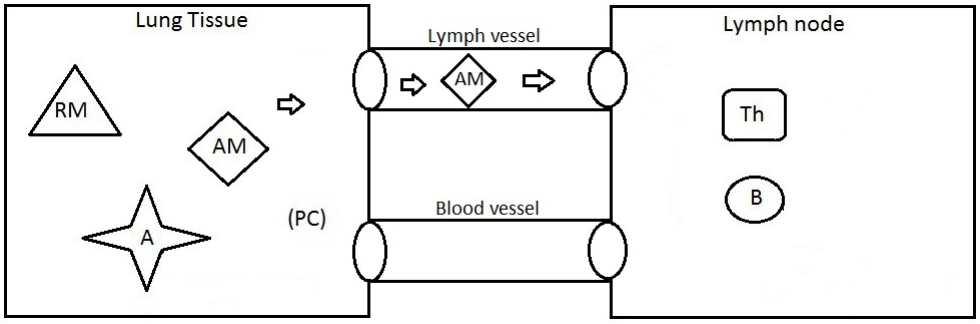

Figure 1: Comunication between local tissue and lymph node; activation of resting macrophages (RM), production of pro-inflamatory cytokines (PC) and migration of activated macrophages (AM) to the lymph node.

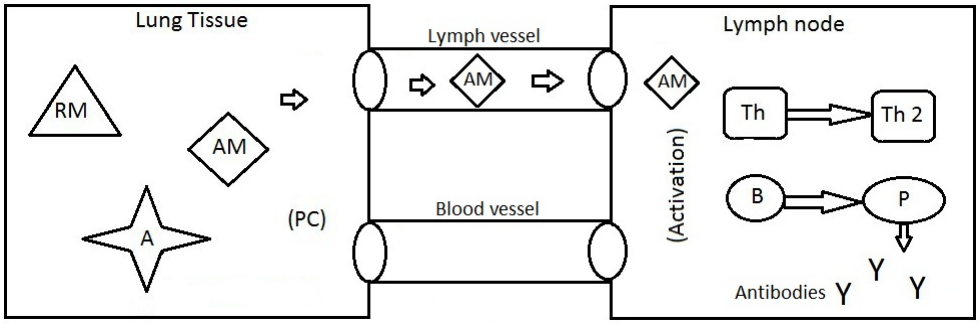

Figure 2: Activated macrophage (AM) stimulate lymphocytes by antigen presenting process; T-cell differentiate in T-helper 2 (Th2) and B-cell differenciate in Plasma Cell (P) which produces antibodies (Y).

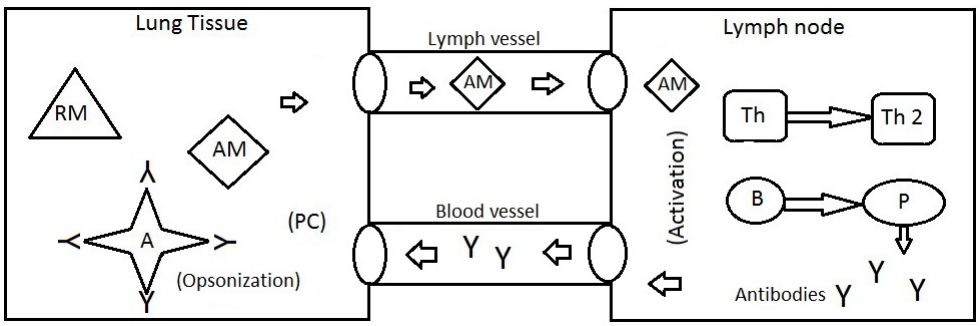

Figure 3: Antibodies (Y) migrate to the lung tissue through blood vessel and opsonize the antigen (A).

This work extends our previous models (Pigozzo et al., 2011; Rocha et al., 2012), enabling the innate IS to activate the adaptive one. To achieve this purpose, a new set of equations, based on the mathematical model of pneumonia described in Marchuk (1997), was included. The main contribution of this work is a mathematical model that reproduces the dynamics of both innate and adaptive IS, coupling for this purpose models of different nature and scales. The meta-model represents a more complete scenario: the dynamics of the cells and molecules inside the lung tissue as well as the communication through lymph and blood vessels with the nearest lymph node. Initially there are resting macrophages located in the tissue and T- and B-cells in the lymph nodes. After the injection of an antigen (A), resting macrophages (RM) become activated macrophages (AM) that start producing pro-inflamatory cytokines (PC) to beacon to other immune cells where to approximate. The AM act as an antigen presenting cell (APC) migrating to the closest lymph node through lymph vessels (Figure 1) and exhibiting the antigen to the lymphocytes which initiates the activation and differentiation of T-cells into T-helper 2 cells (Th2) and activation and differentiation of B-cells into Plasma cells producing antibodies (Figure 2). These antibodies head to the local of the infection in the lung tissue through blood vessels doing what is called opsonization of the antigen, the process by which an antigen is marked for ingestion and destruction by a phagocyte (Figure 3) (Abbas and Lichtman, 2010).

The proposed model uses both PDEs and ODEs to describe the entire dynamics. This is, for the best of our knowledge, the first work that couples PDEs and ODEs to describe the dynamics of innate and adaptive IS into a piece of tissue, including the activation of the adaptive IS by the innate IS.

This work is organized as follows. Section 2 describes the mathematical model used in this work. The IS model presented in this work was simplified when compared to our previous models (Pigozzo et al., 2011; Rocha et al., 2012). The complete model was not used in order to focus on the integration of the two different models: a) local tissue and b) lymph nodes. Section 3 presents its computational implementation. The results obtained by the models are presented in Section 4. Finally, Section 5 draws our conclusions and present our future works.

2 SYSTEM AND METHODS

According to Marchuk (1997), there are several microorganisms that could be aetiological agents of destructive pneumonia. However, the inflammatory and destructive process in lung tissue cannot be started unless there is a malfunctioning of local and general defense mechanisms. Marchuk (1997) considers a scenario of destructive pneumonia induced by *S. aureus* against the background of a defense mechanism malfunction caused by influenza. The multiplication of microorganisms occurs between 10-14 days and causes the disease which, in case of recovery, ends as a result of destruction of bacteria by antibodies, macrophages and neutrophils. Marchuk (1997) uses ODEs to model the processes involved in destructive pneumonia.

In this work, PDEs have been employed to model the spatial and temporal behaviour of the following components: *S. aureus* bacteria (A); resting and activated macrophages (M_R, M_A); and specific antibodies (F). ODEs represent the temporal concentration of T-lymphocytes (T), B-lymphocytes (B) and plasma cells (P) in the Limph Nodes (LN). Macrophages act like APCs, activating the adaptive IS and the production of antibodies. The cellular homeostasis is guaranteed by the addition of an equilibrium term in the equations correspondig to the adaptive IS. The idea is to preserve the minimum amount of adaptive IS cells in the body (Marchuk, 1997). Whithin this spatio-temporal model we consider an homogenization technique in which every portion of the tissue modelled is in contact with both lymph and blood vessels. All the

PDEs are modeled considering homogeneus Neumann boundary conditions.

2.1 PDEs Model

S. Aureus Bacteria (A)

Eq. 1 depicts the model for the *S. Aureus* bacteria. The first term of Eq. 1 models the replication of bacteria at a rate β. Its engulfment by macrophages and other non-specific defense cells is represented by the second and third terms of the same equation: γ_{MA} is the rate for the activation of macrophages and γ_{AM} is the rate for destruction of bacteria by active macrophages. The opsonization process for further phagocytosis in shown in the fourth term: γ_{AF} represents rate for destruction of opsonized bacteria. The last term represents the diffusion where D_A is the bacteria diffusion coefficient.

$$\frac{\partial A}{\partial t} = \beta A - \gamma_{MA} M_R A - \gamma_{AM} A M_A - \gamma_{AF} A F + D_A \nabla A \,. \tag{1}$$

Macrophages ($\mathbf{M}_R$, $\mathbf{M}_A$)

Macrophages are represented in two distinct states: resting (M_R) and activated (M_A). Initially, there is only resting macrophages into the tissue and they become active after exposure to antigens (A). In the active state, they play an important role in presenting and stimulating specific defense cells located in the LN.

The Equation 2 represents the concentration of resting macrophages in the alveolar tissue, in which the first term accounts for their natural decay, the second term represents their activation and the last one is the diffusion term. The natural decay rate is given by m_{MR}, γ_{MA} is the rate in which resting macrophage become active and D_{M_R} is the resting macrophage diffusion coefficient.

$$\frac{\partial M_R}{\partial t} = -m_{MR} M_R - \gamma_{MA} M_R A + D_{M_R} \nabla M_R \,. \tag{2}$$

Equation 3 represents the concentration of active macrophages in the alveolar tissue. Again, the first term models their the natural decay, at a rate of m_{MA}, the second term models their activation, at a rate of γ_{MA}, the third one is the diffusion term, at a rate of D_{MA}.

$$\frac{\partial M_A}{\partial t} = -m_{MA} M_A + \gamma_{MA} M_R A + D_{MA} \nabla M_A - \alpha_M (M_A - M_A^L) \,. \tag{3}$$

The last term of Eq. 3 represents the flux of M_A between the local alveolar tissue and the LN through the lymph vessels. In this equation, M_A^L is the macrophage concentration in the lymph node, which dynamics is described by Eq. 5.

Antibodies (F)

Eq.4 describes the antibody mechanics into the lung tissue. The first term describes the antibodies consumption to defeat bacteria in the opsonization process, at a rate of γ_{FA}. The second term models the diffusion process of antibodies into the tissue, at a rate of D_F, and the last term describes the flux of antibodies between the LN and the tissue, at a rate of α_F.

$$\frac{\partial F}{\partial t} = -\gamma_{FA} F A + D_F \nabla F - \alpha_F \left(F - F^L\right) \,. \tag{4}$$

2.2 ODEs Model

Macrophages (M_A^L)

Eq. 5 represents the flux of active macrophages between the local alveolar tissue and the LN through the lymph vessels, at a rate of α_M

$$\frac{dM_A^L}{dt} = \alpha_M(M_A^T - M_A^L)\,. \tag{5}$$

The concentration of active macrophages in the tissue (M_A^T) is described by Eq. 6.

$$M_A^T = \frac{1}{V_\Omega}\int_\Omega M_A d\Omega\,, \tag{6}$$

where Ω is the simulation domain and V_Ω is its area or volume.

T-lymphocytes (T)

The helper T-lymphocytes are stimulated by active macrophages in the LN and plays an important role in the activation of B-lymphocytes and plasma cells to start the production of specific antibodies against antigens. The first part of Eq. 7 represents the activation of Th2 cells, with the appearance of new cells. b_T is the rate for the stimulation of Th2 cells and ρ_T is the number of descendants Th2 cells created by single division. The second term represents the expenditure of Th2 cells to stimulate B-cells, at a rate of b_p. Finally, the third term models the maintenance of the homeostasis in absence of antigenic stimulation.

$$\frac{dT}{dt} = b_T\left(\rho_T T M_A^L - T M_A^L\right) - b_p M_A^L T B + \alpha_T\left(T^* - T\right)\,. \tag{7}$$

B-lymphocytes (B)

After B-lymphocytes cells have been stimulated by T-cells and active macrophages into the LN, they start to proliferate and turn into plasma cells. Their proliferation is represented by the first term of Eq. 8, in which b_p^b is the rate for the stimulation of B cells and ρ_B is the number of new B-cells. Again, the second term shows the maintenance of the homeostasis.

$$\frac{dB}{dt} = b_p^b\left(\rho_B T M_A^L - T M_A^L B\right) + \alpha_B\left(B^* - B\right)\,. \tag{8}$$

Plasma Cells (P)

The plasma cells are generated from stimulated B-cells, T-cells and active macrophages in the LN.

$$\frac{dP}{dt} = b_p^p\left(\rho_P T M_A^L B\right) + \alpha_P\left(P^* - P\right)\,. \tag{9}$$

The first term of Eq. 9 describes the generation and maturation of plasma cells from stimulated B-cells, in which b_p^p is the rate for the stimulation of plasma cells and ρ_P is the number of new plasma cells. The last term is the maintenance of the homeostasis.

Table 1: Initial conditions for the PDEs model.

Parameter	Position (mm)
A_0	$0 < x < 1,\ 0 < y < 1,\ 0.9 < z < 1$
MR_0	$0 < x < 1,\ 0 < y < 1,\ 0 < z < 1$
MA_0	$0 < x < 1,\ 0 < y < 1,\ 0 < z < 1$
F_0	$0 < x < 1,\ 0 < y < 1,\ 0 < z < 1$

Antibodies (F^L)

Antibodies released by plasma cells in the LN are represented by the Eq. 10.

$$\frac{dF^L}{dt} = \rho_F P - \alpha_F (F^T - F^L)\ . \tag{10}$$

in which the first term of Eq. 10 describes the production of antibodies, at rate ρ_F by plasma cells. The last term describes the flux of antibodies between the LN and the tissue, at a rate of α_F, and F^T is the average number of antibodies in the tissue described by Eq. 11:

$$F^T = \frac{1}{V_\Omega} \int_\Omega F d\Omega\ , \tag{11}$$

where Ω is the simulation domain and V_Ω is its area or volume.

2.3 Initial Conditions and Parameters

The initial conditions, which describe the process of formation of inflammatory site, are shown in Table 1. Table 2 presents the complete set of parameters used in the simulations. Almost all parameters used in the simulation were obtained in Marchuk (1997) applying the necessary unit conversions. The only exceptions are D_A, D_{M_R}, D_{M_A} and D_F, which were estimated by Pigozzo (2011).

3 IMPLEMENTATION

The numerical method employed to implement the mathematical model was the Finite Difference Method (LeVeque, 2007), a method commonly used in the numeric discretization of PDEs. The Finite Difference Method is a method of resolution of differential equations that is based on the approximation of derivatives with finite difference.

A complex part of the resolution of the PDEs is the resolution of the convective term, the chemotaxis term. The development of numerical methods to approximate convectives terms (that in most cases are not linear) have been subject of intense research in the last years (Harten, 1997; Leonard, 1988; Shu and Osher, 1989; Sod, 1978).

Different numerical approaches have been proposed (Marrocco, 2003; Filbet, 2006) to solve this kind of equations. Our implementation is based on the finite difference method for the spatial discretization and the explicit method for the time evolution with an upwind scheme for the convective term of the equation. The upwind scheme discretize the hyperbolic PDEs using a bias for the flux direction given by the signal of the characteristic speeds. The upwind scheme uses an adaptive or solution-sensitive stencil to precisely simulate the direction of information propagation.

Below there is an example of a finite difference operator used in the discretization of the Laplace operator that simulates the diffusion phenomenon in 3D:

Table 2: Complete set of parameters.

Parameter	Value	Unit	Reference
A_0	$1.7 * 10^{-18}$	$cell/mm^3$	(Marchuk, 1997)
β_A	30.0	1 / day	(Marchuk, 1997)
γ_{AM}	$0.6 * 10^{13}$	$mm^3/cell * day$	(Marchuk, 1997)
γ_{AF}	$3.0 * 10^{10}$	$mm^3/cell * day$	(Marchuk, 1997)
D_A	2.0	mm^3/day	(Pigozzo, 2011)
MR_0	$3.4 * 10^{-15}$	$cell/mm^3$	(Marchuk, 1997)
D_{MR}	0.432	mm^3/day	(Pigozzo, 2011)
MA_0	0.0	$-$	$-$
γ_{MA}	$5 * 10^{13}$	$mm^3/cell * day$	(Marchuk, 1997)
α_{MA}	2.5	$1/day$	(Marchuk, 1997)
D_{MA}	3.0	mm^3/day	(Pigozzo, 2011)
b_T	$3.0 * 10^{17}$	$mm^3/cell * day$	(Marchuk, 1997)
ρ_T	2.0	$cell$	(Marchuk, 1997)
b_P	$3.0 * 10^{23}$	$mm^3/cell * day$	(Marchuk, 1997)
α_T	0.01	$1/day$	(Marchuk, 1997)
T^*	$8.4 * 10^{-16}$	$cell/mm^3$	(Marchuk, 1997)
b_P^B	$4.0 * 10^{25}$	$mm^3/cell * day$	(Marchuk, 1997)
ρ_B	16.0	$cell$	(Marchuk, 1997)
α_B	1.0	$1/day$	(Marchuk, 1997)
B^*	$8.4 * 10^{-15}$	$cell/mm^3$	(Marchuk, 1997)
b_P^P	$2.0 * 10^{27}$	$mm^3/cell * day$	(Marchuk, 1997)
ρ_P	3.0	$cell$	(Marchuk, 1997)
α_P	5.0	$1/day$	(Marchuk, 1997)
P^*	$8.4 * 10^{-17}$	$cell/mm^3$	(Marchuk, 1997)
ρ_F	$5.1 * 10^6$	$cell$	(Marchuk, 1997)
α_F	0.43	$1/day$	(Marchuk, 1997)
F^*	$9.5 * 10^{-11}$	$cell/mm^3$	(Marchuk, 1997)
F_0	10^{-10}	$cell/mm^3$	(Marchuk, 1997)
D_F	0.16	mm^3/day	(Pigozzo, 2011)

$$D_O(\frac{\partial^2 O(x,y,z)}{\partial x^2} + \frac{\partial^2 O(x,y,z)}{\partial y^2} + \frac{\partial^2 O(x,y,z)}{\partial z^2}) \approx \tag{12}$$
$$D_O * ((o[x+1,y,z] - 2 * o[x,y,z] + o[x-1,y,z])/deltaX^2))$$
$$+D_O * ((o[x,y+1,z] - 2 * o[x,y,z] + o[x,y-1,z])/deltaY^2))$$
$$+D_O * ((o[x,y,z+1] - 2 * o[x,y,z] + o[x,y,z-1])/deltaZ^2))$$

In Equation 12, O represents the discretization of some types of cells, such as resting and activated macrophages; D_O is the diffusion coefficient of these populations of cells, x, y and z are the position in the space and $deltaX$, $deltaY$ and $deltaZ$ are the space discretization.

In three dimensions, the chemotaxis flux for direction x is as follows:

```
//flux at x-axis
if((CH[x,y,z]-CH[x-1,y,z]) > 0) {
```

```
  flux_left = -(CH[x,y,z]-CH[x-1,y,z])
               * O[x-1,y,z]/deltaX;
} else {
  flux_left = -(CH[x,y,z]-CH[x-1,y,z])
               * O[x,y,z]/deltaX;
}
if(CH[x+1,y,z]-CH[x,y,z] > 0) {
  flux_right = (CH[x+1,y,z]-CH[x,y,z])
                * O[x,y,z]/deltaX;
} else {
  flux_right = (CH[x+1,y,z]-CH[x,y,z])
                * O[x+1,y,z]/deltaX;
}
fluxX = (flux_left + flux_right)/deltaX;
```

We decided to implement our own numerical method to solve the systems of PDEs because a) we have the possibility to parallelize the code; and b) most of the numerical libraries offer few functions that are suitable to our problem. The code was implemented using the C programming language.

4 RESULTS AND DISCUSSION

To show the importance of immune cells, molecules and processes in the dynamics of the immune response, a set of simulations were performed under distinct scenarios. The simulations start with a simple scenario were the cells of the HIS are not considered (case 1). Aiming to analise the importance of the antibodies to the elimination of bacteria, the response is represented firstly by the simulation of only the innate cells (case 2) and then with the complete model including activation of the lymphocytes, production and migration of antibodies to the tissue (case 3). A second wave of antigen was also simulated to understand if the presence of the antibodies would offer a quickier and effective response to the bacteria (case 4).

4.1 Case 1

The purpose of this simple case is to show the diffusive term in the bacteria equation (Eq. 1). Initially the antigen is located only on the portion $z > 0.9mm$ in the three-dimensional domain. As expected, the simulation shows that, without the immune system cells, after a few seconds the bacteria start to spread over the entire domain because of the diffusion (Fig. 4). Furthermore, the replication can also be observed with the increase of the population of *S. aureus*.

4.2 Case 2

Initially, without considering the triggering of acquired response, S. aureus began to lessen with the effect of innate response cells (macrophages) in the first day of simulation. But increases promptly due to the process of bacteria replication (Figure 5). It is important to notify that the damage caused to the local tissue is not under consideration and it is assumed that bacteria grows indefinitely.

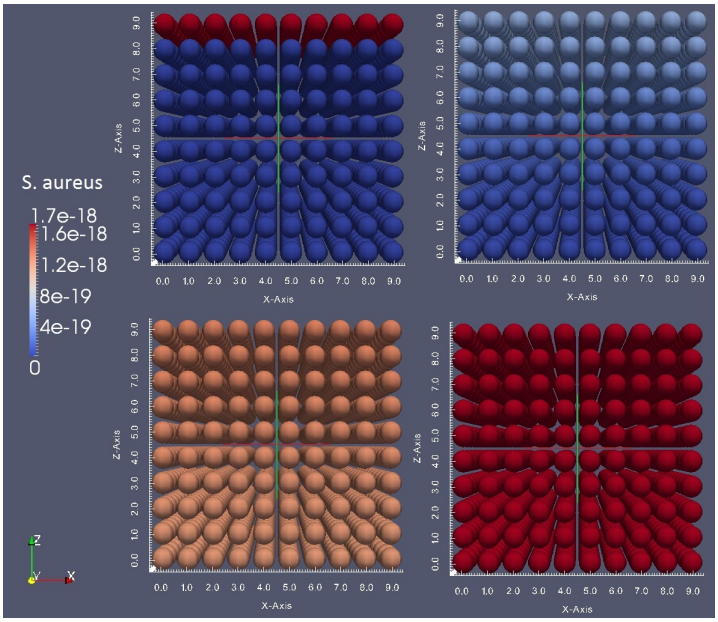

Figure 4: Concentration of *S. aureus*. Upper left depicts the initial condition; upper right, depicts its concentration after 2.8 seconds of simulation; bottom left, after 4 hours and bottom right after 5 hours.

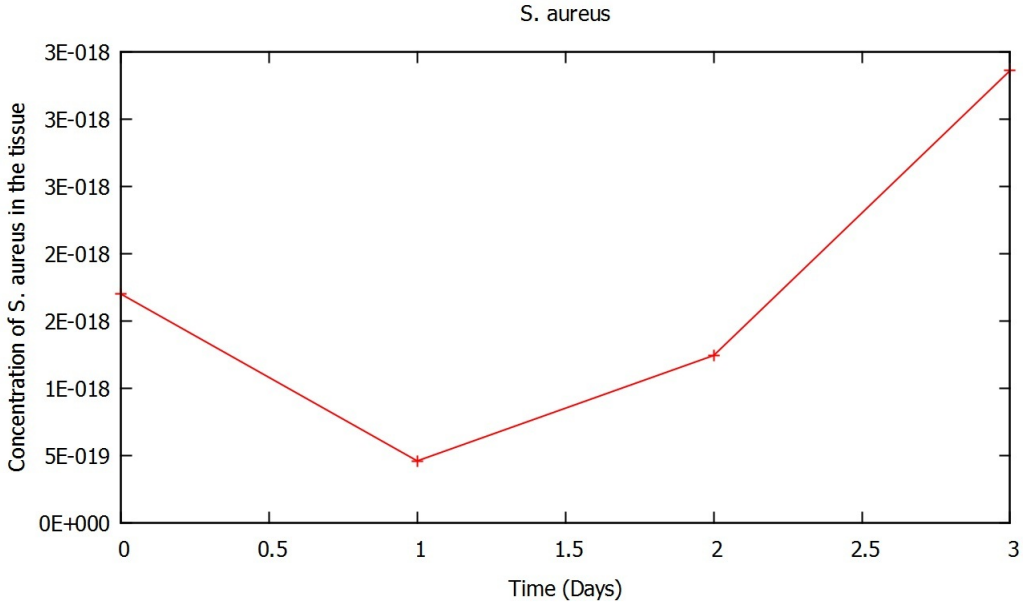

Figure 5: Concentration of *S. aureus* in the absence of the acquired response cells considering its indefinitely growth.

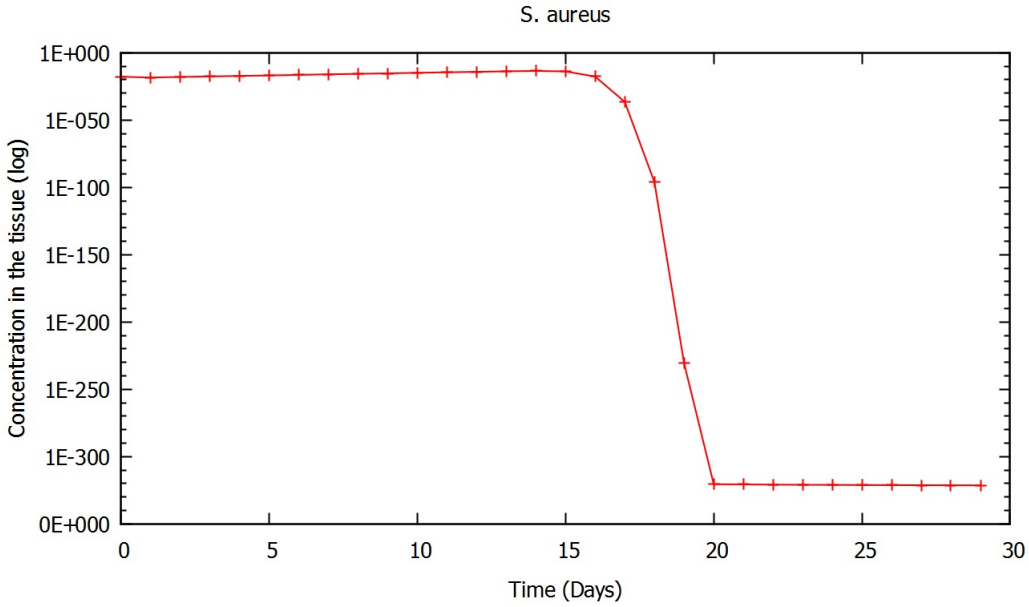

Figure 6: Concentration of *S. aureus* in the presence of antibodies.

4.3 Case 3

The third case represents the complete scenario. Regarding the presence of antibodies in the blood, the concentration of S. aureus grows slowly until the 15^{th} day, when the acquired defense cells have been already stimulated and are able to clear the bacteria concentration (Figure 6). The concentration is dissimilar to the second case without antibodies in the first days due to the small number of antibodies already present in the blood guaranteed by homeostasis.

In this scenario, the increase number of bacteria is a signal to resting macrophages become activated. The activation process increases the number of active macrophages (Figure 7) and reduces the number of resting macrophages in the tissue. Active macrophages leave the tissue and goes to the LN, where they act as APCs, presenting antigens to T cells. This presentation activates the adaptive immune system. T cells in contact with the antigen start their clonal expansion and help the AM with the activation of B cells, and due to this, are consumed, reducing their concentration (Figure 8). Plasma cells start to increase (Figure 9) and produce antibodies (Figure 10), that migrate to the tissue and opsonize the bacteria. The specific response depends mainly on the APC process and although this response is slower, it is effective to handle with the infection: after 20 days of simulation it finishes.

As a consequence of the use of the complete model, the spatial distribution of the *S. aureus* changes significantly when compared to the first case, as illustrated by Figure 11. Although the bacteria spreads over the entire tissue, this time the vigorous and rapid immune response is responsible for extinguishing the bacteria.

4.4 Case 4

A second wave of S. aureus was introduced in the tissue after their first elimination to understand the behavior of the IS modeled. The simulation is carried on equally in comparison with the second case until the 18^{th} day, when the bacteria is inserted. As the acquired response is still active and the cells are at their peak, because their natural decay has not happened yet, the elimination of S. aureus happens unhindered, exceedingly faster than the first response (Figure 12). It is also shown in Figure 12 that S. aureus is still present on the 15^{th} day and completely

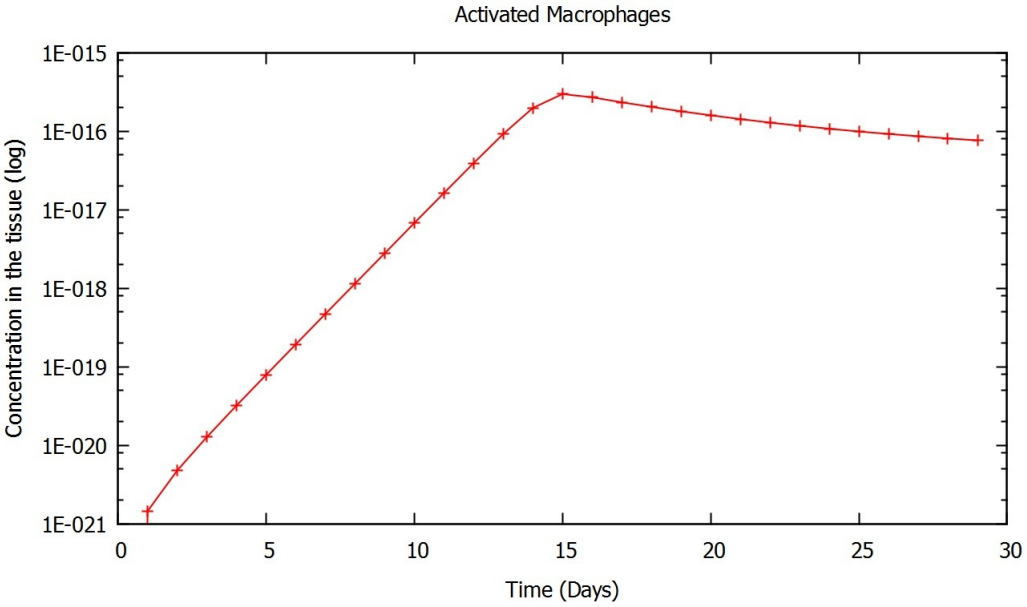

Figure 7: Concentration of macrophages in the tissue.

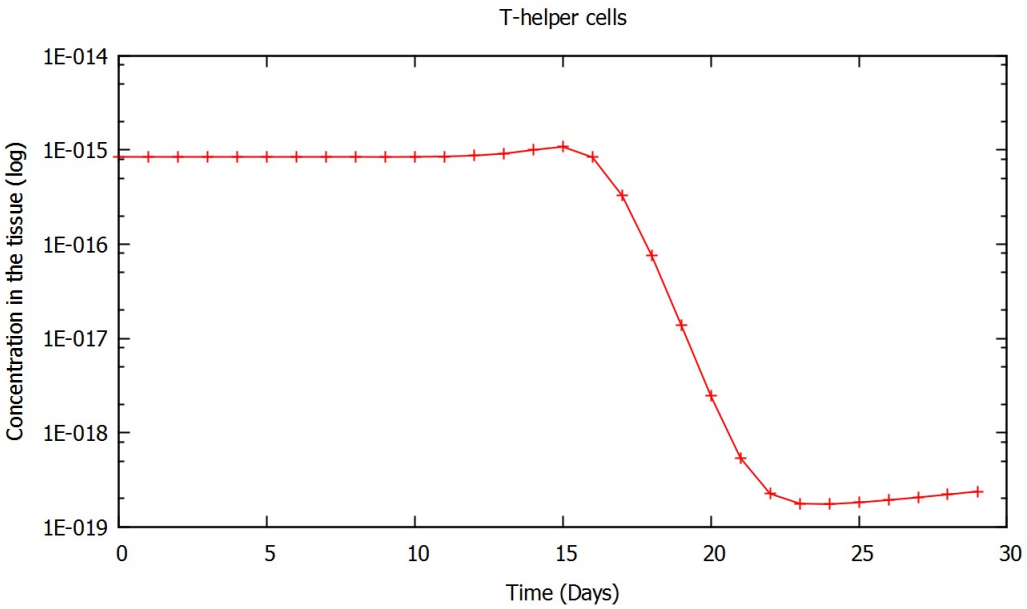

Figure 8: Concentration of T helper cells in the lymph nodes.

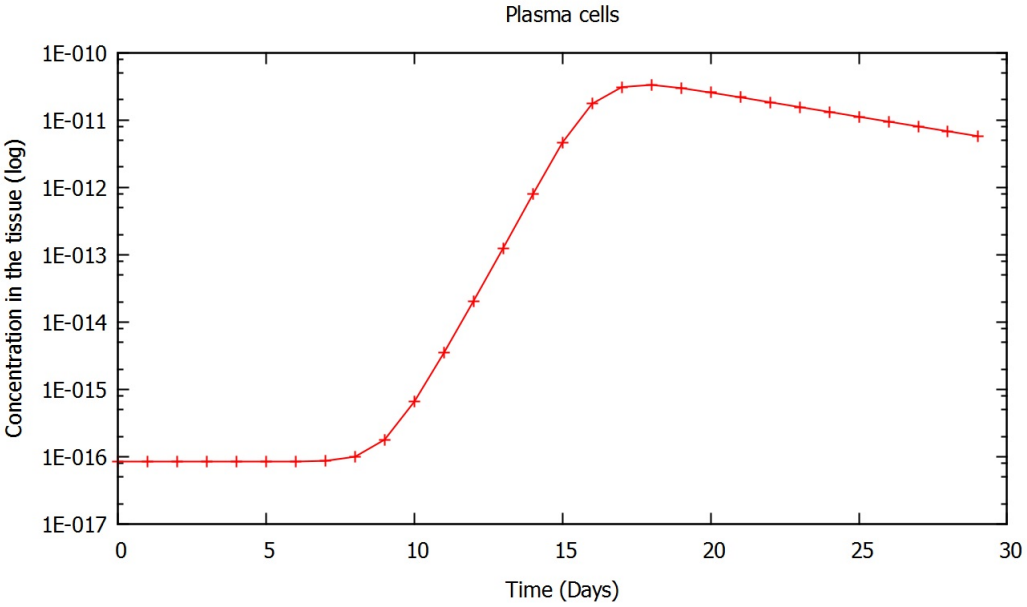

Figure 9: Concentration of plasma cells (activated B-cells) in the lymph node.

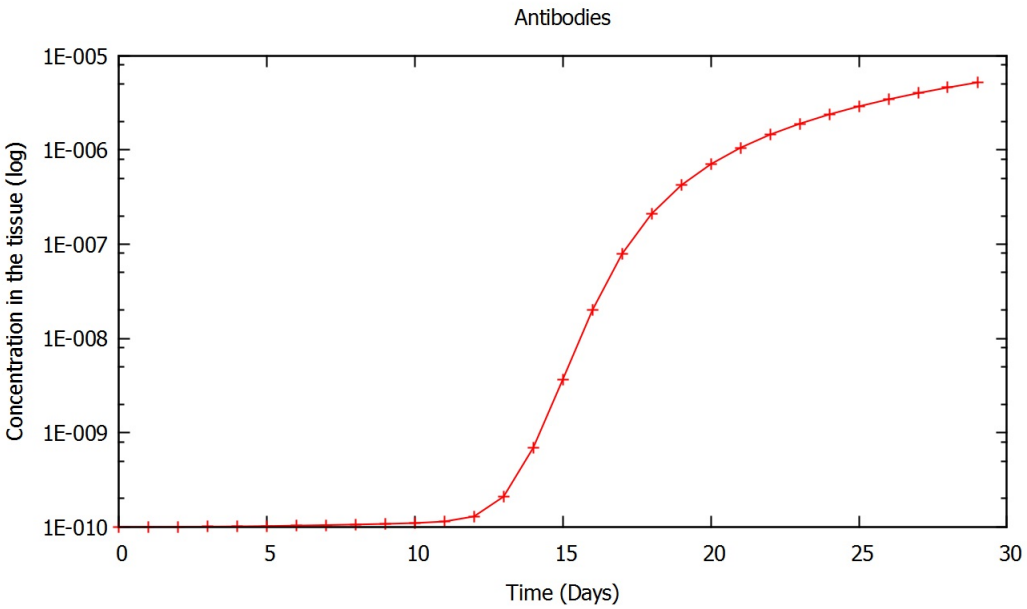

Figure 10: Concentration of antibodies in the tissue.

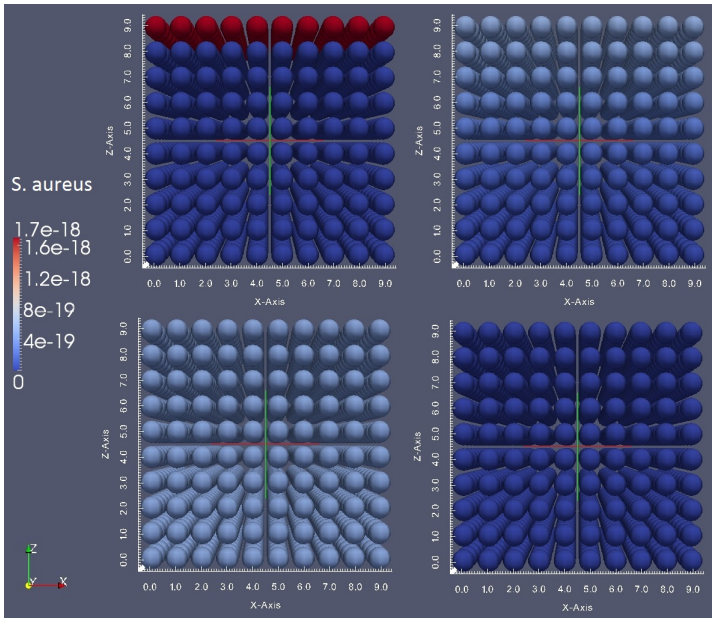

Figure 11: Spatial evaluation of *S. aureus* concentration over 30 days of simulation. Upper left depicts the initial condition; upper right, depicts its concentration after 1 day of simulation; bottom left, after 10 days and bottom right after 30 days.

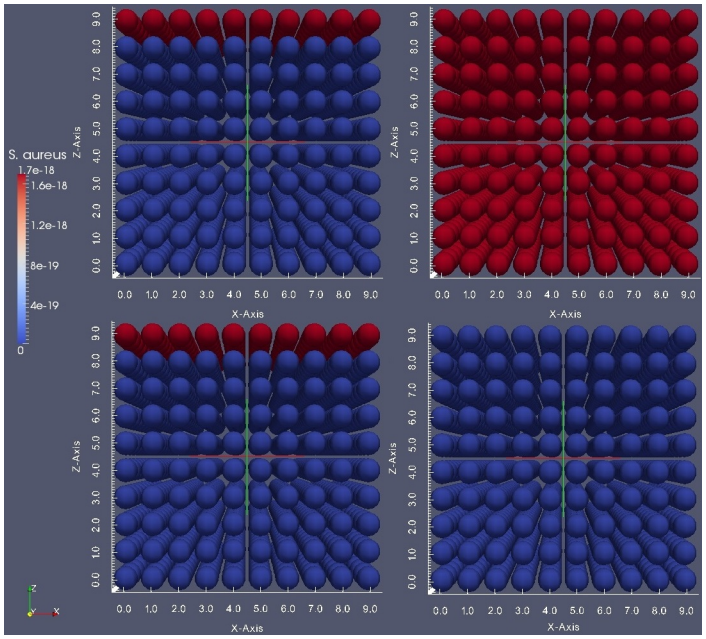

Figure 12: Spatial evaluation of *S. aureus* concentration over 30 days of simulation. Upper left depicts the initial condition; upper right, depicts its concentration after 15 days of simulation; bottom left, after 18 days and bottom right after 19 days.

spread over the tissue. But it is eliminated until the day of the second injection. Instead of starting to grow, the second wave is quickly contained by the IS cells and is eliminated in a matter of hours.

5 CONCLUSION

In this work we presented a mathematical and computational model that simulates the immune response to *S. Aureus* bacteria into a microscopic three-dimensional section of a tissue. To achieve this objective, the model reproduces the initiation, maintenance and resolution of innate and adaptive immune response. A set of PDEs and ODEs are used to model the main agents involved in this processes, like the antigen, macrophages, antibodies, T and B cells.

The main contribution of this work is to establish a general meta-modeling scheme for coupling distinct models of different scales and aspects of the immune system: one of them uses PDEs to model the dynamics into a microscopic three-dimensional section of a tissue and the other one uses ODEs to model the dynamics of some cell into the LN. The model represents the complete scenario: the diffusion of antigens into the tissue and the migration of macrophages to combat the infection. Macrophages also migrate outside the tissue and stimulate the adaptive IS to produce antibodies, which in turn migrate inside the tissue and opsonize the antigens. The proposed model was capable of reproducing qualitatively the spatial and temporal behaviour of resting and activated macrophages as well as specific antibodies. Also, the temporal concentration of T-lymphocytes, B-lymphocytes and plasma cells in the Lymph Nodes were reproduced. However, the specific results obtained by the new model need to be better validated.

We expect from this spatial model to be able to simulate and analyse the evolution of the damage caused to an organ parenchyma, for example, the damage in the lung tissue caused by tuberculosis or pneumonia. Also, as future work, we plan to implement a more complete mathematical model including molecules and others processes involved in the immune responses.

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REFERENCES

Abbas A. and Lichtman A. *Basic Immunology Updated Edition: Functions and Disorders of the Immune System*. Elsevier Health Sciences, 2010.

Baldazzi V., Castiglione F., and Bernaschi M. An enhanced agent based model of the immune system response. *Cellular Immunology*, 244(2):77–79, 2006. International Conference on Immunogenomics and Immunomics, Budapest, Hungary, October 8-12, 2006.

Bezzi M. *Modeling Evolution and Immune System by Cellular Automata*. Rivista del nuovo cimento. Editrice Compositori, 2001.

Carneiro J., Coutinho A., Faro J., and Stewart J. A Model of the Immune Network with B-T Cell Co-operation. I - Prototypical Structures and Dynamics. *Journal of Theoretical Biology*, 182:513–529, 1996.

Chao D.L., Davenport M.P., Forrest S., and Perelson A.S. A stochastic model of cytotoxic t cell responses. *Journal of Theoretical Biology*, 228(2):227–240, 2004.

Filbet F. A finite volume scheme for the patlak–keller–segel chemotaxis model. *Numerische Mathematik*, 104:457–488, 2006.

Gatton M.L. and Cheng Q. Modeling the development of acquired clinical immunity to plasmodium falciparum malaria. *Infect Immun*, 72(11):6538–6545, 2004. ISSN 0019-9567. doi:10.1128/IAI.72.11.6538-6545.2004.

Grilo A., Caetano A., and Rosa A. Agent-Based Artificial Immune System. In *2001 Genetic and Evolutionary computation Conference Late Breaking Papers*. San Francisco, USA., 2001.

Harten A. High resolution schemes for hyperbolic conservation laws. *J. Comput. Phys.*, 135:260–278, 1997. ISSN 0021-9991. doi:10.1006/jcph.1997.5713.

Kesmir C. and De Boer R.J. A Mathematical Model on Germinal Center Kinetics and Termination. *J Immunol*, 163(5):2463–2469, 1999.

Kitano H. Systems biology: A brief overview. *Science*, 295(5560):1662–1664, 2002. doi: 10.1126/science.1069492.

Knop I.O., Pigozzo A.B., Quintela B.M., Macedo G.C., Barbosa C.B., Santos R.W., and Lobosco M. Modeling human immune system using a system dynamics approach. In k. JobbÃągy, R. Magjarevic, and R. Magjarevic, editors, *5th European Conference of the International Federation for Medical and Biological Engineering*, volume 37 of *IFMBE Proceedings*, pages 363–366. Springer Berlin Heidelberg, 2012.

Leonard B.P. Simple high-accuracy resolution program for convective modelling of discontinuities. *International Journal for Numerical Methods in Fluids*, 8(10):1291–1318, 1988. ISSN 1097-0363. doi:10.1002/fld.1650081013.

LeVeque R.J. *Finite Difference Methods for Ordinary and Partial Differential Equations*. Society for Industrial and Applied Mathematics, 2007.

Lundegaard C., Lund O., Kesmir C., Brunak S., and Nielsen M. Modeling the adaptive immune system: predictions and simulations. *Bioinformatics*, 23(24):3265–3275, 2007. ISSN 1460-2059. doi:10.1093/bioinformatics/btm471.

Marchuk G.I. *Mathematical modelling of immune response in infectious diseases*. Mathematics and its applications. Kluwer Academic Publishers, 1997. ISBN 9780792345282.

Marrocco A. Numerical simulation of chemotactic bacteria aggregation via mixed finite elements. *Math. Mod. Num. Analysis*, 37:617–630, 2003.

Perelson A.S., Patrick, and Nelson P.W. Mathematical analysis of hiv-1 dynamics in vivo. *SIAM Review*, 41:3–44, 1998.

Pigozzo A.B. *Implementacão computacional de um modelo matemático do sistema imune inato (in Portuguese)*. Master's Thesis, Federal University of Juiz de Fora, Juiz de Fora - MG, Brazil, 2011.

Pigozzo A.B., Macedo G.C., dos Santos R.W., and Lobosco M. Implementation of a computational model of the innate immune system. In *ICARIS*, pages 95–107. 2011.

Rocha P.A.F., Xavier M.P., Pigozzo A.B., de M. Quintela B., Macedo G.C., dos Santos R.W., and Lobosco M. A three-dimensional computational model of the innate immune system. In *ICCSA 2012*. (Accepted for Publication), 2012.

Shu C.W. and Osher S. Efficient implementation of essentially non-oscillatory shock-capturing schemes,ii. *J. Comput. Phys.*, 83:32–78, 1989. ISSN 0021-9991. doi:10.1016/0021-9991(89)90222-2.

Sloot P.M.A., Chen F., and Boucher C. Cellular automata model of drug therapy for hiv infection. In *Proceedings of the 5th International Conference on Cellular Automata for Research and Industry*, ACRI '01, pages 282–293. Springer-Verlag, London, UK, UK, 2002. ISBN 3-540-44304-5.

Sod G.A. A survey of several finite difference methods for systems of nonlinear hyperbolic conservation laws. *Journal of Computational Physics*, 27(1):1 – 31, 1978. ISSN 0021-9991. doi:DOI:10.1016/0021-9991(78)90023-2.

Sompayrac L. *How the Immune System Works*. Blackwell Publishing, 3 edition, 2008. ISBN 9781405162210.

Stefania B., Sara M., and Giuseppe V. Immune system modelling with situated cellular agents. In *First International Workshop on Multi-Agent Systems for Medicine, Computational Biol-*

ogy, and Bioinformatics, at 4th International Joint Conference on Autonomous Agents and Multiagent Systems (AAMAS 2005), July 25-29, 2005, Utrecht, The Netherlands, 2005. 2005.

Su B., Zhou W., Dorman K.S., and Jones D.E. Mathematical modelling of immune response in tissues. *Computational and Mathematical Methods in Medicine: An Interdisciplinary Journal of Mathematical, Theoretical and Clinical Aspects of Medicine*, 10:1748–6718, 2009.

Tay J.C. and Jhavar A. CAFISS: a complex adaptive framework for immune system simulation. In *SAC '05: Proceedings of the 2005 ACM symposium on Applied computing*, pages 158–164. ACM Press, New York, NY, USA, 2005.

Warrender C.E. *Modeling intercellular interactions in the peripheral immune system*. D.Sc. Thesis, The University of New Mexico, Albuquerque, New Mexico, 2004.

Zorzenon dos Santos R.M. and Coutinho S. Dynamics of hiv infection: A cellular automata approach. *Phys. Rev. Lett.*, 87:168102, 2001. doi:10.1103/PhysRevLett.87.168102.