**Proceeding Series of the Brazilian Society of Computational and Applied Mathematics**

# Modeling of leishmaniasis infection by using multi-agents systems

Viviane Galvão[1]

Instituto de Física, Universidade Federal da Bahia, 40210-340, Salvador – BA

Mestrado Profissional em Bioenergia, Faculdade de Tecnologia e Ciências, 41741-590 Salvador – BA, Brasil

José Garcia Vivas Miranda[2]

Instituto de Física, Universidade Federal da Bahia, 40210-340, Salvador – BA

Roberto Fernandes Silva Andrade[3]

Instituto de Física, Universidade Federal da Bahia, 40210-340, Salvador – BA

**Abstract**. The World Health Organization considers leishmaniasis as one of the six most important tropical diseases in the world. Actually, it is endemic in 88 countries and the different types of this disease affects approximately 12 million of people worldwide. Leishmaniasis is caused by protozoan parasites of the genus *Leishmania*. The mechanisms of the cellular response against leishmaniasis are not completely known. Additionally, there is still a lack of understanding on the metabolism of the parasite. In this way, we have developed and analyzed a computational model for the immune response to *Leishmania major* infection by using multi-agent systems. In our model, we have seven different cell types: *Leishmania major*, CD4-T cell (resting and activated), macrophage (resting, activated, infected, chronically infected), eosinophil (resting and activated), neutrophil, dendritic cell (resting and activated), and keratinocyte. Furthermore, there are void sites to simulate the mobility of the cells. Our model can simulate migration, activation, phagocytosis, and cellular death by lifetime. It was constructed on a three-dimensional cubic lattice. The results show that the kinetics of different cell types does not change for different lattice size. Furthermore, our results suggest that an agent-based approach is a suitable instrument for investigating the cellular interaction.

**Keywords**. multi-agent, leishmaniasis, computational model, immune response, protozoan infection

[1] vivgalvao@gmail.com
[2] vivasm@gmail.com
[3] randrade@ufba.br

 

# 1 Introduction

Leishmaniasis is one of the six most important tropical diseases worldwide. It is caused by a protozoan that belong to the genus Leishmania and, it is classified as a neglected tropical disease. Over 20 species of *Leishmania* are capable of causing human disease. Actually, this disease is endemic in 88 countries, affects around 12 million of people, has an annual incidence around two million cases worldwide, and causes over 50,000 deaths per year. Leishmaniasis is transmitted to humans and animals by the bite of female phlebotomine sandflies [3].

The most common forms of leishmaniasis are cutaneous, which causes skin sores, and visceral, which affects several vital organs. Mice are capable to control *L. major* infection and a cellular and response is developed by the immune system [10,13]. Macrophage is the primary host cell, dendritic cells promotes a CD4 T response, CD4 T cells activate macrophages, and activated macrophages clear the parasite [12] . The knowledge of the progression and control of leishmaniasis is important to identify the responsible factors for the migration of immune cells to the affected tissue. However, this mechanism are not completely understood [13].

Mathematical modeling of disease has become an indispensable tool to investigate the kinetics of immune response. This is possible due to the multiple sources of knowledge about parasite-host interactions and the emergent behavior of a population of immune cells. Recently, some computer models have been used to gain insight into a variety of diseases caused by protozoan. Examples includes Chagas disease [5-7,9], malaria [4], toxoplasmosis [14], and leishmaniasis [1,2,11]. Several approaches used to describe the disease evolution on a cellular level are based on differential equation, cellular automata and multi-agents. Thus, to verify the kinetics of the immune response, we have developed and analyzed a three-dimensional multi-agent-based model for *L. major* infection.

# 2 Computational model

Our computational model description follows the ODD protocol [8].

## 2.1 Purpose

The aim is to investigate the possibility of an agent-based model to simulate different types of cells in the immune response to *L. major*.

## 2.2 State variables and scales

Our computational model was developed in C++ language and it is stochastic. In this way, each simulations will present different results even when the same parameters and initial conditions are used. Our model was constructed on a three-dimensional cubic lattice, consisting of 100×100×100 discrete sites. This regular lattice represents an

DOI: 10.5540/03.2016.004.01.0054  

internal portion of a uniform infection area, hence it has periodic boundary conditions. The agents correspond to cellular groups with a analogous pattern of behavior due to the quantity of cells in the infected area is large.

All actions occur at invariable periods and the description of the infected area is discrete both in time and space. A site can be void or occupied by one distinct type of agent. This model includes seven different cell types: *L. major*, CD4-T cell, macrophage, eosinophil, neutrophil, dendritic cell, and keratinocyte. CD4 T cell, eosinophil, and dendritic cell can be found in two states: resting and activated. Additionally, a macrophage can be found in four states: resting, activated, infected, and chronically infected.

### 2.3 Process overview, scheduling, and initialization

CD4-T cell, macrophage (with exception of the chronically infected), eosinophil, neutrophil, dendritic cell, and keratinocyte can move randomly to void site by using the three-dimensional Moore neighborhood [15]. In this type of neighborhood, each site possess 26 neighboring sites. *L. major* and chronically infected macrophages cannot move, i.e., the position of these two type of agents is invariable. The total number of keratinocyte is constant, but the number of the other agent types can modify during the simulation.

Initially, the spatial distribution pattern of *L. major*, resting cells (macrophages, CD4 T, eosinophil, dendritic cell), neutrophil, and keratinocyte is random. The fraction of keratinocytes is given by the difference between the total number of agents and the total number of *L. major*, the resting cells (macrophages, CD4 T, eosinophil, dendritic cell), and neutrophils.

### 2.4 Submodels

In this simulation, the agents move and interact according to update rules executed at discrete time steps. Each site changes its state according to a local deterministic rule and the state of the all sites is determined through the transition rules. In this way, a illustrative representation to clarify our computational model rules is shown in Figure 1.

## 3 Results and Discussion

In this article, we have developed a multi-agent based model describing the interactions of all cells during the early stages of an infection caused by the protozoan parasite *Leishmania major*. Simulations have been considered for several sets of individual initial conditions. Therefore, every one of parameters were varied and all the steps of the model were equally followed in every one simulation. For each such set, 10 simulations runs were performed to obtain the average values to estimate the best parameters to describe our model. The model steps were equally followed in all simulations.

DOI: 10.5540/03.2016.004.01.0054  

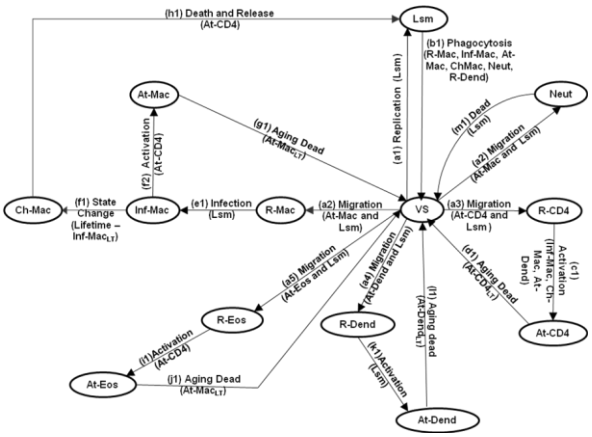


Figure 1: Diagram of interactions for various cell types considered in our *L. major* infection model. (a) If the site is void then: ($a_1$) change it into *L. major* (Lsm) when the number of $L_{sm}$ in its neighborhood is different from zero. ($a_2$) change it into resting macropahe (R-Mac) or neutrophil (Neut) with 50% probability for each one, when both the number of activated macrophage (At-Mac) and Lsm in its neighborhood is different from zero [10]. ($a_3$) change it into resting CD4 T cell (R-CD4) when both the number of activated CD4 T cell (At-CD4) and the number of Lsm in its neighborhood is different from zero [10]. ($a_4$) change it into resting dendritic cell (R-Dend) when both the number of activated dendritic cell (At-Dend) and Lsm in its neighborhood is different from zero [10]. ($a_5$) change it into resting eosinophil (R-Eos) cell when both the number of activated eosinophil (At-Eos) cell and the number of Lsm in its neighborhood is different from zero [10]. (b) If the site is occupied by a Lsm then: ($b_1$) change it into a void site (VS) when the number of Neut or R-Dend or R-Mac or At-Mac or infected macrophage (Inf-Mac) or chronically infected macrophage (Ch-Mac) in its neighborhood is different from zero [12]. (c) If the site is occupied by a R-CD4 then: ($c_1$) change it into an At-CD4 when the number of Inf-Mac or Ch-Mac or At-Dend in its neighborhood is different from zero [12]. (d) If the site is occupied by an At-CD4 then: ($d_1$) change it into a VS when when its age reaches the expected lifetime (At-CD4$_{LT}$). (e) If the site is occupied by a R-Mac then: ($e_1$) change it into an Inf-Mac when the number of Lsm in its neighborhood is different from zero [12]. (f) If the site is occupied by a Inf-Mac then: ($f_1$) change it into Ch-Mac after a lifetime (Inf-Mac$_{LT}$) due to the pathogen replication. ($f_2$) change it into an At-Mac when the number of At-CD4 in its neighborhood is different from zero [10]. (g) If the site is occupied by an At-Mac then: ($g_1$) change it into a VS when its age reaches the expected lifetime (At-Mac$_{LT}$). (h) If the site is occupied by a Ch-Mac then: ($h_1$) change it Lsm when the number of At-CD4 in its neighborhood is different from zero [10]. (i) If the site is occupied by a R-Eos then: ($i_1$) change it into a At-Eos when the number of At-CD4 in its neighborhood is different from zero [10]. (j) If the site is occupied by a At-Eos then: ($j_1$) change it into a VS when its age reaches the expected lifetime (At-Eos$_{LT}$). (k) If the site is occupied by a R-Dend then: ($k_1$) change it into a At-Dend when the number of Lsm in its neighborhood is different from zero [12]. (l) If the site is occupied by a At-Dend then: ($l_l$) change it into a VS when its age reaches the expected lifetime (At-Dend$_{LT}$). (m) If the site is occupied by a Neut then: ($m_l$) change it into a VS when the number of Lsm in its neighborhood is different from zero [10].

DOI: 10.5540/03.2016.004.01.0054  

Figure 2 shows the finite size effects of the used lattice in our study. The curves for *L. major*, CD4 T cell, neutrophil, and dendritic cell show that, for lattices consisting of L = 100, 200, and 300, the cellular kinetics rapidly approaches a stable regime. However, the quantity of macrophage has a slight decrease and the quantity of eosinophil has a tendency to increase and in time. In Figure 2a, we can observe that initially the quantity of *L. major* increases very rapidly. After reaching a maximum when the number of iterations is around 15, it decreases and tends to stabilize around 20% of the attained maximum. This pattern is due to the migration of immune cells to the skin. Additionally, the collapse of all curves indicates that the kinetics has become insensitive to the lattice size.

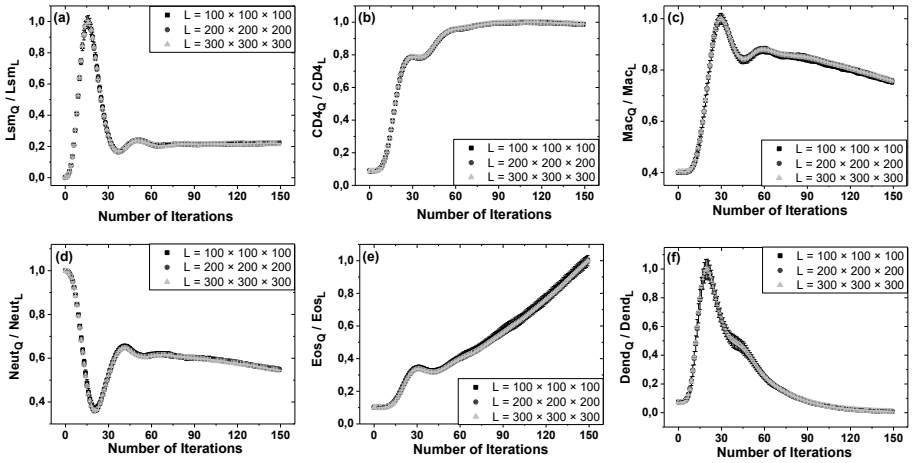


Figure 2: Finite size effects for the immune response to *L. major* for different lattice sizes (L). The specific initial values for agent types were: SO (lattice-site occupation) = 0,8, Lsm = $10^{-4}$, R-CD4 = $10^{-2}$, R-Mac = $2 \times 10^{-2}$, Neut = $2 \times 10^{-2}$, R-Eos= $2{,}5 \times 10^{-4}$, R-Dend = $10^{-4}$, while At-$CD4_{LT}$ = 3, Inf-$Mac_{LT}$ = 10, At-$Mac_{LT}$ = 13, At-$Eos_{LT}$ = 3, and At-$Dend_{LT}$ = 9. a) Kinetics of *L. major*. The drawn points indicate the number of *L. major* agents ($Lsm_Q$) is divided by its largest value during the simulation ($Lsm_L$). b) Kinetics of CD4 T cell. c) Kinetics of macrophage. d) Kinetics of neutrophil. e) Kinetics of eosinophil. f) Kinetics of dendritic cell. As in (a), points indicate number of CD4 T cells ($CD4_Q$), respectively ($Mac_Q$, $Neut_Q$, $Eos_Q$, $Dend_Q$), divided by corresponding largest value ($CD4_L$), respectively ($Mac_L$, $Neut_L$, $Eos_L$, $Dend_L$). (See Figure 1 for the meaning of the labels).

Figure 3 shows the kinetics of *L. major*, CD4 T cells, macrophages, neutrophils, eosinophils and dendritic cells for different fractions of lattice-site occupation. It is important to highlight that, if the quantity of void sites is small, the interaction between the agents becomes more difficult in the model. In this way, our results show that the larger the number of initially occupied sites, the larger is the final fraction of *L. major*, macrophage, and dendritric cell. Also, the final fraction of CD4 T cell and eosinophil tends to become constant. In addition, the final fraction of neutrophil is smaller when the fraction of lattice-site occupied is increased.

DOI: 10.5540/03.2016.004.01.0054  

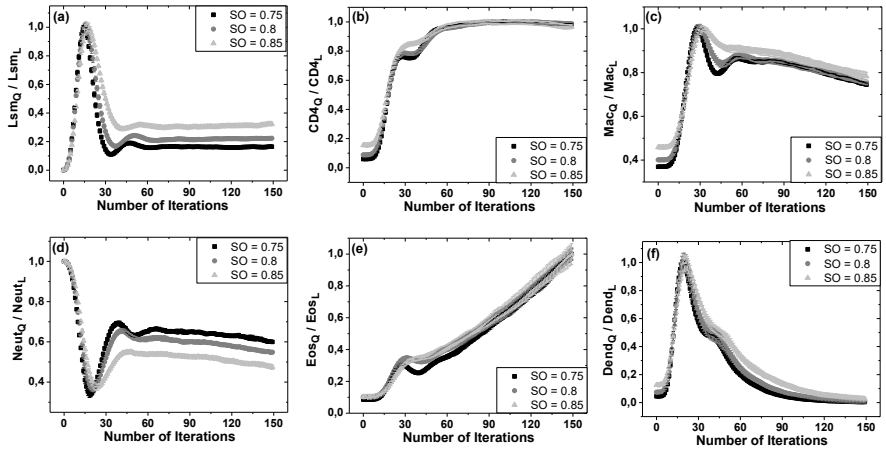


Figure 3. Immune response to *L. major* for different initial fractions of lattice-site occupation (SO). The other parameter values were: L = 100×100×100, Lsm = $10^{-4}$, R-CD4 = $10^{-2}$, R-Mac = $2 \times 10^{-2}$, Neut = $2 \times 10^{-2}$, R-Eos= $2{,}5 \times 10^{-4}$, R-Dend = $10^{-4}$, while At-$CD4_{LT}$ = 3, Inf-$Mac_{LT}$ = 10, At-$Mac_{LT}$ = 13, At-$Eos_{LT}$ = 3, and At-$Dend_{LT}$ = 9. a) Kinetics of *L. major*. b) Kinetics of CD4 T cell. c) Kinetics of macrophage. d) Kinetics of neutrophil. e) Kinetics of eosinophil. f) Kinetics of dendritic cell. (See Figure 1 and 2 for the meaning of the labels).

# 4 Conclusion

We have presented a three-dimensional agent-based model for immune response to *L. major* infection. It can reproduce some cellular properties including migration, activation, phagocytosis, and cellular death by lifetime. Our results suggest that an agent-based approach is a suitable instrument for investigating the cellular interaction. Thus, our computational model can capture the complex system dynamics whose properties depend on the collective behavior of the interacting components.

**Acknowledgement**

This work was supported by CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), and FAPESB (Fundação de Amparo à Pesquisa do Estado da Bahia).

# References

[1] G. M. Dancik, D. E. Jones and K. S. Dorman, Parameter estimation and sensitivity analysis in an agent-based model of *Leishmania major* infection, J. Theor. Biol., vol. 262, 398-412, (2010).

 

[2] M. C. de Almeida and H. N. Moreira, A mathematical model of immune response in cutaneous leishmaniasis, J. Biol. Syst., vol. 15, 313–354, (2007).

[3] P. Desjeux, Leishmaniasis: current situation and new perspectives, Comp. Immunol. Microbiol. Infect. Dis., vol. 27, 305-318, (2004).

[4] J. Ferrer, J. Vidal, C. Prats, J. Valls, E. Herreros, D. Lopez, A. Giro and D. Gargallo, Individual-based model and simulation of *Plasmodium falciparum* infected erythrocyte *in vitro* cultures, J. Theor. Biol., vol. 248, 448–459, (2007).

[5] V. Galvão and J. G. V. Miranda, Modeling the Chagas' disease after stem cell transplantation, Physica A, vol. 388, 1747–1754, (2009).

[6] V. Galvão and J. G. V. Miranda, A three-dimensional multi-agent-based model for the evolution of Chagas disease, Biosystems, vol. 100, 225-230, (2010).

[7] V. Galvão, J. G. V. Miranda and R. Ribeiro-dos-Santos, Development of a two-dimensional agent-based model for chronic chagasic cardiomyopathy after stem cell transplantation, Bioinformatics, vol. 24, 2051–2056, (2008).

[8] V. Grimm, U. Berger, D. L. DeAngelis, J. G. Polhill, J. Giske and S. F. Railsback, The ODD protocol: a review and first update, Ecol. Model., vol. 221, 2760-2768, (2010).

[9] S. C. Isasi, G. J. Sibona and C. A. Condat, A simple model for the interaction between *T. cruzi* and its antibodies during Chagas infection, J. Theor. Biol., vol. 208, 1-13, (2001).

[10] C. A. Janeway Jr., P. Travers, M. Walport and M. J. Shlomchik, Immunobiology: the immune system in health and disease, Garland Science, (2001).

[11] B. M. Langer, C. Pou-Barreto, C. Gonzalez-Alcon, B. Valladares, B. Wimmer and N. V. Torres, Modeling of leishmaniasis infection dynamics: novel application to the design of effective therapies, BMC Syst. Biol., vol. 6, 1-14, (2012).

[12] D. McMahon-Pratt and J. Alexander, Does the *Leishmania major* paradigm of pathogenesis and protection hold for New World cutaneous leishmaniases or the visceral disease?, Immunol. Rev., vol. 201, 206–224, (2004).

[13] H. W. Murray, J. D. Berman, C. R. Davies and N. G. Saravia, Advances in leishmaniasis, Lancet, vol. 366, 1561-1577, (2005).

[14] A. Sullivan, F. Agusto, S. Bewick, C. Su, S. Lenhart and X. Zhao, A mathematical model for within-host *Toxoplasma gondii* invasion dynamics, Math. Biosci. Eng., vol. 9, 647-662, (2012).

[15] M. Wooldridge, An introduction to multiagent systems, John Wiley & Sons, (2002).

DOI: 10.5540/03.2016.004.01.0054  