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# A three-dimensional multi-agent-based model for the evolution of Chagas' disease

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ABSTRACT

A better understanding of Chagas' disease is important because the knowledge about the progression and the participation of the different types of cells in this disease are still lacking. To clarify this system, the kinetics of inflammatory cells and parasite nests was shown in an experiment. Using this experimental data, we have developed a three-dimensional multi-agent-based computational model for the evolution of Chagas' disease. Our model includes five different types of agents: inflammatory cell, fibrosis, cardiomyocyte, fibroblast, and *Trypanosoma cruzi*. Fibrosis is fixed and the other types of agents can move through the empty space. They move randomly by using the Moore neighborhood. This model reproduces the acute and chronic phases of Chagas' disease and the volume occupied by all different types of cells in the cardiac tissue.



## 1. Introduction

Chagas' disease, caused by the protozoan *Trypanosoma cruzi*, affects tens of millions of people worldwide (WHO, 2002). *T. cruzi* parasite is transmitted by a blood-sucking insect of the sub-family Triatominae, or by blood transfusion. Chagas' disease has two distinct phases of progression. The acute phase is characterized by high numbers of *T. cruzi*, intense parasitism and inflammation. In the chronic phase, most of the *T. cruzi*-infected people remain in the asymptomatic or indeterminate form without any signs or clinical symptoms. However, around 30% of them present cardiac complications. Chronic chagasic cardiomyopathy (CChC) is characterized by the presence of inflammatory infiltrates in the heart, interstitial fibrosis, and scarce quantity of *T. cruzi* parasites (Higuchi et al., 2003; Soares et al., 2001a, 2004; Teixeira et al., 2006; Coura, 2007). In this phase, the occurrence of *T. cruzi* is related with a severe or moderate inflammation (Higuchi et al., 2003). The development of fibrosis is caused by the proliferation of fibroblasts and the subsequent deposition of interstitial collagens (Ten Tusscher and Panfilov, 2007).

The complex life cycle of *T. cruzi* has three morphological stages (trypomastigote, amastigote and epimastigote). An infected insect vector eliminates metacyclic trypomastigotes with the feces during the blood meal. Metacyclic trypomastigote enters into the bloodstream through the bite wound or through intact mucosal membranes. This form of *T. cruzi* can invade different types of cells, including macrophages, heart muscle, nerve tissue and digestive tract cells. Inside the cell, trypomastigotes differentiate into intracellular amastigotes. Amastigotes multiply by binary fission and after some divisions, amastigotes transform into trypomastigotes that are released after lyses of the host cell. The circulate parasites can invade other cells or be taken up by the insect vector during a blood meal. In the insect midgut, trypomastigotes transform into epimastigotes, which multiply and migrate to the hindgut. In the hindgut, they differentiate back to metacyclic trypomastigotes and are released in the insect feces (Andrade and Andrews, 2005; Kelly, 2000).

Recently, different theoretical models have been proposed to investigate the kinetics of diseases caused by parasites. Examples include AIDS (Bailey et al., 1992; Corne and Frisco, 2008; Figueiredo et al., 2008), malaria (Ferrer et al., 2007; Hoschen et al., 2000; McKenzie and Bossert, 2005; Zorzenon dos Santos et al., 2007), leishmaniasis (Nelson and Velasco-Hernández, 2002; de Almeida and Moreira, 2007), toxoplasmosis (González-Parra et al., 2009; Kafsack et al., 2007), tuberculosis (Segovia-Juarez et al., 2004; Magombedze et al., 2006) and Chagas' disease (Galvão et al., 2008; Galvão and Miranda, 2009; Isasi et al., 2001; Nelson and Velasco-Hernández, 2002; Sibona and Condat, 2002; Sibona et al., 2005). The inclusion of inflammatory cell, fibrosis, cardiomyocyte and fibroblast is lacking in the evolution models for the Chagas' disease. Thus, we propose in this article a three-dimensional multi-agent-based model for the evolution of Chagas' disease including these types of cells.

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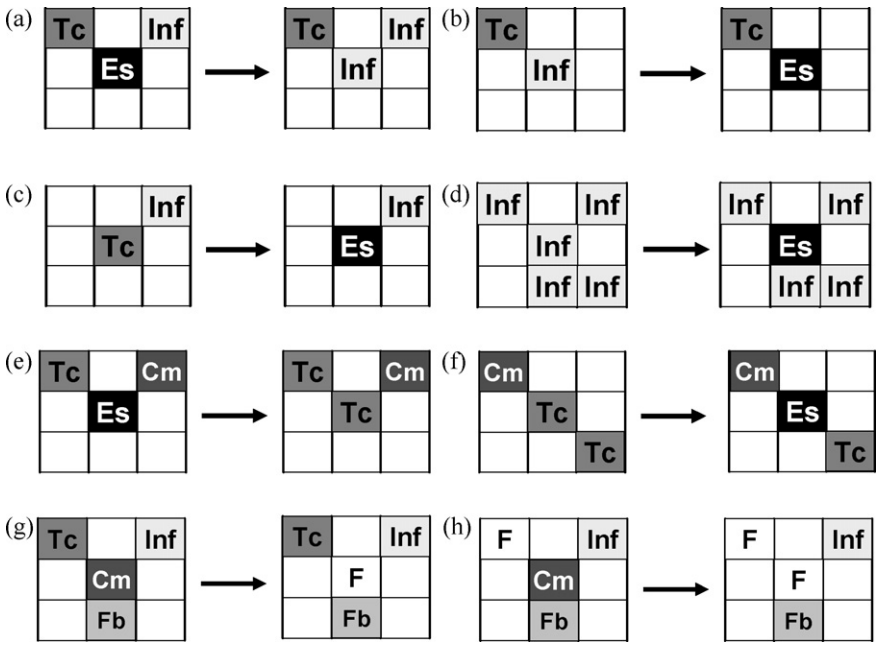


**Fig. 1.** Schematic representation of the transition rules. The Moore neighborhood is represented in two-dimensions for clarity. However, in our model we use the three-dimensional Moore neighborhood. (a) In the neighborhood of an empty space (Es), if the number of *T. cruzi* (Tc) and inflammatory cell (Inf) is different from zero, the Es site changes into Inf (Higuchi et al., 2003). (b) In the neighborhood of an Inf, if the number of Tc is different from zero, the Inf site changes into Es (Soares et al., 2001b). (c) In the neighborhood of a Tc, if the number of Inf is different from zero, the Tc site changes into Es (Soares et al., 2001b). (d) In the neighborhood of an Inf, if the number of Inf is greater than a determined value, the Inf site changes into Es (Andrade, 1999). (e) In the neighborhood of an Es, if the number of Tc and cardiomyocytes (Cm) is different from zero, the Es site changes into Tc (Andrade, 1999). (f) In the neighborhood of Tc, if the number of Tc and Cm is different from zero (de Souza et al., 2003), the Tc site changes into Es. (g) In the neighborhood of a Cm, if the number of Inf, Tc (Andrade, 1999) and fibroblast (Fb) (Ten Tusscher and Panfilov, 2007) is different from zero, the Cm site changes into fibrosis (F). (h) In the neighborhood of a Cm, if the number of Inf (Andrade, 1999), F and Fb (Ten Tusscher and Panfilov, 2007) is different from zero, the Cm site changes into F.

## 2. Computational Model

The description of our computational model follows the standard ODD protocol (Overview, Design concepts, and Details) for individual-based and agent-based models (Grimm et al., 2006).

### 2.1. Purpose

The purpose of this computational model is to understand the participation of different types of cells in the development of Chagas' disease.

### 2.2. State Variables and Scales

We have developed a software program in C++ language to simulate the evolution of Chagas' disease. A three-dimensional lattice consisting of a grid with $100 \times 100 \times 100$ points in size and periodic boundary conditions is employed to represent the cardiac tissue. The biological unit of the lattice simulated is obtained by the comparison with the experiment (Soares et al., 2001b). Our computational model includes different types of agents in which each type corresponds to a different type of cell. Each lattice site represents the space region that can only be occupied by a type of cell. The agents correspond to cellular groups with a similar pattern of behavior because the number of cells in the myocardial tissue is large. In a site, if the number of agent is zero; the site is referred to as empty space. All actions occur at constant intervals called time steps and the description of the chagasic tissue is discrete both in time and space.

This computational model includes five different types of agents: inflammatory cell, fibrosis, cardiomyocyte, fibroblast, and *T. cruzi*. The parameters are the total number of agents, the initial fraction of inflammatory cells, and the initial fraction of fibroblast. The fraction of cardiomyocytes is given by the difference between the total number of agents and the total number of inflammatory cells, fibroblast and *T. cruzi*. The experimental data (Soares et al., 2001b) of 7 months correspond to the 80 time steps of the model; therefore, each time step corresponds to around 2.625 experimental days.

### 2.3. Process Overview and Scheduling

Inflammatory cells, cardiomyocytes, fibroblast, and *T. cruzi* can move through the empty spaces. For simulating the cellular movement, each type of agent is selected randomly and can jump to empty space. These types of agent move randomly by using the three-dimensional Moore neighborhood. In this type of neighborhood, each cell possesses 26 neighboring cells situated in positions above, below, and to the sides (Wolfram, 1986). Fibrosis is fixed, i.e., this type of agent cannot move.

### 2.4. Design Concepts

*Emergence*: Population kinetics and structure emerge from the behavior of different types of cells. The evolution of chagasic tissue is completely represented by local and deterministic rules.

*Sensing*: Agents know their state, they recognize the state of the other agents and they apply the transition rules according to the state of their first neighbors.

*Interaction*: The system evolution is determined by interactions between the different types of agents (inflammatory cell, fibrosis, cardiomyocyte, fibroblast, and *T. cruzi*). The interactions occur in the neighborhood of an agent, i.e., they are locals.

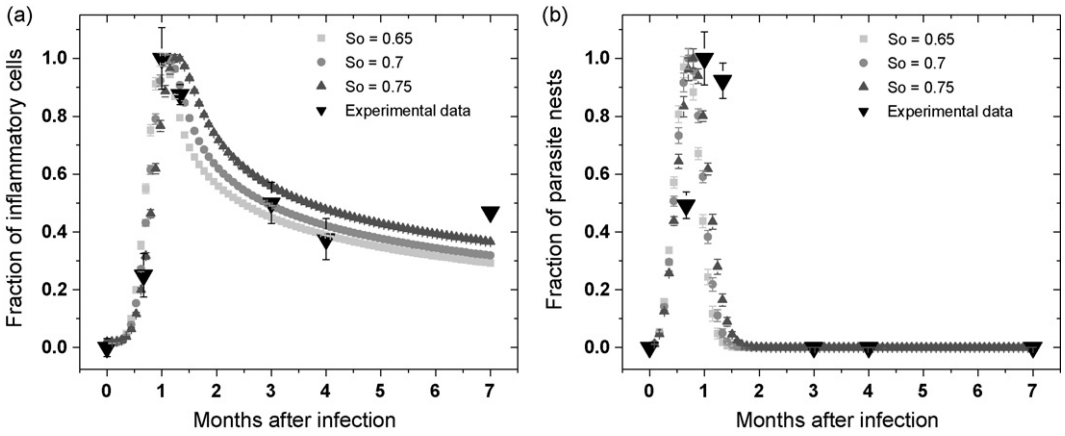


**Fig. 2.** Evolution of Chagas' disease by using different fractions of lattice-site occupation (So). The other parameters used were the initial fraction of inflammatory cells (Inf) equaling $2 \times 10^{-3}$, initial fraction of fibroblast (Fb) equaling $2 \times 10^{-3}$ and the number of inflammatory cells required for death of an inflammatory cell (NInf) is greater than 3. The experimental data were obtained by Soares et al. (2001b). (a) Kinetics of inflammatory cells. (b) Kinetics of parasite nests.

*Observation*: The number of inflammatory cells, parasite nests and quantity of fibrosis are statistically investigated at each time step.

### 2.5. Initialization

Inflammatory cells, cardiomyocytes, fibroblast, and *T. cruzi* have a random distribution. This distribution pattern is based on the experimental data obtained by Soares et al. (2001b). Initially, the cardiac tissue does not possess fibrosis; this type of agent only appears in the time evolution.

### 2.6. Input

We employ the same infective inoculum of 100 *T. cruzi* used by Soares et al. (2001b). Therefore, we use the same quantity of *T. cruzi* in all simulations and we only have one external input.

### 2.7. Submodels

The time evolution is run in the complete lattice and each site changes its state according to a local deterministic rule, which depends only on the neighboring cells. The state of the all sites is determined through the transition rules that depend on a set of rules. This model simulates the acute and chronic phases of Chagas' disease using the cell properties in the chagasic tissue. Our model has eight transition rules for simulate the evolution of Chagas' disease. A schematic representation to explain the transition rules of our model is shown in Fig. 1. The transition rules are as follow:

(i) In the neighborhood of an empty space site, if the number of inflammatory cells and *T. cruzi* is different from zero, the empty space site changes into inflammatory cell (Higuchi et al., 2003). This rule simulates the migration of an inflammatory cell to infected tissue.
(ii) In the neighborhood of an inflammatory cell, if the number of *T. cruzi* is different from zero, the inflammatory cell site changes into empty space (Soares et al., 2001b). This rule simulates the inflammatory cell death by phagocytosis of *T. cruzi*.
(iii) In the neighborhood of a *T. cruzi*, if the number of inflammatory cells is different from zero, the *T. cruzi* site changes into empty space (Soares et al., 2001b). This rule simulates the *T. cruzi* phagocytosis by inflammatory cells.
(iv) In the neighborhood of an inflammatory cell, if the number of inflammatory cells is greater than a determined value, death of inflammatory cells occurs (Andrade, 1999), i.e., the inflammatory cell site changes into empty space. This rule simulates the inflammatory cells death by space and resource competition.
(v) In the neighborhood of an empty space, if the number of *T. cruzi* and cardiomyocytes is different from zero, the empty space site changes into *T. cruzi* (Andrade, 1999). *T. cruzi* replication occurs inside the cardiomyocyte, but our model cannot exactly simulate this replication, because the site can only be occupied by a different type of agent. Therefore, *T. cruzi* replication is simulated in the neighborhood of a cardiomyocyte.
(vi) In the neighborhood of *T. cruzi*, if the number of *T. cruzi* and cardiomyocytes is different from zero (de Souza et al., 2003), death of *T. cruzi* occurs, i.e., the *T. cruzi* site changes into empty space. The death of *T. cruzi* occurs inside the cardiomyocyte, but our model cannot exactly simulate this death, because the site can only be occupied by a different type of agent. Hence, the death of *T. cruzi* by resource and space competition is simulated in the neighborhood of a cardiomyocyte and it occurs more frequently in the acute phase of Chagas' disease.
(vii) In the neighborhood of a cardiomyocyte, if the number of inflammatory cells, *T. cruzi* (Andrade, 1999) and fibroblast (Ten Tusscher and Panfilov, 2007) is different from zero, the cardiomyocyte site changes into a new fibrosis. This rule simulates the formation of new fibrosis areas in the chagasic heart.
(viii) In the neighborhood of a cardiomyocyte, if the number of inflammatory cells (Andrade, 1999), fibrosis and fibroblast (Ten Tusscher and Panfilov, 2007) is different from zero, the cardiomyocyte site changes into fibrosis. This rule simulates the cluster formation of fibrosis by the autoimmune response.

## 3. Results and Discussion

For each set of parameters, the average value of 20 simulation runs was taken in order to better describe the development of Chagas' disease. The parameters optimization was carried out using the best fit corresponding to the experimental data (Soares et al., 2001b) of 7 months. The model steps were equally followed in all simulations. The inflammatory cells and parasite nests were normalized to allow a comparison between computational

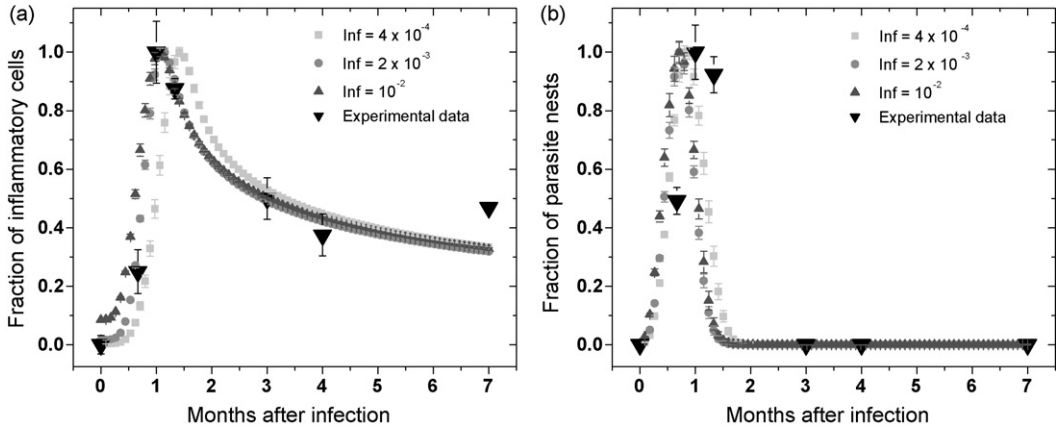


**Fig. 3.** Evolution of Chagas' disease by using different fractions of inflammatory cells. The other parameters used were So = 0.7, Fb = $2 \times 10^{-3}$ and NInf > 3. The experimental data were obtained by Soares et al. (2001b). (a) Kinetics of inflammatory cells. (b) Kinetics of parasite nests. (See Fig. 2 for the meaning of the labels.)

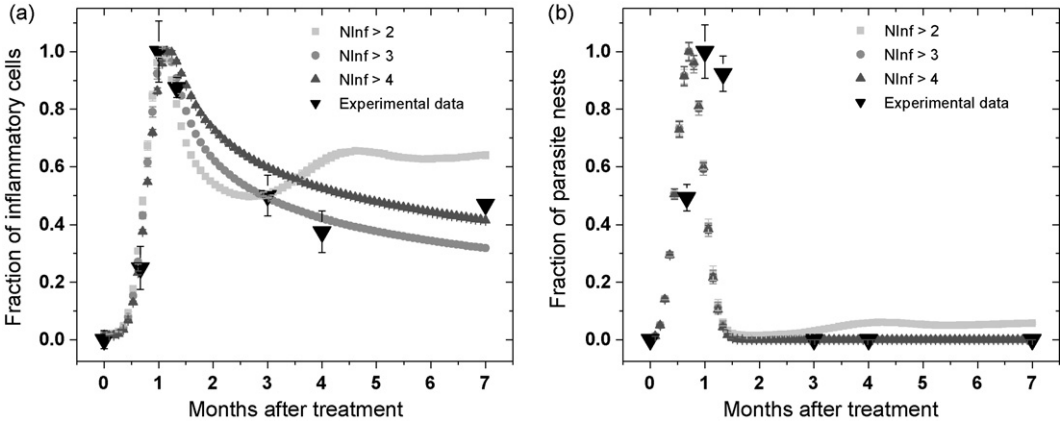


**Fig. 4.** Evolution of Chagas' disease by using different number of inflammatory cells required for death of an inflammatory cell. The other parameters used were So = 0.7, Inf = $2 \times 10^{-3}$ and Fb = $2 \times 10^{-3}$. The experimental data were obtained by Soares et al. (2001b). (a) Kinetics of inflammatory cells. (b) Kinetics of parasite nests. (See Fig. 2 for the meaning of the labels.)

and experimental data. The normalization was done by the same method. All data were divided by the larger value of the respective data set.

We compare the predictions of our multi-agent-based model with the experimental results for the evolution of Chagas' disease until the CChC obtained by Soares et al. (2001b). In this model, IL-4-deficient and wild-type BALB/c mice were infected by inoculation of *T. cruzi* by intraperitoneal route. Groups of mice were sacrificed at 0.66, 1, 1.33, 3, 4 and 7 months after infection. At these time points, the number of parasite nests per square centimeter and inflammatory cells per square millimeter were counted in the heart. After the acute phase, the authors noted that the hearts of wild-type mice had scarce inflammatory foci and the IL-4-deficient mice had scarce inflammatory foci and the IL-4-deficient mice had a visible inflammatory reaction. In addition, in the chronic phase the quantity of parasite nests is very small in both types of mice. We have compared our results with the experimental results of IL-4-deficient mice because these mice are more resistant to *T. cruzi* infection, the myocarditis is exacerbated, and they survive longer than the wild-type.

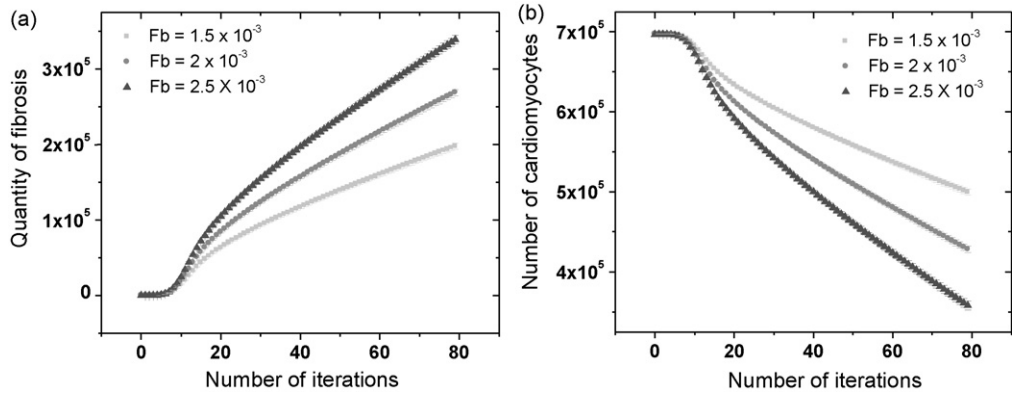


**Fig. 5.** Evolution of Chagas' disease by using different fractions of Fb. The other parameters used were So = 0.7, Inf = $2 \times 10^{-3}$ and NInf > 3. (a) Kinetics of fibrosis progression. (b) Kinetics of cardiomyocytes death. (See Fig. 2 for the meaning of the labels.)

Fig. 2 shows the kinetics of inflammatory cells and parasite nests for different fractions of lattice-site occupation. As our model is three-dimensional, this fraction corresponds to the volume fraction occupied by cells. The best fit of our data with the experimental data was obtained with the fraction of lattice-site occupation 0.7. According to Vinnakota and Bassingthwaighte (2004) the volume fraction occupied by all types of cells in the rat myocardial tissue is $0.694 \pm 0.025$. Hence, our model reproduces the cellular volume of the cardiac tissue. Additionally, our results show that the larger the number of sites occupied, the larger the final fraction of inflammatory cells. This happens because it is more difficult for an inflammatory cell to meet others inflammatory cells once the fraction of empty spaces is small. Also, the quantity of parasite nests spends a little more time to stabilize around zero because it is more difficult for a *T. cruzi* to meet an inflammatory cell when the fraction of empty spaces is small.

The kinetics of inflammatory cells and parasite nests for different fractions of inflammatory cells is shown in Fig. 3. We can observe that the number of inflammatory cells increases rapidly, after it has a gradual reduction and lastly tends to stabilize. The quantity of this type of cell continues decreasing when the number of *T. cruzi* is practically zero due to the occurrence of inflammatory cell death by space competition [rule (iv)]. The number of parasite nests increases very rapidly, after decreases, and lastly is around zero. In the acute phase of Chagas' disease, the number of inflammatory cells and parasite nests is large. In the chronic phase, the number of inflammatory cells tends to become stable and the number of parasite nests is scarce. In this way, our model simulates the acute and chronic phases of this disease.

In Fig. 4 we vary the number of inflammatory cells required for death of an inflammatory cell. Our results show that the difference of one unit in the number of inflammatory cells modifies the behavior of the inflammatory cells. The number of inflammatory cells decreases very rapid when the number of inflammatory cells required for death of an inflammatory cell is greater than 2 and this cause an increase in the number of parasites. Consequently, the number of inflammatory cells increases because the number of parasites is elevated. After this, the number of inflammatory cells and parasites tends to stabilize in a high value. However, the parasite curve is less affected by the variation of this parameter because it does not depend directly on this parameter for the transition rule.

The kinetics of fibrosis progression and cardiomyocytes death for different fractions of fibroblasts is shown in Fig. 5. Our data show that the larger the final fraction of fibrosis, the smaller the final fraction of cardiomyocytes. This is related because several studies on CChC suggest that during the expansion of this disease the fibrosis progression is associated with the cardiomyocyte death (Rossi and Souza, 1999).

According to the experimental data, the best computational parameters of our model to describe the evolution of Chagas' disease were selected. They are the initial fraction of lattice-site occupation equaling 0.7, initial fraction of inflammatory cells equaling $2 \times 10^{-3}$, initial fraction of fibroblast equaling $2 \times 10^{-3}$ and the number of inflammatory cells required for death of an inflammatory cell is greater than 3. The numerical value of inflammatory cells and fibroblast was not compared to experimental data, because the value of these parameters was not determined in the experiment developed by Soares et al. (2001b).

## 4. Conclusion

In this article, we have presented a three-dimensional multi-agent-based model to represent the evolution of Chagas' disease. This model reproduces the acute and chronic phases of *T. cruzi* infection. Therefore, it simulates the kinetics of parasite nests, inflammatory cells, fibrosis progression and cardiomyocyte death. Also, it reproduces the volume occupied by all different types of cells in the myocardial tissue. The main aim is to understand the participation of different types of cells in the development of CChC.

Our results were compared with experimental data (Soares et al., 2001b), excepting for the kinetics of fibrosis progression and cardiomyocytes death, giving a good agreement. This implies that our model rules can be used to understand the evolution of Chagas' disease. Furthermore, different authors propose several hypotheses that have never been investigated by using a proper computational model. The results show that the microscopic rule of the autoimmune response is important for the modelling of CChC. Our data show that the initial fraction of lattice-site occupation and the number of inflammatory cells required for death of an inflammatory cell modify the kinetics of inflammatory cells and parasite nests. Also, the initial fraction of inflammatory cells has less influence on the kinetics of inflammatory cells and parasite nests. This occurs because the immunological system has a rapid autoregulatory response due to the migration [rule (i)] and death [rules (ii) and (iv)]. Finally, the initial fraction of fibroblasts modifies the fibrosis progression and the cardiomyocyte death.

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