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Modeling the Chagas' disease after stem cell transplantation

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ABSTRACT

A recent model for Chagas' disease after stem cell transplantation is extended for a three-dimensional multi-agent-based model. The computational model includes six different types of autonomous agents: inflammatory cell, fibrosis, cardiomyocyte, proinflammatory cytokine tumor necrosis factor-α, *Trypanosoma cruzi*, and bone marrow stem cell. Only fibrosis is fixed and the other types of agents can move randomly through the empty spaces using the three-dimensional Moore neighborhood. Bone marrow stem cells can promote apoptosis in inflammatory cells, fibrosis regression and can differentiate in cardiomyocyte. *T. cruzi* can increase the number of inflammatory cells. Inflammatory cells and tumor necrosis factor-α can increase the quantity of fibrosis. Our results were compared with experimental data giving a fairly fit and they suggest that the inflammatory cells are important for the development of fibrosis.

1. Introduction

The discovery of the pluripotency of adult bone marrow stem cells has opened new perspectives for the treatment of patients with chronic chagasic cardiomyopathy. This disease is caused by the hemoflagellate parasite *Trypanosoma cruzi* and one of the leading causes of heart failure in Latin America. Chagas' disease is transmitted by an insect of the subfamily *Triatominae*, or by blood transfusion. Most of the *T. cruzi*-infected individuals remain asymptomatic. This subclinical state is called the indeterminate form of Chagas' disease. However, around 30% of the *T. cruzi*-infected individuals develop a cardiac complication, in a late phase of the disease. Chronic chagasic cardiomyopathy is characterized by a diffuse inflammatory reaction and a severe fibrosis [1–4]. In the chronic phase of the disease, the presence of *T. cruzi* is associated with chronic inflammatory response [2]. The elevated production of the proinflammatory cytokine tumor necrosis factor-α (TNF- α) causes the fibrosis growth [4].

The regenerative potential of bone marrow stem cell transplantation has been under investigation in experimental models of ischemic cardiomyopathy and chronic chagasic cardiomyopathy [4,5]. A stem cell is a particular type of cell that can renew itself and possesses ability to divide in many different types of specialized cells [5–7]. Experimental evidences have shown that the transplant of bone marrow stem cell can promote apoptosis in non-normal cells and can differentiate into a normal cell of the tissue [5]. An experimental model to describe the effects of adult bone marrow transplant in the chronic chagasic cardiomyopathy was developed by Soares et al. [4]. In this model, bone marrow cells were injected into chronic chagasic mice leading to a considerable reduction in the number of inflammatory cells and in the fibrosis area. The authors suggest that bone marrow stem cells can promote apoptosis of inflammatory cells and fibrosis regression.

The scientific contribution in computational models for parasites includes interaction between *T. cruzi* and antibodies during the acute phase of Chagas infection [8,9], competitive parasite–antibody interaction in the intracellular and

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extracellular phase of the Chagas' disease [10], cell-mediated immune response to Leishmaniasis and Chagas' disease [11], dynamics of *Plasmodium falciparum* invasion of the human erythrocyte cells [12], mathematical model of immune response in cutaneous Leishmaniasis [13], cellular automata model for the dynamical aspects of parasitemia in the blood cycle of malaria [14] and time delay effect in the *Plasmodium* of *Physarum polycephalum* by using the living coupled oscillator system [15].

In recent years, some different theoretical models have been proposed to understand the kinetics of stem cells. These models are based on cellular automata [16], agent systems [17], differential equations [18], co-clustering latent variable models [19], Bayesian network [20,21], lattice [22], stochastic lattice [23], and other mathematical models [24–27]. In this way, we have recently developed a two-dimensional agent-based model for Chagas' disease [28] after bone marrow stem cell transplantation. The main aim of this computational model was to understand the participation of different types of cells in the chagasic tissue regeneration after bone marrow stem cell transplantation. The two-dimensional model only simulated the heart sections and the fibrosis regression had small discrepancies between the computational and experimental data.

In order to better understand the behavior of fibrosis after bone marrow stem cell transplantation, the model was extended here for a three-dimensional multi-agent-based model. Also, the transition rule for fibrogenesis was changed to include the influence of inflammatory cells in the development of fibrosis. The strong point of this type of study lies in the possibility of validating hypothesis about the behavior of different types of cells. In our computational model the hypothesis are presented by rules that simulate the cellular kinetics. The reasons for developing this model are the increase of realism due to the reproduction of chagasic cardiac tissue in three-dimensions and to better comprehend the increase of fibrosis. The advantages of this model in relation to our previous model [28] are to simulate the volume of the heart and the inclusion of inflammatory cells in the fibrosis progression.

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 [29].

2.1. Purpose

The purpose of this computational model is to comprehend how the spatial change affects the contribution of different types of cells in the chronic chagasic cardiomyopathy regeneration after bone marrow stem cell transplantation.

2.2. State variables and scales

The three-dimensional rectangular lattice is composed by a grid of cubic cells, called sites. The lattice consists of $100 \times 100 \times 100$ points in size, which represents the chagasic cardiac tissue. This rectangular lattice possesses periodic boundary conditions and each site represents the region of space which only a type of autonomous agent can occupy. To make the model more realistic each agent represents a single cell. The system description is discrete in time and space and all actions occur at constant intervals called time steps. Each autonomous agent can be present or absent in a particular site. In a site, if the number of agents is zero; the site is referred to as empty space. Therefore, the empty space site is equivalent to space in real system that is not occupied by an agent. In addition, each type of autonomous agent represents a different type of cell.

In our model six different types of agents are distinguished: inflammatory cell, fibrosis, cardiomyocyte, TNF-α, *T. cruzi*, and bone marrow stem cell. The parameters of this model are the total number of autonomous agents and the initial fractions of fibrosis, inflammatory cells, bone marrow stem cells, TNF-α, and *T. cruzi*. The fraction of cardiomyocytes is given by the difference between the total number of agents and the total number of the other types of cells. Our model represents time as discrete time steps with a fixed duration and the time evolution is equally run in the entire lattice. In our model, 1000 time steps correspond to the experimental data [4] of five months; therefore one time step corresponds to approximately 3.6 h of "real time".

2.3. Process overview and scheduling

At each time-step, the same sequence of actions occurs sequentially and builds the configuration of the next step scenario. The inflammatory cells, cardiomyocytes, TNF-α, *T. cruzi*, and bone marrow stem cells can jump to empty space. These types of agents move randomly using the three-dimensional Moore neighborhood. In this case, each site has twenty six adjacent neighbors [30]. Only the fibrosis is fixed. The procedures applied by the different types of agents are described by five rules in the section "Submodels".

2.4. Design concepts

Emergence: Population dynamics and structure emerge from the behavior of cells. The chagasic tissue regeneration is represented entirely by local and deterministic rules, describing, for example, the apoptosis of inflammatory cells and fibrosis reduction.