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Agent based deterministic model of the adult subventricular neurogenesis

M.P. Kurhekar *, U.A. Deshpande

Department of Computer Science and Engineering, Visvesvaraya National Institute of Technology, Nagpur, Maharashtra, 440010, India

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ABSTRACT

There is a significant interest in studying adult subventricular neurogenesis to understand its biological function. Adult subventricular neurogenesis results in migration of neuronal precursors from subventricular zone to the olfactory bulb through the rostral migratory stream where they get converted to neurons. In this paper, we present a deterministic model of adult subventricular neurogenesis. This model captures the essence of neurogenesis by incorporating the neural stem cells, rapidly proliferating intermediate cells and the neurons. It also captures radial dispersion of neurons into the olfactory bulb. Our model incorporates stem cell death (apoptosis) over certain number of stem cell divisions resulting into reduction in the generation of neurons with time, which mimics aging. It demonstrates the steady production of sufficient number of neurons. We prove that our model of adult subventricular neurogenesis is biologically feasible and it overcomes the limitations of previously reported models. We believe that our model will help in devising experiments to further improve the understanding of adult subventricular neurogenesis.

We have performed agent based simulation of the model proposed in this paper. The results of this simulation are given in the Appendix. This program is made available on a publicly accessible website.

1. Introduction

Stem cells and their descendants are the building blocks of life. How stem cell populations guarantee their maintenance and self-renewal, and how individual stem cells decide to transit from one cell stage to another to generate different types of mature differentiated cells are long standing and fascinating questions [1]. There is a significant interest in studying stem cells, both to elucidate their basic biological functions during development and adulthood as well as to learn how to utilize them as new sources of specialized cells for tissue repair. There are several major challenges within the field, which include the identification of new signals and conditions that regulate and influence cell functions, and application of this information towards the design of stem-cell bioprocesses and therapies. Both of these efforts can significantly benefit from the synthesis of biological data into quantitative and increasingly mechanistic models that not only describe, but also predict, how a stem cell's environment can control its fate [2].

One of the reasons for studying the stem cells in the subventricular zone of the brain is that it is one of the only two regions in the adult brain that undergoes active neurogenesis. The other is the hippocampal region of the brain [3,4]. Neurogenesis is the process of formation of new neurons. Adult neurogenesis is important in memory formation and odor discriminations. Alterations in adult hippocampal neurogenesis may result in psychiatric diseases in humans [5]. Age is another factor that affects the functioning of the brain. In fact, how the brain function deteriorates with aging is still not clearly understood. If slowing

* Corresponding author.
E-mail addresses: manishkurhekar@cse.vnit.ac.in (M.P. Kurhekar), uadeshpande@cse.vnit.ac.in (U.A. Deshpande).

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or reversal of brain damage can be achieved by controlling adult neurogenesis, then there is a possibility of gaining some of the lost abilities of the brain functions due to aging. Consequently, a lot of work is being carried out to study the mechanisms involved in the dynamics of the brain cells.

Olfactory bulb facilitates odor encoding and discrimination [6]. Neurogenesis that occurs in the subventricular zone and the olfactory bulb of the brain starts at the base of subventricular zone, where the quiescent stem cells, the *B*-cells reside. These *B*-cells are activated by chemical signals which are generated in the olfactory bulb and are induced to generate proliferating neural stem cells, called as the *C*-cells. These *C*-cells rapidly proliferate and generate neuroblast precursors, called the *A*-cells. These *A*-cells travel through the rostral migratory stream (RMS) to reach the olfactory bulb. Once these *A*-cells reach the olfactory bulb, they move radially outwards to reach the edge of the olfactory bulb, where they get converted to neurons [7,8]. This has been confirmed by the data provided by Wang et al. [9].

Several attempts have been made to model the neurogenesis in the subventricular zone and the olfactory bulb of the brain. A recent one being the paper by Ashbourn et al. [10]. They model the system with partial differential equations assuming that a single chemo-attractant is responsible for cell migration, secreted both by the olfactory bulb and in an endocrine fashion by the cells involved in neurogenesis. The solutions to the system of partial differential equations are compared with the physiological murine process. The solution obtained from partial differential equations over sufficiently long time corresponds to physiologically plausible solutions and they generally obey constraints similar to the conditions reported in-vivo. The model is very complex with large number of parameters and detailed parameter fitting was required for agreement with observed values in murine brain. Their model, although, has ignored the complex radial migration of *A*-cells.

In this paper, we have attempted to deterministically model the neurogenesis in the subventricular zone of the brain. Earlier, we had proposed a deterministic model of the bone marrow [11] but that model lacked any geometry and only local environment affected the fate of the cells. Later we proposed a deterministic model of crypts in the small intestine [12] which had a fixed geometry, but in that model the cells were affected only by the local influencing environment. In this paper, we deterministically model the adult subventricular neurogenesis in which the model has a fixed geometry and the cell fate is also dependent on chemo-attractants that are generated spatially away from the site of proliferation. The theoretical proofs based on the proposed model as well as the outcomes obtained by the agent based modeling simulation reinforce the biological observations of the adult subventricular neurogenesis. This paper is an extension of our earlier conference paper [13]. Compared to the conference paper, this paper contains detailed proofs of all the claims made for the model. This paper also contains Appendix which explains the agent based simulation that is developed for the proposed model and the results obtained.

The paper is organized as follows. In the next section, we describe the model and the rules that govern it. In Section 3, we show that the model provides a steady supply of neurons to the olfactory bulb. In Section 4, we compute the duration of neurogenesis. We discuss the results of the theoretical modeling in Section 5. The details and the results of the agent based simulation are included in Appendix.

2. Model of the adult subventricular neurogenesis

We propose a model of the adult subventricular neurogenesis. The model contains the following basic types of cells:

- **Type-*B* cell (Quiescent Stem cell)**, denoted by *B*, proliferates asymmetrically generating type-*B* stem cell and a new type-*C* proliferative stem cell if the concentration of neurons in the olfactory bulb is less than a threshold, otherwise, it remains quiescent.
- **Type-*C* cell (Proliferative Stem cell)**, denoted by *C*, is a rapidly proliferating cell which either divides symmetrically into two type-*C* cells inside the subventricular zone or divides asymmetrically into a type-*C* cell and a new type-*A* neuroblast precursor cell when it reaches the edge of the rostral migratory stream.
- **Type-$\bar{A}$ cell (Neuroblast precursor cell)**, denoted by *A* or $\bar{A}$, is an intermediate cell which travels along the path known as the rostral migratory stream. These cells have limited proliferation abilities. After reaching the center of the olfactory bulb, these cells travel radially outwards and get converted to neurons once they reach the edge of the olfactory bulb. The *A*-cell denotes the neuroblast precursor cell that is traveling along the rostral migratory stream and the $\bar{A}$-cell denotes the neuroblast precursor cell that is migrating radially outwards in the olfactory bulb.
- **Neurons (Differentiated cell)**, denoted by *N*, is the final product of neurogenesis. Neurons are created after the $\bar{A}$ cells reach near the edge of the olfactory bulb. After generation, the neurons migrate radially outwards and occupy the edge of the olfactory bulb. After maturation, they die leaving empty the space they had occupied earlier.
- **Empty space**, denoted by *E*, represents vacant space.

Along with the above specifications of cell types, we need a few more notations for the model of adult subventricular neurogenesis, which we describe next. In our model, the subventricular zone and the olfactory bulb of the brain can be considered to be represented geometrically as a connected locally finite directed graph. This graph describes the neighborhood of the individual cells.

Let $G = (V, L)$ be a connected, locally finite directed graph that denotes the part of the brain that houses the subventricular zone, the rostral migratory stream and the olfactory bulb. Its vertex set V and edge set L describes the individual cells in the brain and their neighborhood respectively. The vertices are arranged in a fixed shape with subventricular zone at the bottom. Connected to the subventricular zone is a narrow rostral migratory stream. The rostral migratory stream is connected to a bulging olfactory bulb. The directed edges are defined from the cells occupying a lower level to the neighboring cells at the

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