# A Deterministic Model of the Adult Subventricular Neurogenesis

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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 this phenomenon. It demonstrates the steady production of sufficient number of neurons. We prove that our model 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 and the program for agent-based simulation is made available on a publicly accessible website.

## Categories and Subject Descriptors

I.6.3 [**Simulation and Modeling**]: Applications
; J.3 [**Computer Applications**]: Life and Medical Sciences—*Biology and genetics*

## General Terms

Experimentation, Theory

## Keywords

Discrete Modeling, Agent Based Simulation, Modeling of Neurogenesis

## 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 [5]. 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 function, 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 [4].

Neurogenesis that occurs in subventricular zone and 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 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 [2].

Several attempts have been made to model the neurogenesis. A recent one being the paper by Ashbourn et al. [2]. 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 rodent 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 has ignored the complex radial migration of $A$-cells.

In this paper, we deterministically model the adult subventricular neurogenesis in which it has a fixed geometry and the cell fate is dependent on chemo attractants 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

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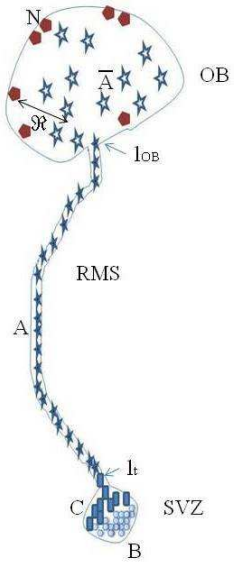


**Figure 1: Schematic diagram showing SVZ, RMS and OB with $B$, $C$, $A$, $\bar{A}$, and $N$ cells.**

the biological observations of the adult subventricular neurogenesis. In the next section, we describe our model and the rules that govern it.

## 2. MODEL OF 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 $B$.
- **Type-$C$ cell (Proliferative Stem cell)**, denoted by $C$.
- **Type-$A$ cell (Neuroblast precursor cell)**, denoted by $A$ or $\bar{A}$.
- **Neurons (Differentiated cell)**, denoted by $N$.
- **Empty space**, denoted by $E$.

Let $G = (V, L)$ be a connected, locally finite undirected 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. For every $u, v \in V$ we denote by $\rho(u, v)$ the distance between these vertices in the shortest-path metric induced by $G$. If $U \subseteq V$ is a nonempty subset of vertices then for every $v \in V$ let $\rho_{U(v)} = min_{u \in U}(u, v)$ be the minimum distance between $v$ and another vertex $u$ contained in set $U$. $N(v)$ denotes the immediate neighborhood of $v$. The levels, termed $l$, are the $y$-axis coordinates and the displacements, termed $d$, are the $x$-axis coordinates for all cells. A corner at the base of subventricular zone can be considered as origin.

The $B$-cells occupy the base of the subventricular zone. These $B$-cells are the quiescent stem cells. The proliferative stem cells, the $C$-cells, occupy all the remaining levels of the subventricular zone above the quiescent stem cells. Every $C$-cell has $\mu$ immediate neighbors. $C$-cells occupy levels till level $l_t$, which marks the beginning of the rostral migratory stream. After this level they get converted to neuroblast precursor cells, the $A$-cells. These $A$-cells are intermediate precursor cells that occupy several levels between the subventricular zone to the olfactory bulb across the rostral migratory stream. After reaching the olfactory bulb, the $A$-cells get converted to $\bar{A}$-cells and start moving radially outwards. After reaching near the edge of the olfactory bulb, these $\bar{A}$-cells get converted to neurons, i.e. the $N$-cells. The mid point of the beginning of the olfactory bulb at level $l_{OB}$ is termed as the center of the olfactory bulb. This is denoted with the $x$-axis and $y$-axis coordinates as ($d_{OBC}$, $l_{OBC}$) in two-dimensional model of space. The edge of the olfactory bulb is assumed to begin at a distance of radius $\Re$ from the center of the olfactory bulb. The $A$-cells can proliferate in the rostral migratory stream, but the proliferation abilities of $A$-cells reduces significantly with each subsequent generation [1]. The direction of all proliferations is towards the olfactory bulb and it is considered to be in the upward direction from the subventricular zone (see Figure 1).

We are now in a position to formally define our model. Let $\Omega$ be the set of states of all the cells of the brain graph. A map $x : V \to \Omega$ is the state of the entire graph. The set of all states of the brain graph $G$ is denoted by $\Omega^V$. A state $x \in \Omega^V$ of graph $G$ at time $t$ is denoted by $x^t$. The state of vertex $v$ at time $t$ is denoted by $x^t(v)$. The state of a vertex is a 5-tuple for $B$-cell, 4-tuple for $\bar{A}$-cell and $N$-cell, and 6-tuple for $C$-cell and $A$-cell. The first coordinate of each tuple denotes the cell type ($B$, $C$, $A$, $\bar{A}$, or $N$). In all cells, the last coordinate denotes simulated time $\tau$ as an internal counter. Finally, the state of an empty space has a single coordinate that denotes its type $E$.

For a $B$-cell, the second coordinate denotes the number of times the stem cell has proliferated. The third and fourth coordinates respectively denote the displacement and the level of the $B$-cell. For a $C$-cell, the second coordinate denotes the number of times the stem cell has proliferated. The third and fourth coordinates respectively denote the displacement and the level of the $C$-cell. The fifth coordinate is a Boolean that denotes if the $C$-cell has to push forward another cell. The second coordinate of $A$-cell denotes its generation (progeny), whereas, the third and the fourth coordinates respectively denote the displacement and the level in the rostral migratory stream. The fifth coordinate is a Boolean that denotes if the cell has to push forward another cell. The second and third coordinates of the $\bar{A}$-cell and the $N$-cell denote the cell's position in the olfactory bulb.

With the above definitions, we now define an iterative operator on all states $\Omega^V$. The rules for each type of cell are applied in the top down order. Note that only one rule for a particular cell would be applied at a particular time instant. We have used $\vee$ for logical-or and $\wedge$ for logical-and. In this model, we assume that the initial state of the graph and the number of neurons, defined by a global variable $NumNeurons$, is known. Note that the last sub-rule in each of the rules is to increment the internal counter.

$x^t(v) = (B, g, d, l, \tau) \Rightarrow x^{t+1}(v) =$

$$\begin{cases} (E) & \text{if } \tau = \Psi \wedge g = \Delta \\ \{(B, g+1, d, l, 0) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge \tau = \Psi \wedge \text{ NumNeurons} < \text{Threshold} \\ \{(B, g+1, d, l, 0) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (C, *, d', l+1, *, *) \wedge \tau = \Psi \\ & \quad \wedge \text{ NumNeurons} < \text{Threshold} \\ (B, g, d, l, \Psi) & \text{if } \forall u \in N(v), x^t(u) = (B, *, *, *, *) \wedge \tau = \Psi \\ (B, g, d, l, \tau + 1) & \text{otherwise} \end{cases} \tag{1}$$

$x^t(v) = (C, g, d, l, f, \tau) \Rightarrow x^{t+1}(v) =$

$$\begin{cases} (E) & if \tau = \Phi \wedge g = \Delta' \\ \{(C, g+1, d, l, 0, \tau) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge l = l_t \wedge f = 1 \\ \{(C, g+1, d, l, 0, \tau) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (A, *, d', l+1, *, *) \wedge l = l_t \wedge f = 1 \\ \{(C, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge l = l_t \wedge \tau = \Phi \\ \{(C, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (A, *, d', l+1, *, *) \wedge l = l_t \wedge \tau = \Phi \\ & \\ \{(C, g+1, d, l, 0, \tau) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge f = 1 \\ \{(C, g+1, d, l, 0, \tau) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (C, *, d', l+1, *, *) \wedge f = 1 \\ \{(C, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge \tau = \Phi \\ \{(C, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (C, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (C, *, d', l+1, *, *) \wedge \tau = \Phi \\ (C, g, d, l, f, \tau + 1) & \text{otherwise} \end{cases} \tag{2}$$

$x^t(v) = (A, g, d, l, f, \tau) \Rightarrow x^{t+1}(v) =$

$$\begin{cases} (E) & \text{if } \tau = \Theta \wedge g = \overline{\Delta} \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (\bar{A}, d', l+1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge l = l_{OB} \wedge f = 1 \\ \{(A, g+1, d, l, 0, 0)\} & \text{if } \forall u \in N(v) x^t(u) \neq (E) \wedge l = l_{OB} \wedge f = 1 \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (\bar{A}, d', l+1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge l = l_{OB} \wedge \tau = (g+1)\Theta \\ \{(A, g+1, d, l, 0, 0)\} & \text{if } \forall u \in N(v) s.t. x^t(u) \neq (E) \wedge l = l_{OB} \wedge \tau = (g+1)\Theta \\ & \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge f = 1 \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (A, *, d', l+1, *, *) \wedge f = 1 \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 0, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (E) \wedge \tau = (g+1)\Theta \\ \{(A, g+1, d, l, 0, 0) \text{ and } x^{t+1}(u) = (A, 0, d', l+1, 1, 0)\} & \text{if } \exists u \in N(v) s.t. x^t(u) = (A, *, d', l+1, *, *) \wedge \tau = (g+1)\Theta \\ (A, g, d, l, f, \tau + 1) & \text{otherwise} \end{cases} \tag{3}$$

$x^t(v) = (\bar{A}, d, l, \tau) \Rightarrow x^{t+1}(v) =$

$$\begin{cases} (E) & \text{if } \tau > \Theta' \\ \{(N, d, l, 0), \text{increment NumNeurons by 1}\} & \text{if distance (d, l) from } (d_{OBC}, l_{OBC}) \text{ is } \geq \Re \\ (\bar{A}, d+\delta, l+\epsilon, 0) & \text{if the position at } (d+\delta, l+\epsilon) \text{ is } (E) \wedge |\delta| \leq 1 \wedge |\epsilon| \leq 1 \\ & \quad \wedge \text{ the signal is in the direction } (d+\delta, l+\epsilon) \\ (\bar{A}, d, l, \tau + 1) & \text{otherwise} \end{cases} \tag{4}$$

$x^t(v) = (N, d, l, \tau) \Rightarrow x^{t+1}(v) =$

$$\begin{cases} \{(E), \text{decrement NumNeurons by 1}\} & \text{if } \tau = \Gamma \\ (N, d+\delta, l+\epsilon, \tau + 1) & \text{if the position at } (d+\delta, l+\epsilon) \text{ is } (E) \wedge |\delta| \leq 1 \wedge |\epsilon| \leq 1 \\ & \quad \wedge \text{ the signal is in the direction } (d+\delta, l+\epsilon) \\ (N, d, l, \tau + 1) & \text{otherwise} \end{cases} \tag{5}$$

$$x^t(v) = (E) \Rightarrow x^{t+1}(v) = (E) \tag{6}$$

Rule (1) is for $B$-cells. The first sub-rule states that if a $B$-cell has had $\Delta$ proliferations then it dies. The second and the third sub-rules state that if the internal counter of a $B$-cell equals $\Psi$, and its immediate neighborhood consists of an empty space or a $C$-cell, then it proliferates if the number of neurons are less than a threshold. The third sub-rule marks a $C$-cell for forward pushing when no empty space is available. The fourth sub-rule specifies that if a $B$-cell's internal counter has reached $\Psi$ but is not surrounded by an empty space or a $C$-cell, then it enters into a quiescent state.

Rule (2) is for $C$-cells. The first sub-rule states that if it has had $\Delta'$ proliferations then it dies. Sub-rules grouped as (2.1) are for a $C$-cell at $l_t$. They state that if a forward parameter to push for a $C$-cell is set to 1 or if its internal counter has reached $\Phi$, then the $C$-cell proliferates asymmetrically into a $C$-cell and an $A$-cell. An $A$-cell is created if there is an empty space in the next level else forward push parameter is set to 1 for an existing $A$-cell in the next level. Sub-rules grouped as (2.2) are for a $C$-cell at levels other than $l_t$. They state that if a forward parameter to push is set to 1 or if its internal counter has reached $\Phi$, then another $C$-cell is created if there is an empty space in the next level else forward parameter is set for a $C$-cell in the next level.

Rule (3) is for $A$-cells. The first sub-rule states that if an $A$-cell has had $\bar{\Delta}$ proliferations then it dies. Sub-rules grouped as (3.1) are for an $A$-cell at $l_{OB}$. They state if forward parameter to push is set to 1 or if its internal counter has reached $(g+1)\Theta$, then the $A$-cell proliferates asymmetrically into an $A$-cell and an $\bar{A}$-cell. An $\bar{A}$-cell is created if there is an empty space in the next level. If there is no empty space, then the newly created $\bar{A}$-cell dies. Sub-rules grouped as (3.2) are for $A$-cell at levels other than $l_{OB}$. They state that if forward parameter to push an $A$-cell is set to 1 or if its internal counter has reached $(g+1)\Theta$, then an $A$-cell is created if in the next level there exists an empty space else forward parameter is set for another $A$-cell. This rule also depicts reduced proliferation of $A$-cells with each generation.

Rule (4) is for $\bar{A}$-cells. The first sub-rule denotes the time $\Theta'$ required for $\bar{A}$-cells maturity. The second sub-rule states that if the $\bar{A}$-cell reaches near the edge of the olfactory bulb, it converts to $N$-cell. The third sub-rule states that the $\bar{A}$-cell moves, if there is an empty space, in the direction of the signal that attracts it towards the edge of the olfactory bulb. This signal is generated by empty spaces on the edge of the olfactory bulb. After every move the counter is reset. The signal of attraction results in radial movement of $\bar{A}$-cells.

Rule (5) is for $N$-cells. The first sub-rule states that $N$-cell dies after $\Gamma$ time steps. The second sub-rule states that $N$-cell moves, if there is an empty space, in the direction of the signal that attracts it towards the edge of the olfactory bulb.

Rule (6) specifies that an empty space does not change.

## 3. RESULTS AND DISCUSSION

Due to lack of space, the detailed theoretical proofs of the properties of our model and the simulation results are given in a technical report [3] that is made available on the website: https://sites.google.com/site/deterministicbrainmodel.

In our model we claim the following:
1. If there exist a $B$-cell in the subventricular zone then a $C$-cell is created within $\Psi$ time steps if the number of neurons are less than a threshold.
2. If there exist two positions $P, Q$ in the subventricular zone that can be occupied by $C$-cells such that initially only one of the positions is occupied by a $C$-cell then the other position will also be subsequently occupied by a $C$-cell.
Thus, we show that stem cells do fill the subventricular zone.

We next show that the system generates enough mature $N$-cells. Specifically we claim:
1. If all positions are occupied by $C$-cells in the subventricular zone then within $\Phi$ time steps:
- An $A$-cell would be created, or
- An $A$-cell will move to the next level, or
- An $A$-cell will become an $\bar{A}$-cell

2. If an $\bar{A}$-cell is present in the olfactory bulb then a $N$-cell will be created within $2\Re\Theta'$ time steps.
A consequence of this is a lower bound on the production of $N$-cells. Specifically, at least one $N$-cell is produced within $\Psi + \Phi\mu l_t l_{OB} + 2\Re\Theta' + 2\Gamma$ time steps.

We consider a unique state in which the subventricular graph has only empty spaces as the *death state* of the system. A state $x^t$ for which there exists a positive integer $k$ such that $x^{t+k}$ is the death state, will be called a *dying out state*. Lastly, we show that the subventricular system eventually enters death state and hence, all states are dying out states.

The model, presented in this paper, is able to capture many of the biologically observed properties of the neurogenesis. The model predicts that the subventricular zone constantly produces newer neurons and eventually reaches the death state due to ageing. It displays homeostatic properties. $\bar{A}$-cells and $N$-cells travel in the olfactory bulb in radial fashion. The model predicts that some $B$-cells would be in quiescent state. Also, the model captures stem cell ($B$-cell) apoptosis.

An agent-based simulation has been developed for the model proposed in this paper. We have implemented the program in the C programming language. The simulation is on a two dimensional grid of size 80 x 30. The program and the results for different time steps are made available on the above mentioned website. In future, we would work on carrying out simulation in three-dimensions.

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