



T.C.
ÜSKÜDAR UNIVERSITY
INSTITUTE OF HEALTH SCIENCES

NEUROSCIENCE DEPARTMENT
NEUROSCIENCE MASTER'S THESIS PROGRAM
MASTER'S DEGREE THESIS

**A THREE-DIMENSIONAL AGENT-BASED MODEL OF ADULT
NEUROGENESIS IN THE SUBVENTRICULAR ZONE OF THE
LATERAL VENTRICLES**

Sama ODEH

Thesis Advisor
Assoc. Dr. Pınar ÖZ

İSTANBUL-2023

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ÖZET

YAN VENTRİKÜLLERDE SUBVENTRİKÜLER BÖLGEDE ERİŞKİN NÖROJENİZİN ÜÇ BOYUTLU AJAN TABANLI BİR MODELİ

Bu tez çalışmasındaki temel amacımız, yetişkin nörogenezinin iki ana nörojenik nişinden biri olan lateral ventriküllerin subventriküler bölgesini 3 boyutlu modelleyerek yetişkin nörogenezinin popülasyon dinamiklerini pratik ve zamanında gözlemlemek ve oluşturmaktır. Nörojenez, maymunlar ve sıçanlar gibi yetişkin memeli beyninde ve bazı çalışmalarda insanlarda iki farklı bölgede varlığını sürdüren nöral kök hücrelerden yeni nöronların ortaya çıkmasıdır: dentat girusun subgranüler bölgesi, hipokampus ve lateral ventriküllerin subventriküler bölgesi. Bizim ilgi alanımız, Tip-B1 hücreleri adı verilen, astrositik özelliklere sahip nöral kök hücrelerin bir alt popülasyonunu içeren, bir kez aktive edildikten sonra bir proliferasyon (simetrik bölünme ve simetrik tüketim) ve daha sonra farklılaşma döngüsüne giren bir alt popülasyonu içeren lateral ventriküllerin subventriküler bölgesidir. geçici olarak çoğalan hücreler olarak da bilinen Tip-C hücrelere dönüşür ve bunlar daha sonra nöroblastlar olarak da adlandırılan Tip-A hücrelere dönüşür. Her birinin sistem üzerindeki etkisini değerlendirmek ve sonraki öngörülemez olayları tahmin etmek amacıyla sıklıkla "ajanlar" olarak adlandırılan çok sayıda öge arasındaki ilişkileri simüle etmeye yönelik çok katmanlı bir sistem aracı olan etmen tabanlı modellemeyi kullanarak, kökeni takip ettik. Tip-B1 hücrelerinin, hareketsizliklerini, aktivasyonlarını, dönüşümlerini ve nişleri ve diğer komşu hücrelerle etkileşimlerini takip edip simüle ederek ve göç ve niş düzenlemesi gibi önemli faktörleri uygulayarak koku alma soğanındaki olgun nöronların son biçimlerine ilerlemesini sağlar. Mevcut literatürü desteklemek üzere, sonuçlarımız B1 tipi hücrelerin çoğalma oranlarında zaman içinde keskin bir artış ve ardından düşüş olduğunu ve farklılaşmanın ardından hızlı ancak sabit C tipi hücre çoğalmasını ve ardından A tipi hücrelere farklılaşmayı göstermektedir.

Anahtar Kelimeler: ajan bazlı modelleme, hesaplamalı model, subventriküler bölge, yetişkin nörogenezi

ABSTRACT

A THREE-DIMENSIONAL AGENT-BASED MODEL OF ADULT NEUROGENESIS IN THE SUBVENTRICULAR ZONE OF THE LATERAL VENTRICLES

Our primary objective in this thesis study is the observation and construction of population dynamics of adult neurogenesis in a practical and timely manner in silico, by three-dimensionally modeling one of the two major neurogenic niches of adult neurogenesis, the subventricular zone of the lateral ventricles. Adult neurogenesis is the persisting emergence of new neurons from neural stem cells in the adult mammalian brain, such as in monkeys and rats, and possibly humans in two distinctive regions: the subgranular zone of the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. Our region of interest is the subventricular zone of the lateral ventricles, which contains a subpopulation of neural stem cells with astrocytic and glial characteristics, called Type-B1 cells, that once activated, enter a cycle of proliferation (symmetric division), symmetrical consumption, and later differentiation into Type-C cells, also known as transiently amplifying cells, that then eventually convert into Type-A cells, also called neuroblasts. By utilizing agent-based modeling, we tracked the lineage progression of Type-B1 cells into their final form of immature neurons in the olfactory bulb by following and simulating their quiescence, activation, differentiation, and by implementing significant factors such as movement and cellular process regulation. In support of existing literature, our results exhibit a sharp rise followed by a constant decline in proliferation rates for Type-B1 cells over time, and upon differentiation, rapid elevation then a decline Type-C cell proliferation, followed by differentiation into Type-A cells, and finally, production of immature neurons.

Keywords: adult neurogenesis, agent-based modeling, computational model, subventricular zone

FORWARD

I would like to express my deep appreciation and thanks to my advisor, Professor Pınar. This work is supported by Üsküdar University.



DECLARATION FORM

I have obtained all the information and documents in this study within the framework of academic rules, I have presented all visual, audio and written information and results in accordance with scientific ethics, I have not made any falsifications in the data I have used, I have referred to the sources I have used in accordance with scientific norms, I hereby declare that it is true, produced by me and written according to Üsküdar University Health Sciences Institute Thesis Writing Guide.



August, 2023

Sama ODEH

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LIST OF SYMBOLS AND ABBREVIATIONS

NSCs: neural stem cells

SVZ: subventricular zone

RMS: rostral migratory stream

OB: olfactory bulb

HANG: hippocampal adult neurogenesis

VANG: ventricular adult neurogenesis

ABM: agent-based modeling

BMP: bone morphogenetic protein

IGF-1: insulin growth factor-1

ECM: extracellular matrix

NGF: nerve growth factor

EGF: epidermal growth factor

BDNF: brain-derived neurotrophic factor

BrdU: 5-bromo-2'-deoxyuridine

GFAP: glial fibrillary acidic protein

1. INTRODUCTION

1.1. Adult Neurogenesis

The theory of neurogenesis (or then-supposed lack thereof) emerged when Santiago Ramon y Cajal, a well-known Spanish histologist, claimed that neurons in the adult brain are fixed, meaning that they never proliferate nor renew (Ramon Y Cajal, 1928; Owji & Shoja, 2019). However, approximately 30 years later when Joseph Altman discovered that neurogenesis persists in the olfactory bulb, the cortex, and the hippocampus through extensive research and experimentation, adult neurogenesis was introduced into the world of neuroscience (Altman, 1962; Altman and Das, 1965). Nonetheless, adult neurogenesis remains a controversy due to the conflicted viewpoints of several researchers. While some studies observed an increase in neurogenesis in the adult brain as it ages, other studies established the complete opposite (Sorrrells et al., 2018; Boldrini et al., 2018). In the adult brain, neurogenesis, which is the process of producing new neurons from neural stem cells (NSCs), also known as pluripotent stem cells, is seen in two specialized areas: the subgranular zone of the dentate gyrus of the hippocampus and the subventricular zone of the lateral ventricles. The dentate gyrus is composed of three layers: the molecular layer, which is primarily occupied by the dendrites of the dentate granule cells; the granule cell layer, which encloses the third layer and is composed primarily of densely packed granule cells; and the hilus, also known as the polymorphic cell layer, which is a region made up of different cell types (Amaral et al., 2007). The subgranular zone is found at the outskirts between the polymorphic cell layer and the granule cell layer, in which NSCs, or Type I cells, reside in a quiescent state until activated (Toni & Schnider, 2016). The process of adult neurogenesis involves several stages, which encompass migration, proliferation, determining fate, differentiating NSCs, maturation, integration into neural networks, and eventual cell death through apoptosis. (Ming and Song et al., 2005). Urban and Cheung observed that an NSC remains quiescent until active, in which it then divides, differentiates, migrates, or undergoes apoptosis. A quiescent cell can divide but is not actively involved in the cell cycle for a set amount of time, according to extensive research by Urban and Cheung. Furthermore, for lifelong tissue homeostasis and regenerative capacity, the exceptional propensity of adult stem cells to maintain quiescence is essential (Urban & Cheung, 2021). We will further elaborate on quiescence in a later section (refer to section 2.4). Upon NSC activation there are two types of cell

division: symmetric and asymmetric division. According to Obernier et al., 2018, there is a third mode of division, symmetrical consumption (Obernier et al., 2018). Symmetric division results in one mother cell (the same cell that is divided into the first round of division) and one daughter cell, while asymmetric division results in one daughter cell (the same cell that is divided into the first round of division) and one neural precursor. Symmetric consumption, however, is the symmetrical production of two transiently amplifying cells, known as type C cells in the subventricular zone (Obernier et al., 2018). Differentiation is the process through which a stem cell changes into a more specialized cell. The subgranular zone (SGZ) and subventricular zone (SVZ) have different microenvironments within their NSC niche; therefore, the differentiation and self-renewal of NSCs in these two regions vary. While most SGZ NSCs divide asymmetrically to give rise to a daughter cell and a neuron or astrocyte, SVZ NSCs tend to maintain their pool by proliferating or undergoing differentiative symmetric cell divisions or symmetrical consumption of type B1 cells (Obernier et al., 2018; Encinas et al., 2011; Bonaguidi et al., 2011). Over the last decades, several *in vivo*, *in vitro*, and *in silico* studies have been established. *In vivo* refers to animal research done on living animals, *in vitro* refers to animal research done in test tubes or laboratory dishes, and *in silico* refers to mathematical experiments performed on computers. Evidently, *in vivo* and *in vitro* adult neurogenesis studies have their setbacks, specifically *in vivo* research, which is mainly due to the intricate and complex nature of both neurogenic niches (Azari & Reynolds, 2016). Cell labeling techniques like 5-Bromo-2'-Deoxyuridine (BrdU)-labeling, which is a thymidine analog inserted into nuclear DNA to identify DNA synthesis, and detect proliferating behavior in active NSCs (Urban & Cheung, 2021). Inactive NSCs maintain strong responsiveness to local signaling cues and can be set into motion by various natural stimuli. Latest research has shed light on the mechanism through which neural stem cells divide and transition into a quiescent phase during brain maturation; however, the extent to which cellular divisions transform with age is still a matter of discussion (Urban et al., 2019; Ahlenius et al., 2009; Capilla-Gonzalez et al., 2014; Kempermann et al., 2018; Shi et al., 2018; Shook et al., 2012; Silva-Vargas et al., 2016). Ahlenius et al. established that mature and aged NSCs displayed comparable proliferation rates when cultivated *in vitro* (Ahlenius et al., 2009). Conversely, Capilla-Gonzalez et al. demonstrated a decrease in the reduction of NSCs using thymidine-labeling in the (SVZ) environment, when contrasting cells from mice aged 2 months and 24 months (Capilla-Gonzalez et al., 2014). In a parallel manner, Shi et al., in a study involving the forebrain ependymal and

subependymal regions of mice aged 2 months and 29 months, noted a decline in the rate of proliferation (Shi et al., 2018). Silva-Vargas et al. recorded a drop in the proliferation pace of stem cells in the V-SVZ zone. Interestingly, Shook et al. reported an increase in the rate of proliferation as age advances (Shook et al., 2012).

1.2. Ventricular-Subventricular Zone of the Lateral Ventricles

The SVZ, the other primary neurogenic niche, is only found in the ependymal cell layer next to the lateral ventricle walls and is made up of Type B cells, mostly quiescent cells with astrocytic features that express glial fibrillary acidic protein (GFAP) (Doetsch et al., 1999; Doetsch et al., 1997; Morshead et al., 1994; Nam & Benzera, 2009). Slow-dividing Type-B cells undergo symmetric consumption that generates Type-C cells, also referred to as transient amplifying cells, and then into neuroblasts, or Type-A cells, which move into the rostral migratory stream and proceed to the olfactory bulb, where they give develop into local interneurons. (Shen et al., 2008; Falcao et al., 2012; Fuentealba et al., 2012; Doetsch et al., 1999; Altman, 1969; Luskin, 1993; Lois & Alvarez-Buylla, 1994; Carleton et al., 2003; Belluzzi et al., 2003). Depending on various intrinsic and extrinsic factors, these cells either remain quiescent (silent and inactive) or active, followed by symmetric or asymmetric division or differentiation to the next type.

2. GENERAL INFORMATION

2.1. V-SVZ Niche

Throughout years of research on adult neurogenesis in the SVZ, several questions emerged regarding the intrinsic and extrinsic influence on the behavior of NSCs. As a result, numerous *in vitro* and *in vivo* studies were established as attempts to answer those questions. Some inquiries are as such: Is NSC fate governed by internal or cell-autonomous events or by niche-cell or cell-cell interactions (Basak et al., 2018)? Is there a signal-based balanced system for the maintenance of SVZ cellular types in the niche (Aguirre et al., 2010)? According to several studies, the Type-B1 cell niche appears to be regulated by numerous factors, cell-cell interaction, growth factors, hormones, vasculature, neural input, cerebrospinal fluid, and even drugs. Therefore, adult neurogenesis in the SVZ is influenced by a combination of intrinsic and extrinsic factors. These factors play a crucial role in regulating the proliferation, differentiation, and survival of NSCs and their progeny in the SVZ. Intrinsic and extrinsic factors include the following:

2.1.1. Intrinsic factors

Intrinsic factors refer to cellular and molecular mechanisms that are inherent to the NSCs themselves. These factors can influence the behavior of NSCs and their ability to generate new neurons.

a) Transcription Factors: Proteins called transcription factors regulate the expression of genes that are involved in a variety of biological activities, including adult neurogenesis. Some transcription factors known to influence adult subventricular neurogenesis include:

- **Sox2:** Maintains neural stem cell identity and proliferation (Favaro et al., 2009).
- **Nkx2.1:** Regulates SVZ neural stem cell differentiation (Butt et al., 2008).
- **Dlx:** Controls the differentiation of neural stem cells into interneurons (Young et al., 2007).

b) Neurotrophic Factors: Neurotrophic factors are proteins that support the survival, differentiation, and maintenance of neurons.

- **Brain-Derived Neurotrophic Factor (BDNF):** A growth factor belonging to the neurotrophin family, BDNF encourages the differentiation and survival of SVZ-derived neuroblasts (Benraiss et al., 2001; Ventriglia et al., 2002).
 - **Epidermal Growth Factor (EGF):** A protein that stimulates SVZ NSC proliferation (Doetsch et al., 2002; Aguirre et al., 2010).
 - **Nerve Growth Factor (NGF):** This neurotrophin is pivotal in determining the destiny, growth, viability, extension, and upholding of specific sets of neurons (Mitsiadis & Pagalla, 2021; Lewin & Carter, 2014; Levi-Montalcini, 1987; Tomellini et al., 2014; Reichardt, 2006) NGF exhibits a weak binding affinity to the transmembrane glycoprotein receptor **p75NTR**, which is found on both neurons and non-neuronal target cells. When activated, this interaction can trigger either the promotion of cell survival or the initiation of apoptosis (Lee et al., 2001; Ibanez & Simi, 2012; Lewin and Carter, 2014).
- c) Cell Adhesion Molecules:** Cell adhesion molecules are proteins that mediate interactions between cells and their environment. They play roles in cell migration and differentiation during neurogenesis.
- **Cadherins:** Cell adhesion molecules that mediate cell-cell adhesion and influence the neuroblast migration to the olfactory bulb (OB) (Snapyan et al., 2009).
- d) Notch signaling pathway:** The Notch signaling pathway controls how cells differentiate and maintain their NSC state.
- Notch1:** A ligand that regulates the balance between self-renewal and differentiation of NSCs (Imayoshi et al. 2010).

2.1.2. Extrinsic factors

Extrinsic factors are external cues and signals that come from the microenvironment surrounding the NSCs. These factors are critical for creating the niche that supports NSC maintenance, proliferation, and differentiation.

a) Neighboring cells: The SVZ contains various cell types, including ependymal cells, astrocytes, and blood vessels. These neighboring cells release signaling molecules that influence NSCs and their progeny. Neighboring cells, such as A cells, ependymal cells, C cells, and other Type-B1 cells, interact according to Obernier et al., with Type-B1 cells via receptor activity (Obernier et al., 2018). Depending on the cellular input, events such as proliferation and differentiation appear to be either reduced or elevated. For instance, GABA release from A cells inhibits Type-B1 cell proliferation, while

diazepam-binding inhibitor protein (DBIP) activity in other Type-B1 cells and Type-C cells stimulates proliferation as well as production of Type-A cells (Fernando et al., 2011; Alfonso et al., 2012; Obernier & Alvarez-Buylla, 2019).

b) Extracellular matrix (ECM): The ECM is an intricate web of proteins, proteoglycans, and other substances that support cells in different tissues structurally and functionally. By affecting cell behavior, migration, proliferation, and differentiation, the ECM in the SVZ plays a critical role in controlling adult neurogenesis (Mercier et al., 2002).

- **NSC-Niche Regulation:** The ECM in the SVZ helps form a niche that maintains NSCs in a quiescent state or supports their activation and proliferation. The interaction between NSCs and ECM components, such as laminins and fibronectins, influences stem cell fate decisions and their ability to self-renew or differentiate into neuronal progenitors (Song et al., 2012; Kerever et al., 2007; Mercier et al., 2002; Chiquet et al, 2009; Garcion et al, 2004)

- **Neuronal Differentiation and Survival:** The ECM's composition and organization also influence the differentiation and survival of immature neurons. Integrins, which are cell-surface receptors that interact with ECM molecules, play a role in transmitting signals that affect neuronal differentiation and promote their survival (Song et al., 2012; Kerever et al., 2007; Mercier et al., 2002; Chiquet et al., 2009; Garcion et al, 2004).

- **Cell Migration and Guidance:** Neural progenitor cells (NPCs) generated in the SVZ need to migrate to their final destinations, such as the olfactory bulb, to become functional neurons. The ECM guides and influences the migration of these cells through interactions with cell adhesion molecules and ECM components like tenascins and chondroitin sulfate proteoglycans (Song et al., 2012; Kerever et al., 2007; Mercier et al., 2002; Chiquet et al, 2009; Garcion et al, 2004).

- **Modulation of Signaling Pathways:** The ECM can regulate various signaling pathways that are critical for neurogenesis. It can affect the activation of growth factors, such as brain-derived neurotrophic factor (BDNF), through interactions with ECM components (Song et al., 2012; Kerever et al., 2007; Mercier et al., 2002; Chiquet et al., 2009; Garcion et al, 2004).

c) Neuronal Activity: Neuronal activity and neurotransmitters can impact adult neurogenesis. Neurotransmitters such as GABA have been shown to influence SVZ adult neurogenesis, which blocks Type-B1 cell proliferation (Obernier & Alvarez-Buylla,

2019). Sensory experiences, learning, and environmental enrichment can stimulate NSC proliferation and survival.

d) Hormones: Hormones play a significant role in regulating VANG, influencing various stages of NSC maintenance, proliferation, and differentiation. Those hormones include the following:

- **Prolactin:** A hormone known for its role in lactation, has also been shown to modulate adult neurogenesis. It can enhance neuroblast production and neuronal differentiation in the SVZ (Shingo et al., 2003).
- **Sex Steroids:** Estrogen and testosterone, the primary sex steroids in females and males respectively, also impact adult neurogenesis. Estrogen enhances neurogenesis in the SVZ, while testosterone has been associated with the modulation of neuronal differentiation (Tanapat et al., 2005).
- **Insulin-Like Growth Factor-1 (IGF-1):** A growth factor that supports cell survival, proliferation, and differentiation. It promotes NSC proliferation and neuronal differentiation in the SVZ (Lichtenwalner et al., 2001).
- **Corticosteroids (Glucocorticoids):** Corticosteroids, such as cortisol in humans and corticosterone in rodents, are stress hormones that can impact neurogenesis. Chronic stress and elevated corticosteroid levels have been associated with reduced neurogenesis in the (SVZ) and the hippocampus (Wong et al., 2015).

2.2. Cell Types

There are three types of cells in the SVZ (Figure 1 & Figure 2): Type-B1 cells, are GFAP-expressing cells (Doetsch et al., 1999) with astroglial characteristics and a basal process that interacts with blood vessels. Type-C cells, EGFR-expressing cells (Lois & Alvarez-Buylla, 1994), also known as transient-amplifying cells, and Type-A cells, doublecortin-expressing cells (Lois & Alvarez-Buylla, 1994) also known as neuroblasts, which migrate to the rostral migratory stream as they divide in clusters toward the OB, where they then differentiate into immature neurons (Obernier et al., 2018; Anthony et al., 2004; Miyata et al., 2001; Noctor et al., 2001; Götz et al., 1998).

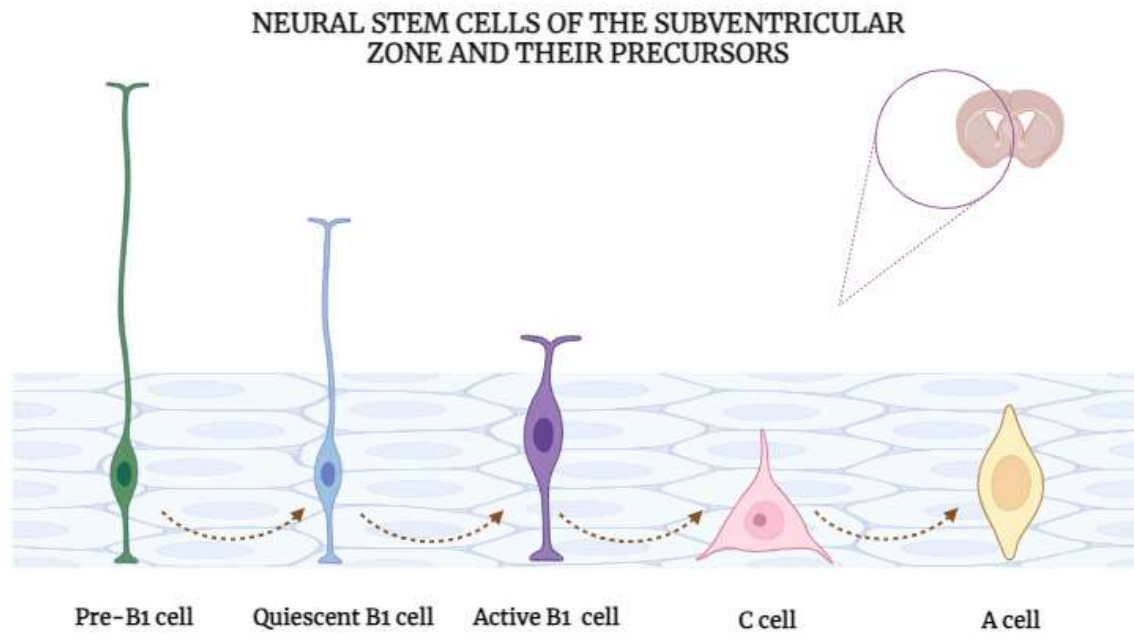


Figure 1: Neural stem cells of the subventricular zone of the lateral ventricles and their progeny.

(Green) Pre-B1 cells, which according to various literature sources (Gaiano et al., 2000; Kriegstein & Alvarez-Buylla, 2009; Spassky et al., 2005; Gao et al., 2014; Tramontin et al., 2003; Götz & Huttner, 2005; Fuentaelba et al., 2015; Merkle et al., 2004; Furutachi et al., 2015), are the embryonic radial glia precursors of Type-B1 cells. (Blue) A quiescent Type-B1 cell is the neural stem cell of the SVZ with astro-radial glial characteristics located along the wall of the ependymal layer of the lateral ventricle (Obernier et al., 2018). (Purple) An active Type-B1 cell, loses its basal process as proliferation and self-renewal initiate, followed by symmetric consumption producing Type-C cells and limited differentiation into Type-C cells. (Pink) A type-C cell, which is a rapidly dividing and transiently amplifying cell, appears to divide 3-4 times before differentiating into Type-A cells (Ponti et al., 2013). (Yellow) A Type-A cell, which is a neuroblast that appears to divide once or twice as it migrates tangentially toward the RMS and radially toward the OB, resulting in a total of 16 Type-A cells and followed by differentiation into local interneurons in the OB (Ponti et al., 2013; Obernier et al., 2018; Anthony et al., 2004; Miyata et al., 2001; Noctor et al., 2001; Götz et al., 1998). Created with BioRender.com.

2.3. Cellular Processes

Cellular processes refer to the various activities that occur within a cell to maintain its function, growth, and reproduction. These processes are essential for the survival of living organisms and are tightly regulated to ensure proper functioning. Cellular processes include:

- a) Proliferation:** NSCs undergo proliferation to increase their numbers, which can occur through symmetric divisions, where both daughter cells are NSCs, or asymmetric divisions, where one daughter cell becomes a neuron or another type of neural cell (Alvarez-Buylla, 2004).
- b) Self-Renewal:** Self-renewal is the process by which NSCs proliferate to form daughter cells. NSCs can divide symmetrically to create two daughter stem cells or asymmetrically to produce one stem cell and one progenitor cell (Song et al., 2012).
- c) Differentiation:** NSCs can differentiate into a variety of neural cell types, including astrocytes, neurons, and oligodendrocytes. This is an important process that helps the nervous system develop and remain healthy (Ming & Song, 2011).
- d) Apoptosis:** Apoptosis, or programmed cell death, is the process in which nonessential cells are eliminated, specifically injured cells, through varying molecular mechanisms, such as the regulation of genetic signals (Renehan et al., 2001).
- e) Migration:** NPCs, which originate from NSCs, can go to particular brain regions where they undergo additional neuronal maturation and integration (Ming & Song, 2011).

LINEAGE PROGRESSION OF SUBVENTRICULAR ZONE NSCs

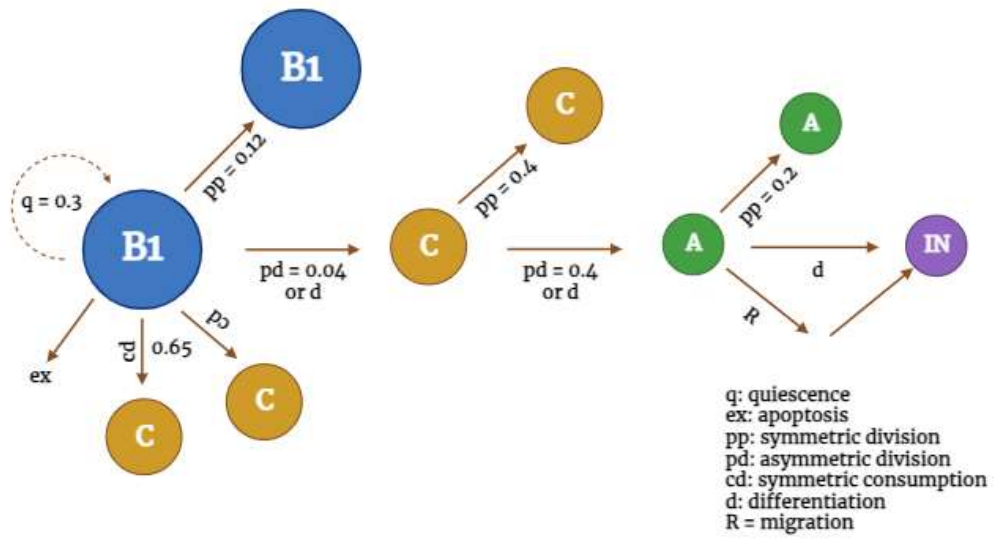


Figure 2: Lineage progression of subventricular zone NSCs.

Probability limits for each event for the different cell types were extracted from Obernier and colleagues' work (Obernier et al., 2018). Created with BioRender.com.

2.4. Quiescence

Cells are quiescent at the G0 or G2 phases of the cell cycle, according to a study by Otsuki & Brand (Urban et al., 2019; Otsuki & Brand, 2018). Quiescence is a dynamically perpetuated mechanism that incorporates a molecular protocol to inhibit long-term specialization, prevent cellular aging, and ensure the cell cycle pause can be undone, even though it is frequently associated with decreased metabolic activity, such as decreased RNA and protein synthesis (Cheung & Rando, 2013). A study has shown that as early as embryonic day 13.5 some NSCs in the ventricular zone of the growing mouse brain begin to slow their rate of division (Fuentealba et al., 2015; Furutachi et al., 2015). Then, until they are later reactivated during postnatal or adult phases, these cells remain in a state of quiescence within the maturing V-SVZ (Cheung & Rando, 2013). For cells with prolonged capability for proliferation, quiescence is important because it protects them from losing the capacity to divide and hinders the accumulation of DNA, protein, and mitochondrial damage. In the absence of these accumulating injuries, malignant alterations or cellular senescence may arise (Cheung & Rando, 2013). The quiescence state of NSCs in both the V-SVZ and SGZ regions is characterized by the

absence of markers related to cell division. Conversely, in the V-SVZ region, NSCs that are currently active can be distinguished by their expression of the epidermal growth factor receptor (EGFR), a protein of the growth factors family, which stimulates the proliferation of NSCs in the SVZ (Aguirre et al., 2010; Codega et al., 2014).

In terms of signaling pathways within the adult mammalian brain, the bone morphogenetic protein (BMP) pathway appears to block the process of neurogenesis while guiding the NSCs toward gliogenesis. Various components associated with this pathway, such as the BMP target inhibitor of differentiation 2 (ID2), the BMP ligands (BMP1, BMP6), and the BMP receptor BMPRII, are all detected in quiescent NSCs (Lim et al., 2000; Mira et al., 2010). This shows that BMP controls NSC proliferation by self-regulation (Llorens-Bobadilla et al., 2015). Therefore, the BMP pathway maintains the quiescent state of NSCs, as demonstrated by the fact that disrupting BMP signaling through the specific removal of the upstream BMPRII receptor initially leads to a temporary upsurge in NSC proliferation, eventually resulting in a gradual reduction of the NSC pool over the long term (Llorens-Bobadilla et al., 2015).

2.5. Rostral Migratory Stream

NSCs migrate during development from their point of origin in the SVZ to their final destination, undergoing differentiation along the way (Altman, 1969; Luskin & Boone, 1994; Curtis et al., 2009; Benraiss et al., 2001; Lois et al., 1996). These cells then become a part of the forebrain's functional neuronal network. According to research (Altman, 1969; Luskin & Boone, 1994; Curtis et al., 2009; Benraiss et al., 2001; Lois et al., 1996), neurogenesis continues even in the adult brain within the SVZ throughout an individual's life, with subsequent cell change occurring, particularly within the OB (olfactory bulb).

The RMS (rostral migratory stream) retains a constant tubular structure in the majority of mammalian species. However, the lumen of this tubular structure gets noticeably smaller in primates like humans (Curtis et al., 2009). Moreover, as opposed to a direct rostral pathway, the RMS in primates travels along a curved trajectory (Curtis et al., 2009). Many species have an unhindered passageway that connects the lateral ventricle and the olfactory ventricle, allowing for continuous cerebrospinal fluid flow and maintaining an undisturbed SVZ between these two areas (Rae, 1994).

The RMS is unique in the rodent brain because its cells form chains, allowing for lateral migration without the need for radial connections. According to studies by Lois and Alvarez-Buylla and Lois et al., these cells travel through a network of glial tubes that offers them directional and orientational cues (Lois et al., 1994; Lois & Alvarez-Buylla, 1994).

On the other hand, the structure of the human RMS is more intricate. Even yet, it has a large number of migratory cells similar to the rodent RMS that eventually evolve into neurons within the OB (Curtis et al., 2007). The human RMS has a trajectory comparable to that of rats, launching along a rostroventral path concerning the striatum. These cells then advance via the olfactory tract until they eventually reach the OB (Curtis et al., 2009).

2.6.Computational Modeling of Adult Neurogenesis

2.6.1. Mathematical models of adult neurogenesis

Given the uncertainty surrounding potential changes in NSC proliferation over time, mathematical modeling can function as a tool for evaluating whether varying hypotheses about shifts in stem cell dynamics are consistent with experimental findings and can generate predictions (Kempermann et al., 2018). Ashborun et al.'s research introduces a mathematical framework that depicts the process of adult neurogenesis in mammals within the SVZ, followed by the movement of cells along the rostral migratory stream to reach the OB (Ashbourn et al., 2012). In this model, it is assumed that a single chemoattractant molecule governs cell migration. This chemoattractant is produced by both the OB and the cells involved in neurogenesis, and it acts as an endocrine signal. Through a sensitivity analysis, it is determined that the parameter settings of the model remain stable even when perturbed, and the entire system displays a level of sensitivity. Many different sets of parameters are randomly generated, revealing that the parameter combinations leading to biologically plausible outcomes generally adhere to conditions comparable to those observed in real-life situations (Ashbourn et al., 2012). A study comparing the current mathematical of NSC behavior in the SVZ (Dabelow et al., 2022) demonstrated different techniques in adult neurogenesis mathematical modeling. A study conducted by Kalamakis and colleagues in 2019 proposed that the behavior of NSCs can be understood by quantifying a rate that reflects the transition between two states:

quiescence and activation. In their analysis, they introduced two parameters, " b " and " p^{stem} ," to account for the age-related increase and decrease in the likelihood of NSC self-renewal (Kalamakis et al., 2019). This framework leads to a situation where NSCs remain in a prolonged quiescent state, resulting in the production of a reduced number of precursor cells (Kalamakis et al., 2019). According to this model, Dabelow and their team have introduced a novel nonlinear feedback NSC model using control theory. In this revised model, instead of considering the previously mentioned parameters as predefined decreasing functions, they are treated as control parameters (Dabelow et al., 2022). In their paper, they initially presented analytical calculations and equations for the models serving as the foundation for their research. This was followed by an overview of the computational algorithm designed to address the control problems within the model. They then provided experimental data for comparison and concluded with a discussion of the different proposed models for the dataset (Dabelow et al., 2022). Additionally, Obernier and colleagues proposed a straightforward mathematical model that outlines the dynamics of various cell types within the SVZ, including Type-B cells, Type-A cells, and Type-C cells (Obernier et al., 2018). Their model for the behavior of Type-B1 cells incorporates observed division patterns from their experiments. In this model, they introduce the parameter " n " to represent the probability of a Type-B1 cell undergoing division within one day. They further categorize the types of division into " pc " for consumption and " ps " for symmetric self-renewal (Obernier et al., 2018). After symmetric consumption, resulting in the production of Type-C cells, these Type-C cells undergo a couple of divisions before differentiating into neuroblasts, which themselves undergo division once or twice (Obernier et al., 2018).

2.6.2. Caveats of current models

The issues outlined below are acknowledged by researchers in the field, who are constantly attempting to enhance mathematical models by including greater biological realism, integrating experimental data, and taking into account the different factors that affect adult neurogenesis.

a) Complexity of Adult Neurogenesis: During adult neurogenesis, complex connections exist between different cell types, signaling pathways, and environmental elements. To enable simulations, computational models frequently need to reduce these

intricate connections. Oversimplification, however, might result in erroneous predictions. (Aimone et al., 2011).

b) Availability of Data: Many elements in adult neurogenesis are yet to be explored; therefore, accurate characterization of models depends on existing experimental evidence. Models that are based on sparse or incomplete data may be insufficiently representative of the underlying biology. (Maass et al., 2002).

c) Computational Resources: Interactions occur at numerous spatial and temporal dimensions during adult neurogenesis. Simulations can become computationally expensive during the construction of detailed models that capture these scales since simulations typically need an enormous amount of processing power. (Mongiat et al., 2009).

d) Dynamic Time Scales: Adult neurogenesis is characterized by dynamic processes that take place on various timelines. It needs particular techniques to accurately model these temporal dynamics and capture both immediate and long-term impacts.

e) Multiple Factors Implementation: Hormonal control, the microenvironment, and neural activity are a few of the variables that affect adult neurogenesis. It is difficult and might require sophisticated strategies to incorporate these aspects into a single model.

f) Spatial Components: Adult neurogenesis encompasses the migration of new neurons to their appropriate locations within the existing neural circuitry. Implementing spatial factors into mathematical models adds complexity and can be difficult to achieve precisely (Mongiat et al., 2009).

g) Experimental Validation: Corroborating computational models of adult neurogenesis demands experimental data for comparison to the model's procedure and results. However, obtaining accurate and comprehensive experimental validation can be difficult due to the dynamic and controversial nature of adult neurogenesis (Simpson et al., 2019).

2.6.3. Agent-based modeling

Throughout the years, different research sectors, such as the business and medical fields, have implemented agent-based modeling (ABM) in their work, mainly because of its impeccable capacity to simulate real-world situations (Bonabeau, 2002; Yu & Bagheri, 2020). At its core, ABM mimics real-world systems, such as biological systems for diseases or cell population dynamics systems, by assigning individual parts of a certain

system as agents and tracking their interactions and decisions via a defined collection of rules, called processes (Bonabeau, 2002; Yu & Bagheri, 2020). ABM is a computational approach used to simulate complex systems by modeling the interactions and behaviors of individual agents within an environment. In ABM, an "agent" is an autonomous entity with specific characteristics, behaviors, and rules that determine how it interacts with other agents and its environment. These agents collectively give rise to emergent properties and behaviors at a system level. A breakdown of the key components of ABM:

- a) **Agents:** Agents are the fundamental units of ABM. Each agent represents an individual entity or decision-maker within the system of the model (Bonabeau, 2002).
- b) **Environment:** The environment is the space or context in which the agents interact. It can be physical, virtual, or conceptual, depending on the system being modeled. The environment provides the context for agent interactions and often defines the rules and constraints governing those interactions (Bonabeau, 2002).
- c) **Interactions:** Agents interact with each other and their environment according to predefined rules and behaviors. These interactions can involve communication, movement, resource exchange, decision-making, and more (Bonabeau, 2002).
- d) **Rules:** Each agent follows a set of rules that dictates its behavior. These rules can be simple or complex and are defined based on the goals, attributes, and strategies of the agent. Rules can include factors like decision-making processes, responses to stimuli, and interactions with other agents (Bonabeau, 2002).
- e) **Emergent properties:** Emergent properties are behaviors or patterns that arise from the interactions of individual agents but aren't directly programmed into the model. These properties can be complex and unpredictable, making ABM a valuable tool for studying systems with nonlinear and interactive dynamics (Bonabeau, 2002).
- f) **Simulation:** ABM involves running simulations where agents interact and make decisions within the defined environment. The simulation progresses in discrete time steps, also known as ticks, allowing agents to update their states and behaviors based on the rules and interactions. By simulating numerous time steps, you can observe how the system evolves (Bonabeau, 2002).

2.6.4. Agent-based approaches

In terms of probability, there are two types of computational models: deterministic and stochastic models. While deterministic models are definite and have specificity in their rules, stochastic models display randomness as a major characteristic. Our ABM is a stochastic, single-cell agent-based model. Most agent-based approaches for adult neurogenesis in the SVZ are simplistic, population-based models. Their conceptual framework of Kurhekar and Deshpande's agent-based deterministic model of the adult subventricular zone effectively represents neurogenesis by including NSCs, quickly dividing intermediary cells and mature neurons. It also stimulates the radial migration of neurons to the OB (Kurhekar & Deshpande, 2015). The model accounts for the natural death of stem cells through apoptosis after a specific number of divisions, leading to a decline in neuron production over time, resembling the aging process (Kurhekar & Deshpande, 2015). Moreover, the model demonstrates a consistent generation of an ample quantity of neurons (Kurhekar & Deshpande, 2015). The researchers provided evidence to support the biological validity of their model concerning adult subventricular neurogenesis (Kurhekar & Deshpande, 2015).

2.7. Importance and Application of Adult Neurogenesis and Mathematical Modeling of Adult Neurogenesis in Neuroscience

The role of adult neurogenesis in neuroscience has yet to be determined definitively (Kaptan & Uzum, 2016). Some hypotheses on what adult neurogenesis involves include: Neurogenesis is critical for the development of neural plasticity and the adaptation of species to their environments. Newborn neurons contribute to the plasticity of the brain, so they enable it to network again, for example, to process information or to compensate for damage. New-born neurons might be more flexible than mature neurons, therefore, they can make connections within neural cells more easily. This is a significant event in terms of memory and learning (Gulyvea, 2017).

2.7.1. Neural plasticity

Neural plasticity, also known as neuroplasticity or synaptic plasticity, refers to the brain's ability to reorganize and adapt by forming new connections between neurons and modifying existing ones. In the context of adult neurogenesis, neural plasticity plays a

critical role in shaping the functional integration of newly generated neurons into existing neural circuits.

- **Learning and Memory:** Neural plasticity is fundamental to learning and memory processes. Adult neurogenesis has been linked to certain forms of learning and memory, and the plasticity of immature neurons allows them to participate in these cognitive functions (Deng et al., 2010).
- **Structural Reorganization:** The incorporation of new neurons through adult neurogenesis can lead to structural changes in neural circuits. Neural plasticity enables the brain to reorganize these circuits to accommodate the addition of new neurons (Toni et al., 2007).
- **Integration of New Neurons:** Arising neurons from adult neurogenesis need to integrate into existing neural circuits to contribute meaningfully to brain function. Neural plasticity allows these neurons to establish synapses with other neurons, thereby participating in information processing (van Praag et al., 2002).
- **Adaptive Responses to Environment:** Neural plasticity allows the brain to adapt to changing environments and experiences. Adult neurogenesis can be influenced by environmental factors, and the plasticity of neural circuits supports the incorporation of new neurons in response to these changes (Li, 2019).
- **Functional Recovery After Injury:** Neural plasticity and adult neurogenesis play roles in functional recovery following brain injury. The formation of new neurons can contribute to rewiring circuits and restoring lost functions.

2.8. Hypothesis

Agent-based stochastic model of VANG in stratified environment possess high explanatory and predictive power and can be used to test hypotheses derived from experimental data.

3. MATERIALS AND METHOD

3.1. Theoretical Framework

It is of significance to note that our 3D-ABM-VANG model is mainly executed in reference to both Dilaray Tüfekçi's 1D-ABM-HANG model and Samet Atbaşı's 3D-ABM-HANG model (Tüfekçi & Öz, 2022; Atbaşı & Öz, 2023).

3.1.1. Objectives

- a) Survey literature for data related to rates of proliferation, differentiation, and migration for each cell type
- b) Establish a 3D-agent-based model using literature data and a preexisting model for adult neurogenesis based on the preexisting 1D-HANG and 3D-HANG models.
- c) Insert characteristics of the VANG biological system into categories of agent attributes, also called initial parameters, cellular processes, cellular activity, and finally the step function.
- d) Implement a background for the 3D-grid, followed by cellular environment simulation.
- e) Build the 3D-grid by integrating the three different layers, followed by tracking cellular lineage.
- f) Integrate standard error and standard deviation tracking of each cell type's population dynamics by constructing plots with a range of 50 to 100 repetitions as the time factors.
- g) Create a visualization model that demonstrates cellular lineage and population growth dynamics.
- h) Collect and integrate data into data frames and excel files.

3.1.2. Choice of cell fate

Cell fate refers to the developmental outcome or identity that a cell assumes during its lifespan. It is a fundamental concept in biology and a key player in identifying numerous processes in biology, including embryonic development, tissue homeostasis, and disease progression. Cell fate is tightly regulated by a combination of genetic, epigenetic, and environmental factors, and understanding the mechanisms that govern

cell fate decisions is a central focus of modern biology (Casey et al., 2020). Hence, the crucial step in building our model is to ascertain the fate of each cell type. Once we establish this fundamental aspect, we can chart the course that each cell type will follow while simulating its cellular processes. Therefore, our method for determining the selection of cell fate involves conducting an extensive review of the existing literature on *in vitro* and *in vivo* studies of adult subventricular neurogenesis (Obernier et al., 2018; Ponti et al., 2013). From this research, we extract data on population percentages related to the rates of cell proliferation, differentiation, and apoptosis for each cell type and integrate them as probability limits. The proliferation rate refers to the number of events that occur per day, while the probability limit refers to the expected probability of any given event. In our scenario, Obernier and colleagues observed that Type-B1 cells predominantly exhibit proliferative behavior. Approximately eighty percent of this cell population engages in symmetric consumption, leading to the generation of Type-C cells, while the remaining twenty percent of Type-B1 cells undergo symmetrical division (Obernier et al., 2018). Following data accumulation, we create a probability bar for the different cellular events per day at a time with their respective values for each cell type and compare them with a random number R that is inserted into the model. Refer to Figure 3 for the probability bar for determining cell fate.

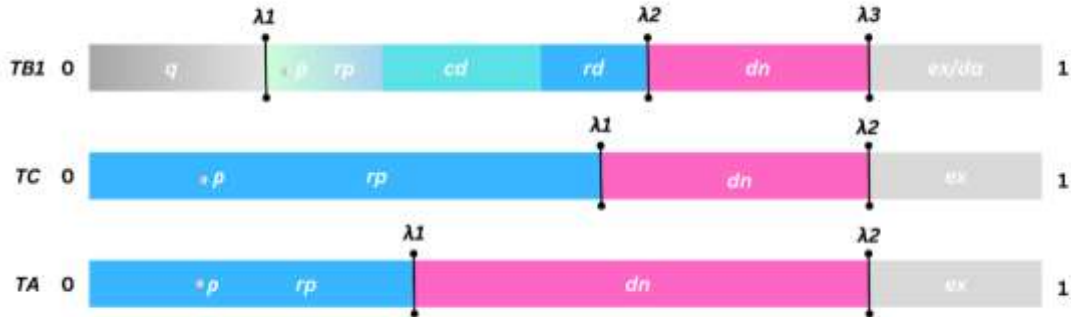


Figure 3: Determination of cell fate.

Cell fate is the identity or developmental consequence that a cell takes on during its existence. The probability limit is the maximum estimated probability of any event, whereas the proliferation rate is the number of events that occur each day.

3.1.3. States

Each cell displays three different states: quiescence, activation, and apoptosis.

a) Quiescence (Q): Quiescence is the cell arrest state of a stem cell, also known as reversible cell cycle arrest (Dabelow et al., 2022). A cell at q can die. The probability that a cell will enter Q with the event q or stay in Q is determined by q_{lim} , where $\tau(t)$ is the age of a certain cell type at time t .

b) Activation (A): A cell leaves q and enters A , which should be followed by either symmetric or asymmetric cell division, symmetric consumption (characteristic of Type-B1 cells as observed by Obernier et al.), or differentiation. In the 1D-HANG model, once a cell enters A , it cannot reenter q ; however, in both the 3D-HANG AND 3D-VANG models, this was allowed, for Type-B1 cells exclusively. An assumption is that an activated cell immediately divides or differentiates; therefore, A is a transient state, and an activated cell cannot die.

c) Apoptosis (ex): Apoptosis, or programmed cell death, is not explicitly a cell state but rather an empty set. When a cell enters apoptosis, it dies and is removed from the map. Any cell can change into an apoptotic state. Cells at the maximum age ($agemax$) undergo apoptosis.

3.1.4. Events

Cellular change happens through typically four events: symmetric and asymmetric cellular division, symmetric consumption, and differentiation. The probabilities of entering cellular division and differentiation are based on rates extracted from experimental data (Error! Reference source not found.) (Obernier et al., 2018).

a) Symmetric cell division (pp): Symmetric cell division produces two daughter cells (one of those cells is the same mother cell however identifying as a daughter cell). Therefore, **pp** is the main source of self-renewal and population growth. The event can (i) originate from q of the mother cell and end in q of both mother and daughter cells, or (ii) originate from A of the mother cell and end in A of both mother and daughter cells. The probability of leaving the original state with the event **pp** is based on the symmetrical division limit (pp_{lim}).

b) Asymmetric cell division (pd): By asymmetric cell division, the mother cell produces a newborn cell of another type. The event can only originate from A and end in A of both mother and daughter cells. The probability of leaving the original state with the event **pd** is based on the asymmetrical division limit (pd_{lim}).

c) **Symmetric consumption (cd)**: Through symmetric consumption, the mother cell produces two newborn cells of another type. It is assumed by experimental data that an NSC is consumed by the next cellular type following initial and prolonged self-renewal processes for stem cell pool maintenance (Obernier et al., 2018). The event can, like asymmetric division, only originate from **A** and end in **A** of both mother and daughter cells. The probability of leaving the original state with the event **cd** is based on the symmetric consumption limit (cd_{lim}).

d) **Differentiation (d)**: Through differentiation, a cell directly converts into another cell type without undergoing any cellular division. This event can only originate from **A** and end in **A**. The probability of leaving the original state with the event **d** is based on the differentiation limit ($diff_{lim}$).

e) **Quiescence (q)**: the event through which a cell transforms from state **Q** to state **A**.

Table 1: Parameters for each cell type with their respective default values (Obernier et al., 2018).

Parameters	T _{B1} Cell	T _c Cell	T _A Cell
pp_{lim}	0.18	0.4	0.16
cd_{lim}	0.65	-	-
pd_{lim}	0.04	0.4	0.14
diff_{lim}	10 times	3 times	3 times
age_{max}	15 days	5 days	5 days
age	0	-	-
age_A	0	-	-
age_{Amax}	10 days	-	-
q_{lim}	0.12	-	-
diff_{count}	0 times	-	-

Table 2: Agent attributes are assigned for each type of event, in terms of next state, next type, and newborn.

Event	Next State	Next State	Newborn
q	Q	C.cell_type	-
pp	A	C.cell_type	C.cell_type
cd	A	C.cell_type	iterated on C.neural_types
pd	A	C.cell_type	iterated on C.neural_types
diff_neural	A	iterated on C.neural_types	-
diff_TB2	A	TB2	-
ex	-	-	-

3.1.5. T_{B1} behavior

T_{B1} cells can either proliferate, asymmetrically self-renew, or differentiate (Obernier et al., 2018). They can symmetrically divide, producing two daughter T_{B1} cells, or get symmetrically consumed by the production of two T_C newborn cells (Obernier & et al., 2018). These cells rarely undergo asymmetric division, in which one daughter cell and T_C cell (Obernier et al., 2018) Assumptions are as follows: A T_{B1} cell can be found in all three states: **q**, **A**, **Ap**. **A**. T_{B1} can remain at **q** pre-activation. A T_{B1} cell enters **A**; this event occurs based on a random number generator (**R/RNG**) and pp_{lim} . After the event, the newborn cell enters **q**. The mother cell resumes aging. Immediately, it then undergoes **pd** and as a result, produces two newborn T_C cells. This event occurs based on **R** and cd_{lim} . A T_{B1} cell can undergo differentiation to a T_C cell directly. A T_{B1} cell can reenter **q**. A T_{B1} cell at age_{max} undergoes apoptosis.

3.1.6. T_C behavior

T_C cells, known as transiently amplifying cells, are the transitional stage between T_{B1} cells and neuroblasts. T_C cells rapidly proliferate or differentiate, but only for a short

period and under high stress of apoptosis (Renehan et al., 2001). Assumptions are as follows: A T_C cell can be found in two states: **A**, **Ap**. T_C cells are generated from T_{B1} cells with **pd** and **d**. A T_C cell might stay at **q** for a short duration of time; however, this state is not assigned as **q**. A T_C cell is immediately at **A**. Post-event, the mother cell continues to age, then immediately undergoes **pd** and as a result, produces a newborn T_A cell. This event occurs based on **R** and pd_{lim} . A T_C cell can undergo differentiation to a T_A cell directly. A T_C cell at age_{max} undergoes apoptosis.

3.1.7. T_A behavior

T_A cells, also known as neuroblasts, can be produced via differentiation from T_C cells. T_A cells rarely proliferate. They undergo differentiation into immature neurons (IN). Assumptions are as follows: A T_A cell can be found in two states: **A**, **Ap**. T_C cells are generated from T_C cells with **pd** and **d**. A T_A cell might stay at **q** for a short duration of time; however, this state is not assigned as **q**. A T_A cell is immediately at **A**. A T_A cell can undergo proliferation, defined by **R** and pp_{lim} . Post-event, the mother cell continues to age. A T_A cell will undergo differentiation to an IN once it has migrated along the RMS and reached the OB. After differentiation, the cell is the same as before **d** and enters **q**. A T_A cell age_{max} undergoes apoptosis.

3.2. Simulation

3.2.1. Model construction

Our model was created using the **Mesa** Python library/package (Error! Reference source not found.), which enables users to quickly build agent-based models using already provided core components (like spatial grids and agent schedulers) or tailored implementations, visualize them using a web-based interface, and analyze the outcomes using Python's data analysis tools. (Kazil et al., 2020). We assigned our agents with different agent classes: '**NPC**: neural progenitor cells for T_{B1} cells, '**TAC**: transiently amplifying cells for T_C cells, and '**NBL**: neuroblasts' for T_A cells. Cellular activity for each newborn cell type was assigned with a 'cellular activity' function within each respective class. As for movement rules and cellular processes, each was assigned its functions named 'move_cells' and 'cellular_processes' which can be called by the cellular activity within each class.

MESA: AN ABM PYTHON LIBRARY

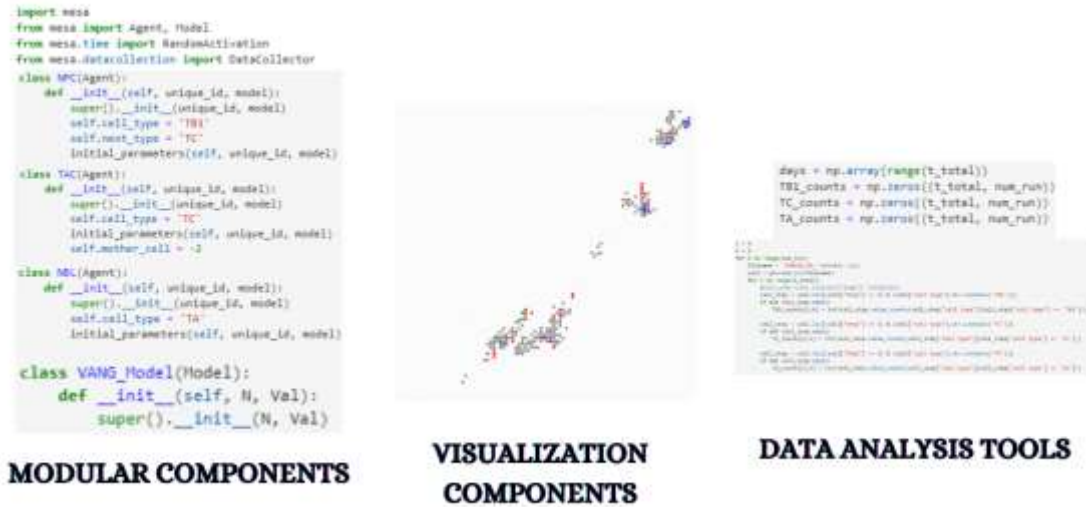


Figure 4: Mesa is an agent-based python package/library that gives access to various tools (Kazil et al., 2020).

3.2.2. Model parameters

Each cell in our model was assigned the following parameters:

- The active age of the cell (no. of days following leaving quiescence)
- The daughter cell type
- The age of the cell
- The location of the cell
- The number of symmetric and asymmetric divisions and symmetric consumptions
- The unique ID of every cell and the ID of the mother cell
- The states and events through every time step for each cell
- Type of the cell at birth and the birth event (i.e., asymmetric cell division, symmetric cell division).

The CanvasGrid package displayed how the cellular population grew spatially with each passing time step. However, this was only employed to obtain the spatial

expansion patterns. Visualization also permits a manual iteration over the graphic user interface (GUI). The recording of cellular activity using parameters described previously was obtained during a looping run with ten repetitions. Each run could last up to 100 days in total.

3.2.3. Agent attributes

Every cell (**agent C**) is created with an agent class that is assigned depending on their birth event and the type of the mother cell. The newborn **T_{B1}**, **T_C**, and **T_A** cells are created with classes **NPC**, **TAC**, and **NBL** respectively. The cell can differentiate into another cell under the same class; therefore, the agent class does not represent the cell type, it only represents the cellular activities available to the newborn cell through its lifespan. The attributes that were assigned to every agent are shown below:

- **C.unique_id**: The identity of C, assigned as a unique number for every agent.
- **C.cell_type**: The cell type for C at **t**.
- **C.event**: The event that occurred for C at **t**.
- **C.state**: The state that C is in at **t**.
- **C.age**: The age of C at **t**.
- **C.age_A**: The active age of C at **t**, which is the number of days after leaving the quiescent state.
- **C.mother_cell**: The unique_id of the mother cell.
- **C.mother_event**: The birth event for C. For example, '**pp**' and '**pd**'.
- **C.daughter_type**: The type of daughter cell that C produces at **t+1**.
- **C.daughter**: The agent that will be assigned for the daughter cell that C produces at **t+1**. The initial value is set as "**None**" and assigned to the respective class type after the event. If the daughter cell is a **T_C** cell, the class is **TAC**. If the daughter is a **T_A** cell, the class is **NBL**.

C.diff_count: The counter for the number of '**pd**' events for C at **t**. In class C, the counter does not reset after the change in the cell type through differentiation; however, the **pd_limit** is summed.

3.2.4. Probability limits

C.pp_limit: The maximum probability for ‘pp’ event to occur for a cell type. This parameter was kept constant in this model for every cell type that has access to this event.

C.pd_limit: The maximum probability for ‘pd’ event to occur for a cell type. This parameter was kept constant in this model for every cell type that has access to this event.

C.rd_limit: The maximum probability for ‘cd’ event to occur for T_{B1} cells.

C.q_limit: The maximum probability for ‘q’ event to occur for T_{B1} cells.

C.diff_limit: The maximum number of ‘pd’ events that are allowed for each cell type. After this, the cell is either pushed for differentiation or apoptosis. The limit was set as 10 for T_{B1} cells and 3 for T_C cells.

C.active_TB1_limit: The maximum active age allowed for T_{B1} cells.

3.2.5. Dictionaries

C.neural_types: Dictionary of available neural lineage cell types in the system that can be accessed through cellular processes. The dictionary includes T_{B1} , T_C , T_A , IN (immature neuron), and N (neuron). This dictionary is used to iterate the cell type in the neural lineage by ‘pd’ and ‘diff_neural’.

C.next_state: The dictionary for the state that C enters at $t+1$. The state is dependent on the event and defined as either **A** (active) or **Q** (quiescent). The respective next_state for each event is given in **Table 1**.

C.next_type: The dictionary for the cell type that is assigned to C at $t+1$. The cell type is dependent on the event. The respective next_type for each event is given in **Table 2**.

C.newborn: The dictionary for the cell type of the daughter cell C produces at $t+1$. The cell type is dependent on the event. The respective newborn for each event is Error! Reference source not found..

3.3. Mathematical Framework

Every cell (agent C_i) is created with an agent class (M_i) that is assigned depending on their birth event (ϵB) and the type (γ) of the mother cell. The newborn T_{B1} , T_C , and T_A cells are created with classes: **NPC**, **TAC**, and **NBL** respectively. The cell can differentiate into another cell under the same class; therefore, the M_i does not represent

the cell type, it only represents the cellular activities (ζ_i) available to the newborn cell through its lifespan. The cellular processes are defined over an event (ϵ), a state (σ), and the consequences of the event. The tracking of events ($\epsilon t \in E_i$) and states ($\sigma t \in S_i$) that occurred through the lifespan of C_i are recorded as an agent attribute.

Four dictionaries are defined as **(1)** for the agent classes available as newborn cells (D_M); where **NPC** is assigned to a newborn T_{B1} cell, **TAC** to a newborn T_C cell, and **NBL** to a newborn T_A cell:

$$D_M = \{NPC, TAC, NBL\} \quad (1)$$

(2) for all cell types included in the system (D_O) with a subset of neural lineage (D_N), where Φ represents the dead cell:

$$D_N = \{T_{B1}, T_C, T_A, IN\} \quad (2)$$

$$D_O = D_N \cup \{T_{B2}, \phi\} \quad (3)$$

(3) for the events available to the cells in the system (D_E), where **q** stands for quiescence, **rp** for symmetric cell division, **cd** for symmetric consumption, **rd** for asymmetric cell division, **dn** for differentiation on neural lineage, **da** for differentiation into an astrocyte and **ex** for apoptosis:

$$D_E = \{q, rp, cd, dn, da, ex\} \quad (4)$$

and **(4)** for the states available to the cells in the system (D_S).

$$D_S = \{Q, A\} \quad (5)$$

The following attributes were assigned to every cell C_i with an agent class M_i and recorded during the simulation for every time step:

$$\begin{aligned}
& \mathbf{UID}: \text{the identity of } \mathbf{C}_i, \text{ assigned as a unique number for every agent.} \\
& \quad \text{For every abbreviation,} \\
& \quad \text{the } \mathbf{UID} \text{ referred to as } \mathbf{i} \text{ within the text.} \\
& \mathbf{MID}: \text{the identity of the mother cell that produced } \mathbf{C}_i. \\
& \mathbf{G}_i(\tau): \text{the cell type of } \mathbf{C}_i \text{ at } \mathbf{t}. \\
& \mathbf{G}_M: \text{the cell type of the mother cell that produced } \mathbf{C}_i. \\
& \quad \text{These cells can only be } \mathbf{T}_{B1}, \mathbf{T}_C, \text{ and, } \mathbf{T}_A. \\
& \mathbf{E}_i(\tau): \text{the event (cellular processes will be initiated) for } \mathbf{C}_i \text{ at } \mathbf{t}. \\
& \mathbf{S}_i(\tau): \text{the state that } \mathbf{C}_i \text{ is in at } \mathbf{t}. \\
& \epsilon \mathbf{B}: \text{the birth event of } \mathbf{C}_i. \\
& \tau(\mathbf{t}): \text{the age of } \mathbf{C}_i \text{ at } \mathbf{t}. \\
& \tau_A(\tau): \text{the active age of } \mathbf{C}_i \text{ at } \mathbf{t}, \\
& \quad \text{which is the number of days since leaving quiescence for } \mathbf{T}_{B1}. \\
& \mathbf{T}_C \text{ and } \mathbf{T}_A \text{ cells are assumed to be active immediately after birth.} \\
& \tau_D(\tau): \text{The total number of asymmetric cell divisions} \\
& \quad \text{and differentiations of } \mathbf{C}_i \text{ at } \mathbf{t}. \\
& \tau_R(\tau): \text{the total number of symmetric cell divisions of } \mathbf{C}_i \text{ at } \mathbf{t}. \\
& \bar{\tau}: \text{the maximum } \tau \text{ allowed for } \mathbf{C}_i, \text{ updated depending on } \mathbf{G}_i(\tau). \\
& \bar{\tau}_A: \text{the maximum } \tau_A \text{ allowed for } \mathbf{C}_i, \text{ updated depending on } \mathbf{G}_i(\tau). \\
& \bar{\tau}_D: \text{the maximum } \tau_D \text{ allowed for } \mathbf{C}_i, \text{ updated depending on } \mathbf{G}_i(\tau). \\
& \bar{\tau}_R: \text{the maximum } \tau_R \text{ allowed for } \mathbf{C}_i, \text{ updated depending on } \mathbf{G}_i(\tau). \\
& \mathbf{M}_J(\tau): \text{the agent class that will be assigned to} \\
& \quad \text{the daughter cell of } \mathbf{C}_i \text{ at } \mathbf{t} + 1. \\
& \mathbf{G}_J(\tau): \text{the cell type that will be assigned to} \\
& \quad \text{the daughter cell at } \mathbf{C}_i \text{ at } \mathbf{t} + 1. \\
& \bar{\alpha}_q: \text{the initial value for the probability of quiescence.} \\
& \bar{\alpha}_{rp}: \text{the initial value for the probability of symmetric cell division.} \\
& \bar{\alpha}_{rd}: \text{the initial value for the probability of asymmetric cell division.}
\end{aligned}
\tag{6}$$

3.3.1. Cellular framework

Iteration of an attribute within a dictionary can be defined as follows with an iterative function (Γ_X):

$$\Gamma x = \begin{cases} k: D_X(k) = Y(t), \\ Z(t+1) = D_X(k+1) \end{cases} \tag{7}$$

An event occurs at every time step since the cell division and differentiation process are all assumed to occur with a duration lower than 24 hours. The age of the cell $\mathbf{C}_i$, τ , is iterated by every time step after its birth.

3.3.1.1. Quiescence

The event **q** does not create any specific consequences, as the cell remains inactive at this stage. The steps that are evaluated in this process (Π_q) are:

$$\Pi_q(C_i) = \begin{cases} G_i(\tau + 1) = G_i(\tau) \\ E_i(\tau) = D_{E,1} \\ S_i(\tau) = D_{S,1} \end{cases} \quad (8)$$

3.3.1.2. Cell division

When the cell C_i undergoes a cell division, C_i is aged (represented by self-renewal, **r**) and a daughter cell (C_j) is produced. If it is a symmetric cell division (**rp**), a daughter cell of the same type is produced (represented by proliferation, **p**). If it is an asymmetric cell division (**rd**), a daughter cell with the cell type next in $\mathbf{D_M}$ is assigned to the newborn cell (represented by differentiation, **d**). If it is symmetric consumption (**cd**), a daughter cell with the cell type next in $\mathbf{D_M}$ is assigned to the newborn cell. The steps that are evaluated in the processes Π_{rp} and Π_{rd} are:

$$\Pi_q(C_i, C_j) = \begin{cases} G_i(\tau + 1) = G_i(\tau) \\ E_i(\tau) = D_{E,2} \\ M_j = M_i \\ G_j(\tau + 1) = G_j(\tau) \\ E_{B,j} = D_{E,2} \\ \tau_{A,i}(\tau + 1) = \tau_{A,i}(\tau) + 1 \\ \tau_{R,i}(\tau + 1) = \tau_{R,i}(\tau) + 1 \\ S_i(\tau + 1) = D_{S,2} \end{cases} \quad (9)$$

$$q(C_i, C_j) = \begin{cases} T_N(G_i, G_j) \\ E_i(\tau) = D_{E,3} \\ T_M(M_i, M_j) \\ G_j(\tau + 1) = G_j(\tau) \\ E_{B,j} = D_{E,3} \\ \tau_{A,i}(\tau + 1) = \tau_{A,i}(\tau) + 1 \\ \tau_{D,i}(\tau + 1) = \tau_{D,i}(\tau) + 1 \\ S_i(\tau + 1) = D_{S,2} \end{cases} \quad (10)$$

3.3.1.3. Differentiation

The cell C_i can differentiate into the next cell type (g) in the neural lineage D_N or into an astrocyte ($D_{O,5}$). These events are represented with event dn and da respectively. When a cell differentiates, the agent class M_i does not change, as there is no newborn cell, but instead, the cell C_i itself is differentiating. Therefore, the lifespan of C_i is iterated with a differentiation process, either Π_{dn} or Π_{da} . The steps that are evaluated in these processes are:

$$\Pi_{dn}(C_i) = \begin{cases} \tau_N(G_i, G_i) \\ E_i(\tau) = D_{E,A} \\ \tau_{A,i}(\tau + 1) = \tau_{A,i}(\tau) + 1 \\ \tau_{D,i}(\tau + 1) = \tau_{D,i}(\tau) + 1 \\ S_i(\tau + 1) = D_{S,2} \end{cases} \quad (11)$$

$$\Pi_{da}(C_i) = \begin{cases} G_i(\tau + 1) = D_{O,5} \\ E_i(\tau) = D_{E,S} \\ \tau_{A,i}(\tau + 1) = \tau_{A,i}(\tau) + 1 \\ \tau_{D,i}(\tau + 1) = \tau_{D,i}(\tau) + 1 \\ S_i(\tau + 1) = D_{S,2} \end{cases} \quad (12)$$

3.3.1.4. Apoptosis

The death of the cell C_i is described with the event ex and the process Π_{ex} . When this event occurs, the cell is also removed from the environment. The steps evaluated in this process are:

$$\Pi_{ex} = \begin{cases} G_i(\tau + 1) = D_{O,6} \\ E_i(\tau) = D_{E,6} \end{cases} \quad (13)$$

3.3.2. Cellular activity

The activities that can occur within the lifespan of the cell C_i are defined for the cell type $G_i(\tau)$. The cellular activities available to a cell depend on its agent class M_i . **NPC** class started with the cell type $G_i(0) = D_{N,1}$, **TAC** with $G_i(0) = D_{N,2}$ and **NBL** with $G_i(0) = D_{N,3}$. Therefore, the cell C_i can only access those for the birth cell type and the next cell types in neural lineage D_N .

3.3.2.1. Cell fate determination

As the **VANG-AB3D** model does not include any mechanics for the intracellular processes, the intracellular state of C_i at the time t (or age τ) is represented with a random constant $\epsilon \in (0, 1)$. ρ is then compared to the probability of the events available to cell type $G_i(\tau)$ as given in Error! Reference source not found.. The probability of events q , rp , cd , and rd are given with the age-dependent probability functions of α_q , α_{rp} , and α_{rd} respectively. The event q is only available to T_{B1} cells, therefore, $\alpha_q = 0$ for T_C and T_A cells. All probabilities for the events the cell C_i can go through eventually sum up to 1 as follows, where β is the probability for apoptosis.

$$\alpha_q(\tau) + \alpha_{rp}(\tau) + \alpha_{cd}(\tau) + \alpha_{rd}(\tau) + \beta(\tau) = 1 \quad (14)$$

The internal stress introduced by aging and activity is reflected in the age-dependent probability functions for events, mainly on rp , and on setting the conditions for cellular activity. The probability of rp decreases by every rp by a factor of $\kappa_{rp} \in (0,1)$ event as:

$$\alpha_{rp}(\tau) = \overline{\alpha_{rp}}(\kappa_{rp})^{\tau_R(\tau)} \quad (15)$$

The event q can be accessed only when $S_i(\tau) = D_{S,1}$, and α_{rd} is set constant. Therefore, the probability equation for events becomes:

$$\overline{\alpha_q} \delta_{(S_i(\tau)=D_{S,1})} + \overline{\alpha_{rp}}(\kappa_{rp})^{\tau_R(\tau)} + \overline{\alpha_{rd}} + \beta' = 1 \quad (16)$$

where β is increased over the initial probability of apoptosis β with the total sum of the decreases in the probability for other events.

3.3.2.2. Type-B1 cell parameters

A $\mathbf{T_{B1}}$ cell is initiated with $G_i(0) = D_{N,1}$ and $S_i(0) = D_{S,1}$. As the cell ages, the probability of remaining in this state is determined as:

$$\delta_q = \delta_{(\tau_A < 1)}(\delta_{(0 < \rho < \alpha_q)} + \delta_{(\alpha_q + \alpha_{rp} < \rho < 1)}) \quad (17)$$

where δ is a conditional operator.

A $\mathbf{T_{B1}}$ cell is allowed to symmetrically divide once and then fall into quiescence. This special condition is defined with the process Π_{rpq} , and the conditions are represented with δ_{rpq} .

$$\Pi_{rpq} = \left\{ \begin{array}{l} G_i(\tau + 1) = G_i(\tau) \\ E_i(\tau) = D_{E,2} \\ M_j = M_i, \\ G_j(\tau + 1) = G_j(\tau) \\ E_{B,j} = D_{E,2} \\ \tau_{A,i}(\tau + 1) = \tau_{A,i}(\tau + 1) \\ \tau_{R,i}(\tau + 1) = \tau_{R,i}(\tau + 1) \\ S_i(\tau + 1) = D_{S,1} \end{array} \right. \quad (18)$$

$$\delta_{rpq} = \delta_{(\tau_A < 1)}\delta_{(\alpha_q < \rho < (\alpha_q + \alpha_{rp}))} \quad (19)$$

A $\mathbf{T_{B1}}$ cell can undergo a cell division, $\mathbf{rp}$ with the conditions represented as δ_{rp} and $\mathbf{rd}$ with the conditions represented as δ_{rd} . The internal stress induced by activity is tracked with τ_A and the maximum τ_A allowed for $\mathbf{T_{B1}}$ cells, $\bar{\tau}_A$. The internal stress induced by $\mathbf{rd}$ is tracked with τ_D and the maximum τ_D allowed for $\mathbf{T_{B1}}$ cell, $\bar{\tau}_D$. $\mathbf{T_{B1}}$ cell is forced toward either direct differentiation on the neural lineage or to apoptosis, with the conditions represented as δ_{dn} and δ_{ex} respectively. A $\mathbf{T_{B1}}$ cell can differentiate into a $\mathbf{T_{B2}}$ astrocyte because of the internal stress induced by aging and activity, with the conditions represented as δ_{da} .

$$\alpha_r = \alpha_{rp} + \alpha_{rd} \quad (20)$$

$$\delta_{rp} = \delta_{(0 < \tau_A < \bar{\tau}_A)}\delta_{(0 < \rho < \alpha_{rp})} \quad (21)$$

$$\delta_{rd} = \delta_{(0 < \tau_A < \bar{\tau}_A)} \delta_{(\alpha_{rp} < \rho < \alpha_r)} \delta_{(\tau_d < \bar{\tau}_d)} \quad (22)$$

$$\delta_{dn} = \delta_{(0 < \tau_A < \bar{\tau}_A)} \delta_{(\alpha_{rp} < \rho < \alpha_r)} \delta_{(\tau_D < \bar{\tau}_D)} \quad (23)$$

$$\delta_{da} = \delta_{(\tau_A \geq \bar{\tau}_A)} \delta_{(\tau < \bar{\tau})} \quad (24)$$

$$\delta_{ex} = \delta_{(\tau_A \geq \bar{\tau}_A)} \delta_{(\tau \geq \bar{\tau})} \quad (25)$$

The cellular activity for a **T_{B1}** cell, where ρ is a random constant that represents the ongoing intracellular processes at the age τ , is given by ζ_{TB1} .

$$\begin{aligned} \zeta_{TB1} = & \delta_q \Pi_q + \delta_{rpq} \Pi_{rpq} + \delta_{rp} \Pi_{rp} + \delta_{cd} \Pi_{cd} + \delta_{rd} \Pi_{rd} + \delta_{dn} \Pi_{dn} + \delta_{da} \delta_{da} \\ & + \delta_{ex} \Pi_{ex} \end{aligned} \quad (26)$$

3.3.2.3. Type-C cell parameters

A newborn cell **T_C** cell is initiated with $\mathbf{G}_i(\mathbf{0}) = \mathbf{D}_{N,2}$ and $\mathbf{S}_i(\mathbf{0}) = \mathbf{D}_{S,2}$. If a **T_{B1}** cell differentiates and continues its life as a **T_C** cell, $\bar{\tau}$, $\bar{\tau}_A$, $\bar{\tau}_D$, and $\bar{\tau}_R$ are iterated from the existing values for the **T_{B1}** cells. Otherwise, these parameters are assigned with the values for the **T_C** cell at birth.

$$\bar{x} = \bar{x}_{TB1} + \bar{x}_{TC}, x \in \{\tau, \tau_A, \tau_D, \tau_R\} \quad (27)$$

T_C cells are transiently amplifying cells; therefore, they rapidly start diving, either **rp** or **rd**, with the conditions represented as δ_{rp} and δ_{rd} respectively.

$$\delta_{rp} = \delta_{(0 < \rho < \alpha_{rp})} \quad (28)$$

$$\delta_{rd} = \delta_{(\alpha_{rp} < \rho < \alpha_r)} \delta_{(\tau_d < \bar{\tau}_d)} \quad (29)$$

$$\delta_{dn} = \delta_{(\alpha_{rp} < \rho < \alpha_r)} \delta_{(\tau_d \geq \bar{\tau}_d)} \quad (30)$$

The internal stress due to age and activity is higher for **T_C** cells, which pushes the cells to apoptosis with a higher probability, with the conditions represented as δ_{ex} .

$$\delta_{ex} = \delta_{(\alpha_r < \rho < 1)} \quad (31)$$

The cellular activity for a T_C cell, where ρ is a random constant that represents the ongoing intracellular processes at the age τ , is given by ζ_{TC} .

$$\zeta_{TC} = \delta_{rp}\Pi_{rp} + \delta_{rd}\Pi_{rd} + \delta_{dn}\Pi_{dn} + \delta_{ex}\Pi_{ex} \quad (32)$$

3.3.2.4. Type-A cell parameters

A newborn Type-A cell is initiated with $\mathbf{G}_i(\mathbf{0}) = \mathbf{D}_{N,3}$ and $\mathbf{S}_i(\mathbf{0}) = \mathbf{D}_{S,2}$. If a T_A cell differentiates and continues its life as a T_A cell, $\bar{\tau}$, $\bar{\tau}_A$ and $\bar{\tau}_R$ iterated from the existing values for the T_A cells. If the cell also differentiated from T_{B1} to T_C that also adds on. Otherwise, these parameters are assigned with the values for T_A cells at birth.

$$\begin{aligned} \bar{x} &= \bar{x}_{TC} + \bar{x}_{TA} \text{ OR } \bar{x} = \bar{x}_{TB1} + \bar{x}_{TC} + \bar{x}_{TA} \\ x &\in \{\tau_A, \tau_D, \tau_R\} \end{aligned} \quad (33)$$

T_A cells are neuroblasts, that can only symmetrically divide (**rp**) and that will differentiate (**dn**) into immature neurons ($\mathbf{D}_{N,4}$), with the conditions represented as δ_{rp} and δ_{dn} respectively.

$$\delta_{rp} = \delta_{(\tau_d < \bar{\tau}_d)} \delta_{(\tau < \bar{\tau})} \delta_{(0 < \rho < \alpha_{rp})} \quad (34)$$

$$\delta_{dn} = \delta_{(\tau_d \geq \bar{\tau}_d)} \delta_{(\tau < \bar{\tau})} \delta_{(\alpha_{rp} < \rho < 1)} \quad (35)$$

The internal stress due to age and activity is high for T_A cells; however, they have a higher probability for differentiation than apoptosis. The apoptosis of T_A cells occurs with the conditions represented as δ_{ex} .

$$\delta_{ex} = \delta_{(\tau_d < \bar{\tau}_d)} \delta_{(\tau < \bar{\tau})} \delta_{(\tau_d \geq \bar{\tau}_d)} \quad (36)$$

The cellular activity for a T_A cell, where ρ is a random constant that represents the ongoing intracellular processes at the age τ , is given by ζ_{TA} .

$$\zeta_{TA} = \delta_{rp}\Pi_{rp} + \delta_{dn}\Pi_{dn} + \delta_{ex}\Pi_{ex} \quad (37)$$

3.3.2.5. Astrocytes and immature neurons

In the SVZ, T_{B1} cells differentiate into another astrocyte subtype called T_{B2} cells, which are assumed to be a reserve or a second population of NSCs; however, because they do not display neurogenic behavior, we chose to abdicate them from our model. Nonetheless, we still include them in our model as the non-neural type T_{B1} cells differentiate after prolonged quiescence. A cell C_i with $G_i(\tau) = D_{O,5}$ will have the class $M_i = D_{M,1}$. All astrocytes are assumed to be in quiescence; therefore, C_i has $S_i(\tau) = D_{S,1}$ when a Type-B1 cell differentiates into it. The cell continues to age (τ increases with every time step); however, it remains in quiescence indefinitely.

INs result from T_A cell differentiation once they reach the OB; therefore, a cell C_i with $G_i(\tau) = D_{N,4}$ will have the class $M_i = D_{M,3}$. All immature neurons are assumed to be in quiescence; therefore, C_i has $S_i(\tau) = D_{S,1}$ when a Type-A cell differentiates into it. The cell continues to age (τ increases with every time step); however, it remains in quiescence indefinitely. The immature neurons are in the OB.

4. RESULTS

4.1. Mesa multi-grid data demonstrate population dynamics similar to those observed in *in vivo* and *in vitro* studies

Our findings revealed patterns of NSC population dynamics that were comparable to those found in a recent *in vivo* and *in vitro* study on adult subventricular neurogenesis (Obernier et al., 2018). According to their findings (Obernier et al., 2018), around 20-30% of the Type-B1 cell population undergoes symmetric self-renewal, whereas the remaining 70-80% is symmetrically consumed by the emergence of Type-C cells. Additionally, they discovered comparable patterns in modes of division across both short- and long-term lineage tracing, with the crucial distinction being the eventual loss of the Type-B1 cell population over time observed in long-term lineage tracing. The short-term scenario is evident in our 3D multigrid, as depicted in Figure 4, where a portion of the Type-B1 cell population self-renews symmetrically for the first couple of days following the initiation of the grid simulation. After a few rounds of self-renewal, Obernier et al. recorded symmetric consumption resulting in Type-C cell production starting from day 3 after labeling (Obernier et al., 2018). Consequently, we detect a rise in the number of Type-C cells starting somewhere between **d0-d10** in the multigrid (Error! Reference source not found.), which is consistent with the data observed by Obernier et al. and Ponti et al. Additionally, Ponti et al. discovered, in their SVZ NSC cell cycle analysis study, that following the first round of division for Type-B1 cells, Type-C cells divide three to four times followed by differentiation to Type-A cells and that this process appears to take place 1 day, as evidenced by the short cell cycle length of Type-B1 cells, standing at 4 hours at a time. Our 3D multigrid supports this data, in which an immediate appearance of Type-C cells is clear as soon as **d0** (Error! Reference source not found.). Moreover, Ponti et al. observed even fewer rounds of proliferation for Type-A cells, which appear to divide once, sometimes twice, before they differentiate into immature neurons (Ponti et al., 2013) This is supported by our results, as evidenced by the smaller number of Type-A cells and the huge production of immature neurons starting from **d10-d90** (Error! Reference source not found., Error! Reference source not found., & Error! Reference source not found.)

4.2. Standard error and standard deviation data provide insight into proliferation rates over time

For the data analysis section of our model, we designed two types of plot graphs for monitoring NSC proliferation rates over time standard error and standard deviation plots. Both standard error and standard deviation are measurements of the spread or heterogeneity of a dataset; however, their calculations and intended uses are different. While standard deviation quantifies the average amount by which each data point in a dataset deviates from the mean of the dataset, standard error quantifies the variability of sample means from multiple samples taken from the same population. The standard error is a measure of the variability of sample means from multiple samples taken from the same population, where it quantifies how much the sample mean is likely to vary from the actual population mean. We calculated the standard error for each cell type in the SVZ: Type B1-cells, Type-C cells, and Type-A cells The data presented in the graphs is the result of the model operating over 100 days and 5 repetitions (Error! Reference source not found., Error! Reference source not found., & Error! Reference source not found.).

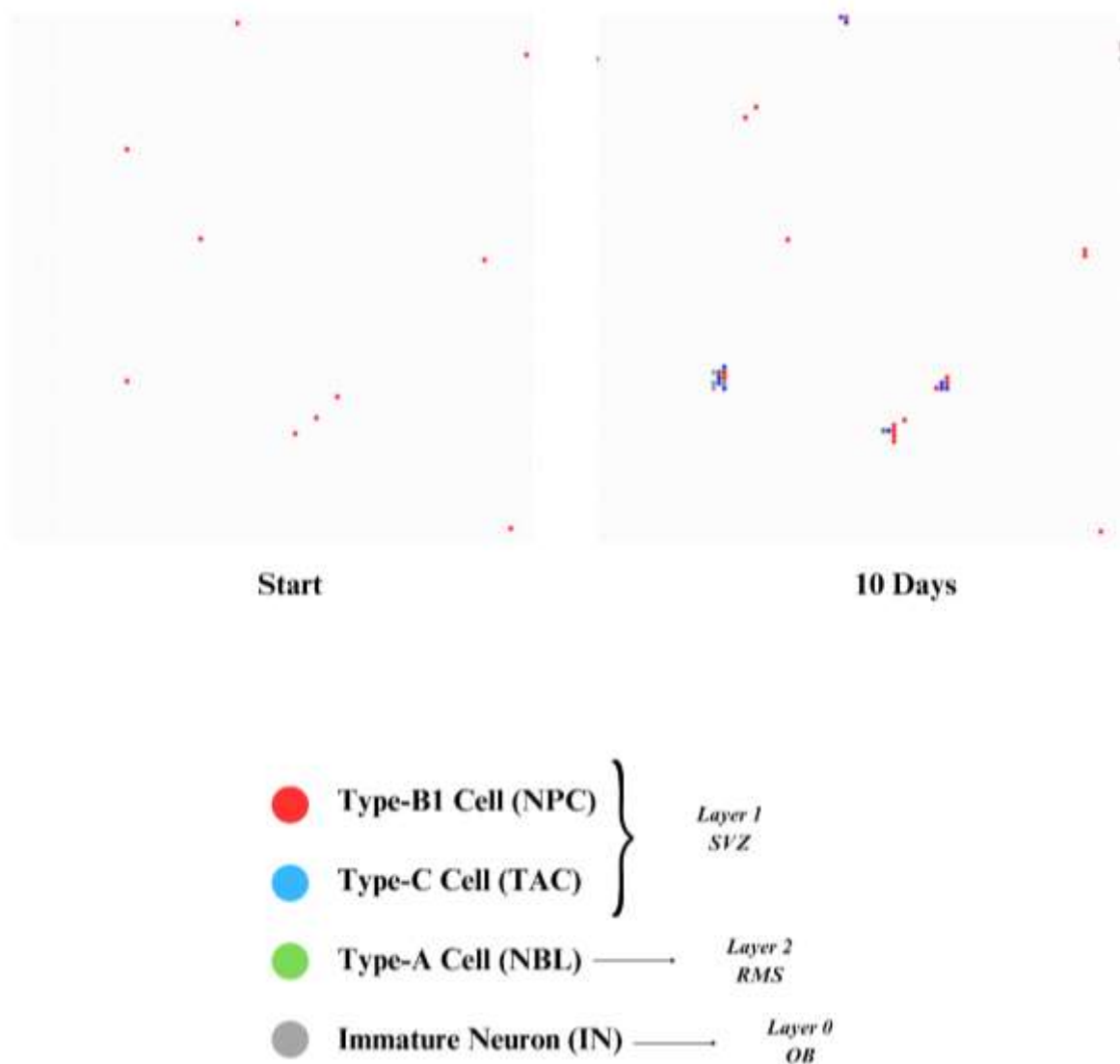


Figure 5: SVZ NSC Population Dynamics on Mesa Multigrid on Day 0 and 10.

Within 10 days of the simulation, we observed a rise in SVZ cellular types: such as Type-B1 cells and Type-C cells.

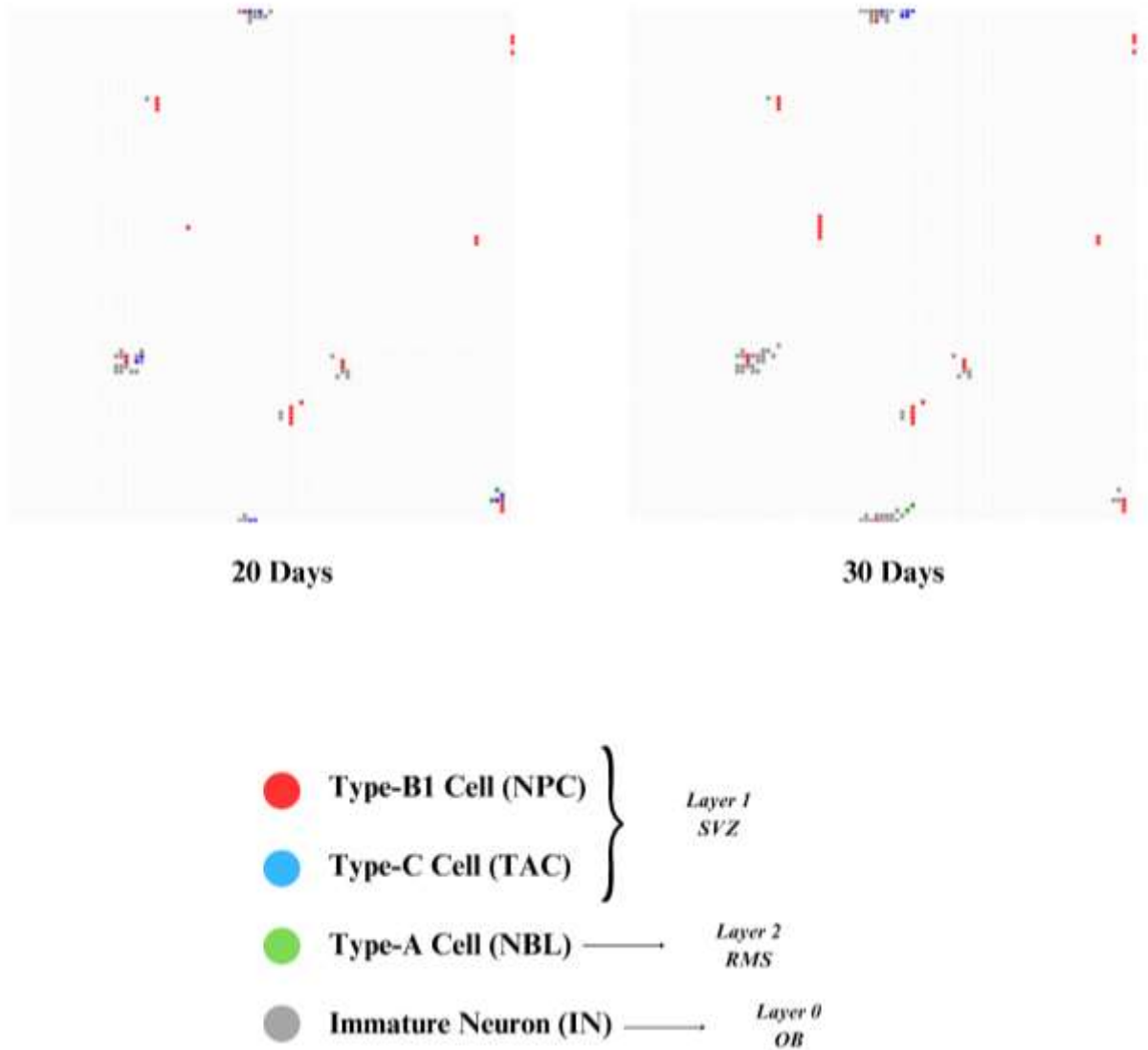


Figure 6: SVZ NSC Population Dynamics on Mesa Multigrid on Days 20 and 30. Twenty days later, there is an observed increase in immature neuron numbers, meaning that after Type-B1 cells are activated, the process of adult neurogenesis is quick, in which almost the majority of the Type-B1 cell population undergoes symmetric consumption, and the remaining percentage either symmetrically self-renews or falls back into quiescence.

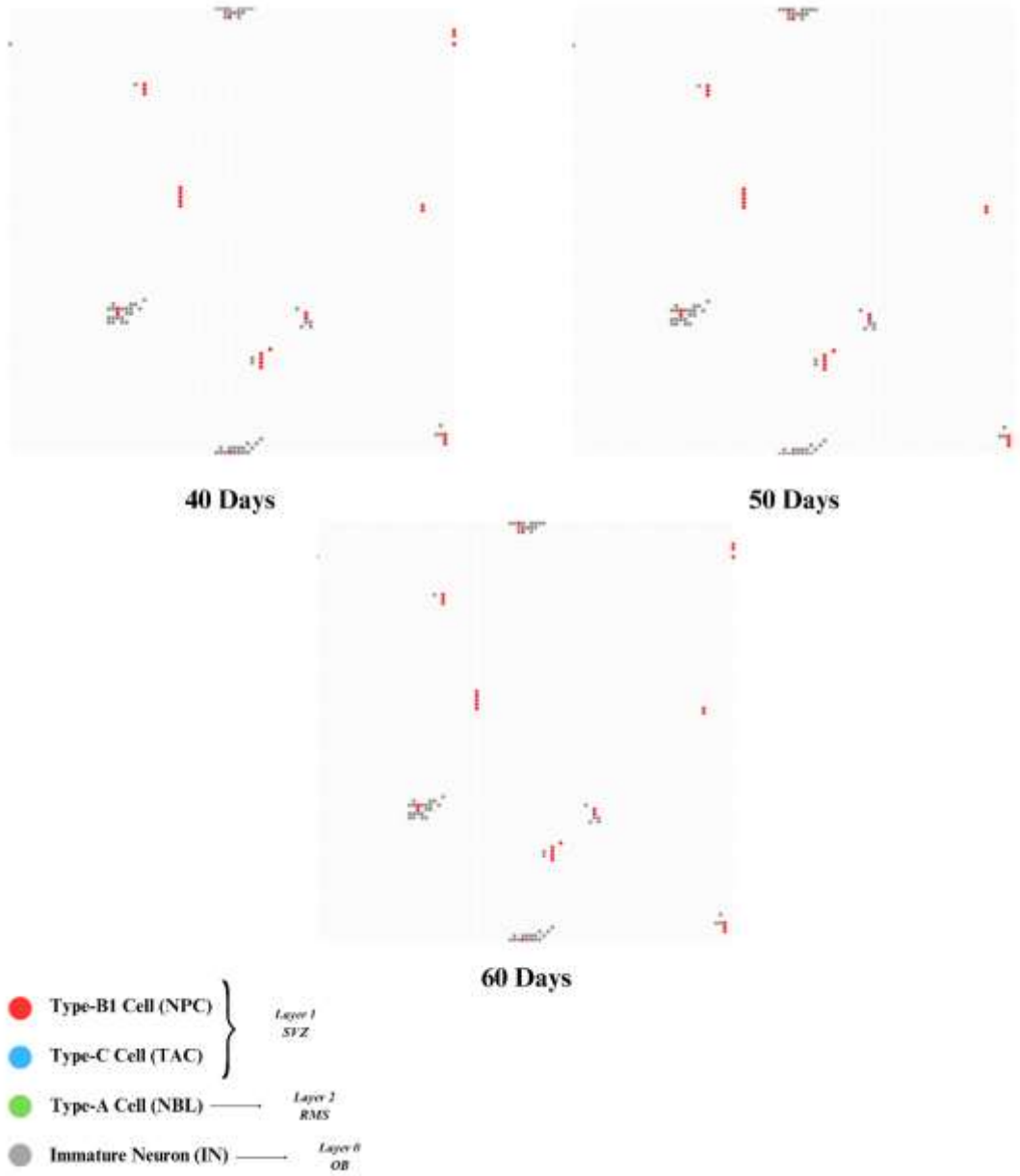


Figure 7: SVZ NSC Population Dynamics on Mesa Multigrid on Days 40, 50 and 60.

Approximately, for the next month, we observe a decline in all the SVZ cellular types, a huge increase in immature neurons, and even some quiescent Type-B1 cells, which according to Obernier et al., could fall back into quiescence upon activation and then remain quiescent for up to five months or more (Obernier et al., 2018).

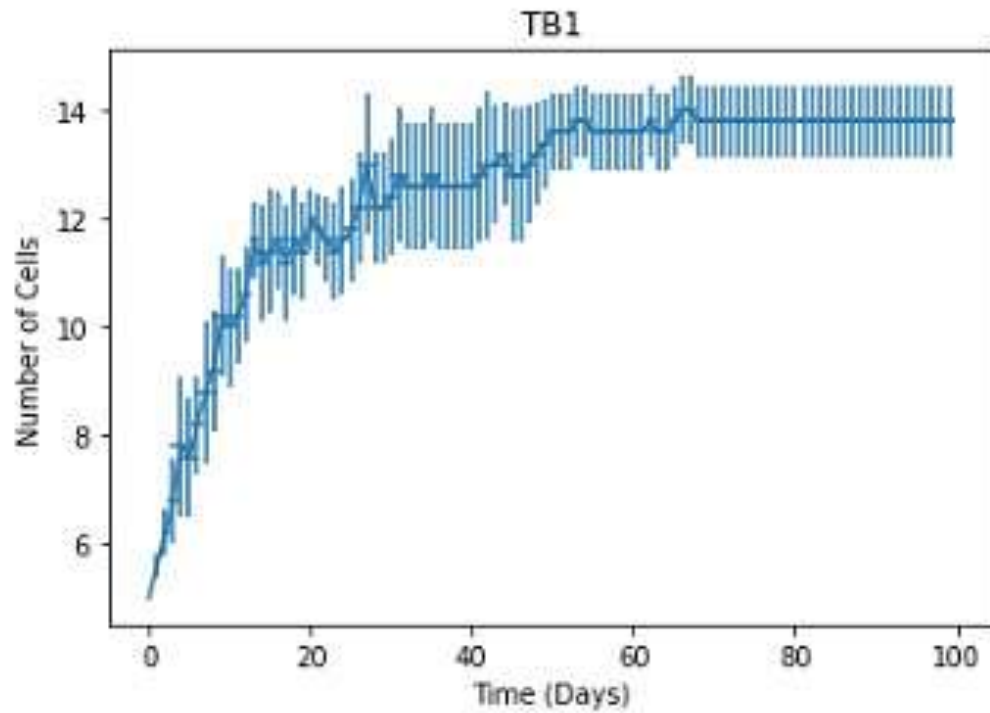


Figure 8: The standard deviation for Type-B1 cells over 100 days and 10 repetitions of the model simulation.

According to the graph above, in the span of 100 days, we observe a gradual increase in Type-B1 cells up to day 50, followed by a constant increase in number up to the 100th-day mark.

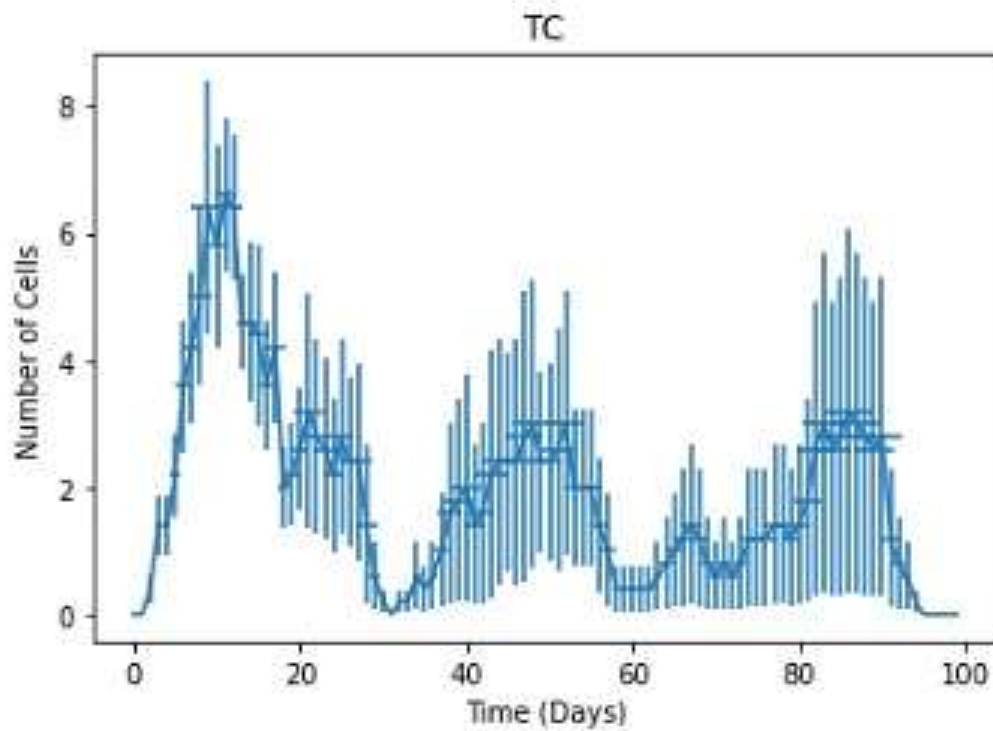


Figure 9: The standard deviation for Type-C cells over 100 days and 10 repetitions of the model simulation.

Typical of Type-C cell behavior, Type-C cells in this graph experience an increase in number around the 10th day, followed by a constant flow of elevation and decline in number up until the 100th day.

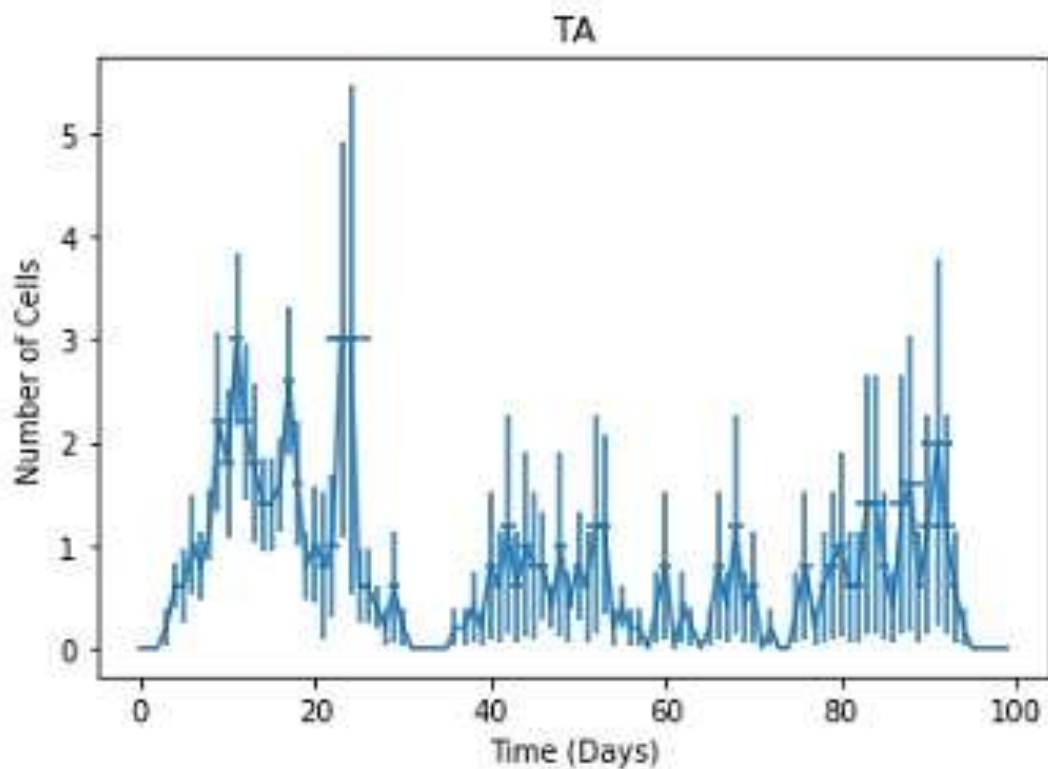


Figure 10: The standard deviation for Type-A cells over 100 days and 10 repetitions of the model simulation.

Like Type-C cells, Type-A cells also appear to display similar numbers following their rise in the SVZ niche, in which we see a sharp surge in their numbers around the three-month mark.

5. DISCUSSION

Current evidence suggests four circumstances regarding SVZ NSC lineage progression **(i)** Type-B1 cells mostly symmetrically self-renews (20%), while the remaining population (80%) undergoes symmetric consumption, which is a process that generates Type-C cells at the expense of Type-B1 cells, also called creating progeny (Obernier et al., 2018); **(ii)** asymmetric division for Type-B1 cells is rarely or seldom occurring; **(iii)** Type-C cells undergo rapid three to four rounds of symmetric cell division before differentiating into Type-A cells (Ponti et al., 2013); **(iv)** Type-A cells divide once or twice before differentiating into immature neurons (Ponti et al., 2013). Obernier et al. also noted that the symmetrically self-renewing fraction of the Type-B1 cell population can reenter quiescence for up to five months, before becoming reactivated and consumed by production Type-C cells (Obernier et al., 2018). However, adult neurogenesis in the SVZ is not solely determined by internal factors such as cell division, specialization, and cell death, or the collective behavior of these cells. Instead, it operates within a complex system influenced by a multitude of factors, as elaborated in earlier sections. These factors encompass interactions between cells, interactions between cells and their microenvironment (the niche), connections between the extracellular matrix and the niche, and the process of cell migration. While our VANG model may appear to be straightforward in terms of the elements we have incorporated, it is, in fact, quite intricate when considering its mathematical framework and the background against which it operates. The fundamental focus of our entire model centers on the dynamics of individual cells within the SVZ niche, as opposed to general population-level dynamics. Presently, our VANG model has limitations due to its lack of integration of cell-cell interactions and cell migration. Our future agenda for this model involves the incorporation of crucial elements, specifically, the inclusion of cellular interactions and the characterization of cell migratory behavior within the VANG system.

6. CONCLUSION AND SUGGESTIONS

Presently, our VANG model has limitations due to its lack of integration of cell-cell interactions and cell migration. Our future agenda for this model involves the incorporation of crucial elements, specifically, the inclusion of cellular interactions and the characterization of cell migratory behavior within the VANG system.



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