Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 18(5): 6288–6304.
DOI: 10.3934/mbe.2021314
Received: 27 May 2021
Accepted: 12 July 2021
Published: 19 July 2021

Research article

Dynamic behavior and stabilization of brain cell reconstitution after stroke under the proliferation and differentiation processes for stem cells

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Abstract: Stem cells play a critical role in regulatory operations, overseeing tissue regeneration and tissue homeostasis. In this paper, a mathematical model is proposed and analyzed to study the impact of stem cell transplantation on the dynamical behavior of stroke therapy, which is assumed to be based on transplanting dead brain cells following a stroke. We transform the method of using hierarchical cell systems into a method of using different compartment variables by using ordinary differential equations, each of which elucidates a well-defined differentiation stage along with the effect of mature cells in improving the brain function after a stroke. Stem cells, progenitor cells, and the impacts of the stem cells transplanted on brain cells are among the variables considered. The model is studied analytically and solved numerically using the fourth-order Runge-Kutta method. We analyze the structure of equilibria, the ability of neural stem cells to proliferate and differentiate, and the stability properties of equilibria for stem cell transplantation. The model is considered to be stable after transplantation if the stem cells and progenitor cells differentiate into mature nerve cells in the brain. The results of the model analysis and simulation facilitate the identification of various biologically probable parameter sets that can explain the optimal time for stem cell replacement of damaged brain cells. Associating the classified parameter sets with recent experimental and clinical findings contributes to a better understanding of therapeutic mechanisms that promote the reconstitution of brain cells after an ischemic stroke.

Keywords: cell replacement; eigenvalue stability analysis; ischemic stroke; numerical simulation; system of ordinary differential equations

1. Introduction

Stem cells (SCs) continue to play an important role in the regulatory processes that govern tissue development, homeostasis, and regeneration [1–3]. This therapy can substitute damaged cells in the brain with transplanted or endogenous cells [4–6]. In addition to their ability to self-renew by replicating themselves, SCs can be categorized into 200 cell types [5, 7]. New neurons are continuously generated in the hippocampus throughout an adult's lifetime, but their number decreases dramatically with age in humans and rodents [8–10]. The newly formed neurons lack the ability to self-repair, which in turn prevents adequate tissue recovery after a brain injury [4]. For instance, approximately 80% of all new neurons are destroyed under the model of a striatum stroke. In addition, endogenous regeneration can only replace approximately 0.2% of the dead neurons [4, 11]. For this reason, stem cell transplantation is a viable alternative for treating brain injuries, such as a stroke, and other medical issues [12–17]. The emergence of stem cell transplantation for several neurological ailments, such as experimental stroke, emphasizes the suitability of this approach in the aftermath of a stroke, which is a major cause of adult disability and mortality worldwide [18, 19].

An ischemic stroke is caused by the occlusion of a cerebral artery by reduced or loss of blood flow in the cerebral region, which results in brain tissue damage. A most promising approach in this regard entails replacing cells in ischemic regions [20–22]. In the case of an ischemic stroke, the underlying rationale for implementing stem cell therapy is to appropriately substitute the infarcted central nervous system tissue [6, 20, 22]. The lost neurons must be replaced so that the neuronal circuitry can be re-established [6, 20, 22, 23]. Moreover, such an approach can provide trophic support to risk-prone tissue within the penumbra that ensconces the infarction area or accelerates cell proliferation, differentiation, migration, and survival (endogenous precursor) [6, 20, 22]. This study considers stem cell usage in the replacement function of damaged brain cells in the case of an ischemic stroke. Rather than examining all possible destinies of the cells being scrounged, this study assesses the overarching mechanism through which brain cell generation occurs. Therefore, instead of considering each neural cell type individually, we place all of them in a group of brain cells that are terminally differentiated. In particular, we combine each neural progenitor lineage-committed cell that progressively loses its ability to self-renew. Several mathematical models of a stroke have been developed so far [24–26]. In these models, only the dynamics of disease and brain inflammation from immune cells, which are linked to how a stroke occurs, are modeled. However, they only model the dynamics of disease and brain inflammation from immune cells, which are linked to how a stroke occurs. Meanwhile, stem cell differentiation and proliferation have been extensively studied, both experimentally and mathematically [27–29]. Furthermore, mathematical models have been adopted to evaluate adult neurogenesis. For example, Ziebell et al. [30] proposed a simple approach for studying hippocampal neurogenesis among adults.

Similarly, Ashbourn et al. [31] proposed a mechanism based on partial differential equations to assess how immature neurons migrate into the olfactory bulb through the rostral migratory stream. They also investigated the parameters that facilitate biologically plausible solutions. Alqarni et al. [32, 33] investigated the dynamic effects of microglia and neural stem cells on brain cells following the generation of neural stem cells and their transplantation, as well as the potential recovery after a stroke.

Ordinary differential equations (ODEs) have been used to model neurogenesis in the olfactory epithelium of a mouse, which represents a cellular layer containing neurons that line nearly half of all cavities in the nasal region [34]. Models exhibiting the considered collation of various cell populations

are notable as a point of departure [34]. Against this backdrop, the present study aims to examine the impact of the stem cells transplanted within seven days on the brain in the stage of recovery from an ischemic stroke. Our study encompasses the impacts of stem cell populations transplanted to replace dead cells in stroke patients, which are then regulated by extracellular signaling feedback. This study aims to explain the concept of symmetry and antisymmetry between brain cells, as well as the role of stem cells in promoting neural cell regeneration after a stroke.

The rest of this paper is organized as follows. In Section 2, we present a mathematical model called stem cells-progenitor cells-brain cells (SPB) and its biological interpretation. We describe the equilibrium points of the model in Section 3. In Section 4, we validate the model's stability. In Section 5, we discuss the numerical experiments. Finally, in Section 6, we conclude this study.

2. SPB model formulation

For a long time, neural cell transplantation has been highlighted for its potential therapeutic application in nearly all neurological ailments affecting the central nervous system, such as strokes [4]. The key function of stem cell transplantation is to reduce or slow down the neurodegenerative damages caused by replacing cells [31]. Stem cells are known to be capable of differentiation, proliferation, and dying [27, 35]. In this regard, progenitor cells undergo differentiation to cells that are differentiated terminally, proliferation through division, and death [27, 35, 36]. The SPB model is based on a neurogenesis system [34] that elucidates the behavior of olfactory epithelium lineage systems under a feedback regulation that governs neuron generation. Three cell populations are modeled by an ODE system, namely stem cells S, progenitor cells P, and brain cells B, with a general form of negative feedback. The biological process of transplanting stem cells into the brain after a stroke serves various functions. The proposed model is assumed to represent the function of replacing dead nerve cells with new nerve cells in the brain [37, 38].

Feedback signals that regulate differentiation and proliferation in various phases are known to mediate coordination and control of cell development in certain tissues [34]. Although feedback control is set up during embryonic expansion, it is continually present within adult mammals, which enables tissues to strongly respond to injuries [34]. We study a system with two possible negative feedback forms: proliferative stem cells and progenitor cells. The form of feedback included in this model is based on that used in [27, 34]. This feedback is chosen because it provides a simple starting point that will not overly complicate the analysis [27, 34]. The proliferation of previous states gets curtailed due to cells that are present within the same and subsequent stages. To attain maturity, the cells must undergo a set of steps related to maturation, which cannot be obviated. Two possible negative feedback forms for proliferative stem cells and progenitor cells are $\frac{p_1}{1+S+P+B}$ and $\frac{p_2}{1+P+B}$, where p_1 and p_2 indicate the proliferation rates of stem cells and progenitor cells, respectively. Mathematically, this type of feedback is called the Hill function [27, 34].

Self-renewal refers to the ability a cell to undergo multiple cycles of cell growth and division while remaining undifferentiated. Self-renewal, according to recent theoretical and experimental models, influences not only the population of stem cells but also the underlying mechanisms through which non-stem cells function. For tissue regeneration, efficacious mature cell production necessitates an

appropriate self-renewal of stem cells [39]. The following ODE describes the behaviors of stem cells:

$$\frac{dS}{dt} = \frac{2p_1 S}{1+S+P+B} - (d_s + \alpha_1)S. \tag{2.1}$$

here, d_s denotes the differentiation rate of stem cells to progenitor cells, and α_1 denotes the death rate of stem cells.

The stem cell population resides at the top of the hierarchy and results in various progenitor cells, which in turn produces precursors that facilitate the formation of mature cells. During the differentiation process, the fact that cells undergo a transition wherein they enter a progenitor state must be considered. The following differential equation illustrates the behavior of progenitor cells:

$$\frac{dP}{dt} = \frac{2p_2 P}{1+P+B} + d_s S - (d_p + \alpha_2)P. \tag{2.2}$$

The dynamics of these cells are determined by several key parameters: α_2 denotes their death rate, and d_p denotes the differentiation rate of progenitor cells to differentiated brain cells, signifying the flux of cells into various differentiation pathways. Note that the formation of mature cells is a multistep process that commences from stem cells and leads to a particular sequence that immature progenitor cells undergo before their transition into maturity [40].

Neural stem cells, which can regenerate themselves during the recovery stage after an ischemic stroke, can keep the mammalian brain active throughout its life [41]. Neurons–as well as glial cells, such as astrocytes–are vulnerable to damage when an ischemic stroke occurs. Therefore, we consider the state of loss in the brain cells in the aftermath of a stroke. Endogenous neural stem cells might not be able to generate enough cells to repair the neurological damage caused by a major disease, such as a stroke [14]. The survival of neural stem cells appears to be hampered as up to 80% of new neurons die within two weeks of their in vivo generation [42]. The following ODE elucidates the behaviors of living brain cells after a stroke:

$$\frac{dB}{dt} = (d_0 - \delta)B + d_P P. \tag{2.3}$$

here, d_0 denotes the endogenous regeneration rate of brain cells and δ denotes the rate of brain cells that die from a stroke.

Thus, the SPB model can be expressed as follows:

$$\begin{aligned}
\frac{dS}{dt} &= \frac{2p_1 S}{1+S+P+B} - (d_s + \alpha_1)S, \\
\frac{dP}{dt} &= \frac{2p_2 P}{1+P+B} + d_s S - (d_p + \alpha_2)P, \\
\frac{dB}{dt} &= (d_0 - \delta)B + d_p P.
\end{aligned} \tag{2.4}$$

For all equations, the populations of stem cells S, progenitor cells P, and brain cells B are positive or equal to zero. In the proposed model, we use the stem cell dose when transplantation occurs as an initial condition, $S(0) = 2 \times 10^8$ [23], set $P(0) = 0$ [27], and determine the initial value of brain cells as $B(0) = 1.5 \times 10^{11}$ [43]. The corresponding schematic of SPB is shown in Figure 1.

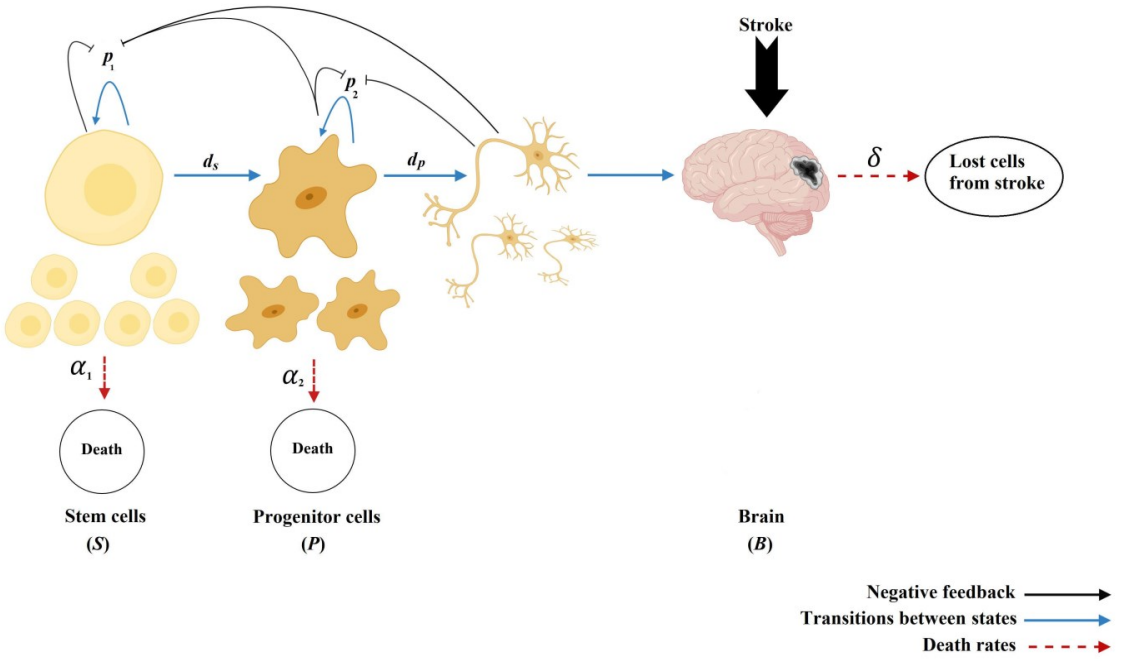

Figure 1. Schematic of the impact of stem cell transplantation in the brain after a stroke.

3. Equilibrium points for the SPB model

The fixed points of the SPB dynamic Eq (2.4) are determined from the following ODEs:

$$\frac{dS}{dt} = 0 \Leftrightarrow \frac{2p_1 S}{1+S+P+B} - (d_s + \alpha_1)S = 0, \tag{3.1}$$

$$\frac{dP}{dt} = 0 \Leftrightarrow \frac{2p_2 P}{1+P+B} + d_s S - (d_p + \alpha_2)P = 0, \tag{3.2}$$

$$\frac{dB}{dt} = 0 \Leftrightarrow (d_0 - \delta)B + d_p P = 0. \tag{3.3}$$

From Eq (3.3), we obtain

$$B = \frac{d_p P}{(\delta - d_0)}. \tag{3.4}$$

By substituting Eq (3.4) into Eq (3.2), we obtain

$$S = P(a_1 - \frac{a_2}{a_3 + P}), \tag{3.5}$$

where

$$a_1 = \frac{\alpha_2 + d_p}{d_s},\ \ a_2 = \frac{2p_2(\delta - d_0)}{d_s(d_p + \delta - d_0)},\ \ a_3 = \frac{\delta - d_0}{\delta - d_0 + d_p},\ \ a_4 = \frac{d_p}{(\delta - d_0)}. \tag{3.6}$$

Then, from Eq (3.1), we obtain
$S = 0$ or $S = b_1 + b_2 P$,

where

$$b_1 = \frac{2p_1 - (d_s + \alpha_1)}{d_s + \alpha_1}, b_2 = \frac{d_p + \delta - d_0}{\delta - d_0}. \tag{3.7}$$

Now, substituting $S = 0$ into Eq (3.5) gives

$$P = 0 \ \ or \ \ P = \frac{a_2}{a_1} - a_3. \tag{3.8}$$

Thus, the first equilibrium point is represented by

$$E_1(S, P, B) = (0, 0, 0)\,. \tag{3.9}$$

When $P = \frac{a_2}{a_1} - a_3$, we obtain the second equilibrium point as follows:

$$E_2(S, P, B) = \left(0, (\delta - d_0)\,\chi, d_p\,\chi\right), \tag{3.10}$$

where

$$\chi = \frac{2p_2 - (d_p + \alpha_2)}{(\delta - d_0)(-d_0 + d_p + \delta)}.$$

Now, after substituting $S = b_1 + b_2 P$ into Eq (3.5), we obtain the third positive equilibrium point as follows:

$$E_3(S, P, B) = (b_1 + \eta\, b_2, \eta, a_4\eta)\,, \tag{3.11}$$

where

$$\begin{aligned}
\eta &= \frac{\eta_1 + (d_0 - \delta)\eta_3}{2(d_0 - d_p - \delta)\nu}, \nu = (d_s + \alpha_1)((d_p + d_s + \alpha_2)(d_0 - \delta) - d_p d_s),\\
\eta_1 &= \sqrt{(d_0 - \delta)^2 \eta_0},\ \ \eta_0 = -4d_s(d_s - 2p_1 + \alpha_1)(d_0 - d_p - \delta)\nu + (\eta_4)^2,\\
\eta_2 &= 2d_s(p_1 + p_2) + 2p_2\alpha_1 - (d_s + \alpha_1)(d_p + \alpha_2 + 2d_s),\\
\eta_3 &= (2d_p d_s(d_s - p_1 + \alpha_1) + \eta_2(\delta - d_0)), \eta_4 = 2d_p d_s(d_s - p_1 + \alpha_1) + \eta_2(\delta - d_0).
\end{aligned}$$

Therefore, we obtain equilibrium points by solving Eq (2.4) to determine the positive equilibrium points if and only if S, P, and B exemplify positive solutions.

Proposition 1 (Nonnegative Equilibrium for the SPB model)**.** *We assume that the equilibrium points for the SPB system, $S; P; B > 0$, satisfy the following conditions:*

- $d_p + \alpha_2 < 2p_2$
- $d_s + \alpha_1 < 2p_1$
- $(d_s + \alpha_1)(d_p + \alpha_2 + 2d_s) < 2(d_s(p_1 + p_2) + p_2\alpha_1)$
- $d_0 < \delta$

Then and only then can there exist nonnegative real steady states.

According to the physiological meaning, we can classify the equilibrium points of SPB Eq (2.4) as follows:

Definition 1. *We define the dead equilibrium point if the stroke is capable of damaging the brain cells in the absence of stem cells in the brain. The steady state of the form $S; P; B = 0$ indicates dead brain cells.*

Definition 2. *We define differentiating progenitor cells into specific types of nerve cells capable of replacing cells that have been damaged. Differentiating progenitor cells to differentiated brain cells is represented by the steady state of the form $P; B > 0, S = 0$.*

Definition 3. *We define replacing dead cells with differentiated cells (mature brain cells) in the brain. The steady state of the form $S; P; B > 0$ indicates that the proliferation and differentiation processes for stem cells are performed for replacing the lost brain cells.*

4. Stability of equilibrium points of the SPB model

For the eigenvalues associated with the equilibrium of the stem cells transplanted in the brain after a stroke, the (3×3) Jacobian matrix of the Eq (2.4) can be expressed as follows:

$$J[\psi] = \begin{bmatrix} F_S[\psi] & F_P[\psi] & F_B[\psi] \\ G_S[\psi] & G_P[\psi] & G_B[\psi] \\ H_S[\psi] & H_P[\psi] & H_B[\psi] \end{bmatrix}, \tag{4.1}$$

where $\psi = [S, P, B]$, $F[\psi] = \frac{dS}{dt}$, $G[\psi] = \frac{dP}{dt}$, and $H[\psi] = \frac{dB}{dt}$.

Theorem 1. *Let us assume a function $f : \Omega \to \Re^3_+$, where Ω is a domain in $\Re^3_+$, and that $E_1 = (0, 0, 0) \in \Omega$ is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part. Then, E_1 denotes an unstable equilibrium point of f.*

Proof. The Jacobian J corresponding to the equilibrium point E_1 is given as

$$J[E_1] = \begin{bmatrix} 2p_1 - (d_s + \alpha_1) & 0 & 0 \\ d_s & 2p_2 - (d_p + \alpha_2) & 0 \\ 0 & d_p & d_0 - \delta \end{bmatrix}. \tag{4.2}$$

where the eigenvalues of the matrix $J[E_1]$ are given by

$$\lambda_1 \;=\; 2p_1 - (d_s + \alpha_1), \lambda_2 = 2p_2 - (d_p + \alpha_2), \; \lambda_3 = d_0 - \delta.$$

From the condition of the equilibrium points, evidently, $\lambda_{1,2} > 0$ and $\lambda_3 < 0$. When the blood supply to the brain is cut off due to a stroke, mature brain cells die [20, 22]. Thus, the first equilibrium point E_1 denotes an unstable point.

Remark 1.
- *Theorem 1 implies that all brain cells die as a result of a stroke prior to stem cell transplantation.*
- *According to the biological meaning of endogenous neural stem cells, the rate of regeneration of these cells is much smaller than that of the neural cells that die from a stroke. Thus, $d_0 < \delta$.*
- *Biologically, an unstable positive equilibrium point emerges where the endogenous neural stem cells can invade the SPB system by eliminating the damage $d_0 > \delta$ if $\lambda_3 > 0$.*

Theorem 2. *Let us assume a function $f : \Omega \to \Re^3_+$, where Ω is a domain in $\Re^3_+$, and that $E_2 = (0, P, B) \in \Omega$ is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part. Thereafter, E_2 is considered as an unstable equilibrium point of f.*

Proof. The Jacobian J corresponding to the equilibrium point E_2 is given by

$$J[E_2] = \begin{bmatrix} b_{11} & 0 & 0 \\ d_s & b_{22} & b_{23} \\ 0 & d_p & d_0 - \delta \end{bmatrix}, \tag{4.3}$$

where

$$\begin{aligned} b_{11} &= \frac{p_1(d_p + \alpha_2) - p_2(d_s + \alpha_1)}{p_2}, \\ b_{22} &= b_{23} = \frac{((d_p + \alpha_2)(d_p - 2p_2 + \alpha_2)(d_0 - \delta_1)}{2p_2(d_0 - d_p - \delta_1)}). \end{aligned}$$

Subsequently, the characteristic equation is given by

$$(\frac{p_1(d_p + \alpha_2) - p_2(d_s + \alpha_1)}{p_2} - \lambda)(-d_p b_{23} - (b_{22} - \lambda)(-d_0 + \delta + \lambda)) = 0, \tag{4.4}$$

Then, the eigenvalues of the characterized Eq (4.4) are given by

$$\begin{aligned} \lambda_1 &= \frac{p_1(d_p + \alpha_2) - p_2(d_s + \alpha_1)}{p_2} > 0, \\ \lambda_{2,3} &= \frac{1}{2}\Big[d_0 + b_{22} - \delta \pm \sqrt{4d_p b_{23} + (-d_0 + b_{22} + \delta)^2}\Big] < 0. \end{aligned}$$

The eigenvalues λ_2 and λ_3 are both negative, whereas λ_1 is positive. Therefore, E_2 denotes an unstable equilibrium point.

Remark 2.
- *Theorem 2 implies that the proliferation of progenitor cells in the absence of stem cells, $(0, P, B) \to \Re^3_+$, causes the progenitor cells to differentiate into mature brain cells.*
- *It is evident that the stability of the equilibrium point E_2 is governed by progenitor cells. As the persistent proliferation of progenitor cells in the absence of stem cells is limited, the differentiating stage is considered unstable.*

Theorem 3. *Let us assume a function $f : \Omega \to \Re^3_+$, where Ω is a domain in $\Re^3_+$, and that $E_3 = (S, P, B) \in \Omega$ refers to an equilibrium point at which all eigenvalues of the Jacobian matrix have negative real parts. Then, E_3 is considered a stable equilibrium point of f.*

Proof. The Jacobian J corresponding to the equilibrium point E_3 is given by

$$J[E_3] = \begin{bmatrix} c_{11} & c_{12} & c_{13} \\ d_s & c_{22} & c_{23} \\ 0 & d_p & d_0 - \delta \end{bmatrix},$$

where

$$\begin{aligned} c_{11} &= -d_s + \frac{2p_1(1+\eta+a_4\eta)}{(1+b_1+(1+a_4+b_2)\eta)^2} - \alpha_1, \\ c_{12} &= -\frac{(2p_1(b_1+b_2\eta)}{(1+b_1+(1+a_4+b_2)\eta)^2}, \\ c_{22} &= \frac{2p_2(1+a_4\eta)}{(1+\eta+a_4\eta)^2} - (\alpha_2+d_p), \\ c_{23} &= -\frac{(2p_2\eta)}{(1+\eta+a_4\eta)^2}. \end{aligned}$$

Subsequently, the characteristic equation is given by

$$M_3\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0 = 0, \tag{4.5}$$

where

$$\begin{aligned} M_0 &= -d_s(c_{13}d_p + a_{12}(-d_0+\delta)) + c_{11}(a_{23}d_p + a_{22}(-d_0+\delta)) > 0, \\ M_1 &= c_{11}c_{22} + c_{11}d_0 + c_{22}d_0 - c_{23}d_p - c_{12}d_s - (c_{11}+c_{22})\delta > 0, \\ M_2 &= -c_{11} - c_{22} - d_0 + \delta > 0,\ M_3 = 1. \end{aligned}$$

Now, we apply the Routh–Hurwitz theorem to $M_3\lambda^3 + M_2\lambda^2 + M_1\lambda + M_0 = 0$, which yields

$$\begin{vmatrix} \lambda^3 & M_3 & M_1 \\ \lambda^2 & M_2 & M_0 \\ \lambda^1 & M^* & 0 \\ \lambda^0 & M_0 & 0 \end{vmatrix}$$

From Proposition 1,

$$\begin{aligned} M_2M_1 - M_0M_3 &= d_s(c_{13}d_p + c_{12}(-d_0+\delta)) - c_{11}(c_{23}d_p \\ &\quad + c_{22}(-d_0+\delta)) + (a_{11}+c_{22}+d_0-\delta)(c_{23}d_p \\ &\quad + c_{12}d_s - c_{11}(c_{22}+d_0-\delta) + c_{22}(-d_0+\delta)) > 0. \end{aligned} \tag{4.6}$$

Then, $M_2, M_0 > 0$ and $M_2M_1 > M_0M_3$, where

$$M^* = \frac{M_2M_1 - M_3M_0}{M_2}. \tag{4.7}$$

Thus,

$$\begin{aligned} M^* &= \frac{1}{(c_{11}+c_{22}+d_0-\delta)}[(c_{11}c_{22}(c_{11}+c_{22})+c_{11}c_{23}d_p \\ &\quad -(c_{12}(c_{11}+c_{22})+c_{13}d_p)d_s)]+(c_{11}+c_{22})d_0 \\ &\quad -c_{23}d_p-(c_{11}+c_{22})\delta > 0. \end{aligned} \tag{4.8}$$

Given that all coefficients in the first column have positive signs, Eq (4.5) has no roots with positive real parts and one of the eigenvalues is negative. For this reason, the equilibrium point E_3 is stable. Hence, the third equilibrium point is stable if both the proliferation rates p_1 and p_2 are high. In addition, if the processes of progenitor cell proliferation are at a high level, they are considered stable, but only under certain restrictions. Similarly, the differentiation rates (d_s and d_p) and death rates (α_1 and α_2) of the stem cells, progenitor cells, and differentiated brain cells increase the rate of transition from stem cells to progenitor cells, differentiated cells, and brain cells. This decreases the rate of restrained feedback from progenitor and differentiated cells to p_1 and p_2, respectively. This finding can be highlighted as a new approach to treat stroke patients.

Remark 3. *The effect of stem cell transplantation on the brain cells during a stroke (which includes cells lost by a stroke) on the dynamic system of the SPB model can be deduced as follows:*

- *Theorem 3 implies that the proliferation and differentiation of stem cells and progenitor cells,* $(S, P, B) \in \Re^3_+$, *facilitate the replacement of the brain cells dead from a stroke with new nerve cells.*
- *From Theorems* 1–3*, we conclude that the instability of the equilibrium without transplantation of stem cells* E_1 *and* E_2 *offers a sufficient condition for the existence of equilibrium with transplantation of stem cells* E_3.
- *Biologically,* $2p_2 > \alpha_2 + d_p$ *and* $2p_1 > \alpha_1 + d_s$*; thus, a stable positive equilibrium point appears where both progenitor and stem cells persist. At this point, the proliferation of the stem and progenitor cells overtakes their loss by death and differentiation, which facilitates the maintenance of their aggregation. The aggregation of progenitor cells also maintains a population of differentiated neural cells as the progenitor cells are transferred to the differentiated brain cells.*
- *The SPB model is deemed stable when the brain reconstitutes the lost cells with the stem and progenitor cells that differentiate into new brain cells.*
- *After a stroke, the differentiated cells can replace the dead cells with new nerve cells, increasing the number of brain cells. As a result, the degree of disability and damage caused by the stroke is reduced [12, 14].*

5. Numerical experiments

Herein, the SPB Eq (2.4) numerically determines the parameters that impact the behavior of the SPB model. The goal of these simulations is to better understand stem cell proliferation, differentiation, parameters, and dynamics to restore the brain cells following a stroke. Table 1 lists the parameters determined through experimental studies [24, 27] and other parameter values obtained using MATHEMATICA programming (11.2, Wolfram Research Inc., Champaign, Illinois, USA). The NDSolve

command was adopted for solving the SPB Eq (2.4) to investigate the impact of stem cells' ability to repair the brain cells by generating new cells after a stroke. All simulations were performed using the Runge-Kutta method of order four (RK4) to obtain more stable and convergent solutions, as shown in Figures 2 and 3, and the residual error demonstrated the precision of the suggested numerical method. The SPB simulations were run with a step size of 10^{-4} and a period of seven days (10,080 min) Also, the simulation results of the SPB model were compared with those of the mathematical model that determined many of the dynamic factors controlling the cell behavior of the stem, progenitor, and differentiated cells when transplanted on melt electrospun scaffolds [27]. A comparison of the results of our study on the role of endogenous neural stem cells in the brain during a stroke and transplanted stem cells in the replacement function indicated that stem cell transplantation can replace dead cells in the brain better than endogenous neural stem cells [32, 33].

Table 1. Parameter values for the SPB model.

Parameters	Values$\times 10^{-3}$	Biological meaning	References
p_1	0.69	proliferation rate of stem cells	[27]
p_2	0.45	proliferation rate of progenitor cells	[27]
d_0	0.0046	endogenous regeneration rate of brain cells	[24]
α_1	0.001	death rate of stem cells	[27]
α_2	0.001	death rate of progenitor cells	[27]
δ	0.12	rate of brain dead cells from stroke	[24]
d_s	0.37	differentiation rate of stem cells to progenitor cells	simulation
d_p	0.26	differentiation rate of progenitor cells to differentiated brain cells	simulation

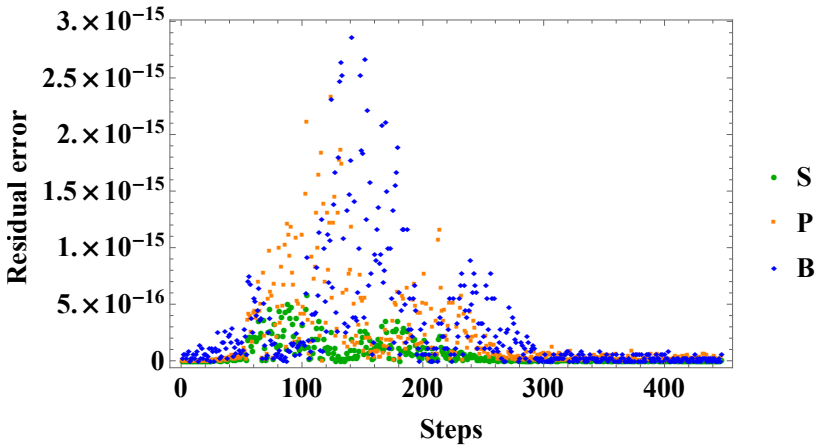

Figure 2. Residual error for the step of the numerical method in the SPB model.

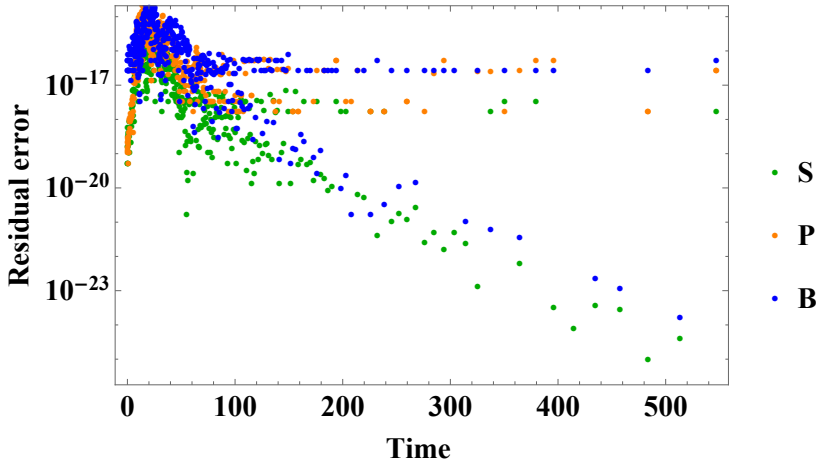

Figure 3. Residual error of the SPB system during time t.

The simulation result obtained for the SPB system indicated that stem cell transplantation can improve stroke recovery by generating new brain cells and replacing those lost due to a stroke. Following a stroke, stem cell transplantation in the brain induces the proliferation and differentiation of new neural cells, which helps to repair neuronal structures and regenerate damaged brain cells based on the SPB simulation results. These dynamics start approximately on the first day after the transplantation of stem cells. The parameters of the SPB model in the simulation are set to $d_s = 0.00037$ and $d_p = 0.00026$.

The numerical results indicate an increase in the stem cell curve, which decreases after 48 h of a stroke onset; this is exemplified by the proliferation and differentiation of stem cells into the progenitor and nerve cells. Furthermore, the population of P begins to differentiate and migrate into the brain during the first three days. In contrast, the population of brain cells B exhibits a shallow increase; it also shifts to a stable curve at approximately seven days, as the brain cells die after a stroke (within three days or more) and grow back after transplantation to replace the dead brain cells, as shown in Figure 4.

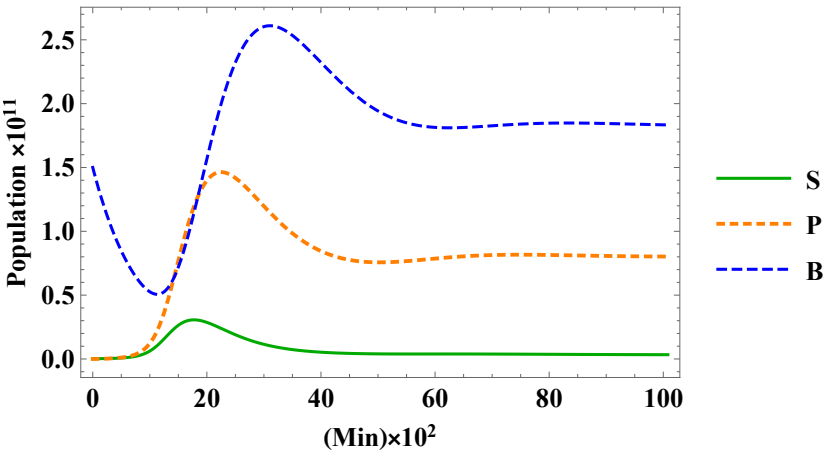

Figure 4. Behavior of the SPB model within seven days.

Biologically, the proliferation and differentiation of stem cells facilitate a reduction in brain damage,

as compared to their absence. The proliferating endothelial cells were found to increase in the ischemic region seven days after stem cell transplantation [44]. Another study showed that one week after a stroke in a rat's brains, the neural stem cells differentiated into neurons and displayed higher numbers after seven days [13, 14]. In addition, approximately three weeks after the transplantation, the stem cells supported endogenous neurons and improved brain functionality in behavioral tests [14, 45]. The numerical simulation results of the SPB model demonstrated the significance and contribution of stem cell transplantation in improving the brain functionality after the cell death caused by an ischemic stroke, as well as the proliferation and differentiation processes of stem cells after being transplanted into the brain.

6. Conclusions

In this study, we developed an SPB Eq (2.4) to evaluate the impact of stem cells cultured on the brain in the aftermath of a stroke by replacing the lost cells with new neurons. The developed model included brain cell reconstitution after a stroke by stem cell subpopulation, which was not considered in previous mathematical models. With an increase in the rate of B, the cultured stem cells began to proliferate and differentiate into mature brain cells after a stroke. The dynamic model of the effects of stem cell transplantation in a stroke was studied both analytically and numerically. The stability of the SPB model can be explained as follows: after a stroke occurs, the brain loses some brain cells; therefore, the number of stem cells transplanted helps the brain to generate new nerve cells, exhibiting a capacity for cell replacement under physiological conditions of the transplanted stem cells. The result of the SPB model simulation revealed the capability of stem cells being transplanted to replace dead cells in the brain if the endogenous neural stem cells fail to reconstitute the lost brain cells after a stroke. Based on these results, the optimal period for stem cell transplantation was set to three to seven days after an ischemic stroke to reduce ischemic zone expansion and increase the number of nerve cells. The analysis and simulation results of the SPB model showed that the efficacy of the treatment depends on the number of stem cells available for transfer to mature brain cells. Numerically, this indicates that the number of brain cells decreased because of a stroke, increased after stem cell transplantation during one week, and peaked at around three days. The results of this study can be used to treat stroke patients, where the differentiated brain cells included in the proposed model are discreted by the state of maturity. In addition, the results can facilitate the study of the rate of neural phenotypes, which can be further divided into three types of brain cells: neurons, astrocytes and oligodendrocytes. The implication of these subtypes can be helpful as the experimental aim is to increase the population of a particular neural cell type, such as neurons.

To investigate the results of our mathematical model and obtain more accurate results, more clinical experiments need to be conducted by considering the properties of stem cells and their role in brain disease therapy. During the analysis, we applied a simple feedback mechanism similar to that used in [34]. This feedback system was applied as a simple starting point. Although this mechanism completely matches other cell systems, there is no evidence that this is a real mechanism for our population. Thus, it will be informative to change the mechanism, as well as the feedback strength, to validate if there is another feedback system that more carefully matches the experimental data. In the future, we hope to extend this study by dynamically validating the ability of pharmacological drugs to support endogenous stem cells to improve stroke therapy. Moreover, we will study cytokine functions in math-

ematical modeling to analyze multistage stem cell transplantation in stroke patients. The presence of cytokine feedback in differential equations can lead to higher consistency and accuracy in real life. Finally, the most important feature of the proposed model is its ability to comprehend the properties of stem cell transplantation therapy, which has been used to treat various brain dysfunctions. The study results will be applied to manage and treat several degenerative diseases, where the affected tissues will progressively degenerate with time.

Acknowledgments

The authors would like to thanks the Universiti Kebangsaan Malaysia for the support of this study by a research grant from the Universiti Kebangsaan Malaysia with code ST-2019-016. Also, the first and third authors would like to acknowledge the University of Bisha and Taibah University in Saudi Arabia for their support.

Conflict of interest

The authors declare no conflict of interest.

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