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Dynamical Simulation of Effective Stem Cell Transplantation for Modulation of Microglia Responses in Stroke Treatment

Awatif Jahman Alqarni [1,2], Azmin Sham Rambely [2,*] and Ishak Hashim [2]

[1] Department of Mathematics, College of Sciences and Arts in Blqarn, University of Bisha, P.O. Box 551, Bisha 61922, Saudi Arabia; aaljhman@ub.edu.sa
[2] Department of Mathematical Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia, UKM Bangi, Selangor 43600, Malaysia; ishak_h@ukm.edu.my
* Correspondence: asr@ukm.edu.my; Tel.: +60-389213244

Abstract: Stem cell transplantation therapy may inhibit inflammation during stroke and increase the presence of healthy cells in the brain. The novelty of this work, is to introduce a new mathematical model of stem cells transplanted to treat stroke. This manuscript studies the stability of the mathematical model by using the current biological information on stem cell therapy as a possible treatment for inflammation from microglia during stroke. The model is proposed to represent the dynamics of various immune brain cells (resting microglia, pro-inflammation microglia, and anti-inflammation microglia), brain tissue damage and stem cells transplanted. This model is based on a set of five ordinary differential equations and explores the beneficial effects of stem cells transplanted at early stages of inflammation during stroke. The Runge–Kutta method is used to discuss the model analytically and solve it numerically. The results of our simulations are qualitatively consistent with those observed in experiments in vivo, suggesting that the transplanted stem cells could contribute to the increase in the rate of ant-inflammatory microglia and decrease the damage from pro-inflammatory microglia. It is found from the analysis and simulation results that stem cell transplantation can help stroke patients by modulation of the immune response during a stroke and decrease the damage on the brain. In conclusion, this approach may increase the contributions of stem cells transplanted during inflammation therapy in stroke and help to study various therapeutic strategies for stem cells to reduce stroke damage at the early stages.

Keywords: cell transplantation; cytokines; ischemic stroke; numerical simulation; runge-kutta method; stability analysis

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1. Introduction

The numbers of stroke-related deaths are increasing, and globally, stroke is now one of the topmost causes of disability and death [1–3]. During an ischemic stroke, the process by which neurons and glial cells die is known as apoptosis or necrosis [4,5]. Resident microglia are triggered by these dead cells and cause the death of other cells based on environmental toxic substances [5–8]. The components of the brain that prevent the invasion of several diseases are the microglial cells, and these cells can also help prevent stroke [7,9]. Dead cells are phagocytized by activated microglia, which also produce toxic cytokines that impact healthy cells [4,9]. The pathophysiology of ischemic stroke is evident through the inflammatory response [5,10]. Directly after arterial occlusion, inflammation begins in the vasculature and then continues throughout the brain, and systemically throughout the disease stages [10,11]. The body generates tightly regulated immune responses that confer detrimental as well as beneficial properties after stroke [12]. Some of the effects of microglia activation include inhibition of brain repair and/or considerable brain damage, including neurogenesis [11,12]. Due to variability effects on inflammatory processes, the immune response following a stroke serves as a strong determinant of brain restoration or increase

the damage in brain [9,11,13]. Thus, inducing stroke recovery-directed modulation of the immune response can offer a potential therapeutic approach [11].

Recently, neurorestorative stem cell-based treatment has been the focus of many stroke studies [1,7]. The extraordinary sophistication of the pathophysiology of ischemic strokes reveals pleiotropic effects on neural stem cells (NSCs), which are potentially therapeutic for both the early (subacute) and chronic phases of stroke [4,7,14]. In addition, after an ischemic stroke for newborn neurons, various obstacles are produced by the generated pathological condition, which makes the use of endogenous repair mechanisms challenging [7,10,15]. Newly formed neurons tend to die, with just $\sim$ 0.2% survival rate for the remaining cells, while others live up to 5 weeks after ischemia [10].

Microglia can be polarized toward the anti-inflammatory and angiogenic phenotype (M_a) with stem cell transplantation [11]. In one study of ischemic rats, the dependent suppression of inflammation emerged as a classical factor secreted by M_a microglia after the demonstration of intracerebral NSC transplantation and was associated with enhanced angiogenesis and functional recovery in terms of microglia polarization [11]. Currently, it is believed that pro-inflammatory microglia (M_p) can exacerbate brain injury, while anti-inflammatory M_a microglia are neuroprotective [4,12,16,17]. Thus, these dual attributes render them appropriate for use in enhancing post-stroke brain recovery, which can be achieved by shifting their balance from the detrimental M_p to the beneficial M_a phenotype [18]. Evidence also shows that the polarization status of microglia can be altered by stem cells (SCs) and, as such, the observed beneficial actions of SCs can be attributed to skewing microglia toward a neuroprotective and neuroregenerative phenotype [11,14]. Thus, it becomes imperative to elucidate the mechanisms of how SCs respond to tissue damage to understand the crosstalk between inflammation and SCs [10,11]. Additionally, a possible intervention point for regenerative therapies can be met through tweaking the effects of inflammation on stem cell behavior [19].

Studies have shown that stroke SCs can offer a viable solution in the future [11,14,15] and correspondingly, scholars have proposed several models of inflammatory processes [5,20,21]. For example, Di Russo et al. [5] modeled the dynamics of inflammation from a stroke: using (i) necrosis and apoptosis, (ii) the activation and inactivation of resident microglia, and (iii) the ratio of neutrophils and macrophages in the tissue, the dynamics of dead cell densities were investigated. Many scholars have also suggested quantitative methods, such as the use of statistical and computational methods, to study adult neurogenesis [22–24]. Along the same lines, systems of a hierarchical cell-constructing model were studied by Nakata et al. [25], where the structure system was controlled by the adult cells. Ziebell et al. [23] introduced a mathematical model that portrayed the various stages of the adult hippocampus and the evolving dynamics of SCs.

The basic framework for our study is a mathematical model of the interplay between microglia and endogenous NSCs during a stroke. Alqarni et al. [4] evaluated potential mechanisms to regulate and stabilize the treatment of microglia inflammation associated with an exogenous stem cell transplantation stroke. Alharbi and Rambely used ordinary differential equations in the formulation of mathematical models to describe the effect of vitamins on strengthening the immune system and its function in delaying the development of tumour cells [26–28]. In addition, Ordinary differential equations (ODEs) have been used to explain disease behavior over time, which has improved therapeutic strategies [4,28,29].

We aim to enhance understanding of the symmetry and antisymmetry of the relationship between the functions of pro-inflammatory and anti-inflammatory microglia with the effect of transplanted stem cells on the immunomodulation of microglia functions during a stroke. We modified a mathematical model for the therapy of the inflammation process in stroke using ODEs. In this paper, we study the roles of stem cell transplantation dynamics via inhibition of inflammation from microglia and stimulate the beneficial function of microglia during a stroke. We investigate the possible mechanisms involved in the dynamics of the transplanted stem cell functions through immune activities.

This paper is organized as follows: In Section 2, a mathematical model called SCs–damage–resting microglia–pro-inflammation microglia– anti-inflammation microglia (SDRPA) is presented. In Section 3, we study the model's equilibrium points. In Section 4, we investigate the model's stability. In Section 5, numerical experiments are discussed. Finally, the study's conclusions are presented in Section 6.

2. Mathematical Representation of the SDRPA Model

In this section, we give a dynamic model for the explanation of the use of transplanted SCs to treat the inflammation produced by microglia during a stroke. The suggested model of therapy stem cell dynamics transplanted in onset stroke shows the interplay between the transplanted SCs and microglia in stroke. The mathematical model is a structure of five differential equations, which are analyzed to find the equilibrium points and to study their stability. Several previous studies have shown the possible therapeutic benefits of transplanted SCs, where the transplantation of pluripotent stem cells in stroke patients has many functions. One of the potential therapeutic of this type of treatment is the immunomodulation of microglia functions during a stroke [11,30].

There are three options for differentiating SCs [31] : (1) symmetrical self-renewal with the possibility σ_S of two SCs, (2) asymmetric self-renewal with the probability of σ_A, where one of the cells denotes the daughter residue a stem cell, whereas another cell does not make this discrimination, and (3) symmetric involvement differentiation with probability of σ_D, where a stem cell has the ability to divide to be two involvement cells. Here we suppose that $\sigma_S + \sigma_A + \sigma_D = 1$ [31]. In this manuscript, we assumed that SCs S reproduce at the rate σ and die at the rate γ_s. Thus, transplanted SCs have considerable influence on the neuroinflammation caused by a stroke because they secrete relevant cytokines to support the anti-inflammation of microglial activation to transform the M_a to M_p phenotype [32]. Therefore, the terms α_4, α_5 and α_6 were designated to describe the direct interactions between SCs and the microglia M_a and M_p. The following equation describes transplanted SCs' behavior during a stroke:

$$\frac{dS}{dt} = [\sigma - \alpha_5 M_a - \alpha_6 M_p - \gamma_s]S.$$

where σ indicates the reproduction rate of SCs, α_5 signifies the stimulating and supporting rate of SCs for M_a, while α_6 indicates the rate of elimination of SCs due to the M_p and γ_s indicates the rate of death of SCs.

During an ischemic stroke, microglia are reactivated and polarized to either a classical type, M_p, by pro-inflammatory cytokines that cause an immune response and lead to secondary damage in the brain; or to a substitutional type, M_a, an anti-inflammatory state caused through anti-inflammatory cytokines, that reduces inflammation and boosts cell repair [33–36]. For mathematical modeling purposes, we supposed that resting immune cells of microglia M_r were produced at a constant rate of α_0, indicating the source rate of the resting microglia cells, which are dying at a constant ratio of γ_0.

The given differential equation describes resting microglia cells' behavior:

$$\frac{dM_r}{dt} = \alpha_0 - (\alpha_1 + \alpha_2 + \gamma_0)M_r.$$

Microglia that are activated by cytokines are caused through dead cells: the M_p phenotype is activated through signals of pro-inflammation cytokine α_1 and the M_a phenotype is activated by signals of anti-inflammation cytokine α_2. Moreover, a shift from M_p to M_a occurs at the rate of parameter α_3, where α_3 is the beginning of transference from pro-inflammatory microglia to anti-inflammatory microglia. The modulation of the immune response is considered an important function of a possible therapeutic approach to improve brain recovery post-stroke [11,19]. Exogenous stem cell transplantation has been demonstrated to modulate the inflammatory immune microenvironment across the ischemic regions of the brain by modulating the functions of the immune cells during the

stroke [11,19,33]. Direct transplant of SCs into the brain after ischemia decreased many inflammatory and immune responses and switched the balance from a pro-inflammatory to anti-inflammatory response of microglia [37]. We present these functions by the rate of parameters α_4 and α_5. The following equations representing microglia M_a and M_p thus take the form:

$$\begin{aligned} \frac{dM_p}{dt} &= \alpha_1 M_r - (\alpha_4 S + \delta_1 D + \alpha_3 + \gamma_1) M_p, \\ \frac{dM_a}{dt} &= \alpha_2 M_r + (\alpha_5 S - \gamma_2) M_a + (\alpha_3 + \alpha_4 S) M_p. \end{aligned}$$

where, δ_1 signifies the rate of damage from microglia related to the production of cytokines, α_4 denotes the rate of amendment of SCs for the function of M_p, and γ_1 and γ_2 are the natural death rate of M_p and M_a, respectively.

Ischemic stroke injury is regarded as a major factor contributing to tissue damage. We assume that the SDRPA model shows that activated microglial cells play complex functions displaying both harmful and beneficial effects, which could include from elimination of cell debris by phagocytosis process and the release of inflammatory cytokines that lead to tissue destruction and increase cell death beyond the primary ischemic region [12,34]. Therefore, the dynamics of dead brain cells after stroke can be explained via the differential equation:

$$\frac{dD}{dt} = [(\delta_2 - r_1) M_p - r_2 M_a] D.$$

where δ_2 indicates the death rate of brain cells due to M_p; and r_1 and r_2 refers to the elimination rates of the damaged cells by M_p and M_a, respectively. Thus, the SDRPA model can be written in the following form:

$$\frac{dS}{dt} = [\sigma - \alpha_5 M_a - \alpha_6 M_p - \gamma_s] S, \tag{1}$$

$$\frac{dD}{dt} = [(\delta_2 - r_1) M_p - r_2 M_a] D, \tag{2}$$

$$\frac{dM_r}{dt} = \alpha_0 - (\alpha_1 + \alpha_2 + \gamma_0) M_r, \tag{3}$$

$$\frac{dM_p}{dt} = \alpha_1 M_r - (\alpha_4 S + \delta_1 D + \alpha_3 + \gamma_1) M_p, \tag{4}$$

$$\frac{dM_a}{dt} = \alpha_2 M_r + (\alpha_5 S - \gamma_2) M_a + (\alpha_3 + \alpha_4 S) M_p. \tag{5}$$

The initial conditions in this model are: $S(0) = S^*$, $D(0) = D^*$, $M_r(0) = M_r^*$, $M_p(0) = M_p^*$, and $M_a(0) = M_a^*$, $0 \leq t < \infty$ where $S(t)$, $D(t)$, $M_r(t)$, $M_p(t)$, and $M_a(t)$ represent the stem cell concentration, dead cells, resting microglia, pro-inflammation microglia, and the anti-inflammation microglia, respectively.

The proposed dynamic model of SDRPA demonstrated by (1)–(5), represents the population behavior of the transplanted SCs, immune cells, and damaged cells in a stroke. Thus, the variables $S(t)$, $D(t)$, $M_r(t)$, $M_p(t)$, and $M_a(t)$ and all parameters are non-negative real, real, and equal to or less than one. The invariant area of SDRPA becomes:

$$\Psi = (S, D, M_r, M_p, M_a) \in \Re_+^5 \tag{6}$$

3. The SDRPA Model's Equilibrium Points

We determine the fixed points of the SDRPA system (1)–(5) from the following:

- $\frac{dS}{dt} = 0 \Leftrightarrow$

$$[\sigma - \alpha_5 M_a - \alpha_6 M_p - \gamma_s] S = 0, \tag{7}$$

- $\frac{dD}{dt} = 0 \Leftrightarrow$

$$[(\delta_2 - r_1)M_p - r_2 M_a]D = 0, \tag{8}$$

- $\frac{dM_r}{dt} = 0 \Leftrightarrow$

$$\alpha_0 - (\alpha_1 + \alpha_2 + \gamma_0)M_r = 0, \tag{9}$$

- $\frac{dM_p}{dt} = 0 \Leftrightarrow$

$$\alpha_1 M_r - (\alpha_4 S + \delta_1 D + \alpha_3 + \gamma_1)M_p = 0, \tag{10}$$

- $\frac{dM_a}{dt} = 0 \Leftrightarrow$

$$\alpha_2 M_r + (\alpha_5 S - \gamma_2)M_a + (\alpha_3 + \alpha_4 S)M_p = 0. \tag{11}$$

The equilibrium points of SDRPA (1)–(5) calculate by solving Equations (7)–(11), we obtain three positive real points of equilibrium by using MATHEMATICA, while the other solutions will be negative. Thus, the first positive equilibrium point is given by:

$$Q_1(S, D, M_r, M_p, M_a) = \left(0, 0, \frac{\alpha_0}{z}, \frac{\alpha_0\alpha_1}{z(\alpha_3 + \gamma_1)}, \frac{\alpha_0(\alpha_1\alpha_3 + \alpha_2(\alpha_3 + \gamma_1))}{z(\alpha_3 + \gamma_1)\gamma_2}\right).$$

where

$$z = \alpha_1 + \alpha_2 + \gamma_0. \tag{12}$$

Next, we represent the second positive equilibrium point as follows:

$$Q_2(S, D, M_r, M_p, M_a) = \left(0, \frac{q}{r_2\ \alpha_2\ \delta_1}, \frac{\alpha_0}{z}, -\frac{r_2\alpha_0\alpha_2}{z\ p}, \alpha_0\frac{\alpha_2(r_1 - \delta_2)}{z\ p}\right),$$

where

$$\begin{aligned} p &= (r_2\alpha_3 + \gamma_2(r_1 - \delta_2)) < 0, \\ q &= -r_2(\alpha_1\alpha_3 + \alpha_2(\alpha_3 + \gamma_1)) + \alpha_1\gamma_2(-r_1 + \delta_2). \end{aligned}$$

The third positive equilibrium point is obtained as follows:

$$Q_3(S, D, M_r, M_p, M_a) = \left(\frac{\beta_3}{\beta_1}, \beta_2, \frac{\alpha_0}{z}, r_2\beta_0, (\delta_2 - r_1)\beta_0\right),$$

where

$$\begin{aligned} \beta_0 &= \frac{\omega}{\alpha_5(-r_1 + \delta_2) + r_2\alpha_6} > 0, \beta_1 = (r_2\alpha_4 + \alpha_5(-r_1 + \delta_2)) > 0, \\ \beta_2 &= \frac{1}{r_2 z\delta_1\beta_1\omega}[(r_1^2 + \delta_2^2)\alpha_0\alpha_1\alpha_5^2 + r_2^2\alpha_4(\alpha_0(\alpha_1 + \alpha_2)\alpha_6 - z\gamma_1\omega) \\ &\quad + r_2(-r1 + \delta_2)(\alpha_0\alpha_5(\alpha_2\alpha_4 + \alpha_1(\alpha_4 + \alpha_6))) - r_1(2\alpha_0\alpha_1\alpha_5^2\delta_2) \\ &\quad -(-r_1 + \delta_2)r_2 z(\alpha_5(\alpha_3 + \gamma_1) + \alpha_4\gamma_2)\omega] < 0, \\ \beta_3 &= -p - \frac{\alpha_0\alpha_2(r_2\alpha_6 + \alpha_5(\delta_2 - r_1))}{z\omega} > 0, \omega = -\gamma_s + \sigma > 0. \end{aligned}$$

Proposition 1. *We assume that the equilibrium points for the SDRPA system, $S; D; M_r; M_p; M_a > 0$ are satisfied under the conditions:*

- $r_1 < \delta_2$
- $\gamma_s < \sigma$

- $\frac{\alpha_0\alpha_2(r_2\alpha_6+\alpha_5(\delta_2-r_1))}{z\omega} < \gamma_2(-r_1+\delta_2) - r_2\alpha_3$
- $r_2\alpha_3 < \gamma_2(\delta_2 - r_1))$
- $r_2(\alpha_1\alpha_3 + \alpha_2(\alpha_3+\gamma_1)) < \gamma_2\alpha_1(\delta_2 - r_1)$

Non-negative real, steady states will then, and only then, exist.

We can study the stability of equilibrium points if they continue to exist constantly over time or constantly change in equilibrium in one direction. We defined three steady states as follows:

Definition 1. *We define the resting microglia activation in a normal brain as the absence of a high activation for these cells when stroke occurs into pro-inflammation microglia and anti-inflammation microglia, the steady-state* $M_r; M_p; M_a > 0$ *and* $D, S = 0$ *implies the functions of the microglia in the onset of a stroke is normal and the microglia do not cause any damage in the brain.*

Definition 2. *We define the starting of the damage by the increased rate of pro-inflammation cytokines where the existence of high activation of microglia will cause damage in brain, the steady-states* $D; M_r; M_p; M_a > 0$*, and* $S = 0$ *imply the damage of the brain cells from the pro-inflammation of microglia by the damaged brain cells from inflammation by microglia due to a stroke without stem cells transplantation.*

Definition 3. *We define the functions of transplanted stem cells on modulation of microglia responses in the brain after stroke, the steady-state of the forms* $S; D; M_r; M_p; M_a > 0$ *is defined by the role of stem cell transplantation in inflammation.*

4. The Equilibrium Points' Stability of the SDRPA Model

A stability study of the SDRPA model for the equilibrium points is performed. By applying the Hartman–Grobman theorem concept [38], the system's 5×5 Jacobian matrix for the eigenvalues associated with transplanted SCs equilibrium in the brain after a stroke (1)–(5) is given by:

$$J[\tau] = \begin{bmatrix} F_S[\varphi] & F_D[\varphi] & F_{M_r}[\varphi] & F_{M_p}[\varphi] & F_{M_a}[\varphi] \\ G_S[\varphi] & G_D[\varphi] & G_{M_r}[\varphi] & G_{M_p}[\varphi] & G_{M_a}[\varphi] \\ H_S[\varphi] & H_D[\varphi] & H_{M_r}[\varphi] & H_{M_p}[\varphi] & H_{M_a}[\varphi] \\ K_S[\varphi] & K_D[\varphi] & K_{M_r}[\varphi] & K_{M_p}[\varphi] & K_{M_a}[\varphi] \\ L_S[\varphi] & L_D[\varphi] & L_{M_r}[\varphi] & L_{M_p}[\varphi] & L_{M_a}[\varphi] \end{bmatrix}.$$

where $\varphi = [S, D, M_r, M_p, M_a], F[\varphi] = \frac{dS}{dt}$, $G[\varphi] = \frac{dD}{dt}, H[\varphi] = \frac{dM_r}{dt}, K[\varphi] = \frac{dM_p}{dt}$, and $L[\varphi] = \frac{dM_a}{dt}$.

Theorem 1. *Given that the function* $g : \Psi \to \Re^5_+$ *where* Ψ *is a domain in* $\Re^5_+$*, and assuming that* $Q_1 \in \Psi$ *is an equilibrium point, where one eigenvalue of the Jacobian matrix has a non-negative real part at minimum. Therefore,* Q_1 *indicates an unstable equilibrium point of* g*.*

Proof. The Jacobian matrix J calculated at the first equilibrium point Q_1 yields: $J[Q_1] = \begin{bmatrix} a_{11} & 0 & 0 & 0 & 0 \\ 0 & a_{22} & 0 & 0 & 0 \\ 0 & 0 & -z & 0 & 0 \\ -\frac{\alpha_0\alpha_1\alpha_4}{z(\alpha_3+\gamma_1)} & -\frac{\alpha_0\alpha_1\delta_1}{z(\alpha_3+\gamma_1)} & \alpha_1 & -\alpha_3-\gamma_1 & 0 \\ a_{15} & 0 & \alpha_2 & \alpha_3 & -\gamma_2 \end{bmatrix}$ where

$$\begin{aligned} a_{11} &= -\frac{\alpha_0(\alpha_2\alpha_5(\alpha_3+\gamma_1)+\alpha_1(\alpha_3\alpha_5+\alpha_6\gamma_2))}{z(\alpha_3+\gamma_1)\gamma_2} - \gamma_s + \sigma, \\ a_{22} &= -\frac{r_2\alpha_0(\alpha_1\alpha_3+\alpha_2(\alpha_3+\gamma_1))}{z(\alpha_3+\ \gamma_1)\gamma_2} + \frac{\alpha_0\alpha_1(-r_1+\delta_2)}{z(\alpha_3+\gamma_1)}, \\ a_{15} &= \frac{\alpha_0\alpha_1\alpha_4}{z(\alpha_3+\gamma_1)} + \frac{\alpha_0\alpha_5(\alpha_1\alpha_3+\alpha_2(\alpha_3+\gamma_1))}{z(\alpha_3+\gamma_1)\gamma_2}, \\ z &= (\alpha_1+\alpha_2+\gamma_0). \end{aligned}$$

We determine the eigenvalues of the matrix $J[Q_1]$ as follows:

$$\begin{aligned} \lambda_1 &= -z < 0, \\ \lambda_2 &= -\frac{\alpha_0(r_2(\alpha_1+\alpha_2)\alpha_3+r_2\alpha_2\gamma_1+\alpha_1\gamma_2(r_1-\delta_2))}{z(\alpha_3+\ \gamma_1)\gamma_2} > 0, \\ \lambda_3 &= -\frac{\alpha_0(\alpha_2\alpha_5(\alpha_3+\gamma_1)+\alpha_1(\alpha_3\alpha_5+\alpha_6\gamma_2))}{z(\alpha_3+\gamma_1)\gamma_2} - \gamma_s + \sigma < 0, \\ \lambda_4 &= -\gamma_2 < 0, \lambda_5 = -(\alpha_3+\gamma_1) < 0. \end{aligned}$$

From Proposition 1, the equilibrium points, it is obvious that $\lambda_2 > 0$. Thus, $J(Q_1)$ has at least one positive root, which denotes that the second equilibrium point Q_1 is unstable. □

Theorem 2. *Given the function $g : \Psi \to \Re^5_+$, where Ψ is a domain in $\Re^5_+$, and assuming that $Q_2 \in \Psi$ is an equilibrium point, then one eigenvalue of the Jacobian matrix has a non-negative real part at minimum. Therefore, Q_2 indicates an unstable equilibrium point of g.*

Proof. The Jacobian matrix J calculated at the second equilibrium point Q_2 yields: $J[Q_2] = \begin{bmatrix} b_{11} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_{24} & -\frac{q}{\alpha_2\delta_1} \\ 0 & 0 & -z & 0 & 0 \\ v\alpha_4 & v\delta_1 & \alpha_1 & \frac{\alpha_1 p}{r_2\alpha_2} & 0 \\ -\frac{\alpha_0\alpha_2\beta_1}{Zp} & 0 & \alpha_2 & \alpha_3 & -\gamma_2 \end{bmatrix}$ where

$$b_{11} = \omega + \frac{\alpha_0\alpha_2(-r_1\alpha_5+r_2\alpha_6+\alpha_5\delta_2)}{zp}, v = \frac{r_2\alpha_0\alpha_2}{zp}, b_{24} = \frac{(-r_1+\delta_2)q}{r_2\alpha_2\delta_1}.$$

The corresponding characteristic equation of the Jacobian $J[Q_2]$, is specified by:

$$(b_{11}-\lambda)(-z-\lambda)(\kappa_0+\kappa_1\lambda+\kappa_2\lambda^2+\lambda^3) = 0.$$

where

$$\kappa_2 = -\frac{p\ \alpha_1}{r_2\ \alpha_2} + \gamma_2, \kappa_1 = \frac{-p\ \alpha_1\ \gamma_2 + q\ v\ (r_1-\delta_2)}{r_2\ \alpha_2}, \kappa_0 = \frac{q\ v\ p}{r_2\ \alpha_2}.$$

Thus, we can obtain the first two eigenvalues:

$$\lambda_1 = \omega + \frac{\alpha_0\alpha_2(-r_1\alpha_5+r_2\alpha_6+\alpha_5\delta_2)}{zp} > 0, \lambda_2 = -z < 0.$$

From Proposition 1, the equilibrium points, it is obvious that $\lambda_1 > 0$. Thus, $J(Q_2)$ has at least one positive root, which denotes that the second equilibrium point Q_2 is unstable. □

Theorem 3. *Given the function $g : \Psi \to \Re^5_+$, where Ψ denotes a domain in $\Re^5_+$, and assuming that $Q_3 \in \Psi$ indicates an equilibrium point, all the Jacobian matrix's eigenvalues have negative real parts at the equilibrium point Q_3. Therefore, Q_3 is assumed as a stable equilibrium point of g.*

Proof. The Jacobian matrix J calculation at the third equilibrium point Q_3 yields: $J[Q_3] = \begin{bmatrix} 0 & 0 & 0 & c_{14} & c_{15} \\ 0 & 0 & 0 & c_{24} & c_{25} \\ 0 & 0 & -z & 0 & 0 \\ c_{41} & c_{42} & \alpha_1 & c_{44} & 0 \\ c_{51} & 0 & \alpha_2 & c_{54} & c_{55} \end{bmatrix}$ where

$$\begin{aligned} c_{14} &= -\frac{\beta_3}{\beta_1}\alpha_6 < 0, c_{24} = \beta_2(-r_1 + \delta_2) > 0 \\ c_{15} &= -\frac{\beta_3}{\beta_1}\alpha_5 < 0, c_{25} = -\beta_2 r_2 < 0, c_{41} = -\beta_0 r_2 \alpha_4 < 0, \\ c_{42} &= -\beta_0 r_2 \delta_1 < 0, c_{44} = -\alpha_3 - \frac{\beta_3}{\beta_1}\alpha_4 - \gamma_1 - \beta_2\delta_1 < 0, \\ c_{51} &= \beta_0\beta_1 > 0, c_{54} = \alpha_3 + \frac{\beta_3}{\beta_1}\alpha_4 > 0, \\ c_{55} &= \frac{\beta_3}{\beta_1}\alpha_5 - \gamma_2 < 0. \end{aligned}$$

The characteristic equation can be written as:

$$(z + \lambda)(\lambda^4 + \eta_3\lambda^3 + \eta_2\lambda^2 + \eta_1\lambda + \eta_0) = 0, \tag{13}$$

Here,

$$\begin{aligned} \eta_0 &= c_{42}c_{51}M_0 > 0, \eta_1 = c_{44}M_6 + c_{41}M_4 - c_{42}M_5 > 0, \\ \eta_2 &= M_1 + M_2 > 0, \eta_3 = -M_3 > 0. \end{aligned}$$

where,

$$\begin{aligned} M_0 &= c_{15}c_{24} - c_{14}c_{25} < 0, M_1 = c_{14}c_{41} - c_{24}c_{42} > 0, \\ M_2 &= -c_{15}c_{51} + c_{44}c_{55} > 0, M_3 = c_{44} + c_{55} < 0, \\ M_4 &= c_{15}c_{54} - c_{14}c_{55} < 0, M_5 = c_{25}c_{54} - c_{24}c_{55} > 0, \\ M_6 &= c_{15}c_{51} < 0. \end{aligned}$$

Thus, we can determine the first eigenvalue:

$$\lambda_1 = -z < 0.$$

Thus, we can use the Routh–Hurwitz theorem for $\lambda^4 + \eta_3\lambda^3 + \eta_2\lambda^2 + \eta_1\lambda + \eta_0 = 0$ [39], giving

$$\begin{vmatrix} \lambda^4 & 1 & \eta_2 & \eta_0 \\ \lambda^3 & \eta_3 & \eta_1 & 0 \\ \lambda^2 & \xi_1 & \eta_0 & 0 \\ \lambda^1 & \xi_2 & 0 & 0 \\ \lambda^0 & \eta_0 & 0 & 0 \end{vmatrix}.$$

Thus, the essential and adequate conditions of all roots contain negative real parts η_i $(i = 1; 3; 4) > 0$ and $\Delta > 0$. Then,

$$\begin{aligned}\Delta &= c_{42}c_{51}M_0(-c_{42}c_{51}M_0M_3^2 - (M_1 + M_2)M_3(c_{41}M_4 - c_{42}M_5 \\ &+ c_{44}M_6) - (c_{41}M_4 - c_{42}M_5 + c_{44}M_6)^2) > 0\end{aligned}$$

From Proposition 1,

$$\xi_1 = \frac{\eta_3\eta_2 - \eta_1}{\eta_3} > 0, \xi_2 = \frac{\xi_1\eta_1 - \eta_0\eta_3}{\xi_1} > 0$$

where

$$\begin{aligned}\xi_1 &= \frac{(M_1 + M_2)M_3 + c_{41}M_4 - c_{42}M_5 + c_{44}M_6}{M_3} > 0 \\ \xi_2 &= c_{41}M_4 - c_{42}M_5 + c_{44}M_6 + \frac{c_{42}c_{51}M_0M_3^2}{(M_1 + M_2)M_3 + c_{41}M_4 - c_{42}M_5 + c_{44}M_6} > 0\end{aligned}$$

Equation (13) has no roots with positive real parts, and only one of its eigenvalues is negative in view of the positive signs of all the coefficients in the first column. The equilibrium point Q_3 is therefore stable. □

Remark 1. *The impact of using SCs transplant on the functions of microglia in stroke onset, represented by the dynamic SDRPA model, can be summarized as follows:*

- *Theorem 1 indicates that the damage, D, can penetrate the SDRPA model, if* $\lambda_2 > 0$.
- *Theorem 2 indicates that the damage,* $D > 0$, *penetrated the brain.*
- *Theorem 3 indicates that stem cell transplantation,* $S > 0$, *modulates the inflammatory environment in a stroke,* $D > 0$.
- *The SDRPA model is considered stable when the immunomodulation from transplanted stem cells can be one of the mechanisms of post-stroke recovery.*

5. Numerical Results and Analysis

This section discusses the utilization of computational models to assess which ones affect the model's behavior and thus explore the numerical solutions of the system ((1)–(5)).

5.1. Determination of Parameters

The SDRPA model involves 18 parameters, including five parameters for the initial conditions of each compartment. Herein, the researchers list several parameters which can be assessed using the experimental studies. Furthermore, for solving the system of ordinary differential equations ((1)–(5)), other parameter values were obtained by simulations through the Software MATHEMATICA with the command NDSolve. The purpose was to assess the SCs' ability to control the functions of immune cells during a stroke. From the simulation of SDRPA model, it can be concluded that there are three parameters that directly affect the behavior of microglia and SCs after transplant, parameter α_4, which represents the rate of amendment of SCs for the function of M_p, parameter α_5, which shows the rate of stimulating and supporting SCs of anti-inflammatory immune cells and, the suppression rate of SCs as a result of damage by pro-inflammatory microglia denoted by the parameter α_6, and the simulation results showed that the effectiveness of stem cell transplantation to modulate pro-inflammation microglia function where the highest rate of SCs will switch the balance from a pro-inflammatory to anti-inflammatory response of microglia as follows: the rate involving SCs was simulated by $\alpha_4 = 50\%, \alpha_5 = 35\%$ and $\alpha_6 = 14\%$. Furthermore, it was obvious that the modulation of microglia responses occurred if the following conditions were satisfied: The rate of stem cell amendment for the function of $M_p >$; and the suppression rate of SCs by M_p, $\alpha_4 > \alpha_6$. Table 1 displays the reference series of values of the parameters. From Figure 1, we can observe various

behaviors depending on the transplant process. In addition, damage continually decreased, while pro-inflammation microglia had a little increase, asides from shifting to a steep curve after approximately 20 h. Furthermore, that anti-inflammation microglia had a high level after stroke onset and transplantation SCs, aside from shifting to a steep and a stable curve at approximately after 20 h to the end of simulation of the recovery stage. It can be seen that after SCs transplanted in the brain the anti-inflammation microglia had a higher level than the pro-inflammation microglia comparing with numerical results evaluating microglia effect on the brain dynamics without SCs transplantation during 72 h of strok as presented in [4]. Additionally, for the concentration of transplanted SCs, there was initial growth and subsequently a reduction over time due to the effects of the treatment on the elimination rate of pro-inflammation microglia. The system was solved numerically, and time concatenation of the solutions were plotted on the system ((1)–(5)) for the parameters to obtain the dynamics of the system. For this, the fourth-order Runge–Kutta method (RK4) was used in all simulations to obtain extra stable and approximate solutions. The time 72 h was chosen for 10^{-4} as the step size for carrying out the simulations of the model [40,41]. Figures 2 and 3 depict the precision of the suggested numerical method presented through the residual error.

Table 1. Parameters values for transplanted stem cells–damaged brain cells–resting microglia–pro-inflammation microglia–anti-inflammation microglia (SDRPA) model.

Parameters	Values	Descriptions	Sources
S^*	1	SCs initial concentration	[31]
D^*	0.4	damage initial concentration	[4]
M_r^*	1	resting microglia initial concentration	[4]
M_p^*	0.1415	pro-inflammation initial concentration	[4]
M_a^*	0.02	anti-inflammation initial concentration	[4]
σ	0.69	the reproduction rate of stem cells	[42]
α_0	0.38	the resting microglia source	[4]
α_1	0.12	activation rate of M_r into M_p	[4]
α_2	0.017	activation rate of M_r into M_a	[4]
α_3	0.11	the rate transference from M_p to M_a	[4]
δ_1	0.2854	the cytotoxic effects due to M_p	[5]
δ_2	0.1	the death rate of brain cells due to M_p	[5]
γ_s	0.1	the natural death rate of S	[42]
γ_0	0.003	the natural death rate of M_r	[4]
γ_1	0.06	the natural death rate of M_p	[4]
γ_2	0.05	the natural death rate of M_a	[4]
r_1	0.05	the decay rate of concentration of the D by M_p	[4]
r_2	0.0125	the decay rate of concentration of the D by M_a	[4]

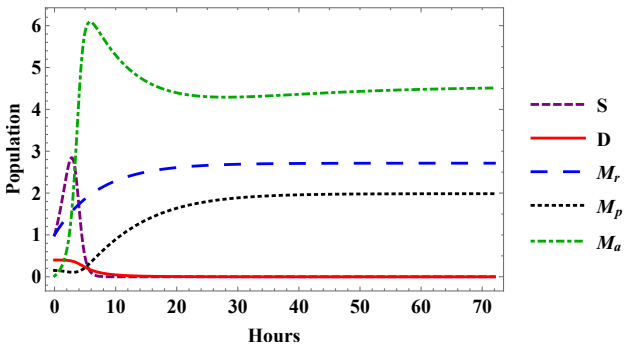


Figure 1. Effectiveness of stem cell transplantation on immune cells' phenotype behavior and dead brain cells within 72 h. Where $\alpha_4 = 0.5314$, $\alpha_5 = 0.3468$ and $\alpha_6 = 0.1419$.

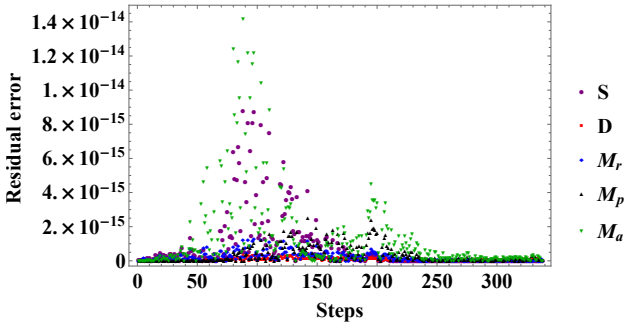


Figure 2. The residual error at several steps for SDRPA model.

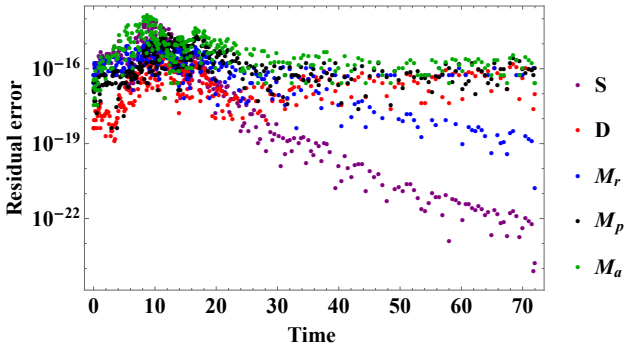


Figure 3. The residual error at time t for SDRPA model.

5.2. Comparison of Experimental Results

Parameter values of resting microglia rates, activation microglia rates, decay rates of concentration of the damage by microglia, reproduction rate of SCs, death rates, and initial conditions, were assumed on the basis of the literature. We assumed that the SCs transplantation influenced transference between the states of microglia activation and could support the anti-inflammation function of microglia, which led to faster recovery. These assumptions were in accordance with the biological understanding of SC functions. In contrast to the findings of our study regarding immune cell functions and the damage during the time of stroke with the SCs effects transplanted with the work in [16,34], we established that the studies agreed in that microglial activation had the contribution of both beneficial and harmful functions in the brain. Furthermore, stem cell transplantation is considered to attenuate ischemia-induced brain injury within hours of transplantation [1,33,40]. The simulation's findings of the model corresponded with the experimental findings for determining the effect of exogenous SCs in the brain during a stroke. We compared the simulation results of the SDRPA model with the numerical results of the effects of dynamic SCs on brain therapy after stroke by endogenous SCs and exogenous SCs. Additionally, we compared the findings in our research to those of [4], and found that stem cell transplantation has the ability to modify the cytokine environment in the brain, especially for early cell transplantation after stroke. For example, transplantation within 1 week caused a reduction in the levels of pro-inflammatory cytokines and growth in the levels of anti-inflammatory cytokines. The results of the SDRPA simulation implied that when neural endogenous SCs failed to grow and assist brain recovery, exogenous SCs were considered the best solution for brain repair processes.

6. Conclusions

Mathematics and computer science fields have worked interactively to better understand biological processes. We modified the model—SDRPA ((1)–(5)) based on the model of Alqarni et al. [4] to study the effectiveness of the role of transplanted exogenous SCs in the brain on the microglia during a stroke. The multifaceted SCs affect the tissue by inhibiting of the pro-inflammation and stimulating the function of the anti-inflammation

microglia. We discussed the results of the dynamical system and the effects of SCs transplanted and microglia during the stroke analytically and numerically. The analysis and simulation results of the system show the ability of transplanted SCs to help the brain by reducing the inflammation on the onset of stroke. Following that, the rate of damage reduced after transplantation. An evident linkage between the mathematical and biological mechanisms was observed. From the analytical results, we can deduce that the stability of the SDRPA model illustrated capacity in the exogenous stem cell implantation, which is significant for immunomodulation. In conclusion, our model may assist in conception of the effectiveness of using SCs transplanted in the brain repair processes. In the outlook, we will extend this study to model strategies that improve, stimulate, and generate the NSCs in the early stage, and where that information could contribute to understanding the effects of therapeutic strategies. We hope to conduct more experimental studies to clinically investigate the results of our mathematical model and to show more precise results. In future studies, it could be interesting to incorporate the dynamics of anti-inflammatory and pro-inflammatory cytokines from microglia and cytokines of endogenous NSCs into the SDRPA model to describe the interaction processes of the different cytokine types in ischemic stroke. Furthermore, we will develop this model by studying the effect of SCs in stimulating endogenous neural cells in a stroke and dynamically validate the ability to support the endogenous stem cells by using pharmacological drugs to improve stroke therapy. In summary, symmetry and antisymmetry are fundamental to understand the role of microglia in ischemic stroke pathobiology constituting a major challenge for the development of efficient immunomodulatory therapies by SCs.

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