Dynamic Modelling of Interactions between Microglia and Endogenous Neural Stem Cells in the Brain during a Stroke

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Abstract: In this paper, we study the interactions between microglia and neural stem cells and the impact of these interactions on the brain cells during a stroke. Microglia cells, neural stem cells, the damage on brain cells from the stroke and the impacts these interactions have on living brain cells are considered in the design of mathematical models. The models consist of ordinary differential equations describing the effects of microglia on brain cells and the interactions between microglia and neural stem cells in the case of a stroke. Variables considered include: resident microglia, classically activated microglia, alternatively activated microglia, neural stem cells, tissue damage on cells in the brain, and the impacts these interactions have on living brain cells. The first model describes what happens in the brain at the stroke onset during the first three days without the generation of any neural stem cells. The second model studies the dynamic effect of microglia and neural stem cells on the brain cells following the generation of neural stem cells and potential recovery after this stage. We look at the stability and the instability of the models which are both studied analytically. The results show that the immune cells can help the brain by cleaning dead cells and stimulating the generation of neural stem cells; however, excessive activation may cause damage and affect the injured region. Microglia have beneficial and harmful functions after ischemic stroke. The microglia stimulate neural stem cells to generate new cells that substitute dead cells during the recovery stage but sometimes the endogenous neural stem cells are highly sensitive to inflammatory in the brain.

Keywords: chemokines; cytokines; eigenvalue stability analysis; neurogenesis; numerical solution; system of ordinary differential equations

1. Introduction

Strokes are diseases that affect the brain, which may cause death and disabilities in mammals [1–3]. When ischemic stroke occurs, the cells surrounding the ischemic area start to die once the outflow of blood declines below 10% of the normal blood influx [1,2]. Cells can die through necrosis or apoptosis [1,4]. Necrosis occurs very quickly after stroke onset; the necrotic cells lead to pollution of the local environment in the brain and damage the surrounding cells through laceration and the release of intracellular contents into the brain [1,4]. On the other hand, apoptosis occurs several hours or days after the stroke onset, where apoptosis occurs in the penumbra and is typically not detrimental to the neighboring cells [1,4]. Due to this, resident microglia are activated by the dead cells causing damage to the surrounding area, which also contributes to an increase of dead brain cells [1,5,6].

Microglia are the assigned immune cells aimed at protecting brain cells from any damage [1,2,7]. Microglia reside within the normal brain as a ubiquitously distributed quiescent cell population

which respond to changes within the system's micro-environment, in order to interact swiftly with diseases [1,8,9]. When microglia are activated their functions change, with increased capacity for phagocytosis and production of cytokines and chemokines [1]. The small secreted proteins, cytokines, which are released by the cells produce a specific effect, especially on inter-cellular interactions and communications [1,5,6]. When cells go through the process of phagocytosis, they are able to identify and consume large particles like pathogens, apoptotic cells, and cellular debris [10].

In living systems, free radicals and oxidants have double functions as both toxic and beneficial complex since they can be either harmful or beneficial to the body [11–13]. The activation of microglia has both beneficial and deleterious effects. The positive effects manifest through the prevention of damage extension by phagocytosis and the production of trophic molecules and anti-inflammatory cytokines, which can be conducive to tissue repair as well as neuroprotection. The harmful effects, which are toxic to tissues, occur primarily through the production of free radicals [12,13]. This reaction is important in removing damaged cells from the brain tissue; however, it can also increase the harm to brain cells by producing free radicals that are toxic to healthy cells [2,14,15]. There has been an increasing amount of evidence suggesting that ischemic inflammation may be vital to the issue of pathogens, as ischemic stroke results not only in damage and neuronal loss but also in sustained neuroinflammation after stroke [3,16,17]. Microglial cells have been shown to take part in the neural analysis associated with adult brain function responsible for the harm occurring in the brain when a stroke occurs [3]. After an ischemic stroke, a dynamic microglial polarization occurs within the harm region [18]. The microglia composition M_1 unleashes proinflammatory cytokines and oxidative mediators that prejudice living neurons, whereas the microglia composition M_2 tends to unleash neurotrophic factors, in order to stop neuronal death and promote brain repair [17,18]. The anti-inflammatory phenotype composition M_2 is capable of manufacturing anti-inflammatory cytokines, which are conducive to inhibiting inflammation and tissue restoration [17–19]. This shows that microglia play both positive and negative roles in stroke [20,21].

In adult brains, neural stem cells (which are active throughout life) are capable of generating different cells [22,23]. Neurogenesis continues for the duration of life in the subventricular zone in all mammalian types, generating new neural stem cells during the recovery stage after ischemic stroke [24–27]. Neural stem cells appear to have many important roles, such as self-renewal and multipotency, replacement of the dead cells, and inhibition of inflammation [22,28–30]. However, endogenous neural stem cells may not be able to generate enough cells to repair the neurological damage caused by a major disease such as stroke [31]. Furthermore, the pathologic environment created after an ischemic stroke poses numerous hurdles for new neurons, which make the utilization of endogenous repair mechanisms more difficult; in particular, in directing the migration and differentiation of endogenous neural stem cells needed to repair the tissue [3,31].

Numerous mathematical models have been proposed for the dynamics of brain diseases, the functions of immune cells in terms of inflammation, and neural stem cell generation. Several models of inflammatory processes have been proposed. For example, the dynamics of inflammation from a stroke were modeled by Di Russo et al. [1] where they studied the dynamics of the densities of cells dead by necrosis and apoptosis, activated and inactivated resident microglia and the proportion of neutrophils and macrophages in the tissue. Mathematical models of inflammation proposed by the authors; Reynolds et al. [32] and Kumar et al. [33] ; for blood cells inflammation. Alharbi and Rambely [34] discussed a mathematical model of the ability of the immune system to inhibit and eliminate abnormal cells, as well as the role of dietary habits in boosting the immune system. Mathematical models for brain diseases have also been proposed by several authors [1,35]. For example, Hao and Friedman [35] described a model for Alzheimer's disease which utilized the microglia. Also, mathematical models have been proposed for compartmental adult neurogenesis. Nakata et al. [36] studied models of a hierarchical cell building system controlled by the mature cells. Ziebell et al. [37] introduced a mathematical model that represents different states of the adult hippocampus and the changing dynamics in stem cells during that time. Cacao and Cucinotta [38]

developed a mathematical model of radiation-induced changes to neurogenesis, while a different study by Huang and Zhang [39] discussed the knowledge of strategies and mechanisms for neural stem cell-based therapies on brain hypoxic-ischemic injury. These studies were all focused on brain diseases and the roles of the immune system in several diseases in the blood or brain. Furthermore, some of the studies focused on the behavior of neural stem cell generation in the subventricular zone. As a starting point, we considered the model which has been recently proposed by Leah et al. [40]. We modified our models based on the model presented by Leah et al. [40], which was derived by studying the behaviors of several types of cells, microglia, brain cells, and the impact of microglial pro-inflammatory factors in living brain cells. In their model, they studied methods to represent interactions between proinflammatory and anti-inflammatory cytokines, types of microglia, and central nervous system (CNS) tissue damage, using clinical data [40].

In our model, we incorporated variables for several cytokines. Furthermore, we introduced the effect of the proinflammation by microglia on brain cells and focused on the brain during the time of stroke. However, we did not consider many types of cytokines. We studied the cytokines as parameters and their influence on the brain. Furthermore, we developed a second model to study the dynamics and stability of the interaction between the damage from microglia and the endogenous neural stem cells in the brain in the recovery stage, in order to study the ability of neural stem cells to heal the brain after stroke. The purposes of this work are to describe the biological interaction between the inflammatory cytokines from microglia and living brain cells in stroke; to study the damage on brain cells during the early stage of stroke over a 72-h duration; to study the interactions between microglia and neural stem cells and the influence of proinflammatory and anti-inflammatory cytokines on brain cells; to analyze the dynamic effect of microglia by stimulating the generation and the proliferation of neural stem cells during the recovery phase after the stroke; and to draw conclusions about the dynamics of neural stem cells to improve the brain after a stroke within a mathematical framework. Our final aim is to understand the positive and negative aspects of this biological process, which could be helpful for the development of therapeutic methods using endogenous neural stem cells in ischemic stroke, by studying the stability of the models.

In Section 2, we present a model—called stroke-microglia-damage (SMD)—of the effect of microglia on the brain during stroke onset, and another model—called stroke-microglia-neural stem cells-recovery (SMNR)—of the interaction between the microglia and neural stem cells and their impact on the brain during a stroke, including analysis of the equilibrium points of the models and their stability states. Numerical experiments of the modified models are detailed in Section 3. Finally, Section 4 presents the conclusions of the study.

2. Mathematical Models

We modified mathematical models of biological processes to investigate the impact of microglia and neural stem cells on the brain by increasing damage or assisting it in the recovery stage in two steps, illustrated by systems of ordinary differential equations. We developed the SMD model based on a model presented by Leah et al. [40], who proposed a mathematical model for neuroinflammation in traumatic brain injury using mathematical modeling with clinical data. The system of ordinary differential equations they derived described the dynamics of biological processes for multiple interactions post-injury. The first model, called the SMD model, that we shall develop describes the roles of microglia in the first 72 h after stroke onset without any generation of neural stem cells, while the second model, called the SMNR model, describes the state from the third day when neural stem cells start to generate. The resting microglia are the immune cells, M_0, which reside in the brain, and will be activated when a stroke occurs to a classic proinflammatory M_1 or an alternative anti-inflammatory M_2 state, where the resting microglia polarizes into two activation states, M_1 or M_2, in reaction to the dead cells from ischemia [18,19]. The cytokines signal for the activation of resting microglia into two phenotypes, proinflammation M_1, and anti-inflammation M_2, microglia denoted by R_1 and R_2, respectively. When microglia cells are activated in stroke, they become either M_1 or M_2

phenotypes. At the start of the stroke, the microglia are biased towards the M_1 phenotype rather than M_2 phenotype, since $R_1 > R_2$. We assume that in stroke onset with this bias towards M_1, the transition rate from M_1 into M_2 phenotype is very small, approximately equal to zero in the first 60 h after stroke onset [1], and the rate of anti-inflammation cytokines, R_2, is at a smaller rate than the rate of proinflammation cytokines, R_1, in the SMD model. We take $R_1 < R_2$ when the rate of proinflammation cytokines, R_1, is at a lower rate than the rate of anti-inflammation cytokines, R_2 in the recovery stage in the SMNR model. Neural stem cells in the subventricular zone from the adult mammalian brain give rise to neuroblasts, which migrate to the injury region and generate new cells [22,28,41]. Microglia have a positive and negative impact on generating neural stem cells [42]. M_1 can impair neural stem cells [18], while M_2 shows the ability to stimulate the generation and the proliferation of neural stem cells N_{sc} Ref. [19]. We focus our model on the mature neural stem cells only in the SMNR because no generation of neural stem cells occurs in this stage of stroke onset.

2.1. Modelling of the Effect of Microglia on the Brain in a Stroke Onset (SMD)

In this study, we modified the dynamic system of the SMD model based on the model presented in [40], which illustrates the behavior of the impact of activated microglia on brain cells in the 72 h following a stroke. We consider a non-linear system of ordinary differential equations, which describes the effects of microglia $M_0(t)$, $M_1(t)$, $M_2(t)$, and the damage from microglia, $D(t)$, on brain cells, $C(t)$, in the 72 h after stroke onset as follows:

$$\frac{dM_0}{dt} = \alpha - \left[R_1 + R_2 + \mu\right]M_0(t).$$

This equation demonstrates that the microglia are activated after an ischemic stroke and are polarized either towards a classic state, M_1, by proinflammatory cytokines, leading to an adaptive immune response and causing additional neuronal damage; or towards an alternative state, M_2, which is the anti-inflammatory phenotype induced by anti-inflammatory cytokines, which is thought to inhibit inflammation and enhance tissue repair [18,19,40]. Although we do not specify the types of cytokines in our models, we focus on the influences of the cytokines which gather in the region of damage; which are determined to either increase M_1 polarization or to change the microglia into the M_2 state. For mathematical modeling purposes, we assume that resting microglia M_0 are generated at a constant rate (α) and die at a constant rate (μ). The function of the activated microglia is to clean up dead cells produced by ischemia and cytokines caused by dead cells [43]. Microglia are activated by the cytokines caused by dead cells: the M_1 phenotype is induced by proinflammation cytokine signals R_1 and the M_2 phenotype is induced by anti-inflammation cytokine signals R_2 [5,17,43]. Furthermore, a shift from M_1 to M_2 may be induced by R_3 signaling [5], where R_3 is the result of a transition from proinflammatory to anti-inflammatory cytokines. This transition only appears in the SMNR model, occurring 60 h after the stroke onset [1]. The following differential equations illustrate the behavior of the activated microglia M_1 and M_2:

$$\frac{dM_1}{dt} = R_1 M_0(t) - \left[\delta D(t) + \gamma_1\right]M_1(t),$$
$$\frac{dM_2}{dt} = R_2 M_0(t) - \gamma_2 M_2(t),$$

where R_1 represents the rate of M_1 activation, R_2 is the rate of M_2 activation, δ is the rate of damage by M_1 activation, γ_1 is the death rate of M_1, and γ_2 is the death rate of M_2. The M_1 phenotype is essential for cell recovery, due to their protection mechanisms against the damage which recruits immune cells to the region of injury. The M_2 phenotype microglia also play a role in reducing damage, by clearing the brain of dead cells and assisting in neurogenesis, as well as inhibiting inflammation. On the other hand, the microglia can also play a negative role, through secretion of damaging proinflammatory cytokines which increase inflammation in the area of healthy cells [5,17]. We consider the damage D caused

by the activated microglia to represent secondary damage in the case of stroke [2,14]. The following differential equation describes this damage:

$$\frac{dD}{dt} = D(t)\big[M_1(t)(\delta - r_1) - \beta_1 C(t) - r_2 M_2(t)\big],$$

where β_1 denotes the rate of effect of damage on brain cells, r_1 denotes the rate of damage clearance by M_1, and r_2 denotes the rate of damage clearance by M_2. In our model, we use the impact of the damage by microglia on the living brain cells, C. The following ordinary differential equation describes this effect on brain cells:

$$\frac{dC}{dt} = C(t)\big[\beta_1 D(t) - \beta_0\big],$$

where β_0 is the rate of cells dying from ischemic stroke.

　　Thus, the SMD model is expressed as follows:

$$\frac{dM_0}{dt} = \alpha - \big[R_1 + R_2 + \mu\big]M_0(t), \tag{1}$$

$$\frac{dM_1}{dt} = R_1 M_0(t) - \big[\delta D(t) + \gamma_1\big]M_1(t), \tag{2}$$

$$\frac{dM_2}{dt} = R_2 M_0(t) - \gamma_2 M_2(t), \tag{3}$$

$$\frac{dD}{dt} = D(t)\big[M_1(t)(\delta - r_1) - \beta_1 C(t) - r_2 M_2(t)\big], \tag{4}$$

$$\frac{dC}{dt} = C(t)\big[\beta_1 D(t) - \beta_0\big], \tag{5}$$

with initial values $M_0(0) = 1$ [1], $M_1(0) = 0.1514$ [1], $M_2(0) = 0.02$ [35], $D(0) = 0.4$ [1], and $C(0) = 0.28$ [35]. Furthermore, we assumed that, in steady state, $M_1 > M_2$ for 72 h and that neural stem cells are not generated.

2.1.1. Equilibrium Points for the SMD Model

　　In this section, we calculate the equilibrium points of the system and determine the parameters for the existence of different types of biological states. We now determine the steady-state solutions as follows:

$$\frac{dM_0}{dt} = \frac{dM_1}{dt} = \frac{dM_2}{dt} = \frac{dD}{dt} = \frac{dC}{dt} = 0.$$

　　Equilibrium points are stable if they remain constant over time or continually balance change in one direction by that in another. We classify three steady states as follows:

Definition 1 (State of the activation of microglia)**.** *We define the microglia that reside in a healthy brain as the absence of a high activation for these cells in the brain when any damage occurs in the region. The steady-state of the form $M_0; M_1; M_2 > 0$ and $D, C = 0$ indicates that the function of immune cells is normal and the microglia do not cause any damage in the brain.*

Definition 2 (State of the beginning of damage from activated microglia M_1)**.** *We define the beginning of the damage by the increased rate of proinflammation cytokines where the existence of high activation of microglia will cause damage to the living brain cells. The steady-state of the form $M_0; M_1; M_2; D > 0, C = 0$ indicates the beginning activation of proinflammation from M_1 microglia.*

Definition 3 (State of the damage from activated microglia in brain cells). *We define the impact of the damage caused by microglia on the living brain cells. The steady state of the form $M_0; M_1; M_2; D; C > 0$ indicates damage of the living brain cells by active microglia.*

Populations of microglia cells (M_0,M_1,M_2), the damage on the tissue by proinflammation, D and the impact of this damage on the living brain cells in the CNS, C are positive or equal to zero for all equations. Thus, we obtain the equilibrium points by solving system (1)–(5) to determine the positive equilibrium points if and only if M_0, M_1, M_2, D and C exemplify the positive solutions.

Proposition 1 (Nonnegative Equilibrium for the SMD model). *We assume the equilibrium points for SMD system, $M_0; M_1; M_2; D; C > 0$ satisfy the following conditions:*

- $\delta > r_1$
- $R_1\gamma_2(-r_1 + \delta) > r_2 R_2 \gamma_1$
- $\alpha R_1 \beta_1 \gamma_2(-r_1 + \delta) > r_2 R_2(\beta_1\gamma_1 + \beta_0\delta)$.

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

Proof. The proof can be clearly found from Definition 1, 2 and 3. □

Hence, the equilibrium point is given as follows:
The equilibrium point for the activation of microglia, E_r

Corollary 1. *The equilibrium point $E_r = (M_0, M_1, M_2, 0, 0)$ exists in $\Re_+^5$ if and only if M_0, M_1, M_2 are the nonnegative roots and $D = 0, C = 0$. This point is given by*

$$E_r = (M_0, M_1, M_2, 0, 0) = \left(\frac{\alpha}{x}, \frac{\alpha R_1}{\gamma_1 x}, \frac{R_2\alpha}{\gamma_2 x}, 0, 0\right). \tag{6}$$

where,

$$x = R_1 + R_2 + \mu.$$

Thus, in the normal state in mammalian brains, we obtain a normal situation when there is no activation of microglia on the brain where $D, C = 0$ given that there is no damage on the brain cells, where the equilibrium point E_r indicated the activation of microglia steady state.
The equilibrium point for high activation of microglia, E_p

Corollary 2. *The equilibrium point E_p exists in $\Re_+^5$ if and only if, M_0, M_1, M_2 and D are the nonnegative roots and $C = 0$. Then, the equilibrium point of proinflammation microglia through 72 h after stroke is given as follows:*

$$E_p = \left(\frac{\alpha}{x}, \frac{r_2 R_2 \alpha}{\gamma_2(-r_1 + \delta)x}, \frac{R_2\alpha}{\gamma_2 x}, \frac{-r_2 R_2 \gamma_1 + R_1 \gamma_2(-r_1 + \delta)}{r_2 R_2 \delta}, 0\right). \tag{7}$$

The model has an equilibrium point for the activation of microglia. During this stage, M_1 has a significant impact. The equilibrium point E_p describes the activation by cytokines which obtains higher proinflammation from R_1 than the rate of the second kind of cytokines R_2 if and only if the rate of damage on the living brain cells by M_1 is more than r_1, which is the clearance damage by the immune cells microglia M_1.
The equilibrium points for the impact of proinflammation microglia M_1 on brain cells, E_d

Corollary 3. *The equilibrium point E_d exists in $\Re_+^5$ if and only if M_0, M_1, M_2, D and C are the nonnegative roots. Then, the equilibrium point E_d has an impact on the damage to the living brain cells through 72 h after stroke onset given as follows:*

$$E_d \;=\; \left(\frac{\alpha}{x}, \frac{R_1\beta_1\alpha}{\kappa x}, \frac{R_2\alpha}{\gamma_2 x}, \frac{\beta_0}{\beta_1}, \frac{(R_1\beta_1\gamma_2(-r_1+\delta)-r_2 R_2\kappa)\alpha}{\beta_1\gamma_2\kappa x} \right), \tag{8}$$

where,

$$\kappa = (\beta_1\gamma_1 + \beta_0\delta).$$

2.1.2. Stability of Equilibrium Points

We now study the stability of equilibrium points for the effect of microglia on brain cells for 72 h without neural stem cells by using definitions 1–3. For the eigenvalues associated without neural stem cell equilibrium in stroke onset, the (5×5) Jacobian matrix of the system (1)–(5) is given by

$$J_1 = \begin{bmatrix} -x & 0 & 0 & 0 & 0 \\ R_1 & -\gamma_1 - D\delta & 0 & -M_1\delta & 0 \\ R_2 & 0 & -\gamma_2 & 0 & 0 \\ 0 & D(-r_1+\delta) & -Dr_2 & -M_2 r_2 - c\beta_1 + M_1(-r_1+\delta) & -D\beta_1 \\ 0 & 0 & 0 & c\beta_1 & D\beta_1 - \beta_0 \end{bmatrix}.$$

1. Stability analysis of equilibrium point, E_r :

Theorem 1. *Suppose that the function $f : \Gamma \to \Re_+^5$ where Γ is a domain in $\Re_+^5$, and suppose that $E_r = (M_0, M_1, M_2, 0, 0) \in \Gamma$ is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part. Then, E_r is an unstable equilibrium point of f.*

Proof. The Jacobian J_1 at equilibrium point E_r is calculated as follows:

$$J[E_r] = \begin{bmatrix} -x & 0 & 0 & 0 & 0 \\ R_1 & -\gamma_1 & 0 & a_{24} & 0 \\ R_2 & 0 & -\gamma_2 & 0 & 0 \\ 0 & 0 & 0 & a_{44} & 0 \\ 0 & 0 & 0 & 0 & -\beta_0 \end{bmatrix},$$

where,

$$a_{24} = \frac{-R_1\alpha\delta}{\gamma_1 x}, \quad a_{44} = \frac{-r_2 R_2\alpha}{\gamma_2 x} + \frac{R_1\alpha(-r_1+\delta)}{\gamma_1 x}.$$

The characteristic equation for the Jacobian $J[E_r]$ is given by

$$(\beta_0 + \lambda)(\gamma_2 + \lambda)(\gamma_1 + \lambda)(x + \lambda)(\lambda + y) = 0. \tag{9}$$

We assume that $x = R_1 + R_2 + \mu$, $y = \frac{r_2 R_2\alpha}{\gamma_2 x} + \frac{R_1\alpha(r_1-\delta)}{\gamma_1 x}$.

Then, the eigenvalues of Jacobian matrix $J[E_r]$ are given by:

$$\lambda_1 \;=\; -x < 0, \quad \lambda_2 = -\beta_0 < 0,$$

$$\lambda_3 \;=\; -\gamma_1 < 0, \quad \lambda_4 = -\gamma_2 < 0, \quad \lambda_5 = -y = \frac{\alpha(-r_2 R_2\gamma_1 + R_1\gamma_2(-r_1+\delta))}{(\gamma_1\gamma_2 x)} > 0.$$

The eigenvalues $\lambda_1, \ldots, \lambda_4$ are negative, but λ_5 is positive. Therefore, E_r is an unstable equilibrium point. □

2. Stability Analysis of Equilibrium point, E_p:

Theorem 2. *Suppose that the function* $f : \Gamma \to \Re_+^5$ *where* Γ *is a domain in* $\Re_+^5$, *and suppose that* $E_p = (M_0, M_1, M_2, D, 0) \in \Gamma$ *is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part and $D > 0$, $C = 0$. Then, E_p is an unstable equilibrium point of f.*

Proof. The Jacobian J_1, at E_p calculated as:

$$J[E_p] = \begin{bmatrix} -x & 0 & 0 & 0 & 0 \\ R_1 & b_{22} & 0 & b_{24} & 0 \\ R_2 & 0 & -\gamma_2 & 0 & 0 \\ 0 & b_{42} & b_{43} & b_{44} & b_{45} \\ 0 & 0 & 0 & 0 & b_{55} \end{bmatrix},$$

where,

$$\begin{aligned} b_{22} &= -\gamma_1 - \frac{(-r_2 R_2 \gamma_1 + R_1 \gamma_2(-r_1 + \delta))}{r_2 R_2} < 0, \quad b_{24} = \frac{r_2 R_2 \alpha \delta}{\gamma_2(r_1 - \delta)x} < 0, \\ b_{42} &= \frac{(-r_1 + \delta)(-r_2 R_2 \gamma_1 + R_1 \gamma_2(-r_1 + \delta))}{r_2 R_2 \delta} > 0, \quad b_{43} = \frac{-(-r_2 R_2 \gamma_1 + R_1 \gamma_2(-r_1 + \delta))}{R_2 \delta}, \\ b_{44} &= \frac{-r_2 R_2 \alpha}{\gamma_2 x} - \frac{r_2 R_2 \alpha(-r_1 + \delta)}{\gamma_2(r_1 - \delta)x} < 0, \quad b_{45} = -\frac{\beta_1(-r_2 R_2 \gamma_1 + R_1 \gamma_2(-r_1 + \delta))}{r_2 R_2 \delta}, \\ b_{55} &= \frac{R_1 \beta_1 \gamma_2(-r_1 + \delta) - r_2 R_2(\beta_1 \gamma_1 + \beta_0 \delta)}{r_2 R_2 \delta} > 0. \end{aligned}$$

From the Jacobian $J[E_p]$, the characteristic equation is given by

$$(\gamma_2 + \lambda)(b_{55} - \lambda)(x + \lambda)(q_2 \lambda^2 + q_1 \lambda^1 + q_0) = 0,$$

where,

$$\begin{aligned} q_2 &= r_2 R_2 \gamma_2(r_1 - \delta)x, \quad q_1 = -R_1 \gamma_2^2(r_1 - \delta)^2 x, \\ q_0 &= -r_2 R_2 \alpha(r_2 R_2 \gamma_1 + R_1 \gamma_2(r_1 - \delta))(r_1 - \delta), \\ x &= R_1 + R_2 + \mu. \end{aligned}$$

By Proposition 1 one of the eigenvalues is positive. So, $J(E_p)$ has one at least positive root, which indicates that the equilibrium point E_p is unstable [44]. □

3. Stability analysis of equilibrium point, E_d:

Theorem 3. *Suppose that the function* $f : \Gamma \to \Re_+^5$ *where* Γ *is a domain in* $\Re_+^5$, *and suppose that* $E_d = (M_0, M_1, M_2, D, C) \in \Gamma$ *is an equilibrium point where all the eigenvalues of the Jacobian matrix have negative real parts at the equilibrium point E_d and $D > 0$, $C > 0$. Then, E_d is a stable equilibrium point of f.*

Proof. The Jacobian J_1 at E_d is calculated as follows:

$$J[E_d] = \begin{bmatrix} -x & 0 & 0 & 0 & 0 \\ R_1 & c_{22} & 0 & c_{24} & 0 \\ R_2 & 0 & -\gamma_2 & 0 & 0 \\ 0 & c_{42} & c_{43} & c_{44} & -\beta_0 \\ 0 & 0 & 0 & c_{54} & 0 \end{bmatrix},$$

where,

$$c_{22} = -\gamma_1 - \frac{\beta_0\delta}{\beta_1} < 0, \quad c_{24} = -\frac{R_1\alpha\beta_1\delta}{(\beta_1\gamma_1 + \beta_0\delta)x} < 0,$$

$$c_{42} = \frac{\beta_0(-r_1 + \delta)}{\beta_1} > 0, \quad c_{43} = -\frac{r_2\beta_0}{\beta_1} < 0,$$

$$c_{44} = -\frac{r_2R_2\alpha}{\gamma_2 x} + \frac{R_1\alpha\beta_1(-r_1 + \delta))}{(\beta_1\gamma_1 + \beta_0\delta)x}$$

$$+ \frac{\alpha(R_1\beta_1\gamma_2(r_1 - \delta) + r_2R_2(\beta_1\gamma_1 + \beta_0\delta))}{\gamma_2(\beta_1\gamma_1 + \beta_0\delta)x} > 0, \quad c_{45} = -\beta_0 < 0$$

$$c_{54} = -\frac{\alpha(R_1\beta_1\gamma_2(r_1 - \delta) + r_2R_2(\beta_1\gamma_1 + \beta_0\delta))}{\gamma_2(\beta_1\gamma_1 + \beta_0\delta)x} > 0.$$

The characteristic equation is given by

$$(\gamma_2 + \lambda)(x + \lambda)(N_3\lambda^3 + N_2\lambda^2 + N_1\lambda + N_0) = 0. \tag{10}$$

Thus, we can find the first two eigenvalues directly:

$$\lambda_1 = -\gamma_2, \quad \lambda_2 = -x.$$

Here, we can apply the Routh–Hurwitz Criterion if and only if [45]:

- $N_2 > 0$,
- $N_0 > 0$,
- $N_2N_1 > N_0N_3$.

where

$$N_0 = \alpha\beta_1\beta_0(\beta_1\gamma_1 + \beta_0\delta)(R_1\beta_1\gamma_2(-r_1 + \delta) - r_2R_2(\beta_1\gamma_1 + \beta_0\delta)) > 0,$$
$$N_1 = \alpha\beta_1^2\beta_0(R_1\gamma_2(-r_1 + \delta)(\beta_1 + \delta) - r_2R_2(\beta_1\gamma_1 + \beta_0\delta)) > 0,$$
$$N_2 = \beta_1\gamma_2(\beta_1\gamma_1 + \beta_0\delta)^2 x > 0, N_3 = \beta_1^2\gamma_2(\beta_1\gamma_1 + \beta_0\delta)x > 0.$$

Since from Proposition 1,

$$N_2N_1 - N_0N_3 = R_1\alpha\beta_1^3\beta_0\gamma_2^2\delta(-r_1 + \delta)(\beta_1\gamma_1 + \beta_0\delta)^2 x > 0.$$

Then, $N_2, N_0 > 0$ and $N_2N_1 - N_0N_3 > 0$,

Now, we apply the Routh–Hurwitz theorem for $N_3\lambda^3 + N_2\lambda^2 + N_1\lambda + N_0 = 0$, giving

$$\begin{vmatrix} \lambda^3 & N_3 & N_1 \\ \lambda^2 & N_2 & N_0 \\ \lambda^1 & N^* & 0 \\ \lambda^0 & N_0 & 0 \end{vmatrix},$$

where,

$$N^* = \frac{N_2 N_1 - N_3 N_0}{N_2},$$

thus,

$$N^* = R_1 \alpha \beta_1^2 \beta_0 \gamma_2 \delta(-r_1 + \delta) > 0.$$

Since all the coefficients in the first column have positive signs; the Equation (10) has no roots with positive real parts and two of the eigenvalues are negative; thus, the equilibrium point E_d is stable. Activated microglia are capable of cleaning dead cells; however, they produce free radicals from brain cells, which increases the damage in brain cells during a stroke. This lead to further death of brain cells [17,32]. □

Remark 1. *The effect of microglia on brain cells in a stroke (which includes activated microglia at stroke onset) on the dynamic system of SMD model can be deduced, as follows:*

- *As a result of Theorem 1 and Definition 1, the damage, D, can invade the SMD system if $\lambda_5 > 0$.*
- *As a result of Theorem 2 and Definition 2, this means that the damage, $D > 0$, invades C.*
- *As a result of Theorem 3 and Definition 3, this means that the damage, $D > 0$, causes the death of C.*
- *The SMD model is stable when the brain cells are affected by the proinflammatory cytokines of microglia; however, when the rate of production of proinflammatory cytokines leads to an increase in damage, the possibility of death of the brain cells is introduced.*

2.2. Modeling the Interaction between Microglia and Neural Stem Cells and Impact on the Brain in Stroke (SMNR)

We formulate the following a non-linear system of ordinary differential equations to describe the interaction between microglial cells and neural stem cells and to investigate the damage to brain cells in the recovery stage after a stroke. This system uses the same equations as the SMD model, but also includes the transition from M_1 to M_2 and the behavior of neural stem cells N_{SC}. The system is as follows:

$$\frac{dM_0}{dt} = \alpha - \left[R_1 + R_2 + \mu\right]M_0(t) \tag{11}$$

$$\frac{dM_1}{dt} = R_1 M_0(t) - \left[R_3 + \delta D(t) + k_1 N_{SC}(t) + \gamma_1\right]M_1(t) \tag{12}$$

$$\frac{dM_2}{dt} = R_2 M_0(t) + R_3 M_1(t) - \left[k_2 N_{SC}(t) + \gamma_2\right]M_2(t) \tag{13}$$

$$\frac{dN_{SC}}{dt} = N_{SC}(t)\left[k_2 M_2(t) + k_1 M_1(t) - \beta_2 C(t) - \sigma\right] \tag{14}$$

$$\frac{dD}{dt} = D(t)\left[\delta M_1(t) - \beta_1 C(t) - r_1 M_1(t) - r_2 M_2(t)\right] \tag{15}$$

$$\frac{dC}{dt} = C(t)\left[\beta_1 D(t) + \beta_2 N_{SC}(t) - \beta_0\right], \tag{16}$$

with initial values $M_0[0] = 1$ [1], $M_1[0] = 0.02$ [35], $M_2[0] = 0.1514$ [1], $N_{SC}[0] = 0.85$ [38], $D[0] = 0.4$ Ref. [1], and $C[0] = 0.28$ [35].

The parameters are real and positive, where R_3 denotes the rate of transition from M_1 to M_2, k_1 is the rate of interaction between neural stem cells and M_1 microglia, k_2 is the rate of interaction between neural stem cells and M_2 microglia, β_2 is the rate of the effect of neural stem cells on brain cells, and σ is the death rate of neural stem cells. The other parameters are the same as in the SMD model. In the SMNR model, $M_1 < M_2$ occurs during the recovery stage, where neural stem cells also start to generate and help the brain. Therefore, microglial activation is important for directing the replacement of damaged or lost cells in the brain.

2.2.1. Equilibrium Points

In this section, we calculate the equilibrium points of the system (11)–(16) and determine the parameter conditions for the existence of the different types of biological states. We find the steady-state solutions as follows:

$$\frac{dM_0}{dt} = \frac{dM_1}{dt} = \frac{dM_2}{dt} = \frac{dN_{SC}}{dt} = \frac{dD}{dt} = \frac{dC}{dt} = 0.$$

We classify three states of steady states:

Definition 4 (The transformation state). *We define the transition cytokines from proinflammation microglia to anti-inflammation (M_1 to M_2). The steady state of the form $M_0; M_1; M_2 > 0$ and $N_{SC}, D, C = 0$ indicates the beginning of recovery stage.*

Definition 5 (The interaction between microglia and neural stem cells state). *We define the interaction between microglia and neural stem cells microglia in which the proinflammation phenotype (M_1) affects negatively on neural stem cells generation and the anti-inflammation phenotype (M_2) stimulates its generation. The steady state of the form $M_0; M_1; M_2; N_{SC} > 0$ and $C, D = 0$, indicates the interaction between brain cells in the recovery stage.*

Definition 6 (The impact of neural stem cells on brain cells state). *We define the impact of generating neural stem cells on brain cells, the steady state of the form $M_0; M_1; M_2; N_{SC}; C > 0$ and $D = 0$ indicates the generation of neural stem cells on brain cells.*

Populations of microglia cells (M_0, M_1, M_2), D, N_{SC} and C are positive or equal to zero. Thus, we obtain the equilibrium points by solving the system (11)–(16) to determine the positive equilibrium points if and only if, M_0, M_1, M_2, D, C exemplify the positive solution. Subpopulation of microglia cells M_0, M_1, M_2, N_{SC}, D and C are positive for all $t > 0$.

Proposition 2 (Nonnegative equilibriums for the SMNR model). *We assume the equilibrium points for the system SMNR is nonnegative for the following conditions given by:*

- $\delta > r_1$
- $\alpha\beta_2 > \beta_0\sigma$
- $R_2\alpha\beta_2 > \beta_0\sigma(R_2 + \mu)$
- $k_1\alpha\beta_2 > k_1\beta_0\sigma + \beta_2\gamma_1\sigma$
- $(k_1\beta_0(R_2 + \mu)\sigma + \beta2(R_3 + \gamma_1)x\sigma < k_1R_1(\alpha\beta_2 - \beta_0\sigma)$
- $k_2\gamma_1 < k_1\gamma_2$
- $k_1k_2\alpha + k_2R_3\sigma + k_2\gamma_1\sigma > k_1\gamma_2\sigma$
- $k_1k_2(R_1 + R_2)\alpha + k_2(R_3 + \gamma_1)x\sigma < k_1\gamma_2x\sigma + \nu$
- $k_1k_2(R_1 + R_2)\alpha + k_2R_3x\sigma + k_1\gamma_2x\sigma > k_2\gamma_1x\sigma + \nu$
- $k_1k_2(R_1 + R_2)\alpha + \nu > k_1\gamma_2x\sigma + k_2(R_3 + \gamma_1)x\sigma.$

Then and only then there exist non-negative real steady states.

Proof. The proof is clearly found from the steady states imposing $(M_0; M_1; M_2; N_{SC}; D; C) > 0$. Thus the models (11)–(16) obtain three points of equilibrium in the recovery stage by using MATHEMATICA. □

The first equilibrium point: the transformation state of microglia from proinflammation to anti-inflammation, E_t

Corollary 4. *The equilibrium point E_t has transformation microglia from proinflammation to anti-inflammation point recovery state from stroke given as follows:*

The equilibrium point $E_t = (M_0, M_1, M_2, N_{SC}, D, C)$ exists in $\Re^6_+$, in the beginning of activation of microglia that inhibits and transfers part of M_1 phenomena to the second M_2 phenomena. Then, $C = 0$, $D = 0$, $N_{SC} = 0$. This point E_t is given by

$$E_t = \left(\frac{\alpha}{x}, \frac{(R_1 \alpha)}{(R_3 + \gamma_1)x}, \frac{\alpha(R_1 R_3 + R_2(R_3 + \gamma_1))}{(R_3 + \gamma 1)\gamma_2 x}, 0, 0, 0 \right), \tag{17}$$

where

$$x = R_1 + R_2 + \mu.$$

The second equilibrium point: the interaction between microglia and neural stem cells on brain cells, E_I

Corollary 5. *The equilibrium point $E_I = (M_0, M_1, M_2, N_{SC}, D, C)$ exists in $\Re^6_+$. At the beginning of the neural stem cells generation, the damage decreases in this state. Then, $C = 0$, $D = 0$. This point is given by*

$$\begin{aligned}
E_I = \Bigg(&\frac{\alpha}{x}, \frac{1}{2k_1(-k_2\gamma_1 + k_1\gamma_2)x}[(R_1 + R_2)(-k_1 k_2 \alpha - k_2 R_3 \sigma - k_2 \gamma_1 \sigma + k_1 \gamma_2 \sigma) \\
&- \mu\sigma[k_2(R_3 + \gamma_1) - k_1\gamma_2] + v], \frac{1}{2k_2(-k_2\gamma_1 + k_1\gamma_2)x}[(R_1 + R_2)(k_1 k_2 \alpha \\
&+ k_2 R_3 \sigma - k_2 \gamma_1 \sigma + k_1 \gamma_2 \sigma) + \mu\sigma(k_2(R_3 - \gamma_1) + k_1\gamma_2)] - v \\
&, \frac{1}{2k_1 k_2 x\sigma}[(R_1 + R_2)(k_1 k_2 \alpha - k_2 R_3 \sigma - k_2 \gamma_1 \sigma \\
&- k_1\gamma_2\sigma) - k_2\mu\sigma(R_3 + \gamma_1) - k_1\gamma_2\mu\sigma + v), 0, 0 \Bigg)
\end{aligned} \tag{18}$$

where,

$$v = \sqrt{(4k_1 k_2 R_1 \alpha(-k_2\gamma_1 + k_1\gamma_2)x\sigma + (k_1 k_2(R_1 + R_2)\alpha + k_2(R_3 + \gamma_1)x\sigma - k_1\gamma_2 x\sigma)^2)}.$$

The third equilibrium point: the effect of generating neural stem cells on brain cells, E_R

Corollary 6. *The equilibrium point $E_R = (M_0, M_1, M_2, N_{SC}, D, C)$ exists in of $\Re^6_+$. When the neural stem cells are generated, the damage fades away in this state. Then, $D = 0$. This point is given by:*

$$\begin{aligned}
E_R = \Bigg(&\frac{\alpha}{x}, \frac{R_1 \alpha \beta_2}{\epsilon_1 x}, \frac{\alpha\beta_2(R_1 R_3 \beta_2 + R_2 \epsilon_1)}{\epsilon_1 \epsilon_2 x}, \frac{\beta_0}{\beta_2}, 0 \\
&, \left(\frac{\beta_2\gamma_2(-k_1\beta_0(R_2 + \mu)\sigma - \beta_2(R_3 + \gamma_1)x\sigma + k_1 R_1 \epsilon_3) + k_2\epsilon_7}{\beta_2\epsilon_1\epsilon_2 x} \right) \Bigg),
\end{aligned} \tag{19}$$

where,

$$\begin{aligned}
\epsilon_1 &= (R_3\beta_2 + k_1\beta_0 + \beta_2\gamma_1), \quad \epsilon_2 = k_2\beta_0 + \beta_2\gamma_2, \\
\epsilon_3 &= (\alpha\beta_2 - \beta_0\sigma), \quad \epsilon_4 = (-k_1\alpha\beta_2 + k_1\beta_0\sigma + \beta_2\gamma_1\sigma), \\
\epsilon_5 &= R_3\beta_2 + k_1\beta_0 + \beta_2\gamma_1, \quad \epsilon_6 = (R_2\alpha\beta_2 - R_2\beta_0\sigma - \beta_0\mu\sigma), \\
\epsilon_7 &= R_1R_3\beta_2\epsilon_3 - R_1\beta_0\epsilon_4 + \epsilon_5\epsilon_6.
\end{aligned}$$

2.2.2. Stability of Equilibrium Points for SMNR Model

We study the stability of the equilibrium points for the second model SMNR by using Definitions 4–6. The first step requires linearization of the system equations that describes the interaction between microglia M_1, M_2, neural stem cells N_{SC}, the damage D in this stage and the impact it has on the brain cells C. The (6×6) Jacobian matrix of the system (11)–(16) is given by:

$$J_2 = \begin{bmatrix}
j_{11} & 0 & 0 & 0 & 0 & 0 \\
R_1 & j_{22} & 0 & -k_1M_1 & -M_1\delta & 0 \\
R_2 & R_3 & j_{33} & -k_2M_2 & 0 & 0 \\
0 & k_1N_{SC} & k_2N_{SC} & j_{54} & 0 & -N_{SC}\beta_2 \\
0 & D(-r_1+\delta) & -Dr_2 & 0 & j_{55} & -D\beta_1 \\
0 & 0 & 0 & c\beta_2 & c\beta_1 & j_{66}
\end{bmatrix},$$

where,

$$\begin{aligned}
j_{11} &= -x, x = R_1 + R_2 + \mu, \quad j_{22} = -R_3 - k_1N_{SC} - \gamma_1 - D\delta, \\
j_{33} &= -k_2N_{SC} - \gamma_2, \quad j_{54} = k_1M_1 + k_2M_2 - C\beta_2 - \sigma, \\
j_{55} &= -M_2r_2 - C\beta_1 + M_1(-r_1+\delta), \quad j_{66} = D\beta_1 + N_{SC}\beta_2 - \beta_0.
\end{aligned}$$

1. Stability analysis of equilibrium point, E_t:

    Theorem 4. *Suppose that the function $f : \Gamma \to \Re_+^6$ where Γ is a domain in $\Re_+^6$, and suppose that $E_t = (M_0, M_1, M_2, 0, 0, 0) \in \Gamma$ is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part. Then, E_t is an unstable equilibrium point of f.*

    Proof. The Jacobian J_2 corresponding to the equilibrium point E_t is given by

$$J[E_t] = \begin{bmatrix}
-x & 0 & 0 & 0 & 0 & 0 \\
R_1 & -R_3 - \gamma_1 & 0 & d_{24} & d_{25} & 0 \\
R_2 & R_3 & -\gamma_2 & d_{34} & 0 & 0 \\
0 & 0 & 0 & d_{44} & 0 & 0 \\
0 & 0 & 0 & 0 & d_{55} & 0 \\
0 & 0 & 0 & 0 & 0 & -\beta_0
\end{bmatrix},$$

where,

$$\begin{aligned}
d_{24} &= -\frac{k_1R_1\alpha}{(R_3+\gamma_1)x}, \quad d_{25} = -\frac{R_1\alpha\delta}{(R3+\gamma_1)x}, \\
d_{34} &= -\frac{k_2\alpha(R_1R_3 + R_2(R_3+\gamma_1))}{(R_3+\gamma_1)\gamma_2 x}, \quad d_{44} = \frac{k_1R_1\alpha}{(R_3+\gamma_1)x} + \frac{k_2\alpha(R_1R_3 + R_2(R_3+\gamma_1))}{(R_3+\gamma_1)\gamma_2 x} - \sigma, \\
d_{55} &= -\frac{r_2\alpha(R_1R_3 + R_2(R_3+\gamma_1))}{(R_3+\gamma_1)\gamma_2 x} + \frac{R_1\alpha(-r_1+\delta)}{(R_3+\gamma_1)x}.
\end{aligned}$$

From the Jacobian matrix $J[E_t]$, the characteristic equation is given by

$$(\beta_0 + \lambda)(R_3 + \gamma_1 + \lambda)(\gamma_2 + \lambda)(x + \lambda)(-\lambda + t_{55})(-\lambda + t_{44}) = 0. \qquad (20)$$

Then, the eigenvalues corresponding to E_t are given by

$$\begin{aligned}
\lambda_1 &= -\beta_0 < 0, \ \lambda_2 = -R_3 - \gamma_1 < 0, \ \lambda_3 = -x < 0, \ \lambda_4 = -\gamma_2 < 0, \\
\lambda_5 &= \frac{k_1 R_1 \alpha}{(R_3 + \gamma_1)x} + \frac{k_2 \alpha (R_1 R_3 + R_2(R_3 + \gamma_1))}{(R_3 + \gamma_1 \gamma_2)x} - \sigma > 0, \\
\lambda_6 &= -\frac{r_2 \alpha (R_1 R_3 + R_2(R_3 + \gamma_1))}{(R_3 - \gamma_1 \gamma_2)x} + \frac{(R_1 \alpha (r_1 - \delta))}{(R_3 + \gamma_1)x} < 0.
\end{aligned}$$

One of the eigenvalues, $\lambda_5 > 0$, then E_t is an unstable point. $\quad\square$

2. Stability analysis of equilibrium point, E_I:

Theorem 5. *Suppose that the function $f : \Gamma \to \Re_+^6$ where Γ is a domain in $\Re_+^6$, and suppose that $E_I = (M_0, M_1, M_2, N_{SC}, 0, 0) \in \Gamma$ is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part and $N_{SC} > 0$. Then, E_I is an unstable equilibrium point of f.*

Proof. The Jacobian matrix J_2 corresponding to the equilibrium point E_I is given by:

$$J[E_I] = \begin{bmatrix}
-x & 0 & 0 & 0 & 0 & 0 \\
R_1 & e_{22} & 0 & e_{24} & e_{25} & 0 \\
R_2 & R_3 & e_{33} & e_{34} & 0 & 0 \\
0 & e_{42} & e_{43} & 0 & 0 & e_{46} \\
0 & 0 & 0 & 0 & e_{55} & 0 \\
0 & 0 & 0 & 0 & 0 & e_{66}
\end{bmatrix},$$

where,

$$\begin{aligned}
e_{22} &= -\frac{\Lambda_1 + v}{2k_2 x\sigma} < 0, \ e_{42} = \frac{\Lambda_2}{2k_2 x\sigma} > 0, \ e_{33} = -\frac{\Lambda_2}{2k_1 x\sigma} < 0, \ e_{43} = \frac{\Lambda_2}{2k_1 x\sigma} > 0, \\
e_{24} &= \frac{-\Lambda_1 + v}{2qx} < 0, e_{34} = \frac{\Lambda_3}{2qx} < 0, \ e_{25} = -\frac{\delta \Lambda_4}{2k_1 qx} < 0, \\
e_{46} &= \frac{\Lambda_7}{2k_1 k_2 x\sigma} < 0, e_{55} = -\frac{\Lambda_5}{2k_1 k_2 qx} > 0, \ e_{66} = \frac{\Lambda_6}{2k_1 k_2 x\sigma} > 0, \\
v &= \sqrt{4k_1 k_2 R_1 \alpha(-k_2 \gamma_1 + k_1 \gamma_2)x\sigma + (k_1 k_2 (R_1 + R_2)\alpha + k_2(R_3 + \gamma_1)x\sigma - k_1 \gamma_2 x\sigma)^2} > 0, \\
\Psi &= x(k_2(R_3 + \gamma_1) + k_1 \gamma_2)\sigma > 0, \Lambda_1 = k_1 k_2(R_1 + R_2)\alpha + k_2 x(R_3 + \gamma_1)\sigma - k_1 x\gamma_2\sigma > 0, \\
\Lambda_2 &= v - \Psi + k_1 k_2(R_1 + R_2)\alpha > 0, \\
\Lambda_3 &= -v + k_1 k_2(R_1 + R_2)\alpha + k_2 x(R_3 - \gamma_1)\sigma + k_1 x\gamma_2\sigma > 0, \\
\Lambda_4 &= -v + k_1 k_2(R_1 + R_2)\alpha + (k_2(R_3 + \gamma_1) - k_1 \gamma_2)x\sigma < 0, \Lambda_5 = k_2^2(r_1 - \delta)(k_1(R_1 + R_2)\alpha \\
&\quad + x(R_3 + \gamma_1)\sigma) + k_1 r_2(v - k_1 x\gamma_2\sigma) + k_2(-k_1 r_2(k_1(R_1 + R_2)\alpha + x(R_3 - \gamma_1)\sigma) \\
&\quad - (r_1 - \delta)(v + k_1 x\gamma_2\sigma)) > 0, \\
\Lambda_6 &= v\beta_2 + k_1 k_2(R_1 + R_2)\alpha\beta_2 - x(k_2\beta_2(R_3 + \gamma_1) + k_1(2k_2\beta_0 + \beta_2\gamma_2))\sigma > 0, \\
\Lambda_7 &= \beta_2(-v - k_1 k_2(R_1 + R_2)\alpha + k_2 x(R_3 + \gamma_1)\sigma + k_1 x\gamma_2\sigma) < 0, \\
q &= k_2 \gamma_1 - k_1 \gamma_2 < 0, x = R_1 + R_2 + \mu > 0.
\end{aligned}$$

From the Jacobian $J[E_I]$, the characteristic equation is given by

$$(e_{66} - \lambda)(\lambda + x)(e_{55} - \lambda)[\lambda^3 + T_2\lambda^2 + T_1\lambda + T_0] = 0, \tag{21}$$

where,

$$\begin{aligned}
T_3 &= -8k_1^3 k_2^2 q^2 x^4 \sigma^3, \quad T_2 = -4k_1^2 k_2 q^2 (k_1(v + \Lambda_1) + k_2\Lambda_2) x^3\sigma^2, \\
T_1 &= 2k_1^2 k_2 q x^2 \Lambda_2 \sigma(-q(v + \Lambda_1) + \Lambda_2(k_1(v - \Lambda_1) + k_2\Lambda_3)\sigma), \\
T_0 &= k_1^2 k_2 q \Lambda_2 x\sigma(\Lambda_1(-\Lambda_2 + \Lambda_3 - 2k_2 R_3 x\sigma) + v(\Lambda_2 + \Lambda_3 + 2k_2 R_3 x\sigma)).
\end{aligned}$$

In Equation (21), the eigenvalue $\lambda = e_{66}$ is distinctly positive, by Proposition 2. Thus, $J(E_I)$ has at least one positive root. Thus, the equilibrium point E_I is unstable [44]. □

3. Stability analysis of equilibrium point, E_R:

Theorem 6. *Suppose that the function* $f : \Gamma \to \Re_+^6$ *where* Γ *is a domain in* $\Re_+^6$, *and suppose that* $E_R = (M_0, M_1, M_2, N_{SC}, 0, C) \in \Gamma$ *is an equilibrium point at which at least one eigenvalue of the Jacobian matrix has a positive real part and* $N_{SC} > 0, C > 0$. *Then,* E_R *is an unstable equilibrium point of* f.

Proof. We now study the stability of the equilibrium point E_R, calculated as:
The Jacobian matrix J_2 estimated at E_R is

$$J[E_R] = \begin{bmatrix}
-x & 0 & 0 & 0 & 0 & 0 \\
R_1 & f_{22} & 0 & f_{24} & f_{25} & 0 \\
R_2 & R_3 & f_{33} & f_{34} & 0 & 0 \\
0 & \frac{k_1\beta_0}{\beta_2} & \frac{k_2\beta_0}{\beta_2} & f_{44} & 0 & -\beta_0 \\
0 & f_{52} & f_{53} & 0 & f_{55} & f_{56} \\
0 & 0 & 0 & 0 & 0 & f_{66}
\end{bmatrix},$$

where

$$\begin{aligned}
f_{22} &= -R_3 - \frac{k_1\beta_0}{\beta_2} - \gamma_1 - \frac{\delta\rho_1}{\beta_2 v_1 v_2 x} < 0, \quad f_{24} = -\frac{k_1 R_1 \alpha\beta_2}{v_1 x} < 0, \quad f_{25} = -\frac{(R_1\alpha\beta_2\delta)}{v_1 x} < 0, \\
f_{55} &= -\frac{(r_2\alpha\beta_2)\rho_2}{v_1 v_2 x} + \frac{R_1\alpha\beta_2(-r_1 + \delta)}{v_1 x} > 0, \quad f_{33} = -\frac{k_2\beta_0}{\beta_2} - \gamma_2, \quad f_{34} = -\frac{k_2\alpha\beta_2\rho_2}{v_1 v_2 x} > 0, \\
f_{43} &= \frac{k_2\beta_0}{\beta_2}, \quad f_{44} = \frac{k_1 R_1 \alpha\beta_2}{v_1 x} + \frac{k_2\alpha\beta_2\rho_2}{v_1 v_2 x} - \sigma > 0, \quad f_{42} = \frac{k_1\beta_0}{\beta_2}, \quad f_{53} = -\frac{r_2\rho_1}{\beta_2 v_1 v_2 x} < 0, \\
f_{56} &= -\frac{\beta_1\rho_1}{\beta_2 v_1 v_2 x} < 0, \quad f_{52} = \frac{(-r_1 + \delta)\rho_1}{\beta_2 v_1 v_2 x} < 0, \quad f_{66} = \frac{\beta_1\rho_1}{\beta_2 v_1 v_2 x} > 0, \\
\rho_1 &= (\beta_2\gamma_2(-k_1\beta_0(R_2 + \mu)\sigma - \beta_2(R_3 + \gamma_1)x\sigma + k_1 R_1(\alpha\beta_2 - \beta_0\sigma)), \\
&\quad + k_2(R_1 R_3 \beta_2(\alpha\beta_2 - \beta_0\sigma)) - R_1\beta_0(-k_1\alpha\beta_2 + k_1\beta_0\sigma + \beta_2\gamma_1\sigma) \\
&\quad + (R_3\beta_2 + k_1\beta_0 + \beta_2\gamma_1)(R_2\alpha\beta_2 - R_2\beta_0\sigma - \beta_0\mu\sigma))) \\
\rho_2 &= (R_1 R_3 \beta_2 + R_2(R_3\beta_2 + k_1\beta_0 + \beta_2\gamma_1)) > 0, \\
v_1 &= (R_3\beta_2 + k_1\beta_0 + \beta_2\gamma_1) > 0, \quad v_2 = (k_2\beta_0 + \beta_2\gamma_2) > 0.
\end{aligned}$$

From the Jacobian $J[E_R]$, the characteristic equation is given by

$$(f_{66} - \lambda)(\lambda + x)(f_{25} f_{34}(-f_{53} k_1 + f_{52} k_2)\beta_0 + f_{25}\beta_2(f_{44} - \lambda)(-f_{33} f_{52} + f_{53} R_3 + f_{52}\lambda) + (f_{55} - \lambda)$$
$$\times((-f_{34} k_2\beta_0 + \beta_2(f_{33} - \lambda)(f_{44} - \lambda))(f_{22} - \lambda) + f_{24}\beta_0(-f_{33} k_1 + k_2 R_3 + k_1\lambda))) = 0. \tag{22}$$

In Equation (22), the eigenvalue $\lambda = f_{66}$ is distinctly positive, by Proposition 2. Thus, $J(E_R)$ has at least one positive root and, so, the equilibrium point E_R is unstable [44]. □

Remark 2. *The effects of microglia and neural stem cells on brain cells in the recovery stage after a stroke, according to analysis of the dynamic system of SMNR, can be deduced as follows:*

- *As a result of Theorem 4 and Definition 4, the neural stem cells, Nsc, can invade the SMNR system if $\lambda_5 > 0$.*
- *As a result of Theorem 5 and Definition 5, this means that the neural stem cells, $Nsc > 0$, can invade C and D.*
- *As a result of Theorem 6 and Definition 6, this means that the neural stem cells, $Nsc > 0$, can eliminate the damage D.*
- *The SMNR model is unstable, given that the model uses mature neural stem cells, where the neural stem cells can help the brain to inhibit inflammation during a stroke; however, it is not always enough to substitute all dead cells with new neural stem cells [3,27].*

3. Numerical Experiments

The aim of this section is to study the parameters of the systems (1)–(5) and (11)–(16), in order to determine those that affect the behavior of the modified models, by using numerical simulations. One of the main problems in modeling and simulating the interactions between microglia and endogenous neural stem cells is that few parameter values are known. Therefore, we listed the parameters which could be determined from the stroke model of [1]. The other parameters were determined from experimental data of other brain injuries which involve similar biological processes. Furthermore, we obtained some parameter values by simulations using the Mathematica software (11.2, Wolfram, Champaign, IL, USA) with the command NDSolve, in order to study the influence of the interactions during the stroke and the possible therapeutic value of neural stem cells. Tables 1 and 2 show the reference sets of parameter values, along with the corresponding simulation results.

**Table 1.** Parameters values for the stroke-microglia-damage (SMD) model.

The SMD Model			
Parameters	**Values**	**Meaning**	**Sources**
α	0.38	Source of resting microglia	[1]
R_1	0.12	Rate the activation of resting microglia into M_1	[1]
R_2	0.017	Rate the activation of resting microglia into M_2	[35]
δ	0.2854	Rate of the damage produced by M_1	[1]
β_1	0.1	Rate of effect the damage on $C(t)$	[1]
β_0	0.05	Rate of dying C through stroke	[1]
μ	0.003	Death rate of M_0	simulation
γ_1	0.05	Death rate of M_1	simulation
γ_2	0.06	Death rate of M_2	simulation
r_1	0.05	Damage clearance by M_1	[1]
r_2	0.0125	Damage clearance by M_2	[1]

The numerical simulations in Tables 1 and 2 appeared in the SMD and the SMNR models. The microglial cells at stroke onset had high proinflammatory activation (i.e., high level of M_1), which caused an increase of damage in the region, affecting brain cells as well as neural stem cells during the 72 h period. On the other hand, when the rate of the anti-inflammatory phenotype microglia (M_2) became higher than that of the M_1, the brain was assisted in recovery and the neural stem cells were stimulated to generate new cells to compensate for lost brain cells. These dynamics started approximately on the third day after stroke onset. The parameters of the SMD model, in the simulation, were fixed as $\mu = 0.003$, $\gamma_1 = 0.05$, and $\gamma_2 = 0.06$. The parameters of the SMNR model, in the simulation, were fixed as $R_3 = 0.11$, $K_1 = 0.75$, $K_2 = 0.91$, $\beta_2 = 0.2$, and $\mu = 0.053$. In the

SMD model, $M_1 > M_2$ and we set $R_1 = 0.12$ [1] and $R_2 = 0.017$ [35]. In the SMNR model, $M_2 > M_1$, the source of resting microglia was $\alpha = 0.38$, and the rate of the anti-inflammatory cytokines (R_2) was greater than that of the proinflammatory cytokines (R_1) in the recovery stage. Accordingly, we set $R_1 = 0.12$ [1] and estimated $R_2 = 0.26$. The dynamics of the systems were given by solving the systems numerically and then plotting the time series of the solutions of the system (1)–(5) and (11)–(16) for the parameters, which were solved using the fourth-order Runge–Kutta (RK4) method to obtain more stable and convergent solutions. The simulations of SMD and SMNR were carried out for the time spans of three days (72 h) and thirty days, respectively with a step size of 10^{-4} in the RK4 method. The SMD model described the inflammatory process where activation of the microglia cells peaks around three days (72 h) from stroke onset [1,2]. Neural stem cells increase the proliferation and the migration from the subventricular zone to the brain in thirty days and peaking around seven days after stroke [3,27]. Therefore, the SMNR model studied thirty days after stroke to investigate the interactions between microglia and neurogenesis after stroke. The accuracy of solutions by using the RK4 method of the SMD model and the best numerical solution of the model was obtained at 38 steps. While the accuracy of solutions by using the RK4 method of the SMNR model and the best numerical solution of the model was obtained at 35 steps. The reliability and accuracy of the proposed numerical method can be seen from the residual error which is shown in Figures 1 and 2. Figure 1 shows the residual error for the SMD model at the number of steps and the residual error at the time. While Figure 2 shows the residual error for the SMNR model at the number of steps and the residual errors at the time. By comparing the results in our study of microglial activation and the damage during the first three days after stroke onset and the recovery stage within the first thirty days after stroke onset with the effects of neural stem cells and those of the study in [40], we found that the studies agreed, in that the extended proinflammatory activation of microglia may inhibit neurogenesis and contribute to additional neuronal loss. Hence, the behavioural responses of microglia can lead to an increase in damage in the brain or its capability to recover. In this study, we focused on the importance and contribution of neural stem cells in transitioning to the recovery stage, as well as the interaction between microglia and neural stem cells. The generation of neural stem cells was considered to lead to a decrease in damage to the brain, compared to their absence. The behaviors of the solutions of the SMD and SMNR models are shown in Figure 3. It can be seen, in the SMD model, that the population of microglial cells M_1 had a shallow increase, asides from shifting to a steep curve at approximately 15–30 h, and peaked at around 72 h. On the other hand, we can observe that M_2 had a low level after stroke onset and, after three days, reached a stable level. The population of M_1 began to shift into the steep curve (the second stage) with an increase of M_2. Furthermore, the damage increased sharply in the initial stage and decreased in the second stage. On the other hand, in the SMNR model, the response of the neural stem cells began after the initial stage, helping the brain cells to repair damaged cells and lost cells, depending on whether the number of living cells was greater than that of the dead cells. As depicted in Figure 3, the curve of neural stem cells increased and then decreased during the 15 days following stroke onset; this can be explained by the ability of neural stem cells to inhibit inflammation, as has been studied in [3], where the survival of neural stem cells seemed to be prevented, with up to 80% of the new neurons dying within two weeks after their generation in vivo. Furthermore, the curve of neural stem cells in Figure 3 reached its peak during the first week, in agreement with studies in rats and mice, where the increase in proliferation of neural stem cells peaked at around 7 days after ischemic injury [27].

Table 2. Parameters values for the stroke-microglia-neural stem cells-recovery (SMNR) model.
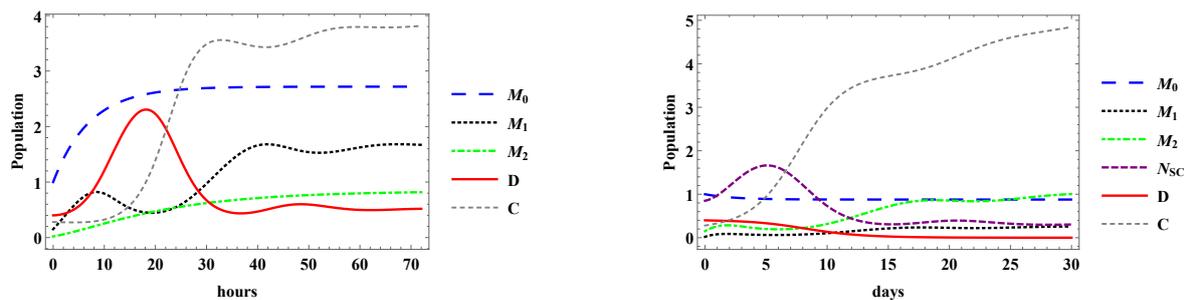
The SMNR Model			
Parameters	**Values**	**Biological Meaning**	**Sources**
α	0.38	Source of resting microglia	[1]
R_1	0.12	Rate the activation of resting microglia into M_1	[1]
R_2	0.26	Rate the activation of resting microglia into M_2	estimated
R_3	0.11	The transition rate of $M_1 \to M_2$	simulation
K_1	0.91	Rate of interaction between M_1 and N_{SC}	simulation
K_2	0.75	Rate of interaction between M_2 and N_{SC}	simulation
δ	0.2854	Rate of the damage produced by M_1	[1]
β_1	0.1	Rate of effect the damage on $C(t)$	[1]
β_2	0.2	Rate of effect N_{SC} on $C(t)$	simulation
β_0	0.05	Rate of dying C through stroke	[1]
μ	0.053	Death rate of M_0	simulation
γ_1	0.015	Death rate of M_1	[35]
γ_2	0.015	Death rate of M_2	[35]
σ	0.015	Death rate of N_{SC}	[38]
r_1	0.05	Damage clearance by M_1	[1]
r_2	0.0125	Damage clearance by M_2	[1]
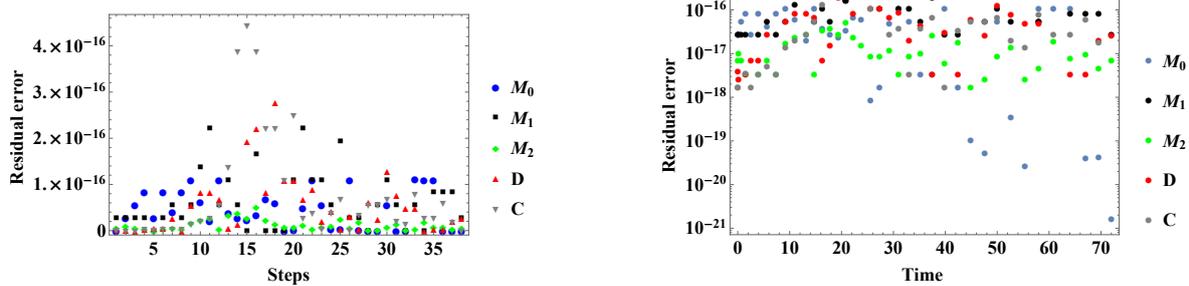
Figure 1. Residual error for the step and time of the numerical method in the SMD model.
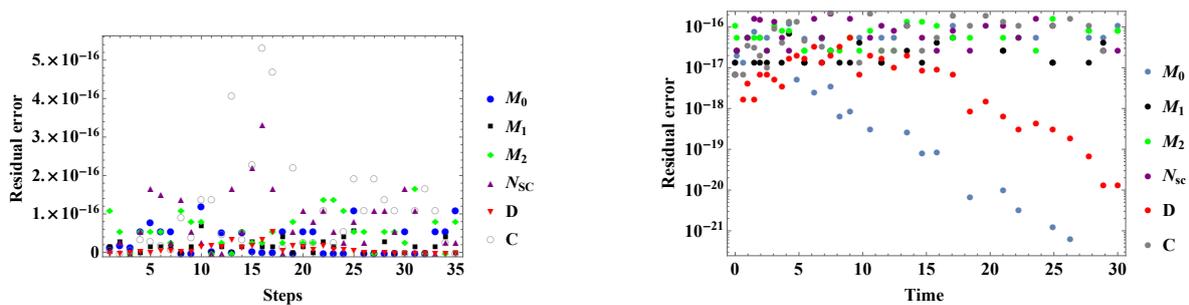
Figure 2. Residual error for the step and time of the numerical method in the SMNR model.

Figure 3. The behaviour of the SMD model within 72 h from stroke onset and the SMNR model within 30 days after stroke onset.

4. Conclusions

We modified two models—SMD ((1)–(5)) and SMNR ((11)–(16))—based on the model of Leah et al. [40], in order to study the impact of the microglial activation stage and the interaction between microglia and neural stem cells during a stroke. The dynamic models of the effects of microglia and the interaction between neural stem cells and microglia in stroke over time were studied both analytically and numerically. From the results of the analysis and simulation of both models, two states of microglial cells (M_1 to M_2) emerged from the resting state. In the first disease stage, the activation of microglial cells went from resting-state microglia to either of the states M_1 or M_2. The results of this interaction led to increased damage in the brain after stroke onset when M_2 was very low, there was no shift from M_1 to M_2, and no generation of neural stem cells occurred in the first 72 h after the stroke. Subsequently, in the recovery stage, the rate of M_1 decreased and the rate of M_2 increased and the neural stem cells began to generate. Subsequent to that, the rate of damage decreased. The instability of the SMNR model can be explained: in the nervous system, the number of endogenous neural stem cells is very low under normal physiological conditions, showing a very limited capacity for cell replacement under normal physiological conditions [20,21]. Understanding the biology in vivo of neural stem cells could lead to new therapeutic strategies for brain repair by endogenous neural stem cells [20,21], encouraging inflammatory inhibition. In conclusion, our modified models can lead to lead to an understanding of the effectiveness risks of the inflammatory responses associated with strokes and their positive and negative effects on the brain in stroke patients, as well as the general dynamics of microglial effects on neural stem cells, both during stroke and in the recovery stage. In the future, we will expand this work to study the mechanisms that improve, stimulate, and generate the neural stem cells in the early stage, and where that information could contribute to understanding the effects of therapeutic strategies. Additionally, it could be interesting to incorporate the dynamics of anti-inflammatory and proinflammatory cytokines from microglia and the cytokines of endogenous neural stem cells into the SMNR model, in order to describe the interaction processes of the different types of cytokines in ischemic stroke.

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References

1. Di Russo, C. A mathematical model of inflammation during ischemic stroke. *Math. Model. Med.* **2010**, *30*, 15–33. [CrossRef]

2. Guruswamy, R.; ElAli, A. Complex roles of microglial cells in ischemic stroke pathobiology: New insights and future directions. *Int. J. Mol. Sci.* **2017**, *18*, 496. [CrossRef]

3. Tobin, M.K.; Bonds, J.A.; Minshall, R.D.; Pelligrino, D.A.; Testai, F.D.; Lazarov, O. Neurogenesis and inflammation after ischemic stroke: What is known and where we go from here. *J. Cereb. Blood Flow Metab.* **2014**, *10*, 1573–1584. [CrossRef] [PubMed]

4. Radak, D.; Katsiki, N.; Resanovic, I.; Jovanovic, A.; Sudar-Milovanovic, E., Zafirovic, S.; Mousad, S.A.; Isenovic, E.R. Apoptosis and acute brain ischemia in ischemic stroke. *Curr. Vasc. Pharmacol.* **2017**, *15*, 115–122. [CrossRef] [PubMed]

5. Anttila, J.E.; Whitaker, K.W.; Wires, E.S.; Harvey, B.K.; Airavaara, M. Role of microglia in ischemic focal stroke and recovery: Focus on toll-like receptors. *Neuro-Psychopharmacol. Biol. Psychiatry* **2016**, *79*, 3–14. [CrossRef] [PubMed]

6. Stonesifer, C.; Corey, S.; Ghanekar, S.; Diamandis, Z.; Acosta, S.A.; Borlongan, C.V. Stem cell therapy for abrogating stroke-induced neuroinflammation and relevant secondary cell death mechanisms. *Prog. Neurobiol. Prog. Neurobiol.* **2017**, *158*, 94–131. [CrossRef]

7. Banjara, M.; Ghosh, C. Sterile neuroinflammation and strategies for therapeutic intervention. *Int. J. Inflamm.* **2017**, *10*, 8385961. [CrossRef]

8. Rajab, N.F.; Musa, S.M.; Ahmad Munawar, M.; Leong, L.M.; Heng, K.Y.; Ibrahim, F.W.; Chan, K.M. Antineuroinflammatory effects of hibiscus sabdariffa Linn.(Roselle) on Lipopolysaccharides-induced Microglia and Neuroblastoma Cells. *Malays. J. Health Sci.* **2016**, *14*, 111–117.

9. Rune, L.; Martin, W.; Daniel, G.; Christina, F.; Lasse, D.; Ishar, D.; Bente, F. Microglial cell population dynamics in the injured adult central nervous system. *Brain Res. Rev.* **2005**, *48*, 196–206.

10. Galloway, D.A.; Phillips, A.E.; Owen, D.R.; Moore, C.S. Phagocytosis in the Brain: Homeostasis and Disease. *Front. Immunol.* **2019**, *10*, 790. [CrossRef]

11. Pham-Huy, L.A.; He, H.; Pham-Huy, C. Free radicals, antioxidants in disease and health. *Int. J. Biomed. Sci. IJBS* **2008**, *4*, 89–96. [PubMed]

12. Di Meo, S.; Reed, T.T.; Venditti, P.; Victor, V.M. Role of ROS and RNS Sources in Physiological and Pathological Conditions. Oxid. Med. *Cell. Longev.* **2016**, *2016*, 1245049. [CrossRef]

13. Fresta, C.G.; Chakraborty, A.; Wijesinghe, M.B.; Amorini, A.M.; Lazzarino, G.; Lazzarino, G.; Tavazzi, B.; Lunte, S.M.; Caraci, F.; Dhar, G.; et al. Non-toxic engineered carbon nanodiamond concentrations induce oxidative/nitrosative stress, imbalance of energy metabolism, and mitochondrial dysfunction in microglial and alveolar basal epithelial cells. *Cell Death Dis.* **2018**, *9*, 245. [CrossRef] [PubMed]

14. Vay, S.U.; Flitsch, L.J.; Rabenstein, M.; Rogall, R.; Blaschke, S.; Kleinhaus, J.; Bach, A.; Fink, G.R.; Schroeter, M.; Rueger, A.M. The plasticity of primary microglia and their multifaceted effects on endogenous neural stem cells in vitro and in vivo. *J. Neuroinflamm.* **2018**, *15*, 226. [CrossRef]

15. Hui-Yin, Y.; Ahmad, N.; Azmi, N.; Makmor-Bakry, M. Curcumin: The molecular mechanisms of action in inflammation and cell death during kainate-induced epileptogenesis. *Indian J. Pharm. Edu. Res.* **2018**, *52*, 32–41. [CrossRef]

16. Hake, I.; Schönenberger, S.; Neumann, J.; Franke, K.; Paulsen-Merker, K.; Reymann, K.; Ismail, G.; Bin Din, L.; Said, I.M.; Latiff, A.; et al. Neuroprotection and enhanced neurogenesis by extract from the tropical plant Knema laurina after inflammatory damage in living brain tissue. *J. Neuroimmunol.* **2009**, *206*, 91–99. [CrossRef]

17. Cherry, J.D.; Olschowka, J.A.; O'Banion, M.K. Neuroinflammation and M_2 microglia: The good, the bad, and the inflamed. *J. Neuroinflamm.* **2014**, *11*, 98. [CrossRef]

18. Ma, Y.; Wang, J.; Wang, Y.; Yang, G.Y. The biphasic function of microglia in ischemic stroke. *Prog. Neurobiol.* **2016**, *157*, 247–272. [CrossRef]

19. Choi, J.Y.; Kim, J.Y.; Kim, J.Y.; Park, J.; Lee, W.T.; Lee, J.E. M_2 phenotype microglia-derived cytokine stimulates proliferation and neuronal differentiation of endogenous stem cells in ischemic brain. *Exp. Neurobiol.* **2017**, *26*, 33–41. [CrossRef]

20. Ahn, S.; Joyner, A. In vivo analysis of quiescent adult neural stem cells responding to Sonic hedgehog. *Nature* **2005**, *437*, 894–897. [CrossRef]

21. Bauer, S . Cytokine control of adult neural stem cells. *Ann. N. Y. Acad. Sci.* **2009**, *1153*, 48–56. [CrossRef] [PubMed]

22. Vieira, M.S.; Santos, A.K.; Vasconcellos, R.; Goulart, V.A.; Parreira, R.C.; Kihara, A.H.; Ulrich, H.; Resende, R.R. Neural stem cell differentiation into mature neurons: Mechanisms of regulation and biotechnological applications. *Biotechnol. Adv.* **2018**, *7*, 1946–1970. [CrossRef] [PubMed]

23. Martínez-Garza, D.M.; Cantú-Rodríguez, O.G.; Jaime-Pérez, J.C.; Gutiérrez-Aguirre, C.H.; Góngora-Rivera, J.F.; Gómez-Almaguer, D. Current state and perspectives of stem cell therapy for stroke. *Med. Univ.* **2016**, *72*, 169–180. [CrossRef]

24. Matarredona, E.R.; Talaveron, R.; Pastor, A.M. Interactions between neural progenitor cells and microglia in the subventricular zone: Physiological implications in the neurogenic niche and after implantation in the injured brain. *Front. Cell. Neurosci.* **2018**, *12*, 268. [CrossRef]

25. Zhang, Z.; Chopp, M. Neural stem cells and ischemic brain. *J. Stroke* **2016**, *18*, 267–272. [CrossRef] [PubMed]

26. Faiz, M.; Sachewsky, N.; Gascón, S.; Bang, K.A.; Morshead, C.M.; Nagy, A. Adult neural stem cells from the subventricular zone give rise to reactive astrocytes in the cortex after stroke. *Cell Stem Cell* **2015**, *17*, 624–634. [CrossRef] [PubMed]

27. Choi, Y.S.; Lee, M.Y.; Sung, K.W.; Jeong, S.W.; Choi, J.S.; Park, H.J.; Kim, O.N.; Lee, S.B.; Kim, S.Y. Regional differences in enhanced neurogenesis in the dentate gyrus of adult rats after transient forebrain ischemia. *Mol. Cells* **2003**, *16*, 232–238.

28. Barkho, B.Z.; Zhao, X. Adult neural stem cells: Response to stroke injury and potential for therapeutic applications. *Curr. Stem Cell Res. Ther.* **2011**, *6*, 327–338. [CrossRef]

29. Ariffin, S.H.Z.; Wahab, R.M.A.; Ismail, I.; Mahadi, N.M.; Ariffin, Z.Z. Stem cells, cytokines and their receptors. *Asia-Pac. J. Mol. Biol. Biotechnol.* **2005**, *13*, 1–13.

30. Lira-Diaz, E; Gonzalez-Perez, O. Emerging roles of microglia cells in the regulation of adult neural stem cells. *Neuroimmunol. Neuroinflamm.* **2008**, *3*, 204–206.

31. Boese, A.C.; Le, Q.S.E.; Pham, D.; Hamblin, M.H.; Lee, J.P. Neural stem cell therapy for subacute and chronic ischemic stroke. *Stem Cell Res. Ther.* **2018**, *9*. [CrossRef] [PubMed]

32. Reynolds, A.; Rubin, J.; Clermont, G.; Day, J.; Vodovotz, Y.; Bard Ermentrout, G. A reduced mathematical model of the acute inflammatory response: I. derivation of model and analysis of anti-inflammation. *J. Theor. Biol.* **2006**, *242*, 220–236. [CrossRef] [PubMed]

33. Kumar, R.; Clermont, G.; Vodovotz, Y.; Chow, C.C. The dynamics of acute inflammation. *J. Theor. Biol.* **2004**, *230*, 145–155. [CrossRef] [PubMed]

34. Alharbi, S.; Rambely, A. A dynamic simulation of the immune system response to inhibit and eliminate abnormal cells. *Symmetry* **2019**, *11*, 572. [CrossRef]

35. Hao, W.; Friedman, A. Mathematical model on Alzheimer'sdisease. *BMC Syst. Biol.* **2016**, *10*, 108. [CrossRef]

36. Nakata, Y.; Getto, P.; Marciniak-Czochra, A.; Alarcón, T. Stability analysis of multi-compartment models for cell production systems. *J. Biol. Dyn.* **2012**, *6*, 2–18. [CrossRef]

37. Ziebell, F.; Martin-Villalba, A.; Marciniak-Czochra, A. Mathematical modelling of adult hippocampal neurogenesis: Effects of altered stem cell dynamics on cell counts and bromodeoxyuridine-labelled cells. *J. R. Soc. Interface* **2014**, *11*, 20140144. [CrossRef]

38. Cacao, E.; Cucinotta, F.A. Modeling impaired hippocampal neurogenesis after radiation exposure. *Radiat. Res* **2016**, *185*, 319–331. [CrossRef]

39. Huang, L.; Zhang, L. Neural stem cell therapies and hypoxic-ischemic brain injury. *Prog. Neurobiol.* **2018**, *173*. [CrossRef]

40. Leah, E.V.; Prerna, R.R.; Raj, G.K.; Amy, K.; Jonathan, E.R. A mathematical model of neuroinflammation in severe clinical traumatic brain injury. *J. Neuroinflamm.* **2018**, *15*, 345. [CrossRef]

41. Zhao, L.; Zhang, J. *Cellular Therapy for Stroke and CNS Injuries*; Springer Series in Translational Stroke Research; Springer: Berlin, Germany, 2015; pp. 34–39.

42. Loane, D.J.; Kumar, A. Microglia in the TBI brain: The good, the bad, and the dysregulated. *Exp. Neurol.* **2016**, *275*, 316–327. [CrossRef] [PubMed]

43. Kim, J.Y.; Kim, N.; Yenari, M.A. Mechanisms and potential therapeutic applications of microglial activation after brain injury. *CNS Neurosci. Ther.* **2015**, *21*, 309–319. [CrossRef] [PubMed]

44. Saha Ray, S.; Sahoo, S. *Generalized Fractional Order Differential Equations Arising in Physical Models*; CRC Press: Boca Raton, FL, USA, 2018.

45. Gantmacher, F.R. *The Theory of Matrices*; American Mathematical Society: Providence, RI, USA, 1959; Volume 2.