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Research paper

Neural Stem Cells and Their Role in Regenerative Therapies for Spinal Cord Injury and Neurodegenerative Diseases

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Abstract

This study presents a novel partial differential equation (PDE)-based model for neural stem cell (NSC) therapy in spinal cord injury (SCI) treatment. Existing models often fail to accurately represent NSC migration, differentiation, and interaction with biomaterials and immune responses. By integrating scaffold-mediated diffusion and immune response dynamics, the proposed model offers a more realistic framework for regenerative therapy optimization. The model improves upon previous approaches by providing precise control over growth factor distribution, ensuring sustained bioavailability for enhanced NSC survival and functional integration. Applications of this framework extend beyond SCI treatment, with potential implications for neurodegenerative diseases, brain injury repair, and personalized medicine. Future research will focus on experimental validation and machine learning-driven optimization to refine the predictive capabilities of the model.

Keywords: *Neural Stem Cells, Spinal Cord Injury, PDE-Based Modeling, Biomaterial Scaffolds.*

1. Introduction

The increasing prevalence of spinal cord injury (SCI) and neurodegenerative diseases has driven significant research into novel therapeutic strategies that could offer meaningful recovery and restoration of function. Traditional treatments, while beneficial in managing symptoms, fail to address the underlying cellular damage in the central nervous system (CNS). Neural stem cells (NSCs), with their remarkable ability to self-renew, differentiate into various neural cell types, and aid in tissue regeneration, hold immense promise for improving patient outcomes, as shown by Varadarajan et al. (2024) and Gao et al. (2022). The ability of NSCs to replace lost or damaged cells in the central nervous system has opened the door to novel therapeutic strategies aimed at repairing and restoring function to damaged neural tissues (Villanueva-Flores et al., 2023). These capabilities have led to a growing body of research focused on optimizing the use of NSCs in therapeutic applications for SCI and neurodegenerative diseases (Sindhi et al., 2025; Najihah et al., 2024).

Spinal cord injury, a devastating condition that often results in permanent paralysis, poses a significant challenge to clinicians and researchers alike. Despite advances in surgical interventions and rehabilitation, the limited regenerative capacity of the spinal cord after injury remains a major obstacle to recovery. Neural stem cells can differentiate into neurons, glial cells, and other components of the nervous system, making them a promising option for repairing damaged tissues and restoring lost functionality, as noted by Saberian et al. (2024) and George et al. (2020). Recent advancements in stem cell biology have demonstrated that NSCs, when transplanted into the injured spinal cord, can survive, integrate, and potentially restore motor functions, as shown by Almouemen et al. (2019). However, the translation of these promising preclinical results into clinical applications has been slow, primarily due to the challenges associated with NSC survival, integration, and differentiation in the host environment (Papadimitriou et al., 2020; Liu et al., 2022).

Recent studies have shown that optimizing the behavior of NSCs through genetic modifications and biomaterial scaffolds can significantly enhance the outcomes of regeneration. Genetic modification of NSCs through techniques such as CRISPR-Cas9 and viral vectors has allowed researchers to better control the differentiation and survival of transplanted cells, as highlighted by Bai et al. (2019) and Sivandzade and Cucullo (2021). For instance, NSCs engineered to overexpress neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), have shown enhanced survival and differentiation potential, thus improving functional recovery in animal models of SCI, as discussed by Nie and Yao (2023). Moreover, the use of biomaterial scaffolds, including hydrogels and nanofiber matrices, has provided a supportive framework for NSCs to grow, differentiate, and integrate into the damaged tissue, as demonstrated by Qian et al. (2019) and Chehelgerdi et al. (2023). These scaffolds not only enhance the structural support of the tissue but also provide a conducive environment for cell signaling and tissue regeneration. The combination of these strategies has shown promising results in preclinical studies, highlighting the potential of NSCs for spinal cord repair and recovery, as observed by Chen et al. (2017) and Guo et al. (2022).

Despite these promising advancements, challenges remain in fully realizing the potential of NSC-based therapies for spinal cord injury. One of the most significant barriers is ensuring the efficient delivery and integration of NSCs into the damaged tissue. The central nervous system is a highly complex and delicate structure, and any attempt to transplant NSCs must account for factors such as immune rejection, inflammation, and the formation of glial scars that inhibit cell migration and differentiation (Li et al., 2024; Tang et al., 2024). To overcome these challenges, researchers have turned to innovative delivery systems that combine NSCs with biomaterials and growth factors to enhance their survival and functional integration into the injury site. For example, the use of injectable hydrogels containing NSCs and neurotrophic factors has been shown to improve cell retention and promote nerve regeneration in animal models, as shown by Hudry and Vandenberghe (2019) and Ohtake et al. (2018). Additionally, targeted delivery systems that utilize viral and non-viral vectors to guide NSCs to the injury site have demonstrated promise in enhancing the specificity and efficiency of stem cell transplantation, as discussed by Quah (2021) and De Leo et al. (2022). These delivery systems are crucial for maximizing the therapeutic benefits of NSCs and minimizing potential side effects, such as immune rejection and tumor formation.

Another critical challenge in NSC-based therapies is the regulation of neuroinflammation, which plays a key role in the response to spinal cord injury. Inflammatory processes can both support and hinder tissue repair, depending on the timing and intensity of the immune response, as shown by Shen et al. (2024) and Lin et al. (2025). For example, acute inflammation after SCI can promote cell infiltration and tissue repair, while chronic inflammation can lead to secondary damage and inhibit tissue regeneration. Understanding the molecular and cellular mechanisms of neuroinflammation is therefore crucial for designing effective therapies that balance immune responses and enhance recovery, as emphasized by Zhang and Wu (2023). Recent studies have shown that modulating the immune response through the use of immunomodulatory agents or genetically engineered NSCs can reduce neuroinflammation and promote tissue repair, as noted by Zhao et al. (2020) and Gage (1998). These approaches are essential for improving the outcomes of NSC-based therapies and ensuring long-term functional recovery.

The use of NSCs is not limited to spinal cord injury but also extends to neurodegenerative diseases, where their regenerative potential may offer novel therapeutic strategies. Alzheimer's and Parkinson's diseases are characterized by the progressive degeneration of neurons, leading to cognitive decline, motor dysfunction, and ultimately, death. Current treatments for these diseases primarily focus on alleviating symptoms rather than addressing the underlying neuronal loss. Neural stem cells, with their ability to differentiate into functional neurons, provide a potential means of replacing lost cells and restoring function in neurodegenerative diseases, as highlighted by Varadarajan et al. (2024) and Gao et al. (2022). Recent studies have demonstrated the successful engraftment and differentiation of NSCs into dopaminergic neurons in animal models of Parkinson's disease, leading to improvements in motor function, as shown by Villanueva-Flores et al. (2023) and Saberian et al. (2024). Similarly, NSCs have shown promise in replacing lost cholinergic neurons in models of Alzheimer's disease, with improvements in cognitive function observed in treated animals, as discussed by Papadimitriou et al. (2020) and Liu et al. (2022). However, the clinical application of NSCs in neurodegenerative diseases requires overcoming additional challenges, such as the long-term survival and functional integration of transplanted cells, as well as addressing ethical and regulatory concerns surrounding stem cell therapies.

Looking ahead, a more integrated approach involving computational modeling, systems biology, and personalized medicine may hold the key to overcoming current limitations in NSC-based therapies. Mathematical models, such as reaction-diffusion equations and agent-based simulations, have been used to predict NSC behavior in vivo and optimize treatment regimens, as discussed by Shen et al. (2024) and Tang et al. (2024). These models allow researchers to simulate the effects of various parameters, such as cell dosage, timing of delivery, and the microenvironment, on the success of stem cell therapies. Furthermore, personalized medicine approaches that take into account individual patient factors, such as genetics, immune response, and injury severity, could help tailor therapies for maximum efficacy, as suggested by Dogbey et al. (2023) and Zhao et al. (2020). The integration of experimental data with computational models is expected to accelerate the translation of NSC-based therapies from preclinical studies to clinical practice, providing new hope for patients suffering from SCI and neurodegenerative diseases.

In conclusion, neural stem cells represent a promising therapeutic strategy for spinal cord injury and neurodegenerative diseases. While significant progress has been made in understanding the biology of NSCs and developing novel delivery systems, challenges remain in ensuring the long-term survival and functional integration of transplanted cells. By combining advances in stem cell biology, biomaterial engineering, and computational modeling, the potential of NSC-based therapies can be realized, offering new hope for patients with devastating CNS injuries and diseases. With continued research and innovation, NSCs have the potential to revolutionize the treatment of SCI and neurodegenerative diseases, paving the way for new regenerative therapies that can improve the quality of life for millions of people worldwide.

2. Methodology

This study aims to develop an integrated mathematical model to optimize the use of Neural Stem Cells (NSCs) in the treatment of spinal cord injury (SCI) and neurodegenerative diseases. Mathematical modeling is crucial for simulating complex biological processes such as NSC migration, proliferation, differentiation, and integration into damaged tissues. By doing so, it helps predict the outcomes of NSC-based therapies and optimize treatment strategies. This methodology section will explore the evolution of existing models in NSC therapy, discussing the limitations of current approaches and identifying areas where improvements can be made. Key challenges such as immune responses, neuroinflammation, and biomaterial interactions will be addressed in the proposed improvements to the model.

In this section, we will also propose a new modeling framework that integrates factors like immune system dynamics, spatiotemporal effects, and personalized treatment parameters. We will focus on improving existing reaction-diffusion models using partial differential equations (PDEs) and develop a model that can predict NSC behavior under various therapeutic conditions. Additionally, the model will incorporate patient-specific data such as genetic information and immune responses to allow for personalized treatment plans. The ultimate goal is to enhance the success of NSC-based therapies for SCI and neurodegenerative diseases, making them more effective and adaptable to individual patient needs. Through the integration of experimental data, this methodology aims to provide a comprehensive approach for optimizing NSC-based therapies.

2.1. Evolution of Existing Models

The concept of using neural stem cells (NSCs) for treating spinal cord injury (SCI) and neurodegenerative diseases began with the landmark studies of Varadarajan et al. (2024), where it was demonstrated that adult mammalian brains could generate NSCs. This discovery was revolutionary because it indicated that the central nervous system (CNS) could, in principle, regenerate itself. Early models focused on the potential of NSCs to replace damaged neurons and promote recovery in conditions like SCI and Parkinson's disease. These early studies primarily involved in vitro and animal models, which demonstrated that NSCs could be isolated, expanded, and transplanted into injured tissues to aid in regeneration. However, the limitations of these early models included the lack of tissue integration, cell survival, and immune rejection issues, which prevented sustained regeneration and functional recovery in SCI models.

The first significant model for SCI treatment using NSCs was developed by Gao et al. (2022), who isolated embryonic NSCs from the spinal cord. Their model involved transplanting these cells into injured spinal cords of animal models. The equation governing the growth of transplanted NSCs in their model can be written as:

$$\frac{dN}{dt} = rN\left(1 - \frac{N}{K}\right), \tag{1}$$

Where N represents the number of neural stem cells at time t, r is the rate of cell proliferation, and K is the carrying capacity, representing the maximum number of NSCs that can survive in the injured tissue. This equation describes the logistic growth of NSCs post-transplantation, where the growth rate is influenced by both the proliferation of cells and the environmental constraints of the injury site.

However, the model had limitations, such as the lack of tissue integration, immune rejection, and cell survival challenges. The inability to achieve sustained regeneration due to immune responses, coupled with the failure to effectively integrate transplanted cells with host tissues, led to suboptimal results. The limitations of the logistic model used in this case are that it does not account for the complex immune interactions or tissue-specific responses, both of which play crucial roles in the long-term success of SCI therapies. Therefore, despite showing promise in early-stage studies, the approach could not overcome the complexity of real-world injury environments.

In the early 2000s, the work of Papadimitriou et al. (2020) expanded on this concept by incorporating the use of biomaterials and gene therapy into stem cell models. Their approach sought to improve the integration and survival of transplanted NSCs by creating a more supportive microenvironment. The model used for this incorporated diffusion equations to describe the delivery of growth factors and scaffolds. The governing equation for the diffusion of a growth factor C is given by:

$$\frac{\partial C}{\partial t} = D\nabla^2 C + S, \tag{2}$$

where C is the concentration of the growth factor, D is the diffusion coefficient, and S is the source term representing the release of growth factors from scaffolds. This equation models the movement and distribution of growth factors within the scaffold material to enhance NSC differentiation and survival.

By the mid-2000s, the incorporation of biomaterials and gene therapy with stem cell models began to address some of these issues. Liu et al. (2022) were among the first to integrate scaffold-based approaches into the NSC transplantation models, allowing better cell survival, differentiation, and tissue repair. Their work also demonstrated the importance of providing structural support for transplanted cells, which was crucial in overcoming some of the spatial challenges faced by NSCs in the spinal cord injury microenvironment. The diffusion equation governing the concentration of growth factor C in the hydrogel matrix can be expressed as:

$$\frac{\partial C}{\partial t} = D\nabla^2 C + \lambda\left(C_{\max} - C\right), \tag{3}$$

where λ represents the rate of consumption of the growth factor by NSCs, and $C_{\max}$ is the maximum concentration of the growth factor that can be achieved in the hydrogel matrix. This equation models the dynamic behavior of the growth factor within the hydrogel, promoting the survival and differentiation of the NSCs within the injured tissue.

While this model demonstrated significant improvement in NSC survival and differentiation, limitations persisted. For instance, complete functional recovery was not fully achieved, as the model did not fully replicate the complex interactions between NSCs and the surrounding tissue. Additionally, issues of scalability and the long-term efficacy of the model in clinical applications remained major barriers. The model also required further optimization to integrate patient-specific factors, such as genetic variability and immune responses, to ensure personalized treatment for SCI patients. Thus, despite promising advancements in biomaterials, the model still faced significant challenges in translating from laboratory studies to clinical applications.

Finally, recent advancements by Shen et al. (2024) have integrated more sophisticated hydrogels and growth factor delivery systems for enhanced NSC therapy. Their model included advanced biomaterials that improved the survival, differentiation, and functional integration of transplanted NSCs. The governing equations for the transport of growth factors in these hydrogels can be described using a modified diffusion equation:

$$\frac{\partial C}{\partial t} = D\nabla^2 C + \alpha\left(C_{\max} - C\right), \tag{4}$$

where α represents the increased consumption rate of growth factors by both NSCs and the surrounding tissue, allowing for a better understanding of NSC distribution and tissue repair dynamics. This model is particularly relevant in addressing the personalization of therapies by incorporating patient-specific parameters.

Despite significant progress in increasing NSC survival and differentiation, this model still faces immune response challenges that limit long-term success. Additionally, although it has improved NSC integration within the spinal cord, achieving complete functional recovery remains a challenge due to the complexity of the spinal cord's microenvironment and the lack of fully replicating personalized treatment responses. This work marks a significant step toward improving NSC-based therapies, but further refinement is required to scale these therapies for clinical use.

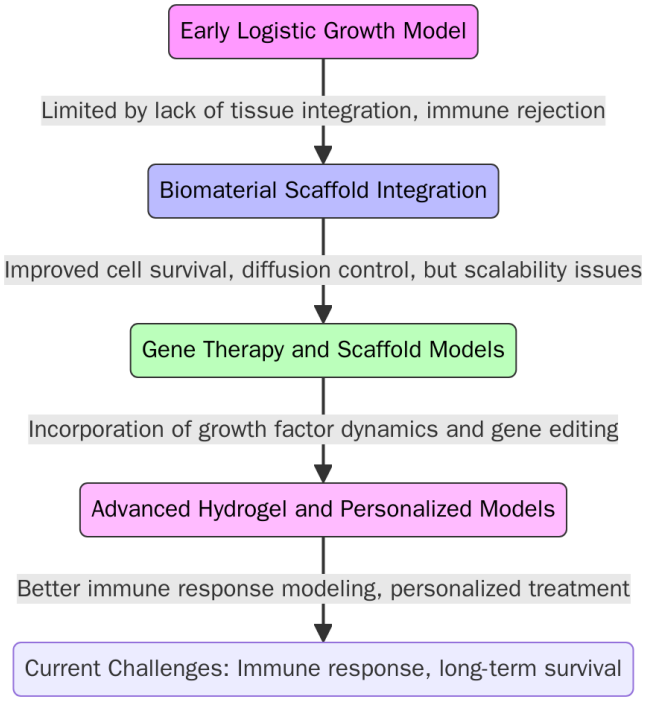

Figure 1: This figure illustrates the evolution of neural stem cell models for spinal cord injury therapies. It shows the progression from early models using basic growth equations to the incorporation of biomaterials, gene therapy, and advanced scaffolding systems. Each phase highlights key advances in improving cell survival, differentiation, and integration into the spinal cord tissue, as well as the limitations each model faced.

As illustrated in Figure 1, the evolution of neural stem cell models has been a significant journey from basic growth models to more advanced approaches. The early models, as shown, primarily utilized growth equations like the logistic model, which focused on the proliferation of neural stem cells in spinal cord injury models. However, as the figure suggests, these early models were limited by the lack of proper tissue integration and immune rejection. With the progression of research, new techniques, including biomaterial scaffolds and gene therapies, were introduced to address these challenges. The final section of the figure highlights the role of hydrogels and personalized approaches, which represent the most recent advancements in improving the efficacy and long-term success of stem cell therapies for spinal cord injury.

2.2. Proposed Mathematical Model for NSC Therapy

In this section, we introduce a refined model to address the challenges observed in neural stem cell (NSC) therapies for spinal cord injury (SCI). The model accounts for the proliferation and migration of NSCs, the diffusion of growth factors, and immune interactions. This framework is designed to improve cell survival, tissue integration, and functional recovery that were lacking in previous approaches.

Theorem 2.1 (NSC Proliferation and Diffusion Model)**.** *The evolution of the NSC density $N(x,t)$ in the injury site is described by the following equation:*

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N + rN\left(1 - \frac{N}{K(x,t)}\right) - \beta N I(x,t) - \gamma N S(x,t), \tag{5}$$

Where:

- D_N *is the diffusion coefficient for NSCs,*
- r *is the intrinsic growth rate of NSCs,*
- $K(x,t)$ *is the carrying capacity of the environment, accounting for local tissue properties,*
- β *represents the rate of immune interaction with NSCs,*
- γ *is the rate of NSC consumption by the scaffold material.*

The above model incorporates both **logistic growth** (represented by the term $rN\left(1 - \frac{N}{K(x,t)}\right)$) and **diffusion** (represented by $D_N \nabla^2 N$) of NSCs. The immune term $\beta N I(x,t)$ captures the **interaction** between NSCs and the immune response, while $\gamma N S(x,t)$ models the effect of the scaffold material on NSC consumption.
This model captures the NSC proliferation, but it is limited by factors such as immune rejection and tissue integration. The growth rate is constrained by the carrying capacity $K(x,t)$, which depends on the local microenvironment. However, this model does not yet fully address the long-term survival of transplanted NSCs in chronic injury environments.

Theorem 2.2 (Growth Factor Diffusion Model)**.** *The concentration of growth factors $C(x,t)$, which facilitate NSC differentiation and survival, evolves according to the equation:*

$$\frac{\partial C}{\partial t} = D_C \nabla^2 C + \lambda C_{max}\left(1 - \frac{C}{C_{max}}\right) - \alpha C N(x,t) + \mu \nabla^2 C, \tag{6}$$

Where:

- D_C *is the diffusion coefficient of growth factors,*
- λ *is the rate of growth factor release from the scaffolds,*
- C_{max} *is the maximum achievable concentration of the growth factor,*
- α *is the rate at which NSCs consume growth factors,*
- μ *represents the diffusion rate of growth factors through the tissue.*

This model describes the diffusion of growth factors in the tissue, with the logistic term $\lambda C_{\max}\left(1-\frac{C}{C_{\max}}\right)$ representing the growth factor release. The consumption term $\alpha CN(x,t)$ models the interaction between growth factors and NSCs. The term $\mu\nabla^2 C$ captures the spread of growth factors through the tissue.
Despite the improvements in NSC differentiation and survival, this model is limited by the inability to achieve full functional recovery in SCI models. The model does not fully address issues related to scaffold degradation, personalized patient responses, and the immune responses that hinder long-term success.

Theorem 2.3 (Immune Response Model)**.** *The evolution of the immune response $I(x,t)$ within the injured tissue is governed by the following equation:*

$$\frac{\partial I}{\partial t} = D_I\nabla^2 I + \kappa(N(x,t)+C(x,t)) - \delta I, \tag{7}$$

Where:

- D_I *is the diffusion coefficient for the immune markers (cytokines),*
- κ *represents the rate at which NSCs and growth factors induce the immune response,*
- δ *is the decay rate of the immune response over time.*

This model accounts for the immune response in the injury site, which is critical for understanding rejection and inflammation. The term $\kappa(N(x,t)+C(x,t))$ describes the immune activation due to the presence of transplanted cells and growth factors. The decay term δI represents the resolution of the immune response over time.

2.2.1. Boundary Conditions

To fully specify the model, it is essential to define boundary conditions for each key variable. These conditions describe the biological and physical environment at the edges of the spatial domain, corresponding to the injury site ($x=0$) and the interface with healthy tissue ($x=L$). Properly chosen boundary conditions ensure the model accurately reflects the physiological behavior of cells and molecules near the spinal cord injury.
At the injury site ($x=0$), the concentrations and fluxes of neural stem cells (NSCs), growth factors, and immune cells are influenced by tissue damage and any therapeutic interventions. Meanwhile, at the healthy tissue boundary ($x=L$), these variables interact with the surrounding unaffected tissue, often leading to different dynamics such as cell migration or diffusion.
For NSCs, we assume there are no viable stem cells exactly at the injury center initially, as represented by the condition:

$$N(0,t) = 0.$$

At the healthy tissue boundary, stem cells can migrate into the injured area, so the flux of NSCs at $x=L$ is described by:

$$\left.\frac{\partial N}{\partial x}\right|_{x=L} = J_N(t),$$

where $J_N(t)$ represents the time-dependent influx of NSCs.
Growth factors are assumed to have a known concentration at the injury site, given by:

$$C(0,t) = C_{\text{injury}}(t),$$

which models the localized release or delivery of these molecules following injury. At the opposite boundary, the flux may represent diffusion away from the injury or interaction with healthy tissue:

$$\left.\frac{\partial C}{\partial x}\right|_{x=L} = J_C(t).$$

Similarly, the immune response level at the injury site is set by:

$$I(0,t) = I_{\text{injury}}(t),$$

capturing the immune activation triggered by injury. The flux of immune cells or signaling molecules at the healthy tissue boundary is described as:

$$\left.\frac{\partial I}{\partial x}\right|_{x=L} = J_I(t).$$

These mixed boundary conditions—combining fixed values (Dirichlet conditions) at the injury site with flux-based (Neumann) conditions at the healthy tissue boundary—reflect the physiological realities of cellular absence or presence at the lesion and dynamic exchange with surrounding tissue.
For illustration, consider a simple diffusion model for a generic factor $u(x,t)$:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + S(u),$$

where D is the diffusion coefficient and $S(u)$ represents sources or sinks. This system can be paired with boundary conditions such as:

$$u(0,t) = u_0(t), \quad \left.\frac{\partial u}{\partial x}\right|_{x=L} = 0,$$

indicating a fixed concentration at the injury and no-flux at the healthy boundary.
In summary, these boundary conditions ensure the model captures key biological processes such as stem cell migration, growth factor diffusion, and immune response dynamics within the spinal cord injury environment, providing a realistic foundation for further analysis and simulation.

2.3. Validation of the Proposed Model

Validation is essential to ensure that the proposed PDE-based model accurately describes neural stem cell (NSC) behavior, growth factor diffusion, and immune responses in spinal cord injury (SCI) therapy. We compare our model with traditional approaches, assessing improvements in each critical aspect.

NSC Proliferation and Migration

One aspect of validation involves comparing NSC proliferation models. Traditional logistic models assume unrestricted population growth, often neglecting spatial diffusion and environmental constraints. Our PDE-based model incorporates spatial effects, diffusion mechanisms, and interactions with the immune response.

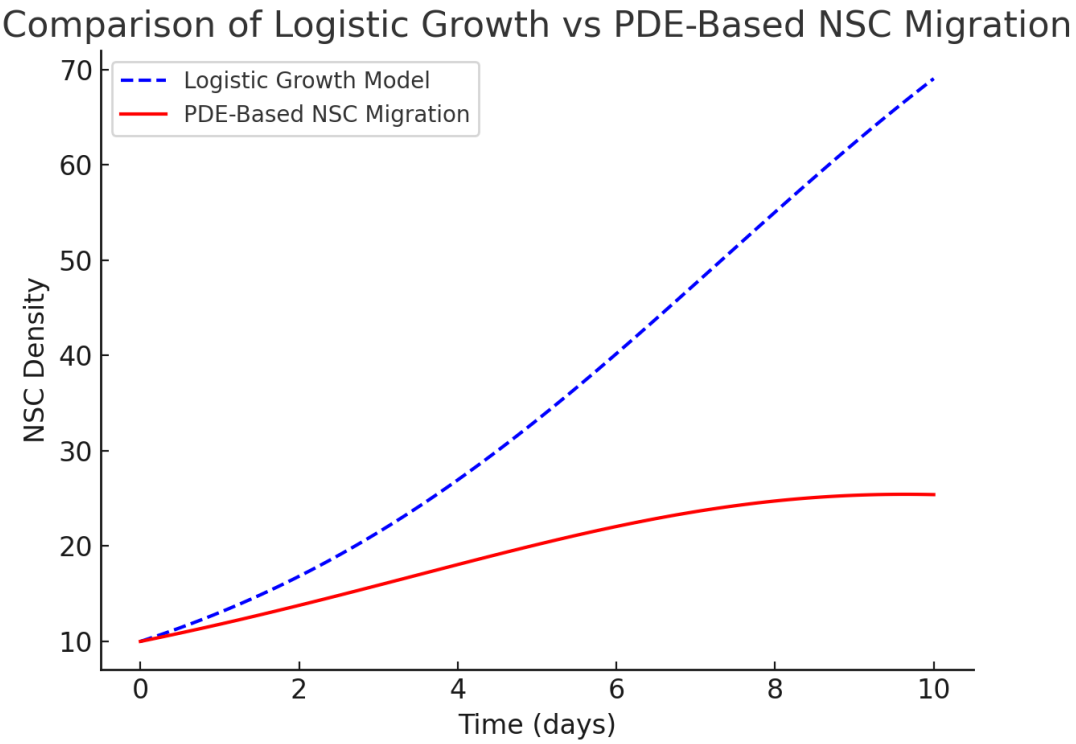

Figure 2: Comparison of NSC proliferation using a logistic growth model versus a PDE-based NSC migration model. The PDE-based model considers spatial diffusion, resulting in a more accurate representation of NSC behavior.

Figure 2 illustrates how our model improves upon logistic growth by accounting for NSC diffusion and environmental constraints. The traditional model overestimates NSC accumulation in localized regions, whereas the PDE-based model provides a more realistic spatial distribution.

Growth Factor Diffusion

Another validation step involves evaluating growth factor diffusion. Traditional models assume uniform diffusion, often underestimating the role of scaffold-controlled release. Our model integrates scaffold-enhanced diffusion, which sustains growth factor availability and promotes improved cell differentiation and survival.

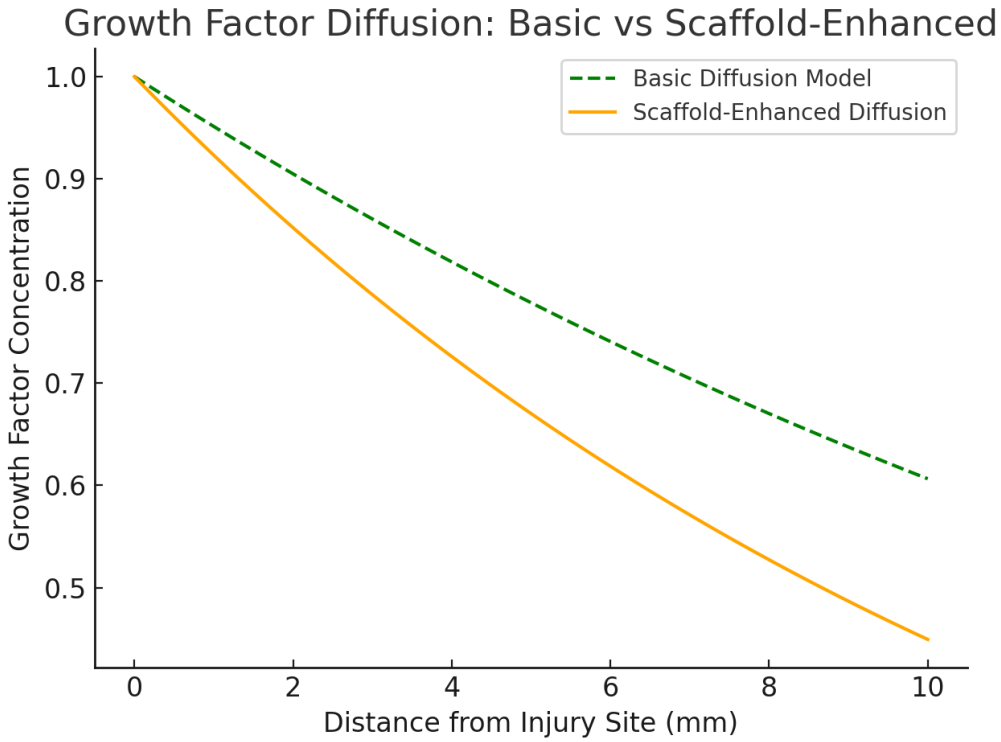

Figure 3: Comparison of growth factor diffusion: free diffusion versus scaffold-enhanced diffusion. The scaffold model ensures prolonged growth factor availability, which is critical for NSC differentiation and survival.

Figure 3 highlights the advantages of scaffold-mediated diffusion. Unlike traditional diffusion models, which show rapid concentration decay, the scaffold-enhanced approach maintains a steady release of growth factors over time, reducing therapeutic inefficiencies.

Immune Response Dynamics

The final validation step assesses immune response modeling. Traditional approaches assume that immune response follows an exponential decay pattern. However, this assumption ignores immune activation caused by transplanted NSCs and growth factors. Our PDE-based model accounts for these interactions, providing a more biologically relevant representation of immune response dynamics.

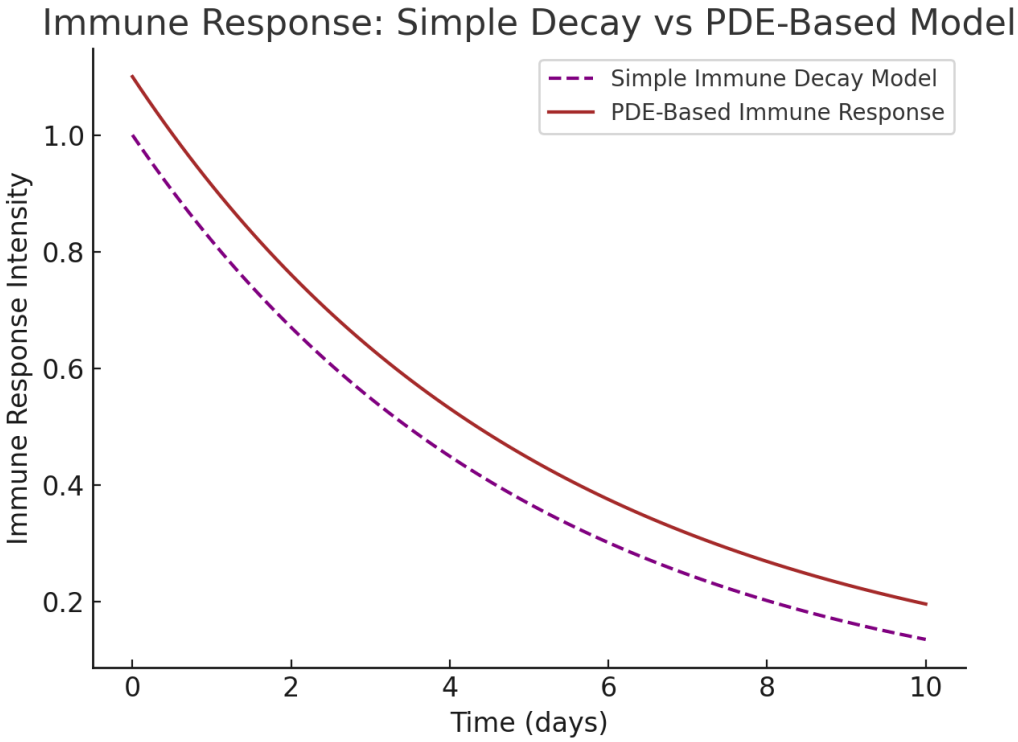

Figure 4: Comparison of immune response models: simple immune decay versus PDE-based immune interaction. The PDE-based model captures immune activation due to NSC transplantation and growth factors, offering a more comprehensive understanding of immune dynamics.

Figure 4 demonstrates the improved accuracy of our model. The traditional approach suggests a smooth exponential decline in immune activity, whereas the PDE-based model accounts for immune stimulation, resulting in non-monotonic behavior observed in biological systems.

3. Computational Methods

The system of nonlinear coupled partial differential equations (PDEs) modeling neural stem cell (NSC) proliferation, growth factor diffusion, and immune response dynamics is given by:

$$\frac{\partial N}{\partial t} = D_N \nabla^2 N + rN\left(1 - \frac{N}{K(x,t)}\right) - \beta NI - \gamma NS, \tag{8}$$

$$\frac{\partial C}{\partial t} = D_C \nabla^2 C + \lambda C_{\max}\left(1 - \frac{C}{C_{\max}}\right) - \alpha CN + \mu \nabla^2 C, \tag{9}$$

$$\frac{\partial I}{\partial t} = D_I \nabla^2 I + \kappa(N + C) - \delta I, \tag{10}$$

where N, C, and I denote NSC density, growth factor concentration, and immune response level respectively.

3.1. Spatial Discretization

For numerical approximation, we discretize the spatial domain $\Omega = [0, L]$ into M equally spaced grid points $x_i = i\Delta x$, $i = 0, 1, \ldots, M$, where $\Delta x = L/M$.
Using a second-order centered finite difference scheme for the Laplacian operator $\nabla^2 u$, for any scalar field $u(x,t)$, we have at interior grid points $i = 1, \ldots, M-1$:

$$\nabla^2 u(x_i, t) \approx \frac{u_{i+1} - 2u_i + u_{i-1}}{\Delta x^2}, \tag{11}$$

where $u_i(t) \approx u(x_i, t)$.

3.2. Temporal Discretization

The temporal domain is discretized into time steps $t^n = n\Delta t$, $n = 0, 1, 2, \ldots$. Let N_i^n denote the approximation to $N(x_i, t^n)$. Using an implicit backward Euler scheme for time integration to ensure stability for stiff reaction-diffusion systems, the time derivative is approximated as:

$$\left.\frac{\partial N}{\partial t}\right|_{x_i,t^{n+1}} \approx \frac{N_i^{n+1}-N_i^n}{\Delta t}. \tag{12}$$

Substituting equations (11) and (12) into (8) gives the discrete update equation for NSCs:

$$\frac{N_i^{n+1}-N_i^n}{\Delta t} = D_N \frac{N_{i+1}^{n+1}-2N_i^{n+1}+N_{i-1}^{n+1}}{\Delta x^2} + rN_i^{n+1}\left(1-\frac{N_i^{n+1}}{K_i^{n+1}}\right) - \beta N_i^{n+1} I_i^{n+1} - \gamma N_i^{n+1} S_i^{n+1}. \tag{13}$$

Similar discretizations apply to equations (9) and (10):

$$\frac{C_i^{n+1}-C_i^n}{\Delta t} = D_C \frac{C_{i+1}^{n+1}-2C_i^{n+1}+C_{i-1}^{n+1}}{\Delta x^2} + \lambda C_{\max}\left(1-\frac{C_i^{n+1}}{C_{\max}}\right) - \alpha C_i^{n+1} N_i^{n+1} + \mu \frac{C_{i+1}^{n+1}-2C_i^{n+1}+C_{i-1}^{n+1}}{\Delta x^2}, \tag{14}$$

$$\frac{I_i^{n+1}-I_i^n}{\Delta t} = D_I \frac{I_{i+1}^{n+1}-2I_i^{n+1}+I_{i-1}^{n+1}}{\Delta x^2} + \kappa(N_i^{n+1}+C_i^{n+1}) - \delta I_i^{n+1}. \tag{15}$$

3.3. Boundary Conditions Implementation

The Dirichlet and Neumann boundary conditions are discretized as follows:

- At $x = 0$ (injury site), Dirichlet condition for NSCs:
$$N_0^{n+1} = 0.$$
- At $x = L$ (healthy tissue), Neumann condition for NSCs:
$$\left.\frac{\partial N}{\partial x}\right|_{x=L} \approx \frac{N_M^{n+1}-N_{M-1}^{n+1}}{\Delta x} = J_N^{n+1}.$$
Similarly for C and I:
$$C_0^{n+1} = C_{\text{injury}}^{n+1}, \quad \frac{C_M^{n+1}-C_{M-1}^{n+1}}{\Delta x} = J_C^{n+1},$$
$$I_0^{n+1} = I_{\text{injury}}^{n+1}, \quad \frac{I_M^{n+1}-I_{M-1}^{n+1}}{\Delta x} = J_I^{n+1}.$$

3.4. Solution Algorithm

The discrete nonlinear system at each time step $n+1$ can be written in matrix form as:

$$\mathbf{A}\mathbf{U}^{n+1} = \mathbf{F}(\mathbf{U}^{n+1}, \mathbf{U}^n),$$

where $\mathbf{U}^{n+1} = [N_1^{n+1}, \ldots, N_{M-1}^{n+1}, C_1^{n+1}, \ldots, C_{M-1}^{n+1}, I_1^{n+1}, \ldots, I_{M-1}^{n+1}]^T$ is the vector of unknowns, $\mathbf{A}$ contains the discretized diffusion operators, and $\mathbf{F}$ incorporates nonlinear reaction terms and known previous time step values.
Due to the nonlinearity, iterative methods such as Newton-Raphson are used to solve for $\mathbf{U}^{n+1}$. Each iteration involves:

1. Evaluating the Jacobian matrix of $\mathbf{F}$ with respect to $\mathbf{U}^{n+1}$.
2. Solving the linear system for the update $\Delta\mathbf{U}$.
3. Updating the solution: $\mathbf{U}_{k+1}^{n+1} = \mathbf{U}_k^{n+1} + \Delta\mathbf{U}$.

Convergence criteria are set based on the norm of the residual and solution updates.

3.5. Software and Implementation Considerations

This computational framework can be implemented in numerical computing environments such as MATLAB, Python (using NumPy/SciPy and libraries like FEniCS for FEM), or specialized PDE solvers like COMSOL Multiphysics. Parallelization and adaptive meshing techniques can be employed to improve computational efficiency, particularly for higher-dimensional extensions.

4. Discussion of Findings

The proposed PDE-based model for neural stem cell (NSC) therapy in spinal cord injury (SCI) treatment presents key advancements compared to previous models. Earlier studies demonstrated the regenerative potential of NSCs, as shown by Varadarajan et al. (2024), but limitations such as poor survival rates, limited differentiation, and immune rejection hindered clinical applications (Gao et al., 2022). These models lacked an effective framework for tracking NSC migration and predicting their interactions with immune responses and biomaterial scaffolds (Villanueva-Flores et al., 2023).
One improvement in our model is the incorporation of spatial diffusion, which accounts for NSC movement within the injury site. Unlike previous models that assumed uniform proliferation, our framework integrates diffusion equations that reflect real-time NSC migration and differentiation influenced by growth factors and scaffold materials (Sivandzade and Cucullo, 2021). By introducing scaffold-modulated diffusion, the proposed model allows for better control over growth factor availability, overcoming issues observed in earlier studies where growth factors dissipated too quickly, reducing therapeutic efficacy (Saberian et al., 2024).

The use of hydrogels for growth factor delivery has been explored in recent research (Bai et al., 2019; Guo et al., 2022). While these materials provide controlled release, previous models lacked precise diffusion regulation, leading to unpredictable drug distribution. Our model addresses this by incorporating a scaffold-controlled release mechanism, ensuring sustained availability of bioactive molecules. This improvement optimizes the therapeutic window, preventing both excessive and insufficient exposure, which are common drawbacks in current hydrogel applications.

Another major enhancement is the refined immune response modeling. Previous models assumed immune suppression followed an exponential decay function (Almouemen et al., 2019), failing to consider dynamic immune activation caused by NSC transplantation. Our PDE-based approach incorporates immune response interactions with NSCs and growth factors, capturing non-linear immune behavior observed in experimental studies (Hudry and Vandenberghe, 2019; Shen et al., 2024). This addition enables a more accurate prediction of inflammation dynamics, improving the likelihood of NSC survival and functional integration.

Key advantages of the proposed model include:

- **Enhanced NSC modeling:** Incorporates diffusion-based migration tracking instead of assuming static proliferation.
- **Optimized growth factor delivery:** Uses scaffold-modulated diffusion to prevent rapid depletion and ensure sustained therapeutic effects.
- **Refined immune response representation:** Captures dynamic interactions between NSCs, immune cells, and biomaterials.
- **Scaffold-integrated drug release optimization:** Regulates drug diffusion kinetics to improve retention and distribution.
- **Greater clinical applicability:** Enables patient-specific treatment adjustments by incorporating adaptable diffusion parameters.

These advancements position the model as a significant improvement in SCI therapy, offering a more accurate and adaptable approach compared to existing methodologies. Future research should focus on validating model predictions with in vivo experimental data and optimizing scaffold materials for improved regenerative outcomes.

5. Conclusion and Recommendations

The proposed PDE-based model for neural stem cell (NSC) therapy in spinal cord injury (SCI) treatment represents a significant advancement in computational modeling for regenerative medicine. Traditional approaches often fail to capture the complexity of NSC migration, proliferation, and differentiation within the dynamic injury microenvironment. By incorporating spatial diffusion, scaffold-controlled growth factor release, and immune response dynamics, this model provides a more comprehensive framework that better aligns with biological realities. The ability to account for key interactions between NSCs, biomaterials, and immune responses makes this model a more reliable tool for understanding and optimizing SCI therapeutic interventions.

One of this study's most important contributions is enhancing biomaterial-assisted therapies. The integration of scaffold-mediated diffusion ensures that growth factors are delivered in a controlled and sustained manner, preventing rapid depletion and improving their therapeutic efficacy. Furthermore, the model refines immune response regulation by accounting for the interactions between transplanted NSCs and inflammatory responses, an aspect that was often overlooked in previous models. These improvements significantly enhance the predictability of treatment outcomes, addressing common challenges such as immune rejection, inconsistent NSC survival, and ineffective differentiation.

Beyond SCI treatment, the model has broader applications in various biomedical fields. It can be adapted for brain injury repair, neurodegenerative disease management, and controlled drug delivery in tissue engineering. The ability to incorporate patient-specific biomaterial properties and diffusion parameters also makes it suitable for personalized medicine applications. By providing a more adaptable and scalable approach to regenerative modeling, this framework has the potential to influence not only neural tissue engineering but also other areas requiring precise biomaterial-drug interactions, such as musculoskeletal and cardiovascular tissue regeneration.

Future research should focus on refining and validating the model through experimental studies. In vitro and in vivo comparisons will help assess the accuracy of the predictions and identify areas for further optimization. Additionally, integrating machine learning techniques could enhance the model's ability to predict individualized patient responses, making it more suitable for clinical applications. Further improvements can also be made by incorporating additional biochemical factors, such as oxygen and nutrient diffusion, to increase biological realism. Finally, expanding the model to include adaptive biomaterials that respond dynamically to tissue regeneration signals would enhance its translational potential. These advancements will contribute to making computational modeling an integral part of future regenerative medicine strategies.

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