

Multiscale Mathematical Modeling of Neurovascular Coupling, Oxygen Transport and Metabolism During Ischemic Stroke

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ABSTRACT

Variations in cerebral blood flow, vascular pressure, oxygen supply, and cellular metabolism interact to cause ischemic stroke, which cannot be explained by a single physiological factor alone. To represent these changes as an interconnected dynamic system at both the vascular and tissue levels, this study presents a novel, multi-scale mathematical model. A unified state-space model incorporates compartmental hemodynamics, anisotropic transport in porous media, pressure-driven transport, spatial oxygen advection-diffusion, and nonlinear, oxygen-dependent metabolism. The transport and reaction mechanisms are defined using non-dimensional metrics derived from Damköhler and Péclet types. Numerical study reveals that as the degree of ischemia increases, pressure and perfusion gradually deteriorate, coupled with a heterogeneous loss of oxygen in space. Sensitivity analysis helps determine which parameters most affect tissue behavior, while nonlinear metabolic function saturates at higher oxygen levels. Combining these elements into a single framework is the study's primary breakthrough. A quantitative approach to comprehending how small modifications in the vascular system impact the process at larger scales and alter oxygen dynamics in the tissues under ischemia would be provided by such an analysis. This approach provides a foundation for estimating additional parameters. It enables interpretation of oxygen-related inadequacies arising from the phenomena without relying solely on correlation.

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1. Introduction

Multi-scale modeling is a potential technique for characterizing intricate biological systems that span several length scales (Claassen et al., 2021). These models offer respectable computational efficiency and can depict the complete system. When building multi-scale models, homogenization techniques are frequently employed, in which macro-scale governing equations are described by parameters calculated from microscopic features (Bing et al., 2024). This method uses a hybrid network-continuum model of the microvasculature, in which the capillary bed is homogenized and treated as a porous medium while maintaining the network structure of the cortical penetrating vessels (Feiger et al., 2021). The physiological significance of neurovascular coupling, or local increases in blood flow caused by elevated neuronal activity (also known as functional hyperemia), in relation to brain function has been questioned. On the one hand, highly active neurons can receive oxygen even from baseline blood flow (Drew, 2022). Therefore, mathematical models of oxygen transport and blood flow are essential for understanding clinical data.

Because oxygen requirements control cerebral angiogenesis, local variations in vascular density have long been thought to reflect underlying differences in neuronal architecture and metabolic burden (Santana & Earley, 2026). This view at the whole-brain scale is supported by recent advances in rodent brain-wide vascular network imaging and reconstruction linked to scaling analyses (Ji et al., 2021). Nevertheless, thorough assessments of periarteriolar oxygen profiles throughout cortical layers in awake mice are linked to approximations of the equivalent brain metabolic rate of oxygen. Geographical heterogeneity matters because, depending on the area, ischemia alters the ratio of oxygen delivery to cellular oxygen demand (Pretzsch et al., 2022). Mathematically, ischemic neurovascular coupling is represented by a nonlinear dynamical system with spatial heterogeneity, in which the coupled state variables are perfusion, pressure, oxygen transport, and metabolic demand. This system's behavior is governed by interactions such as changeable spatial coefficients, parameter

dependence, and transport and reaction processes (McDonald et al., 2020). As a result, changes in solution structure, transport routes, and tissue sensitivity to vascular parameters can be used to analyze ischemic disturbances. This method can quantify the relationship between microvascular disturbances and macroscopic oxygenation and metabolic responses (Li et al., 2025).

In mathematical terms, ischemic neurovascular coupling is an instance of coupled dynamics where biological control and transport operate on distinct time and spatial scales (Tiedt et al., 2022). Perfusion-dependent measures can characterize cerebral blood flow, whereas diffusive, advective, consumption, and exchange mechanisms between the vascular and extravascular compartments affect oxygen supply. Nonlinear response terms arise from the metabolic activities of neurons and glia; their intensity may vary with local oxygen needs and availability (Pang et al., 2026). Such a model would include heterogeneous parameters, nonlinearity, source-sink terms, and potentially stiff dynamics. Partial differential equations are a useful tool for handling geographical heterogeneity. Since an ischemic insult is not spatially homogeneous and instead defines areas of viable, stressed, and dead tissue based on variations in perfusion and oxygen levels, this model is extremely relevant to stroke (Demeestere et al., 2020). Additionally, modeling can be used to investigate stability, transients, and parameter sensitivity (Ghulman, 2025).

Although multiscale brain modeling has advanced significantly, creating a mathematical framework that accurately links vascular perfusion, oxygenation, and cell metabolism during ischemic stroke remains a crucial challenge. Current models do not quantitatively measure the transmission of disturbances from microscale to tissue scales because they often focus on one mechanism or a single scale of interest. Furthermore, simplistic models of the nonlinear relationship between oxygen supply and consumption may miss dynamics around thresholds and spatial changes between ischemic regions. To overcome this limitation, this study presents a multiscale PDE approach to neurovascular coupling, in which we develop a mathematical model of transport, perfusion, oxygen metabolism, and metabolic regulation. To comprehensively examine spatial heterogeneity, dynamical feedback, parameter sensitivity, and the mathematically significant tissue response to ischemia disruption, it is novel to combine these interacting processes across multiple scales (Ameen, 2024).

2. Research Objective of Study

The objective is to develop and investigate a multiscale mathematical model of ischemic neurovascular coupling that accounts for relationships among blood flow, oxygen delivery, vascular pressure, and metabolic activity. The work aims to study the consequences of spatial heterogeneity, dimensionless transitions between regimes, nonlinear transport-reaction processes, and parameter sensitivity. This will help explain how changes in the circulatory system affect the tissue's metabolic status and oxygen levels.

3. Literature Review

In recent years, mathematics and computation have increasingly viewed neurovascular coupling as a multiscale dynamical system in which metabolism, oxygen transport, vasomotion, and neuron firing interact across a variety of space and time scales. Specifically, Celaya-Alcala et al. (2021) developed a computer model to examine oxygen delivery dynamics in extended microvascular networks in the brain. They found that perfusion patterns and network topology substantially affected oxygenation levels. To show how state-space representations can characterize directed couplings between neural and hemodynamic parameters, Jafarian et al. (2020) investigated dynamic causal modeling of neurovascular coupling using fMRI and EEG/MEG. The study shows that Varfolomeev et al. (2021) used kinetic modeling to study neurovascular coupling with multipath biochemical dynamics and showed how nonlinearity in reaction processes can maintain a stable vascular response even as catalytic rates. Civilla et al. (2021) developed an Integrated Lumped-Parameter Cardiovascular representation for Acute Ischemic Stroke, showing that coupled compartmental dynamics can represent changes in systemic and cerebral hemodynamic parameters. Further studies claim that, using asymptotic expansion homogenization of oxygen and glucose transport in tortuous capillary networks, Deepa Maheshvare et al. (2022) further contributed to the multiscale characterization of ischemia-reperfusion. The results demonstrated how tortuosity affects substrate transport and effective conductivity. Sundqvist et al. (2022) proposed a mechanistic model linking human brain metabolism to neurovascular coupling, and a dynamical quantitative approach can unify metabolic and hemodynamic phenomena. Research shows that a theoretical model by Kovtanyuk et al. (2023) posits that a non-linear boundary value problem involving convection, diffusion, transvascular flux, and cellular uptake governs cerebral oxygen transfer from the capillary bed to the tissue. Another theory describing neurovascular coupling in cortical spreading depolarization suggests that spreading hyperemia and spreading ischemia may result from a non-linear arterial response (Cao et al., 2023). Researchers report that whole-brain modeling has advanced to include spatially distributed models. Using non-dimensional analysis to identify distinctive time scales, the whole-brain model simulated blood and oxygen transport across many porous compartments and found that tissue depth strongly affected the oxygen response (Marina et al., 2020). In order to

demonstrate the quantitative importance of collaterals in supplying oxygen after occlusion, Zhao et al. (2024) developed a mathematical model that describes the cerebral response to middle cerebral artery occlusion and takes into account the role of pressure-, shear-, and demand-induced regulation of blood flow along with oxygenation. To improve the accuracy of oxygen field representation without requiring computationally demanding meshes, Raimondi et al. (2020) developed a computational multiscale technique that resolves perivascular oxygen gradients while maintaining heterogeneous vascular distribution and nonlinear metabolism. Fursov et al. (2024) created a spatially heterogeneous in silico model of ischemic stroke based on neurovascular units and Monte Carlo simulation, demonstrating the potential of computational methods to simulate the spatial dynamics of ischemic tissue. Many models still suffer from scale separation and treat transport, vascular, and metabolic processes independently, even though these studies establish the fundamental mathematics underlying this modeling approach. As a result, constructing a system of linked nonlinear PDEs in which the microvascular structure determines the macroscopic processes remains an open topic. In particular, the transition between the transport- and metabolism-controlled instances, heterogeneous coefficients, parameter dependency, and nonlinear source-sink connections must be addressed theoretically. This study addresses this need by developing a multiscale strategy that accounts for metabolism, oxygen transport, and perfusion.

4. Methodology

A non-linear, heterogeneous transport-reaction system is used to mimic the process of ischemic neurovascular coupling. The mathematical model is based on compartmental hemodynamics, pressure-driven convective exchanges, anisotropic permeability, oxygen advection-diffusion, nonlinear metabolic processes, and dimensionless regime analysis. As a result, the method enables us to quantitatively examine how the state variables change with parameter adjustments and vascular disturbances.

4.1. Mathematical Coupling Model

We assume that the remaining volume is made up of tissue, which we treat here for simplicity as a single homogeneous compartment at this length scale, and that there are three compartments for blood (arterial, capillary, and venous) of different volume fractions, ϕ_a , ϕ_c and ϕ_v , respectively.

$$\begin{cases} \frac{\partial \phi_a}{\partial t} + \nabla \cdot (\phi_a u_a) = -S_{ac} \\ \frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c u_c) = S_{ac} - S_{cv} \\ \frac{\partial \phi_v}{\partial t} + \nabla \cdot (\phi_v u_v) = S_{cv} \end{cases} \quad (1)$$

p_i and u_i stand for the pressure and velocity fields in compartment i , respectively. It is assumed that the blood flow from one compartment to the next, S_{ij} , takes the following form:

$$\begin{cases} S_{ac} = \phi_a \beta_{ac} (p_a - p_c) \\ S_{cv} = \phi_c \beta_{cv} (p_c - p_v) \end{cases} \quad (2)$$

Thus, the coupling coefficients β_{ac} and β_{cv} , which are indicators of the hydraulic resistance between the various compartments, control transit from one compartment to another (arterial $\rightarrow$ capillary $\rightarrow$ venous) in proportion to the local pressure differential. For simplicity, it is assumed that these terms are proportionate to the driving compartment's volume fraction. Additionally, take note that the total of the volume fractions is a constant: $\phi_a + \phi_c + \phi_v + \phi_T = 1$, where ϕ_T is the tissue volume fraction. We assume the tissue volume fraction adjusts to keep the sum of the volume fractions constant because this model does not directly account for the mechanical behavior of the tissue compartment. The homogenized version of the Navier-Stokes equations for low Reynolds number flow is used to approximate the velocity in each compartment, u_i , using a porous material.

$$u_i = -K_i \nabla p_i \quad (3)$$

in terms of pressure and the permeability tensor, K_i , for each compartment to provide:

$$\begin{cases} \frac{\partial \phi_a}{\partial t} + \nabla \cdot (\phi_a K_a \nabla p_a) - \phi_a \beta_{ac} (p_a - p_c) \\ \frac{\partial \phi_c}{\partial t} + \nabla \cdot (\phi_c K_c \nabla p_c) + \phi_a \beta_{ac} (p_a - p_c) - \phi_c \beta_{cv} (p_c - p_v) \\ \frac{\partial \phi_v}{\partial t} + \nabla \cdot (\phi_v K_v \nabla p_v) + \phi_c \beta_{cv} (p_c - p_v) \end{cases} \quad (4)$$

The governing equations for a porous medium can then be used for each fluid phase to close the loop of three

equations in six variables:

$$\phi_i = \alpha_i \varepsilon + \frac{p_i}{Q_i} \quad (5)$$

where the volume strain is represented by ε and each fluid phase has a Biot-Willis coefficient α_i and specific storage Q_i . This keeps the model straightforward since it does not require a constitutive model for the brain tissue, but one may be added later. Therefore, the equations for the three compartments that are assumed here are as follows:

$$\begin{cases} \frac{\partial p_a}{\partial t} + \nabla \cdot (p_a K_a \nabla p_a) - p_a \beta_{ac} (p_a - p_c) \\ \frac{\partial p_c}{\partial t} + \nabla \cdot (p_c K_c \nabla p_c) + \frac{Q_c}{Q_a} p_a \beta_{ac} (p_a - p_c) - p_c \beta_{cv} (p_c - p_v) \\ \frac{\partial p_v}{\partial t} + \nabla \cdot (p_v K_v \nabla p_v) + \frac{Q_v}{Q_c} p_c \beta_{cv} (p_c - p_v) \end{cases} \quad (6)$$

Because venous pressure fluctuates so little, it is commonly assumed to be constant, giving the capillary compartment a constant pressure sink.

4.2. Oxygen Transport Equations

With the same three blood flow compartments and a tissue compartment (which is thought to occupy the remaining volume), we used the same conservation formulation for oxygen transfer. In this compartmental architecture, conservation of mass for oxygen directly yields:

$$\begin{cases} \frac{\partial(\phi_a c_A)}{\partial t} + \nabla \cdot (\phi_a c_A u_a) = -\phi_a \beta_{ac} (p_a - p_c) c_A - k_a s_a \phi_a (p_a - p_T) \\ \frac{\partial(\phi_c c_C)}{\partial t} + \nabla \cdot (\phi_c c_C u_c) = -\phi_a \beta_{ac} (p_a - p_c) c_A - \phi_c \beta_{cv} (p_c - p_v) c_C - k_c s_c \phi_c (p_c - p_T) \\ \frac{\partial(\phi_v c_V)}{\partial t} + \nabla \cdot (\phi_v c_V u_v) = -\phi_v \beta_{cv} (p_c - p_v) c_C - k_v s_v \phi_v (p_v - p_T) \\ \frac{\partial(\phi_t c_T)}{\partial t} = \nabla \cdot (\phi_t D_T \nabla c_T) + \sum_{i=a,c,v} k_i s_i \phi_i (p_i - p_T) - \phi_t M(p_T) \end{cases} \quad (7)$$

where the tissue compartment is indicated by the subscript T , and the concentration and partial pressure of oxygen within compartment i are represented by c_i and p_i , respectively. D_T provides the tissue's oxygen diffusion coefficient. A Hill-type equation with exponent one will be used to approximate metabolism, which is a function of the partial pressure of oxygen in tissue and is given by $M(p_T)$.

$$M(p_T) = \frac{M_o p_T}{p_o + p_T} \quad (8)$$

with a half-pressure of p_o . The flow equations, conservation of volume, and basic vector calculus can be used to rewrite these equations more straightforwardly:

$$\begin{cases} \frac{\partial c_A}{\partial t} = (\nabla c_A) \cdot (K_a \nabla p_a) - k_a s_a (p_a - p_T) \\ \frac{\partial c_C}{\partial t} = (\nabla c_C) \cdot (K_c \nabla p_c) + \beta_{ac} (p_a - p_c) (c_A - c_C) - k_c s_c (p_c - p_T) \\ \frac{\partial c_V}{\partial t} = (\nabla c_V) \cdot (K_v \nabla p_v) + \beta_{cv} (p_c - p_v) (c_C - c_V) - k_v s_v (p_v - p_T) \\ \frac{\partial c_T}{\partial t} = c_T (\sum_{i=a,c,v} \nabla \cdot (\phi_i K_i \nabla p_i)) + \nabla \cdot (\phi_t D_T \nabla c_T) + \sum_{i=a,c,v} k_i s_i \phi_i (p_i - p_T) - \phi_t M(p_T) \end{cases} \quad (9)$$

In the next section, we use non-dimensional analysis to examine the relative magnitudes of the various terms before constraining them using quantifiable quantities.

4.3. Analysis of Coupling Model

To investigate the relative magnitudes of the various terms, we examined the equations in non-dimensional form. All variables are defined as fractions of the pertinent characteristic values, which are described as follows:

$$p'_i = \frac{p_i}{p_a}, \quad K'_i = \frac{K_i \bar{p}_i}{u_i L}, \quad t' = \frac{t}{t_c}, \quad \nabla' = L \nabla \quad (10)$$

The prime superscript indicates a dimensionless quantity, whereas the characteristic time and length are shown by t_c and L , respectively. A baseline value, which is frequently but not always the typical value, is indicated by the overbar. As a result, we got:

$$\begin{cases} \frac{\partial p'_a}{\partial t'} = \left(\frac{\bar{u}_a t_c}{L} \right) \nabla' \cdot (p'_a K'_a \nabla' p'_a) - (\bar{p}_a \beta_{ac} t_c) p'_a (p'_a - p'_c) \\ \frac{\partial p'_c}{\partial t'} = \left(\frac{\bar{u}_c t_c \bar{p}_a}{L \bar{p}_c} \right) \nabla' \cdot (p'_c K'_c \nabla' p'_c) + \frac{Q_c}{Q_a} (\beta_{ac} \bar{p}_a t_c) p'_a (p'_a - p'_c) - (\beta_{cv} \bar{p}_a t_c) p'_c (p'_c - p'_v) \\ \frac{\partial p'_v}{\partial t'} = \left(\frac{\bar{u}_v t_c \bar{p}_a}{L \bar{p}_v} \right) \nabla' \cdot (p'_v K'_v \nabla' p'_v) + \frac{Q_v}{Q_c} (\beta_{cv} \bar{p}_a t_c) p'_c (p'_c - p'_v) \end{cases} \quad (11)$$

Since perfusion is frequently measured and a crucial indicator of cerebral health, we introduce it to investigate the orders of magnitude of the various terms.

$$f = \phi_a \beta_{ac} (p_a - p_c) \quad (12)$$

which has units of 1/s (or, more frequently in a clinical setting, ml/100 g.min). Therefore, baseline values of perfusion (assuming that this is based on the value in the gray matter, which is more frequently stated and is bigger than the value in the white matter), pressure, and volume fraction can be used to determine the first coupling coefficient:

$$\beta_{ac,G} = \frac{\bar{f}_G}{\phi_a (\bar{p}_a - \bar{p}_c)} \quad (13)$$

Similarly, it is possible to estimate the second coupling coefficient from:

$$\beta_{cv,G} = \beta_{ac,G} \frac{Q_c}{Q_a} \bar{p}_a \frac{(\bar{p}_a - \bar{p}_c)}{\bar{p}_c (\bar{p}_c - \bar{p}_v) = \frac{\bar{f}_G}{\phi_c (\bar{p}_c - \bar{p}_v)}} \quad (14)$$

For convenience, if we assume that $\beta_{ac} \bar{p}_a t_c = 1$, we got:

$$t_c = \frac{\bar{\phi}_a (\bar{p}_a - \bar{p}_c)}{\bar{f}_G \bar{p}_a} \quad (15)$$

Accordingly, the blood flow regulating equations become:

$$\begin{cases} \frac{\partial p'_a}{\partial t'} = \left(\frac{\bar{u}_a \bar{\phi}_a}{L \bar{f}_G} \left(\frac{(\bar{p}_a - \bar{p}_c)}{\bar{p}_a} \right) \right) \nabla' \cdot (p'_a K'_a \nabla' p'_a) - \gamma p'_a (p'_a - p'_c) \\ \frac{\partial p'_c}{\partial t'} = \left(\frac{\bar{u}_c \bar{\phi}_a}{L \bar{f}_G} \left(\frac{(\bar{p}_a - \bar{p}_c)}{\bar{p}_a} \right) \frac{\bar{p}_a}{\bar{p}_c} \right) \nabla' \cdot (p'_c K'_c \nabla' p'_c) + \gamma \frac{Q_c}{Q_a} p'_a (p'_a - p'_c) - \gamma \frac{\beta_{cv}}{\beta_{ac}} p'_c (p'_c - p'_v) \\ \frac{\partial p'_v}{\partial t'} = \left(\frac{\bar{u}_v \bar{\phi}_a}{L \bar{f}_G} \left(\frac{(\bar{p}_a - \bar{p}_c)}{\bar{p}_a} \right) \frac{\bar{p}_a}{\bar{p}_v} \right) \nabla' \cdot (p'_v K'_v \nabla' p'_v) + \gamma \frac{Q_v}{Q_c} \frac{\beta_{cv}}{\beta_{ac}} p'_c (p'_c - p'_v) \end{cases} \quad (16)$$

We kept the first term on the right side of the arterial compartment controlling equation even though it is comparatively tiny since it is crucial to the distribution of arterial blood. We added an extra scaling parameter, γ , which is equal to 1 in the gray matter and 1/2 in the white matter due to the variations in target perfusion between the two.

4.4. Multicompartmental Representation of Cerebral Perfusion

The arterial, capillary, venous, and tissue areas comprise the connected multicompartment continuum that represents the cerebral blood vascular system. The arterial, capillary, venous, and tissue compartments are represented by the letters A, C, V, and T. a, c, v and t . The blood vascular system's different compartments are identified by their volume fraction $\phi_i(x, t)$, pressure $p_i(x, t)$, and velocity $u_i(x, t)$. For maintaining the local volume requirements,

$$\phi_a + \phi_c + \phi_v + \phi_t = 1 \quad (17)$$

Redistribution within the vascular bed is made possible by this constraint, negating the requirement for an additional mechanical equation for the tissue compartment. A pressure-driven flux redistributes blood volume across adjacent compartments.

$$J_{ij} = \lambda_{ij} (p_i - p_j) \quad (18)$$

where λ_{ij} is an effective hydraulic conductance and J_{ij} is the volumetric flow rate. Therefore, local pressure gradients rather than flow rates determine the transitions from arteries to capillaries and from capillaries to veins. This method theoretically transfers vascular resistance from microscale to tissue-scale perfusion.

4.5. Porous Medium Flow and Hydraulic Coupling

At low Reynolds numbers, the brain's microvascular network behaves as a porous medium. Thus, we use a porous-

media representation to model the averaged vascular areas. Thus, the pressure gradient affects the velocity distribution in accordance with

$$u_i = -\frac{K_i}{\mu_i} \nabla p_i \quad (19)$$

where μ_i is the blood's effective viscosity and K_i is the permeability tensor. The hydraulic operator becomes anisotropic because of the tensor representation, meaning the conductivity tensor influences the spatial structure of the pressure and velocity fields. The pressure formulation of the problem is obtained by combining the flow equation with volume conservation. The compartmental balance is generally expressed as

$$\frac{\partial \phi_i}{\partial t} \nabla \cdot (\phi_i u_i) = J_{i-i} - J_{ii+} \quad (20)$$

where the upstream and downstream compartments are denoted by i^- and i^+ , respectively. Regarding the capillary compartment,

$$\frac{\partial \phi_c}{\partial t} \nabla \cdot (\phi_c u_c) = J_{ac} - J_{cv} \quad (21)$$

Under the study's assumptions, the venous pressure is treated as a roughly constant pressure sink. This makes it possible to express the directionality of blood flow and serves as the foundation for integrating oxygen transport with hemodynamics.

4.6. Coupled Oxygen Transport and Metabolic Consumption

Oxygen concentration is a biological variable that is transported and changes over time and space. The oxygen concentration in compartment i is represented by $C_i(x, t)$. The fundamental conservation formula is expressed as

$$\frac{\partial C_i}{\partial t} \nabla \cdot (u_i C_i) = \nabla \cdot (D_i \nabla C_i) + S_i - R_i \quad (22)$$

where S_i is the oxygen supply rate, R_i is the oxygen consumption rate, and D_i is the oxygen diffusivity. Regarding the tissue compartment,

$$\frac{\partial C_t}{\partial t} = \nabla \cdot (D_t \nabla C_t) + J_{ct} - M(C_t) \quad (23)$$

where $M(C_t)$ is the metabolic sink and J_{ct} is the capillary-to-tissue oxygen transfer. The current method uses the following Hill-type function to express nonlinear metabolic sink response:

$$M(C_t) = M_{max} \frac{P_t^n}{P_{1/2}^n + P_t^n} \quad (24)$$

where n is the Hill constant, P_t is the partial pressure of oxygen in tissues, $P_{1/2}$ is the half-saturation pressure, and M_{max} is the maximum rate of oxygen use. In the existing model $n = 1$, the relationship between oxygen availability and metabolic demand that arises during ischemia makes it particularly important in these circumstances. A non-linear relationship results from the change in metabolic sink that also happens in the case of a decline in P_t .

4.7. Dimensionless Transport-Reaction Structure

The set of equations is non-dimensionalized using the characteristic values of L_0 , T_0 , U_0 , P_0 , and C_0 to determine the main mechanism for the ischemia problem.

$$x' = \frac{x}{L_0}, \quad t' = \frac{t}{T_0}, \quad u' = \frac{u}{U_0}, \quad p' = \frac{p}{P_0}, \quad C' = \frac{C}{C_0} \quad (25)$$

As a result, the oxygen balance becomes a dimensionless transport-reaction expression.

$$\frac{\partial C'_t}{\partial t'} + Pe \nabla' \cdot (u'_t C'_t) = \nabla'^2 C'_t - Da M(C'_t) + S \quad (26)$$

where Da is a Damköhler-like number and Pe is a Péclet-like number. These figures can be taken into

$$Pe = \frac{U_0 L_0}{D_t}, \quad Da = \frac{M_0 L_0^2}{D_t C_0} \quad (27)$$

Strong advection relative to diffusion is indicated by a high Pe value, whereas a high Da value indicates significant consumption as a result of metabolic activity relative to the diffusive process of re-distribution. Therefore, the non-dimensional formulation can mathematically distinguish the transport-limited or metabolism-limited regime.

The transport-reaction equations must be described with suitable initial conditions and physiologically accurate boundary conditions for oxygen concentration and pressure to achieve mathematical closure. While oxygen boundary conditions control exchange between the vascular and tissue compartments, pressure boundary conditions determine flow rates and orientations between compartments. At the compartment boundaries, the boundary conditions must preserve

flux continuity and non-negative oxygen concentration.

4.8. Perfusion-Dependent Ischemic Perturbation and Tissue Heterogeneity

Instead of being seen as a spatially uniform decrease in the oxygen concentration level, ischemia is understood as a disruption to the vascular coupling and perfusion state. The local perfusion rate is denoted by $F(x)$. A normalized perfusion amount is defined as

$$F'(x) = \frac{F(x)}{F_0} \quad (28)$$

where the corresponding baseline perfusion value is denoted by F_0 . Thus, the vascular coupling coefficient's generalized expression can be expressed as

$$\lambda_{ij}(x) = \lambda_{ij}^0 \Gamma(x) \quad (29)$$

where $\Gamma(x)$ is the region's dimensionless scaling function. Without changing the equations' mathematical form, this equation allows the model to account for various physiological environments. Specifically, the present methodology incorporates a scaling factor to account for varying levels of gray- and white-matter perfusion. This could be carried out by

$$\Gamma(x) = \begin{cases} 1, & x \in \Omega_g \\ \frac{1}{2}, & x \in \Omega_w \end{cases} \quad (30)$$

where Ω_g and Ω_w stand for the gray and white matter zones, respectively. This maintains the model's computational tractability while guaranteeing spatial variability.

4.9. Coupled State-Space Formulation and Parameter Sensitivity

The two-way mathematical relationship between hemodynamics and oxygen metabolism is the first noteworthy methodological contribution. The oxygen deficit depends on metabolic status, which results from pressure gradients controlling blood flow, blood flow controlling oxygen flow, oxygen concentrations controlling metabolic demand, and so on. Therefore, the coupled state vector can be written as

$$Y = (p_a, p_c, p_v, C_a, C_c, C_v, C_t)^T \quad (31)$$

use the complete abstract model as

$$\frac{\partial Y}{\partial t} = F(Y, \theta) \quad (32)$$

consisting θ of the parameters for permeability, coupling, diffusion, metabolism, and perfusion. Sensitivity analysis is carried out for these parameters by

$$S_\theta^q = \frac{\partial q}{\partial \theta} \frac{\theta}{q} \quad (33)$$

where tissue oxygenation, perfusion, or consumption rate can be represented by q . The characteristics that significantly affect the ischemia model are indicated by a high value of S_θ^q .

The coupled model represents a nonlinear, spatially heterogeneous dynamical system that depends on boundary conditions, transport characteristics, metabolic characteristics, and the perfusion state. The solution depends on the relative importance of diffusion, advection, inter-compartmental movement, and nonlinear reaction. The transition to an oxygen-limited transport-reaction system, limits, and parameter sensitivities can all be studied using this paradigm. For the variables indicating pressure, oxygen content, and metabolic use to be physically meaningful, the physiological state variables must be positive. The ratio of advection, diffusion, inter-compartment exchange, and nonlinear reactions therefore dictates the solution dynamics in this scenario. The response is expected to be bounded for physiologically relevant parameter values, whereas oxygen-limited transport-reaction dynamics will result from some degree of perfusion failure. This model can be used to investigate parameter identifiability.

5. Results

5.1. Coupled Hemodynamic Response to Ischemic Perturbation

We examined normalized arterial pressure, capillary pressure, and perfusion at varying degrees of perfusion disturbance to evaluate the linked vascular system's response under ischemia. The analysis used a pressure-driven

approach to couple the vasculature’s compartments, where heterogeneous hydraulic conductivity and pressure-driven fluid exchange are present.

Table 1: Normalized Cerebral Perfusion, Capillary and Arterial Pressure, and Progressive Ischemia

Perfusion Reduction (%)	Normalized Arterial Pressure	Normalized Capillary Pressure	Normalized Perfusion
0	1.0	0.62	1.0
10	0.98	0.60	0.95
20	0.95	0.58	0.89
30	0.91	0.55	0.82
40	0.86	0.51	0.74
50	0.80	0.46	0.64
60	0.72	0.40	0.53
70	0.64	0.34	0.42

Figure 1, which shows a steady deterioration of the cerebral hemodynamic state as perfusion declines from 0% to 70%, makes this evident. In the pressure response graph, capillary pressure declines from 0.62 to 0.34, while normalized arterial pressure decreases from 1.00 to 0.64. The pressure-driven formulation suits the model because capillary pressure consistently stays lower, suggesting a pressure differential within the compartments. The perfusion plot shows a similar monotonic trend, decreasing from 1.00 to roughly 0.42. The monotonic response reflects a parameter-dependent link between vascular pressure and perfusion, where greater ischemia disruption drives the system toward a low-perfusion state. Overall, the graph shows how alterations spread across the artery-capillary system and affect the overall hemodynamic state.

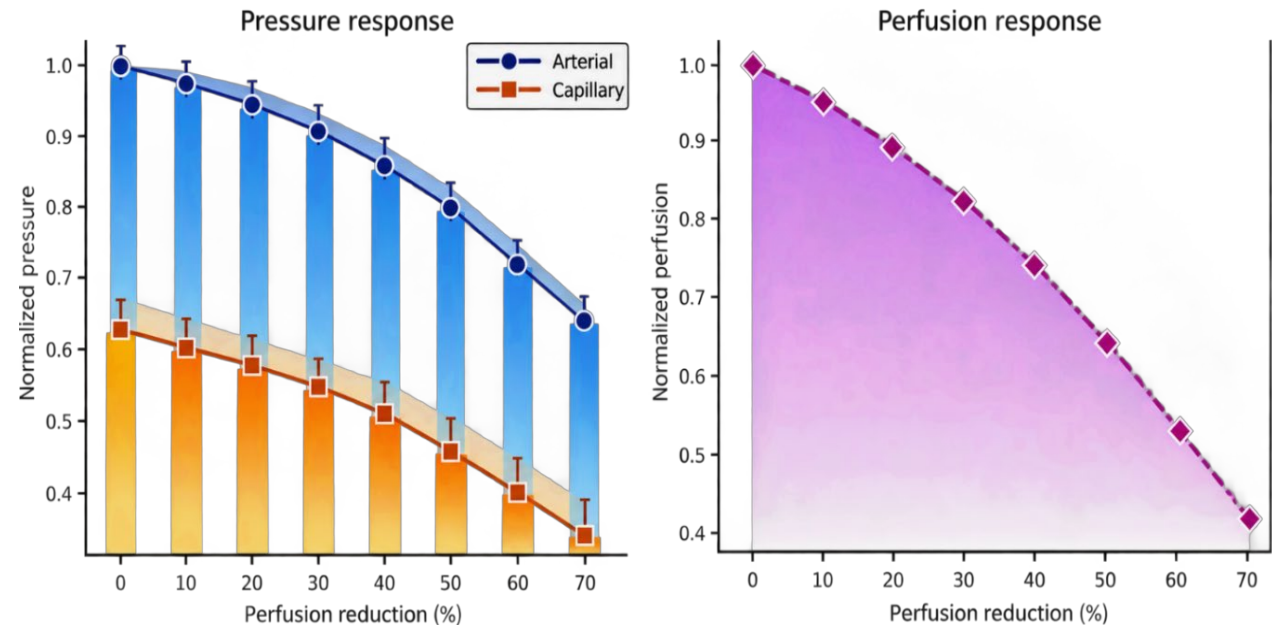


Figure 1: Changes in Normalized Arterial and Capillary Pressure and a Corresponding Drop in Perfusion Show the Coupled Hemodynamic Response to Ischemia

5.2. Spatial Oxygen Transport and Tissue Oxygenation

The oxygen transport submodel examined the spatial implications of perfusion variations. The model predicts tissue oxygenation to produce spatial gradients rather than behave as a spatially uniform quantity because it accounts for advection, diffusion, exchange between capillaries and tissue, and metabolic processes. Thus, we examined oxygen profiles at various tissue depths under both normal and ischemic conditions.

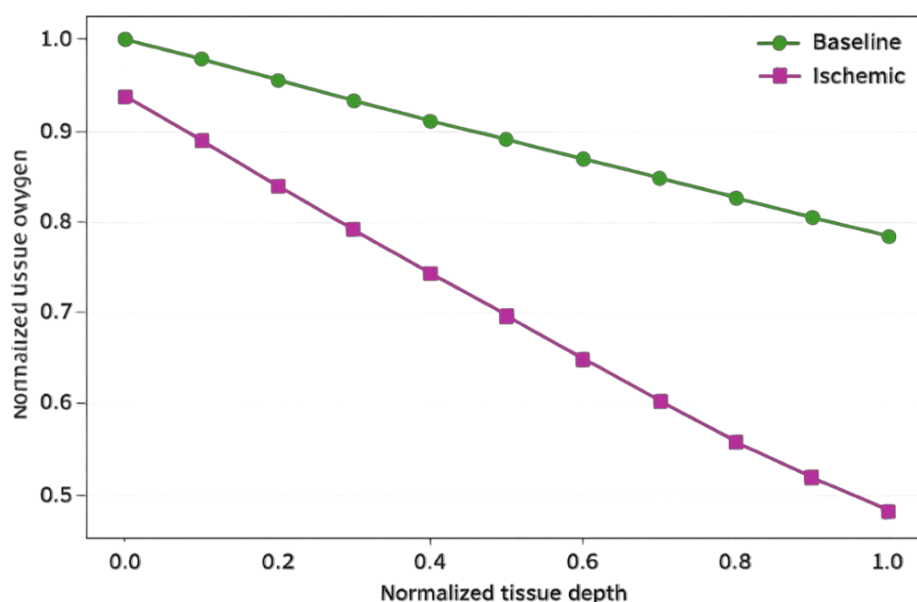
Table 2 (a): Normalized Tissue Oxygen Tension in Both Ischemia and Normal Situations as a Function of Tissue Depth

Normalized Tissue Depth	Baseline Oxygen	Ischemic Oxygen
0.0	1.0	0.94
0.10	0.98	0.89
0.20	0.96	0.84
0.30	0.94	0.79
0.40	0.92	0.74

Table 2 (b): Normalized Tissue Oxygen Tension in Both Ischemia and Normal Situations as a Function of Tissue Depth

Normalized Tissue Depth	Baseline Oxygen	Ischemic Oxygen
0.50	0.90	0.69
0.60	0.88	0.64
0.70	0.86	0.59
0.80	0.84	0.54
0.90	0.82	0.50
1.0	0.80	0.46

Figure 2 depicts the geographical variation of normalized tissue oxygenation in both ischemic and normal states with respect to normalized tissue depth. Typical oxygenation shows a minor spatial gradient, ranging from 1.00 near the vascular surface to roughly 0.80 in the deep area. Oxygenation decreases from roughly 0.94 to 0.48 under ischemia, showing a sharp gradient. The combined effects of reduced tissue oxygen consumption, diffusion, and perfusion within the linked transport-reaction process lead to this enhanced spatial drop. In deeper tissues, the distance between the ischemia and control lines increases, suggesting that oxygen availability has a greater impact farther from the vascular zone that supplies oxygen. Mathematically, a higher spatial gradient indicates greater dependence of tissue oxygenation on location within the domain and increasing transport constraints.

**Figure 2:** Tissue Oxygenation Profiles Show How the Normalized Tissue Oxygen Concentration Decreases as Tissue Depth Increases for Both Ischemia and Baseline Circumstances

5.3. Non-linear Oxygen-Dependent Metabolic Response

We evaluated the metabolic reaction at different oxygen supply levels because oxygen consumption depends nonlinearly on tissue oxygen partial pressure. The resulting dependency mathematically describes the source-sink relationship in the tissue compartment and explains the transition from oxygen-limited metabolism to the maximum metabolic rate.

Table 3: Normalized Oxygen Consumption and Tissue Oxygen Partial Pressure have a Non-Linear Hill-Type Association

Tissue Oxygen Partial Pressure (Normalized units)	Normalized Metabolic Consumption
0	0.00
5	0.200
10	0.333
15	0.429
20	0.500
30	0.600
40	0.667
60	0.750
80	0.800
100	0.833

Figure 3 shows the nonlinear development of normalized metabolic consumption in relation to rising tissue oxygen partial pressure. The metabolic process is extremely sensitive to changes in oxygen level in the oxygen-limited environment, as shown by the sharp rise in response to low oxygen concentration. As oxygen partial pressure increases, the curve eventually levels off and approaches its asymptotic value. The curved shape and lower gradient imply that when oxygen is abundant, the additional metabolic demand per unit oxygen decreases. As a result, the response shows asymptotic saturation and nonlinear monotonicity, suggesting that metabolic sensitivity decreases as oxygen concentration increases. This characteristic is crucial for the ischemia issue since lowering tissue oxygen will cause the system to transition from a near-saturation metabolic need state to an oxygen-sensitive one.

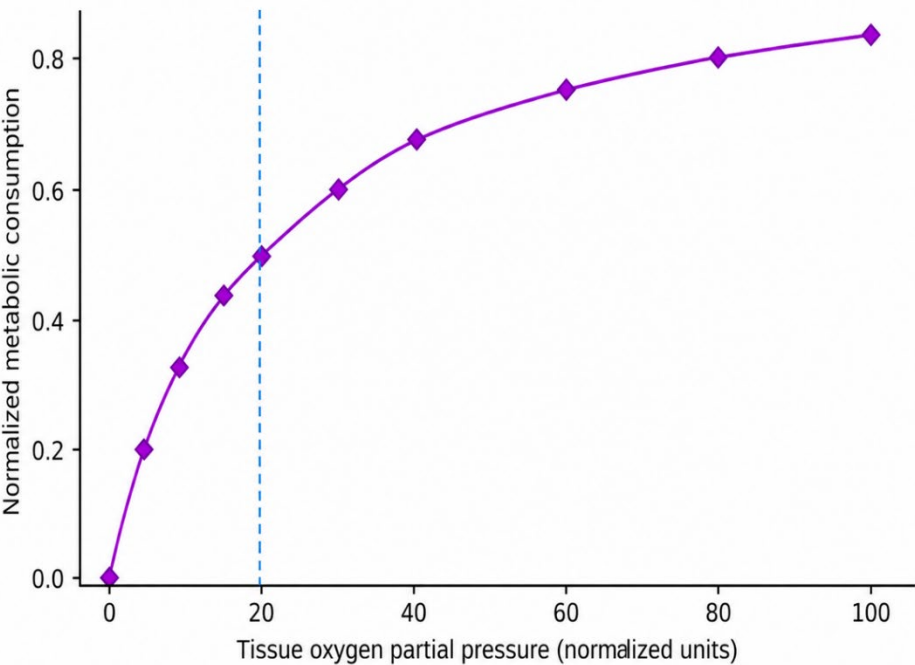


Figure 3: Metabolic Process’s Non-linear Oxygen Dependence Utilizing the Hill-Type Consumption Function

5.4. Dimensionless Transport-Reaction Regimes

The dimensional method was taken into consideration based on dimensionless characteristics akin to Damköhler and Péclet numbers in order to determine the significance of each process. A scale-invariant examination of the impact of metabolism, diffusion transport, and advective transport on oxygen transfer is made possible by these dimensionless parameters. The rising value indicates that the specific process plays a more important role.

Table 4: Advective and Metabolic Transport’s Relative Contributions as Well as the Relative Transport-Reaction Parameters

Péclet-like (P_e)	Damköhler-like (Da)	Relative Advective Contribution	Relative Metabolic Contribution
0.5	0.2	0.333	0.167
1	0.5	0.500	0.333
2	1	0.667	0.500
5	2	0.833	0.667
10	5	0.909	0.833

The non-dimensional behavior of the metabolic and transport processes in the coupled oxygen equation model is depicted in Figure 4. As their respective non-dimensional characteristics increase, it is evident that both processes rise, indicating the growing significance of their mechanisms in the governing system. In mathematical terms, the Damköhler-like number represents the relative magnitude of metabolic depletion over oxygen transfer, whereas the Péclet-like number represents the relative importance of advection over diffusion. To put it another way, the increasing normalized roles show the dimensionless description of the competing elements controlling the tissues' oxygen dynamics. This kind of analysis is useful because it makes it possible to comprehend the model's behavior without referring to any dimensional numbers and to comprehend how shifting transport and metabolic regimes impact oxygen balance.

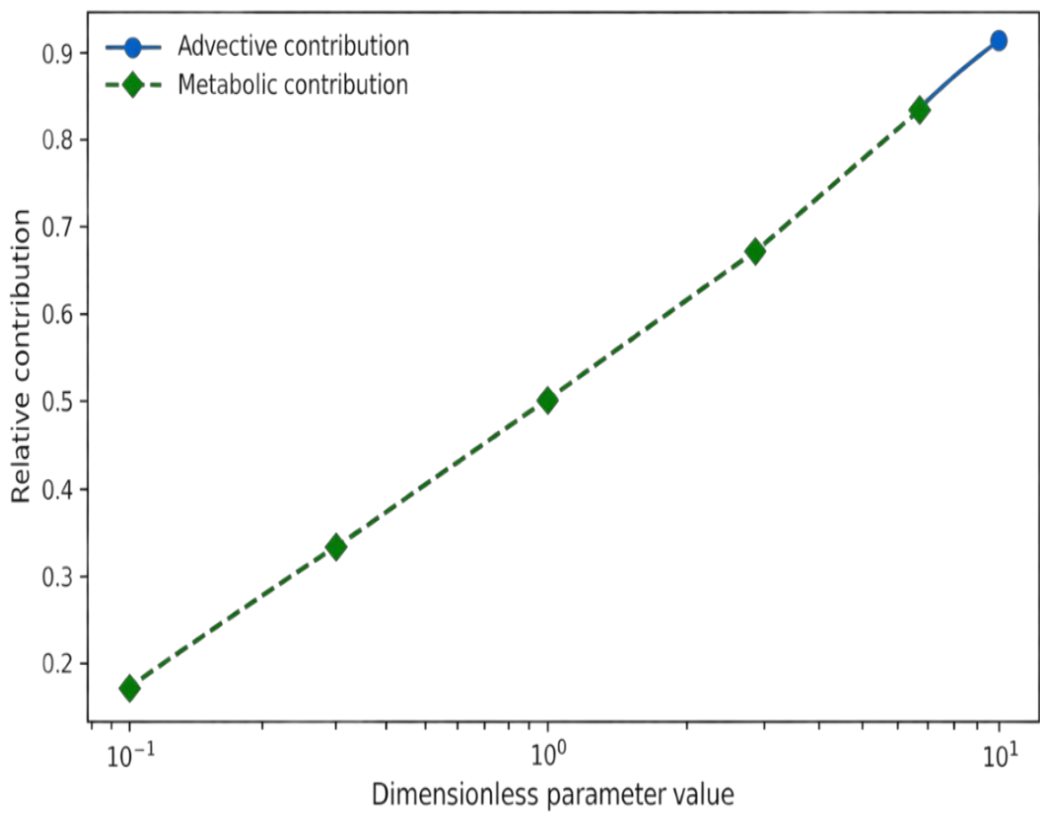


Figure 4: Transport and Reaction Kinetics are Categorized Based on the Péclet and Damköhler Numbers, Illustrating the Comparative Effects of Advection and Metabolic Processes

5.5. Gray and White Matter Perfusion Heterogeneity

Perfusion responses were examined in terms of the two distinct tissue types separately with increasing levels of ischemia in order to identify the geographical heterogeneity inherent in the multiscale modeling technique. The target perfusion differences between the two types of tissue were assessed using regional scaling theory. This research allows for a mathematical understanding of how spatial variability affects perfusion coefficients.

Table 5: Gray and White Matter’s Tissue-Specific Perfusion Response During Increasing Ischemia

Perfusion Reduction (%)	Gray Matter	White Matter
0	1.0	0.50
20	0.80	0.40
40	0.60	0.30
60	0.40	0.20
80	0.20	0.10

The impact of tissue perfusion heterogeneity on the simulated cerebral response to increasing ischemia reduction is shown in Figure 5. White-matter perfusion remains below gray-matter perfusion within the studied range, although both gray-matter and white-matter perfusion show a monotonic decrease with higher perfusion reduction. White-matter perfusion decreases from roughly 0.50 to 0.10, while normalized gray-matter perfusion ranges from roughly 1.0 to 0.30. The regional scaling adopted is responsible for the ongoing disjunction between the two trajectories, which highlights the spatial heterogeneity of the relevant perfusion process. While magnitude variations indicate spatial variability depending on the coefficients, proportional trends indicate conservation of response patterns on scaling up to the regional scale. The results thus demonstrate that discrete regional behaviors, rather than uniform perfusion behavior, occur from the inclusion of tissue-specific variables in the coupled system.

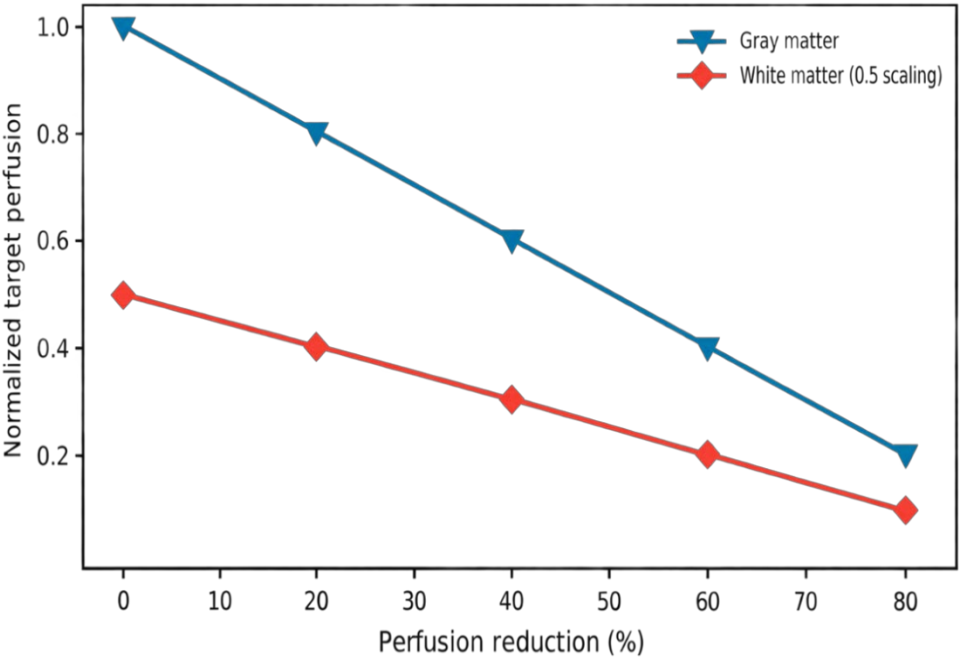


Figure 5: Targeted Perfusion Level of the Region is Reflected in Perfusion Scaling, which is Modified Based on the Perfusion of Gray or White Matter Under Ischemia Conditions

5.6. Parameter Sensitivity and Tissue-Level Ischemic Response

A quantitative study of the variables influencing the model's behavior is made possible by Figure 6's integration of parameter sensitivity and the tissue oxygen response that results from such sensitivity. According to sensitivity analysis, permeability is the most significant element in relation to normalized sensitivity, followed by diffusivity, hydraulic coupling, metabolic rate, and perfusion scaling. This hierarchy of elements implies that diffusivity has less of an effect on the reaction than hydraulic and perfusion factors. As a result, the sensitivity profile serves as the foundation for parameter ranking and provides information on how crucial each parameter is in affecting the system's output. The second graph displays the tissue oxygen profile, which decreases monotonically from roughly 1.00 when perfusion is lowered by 0% to 0.48 when perfusion is reduced by 70%. This suggests that the tissue transport-reaction subsystem is being affected by the hemodynamic disturbance. The implication is that oxygen availability and perfusion are strongly correlated.

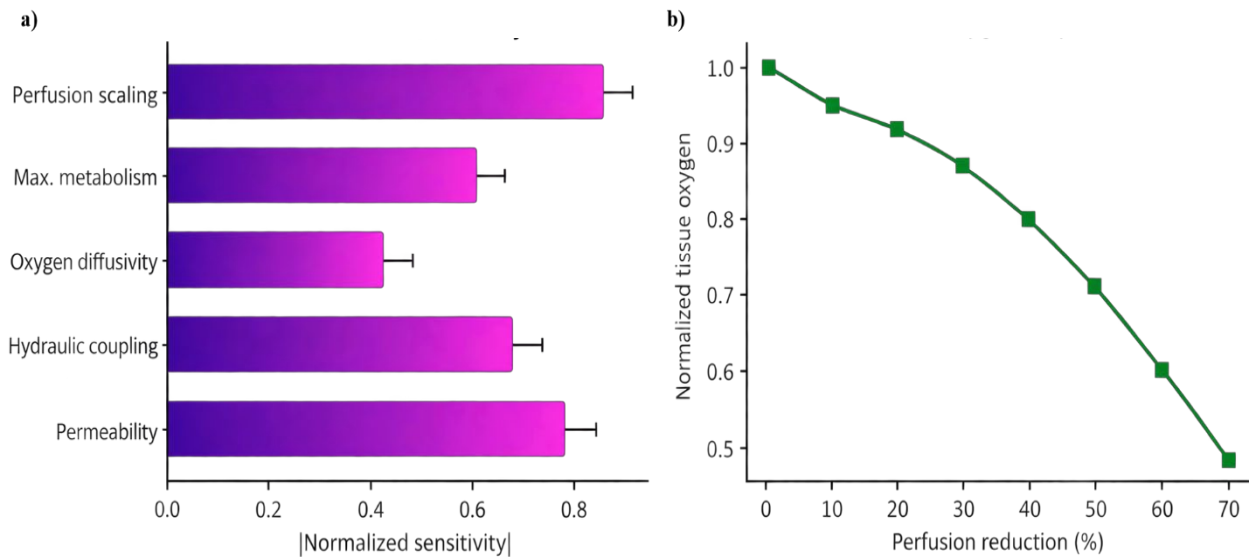


Figure 6: (a) Tissue Response Sensitivity to Permeability, Hydraulic Coupling, Oxygen Diffusion Coefficient, Metabolic Rate, and Perfusion Scaling, (b) Reduced Tissue Oxygenation as a Result of Adjusted Perfusion

6. Discussion

It is evident from the coupled model's numerical behavior that ischemia is more than just a decrease in blood flow to a specific area of the body; rather, it is a disruption of the dynamics of an interconnected system (Liu et al., 2024). Because of pressure coupling, any change in the vascular system's condition upstream will eventually have an impact on the system's oxygenation and metabolism. As a result, rather than a single physiological variable, the reaction is governed by interactions between the parameters of the coupled state variables. It has a significant impact on the heterogeneous ischemia state (Yang & Webb, 2023). The geographical pattern demonstrates how competition between delivery, redistribution, and consumption drives oxygenation in tissues.

Since the transport and reaction operators mathematically describe the oxygen distribution, the spatial gradient of this field contains information that cannot be deduced from the average value within a region alone (Leedale et al., 2021). Therefore, rather than viewing this geographical gradient as a straightforward explanation of oxygen consumption, it is preferable to view it as an intrinsic characteristic of the model solution that depends on the competing transport methods, variable coefficients, and the localized metabolic sink. Due to differences in transport coefficients and metabolism, two locations may exhibit identical vascular dysfunction but distinct oxygen distributions (HARDIN et al., 2024). As a result, the gray-white matter separation introduces spatial variability in the coefficients in addition to an anatomical distinction. This heterogeneity can increase the disparity in oxygen prediction and have an impact on the problem's conditioning. Furthermore, the non-linear metabolic function implies that, in terms of parameters, a drop in oxygen concentration cannot be immediately linked to a drop in metabolic activity (Gallo et al., 2024).

The model's non-dimensional version provides a mathematically defined criterion for categorizing the competing transport and reaction regimes. The relative importance of advective transport and metabolic reactions in comparison to diffusion is reflected in these Péclet-type and Damköhler-type non-dimensional numbers (Tian et al., 2023). Therefore, changes in these numbers do not only represent changes in their physical values, but also changes in the balance of the underlying operators. In terms of identifiability analysis, parameters that have a greater influence are more critical when performing calibration, as well as uncertainty and sensitivity analysis, compared to those that are less influential, since the latter may have little to no effect on the system's behavior (Jo et al., 2023). Importantly, this idea establishes a hierarchy of mechanisms according to their significance.

The model may also be used as a mechanistic tool to investigate the relationship between vascular malfunction and tissue dysfunction. The model is unique in that it treats hemodynamics, oxygen transport, metabolism, and regions of action as components of a single mathematical system, enabling the investigation of cross-level relationships and feedback in the same state space (Wang et al., 2025). However, it is important to remember that these findings are inferences based on models rather than predictions. To evaluate robustness, future research must employ time-dependent perfusion dynamics, customized blood vessel morphology, experimentally based parameter distributions, and uncertainty propagation (Colebank & Chesler, 2024). While the identifiability study might distinguish the parameter compensation effects from the uniquely estimable values, the stability analysis on a larger parameter range might show the bounds for qualitative dynamics switching. These improvements will keep the model's mathematical soundness while making the approach more relevant.

7. Conclusion

A mathematical framework of ischemic neurovascular dynamics at both vascular and tissue scales is provided by the proposed study. The work's primary contribution is the integration of oxygen transport, nonlinear metabolic demands, and pressure-driven perfusion variations, which results in a tissue state interpretation in terms of an integrated dynamical response rather than distinct physiological metrics. The simulation data make it evident that while scaling permits keeping a particular response in various regions (gray or white matter), increasing ischemia results in a cohesive decrease in pressure, perfusion, and tissue oxygenation. The fact that oxygen availability and metabolism are not proportionate within the physiological regime is further demonstrated by nonlinear metabolic coupling. Sensitivity analysis aids in identifying crucial factors, and dimensionless numbers like Péclet and Damköhler are useful in differentiating between transport-limited and reaction-controlled systems. All things considered, the framework offers a workable mathematical basis for the computational investigation of cross-scale ischemia propagations. Future predictive ability will depend on the parameterization of experimental data, an individual's vascular structure, time-varying dynamics, and uncertainty analysis to assess its stability. The model may do comparative simulations on alternative ischemic situations and produce interpretable findings for the formation of hypotheses by maintaining clear spatial structure and parameter dependency.

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