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Hybrid simulation model to study impact of oxygen variability on cellular mechanisms after brain injury

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ABSTRACT

Background: Maintaining adequate oxygen supply is crucial for the proper functioning of the brain, as disruptions in oxygen homeostasis can lead to severe consequences in brain-damaged conditions.

Aims: This study investigates the dynamics of oxygen levels in cells affected by various forms of brain damage, estimating oxygen concentration and the corresponding damage to give overall view between oxygen concentration and brain damage.

Methods: The present paper is a hybrid technique connecting computational engineering and brain medicine. A complete simulation method describing the oxygen distribution in brain and damage occurred due to decreasing oxygen concentration.

Results: The results of this study reveal complex and multifaceted alterations in oxygen homeostasis following brain damage, while initial hypoxic conditions are commonly observed, the data also suggest the subsequent development of localized regions of hyperoxia, potentially due to disruptions in the delicate balance of oxygen supply and demand. These findings shed light on the dynamic and heterogeneous nature of oxygen regulation in the injured brain, with important implications for the understanding of pathological mechanisms and the development of targeted therapeutic strategies.

Conclusion: The insights gained from this research contribute to the growing body of knowledge on the critical role of oxygen in brain function and provide valuable guidance for future investigations and clinical interventions aimed at mitigating the devastating consequences of brain damage.

KEYWORDS: Oxygen diffusion, brain damage, cellular mechanisms, oxygen homeostasis.

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INTRODUCTION

The brain is an extremely metabolically active organ, relying on a continuous supply of oxygen to meet its high energy demands [1]. Disruptions in oxygen homeostasis can have severe consequences for brain function and lead to various neurological disorders, including traumatic brain injury, ischemic stroke, and neurodegenerative diseases [2]. Understanding the complex dynamics of oxygen regulation in brain-damaged cells is crucial for the development of effective therapeutic strategies. Recent studies have shed light on the multifaceted nature of oxygen alterations in the injured brain. Acute hypoxic conditions are commonly observed in the initial stages of brain damage, leading to metabolic disturbances and cell death [3]. However, emerging evidence suggests that the disruption of the delicate balance between oxygen supply and demand can also result in localized regions of hyperoxia, further exacerbating the pathological processes [4]. Advancements in imaging techniques and real-time monitoring have enabled researchers to investigate the spatiotemporal dynamics of oxygen levels within the brain, revealing the heterogeneous and dynamic nature of these alterations [5]. Coupled with investigations into the underlying cellular and molecular mechanisms, these findings have the potential to inform the development of targeted interventions aimed at restoring oxygen homeostasis and mitigating the devastating consequences of brain damage [6-7]. Meshfree collocation numerical method is one of the most recent meshfree methods to solve applied problems, such as oxygen diffusion in sike cells [8-10]. The advantages of such methods gives accurate results compared with other numerical methods as well as its flexibility to simulate and solve problems with difficult and irregular geometries which very close to brain geometry. Researchers in various medical fields typically deal directly with patients' real-life experiences, although the field of applied numerical analysis has entered many different life sciences. With the tremendous development of computing systems, we find that many numerical analysis methods have entered various fields of science, including medicine in its various branches. The dynamics of the human body and the dynamics of its internal structure enable a mathematical model for each part. In the current research, we created a comprehensive

mathematical model that simulates the oxygen concentration in brain cells and the damage resulting from oxygen deficiency [11-13]. This study aims to further elucidate the complex oxygen-related changes in brain-damaged cells, utilizing a comprehensive experimental approach to provide insights into the pathophysiology and potential therapeutic strategies. Oxygen Homeostasis in the Brain The brain is a highly metabolically active organ, requiring a continuous supply of oxygen to meet its energy demands. Intricate mechanisms are in place to maintain oxygen homeostasis within the brain, involving the coordination of cerebral blood flow, oxygen delivery, and cellular utilization [14]. Disruptions in this delicate balance can lead to severe consequences for brain function. Hypoxic Conditions in Brain Damage In the context of brain damage, such as traumatic injury, ischemic stroke, or neurodegenerative disorders, the initial stages are often characterized by hypoxic conditions [15]. The reduced oxygen supply, resulting from compromised cerebral blood flow or impaired oxygen delivery, leads to metabolic disturbances, oxidative stress, and eventually cell death [16]. Numerous studies have investigated the cellular and molecular mechanisms underlying this hypoxic response, including the activation of hypoxia-inducible factors, disruption of mitochondrial function, and the initiation of apoptotic pathways [17]. Emergence of Hyperoxic Regions While the initial hypoxic state has been well-documented, recent research has revealed the development of localized regions of hyperoxia within the injured brain [18]. This phenomenon has been observed in various models of brain damage, including traumatic brain injury and ischemic stroke. The proposed mechanisms underlying this hyperoxic response involve the disruption of the delicate balance between oxygen supply and demand, leading to an uncoupling of cerebral blood flow and metabolic activity. The presence of these hyperoxic regions may further exacerbate the pathological processes, contributing to oxidative stress and secondary injury [19]. Spatiotemporal Dynamics of Oxygen Alterations The complex and heterogeneous nature of oxygen alterations in the injured brain has been the subject of ongoing investigation. Advancements in imaging techniques and real-time monitoring have enabled researchers to study the spatiotemporal dynamics of oxygen levels within the brain [20]. Implications for Therapeutic Interventions Understanding the intricate mechanisms underlying oxygen regulation and alterations in brain-damaged cells is crucial for the development of targeted therapeutic strategies [21]. Interventions aimed at restoring oxygen homeostasis, such as the modulation of cerebral blood flow, optimization of oxygen delivery, or the manipulation of cellular oxygen sensing and utilization pathways, have the potential to mitigate the devastating consequences of brain damage. Ongoing research in this field continues to provide valuable insights that may inform the design of innovative treatments and improve patient outcomes.

MATHEMATICAL FORMULATION

Equations describing spatiotemporal dynamics of oxygen concentration in brain tissue with associated boundary and initial conditions are as follow [22]:

$$\partial C/\partial t = D\nabla^2 C - M(C) + S(x,t) \quad (1)$$

$C(x,t)$: Oxygen concentration at position x and time t

D: Diffusion coefficient of oxygen in brain tissue

$\nabla^2 = \left(\partial^2/\partial x^2 + \partial^2/\partial y^2 + \partial^2/\partial z^2\right)$ Laplacian operator in 3D

M(C): Oxygen consumption rate by cells (metabolism)

$S(x,t)$: Oxygen supply term (from blood vessels)

The consumption rate can be modeled using Michaelis-Menten kinetic [23]:

$$M(C) = \left(V_{\max} \times C\right)/\left(K_m + C\right) \quad (2)$$

$V_{\max}$: Maximum consumption rate

K_m: Michaelis constant (oxygen concentration at half-maximum consumption rate)

$$S(x,t) = \alpha\left(C_b - C\right) \quad (3)$$

α: Mass transfer coefficient

C_b: Oxygen concentration in blood

Initial Condition

$$C(x,0) = C_0(x) \text{ Initial oxygen distribution in the tissue} \quad (4)$$

Boundary Conditions

For a finite domain Ω representing the brain tissue:

Neumann boundary condition (no flux across the tissue boundary):

$$\partial C/\partial n = 0 \quad (5)$$

Where n is the outward unit normal vector to the boundary $\partial\Omega$

Dirichlet boundary condition (fixed oxygen concentration at blood vessels):

$$C = C_b \quad over\ \Gamma \quad (6)$$

Γ Represents the locations of blood vessels within the domain

To account for brain damage, we can introduce spatial dependence to some parameters:

$$D(x) = D_0 \times \left(1 - d(x)\right) \quad (7)$$

$$V_{\max}(x) = V_{\max,o} \times (1 - d(x)) \quad (8)$$

$d(x)$ Damage function ($0 \le d(x) \le 1$) representing the extent of tissue damage at position x

D_0, $V_{\max,o}$ are the baseline values for healthy tissue

Damage Evolution Equation

$$\partial d / \partial t = k_1 \times H(C_{cit} - C) - (k_2 \times d) \quad (9)$$

k_1 : Rate of damage accumulation

k_2 : Rate of damage repair

H : Heaviside step function

C_{cirt} : Critical oxygen concentration below which damage occurs

This system provides a details mathematical framework for modeling oxygen dynamics in brain-damaged cells. It accounts for diffusion, consumption, supply, and the effects of tissue damage on oxygen distribution and utilization. The model can be solved numerically using finite difference or finite element methods, allowing for simulations of various brain injury scenarios and potential therapeutic interventions.

Meshless collocation manipulation

The goal is to model the oxygen distribution and variability in brain tissue after an injury, focusing on cellular-level mechanisms without using a traditional mesh-based approach. For this problem, we can use a meshless collocation method such as the Radial Basis Function (RBF) method [11-13].

Approximate the concentration as follows:

$$c(\mathrm{x}, y, t) \cong \sum_{j=1}^{N_b+N_i} a_j \phi_{ij} + \sum_{j=1}^{N_b} b_j \phi_{ij},\ i = 1,2,..., N_b + N_a \quad (10)$$

Apply equation (10) into equation (1), the latter will be:

$$\frac{\partial c(x,y,t)}{\partial t} = D\left(\sum_{j=1}^{N_b+N_i} a_j \nabla^2 \phi_{ij} + \sum_{j=1}^{N_b} b_j \nabla^2 \phi_{ij} \right) - M(C) + S(x,t) \quad (11)$$

Making use of forward approximation to the time differentiation in equation (11), this will leads to:

$$\frac{1}{\Delta t}\left(c^{k+1} + M^{k+1} - S^{k+1}\right) - \frac{1}{\Delta t}\left(c^{k} + M^{k} - S^{k}\right) = D\left(\sum_{j=1}^{N_b+N_i} a_j \nabla^2 \phi_{ij} + \sum_{j=1}^{N_b} b_j \nabla^2 \phi_{ij} \right)^k \quad (12)$$

c^{k+1}, c^{k} are the concentration at times $(k+1)$ and (k), Δt is the time step, N_b, N_i are boundary and internal nodes, respectively and finally, a_j, b_j are unknown constants to be determined as a major part of the proposed method. Equation (12) can now be re-written as:

$$\left(c^{k+1} + M^{k+1} - S^{k+1}\right) - \left(c^{k} + M^{k} - S^{k}\right) = D.\Delta t.\left(\sum_{j=1}^{N_b+N_i} a_j \nabla^2 \phi_{ij} + \sum_{j=1}^{N_b} b_j \nabla^2 \phi_{ij} \right)^k \quad (13)$$

Next by making use of equation (10) into the left hand side of equation (13) and collecting the terms at the same time step, leads to:

$$\left[\sum_{j=1}^{N_b+N_i} a_j \phi_{ij} + \sum_{j=1}^{N_b} b_j \phi_{ij} - (M - S) \right]^{k+1} = \left(\begin{array}{l} \sum_{j=1}^{N_b+N_i} a_j \phi_{ij} + \sum_{j=1}^{N_b} b_j \phi_{ij} + D.\Delta t \sum_{j=1}^{N_b+N_i} a_j \nabla^2 \phi_{ij} \\ + D.\Delta t \sum_{j=1}^{N_b} b_j \nabla^2 \phi_{ij} + (M - S) \end{array} \right)^k \quad (14)$$

The compact matrix form of equation (14) takes the form:

$$\left(A_{ij} a_j + B_{ij} b_j - (M - S)\right)^{k+1} = \left(C_{ij} b_j + C_{ij}^{*} b_j + (M - S)\right)^{k} \quad (17)$$

A simplified matrix will be:

$$A_{ij} b_j + B_{ij} a_j = c^{\mathrm{sol}} \mathrm{I} \quad (18)$$

Where A_{ij} and B_{ij} defined above, from equation (18), one can get:

$$a_j = B_{ij}^{-1}\mathrm{c}^{\mathbf{sol}}\mathbf{I} - B_{ij}^{-1}A_{ij}b_j \quad (19)$$

Next, let us dealing with the other boundary condition as follows:

$$\mathrm{v}_n(x,y,t)\left(c_{part}-c^{\mathrm{sol}}\right)=D\sum_{j=1}^{N_b+N_i}a_j\frac{\partial}{\partial n}\phi_{ij}+\sum_{j=1}^{N_b}b_j\frac{\partial}{\partial n}\phi_{ij},\ i=1,2,...,N_b+N_a \quad (20)$$

In a compact matrix form, equation (16) can be re-written as:

$$\Phi_{ij}a_j+\Psi_{ij}b_j=\left(\mathrm{D}^{-1}\left(\mathrm{c}^{\mathrm{part}}-\mathrm{c}^{\mathrm{sol}}\right)\right)\mathrm{v}_{\mathrm{j}} \quad (21)$$

From equation (21), one can get the unknown a_j as follows:

$$a_j=\left(\mathrm{D}^{-1}\left(\mathrm{c}^{\mathrm{part}}-\mathrm{c}^{\mathrm{sol}}\right)\right)\Phi_{ij}^{-1}\mathrm{v}_{\mathrm{j}}-\Phi_{ij}^{-1}\Psi_{ij}b_j \quad (22)$$

Equating equations (19) and (22), leads to:

$$\left(\left(\mathrm{D}^{-1}\left(\mathrm{c}^{\mathrm{part}}-\mathrm{c}^{\mathrm{sol}}\right)\right)\right)\Phi_{ij}^{-1}\mathrm{v}_{\mathrm{j}}-\Phi_{ij}^{-1}\Psi_{ij}b_j=\mathrm{c}^{\mathrm{sol}}B_{ij}^{-1}-B_{ij}^{-1}A_{ij}b_j \quad (23)$$

Simplifying equation (23), leads to:

$$b_j=\left(\left(\left(\mathrm{D}^{-1}\left(\mathrm{c}^{\mathrm{part}}-\mathrm{c}^{\mathrm{sol}}\right)\right)\right)\Phi_{ij}^{-1}\mathrm{v}_{\mathrm{j}}-\mathrm{c}^{\mathrm{sol}}B_{ij}^{-1}\right)\left(\Phi_{ij}^{-1}\Psi_{ij}-B_{ij}^{-1}A_{ij}\right)^{-1} \quad (24)$$

Finally, let us deal with the boundary condition given by equation (5), leads to:

$$\frac{\partial}{\partial x}\sum_{j=1}^{N_b+N_i}a_j\phi_{ij}+\sum_{j=1}^{N_b}b_j\phi_{ij}=0,\ i=1,2,...,N_b+N_a \quad (25)$$

In a compact matrix form, equation (25) will be:

$$\mathrm{L}_{ij}a_j=\mathrm{K}_{ij}b_j,\quad \mathrm{L}_{ij}\left(N_b+N_iN_b+N_i\right)\ \&\ \mathrm{K}_{ij}\left(N_b+N_iN_b\right) \quad (26)$$

Equation (26) is a direct relation between the unknown constants a_j & b_j, then:

$$a_j=\mathrm{L}_{\mathrm{ij}}^{-1}\mathrm{K}_{ij}b_j \quad (27)$$

Now then, we have two direct system of relations for the unknown a_j and two systems for b_j one of them is direct and the other is indirect. These relations will be used in two different ways, the first is a computation purpose and the other is a check in the iterative procedure, as will be seen in the next section.

RESULTS

Oxygen dynamics following localized brain injury

A patient has suffered a localized brain injury due to a small ischemic stroke. The model used, is a one cm section of brain tissue over a 60-minute period following the injury. A one-dimensional model of brain tissue, with length 1 cm. The numerical values taken in computation for the parameters are as follows:

Parameter symbol	Parameter description	Numerical value
D	Oxygen diffusion coefficient	2×10^{-5} cm²/s
$V_{\max}$	Maximum oxygen consumption rate	5×10^{-7} mol/cm³/s
K_m	Michaelis constant	1×10^{-6} mol/cm³
C_b	Oxygen concentration in blood	5×10^{-5} mol/cm³
α	Mass transfer coefficient	0.1
C_{cirt}	Critical oxygen concentration	1×10^{-5} mol/cm³
K_1	Damage accumulation rate	0.001
K_2	Damage repair rate	0.0001

- Length of tissue $\ell = 1\ cm$
- Number of grid points $N = 100$
- Spatial resolution $\Delta x = 0.01 cm$
- Time $t = 60$ min
- Time step $\Delta t = 1\mathrm{sec}$
- Number of time steps: 3600
- Label grid points as $x_0, x_1, x_2, ..., x_{99}$
- $x_0 = 0.0\,cm$ *and* $x_{99} = 0.99\,cm$

The numerical procedure proposed is that at each time step (t), you update the value (concentration, potential, temperature, etc.) at each grid point based on your mathematical model (diffusion, reaction, etc.)

Initial Conditions

Uniform oxygen concentration $C(x,0) = 5\times10^{-5}$ mol/cm³

Localized damage at the center $d(x,0) = \exp\left\{-\left((x-0.5)/0.01\right)^2\right\}$

Boundary Conditions

No flux at boundaries $\partial C/\partial x = 0\ \big|_{x=0,x=1\text{cm}}$

At the initial time $t_0 = 0.0$, the Oxygen concentration (mol/cm³) was given as $C(x,0) = 5\times10^{-5}$ mol/cm³, while at time $t_1 = 5.0\,\text{min}, \Delta t = 1.0\,\text{sec}$, Oxygen concentration decreased to $C(x, t=5) = 4.92\times10^{-5}$ mol/cm³ and by growing up the time the Oxygen concentration decreases and reaches $C(x, t=60) = 4.73\times10^{-5}$ mol/cm³. Meanwhile, at the initial stage, there was no damage, and then started to increase from $Damage_{t=0\,\text{sec}} = 0.0$ to $Damage_{t=3600\,\text{sec}} = 0.01$. The oxygen concentration decreases rapidly in the damaged area which is the center of the tissue, oxygen level in the damaged area falls below the critical concentration C_{cirt} within the first five minutes, damage spreads slightly to neighboring regions over time and finally oxygen levels in the periphery decrease slightly due to increased demand from the damaged area. Figure (1) shown both maximum oxygen concentration and the corresponding minimum brain damages at times 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min.

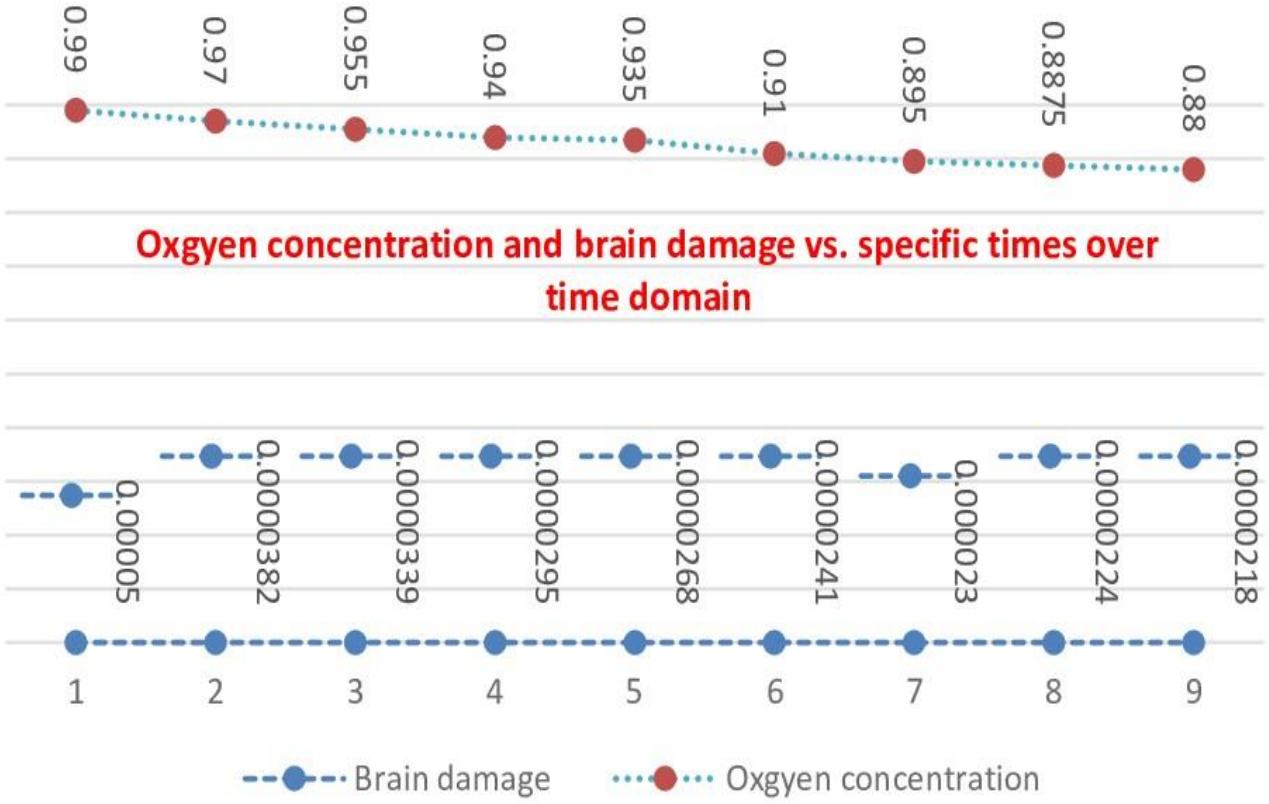

Figure 1: Maximum oxygen concentration and minimum brain damage vs. specific times 5-60 min, time interval 5 min

Traumatic brain injury (TBI)

Patient: 35-year-old male involved in a car accident, resulting in a focal Traumatic brain injury (TBI) in the left frontal lobe. Model geometry is a 2-D brain slice, with dimension 10 cm x 10 cm with grid points (100 x 100 grid points) and the simulation time is taken as 1440 minutes and finally the time step is taken as 0.1 minutes. The numerical values taken in computation for the parameters are as follows:

Parameter symbol	Parameter description	Numerical value
D_0	Oxygen diffusion coefficient in healthy tissue	$2\times10^{-5} cm^2/s$
$V_{\max,0}$	Maximum oxygen consumption rate in healthy tissue	$2\times10^{-4} mol/L/s$

K_m	Michaelis constant	$1\times10^{-3} mol/L$
α	Mass transfer coefficient	0.1
C_b	Oxygen concentration in blood	$0.2\, mol/L$
C_{cirt}	Critical oxygen concentration for damage	$0.01 mol/L$
K_1	Damage accumulation rate	1×10^{-4}
K_2	Damage repair rate	1×10^{-5}
$C_0(x,y)$	Uniform initial oxygen concentration	$0.1 mol/L$

Initial Conditions

$d_0(x,y)=0$ No initial damage

Numerical Results

Oxygen Concentration Distribution

The numerical computation started by plotting the maximum and minimum oxygen concentrations over the overall period of time 24 hours. The concentration started by the initial concentration 0.1 then increased and reached 0.1999 at the end of time, figure (2), meanwhile the concentration decreases from 0.1 to 0.00865 at the end of time.

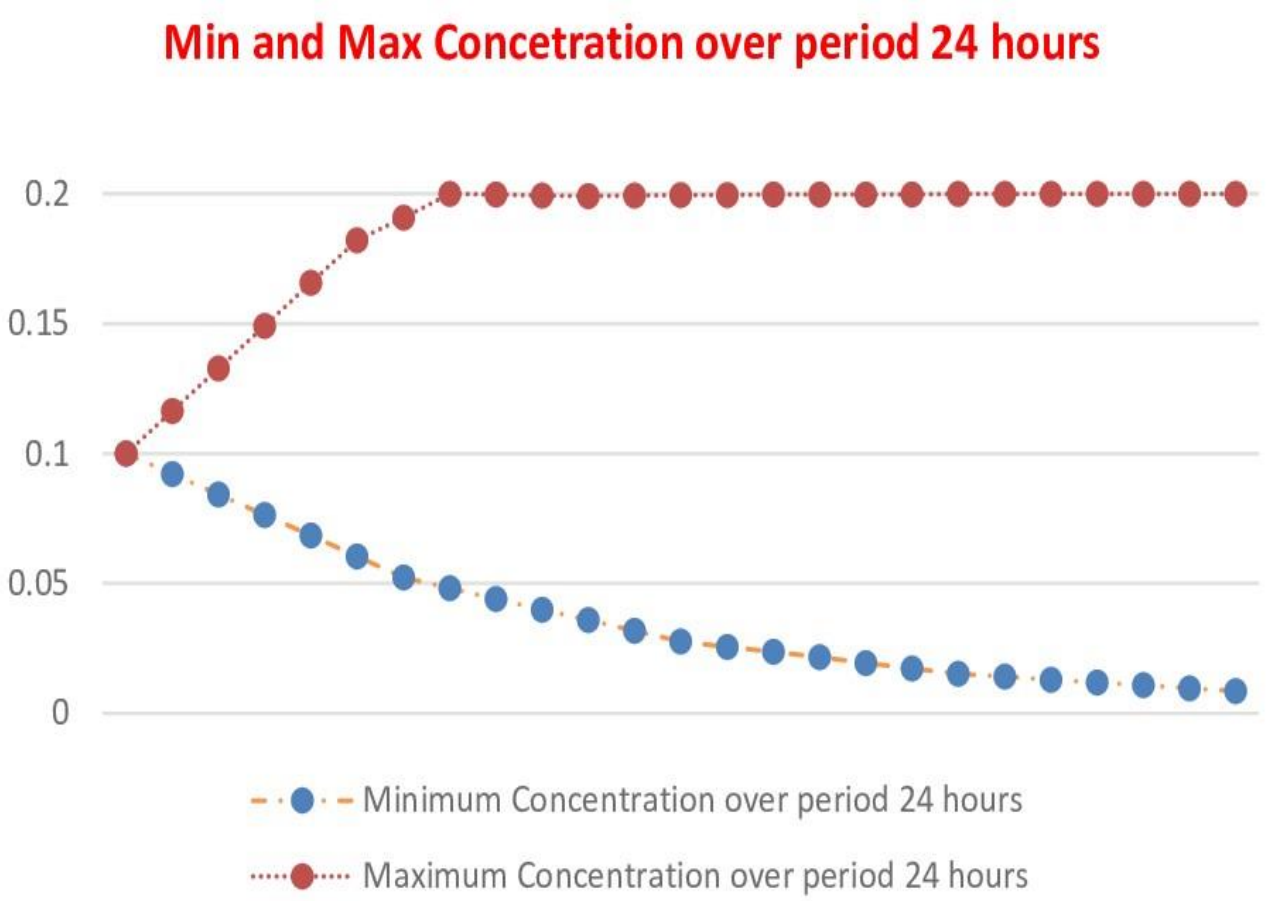

Figure 2: Overall Minimum and Maximum Oxygen Concentration Distribution over a period 24 hours

The next stage of numerical computation is the damage evolution. Also, both minimum and maximum damage evolution are plotted in figures (3), and as seen the time period stopped at time t = 6.11 at which the damage occurred was 0.0573. The overall behavior for maximum and minimum damage evolution between t = 4 hours to t = 6.11 hours are plotted in figure (3), with time step = 0.05

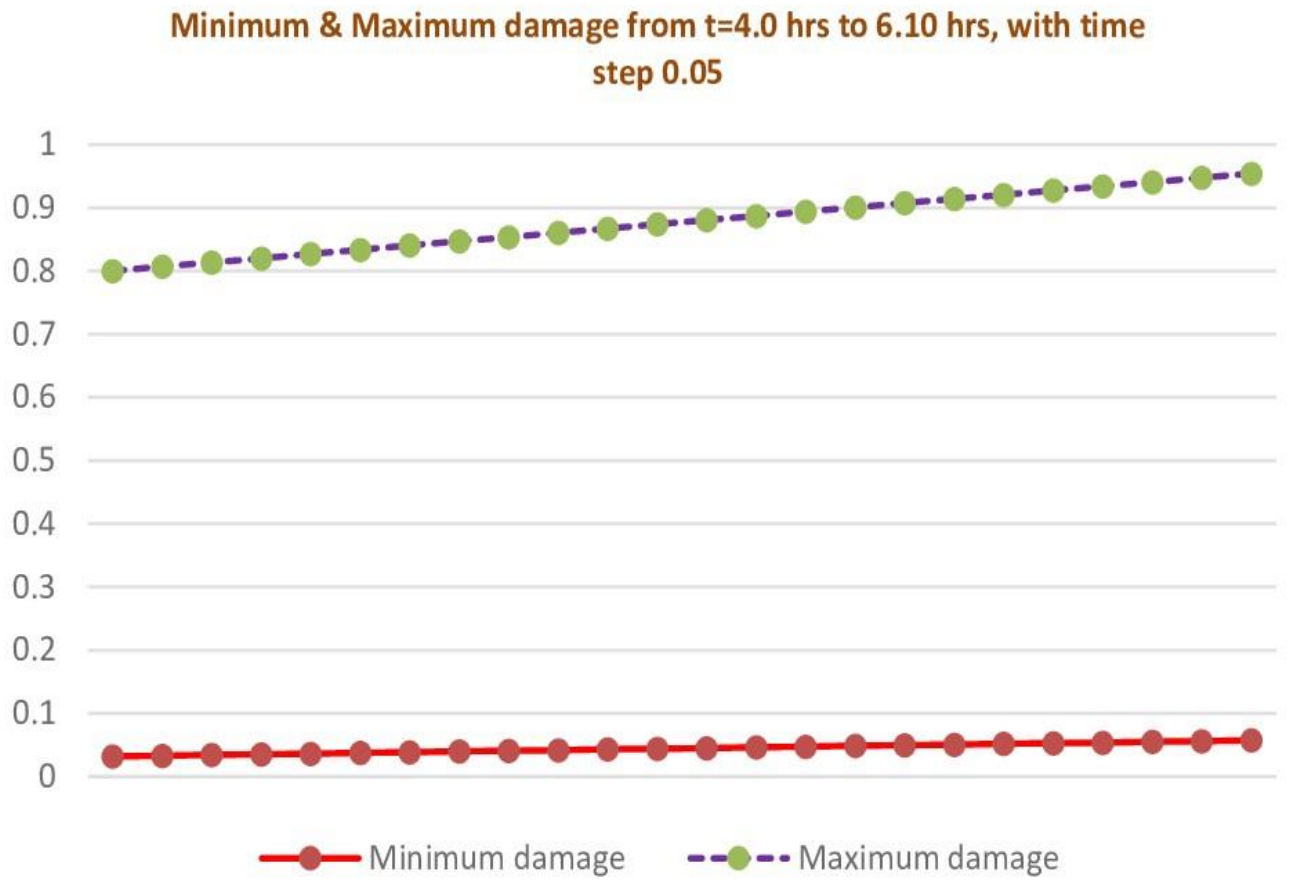

Figure 3: Minimum and maximum damages evolution

CONCLUSION

Oxygen variability following brain injury significantly impacts cellular mechanisms. Hypoxia and hyperoxia can both lead to oxidative stress, mitochondrial dysfunction, and altered neurotransmitter function, exacerbating neuronal damage. Maintaining optimal oxygen levels is crucial to support cellular recovery and minimize secondary injury. Further research is needed to refine oxygen management strategies and improve outcomes for brain injury patients.

Competing interests

I and all authors declare that there is no any competing interests.

Authors' contributions

Maysaa Ali Abdul Khaleq: validation of the data collections, review medical results from numerical computation results

Ammar Yasir Ahmed: review data, analyze numerical results

Wurood Muttalib Farhan: Draft writing

Said Gamil Ahmed: Paper main idea, design software programming for meshfree method, running numerical results, review draft writing, Final approval

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