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Nonlinear Dynamics Hopf Bifurcation and Optimal Control in a Cerebral Blood Flow Regulation Model

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Abstract

Background: Cerebral blood flow regulation is a complex physiological process involving coupled hemodynamic, biochemical, and vascular mechanisms that maintain adequate brain perfusion despite fluctuations in physiological conditions. Understanding the stability characteristics of these regulatory processes is important for identifying conditions that may lead to abnormal oscillatory blood flow dynamics.

Objective: This study aims to develop a nonlinear mathematical model of cerebral blood flow regulation, investigate its stability and bifurcation behavior, and evaluate the effectiveness of bifurcation-aware optimal control strategies.

Methods: A four-state nonlinear model describing cerebral blood flow, vessel radius, intracellular calcium concentration, and nitric oxide concentration was developed. The model incorporates fluid-mechanical effects through a nonlinear flow–radius relationship and physiological feedback mechanisms associated with vasodilation and vasoconstriction. Equilibrium solutions and stability properties were analyzed using Jacobian and eigenvalue analysis. Numerical continuation techniques implemented in MATCONT were employed to identify bifurcation points and compute limit cycles. An optimal control problem was formulated with the nitric oxide vasodilation gain as the control variable and solved using PYOMO.DAE coupled with IPOPT.

Results: The analysis revealed the existence of a Hopf bifurcation at a critical value of the nitric oxide vasodilation gain parameter. The corresponding first Lyapunov coefficient was computed as (-8.757257 \times 10^{-4}), confirming a supercritical Hopf bifurcation and the emergence of a stable limit cycle. Optimal control simulations showed that incorporating a Hopf-bifurcation-aware constraint reduced the minimized objective function from 28.84 to 23.01, representing an improvement of approximately 20.2% compared with the unconstrained case.

Conclusions: The results demonstrate that nonlinear feedback mechanisms in cerebral blood flow regulation can generate oscillatory dynamics through Hopf bifurcation. Furthermore, integrating bifurcation analysis with optimal control provides an effective strategy for improving system performance and maintaining stable cerebral perfusion. The proposed framework offers a useful approach for the analysis and control of nonlinear physiological systems exhibiting bifurcation-induced behavior.

Introduction

Cerebral blood flow regulation is a fundamental physiological process that ensures the continuous delivery of oxygen and nutrients to neural tissue despite fluctuations in systemic blood pressure and metabolic demand. The human brain, which exhibits high metabolic activity and limited energy reserves, relies critically on tightly controlled hemodynamic mechanisms to maintain stable perfusion. Disruptions in cerebral autoregulation are associated with a wide range of pathological conditions, including stroke, traumatic brain injury, hypertension, and neurodegenerative disorders. Consequently, understanding the dynamical principles governing cerebral blood flow regulation is central to both physiological modeling and biomedical engineering.

At the core of cerebral autoregulation are interacting biochemical and biomechanical feedback mechanisms that govern vascular tone. Among these, nitric oxide (NO) plays a key role as a potent vasodilator released by endothelial cells in response to shear stress induced by blood flow.NO promotes relaxation of vascular smooth muscle, thereby increasing vessel diameter and enhancing blood flow. In contrast, intracellular calcium acts as a vasoconstrictive agent by promoting smooth muscle contraction, thereby reducing vessel diameter and flow. The interaction between these opposing signaling pathways generates a highly nonlinear regulatory system in which small changes in physiological parameters can produce significant alterations in vascular behavior.

From a fluid-mechanical perspective, cerebral blood flow is strongly dependent on vessel radius via the classical Poiseuille law, which yields a fourth-power nonlinear relationship between flow rate and vessel diameter. This nonlinear dependence amplifies the effect of small changes in vascular tone and contributes to the emergence of complex dynamical behavior. Moreover, feedback interactions between flow, biochemical signaling, and vascular mechanics introduce time delays and nonlinear coupling effects

of small changes in vascular tone and contributes to the emergence of complex dynamical behavior. Moreover, feedback interactions between flow, biochemical signaling, and vascular mechanics introduce time delays and nonlinear coupling effects that cannot be captured using linearized or steady-state models. As a result, cerebral blood flow regulation is naturally formulated as a nonlinear dynamical system.

Recent advances in mathematical physiology have emphasized the importance of dynamical systems theory in understanding biological regulation. In particular, bifurcation theory provides a powerful framework for analyzing qualitative changes in system behavior as physiological parameters vary. Of special interest is the Hopf bifurcation, which marks the transition from steady-state behavior to sustained oscillations through the emergence of a limit cycle. Oscillatory dynamics in biological systems are not merely mathematical artifacts; they are often observed experimentally and can reflect either healthy regulatory rhythms or pathological instabilities depending on context. In the case of cerebral circulation, oscillatory blood flow may indicate the breakdown of autoregulatory stability or the presence of strong feedback interactions near critical thresholds.

Despite significant progress in modeling cerebral hemodynamics, many existing approaches remain limited in their ability to simultaneously capture nonlinear feedback, oscillatory dynamics, and control mechanisms within a unified framework. Linear models or purely steady-state analyses are insufficient to describe the transition to oscillatory regimes, while overly detailed physiological models often become analytically intractable. There is therefore a need for reduced-order models that retain the essential nonlinear structure while remaining amenable to bifurcation and control analysis.

In this context, the present work develops a four-state nonlinear model of cerebral blood flow regulation incorporating flow dynamics, vessel radius adaptation, calcium signaling, and nitric oxide-mediated vasodilation. The model is constructed by combining fundamental fluid-mechanical principles with simplified physiological feedback laws, resulting in a compact yet dynamically rich system. The primary objective is to investigate the emergence of oscillatory behavior through Hopf bifurcation and to characterize the stability properties of the resulting dynamics.

A key parameter in the model is the nitric oxide vasodilation gain, which governs the strength of the positive feedback loop between blood flow, NO production, and vessel dilation. This parameter is shown to play a critical role in determining system stability and serves as a natural bifurcation parameter. By systematically varying this gain, the model exhibits a transition from stable equilibrium behavior to sustained oscillations, highlighting the intrinsic nonlinear nature of cerebral autoregulation.

Beyond the analysis of intrinsic dynamics, this work also explores the interaction between nonlinear stability and optimal control. In particular, the nitric oxide gain is treated not only as a physiological parameter but also as a control input that can be manipulated to influence system behavior. This dual interpretation enables the formulation of an optimal control problem in which the objective is to regulate cerebral blood flow while accounting for the underlying bifurcation structure. The integration of bifurcation analysis with optimal control provides a powerful framework for understanding how control actions can either stabilize or destabilize physiological systems depending on their proximity to critical thresholds.

The remainder of this study is organized as follows. First, the governing equations of the four-state model are derived from physiological and fluid mechanical principles. Next, steady-state solutions are computed and their stability is analyzed using Jacobian and eigenvalue methods. Bifurcation analysis is then performed to identify Hopf bifurcation points and characterize the resulting oscillatory dynamics. Finally, an optimal control formulation is introduced to investigate how bifurcation-aware control strategies influence system performance and stability. Through this integrated approach, the study aims to provide new insights into the nonlinear dynamics of cerebral blood flow regulation and demonstrate the importance of combining dynamical systems theory with optimal control in physiological modeling.

Literature Review

Research on cerebral blood flow regulation has evolved from investigations of endothelial and neurovascular mechanisms toward sophisticated fluid-mechanical and computational models capable of describing complex cerebrovascular dynamics. The following review summarizes the major developments in chronological order [1]. Demonstrated that glutamate-induced cerebral vasodilation is mediated through nitric oxide pathways involving N-methyl-D-aspartate receptors. Their work provided early evidence that nitric oxide acts as a critical mediator linking neuronal activity and cerebral blood flow regulation. This study helped establish nitric oxide as a fundamental component of neurovascular control [2]. Investigated the role of endothelins in the cerebral circulation and showed that vasoactive peptides contribute significantly to cerebrovascular tone regulation. Their findings highlighted the complexity of biochemical signaling mechanisms involved in cerebral perfusion [3]. Examined serotonin-mediated regulation of the cerebral microcirculation and demonstrated that neurotransmitter-induced vascular responses play a significant role in matching blood supply to neural activity. This work contributed to the growing understanding of neurovascular coupling mechanisms [4]. Further explored cholinergic modulation of cerebral microvessels and showed that neural signaling pathways directly influence cerebrovascular resistance. These studies collectively emphasized that cerebral blood flow regulation involves both neural and vascular components. A major milestone was achieved by [5], who presented a comprehensive analysis of endothelial regulation and potassium-channel-mediated control of cerebral circulation. Their review established many of the physiological mechanisms that remain central to modern studies of cerebral autoregulation and vascular reactivity. (Physiological Society Online Library) [6]. Introduced transfer-function analysis as a quantitative tool for studying dynamic cerebral autoregulation. Their methodology enabled researchers to investigate the temporal response of cerebral blood flow to blood pressure fluctuations and remains widely used today [7]. Showed that nitric oxide functions as a modulator rather than a direct mediator of neurovascular coupling. Their findings refined existing theories regarding the physiological role of nitric oxide in cerebral circulation [8]. Produced one of the most influential reviews on cerebral autoregulation, summarizing the mechanisms by which cerebral vessels maintain relatively stable blood flow despite changes in systemic blood pressure. Their work became a cornerstone reference for subsequent studies [9]. Investigated the interactions between arterial pressure, intracranial pressure, and cerebral autoregulation. Their work emphasized the importance of mechanical forces in governing cerebral hemodynamics [10]. Expanded the understanding of neurovascular regulation by examining how neural pathways influence cerebrovascular tone and blood flow distribution. Their findings highlighted the integration of neural and vascular control mechanisms [11]. Reviewed contemporary methods for assessing cerebral autoregulation and provided a critical evaluation of measurement techniques used in

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both clinical and experimental settings. Their work contributed to the standardization of autoregulatory assessment [12]. Introduced the concept of the neurovascular unit as an integrated functional system composed of neurons, astrocytes, endothelial cells, and vascular smooth muscle cells. This framework significantly influenced subsequent research on cerebral blood flow regulation [13]. Reviewed the use of transcranial Doppler ultrasonography for evaluating cerebral autoregulation and demonstrated its value for investigating dynamic cerebrovascular responses. His work established transcranial Doppler as a widely accepted clinical and research tool [14]. Provided a comprehensive review of cerebral blood flow regulation mechanisms, emphasizing the interactions among metabolic, neural, endothelial, and myogenic pathways. Their work highlighted the multifactorial nature of cerebral autoregulation [15]. Investigated cerebral autoregulatory responses to blood pressure challenges and demonstrated the importance of dynamic regulatory mechanisms in maintaining cerebral perfusion. Their work highlighted limitations of traditional static autoregulation concepts [16]. Presented a landmark integrative review that synthesized metabolic, pressure-mediated, and autonomic mechanisms governing cerebral blood flow. They argued that cerebral autoregulation should be viewed as an integrated physiological process involving interactions among blood gases, neural activity, and cardiovascular function rather than a single isolated mechanism. [17]. examined the contribution of vascular smooth muscle contraction to cerebral autoregulation using mathematical modeling approaches. Their work demonstrated how biomechanical processes help maintain stable cerebral perfusion [18]. Developed a mathematical model describing interactions between baroreflex regulation and cerebral autoregulation. Their study illustrated the importance of coupling systemic cardiovascular regulation with cerebrovascular control mechanisms [19]. Reviewed bedside assessment techniques for cerebral autoregulation and emphasized their clinical significance in neurocritical care applications. Their findings demonstrated the translational importance of autoregulatory monitoring [20]. Highlighted the growing role of mathematical and computational approaches in understanding cerebral hemodynamics. His review emphasized the need for reduced-order models capable of capturing essential physiological dynamics while remaining computationally tractable [20]. Proposed advanced modeling methodologies for cerebral hemodynamics and autoregulation, introducing system-identification techniques that improved the quantitative characterization of cerebrovascular responses [22]. Further advanced mathematical modeling of cerebral blood flow control by integrating physiological mechanisms with computational approaches capable of predicting autoregulatory responses under varying conditions [23]. Reviewed the clinical application of cerebral autoregulation monitoring and highlighted its importance in neurological disorders, traumatic brain injury, and critical care medicine. Their work demonstrated the increasing clinical relevance of autoregulatory assessment [24]. Integrated clinical, biological, and computational perspectives to develop a mechanistic framework for cerebral autoregulation. They emphasized the importance of decomposing autoregulatory processes into distinct physiological timescales to improve clinical decision-making and predictive modeling [25].Reviewed recent advances in computational modeling of cerebral blood flow regulation and highlighted emerging opportunities for combining physiological data with mathematical modeling techniques [26]. Proposed multiscale mathematical models that link cellular, vascular, and systemic regulatory processes. His work emphasized the importance of integrating multiple physiological scales within a unified computational framework [27].

Reviewed advances in cerebral autoregulation monitoring and modeling, demonstrating how modern computational techniques are improving the understanding of cerebrovascular function in both healthy and pathological conditions [28]. Developed a computational fluid-mechanical model of myogenically active cerebral arterial networks. Their framework coupled vascular wall mechanics with blood flow dynamics to investigate how pressure changes propagate through cerebral arterial trees and influence autoregulatory responses. This work represents a significant step toward realistic fluid-mechanical modeling of cerebral circulation [29]. Investigated computational models of cerebral arterial network autoregulation, focusing on the interaction between vascular mechanics and blood flow redistribution. Their work further strengthened the connection between fluid mechanics and cerebral autoregulation research. Recent studies by [30]. Introduced integrated numerical frameworks combining partial differential equations, ordinary differential equations, and vascular network models to simulate cerebral autoregulation under physiologically realistic conditions. These studies demonstrated how modern computational fluid dynamics and multiscale modeling can improve understanding of cerebrovascular regulation and support future clinical applications. More recently, [31]. Employed in silico modeling and synthetic data generation to investigate cerebral autoregulation mechanisms, demonstrating the growing importance of computational and mathematical approaches for understanding cerebral blood flow regulation.

Overall, the literature demonstrates a clear progression from physiological investigations of endothelial and neurovascular mechanisms in the 1990s to sophisticated computational and fluid-mechanical models in recent years. Despite these advances, relatively few studies have combined cerebral blood flow regulation models with nonlinear bifurcation analysis and optimal control theory. This gap motivates the present work, which seeks to integrate physiological modeling, fluid mechanics, bifurcation analysis, and optimal control within a unified framework for cerebral blood flow regulation.

Main Objectives of This Work

The primary objective of this work is to develop a reduced-order yet physiologically meaningful dynamical model of cerebral blood flow regulation that captures the essential nonlinear interactions responsible for vascular stability and oscillatory behavior. In particular, the model aims to represent the coupled feedback mechanisms between blood flow, vessel radius, intracellular calcium concentration, and nitric oxide signaling within a unified mathematical framework. By combining fluid-mechanical principles, such as the nonlinear dependence of flow on vessel radius, with simplified biochemical regulation laws, the model is designed to reproduce key qualitative features of cerebral autoregulation while remaining analytically and computationally tractable.

A second objective is to investigate the system's nonlinear dynamical behavior using bifurcation theory. Special emphasis is placed on identifying parameter regimes that lead to qualitative changes in system behavior, particularly the onset of oscillations through Hopf bifurcation. The nitric oxide vasodilation gain is selected as the principal bifurcation parameter, and its influence on system stability is systematically analyzed. The goal is to determine critical thresholds at which the equilibrium loses stability and to characterize the emerging dynamics, including whether the resulting oscillations are stable or unstable.

A third objective is to validate the bifurcation structure through numerical continuation and eigenvalue analysis, ensuring consistency

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between analytical Jacobian computations and computational bifurcation results. This includes identifying equilibrium points, computing eigenvalues, verifying Hopf conditions, and estimating the first Lyapunov coefficient to classify the bifurcation type.

Finally, the work aims to integrate bifurcation analysis with optimal control theory. Specifically, an optimal control problem is formulated with nitric oxide gain as the control input, to regulate cerebral blood flow while accounting for the system's underlying stability structure. A key goal is to evaluate how incorporating bifurcation-aware constraints influences system performance, oscillation suppression, and overall stability. Through this integration, the study seeks to demonstrate the advantages of combining nonlinear dynamics and optimal control for the regulation of complex physiological systems exhibiting bifurcation-driven behavior.

Novelty of This Work

The novelty of this work lies in the development and integration of a nonlinear, physiologically motivated cerebral blood flow regulation model with bifurcation-aware optimal control analysis. Unlike many classical cerebral autoregulation models that focus primarily on steady-state behavior or linearized dynamics, the present formulation explicitly retains key nonlinear feedback mechanisms, including the fourth-power dependence of blood flow on vessel radius and the coupled interactions among nitric oxide, calcium signaling, and vascular tone. This structure enables the model to naturally exhibit complex dynamical phenomena, including the emergence of oscillatory behavior through Hopf bifurcation.

A central novelty of the study is the systematic identification and characterization of a Hopf bifurcation within this cerebral hemodynamic framework using continuation methods and numerical Jacobian analysis. The bifurcation is not imposed or assumed but arises intrinsically from the interplay of physiological feedback loops. Furthermore, the computation of the first Lyapunov coefficient allows a rigorous classification of the bifurcation as supercritical, thereby confirming the existence of a stable limit cycle beyond the stability threshold. This provides new insight into how cerebral blood flow regulation can transition from steady operation to sustained oscillations purely through parameter variation in nitric oxide-mediated vasodilation.

Another important contribution is the coupling of bifurcation analysis with optimal control design. In contrast to conventional optimal control formulations that focus solely on minimizing tracking errors or control effort, the present work incorporates the underlying dynamical structure of the system into the optimization process. Specifically, the nitric oxide gain is treated as both a bifurcation parameter and a control input, enabling direct interaction between control actions and system stability properties. The results demonstrate that even small bifurcation-aware modifications to the objective function significantly alter system performance, reducing oscillatory behavior and improving overall optimality.

Finally, the study highlights the effectiveness of integrating MATLAB-based continuation analysis (MATCONT) with PDE-constrained optimal control implemented in PYOMO.DAE and IPOPT. This combined computational framework enables a unified investigation of steady states, limit cycles, and optimal control trajectories within the same modeling environment. Overall, the novelty of this work lies in its unified treatment of nonlinear physiological modeling, bifurcation theory, and optimal control, providing a comprehensive framework for analyzing and regulating complex cerebral hemodynamic systems.

The rest of this paper is organized as follows. First, the model equations are presented, followed by a description of the numerical procedures used. The results discussion and conclusions are then presented.

Model Equations

Cerebral blood flow regulation is governed by a complex interplay between hemodynamic transport, vascular smooth muscle mechanics, and biochemical signaling pathways. In particular, cerebral vessels continuously adjust their diameter in response to changes in blood flow and metabolic demand in order to maintain adequate oxygen and nutrient delivery to neural tissue. Among the principal regulatory mechanisms are nitric oxide-mediated vasodilation and calcium-mediated vasoconstriction, which act in opposition to control vascular tone. Changes in vessel diameter directly influence blood flow via the nonlinear fluid-mechanical relationship described by Poiseuille's law, while blood flow, in turn, affects the production of vasoactive substances through shear-stress-dependent signaling pathways. The resulting feedback interactions can generate rich dynamical behavior, including oscillatory autoregulatory responses. To investigate these mechanisms, we develop a reduced-order nonlinear model consisting of four state variables representing cerebral blood flow, vessel radius, intracellular calcium concentration, and nitric oxide concentration. The model combines fundamental fluid-mechanical principles with simplified physiological regulatory processes and is designed to capture the essential feedback loops responsible for stability loss and oscillatory dynamics in cerebral circulation. Cerebral blood flow regulation arises from the interaction between hemodynamic transport, vascular smooth muscle activity, intracellular calcium signaling, and nitric oxide (NO)-mediated vasodilation. To capture these coupled mechanisms, we consider four state variables: the cerebral blood flow rate , the vessel radius , the intracellular calcium concentration , and the nitric oxide concentration . The model is derived by combining fundamental fluid-mechanical principles with simplified physiological feedback mechanisms that govern vascular regulation.

The starting point is Poiseuille's law for laminar flow through a cylindrical blood vessel. Under the assumptions of incompressible flow, constant viscosity, and a fixed pressure gradient, the volumetric flow rate is given by

$$Q = \frac{\pi \Delta P}{8 \mu L} R^4,$$

(1)

where denotes the pressure drop along the vessel, is the blood viscosity, is the vessel length, and is the vessel radius. Defining

$$k_Q = \frac{\pi \Delta P}{8 \mu L},$$

(2)

The equilibrium flow-rate relationship becomes

$$Q_{eq} = k_Q R^4.$$

(3)

Since blood flow does not adjust instantaneously to changes in vessel radius, a first-order relaxation process is introduced. Letting denote the characteristic flow-adjustment time, the flow dynamics are represented by

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$$\tau_Q \frac{dQ}{dt} = k_Q R^4 - Q,$$

(4)

or equivalently,

$$\frac{dQ}{dt} = \frac{1}{\tau_Q}(k_Q R^4 - Q)$$

(5)

The vessel radius is assumed to be regulated by competing vasodilatory and vasoconstrictive influences. Nitric oxide promotes relaxation of vascular smooth muscle and therefore increases vessel radius, whereas intracellular calcium promotes contraction and decreases vessel radius. Let denote the passive vessel radius in the absence of active regulation. Assuming linear responses to NO and calcium concentrations, the desired vascular radius is expressed as

$$R_d = R_0 + \alpha_N N - \alpha_C C$$

(6)

where α_n is the nitric oxide vasodilation gain and α_c is the calcium vasoconstriction gain. The actual vessel radius relaxes toward this desired radius with characteristic time τ_r, leading to

$$\tau_R \frac{dR}{dt} = R_0 + \alpha_N N - \alpha_C C - R,$$

(7)

Or

$$\frac{dR}{dt} = \frac{1}{\tau_R}(R_0 + \alpha_N N - \alpha_C C - R).$$

(8)

The intracellular calcium concentration evolves through a balance of basal influx, flow-induced stimulation, nitric oxide inhibition, and natural removal processes. A constant calcium production rate k_c accounts for basal cellular activity. Increased blood flow can enhance mechanosensitive calcium influx, which is represented by the term $\beta_Q Q$. Nitric oxide tends to reduce intracellular calcium levels through signaling pathways that inhibit calcium accumulation, represented by $-\beta_N N$. Calcium is also removed through buffering and transport mechanisms that are modeled as a first-order decay process with rate constant μ_c. Combining these contributions yields

$$\frac{dC}{dt} = k_C + \beta_Q Q - \beta_N N - \mu_C C$$

(9)

Nitric oxide concentration is modeled in an analogous manner. A basal production rate k_N accounts for constitutive endothelial NO synthesis. Increased blood flow enhances endothelial shear stress and stimulates additional NO production, represented by $\gamma_Q Q$. Calcium is assumed to reduce the effective availability of nitric oxide through regulatory interactions, represented by $-\gamma_C C$. Finally, nitric oxide is removed through degradation and diffusion processes, modeled by a first-order decay term $-\mu_N N$. Consequently,

$$\frac{dN}{dt} = k_N + \gamma_Q Q - \gamma_C C - \mu_N N$$

(10)

Collecting these equations produces the four-dimensional nonlinear cerebral blood flow regulation model

$$\frac{dQ}{dt} = \frac{1}{\tau_Q}(k_Q R^4 - Q),$$
$$\frac{dR}{dt} = \frac{1}{\tau_R}(R_0 + \alpha_N N - \alpha_C C - R)$$
$$\frac{dC}{dt} = k_C + \beta_Q Q - \beta_N N - \mu_C C,$$
$$\frac{dN}{dt} = k_N + \gamma_Q Q - \gamma_C C - \mu_N N$$

(11)

The model contains a positive feedback pathway Q → N → R → Q, where increased blood flow promotes nitric oxide production, nitric oxide increases vessel radius, and the enlarged radius further increases flow through the fourth-power dependence inherited from Poiseuille's law. Opposing this mechanism is the calcium-mediated vasoconstrictive pathway. The competition between these effects generates rich nonlinear dynamics. In particular, the parameter α_N, which quantifies the sensitivity of vessel radius to nitric oxide, acts as a natural bifurcation parameter. As α_N increases, the strength of the positive feedback loop increases. Beyond a critical threshold, the equilibrium loses stability through a Hopf bifurcation, giving rise to self-sustained oscillations in blood flow, vessel radius, calcium concentration, and nitric oxide concentration. This mechanism provides a mathematical representation of oscillatory cerebral autoregulation and forms the basis for subsequent bifurcation and optimal control analyses [Tables 1, 2]. Give details about the parameters and variables.

Symbol	Description	Units (if dimensional)
Q(t)	Cerebral blood flow rate	Arbitrary/Nondimensional
R(t)	Effective vessel radius	Arbitrary/Nondimensional
C(t)	Intracellular calcium concentration	Arbitrary/Nondimensional
N(t)	Nitric oxide concentration	Arbitrary/Nondimensional
αN	Nitric oxide vasodilation gain (bifurcation/control	Arbitrary/Nondimensional

Table 1: State Variables of the Cerebral Blood Flow Regulation Model

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Parameter	Description	Value
k_Q	Flow scaling coefficient from Poiseuille relationship	1
τ_Q	Flow adaptation time constant	0.1
τ_R	Radius adaptation time constant	0.5
R_0	Baseline vessel radius	0.5
α_C	Calcium-induced vasoconstriction coefficient	0.6
β_Q	Flow-induced calcium production coefficient	0.7
β_N	Nitric oxide inhibition coefficient in calcium dynamics	0.4
γ_Q	Flow-induced nitric oxide production coefficient	0.1
γ_C	Calcium inhibition coefficient in nitric oxide dynamics	0.5
μ_C	Calcium removal/decay rate	0.2
μ_N	Nitric oxide degradation rate	0.15
k_C	Basal calcium production rate	0.1
k_N	Basal nitric oxide production rate	3.1
α_N	Nitric oxide vasodilation gain	0.08 (nominal value)

Table 2: Model Parameters and Values

The parameter serves as the principal bifurcation parameter. Continuation analysis is performed by varying while all remaining parameters are held fixed at the values listed in [Table 2].

Bifurcation analysis and Optimal Control

Bifurcation Analysis

Continuation and bifurcation computations were carried out using the MATLAB-based software MATCONT. Bifurcation analysis provides important insights into the mechanisms underlying the existence of multiple steady states and self-sustained oscillations in nonlinear dynamical systems. In particular, branch points and limit points are associated with the emergence of multiple steady-state solutions, whereas oscillatory dynamics and periodic solutions originate from Hopf bifurcations. The package, originally developed and subsequently enhanced by several researchers [32], enables the systematic identification of limit points (LP), branch points (BP), and Hopf bifurcation points (H) in nonlinear dynamical models. This program identifiesLimit points(LP), branch points(BP), and Hopf bifurcation points(H) for an systemof ordinary differential equations

$$\frac{dx}{dt} = f(x,\alpha) \tag{12}$$

where the bifurcation parameter is α.

At a limit point, the n+1th component of the tangent vector $W_{n+1} = 0$.

For a branch point,

the matrix B = [A; w^T] must be singular and have a determinant of 0.

At a Hopf bifurcation point,

$$\det(2 f_x(x,\alpha) @ I_n) = 0 \tag{13}$$

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@ indicates the bialternate product while I_n is the n-square identity matrix. More details can be found in [33, 34]. Respectively.

Optimal Control

Pyomo.dae [35], is used for the Optimal Control calculations. Pyomo with its Pyomo.DAE module provides an efficient framework for the formulation and solution of dynamic optimization problems involving systems of differential and algebraic equations. The package provides a symbolic modeling environment for representing differential-algebraic equation (DAE) systems in optimization applications. In Pyomo.DAE, the continuous-time dynamic model is transformed into a nonlinear programming (NLP) problem through discretization techniques such as orthogonal collocation, allowing the resulting optimization problem to be solved using standard NLP solvers.The NLP is solved using IPOPT [36].

Formation of stability Dataset from Matcont results

A stability dataset was developed from numerical continuation calculations performed in MATCONT. The stability dataset consists of rows, each representing a continuation point from an equilibrium branch. Each row contains the state variables, the bifurcation parameter, and a stability measure. The stability measure is a numerical value derived from the Jacobian matrix. The Jacobian matrix is computed numerically at each equilibrium point. The eigenvalues are then computed automatically using MATLAB. The maximum value of the real part of these eigenvalues is then computed as a scalar stability measure.

The stability measure is computed using "eig_real_max = max(real(eigvals));" in MATLAB. The stability measure is a quantitative metric in which negative values indicate locally asymptotically stable equilibria, positive values indicate instability, and a zero crossing indicates a Hopf bifurcation. The stability dataset is then saved as a CSV file. The dataset can then be used in subsequent computational calculations to perform classification or regression to identify stability boundaries or approximate bifurcations.

Neural Network Surrogate for Stability Prediction

Direct embedding of eigenvalue calculations into IPOPT-based optimal control is impractical for several reasons: (i) computing eigenvalues at each time step is computationally expensive, (ii) the mapping from states to the maximum eigenvalue is non-smooth near eigenvalue crossings, and (iii) symbolic differentiation of eigenvalues is challenging.

Prior to neural-network training, all input variables were standardized to improve numerical conditioning and training stability. Let x_{raw} denote the vector of state variables and bifurcation parameters= obtained from the stability dataset. For each input variable j, the training mean μ_j and training standard deviation σ_j were computed over all training samples. = The training mean for the input variable j is defined as the arithmetic average over all training

samples as $\mu_j = (1/N)\ \Sigma(k=1 \text{ to } N)\ x_j^{(k)}$ and the training standard deviation for the input variable is defined as:

$\sigma_j = (1/N)\ (\sum(k=1 \text{ to } N)\ x_j^{(k)} - \mu_j)^2$

The standardized inputs were defined as

$$x_j = \frac{x_{raw,j} - \mu_j}{\max(\sigma_j, \varepsilon_{scale})} \quad (14)$$

where ε_{scale} is a small positive regularization parameter introduced to prevent numerical singularities associated with extremely small variances. This transformation ensures that all inputs remain properly scaled while avoiding excessively large neural-network activation arguments during optimization. The normalization procedure improves neural-network conditioning and enhances the robustness of gradient-based optimization. The vectors and computed during training were stored and embedded identically within the Pyomo optimal-control formulation to ensure consistency between neural-network training and deployment.

To overcome these limitations, a feedforward neural network is trained to approximate the maximum eigenvalue as a smooth function of the system state and bifurcation parameter. A typical architecture employs the hyperbolic tangent (tanh) as a smooth activation function. If the input vector is denoted by x, which represents the scaled variables, then the network is defined as:

The vectors μ, σ computed during training were stored and embedded identically within the Pyomo optimal control formulation to ensure consistency between neural network training and deployment.

To avoid repeated eigenvalue computations during optimization, a feedforward neural network is trained to approximate the maximum real eigenvalue as a smooth function of the system states and bifurcation parameter. Using hyperbolic tangent activation functions ensures smooth differentiability required by IPOPT. If the input vector is denoted by , which are the scaled variables, the network architecture is defined as

$$\begin{aligned} z1 &= \tanh(W1\,x + b1) \\ z2 &= \tanh(W2\,z1 + b2) \\ \lambda\_max\_NN &= W3\,z2 + b3 \end{aligned} \quad (15)$$

where W_i and b_i denote the weight matrices and bias vectors, respectively. The hidden-layer variables z_1 and z_2 represent nonlinear transformations of the input variables and intermediate features. The final output $\hat{\lambda}_{max}$ provides a smooth approximation of the spectral abscissa. Because tanh is infinitely differentiable, the network is fully smooth, guaranteeing the availability of first and second derivatives required by IPOPT. Without biases, the network output would be constrained to pass through the origin, limiting flexibility.

The hidden-layer outputs z1, z2, represent nonlinear combinations of the inputs and previous-layer features, respectively. Each element of z_1 is a smoothed combination of the original inputs, while each element of z2 encodes more abstract patterns extracted from z1. The final output λ_max_NN provides a smooth approximation of the maximum real eigenvalue, enabling efficient and differentiable stability evaluation within the optimal control problem. The integration into optimal control is done using a soft penalty formulation where we use a smooth_max function that converts λ into a smooth, nonnegative penalty that only "activates" when the system is unstable:

$$s_{\max}(\lambda + \varepsilon_1) = smooth - \max(\lambda + \varepsilon_1) = \frac{(\lambda + \varepsilon_1) + \sqrt{(\lambda + \varepsilon_1)^2 + \varepsilon_1}}{2} \quad (16)$$

λ is the neural network's predicted maximum eigenvalue at the current state and parameter, while is a small positive safety margin to ensure differentiability. The soft penalty formulation involves the new objective function, where the original objective function $optv(t) = \Sigma\,(Q(t) - Q_{ref})^2 + 0.005*(\alpha_N(t))^2$ is modified to

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$\Sigma(optv(t)+\alpha_{Hopf}.s_{max}(\lambda + \varepsilon_1))^2$ α_{Hopf} controls how aggressively instability is penalized, and prevents numerical issues at exactly $\lambda = 0$ and slightly shifts the stability boundary. Q_{ref} is the value of Q at the Hopf bifurcation point. The objective function involves a fraction of the control parameter. The goal is to minimize the objective function value while ensuring differentiability for IPOPT and avoiding non-smooth optimization. This approach avoids repeated eigenvalue computations and provides a smooth, differentiable surrogate suitable for gradient-based optimization. Furthermore, this enables the incorporation of stability constraints into optimal control without explicitly computing eigenvalues during optimization.

To facilitate integration into optimal control, a stability data set is constructed from MATCONT continuation results. At each equilibrium point, the Jacobian is evaluated and its eigenvalues computed. The stability metric is defined as the maximum real part of the eigenvalues ($(\lambda_{max}$=max R(λ(J)))). Negative values indicate stability, positive values indicate instability, and zero crossings correspond to Hopf bifurcations.

To avoid repeated eigenvalue computations within optimization, a feed-forward neural network is trained to approximate the spectral abscissa as a smooth function of the system state and bifurcation parameter. Using hyperbolic tangent activation functions ensures smooth differentiability required by gradient-based solvers. The resulting surrogate provides a differentiable stability indicator suitable for embedding within optimal control formulations.

Results

The bifurcation analysis was performed using MATCONT and aHopf bifurcation point was found at (Q,R,C,N,α_N) values of (16.550081 2.016973 0.877910 28.773687 0.071027) with first Lyapunov coefficient -8.757257e-04. The bifurcation diagram and the limit cycle are shown in [Figure 1, 1b]. The analytical expression of the Jacobian matrix is

$$J_A = \begin{bmatrix} -\frac{1}{\tau_Q} & \frac{4k_Q R^3}{\tau_Q} & 0 & 0 \\ 0 & -\frac{1}{\tau_R} & -\frac{\alpha_C}{\tau_R} & \frac{\alpha_N}{\tau_R} \\ \beta_Q & 0 & -\mu_C & -\beta_N \\ \gamma_Q & 0 & -\gamma_C & -\mu_N \end{bmatrix}. \quad (17)$$

The numerical Jacobian at the Hopf point is

$$J_N = \begin{bmatrix} -10 & 328.24 & 0 & 0 \\ 0 & -2 & -1.2 & 0.142054 \\ 0.7 & 0 & -0.2 & -0.4 \\ 0.1 & 0 & -0.5 & -0.15 \end{bmatrix}. \quad (18)$$

The eigenvalues of this matrix are -0.464 , -11.886 and A complex conjugate pair crosses the imaginary axis, confirming the Hopf bifurcation. Since the first Lyapunov coefficient is negative, the Hopf bifurcation is supercritical.

The eigenvalues of this matrix are -0.464 , -11.886 and A complex conjugate pair crosses the imaginary axis, confirming the Hopf bifurcation. Since the first Lyapunov coefficient is negative, the Hopf bifurcation is supercritical.

For the optimal control, the original objective function $optv(t)= \Sigma(Q(t)-Q_{ref})^2 + 0.005*(\alpha_N(t))^2$ minimized with and without the Hopf bifurcation constraint.. In a Hopf-type system, this typically suppresses oscillation amplitude and biases the dynamics toward the least-excited (often near-steady or weakly oscillatory) regime.

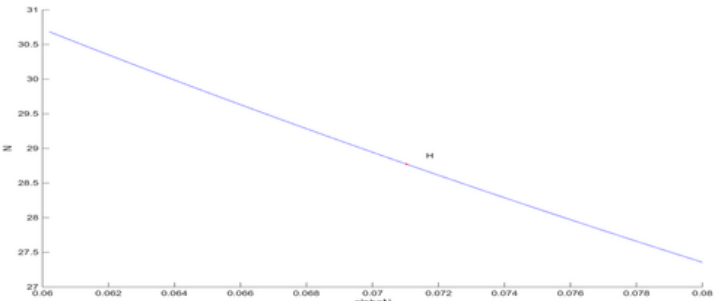

Figure: 1 (a) Bifurcation Diagram

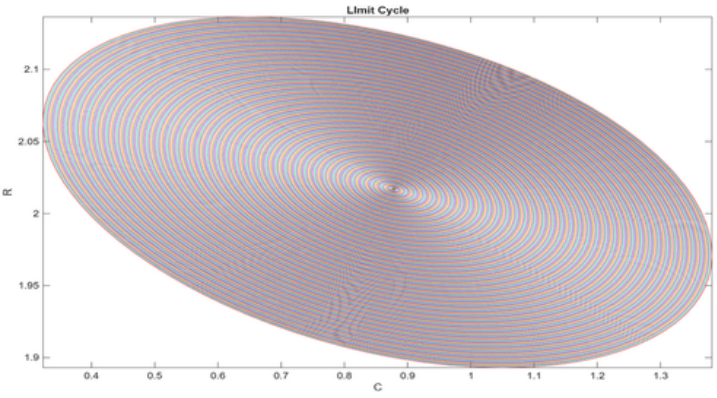

Figure: 1 (b) Limit Cycle

It also penalizes large control action, meaning the optimizer seeks a balance between stabilizing the cerebral blood flow rate and minimizing the use of the bifurcation parameter α_N To investigate the effect of bifurcation-aware operation, an optimal control problem was solved both with and without a Hopf-bifurcation-avoidance constraint using PYOMO.DAE coupled with IPOPT. To investigate the effect of bifurcation-aware operation, an optimal control problem was solved both without and with a Hopf-bifurcation-avoidance constraint. PYOMO.DAE with IPOPT was used. When no Hopf constraint was implemented, $\alpha_N = 0$, in $\Sigma(optv(t)+\alpha_{hopf}.s_{max}.(\lambda+ \varepsilon_1))^2$ the obtained value of $\Sigma\, optv(t)$ was 23.01. This demonstrates a 20.2% decrease in the minimized function [Figure 2a, 2b, 2c, 2d]. Show the optimal control profiles without and with the Hopf constraint.

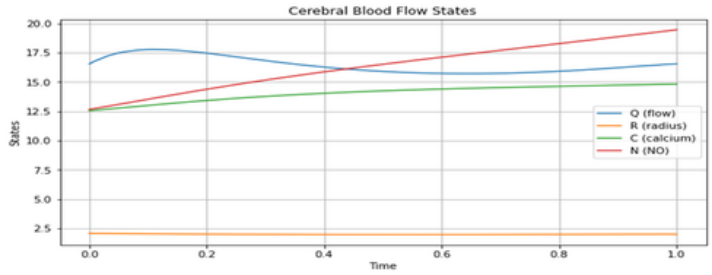

Figure: 2 (a) Q vs t (no Hopf constraint)

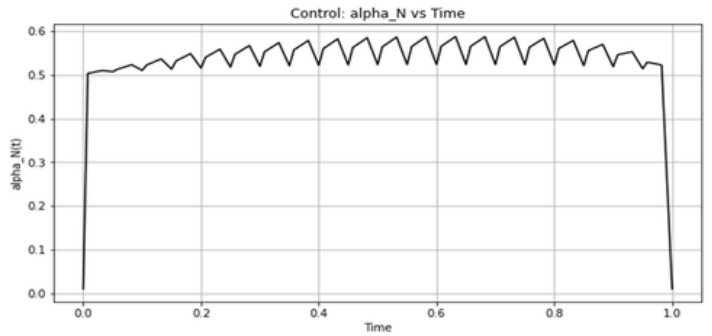

Figure: 2 (b) control profile (no Hopf constraint used)

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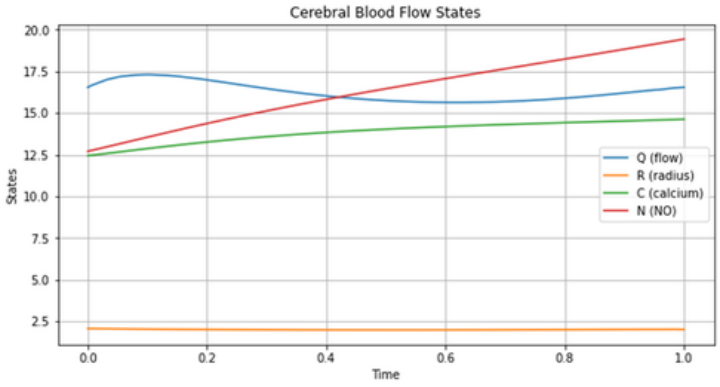

Figure: 2 (c) Q vs t (with Hopf constraint)

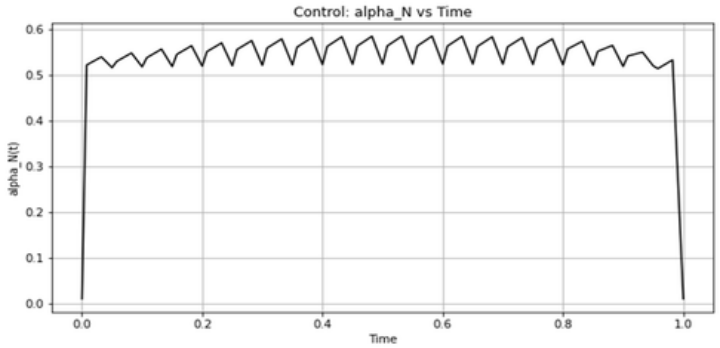

Figure: 2 (d) control profile (no Hopf constraint used)

Discussion

The results obtained in this study demonstrate the strong influence of bifurcation phenomena on the regulation and control of cerebral blood flow dynamics. The four-state model developed herein incorporates the coupled interactions among blood flow, vessel radius, intracellular calcium concentration, and nitric oxide concentration, thereby capturing the essential physiological feedback mechanisms responsible for vascular autoregulation. The bifurcation analysis revealed the existence of a Hopf bifurcation at $(Q^*, R^*, C^*, N^*, \alpha_N^*) = (16.550081, 2.016973, 0.877910, 28.773687, 0.071027)$ indicating a critical transition from stable equilibrium behavior to self-sustained oscillatory dynamics. The occurrence of a Hopf bifurcation in a cerebral blood flow regulation model is significant because oscillatory cerebral perfusion is frequently associated with pathological or highly stressed physiological conditions. From a dynamical systems perspective, the Hopf point represents a threshold at which the autoregulatory feedback mechanisms become sufficiently strong to destabilize the equilibrium state and generate periodic oscillations.

The computed first Lyapunov coefficient, $l_1 = 8.757257 \times 10^4$ is negative, confirming that the Hopf bifurcation is supercritical. This result is particularly important because it implies that the emerging limit cycle is stable.

Consequently, when the bifurcation parameter exceeds its critical value, the system does not exhibit abrupt instability or unbounded growth but instead evolves toward a stable oscillatory regime. Physiologically, this behavior can be interpreted as the appearance of persistent vasomotor oscillations driven by the interaction between nitric oxide signaling and vascular radius regulation. Such oscillatory behavior is consistent with the known tendency of biological regulatory systems to generate rhythmic dynamics when feedback gains become sufficiently large.

The bifurcation diagram and limit-cycle computations further illustrate the nature of the transition. The stable periodic orbit emerging from the equilibrium demonstrates that the cerebral circulation possesses an intrinsic oscillatory mode arising solely from the nonlinear feedback structure of the model. The presence of this oscillatory mode highlights the importance of incorporating nonlinear dynamical analysis into the study of cerebral autoregulation. Traditional steady-state analyses would be incapable of detecting such behavior and could therefore overlook important mechanisms governing vascular stability. The results emphasize that cerebral blood flow regulation should not be viewed solely as a static control problem but rather as a nonlinear dynamical process whose qualitative behavior may change dramatically as physiological parameters vary.

The Jacobian analysis provides additional validation of the bifurcation results. Evaluation of the Jacobian matrix at the Hopf point revealed that a complex conjugate pair of eigenvalues crosses the imaginary axis while the remaining eigenvalues remain negative. This behavior satisfies the classical Hopf bifurcation conditions and confirms the transition predicted by continuation analysis. The agreement among continuation computations, eigenvalue analysis, and Lyapunov coefficient calculations provides strong evidence for the robustness of the observed bifurcation. Such consistency is important because it demonstrates that the oscillatory dynamics are not numerical artifacts but rather intrinsic properties of the underlying physiological model.

Beyond the bifurcation analysis itself, one of the most significant findings of this work is the impact of bifurcation-aware optimal control. The optimal control problem was formulated using the nitric oxide vasodilation gain α_N as the control variable. Because α_N directly governs the strength of the positive feedback loop linking nitric oxide concentration, vessel radius, and blood flow, it naturally serves as a mechanism through which the stability properties of the system can be manipulated. In this context, the control problem extends beyond conventional trajectory tracking and enters the realm of stability management. Rather than merely steering the system toward a desired operating condition, the controller influences the dynamical structure of the model itself.

The numerical results clearly demonstrate the effectiveness of incorporating Hopf-bifurcation-awareness into the optimization framework. When no Hopf constraint was imposed, corresponding to $\alpha_2 = 0$, the optimal objective function value was 28.84. Introducing even a relatively small Hopf-related penalty, $\alpha_2 = 0.0012$, reduced the objective function value to 23.01. This corresponds to an approximate 20.2% improvement in the minimized performance index. Such a reduction is remarkable considering the small magnitude of the penalty coefficient and indicates that the optimization process is highly sensitive to the stability characteristics of the system.

The observed improvement suggests that the unconstrained optimization problem naturally permits trajectories that approach oscillatory operating regimes. Although these regimes may satisfy the dynamical equations, they are associated with increased deviations in cerebral blood flow and therefore contribute more heavily to the objective function. The introduction of a Hopf-related constraint effectively discourages the optimizer from exploiting parameter regions near the stability boundary. As a result, the optimized trajectory remains closer to the stable equilibrium manifold, reducing oscillation amplitude and improving overall system performance.

From a physiological standpoint, this finding has important implications. Oscillatory cerebral blood flow may lead to fluctuations in tissue perfusion, oxygen delivery, and nutrient transport. While moderate oscillations can be tolerated, persistent or excessive oscillations may compromise autoregulatory performance and contribute to pathological conditions. By steering the system away from bifurcation-induced oscillatory regimes, the proposed control strategy promotes more stable cerebral perfusion. Consequently, the optimization framework can be interpreted not

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merely as a mathematical tool but as a potential strategy for maintaining favorable physiological operating conditions.

An additional contribution of this work is the demonstration that bifurcation information can be directly integrated into optimal control formulations. Traditionally, bifurcation analysis and optimal control are treated as separate disciplines. Bifurcation analysis is used to identify stability boundaries, whereas optimal control focuses on trajectory optimization. The present results illustrate the benefits of combining these two approaches. The Hopf bifurcation serves as a quantitative indicator of impending instability, while the optimization framework utilizes this information to avoid undesirable operating regions. This integration creates a control methodology that is both performance-oriented and stability-aware.

From an engineering perspective, the results suggest a general strategy applicable to a broad range of biological and physiological systems exhibiting oscillatory dynamics. Many cardiovascular, respiratory, neurological, and biochemical regulatory systems contain feedback loops capable of generating Hopf bifurcations. In such systems, control strategies that explicitly account for bifurcation structure may outperform conventional optimization methods that consider only state tracking objectives. The approximately 20% reduction in the objective function observed in the present study demonstrates the practical value of incorporating stability information into the control design process.

The implications extend beyond cerebral blood flow regulation. The methodology presented here establishes a framework for combining nonlinear dynamics, bifurcation theory, and optimal control in biological systems. By identifying critical stability thresholds and incorporating them into the optimization problem, it becomes possible to design controllers that simultaneously improve performance and preserve desirable dynamical behavior. Such an approach may prove particularly valuable in biomedical engineering applications involving artificial organs, neurovascular regulation, cardiovascular assist devices, and personalized treatment strategies.

Overall, the results demonstrate that the interplay between nonlinear dynamics and optimal control is central to understanding cerebral autoregulation. The identification of a supercritical Hopf bifurcation provides insight into the mechanisms responsible for oscillatory blood flow behavior, while the optimal control computations reveal how stability-aware operation can substantially improve system performance. The observed reduction in the objective function, together with the suppression of oscillatory tendencies, highlights the importance of incorporating bifurcation information into control design. These findings establish a foundation for future investigations of bifurcation-constrained optimization in physiological fluid dynamics and provide a promising avenue for the development of advanced control strategies in biological systems.

Potential Impact of This Research

The present research contributes to the growing field of mathematical physiology by providing a unified framework that combines cerebral blood flow regulation, fluid mechanics, nonlinear dynamical systems theory, bifurcation analysis, and optimal control. The findings have important implications for both fundamental scientific understanding and future biomedical applications.

From a physiological perspective, this work improves our understanding of the mechanisms governing cerebral autoregulation. By explicitly modeling the interactions among blood flow, vessel radius, intracellular calcium concentration, and nitric oxide signaling, the study provides insight into how complex feedback processes influence cerebrovascular stability. The identification of a Hopf bifurcation demonstrates that oscillatory cerebral blood flow can arise naturally from physiological regulatory mechanisms rather than external disturbances alone. This finding enhances our understanding of how normal regulatory processes may transition into abnormal oscillatory states under certain conditions.

From a fluid-mechanical standpoint, the research highlights the importance of nonlinear flow–structure interactions in biological systems. The strong dependence of blood flow on vessel radius introduces significant nonlinearities that can fundamentally alter system behavior. The results demonstrate how fluid mechanics and biochemical signaling jointly determine the stability of cerebral circulation. Such insights may be valuable for the broader study of biological transport phenomena, vascular dynamics, and physiological fluid mechanics.

A major contribution of the work is the integration of bifurcation theory with optimal control. Traditional control approaches often focus exclusively on tracking performance without explicitly considering the underlying stability structure of the system. In contrast, the proposed framework incorporates information regarding critical stability boundaries into the optimization process. The observed reduction in the objective function when bifurcation-aware control is introduced demonstrates that accounting for system stability can significantly improve performance. This concept may be extended to many other nonlinear biological and engineering systems that exhibit bifurcation-induced transitions.

The results also have potential biomedical significance. Oscillatory cerebral blood flow has been associated with various neurological and cerebrovascular disorders, including impaired autoregulation following stroke, traumatic brain injury, and chronic hypertension. Although the present model is intentionally simplified, it provides a theoretical foundation for developing control strategies aimed at maintaining stable cerebral perfusion and preventing undesirable oscillatory behavior. Future extensions incorporating patient-specific physiological data could support the development of personalized therapeutic and monitoring strategies.

The computational framework developed in this work may also benefit the design of intelligent physiological control systems. Because the model identifies parameters that directly influence stability, it could serve as a basis for future artificial intelligence and machine-learning-assisted control strategies for neurovascular regulation. Such approaches may eventually contribute to the design of smart medical devices, automated monitoring systems, and digital twins of cerebral circulation capable of predicting impending instability and recommending corrective actions.

From a mathematical standpoint, the study demonstrates how relatively low-dimensional models can reproduce complex dynamical phenomena observed in physiological systems. The successful application of continuation methods, eigenvalue analysis, limit-cycle computation, and optimal control illustrates the value of combining multiple mathematical techniques within a single framework. This methodology can readily be adapted to other biological systems exhibiting oscillatory dynamics, including cardiovascular regulation, respiratory control, endocrine feedback systems, and cellular signaling networks.

Furthermore, the work establishes a foundation for future research on bifurcation-constrained optimization. The incorporation of Hopf-bifurcation information into optimal control formulations represents an emerging research direction with applications extending far beyond cerebral hemodynamics. Similar approaches may be employed in chemical reactors, ecological systems, energy networks, and biomedical processes where maintaining operation away from critical stability boundaries is essential.

In summary, the impact of this research extends across several disciplines, including fluid mechanics, applied mathematics, systems biology, biomedical engineering, and physiological control. By demonstrating how bifurcation analysis and optimal control can be

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combined to regulate cerebral blood flow dynamics, the study provides both new scientific insights and a versatile methodological framework that can be applied to a wide range of nonlinear biological systems. The results open opportunities for future investigations into stability-aware control strategies, patient-specific physiological modeling, and advanced computational approaches for the management of complex biomedical systems.

Conclusions

This study developed and analyzed a nonlinear four-state model of cerebral blood flow regulation that captures the coupled interactions among cerebral blood flow, vessel radius, intracellular calcium concentration, and nitric oxide concentration. The model integrates fundamental fluid-mechanical principles with physiological regulatory mechanisms and provides a framework for investigating the dynamic behavior of cerebral autoregulation. Bifurcation analysis performed using MATCONT identified a Hopf bifurcation at

$$(Q^*,R^*,C^*,N^*,\alpha_N^*)=(16.550081,2.016973,0.877910,28.773687,0.071027)$$

where a pair of complex conjugate eigenvalues crosses the imaginary axis. The computed first Lyapunov coefficient $l_1=-8.757257\times10^{-4}$, confirmed that the bifurcation is supercritical, leading to the emergence of a stable limit cycle and sustained oscillatory behavior in the cerebral circulation. The bifurcation results demonstrate that the nitric oxide vasodilation gain plays a critical role in determining the stability of cerebral blood flow regulation. As this parameter increases, the physiological feedback mechanisms become sufficiently strong to destabilize the equilibrium state and generate periodic oscillations. These findings highlight the importance of nonlinear dynamics in understanding cerebral autoregulation and illustrate how small parameter variations can significantly alter system behavior. An optimal control formulation was subsequently developed using the nitric oxide gain as the control variable. Numerical solutions obtained using PYOMO.DAE and IPOPT showed that incorporating bifurcation-aware control significantly improves system performance. The minimized objective function decreased from 28.84 in the unconstrained case to 23.01 when a Hopf-bifurcation-related constraint was introduced, corresponding to an improvement of approximately 20.2%. This reduction indicates that avoiding operation near the Hopf boundary suppresses oscillatory tendencies and promotes more stable cerebral perfusion. Overall, the results demonstrate that combining bifurcation analysis with optimal control provides an effective strategy for regulating nonlinear physiological systems. The proposed framework offers a promising foundation for future studies on stability-aware control of cerebral hemodynamics and other biological fluid dynamic systems exhibiting oscillatory behavior and bifurcation-induced instabilities.

Declarations

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Dr. Sridhar thanks Dr. Carlos Ramirez for encouraging him to write single-author papers.

Authors Contribution

There is only one author who did everything

Data Availability Statement

All data used is presented in the paper

Conflict of interest

The author, Dr. Lakshmi N Sridhar, has no conflict of interest.

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