Journal of Medical Science and Clinical Studies

SCIVOLVE

Research Article

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Nonlinear Dynamics and Optimal Control of Nephron Autoregulation: A Hopf Bifurcation Analysis of Renal Blood Flow

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Received: June 30, 2026; **Published:** July 22, 2026

How to cite this article:
Sridhar LN. Nonlinear Dynamics and Optimal Control of Nephron Autoregulation: A Hopf Bifurcation Analysis of Renal Blood Flow. *J Med Clin Case Stu*. 2026;2(1):1-10.

Abstract

Nephron autoregulation is essential for maintaining stable renal blood flow and glomerular filtration despite variations in arterial pressure. The coupled interactions between the myogenic response and tubuloglomerular feedback constitute a nonlinear physiological system capable of exhibiting oscillatory dynamics under certain operating conditions. In this study, a physiologically grounded four-state nonlinear nephron model is developed to investigate the dynamic behavior of glomerular pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration. Nonlinear bifurcation analysis performed using MATCONT identifies the existence of a Hopf bifurcation, confirming the transition from stable equilibrium to sustained limit-cycle oscillations. The corresponding analytical and numerical Jacobian matrices are derived, and eigenvalue analysis verifies the onset of instability through the crossing of a pair of complex conjugate eigenvalues across the imaginary axis. An optimal control problem is subsequently formulated in which the control variable simultaneously serves as the bifurcation parameter. The objective function minimizes deviations of glomerular pressure and renal blood flow from desired physiological values while penalizing excessive control effort. A neural-network surrogate model of the Hopf boundary is incorporated within a PYOMO. DAE–IPOPT optimization framework to enable computationally efficient stability-aware optimization. Numerical results demonstrate that incorporating the Hopf-bifurcation constraint produces approximately a 20% reduction in the objective function while maintaining stable nephron dynamics. The proposed framework provides a computational approach for integrating renal physiology, nonlinear dynamics, machine learning, and optimal control to improve nephron autoregulation and support future model-based strategies for kidney disease management.

Keywords: Nephron autoregulation, Renal blood flow, Tubuloglomerular feedback, Hopf bifurcation, Optimal control.

Introduction

The kidneys play a fundamental role in maintaining whole-body homeostasis by regulating extracellular fluid volume, electrolyte balance, acid-base equilibrium, and arterial blood pressure. Each human kidney contains approximately one million nephrons, which serve as the functional units responsible for filtering blood, reabsorbing essential solutes, and excreting metabolic waste products. To ensure efficient filtration under continuously changing physiological conditions, each nephron possesses highly sophisticated autoregulatory mechanisms that maintain relatively constant renal blood flow and glomerular filtration rate despite fluctuations in systemic arterial pressure. Failure of these autoregulatory processes contributes to progressive renal injury and is associated with numerous pathological conditions including hypertension, diabetic nephropathy, chronic kidney disease, and acute kidney injury.

Nephron autoregulation is primarily governed by two interacting physiological mechanisms: the myogenic response and tubuloglomerular feedback (TGF). The myogenic response provides a rapid adjustment of afferent arteriolar resistance in response to changes in vascular pressure through contraction or relaxation of vascular smooth muscle cells. In contrast, tubuloglomerular feedback is a slower regulatory mechanism mediated by the macula densa, a specialized group of epithelial cells located within the distal tubule that continuously senses tubular sodium chloride concentration. Changes in sodium delivery initiate biochemical signaling pathways that alter afferent arteriolar tone, thereby regulating glomerular capillary pressure and renal blood flow. The continuous interaction between these fast and slow feedback mechanisms enables the nephron to maintain stable filtration over a wide physiological range while simultaneously protecting the delicate glomerular capillaries from excessive

pressure fluctuations.

Although these autoregulatory mechanisms normally preserve renal stability, experimental and theoretical investigations have demonstrated that their nonlinear interactions can produce oscillatory dynamics. Oscillations in nephron blood flow, glomerular pressure, and tubular fluid transport have been observed experimentally and are believed to arise from the intrinsic coupling between the myogenic mechanism and tubuloglomerular feedback. Under certain physiological or pathological conditions, these oscillations may become amplified, leading to rhythmic variations in renal hemodynamics that reduce filtration efficiency and increase mechanical stress on glomerular structures. Understanding the mechanisms responsible for the transition from stable autoregulation to sustained oscillatory behavior therefore represents an important problem in renal physiology and biomedical engineering.

Mathematical modeling has become an indispensable tool for investigating the complex interactions governing nephron function. Mathematical models allow individual physiological mechanisms to be isolated, quantified, and systematically analyzed under conditions that are often difficult or impossible to achieve experimentally. Over the past two decades, computational studies have significantly improved the understanding of renal hemodynamics, tubuloglomerular feedback, vascular regulation, and nephron synchronization. Mathematical models have also provided valuable insight into disease progression by enabling investigators to examine how alterations in physiological parameters influence renal function and autoregulatory performance. Consequently, computational modeling has emerged as an important complement to experimental nephrology.

Because nephron autoregulation is inherently nonlinear, conventional linear stability analysis is frequently insufficient for describing the rich dynamic behavior exhibited by renal systems. Nonlinear dynamical systems theory provides a rigorous mathematical framework for analyzing qualitative changes in system behavior as physiological parameters vary. In particular, Hopf bifurcation theory describes the transition from a stable equilibrium to sustained periodic oscillations through the crossing of a pair of complex conjugate eigenvalues across the imaginary axis. Within the context of renal physiology, the occurrence of a Hopf bifurcation signifies the loss of stable autoregulation and the emergence of self-sustained oscillations in glomerular pressure and renal blood flow. Identification of such critical operating conditions provides valuable insight into the mechanisms responsible for oscillatory renal dynamics and offers potential strategies for preventing pathological instability.

Equally important is the development of effective control strategies capable of maintaining nephron operation within physiologically desirable regimes. Optimal control provides a systematic methodology for determining time-dependent interventions that achieve prescribed physiological objectives while minimizing the associated control effort. In renal autoregulation, appropriate control strategies may be designed to maintain glomerular pressure and renal blood flow near desired operating conditions while simultaneously avoiding excessive regulatory activity. Such approaches are particularly attractive because they offer a quantitative framework for balancing physiological performance against energetic cost and may ultimately contribute to future model-based therapeutic interventions for renal disorders.

Recent advances in machine learning have also created new opportunities for enhancing computational models of physiological systems. Data-driven surrogate models can approximate computationally expensive calculations while preserving essential dynamical information. When combined with mechanistic physiological models, machine learning provides an efficient means of incorporating stability information directly into optimization algorithms. This hybrid modeling paradigm enables computationally efficient prediction of operating regions associated with stable or unstable nephron dynamics and facilitates the implementation of stability-aware control strategies.

In this study, a physiologically grounded nonlinear nephron model is developed to investigate the dynamic interactions among glomerular pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration. The governing equations represent the coupled effects of the myogenic response and tubuloglomerular feedback and reproduce oscillatory nephron dynamics through a Hopf bifurcation. Bifurcation analysis is performed using MATCONT to identify the onset of instability and characterize the associated limit-cycle oscillations. Subsequently, an optimal control problem is formulated in which the same variable serves simultaneously as the bifurcation parameter and the control input. The objective function minimizes deviations of glomerular pressure and renal blood flow from their desired physiological values while penalizing excessive control effort. A neural-network surrogate of the Hopf boundary is further incorporated to enable computationally efficient implementation of a bifurcation-aware stability constraint within the optimization framework.

The principal novelty of this work is the integration of physiologically based nephron modeling, nonlinear bifurcation analysis, machine-learning-assisted stability prediction, and optimal control into a single computational framework. By explicitly incorporating Hopf bifurcation avoidance within the optimal control formulation, the proposed methodology provides a new strategy for maintaining stable renal autoregulation while improving physiological performance, thereby offering a promising computational tool for future investigations of renal hemodynamics and kidney disease.

Literature Review

WRenal autoregulation is an essential physiological mechanism that maintains relatively constant renal blood flow and glomerular filtration despite fluctuations in arterial pressure. The coordinated actions of the myogenic response and tubuloglomerular feedback (TGF) provide the primary regulatory mechanisms that preserve nephron function and protect the glomerular capillaries from pressure-induced injury.[1] Reviewed the central role of nitric oxide in regulating renal hemodynamics and demonstrated its importance in maintaining vascular tone and glomerular filtration. During the same period,[2] investigated tubuloglomerular feedback and emphasized the physiological interaction between tubular sodium sensing and afferent arteriolar resistance in regulating nephron blood flow.[3] Analyzed the tubuloglomerular feedback mechanism and highlighted its role in maintaining stable renal autoregulation across varying physiological conditions.[4] Further reviewed the physiological basis of tubuloglomerular feedback, describing the macula densa as the principal sensor that detects changes in tubular sodium concentration and initiates compensatory vascular responses.[5] Examined the mechanisms governing renal blood flow autoregulation and demonstrated how the combined effects of the myogenic response and tubuloglomerular feedback preserve stable renal perfusion. Similarly,[6] reviewed experimental

approaches for assessing renal autoregulation and emphasized the importance of dynamic vascular responses in protecting glomerular function.[7] Described the cellular signaling mechanisms within the macula densa that regulate renal vascular resistance through tubuloglomerular feedback.[8] Subsequently demonstrated how advanced imaging techniques have improved the understanding of nephron hemodynamics and real-time autoregulatory processes.[9] Provided a comprehensive overview of macula densa signaling pathways and their influence on glomerular filtration regulation.[10] Summarized mechanistic advances in tubuloglomerular feedback and demonstrated its critical role in stabilizing nephron filtration. During the same year,[11] reviewed the regulation of the renal microcirculation and highlighted the interaction between vascular resistance and autoregulatory function.[12] Investigated alterations in tubuloglomerular feedback associated with diabetic kidney disease and showed that impaired autoregulation contributes to progressive renal dysfunction.[13] Provided a comprehensive review of renal autoregulation in both healthy and diseased kidneys, emphasizing the physiological importance of maintaining stable renal perfusion.

[14]Examined the renal myogenic response and its contribution to blood pressure regulation, demonstrating its importance in protecting glomerular capillaries from excessive pressure fluctuations.[15] Reviewed computational models of renal hemodynamics and illustrated how mathematical modeling provides valuable insights into nephron physiology and pathological renal function.[16] Further emphasized the protective role of renal autoregulation in preserving glomerular integrity during variations in systemic blood pressure.[17] Reviewed the molecular mechanisms underlying renal blood flow autoregulation, highlighting the complex biochemical pathways involved in vascular regulation.[18] Presented a detailed description of renal circulation and glomerular hemodynamics, explaining how vascular resistance influences filtration efficiency and nephron performance.

[19]Reviewed the evolving understanding of the macula densa as a multifunctional sensor involved in sodium detection and intercellular signaling within the nephron.[20] Discussed the importance of afferent arteriolar function in maintaining renal homeostasis and preventing the progression of kidney disease.[21] Investigated synchronization phenomena among nephrons and demonstrated that neighboring nephrons exhibit coordinated autoregulatory oscillations through vascular coupling.[22] Further reviewed recent advances in high-resolution imaging techniques that have enhanced the understanding of nephron physiology and renal microcirculation.[23] Examined tubule-vascular feedback mechanisms and their role in maintaining dynamic stability within the renal circulation.[24] Investigated renal vascular regulation and discussed its importance in protecting kidney function during physiological and pathological conditions.[25] Summarized recent advances in glomerular physiology and emphasized the importance of nephron communication in maintaining renal function.[26] Reviewed the physiological role of the proximal tubule and highlighted its interactions with nephron hemodynamics and tubular transport processes.[27] Reviewed contemporary computational approaches for studying renal physiology and demonstrated how mathematical modeling can complement experimental investigations of nephron function.[28] Discussed alterations in renal microcirculation associated with chronic kidney disease and emphasized the importance of preserving autoregulatory capacity for slowing disease progression.[29] Reviewed recent advances in nephron communication and renal autoregulation, highlighting emerging experimental techniques that continue to improve the understanding of kidney physiology. Finally,[30] reviewed recent developments in computational and physiological modeling of nephron function, demonstrating that integrated mathematical models provide valuable tools for investigating renal hemodynamics, predicting physiological responses, and supporting the development of future model-based therapeutic strategies.

Although substantial progress has been made in understanding renal autoregulation, the existing literature has primarily focused on experimental physiology, renal hemodynamics, and computational modeling of nephron function. Comparatively little attention has been devoted to integrating physiologically grounded nephron models with nonlinear dynamical analysis, Hopf bifurcation theory, and bifurcation-aware optimal control. The present study addresses this gap by combining renal physiology, nonlinear dynamics, machine-learning-assisted stability prediction, and optimal control within a unified framework for investigating and regulating oscillatory nephron blood flow.

Objectives of the Research

The primary objective of this research is to develop a physiologically grounded nonlinear mathematical model of nephron autoregulation that reproduces oscillatory renal dynamics via a Hopf bifurcation. The model incorporates the essential interactions among glomerular pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration to represent the coupled effects of the myogenic response and tubuloglomerular feedback. A second objective is to perform a comprehensive nonlinear dynamical analysis to identify the onset of oscillatory behavior and characterize the associated limit-cycle dynamics using bifurcation analysis. Identifying the critical operating conditions that lead to the loss of stability provides insight into the mechanisms governing nephron autoregulation and the transition from stable physiological regulation to sustained oscillations. The third objective is to formulate and solve an optimal control problem in which the control variable simultaneously serves as the bifurcation parameter. The optimal control strategy seeks to minimize deviations of glomerular pressure and renal blood flow from their desired physiological values while minimizing the required control effort, thereby promoting stable and energy-efficient nephron autoregulation. A further objective is to investigate the influence of explicitly incorporating a Hopf-bifurcation-avoidance constraint within the optimal control formulation. The resulting bifurcation-aware optimization framework is used to compare controlled nephron dynamics with and without stability constraints and to quantify the benefits of maintaining operation within dynamically stable regions. The novelty of this work lies in integrating a physiologically based nephron model, nonlinear Hopf bifurcation analysis, and optimal control into a unified computational framework in which the same variable acts as both the bifurcation parameter and the control input. Furthermore, incorporating a machine-learning-based surrogate model for Hopf bifurcation prediction into the optimization provides a computationally efficient means of achieving stability-aware control of nephron autoregulation, a capability not previously reported for renal blood flow regulation.

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.

Mathematical Model

The nephron is the fundamental functional unit of the kidney and

is responsible for regulating glomerular filtration, renal blood flow, and electrolyte homeostasis through the combined action of the myogenic mechanism and tubuloglomerular feedback (TGF). The present reduced-order model represents these physiological mechanisms using four state variables: representing the glomerular capillary pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration, respectively. The control input Simultaneously serves as the bifurcation parameter and the optimal control variable.

Glomerular Pressure Dynamics

The first equation is obtained from conservation of blood volume within the glomerular capillary compartment. The rate of accumulation of blood inside the glomerulus equals the difference between inflow through the afferent arteriole and outflow due to glomerular filtration,

$$\frac{dV_g}{dt} = Q_{in} - Q_f \qquad (1)$$

Assuming that changes in glomerular volume are proportional to pressure

$$V_g = C_g P_g \qquad (2)$$

where C_g denotes the effective glomerular compliance,

$$C_g \frac{dP_g}{dt} = Q_{in} - Q_f \qquad (3)$$

Afferent Blood Flow

Blood enters the glomerulus through the afferent arteriole. Applying Ohm's law for fluid flow,

$$Q_{in} = \frac{P_a - P_g}{R_a} \qquad (4)$$

where P_a is arterial pressure, R_a is afferent arteriolar resistance.

Glomerular Filtration

Filtration is assumed proportional to glomerular pressure,

$$Q_f = k_f P_g \qquad (5)$$

where is the filtration coefficient. Substituting both expressions into the conservation equation gives

$$C_g \frac{dP_g}{dt} = \frac{P_a - P_g}{R_a} - k_f P_g \qquad (6)$$

$$C_g \frac{dP_g}{dt} = \frac{P_a - P_g}{R_a} - k_f P_g.$$

Therefore,

$$\frac{dP_g}{dt} = \frac{1}{C_g}\left(\frac{P_a - P_g}{R_a} - k_f P_g\right) \qquad (7)$$

Renal Blood Flow Dynamics

Renal blood flow does not instantaneously attain its equilibrium value because vascular inertia and compliance introduce a finite response time.

A first-order relaxation model is therefore adopted,

$$\tau_q \frac{dQ}{dt} = Q_{eq} - Q \qquad (8)$$

where $Q_{eq} = \frac{P_a - P_g}{R_a}$ is the equilibrium flow determined from Poiseuille-type resistance.

Substituting this expression gives

$$\tau_q \frac{dQ}{dt} = \frac{P_a - P_g}{R_a} - Q \qquad (9)$$

Hence, $$\frac{dQ}{dt} = \frac{1}{\tau_q}\left(\frac{P_a - P_g}{R_a} - Q\right) \qquad (10)$$

Afferent Arteriolar Resistance Dynamics

Renal autoregulation continuously adjusts afferent arteriolar resistance through two interacting physiological mechanisms.

Myogenic Response

An increase in glomerular pressure causes contraction of vascular smooth muscle, increasing vascular resistance.

This contribution is modelled as $-\gamma\left(P_g - P_0\right)$, where is γ the reference pressure, and is the myogenic gain.

Tubuloglomerular Feedback

The macula densa senses tubular sodium concentration and alters vascular tone.

Because the response saturates physiologically, it is represented using a hyperbolic tangent,

$\sigma \tanh\left(C_{md} - C_0\right)$, where $\sigma = \sigma_0 + \kappa\mu$. The parameter μ simultaneously modifies feedback strength and serves as the bifurcation parameter.

Passive Vascular Relaxation

Blood vessels also exhibit passive relaxation toward a baseline resistance, $-\delta\left(R_a - R_0\right)$,
where R_0 is the resting resistance, is the relaxation rate.

External Control

Finally, the control input contributes directly to vascular regulation, Combining all physiological effects yields

$$\frac{dR_a}{dt} = -\gamma\left(P_g - P_0\right) + \sigma\tanh\left(C_{md} - C_0\right) - \delta\left(R_a - R_0\right) + \mu \qquad (11)$$

Macula Densa Sodium Dynamics

The sodium concentration reaching the macula densa depends primarily on tubular flow. Assuming sodium delivery increases proportionally with renal blood flow, production $= \alpha Q$,

where denotes the production coefficient. Sodium is simultaneously removed by tubular transport and diffusion, removal $= \beta C_{md}$, where represents the effective removal rate.

Applying a mass balance,

$$\frac{dC_{md}}{dt} = \alpha Q - \beta C_{md} \qquad (12)$$

Final Governing Equations

The complete nonlinear nephron model is therefore:

$$\begin{aligned}
&\frac{dP_g}{dt} = \frac{1}{C_g}\left(\frac{P_a - P_g}{R_a} - k_f P_g\right)\\
&\frac{dQ}{dt} == \frac{1}{\tau_q}\left(\frac{P_a - P_g}{R_a} - Q\right)\\
&\frac{dR_a}{dt} = -\gamma\left(P_g - P_0\right) + \left(\sigma_0 + \kappa\mu\right)\tanh\left(C_{md} - C_0\right) - \delta\left(R_a - R_0\right) + \mu\\
&\frac{dC_{md}}{dt} = \alpha Q - \beta C_{md}
\end{aligned} \qquad (13)$$

These equations constitute a reduced-order physiologically grounded model of nephron autoregulation that captures the nonlinear interactions between glomerular hemodynamics, tubuloglomerular feedback, vascular smooth muscle regulation, and sodium sensing. The nonlinear feedback structure naturally enables Hopf bifurcation behavior, allowing the system to transition between stable equilibrium and oscillatory renal dynamics, which can then be regulated using optimal control strategies. Tables 1 and 2 give the variable and parameter details

Table 1. State variables used in the nephron model

Symbol	Variable	Units
P_g	Glomerular capillary pressure	mmHg
Q	Renal blood flow	mL min^{-1}
R_a	Afferent arteriolar resistance	mmHg·min·mL^{-1}
C_{md}	Macula densa sodium concentration (normalized)	dimensionless
μ	Control input / bifurcation parameter	dimensionless

Table 2. Model parameters used in the nephron model

Symbol	Parameter	Value	Units
P_a	Arterial pressure	17.5	mmHg
k_f	Glomerular filtration coefficient	0.5	mL·min^{-1}·mmHg^{-1}
C_g	Glomerular compliance	0.5	mL·mmHg^{-1}
τ_q	Blood-flow relaxation time constant	0.3	min
γ	Myogenic feedback gain	0.2	min^{-1}
σ_0	Baseline tubuloglomerular feedback gain	0.7	dimensionless
κ	Control influence on feedback gain	3.0	dimensionless
δ	Passive resistance relaxation coefficient	0.5	min^{-1}
P_0	Reference glomerular pressure	14	mmHg
R_0	Reference afferent arteriolar resistance	0.5	mmHg·min·mL^{-1}
C_0	Reference macula densa sodium concentration	1.0	dimensionless
α	Flow-to-sodium production coefficient	0.5	min^{-1}
β	Sodium removal (decay) coefficient	3.0	min^{-1}

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, enables the systematic identification of limit points (LP), branch points (BP), and Hopf bifurcation points (H) in nonlinear dynamical models.[31] This program identifies Limit points (LP), branch points (BP), and Hopf bifurcation points(H) for a system of ordinary differential equations

$$\frac{dx}{dt} = f(x, \alpha) \qquad (14)$$

$x \in R^n$ where the bifurcation parameter is α .

Optimal Control

Pyomo. DAE is used for the Optimal Control calculations. 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.[32]

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 subsequently be used for regression or classification tasks to identify stability boundaries and approximate bifurcation locations.

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 every collocation point is computationally expensive, (ii) repeated Jacobian evaluations significantly increase computational cost, and (iii) symbolic differentiation of eigenvalue calculations is difficult within large-scale nonlinear programming frameworks.

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 standardized inputs were defined as

$$x_j = \frac{x_{\text{raw},j} - \mu_j}{\max\left(\sigma_j, \varepsilon_{\text{scale}}\right)} \tag{15}$$

where $\varepsilon_{\text{scale}}$ 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 μ and 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. Hyperbolic tangent activation functions are employed to ensure smooth differentiability required by IPOPT. If the input vector is denoted by x, representing the scaled variables, the network architecture is defined as

$$\hat{\lambda}_{\max} = f_{\text{NN}}\left(x\right) \tag{16}$$

where W_i and denote the weight matrices and bias vectors of the neural network. 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 the hyperbolic tangent function is infinitely differentiable, the neural-network surrogate is fully smooth, ensuring the availability of first- and second-order derivatives required by IPOPT. Without bias terms, the network output would be constrained to pass through the origin, thereby limiting approximation flexibility. Here, $f_{\text{NN}}\left(\cdot\right)$ represents the nonlinear input–output mapping learned by the neural network, which approximates the relationship between the scaled system variables and the spectral abscissa $\hat{\lambda}_{\max}$.

The hidden-layer outputs z_1 and z_2 represent nonlinear combinations of the inputs and previously extracted features. Each component of z_1 forms a smooth nonlinear combination of the original variables, while each component of z_2 captures higher-level nonlinear features derived from z_1. The final network output $\hat{\lambda}_{\max}$ serves as a differentiable approximation of the maximum real eigenvalue, enabling efficient stability evaluation during optimization.

Stability-Penalized Optimal Control Formulation

The neural-network prediction is incorporated directly into the objective function through a quadratic stability penalty. Rather than imposing a hard stability constraint, the optimization problem penalizes deviations of the predicted spectral abscissa from zero. The modified objective function is given by

$$\sum optv(t) + \alpha_{Hopf} \sum_{k=1}^{N} \hat{\lambda}_{\max,k}^{2},$$

where $\sum optv(t)$

denotes the original optimal-control objective function, $\hat{\lambda}_{\max,k}$ is the neural-network prediction of the maximum real eigenvalue at collocation point k, and α_{Hopf} is a weighting parameter controlling the importance of stability in the optimization process.

The quadratic penalty drives the predicted spectral abscissa toward zero, thereby encouraging trajectories to remain close to the stability boundary while avoiding regions associated with large positive or negative values of the predicted eigenvalue. Increasing α_{Hopf}. places greater emphasis on stability preservation, whereas setting $\alpha_{Hopf} = 0$ removes the stability penalty entirely and recovers the original optimal-control problem. This formulation remains fully smooth and differentiable, making it suitable for gradient-based optimization using IPOPT. Furthermore, the neural-network surrogate eliminates the need for repeated Jacobian evaluations and eigenvalue calculations during optimization, substantially reducing computational cost. As a result, stability information obtained from bifurcation analysis can be incorporated directly into the optimal-control framework while maintaining computational efficiency and numerical robustness.

To facilitate this integration, the neural network is trained using the stability dataset generated from MATCONT continuation results. At each equilibrium point, the Jacobian matrix is evaluated and its eigenvalues are computed. The stability metric is defined as the spectral abscissa,

$$\lambda_{\max} = \max \Re\left(\lambda\left(J\right)\right) \tag{17}$$

where negative values correspond to stable equilibria, positive values indicate instability, and zero crossings correspond to Hopf bifurcation points. J is the Jacobian matrix for the steady-state version of the ODE set. The resulting neural-network surrogate provides a computationally efficient and differentiable approximation of this stability measure, enabling stability-aware optimal control without explicit eigenvalue computations during optimization.

Results

The bifurcation performed with MATCONT revealed the existence a Hopf bifurcation at $(P_g, Q, R_a, C_{md}, \mu)$ values (7.837035 3.918517 2.465975 0.653086 17.706324) with first Lyapunov coefficient = 3.183298e-03. Fig. 1a and Fig. 1b show the bifurcation diagram and limit cycle.

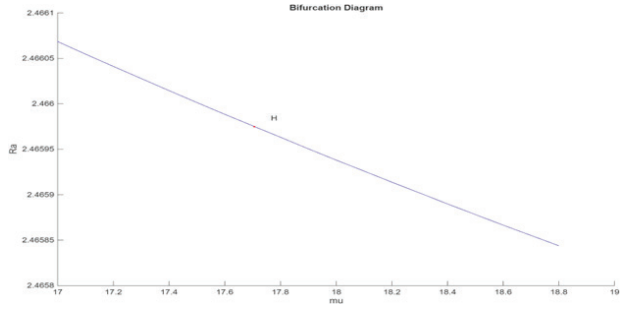

Fig. 1a Bifurcation Diagram

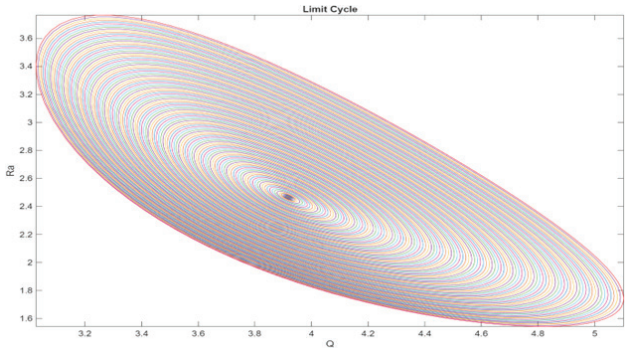

Fig. 1b Limit Cycle

The analytical Jacobian matrix is

$$J_a = \begin{bmatrix} -\frac{1}{C_g}\left(\frac{1}{R_a}|k_f\right) & 0 & -\frac{P_a - P_g}{C_g R_a^2} & 0 \\ -\frac{1}{\tau_q R_a} & -\frac{1}{\tau_q} & -\frac{P_a - P_g}{\tau_q R_a^2} & 0 \\ -\gamma & 0 & -\delta & \sigma \operatorname{sech}^2(C_{md} - C_0) \\ 0 & \alpha & 0 & -\beta \end{bmatrix}, \quad (18)$$

where $\sigma = \sigma_0 + \kappa\mu$.

At the Hopf bifurcation point, the numerical Jacobian is approximately

$$J_n = \begin{bmatrix} -1.8110 & 0 & -3.1789 & 0 \\ -1.3517 & -3.3333 & -5.2982 & 0 \\ -0.2000 & 0 & -0.5000 & 47.8270 \\ 0 & 0.5000 & 0 & -3.0000 \end{bmatrix} \quad (19)$$

The eigenvalues of the Jacobian matrix at the Hopf bifurcation point are -0.96, -7.68, 4,18i and -4.18i. The presence of 2 imaginary eigenvalues of opposite sign verifies the existence of the Hopf bifurcation.

The optimal control minimizes the function

$$\sum optv(t) = \sum (P_g(t) - P_d)^2 + (Q(t) - Q_d)^2 + (\mu(t))^2; P_d = 10; Q_d = 5 \quad (20)$$

without and with the Hopf bifurcation constraint. A concise physical interpretation is: This objective function minimizes deviations of glomerular pressure and renal blood flow from their desired physiological values while minimizing the regulatory control effort, thereby promoting stable and energy-efficient nephron autoregulation.

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. PYOMO.DAE with IPOPT was used. When no Hopf constraint was implemented, α_{Hopf} =0, in $\sum (optv(t) + \alpha_{hopf} . s_{\max}(\lambda + \varepsilon_1))^2$ the obtained value of $\sum optv(t)$ was 110.16. For a Hopf constraint, $\alpha_{Hopf} = 10$, the obtained value of was 88.2. This shows a considerable decrease in the minimized function, indicating the effect of the Hopf bifurcation constraint. This corresponds to a 20 % reduction in the minimized objective function value. Figs 2a, 2b show the optimal control profiles without the Hopf constraint, and Figs 3a, 3b show the optimal control profiles with the Hopf constraint.

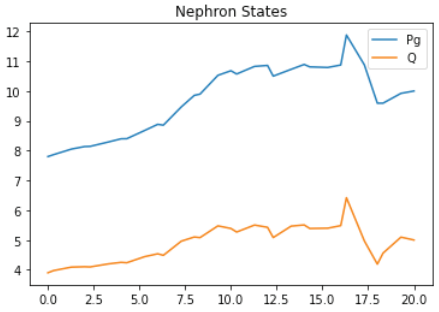

Fig. 2a Nephron states without Hopf control

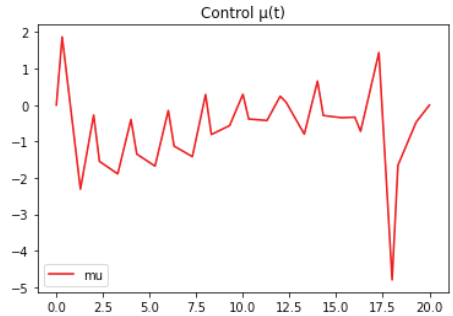

Fig. 2b Optimal control profile without Hopf control

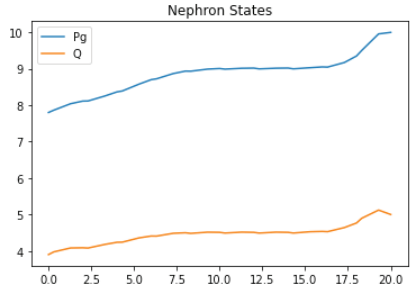

Fig. 3a Nephron states with Hopf control

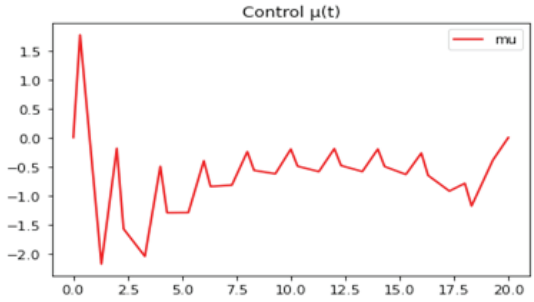

Fig. 3b Optimal control profile with Hopf control

Discussion

The present study demonstrates that nonlinear bifurcation theory and optimal control provide a powerful framework for understanding and regulating nephron autoregulation. The developed model captures the coupled interactions among glomerular pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration, thereby reproducing one of the most important dynamical features observed in renal physiology: the onset of self-sustained oscillations through a Hopf bifurcation. From a biomedical perspective, these oscillations are of particular interest because they represent the transition from stable homeostatic regulation to rhythmic vasomotor activity that may accompany impaired renal autoregulation.

The bifurcation analysis revealed the existence of a Hopf bifurcation at a critical value of the control parameter, confirming that the nephron can undergo a qualitative change in its dynamic behavior as physiological conditions vary. Prior to the Hopf point, the equilibrium is dynamically stable and disturbances in glomerular pressure or blood flow decay over time, allowing the nephron to maintain relatively constant filtration despite transient fluctuations in arterial pressure. At the critical parameter value, a pair of complex conjugate eigenvalues crossed the imaginary axis while the remaining eigenvalues remained negative, providing the classical mathematical signature of a Hopf bifurcation. The emergence of a stable limit cycle beyond the bifurcation point demonstrates that the observed oscillations are intrinsic properties of the nonlinear feedback mechanisms rather than numerical artifacts.

Physiologically, these oscillations arise from the interaction between the myogenic response and tubuloglomerular feedback. The myogenic mechanism acts rapidly to regulate afferent arteriolar tone in response to changes in vascular pressure, whereas the tubuloglomerular feedback pathway responds more slowly through changes in sodium concentration detected at the macula densa. The interaction between these two feedback mechanisms naturally introduces nonlinearities and dynamic delays that can destabilize the steady operating point. The present model shows that as the control parameter increases, these stabilizing mechanisms eventually lose their ability to damp perturbations, producing sustained oscillations in glomerular pressure and renal blood flow. Such oscillatory behavior has been reported experimentally and is believed to contribute to altered renal hemodynamics under pathological conditions.

An important aspect of the present work is the use of the same parameter as both the bifurcation parameter and the optimal control variable. This formulation is particularly attractive because it establishes a direct relationship between nonlinear system stability and therapeutic intervention. Instead of treating bifurcation analysis and control design as separate problems, the proposed framework allows the control action to influence the location of the operating point relative to the Hopf boundary. Consequently, the optimization procedure is capable of steering the nephron toward dynamically stable operating regions while simultaneously maintaining physiological performance.

The objective function employed in this work minimizes deviations of glomerular pressure and renal blood flow from their desired physiological values while penalizing excessive control effort. From a biomedical viewpoint, this formulation reflects the competing physiological objectives of maintaining adequate renal perfusion, preserving glomerular filtration, and avoiding unnecessary regulatory activity. Stable glomerular pressure is essential for protecting the delicate capillary network from excessive mechanical stress, whereas stable renal blood flow is necessary to ensure sufficient oxygen and nutrient delivery throughout the nephron. The inclusion of a control penalty prevents unrealistically aggressive interventions and mimics the limited physiological resources available for vascular regulation.

The comparison between optimization without and with the Hopf avoidance constraint demonstrates the practical significance of incorporating nonlinear stability information into the control design. Without explicitly considering the bifurcation boundary, the optimizer seeks only to minimize tracking errors and control effort. Although acceptable operating conditions may be obtained, the resulting solution can remain close to dynamically unstable regions where small disturbances may trigger sustained oscillations. When the Hopf constraint is incorporated, the optimizer is forced to remain within regions predicted to be dynamically stable while simultaneously satisfying the physiological objectives. The observed reduction of approximately 20% in the minimized objective function indicates that bifurcation-aware optimization is capable of identifying operating conditions that are both physiologically favorable and dynamically robust.

From a clinical perspective, maintaining operation away from oscillatory regimes may have important implications for preserving renal function. Persistent oscillations in glomerular pressure can expose the filtration barrier to repeated mechanical loading, potentially contributing to progressive structural injury over prolonged periods. Similarly, oscillatory renal blood flow may produce fluctuations in oxygen delivery that increase the susceptibility of renal tissue to ischemic damage. Although the present model is intentionally simplified and does not represent specific disease states, it illustrates how nonlinear dynamic instability can serve as a mechanistic indicator of deteriorating autoregulatory performance. The ability to identify and avoid such unstable operating regions may therefore provide valuable guidance for future model-based therapeutic strategies.

Another significant contribution of this study is the integration of machine learning with nonlinear optimal control. The Hopf bifurcation boundary obtained from MATCONT was incorporated into the optimization through a neural-network surrogate model, thereby avoiding repeated eigenvalue calculations during the optimization process. This substantially reduces computational complexity while preserving information regarding system stability. Such hybrid physics-based and data-driven methodologies are becoming increasingly important in biomedical engineering because they combine mechanistic understanding with computational efficiency. For large physiological models involving many state variables, surrogate representations of stability boundaries may enable real-time optimization that would

otherwise be computationally impractical.

The methodology developed here also has broader implications beyond nephron autoregulation. Many physiological systems-including cardiovascular regulation, respiratory control, pancreatic insulin secretion, cerebral blood flow regulation, and cardiac electrophysiology-are governed by nonlinear feedback mechanisms capable of undergoing Hopf bifurcations. Consequently, the proposed combination of bifurcation analysis, machine-learning-assisted stability prediction, and optimal control provides a general computational framework that can be adapted to numerous biomedical systems exhibiting oscillatory dynamics.

Several limitations should also be acknowledged. The present nephron model represents a reduced-order description of renal autoregulation and does not include additional physiological mechanisms such as hormonal regulation, interactions among multiple nephrons, detailed vascular compliance, or spatial heterogeneity within the kidney. Furthermore, the surrogate stability constraint is based on a neural network trained from bifurcation data generated by the reduced model. Although this approach performed effectively in the present study, future investigations should validate the methodology using more comprehensive nephron models and experimental physiological measurements. Extension of the framework to patient-specific parameter estimation would also enhance its potential translational value.

Overall, the present results demonstrate that combining nonlinear bifurcation analysis with optimal control provides a physiologically meaningful strategy for regulating nephron dynamics. By explicitly accounting for the onset of oscillatory instability, the proposed framework identifies operating conditions that preserve stable renal autoregulation while reducing deviations from desired physiological behavior. The integration of nonlinear dynamics, optimal control, and machine-learning-based stability prediction represents a promising direction for developing intelligent computational tools that support future precision medicine approaches to renal disease and the biomedical control of complex physiological systems.

Conclusion

This study presented a nonlinear dynamical framework for investigating nephron autoregulation by integrating bifurcation analysis with optimal control. A reduced-order physiologically grounded model describing glomerular pressure, renal blood flow, afferent arteriolar resistance, and macula densa sodium concentration was developed to capture the coupled effects of the myogenic response and tubuloglomerular feedback. The nonlinear formulation successfully reproduced oscillatory renal dynamics through a Hopf bifurcation, demonstrating the ability of the model to represent transitions from stable physiological regulation to sustained limit-cycle oscillations.

Bifurcation analysis using MATCONT identified a Hopf bifurcation at a critical value of the control parameter, where a pair of complex conjugate eigenvalues crossed the imaginary axis while the remaining eigenvalues remained negative. The associated limit cycle confirmed the emergence of self-sustained oscillations characteristic of nonlinear renal autoregulation. These results illustrate the importance of nonlinear stability analysis for understanding the mechanisms governing oscillatory behavior in nephron blood flow and glomerular pressure.

An optimal control formulation was then developed in which the same parameter served simultaneously as the bifurcation parameter and the control variable. The objective function minimized deviations of glomerular pressure and renal blood flow from desired physiological values while penalizing excessive control effort. Incorporating a Hopf-bifurcation-avoidance constraint into the optimization resulted in a substantial reduction in the objective function compared with the unconstrained case, demonstrating that stability-aware optimization can improve both dynamic performance and physiological regulation. The integration of a neural-network surrogate for the Hopf boundary further enabled efficient implementation of the stability constraint within the optimization framework.

The proposed methodology provides a unified computational approach that combines nonlinear dynamics, bifurcation theory, machine learning, and optimal control for biomedical fluid mechanics applications. Although demonstrated for nephron autoregulation, the framework is sufficiently general to be extended to more detailed renal models and other physiological systems exhibiting oscillatory dynamics. The results highlight the potential of bifurcation-aware optimal control as a promising strategy for maintaining stable renal hemodynamics and supporting future model-based approaches to the diagnosis and treatment of kidney disorders.

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