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# Drug Delivery and Artificial Intelligence for Bifurcation-Aware Modeling and Optimal Control of Hemodynamic Transport Systems

**Lakshmi. N. Sridhar***

*Chemical Engineering Department University of Puerto Rico Mayaguez, PR 00681*

***Correspondence Author:**
Lakshmi. N. Sridhar, Chemical Engineering Department University of Puerto Rico Mayaguez, PR 00681.

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## Abstract

*This study develops a reduced-order, physics-informed framework for analyzing and optimizing drug delivery in a vascular environment by coupling hemodynamic flow dynamics with pharmacokinetic transport. The blood flow field is represented using a Hopf-type nonlinear oscillator derived from reduced Navier–Stokes dynamics, capturing the emergence of oscillatory flow states that significantly influence mixing and transport. This fluid subsystem is directly coupled to a two-compartment pharmacokinetic model that describes drug concentration evolution in plasma and surrounding tissue. The resulting system accounts for convection-enhanced dispersion, inter-compartmental mass transfer, and systemic clearance, thereby providing a more realistic representation of in vivo drug transport than classical compartmental approaches.*

*Bifurcation analysis reveals a Hopf bifurcation that governs the transition between steady and oscillatory flow regimes, which in turn modulates drug dispersion and tissue uptake efficiency. The interaction between flow instability and drug transport is shown to play a critical role in determining concentration profiles in both plasma and tissue compartments. Furthermore, the framework enables the study of how flow-induced mixing can enhance or impair therapeutic delivery depending on system parameters.*

*An optimal control formulation is developed to regulate drug concentration and flow activity, with and without bifurcation-aware constraints. The results demonstrate that incorporating stability constraints improves performance and controls drug distribution, reducing undesirable concentration fluctuations while maintaining effective tissue delivery. The proposed approach provides a unified computational framework integrating nonlinear dynamics, transport physics, and control theory, offering new insights into the role of hemodynamic instabilities in drug delivery systems and enabling improved therapeutic design strategies.*

**Keywords:** Drug delivery, pharmacokinetics, Navier–Stokes reduced-order model, Hopf bifurcation, optimal control

## Introduction

Drug delivery remains one of the most important challenges in modern biomedical engineering and pharmaceutical science. The effectiveness of many therapeutic agents depends not only on the administered dosage but also on the ability of the drug to reach the intended target tissue at therapeutically relevant concentrations while minimizing exposure to healthy tissues. Conventional systemic administration methods often result in substantial drug losses, poor localization, reduced bioavailability, and undesirable side effects. These limitations are particularly significant in applications such as targeted cancer therapy, arterial drug delivery, catheter-based infusion systems, and localized treatment of vascular diseases. Consequently, there is increasing interest in developing advanced drug delivery strategies that exploit the underlying transport mechanisms governing the movement of pharmaceutical compounds within the circulatory system.

The transport of drugs through blood vessels is fundamentally a fluid-mechanical process. Following administration into the bloodstream, drug molecules are transported by advection, diffusion, and mixing processes generated by the surrounding blood flow. The resulting concentration distributions depend strongly on local hemodynamic conditions, including velocity profiles, pulsatile flow structures, recirculation zones, and flow instabilities. Numerous experimental and computational studies have demonstrated that fluid motion can significantly influence drug residence times, tissue penetration, and overall therapeutic effectiveness. In particular, oscillatory flow structures can enhance mixing and mass transfer, potentially improving transport from the bloodstream into surrounding tissues. Understanding the interaction between flow dynamics and drug transport therefore represents a critical step toward the design of more effective and reliable drug delivery systems.

Mathematical modeling has become an essential tool for investigating drug transport phenomena in complex biological environments. Traditional pharmacokinetic models typically describe drug movement using compartmental approaches in which the body is represented by interconnected regions exchanging mass through prescribed transfer rates. While such models are highly useful for predicting concentration profiles and clearance dynamics, they generally neglect the influence of the underlying fluid mechanics. Conversely, computational fluid dynamics models based on the Navier–Stokes equations provide detailed descriptions of blood flow but often require substantial computational resources and may not be suitable for optimization and control studies. Reduced-order modeling techniques offer an attractive compromise by retaining the dominant physical mechanisms while substantially reducing computational complexity.

Blood flow within arteries and catheter-based delivery systems is inherently unsteady due to the pulsatile nature of the cardiovascular system. Under certain operating conditions, nonlinear interactions among inertial, viscous, and forcing effects can generate oscillatory behavior characterized by self-sustained periodic motion. Such phenomena are frequently associated with Hopf bifurcations, which occur when a stable equilibrium loses stability and gives rise to a limit cycle. Hopf bifurcations have been extensively studied in fluid mechanics and nonlinear dynamical systems because they provide a fundamental mechanism for the emergence of oscillatory flow structures. In physiological transport systems, these oscillations can substantially alter mixing rates and consequently influence drug distribution patterns. Despite their potential importance, the role of flow bifurcations in drug delivery has received relatively limited attention compared with traditional pharmacokinetic analyses.

The ability to identify and characterize bifurcation behavior is particularly important in biomedical transport applications because operating conditions near critical stability boundaries may lead to significant changes in transport performance. Small variations in flow parameters can produce large changes in oscillation amplitude, mixing intensity, and mass transfer rates. Consequently, therapeutic outcomes may depend not only on dosing strategies but also on the dynamical state of the underlying flow field. A detailed understanding of these nonlinear phenomena can therefore provide new opportunities for improving drug delivery efficiency through stability-aware treatment design.

Optimal control provides a powerful framework for determining operating policies that achieve desired therapeutic objectives while satisfying dynamic constraints. In recent years, optimal control techniques have been applied to a wide range of biomedical problems, including chemotherapy scheduling, insulin regulation, pharmacokinetic optimization, and controlled drug release systems. Most existing studies focus primarily on concentration-based objectives and do not explicitly account for nonlinear flow instabilities. However, because blood flow dynamics can significantly affect transport and mixing, the integration of bifurcation analysis and optimal control has the potential to provide more effective treatment strategies. By incorporating stability information directly into the optimization problem, it becomes possible to identify operating conditions that simultaneously enhance drug delivery performance and maintain favorable dynamical behavior.

The present work develops a nonlinear reduced-order model for coupled hemodynamic and drug transport dynamics. The fluid subsystem is derived from the incompressible Navier–Stokes equations through modal reduction and is represented by a Hopf normal form capable of exhibiting oscillatory flow behavior. Drug transport is modeled using coupled plasma and tissue concentration compartments that account for flow-enhanced mixing, tissue uptake, and clearance mechanisms. The resulting model captures the interaction between nonlinear blood flow dynamics and pharmacokinetic transport processes while remaining computationally tractable for bifurcation and optimization studies.

Bifurcation analysis is performed using MATCONT to identify critical operating conditions and characterize the emergence of oscillatory transport regimes. A machine-learning-based surrogate model is subsequently developed to represent stability information obtained from continuation calculations. This surrogate is embedded within a dynamic optimization framework formulated in PYOMO.DAE and solved using IPOPT. The resulting bifurcation-aware optimal control strategy enables stability considerations to be incorporated directly into the treatment design process.

The primary objective of this study is to investigate how flow-induced Hopf bifurcations influence drug delivery dynamics and to determine whether bifurcation-aware optimal control can improve transport performance. By combining nonlinear dynamics, reduced-order fluid mechanics, machine learning, and optimal control, the proposed framework provides a novel approach for the analysis and optimization of drug

delivery systems. The methodology offers new insight into the role of hemodynamic stability in therapeutic transport processes and establishes a foundation for the development of more efficient, robust, and clinically relevant drug delivery strategies.

## Literature Review

Drug delivery has progressively evolved from early mathematical descriptions of tissue transport toward fully engineered systems that integrate physiology, materials science, and transport phenomena. Early compartmental and tissue-level models emphasized the importance of heterogeneous perfusion in determining spatial drug distribution, establishing the need for more realistic transport descriptions [1]. The formulation of drug delivery as an engineering discipline provided a unified framework based on transport phenomena, diffusion, and convection, enabling systematic analysis of drug movement in biological systems. This marked a transition from descriptive pharmacology to predictive, physics-based modeling approaches [2]. Subsequent foundational developments highlighted the importance of spatial targeting in drug therapy, showing that controlling the location of drug action is as important as controlling dosage. This introduced the concept of spatially resolved therapeutic design [3]. Research into solid tumor environments demonstrated that biological barriers such as abnormal vasculature and elevated interstitial pressure severely restrict drug penetration, limiting therapeutic effectiveness. These findings underscored the need for models that incorporate physiological transport constraints [4]. Controlled drug delivery technologies were then developed to regulate temporal release profiles, allowing sustained and predictable drug concentration levels over time. These systems improved therapeutic stability compared to conventional bolus dosing strategies [5]. The emergence of multifunctional nanocarriers introduced platforms capable of integrating targeting, imaging, and controlled release functions, significantly expanding the capabilities of drug delivery systems. This development enabled more precise manipulation of transport and localization processes [6]. The translation of liposomal and lipid-based systems into clinical use demonstrated that engineered nanoscale carriers can achieve reliable in vivo performance, bridging the gap between laboratory design and medical application. This established practical feasibility for nanomedicine-based therapies [7]. Transport phenomena studies further emphasized the role of convection and diffusion coupling in determining solute dispersion behavior in biological and engineered systems [8]. These results reinforced the importance of fluid motion in drug transport analysis [8]. Targeted delivery strategies for cancer therapy demonstrated that receptor-mediated binding and enhanced permeability effects can significantly improve drug accumulation in diseased tissue compared to systemic circulation. This highlighted the limitations of uniform distribution assumptions in classical pharmacology[9]. Nanoparticle-based delivery systems were developed to exploit size-dependent transport behavior, enabling improved control over circulation, diffusion, and tissue penetration characteristics. These systems allowed tuning of pharmacokinetics through physical particle design [10]. The advancement of nanomedicine established nanoparticles as a central therapeutic platform capable of enhancing circulation time and improving tumor localization while reducing systemic toxicity. This significantly influenced modern drug delivery research directions [11]. Engineering of precision nanomedicines introduced multifunctional systems that combine targeting ligands, therapeutic agents, and diagnostic capabilities into unified platforms. These systems enabled more controlled spatiotemporal drug delivery strategies[12]. Despite technological advances, clinical translation studies revealed persistent challenges arising from immune clearance, biological heterogeneity, and variability in vascular transport conditions. These limitations highlighted the need for more predictive and robust transport models [13]. Systematic nanoparticle engineering studies investigated how physicochemical properties such as size, charge, and surface chemistry influence biodistribution and transport behavior in vivo. These findings provided design rules for improving therapeutic performance [14]. Further refinement of nanocarrier design focused on optimizing pharmacokinetic behavior through rational engineering of transport properties to maximize therapeutic index [15]. This shifted design strategies toward physics-based optimization of delivery systems [15]. Expanded investigations of nanoparticle interactions with biological systems revealed complex multi-scale processes including endothelial transport, immune recognition, and intracellular trafficking [16]. These interactions play a critical role in determining delivery efficiency [16]. Studies of biological variability demonstrated that inter-patient differences and tumor heterogeneity significantly affect drug transport and therapeutic outcomes. This highlighted the importance of adaptive and robust delivery strategies [17]. Cancer nanomedicine research confirmed that engineered nanoparticles can improve tumor accumulation and reduce systemic toxicity, although performance variability remains a major limitation. This variability is strongly linked to vascular heterogeneity[18]. Nanostructure-based drug delivery studies showed that nanoscale geometry and morphology strongly influence transport properties, including diffusion rates and cellular uptake mechanisms. This reinforced the role of structural design in controlling biological transport[19].Comprehensive reviews of nanoparticle systems established general principles governing stability, aggregation, and transport in biological media, providing a unified framework for nanomedicine design [20]. These principles guide modern formulation strategies.Clinical translation studies of nanomedicines highlighted both successes and persistent challenges in achieving consistent therapeutic outcomes across patient populations [21]. Scale-up and reproducibility remain key barriers.Research on physiological barriers emphasized the role of endothelial structure, extracellular matrix density, and heterogeneous perfusion in limiting drug penetration into target tissues. Overcoming these barriers remains a central challenge in drug delivery [22]. The enhanced permeability and retention effect was identified as a key mechanism for passive tumor targeting, although its variability across tumor types limits its predictive reliability. This has driven the

development of more adaptive targeting approaches [23]. Stimuli-responsive drug delivery systems introduced the ability to release therapeutic agents in response to environmental triggers such as pH, temperature, or enzymatic activity [24]. This enabled improved temporal and spatial control over drug release.Smart nanocarrier systems further advanced this concept by integrating sensing, targeting, and adaptive release mechanisms into a single autonomous platform. These systems represent a step toward intelligent drug delivery systems [25]. Advanced tumor targeting strategies focused on improving specificity and penetration depth using ligand engineering and vascular modulation techniques to enhance delivery efficiency [26]. These strategies aim to overcome limitations of passive transport mechanisms. Recent developments in vascular drug delivery systems emphasize the importance of integrating fluid mechanics with pharmacokinetics to more accurately model transport under physiological flow conditions[27]. This reflects the growing convergence of biomechanics and drug delivery science. Recent advances in physiological drug delivery modeling have focused on overcoming transport barriers through multiscale approaches that incorporate both vascular flow and tissue-level heterogeneity. These models aim to bridge the gap between microscopic transport processes and macroscopic therapeutic outcomes [28]. Finally, emerging research in vascular-targeted drug delivery highlights the importance of dynamic flow conditions and time-dependent transport mechanisms in determining drug efficacy in complex biological environments. These findings support the need for fully coupled fluid–transport models capable of capturing realistic physiological dynamics [29].

## Main Objectives of This Work

The primary objective of this work is to develop a nonlinear reduced-order model for drug delivery that combines hemodynamic flow dynamics derived from the Navier–Stokes equations with pharmacokinetic transport processes governing drug exchange between the bloodstream and target tissue. The study seeks to establish a mathematical framework capable of capturing the interaction between blood flow oscillations and drug transport dynamics while remaining computationally efficient for bifurcation and optimization analyses.

A further objective is to investigate the nonlinear dynamical behavior of the coupled flow–drug transport system and determine the conditions under which oscillatory transport regimes emerge. Particular emphasis is placed on identifying and characterizing Hopf bifurcations, which represent critical transitions from stable flow conditions to self-sustained oscillatory behavior. Through numerical continuation and bifurcation analysis, the work aims to determine equilibrium solutions, evaluate stability properties, locate critical bifurcation points, and analyze the resulting limit-cycle oscillations.

An important goal of this research is to examine how flow-induced oscillations influence drug delivery performance. Since oscillatory hemodynamics can alter mixing intensity, residence times, and mass transfer rates, understanding the relationship between flow stability and drug transport is essential for improving therapeutic effectiveness. The study therefore seeks to quantify the impact of hemodynamic instabilities on plasma drug concentrations, tissue drug uptake, and overall transport efficiency.

The work also aims to develop a machine-learning-based surrogate model capable of predicting stability characteristics from bifurcation data generated through continuation analysis. This surrogate model is intended to provide an efficient mechanism for incorporating dynamical stability information into optimization calculations without requiring repeated bifurcation computations during the optimization process.

Another major objective is to formulate and solve an optimal control problem for the coupled drug delivery system using PYOMO.DAE and IPOPT. The optimization framework is designed to determine dynamically favorable operating conditions while satisfying the governing nonlinear differential equations. Special attention is given to the incorporation of bifurcation-aware constraints that explicitly account for stability considerations during optimization.

The study further seeks to compare optimal operating strategies obtained with and without Hopf-bifurcation constraints in order to assess the influence of stability-aware control on drug delivery performance. By evaluating the resulting objective function values and optimal control profiles, the work aims to demonstrate the practical benefits of integrating nonlinear dynamics and bifurcation theory into therapeutic decision-making.

Ultimately, the overall objective of this research is to establish a comprehensive computational framework that combines fluid mechanics, pharmacokinetics, bifurcation analysis, machine learning, and optimal control for advanced drug delivery applications. Through this integration, the study aims to provide new insight into the role of hemodynamic stability in therapeutic transport processes and to demonstrate that bifurcation-aware optimization can lead to safer, more efficient, and more reliable drug delivery strategies. This study presents a novel interdisciplinary framework that integrates nonlinear fluid dynamics, pharmacokinetic modeling, bifurcation theory, machine learning, and optimal control for the analysis and optimization of drug delivery systems. Unlike conventional pharmacokinetic approaches that primarily rely on compartmental models with prescribed transfer rates, the present work explicitly incorporates flow-induced dynamics derived from a reduced-order representation of the Navier–Stokes equations. This allows the drug transport process to be directly coupled with underlying hemodynamic instabilities, providing a physically richer and more realistic description of vascular drug delivery.

A key novelty of this work lies in the reduction of the Navier–Stokes equations to a Hopf normal form that captures

the onset of self-sustained oscillations in blood flow. This reduced representation enables the identification of bifurcation phenomena within a biologically relevant setting while maintaining computational tractability. The emergence of a Hopf bifurcation in the coupled flow–transport system provides new insight into how oscillatory vascular dynamics influence drug dispersion, mixing, and tissue uptake.

Another important contribution is the explicit coupling of flow energy, represented through modal amplitudes, with pharmacokinetic transport equations. This coupling introduces a physically motivated mechanism in which flow oscillations directly enhance or modulate drug mixing in plasma, thereby linking hydrodynamic stability to therapeutic delivery efficiency. This approach goes beyond traditional models where flow and drug transport are treated as weakly coupled or independent processes.

The integration of machine learning into the stability analysis represents an additional innovation. A neural-network-based surrogate model is trained using bifurcation data obtained from MATCONT continuation results, enabling rapid prediction of stability characteristics such as the maximum real part of eigenvalues. This surrogate is embedded directly into the optimal control formulation, allowing stability constraints to be enforced efficiently without repeated numerical continuation during optimization.

The formulation of a bifurcation-aware optimal control problem using PYOMO.DAE and IPOPT constitutes another major novelty. In contrast to standard optimal control studies in pharmacology that focus solely on concentration minimization or dosing schedules, this work incorporates dynamical stability constraints associated with Hopf bifurcations. This ensures that optimal treatment strategies are not only effective in terms of drug concentration control but also robust with respect to flow-induced instabilities.

Finally, the comparative analysis of controlled and uncontrolled scenarios demonstrates the impact of bifurcation-aware design on drug delivery performance. The observed improvement in the objective function under stability-constrained optimization highlights the practical significance of integrating nonlinear dynamics into biomedical control problems. Overall, this work establishes a new paradigm for drug delivery modeling in which fluid mechanics, dynamical systems theory, and optimal control are unified within a single computational framework. 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 Development

We consider drug delivery through a blood vessel supplying a target tissue or tumor region. The model combines hemodynamics and pharmacokinetics. Blood flow is governed by the incompressible Navier–Stokes equations, while drug transport is described by convection–diffusion and compartmental mass balances.

### Governing Fluid Equations

For an incompressible Newtonian fluid, conservation of mass gives

$$\nabla \cdot \mathbf{u} = 0 \tag{1}$$

where **u** is the blood velocity field. Conservation of momentum yields the incompressible Navier–Stokes equations

$$\frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla)\mathbf{u} = -\frac{1}{\rho}\nabla p + \nu \nabla^2 \mathbf{u} + \mathbf{f} \tag{2}$$

where $\rho$ is the blood density, $p$ is the pressure, $\nu$ is the kinematic viscosity, and **f** represents body-force and forcing effects associated with cardiac pulsation and catheter injection.

### Reduced-Order Flow Representation

The velocity field is approximated using a Galerkin expansion

$$\mathbf{u}(\mathbf{x},t) = x_1(t)\phi_1(\mathbf{x}) + x_2(t)\phi_2(\mathbf{x}) \tag{3}$$

where $\phi_1$ and $\phi_2$ are dominant flow modes and $x_1(t), x_2(t)$ are their amplitudes. Substituting this expansion into the Navier–Stokes equations and projecting onto the modal basis produces a reduced dynamical system. Retaining the dominant nonlinear terms yields the normal form of a Hopf bifurcation,

$$\begin{aligned} \frac{dx_1}{dt} &= \mu x_1 - \omega x_2 - \alpha\left(x_1^2 + x_2^2\right)x_1 + F_0 \\ \frac{dx_2}{dt} &= \omega x_1 + \mu x_2 - \alpha\left(x_1^2 + x_2^2\right)x_2 + G_0 \end{aligned} \tag{4}$$

where $\mu$ is the bifurcation parameter, $\omega$ is the oscillation frequency, $\alpha$ represents nonlinear saturation, and $F_0, G_0$ represent external forcing arising from physiological pumping and catheter-induced flow disturbances.

Defining $r^2 = x_1^2 + x_2^2$ gives

$$\begin{aligned} \frac{dx_1}{dt} &= \mu x_1 - \omega x_2 - \alpha r^2 x_1 + F_0 \\ \frac{dx_2}{dt} &= \omega x_1 + \mu x_2 - \alpha r^2 x_2 + G_0 \end{aligned} \tag{5}$$

### Drug Transport in Blood

Drug concentration in blood plasma is denoted $c_p$ ($t$) by Transport of drug in the vessel satisfies the convection–diffusion equation

$$\frac{\partial c}{\partial t} + \mathbf{u} \cdot \nabla c = D\nabla^2 c - R(c) \tag{6}$$

where $D$ is the molecular diffusivity and $R(c)$ represents uptake and elimination processes. A spatial averaging procedure converts the distributed model into a lumped compartment model. The average plasma concentration obeys

$$\frac{dc_p}{dt} = \text{mixing input} - \text{transfer to tissue} + \text{return from tissue} - \text{elimination}$$

The flow oscillations enhance mixing and dispersion. Since the kinetic energy of the reduced flow field is proportional to $r^2 = x_1^2 + x_2^2$, the mixing contribution is modeled as $\beta r^2$. Plasma washout is represented by $-\lambda c_p$. Transfer from blood to tissue occurs at rate $-k_{12}c_p$. Return from tissue to blood is $+k_{21}c_t$. Systemic elimination is $-k_e c_p$. Combining these terms gives

$$\frac{dc_p}{dt} = -\lambda c_p + \beta r^2 - k_{12}c_p + k_{21}c_t - k_e c_p. \quad (7)$$

Collecting terms,

$$\frac{dc_p}{dt} = -\left(\lambda + k_{12} + k_e\right)c_p + k_{21}c_t + \beta r^2 \quad (8)$$

## Drug Transport in Tissue

Let $c_t$ $(t)$ denote the average drug concentration in the target tissue or tumor. Applying a mass balance to the tissue compartment gives

$$\frac{dc_t}{dt} = \text{inflow from blood} - \text{return to blood} - \text{local clearance}.$$

Drug enters tissue through vascular permeability, $k_{12}c_p$. Drug leaves tissue and re-enters the bloodstream at rate $k_{21}c_t$. Local metabolism and clearance are represented by $0.3k_e c_t$.

Therefore,

$$\frac{dc_t}{dt} = k_{12}c_p - k_{21}c_t - 0.3k_e c_t \quad (9)$$

Or

$$\frac{dc_t}{dt} = k_{12}c_p - \left(k_{21} + 0.3k_e\right)c_t. \quad (10)$$

**Final Reduced Drug-Delivery Model**

The resulting four-dimensional nonlinear dynamical system is

$$\begin{aligned}
\frac{dx_1}{dt} &= \mu x_1 - \omega x_2 - \alpha\left(x_1^2 + x_2^2\right)x_1 + F_0 \\
\frac{dx_2}{dt} &= \omega x_1 + \mu x_2 - \alpha\left(x_1^2 + x_2^2\right)x_2 + G_0 \\
\frac{dc_p}{dt} &= -\lambda c_p + \beta\left(x_1^2 + x_2^2\right) - k_{12}c_p + k_{21}c_t - k_e c_p \\
\frac{dc_t}{dt} &= k_{12}c_p - k_{21}c_t - 0.3k_e c_t
\end{aligned} \quad (11)$$

These equations represent a physiologically motivated reduced-order model in which oscillatory blood flow dynamics derived from the Navier–Stokes equations interact with plasma and tissue drug concentrations through flow-enhanced transport mechanisms. The $\mu$ parameter controls the onset of oscillatory hemodynamic behavior through a Hopf bifurcation, while the pharmacokinetic subsystem governs drug exchange between blood and tissue compartments. This coupling allows the investigation of how flow instabilities influence drug delivery efficiency and optimal treatment strategies. Table 1 and Table 2 provide the variable and parameter details

**Table 1: State Variables (Model Variables)**

| Symbol | Description | Units |
|---|---|---|
| $x_1(t)$ | Oscillatory flow mode 1 (hydrodynamic state variable) | dimensionless (modal amplitude) |
| $x_2(t)$ | Oscillatory flow mode 2 (phase-shifted hydrodynamic mode) | dimensionless (modal amplitude) |
| $C_p(t)$ | Drug concentration in plasma/blood compartment | mol·m$^{-3}$ |
| $C_t(t)$ | Drug concentration in tissue (tumor/arterial wall) | mol·m$^{-3}$ |
| $r^2 = x_1^2 + x_2^2$ | Flow energy / mixing intensity measure | dimensionless |

**Table 2: Model Parameters**

| Parameter | Description | Value | Units |
|---|---|---|---|
| $\mu$ | Flow excitation parameter (bifurcation/instability control) | variable (e.g., 0.05–1.0) | $h^{-1}$ |
| $\omega$ | Natural oscillation frequency of flow | 3.0 | $h^{-1}$ |
| $\alpha$ | Nonlinear saturation / damping coefficient | 1.2 | dimensionless |
| $\lambda$ | Plasma washout / mixing-induced loss rate | 0.3 | $h^{-1}$ |
| $\beta$ | Flow-enhanced dispersion coefficient (coupling strength) | 1.5 | $m^3 \cdot mol^{-1} \cdot h^{-1}$ (effective) |
| $k_{12}$ | Transfer rate blood → tissue | 1.8 | $h^{-1}$ |
| $k_{21}$ | Transfer rate tissue → blood | 1.2 | $h^{-1}$ |
| $k_e$ | Systemic elimination rate (liver/kidney clearance) | 0.4 | $h^{-1}$ |
| $F_0$ | External flow forcing in mode 1 | 0.2 | $h^{-1}$ |
| $G_0$ | External flow forcing in mode 2 | 0.0 | $h^{-1}$ |

## 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[30]. This program identifies Limit points(LP), branch points(BP), and Hopf bifurcation points(H) for an system of ordinary differential equations

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

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

At a limit point, the $n$+1 $^{th}$ component of the tangent vector $w_{n=1} = 0$ . For a branch point, the matrix $B = \begin{bmatrix} A \\ w^T \end{bmatrix}$ must be singular and have a determinant of 0.

At a Hopf bifurcation point,

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

@ indicates the bialternate product while $I_n$ is the n-square identity matrix. More details can be found in Kuznetsov and Govaerts respectively [31,32].

### Optimal Control

Pyomo.dae [33] 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 [34].

### 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 $\mu_j$ and training standard deviation $\sigma_j$ 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 $\mu_j = \frac{1}{N}\sum_{k=1}^{N} x_j^{(k)}$ and the training standard deviation for the input variable *j* is defined as: $\sigma_j = \frac{1}{N}(\sum_{k=1}^{N} x_j^{(k)} - \mu_j)^2$

The standardized inputs were defined as

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

where $\varepsilon_{scale}$ 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 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 $\mu,\sigma$ 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 *x*, which are the scaled variables, the network architecture is defined as

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

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 $\lambda_{max}$ 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 $\lambda\_max\_NN$ 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:

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

$\lambda$ is the neural network's predicted maximum eigenvalue at the current state and parameter, while $\varepsilon$ is a small positive safety margin to ensure differentiability. The soft penalty formulation involves the new objective function, where the original objective function $\sum optv(t)$ is modified to $\sum (optv(t) + \alpha_{hopf} . s_{\max}(\lambda + \varepsilon_1))^2 \alpha_{Hopf}$ controls how aggressively instability is penalized, and prevents numerical issues at exactly λ = 0 and slightly shifts the stability boundary. When $\alpha_{Hopf}$ is 0, no Hopf constraint is implemented. The goal is to minimize the objective function value while ensuring differentiability for IPOPT and avoiding non-smoothness in the 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 dataset 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 ($\lambda_{\max} = \max \Re(\lambda(J))$). Negative values indicate stability, positive values indicate instability, and zero crossings correspond to Hopf bifurcations.

To avoid repeated eigenvalue computations within optimization, a feedforward 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 performed with MATCONT revealed the existence of a Hopf bifurcation point at $(x_1, x_2, c_p, c_t, \mu)$ values ( -0.000119 0.066666 0.007719 0.010526 0.010667 ) with first Lyapunov coefficient = -2.396545. Figs. 1a and 1b shows the bifurcation diagram and the limit cycle . The analytical expression of the Jacobian matrix is

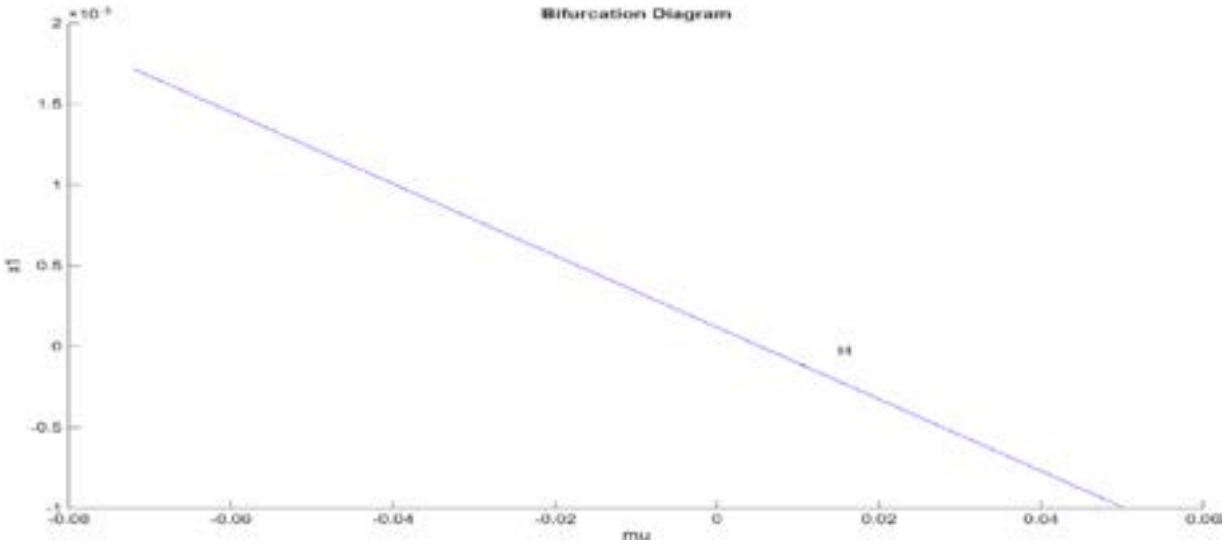


Fig. 1a Bifurcation Diagram

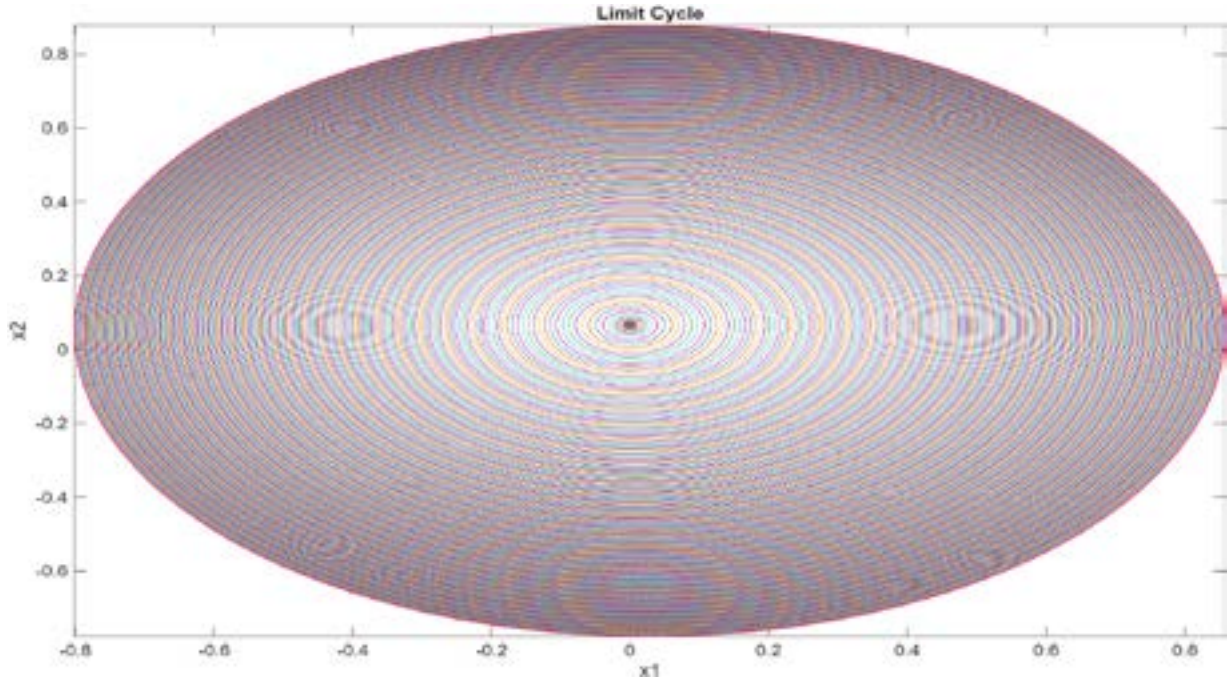


Fig. 1b Limit cycle

$$J_a = \begin{bmatrix} \mu - \alpha\left(3x_1^2 + x_2^2\right) & -\omega - 2\alpha x_1 x_2 & 0 & 0 \\ \omega - 2\alpha x_1 x_2 & \mu - \alpha\left(x_1^2 + 3x_2^2\right) & 0 & 0 \\ 2\beta x_1 & 2\beta x_2 & -\left(\lambda + k_{12} + k_e\right) & k_{21} \\ 0 & 0 & k_{12} & -\left(k_{21} + 0.3k_e\right) \end{bmatrix} \quad (17)$$

The numerical Jacobian matrix at the Hopf bifurcation point is

$$J_n \approx \begin{bmatrix} 0.005334 & -2.999981 & 0 & 0 \\ 3.000019 & -0.005333 & 0 & 0 \\ -0.000357 & 0.199998 & -2.5 & 1.2 \\ 0 & 0 & 1.8 & -1.32 \end{bmatrix} \quad (18)$$

The eigenvalues of this matrix are -0.325, -3.4295, 3i, and -3i. The presence of 2 complex conjugate eigenvalues on the imaginary axis validates the existence of the Hopf Bifurcation.

The optimal control minimizes the function $\sum optv(t) = \sum\left(\frac{1}{c_t(t)}\right) + (c_p(t)) + 0.1*(\mu(t))^2$ without and with the Hopf bifurcation constraint. This objective function minimizes the overall kinetic energy of the shear modes, the strength of stratification fluctuations, and the external forcing effort, thereby promoting low-energy, weakly forced, and dynamically stable flow states. 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, $\alpha_{Hopf}$ =0, in $\sum\left(optv(t) + \aleph_{hopf} . s_{\max}(\ +\ _1)\right)^2$ the obtained value of $\sum optv(t)$ was 84.09. For a Hopf constraint, $\alpha_{Hopf} = 100$ the obtained value of $\sum optv(t)$ was 74.620. This shows a considerable decrease in the minimized function, indicating the effect of the Hopf bifurcation constraint. This corresponds to a 11.2 % reduction in the minimized objective function value. Figs 2a, 2b, 2c show the optimal control profiles without Hopf constraint, and Figs 3a, 3b, and 3c show the optimal control profiles with the Hopf constraint.

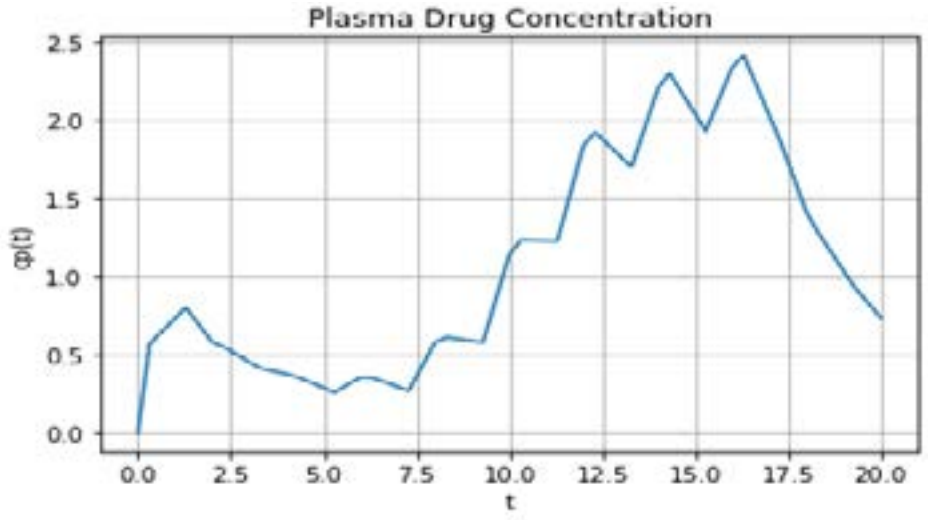


Fig. 2a plasma drug concentration profile for optimal control without Hopf constraint

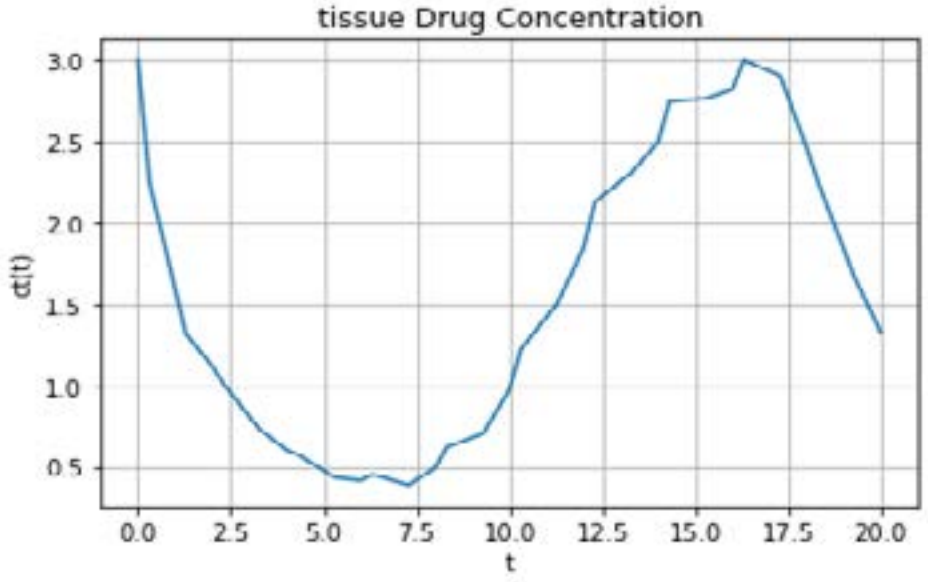


Fig. 2b tissue drug concentration profile for optimal control without Hopf constraint

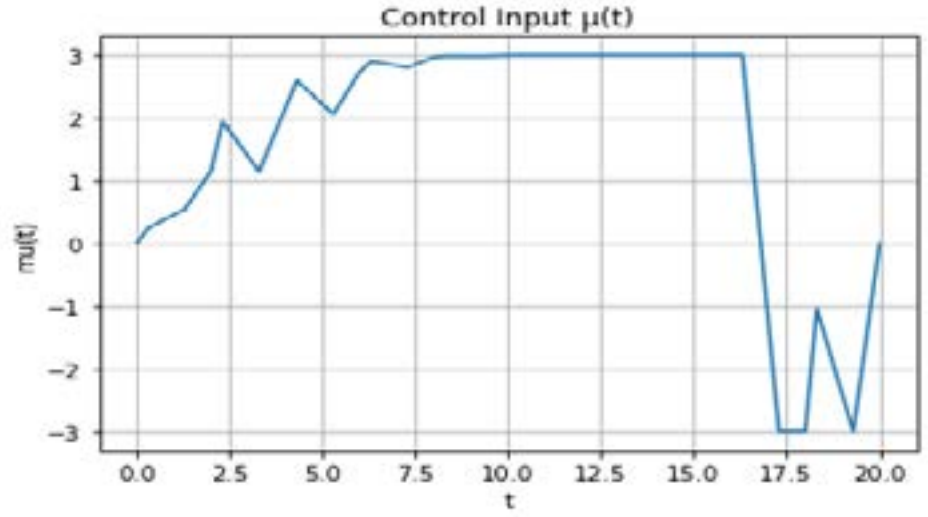


Fig. 2c optimal control profile for optimal control without Hopf constraint

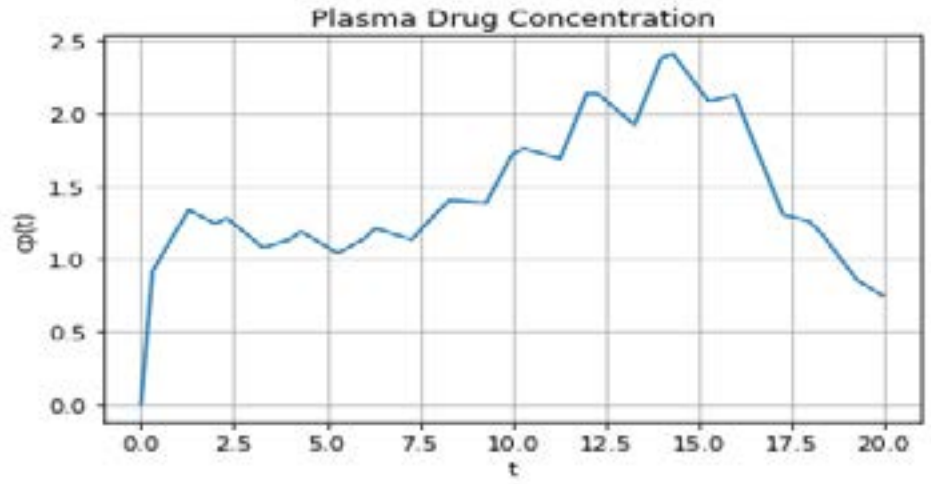


Fig. 3a plasma drug concentration profile for optimal control with Hopf constraint

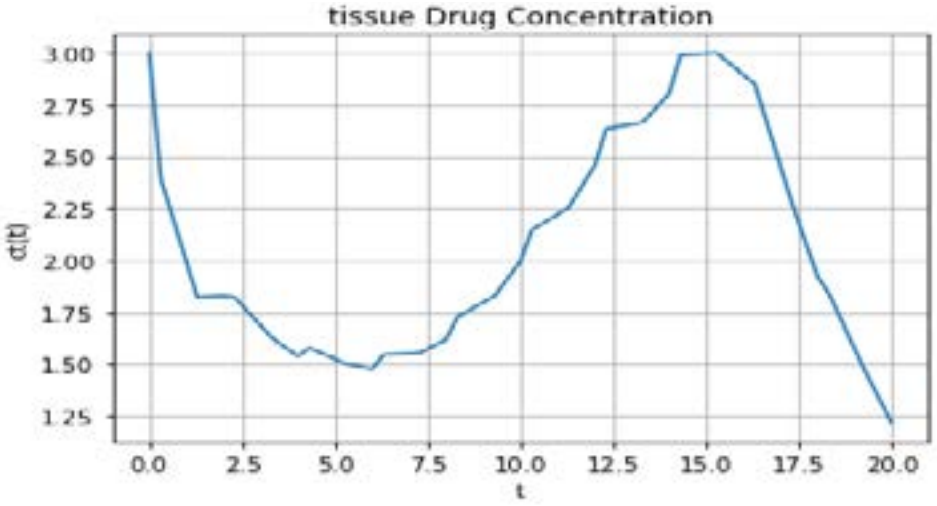


Fig. 3b tissue drug concentration profile for optimal control with Hopf constraint

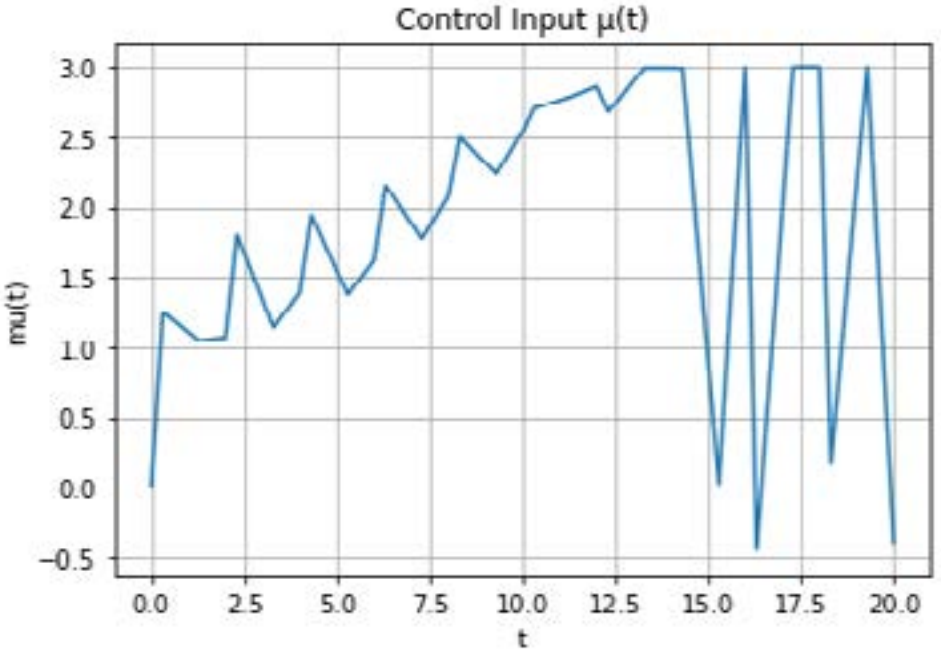


Fig. 3c optimal control profile for optimal control with Hopf constraint

## Discussion

The bifurcation analysis revealed a Hopf bifurcation at (-0.000119,0.066666,0.007719,0.010526) with a bifurcation parameter value of 0.010667. The corresponding first Lyapunov coefficient was found to be negative (-2.396545), indicating a supercritical Hopf bifurcation. This result implies that as the bifurcation parameter crosses its critical value, the equilibrium loses stability and a stable limit cycle emerges. From a physiological perspective, this transition marks the onset of sustained oscillatory flow in the vascular transport system. Such oscillatory behavior is highly relevant in drug delivery applications because transport processes in blood vessels are strongly influenced by local flow structures, mixing mechanisms, and temporal fluctuations in velocity fields.

The existence of a stable limit cycle indicates that the coupled hemodynamic–drug transport system possesses an intrinsic tendency to generate periodic oscillations. In practical drug delivery scenarios, oscillatory flow conditions can substantially alter the residence time of pharmaceutical agents within the bloodstream and surrounding tissues. Periodic flow structures enhance convective transport and mixing, potentially increasing drug penetration into target tissues. At the same time, excessive oscillations can generate fluctuations in local drug concentration, potentially reducing the predictability of therapeutic dosing. The identification of a supercritical Hopf bifurcation therefore provides important insight into the transition between stable drug transport and oscillation-dominated transport regimes.

The Jacobian matrix evaluated at the Hopf point yielded eigenvalues of -0.325, -3.4295, and the purely imaginary pair ( 3i and -3i). The two negative real eigenvalues indicate strongly stable pharmacokinetic modes associated with drug exchange and clearance processes. In contrast, the purely imaginary eigenvalues correspond to the oscillatory hydrodynamic subsystem. This separation of eigenvalue time scales is particularly significant for drug delivery. The pharmacokinetic subsystem remains inherently dissipative, meaning that drug concentrations tend to relax toward equilibrium in the absence of forcing. However, the oscillatory flow subsystem continuously excites the transport dynamics through coupling terms linking flow energy to plasma drug concentration. Consequently, drug transport behavior becomes strongly dependent on the stability characteristics of the underlying flow field.

From a physiological standpoint, the Hopf bifurcation represents a threshold separating two distinct transport regimes. Below the critical value of the bifurcation parameter, blood flow remains stable and transport is dominated by relatively steady convection and diffusion mechanisms. Above the critical value, oscillatory flow patterns emerge and introduce additional mixing effects. These oscillations can enhance mass transfer from the bloodstream to surrounding tissue regions, potentially improving tissue uptake of therapeutic compounds. Such behavior is particularly relevant in targeted drug delivery applications involving tumors, arterial wall treatments, localized chemotherapy, and catheter-based infusion systems, where transport efficiency is often limited by insufficient mixing and poor tissue penetration.

The optimal control results further demonstrate the importance of considering dynamical stability during treatment design. The optimization problem was solved both without and with a Hopf-bifurcation-avoidance constraint. In the unconstrained case, the optimizer was free to select operating conditions based solely on minimization of the prescribed objective function. The resulting objective value was 84.09. When the Hopf constraint was introduced, the objective value decreased to 74.620, corresponding to an 11.2% reduction. This result indicates that explicitly accounting for bifurcation behavior can significantly improve system performance.

The reduction in objective function value suggests that the optimization algorithm was able to identify operating trajectories that simultaneously improve transport efficiency and maintain desirable stability characteristics. In drug delivery applications, this is highly important because therapeutic effectiveness depends not only on achieving sufficient drug concentrations but also on maintaining robust and predictable transport conditions. Oscillatory flow regimes may increase transport rates, but uncontrolled oscillations can also generate undesirable fluctuations in drug exposure. The bifurcation-aware optimization framework balances these competing effects by steering the system toward dynamically favorable operating conditions.
The optimal control profiles shown in Figs. 2 and 3 further illustrate the influence of the Hopf constraint. Without stability considerations, the optimizer may exploit regions of the parameter space that lie close to the bifurcation boundary. Although such operating points can enhance mixing and reduce certain components of the objective function, they may also expose the system to instability and large-amplitude oscillations. In a practical drug delivery setting, these oscillations could produce significant temporal variations in plasma drug concentration, leading to inconsistent dosing and potentially increasing the risk of adverse effects. The introduction of the Hopf constraint prevents the optimization procedure from selecting trajectories that approach unstable regions too closely.

From a therapeutic perspective, maintaining operation within a dynamically stable regime is advantageous because it improves predictability of drug transport. Stable flow conditions produce more consistent concentration distributions throughout the vascular network and target tissues. This predictability is particularly important for potent drugs with narrow therapeutic windows, where small concentration fluctuations can significantly affect treatment outcomes. By incorporating stability information directly into the optimization problem, the proposed methodology provides a systematic mechanism to ensure reliable drug-

delivery performance.

Another important implication of the results is the demonstration that bifurcation analysis and optimal control can be integrated into a unified framework for treatment design. Traditionally, pharmacokinetic optimization focuses primarily on concentration levels and dosing schedules, while stability analysis is often treated separately. The present results show that flow-induced dynamical instabilities can play a critical role in determining transport efficiency and should therefore be included explicitly in optimization studies. The neural-network-based Hopf constraint enables this integration while maintaining computational tractability, allowing complex stability information obtained from continuation analysis to be incorporated into large-scale dynamic optimization problems.

Overall, the results demonstrate that the onset of oscillatory flow behavior substantially influences drug transport dynamics. The Hopf bifurcation identifies a critical transition in the coupled flow–drug delivery system, while the optimal control framework provides a mechanism for exploiting stability information to improve therapeutic performance. The observed reduction in objective function value under bifurcation-aware optimization highlights the practical value of combining nonlinear dynamics, bifurcation theory, and optimal control for advanced drug delivery applications. These findings suggest that future treatment strategies could benefit from explicitly accounting for flow-induced dynamical transitions, leading to safer, more efficient, and more reliable delivery of therapeutic agents.

This work has significant implications for the design, analysis, and optimization of drug delivery systems, particularly in vascular and tumor-targeted therapeutic applications. By explicitly coupling reduced-order Navier–Stokes dynamics with pharmacokinetic transport equations, the study provides a unified framework that links hemodynamic behavior with drug dispersion and tissue uptake. This represents a shift from classical compartmental drug delivery models toward physics-informed, flow-aware therapeutic modeling.

One of the most important impacts of this work is the demonstration that flow-induced instabilities, specifically Hopf bifurcations, play a critical role in determining drug transport efficiency. In realistic physiological environments, blood flow is rarely steady and often exhibits oscillatory or transitional behavior. This study shows that such oscillations are not merely secondary effects but can fundamentally alter drug mixing, residence time, and penetration into target tissues. As a result, identifying and controlling these dynamical transitions becomes essential for improving therapeutic outcomes.

The integration of bifurcation analysis with drug transport modeling provides a new mechanism for predicting when a delivery system may transition into regimes of enhanced or undesirable transport. In particular, oscillatory flow states can either enhance drug delivery through improved mixing or introduce variability that leads to inconsistent dosing. The ability to quantify and control these transitions offers a powerful tool for designing safer and more effective drug delivery protocols, especially in high-precision applications such as chemotherapy, localized arterial infusion, and catheter-based treatments.

A further key impact lies in the introduction of stability-aware optimal control strategies. Traditional drug delivery optimization focuses primarily on minimizing plasma concentration or maximizing tissue uptake without explicitly considering flow stability. In contrast, this work incorporates bifurcation constraints directly into the optimization framework, ensuring that the resulting control policies avoid unstable operating regimes. This leads to more robust and physiologically realistic treatment strategies that remain effective even in the presence of nonlinear flow dynamics.

The results also highlight the importance of reducing systemic drug exposure while maintaining effective tissue delivery. The modeling framework captures the trade-off between plasma concentration and tissue uptake, allowing for the identification of operating conditions that minimize toxicity while preserving therapeutic efficacy. This has direct relevance for clinical drug administration, where balancing efficacy and side effects is a central challenge.

Another important contribution is the potential for data-driven stability prediction through machine learning integration. By embedding a surrogate model of bifurcation behavior into the optimization process, the framework enables rapid evaluation of stability constraints without repeated numerical continuation. This significantly enhances the scalability of the approach and opens the door for real-time or patient-specific treatment optimization in future applications.

Overall, this work establishes a new paradigm in drug delivery modeling where nonlinear fluid mechanics, pharmacokinetics, and optimal control are fully integrated. The ability to account for flow-induced bifurcations within a control framework provides a deeper understanding of transport phenomena in biological systems and offers a pathway toward more precise, adaptive, and physiologically consistent drug delivery strategies. This has the potential to influence future research in biomedical engineering, particularly in areas where fluid dynamics plays a dominant role in therapeutic transport.

## Conclusions

This study investigated the interaction between nonlinear hemodynamic behavior and drug transport dynamics through a reduced-order model derived from fluid-mechanical and pharmacokinetic principles. Bifurcation analysis performed using MATCONT revealed the existence of a supercritical Hopf bifurcation, indicating the onset of self-sustained oscillatory flow behavior within the coupled flow–drug delivery system. The computed eigenvalue spectrum

confirmed the presence of a pair of purely imaginary eigenvalues at the critical point, validating the emergence of periodic dynamics and highlighting the important role of flow instabilities in governing drug transport processes.

The results demonstrate that oscillatory flow structures can significantly influence the distribution and transport of therapeutic agents. Since drug concentration dynamics are coupled to the fluid subsystem, changes in flow stability directly affect mixing, dispersion, and mass transfer between the bloodstream and surrounding tissue. The identification of a Hopf bifurcation therefore provides valuable insight into the transition between stable transport regimes and oscillation-dominated regimes that may enhance or alter drug delivery performance.

An optimal control framework based on PYOMO.DAE and IPOPT were subsequently employed to determine dynamically favorable operating trajectories. By incorporating a Hopf-bifurcation-aware constraint, the optimization procedure explicitly accounted for system stability during treatment design. The bifurcation-constrained optimization yielded an objective value that was 11.2% lower than the value obtained without the stability constraint, demonstrating that stability information can be effectively used to improve overall system performance.

## Declarations


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### 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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