Nonlinear Hemodynamic Control Design via Input-Output Linearization

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Abstract

This paper tackles three-dimensional hemodynamic control problems (left atrial pressure, cardiac output, and mean arterial pressure) via drug therapy, which is a major challenge in treating heart failure. Our proposed approach is a nonlinear control system design based on strict system modeling and controller design. First, the control system was derived as an analytical representation where inputs are multiple drug infusions and outputs are three-dimensional hemodynamics. Second, the controller is designed by input-output linearization technique that conquers the system's nonlinearity and inter-dependency. As a result, the simulation study resulted in the successful convergence of three-dimensional hemodynamics, indicating the controller's validity and the remaining challenges such as control limitation.

1. Introduction

To treat various pathophysiology of acute heart failure (AHF), it is important to maintain overall hemodynamics with multiple drug administration. [1] Maintenance of overall hemodynamics requires simultaneous control of multiple control targets, such as blood pressure, cardiac output, and atrial pressure. A single therapeutic drug administration affects multiple cardiovascular parameters, resulting in multiple changes in overall hemodynamics. While simultaneous administration of multiple drugs increases control reachability, their pharmacologic effects on overall hemodynamics become more complex. Therefore, it is desirable to elucidate the pharmacological effects on overall hemodynamics as a multiple-input and multiple-output (MIMO) system and then to control them in a simplified way that conquers the original complexity.

In previous studies, several closed-loop systems have been developed to automatically adjust drug infusion rates to control the patient's mean arterial pressure (MAP) and/or cardiac output (CO) [2, 3]. There remain concerns that non-target hemodynamics such as left atrial pressure (P_{LA}) is not well controlled, possibly exacerbating pulmonary edema. One study aimed to control three-dimensional hemodynamic control, but the approximation left a stability issue due to the lack of the model analysis [4, 5].

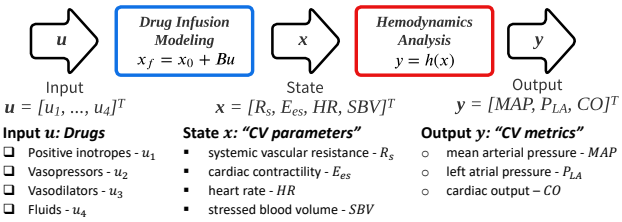

Figure 1: System of drug infusion and hemodynamics

For this three-dimensional hemodynamic control challenge by drug infusions, our methods encompass hemodynamic modeling, drug library development, and nonlinear control design. In modeling, first, the output functions of three-dimensional hemodynamics were analytically derived as the nonlinear functions of four cardiovascular parameters: systemic vascular resistance (R_s), cardiac contractility (E_{es}), heart rate (HR), and stressed blood volume (SBV). Next, a drug library was introduced to model the pharmacological effects against the four cardiovascular parameters. Assuming multiple drug infusion as the system inputs, these four cardiovascular parameters as the system state, and hemodynamics as system outputs, the system structure was mathematically formulated. In the control design, a nonlinear control method based on differential geometry called input-output linearization was applied to linearize this hemodynamic system. For evaluation, the performance of the hemodynamic controller was evaluated in simulation.

2. Methods

2.1. System Modeling

In our system modeling shown in Figure 1, let x denote the *CV parameters* $\boldsymbol{x} := [R_s, E_{es}, HR, SBV]^T \in \boldsymbol{R}^4$. Assuming $\boldsymbol{x}$ is measurable, the patient's initial *CV parameters* $\boldsymbol{x}_0$ are given. Next, let the input $\boldsymbol{u}$ be the drug infusion $\boldsymbol{u} := [u_1, \cdots, u_4]^T \in \boldsymbol{R}^4$ as described in Table 1. The infusion drugs were selected to represent key classes used in treatment of AHF: Dobutamine (DOB) as a positive inotrope, Norepinephrine (NE) as a vasopressor, Sodium Nitroprusside (SNP) as a vasodilator, and Dextran (DEX) as a fluid. Remark that the drug selection is not li-

Table 1: Intervention Drugs for AHF Treatment

Input	Name	Abb.	Unit
u_1	Dobutamine	DOB	[μg/kg/min]
u_2	Norepinephrine	NE	[μg/kg/min]
u_3	Nitroprusside	SNP	[μg/kg/min]
u_4	Dextran	DEX	[ml/kg]

mited to these in our theoretical formulation. Then, let $\boldsymbol{y}$ be the *CV metrics* $\boldsymbol{y} := [MAP, P_{LA}, CO]^T$, which is the control target of three-dimensional hemodynamics.

The following two subsections will introduce the two modelings shown in Figure 1. First, the drug infusion modeling part formulates how drug infusion directly affects *CV parameters* based on their pharmacology. Second, the hemodynamic representation part formulates how the changes in *CV parameters* will in turn affect *CV metrics*.

2.1.1. Drug Infusion Modeling ($\boldsymbol{u} \rightarrow \boldsymbol{x}$)

This part models the multi-dependencies of simultaneous multiple drug infusion when drug effects have converged. The assumptions in this model are a) each drug functions to add its effects linearly to influence *CV parameters* and b) cross-terms of the multiple inputs, e.g., $u_1 \times u_2$ are not considered. Then, our drug infusion model becomes

$$\boldsymbol{x} = \boldsymbol{B}\boldsymbol{u} + \boldsymbol{x}_0 \tag{1}$$

where $\boldsymbol{x}$ shows the *CV parameters* following drug infusion, once updated and converged. The input matrix $\boldsymbol{B}$ is the drug library that represents the multi-dependency effect from each drug to *CV parameters*. In the case of our drug inputs, the drug library matrix is represented by

$$\boldsymbol{B} = \begin{bmatrix} -0.0335 & 3.33 & -0.419 & -0.00725 \\ 3.88 & 26.1 & -1.14 & -0.0135 \\ 8.10 & 24.9 & 0.164 & -0.450 \\ 27.7 & 76.2 & -14.1 & 1.47 \end{bmatrix} \tag{2}$$

based on the pre-identified pharmacological effects [6]. Each element is equivalent to the gain, and the plus or minus sign indicates the direction of the change. For example, drug input u_3 (Sodium Nitroprusside) decreases R_s, E_{es} and SBV while increasing HR, as shown by the gains in column 3 of $\boldsymbol{B}$.

2.1.2. Hemodynamics Derivation ($\boldsymbol{x} \rightarrow \boldsymbol{y}$)

We derived the analytical solution that maps the *CV parameter* $\boldsymbol{x}$ to the *CV metrics* $\boldsymbol{y}$ using approximation [7]. This was derived from the intersection of the *Frank-Starling Curve* and *Guyton's Venous Return Curve* formula [8, 9].

Firstly, the *Frank-Starling Curve* defines the relationship between CO and P_{LA}. The mechanics of the *Frank-Starling Curve* derived in [10] shows

$$CO = \frac{HR \cdot E_{es}}{\beta(E_{es} + \frac{HR}{60} \cdot R_s)} \cdot \ln \frac{P_{LA} + \alpha}{\alpha} \left[\frac{\text{ml}}{\text{min}}\right] \tag{3}$$

where heart rate (HR), systemic vascular resistance (R_s), and left ventricular contractility (E_{es}) are the given *CV parameters* and α and β are constant parameters to define the end-diastolic pressure-volume relationship (EDPVR) [11]. In (3), EDPVR is assumed to be

$$P_{ed} = \alpha\left(\exp\{\beta(V_{ed} - V_0)\} - 1\right) \tag{4}$$

$$\Leftrightarrow V_{ed} = \frac{1}{\beta} \ln \frac{P_{ed} + \alpha}{\alpha} + V_0 \text{ [ml]}. \tag{5}$$

Note that P_{ed} is left ventricular end-diastolic pressure and is equivalent to P_{LA} in the filling phase.

Secondly, we applied *Guyton's Venous Return Curve* to the pulmonary circulation [9, 12],

$$CO = \frac{1}{R_{vp}} \left(\frac{V_p}{C_p} - P_{LA}\right) \left[\frac{\text{ml}}{\text{sec}}\right] \tag{6}$$

where R_{vp} is the resistance for pulmonary venous return, and where C_p and V_p are the compliance and the stressed blood volume in the pulmonary circulation, respectively. Assuming that total stressed blood volume (SBV) is distributed by the compliance ratio of the systemic and pulmonary circulation, V_p is given by

$$V_p \approx \frac{C_p}{C_s + C_p} SBV \tag{7}$$

where C_s is the compliance of the systemic circulation. Substituting V_p in (6) with (7) yields

$$CO = \frac{1}{R_{v_p}} \left(\frac{SBV}{C_p + C_s} - P_{LA}\right) \left[\frac{\text{ml}}{\text{sec}}\right]. \tag{8}$$

Thirdly, solving (3) and (8) with respect to (P_{LA}, CO), the analytical solution of P_{LA} and CO is given by

$$P_{LA} = -\alpha \left(\frac{aW\left(-\frac{b}{a}\exp\left(\frac{c}{a}\right)\right)}{b}\right) - \alpha \text{ [mmHg]} \tag{9}$$

$$CO = -aW\left(-\frac{b}{a}\exp\left(\frac{c}{a}\right)\right) + c \left[\frac{\text{L}}{\text{min}}\right] \tag{10}$$

where $W(\cdot)$ is defined as the Lambert function and

$$a = \frac{1}{1000} \frac{HR \cdot E_{es}}{\beta(E_{es} + \frac{HR}{60} \cdot R_s)} \tag{11}$$

$$b = -\frac{60}{1000} \frac{\alpha}{R_{vp}} \tag{12}$$

$$c = \frac{60}{1000} \frac{1}{R_{vp}} \left(\frac{SBV}{C_s + C_p} + \alpha\right). \tag{13}$$

2.2. Nonlinear Controller

The hemodynamic representation enables a formulation of the discrete nonlinear state equation as

$$\boldsymbol{x}[k+1] = \boldsymbol{f}(\boldsymbol{x}[k]) + \boldsymbol{g}(\boldsymbol{x}[k])\boldsymbol{u}[k] = \boldsymbol{x}_0 + \boldsymbol{B}\boldsymbol{u}[k] \quad (14)$$

$$\boldsymbol{y}[k] = \boldsymbol{h}(\boldsymbol{x}[k]) \quad (15)$$

$$= [P_{LA}(\boldsymbol{x}[k]), CO(\boldsymbol{x}[k]), MAP(\boldsymbol{x}[k])]^T \quad (16)$$

where k indicates the discrete step: a single step is the time duration until the pharmacological effects get a steady state after drug infusion is applied.

Due to the strong nonlinearity of the output function and the multiple-input and multiple-output system, it is challenging to apply the linear control technique. To conquer these challenges, the input-output linearization technique can reformulate the nonlinear system into the linearized system [13]. The key idea is the nonlinear feedback that enables the coordinate transformation based on the feature of differential geometry as shown in Figure 2.

The nonlinear feedback for linearization can be computed by

$$\boldsymbol{u}[k] = \boldsymbol{\alpha}^{+}(-\boldsymbol{\beta} + \boldsymbol{v}[k]) \quad (17)$$

$$\boldsymbol{\alpha} = \begin{bmatrix} a_{11} & \cdots & a_{14} \\ \vdots & & \vdots \\ a_{31} & \cdots & a_{34} \end{bmatrix}, a_{ij} = L_{\boldsymbol{g}_j} h_i(\boldsymbol{x}[k]) \quad (18)$$

$$\boldsymbol{\beta} = [b_1, b_2, b_3]^T, b_i = L_{\boldsymbol{f}} h_i(\boldsymbol{x}[k]) \quad (19)$$

where the Lie Derivative is given by

$$L_{\boldsymbol{f}}\phi(\boldsymbol{x}) := \frac{\partial \phi(\boldsymbol{x})}{\partial \boldsymbol{x}} \boldsymbol{f}(\boldsymbol{x}). \quad (20)$$

Applying this conversion, the linearized system can be represented by

$$\boldsymbol{\sigma}[k+1] = \boldsymbol{A}\boldsymbol{\sigma}[k] + \boldsymbol{B}\boldsymbol{v}[k], \boldsymbol{\sigma} := [h_1, h_2, h_3]^T \quad (21)$$

$$\boldsymbol{A} = \boldsymbol{O}^{3\times 3}, \boldsymbol{B} = \boldsymbol{I}^{3\times 3} \quad (22)$$

where $\boldsymbol{v}$ is a virtual input that can be designed freely and independently to each h_i such as a PI controller:

$$v_i[k] = K_{Pi}(h_i[k] - y_{ri}) + K_{Ii}\sum^{k}(h_i[k] - y_{ri}) \quad (23)$$

where K_{Pi} and K_{Ii} are the proportional and integral gains to ith output function and y_{ri} is the reference value to ith output function.

3. Simulation Results

3.1. Setting

To evaluate the performance of the proposed nonlinear control system, a scenario of AHF is simulated by a patient

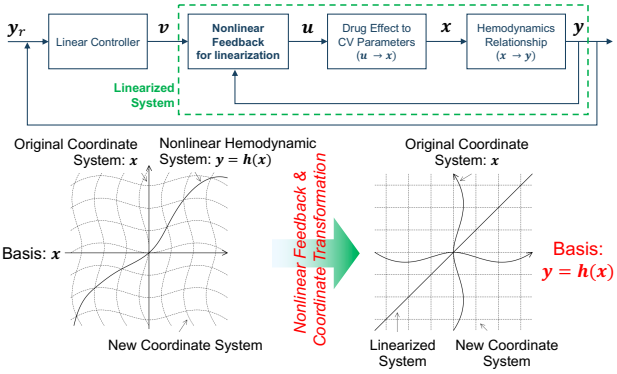

Figure 2: Block diagram and input-output linearization

Table 2: Simulation Parameters

Var.	Name	Value
$\boldsymbol{x}_0$	initial state	$[5.0, 8.0, 100, 200]^T$
$\boldsymbol{h}_r$	control target of $\boldsymbol{h}$	$[7.0, 2.2, 85]^T$
(K_{P1}, K_{I1})	PI gain for $y_1 : MAP$	$(-20, -10)$
(K_{P2}, K_{I2})	PI gain for $y_2 : P_{LA}$	$(-2.0, -1.0)$
(K_{P3}, K_{I3})	PI gain for $y_3 : CI$	$(-0.20, -0.10)$
max k	iteration times	100

having low cardiac output and low blood pressure as given by the initial parameters shown in Table 2. The control objective is to control three-dimensional hemodynamics simultaneously. The control gains were set to control preferentially in the following order: $MAP \to P_{LA} \to CI$.

3.2. Results

The successful results of simultaneous control are shown in Figure 3. Note that the output signals $\boldsymbol{y} = \boldsymbol{h}(\boldsymbol{x})$ are converged in the intended order. The results of state $\boldsymbol{x}$ and input $\boldsymbol{u}$ changes were shown in Figure 4 and Figure 5 respectively.

3.3. Discussion

The proposed nonlinear control design method using input-output linearization showed promising results. One of the benefits of this technique is enabling linear control methods after the nonlinear transformation. For example, the convergence speed is easily controlled to independent hemodynamics thanks to decoupling the interdependencies in the complex hemodynamics into the canonical form shown in the equation (21).

These results also imply some disadvantages or future challenges. For example, the input constraint needs to be explicitly considered in the controller design. In addition, the infusion of DOB and SNP show negative values, while negative DEX input could be avoided by considering Furosemide (FRO) as a diuretic.

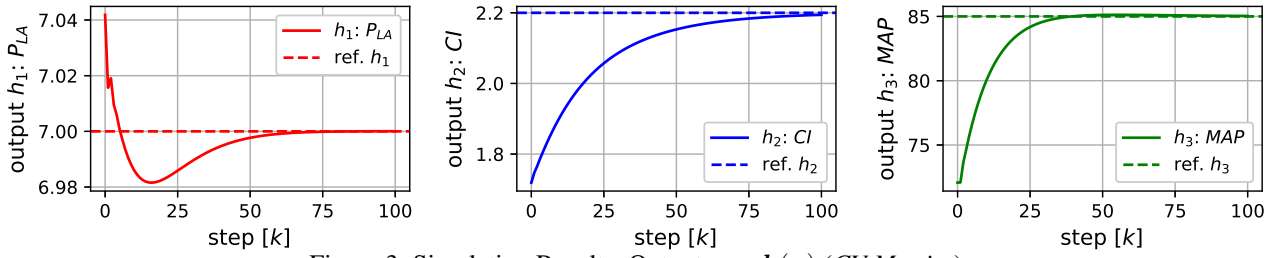

Figure 3: Simulation Results: Output $\boldsymbol{y} = \boldsymbol{h}(\boldsymbol{x})$ (*CV Metrics*)

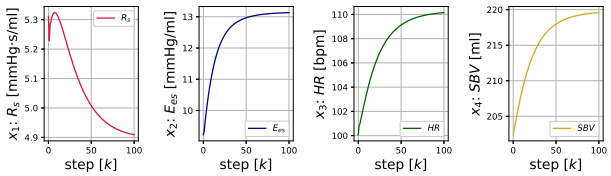

Figure 4: Simulation Results: State $\boldsymbol{x}$ (*CV Parameters*)

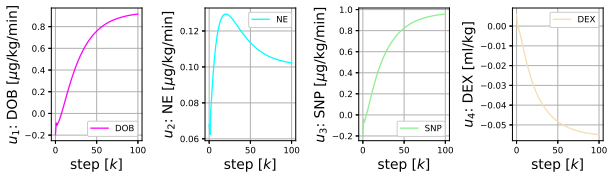

Figure 5: Simulation Results: Input $\boldsymbol{u}$ (Drug Infusion)

4. Conclusion

We proposed a theoretical framework to design a nonlinear controller for a three-dimensional hemodynamic control problem. By combining the representation of the hemodynamic control system and input-output linearization technique, the multiple hemodynamic targets were successfully controlled by multiple drug infusions.

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