

# Control of Hemodynamic and Anesthetic States in Critical Care Patients

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## Abstract

A nonlinear canine circulatory model, which has been used to study the effect of inotropic and vasoactive drugs on hemodynamic variables, has been extended to include propofol pharmacokinetics and pharmacodynamics. Propofol blood concentration is used as measure for depth of anesthesia. The simulation model is used to design and test a control strategy, which simultaneously regulates hemodynamic and anesthetic states in critical care patients. The optimization-based model predictive control strategy assures that constraints imposed on the drug infusion rates are met. The physician always remains “in-the-loop” and, indeed, serves as the “primary controller” by making blood concentration (PFC) setpoint changes based on observations about anesthetic depth.

## 1. Introduction

Critical care physicians maintain certain patient state variables within an acceptable operating range by infusing several drugs. For example, in the case of patients with congestive heart failure, measured variables such as mean arterial pressure (MAP) and cardiac output (CO) are of primary importance and are maintained using sodium nitroprusside (SNP) and dopamine (DPM). In addition, they may be required to administer anesthetics and monitor the depth of anesthesia (DOA) during surgical procedures. The physician uses her/his own senses for other variables which are not easily measured, and often infers anesthetic depth from a number of measurements and patient responses to surgical procedures.

It is desirable to have an automated system which closes the loop on primary variables, but monitors secondary variables and performs diagnostics. This allows the physician to spend more time monitoring the patient for conditions which are not easily measured, and assures that the physician is always “in the loop”. Initial research in this area has focused on single input-single output control of MAP, while more recent work considered the control of several hemodynamic variables by the infusion of multiple drugs. See Fig. 1 for the basic feedback strategy, where sodium nitroprusside (SNP) and dopamine (DPM) are the infused drugs.

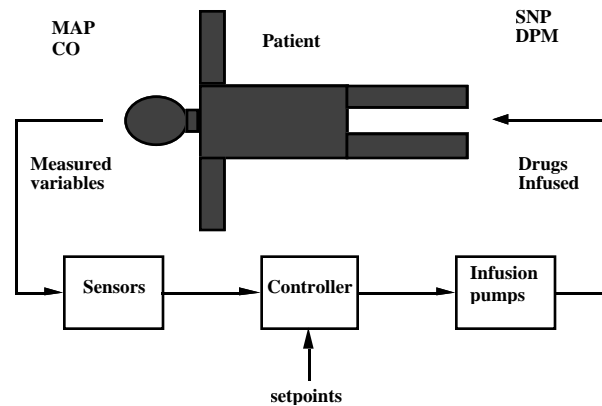


Fig. 1. Basic Two Input-Two Output Drug Infusion Control Diagram. The regulated outputs are MAP and CO, the drugs infused are SNP and DPM.

### 1.1 Control of Hemodynamic Variables

The vast amount of research on blood pressure control was initiated by Slate *et al.* [16], who used a non-adaptive PID controller with empirical rules to control MAP by infusing SNP. Since then, more complex adaptive control schemes have been utilized to overcome the limitations of non-adaptive controllers. See Isaka and Sebald [6] for a review.

There has also been a significant research effort in the simultaneous control of MAP and CO by manipulating the infusion rate of two drugs (usually SNP and DPM). For an example of a multiple model adaptive predictive control approach to this problem see Yu *et al.* [20].

Huang and Roy [5] developed a fuzzy-logic based, automated drug delivery system to control three hemodynamic states by infusing up to four drugs; this system was validated on the nonlinear canine circulatory system model. In Rao *et al.* [13] we present a model predictive control (MPC) approach that provides similar closed-loop responses to Huang and Roy. We assume that a decision analysis unit has already evaluated the patient status and determined the proper model and setpoints for the model predictive control (MPC) strategy. The primary advantage to MPC is the explicit constraint-handling ability.

## 1.2 Control of Anesthetic Variables

Research on control of the depth of anesthesia dates from the 1950's, as reviewed by O'Hara *et al.* [12]. Many of the closed-loop applications have assumed that the depth of anesthesia (DOA) could be related to an easy-to-measure variable. For example, Linkens *et al.* [7] performed a simulation study of the control of muscle relaxation (paralysis) and anesthesia (unconsciousness) using generalized predictive control to manipulate enflurane and pancuronium. Unconsciousness (anesthetic depth) was assumed to be inferred from MAP. Also, Meier *et al.* [8] used fuzzy-logic control to manipulate isoflurane to control MAP.

Roy and coworkers have had an ongoing effort to estimate DOA using middle latency auditory evoked potentials (MLAEP), wavelet transforms, and artificial neural networks (ANN). Nayak and Roy [11] developed a rule-based controller to manipulate isoflurane and control DOA; safety rules based on MAP were also used in the controller design.

Much recent drug infusion work has focused on the use of the intravenous anesthetic agent propofol (PFL). The primary advantages of propofol are that (i) it provides a clear, rapid emergence from anesthesia, and (ii) there is a lack of accumulation, which allows prolonged drug infusion (Sebel [15]). Schuttler *et al.* [14] performed open-loop control of propofol and alfentanil on 20 patients; agreement between measurements and model predictions of blood propofol were generally very good.

## 1.3 Objectives of This Paper

In this paper we are concerned with the simultaneous regulation of hemodynamic and anesthetic states in critical care patients, using propofol as the anesthetic agent. In section 2 we describe the simulation model, and in section 3 we introduce the control structure. In section 4 we present open- and closed-loop simulation results. In section 5 we summarize our results and our current research focus.

## 2. System Description

When implementing a complex control strategy, such as the control of hemodynamic and anesthetic states in critical care patients, it is important to perform detailed simulation studies before moving to animal experiments. Clearly, it is important that the simulation model used is realistic and exhibits qualitatively similar behavior as the physical system. Here we describe extensions to a physiological model which we have used in the past as a basis for control system designs which were later shown to be successful in laboratory experiments.

### 2.1 Physiological Model

The model used in this paper to describe the effect of inotropic and vasoactive drugs on a physiological system was initially developed by Yu *et al.* [18], and has been used (in various forms) in a number of simulation studies (Yu *et al.* [19]; Gopinath *et al.* [3]; Held and Roy [4]; Huang and Roy [5]; Rao *et al.* [13]). We have revised the model to include the pharmacokinetic/pharmacodynamic effects of propofol, based on parameters obtained from Tackley *et al.* [17] and Fragen [1]. The parameters were fine tuned to simulate open-loop results similar to Nakaigawa *et al.* [10].

The model consists of three sets of equations, including (i) circulatory system equations, which describe the effect of specific body parameters on the hemodynamic variables, (ii) drug effect relationships, which describe the influence of the infused drugs on the specific body parameters, and (iii) equations which describe the effect of the arterial baroreceptors in blood pressure regulation. For more details on the model, see Yu *et al.* [18] and Gopinath *et al.* [3].

The model naturally splits into two time scales, involving variables that change during each heartbeat and variables that are constant over a heartbeat. The model is simulated using MATLAB/SIMULINK, which provides a transparent translation of control system design to the nonlinear process. Direct comparisons of different control strategies developed by different researchers is easily performed.

## 2.2 Input and Output Variables

The linear steady-state input/output relationship is

$$y = G u$$

where the output vector is

$$y = [\text{MAP CO MPAP PFC}]^T$$

The input vector is

$$u = [\text{SNP DPM PNP NTG PFL}]^T.$$

The simultaneous hemodynamic/anesthetic control problem exhibits essentially one-way coupling, that is, the propofol infusion affects hemodynamic variables, but the vasoactive drugs have no direct effect on the PFC. Hence we decouple the controllers for PFC and hemodynamic variables.

## 3. Control System Design

### 3.1 Control Structure

The hemodynamic variables, MAP, CO, and MPAP are relatively easy to measure. Although many inroads have been made to infer DOA, it will be some time before it becomes a common controlled output. The DOA is directly related to the PFC in the bloodstream. If the PFC is not measured it can be inferred from a model based on pharmacokinetic parameters. Here we assume that a model

is used to predict the propofol concentration, and that the physician changes the propofol concentration setpoint based on observations of the patient. The physician then serves as an “outer loop controller” in a multivariable cascade control strategy, as shown in schematic form in Fig. 2.

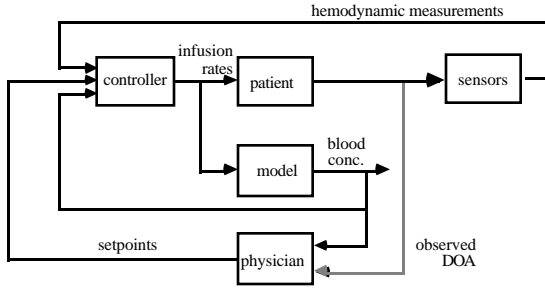


Fig. 2. Control Structure for Hemodynamic Variables and Propofol Blood Concentration.

### 3.2 Model Predictive Control

Model predictive control is an optimization-based approach which has been successfully applied to a wide variety of control problems. The basic idea, shown in Fig. 3, is to select a sequence of  $M$  future control moves to minimize an objective function (usually sum of square of predicted errors) over a prediction horizon of  $P$  sample times. Although a horizon of  $M$  control moves is calculated, only the first move is implemented, a correction for plant-model mismatch is made, and the optimization is performed again. A review of MPC is provided by Garcia *et al.* [2].

Yu *et al.* [20] have applied a variant of MPC (multiple model adaptive-predictive control) to a 2x2 drug infusion problem, while Gopinath *et al.* [3] use a nonlinear model in an MPC framework to control a 2x2 drug infusion system. Since MPC is optimization-based, it handles constrained nonsquare systems quite naturally.

The input-output representation of MPC is based on the finite step response (FSR) or the finite impulse response (FIR) convolution model. This is a nonparametric representation of the process and is simply the open-loop response to a unit step or a unit impulse input. The output prediction based on the impulse convolution model and the history of manipulated variable values  $u$  at the  $k^{\text{th}}$  sampling instant is given by

$$y_k = \sum_{i=1}^N H_i u_{k-i}$$

where  $H_i$  is the  $i^{\text{th}}$  impulse response coefficient matrix.  $N$  is the number of terms in the model, usually chosen to correspond to the settling time of the model.

A general form for the optimization problem at time step  $k$  is

$$\min_{u(k) \dots u(k+M-1)} \sum_{i=k}^{k+P} e_i^T Q e_i + \sum_{i=k}^{k+M} \Delta u_i^T R \Delta u_i$$

$$\begin{aligned} \text{s.t. } \dot{x} &= f(x, u) \\ y &= g(x) \\ e_i &= r_i - y_i \\ u_{\min} &\leq u_i \leq u_{\max} \\ u_{i-1} - \Delta u_{\max} &= u_i = u_{i-1} + \Delta u_{\max} \\ u_i &= u_{k+M-1} \text{ for all } i > k+M-1 \end{aligned}$$

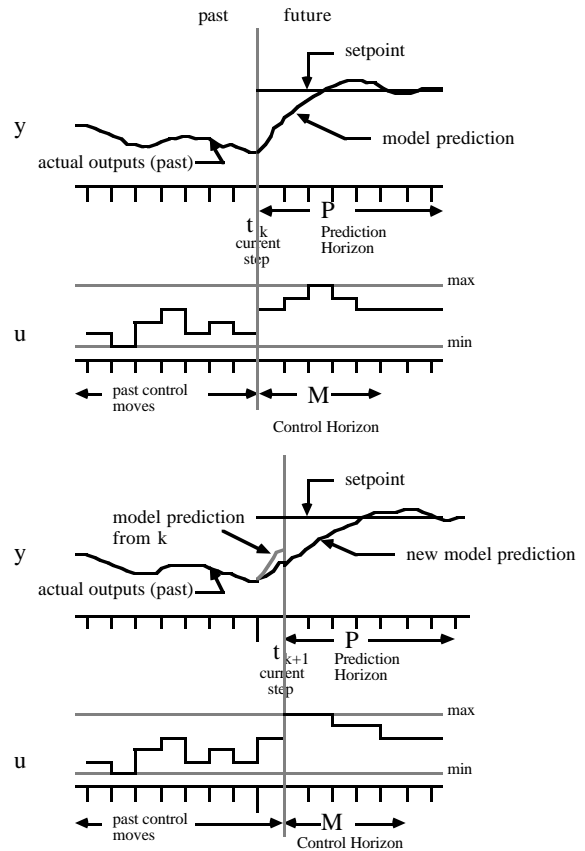


Fig. 3. Model Predictive Control.

where, at step  $i$ ,  $y_i$  is a vector of model predicted outputs,  $e_i$  is a vector of model predicted errors ( $e_i = r_i - y_i$ , where  $r_i$  is the setpoint),  $u_i$  is the vector of manipulated variables, and  $Q$  and  $R$  are output and input weighting matrices. Absolute and velocity constraints on the manipulated variable are included. Although the model is shown in the general continuous form, in this work we use discrete linear step response models. We also use the standard constant additive disturbance assumption to correct for model error for all future time steps.

## 4. Results

Table 1 shows the open-loop gains of the hemodynamic variables to the hemodynamic drugs and anesthesia, for four cases of patient conditions. To generate the open-loop gains, all inputs were step changed from 0 to 1  $\mu\text{g}/\text{kg}/\text{min}$ , except DPM, which was changed from 0 to 6  $\mu\text{g}/\text{kg}/\text{min}$  to avoid the “forbidden zone” (Held and Roy [4]) and PFL which was step changed from 0 to 100  $\mu\text{g}/\text{kg}/\text{min}$ .

Table 1. Open-loop gains for several cases.

Case 1	SNP	DPM	PNP	NTG	PFL
MAP	-9.07	4.94	5.49	-6.17	-5.24
CO	11.97	8.04	-13.40	4.81	0.20
MPAP	-9.85	-2.61	4.05	-9.78	-3.79
PFC	0.00	0.00	0.00	0.00	2.65
Case 2					
MAP	-11.25	2.00	5.34	-8.25	-9.72
CO	8.21	6.46	-20.50	1.27	-1.81
MPAP	-5.49	-1.47	3.49	-5.94	-2.72
PFC	0.00	0.00	0.00	0.00	2.65
Case 3					
MAP	-9.55	4.24	5.66	-6.57	-6.40
CO	12.26	8.13	-14.72	4.97	0.11
MPAP	-9.42	-2.58	3.77	-9.44	-3.91
PFC	0.00	0.00	0.00	0.00	2.65

**CASE 1.** This case is typically associated with congestive heart failure, myocardial infarction or cardiomyopathy. The subject retains only 24 % of its normal heart contractility with 87 mmHg MAP, 65 ml/kg/min CO and 40 mmHg MPAP. This patient is initially conscious and it is desired to maintain MAP between 95-100 mmHg, MPAP between 15-21 mmHg and a minimum CO 95 ml/kg/min while infusing PFL. The PFC setpoint is stepped up gradually from 0 to 5  $\mu\text{g}/\text{ml}$  for the first 5 minutes and 7  $\mu\text{g}/\text{ml}$  thereafter.

Notice that a change in PFL is in an unfavorable direction as the desired setpoint while DPM (second input) is in roughly the same direction as the desired setpoint change, indicating that most of the manipulated variable action (at least in a steady-state sense) will be in DPM. The response time of all variables to a DPM input is much larger than the other inputs. The effective time delay in DPM places limitations on the possible closed-loop speed of response of this system.

The absolute constraints on the manipulated variables are 0 and 10  $\mu\text{g}/\text{kg}/\text{min}$ , except for DPM, where the permissible dosage zone is of 4 to 7  $\mu\text{g}/\text{kg}/\text{min}$  and PFL is constrained between 0 and 600  $\mu\text{g}/\text{kg}/\text{min}$ . The sample time is 0.5 minutes.

Based on the gain matrix, DPM moves all of the outputs in the desired direction of the setpoint change. When the control loops are closed, the anesthetic controller infuses PFL to raise PFC and the hemodynamic controller infuses DPM and NTG to counteract the cardiovascular depression

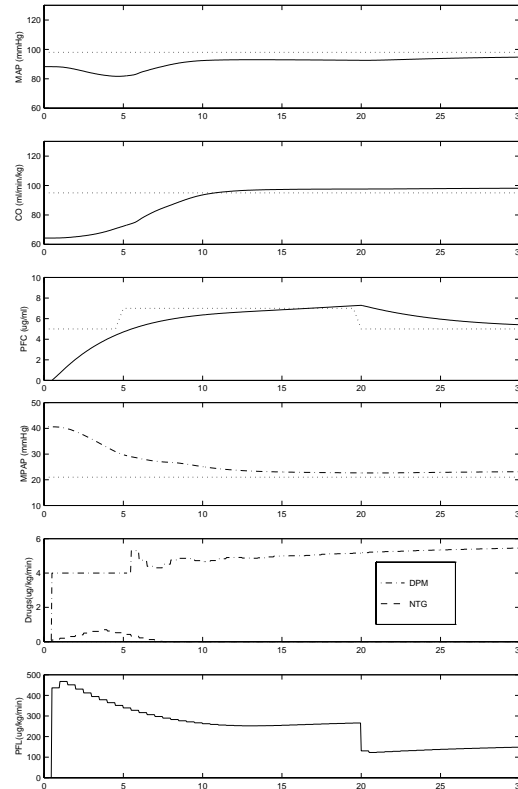


Fig 4. Closed-loop response for Case 1

brought about by PFL and to raise MAP and CO to the desired setpoints. The results are shown in Fig. 4. At around 20 minutes PFC setpoint is lowered back to 5  $\mu\text{g}/\text{ml}$  in order to prevent overdose. The PFL infusion gets lowered suitably while the hemodynamic controller continues to maintain MAP, CO and MPAP in their desired ranges.

**CASE 2** involves a patient retaining 50% of normal cardiac contractility and suffering from a slightly low CO (105 ml/kg/min) and high MAP (120 mmHg) which may be due to post-open heart surgery. It is required to lower MAP to 85-90 mmHg, MPAP between 18-21 mmHg and raise CO to 115 ml/kg/min while also infusing PFL to induce sleep. Again, PFC setpoint is stepped up gradually from 0 to 5  $\mu\text{g}/\text{ml}$  for the first 5 minutes and 7  $\mu\text{g}/\text{ml}$  thereafter.

The open loop-gain matrix for the patient indicates SNP and NTG favourable for lowering MAP and DPM can be seen to aid increase of CO. Again on loop closure, the anesthetic controller infuses PFL to raise PFC and the hemodynamic controller infuses the optimal SNP, NTG and DPM to move MAP and CO to the desired setpoints. The results are shown in Fig. 5.

As the controller continues to manipulate the drug infusion rates it is possible that infusion rate constraints are hit (DPM in this case). In such a situation, the controller will continue to maintain the infusion rates at the optimal maximum in order to avoid drug toxicity. In a real clinical environment, this saturation can trigger an alarm and the

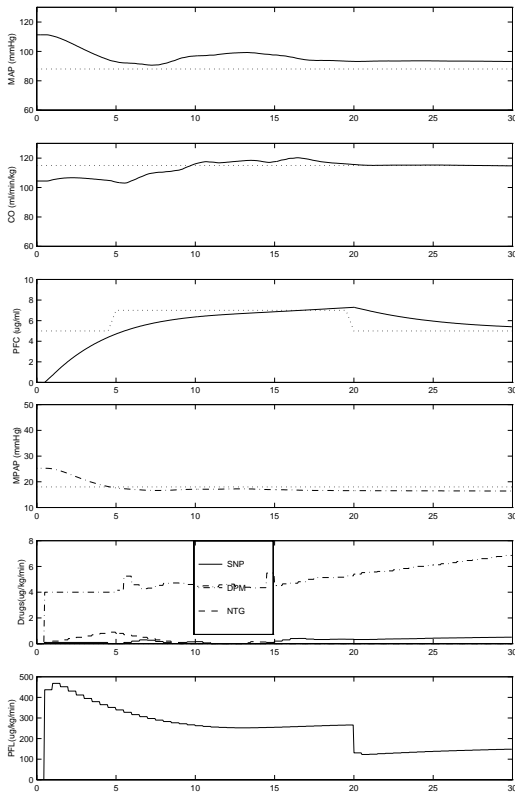


Fig 5. Closed-loop response for case 2

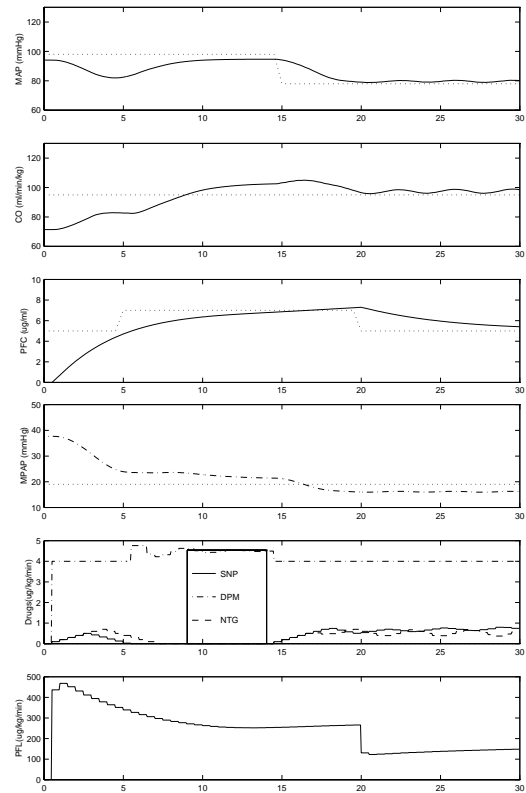


Fig 6. Closed-loop response for case 3

physician can intervene to either relax constraints or make a new decision on the setpoints.

**CASE 3.** A patient retaining 28% of normal contractility is suffering from hypokinesia and minor hypertension. CO must be increased to 95-100 ml/kg/min and MPAP decreased to 18 mmHg. At around 15 minutes, MAP is to be lowered to 75-80 mmHg range. Closed-loop simulations are shown in Fig 6. The controllers can be observed to accommodate these setpoint changes.

We have specified exact setpoints while the real objective is to maintain outputs within a range of values. This could be accomplished by using output constraints, but this can easily lead to infeasible solutions in the optimization problem or to unstable closed-loop behavior.

A problem (or possibly an advantage) of MPC is that there are a large number of tuning parameters available. Many literature studies report SISO cases where only the prediction and control horizons are used as tuning parameters. With a multivariable system, in addition to different weights for each input and output (which could vary with the prediction step), one could have different prediction and control horizon for each output and input. Tuning, then, can be fairly ad-hoc and somewhat of an art, especially since closed-loop stability cannot be guaranteed even for the perfect model case. There has been a recent move in the MPC field to infinite-horizon-based control which can at least guarantee stability for the perfect model case (Muske and Rawlings [9]).

## 5. Summary and Current Work

In this paper we have presented results for control of hemodynamic and anesthetic variables in critical care patients (a simulated canine circulatory model) using a model predictive control strategy. A linear model was used for the model predictions, and closed loop simulations were performed on the nonlinear model. Since drug sensitivities vary from patient to patient, and even within the same patient at different time, it is important to develop strategies which change the patient model on-line. One possible approach, which we have used on two input-two output systems, is multiple model adaptive control (based on using a bank of linear models to capture the nonlinear and uncertain behavior).

The control strategy presented in this paper should be considered part of a hierarchical control structure which involves modules to assess the patient status and to evaluate the effectiveness of the current control strategy. Clearly it is important to always maintain the physician “in the loop” with proper monitoring and alarm functions.

A current research effort is to extend multiple model adaptive control to the problem of simultaneous control of hemodynamic and anesthetic variables. We are also further developing methods to infer anesthetic depth from other readily measured variables.

## NOTATION

e	=	error
G	=	gain matrix
H	=	convolution model
k	=	discrete time step
M	=	control horizon
N	=	model length
P	=	prediction horizon
PFC	=	concentration of propofol
Q	=	output weighting
r	=	setpoint
R	=	input weighting
u	=	input (SNP, DPM, PNP, NTG, PFL)
x	=	state
y	=	output (MAP, CO, MPAP, PFC)
CO	=	cardiac output
DPM	=	dopamine
MAP	=	mean arterial pressure
MPAP	=	mean pulmonary arterial pressure
MPC	=	model predictive control
NTG	=	nitroglycerine
PNP	=	phenylephrine
PFC	=	propofol blood concentration
PFL	=	propofol
SNP	=	sodium nitroprusside

## ACKNOWLEDGMENT

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