

Modeling and Control of Anesthetic and Hemodynamic Drug Infusion

Ramesh R. Rao¹, B. Wayne Bequette^{1*}, Johnnie W. Huang², Rob J. Roy³, and
Howard Kaufman⁴

Departments of ¹Chemical, ²Biomedical Engineering, and ⁴Electrical, Computer and Systems
Rensselaer Polytechnic Institute, Troy, NY 12180 USA
* Email: bequeb@rpi.edu

Department of ³Anesthesiology, Albany Medical Center, Albany, NY 12208 USA

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Kaufman

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 an anesthetic (propofol) pharmacokinetics and pharmacodynamics. The simulation model is used to design and test a control strategy, which simultaneously regulates hemodynamic and anesthetic states in critical care patients.

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. It is desirable to have an automated system which closes the loop on primary variables, monitors secondary variables such as heart rate, 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”. A significant amount of research has been focused on control of drug delivery. Rao *et al.* (1997b) present a detailed discussion on hemodynamic and anesthetic control. 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.

System Description

The model used in this study to describe the effect of inotropic and vasoactive drugs on a physiological system was initially developed by Yu *et al.* (1990a), and has been used (in various forms) in a number of simulation studies (Yu *et al.*, 1990b; Gopinath *et al.*, 1995; Held and Roy, 1995; Huang and Roy, 1996; Rao *et al.*, 1997a). We have revised the model to include the pharmacokinetic/pharmacodynamic effects of propofol, based on parameters obtained from Tackley *et al.*, (1989) and Fragen, (1996). The parameters were fine tuned to simulate open-loop results similar to Nakaigawa *et al.*, (1995). The model is simulated using MATLAB/SIMULINK.

The input variables of the system are the infusion rates of sodium nitroprusside (SNP), dopamine (DPM), phenylephrine (PNP) nitroglycerine (NTG) and propofol (PFL). The output variables are mean arterial pressure (MAP), cardiac output (CO), mean pulmonary arterial pressure (MPAP) and propofol blood concentration (PFC). Since the DOA is not directly measurable, the PFC is used as a measure of DOA. The physician changes the PFC setpoint based on observations of the patient and serves as an “outer loop controller” in a multivariable cascade control strategy, as shown in schematic form in Fig. 1. The simultaneous hemodynamic/anesthetic control problem exhibits essentially one-way coupling, that is, the propofol infusion affects hemodynamic variables, but the hemodynamic drugs have no direct effect on the PFC. Hence we decouple the controllers for PFC and hemodynamic variables.

Model predictive control (MPC) is an optimization-based approach which has been successfully applied to a wide variety of control problems. The basic idea, is to select a sequence of future control moves to minimize an objective function (usually sum of square of predicted errors) over a prediction horizon. One such 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.* (1989).

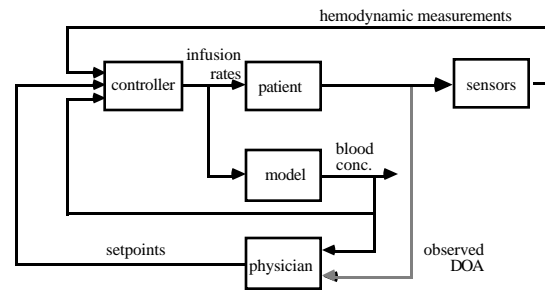


Fig. 1. Control Structure for Hemodynamic Variables and Blood Concentration of Propofol. Notice that the Physician serves as the “outer loop” of a multivariable cascade control strategy.

Results

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 propofol. The PFC setpoint is stepped up gradually from 0 to 5 $\mu\text{g/ml}$ for the first 5 minutes and 7 $\mu\text{g/ml}$ thereafter. The absolute constraints on the manipulated variables are 0 and 10 $\mu\text{g/kg/min}$, except for DPM, where the permissible dosage zone is 4 to 7 $\mu\text{g/kg/min}$ and PFL is constrained between 0 and 600 $\mu\text{g/kg/min}$. The sample time is 0.5 minutes. 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.

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 depression of MAP and CO brought about by PFL and to raise them to the desired setpoints. The results are shown in Fig. 2. At around 20 minutes, PFC setpoint is lowered back to 5 $\mu\text{g/ml}$ 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: This case consists of a patient retaining 100% of normal heart contractility, but is hypertensive initially at 120 mmHg MAP, 130 ml/kg/min CO, and 19 mmHg MPAP. It is required to lower MAP to 95-100 mmHg, MPAP between 18-21 mmHg and maintain a minimum CO of 95 ml/kg/min while also infusing PFL to induce sleep. The PFC setpoint is to be stepped up gradually from 0 to 5 $\mu\text{g/ml}$ for the first 5 minutes, 7 $\mu\text{g/ml}$ for the next 15 minutes and then lowered back to 5 $\mu\text{g/ml}$.

Again in closed loop, the anesthetic controller infuses PFL to raise PFC and the hemodynamic controller infuses the optimal NTG and PNP to lower MAP and CO to the desired setpoints. The results are shown in Fig. 3. At around 15 minutes, an increase in setpoints for MAP and CO is sought. The controller increases PNP dosage and infuses DPM maintaining a lower constraint of 4 $\mu\text{g/kg/min}$ to avoid the forbidden zone. As a result, MAP and CO are observed to increase, but the infusion rates hit constraints (DPM around 17 minutes and PNP around 24 minutes) and the controller continues 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 physician can intervene to either relax constraints or lower the setpoint to the current values. Meanwhile, the anesthetic controller continues to maintain PFC at its setpoint.

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. 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 DOA from other readily measured variables.

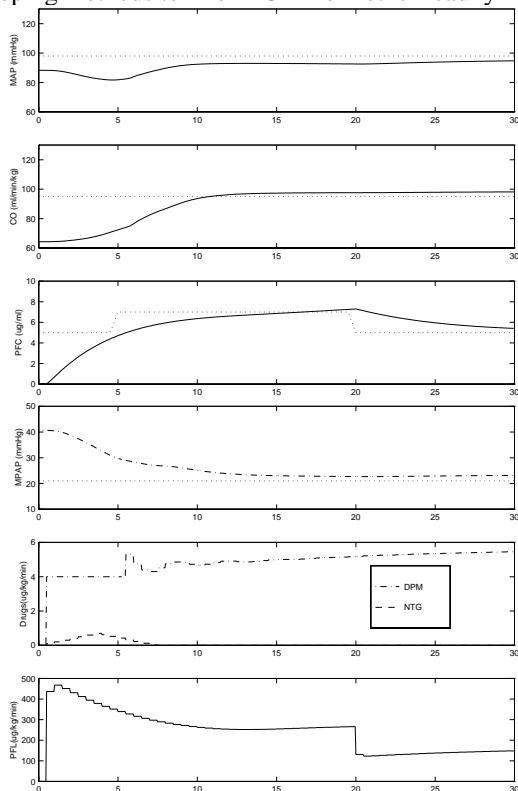


Fig 2. Closed-loop response for Case 1

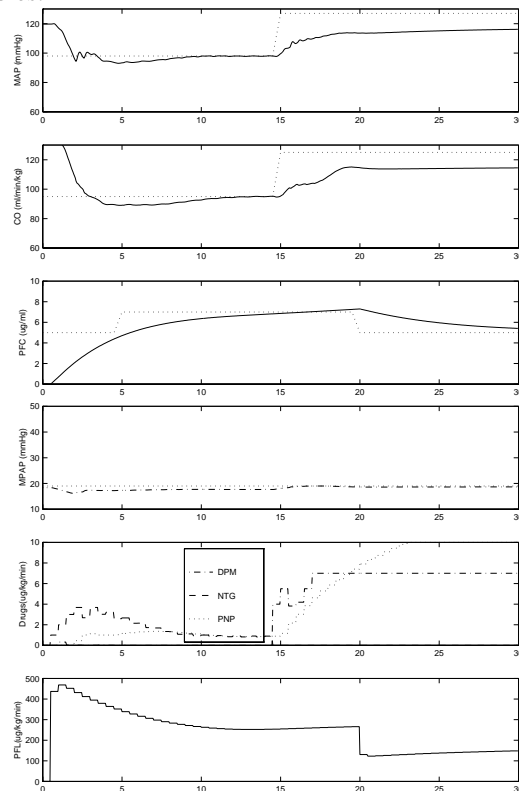


Fig 3. Closed-loop response for case 2

Acknowledgment

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