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Simultaneous Regulation of Hemodynamic and Anesthetic States: A Simulation Study

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Abstract—A model predictive control strategy to simultaneously regulate hemodynamic and anesthetic variables in critical care patients is presented. 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 a measure for depth of anesthesia. The simulation model is used to design and test the control strategy. 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 serves as the ''primary controller'' by making propofol blood concentration setpoint changes based on observations about anesthetic depth. Results are shown for three simulated cases: (i) congestive heart failure, (ii) postcoronary artery bypass, and (iii) acute changes in hemodynamic variables. © *2000 Biomedical Engineering Society.*
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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, physicians 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. The current clinical practice is to use manual adjustment of drug infusion rates with drip intravenous (IV) and/or programmable pumps. The cardiac nurse and physician are responsible for monitoring the measured ''outputs'' (MAP and CO) and adjusting the manipulated ''inputs'' (drug infusion rates), thereby serving as closed-loop controllers. The goal of the research presented in this article is to develop an automated approach to regulate the measured outputs (obtained from currently available sensors) by adjusting the flow rates of programmable pumps (also currently available). This automated approach will free the cardiac nurse and physician of some of the more mundane duties and allow them more time to monitor the patient for conditions that are not easily measured.

Clinical trials have been conducted for the single-input single-output problem of adjusting the infusion rate of sodium nitroprusside to regulate mean arterial pressure using a feedback control algorithm. Our long-term goal is to extend this technology to the multiple input multiple output problem of adjusting several drug and anesthetic infusion rates to regulate several outputs (including depth of anesthesia). It is important to conduct extensive simulation-based studies to be assured of a robust control algorithm (one able to handle extreme patient variability), before moving to animal experiments and clinical trials. The objective of this article is to present the results of an extensive simulation study.

In this article we explore the use of a model predictive control (MPC) strategy to regulate drug infusion. Model predictive controllers are a class of controllers which employ an identifiable model to predict the future behavior of the system over an extended prediction horizon and compute the optimal drug infusion to achieve desired states. An important issue in the design of drug infusion systems is the need to impose bounds on dosages and infusion rates to avoid overdosing or drug toxicity. For example, sodium nitroprusside, used in reduc-

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ing hypertension, should be infused less than 10 $\mu g\,kg^{-1}\,min^{-1}$ to avoid cyanide build up; for the case of low cardiac contractility, dopamine infusion should be maintained within its inotropic range of 4–7 $\mu g\,kg^{-1}\,min^{-1}$. Alternatively, the physician may want to specify an operating range of MAP instead of a specific setpoint. While most control strategies handle such constraints in an ad hoc manner, the primary advantage of MPC is its ability to handle constraints explicitly. Its optimization-based framework allows computation of the optimal infusion rates subject to input and output constraints. For example, constraints on drug infusion rates and output variables (such as maintaining CO above a minimum value) can be explicitly specified and the resulting control action will satisfy them.

Control of Hemodynamic Variables

Initial research in hemodynamic control has focused on single-input single-output control of MAP, while more recent work has considered the control of several hemodynamic variables by the infusion of multiple drugs. A detailed review of blood pressure control is provided by Isaka and Sebald.[10] Recently, Kwok *et al.*[12] reported on clinical trials of automated blood pressure regulation during open-heart surgery. 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 sodium nitroprusside and dopamine). One of the more advanced studies on simultaneous control of CO and MAP utilizing multiple drug infusion was done by Voss *et al.*[20] Yu *et al.*[23] used a multiple model adaptive approach in canine experiments.

Control of Anesthetic Variables

Research on control of the depth of anesthesia dates from the 1950s, and was reviewed by O'Hara *et al.*[14] Manual administration of anesthetics has often produced undesirable oscillations in blood concentration of anesthetic and DOA. Continuous variable-rate infusions have been known to improve the anesthesiologists' ability to titrate the drug to the desired effect.[17] Kenny and White[11] used computer controlled infusion pumps based on pharmacokinetic model equations where programmable pumps deliver anesthetics at variable rates to maintain a desired blood concentration. The infusion profiles are programmed based on prediction using a pharmacokinetic model that describes the drug assimilation and accumulation in the body.

Much recent drug infusion work has focused on the use of the intravenous anesthetic agent propofol (PFL). Propofol is currently gaining widespread acceptance for induction and maintenance of general anesthesia, as well as for sedation and local and regional anesthesia. The primary advantages of propofol are (i) it produces rapid onset of anesthesia, (ii) it provides a clear, rapid emergence from anesthesia, and (iii) there is a lack of accumulation, which allows prolonged drug infusion. Propofol infusion brings about a change in cardiovascular functions such as depression of MAP, CO, heart rate, and vascular resistances. Critical care patients require tight monitoring under the influence of such disturbances and, hence, simultaneous regulation is vital.

Objectives of This Article

In this article, we present model predictive control approaches for simultaneous regulation of hemodynamic and anesthetic states of critical care patients. We use a canine circulatory model to mimic clinical conditions requiring critical care of cardiovascular functions. This control study is a natural extension to earlier work by Rao *et al.*[16] which used MPC for automation of hemodynamic drug infusion.

In the next section, we describe the simulation model of the canine circulatory system and present extensions to incorporate the pharmacokinetics (PK) and pharmacodynamics (PD) of propofol. This provides a realistic simulation platform to design and test advanced control strategies of both hemodynamic and anesthetic states. Then we introduce the model predictive control structure proposed to simultaneously control hemodynamic and anesthetic states. In another section, we present closed-loop simulation results. We then discuss and summarize our results and indicate the focus of our current research.

SYSTEM DESCRIPTION

The overall control objective is to maintain the hemodynamic variables MAP, CO, and mean pulmonary arterial pressure (MPAP) at desired setpoints while simultaneously controlling the anesthetic states (DOA) desired by the anesthesiologist. Sodium nitroprusside is administered for arterial vasodilation; dopamine is used as an inotrope to enhance cardiac performance; phenylephrine (PNP) is an arterial vasoconstrictor and nitroglycerin (NTG) is a venodialator. Control of DOA is achieved by altering the propofol infusion and hence the propofol blood concentration (PFC).

Depending on the patient's status, one or more of the four drugs will be chosen to maintain the three hemodynamic variables. We assume that the attending physician has already evaluated the patient's status and determined the proper model and drug therapy. The model predictive controller uses measurements of the hemodynamic states and determines optimal infusion rates to achieve the desired setpoints.

When implementing a complex control strategy, such as the control of hemodynamic and anesthetic states in critical care patients, it is necessary to perform detailed

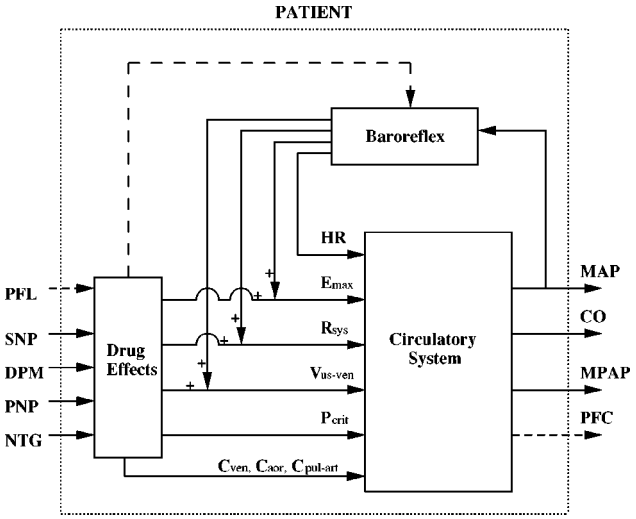

FIGURE 1. Schematic of the physiological model. Details of the baroreflex model are presented in Fig. 2. The extensions made in the nonlinear model for propofol effects are indicated by dashed lines.

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 of a canine circulatory system, which we have used in the past as a basis for control system designs. These were later shown to be successful in laboratory experiments.[15,23]

The model used in this article to describe the effect of inotropic and vasoactive drugs on a physiological system was initially developed by Yu *et al.*[22] and it has been used (in various forms) in a number of simulation studies (for example, by Gopinath *et al.*,[5] by Held and Roy,[6] by Huang and Roy,[8] and by Rao *et al.*[16]). We have revised the model to include the pharmacokinetic/pharmacodynamic effects of propofol based on parameters obtained from Tackley *et al.*[19] and from Fragen.[3] The parameters were fine tuned to simulate and match open-loop results from experiments on dogs reported by Nakaigawa *et al.*[13]

Physiological Model Description

A schematic of the circulatory system model is shown in Fig. 1. The physiological 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. Yu *et al.*[22] used an electric circuit analogy to describe the lumped parameter model of the circulatory system. The forcing function is the time-varying elastance of the heart. The maximum value of this elastance, $E_{\max}$, is used to characterize ventricular contractility. Body compartments and blood vessels are represented as capacitances and the viscous forces and resistance to blood flow in the systemic and pulmonary vasculature are modeled as resistors. MAP is then the voltage measured after the left ventricle, and CO is the current flow measured at that point in the circuit. All the circulatory system elements are described in terms of the following (time-varying) body parameters: (a) heart rate (HR) — affects the contraction time of the ventricle, which in turn affects the cardiac output; (b) maximum elastance ($E_{\max}$) — used to characterize ventricular contractility; (c) unstressed venous volume ($V_{\text{us-ven}}$) — a measure of venous contraction; (d) systemic resistance (R_{sys}) — the resistance to blood flow through the smaller blood vessels; (e) critical closing pressure (P_{crit}) — the minimum pressure required to prevent collapse of blood vessels in the pulmonary circulation; (f) venous and arterial compliances (C_{ven}, C_{aor}, $C_{\text{pul-art}}$) — the capacitance of the blood vessels.

The first set of equations describing the volume-flow relationships for each ''descriptive vessel,'' in the body are of the form

$$\frac{dV_i(t)}{dt} = Q_{i-}(t) - Q_{i+}(t), \tag{1}$$

where i is the vessel being considered ($i = 1, \ldots, 7$), Q_{i-} represents flow in from the previous vessel, and Q_{i+} represents the flow out to the next vessel. There are seven descriptive vessels; the left ventricle, the large arteries, the small arteries, the venous system, the right ventricle, the pulmonary artery, and the pulmonary vein. In addition, the following equation describes the pressure-flow relationships for the large and small arteries (vessels 2 and 3):

$$\frac{dQ_2(t)}{dt} = \frac{P_2(t) - P_3(t)}{L}, \tag{2}$$

where L is a constant inertance element. The next set of equations describes the time dependent concentration of the drugs in the descriptive vessels.

$$\frac{dm_{j,i}(t)}{dt} = (C_d(t)Q(t))_{j,i-} - (C_d(t)Q(t))_{j,i+} - \left(\frac{m(t)}{\tau_{1/2}}\right)_{j,i}, \tag{3}$$

where j refers to the drug and the i represents the vessel being considered. m is the mass of the drug in the vessel,

TABLE 1. Pharmacodynamic parameters (compiled from work of Gopinath *et al.* (Ref. 5) and Huang (Ref. 7). The PFL parameters values are those of Fragen (Ref. 3), and were tuned to match experimental results.

Drug (effect site)	Eff_{max}	p	k_2	EC_{50}
SNP (R_{sys}, P_{crit})	0.635	1.0	0.025	1.706
SNP ($V_{us\text{-}ven}$)	225.0	1.0	0.00625	0.936
DPM (E_{max})	1.3	6.11	1.1316E-3	4.0
DPM (R_{sys})	0.5	1.46	0.0125	92.26
PNP ($V_{us\text{-}ven}$)	32.2	1.0	0.055	1.1
PNP (R_{sys} P_{crit})	0.821	1.0	0.05	1.6
PNP (C_{ven})	0.525	1.0	0.0625	1.8
NTG (R_{sys}, R_{pv})	0.6252	1.0	0.0231	1.91
NTG ($V_{us\text{-}ven}$)	235	1.0	0.01325	1.5
NTG (C_{ven})	0.85	1.0	0.02273	3.851
NTG ($C_{pul\text{-}art}$)	0.462	1.0	0.02354	3.421
PFL (BFC, C_{aor})	0.75	1.0	0.0084	2.5

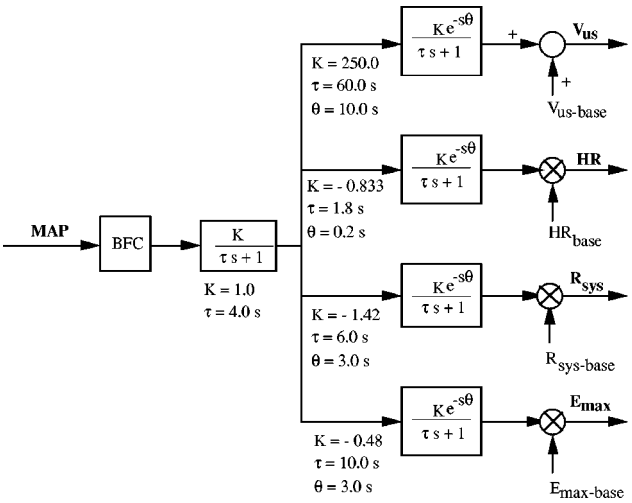

FIGURE 2. Baroreflex model structure, equations, and parameters.

C_d is the drug concentration in the vessel, V is the vessel volume ($C_d = m/V$), and $\tau_{1/2}$ is the half life of the drug.

The pharmacodynamic equations describing the drug-effect relationship are given by the following:

$$\frac{d\mathrm{Eff}(t)}{dt} = k_1 C_d^p(t)(\mathrm{Eff}_{\max} - \mathrm{Eff}(t)) - k_2 \mathrm{Eff}(t); \quad (4)$$

Eff is the quantitative measure of the effect of a drug on its affected parameter in the compartment where the effect is assumed to be concentrated. Eff_{max} is the maximum effect of the drug, p is the power to which the concentration is raised, and k_1 and k_2 are reaction rate constants. The drug-effect parameters on the variables and the relevant chambers in which the drug is assumed are given in Table 1.

The baroreflex model developed by Wesseling *et al.*[21] describes the effects of arterial baroreceptors in short-term MAP regulation. We use a modified version of the baroreflex, shown schematically in Fig. 2. The baroreflex model uses MAP as input to modify $V_{us\text{-}ven}$, R_{sys}, E_{max}, and HR. The baroreflex input (BFC) is calculated as

$$\mathrm{BFC} = \frac{\exp(c(\mathrm{MAP}(t) - \mathrm{MAP}_{ref}))}{1 + \exp(c(\mathrm{MAP}(t) - \mathrm{MAP}_{ref}))} \quad (5)$$

where MAP_{ref} is a nominal value of MAP and c is an empirical constant.

The model naturally splits into two time scales: (i) drug masses and drug-effect variables that remain constant over a heartbeat and (ii) volume, blood flow rate, and baroreflex state variables that change during each heartbeat. The outputs MAP, MPAP, and CO are calculated from the integrated values of vessel flow and pressure relationships. The symptomatic changes in blood pressure and cardiac output associated with patients' conditions and drugs effects can be simulated by altering one or more of the body parameters. For example, one of the causes of congestive heart failure (CHF) is a reduction in the effective contractility of the heart. CHF is modeled by reduction of E_{max} by 50%–70% in the left ventricle. The associated dopamine therapy to increase ventricular contractility affects E_{max}. Vasodilatory action of sodium nitroprusside reducing resistance to blood flow is modeled by reducing R_{sys} and increasing $V_{us\text{-}ven}$. These effects are computed using Eq. (4).

Details of the model equations and parameters are not provided for sake of brevity. The reader is referred to Yu *et al.*[22] and Gopinath *et al.*[5] for a complete description of the model equations and the solution procedure. Huang[7] extended the model to incorporate the effects of phenylephrine and nitroglycerin on venous compliance C_{ven} and pulmonary arterial compliance $C_{pul\text{-}art}$ in the canine circulatory model. In the following sections we propose extensions of the model to incorporate pharmacokinetics and pharmacodynamics of propofol.

Model Extensions for Anesthetic Effects

While physiological models like the one described above provide better insights into drug distribution in the body, they require extensive data. Hence as a first level approximation of anesthetic effects, the pharmacokinetic model adopted in this study is a three compartment model that has been widely used and successfully implemented in clinical practice for open-loop computer assisted target controlled infusions. Shafer and co-workers[18] have developed STANPUMP, a software for computer controlled drug infusion that is freely available at their WWW server. Roy and co-workers reported using STANPUMP with Tackley parameters for estimating propofol concentration in canine experiments during

their investigations of fuzzy logic based DOA estimation using midlatency auditory evoked potential (MLAEP).[9] Although they have used human data for predicting plasma concentrations, their results were good. For our studies we adopt the parameter set of Tackley *et al.*[19]

The three compartment concentration model which describes the distribution and assimilation of a drug is given by the following set of differential equations:

$$\frac{dC_1(t)}{dt} = -[k_{10}+k_{12}+k_{13}]C_1(t)+k_{21}C_2(t) + k_{31}C_3(t)+\frac{I(t)}{V_1}, \quad (6)$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t)-k_{21}C_2(t), \quad (7)$$

$$\frac{dC_3(t)}{dt} = k_{13}C_1(t)-k_{31}C_3(t), \quad (8)$$

where C_i is the drug concentration in compartment i, k_{ij} are the rate constants for drug distribution from compartment i to compartment j (in keeping with the accepted standard in the pharmacokinetic literature), I is the infusion rate and V_1 is the apparent volume of the central compartment. The drug is infused into and eliminated from the central compartment (compartment 1), which essentially constitutes blood or plasma. The drug in the central compartment reversibly distributes between two hypothetical peripheral compartments representing well perfused tissue (compartment 2) and poorly perfused tissues (compartment 3). While anesthesiologists use the model to predict and maintain a desired amount of anesthetic concentration in the blood open loop, we incorporate the model equations to simulate the distribution of propofol in the circulatory system. The drug-effect relationships for propofol are computed using Eq. (4) and the parameters reported in Table 1. With a combined PK/PD mechanism, it is now possible to quantify the magnitude of propofol effects at the active sites.

A number of studies have established that propofol affects cardiovascular parameters such as vascular resistance, arterial compliance, and baroreflex. This in turn causes the depression of MAP, CO, and heart rate. Cullen *et al.*[1] discussed the effect of propofol on baroreflex activity of humans. They showed marked reflex resetting in baseline arterial pressures as reasons for slowing down the heart rate which allowed lower arterial pressure as compared to the awake state. We simulate this effect by altering the MAP_{ref} value associated with the baroreflex input shown in Eq. (5) and Fig. 2. It can be noted that this also alters the systemic vascular resistance as observed in most propofol studies. Based on Deryck *et al.*[2] we also alter arterial compliance C_{aor} in the model equations to simulate the cardiovascular alterations by propofol. The extended anesthetic model combined with the physiological model is now capable of simulating the cardiovascular changes associated with propofol infusion. Predicted propofol concentration is used as a measure of DOA.

Tuning of Model Parameters for Propofol Effects

All of the propofol related parameters used in the model were obtained from a variety of sources of human and animal experiments discussed earlier. Also these studies involved different premedication and the supplementing of opiates and sedatives. Obviously, there is a possibility of error arising in the prediction of hemodynamic and anesthetic states. The parameters hence require tuning and the following procedure was adopted.

The sensitivity of the model to variations in circulatory parameters was analyzed to verify that within the operating range of drug and anesthetic concentrations, the model is capable of simulating changes in MAP and heart rate as observed in experimental studies cited in the literature. The propofol model parameters were then fine tuned by running a number of open-loop simulations to closely reproduce results from experiments. Nakaigawa *et al.*[13] have studied the effects of propofol infusion on cardiovascular hemodynamics, coronary circulation, and myocardial metabolism in open-chested dogs. They presented detailed hemodynamic data and plasma concentration of propofol for various (steady) infusion rates from 6 $mg\,kg^{-1}\,hr^{-1}$ to 21 $mg\,kg^{-1}\,hr^{-1}$. A relevant summary of the experimental results is presented along with those obtained by simulations on our canine circulatory model in Table 2. However, Nakaigawa *et al.*[13] did not report values of hemodynamic variables before propofol infusion, but used results at 6 $mg\,kg^{-1}\,hr^{-1}$ infusion as baseline values. Hence, we provide a more meaningful comparison of our model simulations with their experimental results using normalized values in Fig. 3. Open-loop simulations were performed on the model for each of the infusion rates that lasted 30 minutes. The steady state model predictions of MAP, CO, and heart rate are normalized using the values obtained from the 6 $mg\,kg^{-1}\,hr^{-1}$ data set. Plasma concentrations are presented as is. It can be observed that MAP and plasma concentration values are reasonably close to the experimental values. Even though the experimental heart rate values show nonlinear behavior, model predictions are within acceptable ranges. There is however a large mismatch in the values for cardiac output. Due to the lack of sufficient data, we were unable to match CO values without compromising MAP, HR, and plasma concentration predictions. However, it should be noted that the CO

TABLE 2. Comparison of experimental and simulated results. Mean values of experimental results are reported along with the Standard Error of the Mean ranges in parentheses.

	Propofol Infusion Rate ($mg\,kg^{-1}\,hr^{-1}$)						
Experimental Results (Nakaigawa *et al.* [a])	0	6	9	12	15	18	21
Plasma Concentration (μg/ml)	-	2.9(0.3)	4.3(0.3)	5.4(0.5)	6.4(1.2)	9.4(0.7)	11.5(0.7)
MAP (mm Hg)	-	117(6)	113(8)	108(8)	103(6)	98(5)	93(7)
CO ($ml\,kg^{-1}\,min^{-1}$)	-	140(10)	120(10)	100(10)	90(10)	90(10)	90(10)
HR (beat/min)	-	126(8)	131(8)	128(6)	120(6)	114(6)	108(7)
Simulation Results							
Plasma Concentration (μg/ml)	0.0	2.9	4.3	5.8	7.3	8.7	10.2
MAP (mm Hg)	119	88	81	76	72	69	67
CO ($ml\,kg^{-1}\,min^{-1}$)	131	115	111	108	106	104	103
HR (beat/min)	122	107	104	102	101	99	98

[a]Reference 13.

depression reported from these experiments appears to be unusually large. Propofol is known to cause a minor reduction in CO.

The model is simulated using MATLAB/SIMULINK, which provides a transparent translation of control system design to the nonlinear process. This allows direct comparisons of control strategies developed by different researchers and is now available on the website http://www.rpi.edu/~royr/roy_sftwr.html.

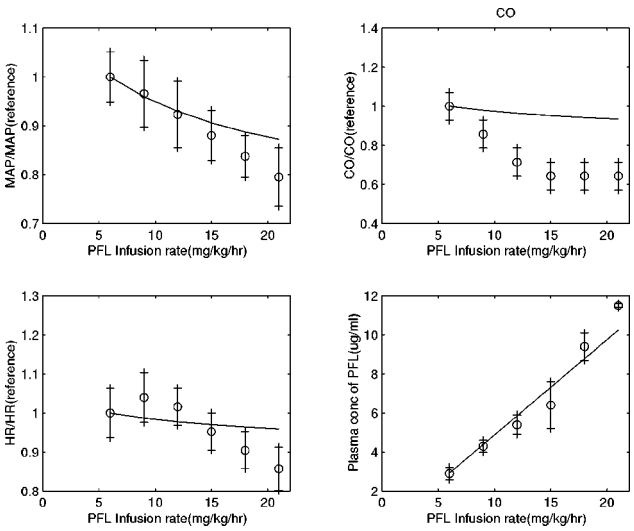

FIGURE 3. Comparison of simulation results with experimental results of cardiovascular changes due to steady propofol infusion. Experimental values are denoted by circles along with the Standard Error of the Mean ranges. Since Nakaigawa *et al.* (Ref. 13) did not provide baseline values at zero propofol infusion, the steady state values for MAP, CO, and HR are normalized based on data for an infusion rate of 6 $mg\,kg^{-1}\,hr^{-1}$.

CONTROL SYSTEM DESIGN

Control Structure

Closed-loop strategies require a feedback signal indicating the measure of MAP, CO, MPAP, and DOA. The measurements of MAP and MPAP can be obtained as frequently as desired. In the past, CO measurement involved techniques such as the Fick method or indicator dilution with sampling time of about 12–15 minutes. Currently available continuous-cardiac-output (CCO) monitors are capable of providing CO measurements every 30 seconds. Several indicators have been suggested for monitoring DOA based on hemodynamics, electroencephalogram (EEG), electromyogram (EMG), auditory evoked potentials (AEPs), and anesthetic concentrations. Although many inroads have been made to infer DOA, it will be some time before it becomes a common controlled output. Since the DOA is directly related to the anesthetic blood concentration we assume that a model is used to predict the propofol concentration (PFC), 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, shown in schematic form in Fig. 4. The simultaneous hemodynamic/anesthetic control problem exhibits essentially one-way coupling, that is, it is assumed that the propofol infusion affects hemodynamic variables (MAP, CO, and MPAP), but the hemodynamic drugs do not interact with propofol directly to affect the propofol blood concentration. Hence we decouple the controllers for PFC and hemodynamic variables.

Model predictive control is an optimization-based approach which has been successfully applied to a wide variety of control problems. MPC uses a model to pre-

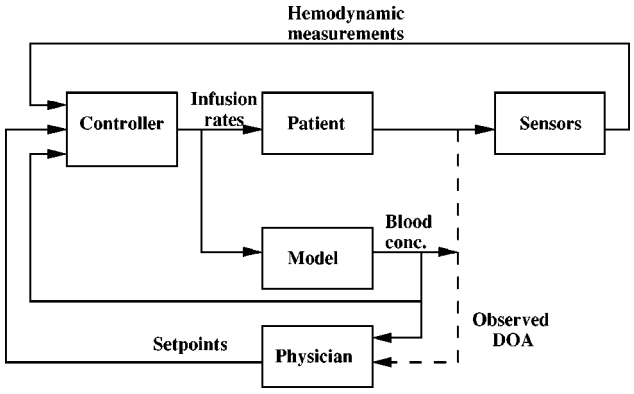

FIGURE 4. Control structure for hemodynamic variables and DOA. PFC is used as an indicator of DOA. Based on model predictions and secondary measurements, a physician serves as an outer-loop controller providing PFC setpoints to maintain the patient in asleep/awake states.

dict the system response to future control moves and optimizes manipulated variables to minimize the predicted error subject to operating constraints. The basic idea, shown in Fig. 5, is to select a sequence of M future control moves to minimize an objective function (usually the sum of the square of predicted errors) over a prediction horizon of P sample intervals. Using a model, the system response to changes in the manipulated variable is predicted. The M moves of the manipulated variables are selected such that the predicted response has minimal setpoint tracking error. Since new measurement information will be available in the next sampling instance, only the first computed change in the manipulated variables is implemented and the optimization is repeated at each sampling interval based on updated measurements of the output variables. A review of MPC is provided by Garcia *et al.*[4] In drug delivery applications, Gopinath *et al.*[5] used a nonlinear prediction model in a MPC framework to control a 2×2 drug infusion system. Yu *et al.*[23] have applied a variant of MPC (multiple model adaptive-predictive control) to a 2×2 drug infusion problem, where a bank of controllers is used to account for nonlinearities.

The manipulated variables (drug infusion rates) u are computed to minimize a quadratic objective function

$$\min_{u(k)\ldots u(k+M-1)} J=\sum_{i=k+1}^{k+P} e_i^T Q e_i+\sum_{i=k}^{k+M-1} \Delta u_i^T R \Delta u_i \tag{9}$$

subject to absolute and rate constraints on the manipulated variables,

$$u_{\min}<u_i<u_{\max},$$

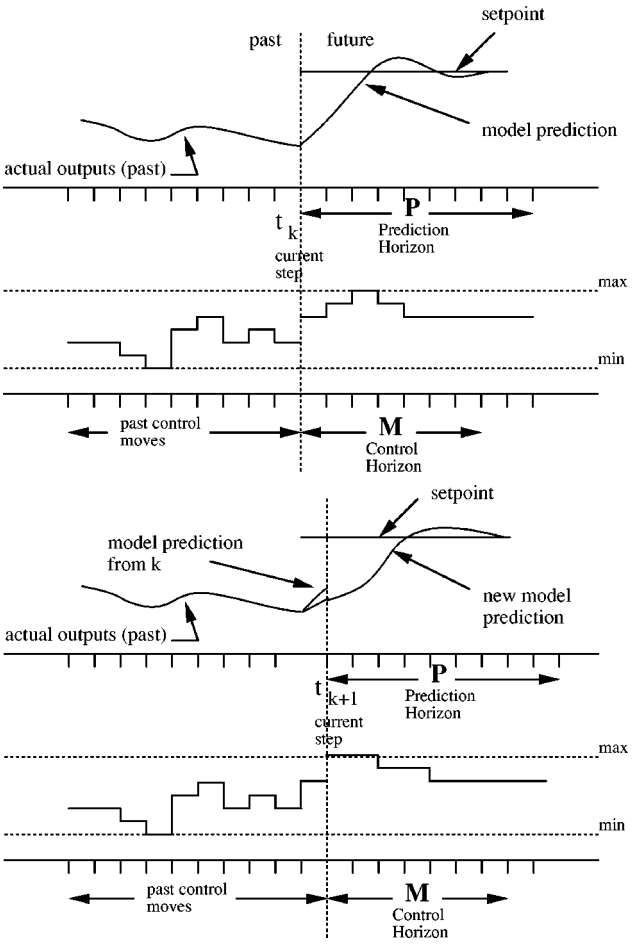

FIGURE 5. Model predictive control: (a) At the current sampling instance *k*, a model is used to predict the output behavior of the system *P* sample intervals into the future based on the past states and *M* future control moves. The future control moves are optimally estimated to minimize predicted error from the setpoint. Feedback is achieved by implementing only the first of the *M* moves. (b) Based on the actual measurements of the output at the *k*+1th instance, the model predictions are corrected as an additive disturbance to account for model mismatch and unmeasured disturbances. The optimization procedure is repeated in a receding horizon framework to compute a new set of moves.

$$u_{i-1}-\Delta u_{\max}\leq u_i\leq u_{i-1}+\Delta u_{\max},$$

where, at each sampling instance i, e_i is a vector of model predicted errors ($e_i=r_i-y_i$), y_i is a vector of model predicted outputs (MAP, CO, MPAP, and PFC) over a prediction horizon of P, r_i is the desired setpoint, u_i is the vector of manipulated variables (SNP, DPM, PNP, NTG, and PFL) over a control horizon M, and Q and R are output and input weighting matrices. The prediction horizon P is chosen on the basis of the open-loop settling time. The control horizon M is used to tighten or detune the controller. In general, larger values of M for an input will result in more aggressive action. This yields

faster response, but the closed-loop system is less robust to disturbances. M is chosen on the basis of an allowed trade-off between these considerations. The output weighting matrix Q is a diagonal matrix used to assign weights to the components of the error function, corresponding to each output in the optimization step. A larger weight for an output will result in tighter control. The input penalty matrix R is also a detuning parameter and is used to penalize control action in the objective function. This parameter is especially useful when a large M is used.

The prediction model is given in a generic form as

$$\dot{x} = f(x,u),$$

$$y = g(x),$$

where the output y is a function of the model states x and the inputs u. The optimization is a quadratic programming (QP) problem and absolute, and rate constraints on the manipulated variable are included as linear inequalities.

The MPC strategy, in its most general form, places no restriction on the type of prediction models or its structure. The model can range from simple linear transfer function to complex nonlinear physiological model described in the previous section. The complexity of the model however increases the computational load and linear approximations are hence used for predictions.

Linear Prediction Model

In this work we use discrete linear step response models. The advantage is that the model can be obtained online, without any assumptions about structural or parametric uncertainties in the model description. 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 is computed by convolving the model impulse response with the history of manipulated variable $(u(k-1), u(k-2), \ldots,)$ from the current sampling instance k and given by

$$y(k) = \sum_{i=1}^{N} H_i u(k-i),$$

where H_i is the ith impulse response coefficient matrix. N is the number of terms in the model, and is usually chosen to correspond to the settling time of the model. This ensures that we use information about any control move that might have been made in the past until the system settles to the steady state arising from that control move. The predicted output at the jth future point is given by

$$y(k+j) = \sum_{i=1}^{j} H_i \Delta u(k+j-i) + \sum_{i=j+1}^{N} H_i \Delta u(k+j-i) + d(k).$$

The prediction of output involves three terms on the right-hand side. The first term includes the present and all future moves of the manipulated variables which are to be determined so as to solve Eq. (9). The second term includes the past values of the manipulated variables and is completely known at time k. The third term is the predicted disturbance which is calculated as the difference between the current measurements and output of the predicted model, i.e., $(d(k) = y_m(k) - y(k))$ at the kth sampling instant. This is the ''additive disturbance'' which accounts for model mismatch and unmodeled disturbances that enter the system and is assumed to be constant over the prediction horizon due to lack of an explicit means of predicting the mismatch or disturbance.

In our simulation framework the nonlinear physiological model serves as the *canine patient* and a linear approximation step response model is used in model predictions.

RESULTS

In this section, we present the simulations to demonstrate the controller performance in setpoint tracking and disturbance rejection.

Due to the limitations of on-line sensors and instrumentation, the control of hemodynamic variables is essentially multirate. Our controller design and simulations are based on the slow sampled variable (CO) with a 0.5 min sampling interval. Normally distributed noise with a standard deviation of 2 mm Hg and 3 $\mathrm{ml\,kg^{-1}\,min^{-1}}$ units was added to the pressure and cardiac output measurements, respectively.

The prediction horizon P is chosen as 20 sample intervals (approximately equal to the settling time of the slowest response in the system) along with a control horizon M of two time steps. The PFL controller uses a control horizon of one time step. The change in output variables is of the same magnitude, but control of MAP is assigned a higher priority over the other two variables. Hence the weights Q in the objective function are assigned in a ratio of 2:1:1 (MAP:CO:MPAP). The input weights R are set to zero and any large changes in drug infusion rate is constrained by imposing velocity constraints as follows:

$$0 \leq \text{SNP,PNP,NTG} \leq 10 \ \ \mu\text{g kg}^{-1}\,\text{min}^{-1},$$

$$4 \leq \text{DPM} \leq 7 \ \ \mu\text{g kg}^{-1}\,\text{min}^{-1},$$

$$|\Delta\text{SNP},\Delta\text{PNP},\Delta\text{NTG}| \leq 0.2 \ \ \mu\text{g kg}^{-1}\,\text{min}^{-1},$$

$$|\Delta\text{DPM}| \leq 0.5 \ \ \mu\text{g kg}^{-1}\,\text{min}^{-1}.$$

The drug velocity constraints thus prevent large fluctuations in drug dosage. Note that dopamine is used as an inotrope and hence the infusion rates are constrained to the inotropic range of 4–7 $\mu\text{g kg}^{-1}\,\text{min}^{-1}$. There are no constraints necessary for propofol delivery. The transient performance criterion for the closed-loop system is a maximum allowable settling time of approximately 10 minutes for MAP and MPAP and 15–20 minutes for CO.

We have specified exact setpoints while the real objective is to maintain outputs within a range of values. For example, CO is usually required to be maintained above 95 $\text{ml kg}^{-1}\,\text{min}^{-1}$. 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. Studies on optimization methods for such infeasibilities are in progress. We present results for cases that require anesthetization and simultaneous control of hemodynamic variables commonly encountered in critical care.

In the following sections we present examples of clinical situations which require simultaneous regulation of hemodynamic and anesthetic states. The efficacy of the model predictive controller is demonstrated by simulating a dog in closed loop using the nonlinear canine circulatory model.

Case 1: Congestive Heart Failure

This case involves maintaining hemodynamic and anesthetic states of a simulated canine under congestive heart failure (Fig. 6). Due to the lowered heart contractility, the MAP and CO are low and require dopamine infusion in the inotropic range. The MPAP is high and nitroglycerin is infused to lower it to normal ranges. Sleep is induced by PFL infusion and the hemodynamic variables are maintained at the desired levels. The canine circulatory model is initialized with values of MAP (88 mm Hg), CO (65 $\text{ml kg}^{-1}\,\text{min}^{-1}$), MPAP (40 mm Hg), retaining 24% of normal baseline contractility of the heart. After stabilizing the hemodynamic variables, a propofol concentration setpoint of 6 μg/ml is sought to induce sleep. Figure 6 shows the results of the controller infusing dopamine, phenylephrine, and nitroglycerin to raise MAP and CO and lower MPAP to the desired setpoints. Propofol infusion begins at 10 minutes and as a result the MAP and CO values are observed to drop. The controller compensates by increasing dopamine and lowering nitroglycerin. At around 40 minutes, the PFC is lowered to 4 μg/ml and the PFL infusion is suitably altered. It can be noted that dopamine infusion is in the meanwhile maintained in its inotropic range of 4–7 $\mu\text{g kg}^{-1}\,\text{min}^{-1}$ and saturates its upper constraint at around 40 minutes. The controller maintains the infusion at this constraint and optimally manipulates the phenylephrine and nitroglycerin infusion. In a clinical environment, the resulting offset can trigger an alarm so that the anesthesiologist can take alternative action such as injecting a short acting drug or increasing the DPM constraint permitting it to act as an α-drug.

Case 2: Post-Coronary Artery Bypass

Patients that have come off bypass are required to be maintained in their sleep state to allow recovery of the circulatory system in the cardiac intensive care unit. PFL is induced to maintain a sleep state and, after several hours, the patient is slowly awakened by stepping down the PFL infusion. Inotropic and vasoactive drugs are also infused to maintain the hemodynamic variables at desired ranges. The post-surgical hypertension is regulated using sodium nitroprusside, while dopamine enhances the heart contractility to improve CO. The MPAP is lowered using nitroglycerin. A simulated dog with 50% baseline contractility, MAP (110 mm Hg), CO (105 $\text{ml kg}^{-1}\,\text{min}^{-1}$) and MPAP (25 mm Hg) requires regulation of its hemodynamic variables at setpoints of 85 mm Hg MAP, 110 $\text{ml kg}^{-1}\,\text{min}^{-1}$ CO and 18 mm Hg MPAP during propofol induction. As in the previous case, a PFC setpoint of 6 μg/ml is desired to induce sleep. Although this procedure of PFL induction and graded reduction lasts several hours, for our simulations we have chosen a shorter time scale for lowering the PFC setpoint (4 μg/ml at 70 minutes and 2 μg/ml at 100 minutes). As seen in Fig. 7, we lower the PFC setpoint after the controller maintains the hemodynamic and anesthetic states steady at desired values. The initial hypertension and the changes associated with PFL infusion are regulated by manipulating the drug infusion.

Case 3: Acute Changes in Hemodynamic Variables

This case is presented to demonstrate disturbance rejection of hemodynamic changes associated with acute interruption (and restoration) of aortic blood flow such as clamping-unclamping in aneurysm repair. Unclamping of an aortic vessel results in hypotension and a drop in CO due to lowered systemic vascular resistance (SVR). We initialize the nonlinear model for a hypertensive dog with lower than normal (70%) baseline contractility. To test the robustness of the model predictive controller we use a linear model identified on a dog with 50% contractility.

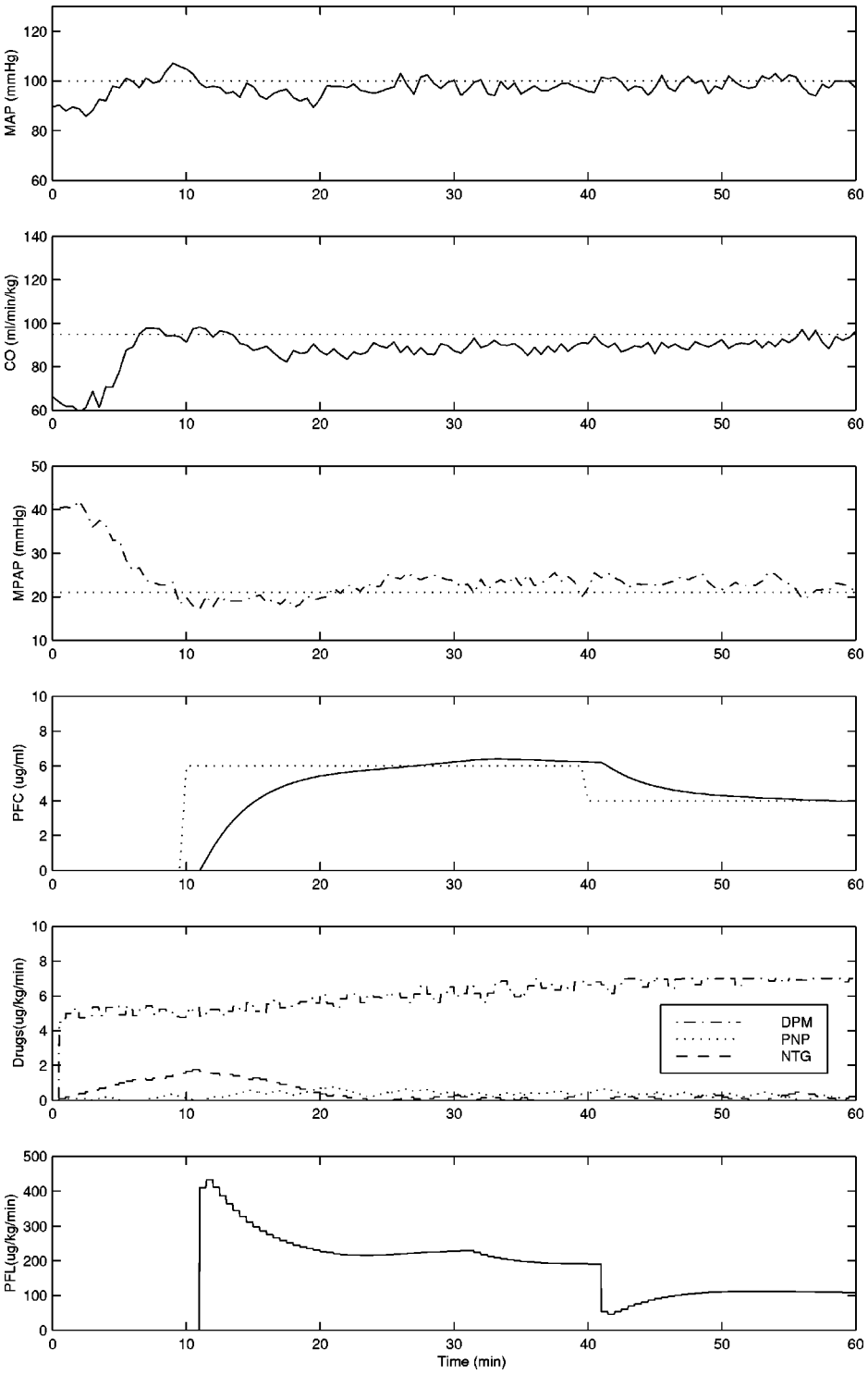

FIGURE 6. Case 1: Simulated canine with CHF requiring maintenance of hemodynamic variables during anesthesia.

MAP is lowered from 110 to 90 mm Hg, while maintaining CO at 110 ml kg^{-1} min^{-1} and MPAP at 18 mm Hg. Like above, the dog is put to sleep with a setpoint of 6 μg/ml. The infusion of sodium nitroprusside controls the lowering of MAP. Dopamine (and phenylephrine to a small extent) counteracts the propofol effects. It is assumed that the patient's artery is declamped at about 35 minutes. To aid in counteracting the hypotension due to declamping the anesthesiologist lowers the setpoint of PFC to 4 μg/ml, just enough not to awaken the patient. At 40 minutes, the PFC setpoint is raised back to 6 μg/ml to ensure good DOA. We simulate the

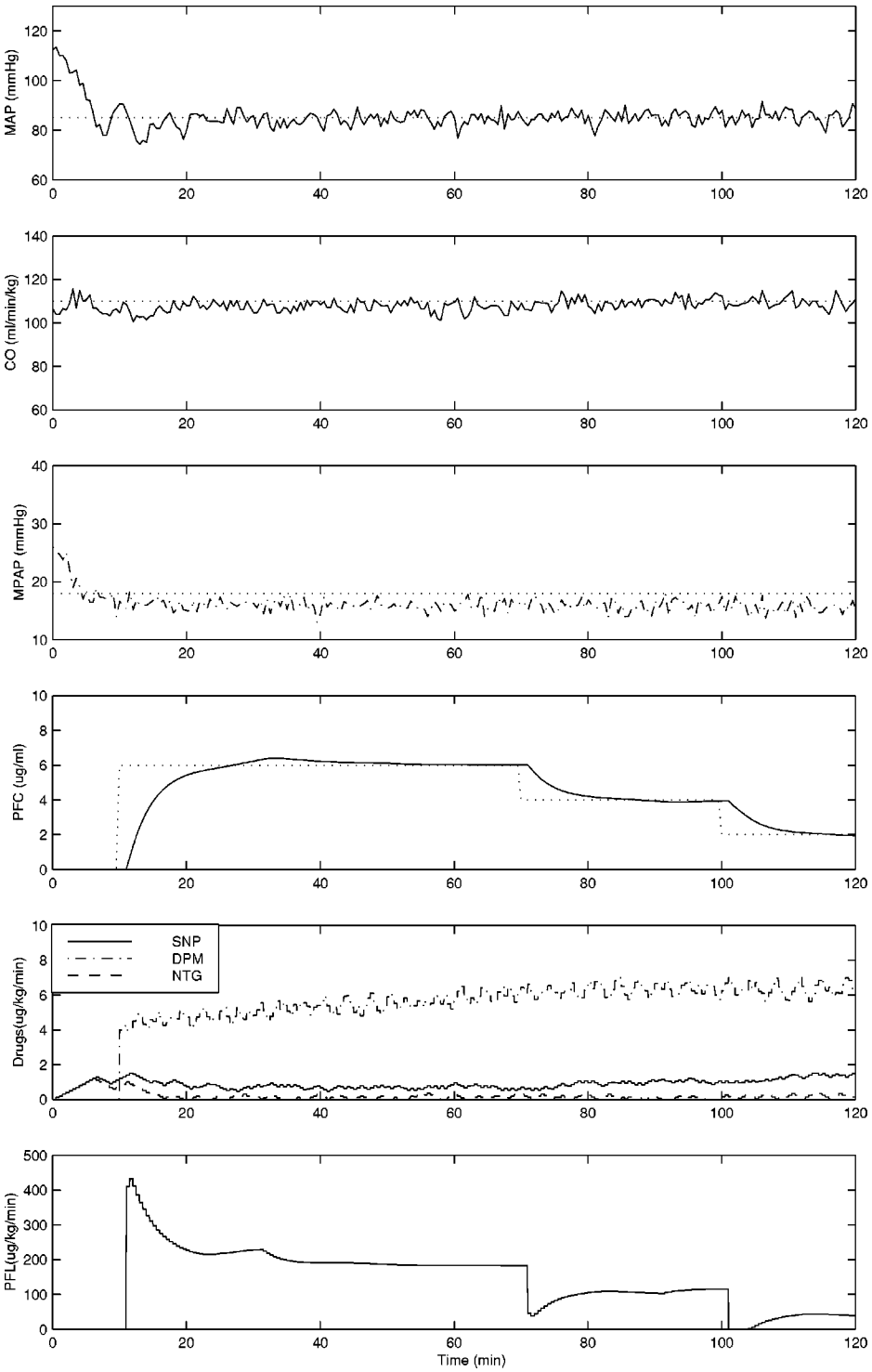

FIGURE 7. Case 2: Control of hemodynamic and anesthetic states of a patient in postbypass intensive care. The sleep state maintained by propofol infusion and the patient is gradually awakened by reducing the propofol dosage. Although this procedure lasts several hours, we have simulated it for shorter time scales after the hemodynamic variables are observed to be stabilized.

declamping by lowering the baseline SVR by about 40% in the model. The SVR value is then slowly ramped up to mimic natural recovery and stabilization. Propofol infusion is initialized at 5 minutes and the PFC setpoint is lowered to 4 μg/ml between 30 and 40 minutes. As shown in Fig. 8, the controller regulates MAP and CO initially using sodium nitroprusside and phenylephrine. The dopamine infusion then assists in regulating MAP, CO, and MPAP throughout the procedure. The drug infusion rates are suitably altered to reject the disturbance associated with a drop in SVR due to declamping.

In all three cases the controller was able to achieve desired performance criteria.

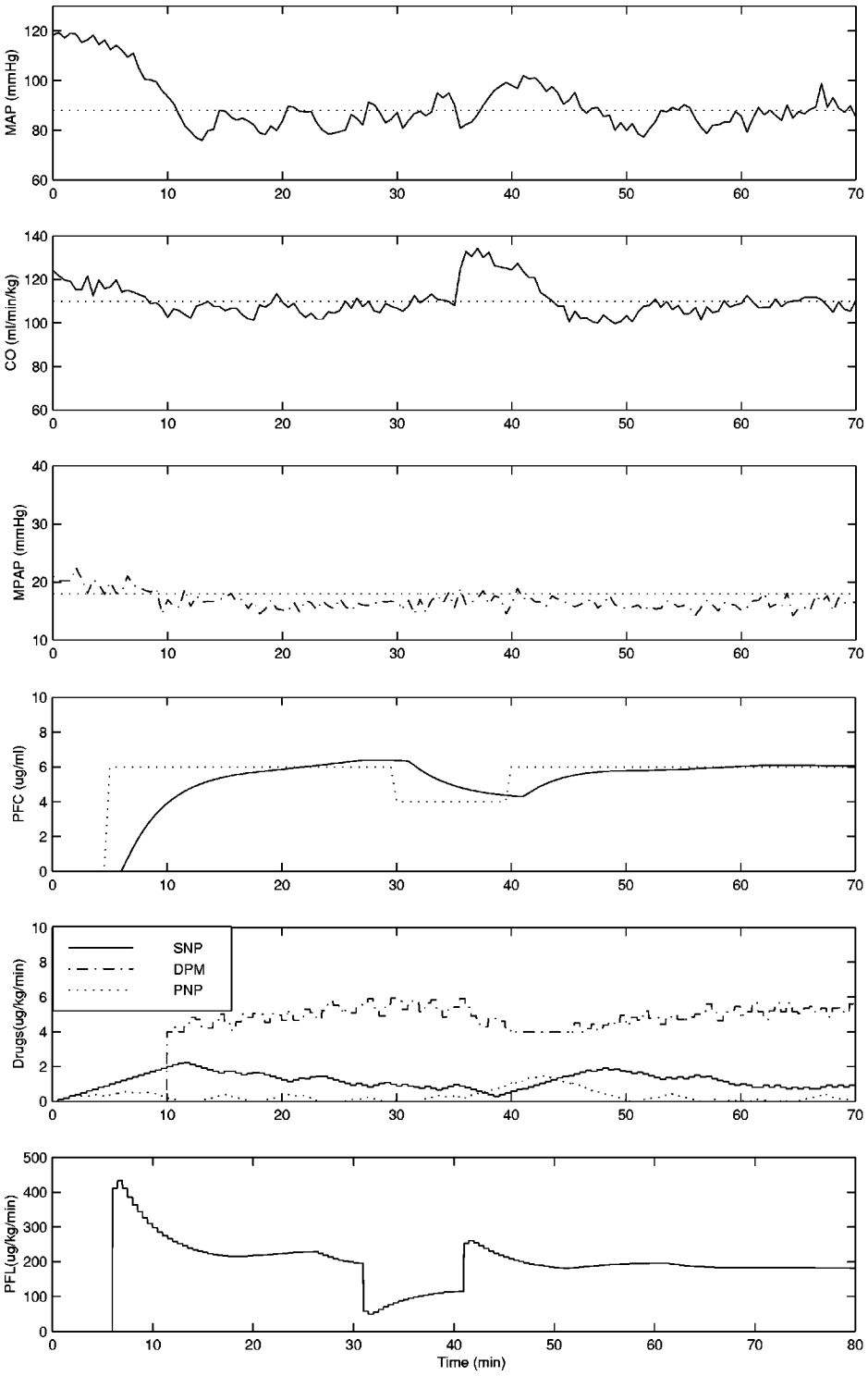

FIGURE 8. Case 3: Simulation of a disturbance such as a sharp drop in SVR associated with aortic declamping on a dog with 70% contractility. To demonstrate the robustness of the controller, a linear model identified based on 50% contractility is used. Declamping is simulated by dropping the SVR values by 40% at about 35 minutes.

DISCUSSION

Automation of drug administration can potentially improve the quality of care in surgical and intensive care environments. We present simulation studies to demonstrate the applicability of model predictive control to automate regulation of blood pressure and cardiac output and anesthetic states. The controller is shown to regulate the hemodynamic variables in the presence of drug dosage constraints. Performance criteria specified in terms of transient settling time (10 minutes for MAP and MPAP and 15–20 minutes for CO) are achieved in all three examples.

Due to the optimization framework, constraints can be

explicitly imposed on both the controlled and manipulated variables. The simulation results presented have absolute and velocity constraints applied on the manipulated variables (drug infusion). In addition, imposing constraints on the controlled variables (outputs) allow specification of operating ranges (such as maintaining cardiac output above 95 $ml\,kg^{-1}\,min^{-1}$). However, this is likely to make the QP problem too restrictive, that is, when computing future moves there may exist no value for which the drug infusion *and* the predicted responses are within the permitted range. Such infeasibilities are usually handled by (1) using a infinite prediction horizon and removing the constraints in the initial portion of the prediction horizon or (2) relaxing the constraints and penalizing the violation (constraint softening). Studies on optimization methods for such infeasibilities are in progress.

The controller uses a prediction model in an optimization framework to compute drug infusion rates. MPC performance relies significantly on the accuracy of the prediction model. This simulation study uses linear step response models and assumes that an accurate linear model is available for each patient condition. In case 3 we show the controller's ability to handle deviations in model accuracy. However, this does not imply that a nominal linear model is sufficient to handle different or all clinical conditions.

To implement this control strategy in a clinical or experimental environment an important issue to be addressed is the availability of prediction models and identification of their associated parameters. Also, drug sensitivities vary from patient to patient, and even within the same patient at different times, so it is important to develop strategies which change the prediction model on line. As stated earlier, the MPC framework places no restriction on the type of model or its structure. Hence we can draw from advances made in areas of adaptive model identification, artificial neural networks, fuzzy logic or rule based mechanisms to provide drug response predictions. Along the same lines, fuzzy logic based supervisory mechanisms[8] can help in choosing a suitable model from a bank of models that mimic various patient conditions. Nonlinear model reduction strategies can also be considered.

SUMMARY AND CURRENT WORK

A model predictive control strategy to control hemodynamic and anesthetic variables in critical care patients is presented. The efficacy of the multivariable controller is demonstrated by closed-loop simulations using a circulatory model of a dog. We have extended a nonlinear canine circulatory model to include hemodynamic changes associated with propofol infusion. The accuracy of predicting propofol effects can be improved subject to availability of more experimental data. Meanwhile, the extended model provides a framework in which to simulate clinical conditions requiring simultaneous control of hemodynamic and anesthetic states. A linear model was used for the model predictions, and closed-loop simulations were performed on the nonlinear model. Since drug sensitivity varies from patient to patient, and even within the same patient at different times, it is important to develop strategies that 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 article should be considered part of a hierarchical control structure which involves modules to assess the patient's status and to evaluate the effectiveness of the current control strategy. Clearly it is important to always keep the physician in the loop through 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 integrate DOA measurements using MLAEP and a hierarchical supervisory module to aid in patient diagnostics.

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