Control of a Nonsquare Drug Infusion System - A Simulation Study

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Abstract

A model predictive control strategy is developed and tested on a nonlinear canine circulatory model for the regulation of hemodynamic variables under critical care conditions. Different patient conditions such as congestive heart failure, post-operative hypertension and sepsis shock are studied in closed loop simulations. The model predictive controller, which uses a different linear model depending on the patient condition, allows constraints to be explicitly enforced. The controller is initially tuned based on a linear plant model, then tested on the nonlinear physiological model; the simulations demonstrate the ability to handle constraints, such as drug dosage specifications, commonly desired by critical care physicians.

Keywords: Biomedical control systems, Drug infusion control, Predictive control, Physiological models

1 INTRODUCTION

Critical care patients have often suffered a "disturbance" to the normal operation of their physiological system; this disturbance could have been generated by surgery or some sort of trauma. The critical care physician is to maintain certain patient state variables within an acceptable operating range. Often the physician will infuse several drugs into the patient to control these states close to the desired values. For example, in the case of critical care patients with congestive heart failure, measured variables that are of primary importance include mean arterial pressure (MAP) and cardiac output (CO). Secondary variables which are monitored, but not regulated as tightly as the primary variables, include heart rate and pulmonary capillary wedge pressure. The physician uses her/his own senses for other variables which are not easily measured, such as depth of anesthesia, and often infers them from a number of measurements and patient responses to surgical procedures.

Constant monitoring and manual regulation of the physiological variables can be tedious and it is desirable to have an automated system to perform such tasks. Research in this area has led to a variety of control strategies ranging from simple linear controllers to complex adaptive and rule based schemes to handle inter- and intra-patient variability in drug responses. With advancements in sensor and instrumentation technology, automated drug infusion systems are also evolving into hierarchical systems as depicted in Figure 1. The inner layer constitutes a controller designed to regulate administration of the drugs based on on-line measurements for primary variables. The supervisory layer provides adaptive functionality to the controller and in addition, monitors secondary variables and performs diagnostics. The hierarchical structure 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 MAP and CO by the infusion of two or more drugs. This paper explores the use of a model predictive control (MPC) strategy to serve as the inner layer 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. An optimizer minimizes a cost function based on the set point tracking error to evaluate a profile of future input moves over a control horizon. Optimal closed-loop feedback is achieved by implementing only the first control move and repeating the complete sequence of steps at subsequent sample time in a "receding horizon" fashion.

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 reducing 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 is to be

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maintained within its inotropic range of 4 to $7\ \mu g\ kg^{-1}\ min^{-1}$. Alternatively, the physician may want to specify an operating range of the output variable 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.

1.1 Drug Infusion Control

The vast amount of research on blood pressure control was triggered mainly by the development of a simple but accurate model of the response to sodium nitroprusside (SNP) infusion by Slate et al. [1]. Initially, they used a PID controller with empirical rules that limited the incremental changes in absolute value of SNP and infusion rate. Potter et al. [2] describe a dedicated bedside control system for monitoring MAP using SNP, glyceryl trinitrate and trimetaphan using proportional-derivative control. As drug sensitivities vary among different patients and within the same patient at different times, more complex adaptive control schemes have been utilized to overcome the limitations of non-adaptive controllers. Meline et al. [3] used proportional-derivative and minimum variance adaptive control to overcome the learning periods associated with adaptive controllers. Ying et al. [4] proposed a fuzzy controller based on expert systems to account for patients sensitivities in arterial pressure control. A detailed review of blood pressure control is provided by Isaka and Sebald [5].

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 dopamine (DPM)). Serna et al. [6] reported on the simultaneous control of CO and MAP using DPM and SNP. McInnis and Deng [7] also investigated a two input-two output system controlling MAP and central venous pressure using vasoactive and inotropic agents. The control algorithm included a bilinear model with a one-step-ahead control law and a recursive least squares identification scheme. One of the more advanced studies on simultaneous control of CO and MAP utilizing multiple drug infusion was done by Voss et al. [8]. The adaptive control algorithm used a Control Advance Moving Average Controller which is a class of extended horizon controllers, with a recursive least squares estimate of model parameters. For an example of a multiple model adaptive predictive control approach to this problem, see Yu et al. [9].

Advanced control strategies have begun to encompass hierarchical approaches to controlling drug infusion. Supervisory layers are incorporated to provide adaptive abilities to accommodate inter- and intra-patient variability as well as aiding the attending physicians with diagnostics and safety monitoring. As a part of an ongoing effort for developing an intelligent control system for drug delivery, Roy and coworkers [10], [11] have developed a fuzzy-logic based, automated drug delivery system to manage hemodynamic states; this system was validated by simulation using a nonlinear canine circulatory system model. The control system features a fuzzy decision analysis module (FDAM) in the supervisory layer to evaluate patient status, and to designate an appropriate therapeutic strategy. A fuzzy hemodynamic management module (HMM) forms the inner controller layer to determine the proper drug dosages based on the current patient states.

In this paper we present a model predictive control (MPC) approach that serves the same purpose as the HMM in Huang and Roy [11], [12] for hemodynamic regulation. We present a description of the controller framework in section 2, discuss MPC in section 3, then show MPC simulation results for a nonlinear canine circulatory system under various patient conditions in section 4.

2 SYSTEM DESCRIPTION

The overall control objective is to maintain three hemodynamic variables MAP, CO and mean pulmonary arterial pressure (MPAP), at desired setpoints by automated infusion of inotropic and vasoactive drugs. SNP is administered for arterial vasodilation; DPM is used as an inotrope to enhance cardiac performance; phenylephrine (PNP) is an arterial vasoconstrictor and nitroglycerine (NTG) is a venodilator. The control system is nonsquare in the sense that there are three output variables (MAP, CO, MPAP) and up to four input variables (SNP, DPM, PNP, NTG). In addition to using cardiovascular drugs, hemodynamic regulation is often achieved using by administering intravenous fluids.

When implementing a complex control strategy, such as the control of hemodynamic states in critical care patients, it is necessary to perform detailed simulation studies before moving to the experimental phase. Clearly, it is important that the simulation model used be realistic and exhibit qualitatively similar behavior as a physical system. We use a nonlinear canine circulatory system model, which closely mimics the dynamics of circulation in a dog, as the *patient*.

2.1 Physiological model for simulating the canine circulatory system

The nonlinear circulatory model used to describe the effect of inotropic and vasoactive drugs on a canine circulatory system was initially developed by Yu et al. [13] and has been used (in various forms) in a number of simulation studies (Yu et al., [14], Gopinath et al., [15]); Held and Roy [16] used it for the control of MAP and CO using DPM and SNP; this model was extended by Huang [10] to study the effect of additional drugs (PNP and NTG), and to include their effect on another output (MPAP). One of the objectives of their work was to assist the physician in distinctively targeting pharmacological treatment of the pulmonary and systemic circulation [11]. Rao et al. [17] make extensions to include pharmacokinetics and pharmacodynamics of the intravenous anesthetic agent propofol (Diprivan) for simulation studies in simultaneous control of hemodynamic and anesthetic states.

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. The model naturally splits into two time scales, involving variables that change during each heartbeat and variables that are constant over a heartbeat. 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_{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. A conceptual diagram is shown in Figure 2. Details of the model equation and parameter values are not provided for sake of brevity. The reader is referred to Yu et al. [13] and Gopinath et al. [15] for a complete description of the model.

The nonlinear model is simulated using the MATLAB/SIMULINK simulation package which provides a transparent translation of control system design (using linear model-based tools) to the nonlinear process. Direct comparisons of different control strategies developed by different researchers is easily performed. The computer code for the nonlinear canine circulatory system model is available for download from the WWW site at
http://www.rpi.edu/∼royr/roy_sftwr.html

2.2 Supervisory Layer

The nonlinear model can be initialized suitably to simulate various *patient* conditions. A fuzzy logic based decision-making module (FDAM) determines the patient status based on estimates of systemic vascular resistance index (SVRI) and pulmonary vascular resistance index (PVRI) along with the measurements of hemodynamic variables. Depending on the patient status, the FDAM recommends administration of one or more of the four drugs to maintain the three hemodynamic output variables. The reader is referred to Huang and Roy [11] for details of the decision making module. For our simulation studies, we assume that the supervisory FDAM module has already evaluated the patient status and determined the proper drug therapy. The model predictive controller, described in the next section, uses measurements of the hemodynamic states and determines optimal infusion rates of the selected drugs to achieve the desired setpoints.

The nonlinear model used in this study makes isovolumic assumptions and, in its present form, cannot be used for simulating cases involving blood volume changes such as fluid loading or hemorrhage. The FDAM however is designed to recommend fluid loading based therapy and in practice, the MPC can be designed to regulate MAP and CO using intravenous fluids to supplement cardiovascular drug administration.

3 MODEL PREDICTIVE CONTROL

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 predict 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 Figure 3, is to select a sequence of M future control moves to minimize an objective function (usually the sum of 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. As 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. [18]. In drug delivery applications, Gopinath et al. [15] use a nonlinear prediction model in an MPC framework to control a 2x2 drug infusion system. Yu et al. [9] have applied a variant of MPC (multiple model adaptive-predictive control) to a 2x2 drug infusion problem, where a bank of controllers are used to account for nonlinearities.

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

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

subject to absolute and rate constraints on the manipulated variables

$$\begin{aligned} u_{min} < \quad & u_i \quad < u_{max} \\ u_{i-1} - \Delta u_{max} \leq \quad & u_i \quad \leq u_{i-1} + \Delta u_{max} \end{aligned}$$

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 over a prediction horizon of P, r_i is the desired setpoint, u_i is the vector of manipulated variables over a control horizon M, and Q and R are output and input weighting matrices. The prediction model is given in a generic form as

$$\begin{aligned} \dot{x} &= f(x, u) \\ y &= g(x) \end{aligned}$$

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.

3.1 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 non-parametric 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 u at the current sampling instance k is 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, 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 j^{th} 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 Equation 1. 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 measured output and output of the predicted model (i.e) $(d(k) = y_m(k) - y(k))$ at the k^{th}

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.

3.2 Open-loop Behavior

In this paper we study cases of patient conditions associated with congestive heart failure, post operative hypertension and sepsis shock.

The linear model required for predictive control is obtained from open-loop step-tests performed on the nonlinear circulatory system model for each of the patient conditions. The nonlinear model parameters are suitably initialized and the responses to step-changes for each drug are recorded during open-loop simulations. All inputs are step changed from 0 to 1 $\mu g\, kg^{-1}\, min^{-1}$, except DPM, which is changed from 0 to 6 $\mu g\, kg^{-1}\, min^{-1}$ due to its low gain in healthy cases and in order to obtain dopamine step responses in its inotropic range of 4 to 7 $\mu g\, kg^{-1}\, min^{-1}$. The step responses of the nonlinear model along with the steady state gains are presented in Figure 4. The response time of all variables to a DPM input is much larger than the other inputs. The nonlinear behavior of the system at different cardiac contractilities (and hence patient conditions) is evident especially in the case of responses to DPM infusion.

The steady state gains also provide insight into the direction and magnitude of control moves. For example, in case 1 (discussed in detail in the next section), the patient retains only 24% of normal contractility and suffers from a low MAP and CO. An increase of MAP and CO is desired. Notice that a change in DPM (second column, Figure 4(a)) 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.

4 MPC 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 multi-rate. While the pressure measurements can be obtained as frequently as desired, CO measurements can only be sampled in 30 second intervals. Hence our controller design and simulations are based on a 0.5 min sampling interval. Normally distributed noise with a standard deviation of 2 units is added to the pressure and cardiac output measurements.

The prediction horizon is chosen as 20 sample intervals (approximately equal to the settling time of the slowest response in the system) along with a control horizon of 2 time steps. The change in output variables are of the same magnitudes, 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 the ratio 2:1:1 (MAP:CO:MPAP). The input weights R are usually specified to penalize aggressive control action in unconstrained situations. We set them to *zero* as large changes in drug infusion rates are constrained by imposing velocity constraints as follows :

$$
\begin{gathered}
0 \leq SNP, PNP, NTG \leq 10\, \mu g\, kg^{-1}\, min^{-1} \\
4 \leq DPM \leq 7\, \mu g\, kg^{-1}\, min^{-1} \\
|\Delta SNP, \Delta PNP, \Delta NTG| \leq 0.2\, \mu g\, kg^{-1}\, min^{-1} \\
|\Delta DPM| \leq 0.5\, \mu g\, kg^{-1}\, min^{-1}
\end{gathered}
$$

The drug velocity constraints thus prevent large fluctuations in drug dosage. Also, having a prediction horizon longer than the control horizon tends to suppress aggressive control action. Note that DPM is used as an inotrope and hence the infusion rates are constrained to the inotropic range of 4 $\mu g\, kg^{-1}\, min^{-1}$ to 7 $\mu g\, kg^{-1}\, min^{-1}$. The transient performance criteria 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 $ml\ kg^{-1}\ min^{-1}$. 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 (discussed later).

4.1 Case 1

This case involves maintaining hemodynamic and anesthetic states of patients under congestive heart failure. Due to the lowered heart contractility, the MAP and CO are low and require DPM infusion in the inotropic range. The MPAP is high and NTG is infused to lower it to normal ranges. The canine circulatory model is initialized for a dog with an MAP (90 mm Hg), CO (65 $ml\ kg^{-1}\ min^{-1}$), MPAP (40 mm Hg) and retaining 24% of normal baseline contractility of heart. The controller is required to elevate MAP and CO to 100 mm Hg and 95 $ml\ kg^{-1}\ min^{-1}$ respectively and lower the MPAP to 18 mm Hg. Figure 5 presents the closed-loop simulation results. The therapeutic strategy recommended by the FDAM in the supervisory layer requires the use of DPM to boost the myocardial contractility and NTG to control the MAP overshoot associated with DPM infusion. The controller maintains DPM infusion its inotropic range. The effective time delay associated with DPM places limitations on the possible closed-loop speed of response of this system, but the desired setpoints are achieved within acceptable settling times. From the open-loop gain values it can be noted that the direction of change of CO due to DPM and NTG are both the same and tighter control of CO to prevent the slight offset is not possible (at least in a steady-state sense). The controller however has minimized this deviation from the setpoint trajectory.

4.2 Case 2

This case presents constraint handling abilities of the model predictive controller. The dog has normal contractility of heart but has a low systemic vascular resistance, which may be caused by a variety of reasons such as sepsis shock; the controller is expected to raise MAP from 120 mm Hg to 130 mm Hg and lower CO to 115 $ml\ kg^{-1}\ min^{-1}$ while maintaining MPAP at 20 mm Hg. PNP infusion is recommended to increase vascular tone. After 15 minutes, we intentionally seek an increase in setpoint of CO to 130 $ml\ kg^{-1}\ min^{-1}$ which saturates the input constraints. The results are shown in Figure 6. As DPM infusion hits the upper constraint of 7 $\mu g\ kg^{-1}\ min^{-1}$, the controller now manipulates the other drug optimally to achieve the desired setpoint as close as possible. In a clinical environment, the resulting offset can trigger an alarm so that the physician can take alternative action such as raising the upper limit for DPM infusion in its α-range for a short while, or injecting a short acting drug.

4.3 Case 3

This case is presented to demonstrate disturbance rejection capabilities and robustness to model sensitivity of the controller. The nonlinear model is initialized to mimic patients suffering from low contractility and hypertension which may occur after open heart surgery. A disturbance in the form of a heart failure is introduced by lowering the baseline contractility. The initial suggested therapy requires infusion of SNP and NTG primarily to lower the MAP and MPAP and raise CO. A dog retaining only 50% of normal contractility with a slightly low CO (105 $ml\ kg^{-1}\ min^{-1}$), high MAP (112 mm Hg) and MPAP (25 mm Hg) is simulated. A setpoint of 88 mm Hg MAP, 18 mm Hg MPAP and 115 $ml\ kg^{-1}\ min^{-1}$ CO is sought. The disturbance is introduced at around 15 minutes by lowering the contractility of the heart to 30% of its baseline value and results in sharp changes in the output variables as shown in Figure 7. It is assumed that the supervisory diagnostic layer detects and correctly identifies the change in patient status and recommends DPM infusion to raise the contractility of the heart. The model predictive controller begins DPM infusion and maintains the necessary SNP infusion rate to counteract the disturbance. Note that the patient's condition has shifted to a different level and, in a strict sense, requires a different model to be used for prediction. However, the optimization strategy is able to accommodate such uncertainties fairly well. A similar but gradual form of a disturbance encountered in critical care is the changes in vascular resistance and altering of baroreflex associated with administration of anesthetics. For example, Propofol causes a 10 to 30% drop in MAP.

5 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. The controller is shown to regulate the hemodynamic variables in the presence of drug dosage constraints. Performance criteria specified in terms of transients settling time (10 minutes for MAP and MPAP and 15-20 minutes for CO) is 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 (i.e) when computing the 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. Evidently, MPC performance relies significantly on the prediction model accuracy. 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 patient 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, 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 approach, supervisory mechanisms, such as the FDAM, can help choose a suitable model from a bank of models that mimic various patient conditions. Nonlinear model reduction strategies can also be considered.

6 SUMMARY

In this paper we have investigated the application of a model predictive control strategy for automation of drug delivery. The controller uses a linear model to compute optimal infusion rates for setpoint tracking and disturbance rejection. Drug dosage and infusion rate constraints are explicitly incorporated and handled in the controller design. Closed loop simulations on a nonlinear canine circulatory model illustrate the ability to regulate hemodynamic variables under various conditions. Enhancement in performance of the controller is closely tied with the model accuracy and needs further efforts in identification and adaptation methodology.

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. It is also important to always maintain the physician "in the loop" with proper monitoring and alarm functions.

Acknowledgment

This research has been supported by a Biomedical Engineering Grant from the Whitaker Foundation and NSF grant BES-9522639.

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Figure Captions

Figure 1: An intelligent control system for monitoring and control of drug infusion. A supervisory layer assists the anesthesiologist in monitoring and diagnostics.

Figure 2: Schematic of the circulatory system model, including baroreflex mechanism and drug effects. Different patient conditions can be simulated by suitable initialization of the circulatory parameters.

Figure 3: 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 setpoint. Feedback is achieved by implementing only the first of the M moves. (b)Based on the actual measurements of the output at the $k+1^{th}$ 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.

Figure 4(a) 24% Contractility (CHF)
Figure 4(b) Normal Contractility
Figure 4(c) 50% Contractility
Figure 4: Open-loop step responses of simulated dog under different baseline contractilities. The input magnitude is 6 for DPM (due to the low gains for healthy heart condition), 1 for the other inputs.

Figure 5: Case 1: Patient with CHF, low MAP, low CO and high MPAP. The setpoints require raising of MAP (90 to 100 mm Hg) and CO (65 to 95 $ml\ kg^{-1}\ min^{-1}$) and lowering of MPAP (40 to 22 mm Hg). DPM increases contractility causing a rise in MAP and CO. NTG infusion places a check on MAP overshoot.

Figure 6: Case 2: Patient with normal MAP, normal or high CO and normal MPAP. MAP is to be raised from 120 to 130 mm Hg. At 15 minutes, the CO setpoint is raised to 130 $ml\ kg^{-1}\ min^{-1}$ intentionally to demonstrate input saturation. The controller maintains DPM infusion at its permissible maximum of 7 $\mu g\ kg^{-1}\ min^{-1}$ while optimizing PNP infusion.

Figure 7: Case 3: Patient initially with 50% baseline contractility, high MAP, low CO and normal-high MPAP. Lowering of MAP (from 112 mm Hg to 88 mm Hg) and MPAP (from 25 mm Hg to 17 mm Hg) is sought. A disturbance is simulated by lowering baseline contractility to 30% at 15 minutes. Based on the sharp drop in CO and MAP the supervisory layer is assumed to recommend infusion of DPM. Subsequently, the controller infuses DPM to reject this disturbance.

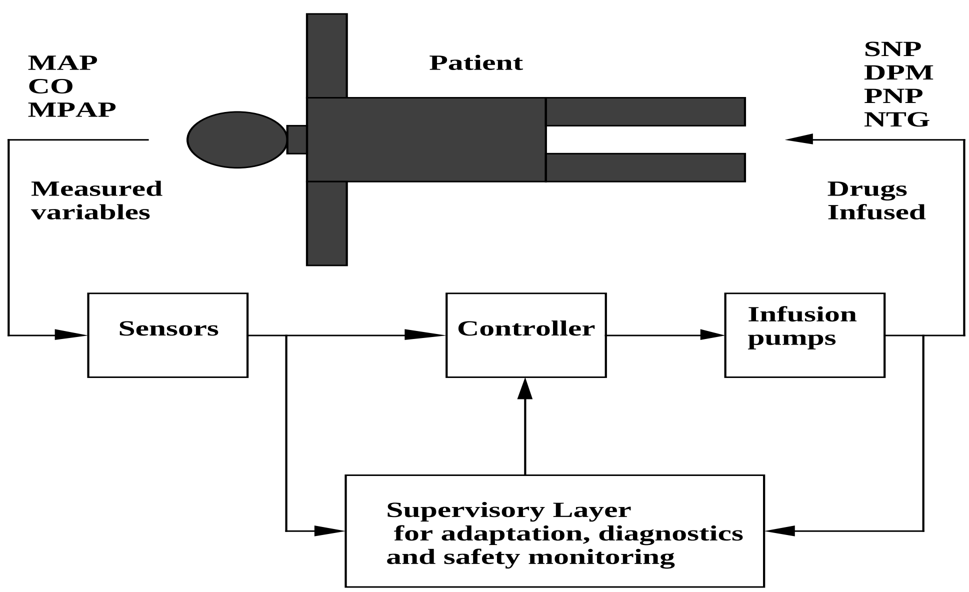


Figure 1: An intelligent control system for monitoring and control of drug infusion. A supervisory layer assists the anesthesiologist in monitoring and diagnostics.

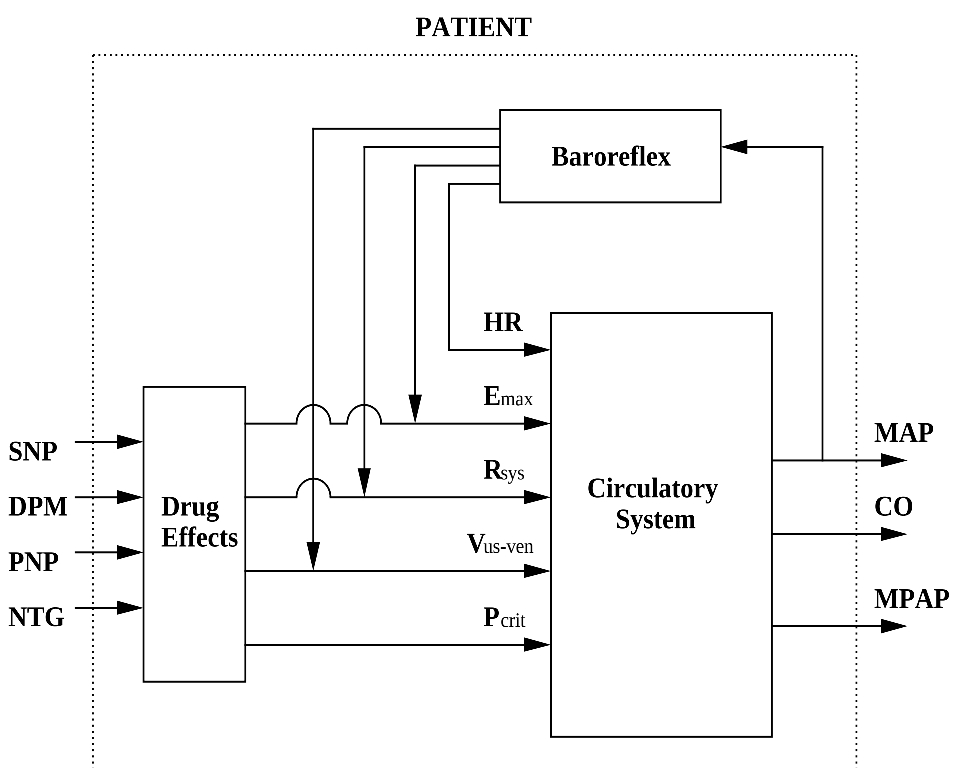


Figure 2: Schematic of the circulatory system model, including baroreflex mechanism and drug effects. Different patient conditions can be simulated by suitable initialization of the circulatory parameters.

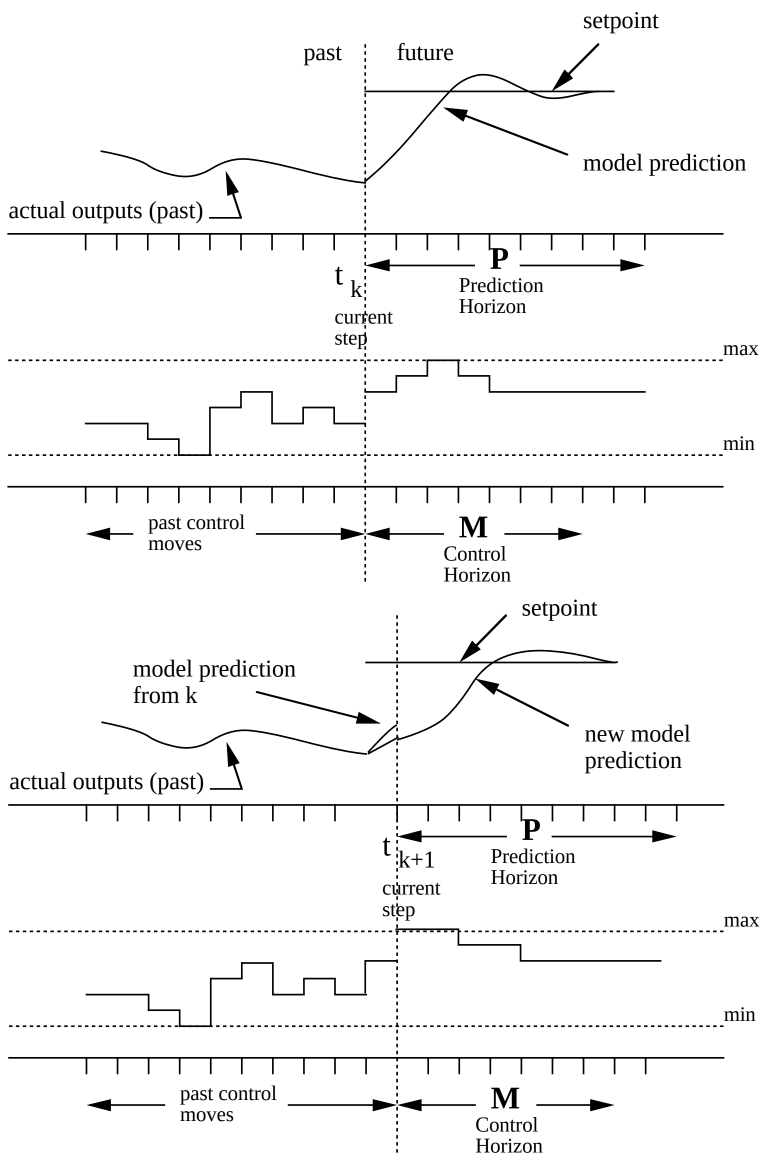
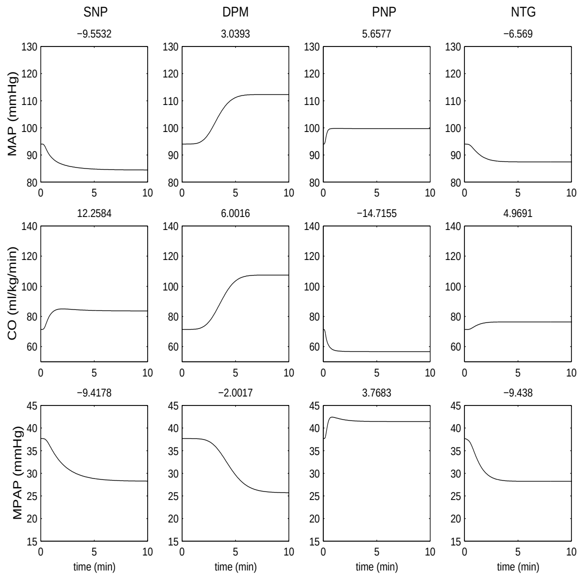
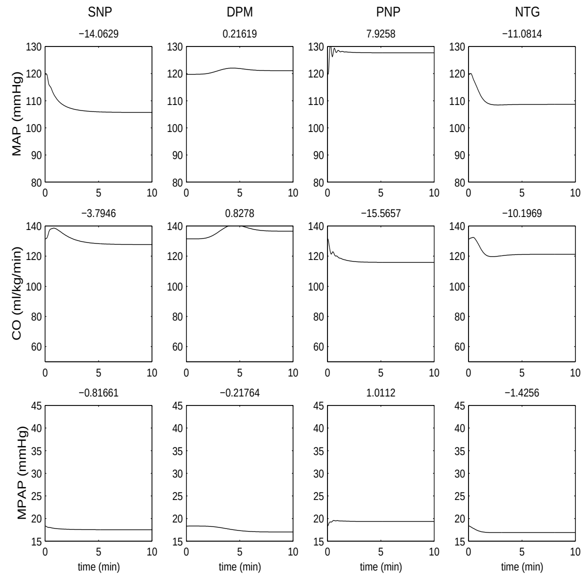


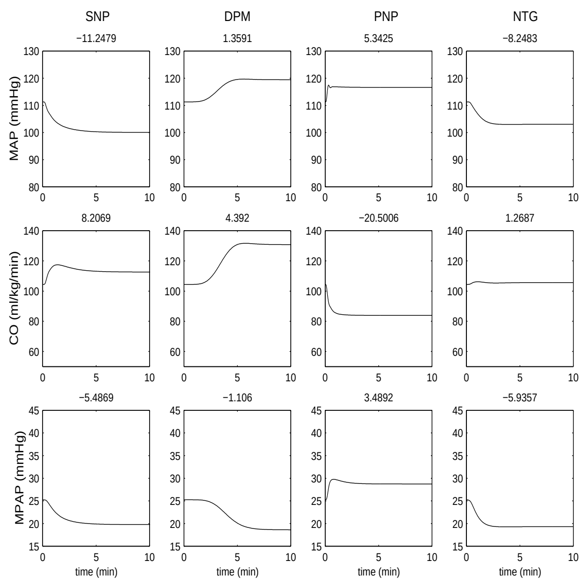
Figure 3: Model Predictive Control: (a)At the current sampling instance k, a model is used to predict the output behavior of the system P sample intervals into the future based on the past states and M future control moves. The future control moves are optimally estimated to minimize predicted error from setpoint. Feedback is achieved by implementing only the first of the M moves. (b)Based on the actual measurements of the output at the $k+1^{th}$ 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.



(a) 24% Contractility (CHF)



(b) Normal Contractility



(c) 50% Contractility

Figure 4: Open-loop step responses of simulated dog under different baseline contractilities. The input magnitude is 6 for DPM (due to the low gains for healthy heart condition), 1 for the other inputs.

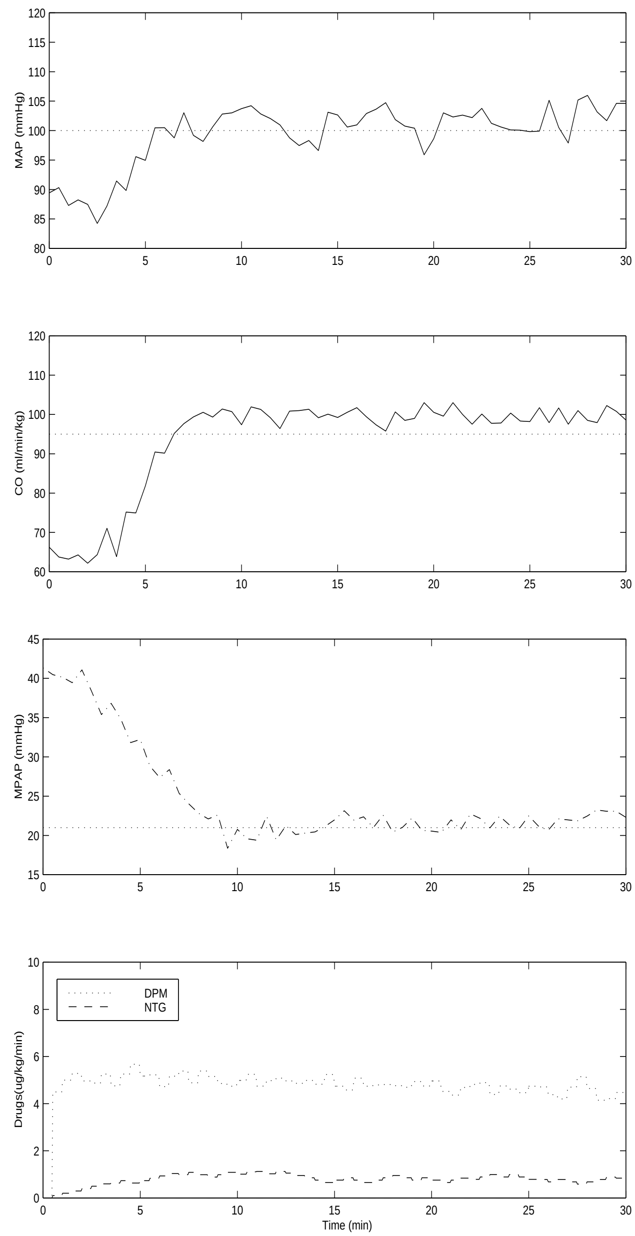


Figure 5: Case 1: Patient with CHF, low MAP, low CO and high MPAP. The setpoints require raising of MAP (90 to 100 mm Hg) and CO (65 to 95 $ml\ kg^{-1}\ min^{-1}$) and lowering of MPAP (40 to 22 mm Hg). DPM increases contractility causing a rise in MAP and CO. NTG infusion places a check on MAP overshoot.

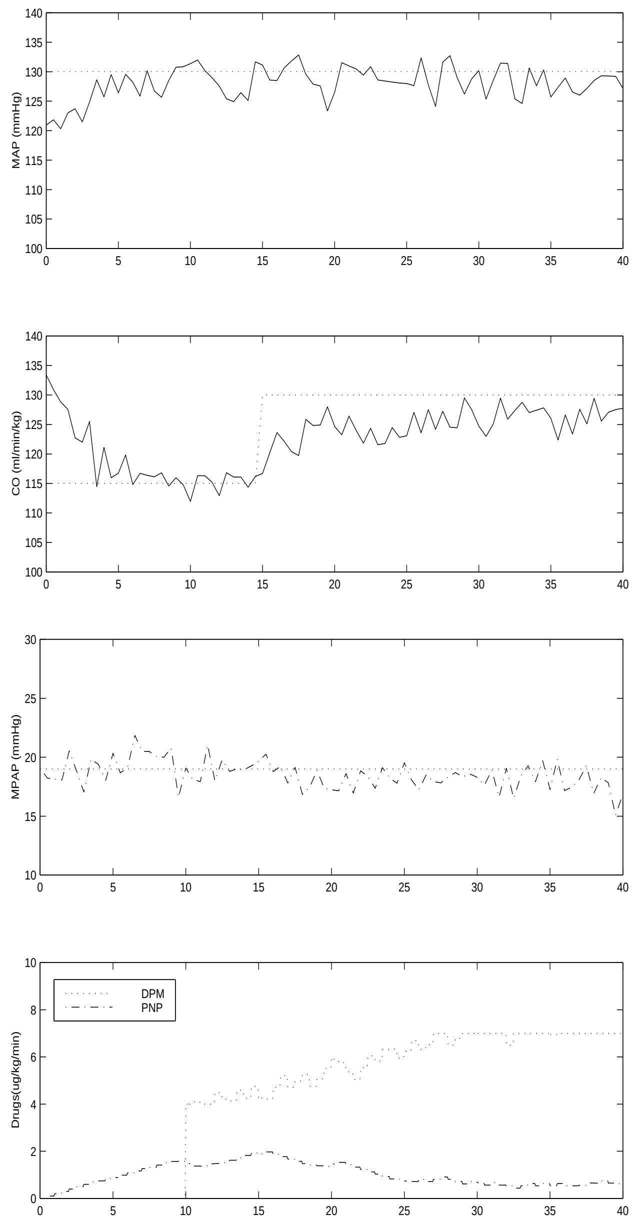


Figure 6: Case 2: Patient with normal MAP, normal or high CO and normal MPAP. MAP is to be raised from 120 to 130 mm Hg. At 15 minutes, the CO setpoint is raised to 130 $ml\ kg^{-1}\ min^{-1}$ intentionally to demonstrate input saturation. The controller maintains DPM infusion at its permissible maximum of 7 $\mu g\ kg^{-1}\ min^{-1}$ while optimizing PNP infusion.

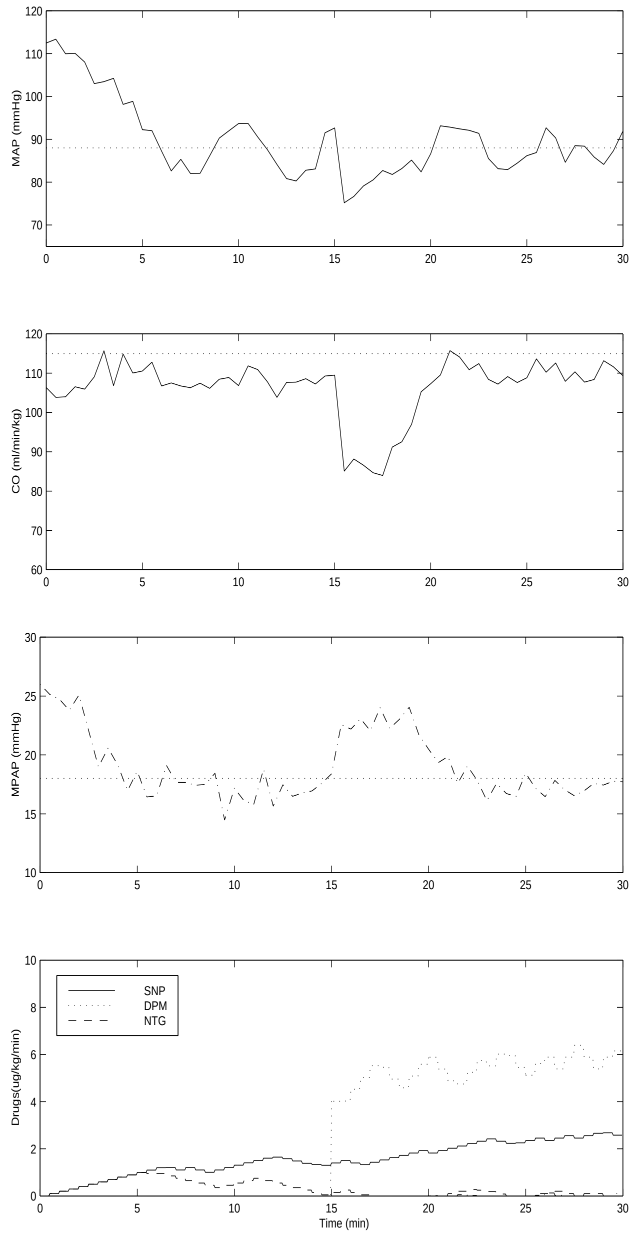


Figure 7: Case 3: Patient initially with 50% baseline contractility, high MAP, low CO and normal-high MPAP. Lowering of MAP (from 112 mm Hg to 88 mm Hg) and MPAP (from 25 mm Hg to 17 mm Hg) is sought. A disturbance is simulated by lowering baseline contractility to 30% at 15 minutes. Based on the sharp drop in CO and MAP the supervisory layer is assumed to recommend infusion of DPM. Subsequently, the controller infuses DPM to reject this disturbance.