MODELING AND CONTROL OF A NONSQUARE DRUG INFUSION SYSTEM

Ramesh R. Rao[1], Johnnie W. Huang[2], B. Wayne Bequette[1*], Howard Kaufman[3] and Rob J. Roy[2]

Departments of [1]Chemical, [2]Biomedical, and [3]Electrical, Computer and Systems Engineering,
Rensselaer Polytechnic Institute
Troy, NY 12180-3590 USA

Abstract: A model predictive control strategy is developed and tested on an nonlinear canine circulatory model for the regulation of hemodynamic variables under critical care conditions. Several cases are studied, including congestive heart failure, post-operative hypertension and a patient that moves from hypertensive to hypotensive conditions. The “nonsquare” (more process inputs than outputs) control system allows the independent management of the hemodynamic and venous circulation. 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 linear plant responses, then tested on the nonlinear plant model; the simulations verify the robustness of the control strategy.

Keywords: Biomedical control systems, 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, and often infers anesthetic depth from a number of measurements and patient responses to surgical procedures.

It is desirable to have an automated system which closes the loop on primary variables, but monitors secondary variables and performs diagnostics. This allows the physician to spend more time monitoring the patient for conditions which are not easily measured, and assures that the physician is always “in the loop”. For example, the physician may observe a low urine output and choose to (a) administer fluids, or (b) administer drugs that increase renal function - dopamine for example, in its dopaminergic range. 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 drugs.

1.1 Drug Infusion Control

The vast amount or 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*. (1979). Initially, they used a non-adaptive PID controller with empirical rules that limited the incremental changes in and absolute value of SNP infusion rate. Since then, more complex adaptive control schemes have been utilized to overcome the limitations of non-adaptive controllers. We will not review these applications because of space constraints; a review of blood pressure control is provided by Isaka and Sebald (1993).

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)). For an example of a multiple model adaptive predictive control approach to this problem see Yu *et al*. (1992).

1.2 Physiological Model

The model used 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) for the control of MAP and CO using DPM and SNP; this model was extended by Huang and Roy (1996) to study the effect of additional drugs (phenylephrine, PNP; nitroglycerin, NTG) and to include their effect on another output (mean pulmonary arterial pressure, MPAP). One of the objectives of their work was to independently control the arterial and venous circulation.

The model consists of three sets of equations, including (i) circulatory system equations, which describe the effect of specific body parameters on the hemodynamic variables, (ii) drug effect relationships, which describe the influence of the infused drugs on the specific body parameters, and (iii) equations which describe the effect of the arterial baroreceptors in blood pressure regulation. A conceptual diagram is shown in Figure 1. For more details on the model, see Yu *et al.* (1990a), and Gopinath *et al*. (1995, 1996).

The model naturally splits into two time scales, involving variables that change during each heartbeat and variables that are constant over a heartbeat. The model is simulated using 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.

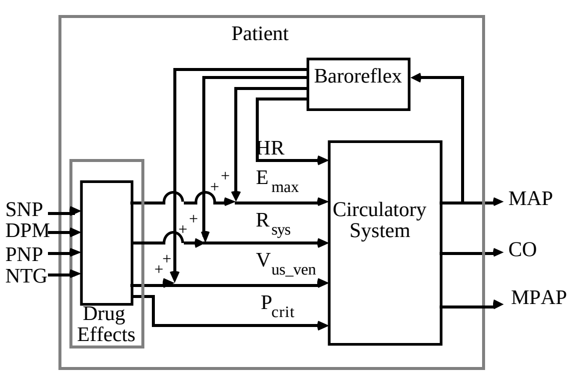

Fig. 1. Schematic of the circulatory system model, including baroreflex mechanism and drug effects.

1.3 Fuzzy Decision Theory-based Control

Huang and Roy (1996) have developed a fuzzy-logic based, automated drug delivery system to manage hemodynamic states; this system was validated on the nonlinear canine circulatory system model. The controller features (1) a fuzzy decision analysis module for patient status evaluation, and to designate an appropriate therapeutic strategy, (2) a fuzzy hemodynamic management module (HMM) to determine the proper drug dosages based on the current patient states, and (3) a therapeutic assessment module to evaluate the effectiveness of the current approach by the HMM.

In this paper we present a model predictive control (MPC) approach that serves the same purpose as the HMM in Huang and Roy (1996). We assume that a fuzzy decision analysis module has already evaluated the patient status and determined the proper model and setpoints for the MPC strategy. The primary advantage to MPC is the explicit constraint-handling ability. We first present a description of the nonsquare system in section 2, discuss MPC in section 3, then show MPC results for the linear and nonlinear plants in section 4.

2. SYSTEM DESCRIPTION

The control system is nonsquare with three output variables (MAP, CO, MPAP) and up to four input variables (SNP, DPM, PNP, NTG). A number of studies have shown how an extra manipulated variable can improve the controllability of a system (for an example, see Morari *et al*., 1985).

2.1 Linear Model

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

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

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

2.2 Open-loop Behavior

In this paper we study three cases, one corresponding to congestive heart failure and two related to post-operative hypertension. The steady-state input/output relationship is

$$y \;=\; G\,u$$

where the output vector is y = [MAP CO MPAP]^T. The input vector is u = [SNP DPM PNP NTG]^T.

In the first case a patient has suffered congestive heart failure and the desired output change is [10 31 –22]. The gain matrix is

$$G \;=\; \begin{bmatrix} -9.07 & 4.94 & 5.49 & -6.17 \\ 11.97 & 8.04 & -13.40 & 4.81 \\ -9.85 & -2.61 & 4.05 & -9.78 \end{bmatrix}$$

This gain matrix was obtained by analyzing the open-loop step responses of the nonlinear model, presented in Fig 2; all inputs were step changed from 0 to 1 μg/kg/min, except DPM, which was changed from 0 to 4 μg/kg/min to avoid the “forbidden zone” (Held and Roy, 1995). Notice that a change in DPM (second column of the gain matrix) is in roughly the same direction as the desired setpoint change, indicating that most of the manipulated variable action (at least in a steady-state sense) will be in DPM. The response time of all variables to a DPM input is much larger than the other inputs. The effective time delay in DPM places limitations on the possible closed-loop speed of response of this system.

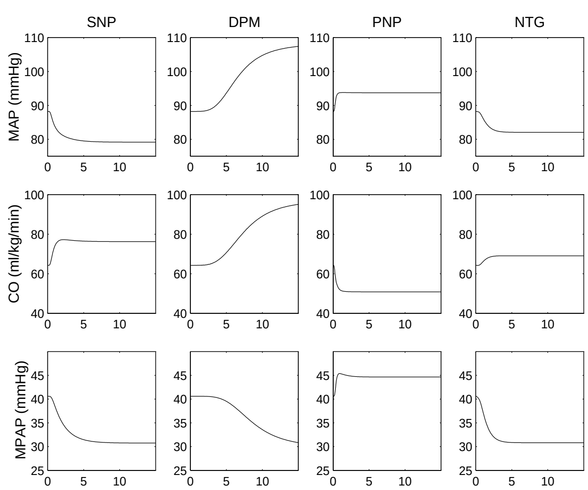

Fig 2. Open-loop step responses, Case 1. The input magnitude is 4 for DPM, 1 for the other inputs.

3. MODEL PREDICTIVE CONTROL

Model predictive control is an optimization-based approach which has been successfully applied to a wide variety of control problems. The basic idea, shown in Fig. 3, is to select a sequence of M future control moves to minimize an objective function (usually sum of square of predicted errors) over a prediction horizon of P sample times. A review of MPC is provided by Garcia *et al*. (1989).

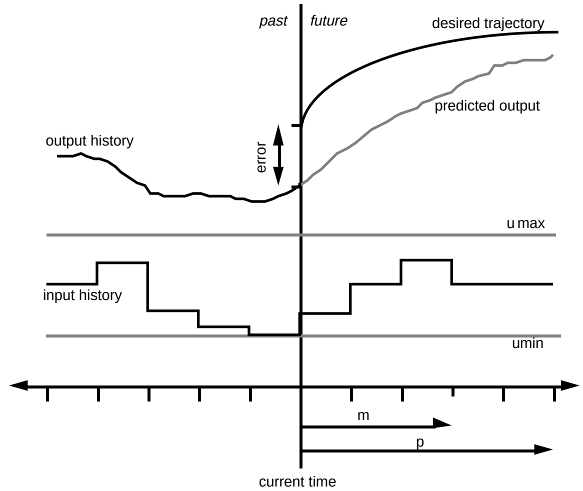

Fig. 3. Model Predictive Control.

Yu *et al*. (1992) have applied a variant of MPC (multiple model adaptive-predictive control) to a 2x2 drug infusion problem, while Gopinath *et al*. (1995) use a nonlinear model in an MPC framework to control a 2x2 drug infusion system. Since MPC is optimization-based, it handles constrained nonsquare systems, such as our 3 output x 4 input system, quite naturally.

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

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

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

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

4. MPC RESULTS

In all of these cases, the model predictive controller was designed based on a linear plant, then simulated on the nonlinear plant.

The parameters used for each case are shown in Table 1. The absolute constraints on the manipulated variables are 0 and 10 μg/kg/min, except for dopamine, where a minimum constraint of 4 is used to avoid the "forbidden zone". 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.

Table 1. Parameters

	Case 1	Case 2	Case 3
P	20	20	20
M	2	2	2
Q	diag(5,3,2)	diag(3,2,5)	diag(5,2,1)
Setpoint	97.5 95 18	87.5 115 18	97.5 100 18
Initial condition	88 64 40	111 104 25	119 131 18

Case 1. MAP Low/CO Low/MPAP High

This case is typically associated with congestive heart failure. Based on the gain matrix, DPM moves all of the outputs in the desired direction of the setpoint change. The results in Figure 4 for the linear plant indicate that only 3 inputs are used by the controller (NTG remains constrained at 0). The results for the nonlinear plant are similar to the linear case, and are shown in Fig. 5. The fuzzy decision module used by Huang and Roy (1996) selected two inputs, DPM and NTG, for case 1 conditions. We compare MPC results for this 2 input case in Fig. 6 and 7. Notice that reasonably good performance is obtained by this 3-output 2-input system. This is because most of the control contribution is made by DPM, in either case.

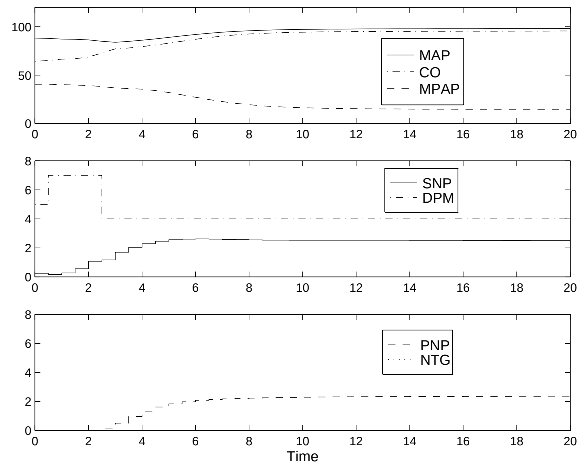

Fig 4. Constrained closed-loop response, linear plant, Case 1. 3-output x 4-input system.

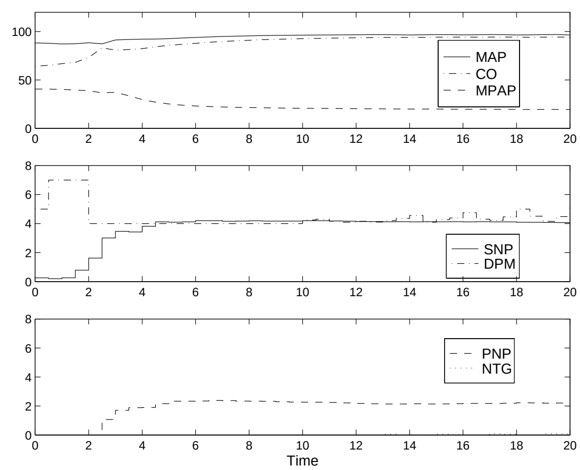

Fig 5. Constrained closed-loop response, nonlinear plant, Case 1. 3-output x 4-input system.

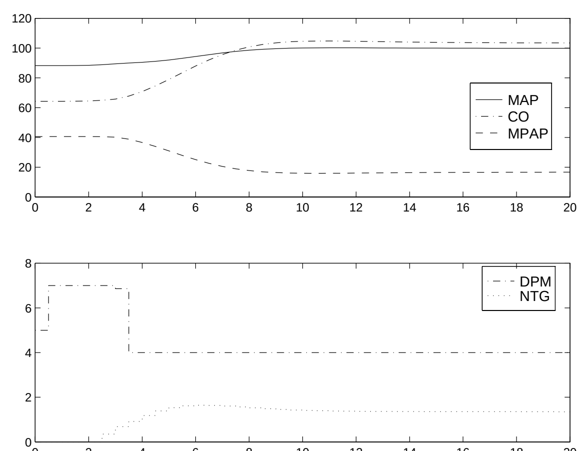

Fig 6. Constrained closed-loop response, linear plant, Case 1. 3-output x 2-input system.

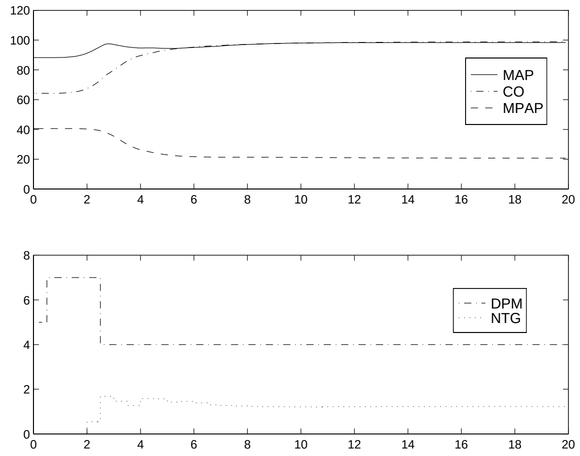

Fig 7. Constrained closed-loop response, nonlinear plant, Case 1. 3-output x 2-input system.

Case 2. MAP High/CO Low/MPAP Normal-High

Patients suffering from hypokinemia and hypertension, possibly due to post-open heart surgery, will often display symptoms consistent with this case. The initial CO setpoint of 115 is further changed to 125 ml/kg/min at 10 minutes. In this case, the manipulated variables used are primarily SNP and DPM. The results for the linear and nonlinear cases are shown in Fig. 8 and 9.

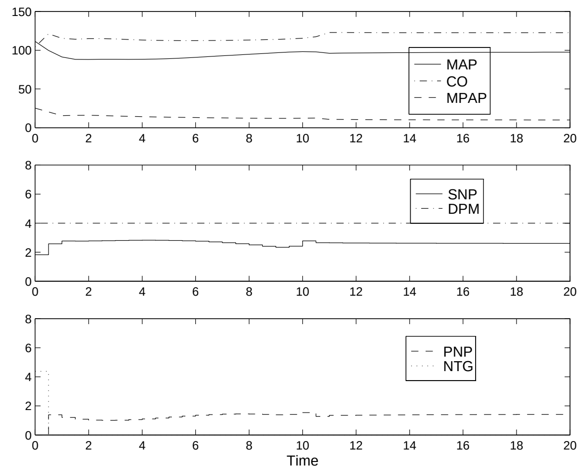

Fig 8. Constrained closed-loop response, linear plant, Case 2. Additional CO setpoint change at 10 min.

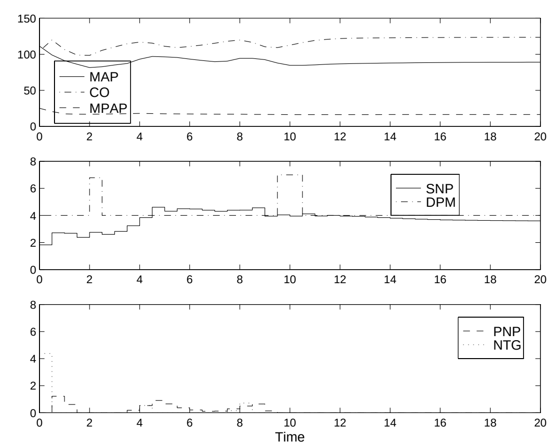

Fig 9. Constrained closed-loop response, nonlinear plant, Case 2. Additional CO setpoint change at 10 min.

Case 3. Hypertensive to Hypotensive

In this case the patient is initially considered hypertensive; after 10 minutes the patient is identified as hypotensive and the setpoints for MAP and CO are changed to 127.5 mmHg and 125 ml/kg/min, respectively. The results for the linear and nonlinear plants are shown in Figures 10 and 11. In all the three cases the controller was able to achieve desirable performance criteria.

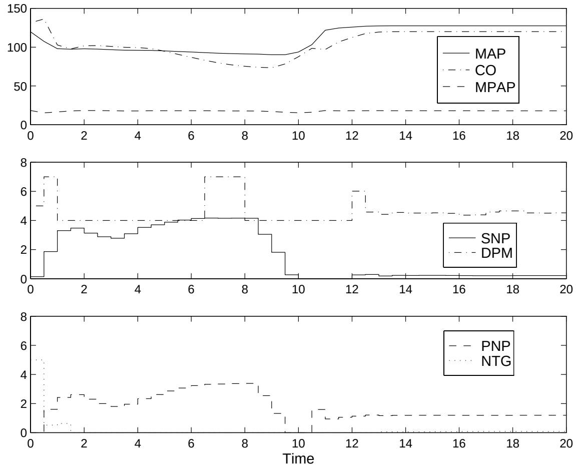

Fig 10. Constrained closed-loop response, linear plant, Case 3. Additional setpoint change at 10 min.

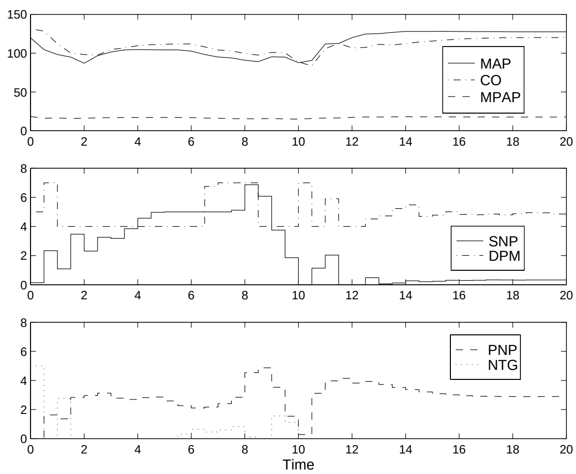

Fig 11. Constrained closed-loop response, nonlinear plant, Case 3. Additional setpoint change at 10 min.

Controller Tuning

A problem (or possibly an advantage) of MPC is that there are a large number of tuning parameters available. Many literature studies report SISO cases where only the prediction and control horizons are used as tuning parameters. With a multivariable system, in addition to different weights for each input and output (which could vary with the prediction step), one could have different prediction and control horizon for each output and input. Tuning, then, can be fairly ad-hoc and somewhat of an art, especially since closed-loop stability cannot be guaranteed even for the perfect model case. There has been a recent move in the MPC field to infinite-horizon-based control which can at least guarantee stability for the perfect model case (Muske and Rawlings, 1993).

SUMMARY

In this paper we have presented results for control of hemodynamic variables in critical care patients (a simulated canine circulatory model) using a "nonsquare" model predictive control strategy. A linear model was used for the model predictions, and simulations where shown for linear and nonlinear plants. The main limitation to this work is the assumption that an accurate linear model is available for each patient condition. 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 "square" 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. It is also important to always maintain the physician "in the loop" with proper monitoring and alarm functions.

NOTATION

e = error
G = gain matrix
H = convolution model
k = discrete time step
M = control horizon
N = model length
P = prediction horizon
Q = output weighting
r = setpoint
R = input weighting
u = input (SNP, DPM, PNP, NTG)
x = state
y = output (MAP, CO, MPAP)

CO = cardiac output
DPM = dopamine
MAP = mean arterial pressure
MPAP = mean pulmonary arterial pressure
MPC = model predictive control
NTG = nitroglycerine
SNP = sodium nitroprusside
PNP = phenylephrine

ACKNOWLEDGMENT

This research has been supported by a Biomedical Engineering Grant from the Whitaker Foundation.

REFERENCES

Garcia, C.E., D.M. Prett, and M. Morari (1989) "Model Predictive Control: Theory and Practice - A Survey," *Automatica*, **25**(3), 335.

Gopinath, R.S., B.W. Bequette, R.J. Roy, H. Kaufman and C. Yu (1995). “Issues in the Design of a Multirate Model-Based Controller for a Nonlinear Drug Infusion System,” *Biotech. Prog.* **11**(3), 318-332.

Gopinath, R.S., B.W. Bequette, H. Kaufman, C.M. Held, J.W. Huang, R.J. Roy (1996). “Drug Infusion Control System Challenge,” *IEEE Trans. Auto. Cont.* (submitted).

Held, C.M and R.J. Roy (1995). “Multiple Drug Hemodynamic Control by Means of a Supervisory-Fuzzy Rule Based Adaptive Control System: Validation on a Model,” *IEEE Trans. Biomed. Eng*. **42**(4), 371-385.

Huang, J.W. and R.J. Roy (1996). “Multiple-Drug Hemodynamic Control Using Fuzzy Decision Theory,” (submitted).

Isaka, S. and A.V. Sebald (1993). “Control Strategies for Arterial Blood Pressure Regulation,” *IEEE Trans. Biomed. Eng*., **40**(4), 353-363.

Morari, M., W. Grimm, M.J. Oglesby and I.D. Prosser (1985). “Design of Resilient Processing Plants - VII. Design of Energy Management Systems for Unstable Reactors - New Insights,” Chem. Eng. Sci., **40**(2), 187-198.

Muske, K. and J.B. Rawlings (1993) “Model Predictive Control with Linear Models,” AIChE J., 39(2), 262-87.

Slate, J.B., L.C. Sheppard, V.C. Rideout and E.H. Blackstone (1979). “A Model for the Design of a Blood Pressure Controller for Hypertensive Patients,” In *IEEE Engineering in Medicine and Biology Conference*, Denver.

Yu, C.L., R.J. Roy and H. Kaufman (1990a). “A Circulatory Model for Combined Nitroprusside-Dopamine Therapy in Acute Heart Failure,” *Medical Progress through Technology*, **16**, 77-88.

Yu, C., R.J. Roy, H. Kaufman, and B.W. Bequette (1990b), "Multiple-Model Adaptive Control Applied to the Multiple-Drug Infusion Problem," *Proceedings of the 1990 Conference on Information Sciences and Systems*, Princeton, NJ, pp. 274-279.

Yu, C.L., R.J. Roy, H. Kaufman and B.W. Bequette (1992) “Multiple-Model Adaptive Predictive Control of Mean Arterial Pressure and Cardiac Output,” *IEEE Trans. Biomed. Eng*., **39**(8) 765-778.