INDIRECT ADAPTIVE CONTROL OF DRUG INFUSION FOR A CIRCULATORY SYSTEM MODEL

by

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Abstract

An indirect adaptive control algorithm using recursive identification and linear quadratic regulation was used to compute the infusion of two drugs in order to control blood pressure and cardiac output in a realistic physiological nonlinear multiple-input multiple-output representation. Two types of recursive identification were considered; namely, conventional recursive least squares (RLS) and a modified version (MRLS) that penalizes large parameter changes.

Results show that the adaptive procedures are capable of controlling the responses to within their specified tolerances and that initial tuning of the adaptation parameters can be reasonably performed using a linearized system model.

1. INTRODUCTION

This paper focuses on indirect adaptive control of a two-input, two-output computer model developed to approximate the hemodynamic responses to the drugs, dopamine and nitroprusside in acute left ventricular pump failure. The controller is used for regulating the blood pressure and cardiac output through the infusion of these two drugs. The way in which a patient responds to these drugs varies from person to person and with time as the condition of the patient changes. This results in variable plant transfer functions. Furthermore, these responses are highly nonlinear with several constraining relationships.

Adaptive control has been used previously in single-output, single-input systems. Xu [1] controlled blood pressure using the drug sodium nitroprusside with a model reference adaptive controller (MRAC) designed by Sobel et al. [2]. He et al. [3] also controlled blood pressure using a multiple model adaptive controller to control blood pressure.

Voss et al. [4] simultaneously controlled cardiac output and blood pressure in dogs through multiple drug infusions using a Control Advance Moving Average Controller (CAMAC). This is an extended horizon controller with a recursive least squares estimator to identify the unknown parameters, which are subsequently used for control calculation.

Barney and Kaufman [6] used the direct MRAC procedure of [2] to control the cardiac output and blood pressure responses of a linear model. They incorporated hard constraints on the dopamine and nitroprusside infusion rates and showed that adaptive control was feasible over a representative range of gains, time constants, and time delays. This direct approach is especially advantageous in that no explicit parameter identification is needed.

However, prior to testing the MRAC on animals, it is important to demonstrate its capabilities with more realistic simulation models. One particular representation amenable to control purposes is the computer model discussed by Yu et al. in [5]. This model was developed to approximate the drug effects of nitroprusside (NP) and dopamine (DP) on a failing heart. The results were obtained by incorporating pharmacodynamic relationships into a nonlinear electrical analog model of the circulatory system. The total drug response included secondary interactions between cardiovascular components.

Because the experimental data from this model closely agreed with clinical results, the direct model reference adaptive control algorithm of [2] along with further modifications proposed by Kaufman et al. [7] was considered by Westvold [8] for calculating drug infusions to control the mean arterial blood pressure (MAP) and cardiac output (CO) responses of this computer model. Digitized versions of the algorithm, along with different output sampling rates, were considered.

Although results to date from using direct MRAC have been quite satisfactory, it is important to note that certain positivity conditions need to be satisfied in order to guarantee that the plant outputs (CO and MAP) asymptotically track the corresponding reference model outputs. Satisfaction of such conditions can be especially difficult for physiological drug infusion models that include significant time delay.

Thus, as an alternative, it is of interest to also explore the performance of indirect adaptive controllers that explicitly incorporate parameter identification. Such an approach also has its limitations in that an identification is needed that will give accurate enough estimates of representative physiological scenarios that involve constant parameters, slowly varying parameters, and parameters with very rapid changes. Furthermore, in order to ensure the accuracy of the parameter estimate, adequate external excitation is required. Design of an identifier that will track parameters with these attributes is a very difficult task. A conventional recursive least squares based procedure with a forgetting factor [9] can, in a noisy environment, usually be tuned to either track only slowly varying parameters or only rapidly varying parameters. This follows since an identification with a forgetting factor corresponding to a short memory will be more responsive to both system changes and to noise effects than an identifier with a forgetting factor corresponding to a larger memory.

Two problems that arise using this algorithm occur when there is insufficient excitation in the input, and when there are collinearities of the input with other inputs or states, i.e., linear state feedback. These problems lead to singularities in the covariance matrix.

More recently, Barron Associates Incorporated (BAI) [13], proposed the Modified Sequential Least Squares Algorithm (MSLS) which reformulates the standard least squares problem to include a term which penalizes changes in the parameter estimates between time steps. This identification method can track time varying parameters, and is robust to the problem of insufficient excitation and data collinearities. The MSLS was used in conjunctions with a receding-horizon optimal controller to control the VISTA/F-16 with a missing left horizontal tail. Bodson [10] derived a recursive version of the MSLS which is a batch algorithm. He showed that the covariance matrix and its inverse are bounded under weak conditions. This new algorithm has been shown to react sufficiently fast due to the choice of a small forgetting factor, and adequately reject noise due to the additional penalizing term when there is insufficient excitation.

Motivated by the successes of the results in reconfigurable flight control, it is of interest to explore the use of the recursive version of the MSLS in indirect adaptive control of drug infusion. The drug infusion problem is described in Section 2.0 and the adaptive controller is presented in Section 3.0. Results are given in Section 4.0, followed by the conclusions and recommendations in Section 5.0.

2. SYSTEM DESCRIPTION

The objective is to lower a patient's blood pressure and to raise or maintain the cardiac output along acceptable trajectories. This is done by calculating the drug infusions that result in an output that meets the specifications. Convergence time is measured as the amount of time necessary for the plant to get within 5 mm Hg for the blood pressure. The controller is considered as having good responses if the plant converges within 10 minutes.

Due to the physical limitations of the system, the control may lie only within certain ranges. A patient cannot receive a negative dosage of a drug. For safety reasons, the dosages should not exceed an upper limit. The ranges that the inputs must lie within are as follows:

$$0 \leq DP \leq 7 \; \mu g/\min \cdot kg$$
$$0 \leq NP \leq 10 \; \mu g/\min \cdot kg$$
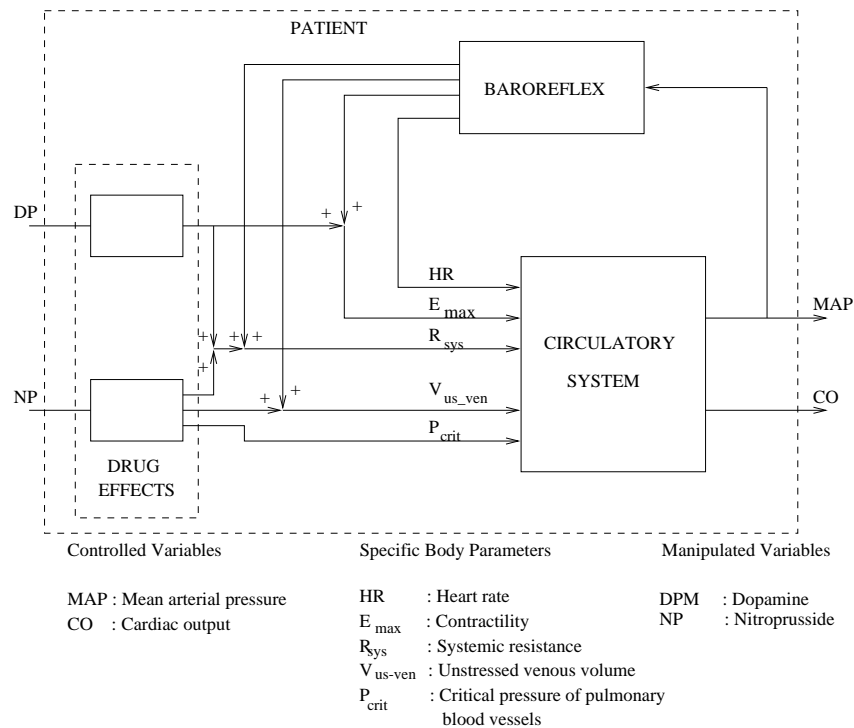
2.2   Model specifications

The objective is to maintain or move the cardiac output (CO) from an initial value in ml/min·kg to a specified find. This blood flow rate is normalized for the body weight of the patient. Too rapid a change in CO is not healthy for the patient and a settling time of about 15 to 20 minutes is reasonable. For mean arterial blood pressure (MAP), a decrease in pressure (mm Hg) from an initial value is needed. This response may change more rapidly than the CO, giving a desired settling time of about five minutes.

2.3   Process Definition

As stated above, the controller was to be validated using the computer model developed by Yu et al. [5]. This model of the cardiovascular system in acute left ventricular (LV) pump failure gives dynamic as well as steady-state data on the drug responses. The drugs considered are dopamine (DP) for the inotropic agent and nitroprusside (NP) as the vasodilator.

The relevant definitions of the model are given in Figure 1, which shows the complete system; Figure 2, which shows the interior of the circulatory system block of Figure. 1; and Figure 3, which shows the interior of the baroflex block of Figure. 1.

The mathematical relations that describe the "drug effects" shown in Figure. 1 and the circulatory system are defined in [5]. These relations consist of a combination of differential equations, algebraic equations, and fitted functions. Some of the required parameter settings for the circulatory system equations are the direct outputs from the baroflex shown in Figure. 3.

Figure 1. Schematic of the nonlinear drug delivery model.

The energy sources of the circulatory system shown in Figure. 1, which in reality correspond to the contracting heart chambers, are modeled as the variable capacitance $(E_{lv})^{-1}$ and $(E_{rv})^{-1}$ as defined in [5].
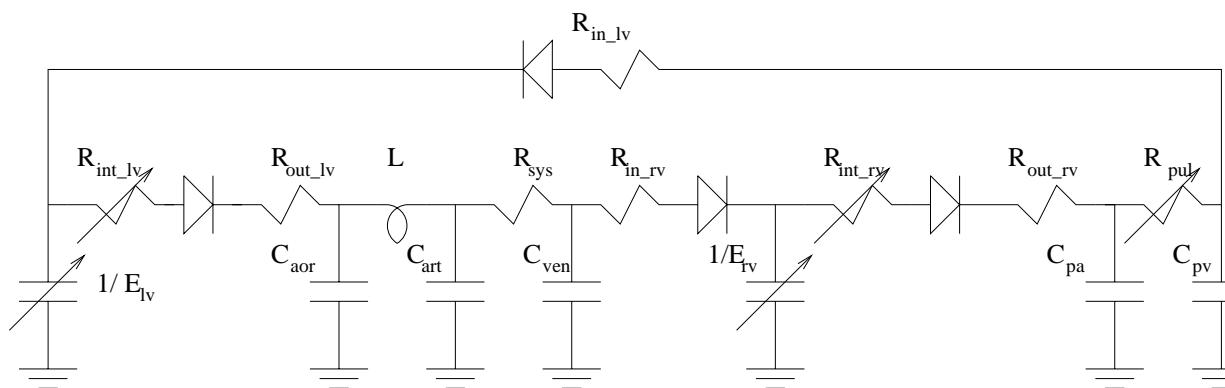
Note in Figure. 2 that the MAP output corresponds to the voltage across the capacitor C_{aor} and the CO output is the current through the resistor labeled as R_{out_lv}.

Physiological descriptions of the background to this model are given in Sections 2.3.1 and 2.3.2.

2.3.1   Circulatory System Representation

In this circulatory model shown in Figure. 2, the heart has two active chambers, the left and right ventricles. These chambers possess time-varying elastances which provide the energy for blood flow. A time-varying elastance can supply energy by imitating a current source. The maximum elastance of a ventricle is used to characterize ventricular contractility. The time-varying elastance of each ventricle is assumed to be a sinusoidal function of time during systole. Each ventricle also possesses an internal viscous impedance which is a linear function of the corresponding peak isovolumic ventricular pressure. The ventricles are passively filled during diastole. The diastolic pressure-volume relationship in both ventricles are assumed to be linear at low pressures and exponential at higher pressures. The roles of the atria during filling are ignored.

The left ventricle is connected to the systemic circulation by an ideal valve while the right ventricle is connected to the pulmonary circulation by a similar device. The systemic vasculature is represented by a lumped parameter model. The structure of the systemic circulation was chosen so as to closely approximate the load the heart sees during ejection. The same guidelines were used in modeling the pulmonary vasculature.

Figure 2. Electrical analog equivalent of the circulatory system.

The systemic and pulmonary compartments are represented by nonlinear capacitors. The pressure-volume relationship of these compliant elements are given in [5]. The independent variables in this model are the volumes of blood in each chamber. The sum of all the volumes of each compartment will give the total blood volume, which is assumed constant. Short-term MAP regulation was simulated using a modified version of the baroflex as proposed in [11] and shown in Fig. 2.
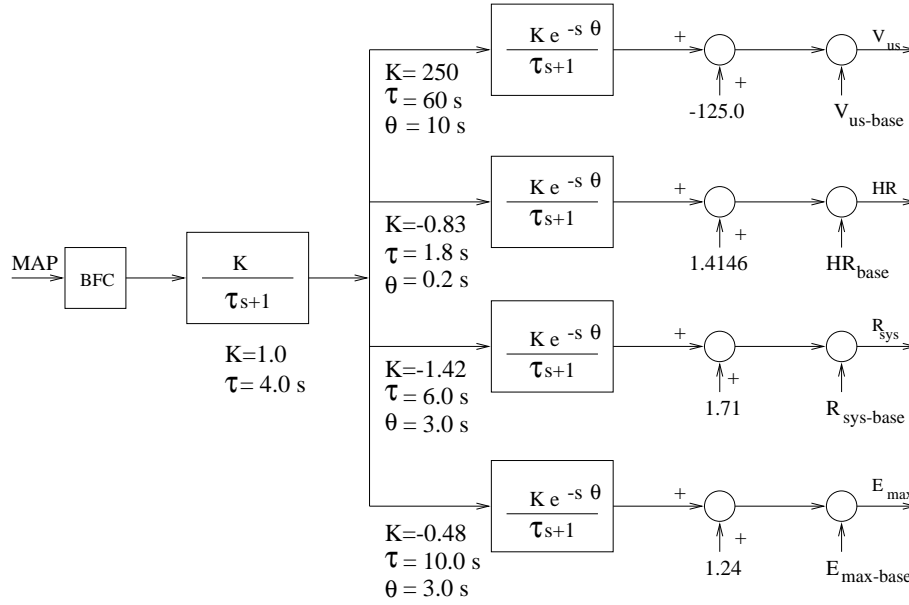
At the start of computation, a volume is assumed in each compartment. Pressures and flow between compartments are then calculated at that instant in time, and the Euler algorithm with an integration step size of 5 milliseconds is used to solve for the new volumes. A steady state was assumed when the volumes at the start of each heart cycle remain constant.

Heart failure was simulated by a decrease in LV contractility. Changes in contractility were taken to be uniform throughout the ventricle. Right ventricular contractility was assumed to be unaffected.

2.3.3   Pharmacodynamics

DP is modelled as a pure inotropic agent;that is, it will raise the baseline contractility of both ventricular chambers. In this study, infusion rates of DP are limited between 0 and 7, which is below its range of alpha adrenergic effects. The response of DP on the heart is assumed to be dependent on the

concentration of the drug in the large arterial compartment.

Figure 3. Schematic of the baroreflex model.

On the other hand, NP has a direct effect on vascular smooth muscle and can possibly alter the characteristics of every element in the model. This model simplified the response of NP to three vascular elements. In the systematic circulation, NP is assumed to decrease systemic resistance and increase the unstressed volume of the venous section. The combined system representation is shown in Fig. 3.

3. ADAPTIVE CONTROLLER DESCRIPTION

The adaptive controller to be applied to the nonlinear simulation model described in Section 2 was designed based upon the use of recursively updated linear discrete models that relate the incremental outputs to the incremental controls. The outputs ΔMAP and ΔCO were respectively chosen on the differences between the actual MAP and CO and their baseline initial values. The increased controls were the actual drug infusions (i.e., difference between computed control and actual baseline values).

A sample time of 30 seconds was used; this is more than adequate for an identification update and corresponding control computation to be performed at each step.

The identified models at each sample were of the form

$$x(k+1) \ = \ F(\theta)x(k) \ + \ G(\theta)u(k) \tag{1}$$
$$y(k) \ = \ H(\theta)x(k) \tag{2}$$

where $x(k)$ is the (nx1) state vector
$y(k)$ is the incremental (2x1) output vector $[\Delta$MAP$, \Delta$CO$]^T$
$u(k)$ is the (2x1) control vector $[$SNP, DOP$]^T$
θ is a vector of parameters to be identified.

The parameter θ is to be estimated online using recursive identification of the controlled autoregressive representation of (1) and (2); namely,

$$A(z^1)y(k) \ = \ B(z^{-1}) \ u(t-nk) \ + \ e(k)$$

where z^{-1} is the delay operator.

$A(z^{-1})$ is a (2x2) polynomial matrix

$B(z^{-1}$ is a (2x2 polynomial matrix

nk represents the actual delay time and e(k) represents the uncertainty.

The estimates of the polynomial coefficients in $A(z^{-1})$ and in $B(z^{-1})$ constitute the parameter θ in (1) and (2). Estimation of these parameters is typically carried out by recursive least squares (RLS) with a forgetting factor. We consider the relation:

$$y(t) = x^T(t)\theta$$

and cost function

$$J = \sum_{i=1}^{N} \lambda^{N-i} e^2(i)$$

where x^T is a (16,1) regression vector, θ is a (16,2) matrix of unknown parameters to be determined and e(i) is the error between the true and estimated outputs. The optimum order of the system was determined by offline identification.

The RLS method can lead to two problems when trying to track varying parameters. First, a small forgetting factor needed to track fast or abrupt parameter variations can cause a large covariance matrix which could lead to covariance 'blow up'. Second as one decreases the forgetting factor, the size of the data window gets smaller and it is more likely that there will exist data collinearities within the data window. To deal with this issue, BAI proposed the MSLS algorithm which prevents singularities in the covariance matrix. This is due to the reformulation of the Least Squares problem; namely, the cost function to be minimized includes a penalization on changes in the parameters between each time step. A weighing factor is included to adjust how much to penalize each parameter variation. The cost function to be minimized is

$$J = \sum_{i=1}^{N} (y(i) - x^T\theta_N)^2 \lambda^{N-i} + \alpha(\theta_N - \theta_{N-1})^2$$

where θ_N corresponds to the parameter estimates at time N.

Setting

$$\frac{dJ}{d\theta} = 0,$$

we get the solution

$$\theta_N = [X^T\tilde{X} + \alpha I]^{-1}[\alpha\theta_{N-1} + \tilde{X}^T y_N]$$
$$= P(t) \cdot B(t)$$

where

$$X^T = [x(1)\ x(2)\ ...\ x(N)]$$
$$\tilde{X}^T = [x(1)\lambda^{N-1}\ x(2)\lambda^{N-2}\ ...\ x(N)]$$
$$y_N{}^T = [y(1)\ y(2)\ ...\ y(N)]$$

We note that the covariance matrix of this algorithm is now

$$P(t) = [X^T\tilde{X} + \alpha I]^{-1}$$

Bodson [10] derived the recursive least squares version (MRLS) of the MSLS:

$$\theta(t+1) = \theta(t) + P(t+1)\ x(t+1)(y(t+1) - x^T(t+1)\theta(t))$$
$$+ \alpha\lambda P(t+1)((\theta(t) - \theta(t-1))$$

To find P(t+1), it is typical in the RLS formulation to use the matrix inversion lemma. However, due to the additional penalty term, the MIL leads to an inversion of a (1+np) by (1+np) matrix, where np is the number of unknown paramaters in the regression vector. Thus, we opt to directly take the inverse.

Given values for θ from the identification, the control is computed from (1) and (2) in a manner so that the system will track a step command (i.e., desired values of MAP and CO) with zero steady-state error. To this effect we augment the system using a new state q(k) which is to be the output of a digital integration (or accumulator) forced by the negative feedback of the output y, giving:

$$x(k+1) = F(\theta)x(k) + G(\theta)u(k) \tag{3}$$

$$q(k+1) = q(k) - H(\theta)x(k) \tag{4}$$

Given this system, a feedback controller will be found by minimizing

$$J = \frac{1}{2} \sum_{k=0}^{\infty} x_k^T Q_x x_k + q_k^T Q_q q_k + u_k^T R u_k$$

The resulting control is then [13]

$$u(k) = K_x x(k) + K_q q(k) \tag{5}$$

where the gain K_x and K_q stabilize the closed-loop system.

For implementation purposes, the digital integration would be forced by the actual error (r-y) and then (4) would be replaced by

$$q(k+1) = q(k) + r - H(\theta)x(k) \tag{6}$$

Since K_x and K_y stabilize the system, a steady state exists so that

$$q(k+1) = q(k) = q_0 \tag{7}$$

and therefore from (6) in steady state

$$y = Hx = r \tag{8}$$

Because implementation of the controller defined in (5) requires full state feedback, a linear observer was used to estimate the state x_k from the output y_k. This observer was also adaptive in the sense that its gain also was updated at each sample to correspond with the estimates of θ.

To initiate the controller, gains were computed using a value of θ from an apriori offline batch identification on the nonlinear simulation model at some selected condition.

4. SIMULATION RESULTS

4.1   Experimental Description and Resuilts

.   Of interest were the cases described in [14]. The first case considered is typically associated with patients suffering from hypokinesis and minor hypertension. The subject retains 28% of normal heart contractility. It is required to raise the MAP to 100 mmHg. This corresponds to a change of +5 mmHg from the baseline value. The CO must be increased to 105 mm/kg/min, a change of +35 mm/kg/min from the baseline value. SNP and DPM were the drugs used to achieve the desired setpoints.

The observer and controller gains were initialized based upon (theta) identified off-line for the 70% contractility model. The simulation lasted 60 minutes. Figure. 4 shows the responses of the three control strategies considered. We see that the control strategy based on the MRLS algorithm had the best performance for both CO and MAP steady state regulation.
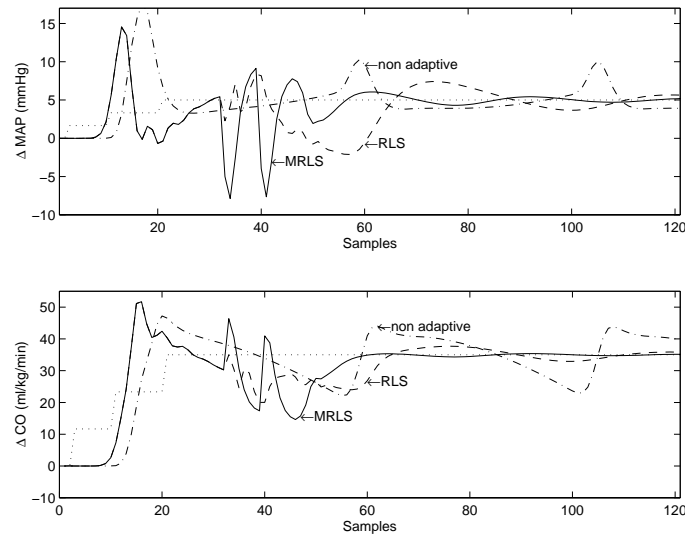
Figure 4. Simulation for Case 1

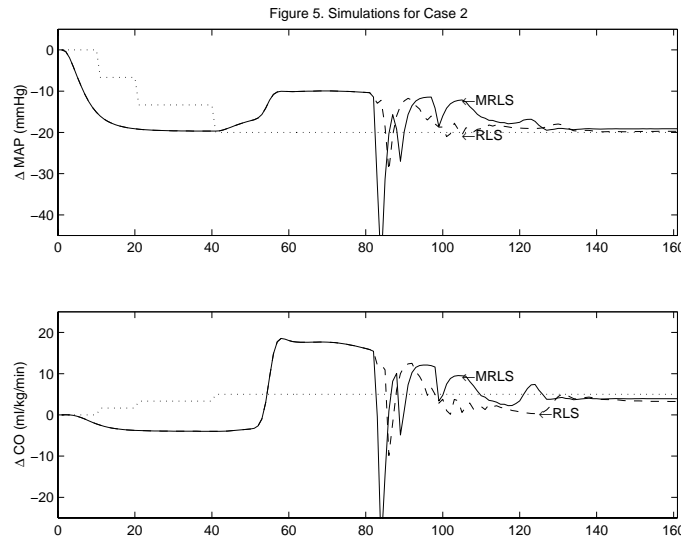| | Time Required to settle within +/-2 band | | Steady State Error | |
	MAP	CO	MAP	CO
MRLS	27	28	-0.18	-0.17
RLS	39.5	51	-0.64	-0.85
Non Adaptive	54	-	1.08	-4.75

Table I: Settling times and steady state error for Case 1.

2)This case is for subjects retaining 50% of normal heart contractility. These patients are suffering from low CO and high MAP. MAP is required to decrease by 20 mmHg, and CO is to increase by 5 ml/kg/min while infusing PFL. The PFC setpoint is maintained at 6 $\mu g/kg/min$ for the first 20 minutes and 4 $\mu g/kg/min$ thereafter to prevent overdose. Again, the gains correspond to an identified 70% contractiltiy model. The simulation lasted 80 minutes and the results are showin in Figure 5. It can be seen from the figure that the infusion of PRP causes the initial drop in MAP and CO values and the closed loop controller uses DPM and NTG to counteract the cardiovascular depression brought about by PFL and to bring MAP and CO to the desired setpoints.

| | Time Required to settle within +/-2 band | | Steady State Error | |
	MAP	CO	MAP	CO
MRLS	62.5	62.5	-0.87	1.06
RLS	65.5	64.5	-0.27	1.75

Table II: Settling times and steady state error for Case 2.

Figure 5. Simulation for Case 2

5. CONCLUSIONS

We have presented an indirect adaptive control algorithm using two different recursive identification methods implemented in linear quadratic control. Three different drugs, DP, SNP, and NTG were used in the closed loop simulations of the nonlinear canine model. Initialization was based on an off-line identification based an autoregressive model. Current research is in further analyzing the performance and robustness of these on line adaptive strategies for controlling hemodynamic variables according to the prescribed therapy.

6. REFERENCES

[1] Xu, X., Kaufman, H., and Roy, R., "Model Reference Adaptive Control of Drug Infusion Rate," 6th IFAC Symposium on Identification, Washington, DC, June 1982, pp. 216-221.

[2] Sobel, K., and Kaufman, H., "Direct Model Reference Adaptive Control for a Class of MIMO Systems," Advances in Control and Dynamic Systems, C.T. Leondes, (ed.), Vol. XXIV, Academic Press, 1986, pp. 245-314.

[3] He, W.G., Kaufman, H., and Roy, R., "Multiple Model Adaptive Control Procedure for Blood Pressure Control," IEEE Trans. Biomed. Eng., 1986, Vol. BME-33, pp. 10-19.

[4] Voss, G.I., Katona, P.G., and Chizeck, H.J., "Adaptive Multivariable Drug Delivery: Control of Arterial Pressure and Cardiac Output in Anesthetized Dogs," IEEE Trans. Biomed. Eng., 1987, Vol. BME-34, pp. 617-623.

[5] Yu, C., Roy, R., and Kaufman, H., "A Circulatory Model for Combined Nitroprusside-Dopamine Therapy in Acute Heart Failure," Medical Progress Through Technology, Kluwer Academic Publisher, 1990, pp. 77-88.

[6] Barney, E.M., and Kaufman, H., "Model Reference Adaptive Control of Cardiac Output and Blood Pressure Through Two Drug Infusions," 5th IEEE Int. Symposium on Intelligent Control, Philadelphia, PA, September 5-8, 1990.

[7] Kaufman, H, I. Barkana, K. Sobel, "Direct Adaptive Control Algorithms", Springer, NY 1998

[8] Westvold, S., H. Kaufman, R.Roy, "Model Reference Adaptive Control of a Circulatory Model for Combined Nitroprusside-Dopamine Therapy", IFAC

Conf on Adaptive Control and Signal Proc., Grenoble, France, July 1992, pp 223-228

[9]   System Identification Toolbox, MATHWORKS, Inc, Natick, MA

[10]   M. Bodson, "An adaptive algorithm with information-dependent data forgetting", ACC, Washington D.C, June 1995, pp. 3484-3489

[11]   Wesseling, K.H. et al, "Baromodulation as the Cause of Short Term Blood Pressure Variability", Proc. of the International Conf on Applications of Physics to Medicine and Biology, (A. Bajzer and Z. Baxa eds), World Scientific Pub, Singapore, 1983, pp247-277

[12]   Lewis, F, and V. Syrmos, "Optimal Control", 2nd ed, Wiley-Interscience, NY 1995

[13]   Monaco, J., D.G. Ward R.L. Barron,, R. Bird, "Implementation and Flight Test Assessment of an Adaptive Reconfigurable Flight Control System", AIAA GNC, New Orleans, 1997

[14]   Rao, R.R, B.W. Bequette, and R.J. Roy "Control of Hemodynamic and Anesthetic States in Critical Care Patients," in Proceedings of Control-97, Sydney, pp158-163 (1997)