Model Reference Adaptive Scheme for Multi-drug Infusion for Blood Pressure Control

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Summary

Using multiple interacting drugs to control both the mean arterial pressure (MAP) and cardiac output (CO) of patients with different sensitivity to drugs is a challenging task which this paper attempts to address. A multivariable model reference adaptive control (MRAC) algorithm is developed using a two-input, two-output patient model. The control objective is to maintain the homodynamic variables MAP and CO at the normal values by simultaneously administering two drugs; sodium nitroprusside (SNP) and dopamine (DPM). Computer simulations were carried out to investigate the performance of this controller. The results show that the proposed adaptive scheme is robust with respect to disturbances and variations in model parameters.

1 Introduction

If blood pressure is controlled and oscillations in the homodynamic variables are reduced, patients experience fewer complications after surgery. In clinical practice, this is usually achieved using manual drug delivery. Given that different patients have different sensitivity and reaction time to drugs, determining manually the right drug infusion rates may be difficult. This is a problem where automatic drug delivery can provide a solution, especially if it is designed to adapt to variations in the patient's model.

Various automatic control techniques have been used to control the hemodynamic variables. Many studies have focused on the infusion of a single drug to lower the patients' blood pressure and maintain it at the desired level using in particular the vasoactive drug sodium nitroprusside SNP [1–8, 13]. Slate and Sheppard [3] used a one-drug patient model and implemented a nonlinear digital proportional-integral-derivative (PID) controller to regulate the mean arterial pressure. Zheng and Zhu [4] developed a multiple-model adaptive scheme (MMAC) based on Fuzzy control. Behbehain [5] proposed an integrating self-tuning control strategy to maintain MAP using SNP. In a recent study Zhu et al. [6] presented an adaptive control algorithm for

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updating time delays and sensitivity of the hemodynamic model. Poterlowicz [7] and Enbiya [8] developed an optimal internal model control system (IMC) to regulate MAP with the SNP drug.

Blood pressure is commonly controlled using more than one drug. Several studies have investigated the automation multiple drug-delivery. Yu et al. [9] developed a computer model to simulate the hemodynamic responses of DPM and SNP in a failing heart. They simulated the circulatory system with a nonlinear electrical analog model with baroreflex feedback. Achuthan et al. [10] used the computer model of [9] to test an indirect adaptive algorithm based on parameter identification and linear quadratic regulation. Voss et al. [11] implemented an adaptive algorithm to control MAP and CO in anesthetized dogs with infusion of sodium nitroprusside and dobutamine. Yu et al. [12] proposed an algorithm that utilized six model predictive controllers to regulate MAP and CO with SNP and DPM. They carried out tests on laboratory animals that were altered to exhibit symptoms of congestive heart failure. Experiments on animal using multi-drug administration were also done by Koivo [14–16], Stern et al. [17] and Kaufman et al. [18].

This paper uses a 2 by 2 patient model with matrix elements represented by first-order transfer functions time delay [19] to investigate the performance of a model reference adaptive control MRAC system. The controller parameters have been adapted using the diagonal 6 by 6 weighting matrices discussed in [19]. Matlab Simulink Toolbox was used to design and simulate the proposed control system.

2 Patient Response Model

The objective of the control system is to decrease the patient's mean arterial pressure and increase the cardiac output to the desired value by tracking the reference signals. The patient hemodynamic model [12] is defined by the linear small-signal first-order transfer function matrix given in equation (1). The drugs used to control the variables CO and MAP are dopamine (DPM) and sodium nitroprusside (SNP). DPM increases both CO and MAP while SNP increases CO and decreases MAP. The drug infusion rates are measured in $(mg/min.kg)$. Cardiac output is measured in $(ml/min.kg)$. Mean arterial pressure is measured in millimeters of mercury $(mmHg)$.

$$\begin{bmatrix} CO \\ MAP \end{bmatrix} = \begin{bmatrix} \frac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} & \frac{K_{12}e^{-T_{12}s}}{\tau_{12}s+1} \\ \frac{K_{21}e^{-T_{21}s}}{\tau_{21}s+1} & \frac{K_{22}e^{-T_{22}s}}{\tau_{22}s+1} \end{bmatrix} \begin{bmatrix} DPM \\ SNP \end{bmatrix} + \begin{bmatrix} D_1 \\ D_2 \end{bmatrix} \tag{1}$$

Where,
K_{ij} - Model gain.
T_{ij} - Time delay (sec.) between the input and the system response.
τ_{ij} - Time constant (sec.).

During clinical evaluations of the patient model, it was observed that disturbances could have an effect on the patient's hemodynamic states, which could lead to an increase/ decrease in blood pressure. Therefore, equation (1) was modified to include the disturbance terms D_1 and D_2 as shown in equation (2), where D_1 and D_2 are small white noise disturbances in CO and MAP.

$$CO = \frac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} \times DPM + \frac{K_{12}e^{-T_{12}s}}{\tau_{12}s+1} \times SNP + D_1$$
$$MAP = \frac{K_{21}e^{-T_{21}s}}{\tau_{21}s+1} \times DPM + \frac{K_{22}e^{-T_{22}s}}{\tau_{22}s+1} \times SNP + D_2 \quad (2)$$

The SIMULINK diagram of the hemodynamic model is shown in fig. 1.

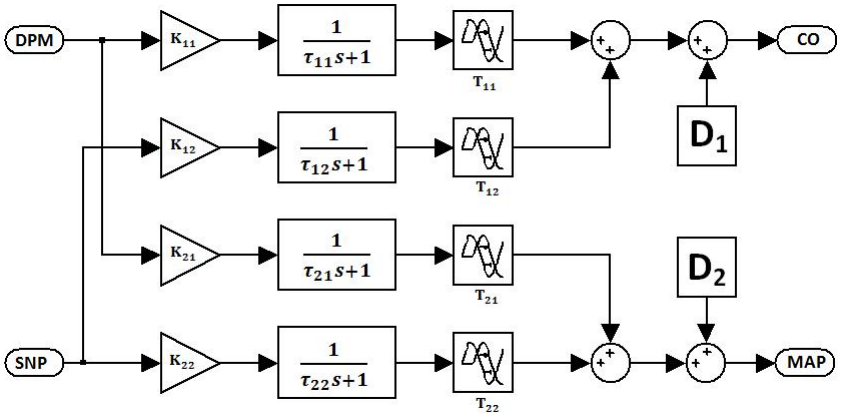

Figure 1: Simulink block diagram of the plant model

The nominal values and range of the parameters in the patient model are given in table 1.

Table 1: Nominal values and range of the parameters in the patient model

Parameters	Nominal	Ranges
K_{11}	5	1 to 12
τ_{11}	300	70 to 600
T_{11}	60	15 to 60
K_{12}	12	-15 to 25
τ_{12}	150	70 to 600
T_{12}	50	15 to 60
K_{21}	3	0 to 9
τ_{21}	40	30 to 60
T_{21}	60	15 to 60
K_{22}	-15	-1 to -50
τ_{22}	40	30 to 60
T_{22}	50	15 to 60

The desired response is represented by the reference model transfer function of CO and MAP shown in equation 3, [19].

$$H(s) = \frac{y_{m_i}(s)}{u_{m_i}(s)} = \frac{1}{\tau_i s+1} \quad (3)$$

y_{m1} and y_{m2} are outputs of the first and second reference model respectively.
u_{m1} and u_{m2} are the inputs of the first and second reference model respectively.

τ_1 = 300 sec. and τ_2 = 90 sec. are the time constants of the reference models chosen produce the desired speed of hemodynamic response. The constraints on normalized drug dosage are selected as follows: $0 \leq DPM \leq 6\ mg\backslash min.kg$ and $0 \leq SNP \leq 10\ mg\backslash min.kg$

3 Model Reverence Adaptive control

Fig.2 shows the diagram of the patient's model and MRAC system. The MATLAB function block is used to obtain the reference signal u_m depending on the patient's case.

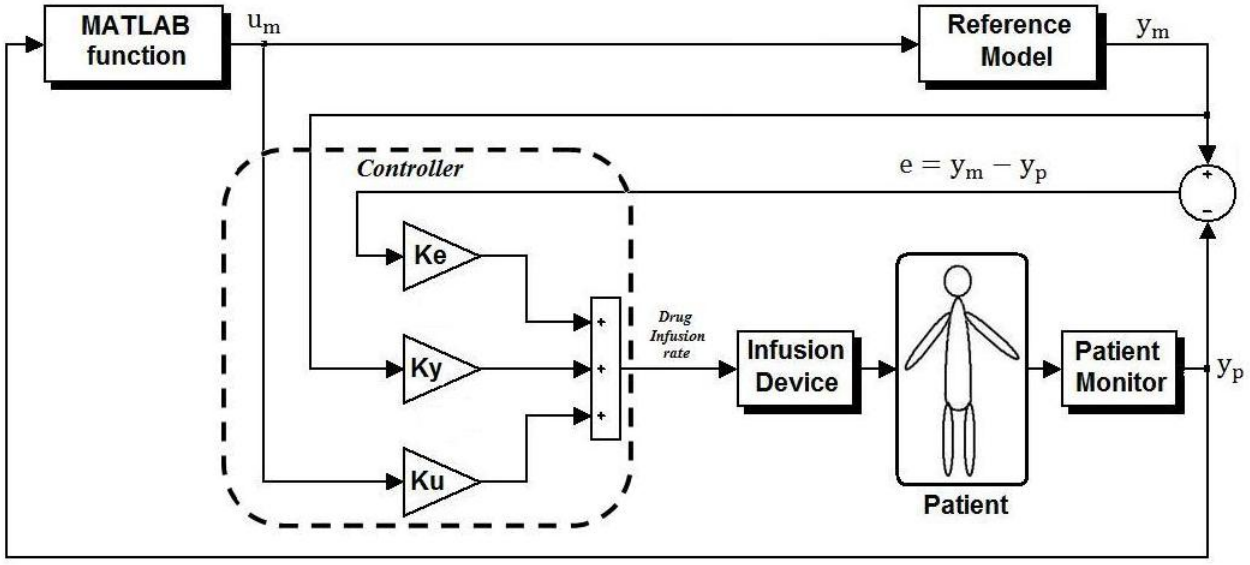

Figure 2: General form of the patient's model with MRAC

The control signal ($u_p(t)$) which presents the drug infusion rate is formulated as a linear combination of the error feedback ($K_e(t) \times e$) and of the two feedforwards reference model output ($K_y(t) \times y_m(t)$) and reference model input ($K_u(t) \times u_m(t)$). The adaptive control law Sobel [20] combines the values of the the tracking error "e", the reference model output "y_m" and the reference model input "u_m" with appropriate adaptive gains (K_y, K_u and K_e). The adaptive control law is given by:

$$U_p(t) = K_y(t)y_m(t) + K_u(t)u_m(t) + K_e(t)[y_m(t) - y_p(t)] \tag{4}$$

$$U_p(t) = K_r(t) \times r(t) \tag{5}$$

$$\begin{aligned} K_r(t) &= [K_e, K_y, K_u] \\ K_r(t) &= K_p(t) + \hat{K}_i(t) \end{aligned} \tag{6}$$

$$r(t) = \begin{bmatrix} e(t) \\ y_m(t) \\ u_m(t) \end{bmatrix} \tag{7}$$

where $e(t) = y_m(t) - y_p(t)$

The adaptive gain vector $K_r(t)$ in (6) is obtained as a combination of integral and proportional gains as follows:

$$K_p(t) = e(t) \times r^T \times A \tag{8}$$

$$\hat{K}_i(t) = e(t) \times r^T \times B \tag{9}$$

where A and B are n_r by n_r (6 x 6) time invariant weighting matrices.

As the system has two inputs and two outputs we have designed two controllers, the function of the first controller is to control the infusion rate of Dopamine (DPM) and the second controls the infusion rate of Sodium nitroprusside (SNP). Fig. 3 illustrates the Simulink block diagram of the system.

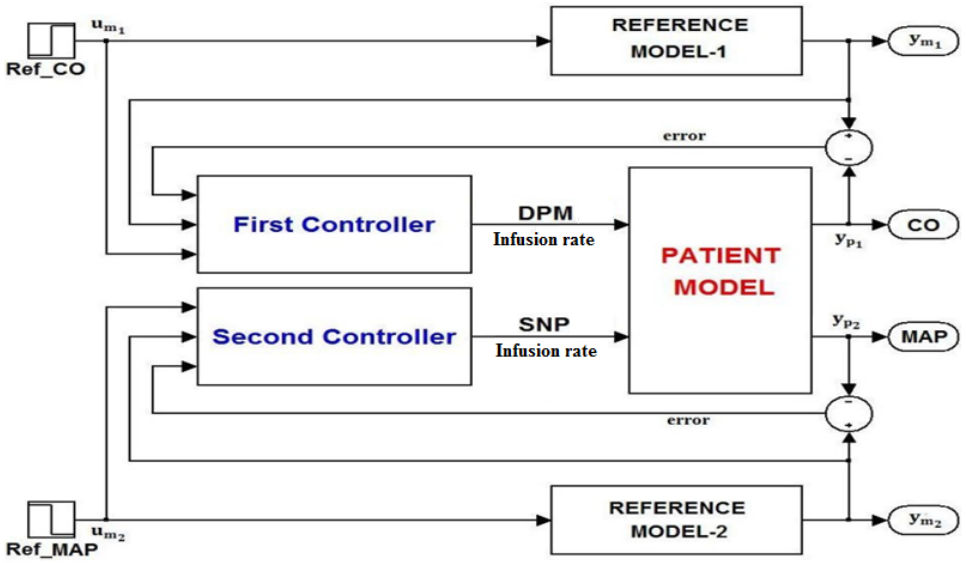

Figure 3: Simulink block diagram of the patient model with the MRAC

4 Control Objectives

The performance of the model reference adaptive controller is investigated by simulating two patients' situations where both MAP and CO are outside the normal values of 120 ($mmHg$) for MAP and 100 ($ml/min.kg$) for CO.

- The initial values of the patients' MAP and CO are chosen as 140 ($mmHg$) and 80 ($ml/min.kg$) respectively. The control objective is to decrease MAP to 120 ($mmHg$) and increase CO to 100 ($ml/min.kg$).

- The initial values of the patients' MAP and CO are chosen as 150 ($mmHg$) and 70 ($ml/min.kg$) respectively. The objective in this case is to decrease MAP by 30 ($mmHg$) and increase CO by 30 ($ml/min.kg$).

5 Simulation Results

The proposed algorithm has been implemented, and tested through a set of experiments by considering two different control objectives as described in section 4.1 and 4.2.

Table 1 lists the nominal values and the range of the parameters of the patient's model which were simulated using Matlab Simulink as shown in figure 3. The simulations were done for different patient's sensitivity. The MRAC has been implemented to compute the drugs infusion rates which are the inputs to the MIMO patient model.

Simulations were conducted for all the parameters values in the range to find by trial and error the best weighting matrices A and B. The proportional and integral gains were then calculated from equation (8) and (9) using these weighting matrices.

In order to compare the performance of our MRAC with that in [19], simulations were also carried out with K_{22} in the range -15, -20, and -50. These are shown in Figure 4, 5 and 6. We observe that the overshoot of both MAP and CO is zero. However, in [19] the mean arterial pressure overshoots by 6% when K_{22} = -20. With regard to the settling within 2%, MRAC showed some improvements when K_{22} = -20.

All the simulations results are summarized in table 2.

Table 2: Simulation results of multi-drug infusion control using MRAC

Hemodynamic variables	K_{22}	Performance Measures	Results using MRAC	[8] results with Non-adaptive PID	[19] results with MRAC
CO	-20	Settling Time (sec)	1232	2790	1440
		Overshoot(mmHg)	Zero	0.32	Little
	-50	Settling Time(sec)	1822	3000	1380
		Overshoot(mmHg)	Zero	1.23	Little
MAP	-20	Settling Time (sec)	543.7	700	1320
		Overshoot(mmHg)	Zero	2.99	1.2
	-50	Settling Time(sec)	508.7	1360	360
		Overshoot(mmHg)	Zero	0.82	Zero

The MRAC performance was also investigated when both MAP and CO are subject to white noise disturbances with variance D_1 and D_2 of 0.0, 0.1, 0.2 and 0.3. The results are depicted in figures 7 to 14 for set point changes of 20 and 30 in CO and -20 and -30 in MAP. These results

demonstrate that the controller copes well with disturbances in the hemodynamic responses. The changes in MAP and CO are very small and the infusion rates are well within the safe range.

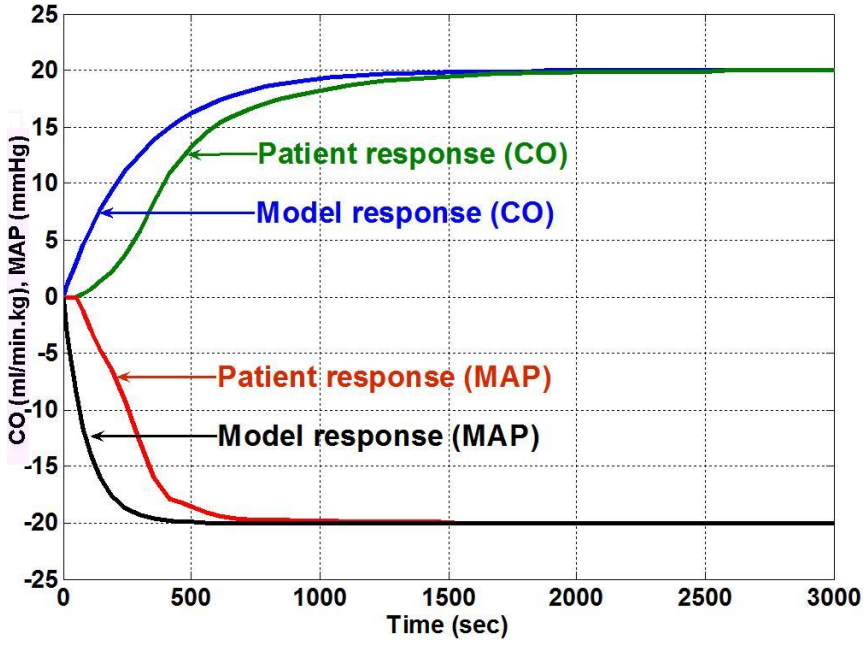

Figure 4: Patient response (CO and MAP) without disturbance, when K_{22} = -15

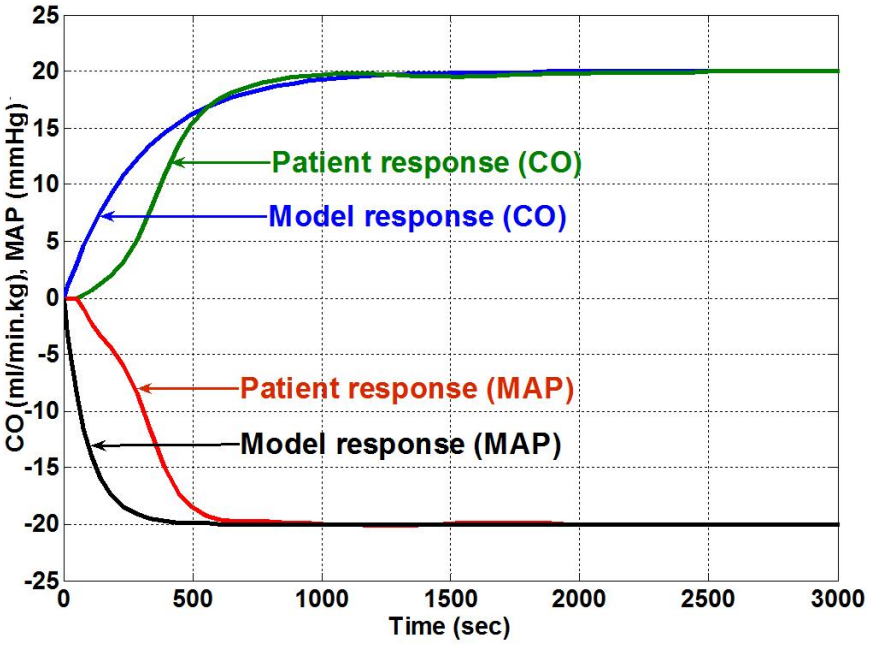

Figure 5: Patient response (CO and MAP) without disturbance, when K_{22}= -20

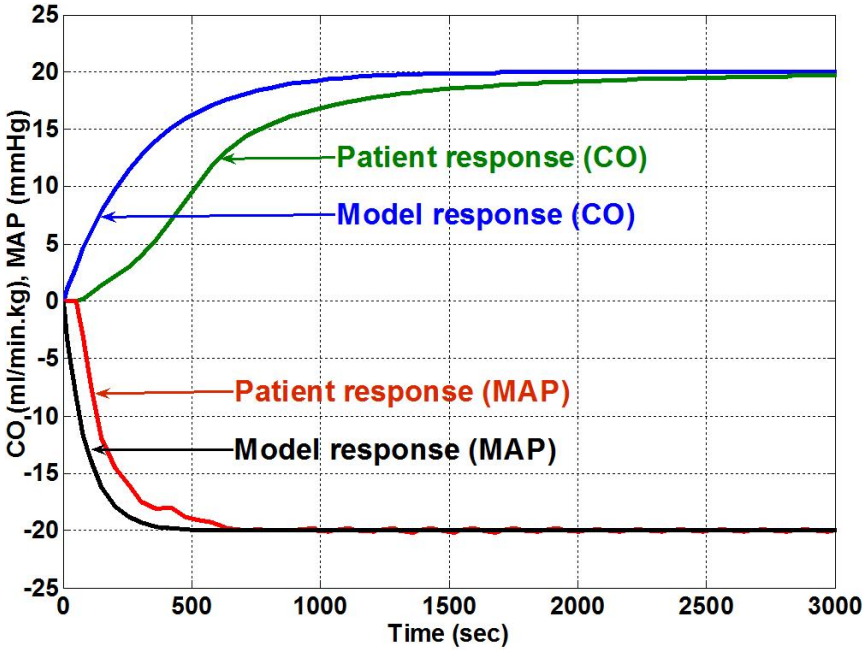

Figure 6: Patient response (CO and MAP), without disturbance, when K_{22}= -50

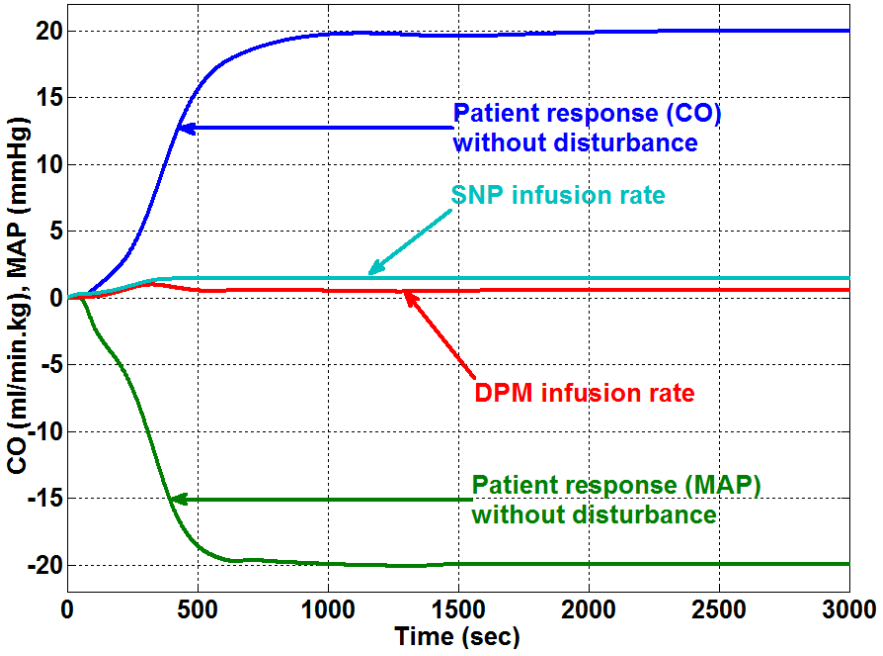

Figure 7: Nominal response without disturbance when set point changes are +20 for CO and -20 for MAP

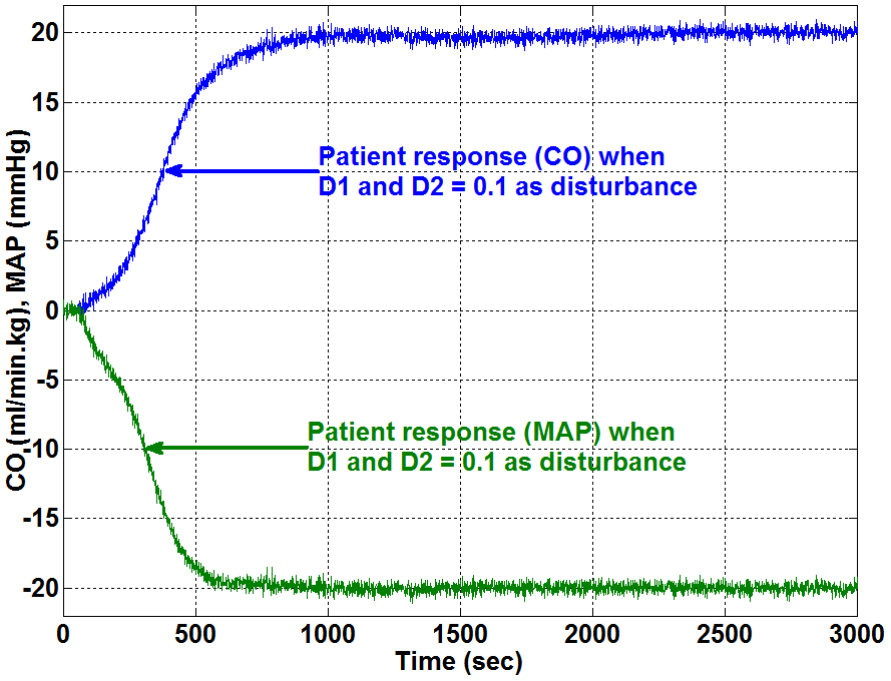

Figure 8: Nominal response with disturbance variance D1=D2=0.1 and set points +20 for CO and -20 for MAP

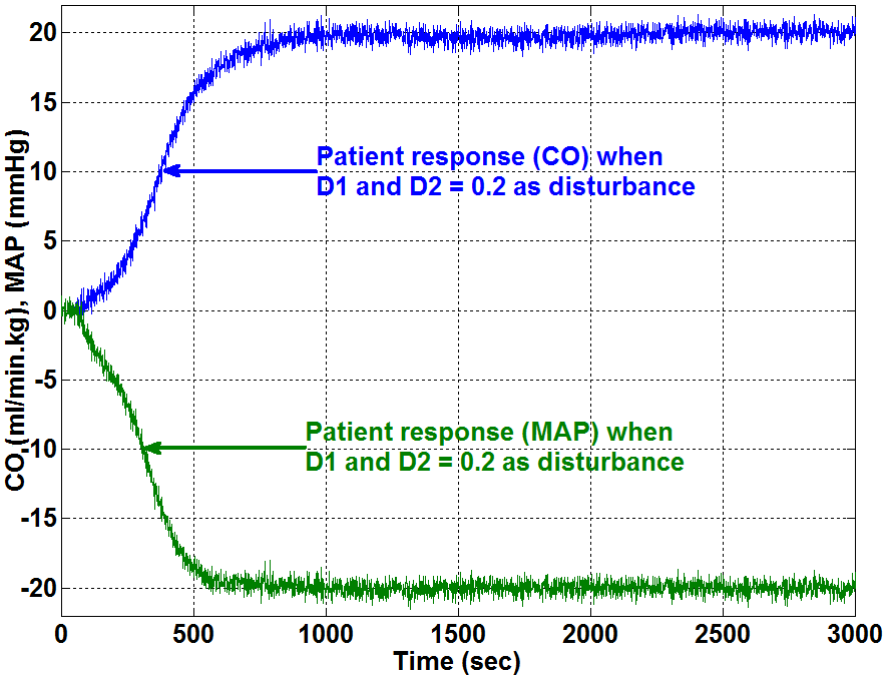

Figure 9: Nominal response with disturbance variance D1=D2=0.2 and set points +20 for CO and -20 for MAP

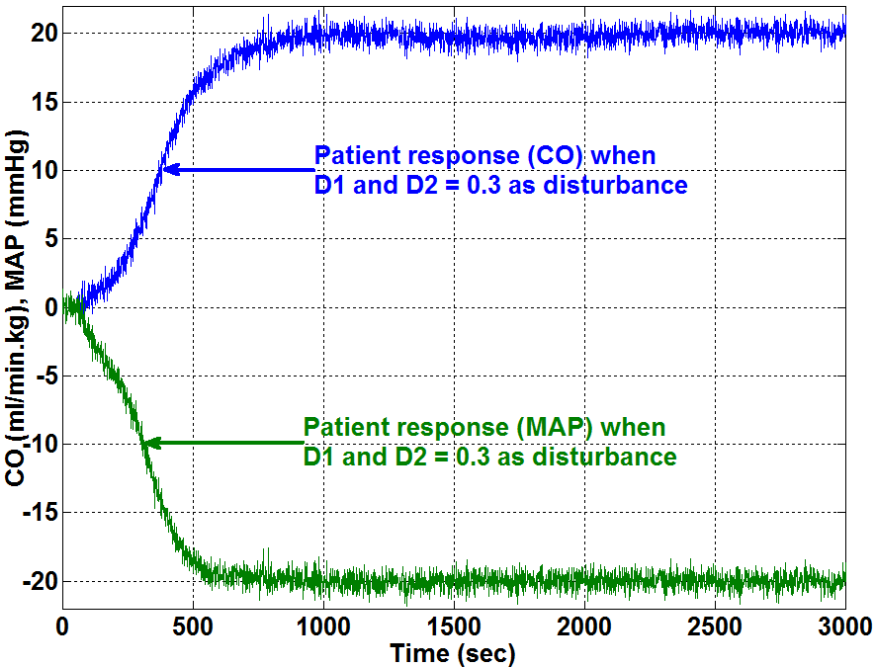

Figure 10: Nominal response with disturbance variance D1=D2=0.3 and set points +20 for CO and -20 for MAP

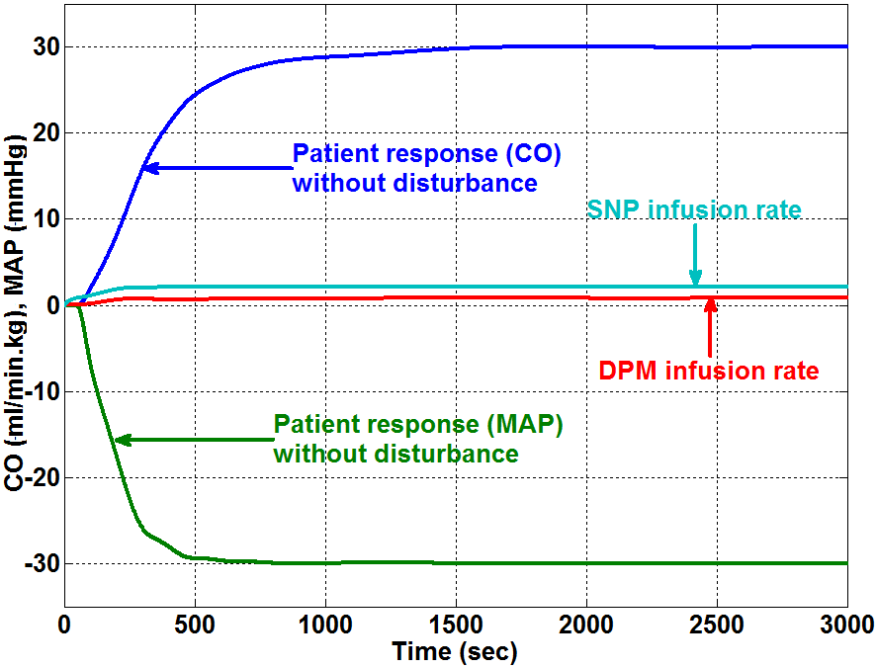

Figure 11: Nominal response without disturbance when set point changes are +30 for CO and -30 for MAP

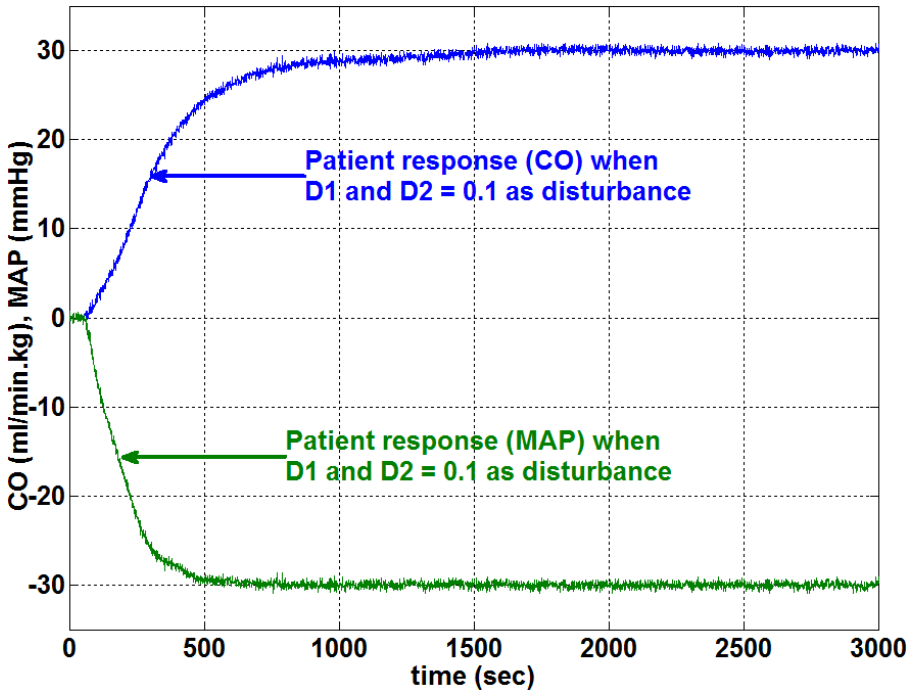

Figure 12: Nominal response with disturbance variance D1=D2=0.1 and set points +30 for CO and -30 for MAP

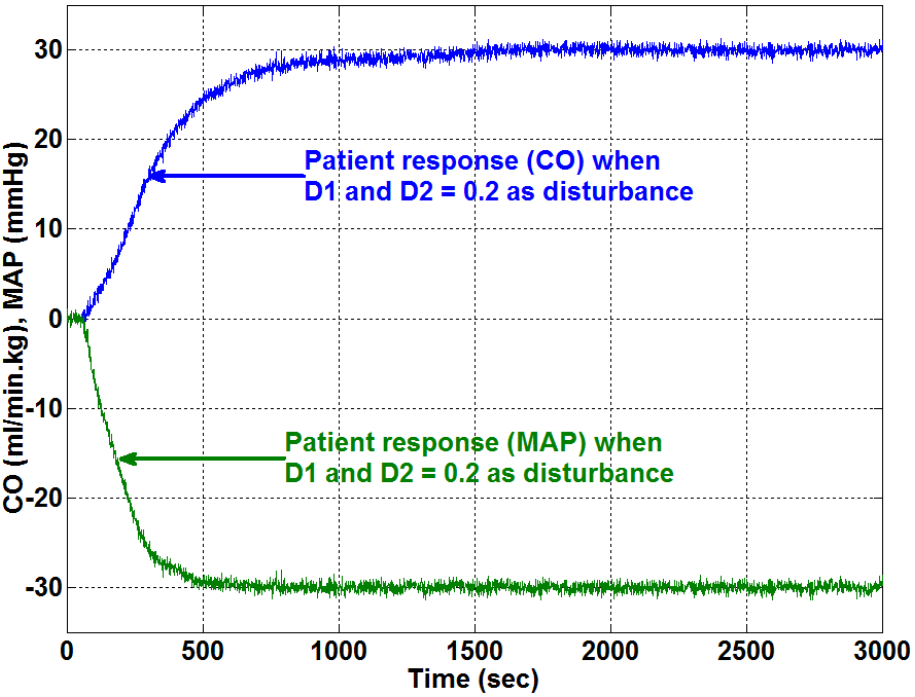

Figure 13: Nominal response with disturbance variance D1=D2=0.2 and set points +30 for CO and -30 for MAP

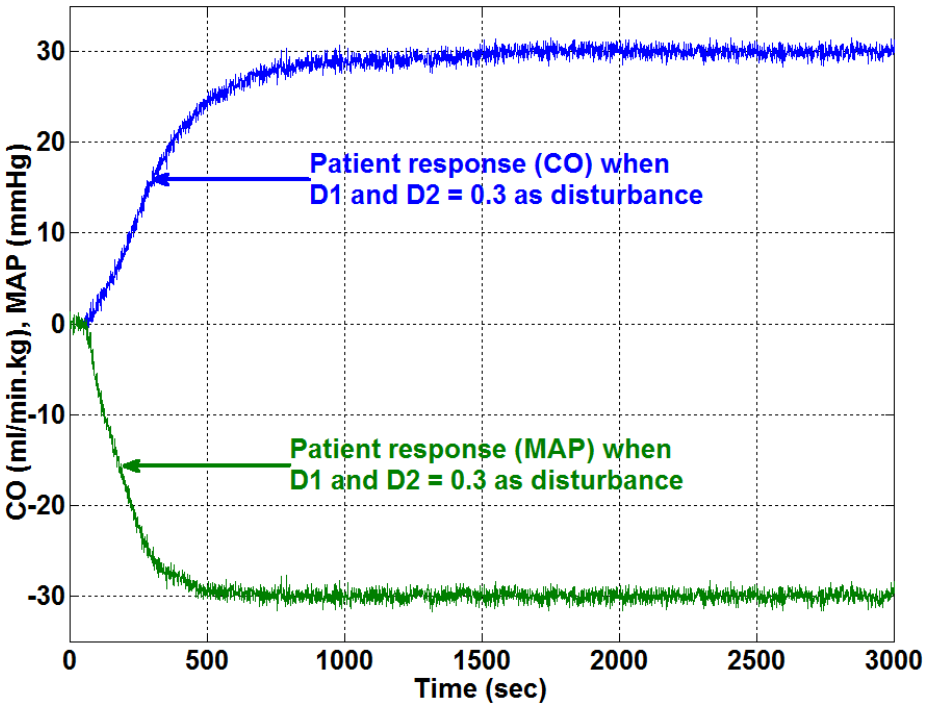

Figure 14: Nominal response with disturbance variance D1=D2=0.3 and set points +30 for CO and -30 for MAP

6 Conclusions

The paper has presented an adaptive multi-drug control scheme for blood pressure control. The proposed scheme was designed and evaluated by simulating variations in patient sensitivity and disturbances in cardiac output and mean arterial pressure. Two drugs were used; dopamine and nitroprusside. The simulation results have confirmed that MRAC is potentially useful for regulating MAP and CO by computing the DPM and SNP infusion rates. The proposed algorithm demonstrated better performance as compared to an non-adaptive PID controller. In the simulations studies the proposed scheme produced better performance compared to reported results, particularly for the updated controller's gain K_{22} (mean arterial pressure gain). This includes shorter settling time and very small or no overshoot when the patient sensitivity K_{22} less than or equal -20. For further work, the proposed controller will be tested with a wide range of patients' sensitivities using more than two drugs.

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