Multi-drug Infusion Control Using Model Reference Adaptive Algorithm

S Enbiya, A. Hossain and F. Mahieddine*

School of Computing, Informatics and Media

*School of Engineering, Design and Technology, University of Bradford, Bradford, UK

{senbiya; m.a.hossain1; f.mahieddine}@bradford.ac.uk

Abstract Control of physiological states such as mean arterial pressure (MAP) has been successfully achieved using single drug by different control algorithms. Multi-drug delivery demonstrates a significantly challenging task as compared to control with a single-drug. Also the patient's sensitivity to the drugs varies from patient to patient. Therefore, the implementation of adaptive controller is very essential to improve the patient care in order to reduce the workload of healthcare staff and costs. This paper presents the design and implementation of the model reference adaptive controller (MRAC) to regulate mean arterial pressure and cardiac output by administering vasoactive and inotropic drugs that are sodium nitroprusside (SNP) and dopamine (DPM) respectively. The proposed adaptive control model has been implemented, tested and verified to demonstrate its merits and capabilities as compared to the existing research work.

1. Introduction

The automatic control of physiological parameters has been considered as important point for several years. One of the particular problems that have been subjected is the control of homodynamic variables such as mean arterial pressure (MAP) and cardiac output (CO). The implementation of automatic control system is very essential to improve

the patient care in order to minimising the workload of the physicians and reducing the costs. The Cardiovascular system has been used to designs control systems for blood pressure control [1]. E. Furutani et al. have developed and implemented a state-predictive servo controller for continuous feedback control of MAP and inference fuzzy rules to avoid the risk and make the patients in safe side during surgical operation [2].

Over the past several years, different approaches have been investigated. Many have focused on the single-input single-output (SISO) control systems to lower the patients' blood pressure and maintain it at desired level using single drug particularly sodium nitroprusside (SNP) [3, 4, 5, 6, 7, 8] and [13]. Fuzzy controller-based MMAC has been presented by H. Zheng and K. Zhu in [3]. The patient model and its response to one drug have been developed and a nonlinear proportional-integral-derivative PID digital controller has been implemented with a minicomputer system to control the MAP by infusion SNP [4]. Adaptive proportional-integral (PI) controller have been implemented for blood pressure regulation using SNP [5]. An integrating self-tuning control strategy has been involved in single drug infusion control system to maintain the MAP using SNP [6]. The Internal model control (IMC) has been implemented on the patient response model to one kind of vasoactive drugs that is SNP [7, 8].

Controlling of homodynamic variables commonly using more than one drug, A nonlinear electrical analog model with a baroreflex feedback, and the MAP was used as the input of a baroreflex to control circulatory variables using a computer model [9] and the indirect adaptive controller based on recursive identification and linear quadratic regulation has been used to control the infusion rates of two drugs [10]. The control advance moving average controller (CAMAC) is one kind of adaptive algorithms has been implemented to control MAP and CO using two drugs [11]. Multiple model adaptive predictive controllers has been designed and implemented to regulate MAP and CO by adjusting the infusion rates of SNP and DPM [12]. The problem of controlling the cardiovascular parameters of a patient using multiple drug administration represents a difficult control problem. Blood pressure control by vasoactive drugs is

essentially a single-input single-output problem and has been successfully solved by Sheppard et al [13], using a PID controller. A continuous optimal controller and an ARMA discrete controller have been used by Koivo [14, 15, 16], also, Stern has used a self-tuning regulator [17], and a model reference adaptive controller implemented by Kaufman [18, 19].

This paper focuses on the performance of the model reference adaptive control (MRAC) of multi-inputs, multi-outputs system (MIMO). The patient model represented by first-order transfer function matrix 2x2 with time delay [19]. The controller parameters have been adapted using the diagonal of time invariant weighting matrices 6x6 [19]. Matlab Simulink Toolbox utilized to design and develops the proposed model.

2. Patient response model

The patient model represented by two inputs and two outputs system as first order model is shown in fig. 1. The objective of the system is to decrease a patient's mean arterial pressure of (20 mmHg) with reference signal (-20) and increase the cardiac output of (20 ml/min.kg) with reference signal (20). The patient response model is defined by a linear small-signal first-order transfer function matrix equation 1as represented in [18]. The drugs which have been used to maintain the homodynamic variables CO, and MAP are dopamine (DPM) and sodium nitroprusside (SNP). The effect of DPM increases both CO and MAP while SNP increases CO and decreases MAP.

$$\begin{bmatrix} CO \\ MAP \end{bmatrix} = \begin{bmatrix} \dfrac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} & \dfrac{K_{12}e^{-T_{12}s}}{\tau_{12}s+1} \\ \dfrac{K_{22}e^{-T_{22}s}}{\tau_{22}s+1} & \dfrac{K_{11}e^{-T_{11}s}}{\tau_{11}s+1} \end{bmatrix} \begin{bmatrix} DPM \\ SNP \end{bmatrix} \quad (1)$$

K_{ij} - Plant gain.

T_{ij} – Time delay between the input and the system response.

τ_{ij} - Time constant.

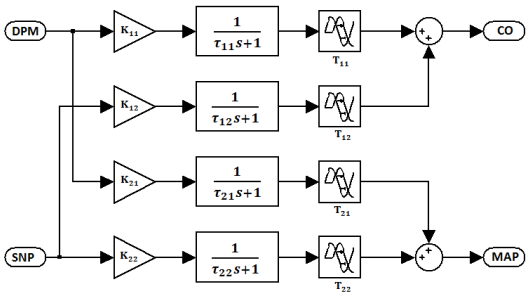

Fig1. Simulink block diagram of the plant model.

The parameters of the patient model have been represented as nominal and ranges values are given in table 1.

parameters	***Nominal***	***Ranges***	***Unit***
K_{11}	5	1 to 12	ml/µg
τ_{11}	300	70 to 600	Sec
T_{11}	60	15 to 60	Sec
K_{12}	12	-15 to 25	ml/µg
τ_{12}	150	70 to 600	Sec
T_{12}	50	15 to 60	Sec
K_{21}	3	0 to 9	$mmHg/[\mu g/min.kg]$
τ_{21}	40	30 to 60	Sec
T_{21}	60	15 to 60	Sec
K_{22}	-15	-1 to -50	$mmHg/[\mu g/min.kg]$
τ_{22}	40	30 to 60	Sec
T_{22}	50	15 to 60	Sec

Table: 1.

The desired response of the patient is represented by reference model transfer function of CO and MAP as in equation 2, [19].

$$\mathrm{H(s)} = \frac{\mathrm{y_{m_i}(s)}}{\mathrm{u_{m_i}(s)}} = \frac{1}{\tau_i s+1} \qquad (2)$$

y_{m_1} and $y_{m_2} are$ the outputs of the first and second reference model respectively.

u_{m_1} and $u_{m_2} are$ the inputs of the first and second reference model respectively.

τ_1= 300sec and τ_2= 90sec.

The limitations of drug dosages presented by E.H. Bamey et al [19] are as follows:

$0 \leq DPM \leq 6\,mg/min.kg$ and $0 \leq SNP \leq 10\,mg/min.kg$

3. Model reference adaptive control

The patient's model with model reference adaptive control (MRAC) is developed based on the underlying control structure as shown in fig. 2. MATLAB function utilized to obtain the reference signal $\mathrm{u_m}$ depending on the patient's case.

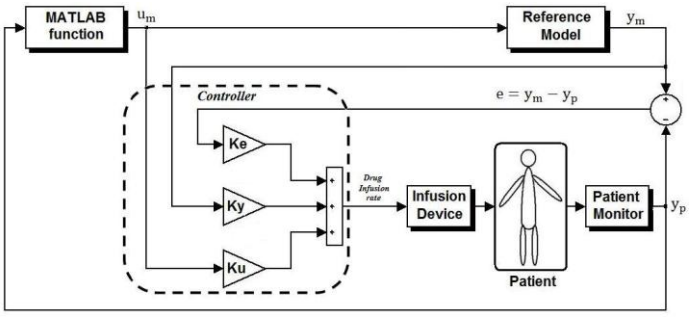

Fig2. General form of the patient's model with MRAC.

The control u is formulated as a linear combination of the error feedback ($\mathrm{K_e e}$) and of the two feedforwards reference model output ($\mathrm{K_y y_m}$) and reference model input ($\mathrm{K_u u_m}$). The algorithm applied generically on MIMO systems which do not satisfy the perfect model following conditions. The order of the plant can be much greater than the order of the reference model. The adaptive control law multiplies the values available for the measurement the tracking error "e", the reference model output "y_m" and the reference model input or reference signal "$\mathrm{u_m}$" with appropriate adaptive gains ($\mathrm{K_y}, \mathrm{K_u}, \mathrm{and}\ \mathrm{K_e}$). The adaptive control law is:

$$\mathrm{U_p(t) = K_y(t) y_m(t) + K_u(t) u_m + K_e(t)[y_m(t) - y_p(t)]} \quad (3)$$

$$\mathrm{U_p(t) = K_r(t) * r(t)} \quad (4)$$

$$\mathrm{K_r(t) = [K_e, K_y, K_u]},$$

$$K_r(t) = K_p(t) + \dot{K}_i(t) \tag{5}$$

$$r(t) = \begin{bmatrix} e(t) \\ y_m(t) \\ u_m(t) \end{bmatrix}, \qquad \text{where} \quad e(t) = y_m(t) - y_p(t) \tag{6}$$

The adaptive gains $K_r(t)$ are obtained as a combination of an integral gain and a proportional gain as shown below.

$$K_p(t) = e(t) * r^T * \overline{T} \tag{7}$$

$$\dot{K}_i(t) = e(t) * r^T * T \tag{8}$$

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

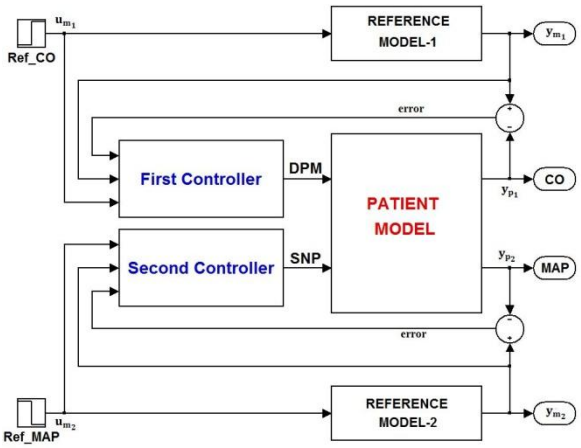

Fig3. Simulink block diagram of the patient model with the MRAC.

4. Simulation results

Table 1 presents the nominal and ranges values of the patient's sensitivity to drugs, in order to take into account the different type of patients and the patient's sensitivity to drug varies from patient to patient. Due to that

the drug infusion controller should be designed to be work well in a real-time environment for a wide range of patients. In the simulation, automatic multiple drug delivery system simulates the MAP and CO using DPM and SNP with different sensitivity. The MRAC has been implemented to control the infusion rate of the drugs. The controller has adapted using the time invariant weighting to make the controller will be suitable for a wide range of patients. The system has been tested using different patient's sensitivity, the parameters value of the patient's model has fixed and change just in the values of K_{22} as (-15, -20, and -50) to expert the performance of the controller. Figures 4, 5 and 6 have shown the simulation results of the patient responses to drugs, and from that we observed the MRAC gives satisfactory results. The results have compared to previous work, and from that we observed our simulation has obtained better response with almost no overshoot and shorter settling time when the patients' sensitivity was -20. The settling time could be $\pm 2\%$ or $\pm 5\%$ from reference point that is ($\pm$20.40 or $\pm$21 to $\pm$19.60 or $\pm$19) when the reference point set at 20 or -20. The values of diagonal matrix and which have been obtained and used to adapt the controller parameters are as following:

$\mathrm{T} = \mathrm{Diag}[1 \times 10^{-5}, 2.8 \times 10^{-8}, 1.1 \times 10^{-6}, 1 \times 10^{-6}, 1 \times 10^{-8}, 1 \times 10^{-10}]$,
$\overline{\mathrm{T}} = \mathrm{Diag}[2 \times 10^{-6}, 1.6 \times 10^{-4}, 2.9 \times 10^{-6}, 1 \times 10^{-7}, 4 \times 10^{-10}, 1 \times 10^{-4}]$.

Figures 4, 5 and 6 illustrate the response of patient's CO and MAP and the desired response characteristics which has been represented by model response. Also we observed that the range of settling time 508.7 - 1822 sec for both CO and MAP, without overshoots.

The simulation results represented that when K_{12} is -4 the desired responses was CO = 19.84 (ml/min.kg) and MAP = -19.96 mmHg from the set point and the in-fusion rates of drugs was DPM = 5.993 (mg/min.kg) and SNP = 2.534 (mg/min.kg). These results shows that infusion rates of DPM and SNP are acceptable, as the infusion rate of DPM did not exceed the limit. This clearly demonstrates better performance as compared to the result represented by E.H. Bamey, et al [19] as shown in table 2 and G. Achuthan [10].

KEY REFERENCE			SIMULATION RESULTS using MRAC	SIMULATION RESULTS using non-adaptive PID	PREVIOUS RESULTS using MRAC as in [19]
Hemodynamic variables	Patient Sensitivity (K_{22})	Responses			
Cardiac output	-20	Settling Time (sec)	1232	2790	1440
		Overshoot (ml/min.kg)	Zero	0.32	Little
	-50	Settling Time (sec)	1822	3000	1380
		Overshoot (ml/min.kg)	zero	1.23	Little
Mean Arterial Pressure	-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

Table: 2.

Table 2 shows the simulation results of multi-drug infusion control using MRAC comparing to previous results and the results which we have obtained using non-adaptive PID controller when patients' sensitivities to drug (K_{22}) were -20 and -50. From these results we observed that MRAC was satisfied to control simultaneously MAP and CO using two drugs. That results have depicted the controller performances in simulation results are better with less settling time and without overshoot comparing to the performance of non-adaptive PID controller when the patients' sensitivities are -20 and -50, while the performances of the proposed algorithm have improved comparing to previous results when K_{22} is equal -20 and without overshoot when the values of K_{22} equal -20 and -50.

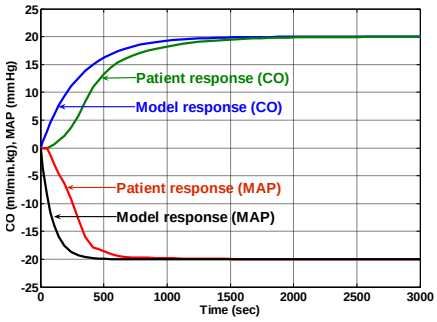

Fig4. Patient response (CO and MAP) when K_{22}= -15.

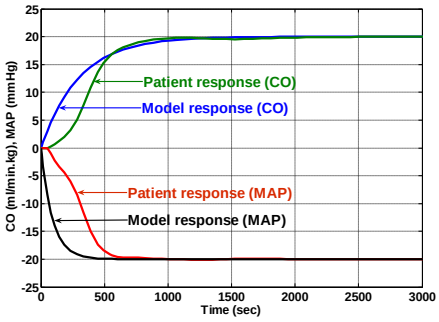

Fig5. Patient response (CO and MAP) when K_{22}= -20.

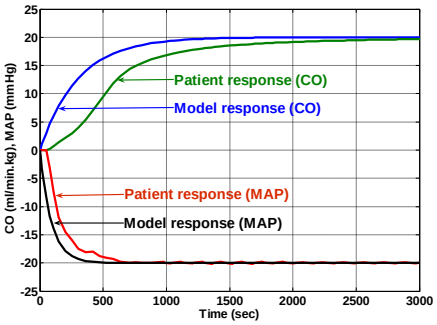

Fig6. Patient response (CO and MAP), when K_{22} = -50.

5. Conclusions

The paper has presented an adaptive multi-drug control scheme for blood pressure control. The proposed scheme was designed and evaluated in simulation study to maintain the nonlinear responses of CO and MAP using two drugs, namely DPM and SNP for the patients of various sensitivities. The simulation results have confirmed that MRAC is potentially useful for regulating the MAP and CO by computing the DPM and SNP infusion rate. The proposed algorithm demonstrated better performance as compared to non-adaptive PID controller and has improved compared to reported results when K_{22} equal -20 with updating the values of the controller's gain. Particularly, the proposed controller offered short settling time and very minimum/no overshoot as compared to the existing reported schemes when the patient sensitivity K_{22} less than or equal -20 . As further work, the proposed controller will be developed to improve its adaptability more for a wide range of patients using more than two drugs.

References

1- P.C.A. Ang, B.W. Ang, K.Y. Zhu (2009) "A Cardiovascular Model for Blood Pressure Control Systems", ICBPE, pp. 1-8.

2- E. Furutani, M. Araki, S. Kan, et al (2004) "An Automatic Control System of the Blood Pressure of Patients under Surgical Operation", Control, Automation, and Systems, International Journal, Vol. 2, pp. 39-54.

3- H. Zheng, K. Zhu (2005) "Automated Postoperative Blood Pressure Control", Journal of Control Theory and Applications, Vol. 3, pp. 207-212.

4- J.B. Slate, L.C. Sheppard (1982) "Automatic Control of Blood Pressure by Drug Infusion", IEE Proc., Vol. 129, pp. 639-645.

5- K.Y. Zhu, H. Zheng D.G. Zhaug (2008) "A Computerized Drug Delivery Control System for Regulation of Blood Pressure", IC-MED. Vol. 2, pp. 1-13.

6- K. Behbehain, R.R. Cross (1991) “A Controller for Regulation of Mean Arterial Blood Pressure Using Optimum Nitroprusside Infusion Rate”, IEEE Trans. On Biomed. Eng. Vol. 38,pp. 513-521.
7- K. Poterlowicz, M.A. Hossain, M.A.A. Majumder (2007) “Optimal IMC System for Blood Pressure Control”, IEEE Proceeding of CS2007, pp. 113-117.
8- S. Enbiya, A. Hossain, F. Mahieddine (2009) “Performance of Optimal IMC and PID Controllers for Blood Pressure Control”, IFMBE Proceedings 24, pp. 89–94.
9- C. Yu, R.J. Roy, H. Kaufman (1990) “A Circulatory Model for Combined Nitroprusside-Dopamine Therapy in Acute Heart Failure”, Med. Prog. Tech., Vol. 16, pp. 77-88.
10- G. Achuthan, Y. Alekseyenko, A. Ishihara, et al (1999) “Indirect Adaptive Control of Drug Infusion For A Circulatory System Model”, Proceedings of the 7th Mediterranean Conference on Control and Automation, pp. 1007-1016.
11- G.I. Voss, P.G. Katona, H.J. Chizeck (1987) “Adaptive Multivariable Drug Delivery: Control of Arterial Pressure and Cardiac Output in Anesthetized Dogs”, IEEE Trans. Biomed. Eng., Vol. BME-34, pp. 617-623.
12- C. Yu, R.J. Roy, H. Kaufman, et al (1992) “Multiple-Model Adaptive Predictive Control of Mean Arterial Pressure and Cardiac Output”, IEEE Trans. Biomed. Eng., Vol. 39, pp. 765-778.
13- L.C Sheppard, J.F Shotts et al (1979) “Computer Controlled Infusion of Vasoactive Drugs in Post Cardiac Surgical Patients”, IEEE-EMBS Denver, Oct. 6-7, pp. 280-284.
14- A.J. Koivo, V.F. Smollen R.V. Barile (1978) “An Automated Drug Administration System to Control Blood Pressure in Rabbits”, Math. Biosc., Vol. 38, pp. 45-56.
15- A.J. Koivo (1980) “Automatic Continuous-Time Blood Pressure Control in Dogs by Mean of Hypotensive Drug Injection”, IEEE Trans. Biomed. Eng., Vol. BME-27, pp. 574-581.
16- A.J. Koivo (1981) “Microprocessor-Based Controller for Pharmodynamical Applications”, IEEE Trans. Auto. Control, Vol. AC-26, pp. 1208-1212.
17- K.S. Stern, B.K. Walker, P.G. Katona (1981) “Automated Blood Pressure Control Using a Self-Tuning Regulator”, IEEE Frontiers Engin. Health Care, pp. 255-258.
18- H. Kaufman, R.J. Roy X. Xu (1984) “Model Reference Adaptive Control of Drug Infusion Rate”, Automatica, Vol. 20, pp. 205-209.
19- E.H. Barney, H. Kaufman (1990) “Model Reference Adaptive Control of Cardiac Output and Blood Pressure through Two Drug Infusions”, Intelligent Control, Proceedings. 5th IEEE International Symposium Vol. 2, pp. 739-744.