PI Controller Based Closed Loop Drug Delivery for the Long Term Blood Pressure Regulation

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***Abstract*- Mean arterial pressure (MAP) is a key variable to decide the performance and operating point of cardiovascular system (CVS) and its maintenance is of vital importance for the human body. This paper focuses on an automatic system to provide closed loop control of MAP. A proportional plus integral controller is proposed for long term arterial blood pressure regulation. This controller is designed so that the actual MAP stays within a narrow range of pressure even under dynamic variations in aldosterone hormone levels. Based on the pressure level change under aldosterone loading, the PI controller administrates sodium infusion and the validity is tested for a seventh order blood pressure regulation model. Simulation results indicate that the controller is capable of avoiding the offset and oscillatory behavior during transients. The settling time is also within acceptable limits. The automated drug delivery is seen to be effective and superior to manual control of ABP regulation. The study presented here opens a potentially viable approach to the design of safer automatic closed loop drug administration technology for the long term blood pressure control.**

***Index Terms*— aldosterone; blood pressure; cardiovascular system; hypertension; nonlinear model; sodium infusion; state model**.

I. INTRODUCTION

The cardiovascular regulatory system is essential to the life and the human body is equipped with various internal feedback control systems which maintain a steady operating point in the face of internal and external disturbances. Under normal conditions, only a narrow range of operating point is desirable. The abnormal regulation of long term arterial blood pressure triggers hypertension or hypotension and the risks associated with altered pressure are studied by many researchers [1]-[2]. Since cardiovascular disease is the world's leading killer its treatment through awareness, treatment and control are of very importance.

In hyper and hypotensive subjects, of mean arterial pressure (MAP) is maintained at a desired level through medical intervention. This is achieved by intravenous infusion of suitable vasodilator or vasoconstrictor drugs. For this, the blood pressure is to be regularly monitored to adjust the dosage of the drug or medicine. MAP monitoring and manual adjustments of drug dose are time consuming and may not be precise. Automatic closed loop drug administration technique can be employed for precise control of MAP [3]-[4]. It is attractive because controlled drug delivery process results in consistency of medication to improve the effectiveness of therapy.

A number of control approaches have been proposed in the past to tackle the short term blood pressure regulation with various strategies, such as PID, optimal, adaptive and fuzzy logic [3], [4]. Although studies have shown that automatic control has the potential of delivering superior performance to manual control of short term regulation, no automated systems have been reported for long term ABP regulation. Employment of human operator to carry out the drug dosage remains the technique of choice in most of the clinical conditions. The reasons for the lack of automatic closed loop controllers are not clear. The nonlinear and cumbersome regulatory process might be the factors which have discouraged from developing the controllers.

The long-term regulation of arterial blood pressure is decided by the fluidic balance condition related to the extracellular fluid volume (ECV), which is provided by the coordinated activity of kidney and cardiovascular system. Fluid volume is maintained through the formation and excretion of urine and electrolytes [1] which are modulated by neural and hormonal activities. Physiological model has been always needed in such cases of system complexity and have received a great deal of attention [5]. In the literature, various models exist based on differential equation models of the physiological regulation process to describe and reproduce some dynamic aspects [1], [2], [6], [7], These models are restricted only to the simulation of some physiological aspects. The physiological system for the long term arterial blood pressure is highly nonlinear and the complex nonlinear interactions of hormonal, neural and fluidic factors make it difficult to assess the individual effect on the ABP regulation. Only few attempts were made for the analysis, parameter estimation and controller design.

Traditional controller design methods based on linear control theory can be effectively applied to small signal model of the system [8]. Control theory is finding numerous applications in physiological systems and systematic design of controlling devices for automation [5], [6]. In general, the linearized model analysis is limited to small variations of inputs and parameters changes and cannot be used for the interpretation of large physiological stresses [9]. Hence, the selection of the linear model structure appropriate for physiological explanation is a critical step. Recently, linear state variable model of the

ABP regulation [6], [10] has been proposed. A variable gain controller based on this state model has been proposed in our previous work [11]. The implementation of this nonlinear controller results in small offsets and requires time consuming two stage calculation. The study presented here represents a Proportional plus Integral (PI) controller which modifies the dynamics of regulation of arterial blood pressure to track the performance of the nonlinear system over a wide range of expected operating levels. The aim is to derive a set of controller parameters which can control a variety of relevant physiological conditions. The performance is well explained by the seventh order linear mathematical model [10] of the long term arterial blood pressure (ABP) regulatory system.

The organization of this paper is as follows. Section II gives the basic state variable description of the model for the long term ABP regulation and the structure of the controlled system. In section III, the simulation results and their comparison have been presented. Section IV includes the discussion including the limitations of the concept. Conclusions are summarized in section V.

II. METHOD

Linear model of the seventh order hormonal controlled long-term regulation model of the ABP regulatory system [6], [10] has been chosen to explain the proposed method. The basic nonlinear model appears to have originated in a previous work by the authors [10]. Detailed description of the system physiology can be found in the literature [1], [2], [7]. The state model equations describing the system are explained in the following sections.

A. State space representation

A seventh order state model is the heart of the analysis and hence the nonlinear model of the long term ABP regulatory system has been transformed to linear version. The dynamic variables associated with first order transfer function blocks in the nonlinear model [10] are taken as the seven states ($\mathbf{X}$) of the model.

$$\left.\begin{aligned}\mathbf{X}(t)&=[x_1(t)\ \ x_2(t)\ \ x_3(t)\ \ x_4(t)\ \ x_5(t)\ \ x_6(t)\ \ x_7(t)]^T\\&=[BRF(t)\ \ ECV(t)\ \ VAS(t)\ \ ENA(t)\ \ AN(t)\ \ AD(t)\ \ AL(t)]^T\end{aligned}\right\} \quad (1)$$

where, BRF: baroresetting feedback, ECV: extracellular volume, VAS: vasculature, ENA: extracellular sodium amount, AN: angiotensin, AD: antidiuretic and AL: aldosterone hormone.

Linearization is accomplished about the normal operating point by taking into account small variations about the point and expanding the nonlinear term into a Taylor's series expansion and neglecting all terms of second and higher derivatives [8]. The nonlinear model has been simulated to determine the equilibrium point under normal conditions. The equilibrium point is taken as MAP=100 mmHg, ECV=15 Litre, ANA=1, AL=1 and NIR=0.1 unit.

State variable representation provides functional relationships in matrix form, by focusing on the interactions and feedback paths among the state variables [5], [8]. The following state model equations given in matrix form describe the complete behaviour of the dynamical system.

$$\begin{aligned}\dot{\mathbf{x}}(t)&=\mathbf{A}\mathbf{x}(t)+\mathbf{B}u(t)+K_S\\y(t)&=\mathbf{C}\mathbf{x}(t)+\mathbf{D}u(t)+K_O\\u(t)&=AL(t),\quad y(t)=MAP(t)\end{aligned} \quad (2)$$

where, u(t); input variable, y(t);output variable,
AL: Aldosterone hormone level.

For the seventh order physiological model, the state matrices are derived under normal operating conditions. These are given in the following set of equations (3).

$$\left.\begin{aligned}A&=\begin{bmatrix}-1.7511e\text{-}4 & -0.0269 & 0.3061 & 0 & -0.0307 & 0 & 0\\ 2.3394e\text{-}6 & -3.1922e\text{-}4 & 0.0035 & 0 & -0.0012 & 0.0101 & 0.7200e\text{-}4\\ 1.9331e\text{-}5 & -0.1293 & -1.3941 & 0 & 0.6488 & 0 & 0\\ 2.3390e\text{-}4 & 5.9447e\text{-}3 & 0.3551 & -0.2666e\text{-}4 & 0.0779 & 0.0924 & 0.1440\\ 5.2311e\text{-}7 & 0.0630 & 8.078e\text{-}4 & -0.4444e\text{-}4 & -0.0673 & 0 & 0\\ -3.0122e\text{-}6 & -0.2639 & 0.0113 & 1.8518e\text{-}3 & -0.0011 & -0.0833 & 0\\ 8.2272e\text{-}8 & -1.1002e\text{-}5 & 0.1259e\text{-}4 & -7.8200e\text{-}5 & 0.0045 & 0 & -0.0166\end{bmatrix}\\B^T&=[0\ \ 0\ \ 0\ \ 1\ \ 0\ \ 0\ \ 0]\\K_S^T&=[0.1289\ \ -0.0084\ \ -0.1906\ \ 1.6861\ \ 0.0676\ \ 0.0881\ \ 0.1789]\\C&=[-0.0098\ \ 1.3309\ \ -15.1170\ \ 0\ \ 1.5189\ \ 0\ \ 0]\\D&=0,\quad K_O=93.632\end{aligned}\right\} \quad \text{.....} \ (3)$$

The initial condition of the state variables is as follows.

$$\mathbf{X}(0)=[0\ \ 15\ \ 1\ \ 2130\ \ 1\ \ 1\ \ 1]^T \quad (4)$$

This compact linear state model has been employed to approximate the dynamics and control actions of the nonlinear mathematical version.

B. Controller design

In this section, the structure of the proportional plus integral (PI) controller proposed for long term control of blood pressure is explained. The proposed controller is designed to maintain MAP under dynamic variations in aldosterone hormone conditions. From the simulation results of the nonlinear [10] and linearized version [6], it is observed that, both the aldosterone (AL) hormone loading and sodium loading cause hypertension. It is observed that, if the sodium infusion is maintained slightly below the normal value, the blood pressure response due to sustained AL loading is eliminated.

In this study the affine linear state model developed in previous section which describes the dynamics of MAP during AL loading and sodium loading is used. The PI controller is used to actuate the infusion rate of sodium by sensing the output signal, MAP. For feedback action the output variable (MAP) which is a function of the state x(t) is considered. The actuating sodium intake rate (NIR) is deciding the extracellular sodium amount (ENA), the fourth state variable (x_4) in our model.

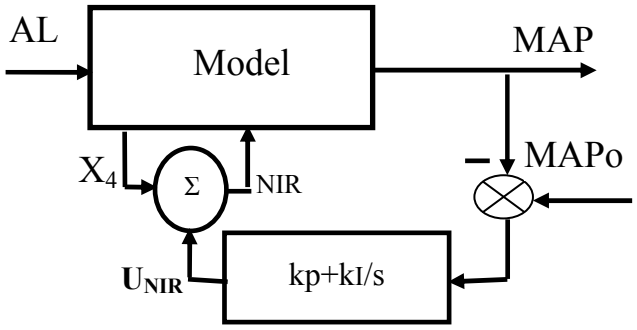

Fig. 1. PI Controller Based Closed Loop System

The controller output (U_{AL}) is decided by the variations in MAP.

$$U_{NIR} = \left(k_P + \frac{k_I}{s} \right) \Delta MAP \qquad (5)$$

$$\Delta MAP = MAP - MAP_o$$

where, k_p is the proportionality constant and k_I is the integral constant, MAP_o: the steady state equilibrium value of MAP.

In the present work the response settling time, maximum overshoot and the steady state error have been considered for defining a successful response. The performance indices were selected such that the closed loop control of MAP should achieve a settling time less than one day with a maximum overshoot of 1mmHg during transients. It is important that MAP should not display serious oscillatory or unstable behavior under any circumstances. An off-line estimation is required in the design of the two coefficients of the control system for meeting various performance indices.

MATLAB® based algorithms were used with least-square error (LSE) criterion to estimate the controller coefficients. The difference in pressure levels is used for the blood pressure maintenance. Computer based controller system performs these operations. Fine tuning of the parameters are required only when large dynamics are involved. Thus, the manual adjustment of the feedback gains is considerably avoided.

A single-input single-output, tunable controller is used to control the sodium infusion. Since the system time constants are relatively larger to that for any drug pump mechanism, the sensor and the pump dynamics are neglected. This represents a fast mode of control. It can be expected that the physical implementation of the controller requires electronic components.

III. RESULTS

The ability of the proposed PI controller to maintain the MAP of hormonal controlled regulation model is to be assessed under aldosterone dysfunctions. The AL dysfunction condition is simulated by increasing the aldosterone hormone level (AL) of the fluid compartments by many times continuously for hours. Increased aldosterone represents hypertensive condition while a reduction leads to hypertensive condition. Table I gives the effect of aldosterone loading on MAP without any feedback controller.

Table I. Effect of Aldosterone Loading

AL	X normal value			
	0.75	1	2	3
MAP	99.1	100	102.9	107

To study the performance of PI controller, the controller parameters are tuned for the best performance and are obtained as follows.

$$k_P=2; \quad k_I=0.01 \qquad (6)$$

Simulation results in Fig. 2 show the role of both the PI and proportional controller. In this simulation aldosterone level was increased by three times for more than one day. If the coefficient k_I is set to zero, the PI becomes a proportional (P) and the P controller provides steady state error as compared to PI controller. Larger k_P reduces error, but causes oscillatory nature. PI controller is effective and provides satisfactory control performance.

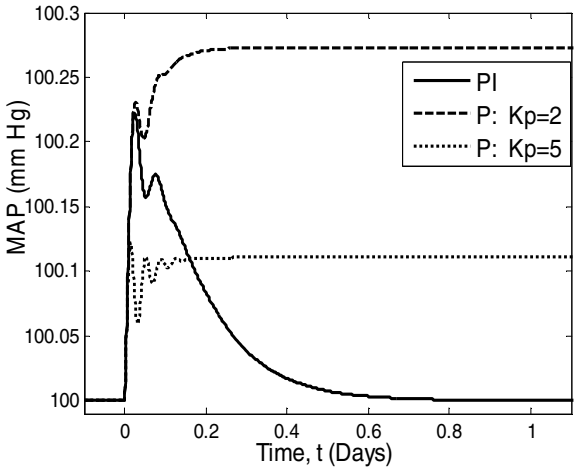

Fig. 2. Comparison of PI- Controller and P- Controller.

Based on the controller values obtained form this simulation, same controller is employed for the dynamic infusion condition.

In the second simulation, the AL dysfunction is extended by dynamic variations in aldosterone hormone level. This is achieved by increasing the AL by 100% by injecting AL continuously for three days. Then it is increased to three times the normal value for another three more days. Increased aldosterone represents hypertensive condition. Then it is reduced to 75% of the normal intake for three more days to simulate the hypertensive condition. Figure shows the variations in the hormone intake rate (AL), controller output (U or U_{NIR}) and controlled output MAP with and without controller.

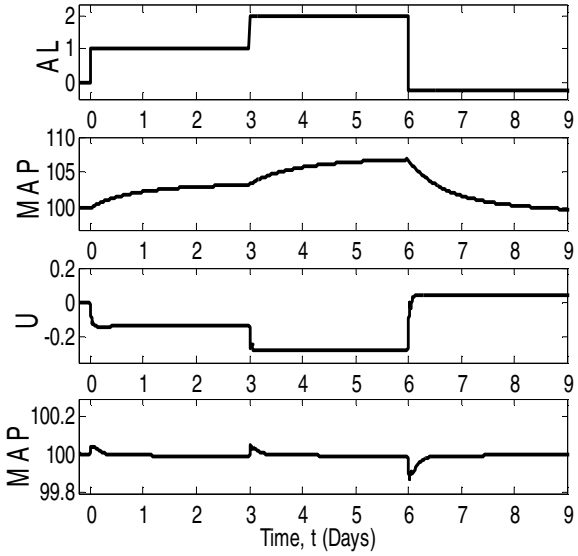

Fig. 3. Performance of the PI controller under Dynamic Aldosterone Loading.

Figure 3 shows the controlled system response. It shows the comparison of MAP response with and without the PI controller for the nonlinear hormonal controlled model. Under dynamic input conditions also the PI-controller performs very well.

IV. DISCUSSION

The intention of the present work is to resolve the effect of aldosterone hormonal stimulation on the long term arterial blood pressure (ABP) regulation. This physiological regulation is decided by the coordinated activities of cardiovascular and renal systems. It is well established that sustained aldosterone dysfunction and sodium intake lead to an increase in MAP representing hypertensive condition with a time constant in hours. The hypertensive response to aldosterone loading can be eliminated if the sodium level is maintained slightly below the normal. In our previous work [11] a nonlinear controller is designed so that the actual MAP stays at a desired level as closely as possible under dynamic variations in sodium intake. In the present work, the effects of sodium electrolyte or equivalent drugs on the regulatory system during aldosterone dysfunction are studied to evaluate the controller function.

Although closed-loop control of short term ABP regulation was suggested in many works, no closed-loop system is developed so far for the long term regulation. It appears surprising that while the advantages of automatic MAP control for short term regulation remain undisputed, no research work or initiative has taken up to develop a controller for the long term arterial blood pressure regulation. CVS variables are difficult to measure and, in general, transients are not reported for system responses. In practice focus has limited to controller design based on the steady state observations. But, in this study the transient response matching is also considered. We consider whether there may be oscillatory behavior associated with the models used, which would make clinical functions uncomfortable.

The proposed proportional plus integral control scheme makes the control system to reset the MAP value to steady state value. The controller output (U_{NIR}) which is the actuator input to the pump is decided by the deviation in MAP. A conventional parameter estimation algorithm using a least-square error (LSE) criterion is sufficient for the off-line estimation and parameter adjustments used for designing the controller for various sodium infusions.

Figure 3 reveals that the PI controller can successfully regulate the MAP to the desired level and maintain the pressure at that level for a patient model with widely variable aldosterone sensitivity. The controller does not provide excessive oscillatory response for the cases considered. Moreover, the results indicate that the controller can effectively eliminate the offset in MAP within a tolerable settling time of few minutes. Predicted pressure levels are closely following the desired level. The deviation at steady state is considerable for a P controller than that of a PI controller. In such conditions PI controller is preferred. Fixed gain controller shows larger settling time. The study presented here represents a promising design step for a long term blood pressure controller not only for the sodium-aldosterone system but for other variables also. In the future, the control strategy should be tested in experimental evaluations to establish its robustness for patient safety and efficacy.

As the drug is to be administered intravenously, an infusion pump is required in the loop. Since the system time constants are large the pump dynamics need not be considered in the design. Also, the dynamics of the MAP measurement and calculating mechanism are also not considered. Since the major aim is to explain the concept of PI controller as a feedback mechanism for the long term ABP regulation, relatively little attention is paid to the physiological variables other than MAP. Though the

sodium intake rate (NIR) is considered as the drug, in actual conditions sodium based drug with its practical limitations should be ascertained. The same approach presented here could be extended to handle other aldosterone related dysfunctions within the system. Although the concept of closed loop control of MAP has been suggested and worked well, further simulations are required to evaluate whether multivariable control may be applicable. In spite of such limitations, it can be concluded that this approach sets the trend for the future of automated drug delivery systems. We propose that PI controller scheme may provide a general platform for the development of safer and more appropriate drug delivery technology.

V. CONCLUSION

We describe the design of a PI controller and investigate whether this can overcome some issues observed with earlier methods for the control of long term arterial blood pressure. This technique applies readily to the seventh order nonlinear hormonal controlled regulation model with aldosterone dysfunction. We show through computational modeling that a control system of this design has improved performance relative to existing methods in its simplicity and robust. The simulation results indicate that it is capable of improved stability tolerable settling time. The findings support further research into PI controller architecture as a feasible approach to the design of automatic closed loop drug administration technologies capable of operating under challenging clinical conditions.

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