International Journal of Engineering Research and Technology.
ISSN 0974-3154 Volume 6, Number 1 (2013), pp. 9-24

http://www.irphouse.com

Multiple Linear State Model Analysis of Nonlinear Blood Pressure Long Term Dynamics using Modified Parameter Estimation

Shahin M. and Maka S.

Associate Professor, Department of Electrical & Electronics Engineering,
Govt. College of Engineering Kannur, Kerala, Pin-670563, India.
** Corresponding Author E-mail: shahinm_tly@rediffmail.com*
Professor, Department of Electrical Engineering,
Indian Institute of Technology, Kharagpur, Pin-721302, India.
E-mail: maka@ee.iitkgp.ernet.in

Abstract:

This paper describes the development of a multiple linear state space model strategy and investigates whether this can overcome some issues observed with earlier methods for the control relevant analysis of the nonlinear dynamics of long term arterial blood pressure regulation. Key features of the work are the state variable representation of the process and parameter tuning technique for parameter identification. Fractional adjustments have been made in the parameters of the basal linear model of the nonlinear process to fit with the data under each selected physiological condition. In matched condition, the nonlinear model can be replaced by the tuned linear state model. A sensitivity study has been performed on the basal linear model to identify the tuning parameters and the realistic bounds. Thus a set of approximate linear models have been developed spanning in the range of expected operation of the nonlinear blood pressure regulatory system. Simulation results indicate that the proposed model is capable of delivering performance in the face of water loading and blood infusion conditions. The linearized model study shows that the model is stable under normal conditions. Thus the actual behavior of nonlinear physiologic mechanisms can be approximated in a better quantitative manner using this multiple model analysis. The attraction of this method is the un-necessity of any initialization procedure for parameter identification, use of conventional least square estimation technique and conventional linearization technique. Findings support further research into multiple tuned model analysis as a potentially viable approach to the analysis of extended blood pressure models.

Key words: blood pressure; cardiovascular system; nonlinear model; parameter tuning: renal failure; state model.

1. Introduction

The cardiovascular system is essential to the life of the human body and possesses a large number of physiological nonlinear control mechanisms to maintain arterial blood pressure (ABP) [1]. The hypertension represents a serious perturbation for the cardiovascular system; which can be experienced by an elevated ABP. Under normal conditions only a relatively narrow range of operating points are compatible with life and, the human body is equipped with internal feedback systems which maintain a suitable and steady operating point in the face of internal and external disturbances. It can be seen that kidneys play an important feedback role in blood pressure regulation. ABP depends on the regulation of the extracellular fluid volume (ECV), a function provided by the kidney through the formation and excretion of urine [2]-[4]. Thus, cardiovascular adjustments to ABP regulation are quite complex and due to this system complexity, physiological model has always been needed in order to understand the dynamic aspects of the physiology of the cardio-renal regulatory system.

A number of approaches have been proposed in the past to tackle this problem, particularly for the experimental and modelling studies regards to the management of blood pressure. A variety of mathematical models have been proposed since the early 1970s and over the last four decades, typically based on modeling the physiology by differential equations. Only one model, ie, from Guyton et al [1], [5], has been considered as the most comprehensive for the regulation of blood pressure. Although the simulation studies have shown that the model has the potential of delivering physiological explanations, it enjoyed very little success with regard to mathematical analysis Several established models of regulation mechanisms are available, but most of the literature is concerned with the characteristics of particular segments such as hormonal systems [6], fluidic regulation [7], and renal systems [2], [8]. Various researchers have shown interest in the development of models of cardio-renal regulatory. The work of Cameron [3] is a medium complex model which involves twelve nonlinear differential equations, but has not included autonomous nervous activity (ANA). Mathematical model due to Uttamsingh et al [2] provides a detailed representation of the kidney in connection with hormonal control. A variety of nervous control pathways due to renal sympathetic activity have been proposed in Karaaslan et al.'s work [4]. These models are restricted to physiological simulation study, but parameter estimation is still difficult. The complex nonlinear interaction of physical, neural and fluidic factors have created difficulty in the analytical solution of the CVS models.

Application of the linearization technique [9]-[11] in studies of nonlinear system dynamics is becoming popular. Linearized model study of a simple CVS model has been performed [12] to analyse the parameter effects. Despite the promising analytical capabilities, no further initiative has been taken to fill this gap to deliver more structural analysis. Another approach, that is useful in modeling studies today, makes use of the state variable approach [13], [14]. Recently, a linear state variable model of the ABP regulation [15], [16] has been proposed enabling mathematical analysis. The complexity of ABP regulation is different in different physiological

conditions. The linearized model analysis is always limited to small variations of inputs and parameters changes. In our previous works, it is observed that the simple linearized model cannot be used for the interpretation of large physiological stresses. Parameter estimation and diagnosis becomes difficult under such conditions [17], [18]. This recognises the necessity to employ multiple model analysis for nonlinear systems [18]- [21]. The current article is focused on parameter tuning of the linear state model to match with the nonlinear physiological responses.

The aim is to develop a multiple state model strategy to explain the performance of the nonlinear system over a wide range of expected operating levels. In this work, we describe the framework for deriving a set of tuned linear models of the blood pressure regulation system, which can simulate a variety of relevant physiological conditions, so as to overcome some issues observed with the earlier methods. Here, the coefficients or parameters of the basal linear state model have been adjusted to fit with the nonlinear response under each specific case. By combining these process models to form a linear approximation of the nonlinear system, the true plant behavior can be approached. We replace the essentially nonlinear model of the CVS by a set of tuned linear models. This helps to understand the individual contributions of the model parameters to the overall regulation, and to increase the possibility of identifying model parameters from data. Another advantage of this approach is the unique linear state model structure with which the mathematical analysis can easily be done. Stability analysis, parameter estimation and feedback control design are now possible with linear control theory [13], [14], [22]. The complexity of nonlinear ABP regulation in different physio-pathological conditions can be clarified by the use of the new co-ordination framework.

The dynamic behavior of a third order nonlinear model of the long-term regulation of ABP has been investigated using the proposed method. Since the aim at this stage is not a profound study of the entire CVS, as a first step, we have adopted the well known intermediate model by Guyton [5]. The model includes three differential equations to represent the most crucial physiological mechanisms responsible for ABP regulation. Its linearized state model has been developed in [15]. A detailed sensitivity study has been performed on the basal linear model to identify the tuning parameters, their basal values and the realistic bounds. The same linear basal model structure is used for all disease simulations. Proper fractional adjustments have been made in the parameters of this basal model to fit with the nonlinear system data under each selected physiological condition, such as water loading. Traditional least square error (LSE) estimation technique has been used for parameter identification [17]. In matched condition, the nonlinear model can be replaced by the tuned linear model to reveal the qualitative and quantitative features of transient as well as the steady states of related variables which may be useful for further diagnosis. Each tuned model can simulate the corresponding physiological stress or condition. Thus a set of approximate linear models have been developed using the modified parameter tuning technique. The stability analysis is also done with the Eigen value concept [13], [14] under each condition.

The organization of this paper is as follows. Section 2 gives the description of the methodology for MPTT. In section 3, the simulation results and their comparison

have been presented. Section 4 includes the discussion including the limitations of the model. Conclusions are summarized in section 5.

2. Model and Methodology

A third order nonlinear mathematical model of the long-term regulation of ABP is selected to analyze the structural behavior and other control aspects using the proposed methodology for the modified parameter tuning technique. Since our aim is not to model the complicated behaviour of entire CVS, the basic nonlinear model originated in Guyton work [5] has been selected; a model which is comparatively less complex, but having certain principal characteristics of the long term arterial blood pressure regulation system. In our previous work this model has been converted into a linear state space model. Detailed description of the system physiology can be found in the literature [1], [5] while control aspects in [16]. The nonlinear equations describing the system are explained in the following sections.

Autonomous nervous activity

The chosen model is divided into three major pathways associated with the circulatory control [1], which provides the conceptual form of the arterial blood pressure regulation process and here we begin the discussion with the topic of autonomous nervous system activities. The autonomous nervous system with baroresetting has been simplified as nonlinear first order block.

$$RO = 14.88 \exp\left(-0.027 MAP\right) \tag{1}$$

$$ANA = RO - 0.000375.BRF \tag{2}$$

$$\frac{d}{dt} BRF = 0.75\left(RO - 0.0005 BRF - 1\right) \tag{3}$$

where, BRF: baroreceptor feedback, RO: receptor output, ANA: autonomous nervous activity, and MAP: mean arterial pressure.

The level of effectiveness on the heart rate is approximated as an autonomic nervous heart multiplier (AHM). Similarly autonomic systemic multiplier (ASM) is related to mean systemic pressure, autonomic venous multiplier (AVM) to venous resistance and, autonomic peripheral multiplier (APM) to total peripheral resistance [18].

$$AHM = 0.3 + 0.7 ANA \tag{4}$$

$$ASM = 0.5 + 0.5 ANA \tag{5}$$

$$AVM = 0.43 + 0.57 ANA \tag{6}$$

$$APM = 0.15 + 0.85 ANA \tag{7}$$

2.2 Cardiovascular system

The mean systemic pressure (MSP), blood volume (BV) and extra cellular volume (ECV) have major roles in the forward loop control of pressure regulatory system [1],

[5]. The non-linear relationship between the mean systemic pressure (MSP), blood volume (BV) and extra cellular volume (ECV) have been written as logistic equations using the curve fitting techniques.

$$BV = -8.87 + \frac{5.475}{\left[0.355 + \exp\left(-\left[ECV + 10.606\right]0.126\right)\right]} \tag{8}$$

$$MSP = -1.218 + \frac{15.45 ASM}{\left[-0.68 + \exp\left(-\left[BV - 9.7\right]0.2\right)\right]} \tag{9}$$

where, ASM is the autonomous systemic multiplier, which is explained in section 2.1.

Thus venous resistance (VR) and total peripheral resistance (TPR) are written in terms of the venous resistance basal value (VR_b) and arterial resistance basal (AR_b). The vasculature (VAS) blocks and the system resistances are taken from [5]. Blood vessel property vasculature has a non linear relation (f_1) with respect to cardiac output (CO).

$$\frac{d}{dt}VAS = -0.4052 VAS + f_1(CO) \tag{10}$$

$$AR = \frac{AR_b}{VAS} \tag{11}$$

$$VR = AVM.\left(\frac{8}{31}VR_b + \frac{1}{31}AR\right) \tag{12}$$

$$TPR = APM.\left(VR_b + AR\right) \tag{13}$$

From the hydraulic principles, we can see that venous return rate (VRR) is the ratio between the pressure differences and venous resistance. It can be seen that cardiac output (CO) is same as the VRR under both transient and steady state.

$$VRR = \frac{\left(MSP - RAP\right)}{VR} \tag{14}$$

$$CO \approx VRR \tag{15}$$

The right atrial pressure (RAP) is under neural control and is approximated as a nonlinear equation given by,

$$RAP = 6.073 \exp\left(\frac{0.0451 CO}{AHM \times ACM}\right) - 7.52 \tag{16}$$

where, ACM is the arterial pressure multiplier to account for the heart muscle contractility which is a nonlinear characteristic (f_2).

$$ACM = f_2\left(MAP\right) \tag{17}$$

$$MAP = CO \times TPR \tag{18}$$

2.3 Renal activity

The role of renal block is crucial in the feedback control of fluid excretion system to

maintain the ABP. The long-term regulation of arterial blood pressure depends on the regulation of the extracellular fluid volume (ECV), a function provided by the kidney through the formation and excretion of urine. Urine output (UO) is taken as a nonlinear function of MAP.

$$UO = f_3(MAP) \tag{19}$$

In the third differential equation representing the fluidic feedback system, the drinking rate (DR) acts as an input.

$$\frac{d}{dt}ECV = DR - UO \tag{20}$$

2.4 State space representation

Since a linear state model provides a better quantitative analysis of the system, a state variable representation of the ABP regulatory system has been developed. Linearization about the operating point (MAP=100 mm Hg, CO= 5 L/minute) has been performed on all the equations, before formulating the model to a state space representation. Three state equations in terms of the state vector x(t), for each of the linearized equations are written. The three dynamic variables associated with first order transfer function blocks are taken as the basic states ($\hat{\mathbf{x}}$) for the model.

$$\hat{\mathbf{x}}(t) = [\hat{x}_1(t), \hat{x}_2(t), \hat{x}_3(t)]^T = [BRF(t), ECV(t), VAS(t)]^T \tag{22}$$

Linearization is accomplished taking into account small variations about the operating point and expanding the nonlinear term into a Taylor's series and neglecting all terms of second and higher derivatives [13]. The incremental variables can be defined as the difference between the actual value and the equilibrium value (with suffice e).

$$y(t) = \Delta MAP(t) = MAP(t) - MAP_e \tag{23}$$

$$u(t) = \Delta DR(t) = DR(t) - DR_e \tag{24}$$

where, u(t): input and, y(t):output.

Now, the actual state variables for the linear model are taken as the incremental states.

$$x_1(t) = \Delta BRF(t) = BRF(t) - BRF_e \tag{25}$$

$$x_2(t) = \Delta ECV(t) = ECV(t) - ECV_e \tag{26}$$

$$x_3(t) = \Delta VAS(t) = VAS(t) - VAS_e \tag{27}$$

The following equations given in vector matrix form describe the complete behaviour of the workable model of the dynamical system, excited by the initial condition vector x(0).

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}u(t) \tag{28}$$

$$y(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}u(t) \tag{29}$$

$$\mathbf{x}(0) = [x_1(0), x_2(0), x_3(0)]^T . \tag{30}$$

This simple model has been employed to analyze its dynamics and control actions. The stability and transient performance, which depends on the eigenvalues, can be evaluated from the state matrix A only. Control system analysis provides functional relationships by focusing on the input-output variables and feedback actions [9], [22]. It is noted that the open loop transfer function (OLTF), GH(s) can be derived from the following characteristic equation.

$$1 + GH(s) = |s\mathbf{I} - \mathbf{A}| = (s + \lambda_1)(s + \lambda_2)(s + \lambda_3) = 0 \tag{31}$$

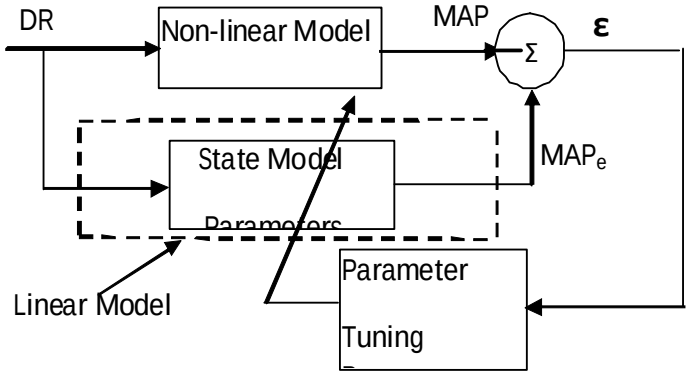
Here, λ_1, λ_2 and λ_3 are the characteristic roots (or, Eigen values) of the denominator polynomial of the closed loop transfer function (CLTF) which are decided by the free parameters of the linearized model. The CLTF analysis is also possible from the state representation, and can be used for simulation.

$$T(s) = \frac{Y(s)}{U(s)} = \mathbf{C}(s\mathbf{I} - \mathbf{A})^{-1}\mathbf{B} + \mathbf{D} \tag{32}$$

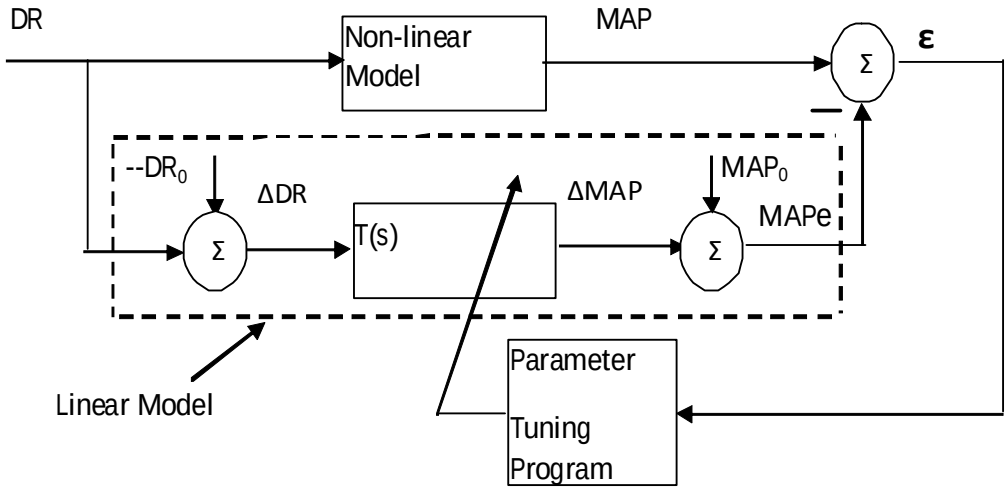
Thus, system approach has been employed to develop a block diagram scheme.

2.5 Modified Parameter Tuning Technique

To investigate the behaviour of nonlinear system under different conditions, more flexible linear state model structure is required instead of fixed parameter architecture. Thus, the nonlinear model of the CVS has been replaced by a set of linear models each corresponding to a specific physiological condition. Whenever the input changes from one level to another, the completely linearized model parameters have been modified to reach the multiple tuned models. The concept is shown in Fig.1. In this section we outline a procedure for the parameter estimation using modified Parameter Tuning Technique (PTT).



(a)



(b)

Figure 1. PTT methodology, a) State space model, b) Transfer function model

The first step is to simulate the nonlinear model to determine the equilibrium point as well as the critical parameters. To investigate the sensitivity of the model response with respect to the nonlinear characteristics, a sensitivity analysis has also been performed. Then the nonlinear model under normal condition has been linearized about the equilibrium point. A sensitivity analysis of the basal linear model has also been required. The study revealed that many of the coefficients have less effect on steady state value of MAP. In the second step the model has been represented as linear state variable model with respect to the selected input and output variables. This basal state model structure but with variable coefficients is maintained for the entire analysis. Open loop and closed loop transfer functions can be determined to arrange the feedback system, if desired. Modified linear models can be derived under each physiological condition, in the next step. Both the linear and nonlinear models are simulated for the selected physiological input and the outputs and are compared. A least square estimation (LSE) algorithm is used to minimize the error by adjusting the parameters of the linear model. Thus we could reach the tuned linear model which can approximately represent the nonlinear model under physiological condition. Linear control theory techniques can be employed to reveal the qualitative and quantitative features of the system dynamics.

3. Results

The proposed technique described in Section 2 has been tested in a number of computational simulations. Since we are interested in examining the results from several points of view, both the dynamic response and the structural properties have been obtained. Simulations were performed for both normal and perturbed conditions of the system.

3.1 Effect of water loading

The technique has been applied to test its ability to reproduce the dynamic behaviour under various physiological stresses. We present here two typical situations. The first case is one in which the water loading experiment is performed for a normal subject. Water loading has been simulated by increasing the water content (DR) of the fluid compartments by five times continuously for fifteen minutes. The immediate effects of increased water intake are the changes in fluidic volume and mean arterial pressure (MAP). Simulation result with the fixed parameter basal model has been presented in a previous publication [15]. The model parameters were tuned such that there is a close agreement between the nonlinear model and tuned linear model.The responses for these models are compared in Fig. 2. Table I shows the predicted MAP under different amounts of drinking rate.

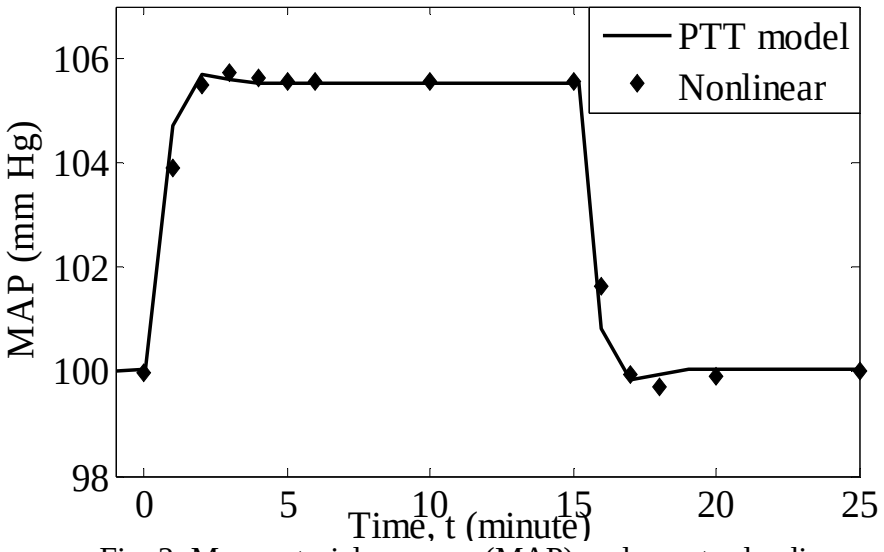


Fig. 2. Mean arterial pressure (MAP) under water loading

Effect of renal shift

The second simulation represents a more challenging environment in which the ABP model is with renal defect as a representative of a typical abnormal condition. Many works [1], [3], [5] report that renal shift leads to hypertension by changing the operating point. To perform the simulation of renal failure, we shift the nonlinear renal characteristic by 10% to the right. Renal failure causes an increased MAP. For a renal impaired patient, the water loading leads to a cumulative effect. The state model coefficients were adjusted for the best fit. The combined effect of this physiological defect with the selected physiological stress (five times the DR) is shown in Fig.3. The comparison shows that parameter tuning provides a better linear approximation by closely following the nonlinear one.

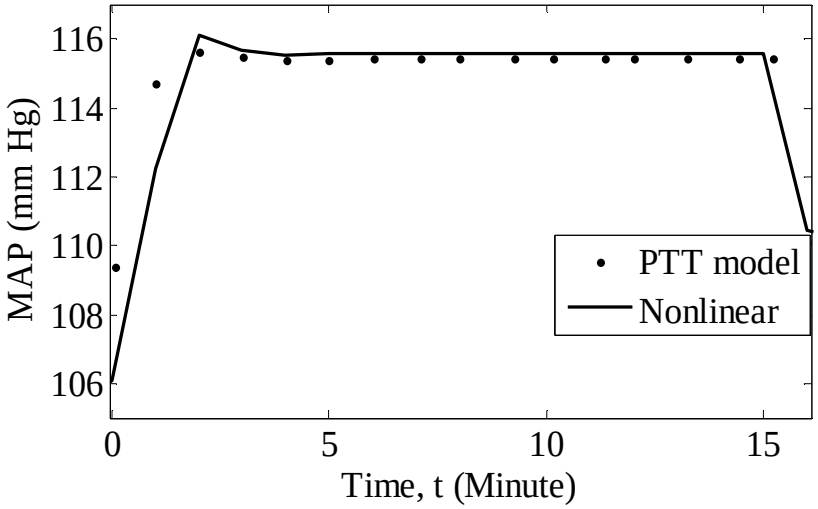


Fig. 3. Mean arterial pressure (MAP) under renal failure.

3.3 Structural Analysis

Effect of input magnitude on the operating point and hence on the system parameters can be assessed from state matrices. Table II shows the system models under different amounts of drinking rate. Effect of parameter tuning can be observed from the matrix coefficients. The location of the poles of the system also depends on the input magnitude. This can be easily noted from the changes in eigenvalues (EV). More interestingly, as the drinking rate (DR) increases to 15 units, system behaves like an over damped one. All the tuned linear models are found to be stable; which establishes that the nonlinear model within the given span of the input variation is stable. Thus it becomes easier to interpret the performance of the system than the nonlinear one.

4. Discussion

The cardiovascular system (CVS) is considered to be a hydraulic system which utilises blood as its working fluid and is characterised in terms of blood pressure and blood flow. Mean arterial pressure (MAP) is one important variable used to describe the system's operating point. The basal value of the ABP, termed as long term ABP is to be maintained within a relatively narrow range of operating points. The abnormal regulation leads to hypertension/ hypotension. They arise from the combined action of many components, and physiological factors [1], [23], [24]. The regulatory system which provides long-term cardiovascular dynamics has a very complex structure, resulting from the non-linear interaction among several different mechanisms: they include fluid volume systems, renal excretory block and circulatory mechanisms. Since significant nonlinearities are involved in the cardio-renal functioning, the diagnosis is difficult to establish. It is very difficult to obtain the analytical solution for the nonlinear model of any order. It is challenging, to analyse or predict the changes in CVS variables mathematically under deregulated conditions.

The nonlinear models available in the literature are powerful for the physiological simulation and interpretation. The traditional control system tools cannot be used for analyzing the nonlinear models. Stability analysis is also not an easy task. Moreover they enjoy very little success for any control system design. Employing linearization to carry out these control tasks remains the technique of choice. At the same time, linearized models cannot be used for the interpretation of large input variations. The reasons for the lack of success of linearization are clear. Linearized model analysis is always limited to small variations of inputs and parameter changes at which the nonlinear properties of the system are less dominant. When the uncertainty range of the parameters is large, the nonlinear characteristics become dominant and the parameter interactions will have a significant effect on the results. Techniques for combating this problem generally revolve around the multiple linear state model based analysis. The work focuses on a multiple tuned linear model framework for the analysis of nonlinear long term ABP regulation system with respect to the various operating conditions.

This paper presents a new approach for parameter tuning technique (PTT) to derive a set of tuned linear models. Proposed methodology is an operating point based parameter estimation scheme to tackle the nonlinearity. From previous studies we observed that the performance of nonlinear system is depending on the input magnitude. Whenever the magnitude changes the operating point shifts leading to an equivalent change in parameters or coefficients. Thus a fixed parameter linear model about the equilibrium point fails to larger inputs. Proper modifications in the coefficients of state model or transfer function are required to match this condition. This leads to multiple tuned linear models. It involves decomposition of nonlinear dynamic performance into multiple linear sections. Extensive sensitivity analysis is required to identify the critical elements. The steps for MPTT are easy to perform. The linearization of actual nonlinear model is straightforward.

Validation of the model consisted of comparing the model response to the nonlinear responses under various physiological conditions. For larger inputs the fixed parameter linear system exhibit larger difference as compared to the nonlinear model under water loading experiment. The simulation results for these cases are summarised in Table I. The key features of the tuned model are generally in agreement with the nonlinear model. It justifies the modification of basal parameters. The simulation results demonstrate other important behaviours of the system also. To study the structural properties of the system, each linear state model is represented as its eigenvalues (EV). Eigenvalues are tabulated in Table II. The results of the linearized model study have shown that the models are stable under these conditions. With increased input level, it can be seen that the system changes from under damped to over damped response establishing that the system properties are input dependent. Since all the tuned models are linear, the system analysis becomes simple from linear control theory point of view. The linear model coefficients can be mapped into a particular nonlinear regime and hence the modified parameters can provide better interpretation to predict the dynamics and control of the nonlinear system.

As a representative of hypertensive condition, renal failure was considered. The nonlinear renal characteristic being in the feedback path for the regulatory system, its

failure is leading to serious perturbations. A shift in the curve or change in the slope parameters is made, the nonlinear properties of the system become dominant and the parameter interactions will have a significant effect on the results. Under such cases, the fixed parameter linear model generally fails. But, the behaviour of the tuned model is matched to that of the nonlinear one using fractional adjustments in the parameters related to renal characteristics. Figure 3 gives the matched responses. The results of the two sets of simulations show that under steady state conditions all the modified linear models are capable of achieving the desired performance requirements. However, a small difference in transient performance can be seen in Fig. 3 for the second case. Upon closer analysis, it can be seen that MAP remains within the allowable error range and hence the parameter tuning based estimation approach achieves a better overall matching. We show through computational modelling that such linear state model analysis, which employs parameter tuning for multiple linear model, is capable of improved performance and a series of advantages over previous approaches in the context of nonlinear model analysis. Thus, these studies can be extended for other diseased conditions also and hence the proposed method suggests how more cardiac problems can be detected with relatively little additional effort.

Present work is also well placed to address a number of physiological questions which would warrant further analysis. One key issue concerns the low order structure of the ABP regulatory system. The selected nonlinear model and hence the proposed linearized model lack many of the circulatory controls that it cannot predict cardiac regulation with a high degree of accuracy. Since our aim is to explain the proposed multiple tuned linear model approach, we paid relatively little attention to the complicated structure of the individual subsystems. However, we hope that the analysis presented here is a very important one conceptually and may extend to enhanced CVS models. Another issue concerns whether regulation of MAP alone is a sufficient condition to ensure overall stability. Present study using support further research. Future work will investigate whether the multiple tuned linear model framework using the state variable approach may be refined by utilising alternative parameter estimation techniques to extend the range of applicability to handle multiple-input multiple-output physiological systems.

Conclusion

This paper focuses on a multiple linear state model framework in order to reproduce the dynamic behavior of the nonlinear long term arterial blood pressure regulatory system. It can be seen that the parameter estimation of the linear state model under different physiological conditions as the heart of the tuning procedure. In this method, the coefficients or parameters of the basal linear model around the equilibrium point have been tuned to match with the nonlinear response under each specific physiological condition. The results of the validation tests have shown that the model sufficiently well predicts the dynamics and control of the system quantitatively. Parameter estimation using PTT promises to provide an important new tool for the characterization of CVS regulation dysfunctions.The use of linear model structure has

allowed us to mathematically demonstrate the stability analysis and structural properties over the expected range of physiological variations which could not be achieved using a nonlinear model or a single linear fixed parameter model, thus conclusively recognising the necessity to employ multiple tuned linear state model analysis for nonlinear systems. Proposed study in the biomedical research area can aid the analysis, control and development of drug delivery technology. This method is very general and could be used not only for the physiological models but for any nonlinear system also.

TABLE I Steady state values of MAP under water loading

Change in DR	Steady state value of MAP		
	Linear	NL extracted	MPTT
5	105.5	105.55	105.55
10	111.01	110.53	110.58
-0.5	99.4	98.3	98.5

TABLE I: System models under different amounts of drinking rate

	Normal	DR=5 units	DR=15 units
A	$\begin{bmatrix} -0.1764e\text{-}3 & -0.02688 & 0.3061 \\ 0.008909 & -1.20622 & 13.7333 \\ 0.5883e\text{-}4 & -0.11406 & -1.5649 \end{bmatrix}$	$\begin{bmatrix} -0.17474e\text{-}3 & -0.01166 & 0.2545 \\ 0.009757 & -0.6465 & 14.1066 \\ 1.5941e\text{-}4 & -0.09691 & -2.8804 \end{bmatrix}$	$\begin{bmatrix} -0.2044e\text{-}3 & -0.02514 & 0.3091 \\ 0.01027 & -1.1565 & 14.2207 \\ 2.2677e\text{-}4 & -0.00581 & -1.9387 \end{bmatrix}$
B	$\begin{bmatrix} 0.09654 \\ 4.3456 \\ 3.2744 \end{bmatrix}$	$\begin{bmatrix} 0.01966 \\ -4.7905 \\ 3.3304 \end{bmatrix}$	$\begin{bmatrix} 0.9975 \\ 0.8008 \\ 0.4626 \end{bmatrix}$
C	$\begin{bmatrix} -0.009801 & 1.3275 & -15.1142 \end{bmatrix}$	$\begin{bmatrix} -0.01076 & 0.7127 & -15.5141 \end{bmatrix}$	$\begin{bmatrix} -0.01115 & 1.2561 & -15.445 \end{bmatrix}$
D	$\begin{bmatrix} 95.2174 \end{bmatrix}$	$\begin{bmatrix} 105.2334 \end{bmatrix}$	$\begin{bmatrix} 98.142 \end{bmatrix}$
EV	$\begin{bmatrix} -0.000375 \\ -1.3855+1.2386i \\ -1.3855-1.2386i \end{bmatrix}$	$\begin{bmatrix} -0.00035091 \\ -1.7634 + 0.34523\,i \\ -1.7634 - 0.34523\,i \end{bmatrix}$	$\begin{bmatrix} -0.0004277 \\ -1.8130 \\ -1.2819 \end{bmatrix}$
T(s)	$\frac{1.328s^2+3.802s+0.001426}{s^3+2.771s^2+3.455s+0.001295}$	$\frac{0.7127s^2+3.5601s+0.001249}{s^3+3.527s^2+3.230s+0.00113}$	$\frac{1.256s^2+2.525s+0.00108}{s^3+3.095s^2+2.325s+0.000994}$

Appendix:

List of constants and variables of the model.

Coefficient	Description	Nominal value	Unit
λ_1	Eigen value 1	0.000375	--
λ_2	Eigen value 2	-1.385+1.238 i	--
λ_3	Eigen value 3	-1.385-1.238 i	--
AR_b	Basal arterial resistance	16.66	mmHg/L/minute
VR_b	Basal venous resistance	3.33	mmHg/L/minute
Variable	Description	Nominal value	Unit
ACM	Autonomic cardiac multiplier	1	--
AHM	autonomic heart multiplier	1	--
ANA	Autonomous nervous activity	1	--
AR	Arterial resistance	16.66	mmHg/L/minute
APM	autonomic peripheral multiplier	1	--
ASM	Autonomic systemic multiplier	1	--
AVM	Autonomic venous multiplier		
BRF	Baroresetting feedback	0	--
CO	Cardiac output	5	Litre
DR	Drinking rate	1	Milli litre/ minute
ECV	Extra cellular volume	15	Litre
MAP	Mean arterial pressure	100	mmHg
MSP	Mean systemic pressure	7	mmHg
RAP	Right arterial pressure	0	mmHg
RO	Baroreceptor output	1	--
TPR	Total peripheral resistance	20	mmHg/L/minute
UO	Urine output	1	Milli litre/ minute
VAS	Vasculature	1	--
VR	Venous resistance	3.33	mmHg/L/minute
$x_1(t)$	State variable 1, ΔBRF	0	--
$x_2(t)$	State variable 2, ΔECV	15	Litre
$x_3(t)$	State variable 3, ΔVAS	1	--

References

[1] Guyton, A.C., 1980, Arterial pressure and hypertension, W.B. Saunders Company, Philadelphia.

[2] Uttamsingh, R.J., Leaning, M.S., Bushman, J.A., Carson, E.R., and Finketstein, L., 1985, "Mathematical model of the human renal system," Medical & Biol. Engg. & Computing, pp. 525-535.

[3] Cameron, W.H., 1977, "A model framework for computer simulation of overall renal functions," Journal of Theoretical Biology, 66, pp.551-572.

[4] Karaaslan, F., Denizhan, Y., Kayserilioglu, A. and Gulcur, H.O., 2005, "Long term mathematical model involving renal sympathetic nerve activity, arterial pressure, and sodium excretion," Annals of Biomedical Engg., 33(11), No. 11, pp. 1607–1630.

[5] Guyton, A.C., Coleman, T.G. and Granger, H.J., 1972, "Circulation: overall regulation," Annual Review of Physiology, 34, pp.13-46.

[6] Blaine, E.H., Davis, J.O., and Harris, P.D., 1972, "A steady state control analysis of the renin-angiotensin-aldosterone system," Circulation Res., 30, pp. 713-730.

[7] Leaning. M.S., Flood, R.L., Cramp, D.G. and Carson, E.R., 1985, "A system of models for fluid-electrolyte dynamics," IEEE Trans. On Biomedical Engg., 32(10), pp.856-866.

[8] Bigelow, J.H., Dehaven, J.C., and Shapley, M.L., 1973, "System analysis of the renal function," Journal of Theoretical Biology, 41, pp. 287-322.

[9] Khoo, M., 2001, Physiological Control Systems, IEEE Series in Biomedical Engg. Metin Akay.

[10] Storace, M., and Feo, O. D., 2004, "Piecewise-linear approximation of nonlinear dynamical systems," IEEE Trans. on Circuits and Systems, 51(4), pp. 830-842.

[11] Oaks Jr., O. J., and Cook, G., 1976, "Piecewise linear control of nonlinear systems," IEEE Trans. on Industrial Electronics and Control Instrumentation, 23(1), pp. 56-63.

[12] Chau, N.P., Safar, M.E., London, G.M. and Weiss, Y.A., 1979, "Essential hypertension: an approach to clinical data by the use of models," Hypertension, 1, pp. 86-97.

[13] Ogata, K., 1998, Modern control engineering, 3rd Ed ., Prentice Hall of India.

[14] Kuo, B.C. and Golnaraghi, F, 2003, Automatic control systems, 8th Ed., John Wiley, Singapore.

[15] Shahin, M. and Maka,S., 2007, "Linear state space model for long-term blood pressure regulation," Int. Journal of Biomedical Engg. and Tech., 1, pp.190-203.

[16] Shahin, M. and Maka,S., 2011, "State Variable Approach to the Analysis of Neural Control of Long Term Blood Pressure Dynamics," Asian Journal of Control, 13(1), pp. 164-176..

[17] O. Nelles, 2001, Nonlinear System Identification, Springer.

[18] Shahin, M., 2011, "Modeling, analysis and control of long term arterial blood pressure regulatory system," PhD Thesis, IIT Kharagpur, India.

[19] Li, Y., and Tan, K. C., 2000, "Linear approximation model network and its formation via Evolutionary computation," Saadhanaa, 25(2), pp. 97-110.

[20] Gao, R., and O'Dwyer, A., 2002, "Multiple model networks for non-linear modeling and control," Proc. of the 3rd Wismar Symposium on Automatic Control, Wismar, Germany, pp. 1-8.

[21] M. Shahin and S. Maka, 2010, "Multiple tuned model approach for the analysis of nonlinear dynamics of the long term blood pressure regulation," *IEEE Proc. of Int. Conf. on Systems in Med. & Biol. - ICSMB 2010*, IIT Kharagpur, pp. 248-252.

[22] Milhourn, H.T., 1966, Application of Control Theory to Physiological Systems, W. B. Saunders, Philadephia.

[23] Julius, S., 1994, "Abnormalities of autonomic nervous control in human hypertension," Cardiovascular drugs and therapy, 8, pp. 11-20.

[24] Folkow, B., 1982, "Physiological aspects of primary hypertension," Physiol. Reviews, 62(2), pp.348-504.