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ASIAN JOURNAL OF SCIENCE AND TECHNOLOGY

ISSN: 0976-3376

Asian Journal of Science and Technology
Vol. 5, Issue 2, pp. 148-152, February, 2014

RESEARCH ARTICLE

CONTROL OF MEAN ARTERIAL PRESSURE BY CARDIAC DRUG INFUSION SYSTEM USING FUZZY LOGIC CONTROLLER

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ARTICLE INFO

Article History:
Received 25th November, 2013
Received in revised form
10th December, 2013
Accepted 12th January, 2014
Published online 28th February, 2014

Key words:
Cardiovascular system,
Mean Arterial Pressure,
Dopamine,
Sodium nitroprusside,
Fuzzy logic controller,
Drug infusion.

ABSTRACT

The control of physiological variables presents specific challenges, mainly due to the highly nonlinear, complex behavior of biological systems. Cardiovascular system stands as a clear example, with critical situations when control is desirable and troublesome in the same time. This paper presents a fuzzy control strategy for blood pressure by automatic infusion of two commonly used drugs, sodium nitroprusside and dopamine respectively. The Mean Arterial Pressure (MAP) is regulated using the Zeigler-Nichols Proportional-Integral and Fuzzy logic controllers (FLC). Simulations study demonstrates the ability of FLC regulates MAP at a nominal and safe value within a reasonable time period. Furthermore, cost reduction by minimized drug consumption and shortened period of clinical treatment is part of the main issues which motivates automation. Performances of control techniques are evaluated based on integral square error and integral absolute error. From the simulation results and from the performance criteria it is observed that FLC controls MAP better than that of conventional PI controller.

INTRODUCTION

Mathematical models are powerful means for studying and realizing complex systems. Investigating the interactions and modeling of physiological systems are also done by the mathematical models. Especially for cardiovascular system (CVS), due to the non-invasive nature of most diagnostic methods, it is hard to obtain hemodynamic parameters directly by performing reproducible experiments on the subjects. As a result, mathematical modeling and computer simulations of the cardiovascular system present a useful means for the understanding of various physiological and pathological phenomena (Rideout, 1991). Computer simulation of complicated physiological models becomes realistic and could provide much valuable information to boost our knowledge in cardiovascular physiology. A range of CVS models have been proposed in the past years. The CVS models differ considerably in complexity depending on the representation from simple one to complex representation of the vascular vessels (Smith, 1999). The CVS models provide a better understanding of the pressure-flow relationships in cardiovascular system. The CVS model appears to be particularly useful in multiple models for pharmacokinetic studies (especially in anesthesiology Gentilini *et al*., 2001). Computer simulations are useful in obtaining concrete knowledge of physical systems from theoretical structure.

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Further, in biomedical research, the use of animals for experiments is expensive, and simulation is often much more cost-effective. Furthermore, in most cases, animals cannot be used multiple times for research. Because of these factors, simulation of equivalent systems may aid in many technological developments as well as in repeated instruction without harming any patients (Bhojwani, 2007). Simulations are realistic, less dangerous, practical, and economical for improving current medical technology. The goal of our work is to realize the mechanisms of the cardiovascular system and to obtain an enhanced mathematical model as well as a simple, compact and inexpensive physical analogy model of the CVS in simulation. Equivalence exists between computational models of cardiovascular function and electrical circuits, a parallel that has been developed since the late 1800's. Years later, Frank introduced the Windkessel model, which comprised of a simple first-order circuit to model arterial dynamics (Hlaváč *et al*., 2004). The complete description of the whole CVS is a very complex task; therefore, modeling of CVS began with simplified models to show only the normal behavior of this system (Shi and Chew, 2009; Noordergraaf, 1963). The mechanical and electrical models are commonly used to represent the cardiovascular system. PHYSBE (Physiological Simulation Benchmark Experiment) model was presented by McLeod (1999). Martin *et al*. (1986) developed fewer compartment models for real- time application. This model is extended by Woodruff *et al*. (1997) to include the pharmacologic model of the cardiovascular drugs. Yu *et al*. (1990) showed the drugs effect on simplified congestive heart

failure model. The regulation of Mean Arterial Pressure (MAP) in the infraction patients is an important control problem. In a typical intensive care or operating room scenario, MAP is usually maintained at their desired values by the controlled infusion of drugs. Two drugs that are commonly used in practice are Sodium Nitroprusside (SNP) and Dopamine (DP). In this study, the compartmental modeling approach (Vinoth *et al*., 2013) is used which allows describing the underlying physiological processes and able to control the Mean Arterial Pressure (MAP). The control of MAP is achieved by implementing various control strategies. In this paper, Z-N control (ZN-PI) and fuzzy logic control (FLC) strategies are incorporated for controlling the MAP. This paper is organized as follows. In Section II, a detailed Drug infusion based CVS model description is introduced and the control techniques are described in Section III. The simulation results and discussion are presented in Section IV and finally the conclusion is drawn in Section V.

Multidrug model of CVS

In our previous work, CVS model is simulated and analysis are carried out and concluded that unstressed volume, systemic resistance, peripheral resistance, left ventricular elastance and right ventricular elastance (V_{usven} , R_{sys} , $R_{0p,}$ E_{maxlv} and E_{maxrv}) are the predominant parameters affecting the MAP. SNP and DP drugs are selected to increase ventricular contractility and to decrease resistance to blood flow. The drugs DP and SNP are interchangeably infused into the CVS model shown in Figure1. Coincidently the target sites of SNP and DP affects the dominant parameters which affect the MAP in the CVS. $E_{max,lv}$ and R_{sa} are modified by the pharmacological effects of DP. DP is inotropic in nature, i.e., it increases ventricular contractility. SNP is a vasodilator and it decreases resistance to blood flow by decreasing R_{sys} and increasing $V_{us,ven}$. The drug infusion therefore affects the controlled variable MAP by these body parameters. An increase in dopamine infusion increases MAP and an increase in nitroprusside infusion reduces MAP.
The therapeutic range of SNP is between 0.0-10.0 µg/kg/min, which is used for both hypertension and acute congestive heart failure. An intermediate infusion range of DP 2-6 µg/kg/min is used for its inotropic effects and safety in acute congestive heart failure. Table IV gives the values of drug parameters defining the site of actions for SNP and DP. The drug distribution and its effect on body are modeled by pharmacokinetics and pharmacodynamics model.

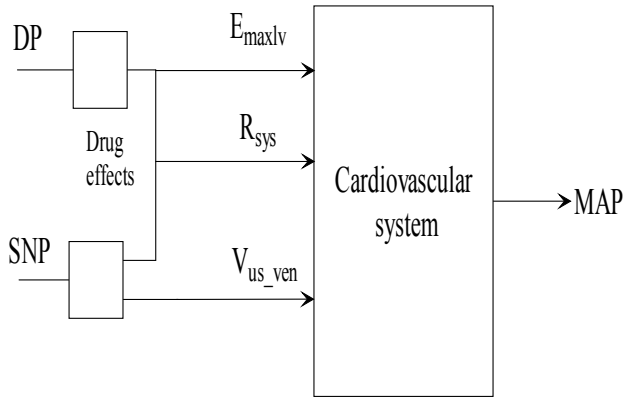

Fig.1. Conceptual diagram of the cardiovascular system with drug effects

The pharmacokinetics in the body compartments is modeled by the following differential equation.

$$\left(\frac{dm}{dt}\right)_j = (\sigma Q)_{j-} - (\sigma Q)_{j+} - \left(\frac{m}{\tau_{1/2}}\right)_j \quad (1)$$

Where,

m is the mass of the drugs at the j^{th} compartment.

σ_{j-} and σ_{j+} are the concentrations of the drugs with the blood flow-in Q_{j-} and blood flow out for each compartment respectively.

$\tau_{1/2}$ is the half life of the drug in the blood vessel.

The concentration of the drug in each compartment is denoted by σ_{dr} and updated by,

$$\sigma_{dr} = \frac{m}{V} \quad (2)$$

Where,
V is the instantaneous volume of the compartment at which the computations are performed.

The pharmocodynamics concentration relationship is given by,

$$\left(\frac{dEff}{dt}\right) = K_1 \sigma_{dr}^{\alpha} \left[Eff\max - Eff\right] - K_2 Eff \frac{dEff}{dt} \quad (3)$$

Where,

E*ff* is the quantitative measure of the effect of a drug on its target sites in the heart chambers or any blood vessel.

E*ff*max is the maximum drug effect

K_1 and K_2 are first and second reaction rate constants,

α is an empirical parameter.

The drug time constant is defined as,

$$\tau = \frac{\tau_{1/2}}{\ln(2.0)} \quad (4)$$

Then the second reaction rate constant is computed with the variables 'x' and 'y' as follows.

$$x = \exp\{\alpha \ln(y)\} \quad (5)$$

Where,

$$y = (i50)\tau / 85.0 \quad (6)$$

Then,

$$K_2 = \frac{K_1}{x} \quad (8)$$

Where,
i_{50} is infusion corresponding to 50% drug effect.

$\tau_{1/2}$ is the time required to reduce the concentration to one half its initial value.

Each parameter is further modified by the drug effects,

$$R_{sys} = R_{sys} - (Eff_{SNP-R_{sys}} + Eff_{DP-R_{sys}})R_{sys} \quad (9)$$

$$E_{max} = E_{max} + (Eff_{DP-E_{max}})E_{max} \quad (10)$$

$$V_{us-ven} = V_{us-ven} + Eff_{SNP-V_{us-ven}} \quad (11)$$

Table 1. SNP and DP drug effect parameters

Parameter	SNP on R_{sys}	SNP on $V_{us,ven}$	DP on E_{max}	DP On R_{sys}
*Eff*max	0.635	225.0	1.3	0.5
α	1.0	1.0	6.11	1.4529
K_2	0.025s^{-1}	0.00625s^{-1}	0.0011316s^{-1}	0.0125s^{-1}
*i*50	1.706 µg/kg/min	0.936 µg/kg/min	4.0 µg/kg/min	92.261 µg/kg/min
$\tau_{1/2}$	15s	15s	120s	120s

Designing of conventional PID controller

Ziegler Nichol's has proposed an open-loop tuning method called process reaction curve method. Optimum controller settings can be obtained for various modes of control by using this method. This method is to approximate a higher order process as first order with dead time. The open-loop response of the process is obtained as 'S' shaped curve or sigmoidal curve as shown in Figure 2.

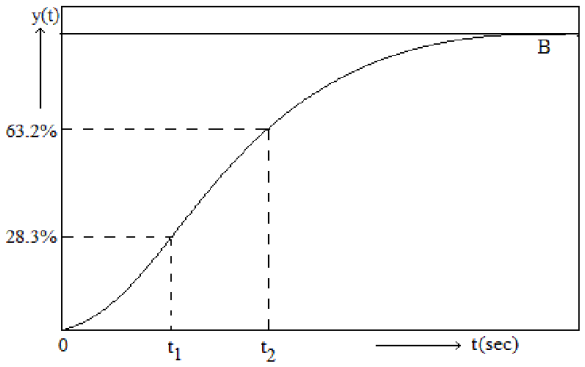

Fig.2. Typical process reaction curve

The process parameters like process gain K_p, time constant τ, dead time t_d are obtained using two point method (Wayne Bequette, 2010).

Time constant $\tau = 1.5(t_2 - t_1)$ (13)

Dead time $t_d = t_2 - \tau$ (14)

Process gain $K_p = \frac{\Delta Output}{\Delta Input}$ (15)

For the obtained model, the PI controller parameters can be determined using Zeigler – Nichols (Z-N) tuning method. The Z-N tuning parameters are given below:

Controller gain $K_c = \frac{0.9\tau}{t_d * K_p}$ (16)

Integral time $T_i = 3.33 * t_d$ (17)

Design of FLC

Fuzzy control is an appealing alternative to conventional control methods when systems follow some general operating characteristics and a detailed process understanding is unknown or traditional system models become overly complex (Mendel, 1995). Fuzzy logic controllers are increasingly applied to many systems with nonlinearity and uncertainty. As the rule base conveys a general control policy, it should be sustained and leaves most of design and tuning work to the scaling gains. Each of the rules of FLC is characterized with an IF and then rules. The set of rules which define the relation between the input and output of fuzzy controller can be found using the available knowledge in the area of designing the system. These rules are defined using the linguistic variables NB, NS, Z, PS and PB. The letters N, P, Z, B, S represent Negative, Positive, zero, Big and Small respectively. All the 25 rules governing the mechanism for each output are explained in Table 2.

Table 2. Rule table for FLC with triangular membership

ERROR \ Change in Error	NB	NS	Z	PS	PB
NB	NB	NB	NS	NS	Z
NS	NB	NS	NS	Z	PB
Z	NS	NS	Z	PS	PS
PS	NS	Z	PS	PS	PB
PB	Z	PS	PS	PB	PB

Simulation results and discussions

In the CVS model with drug effect the MAP is maintained at 93.3mmHg. Initially the MAP will be high to decrease the MAP, at the time of 9th minute SNP is introduced which lowers the MAP. Once the steady state of MAP is attained DP is introduced at the time of 19th minute, which increases MAP. The response of the MAP with the effect of drug infusion is shown in Figure 3.

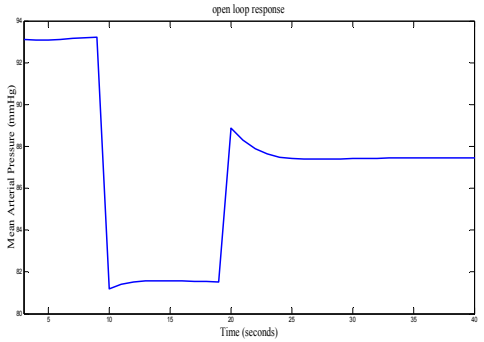

Fig.3. Simulated CVS model with drug effects

From the open loop response a first order process with dead time (FOPDT) model is obtained. From the obtained responses it is inferred that gain of the FOPDT model is 11.68 and 16.27 in terms of mm Hg $(\mu g/kg/min)^{-1}$.

Whereas the time constant is 0.51 seconds and 0.98 second and time delay are 0.18 seconds and 0.2 seconds for SNP and DP respectively.

$$\frac{\Delta MAP}{SNP} = \frac{-11.68}{0.51s+1} e^{-0.18s}$$
$$\frac{\Delta MAP}{DP} = \frac{16.27}{0.98s+1} e^{-0.2s} \quad (18)$$

The drug infusion of CVS has two inputs and one output. If the MAP decreases, effect of DP will act on the output, meanwhile if MAP increases SNP will decrease the MAP. So this model is considered to be single input single output system. The regulation of MAP is achieved by introducing switching controller in closed loop shown in Figure 5.

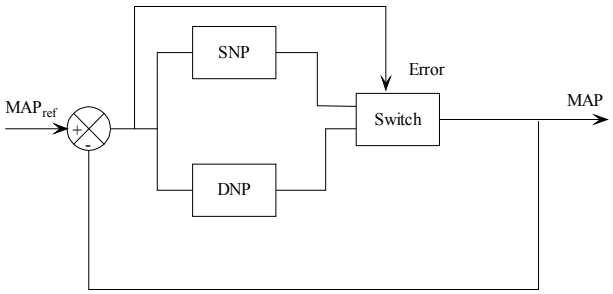

Fig.5.Swithing of Controller to regulate MAP

The model shown in equation 18 is studied in closed loop for PI controller separately. Figure 6 and Figure 7 shows the MAP response to drug infusion of SNP and DP respectively.

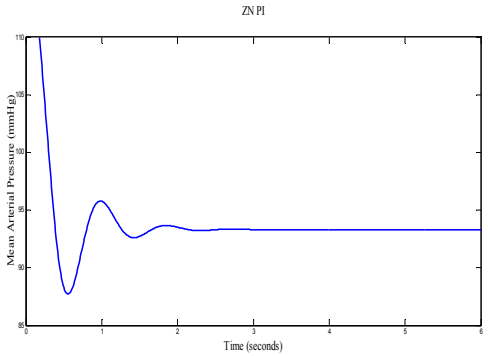

Fig.6. Z-N PI Closed loop response for infusion SNP on CVS

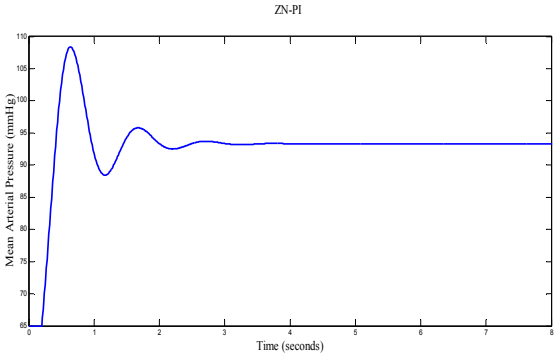

Fig.7. Z-N PI Closed loop response for infusion DP on CVS

From the Figures 6 & 7 it is observed that the under shoot and overshoots present in output. This variation will lead to varying the blood pressure of the patient. Since the variation is not feasible for the patient, ZN-PI controller cannot be used for controlling the MAP practically. To eliminate the overshoot and under shoot in the output FLC is proposed. Figure8 and Figure9 show the fuzzy logic response of SNP and DP respectively.

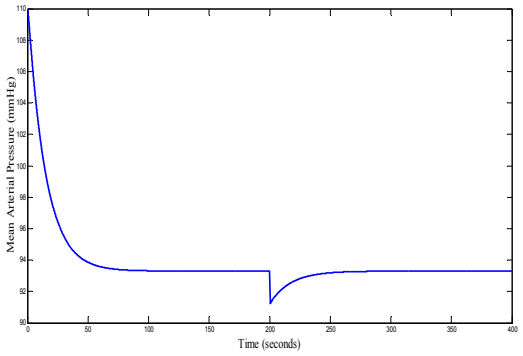

Fig.8. Fuzzy Closed loop response for infusion SNP on CVS

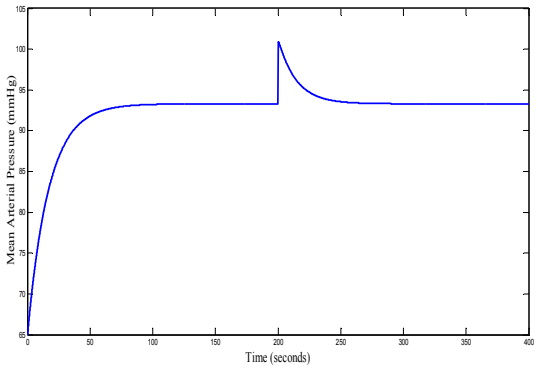

Fig.9. Fuzzy Closed loop response for infusion DP on CVS

From the Figures 8 and 9 it is inferred that MAP response to FLC doesn't have undershoot and overshoot. In Figure 8 it is observed that the SNP based fuzzy controller can able to bring the MAP pressure to 93.3mmHg (normal MAP) with the initial pressure as 110mmHg. From Figure 9 it is observed that the DP based fuzzy controller can also able to maintain the MAP pressure to nominal MAP value of 93.3mmHg.

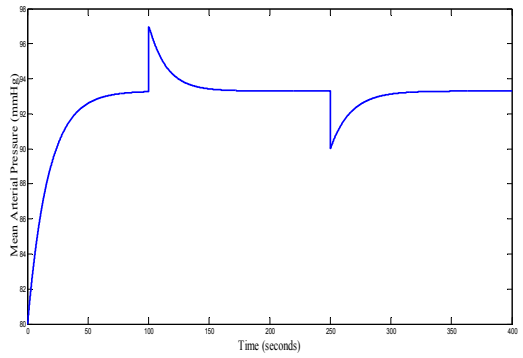

Fig.10. MAP output of switching controller

FLC is implemented in the switching controller technique as shown in fig 5. In switching control technique the controller will be switched according to the error. If the error is positive it means MAP is high, therefore SNP controller will act and increase the MAP. Similarly when the error is negative which is an indication of MAP is low, now DP controller will act to

regulate the MAP. From the Figure10 it is observed that, initially the MAP is lowered by SNP and it continue to maintain MAP. During the post/pre operative or anesthetic conditions MAP can change due to environmental disturbances, in simulation the positive disturbance is given at time t=200seconds and negative disturbance is given at the time t=400 seconds. At t=200 seconds error is positive, so MAP is increased in order to activate the SNP controller and it maintains MAP at 93.3 mmHg. Similarly, at t=400 seconds MAP is decreased and error is negative therefore DP controller acts and maintains MAP at desired value. By comparing Z-N and Fuzzy, from the Z-N PI controller output it is observed that it has overshoot and undershoot which is undesirable in surgical/post operative environment, which is not observed in FLC. FLC is also implemented in switching controller, which showing satisfactory response than Z-N PI. For showing the superiority of FLC, the performance of Z-N PI and fuzzy controller are measured using Integral Square Error (ISE) and Integral Absolute Error (IAE) criteria which are tabulated in Table 3.

Table 3. Performance measures of Z-N PI and Fuzzy

CONTROLLER	ISE(SNP)	IAE(SNP)
Z-N PI CONTROLLER (SNP)	76.79	7.714
FLC (SNP)	11.62	3.408
Z-N PI CONTROLLER (DP)	286.2	46.66
FLC (DP)	165.1	27.93

From the table 3 it is observed that FLC is having less ISE and IAE values compared to Z-N PI which also indicates that FLC's superior performance.

Conclusion

The open-loop behavior of the CVS, in terms of PK-PD points of view, is discussed in this paper. Open loop response is important to model and design of the controller, as it provides a valuable guideline in tuning the controller. In this paper, modeling and control of drug delivery system based on FLC is proposed and applied to control MAP using SNP and DP. Simulation results demonstrate the effectiveness of the proposed FLC to improve the performance of the closed loop control system. In future work, it is proposed to consider the effect of bar receptor effect in the modeling. It is also proposed to maintain more cardiovascular variables like heart rate, cardiac output.

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