Design of an Intelligent Adaptive Drug Delivery System for Arterial Pressure Control

ANDERSON LUIZ DE OLIVEIRA CAVALCANTI
ANDRÉ LAURINDO MAITELLI
Departamento de Engenharia de Computação e Automação
Universidade Federal do Rio Grande do Norte
Av. Senador Salgado Filho s/n, 59072970 Natal
BRAZIL
anderson@dca.ufrn.br http://www.dca.ufrn.br/~anderson

Abstract: -Arterial pressure control is an important task, mostly in postsurgical patients. This work proposes an adaptive system to patient's arterial blood pressure control using sodium nitroprusside. The proposed system uses Proportional-Integral (PI), Fuzzy-PI, rule-based and predictive controllers. To introduce an adaptive characteristic to PI controller, it was used an intelligent fuzzy supervisor with a kind of gain scheduling. This idea can be extended to rule-based and fuzzy-PI controllers. A Pseudo Random Binary Signal (PRBS), with level in accord of patient's drug sensitivity, was used in all controllers to avoid greats decreases in blood pressure in the beginning of control. Also it was used an algorithm to reject wrong measurements in patient's arterial blood pressure. The results obtained consider an adaptive predictive controller and a PI with Fuzzy scheduling considering two simulated patients. In all simulations, the mean arterial pressured considered as reference was 100 mmHg. The simulation results showed that the proposed system has good performance and stabilize the mean arterial pressure with small settling time and small overshoot.

Key-Words: - Adaptive control, arterial blood pressure, intelligent control

1 Introduction

Postsurgical complication of hypertension can occur or to be aggravated in cardiac patients. To decrease the chances of complication it is necessary to reduce elevated blood pressures as soon as possible. A way to reach this objective is to use continuous infusion of vasodilator drugs, such as sodium nitroprusside (SNP) or nipride, that can quickly lower the blood pressure in most patients. An overdose of nitride could, however, cause toxic side effects.

Usually each patient has a different SNP sensibility and it can be time variant. Then, efficient control strategies are necessary to determine the infusion rate of Nipride carefully to achieve the desired blood pressure. Maintaining the desired blood pressure requires constant monitoring of arterial blood pressure and frequently adjusting the drug infusion rate. Manual control of arterial blood pressure by clinical personnel is very demanding, time consuming and, as a result, sometimes of poor quality.

A simplified model describing the relationship between blood pressure decrease and the SNP infusion rate was proposed by Slate [1]. The model include two time delays initially unknown, includes time varying parameters and it can be stochastic and deterministic noises.

Due to the characteristics and simplifications of the model, the used controllers must have characteristics of robustness and adaptation, together with some measure of performance. There are many adaptive controllers: (i) the Model Reference Adaptive Control used, for example, by Payunen et al. [2]; ii) Predictive Adaptive Control, Maitelli & Yoneyama [3]; iii) Intelligent Controllers - specially based in expert, fuzzy, rule-based and neural networks based systems - Polycarpou & Conway [4]; Ying, et al., [5]; Shiek et al., [19]; Held and Roy, [21]; Chen et al., [23]. Another authors use adaptive techniques to mean arterial pressure control (Arsparger et al., [6] – Generalized minimum variance control; Stern et al., [7] – Self-Tuning Regulator). Another controllers that don't use adaptive techniques (Koivo et al., [8]- optimal digital controller, Sheppard, [9] – PID controllers) have a worse performance in comparison with adaptive controllers. In other works the controller is used with a supervisor (Martin et al., [10], e Martin et al., [11]). In these cases, the supervisor is rule based and limits the systems reactions in presence of disturbances. These systems have some problems,

particularly in transient period and in cases with time delays variation or abrupt parameter variations, according the simulations examples showed in Pajunen et al., [2]; Maitelli & Yoneyama, [3]; Maitelli & Silva, [12]; Srinivas et al., [22]; Isaka and Sebald, [17].

Recent works consider a Multi-input, Multi-Output approach using multiple interacting drugs (SNP and Dopamine) to control both the mean arterial pressure (MAP) and cardiac output (CO) of patients with different sensitivity to drugs as in Enbiya et al., [24]. In this paper, however, only the Single-input, Single-output is considered because this approach has demonstrated good results including in children as showed in Spilberg et al., [25].

In this works is proposed an intelligent adaptive controller with supervision applied to the problem. The system consists of a set of controllers and a supervisor that has as main tasks: to make the critical of the measure of patient pressure to limit the infusion rate, to change between controllers and to change the controller parameters. This supervisor is attended by block called Identification, whose function is to estimate the patient parameters in real time.

2 Problem Formulation

In this section, the patient's model and the controllers considered will be presented. The model consists of an uncertain first order model with transport delay.

2.1 Patient's Model

A model of the mean arterial pressure (MAP) of a patient under the influence of sodium nitroprusside (SNP) developed by Slate [1] is given by

$$MAP(k) = P_0 - \Delta P(k) + P_d(k) + n(k) \qquad (1)$$

where MAP is the mean arterial pressure, P_0 is the initial blood pressure, also called a background pressure, ΔP is the change in pressure due to infusion of Nipride, P_d is the change in pressure due to the renin reflex action (Braunwald, [16]) which is the body's reaction to the use of a vasodilator drug, and n(k) is a stochastic background noise. In this paper it is assumed that Po is constant.

A linearized continuous-time deterministic model describing the relationship between the change in the blood pressure and drug infusion rate is, where $\hat{A}(s)$ is the Laplace transform of A(t) function).

$$\Delta\hat{P}(s) = \frac{Ke^{-T_i s}(1+\alpha e^{-T_c s})}{(1+\tau s)}\hat{I}(s) \qquad (2)$$

where ΔP is the change in blood pressure in mmHg, is the infusion rate in ml/h, K is drug sensitivity in mmHg/ml/h, α is the recirculation constant, T_i is the initial transport delay, T_c is the recirculation time delay, and τ is the system time constant, all in seconds.

The discrete-time version of the continuous model (2), required to project an automatic infusion control system is (Pajunen et al., [2]).

$$\Delta P(k) = \frac{q^{-d}(b_1 + b_{m+1}q^{-m})}{1 + a_1 q^{-1}} I(k) \;\; ; \;\; b_1 > 0 \qquad (3)$$

where q^{-1} denotes a unit delay operator. The parameters b_1, b_{m+1} (mmHg/ml/h), a_1 (dimensionless), d and m (multiples of sampling period) are obtained from the continuous model (2).

Typical values of model parameters with sampling time of 15*s* are showed in Table 1.

Table 1: Range of values for parameters of the discrete-time deterministic plant model for sampling time of 15 s

Parameter	Minimum	Maximum	Nominal
b_1	0.053	3.546	0.187
b_{m+1}	0	1.418	0.075
a_1	-0.779	-0.606	-0.741
d	2	5	3
m	2	5	3

We can observe a considerable difference in the values of the patient parameters, strengthening the idea of that the controller must operate with a wide band of parameters of the model. For a given patient, the delays are known (or gotten for a phase of previous identification) and constants for a long period of time. The parameters, however, are considered changeable during the period of control.

Replacing the discrete-time deterministic model (3) in (1) and discarding $P_d(k)$, that has a slow dynamic behavior, we have

$$P_0 - MAP(k) = \frac{q^{-d}(b_1 + b_{m+1}q^{-m})}{1 + a_1 q^{-1}} I(k) - n(k) \quad (4)$$

Adopting the noise model

$$n(k) = -\frac{e(k)}{1 + a_1 q^{-1}} \quad (5)$$

where *e(k)* is a white Gaussian noise with zero mean and variance σ_e^2 and denoting

$$P(k) = P_0 - MAP(k) \quad (6)$$

so that P(k) is the negative change in the blood pressure, (4) becomes

$$\begin{aligned} &P(k) + a_1 P(k-1) = b_1 I(k-d) + \\ &b_{m+1} I(k-d-m) + e(k) \end{aligned} \quad (7)$$

The discrete-time stochastic model for the blood pressure control using infusion of SNP, expressed by (7), is used hereafter for the design of the controllers. The main problem in postsurgical patients is decreasing the arterial pressure, usually in upper values, to suitable levels, typically around 100 mmHg.

The following physical and physiological constraints have to be introduced for this problem:

a) On the input: the acceptable range of the Nipride infusion rate is

$$0 \le \mathrm{I(k)} \le 180\ \mathrm{mL/h} \quad (8)$$

b) On the output: the maximum acceptable rate of change of the patient's MAP per 15*s* sampling interval is

$$\begin{aligned} &|\Delta MAP(k)| = \\ &|MAP(k-1) - MAP(k)| \le 15\ mmHg \end{aligned} \quad (9)$$

These maximum values are chosen considered a patient with 60 Kg and the SNP concentration 200 µg/ml, Chen et al [23]

2.2 Used Controllers

In this section the controllers used to the patient arterial pressure control are described. Specifically, are presented the adaptive predictive and the Fuzzy-PI controllers.

2.2.1 Adaptive Predictive Controller

The model presented in equation (7) was used to the predictive controller design, which is *P(k)* is the negative change in the blood pressure from initial value at instant k (mmHg) and *I(k)* is the SNP rate at instant *k* (ml/h). From this model we can obtain the predicted output *P(k) d* steps ahead, denoted by:

$$\begin{aligned} &\hat{P}(k+d) = \left(-a_1\right)^d P(k) + \sum_{i=1}^{d-1}\left(-a_1\right)^i b_1 I(k-i) + \\ &\sum_{i=1}^{d-1}\left(-a_1\right)^i b_{m+1} I(k-m-i) + b_1 I(k) \end{aligned} \quad (10)$$

Defining

$$\begin{aligned} &K_0 = \left(-a_1\right)^d P(k) + \sum_{i=1}^{d-1}\left(-a_1\right)^i b_1 I(k-i) + \\ &\sum_{i=1}^{d-1}\left(-a_1\right)^i b_{m+1} I(k-m-i) \end{aligned} \quad (11)$$

We can rewrite

$$\hat{P}(k+d) = K_0 + b_1 I(k) \quad (12)$$

Using an objective function that takes in account the deviation between the predicted pressure $\hat{P}(k+d)$ and its reference $P_{ref}(k+d)$ and, at same time, assure zero steady state error,

$$J = \left(\hat{P}(k+d) - P_{ref}(k+d)\right)^2 + \rho\left(\Delta I(k)\right)^2 \quad (13)$$

where ρ is the weighting factor of control signal.
Using (12) we obtain the value of *I(k)* that minimize the objective function (13)

$$I(k) = \frac{(P_{ref}(k+d) - K_0)b_1 + \rho I(k-1)}{b_1^2 + \rho} \quad (14)$$

How the parameters of each patient are initially unknown or/and they can vary during the control process, we use an identifier which consists basically of least squares parameter estimators with forgetting factor, each of one considering a different delay (between 2 and 5) and being executed in parallel. It is used an appropriate delay choose method at each instant.

The equation (7) can be rewriter as

$$P(k) = -a_1 P(k-1) + b_1 I(k-d) + b_{m+1} I(k-d-m) + e(k) \quad (15)$$

Considering d=m and defining

$$\theta(k,d) = \begin{bmatrix} a_1 & b_1 & b_{m+1} \end{bmatrix} \quad (16)$$

and

$$\varphi(k,d) = \begin{bmatrix} -P(k-1) & I(k-d) & I(k-d-m) \end{bmatrix} \quad (17)$$

we have

$$P(k) = \theta(k,d)\varphi^T(k,d) + e(k) \quad (18)$$

It is used recursive estimators, considering different delays d_0 and with forgetting factor λ

$$\hat{\theta}(k,d_0) = \hat{\theta}(k-1,d_0) + K^T(k,d_0)\left(P(k) - \hat{\theta}(k-1,d_0)\varphi^T(k,d_0)\right) \quad (19)$$

$$K(k,d_0) = Q(k,d_0)\varphi^T(k,d_0). \left(\lambda + \varphi(k,d_0)Q(k,d_0)\varphi^T(k,d_0)\right)^{-1} \quad (20)$$

$$Q(k+1,d_0) = \left[I_{3x3} - K(k,d_0)\varphi(k,d_0)\right]Q(k,d_0)/\lambda \quad (21)$$

where $\hat{\theta}(k,d_0)$ is the estimated parameter vector, $Q(k,d_0)$ is the estimated parameter covariance matrix with initial conditions $\hat{\theta}(0,d_0)$ and $Q(0,d_0)$, respectively, Astrom & Wittenmark, [15]. For each delay d_0, we can define the model adequateness index S_{d_0} that represents the quality of model with the delay d_0. This index is given by

$$S_{d_0}(k) = \frac{\mu_{d_0}}{\sum_{d_0} \mu_{d_0}} \quad (22)$$

where $\mu_{d_0}(k)$ is the adequateness measure of the model with delay d_0. The chosen delay in each step is that one that to present the biggest adequateness index. There are many possibilities to the calculation of adequateness index and one of most used is based in the minimum quadratic error, given by

$$\mu_{d_0}(k) = \frac{1}{\sum_{i=1}^{k}\left(P(k) - \hat{\theta}(k-1,d_0)\varphi^T(k,d_0)\right)^2} \quad (23)$$

Using this criteria and an adaptive Linear Quadratic Gaussian (LQG) technique, Hemerly & Davis [20] showed that the delay estimates are consistent and the control is asymptotically stable.
Observe that the denominator of (23) represents the accumulated quadratic error of the model with delay d_0. The better model is that presents the biggest adequateness index.

The denominator of (23) represents the model's accumulated mean squared error.

2.2.2 Fuzzy-PI Controllers

In general, Fuzzy controllers have an input, a processing and an output stages. The input stage converts the sensor values in membership values (fuzzy values).

Fuzzy controllers have one input stage, one processing stage and one output stage. The input stage makes a measure of sensor signals and other kinds of inputs (like switches) and converts the information in appropriate form (fuzzyfication stage). The processing stage execute each appropriate rule and produces an output combining the rules results and finally the output stage converts the preceding combined result in a control signal.

In this work the fuzzy-PI controller is used with the control signal calculated in function of the error and its variation.

The membership functions used are a trapezoidal form showed in Figure 1.

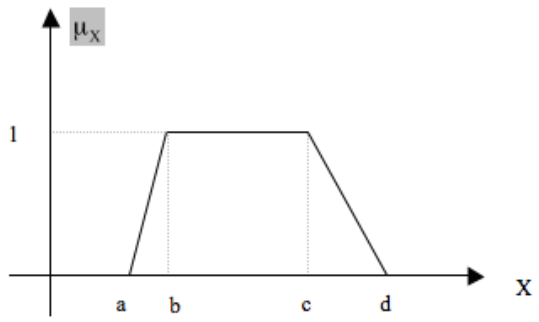

Figure 1- General form of membership functions

For the error are defined 5 fuzzy sets (NL- Negative Large, NS- Negative Small, ZE- Zero, PL- Positive Large, PS- Positive Small), whose membership functions are showed in Table 2, in function of the parameters a, b, c, d of Figure 1.

Table 2: Membership functions for error

Sets e(t)	**a**	**b**	**c**	**d**
NL	-60	-40	-30	-10
NS	-12	-6	-6	-2
ZE	-3	0	0	3
PS	0	6	6	12
PL	10	30	40	60

For the error variation $\Delta e(t)$ are defined the same sets using a scale factor of 1/10 for all values.

For the control signal variation $\Delta I(t)$ are used 5 sets (**NL**- Negative Large, **NS**- Negative Small, **ZE**- Zero, **PL**- Positive Large, **PS**- Positive Small). In this case are used singletons with the values: -90, -30, 0, 30 e 90, respectively.

The Table 3 shows the rules sets used for to calculate $\Delta I(t)$ variable as function of the error and its variation.

Table 3: Rules for the control signal variation.

		e(t)				
		NL	**NS**	**ZE**	**PS**	**PL**
Δe(t)	**NL**	NL	NL	NL	NL	ZE
	NS	NL	NS	NS	ZE	PL
	ZE	NL	NS	ZE	PS	PL
	PS	NL	ZE	PS	PS	PL
	PL	ZE	PL	PL	PL	PL

The table means that if, for example, the error is **NL** and its variation is **NL**, then the signal control variation is **NL**. For the deffuzification are used the mean of maximums method.

2.3 Intelligent Supervisor Proposed

The proposed system consists of a controller's set and an intelligent supervisor, which uses a rule-based fuzzy expert system. The controllers set includes conventional PI, PI-fuzzy, rule based and adaptive predictive controllers, described in previous section. The supervisor take cares of fault detection, physiologic constraints and alarms, and promotes a soft switching between the controllers signals. The controllers performance is evaluate with the aid of the identifier block. The completed block diagram of the proposed system is showed in Figure 2.

The identifier block is composed by least squares estimators with forgetting factor (one estimator for each delay considered), operating in parallel and a chose criteria to decide which is the "better" model in each step.

The following section describes the mean parts of the implemented supervisor. The supervisor make interesting adaptive characteristics to the controllers PI, PI-Fuzzy and rule based, because its parameters are modified in real time, depending on the patient parameters provided by the identifier block.

2.3.1 Initial Stage of Control

Regardless of the controller used, the first 10 steps of control are used for initiating the process of estimating the patient parameters, including the delay, which is considered constant throughout the remainder of the control horizon. We used a signal PRBS (Pseudo Random Binary Signal) with varying amplitude according to the estimated sensitivity of the patient, according to the equation 24:

$$u_{PRBS} = 60 - \frac{60}{3.8}\left|\hat{b}_1(k)\right| \qquad (24)$$

Then we generate a random number x uniformly distributed between 0 and 1. If $x \geq 0.5$ then and u(k)= uPRBS and u(k)=0, otherwise. The idea is to avoid a very large reduction of patient pressure in this initial period and, at the same time, excites him properly to get their parameters, which are important to the rest of the control horizon. The maximum amplitude of the PRBS is inversely proportional to drug patient's sensitivity, given by parameter b_1.

2.3.2 PI Controllers with Fuzzy Scheduling

Initially, the PI controller was tuned empirically considering different values for the parameters b_1 e b_{m+1} related to the sensitivity of each patient, as the range of values shown in Table 1. The Table 4 shows the parameters of the PI controller, tuned empirically on the basis of the aforementioned parameters of the patient. For other values of sensitivity, which implies a variation in the same proportion of b_1 and b_{m+1}, the value of the parameter

K_p should vary in this same proportion, leaving unchanged the value of Ti, due to the linear characteristic of the closed loop system, if the saturation region is not attained.

Table 4: Parameters of PI controller for nominal values of the patient parameters with different delays.

b_1	b_{m+1}	a_1	d=m	K_p	T_r
0.187	0.075	-0.741	2	0.064	8.0
			3	0.077	11.0
			4	0.090	15.0
			5	0.109	22.5

The idea used to give an adaptive feature for the PI controller is utilize a fuzzy system to adjust its parameters. The fuzzy system takes as input the value of b1 and the delay d provided by the identifier block and returns as output the value of the parameters K_p and T_i, the latter being dependent only of the delay.

We define 6 fuzzy sets for the b_1 parameter (VS- Very Small, NM- Nominal, SM- Small, ME- Medium, LA- Large, VL- Very Large) and the parameters of memberships functions (a, b, c, d, e) are showed in Table 5.

Table 5: Membership functions parameters for parameter b_1

Sets b_1	a	b	c	d
VS	0.000	0.050	0.050	0.150
NM	0.075	0.300	0.300	0.500
SM	0.400	0.600	0.600	0.800
ME	0.700	0.900	0.900	1.100
AL	1.000	1.200	1.200	1.400
VL	1.300	1.500	5.000	

We define 6 fuzzy sets for the controller gain Kp (VS- Very Small, NM- Nominal, SM- Small, ME- Medium, LA- Large, VL- Very Large) and the parameters of memberships functions (a, b, c, d, e) are showed in Table 6.

Table 6: Membership functions parameters for K_p

Sets K_p	a	b	c	d
VS	0.0000	0.0100	0.0100	0.0115
NM	0.0105	0.0120	0.0120	0.01425
SM	0.01275	0.0150	0.0150	0.01750
ME	0.01750	0.0250	0.0250	0.04375
AL	0.03125	0.0500	0.0500	0.12500
VL	0.07500	0.1500	0.5000	

The rules for the Kp adjustment as a function of the parameter b_1 are showed in Table 7.

Table 7: Rules for the K_p adjustment

Parameter K_p	**VS**	**NM**	**SM**	**ME**	**LA**	**VL**
	VL	**LA**	**ME**	**SM**	**NM**	**VS**

The mean of maximum defuzzification method (MoM) was used in this case.

The of reset time parameter T_r setting is made according to the estimated delay, as shown in Table 4.

2.3.3 Critical of Read Pressure Value

Another function of the supervisor is to make a critical analysis of the measure patient pressure, avoiding that wrong measures cause a bad controllers reaction inadequate, with drastic consequences for the patient. In case of very rapid change in pressure, caused for example by sampling the pressure, leaks or manipulation in the arterial line, we have no reliable measures of pressure in a few moments, and the supervisor uses the identifier to calculate the predicted value of the pressure that is used to obtain the infusion rate by the controllers until the end of the disturbance is detected, discarding erroneous readings. If the disturbances last a long time the supervisor will notify the operator and stops the infusion (Martin et al, 1992). In this case we are adopting as acceptable at most three consecutive erroneous readings.

In the case of drastic physiological changes in pressure, the supervisor should be able to take action quick and secure. If, for example, the patient has a sudden hemorrhage, his pressure will drop drastically. Still being injected SNP, this can result

in hypotension or even death of the patient. Thus, the supervisor detects fast decreases, but still physiological, in blood pressure and very low values too and immediately stop the infusion of SNP.

In these cases, the infusion of SNP was adjourned until the pressure exceeds a threshold, as (Martin et al, 1992a; Martin et al, 1992b). If the system detects a sudden change in blood pressure, the supervisor rejects it and send to the controller the pressure predicted, until the suppression of the wrong measures or issues are identified with the patient and the infusion is zeroed and the medical staff informed.

3 Results

This section presents the results of applying the developed controllers in the simulation of blood pressure control of a patient. Simulations were made with separate controllers, showing its limitations. The following simulations show the system operating with the Supervisor, considering different operating conditions.

3.1 Adaptive Predictive Controller

Consider a patient with the following nominal parameters:

b_1= 0.187; b_{m+1}= 0.075; a_1= -0.741; m=3

P_0= 150 mmHg; P_{ref}=50 mmHg

(MAP_{ref}= 100 mmHg) and $\sigma_e^2 = 4$ (25)

The Figures 3 and 4 show the system simulation result of the pressure control with the adaptive predictive controller.

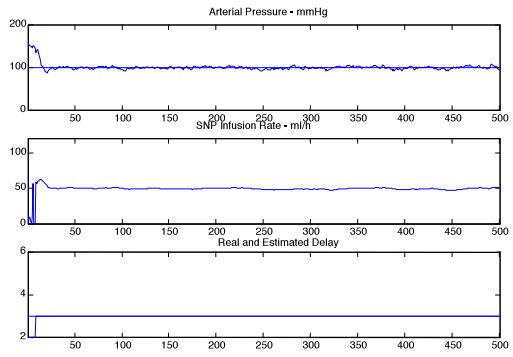

Figure 3: Patient pressure, infusion rate and delay (real and estimated) for the system (25) and adaptive predictive control application

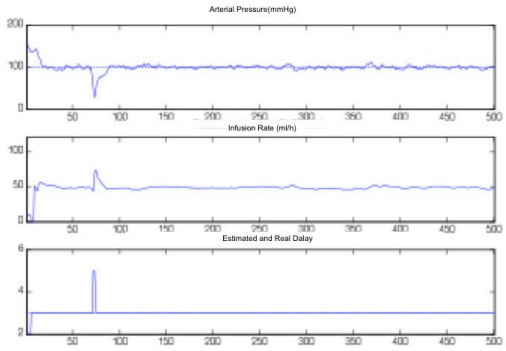

Figure 4: Patient pressure, infusion rate and delay for the system (25) and adaptive predictive control application, with wrong measure pressure

With rejection failure, we have the results given by Figure 5.

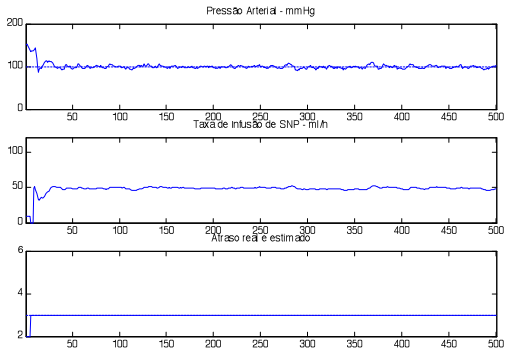

Figure 5: Patient pressure, infusion rate and delay for the system (25) and adaptive predictive control application, with wrong measure pressure and rejection failure

In this case, the supervisor recognizes the failure in the measure blood pressure and during this failure uses its predicted value to replace it.

3.2 PI Controllers with Fuzzy Parameters Scheduling

Consider a patient with the following nominal parameters:

b_1= 0.900; b_{m+1}= 0.360; a_1= -0.741; m=3

P_0= 150 mmHg; P_{ref}=50 mmHg

(MAP_{ref}= 100 mmHg) and $\sigma_e^2 = 4$ (26)

In step 50, was introduced a variation in parameters b_1 and b_{m+1} for 1.200 and 0.480,

respectively. The performance of arterial pressure controlled by a PI controller with fuzzy parameters scheduling is showed in Figure 6.

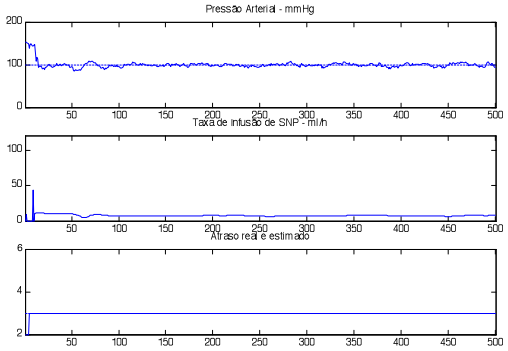

Figure 6: Patient pressure, infusion rate and delay for the system (26) controlled by PI Controller with fuzzy scheduling

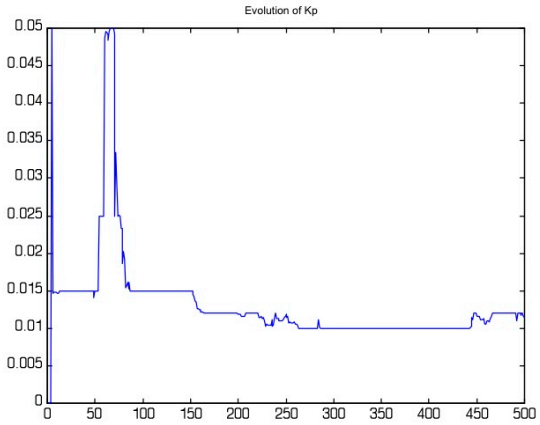

Figure 7- Time evolution of the controller gain K_p

4 Conclusion

In this work we have done the implementation of an intelligent adaptive control scheme to control the blood pressure of a patient. We start from the patient's model and implement various types of controllers: PI, PI-Fuzzy rule-based and predictive controller with adaptive weighting of the control signal, which in this case is the infusion rate. The latter controller requires the use of an identification method in order to estimate the parameters and delays associated to each patient. We used a fuzzy intelligent supervisor to provide an adaptive behavior to the PI controller, making a kind of gain scheduling. This idea can be extended to rule-based controllers and fuzzy-PI, for example.

Another idea is the use, in all the controllers, an initial period of application of a PRBS signal, to estimate the order and the parameters of the patient. The amplitude of this signal is a function of the patient's sensitivity, which may vary to much (from 0.2 to 3.5) and may also vary for the same patient during the control period.

The adaptive predictive controller behaves quite satisfactory for various plant parameters (patient), particularly when large variations occur in the parameters of the patient during the horizon control. An advantage of this type of controller is that it requires practically no tuning parameters set by the user, unlike other controllers. However, its implementation is more difficult and the computational effort is higher in comparison with other controllers evaluated.

An additional aspect addressed was the issue related to the rejection of erroneous measures of the patient's blood pressure. At each step, the pressure value read is compared with the predicted value. If the difference is greater than a predetermined limit, the value read is rejected, and used the predicted value for the duration of the disorder. Meanwhile, the wrong measurements are being considered as non-physiological, in other words, due to errors in the measurement (leaks or manipulation in arterial line, for example). The results show that the proposed scheme is efficient, requiring further improvements to implementations in patients.

The proposed scheme can deal well with patients of different characteristics and slowly time-varying characteristics, rejecting erroneous measures and adapting the parameters of controllers in real time.

References:

[1] Slate, J. B. *Model-Based Design of a Controller for Infusing Nitro-Prusside During Postsurgical Hypertension*. PhD thesis, Univ. Wisconsin-Madison, n0 8028208, Univ. Microfilms Internat., Ann. Arbor, MI, 1980.

[2] Pajunen, G. A.; Steinmetz, M. & Shankar, R. Model Reference Adaptive Control with Constraints for Postoperative Blood Pressure Management. *IEEE Transactions on Biomedical Engineering*, v. 37, p. 679-687, 1990.

[3] Maitelli, A. L. & Yoneyama, T. Suboptimal Dual Adaptive Control for Blood Pressure Management. *IEEE Transactions on Biomedical Engineering*, v. 44, p. 486-497, 1997.

[4] Polycarpou, M. M. & Conway, J. Y. Indirect Adaptive Nonlinear Control of Drug Delivery Systems. *IEEE Transactions on Automatic Control*, v. 43, p. 849-853, 1998.

[5] Ying, H.; McEachern, M.; Eddleman, D. W. & Sheppard, L. C. Fuzzy Control of Mean

Arterial Pressure in Postsurgical Patients with Sodium Nitroprusside Infusion. *IEEE Transactions on Biomedical Engineering*, v. 39, p. 1060-1070, 1992.

[6] Arnspager, J. M.; McInnis, J.; Glover, J. & Normann, N. A. Adaptive Control for Blood Pressure. *IEEE Transactions on Biomedical Engineering*, v. 30, p. 168-176, 1983.

[7] Stern, K. S.; Walter, B. K. & Chizeck, H. J. Automated Blood Pressure Control using a Self-Tuning Regulator. *Proceedings of IEEE 1981 Frontiers of Eng. Health Care Conference*, p. 255-258, 1981.

[8] Koivo, A. J. Microprocessor-based Controller to Pharmacodynamical Applications. *IEEE Transactions on Automatic Control*, v. 26, p. 1208-1213, 1981.

[9] Sheppard, L. C., Computer Control of the Infusion of Vasoactive Drugs. *Ann. Biomedical Engineering*, v. 8, p. 431-444, 1980.

[10] Martin, J. F.; Schneider, A. M.; Quinn, M. L. & Smith, N. T., Improved Safety and Efficacy in Adaptive Control of Arterial Blood Pressure Through the Use of a Supervisor. *IEEE Transactions on Biomedical Engineering*, v. 39, p. 381-388, 1992.

[11] Martin, J. F.; Schneider, A. M.; Quinn, M. L. & Smith, N. T., Supervisory Adaptive Control of Arterial Pressure During Cardiac Surgery. *IEEE Transactions on Biomedical Engineering*, v. 39, p. 389-393, 1992.

[12] [12] Maitelli, A. L. & Silva, C. H. S., Controle Adaptativo da Pressão Arterial com Restrições. *Anais do XV Congresso Brasileiro de Engenharia Biomédica*, v. 1, p.113-114, 1997.

[13] Cruz, V. S. Desenvolvimento de um Supervisor Aplicado ao Problema de Controle Digital da Pressão Arterial, *Anais do 9o Congresso de Iniciação Científica da UFRN*, 1999.

[14] Yen, J.; Largari, R. & Zadeh, L. A., *Industrial Applications of Fuzzy Logic and Intelligent Systems*, New York: IEEE Press, 1995.

[15] Astrom, K. J. & Wittenmark, B., *Adaptive Control*, New York: Addison-Wesley Publishing Company, 1989.

[16] Braunwald, W., *Tratado de Medicina Cardiovascular*, Volume 1, 3a Edição, São Paulo: Livraria Roca LTDA, 1991.

[17] Isaka, S. & Sebald, A., Control Strategies for Blood Pressure Regulation, IEEE *Transactions on Biomedical Engineering*, v. 40, p. 353-363, 1993.

[18] Kwok, K. K.; Shah, S. L.; Firegan, B. A. & Kwong, G. K., An Observational Trial of a Computarized Drug Delivery System on Two Patients, IEEE Transactions on Control Systems Technology", v. 5, n. 4, 1997.

[19] Shieh, J. S.; Linkens, D. A. & Peacock, J. E., Hierarquial Rule-Based and Self-Organizing Fuzzy Logic Control of Depth of Anaesthesia, *IEEE Transactions on Systems, Man and Cybernetics*, Part C, Applications and Reviews, v. 29, n. 1, 1999.

[20] Hemerly, E. M. & Davis, M. H. A., Recursive Order estimation of Stochastic Control Systems, Math Systems Theory, v. 22, p. 323-346, 1989.

[21] Held, C. M & Roy, R. J. (1995), "Multiple Drug Hemodynamic Control by Means of a Supervisory-Fuzzy Rule-Based Adaptive Control System: Validation on a Model", IEEE Transactions on Biomedical Engineering, v. 42, n. 4, p. 371-385.

[22] Sririvas, Y, Timmons, W. D. & Durkin, J., A Comparative Study of Three Expert Systems for Blood Pressure Control, *Expert Systems with Applications*, v. 20, p. 267-274, 2001.

[23] [23] Chen, C. T.; Lin, W. L.; Kuo, T. S. and Wang, C. Y. (1997), "Adaptive Control of Arterial Blood Pressure with a Learning Controller Based on Multilayer Neural Networks", IEEE Transactions on Biomedical Engineering, v. 44, n. 7.

[24] Enbiya, S.; Mahieddine, F.; Hossain, A., Model Reference Adaptive Scheme for Multi-drug Infusion for Blood Pressure Control, *Journal of Integrative Bioinformatics*, 8(3):173, 2011.

[25] [25] Spielberg, D.R.; Barrett, J.S.; Hammer, G.B.; Drover, D.R.; Reece, T.; Cohane, C.A., Schulman, S.R., Predictors of arterial blood pressure control during deliberate hypotension with sodium nitroprusside in children, Anesthesia & Analgesia, Volume 119, Issue 4 - p 867–874, 2014.