Controlling Drug Infusion Biological Systems FREN with Sliding Bounds

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***Abstract*— In this paper, a direct adaptive control for drug infusion of biological systems is presented. The proposed controller is accomplished using our adaptive network called *Fuzzy Rules Emulated Network* (FREN). The structure of FREN resembles the human knowledge in the form of fuzzy IF-THEN rules. After selecting the initial value of network's parameters, an on-line adaptive process based on Lyapunov's criteria is performed to improve the controller performance. The control signal from FREN is designed to keep in the region which is calculated by the modified *Sliding Mode Control* (SMC). The simulation results indicate that the proposed algorithm can satisfy the setting point and the robust performance.**

I. INTRODUCTION

The infusion of sodium nitroprusside in order to lower blood pressure in patients after surgery is an example of the drug infusion problem. There are two general methods for administering the drug [1]. The first one is a bolus injection and the second is a continuously controlled release of the drug. The controller must find the correct dose to decrease the blood pressure to the desired level with out the risk of a drug overdose. The model of a patient's response have been represented in [2]. This model has been used by several controller design studies. The model reference adaptive controller was introduced in [3]. Many multiple-mode adaptive controllers were presented in [4] and [5]. A robust direct model reference adaptive controller was described in [6], in which the control of a dog's mean arterial blood pressure was investigated. Unfortunately, theirs result are based on a linearized nonlinear model and need the accurate mathematical model.

In this paper, our adaptive controller inspired by the hybrid *Sliding Mode Control*(SMC) [7], [8], [9] and a recently proposed adaptive controller called *Fuzzy Rules Emulated Network* (FREN) [10], [11] is presented to cope those problems. The mathematical model of the controlled drug system is not necessary. The structure of FREN resembles the human knowledge in the form of fuzzy control rules and its initial setting of network parameters is intutively selected. After setting its parameters, an on-line adaptation is performed during its operation to fine tune the values. Hence, the controller is able to adapt itself to the change of environment. During the control effort is generated by FREN, the stability can be guaranteed by the bound signals calculated by the modified SMC.

This paper is organized as follows. Section II introduces the overview of the drug infusion model. The bound of the control effort is presented in section III. Then, in section IV, the structure of FREN is introduced. Its usage as a controller is explained in the next subsection. During the operation, all FREN's parameters are adjusted in order to minimize the control error signal. This adaptive method based on the steepest descent or gradient search is presented in subsection IV-B. The criteria for learning rate selection is discussed next. Then the computer simulation results when applying FREN to control the change in blood pressure to the infusion rate of sodium nitroprusside are shown in section V. In the final section, some conclusions are given.

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II. THE DRUG INFUSION MODEL

In [2], a model of a patient's response to the infusion of sodium nitroprusside has been perforned. The transfer function is

$$\frac{\Delta P_d(s)}{I(s)} = \frac{Ke^{-T_i s}(1+\alpha e^{-T_c s})}{\tau s + 1}, \quad (1)$$

where $\Delta P_d(s)$ is the change in mean arterial blood pressure in $mmHg$ and $I(s)$ is the drug infusion rate in mlh^{-1}. Other parameters can be defined as follows:

- K Sensitivity of the patient to the drug $\left(\frac{mmHg}{mlh^{-1}}\right)$,
- T_i Initial transport delay (sec),
- T_c Recirculation transport delay (sec),
- α Recirculation $(-)$,
- τ Lag time constant (sec).

In this paper, the simulation will be done with a discret-time model. Let $\Delta P_d(k)$ and $I(k)$ be the k^{th} sampling of $\Delta p_d(t)$ and $i(t)$, where $\Delta p_d(t)$ and $i(t)$ are invert Laplace transform of $\Delta P_d(s)$ and $I(s)$, respectively. The plant simulation is depicted in Fig. 1, where $\Delta P_d(k)$ and $I(k)$ are denoted by $Y(s)$ and $U(s)$, respectively. The disturbance is generated to follow the patient's environment as shown in Fig. 2.

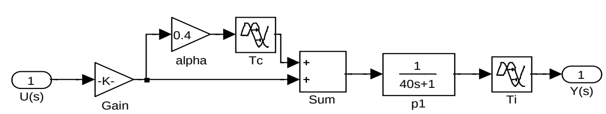

Fig. 1. Drug system

From (1), the controlled drug system can be rewritten as

$$\Delta P_d(k+1) = f(P_d(k),\phi) + g(P_d(k),\phi)I(k) + d(k), \quad (2)$$

or in state equation form as

$$\begin{bmatrix} x_1(k+1) \\ x_2(k+1) \end{bmatrix} = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} x_1(k) \\ x_2(k) \end{bmatrix} + \begin{bmatrix} 0 \\ g(.) \end{bmatrix} u(k) + \begin{bmatrix} 0 \\ f(.) \end{bmatrix} + \begin{bmatrix} 0 \\ d(k) \end{bmatrix}, \quad (3)$$

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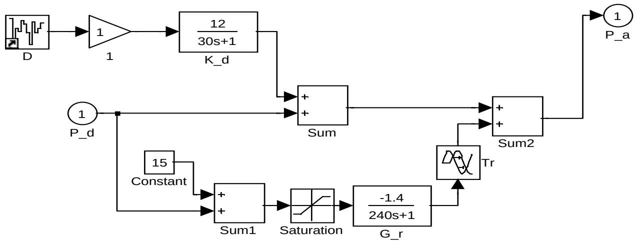

Fig. 2. Disturbance of patient environment and condition

where $x_2(k) = \Delta P_d(k)$, $x_1(k) = \Delta P_d(k-1)$, $u(k)$ is the control signal $I(k)$, $f(.)$ and $g(.)$ are unknown nonlinear functions and $d(k)$ is the bounded disturbance. The system in Eq. (3) with only boundaries of $f(.)$, $g(.)$ and $d(k)$ is used to design the proposed controller as shown in the next section.

III. The Region of the Control Effort

The control effort range is determined by using the modified SMC based on the discrete-time domain. The general N^{th}-order nonlinear discrete-time plant can be written as

$$\begin{bmatrix} x_1(k+1) \\ x_2(k+1) \\ \vdots \\ x_{N-1}(k+1) \\ x_N(k+1) \end{bmatrix} = \begin{bmatrix} a_{1,1} & \cdots & a_{1,N} \\ a_{2,1} & \cdots & a_{2,N} \\ \vdots & \ddots & \vdots \\ a_{N-1,1} & \cdots & a_{N-1,N} \\ a_{N,1} & \cdots & a_{N,N} \end{bmatrix} \begin{bmatrix} x_1(k) \\ x_2(k) \\ \vdots \\ x_{N-1}(k) \\ x_N(k) \end{bmatrix} + \begin{bmatrix} b_1 \\ b_2 \\ \vdots \\ b_N \end{bmatrix} u(k) + \begin{bmatrix} f_1(\boldsymbol{x}) \\ f_2(\boldsymbol{x}) \\ \vdots \\ f_N(\boldsymbol{x}) \end{bmatrix} + \begin{bmatrix} d_1(k) \\ d_2(k) \\ \vdots \\ d_N(k) \end{bmatrix} d(k),$$

or

$$\boldsymbol{x}(k+1) = \boldsymbol{A}\boldsymbol{x}(k) + \boldsymbol{B}_k u(k) + \boldsymbol{F}_k + \boldsymbol{D}_k. \tag{4}$$

Define $s(k)$ as

$$s(k) = \boldsymbol{c}\Big[\boldsymbol{x}(k) - \boldsymbol{x}_d(k)\Big] = \boldsymbol{c}\boldsymbol{e}(k), \tag{5}$$

where $\boldsymbol{x}_d(k)$ be the desired value of $\boldsymbol{x}$ at time k and $\boldsymbol{c} = \begin{bmatrix} c_1 & \cdots & c_N \end{bmatrix} \in R^N$ is a constant matrix, $f : R^N \to R$ and $d_i(k)$ for $i = 1, 2, ..., N$ is unknown disturbance. Note that $\boldsymbol{c}^T$ must not orthogonal to $\boldsymbol{e}$, and the roots of the polynomia $c_N + c_{N-1}z^{-1} + \cdots + c_1 z^{-(N-1)} = 0$ must be kept in the unit circle. From Eq. (4) and (5), $s(k+1)$ can be obtained as

$$s(k+1) = \boldsymbol{c}\boldsymbol{A}\boldsymbol{x}(k) + \boldsymbol{c}\boldsymbol{B}_k u(k) + \boldsymbol{c}\varphi_k - \boldsymbol{c}\boldsymbol{x}_d(k+1), \tag{6}$$

where $\varphi_k = \boldsymbol{F}_k + \boldsymbol{D}_k$. Define the Lyapunov function

$$V(k) = s^2(k), \tag{7}$$

and

$$\begin{aligned} \Delta V(k) &= V(k+1) - V(k), \\ &= s^2(k+1) - s^2(k). \end{aligned} \tag{8}$$

For stability we must have

$$\Delta V(k) < 0 \;\Rightarrow\; s^2(k+1) < s^2(k), \tag{9}$$

thus

$$\Big[s(k+1) + s(k)\Big]\Big[s(k+1) - s(k)\Big] < 0. \tag{10}$$

Assuming that $|\varphi_k| < \Phi_q$, $\boldsymbol{c}\boldsymbol{B}_k > 0$ and

$$\mathcal{A} = \boldsymbol{c}\boldsymbol{x}_d(k+1) - \boldsymbol{c}\boldsymbol{A}\boldsymbol{x}(k). \tag{11}$$

From Eq. (10), there are two possible cases as follows:
Case I: $s(k+1) + s(k) > 0$ *and* $s(k+1) - s(k) < 0$
We obtain

$$-\mathcal{A} + \boldsymbol{c}\boldsymbol{B}_k u(k) + \boldsymbol{c}\varphi_k + s(k) \quad > \quad 0, \tag{12}$$
$$-\mathcal{A} + \boldsymbol{c}\boldsymbol{B}_k u(k) + \boldsymbol{c}\varphi_k - s(k) \quad < \quad 0. \tag{13}$$

Eq. (12) and (13) lead to

$$\frac{\mathcal{A} - \boldsymbol{c}\varphi_k - s(k)}{\boldsymbol{c}\boldsymbol{B}_k} < u(k) < \frac{\mathcal{A} - \boldsymbol{c}\varphi_k + s(k)}{\boldsymbol{c}\boldsymbol{B}_k}. \tag{14}$$

Since

$$\begin{aligned} u_{1p}(k) &= \frac{\mathcal{A} + \boldsymbol{c}\Phi_q + s(k)}{\boldsymbol{c}\boldsymbol{B}_k} \\ &> \frac{\mathcal{A} - \boldsymbol{c}\varphi_k + s(k)}{\boldsymbol{c}\boldsymbol{B}_k}, \\ u_{1n}(k) &= \frac{\mathcal{A} - \boldsymbol{c}\Phi_q - s(k)}{\boldsymbol{c}\boldsymbol{B}_k} \\ &< \frac{\mathcal{A} - \boldsymbol{c}\varphi_k - s(k)}{\boldsymbol{c}\boldsymbol{B}_k}, \end{aligned}$$

we can conclude that

$$u_{1n}(k) < u(k) < u_{1p}(k). \tag{15}$$

Since $u_{1p}(k) > u_{1n}(k)$, it is required that

$$s(k) > -c_N \Phi_q. \tag{16}$$

Case II: $s(k+1) + s(k) < 0$ *and* $s(k+1) - s(k) > 0$
We obtain

$$-\mathcal{A} + \boldsymbol{c}\boldsymbol{B}_k u(k) + \boldsymbol{c}\varphi_k + s(k) \quad < \quad 0, \tag{17}$$
$$-\mathcal{A} + \boldsymbol{c}\boldsymbol{B}_k u(k) + \boldsymbol{c}\varphi_k - s(k) \quad > \quad 0. \tag{18}$$

Eq. (17) and (18) yield

$$\frac{\mathcal{A} - \boldsymbol{c}\varphi_k + s(k)}{\boldsymbol{c}\boldsymbol{B}_k} < u(k) < \frac{\mathcal{A} - \boldsymbol{c}\varphi_k - s(k)}{\boldsymbol{c}\boldsymbol{B}_k}. \tag{19}$$

Since

$$\begin{aligned} u_{2p}(k) &= \frac{\mathcal{A} + c_N\Phi_q - s(k)}{\boldsymbol{c}\boldsymbol{B}_k} \\ &> \frac{\mathcal{A} - \boldsymbol{c}\varphi_k - s(k)}{\boldsymbol{c}\boldsymbol{B}_k}, \\ u_{2n}(k) &= \frac{\mathcal{A} - c_N\Phi_q + s(k)}{\boldsymbol{c}\boldsymbol{B}_k} \\ &< \frac{\mathcal{A} - \boldsymbol{c}\varphi_k + s(k)}{\boldsymbol{c}\boldsymbol{B}_k}, \end{aligned}$$

again we can conclude that

$$u_{2n}(k) < u(k) < u_{2p}(k). \tag{20}$$

Since $u_{2p}(k) > u_{2n}(k)$, it is required that

$$s(k) < c_N \Phi_q. \tag{21}$$

The control effort $u(k)$ will be determined within this boundary using the adaptive network called FREN to be introduced in the next section.

IV. FREN AS CONTROLLER

A. Fuzzy Rules Emulated Network

A general fuzzy inference system can be represented by the IF-THEN rules. For a single input system, these rules may be written as,

RULE i: IF I_{input} IS A_i THEN $B_i = (h_i - k_i)\mu_{A_i} + k_i$

where I_{input} denotes the crisp input of this fuzzy system. This rule indicates that if e belongs to the fuzzy set A_i with the membership value of μ_{A_i} then the fuzzy value of the output of this rule, denoted by B_i, is equal to the linear function of h_i and k_i called Linear Consequence (LC) parameters. After all rules have been processed, the crisp output O_{output} is calculated by

$$O_{output} = \sum_{i=1}^{N} B_i, \tag{22}$$

where N denotes the number of fuzzy rules. When using the proposed FREN as a controller, the structure of the control system becomes as shown in Fig. 3. The FREN receives the error signal $E(k)$ and computes the

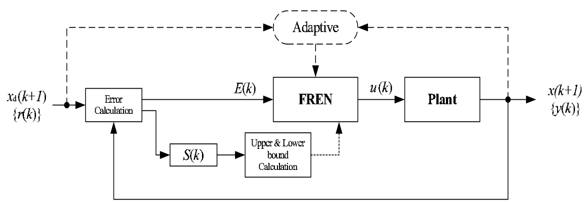

Fig. 3. Control system using FREN

control signal $u(k)$. The plant control signal $u(k)$ is obtained by

$$u(k) = O_{output}, \tag{23}$$

where O_{output} is the output of FREN in (22) and $E(k)$ is the input to FREN or I_{input}. As an example of how the initial value of FREN's parameters are selected, consider the following 4 fuzzy control rules,

RULE 1 IF E IS PL THEN u IS PL
RULE 2 IF E IS PM THEN u IS PM
RULE 3 IF E IS NM THEN u IS NM
RULE 4 IF E IS NL THEN u IS NL.

Assume that the error signal $E \in [-1, 1]$ and the calculated lower and upper bound of the control effort are -2 and 2, respectively, i.e. $u_k \in [-2, 2]$. The value of the control effort, u_k can be set by parameters in LC (e.g. h_i and k_i for $i = 1, 2, 3, 4$.) In this example, h_1 is set to the upper bound ($h_1 = 2$) and h_4 is set to the lower bound ($h_4 = -2$). The other parameters are $h_2 = \frac{h_1}{2} = 1$, $h_3 = \frac{h_4}{2} = -1$, and $k_i = 0$ for $i = 1, 2, 3, 4$. Then, MF parameters are selected to cover the error range. The initial setting of all parameters can be given as:

$$\begin{aligned}
\text{Rule1}: &\quad A_1 = \mu_1(E) = \tfrac{1}{1+\exp[20(E+0.35)]} &&; B_1 = 2A_1,\\
\text{Rule2}: &\quad A_2 = \mu_2(E) = \exp\left(-[\tfrac{E-0.25}{0.15}]^2\right) &&; B_2 = A_2,\\
\text{Rule3}: &\quad A_3 = \mu_3(E) = \exp\left(-[\tfrac{E+0.25}{0.15}]^2\right) &&; B_3 = -A_3,\\
\text{Rule4}: &\quad A_4 = \mu_4(E) = \tfrac{1}{1+\exp[-20(E-0.35)]} &&; B_4 = -2A_4.
\end{aligned}$$

The results of this setting are shown in Fig. 4. Notice that the control effort u_k is within [-2,2].

B. Adaptation algorithm

Since the initial setting of FREN parameters are just rough estimation based on a human expert experience, it is necessary to fine tune these values in order to cope with environmental change and to improve system performance. In this work, an adaptive technique based on the steepest descent technique is proposed to adjust all parameters during system operation. Firstly, we define the objective function as

$$\xi(k) = \frac{1}{2}\Big(r(k) - y(k)\Big)^2, \tag{24}$$

where $r(k)$ and $y(k)$ are the reference and the plant's output signal at time k respectively. The objective is to adjust all of FREN's parameters i.e. shapes of membership function and linear consequences, in order to minimize Eq. (24). The value of parameter P_i is updated at each time step by

$$P_i^{\text{new}} = P_i + \Delta P_i = P_i - \eta_i \frac{\partial \xi}{\partial P_i}, \tag{25}$$

where η_i is called the learning rate of the i-th parameter. The term $\partial\xi/\partial P_i$ is calculated from

$$\frac{\partial \xi}{\partial P_i} = \frac{\partial \xi}{\partial y}\,\frac{\partial y}{\partial u}\,\frac{\partial u}{\partial P_i}, \tag{26}$$

where u is the control signal, i.e. the output of the controller O. Thus

$$\frac{\partial u}{\partial P_i} = \frac{\partial O}{\partial P_i}. \tag{27}$$

This term can be analytically obtained since the network structure is already known.

Other terms in Eq.(26) are approximated by

$$\frac{\partial y}{\partial u} = Y_p \approx \frac{y(k) - y(k-1)}{u(k) - u(k-1)}, \tag{28}$$

and

$$\frac{\partial \xi}{\partial y} = y(k) - r(k) = -E(k). \tag{29}$$

Finally, Eq (25) becomes

$$P_i^{\text{new}} = P_i + \eta_i E(k) Y_p \frac{\partial O}{\partial P_i}. \tag{30}$$

C. Learning Rate Selection

The difficulty in using the adaptive method based on the steepest descent technique is on the selection of appropriate value for the learning rate. Too large value of the learning rate may reduce system stability whereas too small value reduces the system adaptation performance. In this subsection, we discuss how to select an appropriate learning rate which guarantees the stability in Lyapunov's sense. Consider the following Lyapunov function

$$V(k) = \frac{1}{2}\Big(r(k) - y(k)\Big)^2 = \frac{1}{2}E^2(k). \tag{31}$$

The change of Lyapunov function is given by

$$\begin{aligned}
\Delta V(k) &= V(k+1) - V(k)\\
&= \frac{1}{2}\Big(E^2(k+1) - E^2(k)\Big)\\
&= \Delta E(k)\Big(E(k) + \frac{1}{2}\Delta E(k)\Big),
\end{aligned} \tag{32}$$

where $\Delta E(k) = E(k+1) - E(k)$ is the change of error. This can be approximated by

$$\Delta E(k) = \frac{\Delta E(k)}{\Delta P_i}\Delta P_i \approx \frac{\partial E(k)}{\partial P_i}\Delta P_i, \tag{33}$$

for small ΔP_i.

The term $\partial E(k)/\partial P_i$ can be calculated by

$$\frac{\partial E(k)}{\partial P_i} = \frac{\partial E(k)}{\partial y}\,\frac{\partial y}{\partial O}\,\frac{\partial O}{\partial P_i} = -Y_p \frac{\partial O}{\partial P_i}. \tag{34}$$

since $\partial E(k)/\partial y = -1$ and $\partial y/\partial O = \partial y/\partial u = Y_p$.

Using ΔP_i from Eq.(30), the change of the Lyapunov function can then be written as

$$\Delta V(k) = -\eta_i \left(E(k) Y_p \frac{\partial O}{\partial P_i}\right)^2 \left\{1 - \frac{1}{2}\eta_i \left(Y_p \frac{\partial O}{\partial P_i}\right)^2\right\}. \tag{35}$$

According to the stability condition, $\Delta V(k)$ must be less than zero, this yields

$$0 < \eta_i < 2\left(Y_p \frac{\partial O}{\partial P_i}\right)^{-2}. \tag{36}$$

The learning rate η_i should lie in the range indicated by the above relation in order to guarantee system stability.

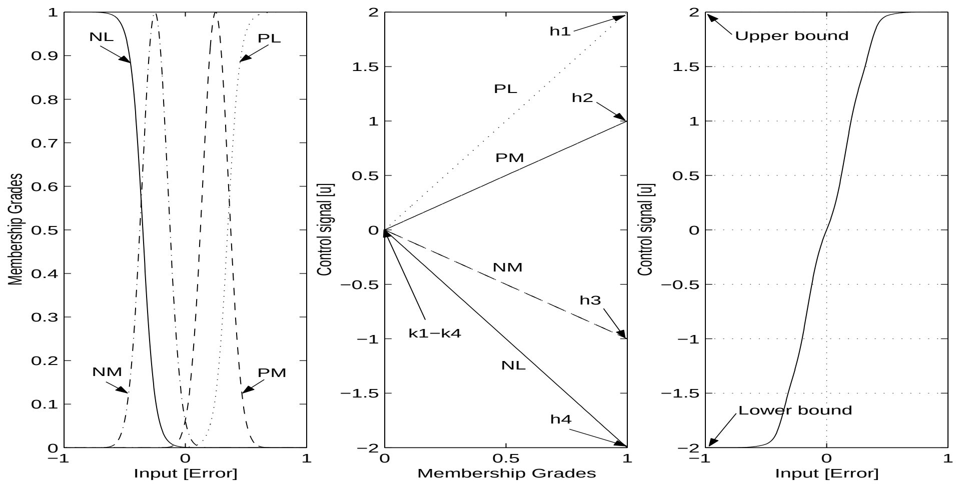

Fig. 4. FREN parameters setting

V. Simulation results

The proposed controller is tested on 3 different patients, the insensitive, the nominal and the sensitive patient. The parameters in Eq. (1) are set as the following:

Parameters	Sensitive	Nominal	Insensitive	Units
K	-9	-0.714	-0.178	$\left(\frac{mmHg}{mlh^{-1}}\right)$,
T_i	20	30	60	(sec),
T_c	30	45	75	(sec),
α	0	0.4	0.4	$(-)$,
τ	30	40	60	(sec).

The sampling time for this simulation is set to 1 sec. The target presure is set to decrease 30 $mmHg$. Denoting the error $e = \Delta P_{setting} - \Delta P$ and u as the control drug rate, the fuzzy control rules of FREN are given by,

Rule 1 If e is PL Then u is PL
Rule 2 If e is PM Then u is PM
Rule 3 If e is NM Then u is NM
Rule 4 If e is NL Then u is NL.

The simulation system is illustrated in Fig. 5. The initial membership functions and LC of FREN are shown in Fig. 6. Both LC and menbership function parameters are adjusted by using Eq. (30). After the learnaing phase around 2,500 epoch, the final membership functions and LC of FREN for the insensitive, the nominal and the sensitive patient are shown on Figs. 7, 8 and 9, respectively. The simulation results of those cases are shown in Fig. 10. In this simulation, the sensitive patient reachs the set point around 10 min. For the insensitive patient case, the blood pressure level reachs the set point in 25min.

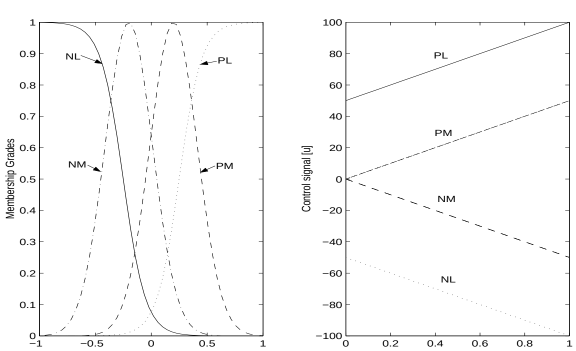

Fig. 6. Initial setting: Membership functions and LC

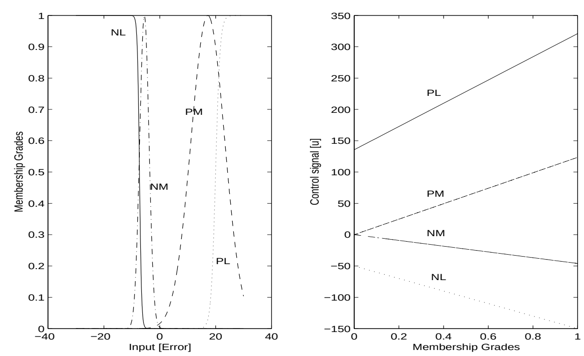

Fig. 7. Final learning: Membership functions and LC of insensitive patient

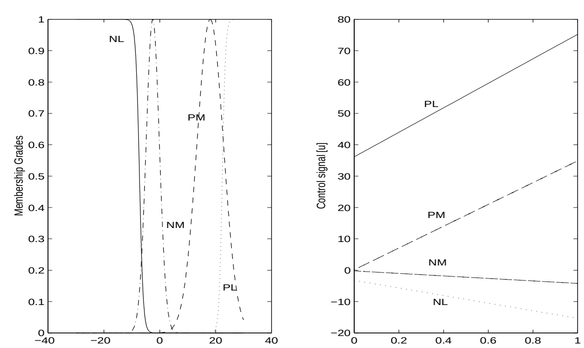

Fig. 8. Final learning: Membership functions and LC of nominal patient

VI. Conclusions

A discrete-time adaptive controller has been introduced to control the drug infusion stated in [2]. This controller is contructed with our adaptable network (FREN) combined with a modified SMC to calculate the control effort bounds. While the control effort is generated by FREN, the control signal must be kept in these bounds. Three the different patients conditions (sensitive, nominal and insensitive) are used to test the controller performance. Finally, from the simulation result, the proposed controller can provide a good response.

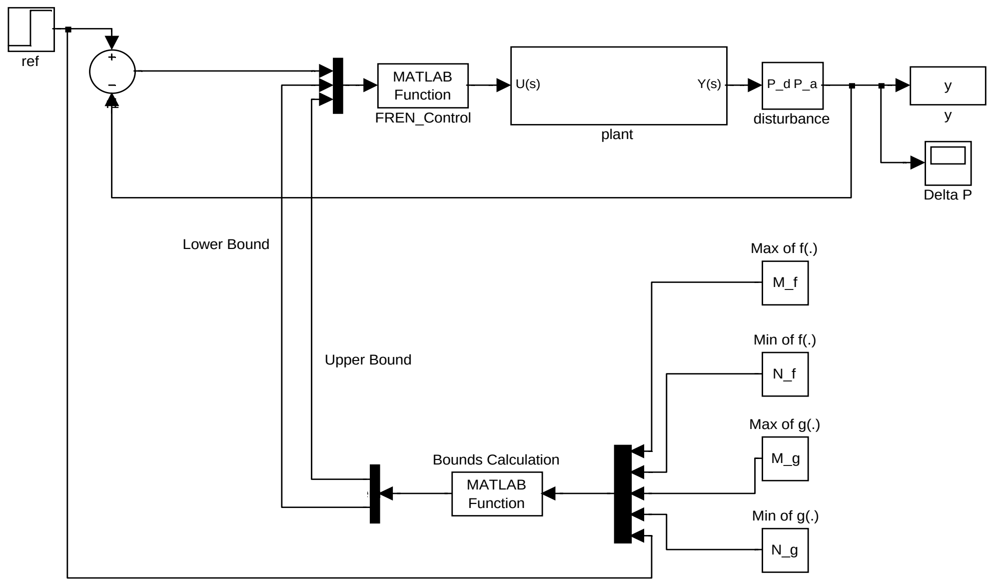

Fig. 5. Drug control system using FREN

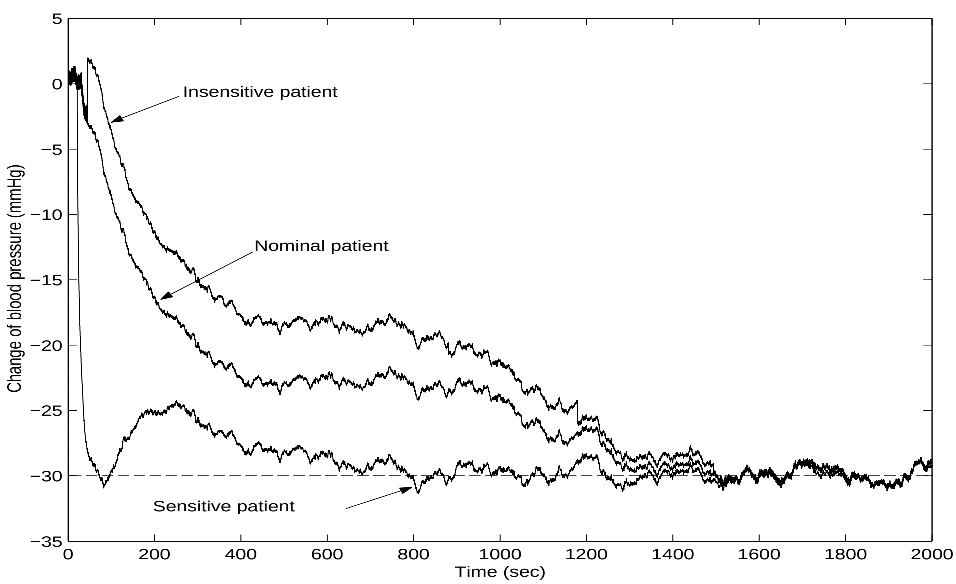

Fig. 10. Simulation results: ΔP and time

VII. ACKNOWLEDGMENTS

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REFERENCES

[1] J. Hahn, T. Edison and T. F. Edgar, "Adaptive IMC control for drug infusion for biological systems," *Control Engineering Practice.*, Vol. 10, pp. 45-56, 2002.

[2] J. B. Slate and L. C. Sheppard, "Automatic control of blood pressure by drug infusion," *IEE Proceedings part A.*, Vol. 9, pp. 639-645, 1982.

[3] H. Kaufman, R. Roy and X. Xu, "Model reference adaptive control of drug infusion rate," *Automatica*, Vol. 20, pp. 205-209, 1984.

[4] J. F. Martin, A. M. Schneider and N. T. Smit, "Multiple-mode adaptive control of blood pressure using sodium nitroprusside," *IEEE Trans. Biomedical Engineering*, Vol. 34, pp. 603-611, 1987.

[5] C. Yu, R. J. Roy, H. Kaufman and B. W. Bequette, "Multiple-mode adaptive predictive control of mean arterial pressure and cardiac output," *IEEE Trans. Biomedical Engineering*, Vol. 39, pp. 765-778, 1992.

[6] C. C. Palerm, B. W. Bequette and S. Ozcelik, "Robust control for drug infusion with time delays using direct adaptive control: Experimental results," *ACC2000 Proceedings*, pp. 2972-2976, 2000.

[7] K. Furuta, "Sliding mode control of a discrete system," *Syst. Contr. Lett.*, Vol. 14, pp. 145-152, 1990.

[8] V. I. Utkin "Sliding mode control in discrete-time and difference systems," *Variable Structure and Lyapunov Control*, A. S. Zinoder, Ed. London, U.K. : Springer-Verlag, pp. 83-103, 1993.

[9] C. Y. Tang and E. A. Misawa, "Discrete variable structure control for linear multivariable systems," *ASME J. Dynamic Syst., Measurment, Contr.*, Vol.122, pp. 783-792, 2000.

[10] C. Treesatayapun, S. Uatrongjit and K. Kantapanit, "Fuzzy graphic rule network and its application on the water bath temperature control system," *ACC 2002 IEEE American Control Conference*, Anchorage,

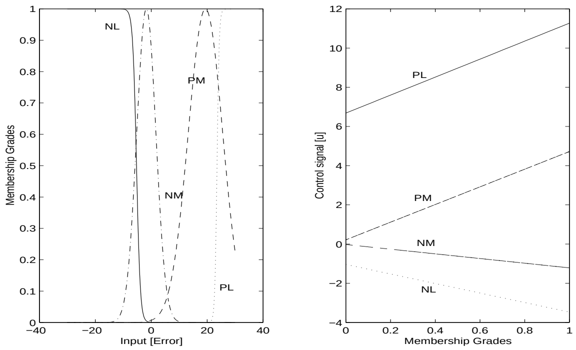

Fig. 9. Final learning: Membership functions and LC of sensitive patient

Alaska, USA, May 2002

[11] C. Treesatayapun and K. Kantapanit, "FGRN nonlinear controller and its applications," *ISIC 2003 IEEE International Symposium on Intelligent Control*, Houston, Texas, USA, Oct 2003