

## Fuzzy Controller for Automatic Drug Infusion in Cardiac Patients

M. Logesh Kumar , R.Harikumar, A. Keerthi Vasan, V.K.Sudhaman

**Abstract:** Control of mean arterial blood pressure and cardiac output is highly desirable in certain operative procedures and in post cardiac operation. This paper emphasizes on a fuzzy controller to control these two variables within the present limits by administering three drugs dopamine, Sodium Nitro Prusside and Phenylephrine which perform the function of increasing heartbeat rate, decreases, increases blood pressure respectively. A fuzzy PD controller with 25 rules is designed to achieve this, which controls the drug delivery unit. This work makes use of few mathematical models whose response to these three drugs mimics the human cardiovascular system. This work can be extended by ASIC Fuzzy control system, which is capable of modeling the cardiovascular mechanism. Till now the usual procedure is that the clinical personal (anesthesiologist) will monitor the changes and will accordingly adjust the infusion rates. The main goals of general anesthesia are adequate hypnosis, analgesia and maintenance of vital functions. For some special kinds of operations neuromuscular block is essential. Furthermore the patient safety and cost reduction as a case of minimized drug consumption and shortened postoperative recovery phases are part of the main issues to motivate automation in anesthesia. Since the beginning of the eighties engineers and physician are working together in the field of the development of closed-loop systems for drug delivery. The work gives a short overview about the development of the automation in drug delivery systems over the last years without the claim of completeness and expressed the much more vision.

**Index Terms**-ASIC Fuzzy control system, closed-loop systems , infusion rates, Phenyl ephrine, Sodium Nitro Prusside,

### I. INTRODUCTION AND MOTIVATION

In clinical practice anesthesiologist has to observe and control a huge amount of hemodynamic and respiratory variables as well as clinical signs of adequate hypnosis and analgesia. In cardiac surgeries a continuous cardiovascular block is needed to guarantee optimal surgical conditions. The remarks are restricted to liquid intravenously injected drugs. This needs a continuous mode for drug application and imply the use of automatic control. Precondition for designing a closed loop control system is a pump which controls the current infusion rate of the injection. With the development of remote controllable infusion pumps led to the design of vaulted control system.

The majority of the used drugs operate not only straight forward to the desired effect. For example the hypnotic drug propofol effects not only on hypnosis level but increase also the analgesia level.

The automated control of hemodynamic variables such as cardiac output and mean arterial pressure has been a goal of many research projects. While the design of such drug infusion controllers has often been based upon simplified linear models, the actual validation procedure requires a more comprehensive nonlinear model that is representative of the circulatory system.

The automated management of hemodynamic variables in patients with critical conditions, in the operating room or the intensive care unit, has been a goal in many different research projects.

A first step was to automate the drug infusion using an open-loop control approach. Programmable pumps are readily available, but the programming however, has to be carried out by a physician, and requires human intervention to respond to changes in the patient's condition, i.e. it lacks an automatic feedback mechanism.

The next stage came with the design of the first closed loop system. Several different approaches in the past decade have been investigated to control arterial pressure by means of vasoconstrictor and vasodilator drugs [1]. Some approaches consider a single-input single-output (SISO) problem by controlling the mean arterial pressure (MAP) with Sodium Nitro Prusside (SNP) [2].

The development of an adequate automated feedback controller is difficult due to the complex, multi-variable, nonlinear behavior of physiological systems [3]. An example of nonlinearity comes from measurements of MAP in dogs, which indicate that the SNP dose response is nonlinear for large changes in pressure [4]. Because of these complexities as well as the significant patient to patient dynamic uncertainties and the presence of time variations in a given patient's response to drug dosages, attention has been given to the use of adaptive and Fuzzy rule based Controllers [5-9]. Few studies had however explored the promising but more difficult field of multiple input-multiple outputs (MIMO) systems.

In 1983 Sema et al. [10] reported on the simultaneous control of CO and MAP using DPM and SNP at Rensselaer Polytechnic Institute. In anticipation of the fact that CO measurements would not be available at a rate faster than once every five minutes, the DPM-CO loop was treated separately from the SNP-MAP loop.

The advantages of this type of controller are its robustness and ability to handle systems with varying and unknown dead times.

With regard to rule-based control systems, Sheppard et al. [11] developed a PD controller in a SISO SNP-MAP configuration. The design considered a PID controller, but after iterative trials and tuning, the integral action was not required in the final version. Although the nominal values of the controller parameters were fixed, the gain of the controller and the infusion rate of the drug were modified on-line following a simple set of rules according to the current and desired MAP and the current infusion rate. This controller was tested on human patients, but only on those that met certain criteria such as the absence of long term drift in the MAP.

In 1990, Neat [12] developed an adaptive drug delivery system for use in regulation of critical care patients suffering from cardiac failure. The approach taken assumed that adaptive control algorithms combined with expert system techniques are necessary to maintain stable patient status within narrow physiological bounds in the presence of large plant uncertainty. To this end, a hybrid controller was presented whose structure was adjusted by an expert system that attempts to match the best control scheme in accordance with the dynamic structure of the plant.

It is important to note that model based predictive control, which can be implemented quite naturally on constrained multivariable systems, has also been considered for drug delivery control systems. The fundamental idea behind MPC is to select a sequence of  $M$  future control moves to minimize an objective function (usually the sum of squares of predicted errors) over a prediction horizon of  $P$  sample times. The model used for the prediction phase can be either linear or nonlinear. Investigators at the University of Alberta [14-16] have designed and evaluated adaptive generalized predictive controllers to regulate MAP with SNP.

Gopinath et al. at Rensselaer [17,18] performed some simulation experiments using multirate, nonlinear model predictive control to regulate MAP and CO in patients with congestive heart failure (CHF). A 38-state nonlinear model developed by Yu [14] and discussed in Section 3.0 was used as the "plant". To reduce the control computation time, a selective linearization technique was used to linearize the model based on trends in the plant-model mismatch. In addition they introduced a novel rule-based override that uses a set of heuristics to initialize dopamine infusion rates to avoid the "forbidden zone" discussed by Held and Roy [13]. A major limitation to this initial effort was the assumption that the state of the patient was known (i.e., entering congestive heart failure), and that the model parameters were perfectly known. For a successful implementation, it would be desirable to be able to identify unknown parameters on-line, for use in the control calculation. However, the full 38-state nonlinear model is too computationally intensive for real-time identification and control. One solution is to develop a reduced-order nonlinear model that adequately describes the drug effects. In all the above cited studies, it is very important to note that the motivation to develop and/or select a particular model for design and validation stems from the inherent difficulties, dangers and time delays inherent to testing the developed control systems on real subjects.

Linear models may not be able to accurately mimic a physiologic system. Further enhancements introduced more variables (typically two-inputs, two-outputs), and also nonlinear, situation specific models.

## II. DESIGN CHALLENGE

With the availability of a representative circulatory system model, it is of interest and importance to develop and validate realistic blood pressure and cardiac output control systems. Such a design study might require:

- 1) The development of representative low order (perhaps linear) models that can be used online for predictive control purposes or even offline for initial control system design.
- 2) The direct design of controllers based upon the response of the nonlinear system model.
- 3) The consideration of combinations of rule based, fuzzy, adaptive, and predictive control algorithms.

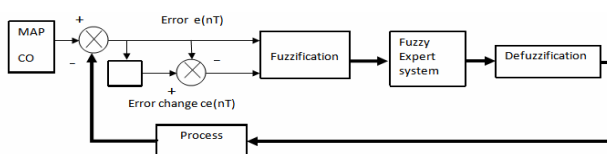


Fig1. Block diagram of fuzzy Control System

## III. MODEL DESCRIPTION

As stated above, a comprehensive nonlinear model that dynamically describes drug effects on the circulatory system was developed by Yu et al. [19]. A schematic of this model is shown in fig 1. A broad division of the model yields three sets of descriptive equations; namely,

- 1) The circulatory system equations, which describe the effect of specific body parameters on the controlled variables MAP and CO,
- 2) The drug effect relationships, which describe the influence of the infused drugs on the specific body parameters, and
- 3) The baro reflex model, which describes the effect of the arterial baroreceptors in short-term MAP regulation.

Different drugs have different effect on the infusion rate as shown below in the table I

Table I. DRUGS AND THEIR EFFECTS

| Drug | Infusion rate(mcg/kg/min) | Effect                            |
|------|---------------------------|-----------------------------------|
| DPM  | 5-10                      | Increases CO,<br>Increases MAP    |
| SNP  | 0.3-4                     | Decreases MPA,<br>Increases CO    |
| PHP  | 5                         | Increases MAP,<br>No effect on CO |

## IV. MODELING EQUATIONS

The fuzzy controller system implemented is an application of fuzzy logic system proposed by L.A.Zadhe in 1965. Fuzzy logic control technique has found many successful industrial applications and demonstrated significant performance improvements. Fuzzy controller design remains a fuzzy process due to the fact that there is insufficient analytic design technique in Contrast with the well developed linear control systems. In standard procedure the design consist of three main parts Fuzzification, Fuzzy logic rule base, and Defuzzification.

The controller here consider the following fuzzy terms.

- NB: negative big
- NM: negative medium
- NS: negative small
- NO: negative zero
- Z : zero
- PO: positive zero
- PS: positive small
- PM: positive medium
- PB: positive big

When a fuzzy controller runs, a numerical error  $e(nT)$  and a numerical rate of change of error  $ce(nT)$  are first fuzzified and respective values are assigned to membership functions following in the universe of discourse. Then the rate of change of controller output is calculated from the membership values of error and rate of change of error by applying the rule base table II. The defuzzification method used is centroid method. The models considered for simulation are equation

[1] for SNP on MAP and equation

[2] for DPM on MAP and CO with different non linearities added to it. The action of PHP on MAP is also taken from same model.

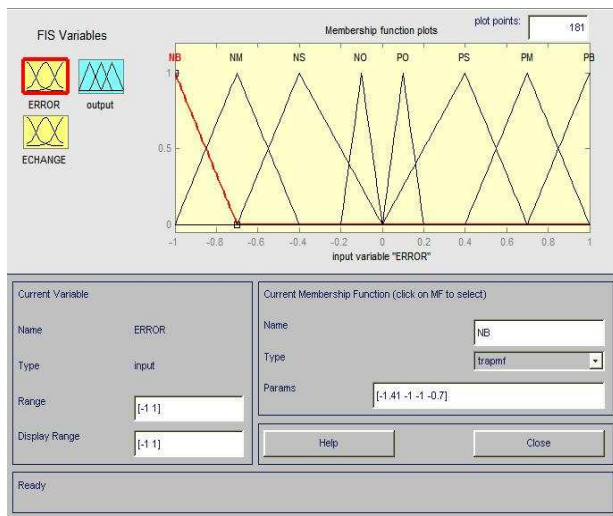


Fig 2. Membership function defined for Controller

$$\frac{P(s)}{S(s)} = \frac{-0.5(1 + 0.2e^{-s45})e^{-s30}}{(1 + 40s)} \quad - (1)$$

$$\frac{C(s)}{D(s)} = \frac{1}{(1 + s10)} \quad - (2)$$

Table II RULE BASE FOR THE PROPOSED CONTROLLER

| ce(nT) \ e(nT) | NB | NM | NS | Z  | PS | PM | PB |
|----------------|----|----|----|----|----|----|----|
| NB             | -  | -  | -  | -  | -  | -  | -  |
| NM             | -  | -  | -  | -  | -  | -  | -  |
| NS             | -  | -  | NB | NB | -  | -  | -  |
| NO             | -  | -  | NO | NO | Z  | -  | -  |
| PO             | -  | -  | PS | PS | Z  | Z  | NO |
| PS             | -  | -  | PS | PS | PS | PO | Z  |
| PM             | -  | -  | PB | PM | PM | PS | PS |
| PB             | -  | -  | PB | PS | PB | PM | PB |

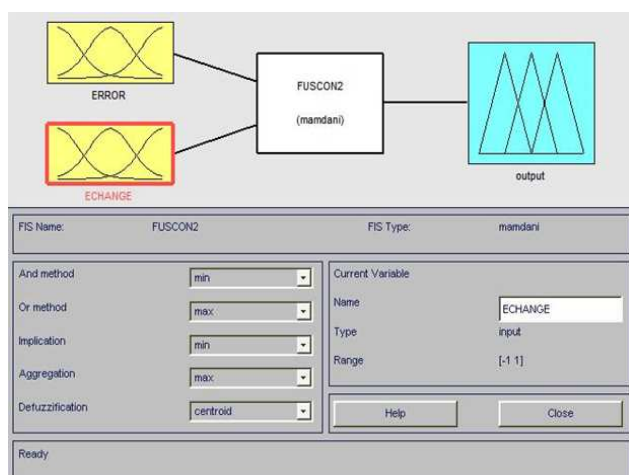


Fig.3. Block diagram of fuzzy Controller Logic

Yu et al. [19] used an electrical circuit analog to describe the lumped parameter model of the circulatory system. The forcing function is the time-varying elastance of the heart. The maximum value of this estimate is used to characterize ventricular contractility. Blood storage capabilities of body compartments and blood vessels are represented as capacitances, and the viscous forces and resistance to blood flow in the systemic and pulmonary vasculature are modeled as resistors. MAP is then the 'voltage' measured after the left ventricle, and CO is the 'current flow' measured at that point in the circuit.

In congestive heart failure (CW, there are usually a number of factors that cause the symptomatic drop in CO and MAP. One of the causes is a reduction in the effective contractility of the heart. Sodium Nitro Prusside (SNP) and dopamine (DPM) are chosen to reduce resistance to blood flow and to increase ventricular contractility. DPM is inotropic in nature, i.e., it increases ventricular contractility and primarily affects Emax, for the prescribed infusion rates of interest. SNP is a vasodilator and reduces resistance to blood flow by reducing Rsys and increasing Vus-ven. This drug also reduces Pcrit, increasing the number of blood vessels in the pulmonary circulation and acilitating blood flow through the lungs at lower pressures. The drug infusion thus affects the controlled variables MAP and CO through these body parameters. An increase in DPM infusion increases MAP and CO, and an increase in SNP infusion reduces MAP but may increase CO.

## V. HEMODYNAMICS

The 38 state variables can be divided into the following two sets, based on their temporal characteristics:

- Variables that remain constant over a heartbeat - these include the drug masses and the drug effect variables.
- Variables that change over a heartbeat such as volume of blood and their flow rates.

The drug-related variables are assumed to remain constant over a heartbeat within their respective compartments since the transport is via the circulation. Changes in values are assumed to take place with fresh inflow of blood into the compartment, which in turn coincides with the heartbeat. The volumes and flow rates within the circulatory compartments however, reflect the changes within a heartbeat.

## VI. PHARMACODYNAMICS

Drug effects on the controlled variables are important in the design and tuning of a controller. SNP effects are primarily a reduction in MAP and a probable increase in CO. The dynamics under normal and CHF conditions are slightly different with respect to rise times and settling times, with the CHF condition exhibiting the slower response. The DPM response is more complex, and depends strongly on the drug dosage at higher doses; the settling time is in the 10-20 minute range with a three to six minute delay. Gingrich and Roy [20] have analyzed the DPM hemodynamic response under CHF, and the model predictions for DPM response closely match their experimental results. Infusion effects can be clearly analyzed from steady-state plots. The MAP-DPM and CO-DPM steady-state plots [18] under varying degrees of baseline contractility (between 7.0 and 1.5 " H g h l ) show the

presence of a 'dead zone' at the low infusions. It should be noted that our model does not simulate conditions corresponding to low infusion rates of DPM. At the higher contractilities, the MAP and CO steady state curves exhibit input multiplicities, with maxima near a DPM infusion of 3.5 ug/kg/min. This can be explained from a physiological standpoint. DPM is modeled as a pure inotropic agent, and increases baseline contractility. If the baseline contractility is already high, then the result is an increase in MAP to values above normal, once infusions are greater than those corresponding to the dead zone. As the steady-state MAP increases due to DPM infusion, the arterial baro-receptors cause increased excitation of the vagal center and further inhibit the vasomotor system, which normally causes vasoconstriction. This results in a lowered heart rate and some vasodilation in the systemic vasculature, causing MAP and CO to decrease. At higher drug doses, the baroreflex response is stronger, and results in lower steady-state MAP and CO. Once the baseline contractility is low DPM, infusion does not increase MAP above normal. This reduces the effect of the baroreflex, and the steady-state curves at lower contractilities do not exhibit any multiplicities. It should also be noted that the effect of DPM is much more pronounced at low contractilities. This is expected, since the drug is inotropic and any effect due to its infusion under normal conditions will be countered by the action of the arterial baroreceptors. It is important to note here that because of the complexities involved in modeling the effects of DPM upon all physiological variables, the present model is not valid for small infusions of DPM, this is reflected in the constraints cited in Section 4.1. The response to dopamine infusion plays a significant role in the design of the control system, primarily due to the variation in speed of response, and the dead zone at low infusions. Accurate scheduling of drug infusion is especially critical when MAP needs to be increased. In the absence of any other drug, MAP can be increased only by the inotropic agent, and it is essential that dopamine infusion be greater than that corresponding to the dead zone. At low infusions, the response may be extremely slow due to very large drug time constants, and the settling time performance criterion may not be met. As suggested by Held and Roy [13], this could be countered by specifying a given region as a forbidden zone for dopamine infusion. This is also common operating practice, and various heuristics are followed by physicians to determine the span of the forbidden zone. The main factors that govern these heuristics in actual practice are the current condition of the patient, patient sensitivity to the drug and the type of action sought.

The model we use here does not reflect the dopaminergic action, and response time constants are assumed to be the primary factors in scheduling dopamine. In this application, we choose the region between 0 and 5 ug/kg/min as the forbidden zone for initial infusion. Normally the drugs are initialized to zero infusion at startup. The desired dopamine infusion profile is then to step up to 4 ug/kg/min whenever the first infusion is requested. After this the subsequent infusion can be subject to the other constraints as given in (5). The high degree of nonlinearity of the system is also clearly seen in the wide range of gains and time constants in the steady-state and transient responses. This underlines the significance of using a rigorous nonlinear model to design the controller.

## VII. CONTROLS-RELEVANT ISSUES

There are several issues that affect controller design for this process. Primary among these are the performance criteria. These determine the manner in which the control objectives must be met, and govern the tuning of the controller. In addition, there are model characteristics that affect implementation. The effects of low DPM infusion were introduced earlier, and point toward the need for some scheduling. Computation time also has an impact on the applicability of the proposed design. Using a complex significant computational load that affects feasibility of real-time implementation. If CO is measured by invasive techniques such as the Hek method or the indicator-dilution method, the drug delivery system is multirate in practical application. CO measurements would typically be available every two to three minutes while MAP would be measured as often as every 30 seconds. This suggests the need to consider multirate control schemes as in [17, 18]. However recent developments enable CO to be measured continuously [21], thus alleviating the need for multirate controllers. The drug delivery controller is responsible for tracking MAP and CO set points that are input by the physician. Since MAP and CO are critical physiological variables, the performance criteria for the controller are based on response time and overshoots to these set points. A typical scenario that might be considered would involve the raising of CO from 80 to 130 ml/kg/min and the lowering of MAP from 120 mmHg to 100 mmHg in a manner such that:

- 1) The transient performance criterion for the closed-loop system has a maximum allowable settling time of approximately 10 minutes for MAP to reach and remain within  $\pm 5$  Hg, and 20-25 minutes for CO to reach and remain within 10% of the commanded change.
- 2) The desired transient response must be achieved subject to the following constraints on the manipulated variables.

## VIII. RATE OF SAMPLING AND CONTROLLER INTERVENTION

Based upon heart rate, the model processes the circulatory values continuously in a loop. The simulated time and the hemodynamic variables are updated in each iteration. Thus the controller can be called from within the program whenever the simulated time for the circulatory model has lapsed the specified interval for the controller intervention. A high rate of intervention may not produce a more desirable performance since various physiological delays and the delays brought about by the pharmacological effects of the infused drugs are present. On the other hand, a low rate of intervention may not be adequate since the patient must be carefully monitored to provide the necessary precautions against any possible further deterioration in the hemodynamic states. The embedded fuzzy logic controller compromises these drawbacks and intervenes the circulatory model every 30 seconds. This amount of time is sufficient for a controller algorithm to process the hemodynamic values from the circulatory system and to produce the appropriate infusion rates. The circulatory model is also sampled at a rate of 1/3 Hz which allows the user to monitor the hemodynamic changes continuously.



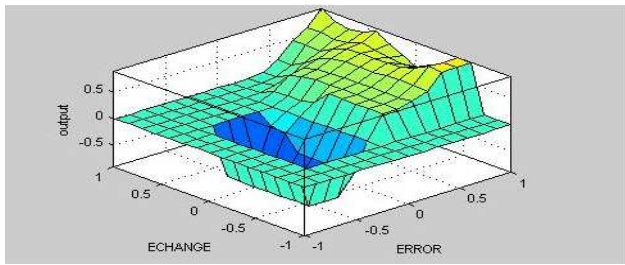


Fig 4. Control surface

## IX. RATE OF DRUG INFUSIONS

At the end of every controller intervention, a new set of infusion rates is generated by the controller. These values are to be sent to a drug delivery unit where the appropriate dosages of each drugs will be infused to the circulatory model. A consideration on the minimal step changes of the drug delivery unit must be made to reflect the actual changes an infusion pump is able to provide. If a different drug other than SNP or DPM is to be used by the controller, a new algorithm must be implemented where the Corresponding parameters in the circulatory model will be modified to properly reflect the clinical effects of the new drug when infused to the system.

## X. RESULTS AND DISCUSSION

The performance of the proposed fuzzy controller is analyzed. For few conditions of MAP & CO the set point for MAP and CO are taken as 100mm Hg & 100ml/kg/min with + 5% allowance. In the first trial initial values of MAP & CO are taken as 80mm Hg and 70ml/kg/min respectively. The controller decided to use only DPM to with a final infusion rate of 7.858 mcg/kg/min and it took 18 mins to achieve this. In the second trial initial value values of MAP&CO are taken as 110mm Hg & 70ml/Kg/min. and it took 18 min and used all three drugs at the rates of 7.81 (DPM), 2.51 (SNP) and 2.34 (PHP) mcg/kg/min. The third trial was with the initial values of 130 mm Hg (MAP) and 70 ml/kg/min (CO). Here CO reached steady state in 17 minutes but MAP had undergone an undershoot of 15 mm Hg and again MAP was. Brought back to set point using PHP in the next 10 mins with drug infusion rates of 6.97(DPM) 3.63 (SNP) and 3.45(PHP) mcg/kg/min. The drop in MAP which stayed for few minutes below the set point was because of the selected sensitivity of MAP to SNP is more than to PHP.

## XI. CONCLUSION

The proposed fuzzy PD controller is a simple FLC with 25 rules. The main problem faced during work is selecting the mathematical models for different drug actions. The performance can be improved by modifying the controller as "self organized FLC" or as a neuro fuzzy controller. This work can be extended by VLSI Fuzzy control system, which is capable of modeling the cardiovascular mechanism under different conditions and for different drugs.

## REFERENCES

[1] L.C. Sheppard, W.F. Holdefer, N.T. Kouchoukos and J.W. W i n , "Analysis of the Multiple Effects of Vasoactive and Positive Inotropic Agents on Cardiovascular System Variables," in Cardiovascular System Dynamics: Models and Mewements, Plenum Press, New York, 1982, pp. 647456.

[2] K.Behbehain, Russel R.C, "A Controller for Regulation of Mean Arterial Blood Pressure Using optimum Nitroprusside infusion rate" , IEEE Trans on Bio-medical Engg., Vol 38,No.6, June 1991.

[3] G.I.Voss, P.G.Katona, " Adaptive multivariable drug delivery: Control of arterial pressure and cardiac output in anesthetized Dogs", IEEE trans on Bio-medical Engineering, Vol. BME-34, No.8, Aug 1987.

[4] J.B. Slate, L.C. Sheppard, V.C. Rideout and E.H.Blackstone, "A Model for Design of a Blood Pressure Controller for Hypotensive Patients," Proc. of the 5th IFAC Symp. Ident@cation Syst. Parameter Estimation, Darmstadt,F.R.Germany, Sept. 24-28,1979.

[5] J.M. Amsparger, B.C. McInnis, Jr, and N.A. Normann, "Adaptive Control of Blood Pressure," IEEE Trans. Biomed.Eng., BME-30168-176.

[6] W.G. He, H. Kaufman, and R. Roy , "Multiple Model Adaptive Control Procedures for Blood Pressure Control,"IEEE Trans. Bwmed. Eng., BME-33:IO-19, 1986.

[7] H. Kaufman, R. Roy, and X. Xu, "Model Reference Adaptive Control of Drug Infusion Rate," Automatica,1984.

[8] J.T. Martin, A.M. Schneider, and N.T. Smith,"Multiple-Model Adaptive Control of Blood Pressure Using Sodium Nitro Prusside," Trans. Biomed. Eng.,BME-34:603-611,1987.

[9] L.J. Meline, D.R. Westenskow, A. Somerville, R.T.Wemick, J. Jacobs, and N.L. Pace, "Evaluation of Two Adaptive Sodium Nitro Prusside Control Algorithms," J. Clin.Monit., 27946,1986.

[10] V. Sema, R. Roy, and H. Kaufman, "Adaptive Control of Multiple Drug Infusion," Proc. of the 1983 American Control Conf., San Francisco, CA, 1983.

[11] L.C. Sheppard, J.F. Shotts, N.F. Roberson, F.D. Wallace and N.T. Kouchoukos, "Computer Controlled Infusion of Vasoactive Drugs in Post Cardiac Surgical Patients," Proc. of the IEEE-EMBS Conf., Denver, CO, Oct. 1979

[12] G.W. Neat, "Expert Adaptive Control: Method and Medical Application,"Ph.D. Thesis, RPI, Troy, NY, 1990

[13] K.Y. Kwok, A.S. Clanachan, B. Finegan, S.L.S Hah. "hng Range Predictive Control of Arterial Blood Pressure," Proc. 29th CDC, Honolulu, HI, pp. 2800-2805,1989.

[14] K.Y. Kwok, SL. Shah, A.S. Clanachan, B.A. Finegan,"Evaluation of a Long-Range Predictive Controller for Computerized Drug Delivery Sytsems," Proc. IFAC Conf. Adaptive Control and Sig. Proc., Grenoble, France, 1992

[15] G.K. Kwong, Kwok, K.E., Finegan, B.A., Shah, S., "Clinical Evaluation of Long-Range Adaptive Control for MAP Regulation,"? Proc. ACC, Seattle, WA, 1995

[16] K.Y. Kwok, SL. Shah, A.S. Clanachan, B.A. Finegan,"Evaluation of a Long-Range Predictive Controller for Computerized Drug Delivery Sytsems," Proc. IFAC Conf.Adaptive Control and Sig. Proc., Grenoble, France, 1992.

[17] R.S. Gopinath, B.W. Bequette, R.J. Roy, H. Kaufman, and C. Yu, "Issues in the Design of a Multirate Model-Based Controller for a Nonlinear Drug Infusion System,"Biotechnology Progress, Vol. 11, No. 3, pp. 318-332.

[18] R.S. Gopinath, B.W. Bequette, R.J. Roy, and H.Kaufman, "Multirate MPC Design for a Nonlinear Drug Infusion Syte"" Proceedings of the 1994 American Control Conference, Baltimore, MD, pp. 102-106.

[19] C. Yu, R.J. Roy, and H. Kaufman , "A Circulatory Model for Combined Nitroprusside-Dopamine Therapy," Medical Progress Through Technology, 16:47-88, Kluwer Academic Publishing, 1990

[20] K.J. Gingrich, R.J. Roy, "Modelling the Hemodynamic Response to Dopamine in Acute Heart Failure," IEEE Trans Bwmed. Eng., 18(3), 1991, pp. 267-272.

[21] M. Yelderman, "Continuous Measurement of Cardiac Output with the Use of Stochastic System Identification Techniques," Journal of Clinical Monitoring, 6:322-332,1990