Available online at www.sciencedirect.com
SCIENCE DIRECT
Computers and Chemical Engineering 29 (2005) 2290–2296
Computers & Chemical Engineering
www.elsevier.com/locate/compchemeng

Modelling and control of drug delivery systems

Pinky Dua, Efstratios N. Pistikopoulos *

Centre for Process Systems Engineering, Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, UK

Received 13 May 2005; accepted 23 May 2005
Available online 14 July 2005

Abstract

This work presents a compartmental model for delivery of drugs under anesthesia and an advanced model based control algorithm for insulin delivery for Type 1 diabetes. The model for anesthesia involves choice of three drugs isoflurane, dopamine and sodium nitroprusside, which allows simultaneous regulation of mean arterial pressure and unconsciousness of the patients. A number of dynamic simulations are carried out to validate the model. For Type 1 diabetes, a parametric programming approach is used to obtain the optimal insulin infusion rate as an explicit function of the state of the patient and the regions in the space of the state of patient where these functions are valid. These explicit functions allow the implementation of blood glucose control on a simple computational software and hardware platform.

Keywords: Anesthesia; Compartmental model; Mean arterial pressure; Type 1 diabetes; Parametric programming

1. Introduction

Modelling and control of drug delivery systems is a multidisciplinary task involving engineers, physicians and mathematicians. A model of a drug delivery system should be detailed enough to capture and reproduce the complex pharmacokinetic and pharmacodynamic effects of the drug, but on the other hand simple enough to design a controller for the optimal delivery of the drugs. This paper considers two drug delivery systems: regulation of anesthesia and insulin delivery for Type 1 diabetes. In Section 2, a model for the delivery of drugs under anesthesia is proposed. The key feature of this model is that it takes into account simultaneous regulation of the mean arterial pressure and unconsciousness of the patients. Section 3 proposes a parametric controller for the regulation of the blood glucose concentration, which can be implemented on a simple computational platform while incorporating constraints on the blood glucose concentration and insulin infusion rate. Concluding remarks are given in Section 4.

2. Modelling anesthesia

Anesthesia is defined as the absence or loss of sensation. In order to provide safe and adequate anesthesia, the anesthesiologist must guarantee analgesia, provide hypnosis, muscle relaxation and maintain vital functions of the patient. To assist access to internal organs and to depress movement response to surgical stimulation, muscle relaxation is necessary. Analgesia is linked with pain relief and at present, there is no specific technique to quantify it. Hypnosis, referred to as depth of anesthesia, is a general term indicating the unconsciousness and absence of post-operative recall of events that occurred during surgery. The electroencephalogram, which is the only non-invasive measure of central nervous system activity while the patient is unconscious, is considered as the major source of information to assess the level of hypnosis, via the Bispectral Index (BIS). Anesthesiologists administer anesthetics and monitor a wide range of vital functions, such as mean arterial pressure (MAP), heart rate, cardiac output (CO), some of which can be measured while the others can be inferred, in order to ensure patient's safety. These vital functions need to be monitored and maintained within tolerable operating ranges by infusing various drugs and/or intravenous fluids.

* Corresponding author. Tel.: +44 207 594 6620; fax: +44 207 594 1129.
E-mail address: e.pistikopoulos@imperial.ac.uk (E.N. Pistikopoulos).

0098-1354/$ – see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.compchemeng.2005.05.014

Automation of anesthesia for monitoring of vital functions is desirable as it will provide more time and flexibility to the anesthesiologist to focus on critical issues, monitor the conditions that cannot be easily measured and overall improve patient's safety. Also, the cost of the drugs will be reduced and shorter time will be spent in the post-operative care unit. There is a significant amount of research in the area of developing models and control strategies for anesthesia (Derighetti, Frei, Buob, Zbinden, & Schnider, 1997; Gopinath, Bequette, Roy, & Kaufman, 1995; Mahfouf, Asbury, & Linkens, 2003; Rao, Palerm, Aufderheide, & Bequette, 2001; Yasuda, Targ, & Eger, 1989; Yasuda et al., 1991a, 1991b; Zwart, Smith, & Beneken, 1972). Gentilini et al. (2001) proposed a model for the regulation of MAP and hypnosis with isoflurane. It was observed that controlling both MAP and hypnosis simultaneously with isoflurane was difficult. Yu et al. (1990) proposed a model for regulating MAP and CO using dopamine (DP) and sodium nitroprusside (SNP), but the control of hypnosis was not considered.

In this work, a compartmental model is proposed, which allows the simultaneous regulation of the MAP and the unconsciousness of the patients. Three major aspects characterise the model: (i) pharmacokinetics, which describes the uptake and distribution of the drugs, (ii) pharmacodynamics which is concerned with the effect of the drugs on the vital functions and (iii) baroreflex which accounts for the reaction of the central nervous system to changes in the blood pressure. The model involves choice of three drugs, isoflurane, DP, and SNP. This combination of drugs allows simultaneous regulation of MAP and hypnosis.

The model is based on the distribution of isoflurane in the human body (Yasuda et al., 1991a) and the works of Gentilini et al. (2001) and Yu et al. (1990). It consists of five compartments organized as shown in Fig. 1. The drugs are distributed among the compartments via the circulatory system and therefore the heart can be taken as if belonging to the central compartment. The transfers from the central compartment to the peripheral compartments, i.e. compartments 2–5 occur via the arteries and the transfers from the peripheral compartments to the central, via the veins. The introduction of drugs can be related to the first compartment as shown on Fig. 1. In the next section, we discuss the pharmacokinetic modelling of the drugs.

2.1. Pharmacokinetic modelling

2.1.1. Respiratory system

The uptake of isoflurane in central compartment occurs via the respiratory system. Considering a well-stirred system, this is modelled as:

$$V\frac{dC_{insp}}{dt} = Q_{in}C_{in} - (Q_{in} - \Delta Q)C_{insp} - f_R(V_T - \Delta) \times (C_{insp} - C_{out}) \quad (1)$$

where C_{insp} is the concentration of isoflurane inspired by the patient (g/mL), C_{in} the concentration of isoflurane in the inlet stream (g/mL), C_{out} the concentration of isoflurane in the outlet stream (g/mL), Q_{in} the inlet flow rate (mL/min), ΔQ the losses (mL/min), V the volume of the respiratory system (mL), f_R the respiratory frequency (1/min), V_T the tidal volume (mL) and Δ is the physiological dead space (mL).

2.1.2. Central compartment

The concentration of isoflurane within the central compartment is given by:

$$V_1\frac{dC_1}{dt} = \sum_{i=2}^{5}\left(Q_i\left(\frac{C_i}{R_i} - C_1\right)\right) + f_R(V_T - \Delta)(C_{insp} - C_1) \quad (2)$$

where C_i is the concentration of the drug in compartment i (g/mL), R_i the partition coefficient between blood and tissues in compartment i and Q_i is the blood flow in compartment i (mL/min).

The infusion of intravenous drugs DP and SNP in the central compartment is modelled as follows:

$$V_1\frac{dC_1}{dt} = \sum_{i=2}^{5}\left(Q_i\left(\frac{C_i}{R_i} - C_1\right)\right) + C_{inf} - \frac{1}{\tau_{1/2}}C_1V_1 \quad (3)$$

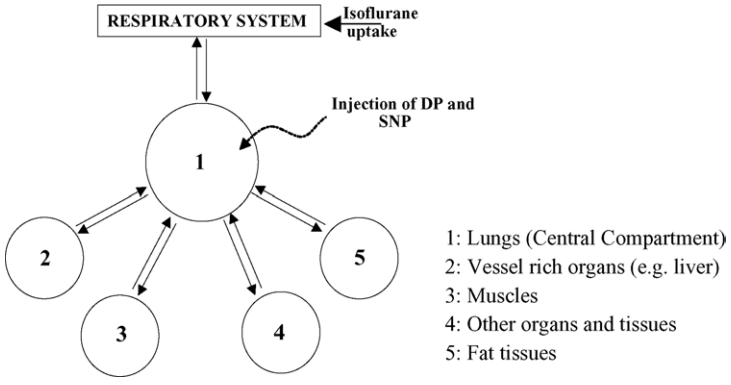

Fig. 1. Compartmental model.

where C_{inf} is the flowrate of the drug infused (g/min), V_i the volume of compartment i (mL) and $\tau_{1/2}$ is the half-life of the drug (min).

2.1.3. Peripheral compartments

Elimination of isoflurane by exhalation and metabolism in liver, the second compartment, is given by:

$$V_2 \frac{dC_2}{dt} = Q_2 \left(C_1 - \frac{C_2}{R_2} \right) - k_{20} C_2 V_2 \tag{4}$$

where k_{20} is the rate of elimination of isoflurane in the second compartment (min^{-1}).

The concentration of isoflurane in compartments 3–5 is given by:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_1 - \frac{C_i}{R_i} \right), \quad i = 3, \ldots, 5. \tag{5}$$

DP and SNP naturally decay in the body, hence the equation for compartments 2–5 is:

$$V_i \frac{dC_i}{dt} = Q_i \left(C_1 - \frac{C_i}{R_i} \right) - \frac{1}{\tau_{1/2}} C_i V_i, \quad i = 2, \ldots, 5. \tag{6}$$

2.2. Pharmacodynamic modelling

2.2.1. Effect of DP and SNP on MAP

DP and SNP indirectly affect MAP via two of the heart's characteristic parameters: maximum elastance (E_{max}) and systemic resistance (R_{sys}). The action of these two drugs on these parameters is given by:

$$\begin{aligned} &\frac{dEff}{dt} = k_1 C_1^N (Eff_{max} - Eff) - k_2 Eff \\ &E_{max} = E_{max,0}(1 + Eff_{DP-E_{max}}) \\ &R_{sys} = R_{sys,0}(1 - Eff_{DP-R_{sys}} - Eff_{SNP-R_{sys}}) \end{aligned} \tag{7}$$

where Eff is the measure of the effect of drug on the parameters of interest, R_{sys} the systemic resistance (mmHg/(mL/min)), E_{max} the maximum elastance (mmHg/mL), $E_{max,0}$ nominal maximum elastance, $R_{sys,0}$ nominal systemic resistance, $Eff_{DP-E_{max}}$ effect of DP on E_{max}, $Eff_{DP-R_{sys}}$ effect of DP on R_{sys}, $Eff_{SNP-R_{sys}}$ the effect of SNP on R_{sys}, k_1, k_2 the rate constants and N is the non-linearity constant.

MAP can be expressed as a function of E_{max} and R_{sys} as:

$$\begin{aligned} &MAP^2 \frac{1}{R_{sys}^2} + 2K^2 MAP - 2K^2 V_{LV} E_{max} = 0 \\ &K = \frac{A_{aorta} A_{LV}}{\sqrt{\rho}\sqrt{A_{LV}^2 - A_{aorta}^2}} \end{aligned} \tag{8}$$

where MAP is the mean arterial pressure (mmHg), A_{aorta} the cross-sectional area of the aorta (cm^2), A_{LV} the cross-sectional area of the left ventricle (cm^2), V_{LV} the mean volume of the left ventricle (mL) and ρ is the blood density (g/mL).

2.2.2. Effect of isoflurane on MAP

Isoflurane affects MAP as follows:

$$MAP = \frac{Q_1}{\sum_{i=2}^{5} (g_{i,0}(1 + b_i C_i))} \tag{9}$$

where $g_{i,0}$ is the baseline conductivities (mL/(min mmHg)) and b_i is the variation coefficient of conductivity (mL/g).

2.2.3. Effect of isoflurane on BIS

There is experimental evidence that a transportation delay exists between the lungs and the site of effect of isoflurane. In order to model this, an effect compartment is linked to the central compartment. The concentration of isoflurane within this compartment is related to the central compartment, which is given by:

$$\frac{dC_e}{dt} = k_{e0}(C_1 - C_e) \tag{10}$$

where C_e is the concentration of isoflurane in the effect compartment (g/mL) and k_{e0} is the kinetics in the effect compartment (min^{-1}).

The action of isoflurane can be then expressed as follows:

$$\begin{aligned} &\Delta BIS = \Delta BIS_{max} \frac{C_e^\gamma}{C_e^\gamma + EC_{50}^\gamma} \\ &\Delta BIS = BIS - BIS_0 \\ &\Delta BIS_{max} = BIS_{max} - BIS_0 \end{aligned} \tag{11}$$

where BIS_0 is the baseline value of BIS (assumed to be 100), BIS_{max} the maximum value of BIS (assumed to be 0), EC_{50} the patient's sensitivity to the drug and γ is the measure of the degree of non-linearity.

2.3. Baroreflex

In this model, baroreflex is obtained from a set of transfer functions relating the mean arterial pressure to the maximum elastance and the systemic resistance and is given by:

$$bfc = \frac{e^{c(MAP - MAP_0)}}{1 + e^{c(MAP - MAP_0)}} \tag{12}$$

where c is the empirical constant (mmHg).

2.4. Model validation

A number of dynamic simulations were performed using gPROMS (2003) to validate the model. First, a simulation was carried out in order to see the effect of isoflurane on MAP. It was observed that a drop in MAP occurs when subjected to an uptake of 1.5 vol.% of isoflurane. MAP drops from 90 to 78 mmHg, which is consistent with the results obtained by Gentilini et al. (2001) during clinical experiments. It was also observed that the elimination of isoflurane was correctly modelled as MAP reaches the value of 90 mmHg as soon as there is no uptake of isoflurane.

Another simulation was performed to see the effect of isoflurane on BIS. General anesthesia corresponds to BIS value between 40 and 65. It was observed that in order to maintain this range, the uptake of isoflurane should be between 0.5 and 1 vol.%.

In order to see the effect of dopamine on MAP, a simulation was performed, where the model was run at steady-state for the first 10 min, then a drop of 20 mmHg in MAP was induced and finally 10 min after the drop, 5 μg/(kg min) of dopamine was infused. It was observed that MAP decreases to 70 mmHg after the drop and then increases to 80 mmHg due to the baroreflex and then finally reaches the steady-state after the infusion of dopamine.

Similarly, another simulation was performed to see the effect of SNP on MAP. It was observed that 1 μg/(kg min) of SNP results in a rapid drop in MAP from 90 to 75 mmHg. It was also observed that SNP should not be infused more than 10 μg/(kg min) since this decreases MAP to 65 mmHg.

Also, in order to validate the model's general behaviour, an anesthetic procedure has been simulated, which consists of five parts: for the first 10 min, it is assumed that the patient is awake. Then isoflurane of 0.6 vol.% is infused alongwith 0.3 μg/(kg min) of SNP to create the anesthetic state and lower the blood pressure to 60 mmHg in order to minimize the possible blood losses. After 800 min, when the steady-state is reached, a drop of 20 mmHg in MAP is induced. It was assumed for the sake of simulation that the anesthesiologist would react only after 5 min of the drop by giving an infusion of 4.5 μg/(kg min) of DP to counteract the drop. Then after 60 min, MAP does not drop and hence DP infusion was stopped. After another 40 min, the uptake of isoflurane and SNP was stopped and it was observed that the patient smoothly wakes up. Fig. 2 shows the results of this simulation.

It must be stressed that this procedure is oversimplified. First, the anesthesiologist would give high dosages of drugs at the beginning of the procedure in order to induce quick response from the patient and then gradually adjust the infusions to keep BIS, MAP, and infusion rates within safe ranges. Also, the patient would be subject to greater number of disturbances starting with the intubation at the beginning of procedure, which was not considered in this simulation. Despite these simplifications, it was observed that the accuracy of the model is not altered by multiple drug infusions.

3. Control of Type 1 diabetes

Diabetes is a disease that affects the body's ability to regulate glucose concentration. There are two main types of diabetes: Types 1 and 2 diabetes. In Type 1 diabetes (also called juvenile diabetes or insulin-dependent diabetes), the pancreas produces insufficient insulin, and exogenous insulin is required to be infused at an appropriate rate to maintain blood sugar levels at normal levels. According to the Diabetes Control and Complications Trial (DCCT) (DCCT, 1993), blood glucose should be controlled within the range of 60–120 mg/dL. If insulin is supplied in excess, the blood glucose level can go well below normal (<60 mg/dL), a condition known as *hypoglycemia*. On the other hand, if insulin is not supplied sufficiently, the blood glucose level is elevated above normal (>120 mg/dL), a condition known as *hyperglycemia*. Both hypo- and hyperglycemia can be harmful to an individual's health. The effects of hypoglycemia are critical on short-term basis, which can lead to diabetic coma and possibly death, while those of hyperglycemia have long-term impacts that have been linked to nephropathy, retinopathy and other tissue damage. Hence, it is very important to control the level of blood glucose in the body to within a reasonable

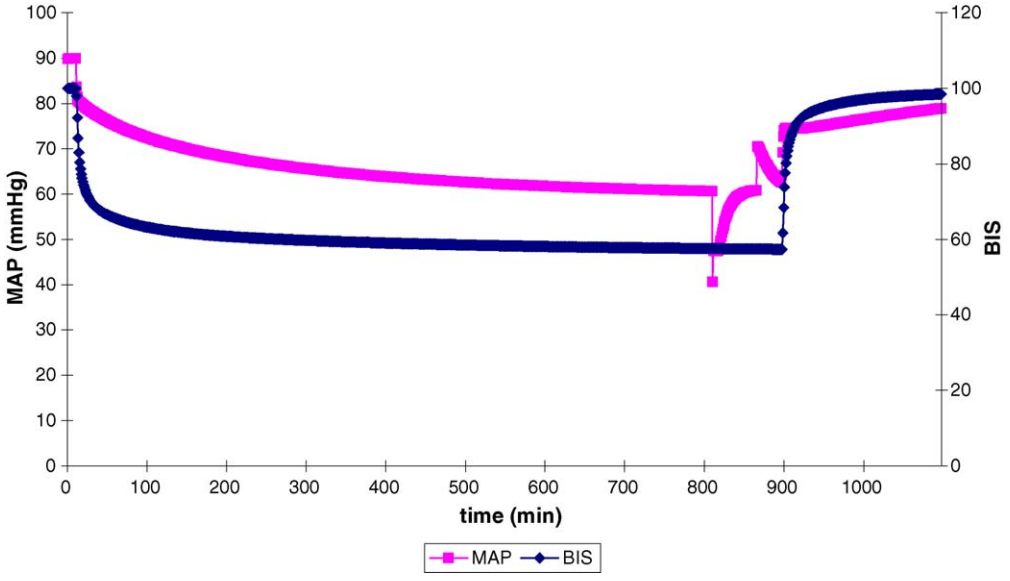

Fig. 2. Simulation of the regulation of MAP and BIS during anesthesia.

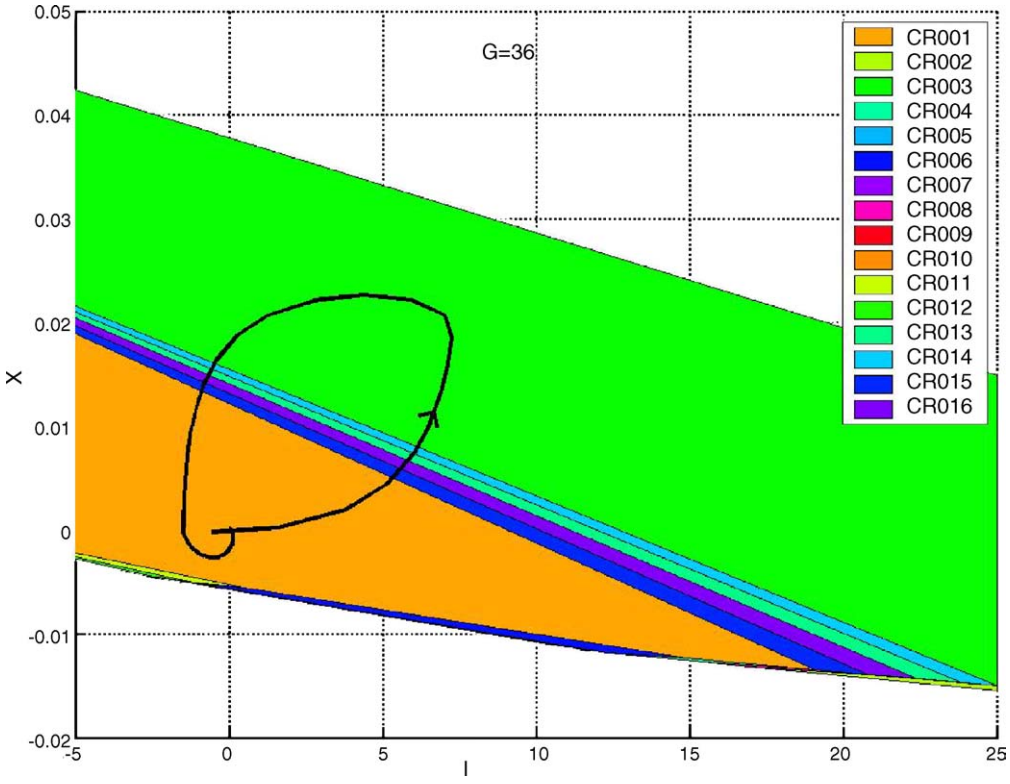

Fig. 3. Critical regions for fixed G.

range (Lynch & Bequette, 2002; Parker, Doyle, & Peppas, 2001).

This can be achieved by developing a control algorithm that can take into account the model of the patient and the constraints on insulin infusion rate and blood glucose concentration. In this work, an advanced model based control technique is proposed that does not require an on-line computer for its implementation. This is based upon parametric control algorithms (Dua, Sakizlis, Dua, Doyle, & Pistikopoulos, 2004; Pistikopoulos, Dua, Bozinis, Bemporad, & Morari, 2002) where the state of the patient is systematically partitioned into a number of polyhedral regions, known as critical regions, and in each of these regions the optimal insulin infusion rate is obtained as an explicit function of the state of the patient (see Appendix A for the theory of model based parametric control). The critical regions for the case of the widely used three-compartment Bergman model (Bergman, Phillips, & Cobelli, 1981) are shown in Fig. 3. In the figure, G, the blood glucose concentration above the basal value, is fixed at 36 mg/dL and I is the insulin concentration above the basal value (mU/L) and X is proportional to insulin concentration in the remote compartment (min^{-1}). The explicit functions can then be stored on simple computational hardware and implementation of the controller reduces to simple function evaluations.

A schematic of the proposed controller implementation is shown in Fig. 4 where a sensor measures the blood glucose concentration and feeds it to the parametric controller, which computes the optimal insulin infusion rate and drives the mechanical pump to infuse the computed amount of insulin. The key advantage of the parametric controller is that a complete road-map of all the possible solutions is available a

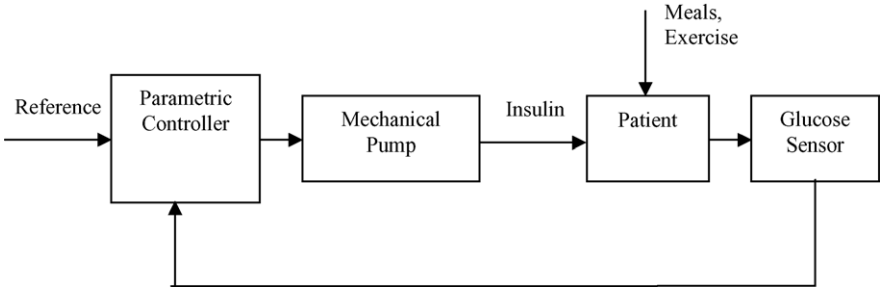

Fig. 4. Closed loop parametric control system.

priori which results in an enhanced feeling of safety. Since a complete road-map of all the possible scenarios is available, an off-line 'fail-safe' analysis for various scenarios can also be carried out.

4. Concluding remarks

Automation of anesthesia is expected to allow the anesthesiologist to focus more on critical aspects during surgery and reduce the amount of drugs infused and the time spent by the patient in the post-operative care unit. A successful implementation of the automation strategy relies on a hi-fidelity model, which can capture the dynamic response of the patient to various drug infusions. In this work, a compartmental model for the automation of anesthesia that takes into account simultaneous regulation of MAP and unconsciousness of the patients has been developed and validated. This paves the way for the development of advanced control and automation strategies for anesthesia. An advanced model based parametric controller for Type 1 diabetes was proposed. This controller provides the optimal insulin infusion rate as an explicit function of the state of the patient, which is expected to greatly simplify the automation of the blood glucose control and reduce patient inconvenience.

Acknowledgements

Pinky Dua would like to acknowledge financial support from the Overseas Research Student Award Scheme (ORS) and the Industrial Consortium of the Centre for Process Systems Engineering. A.P. Muller's contribution to the work on anesthesia is also acknowledged. The work on Type 1 diabetes was carried out in collaboration with Professor Francis J. Doyle III.

Appendix A. Model based parametric control

Consider the following mathematical model of the patient:

$$x_{t+1} = Ax_t + Bu_t \tag{A.1}$$

subject to the following constraints:

$$\begin{aligned} x_{\min} &\le x_t \le x_{\max} \\ u_{\min} &\le u_t \le u_{\max} \end{aligned} \tag{A.2}$$

where $x_t \in R^n$, $u_t \in R^m$, are the state and input vectors, respectively, and the subscripts min and max denote lower and upper bounds, respectively. Typically, x_t and u_t represent G, I, X and the insulin delivery rate, at time interval t, respectively. Model based control problem can then be posed as the following optimization problem:

$$\begin{aligned} \min_U J(U, x(t)) &= x_{t+N_y|t}^{\mathrm{T}} P x_{t+N_y|t} + \sum_{k=0}^{N_y-1} \left[x_{t+k|t}^{\mathrm{T}} Q x_{t+k|t} + u_{t+k}^{\mathrm{T}} R u_{t+k} \right] \\ \text{s.t.} \quad & x_{\min} \le x_{t+k|t} \le x_{\max}, \quad k = 1, \ldots, N_c \\ & u_{\min} \le u_{t+k} \le u_{\max}, \quad k = 1, \ldots, N_c \\ & x_{t+k+1|t} = A x_{t+k|t} + B u_{t+k}, \quad k \ge 0 \\ & u_{t+k} = K x_{t+k|t}, \quad N_u \le k \le N_y \end{aligned} \tag{A.3}$$

where $U = [u_t^{\mathrm{T}}, \ldots, u_{t+N_u-1}^{\mathrm{T}}]^{\mathrm{T}}$, Q and R are constant, symmetric and positive definite matrices, P given by the solution of the Riccati equation, N_y, N_u and N_c the prediction, control and constraint horizons, respectively, K some feedback gain and the superscript T denotes transpose of the vector. Problem (A.3) is solved repetitively at each time t for the current state x_t and the vector of predicted state variables, $x_{t+1|t}, \ldots, x_{t+N_y|t}$ at time $t+1, \ldots, t+N_y$, respectively, and corresponding control actions $u_t, \ldots, u_{t+N_y-1}$ are obtained. The main drawback of model based control problem (A.3) is its extensive online computational effort. This drawback can be overcome by using parametric programming as described next.

The equalities in formulation (A.3) are eliminated by making the following substitution:

$$x_{t+k|t} = A^k x_t + \sum_{j=0}^{k-1} A^j B u_{t+k-1-j} \tag{A.4}$$

to obtain the following Quadratic Program (QP):

$$\begin{aligned} \min_U \ & \frac{1}{2} U^{\mathrm{T}} H U + x_t^{\mathrm{T}} F U + \frac{1}{2} x_t^{\mathrm{T}} Y x_t \\ \text{s.t.} \ & GU \le W + E x_t \end{aligned} \tag{A.5}$$

where $U = [u_t^{\mathrm{T}}, \ldots, u_{t+N_u-1}^{\mathrm{T}}]^{\mathrm{T}} \in R^s$, is the vector of optimization variables, $s = mN_u$, H a constant, symmetric and positive definite matrix and H, F, Y, G, W, E are obtained from Q, R and (A.1) and (A.2).

The QP problem in (A.5) can now be reformulated as a multi-parametric quadratic program (mp-QP) (Bemporad, Morari, Dua, & Pistikopoulos, 2002; Dua, Bozinis, & Pistikopoulos, 2002; Pistikopoulos et al., 2002):

$$\begin{aligned} V_z(x) = \min_z \ & \frac{1}{2} z^{\mathrm{T}} H z \\ \text{s.t.} \ & Gz \le W + Sx_t \end{aligned} \tag{A.6}$$

where $z = U + H^{-1} F^{\mathrm{T}} x_t$, $z \in R^s$ and $S = E + GH^{-1}F^{\mathrm{T}}$.

This mp-QP is solved by treating z as the vector of optimization variables and x_t as the vector of parameters to obtain z as an explicit function of x_t. U is then obtained as an explicit function of x_t by using $U = z - H^{-1}F^{T}x_t$. The final solution is given by U as a set of explicit functions of x_t and the corresponding polyhedral regions in the space of x_t where these functions are valid.

References

Bemporad, A., Morari, M., Dua, V., & Pistikopoulos, E. N. (2002). The explicit linear quadratic regulator for constrained systems. *Automatica*, *38*, 3–20.

Bergman, R. N., Phillips, L. S., & Cobelli, C. (1981). Physiologic evaluation of factors controlling glucose tolerance in man. *Journal of Clinical Investigation*, *68*, 1456–1467.

DCCT—The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *The New England Journal of Medicine*, *329*, 977–986.

Derighetti, M., Frei, C. W., Buob, M., Zbinden, A. M., & Schnider, T. W. (1997). Modelling the effect of surgical stimulation on mean arterial blood pressure. In *Proceedings of the 19th International Conference IEEE/EMBS* (pp. 2172–2175).

Dua, P., Sakizlis, V., Dua, V., Doyle, F. J., III, & Pistikopoulos, E. N. (2004). Model based control for insulin delivery for type 1 diabetics via parametric programming. In *Proceedings of the European Symposium on Computer Aided Process Engineering-14* (pp. 1045–1050).

Dua, V., Bozinis, N. A., & Pistikopoulos, E. N. (2002). A multiparametric programming approach for mixed-integer quadratic engineering problems. *Computers and Chemical Engineering*, *26*, 715–733.

Gentilini, A., Frei, C. W., Glattfelder, A. H., Morari, M., Sieber, T. J., Wymann, R., Schnider, T. W., & Zbinden, A. (2001). Multiasked closed-loop control in anesthesia. *IEEE Engineering in Medicine and Biology*, *20*, 39–53.

Gopinath, R., Bequette, B. W., Roy, R. J., & Kaufman, H. (1995). Issues in the design of a multirate model-based controller for a nonlinear drug infusion system. *Biotechnology Progress*, *11*, 318–332.

gPROMS Introductory User Guide, Release 2.2 (2003). Process Systems Enterprise Limited, London, UK.

Lynch, S. M., & Bequette, B. W. (2002). Model predictive control of blood glucose in type I diabetics using subcutaneous glucose measurements. In *Proceedings of the American Control Conference* (pp. 4039–4043).

Mahfouf, M., Asbury, A. J., & Linkens, D. A. (2003). Unconstrained and constrained generalized predictive control of depth of anaesthesia during surgery. *Control Engineering Practice*, *11*, 1501–1515.

Parker, R. S., Doyle, F. J., III, & Peppas, N. A. (2001). The intravenous route to blood glucose control. *IEEE Engineering in Medicine and Biology*, *20*, 65–73.

Pistikopoulos, E. N., Dua, V., Bozinis, N. A., Bemporad, A., & Morari, M. (2002). On line optimization via off-line parametric optimization tools. *Computers and Chemical Engineering*, *26*, 175–185.

Rao, R. R., Palerm, C. C., Aufderheide, B., & Bequette, B. W. (2001). Automated regulation of hemodynamic variables. *IEEE Engineering in Medicine and Biology*, *20*, 24–38.

Yasuda, N., Targ, A. G., & Eger, E. I. (1989). Solubility of I-653, Sevoflurane, isoflurane and halothane in human tissues. *Anesthesia and Analgesia*, *69*, 370–373.

Yasuda, N., Lockhart, S. H., Eger, E. I., Weiskopf, R. B., Laster, M., Taheri, S., & Peteron, N. A. (1991a). Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesthesia and Analgesia*, *72*, 316–324.

Yasuda, N., Lockhart, S. H., Eger, E. I., Weiskopf, R. B., Johnson, B. H., Freire, B. A., & Fassoulaki, A. (1991b). Kinetics of desflurane, isoflurane and halothane in humans. *Anesthesiology*, *74*, 489–498.

Yu, C., Roy, R. J., & Kaufman, H. (1990). A circulatory model for combined nitroprusside-dopamine therapy in acute heart failure. *Medical Progress through Technology*, *16*, 77–88.

Zwart, A. N., Smith, N. T., & Beneken, J. E. W. (1972). Multiple model approach to uptake and distribution of halothane: The use of an analog computer. *Computers and Biomedical Research*, *5*, 228–238.