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Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes

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Abstract

A nonlinear model predictive controller has been developed to maintain normoglycemia in subjects with type 1 diabetes during fasting conditions such as during overnight fast. The controller employs a compartment model, which represents the glucoregulatory system and includes submodels representing absorption of subcutaneously administered short-acting insulin Lispro and gut absorption. The controller uses Bayesian parameter estimation to determine time-varying model parameters. Moving target trajectory facilitates slow, controlled normalization of elevated glucose levels and faster normalization of low glucose values. The predictive capabilities of the model have been evaluated using data from 15 clinical experiments in subjects with type 1 diabetes. The experiments employed intravenous glucose sampling (every 15 min) and subcutaneous infusion of insulin Lispro by insulin pump (modified also every 15 min). The model gave glucose predictions with a mean square error proportionally related to the prediction horizon with the value of 0.2 mmol L^{-1} per 15 min. The assessment of clinical utility of model-based glucose predictions using Clarke error grid analysis gave 95% of values in zone A and the remaining 5% of values in zone B for glucose predictions up to 60 min ($n = 1674$). In conclusion, adaptive nonlinear model predictive control is

promising for the control of glucose concentration during fasting conditions in subjects with type 1 diabetes.

Keywords: nonlinear control, compartment modeling, Bayesian estimation

1. Introduction

The 'artificial endocrine pancreas' has been the subject of extensive research since the 1970s. The first generation of control approaches was designed for intravenous glucose sampling and intravenous insulin infusion. The initial work was carried out independently by Albisser *et al* (1974) and Pfeiffer *et al* (1974) developing the glucose controlled insulin infusion system (GCIIS) leading to the development of 'Biostator' (Clemens *et al* 1977). In terms of titration algorithms, insulin infusion was linked to the rate of glucose change by Albisser *et al* (1974). The development of advanced algorithms followed (Fischer *et al* 1990, Fisher and Teo 1989, Kienitz and Yoneyama 1993, Ollerton 1989, Salzsieder *et al* 1985, Shichiri *et al* 1983, Swan 1982). A good review of control algorithms based on intravenous insulin delivery is by Parker *et al* (2001).

The subcutaneous delivery of insulin is less invasive than the intravenous insulin delivery and suitable for use with a wearable extracorporal artificial pancreas. However, it has been well recognized that subcutaneous insulin delivery poses problems to efficient glucose control due to the additional delay associated with the absorption of subcutaneously infused insulin (Cobelli and Mari 1985) and only with the availability of short-acting insulin (Howey *et al* 1994) could the next generation of control algorithms have been developed (Brunetti *et al* 1993, Candas and Radziuk 1994, Shichiri *et al* 1998, Shimoda *et al* 1997, Trajanoski and Wach 1998).

The model predictive control (MPC) (Camacho and Bordons 1999) is an emerging methodology to facilitate control of systems with long time delays and open loop characteristics. When combined with adaptive capabilities, it promises to tackle successfully problems such as the control of glucose concentrations in subjects with type 1 diabetes. Model predictive control has been at the forefront of recent research endeavors with contributions, for example, by Parker *et al* (1999) and Lynch and Bequette (2001).

It is within this context that a model predictive controller for use with subcutaneous insulin infusion has been developed with the aim of facilitating control during fasting conditions, such as during overnight fast, with 'infrequent' sampling, i.e. a sample taken every 15 min. This is in recognition that the wearable pancreas may adopt a minimally invasive glucose sensor with a discrete sampling technique and that a combination of a closed-loop control during fasting conditions with open loop characteristics during meals (specifying manually meal related insulin bolus) is a realistic way forward. The controller employs a novel nonlinear model of glucose kinetics based on a detailed double-tracer study by Hovorka *et al* (2002) and adopts Bayesian parameter estimation to facilitate adaptive behavior.

In the following sections, we first describe the underlying glucoregulatory model, then the control strategy, and finally the evaluation focusing on the predictive accuracy of the model.

2. Model of glucose and insulin kinetics

2.1. Introduction

The glucoregulatory model represents the input–output relationship between subcutaneous insulin infusion as input and intravenous glucose concentration as output. Meal ingestion and

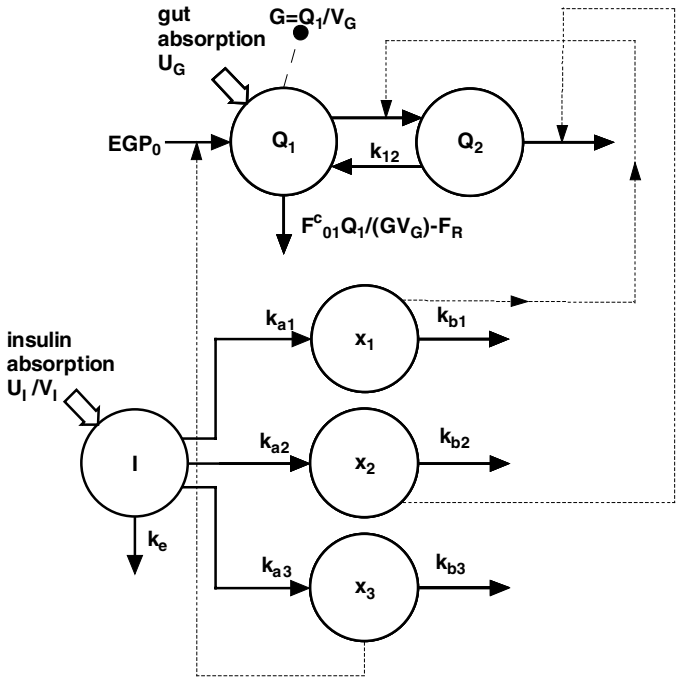

Figure 1. Compartment model of glucose–insulin system. Q_1 and Q_2 represent masses in accessible (plasma) and non-accessible compartments, I represents plasma insulin, x_i represent insulin action on glucose transport, disposal and endogenous glucose production. For more details, see the text.

intravenous glucose infusion represent additional inputs (the latter applicable during clinical studies to recover from hypoglycemia). The model outline is shown in figure 1.

The model consists of a glucose subsystem (glucose absorption, distribution and disposal), an insulin subsystem (insulin absorption, distribution, disposal) and an insulin action subsystem (insulin action on glucose transport, disposal and endogenous production). The model builds on recent experimental and modeling work, which employed glucose tracers to determine structure and parameter values of glucose kinetics in normal subjects during basal conditions and during the intravenous glucose tolerance test (Hovorka *et al* 2002).

2.2. Glucose subsystem

At the heart of the model is a two-compartment representation of glucose kinetics

$$\begin{aligned}\frac{\mathrm{d}Q_1(t)}{\mathrm{d}t} &= -\left[\frac{F^c_{01}}{V_G G(t)} + x_1(t)\right] Q_1(t) + k_{12} Q_2(t) - F_R + U_G(t) + \mathrm{EGP}_0[1 - x_3(t)] \\ \frac{\mathrm{d}Q_2(t)}{\mathrm{d}t} &= x_1(t) Q_1(t) - [k_{12} + x_2(t)] Q_2(t) \\ y(t) &= G(t) = Q_1(t)/V_G\end{aligned} \tag{1}$$

where Q_1 and Q_2 represent the masses of glucose in the accessible (where measurements are made) and non-accessible compartments, k_{12} represents the transfer rate constant from the non-accessible to the accessible compartment, V_G represents the distribution volume of the accessible compartment, y and G is the (measurable) glucose concentration, and EGP_0 represents endogenous glucose production (EGP) extrapolated to the zero insulin concentration.

F_{01}^c is the total non-insulin-dependent glucose flux corrected for the ambient glucose concentration

$$F_{01}^c = \begin{cases} F_{01} & \text{if } G \geqslant 4.5\,\text{mmol}\,\text{L}^{-1} \\ F_{01}G/4.5 & \text{otherwise.} \end{cases} \tag{2}$$

F_R is the renal glucose clearance above the glucose threshold of 9 mmol L^{-1}

$$F_R = \begin{cases} 0.003(G-9)V_G & \text{if } G \geqslant 9\,\text{mmol}\,\text{L}^{-1} \\ 0 & \text{otherwise.} \end{cases} \tag{3}$$

Glucose absorption is a fundamental process affecting postprandial glucose excursions. In our model, the gut absorption rate U_G is represented by a two-compartment chain with identical transfer rates $1/t_{\text{max,G}}$

$$U_G(t) = \frac{D_G A_G t\, \text{e}^{-t/t_{\text{max,G}}}}{t_{\text{max,G}}^2} \tag{4}$$

where $t_{\text{max,G}}$ is the time-of-maximum appearance rate of glucose in the accessible glucose compartment, D_G is the amount of carbohydrates digested, and A_G is carbohydrate bioavailability.

2.3. Insulin subsystem

Insulin absorption is described as

$$\frac{\text{d}S_1(t)}{\text{d}t} = u(t) - \frac{S_1(t)}{t_{\text{max,I}}} \qquad \frac{\text{d}S_2(t)}{\text{d}t} = \frac{S_1(t)}{t_{\text{max,I}}} - \frac{S_2(t)}{t_{\text{max,I}}} \tag{5}$$

where S_1 and S_2 are a two-compartment chain representing absorption of subcutaneously administered short-acting (e.g. Lispro) insulin, $u(t)$ represents administration (bolus and infusion) of insulin, and $t_{\text{max,I}}$ is the time-to-maximum insulin absorption. The insulin absorption rate (appearance of insulin in plasma) is obtained as $U_I = S_2(t)/t_{\text{max,I}}$.

The plasma insulin concentration $I(t)$ is described as

$$\frac{\text{d}I(t)}{\text{d}t} = \frac{U_I(t)}{V_I} - k_e I(t) \tag{6}$$

where k_e is the fractional elimination rate and V_I is the distribution volume.

2.4. Insulin action subsystem

The model represents three actions of insulin on glucose kinetics

$$\begin{aligned} \frac{\text{d}x_1}{\text{d}t} &= -k_{a1}x_1(t) + k_{b1}I(t) \\ \frac{\text{d}x_2}{\text{d}t} &= -k_{a2}x_2(t) + k_{b2}I(t) \\ \frac{\text{d}x_3}{\text{d}t} &= -k_{a3}x_3(t) + k_{b3}I(t) \end{aligned} \tag{7}$$

where x_1, x_2 and x_3 represent the (remote) effects of insulin on glucose distribution/transport, glucose disposal and endogenous glucose production (Hovorka *et al* 2002); k_{ai}, $i = 1, \ldots, 3$, represent deactivation rate constants, and k_{bi}, $i = 1, \ldots, 3$, represent activation rate constants.

2.5. Model constants and parameters

Model quantities were divided into model constants and model parameters with the objective to reduce the number of parameters while retaining the ability to represent the wide range of glucose excursions seen in subjects with type 1 diabetes during physiological conditions.

Table 1. Model constants.

Symbol	Quantity	Value	Source
k_{12}	Transfer rate	0.066 min^{-1}	Hovorka *et al* 2002
k_{a1}	Deactivation rate	0.006 min^{-1}	Hovorka *et al* 2002
k_{a2}	Deactivation rate	0.06 min^{-1}	Hovorka *et al* 2002
k_{a3}	Deactivation rate	0.03 min^{-1}	Hovorka *et al* 2002
k_e	Insulin elimination from plasma	0.138 min^{-1}	Hovorka *et al* 1993
V_I	Insulin distribution volume	0.12 L kg^{-1}	Hovorka *et al* 1993
V_G	Glucose distribution volume	0.16 L kg^{-1}	Hovorka *et al* 2002
A_G	Carbohydrate (CHO) bioavailability	0.8 (unitless)	Livesey *et al* 1998
$t_{\max,G}$	Time-to-maximum of CHO absorption	40 min	Livesey *et al* 1998

Table 2. Model parameters.

Symbol	Quantity	Value[a]	Source
${}^*S_{IT}^{f}$ [b]	Insulin sensitivity of distribution/ transport	51.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al* 2002
${}^*S_{ID}^{f}$ [b]	Insulin sensitivity of disposal	8.2×10^{-4} min^{-1} per mU L^{-1}	Hovorka *et al* 2002
${}^*S_{IE}^{f}$ [b]	Insulin sensitivity of EGP	520×10^{-4} per mU L^{-1}	Hovorka *et al* 2002
EGP_0	EGP extrapolated to zero insulin concentration	0.0161 mmol kg^{-1} min^{-1}	Hovorka *et al* 2002
F_{01}	Non-insulin-dependent glucose flux	0.0097 mmol kg^{-1} min^{-1}	Hovorka *et al* 2002
$t_{\max,I}$	Time-to-maximum of absorption of subcutaneously injected short-acting insulin	55 min	Howey *et al* 1994, Rave *et al* 1999

[a] Mean value of the parameter for the purpose of Bayesian parameter estimation.
[b] Alternative parameterization ${}^*S_{IT}^{f} = k_{b1}/k_{a1}$, ${}^*S_{ID}^{f} = k_{b2}/k_{a2}$ and ${}^*S_{IE}^{f} = k_{b3}/k_{a3}$.

Generally, constants were those quantities which (i) were not *a priori* identifiable (Carson *et al* 1983) or (ii) were unlikely to be identifiable from the data (*a posteriori* non-identifiability).

Table 1 lists model constants and table 2 model parameters.

2.6. Sources of nonlinearity

Nonlinearity of the model arises primarily due to the insulin action on parameters of glucose production, glucose distribution/transport and glucose disposal. This is further confounded by the zero-order glucose disposal representing insulin-independent glucose utilization.

Under fasting conditions, insulin exerts relatively little control over glucose disposal. Model-based results from healthy subjects indicate that insulin-dependent glucose uptake is about 13% of the total glucose turnover (Hovorka *et al* 2002) further supported by model-independent measurements (Best *et al* 1981). At basal conditions, non-insulin-dependent glucose uptake dominates. This is in agreement with studies showing that acute suppression of basal insulin levels has only limited effect on whole-body glucose utilization (<20%, Del Prato *et al* 1995, Edelman *et al* 1990). The relative 'unimportance' of insulin-dependent disposal at basal insulin results in nonlinearity of insulin action in the periphery. Model-based calculations show that raising basal insulin by 50% results in a 50% increment in insulin-dependent glucose uptake but this increases whole body glucose disposal by only about 7% (Hovorka *et al* 2002). However, when insulin-dependent disposal dominates such as at postprandial conditions (plasma insulin >50 mU L^{-1}) insulin has a nearly proportional effect on whole-body glucose disposal.

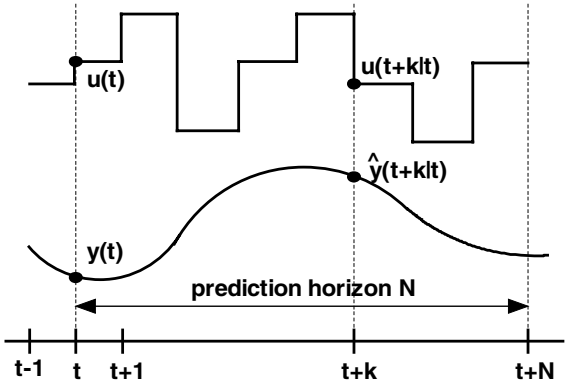

Figure 2. Strategy of model predictive control.

Another source of nonlinearity of insulin action results from the difference in the activation/deactivation profile of the three insulin actions. Insulin activates/deactivates peripheral disposal and EGP quickly (deactivation halftime of about 30 min) whereas glucose distribution/transport is activated/deactivated slowly (deactivation halftime of about 200 min) (Hovorka *et al* 2002). Under fasting conditions, when insulin controls plasma glucose primarily by suppressing EGP, the effect of insulin action will be faster and the action will dissipate also faster than under postprandial conditions when the distribution/transport pathway contributes to glucose control and the attainment/dissipation of the action will take longer.

3. Nonlinear model predictive control with parameter estimation

3.1. Overview

The strategy of model predictive control is shown in figure 2 (Camacho and Bordons 1999). Based on a model, the output trajectory $\widehat{y}(t+k|t)$, $k = 1, \ldots, N$, is estimated for any given control sequence $u(t+k|t)$ over a prediction horizon N. The model primary use is to determine the optimum control sequence, which results in a desired (target) trajectory.

The MPC controller used the nonlinear model specified by (1)–(7). Linearization around the operating point was considered undesirable, see discussion about the sources and the extent of nonlinearity. The full model was retained.

The block diagram of the controller is shown in figure 3. The controller includes the following components: parameter optimizer, target projector, dose optimizer and safety schemes 1–4.

It is known that parameters of the glucoregulatory system differ considerably between subjects (Bergman *et al* 1989) and also exhibit diurnal variations (Lee *et al* 1992, Van Cauter *et al* 1992) although exact quantification of the variation (amplitude and frequency) within a subject is yet to be determined.

In recognition of the variation between and within subjects, the controller adapts itself to the changing environment. This is carried out by re-estimating parameters at each control step, see section on *Bayesian parameter estimation*.

The parameter optimizer estimates model parameters employing glucose measurements from a 'learning window', i.e. a time period immediately preceding the control time. Three lengths of the learning window are predefined, short, medium and long, to be able to deal with both a time-invariant (or slowly varying) underlying system, which is best identified

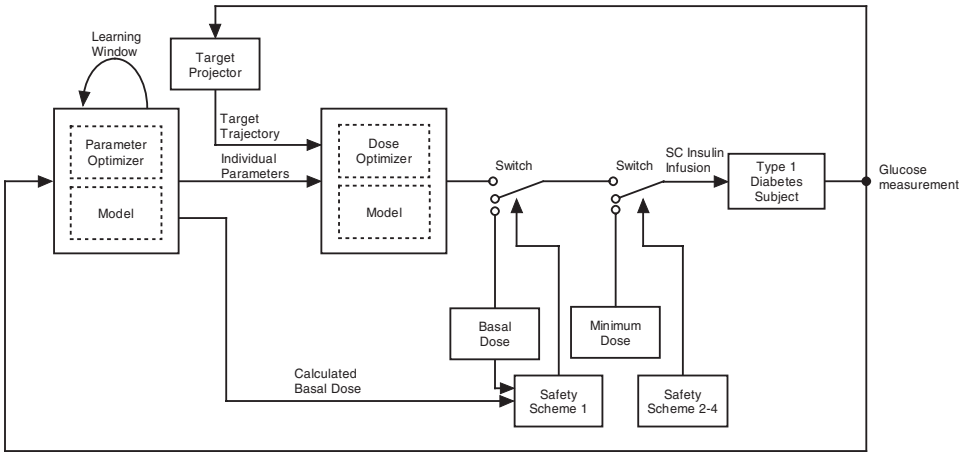

Figure 3. Block diagram of the model predictive algorithm.

over a long learning window, and a time-variant system best identified over a shorter learning window.

The target projector calculates target trajectory, i.e. the desired glucose profile.

The dose optimizer calculates a sequence of insulin infusion rates, which gives best fit to the target trajectory. From this sequence, the first element is returned and is suggested to be infused by the insulin pump. The remaining elements in the sequence are discarded. The dose optimizer adopts nonlinear function minimization as the underlying model is nonlinear.

Control systems must be able to cope with exceptional circumstances (Goriya *et al* 1988). Safety schemes 1–4 protect against system failures and minimize the risk of insulin overdosing and subsequent hypoglycemia.

The controller receives glucose measurements every 15 min and calculates the insulin infusion rate also every 15 min although, in principle, other sampling/control frequencies, equidistant or non-equidistant, are possible without changes to the controller design. The calculated insulin infusion rate is administered as a constant insulin infusion over the 15 min window.

3.2. Bayesian parameter estimation

The model parameters (see table 2) are estimated using the Bayesian approach to avoid problems with posterior identifiability.

The prior multivariate log normal distribution for parameters ${}^*S_{IT}^f$, ${}^*S_{ID}^f$, ${}^*S_{IE}^f$, F_{01} and EGP_0 was obtained from the study by Hovorka *et al* (2002). For the sake of a simpler implementation and numerical stability of the optimization, the multivariate normal distribution was expressed as a linear combination of five univariate independent normal distributions with a zero mean and a unit standard deviation, $p_i \sim N(0, 1)$, $i = 1, \ldots, 5$,

$$\ln\left({}^*S_{IT}^f\right) = a_{11}p_1 + b_1$$
$$\ln\left({}^*S_{ID}^f\right) = a_{12}p_1 + a_{22}p_2 + b_2$$
$$\ln\left({}^*S_{IE}^f\right) = a_{13}p_1 + a_{23}p_2 + a_{33}p_3 + b_3$$
$$\ln(F_{01}) = a_{14}p_1 + a_{24}p_2 + a_{34}p_3 + a_{44}p_4 + b_4$$
$$\ln(\mathrm{EGP}_0) = a_{15}p_1 + a_{25}p_2 + a_{35}p_3 + a_{45}p_4 + a_{55}p_5 + b_5.$$

The random variable transformation technique was adopted to derive coefficients a_{ij} and b_i.

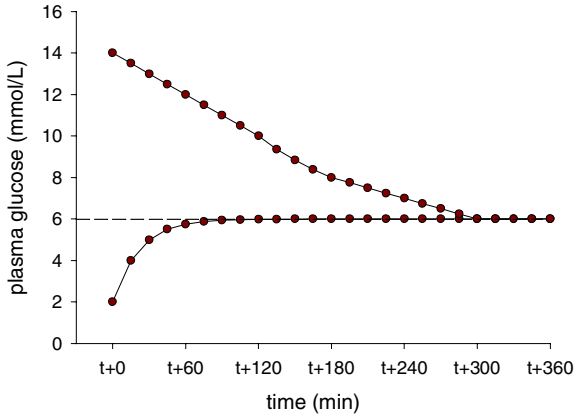

Figure 4. Moving target trajectories associated with high and low glucose concentrations. At glucose concentration > 8 mmol L^{-1}, the trajectory linearly decreases at a rate of 2 mmol L^{-1} per hour; at 6 mmol L^{-1} $<$ glucose $\leqslant 8$ mmol L^{-1}, the linear decrease is 1 mmol L^{-1} per hour. If glucose < 6 mmol L^{-1}, the trajectory exponentially increases with a halftime of 15 min.

The log normal prior of the remaining parameter $t_{\max,I}$ was obtained from literature sources (Howey *et al* 1994, Livesey *et al* 1998) and was again standardized for the purposes of numerical stability and simpler implementation.

The objective function at time t includes a weighted sum of squares of residuals and a penalty due to the distance from prior distributions (the latter collapses into the sum of squares of standardized parameter values due to standardization of random variables)

$$\underset{-2.5\leqslant p_1\cdots p_6\leqslant 2.5}{\arg\min}\left\{\sum_{i=1}^{N_W} w_{t-i}[\hat{y}(t-i\,|\,p_1\cdots p_6)-y(t-i)]^2+\sum_{k=1}^{6} p_k^2\right\} \tag{8}$$

where w_i is the weight reciprocal to the square of the measurement error (coefficient of variation of 2–9% depending on the source of glucose sample), $\hat{y}(i\,|\,p_1\cdots p_6)$ is model predicted glucose concentration at time i given standardized parameters $p_1,\ldots,p_6$, and N_W is the length of the learning window. A running internal assessment of predictive accuracy determines which learning window of 2, 4, or 12 h is to be used.

3.3. Target trajectory

The target trajectory is generated at each time step (see figure 4), using as the starting point the measured glucose concentration $y(t)$, or if that is not available, the model estimated glucose concentration $\hat{y}(t\,|\,p_1\cdots p_6)$.

The target glucose concentration is 6 mmol L^{-1}. When starting above the target value, the target trajectory is linearly declining with a maximum decrease set to a conservative value of 2 mmol L^{-1} per hour to reduce the risk of undershoot. When starting below the target trajectory, a faster exponential normalization of glucose values is specified reflecting the need to recover faster from low glucose values.

3.4. Calculating insulin infusion rate

The control action is the first insulin infusion rate $u(t+1)$ of a control sequence $u(t+1)\cdots u(t+N)$, which is calculated by minimizing an objective function composed

of two components, (i) the adherence of the predicted glucose $\hat{y}(t+i|t)$ to the target trajectory $y(t+i)$ and (ii) the variation in the control sequence

$$\underset{0\leqslant u(t+1)\cdots u(t+N)\leqslant 4}{\arg\min}\left\{\sum_{i=1}^{N}[\hat{y}(t+i|t)-y(t+i)]^2+\frac{1}{k_{\mathrm{agr}}}\sum_{i=1}^{N}[u(t+i)-u(t+i-1)]^2\right\} \tag{9}$$

where k_{agr} is an 'aggressiveness' constant balancing the contribution of the two components.

The prediction horizon N extends over 4 h representing the duration of action of subcutaneously injected short-acting insulin Lispro. The insulin infusion rate is limited to $u(t) \leqslant 4$ U h^{-1} due to technical limitations of insulin pumps.

The aggressiveness constant k_{agr} was determined by assessing safety (the number of hypoglycemia events) and efficacy (e.g. the settling time) during simulation tests with a glucose simulator. The aim was to limit the number of hypoglycemia events while attaining good efficacy (fasting glucose close to the target level). We selected a value of k_{agr} which gave hypoglycemia events (glucose < 3.3 mmol L^{-1}) in less than 5% out of 36 simulated cases and resulted in a mean fasting glucose of around 6 mmol L^{-1}.

3.5. Safety schemes

Four safety schemes are implemented, which override the model-based calculations of the insulin infusion rate. The description of these is beyond the scope of the present paper.

3.6. Implementation

The minimization of (8) and (9) was achieved using the Marquardt algorithm (Marquardt 1963) with the maximum number of iterations set arbitrarily at 50 to limit the run time. Normally, the convergence was achieved within 5 to 30 iterations. An informal investigation using a higher maximum number of iterations did not document an improvement in the performance of the controller.

The current version of MPC was implemented in Microsoft Visual C++ and runs both on a PC (MS Windows NT/98/2000) and a PDA (MS PocketPC). The computational time for a PC (x86 400 MHz) is <5 s and <45 s for PocketPC (iPAQ, Compaq). The PC version of MPC was used in evaluation studies.

4. Evaluation

4.1. Simulation tests

The performance of MPC has been extensively evaluated by simulation tests using a specialized methodology for evaluating glucose controllers (Chassin *et al* 2004). These tests also enabled the system to be tuned prior to real clinical evaluation and suggested acceptable clinical performance (Chassin and Hovorka 2001). Sample evaluation using the simulator is shown in figure 5.

4.2. Clinical experiments

The system was evaluated in 15 clinical experiments in 10 subjects with type 1 diabetes over an 8–10 h period during fasting conditions. Five subjects participated on two occasions.

A representative clinical experiment is shown in figure 6. Detailed evaluation of clinical tests is outside the scope of this document. In a proof-of-concept, six type 1 diabetes subjects

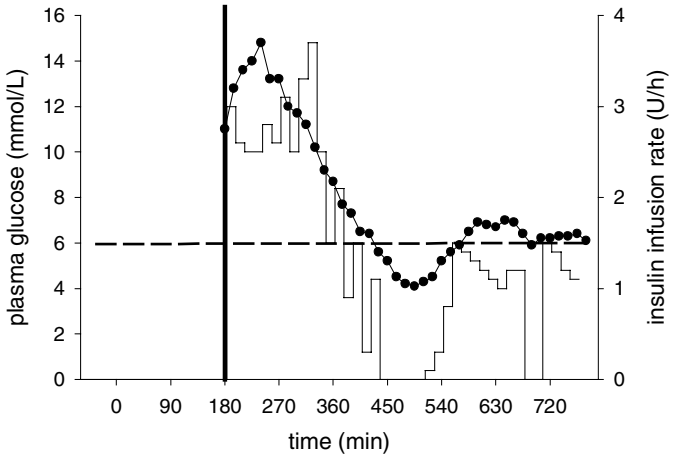

Figure 5. Sample performance of MPC during a simulation test. At time 0 min, the synthetic type 1 diabetes subject had a meal and received insulin bolus. At 180 min (vertical bar), glucose was artificially raised to 11 mmol L^{-1} and the subcutaneous insulin infusion was initiated. MPC calculated the infusion rate every 15 min using intravenous glucose measurements taken also every 15 min.

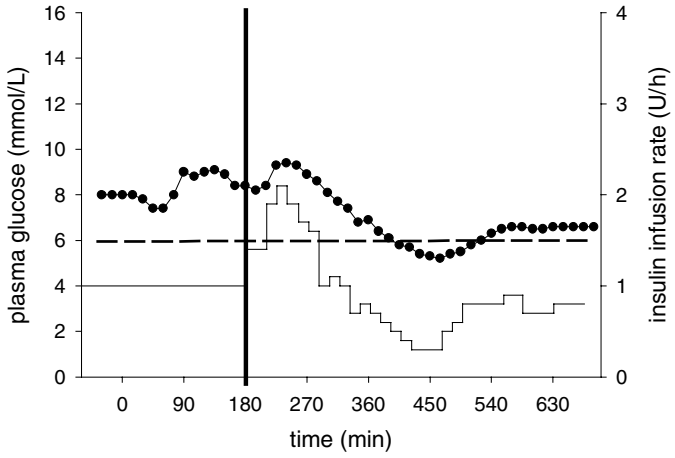

Figure 6. Sample performance of MPC during a clinical test in a male subject with type 1 diabetes (age 59 yr, weight 82 kg, basal insulin dose 27 U/day, HbA_{1C} 8.3%). At time 0 min, subject had a standardized meal (40 g CHO) and received insulin bolus of 6 U. After 180 min of constant insulin infusion, MPC took over the control of the insulin delivery (vertical bar) with sample/control every 15 min.

were controlled over 8 h following a 3 h monitoring period after meal ingestion. The mean glucose concentration was 6.0, 5.8 and 6.3 mmol L^{-1} in the period 2–4 h, 4–6 h and 6–8 h after the start of the control with a decreasing standard deviation of 1.0, 0.6 and 0.4 mmol L^{-1}, respectively. The algorithm was able to achieve and maintain normoglycemia even in the presence of a 30 min delay in glucose measurements mimicking subcutaneous glucose sampling, presenting similar results to those obtained without the measurement delay (Schaller *et al* 2002).

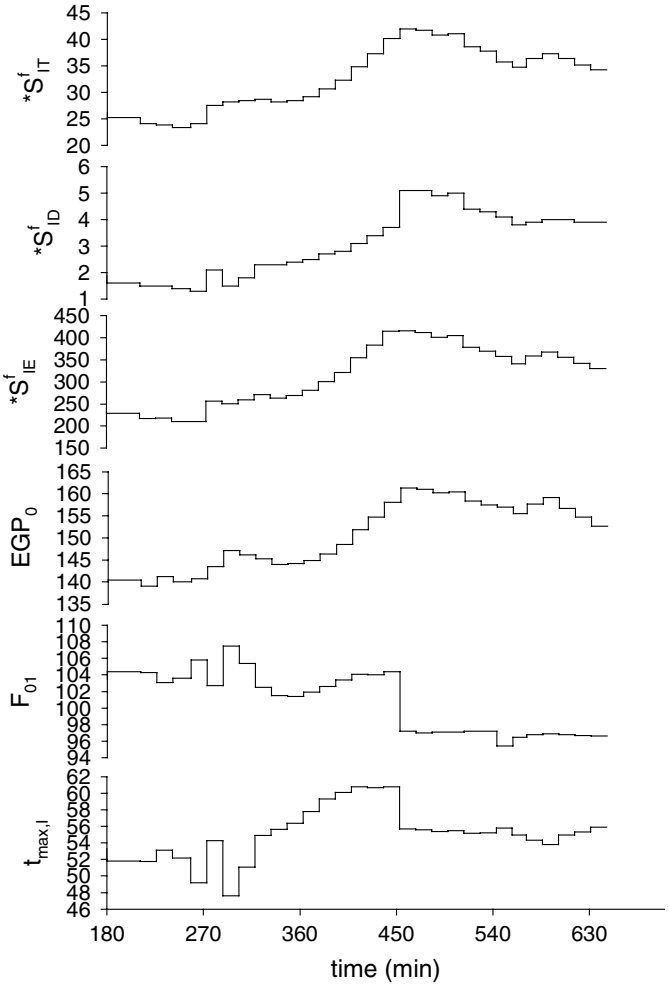

Figure 7. Trace of model parameters estimated by MPC during sample performance shown in figure 6. The units are as follows: ${}^*S^f_{IT}$ and ${}^*S^f_{ID}$ (10^{-4} min^{-1} per mU L^{-1}), ${}^*S^f_{IE}$ (10^{-4} per mU L^{-1}), EGP_0 and F_{01} (μmol^{-1} kg^{-1} min^{-1}), and $t_{\mathrm{max,I}}$ (min).

Figure 7 demonstrates the adaptive capabilities of the controller by plotting the time-evolving model parameters in a clinical experiment shown in figure 6. Figure 7 shows that insulin sensitivities are increasing up to $6\frac{1}{2}$ h postmeal and achieve values about two-fold higher than those at 3 h postmeal. The remaining three parameters also change but the extent of the change is not as striking as when considering insulin sensitivities and the values depart not more than 15% from the population mean.

An example of a study with the measurement delay is shown in figure 8. The 30 min delay represents a 'worst' case scenario and is obtained by adding a physiological delay and a technical delay. The former results from the properties of glucose transport from plasma into the interstitial fluid and is reported to be about 10–15 min although this is still a matter of discussion (Moberg *et al* 1997). The latter 5–10 min delay results from the dead space of the cannula transporting interstitial fluid from the sampling site to the extracorporally positioned glucose sensor. This latter delay is not present when using implantable glucose sensors such as Continuing Glucose Monitoring System (Minimed, Slymar, CA).

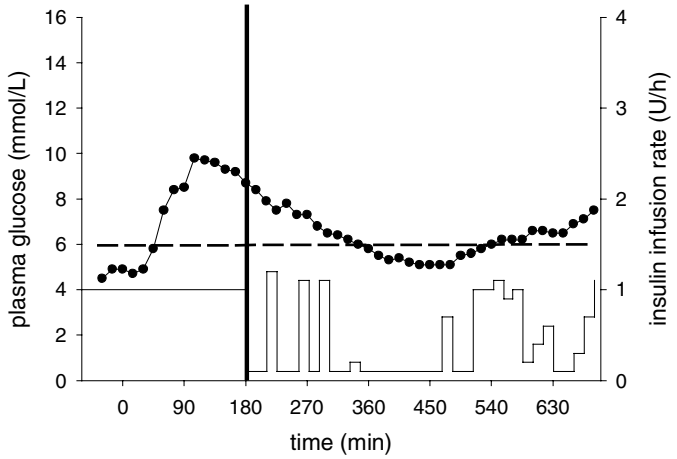

Figure 8. Sample performance of MPC during another clinical test with the same initial conditions and in the same subject as in figure 6. On this occasion, however, glucose concentrations were presented to MPC with a (known) 30 min delay to simulate the measurement delay between plasma and interstitial glucose.

4.3. Model predictive accuracy

Major effort has been dedicated to assess prediction accuracy of the model. For this purpose, data were used from 15 clinical experiments originally designed to test MPC performance.

Model-based predictions for prediction horizons from 15 to 240 min were compared with measured glucose values and the root mean square error (RMSE) was calculated. In total 5256 measured–predicted glucose pairs were obtained.

Prediction accuracy was evaluated for glucose values starting 240 min after food ingestion to avoid the effect of glucose absorption and to have sufficient data to learn individual parameters.

On average, RMSE increased proportionally by 0.2 mmol L^{-1} per 15 min of the prediction horizon. This means that the error associated with predicting 30 min ahead is comparable to a measurement error with a CV of 8% (assuming a glucose concentration of 6 mmol L^{-1}). This implies good accuracy for up to 60–90 min prediction horizon and explains why MPC is able to work well in the presence of the delay in glucose measurements.

Clinical utility of the predictions was further assessed using the Clarke error grid analysis (Clarke *et al* 1987), which assigns pairs of estimated–true glucose concentrations into zones A to E. Zone A implies that correct insulin treatment can be initiated using the estimated glucose concentration. Adjacent zones have progressively lower clinical utility with zone E leading to incorrect (opposite in trend) and potentially dangerous insulin treatment.

Figure 9 shows results for prediction horizon up to 60 min. The majority of points lie in zone A and the remaining in zone B. Prediction horizon up to 240 min (5256 data pairs) gave 66% of pairs in zone A, 33% in zone B, 1% in zone C and 0.1% in zone E.

5. Discussion

The present study describes the development of a nonlinear model predictive controller to achieve and maintain normoglycemia in subjects with type 1 diabetes during fasting conditions. The aim of the controller is to control safely glucose during the night allowing a subject with type 1 diabetes to start the day in normoglycemic conditions.

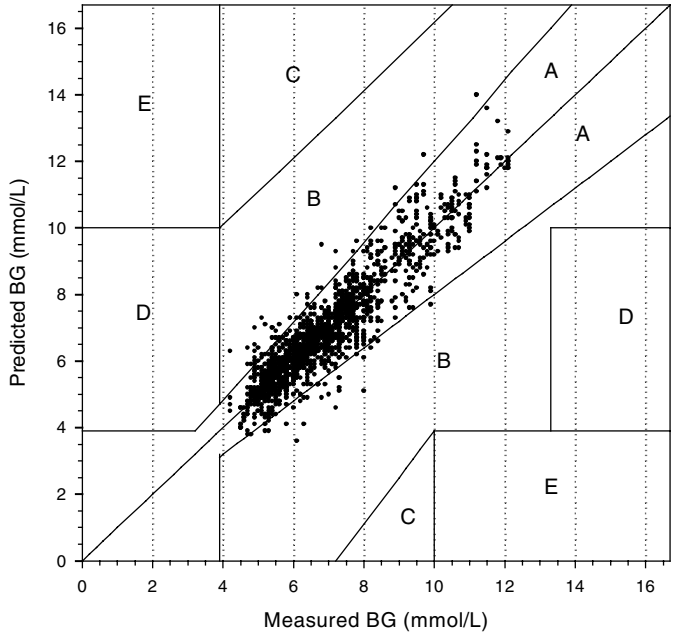

Figure 9. The Clarke error grid analysis for prediction horizon 15–60 min. Data from 15 clinical experiments gave 1674 data pairs with 95% of pairs in zone A and the remaining 5% in zone B.

The controller adopts a nonlinear model of the glucoregulatory system. The novelty of the approach is that model parameters are repeatedly estimated using the Bayesian approach avoiding problems associated with posterior identifiability. This allows adaptation both to a particular subject and to the time-varying characteristics of the glucoregulatory system.

The underlying system is characterized by a long time delay of over 90 min between insulin delivery and its peak action, which results from the superposition of delays associated with insulin absorption from the subcutaneous depot and the duration of insulin action (so-called remote insulin). These difficult conditions promote MPC to be a suitable strategy to approach the problem. MPC also allows for open loop inputs such as meals, manual insulin input, or exercise (after a suitable representation in the model), which could be entered by a subject with type 1 diabetes acting in the supervisory mode.

In both simulation and clinical experiments the controller commenced its operation in postprandial conditions, normally three hours or earlier following meal ingestion and prandial bolus delivery. The information about the meal content in terms of grams of CHO, and the size of the prandial bolus were presented to the controller, which utilized this information by employing the submodel of insulin absorption, see (5), and the submodel of gut absorption, see (4), to generate a gut absorption rate and an insulin absorption rate, respectively. The controller uses this meal-related information as it has a considerable effect on glucose excursions for up to 6 h postmeal.

Important for the present application is the use of informative prior distribution of parameters. The prior distribution specifies the mean and standard deviation of *and* correlation among parameters. The parameter estimation process relies on the prior distribution to achieve posterior identifiability at situations with limited system dynamics and/or short learning periods. Linearization would require recalculation of the prior distribution at each operating point with an unclear effect on the parameter estimation process and subsequently on the controller performance.

Nonlinear MPC has become a field of intense research in response to users' demands for higher performance. A number of approaches/applications have been developed (Balasubramhanya and Doyle 2000, Rangaiah *et al* 2002, Trajanoski and Wach 1998) considering also on-line implementation (Santos *et al* 2001). Nonlinear control is particularly suitable for medical applications where tolerances are small and predictive accuracy is of fundamental importance.

Detailed evaluation of MPC performance during clinical tests is beyond the scope of the present study. The evaluation of predictive accuracy has shown that the model is able to predict plasma glucose up to 60 min ahead with an error comparable to the measurement error. The results for predicting 60 min ahead are excellent with predicting 120 min ahead still clinically good. This good predictive accuracy is a necessary condition for good performance of the controller. The Clarke error grid analysis also supports the clinical utility of the predictions over a wide range of glucose concentrations.

An extracorporal biomechanical portable artificial pancreas will most likely use a glucose sensor measuring interstitial (subcutaneous) glucose, which will further extend system delays. The predictive accuracy of the present controller appears to be sufficient to cope with this additional obstacle to the control of glucose concentration.

The pilot tests and also simulation tests have shown that the controller has to recognize special conditions and recover from them. For this purpose, the four safety schemes have been implemented with the aim of preventing serious hypoglycemia events resulting from insulin overdosing. Hypoglycemia is potentially a life-threatening condition and occurs more often during intensified insulin therapy. Thus every means needs to be employed to facilitate the prevention.

6. Conclusions

Nonlinear model predictive control with adaptive capabilities is well suited to control glucose concentration during fasting conditions in subjects with type 1 diabetes mellitus. Good predictive accuracy of the internal nonlinear model suggests that this approach is suitable for use with subcutaneous glucose sampling and subcutaneous insulin infusion.

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References

Albisser A M, Leibel B S, Ewart T G, Davidovac Z, Botz C K and Zingg W 1974 An artificial endocrine pancreas *Diabetes* **23** 389–404

Balasubramhanya L S and Doyle F J 2000 Nonlinear model-based control of a batch reactive distillation column *J. Process Control* **10** 209–18

Bergman R N, Hope I D, Yang Y J, Watanabe R M, Meador M A, Youn J H and Ader M 1989 Assessment of insulin sensitivity in vivo: a critical review *Diabetes/Metab. Rev.* **5** 411–29

Best J D, Taborsky G J, Halter J B and Porte D Jr 1981 Glucose disposal is not proportional to plasma glucose level in man *Diabetes* **30** 847–50

Brunetti P, Cobelli C, Cruciani P, Fabietti P G, Filippucci F, Santeusanio F and Sarti E 1993 A simulation study on a self-tuning portable controller of blood glucose *Int. J. Artif. Organs* **16** 51–7

Camacho E F and Bordons C 1999 *Model Predictive Control* (Berlin: Springer)

Candas B and Radziuk J 1994 An adaptive plasma glucose controller based on a nonlinear insulin/glucose model *IEEE Trans. Biomed. Eng.* **41** 116–24

Carson E R, Cobelli C and Finkelstein L 1983 *The Mathematical Modeling of Metabolic and Endocrine Systems* (New York: Wiley)

Chassin L J and Hovorka R 2001 Closed-loop glucose control with IV glucose sampling and SC insulin infusion: evaluation by simulation studies *Diabetologia* **44** 221

Chassin L J, Wilinska M E and Hovorka R 2004 Evaluation of glucose controllers in virtual environment: methodology and sample application *Artif. Intell. Med.* at press

Clarke W L, Cox D, Gonderfrederick L A, Carter W and Pohl S L 1987 Evaluating clinical accuracy of systems for self-monitoring of blood-glucose *Diabetes Care* **10** 622–8

Clemens A H, Chang P H and Myers R W 1977 The development of biostator, a glucose controlled insulin infusion system (GCIIS) *Horm. Metab. Res.* 23–33

Cobelli C and Mari A 1985 Control of diabetes with artificial systems for insulin delivery—algorithm independent limitations revealed by a modeling study *IEEE Trans. Biomed. Eng.* **32** 840–5

Del Prato S, Riccio A, Vigili D K, Dorella M, Tiengo A and DeFronzo R A 1995 Basal plasma insulin levels exert a qualitative but not quantitative effect on glucose-mediated glucose uptake *Am. J. Physiol.* **268** E1089–95

Edelman S V, Laakso M, Wallace P, Brechtel G, Olefsky J M and Baron A D 1990 Kinetics of insulin-mediated and non-insulin-mediated glucose uptake in humans *Diabetes* **39** 955–64

Fischer U, Salzsieder E, Freyse E J and Albrecht G 1990 Experimental validation of a glucose insulin control model to simulate patterns in glucose-turnover *Comput. Methods Programs Biomed.* **32** 249–58

Fisher M E and Teo K L 1989 Optimal insulin infusion resulting from a mathematical model of blood glucose dynamics *IEEE Trans. Biomed. Eng.* **36** 479–86

Goriya Y, Ueda N, Nao K, Yamasaki Y, Kawamori R, Shichiri M and Kamada T 1988 Fail-safe systems for the wearable artificial endocrine pancreas *Int. J. Artif. Organs* **11** 482–6

Hovorka R, Powrie J K, Smith G D, Sonksen P H, Carson E R and Jones R H 1993 Five-compartment model of insulin kinetics and its use to investigate action of chloroquine in NIDDM *Am. J. Physiol.* **265** E162–75

Hovorka R, Shojaee-Moradie F, Carroll P V, Chassin L J, Gowrie I J, Jackson N C, Tudor R S, Umpleby A M and Jones R H 2002 Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT *Am. J. Physiol.* **282** E992–1007

Howey D C, Bowsher R R, Brunelle R L and Woodworth J R 1994 [Lys(B28), Pro(B29)]-human insulin A rapidly absorbed analogue of human insulin *Diabetes* **43** 396–402

Kienitz K H and Yoneyama T 1993 A robust controller for insulin pumps based on H-infinity theory *IEEE Trans. Biomed. Eng.* **40** 1133–7

Lee A, Ader M, Bray G A and Bergman R N 1992 Diurnal variation in glucose tolerance *Diabetes* **41** 750–9

Livesey G, Wilson P D, Dainty J R, Brown J C, Faulks R M, Roe M A, Newman T A, Eagles J, Mellon F A and Greenwood R H 1998 Simultaneous time-varying systemic appearance of oral and hepatic glucose in adults monitored with stable isotopes *Am. J. Physiol.* **275** E717–28

Lynch S M and Bequette B W 2001 Estimation-based model predictive control of blood glucose in type I diabetics: a simulation study *Proc. IEEE 27th Annual Northeast Bioengineering Conf.* pp 79–80

Marquardt D W 1963 An algorithm for least squares estimation of nonlinear parameters *J. Soc. Ind. Appl. Math.* **2** 431–41

Moberg E, HagstromToft E, Arner P and Bolinder J 1997 Protracted glucose fall in subcutaneous adipose tissue and skeletal muscle compared with blood during insulin-induced hypoglycaemia *Diabetologia* **40** 1320–6

Ollerton R L 1989 Application of optimal control theory to diabetes mellitus *Int. J. Control* **50** 2503–22

Parker R S, Doyle F J and Peppas N A III 1999 A model-based algorithm for blood glucose control in type I diabetic patients *IEEE Trans. Biomed. Eng.* **46** 148–57

Parker R S, Doyle F J and Peppas N A III 2001 The intravenous route to blood glucose control *IEEE Eng. Med. Biol. Mag.* **20** 65–73

Pfeiffer E F, Thum C and Clemens A H 1974 The artificial beta cell—a continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system) *Horm. Metab. Res.* **6** 339–42

Rangaiah G P, Saha P and Tade M O 2002 Nonlinear model predictive control of an industrial four-stage evaporator system via simulation *Chem. Eng. J.* **87** 285–99

Rave K, Heinemann L, Puhl L, Gudat U, Woodworth J R, Weyer C and Heise T 1999 Premixed formulations of insulin lispro. Activity profiles in type 1 diabetic patients *Diabetes Care* **22** 865–6

Salzsieder E, Albrecht G, Fischer U and Freyse E J 1985 Kinetic modeling of the glucoregulatory system to improve insulin therapy *IEEE Trans. Biomed. Eng.* **32** 846–55

Santos L O, Afonso P A F N, Castro J A A M, Oliveira N M C and Biegler L T 2001 On-line implementation of nonlinear MPC: an experimental case study *Control Eng. Pract.* **9** 847–57

Schaller H C, Schaupp L A, Bodenlenz M, Sommer R, Wutte A, Semlitsch B, Chassin L J, Wilinska M, Hovorka R, Wach P and Pieber T R 2002 Feasibility of the SC-SC route for an extracorporeal artificial pancreas *Diabetes* **51** 462

Shichiri M, Kawamori R, Goriya Y, Yamasaki Y, Nomura M, Hakui N and Abe H 1983 Glycaemic control in pancreatectomized dogs with a wearable artificial endocrine pancreas *Diabetologia* **24** 179–84

Shichiri M, Sakakida M, Nishida K and Shimoda S 1998 Enhanced, simplified glucose sensors: long-term clinical application of wearable artificial endocrine pancreas *Artif. Organs* **22** 32–42

Shimoda S, Nishida K, Sakakida M, Konno Y, Ichinose K, Uehara M, Nowak T and Shichiri M 1997 Closed-loop subcutaneous insulin infusion algorithm with a short-acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas *Front. Med. Biol. Eng.* **8** 197–211

Swan G W 1982 An optimal control model of diabetes mellitus *Bull. Math. Biol.* **44** 793–808

Trajanoski Z and Wach P 1998 Neural predictive controller for insulin delivery using the subcutaneous route *IEEE Trans. Biomed. Eng.* **45** 1122–34

Van Cauter E V, Shapiro E T, Tillil H and Polonsky K S 1992 Circadian modulation of glucose and insulin responses to meals—relationship to cortisol rhythm *Am. J. Physiol.* **262** E467–75