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Performance Limitations Arising in Closed Loop Control of Blood Glucose in Type 1 Diabetes

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Abstract: This paper presents a preliminary study of performance limitations that arise in the closed-loop control of blood glucose, using an autonomous artificial pancreas. It is shown that a major source of limitations is due to model uncertainty, specifically due to the combined effect of the insulin infusion system (IIS), the continuous glucose monitor (CGM) and the human glucose regulatory system. It is argued that the uncertainty associated with each of these elements compromises the achievable closed-loop bandwidth, and, in the presence of disturbances, e.g. meal intake and exercise, the closed-loop response will necessarily be poor. A proposition to overcome this problem is given based on feedforward action.

Keywords: diabetes; artificial pancreas; blood glucose regulation; performance limitations.

1. INTRODUCTION

Diabetes is a major health issue in the world. For example, 8% of the USA population are affected by this disease. Moreover, the incidence of diabetes, as a percentage of the world population, is rapidly growing especially in developing countries. Whilst diabetes can be managed, the treatment is extremely invasive. Hence, there has been a major worldwide effort aimed at developing an artificial pancreas to provide closed loop control of blood glucose concentration. The ultimate goal is to have a system that requires minimal patient intervention. Although important progress has been made, a fully operational autonomous closed loop system is, as of yet, unavailable.

Because of the massive impact of diabetes, there has been a significant effort aimed at developing and comparing different control architectures. This effort is accompanied by claims and counter claims regarding which strategy is best. In this paper, we adopt a different point of view and ask, "What are the fundamental limitations that underly blood glucose control and how can they be addressed?" We believe that this approach has several merits, including (i) understanding the fundamental limitations underlying all control strategies aimed at this problem and (ii) pointing to areas where additional research effort would have the biggest impact.

Diabetes results in inadequate release of insulin. Hence, external insulin analogues must be provided to restore glucose homeostasis. To achieve this, blood glucose must be monitored to ensure that the correct amount of insulin is injected, at appropriate times, to avoid both hypoglycaemia (excessively low glucose concentration) and hyperglycaemia (excessively high glucose concentration). The former is particularly dangerous as it can lead to coma and even death.

Many of the regulation techniques currently in use are dependent upon patient intervention. This can be a difficult task in the face of unpredictable glucose excursions caused by the variability of the system especially after the ingestion of food or the onset of exercise. For example, the efficacy of a pre-meal insulin bolus is highly dependent on the correct estimation of meal carbohydrate content (Ryan et al., 2008) and on estimating the correct time for the infusion (Scaramuzza and Iafusco, 2010). Hence, there has been a major international research effort directed at the development of a system, loosely called artificial pancreas, which interconnects a continuous glucose measurement (CGM) and an insulin infusion system (IIS) to achieve autonomous glucose regulation.

An artificial pancreas consists of three main components, all of which are actively under research and development:

(1) An insulin pump (actuator)
(2) A control algorithm
(3) A blood glucose monitor (sensor)

The prime focus of the current paper relates to the control algorithm. We argue that the actuator and sensor dynamics and limitations are an integral part of the problem and hence the control algorithm has to be designed with their characteristics in mind.

The available literature contains a vast array of ideas that have been proposed as candidates for the control algorithm (Santiago et al., 1978; Fischer et al., 1987; Steil, 2004; Bequette, 2005; Steil and Rebrin, 2005; Hovorka, 2006; Klonoff et al., 2009; Harvey et al., 2010; Lunze et al., 2013). Some of the algorithms under study include:

- PI/PID (with/without feedforward)
- Linear/Nonlinear MPC
- Periodic Control (run-to-run)
- Fuzzy control

Several studies have compared different control strategies. For example, a very recent paper (Luijf et al., 2013) has compared two versions of MPC algorithms (Soru et al., 2012; Patek et al., 2012) against patient self management (open loop). However, an inherent difficulty is that the total set of available strategies are often implemented under different conditions. Hence it is difficult to draw definitive conclusions. Moreover, it has been reported (Luijf et al., 2013) that MPC performs marginally better than manual patient control in terms of mean square tracking error but has the major advantage of reducing the proportion of hypoglycaemic events from 6% to 2%.

In the current paper we will pursue a different point of view. In particular, we will address the issue of fundamental limitations that apply to the artificial pancreas problem. We point to limitations that transcend the choice of any particular control strategy. Our motivation is twofold, namely

(1) to gain an understanding of the key issues which limit achievable performance,
(2) point to areas where additional research efforts might have the biggest impact.

The layout of the remainder of the paper is as follows: Section 2 describes the sources of limitations in artificial pancreas. Section 3 describes a realistic, yet simple, model of the blood glucose regulation system, including actuator and sensor dynamics. Section 4 presents a linearised form of the model. Section 5 develops insights into the fundamental performance limitations that arise from model uncertainty. Section 6 proposes remedial solutions. Section 7 explores the use of feedforward MPC. Section 8 draws conclusions.

2. FUNDAMENTAL LIMITATIONS DUE TO MODEL UNCERTAINTY IN ARTIFICIAL PANCREAS

A central theme in the current paper is that of fundamental limitations. In this context, it is relevant to point to the extensive literature that exists on this topic in the systems and control area, see for example Seron et al. (1997). Indeed, it has been a source of major research effort over the past five decades.

An admittedly simplified summary of the fundamental limitations literature is given below. One way of thinking about the control problem is that of constructing an inverse for the system. Hence fundamental limitations are typically ascribable to inherent difficulties involved in building an inverse (Goodwin et al., 2001). Not surprisingly, pure delays and (multivariable) non-minimum phase zeros are recurring themes in the fundamental limitations literature. Unstable poles are also important since those cannot be cancelled by the controller leading to the need for interpolation constraints. Another source of limitations is model uncertainty, which again inhibits finding a single inverse that applies to all possible models.

In the artificial pancreas problem, model uncertainty is the major source of limitations. Specifically, relative model errors directly translate into relative response errors. This places a lower limit on the achievable response time and hence, on the achievable performance. Importantly, note that these limitations are unavoidable and have nothing to do with the specific control algorithm.

For the sake of simplicity, we distinguish three components in the closed-loop control system of blood glucose, namely:

- The actuator, including the insulin pump and the transportation of insulin from the injection point to the blood stream.
- The blood glucose system, including the biomechanics that link insulin that appear in the plasma to the glucose response.
- The sensor, including the glucose transportation dynamics to the tissue and the sensor dynamics. It is assumed that a continuous glucose monitor is used in the artificial pancreas.

An important observation in the context of the current paper is that each of the aforementioned components has major model uncertainty. For example,

- The action of the insulin pump can depend on a host of factors. From anything like positioning and angle of insertion of the needle to air pressure changes that modify the way the tissue absorbs the insulin (King et al., 2011).
- There exists extremely high inter and intra patient variability that affect the dynamics of glucose regulation. These dynamics are also affected by stress and mood. There are also external disturbances such as food and exercise.
- Continuous glucose monitors usually have their own correction algorithms embedded, which are not publicly available, i.e. the reading is actually a filtered version of the actual measurement. In addition, they need to be periodically calibrated and even body movement can affect the resulting measurement.

Clearly, model uncertainty is a crucial factor in each component. Our goal in the current paper is to raise the issue of unavoidable limitations and present a preliminary study of how these limitations can be addressed in an artificial pancreas.

We will use a linear model for each of the components described above. The use of a nonlinear model is unlikely to improve the situation since the inherent variability of the parameters also applies in the nonlinear case. Thus nonlinear models give additional insight into the underlying dynamics but do not reduce the inter and intra model variability which arises due to other factors.

3. TYPE 1 DIABETES MODEL

In this section we describe a simple, yet realistic model. The model was presented in Kanderian et al. (2009) and

is based on Bergman's minimal model (Bergman, 2005). One advantage of such a model, in the current context, is that Kanderian et al. (2009) reports the identified parameters for a set of subjects, including intraday variability for some of them (see Table 1), hence providing a realistic framework for the characterisation of the uncertainty.

3.1 Actuator:

The following are the associated actuator dynamics:

$$\frac{dI_{SC}(t)}{dt} = -\frac{1}{\tau_1}\cdot I_{SC}(t) + \frac{1}{\tau_1}\cdot\frac{ID(t)}{C_l} \quad (1)$$

$$\frac{dI_p(t)}{dt} = -\frac{1}{\tau_2}\cdot I_p(t) + \frac{1}{\tau_2}\cdot I_{SC}(t) \quad (2)$$

where

- $I_{SC}(t)$: subcutaneous insulin concentration
- $I_p(t)$: plasma insulin concentration
- $ID(t)$: subcutaneous insulin delivery (input)
- τ_1 $[min]$, τ_2 $[min]$: time constants
- C_l $[ml/min]$: insulin clearance

3.2 Patient:

The following are the associated patient dynamics:

$$\frac{dI_{EFF}(t)}{dt} = -p_2\cdot I_{EFF}(t) + p_2\cdot S_I\cdot I_p(t) \quad (3)$$

$$\frac{dG(t)}{dt} = -(GEZI + I_{\mathrm{EFF}}(t))G(t) + EGP + R_A(t) \quad (4)$$

where

- $I_{EFF}(t)$ $[min^{-1}]$: insulin effect on plasma glucose
- $G(t)$ $[mg/dL]$: plasma glucose
- $R_A(t)$ $[mg/dL/min]$: glucose rate of absorption from meals (disturbance)
- S_I $[ml/\mu U]$: insulin sensitivity.
- $GEZI$ $[min^{-1}]$: glucose effect to increase glucose uptake and lower endogenous glucose production at zero insulin.
- EGP $[mg/dl/min]$: endogenous glucose production.

3.3 Sensor

The following are typical sensor dynamics:

$$\frac{dG_{ISF}(t)}{dt} = -\frac{1}{\tau_{SEN}}\cdot G_{ISF}(t) + \frac{1}{\tau_{SEN}}\cdot G(t) \quad (5)$$

where

- $G_{ISF}(t)$: interstitial fluid glucose concentration.
- τ_{SEN} $[min]$: sensor time constant.

3.4 Food absorption

The following are the associated food absorption dynamics:

$$R_A(t) = \frac{t\cdot e^{-\frac{t}{\tau_m}}}{V_G\cdot\tau_m^2}\cdot C_H(t), \qquad t\geq 0 \quad (6)$$

where

- $C_H(t) = C_H\delta(t)$: where C_H are the consumed carbohydrates in $[mg]$ and $\delta(t)$ is a unit impulse at $t=0$.
- V_G $[dl]$: distribution volume for glucose equilibria
- τ_m $[min]$: absorption peak time.

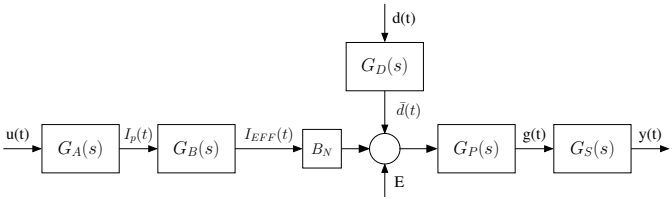

Fig. 1. Block diagram of approximated model

3.5 Exercise

Exercise is also an important factor but is not included in the above model. We will focus primarily on food disturbances but the core conclusions hold, mutatis mutandis, when exercise is added to the problem.

4. MODEL APPROXIMATION

The model described in Section 3 is linear save for equation (4). Assuming that $G(t)$ is regulated close to some nominal value G_o, and $I_{EFF}(t)$ is regulated close to $IEFF_o$, then the equation can be linearised as follows:

$$\frac{dG(t)}{dt} = A_N\cdot G(t) + B_N\cdot I_{EFF}(t) + E_N + R_A(t), \quad (7)$$

where

$$A_N = -(GEZI + IEFF_o)$$
$$B_N = -G_o$$
$$E_N = EGP + IEFF_o\cdot G_o$$

Also, we recognise equation (6) as the impulse response of a simple double pole system where the pole is located at $-1/\tau_m$. With these observations, the model can be represented in block diagram form as in Fig. 1.

In Fig 1, we use the notation,

- $u(t)$: input (subcutaneous delivery *rate*)
- $i(t)$: intermediate variable (*rate of change* of plasma insulin concentration)
- $d(t)$: disturbance (*rate* of consumed carbohydrates)
- E: constant (including EGP *rate*)
- $g(t)$: performance variable (plasma glucose concentration)
- $y(t)$: measured output (interstitial fluid glucose concentration)

In addition, G_A, G_B, G_D, G_P, G_S are five linear transfer functions which take the form:

$$G_A = \frac{k_A}{(\tau_1 s+1)(\tau_2 s+1)}$$

$$G_B = \frac{S_I}{1/p_2\cdot s+1} \qquad G_D = \frac{k_D}{(\tau_m s+1)^2}$$

$$G_P = \frac{1}{(\tau_3 s+1)} \qquad G_S = \frac{1}{\tau_{SEN}s+1}$$

The range of the original parameters is given in Table 1 (see Kanderian et al. (2009)). It is immediately evident that there is a huge range in behaviour. We will argue below that this variability renders high gain feedback impossible.

5. INSIGHTS INTO PERFORMANCE LIMITATIONS

To gain insight into the effect of model uncertainty, we represent each of the blocks in Fig. 1 as a first order lag.

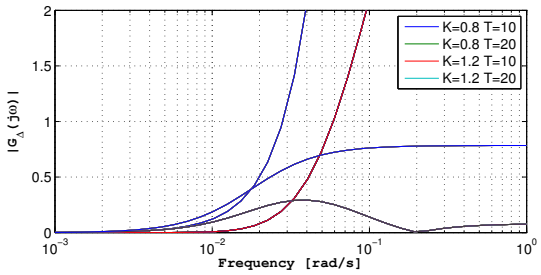

Fig. 2. Multiplicative Model Error G_Δ

We also assume that each transfer function has the same nominal time constant of 30 $[min]$ with a range from 10 to 50 $[min]$. We note that this is consistent with the parameter variation given above. In the sequel, we focus on the total relative model error defined by $G_\Delta = (G_T - G_T^o)/G_T^o$, where G_T is the composite transfer function $G_A \cdot G_B \cdot G_P \cdot G_S$ and G_T^o is its nominal value. Figure 2 shows the magnitude of G_Δ as a function of ω (in radians per minute) for the extreme values of model uncertainty.

From robust control theory (Zhou and Doyle, 1998; Goodwin et al., 2001), we know that a sufficient condition for robust stability is that the product of the closed loop nominal complementary sensitivity function T_o, and G_Δ should have magnitude less than one at all frequencies. Indeed, a margin is required so that $|T_o G_\Delta|$ should be much less than 1, in our case, say 0.5 at all frequencies. The closed loop bandwidth can also be defined (Goodwin et al., 2001) as the frequency where the gain of T_o falls below 0.7. Hence the bandwidth cannot be greater than the frequency where $|G_\Delta|$ reaches 0.7. Based on the above considerations, we see from Fig. 2 that the practical closed loop bandwidth is limited to about $2 \cdot 10^{-2}$ $[rad/min]$. We also note that the nominal bandwidth of the disturbance model is $\omega_d = 1/30 = 3.3 \cdot 10^{-2}$. Hence, any closed loop controller that achieves robust stability *for all possible* parametric variations can only eliminate the disturbance up to about 2 $[rad/min]$.

***Remark** 1.* The reader may wonder why this poor performance has resulted. The key issue is that the parametric uncertainty, in all four transfer functions G_A, G_B, G_P, G_s, means that high gain feedback cannot be used whilst ensuring stability for *all possible* parametric values. The situation would be very different if $\bar{d}(t)$ in Fig. 1 could be measured. If this were possible, then high-gain feedback could be used from $\bar{d}(t)$ to $u(t)$ which would have a major impact on the effect of the disturbance. However, the additional uncertain phase shift introduced by G_P and G_S makes this ideal result unachievable in practice.

6. POSSIBLE REMEDIES

6.1 Adaptive Control

One option to allow a greater achievable feedback bandwidth would be to estimate the parameters appearing in the model from online data obtained from each patient, then the inter-patient variability could be eliminated. It is clear that this strategy must be used to obtain a market-ready artificial pancreas. However, here we will examine a different strategy, namely feedforward MPC. Our aim is to show that feedforward MPC could prove beneficial in its own regard. The joint study of adaptive feedforward MPC is left for future research.

	Minimum Value	Nominal	Maximum Value
τ_1	41	85	131
τ_2	10	40	70
τ_{SEN}	10	15	20
p_2	$9.5 \cdot 10^{-3}$	$1.6 \cdot 10^{-2}$	$2.33 \cdot 10^{-2}$
C_l	540	1250	2010
S_I	$9.64 \cdot 10^{-5}$	$9 \cdot 10^{-4}$	$1.73 \cdot 10^{-3}$
EGP	0.6	2	3.45
$GEZI$	10^{-8}	$3.19 \cdot 10^{-3}$	$6.39 \cdot 10^{-3}$
V_G	104	220	337
τ_m	21	126	231

Table 1. Range of parameter values

6.2 Feedforward

Assume that a mechanism could be developed to make an approximate estimate of the disturbance d. Then, this signal would become available as an extra degree of freedom in the design.

It is important how this extra degree of freedom is utilised. One option would be to use $d(t)$ as a "preview signal" in a standard MPC algorithm. In this context, "preview" denotes prior knowledge of current and future disturbances over the optimisation horizon. However, this is not particularly beneficial since standard MPC uses only one cost function, and hence, the bandwidth available for both preview and feedback is limited by the need to achieve robust stability for all possible parameter values. A key observation in this regard is that, since feedforward involves no signals that depend on the input, then there are never stability issues arising from feedforward. This has motivated recent work described in Carrasco and Goodwin (2011) where a separate cost function is used for the feedback design and for the feedforward design. This enables a much higher bandwidth to be utilised by the feedforward component. We demonstrate the effectiveness of this idea in the sext section.

7. ILLUSTRATING THE ADVANTAGES OF FEEDFORWARD MPC

Here we utilise the linear model described in Section 4. We map the parameter ranges quoted in Section 3 to the equivalent parameters in the linear model – see Table 1. We then consider all different combinations of the extreme and nominal values of the parameters.

A linear observer was used to estimate the model states. The poles of the observer were placed in the range $(0.8, 0.84)$. This yields an observer response time of approximately 20 minutes. The system was sampled with period $h = 1$ $[min]$. Two designs were carried out based on the nominal parameter values as follows.

7.1 Robust Feedback MPC

A robust MPC controller incorporating integral action was designed so that, with a food bolus of 60 $[g]$, the system remains stable and the blood glucose concentration never falls below 50 $[mg/dL]$ *for all possible parameter values.* Note that this is a reasonable lower limit to avoid the

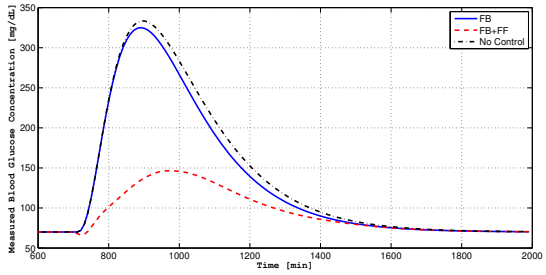

Fig. 3. Output Performance for nominal case

potentially catastrophic impact of hypoglycaemia. This design will be referred to as MPC in the sequel.

***Remark** 2.* Note that the MPC algorithm used in the current study is based on a quadratic cost function. In future work, it would be sensible to use a different cost in the hypoglycaemic region to that used in the hyperglycaemic region.

7.2 Feedforward MPC (FFMPC)

The ideas of Carrasco and Goodwin (2011) were used to design a feedforward component, separate from the feedback MPC previously designed. Based on the nominal model, an MPC problem is solved for the feedforward component. The solution to this problem is then fed to a separate robust MPC problem for the feedback component. The feedforward controller is based only on information of the nominal model and the disturbance, whereas the feedback controller is based on steady state reference values, estimated states from output information, the nominal model, the disturbance and the control input from the feedforward controller. The basic idea is described in more detail in Carrasco and Goodwin (2011). In the sequel, the design that includes a feedback and a feedforward controller will be referred to as FFMPC.

For the example below, a very high bandwidth was assigned to the feedforward controller. On the other hand, the feedback controller bandwidth was reduced so as to achieve stability and satisfactory performance for all possible parameter values. Figure 3 shows simulated results following a food bolus of 60 $[g]$ at time $t = 700$ $[min]$. Figure 3 shows the output response of the nominal system for both robust feedback MPC (FB: solid line), FFMPC (FB+FF: dashed line) and No Control case (dash-dot line), i.e. the control input was constant and set to the steady state value corresponding to an output of 70 $[mg/dL]$. Note that the robust MPC design is marginally better than having no feedback controller. This is due to the need to achieve stability for all parameter values.

7.3 Performance quantification

To provide a quantitative performance comparison, Table 2 presents the mean square error around a setpoint of 70 $[mg/dL]$. The cases shown represent the nominal, best, worst and average performance over all possible combinations of the parameter values. The model used for both the controller and the observer is always based on the nominal parameters.

It can be seen from Table 2 that FFMPC provides an improvement of at least 5:1 over MPC in the nominal and best performance scenarios. Moreover, Table 2 shows the FFMPC strategy provides, on average, an improvement in performance.

	Nominal	Best	Worst	Average
No Control	169.8	11.4	14936.6	2284.9
MPC	164.4	11.6	19345.1	1882.6
FFMPC	33.8	1.8	22724.8	1829.3

Table 2. Mean Squared Error Performance

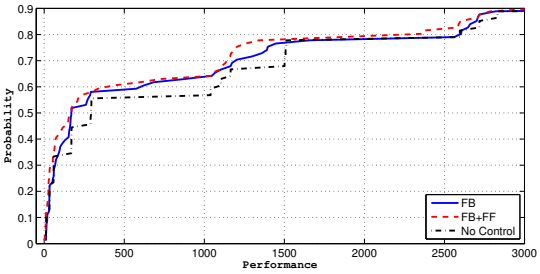

Fig. 4. Cumulative Probability Distribution (zoomed)

***Remark** 3.* Note that the robust MPC design used above is "universal" in the sense that one controller is asked to achieve stability and satisfactory performance for all patients based on a single nominal model. Adaptation of the type described in Section 6.1 would allow the nominal model to be tailored to each individual. This would undoubtedly improve the performance, specially for the extreme cases where the use of feedforward is detrimental. However, variability in the total model would still exist due to the actuator, sensor and intraday variability of the patient. Thus we anticipate that feedforward would still be of great benefit.

7.4 Probabilistic Analysis

Consider a uniform probability distribution on the set of parameters variations, i.e. every combination of parameters has the same probability of being the real system. We can then determine the corresponding cumulative distribution of performance. The results are presented in Figure 4, where three curves are shown, namely the cumulative probability distribution when FFMPC, MPC and No Control scenarios are considered. The plots should be interpreted as follows: the pair (x_o, y_o) describes the probability y_o that a system will have performance equal or better than x_o, for any given curve. Note that Fig. 4 encompasses an ensemble of experiments rather than a single experiment. We conclude from Figure 4 that, under uniform probabilistic uncertainty, feedforward provides better performance than feedback in 90% of cases. Moreover, in the remainder 10% of cases, the feedforward performance is at least 1.5 times better than no control at all.

***Remark** 4.* We have assumed a uniform distribution of the parameters as a worst case scenario since any distribution that has a concentration around the nominal values, e.g a normal distribution, will increase the performance gain obtained by using feedforward.

7.5 Adding Constraints

The results shown above have not considered the effect of constraints. It is sensible to expect certain degradation in the control performance depending on the tightness of

Upper Bound	10^6	$2 \cdot 10^5$	$5 \cdot 10^4$	$4 \cdot 10^4$
No Control	16811.9	16811.9	16811.9	16811.9
MPC	14903.3	14903.3	14906.7	15908.4
FFMPC	974.0	3087.3	14079.6	15843.6

Table 3. MSE Performance with Constraints

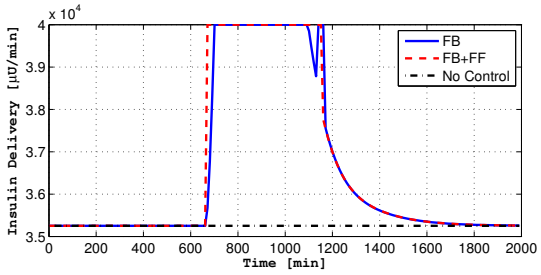

Fig. 5. Insulin delivery with constraints $0 < u(t) < 4 \cdot 10^4$

the constraints. We will examine the nominal case as an illustration. Table 3 presents the achieved mean squared errors as the upper bound on the input is lowered. Fig. 5 shows the *input* for the case $0 < u(t) < 4 \cdot 10^4$. It is clear that the ability of the feedforward component to improve on the regulation of blood glucose decreases as tighter constraints are imposed.

8. CONCLUSIONS

This paper has presented a preliminary study of the fundamental limitations that arise in the feedback control of blood glucose. The key conclusion is that, for realistic variations in the model parameters of the actuator, plant and sensor, then the achievable closed loop bandwidth is severely restricted. On the other hand, feedforward control does not suffer from this limitation. Thus feedforward provides the potential for major performance improvements. These ideas can also be used in a practical scenario, with realistic constraints, by using newly developed ideas of FFMPC, which combines high bandwidth feedforward with the safety net of a robust feedback MPC controller. Our core conclusion from this study is that a blood glucose regulation system based on MPC, or indeed any control algorithm, would be greatly enhanced by supplementing other tools such as online parameter estimation and/or feedforward. Of course, the key caveat in the case of feedforward is that measurements of the disturbances, e.g. food intake and exercise, need to be available. However, we believe that the results presented in the current paper provide a strong incentive to develop tools to make such measurements available.

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