Proceedings of the 17th World Congress
The International Federation of Automatic Control
Seoul, Korea, July 6-11, 2008

Event-based Feedforward Control of a Drug Delivery System for Diabetes Care

Ruoting Yang * **Tzyh Jong Tarn** * **Mingjun Zhang** **

* *Department of Electrical and Systems Engineering, Washington University, St. Louis, MO, USA (e-mail: ryang@ wustl.edu, tarn@ese.wustl.edu).*
** *Department of Mechanical, Aerospace and Biomedical Engineering, University of Tennessee, Knoxville, TN, USA (e-mail: mjzhang@utk.edu)*

Abstract: A new event-based feedforward control method for drug delivery system is presented. Compared with the traditional time-based feedback control, the proposed method shows great potential in dealing with measurement noise and unexpected disturbances. Instead of using time to drive the planner, we determine the reference trajectory with an intelligent event, which is directly derived from measurement. Therefore the proposed method inherits the advantages of both feedback and feedforward. Applications in drug delivery demonstrate promising robustness of this approach.

1. INTRODUCTION

Diabetes mellitus is to a disease in which the patient has difficulty regulating glucose. Today, about 120 million people worldwide suffer diabetes. The diabetes may affect functions of many physiological systems, including retinopathy (blindness), circulatory problems (sensory loss, or even amputation), nephropathy (kidney failure) and heart disease. It has been shown that intensive insulin management can significantly lower the risk of developing complications and slow the progress of existing complications. However, the dosage of insulin must be strictly regulated because excess insulin can cause hypoglycemia and insufficient insulin may cause hyperglycemia.

In early practice, open-loop or semi-open-loop methods have been applied to mimic the insulin secretion of a healthy pancreas. These products are unable to respond to the unexpected change of blood glucose level (BGL), which may arise from irregular food uptake or excessive exercise. In recent years, micro glucose sensors and micro pump shed a light on dealing this problem by developing a closed-loop "Artificial Pancreas". Some state feedback control mechanisms, such as Kienitz [1993], Parker [1999], Bellazzi [2001] and Hovorka *et al* [2004], have been proposed in last decade. The performance of state feedback approaches rely on the quality of feedback. However, the glucose sensors are incapable of providing real-time glucose measurement (usually every ten minutes). The long sampling time causes the poor performance of the state observers. Moreover, the sensor measurements have a long time lag and large noise, which can also affect the qualify of feedback.

Hence, feedforward control becomes very promising in practice. Feedforward controller is planned and calculated offline, while feedback controller can still be applied to compensate for the effect of disturbances and uncertainty, although the feedback may not be very reliable. The most intuitive feedforward design is to construct a nominal input u directly from the inverse dynamics. There are several important contributions based on nonlinear systems, including nonlinear output regulation by (Isidori and Byrnes [1990]), stable inversion by (Devasia [1996]), and causal inversion by (Graichen *et al* [2005]). The basic idea is to plan a sufficiently smooth reference trajectory that connects the initial and terminal setpoints, and then solves the system equations to achieve the nominal input. Hence the inversion-based feedforward approach is divided into two parts: the planner and the controller.

However, in practice, unexpected disturbances often happen during the control process, such as blockage of the infusion system, unplanned food intake. In this paper, we propose a new approach called an event-based feedforward controller, which combines the advantages of both feedback and feedforward control. In this approach, we design the planning trajectory based on output feedback instead of time. The event-based planner is a closed-loop planner, which actively responds to the sensor measurement.

The rest of the paper is organized as follows. In next section, a dynamics model of blood glucose via subcutaneous infusion is introduced. In section 3, the event based inversion feedforward control method is introduced and applied to the blood glucose model. Simulation results in the final section demonstrate the simplicity and robustness of the proposed mechanism.

2. DYNAMICS MODELLING OF BLOOD GLUCOSE REGULATION VIA SUBCUTANEOUS INFUSION

The dynamics modelling of the considered drug delivery system addresses three topics: subcutaneous sensor dynamics, subcutaneous insulin kinetics, and blood glucose kinetics.

The dynamics of the subcutaneous sensor can be written as Steil [2004]:

$$\tau \frac{dS}{dt} = -S + \alpha G + OF \tag{1}$$

where S stands for the sensor value, G represents the blood glucose, OF is the offset current, and τ is the time delay constant. The sensitivity of the sensor is characterized by a constant co-efficient α.

The rapid acting insulin Lispro kinetics with continuous subcutaneous infusion can be described by Shimoda's three-compartmental model (Shimoda [2003]) as follows:

$$\begin{aligned}
\dot{Q}_1 &= -kQ_1 + u, \\
\dot{Q}_2 &= -(\rho + o)Q_2 + kQ_1, \\
\dot{Q}_3 &= -k_e\,(Q_3 - i_b) + \rho Q_2, \\
I &= (Q_3 - i_b)/V_i,
\end{aligned} \tag{2}$$

where Q_1 and Q_2 are the insulin mass (mU/Kg) in the intraperitoneal insulin pools, Q_3 is the plasma insulin mass (mU/kg). I is the plasma insulin concentration (mU/L), and i_b is the basal plasma insulin concentration. u is the intraperitoneal insulin infusion rate ($mU/Kg/min$). k and ρ are the transition rate constants ($\min^{-1}$), and o and k_e are degradation decay rates. The parameter V_i stands for the plasma distribution volume (L/Kg).

The glucose kinetics model is proposed by Bergman [1981] as the well-known "minimal model".

$$\begin{aligned}
\dot{G} &= -XG + P_1(G_b - G) + GI, \\
\dot{X} &= -P_2X + P_3(I - I_b),
\end{aligned} \tag{3}$$

where G is the plasma glucose concentration, and G_b is the basal value; I stands for the plasma insulin concentration, GI is the intravenous glucose uptake and I_b is the basal value. P_1 is a coefficient for glucose effectiveness, and P_3/P_2 measures the insulin sensitivity (Bergman [1981]).

Combining all three dynamics models by letting $x_1 = S - OF$, $x_2 = G$, $x_3 = X$, $x_4 = I$, $x_5 = Q_2$, and $x_6 = Q_1$, then we have a new six-order model for the drug delivery system.

$$\begin{aligned}
\dot{x}_1 &= -\frac{1}{\tau}x_1 + \frac{\alpha}{\tau}x_2 \\
\dot{x}_2 &= -x_2x_3 - P_1(x_2 - G_b) + GI \\
\dot{x}_3 &= -P_2x_3 + P_3(x_4 - i_b) \\
\dot{x}_4 &= \rho x_5/V_i - k_e(x_4 - i_b) \\
\dot{x}_5 &= kx_6 - (\rho + o)x_5 \\
\dot{x}_6 &= -kx_6 + u \\
y &= x_1
\end{aligned} \tag{4}$$

where the parameters are summarized in the following table.

$x_1(mg/dL)$	sensor measured Plasma glucose level
$x_2(mg/dL)$	plasma glucose level
$x_3(\min^{-1})$	interstitial insulin
$x_4(mU/L)$	plasma insulin level
$x_5(mU/Kg)$	Insulin mass in intermediate site
$x_6(mU/Kg)$	insulin mass at the injection site
$P_1(\min^{-1})$	glucose effectiveness
$\frac{P_3(\min^{-1}/mU/L)}{P_2(\min^{-1})}$	insulin sensitivity
$V_i(L/Kg)$	plasma distribution volume
$u(mU/Kg/\min)$	insulin infusion rate
$G_b(mg/dL)$	basal plasma glucose level
$i_b(mU/L)$	basal plasma insulin level
$OF(mg/dL)$	offset current
$\tau(\min)$	time lag constant of sensor
α	sensor sensitivity
$GI(mg/dL)$	intravenous glucose infusion
$k_e, o(\min^{-1})$	insulin degradation rate
$k, \rho(\min^{-1})$	insulin transition rate

Table 1. Physical variables in the dynamics models

3. CONTROL MECHANISMS

3.1 Inversion-based feedforward

Consider a SISO nonlinear system

$$\begin{aligned}
\dot{x} &= f(x) + g(x)u,\ x(0) = x_0, \\
y &= h(x),
\end{aligned} \tag{5}$$

where state $x \in R^n$, input $u \in R$, and output $y \in R$. The vector field $f : R^n \times R \to R^n$ and the function $h : R^n \to R$ are sufficiently smooth.

Inversion-based feedforward problem:

Assume the above system is completely reachable and stabilizable. Given a sufficiently smooth reference trajectory that connects initial and terminal setpoints $(y(0), y(T))$, find a nominal control input u_d and a reference state x_d such that $\dot{x}_d = f(x_d) + g(x_d)u_d$ and $y_d = h(x_d)$. Furthermore, u_d and x_d must satisfy boundary constraints.

Therefore, an inversion-based feedforward problem actually can be divided into two parts: planning a smooth trajectory and finding the bounded nominal input.

Assuming the initial and terminal setpoints are stationary, (Piazzi and Visioli [2001]) construct a sufficiently smooth trajectory as a polynomial

$$y(t) = y_0 + (y_T - y_0)\sum\nolimits_{i=0}^{2r+1} a_i \left(\frac{t}{T}\right)^i,\ t \in [0, T], \tag{6}$$

with the boundary conditions.

$$y(0) = y_0,\ y(T) = y_T,\ y^{(i)}|_{0,T} = 0,\ i = 1, \cdots, r,$$

where r stands for relative degree. A nonlinear system with relative degree r can be transformed into the nonlinear input-output normal form.

$$y^{(r)} = \alpha(y, \dot{y}, ..., y^{(r-1)}, \eta) + \beta(y, \dot{y}, ..., y^{(r-1)}, \eta)u, \tag{7}$$

$$\dot{\eta} = p(y, \dot{y}, ..., y^{(r-1)}, \eta) + q(y, \dot{y}, ..., y^{(r-1)}, \eta)u, \tag{8}$$

where $\alpha(\cdot) = L_f^r h, \beta(\cdot) = L_f^r L_g h$, $p_i(\cdot) = L_f^r \phi_{\eta,i}$ and

$q_i(\cdot) = L_f^r L_g \phi_{\eta,i}$, $\eta = \phi_\eta(x) \in R^{n-r}$ is a supplementary state vector to complete the coordinate diffeomorphism $\phi(x) = [y, \dot{y}, ..., y^{(r-1)}, \eta] = [\xi, \eta]$.

From equation (7), we can solve a unique input in dependence of $\xi, y^{(r)}$ and η.

$$u_d = (y_d^{(r)} - \alpha(\xi_d, \eta))/\beta(\xi_d, \eta) \tag{9}$$

$$\begin{aligned}\dot{\eta} &= q_1(\xi_d, \eta) + q_2(\xi_d, \eta)u_d \qquad (10)\\ &= q_1(\xi_d, \eta) + q_2(\xi_d, \eta)(y_d^{(r)} - \alpha(\xi_d, \eta))/\beta(\xi_d, \eta),\\ &= \bar{Q}(\xi_d, y_d^{(r)}, \eta), \qquad (11)\end{aligned}$$

The system (8) is called internal dynamics, which determines the stability of the inverse system, that is, whether it is a minimum phase or non-minimum phase system.

The solution of the polynomial model is given by

$$y(t) = y_0 + (y_T - y_0)\sum_{i=r+1}^{2r+1} a_i \left(\frac{t}{T}\right)^i,\ t \in [0, T] \tag{12}$$

$$\begin{aligned}a_i &= \frac{(-1)^{i-(r+1)}(2r+1)!}{i \cdot r!(i-(r+1))!(2r+1-i)!},\\ i &= r+1, \cdots, 2r+1.\end{aligned} \tag{13}$$

For example, let r= 6, y_0 = 180, y_T = 90, T = 120, and then

$$\begin{aligned}&[a_7, \cdots, a_{13}]\\ &= [1716, -9009, 20020, -24024, 16380, -6006, 924]\end{aligned}$$

The reference trajectory is shown as a dashed line in Fig. 1.

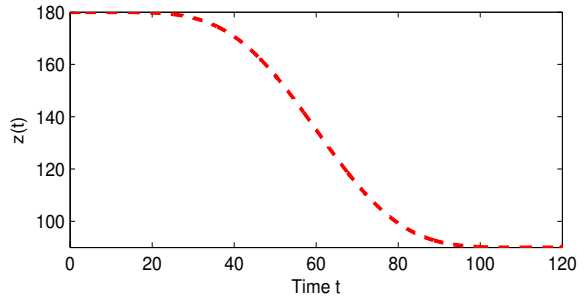

Fig. 1. The smooth transition of planning trajectory.

If the relative degree $r = n$, this special case is termed as feedback linearizable system. This SISO system is also a differentially flat output system (Fliess [1995]), which is completely controllable (van Nieuwstadt [1996]). Then the input-output normal form becomes

$$y^{(n)} = \alpha(y, \dot{y}, ..., y^{(n-1)}) + \beta(y, \dot{y}, ..., y^{(n-1)})u. \tag{14}$$

Given the reference trajectory $y_d, \dot{y}_d, \cdots, y_d^{(n)}$, the inversion-based feedforward control can be easily solved by

$$u_d = (y_d^{(n)} - \alpha(\xi_d))/\beta(\xi_d). \tag{15}$$

If $r \neq n$, the system is partial feedback linearizable, the feedforward control must solve the internal dynamics:

$$\dot{\eta} = \bar{Q}(\xi_d, y_d^{(r)}, \eta), \tag{16}$$

with $2(n-r)$ boundary conditions $\eta(0) = \eta_0$ and $\eta(T) = \eta_T$. By (Graichen *et al* [2005])'s method, $n-r$ unknown parameters are introduced into the reference trajectory.

$$\begin{aligned}y(t) = y_0 + (y_T - y_0)\Bigg[&\sum_{i=r+1}^{2r+1} a_i(p)\left(\frac{t}{T}\right)^i\\ &+ \sum_{i=1}^{n-r} p_i \left(\frac{t}{T}\right)^{i+2r+1}\Bigg],\end{aligned} \tag{17}$$

where $t \in [0, T]$.

Then the internal dynamics (10) can be solved using the MATLAB function bvp4c.

3.2 Event-based planner

A traditional planner predefines the desired reference trajectory, which is a function of time. Unexpected disturbances are not considered in the process of planning. As long as the reference trajectory is given, the planning will not change until replanning occurs. Hence, the planning trajectory loses all its reliability from the moment an unexpected event happens, such as an unexpected intake of sugar.

In recent years, the event-based planner was introduced by Tarn [1996], Xi [1996]. The basic idea of event-based planning and control theory is to design a reference trajectory with respect to an action reference parameter besides time, called an event. An event is defined as a function of system output measurement, so that the planning trajectory is independent of running time. If an unexpected intake of sugar happens, the blood glucose level will not decrease as expected. And the event does not change either, since the event depends on measurement. Therefore, the deviation between the plan and real blood glucose level will not increase as time goes. The scheme of event-based planning and control is illustrated in Fig. 2. The event generator in Figure 2b computes the event on-line based on system output measurements. In this sense, the event-based planner actually is closed-loop, while the traditional time-based planner is open-loop.

Due to the simplicity of computation in the event generator, the event is actually calculated at the same rate as the measurement. Therefore, the event-based and the time-based planner can work at the same sampling rate.

Theorem 1. : If the nonlinear system (5) is asymptotically stable with a time-based controller $u(t)$and the event s is monotonically increasing (non-decreasing) of time t, *i.e.*,

$$\frac{ds}{dt} > 0\ (\frac{ds}{dt} \geq 0). \tag{18}$$

Then this system is (asymptotically) stable under the same controller $u(s)$ based on the event.

Proof: If the original system is asymptotically stable with a controller $u(t)$, then there exists a Lyapunov function $V(t) > 0$ and $\dot{V}(t) < 0$.

Furthermore,

$$\frac{dV(t)}{dt} = \frac{dV(s)}{dt} = \frac{dV(s)}{ds}\frac{ds}{dt} < 0\ .$$

If the event s is monotonically increasing (non-decreasing) with time t, *i.e.*, $ds/dt > 0$ ($ds/dt \geq 0$), then

$$\frac{dV(s)}{ds} < 0\ (\frac{dV(s)}{ds} \leq 0).$$

Hence, for the same controller $u(s)$, this system is asymptotically stable (stable).

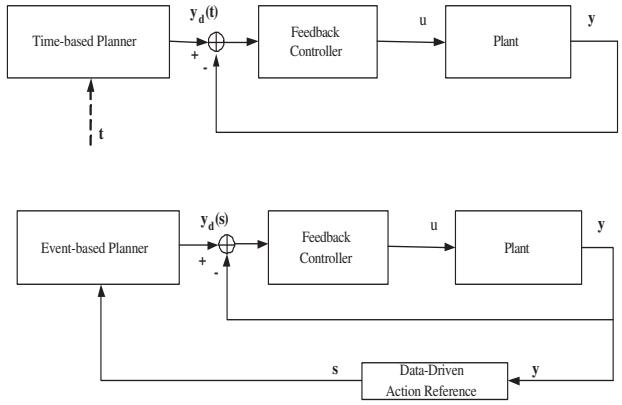

Fig. 2. The time-based planner can be seen as an open-loop planner, while the event-based is a closed-loop planner.

3.3 Event-based feedforward

Fig. 3 is a diagram of the proposed control method. The sensor measurement is directed to the event generator, which translates the measurement into the event online. The event-based planner decides the reference trajectory $y_d, \dot{y}_d, \cdots, \dot{y}_d^{(r)}$ in terms of the event. Then the input effort is derived from a feedforward controller and a feedback controller. Two control efforts are combined to determine the suitable dosage of drug.

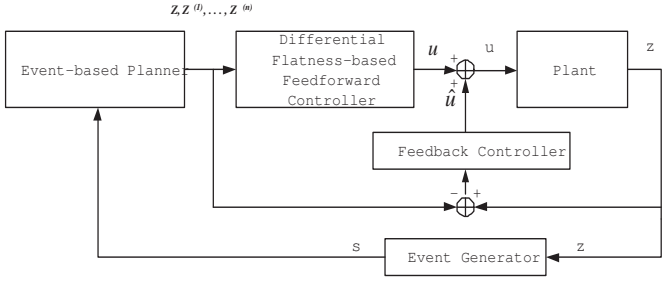

Fig. 3. Diagram of event-based feedforward plus feedback mechanism

Define event s as follows:

$$s_{k+1} = \begin{cases} s_k + \Delta y_k, y_0 - y_k > s_k \\ s_k \quad\quad\quad, y_0 - y_k \leq s_k \\ s_k \quad\quad\quad, y_T - y_k > 0 \end{cases} \tag{19}$$

where $s_0 = 0$, and $\Delta y_k = |y_k - y_{k-1}|$.

Since the time-based reference trajectory is monotonically decreasing, then the event is monotonically increasing. Hence, the stability of an event-based controller is the same as the time-based case. However, when blood glucose level (BGL) suddenly increases in the middle of the control process, the event S will not change. The resulting reference output trajectory remains constant until the BGL comes back to the same level as when disturbance happened. Then the event-based plan resumes from this level.

Using polynomial regression, we can translate the time-based plan (12) to the event-based plan, so that for any feedback y, there exist unique reference trajectory $\dot{y}_d(s), \cdots, \dot{y}_d^{(r)}(s)$.

In the blood glucose regulation model (4), the relative degree r is equal to n. Hence, this is a flat output system, and its nominal input can be directly computed by equation (15).

$$u_d = (y^{(n)} - \alpha(y_d, \dot{y}_d, \cdots, y_d^{(n-1)}))/\beta(y_d, \dot{y}_d, \cdots, y_d^{(n-1)}).$$

However, in the real case, no negative input is allowed, so the negative part of the control should be set to zero. Therefore, a PID feedback controller is applied here to compensate for the effect of losing the negative part. The two DOF control input becomes

$$u = w_1 \Theta(\xi_d, v_d, \dot{v}_d, \ldots, v_d^{(\sigma)}) + w_2 PID(e), \tag{20}$$

where w_1 and w_2 are two constant coefficients.

3.4 Simulation Results

The simulation results are presented in Fig. 4. At the very beginning, the blood glucose level is normal, and then 100 units of glucose are injected. Blood glucose concentration increases to 182.5 mg/dL in 9 minutes. The basal blood glucose level is assumed to be 85 mg/dL (dot dash line), and the safe range must be above 75 mg/dL (dash line).

Before BGL reaches a peak, a simple PD feedback controller is applied. When BGL is at its peak, the event-based planner takes effect and designs the reference trajectory. The two DOF control will provide the majority of the required control input, while the feedback control will compensate for the deviation in the initial setpoint and the lost negative part. If the initial value at the peak is sufficiently close to the initial condition of the reference trajectory, then by the theorem of the continuity and existence of solutions, there exists a unique solution of in the vicinity of the reference trajectory after applying the two DOF control (Theorem 2.6, Khalil [1996]).

Case I: Event-based v.s. time-based, without disturbance and noise (Fig. 4).

The glucose concentration (solid line) reaches the basal level in 110 min, and stays in the safe range after then. Considering the subcutaneous absorption time of insulin analog, this convergence time is acceptable in practice. The input has a maximum rate of 9 U/h, which is below the capacity of insulin pump. Without disturbance, two control methods do not have significant difference in control performance and infusion dosage.

Case II: Event-based v.s. time-based, with disturbance, with sensor noise (Fig. 5).

Assuming Gaussian white noise $N(0, \sigma^2)$, where $\sigma = 3$, is applied in the sensor measurement, the robustness to the sensor noise is tested for both approaches. Also a small dosage of glucose was injected intravenously from 11 min to 40 min as an unexpected disturbance. It is clear that the event-based feedforward control is superior to the time-based method. The event-based method converges in 150 min, while the time-based method converges in 250 min.

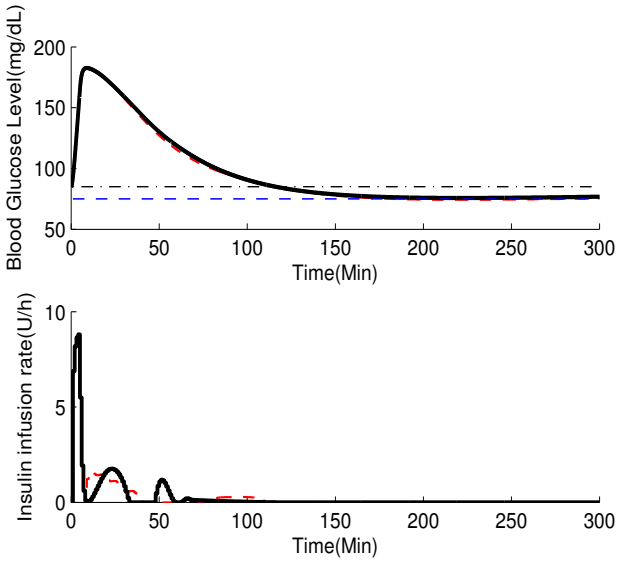

Fig. 4. Event-based method v.s. time-based method in a no disturbance & noise environment. The time-based method is represented by the solid line, while the event-based method is illustrated by the dotted line. Both methods get into the safe range in 110 min. Although control signals of the two methods are of different shapes, the total dosages of drug are similar.

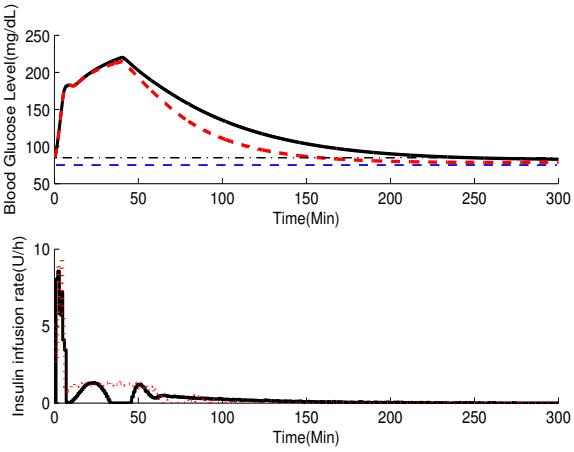

Fig. 5. Event-based method v.s. time-based method with disturbance 3 mg/dL from 11 min to 40 min and Gaussian white noise $N(0, 32)$. Event-based method converges in 150 min, while time-based method converges in 250 min.

Case III: Event-based, Different initial conditions (Fig. 6)

Different initial dosages of glucose (10 - 40 mg/dL) were tested in the simulation. The proposed method is absolutely robust for all the different cases. It is reasonable that the larger initial dosage of glucose will result in the longer control time (from 110 min to 150 min). And the more insulin infusion is required (from 4 U/h to 15.5 U/h).

Case IV: Monte Carlo simulation for event-based method under noise sensor measurement and random initial input (Fig. 7)

Assume initial glucose infusion is a random variable with uniform distribution in $[10, 40]$, and the noise is another

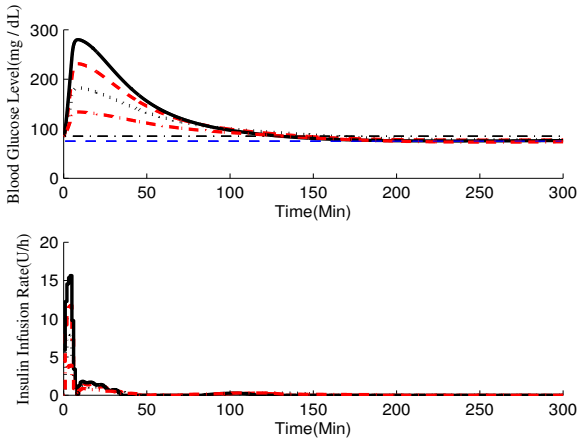

Fig. 6. Event-based control method with inputs of 10 (solid) , 20(dash), 30(dot), and 40(dot dash). All trajectories go into the safe range within 110 min - 150 min.

random variable with Gaussian white noise $N(0, 25)$. Applying Monte Carlo simulation of 100 trials, we can see all trajectories reach basal blood glucose level in 110 - 160 min and no trajectory goes underneath the safe boundary (75 mg/dL). It is evident that the proposed method is very robust under the noise environment. In practice, it is common for a truly normal person to have 160 min convergence time given a large 40 mg/dl initial input and 110 min given a small 10 mg/dl initial input.

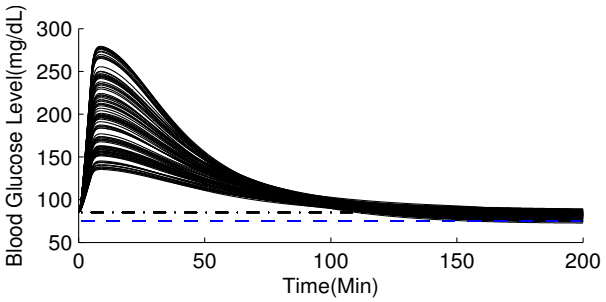

Fig. 7. Monte Carlo simulation for event-based two DOF control method.

The simulation parameters Shimoda [2003], Bergman [1981] are listed in Table 2.

Table 2. Parameters used in simulation

$P_1 = 0.003082$;	$k_e = 0.267$;	$\tau = 1$;
$P_2 = 0.02093$;	$i_b = 0$;	$\rho = 1$;
$P_3 = 0.00001282$;	$V_i = 0.21$;	
$G_b = 85$;	$k = 0.25$;	

3.5 Conclusions

A new event-based feedforward approach to achieve blood glucose regulation is presented in this paper. The approach combines the advantage of both feedforward and feedback, so that feedforward method can respond to the measurement intelligently. Therefore, the proposed method shows promising robustness to unexpected disturbances and sensor noise compared with either pure feedback or feedforward approach. This approach has great potential in the drug delivery system for diabetes care.

3.6 Acknowledge

This material is based upon work supported by the National Science Foundation under Grant No. 0328378.

REFERENCES

K. H. Kienitz, and T. Yoneyama. A robust controller for insulin pumps based on H-infinity theory. *IEEE Transactions on Biomedical Engineering*, 40:1133–1137, 1993.

R. S. Parker, F. J. Doyle III, and N. A. Peppas. A model-based algorithm for blood glucose control in type I diabetic patients. *IEEE Transactions on Biomedical Engineering*, 46:148–157, 1999.

R. Bellazzi, G. Nucci, and C. Cobelli. The subcutaneous route to insulin dependent diabetes therapy. *Engineering in Medicine and Biology Magazine*, 20:54–64, 2001.

R. Hovorka, *et al.* Nonlinear model predictive control of glucose concentration in subjects with type I diabetes. *Physiological measurement*, 25:905–920, 2004.

G. M. Steil, A. E. N. Panteleo, and K. Rebrin. Closed-loop insulin delivery - the path to physiological glucose control. *Advanced Drug Delivery Reviews*, 56: 125–144, 2004.

Y. Matsuo, Shimoda, *et al.* Strict glycemic control in diabetic dogs with closed-loop intraperitoneal insulin infusion algorithm designed for an artificial endocrine pancreas. *J Artificial Organs*, 6: 55–63, 2003.

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

S. Devasia, D. Chen, and B. Paden. Nonlinear inversion-based output tracking. *IEEE Trans. on Automatic Control*, 41: 930–942, 1996.

K. Graichen, V. Hagenmeyer, and M. Zeitz. A new approach to inversion-based feedforward control design for nonlinear system. *Automatica*, 41: 2033–2041, 2005.

A. Piazzi, and A. Visioli. Optimal inversion-based control for the set-point regulation of nonminimum-phase uncertain scalar systems. *IEEE Trans. on Automatic Control*, 46: 1654–1659, 2001.

N. Xi, T.J. Tarn, and A. K. Bejczy. Intelligent planning and control for multi-robot coordination – an event-based approach. *IEEE Transactions on Robotics and Automation*, 12:439–452, 1996.

T.J. Tarn, N. Xi, and A. K. Bejczy. Path-Based Approach to Integrated Planning and Control for Robotic System. *Automatica*, 32:1675–1687, 1996.

A. Isidori, and C.I. Byrnes. Output regulation of nonlinear systems. *IEEE Trans. on Automatic Control*, 35:131–140, 1990.

M. Fliess, J. Levine, P. Martin, and P. Rouchon. Flatness and defect of nonlinear systems: introductory theory and examples. *INT. J. Control*, 61:1327–1361, 1995.

H. K. Khalil. *Nonlinear Systems*, 2nd edn, Upper Saddle River: Prentice-Hall, 1996.

M. van Nieuwstadt, M. Rathinam, and R. M. Murray. Differential flatness and absolute equivalence of nonlinear control systems. *J. Control and Optimization*, 36:1225–1239, 1996.

V. Hagenmeyer, and E. Delaleau. Exact feedforward linearization based on differential flatness. *INT. J. Control*, 76:537–556, 2003.