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

A Closed-loop Artificial Pancreas based on MPC: human-friendly identification and automatic meal disturbance rejection

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Abstract:
Type 1 diabetes is characterized by a lack of insulin production from the pancreas, causing high blood glucose concentrations and requiring external insulin infusion to regulate blood glucose. A novel procedure of "human-friendly" identification testing using multisine inputs is developed to estimate suitable models for use in an artificial pancreas. A human-friendly multisine input signal offers improved identifiability on the dynamics of insulin to glucose, not causing serious deviations from the normal glucose concentration and satisfying insulin delivery pump specifications within acceptable time periods. An integrated formulation of constrained MPC is considered in order to reduce risks of hypoglycemia and hyperglycemia. Furthermore, a set of meal detection and meal size estimation algorithms are developed to improve meal glucose disturbance rejection when incoming meals are unknown. Closed-loop performance is evaluated by simulation studies of a type 1 diabetic individual, illustrating the ability of the MPC-based artificial pancreas strategy to handle measured and unmeasured meals.

1. INTRODUCTION

Type 1 diabetes is characterized by a lack of insulin production from the pancreas causing high blood glucose. Type 1 diabetes currently relies on the insulin therapy that uses subcutaneous insulin infusion to regulate blood glucose concentration. However, it demands significant attention and frequent clinical decisions each day to adjust infusion rates and decide amounts of insulin boluses for meals. The current therapy is a considerable burden to type 1 diabetic subjects and their guardians every day.

Continuous glucose sensors can be coupled with continuous insulin infusion pumps to create a closed-loop artificial pancreas (Hovorka *et al.*, 2004; Bequette, 2005). Closed-loop control algorithms automatically adjust insulin infusion rates to maintain blood glucose at a desired concentration (e.g., $80 \sim 100$ mg/dL). It is desirable to develop efficient model identification techniques to yield accurate models for desirable closed-loop performance.

As in the chemical process industries, the development of a good model inherently requires a trade-off. More frequent and different magnitude changes in the input (insulin delivery rate) result in more deviations of the output (glucose) away from the desired value. A methodology of "human-friendly" identification that accounts for desirable limits in changes in the insulin infusion rate and acceptable deviations from the glucose setpoint with shorter test duration. This idea springs from "plant-friendly" system identification that have been developed for use in manufacturing plants (Lee, 2006). Using *a priori* knowledge, a deterministic multisine input signal is generated for identifying the insulin-to-glucose dynamics.

A novel artificial pancreas strategy using constrained model predictive control is developed in this paper to achieve high-performance closed-loop glucose control for type 1 diabetes. A system of meal detection and meal size estimation is also developed to automatically administer meal insulin boluses as feed-forward action to unmeasured meals. This initial work is verified on the simulation model developed by Hovorka *et al.* (2004) and Wilinska *et al.* (2005). This paper is organized as follows: Section 2 briefs the simulation model for type 1 diabetes, Section 3 gives the generation of multisine input signals. Section 4 details the integrated MPC formulation for glucose control. Section 5 introduces the meal detection and meal size estimation algorithm. Section 6 presents the results of model experiment and evaluation with integrated MPC, and Section 7 provides the summary and conclusions.

2. SIMULATION MODELS FOR TYPE 1 DIABETES

A number of mathematical models have been developed to simulate the dynamics of insulin to glucose. Bolie (1961) presented a pioneering model using two simple differential equations. The Bergman "minimal model" consists of three differential equations for glucose-insulin dynamics (Bergman *et al.*, 1979; Toffolo *et al.*, 1980). The AIDA diabetes software simulator is based on 4 differential and 12 algebraic equations that provides the interactive simulation of insulin and glucose profiles, developed for teaching, demonstration, and self-learning purposes (Patrizio and Lehmann, 2002).

A physiological model using continuous subcutaneous insulin infusion is developed by Hovorka et al. (2004) and modified by Wilinska et al. (2005). The Hovorka model has three compartments of glucose, insulin, and insulin action subsystems, consisting of 9 nonlinear equations. The details for parameter units and values are available in (Hovorka *et al.*, 2004) and (Wilinska *et al.*, 2005). The insulin action subsystem involves insulin sensitivity as a ratio of insulin-to-glucose relationship, we use a 50% reduced insulin sensitivity and 80 *kg* weight for all experiments (Figure 1). Meal glucose absorption dy-

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namics is described by a two-compartment model with equal time constants $t_{max,G}$. Meals with $t_{max,G}$=40 minute are tested in this paper; $t_{max,G}$ indicates that the highest glucose absorption rate occurs 40 minutes after a meal. The open-loop test with a basal rate (1.1 U/hr) and three meals (50g carbohydrate each) is shown in Figure 2.

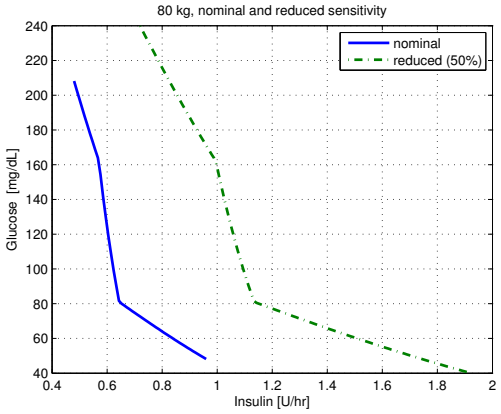


Fig. 1. Steady-state glucose conc. as a function of insulin infusion. Comparison of nominal (published) parameter values with reduced insulin sensitivity (50%), for an 80 kg individual.

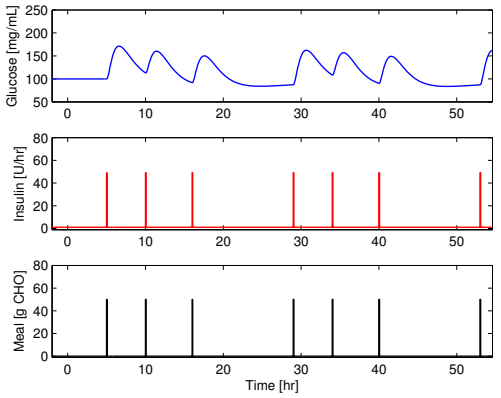


Fig. 2. Response of 80 kg subject with 50% reduced (compared to the published values) insulin sensitivity, to 50 g carbohydrate meals. Comparison of no meal bolus with 12.5 carbohydrate-insulin ratio. Basal rate is 1.10 U/hr.

3. MULTISINE INPUT SIGNAL DESIGNS FOR MODELING EXPERIMENTS

Multisine inputs are deterministic, periodic signals whose power spectrum can be directly specified by the user. A multisine input $u_j(k)$ for the j-th channel of a system with m inputs can be defined as,

$$u_j(k) = \sum_{i=1}^{m\delta} \hat{\delta}_{ji} \cos(\omega_i kT + \phi_{ji}^{\delta}) + \sum_{i=m\delta+1}^{m(\delta+n_s)} \alpha_{ji} \cos(\omega_i kT + \phi_{ji}) + \sum_{i=m(\delta+n_s)+1}^{m(\delta+n_s+n_a)} \hat{a}_{ji} \cos(\omega_i kT + \phi_{ji}^{a}), \quad j = 1, \ldots, m \quad (1)$$

where T is sampling time, N_s is the sequence length, m is the number of channels, δ, n_s, n_a are the number of sinusoids per channel ($m(\delta + n_s + n_a) = N_s/2$), $\phi_{ji}^{\delta}, \phi_{ji}, \phi_{ji}^{a}$ are the phase angles, α_{ji} represents the Fourier coefficients defined by the user, $\hat{\delta}_{ji}, \hat{a}_{ji}$ are the "snow effect" Fourier coefficients (Guillaume *et al.*, 1991), and $\omega_i = 2\pi i/N_s T$ is the frequency grid.

In designing an input signal, the primary frequency band of interest for excitation is determined by the dominant time constants of the system to be identified and the desired closed-loop speed-of-response,

$$\omega_* = \frac{1}{\beta_s \tau_{dom}^H} \leq \omega \leq \omega^* = \frac{\alpha_s}{\tau_{dom}^L} \quad (2)$$

α_s and β_s are parameters that specify the high and low frequency ranges of interest in the signal, respectively for a given range of low and high dominant time constants (defined by τ_{dom}^L and τ_{dom}^H). The input power spectrum via a series of Fourier coefficients must satisfy the primary bandwidth that in consequence determines design parameters such as N_s, n_s, and T (Lee, 2006).

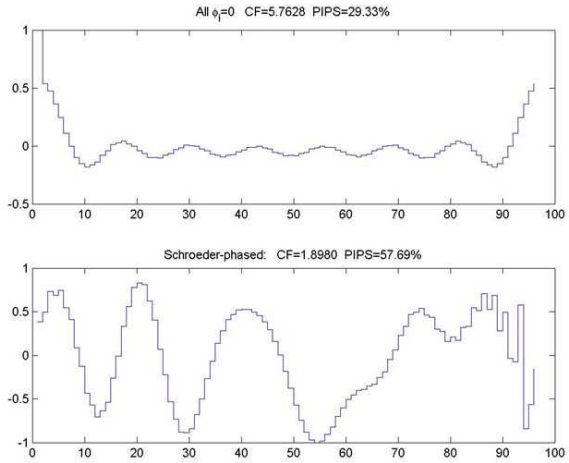


Fig. 3. A comparison of two multisine inputs by different phasing using the identical input power spectrum (Lee, 2006).

One measure that can count for plant-friendliness is the crest factor (CF) that is defined as the ratio of the ℓ_∞ (or Chebyshev) norm and the ℓ_2-norm of a signal,

$$CF(x) = \frac{\ell_\infty(x)}{\ell_2(x)}, \qquad \ell_p(x) = \left[\frac{1}{N_s}\int_0^{N_s} |x(t)|^p dt\right]^{\frac{1}{p}} \quad (3)$$

provides a measure of how well distributed the signal values are over the input span, ranging from 1 to ∞. In Figure 3, the two signals have the identical input power spectrum but the phase realization makes a difference in the time-domain. A multisine signal of a lower crest factor is meaningful for plant-friendliness.

4. INTEGRATED MODEL PREDICTIVE CONTROL

A model predictive controller (MPC) (Muske and Rawlings, 1993) is formulated subject to input and output constraints with a combination of additive output disturbance, state input disturbance, a first-order reference trajectory filter, and a first-order control action filter (see Figure 4). In MPC, a state input disturbance estimated by Kalman filtering and an additive output disturbance compensation are both implemented and are switchable in order to have robust glucose control performance.

A first-order reference trajectory is to avoid aggressive insulin infusions, and a first-order control action filter is to smoothen noise-like insulin infusion rates. When constrained optimization has an infeasible solution, output constraints are released but input constraints are always forced. Specially, a simple pump shut-off scheme is considered to prevent hypoglycemia.

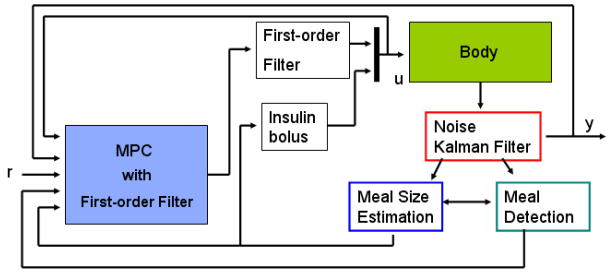


Fig. 4. A schematic diagram of the integrated MPC for closed-loop glucose control.

4.1 MPC Structure with Input Disturbance and Kalman Filtering

An MPC structure with measured and unmeasured step input disturbances is presented in the following

$$\begin{aligned}\begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{d}_{k|k-1}\end{bmatrix} &= \begin{bmatrix}\Phi & \Gamma^d\\ 0 & 1\end{bmatrix}\begin{bmatrix}\hat{x}_{k-1|k-1}\\ \hat{d}_{k-1|k-1}\end{bmatrix} + \begin{bmatrix}\Gamma^u\\ 0\end{bmatrix}u_{k-1|k-1} + \begin{bmatrix}\Gamma^d\\ 0\end{bmatrix}d_{k-1|k-1}\\ \begin{bmatrix}\hat{x}_{k|k}\\ \hat{d}_{k|k}\end{bmatrix} &= \begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{d}_{k|k-1}\end{bmatrix} + L_k\left(y_k - \begin{bmatrix}C & 0\end{bmatrix}\begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{d}_{k|k-1}\end{bmatrix}\right)\\ \hat{y}_{k|k} &= \begin{bmatrix}C & 0\end{bmatrix}\begin{bmatrix}\hat{x}_{k|k}\\ \hat{d}_{k|k}\end{bmatrix} + v_k\end{aligned} \tag{4}$$

where u_k is the input, d_k is the measured disturbance, $\hat{d}_k$ is the unmeasured estimated disturbance, y_k is the measured output, and $\hat{y}_k$ is the estimated output. With assumptions of noise in the input (insulin) and variance in the output (glucose), we consider a Kalman filter to reduce noise effects on the internal state vector. L_k is the Kalman Filter gain calculated as

$$L_k = P_k C^T (CP_kC^T + R)^{-1} \tag{5}$$

where P_k is the error covariance of the state estimate, which is calculated by

$$\begin{aligned}P_k &= \Phi P_{k-1}\Phi^T + (\Gamma^w)Q(\Gamma^{wT})\\ &\quad -\Phi P_{k-1}C^T\left(CP_{k-1}C^T + R\right)^{-1}CP_{k-1}\Phi^T\end{aligned} \tag{6}$$

4.2 Additive Output Disturbance

Another MPC formulation commonly used in the process industry is additive output disturbance rejection. At each time k, model prediction error is corrected as

$$\hat{y}_{k|k} = \hat{y}_{k|k-1} + p_k, \qquad p_k = y_k - \hat{y}_{k|k-1} \tag{7}$$

where it uses the current output measurement to adjust the current model prediction. As a result, the model update is

$$\begin{aligned}\begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{p}_{k|k-1}\end{bmatrix} &= \begin{bmatrix}\Phi & 0\\ 0 & 1\end{bmatrix}\begin{bmatrix}\hat{x}_{k-1|k-1}\\ \hat{p}_{k-1|k-1}\end{bmatrix} + \begin{bmatrix}\Gamma^u\\ 0\end{bmatrix}u_{k-1|k-1} + \begin{bmatrix}\Gamma^d\\ 0\end{bmatrix}d_{k-1|k-1}\\ \begin{bmatrix}\hat{x}_{k|k}\\ \hat{p}_{k|k}\end{bmatrix} &= \begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{p}_{k|k-1}\end{bmatrix} + \begin{bmatrix}0\\ 1\end{bmatrix}\left(y_k - \begin{bmatrix}C & 1\end{bmatrix}\begin{bmatrix}\hat{x}_{k|k-1}\\ \hat{p}_{k|k-1}\end{bmatrix}\right)\\ \hat{y}_{k|k} &= \begin{bmatrix}C & 1\end{bmatrix}\begin{bmatrix}\hat{x}_{k|k}\\ \hat{p}_{k|k}\end{bmatrix}\end{aligned} \tag{8}$$

4.3 Output Constraint Relaxation in Quadratic Programming

The MPC objective function is

$$\min\Phi = \sum_{i=1}^{P} W_y(r_{k+i} - \hat{y}_{k+i|k})^2 + \sum_{i=0}^{M-1} W_{\Delta u}\Delta u_{k+i|k}^2 \tag{9}$$

subject to $\Delta u_{min} \le \Delta u \le \Delta u_{max}$, $u_{min} \le u \le u_{max}$, and $y_{min} \le y \le y_{max}$. While computing the optimal control output, an infeasible solution might be generated with output constraints. If this occurs, we relax the output constraint for solving the quadratic program. However, MPC satisfies input constraints at every sampling time.

4.4 First-Order Reference Trajectory

A reference trajectory is also desirable to assure a smooth return to setpoint

$$\begin{cases} e_{k+i|k} = ae_{k+i-1|k} + (1-a)e_{k|k} \\ r_{k+i|k} = e_{k+i|k} + y_{k|k} \end{cases} \tag{10}$$

where $a = exp(-T/\tau)$, $i = 1...p$, and τ is selected that $r_{k+p|k}$ is settled to r_k within the prediction horizon.

4.5 First-Order Filter for Controller Output

The closed-loop system takes only one step control action out of M_{hor} number of computed control moves. This may generate noise-like control moves particularly under noisy conditions; therefore, a first-order filter is located between the controller and the system for smoothing control moves as

$$\tau_u = \begin{cases} 5 \text{ mins} & dy/dt > 1.5 \text{ [mg/dL min]} \\ 15 \text{ mins} & dy/dt \le 1.5 \text{ [mg/dL min]} \\ 40 \text{ mins} & y < 130 \text{ [mg/dL]} \end{cases} \tag{11}$$

4.6 Insulin Pump Shut-Off for Hypoglycemia

Since hypoglycemia is more critical than hyperglycemia, an adaptive constraint is useful to prevent hypoglycemia by shutting off insulin infusion as

$$if \;\; dy/dt < 0 \;\&\; y < 95mg/dL \quad then \quad u_{max} = 0 \;\; U/hr$$

5. MEAL DETECTION AND MEAL SIZE ESTIMATION

Although the MPC shows good performance to measured meals, unmeasured meals cause high glucose peaks and slow disturbance rejection. A relaxed set of input constraints often lead into hypoglycemia because of excessive insulin infusions from the controller. A system of meal detection and meal size estimation is thus developed to automatically administer meal insulin boluses as feed-forward action to unmeasured meals (Figure 4).

A Kalman filter with three states smoothes the noisy time-domain glucose measurement before the glucose concentration enters the controller (Dassau *et al.*, 2008). If the rate-of-change of the rate-of-change is assumed to be varying in a random fashion, the modeling equations are

$$\begin{bmatrix} g_{k+1} \\ \Delta g_{k+1} \\ \Delta^2 g_{k+1} \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 1 & 1 \\ 0 & 0 & 1 \end{bmatrix}\begin{bmatrix} g_k \\ \Delta g_k \\ \Delta^2 g_k \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} w_k \tag{12}$$

$$y_k = [1\,0\,0]\begin{bmatrix} g_k \\ \Delta g_k \\ \Delta^2 g_k \end{bmatrix} + v_k \tag{13}$$

where g_k is glucose concentration, Δg_k is the first-order derivative, and $\Delta^2 g_k$ is the second-order derivative. The above can be written into

$$x_{k+1} = \Phi x_k + \Gamma^w w_k, \;\; y_k = C x_k + v_k \tag{14}$$

The estimate of state vector is

$$\hat{x}_{k|k-1} = \Phi \hat{x}_{k-1|k-1} \tag{15}$$

and then the estimate is corrected with a Kalman gain

$$\hat{x}_{k|k} = \hat{x}_{k|k-1} + L(y_k - C\hat{x}_{k|k-1}) \tag{16}$$

where L is the steady-state Kalman filter gain and y_k is the measured noisy glucose concentration.

The estimated first-order and second-order derivatives are used for the meal detection and meal size estimation algorithms. An incoming meal is detected when either of the following conditions is satisfied with 5 minute sampling time such that

$$\begin{cases} \Delta y_k \geq 1.2 \;\; \text{and} \;\; \Delta^2 y_{k-1} < 0.45 \text{ and } \;\; \Delta^2 y_k \geq 0.45 \\ \Delta y_k \geq 1.5 \;\; \text{and} \;\; \Delta^2 y_k \geq 0.45 \end{cases} \tag{17}$$

where $\Delta y \equiv [mg/dL\ min]$ and $\Delta^2 y \equiv [mg^2/dL^2\ min^2]$. When a meal is detected at k, a meal size of carbohydrate is estimated with the following FIR filter

$$m(g) = \gamma \; [a_0\ a_1\ ...\ a_n] \times [1 \;\; \Delta^2 y_{k-n+1}\ ...\ \Delta^2 y_k]^T \tag{18}$$

where γ is the sensitivity for meal estimation $(0 < \gamma \leq 1)$, a_i are the coefficients of a FIR filter, and n is the filter length.

For example, a test of [50 50 50]g meals is estimated as [46.1 50.1 53.4]g under noisy condition ($\sigma^2 = 11.0\, mg^2/dL^2$). The meal detected times are 6-9 samples (30-45 minutes) after meal intakes.

6. MODELING EXPERIMENT AND CLOSED-LOOP EVALUATION WITH MPC

6.1 Open-loop Experiment

Firstly, a clinical treatment dataset that involves basal rates and insulin boluses is considered for model identification. A modeling comparison is available from three experiments: (i) insulin bolus test with dt= 0 min, (ii) insulin bolus test with dt = -20 min, and (iii) multisine-based test with dt =0 min. dt denotes a time delay between insulin boluses and meals, e.g., dt=-20 min indicates that insulin boluses are injected 20 minutes prior to meals. Based on *a priori* knowledge, a set of design parameters for a multisine input on the Hovorka simulation is given in Table 1 that produces one cycle of 170 samples (14.17 hours). This multisine signal is adjusted based on the basal insulin rate [1.1 U/hr] so that it moves between 0 and 2.2 [U/hr] as shown in Figure 5.

Open-loop experiments are performed for 56.67 hours [2.36 days]. Three meals of 50g carbohydrates are given for breakfast (7AM), lunch (noon), and dinner (6PM). A noise variance $\sigma^2 = 11.0\, mg^2/dL^2$ is selected as the worst noise condition as a realistic measured noise variance. Figure 6 shows the three experiments where the insulin bolus and multisine-based tests display similar deviations in the output. Particularly, the test using the multisine input as insulin infusion does not generate any serious deviations.

6.2 Modeling Experiments and Subspace Estimation

In this paper, we use subspace modeling for the insulin bolus and multisine tests with a range of $2 \sim 6$ states using the System

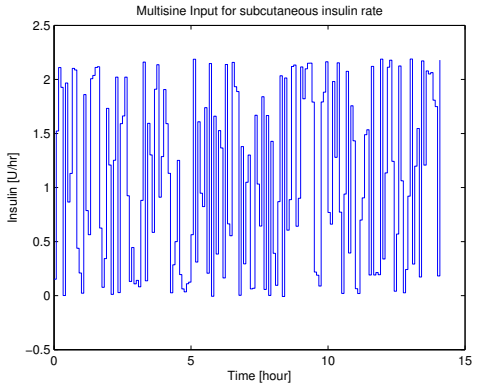


Fig. 5. A multisine input signal for subcutaneous insulin infusion rate for the Hovorka simulation: 1 cycle is 14.17 hours where the sampling time is 5 minutes.

Identification Toolbox in MATLAB (Ljung, 1999). A closed-loop data is used as a validation dataset for all the cases to select the best models; 5-states for the insulin bolus test (dt=0 min), 3-states for the insulin bolus test (dt= -20 min), 5-states for the multisine-based test (dt=0 min). The estimated models are then examined by open-loop prediction, step test, and closed-loop MPC evaluation, as shown in Figure 7.

Table 2 and Figure 7a show the output prediction of the estimated models. All the models have equivalent accuracy for 30 min and 1 hour ahead-of-time predictions, but the multisine test shows the best accuracy at 3 hour prediction. The step tests using 1.1 U/hr indicate an interesting problem; the insulin bolus test (dt=0 min) shows a positive gain for insulin-to-glucose, which is not true for type 1 diabetes. The other models with negative gains provide reasonable closed-loop results in Figure 7c.

Test Ahead-of-Time Prediction (FIT(%))	30 min	1 hour	3 hour
Insulin-bolus (dt=0 min)	74.9	64.2	43.8
Insulin-bolus (dt=-20 min)	74.9	65.3	49.7
Multisine (dt= 0 min)	77.8	69.3	64.2

Table 2. Output predictions of subspace models estimated from the modeling experiment datasets; $FIT\ (\%) = 100 \times (1 - \|\hat{y} - y)\|_2 / \|y - \bar{y}\|_2)$ where $\hat{y}$ is prediction and $\bar{y}$ is mean of the output.

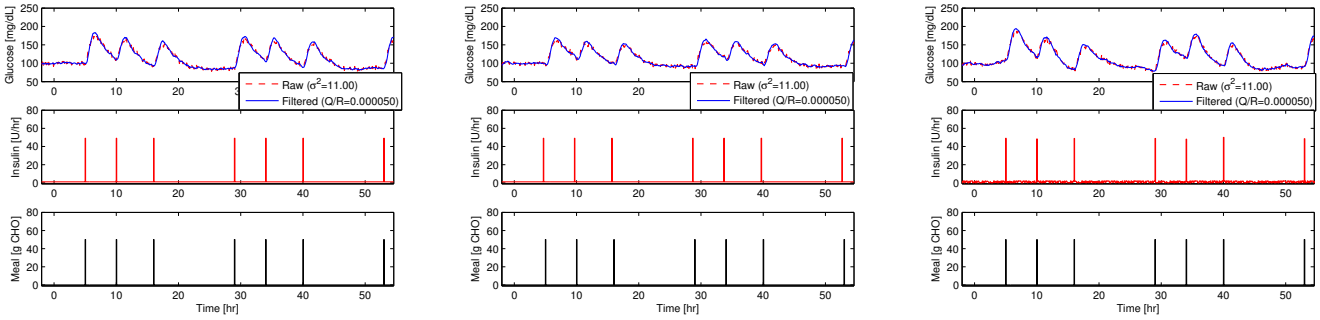
6.3 Closed-Loop MPC Evaluation

In this section, we focus on the subspace model estimated from the multisine test to be evaluated with the integrated MPC formulation. An MPC tuning for glucose control is determined: $P_{hor} = 48$ (4 hours), $M_{hor} = 6$, $W_y = 1$, and $W_{\Delta u} = 10$. Input constraints are $u_{max} = 5.5$ U/hr, $u_{min} = 0$ U/hr, and $\Delta u_{max} = 2.9$ U/hr. Output constraints are given as $y_{max} = 200$ mg/dL and $y_{min} = 99$ mg/dL. Often constrained optimization generates infeasible solutions and constraint violations, and a tight lower bound as 80 mg/dL is not be specified.

The Kalman filtering for disturbance rejection is tuned at $Q/R = 0.00003$ (Q is process noise variance and R is measurement noise variance) (see Eqn. (4)). The first-order reference trajectory filter is assigned with the time constant 15 minutes. The input disturbance rejection by Kalman filtering is used in the MPC; however, it is switched to the additive output disturbance rejection for 15 minutes (3 samples) when measured

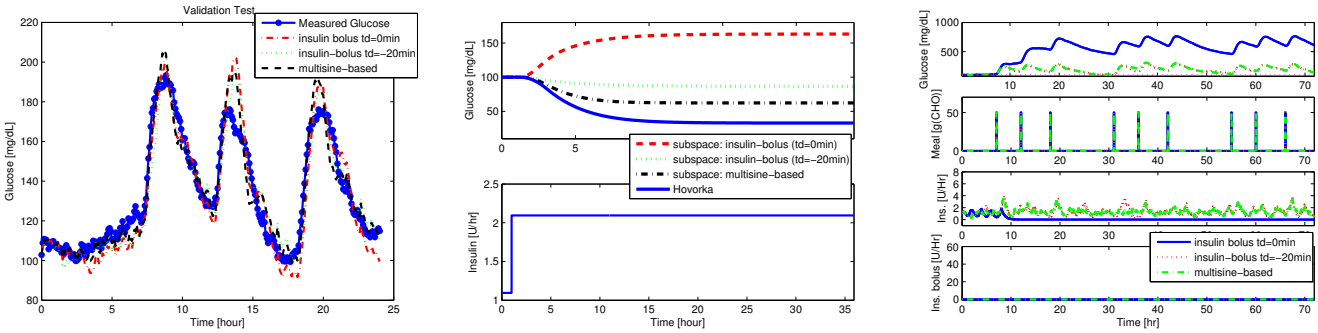
Phasing	α	β	hf	ω_*	ω^*	T (min)	N_s	n_s	1_{cycle} (min)	CF(x)
Guillaume	2	3	0.9	0.0074	0.1	5	170	14	850 (14.7hrs)	1.3994

Table 1. Design parameters of generating a multisine input signal as insulin infusion rate for model identification using the Hovorka simulation.



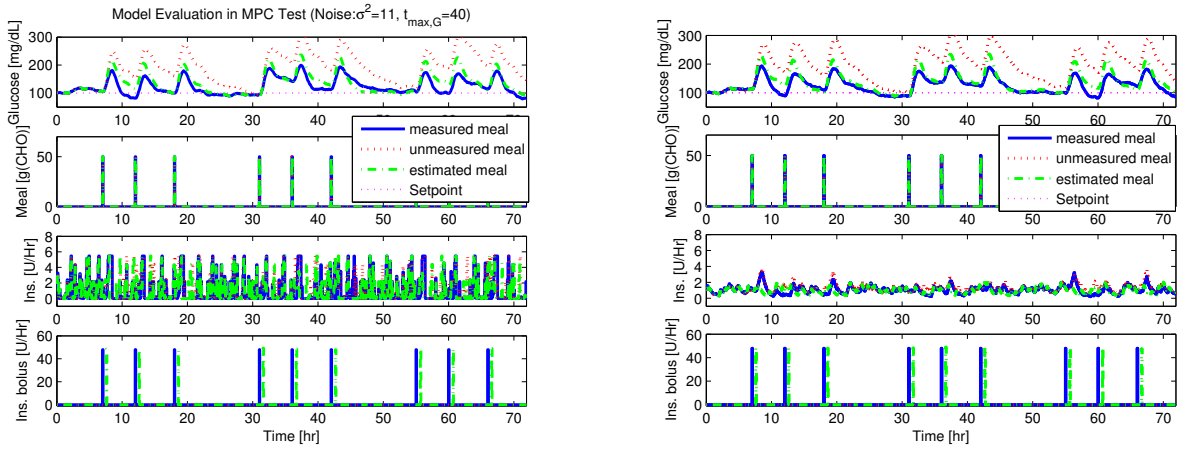
(a) Insulin-bolus, dt=0 min (b) Insulin-bolus, dt=-20 min (c) With multisine input

Fig. 6. Open-loop tests for modeling experiments: insulin bolus test (dt=0 min, a), insulin bolus test (dt= -20 min, b), and multisine based test (dt=0 min, c) under noisy output measurement conditions ($\sigma^2 = 11.0\, mg^2/dL^2$).



(a) Validation (b) Step Test (c) Closed-loop Evaluation

Fig. 7. Model evaluation tests: 1-hour open-loop prediction with (a) a validation data, (b) unit step tests by 1 U/hr, and (c) closed-loop MPC test with unmeasured meals.



(a) Without control action filter (b) With control action filter

Fig. 8. Closed-loop tests with MPC ($P_{hor} = 36$, $M_{hor} = 3$, $W_y = 1$, & $W_{\Delta u} = 5$) for glucose control using the Hovorka simulation under measurement noisy conditions ($\sigma^2 = 11\, mg^2/dL^2$); (a) without and (b) with control action filter.

meal information is given to the MPC or a meal is detected. The sensitivity for the meal size estimation is set to $\gamma = 0.90$.

The closed-loop MPC tests with measured, unmeasured, and estimated meals are shown in Figure 8. Comparing the insulin infusion in Figures 8a and b, the first-order filter in control output reduces noise-like insulin infusion but results in little difference in glucose. Meal insulin boluses on measured meals clearly reduce meal glucose peaks, but the unmeasured meal case shows the highest values for the minimum and maximum glucose concentration because it relies only on insulin by the control output (Table 3). The measured meal case provides the lowest mean absolute deviation (MAD) value, and its glucose concentration is between 81.4 and 193.9 mg/dL. A statistical data analysis of the measured meal and unmeasured cases shows that daily average rates of insulin infusion are [1.51, 1.50, 1.58] U/hr and [1.43, 1.37, 1.38] U/hr, respectively.

The estimated meal case by means of meal detection and meal size estimation presents significant improvement compared to the unmeasured case. Insulin boluses are automatically injected based on the estimated carbohydrates $30 \sim 45$ minutes later from meals. Although the delayed insulin boluses give slightly higher glucose concentration than the measured meal case, it still provides a comparable result to the measured meal without serious over- or underestimated meals.

Test	MAD	Mean	Min	Max
Measured meal case	28.8	125.8	81.4	193.9
Unmeasured meal case	91.0	191.0	96.6	311.4
Estimated meal case	38.6	137.4	87.3	234.9

Table 3. Statistics of the closed-loop data using a subspace model from the multisine-based test.

7. SUMMARY AND CONCLUSIONS

A novel approach of developing the artificial pancreas is presented in this paper, integrating key components for automatic closed-loop glucose control for type 1 diabetes. The human-friendly identification procedure using a multisine input signal improves model quality for use in the artificial pancreas. A clinical test using insulin boluses is not able to produce proper gains of insulin-to-glucose dynamics; the insulin-bolus test with early insulin boluses gives a negative gain, but early insulin boluses might be against the common clinical practice. The test using the multisine signal provides sufficient persistent excitation, leading to a proper gain of insulin-to-glucose.

An effective formulation of constrained MPC is achieved for closed-loop glucose control. The MPC incorporates additive output disturbance, state input disturbance with Kalman filtering, first-order reference trajectory, first-order control action, output constraint relaxation, and pump shut-off methods. The current MPC control performance is, nevertheless, significantly sensitive to input constraint magnitudes.

The measured meal case shows faster meal glucose rejection performance taking advantage of measured meal information. The unmeasured case produces higher glucose concentration which might require different MPC tunings. Although the unmeasured meal case has higher glucose peaks, it reduces glucose concentration slowly without hypoglycemia. The meal size estimator requires additional training for its filter coefficients, and it automatically gives insulin boluses to reduce meal glucose disturbances when a meal is detected. Therefore, satisfactory control performance without meal inputs is achieved.

An efficient strategy of developing the artificial pancreas is presented in this paper by taking advantage of the human-friendly modeling test, integrated MPC formulation, meal detection, and meal size estimation. The proposed closed-loop framework shows acceptable glucose control performance under daily life situations. On-going research incorporates time-varying insulin sensitivity to account for circadian effects such as the well-known dawn phenomenon.

ACKNOWLEDGEMENTS

This research is funded by the Juvenile Diabetes Research Foundation, Grant No. 22-2006-1108.

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