The Intravenous Route to Blood Glucose Control

A Review of Control Algorithms for Noninvasive Monitoring and Regulation in Type I Diabetic Patients

Diabetes mellitus is a disease characterized by the inability of the pancreas to regulate blood glucose concentration. Insulin-dependent, or type I, diabetes is characterized by the destruction of the insulin producing β-cells in the pancreas, such that exogenous insulin is required to control the disease [1]. Inadequate secretion of insulin by the diabetic pancreas results in poor maintenance of normoglycemia (defined as the normal condition with blood glucose concentrations in the 70-100 mg/dL range) with elevated blood glucose concentrations, sometimes upward of 300 mg/dL.

According to the Diabetes Control and Complications Trial (DCCT) Research Group [2, 3], most of the long-term complications associated with diabetes, such as nephropathy and retinopathy, result from sustained hyperglycemia (blood glucose exceeding 120 mg/dL). Hypoglycemia (defined as the condition of blood glucose concentrations less than 60 mg/dL, which is consistent with the DCCT range for low blood sugar) is a short-term concern because it starves the body cells of fuel. This condition is typically caused by the overdelivery of insulin and can lead to insulin shock as well as death.

In healthy patients, the counter-regulatory hormone glucagon would be released in response to hypoglycemia to raise blood glucose concentration. In the diabetic patient, however, the counter-regulatory response is often blunted or absent, and hence less effective [4]. It is therefore important to regulate diabetic patient blood glucose concentrations within tight physiological limits.

This article discusses closed-loop blood glucose regulation algorithms that use the intravenous route for insulin delivery to insulin-dependent diabetic patients. Classical control methods and advanced algorithms using implicit knowledge or explicit models (empirical, fundamental, or “gray-box”) of the diabetic patient are examined. Current research on characterizing patient variability is presented, in the context of a model predictive controller able to adjust to changes in patient glucose and insulin sensitivity.

Overview of Current Treatment and Monitoring Methods

The current treatment methods for insulin-dependent diabetes include subcutaneous insulin injection or continuous infusion of insulin. A review of these methods of blood glucose control by Cobelli, et al., appears elsewhere in this issue. Subcutaneous insulin treatment may require four to five daily injections, which usually correspond with meal-times. The amount of insulin injected is typically based on consideration of a glucose measurement (finger prick), an approximation of the glucose content of the upcoming meal, and the estimated insulin release kinetics from the subcutaneous depot. Lente or ultra-lente (slower release) insulin preparations allow for an overnight release of insulin to prevent highly elevated glucose concentrations in the early morning hours. The continuous infusion insulin pump allows for more predictable delivery due to its constant infusion rate into an intraperitoneal or subcutaneous delivery site. An additional feature of some pumps is their ability to be “primed” so that a bolus of insulin can be released to compensate for anticipated glucose intake.

Either of the above two diabetes treatment methods can result in significant, and sometimes frequent, glucose concentration variations because of the predominantly open-loop nature of the insulin delivery. Intravenous delivery of insulin has significant advantages: (i) rapid delivery with negligible dead-time; (ii) a

Robert S. Parker, Francis J. Doyle III, and Nicholas A. Peppas

1Dept. of Chemical Engineering, University of Delaware
2Dept. of Chemical and Biomedical Engineering, Purdue University
higher percentage of drug reaches the bloodstream, as compared with subcutaneous or intraperitoneal delivery sites; (iii) faster response to insulin over-delivery; and (iv) potential for improved closed-loop controller performance. However, there are shortcomings to this approach as well: (i) indwelling venous catheters may irritate the blood vessel; (ii) the catheter may dislodge from the vein; and (iii) the catheter may occlude (although this problem is present in all catheter delivery devices). Given the significant benefits of utilizing intravenous insulin delivery versus subcutaneous or intraperitoneal approaches, this review will concentrate on intravenous delivery methods for glucose control.

The development of a closed-loop device capable of maintaining normoglycemia over extended periods of time could dramatically improve the quality of life for insulin-dependent diabetic patients (Fig. 1). A device of this type would contain three primary components: (i) a mechanical pump; (ii) an in vivo glucose sensor; and (iii) a mathematical algorithm to regulate the pump given a sensor measurement. Extracorporeal and implantable insulin pumps have been in service for over 15 years [5-7], and recent advances have made available programmable and variable-rate infusion pumps [8].

Current blood glucose monitoring is accomplished through invasive methods, such as a finger prick, but the use of a noninvasive monitor would increase patient comfort and therefore compliance to the insulin therapy. An implantable glucose concentration sensor would measure diabetic patient blood glucose levels on-line and thus eliminate the patient from the feedback loop. A number of research groups are working on implantable glucose sensors (see, for example, [9-11]), and the duration of in vivo sensor reliability continues to increase. This review will focus on the various control algorithms proposed by researchers working on this problem, as well as some new results by the authors on uncertainty characterization and model-based controller synthesis in the presence of uncertainty.

### Intravenous Insulin Delivery Algorithms

**Biostator™ and Nonlinear PID**

Early diabetes regulation work dates to the glucose controlled insulin infusion system (GCIIS) [12] and later to the “Biostator” algorithm and device of Clemens [13]. This feedback controller utilized a low-volume continuous-flow blood glucose sampling mechanism with a dual infusion system (insulin and dextrose) to maintain blood glucose concentration at a user-defined value. The control algorithm was a nonlinear proportional-plus-derivative type structure, using a five-point moving average of glucose measurements to minimize noise effects. While adequate for bedside implementation, implantation would be more difficult due to the additional size associated with the dual-reservoir system necessary for a device of this type. Patient specificity was also an issue, as the algorithm would require individualization prior to its use.

Albisser, et al. [14], studied blood glucose control, also using a two-channel system. Dextrose infusion was regulated by a nonlinear function of glucose concentration, while the infusion of insulin was governed by a projected glucose concentration. This prediction used the current measured value of blood glucose plus an exponential difference factor computed from the four-minute average rate of change of glucose concentration. This factor was designed to emphasize increasing glucose trends over decreasing concentrations. Several patient-dependent or operator-selected parameters were required in this control algorithm.

A comparison of similar methods for artificial β-cell control, based on a glucose measurement and its rate of change, was presented by Broekhuyse, et al. [15]. These algorithms included a modified version of the algorithm in Albisser, et al. [14] by Botz [16] and by Marliss, et al. [17]; a modification of this controller introduced by Kraegen, et al. [18]; two variants of the Biostator algorithm [13,19, 20]; and a linear glucose control algorithm developed by Fischer, et al. [21]. No single controller was found to be uniformly superior, and it was concluded that significant further work in controller development was required to normalize diabetic patient blood glucose concentration.

Bellomo, et al. [22], examined the use of the Biostator control algorithm on diabetic patients but extended its application through the use of a patient model update mechanism. This update occurred over a period defined by the particular parameters being estimated. Rising and falling gains (related to the derivative term in the proportional-plus-derivative type algorithm), as well as the endogenous insulin release and glucose effectiveness, are calculated to minimize the sum-squared error (SSE) between the predicted and actual glucose concentrations over the duration of the current trend in blood glucose (rising or falling). This discrimination, based on the direction of glucose change, is used because of the different controller dynamics desired for the two cases. Other patient-specific coefficients in the controller minimize a quadratic objective function, with terms representing insulin expense and glucose deviation from the basal state. This controller represents a clear advantage over the static Biostator algorithms but still displays significant hyperglycemic peaks during controller operation.

An extended version of the Bergman “minimal model” [23], including insulin antibody binding, was studied by Furler, et al. [24]. The control algorithm was governed by a saturation function that calculated insulin delivery rate as a function of the current glucose measurement. Linear interpolation between the two limits was used to set the rate of insulin infusion. Measurements were taken at intervals of one to four hours, and performance was shown to be superior to a similar control algorithm used in clinical studies [25]. The controller based on the modified saturation function [24] performed well in returning initially hyperglycemic patients to steady state, although no analysis of meal disturbances was performed. It should be noted, however, that this algorithm was not intended for meal disturbance rejection but

![Closed-loop glucose control system](image-url)

1. A closed-loop glucose control system.
Advanced Control Algorithms

Throughout their studies, Salzieder, Fischer, and their coauthors have examined closed-loop control of diabetic patient glucose in dogs and humans [26-29]. For humans, the control algorithms were employed as decision support systems or in simulation studies using individualized patient models. Linear algorithms were employed for insulin delivery based on a glucose measurement using proportional-derivative control [26], pole-placement techniques [28], adaptive methods [27], and modifications of the Biostator algorithm [29]. Fischer and coauthors [27] demonstrated that blood glucose controllers showed markedly improved performance when the controller either adapted on-line or was customized to the specific patient. Of potential concern for these control algorithms is the sampling rate (typically one minute intervals), which is faster than the speed of response of implantable in vivo biosensors [11].

Sorensen [30], using the internal model control framework, developed a detailed compartmental model and a linear model-based controller. To simplify controller synthesis, the 19th-order nonlinear model was approximated by a first-order-plus-time-delay (FOTD) transfer function. The controller resulting from this simplified structure was then implemented in the time domain. Performance was adequate, although improvement through use of a more detailed model in controller design is virtually guaranteed. Also, the controller demonstrated significant performance loss (in terms of ability to reject meal disturbances) when patient parameters differed from those of the model.

An analysis paper by Doyle, et al. [31], examined modeling and experimental techniques for controlling blood glucose. A key observation in their work was that low-order models may not adequately describe the real process and therefore could contain both unacceptable levels of modeling error and significant process-model mismatch. A nonlinear feedforward-feedback controller synthesized using feedback linearization, a nonlinear differential-geometric technique, was the control scheme proposed for glucose regulation. Also proposed was a polymer (gel) device able to act as sensor, controller, and actuator all-in-one. This device would sense glucose as pH changes, and release insulin into the bloodstream according to the pH variation. The control characteristics, such as dynamic behavior and magnitude of release, are designed into the gel through material selection and preparation.

State-dependent Riccati equations were used by Parrish and Ridgely [32] to control blood glucose concentration in diabetic patients. Their controller was designed from a partial linearization of the model developed by Naylor, et al. [33]. This nonlinear full-state feedback control method is limited by an inability to measure several states in the diabetic patient model, such as total stores of glucose and insulin. Cancellation of the nonglucose feedback gains resulted in successful rejection of low-magnitude disturbances, although overaggressive control and increased insulin usage were both observed. The authors used manipulated variable weighting to reduce insulin delivery rates, while maintaining adequate glucose control. Due to the formulation of their controller, the tracking problem demonstrated steady-state offset.

Robust control using the \( H_\infty \) control methodology was the topic of a paper by Kienitz and Yoneyama [34]. Glucose and insulin dynamics were governed by a low-order model containing patient-dependent parameters. The controller was designed based on a nominal patient model, and a set of frequency-dependent weighting functions was tuned to capture the entire expected patient population (based on parameter variations). Patients who are within the design set will, by definition, satisfy the performance criterion because \( H_\infty \) controllers bound worst-case performance. Meal disturbance simulations were promising for the nominal patient. The controller was robust to small amounts of patient uncertainty, but inferences to larger patient variability sets would require retuning of certain controller parameters.

Optimal Control Theory

Using a linear diabetic patient model and a quadratic performance criterion, Swan [35] solved the glucose control problem for the optimal insulin infusion rate. This approach uses optimal control theory and solution of a nonlinear algebraic Riccati equation, and it refines the results of Kikuchi [36, 37], who solved the problem using an approximate solution to the Riccati equation. The insulin delivery rate is a function of both the current insulin and glucose concentrations, although under certain assumptions (no glucose-dependent endogenous insulin release) the insulin state can be removed to yield a solution only in terms of the glucose concentration. The article focused on the initially hyperglycemic diabetic patient, so meal disturbance attenuation was not treated.

Normalization of patient blood glucose in response to both meal consumption and initial hyperglycemia was studied by Fisher and Teo [38]. Various infusion protocols were tested, with the objective being the minimization of sum-squared glucose tracking error. Impulse control (a single injection at time = 0 min) was found to provide superior control in both cases, with perfect reference tracking achievable if a good estimate of the meal was available (under certain assumptions regarding the shape of the meal disturbance and insulin effects). Lim and Teo [39] studied impulse control for the same situations, but in the presence of fuzzy model parameters (patient uncertainty). For the chosen uncertainty set, and again under assumptions about the dynamic behavior of meals and insulin injection, the impulse control method was found to be robust and numerically stable.

Application of optimal control theory to the “minimal model” of Bergman, et al. [23], was undertaken in two studies. One, by Ollerton [40], utilized an integral-squared error (ISE) cost function based on deviation from the desired glucose value. Sampling times of 10 min and
Model-based methods may have an inherent advantage in blood glucose control provided that accurate models are used in controller synthesis.

180 min were studied. The longer sampling time was less sensitive to noise about the basal state, but it had a longer rise time and could also miss significant disturbances that occurred within the inter-sample window. Due to the calculation times experienced, Ollerton discretized the “minimal model” for use in the 10 min sampling time studies. This controller was sensitive to oscillation of the glucose profile about the basal state, and it resulted in physiologically unrealistic insulin profiles characterized by high-amplitude sustained oscillations (ringing). An insensitive model was introduced, most likely based on a type of dead-band control, but no method for its development was discussed.

Fisher [41] performed another study of the “minimal model,” also using an ISE-based objective function. His cost criterion minimized deviations in glucose concentration from a reference value. As a secondary objective, the amount of insulin to perform the corrective action was minimized. The study examined three insulin infusion profiles, determining that an initial injection plus optimal hourly infusion minimized the cost function for an initially hyperglycemic patient. Similar to the control design of Ollerton [40], this algorithm was not robust to patient uncertainty, and it also suffered from the long sampling time (180 min) problem of missing fast or inter-sample disturbances.

Parker, et al. [42], and Parker [43] examined the use of a model predictive controller (MPC), both with and without state estimation, for regulating blood glucose. Controller synthesis was accomplished by linearizing a modified version of the nonlinear patient model from Sorensen [30]. This controller solved an optimization problem with a quadratic objective function at each time step. Terms were included for setpoint tracking over a future prediction time horizon as well as a penalty for insulin delivery. Constraints on insulin delivery rate and rate of change were included in the control algorithm, and the linear controller was evaluated in simulation studies treating the full nonlinear model as the patient. Disturbance rejection and hyperglycemic initial condition simulations showed the efficacy of the controller, which maintained glucose above the hypoglycemic bound of 60 mg/dL, as well as regulated blood glucose within 20 mg/dL of the 80 mg/dL setpoint when challenged with unmeasured 50 g meal disturbances. It was also demonstrated that a nonlinear control algorithm (nonlinear quadratic dynamic matrix control with state estimation [44]) did not radically improve blood glucose control.

**Model-Based Predictive Control Under Patient Uncertainty**

Model predictive control has characteristics that make it an attractive choice for blood glucose concentration regulation. These include (i) the ability to regulate nonlinear systems using a linear algorithm; (ii) inherent input constraint handling; (iii) the explicit prediction of future behavior based on past manipulated variable moves; and (iv) straightforward incorporation of parameter updating. The unconstrained controller guarantees optimal drug delivery through solution of an optimization problem at each time step [45]. Although significant computational power can be required, an analytic solution is available in the unconstrained case [45]. A key benefit of using predictive control in place of a classical control algorithm is the estimation of future glucose behavior based on the past insulin inputs using an explicit model of patient dynamics. As a result, the MPC controller can adjust insulin delivery in response to a predicted hypo- or hyperglycemic excursion well before the event occurs. A feedback-only controller would respond only after the effect of the disturbance manifests itself in the measured output. The patient glucose concentration measurement is used as a feedback signal to correct the predictions for deviations between the internal model and the actual patient dynamics. The human glucose-insulin control problem has inherent input rate and magnitude constraints, as well as an output magnitude constraint, which are all incorporated into the MPC algorithm [45, 46] in a straightforward manner. In the controller development, an implantable glucose sensor is considered with measurements representative of the well-mixed blood being delivered to the organs (an “arterial” glucose measurement). Insulin delivery is assumed to be directly into the venous bloodstream, such that the controller could be utilized in both an implantable device as well as a bedside or portable unit for hospitalized patients. Although research has demonstrated that portal vein insulin delivery is necessary to return the diabetic glucose distribution to that of a healthy patient [47], the choice of delivery location does not have a dramatic impact on the ability to regulate glucose concentration.

Although many of the above control methodologies demonstrated adequate performance, the inherent uncertainty in the model (or patient) typically has not been explicitly addressed. This omission can lead to significant performance degradation should the model parameters not represent the actual dynamics of patient glucose and insulin dynamics. Significant variability among patients, and within a given patient over the course of a day or week, has been documented in the literature [48-51]. To avoid complete retuning of the controller for each patient, while recognizing that some minor patient-to-patient adjustments will be required, the control algorithms utilized in an insulin delivery device must be able to compensate for the uncertainty that exists between the internal model and the actual patient. An adaptation mechanism that updates the controller internal model based on the variability between the predicted glucose concentration and the measured patient glucose concentration is incorporated into the MPC with state estimation (MPCSE) algorithm developed in [42]. The resulting MPC with state and parameter estimation (MPCSPE) algorithm updates selected model parameters through a Kalman filter at each time step [52].

**Uncertainty Characterization**

Uncertainty due to differences between an actual patient and the diabetic patient model may be related to variations in model parameters. A sensitivity analy-
sis, using the modified Sorensen model [30, 43], identified the metabolic terms as most responsible for changes in blood glucose and insulin dynamics, and glucose metabolism is described by the following threshold function:

$$\Gamma_e = E\{A_T + B_T \tanh[C_T(x_i + D_T)]\}$$  \hspace{1cm} (1)

Here the subscript \(i\) is the state vector element involved in the metabolic effect and the \(e\) subscript denotes specific effects within the model, such as the effect of glucose on hepatic glucose production (EIGHGP), the effect of insulin on hepatic glucose uptake (EIPGU), or the effect of glucose on peripheral glucose uptake (EGHGU).

Inter- or intra-patient uncertainty could be classified as either a receptor (\(D_T\)) or post-receptor (\(E_T\)) parameter defect. This uncertainty formulation implies a structured effect of variability on the model, such that the tissues most important to parametric uncertainty are the liver and the peripheral (muscle/fat) tissues.

Parametric sensitivity was determined individually and pair-wise for the glucose metabolic parameters in the diabetic patient model. Mathematically, it was assumed that 50% parametric variability represented a broad range of potential patients. Parameter sets were contrasted using sensitivity in the large [53], where the time-domain SSE between the nominal and parametrically perturbed patient models was the sensitivity criterion. The up-to-four possible parameter pairings were combined with a series of five insulin step changes from the nominal delivery rate in the analysis. A “total sensitivity” was used for comparison, where the total represented the summation of squared errors for: (i) a specified parameter or parameter pair perturbation set, and (ii) the series of insulin step changes.

The most sensitive parameter pairing that resulted from this procedure was EIGHGP-\(E_{T1}\) with EIPGU-\(D_{T1}\), which had 17% more total error than the next highest pairing. A concise graphical analysis is shown in Fig. 2. Variations in the EIGHGP-\(E_{T1}\) parameter had dramatic effects on the process dynamic response, with the ±50% changes shown by the dashed lines. The range of possible process behaviors displayed by the perturbed models was further increased by adding the EIPGU-\(D_{T1}\) parameter variations to those of EIGHGP-\(E_{T1}\). Note that increases in EIGHGP-\(E_{T1}\) and decreases in EIPGU-\(D_{T1}\) produced the worst-case variations shown in Fig. 2. Also, observe that greater variability in process dynamics and steady-state behavior was demonstrated by insulin-sensitive patients (lower dashed and dash-dot lines in the figure), while insulin-resistant patients were dynamically similar, with only moderate steady-state variation.

**Controller Development**

The internal model in MPCSE is described by a discrete-time linear state-space model of the following form:

$$x_m(k + 1) = \Phi x_m(k) + Bu(k)$$  \hspace{1cm} (2)

$$y_m(k) = Cx_m(k).$$  \hspace{1cm} (3)

The model states \(x_m\) mainly represent blood glucose, insulin, or glucagon concentrations and are a linear approximation to those of the actual patient. The input signal \(u(k)\) is the insulin delivery rate, at time \(k\), in mU/min, and the model output \(y_m\) is a linear approximation of the actual patient glucose measurement. This model is constructed from the continuous nonlinear diabetic patient model [30, 43] via analytical linearization followed by discretization, which results in the discrete-time minimum-phase representation. A sample-time of 5 min was used for discretization and controller implementation. Using the internal model of Eqs. (2) and (3), the controller can estimate the state of the patient and the output using the following equations:

$$\hat{x}(k + 1) = \Phi\hat{x}(k) + Bu(k) + K_F[y(k) - C\hat{x}(k)]$$  \hspace{1cm} (4)

$$\hat{y}(k) = C\hat{x}(k).$$  \hspace{1cm} (5)

The Kalman filter, \(K_F\), has several practical applications in the MPCSE algorithm developed here. By updating the internal model with current measurement information using the Kalman filter, patient-model mismatch can be significantly reduced. The Kalman filter can also infer an unmeasured disturbance value so that the controller takes appropriate action to counteract the detected disturbance. Noise filtering is achieved by adjusting the Kalman filter gain based on the reliability of the measurement signal, which reduces noise-induced movement of the manipulated input. Parameter uncertainty is included in the model by changing constants to unknown parameters each having a nominal value. Parameter sensitivities are formulated as additive uncertainties to the linear controller model and are incorporated in the

![Graphical sensitivity analysis. Glucose profiles in response to the insulin step change –22.33 mU/min. Solid: nominal model response; dashed: response bounds for the ±50% variations in EIGHGP-\(E_{T1}\); dash-dot: response bounds for the simultaneous ±50% perturbations in EIGHGP-\(E_{T1}\) and EIPGU-\(D_{T1}\).](image)
The state-space structure through a modification of Eq. (4):
\[
\begin{bmatrix}
\dot{x}(k+1) \\
\dot{\hat{x}}(k+1)
\end{bmatrix} =
\begin{bmatrix}
\Phi & \Phi_w \\
0 & 0
\end{bmatrix}
\begin{bmatrix}
x(k) \\
\hat{x}(k)
\end{bmatrix} +
\begin{bmatrix}
B \\
0
\end{bmatrix} u(k)
\]

The optimization problem solved at each time step by MPC controllers is given by:
\[
\min_{\Delta U(k)} \left\{ \Gamma_y \left[ \Psi_y(k) - \Psi(k) \right] + \Gamma_u \Delta U(k) \right\}.
\]

Here \( \Psi_y \) represents a filtered value of the reference trajectory, and \( \Psi \) is the vector of predicted future measurements calculated from Eqs. (4) and (5). Weighting matrices \( \Gamma_y \) and \( \Gamma_u \) are used to trade off setpoint tracking and manipulated variable movement, respectively. Tuning parameters for this controller are the move horizon \( m \), which defines the number of future moves the controller will calculate, and the prediction horizon \( p \), which governs the distance into the future over which the output will be projected. The unconstrained solution to the objective function given in Eq. (8) is given by:
\[
\Delta U(k) = (H^T \Gamma_y H + \Gamma_u)^{-1} H^T \Gamma_y (\Psi_y(k) - \Psi(k)).
\]

Note that the unconstrained version of the MPCSE algorithm admits a convenient analytical solution that can be implemented easily on a digital chip. In the current controller formulation, input constraints are enforced by clipping, such that the unconstrained solution can be used. The MPCSE controller tuning constants for the case studies below were set \( m = 2, p = 8, \Gamma_y = 1, \Gamma_u = 0, \) and \( \Phi_y = 0.65 \). The matrix \( \Phi_y, 0 \leq \Phi_y < 1 \), is a filter that partially governs the closed-loop rate of response.

Performance of the MPCSE controller with two adjustable parameters was analyzed through simulation by examining the closed-loop behavior resulting from parameter mismatch between the “unknown” nonlinear patient model and the linear internal model. A perturbed patient with EHGGP-EF = 1.1 and EHGPG-DP = -6.4, corresponding to slight insulin insensitivity, was subjected to a 50 g meal disturbance, as modeled in [54], at time \( t = 150 \) min, with results shown in Fig. 3. An initial dynamic transient was observed, where the controller was adjusting to the perturbed parameter vector. The meal disturbance response was qualitatively similar, although the MPCSE controller demonstrated improved performance as evidenced by the 15% decrease in sum-squared tracking error, as compared to the fixed parameter controller (the linear MPCSE controller with no adaptation capability, as implemented in [42]). The associated cost was an insulin delivery increase of approximately 1 unit. The performance improvement was due to the increased aggressiveness of the MPCSE controller and its ability to more accurately adjust the internal model performance to match that of the actual patient.

Performance in the case of parameter perturbation mismatch tested the ability of the MPCSE controller to compensate for unmodeled differences in process dynamics. A glucose intolerant patient (EHHG-DP = -1.9, EHHGPC-DP = -0.25) was subjected to the same 50 g meal disturbance, and the MPCSE controller outperformed the MPCSE controller, demonstrating a 22% decrease in sum-squared tracking error (figure not shown). With the decreased insulin sensitivity, the insulin delivery rate constraint limited the closed-loop response. With the MPCSE controller, it
could be possible to construct a sensitivity-based constraint where patients with significant insulin resistance would have a relaxed upper magnitude constraint on insulin delivery. Incorporating this variable constraint would be a marked improvement over linear MPCSE, where no systematic methodology for constraint relaxation is available.

In addition to parameter mismatch, the MPCSPE controller was able to compensate for slow parameter drifts, even in mismatched parameters. To test this compensation, a week-long simulation, with a ramp change in the EIPGU-E parameter from 0.5 to 0.75 over the first five days (holding constant for the last two days) was performed. The patient consumed three 50 g meals per day, at 0800, 1200, and 1800 hours. Quantitatively, on-line parameter estimation led to an overall SSE reduction of 6% when compared to the MPCSE controller. The small overall performance improvement could be directly tied to the large error contributions of the first few days of the profile, where the input constraints again limited performance. The percentage improvement by day is presented in Table 1. As the ability to reject the disturbance became less affected by the upper bound of the insulin delivery rate, the performance improvement in terms of SSE increased. Note that the aforementioned estimator-based constraint adjustment technique would further improve performance for this case as well, since the early days of the profile would have a relaxed maximum insulin delivery rate.

Conclusions

The review of blood glucose regulation methods presented in this article demonstrates a wide variety of controller synthesis methods, from linear empirical to nonlinear differential geometric techniques. These methods have been implemented in simulation to determine their respective ability to regulate blood glucose concentration. Clearly, no single approach is decidedly superior. A key tenet from robust control theory is that controller performance is directly linked to model accuracy [55]. This implies that model-based methods may have an inherent advantage in blood glucose control provided that accurate models (those validated with patient data) are used in controller synthesis. Patient variability must also be addressed in control design, such that controllers with an adaptation mechanism should offer improved control of blood glucose as patient dynamics change. Promising results have been demonstrated for a model-based predictive controller with state and parameter estimation applied to patients with varying glucose and insulin dynamics.

An artificial pancreas device is not currently available; however, the results surveyed in this article suggest that clinical studies with animals are feasible in the short term. The primary need for constructing an artificial pancreas is as a reliable, long-term in vivo sensor for glucose concentration, a device that is currently unavailable. Several groups are actively pursuing this issue, as described above. The impact of measurement technology on the whole is important. Development of an insulin sensor would potentially add a second measurement to the system, and issues such as time delay and sensor dynamics directly affect closed-loop performance.

The stability of insulin preparations is also important, as intravenous delivery applications would require a monomeric solution. Stability is more generally achieved as a hexamer for injection therapy. For a viable intravenous device, insulin characteristics must be addressed. An additional materials issue relates to the catheter, in terms of fouling and occlusion performance. Additional studies on the effect of catheter structure on insulin activity and methods for improving transport of insulin from the catheter to the bloodstream (for nonintravenous applications) are needed.

The algorithm presented in this work, which is capable of handling some patient variability, is not capable of handling arbitrary parameter values without some “pre-tuning.” If estimates of patient glucose and insulin sensitivity were available, then a controller with similar dynamics could be implemented, with differences between the controller model and the patient handled as described in the MPCSPE controller. The inherent shortcoming here is the dearth of available patient data describing glucose and insulin behaviors in diabetic and healthy individuals. This data would allow a validation of both the patient model, as well as patient uncertainty structures, and hence the construction of accurate models describing inter- and intrapatient variability. An additional concern in the current formulation is the approximation of a nonlinear system by using a linear model with uncertain parameters.

Ongoing work by the authors is exploring methods for capturing variations in the nonlinear patient model using the linear model with variable parameters and measurement data. Fault detection is another algorithmic issue that must be addressed.

### Table 1. Error of the MPCSPE and MPCSE Controllers During the Slow Drift of EIPGU-E, Listed as Sum-Squared Error by Day

<table>
<thead>
<tr>
<th>Day</th>
<th>MPCSE SSE</th>
<th>MPCSPE SSE</th>
<th>% Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.28e+05</td>
<td>1.25e+05</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0.66e+05</td>
<td>0.62e+05</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>0.31e+05</td>
<td>0.28e+05</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0.13e+05</td>
<td>0.11e+05</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>0.075e+05</td>
<td>0.057e+05</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>0.065e+05</td>
<td>0.050e+05</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>0.065e+05</td>
<td>0.050e+05</td>
<td>23</td>
</tr>
</tbody>
</table>

The results surveyed in this article suggest that clinical studies with animals are feasible in the short term for developing an artificial pancreas.
An analysis of the types of faults possible (pump failure, battery drain, catheter occlusion) must be performed and a monitoring technology developed. An update of the patient model, to include effects such as exercise response, diabetic ketoacidosis, and other molecules important to glucose-insulin dynamics, would prove beneficial as well. Clearly, there is much to accomplish before a true artificial pancreas device is developed for the market.

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Robert S. Parker received the B.S. in chemical engineering from the University of Rochester, Rochester, NY, in 1994, and the Ph.D. in chemical engineering from the University of Delaware, Newark, DE, in 1999. Since January 2000, he has been an assistant professor and the Lai Family Foundation New Faculty Fellow in the Department of Chemical and Petroleum Engineering at the University of Pittsburgh, Pittsburgh, PA. Dr. Parker’s research interests include model identification and model-based control with a focus on biomedical and biotechnological systems applications.

Francis J. Doyle III is an associate professor in the Department of Chemical Engineering at the University of Delaware. He received his B.S.E. from Princeton (1985), C.P.G.S. from Cambridge (1986), and Ph.D. from Caltech (1991), all in chemical engineering. After graduate school, he worked at DuPont as a visiting scientist in the Strategic Process Technology Group (1991-1992), then as an assistant/associate professor at Purdue University (1992-1997), and since 1997 at the University of Delaware. His research interests are in process modeling, identification, and control with applications to polymerization systems, pulp and paper processes, and biosystems. He is the recipient of several research awards [NSF N.Y.I. (1992), ONR Young Investigator (1996)] as well as teaching awards [ASEE Section Outstanding Teacher Award (1996), Tau Beta Pi Teaching Award (1996), ASEE Ray Fahien Award (2000)]. In 1998, he was elected as a Fellow of the Institute for Transforming Undergraduate Education (ITUE) at the University of Delaware, and he was elected an academic trustee of CACHE in 1999.

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