IMPLANTABLE ARTIFICIAL PANCREAS FOR DIABETES USING ENZYMATIC BIOSENSORS AND LQG CONTROLLER

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***Abstract*—** The artificial pancreas is a technology in development to help people with diabetes automatically control their blood glucose level by providing the substitute endocrine functionality of a healthy pancreas.

The development of sensors and analysing systems that allow the quick and precise measurement of glucose and sucrose concentrations at a low cost is of great importance in many applications in the medical area, as well as in industrial fermentations and the food industry. Biosensors based on enzymatic reactions connected with analysing systems have been largely used for this purpose, mainly because of the selectivity for the substrate and low response times that these sensors. Recent research on development of the implantable artificial pancreas for treatment of diabetes is reviewed, based on a Medline literature search that focused on glucose sensors, insulin pumps, and pump control systems. To achieve a closed feedback loop, a clinically applicable implantable artificial pancreas requires miniaturization and coordination of three components: an insulin pump, a blood glucose monitor, and a control system. Investigators have developed control algorithms in an effort to stabilize operation of the integrated artificial pancreas in the face of variations in sensor output and pump function.

***Index Terms*--** *Artificial pancreas, Linear Quadratic Gaussian, enzymatic sensor.*

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Introduction

Recent clinical studies have demonstrated that implantable insulin pumps are feasible for satisfactory control of diabetes for over a year, with the major complication being obstruction of the infusion catheter. Research on continuous glucose sensors has predominantly used the glucose-oxidize reaction or near-infrared light spectroscopy.

Implantable glucose oxidize sensors have been limited by local factors causing unstable signal output, whereas optical sensors must overcome interference by substances with absorption spectra similar to glucose. In the industrial area, the great interest is concentrated in the development of analytical instruments which can measure "on line" the substances that are present in bioreactors, thus permitting the monitoring and control of bioprocesses that use glucose and/or sucrose as the substrate.

The goal of the artificial pancreas is two-fold: To improve insulin replacement therapy until glycemic control is practically normal as evident by the avoidance of thecomplications of hyperglycemia, and to ease the burden of therapy for the insulin-dependent. Different approaches under consideration include: The medical equipment approach—using an insulin pump under closed loop control using real-time data from acontinuous blood glucose sensor. The bioengineering approach—the development of a bio-artificial pancreas consisting of a biocompatible sheet ofencapsulated beta cells. When surgically implanted, the islet sheet will behave as the endocrine pancreas and will be viable for years. The gene therapy approach—the therapeutic infection of a diabetic person by a genetically engineered virus which causes a DNA change of intestinal cells to become insulin-producing cells.

Continuous blood glucose monitoring

Technology for continuous blood glucose monitoring supports the mission of the artificial pancreas by: Automatically providing a blood glucose reading every few minutes without finger sticks from the user, monitoring trends pertaining to rising and falling blood sugars, which is helpful in the prediction of blood glucose levels in the immediate future, comparing blood sugar levels and predictions against a high blood sugar threshold, and then prompting the user that a correction bolus from an insulin pump is needed immediately, comparing blood sugar levels and predictions against a low blood sugar threshold, and then prompting the user to reduce the basal insulin from the pump or to eat something.

These capabilities suggest that a stream of real-time data can be used to "close the loop" and control the insulin pump directly. Some issues with the present performance of continuous sensing technology suggest that additional study is needed for application to the artificial pancreas: continuous sensors require calibration a few times a day, by performing a manual blood glucose test with a finger stick, and then entering the blood glucose data into the continuous system for a sensor correction, continuous sensors are measuring interstitial glucose, so there is a time delay between the sensor data and the true blood glucose, automatic control removes the intellect of the user, which can be an additional safeguard when the data is subject to error and must be verified before taking action.

Insulin Therapy

In insulin-dependent persons, blood glucose levels have been roughly controlled using insulin alone. The number of grams of carbohydrate is estimated by measuring foods, and the measurement is used to determine the amount of insulin necessary to cover the meal. The calculation is based on a simple open-loop model: an insulin to carbohydrate ratio (adjusted based on past success) is multiplied by the grams of carbohydrate to calculate the units of insulin needed. That quantity of insulin is then adjusted based on a pre-meal blood glucose measurement (insulin bolus increased for a high blood sugar or insulin bolus delayed and reduced for a low blood sugar). Insulin is injected or infused under the skin, and enters the bloodstream in approximately 15 minutes. After the insulin has acted in the bloodstream, the blood glucose level can be tested again and then adjusted with injection of more insulin, or eating more carbohydrates, until balance is restored. Assuming the design requirement is to truly mimic normal pancreatic delivery of insulin to the liver in order to achieve proper hepatic stimulation, and to cause normal insulin induced functions, until another system is available to deliver portal vein concentrations of insulin, an intravenous infusion device will be needed.

There are notable differences with insulin replacement compared to the function of pancreatic insulin delivery: the insulin dose is predicted based on measured food (where accuracy of measured carbohydrate is difficult) whereas pancreatic insulin is released in proportional response to actual blood glucose levels; pancreatic insulin is released into to the portal vein, where it flows almost directly to the liver, which is the major organ for

storing glycogen (50% of insulin produced is used by the liver); pancreatic insulin is pulsatile which helps maintain the insulin sensitivity of hepatic tissues; injected insulin is delivered subcutaneously (under the skin) but not directly to the bloodstream, so there is a delay before injected insulin begins to reduce blood glucose (although this can be compensated by injecting insulin 15 minutes before eating); insulin which is not delivered intravenously cannot achieve normal momentary concentrations in the portal vein which connects the pancreas to the liver; replacement insulin therapy does not include amylin (although Symlin is now available for use), which can reduce the insulin need by 50%; replacement insulin is dosed as a best compromise between aggressive use for lowering the blood sugar when eating but also conservative use to avoid a post-prandial low blood sugar due to excess insulin, whereas pancreatic function releases insulin aggressively and later includes automatic release of glucagon at the end of an insulin cycle to manage the blood sugar level and avoid hypoglycemia.

An insulin pump to infuse rapid – acting insulin is the first step in simulating the function of the pancreas. The pump can accurately deliver small increments of insulin compared to an injection, and its electronic controls permit shaping a bolusover time to match the insulin profile required for a given situation. The insulin pump is controlled by the pump user to bolus manually based on a recent blood glucose measurement and an estimate of the grams of carbohydrate consumed. This predictive approach is said to be open-loop. Once a bolus has been calculated and delivered, the pump continues to deliver its basal rate insulin in the manner that has been programmed into the pump controls based on the predicted insulin requirements of its user.

While insulin replacement is appreciated as a life saving therapy, its practical use in controlling blood glucose levels sufficiently to avoid the long term complications associated with hyperglycemia is not ideal. Also, it is generally agreed that even with very tight glucose control, there are a significant number of patients who go on to develop all of the life impacting complications of diabetes. Thus, the goal of the Artificial Pancreas should be to normalize carbohydrate and lipid metabolism at a minimum.

Implanted form of artificial pancreas

The new device differs, however, in that it is an implantable device that contains a refillable reservoir of insulin. The device in two and a half inches in diameter and is surrounded by a gel which softens and hardens in response to change in sugar

levels, meaning more insulin is released when sugar levels are high and insulin is not released when sugar levels are too low.

The implantable artificial pancreas would need to be refilled at regular intervals with a tube which would access the device through the skin. Refilling of the device would need to be an every occurrence as is the case with insulin injections.

Implanted Insulin

The device, which is currently dubbed "a self-regulating insulin delivery device," would be implanted in the abdomen. The outside of the device would be made of plastic or metal. There would be no electronic or moving parts, according to Taylor. The device wouldn't need batteries, and because it's not made of biological material, there's no worry of rejection, she said.

The device would house a refillable insulin reservoir that would contain insulin with a protective gel layer. The insulin and gel would need to be replaced approximately every two weeks. That gel layer would react to the presence of sugar (glucose) in the blood.

The gel material contains a lock-and-key chemical interaction that holds the gel together and this is interrupted by the presence of glucose that enters the device gel layer from the fluid surrounding it in the body. When the gel softens, the insulin in it travels much more quickly and reaches the body circulation. Once the insulin has lowered the blood glucose, glucose starts to leave the gel again and the gel hardens, effectively closing the gateway.

This type of insulin delivery more closely mimics the natural delivery of insulin than does an insulin injection, Taylor said. Insulin is a hormone that's necessary for the body to metabolize the carbohydrates in food. Carbohydrates transform into glucose during digestion to provide fuel for the body's cells. But, without insulin, the glucose can't enter the cells and builds up in the bloodstream.

High blood sugar (glucose) levels can eventually lead to serious complications, such as kidney or heart disease and vision problems. But, low blood sugar levels can also be dangerous, even potentially deadly.

Enzymatic Biosensors

The glucose biosensor, a device that changed the lives of millions affected by diabetes, is a one remarkable example of enzyme-based biosensor technology. Enzyme sensors are a major part of biosensorics - technology, which currently represents a mature analogue to instrumental

analytical techniques in areas of clinical diagnostics and is the leading technology in point-of-care analysis.

Enzyme biosensors employ the affinity and selectivity of catalytically active proteins, towards their target molecules. Typically, (enzyme,usually immobilized on/within the surface of transducer - acts as a catalyst when interacting with the analyte, represented by its substrate, inhibitor, co-substrate or co-factor, while the enzyme itself remains unchanged. The transducer converts the effect created by the interaction of enzyme with the analyte, usually into an electrical signal. Depending on the assay type, two fundamental classes of enzyme sensors can be distinguished. First, the enzyme detects the presence of a substrate, or co-substrate/co-factor. This is then, by way of a transducer, used to monitor the increase of enzymatic activity. A typical example is a glucose biosensor. The second group is based on the detection of inhibitors in the presence of a substrate. With this system the decrease of signal (caused by enzyme inhibition) is monitored. The most common example of this approach is the detection of organophosphate compounds used as pesticides or warfare nerve agents. The mode of signal transduction can be electrochemical, optical, resonant (acoustic), thermal etc. The major advantage of all of these approaches is the high sensitivity and specificity of the biorecognition of a single selected analyte.

There have been significant improvements in the field of enzymatic biosensors; the usage of new, genetically engineered enzymes has allowed for improved performance characteristics of current biosensors for the detection of established analytes (glucose, pesticides etc….). Advancement has been the utilization of genetically modified enzymes to detect novel markers. An additional group of improvements is the usage of "non-traditional" transducer materials, e.g. carbon nanotubes (CNT), or different conductive polymers. Remarkable structural and electrical property advancements have enabled new options mainly in the area of electrochemical sensing techn

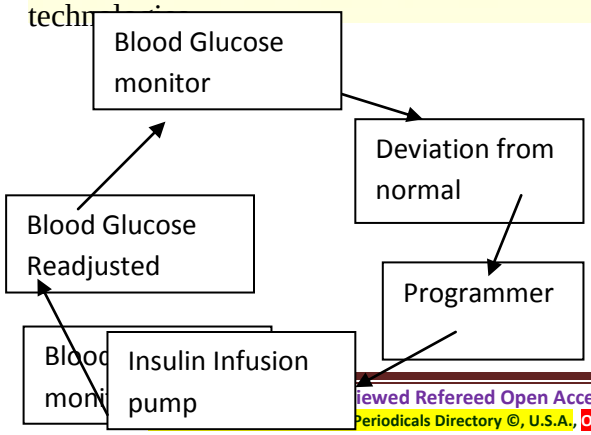

Figure 1 - Conceptual feedback model for artificial glucose control.

Enzymatic sensorsare used for the continuous measurement of glucose and sucrose. The biosensor can be defined as an analytical instrument which uses a biological catalyst in close contact with a suitable transducer that converts the biochemical signal that is produced in a biological reaction into a quantifiable electrical signal (Turner et al., 1987 ; Bowe, 1985). As typical biological components different materials such as enzymes, organelles, membrane components and the whole cells are used. As transducers the most frequently utilized are: potentiometric and amperometric electrodes, termistors and optical receptors. The biological component is normally immobilized in close contact with the transducer surface to increase the response, decrease the interferences and allow its reutilization. After the conversion of the biochemical signal into a quantifiable electrical signal by the transducer, it is itself measured by a biochemical detector which can be easily connected to a computer or to an automated digital system (Brooks et al., 1991).

The high level of substrate concentration present in the bioreactors is the main limitation of the use of enzymatic biosensors, as most of the enzymatic reactions occur in low concentrations of substrate. Thus, a dilution to an optimum concentration for the enzymatic reaction and a draining system are needed for the sample withdrawn from the bioreactor. This step of dilution must be well developed, and thoroughly investigated, because it can introduce signal oscillations producing analysis errors that will certainly change the final results (Valero et al., 1990).

This work presents the experimental assays carried out for the development of enzymatic sensors of glucose and sucrose, based on enzymatic reactions that convert glucose by glucose oxidase and sucrose by invertase (Xu et al., 1989).The development of the sampling line is presented and the results of calibration and the influence of operating conditions are analysed. The concentration of glucose analysed in the calibration tests of the glucose biosensor covered the range from 0.05 to 0.2 g/l, which was possible to extend up to a range from 5.0 to 120 g/l of glucose , using a sampling circuit with the FIA methodology analysis.

EXPERIMENTAL SETUP AND RESULTS

The enzymes utilized in this work were glucose oxidase and invertase from Sigma and the glucose and sucrose solutions were prepared with analysis grade reagents. For analysis and protein determination the Lowry Method was used , and for the measurement of the enzyme

conversion the colorimetric method, based on the Merck glucose oxidase kit, was utilized. The immobilization method for the enzyme in the Sigma glass-supported aminopropyl was of the covalent junction type utilizing 2.5% glutaraldeid (Valdman et al., 1992). The instruments utilized in the experimental tests were specified in each test presented.

Preliminary experiments were carried out in order to define optimal values for temperature, pH and range of glucose and sucrose concentrations. The results obtained and analysed for the sucrose conversion by the invertase are shown in Figures 1a, 1b , 1c.

An enzymatic sensor developed to continuously measure glucose concentration in a Fermenter (Folly, 1996) was actually been extended to measure sucrose concentrations based on the excellent results described previously.

The glucose sensor consisted of a fixed-bed microreactor with glucose oxidase immobilized in glass pearls and through which the sampling fluid was pumped with a Milan peristaltic pump. In this microreactor, a pH electrode (Digimed) was installed to measure the pH change occuring in the glucose reaction present in the solution flowing through the microreactor with the immobilized glucose oxidase. The pH of the reaction was measured with a pH industrial transmitter (Smar). The best values for reaction temperature, pH and glucose solution concentration of the fluid flowing through the microreactor were then determined. The results obtained in these experiments are shown in the Figures 2a , 2b , 2c.

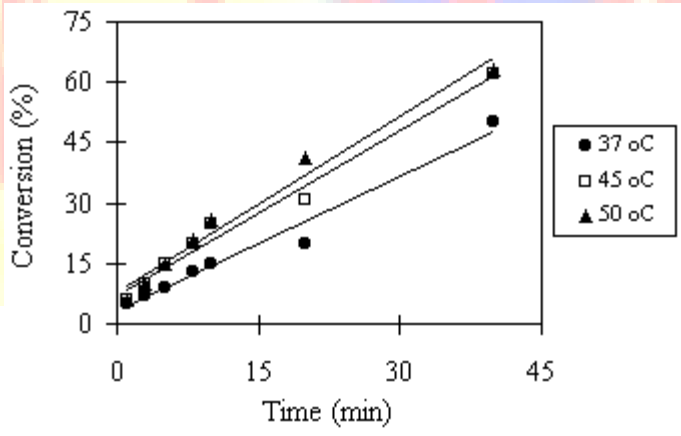

Figure 1a: Effects of temperature changes on sucrose conversion.

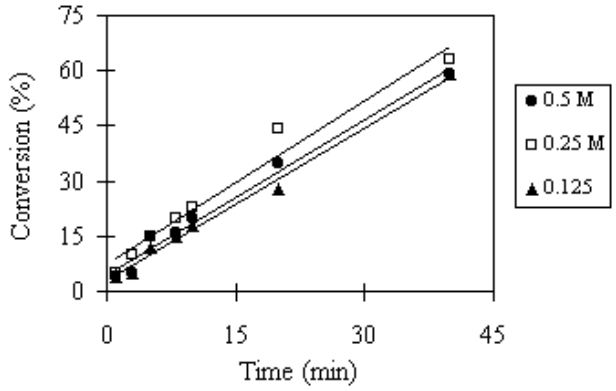

Figure 1b: Effects of sucrose concentration changes on conversion at 45 oC.

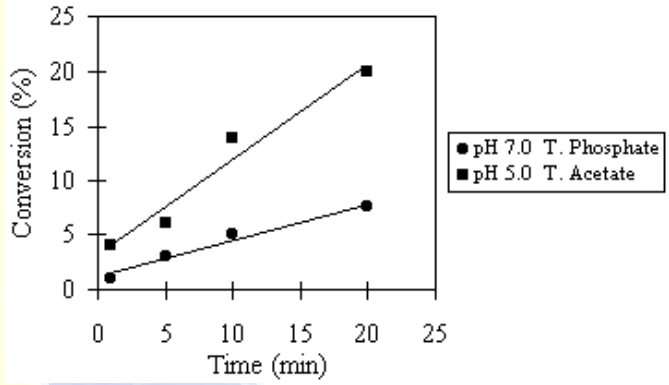

Figure 1c: Effect of pH changes on sucrose conversion at 45□ C.

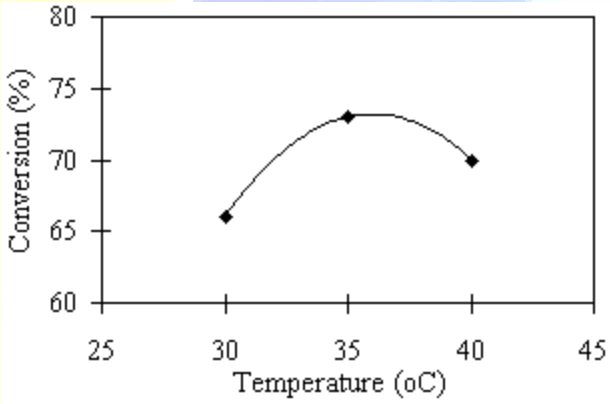

Figure 2a: Effects of temperature changes on glucose conversion.

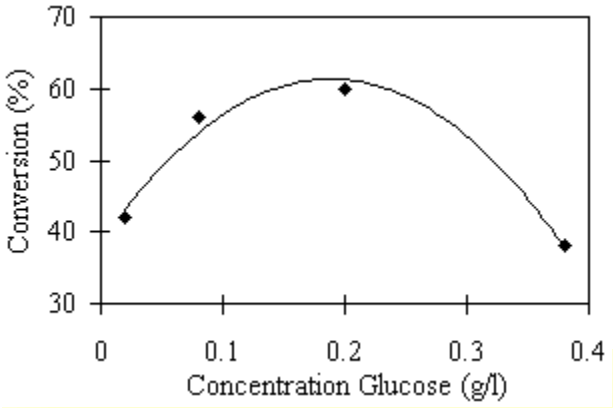

Figure 2b: Effects of glucose concentration changes on conversion at 37□ C.

Figure 3 shows the schematic diagram of the continuous sampling line developed and utilized for the dynamics tests and the calibration of the sensor. Figure 4 shows the calibration curve obtained for the best specified range of concentration obtained from 0.05 to 0.2 g/l, and Figure 5 presents the response curve obtained for a step change input in the glucose solution concentration from 0.1 to 0.2 g/l.

To extend the utilization range of the sensor, another sampling line was developed adapted to an FIA system using the Splitter Technique (Valero et al.,1991). The sampling flow was measured by the sensor of 7.25 ml/min, which made possible an increase in the glucose concentration range to 5 to 120 g/l. The sampling line developed with this methodology is shown in Figure 6 and is composed of one Masterflex eight-channel peristaltic pump , PTFE tubes with ID= 0.8 mm , Omnifit four-way injection valves and a pH meter with a Pharmacia recorder. The calibration curve obtained for this sensor adapted to an FIA system is shown in the Figure 7.

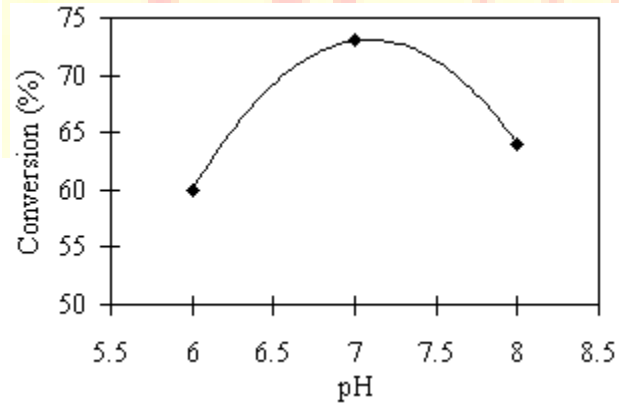

Figure2c: Effects of pH changes on glucose conversion at 37□ C.

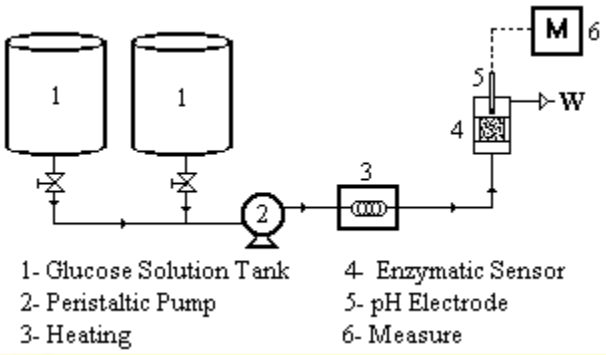

Figure 3: Schematic diagram of the continuous sampling line.

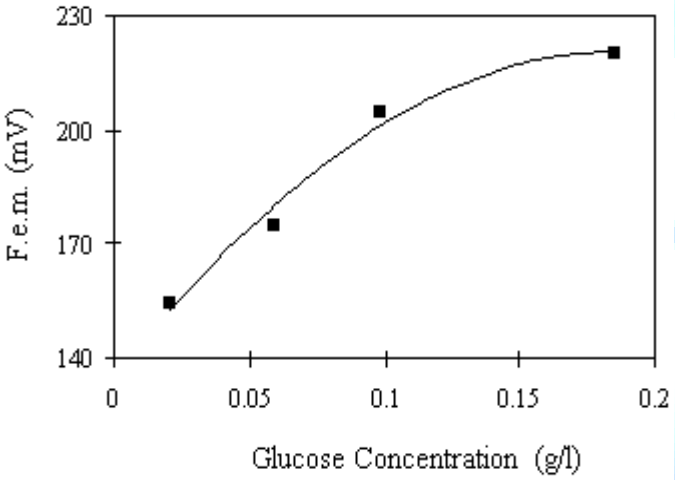

Figure 4: Calibration curve for the glucose sensor.

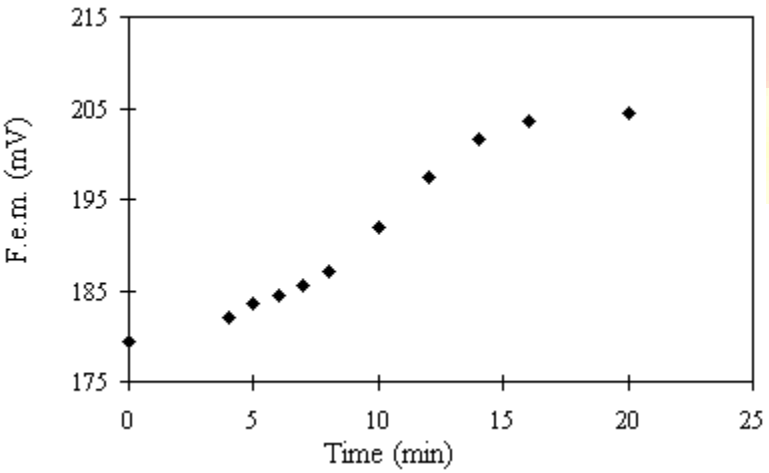

Figure 5: Response curve for the dynamics test of the glucose sensor.

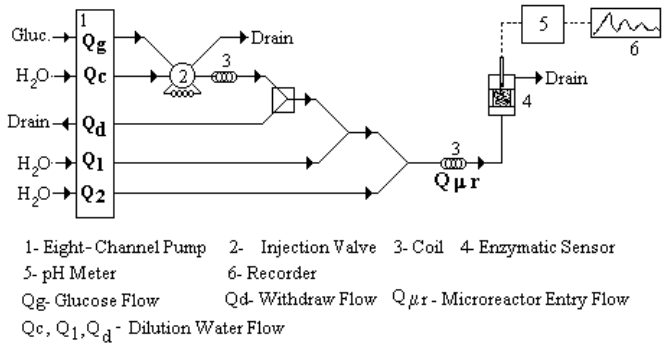

Figure 6: Schematic diagram of the sampling line of the sensor adapted to an FIA system.

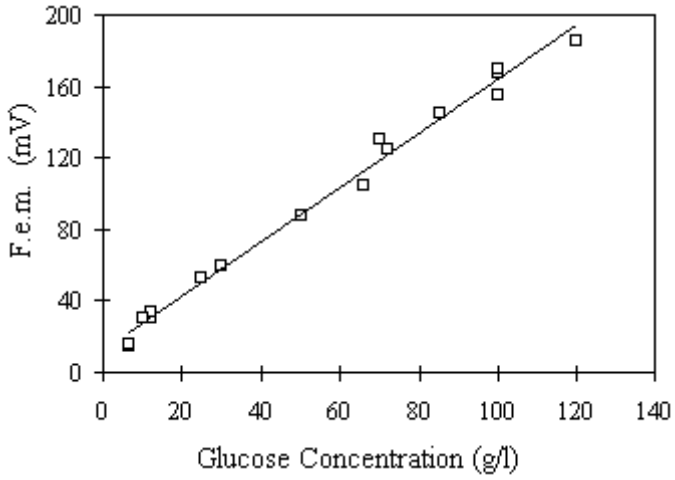

Figure 7: Calibration curve for the sensor adapted to a FIA system.

Linear Quadratic Gaussian-Based Closed-Loop Control of Type 1 Diabetes

In health, blood glucose (BG) is tightly controlled by a hormonal network that includes the gut, liver, pancreas, and brain, ensuring stable fasting BG levels (~80–100 mg/dl) and transient postprandial glucose fluctuations. Diabetes is a combination of disorders characterized by absent or impaired insulin action, resulting in hyperglycemia. Intensive insulin and oral medication treatment to maintain nearly normal levels of glycemia markedly reduces chronic complications in both type 1 diabetes mellitus (T1DM1) and type 2 diabetes mellitus, but may increase the risk of hypoglycemia or even potentially life-threatening severe hypoglycemia, which could result from imperfect insulin replacement reducing warning symptoms and hormonal defenses. Consequently, hypoglycemia has been identified as the primary barrier to optimal diabetes management.4 Thus, the primary purpose of diabetes treatment is optimal control of

postprandial hyperglycemia while avoiding hypoglycemia, which naturally formulates an engineering optimization problem.

Glucose control has been studied for more than three decades and widely different solutions have been proposed. The earliest work was based on intravenous (IV) glucose measurements and both positive (glucose) and negative (insulin) control actuations. Studies by Pfeiffer and Clemens created systems such as a glucose-controlled insulin infusion system or the more well-known Biostator that have been used in hospital settings. Both of these regulators were based on a proportional derivative strategy, where the injected insulin is proportional to the difference between a fixed plasma glucose target and the measured plasma glucose, as well as to the rate of change of plasma glucose. At that time, different types of controllers were also designed based on the prediction of glucose, therefore counteracting the inherent inertia of exogenous insulin compared to the endogenous hormones. The major designs can be found elsewhere. More work followed, spanning a broader range of control theoretic approaches. All systems were based on IV sensing and IV action and most of them relied on modeling of human physiology. Techniques such as pole placement, adaptive control, time domain, worst-case frequency domain, ($H\infty$) and optimization of linear quadratic (LQ) costs were adapted to the problem of glucose control. More recently, there is significant interest in applying model predictive techniques to the control of T1DM. For a review, see Bequette.

Subcutaneous (SC) injection of insulin imposes an additional actuation delay, as exogenous insulin is first transported from the injection site to the central vascular system and only then follows the pathway of IV-injected insulin.

Advances in surgically implantable intravenous sensors and intraperitoneal (IP) insulin pumps have triggered great interest in the control community. However, while it is believed that implantable sensors are closer to intravenous sensing (via blood draws) and are therefore less vulnerable to delays and errors, studies have shown that these sensors suffer from delays nearly equivalent to subcutaneous sensors. Implantable pumps are also believed to be more efficient than SC pumps, mimicking the natural route of insulin delivery (peritoneal injections) more closely. However, all implantable devices require surgery for insertion and have a limited lifetime.

In this article we proposed a methodology for the design of closed-loop feedback controllers based on linear quadratic Gaussian (LQG) control, in which optimal insulin injection are

computed based on CGM. The LQG control design methodology, developed in the 1960s, has been used in many application domains. In LQG control, an actuation signal is computed to minimize squared-error deviations from a nominal operating point, which in the control of diabetes corresponds to tight glycemic regulation around a reference glucose concentration (e.g., 100 mg/dl). An LQG controller comprises two main components—a state observer and a set of feedback gains—both of which are derived from a linear dynamic model of the system being controlled. In modeling the system, the choice of the state vector is made via two antagonistic criteria: the higher the dimension of the model, the more precisely the model can describe observed dynamics and estimate the modeled quantities; however, a high dimension also renders the estimation procedure sensitive to noise in the observed signal (BG), lowering the precision of the state estimate, which can preclude the use of subject-specific regulation due to unobservable states and nonidentifiable parameters.

Model of Glucose–Insulin Dynamics

The Augmented Meal Model (AMM). The baseline model for glucose–insulin kinetics employed in this article is the oral glucose "meal" model of Dalla Man et al., which by construction represents glucose and insulin fluxes during a meal. The structure of the meal model includes a nonlinear gastrointestinal submodel (three states), two glucose compartments, and five insulin-related states and was validated with triple tracer data collected from more than 200 subjects without T1DM. In Dalla Man et al., the model is modified to reflect the lack of pancreatic insulin production in T1DM. Finally, as described previously, we augmented the model to take into account the transport of insulin from subcutaneous injection to blood circulation, and further to the interstitium. We refer to the resulting set of differential equations as the augmented meal model and use the AMM for in silico testing of controllers synthesized from the LQG design methodology.

The Reduced Meal Model (RMM). For control design purposes, we used a reduced version of the AMM, in which we captured the effect of oral glucose via a single equation. Specifically, we modeled the glucose rate of appearance Ra (mg/kg/min) as a first-order lag of the meal disturbance D (mg/kg/min):

$$\dot{R}a(t) = -1\tau meal(Ra(t) - D(t)),$$

where τmeal is the time constant associated with glucose absorption from the gut. The glucose rate of appearance term appears in the type 1 differential equation for plasma glucose Gp(mg/kg) as

$$\dot{G}p(t)=-(k1+kp2)G(t)+k2Gt(t)-Uii(t)-kp3Id(t)+Ra(t)+kp1,$$

where Gt (mg/kg) refers to tissue glucose, Uii (mg/kg/min) refers to insulin-independent glucose utilization, and Id (pmol/liter) refers to the delayed insulin signal associated with endogenous glucose production, where we have assumed there is no glucose renal excretion for the target range of Gp under closed-loop control. The resulting set of differential equations has 11 state variables.

Subject-Specific Parameters for AMM and RMM. Because people are widely different from one another, it is important to tailor both AMM and RMM to the physiology of a particular person. Some model parameters are readily available (e.g., body weight), but most are highly model specific and require data collection before the controller can be activated. For a complete person-specific model we need to estimate most of the model parameters, which will allow the estimator not only to be bias free at steady state, but also capture the complete dynamics of the system. In practice, parameter estimation is cumbersome and must be based on the analysis of glucose, insulin, and BG data collected during standard clinical glucose tolerance tests. The simulation results of this article present the ideal case where, for individual subjects, we assumed complete knowledge of all AMM parameters.

Linear Quadratic Gaussian Control Design

The LQG controller developed consists of two main parts: (i) a state observer (Kalman filter) based on the RMM with subject-specific parameters, linearized around the desired BG operating point, and (ii) a set of linear quadratic regulator (LQR) feedback gains computed from the linearized RMM to minimize a least-squares criterion. Both aspects of the controller are outlined. The continuous-time dynamics of the linearized RMM can be expressed in succinct form, as follows:

$$\dot{X}(t)=AX(t)+Bu(t)+Gw(t)Y(t)=CX(t)+Du(t)+Hv(t)$$

Where,X is the vector of states of the RMM (deviation from reference point), including plasma glucose, tissue glucose, and various insulin states; u represents injected insulin (deviation from reference insulin uop);

and w is the glucose disturbance [D(t) in the AMM and RMM]

Y is a vector representing measurable quantities (offset again by the reference measurement), comprising BG (plus noise) and injected insulin A, B, C, D, G, and H are state space matrices that reflect coefficients of the linearized RMM.

Estimates of the state vector X can be computed dynamically from the observer equation:

$\hat{X}'(t)=A\hat{X}(t)+Bu(t)-L[Y(t)-C\hat{X}(t)-Du(t)]$

where L represents the innovation gain that causes the state estimate to deviate from the open-loop prediction $A\hat{X}(t)+Bu(t)$ based on the difference between what is actually measured and what was predicted to be measured, $Y(t)-C\hat{X}(t)+Du(t)$. The choice of the innovation gain matrix L is critical to the method. In LQG control, we computedL as the optimal Kalman filter gain, assuming (for control synthesis only) that both w and v are white noise processes with covariance matrices chosen to reflect the magnitude of the disturbances and sensor noise. Computationally, this amounts to the solution of an algebraic Riccati equation.

LQ Regulator. The second component of the LQG controller is the set of LQR feedback gains, which transform our estimate of the physiological state of the system into insulin dosing recommendations, as follows

$u(t)=-Ka\hat{X}(t)$.

Note that since u(t) represents the deviation from the reference insulin injection, the actual command to the insulin pump is $[uop-Ka\hat{X}(t)]+$, where $[x]+$ refers to the nonnegative part of x [i.e., $[x]+ = \max(0,x)$], accounting for the constraint that negative boluses cannot be injected. The choice of Ka is critical. Following LQG methodology, we computed Ka through the solution of another Riccati equation so that $\tilde{u}(t)=-Ka\hat{X}(t)$ minimizes the deterministic objective function:

$J(\tilde{X}(0))=\int_{t=0}^{\infty}[\tilde{X}T(t)Q\tilde{X}(t)+\tilde{u}2(t)]dt,$

where (i) the state $\tilde{X}(t)$ is constrained according to the dynamical equations $\tilde{X}(t)=A\tilde{X}(t)+B\tilde{u}(t)$ and (ii) Q is a positive semidefinite matrix of weights that penalize state deviations away from the reference operating point of the controller. In general, matrix Q allows the control designer to specify the states that are of interest (glucose vs insulin, plasma concentration vs other compartment) and the aggressiveness of the regulator (how fast it will try to reach equilibrium, possibly undershooting the target value). For the experimental results of this article, we have chosen Q to be a diagonal matrix, with a common weight qapplied

to all glucose states, and a weight of one applied to all insulin states. The best value ofq depends on the reliability of the sensor and on subject characteristics.

Discretization. Our discussion so far has focused on LQG control as a continuous-

time process; however, in practice, the LQG controller must be implemented as a sampled data format because CGM measurements are only available at discrete intervals and because existing insulin pumps only allow discrete changes to basal patterns or discrete bolus injections. Envisioning scenarios in which sampling intervals change over time, our approach was to design a continuous time LGQ controller, as outlined above, which we then discretized for final implementation. (We did not synthesize a discrete time LQG controller based on a discrete representation of the RMM.) To discretize the state observer, we zero order held the samples and used a piecewise constant measurement signal as input to the continuous time Kalman filter. Next, in computing the bolus associated with each CGM sample, we used a predictive technique in which the bolus amount is computed as an estimate of the amount of insulin that the LQG controller would inject over the subsequent sampling interval.

Results

We evaluated, in silico, subject-specific LQG control and compared it to a previously reported PID controller.40 The purpose of this study was to evaluate the ideal limits of performance associated with LQG control, assuming complete knowledge of all AMM parameters for an in silico population of type 1 diabetic individuals. The evaluation of LQG and comparison to PID was performed in a simulation environment based on the AMM and is similar to the GIM simulator of Dalla

Man and colleagues.43 Our simulation environment included a random CGM sensor noise model developed at the University of Virginia. Our simulation experiments followed the in vivo protocol described by Steil et al.,40 with both CGM sampling and closed-loop control boluses every minute. LQG control versus PID, with one minute CGM samples and bolus updates.

Group Results

To understand the relative performance of LQG versus PID, we designed a simulation experiment involving 10 independent trials (as described earlier) for each of 100 simulated subjects. For each subject, a PID controller was designed according to the specifications of

Steil et al.40 using the AMM to estimate subject-specific metabolic parameters for determining PID coefficients. After running all 1000 trials of the PID controller, we computed the average closed-loop glucose concentration (across all subjects, for the duration of the protocol). Next, for each of the 100 subjects, again assuming full knowledge of each subject's AMM parameters, we designed an LQG controller. We used a common target glucose concentration for all subjects, identified through an iterative process, so that the LQG approach would achieve the same average glucose concentration achieved by the PID approach. Results from this study are presented for four traditional indices of glucose control:

Percent-time BG > 180 mg/dl (PERCH)

Percent-time BG < 70 mg/dl (PERCVL)

Low BG index44 (LBGI)

Minimum glucose concentration (Min_BG)

Results from the 100 subjects (1000 total trials) are shown in Table 1. Note that the subjects spent less time in hyperglycemia on average ($p < 0.001$) under PID control compared to LQG. However, the LQG controller achieved much lower hypoglycemic excursions, with a smaller average PERCVL ($p < 0.001$), smaller average LBGI ($p < 0.001$), and higher Min_BG on average ($p < 0.001$). Average glycemia for the PID controller was 128.2 (mg/dl), whereas average glycemia for the LQG controller was 128.7, not significantly different ($p = 0.65$). [Note that while the average Min_BG for the LQG controller was 81 (mg/dl), a small number of in silico subjects under LQG control experienced hypoglycemic excursions below 70 (mg/dl), resulting in an average PERCVL of 0.3%.]

Table 1.

Average Results from 100 in Silico Subjects (1000 Total Trials)

	PERCH (%)	PERCVL (%)	LBGI	Min_BG (mg/dl)
PID	14.2	8.73	2.25	54
LQG	17.8	0.3	0.33	81

Table 1.Average Results from 100 in Silico Subjects (1000 Total Trials)

CONCLUSIONS

Tests showed that changes in medium conditions had a considerable influence on the conversion of sucrose solutions by invertase. The buffer acetate with a pH of 5.0 and a temperature of 50’ C were the most favourable conditions for larger conversions (50% sucrose).

The biosensor used for measurement of glucose shows very good results, both with continuous measurements and in glucose injection measurements. For continuous flow of the sampling fluid, the concentration range used was from 0.05 to 0.2 g/l, and this range was extended to 5.0 to 120 g/l with the adaptation of this sensor to FIA methodology.

In both cases, the sensor presents a response time of 10 minutes. A similar methodology can be studied for application of a multienzymatic microreactor (glucose oxidase , invertase and mutarotase enzymes) for the continuous measurement of sucrose.

Further study is required to evaluate LQG control in a nonideal case where AMM parameters for individual subjects must be estimated from clinically available data. In ongoing research, we are developing methods for estimating AMM parameters from clinical data using a combination of population average values for some parameters, along with adjusted parameters values that reflect the subject's steady-state glucose and insulin characteristics, insulin clearance, and correction factors.

Future Development

An implanted device full of insulin and glucagon-producing cells. They automatically sense sugar in your blood and produce and release exactly the amount of insulin and other hormones that you need. It’s as if you once again have a fully functioning pancreas. The ß Air bio-artificial pancreas comes which was established 12 years ago with the primary goal of eliminating the need for insulin injections, carbohydrate counting, hypoglycemia and hyperglycemia with a technology which successfully resolves the commonly faced issues in cell-replacement therapy.

The Key Challenges In Implantable Treatments

Beta-02 claims to have solved two key problems with implantable stem cells. First, the body’s immune system tends to attack anything that’s implanted under the skin, requiring immunosuppressive drugs with potentially lethal side effects. Second, the cells that produce

insulin and glucagon are among the most oxygen-hungry in the body. Without access to large amounts of oxygen, the implanted cells tend to die.

Beta-02's solution is a a special delivery system that does not trigger the body's immune system. The device also uses daily injections of oxygen to feed the oxygen-hungry cells inside.

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