and actuators with sufficient authority to influence the controlled variables. As always, plant understanding is key. Biological systems in general are distributed parameter, stochastic, nonlinear, time varying dynamical systems. Process models are often derived from first principles by domain experts, such as theoretical biologists. In some cases data driven models are used. Biological systems tend to exhibit multi-compartmental interactions that are usually not well understood and as a result, the interactions cannot be accurately modeled mathematically. Control engineers have to convert these models into a form that is suitable for controller design. This conversion requires a certain basic understanding of the process that can be somewhat difficult for engineers to obtain, but is well worth the effort.

Most process variables in biological systems can only be measured online, if at all, under clinically controlled conditions such as in a hospital. In many cases measurements are only available at discrete intervals with long associated dead-times. Sensor accuracy has the potential to hinder effective control of the process variables. For example, in Section 4 of this paper, the currently available (off-line) assays cannot detect viral loads below 50 copies per mL of plasma (20 for ultra sensitive assays). Drugs are often the only actuators available to manipulate controlled variables in biological systems. For accurate control a good actuator model is also required as the control signal used is the drug efficacy and not the number of pills. This means that, the dosage to end point efficacy relationship has to be clearly defined for each drug. In cases where more than one drug is used to treat the same condition, then consideration has to be made for issues such as drug–drug interactions as well as the combined efficacy. Lastly design of drug dosing regimens should be done using clinically driven criteria.

Although the five application areas discussed in this paper are diverse they have a number of elements in common. They all involve the use of dynamic models and they deal with problems whose solution will yield significant economic benefits as well as improved quality of life through better therapy. All five problems involve the use of advanced control, particularly model based and optimization based control. Further dynamic models for most of the biomedical applications discussed show a great deal of variability from patient to patient and methods to deal with this variability have to be incorporated into the solution to each problem. Clearly, there are some problems in the biomedical area that lend themselves to data based modeling. The fact that this tutorial does not consider these problems should not be interpreted as indicating their lack of importance.

The biomedical process control area is one that has great growth potential, and one for which the tools used by process control engineers directly apply. However, the biomedical control field has its difficulties as well. One obvious difficulty involves the safety of any proposed new strategy for delivering a drug. If there is any question about the safety of a new drug policy then the policy will not be used. There is the issue of the medical and engineering communities being open to what the other community has to offer. It is important for both engineers and physicians to find collaborators with whom they are able to work effectively. There is also a communication issue since engineers and physicians tend to use different terminology and come at problems from different perspectives. For example engineers talk about lumped parameter systems and physicians use the term compartment models. In spite of these difficulties, the biomedical process control holds tremendous promise. The area is rich with interesting, important and challenging problems, and it is hoped that this tutorial paper will stimulate process control engineers to look further into it.

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I. Glucose control strategies for treating type 1 diabetes mellitus

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1. Introduction

Type 1 diabetes mellitus is a disease characterized by complete pancreatic β-cell insufficiency. The only treatment is with subcutaneous or intravenous insulin injections, traditionally administered in an open-loop manner. Without insulin treatment, these patients die. Insulin was discovered in 1921, and although now it has been purified and manufactured by recombinant DNA technology, one still must individualize the treatment to mimic normal physiology in order to prevent the complications of hyper- and hypoglycemia (elevated glucose levels, and low glucose levels, respectively). The literature documents [1–3] the strong correlation between hyperglycemic excursions and the increase the risk of complications. The Diabetes Control and Complications trial [1] was the landmark study of 1440 type 1 diabetic people randomized into two treatment wings: intensive insulin delivery and standard care. Those people who had mean blood glucose concentrations below 110 mg/dl (glycosylated hemoglobin levels less than 6.0%) had no increase risk for retinopathy, nephropathy and peripheral vascular disease. Those patients who had ele-

vated glycosylated hemoglobin levels had a significant and positive correlation with increased risk. However as the blood glucose concentration was normalized the risk of sever life-threatening hypoglycemia increased up to 10 fold above the risk in those patients with hyperglycemia. Thus the goal of achieving and maintaining normal blood glucose includes accepting the risk of hypoglycemia. A recent long-term study by the DCCT group has confirmed these conclusions [4].

2. Glucose control in healthy individuals

The normal physiologic insulin secretion has two profiles: the basal secretion (to provide a background rate of insulin to the body) and the meal-related bolus secretions. The variables that dictate the basal insulin needs for an individual include growth and development, hormonal status, age, gender, stress levels, health status, and activity level. In addition, the amount and composition of food dictate the meal-related needs [5]. In order to normalize the glucose levels of insulin dependent, type 1 diabetic patients, all variables need to be included into an algorithm for insulin delivery. The insulin requirement can therefore vary from a minimal need of 0.5 units per kilogram per day in quiet times, up to 2.0 units per kilogram per day at maximal stress situations [6]. After an initial dose is prescribed the dose needs to be adjusted and based on the blood glucose level. This method of insulin delivery is fraught with continuous risk of hyper- and hypoglycemia because the moment-to-moment fluctuations in glucose are not adequately treated with intermittent subcutaneous insulin injections [7]. The optimal insulin delivery protocol would therefore be one in which the blood glucose monitoring and insulin dosing would be continuously managed in real-time. The meal-related insulin need also is difficult to derive and allow for the incorporation of carbohydrate into the meal plan and minimize the postprandial glucose peak [8]. The normal pancreas has two phases of insulin delivery, a first phase consisting of an immediate bolus and a second phase of prolonged insulin delivery. The first phase is necessary to depress the glucagon secretion from the pancreatic α-cell and thus turn off the hepatic output of glucose. The variables that dictate the basal insulin needs for an individual include growth and development, hormonal status, age, gender, stress levels, health status, and activity level. The second phase of insulin secretion is needed to metabolize the slower acting carbohydrates. The normal β-cell has its first priory to prevent hyperglycemia. It depends on the α-cell to secrete glucagon to prevent late postprandial hypoglycemia.

The β-cell's response to a rapidly rising blood glucose is to increase the insulin secretion rate, to sustain an absolute blood glucose concentration is to decrease the insulin secretion rate; however, the only way the β-cell can respond to a falling blood glucose concentration is to turn off the insulin secretion. Of course, there is no way the β-cell can retract the insulin once it is given. The β-cell depends on the other counter-regulation hormones to be secreted to buffer the falling glucose concentration. The hormones that play a major role in counter-regulation are glucagon, epinephrine, cortisol and growth hormone. This delicate balance is perfectly orchestrated to maintain blood glucose within a narrow range.

The top portion of Fig. 1 shows the 24-h continuous readout of blood glucose concentrations of a lean, healthy, non-diabetic male who eats between 250 and 300 g of carbohydrate a day, in a random fashion. Despite the variation and timing of his food, exercise and activity level, his blood glucose is maintained at a mean value of 98.5 mg/dl with a standard deviation of 6.1 mg/dl. In contrast, the bottom portion of Fig. 1 shows the 24-h continuous glucose pattern of a type 1 diabetic patient who has a mean blood glucose of 204.7 mg/dl and wide fluctuations of glucose concentrations throughout the day of 102.2 mg/dl, standard deviation. These glucose excursions are implicated as the major risk associated with diabetes for both severe hyperglycemia and hypoglycemia complications. His treatment with insulin injections is not based on these moment-to-moment glucose results, but rather is a standard prescription based on infrequent, intermittent fingerstick glucose monitoring.

3. Artificial pancreas

In order to normalize the glucose levels of insulin dependent, type 1 diabetic patients, the algorithms for the development of an artificial pancreatic islet need to exploit all the measured variables that the normal islet insulin secretion utilizes and quickly increase or decrease the insulin secretory. The insulin secretory rate can therefore vary from a minimal need of 0.5 units per kilogram per day in quiet times, up to 2.0 units per kilogram per day at maximal stress situations. In the case of type 1 diabetic people,

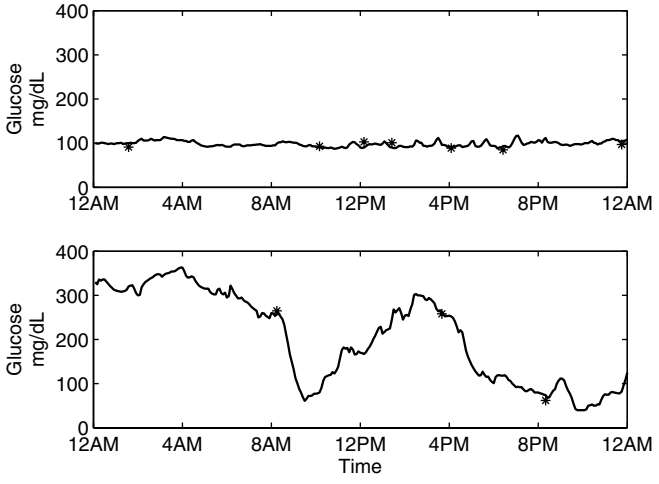

Fig. 1. Twenty-four hour continuous glucose profile for a normal individual (top) and an individual with type 1 diabetes (bottom). The stars denote calibration points for the sensor obtained with a finger stick measurement.

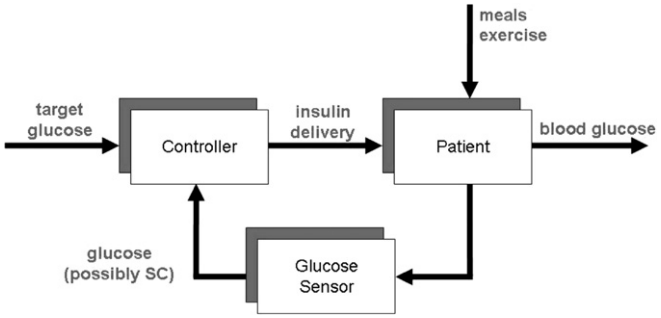

Fig. 2. Block diagram of a glucose feedback control system (SC denotes subcutaneous glucose measurement, as per the current technology).

after an initial dose is prescribed the dose needs to be adjusted and based on the blood glucose level. This method of insulin delivery is fraught with continuous risk of hyper- and hypoglycemia because the moment-to-moment fluctuations in glucose are not adequately treated with intermittent subcutaneous insulin injections. The optimal insulin delivery protocol would therefore be one in which the blood glucose monitoring and insulin dosing would be continuous (real-time). A block diagram of an automated glucose control strategy is shown in Fig. 2.

The meal-related insulin need also is difficult to derive and allow for the incorporation of carbohydrate into the meal plan and the minimization of the postprandial glucose peak.

Perhaps the only way to mimic normal pancreatic function is to provide both the α-cell and the β-cell secretion to maintain as near normoglycemia as possible. Technology needs to be created to monitor glucose frequently and use a glucose-controlled, insulin delivery system to provide the optimal insulin treatment protocol. To this end an artificial pancreatic islet is urgently needed.

4. Control strategies for automated insulin delivery

The challenge of automating insulin delivery for diabetic patients using implantable pumps and glucose sensors has received considerable attention over the last 10–20 years. Recent surveys and tutorials provide excellent overviews of diabetes control strategies from a control engineering perspectives [9–13].

Early diabetes control papers in the 1960s involved clinical studies using both glucose and insulin infusions that were calculated using on–off control or special nonlinear control algorithms (e.g., the ''Biostator'' algorithm). The latter can be interpreted as nonlinear proportional-derivative (PD) controllers that are related to standard gain scheduling technique [11]. Since these early studies, many diabetes control papers have been concerned with automated insulin infusion using standard or modified PID control algorithms. These feedback control strategies are often enhanced by feedforward control action based on a known ''meal challenge'', i.e., an insulin bolus is calculated assuming that the meal time and content are known.

PD controllers have received considerable attention due to concerns that integral control action can lead to insulin overdosing and subsequent hypoglycemia, during and after meals. However, this potential problem can be overcome reduced by judicious use of ''anti-reset windup'' with the integral control action. For most of these PID control papers, the proposed controllers were evaluated in simulation studies of postprandial responses; but a few experimental applications to dogs or humans have also been published. However, direct comparisons of latter papers can be difficult due to differences in the experimental conditions (e.g., intravenous vs. subcutaneous sensors and pumps, different types of insulin and insulin analogs, etc.).

Model-based control strategies have also been proposed for the diabetes control, with model predictive control (MPC) receiving considerable attention in recent years [9,11,13]. MPC strategies are attractive for diabetes control for many of the same reasons that they have been very successful in the process industries [9]: (i) the ability to control both linear and nonlinear processes; (ii) inherent handling of inequality constraints, (iii) prediction of future behavior, and (iv) ease of model parameter updating. Both linear and nonlinear models have been considered. A key issue is the availability of a dynamic model that is reasonably accurate for the current patient conditions.

MPC evaluations for diabetes control problems have demonstrated that improved glucose control can be achieved in comparison with conventional PID control strategies. Most of these evaluations have been on simulation studies. However, a European consortium has reported successful clinical applications based on a nonlinear compartmental model used as the model in an MPC demonstration for insulin delivery [14].

A diabetic person's response to insulin can vary significantly for a variety of reasons. For example, insulin sensitivity varies with the time of day (e.g., the ''dawn phenomena'') and the fitness and health of the individual. Stress and exercise levels also affect a person's insulin sensitivity. Furthermore, the timescales of the variations for a diabetic can vary from hours to months. Thus, a practical automated glucose control strategy will have to be adaptive to some extent in order to accommodate changing and unknown patient conditions. Hovorka [12] has recently published a detailed review of adaptive control strategies for both type 1 and type 2 diabetes. He considers strategies for two types of situations: (i) infrequent glucose measurements are available (e.g., four to seven measurements per day) and (ii), frequent glucose measurements are available (e.g., every 5 min). This survey paper contains an extensive bibliography.

For batch industrial processes, run-to-run control strategies have been successfully used to provide improved control based on experience with one or more recent batches. Run-to-run (R2R) control strategies have also been developed for diabetes control, by considering glucose data for a meal response or an entire day to be the ''batch'' of interest. For example, Zisser et al. [15] reported an experimental

R2R application where the glucose control improved significantly over a two week period based on infrequent glucose measurements, 60 and 90 min after the start of a meal.

In the next section, two successful applications of advanced control strategies to diabetes control are summarized.

5. Applications of advanced process control strategies

Parker et al. [16] were the first to publish a model predictive control approach for the management of glucose levels in type 1 diabetic patients. Their research was a simulation study that employed the Sorensen [17] model as the "virtual patient". They explored several approaches to model development, including: (i) direct identification from patient data using rich signals, (ii) reduced order numerical models that were derived from the original compartmental model, and (iii) linearized versions of the compartmental model coupled with a state estimator. The state estimator was used for inference of the (unmeasured) meal disturbance, providing a form of feedforward control without the need for direct knowledge of the meal. They also explored the estimation of key physiologic parameters on-line, using a Kalman filter.

In simulation studies [16], the MPC with state estimation approach demonstrated that meals would be compensated for without the direct knowledge of meal timing and/or content. The blood glucose levels were controlled to near-normal levels, and there were no significant concerns of hypoglycemia. Thus, this approach advocated a completely patient-free solution with full automation of insulin delivery. Measurement noise and patient uncertainty (parametric mismatch) were also managed, including estimation of key patient parameters. MPC has been tested in numerous clinical trials in Europe, as part of the European ADICOL project, with successes reported for postprandial (post-meal) stabilization [14], as well as 24-h control with ICU patients [21]. This experience demonstrates the promise of advanced algorithms for regulated insulin delivery.

Run-to-run control (or iterative learning control – ILC) is a methodology for dealing with engineering systems that exhibit a cyclic behavior [18]. The key idea is that certain disturbances are persistent across repeated "cycles" in a process (such as raw material impurities in the batch production of a polymer). Instead of repeatedly correcting for the persistence disturbance from an initial (incorrect) condition, this algorithmic approach formulates an update on a time scale of the entire cycle (i.e., one correction allowed at the end of the batch) that minimizes the effect of the persistent disturbance. Viewed from another perspective, the run-to-run algorithm starts on a cycle that is poorly controlled, and refines to the control action over the course of multiple cycles until a nearly perfect controlled cycle is obtained.

In a recent clinical trial, we were able to exploit the 24-h cycle for insulin bolus dosing as a "cycle" that can benefit from run-to-run control [15,19]. We described in subsequent papers a technique for optimizing a patient's insulin therapy (timing, amount) through the use of so called run-to-run control [19,20]. The similarities between the diabetic patient and the batch reactor recipe which motivate the application of this technique are

1. the recipe (24-h cycle) for a human patient consists of a repeated meal protocol (typically 3 meals) with some variance on meal type, timing, and duration,
2. there is not an accurate dynamic model available to describe the detailed glucose response for an individual to the meal profile, and
3. there are selected measurements available that might be used to characterize the "quality" of the response for a 24 h day, including maximum and minimum glucose values.

As noted in the original algorithm reference [19,20], the key elements of the algorithm are that it is *measurement-based* (as opposed to *model-based*) and the independent variable of the control loop is the batch number. Thus a solution is implemented as an open-loop policy for each batch (24-h cycle), and the feedback allows refinement over successive batches (days). Of particular interest in the present context is the fact that the limited measurement information of the patient's blood glucose level is translated into quality measurements (max/min glucose). In this way, the patient's sampling protocol does not need to be rigorously synchronized to a particular time every day, and the resultant quality variables are exactly the type of variables that a medical professional would use to evaluate the efficacy of a particular insulin regimen.

The results of the clinical trial [15] demonstrated a large fraction of the patients responded favorably to the algorithm, and the algorithm's predictions were in line with the medical doctors' recommendations. Continuing studies are addressing the robustness of the algorithm with respect to variability in meal content.

6. Summary

In this section, we have highlighted some of the challenges and promising approaches concerning controller design for an artificial pancreas. The technological challenges associated with the delivery of insulin, as well as the measurement of glucose (e.g., subcutaneously), are quickly coming into focus and the medical technology companies have solutions on the market. One of the key challenges will be the design of robust control strategies to "close the loop" under normal patient lifestyle that includes physical activities, variable meal timing and content, and conditions of illness and stress. Such a control strategy may require patient intervention (e.g., alerting for a meal or exercise), but must be able to maintain a stable glucose level in between meals as well. Perhaps no single control algorithm will accomplish this goal for all patients, and thus different categories of patients will require

alternate algorithms. On the other hand, a common framework, such as MPC, may be quite robust, with individual customization required for patient models, estimation components, and/or cost functions.

Fault detection/diagnostics and monitoring controller performance will be critical factors in the success of an ambulatory artificial pancreas. The glucose control strategy may require adaptation to compensate for unanticipated conditions. For example, model updating or "pattern recognition" to determine the appropriate model for current conditions, for example, a particular stress state. Early trials of MPC with human patients are encouraging [14,21], and many research groups are currently testing these algorithms in diverse patient populations. The next five years will likely witness dramatic progress in the design and evaluation of sophisticated strategies for control of glucose in subjects with type 1 diabetes.

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II. Modeling for anti-cancer chemotherapy design

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1. Overview

Cancer is the most common disease-related cause of death for American adults under age 85 [1]. It is estimated that >$190 billion will be lost to cancer-related effects in 2006, including treatment, lost productivity, etc. [1]. Cancer is a class of diseases characterized by an imbalance in the mechanisms of cellular proliferation (growth) and apoptosis (programmed cell death) [2]. When left untreated, this imbalance results in the growth of cancerous malignancies, including solid tumors and blood–borne disease, among others, and the resulting death of the host organism [3]. Once cancer is detected, it is removed, if possible (in the case of accessible solid tumors), and treatment is initiated. Radiation, surgery, and chemotherapy are common treatment methods [4]. However, it is common for cancer to spread throughout the host organism, a process called *metastasis*, prior to its reaching a detectable size, approximately 1 mm^3. Hence, chemotherapy is often applied alone, or in combination with the above methods, as it is the primary method of non-site-specific treatment and distant metastases require a systemic treatment [5].

2. Cancer as a class of diseases

Some diseases are characterized by the inadequate (or overabundant) supply of a particular endogenous sub-