The Implantable Glucose Sensor in Diabetes: A Bioengineering Case Study

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INTRODUCTION

Since my previous review on this subject that appeared in *Introduction to Bioengineering* in 2000 (*1*), there have been many changes in the field. Most importantly, diabetes has become much more prevalent, especially type 2 diabetes, and the incidence of new cases worldwide has reached epidemic proportions. This has led to widespread concerns that the consequences of the disease, if unabated, may begin to over-tax health care resources in the near future. There has also been remarkable progress in the development of new technologies for addressing the disease. Nevertheless, there remain numerous opportunities for bioengineers, some of which are reviewed here. This article focuses on the rationale for glucose monitoring and advances made at UCSD, and is an abridged version of a more extensive recent review (*2*).

THE CASE FOR NEW GLUCOSE SENSORS

Glucose assay is arguably the most common of all medical measurements. Billions of glucose determinations are performed each year by laypeople with diabetes based on "fingersticking" and by health care professionals based on blood samples. However, new types of sensors capable of continuous glucose monitoring are nearing clinical introduction. Continuous or near-continuous glucose sensors may make possible new and fundamentally different approaches to the therapy of the disease.

The objective of all forms of therapy for diabetes is the maintenance of blood glucose control near normal levels (*3*). The Diabetes Control and Complications Trial (or DCCT) and counterpart studies such as the United Kingdom Prevention of Diabetes Study (UKPDS) have clearly demonstrated (Fig. 1) that lower mean blood glucose levels resulting from aggressive treatment can lead to a reduced incidence and progression of retinopathy, nephropathy, and other complications of the disease (*4,5*). These prospective studies showed definitively that there exists a cause-and-effect relationship between poor blood glucose control and the complications of diabetes. As convenient means for frequent glucose assay were not available at the time, glucose control was assessed in these trials by glycosylated hemoglobin levels (Hb_{A1c}), which indicate blood glucose concentrations averaged over the previous 3-month period. Although Hb_{A1c} levels are useful for assessment of longitudinal blood glucose control, the values indicate only *averaged* blood glucose, rather than blood glucose *dynamics* (i.e., how blood glucose changes with time), and cannot be used for immediate adjustment of therapy. Normalization of blood glucose dynamics may be of equal or greater importance than normalization of average blood

glucose. The results of the DCCT point to the need for practical new approaches to achieve control.

The primary need for a new type of glucose sensor is to facilitate improved treatment of type 1 diabetes. In this case, the insulin producing ability of the pancreas has been partially or fully destroyed due to a misdirected autoimmune process, making insulin replacement essential. The sensor would help avoid the long-term complications associated with hyperglycemia (i.e., above-normal blood glucose) by providing information to specify more timely and appropriate insulin administration. It is now becoming widely appreciated that a new sensor could also be beneficial for people with the more common type 2 diabetes, where a progressive resistance of peripheral tissues to insulin develops, leading to glucose imbalances that can eventually produce long-term clinical consequences similar to type 1 diabetes. Type 2 diabetes is related to obesity, lifestyle and inherited traits. In recent years, the incidence of type 2 diabetes has increased at extraordinary rates in many populations, especially among young people, to the point of becoming a world-wide epidemic (*6*). It is estimated that within 10 years, the prevalence of diabetes may approach 210 million cases worldwide (*7*).

In addition, an automatic or continuous sensor may also have an important role in preventing hypoglycemia (i.e., below-normal blood glucose). Hypoglycemia is caused primarily by a mismatch between the insulin dosage used and the amount of insulin actually needed to return the blood glucose level to normal. Many people with diabetes can reduce the mean blood glucose by adjustment of diet, insulin, and exercise, but when aggressively attempted, this has led to a documented increase in the incidence of hypoglycemia (*8*). Below-normal glucose values can rapidly lead to cognitive lapses, loss of consciousness, and life-threatening metabolic crises. A continuous glucose sensor that does not depend on user initiative could be part of an automatic alarm system to warn of hypoglycemia and provide more confidence to the user to lower mean blood glucose, in addition to preventing hypoglycemia by providing improved insulin dosages. Hypoglycemia detection may be the most important application of a continuous glucose sensor.

Alternatives to sensor-based therapies for diabetes are more distant. Several biological approaches to diabetes treatment have been proposed, including pancreatic transplantation, islet transplantation, genetic therapies, stem cell-based therapies, beta cell preservation, and others. These alternatives require substantial basic research and discovery, and are not likely to be available until far into the future, if eventually feasible.

Although new glucose sensors have the advantage of being closer to clinical introduction, there are certain other advantages as well. Real-time monitoring may lead to an automatic hypoglycemia warning device and entirely new means to implement several present therapies. In addition, the sensor is key to the implementation of the mechanical artificial beta cell. This device would have an automatic glucose sensor, a refillable insulin pump, and a controller containing an algorithm to direct automatic pumping of insulin based on information provided by the sensor. Development of an acceptable glucose sensor has thus far been the most difficult obstacle to implementation of the mechanical artificial beta cell.

THE IDEAL GLUCOSE SENSOR

For the glucose sensor to be a widely accepted innovation, the user must have full confidence in its accuracy and reliability, yet remain uninvolved in its operation and maintenance. Sensor systems under development have yet to reach this ideal, but some promising aspirants are described below. Short of the ideal, several intermediate sensing technologies with limited capabilities may find some degree of clinical application and, if used effectively, may lead to substantial improvements in blood glucose control. Nevertheless, the most complete capabilities will lead to the broadest adoption by users.

PRESENT GLUCOSE SENSING METHODS

The present method for glucose monitoring is based on samples collected by fingersticking. In this method, sample collection involves the use of a lancet to puncture the skin of the fingertip or forearm to produce a small volume of blood and tissue fluid, followed by collection of the fluid on a reagent-containing strip and analysis by a handheld meter. The standard of care requires glucose determination by this method six times per day, but it is widely conceded that most people with diabetes sample only about once a day on average. When sampling is not sufficiently frequent, undetected blood glucose excursions can occur between samples. It has been shown that blood glucose measurements must be obtained every 10 min to detect all blood glucose excursions in the most severe diabetic subjects (*9*), although less frequent sampling may be sufficient for many people with diabetes. The fact that the sampling frequency required to detect all glycemic excursions is not realistically feasible at present indicates that the dynamic control of blood glucose is not actually practiced in diabetes management.

Several hundred physical principles for monitoring glucose have been proposed since the 1960s. Many are capable of glucose measurement in simple solutions, but have encountered limitations when used with blood, employed as implants, or tested in clinically relevant applications. Nevertheless, a few sensors have progressed toward clinical application.

OUR GLUCOSE SENSOR PRINCIPLE

Our sensor approach is based on the immobilized enzymes glucose oxidase and catalase. The enzymes catalyze the following reaction:

$$\text{glucose} + 1/2\ O_2 \rightarrow \text{gluconic acid}$$

The enzymes are immobilized within a gel membrane in contact with the electrochemical oxygen sensor. Excess oxygen not consumed by the enzymatic process is detected by an oxygen sensor and, after comparison with a similar background oxygen sensor without enzymes, produces a differential signal current that is related to glucose concentration.

Enzyme electrode sensors must contact the sample fluid to be assayed and therefore require either sensor implantation or sample extraction (as in the case of fingerstick devices). By employing the enzyme, sensors can have a significant advantage over non-enzymatic sensors of being *specific* for glucose rather than just selective. However, the benefits of enzyme specificity may not be fully realized unless the sensor is properly designed. To achieve the best performance, enzyme electrode sensors must include design features to address enzyme inactivation, biological oxygen variability, mass transfer dependance, and other effects. These issues are engineering challenges that have been addressed in my previous review (*1*).

From the perspective of biocompatibility, sensors can be implanted either in direct contact with blood or with tissues. Biocompatibility in contact with blood depends on the surface properties of the sensor as well flow characteristics at the implant site. Implantation in an arterial site, where the pressure and fluid shear rates are high, poses the threat of blood clotting and is rarely justified. Central venous implantation is considerably safer, and there are examples of other successful implants in this site (e.g., pacemaker leads, catheters).

Implantation of the sensor in a tissue site is safer, but involves other challenges. The sensing objective is to infer blood glucose concentration from the tissue sensor signal, and factors that affect glucose mass transfer from nearby capillaries to the implanted sensor must be taken into account. These factors include: the pattern and extent of perfusion of the local microvasculature, regional perfusion of the implant site, the heterogeneous distribution of substrates within tissues, and the availability of oxygen. There are also substantial differences in performance between short- and long-term implant applications. In the short term, a dominant wound healing response prevails, whereas in the long term, encapsulation may occur. Definitive studies are needed to establish the real-time accuracy of implanted sensors and determine when recalibration is necessary.

This approach has several unique features (*10*). Electrochemical interference and electrode poisoning from endogenous biochemicals are prevented by a pore-free silicone rubber membrane between the electrode and the enzyme layer. This material is permeable to oxygen but completely impermeable to polar molecules that cause electrochemical interference. Appropriate design of the sensor results in sufficient supply of oxygen to the enzyme region to avoid a stoichiometric oxygen deficit (*11*). The differential oxygen measurement system can also readily account for variations in oxygen concentration and local perfusion, which may be particularly important for accurate function of the implant in tissues. Excesses of immobilized glucose oxidase can be incorporated to extend the effective enzyme lifetime of this sensor, a feature not feasible with peroxide- and conductive polymer-based sensors. Co-immobilization of catalase can further prolong the lifetime of glucose oxidase by preventing peroxide-mediated enzyme inactivation, the main cause of reduced enzyme lifetime (*12*). This sensor design also avoids current passage through the body and hydrogen peroxide release into the tissues.

The Long-term Central Venous Sensor

A long-term oxygen-based sensor has been developed as a central venous implant (*10*) (Fig. 2). The sensor functioned with implanted telemetry (*13*) in dogs for >100 days and did not require recalibration during this period (Fig. 3). The central venous site permitted direct exposure of the sensor to blood, which allowed simple verification of the sensor function without mass transfer complications.

These results have lead to several unanticipated conclusions. Although native glucose oxidase is intrinsically unstable, if the sensor is designed appropriately, the apparent catalytic lifetime of the immobilized enzyme can be substantially extended (*14*). Also, the potentiostatic oxygen sensor has been shown to be remarkably stable (*15*) and the oxygen deficit, once thought to be an insurmountable barrier, can be easily overcome by design of the enzyme-containing membrane (*11*). Moreover, the central venous implant site, which is uniquely characterized by slow, steady flow of blood, allows for sufficient long-term biocompatibility with blood.

This arrangement provided an ideal testbed to document the long-term stability and function of the sensor in animals (*10*). In human clinical trials, this system has been reported (*16*) to function continuously for >500 days in humans with <25% change in sensitivity to glucose over that period. This achievement represents a world record for long-term, stable, implanted glucose sensor operation, although there still exist certain hurdles to commercialization.

The Long-term Tissue Glucose Sensor

Notwithstanding the success of the central venous sensor, there is a potential for blood clotting events. Although this potential is be small, it may become significant over many years in individual users. This suggests reservations that may limit clinical acceptance and provides motivation for development of a potentially safer long-term sensor implant in tissues. The successful central venous sensor cannot be simply adopted for use in a safer tissue site, but certain design features of that sensor which promote long-term function, such as immobilized enzyme design, the stable potentiostatic oxygen sensor, and membrane design to eliminate the oxygen deficit, can be incorporated.

The tissue glucose sensor must be designed further to function in the unique environment of tissues. An array of sensors (Fig. 4) from which signals can be averaged is needed to address the heterogeneity of tissues, and there must be signal processing methods to account for variations in microvascular blood flow in tissues.

A systematic approach is required to validate sensor function, based on quantitative experimentation, mass transfer analysis, and accounting for properties of tissues that modulate glucose signals. Several new tools and methods have been developed. A tissue window chamber has been developed that allows direct optical visualization of implanted sensors in rodents, with surrounding tissue and microvasculature, while recording sensor signals (*17*) (Fig. 5). This facilitates determination of the effects of microvascular architecture and perfusion on the sensor signal. A method has been devised for sensor characterization in the absence of mass transfer boundary layers (*18*) that can be carried out before implantation and after explantation to infer stability of the implanted sensor. This allows quantitative assessment of mass transfer resistance within the tissue and the effects of long-term tissue changes. A sensor array having multiple glucose and oxygen sensors has also been developed that shows the range of variation of sensor responses within a given tissue (*17*). This provides a basis for averaging sensor signals for quantitative correlation to blood glucose concentration.

There are opportunities for research on the tissue sensor array. There is a need to understand the effects of physiologic phenomena such as local perfusion, tissue variability, temperature and movement that modulate sensor responses to glucose and affect measurement accuracy. A detailed understanding of these effects and their dynamics is needed for a full description of the glucose sensing mechanism. It must be shown that the sensor array produces a reliable determination of glucose during exercise, sleeping and other daily life conditions.

A complete explanation for the response of every sensor is being sought, whether it is producing "good" or "bad" results, as more can often be learned for sensor improvement from sensors that produce equivocal results than from those that produce highly predictable signals (*20*). As

sensors must be useful for hypoglycemia detection, sensor function must be validated in the hypoglycemic state.

BLOOD GLUCOSE PREDICTION

The ability to monitor blood glucose in real-time has major advantages over present methods based on sample collection that provide only sparse, historical information. There exists, however an additional possibility of using sensor information to *predict* future blood glucose values. It been demonstrated that blood glucose dynamics are not random and that blood glucose values can be predicted using autoregressive moving average (ARMA) methods, at least for the near future, from frequently sampled previous values (*21*) (Fig. 6). Prediction based only on recent blood glucose history is particularly advantageous because there is no need to involve models of glucose and insulin distribution, with their inherent requirements for detailed accounting of glucose loads and vascular insulin availability. This capability may be especially beneficial to children. Glucose prediction can potentially amplify the considerable benefits of continuous glucose sensing, and may represent an even further substantial advance in blood glucose management.

CLOSING THE LOOP

Glucose control is an example of a classical control system. To fully implement this system, there is a need to establish a programmable controller based on continuous glucose sensing, having control laws or algorithms to counter hyper- and hypoglycemic excursions, identify performance targets for optimal insulin administration, and employ insulin pumps. The objective is restore optimal blood glucose control while avoiding over-insulinization by adjusting the program, a goal that may not be possible to achieve with alternative cell- or tissue-based insulin replacement strategies.

Programmable external pumps that deliver insulin to the subcutaneous tissue are now widely used and implanted insulin pumps may soon become similarly available. At present, these devices operate mainly in a pre-programmed or *open-loop* mode, with occasional adjustment of the delivery rate based on fingerstick glucose information. However, experimental studies in humans have been reported utilizing *closed-loop* systems based on implanted central venous sensors and intra-abdominal insulin pumps in which automatic control strategies were employed over periods of several hundred days (*22*). There is a need to expand development of such systems for broad acceptance. Reviews of pump development can be found elsewhere (*23*).

These results demonstrate that an implantable artificial beta cell is potentially feasible, but more effort is required to incorporate a generally acceptable glucose sensor, validate the system extensively, and demonstrate its robust response.

CONCLUSIONS AND OPPORTUNTIES FOR STUDENT INVOLVEMENT

The need for new glucose sensors in diabetes is now greater than ever. Although development of an acceptable, continuous and automatic glucose sensor has proven to be a substantial challenge, progress over the past several decades has defined sensor performance requirements and has focused development efforts on a limited group of promising candidates. The advent of new glucose sensing technologies could facilitate fundamentally new approaches to the therapy of

diabetes. The developments at UCSD provide excellent opportunities for bioengineering students to get involved in research.

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FIGURE CAPTIONS

Figure 1. The Results of the DCCT (*4*). Results show that improved glucose control, measured by a reduction in the fraction of glycosylated hemoglobin, leads to reduced long-term complications of diabetes. Copyright 1993, Massachusetts Medical Society.

Figure 2. Animal prototype long-term central venous glucose sensor with implanted telemetry (*13*). Glucose and oxygen sensors are at the end of the catheters. The telemetry antenna emerges from the top, left. The telemetry body is 2 × 2.5 inches, and is encapsulated in epoxy. This implantable telemetry unit, designed and built by UCSD students, provides a means for reporting all the same measurements from the sensor (i.e., signal currents, electrode voltages, battery status, temperature, etc.) that could be obtained with non-implanted instrumentation. The implant can be reprogrammed to transmit at different rates by passing a magnet in certain sequences. The device is a powerful experimental tool in its own right.

Figure 3. **Response of an implanted intravenous sensor to glucose challenges on day 108 after implantation in a dog (*10*)**. The solid line is the sensor signal and triangles are venous blood glucose assays. Blood glucose excursions with initial rates of 0.28 mM/min were produced by infusions of sterile glucose solutions through an intravenous catheter in a foreleg vein. (Note: 90 mg/dl glucose = 5.0 mM.) Copyright 1990, American Diabetes Association.

Figure 4. Close-up view of tissue glucose and oxygen sensor array (*17*). Sensor array with small (125-µm diameter) independent platinum working electrodes, large (875-µm diameter) common platinum counter electrodes, and a curved common Ag/AgCl reference electrode. The enzyme-containing membrane is not shown. Copyright 2003, American Physiological Society.

Figure 5. An implanted glucose sensor and nearby microvasculature (*2*). Optical image taken in a hamster window chamber. Sensor diameter is 125 µm.

Figure 6. Blood glucose prediction based on recently sampled values (*21*). 10-min prediction in a non-diabetic, average rms error = 0.2 mM. Copyright 1999, American Diabetes Association.

Figure 7. A simple control system for blood glucose. y(out) is the blood glucose concentration, y(sp) is the desired blood glucose, the natural sensor is in the pancreatic beta cell, the plant is the body over which glucose is distributed, and the disturbance is absorption of glucose from the gut via digestion. The control element can be an insulin pump. The control law is an algorithm that directs the pump in response to the difference between measured and target blood glucose.

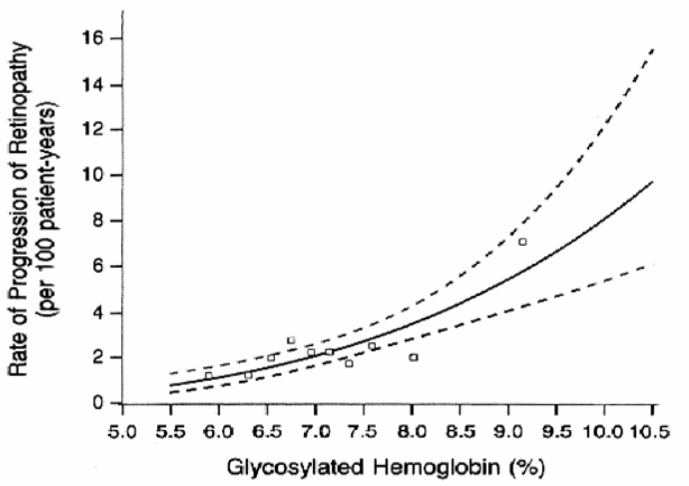
Rate of Progression of Retinopathy
(per 100 patient-years)
16
14
12
10
8
6
4
2
0
5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0 10.5
Glycosylated Hemoglobin (%)

Figure 1.

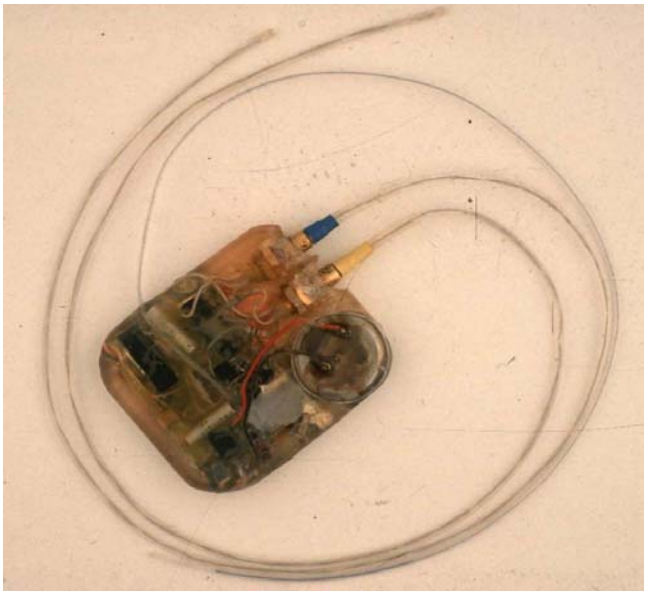

Figure 2.

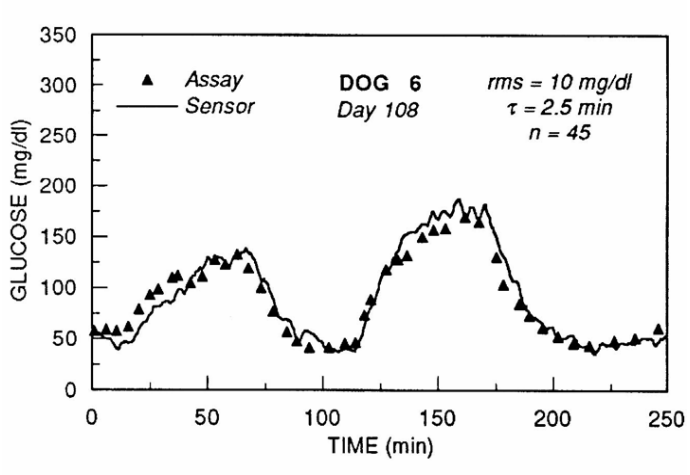
350
300
250
200
150
100
50
0
GLUCOSE (mg/dl)
Assay
Sensor
DOG 6
Day 108
rms = 10 mg/dl
τ = 2.5 min
n = 45
0
50
100
150
200
250
TIME (min)

Figure 3.

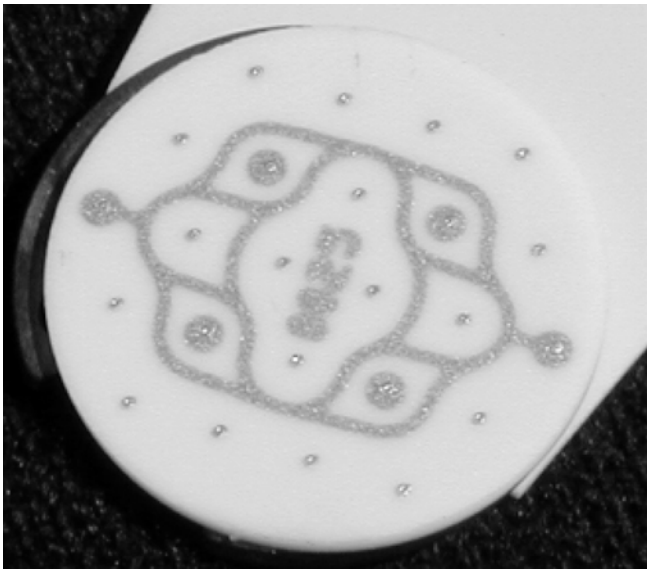

Figure 4.

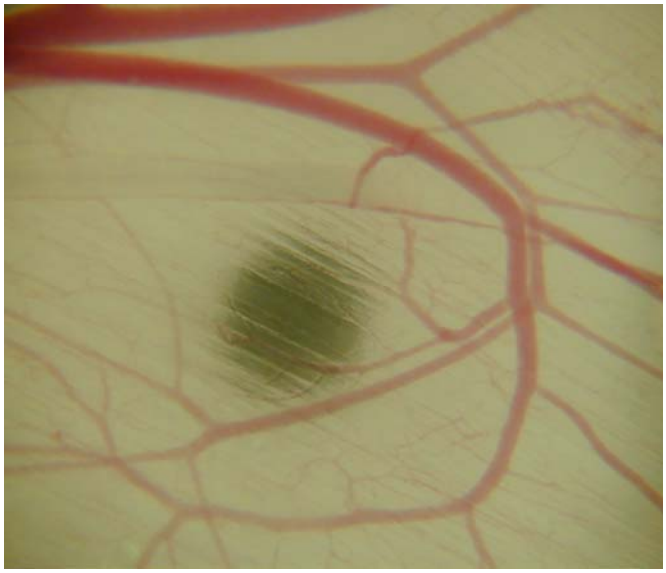

Figure 5.

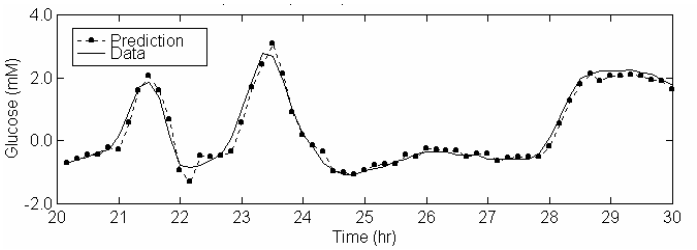
Prediction
Data
Glucose (mM)
Time (hr)
4.0
2.0
0.0
-2.0
20
21
22
23
24
25
26
27
28
29
30

Figure 6.

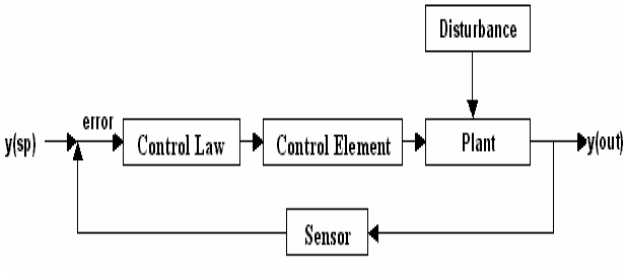
Disturbance
error
y(sp)
Control Law
Control Element
Plant
y(out)
Sensor

Figure 7.