FEASIBILITY OF AN IMPLANTED, CLOSED-LOOP, BLOOD-GLUCOSE CONTROL DEVICE

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Table Of Contents

Abstract:
Data from the Diabetes Control and Complications Trial (DCCT) show that intensive control of blood glucose significantly delays complications of diabetes, such as retinopathy, nephropathy, and neuropathy, compared with conventional therapy consisting of one or two insulin injections per day (2). While much research has gone into developing tighter control mechanisms (including better heuristic models for doctors, better drug delivery devices and more frequent/accurate monitoring systems), the best 'solution' to diabetes would be a completely closed-loop control system that automatically monitors and maintains euglycemia. While other advances may help cognizant and compliant patients achieve stricter blood glucose control, they impose a significant burden on the patient, and preclude successful self-administration by less-apt individuals (young, elderly, mentally-challenged, etc…). This paper is an investigation into the current feasibility of a completely integrated and automated solution. It presents the results of our findings—that there exist technologies that may be integrated to produce a nearly sufficient system—along with a method for mathematically describing and evaluating the performance levels and potentials of different systems. Though our conclusions are not completely new in finding the glucose sensor to be the main deficiency for an integrated control process, our analysis is current, and our evaluation technique should prove useful in the future development of similar devices.

Introduction:
A normal individual's blood glucose level is well-controlled by his/her pancreas. Diabetes is a disease in which the body does not produce or properly use insulin, a hormone that is needed to convert sugar, starches and other food into energy needed for daily life (2). Diabetes is a chronic and potentially disabling disease that represents a major public health and clinical concern (49). Diabetics are at increased risk of developing chronic complications such as heart attacks, strokes, amputations, kidney failure and blindness (49). The majority of the diabetic population can be classified as either type I or type II. Type I, or Insulin-Dependent Diabetes Mellitus (IDDM), accounts for 5-10% of the diabetic population (2) and is characterized by insulin deficiency caused by autoimmune destruction of the ß cells in the pancreatic islets (23). Type II, or Non-Insulin-Dependent diabetes Mellitus (NIDDM), accounts for 90-95% of the diabetic population (2) and is characterized by insulin resistance and impaired insulin secretion (23). Often type 2 diabetes can be controlled through losing weight, improved nutrition and exercise alone (2), but over time, many of these people will develop a dependency for insulin supplements to control their diabetes.

In 1992 it was estimated that 4.5% of the U.S. population had diabetes (49). The health care expenditures for diabetics at the time totaled about $105B, or 14.6% of total U.S. health care expenditures. To exacerbate the impact, it has been suggested that the incidence of undiagnosed diabetics may actually be as high as that of diagnosed diabetics (27). It is clear that with advancement of the disease, the health care expenditures associated with Diabetes are only going to rise. Since a staggering 65% of the health care expenditures for diabetes can be attributed to inpatient care resulting from poor management of the disease and its complications, a significant savings to the health care system could be realized through prevention or effective management of the disease and its complications.

Long-term microvascular and neurological complications are a major cause of morbidity in persons with insulin-dependent diabetes mellitus (IDMM) (18). In 1983, the Diabetes Control and Complications Trials (DCCT) was initiated to compare the effects of intensive and conventional

therapy in IDDM (17). A regime of Intensive therapy for diabetes was designed and compared to a second group using the Conventional therapy methods. The intensive therapy regime was designed to maintain blood glucose levels as close to the nondiabetic range as possible with 3 or more daily insulin injections or treatment with an insulin pump, self-monitoring of blood glucose levels 4 times daily, and monthly outpatient visits with a multidisciplinary diabetes treatment team. The Conventional therapy consisted of 1 or 2 insulin injections per day, daily self-monitoring, and quarterly visits with the diabetes treatment team. A total of 1441 patients were recruited from 1983 through 1989. Ninety-nine percent of the patients completed the study (only 43 dropouts), and more than 95 percent of all scheduled examinations were completed. It was conclusively shown that intensive therapy of patients with IDDM delays the onset and slows the progression of clinically important retinopathy, including vision-threatening lesions, nephropathy, and neuropathy, by a range of 35 to more than 70 percent. The only side effect was that with long-term Intensive therapy, there was an increased risk of severe hypoglycemia. In 1993, the independent data monitoring committee determined that the study results warranted terminating the trial. The DCCT concluded that intensive therapy was successfully carried out, and recommended that *most* patients with IDDM be treated with closely monitored intensive regimens with the goal of maintaining their glycemic status as close to the normal range as safely possible. The DCCT recognized that the time, effort, and costs required for Intensive therapy as carried out in the trials were considerable, and since the resources needed are not widely available, new strategies are needed to adapt methods of intensive treatment for use in the general community at less cost and effort.

A clear drawback to the DCCT was that it had a duration of only10 years and did not allow for the tracking of long-term complications beyond the course of the trials. A follow-up study was initiated by the Diabetes Control and Complications Trial Research Group to develop a simulation model to track lifetime benefits and costs of Intensive therapy as established in the DCCT (19). The purpose of this study was to answer 2 primary questions: If intensive therapy was implemented in all persons with IDDM in the United States who meet demographic and clinical eligibility criteria for enrollment in the DCCT, 1) what would the lifetime benefits and costs of intensive therapy be, and 2) would more costly intensive therapy be preferable to conventional therapy from the perspective of the health care system? The model was developed using the data from the DCCT to extrapolate the long-term complications developed in both the Conventional therapy and the Intensive therapy. The cost-effectiveness analysis included all direct medical costs associated with the disease including those associated with inpatient care, outpatient care, medications, medical equipment, supplies, and laboratory tests. Life-years gained was the primary measure of effectiveness, but several other outcomes were tracked in order to establish the quality-adjusted life-years (QALYs), which is a summary measure used to evaluate both length of life and quality of life. The cumulative lifetime benefits of Conventional and Intensive therapy can also be described as the average number of years a patient will remain free from complications. On average, intensive therapy patients will experience 7.7 additional years of sight, 5.8 additional years free from End Stage Renal Disease (ESRD), and 5.6 additional years free from lower extremity amputation compared with conventional therapy patients (Table 1).

Table 1

Health State	Con. (%)	Int. (%)
Background Retinopathy	98	95
Proliferatvie retinopathy	70	30
Macular edema	56	35
Blindess	34	20
Microalbuminuria	86	64
Albuminuria	46	15
End-stage renal disease	24	7
Neuropathy	57	31
Lower extremity amputation	7	4

Additionally, compared with the Conventional therapy patients, Intensive therapy patients will, on average, gain 15.3 years of life free from any significant microvascular or neurological complication and an associated 5.1 year increase in survival. For the cost effectiveness analysis, with certain assumptions on costs of yearly therapy, it was estimated that the incremental cost per QALY gained was $19,987. This did not account for production losses from lost annual earnings before the age of 65 and for those persons who develop blindness, ESRD, or amputations before the age of 65. If these production losses were taken into account, the incremental cost per QALY gained could be driven well below $2000. In answer to the first question, this study concluded that the lifetime benefits of Intensive therapy markedly exceed the lifetime benefits of conventional therapy, and that the lifetime costs of Intensive therapy (direct medical costs) exceed the lifetime costs of conventional therapy. In answer to the second question, the study concluded that results of the simulation indicate that, under a variety of scenarios, the cost-effectiveness ratio for intensive therapy is well within the range of cost-effectiveness ratios considered to represent a good value ($20,000/QALY or less). But it also recognized that the level of adherence to the DCCT by the patients was very high and that adherence to intensive therapy in the general population with IDDM may be less than that achieved in the DCCT and the long-term benefits may be less. This repeats what the DCCT concluded in that new technologies are needed to help the patient and physician maintain and control Intensive therapy.

Objective:

The work outlined in this paper is towards creating a device which automatically regulates blood glucose levels through closed-loop feedback control. Such a device might eventually be implanted within a patient, but our work will be more preliminary. This paper will outline the materials and methods, and to develop a set of specifications for such a device that would allow it to successfully regulate patient blood glucose. There are four basic blocks in the proposed implementation: Sensors, actuator, software management, and an adaptive algorithm. The central “engine” of this approach is an adaptive filter with multiple inputs and multiple outputs. The ability of this block to function requires sufficient sensor capability, actuator effectiveness, and higher-level software management.

Current Technology:

There are several glycemic control devices available or in development which each display some subset of the traits our device will possess. Among them are fully-implanted insulin delivery systems, Biostator glucose clamps, and insulin pumps (Mini-Med, etc…). No system in current development integrates automated delivery, a sensor suite, and an adaptive algorithm for a complete and robust

blood-glucose control solution. Indeed, the only readily-available, technology-enhanced treatment method is the insulin pump. "The ideal implantable insulin pump (IIP) would be an invisible, durable subcutaneous abdominal device, which in its projected 3-year lifespan would replace three or more insulin injections per day with an initial surgical implantation and clinic visits every 1 or 2 months to refill the insulin reservoir." (33) Patients treated with IIP need to self-monitor their blood glucose regularly to control the dosage of insulin infused. Even if a glucose sensor and control system are added to create an artificial pancreas, regular clinical visits and patient diligence in monitoring glucose control and pump function will be required.

Sensors:

Accurate measurement of blood glucose is essential in the diagnosis and long term management of diabetes (62). The development of a robust sensor with good reliability, sensitivity, repeatability and long life cycle is one of the most critical components in the development of a fully automated "artificial pancreas." (33, 60)

Current blood glucose sensors can be divided into two approaches: electroenzymatic and optical (62). The electroenzymatic sensors, based on polarographic principles, utilize the phenomenon of glucose oxidation with a glucose oxidase enzyme. This chemical reaction can be measured amperometrically or potentiometrically. In the primary optical approach, the attenuated total reflection and infrared absorption spectroscopy is used to measure blood glucose levels. A second optical approach is the fluorescence-based affinity sensor. This uses the immobilized competitive binding of the glucose metabolite and a fluorescein-labeled indicator with receptor sites specific for the measured metabolite and the labeled ligand. A fiber-optic catheter is used to detect changes in fluorescent light intensity, which is related to the concentration of glucose. The majority of the literature available detailed development, testing and analysis of blood-glucose measurement using these types of sensors (40, 24, 60, 47, 33, 58). A patent search run using "Blood Glucose Sensor" as the key words (see appendix A) yielded the same results.

As a result of the findings of these searches, it was found that the type of blood glucose sensors available or in development can be divided into three general categories, but all use the electroenzymatic or optical approach. The most widely used today fall into the "invasive" category. These types of sensor involve the puncture or incision of the skin or insertion of an instrument or foreign material into the body. The next category is really a sub-group of the invasive category titles "implants." The "non-invasive" category is all the sensors that do not fall into the previous two categories. The reason why implants are broken out as a separate group is because in the ideal automated system, the sensor would be part of an integrated sensor/delivery system implanted into the body. Therefore, it is of particular interest to examine the implants as a separate group. Within each of the categories there are groups of sensors that use the same type of technologies in different implementations. Rather than cataloging every permutation, subgroups are identified along with possible implementation concepts.

The majority of the sensors used in the invasive category of applications use an electrode/oxidation method to determine the blood glucose level (25). The sensor uses a platinum electrode and a silver electrode to form part of an electric circuit in which hydrogen peroxide is electrolyzed. The hydrogen peroxide is produced as a result of the oxidation of glucose on a glucose oxidase membrane, and the current through the circuit provides a measure of the hydrogen peroxide concentration, and hence the

glucose concentration, in the vicinity of the sensor. There are two general variations of the electrode based invasive sensors. They are either designed as a needle electrode or as an ion-sensitive field-effect transistor (ISFET) (62). In the needle application, the sensor is in the form of a composite electrode comprising both the platinum and silver electrodes, a glucose oxidase membrane layer, a polyurethane film which is permeable to glucose, oxygen and hydrogen peroxide, and a steel, glass, and plastics supporting structure (26). The composite electrode is attached to the forward end of a catheter that is inserted into a blood vessel or beneath the skin of the subject. In the ISFET, the sensor comprises an electrically insulating substrate; an electrode system formed on the substrate that includes a working electrode and a counter electrode; and a reaction layer formed on the substrate or above the substrate with a space there-between (65). The reaction layer includes a pyranose-oxidizing enzyme. There are many advantages to the ISFET over the electrode sensor. They can be cheaply mass produced as a microminiature sensor with standard Integrated Circuit (IC) micro-fabrication processes. Because of IC capabilities, multiple measurements of glucose or other analytes could be measured simultaneously by including multiple sensors on the same IC. All signal processing can be accomplished on-board the chip, and the entire package would not be more than a few square millimeters in size. Failure of a single sensor is not critical and furthermore, due to the extremely small size of the IC, subcutaneous implantation of the sensor could be accomplished as an outpatient procedure with minor discomfort to the patient. The key challenge to implementation of the ISFET is that satisfactory encapsulation of the ISFET is required in order to protect its electric characteristics, which deteriorate as a result of water vapor entering from the environment (62).

Non-invasive systems most often favor the use of an optically based measurement. The sensor directs infrared light of two or more discrete wavelengths or within a continuous band into body tissue, either transmissively or reflectively (25). A microprocessor then calculates the glucose concentration from a series of such absorbance measurements. If the body tissue is well vascularized, such as a fingertip or ear lobe, then the resulting measurement of glucose approximates the blood glucose concentration. One method of note in this category which does not use an optical measurement, is the measurement of blood analyte concentration by applying a stimulus to an endogenous tissue with a stimulator, detecting a response to the stimulus with a detector, and correlating the detected response of the endogenous tissue to an analyte concentration with a correlator (25). This device relies on blood glucose dependent alterations in the electrophysiological function of peripheral nerves, such as the Median nerve. In essence, this device employs a peripheral nerve as an endogenous glucose sensor. This requires the electrical stimulation of the nerve from an external source.

In the implant sensors category, there are two classes of sensors: electrode method and the optical method. Most of the work towards either one of these systems—when used as an implant—deal with how to take accurate, consistent measurements with high reliability and repeatability and with a long life cycle. While no data point was identified for how long a sensor should remain implanted and function without failure, it is clear that longer is better, and that the degree of difficulty with implantation would be a determining factor in how long it must last. If the patient can replace the sensor without the supervision of a physician and with minor discomfort or difficulty, then the sensor would not need as long a lifecycle. On the other hand, if the implantation procedure requires in-patient thoracic surgery, then the sensor needs a considerably longer lifecycle (3-10 years).

One of the patents (55) deals strictly with sensor surface architecture in order to promote the longevity of any implanted sensor without buildup of a Foreign Body Capsule as part of the body's response to

the introduction of a foreign material. To whatever extent possible, the contribution of an implant's geometry (as contrasted with its composition) to the host response must be analyzed and accounted for in the successful deployment of any implant (64). The primary goal of this technology is to encourage the formation of vasculature in the sensor interface area to allow the accurate measurement of glucose levels by either the electrode method or the optical method. Six sensors were tested with this implantation method and charted an average lifetime of 84 days with one of the sensors lasting less than 10 days and another yielding optimal data to 150 days.

Unfortunately, there is not a good sensor available for long-duration implantation that is critical to an integrated, implantable artificial pancreas. Certainly there are promising technologies in development, but many issues have yet to be resolved. Because of this, a recommendation for one method over another cannot be made at this time, though the ISFET seems to have the most advantages of allowing a powerful micro-miniature package with an array of sensors and on-board signal processing while being cheap to mass-produce. However, recommendations for sensor characteristics are presented in the following table. These are made with the goal of helping to identify what needs to be improved in order to make the sensor an effective component of the artificial pancreas. Some data from the literature exists to back the specifications, but many require additional investigation.

Implantable Blood Glucose Sensor Specifications

Parameter	Specification	Comments
Biocompatability	Must survive long-duration implantation in chemically harsh environment of human body.	(Thevenot 1982)
Sensitivity	2-5% of actual glucose level	In vitro glucose determination (Thevenot 1982)
Range	20 to 200 mg/dl (1 to 100 mM)	Vary linearly with glucose level in the hyper- and hypoglycemia range (Thevenot 1982)
Temperature dependence	2-4%/°C (max)	(Thevenot 1982)
Drift	Zero *or* easy calibration	(Thevenot 1982)
Calibration	in vivo	Calibrating in vivo is essential since the sensitivity in vivo is different from in vitro (Poitout 1993)
Life cycle	1 year	Dependent upon ease of implantation and other complicating factors in sensor design and biological rejection of a foreign body which degrades sensor performance. (Gough 1995)
Response time	30s or less	(Oberhardt 1982)
Sampling rate	every 10s averaged over 1-min intervals	(Oberhardt 1982)
Miniaturization	As low invasive as possible	(Oberhardt 1982)
Power	Low power and rechargeable	(Oberhardt 1982)

Actuators: the delivery device

Devices that administer drugs to patients typically fall into one of two categories: invasive or noninvasive to the body. These are very broad categories, however, because the delivery system is often quite specific to the therapeutic agent being delivered. The size, composition, stability, and pharmacokinetics of a drug may further limit the route or method of delivery to say, an invasive infusion pump that delivers insulin subcutaneously rather than transdermally. Therefore we will discuss the different specific routes of delivery, such as oral, transdermal, and pulmonary delivery, as well as look at controlled release systems.

Perhaps the most preferable way to deliver a drug is still via the mouth. This is true for a few reasons. Oral delivery does not require sterile drug formulations, whereas direct delivery to the bloodstream would require sterility of the drug. Also, most other routes of delivery fall into the invasive category and are not as likely to gain patient compliance because of ease of use and potential pain to the patient. It is also cheap. However, the biggest problem with oral delivery is the digestive tract, which has mechanisms to degrade protein therapeutics. Pepsin, trypsin, chymotrypsin, and other proteases and peptidases as well as the acidic pH environment all foil attempts of delivery via the gastrointestinal tract. The intestinal lining is also quite impermeable to high molecular weight drugs. This is why other routes of delivery have been sought.

This is not to say that other methods of delivery are inherently poor compared to oral methods. In fact, the ideal delivery system would deliver necessary amounts of drug directly to the target tissue, leaving the rest of the body alone. This is not the case with oral formulations, which typically saturate the entire body with the drug in order to achieve the necessary quantity of drug near the target. This is the cause of many undesirable side effects.

Oral Delivery

Drugs formulated for oral delivery take the form of compressed tablets, gelatin capsules, and liquids. Oral delivery has been reserved for small molecules rather than peptides because of the problems alluded to earlier. However, efforts at overcoming the lumenal proteases, such as trypsin, chymotrypsin, carboxypeptidases, and brush border aminopeptidases are not unheard of. This typically involves either a structural change in the drug, inhibition of the lumenal proteases, or protection of the drug (36 p218). A structural change would involve modifying the ends of the polypeptide, either by acylation or alkylation, or changing the conformation, chirality or the amino acids themselves. Protease inhibitors can also help the drug survive the protease attack. For example, aprotinin, a soybean trypsin inhibitor, has been shown to increase oral insulin absorption (36 p220). Sheltering the peptide drug from degradation is another approach. For example, multiple emulsions and pH sensitive polymeric devices that degrade at the right pH ensure delivery to the right part of the gastrointestinal tract at the right time.

These approaches have been used with limited success, and for the most part, protein therapeutics are just not amenable to oral delivery. Even if degradation can be avoided, the uptake by the intestinal wall, or lack thereof, still presents a problem. For example, at their best, only 1% of drugs such as lysine, vasopressin, and insulin ever get absorbed in their native forms through the intestinal lining (36 p220).

Transdermal Delivery

The skin is probably one of the most accessible organs of the human body and is an attractive target for noninvasive drug delivery. It receives roughly 1/3 of the body's blood supply and lacks proteolytic enzymes (37). It also offers the possibility of circumventing gastrointestinal degradation and first-pass elimination by the liver.

The skin has been used traditionally for topical application of dermatological drugs but transdermal delivery systems are available. For example, a transdermal patch that releases scopolamine for motion sickness was one of the first products developed. There have also been transdermal products on the market for treating hypertension, postmenopausal syndromes, and nicotine addiction.

One mechanism for transdermal delivery is iontophoresis, which uses an electric current to induce migration of charged molecules. Electrodes are attached to the skin and a current passed through them. The drug reservoir electrode delivers the drug, which permeates the dermis and finds its way into the capillary network. (See Figure 1) It is hypothesized that the electric potential alters skin permeability and enhances absorption of the drug by opening pores in the stratum corneum, the outer most part of the epidermis. It does this by rearranging the alpha helices in keratin and encouraging flow of ions to counter dipole formation. When a direct current is applied, the stratum corneum becomes polarized, which tends to act against the applied electrical field. To overcome this, iontophoresis is best done in a pulsed mode so that the skin has a chance to recover by discharging the current during the off periods.

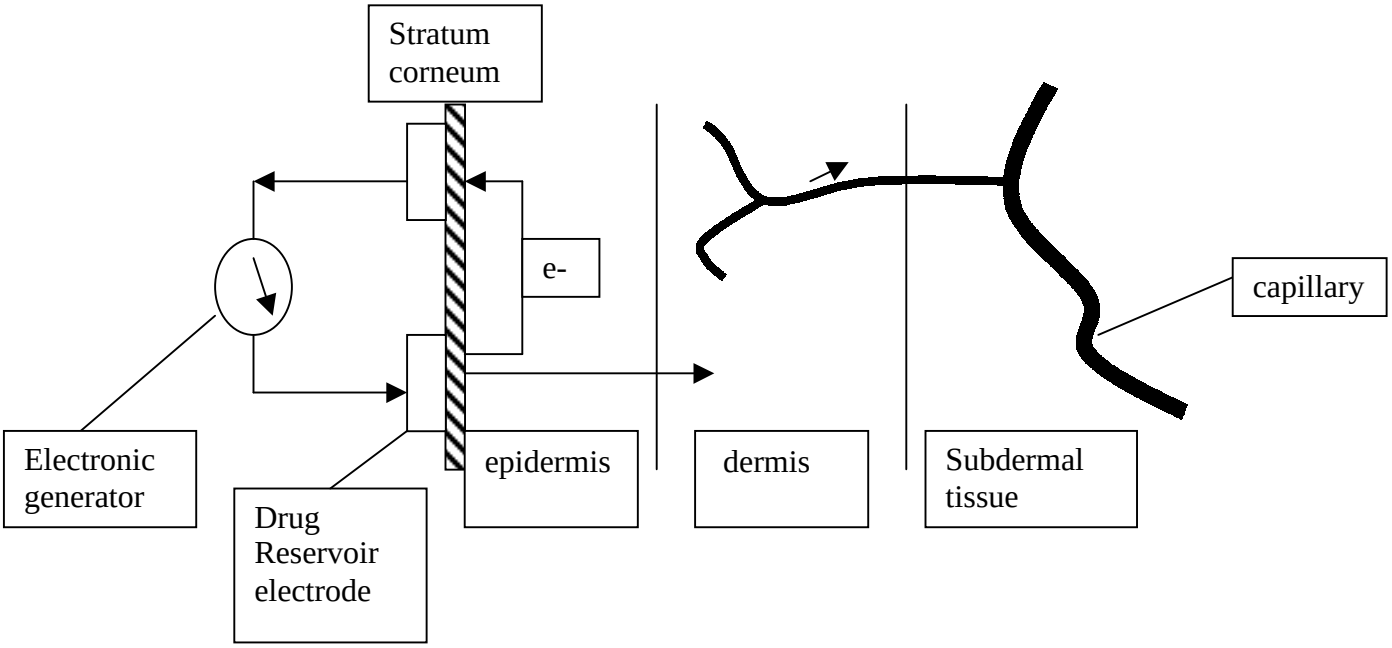


Fig.1

In diabetic hairless rats, a maximum enhancement factor of 37 for increased permeability to insulin was achieved. The enhancement factor was defined as the ratio of skin permeation rate with iontophoresis to that without a current of 4 mA for 80 minutes (56).

Similarly, low-frequency ultrasound waves in the 20 kHz range can also shuttle insulin past the skin in a process called sonophoresis (43).

These technologies are not without their disadvantages, however. Iontophoresis has been found to have a maximum delivery dose of 1 mg/day while ultrasound transdermal delivery is limited to 30 μm particles (13).

Pulmonary Delivery

Another noninvasive route is via inhalation. Despite the amount of new research into inhalable drugs, inhalation therapy is not new. Aromatherapy has been practiced for many millenia, although often without scientific basis. However, the fact that the lung has a surface area the size of a tennis court (~75 m^2) capable of absorption into the bloodstream is very tantalizing for those in the drug delivery field. The respiratory tract also has high permeability and pharmacokinetics that resemble intravenous delivery (61).

The walls of the lung are very thin (about 0.1 to 1 μm) at the fine structures at the end of the airway called the alveoli. When a drug is inhaled, it can reach the entire surface in a few seconds and be absorbed either by diffusion or pinocytosis. However, several factors affect the bioavailability of the drug, that is, how much of it exactly reaches systemic circulation. These include the molecular weight of the drug and its ability to break past the mucociliary epithelia cells and other defense mechanisms.

It has been found that low molecular weight compounds dissolve more readily than larger molecules in the lung. This is in agreement with studies which show a good correlation between the size and the time required for maximum blood plasma concentration, T_{max}. (See table 2)

Table 2

Peptide Compounds	Molecular Weight (Daltons)	T_{max}, hr
Calcitonin	4318	0.25
Insulin	5700	0.25
Interferon-alpha (glycos.)	19000	6.0
Albumin	68000	20.0

Because smaller drugs less than 20 kDa reach the alveoli more easily and are absorbed faster, they tend to have pharmacokinetics like that of intravenous injection, whereas larger drugs tend to have a slow sustained release into the bloodstream.

One barrier in the respiratory tract is the mucus-covered ciliated epithelia which beat at around 1000 to 1500 beats per minute to remove foreign substances (1 p93). This is significant because any drug particles that stop short of the alveoli can become trapped by the mucus and removed from the body. It has been found that aerosolized drugs that are near spherical and monodispersed in the respirable range of 3 μm tend to have a better chance at being deposited deep into the alveoli.

Another barrier is the immune system. Alveolar macrophages engulf any foreign particles in the lung that it can. There are also antibody-mediated immunological responses which may lead to the destruction of the drug before it ever reaches the bloodstream.

The alveoli also contain enzymes such as chymotrypsin and other endopeptidases which can further degrade a peptide drug.

These obstacles, in conjunction with factors such as drug loss in the device, allow a drug deposition of only about 20 to 50% of the original dose into the peripheral lung (1 p96).

The devices used for inhalation vary, but the first ones on the market were metered-dose inhalation (MDI) devices. Traditionally, these incorporated drugs in a mixture of propellant such as trichlorofluoromethane and dichlorodifluoromethane. Trichlorofluoromethane is inert and allows regulation within 35 and 75 psig while dichlorofluoromethane is actually used to aerosolize the drug. However, with the banning of chlorofluorocarbons in 1996 to protect the ozone, other devices have come forward. For example, piezoelectric devices which produce a spray from a single drop of solution have been tried. Also, dry powder inhalers (DPI) deliver predetermined doses of dry powdered drug as a fine mist. These devices are self-contained and usually have a metering system. Sometimes, in liquid preparations, surfactants such as sorbitan trioleate may be added to stabilize the drug as well as lubricate the valve.

Recently, companies such as Alkermes AIR and Inhale have been trying to get devices which deliver inhalable insulin approved by the FDA. These devices atomize powdered insulin inside a chamber and allow the patient to breathe in the aerosol directly from the chamber. The chamber can hold 200 mL of air concentrated with insulin, which the patient inhales from. This device is in phase III clinical trial. Dura Pharmaceuticals uses a similar device which it is developing in conjunction with Eli Lilly (30).

Although there are advantages with pulmonary delivery, such as its noninvasiveness, a key problem is its low bioavailability, which, for example, is around 20% for inhalable insulin (14). This occurs for a number of reasons, among them device inefficiency, drug incompatibility, and the pulmonary barriers mentioned earlier. However, the outlook on inhalable drugs is actually fairly promising.

Controlled Release

Aside from route specific delivery devices, there are also devices which strive to control the delivery of the drug as a function of time. One example, which is still in use today, is the insulin pump. Insulin is dispensed from glass or plastic cartridges that need to be refilled with insulin every few days. The unit is typically the size of a pager and capable of holding 3 milliter or about 300 units of insulin. These pumps automatically give patients a basal rate of insulin through a catheter below the stomach. They also allow patients to artificially bolus, or spike, their insulin levels before meals.

Other controlled release technologies tend not to be as bulky as the infusion pump. One example is the depot system for drug delivery. Depot devices are made of biodegradeable polymers, liposomes, permeable polymers, and microspheres, to name a few. They are typically fashioned in shapes that favor a zero-order release, that is, sustained release independent of the concentration of the drug. In these systems the polymeric matrix can be made of starch, collagen, hydrogels, or polyanhydrides, etc. They are safe and biodegradeable. For example, a common polymer used in these applications is polyester of lactic acid and its copolymer with glycolic acid, which degrade into lactic and glycolic acids through ester hydrolysis. These byproducts are natural human metabolic compounds so they pose no harm.

Depot systems slowly release the drug encapsulated within it as it slowly degrades, creating pores which increase drug diffusion. There are also considerations for the kind of degradation. Some polymers erode from the surface while others break off in pieces. For example, Poly(D,L-lactide-coglycolide) tends to hydrate and erode in bulk (14). In contrast, the polymer used in Gliadel, poly[1,3-bis(carb-oxyphenoxy)propane-co-sebacic acid]), tends to erode more steadily from the surface (32). Gliadel was used to deliver carmustine, a drug used to stop brain cancer cells from dividing, locally through implantation in the vicinity of the tumor after surgery.

In these polymeric systems, the drug has to be embedded in the matrix prior to delivery. This usually involves some type of microencapsulation procedure such as the double emulsion method, in which the protein drug is homogenized with the polymer, emulsified in water, and then diluted and dried to form microspheres containing the drug.

There are also other methods of controlling release. An example is through osmosis. In osmotically driven devices, a membrane separates the drug from another compartment that contains an osmotic driving agent such as sodium chloride that pulls in water when placed in an aqueous environment. (See Figure 2) The increased pressure on the membrane slowly pushes the drug out through a small aperture. This type of system has the advantage of uniform controlled release regardless of the drug's physicochemical properties. However, the drug streams out as highly concentrated material, and this may be toxic in some cases.

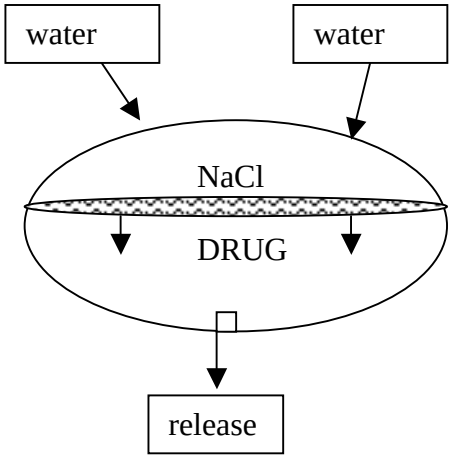
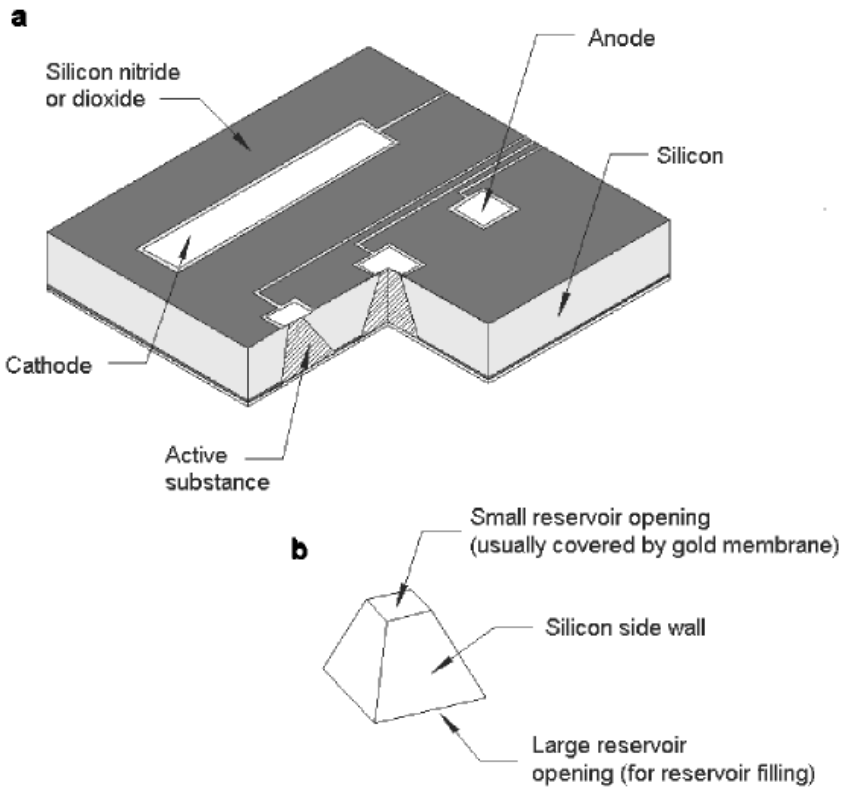


Fig. 2

Another example is the use of microchip technology to deliver drugs. One group has constructed a 1.7 cm silicon square chip with a height of 0.31 mm capable of accommodating 34 drug reservoirs (51). (See Figure 3) Each of the drug reservoirs is filled by microinjection or inkjet printing methods, capped and protected by a 0.3 μm gold layer that dissolves when 1 volt is applied to it in the presence of chloride ions. The dissolution of the gold cap releases the drug in the reservoir. The group has demonstrated that pulsatile release from each individual reservoir is possible. This gives more flexibility in terms of delivery, especially for drugs such as insulin. However, each of the reservoirs

may not contain enough drug for sustained use. For example, insulin, which is needed in the gram level, may not work very well in such a system. Nevertheless, the microchip delivery technology is a great step forward and may be applicable for delivery of small antidiabetic drugs such as sulfonylureas.



Source: (15)

Fig. 3

Which actuator then?

Although there exist many drug delivery options for glycemic control, many of the ones referenced earlier are in early stages of development. Thus, we will make use of what's currently available at the moment. We envision initially using an external infusion pump actuator similar to the ones manufactured by MiniMed (508) and Disetronic (V100) (42). These devices are relatively light (~100 grams) and capable of incremental delivery of 0.1 U of insulin with a +/- 2% error rate. They are also designed to be water resistant. However, their batteries only lasts a few months. The infusion pump in the integrated system would have to last at least for one year. Ultimately, our device would consist of at least two of these actuators delivering active and counteractive agents that will keep patient blood glucose levels within a desirable range. One reservoir would deliver a fast acting insulin such as Lispro while the other would deliver glucose and/or glucagons to counter hypoglycemia. (See Figure 4) We would need two syringe pumps to avoid cross-contamination of drug reservoirs. Although we will initially use syringe pumps, we will switch to other more sophisticated actuators as they become available and our system becomes more robust and tested.

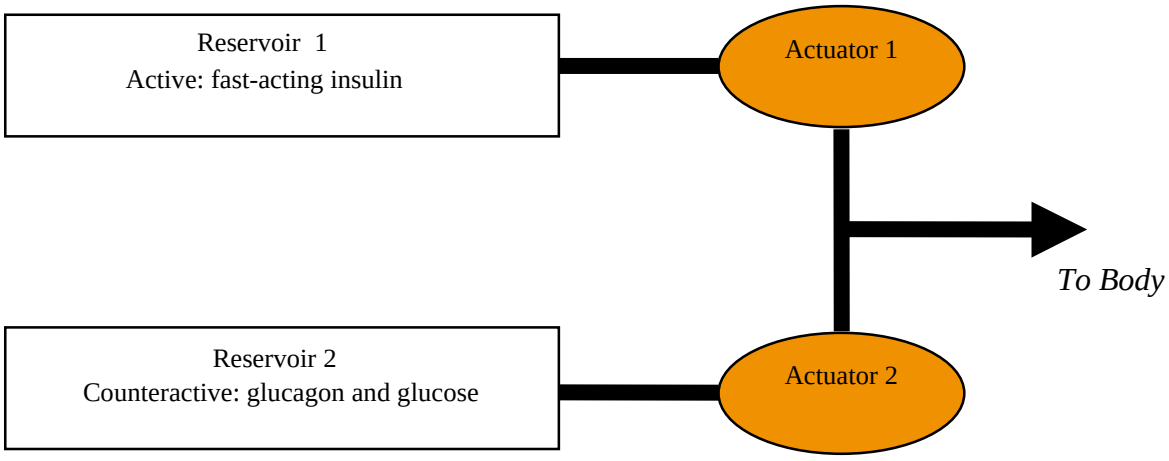


Fig. 4

Management Software:
To achieve a closed feedback loop, a clinically applicable implantable artificial pancreas requires miniaturization and coordination of three components: an actuator for drug-delivery, a sensor suite for blood glucose monitoring, and a control system to properly determine and meet treatment needs. The ultimate goals of fully automatic glucose control by an artificial pancreas include prevention or delay of chronic complications of diabetes, lowered risk of hypoglycemia, and less patient inconvenience and discomfort than with multiple daily glucose self-tests and insulin injection. 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. 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 (33). It is currently considered that the sensors are really the rate-limiting step to a working artificial pancreas (16).

Implanting a device to regulate blood glucose requires great reliance on, and confidence in, technology. The management system must be able to sample, filter, and interpret both the glucose sensor data and the output of the control algorithm; compare the reading with allowable levels and historical data profiles; predict and correct, if necessary, dangerous trends; and accurately calculate feedback to the control algorithm to achieve an output of just enough insulin to maintain normoglycemia. This process must operate correctly all of the time, because errors could lead to severe hypo- or hyperglycemia.

In anticipation of the development of a glucose sensor to complete the artificial pancreas, investigators have prepared control algorithms with which to operate the required feedback loop (9, 35). The systems do not require much computing power relative to that presently available. A 1993 study used an Intel processor at 5 MHz, compared with the 200-MHz processors now carried by most electronics stores (9).

The control system must be sophisticated enough to compensate for variation in all measured parameters. For example, glucose sensor readings will include random error and will drift over time. The control system must be able to decide whether to accept or ignore an extreme sensor reading. This is important because the sensor reading is used by the control algorithm not only to determine the amount of insulin infused, but to recalibrate continuously the basic equations establishing how much insulin is required to reduce blood glucose by a given amount. This insulin dose-response relationship varies by body weight and metabolic function, and must be constantly recomputed using the entire sensor and actuator data history. The system must also be programmed to recognize sensor malfunction, when it must stop the recalibrating in the control algorithm, revert to a baseline profile, and sound a warning. (33)

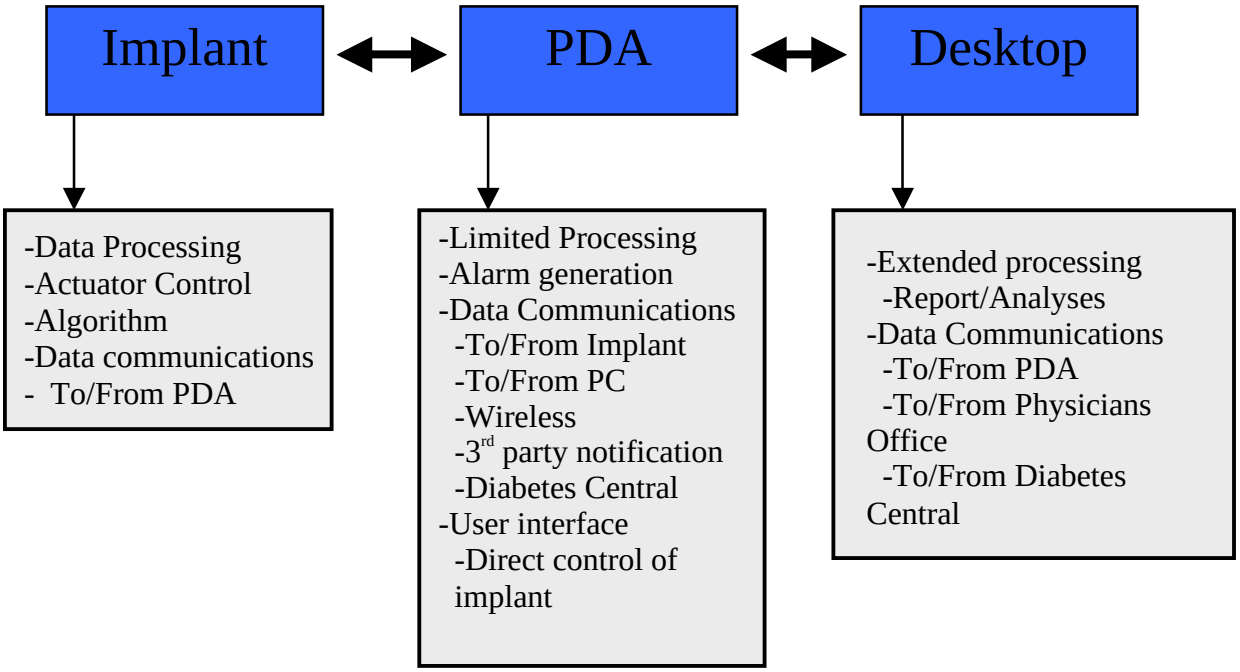
At the other side of the loop, the rate of insulin infusion ordered by the control system may not represent the actual amount of insulin delivered into the body (usually as a result of catheter obstruction [48].) The control system must be able to recognize obstruction. This could be done indirectly by evaluating sudden increase in the delivery rate or pressure being ordered from the pump, or directly by use of a flow sensor at the tip of the catheter. It must also alert the patient or a third party.

The control system must be reliable enough not to respond to random errors in sensor readings and yet flexible enough to respond quickly to substantial insulin needs, such as after a large meal, without overreacting and producing hypoglycemia (47). Uncertainty in sensor measurements and insulin absorption produces a risk of instability in the control system. Previous attempts at computerized control systems have utilized complex mathematical treatments such as H-infinity theory for control algorithm design (35). One control strategy involves a clinician-determined weight factor Q that can be varied on a range between toleration of moderate hyperglycemia, to strict control at the risk of hypoglycemia (33). In our proposal this risk is addressed both by the control algorithm itself and by the analysis and feedback aspects of the management system (which might include physician input). It is generally recognized that development of a stable control system is feasible with current mathematical and computing tools (33).

One challenge for any control system is the initial calibration of the artificial pancreas. For a glucose sensor, the device produces an electric current that relates uniquely to glucose concentration, but the equation relating the two parameters varies by individual and sensor. To determine the value of parameters for this equation, most systems require sensor voltage and blood glucose to be measured independently and simultaneously two or more times (33). Typically, a patient might have fasting blood glucose and sensor voltage measured, then have the measurements repeated after oral glucose administration, and have results entered into a computer system. As an illustration of this method, Poitout et al. (47) employed a real-time sensor calibration procedure in human subjects that resulted in 95% of sensor estimations differing from the measured plasma glucose by <1.72 mmol/l in a representative experiment. The problems of sensor drift over time in vivo would necessitate programming the artificial pancreas to recalibrate itself automatically and continuously after the original basal parameters are set. In our proposal this initial calibration is used for the training phase of the control algorithm, and the re-calibration is performed continuously as part of its operation. The management software, while handling all of the communication and severely nonlinear decisions (such as alarm), also tracks the input and output in order to forecast trends and spot anomalies.

Jaremko and Rorstad state that, "[T]he control system for an artificial pancreas must be carefully designed for stability in the face of variable sensor readings and a changeable insulin dose-response relationship, and it must be painstakingly calibrated on initial implantation. However, these tasks should be feasible for modern computers and mathematical modeling techniques (33)." In view of (9), (35), and (47) it is clear that technology for diabetes management and control software has been feasible at least since 1993; progress in miniaturization and advances in the computer industry in general have made available computing power smaller, faster, and more powerful. It should be noted that the software envisioned in (9) and (35) was envisioned as being onboard an implanted device; our proposal needs only the control algorithm software to be onboard the implanted device. This gives us the flexibility of both a more sophisticated management system and the ability to update easily in a Palm-Pilot-sized external device. Diabetes management software (open loop) already exists which runs on a hand-held device. For example, Diabetes Tracker (pdasoftnet), and GlucoPilot (SoftCare Clinical Informatics) are both for Palm Pilot. In addition to these tracking, graphing, and database functions, software exists which uses the kind of trend-recognition and forecasting applications we envision as valuable applications for study and safety in our management system. For example, Wall Street Financial Assistant (Beiks LLC) contains a database tool, and Documents to Go (DataViz, Inc.) contains a forecasting tool. TinySheet (iambic software), which imitates Excel could have a forecasting tool built in (Sam Savage, author of What's Best!, an Excel add-in with forecasting capability.) Current hand-held devices, such as Palm Pilot, already have more computing power than will be needed by our system. Current software for these devices already have the kind of applications our management system will require. It is clear that a software management system such as that we envision could be written, tailored specifically for the specific needs of glucose sensor and insulin delivery monitoring, and able to be mounted in a small hand-held-size or wearable device. In addition to these capabilities, it is recommended that commercially available technologies be integrated into the system to increase the usability and versatility of the device. Wireless communications to send data directly to a computer, a "Diabetes Central" processing center, third party paging notification in the event of an emergency or for patients that are either too young, mentally incapable, aged, or otherwise physically incapable of self-management, and direct communication to a personal physician are all existing technologies which could easily be implemented in the overall architecture. The following diagram outlines the relationship between the various management software and the hardware.

Relationship Between Management Software and Hardware Components



Introduction to Prior Art in Control Systems Analysis/Application to Blood Glucose In Diabetes Patients

Control:

The study of controls is the study of the dynamic interactions between systems, or blocks within a system, with the goal of understanding how to make that system behave within given specifications. A simple example of controls (to think about, but not to implement) is determining how to keep an airplane steady, and at a specified altitude, during flight. Typically, as in the airplane example, the controlling entity (maybe the pilot, maybe the autopilot system) will have some way to measure, or sense, system conditions. Also, to be effective, the controller requires actuators—things which perform actions on the system—to affect the system state. Figure 5 shows an abstract diagram of a control system.

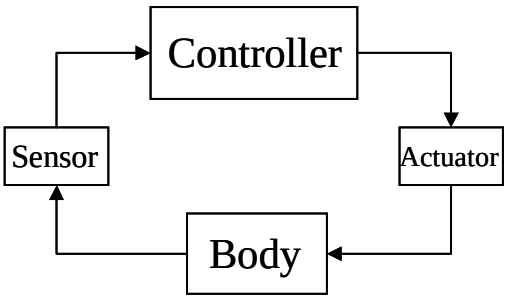


Figure 5: General control block diagram. Complete feedback loop.

The most prevalent feature of most control systems is that they form a loop. It is because of this completed loop (often called the 'feedback loop,' though there are also 'feedforward' paths) that control algorithms work at all. Indeed, a pilot without sufficient knowledge of his or her plane's state (speed, altitude, pitch, etc…) could not be expected to fly very well. If we were to blind such a pilot, we would be "opening the loop," and hampering the control of the plane.

The body's method of regulating diabetes is a highly integrated control system involving a complex suite of sensors and actuators at several levels from molecular and cellular through the endocrine organ system. Patients who suffer from diabetes have trouble with some part of this glycemic control system, to the effect that their blood glucose levels are poorly controlled. They require intervention to aid in the control effort. By attacking this as a 'controls' problem, an engineering solution might be such an intervention, and what follows is a review of previous efforts that take this tack. Because the closed loop is so central to control theory, these prior methods are organized by the extent to which their loop is closed. Further sub-division separates those control methods that change over time (adaptive) from those which do not (static, or non-adaptive).

Partially-closed-loop Control:
Current clinical approaches are best characterized as partially-closed-loop, heuristic, adaptive control. They are adaptive because patients will typically receive check-ups from their doctors in order to alter treatment regimens over time. The control loop is only partially-closed for two reasons (see 65). The first is because of the removal between the adaptation algorithm (doctor) and the imperfect data (patient blood-glucose measurements). Both inaccuracy of data and poor communication of that data impact the sensor effectiveness. The second 'loop-opener' is patient inability or unwillingness to properly actuate their treatments (insulin, exercise, etc…). The ways to tighten the control loop in the face of these troubles are three: better education of patients, better monitoring, and development of better heuristics to assist dosing decisions. Better education and monitoring are clear goals that are best discussed elsewhere. Here we focus on the development of the heuristics.

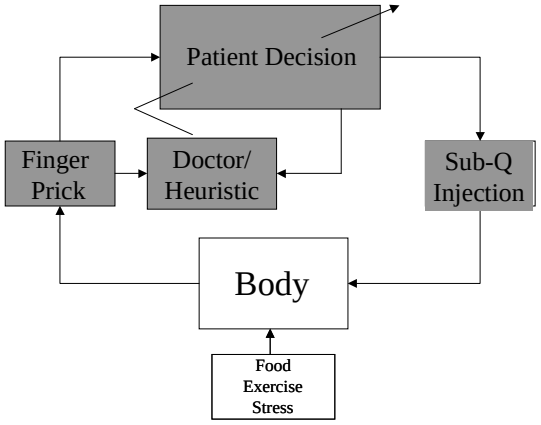


Figure 6: Clinical control diagram. Heuristic, adaptive, partially-closed-loop.
Grey blocks represent loop defects.

There has been an enormous amount of work (by every clinician treating diabetes, everywhere) in developing heuristic methods for treating diabetes, and these methods have been tested and refined via clinical studies. The 'rule of 1800' and the 'rule of 1500' are examples of such heuristic techniques

that physicians use to prescribe insulin regimens to their patients based upon how their blood-glucose is affected by insulin doses (34). These techniques, while clearly not accounting for inter-patient variability, are terribly hampered in attempts to account for intra-patient changes by the relatively-poor feedback that is consistently present between patient and doctor. Communication theory (Nyquist Sampling Theorem) relates the accuracy with which we can reconstruct a signal based upon our sampling rate. A simple back-of-the-envelope calculation tells us that we will not have a faithful reconstruction of the patient's blood-glucose levels by sampling at the typical four measurements per day.[1] This is not to imply that these heuristics do not help patients: it has been shown in the Diabetes Complication and Control Trial (DCCT) (18) that intensive insulin therapy (IIT) significantly reduces the risks associated with chronic hyperglycemia. However, the increased time and money costs associated with IIT motivate further study.

Other partially-closed-loop systems that have been developed are the model-based Diabetes Advisory System (DIAS) (3), and the Automated Insulin Dosage Advisor (AIDA) (38). Model-based systems begin their treatment by abstracting the human as a set of compartments that interact via certain rules. In the case of diabetes care, a common, simple model involves identifying a differential equation that governs the relationship between insulin concentration in the blood and gluconeogenesis rates in the liver. AIDA uses a model-based method of dosing insulin via prediction/verification cycles, with significant heuristics in model assessment and initial conditions. Retrospective tests have been effective for individual patients, but only 80% of patients had reliably-predicted, meal-effected glucose levels within an RMS error of 34.5 mg/dl over 5-6 days(39). Qualitatively, the model requires 17 parameters, but assumes 15 of these to be fixed, allowing variation only in the remaining two. DIAS, in contrast, has no heuristic components: it is completely model-driven and uses a complex Bayesian network of glucose-insulin interactions as a framework. It then requires blood glucose measurements (finger-prick reports), carbohydrate intake, and past insulin injection information to devise a current dose proposal/treatment regimen. While results of blinded studies have been positive for the ability of the DIAS to outperform doctors in lowering HbA1c over a set period of time, the results are not statistically significant. (29). Indeed, though the complication of the model makes it more malleable to inter- and intra-patient variability, it also makes the entire system vulnerable to error, and raises start-up calibration issues. Further, in both AIDA and DIAS, the variations allowed are typically only adjusted from patient to patient, and not intra-patient (over time). Due to complexity and measurement inability, neither can readily adapt its model structure nor patient parameters to reflect intra-patient changes. This adds doubt to their abilities for broad-population glycemic control applications.

So, while AIDA and DIAS address some of the cost and communication issues, they still require adjustment as well as patient attention, accuracy, and ability to self-medicate. Many clinicians feel that the error bars on their work are largely due to imperfect follow-through by the patient, or the patient's inability to dose insulin (especially among certain patient populations such as adolescents and the elderly)(10). Indeed, other innovations such as the insulin pump are helping to reduce these types of errors. However, once the loop of control is broken there is clear agreement in Medicine, and solid theoretical support in Engineering, that the open loop versions will never work as well as their similarly-constructed but closed-loop counterparts (basic control theory). Hence, much research has been done to develop systems that take the patient out of the loop.

[1] Assuming three meals per day, each causing one 'cycle' of blood glucose level, the smallest maximum frequency content is 3 cycles/day. To faithfully reconstruct a signal, we must sample at strictly greater than twice the maximum frequency, or above 6 samples per day. Thus, 4 measurements per day is insufficient.

Closed-loop Control:
Some solutions have 'taken the patient out of the loop' (thus helping to close in on control) by integrating an automatic sensor, an algorithm, and a therapy delivery actuator into a single device. The sensors and actuators in these systems are discussed elsewhere. This section presents several closed-loop control algorithms and their results.

Non-adaptive/quasi-static strategies:
Proportional Integrator Differentiator (PID) controllers are very common in other areas of control, and were used as early as 1979 by Clemens in the well-known Biostator (15). This device incorporates a non-linear PID controller and a moving-average for noise rejection to strongly control patient blood glucose levels. Despite its success at maintaining control, the Biostator algorithm requires continuous intravenous sensing (blood glucose measurement) and actuation (insulin and dextrose), which are impossible in a portable device. It also requires significant manual tuning to fit each patient. This begins to open the loop again as it requires operator intervention to set up and update the device as the patient's parameters change. Several different PID controllers, each with a different twist, were compared by Broekhuyse et al (8), each displaying limited success, and none clearly superior. The main drawbacks with these PID controllers are their dependence on either model parameters or continuous sensor information. Despite adding a patient model update algorithm (weak adaptation) to help adapt these PID models (6) to patient variations, hyperglycemic peaks hampered successful operation.

Pole-assignment strategies have also been attempted. These methods begin with a differential equation mediated, compartmental model glucose-insulin interactions, and cast control as a filtering problem. After identifying and plugging in the parameters for the differential equations, these methods 'place poles' in the s-plane to compute algorithmically the required insulin dose given a set of glucose measurements. While such filters are physically easy to implement, and control well-understood systems well, they face the same trouble as the PID controllers in that the parameters are difficult to attain, and change over time. (53, 21). Because of the tremendous sensitivity of these algorithms to inter- and intra-patient variations, the problem of glycemic control has turned its focus to adaptive algorithms.

Adaptive strategies:
Adaptive filtering is a well-developed field that includes several basic topologies (28) that allow not only outputs of the filter to be changed over time, but also the method by which those outputs are generated. In other words, the filter continuously monitors its own success through a defined metric, and is equipped with the capability of altering its own processing scheme to better meet the success criterion. There are two basic ways in which adaptation has been used to address glycemic control: model-parameter estimation and simultaneous model and model-parameter estimation. Both of these are variations of "plant identification" in Haykin (28), and both have been integrated into a system that uses the 'current' plant model to predict glucose levels based on current and past insulin injections, and assigns an insulin regimen to deal with this.

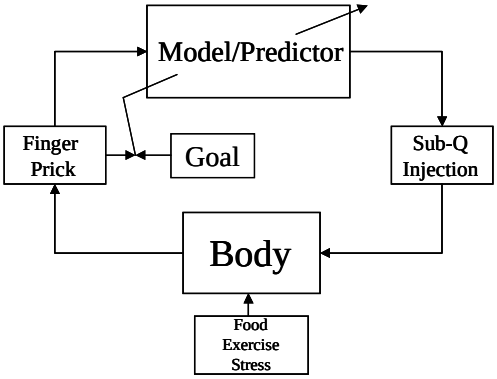


Figure 7: Adaptive, closed loop control diagram.

Brunetti et al (1993) (9) developed a linear adaptive system for parameter identification in a model-based approach. As shown in 7, this method addresses the problem of defining unknown model parameters by allowing the adaptive structure to determine the parameters for itself. While performance with these algorithms has been tested mainly *in silico*, the results are promising in their elimination of the need for constant adjustment to deal with patient variability. However, there are still issues with integration to implantable devices due to sensor limitations (mostly sampling rate). Additionally, the limits of performance will eventually be limited by the accuracy of the original plant model.

Candas et al (11) developed a similar method for adaptively identifying missing/changing model parameters, but they used a nonlinear model. Explaining that this modification could allow their algorithm to better-suit itself to the conceivable nonlinearities in the system, they tested the device on three diabetic pigs. Indeed, though the study was limited, the preliminary results indicated a marked improvement in performance over previous attempts to maintain euglycemia in the presence of "large and rapid variations in insulin action." Still, the required sensor sampling rate is between 2 and 7 minutes (rapidly changing and moderately stable glucose perturbation respectively.) Unfortunately, this far exceeds current sensor technology.

Trajanoski et al (59) also developed a non-linear adaptive system. The feedback adaptation for this method goes a step further than the methods described above: it allows for adaptation of the model parameters as well as the model structure itself. While the model begins as inherently nonlinear (as with the Candas model), the adaptation is partially accomplished through a nonlinear neural network. Simulation testing found the method to be insensitive to high amounts of noise and/or time delays, but "control limitations due to subcutaneous insulin administration make additional action from the patient necessary at mealtime." This is adequate for control, but is a clear deficiency for a fully integrated control scheme.

Indeed, Bellazzi et al (5), and Parker et al (45), in their recent review articles both state that the major stumbling block to the development of automatic glycemic control is sensor technology. The success of a device as straight-forward as Biostator displays that control algorithms are already in place to impose euglycemia given sufficient sensor and actuator technology. However, given that sensor technologies continue to be a limiting factor, with sampling rates of 2 minutes nowhere in sight, it remains an open problem to close the loop while mitigating sampling requirements.

Control Algorithm product:
The previous control discussion reveals that there is significant work that has been done in the area of control via system identification, with specific application to the problem of blood glucose control (5, 11, 59). Comparing the results of adaptive to non-adaptive solutions, it is clear that adaptive controllers solve several of the problems commonly faced by the non-adaptive methods, especially including intra-patient variability with time, and insensitivity to glucose sensor requirements. Given that diabetes is a progressive disease, an adaptive strategy is most appropriate. However, the problem remaining for controllers is the ability to function sufficiently given insufficient glucose sensor information.

Depending on the way that the problem is posed, and the resulting structure of the adaptive algorithm, there are a few ways to address this problem. Our proposed direction for automatic, closed-loop adaptive controllers is toward linearized, adaptive modeling, with the addition of both multiple inputs and an H_∞ method for characterizing system performance and potential.

MIMO:
Despite significant attempts to uncover multiple-input, multiple-output (MIMO) blood glucose control algorithms, it seems that previous research efforts have focussed on single-input, single-output (SISO) or SIMO systems. The reasons for this focus are two-fold: more sensors means more hassle/integration issues, and our objective is simply the control of blood glucose. However, in the face of insufficient blood glucose sensors (either frequency or inaccuracy), one must look for degrees of freedom, and begin making trade-offs. Indeed, our problem in this endeavor is to get as much information, as quickly as possible, to be able to appropriately supply insulin (and possibly other agents) and successfully control blood glucose. While there are good models for insulin-glucose metabolism in the human body, and adaptive realization of appropriate parameters are nearly good enough, it is remiss to overlook the many coherent and orthogonal noise sources that could be recognized. Though it would be better if an algorithm could control without these factors, the adversity of insufficient glucose sensors compels us to suggest incorporating them. There are many factors to consider, and an analysis of which are best and easiest to implement is certainly required. Our suggestions for new measurement include: cortisol levels, epinephrine/norepinephrine levels, and physical activity level. Though these are not uniquely associated with poor blood glucose control, they can have a significant effect on insulin-mediated glucose metabolism. The 'dawn phenomenon' is an example of an insulin-glucose interaction that is not well-modeled by compartment models without the addition of sensor information regarding cortisol levels. (34).

H_∞ Characterization:
Though the non-linear modeling has been reasonably successful, we propose that the ability to dynamically characterize the performance of our system in a closed-form way that evaluates both system and sensor errors will provide a superior adaptation strategy. Appendix B presents relevant control theory in a general and rigorous fashion, and specifically relates the application of H_∞ theory to the problem of blood glucose control. It also explains the necessity for a linearized model. While this type of analysis has been applied to regulation of diabetes (35), our formulation represents a real stride in the ability of the system to explicitly identify trade-off decisions. This capability could be important in the actual development of an implantable device, especially in the comparison of competing linearized algorithms. Of most direct importance, this performance characterization can evaluate feasibility of a control within specified bounds, and suggest dimensions of flexibility for system

optimization. It also would enable direct evaluation of the usefulness of additional sensors, and would allow developers to decide which provide the best help in controlling glucose.

Implementation:
The bulk of the work outlined in this paper addresses the shortcomings of current artificial pancreas approaches. It provides recommendations on how and what should be implemented to improve these devices. In order to be thorough, the following table provides an approach to a method of implementation of these recommendations. This is centered around the development of the adaptive algorithm and simulation. Once this has been proven to be a sound concept with improved simulated glucose control, then further investment in animal and human modeling could occur.

Recommended Implementation Approach

	Development Stage	Sensors	Actuator	External Device	Management Software	Algorithm
Simulation Stages	Simulation without Sensors	None	None / One	None	Input/output, continuous monitoring, user interface, analysis & forecasting for pre-emptive alert decision trees	Simulating inputs to test SISO & SISO via MIMO
	Simulation with Sensors	1. 1 Glucose 2. Multiple Glucose 3. Other sensors	None	None	Same as above	SISO via MIMO
1. Animal Model Testing 2. Human Testing Stages	External Actuator 1 External Sensor	1 Glucose	External Insulin Pump	Sensor sends data to external control device external control device sends data to actuator and to desktop system	All of above plus desktop software for archiving, reports, graphing, communication with physician	External device implements algorithm
	Implanted Actuator Multiple External Sensors	1. 1 Glucose 2. Multiple Glucose 3. Other sensors	Implanted Insulin Pump	Same as above	All of above	External device implements algorithm
	Integrated Actuator 1 Sensor	1 Glucose	Implanted Insulin Pump	All of above plus external device monitors data, communicates with desktop, controls Implant	All of above	Sensor, actuator, & algorithm integrated in implant
	Integrated Actuator Multiple Sensors	1. 1 Glucose 2. Multiple Glucose 3. Other sensors	Implanted Insulin Pump		All of above plus Alarms, forecasting	Sensor, actuator, algorithm integrated in implant

Conclusions:

It is clear from the literature that the sensor is the weakest link in current artificial pancreas attempts. We propose that a MIMO linearized adaptive filter with dynamic performance characterization derived from H_∞ theory can help evaluate and overcome the shortcomings of current systems. The algorithm is central to the overall development effort and is the key place to start with this approach. One advantage to this approach is that the algorithm will perform independently of advances in technology—they will be "plug-and-play" improvements. While a long-duration implantable sensor may not be available today, the system can be developed such that the sensor, when it becomes available, can be integrated. Actuator options are discussed, and also proposed are increased capabilities in management software, including wireless communications and 3rd-party notification. An approach is proposed to proceed with the development of an integrated artificial pancreas centered about this adaptive algorithm/characterization tool, utilizing an incremental implementation designed to prove each technology enhancement without exceeding state-of-the-art capabilities, yet improving overall management of Glycemic Control.

References

1. Adjei AL. Gupta PK, 1997, Inhalation Delivery of Therapeutic Peptides and Proteins.
2. American Diabetes Association, 2001, www.diabetes.org/ada/facts.asp, *ADA Website*.
3. Andreassen S, Benn J, Hovorka R, Oleson KG, and Carson ER, 1994, A probabilistic approach to glucose prediction and insulin dose adjustment: Description of metabolic model and pilot evaluation study *Comput Methods Programs Biomed* 41: 183-203.
4. Belazzi R, Nucci G, Cobelli C, 2001, The subcutaneous route to insulin-dependent diabetes treatment, *IEEE Eng Med & Biol Mag* 20(1):54-64.
5. Bellazi R, Siviero C, Stefanelli M, and De Nicolao G, 1995, Adaptive controllers for intelligent monitoring, *Artif Intell Med* 7:515-540.
6. Bellomo G, Brunetti P, Calabrese G, Mazzotti D, Sarti E, and Vicenzi A, 1982, Optimal feedback glycaemia regulation in diabetics, M*ed & Biol Eng & Comput* 20:329-335.
7. Boyd S, and Barratt C, 1991, Linear Controller Design: Limits of Performance.
8. Broekhuyse HM, Nelson JD, Zinman B, and Albisser AM, 1981, Comparison of algorithms for the closed-loop control of blood glucose using the artificial beta cell, *IEEE Trans Biomed Eng* BME-28: 678-687.
9. Brunetti P, Cobelli C, Cruciani P, Fabietti PG, Filipucci F, Santeusanio F, Sarti E, 1993, A simulation study on a self-tuning portable controller of blood glucose. *Int J Artif Organs* 16:51-57.
10. Buckingham B, personal communication, 1 May 2001.
11. Candas B, Radziuk J,1994,An adaptive plasma glucose controller based on a nonlinear insulin/glucose model, *IEEE Trans Biomed Eng* 41:116-124.
12. Carson ER, Deutsch T, 1992, A spectrum of approaches for controlling diabetes, *IEEE Control Systems Ma*g 12(12):25-31.
13. Cleland JL, et al, 2001, Emerging protein delivery methods, *Current Opinion in Biotechnology* 2001 12:212-219.
14. Cleland JL, 2001, class lecture.
15. Clemens AH, 1979, Feedback control dynamics for glucose controlled insulin infusion system, Med Prog Technol 6:91-98.
16. *Comput Methods Programs Biomed* ,1996 Jan:49(1):105-115.
17. The Diabetes Control and Complications Trial Research Group, 1990, Diabetes Control and complications Trial (DCCT) update, *Diabetes Care*. 13:427-433.
18. The Diabetes Control and Complications Trial Research Group, 1993, The Effect of Intensive Treatment of Diabetes On the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *The New England Journal of Medicine*. 329(14):977-98.
19. The Diabetes Control and Complications Trial Research Group. 1996. Lifetime Benefits and Costs of Intensive Therapy as Practiced in the Diabetes Control and Complications Trial, *Journal of the American Medical Association*.,276(17): 1409-1415.
20. Fischel-Ghodsian F, Newton JM, 1993, Simulation and optimisation of a self-regulating insulin delivery system, *J Drug Targeting* 1:6780.
21. Fischer U, Salzsieder E, Freyse E-J, and Albrecht G, 1990, Experimental validation of a glucose-insulin control model to simulate patterns in glucose turnover, *Comput Meth Prog Biom*ed 32:249-258.
22. Fischer U, Schenk W, Salzsieder E, Albrecht G, Abel P, and Freyse E-J, 1987, Does physiological blood glucose control require an adaptive strategy? *IEEE Trans Biomed Eng* BME-34:575-582.
23. Ganong WF, 1997, Review of Medical Physiology (18th Edition) pg. 332 Appelton and Lange.
24. Gough DA, Armour JC, 1995, Perspectives in Diabetes. Development of the Implantable Glucose Sensor. What are the prospects and why is it taking so long? *Diabetes* 44:1005-1009.

25. Gozani SN, *Apparatus and methods for non-invasive blood analyte measurement*, US Patent #5,752,512, 5/19/98.
26. Gross, et al, Analyte-controlled liquid delivery device and analyte monitor, US Patent #'s 5,820,622, 10/13/98; 5,807,375, 10/15/98; and 5,800,420, 10/1/98.
27. Harris M, Hadden W, Knowler W, Bennett P, 1987, Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in the U.S. population age 20-74 yr. *Diabetes*. 36:523-534.
28. Haykin S, 1996, Adaptive Filter Theory, 3rd Ed Ch 2, Prentice Hall, NJ.
29. Hejlesen OK, Andreassen S, Frandsen NE, Sorensen TBB, Sando SH, Hovorka R, and Cavan DA, 1998, Using a double-blind controlled clinical trial to evaluate the function of a diabetes advisory system: A feasible approach, *Comput Methods Programs Biomed* 52:165-173.
30. Henry C, Special Delivery, 2000, *Chem & Eng New*s 78:49-65.
31. Hepp KD, 1994, Implantable insulin pumps and metabolic control, *Diabetologia* 37 (Suppl 2): S108-S111.
32. Hilt D, 1998, *Modern Drug Discovery* 1(1):30-42.
33. Jaremko J, Rorstad O, 1998, Advances toward the implantable artificial pancreas for treatment of diabetes, *Diabetes Care* 21:444-450.
34. Kalinyak J, personal communication, 13 Apr 2001.
35. Kienitz KH, Yoneyama T, 1993, A robust controller for insulin pumps based on H-infinity theory, *IEEE Trans Biomed Eng* 40:1133-1137.
36. Klegerman ME, Groves MJ, 1992, Pharmaceutical Biotechnology: Fundamentals and Essentials.
37. Lee V, 1991, Peptide and Protein Drug Delivery.
38. Lehman ED, Deutsch T, Carson ER, and Sonksen PH, 1994, AIDA: an interactive diabetes advisor, *Comput Methods Programs Biomed* 41:183-203.
39. Lehmann ED, Hermany I, and Deutsch T, 1994, Retrospective validation of a physiological model of glucose-insulin interaction in type 1 diabetes mellitus, *Med Eng Phys* 16:193-202.
40. Oberhardt BJ, et al, 1982, Glucose sensor characteristics for miniaturized portable closed-loop insulin delivery: A step toward implantation, *Diabetes Care* Vol 5 #3:213-217.
41. MedData Inc., http://www.meddatai.com.
42. MiniMed Inc, www.minimed.com.
43. Mitragotri S, Blankschtein D, Langer R, 1995, Ultrasound-Mediated Transdermal Protein Delivery, *Science* 260:850-853.
44. Oberhardt BJ, et.al, 1982, Glucose sensor characteristics for miniaturized portable closed-loop insulin delivery: A step toward implantation, *Diabetes Care* Vol. 5 #3: 213-217.
45. Parker R, Doyle F, Peppas N, 2001, The intravenous route to blood glucose control, *IEEE Eng Med & Biol Mag* 20(1):65-73.
46. Point Study Group, 1998, One-year trial of a remote-controlled imnplantable insulin diffusion system in type 1 diabetic patients, *Lancet* ii:866-869.
47. Poitout V, Moatti-Sirat D, Reach G, Zhang Y, Wilson GS, Lemonnier F, Klein JC, 1993, A glucose monitoring system for on line estimation in man of blood glucose concentration using a miniaturized glucose sensor implanted in the subcutaneous tissue and a wearable control unit, *Diabetologia* 36:658-663.
48. Renard E, Baldet P, Picot MC, Jacques-Apostol D, Costalat G, Bringer J, Jaffiol C, 1995, catheter complications associated with implantable systems for peritoneal insulin delivery: an analysis of frequency, predisposing factors, and obstructing materials, *Diabetes Care* 18:300-306.
49. Rubin R.J., Altman WM, Mendelson DN, 1992 ,Health Care Expenditures for People with diabetes Mellitus, *Journal of Clinical Endocrinology and Metabolism*. 78: 809A-809F.
50. Savage S, personal communication, 11 June 2001.
51. Santini JT, Cima MH, and Langer R, 1999, A controlled-release microchip, *Nature* 397:335-338.

52. Saudek CD, Selam JL, Pitt HA, Waxman K, Rubio M, Jeandidier N, Turner D, Fischell RE, Charles MA, 1989, A preliminary trial of the programmable implantable medication system for insulin delivery, *N Engl J Med* 321:574-579.
53. Shimoda S, et al, 1997, Closed-loop subcutaneous insulin infusion algorithm with a short acting insulin analog for long-term clinical application of a wearable artificial endocrine pancreas, *Frontiers Med Biol Eng* 8:197-211.
54. Shults MC, Rhodes RK, Updike SJ, Gilligan BJ, Reining WN, 1994, A telemetry-instrumentation system for monitoring multiple subcutaneously implanted glucose sensors, *IEEE Trans Biomed Eng* 41:937-942.
55. Shults, et al, *Device and method for determining analyte levels*, US Patent #6,001,067, 12/14/2000.
56. Siddiqui O, et al, 1987, *J Pharm Sci* 26:341.
57. Sternberg F, Meyerhoff C, Mennel FJ, Bischof F, Pfeiffer EF, 1995, Subcutaneous glucose concentration in humans: real estimation and continuous monitoring, *Diabetes Care* 18:1266-1269.
58. Thevenot DR, 1982, Problems in adapting a glucose-oxidase electrochemical sensor into an implantable glucose-sensing device, *Diabetes Care* Vol 5 #3:184-189.
59. Trajanoski Z, Wach P, 1998, Neural predictive controller for insulin delivery using the subcutaneous route, *IEEE Trans Biomed Eng* 45:1122-1134.
60. Updike SJ, et al, 1982, Implanting the glucose enzyme electrode: Problems, progress, and alternative solutions, Diabetes care Vol 5 # 3:207-212.
61. Wall DA, 1995, Pulmonary absorption of peptides and proteins, *Drug Delivery* 2: 1-20.
62. Webster JG, 1998, Medical Instrumentation: Application and Design, Third edition, Wiley, 477-482.
63. Widrow B, Stearns S, 1984, Adaptive Signal Processing, Prentice Hall, NJ.
64. Woodward SC, 1982, How fibroblasts and giant cells encapsulate implants: Consideration in design of glucose sensors, *Diabetes Care* Vol 5 #3:278-281.
65. Yoshioka, et al, Bionsensor, US Patent # 5,651,869, 7/29/97.

Appendix A: "Blood Glucose Sensor" Patent Search Results

	Patent #	Patent Title
1	6,210,922	Serum free production of recombinant proteins and adenoviral vectors
2	6,159,147	Personal computer card for collection of real-time biological data
3	D433,755	Glucose sensor
4	6,144,837	Method and apparatus for interactively monitoring a physiological condition and for interactively providing health-related information
5	6,122,536	Implantable sensor and system for measurement and control of blood constituent levels
6	6,110,746	Peptides derived from human heat shock protein 60 for treatment of diabetes, compositions, methods and kits
7	6,088,605	Method and apparatus for non-invasive blood glucose sensing
8	6,049,727	Implantable sensor and system for in vivo measurement and control of fluid constituent levels
9	6,001,067	Device and method for determining analyte levels
10	5,997,501	Intradermal drug delivery device
11	5,995,860	Implantable sensor and system for measurement and control of blood constituent levels
12	5,854,074	Dispensing instrument for fluid monitoring sensors
13	5,848,991	Intradermal drug delivery device and method for intradermal delivery of drugs
14	5,820,622	Analyte-controlled liquid delivery device and analyte monitor
15	5,810,199	Dispensing instrument for fluid monitoring sensor
16	5,807,375	Analyte-controlled liquid delivery device and analyte monitor
17	5,800,420	Analyte-controlled liquid delivery device and analyte monitor
18	5,795,859	Peptide which abrogates TNF and/or LPS toxicity
19	5,795,723	Expression of neurogenic bHLH genes in primitive neuroectodermal tumors
20	5,786,584	Vial and cartridge reading device providing audio feedback for a blood glucose monitoring system
21	5,771,891	Apparatus and method for non-invasive blood analyte measurement
22	5,752,512	Apparatus and method for non-invasive blood analyte measurement
23	5,739,238	Alkoxysilyl-functional oligomers in curable silane polymer compositions
24	5,738,244	Dispensing instrument for fluid monitoring sensors
25	5,695,995	Neurogenic differentiation (neurod) genes
26	5,665,477	Hydrogel adhesive for attaching medical device to patient
27	5,665,065	Medication infusion device with blood glucose data input
28	5,660,791	Fluid testing sensor for use in dispensing instrument
29	5,651,869	Biosensor
30	5,632,410	Means of handling multiple sensors in a glucose monitoring instrument system
31	5,630,986	Dispensing instrument for fluid monitoring sensors

Appendix A: "Blood Glucose Sensor" Patent Search Results Con't

	Patent #	Patent Title
32	5,601,435	Method and apparatus for interactively monitoring a physiological condition and for interactively providing health related information
33	5,594,100	Epitope for prevention of type I diabetes
34	5,575,403	Dispensing instrument for fluid monitoring sensors
35	5,558,640	System for infusion of medicine into the body of a patient
36	5,527,288	Intradermal drug delivery device and method for intradermal delivery of drugs
37	5,510,266	Method and apparatus of handling multiple sensors in a glucose monitoring instrument system
38	5,508,030	Creating new capillary blood pools for practicing bidirectional medicine
39	5,474,065	Non-invasive fetal probe
40	5,411,551	Stent assembly with sensor
41	5,370,114	Non-invasive blood chemistry measurement by stimulated infrared relaxation emission
42	5,264,103	Biosensor and a method for measuring a concentration of a substrate in a sample
43	5,231,993	Blood sampler and component tester with guide member
44	5,231,988	Treatment of endocrine disorders by nerve stimulation
45	5,209,231	Optical glucose sensor apparatus and method
46	5,208,147	Means for measuring a characteristic in a sample fluid
47	5,114,859	Method for measuring a characteristic in a sample fluid
48	5,002,572	Biological implant with textured surface
49	4,953,552	Blood glucose monitoring system
50	4,805,624	Low-potential electrochemical redox sensors
51	4,679,562	Glucose sensor
52	4,538,616	Blood sugar level sensing and monitoring transducer
53	4,494,950	Plural module medication delivery system