Journal of Diabetes Science and Technology
Volume 1, Issue 1, January 2007

REVIEW ARTICLE

The Artificial Pancreas: How Sweet Engineering Will Solve Bitter Problems

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Abstract

An artificial pancreas is a closed-loop system containing only synthetic materials which substitutes for an endocrine pancreas. No artificial pancreas system is currently approved; however, devices that could become components of such a system are now becoming commercially available. An artificial pancreas will consist of functionally integrated components that will continuously sense glucose levels, determine appropriate insulin dosages, and deliver the insulin. Any proposed closed loop system will be closely scrutinized for its safety, efficacy, and economic impact. Closed loop control utilizes models of glucose homeostasis which account for the influences of feeding, stress, insulin, exercise, and other factors on blood glucose levels. Models are necessary for understanding the relationship between blood glucose levels and insulin dosing; developing algorithms to control insulin dosing; and customizing each user's system based on individual responses to factors that influence glycemia. Components of an artificial pancreas are now being developed, including continuous glucose sensors; insulin pumps for parenteral delivery; and control software, all linked through wireless communication systems. Although a closed-loop system providing glucagon has not been reported in 40 years, the use of glucagon to prevent hypoglycemia is physiologically attractive and future devices might utilize this hormone. No demonstration of long-term closed loop control of glucose in a free-living human with diabetes has been reported to date, but many centers around the world are working on closed loop control systems. It is expected that many types of artificial pancreas systems will eventually be available, and they will greatly benefit patients with diabetes.

J Diabetes Sci Technol 2007;1(1):72-81

Introduction

A closed-loop abiotic artificial pancreas system to control blood glucose levels is a potential cure for diabetes. This approach to glucose measurement, determination of the proper insulin dose, and delivery of insulin can result in physiologic glycemic levels without fingerstick blood glucose measurements, insulin injections, or hypoglycemic events. In spite of difficult problems that remain to be solved, recent engineering advances have produced individual components that can be combined into closed-loop systems, as well as several investigational closed-loop systems that have actually controlled blood glucose under defined conditions without human input. This article summarizes where we are now and where we are heading in the field of the artificial pancreas.

Definition

The definition of an artificial pancreas is a device or system of integrated devices containing only synthetic materials, which substitutes for an endocrine pancreas by sensing the blood glucose level, determining the amount of insulin needed, and then delivering the appropriate amount of insulin. The three components of an artificial pancreas are:

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Abbreviations: (ADICOL) Advanced Insulin Infusion using a Control Loop, (MPC) model predictive control, (PID) proportional integral derivative control

Keywords: artificial, closed-loop, control, diabetes, glucose, pancreas

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1) an automatic glucose monitor; 2) an automatic insulin delivery system; and 3) an algorithm to link blood glucose levels with insulin delivery.

Current Status

No artificial pancreas is currently commercially available, but components that could go into an artificial pancreas are now becoming commercially available. At this time, multiple versions of entire systems are currently under investigation in humans, animals, and in computerized models.

Significant technical, administrative, marketing, and financial problems will have to be solved in order to develop a safe and effective artificial pancreas. The technical problems include how to develop: 1) a very accurate continuous subcutaneous sensor with little lag time between fluctuations in measured glucose levels; 2) a physiologic method for delivering insulin; and 3) a robust controller to provide sufficient insulin to attain physiologic levels of glycemia within a narrow safe range. Furthermore, if an artificial pancreas is engineered, the device will undergo extremely rigorous scrutiny from such political sectors as: 1) regulatory agencies (concerned with safety); 2) insurance companies (concerned with efficacy); and 3) the legal system (concerned with liability), which is a potential arena for devastating lawsuits against the manufacturing and medical communities in the event of device failure.

To date, at least seven types of continuous glucose sensors, three types of insulin delivery systems, four types of insulin[1-12] and four types of algorithms[9,13-16] have been reported to be under investigation for use in an artificial pancreas. Hundreds of unique closed-loop systems could therefore emerge from assembling various combinations of these components.

The ultimate purpose of developing better glucose monitoring and insulin delivery technologies is to combine these two processes by way of an algorithm, into an automatic closed-loop system. The artificial pancreas could be controlled by a formula designed to mimic a model of natural islet cell function so that the same amount of insulin, would be released, both basally and after meals by the artificial pancreas, similar to what a natural pancreas would release. The first artificial pancreas systems will contain both external and internal hardware. The early devices will probably control basal insulin delivery automatically and require manual insulin programming at mealtimes.[17] Only a few dozen studies on human subjects receiving these devices or systems have been reported to date. Most of these subjects were treated for less than a few days, and much more research is needed to demonstrate that any of these projects is reliable in a variety of circumstances.

Closed-Loop Control Compared to Open-Loop Control

The artificial pancreas is a closed-loop insulin delivery device. Open-loop control and closed-loop control devices differ in: 1) their input (how continuous); 2) their controller (how automatic); 3) and their output (how continuous). An open-loop controller receives intermittent input and utilizes a manual controller to deliver intermittent output. Intensive insulin therapy for insulin-requiring diabetes is currently managed by open-loop control with intermittently monitored glucose levels resulting in intermittently administered insulin doses that are manually administered by a patient using a written algorithm. Such currently available intensive therapy can be contrasted to glucose management by a closed-loop system, which for control of blood glucose in patients with diabetes is known as an artificial pancreas. In this case, glucose levels are monitored continuously, which results in continuously infused insulin dosed according to a computerized algorithm without a need for patient input. Compared to currently applied intensive therapy, an artificial pancreas can potentially result in: 1) less glycemic variability; 2) less hypoglycemia; 3) less pain from pricking the skin to check the blood glucose and deliver insulin boluses; and 4) less overall patient effort.

Technical problems to be solved

Technical problems of components and integrated systems

In order to build an artificial pancreas, technical problems with each of the three major individual components of the device (the continuous sensor, the pump and the control system) must be solved. In addition, once the individual components are optimized for integration, then problems with the integrated system will also need to be solved.

Sensor problems

An implanted continuous sensor may malfunction for many reasons. These include: 1) calibration drift; 2) a lag between concentrations of arterial blood glucose and interstitial fluid glucose during rapid fluctuations; 3) sensor fouling; 4) rejection and fibrosis; and 5) local inflammatory complications.

The reading from an implanted sensor can drift.[18] Almost all continuous glucose sensors that are in use or under development require regular blood glucose checks to maintain proper calibration. Even a few daily blood glucose checks spoil the sense of freedom that could derive from a fully automatic closed-loop system. Additionally, a lag may exist between rapidly fluctuating blood glucose levels and

interstitial fluid glucose levels. The magnitude of the lag may be no more than around 5 minutes[19, 20] with a freshly inserted subcutaneous glucose sensor, but after prolonged implantation, the sensor surface may become increasingly fouled with fibrotic material and the lag time progressively increases. Calibration drift can be overcome by regular calibration of a sensor against a reference assay.

At least seven types of invasive or minimally invasive continuous glucose sensors[21,22] have been reported to be under investigation for use in an artificial pancreas. These include: 1) a subcutaneous needle-type sensor containing glucose oxidase;[1,5,10] 2) a subcutaneous needle-type sensor containing ferrocene;[2] 3) an intravenous subcutaneous needle-type sensor containing glucose oxidase;[8] 4) a subcutaneous array of multiple simultaneously measuring glucose oxidase sensors;[12] 5) a microdialysis system for extracting and measuring interstitial fluid enzymatically;[3,4,7] 6) a viscometric system for removing and measuring interstitial fluid;[11] and 7) a continuous intravenous in-line glucose oxidase sensor.[6] These studies included no more than twelve subjects and lasted no more than 48 hours,[3-12] except for one trial that was reported to last for 14 days.[2]

Insulin Delivery Problems

An implanted or external insulin reservoir, comprising part of an artificial pancreas, might develop many problems, depending on the delivery site. These include: 1) the absence of currently available mechanical systems that can simulate the physiologic non-glucose stimuli which trigger insulin release;[23] 2) non-physiologic delivery of infused insulin into the portal circulation by way of either: a) the systemic circulation (with an external insulin pump) because of a long delay in both absorption into the bloodstream and following absorption an additional delay in reaching the liver; or b) the peritoneum (with an implanted insulin pump), because of some delay, even by this route, in reaching the liver;[24] 3) insulin denaturation within the insulin reservoir;[25] 4) local and systemic complications from controlled insulin delivery, including improper dosing;[26] and 5) surgical and anesthesia risks of implantation and explantation.

Four routes of insulin delivery systems have been reported to be under investigation for use in closed-loop systems. These include: 1) subcutaneous;[2,3,4,7,10,11] 2) intraperitoneal;[8] 3) peripheral intravenous;[5-7] and 4) portal intravenous[9] although these last two routes would be suitable only for hospitalized patients. The types of insulin that have been studied for this purpose include: 1) Regular U 100;[5,12] 2) Regular U 40;[6,9] 3) Regular U 400;[8] 4) Lispro;[2,3,4,7,10,11] and 5) Insulin aspart and insulin glulisine will probably also be tested in a closed-loop system in the future. Reviews have been published covering controlled insulin delivery technologies and short acting insulins.[24,27,28,29]

Controller Problems

A controller in an artificial pancreas is a software algorithm that determines the amount of bolus and basal insulin needed in response to slow fluctuations in glucose levels between meals and rapid rises in glucose levels at mealtimes. Controllers currently under development lack three important elements: 1) sufficiently robust models of glucose homeostasis for predicting necessary doses of insulin in various situations;[30-33] 2) practical solutions to the one-way problem which is that current closed-loop systems cannot treat hypoglycemia, so to avoid overshoot they must undertreat hyperglycemia; 3) effective solutions to the tradeoff between specificity and sensitivity in detecting prandial spikes in glucose levels, because when the glucose level rises sharply it is necessary to avoid responding to "noise" which is a random fluctuation in the glucose level and not a true mealtime spike (specificity), but it is also necessary to avoid a delay in responding rapidly to mealtime surges in glucose levels (sensitivity).[34] An inappropriate bolus can result in hypoglycemia and a delayed bolus can result in excessive postprandial glucose levels.[35] This third problem can be solved by decreasing the device's sensitivity to rapid increases in glucose and requiring the patient to manually trigger the device at mealtime to affect a prandial bolus of insulin. Basal delivery of insulin in eventual closed-loop systems will likely also be subject to patient override, but the more input required from the patient, the further the system will be from providing true closed-loop control. Of the three components of an artificial pancreas, controllers appear to be the furthest from being ready to incorporate into a closed-loop system.

Integrated System Problems

When an artificial pancreas is developed, outcomes data will be required in order for this tool to become widely adopted. Initially, the technology will probably be expensive and require considerable training. It will be necessary for developers of an artificial pancreas to demonstrate: 1) *safety*, because the system's algorithm must protect against severe hypoglycemia to prevent morbidity, product recalls, and lawsuits; 2) *effectiveness* because it is not known to what degree closed-loop control (compared to current intensive therapy) will produce improved mean glucose levels and decreased glucose variability; and 3) *cost-effectiveness* because the economic impact of improved control and decreased glucose variability with such a system will need to be measured and found to be attractive in order to convince payers to provide reimbursement for this technology.

Building a controller for a Closed-loop system

Of the three components of an artificial pancreas, controllers have been written about the least. A closed-loop controller utilizes formulas, known as models that have been verified by empirically collected data, to determine insulin dosages based on patterns of glycemia.

Models

A model is a simplified representation of a more complex system. Mathematical models of glucose homeostasis are used in the construction of controllers for an artificial pancreas.[36] Models are: *useful* to understand the relationship between blood glucose levels and insulin dosing, *necessary* for the development of algorithms to control an off-the-shelf artificial pancreas, and *critical* to customize each user's artificial pancreas with insulin dosing management for that user. In order to predict blood glucose concentrations, a model must incorporate such information as: 1) the effect of the blood glucose concentration and changes in the blood glucose concentration on beta cell insulin release; 2) the effect of exogenous insulin delivery into the subcutaneous or intravenous compartments on blood insulin levels; 3) the effect of food intake on glucose appearance into the circulation; and 4) the effect of a change in glucose appearance into the bloodstream combined with specified insulin levels on blood glucose concentrations.[15]

Glucose Homeostasis

The pattern of physiologic insulin release in response to a rapid rise in blood glucose is the best understood part of the glucose homeostasis model, which describes maintenance of physiologic glycemia. Insulin release in response to a glucose challenge is known to be characterized by an early first phase of release within about 10 minutes and a later second phase of release which progressively increases from around 20-60 minutes following the acute glucose challenge.[37] The beta cell response to a glucose challenge is proportional to both the concentration and rate of rise or fall in the blood glucose level.

Models of glucose homeostasis are comprised of multiple elements related to carbohydrates entering the system or to psychological stress, which will raise the blood glucose level and factors like insulin and exercise, which will lower the blood glucose level. Many investigators have attempted to collect empirical data about the factors that affect glycemia and to create a model for each part of the entire process. In spite of the creation of various pieces of an overall model, no model exists that has been demonstrated to faithfully mimic the control of blood glucose exercised by the pancreas.[38,39]

Types of control algorithms for insulin release

Four types of control algorithms based on models have been reported to determine insulin release in response to an acute rise in the blood glucose level, such as what occurs with carbohydrate ingestion. These algorithms include: 1) Proportional-Integral-Derivative Control (PID);[15,40] 2) and 3) Proportional-Derivative Control (PD) both with[14] and without[9] a fading memory component; and 4) Model Predictive Control (MPC).[13,16,35] The first three types of algorithms are all forms of PID control. Additional types of control based on neural networks incorporating MPC,[41] rule-based fuzzy logic without models or algorithms,[42] and an analysis and/or synthesis technique that attempts to design the best performing controller, known as H-infinity control,[42,43] have been used in simulated patients, but these methods have not been published for any *in vivo* system. These types of control systems are all intended to return the elevated blood glucose level back down to baseline levels, but each technique responds to different stimuli. Many of the published simulations of glucose control papers assume a high initial blood glucose concentration, apply feedback control to bring the glucose to the setpoint, and do not incorporate meal challenges which would raise the glucose level again. In this field of research, in vivo testbed systems, which include meal challenges and insulin delivery by way of a subcutaneous or intraperitoneal route, have produced by far the most practical data for developing closed-loop systems.

All of these control systems function like tools that can assist a lost driver reach a destination. The destination in this case is a predefined glucose concentration set point. The difference between these two types of systems is that PID and PD control are like a roadmap, and if the driver is off course, then such a system *reacts* by returning the driver to the street, where the driver went off course, to reestablish the correct path to the target. MPC control, on the other hand, is like a Global Positioning System and if the driver is off course, then it *acts* by bringing the driver to the target by establishing a new correct path to the target.

Available components of an artificial pancreas

Product integration

Over the past five years glucose monitoring and insulin delivery have been facilitated by development of devices that perform more than a single task.[45,46] Mechanical integration occurs when two or more devices are located in physical proximity to each other, but lack mutual communication. The first integrated products offered only mechanical integration. They contained a blood glucose monitor and an insulin delivery syringe housed within the same package,

but the two components functioned completely separately without any communication between them.

Isolated components

At this time, six continuous glucose sensors are approved for use in the US or Europe. These include the CGMS Gold (Medtronic Diabetes, Northridge, California),[47] the GlucoWatch GW2B (Animas Corporation, Frasier, Pennsylvania),[48] the Guardian (Medtronic Diabetes, Northridge, California),[49] the Guardian RT (Medtronic Diabetes, Northridge, California),[50] the STS (Dexcom, San Diego, California),[51] and the GlucoDay (A. Menarini, Milan, Italy).[21] The first five of these are approved for use in the United States and all six are approved for use in Europe. An additional continuous glucose monitors that is currently being evaluated by the FDA for approval in the United States is the Navigator (Abbott Diabetes Care, Alameda, California).[52] An artificial pancreas must process realtime glucose readings, so the CGMS Gold, which provides only retrospective data, would not be a suitable component. All the other continuous monitors provide realtime glucose readings, although not all of these devices are widely available at this time. It is expected that additional continuous glucose monitors will become available after the Clinical Laboratory Standards Institute, working with Diabetes Technology Society, develops performance guidelines for these monitors for American and international medical device regulatory agencies.[53]

Current commercially available insulin pumps deliver insulin continuously and subcutaneously. Two pumps are also available on a limited basis to research subjects in Europe only for delivering insulin into the peritoneum. All of these devices are manually controlled by the patient to deliver basal and mealtime boluses at rates selected according to individual glycemic patterns. Insulin pump therapy into the skin is well established and not associated with significant morbidity.[54] The implanted 2007 Pump (Medtronic Diabetes, Northridge, California) and the Diaport Percutaneous Port System (Disetronic, Burgdorf, Switzerland) are both available on a restricted basis to patients in Europe for long-term intraperitoneal insulin delivery.

The implanted 2007 Pump consists of three components: 1) a negative-pressure insulin reservoir that is implanted into the abdominal wall subcutaneous space; 2) a delivery catheter tip that is implanted into the peritoneum; and 3) a portable personal pump communicator that the patient uses to control the insulin delivery rate. To insert the 2007 Pump, a surgeon dissects the right upper quadrant and sets the 6-ounce pump into a pump pocket in the abdomen wall. The catheter tip is then inserted into the peritoneum.[55,56] To maintain this pump, the reservoir is refilled every 1.5 – 3 months with special dedicated Regular insulin called Hoe21PH. A side port in the reservoir permits flushing of the catheter independently of the reservoir.[57] The use of implanted insulin pump treatment has been particularly well received in France. Implanting centers there have joined to form an association called the EVADIAC (Diabete du Traitement par Implants Actifs) Study Group.[58]

The Diaport Percutaneous Port System facilitates delivery of insulin from an external pump directly into the peritoneum by way of an infusion set that is inserted into the peritoneum through the bloodless umbilical vein. The infusion set connects to an external pump. Any type of rapidly acting insulin used for subcutaneous pump therapy can also be used for intraperitoneal pump therapy. A catheter obstruction can be cleared by removing and flushing the catheter. Intraperitoneal insulin delivery increases portal vein insulin delivery and lowers peripheral levels of insulin, and both of these changes result in a more physiologic delivery of insulin.[59] When an insulin pump and reservoir are extracorporeal, it is easier to refill the insulin supply and change batteries. Furthermore, there is no risk of insulin denaturing in a reservoir outside the body. Inside the body, however, the temperature may be too warm for long-term insulin storage.

Trends in integrated systems

A current trend in insulin pump design is progressively smaller sizes to the point where they contain insufficient surface area for control buttons. Control functions are being assumed by handheld portable devices that wirelessly determine the rate and timing of insulin delivery. An integrated sensor-augmented pump, The Paradigm REAL-Time System (Medtronic Diabetes, Northridge, California), was approved by the FDA this year. This system consists of a CGMS Guardian RT real time glucose sensor and an insulin pump.[60]

Another trend in integration is for the pump controller to be engineered to also serve as a blood glucose monitor, so that the controller's screen can also display the latest capillary blood glucose value and a recommended dose of continuously infused rapidly acting subcutaneous insulin. Bolus dosage controllers embedded into insulin pumps use pre-programmed values for insulin sensitivity, carbohydrate sensitivity, and a target postprandial glucose level. The controller receives ongoing updated information about the currently measured glucose level as well as the timing and amount of all recent short-acting boluses of insulin that might necessitate discounting the recommended current dose because of a persistent effect of on-board insulin. The

amount of on-board insulin can be discounted according to a duration of activity curve that may be selected from a family of curves, or else a particular curve may be selected as the default curve. The planned carbohydrate intake is the only mealtime information needed to calculate a bolus dose of insulin appropriate for the patient's current glucose level, insulin sensitivity, carbohydrate sensitivity, recent dosing of short-acting insulin, and target postprandial glucose level. This amount is generally determined right at mealtime and then programmed into the controller.[61] Software that analyzes glucose values has been reported to predict an optimal total daily dose of insulin, without specifying how to modify each individual dose of insulin.[62]

Evaluating Performance of a closed-loop system

An important goal of diabetes therapy is improvement in the mean blood glucose level, as reflected by the A1c level. With real time continuous glucose monitoring, it is possible to decrease the amount of time spent in the hypoglycemic and hyperglycemic ranges without necessarily improving the mean blood glucose or the A1c level.[51,63] Furthermore, the A1c level, which can require 2-3 months to fully change in response to a new level of mean glycemia, may not be a useful measure if a particular treatment is used only for only a few days or weeks.[64,65] Because glycemic variability, independent of A1c, may be a significant risk factor for microvascular complications,[66] it could be useful to develop a score to evaluate the performance of an artificial pancreas that incorporates both mean control and variability. Time spent hypoglycemic or hyperglycemic would lower the score. One measure of artificial pancreas performance addresses the glycemic variability issue by assessing both pre-meal and post-meal glucose levels.[67] Fasting and postprandial glucose levels are each assigned to one of six scored performance zones. The score for both of these two states is a multidimensional score comprising the percentages of time spent in each performance zone. A high percentage of time spent close to target is an indication of controller efficacy and a low percentage of time spent far from the target is an indication of controller safety. A similar proposal for classifying the performance of an algorithm-driven protocol for hourly bolus intravenous insulin therapy to achieve tight glucose control in hospitalized patients with diabetes was also based on the percentage of time spent in the target range.[68]

Closed-Loop Systems

Past

The first artificial pancreas was developed in 1964 by a Beverly Hills, California internist, Dr. Arnold Kadish. His device sampled and measured venous blood every 15 seconds. The device delivered either insulin (for blood glucose above 150 mg/dl) or glucagon (for blood glucose below 50 mg/dL) to maintain the blood glucose level within a range of 50-150 mg/dL. The device was the size and shape of a large backpack and not compatible with free-living.[69] This idea of delivering two hormones – one for high and one for low glucose levels – has been replaced, because of the complexity of the instrument, by a variety of current experimental systems, which virtually all depend exclusively on insulin to overcome hyperglycemia but do not deliver a specific remedy for hypoglycemia.

In 1974 Albisser and colleagues reported the use of an extracorporeal *artificial pancreas* system to maintain glycemia in the normal range during consumption of meals.[70,71] That same year Pfeiffer and colleagues also reported use of a computerized glucose controlled insulin infusion *artificial beta cell* system.[72] All this work led to development of the commercial product for inpatient control of blood glucose, the Biostator, which was produced by Miles Laboratory. This device is no longer being manufactured, but is still used in research laboratories. Shichiri and colleagues reported the development of a prototype *artificial beta cell* in the late 1970's.[73-76] This system was later the basis for a commercial bedside closed-loop research system, the STG-22 (Nikkiso Ltd., Tokyo, Japan), which is still being manufactured. Both devices were designed to sample blood from and deliver insulin into the intravenous space. They were never suitable for free-living patients outside of a hospital or research facility.

Closed-loop devices with intravenous blood sampling and insulin delivery are used for glucose clamp studies to characterize new hypoglycemic agents[77] and locate very small insulinomas, which are too small to see at surgery or on preoperative imaging studies.[78] The glucose infusion rate necessary to maintain euglycemia reflects the agent's pharmacodynamic properties. When this rate falls precipitously during an exploration for such a tumor and a sequential excision of pancreatic slices, then the most recently excised slice is identified as containing the insulinoma.

Present

No demonstration of long-term closed-loop control of glucose in a free-living human with diabetes has been reported to date. The in vivo results that have been reported consist of closed-loop control of animals with diabetes and very short-term control of patients with diabetes. Reports of closed-loop systems are described briefly below.

Animal studies

Kan and colleagues in Japan have developed a closed-loop system for glucose control. The sensor is part of a STG-22 apparatus for intravenous glucose sampling and insulin delivery, and the algorithm is a combination of proportional control and model predictive control. This combined algorithm achieved target glycemic levels faster than either algorithm used alone in a set of pancreatectomized dogs.[6]

Ward and colleagues in the United States have reported the use of a nonlinear proportional derivative control algorithm with a fading memory component to automatically control intravenous insulin delivery in alloxan-treated ketosis-prone diabetic rats. A subcutaneous amperometric sensor array was used.[12]

Human Studies

ADICOL: The ADICOL (Advanced Insulin Infusion using a Control Loop) European multinational project was funded by the EC from 2000-2003 and developed an artificial pancreas system that contained a microdialysis system to sample interstitial fluid, which they called *open flow microperfusion*. The fluid glucose concentration was measured with an enzymatic sensor. A series of modeling studies as well as human trials were conducted on fasting and fed subjects.[79-88] Because these studies did not use a functioning subcutaneous sensor, intravenous glucose measurements were used both in real time and with simulated (i.e., delayed by 30 minutes) subcutaneous glucose readings. A Model Predictive Control algorithm was developed for the project.[89] Later, both the microperfusion sampling system and a viscometric glucose monitoring system were each used in human subjects to enhance the model for glucose kinetics.[11] This group is now developing an MPC controller for closed-loop subcutaneous insulin infusion.[86, 89]

Australia: A team reported a closed-loop system for patients hospitalized in an intensive care unit.[5] The system utilized a subcutaneous CGMS sensor, an intravenous insulin infusion setup, and a controller based on a proportional integral algorithm. The control algorithm, however, was not satisfactory.

France: A group has reported work with a closed-loop system, called the long-term Sensor System that contains an intravenous long term enzymatic sensor, an implantable insulin pump that delivers drug into the peritoneum, and a controller with a PD algorithm. This is the only closed-loop system utilizing intravenous sensing and intraperitoneal insulin delivery.

Germany: A group is developing a continuous glucose sensor that utilizes microdialysis to sample interstitial fluid and an enzymatic amperometric glucose measurement. The sensor has been combined with a subcutaneous insulin infusion system and a Model Predictive Control algorithm.

Japan: A group has reported four types of combination systems and the world's longest duration of benefit in their subjects: up to 14 days. They have reported interstitial fluid sampling by microdialysis and glucose measurement by a needle sensor utilizing either glucose oxidase or ferrocene. They have delivered insulin subcutaneously and intraperitoneally with a PD controller.[6, 9, 73-76] Their results, however, were not replicated by an English group that used the same control method.[87]

Corporate: A group from Medtronic Diabetes has done pioneering work in PID control and has tested their algorithm in dogs and humans with subcutaneously measured glucose (using their own commercially available CGMS) and subcutaneously delivered insulin.[10] A preliminary report from a collaboration between investigators at Yale University and Medtronic Diabetes has demonstrated the feasibility of such a system in children.[90] A team from Roche Diagnostics has reported a proprietary microdialysis sampling method, known as SCGM1, to obtain interstitial fluid. The glucose content is then measured enzymatically. Insulin is administered subcutaneously by way of an MPC controller.[7]

Future

Multiple versions of artificial pancreas systems will probably be developed because of the many choices of features available. A future artificial pancreas might measure interstitial fluid glucose or intravascular glucose and deliver insulin through either an external pump or an implanted pump. The insulin delivery route might be into either the subcutaneous or intraperitoneal space for any patient or the intravascular space for inpatients. The controller of insulin delivery might utilize one of several types of control algorithms and might function fully automatically or through some combination of patient-controlled bolus dosing for meals and autonomous dosing for basal delivery between meals. No closed-loop system providing glucagon to prevent inadvertent hypoglycemia due to excessive insulin administration has been reported in 40 years. The use of glucagon in an artificial pancreas system would be physiologically attractive because it could permit more aggressive insulin dosing with less risk of overshoot hypoglycemia. When current bitter technical problems that are delaying development of an artificial pancreas are solved, then the benefits for people with diabetes will be very sweet.

Acknowledgements:

The author thanks Gerold Grodsky and B. Wayne Bequette for their advice and assistance with this manuscript.

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