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Review Article

The future of open- and closed-loop insulin delivery systems

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Abstract

We have analysed several aspects of insulin-dependent diabetes mellitus, including the glucose metabolic system, diabetes complications, and previous and ongoing research aimed at controlling glucose in diabetic patients. An expert review of various models and control algorithms developed for the glucose homeostasis system is presented, along with an analysis of research towards the development of a polymeric insulin infusion system. Recommendations for future directions in creating a true closed-loop glucose control system are presented, including the development of multivariable models and control systems to more accurately describe and control the multi-metabolite, multi-hormonal system, as well as in-vivo assessments of implicit closed-loop control systems.

Introduction

An important aspect of diabetes management is the improvement of our understanding of how homeostasis is affected by external disturbances. From an engineering point of view homeostasis denotes the steady state of a biological system with disturbances leading to dynamic behaviour characterized by instability issues. Thus, to provide homeostatic control with respect to the body's plasma glucose levels, several processes must be analysed and understood.

First among them is how a healthy patient is able to regulate his or her glucose levels, both throughout the day and in response to non-steady-state conditions. Second, the differences between the diabetic patient and the healthy patient must be understood in order to establish which system elements need to be controlled, what constraints exist, and which manipulated variables can be used in developing a control scheme. Finally, it is important to evaluate previous work performed in the area of glucose control, with respect to modelling explicit closed-loop control, and implicit closed-loop devices.

Glucose metabolism

Discussions on glucose metabolism and complications associated with glucose control can provide significant understanding of the diabetes management process (Puckett 1992; LeRoith et al 2000; Larsen et al 2003; Greenspan & Gardner 2004; Guyton & Hall 2006). It is well known that for adenosine triphosphate (ATP) synthesis, the body uses glucose. Therefore, glucose is the primary metabolite required for the body to function properly.

In a healthy individual, the basal glucose level is approximately 80–90 mg dL^{-1}. Although there is usually an abrupt concentration increase associated with ingesting a meal, especially one high in carbohydrates, the plasma glucose levels of a healthy individual seldom go over 120–140 mg dL^{-1}. If the plasma levels are higher than homeostatic levels, the excess glucose is taken into liver and muscle cells and stored as glycogen. However, there is an upper limit on the amount of glycogen that can be stored, and additional glucose is usually converted to fat.

When the glucose concentration is below the basal level, the liver produces glucose endogenously through glycogenolysis, in which the stored glycogen of the liver is catabolized to form glucose, and gluconeogenesis, in which amino acids and fatty acids stored in the liver are converted to glucose. Hormones play a major role in nearly every significant glucose metabolic process. The primary hormones, including insulin, glucagon, adrenaline

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(epinephrine), and certain gastrointestinal hormones, of which glucagon-like peptide-1 (GLP-1) is the most important, all play significant roles in allowing the healthy individual to maintain glucose at basal levels.

Insulin is primarily responsible for two effects. First, insulin binding to muscle and liver cells results in an order of magnitude increase in glucose uptake into those cells. Second, insulin is primarily responsible for the conversion of glucose in excess of that required for maximum glycogen storage into fat. Furthermore, insulin is responsible for the uptake of amino acids and fatty acids into the liver cells, which allows the liver cells to have enough starting materials to produce glucose via gluconeogenesis.

Insulin is produced in the beta cells of the pancreas. The basal insulin secretion is approximately 25 ng min^{-1} kg^{-1} body weight. As glucose ingestion causes the plasma glucose concentration to increase, the secretion rate of insulin is increased. The secretion rate is usually increased by an order of magnitude within 3–5 min of glucose elevation.

Glucagon is primarily responsible for providing the counter-regulatory response in glucose control. As glucose levels descend to below the basal level, usually a result of either fasting or exercise, glucagon binds to liver cells to stimulate glycogenolysis and gluconeogenesis. The binding of glucagon to liver cells also increases the uptake of amino acids and fatty acids, resulting in increased glucose production via gluconeogenesis. Finally, glucagon binding to adipose cells results in the endogenous production of fatty acids to be used in glucose production. Like insulin, glucagon is produced in the pancreas. Glucagon is released during exercise and during episodes of hypoglycaemia (Guyton & Hall 2006).

Like glucagon, the secretion of adrenaline results in increased gluconeogenesis. It also results in the increased mobilization of fatty acids for use in gluconeogenesis. However, unlike glucagon, adrenaline, combined with noradrenaline (norepinephrine), constricts the size of blood vessels and dramatically decreases the flow of blood to other tissues. This results in decreasing the uptake of glucose into the other cells. The secretion of both glucagon and adrenaline/noradrenaline increases in response to exercise. Adrenaline and noradrenaline are also secreted in high stress situations and when the plasma glucose concentration decreases well below the threshold level for glucagon release.

For reasons not completely understood, incretin hormones, of which GLP-1 is the most significant, are released in response to a meal. The incretin effect results in an increase in both pancreatic insulin production and secretion. This results in an increase in plasma insulin even before hyperglycaemia is observed. In addition, the incretin effect also plays a direct role in regulating plasma glucose levels, independent of any role it has in increasing insulin levels.

Diabetes mellitus

Diabetes mellitus is characterized by a breakdown in the glucose metabolic process. Of more interest to this research is Type 1 diabetes, in which the pancreas is unable to provide the necessary level of insulin to control plasma glucose levels. Type 1 diabetes is an autoimmune disease in which the body destroys its pancreatic beta cells. This autoimmune process normally occurs early in a person's life, with later cases normally occurring when a person is in his or her early to mid 20s. For Type 1 diabetic patients and a large number of Type 2 diabetic patients, insulin must be provided from a source other than the pancreas.

For a Type 1 diabetic patient, the insulin levels will be based entirely on the quality of control that is being provided. If the amount of insulin provided is not enough, more glucose will be produced in the liver than can be taken up into cells, resulting in hyperglycaemia. If the hyperglycaemic state is maintained for an extended period of time, the diabetic patient will suffer many consequences (Guyton & Hall 2006). Firstly, the increased level of glucose in the blood changes the osmotic balance of the body, resulting in the loss of water from and ultimately the dehydration of many of the body's cells. Secondly, as the glucose levels increase in the body beyond a threshold of approximately 200 mg dL^{-1}, glucose is no longer able to be reabsorbed in the kidneys and begins to be passed in urine. The high levels of glucose in urine result in changes in the osmotic balance of urinary fluid, resulting in the passing of other fluids and electrolytes not normally passed. The presence of high glucose itself in the body can actually destroy tissue walls, including the walls of blood vessels, kidneys, eyes and limbs. Diabetic patients are at higher risk for heart failure and kidney failure. In addition, it is not uncommon for diabetic patients to suffer blindness, and often limbs have to be removed because of the development of gangrene. As a final effect of frequent hyperglycaemia, the inability of the body to use glucose as fuel results in the body's switching to fat metabolism and protein metabolism. This can result in the body's pH dropping to dangerous levels that can result in death from acidosis, or in the body consuming the proteins of its tissues, also resulting in death.

While hyperglycaemia could perhaps be prevented by purposely providing more insulin than required for glucose utilization, hypoglycaemia would result from providing too much insulin. The amount of insulin available in the blood has a direct effect on the amount of glucose being taken into the cells of the liver and muscle cells. As the insulin availability increases, so does the uptake of glucose into the liver and muscle cells, regardless of the needs of other cells. This is problematic because glucose is the only nutrient that can be used by certain cells in sufficient quantity to allow them to sufficiently perform their metabolic processes.

The most important of these include the brain and the retina. If the brain is unable to get the necessary glucose to perform its metabolic functions, death will result. Adding to the severity of the problem is that if the pancreas is regularly increasing its glucagon output to increase the glucose levels in response to hypoglycaemia, it will eventually become insensitive to the low glucose levels, and eventually hypoglycaemia will not result in the production of glucagon. The central nervous system is responsible for the production of adrenaline, and so this low level of hypoglycaemia will result in the secretion of adrenaline as well. Therefore, to maintain healthy basal conditions, it is very important that a diabetic patient be able to exercise tight glucose control by using carefully determined insulin dosages.

When a diabetic patient eats a meal, the outcome again strongly depends on the quality of insulin therapy. Specifically,

the patient's glucose levels will depend on both the amount of insulin administered and the time of administration. If insulin levels are too low, two dramatic effects will result in extreme hyperglycaemia. First, there will not be enough insulin to allow the glucose to be taken into the liver and peripheral cells. Second, the low insulin levels will result in relatively high glucagon levels, which will actually result in even higher levels of glucose in the blood.

In addition to the amount of insulin administered for a meal, the time of administration plays a major role in maintaining normoglycaemic conditions. This time usually corresponds with the production of the GI hormones associated with the meal. If the administration is too early, the result will be the onset of hypoglycaemia before the meal is absorbed and hyperglycaemia near the end of the meal, as there will not be sufficient insulin to allow the glucose infusion from the end of the meal to be utilized. If the insulin is administered too late, hyperglycaemia will result at the beginning of the meal and hypoglycaemia will result at the end of the meal or shortly after.

During exercise, if too much insulin is present in the body before exercise, the result will be an increase in glucose uptake in the liver and periphery, and the inhibition of both glucose and fatty acid production. The fatty acid levels do not increase, and so the glucose utilization by the cells increases. The consequence of all of these effects is the onset of hypoglycaemia, a common occurrence during exercise for diabetic patients.

When too little insulin is present during exercise, the result will be hyperglycaemia. This is not a problem during exercise, as the increased glucose levels provide additional fuel that can be used. However, once exercise has been completed, the patient now has higher glucose levels than normal, and there is no effort by the body to restore the levels to normal.

As discussed in the previous paragraphs, diabetes can result in very serious consequences for both hyper- and hypoglycaemia. The ability to live a life of nearly the same quality as a healthy patient largely depends on the ability of the patient to provide the right amount of insulin at the right time. To achieve this optimal type of administration, several insulin delivery methods have been proposed and developed.

Review of insulin delivery techniques

To effectively control glucose in Type 1 and some Type 2 diabetic patients, insulin must be administered in such a way that neither hyper- nor hypoglycaemic episodes are regularly experienced. Several different insulin administration techniques have been studied. Several other methods have been proposed and are the focus of current research. Each method can be classified by the type of control provided and by the site at which insulin is delivered. Each will be discussed below.

Open-loop methods

Open-loop methods of insulin delivery focus on a patient administering insulin to his or herself at different times of the day. The purpose here is to briefly describe open-loop methods of control. The interested reader is directed to Parker (2004) for a more thorough review of the open-loop route.

The most common method of open-loop insulin delivery is the subcutaneous insulin injection. Patients will often inject a slow-acting insulin formulation in the morning to provide the basal insulin requirement throughout the day. This analogue, known as insulin glargine, is developed by modifying certain amino acids on the different insulin chains (Parker 2004). Once altered, it is able to provide a steady release of insulin all day. In addition to the basal requirement, patients will inject insulin into subcutaneous tissue before meals. The amount of insulin to inject will depend on a measurement of glucose and on an estimate of the amount of food that is about to be eaten. To provide rapid insulin during this situation, a fast-acting insulin formulation such as insulin aspart or insulin lispro is used. This method suffers from the requirement of three or more daily injections into a layer of subcutaneous tissue. In addition, because the injected insulin must diffuse through the subcutaneous tissue to be absorbed into the bloodstream, and because some of this insulin may be degraded in the subcutaneous tissue during this diffusion, not all of the injected insulin will be available in the body. Also, the diffusion across the subcutaneous layer will create an additional time delay in addition to the delay associated with insulin binding to mediate glucose uptake. Finally, because the insulin will go straight from the subcutaneous layer to the bloodstream, the first-pass effect, in which approximately 40% of insulin secreted from the pancreas is degraded in the liver before reaching the bloodstream, will not occur. This will result in increased uptake into the muscle cells and decreased uptake into the liver relative to a healthy patient.

An improvement to the insulin injection is the externally worn insulin pump. The pump is always attached to the diabetic patient, and a basal amount of insulin is provided throughout the day. When the patient is going to modify his or her insulin delivery because of a meal or exercise, the insulin infusion rate can be modified. Pumps have recently been developed to determine the bolus size for a given situation (Medtronic MiniMed 2007a). The patient must input his or her blood glucose levels and an estimate of the size of the load (meal size or exercise load) and the change in infusion will be determined. This type of administration has two primary advantages over injections. First, because the pump has a catheter that is always in contact with the patient, multiple insertions will not be required, increasing the quality of life for the patient. The exception is when the catheter is periodically changed, but this is still significant improvement to the three or more injections usually required. The second advantage is the ease in which a change in the insulin infusion can be made. If a patient were to eat a different amount of food than projected, or were to exercise for a different duration, the insulin rate can be adjusted to account for this. However, the disadvantages associated with subcutaneous delivery still exist. Furthermore, the patient is required to wear a pager-sized device at the abdominal area. Such a device would definitely be noticeable and would have a definite impact on the quality of life for the patient.

In addition to subcutaneous delivery, other open-loop methods have been proposed that take advantage of other administration sites. Recently, the Food and Drug Administration has approved the use of Exubera, an inhaled form of insulin, to be used by insulin-dependent diabetic patients

(McMahon & Arky 2007). The biggest advantage of such a technique is the increase in patient compliance, as a result of no longer having to receive injections or having to wear an external pump. However, several disadvantages exist. First, the bioavailability of inhaled insulin is less than that of a subcutaneous infusion. In addition, a slow releasing insulin analogue has not been developed in an inhaled form, so basal administration is still necessary. Finally, because the absorption rate of insulin via the lungs can vary significantly for circumstances such as if a patient smokes or develops a cold, the dose must be carefully determined. Over-absorption of insulin can easily result in severe hypoglycaemia (Parker 2004).

In addition to inhalation, NIH funding is currently being applied toward the development of oral insulin delivery. Like the inhalation route, the oral route would in theory prevent the patient from having to receive multiple daily injections. However, there are drawbacks to oral delivery. The first disadvantage of the oral route is the difficulty in maintaining the integrity of insulin in the harsh environment of the stomach. Insulin must be able to pass through the stomach and into the intestines for absorption into the bloodstream. However, the acidic gastric environment will degrade insulin, requiring a protective vehicle to allow the insulin to pass safely to the small intestine. Peppas (2004a) has developed a biomaterial for oral delivery of proteins that protects them in the harsh stomach environment and releases them in the higher pH environment of the small intestine. While protein degradation is one main cause of low bioavailability for protein delivery, another disadvantage of oral delivery is the low bioavailability associated with poor absorption from the intestine into the bloodstream (Morishita & Peppas 2006). Ongoing research in many labs, including the Peppas laboratory, is currently focused on improving the transport of insulin across the intestinal epithelium.

In addition to oral and inhaled insulin delivery, other proposed methods include delivery via the eyes, skin, and nasal passages (Parker 2004). All open-loop delivery systems require some level of patient or doctor involvement in the insulin administration. This will require a blood glucose measurement, an estimate of the meal to be consumed, and a calculation to determine an empirical estimate of the insulin requirement. With the exception of the insulin pump, the open-loop method requires a patient to live a predictable lifestyle, one in which his or her meal is prepared specifically for the given insulin bolus and exercise must be performed only in accordance with the insulin received.

Closed-loop delivery

An effective alternative to open-loop insulin delivery is closed-loop delivery, in which the involvement of the patient in maintaining glucose control is minimal. Such a system would be able to determine the insulin requirement in real time, regardless of the situation, and deliver the proper insulin dosage. It would be able to change the infusion as the patient's activity changes and, ideally, would exist internally, eliminating the requirement of wearing external equipment. Such a system would also aim to significantly reduce the number of injections required or to eliminate them altogether. The ideal method of closed-loop delivery would be to repair the body's natural ability to infuse insulin. One method to achieve this would be the pancreas transplant. Ideally, the transplantation of a healthy pancreas would enable a diabetic patient to produce insulin as a healthy patient. However, there are many shortcomings associated with this approach. First, this method depends strongly on the availability of a healthy pancreas for transplantation. Second, the body of a pancreas recipient often undergoes an immune response that ultimately rejects the foreign organ (Parker 2004).

Another natural method would be to restore to the patient's pancreas the ability to naturally secrete insulin as a healthy patient (Bouwens & Rooman 2005). While such a method has promise, a great deal of research must be performed before this type of therapy can be useful to man. A third method involves implanting encapsulated islet cells from a healthy pancreas, in the hopes that the immune response associated with the foreign pancreas can be avoided. At the same time, the islet beta cells will be able to produce insulin as a healthy pancreas would. This method is the subject of much ongoing research (Parker 2004).

While natural pancreatic restoration methods are ideal, research must still be completed to determine the feasibility of these methods becoming reality. Perhaps a more realistic method of closed-loop control involves engineered solutions. First is the idea of explicit closed-loop control, in which a glucose sensor, an insulin infusion algorithm, and an insulin pump are used to form an artificial pancreas. Second is the idea of implicit closed-loop control, in which polymeric material is able to act as the sensor, control algorithm and infusion system. To test the validity of such methods, simulations are performed by first developing a model of the infusion and then implementing the infusion model with a model of glucose dynamics within a diabetic patient. Patient modelling, explicit closed-loop control, and implicit closed-loop control will now be discussed.

Diabetic patient models

Models describing the important metabolite and hormone dynamics in diabetic patients have been developed since 1960 to gain understanding of the glucose homeostasis system and to simulate what effect certain therapies would have on the patient. This review covers different models developed during the last few decades. Others have written reviews on the models and described their various advantages and shortcomings. The interested reader is directed to Sorensen (1985), Puckett (1992), Parker & Doyle (2001) and Steil et al (2005) for more insight.

Patient models can be broken down into two main groups. On one side is the pharmacokinetic model, in which elimination and absorption kinetics are described for each species, and a theoretical number of compartments is determined based on elimination and absorption data (Holz & Fahr 2001). The second Type 1 is the physiologically explanatory model, in which an organ system is considered to be a compartment, and mass balances are written for each organ system by considering convection resulting from blood flow, diffusion from blood to within organ cells, and metabolic processes (Himmelstein & Lutz 1979; Bischoff 1987). Both types have been developed in the past. While the pharmacokinetic models have the advantage of being easier to identify from experimental data, Doyle et al (1995) have shown that

more complex models may be needed to provide the necessary accuracy for effective control studies.

The first known pharmacokinetic model for glucose regulation was developed by Bolie (1960). The model consisted of one linear equation for insulin and one for glucose. Elimination and absorption kinetics were described by first-order rate equations. While developed for a healthy patient, assuming that insulin secretion was simply proportional to glucose, the diabetic patient can be described by setting the first-order insulin secretion rate constant to zero. Ackerman et al (1965) modified the model by tying insulin and all other hormones involved in glucose regulation together as a single variable. The model form remained the same however. The main criticisms of these models are that they represent a clear oversimplification of the glucose regulatory system. Besides the fact that insulin or hormone secretion is more complex than a simple first-order process, the use of a single insulin or hormone compartment has been criticized by multiple reviewers, including Sorensen (1985) and Parker & Doyle (2001).

Frost et al (1973) developed a two-compartment pharmacokinetic model for insulin in healthy and diabetic patients. For healthy patients, the insulin secretion rate is given as an exponential function of glucose. For diabetics the secretion is taken to zero. Insulin elimination was taken to be a nonlinear saturation function of insulin for healthy patients and a first-order process for diabetic patients. Frost himself admits that this also is an oversimplification, but notes a strong fit to patient data. His two compartment model with nonlinear sinks is also an improvement over the earlier developed models.

Sherwin et al (1974) and Cerasi et al (1974) simultaneously developed a three-compartment pharmacokinetic model in which a central compartment is continuously exchanging insulin with two side compartments. While more complex with respect to the number of insulin compartments, insulin appearance and elimination from each compartment, it is modelled as first-order elimination kinetics. The model of Cerasi also has six linear ordinary differential equations (ODEs) to describe physiological insulin secretion. While the three insulin compartments are said to provide more physiological accuracy than the one compartment models previously used, the one compartment glucose model of Cerasi is likely inaccurate. Insel et al (1975) developed a three-compartment glucose model that included nonlinear terms to account for insulin effects on glucose uptake. However, the nonlinear term is effectively zero order with respect to insulin, and thus does not really effectively show accurate insulin effects in glucose consumption.

The majority of pharmacokinetic models developed since then have been modifications of the original pharmacokinetic models previously developed. Tranberg & Dencker (1978) developed a two-compartment insulin model very much like that of Frost. Home et al (1982) and Kobayashi et al (1983) both used a one-compartment model to fit kinetic parameters from patient data. Hipszer et al (2005) recently used the one-, two-, and three-compartment insulin models to fit insulin data from diabetic patients, concluding that a single insulin compartment was all that was needed to describe insulin kinetics. Salszieder et al (1985) developed a one-compartment model for both insulin and glucose, but increased model complexity in two ways. First, they assumed that glucose production and uptake were best expressed as differential equations. Second, they assumed that insulin accumulation was a function both of the glucose concentration and the derivative of the glucose concentration, an assumption which, as discussed later, forms the basis of many of the control systems designed for glucose control. Parker & Doyle (2001) indicated that this model was not able to accurately describe faster dynamic processes associated with glucose regulation.

Perhaps the most widely used pharmacokinetic model to describe glucose and insulin kinetics is the minimal model developed by Bergman et al (1979). The authors chose from seven different pharmacokinetic model structures, including some of the previously developed models, to select the model structure displaying both a strong representation of intravenous glucose tolerance test (IVGTT) data and physiological relevance. The model consists of a single glucose compartment and two insulin compartments. The pharmacokinetic diagram is given in Figure 1. Glucose elimination is considered to be a nonlinear function of both glucose and a term representing insulin that is bound to liver and peripheral cells. While originally developed based on animal studies, the model was later applied to studies in man (Bergman et al 1981a, b), to an oral glucose tolerance test (OGTT) (Dalla Man et al 2005), and to a mixed meal test (Caumo et al 2000).

There have been several published studies displaying the shortcomings of the minimal model, including the work of Quon et al (1994) and Finegood & Tzur (1996). Both groups found that the minimal model did not accurately quantify the relative contributions of insulin and glucose with respect to glucose uptake. Cobelli et al (1998) later determined that the problem stemmed from the use of a single glucose compartment. This led to efforts to develop an improved minimal model, beginning with a two-compartment glucose model (Caumo et al 1999; Cobelli et al 1999), and ultimately leading to the recently developed hot IVGTT two-compartment minimal model (Toffolo & Cobelli 2003). The model continues to be improved today (Krudys et al 2005).

More recently, control engineers have gained an interest in the pharmacokinetic model developed by Hovorka et al

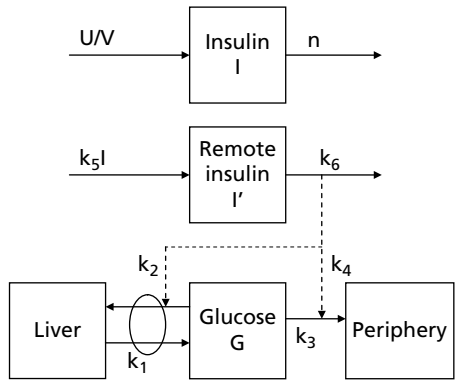

Figure 1 Pharmacokinetic diagram of the minimal model. Solid lines represent material appearance or disappearance, and dashed lines represent contributions toward the kinetic appearance or disappearance. The k_is represent the rate coefficients for each term with respect to the kinetic process.

(2002, 2004). In a similar manner to Bergman and Cobelli with the minimal model, Hovorka et al (2004) proposed a number of different models before deciding on the one that best fit the data as well as corresponded to physiology. The model diagram is given in Figure 2. It uses two glucose compartments and three insulin-action compartments, describing the appearance and elimination of each species as a first-order process. While there is only a single actual insulin compartment, three different types of insulin action are described and assumed to differ with respect to their ability to affect glucose metabolism. This coincides well with the original claims of minimal model critics, which may have a lot to do with its rapid acceptance among control engineers. Wilinska et al (2005) recently improved upon the model to more accurately describe the kinetics associated with subcutaneous insulin delivery.

The second major type of patient model is the one that describes biochemical species dynamics at each significant organ site. These models are developed by selecting as the main compartments only those organs in which significant species appearance or disappearance occur, and writing mass balances accordingly (Himmelstein & Lutz 1979). The first model of this type was developed by Foster et al (1973). This model assumed a glucose compartment for blood, muscle and the liver, while assuming a single compartment each for insulin, glucagon and fatty acids. Guyton et al (1978), which included Foster, increased the complexity of Foster's model. A central organs compartment was added to the glucose model, insulin secretion from the pancreas was made more complex, and diffusion was included in the transport equations. Sorensen (1985) improved Guyton's work by dividing the central organs compartment into the brain and gut compartments and by including the counter-regulatory effects of glucagon. A model diagram of Sorensen's glucose model is given in Figure 3. The model of Foster et al (1978) is the only one to include fatty acid metabolism.

Other physiologically relevant models include the glucose model of Tiran & Galle (1975), the insulin model of Tiran et al (1979), the model of Cobelli et al (1981), and the model of Puckett (1992). The many parameters of Tiran's models were estimated using dog data. The models also did not include the effects of glucagon. The models are also given in transfer function form, meaning that they represent linear representations of the systems. The model of Cobelli considers glucose to be a single subsystem, and contradicts his own minimal model improvements made years later. Puckett developed a model very similar to Sorensen's, but did not include glucagon effects, and removed all transport terms besides the metabolic sources and sinks. In this way, her model represents a multi-compartment pharmacokinetic model. As such, any dynamics associated with other transport will not be captured by this model.

While Sorensen's model has been the most widely used physiological model with respect to glucose control, it has been criticized for not accurately representing observed glucose behaviour in diabetic patients. Steil et al (2005) have pointed out that the model underpredicts the threshold glucose concentration at which insulin action becomes saturated.

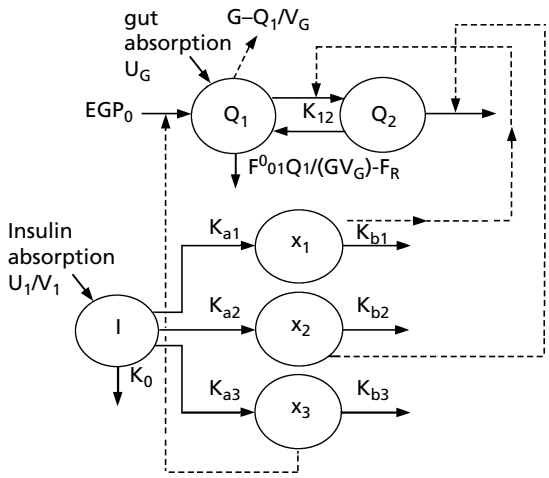

Figure 2 Pharmacokinetic diagram from the Hovorka model (Hovorka et al 2004). Q_1 and Q_2 represent the mass of glucose in compartments 1 and 2, respectively. I represents plasma insulin, and x_1, x_2, and x_3 represent insulin action toward glucose uptake, production and exchange between the two compartments, respectively. Solid lines represent kinetic appearance or disappearance. Dashed lines represent action by insulin. Large solid arrows represent a single non-continuous source of either glucose or insulin.

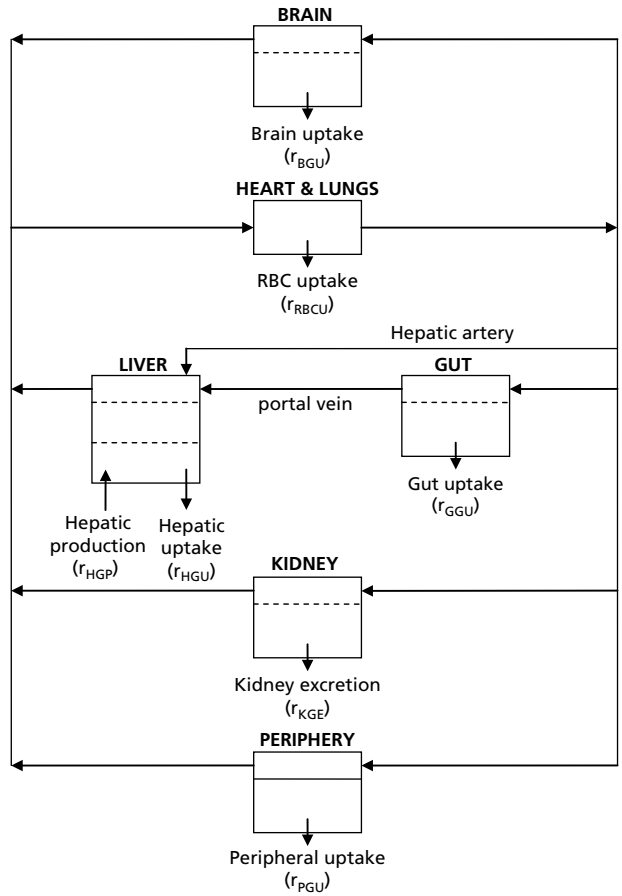

Figure 3 Flow diagram of the Sorensen glucose model (Sorensen 1985).

They also mentions that the model poorly represents the glucose concentration of a patient with zero insulin and that the sharp drop in glucose that is experienced by patients whose insulin levels rise quickly is also not predicted. However, despite these shortcomings, it remains the most physiologically accurate model developed to date. In addition to the development of a model, the model parameters must be accurately estimated to ensure reasonable simulation results. While the assumed accuracy of physiological models relative to pharmacokinetic models makes them enticing for control simulations, they suffer from the drawback of having tens to hundreds of parameters that must be identified. Specific patient metabolic rates cannot usually be measured, and so many different techniques have had to be used to estimate model parameters. Some authors, such as Bolie (1960), Guyton et al (1978), Tiran & Galle (1975), Tiran et al (1979), and Sorensen (1985), used average reported parameters, such as compartment volumes and blood flows. Sorensen and Bolie chose to extrapolate human parameters from reported dog and rat parameters, assuming a linear relationship based only on bodyweight. In other instances, specific data were acquired that allowed specific model parameters to be determined, such as most of the kinetic parameters of Sorensen's model and the diffusion terms of Tiran's models. Most often, however, the model parameters were estimated by comparing model responses to glucose and insulin data, and selecting the parameter set minimizing the sum of the squared residuals. It would appear that the lower order models have an advantage in that they can be estimated with a single set of glucose or insulin data, whereas the larger models will have to either assume average parameters values from literature or be able to use experimental data for a specific biochemical species in a specific tissue compartment. Finally, it should be noted that most average patient parameter values are given for a 70 kg adult male, independent of age, and that values for a patient not matching this description would still have to be determined, either through experiment or approximation.

Explicit closed-loop control

By utilizing the principles of process control, the body can be treated as a chemical process. Glucose metabolism can be simplified to the control of a single variable, glucose, through the use of a single manipulated variable, insulin. The effectiveness of such methods depends on the effective development of glucose sensors, insulin pumps, and control algorithms relating the insulin infusion to past, present and predicted glucose values.

The development of improved glucose sensing methods is probably the most active component of research being applied toward the development of an explicit closed-loop system. Even without the pump and algorithm, the use of a glucose sensor that is able to give frequent blood glucose measurements in real time is a dramatic improvement to drawing blood via a fingerstick and measuring glucose directly. Joseph & Torjman (2004) summarized the different types of sensors being developed, including sensor design and biological issues associated with each. Among the sensors discussed are those implanted in either the subcutaneous tissue or the bloodstream. Most invasive sensors are based on enzyme catalysed glucose oxidation. One issue associated with implanted sensors is the immune response of the body to foreign species. This can reduce the life of the sensor and can also interfere with its ability to give accurate readings. Another issue is the frequency of measurements. Medtronic MiniMed (Northridge, CA) has developed external sensors capable of giving measurements less than 5 min apart (Medtronic MiniMed 2007b). However, the device is not implantable. Devices implanted in the subcutaneous tissue also have the issue of not reading the actual glucose values of blood. The diffusion of glucose from blood to the subcutaneous tissue can result in time delays of approximately 10 min. Schmidtke et al (1998) and Freeland & Bonnecaze (1999) have worked on developing dynamic models so that blood glucose values can be inferred from subcutaneous values. Much research is still needed, however, to develop implantable devices that can frequently report accurate glucose values for long periods of time (Colberg 2005; Ginsberg 2005). In addition, the lack of developed sensor technology for the other biochemical species to be determined in real time severely limits the possibilities of control to be based on glucose measurements only.

The second mechanical component of the system is the insulin infusion pump. Insulin pumps currently developed by Medtronic MiniMed are able to provide rapid-acting insulin throughout the day either as a basal pulse or as a bolus for a meal (Medtronic MiniMed 2007c). With the patented 'Bolus Wizard' the insulin bolus will be calculated based on the size of the meal and the current glucose measurement. However, implantation of such a device is still a work in progress. Many issues must be resolved, including the immune response of the body, the location of the device, and how often the pump's insulin must be replaced. While Renard (2002) argues that the pump should be placed within the peritoneum, a device planted under the skin may be easier to refill. However, such a device would likely be supplying insulin to the subcutaneous tissue, and delivery would not be like that of a healthy patient.

Parker et al (2001) reviewed many of the algorithms developed for glucose control before 2000. Bequette (2005) also reviewed many of the older developments while reviewing algorithms developed through 2005. The aim of this work is to summarize those reviews and to review algorithms developed since 2005.

The first algorithm of real significance with respect to the development of the artificial pancreas was proposed by Albisser et al (1974). This algorithm provided insulin when glucose was higher than the desired level and dextrose when glucose was lower than desired. The dextrose infusion rate was proportional to glucose infusion, and the insulin infusion rate was based on a nonlinear proportional plus derivative (PD) algorithm. The 'Biostator' algorithms (Clemens 1979) improved upon Albisser's work to try to improve the response of blood glucose to a meal. This algorithm suffered from many problems. First, the control algorithm consisted of many patient-dependent parameters, meaning the algorithm would have to be developed for a specific patient (Parker et al 2001). If patient parameters changed over time, the algorithm may also have to be reprogrammed. The second major problem is that the derivative was calculated using finite difference

for the previous four measurements (Bequette 2005). Each measurement was one minute apart, and so the rate immediately after the beginning or end of a meal will inevitably suffer from a time lag before it is properly adjusted. In addition, measurement noise associated with any of the four points could also dramatically affect the infusion rate. Many authors (Parker et al 2001) tried to create improvements to the Albisser's algorithm, but no controllers were found to outperform the original nonlinear PD algorithm.

As validation that the PD algorithm is indeed the best representation, Nomura et al (1984) studied the response of beta cells of healthy rats to a step disturbance of glucose. Glucose was infused at a constant rate, and the insulin concentration was noted with time. A biphasic response was observed, and the time constants associated with each phase were estimated. The biphasic response of the pancreas is shown in Figure 4. Steil et al (2004) investigated Albisser's algorithm and the algorithms of 'Biostator' while also proposing a proportional plus integral plus derivative (PID) algorithm for insulin infusion. Controller effectiveness was studied by performing simulations using the model of Cobelli et al (1981). For the simulation, the model was initially in the hyperglycaemic state, and the ability of the controller to return glucose levels to normal was investigated. The algorithm has been implemented in the implantable pumps of Medtronic MiniMed, and the ability to return glucose levels to normal in hyperglycaemic diabetic dogs was observed. The pump was also implanted into volunteers, and the control algorithm was demonstrated to result in both hyperglycaemia after the consumption of a meal and hypoglycaemia after the meal. An argument against the use of PID controllers to mimic the biphasic insulin profile is made by Bequette (2005), who argues that such a response can be the result of any control system in which integral action is present, and that internal model controllers can also have the same response. He also argues that integral control can result in hypoglycaemia as a result of infusing too much insulin.

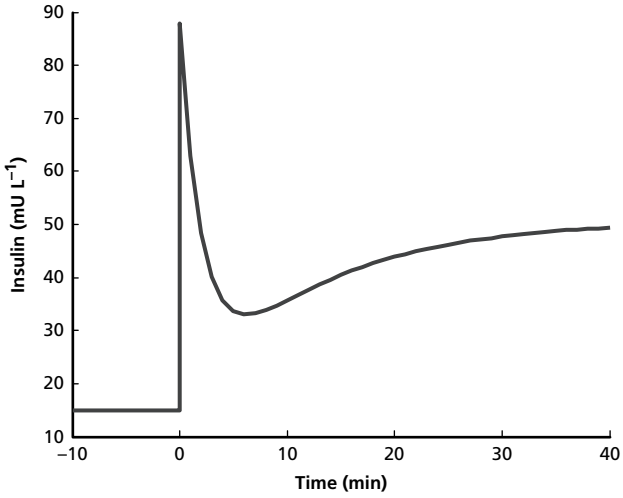

Figure 4 Biphasic insulin response to step increase in glucose, as modelled by Nomura et al (1984). At time zero the glucose concentration is increased from 80 to 160 mg dL^{-1} and maintained at the new level. A basal insulin concentration of 15 mU L^{-1} was assumed, as the results of the model simulation are given as insulin levels above basal. At the time of the glucose change, a sharp spike in insulin occurs, known as first phase release. This response falls off rapidly, followed by a second delayed release phase that gradually increases to the steady-state insulin value.

Many authors have studied control algorithms by performing simulations using the well known patient models. Furler et al (1985) investigated the use of a semiclosed-loop algorithm based only on current glucose levels by performing simulations with the minimal model. The ability to return glucose levels from hyperglycaemia to normal was observed, but no attempt was made to prevent glucose levels from approaching hyperglycaemia after consumption of a meal. Sorensen (1985) developed an internal model controller, and simulations were performed using his developed patient model. The controller is able to keep glucose levels under 140 mg dL^{-1} during a 100 g oral glucose tolerance test (OGTT). Parker et al (2001) showed that the effectiveness of the controller is highly parameter dependent and that changing the model parameters results in the controller no longer being able to reject the disturbance.

Recent efforts in algorithm development have focused on advanced control methods. Among the first advanced control systems were the optimal controllers developed by Ollerton (1989) and Fisher (1991). Ollerton used optimal control to minimize the integral of the squares of the differences between a glucose measurement and the glucose set point. The minimal model was discretized with a 10-min sampling interval, and the insulin infusion profile minimizing the objective function was chosen as the optimal profile. A 180-min sampling time is also used, but such a long sampling time would be unable to correct for a meal disturbance that was present in between the samples. The author shows that the algorithm is able to return an initially hyperglycaemic patient to normal levels, even in the presence of a 100 g/day infusion of glucose. However, the algorithm is unconstrained with respect to the states, inputs and outputs, and the optimal solution results in insulin levels below 0 mU L^{-1}, which are not physically attainable. Even with negative insulin levels, the control system is unable to prevent the onset of hypoglycaemia. Fisher also used the integral squared error objective function to apply optimal control to the minimal model, but chose three different semiclosed-loop insulin delivery systems to investigate. The first system comprised a basal infusion and injections when necessary, the second consisted of an infusion pump only that was optimized every hour, and the third system consisted of the optimal hourly infusion and the injection when needed. The optimal injection and pump infusion, where applicable, were determined using the objective function. Fisher showed that the best controllers consisted of the optimal insulin injection, and that the optimal infusion alone would not be able to reject a meal disturbance without the onset of hypoglycaemia.

Other methods of advanced control that have been applied include the application of H_∞ control by Parker et al (2000). The authors applied H_∞ control to a modified version of Sorensen's model in which model parameter uncertainty was considered. The control was applied after the model was reduced. Simulations showed that neither hyper- nor hypoglycaemia were approached.

The most recent developments in closed-loop control have focused on model predictive control (MPC) to provide the optimal control profile while considering constraints. Given measured outputs, model parameters are estimated using state estimation, and an objective function is solved based on the model prediction of the future glucose trajectory resulting from that particular insulin profile. Parker et al (1999) developed a model-based algorithm employing a linearized version of the Sorensen model, a Kalman filter, and a linear quadratic objective function. Like other methods applied to Sorensen's model, neither hyper- nor hypoglycaemia were approached. Lynch & Bequette (2001) applied linear MPC to the Sorensen model by using the minimal model to determine the insulin infusion profile. The authors later applied MPC directly to the minimal model, showing that neither hyper- nor hypoglycaemia were approached during a meal (Lynch & Bequette 2002). Hovorka et al (2004) applied nonlinear MPC to Hovorka's original model. While the authors were able to show that nonlinear MPC used along with an injection at mealtime was able to reduce hyperglycaemia and prevent hypoglycaemia, no work was presented in which only the MPC controller was used.

Diaz et al (2005) applied predictive functional control to Carson's model. While able to simulate the reduction of hyperglycaemia during a meal and the prevention of hypoglycaemia, the results were achieved by utilizing insulin infusion rates that could lead to hyperinsulinism (Guyton & Hall 2006) and that may be infeasible for today's insulin infusion pumps. Finally, Agar et al (2002) developed an online simulation tool employing MPC to control a patient using Puckett's model as both model and patient.

Implicit closed-loop control

The development of an effective explicit closed-loop control system depends on the ability of engineers to develop an effective sensor for each output, an effect control algorithm that allows the controlled variables to be maintained at normal levels during many different conditions, and an effective infusion pump. The pump and the sensor must be attached to or implanted in the body and they must be able to respond quickly to the changing environment.

An alternative that removes the necessity of developed equipment is the implicit closed-loop control system, in which a chemical system is acting as all three components of the control system. The system, which contains insulin, is able to modify its insulin release profile in response to a change in the local environment. By mechanically changing in response to its environment, the system acts as a sensor. By releasing insulin through natural transport processes, the device acts as the infusion system. By being optimally designed to release the right amount of insulin for each condition, the device development is the control algorithm.

The required stimulus is the state of the local environment, and so a logical candidate to serve as such a device is the environmentally responsive hydrogel. Hydrogels are crosslinked hydrophilic polymer networks that are able to absorb large amounts of water (Peppas 2004b). The functional groups of the polymer backbone can be modified to allow the hydrogel to swell or deswell in response to many different stimuli, including pH and temperature.

To be used as glucose sensors, Albin et al (1987), as well as Schwarte et al (1998) and Podual et al (2000a, b), have incorporated enzyme-catalysed glucose oxidation into the hydrogels by immobilizing glucose oxidase into the gel network. Since one of the reaction products is gluconic acid, it is logical to develop the gels to be pH-responsive. The release of insulin should increase in response to increased glucose, and so it is also natural that the hydrogel system be designed to swell in response to an increase in acid concentration, or a pH decrease.

Hydrogel systems that are responsive to pH changes can be divided into two groups. The first are the anionic hydrogels that swell in response to a high pH. These gels contain acid groups that deprotonate at a high pH. This ionization results in repulsions among functional groups within the chains. Examples of anionic hydrogels include the poly(methacrylic acid-graft-ethylene glycol) gels developed by Peppas (2004a) for oral delivery, and the poly(N-isopropylacrylamide-co-methacrylic acid) gels developed to serve as chemomechanical oscillators (Leroux & Siegel 1999; Dhanarajan et al 2002). Cationic hydrogels are hydrogels that swell in response to a decrease in pH. These gels contain basic functional groups, such as methacrylates. Below the pK_a of the functional group, the functional groups become protonated, which results in a change in hydrophilicity of the network, causing an increase in water uptake into the gel (Podual et al 2000a). This results in increased swelling at the pH below the pK_a of the functional groups.

Many people have studied the swelling and release characteristics of pH-sensitive cationic hydrogels. Firestone & Siegel (1991) investigated the swelling kinetics of copolymer gels of methacrylic acid and dimethylaminoethyl methacrylate, poly(MMA-co-DMAEM), as a function of pH, ionic strength, and temperature, showing that these systems can take in as much as eight-times their collapsed weight in water. Siegel et al (1992) showed that the pK_a of the buffer solution had a strong effect on the swelling of these gel systems. Firestone & Siegel (1988) showed that these systems were able to demonstrate oscillatory swelling and deswelling, and that successive pH increases with time resulted in successive deswelling to a specific swelling ratio. Cornejo-Bravo & Siegel (1993) studied water sorption for copolymers of diethylaminoethyl methacrylate and methyl methacrylate (poly(DEAEM-co-MMA)), but no dynamic swelling or release results were given. Finally, Siegel et al (1988) investigated the release of caffeine from a hydrogel disk approximately 13-mm in diameter and 0.33-mm thick, and the effects of buffers on release (Cornejo-Bravo & Siegel 1995). At pH 3, the loaded disk no longer released caffeine at approximately 100 min from the start of the experiment. The completion time had increased to 200 min for pH values of 5 and 7. All of Siegel's swelling studies showed the gels reaching their equilibrium swelling ratios in the order of hours.

In our laboratory, we have investigated the swelling and release of pH-sensitive cationic hydrogels as well. Hariharan & Peppas (1996) studied dynamic and equilibrium swelling for a poly(diethylaminoethyl methacrylate-co-hydroxyethyl methacrylate) (poly(DEAEM-co-HEMA)), poly(diethylaminoethyl acrylate-co-hydroxyethyl methacrylate) (poly(DEAEA-co-HEMA), and also poly(methacrylaminopropyl ammonium

chloride-co-hydroxyethyl methacrylate) (poly(MAPTAC-co-HEMA)). They were able to demonstrate that poly(DEAEA-co-HEMA) showed no water sorption at pH 8, while the gels were able to uptake more than 10-times the weight of the collapsed gel at pH 3. Using poly(DEAEM-co-HEMA) they demonstrated that 1-mm thick disks would reach equilibrium swelling in approximately 3 h, displaying weight swelling ratios ranging from 1.5- to 2.5-times the original weight of the gel. Ende et al (1995) performed release studies of oxprenolol HCl from poly(DEAEA-co-HEMA) and poly(DEAEM-co-HEMA). Maximum drug release was observed to occur from 1-mm disks within 12 h for poly(DEAEA-co-HEMA) and in the order of one day for poly(DEAEM-co-HEMA), with rapid release occurring in the first 5 h, followed by slower release until the device no longer released.

Increasing the number of functional groups results in a lower transition pH for swelling, and so cationic hydrogels of poly(diethylaminoethyl methacrylate-co-ethylene glycol monomethyl ether monomethacrylate) (poly(DEAEM-g-EGMMA)) were developed by Podual et al (1998, 2000a, b, c) and Schwarte et al (1998). A small amount of PEGMMA was added to the gels to impart stealth capabilities in the body, preventing a rapid immune response from occurring. The gels displayed a transition pH of around 7.1, and displayed volume swelling ratios ranging from 8 for highly cross-linked gels to over 40 for lightly cross-linked devices. Dynamic studies showed that disks measuring 1-cm diameter and 1-mm thick would reach equilibrium swelling in response to a pH change below the transition pH in approximately 5–6 h. Microparticles of poly(DEAEM-g-EGMMA) were developed, and results showed that the gels reached equilibrium swelling nearly instantaneously to a decrease in pH below the transition pH (Podual et al 2000b). The gels were also shown to be glucose sensitive by observing their swelling in solutions of different glucose concentrations (Podual et al 2000c). Finally, insulin release was demonstrated in response to change in glucose. Insulin was shown to be completely released from the system within 20 min (Podual et al 1998).

Based on the currently developed formulations of poly(DEAEM-g-EGMMA), the hydrogel system would function as an implicit closed-loop system by way of the following mechanism, as shown in Figure 5. Small hydrogel particles would be injected directly into the bloodstream, where they would be protected from the body's immune response by the ethylene glycol grafts. As the glucose concentration of the blood increases, there will be increased diffusion of glucose to within the gel system. Within the gel, the presence of immobilized glucose oxidase will result in the enzyme catalysed oxidation of glucose, forming gluconic acid. This acid formation will result in a slight pH change. The pH change will not be large because of the presence of buffers in the bloodstream, most importantly the bicarbonate buffer system (Guyton & Hall 2006). When the pH decreases below the transition pH of the gel, swelling will occur, resulting in an increase in the diffusivity of species from the gel by up to a factor of ten. This results in an order of magnitude increase in insulin infusion from the gel, which results in increased glucose uptake. As the glucose concentration decreases, oxidation will decrease, and as hydrogen ions naturally diffuse out of the gel, the pH will increase again, resulting in a collapse of the particle.

There have been a number of modelling efforts associated with hydrogels. These can be grouped according to the various steps in the swelling and release process. A review of the different models assuming different transport mechanisms and different methods of viscoelastic chain relaxation was written by Podual (1998). With respect to the development of control relevant transport models, Lustig & Peppas (1988) developed scaling laws to describe the diffusion of solutes in hydrogels that do not exhibit swelling behaviour. Harland

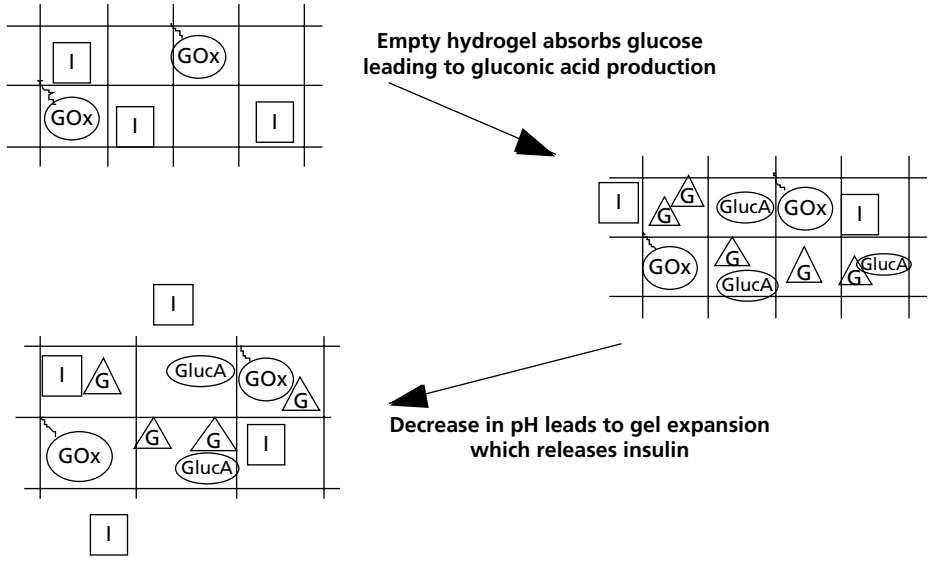

Figure 5 Schematic of mechanics of pH-responsive cationic hydrogels with glucose oxidase, based on the work of Podual (1998). Glucose appearance results in the production of gluconic acid, which decreases the system pH. pH-induced swelling results in increased diffusion of insulin from within the gel. As glucose is utilized, the mechanism is reversed.

et al (1988) modelled the combined dissolution and diffusion of a drug that was released from the non-swelling system. Hariharan & Peppas (1993) and Albin et al (1987) developed models describing swelling and release from pH-responsive hydrogel films, whilst Podual et al (2004) and Podual & Peppas (2005) developed models describing swelling and release from poly(DEAEM-g-EGMMA) spherical particles. To the knowledge of the authors, there have been no previous attempts to simulate the response of pH-responsive hydrogels in-vivo.

Conclusions and future directions

This expert review has addressed engineering aspects associated with the control of glucose metabolism, diabetes, and current and proposed therapeutic methods for treating diabetes, including all pertinent patient models, control algorithms, and efforts toward developing an implicit closed-loop control system. As the diabetes problem gains more acceptance as one of multiple inputs and perhaps multiple outputs, future modelling and closed-loop control efforts for glucose homeostasis will be based on species in addition to glucose and insulin. Roy & Parker (2006, 2007) have recently developed a fatty acid minimal model, and control systems utilizing both insulin and glucagon are currently being studied (El Khatib et al 2007), demonstrating the transition to more complex models and systems. Future efforts toward implicit closed-loop control will include in-vivo assessments of hydrogel swelling and release. While patient testing is still a few years away, simulations based on developed patient models and polymeric delivery system models will assist in the design process by allowing researchers to investigate the in-vivo effectiveness of many different formulations. These developments, as well as future developments in oral insulin delivery, ensure that great progress will continue to be made toward the development of improved insulin therapy.

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