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REVIEW ARTICLE

EXPLORING CLOSED-LOOP ARTIFICIAL PANCREAS USE IN TYPE 1 DIABETES

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SUMMARY

Near-normal glucose control without hypoglycemia remains an elusive goal for patients with diabetes who require chronic insulin treatment. Building an electromechanical replacement for lost beta cell function has been a target for more than 40 years. Recent progress has been made with the advent of reasonably reliable continuous glucose sensing, miniaturized insulin infusion devices and powerful microcomputers. An important limitation remains with the need to sense glucose and infuse insulin subcutaneously, as this compartment delays both information about blood glucose and changes to insulin exposure. This has shifted the focus of research onto the development of computer programs that can forecast metabolic requirements to compensate for the lack of immediate access to metabolic information and delayed insulin effects. Recently developed tools for in silico testing of these algorithms will hopefully accelerate the emergence of effective and safe computer-assisted insulin infusion systems and remove the hypoglycemia threat from insulin therapy, while enabling closer-to-normal glycemic control throughout the day and requiring no or only limited user inputs.

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INTRODUCTION

Why do we need a closed-loop artificial pancreas? Unlike many other hormones, insulin has profound and irreversible systemic effects, both short- and long-term. Owing to this fundamental property, the lack of short-term adjustment of exposure or other countermeasures, subcutaneously injected insulin has a low therapeutic index. The main health risks are hypoglycemia and its associated neurological sequelae. Hypoglycemia is especially prevalent in children and adolescents treated with insulin (1), and fear thereof keeps many patients in a suboptimal glucose range (2). While continuous glucose monitoring options, optimized insulin formulations and generally better patient training have improved glycemic control, they have not abolished the risk of misdosing and resulting hypoglycemia. Newer insulin formulations that may offer a better therapeutic index are in early development, e.g., nanoparticles based on glucose-sensitive membranes (3, 4), and efforts to treat patients with immunosuppressive drugs, alone or in combination with transplanted islets, continue (5, 6).

However, an electromechanical closed-loop artificial pancreas remains a viable near-term option to achieve lasting near-normal glycemic control without hypoglycemia. The system is principally composed of a sensor, a computer and a pump (Fig. 1). Blood or interstitial fluid is drawn into a glucose analyzer. A computer program converts glucose information and specific user inputs, e.g., with regard to meals, into instructions to deliver insulin at various rates directly into the bloodstream or subcutaneous tissue. Additionally, glucose or hormones such as glucagon can be administered by another pump upon detection of hypoglycemia trends by some devices.

A BRIEF HISTORY OF THE ARTIFICIAL ENDOCRINE PANCREAS

As early as 1959, the idea for an implantable artificial endocrine pancreas (7) was proposed but was only realized in the late 1970s. The first such device, the Biostator® (Miles Laboratories, Elkhart, IN, USA), was a large, desktop-sized apparatus dependent on an external power supply. It was developed on the basis of prior (1974) studies by research teams in Canada (8) and Germany (9). A similar device was developed shortly thereafter by an Osaka University group (10). All these early devices withdrew venous blood continuously to measure blood glucose levels ex vivo and delivered in turn insulin or glucose as needed intravenously, usually by a double lumen catheter

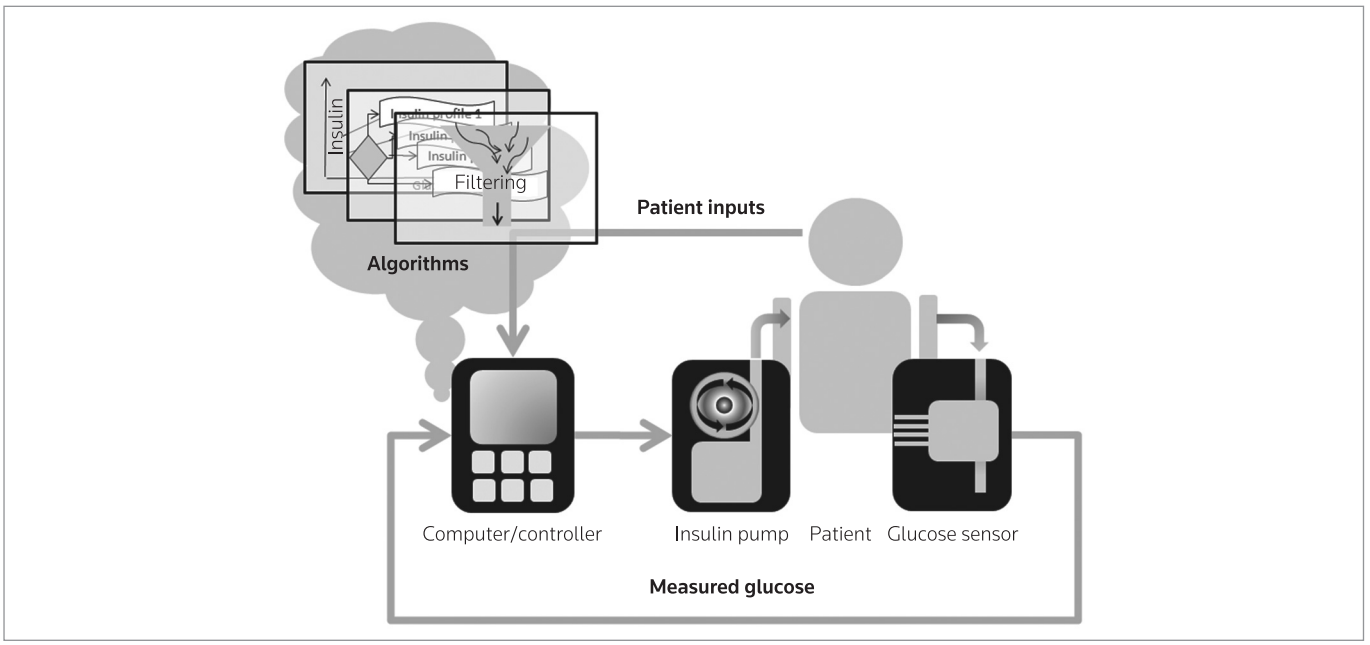

Figure 1. Scheme of a portable closed-loop artificial endocrine pancreas consisting of a controller, an insulin delivery device and an automated glucose sensor. The three elements can be separate and connected by wire or wirelessly, or incorporated all into one possibly implantable device.

placed in the lower forearm of the patient. Although very simple in layout, the Biostator® was able to almost normalize blood glucose in patients with type 1 diabetes for several days, the principal limitations being the need to keep patients hospitalized and largely in bed while having to maintain sufficient venous access throughout that time. Even more limiting was the need to constantly recalibrate the amperometric glucose sensors and replace the glucose oxidase-containing membrane, sometimes a few times over a single day.

Notwithstanding its lack of practical use as an outpatient treatment for diabetes, the Biostator® (and its successors) remains in use to study metabolic parameters such as insulin sensitivity or glucose disposal in a highly standardized fashion, and quantify the effects of new drugs on insulin secretion or insulin formulations on metabolic activity (11, 12). However, over the following 40 years and despite great effort, the concept of intravascular glucose measurement and insulin delivery proved too challenging for a portable design, although an advanced system was courageously tested using a glucose sensor implanted by direct jugular access in the superior vena cava and connected by a subcutaneous lead to an implanted pump delivering insulin intraperitoneally (13). With one exception that uses intraperitoneal insulin delivery (14), all current prototypes for a portable outpatient closed-loop system have adopted the subcutaneous route for both glucose measurement and insulin delivery to avoid the hassle and risks of long-term implanted intravascular or intraperitoneal catheters.

DESIGN CHALLENGES

Physiological systems are very complex, as emphasized by Warren Weaver, a pioneer of mathematical modeling who once stated that "classical physics is organized simplicity, statistical mechanics is chaotic complexity, and biology is organized complexity" (15). Hence, modeling biological systems such as beta cells either requires explicit consideration of all its structural features and functional interrelations with other systems, or successful computer-based simulation of systems that cannot be incorporated to provide appropriate insulin infusion rates. Islets are an integral part of a complex system designed to optimize postabsorptive nutrient disposition, with multiple afferent and efferent pathways, including neural, paracrine and hormonal pathways (Fig. 2). The challenge from an engineering perspective is to decide which aspects are essential to integrate into the sensory, computing and hormone replacement aspects of an artificial endocrine pancreas. A reductionist approach is necessary to achieve an acceptable balance between design simplicity, reliability of components and feasibility of the drug administration route. The challenge then is to create computational bridges for what cannot be mimicked with present medical technology: instant determination of blood glucose coupled to equally instant and short-lived insulin infusion into the portal circulation. This ultimately requires the creation of a sort of artificial intelligence that can learn, based on limited inputs, to adapt to an individual's unique life style and physiological makeup, and, given the device-related lag times for glucose sensing and insulin action, reliably forecast metabolic needs over a considerable time horizon. As will be discussed below, while significant progress has been made in the glucose-sensing and insulin delivery areas, the greater challenge remains to create the "brains" smart enough to provide safe and effective blood glucose control, with little or no human intervention required.

INPUT VARIABLES

The simplest approach is to assume that the beta cell reacts to changes in ambient glucose by changing the insulin secretory

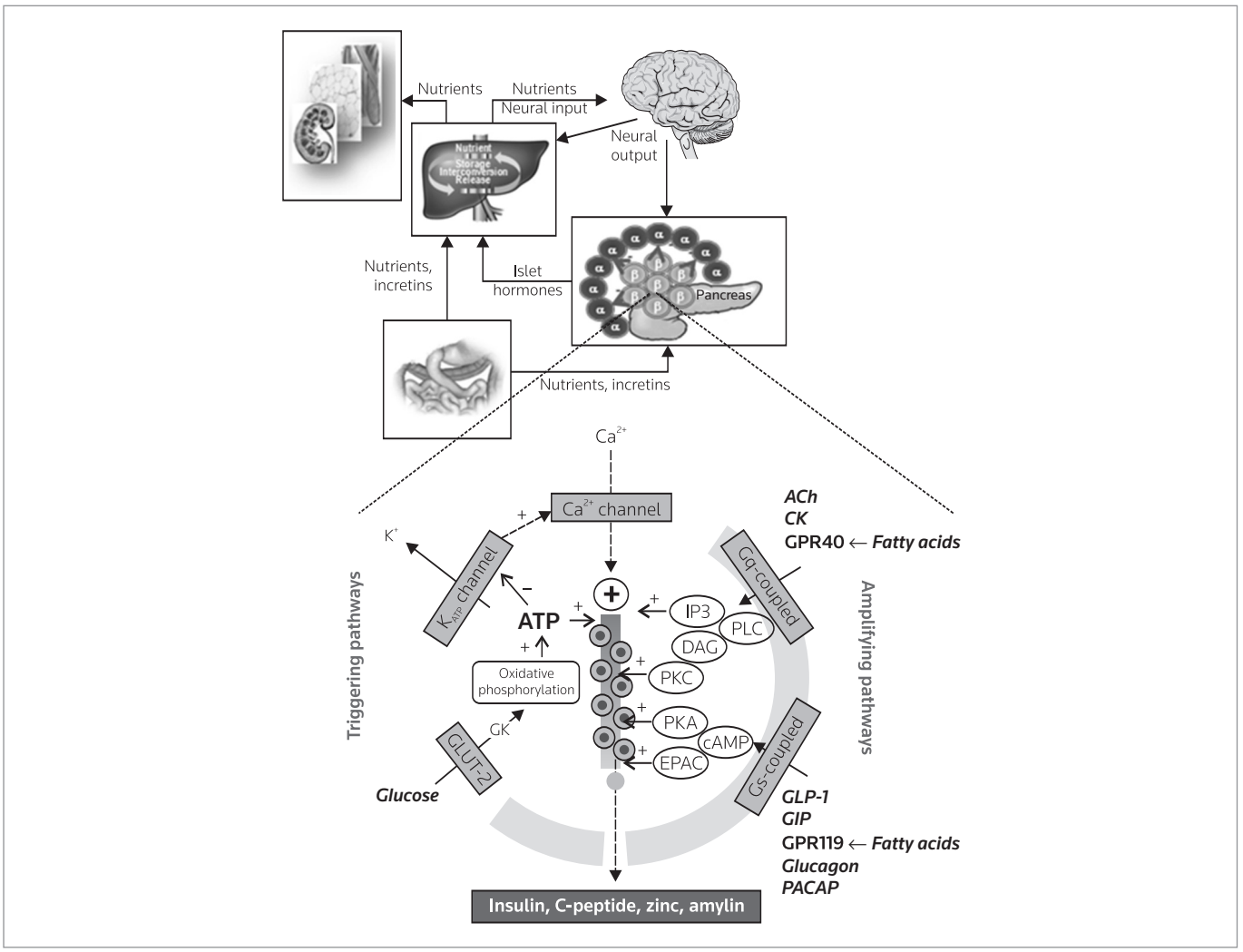

Figure 2. Scheme of the endocrine pancreas and beta cells embedded in multiple control loops to coordinate the secretion of insulin and other islet cell hormones. Abbreviations: ACh, acetylcholine; CK, cholecystokinin; GPR, G protein-coupled receptor; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; PACAP, pituitary adenylate cyclase-activating polypeptide; IP3, inositol triphosphate; PLC, phospholipase C; DAG, diacylglycerol; PKC, protein kinase C; PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; EPAC, exchange protein directly activated by cAMP 1; GLUT-2, glucose transporter type 2; GK, glucokinase.

response in a linear fashion. This is in fact the principle based on which many patients adjust their subcutaneous insulin dose, albeit often with less than satisfactory outcomes (16, 17). In addition, knowing the lack of immediate ability to modulate insulin concentration via the subcutaneous delivery route, anticipatory dosing is mandatory, i.e., the insulin requirement for a given meal has to be accurately estimated to avoid postprandial hypoglycemia and minimize hyperglycemia. In addition, information about impending conditions that may have a profound impact on metabolism may also have to be inputted by the user, e.g., meals or exercise.

OUTPUT VARIABLES

An additional question is whether insulin is the only hormone requiring replacement: beta cells produce and co-secrete with insulin a number of other potentially useful peptides, e.g., amylin. Amylin is co-secreted with insulin and exerts potentially useful actions, such as delayed gastric emptying, reduced glucagon secretion and increased satiety, all of which can help dampen postprandial glucose excursions (18). The availability of more stable analogues such as pramlintide could facilitate incorporation into a closed-loop infusion system. In addition, while suppression of glucagon secretion by insulin is key in type 1 (19) and type 2 (20) diabetes, particularly at meals, intravenous insulin delivery can normalize peripheral glucagon levels (21). Including a counterregulatory hormone such as glucagon is potentially useful for periods of prolonged fasting, e.g., overnight, to mitigate hypoglycemia. The principal issues are increased device size and complexity, and the susceptibility of hormones like glucagon to rapidly denature in a liquid formulation.

IMPACT ON A PRACTICAL CLOSED-LOOP SYSTEM

Although counterintuitive, the significant limitations of designing a device for the sensing of multiple metabolites and drug delivery components for multiple factors dominate most concepts for an artificial endocrine pancreas, rather than designing components around a near-perfect model of an electromechanical beta cell replacement device. The latter might attempt to include a greater number of input and output signals, and a different route for insulin, e.g., intraperitoneal, and may include other secreted beta cell products, e.g., amylin, which may enhance insulin action and slow gastric emptying. However, the technical and practical hurdles are considerable, even with today's technology, and knowledge of beta cell physiology is still evolving. For example, the importance of incretin hormones to amplify early insulin secretion was only realized in the 1990s.

Most current concepts for a portable closed-loop artificial pancreas are based on interstitial/subcutaneous sensing of glucose and subcutaneous delivery of insulin. The challenges of this approach can be summarized as follows:

• Subcutaneous glucose sensing

– A large (5-10 minutes) delay exists between measured interstitial glucose and actual blood glucose (22). In combination with intrinsic sensor-related delays, the measurement process can thus take up to 30 minutes (23, 24) before information becomes available for the controller to compute changes in insulin infusion rates.

– The accuracy of measured glucose is limited to approximately 70-80% based on the Clarke error grid (25, 26), even with frequent calibration. Thus, data noise and sensor drifting can become a source of misdosing.

• Subcutaneous insulin delivery

– As with glucose sensing, transfer of insulin from the interstitial space of administration to the blood, and ultimately, the site of action, is delayed even with fast-acting insulin analogues: peak glucose-lowering activity is not observed before 45-50 minutes after start of delivery to the subcutaneous space, while the formation of a drug depot in the subcutaneous space increases the risk of continued and potentially inappropriate rise of insulin levels (27).

– Although rare nowadays, subcutaneous delivery of peptide hormones increases the risk for local and systemic immunological reactions to the drug, including the formation of antibodies that can further contribute to protracted insulin pharmacokinetics.

– Drug stability (denaturation, aggregation) also remains a concern, although use of biocompatible materials for the drug reservoir and catheter has reduced the magnitude of the issue (28).

GLUCOSE SENSING

An accurate and reliable continuous glucose measurement (CGM) device has been the bottleneck of closed-loop systems from the onset (29, 30). Currently available CGM devices can achieve a median relative absolute difference between sensor and reference glucose measurements of ≤ 5% (31-33), which should be compatible with the needs of closed-loop glucose control as long as calibration schedules are adhered to. As discussed above, glucose measured by CGM devices also has a significant time lag to blood glucose values. Data processing techniques that filter out noise add to this delay and are device-dependent. The CGM DexCom™ (Dexcom, San Diego, CA, USA) lags by 6 minutes, and an 8- to 15-minute time lag has been reported for the FreeStyle Navigator® (25, 34) and the Guardian® (Medtronic Minimed, Northridge, CA, USA) CGMs (24, 35).

From the closed-loop viewpoint, more important than differences in the time lag are transient and persistent deviations between glucose values measured by the sensor and the actual blood glucose levels. Transient deviations occur over 1-4 hours and may relate to intermittent, bidirectional changes in sensor sensitivity and mechanical perturbations, including temporal sensor dislodgement (36). Persistent deviations are caused mainly by erroneous calibration with fingerstick glucose measurements, or an inappropriate calibration algorithm, or by persistent drift of sensor sensitivity. Underreading of blood glucose levels is the smaller problem, as additional insulin can be delivered once sensor levels recover (37). However, overreading may initiate overdelivery of insulin and increase the risk of hypoglycemia.

FULLY AUTONOMOUS VERSUS HYBRID CONTROL

The attractiveness of a hybrid system is based on the ability of the user to mimic anticipatory aspects of normal physiology, especially with regard to two common situations that can induce very rapid and profound changes in glycemia: food intake and physical exercise. These situations are not adequately addressed by mere retrospective glucose monitoring, as they normally involve a host of non-glucose inputs. Especially the ingestion of large meals may pose a significant challenge to closed-loop systems, as insulin is delivered on the basis of (delayed) glucose excursions only, without prior information about timing or size of the meal (38, 39). The rate of change in the glucose concentration could be employed to signal the start of a meal (40), but glucose concentrations may also rise for other reasons. A more straightforward way may thus be to abandon the fully automatic mode and have the patient inform the semi-closed loop system about the time and size of an impending meal, and have the controller provide advice on insulin dosing (41), or, alternatively, automatically increase insulin delivery based on the estimated carbohydrate content of the meal (42).

Management of food ingestion normally involves a large variety of sensory/neural and endocrine inputs to the beta cell that modulate early insulin release (43-48). By contrast, retrospective, solely glucose sensing-based closed-loop insulin delivery may fail to optimally control meal-induced hyperglycemia. This can be improved by open-loop insulin infusion with meals that mimics the physiological early insulin release at meals (49-51). Thus, a key to improving postprandial glucose excursions in closed-loop systems may be to start meal-related insulin delivery by infusing an insulin spike at the very beginning of the meal: administration of such a priming bolus, between 20 and 50% (52) or 50 and 75% (53) of the estimated total insulin requirement, or even administration of a fixed bolus of two units (54), have all been associated with reduced postprandial hyperglycemia and without an increased risk for hypoglycemia.

Another example for potentially useful user input is exercise: exercise can induce highly variable glucose responses, mainly hypo-

glycemia (55), which may occur either during or shortly after exercise but can also be delayed by several hours (56, 57). However, intense exercise may also produce hyperglycemia (58). Either way, manual input of exercise may be coupled with an intensity estimate, and/or heart rate monitoring (59) to trigger suspension of insulin infusion during closed-loop delivery may be options to reduce the risk for hypoglycemia. Pre-emptive carbohydrate intake or dual hormone treatment with glucagon as a hormone to stimulate hepatic glucose secretion could be added to minimize the risk of hypoglycemia, and suggestions by the device computer based on past situations may offer an additional guide for the patient. One has to emphasize, however, that intensive patient training will be paramount to ensure that user inputs with regard to calibration of glucose are accurate, or the time and magnitude of meal size or intensity of exercise are appropriate and consistent.

CONTROLLER ALGORITHMS

To develop an insulin infusion algorithm for a closed-loop artificial pancreas, mathematical models and computer algorithms to compute appropriate insulin infusion rates are required. For the intravenous glucose-sensing and insulin-infusing systems, relatively simple algorithms suffice based on both proportional and derivative (first-order) glucose-dependent functions (8, 60, 61). However, by lacking the ability to instantly measure blood glucose with subcutaneous access or to acutely impact systemic insulin exposure with subcutaneous infusion, the key performance parameter for any automated or even semi-automated (hybrid) insulin delivery system hinges on its excellence in anticipating blood glucose changes. Thus, while the original algorithms for the Biostator® used simple linear equations with first-order dynamics, current algorithms take advantage of the lessons learned from more advanced in silico modeling of carbohydrate metabolism, such as Cerasi's three-compartment model (62) or Bergman/Cobelli's minimal model (63).

In the proportional–integral–derivative (PID) algorithm, pioneered by Steil and colleagues (64), the proportional element refers to the change of insulin infusion required to correct the gap between actual and target glucose. The derivative element is incorporating the rate of glucose change to accelerate insulin delivery when the rate of changes in glucose concentration is high and slow it when that rate is low. The integral element is to consider the time of exposure already spent on a certain glucose level. This is useful when proportional and derivative elements would not trigger a change in insulin infusion yet the patient remains in a less than desirable glucose range. In this model, the derivative element mimics the first phase, and the proportional element the second phase of insulin secretion. The integral element is part of the second-phase element, to address persistent postabsorptive or fasting hyperglycemia. However, PID is a relatively rigid approach, as only one solution for all time points is being calculated. Thus, in silico tuning is required to optimize the control parameters, as even relatively small deviations, such as those generated by data noise or transient sensor drift, may result in inappropriate insulin infusion rates over time when using suboptimal parameters for a given patient. An approach to correct this weakness of PID algorithms is the fading memory proportional derivative (FMPD) method, where the integral element is removed and recent glucose measurements are weighed more heavily than older ones to accelerate adaptation. This algorithm appears to work well in insulin-deficient animals (65).

While the PID model uses glucose inputs to forecast insulin delivery, the "inversion" algorithm is based on a glucoregulatory patient model which translates an optimal insulin exposure into subcutaneous insulin infusion rates based on known pharmacokinetic parameters for insulin (66). The in silico results for such an algorithm have been recently published (67) and showed that 63% of the time normoglycemia for the full closed-loop control can be achieved, and that this can be increased to 96% for the semi-closed (or hybrid) loop control simulation where meal information is inputted.

The model predictive control (MPC) algorithm addresses the same issue by iteratively recalculating optimal insulin infusion rates based on predicted glucose changes for a limited time interval before resetting itself (68). Thus, the important difference compared to PID is the use of a chain of microsimulations of glucose and resulting insulin needs rather than the rigid, reference glucose-based approach PID algorithms are based on, promising increased flexibility in the presence of dynamic changes, e.g., driven by variable size, composition or consumption times of meals. As illustrated in Figure 3, a PID algorithm may be more sluggish to adapt, possibly overdosing insulin in a given situation, whereas MPC may be faster in reducing insulin in anticipation of reduced requirements. At least in a computer-based simulation using the Virginia/Padova Simulator, MPC proved to be superior to PID (69). Also, an extend-

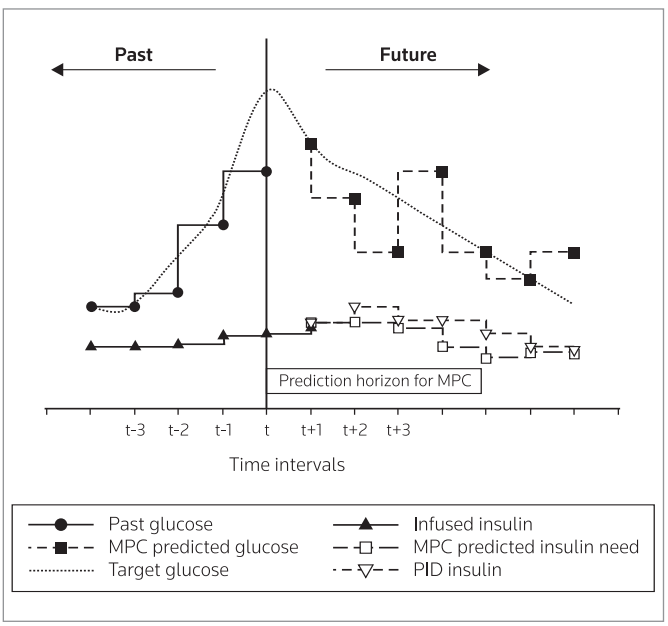

Figure 3. Comparison of proportional–integral–derivative (PID) and model predictive control (MPC) algorithms. PID algorithms use a quasi-continuous approach (limited by the sampling interval) to estimating required insulin doses based on actual and past glucose values, both absolute and slope. In the presence of significant deviations from a smooth trend, PID algorithms will attempt to return patients' glucose levels to levels originally expected. By contrast, MPC algorithms will charter a new course based on a time-limited model-based forecast; in this example, a prediction horizon of t+5, followed by a re-start and new forecast once that time window has elapsed.

ed model to include the asymmetry of risk (hypoglycemia acutely imparts severe health risks, whereas hyperglycemia does not), and the irreversible nature of insulin action (at least in the absence of a specific antidote) has recently been shown to reduce the risk of avoidable hypoglycemia by > 50% compared to non-risk-adjusted algorithms (70). As a result, MPC-based models such as the Zone MPC (USC Santa Barbara) and the Padova MPC (University of Padova, Italy) are currently the most often researched and most promising approaches to address the inherent challenges of subcutaneous glucose measurement and insulin infusion-based systems. The Padova MPC is currently being tested in a JDRF-supported trial (http://www.clinicaltrials.gov/ct2/show/NCT01271023?term=control+to+range&rank=1).

PID, reverse PID and MPC algorithms are strictly deterministic, and use all inputted data without consideration for data noise or sensor error, unless a model for such non-white noise is successfully included in the algorithm (71). Without such correction, these algorithms are susceptible to instability when a large number of inconsistent data are fed into the controller, and potentially result in significantly incorrect estimates for insulin requirements. Approaches to mitigate this risk add a rule-based safety layer that constrains insulin delivery (71, 72), or suspend insulin infusion in the presence of falling or low glucose (73), or perform filtering of data by, e.g., "H2-infinity loop" or "fuzzy" algorithms. H-infinity (H_∞) filtering, also known as minimax filtering, attempts to minimize the peak value of certain closed-loop frequency response functions, i.e., the "worst-case" estimation error (74). However, results from in silico testing have not yet been published (75). "Fuzzy logic", on the other hand, filters noisy data by applying empirical knowledge, "common sense" in a way, to reduce large amounts of data (glucose in this instance) to a more manageable (for the algorithm) volume (76, 77). Both of these approaches command significantly more complex mathematics, and it remains to be seen whether they can offer significant advantages over MPC-based algorithms.

As an alternative to the above algorithmic approaches, neural networks are designed to "self-evolve" as an expert system and become uniquely tuned with individual patients. The two guiding principles of neural networks are associative mapping (storing the relationships among glucose patterns), in which the network learns to produce a particular pattern on the set of input signals, i.e., glucose levels, whenever another particular pattern is applied on the set of input units, and regularity detection, in which networks learn to respond to particular properties of the input patterns, i.e., infusion of insulin (78, 79). However, in silico or in vivo comparative testing has not yet been published.

It is important to remember at this juncture that currently no algorithm has been sufficiently tested in the clinic, i.e., long-term and in a large and diverse patient population, to be recommended for outpatient use. While animal studies are relatively easy to conduct, most animal models are either not truly representative of human diabetes, or lack the longevity to permit long-term testing. Thus, in silico modeling is beginning to replace preclinical models as a proof-of-concept tool for closed-loop algorithms (80). The Virginia/Padova Simulator was FDA-approved in 2008 to be a substitute for animal testing, and is now commercially available as Simulink®/MATLAB® through the medical research firm The Epsilon Group. The FDA has also published important guidance in June 2011 for a subset of closed-loop devices, "low glucose suspend" systems, that stop or reduce insulin infusion in the presence or in anticipation of impending hypoglycemia (81). The guidance includes in silico testing as an acceptable method of providing evidence for safety in lieu of conventional animal testing. However, it is not yet clear whether the agency would extrapolate this guidance to closed-loop systems.

The second challenge for closed-loop algorithms is to take into account issues other than lag time arising from subcutaneous insulin administration. There is some evidence that closed-loop systems when using peripheral intravenous insulin administration are not capable of fully normalizing plasma glucose and other metabolic markers in humans (82, 83). As with open-loop subcutaneous administration of insulin, closed-loop systems produce significant hyperinsulinemia in peripheral blood. Early on, the unphysiological route of insulin delivery was blamed, and studies in experimental diabetes models seemed to confirm that intraportal insulin delivery is more likely to be capable of completely restoring metabolism (not just plasma glucose), while reducing peripheral insulin exposure (84, 85). Studies in humans also appear to support the notion that intraportal insulin delivery is superior to peripheral administration routes (86). However, in the presence of minimal but preserved exposure of the liver to endogenous insulin, intraportal delivery of exogenous insulin may not be as essential as much as in situations of complete insulin deficiency, such as type 1 diabetes. Given the infeasibility of chronic intraportal insulin delivery via permanent catheters (bleeding, thrombosis, infection risks) and, to a similar extent, that of chronic intraperitoneal delivery as a next-best option (catheter inflow obstruction, adhesions, infection and perforation risks), complete metabolic normalization may likely remain an elusive goal unless more biocompatible ways of intraportal insulin delivery become available.

This leaves the subcutaneous delivery route as the only feasible option for the time being. However, this route also adds additional problems, e.g., lag times between start of infusion and significantly increased peripheral insulinemia, as discussed above, with the maximum blood glucose-lowering effect occurring only after up to 90-120 minutes have passed (29). Thus, in order to prevent late-onset hypoglycemia, high glucose levels have to be normalized slowly even during closed-loop delivery. Methods to account for insulin "on board" have been suggested to protect against insulin overdosing (74). Thus, these pharmacokinetic limitations should be considered in closed-loop algorithms. In addition to time lags, insulin absorption from the subcutaneous depot varies by up to fourfold between subjects, and as much as 50% within subjects (87). While a more modest 20-25% within-subject variability has been reported in healthy patients under controlled conditions (88), variability in subcutaneous blood flow may be higher in patients with diabetes. Such short-term unpredictability requires a more sophisticated effort from an insulin controller perspective, including a learning mode to adjust to individuals' subcutaneous absorption characteristics. Insulin requirements also vary both day to day and hour to hour owing to circadian and diurnal cycles such as the "dawn phenomenon", an early morning increase of glucose (89), or at times of illness and stress (90). In addition, insulin requirements vary by age and are generally lower in younger individuals compared with adults (91, 92). For these slower and more consistent changes, automatic adaptation of insulin infusion rates is likely expected to be of benefit.

In conclusion, there are currently a number of competing model systems for the control of insulin (and possibly glucagon) infusion being evaluated. Since a well-characterized in silico test bed is now available, more comparative data should be forthcoming in the near future to determine which will be most capable of compensating for the numerous challenges provided by subcutaneous glucose measurement and insulin delivery, and suitable for extended, long-term in-human testing of closed-loop or hybrid systems.

BEDSIDE CLOSED-LOOP SYSTEMS

Bedside closed-loop systems are no longer broadly available. Clinical use has thus been sparse and limited to proof of concept, e.g., in the management of diabetic coma or diabetic ketoacidosis (93), intrasurgical stabilization of diabetic subjects (94-96), during delivery (97), hemodialysis (98) or the management of insulinoma-associated hypoglycemia (99).

More commonly nowadays, bedside systems are used in research settings to, e.g., determine insulin sensitivity in clamp studies (100), or the pharmacodynamic profile of new diabetes medications.

PORTABLE CLOSED-LOOP SYSTEMS – CURRENT PROTOTYPES

In 2006, Steil et al. built a prototype that is based on the Guardian® CGM, a Paradigm® 715 insulin pump (Medtronic MiniMed, Northridge, CA, USA) and a PID algorithm (101). This system has been used in 34 patients (39), including adolescents and adults, over approximately 30 hours, and compared to open-loop control. Mean glucose levels were not different between the open and closed loop (133 ± 63 mg/dL vs. 133 ± 52 mg/dL; $P > 0.65$). However, glucose was more often (75%) within the target range of 70-180 mg/dL with closed loop versus 63% for open loop. The incidence of biochemical hypoglycemia (blood glucose < 60 mg/dL) was similar under the two treatments, and there were no episodes of severe hypoglycemia (Table I).

Software described by Dassau et al. (102) supports a modular system (MDLAP) via wireless connections to a range of available sensors and pumps, and is compatible with different control algorithms (Table I). Using a fuzzy logic controller, this system has been tested over up to 24 hours in a small group of patients with type 1 diabetes in good control (mean HbA1c = 6.6 ± 0.7%). During closed-loop control, 73% of the sensor values ranged between 70 and 180 mg/dL, 27% were > 180 mg/dL and none were < 70 mg/dL (40).

A manual closed loop with an MPC controller has been used in 17 children and adolescents (103), 24 adults (104) and 10 pregnant women over a 22-hour period (105). In the pediatric population, target glucose levels were more often achieved than with standard care (52% vs. 39%; $P = 0.06$), with no glucose values < 36 mg/dL. In the adult study, the closed loop also increased the number of in-target glucose levels by about 28%, while eliminating nocturnal glucose values < 36 mg/dL. In 10 pregnant patients, target glucose was achieved in 84% of recorded glucose measurements, without nocturnal hypoglycemia.

An automated version, which combines the FreeStyle Navigator® CGM with a Deltec Cozmo® pump (Smiths Medical, Ashford, UK), has been evaluated in adolescents over 12 hours (Table I). Plasma glucose remained in the near-normal range, as did plasma insulin (73).

Given the persistent threat of hypoglycemia even with closed-loop systems, prototypes for dual-hormone delivery (53, 87) have been evaluated in small trials and shown to reduce the frequency of severe hypoglycemia, albeit at the expense of higher average glucose levels.

GLYCEMIC TARGETS

There are no generally agreed upon glucose control targets for closed-loop devices. Thus, in alignment with the Diabetes Control and Complications Trial (DCCT) (106) and an American Diabetes Association (ADA)-supported HbA1c goal of 7%, target glucose levels should be set to 70-120 mg/dL for fasting/preprandial and to < 180 mg/dL for postprandial glucose, but may differ in individuals based on special circumstances, e.g., pregnancy. Alternatively, current American Association of Clinical Endocrinology (AACE) guidelines (107) recommend fasting < 110 mg/dL, postprandial < 140 mg/dL, consistent with a lower HbA1c target of 6.5%. However, since the greater benefit of closed-loop devices may be the avoidance of hypoglycemia rather than the control of postprandial hyperglycemia, continuous glucose measurement systems may provide more useful evidence of benefit. Since all current prototypes already use CGMs, a large amount of data will be available not only for the controller but also for the patient and the treating physician to evaluate. A number of numerical and graphical output options to document the percentage of glucose values within and outside the target range could be pursued to assess improvement in control beyond periodic HbA1c determinations, as proposed by Kovatchev (108). Thus, linking the device to lap- or desktop devices is recommended to generate easy-to-understand graphical outputs, which in turn might help patients to identify opportunities for further optimization, e.g., with regard to inputs on exercise or meals.

CONCLUSIONS AND OUTLOOK

Miniaturization and improved reliability of components, and more sophisticated computer programs to bridge system-inherent deficiencies, have improved the feasibility of a portable, closed-loop artificial endocrine pancreas. The availability of in silico testing should further accelerate the evaluation of suitable programs, while the emergence of a regulatory pathway for device approval should encourage commercial developers. However, the current concepts will probably not lead to completely autonomous systems given the limited (glucose only) and delayed (interstitial glucose) input. Additional input from a well-trained user to mimic anticipatory adjustments of insulin (meal, exercise) may remain necessary to maximize the number of on-target glucose values and minimize the hypoglycemia risk. Such hybrid systems may also have the advantage of enhancing user knowledge and training as a result of an ongoing "dialogue" between controller and patient, at least during daytime. The greatest contribution of the fully automated mode may be overnight control of glycemia when reconciling avoidance hypoglycemia with the mitigation of early-morning hyperglycemia, and may more likely be possible than with current open-loop insulin infusion or long-acting human insulin analogues.

Table I. *Clinical studies with closed-loop systems.*

Control type	Sample size	Algorithm	Sensor/pump	Sampling interval (min)	Results (% glucose values in target range vs. open loop)	Ref.
Closed loop (24 hours)	10	MPC	FreeStyle Navigator/ Deltec Cozmo	15	68-77% (early, late pregnancy)	105
Closed loop (15 hours)	20	MPC	FreeStyle Navigator/ Omnipod	15	78% vs. 64%	
Closed loop (29 hours)	10	PID	Medtronic Minimed/ Medtronic 511	1	75% vs. 63%	39
Closed loop (24 hours)	7	Fuzzy logic	FreeStyle Navigator or STS Seven/OmniPod CSII	5	73%	38
Closed loop (37 hours)	17	PID	Medtronic Minimed/ Medtronic Paradigm	1-5	85% vs. 58%	52
Closed loop (48 hours)	8	PID	Medtronic Minimed/ Medtronic MMT (IP)	1-5	39% vs. 28%	14
Closed loop overnight 12 hours	12	MPC	Medtronic Guardian/ Deltec Cozmo	15	52% vs. 39%	103
Closed loop overnight 12 hours	14	MPC	FreeStyle Navigator/ Deltec Cozmo	15	53% vs. 55%	103
Closed loop overnight 12 hours	12	MPC	FreeStyle Navigator/ Deltec Cozmo	15	78% vs. 43%	103
Closed loop overnight 12 hours	12	MPC	FreeStyle Navigator/ Deltec Cozmo	15	74% vs. 53%	104
Closed loop overnight 12 hours	8	MPC	FreeStyle Navigator/ Deltec Cozmo	15	58% vs. 42%	73
Closed loop bihormonal 28 hours	7	FMPD	DexCom Seven Plus or Medtronic Guardian	5	63% reduction of hypoglycemia	53
Closed-loop bihormonal	27	MPC (insulin) PID (glucagon)	GlucoScout/ Deltec Cozmo	5	74% vs. 62%	87

MPC, model predictive control; PID, proportional–integral–derivative.

DISCLOSURES

The author is an employee of Takeda Global Research and Development, Inc.

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