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The artificial pancreas: current status and future prospects in the management of diabetes

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Recent advances in insulins, insulin pumps, continuous glucose-monitoring systems, and control algorithms have resulted in an acceleration of progress in the development of artificial pancreas devices. This review discusses progress in the development of external systems that are based on subcutaneous drug delivery and subcutaneous continuous glucose monitoring. There are two major system-level approaches to achieving closed-loop control of blood glucose in diabetic individuals. The unihormonal approach uses insulin to reduce blood glucose and relies on complex safety mitigation algorithms to reduce the risk of hypoglycemia. The bihormonal approach uses both insulin to lower blood glucose and glucagon to raise blood glucose, and also relies on complex algorithms to provide for safety of the user. There are several major strategies for the design of control algorithms and supervision control for application to the artificial pancreas: proportional–integral–derivative, model predictive control, fuzzy logic, and safety supervision designs. Advances in artificial pancreas research in the first decade of this century were based on the ongoing computer revolution and miniaturization of electronic technology. The advent of modern smartphones has created the ability to utilize smartphone technology as the engineering centerpiece of an artificial pancreas. With these advances, an artificial or bionic pancreas is within reach.

Keywords: artificial pancreas; continuous glucose monitoring; insulin infusion; insulin; algorithms

Introduction

Glucose homeostasis in humans is a superb example of closed-loop regulation of a vital physiological parameter. In nondiabetic individuals, the pancreas is able to sense changes in blood glucose and respond by stimulating the release of insulin via the β cells to lower blood glucose or glucagon via the α cells to increase blood glucose. In insulin-dependent diabetes, however, β cell function is impaired and the homeostatic equilibration of blood glucose is no longer present. Long-term effects of elevated blood glucose, or hyperglycemia, include a range of microvascular complications including retinopathy, nephropathy, and neuropathy. Diabetes is the leading cause of blindness, kidney disease, and amputation in the United States and Europe. The landmark Diabetes Control and Complications Trial published in 1993 found, however, that maintenance of near normal glucose levels reduced the risk of long-term microvascular complications.[1] In 2005, the publication of the "Epidemiology of Diabetes Interventions and Complications" study found that despite the multifactorial etiology of heart disease, intensive insulin therapy in patients with type 1 diabetes was shown to reduce the incidence of nonfatal myocardial infarction, stroke, or death from cardiovascular disease.[2]

Patients with insulin-dependent diabetes must measure their blood glucose with medical devices and administer insulin by multiple daily injections or by continuous subcutaneous insulin infusion (using a pump) to prevent hyperglycemia. In the absence of endogenous closed-loop or feedback regulation of glucose, the use of exogenous

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insulin invariably leads to episodes of hypoglycemia. The acute dangers of hypoglycemia, including discomfort, mental confusion, loss of consciousness, seizure, and death, are widely regarded as the primary limiting factor in the treatment of insulin-dependent diabetes.[3] Hypoglycemia can be managed by the administration of fast-acting carbohydrates that are rapidly metabolized by the body into glucose. In some cases, patients require assistance from others to administer subcutaneous injections of glucagon to elevate their blood glucose when they are unable to consume carbohydrates due to the severity of the hypoglycemic event.

Physicians, scientists, and engineers have worked for the past 50 years to develop complex medical devices for patients with diabetes that emulate the pancreatic regulation of glucose in otherwise healthy individuals. Research groups in Canada, Germany, France, Australia, and Japan in the 1970s and 1980s were able to demonstrate proof of principle of the feasibility of automated control of glucose.[4–13] Albisser *et al.* were among the first to describe an "artificial endocrine pancreas" in a paper published in 1974.[4] They noted that the healthy pancreas secretes insulin as required to maintain blood glucose within normal physiologic limits. They referred to an artificial pancreas as a "computerized control system . . . which closely simulates this particular endocrine function of the pancreas." The patient's instantaneous blood glucose was determined from a custom laboratory instrument measuring venous glucose concentration that output the data to a laboratory computer. Algorithms in the computer, using both the instantaneous glucose and the rate of change, then calculated the appropriate infusion of insulin and dextrose needed to maintain the subject's blood glucose within the normal range. These systems relied upon intravascular administration of glucose and insulin or other components with a high level of complexity and could be used only under carefully supervised inpatient conditions.

Although some authors have used the term *bionic pancreas*, in this paper we use the term *artificial pancreas* or *closed-loop* to refer to a range of applications in which input from a continuous glucose-monitoring (CGM) system is used to calculate the appropriate insulin, and in some applications the appropriate glucagon infusion, necessary to achieve a specified target glycemia. This is consistent with the broad definition of artificial pancreas devices given in the November 2012 guidance from the U.S. Food and Drug Administration (FDA) on this topic.[14] It is relevant to note here that artificial pancreas or closed-loop systems often differ in the degree of control and intervention allowed. Some artificial pancreas devices require open-loop delivery of insulin for meals (sometimes referred to as *meal announcement*) with estimated grams of carbohydrate. Other approaches require simple announcement of meals (small, medium, or large breakfast, lunch, or dinner). Similarly, some artificial pancreas systems rely on open-loop supplementation with fast-acting carbohydrates to treat actual or impending hypoglycemia, whereas others, most notably those using exogenous glucagon as a means of raising glucose levels, do not. These are important considerations to bear in mind when comparing clinical results from different closed-loop studies.

Recent advances in insulins, insulin pumps, continuous glucose-monitoring systems, and control algorithms have resulted in a dramatic acceleration of progress in the development of artificial pancreas devices ultimately intended for use in the outpatient setting. In the last 3 years alone, there have been numerous excellent reviews of progress made in the field of artificial pancreas research.[15–21] Accordingly, it is not our intent in this paper to provide a single exhaustive, comprehensive review of the entire field, but rather to provide a more general overview intended for the nonspecialist. There are in principle multiple approaches to achieving an artificial pancreas, including the use of fully implanted insulin-infusion systems and fully implanted continuous glucose sensors. Despite promising initial results with a fully implanted closed-loop system as described by Renard *et al.*, there is little or no active research using this approach at the present time.[22,23] In this review, therefore, we have limited our discussion to external systems that are based on subcutaneous drug delivery and subcutaneous continuous glucose monitoring.

A critical enabling technology for current artificial pancreas systems is the continuous glucose-monitoring system used to provide input to the control algorithms. Accordingly, we review the state of the art in continuous glucose monitoring. We believe that recent advances in the accuracy and performance of the latest generation of continuous glucose monitoring have placed the field of artificial

pancreas research on the threshold of prototype commercial devices and large-scale outpatient feasibility studies.

We discuss the two major system-level approaches to achieving closed-loop control of blood glucose in diabetic individuals. The unihormonal approach uses only insulin to reduce blood glucose and relies on complex safety-mitigation algorithms to reduce the risk of hypoglycemia. The bihormonal approach uses both insulin to lower blood glucose and glucagon to raise blood glucose, but also relies on complex algorithms to provide for the safety of the user.

In this review, we discuss a number of the major strategies for the design of control algorithms and supervision control for application to the artificial pancreas: proportional–integral–derivative (PID), model predictive control (MPC), fuzzy logic (FL), and safety supervision designs. We provide examples from each of the major classes of control algorithms describing the actions of the controller designed to produce improved glycemic outcomes.

We also discuss the impact of new technologies on artificial pancreas applications that could, in principle, be brought to the market within the next few years. Advances in artificial pancreas research in the first decade of this century were based on the ongoing computer revolution and the miniaturization of electronic technology. Few researchers in the field were able to anticipate the potentially revolutionary implications of the smartphone revolution that began with the introduction of the original iPhone in 2007. In the early designs of prototype artificial pancreas systems, there was a tacit assumption that the control algorithm and component communication capability would be colocated on a miniaturized insulin infusion pump. In subsequent years, the development of patch pump technology with standalone pump controllers created the option of incorporating the control algorithms and communications into the standalone pump controller. More recently, the advent of modern smartphones has raised yet another option, namely, the ability to utilize smartphone technology as the engineering centerpiece of an artificial pancreas. Indeed, this is the approach taken by the University of Virginia (UVA) with the Diabetes Assistant (DiAs) platform.[24]

Two new applications of artificial pancreas technology are now possible immediately based on this new technology: remote monitoring and advisory systems. The connection of continuous glucose-monitoring systems to smartphones has created the opportunity for patient caregivers to receive push notification alerts when the patient's blood glucose rises above or falls below predesignated threshold values.[25] In addition to remote monitoring, smartphone technology may make it possible to provide patients with advisory systems or decision-support systems while on current basal-bolus open-loop therapy that benefit from control algorithms that are under development for the artificial pancreas.[26]

Finally, we briefly discuss progress made in recent years in addressing five remaining challenges to successful closed-loop control: exercise, the effect of concurrent illness, large carbohydrate meals, inadequate insulin pharmacokinetics, and commercial issues associated with integrating continuous glucose monitors, insulin pumps, and closed-loop algorithms from different commercial entities.

Basic functionality of the artificial pancreas

The fundamental technical problem associated with today's artificial pancreas was well described over 30 years ago in a paper entitled "Algorithms for adjustment of insulin dosage by patients who monitor blood glucose" and written in response to the advent of home blood glucose monitoring.[27,28] The advent of self-monitoring of blood glucose (SMBG) in the 1970s meant that, for the first time since the discovery of insulin, patients with diabetes had the ability to obtain real-time data on their blood glucose value. The purpose of the paper was to propose a set of algorithms to assist patients in making real-time optimum therapeutic decisions based on the blood glucose meter data for additional insulin in response to hyperglycemia. In addition, algorithms were also presented in the paper for improved glycemic control associated with a change in insulin sensitivity due to intercurrent illness or unusual levels of physical exercise. These are virtually the same issues that are addressed by current state-of-the-art artificial pancreas systems using a wide range of technology that was not only unavailable 30 years ago, but difficult to imagine as well. However, the development of technology in the intervening years has created a new opportunity to use a combination of sensor technology, insulin-delivery technology, and microelectronics to automate the application of

such algorithms and permit patients to better maintain their blood glucose levels in the normal range. Current approaches to the artificial pancreas, described below, attempt to do precisely this.

There are three major functional components of the modern artificial pancreas: a continuous glucose-monitoring system, an insulin-infusion pump, and a control algorithm. One of the first continuous glucose sensors was developed by Updike in 1967 using glucose oxidase immobilized in a biocompatible membrane.[29–31] The first modern commercial continuous glucose-monitoring system was a similar electrochemical sensor developed by Mastrototaro *et al.*[32,33] In both of these examples, the glucose sensor is inserted through the skin and placed at a depth of 8–12 mm in the subcutaneous tissue. The sensor measures glucose in the interstitial fluid rather than the blood. Glucose is determined from a catalytic reaction based on the enzyme glucose oxidase immobilized into a polymeric membrane covering an electrode sensing element.

The first insulin pumps were also developed in the late 1970s and immediately demonstrated the potential for improving the quality of life and clinical outcomes for patients with diabetes.[34–38] Modern pumps are small, reliable electromechanical devices that are used to provide a programmed infusion of insulin into the subcutaneous tissue. Pumps consist of a refillable insulin cartridge, a pump mechanism, and a programmable user interface, which can be used by the patient to establish a basal infusion rate or to give a discrete bolus for coverage of a meal or for correction of hyperglycemia. Over the three decades since the introduction of insulin pumps, advances in microelectronics and consumer electronics have improved both the functionality and usability of the technology. The third functional component of the basic artificial pancreas is the control algorithms incorporated into a microprocessor device that provide real-time insulin-infusion dosing decisions based on the data input from the continuous glucose monitor, the insulin pump, and other vital ancillary information included in the algorithms. One of the earliest modern algorithm approaches to the artificial pancreas was the MPC algorithm proposed by Parker *et al.* in 1999.[39] The approach taken by Parker and Doyle to control insulin delivery for patients with type 1 diabetes consisted of a model of the diabetic patient physiology. The model of the glucose insulin dynamics was used to predict future glucose based on accumulated data on the insulin administered to the patient and resulting glucose values. The use of a model-based predictive algorithm permits insulin-dosing instructions to be given for a future predicted glucose value, thereby helping to mitigate the problems resulting from the temporal delays associated with the slow action of subcutaneously administered insulin. Hovorka *et al.* have developed another MPC algorithm based on a nonlinear model of the diabetic patient physiology.[40] MPC has been used by many other leading researchers in the field of artificial pancreas research.[41,42] A different early approach to the development of artificial pancreas control algorithms was the PID strategy first proposed in the context of diabetes management by Steil *et al.*[43,44] We discuss below various examples of MPC, PID, FL, and other logical supervision algorithms as examples of unihormonal or bihormonal approaches to the artificial pancreas.

Accuracy and lag time of continuous glucose-monitoring systems

The first generations of continuous glucose monitors approved by the FDA beginning in 1999 were able to provide significant clinical benefits as an adjunct to standard SMBG, but were widely acknowledged to have insufficient accuracy and reliability for use in automated closed-loop or artificial pancreas applications. In a report on recent closed-loop feasibility studies, Kovatchev *et al.* highlighted a number of limitations of current CGM systems, specifically, transient loss of sensitivity and random noise, which negatively affect the input data provided by CGM devices to control algorithms.[45] In a review paper on recent developments in artificial pancreas research, Thabit and Hovorka similarly identified the progress in continuous glucose sensing as an important element responsible for recent progress in the field, but they too highlighted some of the remaining challenges with continuous glucose-monitoring systems:

> Suboptimal accuracy and reliability remain one of the biggest obstacles for closed-loop systems. Commercially available CGM systems can achieve a median relative absolute difference between sensor and reference glucose measurements of 15% or less, which should be commensurate with closed-loop

glucose control. However, transient and persistent deviations of greater magnitude occur. Transient deviations relate to temporal loss or increase of sensor sensitivity or mechanical perturbation including temporal sensor dislodgment. Persistent deviations are caused by erroneous calibration, an inappropriate calibration algorithm, or slow drift of sensor sensitivity. When a sensor over reads blood glucose levels, the persistent deviations pose the greatest challenge to safe closed-loop insulin delivery, as insulin over delivery may occur, thus increasing the risk of hypoglycemia.[16]

In the case of bihormonal closed-loop control, Castle *et al.* have noted in their clinical studies that "sensor overestimation of glucose clearly led to a delay in glucagon delivery. Not surprisingly, delivery of glucagon at a lower starting glucose value resulted in more cases of hypoglycemia."[46]

Two widely accepted metrics for assessing the accuracy of continuous glucose-monitoring systems are the mean absolute relative difference (MARD) and the Clarke error grid. The MARD provides a single parameter to assess the average error of a continuous glucose-monitoring system compared to a reference measurement. The MARD is defined as the sum of all temporally matched pairs of the absolute value of the difference between the CGM measurement and the reference measurement, divided by the reference measurement. A low MARD value denotes a small average error and hence a high level of accuracy. The most accurate blood glucose meters used for SMBG have reported MARD values of 6–8% compared with high-precision instruments used for measuring glucose, such as the Yellow Springs Instrument glucose analyzer, in clinical or research laboratory settings. The effect of compartment differences in glucose concentration between the interstitial fluid and venous or capillary blood may set a theoretical lower limit for accuracy of CGM devices measuring interstitial fluid glucose of 8–10%. High values of MARD, such as 20% or higher, denote a large average error but may also reflect the presence of larger outlier values with individual errors of 30–40% or more.

The Clarke error grid was first proposed as a means of assessing the clinical relevance of patient estimates of their own blood glucose compared to measurements made on first-generation home blood glucose monitors.[47] The Clarke error grid has been generalized as a method of assessing the clinical accuracy of measurements made on new blood glucose–monitoring devices (plotted on the *y*-axis) compared with established reference methods (plotted on the *x*-axis).[48] The graph is divided into five regions or zones (A, B, C, D, and E). Points in zone A are defined as having glucose values that differ from reference measurements by 20% or are within the hypoglycemic range (70 mg/dL or less) when the reference value is also in the hypoglycemic range. Zone A is referred to as clinically accurate because therapeutic decisions based on measurements in this zone would likely lead to an appropriate clinical result. High values of the percentage of points in the Clarke error grid A zone denote a high level of accuracy. The most accurate home blood glucose meters, for example, often have Clarke error grid A zone percentages of 96–97% compared with laboratory reference values. Points in zone B are defined as having deviations from the reference measurement in excess of 20% but not likely to lead to clinically deleterious treatment decisions. In the early days of continuous glucose monitoring, it was a relatively commonplace practice to report the combined percentage of points in the Clarke error A and B zones as a means of reporting CGM accuracy. We do not believe, however, that this is appropriate for artificial pancreas applications, because the B zone may contain points that could lead to dangerous overdelivery of insulin (e.g., a CGM reading of 200 mg/dL compared with a reference blood glucose reading of 100 mg/dL).[47]

The improvement in accuracy and reliability of continuous glucose-monitoring systems over the past decade can be seen simply by reviewing the peer-reviewed literature on accuracy for a single manufacturer. Garg *et al.* found that the first-generation Dexcom (San Diego, CA) continuous glucose-monitoring system, the short-term sensor (STS), was able to reduce glycemic variability in patients using the device, but aggregate sensor data showed an average error or MARD of 19%, and only 49% of the data were in the clinically accurate Clarke error grid A zone (95% of all points were in the clinically accurate A zone or the benign error B zone).[49] The accuracy of the second-generation Dexcom continuous glucose-monitoring system, the Dexcom SEVEN®, was improved relative to the first-generation

product. The MARD was reduced to 16.7% and the percentage of points in the clinically accurate Clarke error grid A zone was increased to 70% (the percentage of points in the combined A + B zone was 97.8%).[50] Wentholt and DeVries acknowledged the improvement in sensor accuracy represented by the Dexcom SEVEN in an article entitled "An analysis of the SEVEN system: have we reached the summit of needle-type sensor accuracy?"[51] They wrote, "It is unknown what the future holds, but there certainly seems much to be gained from improved calibration procedures . . . it is hoped that this will translate into improved sensor use and thereby improved glycemic control." In fact, improved calibration procedures did play a role in the subsequent advances in accuracy and performance of both the third-generation Dexcom SEVEN PLUS® and the fourth-generation Dexcom G4 PLATINUM® continuous glucose-monitoring system. The pivotal trial data for the Dexcom G4 PLATINUM submitted to the FDA and reported by Christiansen *et al.* found that the MARD was reduced to 13.2% and the percentage of points in the clinically accurate Clarke error grid A zone was increased to 79%.[52] Consistent with the comment cited by Wentholt *et al.* above, Garcia *et al.* have described further improvements to the G4 PLATINUM continuous glucose monitoring based on changes in the calibration algorithms and the denoising algorithms resulting in a reduction of the MARD to 11.7%.[53] The Institute for Technology Research and Development at the University of Ulm, Germany, recently evaluated the performance of several currently commercially available continuous glucose-monitoring systems. Subjects wore duplicate systems so that the investigators reported both MARD and sensor-to-sensor differences as measured by the precision absolute relative difference (PARD).[54,55] The results are shown in Table 1.

Table 1. Comparison of accuracy metrics for four currently available continuous glucose-monitoring systems[54,55]

Continuous glucose-monitoring system	Mean absolute relative difference (MARD)	Precision absolute relative difference (PARD)
Abbott Navigator	12.4 ± 3.6%	10.1 ± 4.1%
Medtronic Enlite	16.4 ± 6.9%	16.7 ± 3.8%
Dexcom SEVEN PLUS	16.7 ± 3.8%	15.4 ± 4.2%
Dexcom G4 PLATINUM	10.9 ± 1.5%	7.3 ± 1.9%

Similar advances in sensor accuracy have been reported by the University of Ulm group when evaluating a prototype of a novel continuous glucose-monitoring system under development by Roche.[56] They found a MARD of 9.2 ± 2.1%, a PARD of 7.6 ± 2.3%, and 83.4% of the CGM results in the clinically accurate Clarke error grid A zone (98.7% in the combined A + B zone). In addition, Hoss *et al.* recently reported on a new third-generation prototype version of the Abbott Navigator continuous glucose monitor (Abbott, Alameda, CA), which had a MARD of 12.2% and 88% in the clinically accurate A zone of the consensus error grid (98.6% in the combined A + B zone).[57] It is unknown whether the results with the Roche and Abbott prototypes will be sustained when moving to production versions.

Uncertainties in the physiological lag time between blood glucose and interstitial fluid glucose are often cited as a possible impediment to the use of continuous glucose-monitoring data as input to closed-loop algorithms. As noted above, transdermally inserted glucose sensors measure glucose in the interstitial fluid and not in blood itself. Many early reports suggested lag times from 4 to 40 min.[58–61] However, recent research by numerous investigators has found that the true physiological lag time between blood glucose and interstitial fluid glucose is no greater than 5–10 min. Wientjes and Schoonen used the results of microdialysis measurements and theoretical calculations of glucose transport in subcutaneous adipose tissue to conclude that the physiological lag time between blood and interstitial fluid glucose was negligible.[62,63] Voskanyan *et al.* summarized their extensive experience with electrochemical sensors, noting that the use of mathematical filters to smooth noisy raw sensor data appeared to be the single most important factor in giving the appearance of a large lag time between blood and interstitial fluid glucose.[64,65] Finally, Basu *et al.* have used radiotracer methods to measure the actual physiological lag time between intravascular glucose and interstitial fluid glucose. They assessed plasma and microdialysis samples for the appearance and decay of glucose in the blood and interstitial fluid, respectively, after sequential glucose

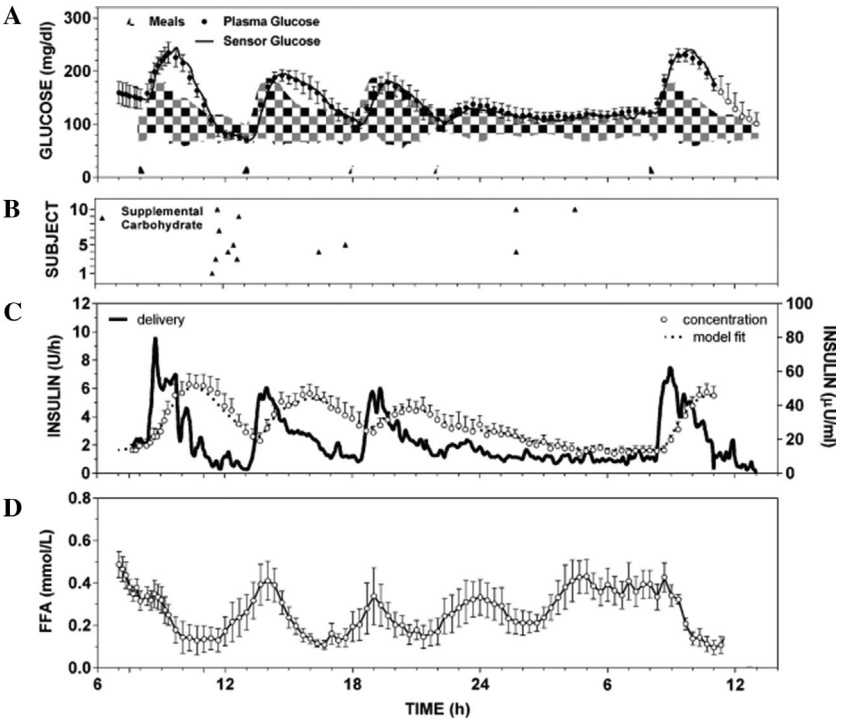

Figure 1. Glucose, carbohydrate, insulin, and free fatty acids (FFA) averaged over ten subjects, illustrating the performance of an early PID closed-loop algorithm.[43]

tracers administered intravenously and found a 5–6 min delay between blood glucose and interstitial fluid glucose.[66]

Two major approaches to glucose regulation in the artificial pancreas: unihormonal and bihormonal

As noted above, there are two major system-level approaches to achieve closed-loop control of blood glucose in diabetic patients: the unihormonal approach using insulin only to lower blood glucose and the bihormonal approach using insulin to lower blood glucose and glucagon to raise blood glucose. The bihormonal approach may be expanded to include the use of pramlintide to delay gastric emptying and downregulate endogenous hyperglucagonemia, thereby providing still further improvements in glycemic control.[67]

The first successful feasibility studies of the unihormonal approach were done by Steil *et al.* using a PID control algorithm.[43,44] These studies were performed using the Medtronic MiniMed® CGM system and a Medtronic 511 Paradigm™ insulin pump, both of which were able to communicate telemetrically with a laptop computer. Figure 1 from the 2006 paper by Steil *et al.* depicts the sensor glucose, supplemental carbohydrate, and insulin delivery averaged for the ten subjects in the study.

The original formulation of the PID approach may have been prone to iatrogenic hypoglycemia because the integral component could drive insulin delivery based on the difference between the instantaneous glucose and the target glucose even when there was a large amount of insulin on board (IOB). In these studies, insulin dosing for meals was controlled by the closed-loop algorithm and there was no prior meal announcement or manual delivery of insulin before the meal. In 2011, Steil *et al.* published a modification of their PID algorithm incorporating the explicit use of insulin feedback on the forward delivery of insulin.[68] This led to improved glucose values, but still required some open-loop administration of carbohydrates to treat real or imminent hypoglycemia. In a recent commentary, Steil noted further that the use of the insulin feedback in the PID approach may have alleviated some of the concerns about overadministration of insulin: "The clinical results achieved to date with PID control

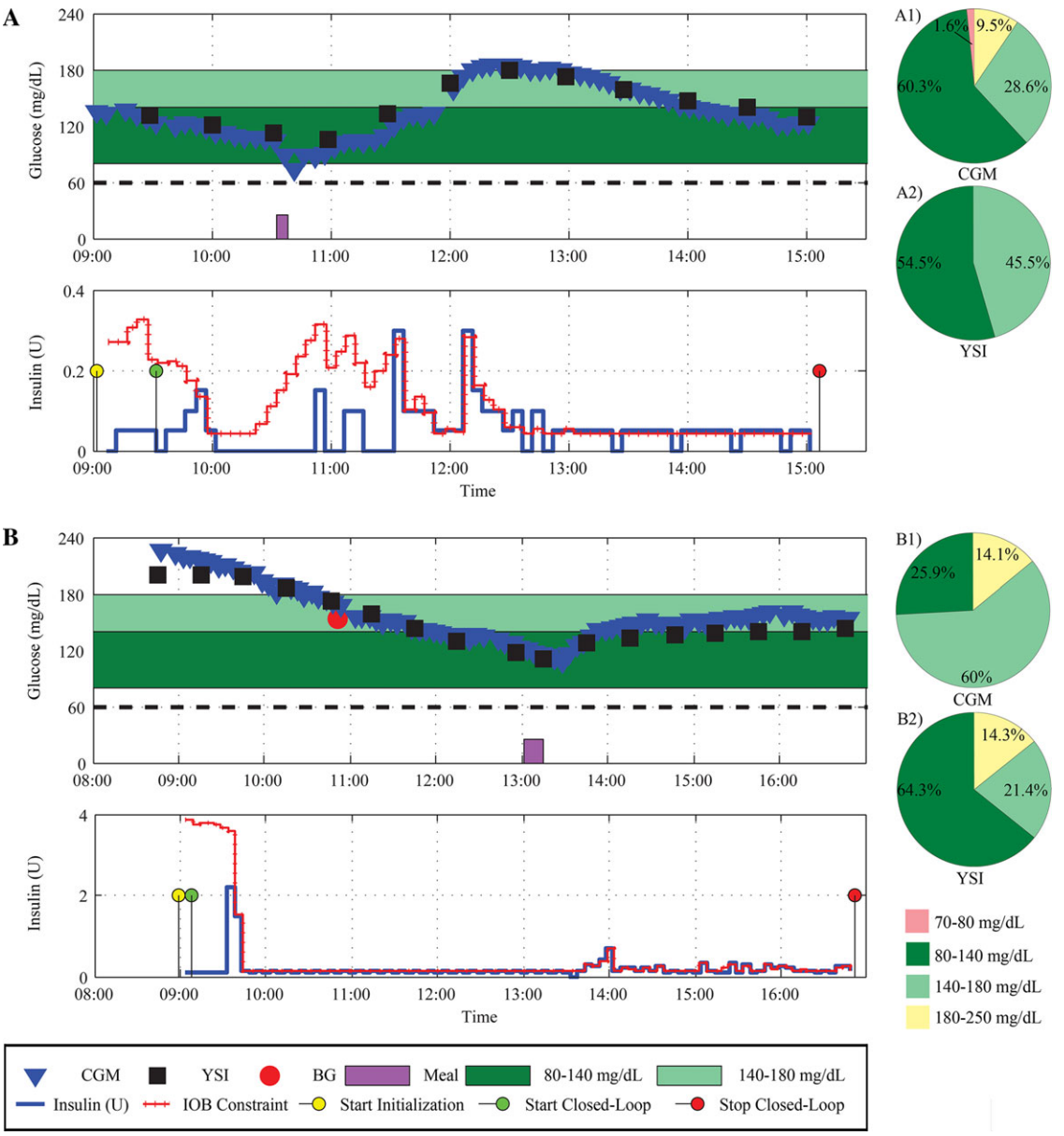

Figure 2. Glucose and insulin from two closed-loop clinical studies done with the UCSB personalized multiparametric MPC algorithm.[74]

have improved as changes in the algorithm have been effected to meet those challenges."[69]

MPC describes a broad approach to closed-loop algorithms that has many different implementations depending on the details, type, and order of the model used to relate the action of insulin delivery (the actuator) to the effect on the subject's glucose level (the objective or cost function). The MPC approach taken by Doyle *et al.* at the University of California Santa Barbara (UCSB) incorporates safety constraints to address the same issue noted above in the PID approach. The use of a dynamic safety constraint based on projecting the effect of the insulin on board on future glucose was described by Ellingsen *et al.* and included a discussion of improved estimates of insulin correction factor, insulin-to-carbohydrate ratio, and the estimates of insulin decay curves in the body.[70]

"Control to zone" design of MPC was recently reported in several publications where the control objective is to bring glycemic levels into an acceptable zone or range rather than to a strict and artificial target.[71–73] Dassau *et al.* summarized the results of the work of their group in a paper published in 2013 entitled "Clinical evaluation of a personalized artificial pancreas," which used a personalized model for each individual subject using multiparametric MPC.[74] The study used Dexcom SEVEN and SEVEN PLUS continuous glucose-monitoring systems and an Insulet OmniPod insulin pump connected wirelessly to a laptop computer running the artificial pancreas system (APS) software system developed at UCSB.[75] The study had three objectives: (1) normalizing glucose levels independent of the initial glucose value, (2) maintaining glucose values in the normal range (euglycemia), and (3) minimizing postprandial glucose excursions associated with small unannounced meals (25–35 g carbohydrate).

"The advantage of an MPC strategy is its ability to incorporate an explicit model of the glucose–insulin system. The controller compares the model-predicted output with the actual output (glucose concentration), calculates the next manipulated input value (insulin delivery), and updates the prediction with new measurements at each control cycle." Figure 2 reproduces the clinical results from two closed-loop clinical studies using the UCSB personalized multiparametric MPC. As illustrated, the controller is constrained by the IOB estimation from overdelivery of insulin that may result with hypoglycemia. This dynamic constraint is relaxed as glucose levels change, allowing more control action or restricting it as shown (Fig. 2B).[74]

A modular design to the artificial pancreas was suggested by Kovatchev*et al.*[76] and Patek *et al.*[77] at the University of Virginia (Charlottesville, Virginia); the system can be divided into controller and safety modules, as well as a communication module. Other groups have also recently published their results using rule-based algorithms for overnight closed-loop control.[78] An example of a modular strategy is a combination of a controller with a safety system and a communication layer, as suggested in the Juvenile Diabetes Research Foundation (JDRF) control-to-range study.[77] A variation on this hierarchical control strategy where each module is tasked with different object points is suggested by the University of Virginia, where their modular system relies upon four separate algorithm components to optimize glycemic values within various safety constraints. The first component of the UVA system is the safety supervision module (SSM), which dampens the delivery of insulin in inverse proportion to the predicted risk of hypoglycemia using a model-based estimation of the patient's metabolic state.[79,80]

The second component is a module for the prevention of hyperglycemia, the hyperglycemia safety system (HSS), which uses a combination of the SSM metabolic estimation procedure and an insulin-on-board calculation that compares the actual insulin on board with the ideal insulin on board needed to achieve euglycemia. The combination of the HSS and SSM is called the unified safety system. The UVA system also contains a dual visual display of the patient's glycemic state on a smartphone based on the concept of the green, yellow, and red traffic light display for both hypoglycemia and hyperglycemia. When the traffic light is green, the risk for hypoglycemia or hyperglycemia is low and no action by the algorithm or the patient is needed. When the traffic light is yellow, there is a discernible risk and the algorithm initiates alteration of insulin to address the situation. When the traffic light is red, there is a high risk of real or impending hypoglycemia or hyperglycemia, and external action by the patient, such as the ingestion of rescue carbohydrates or administration of a correction bolus, may be required.

The third module is a meal safety system (MSS) which is used to respond to increases in glucose owing to consumption of a meal. After an announced meal (i.e., after the closed-loop algorithms have been informed by the patient that he or she is eating a meal), if there is no imminent risk of hypoglycemia, the MSS component of the closed-loop algorithm increases the basal rate up to three times the preprogrammed value. Insulin is attenuated by the action of the MSS module after a meal when the glucose decreases (e.g., to 110 mg/dL) and the insulin is attenuated. When the continuous glucose monitor detects a rise in glucose, the remaining insulin required for the meal (not yet provided as part of the increased basal infusion of insulin) is infused as a single bolus.

The fourth and final module in the UVA modular system is the hyperglycemia-mitigation system (HMS). The HMS module predicts the

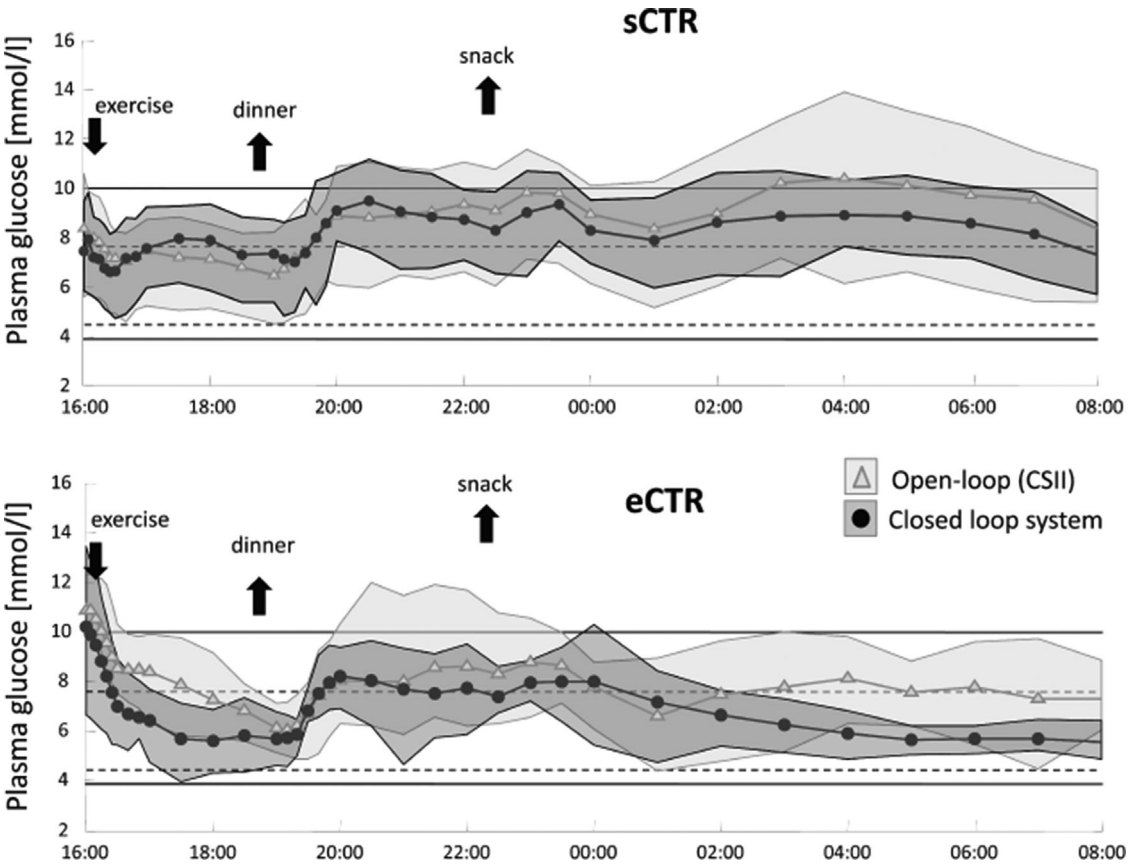

Figure 3. The mean and quartile range of plasma glucose for the UVA standard control-to-range (sCTR) algorithm and the enhanced control-to-range (eCTR) algorithm.[81]

estimated glucose 30–60 min forward in time, and if the forecast indicates a glucose value above the hyperglycemia threshold of 180 mg/dL, the HMS uses the insulin-on-board information from the pump and provides a correction bolus calculated as 60% of the correction bolus needed to achieve euglycemia. HMS can repeat such hyperglycemic correction boluses every hour as needed.

The most recent results using the modular approach to the artificial pancreas with control, safety, and communication modules were published in 2012 in a paper entitled "Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia."[81] The components used in this study were either a Dexcom SEVEN PLUS or an Abbott Navigator® continuous glucose monitor and an Insulet Omnipod insulin pump communicating wirelessly with a laptop computer—all of which were integrated through the UCSB APS.[75] The study compared two modular closed-loop algorithms designed to achieve an optimum control to range: standard control to range (sCTR) and enhanced control to range (eCTR). The difference between these two algorithms was described by the authors:

> The first system, sCTR, included an SSM mitigating the risk for hypoglycemia, and a sCTR algorithm activated when hyperglycemia was predicted. The task of sCTR was to prevent hypoglycemia and mitigate extreme hyperglycemia, without truly aiming for optimal glucose control. The second system, eCTR, included the same SSM to prevent hypoglycemia but coupled with a more sophisticated MPC algorithm. The task of eCTR was optimal glucose control within a target range.

Figure 3 depicts the mean and quartile range of the plasma glucose for each of these algorithm

Figure 4. (Left) The DiAs smartphone used in recent UVA outpatient artificial pancreas studies with the closed-loop control algorithms operating on a smartphone rather than a laptop computer. (Right) A patient holding the DiAs smartphone next to the Dexcom CGM and Insulet insulin pump on her abdomen.[45]

approaches, each comparing open-loop to closed-loop control.

Using the sCTR algorithm, a subsequent study by the University of Virginia group demonstrated the feasibility of outpatient closed-loop control using the Dexcom SevenPlus continuous glucose-monitoring system and an Insulet Omnipod insulin pump communicating directly to a specially configured Android smartphone designated the DiAs, rather than to a laptop computer.[45] A photograph of the DiAs platform used in the study is shown in Figure 4.

Phillip *et al.* have used an FL system to emulate the expert decision-making algorithms used by medical personnel in providing treatment recommendations to patients.[82–84] Mauseth *et al.* have also developed an independent FL system using experience gleaned by the algorithm developers from their previous work in the aviation industry.[85,86] In 2013, Phillip *et al.* published the results of a clinical study using their FL controller, MD-Logic, for overnight or nocturnal closed-loop control in a diabetes camp.[87] The components used in this study were a Medtronic Enlite continuous glucose monitor and a Medtronic Paradigm Veo insulin pump communicating wirelessly with a laptop computer. The study found that the MD-Logic system was able to lower the mean overnight glucose from 140.4 mg/dL in the open-loop arm to 126.4 mg/dL in the closed-loop arm while at the same time reducing the incidence of hypoglycemic events threefold between the two groups. This is an important result for two reasons: first, it demonstrated the successful use of an early-stage artificial pancreas device in a true outpatient setting, a diabetes camp; and second, it demonstrated the potential of current artificial pancreas technology to achieve overnight closed-loop control of glycemia. Glycemic control in the two arms of the MD-Logic overnight closed-loop control camp study, along with both basal and bolus insulin dosing, are shown in Figure 5.

There have been two prominent research groups in recent years that have advocated and evaluated the bihormonal approach to closed-loop control: Ward *et al.* at Oregon Health Sciences University and Damiano *et al.* at Boston University and the Massachusetts General Hospital. These two approaches differ slightly in the frequency and amount of glucagon delivered. In the Oregon system, glucagon is given relatively infrequently—on average, only once or twice daily—for purposes of reversing overt or impending hypoglycemia. In the Boston

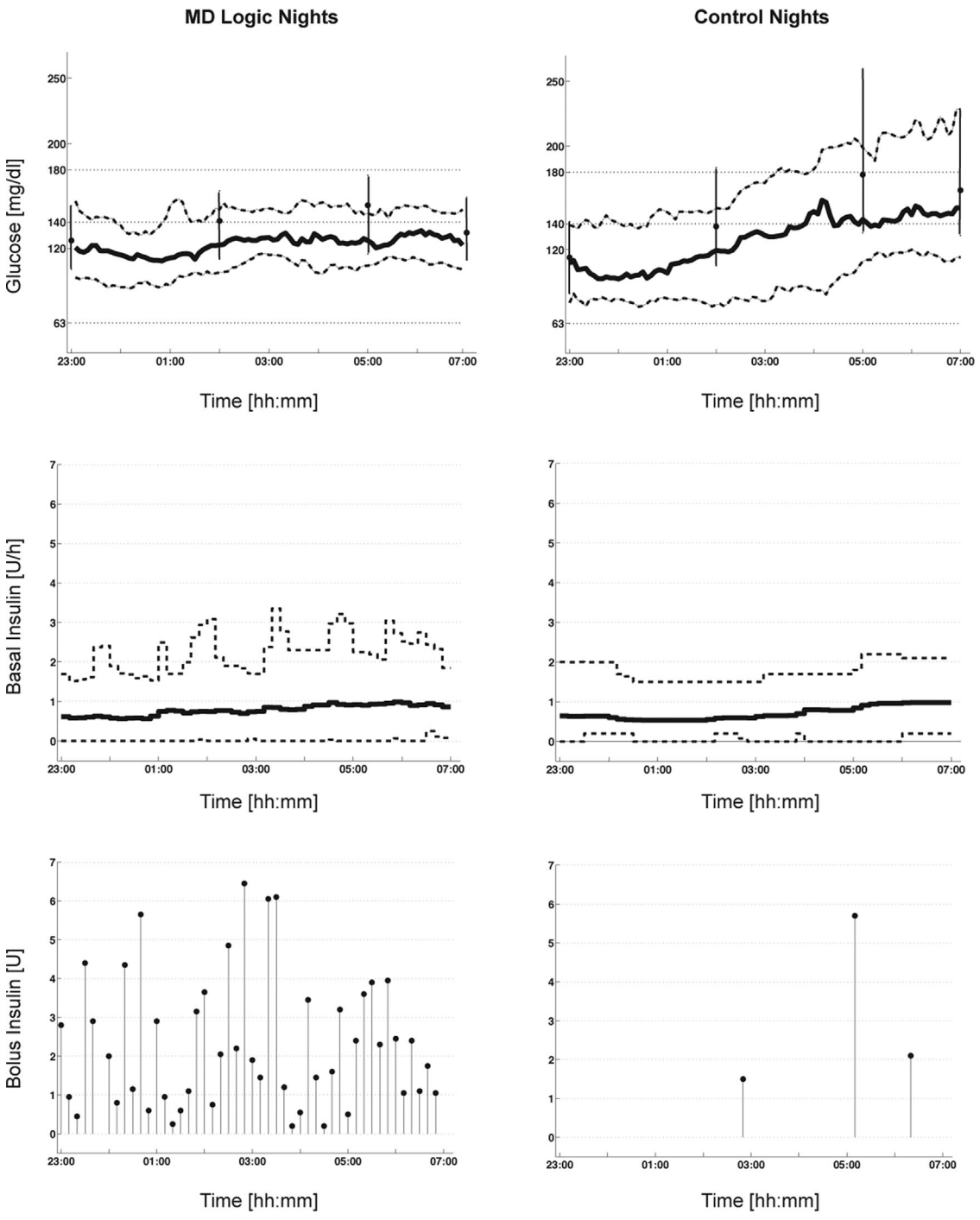

Figure 5. (A) Shows the glucose (median and quartile), basal insulin (median and quartile), and bolus insulin (total for all subjects) for the overnight closed-loop arm of the study. (B) Shows the same for the overnight open-loop arm.[87]

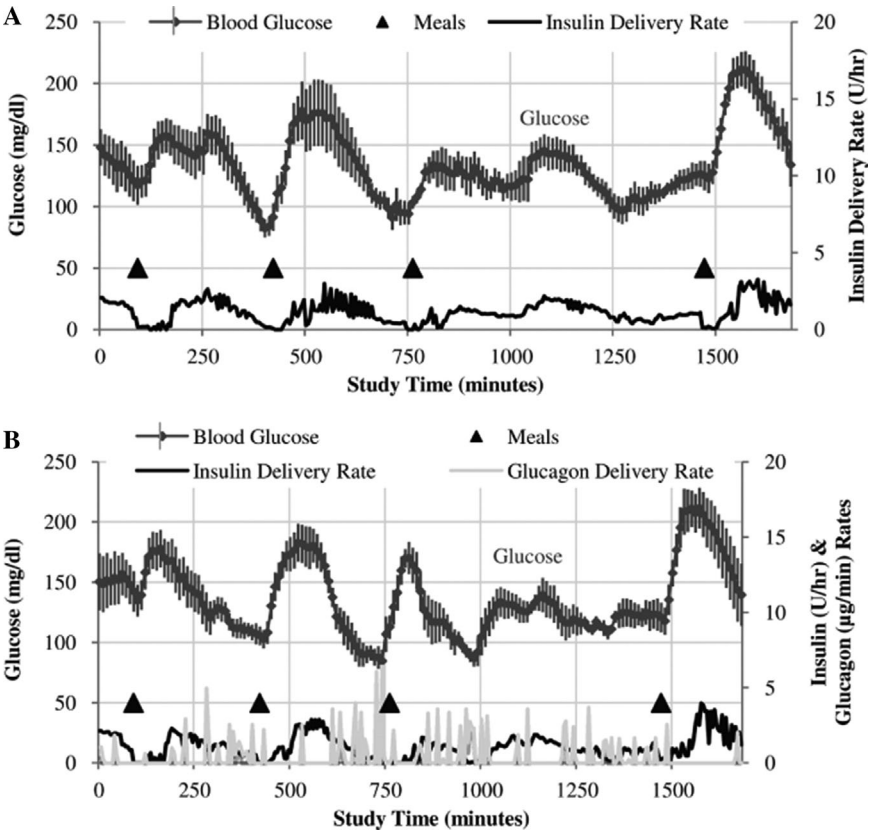

Figure 6. Glucose, insulin, glucagon, and meals from a bihormonal artificial pancreas study with two different patterns of glucagon administration.[90]

system, glucagon is given more frequently—often 20 or more times daily, albeit in smaller dosages—for the purpose of preventing hypoglycemia and maintaining euglycemia. The Boston approach appears to permit the controller to achieve a more rapid time to target than is often observed in unihormonal systems, while the Oregon system may minimize some of the uncertainties associated with chronic use of glucagon.

The Oregon group has published numerous papers on their approach to bihormonal closed-loop control.[88–91] In a study published by Castle *et al.* in 2010, they showed that the bihormonal approach to closed-loop control allowed subjects to achieve improved glycemic control with little or no risk of hypoglycemia. Subjects in the study wore two continuous glucose monitors—either Dexcom SEVEN PLUS or a Medtronic Guardian® Real-Time continuous glucose monitor. Insulin was administered subcutaneously using an Animas insulin pump. Glucagon was administered subcutaneously using a Medfusion 2001 syringe pump. All of the artificial pancreas device components were configured to communicate wirelessly with a laptop computer containing the control algorithms. At the time of this study, and indeed, at the present time, there is not a long-term stable, soluble formulation of glucagon, hence a new glucagon solution had to be prepared every 8 hours. One important feature of the algorithm used by Castle *et al.* is that it reduces the gain on the parameter controlling insulin dosing after administration of glucagon. This prevents insulin from being given in response to the rise of glucose following treatment of hypoglycemia by glucagon. The relatively infrequent use of glucagon in this bihormonal artificial pancreas system is designed to reduce the likelihood of relying on a potentially unstable balance between insulin and frequent glucagon to achieve euglycemia. Figure 6 shows the glucose levels, insulin delivery, and glucagon delivery from a 2010 paper comparing unihormonal (insulin only) closed-loop

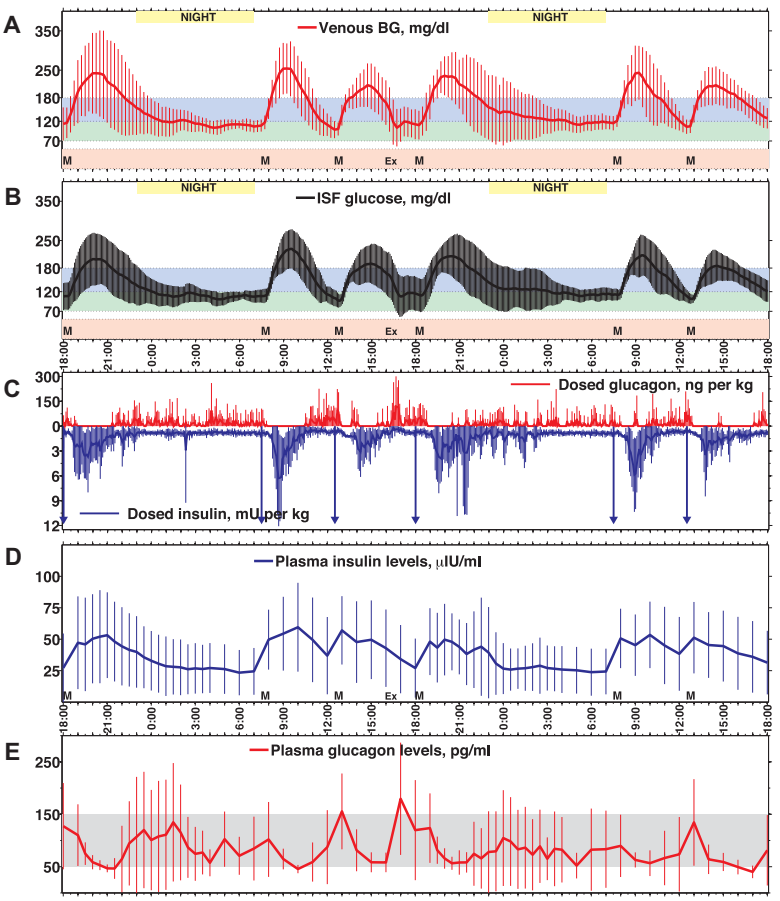

Figure 7. The mean and standard deviation of (A) the plasma glucose, (B) the continuous glucose monitor data, (C) insulin and glucagon doses, (D) plasma insulin levels, and (E) glucagon levels are shown for all six subjects from the Boston University bionic pancreas study.[92]

control with bihormonal (insulin and glucagon) closed-loop control.[90] Unihormonal and bihormonal control were roughly comparable, except that the incidence of hypoglycemia was reduced with the bihormonal approach.

The Boston group also has been a staunch proponent of the bihormonal approach to closed-loop control, which they have described as a "bionic pancreas."[92–94] The Boston bionic pancreas utilizes a customized MPC algorithm for the insulin infusion that includes a pharmacokinetic model of the absorption and clearance of insulin lispro from the body. Glucagon administration is controlled by a proportional derivative algorithm to prevent or treat glucose excursions below 100 mg/dL. Russell *et al.* reported on pilot studies with six subjects in a 2012 paper.[92] The components used in this study were an Abbott FreeStyle Navigator continuous glucose monitor and two Insulet OmniPod® insulin pumps—one for insulin and the other for glucagon. All of the components were configured to communicate wirelessly with a laptop computer containing the bihormonal control algorithms. The mean and standard deviation of the plasma glucose, the continuous glucose monitor data, insulin and glucagon doses, plasma insulin levels, and plasma glucagon levels are shown in Figure 7 for their six subjects.

A recent paper by El-Khatib *et al.* reported on the further development of their bihormonal artificial pancreas.[95] In this paper, they also discussed in greater detail their approach to simplifying meal boluses, noting that a fully automated artificial pancreas device would not require open-loop meal announcements. Their adaptive meal-priming

system uses a simple meal notification provided by the user, and the algorithm then "automatically adjusts the size of 'breakfast', 'lunch,' and 'dinner' doses by administering 75% of the average prandial insulin provided for previous meals at that time of day."

The roadmap to an artificial pancreas and the impact of new technologies

In an influential paper entitled "Can We Really Close the Loop and How Soon? Accelerating the Availability of an Artificial Pancreas: A Roadmap to Better Diabetes Outcomes," published in 2009, Kowalski proposed a path for research on the artificial pancreas that has been the basis for much of the advances in research in the field in recent years.[96] In summary, the Kowalski roadmap has the following elements: (1) very-low glucose insulin pump shut-off with the goal of reducing severe hypoglycemia exposure and hypoglycemic seizures; (2) predictive hypoglycemia-minimizing system with the goal of reducing hypoglycemia exposure below current estimated averages of 1–2 h/day; (3) predictive hypoglycemia- and hyperglycemia-minimizing system, with the goal of reducing hypoglycemic exposure, as above, and reducing hyperglycemic exposure from current estimated averages of 7–8 h/day; (4) overnight closed-loop control—nocturnal closed loop with the goal of automating to a euglycemic set point overnight, with meal announcement during the day based on hypoglycemia and hyperglycemia minimization; (5) full diurnal closed-loop control with or without meal announcement, but requiring occasional treatment for hypoglycemia with fast-acting carbohydrates; and (6) full diurnal closed-loop control with a bihormonal system with no meal announcement and with the use of glucagon administered automatically to prevent hypoglycemia as required.

Bergenstal *et al.* and Ly *et al.* have published papers on the use of the low-glucose or *threshold suspend* system, showing a reduction in the incidence of severe hypoglycemia in the intervention arm.[97,98] In October 2013, the FDA approved a low glucose or threshold glucose suspend system, the Medtronic 530G system, consisting of a continuous glucose monitor integrated into an insulin pump system. The 530G system suspends basal insulin infusion when the continuous glucose monitor in the system detects glucose below a predesignated threshold value. In an editorial on the significance of the Bergenstal paper, Hirsch noted that for low-glucose or threshold-glucose suspend using a sensor-augmented pump system to be effective in preventing nocturnal hypoglycemia, "the CGM device would have to be accurate at hypoglycemic levels to suspend at the appropriate times." Moreover, he found it surprising that the median duration of suspension during nocturnal events was only 11.9 min, making it unlikely that such a brief suspension of insulin infusion was solely responsible for reducing the hypoglycemic exposure. Despite these concerns, he wrote further that it was "reassuring and exciting" that nocturnal hypoglycemic exposure and event rates were reduced by 38% and 32%, respectively, but raised concerns about short duration of the study and the effectiveness in a broader patient population.[99] Although this represents a small step on Kowalski's roadmap, it does represent a milestone in terms of regulatory approval of devices of this type.

At the time the roadmap above was proposed, there were few clinical studies showing the success of overnight closed-loop or automatic diurnal regulation of glucose levels. A slow methodical progression from low-glucose suspend, to predictive low-glucose suspend, to hypoglycemia and hyperglycemia minimization, to overnight closed-loop control appeared to be a reasonable, conservative development strategy. In the last few years, however, numerous artificial pancreas clinical studies have demonstrated improved glucose control overnight and during the day. At the time the Kowalski roadmap was proposed, the accuracy and reliability of continuous glucose-monitoring systems was widely assumed to be insufficient to achieve full diurnal closed-loop control either with or without meal announcement. Finally, there had been few, if any, human clinical studies addressing the technical challenges associated with bihormonal control. As discussed above, there have been numerous clinical studies demonstrating favorable results on overnight closed-loop control and on diurnal closed-loop control. The accuracy and reliability of continuous glucose-monitoring systems has improved dramatically. There have been numerous successful studies using the bihormonal approach. In short, it may now be possible to skip the original proposed intermediate steps of predictive

low-glucose suspend, hypoglycemia and hyperglycemia minimization, and overnight closed-loop control, and proceed directly to diurnal closed-loop control with either the unihormonal or bihormonal approach.

In addition, the rapid development of smartphone technology over the last several years has created an opportunity to introduce various applications of artificial pancreas technology that were not possible to envision when the Kowalski roadmap was first proposed. The use of smartphones as the hub of artificial pancreas prototype devices is becomingly increasingly widespread. As Kovatchev *et al.* have stated:

> Further progress toward bringing closed-loop control to the outpatient setting depends on an artificial pancreas platform that is based on a readily available, inexpensive, wearable hardware, computationally capable of running closed-loop control algorithms, wirelessly connectable to CGM devices and insulin pumps, and capable of broadband communication for the participants in outpatient clinical trials. A logical host for such a portable artificial pancreas platform is a contemporary smart phone, a consumer electronics device that meets virtually all of these aforementioned requirements.[45]

The connectivity associated with smartphone technology has also made possible another application of the technology that was not envisioned in the original Kowalski roadmap. Internet-based remote monitoring of glucose values was used in many of the early artificial pancreas studies to allow investigators to follow the course of a closed-loop clinical study from a distance. Place *et al.* have described a system used by researchers in the United States and France working on joint clinical studies to evaluate artificial pancreas devices.[100] In these studies, smartphone-based artificial pancreas devices continuously broadcast data to a secure centralized server so that researchers in other cities or countries could then log on via a regular internet browser and observe the closed-loop clinical study in real-time. O'Grady *et al.* have reported on a similar system, the Medtronic Portable Glucose Control System, consisting of two subcutaneous glucose sensors, an insulin pump, and control algorithms and wireless connectivity housed in a Blackberry Storm smartphone platform.[101] The authors note that the remote monitoring capabilities available in their system may facilitate physician supervision of future home studies of artificial pancreas devices.

Moreover, it was quickly realized that remote monitoring based on emerging smartphone technology might represent an important spin-off of artificial pancreas technology. In 2009, Dassau *et al.*, in a paper entitled "Enhanced 911/global position system wizard: a telemedicine application for the prevention of severe hypoglycemia—monitor, alert, and locate," proposed using smartphone-based remote monitoring technology to assist in the prevention of severe hypoglycemia.[25] "In addition to providing a safety layer to a future artificial pancreas, this system also can be easily implemented in current continuous glucose monitors to help provide information and alerts to people with diabetes."

The impact of this telemedicine application was enhanced further by the development of additional algorithms for hypoglycemia detection.[102,103]

The potential clinical benefits of remote monitoring to reduce the incidence and duration of nocturnal hypoglycemia were shown in a study by DeSalvo *et al.* in a diabetes camp.[47] In this study, the remote monitoring capability developed by Place at the University of Montpellier and Keith-Hynes at the University of Virginia for monitoring the progress of closed-loop clinical studies was deployed in a diabetes camp. The system used the Dexcom G4 PLATINUM receiver connected by a mini-USB cable to an Android smartphone that transmitted real-time CGM data over a wireless network deployed throughout the camp. Doctors were able to monitor 10 subjects (campers) at a time throughout the night and intervene with rescue carbohydrates when the CGM glucose values reached 70 mg/dL. Compared to a control group of an equal number of subjects wearing a CGM device but not receiving assistance dictated by remote monitoring, the subjects (campers) in the remote monitoring had a one-third reduction of hypoglycemic events defined as less than 70 mg/dL lasting 1 h or more. There were no episodes of hypoglycemia defined as less than 50 mg/dL in the remote monitoring with a duration greater than 30 min, whereas in the control group there were nine episodes lasting 30 min or longer and six episodes lasting 1 h or longer. In this study, CGM was monitored in real-time by medical personnel who responded to the threshold

alerts and provided treatment for hypoglycemia to the subjects. In practice, the use of smartphones and programs hosted on distributed computers connected by the Internet (cloud computing) could provide parents, spouses, and other designated caregivers with event-based notifications (e.g., text messages) that would allow them to provide assistance to the patients if needed. The authors concluded, "Remote monitoring using CGM at diabetes camps is feasible and effective in reducing the risk of prolonged nocturnal hypoglycemic events . . . Remote monitoring may be a valuable tool for augmenting the ability of CGM systems in routine clinical use to prevent severe nocturnal hypoglycemia."

Despite the successful repeated use of remote monitoring to allow medical staff supervision of artificial pancreas studies and the potential to use remote monitoring to assist patients in preventing hypoglycemia, the reliance of artificial pancreas devices on smartphone technology has been met with some criticism. Real-time physician supervision of commercial artificial pancreas systems seems to be an unnecessary and economically unfeasible application of the technology. However, the use of automated push notifications to patients and caregivers in the event of detected or suspected artificial pancreas component failure may be both clinically helpful and economically viable. Remote monitoring of commercial artificial pancreas devices may be valuable as well as a component of postmarket surveillance of system performance.

The use of smartphones as controllers for artificial pancreas systems has also come into question, despite the success of the University of Virginia DiAs platform studies, because of the difficulties associated with obtaining regulatory approval of the smartphone as a class III (high risk) medical device. Regulatory experts have raised questions about the potential deleterious effects of downloaded smartphone applications on artificial pancreas algorithms running on a smartphone, as well as the uncertainties associated with periodic upgrades of the smartphone operating systems. In addition, the regulatory review process for a smartphone as a component of a class III medical device is not currently known. A number of continuous glucose monitor manufacturers are proceeding with plans to display data on smartphones that should enable patients to view their data more frequently and avoid the stigma, particularly among adolescents, associated with having to use a separate medical device. However, the FDA may require them to also provide a separate receiver as well. More importantly, the use of smartphones not only for display of sensor data but also for control of an insulin pump does pose a number of legitimate questions relating to safety and reliability. We are optimistic, however, that there may be a combination of hardware and software solutions that allow for smartphones to be used in this capacity.

In addition, advances in cloud computing make it possible for caregivers to access on demand the real-time glucose values of family members or loved ones at any time throughout the day or night. The computational power on the latest generation of smartphones, plus access to additional data processing available on cloud-based platforms, makes it possible to provide patients with recommendations for improved treatment action using the same or similar control algorithms used in the artificial pancreas. The widespread use of advisory or decision-support systems may be an important application of artificial pancreas technology that reduces the burden of diabetes and improves glycemic control in patients. In a paper entitled "Smart telemedicine support for continuous glucose monitoring: the embryo of a future global agent for diabetes care," Rigla has proposed accelerated research and development efforts designed to integrate current generations of continuous glucose monitors with smartphones to create telemedicine monitoring platforms.[104] In the paper, Rigla envisioned the telemedicine monitoring platform containing complex algorithms run locally or remotely to provide clinical decision support to both patients and physicians.

Five remaining challenges for the artificial pancreas

Despite the substantial progress made in recent years and summarized above in the field of artificial pancreas research, there remain a number of challenges to successful development of commercial artificial pancreas devices. These challenges, as noted above, include the effect of exercise, concurrent illness, large carbohydrate meals, the pharmacokinetics of current subcutaneous insulin, and integration of the three major functional components of an artificial pancreas into a single commercial device.

There is extensive ongoing research into the effects of exercise on the stability of closed-loop control and the associated increased risk of

hypoglycemia.[105,106] The bihormonal approach may be especially helpful in addressing the challenges associated with maintaining euglycemia during periods of strenuous physical exercise, although there may be limits to the effectiveness of glucagon in raising blood glucose in special cases in which subjects have participated in high-intensity long-duration exercise such as competitive cycling or long-distance running. The effect of changes in a person's insulin sensitivity or resistance based on concurrent illness or medication is also an active area of research.[89] The effect of meals, especially large-carbohydrate meals, on postprandial glucose values is similarly an ongoing focus of research.[86] The development of new analog insulins with further improvements in pharmacokinetics (i.e., more rapid onset and shorter duration of action) should facilitate better glycemic control, including more rapid treatment of hyperglycemia and the more effective modulation of insulin infusion to reverse actual or impending hypoglycemia. Cengiz has recently reviewed different approaches for creating insulins with more favorable pharmacokinetics for artificial pancreas applications.[107] There are at least five different approaches to developing insulins with more rapid absorption: localized heating, topical pharmacologic treatments, inhaled insulins, interperitoneal delivery, and new pharmacologic formulations of insulin (e.g., Fiaspart, under development by Novo Nordisk).

One of the most important challenges in the field of artificial pancreas research and development is the commercial integration of state-of-the-art technology, including continuous glucose monitoring, insulin infusion systems, and closed-loop algorithms. Ideally, commercial embodiments of artificial pancreas devices would include the most accurate and reliable continuous monitors, the most reliable and user-friendly insulin- and glucagon-infusion systems, and the most efficacious control algorithms in a single package. It seems unlikely for the foreseeable future that any one of the existing diabetes technology companies will be able to develop and manufacture all three of the state-of-the-art components (pump, sensor, and algorithms) required for a commercial artificial pancreas device themselves. An alternative strategy might be for a new company to be created for the purpose of establishing multiple business partnerships to obtain access to the best glucose sensor technology, the best pump technology, and the best control algorithms from a number of different companies or universities and take responsibility for their integration into a single artificial pancreas device. This new company would be responsible not only for the engineering integration, the verification, and the validation, but also for the clinical studies and regulatory filings to obtain approval from the FDA. There are ample precedents, in fact, in other areas of critical system technology—such as commercial aviation, in which the company responsible for the manufacture and release of an aircraft acquires critical components, such as jet engines, navigation systems, and avionics, among other things, from third-party vendors and takes responsibility for the engineering integration, verification, and validation as well as the commercialization of the aircraft. This may represent a faster and more viable path for the development of commercial artificial pancreas systems than to wait for a single large company to develop or acquire all the best available artificial pancreas components themselves.

Summary and conclusion

In the unihormonal approach, there are a number of possible commercial embodiments of closed-loop technology that could have a positive impact on patients within the next 5 years. We believe that overnight closed-loop control may be an achievable goal for near-term artificial pancreas device development. In addition to the work cited above by Phillip *et al.*, Hovorka *et al.* have also obtained excellent results with their nonlinear MPC algorithm used for overnight closed-loop control.[108–110] Hypoglycemia and hyperglycemia minimizers such as those described above for the UCSB MPC algorithms or the University of Virginia modular closed-loop algorithms may also be feasible in the next several years. The Cambridge group has also shown successful control of basal insulin delivery for up to 36 h using closed-loop control algorithms.[111] However, as mentioned above, given the rapid progress in the field, it may be possible to skip these intermediate steps and proceed directly to full diurnal closed-loop control with either the unihormonal or bihormonal approach.

In the case of the bihormonal approach, similar advances as those outlined above are possible in principle in the near future, but there are two significant additional challenges in terms of the

availability of the required technology. Progress has been made in recent years by a number of researchers and pharmaceutical companies in developing a stable, soluble form of glucagon.[112] However, none of these compounds have yet been approved by the FDA, and the process for obtaining approval of a new drug can be long and arduous. Moreover, there would need to be regulatory approval for chronic use of glucagon. In addition, there is not currently an insulin pump with a dual-cartridge system capable of continuous subcutaneous infusion of both insulin and glucagon. We do not foresee any insurmountable technological obstacles to the development of a dual-chamber pump, but medical device development can be costly and time consuming and it is difficult to predict when such a technology might be available.

Significant progress has been made by many groups using different approaches to achieving improved glycemic control with artificial pancreas devices, but it can be difficult to compare the results of clinical studies directly because of the high level of heterogeneity in the study design and protocols, as well as differences reporting clinical outcomes. In addition, many published papers do not provide sufficient data for independent researchers to determine all the relevant details in the study (e.g., the details of meal bolusing or the frequency of unscheduled open-loop interventions with fast-acting carbohydrates to prevent hypoglycemia or insulin injections to prevent hyperglycemia). It would also be helpful in assessing system robustness and reliability for authors to note the frequency and extent of technical support provided by clinical or engineering staff to troubleshoot the systems used in studies. In recent years, a number of groups (e.g., Boston University, UCSB, and the University of Virginia) have embraced the use of online supplementary data options in many journals to provide this information on their studies. We encourage others to do so as well in the future.

In summary, we believe that advances in the accuracy and performance of continuous glucose-monitoring systems have made it possible to provide input data to closed-loop algorithms suitable for the development of commercial prototypes of artificial pancreas devices. In addition, advances in the safety and effectiveness of control algorithms have been repeatedly demonstrated in feasibility studies done by numerous groups around the world using a variety of control strategies or approaches. The next phase of artificial pancreas research will likely focus on further engineering integration and testing of prototype systems followed by extensive clinical testing in the outpatient setting.

Conflicts of interest

Dr. Peyser is a consultant to Dexcom and holds stock in the company. Dr. Dassau is an employee of the University of California Santa Barbara and has participated in the development of the UCSB algorithms described in this paper. Dr. Breton is an employee of the University of Virginia and has participated in the development of the UVA algorithms described in this paper. Dr. Skyler is a member of the Board of Directors of Dexcom and holds stock in the company.

References

1. The Diabetes Control and Complications Trial Research Group. 1993. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* **329:** 977–986.
2. Nathan, D.M. *et al.* 2005. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N. Engl. J. Med.* **353:** 2643–2653.
3. Cryer, P.E. 1994. Banting lecture. hypoglycemia: the limiting factor in the management of IDDM. *Diabetes* **43:** 1378–1389.
4. Albisser, A.M. *et al.* 1974. An artificial endocrine pancreas. *Diabetes* **23:** 389–396.
5. Clemens, A.H., P.H. Chang & R.W. Myers. 1977. The development of Biostator, a glucose controlled insulin infusion system (GCIIS). *Horm. Metab. Res.* Suppl. 7: 23–33.
6. Albisser, A.M. *et al.* 1974. Clinical control of diabetes by the artificial pancreas. *Diabetes* **23:** 397–404.
7. Pfeiffer, E.F., C. Thum & A.H. Clemens. 1974. The artificial beta cell–a continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm. Metab. Res.* **6:** 339–342.
8. Kerner, W. *et al.* 1976. Attempts at perfect normalization of glucose tolerance test of severe diabetics by artificial beta cell. *Horm. Metab. Res.* **8:** 256–261.
9. Kraegen, E.W. *et al.* 1979. Development of a closed-loop artificial pancreas. *Horm. Metab. Res. Suppl.* **8:** 38–42.
10. Mirouze, J. *et al.* 1977. Evaluation of exogenous insulin homoeostasis by the artificial pancreas in insulin-dependent diabetes. *Diabetologia* **13:** 273–278.
11. Shichiri, M. *et al.* 1984. The development of wearable-type artificial endocrine pancreas and its usefulness in glycaemic control of human diabetes mellitus. *Biomed. Biochim. Acta.* **43:** 561–568.
12. Goriya, Y. *et al.* 1979. The development of an artificial beta cell system and its validation in depancreatized dogs:

the physiological restoration of blood glucose homeostasis. *Med. Prog. Technol.* **6:** 99–108.
13. Kawamori, R. *et al.* 1978. Importance of insulin secretion based on the rate of change in blood glucose concentration in glucose tolerance, assessed by the artificial beta cell. *Acta Endocrinol. (Copenh).* **87:** 339–351.
14. Guidance for Industry and Food and Drug Administration Staff: The Content of Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications for Artificial Pancreas Device Systems. November 9, 2012. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259305.pdf.
15. Cobelli, C., E. Renard & B. Kovatchev. 2011. Artificial pancreas: past, present, future. *Diabetes* **60:** 2672–2682.
16. Thabit, H. & R. Hovorka. 2012. Closed-loop insulin delivery in type 1 diabetes. *Endocrinol. Metab. Clin. North Am.* **41:** 105–117.
17. Kumareswaran, K., M.L. Evans & R. Hovorka. 2012. Closed-loop insulin delivery: towards improved diabetes care. *Discov. Med.* **13:** 159–170.
18. Hovorka, R. 2011. Closed-loop insulin delivery: from bench to clinical practice. *Nat. Rev. Endocrinol.* **7:** 385–395.
19. Elleri, D., D.B. Dunger & R. Hovorka. 2011. Closed-loop insulin delivery for treatment of type 1 diabetes. *BMC Med.* **9:** 120.
20. McCall, A.L. & L.S. Farhy. 2013. Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. *Minerva Endocrinol.* **38:** 145–163.
21. Renard, E., C. Cobelli & B.P. Kovatchev. 2013. Closed loop developments to improve glucose control at home. *Diabetes Res. Clin. Pract.* **102:** 79–85.
22. Renard, E. *et al.* 2006. Artificial beta-cell: clinical experience toward an implantable closed-loop insulin delivery system. *Diabetes Metab.* **32:** 497–502.
23. Renard, E. 2008. Clinical experience with an implanted closed-loop insulin delivery system. *Arq. Bras. Endocrinol. Metabol.* **52:** 349–354.
24. Keith-Hynes, P. *et al.* 2013. DiAs user interface: a patient-centric interface for mobile artificial pancreas systems. *J. Diabetes Sci. Technol.* **7:** 1416–1426.
25. Dassau, E. *et al.* 2009. Enhanced 911/global position system wizard: a telemedicine application for the prevention of severe hypoglycemia—monitor, alert and locate. *J. Diabetes Sci. Technol.* **3:** 1501–1506.
26. Rigla, M. *et al.* 2007. A telemedicine system that includes a personal assistant improves glycemic control in pump-treated patients with Type 1 diabetes. *J. Diabetes Sci. Technol.* **1:** 505–510.
27. Schade, D.S. *et al.* 1983. *Intensive Insulin Therapy*. Princeton, N.J.: Excerpta Medical.
28. Skyler, J.S. *et al.* 1981. Algorithms for adjustment of insulin dosage by patients who monitor blood glucose. *Diabetes Care* **4:** 311–318.
29. Updike, S.J., M.C. Shults & M. Busby. 1979. Continuous glucose monitor based on an immobilized enzyme electrode detector. *J. Lab. Clin. Med.* **93:** 518–527.
30. Updike, S.J., M. Shults & B. Ekman. 1982. Implanting the glucose enzyme electrode: problems, progress, and alternative solutions. *Diabetes Care* **5:** 207–212.
31. Updike, S.J. & G.P. Hicks. 1967. The enzyme electrode. *Nature* **214:** 986–988.
32. Johnson, K.W. *et al.* 1992. In vivo evaluation of an electroenzymatic glucose sensor implanted in subcutaneous tissue. *Biosens. Bioelectron.* **7:** 709–714.
33. Mastrototaro, J. 1999. The MiniMed continuous glucose monitoring system (CGMS). *J. Pediatr. Endocrinol. Metab.* **12**(Suppl. 3): 751–758.
34. Tamborlane, W.V. *et al.* 1980. Outpatient treatment of juvenile-onset diabetes with a preprogrammed portable subcutaneous insulin infusion system. *Am. J. Med.* **68:** 190–196.
35. Sherwin, R.S. *et al.* 1980. Treatment of juvenile-onset diabetes by subcutaneous infusion of insulin with a portable pump. *Diabetes Care* **3:** 301–308.
36. Tamborlane, W.V. *et al.* 1979. Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N. Engl. J. Med.* **300:** 573–578.
37. Pickup, J.C. *et al.* 1978. Insulin via continuous subcutaneous infusion. *Lancet* **2:** 988–989.
38. Pickup, J.C. *et al.* 1978. Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br. Med. J.* **1:** 204–207.
39. Parker, R.S., F.J. Doyle III & N.A. Peppas. 1999. A model-based algorithm for blood glucose control in type 1 diabetic patients. *IEEE Trans. Biomed. Eng.* **46:** 148–157.
40. Hovorka, R. *et al.* 2004. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol. Meas.* **25:** 905–920.
41. Cobelli, C. *et al.* 2009. Diabetes: models, signals, and control. *IEEE Rev. Biomed. Eng.* **2:** 54–96.
42. Schmidt, S. *et al.* 2013. Model-based closed-loop glucose control in type 1 diabetes: the DiaCon experience. *J. Diabetes Sci. Technol.* **7:** 1255–1264.
43. Steil, G.M. *et al.* 2006. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes* **55:** 3344–3350.
44. Weinzimer, S.A. *et al.* 2006. Reduction of post-prandial glucose excursions during closed-loop (CL) feedback-controlled insulin delivery with a manual priming bolus: 029. *Pediatr. Diabetes* **7**(Suppl.): 67–68.
45. Kovatchev, B.P. *et al.* 2013. Feasibility of outpatient fully integrated closed-loop control: first studies of wearable artificial pancreas. *Diabetes Care* **36:** 1851–1858.
46. Castle, J.R. *et al.* 2010. Factors influencing the effectiveness of glucagon for preventing hypoglycemia. *J. Diabetes Sci. Technol.* **4:** 1305–1310.
47. Cox, D.J. *et al.* 1985. Accuracy of perceiving blood glucose in IDDM. *Diabetes Care* **8:** 529–536.
48. Clarke, W.L. *et al.* 1987. Evaluating clinical accuracy of systems for self-monitoring of blood glucose. *Diabetes Care* **10:** 622–628.
49. Garg, S. *et al.* 2006. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* **29:** 44–50.

50. Zisser, H.C. *et al.* 2009. Accuracy of the SEVEN continuous glucose monitoring system: comparison with frequently sampled venous glucose measurements. *J. Diabetes Sci. Technol.* **3:** 1146–1154.
51. Wentholt, I.M. & J.H. DeVries. 2009. An analysis of the SEVEN system: have we reached the summit of needle-type sensor accuracy? *J. Diabetes Sci. Technol.* **3:** 1155–1157.
52. Christiansen, M. *et al.* 2013. A new-generation continuous glucose monitoring system: improved accuracy and reliability compared with a previous-generation system. *Diabetes Technol. Ther.* **15:** 881–888.
53. Garcia, A. *et al.* 2013. Dexcom G4AP: an advanced continuous glucose monitor for the artificial pancreas. *J. Diabetes Sci. Technol.* **7:** 1436–1445.
54. Freckmann, G. *et al.* 2013. Performance evaluation of three continuous glucose monitoring systems: comparison of six sensors per subject in parallel. *J. Diabetes Sci. Technol.* **7:** 842–853.
55. Pleus, S. *et al.* 2013. Performance evaluation of a continuous glucose monitoring system under conditions similar to daily life. *J. Diabetes Sci. Technol.* **7:** 833–841.
56. Zschornack, E. *et al.* 2013. Evaluation of the performance of a novel system for continuous glucose monitoring. *J. Diabetes Sci. Technol.* **7:** 815–823.
57. Hoss, U. *et al.* 2013. Continuous glucose monitoring in the subcutaneous tissue over a 14-day sensor wear period. *J. Diabetes Sci. Technol.* **7:** 1210–1219.
58. Jansson, P. *et al.* 1988. Characterization by microdialysis of intracellular glucose level in subcutaneous tissue in humans. *Am. J. Physio.* **255:** 218–220.
59. Bolinder, J., U. Ungerstedt & P. Arner. 1992. Microdialysis measurement of hte absolute glucose concentration in subcutaneous adipose tissue allowing glucose monitoring in diabetic patients. *Diabetologia* **35:** 1177–1180.
60. Hagstrom, E. *et al.* 1990. In vivo subcutaneous adipose tissue kinetics after glucose ingestion in obesity and fasting. *Scand. J. Clin. Invest.* **50:** 129–136.
61. Bolinder, J. *et al.* 1989. Nicrodialysis of subcutaneous adipose tissue in vivo for continuous glucose monitoring in man. *Scand. J. Clin. Invest.* **49:** 465–474.
62. Wientjes, K.J. & A.J. Schoonen. 2001. Determination of time delay between blood and interstitial adipose tissue glucose concentration change by microdialysis in healthy volunteers. *Int. J. Artif. Organs* **24:** 884–889.
63. Schoonen, A.J. & K.J. Wientjes. 2003. A model for transport of glucose in adipose tissue to a microdialysis probe. *Diabetes Technol. Ther.* **5:** 589–598.
64. Voskanyan, G. *et al.* 2007. Putative delays in interstitial fluid (ISF) glucose kinetics can be attributed to the glucose sensing systems used to measure them rather than the delay in ISF glucose itself. *J. Diabetes Sci. Technol.* **1:** 639–644.
65. Rebrin, K., N.F. Sheppard, Jr. & G.M. Steil. 2010. Use of subcutaneous interstitial fluid glucose to estimate blood glucose: revisiting delay and sensor offset. *J. Diabetes Sci. Technol.* **4:** 1087–1098.
66. Basu, A. *et al.* 2013. Time lag of glucose from intravascular to interstitial compartment in humans. *Diabetes* **2:** 4083–4087
67. Micheletto, F. *et al.* 2013. In silico design of optimal ratio for co-administration of pramlintide and insulin in type 1 diabetes. *Diabetes Technol. Ther.* **15:** 802–809.
68. Steil, G.M. *et al.* 2011. The effect of insulin feedback on closed loop glucose control. *J. Clin. Endocrinol. Metab.* **96:** 1402–1408.
69. Steil, G.M. 2013. Algorithms for a closed-loop artificial pancreas: the case for proportional-integral-derivative control. *J. Diabetes Sci. Technol.* **7:** 1621–1631.
70. Ellingsen, C. *et al.* 2009. Safety constraints in an artificial pancreatic β-cell: an implementation of model predictive control with insulin-on-board. *J. Diabetes Sci. Technol.* **3:** 536–544.
71. Grosman, B. *et al.* 2010. Zone model predictive control: a strategy to minimize hyper- and hypoglycemic events. *J. Diabetes Sci. Technol.* **4:** 961–975.
72. Gondhalekar, R., *et al.* 2013. Periodic-zone model predictive control for diurnal closed-loop operation of an artificial pancreas. *J. Diabetes Sci. Technol.* **7:** 1446–1460.
73. van Heusden, K. *et al.* 2012. Control-relevant models for glucose control using a priori patient characteristics. *IEEE Trans. Biomed. Eng.* **59:** 1839–1849.
74. Dassau, E. *et al.* 2013. Clinical evaluation of a personalized artificial pancreas. *Diabetes Care* **36:** 801–809.
75. Dassau, E. *et al.* 2008. Modular artificial β-cell system: a prototype for clinical research. *J. Diabetes Sci. Technol.* **2:** 863–872.
76. Kovatchev, B. *et al.* 2009. Control to range for diabetes: functionality and modular architecture. *J. Diabetes Sci. Technol.* **3:** 1058–1065.
77. Patek, S. *et al.* 2012. Modular closed-loop control of diabetes. *IEEE Trans. Biomed. Eng.* **59:** 2986–2999.
78. Capel, I. *et al.* 2013. Artificial pancreas using a personalized rule-based controller achieves overnight normoglycemia in patients with type 1 diabetes. *Diabetes Technol. Ther.* **16:** 172–179.
79. Clarke, W.L. *et al.* 2009. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: the Virginia experience. *J. Diabetes Sci. Technol.* **3:** 1031–1038.
80. Hughes, C.S. *et al.* 2010. Hypoglycemia prevention via pump attenuation and red-yellow-green "traffic" lights using continuous glucose monitoring and insulin pump data. *J. Diabetes Sci. Technol.* **4:** 1146–1155.
81. Breton, M. *et al.* 2012. Fully integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near normoglycemia. *Diabetes* **61:** 2230–2237.
82. Atlas, E. *et al.* 2010. MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care* **33:** 1072–1076.
83. Miller, S. *et al.* 2011. Automatic learning algorithm for the MD-logic artificial pancreas system. *Diabetes Technol. Ther.* **13:** 983–990.
84. Nimri, R. *et al.* 2012. Feasibility study of automated overnight closed-loop glucose control under MD-logic artificial pancreas in patients with type 1 diabetes: the DREAM Project. *Diabetes Technol. Ther.* **14:** 728–735.

85. Mauseth, R. *et al.* 2010. Proposed clinical application for tuning fuzzy logic controller of artificial pancreas utilizing a personalization factor. *J. Diabetes Sci. Technol.* **4:** 913–922.
86. Mauseth, R. *et al.* 2013. Use of a "fuzzy logic" controller in a closed-loop artificial pancreas. *Diabetes Technol. Ther.* **15:** 628–633.
87. Phillip, M. *et al.* 2013. Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N. Engl. J. Med.* **368:** 824–833.
88. Ward, W.K., J.R. Castle & J. El Youssef. 2011. Safe glycemic management during closed-loop treatment of type 1 diabetes: the role of glucagon, use of multiple sensors, and compensation for stress hyperglycemia. *J. Diabetes Sci. Technol.* **5:** 1373–1380.
89. El Youssef, J. *et al.* 2011. A controlled study of the effectiveness of an adaptive closed-loop algorithm to minimize corticosteroid-induced stress hyperglycemia in type 1 diabetes. *J. Diabetes. Sci. Technol.* **5:** 1312–1326.
90. Castle, J.R. *et al.* 2010. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care* **33:** 1282–1287.
91. Bakhtiani, P.A. *et al.* 2013. A review of artificial pancreas technologies with an emphasis on bi-hormonal therapy. *Diabetes Obes. Metab.* **15:** 1065–1070.
92. Russell, S.J. *et al.* 2012. Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. *Diabetes Care* **35:** 2148–2155.
93. El-Khatib, F.H. *et al.* 2010. A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci. Transl. Med.* **2:** 1–12.
94. Russell, S.J. *et al.* 2010. Efficacy determinants of subcutaneous microdose glucagon during closed-loop control. *J. Diabetes Sci. Technol.* **4:** 1288–1304.
95. El-Khatib, F.H. *et al.* 2014. Autonomous and continuous adaptation of a bihormonal bionic pancreas in adults and adolescents with type 1 diabetes. *J. Clin. Endocrinol. Metab.* DOI: jc20134151. Jan 31 [Epub ahead of print].
96. Kowalski, A.J. 2009. Can we really close the loop and how soon? accelerating the availability of an artificial pancreas: a roadmap to better diabetes outcomes. *Diabetes Technol. Ther.* **11:** S113–S119.
97. Bergenstal, R.M. *et al.* 2013. Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N. Engl. J. Med.* **369:** 224–232.
98. Ly, T.T. *et al.* 2013. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* **310:** 1240–1247.
99. Hirsch, I.B. 2013. Reducing hypoglycemia in type 1 diabetes: an incremental step forward. *Diabetes Technol. Ther.* **15:** 531–532.
100. Place, J. *et al.* 2013. DiAs web monitoring: a real-time remote monitoring system designed for artificial pancreas outpatient trials. *J. Diabetes Sci. Technol.* **7:** 1427–1435.
101. O'Grady, M.J. *et al.* 2012. The use of an automated, portable glucose control system for overnight glucose control in adolescents and young adults with type 1 diabetes. *Diabetes Care* **35:** 2182–2187.
102. Dassau, E. *et al.* 2010. Real-time hypoglycemia prediction suite using continuous glucose monitoring: a safety net for the artificial pancreas. *Diabetes Care* **33:** 1249–1254.
103. Harvey, R.A. *et al.* 2012. Design of the health monitoring system for the artificial pancreas: low glucose prediction module. *J. Diabetes Sci. Technol.* **6:** 1345–1354.
104. Rigla, M. 2011. Smart telemedicine support for continuous glucose monitoring: the embryo of a future global agent for diabetes care. *J. Diabetes Sci. Technol.* **5:** 63–67.
105. Dalla Man, C., D.M. Breton & C. Cobelli. 2009. Physical activity into the meal glucose-insulin model of type 1 diabetes: in silico studies. *J. Diabetes Sci. Technol.* **3:** 56–67.
106. van Bon, A.C. *et al.* 2011. Exercise in closed-loop control: a major hurdle. *J. Diabetes. Sci. Technol.* **5:** 1337–1341.
107. Cengiz, E. 2013. Closer to ideal insulin action: ultra fast acting insulins. *Panminerva Med.* **55:** 269–275.
108. Hovorka, R. *et al.* 2011. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. *BMJ* **342:** d1855.
109. Elleri, D. *et al.* 2012. Evaluation of a portable ambulatory prototype for automated overnight closed-loop insulin delivery in young people with type 1 diabetes. *Pediatr. Diabetes.* **13:** 449–453.
110. Kumareswaran, K. *et al.* 2011. Meta-analysis of overnight closed-loop randomized studies in children and adults with type 1 diabetes: the Cambridge cohort. *J. Diabetes Sci. Technol.* **5:** 1352–1362.
111. Elleri, D. *et al.* 2013. Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. *Diabetes Care* **36:** 838–844.
112. Jackson, M.A. *et al.* 2012. Stable liquid glucagon formulations for rescue treatment and bi-hormonal closed-loop pancreas. *Curr. Diab Rep.* **12:** 705–710.