Trends in Endocrinology & Metabolism

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REVIEWS

Review

A Century of Diabetes Technology: Signals, Models, and Artificial Pancreas Control

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Arguably, diabetes mellitus is one of the best-quantified human conditions: elaborate *in silico* models describe the action of the human metabolic system; real-time signals such as continuous glucose monitoring are readily available; insulin delivery is being automated; and control algorithms are capable of optimizing blood glucose fluctuation in patients' natural environments. The transition of the artificial pancreas (AP) to everyday clinical use is happening now, and is contingent upon seamless concerted work of devices encompassing the patient in a digital treatment ecosystem. This review recounts briefly the story of diabetes technology, which began a century ago with the discovery of insulin, progressed through glucose monitoring and subcutaneous insulin delivery, and is now rapidly advancing towards fully automated clinically viable AP systems.

Introduction: the Previous Century

Classic studies have shown that many of the microvascular and macrovascular complications of diabetes can be predicted by average glycemia (typically measured by **hemoglobin A1c (HbA_{1c})**, see Glossary) and/or by glycemic variability, and can be reduced by intensive insulin therapy in type 1 diabetes [1,2], and/or by medication in type 2 diabetes [3]. However, in both type 1 and type 2 diabetes, the risk for hypoglycemia was identified as, and remains, the primary barrier to optimal glycemic control [4,5]. Thus, diabetes poses a life-long optimization problem: reduce HbA_{1c} while simultaneously avoiding hypoglycemia [5]. Traditional external insulin replacement through multiple daily injections has not been nearly as efficient as the natural endogenous insulin secretion of the pancreatic β cells and, as a result, acute events have occurred and continue to occur, exposing patients to severe hypoglycemia. The pathophysiology of this phenomenon has been studied extensively: imperfect intensive insulin treatment may reduce the warning symptoms and hormonal defenses against hypoglycemia leading to defective counter-regulation and hypoglycemia unawareness [6–10]; all of which make external blood glucose (BG) regulation even more challenging.

For the 40 years following the landmark discovery of insulin in 1921, the primary diabetes technology has been a syringe used to inject insulin. This began to change in the early 1960s, when an intravenous insulin and glucagon pump was introduced [11] (Figure 1), opening the way to intravenous BG control designs emerging in the 1970s [12–14]. In 1977, one of these designs [13] resulted in the first commercial **artificial pancreas (AP)** – the Biostator [15] – a large (refrigerator-sized) device that has been used extensively for glucose-control research [16]. Thus, the AP idea is not new – it can be traced back decades ago to these studies, which have demonstrated the possibility for external BG regulation using intravenous BG measurement and infusion of insulin and glucose [11–16]. The first commercial subcutaneous insulin pump – the Auto Syringe – was introduced in the 1970s (Figure 1), and by the end of the decade, the first trials demonstrating the feasibility of **continuous subcutaneous insulin infusion (CSII)** were reported in the UK [17] and the USA [18]. It has been a long journey, however, from these early systems to the contemporary technological management of diabetes – the merger of

Highlights

Classic studies have shown that the complications of diabetes can be reduced by strict glycemic control. However, the risk of hypoglycemia remains the primary barrier to intensive therapy; thus, people with diabetes face a life-long optimization problem: reduce their HbA_{1c} while simultaneously avoiding hypoglycemia.

Contemporary technologies, such as CGM and CLC (known as the AP), offer the best solution to this optimization problem, particularly in type 1 diabetes.

The advancement of these technologies is enabled by decades of studies aiming to develop elaborate *in silico* models describing the action of the human metabolic system, process CGM data and other metabolic signals, and automate insulin delivery.

As a result, 100 years after the discovery of insulin, the technology is entering the stage of fully automated portable AP systems providing real-time, long-term optimal control of diabetes in patients' natural environments.

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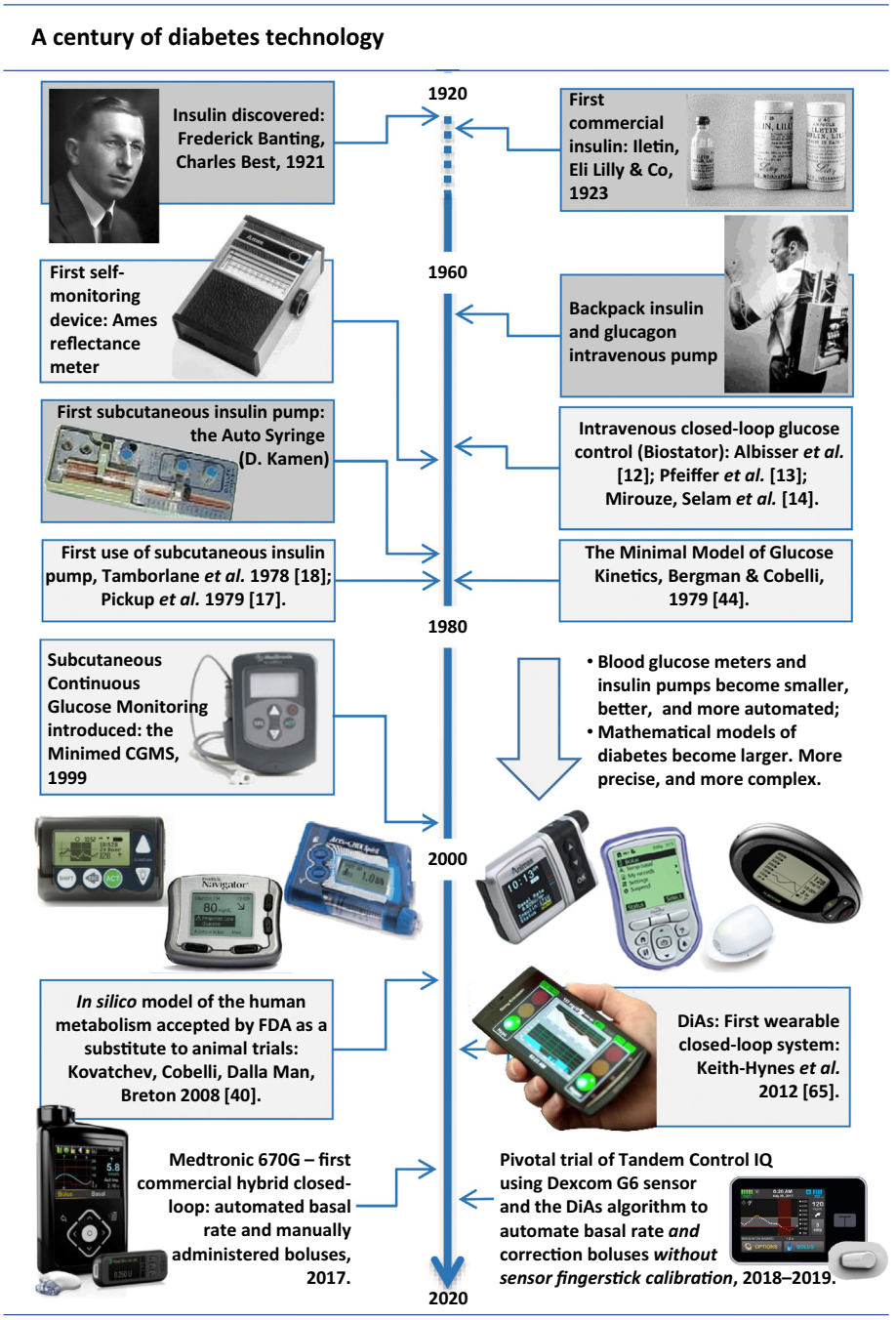


Glossary

Artificial Pancreas (AP): the popular name for CLC of diabetes; also known as automated insulin delivery. Generally refers to a system that combines CGM and CSII run by a control algorithm (Controller) that reads CGM and possibly other data and directs insulin delivery.

Continuous glucose monitoring (CGM): typically refers to minimally invasive subcutaneous sensors (although implantable sensors also exist), which sample interstitial glucose frequently; for example, every 5 min. rtCGM refers to sensors transmitting and/or displaying the data automatically without the patient's involvement. iCGM, also known also as FGM, is a form of CGM requiring the sensor to be queried (flashed) to produce data. FGM is not usable for automated CLC.

Continuous Subcutaneous Insulin Infusion (CSII): an insulin pump.

Hemoglobin A1c (HbA_{1c}): classic marker of average glycemia, widely accepted to gauge clinical trial outcomes and guide clinical practice.

Low Glucose Suspend (LGS) and predictive LGS (PLGS): systems that use CGM data to discontinue insulin delivery if a low BG threshold is crossed (LGS) or is predicted to be crossed (PLGS); sometimes referred to as entry-level controllers.

Model-predictive control (MPC): one of the major classes of CLC algorithms used by a number of contemporary AP systems, which is based on a mathematical model of the human metabolism predicting BG fluctuations and thereby compensating for the inherent time delays of insulin delivery; PID controllers are popular as well, but lack the predictive capabilities of MPC.

Sensor-augmented pump (SAP): therapy that combines CGM with CSII, without communication between the two; typically used as control condition in AP studies.

Time in range (TIR): widely used metric of glycemic control reflecting the percent CGM readings within a certain range. Commonly accepted ranges are 70–180 mg/dl (overall) or 80–140 mg/dl (overnight).

Figure 1. Discovery of Insulin in 1921 Marked the Beginning of Diabetes Technology Development. By the late 1970s continuous subcutaneous insulin delivery (CSII) and early intravenous control algorithms became available. Continuous glucose monitoring (CGM) was introduced in 1999. Since the 2000s, CSII devices have become smaller and more reliable, CGM more precise, and control algorithms have overcome the challenges of subcutaneous glucose sensing and subcutaneous insulin delivery. The first experimental wearable system suitable for outpatient use was introduced in 2012, and the first commercial hybrid closed loop became available in 2017; pivotal trials of new generations of closed-loop control systems are now under way. Abbreviation: DiAS, Diabetes Assistant. [12–14,17,18,44,62]

continuous glucose monitoring (CGM), CSII via insulin pump, and a mathematical algorithm (Controller), into a subcutaneous closed-loop control (CLC) AP system that automates insulin delivery and facilitates BG regulation, so far primarily in type 1 diabetes.

This review takes a brief look at the key components of contemporary diabetes technology and describes the most recent advances in AP development and clinical translation. Following the tradition established by previous reviews of the diabetes technology field [19,20], three specific topics are emphasized: (i) signals, in particular CGM, which provides input data for the contemporary treatment of diabetes; (ii) *in silico* models and computer simulation, which enabled technology development and replaced animal trials in the preclinical testing of AP algorithms; and (iii) control, in its ultimate real-time implementation as an AP system. The key message is that the AP is a network of devices, perhaps the first medical network responsible for minute-to-minute critical treatment decisions, in countless constantly shifting surroundings, over many years of use. It is therefore imperative for the system components, CGM, CSII, and Controller, to be seamlessly integrated and thoroughly tested *in silico* and *in vivo* prior to their clinical deployment. Figure 1 depicts some of the milestones of the progress of diabetes technology in the past century, with particular emphasis on BG monitoring and control:

Signals: Enabling Real-Time Monitoring of Diabetes

In 1969, the first portable BG meter – the Ames Reflectance meter – was manufactured (Figure 1) and, until 1999, self-monitoring of blood glucose (SMBG) requiring a fingerstick and collection of a blood drop was the only BG measurement available for ambulatory use. The leap towards minimally invasive subcutaneous glucose monitoring was made at the turn of the 21st century with the introduction of CGM devices by Medtronic, Abbott, Dexcom, and others [21–23]. It is important to know, however, that these devices measure glucose concentration from a different blood compartment – the interstitium – which introduces an additional (presumably diffusion) process between blood and interstitial glucose (IG) [21]. As a result, BG is different from IG and this difference presented a major challenge to the accuracy of early CGM devices. The formulation of the push–pull phenomenon offered arguments for a more complex BG–IG relationship than a simple constant or directional time lag [24] and, indeed, most studies observed that IG lagged behind BG by 4–10 min, regardless of the direction of BG change [25,26]. To account for the gradient between BG and IG, CGM devices have been typically calibrated with capillary BG readings. Successful calibration would adjust the amplitude of IG fluctuations with respect to BG, but would only partially mitigate the time lag due to BG-to-IG glucose transport. In addition, errors from calibration, loss of sensitivity, and random noise confound further the data produced by CGM sensors [27]. Nevertheless, over the years the accuracy of CGM has been steadily increasing and has reached a point where CGM readings could be used as a replacement for traditional BG measurement without calibration with capillary blood. For example, a few years ago the Dexcom G4 Platinum and G5 CGMs used algorithmic signal processing to improve their accuracy and obtain replacement clearance from the FDA [28]. In 2018, the new version of these devices – G6 – was approved by the FDA for use without fingerstick calibration, thereby potentially eliminating a major nuisance of diabetes monitoring.

Over the last decade, the clinical utility of CGM has been demonstrated by a number of studies that have documented its benefits in children and adults, and charted guidelines for its use [29–33]. A version of CGM using on-demand retrieval of frequently sampled glucose traces was introduced by Abbott and became known as intermittently viewed CGM (iCGM), or flash glucose monitoring (FGM); also available without fingerstick calibration and primarily aimed at the management of type 2 diabetes [34,35]. The differences between

real-time CGM and iCGM, were recently summarized by the International Consensus on Use of CGM as follows:

> Real-time continuous glucose monitoring (rtCGM) and intermittently viewed CGM (iCGM) address many of the limitations inherent in HbA1c testing and SMBG. rtCGM uniformly tracks the glucose concentrations in the body's interstitial fluid, providing near real-time glucose data; iCGM uses similar methodology to show continuous glucose measurements retrospectively at the time of checking. Both rtCGM and iCGM facilitate monitoring of time spent in the target glucose range (**time in range; TIR**). However, only rtCGM can warn users if glucose is trending toward hypoglycemia or hyperglycemia. With iCGM, these trends can only be viewed after physically scanning the sensor [36].

Alternatives to subcutaneous CGM were recently presented by new implantable sensors, which have demonstrated the potential for long-term (up to 6 months) continuous use [37]. Other signals relevant to the human metabolism, for example, heart rate or motion sensing, have been used to successfully improve the automated control of diabetes, particularly around challenges such as physical activity [38,39], but the routine use of these additional signals is still away from mainstream.

In Silico Models: Abandon Animal Trials

In January 2008, in an unprecedented decision, the FDA accepted a computer simulator as a substitute to animal trials for the testing of CLC strategies, which accelerated the development of AP algorithms and effectively eliminated animal studies from this field. The simulation environment that was granted this designation was built upon 30 years of metabolic modeling studies and contained *in silico* images of 300 virtual subjects with type 1 diabetes [40]. Each of these images corresponded to one specific configuration (vector) of individual parameters; rate constants in a large model of the human metabolism derived from the quantitative understanding of the network of interactions presented in Figure 2 [41]. In health, BG levels are regulated by the pancreas, gut, liver, muscle, kidneys, and brain. BG levels increase with food containing carbohydrates, and glucose is also produced by the body (mainly by the liver), after which it is distributed and utilized through both insulin-independent (e.g., central nervous system and red blood cells) and insulin-dependent (muscle and adipose tissues) pathways. Insulin, secreted by the pancreatic β cells in response to elevated BG levels and signals from the gut (incretin effect [42,43]), is the primary regulator of glucose homeostasis. Insulin action depends on rate constants that are usually referred to as insulin sensitivity and β-cell responsivity [19]. In pathophysiology, the control is degraded. In type 2 diabetes, the network in Figure 2 is largely preserved, but insulin secretion is deficient relative to hepatic and peripheral insulin resistance. In type 1 diabetes, insulin secretion is virtually absent, while glucagon secretion from α cells is still preserved, which removes the insulin-dependent pathways and lowers BG levels; therefore, BG can only go up, leading to hyperglycemia. Thus, in type 1 diabetes insulin replacement is mandatory.

The Minimal Model of Glucose Kinetics, introduced in 1979 (Figure 1), was the first to represent the glucose–insulin control network in formal mathematical terms, and is still in use to date [44]. Fast forward to 2007, the minimal model methodology has evolved into elaborate quantitative understanding of the human metabolic system, which allowed its comprehensive description, fully implementing the body of knowledge about metabolic regulation into large, nonlinear models of high order, with a large number of parameters [41]. In addition, two other types of models were introduced that describe: (i) the changes of the metabolic system triggered by external disturbances, for example, physical activity/exercise; and (ii) the time delays associated with subcutaneous insulin delivery (Figure 2) [45]. In combination, these models marked a critical step towards accelerating the progress of AP development – simulation allowed rapid *in silico* testing of CLC

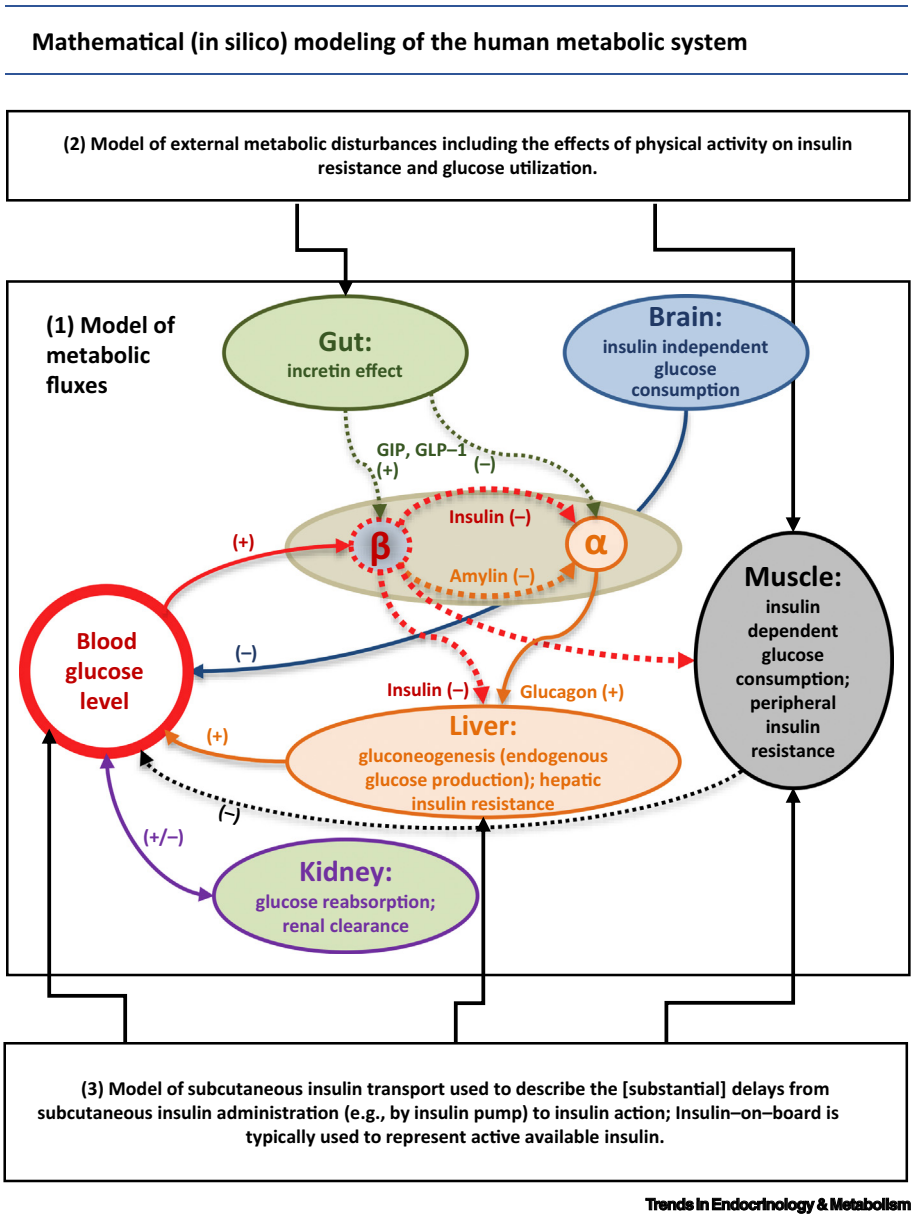


Figure 2. Three Mathematical Models Are Typically in Play to Describe the Action of the Human Metabolic System in Diabetes and the Effects of Insulin Treatment. (1) Model of the internal metabolic fluxes and glucoregulatory responses triggered by blood glucose fluctuation; (2) model of the influence of external disturbances such as food and exercise; and (3) model of treatment describing subcutaneous glucose sensing and insulin delivery. The metabolic models are typically compartmental, using differential equations governed by rate constants to describe the metabolic system in action, that is, the fluxes between various compartments such as gut, liver, kidney, muscle, and brain. At the center is β-cell insulin production, deficient or absent in diabetes, and the release of glucagon from the α cell. Abbreviations: GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

algorithms and opened the field for efficient and cost-effective *in silico* preclinical trials leading directly to human studies. Simulation experiments now allow any CGM device, any insulin pump, and any control algorithm to be linked in a closed-loop system *in silico*, prior to their deployment in clinical trials. With this methodology, any meal and insulin delivery scenario can be pilot-tested efficiently and, most importantly, extreme scenarios that cannot be tested safely

in vivo can be played multiple times to ensure adequate response of the treatment approach [46]. A detailed account of the metabolic models and the simulators of the human metabolic system developed to date is included in a recent review [47]. We need to emphasize, however, that good *in silico* performance of a control algorithm does not guarantee *in vivo* performance – it only helps test extreme situations and the stability of the algorithm, and rule out inefficient scenarios. Thus, computer simulation is only a prerequisite to, but not a substitute for, clinical trials.

Control: the AP

The contemporary AP systems have resulted from nearly 100 years of advances in diabetes technology and, as with any other technology, their development has accelerated dramatically in the past decade. In 2009, *JAMA* stated that the AP may soon be a reality [48]. In 2012, a *Nature* Outlook featured the topic of AP [49], and a News Focus in the January 10, 2014 issue of *Science* [50] highlighted the same topic. These newsflashes reflected rapidly growing academic and industrial efforts focused on the development of CLC systems using CGM coupled with subcutaneous insulin pumps. First steps towards fully automating the glucose control in diabetes using CGM and CSII linked via a CLC algorithm, were taken by the early work of Steil [51] and Hovorka [52]. Various types of control algorithms were introduced ranging from relatively straightforward proportional–integral–derivative (PID) controllers [51] to complex model-predictive control (MPC) algorithms [52] and dual-hormone control that added glucagon to combat hypoglycemia [53]. In 2006 the JDRF Artificial Pancreas Project was initiated, sponsoring several centers in the USA and Europe to carry out CLC research. In 2008 the National Institutes of Health launched an AP initiative and in 2010 the European AP@Home consortium was established. A roadmap towards a viable AP was accepted, which included several sequential steps, beginning with automated mitigation of hypoglycemia and progressing through control-to-range and control-to-target towards fully automated, possibly multihormonal, AP [54]. By 2010 the AP became a global research topic engaging physicians and engineers in an unprecedented collaboration. A number of inpatient studies established the feasibility of automated subcutaneous CLC in the hospital setting [55–59]. Most of these studies pointed out the superiority of CLC over CSII in terms of: (i) increased time within target range (typically 70–180 mg/dl); (ii) reduced incidence of hypoglycemia; and (iii) better overnight control.

Wearable AP

The first outpatient studies took a laptop-based AP system to a camp setting, where children with diabetes were controlled overnight by the MD-logic probabilistic control algorithm [58,60]. Comparing the AP with **sensor-augmented pump (SAP)** therapy, this multicenter, multinational, randomized, crossover trial showed significantly reduced incidence of night-time glucose levels below 63 mg/dl (7 vs. 22 episodes on AP vs. SAP) and significantly tighter overnight control: median values for the individual mean overnight glucose levels were 126.4 mg/dl on AP versus 140.4 mg/dl on SAP [60]. This same system was then taken to patients' homes, achieving similar results [61]. However, as with all previous inpatient trials, these first outpatient studies used a system that was based on laptop computers, still cumbersome and unsuitable for routine ambulatory use. In the *Nature* [49] and *Science* [50] reviews cited earlier, a common photograph appeared of a smartphone presenting a dual traffic-light display – the face of the first portable AP platform – the Diabetes Assistant (DiAs) developed at the University of Virginia in 2011 (Figure 1). DiAs was built using an Android smartphone as a computational hub and included a graphical user interface designed for the patient [62] and a Web-based remote monitoring system [63]. DiAs was used in a number of clinical trials (including long-term studies at home) at ten clinical centers in the USA and Europe [64–69], and in the first 'stress test' of an AP system – the AP Ski Trial, which involved children with type 1 diabetes wearing DiAs during 5-day winter-sport camps in Virginia, Colorado, and California [70]. This experimental

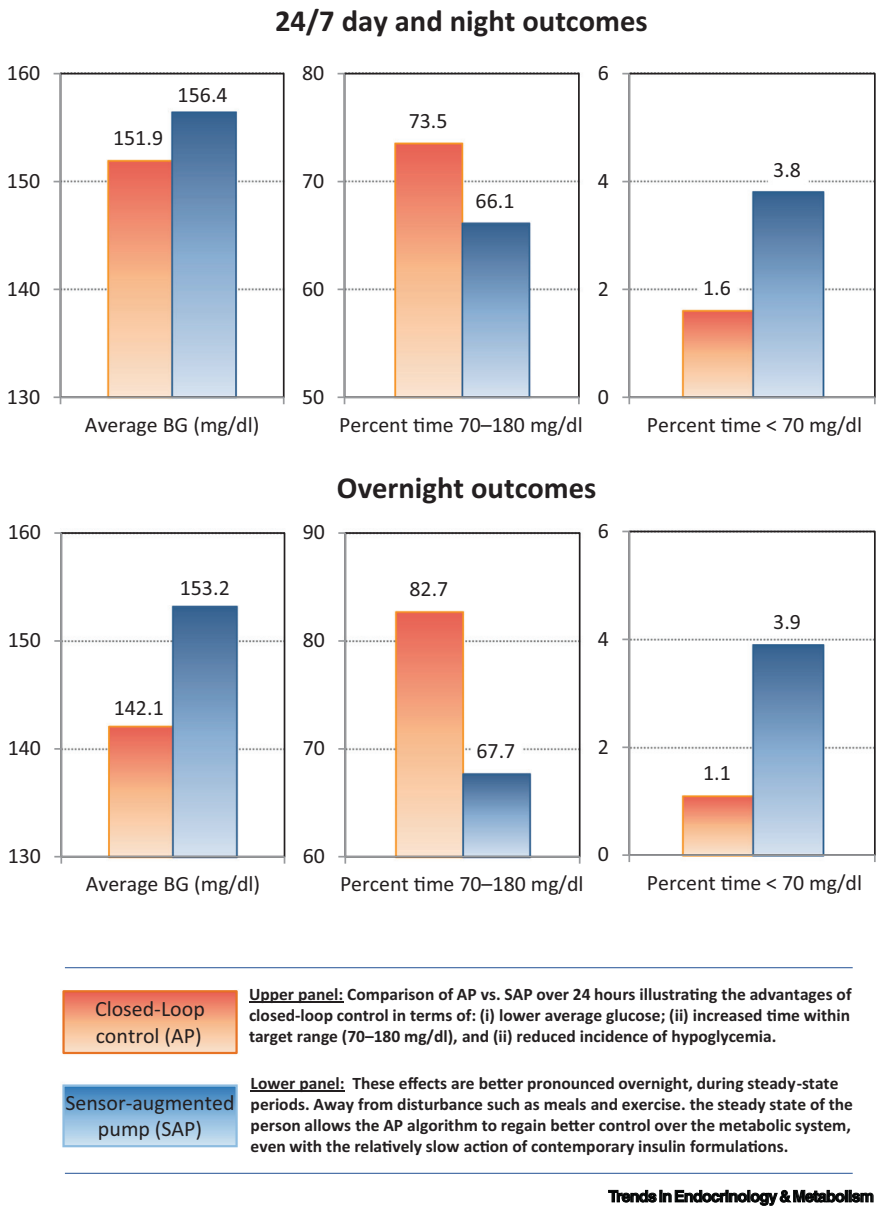


Figure 3. Meta-Analysis of Outpatient Mobile Artificial Pancreas (AP) Studies using DiAs by the end of 2015. Upper Panel: comparison of AP versus sensor-augmented pump (SAP) over 24 h illustrating the advantages of closed-loop control in terms of: (i) lower average glucose; (ii) increased time within target range (70–180 mg/dl); and (iii) reduced incidence of hypoglycemia. Lower Panel: these effects are better pronounced overnight, during steady-state periods. Away from disturbance such as meals and exercise. The steady state of the person allows the AP algorithm to regain better control over the metabolic system, even with the relatively slow action of contemporary insulin formulations. Abbreviation: BG, blood glucose.

device set a precedent for one of the two types of home AP systems – Mobile AP using a smart phone to connect to CGM and CSII, run the Controller and, possibly, connect to the Cloud. Figure 3 presents a meta-analysis of 18 clinical trials completed by the end of 2015, which enrolled 320 patients with type 1 diabetes, yielding approximately 155 000 h of data [64–69].

Multisignal and Multihormonal AP

Physical activity was identified as a major challenge to automated control by early inpatient studies, which focused on exercise increasing the risk for hypoglycemia and its possible reduction through CLC [59,71,72]. Various algorithm adaptation methods were tested [73–76], and it was generally accepted that the rapid changes in insulin sensitivity and glucose utilization during exercise are difficult to mitigate by manipulating insulin delivery alone; thus, additional signals or, possibly, additional hormones were needed to detect and mitigate these changes faster [72]. Indeed, it was shown that additional signals, such as motion sensing or heart rate monitoring could mitigate the effects of physical activity [38,39,77,78]. Dual-hormone systems using glucagon to counter the effects of insulin overdelivery and prevent hypoglycemia were introduced [53] and tested in inpatient and outpatient studies [79–81]. The relative benefits of adding glucagon to insulin-only AP systems have been assessed in direct comparison studies, and were generally limited to mitigation of hypoglycemia associated with exercise [82–85]. According to a recent review [86]: 'Glucagon may therefore serve an important role in the artificial pancreas system during aerobic exercise as a result of the rapid change in glucose levels and the inability of insulin reduction or suspension to compensate because of the prolonged duration of action of insulin. Insulin suspension may be sufficient, however, for preventing the gradual, delayed onset of post-exercise hypoglycemia.' Given the complexity of the technology – a dual-chamber pump using stable glucagon to counter hypoglycemia – the future of insulin-plus-glucagon systems remains uncertain. Meanwhile, other candidate hormones, such as amylin, glucagon-like peptide (GLP)-1 receptor agonists, or sodium glucose transport protein (SGLT) inhibitors, are considered for dual-hormone AP use; but, these studies are still in their infancy.

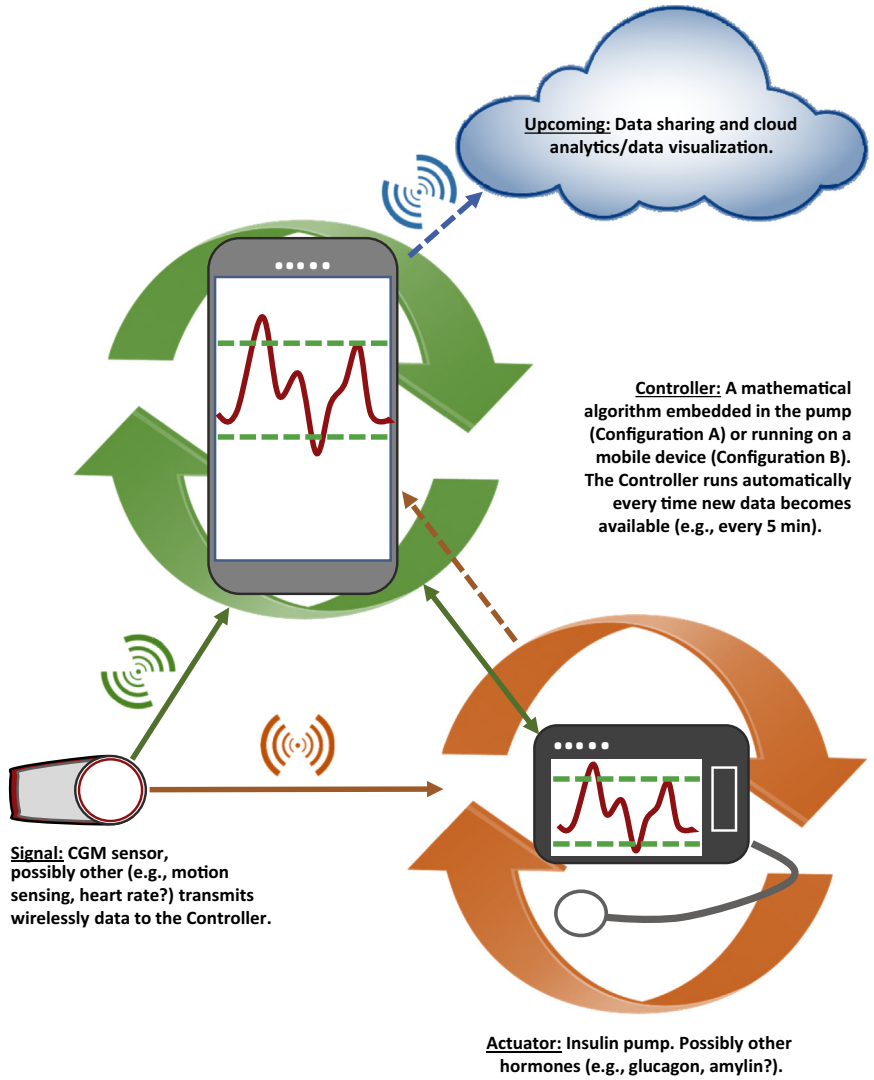
System Integration: the First Step towards Routine Clinical Use

Low Glucose Suspend (LGS) is considered a precursor to AP because of the automated data transfer from CGM to the insulin pump – a system integration that was a critical step in AP development. In this type of system, the insulin pump 'listens' to a CGM and suspends insulin delivery if the CGM value crosses a certain predefined low BG threshold; for example, 70 mg/dl. Predictive LGS (PLGS) takes this functionality one step further and discontinues insulin delivery if BG levels are predicted to fall below a threshold by a mathematical formula. The ASPIRE trial showed a 38% reduction in nocturnal hypoglycemia compared with CGM alone without increasing HbA_{1c} [87]; a subsequent study achieved similar results [88]. PLGS algorithms brought these type of systems to a higher level of computational sophistication [89]; both LGS and PLGS are now commercially available and are part of clinical practice; for example, Medtronic's MiniMed 630G is a LGS system and Tandem's Basal-IQ uses PLGS. However, LGS and PLGS are still binary off–on insulin 'switches'; they lack the defining property of a CLC algorithm – feedback estimation of the patient state using CGM and insulin delivery data to modulate insulin delivery up or down in real time, depending on the needs of the person at any moment. Nevertheless, these integrated systems created the hardware needed for including a control algorithm directly in an insulin pump, that is, Embedded AP. Figure 4, Key Figure presents the schematics of contemporary CLC systems: depending on the location of the Controller, the system is Mobile or Embedded, but in either case the key components are: a real-time CGM producing the signal used for control, typically a glucose reading every 5 min; an actuator – the pump delivering insulin, and a 'brain' in between, that is the control algorithm. The data exchange between these devices is typically wireless and some systems provide a Cloud connection for remote monitoring and advanced applications.

It is likely that both Embedded and Mobile AP systems will continue to coexist and share functionalities in the future. For example, smartphone apps will continue to accompany CGM and AP systems, transferring some of the medical functions of these devices to consumer electronics.

Key Figure

Schematic of a Closed-Loop Control System



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Such an approach offers certain advantages not only to the initial research phase of AP development (e.g., DiAs), but potentially to routine clinical use. (i) Contemporary smartphones are readily available, capable of running high-demand computations, wirelessly connectable to various devices, and capable of broadband communication with the Cloud. (ii) No current insulin pump offers similar capabilities, thus the demand for more flexibility could drive adoption. (iii) The technological life cycle of a smart phone is several months, as opposed to several years for insulin pump controllers; thus use of consumer electronics allows keeping up with contemporary user interface appearance and device form factor. (iv) Psychological studies show that many patients, particularly children and teenagers, are reluctant to use their insulin pump in public, missing boluses and slipping into poor glycemic control when privacy is limited, for example, during school days; however, no one is embarrassed to use a smartphone, and that may be a key to better patient engagement and better glucose control.

Concluding Remarks and Future Perspectives

In 2018, the National Library of Medicine (PubMed) included 132 publications in the AP field, and in the first 6 weeks of 2019, 25 additional papers were published. This continues a trend of over 100 scientific publications per year since 2015 and confirms the growing prominence of AP for the treatment of diabetes. AP systems were pilot-tested, and were found effective, in pregnant women with type 1 diabetes [90], and in people with type 2 diabetes on insulin therapy [91]. Several meta-analyses were published, confirming the efficacy of the AP for diabetes control [92–94]. For example, a recent meta-analysis including 40 studies with 1027 participants found that the proportion of time in the target range of 70–180 mg/dl was significantly higher with AP, both overnight and over 24 h (weighted mean differences of 15.1% and 9.6%, respectively); AP also reduced the time below 70 mg/dl (weighted mean difference – 1.5%) [93]. These new results are similar to the 2015 meta-analysis presented in Figure 3, which showed time-in-target improvement of 15% overnight and a 2.2% reduction of time below 70 mg/dl. Overall, the studies to date have produced promising results, which is somewhat remarkable, given that the AP systems used in most of the trials pooled by meta-analyses were highly experimental and cumbersome; for example, minicomputers of tablets carried around by the study participants. We can therefore expect that with improved form factors and system usability, the outcomes will become more stable and, perhaps, better. Research results continue to be translated to clinical practice: two new systems are featured at the end of the timeline in Figure 1 – the Medtronic MiniMed 670G [95,96] and the Tandem Control-IQ [97]. Following a pivotal trial [95] and regulatory approval in 2017, the MiniMed 670 is now commercially available and used clinically. This is a Hybrid closed-loop system, which modulates automatically the insulin pump basal rate to mitigate both hypo- and hyperglycemia, but does not administer automated insulin boluses; for example, corrections after a meal. The Tandem Control-IQ uses a Dexcom G6 sensor that does not require fingerstick calibration and an advanced Controller that modulates basal rate, administers automated insulin corrections, and has a dedicated safety system monitoring the work of the Controller to safeguard against hypoglycemia. A pilot study of Control-IQ has been published [97] and the system has now completed a multicenter pivotal trial (NCT 03563313).

Outstanding Questions

What are the most important directions for future glucose sensor development? More accurate? More durable and reliable? Less invasive? All of the above?

Are other sensors, for example, insulin, lactate, potentially contributing to better glycemic control?

What is the best route to fully automated CLC that does not require any user intervention prior to, or during, abrupt events such as unannounced meal or exercise? Is tracking human behavior and building behavioral action profiles a viable alternative?

What is the utility of additional real-time signals, for example, motion sensing, heart rate, and geolocation, for the improvement of diabetes control? Early studies have shown marginal improvement, particularly around the management of the effects of physical activity, but comprehensive multisignal control of diabetes is still elusive.

What is the utility of additional hormones, for example, glucagon, amylin, or GLP-1 receptor agonists and SGLT inhibitors, for the improvement of diabetes control? In type 2 diabetes, new medications are showing promising results in clinical trials and in clinical practice. It is less clear whether these compounds would add tangible improvement to the automated treatment of type 1 diabetes, particularly in view of increased technological complexity.

Mobile CLC running in an app, or algorithm embedded in the insulin pump? Can they coexist and complement each other in the same system?

Figure 4. Configuration A (green): embedded closed-loop control. The control algorithm is run by the insulin pump, which receives data directly from the continuous glucose monitoring (CGM) sensor. Optionally, the pump communicates data to a mobile device and from there to the Cloud. Configuration B (orange) mobile closed-loop control: the control algorithm is run by a mobile device, which receives data from the CGM and from the insulin pump, and controls the insulin pump. Typically, the mobile device transmits data to the Cloud.

We can therefore conclude that, a century after the discovery of insulin, viable AP technology is within reach and entering mainstream clinical practice. The AP is a mobile medical network consisting of several devices, CGM, Controller, and insulin pump, which work in concert to optimize the control of diabetes in real time. Thus, connectivity between devices is paramount and issues such as security of interdevice communication are being vigorously addressed. While currently targeting insulin replacement in type 1 diabetes, similar automated technologies are being tested and have potential for the treatment of type 2 diabetes as well. The AP user interface is generally multifunctional, offering more possibilities that a CGM or insulin pump display; thus, the limits of safe AP operation should be clearly defined and explained to the user, to healthcare professionals, and to significant others. Exceeding system capabilities carries risks with any device, but can be particularly harmful with medical equipment.

In summary, a number of studies in the past decade have confirmed that AP is a feasible treatment for diabetes; its digital-network structure is well defined, and at least two configurations – Mobile and Embedded – are in play in contemporary systems. First-generation control algorithms are already out, and research continues in multiple new directions including better sensors and new advanced multisignal and, possibly, multihormonal controllers (see Outstanding Questions). Thus, AP is here to stay, and is on its way to fulfill its promise as the digital-age optimal treatment for diabetes.

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Disclaimer Statement

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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 of insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 329, 978–986
2. Lachin, J.M. and *et al.*DCCT/EDIC Research Group (2008) Effect of Glycemic Exposure on the Risk of Microvascular Complications in the Diabetes Control and Complications Trial revisited. *Diabetes* 57, 995–1001
3. UK Prospective Diabetes Study Group, UKPDS (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. *Lancet* 352, 837–853
4. Cryer, P.E. (1994) Hypoglycaemia: The limiting factor in the glycaemic management of IDDM. *Diabetes* 43, 1378–1389
5. Cryer, P.E. (2014) Glycemic goals in diabetes: trade-off between glycemic control and iatrogenic hypoglycemia. *Diabetes* 63, 2188–2195
6. White, N.H. *et al.* (1983) Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N. Engl. J. Med.* 308, 485–491
7. Cryer, P.E. and Gerich, J.E. (1985) Glucose counterregulation, hypoglycemia, and intensive therapy of Diabetes Mellitus. *N. Engl. J. Med.* 313, 232–241
8. Amiel, S.A. *et al.* (1987) Defective glucose counterregulation after strict glycemic control of insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 316, 1376–1383
9. Amiel, S.A. *et al.* (1988) Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 37, 901–907
10. The Diabetes Control and Complications Trial Research Group (1997) Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46, 271–286
11. Kadish, A.H. and Automation control of blood sugar (1964) A servomechanism for glucose monitoring and control. *Am. J. Med. Electron.* 39, 82–86
12. Albisser, A.M. *et al.* (1974) An artificial endocrine pancreas. *Diabetes* 23, 389–396
13. Pfeiffer *et al.* (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
14. Mirouze, J. *et al.* (1977) Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. *Diabetologia* 13, 273–278
15. Clemens, A.H. *et al.* (1977) The development of Biostator, a glucose-controlled insulin infusion system (GCIIS). *Horm. Metab. Res.* Suppl 7, 23–33
16. Santiago, J.V. *et al.* (1979) Closed-loop and open-loop devices for blood glucose control in normal and diabetic subjects. *Diabetes* 28, 71–84
17. Pickup, J.C. *et al.* (1978) Continuous subcutaneous insulin infusion: an approach to achieving normoglycaemia. *Br. Med. J.* 1, 204–207
18. Tamborlane, W.V. *et al.* (1978) 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
19. Cobelli, C. *et al.* (2009) Diabetes: Models, Signals, and Control. *IEEE Rev. Biomed. Eng.* 2, 54–96

20. Cobelli, C. *et al.* (2011) Artificial pancreas: past, present, future. *Diabetes* 60, 2672–2682
21. Rebrin, K. *et al.* (1999) Subcutaneous glucose predicts plasma glucose independent of insulin: Implications for continuous monitoring. *Am. J. Physiol. Endocrinol. Metab.* 277, E561–E571
22. Mastrototaro, J.J. (2000) The MiniMed continuous glucose monitoring system. *Diabetes Technol. Ther.* 2, S13–S18
23. Feldman, B. *et al.* (2003) A continuous glucose sensor based on wired enzyme technology – results from a 3-day trial in patients with type 1 diabetes. *Diabetes Technol. Ther.* 5, 769–778
24. Wentholt, I.M.E. *et al.* (2004) Relationship between interstitial and blood glucose in type 1 diabetes patients: delay and the push-pull phenomenon revisited. *Diabetes Technol. Ther.* 9, 69–175
25. Boyne, M. *et al.* (2003) Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 52, 2790–2794
26. Kulcu, E. *et al.* (2003) Physiological differences between interstitial glucose and blood glucose measured in human subjects. *Diabetes Care* 26, 2405–2409
27. Kovatchev, B.P. and Clarke, W.L. (2008) Peculiarities of the continuous glucose monitoring data stream and their impact on developing closed-loop control technology. *J. Diabetes Sci. Technol.* 2, 158–163
28. Facchinetti, A. *et al.* (2013) Real-time improvement of continuous glucose monitoring accuracy: the smart sensor concept. *Diabetes Care* 36, 793–800
29. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group (2008) Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N. Engl. J. Med.* 359, 1464–1476
30. Battelino, T. *et al.* (2012) The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 55, 3155–3162
31. New, J.P. *et al.* (2015) Continuous glucose monitoring in people with diabetes: the randomized controlled Glucose Level Awareness in Diabetes Study (GLADIS). *Diabet. Med.* 32, 609–617
32. Rachmiel, M. *et al.* (2015) The use of continuous glucose monitoring systems in a pediatric population with type 1 diabetes mellitus in real-life settings: the AWeSoMe Study Group experience. *Acta Diabetol.* 52, 323–329
33. Beck, R.W. and *et al.*DIAMOND Study Group (2017) Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 317, 371–378
34. Heinemann, L. and Freckmann, G. (2015) CGM versus FGM; or, continuous glucose monitoring is not flash glucose monitoring. *J. Diabetes Sci. Technol.* 9, 947–950
35. Fokkert, M.J. *et al.* (2017) Performance of the FreeStyle Libre Flash glucose monitoring system in patients with type 1 and 2 diabetes mellitus. *BMJ Open Diabetes Res. Care* 5, e000320
36. Danne, T. *et al.* (2017) International consensus on use of continuous glucose monitoring. *Diabetes Care* 40, 1631–1640
37. Kropff, J. *et al.* (2017) Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE study: a 180-day, prospective, multicenter, pivotal trial. *Diabetes Care* 40, 63–68
38. Breton, D. *et al.* (2014) Adding heart rate signal to a control-to-range artificial pancreas system improves the protection against hypoglycemia during exercise in type 1 diabetes. *Diabetes Technol. Ther.* 16, 506–511
39. Turksoy, K. *et al.* (2014) An integrated multivariable artificial pancreas control system. *J. Diabetes Sci. Technol.* 8, 498–507
40. Kovatchev, B.P. *et al.* (2009) *In silico* preclinical trials: A proof of concept in closed-loop control of type 1 diabetes. *J. Diabetes Sci. Technol.* 3, 44–55
41. Dalla Man, C. *et al.* (2007) Meal simulation model of the glucose-insulin system. *IEEE Trans. Biomed. Eng.* 54, 1740–1749
42. Nauck, M.A. *et al.* (1986) Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J. Clin. Endocrinol. Metab.* 63, 492–498
43. Drucker, D.J. and Nauck, M.A. (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 368, 1696–1705
44. Bergman, R.N. *et al.* (1979) Quantitative estimation of insulin sensitivity. *Am. J. Phys.* 236, E667–E677
45. Dalla Man, C. *et al.* (2014) The UVA/ Padova Type 1 Diabetes Simulator: new features. *J. Diabetes Sci. Technol.* 8, 26–34
46. Viceconti, M. *et al.* (2017) In silico assessment of biomedical products: the conundrum of rare but not so rare events in two case studies. *J. Eng. Med.* 231, 455–466
47. Chase, J.G. *et al.* (2018) Improving glycemic control in critically ill patients: personalized care to mimic the endocrine pancreas. *Crit. Care* 22, 182
48. Friedrich, M.J. (2009) Artificial pancreas may soon be a reality. *JAMA* 301, 1525–1527
49. Dolgin, E. (2012) Managed by machine. *Nature* 485, S6–S8
50. Clery, D. (2014) A pancreas in a box. *Science* 343, 133–135
51. Steil, G.M. *et al.* (2006) Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes* 55, 3344–3350
52. Hovorka, R. *et al.* (2004) Closing the loop: the ADICOL experience. *Diabetes Technol. Ther.* 6, 307–318
53. El-Khatib, F.H. *et al.* (2010) A bihormonal closed-loop artificial pancreas for type 1 diabetes. *Sci. Transl. Med.* 2, 27ra27
54. 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
55. Weinzimer, S.A. *et al.* (2008) Fully automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care* 31, 934–939
56. 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
57. Hovorka, R. *et al.* (2010) Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 375, 743–751
58. Atlas, E. *et al.* (2010) MD-logic artificial pancreas system: a pilot study in adults with type 1 diabetes. *Diabetes Care* 33, 1072–1076
59. Breton, M.D. and *et al.*on behalf of The International Artificial Pancreas (iAP) Study Group (2012) Fully-integrated artificial pancreas in type 1 diabetes: modular closed-loop glucose control maintains near-normoglycemia. *Diabetes* 61, 2230–2237
60. Phillip, M. *et al.* (2013) Nocturnal glucose control with an artificial pancreas at a diabetes camp. *N. Engl. J. Med.* 368, 824–833
61. Nimri, R. *et al.* (2013) The "glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. *Pediatr. Diabetes* 14, 159–167
62. 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
63. 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
64. Cobelli, C. *et al.* (2012) Pilot studies of wearable artificial pancreas in type 1 diabetes. *Diabetes Care* 35, e65–e67
65. 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
66. Anderson, S.M. *et al.* (2016) Multinational home use of closed-loop control is safe and effective. *Diabetes Care* 39, 1143–1150
67. Renard, E. *et al.* (2016) Day and night closed loop glucose control in patients with type 1 diabetes under free-living conditions: comparison of a single-arm, 1-month experience to results of a previously reported feasibility study of evening and night at home. *Diabetes Care* 39, 1151–1160
68. Del Favero, S. *et al.* (2016) Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe. *Diabetes Care* 39, 1180–1185
69. Kovatchev, B.P. *et al.* (2017) Feasibility of long-term closed-loop control: a multicenter 6-month trial of 24/7 automated insulin delivery. *Diabetes Technol. Ther.* 19, 18–24
70. Breton, M.D. *et al.* (2017) Closed loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the artificial pancreas ski study. *Diabetes Care* 40, 1644–1650

71. Sherr, J.L. *et al.* (2013) Reduced hypoglycemia and increased time in target using closed-loop insulin delivery during nights with or without antecedent afternoon exercise in type 1 diabetes. *Diabetes Care* 36, 2909–2914
72. Riddell, M.C. *et al.* (2015) Exercise and the development of the artificial pancreas: one of the more difficult series of hurdles. *J. Diabetes Sci. Technol.* 9, 1217–1226
73. Jayawardene, D.C. *et al.* (2017) Closed-loop insulin delivery for adults with type 1 diabetes undertaking high-intensity interval exercise versus moderate-intensity exercise: a randomized, crossover study. *Diabetes Technol. Ther.* 19, 340–348
74. Huyett, L.M. *et al.* (2017) Outpatient closed-loop control with unannounced moderate exercise in adolescents using zone model predictive control. *Diabetes Technol. Ther.* 19, 331–339
75. Pinsker, J.E. *et al.* (2018) Evaluation of an artificial pancreas with enhanced model predictive control and a glucose prediction trust index with unannounced exercise. *Diabetes Technol. Ther.* 20, 455–464
76. Bally, L. and Thabit, H. (2018) Closing the loop on exercise in type 1 diabetes. *Curr. Diabetes Rev.* 14, 257–265
77. Jacobs, P.G. *et al.* (2015) Incorporating an exercise detection, grading, and hormone dosing algorithm into the artificial pancreas using accelerometry and heart rate. *J. Diabetes Sci. Technol.* 9, 1175–1184
78. Cinar, A. (2017) Multivariable adaptive artificial pancreas system in type 1 diabetes. *Curr. Diab. Rep.* 17, 88
79. Russell, S.J. *et al.* (2014) Outpatient glycemic control with a bionic pancreas in type 1 diabetes. *N. Engl. J. Med.* 371, 313–325
80. Russell, S.J. *et al.* (2016) Day and night glycaemic control with a bionic pancreas versus conventional insulin pump therapy in preadolescent children with type 1 diabetes: a randomised crossover trial. *Lancet Diabetes Endocrinol.* 4, 233–243 Erratum in: *Lancet Diabetes Endocrinol*. 2018 6:e3
81. El-Khatib, F.H. *et al.* (2017) Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. *Lancet* 389, 369–380
82. Haidar, A. *et al.* (2016) Single- and dual-hormone artificial pancreas for overnight glucose control in type 1 diabetes. *J. Clin. Endocrinol. Metab.* 101, 214–223
83. Taleb, N. *et al.* (2016) Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. *Diabetologia* 59, 2561–2571
84. Jacobs, P.G. *et al.* (2016) Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. *Diabetes Obes. Metab.* 18, 1110–1119
85. Castle, J.R. *et al.* (2018) Randomized outpatient trial of single- and dual-hormone closed-loop systems that adapt to exercise using wearable sensors. *Diabetes Care* 41, 1471–1477
86. Peters, T.M. and Haidar, A. (2018) Dual-hormone artificial pancreas: benefits and limitations compared with single-hormone systems. *Diabet. Med.* 35, 450–459
87. Bergenstal, R.M. *et al.* (2013) Threshold-based insulin-pump interruption for reduction of hypoglycemia. *N. Engl. J. Med.* 369, 224–232
88. 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
89. Beck, R.W. *et al.* (2014) Frequency of morning ketosis after overnight insulin suspension using an automated nocturnal predictive low glucose suspend system. *Diabetes Care* 37, 1224–1229
90. Stewart, Z.A. *et al.* (2016) Closed-loop insulin delivery during pregnancy in women with type 1 diabetes. *N. Engl. J. Med.* 375, 644–654
91. Thabit, H. *et al.* (2017) Closed-loop insulin delivery in inpatients with type 2 diabetes: a randomised, parallel-group trial. *Lancet Diabetes Endocrinol.* 5, 117–124
92. Weisman, A. *et al.* (2017) Effect of artificial pancreas systems on glycaemic control in patients with type 1 diabetes: a systematic review and meta-analysis of outpatient randomised controlled trials. *Lancet Diabetes Endocrinol.* 5, 501–512
93. Bekiari, E. *et al.* (2018) Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. *BMJ* 361, k1310
94. Karageorgiou, V. *et al.* (2019) Effectiveness of artificial pancreas in the non-adult population: A systematic review and network meta-analysis. *Metabolism* 90, 20–30
95. Bergenstal, R.M. *et al.* (2016) Safety of a hybrid closed-loop insulin delivery system in patients with type 1 diabetes. *JAMA* 316, 1407–1408
96. Garg, S.K. *et al.* (2017) Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes Technol. Ther.* 19, 155–163
97. Brown, S. *et al.* (2018) First look at control-IQ: a new-generation automated insulin delivery system. *Diabetes Care* 41, 2634–2636