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REVIEW ARTICLE

The Next Generation of Artificial Pancreas Control Algorithms

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Abstract

Creating a wearable artificial pancreas (AP) by closing the loop between a glucose sensor and an insulin infusion pump has the potential to significantly impact the complications associated with and improve the quality of life of diabetic individuals. Despite recent progress on glucose sensor and insulin infusion technologies, control algorithms built on the simple glucose value efferent and insulin dose afferent model are not efficient and reliable. Based on glucose regulatory mechanisms known to date, their impairment in the diabetic state, and fundamental principles of control theory, some corrections to the present course of research are proposed to facilitate the removal of this barrier. A greater emphasis on model predictive controllers or controllers that exploit a mathematical representation, or model, of the patient's own physiology is proposed. Whole-body physiologically based pharmacokinetics–pharmacodynamics-type models hold the best odds for enabling a successful closed-loop AP. However, two major improvements to the diabetes modeling state of the art are required to make them practical for daily care: integrating hypothalamus–pituitary–adrenal axis and gastrointestinal tract submodels. Although there are simple representations of these in current existence, large concerted efforts between experimentalists and modelers will be required to enhance their accuracy. Finally, changes in hardware that complements controller performance are suggested. For instance, the development of dual control inputs of insulin and glucagon could relax tolerances on controller accuracy.

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Introduction

Renewed efforts have been taking place to make the artificial pancreas (AP) a reality. The AP remains a viable therapeutic alternative pending a biological cure, which would require either regeneration or transplantation of normal β cells with long-term success. In the normal pancreas, a significant variety of hormonal, substrate, and neuronal signals are continuously transduced (sensed), and the appropriate responses in the form of insulin, amylin, glucagon, and somatostatin are continuously secreted. In the current approach, the AP proposes to mimic those functions by linking a glucose sensor to an insulin pump via a computer control algorithm.[1,2] The goal is to obtain a safe, effective, and affordable device that operates continuously by mimicking the pancreas, requiring minimal patient or professional intervention.

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Abbreviations: (AP) artificial pancreas, (GIP) gastric inhibitory peptide, (GIT) gastrointestinal tract, (GLP-1) glucagon-like peptide 1, (HPA) hypothalamic–pituitary–adrenal axis, (MPC) model-predictive controller, (PB-PK-PD) physiologically based pharmacokinetics–pharmacodynamics, (PID) proportional-integral-derivative controller

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There is justified optimism for this approach, although some limitations are to be expected. Clinical trials have shown that continuous glucose monitoring with patient-administered insulin does result in tighter control than traditional clinical practice.[3,4] Moreover, large longitudinal clinical trials have confirmed that intensive glucose monitoring with informed insulin dosing is effective in reducing the risks of related complications and delaying,[5–7] but not halting,[8,9] glucose control deterioration. Also, it is not clear if it can be effective for poorly controlled diabetic patients.[9] In short, the AP promises freedom from multiple daily finger pricks and injections with the bonus of tighter control for a significant portion of the diabetes disease continuum.

Today, glucose sensing and insulin pump technologies have matured to the point of making the AP viable. However, an efficient and reliable control algorithm to close the glucose–insulin loop has thus far remained elusive, despite numerous attempts (see reviews by Hovorka *et al.*[1] and Klonoff[2]). The necessary ingredients for building such an algorithm are delineated in this article and, while doing so, some corrections to the present course of AP research are proposed.

First, it is instructive to overview the current knowledge on glucose regulation.

Whole-Body Glucose Regulation vs the Artificial Pancreas

It is currently known that at least 10 hormones participate closely in glucose regulation, with several more controlling related functions such as satiety, digestion, and growth (**Table 1**). The central nervous system also plays an important role by modulating the responses of endocrinal and other tissues according to a variety of inputs, including the circadian rhythm.[10] It is also important to bear in mind that our knowledge of these complex mechanisms is still expanding rapidly. For instance, it has been discovered that mice lacking osteocalcin show glucose intolerance, insulin resistance, and β-cell deficiency.[11] Because the same gene is present in humans, this finding suggests that the skeletal system may be pivotal in regulating our glucose metabolism.

Table 1.
Known Hormones Directly Involved with Glucose Regulation

Hormone	Tissue/organ	Secretagogues	Action
Insulin	β cells (pancreas)	Glucose, fatty acids, amino acids, incretins (GLP-1, GIP)	Promotes uptake and storage of glucose, lipids, and amino acids in various tissues
Amylin	β cells (pancreas)	Same as insulin	Suppresses glucagon secretion Slows down gastric emptying Promotes satiety
Incretins (GLP-1, GIP)	Gastrointestinal tract (L and K cells)	Meal ingestion	Amplifies first-phase secretion of insulin Stimulates late-phase insulin secretion Slows down gastric emptying Suppresses glucagon secretion
Somatostatin	δ cells (pancreas) stomach intestine brain	Growth hormone	Suppresses the secretion of various hormones, including growth hormone and gastrointestinal hormones
Glucagon	α cells (pancreas)	Glucose <70 mg/dl	Promotes glycogenolysis and gluconeogenesis
Catecholamines (epinephrine, norepinephrine)	Adrenal glands (medulla)	Glucose <70 mg/dl	Suppresses insulin secretion Promotes glucagon secretion Mobilizes gluconeogenesis substrates Promotes hepatic glucose production and lipolysis
Growth hormone	Pituitary	Glucose <65 mg/dl, sleep, exercise, ghrelin, dietary protein	Suppresses liver glucose uptake Promotes gluconeogenesis Promotes lipolysis
Cortisol	Adrenal glands (cortex)	Glucose <60 mg/dl	Promotes glycogenolysis, lipolysis, and proteinolysis Mobilizes amino acids and ketone bodies

Figure 1 summarizes the known hormones, their endocrine glands, secretagogues, and actions that contribute to glucose regulation as understood today. In the healthy human subject, glucose is maintained at a midnormal range of 88 to 96 mg/dl (4.9 to 5.3 mmol/liter).[12] Upon ingestion of a meal, incretins help prepare the pancreas for the imminent surge of blood glucose. The incretins glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), secreted by specialized cells in the gastrointestinal tract (GIT), promote the first-phase secretion of insulin in proportion to the glucose content of the meal even before its appearance in the bloodstream.[13] This constitutes an anticipatory or feed-forward control loop. Insulin promotes the uptake of glucose primarily in skeletal muscle, adipose tissues, and liver and of proteins in various tissues and suppresses lipolysis. Amylin is cosecreted with insulin by β cells in the pancreas. Amylin, in combination with GLP-1 and GIP, helps reduce the total insulin demand by slowing gastric emptying and promoting satiety.[14,15] Insulin and amylin also seem to suppress the release of glucagon, further attenuating the postprandial glucose peak.[14] Incretins also influence the late phase of insulin secretion.[13]

During hypoglycemia, the normal body has a series of redundant safeguards at its disposal to maintain an adequate glucose supply for the brain. As glucose lowers below ~80 mg/dl, insulin secretion halts, thus favoring the ongoing renal and hepatic glucose productions. If levels keep falling to ~70 mg/dl, glucagon and catecholamine (epinephrine and norepinephrine) secretions are activated in the pancreas and adrenal glands, respectively. These hormones quickly activate multiple pathways that work synergistically to counter hypoglycemia. Glucagon sets

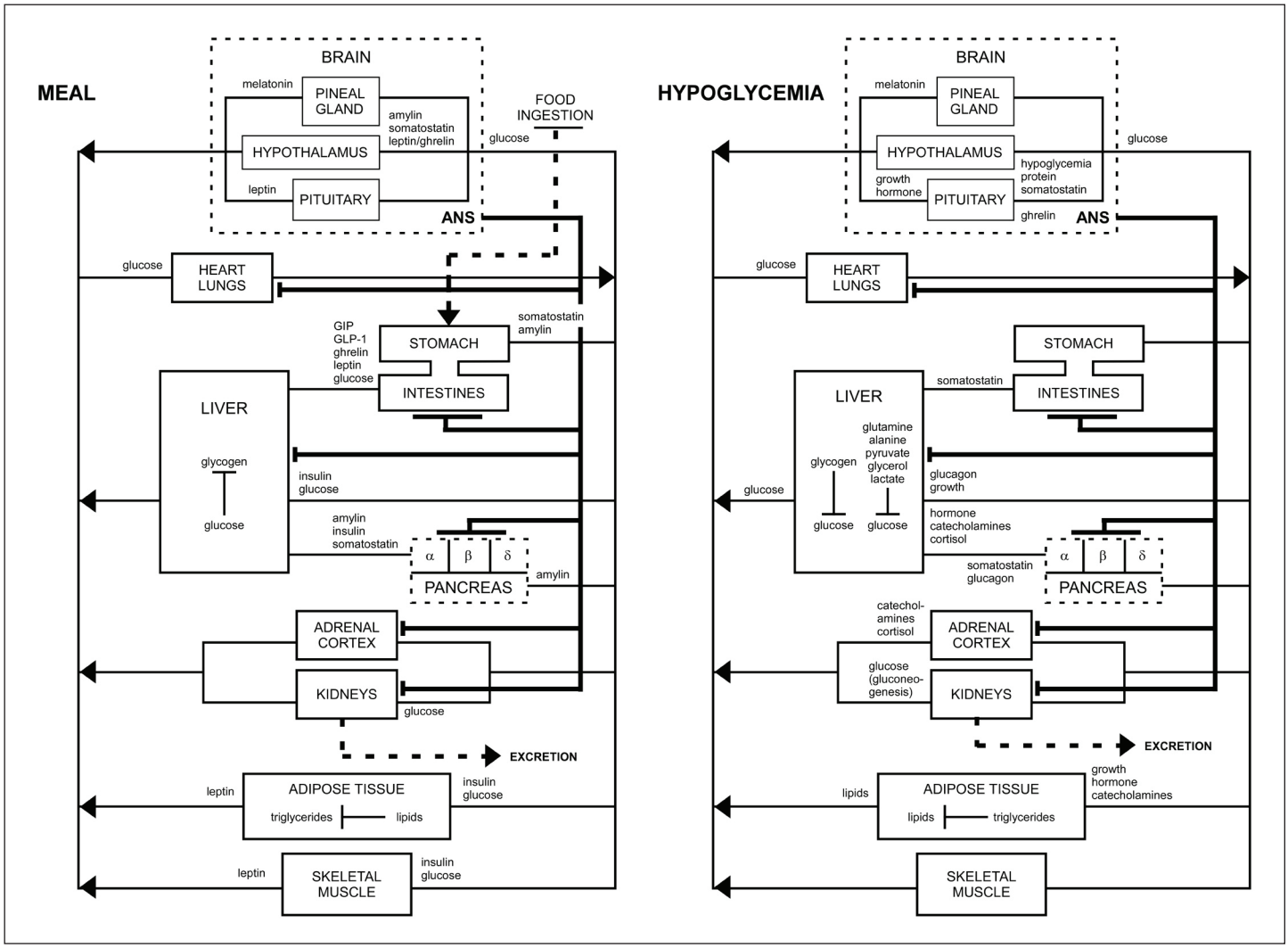

Figure 1. Schematic representations of hormonal cues following a meal (left) and hypoglycemia (right). Organs (boxes) involved in energy homeostasis are interconnected by major arteries and veins (lines and arrows). Hormones secreted by a given organ are shown downstream of that organ and, conversely, hormonal targets are depicted upstream of the target organ. The autonomous nervous system (ANS) pathways are represented by thick solid lines, but its regulation of blood flow is omitted. Storage and production of substrates by the liver and adipose tissues are also shown. Related hormones regulating satiety and the circadian rhythm are included.

off hepatocytes to produce glucose from stored glycogen (glycogenolysis) and from glycerol, lactate, and amino acids (gluconeogenesis). Catecholamines amplify the effect of glucagon directly by facilitating its secretion and costimulating hepatic glucose production and indirectly by mobilizing gluconeogenic substrates. Falling levels of insulin favor sensitive lipolytic pathways to release lipids. If hypoglycemia is prolonged over several hours, growth hormone (<65 mg/dl) and cortisol (<60 mg/dl) are secreted to help recruit alternative fuels via lipolysis, proteinolysis, and ketogenesis. At even lower glucose levels, brain functions become impaired.

Improving the Software

The preceding overview, albeit brief, suggests that glucose and related energy regulatory networks possess a complexity that eclipses the control potential of any glucose–insulin AP, and even more so in disease conditions where the pancreas is not the only affected organ. It appears the logical error commonly made is that since the therapeutic goal is to keep plasma glucose within physiological concentrations, glucose concentration is the only relevant biomarker for adjusting insulin dosage, and indeed the dosage of any diabetes drug. This statement can only be correct if all other substrates, hormones, and neuronal signals are either negligible (insensitive) or simply follow glucose concentration fluctuations (redundant).

Physiology and clinical experience gives us further indication that other biomarkers cannot be ignored. For instance, serum cortisol, hepatic glycogen stores, and expression levels of glucose transporters are neither negligible nor redundant as they will modify the relationship between insulin and glucose within a patient. Hence, operating with only a glucose sensor renders the AP severely starved for information. Lacking a complicated array of sensors, this conundrum can only be solved if the controller estimates the missing pieces. The estimation process requires the use of a mathematical model and supplemental user-inputted data. These algorithms are called model predictive controllers (MPC).

In model-less controllers, the error, or the difference between the output (glucose concentration) and the desired set point value (normoglycemia), is used to calculate a change in the input (insulin). A common example of this is the proportional-integral-derivative controller (PID). In contrast, MPC uses an internal model to predict future outcomes from past and current states and then uses a mathematical tool called cost function minimization to find a sequence of control inputs to reach the desired future outcome. Alternatively, Kalman or Particle filters could be employed instead of cost function minimization.

In general, model-less controllers cannot outperform MPC provided that the model is reasonably accurate. In diabetes care this becomes clear if one considers the fact that the same patient may have similar glucose readings at the same time of the day and on consecutive days but still reacts completely differently to the same insulin dose. Suppose there was a higher excursion after breakfast on day 2 caused by an increase in hepatic glycogen stores that occurred overnight due to a late-night snack. The MPC fitted with a good model would have been able to take this into account (provided the patient did not forget to input the content of the meal into the AP) and discriminate between the two situations. The larger glucose excursion on day 2 after breakfast would have been predicted by the MPC and the insulin dosage adjusted accordingly and delivered preemptively with a manual trigger. The model-less controller, however, would have given the same triggered response as the day before, resulting in poorer subsequent control.

The MPC is especially useful for multivariate nonlinear systems such as the human body and has been employed successfully in continuous drug delivery and anesthesia.[16–18] Recently, clinical trials have leaned toward the use of MPC[19–21] with the exception of Medtronic MiniMed's PID controller.[22] MPCs, even when the model was simply a set of heuristic rules,[20] have demonstrated better performance than PID control with patient-specific fine-tuned gains.[23] However, this result is debatable, as clinical trials comparing PID and MPC approaches directly under equal conditions have not been carried out. Perhaps the main culprits are the notorious time lags associated with insulin analog kinetics and subcutaneous glucose sensing, which are particularly detrimental to the performance of PID controllers. In the case of MPC, such lags can be built into the model, allowing the controller to compensate for it. Conversely, PID controllers have no means to account for delays and must rely on external signal filtering to ameliorate this effect.

How accurate does the MPC model have to be? Clearly, any physiological model could range from having no correlation to the real organism to having a perfect correlation. It is not hard to imagine that an ideal model would need to faithfully capture every biochemical and physical process in every tissue related to the disease. Because this is not feasible in the foreseeable future,

the most detailed model that can be afforded with experimental data presently available is needed. While this statement may seem trivial, current practice suggests otherwise. To this date, minimal models of glucose regulation are still vigorously researched,[24] even though whole-body physiologically based pharmacokinetics–pharmacodynamics (PB-PK-PD)-type models with varying degrees of complexity and accuracy have been proposed and validated in controlled experiments for some time.[25–32] Minimal models and PB-PK-PD models are similar in that they both use well-stirred reactor abstractions (referred to as compartments). The difference lies in that minimal model compartments subsume a large collection of tissues and organs (e.g., peripheral organs) to obtain the smallest possible set of equations, whereas PB-PK-PD models treat each organ or tissue as (more or less) separate compartments (e.g., brain, liver, pancreas, kidneys, adipose tissues) and subcompartments (e.g., erythrocytes, plasma, interstitium, tissue cells).

Any good modeling practice should strive to maximize the utilization of available data while keeping the number of assumptions to a minimum. In the PB-PK-PD approach, data utilization is maximized by breaking down compartments into their constituent organs, tissues, cells, organelles, and so on when data are available to calibrate those submodels independently. This gives rise to semiempirical submodels or models based on sound biochemical and physical principles with a few parameters fitted to reproduce experimental data. A good example of this is the pancreas model by Sorensen.[29] At even higher resolutions, sometimes it is possible to create submodels where most parameters could, at least in principle, be measured directly, thus bypassing the need for fitting. By reaching for a direct correspondence between physiological model and real organism, data utilization is maximized and the number of assumptions is minimized.

A desirable side effect of maintaining a close correspondence between model and reality is that the MPC is better able to accommodate interpatient pathophysiological variations, which are considerable in diabetes and indeed in many other conditions. The idea is that the AP "learns the patient" based on its past performance to continuously improve future control. The close correspondence could also allow the patient to meaningfully change some of the parameters: if the patient loses 5 pounds he or she just enters the new weight into the AP and insulin injection rates are recalculated accordingly. Here, patient vitals (body type, gender, age, etc.) and other easily available data (hemoglobin A1c, time of last hypoglycemic episode, subjective mental stress level, etc.) could be used for the initial calibration to increase reliability during early use of the AP.

So far, most if not all MPC trials have been performed on individuals with type 1 diabetes under well-controlled conditions. Daily life, however, is not well controlled: we eat complex foods, exercise, sleep, get sick, and so on. This will require increasingly sophisticated modeling, including stress and nutrition data as well. To this end, the next advances in diabetes modeling should include the development and integration of submodels of the hypothalamic–pituitary–adrenal (HPA) axis and the gastrointestinal tract. The HPA axis is essential in capturing the response and adaptation to physical and mental stress and diurnal cycles, as well as their impairment in the diabetic state.[33,34] All diabetes models to date have lacked this key system, even though simple models of the HPA axis exist.[35–38] A GIT submodel is needed, at a minimum, to relate the ingestion of several meals a day to a time trajectory of glucose appearance in the bloodstream. Examples of this are available,[31,39,40] even though model-independent testing against mixed meal data was completed only recently.[40] A more adequate, albeit considerably more complex, GIT model should predict the appearance rate of carbohydrates, fats, proteins, and water as a function of meal composition and hormonal signals. The HPA and GIT are highly complex subsystems, and the development of adequate models will require large amounts of experimental data, a significant portion of which do not presently exist. In addition, their integration will also require concurrent enhancements to the existing PB-PK-PD models to make them compatible. As a result, large and concerted research efforts will be required between experimentalists and modelers. Despite the difficulties, some researchers have already begun to make inroads toward this end.[39,41–43]

Improving the Hardware

From the assertion that an information-starved, glucose–insulin AP places stringent tolerances on model accuracy, it follows that an implementation that senses one or more species in addition to glucose, or infuses one or more drugs in addition to insulin, would greatly relax those tolerances (also called a multi-input–multi-output controller). Ideally, for sensing, one would like to measure species that vary independently from each other under most situations ("orthogonal" species). The goal here is to constrain the solution space or, in other words, to reduce the uncertainty in the control inputs estimated by the

internal model as much as possible. The corollary also holds. If a MPC possesses a model sophisticated enough, the AP should be able to compensate for noise or drift in the sensor by partially relying on model predictions of the measured variable at future time points. In this way, the reliability of glucose sensors could be improved or, equivalently, the interval between sensor calibrations increased.

Integrating even just one additional control input in addition to insulin could have a similar or perhaps greater impact in relaxing model accuracy tolerances. Historically, the only choice for additional control has been glucagon, and the last study, using an insulin and glucagon intravenous approach, was published in 1977.[44] Recently, however, an animal study has reintroduced the idea, this time via the subcutaneous route and showing encouraging results.[45] Glucagon is the logical choice as it is the only known insulin counterregulatory pancreatic hormone, is fast acting, and its secretion is usually altered, deficient, or entirely absent in diabetic individuals. In contrast to fast-acting sugars, glucagon modulates multiple internal regulatory mechanisms. Glucagon is stable for months in powder form but must be used promptly upon reconstitution. It may be prepared periodically and loaded into existing portable insulin pumps.[45] Alternatively, a dilution step could be adapted to the pump so that reconstitution occurs right before injection. Still, pramlintide, an amylin analog, should not be discounted, as it has been shown to greatly reduce the need for insulin and to improve long-term control.[15,46,47]

Current approaches typically detune insulin input to minimize the risk of hypoglycemia.[2] This detuned approach is contraindicated in the therapeutic model of tight glucose concentration control. The higher control aggressiveness afforded by the inclusion of a glucagon pump could simultaneously tighten glucose excursions and drastically reduce hypoglycemia risk, a strategy that could be enhanced further with amylin analogs, perhaps by premixing it with insulin prior to infusion. Paradoxically, it may turn out that developing a more complex AP with dual insulin/glucagon control inputs may actually be a more readily attainable goal than using only insulin. That is, increasing hardware complexity in order to decrease software complexity may turn out to be the right prescription.

Conclusions

The artificial pancreas holds the promise for future freedom from multiple daily finger pricks and injections with a potential bonus of tighter control for a significant portion of the diabetes disease continuum. However, an efficient and reliable control algorithm to close the glucose–insulin loop has yet to be developed.

An overview of the current knowledge of glucose regulatory networks suggests a complexity that eclipses the control potential of any glucose–insulin AP. Because only a glucose sensor is available, the paucity of information about the patient's internal physiological state can only be remedied by a controller that estimates the missing parameters via a mathematical model (model predictive controller) while relying on supplemental user-inputted data. For the model, whole-body physiologically based pharmacokinetics–pharmacodynamics-type models hold the best odds for enabling a successful closed-loop AP because they retain as much direct correspondence to the real organism as possible. This characteristic allows the accuracy to improve as more data become available, such as when the AP is "learning the patient" or using past performance to improve future control.

To enable adequate control in daily life situations, the next advances in diabetes modeling should move toward the development and integration of submodels of the HPA axis and the GIT. The HPA is essential in capturing the response and adaptation to stressors and diurnal cycles, as well as their impairment in the diabetic state, whereas a GIT model is required for predicting the appearance of nutrients in the bloodstream following the consumption of meals. In this context, this expanded model should also become valuable in patient education, for health-care provider training, as a "virtual diabetic" testbed simulator for benchmarking different noise filtering and control strategies, and for academic and industrial research. On the hardware side, more emphasis should be placed in developing a dual insulin/glucagon portable pump while continuing to enhance glucose sensing technology to ease the level of sophistication required from the controller.

It is well known that interpatient variance can be rather large, especially in a complex metabolic disease. Nevertheless, modelers commonly test their predictions against population averages without ever attempting to reproduce the individual. Even in a cohort of normal subjects, controlled experiments have shown that postprandial peaks typically have a standard deviation relative to the mean of ~30% in glucose and ~100% in insulin,[43] so modeling the individual using only population-averaged data may partially account for the limited successes in attaining efficient and reliable control.

Despite the challenges highlighted here, the current trajectory should be able to close the loop and deliver the first portable glucose–insulin AP in the near future. This could constitute a major therapeutic breakthrough due to the enormous leap in the volume of patient-specific data accessible via continuous glucose monitoring coupled to the intensive care afforded by a semiautonomous insulin pump. Nevertheless, the first generation of AP should not be expected to approach the performance of a real pancreas and periodic intervention will still be required. The battle against diabetes is ongoing, and the glucose–insulin AP could be an important step along the way.

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