The Artificial Pancreas

Jerry Radziuk

The discovery of insulin was lifesaving. However, it converted type 1 diabetes, which had been an acute and lethal disease, into a chronic disease, with its attendant complications. It had long been considered—and was clearly demonstrated in the Diabetes Control and Complications Trial (1)—that microvascular complications such as retinopathy, nephropathy, and neuropathy (as well as micro- and macrovascular legacy effects) were improved with intensive glucose control—that is, when circulating glucose levels were closer to those seen in the nondiabetic state. This entailed increased involvement on the part of a person with diabetes in their management: glucose monitoring, frequent insulin injections, or continuous subcutaneous insulin infusion (CSII). It also increased the risk of hypoglycemia. The mitigation of this trade-off, as well as controlling "brittle" diabetes, improving the quality of life of the person with diabetes, and the availability of the necessary technology, has motivated the evolution of self-managed intensive control into automated control.

Indeed, the artificial pancreas has been a major goal of research in type 1 diabetes since exogenous insulin became available. Articles on the automated control of glycemia in the absence of endogenous insulin (2,3) were published on (almost) the 50th anniversary of the discovery of insulin. This early version of the artificial pancreas depended on very frequent, automated measurements of blood glucose and an intravenous delivery of insulin. It was also bulky. Nevertheless, over the short term, it could maintain near normoglycemia. Initial versions operated using versions of a proportional (P) controller (4):

$$u_P = K_1 \cdot [g(t) - g_{target}] \quad (1)$$

where u_P is the insulin infusion rate, $g(t)$ the blood glucose concentration, g_{target} the target concentration, and K_1 the proportionality constant. Subsequent versions incorporated derivative (D) control:

$$u_D = K_2 \cdot dg(t)/dt \cong K_2 \cdot [g(t) - g(t-1)] \quad (2)$$

Essentially, this allows improved projections of glucose values into the future and thus better control of these future values. Albisser et al. (4) already demonstrated much tighter control with a proportional plus derivative (PD) controller compared with a simple P controller. It is notable that this controller infused glucose intravenously when glucose levels threatened to fall too far.

While unequivocally demonstrating feasibility, this early controller also illustrates *1*) the impractical nature of an intravenously based controller, *2*) the empirical nature of the P/PD controllers, and *3*) the difficulty of balancing tight control using insulin alone with the possibility of hypoglycemia.

The article by Breton et al. (5) in this issue of *Diabetes*, in turn, illustrates the progress that has been made in the last 40 years.

SUBCUTANEOUS ROUTE

The advent of CSII and, more recently, subcutaneous glucose monitoring, together with advances in technology, has allowed the development of a portable artificial pancreas. Here too, PD controllers have been applied with good results, at least in a computer simulation (6). The standard control-to-range (sCTR) protocol used in the Breton report is based on a simple linear model (7), which would also be similar to a PD controller.

MODEL-BASED CONTROL

Although P/PD controllers may appear empirical, they do have a basis in physiology, as illustrated by the fitting of intravenous glucose tolerance and hyperglycemic clamp data using proportional-integral-derivative control for insulin secretion (8). An integral control function has thus been added:

$$\begin{aligned} u_I(t) &= K_3 \cdot \int_0^t [g(\tau) - g_{target}] d\tau \\ &\cong u_I(t-1) + K_3 \cdot [g(t) - g_{target}] \\ &\sim K_3 \sum_i [g(t-i) - g_{target}] \end{aligned} \quad (3)$$

This control component provides the second-phase response to glucose excursions, such as those following meals. Since the glucose signal for insulin secretion will dissipate with time, a "forgetting factor" can be applied to the summations inherent in $u_I(t)$ (8). u_P and u_D, on the other hand, correspond to basal and first-phase control. Proportional-integral-derivative control has achieved near-normal overnight glycemia with improved postprandial excursions (9).

It can be seen that the total input, $u(t)$, becomes

$$u(t) = u_P + u_D + u_I \sim \sum_i K_i \cdot [g(t-i) - g_{target}] \quad (4)$$

with a number of the K_i the same.

A generalization of equation 4 leads to the model used by Breton et al. (5):

$$\delta g(t) \cong \sum_{i=1}^{n} \alpha_i \delta g(t-i) + \sum_{i=1}^{n_u} \beta_i \delta u(t - t_u - i) + \sum_{i=1}^{n_d} \gamma_i d(t-i) \quad (5)$$

with the δ signifying a change from basal levels or rates. $d(t)$ corresponds to the exogenous meal input (determined

From the Departments of Medicine and of Cellular and Molecular Medicine, University of Ottawa; the Department of Medicine, The Ottawa Hospital; and the Ottawa Hospital Research Institute, Ottawa, Ontario, Canada.
Corresponding author: Jerry Radziuk, jradziuk@uottawa.ca.
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by gastric emptying/absorption), t_u is the delay in insulin absorption from the subcutaneous injection site, and $\alpha_i,\beta_i,\gamma_i$ are constants (10). Using this model and minimizing a cost function (which establishes the "penalties" assessed for deviation from basal glycemia or a desired postprandial glucose profile, for infusing too much insulin, etc.), model predictive control yields the next (incremental) infusion rate, $\delta u(t)$. This corresponds to the enhanced control-to-range (eCTR) used in ref. 5. Comparing sCTR and eCTR therefore, this article shows convincingly that as the model becomes more comprehensive, glucose variability decreases, and the time spent in near normoglycemia and in a tight glycemic range increases.

INCIDENCE OF HYPOGLYCEMIA

As shown by the Diabetes Control and Complications Trial, tighter glucose control has been associated with an increased incidence of hypoglycemic episodes (1,11). Breton et al. show that using eCTR, more precise control (increased time in near normoglycemia and in tight control) can be achieved without increased hypoglycemia compared with patient-managed CSII. This is an important result. On the other hand, with the less rigorous control of the sCTR approach, time in near normoglycemia also increased and time in tight control did not, but hypoglycemic episodes decreased from 1.08 to 0.4 events/patient, with a sixfold reduction in overnight hypoglycemia. The groups are different and therefore difficult to compare, although feasible comparisons have been made. There is an implication, however, that the association of tight control with hypoglycemia has not yet been eliminated. This too is important. In the future, it will be valuable to compare control strategies in the same patients to gain more insight on the limits of the control in the face of hypoglycemia.

Inspection of Fig. 1 shows why, with subcutaneous insulin administration, it will continue to be difficult to achieve the responsivity in insulin concentrations and, therefore, action to avoid hypoglycemia. A model of insulin action is shown with a subcutaneous compartment, a circulatory compartment, and an effect compartment, which represents the action of insulin. With respect to glucose, the acute actions are the removal of glucose (primarily in muscle) and the suppression of glucose production (primarily in the liver). The top two panels show schematics for insulin response following its intravenous injection. It can be seen that insulin is cleared very rapidly (minutes) and the effect extends for no more than 2 h. After a subcutaneous injection (lower panels), circulating (rapid-acting) insulin lispro is not cleared completely for about 4 h, with its action extending past 6 h. Because the onset of action is much slower than with intravenous insulin, more insulin would be needed to initially cover a perturbation such as a meal. The additional insulin would be sequestered and released gradually (note the slow offset), past the time when the glucose excursion has waned. The surplus insulin would then contribute to hypoglycemia, unless rescue measures are taken. These dynamics thus set the limit of what can be accomplished with current

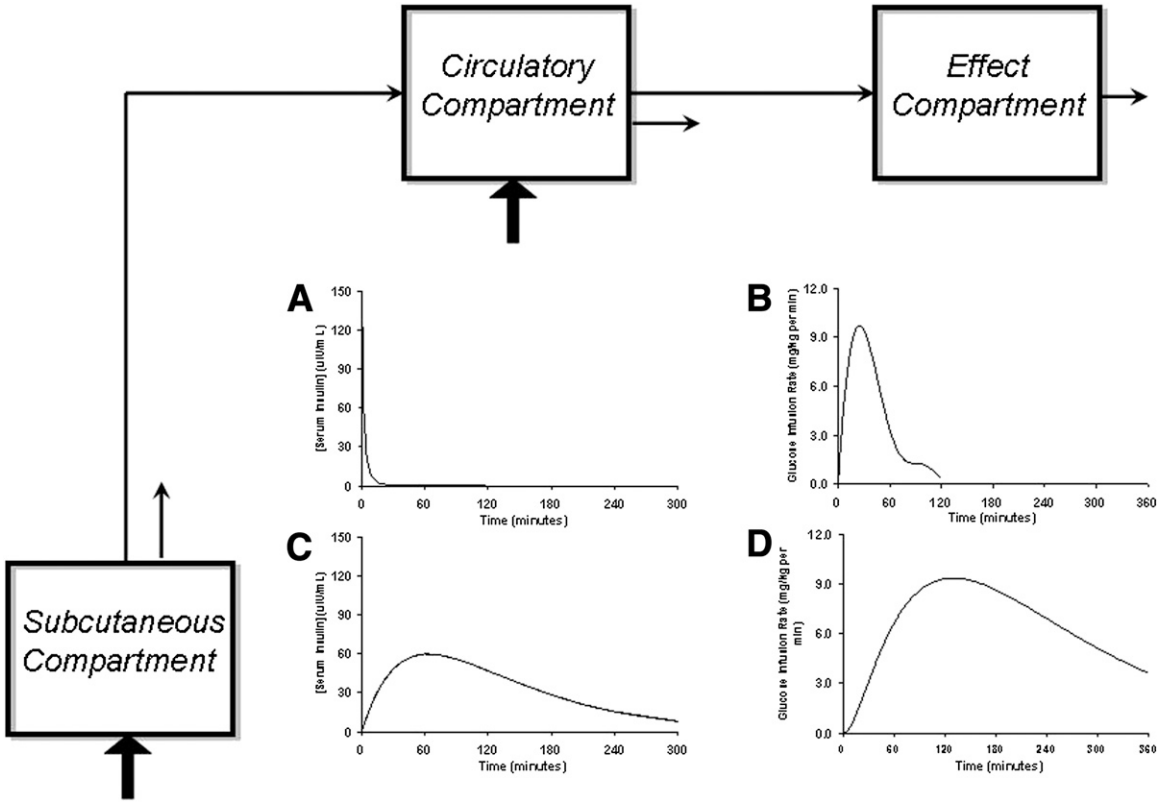

FIG. 1. A simplified model of insulin kinetics/dynamics is shown. Insulin enters either directly into the circulation or is subcutaneously administered. It enters the circulation from where it exerts its action—represented by the effect compartment. *A* and *B*: Insulin concentrations (*A*) and action (*B*; glucose infusion rates during euglycemic glucose clamp). Subcutaneously administered insulin first enters this compartment from where it is absorbed into the circulation. *C* and *D*: Plasma insulin concentrations (*C*) and action (*D*) after subcutaneous lispro insulin injection. Schematics in *A* and *B* are from our unpublished data; *C* and *D* are abstracted from ref. 12.

rapid-acting insulins, no matter how good the prediction of concentrations.

Strategies that have been or could be used to minimize hypoglycemia follow.

Mitigating the effect of insulin when hypoglycemia is projected. In the original controller of Albisser et al. (2), insulin was stopped and glucose infused to prevent hypoglycemia. This was possible since infusions were intravenous, which is not practicable long term. Alternately, automated subcutaneous glucagon administration has recently been implemented in a bihormonal controller, and preliminary data have demonstrated this to be effective (13)—at least under some conditions (14). As an alternative, Breton et al. (5) have implemented a high level safety supervision module (SSM) in their controller, which acts independently of the CTR modules and attenuates the infusion of insulin as a function of the risk of hypoglycemia. Alarms are also built in. Although the number of interventions by the SSM was not specified, clearly hypoglycemia is decreased relative to the degree of glycemic control, both for the sCTR and eCTR. Although it may degrade the optimization of, for example, the eCTR, the SSM is a critical and innovative modular approach to minimizing hypoglycemic events. The risk and possible extent of hypoglycemia can be extrapolated partly from estimates of "insulin on board," or the amount of insulin accumulated in the three compartments of Fig. 1 and their rates of removal.

Alternative models. Model predictive control of glucose concentration has also been implemented in diabetic subjects using an expanded version of the model shown in Fig. 1 (15). It incorporates the inherent nonlinearity of the glucoregulatory system by acknowledging that it is the parameters of glucose metabolism (clearance, transport, production) that are dependent on insulin in the effect compartment. As such models evolve, it will be important to compare them to each other to determine whether structural isomorphism of models with physiology provides improvements in control.

Accelerated insulin absorption. As seen in Fig. 1, the limiting factor in how insulin in a closed-loop setting responds to changes in glycemia is its absorption from subcutaneous sites. Rapid-acting insulins have decreased the absorption time but, as shown in Fig. 1 (insulin lispro), the pharmacokinetics/dynamics are still a long way from intravenous insulin. Further acceleration of absorption is needed. An example of such an effort is the intradermal administration of (rapid-acting) insulin (12), which demonstrates a more rapid onset of absorption of insulin lispro and therefore a more rapid action.

Tissue targeting. Insulin secretion takes place essentially into the portal vein. The liver is therefore the initial target of newly secreted insulin. This matters (16) both acutely for the suppression of hepatic glucose production and for the chronic maintenance of systemic insulin sensitivity. Nearly half of insulin administered intraperitoneally appears first in the portal vein (17). Intraperitoneal insulin has therefore been used for a long time in attempts to improve control (18), has been found to reduce severe hypoglycemia (19), and has been used in a closed loop system with a subcutaneous glucose sensor (20).

Ideal control by an artificial pancreas would therefore encompass autonomous (without patient input) control with normalization both of glycemia and of the glucose fluxes that contribute to it under all physiological circumstances. It would dramatically reduce the complications that arise from their dysregulation. Such closed-loop control without subject input to signal meals and their content, or to indicate the initiation of exercise, can likely only be achieved if insulin kinetics and action approach that of intravenous insulin (Fig. 1*A* and *B*)—accompanied by even more accurate glucose sensing. The pharmacokinetics/dynamics of rapid-acting analogs and formulations (Fig. 1*C* and *D*) will meanwhile set the limits of this control. Astute modeling, as demonstrated in ref. 5, will allow approaching these limits as closely as possible. The clinical and attainable aim of these interventions with current technologies is clearly to achieve intensive control that is consistent across the diabetic population. Achieving this goal would minimize patient decision-making, as well as diabetes-associated morbidities including hypoglycemia and progression of longer-term complications.

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