



NIH Public Access

Author Manuscript

IEEE Rev Biomed Eng. Author manuscript; available in PMC 2010 October 8.

Published in final edited form as:

IEEE Rev Biomed Eng. 2009 January 1; 2: 54–96. doi:10.1109/RBME.2009.2036073.

Diabetes: Models, Signals, and Control

Claudio Cobelli,

Department of Information Engineering, University of Padova, Via Gradenigo 6B, 35131 Padova, Italy

Chiara Dalla Man,

Department of Information Engineering, University of Padova, Via Gradenigo 6B, 35131 Padova, Italy

Giovanni Sparacino,

Department of Information Engineering, University of Padova, Via Gradenigo 6B, 35131 Padova, Italy

Lalo Magni,

Department of Computer Engineering and Systems Science, University of Pavia, Via Ferrata 1, 27100 Pavia, Italy

Giuseppe De Nicolao, and

Department of Computer Engineering and Systems Science, University of Pavia, Via Ferrata 1, 27100 Pavia, Italy

Boris P. Kovatchev

Department of Psychiatry and Neurobehavioral Sciences, P.O. Box 40888, University of Virginia, Charlottesville, VA 22903 USA

Claudio Cobelli: cobelli@dei.unipd.it

Abstract

The control of diabetes is an interdisciplinary endeavor, which includes a significant biomedical engineering component, with traditions of success beginning in the early 1960s. It began with modeling of the insulin-glucose system, and progressed to large-scale *in silico* experiments, and automated closed-loop control (artificial pancreas). Here, we follow these engineering efforts through the last, almost 50 years. We begin with the now classic minimal modeling approach and discuss a number of subsequent models, which have recently resulted in the first *in silico* simulation model accepted as substitute to animal trials in the quest for optimal diabetes control. We then review metabolic monitoring, with a particular emphasis on the new continuous glucose sensors, on the analyses of their time-series signals, and on the opportunities that they present for automation of diabetes control. Finally, we review control strategies that have been successfully employed *in vivo* or *in silico*, presenting a promise for the development of a future artificial pancreas and, in particular, discuss a modular architecture for building closed-loop control systems, including insulin delivery and patient safety supervision layers. We conclude with a brief discussion of the unique interactions between human physiology, behavioral events, engineering modeling and control relevant to diabetes.

Index Terms

Artificial pancreas; automatic control; identification; parameter estimation; physiological systems; sensors; signal processing

I. Introduction

Diabetes is a common metabolic disorder characterized by chronic hyperglycemia that leads to microvascular and macrovascular complications [1]–[5]. These complications include limb loss, blindness, ischemic heart disease, and end-stage renal disease. Diabetes is broadly classified into two categories, type 1 diabetes and type 2 diabetes. Both arise from complex interactions between genes and the environment, however their pathogenesis is distinct. Type 1 diabetes is the result of immune-mediated destruction of the beta-cells in the islets of Langerhans—the site of insulin secretion and production. In general, the disease occurs in childhood and adolescence (although it can occur at all ages) and is characterized by absolute insulin deficiency. Consequently, affected individuals require insulin therapy to control hyperglycemia and sustain life. As a rule, obesity does not play a part in the pathogenesis of type 1 diabetes, although obesity in type 1 diabetes is associated with the development of cardiovascular complications. In contrast, type 2 diabetes occurs because insulin secretion is inadequate and cannot overcome the prevailing defects in insulin action, resulting in hyperglycemia. Excess caloric intake, inactivity, and obesity all play parts in the pathogenesis of type 2 diabetes. In general, it is a disease that occurs with increasing frequency with increasing age and is uncommon before age 40 (although there are important exceptions). In addition, people with type 2 diabetes are more likely to have associated adverse cardiovascular risk factors such as dyslipidemia and hypertension. Prediabetes, i.e., impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is an intermediate condition in the transition between normality and diabetes. People with IGT or IFG are at high risk of progressing to type 2 diabetes, although this is not inevitable. Both type 2 diabetes and prediabetes are recognized risk factors for overt cardiovascular disease and related metabolic complications and are major components of health care spending [6], [7]. Rapid urbanization and societal affluence of global migrating populations has been suggested as major risk factors for the observed exploding prevalence of prediabetes and type 2 diabetes with consequent rising trends in cardiovascular risks [8]. IFG is a rapidly emerging form of prediabetes with a 20%–30% risk of progression to diabetes over 5–10 years. This risk is even greater if individuals have both IFG and IGT. Furthermore, both IFG and IGT are linked to increased risk for cardiovascular events [6], [7] in the Caucasian population. Ninety percent of the world population with diabetes is type 2 with type 1 diabetes comprising between 5%–10%. It is plausible that the relative frequency of type 1 and type 2 diabetes will change with rising trends in the prevalence of type 2 diabetes, obesity, and prediabetes in the developing world.

Over time, diabetes leads to complications, in particular: diabetic retinopathy, which leads to blindness; diabetic neuropathy, which increases of the risk of foot ulceration and limb loss; and diabetic nephropathy leading to kidney failure. In addition, there is an increased risk of heart disease and stroke with 50% of people with diabetes dying of cardiovascular disease and stroke. Finally, the overall risk of dying among people with diabetes is at least double the risk of their peers without diabetes. The World Health Organization (WHO) estimates than more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes. When ranked by cause-specific mortality, diabetes is the fifth cause of death, after communicable diseases, cardiovascular diseases, cancer and injury [8]. Almost 80% of diabetes death occurs in low- and middle-income countries. WHO projects that diabetes deaths will increase by more than 50% in the next ten years without urgent action. Most notably, diabetes is projected to increase by over 80% in upper-middle income countries between 2006 and 2015. Diabetes and its complications impose significant economic consequences on individuals, families, health systems, and countries. WHO estimates that over the next ten years (2005–2015) China will lose \$558 billion in national income due to heart disease, stroke, and diabetes alone.

Given the complexity of the disease it is not surprising that diabetes is fought with a battery of tools spanning over several disciplines, from cellular biology to pathophysiology to pharmacology to chemistry, physics, and engineering to transplantation to patient management to health care (Fig. 1). Dynamic system models are an essential ingredient of virtually all of these strategies. However, in this review we have to limit our scope; thus, we will not be able to discuss modeling in the areas of patient management [9], [10] and health care intervention strategies [11]–[14], or in the emerging area of systems biology [15], [16]. We will first focus on two mechanistic, physiologically based classes of models: minimal (coarse) models which describe the key components of the system functionality and are capable of measuring crucial processes of glucose metabolism and insulin control in health and diabetes; maximal (fine-grain) models which include comprehensively all available knowledge about system functionality and are capable to simulate the glucose-insulin system in diabetes, thus making it possible to create simulation scenarios whereby cost effective experiments can be conducted *in silico* to assess the efficacy of various treatment strategies. Then, we discuss the crucial role of models to enhance the interpretation of glucose and insulin time-series signals. Finally, we discuss recent strategies, in particular Model Predictive Control aiming for closed-loop control of type 1 diabetes (known as artificial pancreas), where models also play an important role.

II. Glucose-Insulin Control System

Glucose concentration is tightly regulated in health by a complex neuro-hormonal control system [1], [2]. Insulin is the primary regulator of glucose homeostasis, i.e., it promotes glucose utilization and inhibits glucose production. A battery of counterregulatory hormones are also at work, i.e., glucagon, epinephrine, cortisol, and growth hormone, which defend, on different time scales, the body from life-threatening hypoglycemia. Both hypoglycemia counterregulation and insulin control are neuro-mediated.

In this review, we focus on the glucose-insulin control system which is not only the most studied in terms of modeling, but also the one where modeling has had major impact in diabetes research and therapy. A high-level scheme of this system is shown in Fig. 2. Glucose is produced (mainly by the liver), distributed, and utilized in both insulin-independent (e.g., central nervous system and red blood cells) and insulin-dependent (muscle and adipose tissues) tissues. Insulin is secreted by pancreatic beta-cells, reaches the system circulation after liver degradation, and is peripherally cleared primarily by the kidneys. The glucose and insulin systems interact by feedback control signals, e.g., if a glucose perturbation occurs (after a meal), beta-cells secrete more insulin in response to increased plasma glucose concentration and in turn insulin signaling promotes glucose utilization and inhibits glucose production so as to bring rapidly and effectively plasma glucose to the preperturbation level. These control interactions are usually referred to as insulin sensitivity and beta-cell responsivity. In pathophysiology, the control is degraded. In type 2 diabetes this degradation is initially presented as prediabetes, characterized by progressive deterioration of both insulin sensitivity and beta-cell responsivity. In type 1 diabetes, beta-cells rapidly become virtually silent and insulin must be provided exogenously by the patient attempting to compensate for hyperglycemia. However, insulin treatment may risk potentially severe hypoglycemia and thus people with type 1 diabetes face a life-long behavior-controlled optimization problem: to maintain strict glycemic control and reduce hyperglycemia, without increasing their risk for hypoglycemia. Blood glucose is both the measurable result of this optimization and the principal feedback signal to the patient for his/her control of diabetes. Several types of models assist the optimization of diabetes control.

III. Minimal Models

A. Rationale

Minimal models must be parsimonious and describe the key components of system functionality. Thus, a sound modeling methodology must be used to select a valid model, i.e., a well founded and useful model which fulfills the purpose for which it was formulated [17]. Briefly, it is reasonable to assume that a good minimal model will not be a large-scale one: not every known substrate/hormone needs to be included because the macro-level response of the system would be relatively insensitive to many micro-level relationships. In addition, because it is not possible to estimate the values of all system parameters from *in vivo* dynamic data, many of the unit processes must be lumped together. Therefore, desirable features of a minimal model include: 1) physiologically based; 2) parameters that can be estimated with reasonable precision from a single dynamic response of the system; 3) parameters that vary within physiologically plausible ranges; and 4) ability to describe the dynamics of the system with the smallest number of identifiable parameters. Given a set of dynamic data, e.g., plasma concentration measurements after a perturbation, one generally proceeds by proposing a series of system models, beginning with the simplest and systematically increasing the complexity by including more known physiological detail. Each of the series of system models is then tested for *a priori* identifiability and subsequently numerically identified from experimental data in which samples are taken at frequent intervals, and for which measurements are made with utmost care (to reduce the influence of measurement error on the choice of a model). A number of quantitative tools are available to select the most parsimonious from a series of models, including testing the residuals, parameter precision, parsimony criteria, and parameter plausibility. Also of importance is the validation of the model-derived measures against those provided by an independent technique. All these methodological aspects have received systematic attention; books are available which cover in details all aspects of model identification and validation [17], [18]. In Section III-B, we discuss minimal models used to understand/measure glucose metabolism and insulin control; in Section III-C we discuss insulin secretion and glucose control; Section III-D reviews briefly some recent clinical studies where certain models discussed below have been successfully employed.

B. Glucose System

Understanding quantitatively the glucose system requires dynamic data, e.g., glucose or a tracer-glucose perturbation, and a system model, e.g., a compartmental model [18].

1) Insulin Action: Steady State—To study glucose kinetics in steady state, a tracer is needed. Tracer theory shows that linear time-variant compartmental models are accurate [19], thus allowing the use of a sum of exponential models (input–output models) to understand the number of compartments needed to describe the system. Insel *et al.* [20] were the first showing that a three compartment model is required to describe basal glucose kinetics (Fig. 3, top panel). This was later confirmed by Cobelli *et al.* [21], albeit a different model structure was postulated (Fig. 3, middle panel). The compartmental structure has been validated in animal experiments [22]. Both models incorporated *a priori* physiological knowledge to achieve unique identifiability. As noted in [21], the exchange kinetics between compartment 1 and 2 is much faster than between 1 and 3; thus, it is reasonable to use a simpler model (Fig. 3, bottom panel) with compartments 1 and 2 aggregated into a new single compartment 1 (e.g., after the first 2–3 min following tracer injection, only a two-compartment model is resolvable from the data).

Steady state allows a safe use of linear modeling strategies, so it is not surprising that the first quantitative studies on the effect of insulin on glucose kinetics were performed by artificially inducing an elevated insulin steady state with glucose clamp at basal level and performing a

tracer study. As an example, Fig. 4 shows the model-derived parametric representations of basal and elevated-insulin state obtained in [21] and [23] by identifying the tracer model of Fig. 3 (middle panel). If one compares the parameter values in the two steady states, an insulin effect on the rate constants into and out of compartment 3 is detected, slowly equilibrating tissues, presumably insulin-dependent tissues. In fact, not only parameter k_{03} , which describes irreversible removal, increases, but also the exchange parameters with the accessible pool, k_{31} and k_{13} , increase and decrease, respectively.

Multiple steady-state tracer data allow not only inference of the effect of insulin on glucose masses, fluxes, and rate parameters, but also on the timing and magnitude of insulin control [20]. A model of insulin kinetics was studied at basal glucose with the glucose clamp technique and it was shown, for the first time, that it is not plasma insulin but insulin in a large slowly equilibrating compartment that mimics the time course of glucose utilization (Fig. 5). The authors performed three separate experiments in each individual: primed continuous infusion of insulin, primed continuous infusion of a glucose tracer, and glucose clamp with a variable infusion, and were able to identify the 12-parameter combined glucose (tracer and trace) and insulin model of Fig. 6. The two steady-state glucose systems were quantified in detail and the model revealed their ability to quantify the action of insulin on glucose utilization (with glucose production suppressed). In order to describe glucose utilization (equal to the glucose infusion rate), this approach followed Sherwin *et al.* finding [24] where glucose utilization from compartment 2 was related to insulin in the remote compartment 3 by a linear function, $k_{03} = \alpha + \beta$ compartment 3, thus deriving a measure of insulin effectiveness, defined as the derivative of glucose utilization with respect to insulin in the remote compartment 3.

2) Insulin Action: Nonsteady State—Multiple steady-state tracer studies have been very informative, but also very complex in terms of required protocols and models. Is there a possibility to take advantage of the rich information content of a glucose dynamic perturbation, illustrated in Fig. 7, e.g., an intravenous glucose tolerance test (IVGTT), or a meal or an oral glucose tolerance test (OGTT)? In other words, is it possible to derive a measure of key control points of the glucose regulatory system, such as insulin sensitivity, i.e., the ability of insulin to control glucose production and utilization (Fig. 2), by simply exploiting the information content of the measured plasma glucose and insulin concentrations after the perturbation? The quest for answers inspired the minimal modeling strategy development at the end of the 1970s/early 1980s [25], [26], which has been, and still is, very successful [27], [28]. The simplest model describing the responses of plasma glucose and insulin to an oral or intravenous administration of glucose, was the pioneering study of Bolie in 1961 [29]

$$\begin{cases} \dot{G}(t) = -a_1 G(t) - a_2 I(t) + J(t) \\ \dot{I}(t) = a_3 G(t) - a_4 I(t) \end{cases} \quad (1)$$

where G , I denote plasma glucose and insulin, respectively, and J is glucose input which can be either an intravenous injection or the absorption rate of glucose during a meal or an oral glucose tolerance test. The model assumed that glucose disappearance was a linear function of both glucose and insulin, that insulin secretion was proportional to glucose, and that insulin disappeared in proportion to plasma insulin concentration. With various minor modifications this model has been used in conjunction with intravenous injections or infusions [29]–[31] and also during an oral glucose tolerance test [32]–[34] to obtain a four-parameter representation of glucose metabolism in various states of glucose intolerance, including diabetes. This model is *a priori* and *a posteriori* (numerically) identifiable, but it is too simple to be an adequate representation of the glucose-insulin system. First, the assumed linear relationship between insulin secretion and glucose has no experimental basis; in fact, the relationship between insulin

secretion rate and glucose is dynamically very complex. Second, this model does not explicitly consider the complex interactive control of hepatic glucose production and uptake by glucose and insulin. Thus, this first model can be criticized as representing complex metabolic interactions in too simplistic terms to adequately represent the complex dynamical patterns that characterize the response of the metabolic system to exogenous perturbation.

Dynamic perturbations: The modeling methodology outlined in the Section III-A was first employed to define the so-called glucose minimal model, the goal being the estimation of insulin sensitivity from an IVGTT [25]. To facilitate the model selection process, system decomposition or partition analysis was introduced [35]. In fact, to describe plasma glucose and insulin data measured in an organism there is the need to simultaneously model not only the glucose but also the insulin system and their interactions. This means that, in addition to model insulin action, one also has to model glucose-stimulated insulin secretion. Since models are, by definition, “wrong,” an error in the insulin secretion model would be compensated by an error in the insulin action model, thus introducing a bias in insulin sensitivity. To avoid this interference that is so common in physiological studies, the dynamic contribution of a subsystem can be eliminated. Such a “loop-opening” can be accomplished in a several ways by gross surgical manipulation of the systems, by using an external feedback loop to clamp the level of specific system variables, or by infusing certain substances that inhibit the endogenous elaboration of some feedback signals. All of these techniques are invasive, and most are not applicable to humans, at least on a routine basis. In contrast, model-based system decomposition [25], [35] is an artificial “loop cut”: the system is decomposed in two subsystems which are linked together by measured variables (Fig. 8); the insulin subsystem represents all tissues secreting, distributing and degrading insulin, and the glucose subsystem represents all tissues producing, distributing and metabolizing glucose. When the system is perturbed, e.g., by a glucose injection, and the time courses of plasma glucose, G and insulin I , are measured, then the time courses of G and I can be considered in terms as “input” (assumed known) and “output” (assumed noisy) of the beta-cell and glucose subsystems, respectively. Models are then proposed not for the whole system but for each of the subsystems, independently, thus considerably reducing the difficulties of the modeling exercise. This way, the difficulties of modeling the beta-cell do not interfere with modelling insulin action on glucose-consuming tissues and vice versa (see Section III-C). Seven models of increasing complexity were proposed to explain plasma glucose concentration by using plasma insulin as the known input. The chosen minimal model (Fig. 9, left panel) assumes that glucose kinetics can be described with one compartment (the early portion of glucose data is not considered) and that remote (with respect to plasma) insulin controls both net hepatic glucose balance and peripheral glucose disposal:

$$\begin{cases} \dot{Q}_1(t) = NHGB(Q(t), I'(t)) - R_d(Q(t), I'(t)) + D \cdot \delta(t) & Q(0) = Q_b \\ \dot{I}'(t) = -k_3 \cdot I'(t) + k_2 \cdot [I(t) - I_b] & I'(0) = 0 \\ G(t) = \frac{Q(t)}{V} \end{cases} \quad (2)$$

where Q is plasma glucose mass, with Q_b denoting its basal value; I is plasma insulin concentration, with I_b denoting its basal value, $I'(t)$ above basal remote insulin; D is the glucose dose; V is the glucose distribution volume, and k_2 and k_3 are rate parameters.

NHGB is the net hepatic glucose balance, which depends upon plasma glucose and remote insulin I'

$$\text{NHGB}(Q(t), I'(t)) = \text{NHGB}_0 - [k_5 + k_6 \cdot I'(t)] \cdot Q(t) \quad (3)$$

and R_d the rate of glucose disappearance from the peripheral tissues, also function of plasma glucose and remote insulin, I'

$$R_d(Q(t), I'(t)) = R_{d0} + [k_1 + k_4 \cdot I'(t)] \cdot Q(t). \quad (4)$$

This nonlinear model requires a reparameterization in order to become *a priori* uniquely identifiable (details in [17])

$$\begin{cases} \dot{Q}(t) = -[p_1 + X(t)] \cdot Q(t) + p_1 \cdot Q_b + D \cdot \delta(t) & Q(0) = Q_b \\ \dot{X}(t) = -p_2 \cdot X(t) + p_3 \cdot [I(t) - I_b] & X(0) = 0 \\ G(t) = \frac{Q(t)}{V} \end{cases} \quad (5)$$

with $X(t) = (k_4 + k_6)$. $I'(t)$; $p_1 = k_1 + k_5$; $p_2 = k_3$; $p_3 = k_2 \cdot (k_4 + k_6)$; $p_4 = \text{NHGB}_0 - R_{d0} = p_1 \cdot Q_b$. X is insulin action, p_1 is the fractional (i.e., per unit distribution volume) glucose effectiveness measuring glucose ability per se to promote glucose disposal and inhibit glucose production; p_2 is the rate constant of the remote insulin compartment from which insulin action is emanated; p_3 is a scale factor governing the amplitude of insulin action. The model allows the estimation of insulin sensitivity as

$$S_i^{\text{IVGTT}} = \frac{p_3}{p_2} \cdot V \quad (\text{dl/kg/min per } \mu\text{U/ml}). \quad (6)$$

A novel feature of the model was that insulin action did not emanate from plasma but from a compartment remote from plasma. This was a model ingredient requested by data and modeling methodology, in agreement with [24]. Only later this remote compartment was experimentally proven in dog studies to be the interstitial fluid [27].

In numerous studies reviewed in [27], insulin sensitivity estimated with the minimal model has been shown to strongly correlate to that measured with the euglycemic-hyperinsulinemic clamp [36], calculated as the steady-state glucose infusion rate divided by basal glucose times the above basal increase in insulin concentration. This technique is usually considered the gold standard to measure insulin sensitivity in humans. However, it is labor-intensive and requires glucose and insulin pumps to be frequently manipulated by a trained physician; moreover, the method is “nonphysiological” since in normal life conditions a constantly elevated insulin concentration not coordinated with a concomitant rise in glucose is never experienced. The minimal model has been widely employed by more than one thousand papers since its introduction in 1979 (counted until mid 2009); in the last five years alone around 55 papers/year have been published.

S_i^{IVGTT} is essentially a steady-state measure, i.e., it does not account for how fast or slow insulin action takes place. Recently, a new dynamic insulin sensitivity index, $S_i^{\text{D-IVGTT}}$, was introduced and shown to provide a more comprehensive picture of insulin action on glucose metabolism

than S_I^{IVGTT} , especially in diabetic subjects who exhibit both low and slow insulin action [37].

Glucose kinetics requires at least a two compartment description [21]. Undermodeling the system, i.e., using one instead of two compartments during the highly dynamic IVGTT perturbation, can introduce bias in glucose effectiveness and insulin sensitivity, being over- and under-estimated, respectively [38]–[40]. A two compartment glucose minimal model has been proposed [41], [42], but this requires *a priori* knowledge on the two glucose exchange parameters [21], [23], [43], [44]. By incorporating this *a priori* knowledge and using a Bayesian Maximum *a posteriori* estimator, the accuracy of both glucose effectiveness and insulin sensitivity has been shown to improve.

Like the glucose clamp technique, the IVGTT is nonphysiological, albeit to a lesser extent. Because it is important to measure insulin sensitivity in the presence of physiological changes in glucose and insulin concentrations, e.g., during a meal or OGTT, a different approach is needed to describe glucose kinetics in the gastrointestinal tract. The oral glucose minimal model (OMM) builds on the IVGTT minimal model by parametrically describing the rate of appearance of glucose into plasma (R_a) [45]. The model (Fig. 9, right panel) has a new mass balance equation

$$\dot{Q}(t) = -[p_1 + X(t)] \cdot Q(t) + p_1 \cdot Q_b + Ra(t, \alpha) \quad Q(0) = Q_b \quad (7)$$

with $\alpha = [\alpha_1, \alpha_2, \dots, \alpha_N]$ the parameter vector describing R_a . Insulin sensitivity, S_I^{ORAL} , can be derived from model parameters as reported in (6). A piecewise linear description for R_a with eight parameters is reasonably flexible to accommodate meal or OGTT data. The addition of parameters α renders the model more complex and it can be shown that the OMM is not *a priori* uniquely identifiable because V is nonidentifiable and p_1 is nonuniquely identifiable (two solutions). Thus, there is the need to assume V and p_1 to be known, usually fixed to population values. To improve numerical identifiability, a Maximum *a Posteriori* Bayesian estimator is used exploiting some prior on p_2 and a constraint on R_a , related to the total amount of glucose appearing in the circulation. S_I^{ORAL} has been precisely estimated and has been validated by comparison with both multiple tracer [46] and glucose clamp [47] techniques. Given the potential of the method for large scale clinical trials, a reduces protocol, e.g., a 2h-7 samples OGTT, has been designed and show to perform as well as a full protocol, e.g., a 5h-11 samples OGTT [54].

For both OGTT and MTT the new dynamic index $S_I^{D\text{ORAL}}$ has been shown to have the same beneficial effects on assessing insulin action as for IVGTT [37].

Dynamic perturbations with tracer: The IVGTT and oral minimal models are providing a composite “liver plus peripheral tissues” measure of insulin action (Fig. 9). Is it possible to dissect insulin action on the liver and peripheral tissues? Yes, if a glucose tracer is added to the IVGTT or meal/OGTT, thanks to the tracer’s ability to separate glucose utilization from production. The labeled IVGTT, both radio- (e.g., $[3 - {}^3\text{H}]\text{-glucose}$) and stable- (e.g., $[6, 6 - {}^2\text{H}_2]\text{-glucose}$) label, was first interpreted with one [48]–[51] and, subsequently, with a two-compartment minimal model [52], [53], [55], [56] which has been shown to be more accurate. The model proposed in [52] and [53] is shown in Fig. 10. It is assumed that insulin-independent glucose utilization takes place in the accessible compartment while insulin-dependent glucose utilization consists of two components, one constant, R_{d0} , and the other proportional to glycemia. Insulin-dependent glucose utilization is parametrically controlled by insulin in a

compartment remote from plasma. Details on model identifiability can be found in [52] and [53]. From the uniquely identifiable parameterization important indices such as glucose effectiveness, glucose clearance, and insulin sensitivity, can be estimated.

More recently, a labeled meal/OGTT was introduced and interpreted with the oral tracer minimal model [57]. A stable isotope glucose tracer (e.g., $[1 - ^{13}\text{C}]$ -glucose or $[6, 6 - ^2\text{H}_2]$ -glucose) is normally used and from the oral tracer dose and plasma measurements of glucose tracer one can calculate the exogenous glucose (G_{exo}), i.e., coming from the meal/OGTT.

The model describing G_{exo} data is given by [57]

$$\begin{cases} \dot{Q}^*(t) = -[p_1^* + X^*(t)] \cdot Q^*(t) + Ra(t, \alpha) & Q^*(0) = 0 \\ \dot{X}^*(t) = -p_3^* \cdot X^*(t) + p_3^* \cdot [I(t) - I_b] & X^*(0) = 0 \\ G_{\text{exo}}(t) = \frac{Q^*(t)}{V^*} \end{cases} \quad (8)$$

where * denotes tracer variables and parameters.

The disposal insulin sensitivity index, $S_I^{*\text{ORAL}}$, i.e., insulin action on glucose disposal only, is

$$S_I^{*\text{ORAL}} = \frac{p_3^*}{p_2^*} \cdot V^* \quad (\text{dl/kg/min per } \mu\text{U/ml}). \quad (9)$$

The model shares the same input, $Ra(t, \alpha)$, of the oral minimal model [(7)]. Thus, these two models can be simultaneously identified from the measurements G_{exo} and G and there is no need for using Bayesian priors for p_2 and p_2^* to improve numerical identifiability. However, knowledge of V^* and p_1^* is still needed.

$S_I^{*\text{ORAL}}$ has been validated against the multiple tracer [57] and the glucose clamp [47] techniques.

An unexpected finding commented in [47] was $S_I^{*\text{ORAL}}$ to be very close to (sometimes higher than) S_I^{ORAL} , which implies a negligible (or negative) action of insulin on the liver since hepatic insulin sensitivity $S_I^{\text{L ORAL}} = S_I^{\text{ORAL}} - S_I^{*\text{ORAL}}$. The principal suspect was the mechanistic description of endogenous glucose production (EGP), an ingredient of S_I^{ORAL} [58]. To address this issue, model-independent EGP profiles [59] were used.

The minimal model EGP description is

$$EGP(t) = EGP_b - GE^L \cdot [G(t) - G_b] - X^L(t) \cdot G(t) \quad EGP(0) = EGP_b \quad (10)$$

where EGP_b is the basal EGP, GE^L liver glucose effectiveness, G is glucose concentration, G_b its basal value, X^L is liver insulin action (deviation from basal) which follows the dynamic equation

$$\dot{X}^L(t) = -p_2 \cdot X^L(t) + p_3^L \cdot [I(t) - I_b] \quad X^L(0)=0 \quad (11)$$

where p_2 is a rate constant describing the dynamics of insulin action on glucose production (assumed the same as on glucose utilization) and p_3^L is the scale factor governing the amplitude of hepatic insulin action.

When tested against EGP data, the model failed, i.e., it was unable to fit the data, and provided imprecise and physiologically implausible parameter estimates. This finding supported our hypothesis that the mechanistic description of EGP included in the minimal model is incorrect, and this may be the cause of the unreliable (negative) estimate of hepatic insulin sensitivity obtained with the minimal model.

Other models were tested, with the goal to find an EGP description that is suitable for incorporation in the minimal model instead of (10); the best one was

$$EGP(t) = EGP_b - k_G \cdot [G(t) - G_b] - X^L(t) - X^{Der}(t) \quad EGP(0)=EGP_b \quad (12)$$

with X_L defined as

$$\begin{cases} \dot{X}_1(t) = -p_2^L \cdot X_1(t) + p_3^L \cdot [I(t) - I_b] & X_1(0)=0 \\ \dot{X}^L(t) = -p_2^L \cdot X^L(t) + p_3^L \cdot X_1(t) & X^L(0)=0 \end{cases} \quad (13)$$

and

$$X^{Der}(t) = \begin{cases} k_{GR} \cdot \frac{dG(t)}{dt}, & \text{if } \frac{dG(t)}{dt} \geq 0 \\ 0, & \text{if } \frac{dG(t)}{dt} < 0 \end{cases} \quad (14)$$

where p_2^L is a rate constant describing the dynamics of insulin action on glucose production (assumed here to be different from that on glucose utilization), p_3^L is the scale factor governing the amplitude of hepatic insulin action, and k_{GR} is a parameter governing the magnitude of glucose derivative control.

This model is different from the minimal-model EGP description. First, insulin action it is not multiplied by glucose concentration, which means that glucose and insulin act independently on the liver. In fact, while insulin modulates glucose utilization by moving the glucose transporter GLUT-4 to cell membrane and thus the glucose utilization clearly depends on glucose level, the insulin-stimulated inhibition of production follows different paths. In addition, insulin action on glucose production has a different time course from insulin signalling on glucose disposal. Finally, the model incorporates the accepted notion that a portal insulin signal (here is approximated by glucose derivative) controls the rapid suppression of EGP [60]. Hepatic insulin sensitivity is given by

$$S_I^{L\text{ORAL}} = \frac{p_3^L}{p_2^L} \cdot \frac{1}{G_b} \quad (\text{dl/kg/min per } \mu\text{U/ml}) \quad (15)$$

with G_b basal glucose concentration and p_2^L and p_3^L defined above.

This model has been recently coupled with oral tracer minimal model (unpublished); thus, hepatic [$S_I^{L\text{ORAL}}$, (15)] and disposal insulin sensitivity ($S_I^{*\text{ORAL}}$, (9)] can be simultaneously estimated from a single-tracer experiment using total glucose, exogenous glucose, and insulin concentrations. The whole-body insulin sensitivity is $S_I = S_I^{*\text{ORAL}} + S_I^{L\text{ORAL}}$, thus, the relative role of the liver versus periphery can be determined in percentage. Our results show that during a meal $S_I^{L\text{ORAL}}$ represents 34% of total insulin action.

Both unlabelled and tracer IVGTT and oral minimal models are powerful tools to measure a number of indices characterizing the control that glucose and insulin exert on glucose metabolism. These indices are of utmost importance for the understanding and treatment of pathophysiology, from glucose intolerance to diabetes. Even more importantly, the combined use of the unlabelled and labeled minimal models, thanks to the tracer-to-tracee indistinguishability principle [19], allows us to move from a parametric indices to a flux portrait.

Consider the IVGTT probe. Glucose utilization can be calculated from the uniquely identifiable parameterization of the model of Fig. 10 as

$$U(t) = k_{01}(t) \cdot Q_1(t) + [k_{02} + X^*(t)] \cdot Q_2(t) \quad (16)$$

where Q_1 and Q_2 are glucose masses in compartments 1 and 2, respectively.

Endogenous glucose production can be calculated by using the endogenous glucose concentration, G_{end} , i.e., the component of total glucose concentration measured in plasma due to glucose production, which can be calculated in a model-independent fashion [61]. G_{end} is related to the endogenous glucose production, EGP, by the integral equation

$$G_{\text{end}}(t) = \int_0^t h(t, \tau) \cdot EGP(\tau) \cdot d\tau + G_b \cdot h(t, 0) \quad (17)$$

where $h(t, \tau)$ is the time-varying impulse response of the glucose system, given by the tracer minimal model of Fig. 10, and G_b is basal glucose. EGP can be estimated by deconvolution, e.g., the stochastic deconvolution method [62]. In [61], EGP estimation has been validated against that obtained by a dual tracer-to-tracee clamp technique, which provided a virtually model-independent estimation (Fig. 11). A similar modeling strategy has also been used in [63].

Recently, Krudys *et al.* [64] have proposed a structural model of EGP during an IVGTT. EGP depends on the amount of releasable glucose in the liver and has an inhibitory function which is related to remote insulin. The model reconstructed EGP was validated against that obtained

via deconvolution and the tracer-to-tracee clamp technique [64]. The model also provided some indices of glucose and insulin control on EGP which have been recently refined [65].

As for the IVGTT, relevant glucose fluxes can also be derived from meal and OGTT data. Glucose rate of appearance, R_a , can be reconstructed from the simultaneous identification of the two models of (7) and (8). Moreover, glucose utilization can be calculated as

$$U(t) = [p_1^* + X^*(t)] \cdot Q(t). \quad (18)$$

The time course of endogenous glucose production $EGP(t)$ can be reconstructed with the model described in [58] and reported in (12). In this case, in addition to EGP profile, the model provides quantitative indices of hepatic insulin sensitivity [(15)] and glucose effectiveness as well as (unlike the Krudys model) an index quantifying hepatic insulin sensitivity.

Alternatively, $EGP(t)$ can also be estimated by stochastic deconvolution from endogenous glucose concentration data, G_{end} [66]. Unlike IVGTT, during meal and OGTT the single compartment model can be used to describe glucose kinetics; thus, $h(t, \tau)$ is the impulse response of the system of (8). Moreover, if a single glucose tracer is orally administered, $h(t, \tau)$ can be determined by fixing V^* and p_1^* to population values.

EGP and R_a time courses reconstructed with both models and deconvolution have been validated against the triple tracer technique [59], [67], [68] which provided virtually model-independent estimates of such glucose fluxes (Fig. 12) [58].

3) From Whole-Body to Organ/Tissue—While whole-body models can provide important quantitative information on insulin action, it is important but at the same time remarkably difficult, to noninvasively measure the processes of glucose transport and metabolism at the organ level. A crucial target tissue of glucose metabolism is the skeletal muscle. Impaired insulin transport within the muscle is a well-recognized characteristic of a number of metabolic diseases, including type 2 diabetes, obesity, hypertension, and cardiovascular disease [69]. Understanding its causes requires us to segregate and quantify *in situ* the major individual steps of glucose processing, particularly those of glucose delivery, transport in and out of the cell, and phosphorylation (Fig. 13).

There are two major experimental techniques to tackle this problem, both employing tracers with glucose metabolism at steady state. The classical experimental approach is based on the multiple tracer dilution [70]. This model consists of the simultaneous injection, upstream of the organ, of more than one tracer which allows the separate monitoring of the individual steps of glucose metabolism. For example, in the case when the objective of the experiment is the measure of all the elementary processes (convection, diffusion, transport, and metabolism), usually one can simultaneously inject upstream of the organ (artery) and measure downstream (vein) a first tracer that is distributed only in the capillary bed (intravascular tracer), a second that is subject to the bidirectional exchange through the capillary membrane (extracellular tracer), a third that also permeates the cell through the sarcolemma (permeating not metabolizable tracer), and, finally, a fourth that is also metabolized (permeating metabolizable tracer). These tracers must obviously be distinguishable once they reach the organ outflow. The venous outflow curves must then be analyzed by means of a physiological system model. More recently, the positron emission tomography (PET) noninvasive imaging technique was proposed. Using appropriate tracers, PET can provide highly specific and rich biochemical information if applied in dynamic mode, i.e., sequential tissue images acquired following a bolus injection of tracer so that the time course of the tissue metabolism can be monitored.

Again, a physiological system model is needed to interpret the data. Unlike the multiple tracer dilution technique, here tracers cannot be injected simultaneously but only sequentially.

Multiple tracer dilution data can be interpreted with both linear distributed parameter (see reviews [18] and [71] and compartmental organ models [72]. The only application to glucose metabolism of distributed parameter models has been in an isolated and perfused heart [70]. In contrast and despite short history, compartmental organ models have been more intensively applied to interpret multiple tracer dilution data in the human skeletal muscle. A compartmental model has been proposed [73] describing the transmembrane transport of glucose. The model has been developed from multiple tracer dilution data obtained in human skeletal muscle *in vivo* using two tracers, one extracellular ($L - [^3H]\text{-glucose}$) and the other permeant, nonmetabolizable ($[^{14}\text{C}]\text{-3-O-methyl-D-glucose}$). This allows us to estimate with very good precision the rate constants of glucose transport into and out of the cell. Consequently, this model allowed us to study the enhancing effect of insulin on muscle glucose transport parameters in nondiabetic subjects [73] and identified the presence of a localized defect in insulin control in non-insulin-dependent diabetic (NIDD) patients [74]. This compartmental model has been extended [76] to describe the kinetics of a third tracer, permeant nonmetabolizable ($[^3\text{H}]\text{-glucose}$). The gain obtained by adding to the experimental protocol a third tracer is immense. This ultimately allowed us to quantify a model of the tracee and therefore study not only the rate constants of transport and phosphorylation but also the bidirectional glucose flux through the cell membrane, the phosphorylation flux, and the intracellular concentration, in nondiabetic, obese and diabetic subjects [75]–[77]. This allowed important physiological results to be obtained. Among these, it was possible to show that the insulin control on both transmembrane transport and phosphorylation flux in subjects affected by NIDDM is much less efficient with respect to nondiabetic subjects [76], [77]. Therefore, the model enabled demonstration of the fact that cellular transport plays a very important role in the insulin resistance associated with NIDDM.

PET data can be analyzed by several modeling strategies with regional compartmental modeling being the most powerful approach to connect organ or tissue concentration data into measures of physiological parameters. In this respect, the brain glucose model by Sokoloff *et al.* [78] has been a landmark. The selected tracer for studying glucose metabolism in skeletal muscle (but also in the brain and myocardium) is $[^{18}\text{F}]\text{-fluorodeoxyglucose}$ ($[^{18}\text{F}]FDG$), a glucose analog. The ideal tracer would be $[^{11}\text{C}]\text{-glucose}$ but the interpretative model by having to account for all metabolic products along the glycolysis and glycogen synthetic pathways would be unreasonable from the limited information content of PET data. The advantage of $[^{18}\text{F}]FDG$ is that a simpler model can be adopted. In fact, $[^{18}\text{F}]FDG$ once in the tissue, similarly to glucose, can either be transported back to plasma or can be phosphorylated to $[^{18}\text{F}]FDG - 6 - \text{phosphate}$, $[^{18}\text{F}]FDG - 6 - \text{P}$. The advantage is that $[^{18}\text{F}]FDG - 6 - \text{P}$ is trapped in the tissue and released very slowly. In other words, $[^{18}\text{F}]FDG - 6 - \text{P}$ cannot be metabolized further, while glucose-6-P does so along the glycolysis and glycogen synthesis pathways. The major disadvantage of $[^{18}\text{F}]FDG$ is the necessity to correct for the differences in transport and phosphorylation between the analog $[^{18}\text{F}]FDG$ and glucose. A correction factor called lumped constant (LC) can be employed to convert $[^{18}\text{F}]FDG$ fractional uptake (but not the $[^{18}\text{F}]FDG$ transport rate parameters) to that of glucose. LC values in human skeletal muscle are available [79], [80]. In order to provide rate constants of transport and phosphorylation of $[^{18}\text{F}]FDG$ in skeletal muscle, a four-compartment model (plasma, extracellular, tissue $[^{18}\text{F}]FDG$, and $[^{18}\text{F}]FDG - 6 - \text{P}$) with five rate constants has been proposed [81]. The model (Fig. 14) is described by

$$\begin{aligned}\dot{C}_c(t) &= K_1 C_p(t) - (k_2 + k_3) C_c(t) + k_4 C_e(t) \quad C_c(0) = 0 \\ \dot{C}_e(t) &= k_3 C_c(t) - (k_4 + k_5) C_e(t) \quad C_e(0) = 0 \\ \dot{C}_m(t) &= k_5 C_e(t) \quad C_m(0) = 0\end{aligned}\tag{19}$$

$$C(t) = (1 - V_b)(C_c(t) + C_e(t) + C_m(t)) + V_b C_b(t)\tag{20}$$

where C_p is $[^{18}\text{F}]$ FDG plasma arterial concentration, C_c is extracellular concentration of $[^{18}\text{F}]$ FDG normalized to tissue volume, C_e $[^{18}\text{F}]$ FDG is tissue concentration, C_m $[^{18}\text{F}]$ FDG – $6 - P$ is tissue concentration, C is total ^{18}F activity concentration in the ROI, K_1 [ml/ml/min] and k_2 [min^{-1}] are the exchanges between plasma and extracellular space, k_3 [min^{-1}], k_4 [min^{-1}] is the rate of transport in and out of cell, and k_5 [min^{-1}] is the rate of phosphorylation. V_b is the fractional blood volume in the region of interest, and C_b is the whole blood tracer concentration. From the model one can calculate the fractional uptake of $[^{18}\text{F}]$ FDG, K [ml/ml/min]

$$K = \frac{K_1 k_3 k_5}{k_2 k_4 + k_2 k_5 + k_3 k_5}\tag{21}$$

and, by using LC value and the glucose basal plasma concentration value, the glucose fractional uptake. $[^{18}\text{F}]$ FDG rate constants of transport and phosphorylation are inefficient in obesity and type 2 diabetes, but these defects can be substantially reversed with weight loss [82].

To move to a glucose representation a multi-tracer positron emission tomography (PET) imaging method is needed [83], which allows the simultaneous assessment of blood flow, glucose transport, and phosphorylation in the skeletal muscle. The method employs three different PET tracers (Fig. 15) injected at different times, and allows us to quantify blood flow from $[^{15}\text{O}]$ H₂O images with one- compartment two-rate constant model; glucose transport from $[^{11}\text{C}]$ 3-OMG images with a three compartment four-rate constant model; and, finally, glucose phosphorylation by combining $[^{18}\text{F}]$ FDG fractional uptake with $[^{11}\text{C}]$ 3-OMG rate constants. The $[^{11}\text{C}]$ 3-OMG model is a simpler version of that of (19), (20) since $[^{11}\text{C}]$ 3-OMG is not phosphorylated. This multi-tracer model-based PET imaging method has shown that glucose transport from plasma into interstitial space is virtually identical to tissue perfusion and not affected by insulin; insulin significantly increases both glucose transport and phosphorylation modulating distribution of control among delivery, transport, and phosphorylation (glucose delivery and transport contribute nearly equally to the control of glucose uptake accounting for 90% of control together); predominately oxidative muscles (soleus) have higher perfusion and higher capacity for glucose phosphorylation than less oxidative muscles (tibialis).

C. Insulin System

Here, we describe some models of the insulin system and the control exerted by glucose on insulin secretion.

1) Insulin Kinetics—To study insulin kinetics in the steady state a tracer would be the ideal probe. Tracer studies have been performed, e.g., by using radioactive isotopes of iodine or hydrogen, but ideal tracer prerequisites such as tracer-tracee indistinguishability and nonnegligible perturbation, are not completely met. The majority of insulin kinetic studies have been performed by pulse injection or infusion. However, the administration of a nontracer

amount of insulin has two undesired effects: first, it may induce hypoglycemia, which in turn could trigger counterregulatory response that may affect insulin kinetics; second, it inhibits insulin secretion, thus the measured insulin concentration contains a time-varying endogenous component. These confounding effects can be avoided by designing a rather complex experiment, where hypoglycemia is prevented by variable glucose infusion (glucose clamp technique), and endogenous insulin secretion is suppressed by somatostatin infusion.

In the physiological concentration range (up to 100–150 $\mu\text{U}/\text{ml}$) where insulin kinetic is approximately linear, various linear compartmental models have been proposed [84], following the landmark model of Sherwin *et al.* [24] (already discussed, see Fig. 6, upper panel). Some of these models are shown in Fig. 16. The two-compartment structure is derived by noting that compartments 1 and 2 in the model of Fig. 6 (upper panel) are in rapid equilibrium. SR^{post} is the posthepatic insulin secretion rate, i.e., the flux of newly secreted insulin that reaches plasma after the first passage through the liver. The two models differ in terms of the site of irreversible loss: plasma (Fig. 17, top panel), or peripheral tissues (Fig. 16, middle panel). Both models are *a priori* uniquely identifiable. Typical numerical values of their parameters are shown in the figure. In the situation where a two-compartment model cannot be resolved from the data, the single compartment model (Fig. 16, bottom panel) can be used.

In the supraphysiological range, nonlinear or linear time-varying insulin kinetics model are more appropriate. A relatively simple nonlinear two-compartment model, similar to that of Fig. 16, upper panel, has been proposed by Frost *et al.* [85], with linear transfer rate k_{12} and k_{21} but nonlinear irreversible loss k_{01} described by the Michaelis-Menten relation. However, the relatively high number of model parameters (six) poses some problems in deriving precise estimates for all of them. A nonlinear five-compartment model has been proposed by Hovorka *et al.* [86], which also incorporates a description of insulin kinetic at the receptor level. Alternatively, linear time-varying models has also been formulated, e.g., that of Morishima *et al.* [87], which assumes constant k_{12} and k_{21} and time-varying $k_{01}(t)$.

2) Insulin Secretion—The problem of estimating the secretion profile *in vivo* during perturbation from plasma concentration measurements is a classic input estimation problem for which deconvolution offers the classic solution. However, it is not possible to infer on pancreatic secretion from plasma insulin concentration data; it is only possible to derive its component appearing in plasma, or the posthepatic insulin secretion, which is approximately equal to 50% of the pancreatic secretion. This problem can be bypassed if C-peptide concentration is measured during the perturbation and used to estimate insulin secretion since C-peptide is secreted equimolarly with insulin, but it is extracted by the liver to a negligible extent (Fig. 17). In other words, plasma C-peptide concentration well reflects, apart from the rapid liver dynamics, C-peptide pancreatic secretion, which coincides with insulin secretion.

Since there is solid evidence that C-peptide kinetics are linear in a wide range of concentration, the relationship between above basal pancreatic secretion (SR, the input), and the above basal C-peptide concentration measurements (C, the output) is the convolution integral

$$C(t) = \int_0^t h(t - \tau) \cdot SR(\tau) \cdot d\tau \quad (22)$$

where h is the impulse response function of the system. SR profile during a perturbation can be reconstructed by solving the inverse problem, which is deriving SR by deconvolution, given C and h . The knowledge of the impulse response h is a prerequisite. This requires an additional experiment on the same subject, consisting of a bolus of C-peptide and a concomitant infusion

of somatostatin to inhibit endogenous C-peptide secretion. Usually, C-peptide concentration data are then approximated by a sum of two exponential models that, after normalization to the C-peptide dose, provide the impulse response function [88], [96]. Deconvolution methods have been applied to estimate the secretion profile in various physiological states [89], [90] and during both intravenous and oral glucose tolerance tests [91]–[93].

To eliminate the need for a separate experiment to evaluate the impulse response function, a method has been proposed [94] to derive C-peptide kinetic parameters in an individual based on data about his or her age, weight, height and gender. Secretion reconstructed by deconvolution, with the impulse function evaluated from either the C-peptide bolus experiment or the population parameters are similar [94], indicating that the population values allow a good prediction of individual secretion profiles.

As for pancreatic insulin secretion, an indirect measurement approach is essential to quantify hepatic insulin extraction in humans since the direct measurement requires invasive protocols, with catheters placed in a artery and hepatic vein [84]. Deconvolution offers a possible solution since by comparing pancreatic secretion rate (SR) obtained from C-peptide data and posthepatic secretion (SR^{post}) obtained from insulin data—one can estimate hepatic extraction E as

$$E(t) = \frac{SR(t) - SR^{post}(t)}{SR(t)}. \quad (23)$$

Estimation of SR^{post} by deconvolution is straightforward if insulin levels are in the physiological range since the kinetic model is linear, while it becomes more problematic if insulin levels are supraphysiological. In this last case, the link between SR^{post} and insulin concentration (I) is given by

$$I(t) = \int_0^t g(t, \tau) \cdot SR^{post}(\tau) \cdot d\tau \quad (24)$$

with $g(t, \tau)$ representing the impulsive response of the linear time-varying insulin kinetic system.

3) Beta-Cell Function—Deconvolution allows us to measure in a virtually model-independent way insulin secretion after a glucose stimulus. However, giving a mechanistic description of pancreatic insulin secretion as a function of plasma glucose concentration has the advantage to provide quantitative indices of beta-cell function.

The minimal modeling methodology is similar to that employed to derive the glucose minimal model: the system is decomposed in two subsystems (Fig. 8.), but this time we look at the insulin subsystem with plasma glucose, G , considered the “input” (assumed known) and C-peptide, C , the “output” (assumed noisy).

Since the secretion model is identified on C-peptide measurements taken in plasma, it must be integrated into a model of whole-body C-peptide kinetics, which has two compartments [88].

During IVGTT, the above-basal insulin secretion [97] is given by (Fig. 18, left)

$$SR(t) = m \cdot F(t) \quad (25)$$

with F the ready releasable insulin described by

$$\dot{F}(t) = -m \cdot F(t) + Y(G, t) \quad F(0) = F_0 \quad (26)$$

with F_0 the amount of insulin released immediately after the glucose stimulus; $Y(G, t)$ is the provision of new insulin, which depends on glucose level

$$\dot{Y}(G, t) = -\frac{1}{T} \cdot [Y(G, t) - Y(G, \infty)] \quad Y(0) = 0 \quad (27)$$

and

$$Y(G, \infty) = \begin{cases} 0 & \text{if } G(t) < h \\ \beta \cdot [G(t) - h] & \text{if } G(t) \geq h \end{cases} \quad . \quad (28)$$

In other words, insulin secretion consists of two components: first and second phase secretion. First phase secretion is portrayed by a rapidly turning-over compartment (2 min) and likely represents exocytosis of previously primed insulin secretory granules (commonly called readily releasable). It exerts derivative control, since it is proportional to the rate of increase of glucose from basal up to the maximum through a parameter [28], Φ_1 , which defines the first responsivity index

$$\Phi_1 = \frac{F_0}{\Delta G} \quad (29)$$

with ΔG the difference between peak and basal glucose concentration.

Second phase insulin secretion is believed to be derived from the provision and/or docking of new insulin secretory granules that occurs in response to a given (i.e., proportional to) glucose concentration, through a parameter Φ_2 , which defines the second phase responsivity index, and reaching the releasable pool with a delay time constant, T

$$\Phi_2 = \beta. \quad (30)$$

The meaning of Φ_2 and T can be explained by analyzing model parameters under the above-basal step increase of glucose: provision tends with time constant T towards a steady state, which is linearly related to the glucose step size through parameter Φ_2 . T presumably represents the time required for new “readily releasable” granules to dock, be primed, then exocytosed. In addition to Φ_1 and Φ_2 , a basal responsivity index can also be calculated, Φ_b . Finally, a single total index of stimulated beta-cell responsivity, Φ_{IVGTT} , can be derived by combining Φ_1 and Φ_2 . Of note, in [97] it has been shown that population values are also a good predictor of the

individual kinetic parameters. However, additional uncertainty is brought in by the population approach [98], which can be taken into account into a Bayesian setting via Markov Chain Monte Carlo [99].

Beta-cell function can also be assessed from an oral test, such as meal or OGTT. An oral glucose test differs from IVGTT in several important aspects including the route of delivery with the associated incretin hormone secretion, the more physiological and smoother changes in glucose, insulin, and C-peptide concentrations, and, during a mixed meal, the presence of non-glucose nutrients stimulation, i.e., amino acids and fat. Various models have been proposed to assess beta-cell function during a meal and OGTT [95], [100]–[102]. All of them share the model of C-peptide kinetics described above, but differ on the assumption on how glucose controls the secretion. The oral C-peptide minimal model proposed by Breda *et al.* [101] Fig. 18 (right) maintains basically all of the previous model ingredients employed in the IVGTT model, with the exception of the fast turning over insulin releasable pool (F , which is not evident under these conditions) to describe the data. In particular, both a rate of change of glucose component of insulin secretion and a delay between glucose stimulus and beta-cell response have been shown to be necessary to fit the data [103]. Model equations are

$$SR(t)=Y(G, t)+SR_d(G, t) \quad (31)$$

with $Y(G, t)$ described by (27) and (28), also called a static component of insulin secretion, and $SR_d(G, t)$ the dynamic component of insulin secretion

$$SR_d(G, t)=\begin{cases} K \cdot \frac{dG(t)}{dt} & \text{if } \frac{dG(t)}{dt} \geq 0 \\ 0 & \text{if } \frac{dG(t)}{dt} < 0 \end{cases}. \quad (32)$$

Thus, this model features a dynamic component that senses the rate of change of glucose concentration, and a static component that represents the release of insulin that, after a delay, occurs in proportion to prevailing glucose concentration. Similarly to the IVGTT, where first, Φ_1 , and second phase, Φ_2 , beta-cell responsivity indices were defined, from the oral model dynamic, Φ_d ($= K$), and static Φ_s ($= \beta$) responsivity indices can be derived. Basal responsivity index, Φ_b , can be obtained as a ratio between basal secretion and basal glucose. A total responsivity index, Φ_{ORAL} , which combines Φ_d and Φ_s , can also be derived.

The model has been successfully used by Toffolo *et al.* [104] during “up&down” intravenous glucose infusion and by Steil *et al.* [105] for describing hyperglycemic clamp C-peptide data as well as meals, thus providing further independent evidence for its validity. In contrast to the IVGTT model where the derivative component of first phase secretion was operative only during the first few minutes as the plasma glucose concentration increased from a “basal” to “maximal” concentration, the relatively gradual pattern of glucose appearance observed during oral tests necessitated the presence of a secretion component proportional to glucose rate of change that contributed to the model for the first 60–90 minutes. In addition, and similar to IVGTT, a component of insulin secretion proportional to glucose, characterized by a delay time T (presumably reflecting at least in part the time it takes for new granules to reach the releasable pool), that contributed throughout the experimental period, was also necessary. As discussed above, Φ_d is markedly different from its IVGTT counterparts Φ_1 . In fact, during IVGTT first phase component only contributed during the first 4–6 minutes and the proportional component for the rest of test. Thus, it is probable that Φ_d and Φ_1 are assessing different aspects of the insulin secretory pathway. In particular, Φ_d presumably could also reflect multiple distal steps including the rate of granule docking, priming as well as exocytosis.

The model proposed by Hovorka *et al.* [95] assumes an instantaneous linear control of glucose on insulin secretion; i.e., there is no delay between glucose stimulus and beta-cell response. The model proposed by Cretti *et al.* [100] describes insulin secretion with the static component of glucose control of the C-peptide minimal model; thus, it is characterized by a delay but does not include any dynamic, i.e., rate of change, glucose control. Interestingly, the same authors have recently included a dynamic control to describe first phase secretion in a subsequent report [106]. The model proposed by Mari *et al.* [102], similarly to the oral model shown in Fig. 18 right, has both a proportional component and a component responsive to the rate of change of glucose, but there is no delay between glucose signaling and supply of new insulin to the circulation. The authors choose to account for the expected inability of a proportional plus derivative glucose control to account for C-peptide measurements with a time-varying term correcting only the static component of insulin secretion, which has been called the potentiation factor. In simple words, the potentiation factor is a time-varying correction term that mathematically compensates for the proportional plus derivative description deficiency.

4) Disposition Index—It is worth noting that beta-cell function needs to be interpreted in light of the prevailing insulin sensitivity. One possibility is to resort to a normalization of beta-cell function based on the disposition index paradigm, first introduced in 1981 [35], and recently revisited in [28], where beta-cell function is multiplied by insulin sensitivity. This concept, self-evident in Fig. 8, is more clearly illustrated in Fig. 20 (left). While regulation of carbohydrate tolerance is undoubtedly more complex, it is conceived that glucose tolerance of an individual is related to the product of beta-cell function and insulin sensitivity. In essence, different values of tolerance are represented by different hyperbolas, i.e., $DI = \text{beta-cell function} \times \text{insulin sensitivity} = \text{const}$. If an individual's beta-cells respond to a decrease in insulin sensitivity by adequately increasing insulin secretion (state II) the product of beta-cell function and insulin sensitivity (the disposition index) is unchanged, and normal glucose tolerance is retained. In contrast, if there is an inadequate compensatory increase in beta-cell function to the decreased insulin sensitivity (state 2), the individual develops glucose intolerance. Thanks to its intuitive and reasonable grounds, this measure of beta-cell functionality, which was first introduced for IVGTT, has become the method of choice also with the meal and OGTT test. Thus, disposition indices DI_1 , DI_2 , DI_{IVGTT} or DI_d , DI_s ,

DI_{ORAL} can be calculated by multiplying responsivity indices Φ_1 , Φ_2 , Φ_{IVGTT} by S_i^{IVGTT} (for IVGTT) or by multiplying responsivity indices Φ_d , Φ_s , Φ_{ORAL} by S_i^{ORAL} (for meal/OGTT) to determine if the first phase, second phase, global beta-cell function is appropriate in light of the prevailing insulin sensitivity. Another important use of the disposition index paradigm is the monitoring in time of the individual components of tolerance and the assessment of different treatment strategies. It is easily appreciated from Fig. 20 (right) the importance of segregating glucose tolerance into its individual components of beta-cell responsivity and insulin sensitivity: subject x is intolerant due to its poor beta-cell function while subject y has a poor insulin sensitivity and these two individuals need opposite therapy vectors. However, the glucose-insulin feedback system is more complex than the hyperbola paradigm. The relation between beta-cell function and insulin sensitivity is certainly describable by a nonlinear inverse relationship but is in all likelihood more complex than a simple hyperbola, i.e., the relation is more likely $DI = \text{beta-cell function} \times (\text{insulin sensitivity})^\alpha = \text{constant}$. In addition, this simple concept hides several methodological issues which, unless fully appreciated, could lead to errors in interpretation. Some critical questions are: is it true that the hyperbolic relationship holds in a population? How should the disposition indices be used in comparing populations, i.e., should the individual values be averaged, or should the disposition index be estimated directly in the population? How should the population variability accounted for? Also, since the effect of insulin on peripheral tissues is also determined by the amount of insulin to which the tissue is exposed, hepatic insulin extraction may come into play (see the following) and

provide yet another dimension to the relationship between insulin secretion and action portrayed in Fig. 20. Some of these aspects have been recently examined in [28] and [107].

5) Hepatic Insulin Extraction—Minimal models also provide an approach to assess hepatic insulin extraction. In fact, SR can be assessed from the model of C-peptide kinetics and secretion identified from C-peptide and glucose measured during IVGTT or meal or OGTT. By following a similar approach, SR^{post} can be assessed by insulin and glucose data. In particular, insulin-modified IVGTT experiment, i.e., an IVGTT associated with short insulin infusion given between 20 and 25 minutes after the glucose bolus, offers definitive advantages with respect to the standard IVGTT since the insulin infusion generates an additional disappearance curve that greatly facilitates the simultaneous estimation of insulin kinetic and secretion parameters. Hepatic insulin extraction can then be calculated from SR and SR^{post} profiles [106]. During meal and OGTT the situation is more complicated, however, a recent study [108] proposes a population model, which, similarly to the widely used Van Cauter formulas [94], allows us to calculate insulin kinetic parameters from subject anthropometric characteristic, such age, gender, body surface area, etc., avoiding the necessity to infuse exogenous insulin. From pre- and post-hepatic insulin secretion rates, hepatic insulin extraction time course can be derived as for the IVGTT. In addition, from pre- and post-hepatic model parameters an index of hepatic extraction can also be calculated [108], [109].

D. Clinical Studies

It is well beyond the scope of this contribution to review model-based pathophysiological studies. However, it may be helpful for the reader to refer to specific instances where an answer to a diabetes-related question has been provided by a systematic use of models. For instance, the battery of oral glucose, C-peptide, and insulin models have been used in studying: the effect of age and gender on glucose metabolism [59]; the effect of anti-aging drugs [110]; the influence of ethnicity [111]; insulin sensitivity and beta-cell function in nondiabetic [112] and obese [113] adolescents; the pathogenesis of prediabetes [114]–[116] and type 2 diabetes [117], [118].

IV Maximal Models

A. Rationale

In contrast to minimal, maximal (fine-grain) models are comprehensive descriptions attempting to fully implement the body of knowledge about metabolic regulation into a generally large, nonlinear model of high order, with a large number of parameters. This class of models cannot, in general, be identified, i.e., without massive experimental investigation on a single individual it is not possible to relate with confidence alterations in the dynamics of blood-borne substances to specific changes in parameters of a comprehensive model. This means that these models are not generally useful for the quantification of specific metabolic relationships—their utility is in the possibility for system simulation.

Simulation is a powerful investigative tool, particularly in the engineering disciplines where the system structure and function is usually “known” and equations can be written based on first principles. In contrast, a physiological system is largely “unknown” in terms of structure and function, i.e., equations can always be written but the problem is model validity. Although strategies for validation of a complex (versus simple) model have been delineated [17], [119], the difficulties of the problem remain.

In metabolism and diabetes, large scale models have been of value as research tool, i.e., to test a theory or incompatibilities of theories. A classic is the insulin secretion model of Grodsky [120] where in order to describe insulin secretion patterns in response to a variety of glucose

stimuli, he postulated that insulin granules were not a homogeneous pool. While the threshold hypothesis he introduced (i.e., each granule has a certain glucose threshold above which it releases the content) has gained little support from subsequent experiments, the non-homogeneity of insulin-containing granules pool is today an accepted notion and various beta-cell biology theories have been put forward. Another example is the glucose-insulin simulation model by Sturis *et al.* [121], which offered an explanation of why wide ultradian oscillations (period of ~120 min in humans) occur in insulin and glucose profiles in various physiological conditions, stating that they can originate from the interaction between the glucose and insulin subsystems without the need to invoke the presence of a pancreatic pacemaker operating at these frequencies.

Another important area for maximal models is their use as test beds for examining the empirical validity of models intended for clinical applications. For instance, in [122] and [123] the consequences of undermodeling the glucose system by using the classic IVGTT single compartment minimal model has been studied by using a richer IVGTT two compartment glucose-insulin simulation model.

Finally, simulation models have been proven useful in a teaching setting as heuristic devices providing easy and quick answers to “what...if” questions. Some good examples on simulators being an efficient library of physiological knowledge are [124]–[126].

A classic simulation is *in silico* experimentation, which in disciplines like engineering is carried out in everyday life; a recent success is the Boeing 777 jetliner, which has been recognized as the first airplane to be 100% digitally designed and assembled in a computer simulation environment. This important use of simulation has not had the expected impact in metabolism and diabetes. However, there are situations where *in silico* experiments with complex models could be of enormous value. In fact, it is often not possible, appropriate, convenient, or desirable to perform an experiment on the glucose system, because it cannot be done at all, or it is too difficult, too dangerous, or unethical. In such cases, simulation offers an alternative way of *in silico* experimenting on the system. Simulation models have been published and used to examine various aspects of diabetes control, e.g., for assessing different control algorithms and different insulin infusion routes [122], [127]–[138]. Although the confidence in their results is certainly higher than that obtained using as simulator the glucose minimal model [25] (extensively misused for this purpose and recently being the core of the Medtronic Virtual Patient [139]), the impact has been very modest. All these models are average population models and as a result their capabilities are generally limited to prediction of population averages that would be observed during clinical trials. An average-model approach is not realistic for *in silico* experimentation. A different approach is needed in order to provide valuable information about the safety and the limitations of control algorithms, or to guide and focus emphasis of clinical studies, or to rule out ineffective control scenarios in a cost-effective manner prior to human use. It is necessary to have a diabetes simulator equipped with a cohort of *in silico* subjects that spans sufficiently well the observed interperson variability of key metabolic parameters in the general population of people, say with type 1 or type 2 diabetes.

In the following, we discuss in detail a whole-body glucose-insulin simulator and an organ/cellular-level insulin secretion simulator. The healthy state glucose-insulin simulator is presented first, then prediabetes and type 2 diabetes version are discussed. Finally, we describe the type 1 diabetes simulator, which was recently accepted by FDA as a substitute of preclinical animal trials for certain insulin treatments [140].

B. Healthy State Simulator

The rationale was to identify the glucose-insulin meal simulation model [137], developed on average data, in each of 204 nondiabetic individuals. All these subjects underwent a triple tracer

meal protocol which provided virtually model-independent estimates of crucial fluxes of the system, i.e., the rate of appearance in plasma of ingested glucose, glucose production, glucose utilization, and insulin secretion [59]. This flux information was key to developing with confidence a large scale maximal model, i.e., with only plasma glucose and insulin concentration this exercise is practically impossible since one cannot obtain a good description of the multiple system fluxes (Fig. 20). Fig. 21 shows the database and allows appreciation of the relevance of interindividual variability. Thanks to this rich “concentration and flux” representation, the glucose-insulin system model was identified by resorting to a subsystem forcing function strategy, which minimizes structural uncertainties in modeling the various subsystems. The rationale is shown in Fig. 22. As an example consider the glucose utilization subsystem (see [137] for details). Glucose kinetics is described with a two compartment model. Insulin-independent utilization takes place in the first compartment, is constant, and represents glucose uptake by the brain and erythrocytes (F_{cns})

$$U_{ii}(t) = F_{cns}. \quad (33)$$

Insulin-dependent utilization takes place in the remote compartment and depends nonlinearly (Michaelis–Menten) from glucose in the tissues

$$U_{id}(t) = \frac{V_m(X(t)) \cdot G_t(t)}{K_m + G_t(t)} \quad (34)$$

where $G_t(t)$ is glucose mass in the insulin-dependent tissues and $V_m(X(t))$ is assumed to be linearly dependent on a remote insulin $X(t)$

$$V_m(X(t)) = V_{m0} + V_{mx} \cdot X(t). \quad (35)$$

X (pmol/L) is insulin in the interstitial fluid described by

$$\dot{X}(t) = -p_{2U} \cdot X(t) + p_{2U}[I(t) - I_b] \quad X(0) = 0 \quad (36)$$

where I is plasma insulin, suffix b denotes basal state, and p_{2U} is rate constant of insulin action on the peripheral glucose utilization.

Total glucose utilization U is thus

$$U(t) = U_{ii}(t) + U_{id}(t). \quad (37)$$

For each of the 204 subjects included in the database, the glucose kinetics model equipped with (33)–(37) was numerically identified using the measured glucose utilization (U) and concentration (G) as output and plasma insulin, endogenous glucose production and glucose rate of appearance as known inputs (Fig. 22, bottom left panel).

The other subsystems of Fig. 22 have been identified following a similar strategy (more details can be found in [137]).

The model consists of 12 differential equations and 35 parameters, 26 of which are free and nine derived from steady-state constraints.

From the 204 subjects model parameters and their joint probability distribution in the healthy population were reconstructed. Since most parameters were approximately log-normally distributed, this probability distribution is uniquely defined by the average vector and the covariance matrix of the log-transformed parameter vector. Given the joint distribution, virtual subjects can be generated, i.e., say 1000 realizations of the log-transformed parameter vector can be sampled randomly from the multivariate normal distribution, thereby producing 1000 virtual *in silico* “subjects.”

Fig. 23 shows examples of daily glucose patterns in some generated *in silico* subjects.

C. Prediabetes and Type 2 Diabetes Simulator

A prediabetes and type 2 diabetes simulators would be very useful to assess the efficacy of various drug therapies before performing experiments in humans. A triple tracer protocol meal data base, similar to that available in nondiabetics, was available for 35 prediabetic and 23 type 2 diabetic subjects. The same modeling strategy developed for the Healthy State Simulator was adopted. The model consists of 12 differential equation and 35 parameters (26 of which are free) [137], [138]. The simulator can generate cohorts of virtual subjects, thus enabling various diabetes treatments to be assessed rapidly in cost-effective *in silico* experiments.

D. Type 1 Diabetes Simulator

A type 1 diabetes version of the simulator would be critical for the preclinical testing of control strategies in artificial pancreas studies. Arguably, large-scale simulations would account better for intersubject variability than small-size animal trials and would allow for more extensive testing of the limits and robustness of control algorithms. A first necessary modification was the substitution of insulin secretion subsystem with an exogenous insulin delivery subsystem, e.g., a subcutaneous (sc) insulin pump an associated model of insulin kinetics and absorption. Subcutaneous insulin transport has been extensively modeled and quantitative models exist [142], [285], [286] which allowed both the estimation of the timing and duration of insulin action from insulin pump data, and their computer simulation in *in silico* experiments. One approach includes a two-compartment model approximating nonmonomeric and monomeric insulin fractions in the subcutaneous space [285], which can serve as a base for the translation of the insulin signal from the pump to insulin in the circulation.

A much more difficult task was the description of the inter-subject variability, since even single-tracer studies in type 1 diabetes are scarce. In order to obtain parameter joint distributions in type 1 diabetes from those in the healthy state, we assumed that the intersubject variability was the same (same covariance matrix), but certain clinically relevant modifications were introduced in the average vector. The model consists of 13 differential equation and 35 parameters (26 of which are free and nine derived from steady-state constraints). The simulator has been tested by several experiments in adults, adolescents, and children to assess the validity of the cohort of *in silico* subjects. The simulator (Fig. 24) is equipped with 100 virtual adults, 100 adolescents, and 100 children, spanning the variability of the T1DM population observed *in vivo*. In addition to virtual “subjects,” the simulator is equipped with mechanisms reproducing CGM errors, e.g., virtual “sensors” that can be placed on the “subjects” for *in silico* closed-loop control experiments. Subcutaneous insulin delivery is modeled as well, which allows placing virtual “insulin pumps” on the subjects for full-scale open- or closed-loop control experiments with any predefined treatment scenario. In January 2008, the simulator was accepted by the Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas studies and has been

adopted by the JDRF Artificial Pancreas Consortium as a primary test bed for new closed-loop control algorithms. The simulator was immediately put to its intended use with the *in silico* testing of a new Model Predictive Control algorithm [141], and in April 2008, an investigational device exemption (IDE) was granted by the FDA for a closed-loop control clinical trial (see Section VI). This IDE was issued solely on the basis of *in silico* testing of the safety and effectiveness of the proposed artificial pancreas algorithm, an event that sets a precedent for future preclinical studies. Thus, the following paradigm has emerged: 1) *in silico* modeling could produce credible preclinical results that could substitute certain animal trials and 2) *in silico* testing yields these results in a fraction of the time and the cost required for animal trials. However, one needs to emphasize that good *in silico* performance of a control algorithm does not guarantee *in vivo* performance; it only helps to test extreme situations and the stability of the algorithm and to rule out inefficient scenarios. Thus, computer simulation is only a prerequisite to, but not a substitute for, clinical trials.

In addition to the simulator described above [137], [247], another simulation environment has been developed with the core glucose-insulin model detailed in [136] which is used by the University of Cambridge in the JDRF Artificial Pancreas Program. The model [136] has been built for being the model ingredient of a closed loop MPC algorithm. The model, coupled to a subcutaneous insulin kinetic model [142], consists of 11 differential equations and 20 parameters. The strategy to describe the population variability differs from that described above. The simulator presently includes 18 type 1 synthetic subjects defined by 20 parameter sets. A subset of six parameters was estimated from experimental data collected in type 1 subjects and the remaining 14 obtained from the literature. An important use has been the assessment of hypoglycemia and hyperglycemia risk during overnight with closed-loop Model Predictive Control versus open-loop insulin delivery [143].

E. Insulin Secretion

Another useful application of simulation models is hypothesis pilot testing. For instance, simulation models have been used to investigate the cellular mechanisms which lead pancreatic beta-cells to secrete insulin. Beta-cells show bursting electrical activity and oscillatory calcium levels and insulin secretion and modeling has contributed significantly to the understanding of the generation of these rhythmic patterns (see reviews in [144] and [145]). However, surprisingly little work has been done on detailed modeling insulin secretion. Already in the 1970s, Grodsky [120] and Cerasi *et al.* [146], among others, modeled the pancreatic insulin response to various kinds of glucose stimuli, but these models were phenomenological due to the limited knowledge of the beta-cell biology at that time. Only recently has the knowledge of the control of the movement and fusion of insulin granules increased to a level where it is possible to formulate mechanistically based models. Here, we discuss some recent developments on cellular simulation models of insulin secretion serving as research tool at organ level to pilot-test new theories.

Grodsky [120] proposed that insulin was located in “packets,” plausibly the insulin containing granules, but also possibly entire beta-cells. Some of the insulin was stored in a reserve pool, while other insulin packets were located in a labile pool, ready for release in response to glucose. The labile pool was responsible for the first phase of insulin secretion [120], while the reserve pool was responsible for creating a sustained second phase. This basic distinction has been, at least partly, confirmed when the packets are identified with granules [147], [148]. Moreover, Grodsky [120] assumed that the labile pool is heterogeneous in the sense that the packets in the pool have different thresholds with respect to glucose, beyond which they release their content. This assumption was necessary for explaining the so-called staircase experiment, where the glucose concentration was stepped up and each step gave rise to a peak of insulin. There is no supporting evidence for granules having different thresholds [149], but

Grodsky [120] mentioned that cells apparently have different thresholds based on electrophysiological measurements. Later, Jonkers and Henquin [150] showed that the number of active cells is a sigmoidal function of the glucose concentration, as assumed by Grodsky [120] or the threshold distribution.

Recently, Pedersen *et al.* [151] unified the threshold distribution for cells with the pool description for granules, thus providing an updated version of Grodsky's model, which also takes into account recent knowledge of beta-cell biology. The model scheme is shown in Fig. 25 (top panel). It includes mobilization of secretory granules from a very large reserve pool to the cell periphery, where they attach to the plasma membrane (docking). The granules can mature further (priming) and attach to calcium channels, thus entering the "readily releasable pool" (RRP). Calcium influx provides the signal triggering membrane fusion, and the insulin molecules can then be released into the extracellular space. Also included is the possibility of so-called kiss-and-run exocytosis, where the fusion pore reseals before the granule cargo is released. For the mathematical formulation the mobilized and docked pools have been lumped into a single "intermediate pool" (Fig. 25, lower panel). The glucose-dependent increase in the number of cells showing a calcium signal [150] was included by distinguishing between readily releasable granules in silent and active cells. Therefore, the RRP is heterogeneous in the sense that only granules residing in cells with a threshold for calcium activity below the ambient glucose concentration are allowed to fuse. Hence, the model provides a biologically founded explanation for the heterogeneity assumed by Grodsky [120] and it is able to simulate the characteristic biphasic insulin secretion pattern in response to a step in glucose stimulation, as well as the secretory profile of the staircase stimulation protocol (Fig. 26). The model is a classic compartmental one, except from the description of the RRP. The intermediate pool I develops according to the mass-balance equation

$$\frac{dI(t)}{dt} = M(G, t) - r \cdot I(t) - p^+ \cdot I(t) + p^- \cdot \int_0^\infty h(g, t) \cdot dg \quad (38)$$

where M is the mobilization flux, and r is the rate of reinternalization. The last term describes the flux of granules loosing the capacity of rapid exocytosis. Mobilization has been modeled similarly to Grodsky (1972) by a first-order differential equation.

The RRP is described by a time-varying density function $h(g, t)$ indicating the amount of insulin in the RRP in beta-cells with a threshold between g and $g + dg$. Granules are primed with rate p^+ and are assumed to loose the capacity of rapid exocytosis with rate p^- . Moreover, if the granule is in a triggered beta-cell it will fuse with rate f^+ . This leads to the equation

$$\frac{dh(g, t)}{dt} = p^+ \cdot I(t) \cdot j(g) - p^- \cdot h(g, t) - f^+ \cdot h(g, t) \cdot \theta(G - g) \quad (39)$$

Here, $\theta(G - g)$ is the Heaviside step function, which is 1 for $G > g$ and zero otherwise, indicating that fusion only occurs when the threshold is reached. I is total intermediate pool, and the priming flux $p^+ I$ distributes among cells according to the fraction of cells with threshold g described by the time-constant function $j(g)$. Thus, priming is assumed to occur with the same rate in all cells, but the model takes into account the fraction of cells with the corresponding threshold. The secretion rate is proportional to the size of the fused pool F (Fig. 25, bottom panel).

An interesting property of beta-cells that was included in Grodsky's model is so-called derivative control, i.e., the fact that the pancreas senses not only the glucose concentration but also its rate of change. Modeling at whole-body level has shown that this property is necessary for explaining data, e.g., both IVGTT and OGTT&MTT [101], [152]. Derivative control arises from the threshold hypothesis as explained by Grodsky [120] and in greater detail by Licko [153]. Due to the threshold on cells, the model by Pedersen [151] also possesses derivative control, which is only active when $dG/dt > 0$. It is of interest to understand, and is currently under investigation, how the subcellular parameters relate to beta-cell responsiveness measured by whole-body minimal models, i.e., Φ_1 , Φ_2 for IVGTT and Φ_d , Φ_s for OGTT&MTT, e.g., which steps of glucose stimulated insulin secretion are impaired in diabetics.

V. Signals

A. Rationale

Historically, the use of signal analysis techniques in the study of diabetes physiology started in the late 1970s with the quantification of blood glucose (BG) concentration and other substances, such as insulin, C-peptide, and glucagon during in-hospital monitoring. Some of the principal approaches are discussed in Section V-B.

Routine field observation of BG fluctuation began with the advent of self-monitoring (SMBG), which typically provides 2–5 BG capillary BG samples per day analyzed by portable glucometers. This opened the possibility of studying individuals' glucose fluctuation (and thus the effectiveness of their therapy) during natural conditions for extended periods of time. The principal methods for analysis of SMBG data include statistical approaches and risk assessment and are presented in Section V-C.

In the last ten years, new continuous glucose monitoring (CGM) systems capable of monitoring glucose concentration frequently (e.g., every 5 minutes) for several days have begun to emerge. Most of CGM systems are minimally invasive and portable, measuring glucose subcutaneously and assessing BG concentration indirectly via interstitial fluid sampling. Even if certain accuracy issues are still unsolved, CGM sensors open new possibilities in diabetes management, showing encouraging treatment results and potential for real-time prevention of hypo- and hyper-glycemia. Methodologies and applications concerning CGM sensor data are discussed in Section V-D.

B. Physiological Signals

1) Glucose-Insulin Oscillations—According to a recent review, four time scales of BG fluctuation have been identified: 5–15 min corresponding to pulsatile secretion of insulin; 60–120 min corresponding to intrinsic oscillatory phenomena; 150–500 min accounting for meals, insulin injection, and other external schedules, and ~700 min corresponding to circadian rhythm [154]. The Nyquist sampling period sufficient to follow the intrinsic blood glucose dynamics in diabetes was estimated at 10 minutes [155]. The temporal relationship between insulin oscillation and plasma glucose excursions has been attributed to a feedback loop between beta cell action and endogenous glucose production [156]. It has been established that the ability of glucose to entrain ultradian insulin secretion patterns is disturbed in diabetic and prediabetic individuals [157]–[159], but the exact role of oscillations in the glucose regulation systems is still under investigation [160].

2) Peak Detection and Spectral/Correlation Analysis—Most of the approaches employed in the 1980s and early 1990s to study glucose and insulin oscillations can be traced back to peak-detection methods and spectral/correlation analysis. Peak-detection methods

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

provide information on pulse amplitude and location [161]–[164], while spectral/correlation analysis seeks to identify cycles in time series [165], [166]. These methods can be easily modified to assess the concordance of peaks and the cross-spectrum/correlation function in order to study the dynamic relationship between paired time series, e.g., glucose and insulin [167]–[170]. However, in situations where pulses are brief, small in amplitude, and irregular, peak detection is difficult. Spectral/correlation analysis is hard to apply to short and noisy time series, or when the observed cycles are inherently irregular. Finally, both peak-detection and spectral/correlation analysis ignore the morphology of the pulses and cannot detect e.g., changes in the pattern of episodic insulin release which is characteristic of some physiological and patho-physiological states. Overcoming these limitations may require the use of different data analysis tools, such as the ApEn described as follows.

3) Hormone Pulsatility and Approximate Entropy—Approximate Entropy (ApEn) is a method developed in the early 1990s [171] to quantify the “regularity” of a time series. ApEn detects changes in underlying episodic behavior not reflected in peak occurrences or amplitudes. To do so, ApEn assigns a nonnegative number to a time series, with larger values corresponding to greater apparent temporal irregularity in the hormone release pattern over time. Two input parameters, m and r , must be specified to compute ApEn, which then measures the logarithmic likelihood that runs in the patterns that are close (within r) for m contiguous observations remain close (within the same tolerance r) on the next incremental comparisons [172]. An extension of this theory has also been proposed to analyze the synchrony of two time series belonging to the same physiologic network through the Cross Approximate Entropy index [173].

To a large extent, ApEn is complementary to peak detection and spectral analysis in that it evaluates both dominant and subordinate patterns in concentration-time series [174]. Given its ability to detect changes in underlying episodic behavior which will not be reflected in pulse occurrences or their characteristics, ApEn acts as a “barometer” of feedback system change in many coupled systems. ApEn has been utilized to probe the regulation of several hormones including growth hormone [175], aldosterone [176], cortisol [177], insulin [178], and glucagon [179]. Specific to diabetes, it has been reported that insulin secretion patterns are more irregular in healthy older and obese individuals and patients with prediabetes or type II diabetes mellitus than in young, nonobese, nondiabetic subjects [156]–[159]. It was hypothesized that this may in part reflect failure of negative feedback by glucose, and that disorderly insulin secretion patterns in aging and prediabetes accompany insulin resistance [160]. Methodologically it has also been discussed how, e.g., in hormone secretion studies, the discrimination power of ApEn from plasma concentration time series can be influenced by their kinetics [180], [181].

C. Self Monitoring of Blood Glucose

1) Blood Glucose Self-Monitoring—Blood glucose self-monitoring (SMBG) is typically comprised of several episodic BG readings per day. When rather large time intervals are monitored in a given patient, several tools can be used to analyze SMBG time series. For instance, in [182] and [183], the expected cyclo-stationary behavior of glucose was investigated by decomposing the SMBG time series into a cyclic component, that expresses the daily pattern, and a trend component, that describes long-term variations, by a Bayesian method implemented by Monte Carlo Markov chains. Another approach, widely accepted to analyze SMBG time series, is risk analysis. A key element to the interpretation of SMBG signals is the use of the BG Risk Space, which was introduced over ten years ago and was based on a transformation of the BG scale that corrects an inherent asymmetry of the hypoglycemic versus hyperglycemic ranges [184]. The steps of the SMBG data risk analysis are as follows.

2) Symmetrization of BG Scale—The BG measurement scale is asymmetric: the hypoglycemic range (below 70 mg/dl) is much narrower numerically than the hyperglycemic range ($BG > 180$ mg/dl). This asymmetry creates a number of computational problems and challenges. For example, a BG excursion from 180 to 240 mg/dl is much larger numerically than a BG excursion from 70 to 50 mg/dl, yet the second excursion carries much greater risk to the patient. The asymmetry of the BG scale can be corrected by using

$$f(BG, \alpha, \beta) = [(\ln(BG))^{\alpha} - \beta] \quad (40)$$

where $\alpha, \beta > 0$ are parameters determined from the assumptions

$$A1: f(600, \alpha, \beta) = -f(20, \alpha, \beta) \quad (41)$$

and

$$A2: f(180, \alpha, \beta) = -f(70, \alpha, \beta). \quad (42)$$

By multiplying by a third parameter γ we fix the minimal and maximal values of the transformed BG range at $-\sqrt{10}$ and $\sqrt{10}$ respectively. When solved numerically under the restriction $\alpha > 0$, these equations give: $\alpha = 1.084$, $\beta = 5.381$, and $\gamma = 1.509$. These parameters are sample independent and were fixed in 1997 [184].

3) BG Risk Space—After fixing the parameters of $f(BG)$, we define the quadratic function $r(BG) = 10.f(BG)^2$, which defines the BG risk space. The function $r(BG)$ ranges from 0 to 100. Its minimum value is 0 and is achieved at $BG = 112.5$ mg/dl, a safe euglycemic BG reading, while its maximum is reached at the extreme ends of the BG scale 20 mg/dl and 600 mg/dl. Thus, $r(BG)$ can be interpreted as a measure of the risk associated with a certain BG level. The left branch of this parabola identifies the risk of hypoglycemia, while the right branch identifies the risk of hyperglycemia [185]. Fig. 27 visualizes this concept by a 72-hour CGM trace of a patient with T1DM: each CGM reading is processed in two steps: 1) application of the symmetrization formula [184], and 2) application of the quadratic risk function that assigns increasing weights to larger BG deviations towards hypo- or hyper-glycemia [185]. As seen in Fig. 27, a hypoglycemic episode occurring at hour 30 of observation is hardly visible in BG scale, but is well pronounced in risk space. Conversely, a hyperglycemic excursion at hour 54 is numerically reduced in risk space, which corresponds to the notion of relative risk it carries.

The conversion of the BG data into risk values has profound implications not only for the interpretation of the BG signal, but for control as well because similar emphasis is placed on the hypoglycemic and hyperglycemic ranges; the normal BG range (70–180 mg/dl) is given less weight, thus variability contained within normal range carries less risk than excursions outside of this range; excursions into extreme hypo- and hyper-glycemia get progressively increasing risk values.

4) SMBG-Based Risk Metrics—In addition, the conversion of BG data into risk space has resulted in established metrics for the risk for hypoglycemia and glucose variability in general. Let x_1, x_2, \dots, x_n be a series of n BG readings, and let:

1. $r_l(BG) = r(BG)$ if $f(BG) < 0$ and 0 otherwise;

2. $rh(BG) = r(BG)$ if $f(BG) > 0$ and 0 otherwise.

The Low Blood Glucose [Risk] Index (LBGI) and the High BG [Risk] Index (HBGI) are then defined as:

$$LBGI = \frac{1}{n} \sum_{i=1}^n rl(x_i) \quad (43)$$

and

$$HBGI = \frac{1}{n} \sum_{i=1}^n rh(x_i) \quad (44)$$

respectively.

The LBGI, which is based on the left branch of the BG Risk Function $r(BG)$ has been validated as an excellent predictor of future significant hypoglycemia [186], [187]. The LBGI also provides means for classification of the subjects with regard to their long-term risk for hypoglycemia into: minimal, low, moderate and high-risk groups, with LBGI of below 1.1, 1.1–2.5, 2.5–5.0, and above 5.0, respectively [187], and has been used for short term prediction of hypoglycemia as well [188], [189]. By definition, the LBGI is independent from hyperglycemic episodes.

Further, we define the Average Daily Risk Range (ADRR), which is a measure of overall glycemic variability based on $r(BG)$ and computed as follows.

1. Let $x_{11}, x_{12}, \dots, x_{n1}$ be a series of n_1 SMBG readings taken on Day 1.
2. Let $x_{12}, x_{22}, \dots, x_{n2}$ be a series of n_2 SMBG readings taken on Day 2.
-
3. Let $x_{1M}, x_{2M}, \dots, x_{nM}$ be a series of n_M SMBG readings taken on Day M.

Thus, $n_1, n_2, \dots, n_m > 3$ and the number of days of observation M is between 14 and 42 (two to six weeks). Further, let

$$LRi = \max(rl(x_{1i}), rl(x_{2i}), \dots, rl(x_{ni}))$$

and

$$HRi = \max(rh(x_{1i}), rh(x_{2i}), \dots, rh(x_{ni})) \text{ for day } #i; i=1, 2, \dots, M.$$

The Average Daily Risk Range is then defined as

$$ADRR = \frac{1}{M} \sum_{i=1}^M [LR^i + HR^i]. \quad (45)$$

The ADRR has been shown superior to traditional measures in terms of risk assessment and prediction of extreme glycemic excursions [190]. Specifically, it has been demonstrated that classification of risk for hypoglycemia based on four ADRR categories: low risk: ADRR < 20; low-moderate risk: 20 <= ADRR < 30; moderate-high risk: 30 <= ADRR < 40, and high risk: ADRR > 40, resulted in over six-fold increase in risk for hypoglycemia from the lowest to the highest risk category [190].

D. Continuous Glucose Monitoring Time Series

Subcutaneous continuous glucose monitors (CGM) assist the treatment of diabetes by providing frequent data for the dynamics of BG. Recent studies have documented the benefits of CGM [191]–[193] and charted guidelines for clinical use [194] and its future as a precursor to closed-loop control [195]. However, while CGM has the potential to revolutionize the control of diabetes, it also generates data streams that are both voluminous and complex. The utilization of such data requires an understanding of the physical, biochemical, and mathematical principles and properties involved in this new technology. It is important to know that CGM devices measure glucose concentration in a different compartment—the interstitium. Interstitial glucose (IG) fluctuations are related to BG presumably via diffusion process [196], [197]. This leads to a number of issues, including distortion (which incorporate a time lag) and calibration errors, and necessitates the development of methods for their mitigation. In particular, it is necessary to consider that, since the BG to IG kinetics acts as a low-pass filter, the frequency content of interstitial glucose is different from that of blood glucose [198], [199].

1) CGM Sensor Calibration—CGM sensor calibration accounts for the gradient between BG and IG. Typically, CGM devices are calibrated with capillary glucose, which brings the (generally lower) IG concentration to BG levels. The factors pertinent to successful calibration and the effects of calibration errors have been extensively studied in the past few years [200]–[203]. Alternative calibration methods based on decomposition of the sensor errors and on the use of diffusion models have been studied as well [204], [205]. Various calibration functions are adopted by researchers and industry, but most have a certain linear component using a 2-point linear regression model: $y = ax + b$, where a and b are calibration parameters which are determined by fitting them against a couple of reference $BG(y)$ and raw CGM current $CGM(x)$ levels collected at the same time. However, this procedure can be suboptimal, because it does not take into account distortions introduced by BG-to-IG kinetics. The DirecNet Study Group [200], analyzed the improvement in CGMS sensor accuracy by retrospectively modifying the number and timing of the calibration points and established that the timing of the calibration points is quite important. In particular, performing calibrations during periods of relative glucose stability, i.e., where the point-to-point difference due to the BG-to-IG kinetics is minimized, significantly improves the accuracy. An approach presented by Kuure-Kinsey *et al.* [206] uses dual-rate Kalman filter to improve the accuracy of CGM data. The procedure exploits episodic SMBG readings and estimates in real-time the sensor gain. A critical aspect of this algorithm is that it does not embed any BG-to-IG kinetics model. A more comprehensive description of the CGM measurement process was done by Knobbe and Buckingham [201]. In their work, BG-to-IG kinetics model was explicitly taken into account in order to reconstruct BG levels in continuous time from CGM measurements by an Extended Kalman Filter potentially able to deal with a multiplicative calibration error. However, successful calibration would adjust the amplitude of IG fluctuations with respect to BG, but would not eliminate the possible time lag due to BG-to-IG glucose transport and the sensor processing time (instrument delay).

2) CGM versus BG—Because the time lag typically associated with CGM could greatly influence CGM applications, a number of studies were dedicated to its investigation [207]–

[211], yielding various results. For example, it was hypothesized that if glucose fall is due to peripheral glucose consumption the physiologic time lag would be negative, i.e., fall in IG would precede fall in BG [196], [212]. In most studies, however, IG lagged behind BG by 4–10 min, regardless of the direction of BG change [196], [207], [208]. The formulation of the push-pull phenomenon offered reconciliation of these results and provided arguments for a more complex BG-IG relationship than a simple constant or directional time lag [211]. In addition, loss of sensitivity and random noise confound CGM data [213]–[215]. Thus, while the accuracy of CGM is increasing, it is still below the accuracy of direct BG measurement [216]–[219] and may be reaching a physiological limit of s.c. glucose monitoring.

Consequently, it is now recognized that the glucose monitor remains the main limiting factor in the development of diabetes control systems [220]–[223]. Less recognized is the fact that the algorithms retrieving CGM data also have a major contribution to the clinical success of these devices. In order to provide the best data possible, CGM signal processing is needed. Of primary importance are methods for: tracking CGM data integrity, including CGM data filtering (denoising); predicting glucose fluctuations which has the potential to mitigate the effects of a time lag; generating predictive alarms that could produce appropriate warning for upcoming extreme glycemic events (e.g., hypoglycemia) and would thereby assist the behavioral self-regulation of diabetes. Available techniques for filtering, prediction, and alert generation have been recently reviewed in [224].

3) Filtering—In general, denoising filters start from the following equation:

$$y(t)=u(t)+v(t) \quad (46)$$

where $y(t)$ is the glucose level measured at time t , $u(t)$ is the true, unknown, glucose level and $v(t)$ is random additive noise. The purpose of filtering is then recovering $u(t)$ from $y(t)$. Given the expected spectral characteristics of signal and noise, e.g., signal is lowpass and noise is white, (causal) low-pass filtering represents the most natural candidate to separate signal from noise in online applications. One major problem in low-pass filtering is that, because signal and noise spectra overlap, it is not possible to remove noise $v(t)$ from the measured signal $y(t)$ without distorting the true signal $u(t)$. In particular, distortion results in a delay affecting the estimate $\hat{u}(t)$ with respect to the true $u(t)$: the more the filtering, the larger the delay. Thus, a clinically significant filtering issue is reaching a compromise between the regularity of $\hat{u}(t)$ and its delay with respect to the true $u(t)$.

In the literature, real-time denoising of CGM signals has been addressed, both by sensor manufacturers and university researchers. The information of signal processing in commercial CGM devices is generally proprietary, but some results seem to indicate that moving-average (MA) filters with fixed parameters are often used. Methods which indirectly can address the denoising issue can be found in Chase *et al.* [214], Knobbe *et al.* [201] Palerm *et al.* [226], and Kuure-Kinsey *et al.* [206]. An explicit dealing with the denoising problem is made in the recent work by Facchinetto *et al.* [225]. In this paper, a Bayesian estimation approach was implemented by Kalman filtering for the real-time denoising of CGM signals. A key feature of the method is that, thanks to the incorporation of a stochastically based smoothing criterion, it can individualize filter parameters and hence the regularization amount according to the signal-to-noise ratio (SNR) of the specific CGM signal. In particular, the approach is able to cope with different sensors, interindividual and intraindividual SNR variability of CGM data. The performance of this new approach was assessed using Monte Carlo simulations and 24 CGM datasets and compared to a moving average filtering with fixed parameters. Fig. 28 shows two CGM time series (gray profiles) taken from the Monte Carlo simulation of [225] and obtained by adding, to a reference profile, a white Gaussian noise sequence with variance σ^2

$= 4 \text{ mg}^2/\text{dl}^2$ (top panel) and $\sigma^2 = 49 \text{ mg}^2/\text{dl}^2$ (bottom panel). Data from a burn-in interval (shaded box) were used to estimate σ^2 : notably, the numerical values estimated for σ^2 (reported in the shaded box) are very close to the true ones. Thanks to the self-tunable parameters individualization, in both simulations the Kalman filter denoises optimally noisy CGM data (black lines in Fig. 28). On real data, results showed that, for comparable signal denoising, the delay introduced by the Kalman filter is about 35% less than that obtained by MA [225].

4) Prediction—A multitude of methods has been proposed for the near-term (up to 45 minutes) prediction of glucose fluctuations. Most of these methods are based on time-series modeling techniques [227]–[233], but neural networks [234], [235] and other physiological structural models [236] have been used as well. Some of the approaches based on time-series modeling are briefly described as follows.

A typical CGM-based predictor would be based on a local approximation of the CGM time series by a first-order polynomial:

$$u_i = \alpha \cdot t_i + \beta \quad (47)$$

or by a first-order autoregressive (AR) model corresponding to the following time-domain difference equation

$$u_i = a \cdot u_{i-1} + w_i \quad (48)$$

where $i = 1, 2, \dots, n$ is the order of glucose samples collected until the n th sampling time t_n and $\{w_i\}$ is a random white noise process with zero mean and variance σ^2 . The prediction strategy then works as follows: Let θ be the vector of the parameters of the model employed to describe the glucose time series, at each sampling time t_n . A new value of θ is determined by fitting past glucose data $u_n, u_{n-1}, u_{n-2}, \dots$ by weighted linear least squares. Once θ determined, the model is used to calculate the prediction of glucose level Q steps ahead, i.e., \hat{u}_{n+Q} . The product $Q \cdot T_s$, where T_s is the sensor sampling period, gives the so-called prediction horizon (PH). The necessity of having a time-varying θ is obvious in the model of (47). For the AR model of (48), the use of a time-invariant θ e.g., identified in a burn-in interval, would produce inaccurate predictions because of nonstationarity of CGM time series, which, in the case of low-order model, calls for a time-varying modeling strategy [230]. In the estimation of θ the past data participate with different relative weights. A typical choice is to employ exponential weighting, i.e., μ^k is the weight of the sample taken k instants before the actual sampling time, with the forgetting factor μ within the range $(0, 1)$ termed forgetting factor. In [233], the forgetting factor is modulated in order to account for sudden changes of glucose dynamics.

Reifman *et al.* [228] employed a different approach, which exploited a high-order AR model (order 10) which was first fitted, in each subject, in a burn-in interval and then used within the prediction algorithm for the rest of the time series. A price to be paid for this approach is an increased model complexity which requires the use of a rather long burn-in interval (about 2000 samples, or ~ 36 h). Moreover, given the high number of parameters to be estimated, this AR model would be overly sensitive to noise. Indeed, a “regularization constraint” was placed on the AR coefficients in order to decrease their sensitivity to the data. Furthermore, the prediction algorithm of [228] has been assessed on retrospectively smoothed CGM data.

A stochastic nonparametric approach, similar to that employed in [225] for denoising, was proposed for prediction purposes in [237]. The idea of the method is to exploit the available *a priori* information on the smoothness of CGM signal, formalized through a stochastic model

including the multiple integration of a white noise process. After having placed the problem in a state-space setting, a Kalman Filtering methodology is used to predict glucose level within a given PH. The approach was tested on 13 data sets of Minimed CGM data (5 min sampling) during a hypoglycemic clamp (4 hour data). Three different PH were tested, PH = 10, 20, and 30 min. The parameters of the Kalman filter were empirically determined, in a retrospective fashion, in order to “maximize” sensitivity and specificity. The authors reported that the prediction performance, in this well-controlled hypoglycaemic clamp situation, was satisfactory in terms of sensitivity and specificity. No quantitative estimates of the prediction delays were reported.

5) Hypoglycemia and Hyperglycemia Alerts—A special class of predictive methods concerns the generation of alarms forewarning the patient about upcoming extreme glycemic events, e.g., hypo- or hyper-glycemia. These methods have rapidly evolved from a concept [238] to implementation in CGM devices, such as the GuardianRT (Medtronic, Norhridge, CA) [239] and the Freestyle Navigator (Abbott Diabetes Care, Alameda, CA) [178]. Discussion of the methods for testing of the accuracy and the utility of such alarms has been initiated [178], [240], [241], and the next logical step—prevention of hypoglycemia via shutoff of the insulin pump—has been undertaken [242].

VI. Control

A. Rationale

As already noted in Section II, a patient with type 1 diabetes faces a life-long behavior-controlled optimization problem: the administration of external insulin to control glycemia enters a stochastic scenario where hyperglycemia and hypoglycemia may not be easily prevented by open-loop therapy. The adjustment of therapy, i.e., basal insulin delivery and premeal boluses, on the basis of a few daily fingerstick blood glucose measurements, can be seen as rudimentary way to close the loop. Clearly, the few daily measurements, albeit very important, considerably limit the effectiveness of the feedback action.

Closed-loop glucose control uses in contrast frequent measurements. This subject has been discussed by numerous research papers since the 1960s, and several surveys are now available [223], [243]. The purpose here is to review recent developments by taking into account some guidelines. In particular, attention is focused on the subcutaneous sc-to-sc control route, i.e., on control systems adopting noninvasive sc insulin pumps and sc CGM devices. Therefore, contributions specific to intensive care patients or those dealing with glucagon pumps are not dealt with. Recent years have witnessed the development of more realistic models of glucose metabolism, as well as the first trials testing closed-loop glucose control systems in people. In view of this, another inclusion criterion is the validation platform: we will only consider control algorithms validated in clinical *in vivo* trials or in advanced *in silico* experiments, which provide accurate description of dynamic phenomena and/or incorporate interindividual variability [137], [244], [245]. The ideal *in silico* experiment not only provides a detailed simulation of metabolic processes but is also capable of running simulations on a large virtual population of patients. The importance of these models for testing glucose control algorithms is confirmed by the fact that the FDA has accepted *in silico* trials conducted with a large-scale *in silico* model as a substitute of the preclinical animals studies, which are usually needed to authorize clinical trials in humans [140]. In [246] and [247], some guidelines for *in silico* proof-of-concept testing of artificial pancreas control algorithms are proposed. A critical step of a full-scale *in silico* testing should involve not only controller software but also hardware elements, including the communication interface between the controller and the glucose sensor and insulin pump [248].

The problem of maintaining glucose levels within a predefined range by acting on insulin delivery is a control problem with a number of more or less specific features. The controlled variable is glucose utilization, the measured output is the sc glucose provided by the CGM, and the clinical criterion for success is plasma glucose. There is one manipulated variable (also called control input), namely the insulin delivered by the sc pump that can be acted upon by either the patient or the control systems to regulate plasma glucose. The system is subjected to disturbances, the most important one being the meals. It is important to note that this disturbance may be announced, approximately known, or even predictable. Such knowledge is routinely exploited in conventional insulin therapy in order to compute premeal boluses. Among other disturbance inputs, one may mention physical exercise that is known to acutely increase glucose utilization and chronically modify insulin sensitivity.

The dynamics of the system linking sc insulin to sc glucose consist of a cascade of three subsystems: the sc insulin having plasma insulin as output, the insulin-glucose metabolism nonlinear model having plasma glucose as output, and the sc glucose subsystem having sc glucose as output. As a result, sc insulin infusion poses major challenges to control algorithms due to the significant time needed for insulin absorption, diffusion, and action. With the advent of new rapid-acting insulin analogues that have been developed to more closely approximate the physiology of meal-related insulin secretion (e.g., lispro, aspart, glulisine) this time is now one hour or less [287], [288], which is still far inferior to the rate of insulin response in health. Such large time delays are relatively inconsequential in a steady (fasting) state, but have a major impact during system disturbances (e.g., meals, exercise). Recently, it has been found that, due to the “smoothing” inherent with sc insulin transport, small 15-min insulin boluses are indistinguishable from continuous basal rate [289], which allows designing control algorithms with up to a 15-min actuation rate, an approach that may be superior to the traditional bolus + continuous basal rate in terms of both computational and insulin pump energy efficiency. Further, the effect of meals on plasma glucose is characterized by an absorption delay whose time constant is in the order of hours. Overall, the sc system dynamics is nonlinear and affected by substantial delays, making the design of effective sc closed-loop control algorithms all but a trivial task. In addition, control must also face the significant inter- and intra-patient variability, meaning that it may be virtually impossible to apply the same controller to different patients and that even the same patient may show large variations at different days. Another issue is the presence of intrinsic input constraints, in that the manipulated input variable, e.g., insulin, is nonnegative. Moreover, there are also output constraints on the controlled variable in that plasma glucose should never go below a hypoglycaemia threshold, e.g., 60 or 70 mg/dl. On the other hand, in order to prevent long-term complications, hyperglycemia should be avoided as well. Finally, it is important to realize that closed-loop control is not without risks. For instance, in presence of hyperglycemia following a meal the regulator is likely to react by delivering more insulin, whose effect will not be immediately apparent due to intrinsic system delays. Then, insulin given in excess and too late may act when meal effect has ceased, so that hypoglycemia becomes unavoidable even if the insulin pump is shut off.

B. Architecture of Glucose Control

The availability of CGM measurements opens the way to different types of closed-loop control strategies, ranging from simple short-term safety-oriented interventions to long-term therapy-optimization schemes. In order to classify and organize the review of the literature, we refer to a recent paper that has proposed a layered architecture for artificial pancreas systems [249] (Fig. 29). The layers are characterized by the time-scale of their operations. At the bottom, the fastest layer is in charge of safety requirements. Possible algorithms include pump shutdown, insulin on board (IOB), and the so-called “brakes.” Immediately above, there is the real-time control layer that decides insulin delivery on the basis of latest CGM data, previous insulin

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

delivery, and meal information. Typical algorithms are either Proportional Integral Derivative (PID) or Model Predictive Control (MPC) regulators. The top layer, called offline control tuning, uses clinical parameters and historical data to tune the real-time control layer. In this case, the methods include individual controller calibration strategies, run-to-run (R2R) control algorithms, and behavioral analysis of patient lifestyle. Each layer processes available information (experimental measurements and patient's inputs) to take decisions that are passed to a lower layer. Each layer can override commands from an upper layer if this is either useful or necessary: a typical example may be provided by the safety layer zeroing insulin administration decided by the real-time control module.

It is interesting to note that activation of all layers is not strictly necessary. Within a traditional therapy consisting of basal insulin and meal-compensating boluses, use of the CGM information may be limited to safety interventions when the patient is at risk of hypoglycemia. For instance, the real-time control layer may be omitted, in which case the offline layer would just be in charge of adjusting basal insulin and premeal insulin boluses using historical information.

C. Safety Algorithms

The idea behind control algorithms pertaining to the safety layer is to exploit CGM data to improve patient's safety. Since the main short-term risk is hypoglycemia, the safety algorithms discontinue or reduce basal insulin to prevent dangerous decreases of blood glucose level.

The simplest strategy is pump shutoff when hypoglycemia is predicted. This approach has been shown to reduce the risk of nocturnal hypoglycemia [242], [250]. A possible drawback is that the use of an on-off control law for basal insulin, similar to bang-bang or relay control, may induce undesired oscillations of plasma glucose. In fact, if the basal insulin is higher than that needed to keep the glycemic target, the recovery from hypoglycemia would be followed by application of the basal that will cause a new shut-off occurrence. The cycle of shut-off interventions yields an insulin square wave that induces periodic oscillation of plasma glucose.

An alternative approach relies on insulin-on-board (IOB) computation [251]. The amount of IOB should never exceed a quantity that can cause future hyperglycemia. This assessment of the amount of on-board insulin, though approximate, offers a practical way to prevent hypo phenomena. Moreover, the IOB computation is simple enough to be included within a safety module that should act when upper layers have failed.

The third approach, the so-called "brakes" [252], which assess the risk associated with glucose values and reduce the delivered insulin accordingly. The main advantage, compared to the shut-off approach, is the ability to finely adapt intervention to the estimated risk. A possible improvement may regard risk assessment that could take into account past CGM and insulin history and not only the current CGM value. With this respect, the complex risk prediction algorithms may be incompatible with simplicity and robustness requirements of a safety module.

Recently, it has been proposed that implementation of "semi closed-loop" glucose control, only using the safety module, without the real-time control, could offer a first step towards full-closed loop control [253]. However, the philosophy of pure safety (act only to prevent hypoglycemia) needs to be adopted with caution, particularly in a system characterized by slow dynamics where prevention is much more efficient than correction. Nevertheless, in the presence of a real-time control module, safety algorithms may play an important role, especially if they are based on simple and physically grounded computations and offer a recovery strategy from physical or algorithmic failures of real-time controllers.

D. Real-Time Control

1) Feedback and Feedforward Control—There are two classes of control schemes: open- and closed-loop. Both classes of control schemes aim to keep the controlled variable (e.g., blood glucose) within the admissible or desired range, compensating for disturbances and uncertainties by acting on the manipulated variable (e.g., insulin). The main difference is that open-loop methods do not employ real-time measurements in order to take their decisions, whereas closed-loop control exploits measurements correlated with the variable under control to react to uncertainties and disturbances.

A fully open-loop scheme would correspond to a fixed therapy (for instance consisting of basal insulin administration throughout the day and insulin boluses at meal times), based on patient characteristics, without plasma glucose measurements. The open-loop therapy could, however, exploit knowledge of external disturbances, e.g., adapting the boluses to the predicted meal amount. The use of knowledge on an external disturbance in order to compensate in advance for its effects is a feedforward action. In principle, if the patient dynamics and external disturbances were perfectly known, it would be possible to design an open-loop insulin profile ensuring the desired glycemic control. In real life, however, both the patient dynamics and presence and size of external disturbances are far from being perfectly known. Hence, there is the need of corrections that must be based to the actual patient state. In fact, in the conventional therapy, occasional fingerstick glucose measurements are used to trigger corrective actions in order to react to deviations from the nominal profile that the open-loop control is expected to produce. This gives rise to a kind of partially closed-loop control scheme. However, few daily measurements are insufficient to change the nature of a control strategy which relies heavily on feedforward compensation.

With the commercial availability of CGM, it has become possible to design minimally invasive closed-loop control schemes based on frequent output measurements. In particular, the effect of external disturbances (e.g., meal and exercise, but also changes of insulin sensitivity) can be corrected based on their effect on glucose levels. In presence of an excessive rise of glucose, the controller is alerted by the CGM signal and can increase insulin delivery. Conversely, an undesired decrease of glycemia can trigger the reduction of basal insulin delivery.

A purely closed-loop control scheme would decide instantaneous insulin delivery on the basis of CGM signal alone. This would bring several advantages. First, any undesired glucose level would be accounted for in real time by suitable corrections of insulin rate. Moreover, being based on the measured effects of disturbances, corrections are applied without need for explicit knowledge or modeling of such disturbances. For example, an unexpected meal would be dealt with by reacting to the consequent glucose rise. If all this were possible and effective, improved quality of life would be apparent, as any change of meals and habits would be dealt with similarly to glucose control in health. Unfortunately, the sc delays described above present a major stumbling block on the way to a purely closed-loop control strategy: The action of insulin on plasma glucose is subject to significant delays so that effects of reactions to undesired glucose level may arrive too late to prevent hyper- or hypo-glycemic episodes. This problem is further exacerbated by the inherent delay between plasma glucose and the CGM signal. For a closed-loop controller, the worst case scenario is when a fast acting disturbance has to be counteracted by a manipulated variable whose action is delayed by the system dynamics. In this context, attempts to speed up the responsiveness of the closed-loop system may even result in an unstable behavior. For example, an excessive closed-loop insulin administration following postprandial hyperglycemia is likely to cause a hypoglycemic episode. This kind of intrinsic performance limitation is well known in control: in presence of significant delays in the route from manipulated (s.c. insulin) to the controlled variable (plasma glucose), the designer must settle for a relatively slow response time (i.e., the time needed for desired glycemia to be restored). These considerations suggest that the closed-loop control action

should not be abrupt and favour gradual corrections. However, a poorly aggressive control is not likely to provide good postprandial glycaemic attenuation, when a large and sudden disturbance is to be counteracted.

The problem of finding a tradeoff between nocturnal regulation, well suited to mild control actions, and postprandial regulation, calling for prompt and energetic correction has been pointed out in [254] with reference to previous closed-loop trials [255]–[257] where good nocturnal regulation was to the detriment of breakfast control quality. This dilemma can be escaped by a control scheme that combines feedforward and feedback actions [254], [258] (Fig. 30). In particular, feedback control actions are applied only as corrections that are summed to a “conventional” insulin administration (feedforward action) made of a basal profile and premeal boluses calibrated on the presumed meal amount. Associated with the feedforward action is a nominal glucose profile which represents the expected consequence of the conventional therapy. The closed-loop regulator bases its actions on the difference between the CGM signal and this nominal profile. If the difference is zero, no closed-loop correction is applied and the patient is subject to the conventional therapy alone. Although in practice the difference will always be nonzero, a well-designed feedforward action will require small-size feedback corrections. The major advantage is the possibility of combining prompt and energetic compensation of meals (through the feedforward bolus) with the robustness of closed-loop control capable of adapting to unpredicted events, disturbances, and changes in patient’s dynamics.

2) Models for Control—The deployment of a controller, especially a closed-loop one, relies heavily on mathematical models. It is worth noting that the requirements posed to models may vary depending on the different phases: design, tuning, and validation.

Most control design methods make use of compact models, whose main task is capturing system dynamics on the time scale regulation is concerned with. In this respect, linear time-invariant models may be obtained by linearization of either the average insulin-glucose *in silico* model or the minimal model. In the former case, order reduction methods may be employed to eliminate redundant state variables. Another way to obtain a linear time-invariant model is by black-box identification techniques applied to patient’s data, e.g., to identify ARMAX models. Some nonlinear control strategies such as Nonlinear Model Predictive Control, described as follows, can rely directly on nonlinear models such as the insulin-glucose *in silico* model or the minimal model (nonlinear black-box models, e.g., Nonlinear ARMAX, can be considered as well).

In the tuning and validation stages, it is convenient to run simulations that mimic the real system dynamics as faithfully as possible, so that large scale simulation models are particularly useful. In control engineering, it is a common practice to design a controller on some simple model (low-order linear time-invariant, for instance) and validate it on a detailed simulator of the system under control. Recalling that the insulin-glucose *in silico* model characterizes a population of virtual patients it is even possible to tune the controller parameters through *in silico* trials that compare the performances of different parameters values on the whole *in silico* population.

In the following review of glucose control strategies, the role and type of associated models will be pinpointed for each control method. In any case, a common feature of models for control design is instrumental to the achievement of satisfactory regulation performances rather than striving for the best possible description of all physiological phenomena.

3) PID Control—The classical PID control scheme is the most widespread in the control of industrial processes due to its simplicity, flexibility, and ease of tuning. In particular, the tuning

of the controller parameters can be done without a mathematical model of patient's metabolism, simply using empirical rules.

It is therefore not surprising that some of the first sc-to-sc control experiments used a PID controller [259], [260], [290], [291]. Among its pros, there is the possibility of relating the PID tuning parameters to the biometric parameters of the patient [259]–[261].

However, one issue concerning PID is the merit of the integral action. In fact, integral action is usually included in industrial regulators because, provided that the closed-loop system is stable, its presence guarantees asymptotic zero-error regulation. In the case of glucose control, this would correspond to the asymptotic convergence of glycemia, in absence disturbances, towards the assigned setpoint. Recalling that meals are to be regarded as disturbances, the assumption is unrealistic, which makes the asymptotic zero-error property much less appealing. There is a further concern, relative to the transient response to disturbances, which is even more critical: Consider a closed-loop stable linear system having in the loop a controller with an integral action and assume that the initial state is at the equilibrium with output equal to the setpoint. If an external transient disturbance is applied, it can be easily demonstrated that the integral over time of the difference between the resulting output and the equilibrium output is equal to zero. The glucose metabolism is nonlinear but nevertheless it may be approximated by a linear system in a neighborhood of the equilibrium point. As observed by [243], this means that after a meal, which makes glycemia exceed the desired value, there will always be an undershoot, i.e., a glucose transient that takes values below the glycemia setpoint and whose area is comparable the area of the previous overshoot above the setpoint. For these reasons, it may be convenient to turn to PD controllers, i.e., without the integral action. In particular, [262] can be regarded as a PD controller, in that it adapts the basal insulin depending of glucose value (proportional action) and its variation in the past 30 min (which replaces the derivative action).

PID control suffers from the same problems already highlighted. Due to the presence of substantial delays in the insulin-to-glucose route, one has to design a scarcely aggressive controller which, however, may react less promptly and effectively to meals than the usual premeal boluses of the conventional therapy. As already mentioned, in order to improve performance, a possibility is to add a feedforward action, so as to recover the promptness of meal compensation. Although MPC strategies appear better suited to incorporate predictions on the future effects of meals, an attempt has been made along this direction by [261], where the authors present a controller switching between PID regulation and bolus administration in proximity of meals. In any case, irrespective of the adopted tuning procedure or the presence of a feedforward action, PID controller will be subject to saturations and therefore an anti-windup implementation is always needed.

4) MPC—In recent years MPC [263] has emerged as the most promising approach to glucose control. The main ingredients of MPC are: the model, the cost function, and the constraints. The model is needed in order to be able to predict the future states and outputs of the system as a function of the current state, future values of the manipulated variables, and future values of measurable or predictable disturbances (Fig. 31). It can be linear or nonlinear, continuous-time or discrete-time, state-space or input-output, black-box, grey-box, or white-box. The cost function measures the quality of closed-loop control. Usually, but not necessarily, it is a quadratic penalty

$$J(k) = \sum_{i=0}^N (q(y_o(k+i) - y(k+i))^2 + (u_o(k+i) - u(k+i))^2) \quad (49)$$

on future deviations (whose number is a design parameter called prediction horizon) of the output from the setpoint y_0 and may include also a quadratic penalty on future control actions that can be the difference of the input u with respect to a reference u_0 or the variation along the time $\Delta u = u(k) - u(k-1)$. Finally, there may be constraints on the manipulated variables (insulin delivery rates by the pump is greater than zero and less than some maximal value)

$$u_{\min} \leq u \leq u_{\max} \quad (50)$$

$$\Delta u_{\min} \leq \Delta u \leq \Delta u_{\max} \quad (51)$$

and also on the controlled ones (glycemia in the admissible range)

$$y_{\min} \leq y \leq y_{\max}. \quad (52)$$

The rationale behind MPC is rather simple: at each time point we compute the sequence of future input moves optimizing the cost function subject to the constraints. Then, only the first control move is applied. At the next step, the procedure is repeated by translating the predictions and control horizons: an optimization is again performed and only the first input move is applied. The principal merit of MPC is that it reduces the control design problem to a sequence of finite-horizon optimization problems, which makes it possible to deal with nonlinear system models, input and output constraints, multiple inputs and outputs, and possible knowledge regarding the dynamics of disturbances. Finally, the tuning of the regulator can follow a rather straightforward trial-and-error procedure: if the control action is sluggish, it suffices to adjust the cost function increasing the weight on the controlled output, i.e., glycemia. In the simplest implementation, after finding reasonable values for the control and prediction horizons (e.g., a unique value covering the duration of typical post-meal transients), the tuning reduces to the calibration of a scalar aggressiveness parameter [270]. As already mentioned, the core of MPC is a mathematical model able to predict the future evolution of the system under control. In fact, different MPC schemes are obtained depending on the nature and complexity of the adopted model.

Nonlinear Model Predictive Control (NMPC) assumes a nonlinear patient model and keeps into account input and output constraints. In this case, explicit solution of the finite-horizon optimization problem does not exist, and the price to pay for an accurate description of the nonlinear dynamics is the need for online iterative optimization within the algorithm. This may preclude the adoption of NMPC within commercial devices, for both engineering and regulatory reasons. Moreover, standard NMPC algorithms assume knowledge of the current state variables, so that it is necessary to include also a state observer or a Kalman filter whose design and tuning may not be straightforward. A final problem is the difficulty of obtaining reliable individual models of insulin-glucose dynamics, as interindividual variability may hinder the use of an average model.

NMPC is however of particular interest as a touchstone for other simpler MPC schemes. A study has indeed demonstrated a distinct improvement over linear MPC [141] on the average *in silico* patient of the insulin-glucose *in silico* model. Experiments on real patients using NMPC have also been performed [136], [264], [265]. The need for an individual model has been overcome by online recursive identification of model parameters within a Bayesian setting. Given that experimental data alone may not guarantee parameter identifiability, the

Bayesian priors play a key role. Moreover, a formal demonstration of stability and robustness properties of the closed-loop system is obstructed by the complex interplay between on line recursive identification and nonlinear control.

Linear Model Predictive Control (LMPC) uses an approximate linear model of the insulin-glucose dynamics, which produces a substantial algorithmic simplification. The linear model can have different sources. For instance, it may be obtained from the linearization of a more complex nonlinear average patient model around a suitable working point; however such an approach would suffer from the lack of individualization. To overcome this limitation, one possibility is to resort to black-box identification of an individual patient model from data collected on the same individual subject to conventional therapy. In practice, time series of insulin, CGM data, and meal information are used to identify an ARMAX model with two inputs (sc insulin and meals) and one output (sc glucose). A necessary condition to ensure good identifiability properties of ARMAX models is the so-called persistent excitation property of input signals, which should not be collinear between each other and whose spectrum should excite an adequate number of frequencies. Unfortunately, the meals and insulin boluses of the conventional therapy turn out to be collinear and, due to this lack of excitation, the identification algorithm may even fail to correctly estimate the sign of the gains from insulin and meals to sc glucose [266]. As a remedy, it has been proposed to use split and/or delayed insulin boluses to improve the joint excitation properties of the inputs [254], [266] (see also [267] for further optimal design issues in the identification of insulin-glucose models).

A remarkable property of constrained LMPC is the existence of a closed-form solution under the form of a piecewise constant control law that can be computed off line, e.g., in [268] an application to simulated patients is reported. The main drawback of this LMPC scheme, that goes under the name of explicit multiparametric MPC, is the need of finding the appropriate control gain for the current state, a task that involves searching among a potentially very high number of regions in the state space. This can be avoided by computing on line the optimal solution via quadratic programming methods [258], which could be a computationally advantageous alternative to explicit multiparametric MPC. It is worth noting the possibility of including IOB among the constraints of the optimization problem, to embed certain safety constraints already within the real-time control module [258], [269].

It is unlikely that the first commercial realizations of an artificial pancreas will include overly complex computational algorithms. This motivates the interest for the simplest possible LMPC scheme, which is input-output unconstrained LMPC. This particular MPC scheme neglects constraints and uses a linear model in input-output form, e.g., an ARX- or ARMAX-type model. There is no need for online optimization algorithms, because the unconstrained optimization problem admits a closed-form solution that calculates the insulin rate as a simple linear combination of previous insulin rates, previous CGM values, and meal amounts (when known). The use of an input-output model, instead of state-space model, alleviates the need for a state observer, which is a further simplification. A clinical trial on 20 patients has been recently carried out using unconstrained LMPC [255]–[257], showing a five-fold reduction of nocturnal hypoglycemia episodes and an improvement of overnight percent time within the target range of 70–140 mg/dl, with respect to conventional open-loop control [255] (Fig. 32). The LMPC controller was based on an average patient model, but the regulator aggressiveness was personalized keeping into account easy-to-measure individual clinical parameters. To improve breakfast regulation, which was slightly worse than open-loop, an unconstrained LMPC with feedforward action has been proposed [249]. Generalized Predictive Control (GPC), a classic type of input-output unconstrained LMPC, has been experimented with on diabetic swine using both insulin and glucagon as inputs. A first trial used an adaptive GPC (i.e., with model parameters adapted on line) employing insulin or glucagon depending on the sign of the difference between measured glycemia and its target value [271]. In a second trial,

GPC was used to compute the insulin rate while, to speed up glucagon administration, the regulation of this second input was decided by a PD controller [272]. The main drawbacks of unconstrained LMPC are the use of a simplified linear model and the neglect of constraints, especially the one on minimal admissible glycemia. However, these drawbacks may be compensated by the advantage of a very simple implementation, especially if this real-time controller is part of a modular architecture including a safety module responsible for hyperglycemia prevention.

5) Real-Time Detection and Estimation—As already mentioned, controllers based on state feedback require the knowledge of the state of the insulin-glucose system. Even for the simplest models, the available measurements do not give access to the full state vector, so that real time algorithms for state observation are needed (see [143], [273], and [292]). State estimation is important not only for control properties, but can also be easily extended to prediction. In particular, it can be used to predict hypoglycemia [274], [275] and possibly trigger safety actions such as pump shutoff or attenuation. Nevertheless, insofar as a state observer or a Kalman filter rely heavily on a complex model not easily personalized to the specific patient, caution should be used in their use as safety algorithms.

The knowledge of meal time and amount plays an important role in that it can substantially help choosing the correct insulin profile for restoring glycemic control. An ideal artificial pancreas would be completely automatic, dispensing the patient from providing meal information to the device. In this context, a meal detection and estimation module [258], [276], [277] could greatly help the controller reacting properly to the glucose rise following a meal. However, in an s.c.-s.c. glucose control system, the delay introduced by meal detection and estimation would add to the intrinsic delays in the sc-to-sc route, thus degrading the effectiveness of meal compensation compared to the use of an appropriate premeal bolus. In any case, even if the patient were asked to provide meal confirmation to the control device, it would still be necessary to recover from a user's error by giving the device the capability to automatically detect unannounced meals.

E. Strategies for Control Tuning

1) Measuring Control Performance on Population—Although several classic control metrics exist for assessing the quality of glycemic control [278], some additional issues emerge. In particular, it does not suffice to develop an algorithm that performs satisfactorily on a single subject either real or simulated. As a matter of fact, given the great interindividual variability, it is of paramount importance to guarantee satisfactory performance on the entire population of patients. This motivated the introduction of the so-called Control Variability Grid Analysis (CVGA) [279], which associates to each patient a point in a plane (Fig. 33). The two coordinates correspond, via a nonlinear transformation, to the minimal and maximal glucose value in the considered time interval. The lower left corner is associated with ideal glycemic control while high x -values correspond to hypoglycemic episodes and high y -values to hyperglycemic episodes. The plane is partitioned into nine regions corresponding to different levels of glycemic control quality, from A (best) to E (worst). In this way, the results from a real or simulated trial can be visualized by plotting the patients as a cloud of points onto the CVGA and summarized by counting the percentage of points in the nine regions. Using the CVGA, comparison with either conventional open-loop control or another closed-loop controller is immediate. Of course, a good controller will bring as many patients as possible in the A and B regions. Preliminary to a clinical study, the controller can be applied to an *in silico* population, representative of the real population, and the performance assessed on the CVGA. If they are unsatisfactory, the controller can be modified and tested again by repeating the *in silico* trial. The procedure is iterated until glycemic control is acceptable for all the virtual patients.

2) Robustness versus Personalization of Controller Parameters—The ideal artificial pancreas should perform safely and satisfactorily in all patients. To achieve this, the designed controller should be highly robust against uncertainties in the system dynamics, either due to interindividual or intraindividual variability. Experiments conducted in *in silico* patients have shown that, a fixed controller yields largely disparate performances when applied to different patients; hence, there is need for a personalization of the control algorithm. Given the difficulty of identifying accurate individual models, the direct tuning of controller parameters has been investigated on the basis of few biometric and clinical parameters (body weight, total daily insulin, basal insulin delivery, carb ratio, etc.) characterizing the physiology of each individual. This can be done for both PID regulators [261] and MPC ones [143], [255]–[257]. In particular, for MPC the relation between biometric and physiological patient's parameters and the optimal scalar aggressiveness parameter of the controller can be determined through a sequence of *in silico* trials [255]–[257].

3) Run-to-Run Control and Behavioral Analysis—An offline module may be in charge of adapting the control strategy on a daily or weekly basis through the monitoring of the outcomes achieved by the real-time control module. This corresponds to a further closed-loop working on a coarser time scale. This type of problem, called run-to-run (R2R) control, has been extensively studied in the control of chemical and manufacturing processes [293]. The rationale of R2R control is rather simple: the parameter to be adjusted is corrected on the basis of the outcome of the last run. Proportional and proportional-integral control schemes are the most widely used ones. The first applications to glucose control regarded the iterative adjustment of the basal and boluses forming the conventional open-loop therapy [280]–[282]. It goes without saying that if the glucose controller includes a feedforward action, it may still benefit from this kind of R2R control. More recently, R2R control has been applied also to the tuning of the controller parameters [254] where adjustment of the controller aggressiveness is considered. An iterative tuning based on the last 24 hours may also be performed continuously via iterative learning control techniques [283].

Finally, stochastic models of patient's behavior may be very helpful in order to design and recursively update the parameters (basal and boluses) of the conventional therapy. A formal stochastic model of the process of self-treatment in diabetes (e.g., regular meals, exercise, as well as random treatment deviations) and its potential to generate system challenges can be very useful in that regard, giving a probabilistic interpretation of the observed patterns [294], [295]. Specifically, behavioral self-regulation of diabetes can be approximated by a periodic renewal process that has a significant random component. Such a periodic pattern causes downward and upward BG shifts that, with certain probability, can result in extreme events, such as severe hypoglycemia or major hyperglycemia. The parameters of this process are individual, contingent on behavioral interpretation (a person's ability to control his/her BG within near-normal limits) and physiology (e.g., a hypoglycemic episode would increase the risk for recurrent hypoglycemia). It has been shown that such an approach is capable of quantifying patterns of diabetes self-management [296] and is particularly useful for understanding the causes of severe hypoglycemia. These studies have demonstrated a quantifiable relationship between stochastic patterns of self-treatment behavior and subsequent occurrence of hypoglycemic episodes [297], [298]. Integrating behavior and physiology into a common framework has also enabled the computer simulation of patterns related to counterregulatory depletion, HAAF, and recurrent hypoglycemia [299].

VII. Conclusion

Approached from a biomedical engineering point of view, the bio-behavioral control of insulin-dependent diabetes (type 1 or insulin-treated type 2) is therefore comprised of: 1) physiologic processes depending on a person's metabolic parameters such as insulin sensitivity and

counterregulation, which could suffer from occasional depletion of counterregulatory reserves occurring with repeated hypoglycemia, and 2) behaviorally triggered processes of glucose fluctuations (e.g., regular postprandial glucose excursions) interrupted by generally random hypoglycemia-triggering behavioral events (e.g., insulin overdose, missed food, or excessive exercise). Fig. 34 presents the dual-layer structure of the engineering understanding of diabetes and places in context the unique combination of mathematical modeling, signal processing, and optimal control reviewed in this contribution. Specifically, Layer 1 represents the puzzle of physiological and behavioral interactions predetermining the specific parameters of each individual with diabetes. Each puzzle piece represents a specific subsystem pertinent to glycemic control: the *glucose system*, reflecting the appearance and the elimination of exogenous or endogenous carbohydrates, the *insulin system* that controls the dynamics of insulin-mediated carbohydrate metabolism, the counterregulatory system which is of enormous relevance to diabetes and is presented by *hypoglycemia*—the primary obstacle to diabetes control, and the *patient behavior*, which serves as a generator of events (e.g., meals, physical activity, human errors) resulting in metabolic perturbations. Completing the puzzle, the processing of these perturbations depends on individual physiologic parameters of glucose appearance, insulin sensitivity, and counterregulation. The interplay between behavior and biology results in glucose variability, which is the primary observable signal for optimal diabetes control. Layer 2 represents the engineering tools available to contemporary diabetes control. We have discussed several types of mathematical *models* which over the past 40–50 years have become increasingly elaborate, with recent trends also moving from single individual to population [300] by describing inter-subject variability in a stochastic framework where individual data and anthropometric and metabolic characteristics are explicitly taken into account [301]–[304]. A milestone in this line of research was the introduction of the minimal modeling concept, which established in 1979, the framework for a host of subsequent studies of the human glucose metabolism. A more contemporary milestone has been achieved in 2008, when the first model-based computer *simulator* of the human metabolic system was accepted as a viable tool for the preclinical testing of control algorithms, essentially alleviating the need for costly and time-consuming animal trials. The progress in modeling was supported by other technological developments, most importantly by the advent of continuous glucose monitoring, which provided detailed *signals* that could be used as inputs for optimizing glucose control. Finally, a number of *control* algorithms have been used and are recently under development with the goal to assist, and ultimately automate, the glycemic control in diabetes.

We can therefore conclude that the formal understanding and description of glucose-insulin metabolism in health and diabetes is, arguably, one of the most advanced applications of biomedical engineering to the life sciences. A rich background exists of models, metrics, and algorithms, and this contribution attempts to provide a systematic review of a number of them. We have to admit, however, that many more metabolic models exist that fall out of the scope of this review. This is because our goal is to follow a specific line of research that led from the first comprehensive model of glucose-insulin dynamics, through detailed simulation of the human physiology, to the first attempts for automated closed-loop control. Future reviews will therefore discuss problems not addressed by this manuscript.

Acknowledgments

The authors thank Dr. A. Vella and Dr. A. Basu, Mayo Clinic, Rochester, MN; Dr. A. Avogaro, Dr. G. Toffolo, Dr. A. Bertoldo, and Dr. A. Facchinetto, University of Padova, Padova, Italy; Dr. L. Farhi, Dr. M. Breton, and Dr. S. Patek, University of Virginia, Charlottesville, VA, for their contributions to this review.

References

1. Pickup, JC.; Williams, G. *Textbook of Diabetes* 2. Oxford, U. K: Blackwell; 1991.

2. Wilson, RH.; Foster, DW.; Kronenberg, HN.; Larsen, PR. William Textbook of Endocrinology. 9. Philadelphia, PA: Saunders; 1998.
3. [Online]. Available: www.ada.org
4. [Online]. Available: www.easd.org
5. [Online]. Available: www.idf.org
6. Meigs JB, Nathan DM, D'Agostino RB, Wilson PW. Fasting and postchallenge glycemia and cardiovascular disease risk: The Framingham offspring study. *Diabetes Care* 2002;25:1845–1850. [PubMed: 12351489]
7. The DECODE Study Group. Glucose tolerance and mortality: Comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999;354:617–621. [PubMed: 10466661]
8. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782–787. [PubMed: 11742409]
9. Carson ER, Deutsch T, Leicester HJ, Roudsari AV, Sönksen PH. Challenges for measurement science and measurement practice: The collection and interpretation of home-monitored blood. *Measurement* 1998;24:281–293.
10. Montani S, Magni P, Bellazzi R, Larizza C, Roudsari AV, Carson ER. Integrating model-based decision support in a multi-modal reasoning system for managing type 1 diabetic patients. *Artificial In-tell Medicine* 2003;29:131–151.
11. Palmer AJ, Weiss C, Sendi PP, Neeser K, Brandt A, Singh G, Wenzel H, Spinas GA. The cost-effectiveness of different management strategies for type 1 diabetes: A Swiss perspective. *Diabetologia* 2000;43:13–26. [PubMed: 10672449]
12. Valentine WJ, Palmer AJ, Nicklasson L, Cobden D, Roze S. Improving life expectancy and decreasing the incidence of complications associated with type 2 diabetes: A modelling study of HbA1c targets. *Int J Clin Pract* 2006;60:1138–1145. [PubMed: 16939559]
13. Eddy DM, Schlessinger L. Archimedes: A trial-validate model of diabetes. *Diabetes Care* 2003;26:3093–3101. [PubMed: 14578245]
14. Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. *Diabetes Care* 2003;26:3102–3110. [PubMed: 14578246]
15. Kitano H, Oda K, Kimura T, Matsuoka Y, Csete M, Doyle J, Muramatsu M. Metabolic syndrome and robustness tradeoffs. *Diabetes* 2004;53:S6–S15. [PubMed: 15561923]
16. Schadt EE. Molecular networks as sensors and drivers of common human diseases. *Nature* 2009;46:218–223. [PubMed: 19741703]
17. Cobelli, C.; Carson, ER. Introduction to Modeling in Physiology and Medicine. New York: Elsevier/Academic; 2008.
18. Carson, ER.; Cobelli, C. Modelling Methodology for Physiology and Medicine. San Diego, CA: Academic; 2001.
19. Cobelli, C.; Foster, D.; Toffolo, G. Tracer Kinetics in Biomedical Research. Boston, MA: Kluwer; 2000.
20. Insel PA, Liljenquist JE, Tobin JD, Sherwin RS, Watkins P, Andres R, Berman M. Insulin control of glucose metabolism in man: a new kinetic analysis. *J Clin Invest* 1975;55:1057–1066. [PubMed: 15959962]
21. Cobelli C, Toffolo G, Ferrannini E. A model of glucose kinetics and their control by insulin, compartmental and noncompartmental approaches. *Math Biosci* 1984;72:291–315.
22. Gastaldelli A, Schwarz JM, Caveggion E, Traber LD, Traber DL, Rosenblatt J, Toffolo G, Cobelli C, Wolfe RR. Glucose kinetics in interstitial fluid can be predicted by compartmental modeling. *Amer J Physiol* 1997;272:E494–E505. [PubMed: 9124557]
23. Ferrannini E, Smith DJ, Cobelli C, Toffolo G, Pilo A, DeFronzo RA. Effect of insulin on the distribution and disposition of glucose in man. *J Clin Invest* 1995;76:357–364. [PubMed: 3894421]
24. Sherwin RS, Kramer KJ, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R. A model of the kinetics of insulin in man. *J Clin Invest* 1974;53:1481–1492. [PubMed: 4856884]
25. Bergman RN, Ider YZ, Bowden CR, Cobelli C. Quantitative estimation of insulin sensitivity. *Amer J Physiol* 1979;236:E667–E677. [PubMed: 443421]

26. Bergman RN, Cobelli C. Minimal modeling, partition analysis, and the estimation of insulin sensitivity. *Fed Proc* 1980;39:110–115. [PubMed: 6985867]
27. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes* 1989;38:1512–1527. Review. [PubMed: 2684710]
28. Cobelli C, Toffolo GM, Dalla Man C, Campioni M, Denti P, Caumo A, Butler P, Rizza R. Assessment of beta-cell function in humans, simultaneously with insulin sensitivity and hepatic extraction, from intravenous and oral glucose tests. *Amer J Physiol Endocrinol Metab* Jul;2007 293(1):E1–E15. [PubMed: 17341552]
29. Bolie VW. Coefficients of normal blood glucose regulation. *J Appl Physiol* 1961;16:783–788. [PubMed: 13870789]
30. Segre G, Turco GL, Vercellone G. Modeling blood glucose and insulin kinetics in normal, diabetic and obese subjects. *Diabetes* 1973;22:94–103. [PubMed: 4687648]
31. Ceresa F, Ghemi F, Martini PF, Martino P, Segre G, Vitelli A. Control of blood glucose in normal and in diabetic subjects. Studies by compartmental analysis and digital computer technics. *Diabetes* 1968;17:570–578. [PubMed: 5675317]
32. Ackerman, Rosevear JW, McGuckin WF. A mathematical model of the glucose tolerance test. *Phys Medicine Biol* 1964;9:203–213.
33. Gatewood LC, Ackerman E, Rosevear JW, Molnar GD, Burns TW. Tests of a mathematical model of the blood-glucose regulatory system. *Comput Biomed Res* 1968;2:1–14. [PubMed: 5743536]
34. Gatewood LC, Ackerman E, Rosevear JW, Molnar GD. Simulation studies of blood-glucose regulation: Effect of intestinal glucose absorption. *Comput Biomed Res* 1968;2:15–27. [PubMed: 5743535]
35. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: Measurement of insulin sensitivity and beta-cell sensitivity from the response to intravenous glucose. *J Clin Invest* 1981;68:1456–1467. [PubMed: 7033284]
36. De Fronzo RA, Tobin JD, Andres R. Glucose clamp technique: A method for quantifying insulin secretion and resistance. *Amer J Physiol* 1979;237:E214–E223. [PubMed: 382871]
37. Pillonetto G, Caumo A, Cobelli C. Dynamic insulin sensitivity index: Importance in diabetes. *Amer J Physiol*. PMID: 19920215, to be published.
38. Cobelli C, Bettini F, Caumo A, Quon MJ. Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. *Amer J Physiol* 1998;275:E1031–E1036. [PubMed: 9843746]
39. Finegood DT, Tzur D. Reduced glucose effectiveness associated with reduced insulin release: An artifact of the minimal model method. *Amer J Physiol* 1996;271:E485–E495. [PubMed: 8843742]
40. Quon MJ, Cochran C, Taylor SY, Eastman RC. Non-insulin-mediated glucose disappearance in subjects with IDDM. Discordance between experimental results and minimal model analysis. *Diabetes* 1994;43:890–896. [PubMed: 8013753]
41. Cobelli C, Caumo A, Omenetto M. Minimal model SG over-estimation and SI underestimation: Improved accuracy by a Bayesian two-compartment model. *Amer J Physiol* 1999;277:E481–E488. [PubMed: 10484360]
42. Callegari T, Caumo A, Cobelli C. Bayesian two-compartment and classic single-compartment minimal models: Comparison on insulin modified IVGTT and effect of experiment reduction. *IEEE Trans Biomed Eng* Dec;2003 50(12):1301–1309. [PubMed: 14656059]
43. Cobelli C, Ruggeri A. Optimal design of sampling schedules for studying glucose kinetics with tracers. *Amer J Physiol* 257Endocrinol Metab 1989;20:E444–E450.
44. Hovorka R, Eckland DJA, Halliday D, Lettis S, Robinson CE, Bannister P, Young MA, Bye A. Constant infusion and bolus injection of stable-label tracer give reproducible and comparable fasting HGO. *Amer J Physiol* 273Endocrinol Metab 1997;E192–E201.
45. Dalla Man C, Caumo A, Cobelli C. The oral glucose minimal model: Estimation of insulin sensitivity from a meal test. *IEEE Trans Biomed Eng* Mar;2002 49(3):419–429. [PubMed: 12002173]
46. Dalla Man C, Caumo A, Basu R, Rizza RA, Toffolo G, Cobelli C. Minimal model estimation of glucose absorption and insulin sensitivity from oral test: Validation with a tracer method. *Amer J Physiol* 2004;287:E637–E643.

47. Dalla Man C, Yarasheski KE, Caumo A, Robertson H, Toffolo G, Polonsky KS, Cobelli C. Insulin sensitivity by oral glucose minimal models: Validation against clamp. *Amer J Physiol* 2005;289:E954–E959.
48. Cobelli C, Pacini G, Toffolo G, Saccà L. Estimation of insulin sensitivity and glucose clearance from minimal model: New insights from labeled IVGTT. *Amer J Physiol* 1986;250:E591–E598. [PubMed: 3518490]
49. Avogaro A, Bristow JD, Bier DM, Cobelli C, Toffolo G. Stable-label intravenous glucose tolerance test minimal model. *Diabetes* 1989;38:1048–1055. [PubMed: 2753235]
50. Caumo A, Giacca A, Morgese M, Pozza G, Micossi P, Cobelli C. Minimal models of glucose disappearance: Lessons from the labelled IVGTT. *Diabet Med* 1991;8:822–832. [PubMed: 1837509]
51. Avogaro A, Vicini P, Valerio A, Caumo A, Cobelli C. The hot but not the cold minimal model allows precise assessment of insulin sensitivity in NIDDM subjects. *Amer J Physiol* 1996;270:E532–E540. [PubMed: 8638702]
52. Vicini P, Caumo A, Cobelli C. The hot IVGTT two-compartment minimal model: Indexes of glucose effectiveness and insulin sensitivity. *Amer J Physiol* 1997;273:E1024–E1032. [PubMed: 9374690]
53. Toffolo G, Cobelli C. The hot IVGTT two-compartment minimal model: An improved version. *Amer J Physiol Endocrinol Metab* 2003;284:E317–E321. [PubMed: 12388140]
54. Dalla Man C, Campioni M, Polonsky KS, Basu R, Rizza RA, Toffolo G, Cobelli C. Two-hour seven-sample oral glucose tolerance test and meal protocol: Minimal model assessment of beta-cell responsivity and insulin sensitivity in nondiabetic individuals. *Diabetes* 2005;54:3265–3273. [PubMed: 16249454]
55. Caumo A, Cobelli C. Hepatic glucose production during the labeled IVGTT: Estimation by deconvolution with a new minimal model. *Amer J Physiol* 1993;264(5 pt 1):E829–E841. [PubMed: 8498505]
56. Hovorka R, Shojaee-Moradie F, Carroll PV, Chassin LJ, Gowrie IJ, Jackson NC, Tudor RS, Umpleby AM, Jones RH. Partitioning glucose distribution/transport, disposal, and endogenous production during IVGTT. *Amer J Physiol Endocrinol Metab* 2002;282(5):E992–E1007. [PubMed: 11934663]
57. Dalla Man C, Caumo A, Basu R, Rizza RA, Toffolo G, Cobelli C. Measurement of selective effect of insulin on glucose disposal from labeled glucose oral test minimal model. *Amer J Physiol* 2005;289:E909–E914.
58. Dalla Man C, Toffolo G, Basu R, Rizza RA, Cobelli C. Use of labeled oral minimal model to measure hepatic insulin sensitivity. *Amer J Physiol Endocrinol Metab* 2008;295:E1152–E1159. [PubMed: 18765681]
59. Basu R, Dalla Man C, Campioni M, Basu A, Klee G, Jenkins G, Toffolo G, Cobelli C, Rizza RA. Mechanisms of postprandial hyperglycemia in elderly men and women: Gender specific differences in insulin secretion and action. *Diabetes* 2006;55:2001–2014. [PubMed: 16804069]
60. Cherrington AD. Control of glucose uptake and release by the liver in vivo. *Diabetes* 1999;48:1198–1214. [PubMed: 10331429]
61. Vicini P, Zachwieja JJ, Yarasheski KE, Bier DM, Caumo A, Cobelli C. Glucose production during an IVGTT by deconvolution: Validation with the tracer-to-tracee clamp technique. *Amer J Physiol* 1999;276:E285–E294. [PubMed: 9950788]
62. De Nicolao G, Sparacino G, Cobelli C. Nonparametric input estimation in physiological systems: Problems, methods, case studies. *Automatica* 1997;33:851–870.
63. Hovorka R, Jayatillake H, Rogatsky E, Tomuta V, Hovorka T, Stein DT. Calculating glucose fluxes during meal tolerance test: A new computational approach. *Amer J Physiol Endocrinol Metab* 2007;293(2):E610–E619. [PubMed: 17519281]
64. Krudys KM, Dodds MG, Nissen SM, Vicini P. Integrated model of hepatic and peripheral glucose regulation for estimation of endogenous glucose production during the hot IVGTT. *Amer J Physiol Endocrinol Metab* 2005;288:E1038–E1046. [PubMed: 15632105]
65. Tokuyama K, Nagasaka S, Mori S, Takahashi N, Kusaka I, Kiyonaga A, Tanaka H, Shindo M, Ishibashi S. Hepatic insulin sensitivity assessed by integrated model of hepatic and peripheral glucose regulation. *Diabetes Technol Therapeutics* 2009;11(8):487–492.

66. Chierici M, Toffolo G, Basu R, Rizza RA, Cobelli C. Postprandial endogenous glucose production from a single tracer labeled meal: Validation against a triple tracer protocol. *Diabetes* 2007;56(supp 1):155-OR.
67. Toffolo G, Basu R, Dalla Man C, Rizza RA, Cobelli C. Assessment of postprandial glucose metabolism: Conventional dual versus triple tracer method. *Amer J Physiol Endocrinol Metab* 2006;291:E800–E806. [PubMed: 16720627]
68. Toffolo G, Dalla Man C, Cobelli C, Sunehag AL. Glucose fluxes during OGTT in adolescents assessed by a stable isotope triple tracer method. *J Pediatr Endocrinol Metab* 2008;21:31–45. [PubMed: 18404971]
69. Bonora E, Moghetti P, Zancanaro C, Cigolini M, Querena M, Cacciatori V, Corgnati A, Muggeo M. Estimates of *in vivo* insulin action in man: Comparison of insulin tolerance tests with euglycemic and hyperglycemic glucose clamp studies. *J Clin Endocrinol Metab* 1989;68:374–378. [PubMed: 2645308]
70. Kuikka J, Levin M, Bassingthwaite JB. Multiple tracer dilution estimates of D- and 2-deoxy-D-glucose uptake by the heart. *Amer J Physiol* 1986;250:H29–H42. [PubMed: 3510568]
71. Bassingthwaite, JB.; Goresky, CA. *Handbook of Physiology—The Cardiovascular System. Microcirculation*. Bethesda, MD: Amer. Soc. Physiology; 1984. Modeling in the analysis of solute and water exchange in the microvasculature.
72. Jacquez, JA. *Compartmental Analysis in Biology and Medicine*. 2. Ann Arbor, MI: Univ. Michigan Press; 1985.
73. Cobelli C, Saccomani MP, Ferrannini E, DeFronzo RA, Gelfand R, Bonadonna RC. A compartmental model to quantitate *in vivo* glucose transport in the human forearm. *Amer J Physiol* 1989;257:E943–E958. [PubMed: 2692459]
74. Bonadonna RC, Saccomani MP, Seely L, Starick Zych K, Ferrannini E, Cobelli C, DeFronzo RA. Glucose transport in human skeletal muscle: The *in vivo* response to insulin. *Diabetes* 1993;42:191–198. [PubMed: 8093605]
75. Saccomani MP, Bonadonna RC, Bier DM, De Fronzo RA, Cobelli C. A compartmental model to measure the effects of insulin on glucose transport and phosphorylation in human skeletal muscle. A triple tracer study. *Amer J Physiol* 1996;270:E170–E185. [PubMed: 8772490]
76. Bonadonna RC, Del Prato S, Bonora E, Saccomani MP, Gulli G, Natali A, Frascerra S, Pecori N, Ferrannini E, Bier DM, Cobelli C, De Fronzo RA. Roles of glucose transport and glucose phosphorylation in muscle insulin resistance of NIDDM. *Diabetes* 1996;45:915–925. [PubMed: 8666143]
77. Pendergrass M, Bertoldo A, Bonadonna RC, Nucci G, Mandarino L, Cobelli C, DeFronzo RA. Muscle glucose transport and phosphorylation in type 2 diabetic, obese nondiabetic, and genetically predisposed individuals. *Amer J Physiol Endocrinol Metab* 2007;292:E92–E100. [PubMed: 16896161]
78. Sokoloff L, Reivich M, Kennedy C, Des-Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M. The [¹⁴C]deoxyglucose method for the measurement of local cerebral glucose utilization: Theory, procedure, and normal values in the conscious and anesthetized albino rat. *J Neurochem* 1977;28:897–916. [PubMed: 864466]
79. Utriainen T, Mäkimattila S, Lovisatti S, Bertoldo A, Bonadonna RC, Weintraub S, De Fronzo R, Cobelli C, Yki-Järvinen H. Lumped constant for [¹⁴C]deoxy-D-glucose in human skeletal muscle. *Diabetologia* 1998;41:A187.
80. Kelley DE, Williams KV, Price JC, Goodpaster B. Determination of the lumped constant for [¹⁸F] FDG in human skeletal muscle. *J Nucl Med* 1999;40:1798–1804. [PubMed: 10565773]
81. Bertoldo A, Peltoniemi P, Oikonen V, Knuuti J, Nuutila P, Cobelli C. Kinetic modeling of [(¹⁸F) FDG in skeletal muscle by PET: A four-compartment five-rate-constant model. *Amer J Physiol Endocrinol Metab* 2001;281:E524–E536. [PubMed: 11500308]
82. Williams KV, Bertoldo A, Kinahan P, Cobelli C, Kelley DE. Diabetes 2003;52:1619–1626. [PubMed: 12829624]
83. Bertoldo A, Pencek RR, Azuma K, Price JC, Kelley C, Cobelli C, Kelley DE. Interactions between delivery, transport, and phosphorylation of glucose in governing uptake into human skeletal muscle. *Diabetes* 2006;55:3028–3037. [PubMed: 17065339]

84. Ferrannini E, Cobelli C. The kinetics of insulin in man. I. General aspects. *Diabetes Metab Rev* 1987;3:335–363. [PubMed: 3552526]
85. Frost DP, Srivastava MC, Jones RH, Nabarro JD, Sonksen PH. The kinetics of insulin metabolism in diabetes mellitus. *Postgrad Med J* 1973;49(Suppl 7):949–954. [PubMed: 4772466]
86. Hovorka R, Powrie JK, Smith GD, Sönksen PH, Carson ER, Jones RH. Five-compartment model of insulin kinetics and its use to investigate action of chloroquine in NIDDM. *Am J Physiol* 1993;265:E162–E175. [PubMed: 8338148]
87. Morishima T, Pye S, Bradshaw C, Radziuk J. Posthepatic rate of appearance of insulin: Measurement and validation in the nonsteady state. *Amer J Physiol* 1992;263:E772–E779. [PubMed: 1415699]
88. Eaton RP, Allen RC, Schade DS, Erickson KM, Standerfer J. Prehepatic insulin production in man: Kinetic analysis using peripheral connecting peptide behavior. *J Clin Endocrinol Metab* 1980;51:520–528. [PubMed: 6997329]
89. Polonsky KS, Licinio-Paixao J, Given BD, Pugh BDW, Rue P, Galloway J, Garrison T, Frank B. Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients. *J Clin Invest* 1986;51:98–105. [PubMed: 3511094]
90. Polonsky KS, Given BD, Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest* 1988;81(2):442–448. [PubMed: 3276730]
91. Shapiro ET, Tillil H, Rubenstein AH, Polonsky KS. Peripheral insulin parallels changes in insulin secretion more closely than C-peptide after bolus intravenous glucose administration. *J Clin Endocrinol Metab* 1988;67(5):1094–1099. [PubMed: 3053748]
92. Tillil HE, Shapiro ET, Miller MA, Garrison T, Frank BH, Galloway JA, Rubenstein AH, Polonsky KS. Dose-dependent effects of oral and intravenous glucose on insulin secretion and clearance in normal humans. *Amer J Physiol* 1988;254(3 pt 1):E349–E357. [PubMed: 3279811]
93. Sparacino G, Cobelli C. A stochastic deconvolution approach to reconstruct insulin secretion rate after a glucose stimulus. *IEEE Trans Biomed Eng* Apr;1996 42(4):512–529. [PubMed: 8849464]
94. Van Cauter E, Mestrez FF, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. *Diabetes* 1992;41:368–377. [PubMed: 1551497]
95. Hovorka R, Chassin L, Luzio SD, Playle R, Owens DR. Pancreatic beta-cell responsiveness during meal tolerance test: Model assessment in normal subjects and subjects with newly diagnosed non-insulin-dependent diabetes mellitus. *Clin Endocrinol Metab* 1998;83:744–750.
96. Polonsky KS, Given BD, Pugh W, Licinio-Paixao J, Thompson JE, Garrison T, Rubenstein AH. Calculation of the systemic delivery rate of insulin in normal man. *J Clin Endocrinol Metab* 1986;63:113–118. [PubMed: 3519643]
97. Toffolo G, De Grandi F, Cobelli C. Estimation of beta-cell sensitivity from intravenous glucose tolerance test C-peptide data. Knowledge of the kinetics avoids errors in modeling the secretion. *Diabetes* 1995;44:845–854. [PubMed: 7789653]
98. Magni P, Bellazzi R, Sparacino G, Cobelli C. Bayesian identification of a population compartmental model of C-peptide kinetics. *Ann Biomed Eng* 2000;28:812–823. [PubMed: 11016418]
99. Magni P, Sparacino G, Bellazzi R, Toffolo GM, Cobelli C. Insulin minimal model indexes and secretion: Proper handling of uncertainty by a bayesian approach. *Ann Biomed Eng* 2004;32:1027–1037. [PubMed: 15298440]
100. Cretti A, Lehtovirta M, Bonora E, Brunato B, Zenti MG, Tosi F, Caputo M, Caruso B, Groop LC, Muggeo M, Bonadonna RC. Assessment of beta-cell function during the oral glucose tolerance test by a minimal model of insulin secretion. *Eur J Clin Invest* 2001;31:405–416. [PubMed: 11380592]
101. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C. Oral glucose tolerance test minimal model indexes of β -cell function and insulin sensitivity. *Diabetes* 2001;50:150–158. [PubMed: 11147781]
102. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E. Meal and oral glucose tests for assessment of beta-cell function: Modeling analysis in normal subjects. *Am J Physiol Endocrinol Metab* 2002;283:E1159–E1166. [PubMed: 12388151]
103. Breda E, Toffolo G, Polonsky KS, Cobelli C. Insulin release in impaired glucose tolerance: Oral minimal model predicts normal sensitivity to glucose but defective response times. *Diabetes* 2002;51:S227–S233. [PubMed: 11815484]

- NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript
104. Toffolo G, Breda E, Cavaghan MK, Ehrmann DA, Polonsky KS, Cobelli C. Quantitative indexes of beta-cell function during graded up&down glucose infusion from C-peptide minimal models. Amer J Physiol Endocrinol Metab 2001;280:E2–E10. [PubMed: 11120653]
 105. Steil GM, Hwu C, Janowski R, Hariri F, Jinagouda S, Darwin C, Tadros S, Rebrin K, Saad MF. Evaluation of insulin sensitivity and beta-cell function indexes obtained from minimal model analysis of a meal tolerance test. Diabetes 2004;53:1201–1207. [PubMed: 15111487]
 106. Weiss R, Caprio S, Trombetta M, Taksali SE, Tamborlane WV, Bonadonna RC. Beta-cell function across the spectrum of glucose tolerance in obese youth. Diabetes 2005;54:1735–1743. [PubMed: 15919795]
 107. Denti, P.; Salinger, D.; Vicini, P.; Toffolo, G.; Cobelli, C. A nonlinear mixed-effects approach to the estimation of the glucose disposition index. Proc. PAGE 2009 Meeting; St. Petersburg, Russia. Jun. 23–26, 2009;
 108. Campioni M, Toffolo GM, Basu R, Rizza RA, Cobelli C. Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters. Amer J Physiol Endocrinol Metab. Aug 11;2009 [Epub ahead of print].
 109. Toffolo G, Campioni M, Basu R, Rizza RA, Cobelli C. A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. Amer J Physiol Endocrinol Metab 2006;290(1):E169–E176. [PubMed: 16144811]
 110. Nair KS, Rizza RA, O'Brein P, Short KR, Nehra A, Vittone JL, Klee GG, Basu A, Basu R, Cobelli C, Toffolo G, Dalla Man C, Tindall DJ, Melton LJ, Smith GE, Khosla S, Jensen MD. Effect of two years dehydroepiandrosterone in elderly men and women and testosterone in elderly men on physiological performance, body composition and bone density. New England J Med 2006;355:1647–1659. [PubMed: 17050889]
 111. Petersen KF, Dufour S, Feng J, Befroy D, Dzuira J, Dalla Man C, Cobelli C, Shulman G. Increased prevalence of insulin resistance and non-alcoholic fatty liver disease in asian indian men. PNAS 2006;103:18273–18277. [PubMed: 17114290]
 112. Sunehag AL, Dalla Man C, Toffolo G, Haymond MW, Bier DM, Cobelli C. Beta-Cell function and insulin sensitivity in adolescents from an OGTT. Obesity 2009;17:233–239. [PubMed: 19057529]
 113. Cali AM, Dalla Man C, Cobelli C, Dziura J, Seyal A, Shaw M, Allen K, Chen S, Caprio S. Primary defects in beta-cell function further exacerbated by worsening of insulin resistance mark the development of impaired glucose tolerance in obese adolescents. Diabetes Care 2009;32:456–461. [PubMed: 19106382]
 114. Bock G, Dalla Man C, Campioni M, Chittilapilly E, Basu R, Toffolo G, Cobelli C, Rizza RA. Pathogenesis of pre-diabetes: Mechanisms of fasting and postprandial hyperglycemia in people with impaired fasting glucose and/or impaired glucose tolerance. Diabetes 2006;55:3536–3549. [PubMed: 17130502]
 115. Bock G, Chittilapilly E, Basu R, Toffolo G, Cobelli C, Chandramouli V, Landau BR, Rizza RA. Contribution of hepatic and extrahepatic insulin resistance to the pathogenesis of impaired fasting glucose: Role of increased rates of gluconeogenesis. Diabetes 2007;56:1703–1711. [PubMed: 17384334]
 116. Bock G, Dalla Man C, Campioni M, Chittilapilly E, Basu R, Toffolo G, Cobelli C, Rizza RA. Effects of nonglucose nutrients on insulin secretion and action in people with pre-diabetes. Diabetes 2007;56:1113–1119. [PubMed: 17395750]
 117. Basu A, Dalla Man C, Basu R, Toffolo G, Cobelli C, Rizza RA. Effects of type 2 diabetes on insulin secretion, insulin action, glucose metabolism. Diabetes Care 2009;32:866–872. [PubMed: 19196896]
 118. Dalla Man C, Bock G, Giesler PD, Serra DB, Saylan Ligueros M, Foley JE, Camilleri M, Toffolo G, Cobelli C, Rizza RA, Vella A. Dipeptidyl peptidase-4 inhibition by vidagliptin and the effect of insulin secretion and action in response to meal ingestion in type 2 diabetes. Diabetes Care 2008;32:14–18. [PubMed: 18931099]
 119. Cobelli C, Carson ER, Finkelstein L, Leaning MS. Validation of simple and complex models in physiology and medicine. Amer J Physiol Endocrinol Metab 1984;246:R259–R266.
 120. Grodsky GM. A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling. J Clin Invest Aug;1972 51:2047–2059. [PubMed: 4559946]

121. Sturis J, Polonsky KS, Mosekilde E, Van Cauter E. Computer model for mechanisms underlying ultradian oscillations of insulin and glucose. *Amer J Physiol* 1991;260:E801–E809. [PubMed: 2035636]
122. Vicini P, Caumo A, Cobelli C. Glucose effectiveness and insulin sensitivity from the minimal models: Consequence of undermodeling assessed by Monte Carlo simulation. *IEEE Trans Biomed Eng* Jan;1999 46(1):130–137. [PubMed: 9932334]
123. Caumo A, Vicini P, Zachwieja J, Avogaro A, Yarasheski K, Bier D, Cobelli C. Undermodeling affects minimal model indexes: Insights from a two-compartment model. *Amer J Physiol* 1999;276:E1171–E1193. [PubMed: 10362630]
124. Lehmann ED, Chatu SS, Hashmy SS. Retrospective pilot feedback survey of 200 users of the AIDA Version 4 Educational Diabetes Program. 1—Quantitative survey data. *Diabetes Technol Ther* 2006;8:419–432. [PubMed: 16800766]
125. Rutscher A, Salzsieder E, Thierbach U, Fischer U, Albrecht G. Kadis—A computer-aided decision support system for improving the management of type-1 diabetes. *Exp Clin Endocrinol* 1990;95:137–147. [PubMed: 2335180]
126. Salzsieder E, Fischer U, Stoewhas H, Thierbach U, Rutscher A, Menzel R, Albrecht G. A model-based system for the individual prediction of metabolic responses to improve therapy in type I diabetes. *Horm Metab Res Suppl* 1990;24:10–19. [PubMed: 2272613]
127. Srinivasan R, Kadish AH, Sridhar R. A mathematical model for the control mechanism of free fatty acid-glucose metabolism in normal humans. *Comput Biomed Res* 1970;3:146–166. [PubMed: 5431933]
128. Fridlyand LE, Harbeck MC, Roe MW, Philipson LH. Regulation of cAMP dynamics by Ca²⁺ and G protein-coupled receptors in the pancreatic beta-cell: A computational approach. *Amer J Physiol Cell Physiol* Dec;2007 293:C1924–C1933. [PubMed: 17928534]
129. Cobelli C, Federspil G, Pacini G, Salvà A, Scandellari C. An integrated mathematical model of the dynamics of blood glucose and its hormonal control. *Math Biosci* 1982;58:27–60.
130. Cobelli C, Mari A. Validation of mathematical models of complex endocrine-metabolic systems: A case study on a model of glucose regulation. *Med Biol Eng Comput* 1983;21:390–399. [PubMed: 6350741]
131. Cobelli C, Ruggeri A. Evaluation of portal/peripheral route and of algorithms for insulin delivery in the closed-loop control of glucose in diabetes. A modeling study. *IEEE Trans Biomed Eng* Jan; 1983 BME-30(1):93–103. [PubMed: 6339366]
132. Salzsieder E, Albrecht G, Fischer U, Freys EJ. Kinetic modeling of the glucoregulatory system to improve insulin therapy. *IEEE Trans Biomed Eng* Jun;1985 32(6):846–855. [PubMed: 3902618]
133. Sorenson, JT. PhD dissertation. Dept. Chemical Eng., Massachusetts Inst. Technology; 1985. A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes.
134. Lehmann ED, Deutsch T. A physiological model of glucose-insulin interaction in type 1 diabetes mellitus. *J Biomed Eng* 1992;14:235–242. [PubMed: 1588781]
135. Andreassen S, Benn JJ, Hovorka R, Olesen KG, Carson ER. A probabilistic approach to glucose prediction and insulin dose adjustment: Description of metabolic model and pilot evaluation study. *Comput Methods Programs Biomed* 1994;41:153–165. [PubMed: 8187463]
136. Hovorka R, Canonico V, Chassin LJ, Haueter U, Massi-Benedetti M, Federici MO, Pieber TR, Schaller HC, Schaupp L, Vering T, Wilinska ME. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiol Meas* 2004;25:905–920. [PubMed: 15382830]
137. Dalla Man C, Rizza RA, Cobelli C. Meal simulation model of the glucose-insulin system. *IEEE Trans Biomed Eng* Aug;2007 54(8):1740–1749. [PubMed: 17926672]
138. Dalla Man, C.; Cobelli, C. A pre & type 2 diabetes simulator for *in silico* trials. Proc. Ninth Diabetes Technology Meeting; San Francisco, CA. 2009. accepted for publication
139. Kanderian SS, Weinzimer S, Voskanyan G, Steil GM. Identification of intraday metabolic profiles during closed-loop glucose control in individuals with type 1 diabetes. *J Diabetes Sci Technol* 2009;3:1047–1057. [PubMed: 20144418]

140. Kovatchev BP, Breton MD, Dalla Man C, Cobelli C. *In silico* model and computer simulation environment approximating the human glucose/insulin utilization. Food and Drug Administration Master File MAF 2008:1521.
141. Magni L, Raimondo DM, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Model predictive control of glucose concentration in type I diabetec patients: An *in silico* trial. *Biomed Signal Processing Contr* 2009;4:338–346.
142. Wilinska M, Chassin LJ, Schaller HC, Schaupp L, Pieber TR, Hovorka R. Insulin kinetics in type-I diabetes: Continuous and bolus delivery of rapid acting insulin. *IEEE Trans Biomed Eng* Jan;2005 52(1):3–12. [PubMed: 15651559]
143. Wilinska ME, Budiman ES, Taub MB, Elleri D, Allen JM, Acerini CL, Dunger DB, Hovorka R. Overnight closed-loop insulin delivery with model predictive control: Assessment of hypoglycemia and hyperglycemia risk using simulation studies. *J Diabetes Sci Technol* 2009;3:1109–1120. [PubMed: 20144424]
144. Bertram R, Sherman A, Satin LS. Metabolic and electrical oscillations: Partners in controlling pulsatile insulin secretion. *Amer J Physiol Endocrinol Metab* Oct;2007 293:E890–E900. [PubMed: 17666486]
145. Pedersen MG. Contributions of mathematical modeling of beta-cells to the understanding of beta-cell oscillations and insulin secretion. *J Diabetes Sci Technol* Jan;2009 3:12–20. [PubMed: 20046647]
146. Cerasi E, Fick G, Rudemo M. A mathematical model for the glucose induced insulin release in man. *Eur J Clin Invest Aug*;1974 4:267–278. [PubMed: 4424575]
147. Daniel S, Noda M, Straub SG, Sharp GW. Identification of the docked granule pool responsible for the first phase of glucose-stimulated insulin secretion. *Diabetes Sep*;1999 48:1686–1690. [PubMed: 10480595]
148. Olofsson CS, Göpel SO, Barg S, Galvanovskis J, Ma X, Salehi A, Rorsman P, Eliasson L. Fast insulin secretion reflects exocytosis of docked granules in mouse pancreatic B-cells. *Pflugers Arch May*;2002 444:43–51. [PubMed: 11976915]
149. Nesher R, Cerasi E. Modeling phasic insulin release: Immediate and time-dependent effects of glucose. *Diabetes Feb*;2002 51(Suppl 1):S52–S59.
150. Jonkers FC, Henquin J-C. Measurements of cytoplasmic Ca²⁺ in islet cell clusters show that glucose rapidly recruits beta-cells and gradually increases the individual cell response. *Diabetes Mar*;2001 50:540–550. [PubMed: 11246873]
151. Pedersen MG, Corradin A, Toffolo GM, Cobelli C. A subcellular model of glucose-stimulated pancreatic insulin secretion. *Philos Transact Roy Soc A Oct*;2008 366:3525–3543.
152. Toffolo G, Breda E, Cavaghan MK, Ehrmann DA, Polonsky KS, Cobelli C. Quantitative indexes of beta-cell function during graded up&down glucose infusion from C-peptide minimal models. *Am J Physiol Endocrinol Metab Jan*;2001 280:E2–E10. [PubMed: 11120653]
153. Licko V. Threshold secretory mechanism: A model of derivative element in biological control. *Bull Math Biol Feb.–Apr*;1973 35:51–58. [PubMed: 4783702]
154. Rahaghi FN, Gough DA. Blood glucose dynamics. *Diabetes Technol Therapeutics* 2008;10(2):81–94.
155. Gough DA, Kreutz-Delgado K, Bremer TM. Frequency characterization of blood glucose dynamics. *Ann Biomed Eng* 2003;31(1):91–97. [PubMed: 12572659]
156. Porksen N, Hollingdal M, Juhl CB, Butler P, Veldhuis JD, Schmitz O. Pulsatile insulin secretion: Detection, regulation and role in diabetes. *Diabetes* 2002;51:S245–S254. [PubMed: 11815487]
157. Meneilly GS, Ryan AS, Veldhuis JD, Elahi D. Increased disorderliness of basal insulin release, attenuated insulin secretory burst mass, and reduced ultradian rhythmicity of insulin secretion in older individuals. *J Clinical Endocrinol Metab* 1997;82:4088–4093. [PubMed: 9398719]
158. Meneilly GS, Veldhuis JD, Elahi D. Disruption of the pulsatile and entropic modes of insulin release during an unvarying glucose stimulus in elderly individuals. *J Clin Endocrinol Metab* 1999;84:1938–1943. [PubMed: 10372690]
159. Schmitz O, Porksen N, Nyholm B, Skjaerback C, Butler PC, Veldhuis JD, Pincus SM. Disorderly and nonstationary insulin secretion in relatives of patients with NIDDM. *Amer J Physiol* 1997;272:E218–E226. [PubMed: 9124326]

160. Veldhuis JD, Keenan DM, Pincus SM. Motivations and methods for analyzing pulsatile hormone secretion. *Endocrine Rev* 2008;29:823–864. [PubMed: 18940916]
161. Merriam G, Wachter K. Algorithms for the study of episodic hormone secretion. *Amer J Physiol* 1982;243:E310–E318. [PubMed: 6889816]
162. Oerter KE, Guardabasso V, Rodbard D. Detection and characterization of peaks and estimation of instantaneous secretory rate for episodic pulsatile hormone secretion. *Comput Biomed Res* 1986;19:170–191. [PubMed: 3754800]
163. Van Cauter E. Estimating false positive and false negative errors in analysis of hormone pulsatility. *Amer J Physiol* 1988;254:E786–E794. [PubMed: 3377077]
164. Urban RJ, Kaiser DL, Van Cauter E, Johnson ML, Veldhuis JD. Comparative assessments of objective peak-detection algorithms. II. Studies in men. *Amer J Physiol* Jan;1988 254(1 Pt 1):E113–E119. [PubMed: 3337224]
165. Sturis J, Van Cauter E, Blackman JD, Polonsky KS. Entrainment of pulsatile insulin secretion by oscillatory glucose infusion. *J Clin Invest* 1991;87:439–445. [PubMed: 1991830]
166. Grambsch P, Meller MH, Grambsch PV. Periodograms and pulse detection methods for pulsatile hormone data. *Stat Med* 30 2002;21(16):2331–2344.
167. Simon C, Brandenberger C, Follenius M, Schlienger J. Alteration in the temporal organization of insulin secretion in type 2 diabetic patients under continuous enteral nutrition. *Diabetologia* 1991;34:435–440. [PubMed: 1909248]
168. Sturis J, Polonsky KS, Shapiro T, Blackman JD, O'Meara N, Van Cauter E. Abnormalities in the ultradian oscillations of insulin secretion and glucose levels in type 2 diabetic patients. *Diabetologia* 1992;35:681–689. [PubMed: 1644248]
169. O'Meara NM, Sturis J, Van Cauter E, Polonsky KS. Lack of control by glucose of ultradian insulin secretory oscillations in impaired glucose tolerance and in non-insulin-dependent diabetes mellitus. *J Clin Invest* 1993;92:262–271. [PubMed: 8325993]
170. Hollingdal M, Juhl CB, Pincus SM, Sturis J, Veldhuis JD, Polonsky KS, Pørksen N, Schmitz O. Failure of physiological plasma glucose excursions to entrain high-frequency pulsatile insulin secretion in type 2 diabetes. *Diabetes* Aug;2000 49(8):1334–1340. [PubMed: 10923634]
171. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Nat Acad Sci USA* 1991;88:2297–2301. [PubMed: 11607165]
172. Pincus SM. Quantification of evolution from order to randomness in practical time series analysis. *Methods Enzymol* 2004;240:68–89. [PubMed: 7823854]
173. Pincus SM, Mulligan T, Iranmanesh A, Gheorghiu S, Godschalk M, Veldhuis JD. Older males secrete luteinizing hormone and testosterone more irregularly, and jointly more asynchronously, than younger males. *Proc Nat Acad Sci USA* 1996;93(24):14100–14105. [PubMed: 8943067]
174. Evans WS, Farhy LS, Johnson ML. Biomathematical modeling of pulsatile hormone secretion: A historical perspective. *Methods Enzymol* 2009;454:345–366. [PubMed: 19216934]
175. Friend K, Iranmanesh A, Veldhuis JD. The orderliness of the growth hormone (GH) release process and the mean mass of GH secreted per burst are highly conserved in individual men on successive days. *J Clin Endocrinol Metab* 1996;81:3746–3753. [PubMed: 8855833]
176. Siragy HM, Vieweg WV, Pincus S, Veldhuis JD. Increased disorderliness and amplified basal and pulsatile aldosterone secretion in patients with primary aldosteronism. *J Clin Endocrinol Metab* 1995;80:28–33. [PubMed: 7829626]
177. Van den Berg G, Pincus SM, Veldhuis JD, Frolich M, Roelfsema F. Greater disorderliness of ACTH and cortisol release accompanies pituitary-dependent Cushing's disease. *Eur J Endocrinol* 1997;136:394–400. [PubMed: 9150699]
178. McGarraugh G, Bergenstal R. Detection of hypoglycemia with continuous interstitial and traditional blood glucose monitoring using the FreeStyle Navigator Continuous Glucose Monitoring System. *Diabetes Technol Therapeutics* 2009;11(3):145–150.
179. Meier JJ, Kjems LL, Veldhuis JD, Lefèbvre P, Butler PC. Postprandial suppression of glucagon secretion depends on intact pulsatile insulin secretion: Further evidence for the intraislet insulin hypothesis. *Diabetes* 2006;55(4):1051–1056. [PubMed: 16567528]

180. Sparacino G, Bardi F, Cobelli C. Approximate entropy studies of hormone pulsatility from plasma concentration time series: Influence of the kinetics assessed by simulation. *Ann Biomed Eng* Jun; 2000 28(6):665–676. [PubMed: 10983712]
181. Veldhuis JD, Johnson ML, Veldhuis OL, Straume M, Pincus SM. Impact of pulsatility on the ensemble orderliness (approximate entropy) of neurohormone secretion. *Amer J Physiol Regul Integr Comp Physiol* Dec;2001 281(6):R1975–R1985. [PubMed: 11705784]
182. Bellazzi R, Magni P, De Nicolao G. Bayesian analysis of blood glucose time series from diabetes home monitoring. *IEEE Trans Biomed Eng* Jul;2000 47(7):971–975. [PubMed: 10916270]
183. Magni P, Bellazzi R. A stochastic model to assess the variability of blood glucose time series in diabetic patients self-monitoring. *IEEE Trans Biomed Eng* Jun;2006 53(6):977–985. [PubMed: 16761824]
184. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke WL. Symmetrization of the blood glucose measurement scale and its applications. *Diabetes Care* 1997;20:1655–1658. [PubMed: 9353603]
185. Kovatchev BP, Straume M, Cox DJ, Farhy LS. Risk analysis of blood glucose data: A quantitative approach to optimizing the control of insulin dependent diabetes. *J Theoretical Medicine* 2001;3:1–10.
186. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke WL. Assessment of risk for severe hypoglycemia among adults with IDDM: Validation of the low blood glucose index. *Diabetes Care* 1998;21:1870–1875. [PubMed: 9802735]
187. Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA, Clarke WL. Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using Self-Monitoring Blood Glucose (SMBG) Data. *Diabetes Technol Therapeutics* 2003;5(5):817–828.
188. Cox DJ, Gonder-Frederick LA, Ritterband L, Clarke WL, Kovatchev BP. Prediction of severe hypoglycemia. *Diabetes Care* 2007;30:1370–1373. [PubMed: 17363757]
189. Kovatchev BP, Cox DJ, Farhy LS, Straume M, Gonder-Frederick LA, Clarke WL. Episodes of severe hypoglycemia in type 1 diabetes are preceded, and followed, within 48 hours by measurable disturbances in blood glucose. *J Clin Endocrinol Metab* 2000;85:4287–4292. [PubMed: 11095469]
190. Kovatchev BP, Otto E, Cox DJ, Gonder-Frederick LA, Clarke WL. Evaluation of a new measure of blood glucose variability in diabetes. *Diabetes Care* 2006;29:2433–2438. [PubMed: 17065680]
191. Deiss D, Bolinder J, Riveline J, Battelino T, Bosi E, Tubiana-Rufi N, Kerr D, Phillip M. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. *Diabetes Care* 2006;29:2730–2732. [PubMed: 17130215]
192. Garg K, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S, Jovanovic L. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor. *Diabetes Care* 2006;29:44–50. [PubMed: 16373894]
193. The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *New England J Medicine* 2008;359:1464–1476.
194. Hirsch IB, Armstrong D, Bergenstal RM, Buckingham B, Childs BP, Clarke WL, Peters A, Wolpert H. Clinical application of emerging sensor technologies in diabetes management: Consensus guidelines for continuous glucose monitoring. *Diabetes Technol Therapeutics* 2008;10:232–246.
195. Hovorka R. The future of continuous glucose monitoring: Closed loop. *Current Diabetes Rev* 2008;4:269–279.
196. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: Implications for continuous monitoring. *Amer J Physiol Endocrinol Metab* 1999;277:E561–E571.
197. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF. Interstitial fluid glucose dynamics during insulin-induced hypoglycemia. *Diabetologia* 2005;48:1833–1840. [PubMed: 16001232]
198. Breton MD, Shields DP, Kovatchev BP. Optimum subcutaneous glucose sampling and Fourier analysis of continuous glucose monitors. *J Diabetes Sci Technol* 2008;2:495–500. [PubMed: 19885217]
199. Miller M, Strange P. Use of Fourier models for analysis and interpretation of continuous glucose monitoring glucose profiles. *J Diabetes Sci Technol* 2007;1:630–638. [PubMed: 19885131]

200. Buckingham BA, Kollman C, Beck R, Kalajian A, Fiallo-Scharer R, Tansey MJ, Fox LA, Wilson DM, Weinzimer SA, Ruedy KJ, Tamborlane WV. Diabetes Research In Children Network (Direcnet) Study Group. Evaluation of factors affecting CGMS calibration. *Diabetes Technol Therapeutics* 2006;8(3):318–325.
201. Knobbe EJ, Buckingham B. The extended Kalman filter for continuous glucose monitoring. *Diabetes Technol Therapeutics* 2005;7(1):15–27.
202. Lesperance LM, Spektor A, McLeod KJ. Calibration of the continuous glucose monitoring system for transient glucose monitoring. *Diabetes Technol Therapeutics* 2007;9(2):183–190.
203. Lodwig V, Heinemann L. Glucose Monitoring Study Group. Continuous glucose monitoring with glucose sensors: Calibration and assessment criteria. *Diabetes Technol Therapeutics* 2003;5(4):572–586.
204. Facchinetto A, Sparacino G, Cobelli C. Reconstruction of glucose in plasma from interstitial fluid continuous glucose monitoring data: Role of sensor calibration. *J Diabetes Sci Technol* 2007;1(5):617–623. [PubMed: 19885129]
205. King CR, Anderson SM, Breton MD, Clarke WL, Kovatchev BP. Modeling of calibration effectiveness and blood-to-interstitial glucose dynamics as potential confounders of the accuracy of continuous glucose sensors during hyperinsulinemic clamp. *J Diabetes Sci Technol* 2007;1:317–322. [PubMed: 19756217]
206. Kuure-Kinsey M, Palerm CC, Bequette BW. A dual-rate Kalman filter for continuous glucose monitoring. *Proc IEEE Conf Eng Medicine Biology Soc* 2006;1:63–66.
207. Boyne M, Silver D, Kaplan J, Saudek C. Timing of changes in interstitial and venous blood glucose measured with a continuous subcutaneous glucose sensor. *Diabetes* 2003;52:2790–2794. [PubMed: 14578298]
208. Kovatchev BP, Shields DP, Breton MD. Graphical and numerical evaluation of continuous glucose sensing time lag. *Diabetes Technol Therapeutics* 2009;11:139–143.
209. Kulcu E, Tamada JA, Reach G, Potts RO, Lesnoy MJ. Physiological differences between interstitial glucose and blood glucose measured in human subjects. *Diabetes Care* 2003;26:2405–2409. [PubMed: 12882870]
210. Voskanyan G, Keenan DB, Mastrototaro JJ, Steil GM. 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* 2007;1(5):639–644. [PubMed: 19885132]
211. Wentholt IME, Hart AAM, Hoekstra JBL, De-Vries JH. Relationship between interstitial and blood glucose in type 1 diabetes patients: Delay and the push-pull phenomenon revisited. *Diabetes Technol Therapeutics* 2004;9:169–175.
212. Wientjes KJ, Schoonen AJ. Determination of time delay between blood and interstitial adipose tissue glucose concentration change by microdialysis in healthy volunteers. *Int J Artificial Organs* 2001;24:884–889.
213. Breton MD, Kovatchev BP. Analysis, modeling, and simulation of the accuracy of continuous glucose sensors. *J Diabetes Sci Technol* 2008;2:853–862. [PubMed: 19750186]
214. Chase JG, Hann CE, Jackson M, Lin J, Lotz T, Wong XW, Shaw GM. Integral-based filtering of continuous glucose sensor measurements for glycaemic control in critical care. *Computer Methods and Programs in Biomedicine* 2006;82(3):238–247. [PubMed: 16647157]
215. Kovatchev BP, Clarke WL. Peculiarities of the continuous glucose monitoring data stream and their impact on developing closed-loop control technology. *J Diabetes Sci Technol* 2008;2:158–163. [PubMed: 19578532]
216. Clarke WL, Kovatchev BP. Continuous glucose sensors—Continuing questions about clinical accuracy. *J Diabetes Sci Technol* 2007;1:164–170. [PubMed: 19888401]
217. Garg SK, Smith J, Beatson C, Lopez-Baca B, Voelmlle M, Gottlieb PA. Comparison of accuracy and safety of the SEVEN and the navigator continuous glucose monitoring systems. *Diabetes Technol Therapeutics* 2009;11:65–72.
218. Kovatchev BP, Anderson SM, Heinemann L, Clarke WL. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. *Diabetes Care* 2008;31:1160–1164. [PubMed: 18339974]

219. The Diabetes Research in Children Network (DirecNet) Study Group. The accuracy of the guardian RT continuous glucose monitor in children with type 1 diabetes. *Diabetes Technol Therapeutics* 2008;10:266–272.
220. De Block C, Vertommen J, Manuel-y-Keenoy B, Van Gaal L. Minimally-invasive and non-invasive continuous glucose monitoring systems: Indications, advantages, limitations and clinical aspects. *Current Diabetes Rev* 2008;4(3):159–168.
221. Ginsberg BH. The current environment of CGM technologies. *J Diabetes Sci Technol* 2007;1(1):118–121.
222. Klonoff DC. Continuous glucose monitoring: Roadmap for 21st century diabetes therapy. *Diabetes Care* 2005;28:1231–1239. [PubMed: 15855600]
223. Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabetic Medicine* 2005;23:1–12. [PubMed: 16409558]
224. Sparacino G, Facchinetto A, Maran A, Cobelli C. Continuous glucose monitoring time series and hypo/hyperglycemia prevention: Requirements, methods, open problems. *Current Diabetes Rev* 2008;4(3):181–192.
225. Facchinetto A, Sparacino G, Cobelli C. An on-line self-tunable method to denoise CGM sensor data. *IEEE Trans Biomed Eng*. to be published. 10.1109/TBME.2009.2033264
226. Palerm CC, Willis JP, Desemone J, Bequette BW. Hypoglycemia prediction and detection using optimal estimation. *Diabetes Technol Therapeutics* 2005;7:3–14.
227. Gani A, Gribok AV, Rajaraman S, Ward WK, Reifman J. Predicting subcutaneous glucose concentration in humans: Data-driven glucose modeling. *IEEE Trans Biomed Eng* Feb;2009 56(2):246–254. [PubMed: 19272928]
228. Reifman J, Rajaraman S, Gribok A, Ward WK. Predictive monitoring for improved management of glucose levels. *J Diabetes Sci Technol* 2007;1(4):478–486. [PubMed: 19885110]
229. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetto A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time-series. *IEEE Trans Biomed Eng* 2007;54(5):931–937. [PubMed: 17518291]
230. Sparacino G, Zanderigo F, Maran A, Cobelli C. Continuous glucose monitoring and hypo/hyperglycemia prediction. *Diabetes Res Clin Pract* 2006;74(Suppl 2):S160–S163.
231. Choleau C, Dokladal P, Klein JC, Ward WK, Wilson GS, Reach G. Prevention of hypoglycemia using risk assessment with a continuous glucose monitoring system. *Diabetes Nov*;2002 51(11):3263–3273. [PubMed: 12401718]
232. Cameron F, Niemayer G, Gundy-Burlet K, Buckingham B. Statistical hypoglycemia prediction. *J Diabetes Sci Technol* 2008;2(4):612–621. [PubMed: 19885237]
233. Eren-Oruklu M, Cinar A, Quinn L, Smith D. Estimation of future glucose concentrations with subject-specific recursive linear models. *Diabetes Technol Therapeutics* 2009;11(4):243–253.
234. Pappada SM, Cameron BD, Rosman PM. Development of a neural network for prediction of glucose concentration in type 1 diabetes patients. *J Diabetes Sci Technol* 2008;2(5):792–801. [PubMed: 19885262]
235. Pérez-Gandía C, Facchinetto A, Sparacino G, Cobelli C, Gómez EJ, Hernando ME. Artificial neural network algorithm for on-line glucose prediction from continuous glucose monitoring. *Diabetes Technol Ther*. 2009 in press.
236. Stahl F, Johansson R. Diabetes mellitus modeling and short-term prediction based on blood glucose measurements. *Math Biosci* 2009;217(2):101–117. [PubMed: 19022264]
237. Palerm C, Bequette W. Hypoglycemia detection and prediction using continuous glucose monitoring—A study on hypoglycemic clamp data. *J Diabetes Sci Technol* 2007;1:624–629. [PubMed: 19885130]
238. Heise T, Koschinsky T, Heinemann L, Lodwig V. Glucose Monitoring Study Group. Hypoglycemia warning signal and glucose sensors: Requirements and concepts. *Diabetes Technol Therapeutics* 2003;5(4):563–571.
239. Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro J. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: The Guardian continuous monitoring system. *Diabetes Technol Therapeutics* 2004;6(2):105–113.

240. Noujaim SE, Horwitz D, Sharma M, Marhoul J. Accuracy requirements for a hypoglycemia detector: An analytical model to evaluate the effects of bias, precision, and rate of glucose change. *J Diabetes Sci Technol* 2007;1(5):653–668.
241. Ward WK. The role of new technology in the early detection of hypoglycemia. *Diabetes Technol Therapeutics* 2004;6(2):115–117.
242. Buckingham B, Cobry E, Clinton P, Gage V, Caswell K, Kunselman E, Cameron F, Chase HP. Preventing hypoglycemia using predictive alarm algorithms and insulin pump suspension. *Diabetes Technol Therapeutics* 2009;11(2):93–97.
243. Bequette BW. A critical assessment of algorithms and challenges in the development of a closed-loop artificial pancreas. *Diabetes Technol Therapeutics* 2005;7:28–47.
244. Wilinska ME, Chassin LJ, Hovorka R. *In silico* testing—Impact on the progress of the closed loop insulin infusion for critical ill patient project. *J Diabetes Technol* 2008;2(3):417–423.
245. Hovorka R, Chassin LJ, Ellmerer M, Plank J, Wilinska ME. A simulation model of glucose regulation in the critically ill. *Physiol Meas* 2008;29:959–978. [PubMed: 18641427]
246. Patek SD, Bequette BW, Breton M, Buckingham BA, Dassau E, Doyle FJ III, Lum J, Magni L, Zisser H. *In silico* preclinical trials: Methodology and engineering guide to closed-loop control in T1DM. *J Diabetes Sci Technol* 2009;3(2):269–282. [PubMed: 20144358]
247. Kovatchev BP, Dalla Man C, Cobelli C. In silico preclinical trials: A proof of concept in closed-loop control of type 1 diabetes. *J Diabetes Sci Technol* 2009;3:44–55. [PubMed: 19444330]
248. Dassau E, Palerm CC, Zisser H, Buckingham BA, Jovanovic L, Doyle FJ III. In silico evaluation platform for artificial pancreatic, β -cell development—A dynamic simulator for closed-loop control with hardware-in-the-loop. *Diabetes Technol Ther* 2009;11(3):187–194. [PubMed: 19191486]
249. Kovatchev BP, Patek S, Dassau E, Doyle FJ III, Magni L, De Nicolao G, Cobelli C. Control-to-range for diabetes functionality and modular architecture. *J Diabetes Sci Technol* 2009;3(5):1058–1065. [PubMed: 20144419]
250. Cengiz E, Swan KL, Tamborlane WV, Steil GM, Steffen AT, Weinzimer SA. Is an automatic pump suspension feature safe for children with type 1 diabetes? An exploratory analysis with closed-loop system. *Diabetes Technol Therapeutics* 2009;11(4):207–210.
251. Zisser H, Robinson L, Bevier W, Dassau E, Ellingsen C, Doyle FJ III, Jovanovic L. Bolus calculator: A review of four “smart” insulin pumps. *Diabetes Technol Ther* 2008;10(6):441–444. [PubMed: 19049372]
252. Patek, SD.; Breton, MD.; Hughes, C.; Kovatchev, BP. Control of hypoglycemia via estimation of active insulin, glucose forecasts, and risk-based insulin reduction. Proc. 2nd Advanced Technol. Treatment for Diabetes; Athens, Greece. 2009.
253. Kowalski AJ. Can we really close the loop and how soon? Accelerating the availability of an artificial pancreas: A roadmap to better diabetes outcomes. *Diabetes Technol Therapeutics* 2009;11:S113–S119.
254. Magni L, Forgione M, Toffanin C, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Run-to-run tuning of model predictive control for type I diabetic subjects: An *in silico* trial. *J Diabetes Sci Technol* 2009;3(5):1091–1098. [PubMed: 20144422]
255. Kovatchev BP, Anderson S, Breton M, Patek S, Clarke W, Bruttomesso D, Maran A, Costa S, Avogaro A, Dalla Man C, Facchinetto A, Guerra S, Magni L, Raimondo DM, De Nicolao G, Renard E, Cobelli C. Personalized subcutaneous model-predictive closed-loop control of T1DM: Pilot studies in the USA and Italy. *Diabetes Jun;2009 58(Suppl 1):A60–A60.*
256. Bruttomesso D, Farret A, Costa S, Marescotti MC, Vettore M, Avogaro A, Tiengo A, Dalla Man C, Place J, Facchinetto A, Guerra S, Magni L, De Nicolao G, Cobelli C, Renard E, Maran A. Closed-loop artificial pancreas using subcutaneous glucose sensing & insulin delivery, and a model predictive control algorithm: Preliminary studies in Padova and Montpellier. *J Diabetes Sci Technol* 2009;3(5):1014–1021. [PubMed: 20144414]
257. Clarke WL, Anderson SM, Breton MD, Patek SD, Kashmer L, Kovatchev BP. Closed-loop artificial pancreas using subcutaneous glucose sensing and insulin delivery and a model predictive control algorithm: The Virginia experience. *J Diabetes Sci Technol* 2009;3(5):1031–1038. [PubMed: 20144416]

258. Lee H, Buckingham BA, Wilson DM, Bequette BW. A closed-loop artificial pancreas using model predictive control and a sliding meal size estimation. *J Diabetes Sci Technol* 2009;3(5):1082–1090. [PubMed: 20144421]
259. Steil GM, Pantaleon AE, Rebrin K. Closed-loop insulin delivery—The path to physiological glucose control. *Adv Drug Deliv Rev* 2004;56:125–144. [PubMed: 14741112]
260. Steil GM, Rebrin K, Darwin C, Hariri F, Saad MF. Feasibility of automating insulin delivery for the treatment of type 1 diabetes. *Diabetes* 2006;55(12):3344–3350. [PubMed: 17130478]
261. Marchetti G, Barolo M, Jovanovic L, Zisser H, Seborg DE. An improved PID switching control strategy for type 1 diabetes. *IEEE Trans Biomed Eng* 2008;55(3):857–865. [PubMed: 18334377]
262. Wang Y, Percival MW, Dassau E, Zisser HC, Jovanovic L, Doyle FJ III. A novel adaptive basal therapy based on the value and rate of change of blood glucose. *J Diabetes Technol* 2009;3(5):1099–1108.
263. Magni, L.; Raimondo, DM.; Allgower, F., editors. New York: Springer Verlag. 2009. Nonlinear Model Predictive Control: Towards New Challenging Applications; p. 384Springer Lecture Notes in Control and Information Sciences series
264. Hovorka R, Chassin LJ, Wilinska ME, Canonico V, Akwi JA, Federici MO, Massi-Benedetti M, Hutzli I, Zaugg C, Kaufmann H, Both M, Vering T, Schaller HC, Schaupp L, Bodenlenz M, Pieber TR. Closing the loop: The adicol experience. *Diabetes Technol Therapeutics* 2004;8(3):307–318.
265. Schaller HC, Schaupp L, Bodenlenz M, Wilinska ME, Chassin LJ, Wach P, Vering T, Hovorka R, Pieber TR. On-line adaptive algorithm with glucose prediction capacity for subcutaneous closed loop control of glucose: Evaluation under fasting conditions in patients with type 1 diabetes. *Diabetic Medicine* 2006;23:90–93. [PubMed: 16409572]
266. Finan DA, Palerm CC, Doyle FJ III, Seborg DE, Zisser H, Bevier WC, Jovanovic L. Effect of input excitation on the quality of empirical dynamic models for type 1 diabetes. *AIChE J* 2009;55:1135–1146.
267. Galvanin F, Barolo M, Macchietto S, Bezzo F. Optimal design of clinical tests for the identification of physiological models of type 1 diabetes mellitus. *Ind Eng Chem Res* 2009;48(4):1989–2002.
268. Dua P, Doyle FJ III, Pistikopoulos EN. Model-based blood glucose control for type 1 diabetes via parametric programming. *IEEE Trans Biomed Eng* Jun;2006 53(6):1478–1491. [PubMed: 16916082]
269. Ellingsen C, Dassau E, Zisser H, Grosman B, Percival MW, Jovanovic L, Doyle FJ III. Safety constraints in an artificial pancreas beta cell: An implementation of model-predictive control with insulin on board. *J Diabetes Sci Technol* 2009;3:536–544. [PubMed: 20144293]
270. Magni L, Raimondo DM, Bossi L, Dalla Man C, De Nicolao G, Kovatchev B, Cobelli C. Model predictive control of type 1 diabetes: An in silico trial. *J Diabetes Sci Technol* 2007;1:804–812. [PubMed: 19885152]
271. El-Khatib FH, Jiang J, Damiano ER. Adaptive closed-loop control provides blood glucose regulation using dual subcutaneous insulin and glucagon infusion in diabetic swine. *J Diabetes Sci Technol* 2007;1:181–192. [PubMed: 19888405]
272. El-Khatib FH, Jiang J, Damiano ER. A feasibility study of bihormonal closed-loop blood glucose control using dual subcutaneous infusion of insulin and glucagon in ambulatory diabetic swine. *J Diabetes Sci Technol* 2009;3(4):789–803. [PubMed: 20144330]
273. Gillis R, Palerm CC, Zisser H, Jovanovic L, Seborg DE, Doyle FJ. Glucose estimation and prediction through meal responses using ambulatory subject data for advisory mode model predictive control. *J Diabetes Sci Technol* 2007;1(6):825–833. [PubMed: 19885154]
274. Palerm CC, Willis JP, Desemone J, Bequette BW. Hypoglycemia prediction and detection using optimal estimation. *Diabetes Technol Therapeutics* 2005;7(1):3–15.
275. Palerm CC, Bequette BW. Hypoglycemia detection and prediction using continuous monitoring—A study on hypoglycaemic clamp data. *J Diabetes Sci Technol* 2009;1(5):624–629. [PubMed: 19885130]
276. Dassau E, Buckingham BA, Bequette BW, Doyle FJ III. Detection of a meal using continuous glucose monitoring: Implications for an artificial β -cell. *Diabetes Care* 2008;31(2):295–300. [PubMed: 17977934]

277. Cameron F, Niemeyer G, Buckingham BA. Probabilistic evolving meal detection and estimation of meal total glucose appearance. *J Diabetes Sci Technol* 2009;3(5):1022–1030. [PubMed: 20144415]
278. Clarke WL, Kovatchev BP. Statistical tools to analyze CGM data. *Diabetes Technol Theraputics* 2009;11:S45–S54.
279. Magni L, Raimondo DM, Dalla Man C, Breton M, Patek S, De Nicolao G, Cobelli C, Kovatchev B. Evaluating the efficacy of closed-loop glucose regulation via control-variability grid analysis (CVGA). *J Diabetes Sci Technol* 2008;2:630–635. [PubMed: 19885239]
280. Zisser H, Jovanovic L, Doyle FJ III, Ospina P, Owens C. Run-to-run control of meal-related insulin dosing. *Diabetes Technol Ther* 2005;7(1):48–57. [PubMed: 15738703]
281. Palerm CC, Zisser H, Jovanovic L, Doyle FJ III. Arun-to-run framework for prandial insulin dosing: Handling real-life uncertainty. *Int J Robust Nonlin Sep*;2007 17(13):1194–1213.
282. Palerm CC, Zisser H, Jovanovic L, Doyle FJ III. A run-to-run control strategy to adjust basal insulin infusion rates in type 1 diabetes. *J Process Contr Mar.–Apr*;2008 18(3–4):258–265.
283. Wang Y, Dassau E, Doyle FJ III. Closed-loop control of artificial pancreatic β -cell in type 1 diabetes mellitus using model predictive iterative learning control. *IEEE Trans Biomed Eng*. to appear.
284. Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H. The burden of mortality attributable to diabetes: Realistic estimates for the year 2000. *Diabetes Care* 2005;28:2130–2135. [PubMed: 16123478]
285. Dalla Man C, Raimondo DM, Rizza RA, Cobelli C. GIM, simulation software of meal glucose-insulin model. *J Diabetes Sci Technol* 2007;1:323–330. [PubMed: 19885087]
286. Nucci G, Cobelli C. Models of subcutaneous insulin kinetics. A critical review. *Comput Methods Programs Biomed* 2000;62:249–257. [PubMed: 10837910]
287. Roach P. New insulin analogues and routes of delivery: Pharmacodynamic and clinical considerations. *Clin Pharmacokinet* 2008;47:595–610. [PubMed: 18698880]
288. Rossetti P, Porcellati F, Fanelli CG, Perriello G, Torlone E, Bolli GB. Superiority of insulin analogues versus human insulin in the treatment of diabetes mellitus. *Arch Physiol Biochem* 2008;114:3–10. [PubMed: 18465353]
289. Chan A, Breton MD, Kovatchev BP. Effects of pulsatile subcutaneous injections of insulin lispro on plasma insulin concentration levels. *J Diabetes Sci Technol* 2008;2:844–852. [PubMed: 19590755]
290. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV. Fully automated closed-loop insulin delivery versus semi-automated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care* 2008;31:934–939. [PubMed: 18252903]
291. Panteleon AE, Loutseiko M, Steil GM, Rebrin K. Evaluation of the effect of gain on the meal response of an automated closed-loop insulin delivery system. *Diabetes* 2006;55:1995–2000. [PubMed: 16804068]
292. Patek SD, Breton MD, Chen Y, Solomon C, Kovatchev B. Linear quadratic gaussian-based closed-loop control of type 1 diabetes. *J Diabetes Sci Technol* 2007;1(6):834–841. [PubMed: 19756210]
293. Moyne, J.; del Castillo, E.; Hurwitz, AM. Run-to-Run Control in Semiconductor Manufacturing. Boca Raton, FL: CRC; 2001.
294. Gonder-Frederick LA, Cox DJ, Kovatchev BP, Schlundt D, Clarke WL. Biopsychobehavioral model of risk of severe hypoglycemia. *Diabetes Care* 1997;20:661–669. [PubMed: 9097000]
295. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Schlundt D, Clarke WL. Stochastic model of self-regulation decision making exemplified by decisions concerning hypoglycemia. *Health Psychol* 1998;17:277–284. [PubMed: 9619478]
296. Patek, SD.; Breton, MD.; Cobelli, C.; Dalla Man, C.; Kovatchev, BP. Adaptive meal detection algorithm enabling closed-loop control in type 1 diabetes. Proc. 7th Diabetes Technology Meeting; San Francisco, CA. 2007.
297. Clarke WL, Cox DJ, Gonder-Frederick LA, Julian DM, Kovatchev BP, Young-Hyman D. The bio-psycho-behavioral model of severe hypoglycemia II: Self-management behaviors. *Diabetes Care* 1999;22:580–584. [PubMed: 10189535]
298. Cox DJ, Gonder-Frederick LA, Kovatchev BP, Young-Hyman D, Schlundt D, Julian DM, Clarke WL. Bio-psycho-behavioral model of severe hypoglycemia: II understanding causes of severe hypoglycemia. *Diabetes Care* 1999;22:2018–2025. [PubMed: 10587836]

299. Breton MD, Clarke WL, Farhy LS, Kovatchev BP. A model of self-treatment behavior, glucose variability, and hypoglycemia-associated autonomic failure in type 1 diabetes. *J Diabetes Sci Technol* 2007;1:331–357. [PubMed: 19606264]
300. Davidian, M.; Giltinan, DM. Nonlinear Models for Repeated Measurement Data. Boca Raton, FL: Chapman & Hall/CRC; 1998.
301. Denti P, Bertoldo A, Vicini P, Cobelli C. Nonlinear mixed effects to improve glucose minimal model parameter estimation: a simulation study in intensive and sparse sampling. *IEEE Trans Biomed Eng* Sep;2009 56(9 pt 1):2156–2166. [PubMed: 19380266]
302. Denti, P.; Bertoldo, A.; Vicini, P.; Cobelli, C. Covariate Selection for the IVGTT Minimal Model of Glucose Disappearance. Proc. 18th Population Approach Group in Europe Meeting; St. Petersburg, Russia. 2009. [Online]. Available: <http://www.page-meeting.org/default.asp?abstract=1642>
303. Silber HE, Jauslin PM, Frey N, Gieschke R, Simonsson US, Karlsson MO. An integrated model for glucose and insulin regulation in healthy volunteers and type 2 diabetic patients following intravenous glucose provocation. *J Clin Pharmacol* 2007;47:1159–1171. [PubMed: 17766701]
304. Jauslin PM, Silber HE, Frey N, Gieschke R, Simonsson US, Jorga K, Karlsson MO. An integrated glucose-insulin model to describe oral glucose tolerance test data in type 2 diabetics. *J Clin Pharmacol* 2007;47:1244–1255. [PubMed: 17906159]

Biographies



Claudio Cobelli (M'84–SM'90–F'01) was born in Bressanone (Bolzano), Italy, on February 21, 1946. He received the Ph.D. degree (Laurea) in electrical engineering from the University of Padova, Padova, Italy, in 1970.

From 1970 to 1980, he was a Research Fellow of the Institute of System Science and Biomedical Engineering, National Research Council, Padova. From 1973 to 1975 and 1975 to 1981, he was an Associate Professor of biological systems at the University of Florence and Associate Professor of biomedical engineering at the University of Padova, respectively. In 1981, he became a Full Professor of biomedical engineering at the University of Padova. Since

2000, he has been an Affiliate Professor of bioengineering at the University of Washington, Seattle. Since 2000, he has been Chairman of the Graduate and Ph.D. Program on bioengineering at the University of Padova. His main research activity is in the field of modeling and identification of physiological systems, especially endocrine-metabolic systems. He has published around 280 papers in internationally refereed journals. He is Coeditor of *Carbohydrate Metabolism: Quantitative Physiology and Mathematical Modeling* (Chichester: Wiley, 1981), *Modeling and Control of Biomedical Systems* (Oxford: Pergamon, 1989), and *Modeling Methodology for Physiology and Medicine* (New York: Academic, 2000). He is Coauthor of *The Mathematical Modeling of Metabolic and Endocrine Systems* (New York: Wiley, 1983); *Tracer Kinetics in Biomedical Research: from Data to Model* (London: Kluwer Academic/Plenum, 2001) and *Introduction to Modeling in Physiology and Medicine* (San Diego: Academic, 2008).

Dr. Cobelli is currently an Associate Editor of IEEE Transactions on Biomedical Engineering and *Diabetes*. He is on the Editorial Board of the *American Journal of Physiology: Endocrinology and Metabolism*, *Diabetes*, and *Journal of Diabetes Science & Technology*. In the past he has been Associate Editor of *Mathematical Biosciences* and on the Editorial Board of *Control Engineering Practice*, *Diabetes, Nutrition and Metabolism*, *Diabetologia*, and *American Journal of Physiology: Modeling in Physiology*. He has been Chairman (1999–2004) of the Italian Biomedical Engineering Group and has been Chairman (1990–1993 and 1993–1996) of IFAC TC on Modeling and Control of Biomedical Systems. He is Fellow of BMES.



Chiara Dalla Man was born in Venice, Italy, on March 2, 1977. She received the Ph.D. degree (*Laurea cum laude*) in electronics engineering from the University of Padova, Padova, Italy, in 2000. She also received the Ph.D. degree in biomedical engineering from the University of Padova, and City University London, U.K., in 2005.

From March to September 2004, she was a Visiting Ph.D. Student at the Centre of Measurements and Information in Medicine, City University London, U.K. From 2005 to 2007, she was a Post-Doctoral Research Fellow with the Department of Information Engineering of

Padova University. Since October 2007, she has been an Assistant Professor in the Faculty of Engineering of Padova University. Her research interests include the field of mathematical modeling of metabolic and endocrine systems.

Dr. Dalla Man is on the Editorial Board of *Journal of Diabetes Science and Technology*.



Giovanni Sparacino was born in Pordenone, Italy, on November 11, 1967. He received the Doctoral degree in electronics engineering *cum laude* from the University of Padua, Padua, Italy, in 1992, and the Ph.D. degree in biomedical engineering from the Polytechnic of Milan, Milan, Italy, in 1996.

Since 1997, he has been with the University of Padua: from 1997 to 1998, he was a Research Engineer at the Faculty of Medicine; from 1999 to 2004, he was an Assistant Professor at the Faculty of Engineering; since 2005, he has been an Associate Professor of biomedical engineering at the Faculty of Engineering. His scientific interests include deconvolution and parameter estimation techniques for the study of physiological systems, hormone time-series analysis, continuous glucose monitoring, and measurement and processing of evoked potentials.



Lalo Magni was born in Bormio, Italy, in 1971. He graduated with full marks and honors (*summa cum laude*) in computer engineering from the University of Pavia, Pavia, Italy, in 1994. He received the Ph.D. degree in electronic and computer engineering in 1998.

From January 1999 to December 2004, he was an Assistant Professor at the University of Pavia, where he has been an Associate Professor since January 2005. From October 1996 to February 1997 and in March 1998, he was at CESAME, Université Catholique de Louvain, Louvain La Neuve, Belgium. From October to November 1997, he was at the University of Twente with the System and Control Group in the Faculty of Applied Mathematics. His current research interests include nonlinear control, predictive control, robust control, process control and glucose concentration control in subjects with diabetes. His research is witnessed by more than 40 papers published in international journals.

Dr. Magni was a Plenary Speaker at the 2nd IFAC Conference “Control Systems Design” (CSD’03), in 2003. In 2005, he was a Keynote Speaker at the NMPC Workshop on Assessment and Future Direction. In 2003, he was a Guest Editor of the Special Issue “Control of Nonlinear Systems with Model Predictive Control” in the *International Journal of Robust and Nonlinear Control*. He served as an Associate Editor of the IEEE Transactions on Automatic Control. He is an Associate Editor of *Automatica*. He was subarea Chair for the area “Nonlinear systems optimal and predictive control” at the IFAC Symposium on Nonlinear Control Systems (NOLCOS 2007). He organized the NMPC Workshop on Assessment and Future Direction in September 2008 in Pavia.



Giuseppe De Nicolao (SM’01) received the degree in electronic engineering from the Polytechnic of Milan, Italy.

From 1987 to 1988, he was with the Biomathematics and Biostatistics Unit of the Institute of Pharmacological Researches “Mario Negri”, Milano. In 1988, he joined the Italian National Research Council (CNR) as a Research Scientist at the Center of System Theory in Milan, Italy. From 1992 to 2000, he was an Associate Professor and, since 2000, he has been a full Professor of model identification in the Department of Computer Science and Systems Engineering of the University of Pavia, Pavia, Italy. In 1991, he held a visiting fellowship at the Department of Systems Engineering of the Australian National University, Canberra. His research interests include Bayesian learning, neural networks, model predictive control, optimal and robust filtering and control, deconvolution techniques, modeling, identification and control of biomedical systems, advanced process control and fault diagnosis for semiconductor manufacturing. On these subjects he has authored or coauthored more than 100 journal papers and is coinventor of two patents.

Dr. De Nicolao was a Keynote Speaker at the IFAC workshop on “Nonlinear model predictive control: Assessment and future directions for research”. From 1999 to 2001, he was an Associate Editor of the IEEE Transactions on Automatic Control and, since 2007, he has been an Associate Editor of *Automatica*.



Boris P. Kovatchev received the Ph.D. degree in mathematics (probability and statistics) from Sofia University “St. Kliment Ohridski,” Bulgaria, in 1989.

Currently, he is a Professor in the Department of Psychiatry and Neurobehavioral Sciences and Adjunct Professor of Systems and Information Engineering, University of Virginia, Charlottesville. He is Head of Section Computational Neuroscience and Director of the University of Virginia Diabetes Technology Program. His research expertise is in biomathematics, specifically modeling of biologic and behavioral processes. In the past 15 years he has been involved in various aspects of diabetes technology development, as well as in the development of quantitative strategies for neurobiological problems. Currently, he is the Principal Investigator of two large projects funded by the National Institutes of Health, and the Principal Investigator of the JDRF Artificial Pancreas Project at the University of Virginia. He is also involved in industry-sponsored translational research. He is author of over 100 scientific publications and coauthor of the textbook *Invitation to Biomathematics* (Academic, 2008). His academic work includes participation in several international boards and NIH study sections. He holds five patents and is author of 15 other inventions that are currently at various stages of the patenting process.

Dr. Kovatchev is an Associate Editor of IEEE Transactions on Biomedical Engineering and member of the Editorial board of the *Journal of Diabetes Science and Technology*.

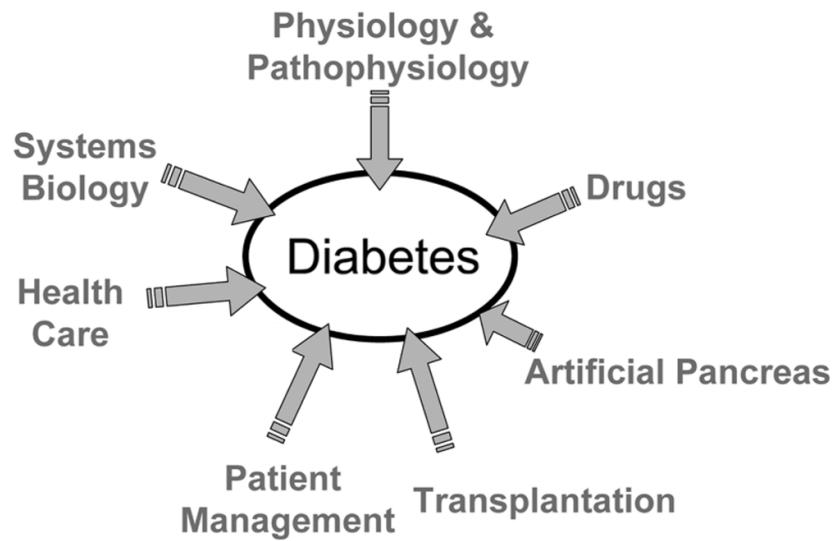


Fig. 1.
Disciplines which contribute to diabetes control.

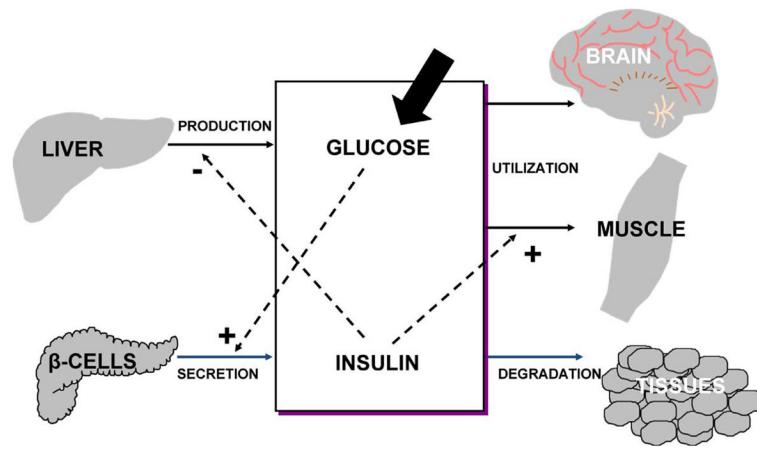
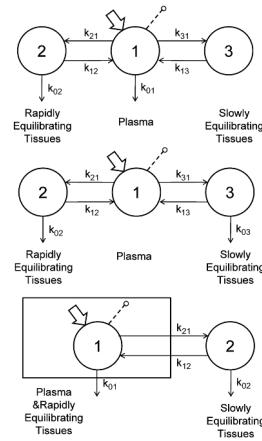
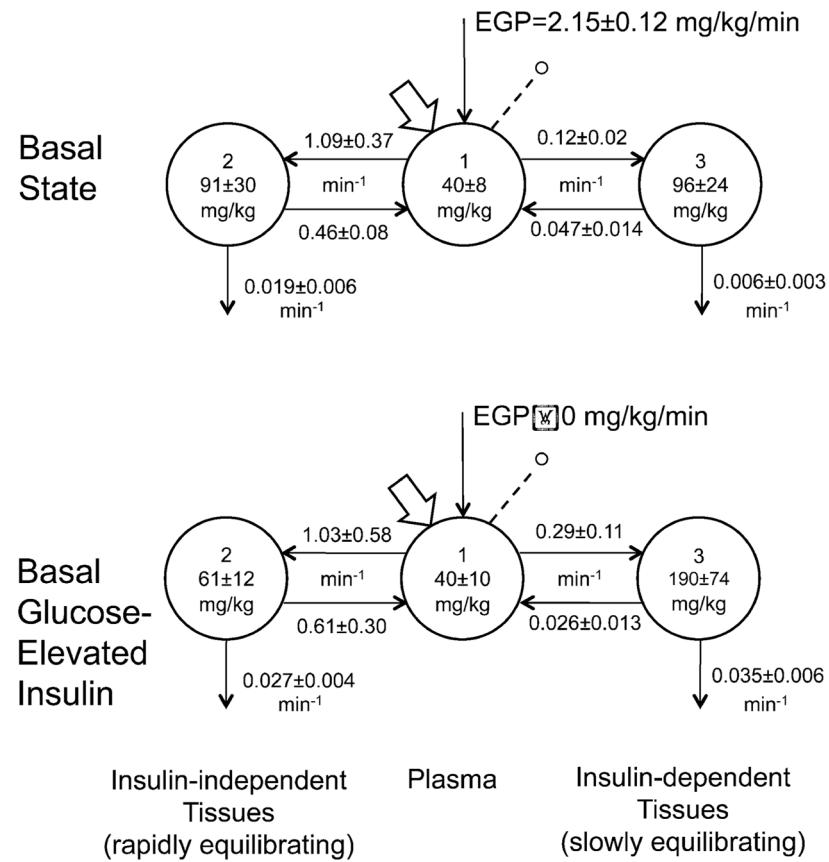


Fig. 2.
Scheme of the glucose-insulin system.

**Fig. 3.**

Compartmental model of glucose kinetics in steady state. Upper panel: three compartment model with glucose utilization taking place in plasma and rapidly equilibrating tissues; Middle panel: three compartment model with glucose utilization taking place in slowly and rapidly equilibrating tissues; Lower panel: compartment model with glucose utilization taking place in plasma + rapidly equilibrating tissue and slowly equilibrating tissues.

**Fig. 4.**

Model of glucose kinetics in steady state: model-derived parametric representation at basal (upper panel) and elevated insulin (lower panel). EGP denotes endogenous glucose production.

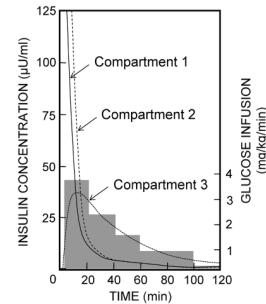


Fig. 5.

Comparison among insulin concentration in plasma (compartment 1), rapidly (compartment 2) and slowly (compartment 3) equilibrating tissues with glucose utilization measured with glucose clamp technique. Compartment 3 mimics the time course of glucose infusion (=utilization).

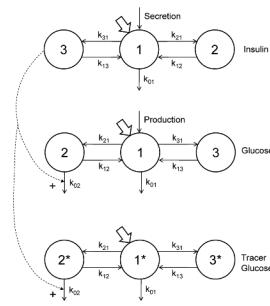


Fig. 6.

Compartmental models of insulin (upper panel), glucose (middle panel), and tracer glucose (lower panel) kinetics.

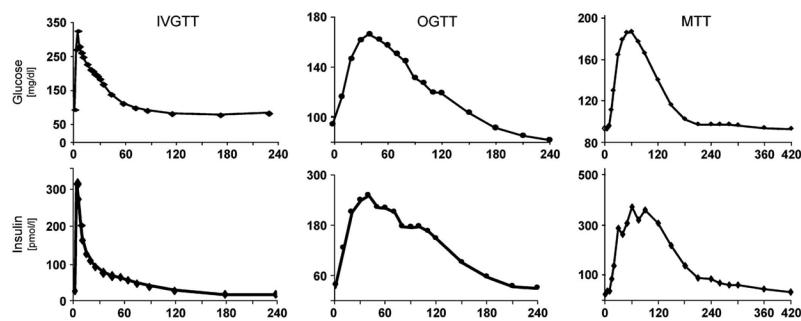


Fig. 7.

Plasma glucose (upper) and insulin (lower) concentrations measured during IVGTT (right), OGTT (middle), and MTT (left, panel).

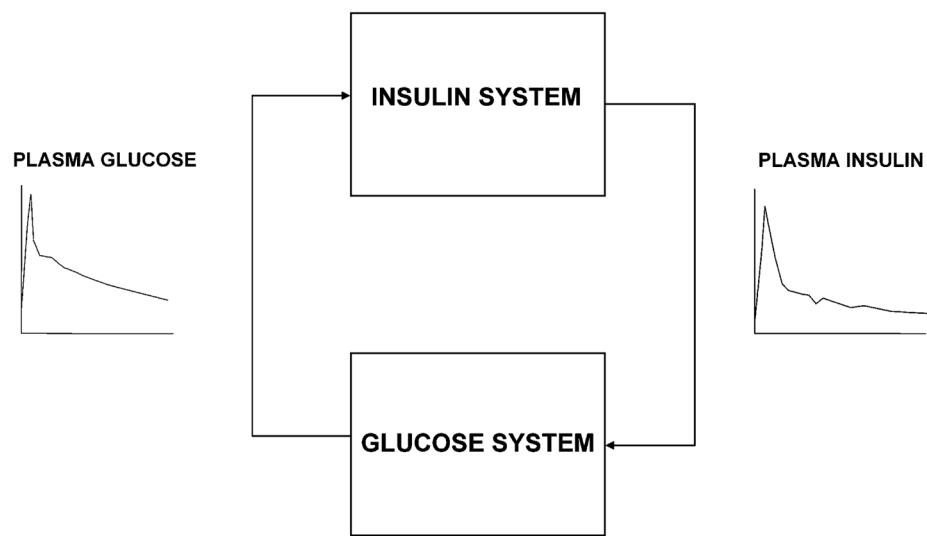


Fig. 8.
Decomposition of glucose-insulin system into glucose and insulin subsystems.

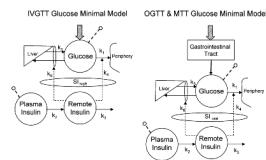
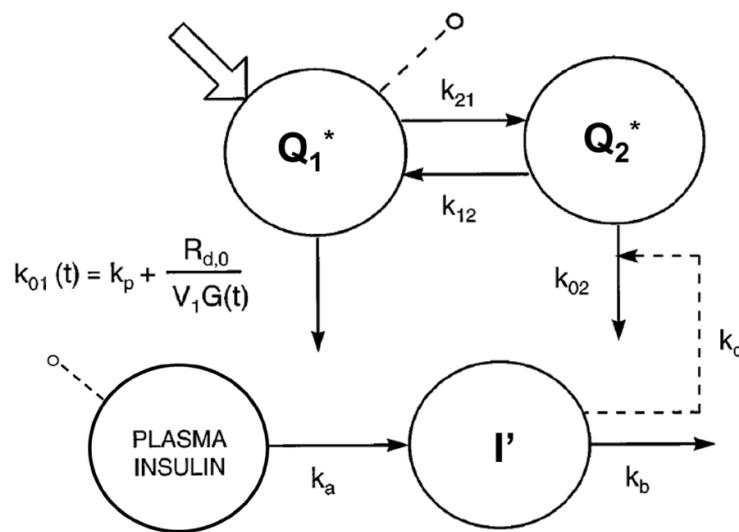


Fig. 9.
Left panel: IVGTT glucose minimal model. Right panel: OGTT/MTT glucose minimal model.

**Fig. 10.**

Two compartment model of tracer glucose kinetics. The insulin-independent glucose utilization takes place in the accessible compartment (Q_1^*) while insulin-dependent glucose utilization consists of two components, one constant, $R_{d,0}$, and the other proportional to glycemia. Insulin-dependent glucose utilization is parametrically controlled by insulin in a compartment remote from plasma (I').

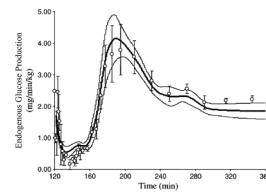


Fig. 11.

Endogenous glucose production estimated with the dual tracer technique (open circles, vertical bars represents standard deviation) and with deconvolution (continuous line).

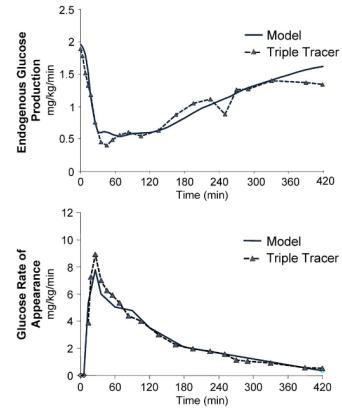


Fig. 12.

Comparison between endogenous glucose production (upper panel) and rate of appearance of glucose (lower panel) during a meal reconstructed with models and triple tracer model-independent method.

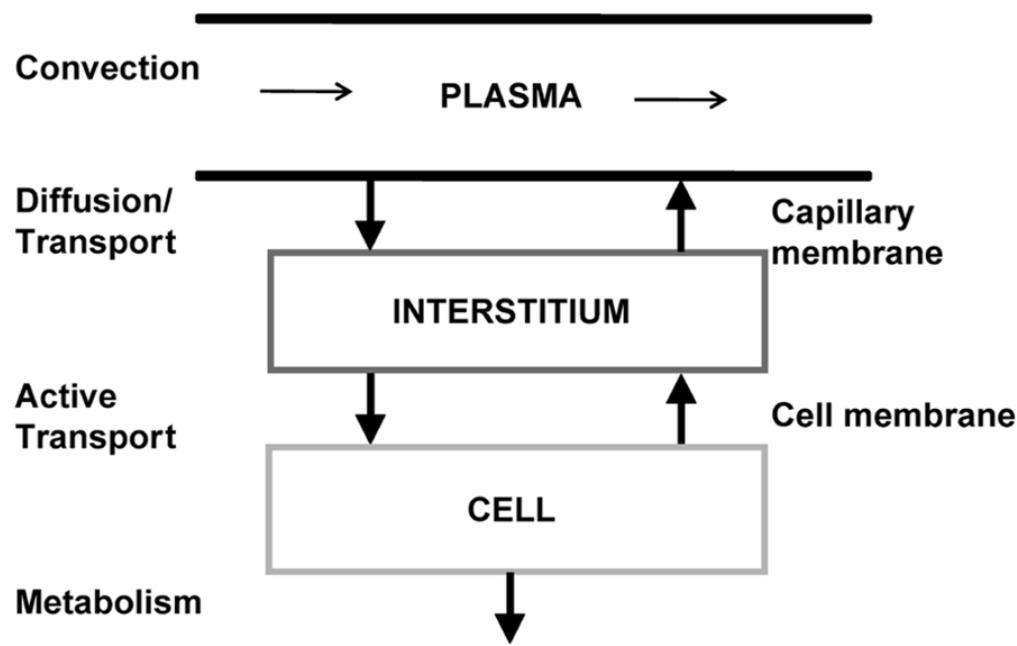
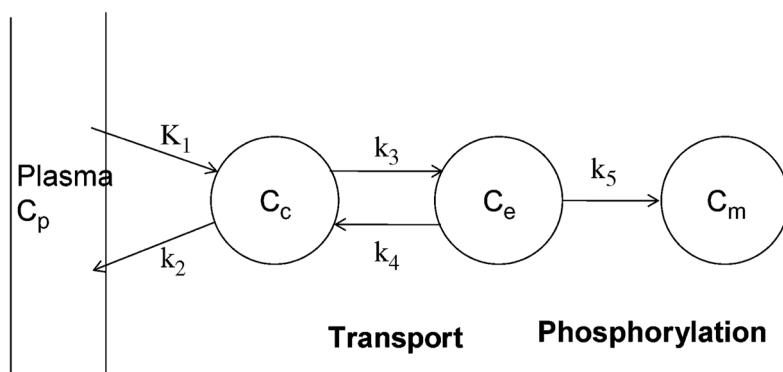


Fig. 13.

Major glucose processing: diffusion to/from the intersitium, active transport in and out of the cell, and phosphorylation/metabolism.

**Fig. 14.**

The 5 k model of $[^{18}\text{F}]$ FDG in skeletal muscle: C_p is $[^{18}\text{F}]$ FDG plasma arterial concentration, C_c extracellular concentration of $[^{18}\text{F}]$ FDG normalized to tissue volume, C_e $[^{18}\text{F}]$ FDG tissue concentration, C_m $[^{18}\text{F}]$ FDG – 6 – P tissue concentration, total ^{18}F activity concentration in the ROI, K_1 [$\text{ml}/\text{ml}/\text{min}$] and k_2 [min^{-1}] the exchange between plasma and extracellular space, k_3 [min^{-1}] and k_4 [min^{-1}] transport in and out of cell, k_5 [min^{-1}] phosphorylation.

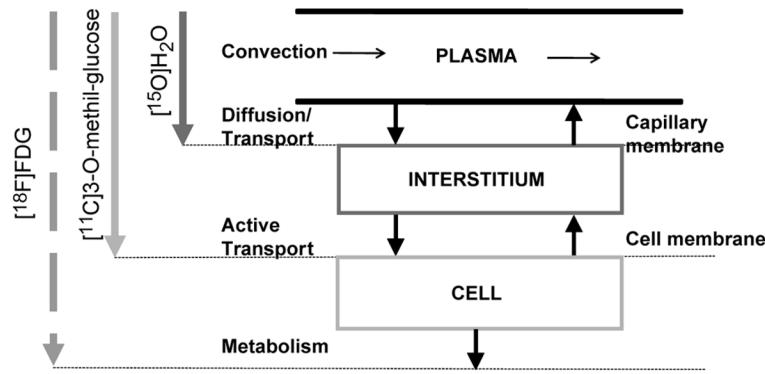
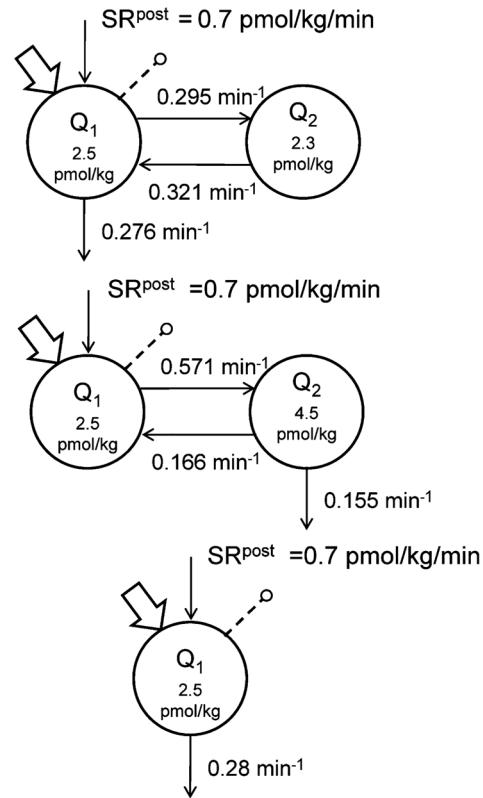


Fig. 15.

Employment of PET tracers to study glucose diffusion through capillary membrane, active transport into the cells and metabolism.

**Fig. 16.**

Compartmental models of insulin kinetics. Upper panel: two compartment model with insulin degradation in the accessible compartment; Upper panel: two compartment model with insulin degradation in the remote compartment; Upper panel: one compartment model.

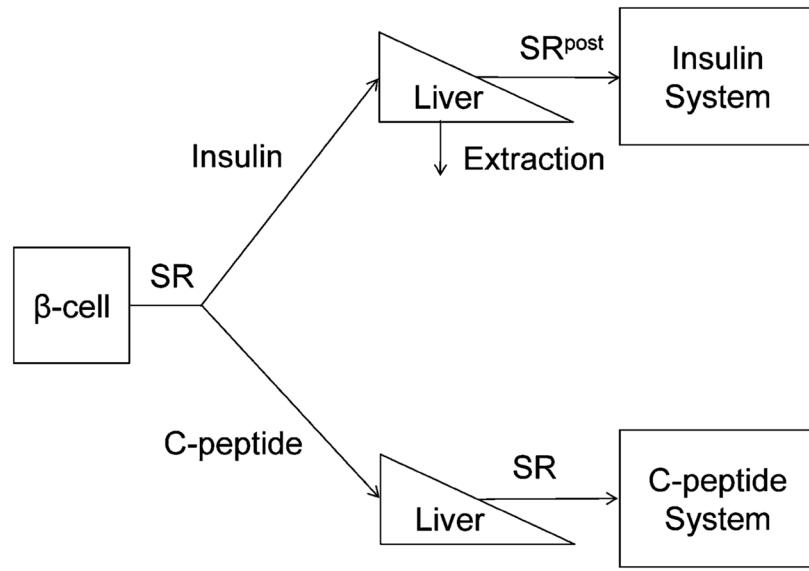
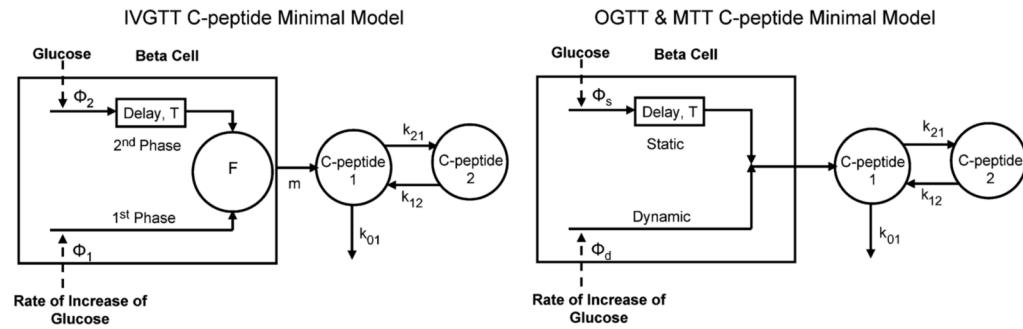
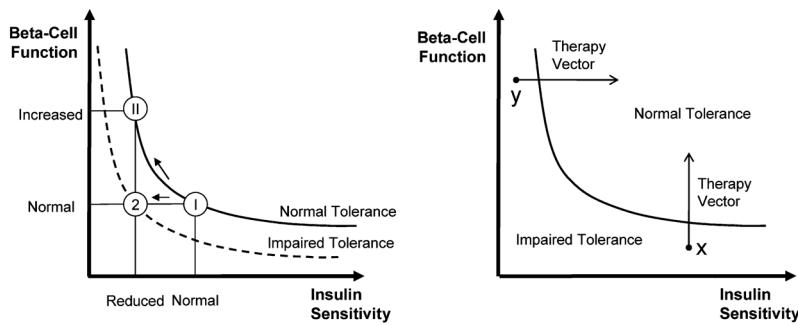


Fig. 17.

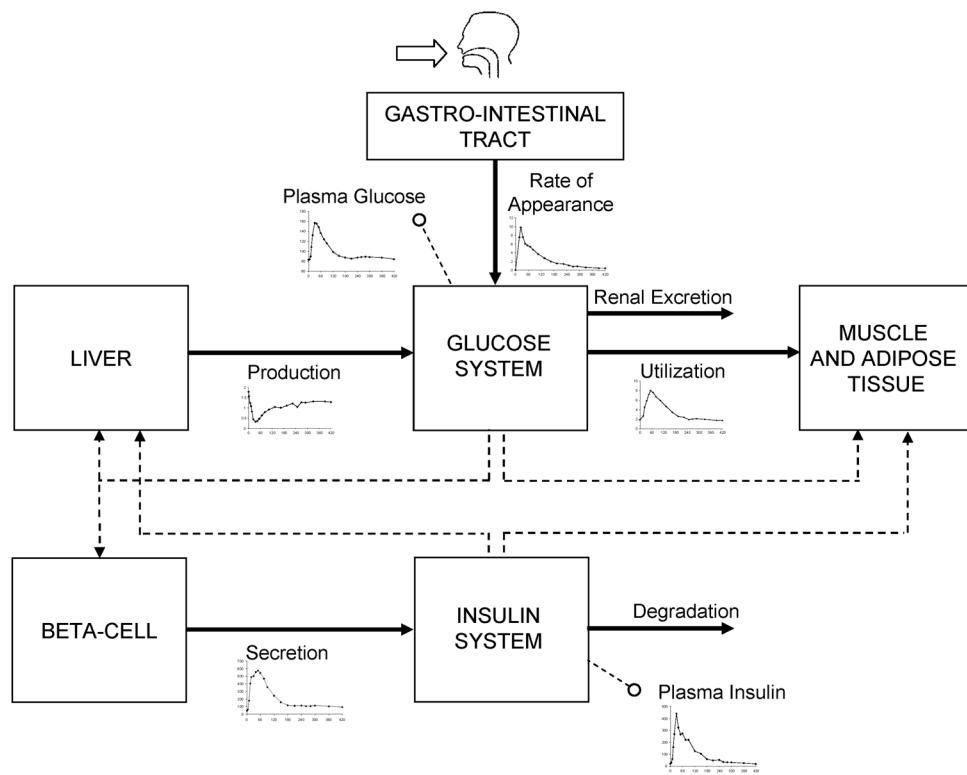
Schematic representation of insulin (upper) and C-peptide (lower) pancreatic secretion and kinetics. Insulin is secreted by the beta-cells in the portal vein and extracted by the liver before it appears in plasma; C-peptide is secreted by the beta-cells, equimolarly to insulin, passes through the liver, before it appears in plasma, but is not extracted.

**Fig. 18.**

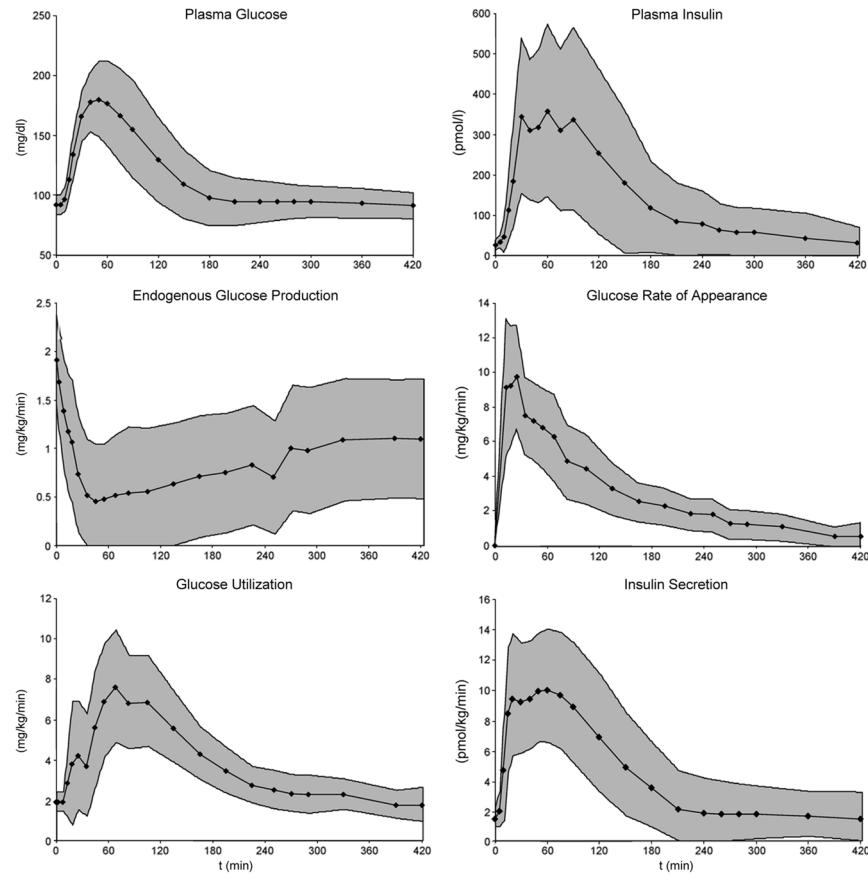
Left panel: IVGTT C-peptide minimal model. Right panel: OGTT/MTT C-peptide minimal model.

**Fig. 19.**

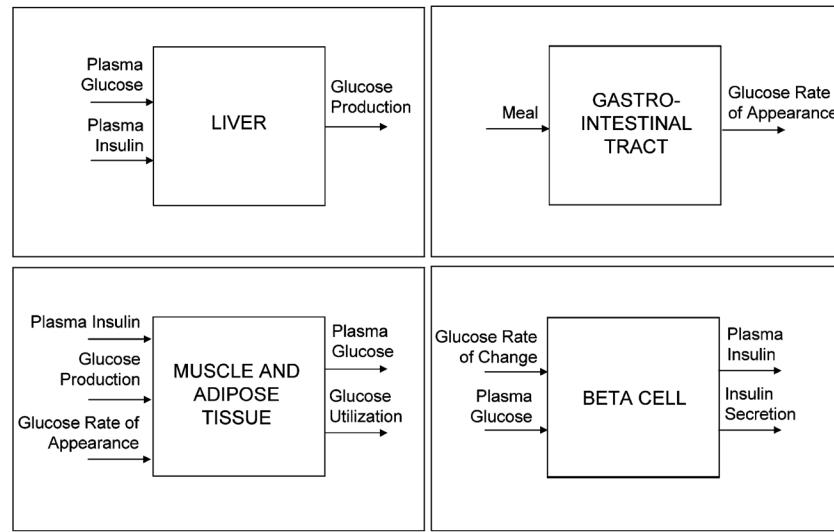
Disposition index paradigm. Left panel: a normal individual could be represented by state I; if beta-cells respond to a decrease in insulin sensitivity by adequately increasing insulin secretion (state II) the product of beta-cell function and insulin sensitivity (the disposition index) is unchanged, and normal glucose tolerance is retained. In contrast, if there is not an adequate compensatory increase in beta-cell function to the decreased insulin sensitivity (state 2) the individual develops glucose intolerance. Right panel: importance of segregating glucose tolerance into its individual components of beta-cell responsiveness and insulin sensitivity. Subject x is intolerant due to its poor beta-cell function while subject y has poor insulin sensitivity; these two individuals need opposite therapy vectors.

**Fig. 20.**

Scheme of the glucose-insulin control system which relates measured plasma concentrations, i.e., glucose and insulin, to glucose fluxes, i.e., rate of appearance, production, utilization, renal extraction, and insulin fluxes, i.e., secretion and degradation.

**Fig. 21.**

Mixed meal data base (average of 204 nondiabetic subjects, grey area represents $\text{mean} \pm 1\text{SD}$ range). Top panel: glucose (left) and insulin (right) concentrations. Middle panel: endogenous glucose production (left) and glucose rate of appearance (right). Bottom panel: glucose utilization (left) and insulin secretion (right).

**Fig. 22.**

Unit process models and forcing function strategy: endogenous glucose production (top left panel); glucose rate of appearance (top right panel); glucose utilization (bottom left panel); insulin secretion (bottom right panel). Entering arrows represent forcing function variables, outgoing arrows are model output.

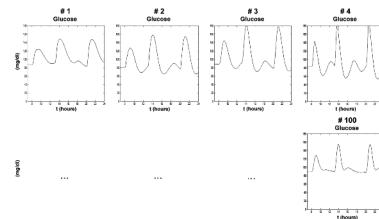


Fig. 23.
Example of daily glucose concentration in some generated *in silico* subjects.

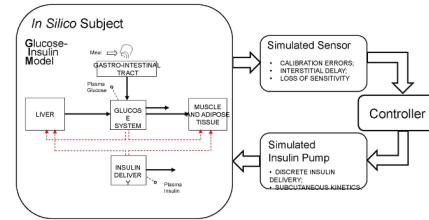
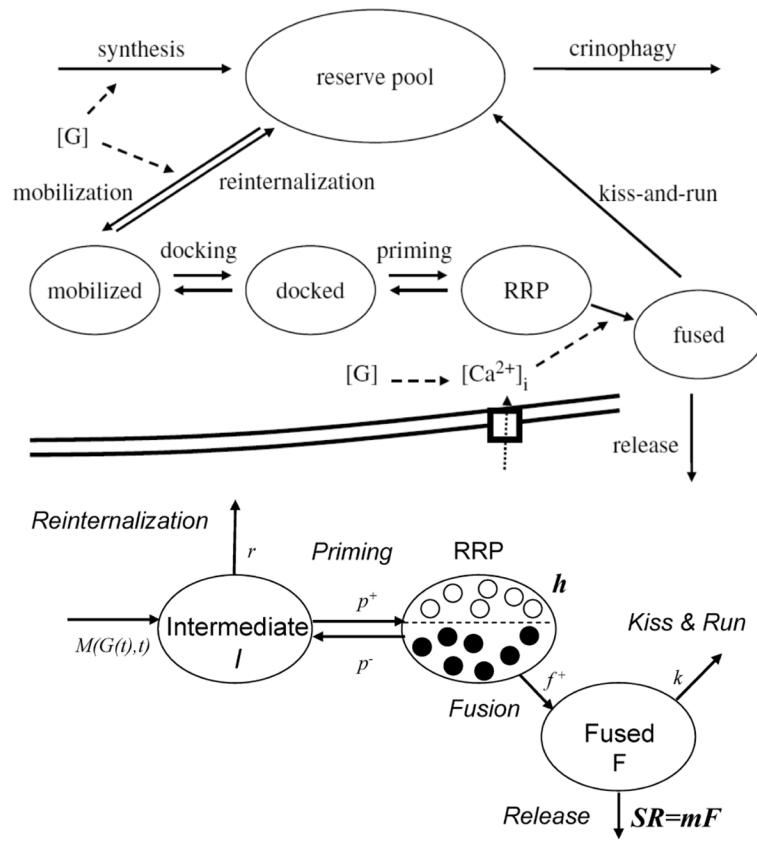


Fig. 24.

Employment of the type 1 diabetes simulator for testing closed-loop control algorithm for insulin infusion.

**Fig. 25.**

Upper panel: overview of the *in silico* model of insulin secretion which includes mobilization of secretory granules from a very large reserve pool to the cell periphery, where they attach to the plasma membrane (docking). The granules can mature further (priming) and attach to calcium channels, thus entering the “readily releasable pool” (RRP). Calcium influx provides the signal triggering membrane fusion. Lower panel: mathematical formulation of the model.

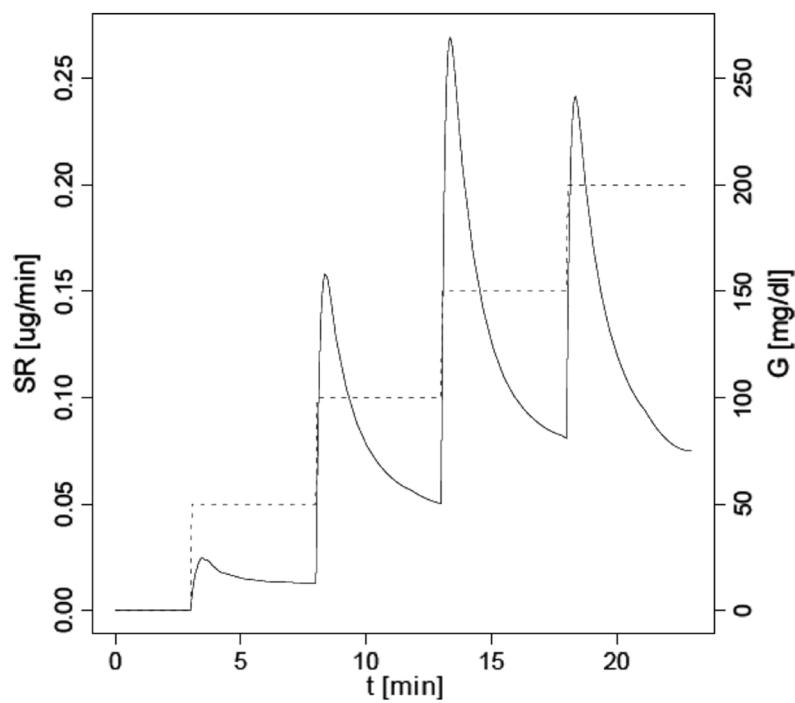


Fig. 26.

Simulation results: insulin secretion (SR) in response to the staircase glucose stimulation (G).

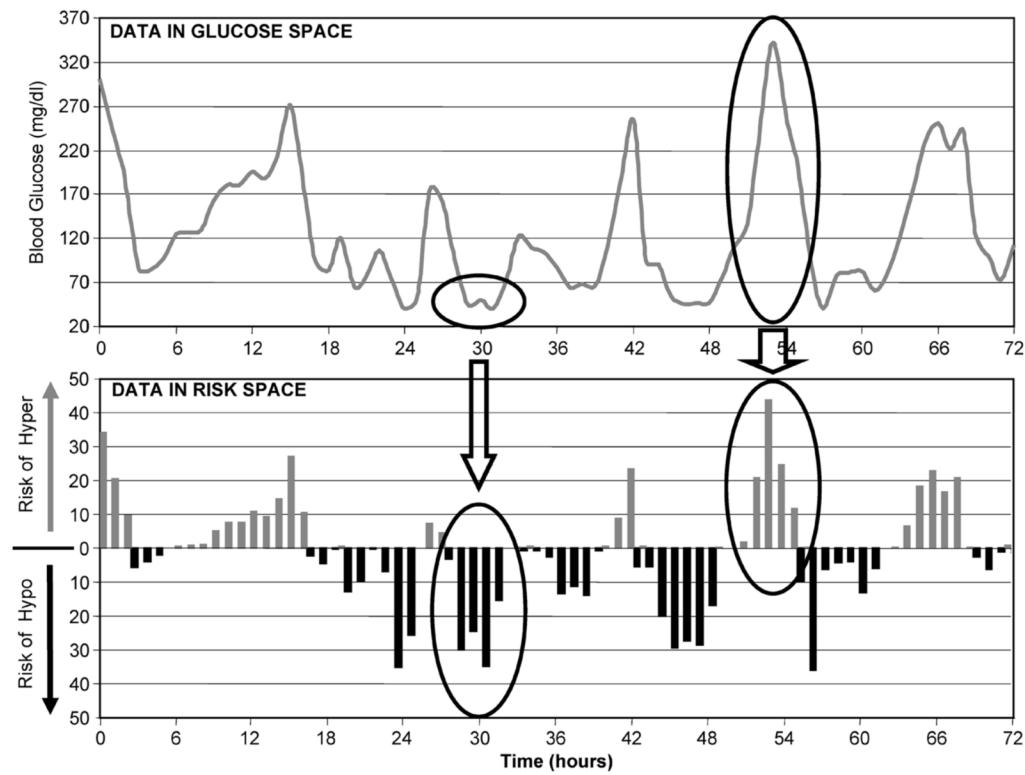


Fig. 27.
Transforming BG data into risk space equalizing the hypoglycemic and hyperglycemic blood glucose ranges.

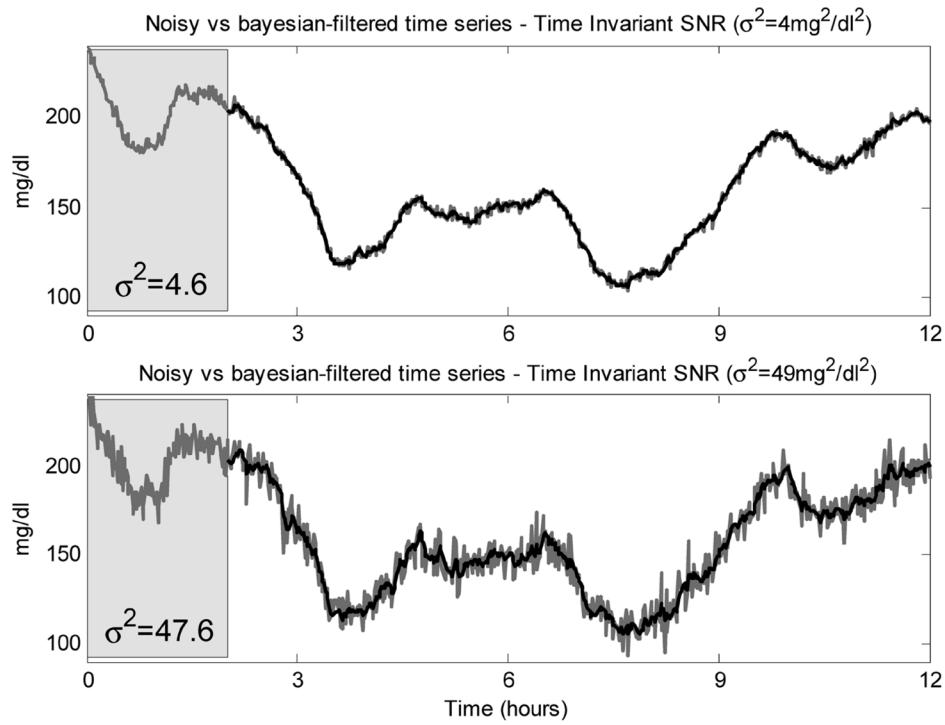


Fig. 28.

Two simulated CGM profiles obtained with different noise variance. Noisy (gray line) versus Kalman filtered (black) signals. Shaded areas correspond to the burn-in intervals.

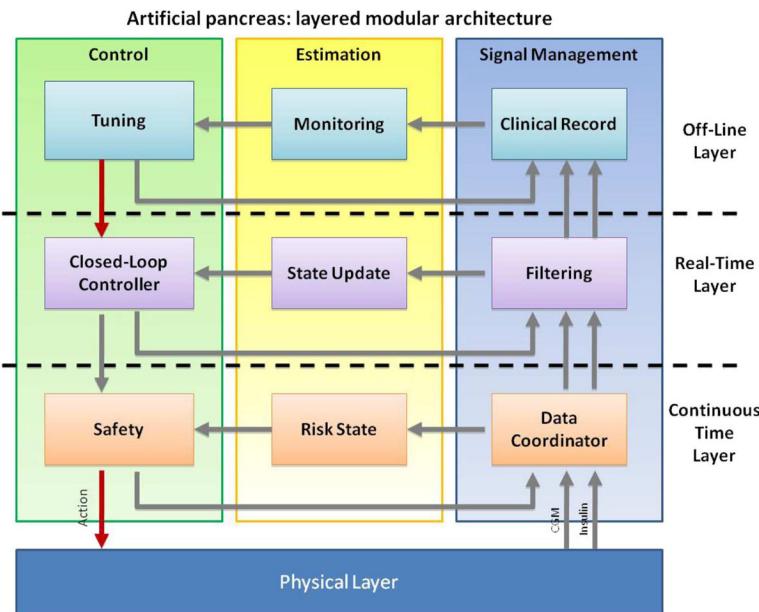


Fig. 29.

Modular layered architecture of the artificial pancreas. The layers work on different time scales: the fastest one deal with safety maintenance, the middle one with real-time closed-loop control, and the top one with tuning and supervision on a daily or longer time scale. Three main functionalities are included in each layer: control, estimation, and data management. Decision flow is from top to bottom and information flow is from bottom to top. A layer can override decisions suggested by its upper layer, e.g., for safety reasons.

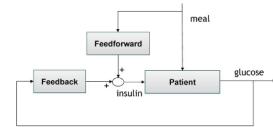
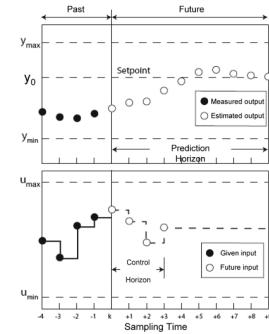


Fig. 30.

Block diagram of a closed-loop glucose control systems including a feedforward action. Information on meal time and amount is used to generate a feedforward action, typically under the form of a premeal bolus. The insulin control signal is obtained as the sum of the feedforward action and the feedback computed by the controller on the basis of glucose sensing.

**Fig. 31.**

MPC prediction scheme: given the model, past inputs and outputs, the future outputs are predicted as a function of future inputs.

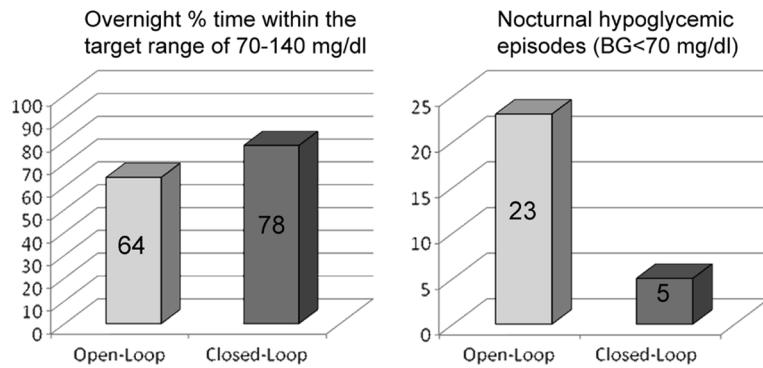


Fig. 32.

Results of a recent clinical trial that compared conventional open-loop therapy to closed-loop glucose control using Linear Model Predictive Control. Closed-loop control achieved an increase of overnight percent time within the target range and an almost five-fold reduction of the number of nocturnal hypoglycemic episodes.

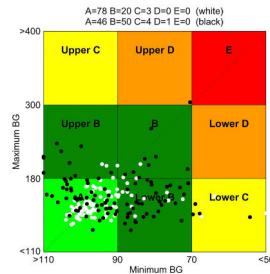


Fig. 33.

An example of CVGA plot. Each patient is represented by a point in the CVGA plane whose coordinates correspond to the minimal and maximal glycemia reached during the monitored time period (note that the axis of the minimal glycemia is reverted). Regulation improves as the points get closer to the lower left corner, corresponding to ideal euglycemia. The glycemic regulation of two populations (white and black circles) is compared. The greater percentage of patients within the A region indicates that the white-dot population achieves better glycemic control compared to the black-dot population.

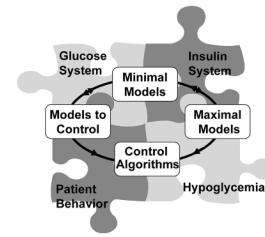


Fig. 34.

Dual-layer bio-behavioral structure of diabetes modeling and control: Layer 1 includes the puzzle of physiologic and behavioral characteristics that determine the specifics of each individual. Layer 2 includes the engineering approaches available to support the optimization of diabetes control.