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Reviews

Mathematical modelling of glucose dynamics

Benoit Huard and Gemma Kirkham

Abstract

The accurate regulation of glucose within humans is an essential feature of homeostasis. It optimises energy release in the muscles and organs. Glucose rhythms driven by internal and external stimuli have been physiologically observed in humans and modelled mathematically to provide a solid framework for understanding these processes in a qualitative and quantitative manner. In this article, we review the latest contribution of mathematical modelling to the understanding and prediction of dynamics within the glucose regulation system.

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Keywords

Glucose regulation, Mathematical modelling, Insulin, Glucagon, Diabetes, Differential equations.

Introduction

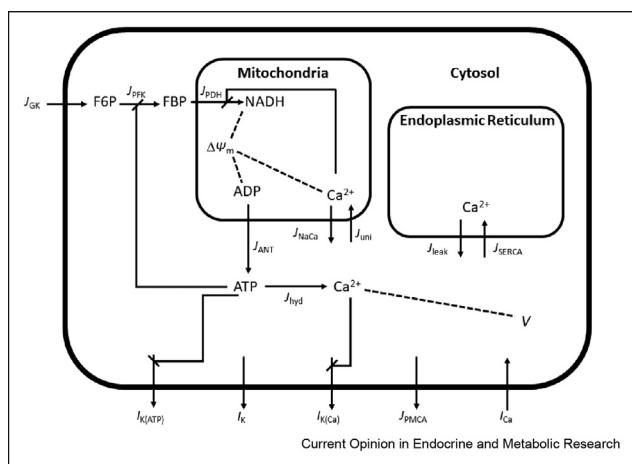
The mathematical modelling of physiological regulation is an important theoretical tool for furthering the understanding of biological processes, and devising quantitative markers of both healthy regulation and pathogenesis in the healthy and non-healthy regimes [5]. In conjunction with the increased use of wearable monitoring devices [36], it thus comes as an indispensable instrument for informing clinical practice, tracking the progression of diabetes [29], and devising optimal treatment strategies that integrate natural rhythms [26]. Glucose regulation is an integral part of

the endocrine system [77] and is the result of complex biochemical interactions occurring within the plasma, muscles and organs. Two main modelling strands prove useful for understanding these interactions. Many studies investigate mechanisms at the cellular level to understand patterns of insulin and glucagon release or glucose absorption, while others regard regulation at the system level, focusing on key physiological functions. Such models provide a framework for assessing glucose regulation efficiency in an individual and determining personalised conditions for the successful implementation of an automated insulin distribution system [12,19,38].

Dynamics within the Langerhans islets

The secretion of insulin operates in a pulsatile manner with a period of about 5 min and is triggered within β cells in response to variations in glucose levels, especially following meals. It is released in two phases, which are principally modulated by the ATP/ADP ratio which increases following the entry of glucose into the cell through the cellular membrane, while Ca^{2+} waves facilitate the exocytosis of insulin granules [37,58]. Recent models provide evidence for intracellular interconnected feedback mechanisms involving Ca^{2+} signalling and metabolic oscillations.

One such model is the integrated oscillator model (IOM) [11,46], which builds upon the previous dual oscillator model [47] and contains an additional key Ca^{2+} feedback to glycolysis [43,46]. It integrates bidirectional feedback between electrical activity and glycolytic oscillations within a single β -cell along with mitochondrial dynamics [43] to embed energy production mechanisms (Figure 1). The model incorporates cellular and mitochondrial membrane potentials, along with Ca^{2+} , ATP, and fructose phosphates (fructose 1,6-bisphosphate FBP, and fructose 6-phosphate F6P), the dynamics of which are described by a set of eleven differential equations along with a number of fluxes and ionic currents. The oscillations produced by the model (Figure 2) are in line with experimental results on mice β cells, including bursting oscillations in the cellular membrane potential. The model is able to reproduce numerous key experimental findings of pulsatile insulin secretion, notably the presence of compound oscillations and the sawtooth oscillations in FBP (see Figure 2) [46] and in the pyruvate kinase activity reporter (PKAR) signal, which is a biosensor engineered to monitor glycolytic activity [48].

Figure 1

Modular diagram for the integrated oscillator model of a single mouse β cell, including membrane potentials, Ca^{2+} , ATP, ADP, fructose phosphates, and key ionic currents and fluxes [43].

The modelling highlights the importance of the tetrameric enzyme phosphofructokinase (PFK), which is responsible for the catalysis of the initial reaction in glycolysis, and thus has a crucial role in the genesis of oscillations [42]. Mouse experiments supplemented with this augmented mathematical model has shown that β cells deprived of phosphofructokinase M (PFK-M) keep their ability to produce pulsatile insulin secretion thanks to isoforms of the enzyme [44]. In turn, the IOM has been used along with the model from Cha et al. [16] and the phantom bursting model in [45] to study how the ATP/ADP ratio varies in response to glucose levels in the presence of K(ATP)-driven Ca^{2+} bursting oscillations in [43].

In humans, the bursting of pituitary cells also occurs in pseudo-plateaus, showing additional smaller amplitude bursts in the plateau areas. These mixed-mode oscillations were studied in [7] using a modified version of the Hodgkin-Huxley model. The model was reduced to a 3D slow-fast system in which the maximal conductance of the potassium human Ether-à-go-go-Related Gene (hERG) channel can be used as a bifurcation parameter to generate the hyperpolarisation, spiking and mixed-mode oscillatory bursting states.

The modelling of interactions between β cells within the islets of Langerhans can be achieved by regarding the system as a weighted network connected through gap junction channels. In particular, this approach has been used in [61] to provide synchronisation conditions on the connectivity matrix for homogeneous (all active) and heterogeneous (including a fraction of silent cells) populations of β cells, which are individually assumed to satisfy Pernarowski's model of bursting [24,59]. An

appropriate Lyapunov function was constructed to obtain synchronicity constraints [61]. While this modelling study assumes uniformity of behaviour (and model parameters) in the β cell population, which is a common assumption in the non-diabetic, the approach could be modified to account for some heterogeneity.

In contrast, the glucagon-secreting α cells are known to exhibit a much larger inter-cell variability, which requires the usage of models with a wide range of parameters to match physiological observations [49]. In addition, modelling taking into account noise [25] and paracrine signalling [49,73] have demonstrated their important role in the pulsatile secretion of glucagon. Similarly, a recent model of α , β , δ cell interactions suggest that the inhibition of glucagon secretion in the presence of elevated glucose levels is partly achieved through the action of β cells onto somatostatin secretion in δ cells [13]. The recent discovery of the importance of innervation between pancreatic cells may shed further light on intrapancreatic regulatory activity [75].

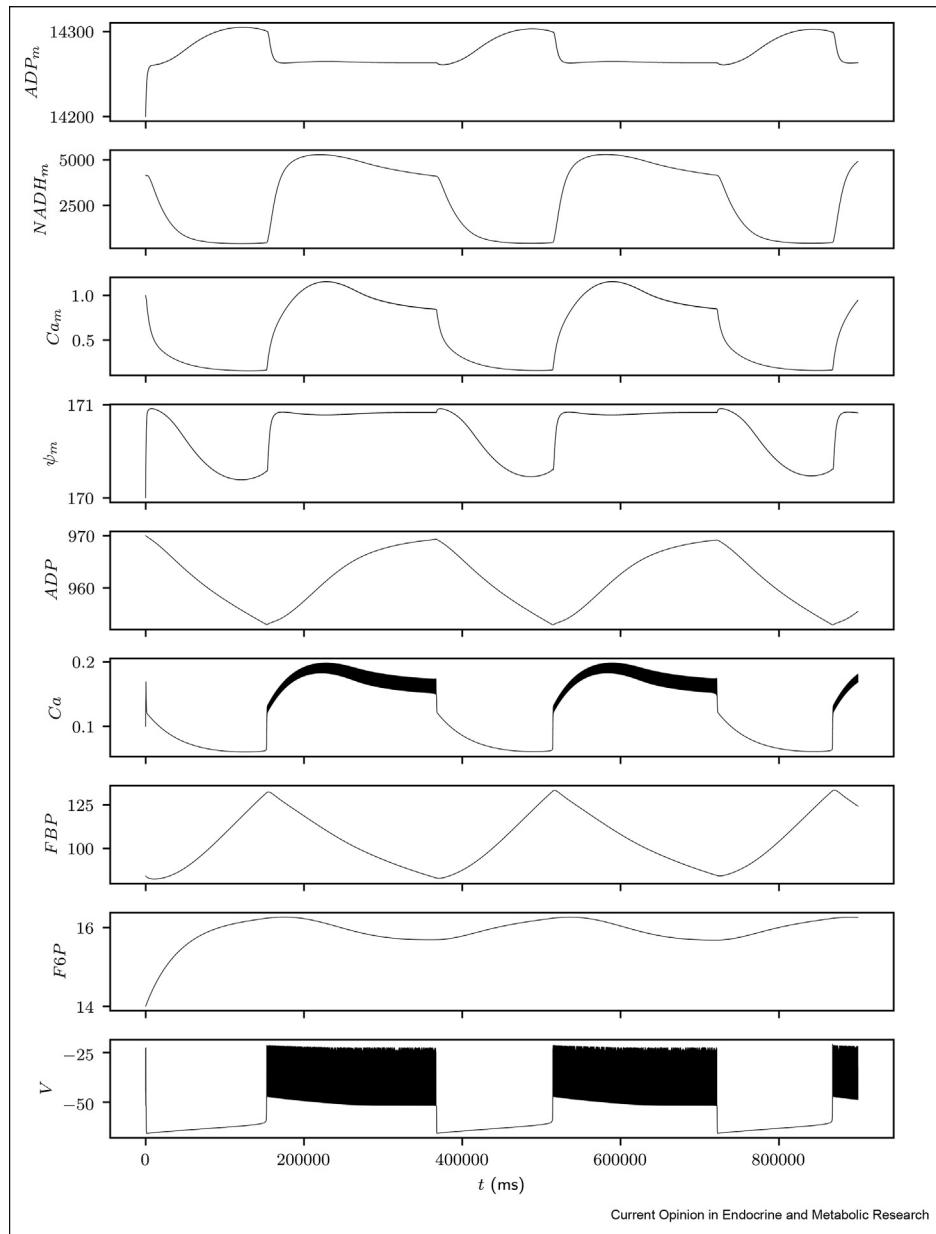
System level models

The entrainment of insulin release by glucose stimuli has also been observed at the ultradian level, with tightly coupled glucose-insulin oscillations (period ~ 80 –180 min) emerging in fasting, meal ingestion, continuous enteral and intravenous nutrition conditions [63]. A large part of the mathematical study of glucose-insulin ultradian rhythms takes its roots in the modelling work of Sturis et al. [66–68], within which the delay inherent to hepatic glucose production is regarded as a mechanism for explaining these oscillations. In recent years, extensions of this model have been used to provide more robust systems of the intravenous glucose tolerance test (IVGTT) [9,10] or to include different infusion patterns. When focusing solely on plasma glucose (G) and insulin levels (I), two feedback loops taking into account secretion times inherent to hepatic glucose and pancreatic insulin synthesis and transport are typically modelled using nonlinear equations of the form

$$\dot{G}(t) = G_m(t) - f_2(G) - f_3(G)f_4(I) + f_5(I(t - \tau_2)), \quad (1)$$

$$\dot{I}(t) = I_m(t) + f_1(G(t - \tau_1)) - d_I I, \quad (2)$$

as first introduced in [40]. Here, f_1 represents insulin secretion (with a constant delay $\tau_1 \sim 5$ –15 min), f_2 is the insulin independent glucose utilisation, f_3f_4 stands for the insulin dependent glucose utilisation and f_5 models hepatic glucose production (with a constant delay $\tau_2 \sim 35$ –50 min), which is assumed to be triggered by low insulin levels. As such, functions f_1, f_2, f_3 and f_4 are positive functions of their arguments, while f_5 decreases as insulin levels increase. The glucose infusion $G_m(t)$ is typically

Figure 2

Simulation of oscillations in the Integrated Oscillator Model, as implemented in [43]. V : β cell membrane potential, ψ_m : mitochondrial membrane potential, Ca , Ca_m : mitochondrial Ca^{2+} , F6P: Fructose 6-phosphate, FBP: Fructose 1,6-bisphosphate, ADP: adenosine diphosphate in cytosol, ADP_m : adenosine diphosphate in mitochondria, $NADH_m$: nicotinamide adenine dinucleotide + hydrogen.

chosen as constant [40,41,34,33,15] or representing meals [17,18]. The delays have a crucial effect on the production of oscillations and on the resulting glucose and insulin amplitudes [15,33,41]. It was shown using interval maps in the one delay case (that is when $\tau_1 = 0$, reducing to a model studied in the studies by Bennett et al., Engelborghs et al. [8,23]) that a global bifurcation exists and is responsible for the presence of oscillations [3]. Such a phenomenon is numerically evidenced and also expected in the two-delay model (2) [40,39]. To approximate the limit cycle in the two-delay model with a constant glucose

infusion using a perturbative scheme, the following simplified model

$$\dot{G}(t) = G_{in} - \alpha_1 G - \alpha_2 GI + \frac{\alpha_3}{I(t - \tau_2) + K_2} \quad (3)$$

$$\dot{I}(t) = \frac{b_1 G(t - \tau_1)^2}{G(t - \tau_1)^2 + K_1^2} - b_2 I, \quad (4)$$

was investigated in [15]. Delay-dependent conditions were formulated for the existence of a supercritical Hopf bifurcation, which is the process by which gradually increasing the value of a parameter (e.g. glucose input) leads to oscillations. Explicit approximate equations for glucose and insulin amplitudes were obtained in terms of the model parameters [14,15]. In particular, these expressions provide a proxy for directly estimating the maximal and minimal values for glucose and insulin oscillations for a given level of insulin resistance. It is worth emphasising that such formulas have been obtained under the assumption that delays are discrete and constant. An IVGTT model with an interval delay was introduced by Shi et al. [64].

The impact of different patterns of insulin therapies on the dynamics of systems of the form (2) has been investigated in numerous studies [72,32,33,74].

The model was recently further extended to consider glucagon dynamics, introducing A as the plasma glucagon concentration (ng/L), whilst incorporating both the glucagon secretion rate and the body's glucagon clearance rate. The resulting model is shown in (5) and schematically represented in Figure 3. In response to the physiological observation that both glucose and insulin levels determine glucagon secretion, the function $f_5(I(t - \tau_2))$ in the initial model has been replaced with terms reflecting the hepatic glucose uptake (HPU) and hepatic glucose production (HGP), which are respectively modelled by $f_5(G)f_6(I)$ and $f_7(I(t - \tau_2))f_8(A)$. It is shown analytically that HPU and

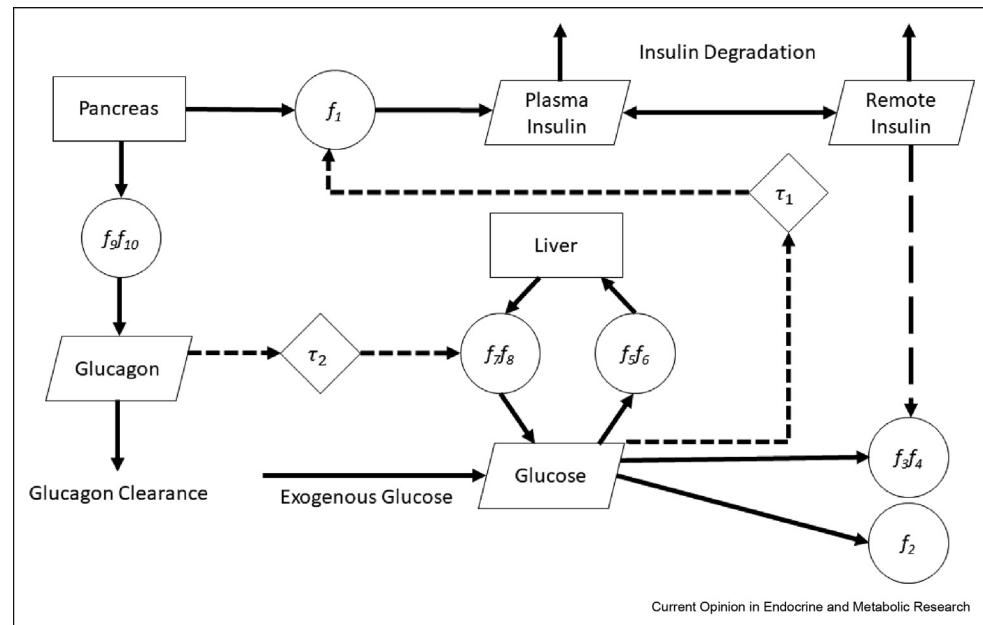
HGP must counterbalance each other for oscillations to occur. This modification allows the recently introduced concept of glucagon resistance to be acknowledged within the model, with moderate levels of glucagon being incapable of stimulating HGP when the shape of the function significantly changes. Moreover, τ_2 now represents the delay from when glucagon binds to the liver to the subsequent release of glucose rather than the time between the suppression and diminishment of HGP in the presence of increased insulin levels [20].

$$\begin{aligned}\dot{G}(t) &= G_m(t) - f_2(G) - f_3(G)f_4(I) - f_5(G)f_6(I) \\ &\quad + f_7(I(t - \tau_2))f_8(A), \\ \dot{I}(t) &= I_m(t) + f_1(G(t - \tau_1)) - d_I I \\ \dot{A}(t) &= f_9(G)f_{10}(I) - d_A A.\end{aligned}\quad (5)$$

A simple system describing insulin-mediated glucagon dynamics through C-peptide data has been devised recently by Morettini et al. [50] to provide a minimal model of the oral glucose tolerance test.

In order to pass from controlled glucose inputs to real-life glucose predictions in the presence of meals and insulin injections, the Arleth model is sometimes used to infer glucose absorption timings from levels of proteins, lipids, sugar, and starch in the stomach and of carbohydrates in the intestine [4]. This approach was recently implemented by Gyuk et al. [27] in conjunction with a simplified delay model devised in

Figure 3



Flow chart for the glucose–insulin–glucagon model (5).

[55] to make glucose-insulin predictions. Personalised model parameters were optimised to match CGM data collected on insulin-dependent type 2 diabetic individuals.

In non-clinical circumstances, it is also fruitful to consider the dynamics of ghrelin, which modulates food appetite. This hormone is secreted mainly in the stomach although its inhibition signalling occurs in the intestine. This additional feedback was embedded in a recent multi-compartment model [6] and the dynamics in the presence of three meals were compared with experimental data from 10 individuals. Although the current model did not include the effect of insulin on ghrelin release, which remains to be elucidated, the model satisfactorily reproduced the available data for ghrelin and insulin levels, and food volumes remaining in the gastrointestinal tract over a 24 h window. Furthermore, to acknowledge the fact that insulin secretion is impacted by the presence of free fatty acids, their contribution was incorporated into a simple three-equation delay model [52] which generalises a model of the intravenous glucose tolerance test [41]. In particular, the insulin secretion term in the model comprised an additional contribution of free fatty acids. This enabled the authors to investigate quantitatively the contribution of this effect before and after bariatric surgery.

A separate in-depth model using Topp's model [70] and incorporating leptin as well as lipolysis and lipid oxidation in relation to glucose uptake was introduced by Sweatman [69]. The study explores the changes of various biomarkers under the conditions of several diets, assessing the changes to plasma glucose and insulin concentrations. It makes predictions surrounding insulin and leptin sensitivity and the relevant impact on both insulin and glucagon secretion rates. The model has the capability to predict trajectories to lean and overweight type 2 diabetes, along with nondiabetic states with raised fat mass.

Two models created by Panunzi, de Gaetano et al., namely the single delay model (SDM) for IVGTT [56] (a minimal one-delay model of the form (2)) and the extended model [21] (which models β cells as heterogeneous firing units) have been supplemented with insulin-independent glucose utilisation [22]. The updated SDM was then used to fit a large number of glucose-insulin series generated with the extended model. The interplay between the two models allowed the authors to discuss the link between the degree of nonlinearity in insulin secretion and the volume of the pancreatic reserve.

Several larger-scale multi-organ models integrate a very extensive number of biological variables separated in multiple compartments, for which production, diffusion,

utilisation, and clearance processes lead to large systems of balance equations simulating whole-body dynamics. Among these, UVA Padova is patented for usage in closed-loop delivery systems [71]. A similar multi-organ model was introduced in [30], supplementing the previous model of Nyman et al. [54] through the introduction of the effect of blood flow on glucose uptake in adipose tissue and by updating postprandial glucose uptake in organs and muscles. Another very comprehensive model is that of Sorenson [65], devised by considering a large number of physiological functions along with parameter values estimated from the clinical literature. In a recent revision of this model [57], an additional subsystem was added to incorporate intestinal glucose absorption, present the complete set of equations in a concise manner and provide an online implementation of the modified model. The model provides predictions comparable to the UVA-Padova and the Hovorka model in *in silico* simulations [60]. While similar, the model from Sarkar et al. [62] was calibrated using patient data over several years and as such, focuses on long term dynamics and aims at providing estimates for the progression of type 2 diabetes in an individual.

As the phenomenological understanding of physiological regulation evolves, it is important to use this knowledge to devise enhanced estimators of insulin (and glucagon) resistance. It has been recognised that current biomarkers may not be informative enough for discriminating between the different pathways that may lead to type 2 diabetes. Building on a model from Topp et al. [70], the model by Ha and Sherman [29] incorporates distinct feedback mechanisms for hepatic and peripheral insulin sensitivity onto β cell mass dynamics and hyperinsulinemia. The model enables the tracking of two main pathways to type 2 diabetes depending on which pre-diabetes symptom arises first, namely fasting hyperglycaemia or impaired glucose tolerance in the oral glucose tolerance test. They performed longitudinal simulations over a period of five years with an assumed initial decline in peripheral and hepatic insulin sensitivity. The model provides a framework for devising optimised therapy in the early stages of diabetes, targeting the specific insulin resistance phenotype.

Furthermore, although Bergman's minimal model [9,10] has the power to estimate insulin sensitivity (S_i) during an IVGTT, discrepancies have risen in the accuracy of the model when comparing S_i across different ethnic groups. The S_i is underestimated in individuals with a large acute insulin response. This article evaluates the differences of S_i when calculated using the minimal model versus using the hyperinsulinemic euglycemic clamp. It concludes that the latter, measuring S_i directly, is more reliable than the simulation in the minimal model and care should be taken when analysing results across different ethnic groups [28].

Exercise has a direct impact on glucose dynamics in individuals with type 1 diabetes, hence, incorporating exercise-induced changes is important in the development of a safe artificial pancreas. Alkhateeb et al. [2] propose six variations of the Bergman minimal model [10] to simulate the physiological effects of moderate exercise, validating the results by comparing with existing clinical data and simulations with the Hovorka model [31]. The model portrays that glucose effectiveness is dependent on exercise intensity and the increased insulin sensitivity was seen to be proportional to both the intensity and duration.

Finally, it is worth emphasising that the large quantity of data obtained through continuous glucose monitoring (CGM) provides a highly valuable resource for the training of artificial neural networks. As such, machine learning methods are taking an increasingly large share of the literature on glucose dynamics prediction, with a large body of work being concerned with the prediction of hypoglycaemia (see [51] for a review). While various studies obtain glucose predictions based solely on long-term CGM data, others make use of other physiological data (e.g. insulin, physical activity, heart rate, meals) as well as dynamical models. The approach of using neural networks trained with CGM in combination with glucose absorption models (such as the one from Arleth [4]) was shown to provide more reliable estimates than CGM data alone [35], especially when the responses to meals is to be predicted. Recent research carried out to understand the role of glucose transporters in intestinal glucose absorption (especially GLUT2 [1,53]) should lead to further improvements in predictive models of glucose uptake. Similarly, further modelling is required for evaluating the effect of rhythms in the hypothalamic–pituitary–adrenal axis and their impairment on pancreatic secretion and insulin sensitivity [76,77]. Such modelling studies should enable a better glycemic control that preserves healthy dynamical rhythms.

Conflict of interest

Nothing declared.

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