Mathematical modelling of glucose dynamics

Benoit Huard*, Gemma Kirkham

Department of Mathematics, Physics and Electrical Engineering
Northumbria University

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 paper, we review the latest contribution of mathematical modelling to the understanding and prediction of dynamics within the glucose regulation system.

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 minutes 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.

*Corresponding author
Email address: benoit.huard@northumbria.ac.uk (Benoit Huard)

Preprint submitted to Current opinion in endocrine and metabolic research (accepted version) *May 2022*

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].

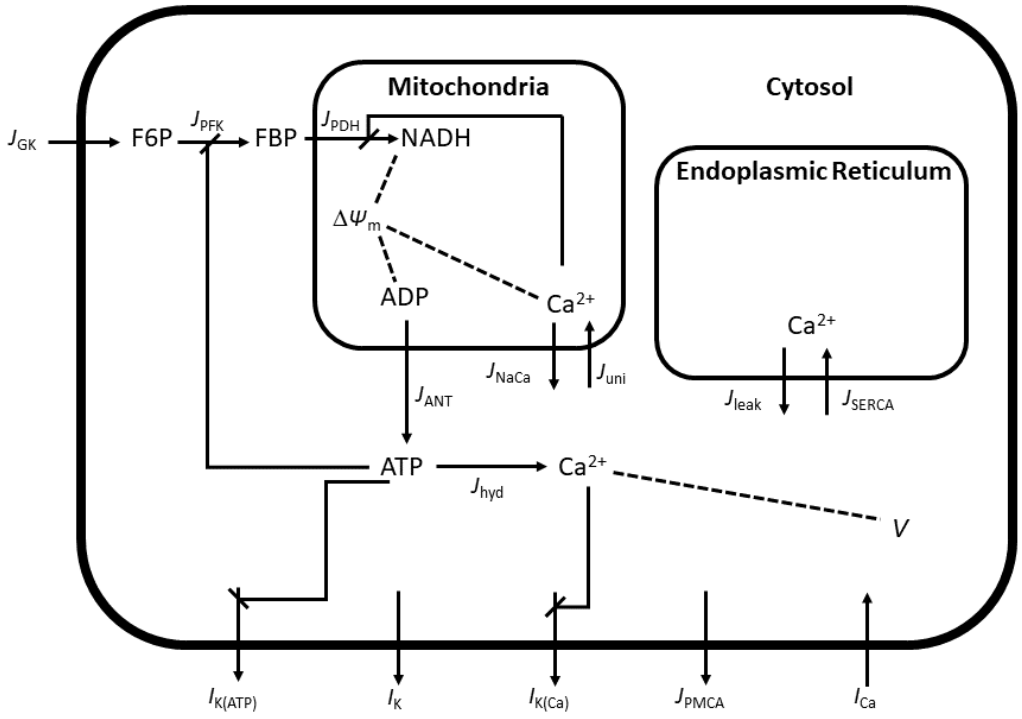

Figure 1: Modular diagram for the Integrated Oscillator Model of a singular mouse β cell, including membrane potentials, Ca^{2+}, ATP, ADP, fructose phosphates and key ionic currents and fluxes. After [43].

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].

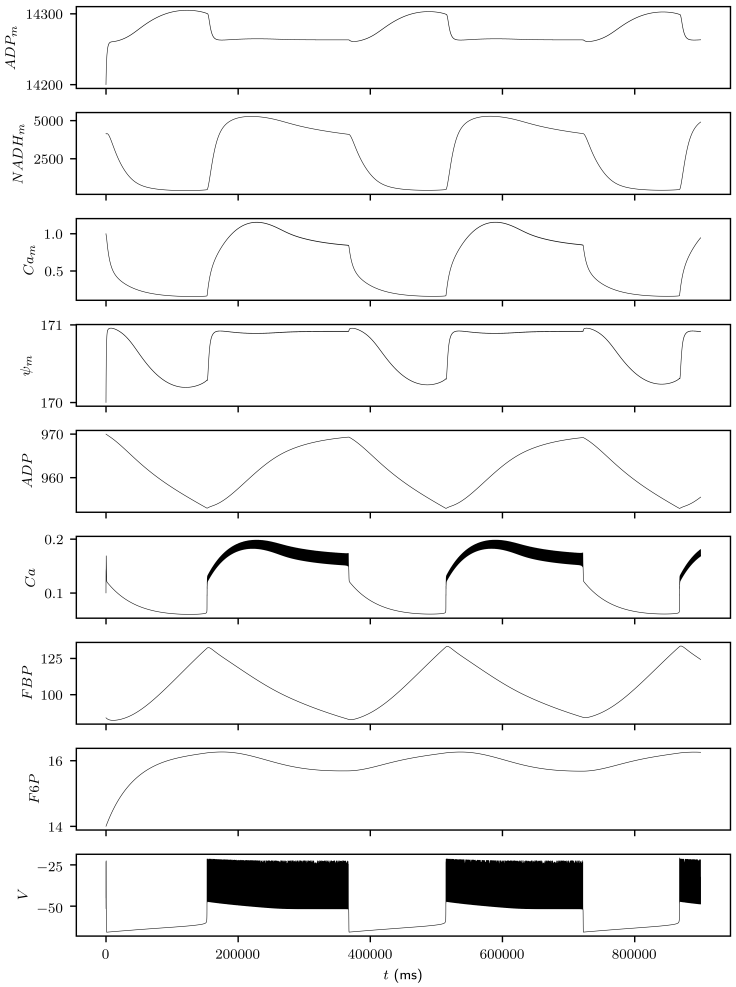

Figure 2: Simulation of oscillations in the Integrated Oscillator Model, as implemented in [43]. V: β cell membrane potential, ψ_m: mitochondrial membrane potential, Ca:, Ca_m : mitochrondrial Ca^{2+}, F6P: Fructose 6-phosphate, FBP: Fructose 1,6-bisphosphate, ADP: adenosine diphosphate in cytosol, ADP_m: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

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 $\sim$ 80-180 minutes) 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, 67, 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

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

$$\dot{I}(t) = I_{in}(t) + f_1(G(t-\tau_1)) - d_i I, \quad (2)$$

as first introduced in [40]. Here, f_1 represents insulin secretion (with a constant delay $\tau_1 \sim$ 5-15 minutes), f_2 is the insulin independent glucose utilisation, $f_3 f_4$ stands for the insulin dependent glucose utilisation and f_5 models hepatic glucose production (with a constant delay $\tau_2 \sim$ 35-50 minutes), 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 $G_{in}(t)$ is typically 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 [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

$$\dot{G}(t) = G_{in} - a_1 G - a_2 G I + \frac{a_3}{I(t-\tau_2) + K_2} \quad (3)$$

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

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 HPG 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].

$$\begin{aligned} \dot{G}(t) &= G_{in}(t) - f_2(G) - f_3(G)f_4(I) - f_5(G)f_6(I) + f_7(I(t-\tau_2))f_8(A), \\ \dot{I}(t) &= I_{in}(t) + f_1(G(t-\tau_1)) - d_i I \\ \dot{A}(t) &= f_9(G)f_{10}(I) - d_a A. \end{aligned} \tag{5}$$

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 [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 hour window. Furthermore, to acknowledge the fact that insulin secretion is

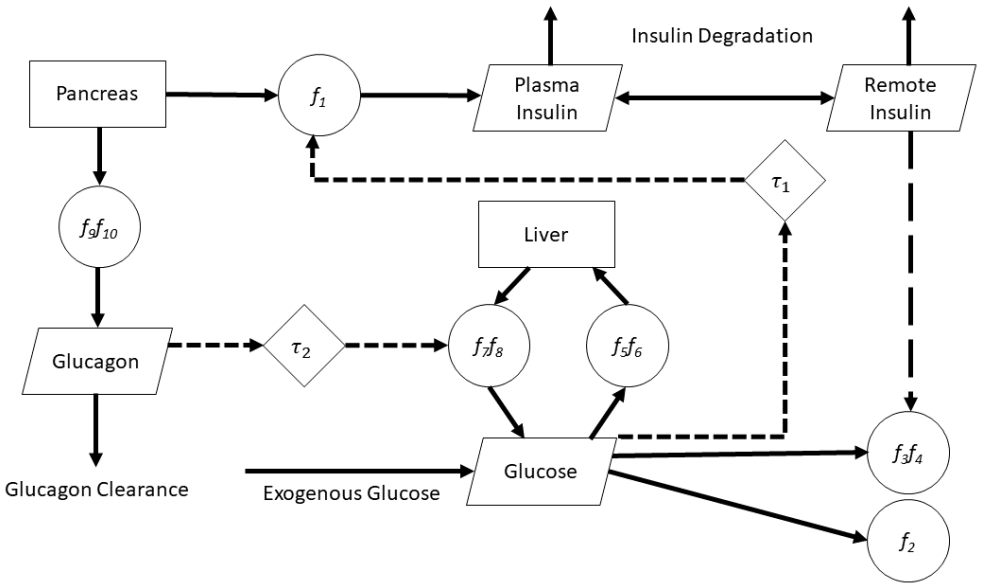

Figure 3: Flow chart for the glucose-insulin-glucagon model (5).

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 and collaborators, 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 hyperinsulinimia. 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 (Si) during an IVGTT, discrepancies have risen in the accuracy of the model when comparing Si across different ethnic groups. The Si is underestimated in individuals with a large acute insulin response. This paper evaluates the differences of Si when calculated using the minimal model versus using the hyperinsulinemic euglycemic clamp. It concludes that the latter, measuring Si 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.

Interest. Authors declare no competing interests.

References

[1] Nima Afshar, Soroush Safaei, David P Nickerson, Peter J Hunter, and Vinod Suresh. Computational modelling of glucose uptake by SGLT1 and apical GLUT2 in the enterocyte. *Frontiers in physiology*, 12, 2021.

[2] Haneen Alkhateeb, Anas El Fathi, Milad Ghanbari, and Ahmad Haidar. Modelling glucose dynamics during moderate exercise in individuals with type 1 diabetes. *Plos one*, 16(3):e0248280, 2021.

[3] Maia Angelova, Gleb Beliakov, Anatoli Ivanov, and Sergiy Shelyag. Global stability and periodicity in a glucose-insulin regulation model with a single delay. *Communications in Nonlinear Science and Numerical Simulation*, 95:105659, 2021.

[4] Tom Arleth, Steen Andreassen, Marco O Federici, and Massimo M Benedetti. A model of the endogenous glucose balance incorporating the characteristics of glucose transporters. *Computer methods and programs in biomedicine*, 62(3):219–234, 2000.

[5] Mostafa Bakhti, Anika Böttcher, and Heiko Lickert. Modelling the endocrine pancreas in health and disease. *Nature Reviews Endocrinology*, 15(3):155–171, 2019.

[6] Massimo Barnabei, Alessandro Borri, Andrea De Gaetano, Costanzo Manes, Pasquale Palumbo, and Jorge Guerra Pires. A short-term food intake model involving glucose, insulin and ghrelin. *Discrete & Continuous Dynamical Systems-B*, 2021.

[7] Simone Battaglin and Morten Gram Pedersen. Geometric analysis of mixed-mode oscillations in a model of electrical activity in human β cells. *Nonlinear Dynamics*, 104(4):4445–4457, 2021.

[8] DL Bennett and SA Gourley. Global stability in a model of the glucose-insulin interaction with time delay. *European Journal of Applied Mathematics*, 15(2):203–221, 2004.

[9] R N Bergman, Y Z Ider, C R Bowden, and C Cobelli. Quantitative estimation of insulin sensitivity. *American Journal of Physiology-Endocrinology and Metabolism*, 236(6):E667, June 1979.

[10] RN Bergman, DT Finegood, and SE Kahn. The evolution of β-cell dysfunction and insulin resistance in type 2 diabetes. *European journal of clinical investigation*, 32:35–45, 2002.

[11] Richard Bertram, Leslie S. Satin, and Arthur S. Sherman. Closing in on the Mechanisms of Pulsatile Insulin Secretion. *Diabetes*, 67(3):351–359, February 2017.

[12] Charlotte K Boughton and Roman Hovorka. New closed-loop insulin systems. *Diabetologia*, 64(5):1007–1015, 2021.

[13] LJB Briant, TM Reinbothe, I Spiliotis, C Miranda, B Rodriguez, and P Rorsman. δ-cells and β-cells are electrically coupled and regulate α-cell activity via somatostatin. *The Journal of physiology*, 596(2):197–215, 2018.

[14] Adam Bridgewater. *Mathematical description of the ultradian oscillations in the glucose-insulin regulatory system*. PhD thesis, Northumbria University, 2018.

[15] Adam Bridgewater, Benoit Huard, and Maia Angelova. Amplitude and frequency variation in nonlinear glucose dynamics with multiple delays via periodic perturbation. *Journal of Nonlinear Science*, 30(3):737–766, 2020.

[16] Chae Young Cha, Yasuhiko Nakamura, Yukiko Himeno, JianWu Wang, Shinpei Fujimoto, Nobuya Inagaki, Yung E Earm, and Akinori Noma. Ionic mechanisms and Ca^{2+} dynamics underlying the glucose response of pancreatic β cells: a simulation study. *Journal of General Physiology*, 138(1):21–37, 2011.

[17] Cheng-Liang Chen and Hong-Wen Tsai. Modeling the physiological glucose–insulin system on normal and diabetic subjects. *Computer methods and programs in biomedicine*, 97(2):130–140, 2010.

[18] Cheng-Liang Chen, Hong-Wen Tsai, and Sio-Si Wong. Modeling the physiological glucose–insulin dynamic system on diabetics. *Journal of Theoretical Biology*, 265(3):314–322, August 2010.

[19] Claudio Cobelli, Eric Renard, and Boris Kovatchev. Artificial pancreas: past, present, future. *Diabetes*, 60(11):2672–2682, 2011.
[20] Reed B. Cohen and Jiaxu Li. A novel model and its analysis on the metabolic regulations of glucose, insulin, and glucagon. *SIAM Journal on Applied Mathematics*, 81(6):2684–2703, January 2021.
[21] Andrea De Gaetano, Claudio Gaz, Pasquale Palumbo, and Simona Panunzi. A unifying organ model of pancreatic insulin secretion. *PloS one*, 10(11):e0142344, 2015.
[22] Andrea De Gaetano, Claudio Gaz, and Simona Panunzi. Consistency of compact and extended models of glucose-insulin homeostasis: The role of variable pancreatic reserve. *Plos one*, 14(2):e0211331, 2019.
[23] Koen Engelborghs, V Lemaire, J Belair, and Dirk Roose. Numerical bifurcation analysis of delay differential equations arising from physiological modeling. *Journal of mathematical biology*, 42(4):361–385, 2001.
[24] Haniyeh Fallah. Symmetric fold/super-hopf bursting, chaos and mixed-mode oscillations in Pernarowski model of pancreatic beta-cells. *International Journal of Bifurcation and Chaos*, 26(09):1630022, 2016.
[25] Virginia González-Vélez, Anthony Piron, and Geneviève Dupont. Calcium oscillations in pancreatic α-cells rely on noise and ATP-driven changes in membrane electrical activity. *Frontiers in physiology*, page 1515, 2020.
[26] Azure D Grant, Dana M Lewis, and Lance J Kriegsfeld. Multi-timescale rhythmicity of blood glucose and insulin delivery reveals key advantages of hybrid closed loop therapy. *Journal of Diabetes Science and Technology*, page 1932296821994825.
[27] Péter Gyuk, István Vassányi, and István Kósa. Blood glucose level prediction for diabetics based on nutrition and insulin administration logs using personalized mathematical models. *Journal of Healthcare Engineering*, 2019, 2019.
[28] Joon Ha, Ranganath Muniyappa, Arthur S Sherman, and Michael J Quon. When MINMOD artifactually interprets strong insulin secretion as weak insulin action. *Frontiers in physiology*, 12:508, 2021.
[29] Joon Ha and Arthur Sherman. Type 2 diabetes: one disease, many pathways. *American Journal of Physiology-Endocrinology and Metabolism*, 319(2):E410–E426, 2020. PMID: 32663101.
[30] Tilda Herrgårdh, Hao Li, Elin Nyman, and Gunnar Cedersund. An updated organ-based multi-level model for glucose homeostasis: organ distributions, timing, and impact of blood flow. *Frontiers in physiology*, 12:619254, 2021.
[31] Roman Hovorka, Valentina Canonico, Ludovic J Chassin, Ulrich Haueter, Massimo Massi-Benedetti, Marco Orsini Federici, Thomas R Pieber, Helga C Schaller, Lukas Schaupp, Thomas Vering, et al. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. *Physiological measurement*, 25(4):905–920, 2004.
[32] Mingzhan Huang, Jiaxu Li, Xinyu Song, and Hongjian Guo. Modeling impulsive injections of insulin: towards artificial pancreas. *SIAM Journal on Applied Mathematics*, 72(5):1524–1548, 2012.
[33] Benoit Huard, Adam Bridgewater, and Maia Angelova. Mathematical investigation of diabetically impaired ultradian oscillations in the glucose–insulin regulation. *Journal of theoretical biology*, 418:66–76, 2017.
[34] Benoit Huard, JF Easton, and Maia Angelova. Investigation of stability in a two-delay model of the ultradian oscillations in glucose–insulin regulation. *Communications in Nonlinear Science and Numerical Simulation*, 26(1-3):211–222, 2015.
[35] Rebaz AH Karim, István Vassányi, and István Kósa. After-meal blood glucose level prediction using an absorption model for neural network training. *Computers in Biology and Medicine*, 125:103956, 2020.
[36] Dae Wook Kim, Eder Zavala, and Jae Kyoung Kim. Wearable technology and systems modeling for personalized chronotherapy. *Current Opinion in Systems Biology*, 21:9–15, 2020.
[37] Christiane Klec, Gabriela Ziomek, Martin Pichler, Roland Malli, and Wolfgang F Graier. Calcium signaling in ß-cell physiology and pathology: a revisit. *International journal of molecular sciences*, 20(24):6110, 2019.
[38] Dana Lewis. How it started, how it is going: the future of artificial pancreas systems (automated insulin delivery systems). *Journal of Diabetes Science and Technology*, 15(6):1258–1261, 2021.
[39] J Li and Y Kuang. Analysis of a model of the glucose-insulin regulatory system with two delays. *SIAM J Appl Math*, 63(3):757–76, 2007.
[40] Jiaxu Li, Yang Kuang, and Clinton C Mason. Modeling the glucose–insulin regulatory system and ultradian insulin secretory oscillations with two explicit time delays. *Journal of theoretical biology*, 242(3):722–735, 2006.
[41] Jiaxu Li, Minghu Wang, Andrea De Gaetano, Pasquale Palumbo, and Simona Panunzi. The range of time delay and the global stability of the equilibrium for an IVGTT model. *Mathematical Biosciences*, 235(2):128–137, February 2012.
[42] Isabella Marinelli et al. *Advanced mathematical modelling of pancreatic β-cells*. PhD thesis, Basque Center for Applied Mathematics, 2019.
[43] Isabella Marinelli, Patrick A. Fletcher, Arthur S. Sherman, Leslie S. Satin, and Richard Bertram. Symbiosis of

electrical and metabolic oscillations in pancreatic β-cells. *Frontiers in Physiology*, 12, 2021.

[44] Isabella Marinelli, Vishal Parekh, Patrick Fletcher, Benjamin Thompson, Jinhua Ren, Xiaoqing Tang, Thomas L Saunders, Joon Ha, Arthur Sherman, Richard Bertram, et al. Slow oscillations persist in pancreatic β cells lacking phosphofructokinase M. *Biophysical journal*, 121(5):692–704, 2022.

[45] Isabella Marinelli, Benjamin M Thompson, Vishal S Parekh, Patrick A Fletcher, Luca Gerardo-Giorda, Arthur S Sherman, Leslie S Satin, and Richard Bertram. Oscillations in K (ATP) conductance drive slow calcium oscillations in pancreatic β-cells. *Biophysical Journal*, 2022.

[46] Joseph P. McKenna and Richard Bertram. Fast-slow analysis of the integrated oscillator model for pancreatic β-cells. *Journal of Theoretical Biology*, 457:152–162, 2018.

[47] Joseph P McKenna, Raghuram Dhumpa, Nikita Mukhitov, Michael G Roper, and Richard Bertram. Glucose oscillations can activate an endogenous oscillator in pancreatic islets. *PLoS computational biology*, 12(10), 2016.

[48] Matthew J Merrins, Aaron R Van Dyke, Anna K Mapp, Megan A Rizzo, and Leslie S Satin. Direct measurements of oscillatory glycolysis in pancreatic islet β-cells using novel fluorescence resonance energy transfer (FRET) biosensors for pyruvate kinase M2 activity. *Journal of Biological Chemistry*, 288(46):33312–33322, 2013.

[49] Francesco Montefusco, Giuliana Cortese, and Morten G Pedersen. Heterogeneous α-cell population modeling of glucose-induced inhibition of electrical activity. *Journal of theoretical biology*, 485:110036, 2020.

[50] Micaela Morettini, Laura Burattini, Christian Göbl, Giovanni Pacini, Bo Ahrén, and Andrea Tura. Mathematical model of glucagon kinetics for the assessment of insulin-mediated glucagon inhibition during an oral glucose tolerance test. *Frontiers in endocrinology*, 12:611147, 2021.

[51] Omer Mujahid, Ivan Contreras, and Josep Vehi. Machine learning techniques for hypoglycemia prediction: Trends and challenges. *Sensors*, 21(2):546, 2021.

[52] Anarina L Murillo, Jiaxu Li, and Carlos Castillo-Chavez. Modeling the dynamics of glucose, insulin, and free fatty acids with time delay: The impact of bariatric surgery on type 2 diabetes mellitus. *Mathematical Biosciences and Engineering: MBE*, 16(5):5765, 2019.

[53] Richard J Naftalin. Does apical membrane glut2 have a role in intestinal glucose uptake? *F1000Research*, 3, 2014.

[54] Elin Nyman, Cecilia Brännmark, Robert Palmér, Jan Brugård, Fredrik H Nyström, Peter Strålfors, and Gunnar Cedersund. A hierarchical whole-body modeling approach elucidates the link between in vitro insulin signaling and in vivo glucose homeostasis. *Journal of Biological Chemistry*, 286(29):26028–26041, 2011.

[55] Pasquale Palumbo, Pierdomenico Pepe, Simona Panunzi, and Andrea De Gaetano. Glucose control by subcutaneous insulin administration: a dde modelling approach. *IFAC Proceedings Volumes*, 44(1):1471–1476, 2011.

[56] Simona Panunzi, Pasquale Palumbo, and Andrea De Gaetano. A discrete single delay model for the intra-venous glucose tolerance test. *Theoretical Biology and Medical Modelling*, 4(1):35, September 2007.

[57] Simona Panunzi, Marcello Pompa, Alessandro Borri, Vincenzo Piemonte, and Andrea De Gaetano. A revised Sorensen model: Simulating glycemic and insulinemic response to oral and intra-venous glucose load. *Plos one*, 15(8):e0237215, 2020.

[58] Morten Gram Pedersen, Alessia Tagliavini, and Jean-Claude Henquin. Calcium signaling and secretory granule pool dynamics underlie biphasic insulin secretion and its amplification by glucose: experiments and modeling. *American Journal of Physiology-Endocrinology and Metabolism*, 316(3):E475–E486, 2019.

[59] Mark Pernarowski. Fast subsystem bifurcations in a slowly varying lienard system exhibiting bursting. *SIAM Journal on Applied Mathematics*, 54(3):814–832, 1994.

[60] Marcello Pompa, Simona Panunzi, Alessandro Borri, and Andrea De Gaetano. A comparison among three maximal mathematical models of the glucose-insulin system. *Plos one*, 16(9):e0257789, 2021.

[61] A Ruiz-Silva. Synchronization patterns on networks of pancreatic β-cell models. *Physica D: Nonlinear Phenomena*, 416:132783, 2021.

[62] Joydeep Sarkar, Gaurav Dwivedi, Qian Chen, Iris E Sheu, Mark Paich, Colleen M Chelini, Paul M D'Alessandro, and Samuel P Burns. A long-term mechanistic computational model of physiological factors driving the onset of type 2 diabetes in an individual. *PloS one*, 13(2):e0192472, 2018.

[63] Leslie S Satin, Peter C Butler, Joon Ha, and Arthur S Sherman. Pulsatile insulin secretion, impaired glucose tolerance and type 2 diabetes. *Molecular aspects of medicine*, 42:61–77, 2015.

[64] Xiangyun Shi, Yang Kuang, Athena Makroglou, Sriprakash Mokshagundam, and Jiaxu Li. Oscillatory dynamics of an intravenous glucose tolerance test model with delay interval. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 27(11):114324, November 2017.

[65] John Thomas Sorensen. *A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes.* PhD thesis, Massachusetts Institute of Technology, 1985.

[66] Jeppe Sturis, Carsten Knudsen, Niall M O'Meara, Jesper S Thomsen, Erik Mosekilde, Eve Van Cauter, and Kenneth S Polonsky. Phase-locking regions in a forced model of slow insulin and glucose oscillations. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 5(1):193–199, 1995.

[67] Jeppe Sturis, NM O'Meara, Edith Timothy Shapiro, JD Blackman, Hartmut Tillil, KS Polonsky, and Eve Van Cauter. Differential effects of glucose stimulation upon rapid pulses and ultradian oscillations of insulin secretion. *The Journal of Clinical Endocrinology & Metabolism*, 76(4):895–901, 1993.

[68] Jeppe Sturis, Kenneth S Polonsky, Erik Mosekilde, and Eve Van Cauter. Computer model for mechanisms underlying ultradian oscillations of insulin and glucose. *American Journal of Physiology-Endocrinology And Metabolism*, 260(5):E801–E809, 1991.

[69] Catherine ZW Hassell Sweatman. Mathematical model of diabetes and lipid metabolism linked to diet, leptin sensitivity, insulin sensitivity and VLDLTG clearance predicts paths to health and type ii diabetes. *Journal of Theoretical Biology*, 486:110037, 2020.

[70] Brian Topp, Keith Promislow, Gerda Devries, Robert M Miura, and Diane T Finegood. A model of β-cell mass, insulin, and glucose kinetics: pathways to diabetes. *Journal of theoretical biology*, 206(4):605–619, 2000.

[71] Roberto Visentin, Enrique Campos-Náñez, Michele Schiavon, Dayu Lv, Martina Vettoretti, Marc Breton, Boris P Kovatchev, Chiara Dalla Man, and Claudio Cobelli. The UVA/Padova type 1 diabetes simulator goes from single meal to single day. *Journal of diabetes science and technology*, 12(2):273–281, 2018.

[72] Haiyan Wang, Jiaxu Li, et al. Mathematical modeling and qualitative analysis of insulin therapies. *Mathematical Biosciences*, 210(1):17–33, 2007.

[73] Margaret Watts, Joon Ha, Ofer Kimchi, and Arthur Sherman. Paracrine regulation of glucagon secretion: the $\beta/\alpha/\delta$ model. *American Journal of Physiology-Endocrinology and Metabolism*, 310(8):E597–E611, 2016.

[74] Jin Yang, Sanyi Tang, and Robert A. Cheke. Modelling the regulatory system for diabetes mellitus with a threshold window. *Communications in Nonlinear Science and Numerical Simulation*, 22(1–3):478–491, May 2015.

[75] Yu Hsuan Carol Yang, Linford JB Briant, Christopher A Raab, Sri Teja Mullapudi, Hans-Martin Maischein, Koichi Kawakami, and Didier YR Stainier. Innervation modulates the functional connectivity between pancreatic endocrine cells. *Elife*, 11:e64526, 2022.

[76] Eder Zavala, Carlos A. Gil-Gómez, Kyle C. A. Wedgwood, Romana Burgess, Krasimira Tsaneva-Atanasova, and Marco A. Herrera-Valdez. Dynamic modulation of glucose utilisation by glucocorticoid rhythms in health and disease. *bioRxiv*, 2020.

[77] Eder Zavala, Kyle CA Wedgwood, Margaritis Voliotis, Joël Tabak, Francesca Spiga, Stafford L Lightman, and Krasimira Tsaneva-Atanasova. Mathematical modelling of endocrine systems. *Trends in Endocrinology & Metabolism*, 30(4):244–257, 2019.