Mathematical Modelling and Numerical Simulation with Applications, 2022, 2(4), 244–251

https://www.mmnsa.org
ISSN Online: 2791-8564 / Open Access
https://doi.org/10.53391/mmnsa.2022.020

RESEARCH PAPER

Mathematical modelling of a glucose-insulin system for type 2 diabetic patients in Chad

Adam Hassan Adoum [1,†], Mahamat Saleh Daoussa Haggar [2,†] and Jean Marie Ntaganda [3,†,*]

[1]Department of Mathematics, University Adam Barka d'Abeche, Faculty of Sciences and Techniques (FAST), Chad, [2]Laboratory of Modeling, Mathematics, Computer Science, Applications and Simulation (L2MIAS), Department of Mathematics, Faculty of Exact and Applied Sciences, University of N'djamena, Chad, [3]Department of Mathematics, College of Science and Technology, School of Science, University of Rwanda, Rwanda

*Corresponding Author
†adamhassan2009@yahoo.fr (Adam Hassan Adoum); msdhaggar@gmail.com (Mahamat Saleh Daoussa Haggar); jmnta@yahoo.fr (Jean Marie Ntaganda)

Abstract

In this paper, we focus on modelling the glucose-insulin system for the purpose of estimating glucagon, insulin, and glucose in the liver in the internal organs of the human body. A three-compartmental mathematical model is proposed. The model parameters are estimated using a nonlinear inverse optimization problem and data collected in Chad. In order to identify insulin and glucose in the liver for type 2 diabetic patients, the Sampling Importance Resampling (SIR) particle filtering algorithm is used and implemented through discretization of the developed mathematical model. The proposed mathematical model allows further investigation of the dynamic behavior of hepatic glucose, insulin, and glucagon in internal organs for type 2 diabetic patients. During periods of hyperglycemia (i.e., after meal ingestion), whereas insulin secretion is increased, glucagon secretion is reduced. The results are in agreement with empirical and clinical data and they are clinically consistent with physiological responses.

Key words: Mathematical model; Type 2 diabetes patients; glucose; insulin; estimation; internal organs
AMS 2020 Classification: 92B05; 37N25; 34A45; 65L05

1 Introduction

Diabetes is a disease that cannot be cured (chronic) but can be treated. It is due to an abnormal increase in glucose [1]. This disease has become a major world health problem, particularly in Chad. Like all developing countries, Chad is paying heavy consequences due to this disease. Chad, the second largest country and the third most overcrowded country in Central Africa, is in the midst of a transition from this disease [2]. According to the report of the International Diabetes Federation, 425 million people worldwide were living with the disease in 2015 and this number may increase to an estimated 622 million in 2040 [3]. In 2013, 231290 Chadians had diabetes [4], this number may be significant in the future. All these results make diabetes a real public health problem. There are two main types of diabetes: type 1 diabetes, which affects 10 percent of the affected population and type 2 diabetes, which affects the remaining percent [5, 6]. Type 2 diabetes is therefore important in terms of severity. Consequently, many researchers are trying to find methods to diagnose and treat this disease. Generally, disease dynamics is investigated throughout the application of the mathematical models [7, 8, 9]. One approach is to find a mathematical model that can describe

➤ **Received:** 15.11.2022 ➤ **Revised:** 24.12.2022 ➤ **Accepted:** 27.12.2022 ➤ **Published:** 30.12.2022

the dynamics of the glucose-insulin system in order to analyze, interpret and predict the results. One of the approaches used is to find a mathematical model capable of describing the dynamics of the glucose-insulin system in order to predict, analyze and interpret the results. In literature, much effort has been made recently to analyze [10] and to develop mathematical models of type 2 diabetes [11, 12, 13, 14]. The objective of this paper is to propose a mathematical model of the glucose-insulin system suitable for type 2 diabetic patients in Chad. The glucagon, insulin, and hepatic glucose in internal human organs are estimated using Sampling Importance Resampling (SIR) algorithm. The mathematical model parameters are estimated using a nonlinear inverse optimization problem and data collected in Chad.
This paper is structured as follows: Materials and methods are presented in Section 2. It deals with data sources and mathematical model equations. Section 3 focuses on the estimation of the parameters of the model. The numerical tests are given in Section 4 while concluding remarks are presented in Section 5.

2 Materials and methods

Data set

The data are collected in the laboratory of the hematology department at regional Abéché hospital in Chad for a period of one month from 23, January 2019 to end 23, February 2019. Moreover, 900 exams should be done, but we faced some challenge including lack of material such as glucose meter, lower number of enumerators and financial means to organize the transport of participants who live so far from the hospital to come early morning in a fasting state. Consequently, the data have been collected only for 96 participants and 75 among them have type 2 diabetes.

Model equations

More multiple pancreatic hormones are involved in glucose homeostasis [15], but the potent hormone regulators of both glucose appearance and disappearance in the circulation are insulin and glucagon. Indeed, insulin is the key regulatory hormone of glucose disappearance, and glucagon is a major regulator of glucose appearance. Consequently, the deficiency of these hormones is the main cause of type 2 diabetes. During the fed state, the rate of gastric emptying is the major determinant source of circulating glucose and other sources of how glucose appears in the circulation are derived from hepatic processes. Glucagon plays a major role in sustaining plasma glucose during fasting conditions by stimulating hepatic glucose production. During the first 8-12 hours of fasting, glucagon facilitates this process and thus promotes glucose appearance in the circulation throughout the glycogenolysis mechanism [16]. Over longer periods of fasting, glucose, produced by gluconeogenesis, glucose is released from the liver which is the sole source of endogenous glucose production. Most tissues have the ability to hydrolyze glycogen and glucose removal into skeletal muscle and adipose tissue is driven mainly by insulin in the immediate post-feeding state [16]. In addition, insulin contributes to augmenting glucose uptake in peripheral tissues and in the liver by affecting the activity of different enzymes. The peripheral insulin resistance and relative insulin deficiency in type 2 diabetic patients have resulted in low glucose uptake rates by muscle cells and adipose tissue cells [17]. The studies show that insulin-induced stimulation effects on hepatic glucose uptake and hepatic glucose production rate are impaired in type 2 diabetic patients. This leads to reduced hepatic glucose uptake [18]. A type 2 diabetic patient is experienced with postprandial β-cell action that becomes abnormal due to the loss of immediate insulin response to a meal [19]. Therefore, hyperglycemia in type 2 diabetic patients is caused by the resistance of peripheral insulin resistance coupled with progressive β-cell failure and decreased availability of insulin and other hormones that is amylin (a neuroendocrine hormone coexpressed and consecrated with insulin by pancreatic β-cells in response to nutrient stimuli, and GLP-1 (more potent incretin hormone secreted in greater concentrations and is more physiologically relevant in humans) [20]. Due to high glucose level that can induce vascular endothelial cell dysfunction and affect blood viscosity and arterial wall tension, type 2 diabetes patients are at higher risk for the development of vascular complications than non-diabetic persons [21].
Due to such a high demand for understanding the blood flow characteristics in type 2 diabetic patients, in this study, we develop the mathematical model of type 2 diabetes patients.
We propose a three-compartmental mathematical model where the compartments are the vascular and tissues compartment, liver compartment and pancreas compartment. The state variables are are glucagon (Γ), insulin (I_p), hepatic glucose (G_L), glucose (G). Taking into consideration the diagram model illustrated in Figure 1.
The model equations are as follows:

$$\begin{cases} V^{\Gamma}\dfrac{d\Gamma(t)}{dt} = n_{\Gamma}G^{\alpha}I_p - p_1\Gamma, \\ V^{I_p}\dfrac{dI_p(t)}{dt} = n_{I_p}G^{\delta} - p_2I_p, \\ V^{G_L}\dfrac{dG_L(t)}{dt} = n_{G_L}\Gamma^{\beta} - p_3G_L + p_4G + R_{PGL}, \\ V^{G}\dfrac{dG(t)}{dt} = p_3G_L + n_GI_p^{\gamma} - p_5G + R_{meal}, \end{cases} \tag{1}$$

where n_i denotes the rate of blood coming indirectly in compartment i ($i = \Gamma, I_p, G_L\ G$) from vascular circulation. α, β, γ and δ are the constants to be estimated and refer to the non-linearity of the corresponding determinant variable. The parameters and variables are described in Table 1.

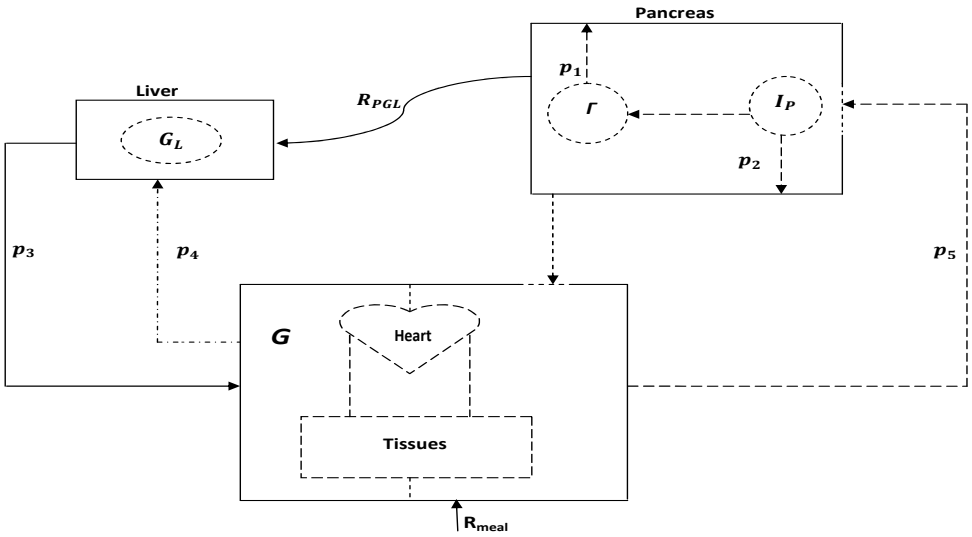

Figure 1. Diagram of the mathematical model. The dash lines notify that a certain quantity of mass flows non-linearly from one compartment/sub-compartment to another. The dashed dot line between the heart-tissues compartment means that a small quantity of glucose is transmitted to the liver compartment.

Parameter/Variable	Description	Unit
	Variables	
Γ	Number of glucagon secreted by the α-cells to release glucose stored in the liver	pg/ml
I_P	Concentration of the insulin secreted by the beta (β)-cells and poured into blood to make penetrate and store in the liver the surplus of the glucose level found in the blood	$\mu U/dl$
G	Glucose concentration in the heart and tissues	mg/dl
G_L	Glucose concentration in the liver	mg/dl
	Parameter to be estimated (Rate)	
n_Γ	Rate of blood coming to glucagon sub-compartment in the pancreas	$(dl)^2/\mu U.min$
n_{I_p}	Rate of blood coming to insulin sub-compartment in the pancreas	$dl.\mu U/mg.min$
n_{G_L}	Rate of blood coming to in the liver	dl/min
n_G	Rate of blood in heart and tissues	$\mu U.mg/dl.min$
p_1	Rate of glucagon from the pancreas to the blood	dl/min
p_2	Rate of insulin from the pancreas to the blood	dl/min
p_3	Rate of glucose from the liver to the heart and tissues	dl/min
p_4	Rate of glucose from the blood to liver (Few quantity)	dl/min
p_5	Rate of glucose from the blood to pancreas	dl/min
R_{meal}	Rate of glucose in human body after meal	mg/min
R_{PGL}	Rate of insulin from pancreas to the blood through the liver	mg/min
	Parameter from literature	
V^Γ	Volume of glucagon in glucagon sub-compartment	dl
V^{I_p}	Volume of insulin in insulin sub-compartment	dl
V^{G_L}	Volume of glucose in the liver compartment	dl
V^G	Volume of glucose in the heart and tissues	dl

Table 1. Description of variables and parameters of the mathematical model

3 Estimation of parameters

We consider that the volumes are obtained from literature and they are presented in Table 2 [14].

Parameter	Value	Parameter	Value
V^G	11.6	V^Γ	113.1
V^{G_L}	25.1	V^{I_p}	67.4

Table 2. Parameters used from the literature [14]

To estimate other parameters, let

$$\mu = \left(n_\Gamma, n_{I_p}, n_{G_L}, n_G, p_1, p_2, p_3, p_4, p_5, R_{meal}, \alpha, \beta, \gamma, \delta, R_{PGL}\right)'$$

be a vector of parameters to be estimated. We fix a positive parameter and we consider the following discretisation of the interval

$[0, T_{\max}]$,

$$t_k = \frac{kT_{\max}}{N},$$

where $T_{\max}$ denotes a positive time parameter. For a positive integer parameter N and $G^\sigma(t_k)$ corresponding data measurement of real values $G(t_k)$ at time t_k we take

$$\underline{G}^\sigma = (G^\sigma(t_1), \ldots, G^\sigma(t_N))'. \tag{2}$$

The superscript σ is the perturbation parameter due to some imprecision on measured data [22]. The identification of parameters can be done by formulating nonlinear inverse problem which is solved using regularization techniques [23]. Let $\underline{G}$ be vector solutions in $\mathbb{R}^N$ at time grid points of the system (1) depending of the parameter vector u. We want to solve the coefficient identification problem

$$J(\mu) = \|\underline{G} - \underline{G}^\sigma\|^2,$$

where $\underline{G}^\sigma$ is given by (2).

This inverse problem can be formulated as follows. Find $\mu^* = \left(n_\Gamma^*, n_{I_p}^*, n_{G_L}^*, n_G^*, p_1^*, p_2^*, p_3^*, p_4^*, p_5^*, R_{meal}^*, \alpha^*, \beta^*, \gamma^*, \delta^*, R_{PGL}^*\right)'$ such that

$$\mu^* = \arg\min_{\mu} J(\mu), \tag{3}$$

subject to (1). We should notify that the (3) is not linear inverse problem and it is ill-posed. This means that little perturbation on data produces a solution that is very different of the original ones. Furthermore, the solution μ does not depend continuously on the data. To find the regularization of the problem (3), we use Tikhonov techniques (See [23] for details). Therefore, this problem becomes Taking $\omega = \left(n_\Gamma, n_{I_p}, n_{G_L}, n_G, p_1, p_2, p_3, p_4, p_5, R_{meal}, \alpha, \beta, \gamma, \delta, R_{PGL}\right)'$, find $\underline{\tilde{\mu}}^\theta$ solution of

$$J(\underline{\tilde{\mu}}^\theta) = \min_{\omega} J^\theta(\omega), \tag{4}$$

subject to (1) where we have set

$$J^\theta(\omega) = \|\underline{G} - \underline{G}^\sigma\|^2 + \theta \|\mathcal{L}\omega\|^2, \tag{5}$$

for good θ such that $\underline{\mu}^\theta$ converges to the solution $\underline{\mu}$ as $\theta \to 0$. Here $\mathcal{L}$ is an operator used for stabilization (i.e., $\mathcal{L}$ is the identity, a differentiation operator, etc.). The solution of (4) subject to (1) is obtained using the Least square method and the data collected in Chad. The numerical simulations are carried out using Matlab built-in function *fmincon* which allows solving constrained optimization problems. The parameters estimated are shown in Table 3.

Estimated parameter	Value
n_Γ	0.6005
n_{I_p}	1.1938
n_{G_L}	1.3845
n_G	0.5479
p_1	1.0343
p_2	1.5477
p_3	1.3693
p_4	0.7866
p_5	1.9521
R_{meal}	101.4078
α	0.0506
β	0.5151
γ	0.0545
δ	0.0505
R_{PGL}	0.5539

Table 3. Estimated model parameters

4 Numerical tests

The measurement of glucose and insulin from different parts of the body needs to take blood samples to determine their concentration. However, to take blood samples from many internal body organs for instance heart and the liver is clinically impossible. We solve this problem, we can estimate concentrations of these parameters using measurements from peripheral tissues along with a mathematical model and a filtering algorithm. Sampling Importance Resampling (SIR) algorithm is one of the methods that can give the estimated solution. For more details about the SIR algorithm, we refer the readers to [24, 25]. The data collected

in Chad is the glucose measured in the tissues of patients. In our simulation we estimate glucose in the liver, insulin and glucagon in the pancreas by taking this measured glucose as measurements. We assume that noisy measurements of glucose in tissues and the heart are available measured data. To apply the SIR algorithm, we consider a fixed-step backward difference approximation by

$$\frac{dX}{dt} \approx \frac{X_k - X_{k-1}}{\Delta t}, \quad 0 \leq t \leq T_{\max}, \tag{6}$$

where

$$X_k = \left(\Gamma_k, I_{p,k}, G_{L,k}, G_k\right)^t, \tag{7}$$

and

$$X_k = X(t_k).$$

If M denotes the total number of discretization intervals we have

$$X_k = X_{k-1} + \Delta t,$$

where $\Delta t = \frac{T_{\max}}{M}$ is step.
Let set

$$F_{k-1}(X_{k-1}) = (F_1(X_{k-1}), F_2(X_{k-1}), F_3(X_{k-1}), F_4(X_{k-1}))^t,$$

which refers to the dynamic equations with

$$\begin{aligned}
F_1(X_{k-1}) &= \left(1 - \frac{\Delta t}{V^\Gamma} p_1\right) \Gamma_{k-1} + \frac{\Delta t}{V^\Gamma} n_\Gamma G_{k-1}^\alpha I_{p,k-1}, \\
F_2(X_{k-1}) &= \left(1 - \frac{\Delta t}{V^{I_p}} p_1\right) I_{p,k-1} + \frac{\Delta t}{V^{I_p}} n_{I_p} G_{k-1}^\delta, \\
F_3(X_{k-1} &= \left(1 - \frac{\Delta t}{V^{G_L}} p_3\right) G_{L,k-1} + \frac{\Delta t}{V^{G_L}} \left(n_{G_L} \Gamma_{k-1}^\beta + p_4 G_{k-1} + R_{PGL}\right), \\
F_4(X_{k-1} &= \left(1 - \frac{\Delta t}{V^G} p_5\right) G_{k-1} + \frac{\Delta t}{V^G} \left(p_3 G_{L,k-1} + n_G I_{p,k-1}^\gamma + R_{meal}\right).
\end{aligned} \tag{8}$$

Using (8) our state dynamic model (1) is estimated recursively by the following compact form

$$\begin{cases} X_k = F_{k-1}(X_{k-1}) + v_{k-1}, \\ Y_k = PX_k + e_{k-1}, \end{cases} \tag{9}$$

where we set $Y_k = G_k$ that is measurement of glucose in tissues, v_{k-1} and e_{k-1} are the stochastic process and measurement noise, respectively and they are independent and identically distributed (i.i.d.). P denotes the matrix from the equations modelling the sensors referred to as the measurement model given as

$$P = (0, 0, 0, 1)^t.$$

In numerical simulation, we consider $M = 100$, $T_{\max} = 300$ minutes, $N = 1000$ particles and we assume that the state X_0 and state measurement noises have a Gaussian probability density function that is $X_0 \sim \mathcal{N}(0, 5)$, $v_k \sim \mathcal{N}(0, 20)$ and $e_k \sim \mathcal{N}(0, 1)$ where $\mathcal{N}$ means normal distribution. The numerical results are illustrated in the Figure 2, 3 and 4.
Figure 2 shows the concentration of glucagon in the pancreas using SIR implemented on the mathematical model. There is not a significant variation of this parameter that plays a crucial role in the regulation of blood glucose. This means that blood glucose is not regulated for a type 2 diabetic patient. The pancreatic insulin decreases as shown in the Figure 3. Therefore, there is no role of both insulin and glucagon as regulators of blood glucose. During periods of hyperglycemia (i.e., after meal ingestion), whereas insulin secretion is increased, glucagon secretion is reduced. All those results are justified by the increase of glucose in the liver (See Figure 4). Hence, the liver affects insulin concentrations, since about 50% of insulin is extracted at first passage, and this fraction may be reduced in the insulin-resistant liver, leading to hyperinsulinemia [26]. The elevated rate of hepatic glucose production (HGP) is a major cause of fasting hyperglycemia and a lack of suppression of HGP may contribute to postprandial hyperglycemia. Through an increased secretion of triglyceride, the liver may also contribute to peripheral insulin resistance and thereby further increase postprandial hyperglycemia [26].

5 Concluding remarks

The mechanical behaviour of the glucose-insulin system depends on the type of mathematical model that describes its dynamics. The simple mathematical model should describe accurately this system vis-a-vis the diseases that affect it. In this work, we have proposed a three-compartmental mathematical model for type 2 diabetic patients that describes the variation of glucose and insulin in Chad context based on data collected at Abéché hospital. To estimate the dynamics of glucagon, insulin and hepatic glucose in internal organs of the human body, the Sampling Importance Resampling (SIR) particle filtering algorithm is used and implemented using the developed mathematical model. Numerical results show that the new glucose-insulin system model

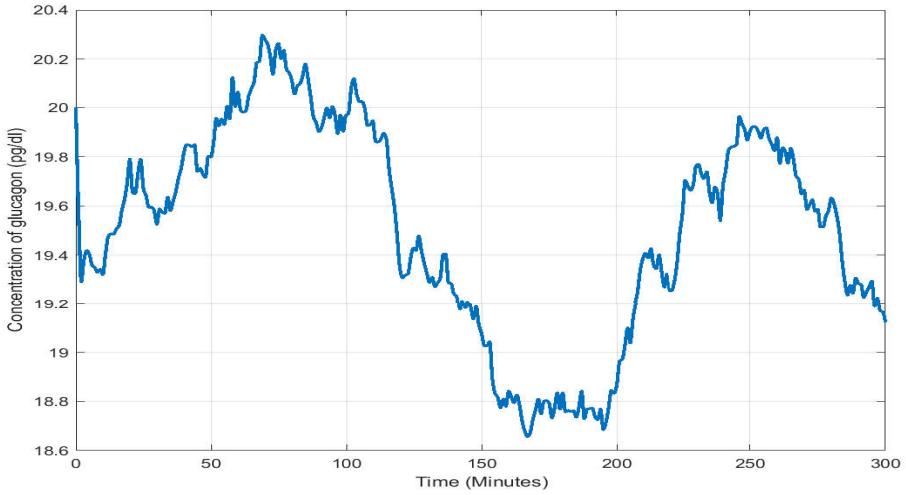

Figure 2. Variation of glucagon in the pancreas

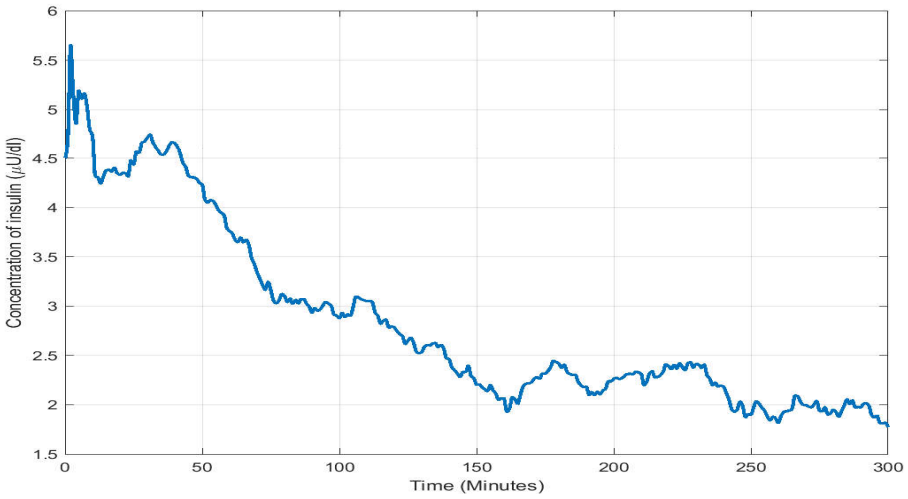

Figure 3. Variation of insulin in the pancreas

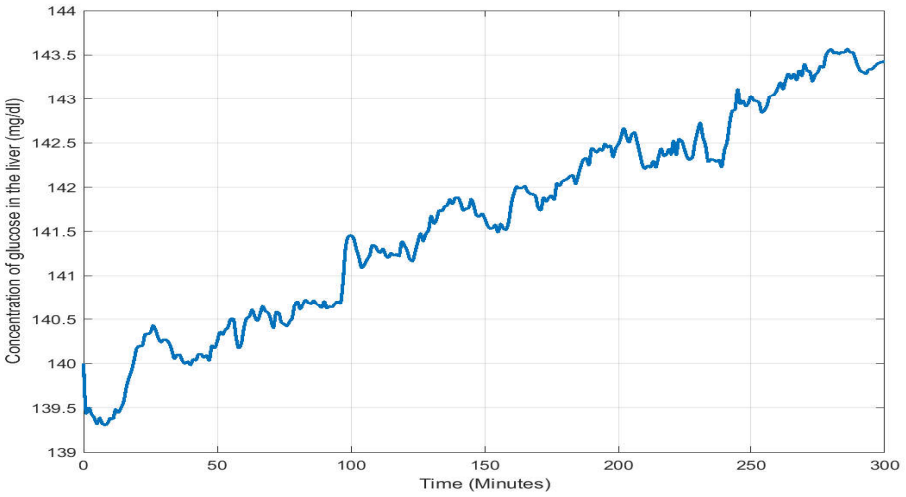

Figure 4. Variation of glucose in the liver

introduced fits with the clinical data and they are clinically consistent with physiological responses. Indeed, insulin secretion increases while glucagon secretion reduces due to periods of hyperglycemia. The proposed mathematical model can also be used by physiologists and other experts in medicine for monitoring the glucose-insulin system.

Declarations

Consent for publication

Not applicable.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

Not applicable.

Author's contributions

A.H.A.: Conceptualization, Investigation, Methodology, Software, Writing - Original Draft, M.S.D.H.: Investigation, Methodology, Writing - Original Draft, J.M.N.: Methodology, Supervision, Validation, Writing - Review and Editing. All authors discussed the results and contributed to the final manuscript.

Acknowledgements

Not applicable.

References

[1] Tolić, I.M., Mosekilde, E., & Sturis, J. Modeling the insulin–glucose feedback system: the significance of pulsatile insulin secretion. *Journal of Theoretical Biology*, 207(3), 361–375, (2000). [CrossRef]
[2] https://fr.wikipedia.org/wiki/Afriquecentrale, 2022, Access Date: 15th May 2022.
[3] International Diabetes Federation (IDF), Atlas, Seventh edition, 2015, Access Date: 15th May 2022.
[4] International Diabetes Federation (IDF), Atlas, Sixth edition, 2013, Access Date: 5th June 2022.
[5] https://www.diabete.qc.ca/fr/comprendre-le-diabete/tout-sur-le-diabete/types-de-diabete/le-diabete-de-type-2, Access Date: 5th June 2022.
[6] Lin, C.W. Modeling glucose-insulin kinetics and development of type 2 diabetes in offspring of diabetic parents. Ph.D. Thesis, University of Iowa, (2011). [CrossRef]
[7] Joshi, H., & Jha, B. K. Chaos of calcium diffusion in Parkinson's infectious disease model and treatment mechanism via Hilfer fractional derivative. *Mathematical Modelling and Numerical Simulation with Applications*, 1(2), 84–94, (2021). [CrossRef]
[8] Joshi, H., Jha, B.K., & Yavuz, M. Modelling and analysis of fractional-order vaccination model for control of COVID-19 outbreak using real data. *Mathematical Biosciences and Engineering*, 20(1), 213–240, (2023). [CrossRef]
[9] Durai, P., Xavier, F., Zubair, B., & Fuqian, S. Fractional Reaction-Diffusion Model for Parkinson's Disease. In: Pandian, D., Fernando, X., Baig, Z., Shi, F. (eds) Proceedings of the International Conference on ISMAC in Computational Vision and Bio-Engineering 2018 (ISMAC-CVB). ISMAC 2018. Lecture Notes in Computational Vision and Biomechanics, vol 30. Springer, Cham. [CrossRef]
[10] Uçar, S., Özdemir, N., Koca, İ., & Altun, E. Novel analysis of the fractional glucose-insulin regulatory system with non-singular kernel derivative. *The European Physical Journal Plus*, 135(5), 414, (2020). [CrossRef]
[11] Vahidi, O., Kwok, K.E., Gopaluni, R.B., & Sun, L. Development of a physiological model for patients with type diabetes mellitus. In Proceedings of 2010, *American Control Conference*, pp.2027–2032, Mariott Waterfront, Baltimore, MD, USA, (2010). [CrossRef]
[12] Vahidi, O. Dynamic Modeling of Glucose Metabolism for the Assessment of Type II Diabetes Mellitus. Ph.D. Thesis, The University of British Columbia, (2013).
[13] Vahidi, O., Kwok, K.E., Gopaluni, R.B., & Sun, L. Developing a physiological model for type II diabetes mellitus. *Biochemical Engineering Journal*, 55(1), 7–16, (2011). [CrossRef]
[14] Sorensen, J.T. A physiologic model of glucose metabolism in man and its use to design and assess improved insulin therapies for diabetes. Ph.D. Thesis, USA: Massachusetts Institute of Technology, (1985).
[15] Moore, C.X., & Cooper, G.J. Co-secretion of amylin and insulin from cultured islet β-cells: modulation by nutrient secretagogues, islet hormones and hypoglycemic agents. *Biochemical and Biophysical Research Communications*, 179(1), 1–9, (1991). [CrossRef]
[16] Aronoff, S.L., Berkowitz, K., Shreiner, B., & Want, L. Glucose metabolism and regulation: beyond insulin and glucagon. *Diabetes Spectrum*, 17(3), 183–190, (2004). [CrossRef]
[17] Basu, A., Basu, R., Shah, P., Vella, A., Johnson, C.M., Nair, K.S., Jensen, M.D., Schwenk, W.F. & Rizza, R.A. Effects of type 2 diabetes on the ability of insulin and glucose to regulate splanchnic and muscle glucose metabolism: evidence for a defect in hepatic glucokinase activity. *Diabetes*, 49(2), 272–283, (2000). [CrossRef]
[18] Iozzo, P., Hallsten, K., Oikonen, V., Virtanen, K.A., Kemppainen, J., Solin, O., Ferrannini, E., Knuuti, J., & Nuutila, P. Insulin-mediated hepatic glucose uptake is impaired in type 2 diabetes: evidence for a relationship with glycemic control. *The Journal of Clinical Endocrinology & Metabolism*, 88(5), 2055–2060, (2003). [CrossRef]

[19] Kahn, S.E. The importance of the beta cell in the pathogenesis of type 2 diabetes mellitus. *The American Journal of Medicine*, 108(6), 2-8, (2000). [CrossRef]
[20] Toft-Nielsen, M.B., Damholt, M.B., Madsbad, S., Hilsted, L.M., Hughes, T.E., Michelsen, B.K., & Holst, J.J. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *The Journal of Clinical Endocrinology & Metabolism*, 86(8), 3717-3723, (2001). [CrossRef]
[21] Igari, K., Kudo, T., Uchiyama, H., Toyofuku, T., & Inoue, Y. Quantitative evaluation of microvascular dysfunction in peripheral neuropathy with diabetes by indocyanine green angiography. *Diabetes Research and Clinical Practice*, 104(1), 121-125, (2014). [CrossRef]
[22] Ntaganda, J.M., Niyobuhungiro, J., Banzi, W., Mpinganzima, L., Minani, F., Gahutu, J.B., Dusabejambo, V., & Kambutse, I. Mathematical modelling of human cardiovascular-respiratory system responses to exercise in Rwanda. *International Journal of Mathematical Modelling and Numerical Optimisation*, 9(3), 287-308, (2019). [CrossRef]
[23] Hanke, M. (2000). Iterative regularization techniques in image reconstruction. In Surveys on solution methods for inverse problems (pp. 35-52). Springer, Vienna. [CrossRef]
[24] Arulampalam, M.S., Maskell, S., Gordon, N., & Clapp, T. A tutorial on particle filters for online nonlinear/non-Gaussian Bayesian tracking. *IEEE Transactions on Signal Processing*, 50(2), 174-188, (2002). [CrossRef]
[25] Doucet, A., Godsill, S., & Andrieu, C. On sequential Monte Carlo sampling methods for Bayesian filtering. *Statistics and Computing*, 10(3), 197-208, (2000). [CrossRef]
[26] Staehr, P., Hother-Nielsen, O., & Beck-Nielsen, H. The role of the liver in type 2 diabetes. *Reviews in Endocrine & Metabolic Disorders*, 5(2), 105-110, (2004). [CrossRef]

Mathematical Modelling and Numerical Simulation with Applications (MMNSA) (https://www.mmnsa.org)