Prediction of blood glucose in type 1 diabetics using a Hybrid Model based on Agents

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***Abstract* — The number of Diabetes Mellitus cases has constantly grown in recent decades around the world. Thus, numerous mathematical and agent-based models have been proposed to shape the human glucose-insulin regulatory system and its ultradian oscillations. However, the most current models do not have the ability to learn constantly in order to increase the prediction of human blood glucose from 30 minutes to approximately 8 hours. In order to contribute to the improvement of these mechanisms, this research project presents an autonomous reactive model to inputs such as physical activity, quantity and type of insulin, as well as food intake, in order to predict the oscillation of glucose concentration in the human bloodstream for approximately 8 hours in type 1 diabetic patients. The main property of the proposed model is to combine a discrete modeling approach, agent-based model, with continuous model to form a hybrid model. This model is based on the schematic diagram of the human glucose-insulin regulatory system, and each agent within the physiological process will follow a mathematical model to characterize its functions and interactions. The use of agents representing, for example, the pancreas and its alpha and beta cells, tends to facilitate the process of learning from the variable's values related to each patient, and deliberation of which of them should be re-fed into the mathematical model (differential equations). The end result tends to identify the behavior of each type 1 diabetic with their respective glucose variation for 8 hours and create recurrent and subjective recommendations.**

***Keywords* – Diabetes Mellitus; mathematical model; agent-based model; predict; glucose concentration.**

Classification: doctorate degree.
Category: Beginner.

I. Introduction

Current society has changed their lifestyle with the increase of sedentarism associated with the consumption of industrialized foods with high energy density. The number of the diabetes cases has tripled in the USA since 1990 [3] and reach more than 16 million in Brazil [11]. Public policies aimed at adults, children and adolescents, associated with a model that can facilitate the circadian routine of a diabetic are necessary and emerging to reduce the advance of this chronic disease [6]. The ease of access to software in devices with low computational capacity may facilitate the integration of diabetic patients with a model capable of predicting the oscillation of glucose in the bloodstream [9]. In fact, users/patients from different places with specific diseases are encouraged to perform most of their checks through a software or device [5].

The nature of the human organism necessitates a model that mimic this dynamic exchange of information across its components. In our research project, we typically link descriptions of human glucose-insulin regulatory system (HGIRS) described in Fig. 1. In Fig. 1, the solid lines denote production/consumption of a substrate (glucose or insulin), dotted lines denote inhibition by a substrate, and dashed lines denote encouragement by a substrate. Ingested food, for example carbohydrates or fat, is converted to glucose, which the human body uses to supply their processes . Glucose also stimulates pancreatic ß-cells to produce insulin [9]. However, note here that there isn't connection between pancreatic ß-cells and insulin in this diagram because is a HGIRS from type 1 diabetic (T1D). In the case of T1D, the pancreas is incapable of producing insulin, and so healthy glucose levels can only be maintained through the injection of external insulin. It is not possible to induce stable glucose oscillations under these conditions, but we can determine how much insulin is required to keep glucose within range of 80-120 mg/dl of the blood in the human bloodstream [9]. In our research project, we involved a dichotomy about insulin concentration in bloodstream: identify which type (basal or fast-acting) and quantify what insulin is needed to maintain glucose levels in the appropriate range in bloodstream (80-120 mg/dl), during all day long.

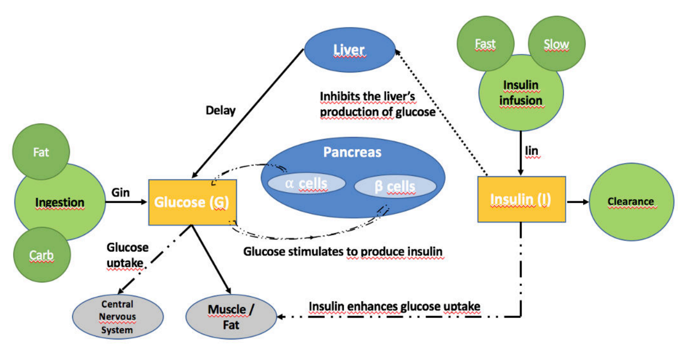

Fig. 1. Human glucose-insulin regulatory system (HGIRS): T1D

The central nervous system (CNS) processes glucose without insulin, whereas insulin enhances glucose uptake by muscle and fat cells. Thus, when blood glucose (BG) levels are high or before daily meals, insulin infusion by injection is necessary to stimulate glucose uptake and to slow the production of further glucose from the liver [9]. When BG levels are low, the most part of the time is necessary to ingest food and the liver's production of glucose speeds up. This feedback loop helps to keep a person's BG levels in a state of oscillatory homeostasis [9].

ABMs are discrete models that utilize individual entities known as agents, here representing individual organs and hormones represented in Fig. 1. Each agent is autonomous and behaves based on decisions from the set of rules, interactions, and states given to it, leading the heterogeneity among agents. Agents can receive inputs from environment, influencing their decision making, and can also have the ability to alter their environment. The models that combine aspects of both continuous and discrete model are commonly referred to as hybrid models [4]. Hybrid ABSs arise when continuous models are used to describe part of overall model, such as the environment and parts of decision-making processes.

Computational models are used in living organisms in order to understand, translate and predict their behavior. When building our hybrid model represented in Fig. 2, four different areas could be considered: (1) how to *construct a model* – create a mathematical formulation that is able to recapitulate the dynamics of a human glucose-insulin regulatory system (systemic part of a living organism), (2) how to *solve a model* – determining the most efficient way to solve the underlying mathematics [4], (3) how to *analyze models* - calibrate and validate the model and then make and understand model predictions [4], and (4) *agent-based model* (*ABM*) – responsible to learn and store the individual parameters from each patient, to characterize the behavior from them and re-fed into mathematical model.

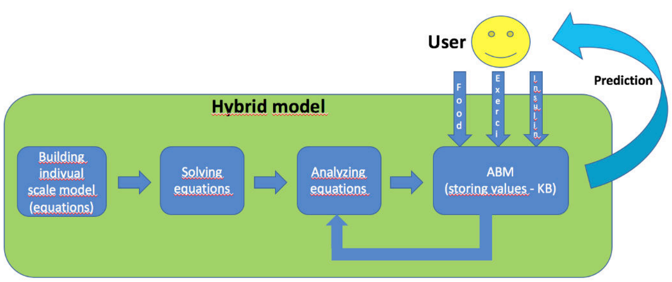

Fig. 2. Considerations for building our hybrid model

We focus this research to build a Hybrid Agent-based Model where an ABS (discrete) is informed by differential equation models (continuous), operating at same environment (organism): HGIRS. The use of continuous models is to describe the dynamics of the HGIRS and agent-associated reactions that occur at the same space and scale, and influence agent decision-making processes.

A. Current research

With no known cure for diabetes, lifelong treatment is generally the only option. T1D patients must monitor their BG levels throughout the day and take corrective action whenever they are hyper or hyploglicemic [14]. There has been a recent of interest in human BG prediction due to its role in closed loop control for the artificial pancreas [5]. This research upon a foundation of previous models of the human glucose and insulin system, based only on differential equations but not with the focus of prediction, but on immediate recommendations [9][10]. However, the Artificial Intelligence, but exactly the Machine Learning has helped improve the prediction of glucose in human blood. In [14], the focus of the research was on the prediction of 30 minutes and also hypoglycemia only, using physiological and regression models.

Compared with the models already created, the our model aims to predict the glucose level in T1D patients for 8 hours simply because of the average sleep time of a patient in order to avoid nocturnal hypoglycemia. The joint use of the mathematical model to simulate the SRGI and the constant calibration of the values of the parameters through the agents, as the insulin sensitivity, tends to facilitate the prediction.

II. Methodology

The method adopted in the development of the present work is the Applied Research based on the hypothetical-deductive approach, using references available in the specialized literature for the definition of the problem, specification of hypotheses and analysis of such hypotheses [13]. The proposed model is specified by means of a prototype, based on agents and differential equations, that allows the validation of the hypotheses that serve as basis for the design of the model.

The first phase of this work consists of a seven-step study. The first is the study of articles referring to endocrinological medicine [10][16]. The second focuses on the construction of mathematical models, but specifically differential equations, in order to replicate the behavior of HGIRS. In this step the Matlab software is used, so with your fsolve feature. The third step is based on the analysis of the various functionalities of ABSs in order to understand the possible advantages of its use in a HGIRS [17]. The fourth step focuses on the study of how an ABS can be applied to simulate a HGIRS, as well as in combination with the continuous part (differential equations). The fifth step is based on the verification and study of the programming language named Jason. Jason is to develop the ABS which allows its implementation, and evaluation in a simulation environment with support for communication between agents. The sixth stage focuses on the construction of the final model, with the objective of predicting the oscillation of glucose in the blood of a T1D patient, using our hybrid model. Finally, the seventh step consists in calibrating the model with some T1D patients, in order to measure to the accuracy in the reached values. Initially, the calibration will be with only one T1D patient. In the last step, the T1D patient can use modern devices for continuous monitoring of blood glucose level.

III. Hybrid Model

A. *Mathematical model*

The glucose concentration (G) can increase via two pathways: ingestion and endogenous production [9]. Initially, we only model glucose release from ingestion, which we represent by the glucose intake rate ***Gin***. We make this term periodic (in the case of multiple daily meals) (1) with ultradian glucose oscillations. In this way, we can consider carbohydrates and fat when are consumed, each one with different metabolism to generate glucose into HGIRS. Primarily, we model glucose from the liver, commonly called hepatic production (***HGP***), and we make this term constant (1).

The glucose concentration (G) can decrease via two pathways, namely: utilization by the Central Nervous System (CNS) and utilization by muscle and fat cells [9]. Glucose utilization by the CNS does not depend on insulin concentration; these cells will use all of the glucose available to them up to a threshold [9]. Equation (1) primarily uses this term constant (***CNSGU***). On the other hand, muscle and fat cells, do rely on the presence of insulin to take up glucose; thus, we represent their consumption with the product ***f1(G(t))*f2(I(t))***. Here we arrive at the first complication that diabetic illness introduces; the muscle and fat cells from people with T1DM depends on external insulin to take up glucose from the bloodstream as easily as the corresponding cells of a person without diabetes [9]. The scaling factor μ accounts for this; μ can take values from 0 to 1, with corresponding to no ability for muscle and fat cells to take up glucose (T1D), and 1 corresponding to the glucose uptake ability of a person without diabetes. The additional factor, **[1+(E-Em)]** (1), accounts for the positive effect of exercise on insulin sensitivity [7]. Here, ***E*** corresponds to minutes of physical activity (MPA) per day, as defined by [12]. 60 minutes per day of MPA (**Em** = 60) is considered average; any less than this decreases glucose tolerance and any more increases glucose tolerance.

There is only one pathway by which the insulin concentration can increase in T1D: insulin infusion ***Iin*** (external) (2) because T1D does not have insulin production from pancreatic ß-cells. We make this term periodic (in the case of multiple insulin infusion before daily meals) (2) with ultradian glucose oscillations. We let the insulin infusion rate ***Iin*** be a periodic term since only make sense if glucose intake is also periodic. Finally, there is one significant way for insulin concentration to decrease, which is through metabolism by human insulin-degrading enzyme (IDE) [1]. As an enzymatic reaction, we quantify insulin degradation with Michaelis-Menten kinetics using the term ***VmaxI(t) / (Km+I(t))*** (2). Here, ***Vmax*** is the maximum insulin clearance rate and ***Km*** is the enzyme's half-saturation value [18].

We can represent these processes mathematically by:

$$G' = Gin + HGP - CNSGU - \mu[1+(E-Em)]*f1((Gt))*f2(I(t)) \quad \textbf{(1)}$$

$$I' = Iin - (VmaxI(t) / Km+I(t)) \quad \textbf{(2)}$$

This mathematical model provide the framework upon which we base our analysis of human glucose and insulin dynamics [9]. We are in the development phase of the functions f1 and f2, to represent the consumption of glucose in relation to the application of insulin.

B. *Agent-Based Model (ABM)*

The agent-based model within our hybrid model works cooperatively using the BDI model (Belief, Desire and Intention) [19]. The proposed model has as important characteristic: the ability of communication between all the agents that compose it. The cooperation between agents is an important feature used in a way that is implicit in the model plans. The proposed model is not purely reactive because agents, in addition to continuously responding to environmental changes (HGIRS), try to systematically achieve their goals calling their functions. A knowledge base (KB) is used by each agent in order to store information needed to achieve individual goals and model goals [19].

The diagram described in Fig. 3 represents the agents that make up the HGIRS, and their possible state and actions. In addition, there are resources that can be inserted or released by the agents, such as glucose and insulin. For the model to be effective, it must assure some essential accuracy characteristics for data obtained based on information entered by the user/patient, such as BG value (mg/dl), amount of carbohydrate and fat ingested, type and time of physical exercise, besides the types and quantity of each insulin (basal and fast effect).

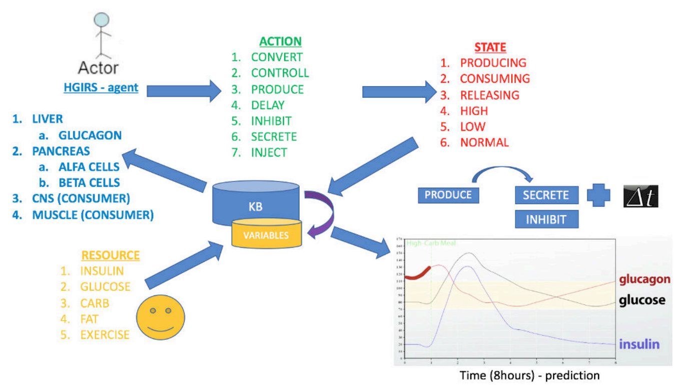

Fig. 3. Agent-based model diagram

In a predictive way, the proposed model aims to guarantee these characteristics by means of the agents (organs and hormones), representing the HGIRS. The model can to store the inserted values from user and to maintain the accuracy of the glucose oscillation curve in the blood, for at least 8 hours. An agent can accumulate knowledge based on previous experiences and, consequently, perform a task more efficiently than in previous executions [8]. The behavior of the agents, their actions, the relationship between them and their respective function calls are based on differential equations. From the learning curve of each patient, the predictive values reached in the BG oscillation curve tend to be more precise, so that the agents feed the model, and consequently to the variables of the differential equations.

We are in the development phase of the ABS to represent the HGIRS based in differential equations and to predict the behavior of concentration of glucose in human blood. There are many well-known agent languages that combine declarative and imperative features (hybrid approach). Primarily, we define to use Jason [2], that is an interpreter, for an extended version of AgentSpeak(L) [15]. Jason was chosen due to be fully customisable in Java and to have a clear notion of the agent-based environment, in our case the HGIRS.

IV. CONCLUSIONS

With this research project, we have proposed a hybrid model (discrete and continuous) to predict the oscillation of glucose in the bloodstream of T1D. This model aims to replicate fundamental behaviors of the HGIRS, in order to better understand and predict the model behavior as a whole. The main idea is that, through the minimum of possible information provided by the user/patient, as well as type and quantity of food, insulin and exercise, to know with accuracy the oscillation of glucose levels in T1D for at least 8 hours. The use of an ABS, being that each component of HGIRS is an agent, tends to facilitate the process of storing the values in an individualized way and reusing them. Through the model, a personalized treatment can be suggested for each user/patient, so that the glucose levels remain between 80-120 mg/dl of blood, cooperating with the current medical recommendations.

In this way, T1D patients with the possession of this model can have the freedom to live with more tranquility, especially in moments of sleep, avoiding hyperglycemia and hypoglycemia.

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