Developing a Dynamic Bio-inspired Intelligent System to Support Diabetic Patients

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Abstract.
This paper proposes a new biologically-inspired phenomenological model of insulin release that can be used to continuously monitor a person with diabetes and therefore recommend insulin dose and predict events. Given all the parameters and conditions that have to be met in order to achieve stability, the proposed insulin-release system will be considered as highly non-linear and dynamical. The resulting model will study the mechanisms that keep the system from reaching a chaotic state (diabetes), based on the property of self-organised criticality. This property was selected since it has been previously identified and studied in other dynamical biological systems. The proposed model will then be used as part of a model-based reasoning system that aims to support patients with diabetes.

1 Introduction

Regulation of insulin and glucose in the human body is part of a complex dynamical system, whose understanding and study is highly relevant for the management of diabetes. This system is in turn influenced by factors such as meal intake, heart rate, exercise, sleep, and other factors. Research and development on the insulin release system, also known as the artificial pancreas, can be traced back at least 50 years [1]. The models, signals, and control algorithms involved in the design of the insulin-release clinical system are the three most relevant areas of study. This research has facilitated the advancement of continuous glucose monitoring technologies, and the development of medical devices that assist type 1 diabetic patients in self-management of their condition.

Significant improvements have been made in continuous glucose monitoring technologies, and several control techniques have been tested and implemented on medical devices. However, in the context of modelling, it was found that a significant discrepancy exists between the physiological understanding and the low-level mechanisms that permit the physiological state [2]. This finding is the main motivation for the development of the model proposed in this paper. The modelling approach will be improved by studying the phenomenological aspects of insulin release using mathematical properties.

This paper summarizes the preliminary research that was conducted, as well as the modelling approaches that will be considered in order to construct the

research proposal. The model will then be used to identify how individual diabetes patients are influenced by different factors such as carbohydrate intakes, hormones, physical exercise and so on, and therefore support them in their required insulin doses.

2 Preliminary research on Bio-Inspired Models

To better understand the features of the model proposed in this research, physiological and mathematical models were studied. Among the physiological models analysed, minimal and maximal models were identified as the main models considered for CGM technology development. For the purpose of this research project, further studying of the phenomenological aspects of insulin-release using mathematical properties will be conducted. This was decided given a few misrepresentations found in physiological models, which are briefly also detailed in this section.

2.1 Physiological models

A physiological model is defined as the qualitative or quantitative representation of an actual physiological system. Quantitative physiological modelling is preferred, and considered to be more useful, as it provides a mathematical representation characterized by differential equations [5]. The most commonly used approach for the artificial pancreas system is compartmental modelling [4], a special case of physiological modelling where the movement of a substance between compartments is described. Furthermore, there are two classes of physiologically-based models for the artificial pancreas system, both described in this section: maximal models and minimal models.

Minimal models focus on explaining the key components of the system and measuring essential processes involved in healthy state and diabetes. One of the earliest models documented is the one developed by Bergman and colleagues back in the 70s [1]. The aforementioned model has undergone several modifications to include additional compartments and incorporate the effects of disturbances such as meal or exercise. Other examples of minimal models include the compartmental approaches proposed by Insel, et. al. and Cobelli et. al. in [2] which attempt to measure and understand glucose metabolism and its regulation by insulin.

Maximal models attempt to simulate the glucose insulin system using all available knowledge of functionality, thus allowing the researcher to carry out experiments in particular scenarios [3]. Useful information on the general functions of the system has been collected. One of the most representative examples is that of the GIM (Glucose Insulin Model) simulation software, which was designed based on the model proposed by Chiara Dalla Man, Robert A. Rizza, and Claudio Cobelli [4], consisting of 12 differential equations and 35 parameters. This software has been useful to simulate healthy state subjects, type 2 diabetic

subjects, and impaired glucose-tolerant subjects in two main scenarios: meal and daily life. The model developed by Grodzky, Jonkers and Henquin [9], was able to demonstrate the number of active cells is a sigmoidal function of glucose concentration, and suggest that insulin release is subject to different thresholds .

Minimal models are commonly used to analyse the data obtained from glucose tolerance tests. Although the results obtained prove useful, they tend to misrepresent the actual dynamics of the glucose-insulin system given that they are modelled in steady state. Some misrepresentation is also observed in maximal models, given that several of the parameters used in the system are derived from steady-state conditions.

Several other studies have been conducted in an attempt to understand the insulin release phenomenon in the human pancreas, these include glucose tolerance tests and in vitro studies (see [2] and [9]).

After revising the state-of-the-art in physiological modelling for the artificial pancreas, it was concluded that these models alone would not be sufficient for the development of this research project. The studied models have been able to provide useful information about the phenomenon of insulin release in the pancreas, and they provide solid evidence of progress in the field. However, it is considered that the models do not accurately represent the physiological state as they provide a generalized mathematically reduced approach, rather than a detailed representation on the phenomenon of insulin-release. It was thus decided to explore a different set of methods to further develop the research project. These are presented in the subsequent section of this article.

2.2 Computational models and properties

This section introduces the property of self-organized criticality, Turing mechanisms, and two reaction-diffusion systems that will be considered as the foundation for the development of the model. These properties and systems have been chosen since they have been previously studied and identified in biological systems. While physiological models focus on representing the physical interactions of the system, the following systems and properties focus on describing complex mathematical scenarios, such as chemical reactions and/or the interaction between an activator and an inhibitor.

The property of self-organized criticality is particular to dynamical systems that are attracted to a critical point; for the past decade it has been identified and studied in biological systems. It has proven useful in defining and understanding neuronal communication, the functionality of protein families, pattern formation in biological systems, among others [11].

Turing mechanisms have been useful in research related to pattern formation, particularly in biological patterns such as the scales of fish, the formation of a

foetus and, at a more molecular level, pattern formation in cellular slime mould and calcium activity [7]. The model which can assist in studying these mechanisms is the two-variable Lengyel-Epstein model; a model for the photosensitive chlorine dioxide-iodine-malonic acid reaction (CDIMA). It has proven useful for investigating the continuous effect of external influence on Turing pattern formation. (see [7] and [8])

Reaction-diffusion systems and models are also used to describe pattern formation phenomena (including Turing patterns), particularly in systems that involve the interaction of many components. The model of interest for the purpose of this project is the Gray-Scott model, given the wide range of spatio-temporal dynamics it supports [10]. This model describes auto-catalytic chemical reactions of type: $A + 2B \rightarrow 3B$; $B \rightarrow C$, where the first equation represents an auto-catalytic process. It is possible to observe a wide range of dynamics when the input to the reactor is a continuous uniform flow of species A. The system can have up to three homogeneous steady-states: one trivial, and two non-trivial.

Another system of interest is the Brusselator. This system represents the interaction between a reactor and an inhibitor, and is nowadays considered one of the simplest reaction-diffusion systems capable of generating complex spatial patterns [13]. The proposed activator-inhibitor interaction is a well-known principle to explain pattern formation in chemical, ecological, physical, and biological systems.

3 Criticality analysis of the insulin-release system

Three possible approaches to improve the modelling methodology were identified during the preliminary research stage. The approaches were identified based on findings from physiological models that indicate the presence of criticality in the system. The approaches are described in the following subsections and will have to be analysed and simulated in order to fulfil the aim of the research project.

3.1 Finding 1: Non linearity and dynamical requirements

In mathematical terms, the insulin release system has to be considered as highly non-linear and dynamical. Given all of the parameters involved and the conditions needed to reach stability, it qualifies as one of the dynamical systems that is attracted to a critical point, this critical point being a normal glucose level. The low- level mechanisms of insulin release which control the system so that it does not become chaotic (diabetes), have to be studied to gather a wider knowledge on the effect they have over the global state of stability [12]. This will be achieved by studying the property of criticality observed in the insulin-release system.

3.2 Finding 2: Identification of critical patterns

A recent study has found that local feedback has a direct effect on the orientation of the Turing pattern in a system, and can change the global or local dynamics in it [7]. These findings can assist in understanding and defining the communication mechanisms followed by beta cells which lead to the release of insulin. This will be achieved by adding constraints to the insulin-release system, such as thresholds and external stimuli (e.g. meal and exercise). By adding these disturbances to the system, it will be possible to observe the effect on the insulin-release pattern, and whether or not it converges to a critical point.

3.3 Finding 3: Insulin delivery as a wave function

In the study by Jonkers and Henquin [9] it was demonstrated how beta cells are recruited in accordance with the sensed concentration of glucose, given that they have different threshold sensitivities to it. The study also shows how the behaviour of a single cell can be extrapolated to the behaviour of the islet (cluster) it is associated with. This property can indicate that the propagation of insulin secretion behaves as a wave function. The control of such a system has been studied by Y. N. Kyrychko et. al [10]. Where an activator/inhibitor control was applied on a Gray-Scott model based system, convergence to stability was achieved regardless of the chaotic nature of the system.

In the following stage of development, the low level mechanisms of insulin release will be simulated to observe their influence on stability at a global level. This will be achieved using coupled oscillators to represent the interaction of pancreatic β-cells, which represents the foundation for the development of the proposed model.

4 Bio-Inspired Model-Based Reasoning

In model based reasoning, an explicit model of the behaviour of the system is used to predict its reaction given a set of initial conditions and constraints. The predicted behaviour is then compared with the actual system and if discrepancies are found and assuming that the model is accurate then the reasoning mechanism can adapt the model to detect and identify the discrepancies. According to Herrero et al, [6] model-based reasoning has been proposed in different areas related to diabetes: Safety of monitoring devices, artificial pancreas, and prediction of hypoglycaemia.

In this research we propose to use a dynamic bio-inspired mathematical model to better model patient assimilation of glucose. The model will then be part of a MBR system that will be used to monitor a patient, detect when insulin is needed and identify the doses required.

The simulation and validation of the model will be performed using real patient data, which will be facilitated given the collaboration with Pepper project EU (http://www.pepper.eu.com/)

5 Conclusion

This paper proposes the development of a bio-inspired mathematical model of insulin release. Three approaches to assist in studying the property of criticality in the insulin-release system have been identified, and will be considered to develop the model. There is no evidence suggesting that the mathematical properties and models listed in this document have been used to model the phenomenological aspects of insulin release in the pancreas. A major advantage of using them is their capability of explaining complex dynamical systems using a simpler mathematical approach. Implementing this novel methodology could help fill in some gaps in physiological modelling, such as the inclusion of disturbances and non-linearities present in the system.

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