

Parallel Session
Physiology IV

MODELLING THE INTERPLAY OF TWO GLYCEMIC BIOMARKERS FOR PATIENT-SPECIFIC MONITORING OF DIABETES

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Keywords: Biomathematics, Age-structured models, Diabetes, Hematology.

Diabetes mellitus encompasses a group of metabolic disorders characterized by high blood sugar concentration and irregular insulin levels. It has been recognized as one of the largest global health emergencies of the 21st century. Nearly 9% of the adult population worldwide has diabetes [1, 2]. Currently, the standard for estimating a patient's average blood glucose concentration (AG) includes measuring both the blood glucose under fasting conditions together with the fraction of glycated hemoglobin (HbA_{1c}). A well-known conversion table between the HbA_{1c} fraction and the AG, the so-called ADAG formula [3], exists which is widely employed in the clinic. The use of HbA_{1c} for screening and diagnosis of diabetes displays a much smaller intra-individual biological variability with respect to that of plasma glucose and it is not influenced by sudden glycemic variations. It provides a strong correlation with AG over a preceding time frame of 2-3 months [4].

However, there exist important limitations in the use of HbA_{1c}. Besides exhibiting *in vivo* effects due to physiological conditions such as pregnancy, age and genetic determinants, it cannot capture fluctuations in the blood glucose concentration such as short hyper- and hypoglycemia episodes, which may be triggered by pathological conditions evidencing a prediabetic state of a patient.

In this contributed talk a mathematical model describing the dynamics of glucose, HbA_{1c} and another form of hemoglobin, known as HbA_{1d}, which exhibits a much faster kinetics, will be presented. Our theoretical approach describes the processes of HbA_{1c} and HbA_{1d}

formation inside red blood cells (RBCs) by means of chemical reaction kinetic differential equations and incorporates the age-structure of RBC populations. Our model is further validated with a large database of over 11000 patients and is able to capture pathological processes that cannot be detected with the current gold standard ADAG formula, widely used in the clinic [5].

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**DESIGN OF A CONTROL LAW FOR INSULIN
RESISTANT PATIENTS BY MEANS OF A SIMPLE
GLUCOSE/INSULIN SYSTEM MODEL**

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Keywords: Glucose-insulin system, Glycemia control, Insulin resistance, Mathematical models, Parameters estimation.

Control of glycemia by automatic insulin pumps for diabetic patients is a relevant issue, strongly debated in recent years.

Type-1 Diabetes Mellitus (T1DM) is a metabolic disorder consisting in a lack of production of insulin, while in Type-2 Diabetes Mellitus (T2DM) patients the hormone is produced, although this production is impaired, and a low insulin sensitivity does not allow to properly decrease plasmatic glucose levels. In both cases, a therapy consisting in an additional external administration of insulin can be performed.

In order to have accurate predictions of the insulin amount to be supplied to a T2DM patient to restore euglycemia, a good mathematical model of the glucose-insulin system is mandatory. While several such models have been published, in 2007 a relatively simple discrete-delay model (Panunzi, Palumbo - 2007, henceforth compact model) showed excellent performance in fitting Intra-Venous Glucose Tolerance Test (IVGTT) data. Subsequently a much more complicated “pulsatile” mechanistic model (Palumbo 2010, De Gaetano 2015, henceforth extended model) was shown to reproduce a wide array of diverse experiments (low and high frequency insulinemia oscillations, accentuated by constant glucose administration; entrainment of insulinemia oscillations by pulsatile glucose administration; IVGTT response in varying states of health, pre-diabetic and diabetic conditions; insulin secretion waveforms in response to shaped glycemia perturbations in vitro).

The present work shows that a basic glycemia control law can be used taking advantage of the simple and effective form of the compact model; by properly tuning the three parameters of the control law with the aim of reproducing a “normal” glycemia trend, the controller can be implemented in an external device delivering insulin, and it is shown that it performs very well both in the transitory and in the steady state conditions restoring euglycemic concentrations.

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PERTURBATION ANALYSIS OF A DELAYED MODEL OF GLUCOSE-INSULIN REGULATION

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Keywords: Diabetes, Delay differential equations, Lindstedt's method.

Homeostasis is a living organisms' ability to maintain a dynamic equilibrium in response to environmental changes. This equilibrium results from negative feedback loops that occur within the body, and can be thought of as a steady state which may be either: stable, leading to constant levels over time; or unstable, leading to sustained oscillations [3]. Examples of homeostatic processes include: the regulation of glucose levels; temperature; calcium levels; blood pH levels; and blood pressure, and a disruption to these can have devastating consequences for an individual. Diabetes mellitus, a disease which inhibits the body to maintain the glucose level within a healthy range, is a key example of a failure in the process of homeostasis. This contribution focuses on the ultradian oscillations of glucose and insulin which occur in patients without diabetes mellitus [4], but are eventually lost in patients with type 2 diabetes [2]. More specifically, we look to model the effect of diabetic parameters on the amplitude and period of the oscillations. This is done by using Lindstedt's perturbative method on a reduced one-delay model of the glucose-insulin system used in [1] to obtain approximate analytical expressions for the limit cycle. The model is then extended to include a commensurate delay. In both cases, the approximate expressions for the amplitude and period are a close match to the numerical solution, allowing us to describe quantitatively the contribution of each model parameter to the oscillations.

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**STRUCTURED MODELS AS A MATHEMATICAL TOOL
TO DESCRIBE DIABETES EVOLUTION**

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Keywords: Modeling, Diabetes.

In structured models, the aggregate of individuals of a population is characterized with respect to the value of the structure variable, which represents the quantity of interest. While important classical models of this kind were developed with respect to age and size, in the present study we propose a glycemia-structured population model, based on a linear PDE with variable coefficients and characterized by three glycemia-dependent functions: a mortality rate, a youth population profile and an average worsening rate. In addition to studying the formal properties of the solution, both in the transient and in the equilibrium conditions, we identify key parameters and functions of the model from real-life data and hypothesize some plausible modifications of the rate functions to obtain a more beneficial behavior, which can also offer some insights in view of possible public health intervention strategies. Preliminary simulations seem to offer a good approximation of observed reality and of the features expected in the clinical setting.