MP Modelling of Glucose-Insulin Interactions in the Intravenous Glucose Tolerance Test

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ABSTRACT

The Intravenous Glucose Tolerance Test is an experimental procedure used to study the glucose-insulin endocrine regulatory system. An open problem is to construct a model representing simultaneously the entire regulative mechanism. In the past three decades, several models have appeared, but they have not escaped criticisms and drawbacks. In this paper, the authors apply the Metabolic P systems theory for developing new physiologically based models of the glucose-insulin system, which can be applied to the IVGTT. Ten datasets obtained from literature were considered and an MP model was found for each, which fits the data and explains the regulations of the dynamics. Finally, each model is analysed to define a common pattern which explains, in general, the action of the glucose-insulin control system.

Keywords: Biomathematical Discrete Modelling, Diabetes, Intravenous Glucose Tolerance Test, Metabolic P Systems, Personalized Glucose-Insulin Dynamics

1. INTRODUCTION

Glucose is the primary source of energy for body cells. It is transported from the intestines or liver to body cells via the bloodstream, and is absorbed by the cells with the intervention of the hormone insulin produced by the pancreas. Blood glucose concentration is a function of the rate of glucose which enters the bloodstream, the glucose appearance, balanced by the rate of glucose which is removed from the circulation, the glucose disappearance. Normally, in mammals this concentration is tightly regulated as a part of metabolic homeostasis. Indeed, although several exogenous factors, like food intake and physical exercise, affect the blood glucose concentration level, the pancreatic endocrine hormones insulin and glucagon1 keep this level in the range 70 – 110 mg/dl. When the blood glucose concentration level is high, the pancreatic β−cells release insulin which lowers that concentration by inducing the uptake of the excess glucose by the liver and other cells and by inhibiting hepatic glucose production. On the contrary, when the glucose level is low, the pancreatic α−cells release glucagon that
results in increasing the blood glucose level by acting on liver cells and causing them to release glucose into the blood (Figure 1).

If the plasma glucose concentration level is constantly out of the usual range, then we are in presence of blood glucose problems. In particular, when this level is constantly higher than the range upper bound (which is referred to as hyperglycemia), we are in presence of Diabetes: a dreadfully severe and pervasive illness which concerns a good number of structures in the body. Diabetes is classified into two main categories known as type I and type II, respectively. Type I, 5–10% of all categories of diabetes, results from autoimmune destruction of β-cells and the pancreas is no longer capable of making insulin. Therefore, daily insulin injections are necessary. Diabetes of type II refers to the remaining 90% and occurs when the pancreas produces insulin but cells fail to use it properly. In both the types of diabetes, the illness can lead to several complications like retinopathy, nephropathy, peripheral neuropathy and blindness. This motivates researches to study the glucose-insulin endocrine regulatory system. In particular, the glucose-insulin system has been the object of repeated mathematical modelling attempts. The majority of the proposed models were devoted to the study of the glucose-insulin dynamics by considering experimental data obtained by the intravenous glucose tolerance test, shortly IVGTT, and the oral glucose tolerance test, shortly OGTT. In these models, the insulin-glucose system is assumed to be composed of two linked subsystems modelling the insulin action and the glucose kinetics, respectively. Since the action of insulin is delayed with respect to plasma glucose, the subsystems of insulin action typically includes a delay.

The intravenous glucose tolerance test focuses on the metabolism of glucose in a period of 3 hours starting from the infusion of a bolus of glucose at time t = 0. It is based on the assumption that, in a healthy person, the glucose concentration decreases exponentially with time following the loading dose (Figure 2). It has been recommended as a method to assess the use of insulin in order to identify subjects which may be diabetics (National Diabetes Data Group, 1979). However, considering the limits of the existing mathematical models, a need exists to have reliable mathematical models representing the glucose-insulin system. The mere fact that several models have been proposed (Boutayeb & Chetouani, 2006; Makroglou, Li, & Kuang, 2006; Mari, 2002) shows that mathematical and physiological considerations have to be carefully integrated when attempting to represent the glucose-insulin regulatory mechanism. In particular, in order to model the IVGTT, a reasonably simple model is required. It has to have a few parameters to be estimated and has to have dynamics consistent with physiology and experimental data. Further, the model formulation, while applicable to model the IVGTT, should be

Figure 1. The glucose homeostasis
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Evolutionary Modeling and Industrial Structure Emergence
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