

# Insulin Metabolism Models for Children with Type 1 Diabetes

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## INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease resulted from insufficient secretion of hormone insulin. DM is mainly classified into Type 1 (or insulin dependent diabetes), which is characterized by absence of insulin secretion, due to destruction of the  $\beta$ -cells of pancreas, and Type 2 (or insulin independent diabetes), which is characterized by reduced action of insulin. This dysfunction of insulin results in many short- (hypoglycaemia, hyperglycaemia) and long-term (like neuropathies, nephropathies, retinopathies, and so on) complications. The result of the Diabetes Control and Complications Trial (DCCT) (DCCT Research Group, 1993) and the U.K. Prospective Diabetes Study (UK-PDS) (UKPDS Group, 1998) indicate that the intensive glucsaemic control reduces many short- and long-term complications of DM.

The ultimate goal in management of DM is the development of an automatic “closed-loop” system, well known as “artificial pancreas,” able to simulate accurately the glucose-insulin metabolism and maintain glucose levels of a diabetes patient into physiological levels (70–110 mg/dl for a healthy person). A “closed-loop” system for DM comprises three primary components: (i) an accurate frequent or continuous glucose measurement system, (ii) an insulin delivery system, and (iii) a control system able to change the dose of

delivered insulin, with respect to the requirement of glucose levels in desired range. Currently, individuals with Type 1 Diabetes Mellitus (T1DM) measure their glucose levels using either conventional finger-stick glucose meters (three to four times per day), or continuous glucose monitoring systems (CGMS), and choose their insulin delivery method between multiple daily injection (MDI), and continuous subcutaneous insulin infusion (CSII). The most appropriate algorithms to close the loop seems to be those based on model predictive control—MPC (Bequette, 2005). In a MPC controller, a model is used for the prediction of current and future insulin delivery parameters based on estimation on future glucose concentrations, while an optimizer finds the optimum insulin delivery parameter values in order to maintain future glucose values inside the desired range.

The models for the predictions of glucose values simulate the glucose-insulin metabolic system, which is characterized by high complexity and nonlinearity. Several mathematical models (MMs) have been proposed for the simulation of glucose-insulin metabolism for T1DM patients taking into consideration previous glucose measurements, type, and dose of insulin intake, and food intake, while recently, artificial neural networks (NN) have been proposed for simulation of glucose—insulin metabolism.

The aim of this article is to describe how NN have been applied for the simulation of glucose—insulin metabolism, and to present two NN based personalized models for children with T1DM. The models, which are able to make short-term glucose predictions, are based on the combined use of MMs and NNs. The models are comparatively assessed using data about glucose levels, insulin intake, and diet during previous time periods, from four children with T1DM.

## **BACKGROUND**

Many computer-based simulations of glucose-insulin metabolism systems have been proposed in order to predict short-term glucose levels, and avoid hypoglycaemic and hyperglycaemic events. Usually, these systems, using among others glucose data from finger-stick glucose meters, are based on Compartmental Models (CMs). CMs represent a type of MMs commonly used for modeling complex dynamics systems, such as the physiological systems (Brown & Rothery, 1993; Cobelli & Foster, 1998). CMs have been used in order to estimate the way in which changes in insulin dosage affect blood glucose levels (Puckett & Lightfoot, 1995). Furthermore, a pharmacokinetic model has been developed by Berger and Rodbard (1989) for the simulation of plasma insulin and glucose dynamics after subcutaneous injection of insulin for the prediction of the expected time course of plasma glucose in response to a change in the insulin dose, timing or regime. This model has been improved by Lehmann and Deutsch (1992), by taking into consideration the absorption, in quantitative terms, of carbohydrates contained in the food. The widespread use of the resulted physiological model, known as AIDA, though being one of the most popular physiological models of glucose-insulin interaction for T1DM patients, it has been limited, due to uncertainties associated with the estimation of blood glucose profiles. These uncertainties have been addressed by Andreassen, Benn, Hovorka, Olesen, and Carson (1994) using causal probabilistic networks, for both the hourly prediction of blood glucose levels and the insulin dose adjustment. The obtained results have shown that this approach is able to identify and predict nocturnal hypoglycaemia (Cavan, Hovorka, Hejlesen, Andreassen, & Sönksen, 1996).

The acceptance of the aforementioned models was limited, because these systems take into account only a confined number of the factors associated with glucose

metabolism, and they are not easily individualized to accurately simulate metabolic processes for a specific T1DM patient. In order to overcome the aforementioned difficulties, the use of NNs for the simulation of glucose-insulin metabolism has been proposed. NNs are a powerful tool in handling complex, nonlinear problems, due to their ability to be trained in order to handle unknown information hidden in the data (Haykin, 1999). Specifically, the information about blood glucose levels, insulin intake, and observed hypoglycemia symptoms have been used as input to a system consisting of two NN models in a chained scheme (Mougiakakou & Nikita, 2000; Mougiakakou, Nikita, Protonotarios, & Matsopoulos, 1998). The output of the first NN provides estimation for the insulin regime, while the output of the second NN estimate the appropriate insulin doses. Furthermore, inputs related to the insulin type and time of injection, carbohydrate and time of meal, exercise, blood glucose measurements, and special events (stress, pregnancy, and so on) from a T1DM patient have been fed to a NN resulting in a satisfactory accuracy in the prediction of blood glucose levels (Sandham, Hamilton, Japp, & Patterson, 1998). A comparative study of different NN approaches for the prediction of short-term blood glucose levels for T1DM patients has shown that the use of NNs is promising for the simulation of glucose metabolism (Tresp, Briegel, & Moody, 1999). Moreover, a hybrid system combining the principal component method with a NN has been proposed for the prediction of blood glucose levels in diabetic patients (Liszka-Hackzell, 1999). Recently, the use of a NN trained by the Levenberg-Marquardt (LM) algorithm has been presented, in order to predict the blood glucose concentration in T1DM patients (Zitar, 2003), with promising results. Finally, a hybrid model based on the combined use of MMs and NNs has been proposed for the short-term prediction of glucose levels in T1DM patients based on measured blood glucose levels, insulin intake, and description of food intake, along with the corresponding time (Mougiakakou, Prountzou, & Nikita, 2005).

## **MODELING OF GLUCOSE: INSULIN METABOLISM FOR CHILDREN WITH TYPE 1 DIABETES MELLITUS**

In this article, two glucose-insulin metabolism models for children with T1DM are presented. The models, which are personalized and able to make short-term

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