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Structural identifiability and indistinguishability analyses of the Minimal Model and a Euglycemic Hyperinsulinemic Clamp model for glucose–insulin dynamics

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ABSTRACT

Many mathematical models have been developed to describe glucose–insulin kinetics as a means of analysing the effective control of diabetes. This paper concentrates on the structural identifiability analysis of certain well-established mathematical models that have been developed to characterise glucose–insulin kinetics under different experimental scenarios. Such analysis is a pre-requisite to experiment design and parameter estimation and is applied for the first time to these models with the specific structures considered. The analysis is applied to a basic (original) form of the Minimal Model (MM) using the Taylor Series approach and a now well-accepted extended form of the MM by application of the Taylor Series approach and a form of the Similarity Transformation approach. Due to the established inappropriate nature of the MM with regard to glucose clamping experiments an alternative model describing the glucose–insulin dynamics during a Euglycemic Hyperinsulinemic Clamp (EIC) experiment was considered. Structural identifiability analysis of the EIC model is also performed using the Taylor Series approach and shows that, with glucose infusion as input alone, the model is structurally globally identifiable. Additional analysis demonstrates that the two different model forms are structurally distinguishable for observation of both glucose and insulin.

1. Introduction

There are now more than 285 million and 344 million individuals in the world that are known to suffer from diabetes and impaired glucose tolerance (IGT), respectively, and it is estimated that these figures will rise up to 439 million for diabetes and 472 million for IGT in year 2030 [1]. The study of diabetes, IGT, glucose–insulin pathology and related subjects has therefore become increasingly important in order to try to reduce the numbers suffering from these preventable phenomena.

Diabetes is a condition caused by high levels of blood glucose due to insufficient or no insulin production in the body. Diabetes sufferers generally have reduced insulin sensitivity. It is a serious illness and has increasingly affected a larger population worldwide over more recent years due to exposure to many risk factors such as unhealthy lifestyles, excessive diet and lack of physical activity [1–4]. The disease is classified into four main categories: Type 1, Type 2, gestational diabetes mellitus and other specific types [2].

Type 1 Diabetes is caused by a disorder of the autoimmune system resulting in the damaging of pancreatic cells

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that produce insulin and results in a dramatic reduction or loss of insulin production. It often occurs in young children, but can occur at any age. Type 1 Diabetes patients rely on the administration of insulin on a daily basis for survival. Type 2 Diabetes comprises approximately 90% of diabetes cases [1,2] and is caused by insulin resistance in the body. It normally occurs later in life, and may be due to an individual's lifestyle and eating patterns, but in some cases the causes are also unknown [1,2,5,6]. Type 2 Diabetes patients are usually required to closely manage and control their diet and blood glucose, but they may not necessarily be dependent on daily insulin administration for survival [2].

The key factor that causes diabetes is insufficient or lack of insulin production affecting glycemic metabolism within the body. The disease often leads to other diseases such as renal failure, blindness, polyneuropathy, increased risk of infection, cardiovascular disease, stroke and death, even if treated [1,2,5,6]. Patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) suffer from abnormal (non-diabetic) hyperglycemia and they often develop Type 2 Diabetes later in life, however 30% of the sufferers regain normal glucose tolerance over a period of years [4]. Hence, researchers within biological, medical and pharmaceutical fields are keen to find solutions to improve and control the condition of diabetes and other glucose intolerance sufferers.

For the past 30 years, many mathematical models have been developed to describe glucose and insulin kinetics in an attempt to provide effective control of diabetes. A robust, valid and verified model offers the capability of predicting glucose and insulin pathophysiology within an individual or diabetes sufferer, subject to different treatment scenarios, thus hopefully reducing the need for and level of experimentation. It is extremely important that modellers are confident that they can identify and estimate all of the unknown parameters within such models through the system observations available for any subsequent predictions to be meaningful. Structural identifiability and indistinguishability analyses play important roles in this process prior to any form of model simulation and parameter fitting.

Structural identifiability arises from the inverse problem of inferring from the known, or assumed, properties of a system of a suitable model structure and estimates for the corresponding rate constants and other parameters. Structural identifiability analysis considers the uniqueness of the unknown model parameters from the input–output structure corresponding to proposed experiments to collect data for parameter estimation (under an assumption of the availability of perfect, noise-free data). The existence of noise-free data is assumed for *a priori* structural (non-numerical) identifiability analysis purposes. An important rationale for performing structural identifiability analysis is to confirm whether any of the unknown parameters present within the postulated model are unidentifiable from the observations available on the system. This is particularly important for those parameters that have practical significance. Under such circumstances if any parameters are unidentifiable, under perfect, noise-free conditions, then any subsequent estimation of these parameters from data with the presence of noise would prove meaningless. Structural identifiability analysis is therefore an important, but often overlooked, theoretical pre-requisite to experiment design, system identification and parameter estimation, since numerical estimates for unidentifiable parameters are effectively meaningless. If parameter estimates are to be used to inform about intervention or inhibition strategies, or other critical decisions, then it is essential that the parameters be uniquely identifiable. Modellers often tend to neglect such analysis due to the ease of use of modern computer software that allows users to estimate unknown parameters almost unconditionally [7].

The intention of this paper is to establish whether the parameters from well established models that are used for the analysis of glucose-insulin dynamics are indeed structurally identifiable or otherwise from the observations commonly available.

Structural indistinguishability for systems models is concerned with determining the uniqueness between possible candidates for the model (or mechanism) structure. The analysis is concerned with whether the underlying possibilities for the parameterised mathematical model can be distinguished using the inputs (perturbations or interventions) and observations (or measurements) available for the system under investigation [8].

The parameter insulin sensitivity is incorporated in many different models for glucose–insulin kinetics and plays a highly important role as it provides information on factors such as glucose intolerance and insulin resistance in individuals. This key parameter is also used as a measure to determine whether the sufferer shows signs of developing a glucose metabolism disorder, diabetes or other related diseases. To quantify the index of insulin sensitivity, tests, such as the Oral Glucose Tolerance Test (OGTT), the Intravenous Glucose Tolerance Test (IVGTT), the Euglycemic Hyperinsulinemic Clamp (EIC) and Hyperglycemic Clamp can be used [9,10].

Among all the models that describe glucose and insulin kinetics and dynamics, the most commonly accepted mathematical model is the so called "Minimal Model" which was originally developed by Bergman and colleagues [9]. These authors claimed that the model is numerically identifiable as the model satisfactorily fitted the data collected from a variety of experiments on animals. The model is widely used in clinical and scientific settings and is universally accepted, including FDA approval for clinical use. A structural identifiability analysis has only seemingly been carried out for a modified version of the Minimal Model, named the "new Minimal Model". This analysis used the Taylor or Power Series Expansion of the model solution where it was claimed that the model is only identifiable with added constraints or *a priori* knowledge [11–13].

In this paper, structural identifiability analyses for both the original and extended forms of the Minimal Models have been carried out, as far as the authors are aware, for the first time for the particular model structures considered. Due to well-known difficulties in simultaneously performing parameter estimation for glucose clamp data using the extended Minimal Model, due to its structure, the model developed by Umberto Picchini and group members [14] to describe the glucose and insulin dynamics when applying the Euglycemic Hyperinsulinemic Clamp was considered for such experiments/observations.