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On the use of continuous glucose monitoring systems to design optimal clinical tests for the identification of type 1 diabetes models

Federico Galvanin, Massimiliano Barolo, Fabrizio Bezzo*

CAPE-Lab – Computer-Aided Process Engineering Laboratory, Dipartimento di Ingegneria Industriale, Università di Padova, via Marzolo 9, I-35131 Padova PD, Italy

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ABSTRACT

The identification of individual parameters of detailed physiological models of type 1 diabetes can be carried out by clinical tests designed optimally through model-based design of experiments (MBDoE) techniques. So far, MBDoE for diabetes models has been considered for discrete glucose measurement systems only. However, recent advances on sensor technology allowed for the development of continuous glucose monitoring systems (CGMSs), where glucose measurements can be collected with a frequency that is practically equivalent to continuous sampling. To specifically address the features of CGMSs, in this paper the optimal clinical test design problem is formulated and solved through a continuous, rather than discrete, approach. A simulated case study is used to assess the impact of CGMSs both in the optimal clinical test design problem and in the subsequent parameter estimation for the identification of a complex physiological model of glucose homeostasis. The results suggest that, although the optimal design of a clinical test is simpler if continuous glucose measurements are made available through a CGMS, the noise level and formulation may make continuous measurements less suitable for model identification than their discrete counterparts.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a metabolic disease of the glucoregulatory system affecting millions of people worldwide and causing the expenditure of millions of euros every year for health care [1]. This disease is characterized by the absence of endogenous insulin secretion resulting in the total inability of a diabetic subject to adequately regulate the blood glucose levels (glycemia) in the body. For T1DM care, one of the most promising therapies derives from the use of an artificial pancreas, an external piece of equipment based on a continuous glucose measurement sensor, a control algorithm for the calculation of the appropriate insulin amount to be delivered, and a micropump for continuous insulin administration. The development of an artificial pancreas is firmly related to the availability of a reliable and detailed physiological model of glucose homeostasis [2]. An accurate dynamic simulation model of the glucose–insulin system can be useful to assist diabetes care and test glucose sensors as well as insulin infusion algorithms [3]. A model can be particularly important for controller design and tuning [4,5] and, if a model-based control approach is employed (e.g. model predictive control), it may become part of the control scheme

* *Corresponding author*. Tel.: +39 049 827 5468; fax: +39 049 827 5460.
E-mail address: federico.galvanin@unipd.it (F. Galvanin).
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itself [6,7]. Furthermore, the model may be used as a "virtual subject" to mimic a subject's response in the development of proposed insulin treatments or decision support systems for diabetes care. The availability of a validated, robust and detailed model tailored to an individual subject can provide substantial benefits both to the clinician, who could devise a customized diabetes care solution for the subject, and to the engineer, who could design and test specifically tailored conventional or advanced glucose control strategies.

Given the high inter- and intra-variability of the individual responses, a generic model of T1DM should be tailored to an individual subject by estimating the set of individual model parameters in a statistically sound way. Standard clinical tests [8] have been proposed and are currently used to help diagnose diabetes and to identify the parameters of simple models of glucose homeostasis, but, as long recognized [9], the optimal input excitation to identify the metabolic parameters precisely could be different from that provided during a standard test. The identification procedure can be costly and very time consuming because the system may exhibit identifiability issues [10], or there may be a mismatch between the model and the actual system to be represented such that the candidate model structure is not suitable to represent the system (i.e. the subject affected by diabetes) in an adequate way, or reliable data may be difficult and expensive to obtain. The notion of identifiability addresses the question of whether it is possible to obtain unique solutions for unknown parameters of interest in a mathematical model from data collected in well-defined stimulus-response experiments performed on a dynamic system represented by the model.

Identifiability can be seen as a structural property of the model itself and must be considered as a necessary prerequisite for a reliable parameter estimation. The property can be tested before (a priori identifiability) or after (a posteriori identifiability) an experiment is carried out and data are collected. A priori identifiability analysis can be performed, under ideal conditions of noise-free observations and error-free model structure, either on a specific region of the parameter space at assigned experimental conditions (*local* identifiability), or on the entire space of variability of model parameters for any admissible experimental condition (*global* identifiability) [11]. A priori global identifiability can be tested for linear models [10,12] and nonlinear dynamic models adopting techniques based on power series expansion, direct testing or differential algebra tools [13]. Computer algebra programs have been developed for assessing the a priori global identifiability of nonlinear dynamic models described by differential equations involving polynomial or rational functions [14]. However, the extension of these methods to complex nonlinear dynamic models of generic form remains an extremely challenging task, and the computational efficiency of the available algorithms strongly depends on the order of the nonlinear system and the number of measured states [15]. Furthermore, it should be pointed out that a priori identifiability does not necessarily imply a posteriori "practical" identifiability (i.e. identifiability from data in the presence of measurement errors and/or model uncertainty). Conversely, local a priori identifiability of large nonlinear differential systems of generic form can be assessed by sensitivity-based identifiability analyses, where the property is evaluated with respect to a specific point in the parameter space without considering the model structure [13]. In fact, as observed by Söderström and Stoica [16], the identifiability of a dynamic system is not exclusively related to the model structure, but also to the level of excitation that can be realized while performing an identification experiment. Model-based design of experiments (MBDoE) techniques can provide a valid support to model identification, detecting a suitable set of excitation patterns that ensure the practical identifiability of complex nonlinear dynamic models [17]. The effectiveness of MBDoE has been demonstrated in a wide range of applications [18]. Quite recently, Galvanin et al. [19,20] showed that MBDoE can be effectively exploited to tackle the identifiability issues of complex physiological models of T1DM, allowing the design of alternative test protocols, and thus enabling a statistically sound estimation of the parametric set of detailed models of glucose homeostasis in an individual. The optimal settings for the clinical test are identified through an optimization procedure delivering the temporal patterns and quantities of glucose and/or insulin administration, and the sampling schedules of the glucose concentration measurements. The result is a "metabolic portrait" of a subject affected by T1DM in terms of his/her model parameters.

The usual MBDoE procedure assumes discrete blood sampling and off-line analyses. However, recent advancements in sensor technology allow for the development of continuous glucose monitoring systems (CGMSs) where the glucose levels can be continuously measured over a 24-h period [21]. Although several accuracy issues must still be addressed when CGMSs are used, including the need of calibration and the lag time between blood glucose and interstitial glucose readings [22], CGMSs allow patients to view an approximation of their blood glucose levels every 5–10 min and permit a fine-tuning of a patient's glycemic control that is not possible with self-monitoring of blood glucose. Therefore, also thanks to the recent advances in continuous subcutaneous insulin infusion pumps, CGMSs do provide a precious contribution to the glycemic control via the subcutaneous route [4,23].

On such a perspective, CGMSs may open new possibilities also for the design of clinical tests aimed at identifying detailed models of T1DM. In fact, the availability of much more frequent glucose measurements is expected to enrich the information content of each single clinical test, possibly making the model parameter identification exercise easier. However, it should also be noted that CGMS readings are usually less precise and accurate than the ones realized through discrete blood sampling [24], and this may offset the benefit deriving from the increased number of measurements.

The purpose of this paper is to discuss the possibility to use a CGMS within an MBDoE approach to model parameter identification. A simulated example will be considered to assess whether a CGMS may be really useful to optimally design a clinical test for the parameter identification of a detailed model of glucose homeostasis. Parameter identification in the presence of continuous (CGMS) or discrete (blood sampling and off-line analysis) glucose measurements will be carried out, and the relative merits of the two approaches will be