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Shedding light on grey noise in diabetes modelling

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ABSTRACT

Glycaemia of outpatients with diabetes is very difficult to model due to sparse, low quality data, inter- and intra- patient variability and a myriad of other factors that have significant, but intermittent effects. For model-based control strategies, such factors can contribute non-random grey noise that can confound patient-specific models, and reduce prediction confidence. Incorporating such factors in glycaemic models would significantly improve control if the data available allows practical identifiability of these model parameters. This review compares and analyses models that capture the glycaemic grey-noise impact of nutrition, stress and illness, exercise and circadian rhythms are compared and considered in the context of practical application to model-based outpatient diabetes management.

Candidate models to capture glycaemia in outpatients with diabetes must be considered in the context of the data needed to identify the models, the ability of the model to adapt to the patient state, and the practical identifiability of the models for a particular data quality. In particular, the outpatient environment presents challenges for acquiring quality data and gold-standard methods of measurement are frequently infeasible. Only models that can be practically identified using the type and quality of data available in an outpatient setting should be considered, thus informing model development. Furthermore, the candidate models should also be capable of capturing inter- and intra- patient variability in the heterogeneous metabolism of individuals with diabetes. Finally, practically identifiable models need to also be identifiable over a clinically acceptable time period so the models are useful in context for managing diabetes.

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1. Introduction

Diabetes mellitus is a metabolic syndrome characterised by endogenous inability to control glycaemic excursions [1]. In type 2 diabetes mellitus (T2DM) there is often a substantial reduction in the efficiency of insulin to clear circulating blood glucose [1]. Injecting exogenous insulin to restore normoglycaemia after a postprandial excursion is a necessary therapy for those with type 1 diabetes (T1DM) and is often beneficial for those with T2DM [1].

However, estimating optimal insulin doses can be difficult. The traditional factors determining a postprandial dose are meal carbohydrate content and nominal insulin sensitivity (*SI*). However, a host of smaller confounding factors accompany these factors [2–10]. Uncertainty introduced by confounding factors can cause individuals to take conservative doses for fear of hypoglycaemia [1], reinforcing mild hyperglycaemia and increased incidence of diabetic complications [1,11–13].

Mathematical modelling of physiological systems is a widely used science with many applications in glycaemia [14,15]. In particular, improved outcomes in critical care have been achieved through glycaemic modelling and control [15–19]. Extensive research has also been carried out into closed-loop control for outpatients with diabetes [20–26], although these methods are not currently ready for standard care [27]. Model-based analysis can also be useful for clinical diagnostics in glucose tolerance and insulin sensitivity tests [28–34], and is also used to inform insulin doses in self-managed blood glucose therapy [35–37].

What is common is that these applications tend to involve identification of patient-specific physiological parameters from available data, either for a population or specific to the patient at that time. For control applications, these parameters are used in conjunction with measured data and existing algorithms to determine an appropriate insulin dose to restore glycaemic excursions to pre-defined targets. Thus, unmodelled, non-random factors that affect this identification impact control safety and quality, and thus compliance.

Comparatively simple models that contain few variables have proven to be effective for glycaemic prediction and control in critical care [38,39], primarily because they can be robustly identified [40,41]. However, in outpatient diabetes there are significantly more environmental stimuli present. These stimuli have the potential to contribute confounding behaviours and variability to the glycaemic signal that are not measured or included in the model.

For example, psychological factors, such as stress and depression, have been shown to influence glycaemic outcomes, tending patients toward hyperglycaemia [1,3,42,43], and exercise is a major source of glycaemic disturbance and can potentially cause hypoglycaemia [23,44,45]. When factors such as exercise and stress are not modelled, they contribute to non-random 'grey noise' in the data and confound attempts to capture the patient's true glycaemic metabolism. Hence, capturing grey noise would ultimately lead to more precise prediction in glycaemic levels and thus, improved glycaemic control.

To fully and effectively model the glycaemic excursions of diabetes outpatients, the models employed should attempt to minimise (by design) the grey noise by including additional behaviours in conjunction with patient-specific parameters. However increasing the size and complexity of the models also increases risk of model structural [46–50] and practical [40,41,51,52] non-identifiability. Parameters must be 'identifiable' for sensible estimation.

Structural identifiability analyses are concerned with distinct model input-output roles and assume perfect, continuous data [46–50]. For a model to be considered structurally identifiable, no two parameters, or combination of parameters, can be allowed to describe the same specific behaviour. Structurally non-identifiable models lead to non-unique solutions and typically poor prediction of physiological response to therapy, increasing risk for therapy application.

Similarly, practical identifiability is a growing field of analysis that considers the model and its dynamics with respect to the quality of the data available [40,41,51,52]. Given measurement error and limited data quantity, two parameters capturing similar, but structurally distinct, behaviours can appear to describe the same behaviour. Parameter trade-off then results in poor parameter estimates, despite strong adherence of the overall identified model to the measured data, leading to poor prediction and thus poor or unsafe decision support. For this reason, practical non-identifiability can be much more difficult to recognise and diagnose than structural non-identifiability. Thus, when the goal of model-based analysis is to capture a critical subject-specific state for control, it is important that only practically identifiable models are used.

Glucose-insulin dynamic models are the pivotal element of any glycaemic control algorithm and have already been extensively reviewed in the field [14,53–55]. Hence, these models are not reviewed specifically here and are not the focus of the present work. Rather, this review seeks to draw attention to important grey-noise effects in diabetes that can significantly affect management and interpretation of data, and to provide a qualitative assessment and comparison of the representative modelling efforts to date and their applicability to the outpatient environment. The