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## A model describing the multiphasic dynamics of mixed meal glucose responses in healthy subjects

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**Abstract.** Modelling of the glucose metabolism for the purpose of improving the diagnosis and therapy of diabetes mellitus has been the subject of research for decades. Despite this effort, conventional models describing postprandial glucose profiles of healthy subjects fail to include the phenomenon of biphasic glucose responses. Continuous glucose monitoring data recorded from five healthy subjects show that mono- and biphasic glucose responses from regular meals are equally common. We therefore developed a suitable parametric model, capable of producing mono- as well as biphasic meal responses. It is expressed by linear second order differential equation with a dual Gaussian input function. Additionally, a simple method for classifying meal responses into mono- or biphasic profiles was developed. Model inversion was performed using a fully Bayesian method.  $R^2$  values of model output compared to CGM data was  $91.6 \pm 8.3$  %, indicating the models ability of accurately describing a wide range of mixed meal glucose responses. Parameters were found to be associated with characteristics of individual meals. We suggest that the model could be used to objectively assess postprandial hyperglycemia, one of the main measures for glycemic control.

**Keywords:** healthy subjects, input function, postprandial glucose dynamics, system identification.

### 1 Introduction

Diabetes mellitus is one of the most common metabolic disorders and manifests itself by a failure of the body to regulate the concentration of glucose in the blood in a healthy range. In this context, various diagnostic and therapeutic methods rely on knowledge of the underlying mechanisms of glucose regulation. For that reason, mathematical modelling of the glucose metabolism in the healthy as well as the diabetic state has gained much attention in research over the past decades. Hereby, one of the main focus points has been the metabolism in a postprandial state, modelled with the help of corresponding profiles glucose and other substances, e.g. insulin. The level of biomedical detail incorporated into those models is thereby strongly dependent on the experimental data available for model identification [1].

By analyzing postprandial glucose profiles from healthy subjects consuming mixed meals, i.e. meals containing carbohydrates as well as fat and protein, the occurrence of two distinct peaks rather than only one single peak in the profiles has been reported [2]. A similar effect has also been described with a pure glucose meal during an oral glucose tolerance test (OGTT) [3]. At present day, the occurrence of biphasic glucose responses has not been incorporated into models describing the postprandial glucose metabolism from mixed meals. Conventional models are only capable of producing monophasic (single peak) responses, including the well-established and highly influential simulation model by *Dalla-Man et al.* [4]. In those models it is common to use various types of input functions to model the impact of food on the glucose concentration. These input functions can be an impulse (e.g. [5]), of trapezoidal/triangular shape [6] or be described by the general functional form  $f(t) = t \exp(-t)$  or  $f(t) = t \exp(-t^2)$  [7, 8].

In this paper we present a model capable of describing monophasic as well as biphasic responses from mixed meals by introducing a type of input function, often used in the modelling of hormone secretion patterns [9]. The model was designed to be identified using only data from continuous, subcutaneous glucose monitoring (CGM). We demonstrate that the model possess enough flexibility to describe responses of greatly varying shape from different meals and that parameters of the model are related to the characteristics of the meal. Secondly we introduce a simple method for classifying meal responses as mono – or biphasic, based on similar process developed for sparsely sampled glucose data during an OGTT [3].

In doing so, we want to establish a method for objectively characterizing the postprandial glucose exposure under realistic conditions. Such a tool could be used to improve the assessment of the overall state of glycemic control in individuals affected by diabetes mellitus.

## 2 Methods

### 2.1 Data Collection

CGM data was collected from five healthy male subjects (Age: 26-47, BMI: 25.2-30.2 kg/m<sup>2</sup>) undergoing inpatient monitoring at the Human Metabolism Research Unit at the University Hospitals Coventry and Warwickshire, UK. For that, the Freestyle Navigator 2 CGM system (Abbot Diabetes Care Inc., 1360 South Loop Road, Alameda CA, USA) providing a 10-min sampling period was utilized. After a sufficient sensor “warm up” period, 18 hours of consecutive glucose data, collected between 09:00 and 03:00 the following day was recorded. During this time, subjects consumed a total of four meals and performed two 30 min periods of light stepping exercise at 12:30 and 16:30. The meals consisted of standard western menu items and were identical for all subjects, with only the amounts adapted to ensure an isocaloric diet. In detail, the share of calories from carbohydrates and the overall share of the total daily calorie intake in percent for each meal were as follows: breakfast (52 / 25), lunch (44 / 34), dinner (47 / 26) and snack (74 / 15).

Prior to the study, appropriate ethical approval including the compliance with the Ethical Principles for Medical Research on Human Subjects set by Declaration of Helsinki was granted (REC Reference: 13/WM/0327).

## 2.2 Model Formulation

The basis for the model formulation is formed by the fact that the metabolism of a healthy person attempts to maintain glucose homeostasis, meaning that an inflow of glucose to the blood from a meal and the subsequent rise in concentration is rapidly compensated by the endocrine system. The model itself was adapted from previous publications [10, 11] and consists of a linear second-order differential equation with a novel, nonlinear input function:

$$\ddot{x}(t) + \theta_1 \dot{x}(t) + \theta_2 x(t) = f(t, \theta) \quad (1)$$

$$x(0) = x_{01} \quad \dot{x}(0) = x_{02} \quad (2)$$

$$y(t) = x(t) + \varepsilon \quad \varepsilon \sim N(0, \lambda^2) \quad (3)$$

$$f(t, \theta) = \frac{\theta_4}{\sqrt{10\pi}} \exp\left(-\frac{(t-\theta_3)^2}{10}\right) + \frac{\theta_6}{\sqrt{100\pi}} \exp\left(-\frac{(t-\theta_5)^2}{100}\right). \quad (4)$$

The new external input function  $f(t, \theta)$  acts on the system describing the glucose concentration  $x(t)$ . In (3), the process of observing the CGM data  $y(t)$  is described as having a Gaussian distributed measurement error  $\varepsilon$  with zero mean and standard deviation  $\lambda$ . In (1) the linear system behavior is governed by the evolution parameters  $\theta_1$  and  $\theta_2$  with the initial conditions  $x_{01}$  and  $x_{02}$  being described in (2).

The input  $f(t, \theta)$  is defined through the summation of two Gaussian distributions and introduces additional evolution parameters  $\theta_3$  to  $\theta_6$ . By adapting these parameters, it is possible to induce both mono- and biphasic glucose responses from the model. It was designed to represent the biphasic process of glucose absorption. The first component of (4) models an initial inflow of glucose from carbohydrates, whereas the second component describes mixed and delayed effects of carbohydrates, fat and protein in the food. The widths of the two components (corresponding to the standard deviation of a Gaussian) were chosen to produce sharp or flat responses, associated with carbohydrates or fat/protein, respectively [12]. This gives the model the ability to produce a wide variety of responses to different meals as can be seen in Fig. 1.

## 2.3 Parameter Estimation

Equations (1)-(4) specify a total of nine parameters that have to be estimated from the CGM data only. The two initial conditions in expression (2) were fixed, because the dynamics of the model are mainly driven by the input function and therefore have little effect on the model output. This leaves a total of seven unknown parameters, i.e. the evolution parameters  $\theta_1$  to  $\theta_6$  and the measurement error  $\lambda$ , to be identified during model inversion. For that, a variational Bayesian numerical method was employed. It is a fully

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Bayesian method, allowing the identification of nonlinear models formulated with ordinary as well as stochastic differential equations [13]. By using Bayesian approach, all unknown parameters are characterized by probability distributions rather than fixed values. Furthermore, any existing information about the parameters can be included into prior distributions. The particular inference method has been proven to be useful and robust by past research [10, 14].

Based on findings from a previous study [12] and the experimental schedule, the sections of CGM data under meal influence were extracted for each of the 20 recorded meals (see dashed vertical lines in Fig. 1). From that, the value of  $x_{01}$  was set to the first CGM value of the respective meal and  $x_{02}$  to the difference of the second and first measurement point. Additionally the offset of the CGM data was corrected by subtracting a basal glucose concentration value estimated as average between the first and last measurement point of each meal. This is justified by the fact that baseline levels on the timescale of one peak can be considered constant. After that, all seven model parameters were estimated for each individual meal.

All prior distributions utilized existing information to a varying extent. The prior for the measurement error  $\lambda$  was set to in accordance with the experimentally derived value of  $0.9 \pm 0.8$  mmol/L for the used CGM device [15]. The priors for the normally distributed evolution parameters ( $\theta_1$  to  $\theta_6$ ) were chosen to reflect physiologically sensible ranges or based on previous findings with a similar model structure [10].

All derivations were done in MATLAB 2015b (The MathWorks, Inc., 1 Apple Hill Drive, Natick MA, USA). An implementation of the inference method is published as an open-source library of MATLAB functions [16].

## 2.4 Classification of Meal Responses

The meal responses were classified according to the number of significant peaks within the response into the categories “monophasic” for one and “biphasic” for two peaks. Based on the previously mentioned publication by *Tschritter et al.* [3], the following criteria for detecting peaks were developed: a continuous rise in BG level by at least 0.5 mmol/L or duration of 30 min and a subsequent continuous drop in BG level by at least 0.5 mmol/L or duration of 30 min. An automated algorithm applying these criteria to the meal responses was implemented.

## 3 Results

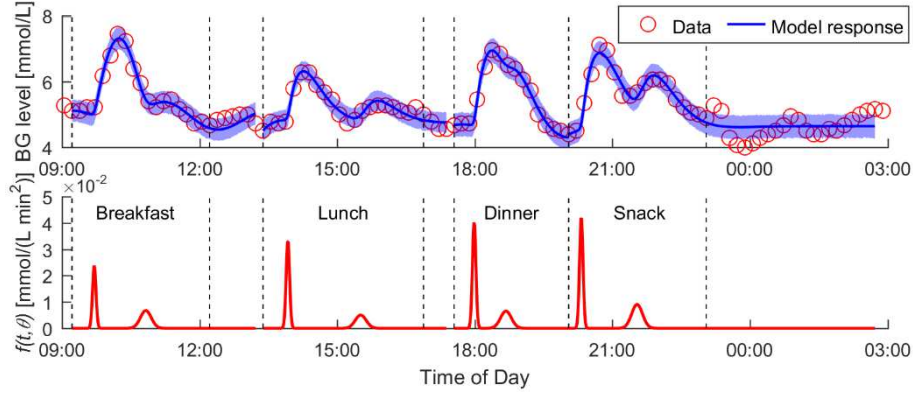
The quality of the model fit was evaluated using the coefficient of determination ( $R^2$ ). The overall mean and standard deviation for  $R^2$  are 91.6 and 8.3 %, respectively. An example of model output is given in Fig.1. The classification of the meal responses yielded an exact 50 % split between monophasic and biphasic.

In order to increase the understanding in the inferred evolution parameters  $\theta_1$  to  $\theta_6$ , they were transformed into the following, more meaningful quantities:

$$\tau = \frac{2\pi}{\sqrt{\theta_2}} \quad \zeta = \frac{\theta_1}{2\sqrt{\theta_2}} \quad \Delta_T = \theta_5 - \theta_3 \quad \Phi_F = \frac{\theta_4}{\theta_6} \quad (5)$$

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In (5),  $\tau$  is the period of natural oscillation of the system in minutes and  $\zeta$  the damping factor (dimensionless).  $\Delta T$  describes the time difference between the two peaks of the input function in minutes and  $\Phi_F$  the ratio between the intensities associated with the peaks (dimensionless).



**Fig. 1.** Top: example of model outputs with uncertainty. Bottom: plots of the respective input functions  $f(t, \theta)$ . The dashed vertical lines mark beginning and end of every meal period. Here breakfast and dinner were classified as monophasic responses, whereas lunch and the snack were classified as biphasic.

Median values and interquartile ranges of all parameters grouped by meals are displayed in Table 1. The mean and standard deviation of  $\lambda$  over all responses are 0.32 and 0.04 mmol/L, respectively.

**Table 1.** Parameters grouped according to meals. Values are given as median [IQR].

Meal	$\tau$ [min]	$\zeta$	$\Delta T$ [min]	$\Phi_F$	$\lambda$ [mmol/L]
Breakfast	136	0.61	67.6	1.55	0.37
	[116-146]	[0.37-0.67]	[62.4-81.2]	[1.02-1.80]	[0.30-0.39]
Lunch	193	1.09	94.2	2.11	0.29
	[124-205]	[0.81-1.93]	[86.9-97.2]	[1.44-2.36]	[0.28-0.34]
Dinner	126	0.46	50	1.3	0.32
	[94-135]	[0.41-0.55]	[39.7-2.9]	[1.11-2.38]	[0.32-0.33]
Snack	138	0.79	72.2	1.47	0.32
	[121-179]	[0.36-1.15]	[66.2-78.3]	[1.33-1.56]	[0.31-0.34]

## 4 Discussion

Our experiments confirm previous findings, regarding the biphasic nature of mixed meal glucose responses [2]. The classification results show that biphasic responses are as common as monophasic responses, justifying the premise of this work and the need to include this phenomenon in realistic models. Apart from that, the main contribution of this work is the addition of an input function to an otherwise established model,

allowing the description of a wide range of mono- and biphasic glucose responses. The functional form of two overlapping Gaussians is novel in the context of describing glucose dynamics and enables a high degree of flexibility by allowing the adjustment of the intensity and the timing of the peaks.

In Fig. 1 the capability of the model to accurately describe different degrees of biphasic and monophasic responses is exemplified. The results from the analysis of  $R^2$  values confirm this impression and show the model's ability to fit the data well.

Due to the small number of responses recorded per meal, the use of statistical testing in the analysis of parameters was intentionally forgone. Nevertheless, it is possible to infer information about the explanatory power of the model upon inspection of the parameters (Table 1). In comparison with other meals, the parameters  $\tau$  and  $\Delta T$  are increased during lunch. This implies that the high overall calorie (34 % of total daily carbohydrate intake) and especially fat/protein content (56% of calories) could cause prolonged hyperglycemia. The same argument can be made for the damping parameter  $\zeta$ , also being increased during lunch, compared to other meals. This suggests that these parameters are related to the food characteristics. On the other hand, the results of parameter  $\Phi_F$  do not clearly support the physiological interpretation of the input function as being related to the carbohydrate and fat/protein content of the food. Here, no similarities between ratios of macronutrients in the food and  $\Phi_F$  were found.

In terms of the measurement error  $\lambda$ , the inferred values ( $0.32 \pm 0.04$  mmol/L) lie well within the uncertainty limits reported in literature ( $0.9 \pm 0.8$  mmol/L) [15]. Additionally, the small standard deviation of  $\lambda$  is a sign of consistent model fitting.

In terms of experimental design, the time difference between meals as well as the time difference between exercise and meal was short. This could have been a limiting factor in the modelling process due to overlapping effects of meals or meals and physical exertion. Additionally, the homogeneity and limited size of the study population hindered the explanatory power of results as well as the ability to relate the model parameters to physiological characteristics.

Based on previous findings in our group [10], this work can be considered as a further step towards our goal of improving the evaluation of glycemic control in people affected by diabetes mellitus. In particular, the model could be used to objectively assess postprandial hyperglycemia, one of the main measures for glycemic control [17]. Future experiments will focus on isolating the effects of different macronutrients and include subjects with different stages of impaired glucose tolerance and DM type 2.

### Conflict of interest

The authors declare that they have no conflict of interest.

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