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Multi-Step Approach for Sensitivity Analysis for a Unified Model of Glucose-Insulin Metabolism ⋆

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Abstract: Mathematical models of biomedical systems often have a high number of uncertain parameters that are difficult or even impossible to estimate precisely. In order to be able to adequately describe the system, it must be known how large the influence of which factors is on the model behavior and how uncertainties in the parameters affect the model accuracy. Sensitivity analysis (SA) offers a possibility to examine to what extent the variance of the model output can be described by the variability of the input factors. In this paper, a multi-step SA is fulfilled for a unified model of glucose-insulin metabolism that consists of an Elementary Effects Test for screening purposes, a functional principal component analysis for dimensionality reduction of the model output variance and a variance-based approach to determine the sensitivity indices. The concept is tested on several scenarios for type 1 and type 2 diabetic patients, as well as non-diabetics. Results show that parameters are of different importance, depending on the type and scenario studied, which should be considered in a further system analysis.

Keywords: Diabetes mellitus, sensitivity analysis, functional principal components, EET, VBSA

1. INTRODUCTION

Diabetes mellitus is a chronic disorder in which the body is no longer able to maintain glucose-insulin homeostasis on its own. People who have been diagnosed diabetes need lifelong therapy, along with permanent measurement of blood glucose concentration and insulin administration. Modeling and simulation of metabolic processes can help understanding the underlying mechanisms of this disorder and is a key step towards system analysis, model driven controller design, individual parameter identification or state estimation processes (Eberle and Ament (2012); Russell (2008); Tolks and Ament (2017)). A methodological review about models, signals, and control within the area of diabetes is given by Cobelli et al. (2009).

Parameters identified from experimental data in real-life are often subject to a high degree of uncertainty. In order to be able to deal with these uncertainties, sensitivity analysis (SA) techniques can be used to quantify the influence of parameters on model quality.

SA is widely used in systems biology (Sumner et al. (2012)) or environmental modeling (Pianosi et al. (2016)) and one key area is to identify those input factors that contribute most to the variation in the model output. A systematic review on SA techniques is given in Pianosi et al. (2016).

When the model output is scalar, e.g. an aggregated statistical information or the sum of squared errors, a set of quantitative sensitivity indices describe the variance in that variable induced by variation of the input factors. However, in biomedical systems often the dynamic behavior over time is of interest. Thus, the model outputs are functions of time and consequently the sensitivity indices are also time-dependent. This gives information on how influential parameters are at certain time-points (Marino et al. (2008)).
As an alternative scalar features can be derived from the model output and the indices can be calculated thereof. First proposed by Campbell et al. (2006) and applied on biological systems by Sumner et al. (2012) functional principal components seems to be an expedient method to convert vectorial model outputs into an alternative format. It aims to transforming functional data in a set of basis functions that represents the most important features of the model output. Afterwards, a standard SA method can be applied to the coefficients of the principal components to determine most relevant input factors.

In addition to questions such as local or global SA or qualitative and quantitative SA, computational considerations also play a role. Particularly in biological systems, many parameters are often involved that require efficient algorithms or methods. To reduce computational cost a multi-step SA is suggested here. It consists of a screening technique for all parameters of the model. The indices are then determined using the Elementary Effects Test (EET) that results in a qualitative ranking of the factors. From that, a reduced set with only the most influential parameters is build. Finally, a variance-based sensitivity analysis (VBSA) is applied for this set to obtain quantitative information about the sensitivity indices. These are the first-order and total-order effects, which describe influence of a single parameter on the variance of the model output and interactions between input factors, respectively.

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2. MODEL OF THE GLUCOSE-INSULIN METABOLISM

The model of glucose-insulin-glucagon regulation incorporated here is a unified system that enables simulating non-diabetics, type 2, and type 1 patients and is presented in (Tolks et al., 2019, accepted).
The unified model implements components of two widely used diabetes models: the UVA/Padova type 1 diabetes mellitus simulator (T1DMS) by Dalla Man et al. (2014) to simulate patients with type 1 diabetes (T1DM). And second, the meal simulation model presented in Dalla Man et al. (2007a,b). While the first model is widely used for in-silico trials and testing of closed-loop algorithms (artificial pancreas), was the second one added into the unified model in order to simulate non-diabetic people (TNDM) and patients having diagnosed type 2 diabetes (T2DM). Differences in the models result on one side in the possibility of subcutaneous administration of insulin and glucagon and on the other side in the modeling of pancreatic secretion and distribution of insulin in the body.
A combination of the previously separated models allows a comprehensive view on the dynamic behavior of glucose-insulin metabolism with a common set of differential equations which enables comparisons over several populations. The model is written in nonlinear state space form with 20 states and 40 independent variables that determine the metabolic behavior. A set of parameters characterizes an individual and his current health status, and different manifestations of the disorder can be described by altered parameter vectors. The variations are determined by the covariance of the parameters among each other and their distribution, that is log-normal for most.
The model has three outputs: plasma glucose levels, concentration of glucose in the subcutaneous space (CGM), and plasma insulin concentration. Here, the CGM signal is used as the output on which the input factors are tested. Since insulin measures can only be carried out under lab conditions and blood glucose records are only available a few times a day, continuous glucose measurements are best suited in real situations. Note that no sensor errors were assumed here.
Simulations are possible for TNDM, T2DM, and T1DM subjects. Differences in the model output for the three groups result only from different values of the respective parameters. Therefore, the unified model is appropriate for parameter studies.

New developments of the T1DMS by Visentin et al. (2018) introduce time-variant parameters and extended insulin dosage forms. But they are not considered here.

3. METHODS

3.1 Concept and workflow

Since the model has many influential factors and quantitative techniques for sensitivity analysis are computationally expensive, the method presented here is a multi-step SA using a screening technique, a parameter reduction and a subsequent quantitative SA, Fig. 1.
First, a screening over the whole parameter vector is carried out by applying the Elementary Effects Test. Model evaluation results in a time-dependent output signal for each sample. Next, functional principal component analysis (FPCA) is used to explain the variance in the model output with a minimal set of orthonormal basis functions. For each of the principal components (PCs) the Elementary Effects (EE) can then be calculated.

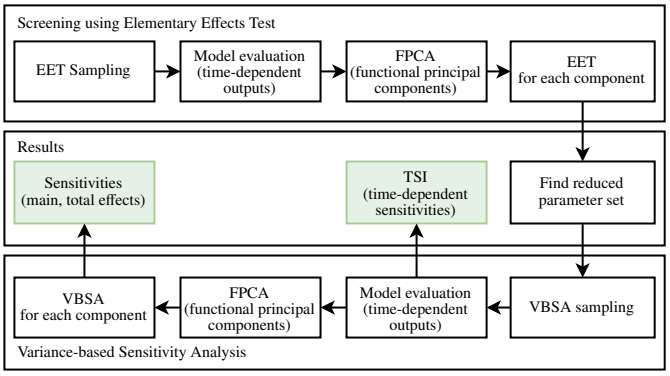

Fig. 1. Proposed workflow: First, a screening is fulfilled using the Elementary Effects Test (EET) and the most relevant parameters are selected. Second, variance-based sensitivity analysis (VBSA) follows. The model outputs are time-dependent and thus time-dependent sensitivities (TSI) can be calculated. Moreover, functional principal component analysis (FPCA) is used as an input for the SA techniques.

From that, only factors with a high EE are chosen. That means for the following steps only a reduced parameter set is used.
Second, the main sensitivity analysis is fulfilled using a variance-based technique. Again, the model must be evaluated for all samples. Sensitivity indices can be calculated for each time step of the time-variant output and gives insights into the dynamics of the indices during the entire time course.
As mentioned before, the model output variance can be described by a set of basis functions. And finally, first-order and total-order effects can be computed for each PC. The entire procedure is carried out for the three diabetes groups, and also for various scenarios, see comparison in Section 4. Furthermore, a log-normal distribution for all parameters is assumed for all sampling procedures, also taking into account their covariance. Means are set to the average patient in each group and the standard deviation to ±25 % of the corresponding nominal value.

For screening, four scenarios were selected to reflect specific aspects of daily life. Likewise, they excite various parts of the model so parameters are revealed that are more or less active during the several situations. A meal ingestion scenario with 60 g of carbohydrate intake and a steady-state simulation was performed. The first one is assumed to show parameters mainly connected to the digestive tract and the glucose homeostasis processes. The latter to reveal factors for maintaining basal state. The third scenario includes an insulin bolus given in addition to the meal in T2DM and T1DM. In the last scenario, only an insulin bolus is administered, allowing parameters that are only related to insulin processing to be determined separately.
For VBSA, only two scenarios have been chosen which reflect the most common daily life situations. This is the meal ingestion case for TNDM, and the same scenario including an additional insulin bolus at meal time for T2DM and T1DM.

In general, the model formulation is given by

$$y(t) = f(t, u, \boldsymbol{X}) \tag{1}$$

with $y(t)$ the time-varying output, u the input signal, and $\boldsymbol{X}$ a vector of M input factors also referred to as parameters of the model. The factors are assumed to be independent of each other and its uncertainty is given by a probability function.
Depending on the SA method used, N parameter sets are sampled and the model is evaluated for each sample.

3.2 Factor screening and ranking

A well established method for screening and factor ranking is the method of Morris or Elementary Effects Test (EET). It is a multiple start approach in which the output perturbation is determined by multiple points within the input space that are deflected by a finite difference (Pianosi et al. (2016)). For the i-th input factor the sensitivity index S_i is calculated as

$$S_i = \frac{1}{r}\sum_{j=1}^{r} EE^j \tag{2}$$
$$= \frac{1}{r}\sum_{j=1}^{r} \frac{f\left(\bar{x}_1^j, \ldots, \bar{x}_i^j + \Delta_i^j, \ldots, \bar{x}_M^j\right) - f\left(\bar{x}_1^j, \ldots, \bar{x}_i^j, \ldots, \bar{x}_M^j\right)}{\Delta_i^j} c_i$$

where r is the number of finite differences, Δ_i^j is the perturbation of the i-th parameter, and c_i a scaling factor to deal with different units of measurements. To compute the EE, the SAFE toolbox developed by Pianosi et al. (2015) is used.
The computational cost to derive both sets of indices is $r(M+1)$, with $M = 37$ parameters and $r = 100$ finite differences which is much lower than variance-based methods.

3.3 Transforming the functional model output

As the model output is a time series one searches for an expansion of the functional output in an appropriate coordinate system, i.e., in terms of an appropriate set of basis functions, followed by a SA of the coefficients of the expansion (Campbell et al. (2006)). The variance V of the output can be described by a set of K basis functions $\boldsymbol{\phi}(t)$ and coefficients $\boldsymbol{C}$ as

$$\mathrm{V}(t) = \boldsymbol{C}\boldsymbol{\phi}^T(t), \quad \boldsymbol{y} \in \mathbb{R}^{N,T}, \boldsymbol{C} \in \mathbb{R}^{N,K}, \boldsymbol{\phi} \in \mathbb{R}^{T,K}, \tag{3}$$

with N denoting the number of samples and T denoting the number of time points. Output $y_j(t)$ can be rewritten from (3) as

$$y_j(t) \approx \bar{y}(t) + \sum_{k=1}^{K} c_{jk}\phi_k(t), \quad j = 1 \ldots N, \tag{4}$$

where $\bar{y}(t)$ is the mean function over all realizations $y_j(t)$. The j-th output is therefore an approximation of the mean function and the variance explained by a set of K basis functions.
Further details about theory and how to derive coefficients and PCs can be found in Müller (2005); Yao et al. (2005). Algorithms are implemented in the PACE toolbox (Fan (2015)).

3.4 Quantitative sensitivity analysis

Variance-based sensitivity analysis (VBSA) belongs to a class of global sensitivity analysis techniques and has been broadly described, e.g. in Saltelli et al. (2010); Marino et al. (2008). The first-order indices S_i are a quantity for the direct contribution of an input factor to the variance of the output:

$$S_i = \frac{\mathrm{V}_{\boldsymbol{X}_i}\left[\mathrm{E}_{\boldsymbol{X}_{\sim i}}(\boldsymbol{Y} \mid \boldsymbol{X}_i)\right]}{\mathrm{V}(\boldsymbol{Y})}. \tag{5}$$

S_{T_i} are the total-order indices and measure the first and higher order contributions of factor $\boldsymbol{X_i}$:

$$S_{T_i} = \frac{\mathrm{E}_{\boldsymbol{X}_{\sim i}}\left[\mathrm{V}_{\boldsymbol{X}_i}(\boldsymbol{Y} \mid \boldsymbol{X}_{\sim i})\right]}{\mathrm{V}(\boldsymbol{Y})} = 1 - \frac{\mathrm{V}_{\boldsymbol{X}_{\sim i}}\left[\mathrm{E}_{\boldsymbol{X}_i}(\boldsymbol{Y} \mid \boldsymbol{X}_{\sim i})\right]}{\mathrm{V}(\boldsymbol{Y})}. \tag{6}$$

$\mathrm{V}_{\boldsymbol{X}_i}\left[\mathrm{E}_{\boldsymbol{X}_{\sim i}}(\boldsymbol{Y} \mid \boldsymbol{X}_i)\right]$ is the expected reduction in variance that would be obtained if $\boldsymbol{X}_i$ could be fixed and $\mathrm{E}_{\boldsymbol{X}_{\sim i}}\left[\mathrm{V}_{\boldsymbol{X}_i}(\boldsymbol{Y} \mid \boldsymbol{X}_{\sim i})\right]$ is the expected variance that would be left if all factors but $\boldsymbol{X_i}$ could be fixed (Saltelli et al. (2010)).

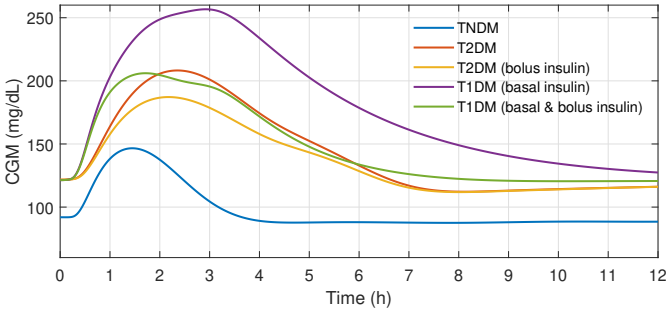

Fig. 2. Mean functions of the model output taken from EET for three diabetes types and different scenarios ($N = 4100$ samples each): In all cases a 60 g carbohydrates meal was given at $t = 0$. TNDM got only the meal, diabetics received the meal with and without insulin bolus at meal time (7 U), whereas T1DM additionally got an optimal basal insulin.

The computational cost to derive both sets of indices is $N(M+2)$, with $M = 15$ denoting the number of parameters and $N = 20000$ is the number of samples which leads to 340000 simulations in total. To compute the VBSA indices, the SAFE toolbox presented by Pianosi et al. (2015) is used.

Time-varying sensitivity indices $S_i(t)$ and $S_{T_i}(t)$ show how the significance of a parameter changes over a time interval and thus provide insights into the dynamics of a system when parts of a system are more or less active than others. The indices can be calculated at specific time points that are known to be important or over the entire time course using the scheme described in Section 3.4. This method is also outlined in Marino et al. (2008). Results can be found in Fig. 4.

4. RESULTS

Figure 2 shows the averaging functions of the model output for the different diabetes groups and scenarios. The simulation data was derived from EET sampling. In each scenario a meal of 60 g carbohydrates was given at the beginning of the simulation and subcutaneous glucose concentrations (model output CGM) rises in all subjects. Basal glucose level in T2DM and T1DM are assumed to be in the normal-glycemic range, but higher then in normal subjects. For TNDM glucose level declines quickly into steady-state after 4 h. T1DM was simulated given an optimal basal insulin to remain in steady-state ($\approx$20 mU/ min). Additionally, in one scenario (green solid line) an insulin bolus at meal time was administered. The optimal basal and bolus calculation is described in Dalla Man et al. (2014). Simulation results show that without bolus insulin glucose concentration remains in the hyperglycemic range for a long time until steady-state is reached at the end of the simulation (purple line). Better results are achieved with the optimal insulin bolus. T2DM was simulated with (yellow line) and without (red line) insulin bolus, too, and has a similar behavior as T1DM. In all scenarios considered, the disturbance caused by the meal is compensated by the effect of insulin secretion or externally administered bolus. It can be seen that there exists a dynamic behavior with different time scales due to meal ingestion and a steady-state part at the end of the observation period.

Since the model output is time-variant functional principal component analysis (FPCA) was performed to approximate the output variance by a small set of FPCs as described in Eq. (3). It turned out that in all examined scenarios only three FPCs

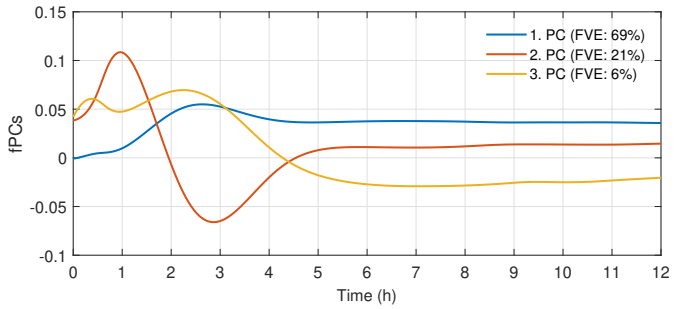

Fig. 3. Time course of the functional principal components (FPCs) for TNDM and the meal ingestion scenario computed after EET sampling. Only 3 FPCs explain 96 % of the variability in the output (fraction of variance explained, FVE). The first PC explains a slow transition into steady-state, whereas the second and third FPCs account for the fast dynamics in the system.

were required to explain more than 90 % of variability. Their time course is exemplarily plotted in Fig. 3 for the non-diabetic case and a meal ingestion scenario. As shown in the graph the first FPC explains 69 % of variability, whereas the second and third FPCs account for 21 % and 6 %, respectively. Looking at the time course, it is noticeable that the first FPC has a slower dynamic towards a stationary end value.

Now, for each type and scenario there exists a set of functional principal components $\boldsymbol{\phi}(t)$ and scores $\boldsymbol{C}$ from which the EEs can be calculated. They are reported in the left column of Fig. 5 (results for TNDM and the 15 most influential factors only) and on the left side in Table 1. The indices must be separately interpreted for each FPC. Looking at the mean values of the first FPC in Fig. 3 factor G^b is most important compared to all others. This makes sense regarding the time course of the first FPC and, since G^b is the stationary value of the CGM output, an alteration directly induces variance. Effects for the second component are high for the meal related parameter b and also for factors of glucose transport k_1, k_2 and insulin kinetic m_6 which is in accordance to the dynamic time course of the second FPC in Fig. 3. The third component only accounts for 6 % variability and incorporates all less sensitive values.
The computational cost was 17 min for model evaluations and additional 139 min for the FPCA, for each of the 10 cycles.

After screening of the full parameter set for all scenarios the most influential factors were chosen for variance-based sensitivity analysis. For this, every group was considered independently but all scenarios and FPCs were regarded together in each group. Then, the 15 unique parameters with the highest mean value given by the EET were selected. They are shown in Figure 5 and in Table 1. It is noticeable that certain parameters are important in all types and scenarios such as basal glucose level G^b, glucose distribution volume V_G, or glucose rates k_1 and k_2. Likewise, factors for meal intake (b, k_{max}, k_{min}) or V_{mx}, which is part of the insulin-dependent glucose utilization, must be taken into account. For T1DM time constants to model subcutaneous insulin kinetics k_d, k_{a1}, and k_{a2} are also important. Some parameters like k_g, the time-lag between plasma and subcutaneous glucose concentration do not have much influence on the variance of the output. Nevertheless, it should be considered in parameter identification or control design as it is an important link between the two glucose measures.

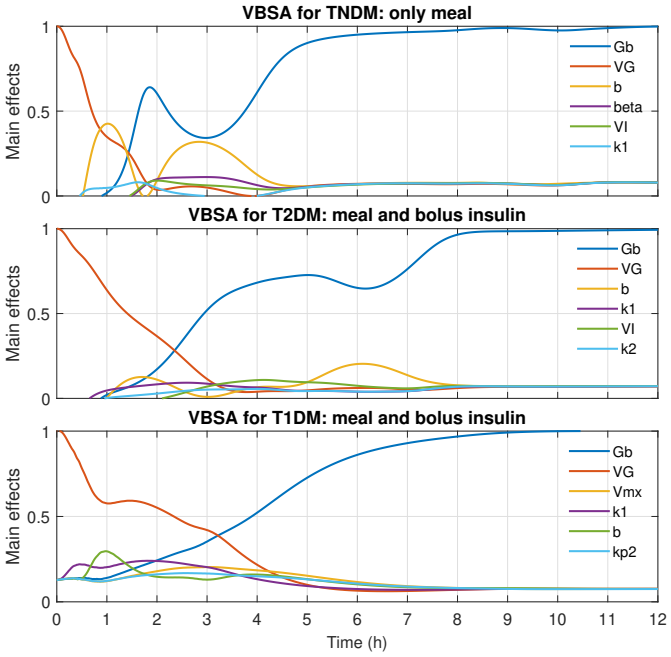

Fig. 4. Time-varying SIs: VBSA was performed for the three scenarios using the reduced parameter set and $N = 20000$ samples. Only the six indices with the highest time-integrated main effects are shown in the graph.

VBSA was fulfilled using a reduced set of 15 parameters for each diabetes type. In contrast to the EET where different scenarios were investigated, here, only the most likely setting for each type was considered. This is the single meal scenario for TNDM and for T2DM and T1DM a meal ingestion with additional optimal insulin bolus. Sobol sampling method was used to generate the input factors. Computational time was 30 h per scenario (four cores at 3.6 GHz parallel, 32 GB RAM).
After model evaluation, the time-dependent sensitivity indices were calculated for each time step. This gives insights into the impact of input factors at certain times and it can be assumed that some parameters have a stronger influence on the dynamic behavior of the model and others on the stationary behavior.
This can be seen in Fig. 4 for three scenarios. Sensitivity of parameter G^b, which is the basal glucose concentration in blood plasma and therefore determines stationary final value, is increasing with time and remains at its maximum when steady-state is reached as it can be seen in the mean functions depicted in Fig 2. Parameter b is mainly related to meal ingestion in the gastric emptying function, which is delayed in T1DM and T2DM subjects, compared to the TNDM, and is negatively related to G^b. Parameters k_1 and k_2 are rate constants with which glucose is exchanged between blood plasma and surrounding tissues. Their SIs are nearly stable over the whole time course in all types. The pancreatic responsivity to glucose is given by parameter β. It is active during the transient part in TNDM and assumed to be deteriorated in T2DM and absent in T1DM.
Second, to derive a scalar feature from the dynamic model output, functional principal component analysis was again applied and a set of FPCs is produced that describes the main types of variance in the CGM signal. Then, for each component, the sensitivity indices were computed as an indicator for the importance of the model parameters described by the corresponding functional component. As it was shown for the EET, sensitivity indices must be interpreted separately for each component.

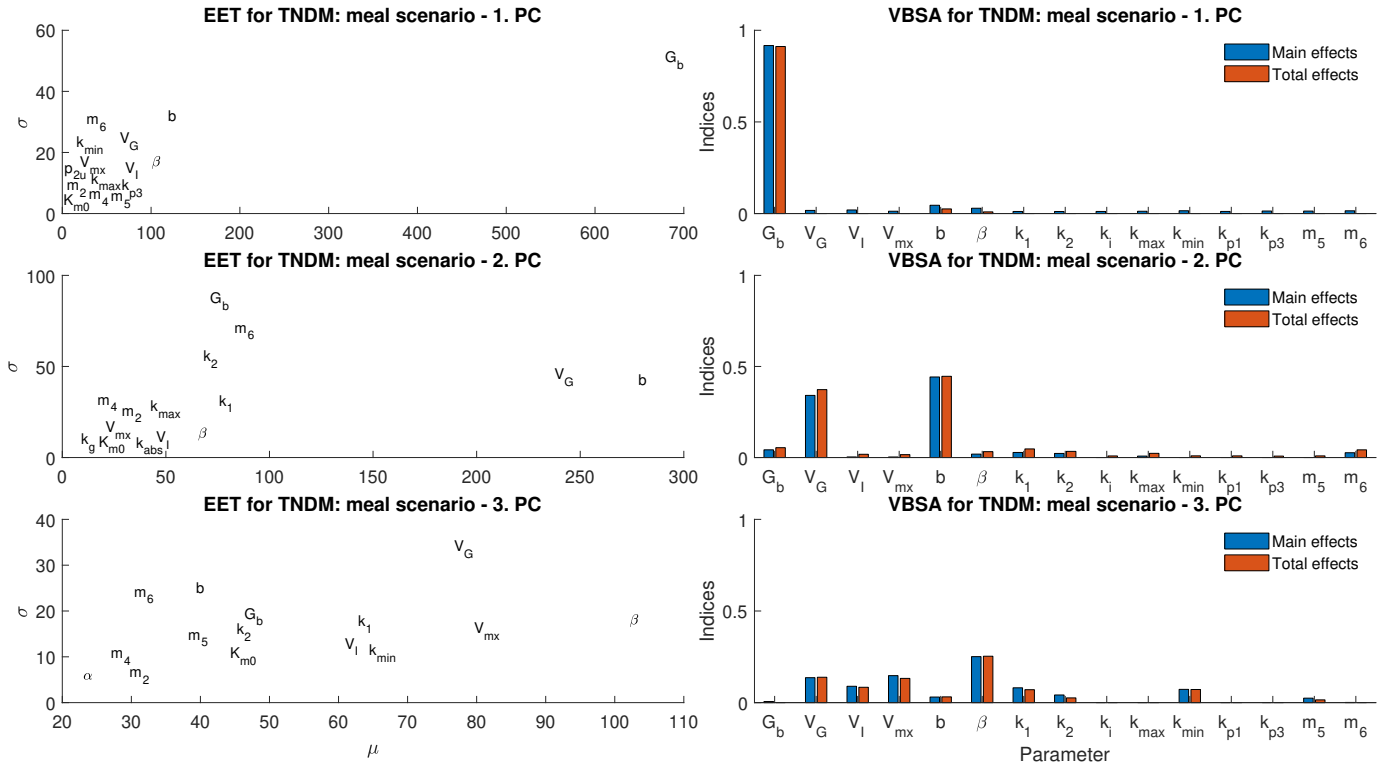

Fig. 5. Parameter sensitivities with regard to the three principal components (PCs) of the CGM model output for the TNDM case and the OGTT scenario. The left column shows the mean μ and standard deviation σ of the Elementary Effects Test (first 15 parameters with the highest mean are shown only). A high mean stands for a strong impact of a parameter on the model output variance and a high standard deviation indicates nonlinear dependencies or interactions between different variables. On the right side the main and total effects calculated with a variance-based sensitivity analysis is given. Main effects quantify the level of variance caused by each individual parameter in the model output. Total effects are a measure of the variability in the model output when parameters interact in combination. Results for T2DM and T1DM cases are summarized in Table 1.

Table 1. Mean values of EET and main effects of VBSA for different diabetes types and scenarios, respectively (reduced parameter set, rounded). All sensitivities were calculated for each principal component (indices 1–3). If no entry exists, the parameter was not considered in the corresponding subject or the scenario.

	EET									VBSA								
	TNDM: meal			T2DM: meal & bolus			T1DM: meal & bolus			TNDM: meal			T2DM: meal & bolus			T1DM: meal & bolus		
	μ_1	μ_2	μ_3	μ_1	μ_2	μ_3	μ_1	μ_2	μ_3	S_1	S_2	S_3	S_1	S_2	S_3	S_1	S_2	S_3
G_b	690.0	76.0	47.5	902.2	104.1	33.6	771.6	365.4	52.9	0.9	0.0	0.0	0.9	0.0	0.0	0.7	0.2	0.1
V_G	43.1	242.6	78.3	74.3	403.2	73.9	440.6	370.1	33.9	0.0	0.3	0.1	0.0	0.6	0.0	0.2	0.5	0.0
V_I	67.0	42.8	62.9	102.1	15.9	67.1	44.2	21.1	9.1	0.0	0.0	0.1	0.0	0.0	0.1	-	-	-
k_{abs}	16.3	38.7	6.9	21.2	91.5	48.3	35.9	23.6	15.2	-	-	-	0.0	0.0	0.0	-	-	-
k_{max}	23.1	46.7	6.2	15.0	78.5	30.4	26.4	109.0	74.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
k_{min}	45.6	17.8	64.8	6.3	70.4	54.0	29.7	118.6	54.8	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1
b	124.3	280.2	40.0	43.2	227.0	68.5	47.2	151.0	142.2	0.0	0.4	0.0	0.0	0.2	0.0	0.0	0.1	0.4
k_1	11.9	79.6	62.6	76.4	168.3	36.1	203.2	164.9	21.8	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.1	0.0
k_2	8.8	71.7	47.2	54.4	110.9	29.0	153.0	127.3	20.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0
k_{p1}	13.7	21.0	9.2	39.4	33.1	83.1	-	-	-	0.0	0.0	0.0	0.0	0.0	0.1	-	-	-
k_{p2}	1.4	5.2	5.5	3.7	7.4	2.7	109.3	13.3	57.5	-	-	-	-	-	-	0.0	0.0	0.1
k_{p3}	41.8	6.1	14.5	53.9	23.9	13.2	46.7	23.7	18.4	0.0	0.0	0.0	-	-	-	-	-	-
k_{p5}	9.6	3.5	5.7	16.7	5.4	16.8	2.4	1.4	1.0	-	-	-	-	-	-	0.0	0.0	0.0
m_2	34.6	26.6	30.4	58.3	34.4	36.1	-	-	-	-	-	-	0.0	0.0	0.0	-	-	-
m_5	31.6	16.0	39.6	52.7	25.8	52.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	-	-
m_6	51.0	87.9	31.8	73.5	125.7	128.6	-	-	-	0.0	0.0	0.0	0.0	0.0	0.3	-	-	-
V_{mx}	29.1	37.2	81.5	70.9	37.4	73.7	180.1	17.3	95.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.2
K_{m0}	19.2	23.1	46.5	53.5	30.6	53.2	64.4	15.4	31.5	-	-	-	-	-	-	0.0	0.0	0.0
β	99.7	67.7	102.9	125.2	28.2	101.4	-	-	-	0.0	0.0	0.3	0.0	0.0	0.1	-	-	-
k_i	10.7	15.4	18.5	28.1	6.8	38.7	19.8	8.2	26.5	0.0	0.0	0.0	-	-	-	-	-	-
n	11.4	18.5	8.7	27.9	32.0	22.4	47.2	18.2	11.5	-	-	-	-	-	-	0.0	0.0	0.0
k_{a1}	0.0	0.0	0.0	9.0	21.0	6.0	52.1	23.8	15.9	-	-	-	-	-	-	0.0	0.0	0.0
k_{a2}	0.0	0.0	0.0	6.3	22.7	5.3	131.1	58.2	55.0	-	-	-	-	-	-	0.0	0.0	0.1
k_d	0.0	0.0	0.0	4.8	16.0	4.4	93.3	24.2	45.8	-	-	-	-	-	-	0.0	0.0	0.0

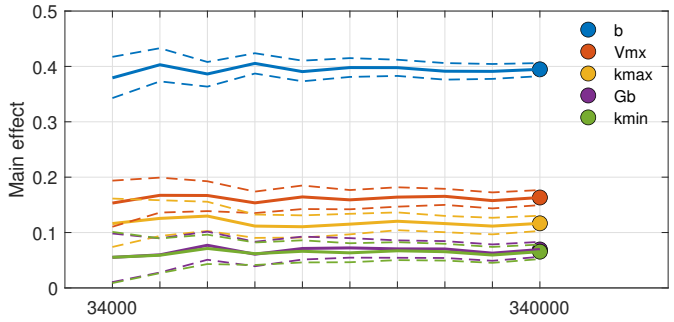

Fig. 6. Convergence plot of main effects for T1DM (3. PC), generated by VBSA bootstrapping. Solid lines represent the input factors, dashed lines confidence bounds.

The first-order and total-order effects returned by the VBSA method are depicted in the right column of Fig. 5 for the non-diabetic case and are summarized for all groups on the right side of Table 1. The results coincide with those of the EE presented in the previous section. The same input variables were identified to be important. There are only minimal differences between main and total order effects visible. This indicates only minor interaction between parameters. It has to be noted that some total effects are lower then their corresponding main effect. This could be an indicator for the presence of correlations between the input factors and needs further investigation.

Finally, to assess quality of the VBSA technique a convergence analysis was performed to proof whether indices are dependent on the number of evaluations. Bootstrapping can address this question easily since no additional or new model evaluations must be executed. Figure 6 exemplarily shows the convergence plot for five most influential parameters for the third PC for the T1DM case. The estimated indices converge to a stable value with increasing sample size. The confidence intervals also shrink as the number of samples increase, so it can be assumed that the indices found can be trusted.

5. CONCLUSION

We presented a multi-step sensitivity analysis technique applied on a unified model of glucose-insulin metabolism. Because quantitative parameter studies with many input factors require a very high computational effort, screening and ranking methods as EET are a good first choice to reduce the parameter space to an affordable degree. Afterwards, a quantitative sensitivity measure as VBSA can be used to determine first-order and total-order indices. When considering time-dependent model outputs a method must be found to derive a scalar representation. We have shown this using a set of functional principal components as an approximation of the output signal.
The study was performed comparing certain diabetes types and scenarios. Results show different influences of the input factors on the model output variance.
Parameters found to have a high impact on the output variance are a starting point for further model analysis.

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