Glucose-insulin metabolism model reduction and parameter selection using sensitivity analysis

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***Abstract*— Glucose-insulin metabolism models are useful tools for research on diabetes, in development of diabetes-related medical devices like artificial pancreas systems, insulin pumps and continuous glucose monitors, and may also play a role in personalized decision support tools for people with diabetes. Such models are often highly nonlinear with many parameters that are person dependent. An example is the model used in the UVa/Padova T1DM simulator, which has a large number of states and parameters. It is desirable to be able to personalize such models through parameter identification based on limited glucose, meal and insulin data obtainable from free-living settings, as opposed to clinical research settings that have traditionally been required. In this paper we use the UVa-Padova T1DM simulator model in a case study to investigate observability of the model under different measurements, and the identifiability of its parameters as a function of the model's inputs and outputs. Structural identifiability is discussed and briefly investigated using the nonlinear Observability Rank Condition. Practical identifiability is discussed and investigated using sensitivity and Fisher information matrix analysis. We show how such analyses can be used to guide model reduction for improved identifiability, or to select the most proper subset of parameters to estimate.**

I. Introduction

Diabetes is a disease affecting a large portion of the world's population, with a global prevalence of 9% and rising [1]. Once a person is diagnosed with diabetes, control of the blood glucose level to within a normal range is required to avoid acute and chronic consequences of the disease. In Type 1 Diabetes Mellitus (T1DM) this control is achieved by using injections of insulin, either by using syringes, insulin pens or insulin pumps, however the control problem is not trivial and many diabetes patients suffer from poor glycemic control. The most dangerous acute consequences of poor control are severe hypoglycemia or ketoacidosis, both of which can be fatal. The diabetes patient is also at increased risk of long term adverse effects like cardiovascular disease, neuropathy (nerve damage), retinopathy (damage to the retina, causing blindness) and kidney failure.

Glucose-insulin metabolism models describe the interplay between blood glucose, insulin and other relevant variables in humans. The UVa/Padova T1DM S2013 simulator (T1DMS) is based on one such model [2], [3]. T1DMS has been accepted by the US Food and Drug Administration (FDA) for use in simulation studies of equipment that measures and/or manipulates the blood glucose level, e.g. sensor augmented insulin pumps and artificial pancreas systems. Such in silico studies may be performed in addition to or in place of some of the in vivo animal or human clinical studies required to approve a new medical device or equipment. This benefits device manufacturers and people with diabetes by cutting costs and time to market of such equipment. The simulator has 300 predefined parameter sets, called virtual patients, grouped into 100 adults, 100 adolescents and 100 children. The parameter set for each virtual patient has been drawn randomly from a joint parameter distribution describing each group [3]. This parameter distribution has been found through more than 30 years of medical experiments using measurements of plasma glucose, insulin and glucagon, including use of radioactive tracer labeling techniques to identify subsystems within the model. Such detailed data are called "clinical research data" in the following.

For simulation use, the T1DMS model is fit for purpose, as the parameters are considered known once a virtual patient is selected. Other uses of the model are possible, and in principle the model parameters can be adapted to patient data to get personalized models. Such a model could be incorporated into medical devices that control blood glucose, like sensor augmented insulin pumps or artificial pancreas systems, to provide glucose predictions that can be used to compute optimal insulin inputs. A model well fitted to an individual could also be used in decision support tools for individuals that do not use insulin pumps, e.g. by giving advice about the insulin dosage, or tracking patient parameters over time. In order for such personalization to be practically feasible, the parameters must be possible to identify based on obtainable measurements in free-living settings. Such data are called "free-living data" in the following, and comprise of infrequent glucose measurements obtained through Self Monitoring of Blood Glucose (SMBG) meters and/or frequent glucose measurements from a Continuous Glucose Monitor (CGM), insulin dosages (basal and bolus) and meal information.

The intended use of the T1DMS model is simulation, and the model is generally considered unidentifiable from free-living data [4]. It is possible that a personalized model with good prediction ability can be achieved by an identification procedure that first performs a classification of the glucose data to select an initial parameter set (i.e. select the predefined virtual patient that best fits the data), then optimizes a small subset of parameters in the vicinity of the initial parameter set. In this use case it is important to know which

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parameters are possible to estimate from the data, and which parameters are best to fix or compute from other patient measurements, e.g. body mass.

This paper discusses methods for investigating identifiability of parameters in nonlinear state-space models, using the T1DMS model as a case study. It is shown how the methods can be used to guide model reduction, or select a subset of parameters to estimate.

II. UVa/Padova T1DM simulator model overview

We used the S2013 version of the T1DMS model, which is described in slightly differing ways in the literature [3], [4]. A short introduction to the model is given here, for more details see the references. A useful overview of the model equations is given in Fig. 2 of [5]. We provide an inference graph representation of the T1DMS model in Fig. 1.

The model is a compartmental model with plasma, liver, subcutaneous (SC) and utilization tissue compartments. The main variables modeled are

- Glucose, the 'universal fuel' of the body
- Insulin, a hormone with a blood glucose lowering effect
- Glucagon, a hormone with a blood glucose raising effect.

A. System equations

The T1DMS model is of the form:

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{p}) + \mathbf{g}(\mathbf{u}, \mathbf{p}) \tag{1}$$

where $\mathbf{x}$ is the state, $\mathbf{u}$ is the input and $\mathbf{p}$ is a vector of parameters. The state vector $\mathbf{x}$ and input vector $\mathbf{u}$ of the model are:

$$\mathbf{x} = \begin{bmatrix} G_p \\ G_t \\ G_s \\ I_p \\ H \\ I_l \\ I' \\ I_{sc1} \\ I_{sc2} \\ X \\ X^L \\ H_{sc1} \\ H_{sc2} \\ SR_H^s \\ X^H \\ Q_{sto1} \\ Q_{sto2} \\ Q_{gut} \end{bmatrix} \begin{array}{l} \text{- Plasma glucose [mg/kg]} \\ \text{- Tissue glucose [mg/kg]} \\ \text{- Subcutaneous glucose [mg/dL]} \\ \text{- Plasma insulin [pmol/kg]} \\ \text{- Plasma glucagon [ng/L]} \\ \text{- Liver insulin [pmol/kg]} \\ \text{- Intermediate insulin conc. [pmol/L]} \\ \text{- SC insulin compartment 1 [pmol/kg]} \\ \text{- SC insulin compartment 2 [pmol/kg]} \\ \text{- Insulin action in tissue [pmol/L]} \\ \text{- Insulin action in liver [pmol/L]} \\ \text{- SC glucagon compartment 1 [ng/L]} \\ \text{- SC glucagon compartment 2 [ng/L]} \\ \text{- Glucagon secretion [ng/L min]} \\ \text{- Glucagon action [ng/L]} \\ \text{- Glucose content in upper stomach [mg]} \\ \text{- Glucose content in lower stomach [mg]} \\ \text{- Glucose content in gut [mg]} \end{array}$$

$$\mathbf{u} = \begin{bmatrix} D \\ IIR \\ H_{inf} \end{bmatrix} \begin{array}{l} \text{- Meal glucose intake [mg]} \\ \text{- Insulin infusion rate [pmol/kg min]} \\ \text{- Glucagon infusion rate [ng/L min]} \end{array}$$

The three inputs affect one state each, Q_{sto1}, I_{sc1} and H_{sc1}, respectively, in an additive and linear fashion. A special feature of the meal glucose intake D is its use as a kind of parameter affecting the computation of Q_{sto2} and Q_{gut} through the function k_{empt}. This lets the model remember the size of the last meal (see [3] for details).

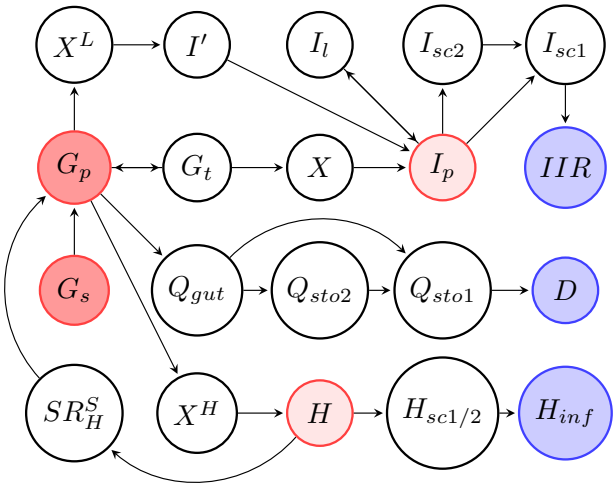

Fig. 1. Inference graph representation of the T1DMS model. White and red circles are states. Dark red states can be measured in a free-living setting, light red states can be measured in research settings. Blue circles are inputs. An edge in the graph from state A to state B signifies that the differential equation governing A has terms containing B, implying that information about B can be inferred by monitoring A [6]. All states are self-referencing, but the loop edges usually signifying this has been removed from the graph to reduce clutter.

The state transition functions $\mathbf{f} = [f_1 \cdots f_{18}]^\top$ are not repeated here. For the discussion in this paper it is relevant to mention that less than half of the functions in $\mathbf{f}$ are nonlinear. The nonlinear functions are those describing the dynamics of states G_p, G_t, Q_{sto2}, Q_{gut}, X^H, H and SR_H^s. The nature of the nonlinearities include ramp functions, rational functions of the states (Michaelis-Menten kinetics), logarithms and hyperbolic tangent functions. Ramp functions are zero when some quantity is less than a threshold, and linear when above the threshold. An example of a ramp function is the function for renal excretion which is part of the equation for $\dot{G}_p$, given by:

$$E = -k_{e1} \max[(G_p(t) - k_{e2}), 0] \tag{2}$$

B. Measurement equations

The measurements that can be done relatively easily on this system in a clinical experiment setting are discrete time measurements of the plasma glucose, G_p, plasma insulin, I_p, and plasma glucagon, H. These measurements can in theory be taken quite frequently, but a practical lower sampling interval limit is one sample every 5 minutes for short periods, usually a longer sampling interval is used. The measurements are normally performed through venous blood sampling analyzed using laboratory analyzers, and are affected by noise.

Outside clinical research settings, a person with diabetes measures his/her blood glucose level using a SMBG meter, using finger capillary blood and getting a result within seconds. SMBGs are less accurate than laboratory blood

glucose methods. Another drawback of such measurements in a parameter identifiability context is that they are usually not performed often, the sampling frequency varies from person to person, and can be as seldom as once a day.

Continuous glucose monitors (CGMs) alleviate this problem by providing a new glucose estimate frequently, typically every 5 minutes. CGMs have a small electrochemical glucose sensor inserted subcutaneously. The glucose level in the SC space is modeled by the state G_s in the T1DMS model, which is delayed compared to the G_p state through first order linear dynamics:

$$\dot{G}_s = -\frac{1}{T_s}(G_s - \frac{G_p}{V_G}) \tag{3}$$

where V_G is one of the parameters in $\mathbf{p}$.

The fact that CGM measurements are not a direct measurement of the plasma glucose has implications for the observability/identifiability when using CGM signals as the measurement.

To summarize the measurement equation, it is linear, discrete-time of the form $\mathbf{y}_k = \mathbf{h}(\mathbf{x}(t_k), \mathbf{p}) = \mathbf{H}(\mathbf{p})x(t_k)$. If all possible measurements are performed, we have

$$\mathbf{y} = \begin{bmatrix} y_{pg} \\ y_{sg} \\ y_{pi} \\ y_{ph} \end{bmatrix} \begin{matrix} \text{- Plasma glucose } [\mathrm{mg/dL}] \\ \text{- SC glucose } [\mathrm{mg/dL}] \\ \text{- Plasma insulin } [\mathrm{pmol/L}] \\ \text{- Plasma glucagon } [\mathrm{ng/L}] \end{matrix}$$

$$\mathbf{H} = \begin{bmatrix} \frac{1}{V_G} & 0 & 0 & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & \frac{1}{V_I} & 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & \cdots & 0 \end{bmatrix}$$

The two last rows of $\mathbf{H}$ and $\mathbf{y}$ are only present in a clinical experiment setting, since insulin and glucagon measurements can only be measured using laboratory methods.

C. Parameters

The parameters of the model are many, and they span a range of uncertainty and dynamics. Some parameters are nearly constant across individuals, others are person-dependent but constant, and some are time-varying [7], and can even be situation dependent. Some parameters are more related to the last ingested meal than to the person, and some are directly measurable, e.g. body weight.

III. Observability and identifiability

When a system is *observable* one is able to infer the initial state given the inputs and outputs (measurements) since the initial time. When a system is *identifiable* it is possible to identify the values of the parameters of the system from the same data. Any system with parameters given by the parameter vector $\mathbf{p}$ can be transformed into a new system where the parameters are made part of an augmented state vector consisting of the states *and* the parameters, $\mathbf{x}_a = [\mathbf{x}^\top \ \mathbf{p}^\top]^\top$, where the parameters are often assumed to have no dynamics, i.e. $\dot{\mathbf{p}} = \mathbf{0}$. This means that any identifiability problem can be considered a special case of an observability problem [8].

A. Structural observability

For linear systems, observability at at a point $\mathbf{p}$ in parameter space is determined by the Kalman rank condition, i.e. computing the observability matrix of the system and checking that is has rank equal to the dimension of the state vector. The nonlinear counterpart to this is the Nonlinear observability rank condition (NORC) [8], [9].

A system may be non-observable due to structural causes, but also due to specific parameter values. As an example of the latter, the following system with two states and one measurement

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \end{bmatrix} = \begin{bmatrix} -1 & 1 \\ 0 & -a \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}, \quad y = x_1 + x_2 \tag{4}$$

is observable except if a=2, for this exact value of a the rank of the observability matrix collapses to 1. A system like this, which is observable except in a set of Lebesgue measure zero in parameter space, is said to be structurally observable. If a system is structurally unobservable there are fundamental observability problems in the model due to its structure, and it is impossible and thus meaningless to try to estimate its states and parameters, regardless of the parameter values. Structural observability in nonlinear systems can be determined using graph theory as described in [6]. From the inference graph of the T1DMS model shown in Fig. 1 we see that all states except G_s influence G_p. This means that the model is structurally observable when G_p and G_s are measured. The minimal sensor setup that gives a structurally observable system is to measure only G_s.

B. Practical observability

The question of practical observability is different from structural observability, as it is based on a set of input and output data, where the measurements can be infrequent and noisy. It is also called *a posteriori observability*, reflecting its use *after* data has been collected from the system. Note that data collection can be and is often done synthetically through simulation of the system.

IV. Methods

This section gives an introduction to the methods used to investigate the observability and identifiability of the T1DMS model in this work.

A. Nominal trajectory

Some of the methods to be presented require a nominal trajectory to base the observability and identifiability analysis on. The nominal trajectory we used in this study was constructed from data from patient 559 in the OhioT1DM dataset [10], and a scenario spanning two days was used. Nominal parameters $\mathbf{p}_0$ were found through manual tuning to make the simulated curve approximate the measurements. While this method for choosing the nominal trajectory is somewhat ad hoc, it makes sure that the nominal trajectory

and parameter set that we base the sensitivity analysis on is realistic and relevant to describe the patient.

B. Nonlinear observability rank condition

NORC is computed by finding Lie derivatives of the output function. If the measurement equation is time invariant and independent of the control inputs the Lie derivative is

$$L_f = \mathbf{f}^\top \frac{\partial}{\partial x} \tag{5}$$

The following matrix of Lie derivatives must be computed for the system, and the rank of the matrix must be determined:

$$\mathbf{dO} = \begin{bmatrix} \frac{\partial h}{\partial x_1} & \cdots & \frac{\partial h}{\partial x_n} \\ \frac{\partial L_f h}{\partial x_1} & \cdots & \frac{\partial L_f h}{\partial x_n} \\ \vdots & \vdots & \vdots \\ \frac{\partial L_f^{n-1} h}{\partial x_1} & \cdots & \frac{\partial L_f^{n-1} h}{\partial x_n} \end{bmatrix} \tag{6}$$

In general the terms of the matrix will contain the states and the parameters of the system, meaning that the rank of the matrix and therefore also the observability of the system is dependent on the state and parameter vectors. Therefore one may use it to determine the observability given some state $\mathbf{x}$ and parameter vector $\mathbf{p}$.

The NORC answers the question of whether it is theoretically possible to identify the values of the states when given *complete, noise free and continuous data*. All these prerequisites are obviously never satisfied in the glucose/insulin system. This means that even if the NORC analysis concludes that the structure is observable, it may still not be practically observable; to determine that, the methods of the next section are needed. Nevertheless, the NORC analysis may still provide some insights into the system.

C. Sensitivity analysis

Sensitivity analysis can be used to determine practical identifiability of parameters. A nominal trajectory starting at initial state $\mathbf{x}_0$ using a nominal parameter vector $\mathbf{p}_0$ and a scenario of inputs $\{\mathbf{u}_k\}$ is used to investigate the identifiability locally around this trajectory.

The method starts by computing $\mathbf{S}_x(k)$, the $n_x \times n_p$ parameter-to-state sensitivity matrix $\frac{\partial \mathbf{x}}{\partial \mathbf{p}^\top}$ for each time step k along the nominal trajectory. $\mathbf{S}_x$ can be found through numerical integration over a time interval that spans the available measurements, with initial values $\mathbf{x}(0) = \mathbf{x}_0$ and $\mathbf{S}_x(0) = 0$:

$$\dot{\mathbf{S}}_x = \frac{\partial \mathbf{f}}{\partial \mathbf{x}^\top}\mathbf{S}_x + \frac{\partial \mathbf{f}}{\partial \mathbf{p}^\top} \tag{7}$$

where (7) follows from differentiating (1) with respect to $\mathbf{p}$ [11]. The discrete-time version is:

$$\mathbf{S}_x(k+1) = \left(\mathbf{I} + \frac{\mathrm{d}\mathbf{f}}{\mathrm{d}\mathbf{x}^\top}\Delta t\right)\mathbf{S}_x(k) + \frac{\mathrm{d}\mathbf{f}}{\mathrm{d}\mathbf{p}^\top}\Delta t \tag{8}$$

where Δt is the time step of the simulation. In this work we found the matrices $\frac{\mathrm{d}\mathbf{f}}{\mathrm{d}\mathbf{x}^\top}$ and $\frac{\mathrm{d}\mathbf{f}}{\mathrm{d}\mathbf{p}^\top}$ using finite differences at each simulation step, using perturbations of the parameters that are based on a fraction of the range of values the parameter can take.

The parameter-to-output sensitivity matrix $\mathbf{S}_y$ is constructed row by row, with row k given by $\mathbf{H}\mathbf{S}_x(k)$. This matrix has a row for every step of the simulation. A smaller $\mathbf{S}_{y,meas}$ matrix is also computed that only contains the rows of $\mathbf{S}_y$ corresponding to times where a measurement is available (every 5 minutes in our scenario).

Once $\mathbf{S}_y$ has been found we can analyze it as follows:

1) If there are columns in $\mathbf{S}_y$ containing all zeros, there is no information about the corresponding parameter, and it is therefore not identifiable from the data. We call these "no-information parameters".
2) If all values in a column of $\mathbf{S}_y$ are small, there is little hope of identifying the corresponding parameter from real data. The limit for what "small" is depends on the noise of the measurement system. For glucose measurements, any change of glucose concentration less than 5 $\mathrm{mg/dL}$ (0.28 $\mathrm{mmol/L}$) is not reliably discernible with an SMBG or CGM measurement, and we have used this as a lower threshold. Any column in $\mathbf{S}_y$ having max absolute value lower than this threshold are considered "low-information parameters".
3) $\mathbf{S}_y^{reduced}$ is constructed from $\mathbf{S}_y$ by removing "no-information" and "low-information" columns
4) Singular value decomposition (SVD) of the $\mathbf{S}_y^{reduced}$ matrix generates a set of singular values (SV) and corresponding right singular vectors (RSV) that can be analyzed as in Stigter et al. [12], by looking for a gap in the singular values. The column removal done to produce $\mathbf{S}_y^{reduced}$ makes it likely that several of the SVs that would otherwise be near zero have already been eliminated. The RSV corresponding to the smallest SV contains information about the linear combination of parameters that is most unidentifiable. Parameters with strong linear correlation in the $\mathbf{S}_y^{reduced}$ need to be reduced from the model by being combined or fixed or otherwise eliminated.
5) The reduction is performed, new $\mathbf{S}$ matrices are computed, and the analysis is performed again.
6) When to stop the process is not clear. It can be done by analyzing the variance of parameter estimates [13]. Other studies have used thresholds for the SVs, [14], stopping when the smallest SV is larger that a given limit. In our work we focused on the smallest SVs, which lead to those parameters that are most clearly unidentifiable, to find the first parameters to reduce from the model.

We call the no-information, low-information and linearly correlated parameters found through SVD analysis the "identifiability signature", following Stigter et al [12]. The above method also has many similarities with the methods presented by other researchers in this area [15], [13], [14].

D. Fisher Information Matrix analysis

Fisher's Information Matrix (FIM) is given by

$$\begin{aligned}\text{FIM} &= E\left\{\left(\frac{\partial \ln p(z|\mathbf{p})}{\partial \mathbf{p}}\right)\left(\frac{\partial \ln p(z|\mathbf{p})}{\partial \mathbf{p}}\right)^{\top}\right\} \\ &= -E\left\{\frac{\partial}{\partial \mathbf{p}}\left(\frac{\partial \ln p(z|\mathbf{p})}{\partial \mathbf{p}}\right)\right\}\end{aligned} \tag{9}$$

where z is the measurement, $\mathbf{p}$ is the parameter vector and $p(z|\mathbf{p})$ is the likelihood function. A practical approximation of the FIM is [11]:

$$\text{FIM} = \sum_{k=1}^{N} \mathbf{S}_x(k)^{\top}\mathbf{H}^{\top}\mathbf{R}^{-1}\mathbf{H}\mathbf{S}_x(k) \tag{10}$$

where $\mathbf{R}$ is the covariance matrix of the measurement(s).

As with $\mathbf{S}_y$ we can compute the FIM for all time steps of the simulation or only for those where measurements are available. The inverse of the FIM is a covariance matrix called the Cramer-Rao Lower Bound (CRLB). The CRLB can be used to determine the theoretical lower limit of covariance that can be achieved for each parameter given the measured data. When the FIM is noninvertible, rows or columns that are zero signify that there was no information in the measurements about the corresponding parameter. Also, further insights can be gained by computing the correlation coefficients from the CRLB. The condition number of the FIM can be used to determine how close it is to singularity, and eigenvalues and eigenvectors of the FIM can be used to determine which parameters that are highly correlated or what combination of parameters that are most estimable. The scaling by $\mathbf{R}^{-1}$ adds the possibility of investigating different sensor noises and their influence on parameter identifiability.

The FIM and $\mathbf{S}_y$ matrix analyses give similar insights about unidentifiable parameters. We based our analysis mainly on the sensitivity matrix, as we found it to be more intuitively interpretable than the FIM. Stigter et al. [12] also claim that rank tests based on the FIM is less precise than rank tests based directly on the sensitivity matrix.

The T1DMS model was implemented based on the referenced articles, and a framework for simulating it and computing sensitivity matrices and FIM was implemented.

V. Results

A. NORC analysis of the T1DMS model

The beginning of the $\mathbf{dO}$ matrix was computed for the T1DMS model system equations using the unaugmented state vector and only y_{gp} measurements, i.e. $\mathbf{H} = [\frac{1}{V_G}\ 0\ 0\ 0 \cdots 0]$. The computed matrix is quite sparse for the top rows, then gets more and more dense with more and more complex terms as the level of differentiation increases.

We observed that the computation of the $\mathbf{dO}$ matrix branches several times due to the ramp-like nonlinearities of the model, meaning that $\mathbf{dO}$ and its rank differs throughout the state space depending on which side of the ramps we are. For example, the value of G_p divides the state space into at least 4 parts, since the renal excretion function E and the insulin dependent glucose utilization function U_{id} include conditionals on the value of G_p. It was found that the matrix is different for the G_p intervals (0,$V_G G_{th}$), ($V_G G_{th}$,G_{pb}), (G_{pb},k_{e2}) and (k_{e2}, G_{max}). Similar effects occur also for other variables, e.g. X^H. These state space 'dividing lines' are possible to read out of the model equations directly.

It is intuitive that parameters that are only in effect when a ramp is active, are unobservable when the system is in an area of state space where the ramp is inactive, since those parameters are then multiplied by zero and cannot affect the output. An example of this is given by the equation for renal excretion in (2), where neither k_{e1} nor k_{e2} is observable when $G_p < k_{e2}$.

Another observation is that the column in the $\mathbf{dO}$ matrix corresponding to G_s has all zero elements, indicating that G_s is unobservable when only plasma glucose is measured. This is obviously true, since the G_s state only exists in order to model the CGM measurement, and does not affect any other state. When both SMBG and CGM measurements are available, the G_s state obviously is observable, as it is directly measured by y_{cgm}. This can also be seen directly from the graph in Fig. 1, as G_s has information about G_p but not the other way around.

B. Model reduction based on sensitivity analysis

When $\mathbf{S}_y$ was computed for the chosen nominal trajectory, we saw that it provided no information about parameters δ, k_{h1}, k_{h2}, and k_{h3}, seen as all zeroes in columns of $\mathbf{S}_y$ corresponding to these parameters. The k_{h1}, k_{h2}, and k_{h3} parameters get zero information by running our scenario because they are part of the SC glucagon subsystem and no SC glucagon was given in the scenario. Adjusting the scenario to include such inputs makes $\mathbf{S}_y$ have values also for these parameters.

The δ parameter is part of the glucagon kinetics and secretion equations of the T1DMS model, affecting the glucose through X^H and H. The reason why we got zero information about δ from the tested scenario, is more involved: H is only affected by δ when plasma glucose is decreasing, and H in turn only affects X^H if $H > H_b$. Thus the scenario must produce a situation where $H > H_b$ and $\dot{G}_p > 0$ simultaneously for δ to have any effect on the output. The tested scenario did not provide this.

In initial testing with a data set with glucose values less than 180 $\mathrm{mg/dL}$, we also found zero information about parameters k_{e1} and k_{e2}. The scenario-dependent identifiability of these parameters was also seen in the NORC analysis of Sec. V-A. The renal excretion threshold was not exceeded by the nominal trajectory in the initial tests. Adjusting the scenario by increasing meal doses raised plasma glucose above the k_{e2} threshold for parts of the trajectory, and recomputing $\mathbf{S}_y$ for this adjusted scenario resulted in non-zero columns corresponding to k_{e1} and k_{e2}. This illustrates that parameter identifiability depends on which parts of the state space has been visited, which again depends on which inputs have been applied to the system. Sensitivity analysis can point out problems with the input data related to parameter identifiability. Importantly, the nominal parameter

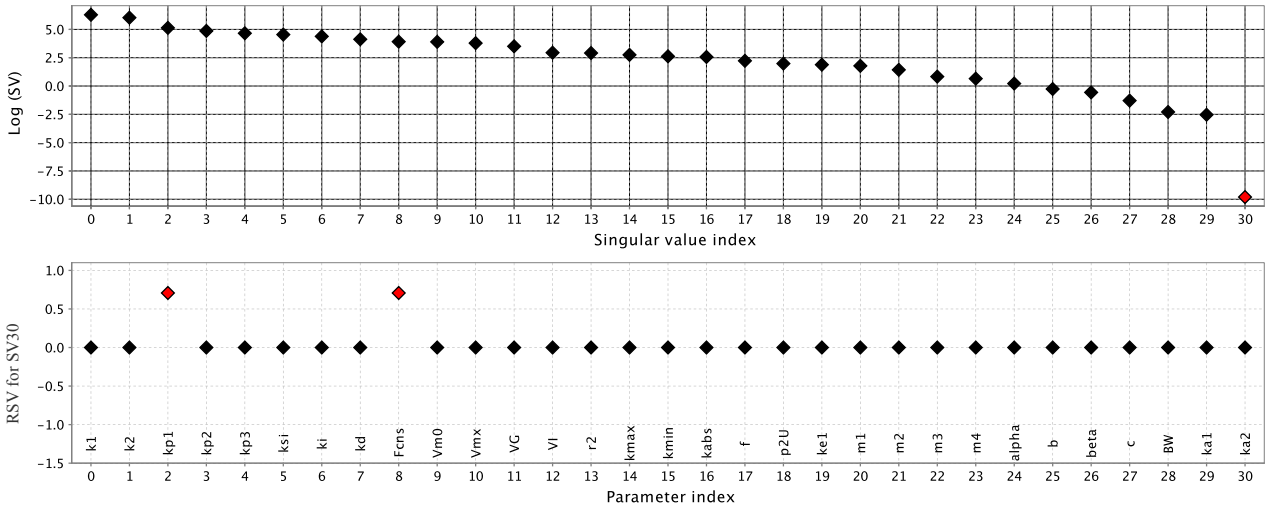

Fig. 2. *Top:* Singular values (SV) of the $\mathbf{S}_y^{reduced}$ matrix. *Bottom:* Right singular vector (RSV) corresponding to the smallest singular value. The RSV has values for k_{p1} and F_{cns}, indicating that these parameters are highly correlated and cannot be individually identified. The selected SV and the significant elements of the corresponding RSV are marked in red.

vector also influences the analysis. If for instance the nominal parameter vector has a very high value for k_{e2}, this could cause k_{e1} and k_{e2} to be flagged as having no information in the sensitivity analysis.

The parameters that never go above sensitivities of 5 $\mathrm{mg/dL}$ per parameter unit were considered to have too low information to be possible to estimate from real data; these were k_H, K_{m0}, r_1, k_{e2}, n, ρ, G_{th}, T_s and SR_H^b. These parameters should be set to fixed values, and values for some of these are suggested in the literature, e.g. G_{th} = 60 $\mathrm{mg/dL}$.

The plot of SVs and the RSVs corresponding to the smallest SV is given in Fig. 2. We see that the smallest SV is significantly lower than the rest. The parameters k_{p1} and F_{cns} make up the RSV of the smallest SV. Looking at the sensitivity curves, i.e. the data in the columns of $\mathbf{S}_y$ corresponding to these parameters, we see that they are perfectly anti-correlated. Looking at the system equation for these two parameters we can see why: They are both additive parameters in different parts of the equation for $\dot{G}_p$. They can not be separately distinguished in the output, only their sum can be estimated. F_{cns} was fixed to the literature default value (1.0) and removed from the set of considered parameters. The analysis was repeated to produce a new set of SVs and RSVs, and the new smallest SV and its corresponding RSV was analyzed. Continuing this process points to several other combinations of parameters that are difficult or impossible to distinguish using only free-living data. Initial findings from the sensitivity analysis and suggested model reductions to move towards identifiability from free-living data are given in Table I.

TABLE I

INDISTINGUISHABLE PARAMETERS FOUND THROUGH SVD ANALYSIS OF THE SENSITIVITY MATRIX $\mathbf{S}_y$

Parameter combination	**Suggested model reduction**
k_{p1}, F_{cns}	Nominal value for F_{cns}
$m_1, m_2,$ m_3, m_4	Use nominal values or eliminate I_l (The I_l state is governed by m_1 to m_4 [4])
r_1, r_2	Use nominal values
k_{a2}, k_{a1}, k_d	Combine to one common time constant

C. Other findings from sensitivity and FIM analysis

We performed tests where we varied some of the inputs to the sensitivity calculation. Firstly we checked the influence of using sensitivity data only at the times of CGM measurements (every 5 minutes), by analyzing the $\mathbf{S}_{y,meas}$ matrix instead of the full $\mathbf{S}_y$. We found through similar analysis as reported above that reducing the sampling to once every 5 minutes did not alter the identifiability signature. This indicates that the 5 minute sampling rate of most CGM systems is sufficiently frequent to allow identification.

We also tried to switch to measuring G_p instead of G_s, this emulates using SMBG data instead of CGM data. We kept the sampling interval of 5 minutes also for the SMBG measurements. While such frequent SMBG data are unrealistic in real life, it was done here to investigate whether something can be gained identifiability-wise by having a more direct measurement of the plasma glucose. Said differently; we would like to investigate whether the slight low-pass filtering of the G_p to G_s dynamics that blurs some of the details of the glucose signal, has an impact on parameter identification. Redoing the sensitivity analysis based on SMBG measurements G_p we saw that T_s from Eq. 3 was flagged as "no information", and V_G is flagged as a "low information" parameter. This is natural given that we no longer measure G_s and thus T_s cannot influence our measurement. Otherwise, the same identifiability signature as with CGM measurement was found, suggesting that measuring SMBG is not clearly superior to measuring CGM with regards to identification of the most identifiable parameters when using free-living data. This is

reassuring given that free-living SMBG measurements are quite infrequent and basing identification on frequent SMBG would be impractical.

By varying the parameter T_s in the nominal parameter set we could investigate the effect of having CGM measurements with more or less physiological lag, which is interesting since this parameter is known to have between-individual and between-sensor variations [16]. Even with large values of T_s (60 $\mathrm{minutes}$) we see surprisingly similar identification signatures, and if we compute the trace of the FIM matrix for the different T_s values we see that it decreases only slightly with increasing T_s. This is an indication that many of the most identifiable parameters in the T1DMS model affect mean glucose level and long-term varying dynamics, and these are roughly as identifiable using CGM measurements as when we use frequent SMBG measurements.

The final input variation we investigated was the influence of scenario length. We expanded the two-day scenario we had been looking at to include three more days, then re-ran the analysis, getting the same results in terms of identifiability signature as with two days. Reducing the scenario to only include 1 day resulted in more low-information parameters. This is because one day of data may well lead to a trajectory that does not go into certain areas of state space. As an example, r_1 and r_2 show up as identifiable for some scenario lengths and not identifiable from others. Looking at the equations for r_1 and r_2 [4] we see that they are related to the so-called risk function controlling endogenous glucose production during hypoglycemia or near-hypoglycemia. These parameters only affect the output when plasma glucose is below a threshold G_b. I.e. r_1 and r_2 are only identifiable in scenarios that include hypoglycemic or near-hypoglycemic episodes. A longer scenario that spans more days increases the probability that such areas of the state space are explored.

VI. Discussion

The NORC analysis provides some insights, but the full resulting $\mathbf{dO}$ matrix is difficult to compute and interpret. In our view the NORC analysis is fundamentally unsatisfactory, as it only gives a yes/no answer to the observability question if we have *continuous, perfect measurements*. This makes it less applicable to use in a glucose/insulin model, where measurements are infrequent and noisy.

Sensitivity and FIM analyses are more relevant to the problem at hand, and provides useful information about unidentifiable parameters in the T1DMS model when attempting to use only free-living data for identification. The information can be used to eliminate the unidentifiable aspects of the model by reducing it. We imagine that an iterative process of reformulation and new sensitivity analysis is needed to guide the model reduction towards a model that is identifiable from free-living data. It must be emphasized that some of the model reductions suggested in this work will have no influence on the simulation results (e.g. fixing F_{cns}) while others represent a fundamental change to the model that will necessarily decrease the detail level and fidelity of the model (e.g. the suggested elimination of the I_l state).

Parameters found to be unidentifiable should be excluded from identification, but the best way to eliminate or exclude a parameter is not always clear, and it usually requires detailed knowledge about the model and the system it represents. In the case of F_{cns} and k_{p1} we may choose to use nominal values for one of them or to combine them into a new parameter. F_{cns} describes the energy consumption of the central nervous system, a fairly fixed quantity across individuals, while k_{p1} describes the basal endogenous glucose production, which is likely to vary more across individuals. In this case it makes sense to fix F_{cns}. In other cases, where the between-individual parameter variation is similar for the parameters considered for elimination, or unknown, a combined parameter may be more appropriate. In this case it is likely better to create one new parameter that gets a new physiological meaning, than to fix one parameter and estimate the other, ending up with two parameters having "wrong" values.

The sensitivity and FIM analysis relies on a nominal trajectory based on a set of inputs and a nominal parameter set, and the conclusions of the analysis is applicable in the vicinity of that trajectory. We based our nominal trajectory on real data, as explained in Sec. IV-A. There are many parameter sets that would provide as good a fit as the one we selected, and since the values of the nominal parameter set has an impact on the analysis, an unfortunate choice of nominal parameters may cause false conclusions on parameter identifiability. This is also commented by Stigter et al. [12] and they demonstrate that combining the sensitivity matrices from several trajectories using different nominal parameter vectors results in improved detection of unidentifiable parameters. This will be further investigated, along with automation of the generation of feasible nominal trajectories and parameter vectors from real data sets, instead of the manual process we employed here. The fact that the analysis is scenario-dependent implies that it is sensible to use data from several individuals in the sensitivity analysis that guides the model reduction, to ensure that model features that are needed to describe some patient subgroups are not eliminated by the model reduction. The initial findings on possible model reduction and influence of experiment factors we found in Sec. V-C should be re-investigated using more trajectories.

The T1DMS model is a complex use case for the identifiability methods discussed. Finding an identifiable version of this model through systematic model reduction is an interesting alternative to the more minimal models recently presented [17], since the T1DMS model is backed by large amounts of data and studies, whereas the more minimal models have less physiological evidence.

A. Other applications of the method

The sensitivity and FIM analysis method we describe has several other possible applications. The method can be used to:

- Judge the suitability of a data set for parameter identification, to decide if parameter identification should be

attempted or not

- Detect that a dataset contains too little information to identify all parameters of a model, and guide the choice of which parameters to keep out of the identification procedure. This could be advantageous to reduce the computation time, since it reduces the dimension of the optimization problem. It is also better to leave unidentifiable parameters at nominal values than to identify more or less random values for them based on data that did not really contain information about them.
- Design physical experiments for parameter estimation, in that it points to regions of state space that should be avoided or visited, as well as measurements that should be included, in order to yield identifiability of a given model. It can guide experiment design to produce the most information-rich data set for parameter identification, given a set of constraints like session length, patient safety and input limitations.

An example of the last point could be to design the optimal parameter identification experiment for initial adaptation of a glucose-insulin model in an artificial pancreas system.

Although the sensitivity and FIM analysis methods we presented here were applied to glucose-insulin metabolism modeling, the method is generic and should be transferable and relevant to many other areas where complex state-space models are employed.

VII. Conclusion

Methods for investigating observability and identifiability in nonlinear systems were discussed and demonstrated on the UVa/Padova T1DM simulator model. Sensitivity analysis and Fisher Information Matrix analysis is a practical and readily applicable way to determine which parameters are indistinguishable from each other under a given input scenario and measurement regime, following a nominal trajectory of interest. The analysis has pointed to parameters and combinations of parameters in the model that need to be reduced in order to move towards identifiability from free-living data (CGM, SMBG, meal and insulin data), and we have shown how sensitivity and FIM analysis can guide model reduction. A simplified model that can be identified from free-living data and is backed by the physiological evidence embedded in the UVa/Padova T1DM simulator model would be useful in many applications, including artificial pancreas. Further work will further develop the methods presented here to produce a reduced T1DMS model and investigate the advantages of such a model compared to other models.

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