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ORIGINAL ARTICLE

Robust Fault Detection System for Insulin Pump Therapy Using Continuous Glucose Monitoring

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Abstract

Background:

The popularity of continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, as a way to deliver insulin more physiologically and achieve better glycemic control in diabetes patients has increased. Despite the substantiated therapeutic advantages of using CSII, its use has also been associated with an increased risk of technical malfunctioning of the device, which leads to an increased risk of acute metabolic complications, such as diabetic ketoacidosis. Current insulin pumps already incorporate systems to detect some types of faults, such as obstructions in the infusion set, but are not able to detect other types of fault such as the disconnection or leakage of the infusion set.

Methods:

In this article, we propose utilizing a validated robust model-based fault detection technique, based on interval analysis, for detecting disconnections of the insulin infusion set. For this purpose, a previously validated metabolic model of glucose regulation in type 1 diabetes mellitus (T1DM) and a continuous glucose monitoring device were used. As a first step to assess the performance of the presented fault detection system, a Food and Drug Administration-accepted T1DM simulator was employed.

Results:

Of the 100 *in silico* tests (10 scenarios on 10 subjects), only two false negatives and one false positive occurred. All faults were detected before plasma glucose concentration reached 300 mg/dl, with a mean plasma glucose detection value of 163 mg/dl and a mean detection time of 200 min.

Conclusions:

Interval model-based fault detection has been proven (*in silico*) to be an effective tool for detecting disconnection faults in sensor-augmented CSII systems. Proper quantification of the uncertainty associated with the employed model has been observed to be crucial for the good performance of the proposed approach.

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Abbreviations: (CGM) continuous glucose monitoring, (CSII) continuous subcutaneous insulin infusion, (FDA) Food and Drug Administration, (IVP) initial-value problem, (MIA) modal interval analysis, (ODE) ordinary differential equation, (T1DM) type 1 diabetes mellitus

Keywords: diabetes fault detection, insulin pump therapy, interval analysis, model-based, robustness

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Introduction

According to a meeting[1] of insulin pump experts on insulin pump safety, which was conducted at the request of the U.S. Food and Drug Administration (FDA), insulin pump designs have made great progress in improving the quality of life of people with diabetes, but much more remains to be done to improve safety measures.

Potential safety issues include users disconnecting their pumps without first terminating ongoing delivery, which results in insulin leakage and miscalculation of the amount infused. Another example occurs when, under circumstances not detected by the user, the infusion set becomes disconnected and prevents insulin from reaching the user. Such circumstances include the infusion set needle being caught on the infusion site tape or the needle being pulled out during sleep. These examples show that it is critical that insulin pumps detect and inform users about accidental pump or infusion set disconnections in a timely manner, a feature that is not supported by currently available insulin pumps.

The idea of using fault detection techniques to detect failures in insulin pump therapy combined with continuous glucose monitoring (CGM) is not new and has been previously proposed by other authors. Finan and coauthors[2] proposed a multivariate statistical technique to detect insulin pump leakages and glucose sensor bias. Kovacs and associates[3] applied a model-based technique based on linear parameter varying modeling, using the Bergman minimal model,[4] in the context of critically ill patients. Vega-Hernandez and coworkers[5] employed another model-based fault detection technique for increasing security in an artificial pancreas using the mathematical model developed by Hovorka and colleagues.[6] A model-based approach using a Kalman estimator for detecting failures in both continuous subcutaneous insulin infusion (CSII) and CGM to improve safety during overnight glycemic control was presented by Facchinetti and associates.[7]

In this article, we propose, for the first time to our knowledge, the use of a validated robust model-based fault detection technique[8] to detect faults in insulin pump therapy in combination with CGM. The proposed robust fault detection technique has already been applied successfully in other engineering problems such as for detecting failures in chemical and petrochemical plants.[9]

Controlling blood glucose levels in type 1 diabetes mellitus (T1DM) is a complex problem incorporating many variables with significant levels of variability, such as insulin sensitivity, and uncertainty, such as carbohydrates intake and exercise.[10] Thus existing mathematical models of the glucoregulatory system for T1DM subjects[4,6] are approximations of reality. Furthermore, CGM accuracy[11] is far from being optimal, mainly due to the fact that glucose is measured in the interstitial compartment instead of in the blood compartment.[12] Note that this lack of accuracy is currently one of the main barriers for mainstream utilization of CGM. Thus dealing with all this variability, uncertainty, and lack of accuracy is a crucial point in order to build a reliable model-based fault detection system to detect failures in insulin pumps.

Unlike other previously proposed model-based approaches, our fault detection system is able to handle high levels of uncertainty associated with CSII in T1DM. The presented approach manages uncertainty by using interval analysis[13] in the process of modeling and simulation. By using interval analysis, our technique is able to minimize the false alarms ratio while maintaining a high level of fault sensitivity.

Materials and Methods

Analytical Redundancy

Analytical redundancy is a method to detect faults that compares the behavior of a real system to a model-based reference system. A fault is detected when they are inconsistent.[14] The main problem is that these two behaviors are seldom the same, because the model is, by definition, inaccurate, i.e., it is an approximate representation of the system. This is the consequence of the uncertainties of the system and the procedure of systems' modeling. This problem is usually solved by setting a threshold for the residual (R; i.e., difference between the model behavior and the actual system) over which the system is considered to be faulty. **Figure 1** shows a graphical representation of the analytical redundancy concept. Nevertheless, selecting such a threshold can be a difficult task because it may not be constant over time, and an adaptive threshold might be required. One way to overcome this limitation is by including the uncertainty of the system in the modeling procedure.

Interval Analysis

One way to account for uncertainty is to take the model parameters, measurements, and initial states as interval values.[13] Intervals only contain information about upper and lower bounds; thus, in using intervals, no assumptions are made about the probability distribution of the uncertainty or about the independence or correlation of parameters.

The simulation of a real-valued model produces a trajectory for each output variable, which is a curve representing the evolution of the variable of the system across time. In the case of a model involving interval values, a set of curves (a band) represents the evolution of each variable.

For obtaining such a reference band, we used interval analysis for solving interval-valued initial-value problems (IVPs).[13] These methods provide numerically reliable enclosures of the exact solution at sample times t_0, t_1,...,t_n. However, interval methods have a reputation of yielding highly overestimated bands. This is due primarily to the dependency (multiple instances of some variables) problem, which is inherent in interval arithmetic, and the wrapping problem, which arises when interval calculations are done in state space.

The approach described here pursues a band that is guaranteed to be complete (i.e., includes all the possible behaviors of the model), but without the large overestimation associated with interval methods that would make the approach impractical. For obtaining this complete, slightly overestimated band, we propose the use of modal interval analysis (MIA; for a complete introduction, see Reference 15), which has been proven to be an effective way to reduce overestimation in interval computations.[16]

Interval Model-Based Fault Detection

We consider a model-reference described by the following nonlinear, ordinary differential equation (ODE) model:

$$x' = f(x,\theta), x(0) = x_0, \quad (1)$$

$$y = h(x,\theta), \quad (2)$$

where x is the m-dimensional state vector, θ is a p-dimensional time-invariant parameter vector, and y is the r-dimensional output vector. Output measurements $\hat{y}_j$ at $t = t_j$ are available with error $v_j = \hat{y}_j - y_j$, where $y_j = h(x_j,\theta)$ and $x_j = x(t_j)$. The initial states x_0 are assumed to lie in a known interval X_0. The parameter vector θ is assumed to be constant and to belong to a known interval Θ, which represents the set of parameter values for a fault-free system.

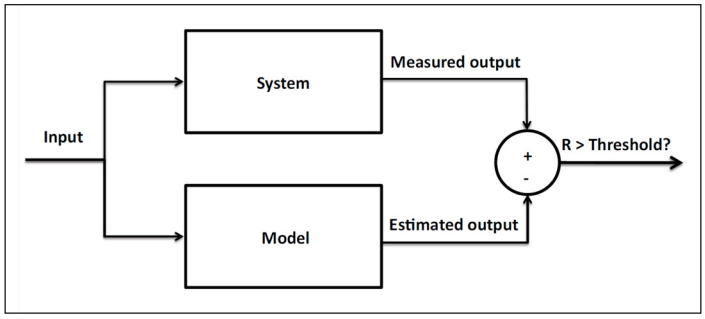

Figure 1. Analytical redundancy diagram. Given the same input for the actual system and a model of the system, the measured output is compared with the estimated output (residual). If the residual (R) is bigger than a predefined threshold, the system is considered to be faulty.

The measurement error v_j is bounded and assumed to belong to a known interval V_j at each t_j. Therefore the output vector y_j belongs to a known box $Y_j = \hat{y}_j - V_j$. The structure of the model, that is, the function $f(x,\theta)$, is assumed to be known (if the model structure is not known with certainty, or if the model structure is poorly chosen, wider parameter intervals may be needed to fully capture normal behaviors). We assume that f and h are continuously differentiable with respect to the uncertain quantities x (initial states x_0 and parameters θ).

The simulation of a model produces a trajectory for each output variable, which is a curve representing the evolution of the variable of the system across time: $y(t), t = t_0, \ldots, t_n$. In the case of an interval model, as it is a set of models indeed, a set of curves (a band) represent the evolution of each variable. The limits of the band are

$$Y(t) = [\min(y(t)), \max(y(t))],\ t_0, \ldots, t_n. \quad (3)$$

The band of system output, generated using the parametric model with the set of parameter values, describes the fault-free system behavior. A fault is reported when the output $y(t)$ lies outside the boundary of the band. The goal is to report faults as soon as possible and to avoid false alarms. A fault is detected when the measurement $\hat{y}(t)$ of the output $y(t)$ is not contained in the estimated output band $Y(t)$. That is,

$$\hat{y}(t) \notin Y(t). \quad (4)$$

Note that we can only say that a fault occurs when the previous statement is satisfied, but we cannot say that the system is not faulty if the previous statement

is not satisfied. This is due to the fact that a fault can be masked by its own dynamics. Furthermore, two simultaneous faults could counteract each other, resulting in an apparently normal behavior.

In fact, if $y(t)$ can be measured $\hat{y}(t)$, the measurement is, in general, not accurate because of the uncertainty associated to the measuring procedure. If this inaccuracy is not considered, false alarms can be generated. One option to take this inaccuracy into account is to use interval measurements $\hat{Y}(t)$. Then a fault is detected when the intersection of the two bands is empty. That is,

$$\hat{Y}(t) \cap Y(t) = \emptyset. \quad (5)$$

Thus the previously stated fault detection problem is reduced to solving an initial IVP with interval-valued parameters and/or initial values.[17] Nevertheless, this is, in general, a challenging problem due to the overestimation phenomenon associated with interval computations. This drawback can be lessened using an error-bounded estimation[18] of the exact band $Y(t)$ since a fault is also detected if

$$\hat{Y}(t) \cap Y_{out}(t) = \emptyset, \quad (6)$$

where $Y_{out}(t)$ is an external error-bounded estimation of $Y(t)$, i.e., $Y(t) \subseteq Y_{out}(t)$, which usually is much easier to obtain than $Y(t)$ although it detects less faults than $Y(t)$. If determining $Y_{out}(t)$ is still very time consuming, its computation can stop either when a fault is detected or when a predefined timeout is reached. **Figure 2** graphically describes our interval model-based fault detection approach.

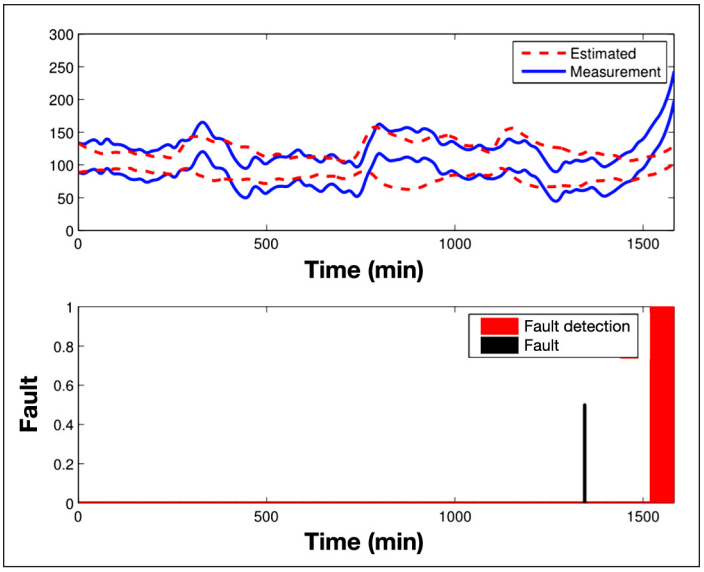

Figure 2. Graphic representation of an interval model-based fault detection approach. In the upper graph, the blue solid curve represents the interval measurements and the red dashed curve represents the estimated output. In the lower graph, the black short bar indicates the time the fault occurs and the red long bar indicates the time the fault is detected. Note that the moment the fault is detected is when the two bands are not intersecting.

Sliding Time Windows

When simulating ODE systems, the goal is to estimate the states of a system knowing some initial ones and the inputs to the system. Therefore, as the simulation goes on, the time distance between the time point, which is being estimated, and the initial one is always increasing. In the case of an IVP with interval-valued parameters and/or initial values, this would mean that the computing effort is also increasing together with the overestimation, and at some time point, the problem may become intractable. This problem can be solved by using a sliding time window.[8]

In fault detection, data from the system is needed to compare the real system behavior and the reference one, which is obtained analytically. Therefore, any time point can be considered as an initial one, and the estimation of the value of a variable at time point t can be calculated starting from the initial time point $t_0 = 0$, which is represented by $Y(t|t_0)$, or $Y(t|t_j)$ from any other time point t_j, $0 < t_j < t$. So the necessary computing effort can be limited by fixing a maximum length $w = t - t_j$. This is especially important in real-time applications, where the computation time is limited by the sample time.

The fault detection results obtained using several window lengths is better, i.e., there are fewer missed alarms (false negatives), than the ones obtained using a single window length, whatever the length is in the latter case. The reason for this improvement lies in the fact that a fault can be detected, or not, depending on the window length.

As the necessary computing effort to calculate $Y(t|t - w_1)$ is greater than the one to calculate $Y(t|t - w_2)$ when $w_1 > w_2$, the logical strategy is to first use the shortest window length, and if no fault is detected, then use the second shortest window length and so on until the maximum window length is reached, thus saving computing effort and minimizing the rate of false negatives. Note that the number of used windows and their lengths depend on the available computing time.

Experimentally, it has been observed that longer windows have longer detection times. Then it could seem that shorter windows are better. This is not true. For instance, shorter windows do not detect slow drifts, because the envelope "follows" the measurement. The experiments show that longer windows do not detect short duration faults, because the duration of the fault is shorter than the detection time. On the other hand, longer windows tend to be wider, because the uncertainty is accumulated though the window. Therefore, there are faults that can only be detected with shorter windows. Note that the analytical determination of the optimal window length remains an open problem.

The algorithm implementing our interval model-based fault detection system is summarized in **Table 1**. Where, *Data* is a vector containing system inputs and measurements, *Windows* is a vector of sliding time window lengths, Y_{out} is an external approximation of the band encompassing all the possible dynamic behaviours of the ODE system, *Solver* is an interval-based IVP solver (see Solving Initial-Value Problems Using Modal Interval Analysis), and $\hat{Y}(t)$ is the current interval measurement.

Table 1.
Interval Model-Based Fault Detection Algorithm

Fault detection algorithm (in: model, data, windows; out: fault)

1. for each sample time t do
2. *Fault* = false;
3. for each sliding time window length i do
4. $Y_{out}(t|t - window_i) = Solver(Model, Data, window_i)$
5. if $Y_{out}(t|t - window_i) \cap \hat{Y}(t) = \varnothing$ then
6. *Fault* = true; break
7. endfor
8. endfor

Type 1 Diabetes Subject Model

Several metabolic models of different complexities have been proposed to represent the glucose–insulin dynamics of a T1DM subject.[4,6,19] However, their suitability depends on the purpose for which they are used. For instance, the sophisticated model proposed by Dalla Man and coauthors[19] is suitable for creating a T1DM subject simulator[20] but is not a useful prediction model for a model predictive controller since its complexity makes it difficult to identify its parameters. On the other hand, the minimal model proposed by Bergman and colleagues[4] may not be sophisticated enough to be used in a T1DM simulator, but it may be suitable for model predictive control and other algorithms that require glucose estimation, such as the current model-based fault detection approach.

In the present work, a composite metabolic model formed by the endogenous minimal model,[4] the glucose absorption model, and the subcutaneous insulin absorption model[6] have been employed. A linear version of this model was successfully used by Gillis and associates[21] to predict glucose levels using a Kalman filter state estimation with meal announcement and a prediction horizon of 45 min.

The Bergman minimal model is represented by the following equations:

$$\dot{G}(t) = -[S_G + X(t)]G(t) + S_G G_b + \frac{R_a(t)}{V_G}, \quad (7)$$

$$\dot{X}(t) = -p_2 X(t) + p_2 S_I [I(t) - I_b], \quad (8)$$

where G is plasma glucose concentration with $G(0) = G_b$; I is plasma insulin concentration with $I(0) = I_b$, where b denotes basal values; X is insulin action on glucose production and disposal with $X(0) = 0$; V_G is the distribution volume; and S_G, S_I, and p_2 are model parameters. Specifically, S_G is the fractional (i.e., per unit distribution volume) glucose effectiveness, which measures glucose ability *per se* to promote glucose disposal and inhibit glucose production; S_I is the insulin sensitivity; p_2 is the rate constant describing the dynamics of insulin action; and R_a is the rate of glucose appearance.

In order to represent the subcutaneous insulin infusion, an existing model of subcutaneous insulin absorption was incorporated into the Bergman minimal model.[6] This model is expressed by

$$\dot{I}(t) = -k_e I(t) + \frac{S_2(t)}{V_I t_{maxI}} \quad (9)$$

$$\dot{S}_1(t) = u(t) - \frac{S_1(t)}{t_{maxI}} \quad (10)$$

$$\dot{S}_2 = \frac{S_1(t) - S_2(t)}{t_{maxI}} \quad (11)$$

where k_e is the first-order decay rate for insulin in plasma, $u(t)$ subcutaneous insulin infusion rate, V_I is the distribution volume of plasma insulin, t_{maxI} is the time to maximum insulin absorption, and $S_1(t)$ and $S_2(t)$ are a two-compartment chain representing absorption of subcutaneously administered short-acting (e.g., lispro) insulin.

In order to represent the glucose absorption after the ingestion of a mixed meal, a modified version of the Hovorka gastrointestinal absorption model[6] was

incorporated to the Bergman minimal model. The model was modified because the original one was not able to represent the glucose absorption dynamics of certain mixed meals, especially the ones where a second absorption peak is observed due to a delayed absorption. The modified model equations are

$$\dot{F}(t) = \frac{1}{t_{maxG}}\left(-F(t) + A_G D_G(t) + (0.9 - A_G)D_{G_d}(t)\right), \quad (12)$$

$$\dot{R}_a(t) = \frac{1}{t_{maxG}}\left(-R_a(t) + F(t)\right), \quad (13)$$

where R_a is the plasma appearance of glucose; F is the glucose appearance in the first compartment; D_G is the amount of carbohydrates ingested at time t; D_{G_d} is the amount of carbohydrates absorbed at time $t_{meal} + t_{delay}$ during a certain time interval $t_{interval} = [t_{meal} + t_{delay}, t_{meal} + t_{delay} + interval]$, being $D_{G_d}(t_{interval}) = D_G(t_{meal})/interval$ and $interval$ fixed to 60 min; A_G is carbohydrate bioavailability; and t_{maxG} is the time of maximum glucose rate of appearance in the accessible glucose compartment. Note that $interval$ was empirically fixed to 60 min in order to smooth the transition between the two absorption peaks, but it could also be an additional parameter to identify.

Solving Initial-Value Problems Using Modal Interval Analysis

As already mentioned in Interval Analysis, interval computations have the problem of overestimating results because of the multiple instances of variables. In order to compute, in an efficient way, a tight external approximation of the model output ($G(t)$), MIA was employed. For this purpose, the model presented in Type 1 Diabetes Subject Model was discretized using a first forward difference derivative approximation (1 min step size). Such an approximation was proven to provide equivalent results to the continuous form of the model. Then symbolic manipulations were carried out in order to eliminate multiple instances of variables. Finally, optimality theorems from MIA[15] were applied to minimize the overestimation due to the multiple instances of variables that could not be eliminated. Thus the following equations were obtained:

$$S_1(k+1) = S_1(k) + \left(u(k) - \frac{dual(S_1(k))}{t_{maxI}}\right)T_S \quad (14)$$

$$S_2(k+1) = S_2(k) + \frac{S_1(k) - dual(S_2(k))}{t_{maxI}}T_S, \quad (15)$$

$$I(k+1) = I(k)(1 - k_e T_S) + \frac{S_2(k)}{t_{maxI}V_I}T_S, \quad (16)$$

$$F(k+1) = F(k) + \left(\frac{1}{t_{maxG}}\left(A_G D_g(k) - dual(F(k)) + (0.9 - A_G)\, D_{G_d}(k)\right)\right)T_S, \quad (17)$$

$$R_a(k+1) = R_a(k) + \frac{F(k) - dual(R_a(k))}{t_{maxG}}T_S, \quad (18)$$

$$X(k+1) = X(k) + p_2(S_I I(k) - dual(X(k)))T_S, \quad (19)$$

$$G(k+1) = G(k)(1 - X(k))\, T_S + S_G(G_b - dual(G(k))T_S + \frac{R_a(k)}{V_G}T_S, \quad (20)$$

where k indicates the current sample, T_S is the sample time (i.e., 1 min), and $dual$ is a modal interval operator defined as $dual([a,b]) := [b,a]$, with a being the lower bound of an interval and b the upper bound. Note that, despite using the same notation, variables and parameters in **Equations (14)–(20)** are their interval counterparts.

In order to solve the previous interval ODE system, the initial states were set to zero, with the exception of $G(0)$ and $I(0)$, which were set to their basal values (G_b and I_b). The algorithm for solving the interval ODE system consists of an iterative loop that sequentially evaluates **Equations (14)–(20)** using MIA arithmetic. For this purpose, a MIA arithmetic library[16] was implemented in Matlab®. Since most of **Equations (14)–(20)** satisfy optimality conditions of MIA,[15] the resulting interval computations do not produce much overestimation. In the case that these optimality conditions would not have been satisfied, the f^* algorithm[16] could have been employed to reduce such overestimation.

When using the sliding time window strategy presented earlier, at each simulation step, the states of the model are set to their corresponding values at the beginning of the simulation window (e.g., $X(0) = X(k - window)$), with the exception of $G(0)$, which is set to the actual glucose measurement at the beginning of the window (i.e., $G(0) = \hat{G}(k - window)$) with the corresponding uncertainty.

Regarding the length of the sliding time window, a single 60 min window length was selected. The selection of a 60 min window was done experimentally by trying different window lengths (e.g., 30, 60, and 90 min) and taking the one that provided better results in terms of

shortest detection times and less false negatives. Since the studied problem only presents one type of fault (i.e., pump disconnection) and the window length depends on the type of fault and its duration, the utilization of multiple sliding time windows was considered unnecessary.

Finally, note that estimated blood glucose $G(k + 1)$ in **Equation (20)** corresponds to Y_{out} in **Table 1** and that the continuous glucose measurements (G_{cgm}) correspond to $\hat{Y}$ in **Table 1**.

Estimation of Interval Parameters

One common difficulty when using interval analysis for solving IVPs is to define the intervals associated with model parameters and initial conditions of the ODE system. One way to tackle this problem is to use parameter identification techniques based on interval analysis.[22] However, these techniques, even if they are numerically sound, are usually very conservative in terms of the size of the provided intervals. Another technique to define such intervals consists of using classic parameter identification techniques (i.e., least squares) over different sets of data and to take the minimum and maximum identified value for each parameter.[23] In the present work, since the T1DM simulator[20] does not incorporate intrasubject variability, interval parameters were only used to deal with the errors introduced in the modeling process and the errors associated with measurements. In order to define such intervals, classic parameter identification techniques were employed to calculate the center of such intervals. Then the width of the intervals was defined based on empirical and experimental evidence.[24] Even if some degree of experimental evidence was used to set the magnitude of the intervals, the main criteria consisted of ensuring that the interval model estimate was able to encompass, as much as possible, the reference behavior during the identification phase (see **Figure 3**).

Center of Interval Parameters

For calculating the center of the interval parameters, the *fmincon* optimization algorithm from the Matlab Optimization Toolbox (2010b, The Matworks, Natick, MA) was used to minimize the sum of squared errors between a discrete version of the T1DM model [**Equations (14)–(20)**] and the experimental data. Note that the three employed models were identified separately in order to avoid identification problems.

To identify the glucose absorption model parameters (t_{maxG}, t_{delay}, and A_G), meal protocol (i.e., carbohydrates and intake times) and glucose rate of appearance (R_a) data were used, respectively, as input and output data. Note that R_a data are difficult to obtain in normal clinical practice because it requires the use of a complex multitracer oral glucose protocol.[25] However, different approaches[26,27] have been proposed for estimating from plasma glucose and plasma insulin concentration data that could be used for this purpose. For the sake of simplicity, reference R_a data from the T1DM simulator[20] were used in this work. To identify the subcutaneous insulin absorption model parameters (k_e, V_I, and t_{maxI}), CSII data and plasma insulin measurements (I_p) from the T1DM simulator were used. Finally, CSII data, meal protocol, and CGM data were employed to identify the parameters of the endogenous model (SI, VG, SG, and p_2). Note that previously identified model parameters for R_a and subcutaneous insulin absorption models were used for identifying the endogenous model parameters.

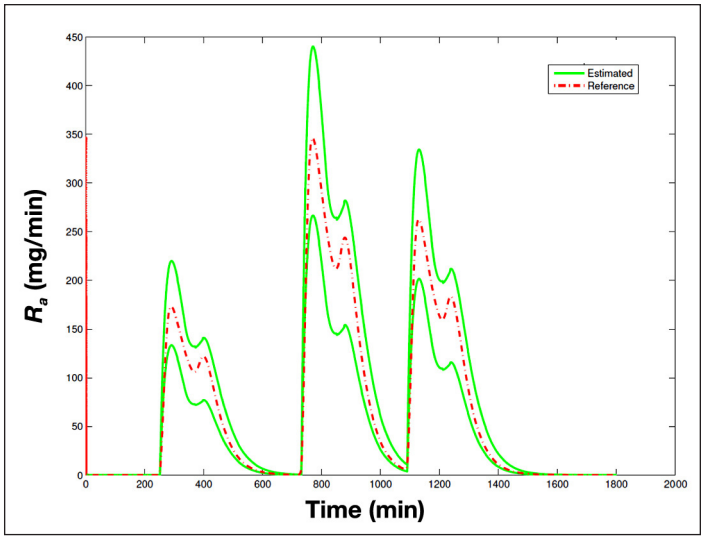

Figure 3. Interval estimation of R_a (solid green linecurve) versus reference value from the T1DM simulator (dotted red linecurve). The data corresponds to a scenario with three meals.

Width of Interval Parameters

Table 2 shows the selected uncertainty for each of the parameters and inputs of the model. Note that parameters and inputs with higher variability,[24] such as insulin sensitivity (S_I), time to maximum insulin

Table 2.
Uncertainty on Model Parameters and Inputs of the Type 1 Diabetes Mellitus Model Expressed in Percentage

S_I 10	p_2 5	V_G 3	S_G 3	t_{maxI} 10	V_I 3	G_b 5
k_e 5	A_G 5	t_{maxG} 5	BW 1	u 1	D_G 10	I_b 5

absorption (t_{max1}), and carbohydrate intake (D_G), have higher uncertainty than other parameters with less variability, such as glucose and insulin distribution volumes (V_G and V_I), body weight (BW), and insulin infusion (u). The corresponding intervals can be easily obtained as $X = [x - n\%x, x + n\%x]$, where x is the estimated value and n is the corresponding percentage uncertainty.

Figure 3 shows an example of R_a interval estimation together with the reference value from the T1DM simulator.

It is important to mention that, in a real clinical scenario, this uncertainty should be individualized to each diabetes subject in order to cope with intrasubject variability. For this purpose, the method proposed by Kirchsteiger and associates[23] could be employed.

As far as the error associated with the continuous glucose measurements (G_{cgm}) is concerned, a ±20 mg/dl error was considered.[11] Nevertheless, the CGM noise model of the T1DM produces differences with respect to plasma glucose values up to 40%, which can be considered unrealistic for current CGM devices. Finally, note that the dynamic lag between the plasma and interstitial glucose compartments has not been modeled. However, the considered uncertainty associated with the CGM measurement already incorporates the error due to modeling approximation.

In Silico *Protocol*

As a first step to assess the performance of the presented fault detection system, a FDA-accepted T1DM simulator was employed.[20] It must be noted that the model implemented in the T1DM simulator[19] is much a more sophisticated model than the one employed in the present work (i.e., 11 versus 35 parameters). Despite the mismatch with the reality being shown to be larger, the T1DM simulator is a suitable platform for testing the proposed fault detection approach because it is able to replicate this mismatch to a certain degree.

Thus the T1DM simulator was used to generate the required data (i.e., plasma insulin, plasma glucose, and glucose rate of appearance) for the testing of the fault detection technique. For this purpose, 10 adult subjects of the academic version of the simulator were selected. In order to tune the basal–bolus therapy, a protocol consisting of adjusting the basal insulin rate in order to get a basal glucose level (G_b) close to 100 mg/dl and adjusting the insulin-to-carbohydrate ratio in order to minimize the postprandial peak and to avoid hypoglycemia was used. Two meal protocols (i.e., different meal ingestion times and different amounts of ingested carbohydrates) were employed (see **Table 3**).

Table 3.
Meal Protocols Used to Identify the Model Parameters (Protocol 1) and Testing the Fault Detection Algorithm (Protocol 2)

Protocol	Breakfast	Lunch	Dinner
1	6 AM (30 g)	2 PM (60 g)	8 PM (45 g)
2	6 AM (60 g)	1 PM (70 g)	7 PM (30 g)

Protocol 1 was used to identify the model parameters while protocol 2 was used to test the fault detection technique. The idea of using two different protocols for tuning the model and testing the fault detection algorithm was to create a more realistic benchmark. Nevertheless, it is important to emphasize that the T1DM simulator is an approximation of the glucose–insulin dynamics of a T1DM subject and it does not include the variations of insulin sensitivity during the day and other perturbations such as physical exercise or stress.

For each subject, 10 random faults were generated in a period of 24 h. However, a 30 h simulation period was used in order to have enough time to detect faults occurring at the end of the 24 h period. The faults represented a complete suppression of the insulin infusion, which is equivalent to the disconnection of the infusion system. To evaluate the performance of the algorithm, different metrics were employed: time interval between the occurrence fault and its detection (time); plasma glucose concentration at the moment of detection; insulin not delivered until the fault is detected (lost insulin); and false negatives and false positives, where a false negative is defined as a fault not detected before 400 min. Finally, although there is no consensus definition of what constitutes diabetic ketoacidosis in terms of plasma glucose concentration,[28] a threshold of 300 mg/dl was established as a safety limit to evaluate the performance of the fault detection system.

Results

Table 4 shows a summary of the results. Despite the detection interval being occasionally long, all faults were detected before the plasma glucose concentration reached the predefined safety limit (300 mg/dl). Note that the variability of the results between subjects is significant. This is due to the very different glucose–insulin dynamics of the subjects. Also noticeable was

the low ratio of false negatives (2 out of 100 faults) and false positives (1 out of 1257 h of nonfaulty simulation), which demonstrates the robustness of the proposed approach. **Figure 4** shows an example of fault detection corresponding to subject adult 3, and **Figure 5** shows an example of a false positive in subject adult 6.

Table 4.
Fault Detection Results for the 10 Adult Subjects of the Type 1 Diabetes Mellitus Simulator[a]

Subject	Time (min)	Moment of detection (mg/dl)	Lost insulin (U)	False negative/ false positive
1	390 ± 59	185 ± 38	11.7 ± 1.8	1/0
2	204 ± 28	128 ± 32	6.4 ± 2.5	0/0
3	191 ± 24	176 ± 31	6.4 ± 2.8	0/0
4	161 ± 33	163 ± 52	4.7 ± 1.5	0/0
5	297 ± 52	161 ± 36	9.2 ± 5.8	0/0
6	170 ± 33	170 ± 33	7.6 ± 4.2	0/1
7	160 ± 32	156 ± 15	4.4 ± 0.6	0/0
8	196 ± 39	155 ± 13	7.1 ± 1.6	0/0
9	318 ± 49	210 ± 33	11.2 ± 2.6	1/0
10	330 ± 86	162 ± 55	10.8 ± 4.0	0/0
Total	200 ± 43	163 ± 34	7.3 ± 2.7	2/1

[a] Results are expressed as median ± standard deviation.

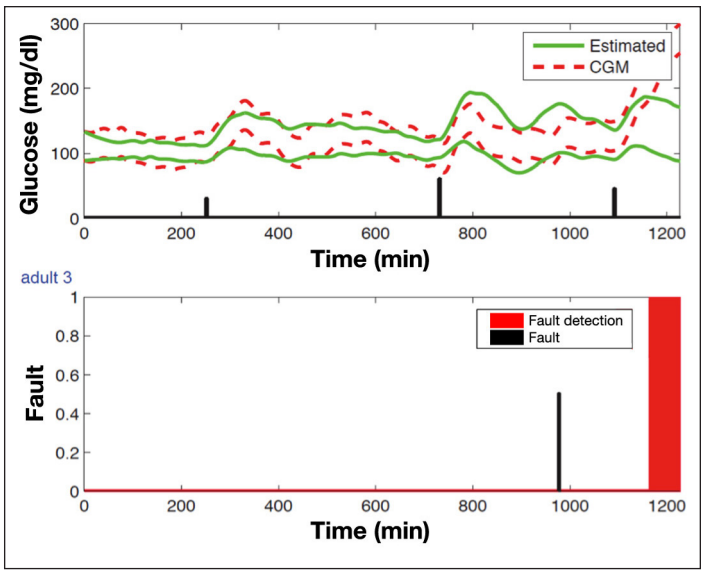

Figure 4. Example of fault detection in subject adult 3. In the upper graph, the black short bar indicates carbohydrate intakes (time and amount), the red dashed curve represents the interval measurements, and the green solid curve represents the estimated interval output. In the lower graph, the black short bar indicates the time the fault occurs and the long red bar indicates the time the fault is detected.

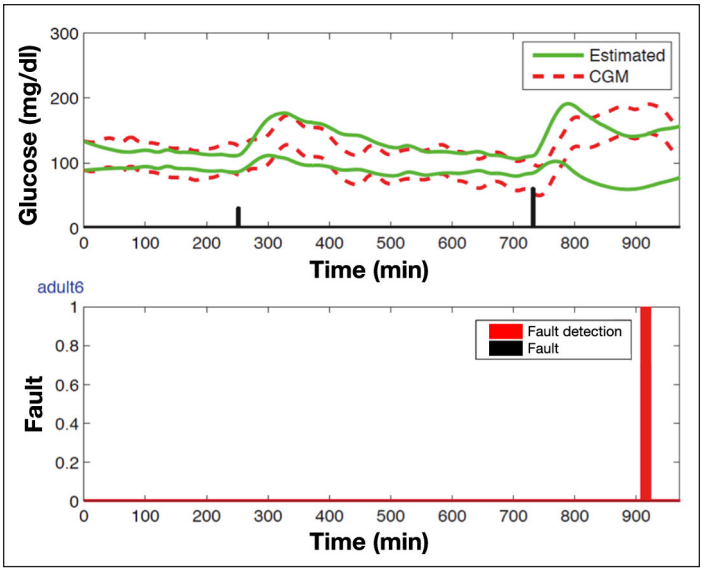

Figure 5. Example of false positive in subject adult 6. In the upper graph, the black short bar indicates carbohydrate intakes (time and amount), the red dashed curve represents the interval measurements, and the green solid curve represents the estimated interval output. In the lower graph, the black short bar indicates the time the fault occurs, and the long red bar indicates the time the fault is detected. Note that, around 900 min, the estimated interval output falls slightly below the interval measurement, producing a false positive.

Discussion

Interval model-based fault detection has been proven to be an effective robust tool for detecting faults in CSII systems using CGM. In particular, disconnection of the insulin infusion set, which currently available insulin pumps are not able to detect, has been successfully detected. The proposed technique has been validated using a FDA-approved T1DM simulator, which is an accepted method for *in silico* testing of glucose controllers before clinical trials.

The proposed fault detection technique uses the well-known principle of analytical redundancy. Interval analysis has been used to account for uncertainties in model parameters, measurements, and inputs. In particular, MIA was successfully used to deal with the problem of numeric overestimation associated with interval computations, which can make the fault detection technique less sensitive or even useless if the overestimation is too big. Although it is not addressed in this article, MIA allows quantifying such overestimation by computing an inner approximation of the exact band. Then, by comparing the outer and inner approximations, it is possible to have an estimate of such overestimation.

Although interval analysis approaches have the reputation of being computationally complex, this is not the case

for the current application thanks to the use of MIA. Note that the same problem could not be solved using standard interval arithmetics due to the extreme overestimation of the results (i.e., trumpet effect). An alternative to MIA could be the use of Taylor models combined with interval analysis[17] or the use of interval constraint propagation combined with branch-and-bound techniques.[22] However, the comparison of these techniques with MIA is out of the scope of this article.

Intervals associated with model inputs, measurements, and model parameters were selected based on technical specifications of the employed medical devices and clinical knowledge. However, some of these intervals were readjusted in order to guarantee that the interval model estimate was able to encompass the reference behavior during the identification phase. It is important to remark that, in a real clinical scenario, these intervals should be adjusted according to physiological and metabolic characteristics of the subject. In the case of parameters that have a strong intraday variability, such as insulin sensitivity, different interval values could be used along the day since trying to cope with all the variability in a single interval would lead to low fault sensitivity.

Of the 100 *in silico* tests, only two false negatives and one false positive occurred. These results demonstrate the robustness and high sensitivity of the proposed approach. However, the used T1DM simulator does not account for intrasubject variability and other perturbations such as physical exercise or psychological stress. For this reason, more tests using actual clinical data need to be carried out for a final validation of the proposed method.

Although the presented technique has only been used to detect one type of fault in CSII systems (i.e., disconnection of the insulin infusion set), it could also be used to detect other types of fault in the insulin infusion set such as leakages. Furthermore, the same approach could be used to detect faults in the CGM system (i.e., sensor drift or loss of sensitivity) or even to detect unexpected variations in the T1DM subject glucose dynamics (i.e., illness). However, these types of faults may take longer to detect due to their slower dynamics.

It is important to remark that this fault detection method only detects discrepancies between the model and the real system. So in a general setting where different faults can occur, it can only detect if there is a fault in the system but cannot determine which one. In order to diagnose which fault is causing the discrepancy, a fault diagnosis module could be employed.[14]

Commercially, the proposed fault detection technique could be easily integrated in a dual CSII–CGM (sensor-augmented pump) system such as the Paradigm Veo (Medtronic, Northridge, CA) or Vibe (Animas Corporation, Westchester, PA). However, in order to integrate the proposed techniques with such technology, a certain level of user intervention would be required in order to account for the amount of ingested carbohydrates and the type of absorption of the ingested meal (e.g., slow, medium, and fast). Since estimating the type of absorption of a meal is not common in standard insulin therapy, a library of different types of mixed meal[29] could be provided to the user in order to facilitate this task. Furthermore, some tuning of the fault detection algorithm would be required before its utilization. First of all, the employed model would need to be individualized for each subject using retrospective clinical data. In real practice, this could be done using retrospective CGM data, basal insulin infusion rates, times and amounts of insulin boluses obtained from the subjects' insulin pumps, and subject-reported estimates of the times and carbohydrate content of meals.[30] Then a graphical user interface would be provided to the clinicians in order to upload such data. Finally, an algorithm would automatically analyze these data, determine the center of intervals (i.e., parameter identification), and quantify the width of the intervals based on the variability of data.

Another parameter that could be tuned is the length of the sliding time window. Once a fault has been detected, an alarm (i.e., acoustic or vibration signal) could be used in order to alert the user.

Finally, the proposed technique has been used to supervise the current basal–bolus therapy in CSII, but it could also be easily integrated in an artificial pancreas framework.[10]

Conclusions

Interval model-based fault detection has been proven (*in silico*) to be an effective tool for detecting faults in sensor-augmented CSII systems. Although the presented methodology is numerically sound (i.e., robust), the wrong quantification of the involved uncertainty may lead to the occurrence of false negatives or false positives. Therefore, setting the right size of the intervals associated with model inputs, measurements, and model parameters is crucial for the good performance of the approach proposed.

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