Robust Fault Detection System For Insulin Pump Therapy using Continuous Glucose Monitoring

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Abbreviations: FDA (Federal Drug Administration); CSII (Continuous Subcutaneous Insulin Infusion); CGM (Continuous Glucose Monitoring); T1DM (Type 1 Diabetes Mellitus); MIA (Modal Interval Analysis); ODE (Ordinary Differential Equation); IVP (Initial-Value Problem).

Key Words: Insulin pump therapy; diabetes, fault detection; model-based; robustness; interval analysis.

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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 glycaemic control in diabetic patients has increased over the last years. Despite the therapeutic advantages of using CSII have been substantiated, the use of CSII has also been associated with an increase in the risk of technical malfunctioning of the device, leading to an increased risk of acute metabolic complications, such as severe hypoglycaemia and 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 type of faults such as the disconnection or leakage of the infusion set.

Methods

In this paper, we propose the utilisation of 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 and

a continuous glucose monitoring device were used. As a first step to assess the performance of the presented fault detection system, a FDA-accepted type 1 diabetes mellitus simulator was employed.

Results

Of the 100 *in-silico* tests (10 scenarios on 10 subjests), only 2 false negatives and 1 false positive occurred. All faults were detected before plasma glucose concentration reached 300 mg/dL, with a mean plasma glucose detetion value of 163 mg/dL and a mean detection time of 200 minute.

Conclusions

Interval model-based fault detection has been proven (*in-silico*) to be an effective tool for detecting faults in sensor-augmented continuous subcutaneous insulin infusion (CSII) systems. Quantificating the uncertainty associated to the supervised system has been seen to be crucial for the good performace of the proposed approach.

1 Introduction

According to a recent meeting [1] of insulin pump experts on insulin pump safety at the request of the US 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.

For example, many users disconnect their pumps without terminating ongoing delivery first. This results in insulin leakage and miscalculation of the amount infused. Another example is when, under circumstances not detected by the user, the infusion set becomes disconnected, preventing 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/infusion set disconnections in a timely manner, a feature that, unfortunately, insulin pumps currently on the

market do not support.

The idea of using fault detection techniques for detecting failures in insulin pump therapy combined with continuous glucose monitoring (CGM) is not new and has been previously proposed by other authors. In [2], a multivariate statistical technique was proposed to detect insulin pump leakages and glucose sensor bias. In [3], a model-based technique based on Linear Parameter Varying (LPV) modelling, using the Bergman minimal model [4], was applied in the context of critically-ill patients. In [5], another model-based fault detection technique for increasing security in an artificial pancreas using the mathematical model developed in [6]. More recently, a model-based approach using a Kalman estimator for detecting failures in both CSII and CGM to improve safety during overnight glycemic control has been presented [7].

In this paper, 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 continuous glucose monitoring. The proposed robust fault detection technique has already been successfully applied in other engineering problems such as for detecting failures in chemical and petrochemical plants [9].

Controlling blood glucose levels in type 1 diabetes is a complex problem affected by many variables with significant levels of variability (i.e., insulin sensitivity) and uncertainty (i.e., carbohydrates intake, exercise, etc) [10]. Thus, existing mathematical models of the gluco-regulatory system for type 1 diabetic subjects [4, 6] are just rough approximations of the reality. Furthermore, whereas CSII is a well-established technology, CGM [11] is a relatively young technology and its accuracy is still one of the main barriers for its mainstream utilization [12]. 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 allows to handle in an elegant way the high levels of uncertainty associated with the present problem. The way our approach deals with this uncertainty is by using interval analysis [13] in the process of modelling and simulation. By using interval analysis, our technique is able to minimise the false alarms ratio while maintaining a high level of fault sensitivity.

2 Materials and Methods

2.1 Analytical Redundancy

Analytical redundancy is a method to detect faults that compares the behaviour of a real system with respect to a reference one obtained from a model of the system. A fault is detected when they are inconsistent [14]. The main problem is that these two behaviours 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' modelling. This problem is usually solved by setting a threshold for the residual (R) (i.e. difference between the model behaviour 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 since it may not be constant over time and an adaptive threshold may be required. One way to overcome this limitation is by including the uncertainty of the system in the modelling procedure.

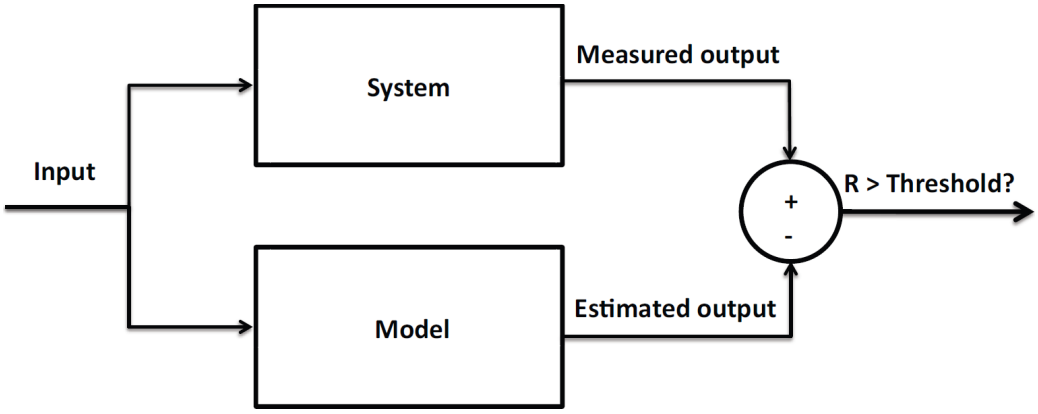

Figure 1: Analytical redundancy diagram. Given the same input for the actual system and a model of the system, the measured output is compared with the estimated output (residual). If the residual (R) is bigger than a predefined threshold, the system is considered to be faulty.

2.2 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 behaviours 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 Model Inteval Analysis (MIA) (for a complete introduction see [15]), which has been proven to be an effective way to reduce overestimation in interval computations [16].

2.3 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.

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 behaviours). 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) represents the evolution of each variable. The limits of the band are

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

The band of system output, generated using the parametric model with the set of parameter values, describes the fault-free system behaviour. Once faults occur, the output $y(t)$ will lie outside the boundary of the band, and then a fault is reported. The goals of fault detection are to report faults as soon as possible if they occur, and to avoid false alarms. Then, a fault is detected when the measurement $\hat{y}(t)$ of the output $y(t)$ is not contained in the estimated outp

ut band $Y(t)$. That is

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

Note that we can only say that a fault occurs when the previous statement is satisfied, but we cannot say that the system is non-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 behaviour.

In fact, if $y(t)$ can be measured ($\hat{y}(t)$), the measurement is, in general, not accurate due to 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 using interval measurements $\hat{Y}(t)$. Then, a fault is detected when the intersection of the two bands is empty. That is

$$\hat{Y}(t)\cap Y(t)=\varnothing. \tag{5}$$

Thus, the previously stated fault detection problem is reduced to solving an initial value problem (IVP) with interval-valued parameters and/or initial values [17]. Nevertheless, this is, in general, a challenging problem due to the overestimation phenomenon associated to the interval

computations. This drawback can be softened using an error-bounded estimation [18] of the exact band $Y(t)$ since a fault is also detected if

$$\hat{Y}(t) \cap Y_{out}(t) = \varnothing, \tag{6}$$

where $Y_{out}(t)$ in 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 the obtainment of $Y_{out}(t)$ 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 the presented interval model-based fault detection approach.

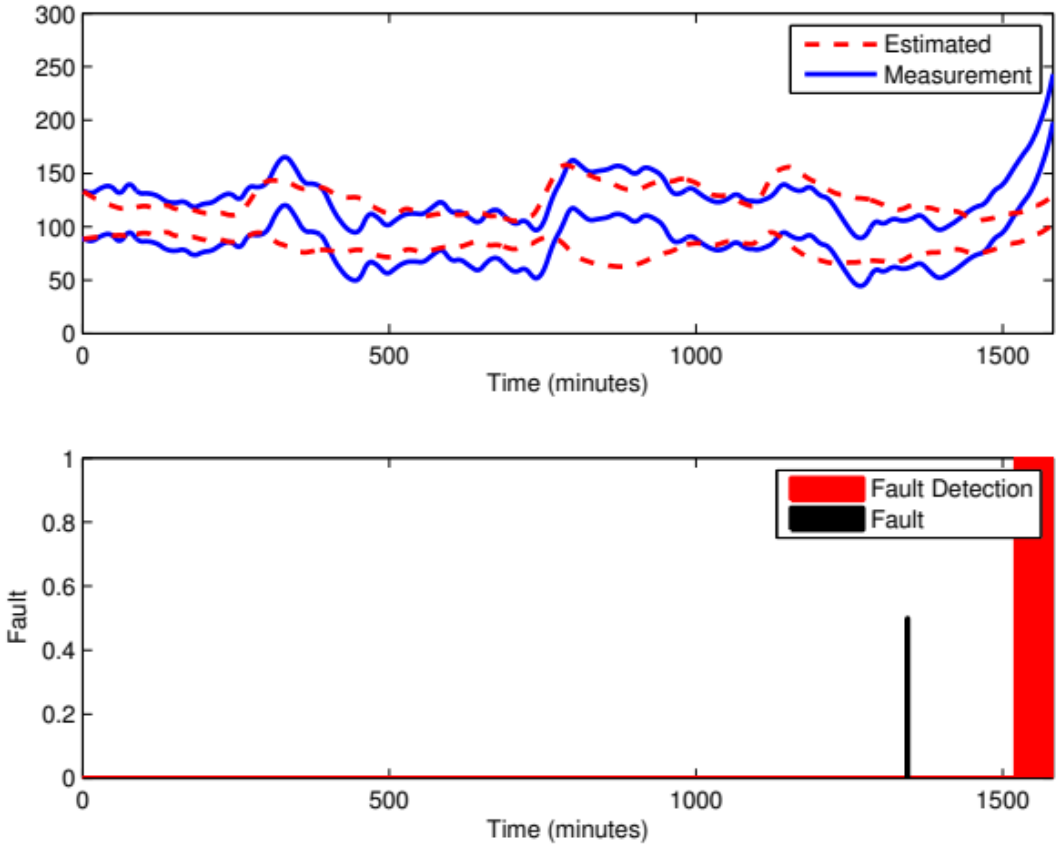

Figure 2: Graphic representation of an interval model-based fault detection approach. In the upper graph, blue solid line represents the interval measurements and red dashed line the estimated output. In the lower

graph, black short bar indicates the time the fault occurs and 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.

2.3.1 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 IVP with interval-valued parameters and/or initial values, this means 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 means of the utilisation of a sliding time window [8].

In fault detection, data from the system are needed to compare the real system behaviour 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 a time point t can be calculated starting from the initial time point $t_0=0$, which is represented by $Y(t \vee t_0)$, or $Y(t \vee t_j)$ 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 less missed alarms, than the ones obtained using a single window length, whatever the length 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 $Y(t \vee t-w_1)$ is larger than the one to calculate $Y(t \vee t-w_2)$ when $w_1>w_2$, the logical strategy is to first use the shortest window length and stop

when a fault is detected, thus saving computing effort and minimising the rate of missed alarms. The maximum window length used depends on the available computing time and on the accuracy of the used model.

The algorithm implementing the presented interval model-based fault detection system is summarised in **Table 1**. Where, *Data* is a vector containing system inputs and measurements, *Wins* 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 **Section 2.5**) and $\hat{Y}(t)$ is the current interval measurement.

FD Algorithm(**In:** $Model$, $Data$, $Wins$, **Out:** $Fault$)

1. **for** each sample time **do**
2. $Fault = \textbf{false}$;
3. **for** $i = 1$ **to** $i \leq size(Wins)$
4. $\quad Y_{out}(t|t - Wins(i)) = Solver(Model, Data, Wins(i))$
5. $\quad$ **if** $Y_{out}(t|t - Wins(i)) \cap \hat{Y}(t) = \emptyset$ **then**
6. $\quad\quad Fault = \textbf{true}$; **break**
7. $\quad$ **else** $i = i + 1$
8. **endfor**

Table 1: Interval model based fault detection algorithm.

2.4 Type 1 Diabetic Subject Model

Several metabolic models of different complexities have been proposed to represent the glucose-insulin dynamics of a type 1 diabetic (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 et al. [19] is suitable for creating a type 1 diabetic subject simulator [20], but is not as useful as prediction model for a model predictive controller (MPC), since its complexity make

it difficult to identify its parameters. On the other hand, the minimal model proposed by Bergman et al. [4] may not sophisticated enough to be used in a T1DM simulator, but it may be suitable for MPC control and other algorithms that require glucose estimation or forcasting, 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 from [6] have been employed. A linear version of this model was successfully used by Gillis and colleagues [21] to predict glucose levels using a Kalman filter state estimation with meal announcement and with a prediction horizon of 45 minutes.

The Bergman minimal model is represented by the equations

$$\dot{G}(t) = -\left[S_G + X(t)\right]G(t) + S_G G_B + \frac{R_a(t)}{V_G}, \tag{7}$$

$$\dot{X}(t) = -p_2 X(t) + p_2 S_1\left[I(t) - I_b\right], \tag{8}$$

where G is plasma glucose concentration with $G(0) = G_b$, I is plasma insulin concentration with $I(0) = I_b$, where suffix 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

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

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

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

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, $S_1(t)$ 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 gastro-intestinal 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

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

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

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 $t_{interval} = \left[t_{meal} + t_{delay}, t_{meal} + t_{delay} + interval\right]$, being $D_{G_d}(t_{interval}) = D_G(t_{meal})/interval$ and *interval* fixed to 60 minute; 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 minute in order to smooth the transition between the two absorption peaks, but it could also be an additional parameter to identify.

2.5 Solving IVPs using Modal Interval Analysis

As already mentioned in **Section 2.2**, interval computations have the problem of overestimating the results due to 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 **Section 2.4** was discretized using a first forward difference derivative approximation (1 minute 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 minimise the overestimation due to the multiple instances of variables that could not be eliminated. Thus, the following equations were obtained,

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

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

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

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

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

$$X(k+1)=X(k)+p_2\left(S_I I(k)-dual(X(k))\right)T_S, \tag{19}$$

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

where k indicates the current sample, T_s is the sample time (i.e. 1 minute) and *dual* is a modal interval operator defined as $dual([a,b]):=[b,a]$, being a 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 $I(0)$ that 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 the **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 $f^{\dot{c}}$ algorithm [16], based on branch-and-bound techniques and MIA, could have been employed to reduce such overestimation.

When using the sliding time window strategy presented in **Section 2.3.1**, at each simulation step, the states of the model are set to their corresponding values at the beginning of the simulation window (e.g. $X(0)=X(k-win)$), with the exception of $G(0)$ that is set to the actual glucose measurement at the beginning of the window (i.e. $G(0)=\hat{G}(k-win)$) with the corresponding uncertainty.

Regarding the length of the sliding time window, a 60 minute window length was proved to be effective in terms of sensitivity and specificity. Therefore, the use of multiple window lengths was not considered necessary. In the case of different type of faults with different dynamics, the use of multiple window lengths could be considered.

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}) corresponds to $\hat{Y}$ in **Table 1**.

2.6 Estimation of Interval Parameters

One common difficulty when using interval analysis for solving IVPs is to define the intervals associated to model parameters and initial conditions of the ODE system. One way to tackle this problem is using 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 intra-subject variability, interval parameters were only used to deal with the errors introduced in the modelling process and the errors associated to measurements. In order to define such intervals, classic parameter identification techniques were employed to calculate the centre 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 define 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 behaviour during the identification phase (see **Figure 3**).

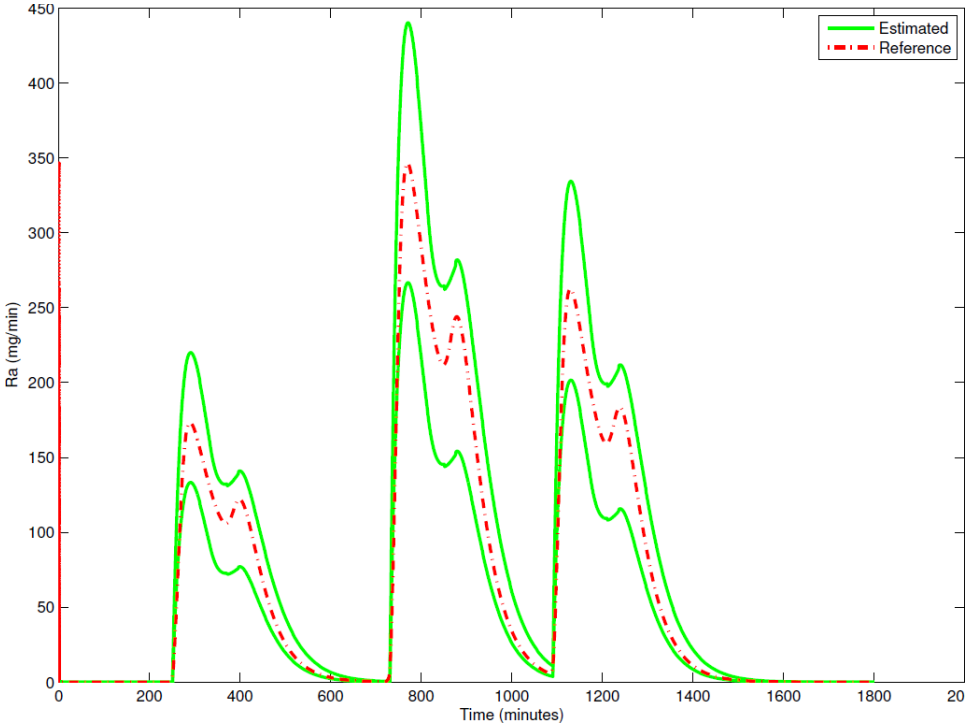

Figure 3: Interval estimation of R_a (solid green line) vs. reference value from the T1DM simulator (dotted red line). The data corresponds to a scenario with 3 meals.

(18)

2.6.1 Center of Interval Parameters

For calculating the centre of the interval parameters, the *fmincon* optimisation 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 3 employes models were identified separately in order to avoid identifiability problems.

To identify the glucose absorption model parameters (t_{maxG}, t_{delay} and A_G), the meal protocol (i.e., carbohydrates and intake times) and glucose rate of appearance (R_a) data were respectively used as input and output data. Note that R_a data is difficult to obtain in normal clinical practice, since it requires the use of a complex multi-tracer oral glucose protocol [25]. However, different approaches [26, 27] have been proposed for estimating R_a 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 (s.c.) 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 (S_I, V_G, S_G and p_2). Note that previously identified model parameters for R_a and s.c. insulin absorption models were used for identifying the endogenous model parameters.

2.6.2 Width of Interval Parameters

Table 2 shows the selected uncertainty for each one 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 absorption (t_{maxI}) 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 $X=\left[x-n\%\,x\,,x+n\%\,x\right]$, 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.

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

Table 2: Uncertainty on model parameters and inputs of the T1DM diabetic model expressed in percentage (%).

It is important to remark that in a real clinical scenario, this uncertainty should be individualized to each diabetic subject in order to cope with intra-subject variability. For this purpose, the method proposed in [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 of 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 modelled. However, the considered uncertainty associated to the CGM measurement already incorporates the error due this modelling approximation.

2.7 *In-Silico* Protocol

As a first step to assess the performance of the presented fault detection system, a FDA-accepted type 1 diabetes mellitus simulator (T1DM simulator) was employed [20]. It is important to remark 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 vs. 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, the 10 adult diabetic 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 minimise the post-prandial peak and to avoid hypoglycaemia was used. Two meal protocols (i.e. different meal ingestion times and different amounts of ingested carbohydrates) were employed. The first meal protocol (6am (30g), 2pm (60g) and 8pm (45g)) was used to identify the model parameters while the second one (6am (60g) 1pm (70g) 7pm (30g)) was used to test the fault detection technique. The idea of using two different scenarios for tuning the model and testing the fault detection algorithm was to create a more realistic benchmark. Nevertheless, it is important to emphasise 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 hours. However, a 30 hours simulation period was used in order to have enough time to detect faults occurring at the end of the 24h period. The faults consisted in a complete suppression of the insulin infusion, which in 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 (G Detect.); insulin not delivered until the fault is detected (Lost Insulin); false negatives (FN) and false positives (FP),

being a false negative a fault not detected before 400 minutes. Finally, although there is no consensus definition of what constitutes diabetic ketoacidosis in term of plasma glucose concentration [28], a threshold of 300 mg/dL was establish as a safety limit to evaluate the performance of the fault detection system.

3 Results

Table 3 shows a summary of the results. Despite the detection interval being occasionally long, all faults were detected before the plasma glucose concentration reached the pre-defined 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 hours of non-faulty simulation), which demonstrates the robustness of the proposed approach. **Figures 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.

Subj	Time (min)	G Detect. (mg/dL)	Lost Insulin (U)	FN/FP
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

Table 3. Fault detection results for the 10 adult subjects of the T1DM simulator. Results are expressed as $Median \pm SD$.

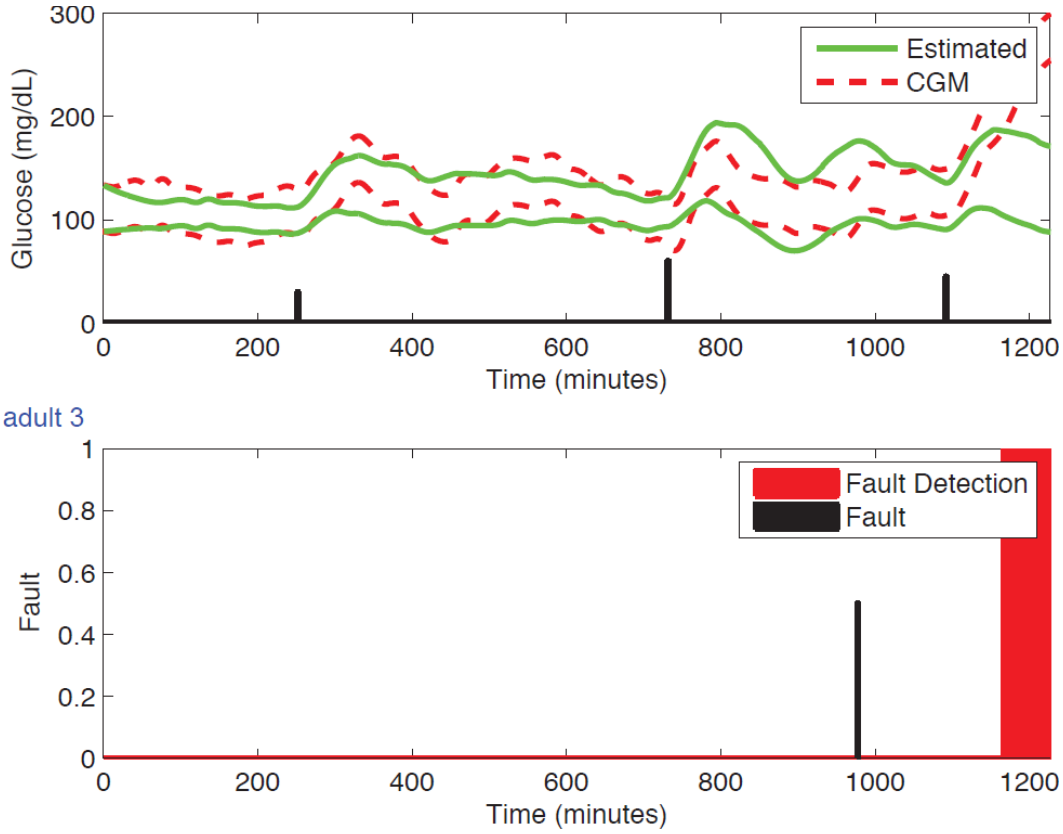

Figure 4: Example of fault detection in subject adult #3. In the upper graph, red dashed line represents the interval measurements and the green solid line the estimated interval output. In the lower graph, black short bar indicates the time the fault occurs and red long bar indicates the time the fault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

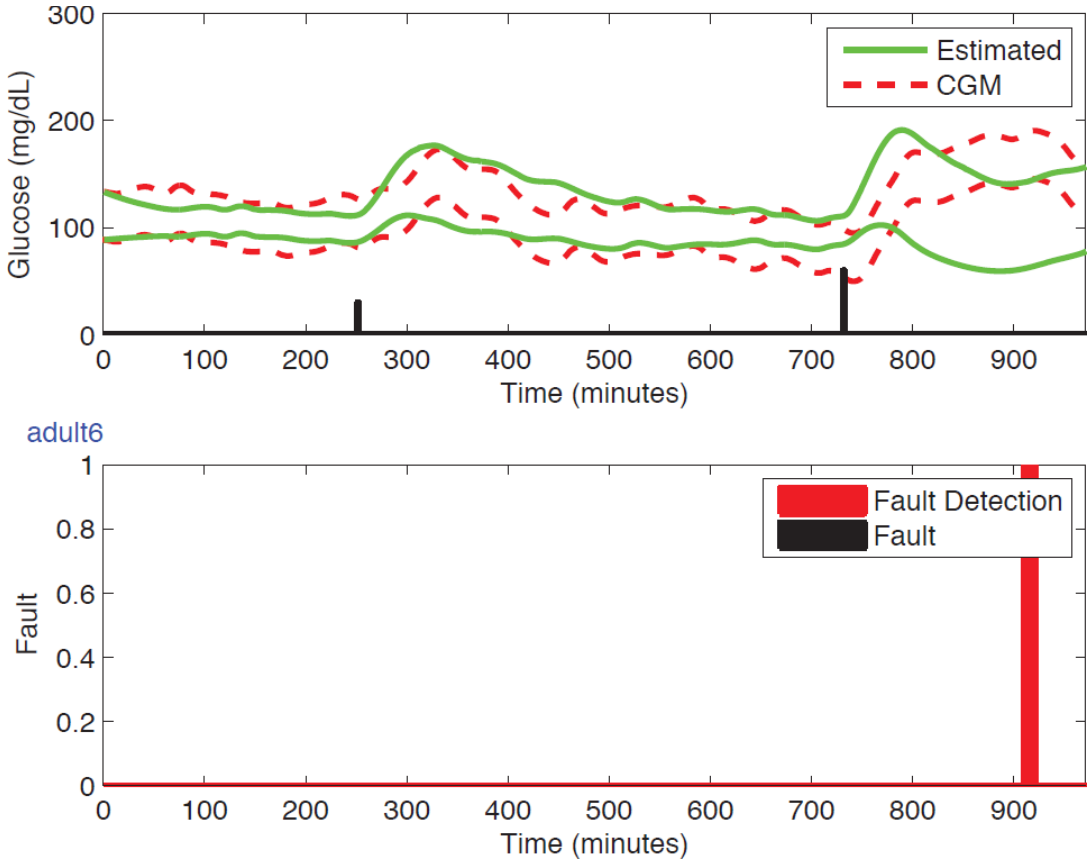

Figure 5: Example of false positive in subject adult #6. Note that around minute 900 the estimated interval output slightly falls below the interval measurement producing a false positive.

4 Discussion

Interval model-based fault detection has been proven to be an effective robust tool for detecting faults in continuous subcutaneous insulin infusion (CSII) systems using continuous glucose monitoring (CGM). In particular, disconnection of the insulin infusion set, which current available insulin pumps are not able to detect, has been successfully detected. The proposed technique has been validated using an FDA-approved type 1 diabetic (T1DM) simulator, which is an accepted method for *in-silico* the 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, Modal Interval Analysis (MIA) was successfully used to deal with the problem of numeric overestimation associated to 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 paper, 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, it 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 paper.

Intervals associated to 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 behaviour 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 intra-day variability, such as insulin sensitivity, different interval values could be used along the day, since trying to cope with all of the variability in a single interval would lead to low fault sensitivity.

Of the 100 *in-silico* tests, only 2 false negatives and 1 false positives occurred. These results demonstrate the robustness and high sensitivity of the proposed approach. However, the used

T1DM simulator does not account for intra-subject variability and other perturbation such as physical exercise or phycologic 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 been only 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 type of faults 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 detect discrepancies between the model and the real system. So, in a general setting where different faults can occur, it only can 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, USA) or Vibe (Animas Corporation, PA, USA). 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 type of mixed meals [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 utilisation. First of all, the employed model would need to be individualised for each subject using retrospective clinical 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].

5 Conclusions

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

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