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Detecting Failures of the Glucose Sensor-Insulin Pump System: Improved Overnight Safety Monitoring for Type-1 Diabetes

Andrea Facchinetti, *Member IEEE*, Simone Del Favero, Giovanni Sparacino, and Claudio Cobelli*, *Fellow IEEE*

***Abstract*— New sensors for real-time continuous glucose monitoring (CGM) and pumps for continuous subcutaneous insulin infusion (CSII), possibly mounted on the same device, opened new scenarios for Type-1 diabetes treatment. However, possible failures of either CGM or CSII can expose diabetic patients to risks that can be dangerous especially overnight. In this contribution we present a proof-of-concept method, developed in a state-space context and implemented through a Kalman estimator, to detect in real time possible overnight failures of the sensor-pump system by simultaneously using CGM and CSII data. The method is tested on two simulated and one real subject. Results show that the method is able to correctly generate alerts for sensor-pump failures and stimulates further investigation on its development.**

I. INTRODUCTION

DIABETES is a disease which causes abnormal glycemic values due to the inability of the pancreas to produce insulin (Type-1 diabetes) or to the inefficiency of insulin secretion and action (Type-2 diabetes). Patients affected by diabetes need to monitor their glycemic level during all day in order to control it and take countermeasures to keep it inside the normal range of 70-180 mg/dL as much as possible. Especially in Type-1 patients, diabetes management is normally based exogenous insulin infusions, whose scheduling and dosages are tuned on the basis of 3-4 finger-stick glucose measurements per day. Recently, new technologies have been developed in order to improve and facilitate diabetes therapy: sensors for Continuous Glucose Monitoring (CGM), minimally invasive devices which return real-time glucose measures every 1-5 minutes for up to 7 days [1]; pumps for continuous subcutaneous insulin infusion (CSII) which allow a more effective and physiological delivery of insulin [2]. Moreover, it has been demonstrated that their simple combination in an single device, the so-called sensor-augmented pump, allows a further reduction of time spent in hypoglycemia and hyperglycemia [3].

The availability of CGM sensors and CSII pumps gave new stimulus to the development of the so-called artificial pancreas, a system based on a closed-loop control algorithm that, receiving in input the glycemic value measured by CGM and other individual parameters, is able to infuse via CSII pump the optimal insulin dosage in order to keep glycemia in the normal range [4]. In such a system, a prompt detection of possible failures in either the CGM sensor or CSII pump is crucial for safety. Failures during day-time are less critical because the patient is awake and can promptly fix them. More dangerous is the night-time scenario, in which the patient is asleep and cannot take a timely countermeasure. Fig. 1 shows CGM (blue line) and injected insulin (blue bars) data in a representative Type-1 diabetic patient during night-time (23h00m-07h00m) in one of the experiments documented in [5]. As one can note, two unrealistic sudden falls on the CGM profile are visible around time 01h30m and 06h20m, which can be classified as spurious when one looks at the reference plasma glucose (red stars) measured in parallel.

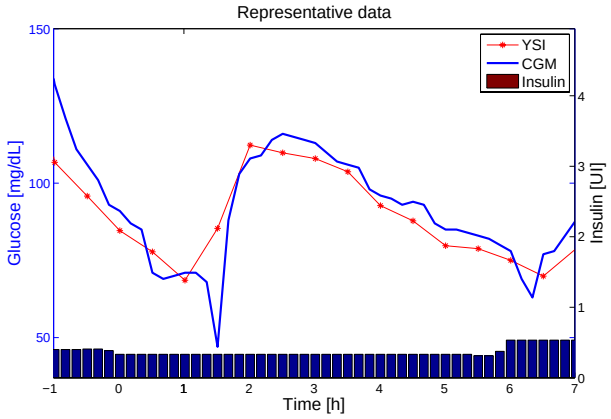

Fig. 1. Data collected during night-time (23h00m-07h00m) in a representative subject: CGM signal (blue line), insulin injected (blue bars), and reference YSI plasma glucose (red stars). Two unrealistic sudden falls on CGM profile are visible around time 01h30m and 06h20m

The aim of this work is to investigate if it is possible to detect overnight failures as those of Fig. 1 by resorting to a state-space model of CGM and CSII data suitably identified and used in predictor-form via a Kalman estimator.

II. METHODS

A. The failure-detection method

The failure-detection method (FDM) consists of four main steps:

1) Identification of a model, personalized on the patient, which describes the relationship between glucose level measured by CGM and insulin injected by the CSII pump;

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A. Facchinetti, S. Del Favero, G. Sparacino, and C. Cobelli* are with the Department of Information Engineering, University of Padova, Via G. Gradenigo 6/B, 35131 Padova, Italy (phone: +39 049 827 7803; fax: +39 049 827 7826; e-mail: {facchine,sdelfave,gianni,cobelli}@dei.unipd.it)

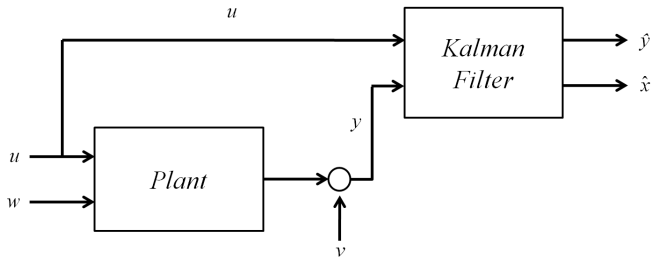

Fig. 2. Structure of the Kalman estimator. *Plant* denotes the system modeled using N4SID in step 1) of the algorithm, while the *Kalman filter* is created in step 2) on the base of the *Plant* model. Input *u* is the insulin injected by the pump, *w* and *v* are white noises, *y* is the glucose level measured by the CGM sensor, outputs $\hat{y}$ and $\hat{x}$ are the 1-step ahead predicted glucose level and predicted state-vector, respectively.

2) Derivation of a model-based Kalman filter estimator to obtain a real-time prediction of the future glucose level together with its variance;
3) Comparison between the glucose prediction and the next CGM sample;
4) Generation of a *failure alert* if the CGM sample is far from the predicted value.

Step 1). We resort to a discrete state-space model in the innovation form

$$x(t+Ts) = Ax(t) + Bu(t) + Ke(t) \quad (1)$$
$$y(t) = Cx(t) + Du(t) + e(t) \quad (2)$$

in which $x(t) \in \mathbb{R}^n$ is the state vector at discrete time t, $u(t) \in \mathbb{R}$ is the insulin injected by the pump at time t, $e(t) \in \mathbb{R}$ is the innovation, a white noise of variance Var$[e]$ estimated form the data, and $y(t)$ is the glucose level measured by the CGM sensor at time t. Our implementation in Matlab®(Version R2010a, The MathWorks, Inc, Natick, MA) employed the N4SID approach (*n4sid* function of the *System Identification Toolbox*), a numerical algorithm for subspace state identification, see [6] for details.

Step 2). From the so-identified model, we derive a discrete-time Kalman predictor, see Fig. 2. The Kalman filter inputs are CGM $y(t)$ and insulin $u(t)$, and the output is the 1-step head prediction of CGM $\hat{y}(t|t-Ts)$. Since N4SID gives a model in innovation form, the Kalman filter prediction can be obtained simply computing at each time instant the innovation

$$e(t) = y(t) - \hat{y}(t|t-Ts)$$

and plugging $e(t)$ in (1):

$$\hat{x}(t+Ts|t) = A\hat{x}(t|t-Ts) + Bu(t) + Ke(t)$$
$$\hat{y}(t|t-Ts) = C\hat{x}(t|t-Ts) + Du(t)$$

Step 3). The prediction of the Kalman filter $\hat{y}(t|t-Ts)$ is compared with the next glucose level measured by the CGM sensor, i.e. $y(t)$. The comparison consists in evaluating if $y(t)$ overcomes the confidence interval given by $(\hat{y}(t|t-Ts) - kSD, \hat{y}(t|t-Ts) + kSD)$, where SD is the standard deviation of the estimated value and k a suitable positive integer. Once again, since the identified model is innovation form [7], SD is simply the square root of the innovation variance,

$$SD = \sqrt{\text{Var}[e]}$$

and Var$[e]$ is estimated by N4SID form the data.

Step 4). For failure alert generation, in this preliminary implementation, every time $y(t)$ overcomes the confidence interval $(\hat{y}(t|t-Ts) - kSD, \hat{y}(t|t-Ts) + kSD)$, a *failure alert* is generated.

B. The database

1) Real Subject: one dataset has been extracted from a larger database which consists of several open-loop and closed-loop experimental trails [5]. The specific dataset consists of two blocks of data of about 20-hour length, collected on the same patient, the first is relative to the open-loop experiment (i.e. with standard insulin therapy), and the second is relative to the closed-loop one. Each block is composed by: a CGM time series, measured with the FreeStyle Navigator (Abbott Diabates Care, Alameda, CA), with one sample every 10 min; information about insulin infusion, delivered through the Omnipod system (Insulet Corp, Bedford, MA); and frequently sampled blood glucose (BG) values drawn by using YSI instrument (YSI Incorporated, Yellow Spring, OH). Because each set of data has been collected on different time grids, each time series has been first interpolated by resorting to a Bayesian smoothing procedure [8], and then resampled in a 10-min evenly spaced grid. It has been shown in [9] that the coupling between injected insulin and meal intake in traditional open-loop therapy strongly affects the quality of the identified model. In view of this, model identification will be performed on closed-loop part of the dataset, which has significantly less coupled inputs, while FDM will be tested on the open-loop part of the dataset.

2) Simulated Subjects: the real subject data allowed us to construct two *in silico* subjects. Starting from reference plasma glucose (YSI data), we generated a simulated faultless CGM time series. On this time series simulated faults were introduced at specified times in order to challenge FDM to detect all and only the simulated faults. The generation of a faultless CGM time series from YSI data is possible because YSI values have been frequently sampled (in the original grid, one sample every 30 minutes). Since YSI is measured in plasma, while CGM is measured in the interstitial fluid, we first obtained interstitial glucose (IG) data from BG by convolving YSI measures with a single-exponential function $h(t) = \frac{g}{\tau} e^{\frac{-t}{\tau}}$ which is usually exploited to describe the plasma-to-interstitial fluid kinetics [10]. In the specific, we set $g = 1$ and $\tau = 15$ minutes. Finally, in order to simulate CGM data, which are a noisy version of IG, a zero-mean white Gaussian noise with variance $\sigma^2 = 2$ mg^2/dL^2 has been added to IG profile. These values are representative and similar to other used literature [11].

In the first simulated scenario (Simulation 1), an unreliable fall, similar to ones observed on the representative patient of

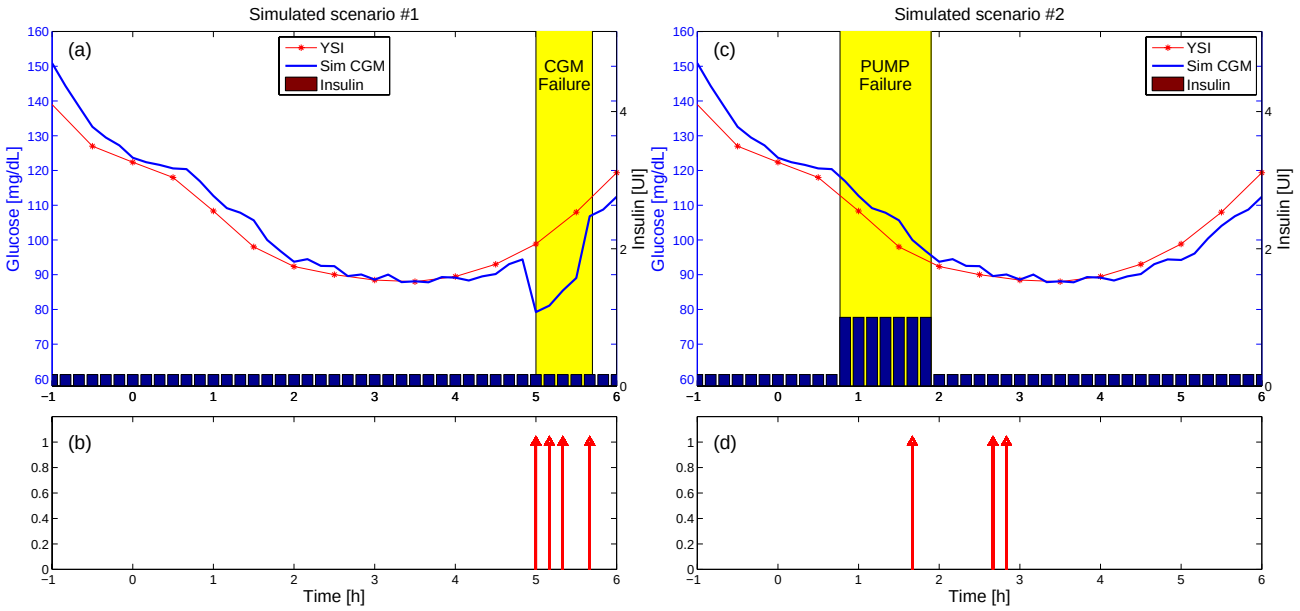

Fig. 3. Simulated data. (a) CGM failure scenario (location of CGM failure is evidenced in yellow): CGM signal (blue line), injected insulin (blue bars), and reference plasma glucose (red stars). (c) Pump failure scenario (location of pump failure is evidenced in yellow): CGM data (blue line), injected insulin (blue bars), and reference plasma glucose (red stars) are shown. (b) and (d) *Failure alerts* generated by FDM (red arrows).

Fig. 1, has been added to the CGM time series. This CGM failure consists in a spurious decrease in CGM data of 15 mg/dL in the time window 05h00m-05h30m.

In the second simulate scenario (Simulation 2), an insulin pump failure has been introduced. The original night basal insulin infusion from 00h50m to 01h50m, which has been delivered to the patient, has been increased to 1 for 7 consecutive samples. This replacement has the aim of simulating a condition in which the quantity that has been delivered is different from the one stored and visualized by the pump device. Fig. 3 depicts both the simulated scenarios. Panels (a) and (c) show the simulated CGM (blue line) and insulin infusion (blue bars) data. YSI data (red stars), not used by FDM, are also reported to evidence the real behavior of glucose concentration. Simulated failures are highlighted by the yellow boxes.

III. RESULTS

A. FDM training

The state-space model has been identified on the training set, using overnight insulin data and simulated CGM data. The choice of not using the original CGM values is due to the fact that we do not want FDM to learn failures. The best dimension of the state vector has been set equal to 3. The number k of SD values which compose the confidence interval has been set to 3, which is a reasonable compromise in order to evidence dangerous outliers.

B. Simulated data

Simulation 1 (CGM failure). Panel (b) of Fig. 3, which is relative to the CGM failure scenario of panel (a), depicts with red spikes all time instants in which FDM generated a *failure alert*. A total of 4 alerts have been given, located at 05h00m, 05h10m, 05h20m, and 05h40m. All of them are exactly in correspondence of the simulated failure. The first three alerts are generated as consequence of the rapid decrease of CGM (beginning of the failure). The last alert, on the other hand, is due to the rapid increase which characterizes the end of the failure. This results evidence that FDM is able to correctly and promptly detect such a kind of event. No false positives have been generated.

Simulation 2 (pump failure). Panel (d) shows the results of the application of FDM to the pump failure scenario on panel(c). FDM generated three *failure alerts*. The first is located at time 01h40m, about 40 minutes after the beginning of the failure, and the other two at time 02h40m and 02h50m. All alerts can be associated to not-detected changes in CGM behavior. In fact, the rapid increase of the total amount of insulin injected should have reduced the glycemic concentration more than what has been measured by CGM, but this did not happen. Of note is that all three alerts are delayed with respect of the beginning of the failure. This is not surprising, in fact the effect of insulin action on glycemic concentration can be observed only after 40-50 minutes because of both physiological and technological delays [4], [12].

C. Real data

Fig. 4 (a) presents the real scenario observed during the experiment. As in Fig. 3, CGM data (blue line), insulin infusion (blue bars), and YSI data (red stars) are displayed. Analyzing the data, no problems have been detected in the insulin pattern. On the other hand, the CGM profile presents a sequence of oscillations (00h40m-01h40m) and a loss of sensitivity (04h50m-05h30m) that are not present on YSI measures. These two events can be considered as failures.

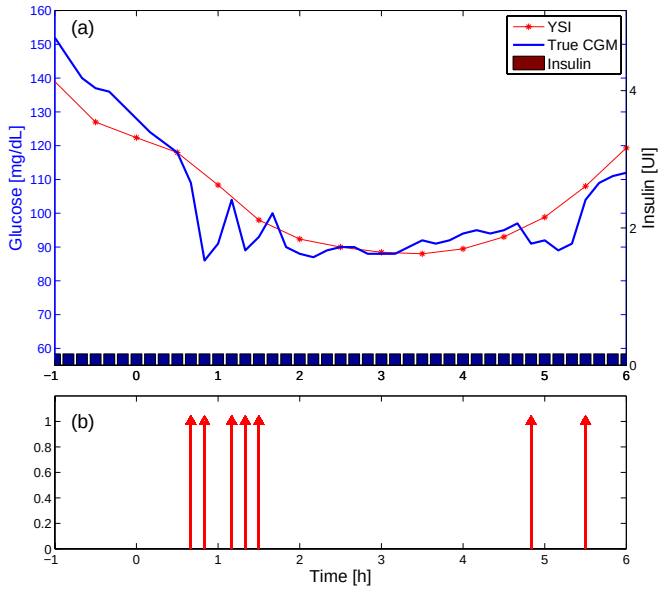

Fig. 4. Real data. (a) CGM signal (blue line), injected insulin (blue bars), and reference plasma glucose (red stars). (b) *Failure alerts* generated by FDM (red arrows).

The results of the application of FDM are displayed in panel (b). Six *failure alerts* have been generated. Four are in correspondence of the sequence of oscillations on CGM data, while the other two have been generated at the beginning (04h50m) and at the end (05h30m) of the second episode. No false positives have been generated.

IV. CONCLUSIONS

CGM sensors and CSII pumps are new technologies that can significantly improve therapy and quality of life in diabetic patients. However, as any electronic system, they are not free form failures. In this work, we presented a method to detect in real time some of the possible failures of the sensor-pump system during the night period on the base of CGM and CSII data. Results obtained on two simulations demonstrated that such a system is able to satisfactory detect both CGM and pump failures. Results on the real dataset confirmed those on simulation. Although the present work is largely still out a proof-of-concept, from the preliminary analysis made, sensor failures seem more easily detectable than pump failures. This can be explained by the fact that the gain of FDM has been tuned to catch short-term errors in the CGM-pump system. Since changes in the insulin basal pattern during the night can be observed on CGM only after some time, as well as the effect of long-term failures in CGM such as drifts, a proper tuning of the gain of FDM together with a longer prediction horizon appear to be required to track such events.

Further works will concern: method assessment on a larger simulated dataset, for instance by resorting to the UVa/Padova Type-1 Diabetic Simulator [13], which will allow to reproduce more harmful scenarios, especially concerning pump failures (e.g. simulating basal insulin infusions greater than the ones visualized to the user); the use of longer prediction horizons, to track long-term failures; and the evaluation under different input combinations. From the methodological point of view, other identification techniques, which can take into account feedback, will also be considered.

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