Detecting Sensor and Insulin Infusion Set Anomalies in an Artificial Pancreas

Nihat Baysal, Fraser Cameron, Bruce A. Buckingham, Darrell M. Wilson, B. Wayne Bequette

Abstract—Continuous subcutaneous insulin infusion pumps and continuous glucose monitors enable individuals with type 1 diabetes to achieve tighter blood glucose control, and are critical components in a closed-loop artificial pancreas. Insulin infusion sets can fail and CGM sensor signals can suffer from a variety of anomalies. In this paper algorithms are developed to detect infusion set failures and sensor signal anomalies; both in-patient and outpatient studies are presented. A threshold-based method, based on high glucose concentrations, is shown to be adequate to detect infusion set failures. Pressure-induced sensor attenuation (PISA), which can occur when a subject rolls over and puts pressure on their sensor, is a particularly challenging problem. An algorithm based on non-physiological rates-of-change, coupled with a maximum attenuation time window, is developed to detect and compensate for PISAs. These algorithms can be used either in advisory mode for current open-loop technology, as well as an additional safety/fault detection layer as part of a fully closed-loop artificial pancreas.

I. BACKGROUND

INDIVIDUALS with type 1 diabetes mellitus (T1DM) must inject insulin to regulate their blood glucose concentration. T1DM individuals often begin with basal-bolus therapy, where they give themselves one injection of long-acting insulin, to cover their “steady-state” (basal) needs, and several injections of rapid-acting insulin, often to cover their meal carbohydrates, each day. During the past twenty years, more and more people with T1DM have begun to use continuous insulin infusion pumps, which deliver micro-boluses throughout the day, to achieve steady-state needs; they then use the pump to give boluses (higher delivery rates for brief periods of time) to cover their meal-related insulin needs. More recently, continuous glucose monitors (CGM) provide measurements related to the blood glucose values, typically at 1 to 5 minute intervals; the sensor itself resides just underneath the skin, therefore measuring the interstitial fluid glucose levels. With the two components, actuator and sensor, of a closed-loop system commercially available, it is natural to think about interfacing them with a controller to form a closed-loop artificial pancreas.

The progression towards a closed-loop artificial pancreas has been naturally occurring in stages. CGM signals can be used to provide a warning if an individual is in danger of becoming hypoglycemic (low blood glucose) or hyperglycemic within the near future (Palerm and Bequette, 2007). Further, particularly if an individual does not respond to hypoglycemic alarms, the pump can be turned off in a low glucose suspend system (Choudhary et al., 2011; Cameron et al., 2012a). A control-to-range strategy is used to maintain glucose between lower and upper limits, while minimizing the changes in insulin infusion from basal rates (Kovatchev et al., 2009; Grosman et al., 2010). Control to a specific setpoint can be implemented in the form of PID (Weinzimer et al., 2008; Palerm, 2011; Steil et al., 2011), MPC (Hovorka et al., 2004; Cameron et al., 2011; Percival et al., 2011; Soru et al., 2012), as well as other algorithms.

While there has been much progress towards the development of a closed-loop artificial pancreas during the past five years (for a review, see Bequette (2012)), there remain some critical challenges to full-scale commercial development. In this paper we focus on two critical challenges: sensor anomalies, and insulin infusion set failures. We first provide examples of each in Sections II and III, then discuss various approaches/algorithms to solve these problems in Sections IV and V.

II. SENSOR ANOMALIES

CGM signals can be corrupted by measurement noise, biased by miscalibration, suffer from communication dropouts, and can attenuate due to the compression/tension of the tissue where the probes reside. Detecting and compensating for these errors and artifacts is critical to preventing erroneous clinical decisions to be made based on the sensor outputs. These problems can be exacerbated by the controller lead action necessary to compensate for the 3-10 minute time-lag (Rebrin et al., 1999; Steil et al., 2003) between the blood glucose levels that we wish to regulate and the interstitial fluid glucose levels that are measured by the sensors.

Here we divide the sensor anomalies into three types: fouling, dropouts, and attenuations.

II.1 Sensor Fouling

Over time the sensor gain changes, due to fouling of the sensor in contact with the skin tissues. This can occur due to knocking or displacing sensor, or through a bodily reaction to the electrode penetrating into the skin. Primarily this manifests as a slow decrease in the sensor gain over time, although some motion can restore circulation and restore the sensor gain; see Fig 1 for an example of sensor fouling. Currently, fouling is primarily handled by frequent recalibration of the sensor using reference glucose fingerstick measurements.
II.2 Sensor Communication Dropouts

There are often periods of time where there is a loss of signal from the sensor, or the controller does not receive the signal, as shown in Fig. 2.

Acting intelligently during sensor dropouts requires extrapolating the sensor readings and uncertainty into the gap. A Kalman predictor (without the measurement update) can be used for short-term predictions in this situation. For longer time periods it is necessary to provide a CGM loss-of-signal alarm or (particularly if there is no response to the alarm overnight) revert to basal insulin delivery.

II.3 Sensor Signal Attenuation

A major challenge is pressure-induced sensor attenuation (PISA), which can occur when an individual rolls over on their sensor\(^1\); an example is shown in Fig. 3 where there are several consecutive time periods with sensor attenuation. Any control algorithm acting on the raw, attenuated, signals would likely shut-off the pump, leading to unnecessarily high mean glucose values. An example of this is shown clearly in Fig. 4, where a predictive pump shut-off (PSO) algorithm has shut-off the pump for a period of time where there is clearly a PISA.

\(1\) We have previously referred to these as nocturnal sensor attenuation (NSA), since it frequently happens overnight.

Detailed analyses of the biomechanical issues related to signal attenuation are given by Helton et al. (2011a,b).

III. INSULIN INFUSION SET FAILURE

Detecting failures in the actuator, the insulin infusion pump, is as important as ignoring sensor anomalies. Some Infusion set failures (ISF) can be detected internally by the pump (high pressure), while others can only be detected with more information.

III.1 Insulin Pump Alarms

Insulin infusion pumps have high pressure and related alarms, to alert the user when a catheter occlusion has likely occurred. van Bon et al. (2012) note that, depending on the basal insulin infusion rate, it may take 2-4 hours after an occlusion before the alert is activated.
III.2 Infusion Set Problems

Infusion sets typically last 3-5 days before the infusion site fails. During normal operation the pump creates a bubble of insulin under the skin. The insulin then osmoses into the bloodstream and acts. The body can react to this invasion through swelling and/or pain at the site. Swelling or skin contortions can allow insulin to leak out of the body, creating a mismatch between commanded and delivered insulin. This in turn leads to poor control due to inadequate insulin, as evidenced by high glucose levels. An example of a set failure is shown in Fig. 5; the glucose continues to rise after the set failure, with essentially no response to the insulin bolus commands given to the pump.

IV. Pressure-Induced Sensor Attenuation Detection

A sudden decrease in glucose levels that violates physiological limits on rate-of-change is the major characteristic of a nocturnal sensor attenuation. In order to decide when a PISA ends, upcoming CGM data should be evaluated for at least 15 minutes or three readings and an increasingly negative rate-of-change should be observed. There are two approaches for the detection and the recovery of nocturnal sensor attenuations: If the whole trajectory of CGM readings are known, the retrospective analysis gives better results than the real-time analysis which is aimed to be applied during real-time operations. The retrospective analysis method is particularly useful as an automated way of analyzing large amounts of out-patient data for sensor anomalies; out-patient data does not have reference glucose values to serve as a reference standard for the CGM signal.

IV.1 Retrospective

The retrospective detection assumes that signal attenuations are large, high frequency, negative disturbances to the glucose concentrations, and uses a weighted least-squares fit to the CGM readings and a trust calculation to determine the weighting applied to each reading.

The least-squares fit selects the glucose estimates that minimize a weighted disagreement with the CGM readings and the second derivative of the glucose level. The trust calculation sets the weights for each CGM reading according to how far they fall below the estimated glucose levels. Full weighting is given to readings that are less than 10 mg/dL below the glucose estimates. The two steps are iterated until the estimated glucose levels converge.

IV.2 Real-time

In real-time operation, it is essential to detect when the CGM readings become attenuated and when they return to normal (recovered). The following parameters are used to decide whether a signal is attenuated or just recovered from previous attenuation:

- CGM rate of change (first derivative)
- Kalman filter likelihood
- Rate of change of CGM increase rate (second derivative)
- Maximum attenuation time window

IV.3 Results

Both the retrospective and real-time analysis methods are tested by using the night-time data obtained from in-patient studies where reference YSI (“gold standard” laboratory measurements) glucose values were also recorded along with CGM measurements. Note that neither the retrospective nor the real-time methods make use of the reference glucose values – these are used to better understand the limitations to the CGM devices. For out-patient studies, since the subjects are in a home environment, there are no reference glucose values available.

There are four examples given in Fig. 6 in which the recorded CGM measurements and YSI values are given in black crosses and red squares. Retrospective analysis uses all CGM readings and smooths them out to create the weighted distribution (green line). In real-time analysis, CGM readings are handled consecutively, assuming that upcoming data point is not known and the method predicts whether the glucose measurement is attenuated. In these examples the negative rate of change in glucose measurement (first derivative) of 2.5 mg/dL is taken as the threshold for attenuation. If there is a CGM signal dropout for more than 10 minutes, the projected glucose value coming from the Kalman predictor is used to calculate the derivative. Once the signal is flagged as attenuated, the method starts checking the rate of change in CGM measurement increase (second derivative). At this time the minimum PISA time window of 15 minutes or at least three CGM readings (Kalman predicted, if necessary) is needed to detect a recovery from attenuated state. When two consecutive negative second derivative values are obtained within the maximum PISA window of 120 minutes, the method flags the reading as recovered. The PISA results are given in Fig. 6 with blue arrowheads. In the top left plot, after a few CGM signals there is a long period without an available signal; and there appears to be an initial calibration error. The top right plot illustrates a case with multiple consecutive PISAs, also there is some bias in the CGM value towards the end of the time frame. The bottom left bottom shows a well-
controlled glucose level with a single PISA. Finally, the bottom right plot has one major period with a PISA, and a substantial increase in glucose during the second-half of the data.

![Figure 6](image6.png)

**Figure 6.** Real-time and retrospective detection of pressured-induced sensor attenuations (PISA) in four different patients. Predicted invalid reading regions are shown in blue arrowheads (▲). Green line indicates retrospective estimate values based on valid glucose measurements. CGM measurements and YSI values are given in black crosses (+) and red squares (●), respectively. Neither the retrospective nor real-time methods make use of the reference glucose values.

## V. Infusion Set Failure Detection

Insulin set failures can be detected directly by pump pressure sensors, indirectly by a lack of insulin action on glucose, or even more indirectly through a loss of glucose control. The model-based method covers the second option while the multivariate statistical analysis and threshold approaches cover the third.

### V.1 Model-Based Analysis (MBA)

Using an interactive multiple model method (Cameron 2012b) we postulate one case where insulin is fully effective and another where insulin is completely ineffective. While both cases evolve over time according to its fit with the data, the probability of the failure case is repeatedly added to by 1% of the non-failure case. This reflects the chance that a set will have just failed. The relative probability of the failure case is thresholded to serve as an alarm of set failure. This method, since it uses the analytic redundancy of glucose and insulin has the potential to detect set failures before the glucose level becomes dangerously elevated.

### V.2 Multivariate Statistical Analysis (MSA)

Set failures tend to result in elevated, rising glucose levels. The MSA approach uses the slope of the glucose level calculated over the last two hours. In addition it tests the last 10 readings over the last 45 minutes against the principal direction. The principal direction was calculated as the direction corresponding to the largest singular value for 10 simulated data sets. A set failure is detected then if the slope and magnitude in the principal direction are outside a preset region (Rojas 2011a, Rojas 2011b).

### V.3 Threshold Detection

If the infusion set has failed, then less insulin is being delivered and the glucose levels will rise unless more insulin is added. We can detect this rise through a simple glucose threshold of 305 mg/dL. Additionally, to prevent excessive false positives, we impose a 6 hour delay between set failure alarms. Lastly, to prevent false alarms at the replacement of a failed set, alarms are withheld until the glucose level is first below 250 mg/dL.

### V.3 Results

Data was collected from 88 insulin set insertions under two protocols. In each of the insertions, the patients were instructed to keep the sets in until forced to remove them by pain, inflammation, or failure. 15 sets had failed correction boluses, the glucose level did not drop by 50 mg/dL. The time of the set failure was determined retrospectively as the center of the trough before the failure. The results of the three methods are summarized in Table 1, with an example in Fig. 7. Since a set failure is an event with duration, we describe the detection performance in terms of the percent detected, the time after the failure’s start, and the glucose level at detection. To provide the other side of the metrics the number of false positives are reported.

![Figure 7](image7.png)

**Figure 7.** Glucose and insulin over the life of an insulin infusion set. ‘Set Failure’ indicates the likely start of the failure. The grey, red, and black diamonds show online set failure detection using the model, data, and threshold based detectors respectively.

### Table 1: Comparative Set Failure Detection Results.

<table>
<thead>
<tr>
<th>Method</th>
<th>TP day</th>
<th>TP/TP+F (%)</th>
<th>Median Time to Detection (min)</th>
<th>Glucose at Detection (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBA</td>
<td>0.43</td>
<td>0.73</td>
<td>181</td>
<td>277</td>
</tr>
<tr>
<td>MSA</td>
<td>0.36</td>
<td>0.73</td>
<td>240</td>
<td>315</td>
</tr>
<tr>
<td>Threshold</td>
<td>0.33</td>
<td>0.73</td>
<td>225</td>
<td>313</td>
</tr>
</tbody>
</table>

### Conclusions and Future Work

Currently we are conducting out-patient (in-home) studies of a pump suspension algorithm (low glucose suspend) to mitigate overnight hypoglycemia. These studies, like those on the closed-loop artificial pancreas, require methods to
prevent inappropriate suspensions from sensor anomalies, and methods to prevent nights spent with failed insulin pumps. With effort and testing, these methods will serve as the basis for protecting patients both for pump suspension therapy and closed-loop therapy in the future.

ACKNOWLEDGMENT

We wish to acknowledge our colleagues Winston Garcia-Gabin and Ruben Rojas for the MSA methods for infusion set failure detection.

LITERATURE CITED


