

**Formal verification of Artificial Pancreas**

by

**Suhas Akshar Kumar**

B.E., People's Education Society Institute of Technology, 2013

A thesis submitted to the

Faculty of the Graduate School of the

University of Colorado in partial fulfillment

of the requirements for the degree of

Master of Science

Department of Electrical Energy and Computer Engineering

2016

This thesis entitled:  
Formal verification of Artificial Pancreas  
written by Suhas Akshar Kumar  
has been approved for the Department of Electrical Energy and Computer Engineering

---

Prof. Sriram Sankaranarayanan

---

Prof. Pavol Cerny

---

Dr. David Maahs

Date \_\_\_\_\_

The final copy of this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

## Abstract

Suhas Akshar Kumar, (M.S., Electrical Energy and Computer Engineering)

Formal verification of Artificial Pancreas

Thesis directed by Prof. Sriram Sankaranarayanan

Modern medical devices like artificial pancreas system are safety critical. Malfunction of these devices can cause death or serious injury to the people using them. The artificial pancreas run complex control algorithms and there is a need to verify these control algorithms to minimize or eliminate failures during every day use by patients. Current clinical trials test these devices only for a few patients and do not test for the wide range of failure scenarios that could occur during daily use. Automated formal verification can test for corner case failure conditions that could be addressed before production. This thesis presents an approach to perform formal verification of artificial pancreas system using S-Taliro, a tool for testing for metric temporal logic (MTL) specification on Matlab(tm) based models. A spline based approach is used to test for properties related to the controller and a model based approach is used to test properties related to the closed loop system. A non deterministic predictive model is built using clinical data and future directions to check these predictive models are discussed. Violations are found for both the model based approach as well as the spline based approach. Violations are visualized and discussed and remedies are suggested. A non deterministic model is built using data and the model is simulated. Ideas about checking this model is presented. The violations can be used by the control system designer to find the root cause of the failure and to design a new controller that satisfies the specified properties. Violations from the spline based approach can be used to find such scenarios in actual

data and the information can be used to correct for such failures in the future controller designs. The non deterministic model built from patient data can be used to test controller's performance on individual patients.

## **Dedication**

To my parents Mrs V.K Geetha and Mr Akshar Kumar for always being there for me.

## Acknowledgements

I thank Sriram, my advisor during the 2 years at University of Colorado, Boulder. Under his guidance, I have learnt everything I know about cyber physical systems. This thesis would not be possible but for his constant support and encouragement.

Thanks to Faye Cameron for all the discussions and advice. Thanks to Dr David Maahs for the constant guidance in my research and also being part of my committee. I would like to thank Prof Pavol Cerny for being part of my committee and for the valuable feedback.

Thanks to the faculty at PES Institute of Technology and University of Colorado Boulder for my education. Thanks to my research group: Vris, Amin, Alex, Ashutosh and Hadi. I am grateful to Aditya for his ideas and suggestions. Thanks to my friends in Boulder for making my stay here exciting. Thanks especially to Sanket, Ankit, Pratap, Krishna, Sesha and Swapnil. Lastly, I want to thank my parents and my sister Spurthy for the constant love and support.

## Contents

<b>Chapter</b>	<b></b>
<b>1</b>	<b>1</b>
1.1	1
1.2	2
1.3	3
1.4	4
<b>2</b>	<b>6</b>
<b>3</b>	<b>8</b>
<b>4</b>	<b>9</b>
4.1	9
<b>5</b>	<b>12</b>
5.1	13
5.1.1	13
5.1.2	14
5.2	14
<b>6</b>	<b>16</b>
6.1	17
6.2	18

6.2.1	S-Taliro . . . . .	18
6.3	Properties and Results . . . . .	19
6.3.1	Control during low glucose levels . . . . .	19
6.3.2	Control during high glucose levels . . . . .	20
6.3.3	Comparing Closed and Open Loop Performance . . . . .	23
6.4	Discussion . . . . .	24
<b>7</b>	<b>Spline Based Testing</b>	<b>26</b>
7.1	Spline Model using SLM tools . . . . .	26
7.1.1	Splines . . . . .	27
7.1.2	Spline interpolation . . . . .	27
7.1.3	SLM Tools . . . . .	28
7.2	S-Taliro testing using spline model . . . . .	28
7.3	Properties and results . . . . .	28
7.4	Limitations . . . . .	30
7.5	Discussion and Conclusion . . . . .	30
<b>8</b>	<b>Delay Coordinate Embedding</b>	<b>34</b>
8.1	Introduction . . . . .	34
8.2	Non Deterministic model . . . . .	35
8.3	Delay Coordinate embedding . . . . .	36
8.4	Implementation . . . . .	36
8.4.1	Tries . . . . .	37
8.5	Simulation . . . . .	38
8.6	Ideas for verification of the model . . . . .	39
	<b>Bibliography</b>	<b>41</b>

## Tables

### Table

1.1	Pathway to the artificial pancreas project with representative papers showing technological feasibility. Source: Juvenile Diabetes Research Foundation (JDRF). See [28] for a recently proposed revised pathway. . . . .	4
6.1	Inputs to the closed-loop simulator. . . . .	19

## Figures

### Figure

1.1	Closed loop schematic diagram of the overall artificial pancreas system. . . . .	3
4.1	Schematic diagram of the hypo/hyper minimizing controller. . . . .	10
6.1	Illustration of the overall robustness-guided falsification setup. . . . .	16
6.2	Structure of a physiological insulin-glucose regulatory model. . . . .	17
6.3	Timeline of simulated events for the closed loop simulation. . . . .	18
6.4	Violation of property 1.1 . . . . .	20
6.5	Violation of property 1.2 . . . . .	21
6.6	Violation of property 1.3 . . . . .	21
6.7	Violation of property 1.4 . . . . .	22
6.8	Violation of property 2.1, 2.2 and 2.3 . . . . .	23
6.9	Violation of property 3.1 . . . . .	24
6.10	Violation of property 3.3 . . . . .	25
7.1	some splines . . . . .	27
7.2	property 1 . . . . .	29
7.3	property 2 . . . . .	32
7.4	property 3 . . . . .	32
7.5	property 4 . . . . .	32
7.6	property 6 . . . . .	33

7.7	property 7 . . . . .	33
8.1	Resulting time series after preprocessing . . . . .	37
8.2	Resulting time series after preprocessing . . . . .	38
8.3	Plot of the insulin on board curve . . . . .	39
8.4	Resulting insulin time series after binning . . . . .	40
8.5	Resulting glucose time series after binning . . . . .	40
8.6	Plot of the simulation curve . . . . .	40

# Chapter 1

## Introduction

This thesis presents two case studies on the use of robustness guided falsification techniques to falsify properties for the artificial pancreas. It further presents ideas on testing properties on models of insulin glucose dynamics built using actual patient data.

### 1.1 Type 1 Diabetes

Type 1 Diabetes (T1D) is a disease that occurs when the immune system destroys beta cells in the pancreas, the ability of the pancreas to secrete insulin is lost, since beta cells secrete insulin. Insulin is a key hormone in the regulation of glucose in the body. With the loss of regulation of glucose in the body, glucose in the blood can drop to below a threshold which can cause hypoglycemia or it can increase to levels above a threshold which can cause hyperglycemia. If left untreated mild hypoglycemia can cause fainting, Severe hypoglycemia can cause seizures, coma or even death. Likewise mild hyperglycemia over time can cause damage to organs like kidneys. Severe untreated hyperglycemia can cause a condition called ketoacidosis, this happens when there not enough insulin the body, without insulin the body cannot use glucose in the body, so the body breaks down fat, in this process waste products called ketones are produced the body cannot handle large amounts of ketones. Type 1 diabetes is usually treated using multiple daily injections of insulin. Recently, manually controlled insulin pump that deliver insulin subcutaneously is used as a treatment. The pump can be set to the control the rate of insulin delivery over time(basal insulin), the patient has to manually set the pump to deliver extra insulin before the meal(bolus

insulin) and also has to decrease the insulin delivery during physical activity. The disadvantage of this approach is that the patients have to be trained in using these devices and is error prone. Patients with T1D have an active role in the tight control of glucose in their body. This includes counting the amount of carbohydrates ingested from meals, monitoring glucose continuously either by a continuous glucose monitor or by other devices, and injecting the right amount of insulin at the right time. Many children and adolescents are diagnosed with T1D, which requires constant consistent care from parents. It is hard for children to manually count carbohydrates from meals and monitor blood sugar. Further, night time control of glucose is further complicated because the patient or the caregiver is asleep. The main danger with external insulin control is that delivering too much insulin can bring the blood glucose level down to dangerous levels which causes hypoglycemia. Delivering little insulin causes the blood glucose levels to rise and over time, results in long term damage to kidneys, eyes and peripheral nerves. Recently, ideas have been proposed for a device that performs automatic insulin control using closed loop control systems that use data from continuous glucose monitors and an insulin pump, inject the right amounts of insulin at the right time to ensure tight glycemic control in patients. This eases the burden of glycemic control on the patients and helps improve reliability in controlling glucose. This thesis discusses techniques to test these devices automatically using formal verification techniques for checking correctness properties of these systems.

## 1.2 Artificial pancreas project

The artificial pancreas project envisions a complete control system to automate the delivery of insulin that can be used as "de facto" cure for type 1 diabetes. To this end, it lays out stages of development for the device that would ultimately result in a very reliable and robust device that could be used to treat type 1 diabetes.

As shown in figure 1.1, the artificial pancreas consists of a continuous glucose monitor(CGM), an insulin pump that delivers insulin and a controller in closed loop that decides the amount of insulin to deliver based on the CGM measurements. Table 1.1 shows the stages of artificial pancreas

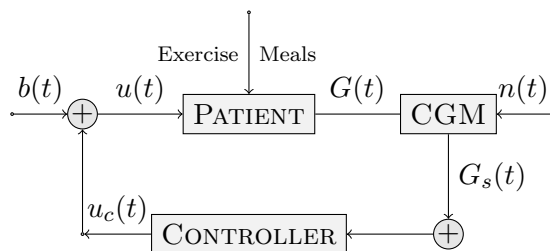


Figure 1.1: Closed loop schematic diagram of the overall artificial pancreas system.

that the juvenile diabetes research foundation(JDRF) envisions. The first generation device called the "very low glucose pump shutoff" shuts off the pump when it senses that the current CGM measurement is below a known threshold for hypoglycemia. The next generation device called the "Hypoglycemia minimizer" shuts off the pump if it predicts that the blood glucose would go below a threshold for hypoglycemia. The next device is the same as the "hypoglycemia minimizer" but it also minimizes hyperglycemia by introducing insulin when the blood glucose levels in the blood are high. The 4th generation device also gives an option to the user to introduce a manual insulin bolus in anticipation of meals, the next generation device automatically applies a bolus in anticipation of meals eliminating the need for user input. and finally the final version of the device uses glucagon in addition to insulin to achieve bidirectional control.

### 1.3 The need for verification

The artificial pancreas project could help in treating and curing Type 1 diabetes by automatically keeping patient's blood glucose in the euglycemic range and with minimal manual supervision. The patient could be exposed to many risks by using the Artificial pancreas system. If the artificial pancreas injects too much insulin, the patient's blood glucose level could go below the hypoglycemia threshold and which could cause the patient to go into coma or it could cause death. Also, if the artificial pancreas injects inadequate insulin in response to a meal then the patient could suffer from ketoacidosis. The control algorithm should provide reliable and robust response to unpredictable events like meals, physical activity and physical failures of pump and sensors. The software in the

Table 1.1: Pathway to the artificial pancreas project with representative papers showing technological feasibility. Source: Juvenile Diabetes Research Foundation (JDRF). See [28] for a recently proposed revised pathway.

ID	Description	Refs.
1	Low Glucose Pump Shutoff Pump shutoff during hypo.	[34]
2	Hypoglycemia Minimizer Pump shutoff for predicted hypo.	[10]
3	Hypo./Hyper. Minimizer #2 + additional insulin when glucose above threshold	[4, 36, 22]
4	Hybrid Closed Loop Closed loop insulin delivery with manual bolus	[25, 24, 23]
5	Fully Automated Closed Loop #4 with no manual boluses	[7, 8, 9, 13, 31, 26, 15]
6	Multi-hormone Closed Loop Use glucagon and insulin	[18, 17]

artificial pancreas should likewise be tested for the absence of runtime errors.

As medical devices become complex with many features and their use in everyday life increases, it is necessary to test these devices thoroughly before their release into the market. As of now, staged clinical trials are used to test these devices. Since, newer devices have complex control software to support their features, clinical trials, with their limited sample size are not enough to test many corner cases that could show up during widespread use. There is a need for continuous post market testing and remote monitoring in the population to find these corner case defects [21]. Correcting defects found in the field are expensive to fix, therefore these devices are tested in closed loop with *in-silico* complex models of human physiology.

## 1.4 Contributions

This thesis studies the *predictive hypoglycemia/hyperglycemia minimizer device* which is used to treat patients with type 1 diabetes . The controller consists of a Kalman filter which predicts future values of glucose based on past noisy samples. Further, using this predicted value and other rules, the controller either shuts off the pump, increases the basal rate or continues with normal delivery. The controller also processes the signal to detect sensor dropouts and pressure induced

sensor attenuation. There have been trials conducted on an previous version of this controller. The trials documented the efficacy of the controller in regulating glucose in the euglycemic range for the participants [8, 30]. This thesis uses simulation based falsification techniques to find violations of properties that specify the correct operation of the artificial pancreas system. In the first study the insulin glucose dynamics is modeled using the Dalla Man model [14, 32]. in the Matlab(tm) environment, the *predictive hypoglycemia/hyperglycemia minimizer device* controller which is specified in the Matlab(tm) environment is used in closed loop with this device, the combined closed loop is verified using a tool called S-Taliro [3] also written for use in the Matlab(tm) environment. S-Taliro uses the technique of robustness based falsification [19, 20] and it adjusts the input to the system in a systematic way to guide the system to a property violation . The properties are specified in the Metric temporal logic formula. The second study using a simple spline model instead of physiological model to test the closed loop system. In this case, only properties related to the controller can be tested because the spline model is not representative of the insulin glucose dynamics of the body. The glucose input to the controller is generated by using the shape language modeling toolbox that generates arbitrary piecewise polynomial functions that satisfy constraints on the derivatives and its values. These arbitrary curves do not act as representative of the glucose variation in the body, but they act as worst case inputs that the controller could encounter. Therefore, this technique tests the controller for worst case glucose input patterns. The third study builds a "non deterministic" black box model of the human insulin glucose dynamics using data from a clinical trial called the pump shutoff study(PSO3). This is done to get a better representative model of the insulin glucose dynamics from real data. Further, ideas are presented on how to verify this "non deterministic" model. The model is also built to ensure that it is amenable to verification.

## Chapter 2

### Related Work

Recently there has been a lot of work in modeling and analysis of closed loop medical devices, these include pacemakers, implanted cardiac defibrillators. These studies explore formal specifications for physiological models, formal verification techniques to verify closed loop models and the use of physiological models to test control software. This thesis aims to test the hypo/hyper minimizer control software using the Dalla Man model of the human insulin-glucose regulatory systems. There have been many detailed models of the human insulin-glucose regulation system developed over the past 50 years. These include the Bergman minimal model [5, 6], Dalla Man et al [32, 14, 33] and Hovorka et al model [25, 44]. These models have been quite successful in capturing the insulin glucose dynamics in the human body. However these models are average and capture the average population dynamics and not individual variability, it is necessary to model individual patient variation and to model sensor and pump errors in the simulations. The model by Kovatchev et al [27] was accepted by the Food and Drug Administration as a substitute for clinical animal trials for insulin treatments. These models can be used to test the control algorithms in the computer via simulations [31, 37]. This reduces time and cost when compared with animal trials. These simulations use a *virtual clinical protocol* to specify external inputs like meal timing, meal calories, and insulin bolus. The simulation is performed for different patient parameter sets and inputs and results obtained from simulation can be used to reason about the safety and efficacy of the controller. Results from the simulation can be analyzed to compute metrics like time in the hypoglycemia, time in the hyperglycemia. This thesis uses a technique to perform exhaustive search

that searches over a large space of possible inputs to the simulation. It also searches for worst case scenarios that violate properties specified by the user and expressed in a specification language like Metric Temporal Logic [29]. This thesis also builds on [11]. The RV:Runtime Verification paper performed an exhaustive analysis of a PID controller [42] which is built from descriptions from published literature. The MEDCPS paper tests a controller in loop rather than working with models built from descriptions. The challenges of working with software in a loop is building interfaces between the plant model and the control software. This thesis includes another approach of using splines as the patient model and does not include complicated physiological models which makes the simulation faster and also tests for scenarios not probable with physiological models.

This work is also related to that of Chen et al [12], where symbolic decision procedures are applied to find patient parameter ranges for which a PID controller can be shown to be safe. Beyond the choice of a different verification approach, Chen et al focus on capturing a range of variations of patient parameters whereas our approach captures variations in the inputs (meals, bolus, CGM noise). Furthermore, this approach works with the actual software-in the-loop setup rather than using a model of the controller.

## Chapter 3

### Structure of the thesis

The thesis starts out by describing the pump shut off controller in chapter 4. This controller is used in the first two studies. This chapter describes the over all architecture of the *hypo/hyper controller*, describes the Kalman filter, the principle on which the controller is built on. It also describes the algorithm of the controller. Next, chapter 5 presents S-Taliro. It describes the robustness guided technique to perform falsification. It describes the S-Taliro tool and how it performs the robustness guided falsification. Chapter 6 presents the DallaMan model study. This chapter describes the DallaMan model, the subsystems of the DallaMan model. Next it presents the closed loop system consisting of the controller described in chapter 4, S-Taliro described in chapter 5. It presents the properties that are tested on the closed loop and the open loop system. It presents the falsifications of the properties and suggested remedies for those violations. Next, chapter 7 presents spline based testing technique. It describes the spline based model. It presents the Shape modeling toolbox used to generate splines with constraints. It describes the closed loop consisting of the model and the spline based model. It presents properties that are tested on the closed loop system. Next, it presents falsifications of the properties. The last chapter presents the PSO3 data and the "non deterministic" model built using the PSO3 data. It presents the idea on binning and it describes how the model is represented using a trie. The model is simulated and then ideas on verification of these models are presented.

## Chapter 4

### Pump Shut-Off Controller

Figure 4.1 shows the overall schematic of the hypo/hyper minimizer algorithm. This is an advanced version of the controller originally described by Cameron et al. [10]. The original system used a Kalman filter based prediction algorithm to shut off the pump when it predicted that the glucose would go below a hypoglycemia threshold. The new version of the controller also increases the basal insulin when it predicts that the glucose in the blood is going high, therefore reducing hyperglycemia. There have been clinical trials testing the efficacy of the controller, these trials show that patients spend more time in the euglycemic range during the trials.

#### 4.1 Kalman filter

As discussed in [10], A standard model is used to build the kalman filter

$$x_{k+1} = \Phi x_k + w_k$$

$$y_k = C x_k + v_k$$

Where  $x$  is the state vector,  $y$  is a output vector,  $w$  and  $v$  are random disturbances and  $k$  is the discrete time sample. Here,

$$x_k = \begin{bmatrix} g \\ d \end{bmatrix} \quad \Phi = \begin{bmatrix} 1 & 1 \\ 0 & 1 \end{bmatrix} \quad C = \begin{bmatrix} 1 & 0 \end{bmatrix}$$

Here,  $g$  is the blood glucose concentration,  $d$  is the change in glucose concentration from one sample to the next,  $y$  is the measured glucose(sensor signal),  $v$  is the sensor noise.  $w$  has covariance

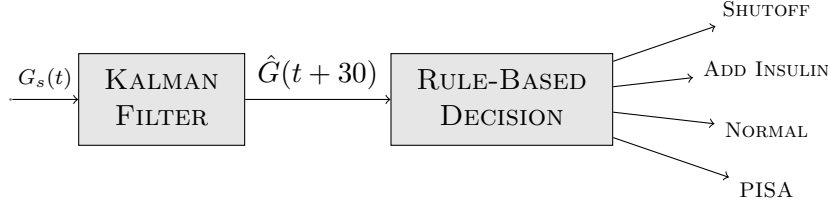


Figure 4.1: Schematic diagram of the hypo/hyper minimizing controller.

$q$  and  $v$  has covariance  $R$ . The Kalman filter assumes an initial estimate of the system state  $\hat{x}_o = \begin{bmatrix} CGM(0) \\ 0 \end{bmatrix}$  and the covariance  $P_0 = \begin{bmatrix} 36000 & 0 \\ 0 & 1000 \end{bmatrix}$ , here  $CGM(0)$  is the first CGM reading. The state estimate is propagated at each step with the following equations.

$$\begin{aligned}\hat{x}_{k|k-1} &= \Phi \hat{x}_{k-1|k-1}, \\ \hat{P}_{k|k-1} &= \Phi \hat{P}_{k-1|k-1} \Phi^T + Q,\end{aligned}$$

where  $k$  represents the current time step and  $k-1$  represents the previous time step, when CGM measurement are available state estimate is updated as:

$$\begin{aligned}\hat{L}_{k|k-1} &= P_{k|k-1} C^T (C \hat{P}_{k|k-1} C^T + R)^{-1} \\ \hat{x}_{k|k} &= \hat{x}_{k|k-1} + L_{k|k-1} (y_k - C \hat{x}_{k|k-1}) \\ P_{k|k} &= P_{k|k-1} - L_{k|k-1} C P_{k|k-1}\end{aligned}$$

When the glucose readings are not available the state estimate is propagated as

$$\hat{x}_{k|k} = \hat{x}_{k|k-1} \hat{P}_{k|k} = \hat{P}_{k|k-1}$$

When glucose readings are not available for at least 20 min then the state estimate is propagated as:

$$\begin{aligned}\hat{L}_{k|k-1} &= P_{k|k-1} C^T (C \hat{P}_{k|k-1} C^T + R \cdot \gamma)^{-1} \\ \hat{x}_{k|k} &= \hat{x}_{k|k-1} + L_{k|k-1} (140 - C \hat{x}_{k|k-1}) \\ P_{k|k} &= P_{k|k-1} - L_{k|k-1} C P_{k|k-1}\end{aligned}$$

Here,  $\gamma = 1000$  is a tuning parameter that determines the speed at which the estimate reverts to initial conditions. The Kalman filter processes the CGM readings and estimates the current glucose and first derivative and based on the estimated derivatives it predicts the value  $G_p(t+30)$  of blood glucose levels 30 minutes into the future. The following actions are performed based on the future predicted glucose readings.

- A. SHUTOFF: shut down the pump for a particular time interval.
- B. ADD INSULIN: infuse extra insulin.
- C. NORMAL: continue the current basal rate.
- D. PISA: Alert the user of the pressure induced sensor attenuation incident.

The algorithm also consists of set of rules to ensure patient safety the rules are:

1. The pump is allowed to be shut off for a maximum of 120 minutes every 150 minutes and the pump can be shut off for a maximum of 180 minutes every night.
2. The pump is shut off when the predicted glucose is below 80mg/dl and if it raises above 100mg/dl.

The algorithm also has rules to detect pressure induced sensor attenuation, this happens when the pressure is applied on the sensor causing it malfunction and report false glucose values.

## Chapter 5

### Robustness-Guided Testing

This chapter describes robustness guided falsification testing to test closed loop control systems. This approach combines the notion of robustness of temporal logic formulas with stochastic optimization techniques. Model based falsification techniques search for behaviors of a system that violate a given property  $\mathcal{P}$ . Robustness based falsification is discussed in detail in [1, 11]. This discussion is excerpted from a previous survey on this topic Cameron et al [11]. Falsification techniques can be symbolic, which explores the system behavior using a constraint solver, it could also be numeric, which uses a numerical simulation of the model to find the property violations. There are many constraint solvers that support richer logics that have improved symbolic falsification techniques, but these techniques are typically restricted to linear models that involve linear controllers. Symbolic model checkers for non linear models and nonlinear controllers are a topic for ongoing research. These techniques don't scale well and have to be adapted to software like Matlab(tm), Simulink(tm)/Stateflow(tm), which are widely used in industry to model nonlinear plants with nonlinear control systems. Simulation based falsification techniques perform repeated simulations of the system under various inputs and initial conditions. They also use results of past simulations to guide the future inputs to the system. Simulation based falsifications techniques have two main advantages (a) They can handle the system as a blackbox. This is useful because the models specified in frameworks like Simulink, Stateflow(tm) have semantics that change over successive versions of Matlab(tm). Black box models can be drawback because knowledge of the model helps in performing efficient simulations. (b) Simulations are cheap and parallelizable and

can be performed accurately for large non linear systems which are hard to deal with symbolic checkers. The disadvantage of using numerical simulation is that the simulations are approximate and they may deviate from the actual trajectories due to numerical errors.

## 5.1 Robustness Guided Falsifications

Robustness based falsification are based on two ideas (a) A notion of trace robustness is defined as a metric that captures how "close" the trace is to a violation. A trace with smaller robustness is closer to a violation when compared to a trace that has a larger robustness [19, 38]. (b) the robustness metric is used to select inputs that guides the system to decreasing robustness therefore towards property violations [35, 1, 3]. Inputs are selected that minimize the robustness as an objective function by solving the global optimization problem using techniques such as Nelder-Mead, simulated annealing [35, 1], ant-colony [2] optimization or the cross entropy method [40].

### 5.1.1 Description

Now the robustness guided approach for falsifying metric temporal logic will be described. The robustness of a trace measures how close the trace is to violate the property. Let  $\mathbf{x} : \mathbb{R}_{\geq 0} \rightarrow X$  be a trajectory mapping  $t \geq 0$  to state  $\mathbf{x}(t) \in X$  and  $\phi$  be a MTL property.

**Definition 1 (Robustness metric):** The robustness of  $\mathbf{x}(\cdot)$  w.r.t  $\phi$  is a real number

$\rho(\mathbf{x}, \phi)$  that has the following properties: (a)  $\rho(\mathbf{x}, \phi) > 0$  if  $\mathbf{x} \models \phi$  and (b)  $\rho(\mathbf{x}, \phi) < 0$  if  $\mathbf{x} \not\models \phi$ .

Furthermore, the magnitude  $v: -\rho(\mathbf{x}, \phi)$ —denotes the maximum radius of a cylinder around the trace  $\mathbf{x}$  so that any other trace in the cylinder also has the same outcome for  $\phi$  as  $\mathbf{x}$ . Robustness for a given trace and property can be computed efficiently using polynomial time in the size of the formula and the number of sample points in the trace[cite]. for convex sets as atomic predicates this requires solving convex optimization problems. However, in practice, the predicates are described by boxes or half-spaces, and the robustness computation can be optimized significantly.

### 5.1.2 From Robustness to Falsifications:

The problem of finding a violation can be reformulated as that of finding a trace of negative robustness. First, an optimization problem of finding a minimum robustness trace can be found,  $\rho^*$  :  $minimize_{x \in Traces} \rho \mathbf{x}, \phi$ . If the minimum robustness  $\rho < 0$ , then we can say that the system violates the property and the trace  $\mathbf{x}^*$  that corresponds to the violation is obtained. Since the robustness function can be quite complicated, global optimization algorithms such as simulated annealing[cite], ant-colony optimization[2], genetic algorithms or cross entropy method can be applied to this problem. If a negative robustness trace is found, then the simulation can be stopped and the property is said to be violated. If not, the least robust trace is returned to the user for the user to understand how close the system gets towards violating the property and during what circumstance.

## 5.2 S-Taliro

The Figure shows a schematic of the S-Taliro tool <sup>1</sup>, it is a robustness guided falsification tool that supports MTL properties [3]. S-Taliro is implemented inside Matlab(tm) and supports models described in Simulink/Stateflow(tm). The tool uses an inbuilt simulator and computes the robustness of a trace. The resulting robustness is used as an objective function by a global optimization engine that seeks to minimize this value. The global optimizer decides on future test inputs to the simulator based on past inputs and the robustness of the resulting traces. Since no global optimization algorithm can guarantee finding a global minimum, multiple global optimization algorithms such as simulated annealing, uniform random exploration, ant colony optimization, cross entropy method and genetic algorithms are used. If S-Taliro fails to find a violation, it returns the least robust trace, through which we can find a relaxed property that can be satisfied. S-Taliro is available as an open source tool <sup>2</sup>, and is built to be extensible through the addition of new solvers and alternative robustness computation techniques. The latest version uses multiple cores

<sup>1</sup> S-Taliro stands for System Temporal Logic RObustness

<sup>2</sup> Cf. <https://sites.google.com/a/asu.edu/s-taliro/s-taliro>

to perform numerous simulations in parallel. It also supports features such as property-directed parameter tuning for models and requirements. These features will be enhanced in future releases of the tool.

## Chapter 6

### Dalla-Man Model Study

This chapter describes the first of two studies dealing with verification of the hypo/hyperglycemia minimizer. This study first builds a simulator of the Dalla Man model in closed loop with the hypo/hyperglycemia minimizer. The Dalla Man model [32, 14, 33] is a physiological model that models the human insulin-glucose dynamics with meals and insulin as inputs. Interesting properties about the closed loop are formulated and these properties are tested for violations using simulation based falsification using the S-Taliro [3] tool. S-Taliro provides violations for 8 out of 10 properties formulated, and provides the output that approaches "closest" to violation for the remaining properties. Figure 6.1, displays the schematic for the S-Taliro tool.

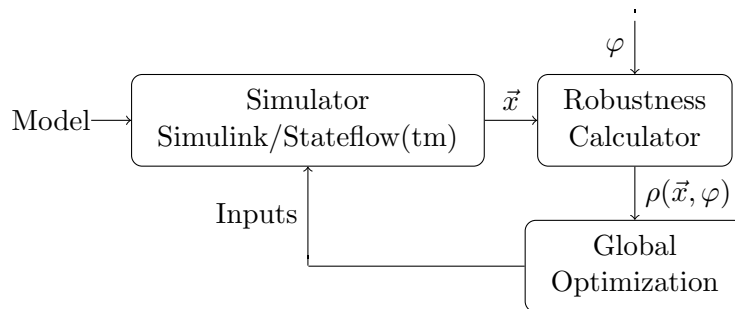


Figure 6.1: Illustration of the overall robustness-guided falsification setup.

## 6.1 Physiological models

There has been a lot of work in physiological modeling of the human insulin-glucose dynamics in the human body starting with the seminal work by Bergman, Cobelli and others [5, 6]. There have been recent studies by DallaMan [32, 14, 33] and Hovorka et al [25, 44].

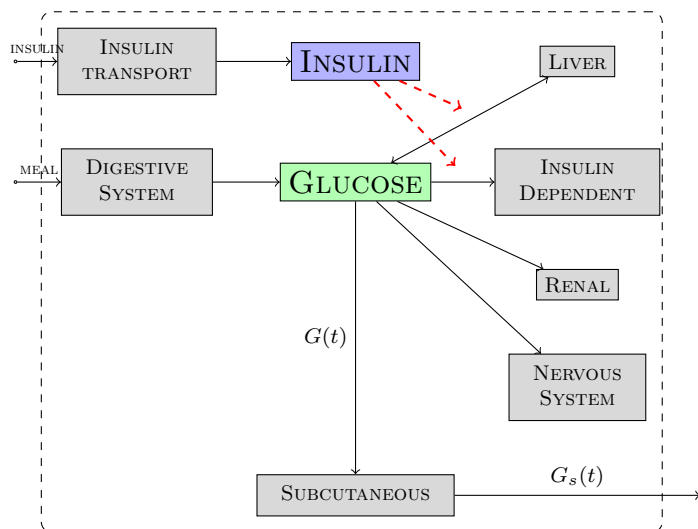


Figure 6.2: Structure of a physiological insulin-glucose regulatory model.

The main idea between these models is to write balance equations that capture the entry, storage, uptake and excretion of both insulin and glucose. They capture the influence of plasma insulin levels on the uptake of glucose and endogenous production of glucose by the liver. The model is a nonlinear ordinary differential equation, due to the fact that the influence of plasma insulin on endogenous glucose production, and insulin dependent glucose uptake is nonlinear. The model can also exhibit hybrid mode behavior because the renal clearance switches on only when  $G(t) \geq G_r$ , a renal clearance threshold parameter (around 180mg/dl). For this study, the DallaMan et al [32, 14, 33] model is used, this model is a nonlinear ordinary differential equation (ODE) system with 10 state variables. It can be used for *in silico* or virtual clinical trials instead of animal trials, and is approved by the FDA.

## 6.2 Study setup

The input to the model is the bolus, basal insulin and meals, and the output is the glucose value. The simulation has the following parameters that are set. (a) The initial state of the patient physiological model, (b) the timing of the meals and their carbohydrate content, (c) noise in the CGM readings, (d) parameters for the physiological model of a particular patient. The overall timeline of events for the simulation is shown in the figure 6.3, the simulation models a common scenario where a patient eats dinner and a night snack. The meal timings and carbohydrates can be varied over a range. The simulation incorporates another common scenario where a patient applies a bolus anytime between 20 minutes before a meal to 20 minutes after a meal. This is seen in 6.1. The amount of bolus injected as measured by the CHO to insulin ratio is also varied. The simulation also assumes that the controller is started at  $t = 50$  min and the includes a range of values for sensor noise.

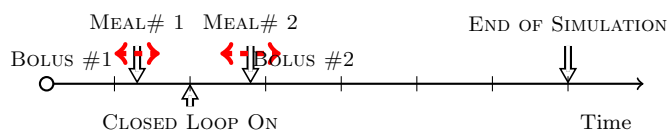


Figure 6.3: Timeline of simulated events for the closed loop simulation.

### 6.2.1 S-Taliro

S-Taliro takes the overall closed loop model and searches over the space of inputs to find property violations. The tool formulates a total of 127 inputs that includes 120 sensor noise values. S-Taliro is run for upto 7 times for each property, this allows us to discover multiple violations. Uniform random heuristic was used rather than simulated annealing, probably because of the large search space.

Table 6.1: Inputs to the closed-loop simulator.

INPUTS	RANGE
Meal #1 Time	[20, 40]mins
Meal # CHO	[60, 150]gms
Meal #2 Time	[180, 300]mins
Meal #2 CHO	[0, 60]gms
Insulin Bolus Delta	$[-20, 20]textmins$
Insulin-CHO Ratio	[0.05, 0.2]U/gm
Open Loop Basal	[0.01, 0.1]U/hr
Controller Start Time	{50mins}
Sensor noise ( $\sim 120$ inputs)	$[-20, 20]mg/dl$

### 6.3 Properties and Results

This section describes the properties that we wish to test for in the overall closed loop.

#### 6.3.1 Control during low glucose levels

An important objective of the controller is to turn off the pump in the event of impending hypoglycemia. So an important question to ask is whether the controller resumes basal insulin or deliver extra bolus insulin when the patient is already under hypoglycemia.

**Property 1.1** :Is it possible for basal insulin to be resumed when  $G(t) \leq 70$  mg/dl and when the pump is shutoff and the total shutoff time and the current shutoff time window are below their upper limits. S-Taliro found 5 violations. As seen in figure 6.4. The circled region shows the violation wherein insulin delivery is resumed under hypoglycemia. The main cause for this violation is the noise pattern in the CGM spoofs the controller to assume the glucose value is increasing and therefore increases the insulin. This can be avoided by adjusting the gains of the Kalman filter to be more robust to noise. It can also be avoided by requiring the glucose levels to cross a minimal threshold before resuming insulin delivery.

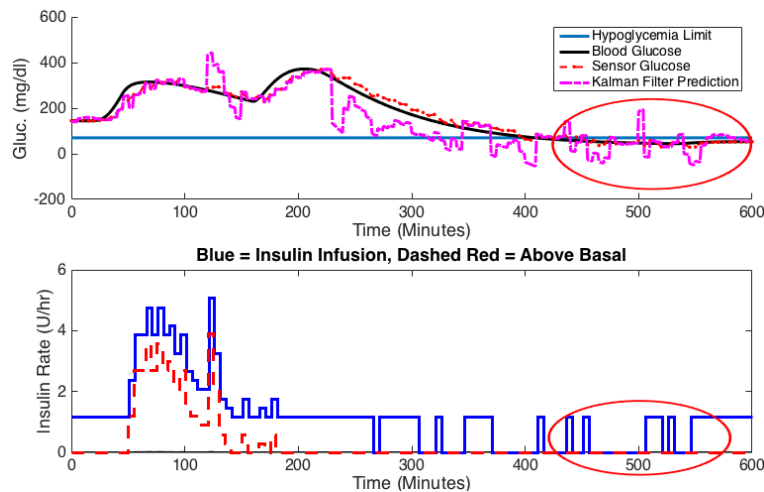


Figure 6.4: Violation of property 1.1

**Property 1.2** : Is it possible for additional insulin to be commanded when  $G(t) \leq 80$  mg/dl S-Taliro could not violate this property, but the near violation shown in figure 6.5 that is presented demonstrates that extra insulin can be added near a hypoglycemic region ( $G(t) \approx 90$  mg/dl).

**Property 1.3** : Is it possible for additional insulin to be commanded and subsequently the pump shutoff within 30 min: We see that the temporary glitch caused by the CGM noise causes the controller to briefly command a small amount of extra insulin and then shutting the pump down immediately. Again this scenario can be avoided by requiring a minimal threshold for CGM value before additional insulin is commanded and also adjusting the Kalman filter gain values. This is observed in figure 6.6.

**Property 1.4** : Let  $\gamma$  be the ratio of total pump shutoff time divided by the total time under hypoglycemia. Can  $\gamma \leq 0.7$ . Will the pump be shutoff for less than 70% of the time under hypoglycemia? The violation for this property is shown in figure 6.7.

### 6.3.2 Control during high glucose levels

It is necessary to test P2.1 Can the pump be shutoff when  $G \geq 300$  mg/dl.

P2.2 Can the total time under hyperglycemia  $G \geq 180$  mg/dl exceed 70% of

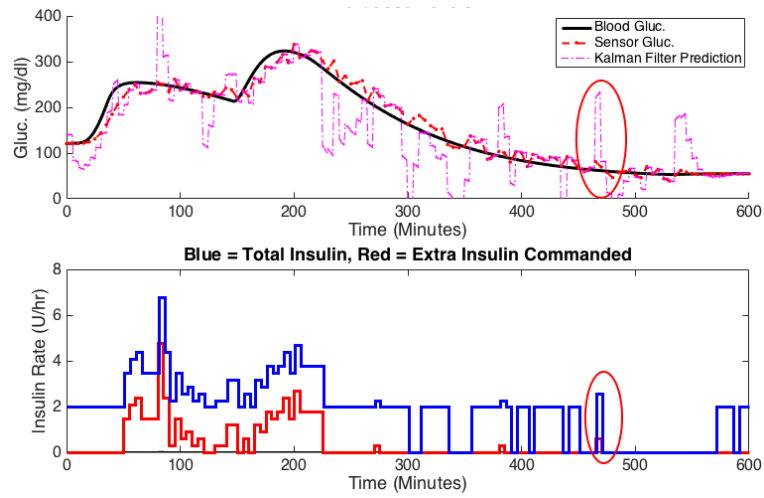


Figure 6.5: Violation of property 1.2

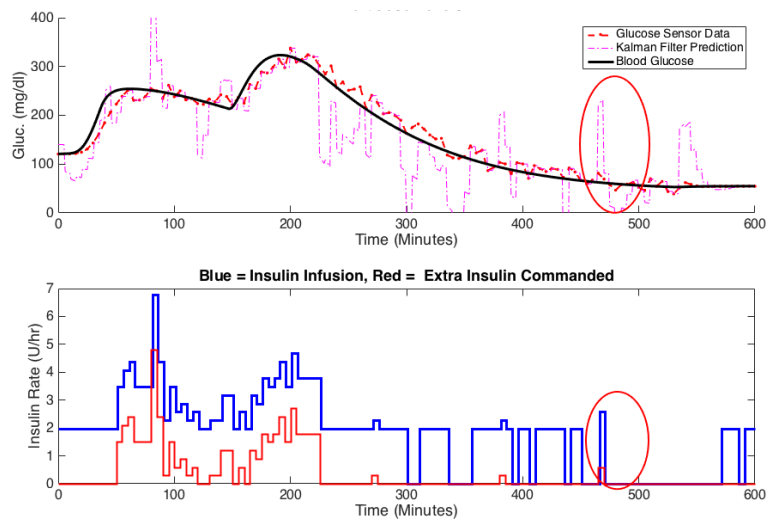


Figure 6.6: Violation of property 1.3

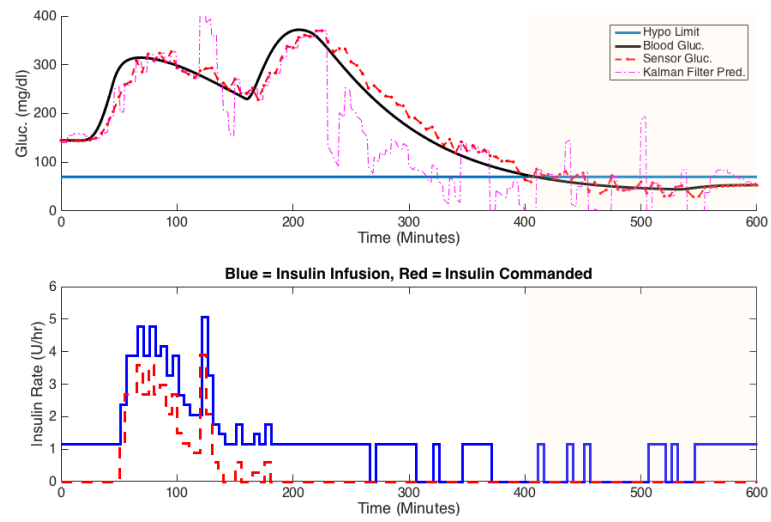


Figure 6.7: Violation of property 1.4

the total simulation time?.

P2.3 Can the total time under hyperglycemia  $\geq 300$  mg/dl exceed 3 hrs?.

As shown in figure 6.8, S-Taliro found that all three properties are violated by a single trace. The pump shutdown is the result of sensor noise and the extended time in hyperglycemia is due to inadequate meal bolus. The controller does not infuse enough extra insulin to rectify this situation for this simulation.

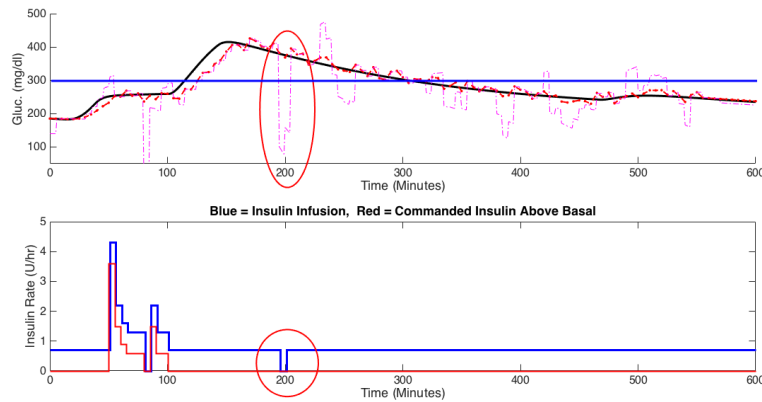


Figure 6.8: Violation of property 2.1, 2.2 and 2.3

### 6.3.3 Comparing Closed and Open Loop Performance

It is important to test properties that compare the performance of closed loop and open loop for identical meals, insulin basal and bolus and starting patient physiological state. This comparison is hard in a clinical setting but quite easy in silico, due to mathematical models.

**Property 3.1** : Is it possible for closed loop hypoglycemia whereas the open loop blood glucose value remains above 80 mg/dl? the least robust violation is shown in figure 6.9, it is seen that the blue curve which represents the open loop glucose stays well above the black curve which represents the closed loop glucose.

**Property 3.2** : Is it possible for the closed loop hyperglycemia above 300 mg/dl whereas the open loop blood glucose level remains below 180 mg/dl? This property is not violated, which means the hyperglycemia can go untreated.

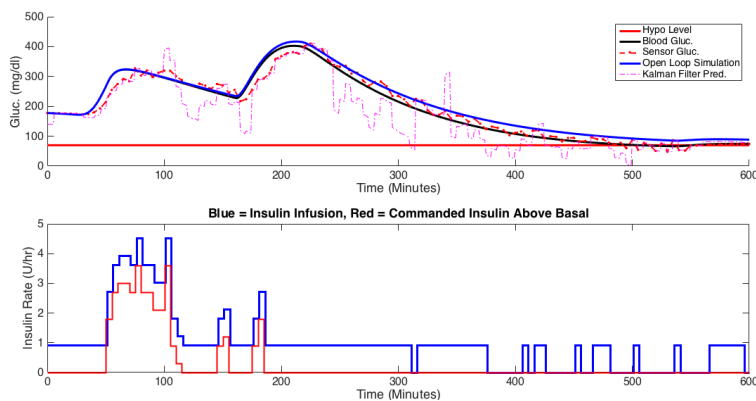


Figure 6.9: Violation of property 3.1

**Property 3.3** : Let  $\rho$  represent the ratio of time in the euglycemic range for the closed loop vs. time in range for the open loop. Is it possible that  $\rho < 0.7$  ? It is seen in the figure that the black curve representing closed loop hyperglycemia spends less time in the euglycemic region than the blue curve.

## 6.4 Discussion

We find violations to 8 of the 10 properties and a near violation for one more. It is important to note that the CGM noise pattern seems to be the single most important cause of these violations. S-Taliro uses a range of  $[-20, 20]$  mg/dl as bounds on the error for each CGM readings. Incorporating more realistic constraints on the CGM noise patterns introduced by S-Taliro is one way to ensure that the results are valid. The lack of modeling for counter regulatory processes makes the physiological model potentially less accurate for hypoglycemia. Incorporating recently proposed models that include counter regulation terms is an important step to make the model more representative to the underlying insulin glucose dynamics. The simulations carried out by S-Taliro are quite expensive, therefore parallel simulations must be performed going forward to increase the number of simulations that are performed.

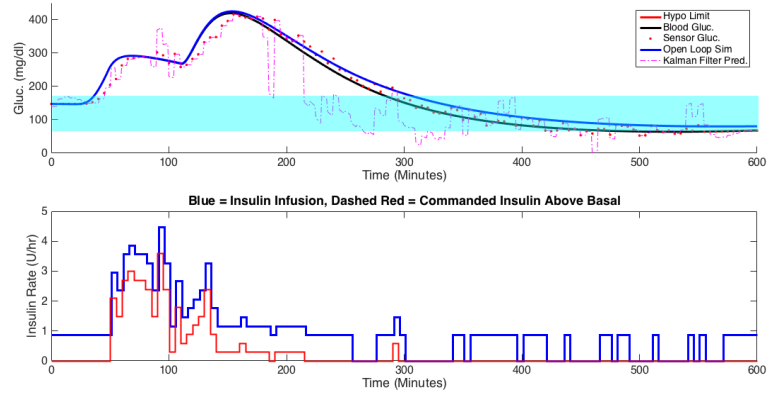


Figure 6.10: Violation of property 3.3

## Chapter 7

### Spline Based Testing

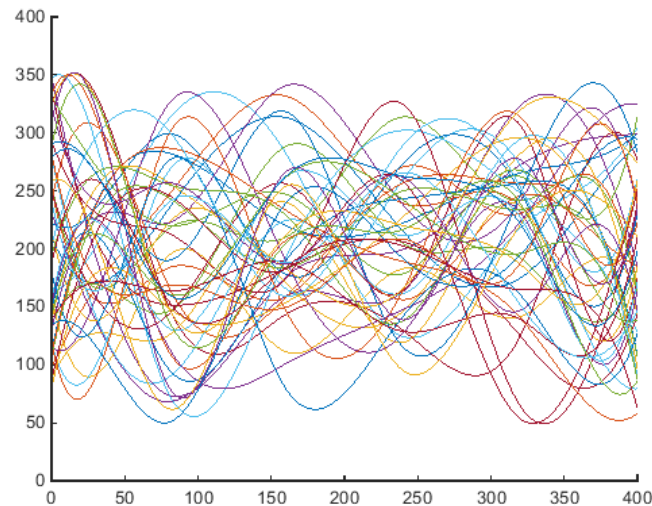
Searching for falsifications with the Dalla Man model [32, 14, 33] and the pump shutoff controller in closed loop is computationally expensive. This chapter introduces a spline based method to just test the controller, in this method arbitrary curves with specified constraints are used as the model. The glucose curves are used as measurements by the controller, and S-Taliro [3] is used to falsify the metric temporal logic formula specified. This method of spline based testing generates splines to "spoof" glucose inputs to the controller. In view of the controller, the glucose measurements are actual measurements from the glucose sensor. The controller has a predefined basal profile that is usually set by the patient. S-Taliro is then used to modify the control points of the splines to falsify the stated MTL property.

#### 7.1 Spline Model using SLM tools

Splines are used to model the glucose variation in the body, splines are used because of the smoothness properties, its first and second derivatives are continuous. Formally splines are piece wise polynomial functions. To generate particular shapes of the glucose profile, control points are defined and then a spline is used as an interpolant to generate a glucose profile. But the problem with spline interpolation is that values at the start and end of the curves are unconstrained, this is unrealistic as a model for glucose profile because glucose values in patients are in the range [50, 300] mg/dl. The derivatives of the curves generated by the splines are also unconstrained, and practically glucose values in patients have maximum values of  $\pm 5$  mg/dl/min. A toolbox called

shape language modeling(SLM) [16] is used to generate spline that pass through control points and satisfy the constraints on derivatives and the end point values. Figure 7.1 shows the various splines generated by the SLM toolbox.

Figure 7.1: This figure shows random splines that is generated by the SLM toolbox.



### 7.1.1 Splines

A spline is piecewise polynomial on an interval  $[a, b]$  with sub intervals  $T_0, T_1, T_2, \dots, T_n$  such that  $T_0 = \{t | t_0 \leq t < t_1\}, T_1 = \{t | t_1 \leq t < t_2\}$  such that  $y(t) = P_1(t)$  for  $t \in T_0$   $y(t) = P_2(t)$  where  $P_0, P_1, \dots$  are polynomials. The highest order of the polynomials  $P_i(t)$  is the order of the spline. It is preferable to use a spline of order greater than three to ensure that it is smooth, the first and the second derivative of a smooth curve exists.

### 7.1.2 Spline interpolation

To generate an arbitrary curve, control points or "knots" are selected through which the curve will pass through  $\{(x_i, y_i) : i = 0, 1, \dots, n\}$ , between each pair of points  $(x_{i-1}, y_{i-1})$  and  $(x_i, y_i)$  with polynomials  $y = q_i(x), i = 1, 2, \dots, n$ . with the additional restriction that the first and the

second derivatives be continuous at all points, including the boundary. This is achieved by using a 3rd degree spline as the interpolant. The solution for the coefficients of the interpolants are got by solving linear equations. One disadvantage of using the cubic interpolant is that the we cannot constrain the derivatives nor the maximum and the minimum values of the generated curve [41]. The next section talks about how this disadvantage is overcome.

### 7.1.3 SLM Tools

Shape language modeling toolbox is used to generate spline that pass through control points and also satisfy the constraints on its derivatives. It uses the principle of least squares to find a curve that tries to pass through the "knots" and also satisfy constraints like monotonicity. Some of the other constraints that could be used are, 'ConcaveDown', 'ConcaveUp', 'Decreasing', 'Increasing', 'LeftSlope', 'LeftValue', 'RightSlope', 'RightValue'. After specifying the constraints we then fit a model from data, this function solves the optimization problem that return the spline model. the spline model contains piece wise polynomials which can be evaluated using the Matlab(tm) function ppval.

## 7.2 S-Taliro testing using spline model

The inputs to S-Taliro are 1.The system model 2. properties. Here the system model is the spline model in closed loop with the pump shutoff controller. S-Taliro then changes the input automatically to find a violation of the property of interest. To be precise, it alters the control points of the constrained spline to find a violation.

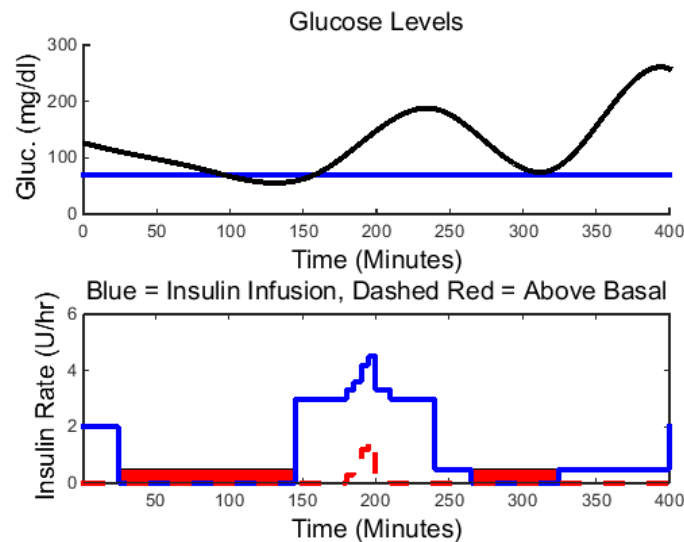
## 7.3 Properties and results

The following properties are defined and tested.

**Property 1** The controller must ensure that the pump is shutdown when the patient's glucose is already low because that is the function of the controller. There is a high risk of hypoglycemia if basal insulin is on and the patient's glucose is pulled down even further. therefore, "The Pump

must be shut down whenever glucose is below 70 mg/dl". This is encoded in S-Taliro as an MTL formula  $\phi_1 = \langle \langle [30, 380](a/\wedge b) \rangle \rangle$ , where a is "glucose is below 70 mg/dl" and b is "pump must be shut down". This MTL property is read as eventually its the case the glucose is below 70 mg/dl and the pump is shut down". The violation of this property is shown in figure 7.2.

Figure 7.2: This is the violation of property 1, it is seen at time  $t = 145$  to  $t=160$  that the patient is under hypoglycemia(insulin goes below 70 mg/dl) and pump is shut off.



**Property 2** It is necessary to ensure that the pump doesnt misread the glucose and adds extra insulin but realizes later and shuts the pump down. Therefore, The pump must not be shut down within 30 minutes of adding extra insulin. This is encoded in S-Taliro as an MTL formula  $\phi_2 = \langle \langle (a/\wedge(\langle \langle [0, 30]b \rangle \rangle)) \rangle \rangle$  where a is "Extra insulin added" and b is "pump is not shut down". The violation of this property is shown in figure 7.3.

**Property 3, 4, 5** The pump can also add extra insulin because when it thinks there is an impending risk of hyper glycemia. This is risky because if extra insulin is added in a low glucose region, it could drag the body down to hypoglycemia. It is important to ask the question, "Is extra insulin ever introduced by the controller when blood glucose is below 120 mg/dl or 100 mg/dl or 90 mg/dl". This is encoded in S-Taliro as an MTL formula  $\phi = \langle \langle (a/\wedge b) \rangle \rangle$  where a is extra insulin is

added” and b is ”glucose is less than 120 mg/dl”?. Minor violations were found for property 3 and 4 as seen in figure 7.4 and figure 7.5, but no violations were found for property 5 after S-Taliro running for 8 hours.

**Property 6** We expect the pump to be shut off during the majority of the time for hypoglycemia. We expect the pump to be shutoff for at least 70% of the time during a hypoglycemic incident. This is encoded in S-Taliro as an MTL formula  $\phi_6 = \Box(t - > c)$ , where t is ”time under hypoglycemia is at least 10 min and at most 120 minutes” and c is ”pump shut off time is greater than 0.7 time under hypoglycemia. Which is read as ”always if the patient is under hypoglycemia then then pump shut off time is greater then the time under hypoglycemia”. The violation for this property is shown in figure 7.6.

**Property 7** We expect the pump to be shutoff when the glucose derivative is negative. It is important to ask the question, is Extra insulin is added when glucose derivative is negative?. This is encoded in S-Taliro as an MTL formula  $\phi_7 = \Box(\Box(f \wedge e) \rightarrow g)$ , where f is ”glucose rate is below -2 mg/dl” and e is ”extra insulin is infused”, is it read as ”is it true that eventually glucose rate is below -2 mg/dl and extra insulin is infused?”. The violation for this property is shown in figure 7.7.

## 7.4 Limitations

This study does not use physiological models, and the glucose curves generated do not represent actual patient glucose values. So it is not guaranteed that the glucose curves can be found in real patients. However it gives us any worst case scenarios that can occur. Therefore this study can test for properties that are only specific to the controller and not the patient model.

## 7.5 Discussion and Conclusion

In this method we can test for wide variety of scenarios, scenarios which may not be practical in the field. But once we find falsifications we can then check clinical data like PSO3(pump shutoff controller study 3) to check if scenarios similar to the falsification is found in the data. Or we could

give an advisory so that an expert can closely examine.

Figure 7.3: This is the violation of property 2 , it is seen at time  $t = 30$  insulin is infused and  $t=45$  that pump is shut off.

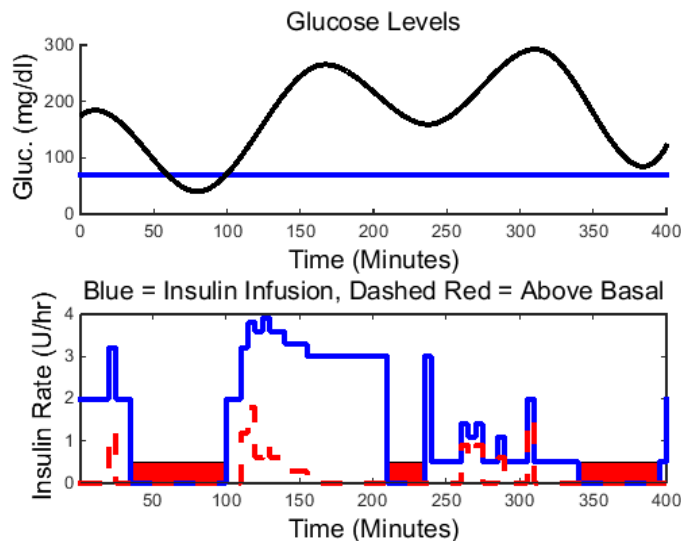


Figure 7.4: This is the violation of property 3

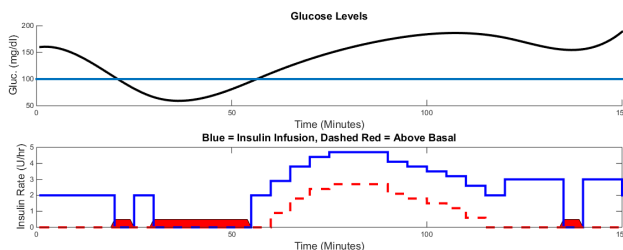


Figure 7.5: This is the violation of property 4

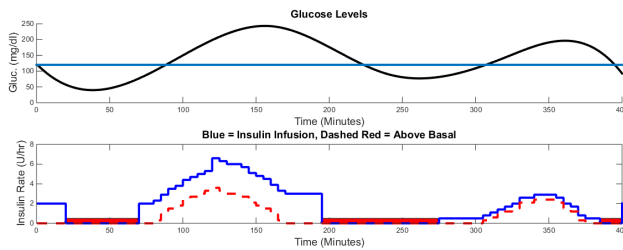


Figure 7.6: This is the violation of property 6 , it is seen that the pump is shutoff for less than 70% of the time of hypoglycemia.

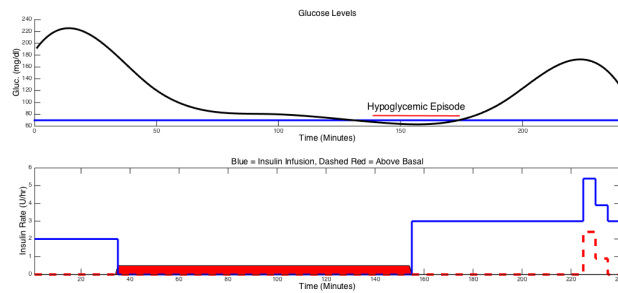
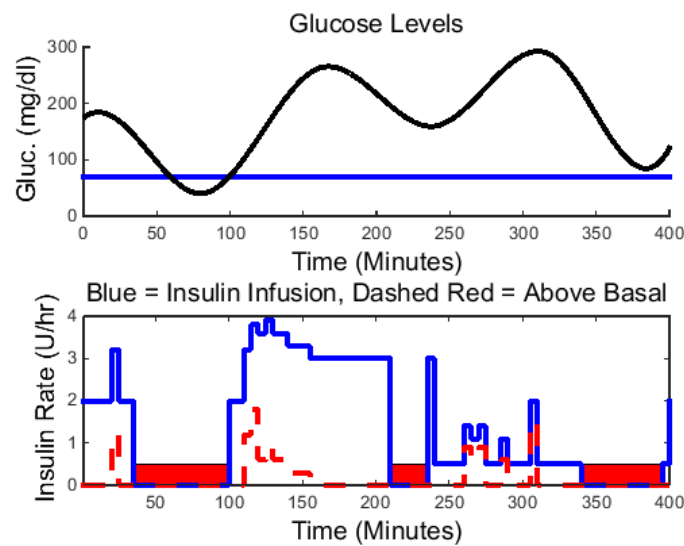


Figure 7.7: This is the violation of property 7 , it is seen that extra insulin is commanded when the derivative of the insulin is negative.



## Chapter 8

### Delay Coordinate Embedding

The first two studies in this thesis used physiological ordinary differential equation models that were built from understanding the underlying physiology. However, This chapter proposes a "nondeterministic" quantitative model that predicts a likely range of next time values of blood glucose of a patient with type 1 diabetes from the current value. This approach is based on a process of "binning" data points from the PSO3 pump shutoff study [39] to obtain possible next step glucose values given the current state ranges of values. The binned data points are collected and stored in a trie data structure, the trie data structure is used for fast lookups and easier nearest neighbor searches. The model is simulated and ideas about its verification are presented.

#### 8.1 Introduction

The physiological models like the Bergman model [5, 6] and Dalla Man model [32, 14, 33] are based on a population and not built for a particular patient. These models are also continuous and computationally inefficient to use for verification. Since the underlying insulin dynamics are very complex its a good idea to build a model from the data to capture situations that occur in the field, but which may not occur during model simulations, we can also choose a model that is computationally efficient to verify and to reason about. We could use three broad approaches to model the insulin glucose dynamics. (a) white box modeling wherein the model is built using first principles, this is very complex and impractical. (b) grey box model, these models are built using some prior simplified knowledge of the system but contains free parameters that needs to

be estimated. havorka et al [25, 44] uses this approach to learn the model online. (c) black box modeling, here we want to get a model that fits the data well even if the model we obtain does not fit the prior knowledge of the dynamic system. However we can choose some model structures which have been used traditionally to represent dynamic systems. However choosing the right model structure is an arbitrary process, but it also gives us the flexibility to choose the model to suit our specific application needs. We choose a black box approach to modeling since we want a model that represents the data well and is computationally cheap to verify.

## 8.2 Non Deterministic model

The PSO3 data is used in this study, more information can be found at [39]. In the following discussion, we model time in the increments of basic step  $\delta > 0$  and time intervals of  $t = 0, \delta, 2\delta, \dots$ , in the implementation  $\delta = 20min$ .  $G(t)$  is the blood glucose values as measured by a continuous glucose monitor and  $i(t)$  represent the *insulin on-board* for a patient. The insulin on board represents the current active insulin in the blood ready to act on glucose levels. The non deterministic model provides a possible range for the values for  $G(t + \delta)$ , given the values  $G(t), i(t)$ , the current glucose value and the current insulin on board value. The predicted glucose value is a range of glucose values and all values in the range are equally probable. This flexibility of having a range of predicted glucose values allows for exploration of worst case behaviors, this exploration is computationally expensive.

-The PSO3 data has data for many patients and each patient is associated with many sessions  $j = 1, \dots, N$ , for each session ID  $j$  and some time interval  $[0, T]$ , we obtain samples for  $G_j(t), i_j(t)$ .

-The range of values of  $G(t)$  and  $i(t)$  is partitioned into bins such that there are almost equal number of elements in all the bins.

-Now, we go through the data and collect for each time, the pair  $(B_{g(t)}, B_{i(t)})$  is associated with the future glucose bin associated with that measurement  $B_{g(t+\delta)}$ . If we find a new future glucose bin for the same pair of glucose and insulin bin, we associate the new value with the bin as well.

The resulting table of associations represent our system.

### 8.3 Delay Coordinate embedding

The approach described above predicts a future value based on only the current value without considering the history. For example the data point  $(G_j(t), i_j(t))$  on rising glucose levels is qualitatively different from the same set of values on falling glucose values. A better model can be obtained if the binning was based on a small segment of the past history, we can bin based on the sequence of the past  $p$  values of blood glucose levels.  $G_j(t - p\delta), \dots, G_j(t - \delta), i_j(t)$ . In our implementation, 3 past values are considered. This is a generalization of the previous binning approach which does not take the past values of glucose into account. This is very similar to the idea of delay coordinate embedding in dynamical systems theory [43].

### 8.4 Implementation

The PSO3 data is first preprocessed and then the insulin on board time series and CGM time series is computed.

**Preprocessing of data** The PSO3 protocol is described in [cite]. The PSO3 data contains the following data for each session, basal rate, bolus value and times of measurement, CGM values and times of measurements. The insulin of board is computed by using the basal rate and the bolus values, the CGM values are in the increments of 5 mins, the CGM values are interpolated to get values in the increments of 1 min. figures 8.1 and 8.2 shows the resulting time series after preprocessing. The time series is now discretized by binning values into ranges, figures 8.5 and 8.4 shows the resulting binned time series.

**Insulin on board** Insulin on board is the amount of insulin that is still active in the body after being used up by the body, it is computed for the bolus rate. As seen in the figure 8.3, at around 100 minutes, 35% of the insulin is remaining in the blood, at 200 minutes 10% of the insulin

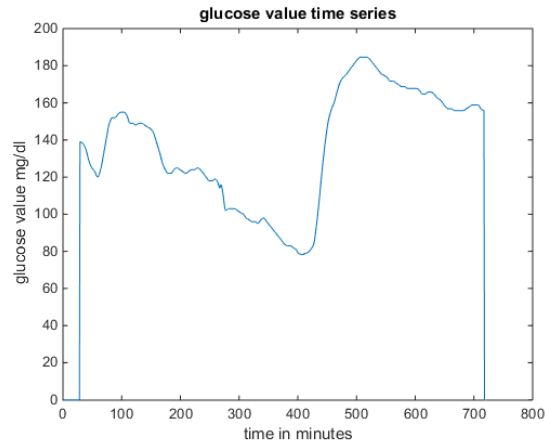


Figure 8.1: Resulting time series after preprocessing

remains in the blood.

**Collecting data** The IOB and CGM time series starts from 5PM and extends upto 5AM in the morning, data that is outside this range is ignored. The non deterministic quantitative model is built for each patient and not for the population. In this study the model is built for the patient identified by 'PSO3-001-0001'. The data is collected from time  $T = 240$  min of the time series and the following tuple is collected  $G(t - 40), G(t - 20), i(t), G(t), G(t + 20)$ , where  $G(t)$  is the glucose time series and  $i(t)$  is the insulin on board time series. for time  $240 \leq t \leq 600$ , the data is started from time  $t = 240$  to ignore any effect of meals eaten before 9 PM. Each of the 5 tuple is inserted into the trie data structure.

#### 8.4.1 Tries

The chapter introduces the trie data structure and gives details about its implementation to store the resulting data collected from the time series. The trie data structure is used to help in fast lookups and for simple nearest neighbor searches. The name trie comes from its use for retrieval. A trie is used to store data that has a key and a value, it is like a dictionary, In our case the key is the four tuple  $G(t - 40), G(t - 20), i(t), G(t)$  and our value is  $G(t + 20)$ , since we can encounter

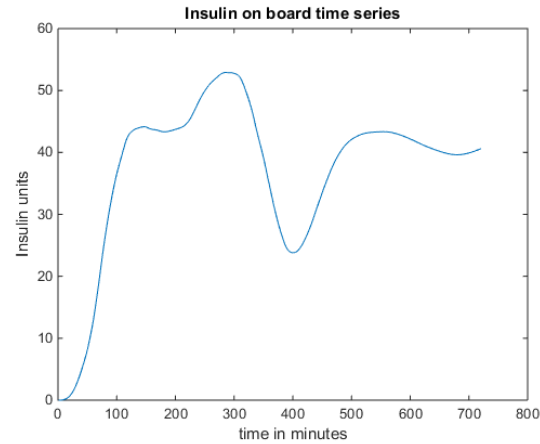
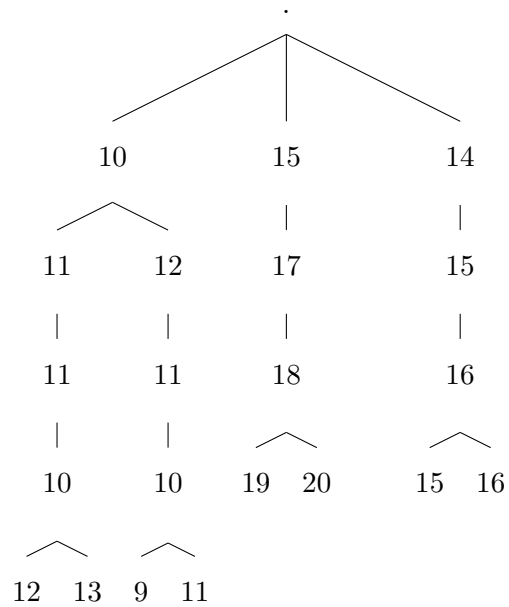


Figure 8.2: Resulting time series after preprocessing

different future values for the same past values.



## 8.5 Simulation

Once the trie model is built, it is simulated, the simulation is started with an initial condition represented by a tuple, the insulin on board is the input to the model and the past glucose bins is appended with the current iob bin, this new tuple is queried from the trie and possible future values are obtained. The future values obtained are used as the current glucose bin and these are

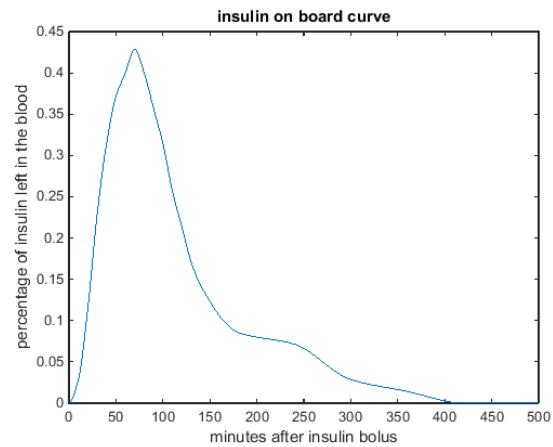


Figure 8.3: Plot of the insulin on board curve

appended to the past glucose values to obtain new tuples. This process is repeated to obtain the entire trace for the simulation. Figure 8.6 shows the simulation trace of one of the simulations.

## 8.6 Ideas for verification of the model

This model can be used to verify a closed loop system consisting of this model in closed loop with a controller. The controller has to be discretized and we can observe the trace of the system to verify properties.

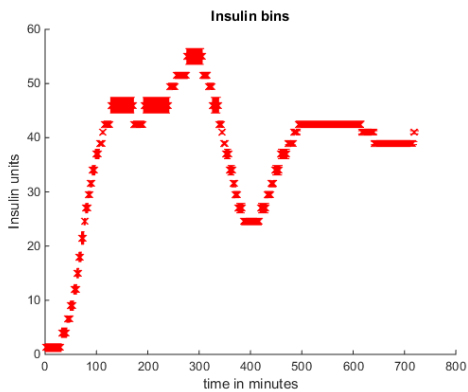


Figure 8.4: Resulting insulin time series after binning

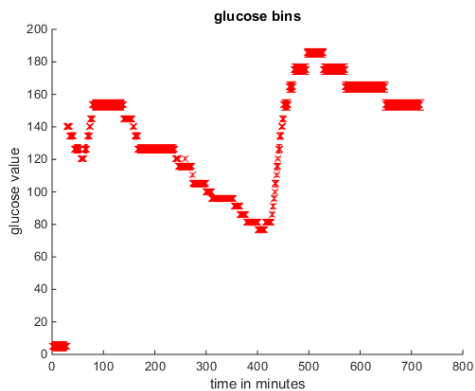


Figure 8.5: Resulting glucose time series after binning

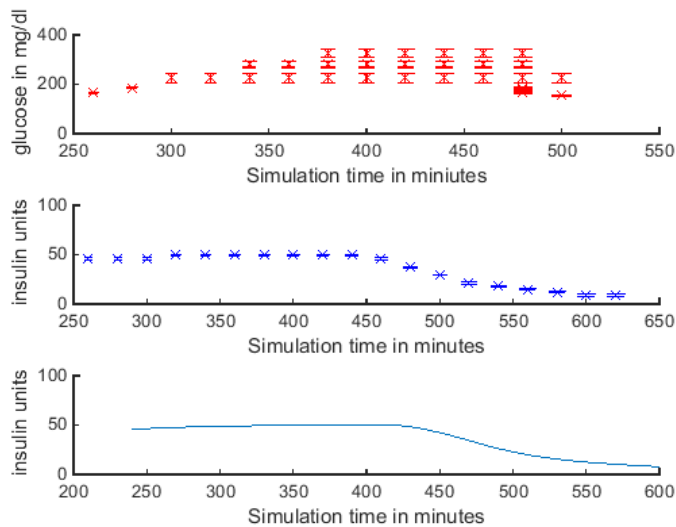


Figure 8.6: Plot of the simulation curve

## Bibliography

- [1] Houssam Abbas, Georgios Fainekos, Sriram Sankaranarayanan, Franjo Ivancic, and Aarti Gupta. Probabilistic temporal logic falsification of cyber-physical systems. Trans. on Embedded Computing Systems (TECS), 12:95–, 2013.
- [2] Yashwanth Singh Rahul Annapureddy and Georgios E. Fainekos. Ant colonies for temporal logic falsification of hybrid systems. In Proceedings of the 36th Annual Conference of IEEE Industrial Electronics, pages 91 – 96, 2010.
- [3] Yashwanth Singh Rahul Annapureddy, Che Liu, Georgios E. Fainekos, and Sriram Sankaranarayanan. S-talro: A tool for temporal logic falsification for hybrid systems. In Tools and algorithms for the construction and analysis of systems, volume 6605 of LNCS, pages 254–257. Springer, 2011.
- [4] Eran Atlas, Revital Nimri, Shahar Miller, Eli A. Grunberg, and Moshe Phillip. MD-Logic artificial pancreas system: A pilot study in adults with type 1 diabetes. Diabetes Care, 33(5):1072–1076, May 2010.
- [5] R. N. Bergman and J. Urquhart. The pilot gland approach to the study of insulin secretory dynamics. Recent Progress in Hormone Research, 27:583–605, 1971.
- [6] Richard N. Bergman. Minimal model: Perspective from 2005. Hormone Research, pages 8–15, 2005.
- [7] F. Cameron. Explicitly Minimizing Clinical Risk through Closed-loop Control of Blood Glucose in Patients with Type 1 Diabetes Mellitus. PhD thesis, Stanford University, 2010.
- [8] F. Cameron, B. Wayne Bequette, D.M. Wilson, Bruce Buckingham, Huyjin Lee, and Günter Niemeyer. Closed-loop artificial pancreas based on risk management. J. Diabetes Sci Technol., 5(2):368–79, 2011.
- [9] F. Cameron, Günter Niemeyer, and B. Wayne Bequette. Extended multiple model prediction with application to blood glucose regulation. Journal of Process Control, 22(8):1422–1432, Sep 2012.
- [10] F. Cameron, Darrell M. Wilson, Bruce A. Buckingham, Hasmik Arzumanyan, Paula Clinton, H. Peter Chase, John Lum, David M. Maahs, Peter M. Calhoun, and B. Wayne Bequette. Inpatient studies of a kalman-filter-based predictive pump shutoff algorithm. J. Diabetes Science and Technology, 6(5):1142–1147, 2012.

- [11] Faye Cameron, Georgios Fainekos, David M. Maahs, and Sriram Sankaranarayanan. Towards a verified artificial pancreas: Challenges and solutions for runtime verification. In Proceedings of Runtime Verification (RV'15), volume 9333 of Lecture Notes in Computer Science, pages 3–17, 2015.
- [12] Sanjian Chen, Matthew OKelly, James Weimer, Oleg Sokolsky, and Insup Lee. An intraoperative glucose control benchmark for formal verification. In 5<sup>th</sup> IFAC conference on Analysis and Design of Hybrid Systems (ADHS), Oct 2015.
- [13] Claudio Cobelli et al. and AP@Home Consortium. First use of model predictive control in outpatient wearable artificial pancreas. Diabetes Care, 37(5):1212–1215, May 2014.
- [14] Chiara Dalla Man, Robert A Rizza, and Claudio Cobelli. Meal simulation model of the glucose-insulin system. IEEE Transactions on Biomedical Engineering, 1(10):1740–1749, 2006.
- [15] E Dassau, H Zisser, Harvey R.A., Percival M.W., B. Grosman, W Bevier, E Atlas, S Miller, R Nimri, L Jovanovic, and Doyle F.J. Clinical evaluation of a personalized artificial pancreas. Diabetes Care, 36(4):801–9, 2013.
- [16] John D’Errico. Slm - shape language modeling, jun 2009.
- [17] Firas El-Khatib, J. Jiang, and Edward R. Damiano. Adaptive closed-loop control provides blood-glucose regulation using dual subcutaneous insulin and glucagon infusion in diabetic swine. J Diabetes Sci Technol., 1(2):181–92, 2007.
- [18] Firas H. El-Khatib, Steven J. Russell, David M. Nathan, Robert G. Sutherlin, and Edward R. Damiano. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci. Transl. Med., 2, April 2010.
- [19] Georgios Fainekos and George J. Pappas. Robustness of temporal logic specifications for continuous-time signals. Theoretical Computer Science, 410:4262–4291, 2009.
- [20] Georgios E. Fainekos. Robustness of Temporal Logic Specifications. PhD thesis, Department of Computer and Information Science, University of Pennsylvania, 2008.
- [21] Gregory P. Forlenza, Sriram Sankaranarayanan, and David M. Maahs. Refining the closed loop in the data age: Research-to-practice transitions in diabetes technology. Diabetes Technology & Therapeutics, 17(5), 2015.
- [22] B Grosman, E Dassau, H.C Zisser, L Jovanovic, and Doyle F.J. Zone model predictive control: A strategy to minimize hyper- and hypoglycemic events. J Diabetes Sci Technol., 4(4):961–75, 2010.
- [23] R. Hovorka, J. M Allen, D. Elleri, L. J. Chassin, J. Harris, D. Xing, C. Kollman, T. Hovorka, A. M. Larsen, M. Nodale, A. De Palma, M. Wilinska, C. Acerini, and D. Dunger. Manual closed-loop delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. Lancet, 375:743–751, February 2010.
- [24] R. Hovorka, V. Canonico, L.J. Chassin, U. Haueter, M. Massi-Benedetti, M.O. Federici, T.R. Pieber, H.C. Shaller, L. Schaupp, T. Vering, and M.E. Wilinska. Nonlinear model predictive control of glucose concentration in subjects with type 1 diabetes. Physiological Measurement, 25:905–920, 2004.

- [25] R. Hovorka, F. Shojaee-Moradie, P.V. Carroll, L.J. Chassin, I.J. Gowrie, N.C. Jackson, R.S. Tudor, A.M. Umpleby, and R.H. Hones. Partitioning glucose distribution/transport, disposal and endogenous production during IVGTT. Am. J. Physiol. Endocrinol. Metab., 282:992–1007, 2002.
- [26] B Kovatchev, C Cobelli, E Renard, S Anderson, M Breton, S Patek, W Clarke, D Bruttomesso, A Maran, S Costa, A Avogaro, C Dalla Man, A Facchinetti, L Magni, G De Nicolao, J Place, and A Farret. Multinational study of subcutaneous model-predictive closed-loop control in type 1 diabetes mellitus: summary of the results. J Diabetes Sci Technol., 4(6):1374–81, 2010.
- [27] B. P. Kovatchev, M. Breton, C. D. Man, and C. Cobelli. In silico preclinical trials: a proof of concept in closed-loop control of type 1 diabetes. J Diabetes Sci Technol, 3(1):44–55, Jan 2009.
- [28] Aaron Kowalski. Pathway to artificial pancreas revisited: Moving downstream. Diabetes Care, 38:1036–1043, June 2015.
- [29] Ron Koymans. Specifying real-time properties with metric temporal logic. Real-Time Systems, 2(4):255–299, 1990.
- [30] David Maahs, Elizabeth Mayer-Davis, Franziska Bishop, L. Wang, M. Mangan, and Robert G. McMurray. Outpatient assessment of determinants of glucose excursions in adolescents with type-1 diabetes. Diabetes Technology and Therapeutics, 14(8):658–664, Aug 2012.
- [31] L. Magni, D.M. Raimondo, L. Bossi, C. Dalla Man, G. De Nicolao, B. Kovatchev, and C. Cobelli. Model predictive control of type 1 diabetes: an in silico trial. J. Diabetes Science and Technology, 1(6):804–12, 2007.
- [32] Chiara Dalla Man, M. Camilleri, and Claudio Cobelli. A system model of oral glucose absorption: Validation on gold standard data. Biomedical Engineering, IEEE Transactions on, 53(12):2472–2478, dec. 2006.
- [33] Chiara Dalla Man, F. Micheletto, D. Lv, M. Breton, Boris Kovatchev, and Claudio Cobelli. The UVA/PADOVA type 1 diabetes simulator: New features. J. Diabetes Science and Technology, 8(1), January 2014.
- [34] Medtronic Inc. “paradigm” insulin pump with low glucose suspend system, 2012. Cf. [http://www.medtronicdiabetes.ca/en/paradigm\\_veo\\_glucose.html](http://www.medtronicdiabetes.ca/en/paradigm_veo_glucose.html).
- [35] Truong Nghiem, Sriram Sankaranarayanan, Georgios E. Fainekos, Franjo Ivančić, Aarti Gupta, and George J. Pappas. Monte-carlo techniques for falsification of temporal properties of non-linear hybrid systems. In Hybrid Systems: Computation and Control, pages 211–220. ACM Press, 2010.
- [36] R Nimri, I Muller, E Atlas, S Miller, O Kordonouri, N Bratina, C Tsioli, M.A. Stefanija, T Danne, T Battelino, and Phillip M. Night glucose control with md-logic artificial pancreas in home setting: a single blind, randomized crossover trial-interim analysis. Pediatric Diabetes, 15(2):91–100, March 2014.
- [37] S.D. Patek, B.W. Bequette, M. Breton, B.A. Buckingham, E. Dassau, F.J. Doyle III, J. Lum, L. Magni, and H. Zisser. In silico preclinical trials: methodology and engineering guide to closed-loop control in type 1 diabetes mellitus. J Diabetes Sci Technol., 3(2):269–82, 2009.

- [38] A. Rizk, G. Batt, F. Fages, and S. Soliman. On a continuous degree of satisfaction of temporal logic formulae with applications to systems biology. In 6th International Conference on Computational Methods in Systems Biology, number 5307 in LNCS, pages 251–268. Springer, 2008.
- [39] John Lum Roy Beck, Bruce Buckingham. Reduction of Nocturnal Hypoglycemia by Using Predictive Algorithms and Pump Suspension: An Outpatient Pilot Feasibility and Efficacy Study . ClinicalTrials.gov, Jun 2015.
- [40] Sriram Sankaranarayanan and Georgios E. Fainekos. Falsification of temporal properties of hybrid systems using the cross-entropy method. In HSCC, pages 125–134. ACM, 2012.
- [41] Patricia L. Smith. Splines as a useful and convenient statistical tool. The American Statistician, 33(2):57–62, 1979.
- [42] Garry M. Steil. Algorithms for a closed-loop artificial pancreas: The case for proportional-integral-derivative control. J. Diabetes Sci. Technol., 7:1621–1631, November 2013.
- [43] Andreas S. Weigend and Neil A. Gershenfeld. Time Series Prediction: Forecasting the Future and Understanding the Past. Addison-Wesley, Reading, Massachusetts, 1994.
- [44] M.E. Wilinska, L.J. Chassin, C. L. Acerini, J. M. Allen, D.B. Dunber, and R. Hovorka. Simulation environment to evaluate closed-loop insulin delivery systems in type 1 diabetes. J. Diabetes Science and Technology, 4, January 2010.