Linearization based Safety Verification of a Glucose Control Protocol

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Introduction

Medical cyber-physical systems: multiple medical devices coordinate and control with each other and provide closed loop control to the patient

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Medical cyber-physical systems: multiple medical devices coordinate and control with each other and provide closed loop control to the patient

Challenges in verifying safety in these systems

- These systems are **non–scalable** due to **state–space explosion**
- Guatanteeing **safety** in presence of significant **physiological variabilities** among patients over long **time horizons** is hard

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Related Works

[1][2][3] deal with safety verification on various case studies in medical cyber–physical systems

- all of them suffer from scalability issues
- no systematic approach to address them

[1] provides a formal verification framework of an intra–operative glucose control benchmark of Dallaman's glucose–insulin regulatory protocol [4]

- due to variability of the model and state parameters, full system verification was not feasible

[1] Sanjian Chen, Matthew O'Kelly, James Weimer, Oleg Sokolsky, and Insup Lee. An intraoperative glucose control benchmark for formal verification. IFAC-PapersOnLine, 2015.
[2] Lenardo C Silva, Hyggo O Almeida, Angelo Perkusich, and Mirko Perkusich. A model-based approach to support validation of medical cyber-physical systems. Sensors, 2015.
[3] Anitha Murugesan, Oleg Sokolsky, Sanjai Rayadurgam, Michael Whalen, Mats Heimdahl, and Insup Lee. Linking abstract analysis to concrete design: A hierarchical approach to verify medical cps safety. In ICCPS'14.
[4] Chiara Dalla Man, Robert A Rizza, and Claudio Cobelli. Meal simulation model of the glucose-insulin system. IEEE Transactions on biomedical engineering, 2007.

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Dallaman’s Model

1. a glucose–insulin regulatory protocol for intra–operative Type 1 diabetic patients
2. consists of 7–states with an insulin sub–model (5 states) and a glucose sub–model (2 states)

$$\dot{I}_p(t) = -(m_2 + m_4)I_p(t) + m_1 I_l(t) + u(t) \times 10^2 / BW$$

$$\dot{X}(t) = P_{2U} / V_i I_p(t) - P_{2U} X(t) - P_{2U} I_b$$

$$\dot{I}_1(t) = k_i / V_i I_p(t) - k_i I_1(t)$$

$$\dot{I}_d(t) = k_i I_1(t) - k_i I_d(t)$$

$$\dot{I}_l(t) = m_2 I_p(t) - (m_1 + m_3)I_l(t)(ku$$

$$\dot{G}_p(t) = - k_1 G_p(t) + k_2 G_t(t) - F_{snc} + m(t) \times 10^3 / BW + \max(0, k_{p1} - k_{p2} G_p(t) - k_{p3} I_d(t)) - 1 -$$

$$\max(0, k_{e1}(G_p(t) - k_{e2}))$$

$$\dot{G}_t(t) = - (V_{m0} + V_{mx} X(t)) G_t(t) / (K_{m0} + G_t(t)) + k_1 G_p(t) - k_2 G_t(t)$$

Dallaman’s Model

3. output of the model is given by

$$y(t) = G_p / V_g$$

4. consists of 18 model parameters

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Proportional Derivative Controller

- Total insulin **u(t)** that enters the blood stream is given by–

$$u(t) = u_c(t) + u_b(t)$$

where $u_c(t)$ is the continuous intravenous infusion rate and $u_b(t)$ is the bolus input impulse

- Glucose input **m(t)** is an impulse input in the form of dextrose

Proportional Derivative Controller

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Working Principle of the PD–controller

1. Clinicians sample the blood glucose levels of the patients periodically at an interval of 30 minutes
2. Based on the current blood glucose level y(k) and previous blood glucose level y(k–1), either insulin or glucose needs to be administered to maintain the glucose level within a normal range (70–130mg/dL) [5]

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[5] Benjamin A Kohl, Sanjian Chen, Margaret Mullen-Fortino, and Insup Lee. Evaluation and enhancement of an intraoperative insulin infusion protocol via in-silico simulation. In Healthcare Informatics (ICHI), , IEEE, 2013.

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Formal Verification Framework

1. Our formal verification framework consists of the **Dallaman's model** integrated with the **Proportional Derivative Controller**
2. The state diagram of the hybrid model is captured by **hybrid automata**
3. The state of a patient in a particular mode is captured by a set of differential equations
4. Every discrete transition leads to a mode switch in the patient
5. The unsafe region is captured by a **dead state ("Not Safe" mode)** where the blood glucose value lies **outside the normal range**. Once a patient enters this mode, he can never reach the accepting states

Formal Verification Framework

1. Every patient goes through a **pre–operative monitoring phase**.

2. If the blood glucose level remains within a **normal range (70–130mg/dL)** in this period, the patient is operated upon.

3. Otherwise, the surgery is postponed till the blood glucose level comes to a stable region.

4. Based on the pre–operative monitoring period, two possible cases are –

   Case 1: A pre–operative monitoring phase of 30 minutes.

   Case 2: A pre–operative monitoring phase of unbounded duration during which the PD–controller works at every 30 minutes to bring down the blood glucose level within normal range.

5. A **protocol–control phase**, during which the PD–controller works at **every 30 minutes** and updates the control inputs according to the blood glucose level of the patient. The patient goes into the **"Not Safe" mode** if the blood glucose level is not within the **normal range of 60–150mg/dL**.

Formal Verification Framework

The state matrix x(t) and the input matrix inp(t) of our model is given by–

$$x(t) = \begin{bmatrix} I_p(t) \\ X(t) \\ I_1(t) \\ I_d(t) \\ I_l(t) \\ G_p(t) \\ G_t(t) \end{bmatrix} \qquad inp(t) = \begin{bmatrix} u(t) \\ m(t) \end{bmatrix}$$

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Objective

"*To verify that the patient is safe and the system does not enter the Not Safe mode.*"

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Challenges in Verification : Due to large variations in the parameter values, full–time verification of the Dallaman's model turns out to be infeasible for some cases

An alternative approach to verify such a non–linear system is to approximate the model using some linearization technique.

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Linearized Model

applied Jacobian Linearization [6] to linearize the hybrid model

[6] Mohammed Dahleh, Munther A Dahleh, and George Verghese. Lectures on dynamic systems and control. A+ A, 4(100):1–100, 2004.

Linearized Model

applied Jacobian Linearization [6] to linearize the hybrid model

Step 1: Equate each state equation in the state matrix to 0 to get the initial **equilibrium points** corresponding to each state function.

Step 2: Take **partial derivatives** of each of these equations w.r.t. ***x*** and ***inp*** respectively, we get the state update functions in the form of

$$dx/dt = A\ \delta_{x}(t) + B\ \delta_{inp}(t)$$

The output is in the form

$$y(t) = C\ \delta_{x}(t) + D\ \delta_{inp}(t)$$

where each of A,B,C,D are matrices at the equilibrium points.

[6] Mohammed Dahleh, Munther A Dahleh, and George Verghese. Lectures on dynamic systems and control. A+ A, 4(100):1–100, 2004.

Error in Linearization

- The error in linearization is given by

  $E(x) = f(x) - L(x)$

  where f (x) and L(x) are the non-linear and the corresponding linearized model respectively
- The error in linearization is bounded by $M(x-a)^2 / 2$, where M is the maximum value of $|f''|$ in the interval [a, x], where 'a' is the equilibrium point
- The **Hessian matrix** stores the **second order partial derivatives** of the function f(x)
- The error terms are functions of the model parameters
- Substitute the nominal values of the parameters into the error terms to get the minimum and maximum error of the model

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Formal Verification Experiments

- verified both the models on a machine with **Intel Core i7, 3.4 GHz processor** and **4GB RAM** with **Linux operating system**
- verified the hybrid models using **dReach−dReal version 3.16.09.01** [7]
- dReach−dReal has no support to represent linear systems
- verified the linearized model using **SAL** verification tool [8]

[7] Soonho Kong, Sicun Gao, Wei Chen, and Edmund Clarke. dreach: δ-reachability analysis for hybrid systems. In International Conference on Tools and Algorithms for the Construction and Analysis of Systems,Springer, 2015.

[8] Saddek Bensalem, Vijay Ganesh, Yassine Lakhnech, C´esar Mu noz, Sam Owre, Harald Rueß, John Rushby, Vlad Rusu, Hassen Sa¨ıdi, N. Shankar, Eli Singerman, and Ashish Tiwari. An overview of SAL. In C. Michael Holloway, editor, LFM 2000: Fifth NASA Langley Formal Methods Workshop, Hampton, VA, jun 2000. NASA Langley Research Center.

Formal Verification Experiments

dReach–dReal

1. a safety verification tool capable of supporting non–linear systems
2. solved the safety verification problem by checking the bounded δ –complete reachability analysis of the system, where δ denotes verification error
3. path length refers to the number of discrete transitions from one state to another in a hybrid model
4. path length in dReach denotes the depth upto which the state space has been explored

SAL

1. SAL tool supports verification of a model based on fixed point values of the parameters
2. To fully verify the linearized model, we ran multiple fixed point verification of the SAL model for all the parameters within their range

Formal Verification Experiemnts

- full system verification of the hybrid models with full parameter ranges did not scale for a path length greater than 7
- For the verification of the linearized Dallaman's model, we sampled each parameter range into intervals of upto 4, depending on the range of the parameter and their variation in the running time within that range
- On sampling the 18 model parameters into intervals of upto 4, we have 8192 calls to the SAL model for every full verification run of the linearized model
- calculated the error in linearization by substituting the nominal values of the parameters in the error terms and added the error with the linearized model
- full system verification of the hybrid model does not scale in dReach
- full system verification of the linearized model becomes verifiable in SAL with approximately 2x faster execution time for a path length of 7

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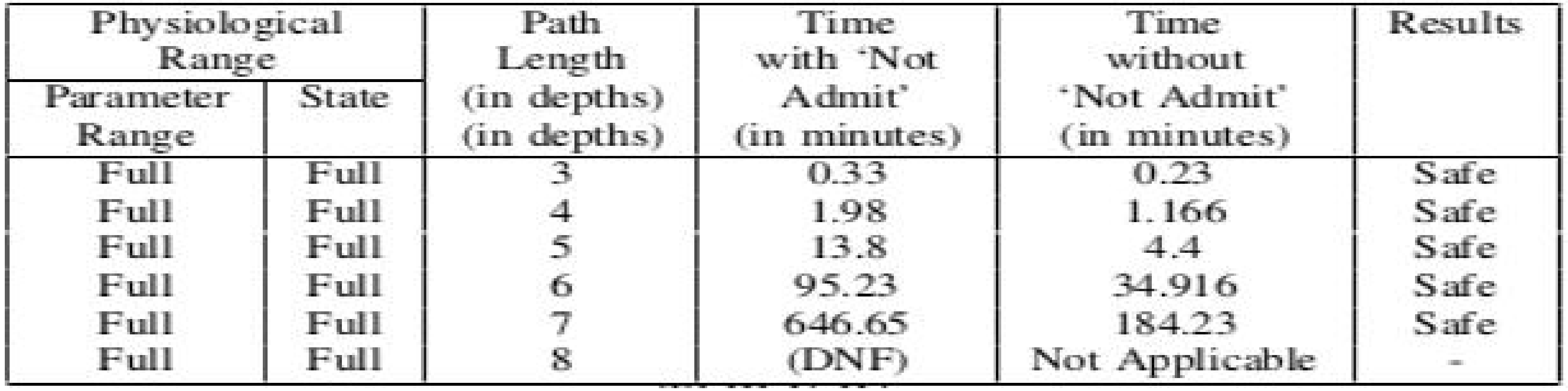
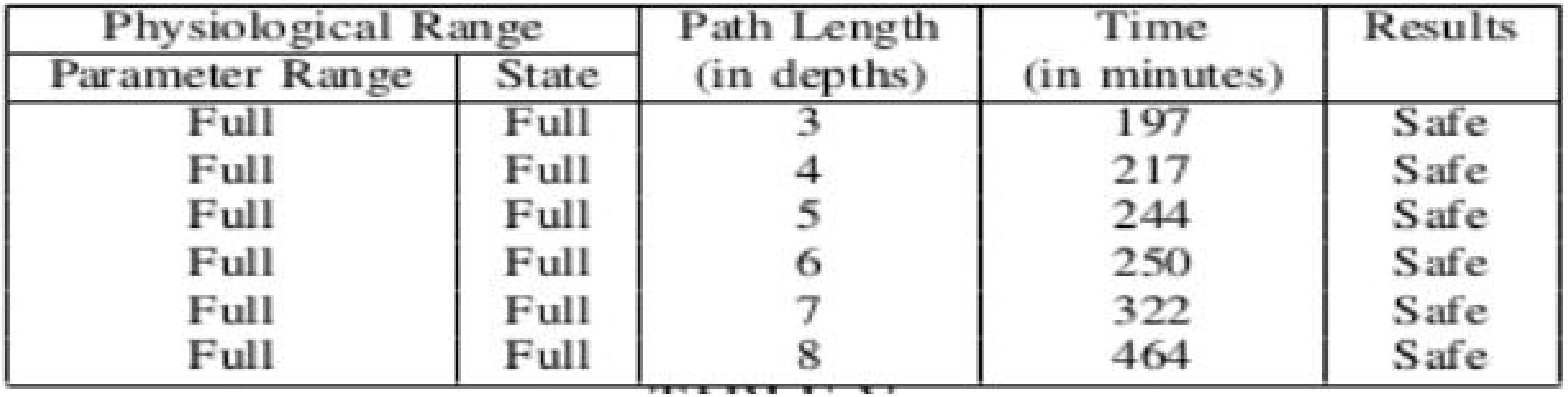
Formal Verification Results



Physiological Range		Path Length (in depths) (in depths)	Time with ‘Not Admit’ (in minutes)	Time without ‘Not Admit’ (in minutes)	Results
Parameter Range	State				
Full	Full	3	0.33	0.23	Safe
Full	Full	4	1.98	1.166	Safe
Full	Full	5	13.8	4.4	Safe
Full	Full	6	95.23	34.916	Safe
Full	Full	7	646.65	184.23	Safe
Full	Full	8	(DNF)	Not Applicable	-

Verification of Dallaman's hybrid model in dReach



Physiological Range		Path Length (in depths)	Time (in minutes)	Results
Parameter Range	State			
Full	Full	3	197	Safe
Full	Full	4	217	Safe
Full	Full	5	244	Safe
Full	Full	6	250	Safe
Full	Full	7	322	Safe
Full	Full	8	464	Safe

Verification of linearized Dallaman's model in SAL

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Conclusion

- a formal verification framework for verification of a famous glucose control physiological model, the Dallaman's model
- verified the hybrid model in dReach
- verification of the hybrid model becomes non–scalable in large time horizons due to exponential blow up of the state space
- linearized our model using Jacobian Linearization technique
- calculated the error in linearization
- verified the linearized model in SAL

References

[1] Sanjian Chen, Matthew O’Kelly, James Weimer, Oleg Sokolsky, and Insup Lee. An intraoperative glucose control benchmark for formal verification. IFAC-PapersOnLine, 2015.

[2] Lenardo C Silva, Hyggo O Almeida, Angelo Perkusich, and Mirko Perkusich. A model-based approach to support validation of medical cyber-physical systems. Sensors, 2015.

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[8] Saddek Bensalem, Vijay Ganesh, Yassine Lakhnech, C ésar Mu noz, Sam Owre, Harald Rueß, John Rushby, Vlad Rusu, Hassen Sa ïdi, N. Shankar, Eli Singerman, and Ashish Tiwari. An overview of SAL. In C. Michael Holloway, editor, LFM 2000: Fifth NASA Langley Formal Methods Workshop, Hampton, VA, jun 2000. NASA Langley Research Center.

THANK YOU