IEEE CDC 2014

Workshop Title:

Recent advances in modeling and control for Diabetes treatment

Organizers:

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Workshop length:

The proposed workshop length is one full day (1 morning session + 1 afternoon session).

1 List of presenters with short bios

Frank Doyle, University of California at Santa Barbara (UCSB), USA

Frank Doyle holds the Duncan and Suzanne Mellichamp Chair in Process Control in the Department of Chemical Engineering, as well as appointments in the Electrical Engineering Department, and the Biomolecular Science and Engineering Program at UC, Santa Barbara. He is the Director of the UCSB/MIT/Caltech Institute for Collaborative Biotechnologies, and is the Associate Dean for Research in the College of Engineering. He received a B.S.E. degree from Princeton, C.P.G.S. from Cambridge, and Ph.D. from Caltech, all in Chemical Engineering. Prior to his appointment at UCSB, he has held faculty appointments at Purdue University and the University of Delaware, and held visiting positions at DuPont, Weyerhaeuser, and Stuttgart University. He has been recognized as a Fellow of multiple professional organizations including: IEEE, IFAC, AIMBE, and the AAAS. He served as the editor-in-chief of the IEEE Transactions on Control Systems Technology from 2004-2009, and was the Vice President for Publications in the Control System Society from 2011-2012. His research interests are in systems biology, network science, modeling and analysis of circadian rhythms, and drug delivery for diabetes.

Wayne Bequette, Rensselaer Polytechnic Institute, USA

B. Wayne Bequette is a Professor of Chemical and Biological Engineering, and Associate Director of the Center for Automation Technologies & Systems (CATS) at Rensselaer Polytechnic Institute. In that capacity is a member of the Smart Manufacturing Leadership Coalition, a non-profit organization involved in the development and deployment of Smart Manufacturing Systems. His research spans a wide range of topics, from biomedicine and healthcare to energy and sustainability. Dr. Bequette is currently developing a closed-loop artificial pancreas for individuals with type 1 diabetes; this system automatically adjusts an insulin infusion pump based on signals from a continuous glucose monitor, In addition to testing these prototypes in a clinical environment, over 2000 patient-nights of in-home overnight studies have been conducted.

Claudio Cobelli, Università di Padova, ITALY

Claudio Cobelli is Full Professor of Bioengineering at the University of Padova, Padova, Italy. His major research activity is in modeling, identification and control of metabolic systems, and is mainly supported by NIH, JDRF and European Community. He has published more than 400 papers in peer reviewed journals and is co-author of 8 textbooks. He is presently Associate Editor of Journal of Diabetes Science and Technology and on the Editorial Board of Diabetes; Medical & Biological Engineering & Computing, and Diabetes, Technology & Therapeutics; he has been Associate Editor of Mathematical Biosciences and IEEE Transactions on Biomedical Engineering. He has been Chairman (1990-1993 & 1993-1996) of IFAC TC on Modeling and Control of Biomedical Systems. He is Fellow of Institute of Electrical and Electronic Enginering (IEEE), Biomedical Engineering Society (BMES) and American Institute for Medical and Biological Engineering (AIMBE). In 2010 he received the Diabetes Technology Artificial Pancreas Research Award.

Boris P. Kovatchev, University of Virginia

Dr. Boris P. Kovatchev is Professor at the University of Virginias (UVA) School of Medicine, Adjunct Professor at the School of Engineering and Applied Science, and the founding Director of the UVA Center for Diabetes Technology. He received his Ph.D. degree in Mathematics from Sofia University St. Kliment Ohridski, Bulgaria in 1989. Kovatchev has a 20-year track record in mathematical modeling and computing, with primary focus on translational diabetes research. Currently, he is the Principal Investigator of several large projects dedicated to the development and clinical testing of closed-loop control and advisory systems for diabetes, including: (i) NIH Diabetes Impact Project DP3 DK 101055 at UVA and Stanford University; (ii) the JDRF Artificial Pancreas Project at UVA a multi-center study that along with UVA involves the Universities of Padua (Italy), Montpellier (France), Stanford University, UC Santa Barbara, and the Sansum Diabetes Research Institute; (iii) NIH RO1 DK 085623 at UVA and Padua, and (iv) NIH RO1 DK 051562 focusing on the control of glucose variability. Kovatchev is also Co-Principal Investigator of a multi-center NIH Diabetes Impact Project (DP3 DK 094331) at UC Santa Barbara, UVA, and the Mayo Clinic and leads several industry-sponsored studies. His projects resulted in in the [only] computer simulator of the human metabolic system accepted by FDA as a substitute to animal trials for the pre-clinical testing of insulin treatments, and in the first [worldwide] outpatient trials of portable artificial pancreas. Kovatchev is author of 143 peer-reviewed publications and is a member of the editorial boards of IEEE Transactions on Biomedical Engineering and the Journal of Diabetes Science and Technology. He holds 38 U.S. and international patents and has numerous patent applications currently pending. In 2008 he received the U.S. Diabetes Technology Leadership Award; in 2011 he was named the UVAs Edlich-Henderson Inventor of the Year, and in 2013 he was the recipient of JDRFs Gerold and Kayla Grodsky Award presented for outstanding scientific contributions to diabetes research.

David Price, Medical Affairs - Dexcom

Dr. Price is Vice President of Medical Affairs at Dexcom. His many responsibilities include the design and interpretation of Dexcom clinical trials and usability studies, providing oversight and collaboration on investigator- initiated studies, developing publications, and providing clinical input into product development and risk management processes. Dr. Price previously worked at LifeScan and was responsible for developing clinical decision support solutions and clinical research. He has numerous patent applications related to applying decision support to medical devices. Dr. Price was a clinical fellow at the Joslin Diabetes Center and Harvard Medical School. From 1986-2002, he was in private clinical practice as a diabetologist in Santa Rosa, Ca. During this period, he served as an investigator for numerous pharmaceutical and device trials related to diabetes and metabolism. He is a fellow of the American College of Endocrinology and held a clinical faculty appointment at University of California in San Francisco from 1990-2001. Dr. Price has authored many publications and has lectured extensively on diabetes related topics to physicians, nurses, and the general public. His internship and residency were completed at the Maine Medical Center. His medical degree is from the Ohio State University College of Medicine, and his undergraduate baccalaureate degree from Washington University in St. Louis. Dr. Price is from Cleveland, Ohio.

Howard Zisser, Insulet Corporation

Howard Zisser is Medical Director at Insulet Corporation, Adjunct Professor at the Department of Chemical Engineering, University of California at Santa Barbara and Visiting Associate in the Division of Chemistry and Chemical Engineering of the California Institute of Technology.

Bruce A. Buckingham, Stanford University

Bruce Buckingham, M.D. is a Professor of Pediatric Endocrinology at Stanford University and Packard Childrens Hospital. Dr. Buckinghams research interests have focused on continuous glucose monitoring in children and closing-the-loop. These efforts are being funded by the JDRF, NIH and the Helmsley Foundation and are currently focused on preventing nocturnal hypoglycemia with a predictive low-glucose suspend system, and full overnight closed-loop. Other closed-loop studies are focused on 24/7 closed loop in the ambulatory setting and assessing ways to improve insulin infusion sets to prolong their wear.

Lane Desborough, Medtronic Lane Desborough is the Chief Engineer for the Insulin Delivery / Closed Loop business unit of the Diabetes division of Medtronic, Inc. in Northridge California. He is responsible for sourcing new concepts to advance diabetes management in alignment with a vision of customer-focused solutions, as well as advancing the organization's adoption of new technologies and capabilities. Examples include model based development, human-centered automation, statistics, big data, frugal innovation, system safety engineering, and lean development.

Lane received engineering degrees from the University of Waterloo and Queen's University, specializing in chemical engineering process control. Prior to joining Medtronic in 2010, he spent 18 years working for Nova Chemicals, Honeywell, and General Electric. He lives with his wife and three children in Thousand Oaks, California and enjoys marathon running and sailboat racing. He serves on the board of Insulindependence.org, a nonprofit member association dedicated to uniting, expanding and supporting the active diabetes community.

2 Abstract

The proposed full day workshop is jointly organized by two IEEE CSS technical committees as part of their activities: the IEEE CSS Technical Committee on System Identification and Adaptive Control (chaired by Diego Regruto) and the IEEE Technical Committee on Medical and Health Care Systems TC-MHCS (chaired by Daniel Rivera). Diabetes is a common metabolic disorder characterized by chronic hyperglycemia that leads to a number of critical health complications including limb loss, blindness and ischemic heart disease, just to cite a few. Unfortunately, the traditional approach to the management of diabetes, based on multiple daily subcutaneous insulin injections, is inadequate in many cases. For this reason, significant research efforts have been devoted in the last decades to overcome the limitations of the traditional medical practice. Although the idea of feedback control of the blood glucose dynamics can be traced back to the 70s, recent technological advances in the fields of implantable glucose sensor and programmable insulin pump of small size have paved the way to the realization of an artificial pancreas, i.e. a feedback control system designed for computing in real-time the best possible insulin delivering strategy on the basis of a mathematical model of the diabetic patient.

The workshop objective is (i) to provide to the control community a tutorial overview of the recent advances in the field of modeling and control for diabetes care and (ii) to stimulate interaction between the control community and the medical/biomedical industry community on the subject of diabetes care. In order to meet such objectives, the workshop proposers have brought together eight speakers taken among the most renowned leading experts in the areas of modeling and control for diabetes care (four from the control and biomedical engineering academic research community, and four from the medical/industry community). The eight proposed lectures will span, in a tutorial fashion, some of the most significant aspects of the problem ranging from modeling of the diabetic patient dynamics to closed-loop control and continuous glucose monitoring sensor design. Open problems representing challenging opportunity for the control/system identification research community will also be presented.

3 Brief statements of the workshop goals

By bringing together leading researchers in the fields of modeling and control for diabetes care, including also industry or medical speakers, the organizers propose a set of tutorial lessons aimed at:

(i) reviewing the fundamental aspects and difficulties related to the problem of modeling and control for blood glucose regulation in patients affected by Type I diabetes;

(ii) provide a report on the recent advances obtained in this field highlighting the crucial role played by control theory;

(iii) provide to the control community a list of challenging open problems that still need to be solved in order to realize an effective artificial pancreas systems

4 Brief description of the intended audience

We believe that the proposed workshop will benefit the identification/control community as well as other communities, e.g., signal processing, biomedical engineering. We believe that the potential audience of this workshop comprises a relatively large number of CDC participants. The workshop will be the opportunity for a lively and productive interaction between academic and industry experts of the field.

5 Proposed Workshop structure and contents

The workshop consists of two parts. The first part comprises a set of tutorial lectures aimed at presenting the fundamental concepts and some recent results about modeling and control for diabetes care developed by leading researcher in the field of control and biomedical engineering. The second part is explicitly devoted to show the point of view of the industrial and medical community on the subject.

PART I: Modeling and control for diabetes care: review of fundamental concepts and recent advances

The first part consists of the 4 talks listed below.

(I.1) Title: *Closed-Loop Artificial Pancreas Systems: overview and recent clinical advancements*

Speaker: F. Doyle

Brief summary: In this overview talk, we describe and evaluate Artifical Pancreas (AP) technology to gain further momentum toward outpatient trials and eventual approval for widespread use. We enumerate the design objectives, variables, and challenges involved in AP development, followed by a discussion of recent clinical advancements. Thanks to the effective integration of engineering and medicine, the dream of automated glucose regulation is nearing reality. Consistent and methodical presentation of results will accelerate this success, allowing head-to-head comparisons that will facilitate adoption of the AP as a standard therapy for type 1 diabetes.

(I.2) Title: *Steps Towards a Closed-loop Artificial Pancreas for Type 1 Diabetes*

Speaker: W. Bequette

Brief summary: The pancreas in individuals with Type 1 diabetes mellitus (T1DM) no longer produces insulin and, therefore, these individuals must inject insulin to regulate their blood glucose concentration. The goal of this research is to develop a closed-loop artificial pancreas (AP), composed of a continuous glucose sensor, insulin pump and a control algorithm that automatically adjusts the pump to maintain desired glucose levels. Our research has proceeded in several phases, developing (i) alarms to warn of impending hypoglycemia (low blood sugar), (ii) a predictive low glucose suspend (PLGS) system to avoid overnight hypoglycemia, (iii) a combined overnight hypo- hyperglycemia mitigation, and (iv) a fully closed-loop day/night risk management based strategy. The PLGS system has undergone extensive clinical testing, including over 2000 nights of at-home studies that confirmed a tremendous decrease in hypoglycemic risk compared to standard care. Our major upcoming study involves the development of a portable ambulatory closed-loop system, which will be tested in hotel and at-home studies.

(I.3) Title: *The Artificial Pancreas Simulator: Recent Developments in Modeling.*

Speaker: C. Cobelli

Brief summary: Simulation and modeling have allowed in recent years an acceleration in the artificial pancreas research. The talk will review the recent developments on in silico patient and glucose sensor modeling.

(I.4) Title: *Modular Architecture of Closed-Loop Control in Diabetes: Aligning Physiology with Control Design.*

Speakers: B. Kovatchev

Brief summary: The success of the closed-loop control of diabetes (known as the artificial pancreas) is contingent upon the interaction between a network of physiologic and behavioral processes specific to each patient and an individually-tailored control system. Thus, to ensure the transition of the artificial pancreas to everyday ambulatory use and widespread clinical acceptance, the control algorithm design needs to reflect physiology and behavior. In this presentation, we discuss a multi-layer architecture consisting of dedicated algorithmic modules responsible for identification and handling of underlying physiological and behavioral processes such as circadian hormonal rhythms, hepatic glycogen depletion resulting from recurrent hypoglycemia, and transient variations in insulin sensitivity triggered by behavioral events (e.g. alcohol, exercise).

PART II: Modeling and control for diabetes care: recent advances in the medical and industrial community

The second part consists of the 4 talks listed below.

(II.1) Title: *The evolution of Continuous Glucose Monitoring (CGM) performance, an essential component closed loop systems*

Speaker: D. Price

Brief summary: In 2001, only one RT-CGM device, GlucoWatch Biographer (Cygnus, Redwood City, CA) was commercially available.30 By 2005, four RT-CGM systems had been approved for use in the U.S. or carried CE marking for use in Europe. These included the GlucoWatch G2 Biographer (GW2B; Cygnus, Redwood City, CA), Guardian RT (Medtronic, Northridge, California, USA), GlucoDay (A. Menarini Diagnostics, Florence, Italy) and Pendra (Pendragon Medical, Zurich, Switzerland). A fifth device, Dexcom STS (Dexcom, ADDRESS) was approved in 2006. By 2008, the Dexcom Seven and the FreeStyle Navigator Continuous Glucose Monitor (Abbott Laboratories, Alameda, CA) were commercially available. All of the aforementioned products have been withdrawn from the market or supplanted by newer and improved products from the same manufacturers. Currently, there are four RT-CGM systems commercially available in the US: Dexcom G4 PLATINUM system; Medtronic Guardian Real Time system; Medtronic Paradigm Real Time insulin pump with Sof-Sensor; and Medtronic 530 G with Enlite Sensor. A number of other systems are in use or are awaiting regulatory approval in Europe. These new devices have demonstrated increasingly greater accuracy than their predecessors as assessed by a commonly used accuracy metric, the mean absolute relative difference (MARD). MARD measures the difference between RT-CGM sensor readings and paired glucose values obtained through laboratory reference methodology. Whereas, the MARD values of the CGM systems approved by the FDA from 2001 through 2006 ranged from 19.7% 31 to 26.0%,32 the MARD values for two of the most recently approved CGM systems were reported to range from 11% to 13% for one device 33, 34 and 14% to 18% for another device. In addition, the current systems have reduced data gaps and diminished sensors with large errors that could result in erroneous insulin administration or missed detection of hypoglycemia. The enhanced accuracy of current systems, relative to past burdens, should facilitate safe and effective closed loop systems.

(II.2) Title: *Ultra rapid insulins in closed loop AP systems*

Speaker: H. Zisser

Brief summary: Currently available commercial insulins have a relatively sluggish onset of action, which can lead to sub-optimal closed-loop control. Novel insulins and insulin delivery methods with be discussed including clinical data using intraperitoneal and inhaled insulin.

(II.3) Title: *Overnight Closed-Loop for Type 1 Diabetes: many algorithms, similar results.*

Speaker: B. A. Buckingham

Brief summary: Overnight closed-loop avoids major day time disturbances in glucose control associated with meals and exercise. It is a time of great concern for people with diabetes since they are asleep, unaware of their glucose levels and majority of hypoglycemic seizures occur at night with the risk of "DEAD-in-bed" syndrome. One issue is subjects lying on their sensor causing nocturnal attenuations in the glucose signal. The first step is to prevent lows with predictive low glucose suspend algorithms, and then employ full closed-loop algorithms overnight. PID, MPC, and fuzzy logic algorithms have all been used to good effect in research center studies, and are now being using in the home environment.

(II.4) Title: *Practical Challenges And Opportunities With Modeling Glucose Dynamics In People With Type 1 Diabetes.*

Speaker: L. Desborough

Brief summary: Good experiments yield good data, good data yield good models, good models yield good predictions, and good predictions yield good control. Thus dynamic models of glucose dynamics are foundational to the development of closed loop insulin delivery systems to reduce task burden for people with type 1 diabetes. The modeling path to the so-called Artificial Pancreas is fraught with peril: nonlinearities, non-Gaussian distributions, short sample lengths, nonquadratic loss functions, inaccurate sensing, inconsistent recording, missing data, sensor artifacts, unmeasured inputs, coincident inputs, lack of persistent excitation, small datasets, and varying plant dynamics are just some of the challenges associated with developing accurate, individualized models. These challenges and our progress towards addressing them at Medtronic Diabetes will be discussed.

6 Prerequisites

Due to the tutorial nature of the workshop the audience is not expected to satisfy any specific prerequisites. We are strongly convinced that, by attending the workshop, experts in control/system identification theory will take the opportunity to become aware of a number of exciting research challenge.