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SYMPOSIUM

Progress in Development of an Artificial Pancreas

David C. Klonoff, M.D., FACP,[1] Claudio Cobelli, Ph.D.,[2] Boris Kovatchev, Ph.D.,[3] and Howard C. Zisser, M.D.[4]

Abstract

This issue of *Journal of Diabetes Science and Technology* contains a collection of 12 original articles describing the latest advances in the development of algorithms for controlling insulin delivery in an artificial pancreas. Algorithms presented in this issue are affected by numerous quantifiable factors, including insulin pharmacokinetics, timing of meal carbohydrate appearance, meal size, amount of exercise, presence of stress, day-to-day variations in insulin sensitivity, insulin time-activity profiles, accuracy of glucose monitor calibration, metabolic profiles of both adults and neonates, and risks of hypoglycemia/hyperglycemia. These articles present theoretical advances in insulin delivery algorithms from modeled *in silico* patients, as well as clinical data from actual patients who have used closed loop systems. The novel approaches described in these articles are expected to bring us much closer to realization of a commercially available closed loop system for controlling glucose levels in patients with diabetes.

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Introduction

This issue of *Journal of Diabetes Science and Technology* presents a collection of 12 original articles describing the next generation of advances for creating an artificial pancreas. The articles focus on new developments in insulin delivery algorithms as opposed to new glucose sensors or insulin delivery hardware. This symposium has been coedited by Claudio Cobelli, Boris Kovatchev, and Howard Zisser. Development of an artificial pancreas is a major goal of scientists, engineers, and clinicians in the diabetes technology community.[1] This type of system will provide automated insulin delivery with better blood glucose levels, less variability, fewer episodes of hypoglycemia, and less time spent on making decisions than any open loop system can deliver.

Journal of Diabetes Science and Technology is closely covering artificial pancreas technology. In November 2007, this journal published the first collection or symposium of articles focused on this type of system, which was entitled "Artificial Pancreas: Closed Loop Control of Glucose Variability in Diabetes."[2–5] These articles described various algorithms for achieving control in type 1 diabetes. The symposium was coedited by B. Wayne Bequette, Claudio Cobelli, and Boris Kovatchev.

Author Affiliations: [1]Mills-Peninsula Health Services, San Mateo, California; [2]University of Padova, Padova, Italy; [3]University of Virginia, Charlottesville, Virginia; and [4]Sansum Diabetes Research Institute, Santa Barbara, California

Abbreviations: (FDA) Food and Drug Administration, (IOB) insulin on board, (MPC) model predictive control

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Corresponding Author: David C. Klonoff, M.D., FACP, Mills-Peninsula Health Services, 100 South San Mateo Drive, Room 5147, San Mateo, CA 94401; email address dklonoff@yahoo.com

Algorithm Development

The field of algorithm development for closed loop control has progressed since 2007. A major advance since then has been development of an *in silico* diabetes simulator against which to test algorithms.[6] This simulator is now used by many researchers as a tool for computer-aided development of control algorithms and is accepted by the Food and Drug Administration (FDA) as a substitute for animal trials in the preclinical setting. The articles in this year's symposium focus on algorithms, which are determined by an even greater number of factors than ever before. Algorithms presented in this issue are affected by numerous quantifiable factors, including insulin pharmacokinetics, timing of meal carbohydrate appearance, meal size, amount of exercise, presence of stress, day-to-day variations in insulin sensitivity, insulin time-activity profiles, accuracy of glucose monitor calibration, metabolic profiles of both adults and neonates, and risks of hypoglycemia/hyperglycemia. In addition to presenting theoretical advances in insulin delivery algorithms from modeled *in silico* patients, this symposium also presents clinical data from actual patients who have used closed loop systems.

Symposium Articles

This year's artificial pancreas symposium in *Journal of Diabetes Science and Technology* contains 12 original articles. (1) In the 1st article, Bequette and colleagues use glucose infusion rates from glucose clamp studies to generate insulin time-activity profiles to develop insulin-on-board (IOB) curves. The effects of bias of handheld blood glucose meters on IOB curves are modeled in order to assess whether these monitors can be used in glucose clamp studies of insulin sensitivity.[7] (2) In the 2nd article, Bruttomesso and colleagues apply both a model predictive control (MPC) algorithm and open loop control on a set of patients with type 1 diabetes. Results of both types of control are compared in terms of mean glucose levels, percentage of time spent in the hyperglycemic range, postprandial glucose levels, and episodes of severe hypoglycemia.[8] (3) In the 3rd article, Cameron and colleagues describe an algorithm to detect the presence of a meal and to detect the shape and total appearance of the meal. They go on to validate the performance of this algorithm both as a stand-alone formula and in cooperation with a controller on an FDA-approved type 1 diabetes simulator.[9] (4) In the 4th article, Clarke and colleagues use a new personalized MPC algorithm for determining insulin dosages. They compare the performance of this algorithm to that of an open loop system for controlling glucose levels both overnight and for 4 hours after a standardized meal.[10] (5) In the 5th article, Hernando and colleagues present an automatic data processing risk management system to alert the physician about out-of-range glucose values and to shut off insulin infusion during hypoglycemia. They test their algorithm on a cohort of ambulatory type 1 subjects and on a simulated population. (6) In the 6th article, Kanderian and colleagues present closed loop algorithms that incorporate intraday variations in three metabolic parameters: variance in insulin sensitivity, the effect of glucose intake without insulin on board, and endogenous insulin production without insulin on board. They calculate how a closed loop control algorithm is improved by incorporating these three factors, which vary each day, along with the initial glucose concentration, basal insulin rate, meal carbohydrate content, and basal insulin concentration.[12] (7) In the 7th article, Kovatchev and colleagues introduce a class of algorithms called control to range for optimizing insulin dosing. This construct includes a range correction module for adjusting the insulin delivery rate to avoid abnormal glucose excursions and a safety supervision module for assessing the risk of hypoglycemia to attenuate or discontinue insulin infusion when necessary.[13] (8) In the 8th article, Le Compte and colleagues present a model predictive controller for the neonatal patient population. In a neonatal intensive care unit, these investigators compare the performance of this controller against retrospective control for safety and efficacy.[14] (9) In the 9th article, Lee and colleagues present a model predictive control algorithm for closed loop control that includes three novel components: meal detection and meal size estimation features, IOB constraints, and an insulin shut-off piece to avoid hypoglycemia. They then compare the results of using a model predictive control algorithm on a modeled population with or without these additional components.[15] (10) In the 10th article, Magni and colleagues propose an algorithm for closed loop control capable of automatic tuning according to the amount of insulin sensitivity. They test the performance of this algorithm on a cohort of virtual subjects.[16] (11) In the 11th article, Wang and colleagues propose a control algorithm for insulin dosing that utilizes a grid of nine zones defined by every combination of three possible absolute glucose values and three possible rates of change of the glucose value. Each zone defines a multiplier factor for the basal insulin rate. An algorithm containing these nine basal rate multipliers is tested on a simulated population.[17] (12) In the 12th article, Wilinska and colleagues present a proposed MPC algorithm for glucose control. They test this algorithm and compare the incidence of hypoglycemia for a simulated type 1 population with the incidence for a similar group of actual patients who are receiving open loop control.[18]

Conclusions

The authors whose articles are presented in this symposium are steadily advancing the field of algorithms for an artificial pancreas. Many new developments in algorithmic control are expected in the near future as we progress toward a commercial product. In 2011, *Journal of Diabetes Science and Technology* will present its third artificial pancreas symposium to chronicle further advances in this field. It is expected that the ideas presented in this 2009 symposium will lead to questions and hopefully also to answers about how to control an artificial pancreas system by regulating insulin infusion to stabilize glucose levels.

An artificial pancreas does not necessarily need to mimic the work of the healthy human pancreas to treat diabetes. It is only necessary for such a system to achieve similar glycemic results. Analogously, an airplane does not mimic bird flight, but achieves the intended result of air travel. The goal for developers of artificial pancreas systems remains to develop a smart system that can approximate the effect of a human pancreas in controlling blood glucose levels.

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