

## **Large lecture geared toward a generalized, non-specialist audience**

### **Title: The artificial pancreas for patients with type 1 diabetes**

In this lecture, I will start with a historical review of type 1 diabetes, starting from its recognition as far back as 1500 BCE by the ancient Egyptians and Indians (who named the condition “honey urine” as the urine of patients was attracting ants and flies). I will then review major historical attempts to treat type 1 diabetes and how the disease was invariably fatal until Sir Frederick Banting discovered insulin in 1922. The discovery of insulin was a dramatic breakthrough that saved millions of lives and transformed the disease from fatal to a chronic condition requiring life-long insulin replacement therapies. I will share photos<sup>1</sup> and stories of the historic events of insulin discovery and early insulin use.

I will then review the post-insulin era, and how we realized that conventional insulin therapy is insufficient and that patients would still develop long term devastating complications (blindness, kidney failure, lower extremity amputations, etc). I will present the landmark DCCT trial and how it transformed our treatment goals and introduced the concept of tight glucose control. I will present day-to-day difficulties in achieving tight glucose control, and the reasons 75% of the patients have poor glucose control.

I will then present technological advances in the treatment of diabetes, starting from the first infusion pump developed in the 1960s<sup>2</sup>. I will briefly review the evolution of glucose meters, continuous glucose sensors, and infusion pumps and detail how these advances motivated the research, starting a few years ago, towards the development of a portable artificial pancreas. I will present the basic principles of the artificial pancreas, its different configurations, and the results of early human trials by teams from Europe, US, and our team. I will explain why the artificial pancreas is considered the “Holy Grail” and the most promising therapy for diabetes.

I will then explain in simple terms the concept of feedback control systems (which is the basis of the artificial pancreas) and show examples of how these systems appear in many natural biological and physiological systems and human-made engineering systems. I will explain that although the system is called the artificial pancreas in the scientific literature and the media, it is developed using mathematical and engineering concepts and not by copying the physiological functionality of the pancreas. I will then draw an analogy to building airplanes using engineering concepts and not by copying the physiological functionality of flying birds.

Finally, the future of the development of the artificial pancreas will be presented, and what technological, scientific, ethical, and regulatory hurdles we still need to be overcome before the system becomes commercially available. Early studies of psychosocial aspects of the artificial pancreas and patients perspectives on its use will be presented. I will finish the talk by playing a small video of a young girl who participated in one of our studies, and was interviewed by CBC TV. When she was asked what she thought of her experience, she responded: “a lot of catheters”. She did not talk about how amazing it would be to have no more hypoglycemia events, no need to fear seizures, reduction of long term complications, and flexibility of food intake and exercise. Instead, her first thought was that extra needle the system needs. It was a clear message to us that we should never forget that it is those children who will eventually use the system, and as important glucose control and reduction of hypoglycemia are, patients’ priorities might be completely different and that we should ensure that we accommodate their needs.

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<sup>1</sup> See for example: <http://usvsth3m.com/wp-content/uploads/2014/10/6hCjyow.jpg>

<sup>2</sup> <https://pbs.twimg.com/media/BTDosp9CEAAqjh4.jpg:large>

## **Lectures accessible to a broad departmental audience in my field**

I propose to present the three lectures in three different departments: Division of Endocrinology, Department of Electrical and Computer Engineering, and Department of Mathematics.

### **1. Division of Endocrinology Talk**

#### **Title: Understanding the benefits of glucagon in the artificial pancreas**

In this talk, first, basic glucagon physiology in health and diabetes will be reviewed with its current clinical use. I will then present the concept of the single-hormone (insulin alone) artificial pancreas and results from in-patient and early out-patient studies from our group and others showing its improved safety and efficacy compared to conventional pump therapy. I will then present the concept of using glucagon in the artificial pancreas as an adjunct to insulin, and the potential this approach has to further reduce hypoglycemia in comparison to the single-hormone artificial pancreas. Whether the clinical benefits of adding glucagon to the artificial pancreas justifies the increased costs and device complexity is arguably the current biggest question in the field. We are the only team developing both artificial pancreas systems and systematically comparing the two. I will present published and unpublished results from six randomized controlled trials comparing the two systems in different conditions (exercise, night, out-patient, etc.) and populations (pediatrics, adults, hypoglycemia unaware patients, etc.). Finally, future planned studies and unanswered questions will be discussed.

This talk will be partially based on [10, 14, 17, 21, 22, 27, 28] (see my CV), papers from other groups, and unpublished data from our group.

### **2. Department of Electrical and Computer Engineering Talk**

#### **Title: Closed-loop control of glucose levels in patients with type 1 diabetes: Challenges and open problems.**

From a theoretical standpoint, developing the artificial pancreas is a control engineering problem. The artificial pancreas delivers insulin and glucagon into the body as guided by a control algorithm that relies on continuous glucose sensor readings. However, the control problem is challenged by the large intra- and inter-patient variability, sensor inaccuracies, and the time-lag in subcutaneous insulin absorption. I will present different control strategies that have been proposed in the literature for this problem such as proportional-integral-derivative controller, model predictive control, and fuzzy control. Special attention will be paid to controllers that have been tested clinically. I will then present our controller in detail, based on adaptive model predictive control combined with Kalman filtering, and show its performance.

Currently, patients need to calculate the carbohydrate content of every meal they eat and administer a matching insulin dose. This is a challenging task for most patients and calculation error might lead to post-meal low or high glucose levels. I will present a novel control algorithm for the artificial pancreas that would alleviate the burden of carbohydrate counting from the patients. This would be achieved by giving a small carbohydrate-independent pre-meal insulin bolus, and then giving the remaining needed insulin following sensor reading excursions as guided by the control algorithm. Due to delays in insulin absorption, the algorithm should reliably predict future meal-glucose appearance in the blood and be able to deliver matching insulin. This prediction by the algorithm is equivalent to what the patients do now in calculating

the carbohydrate content of a meal before eating, but the algorithm estimates the carbohydrate content using post-meal glucose excursions as measured by the sensor. These estimation and control algorithms were tested in a clinical trial and the results will be presented.

This talk will be partially based on [14, 16, 17, 22, 25] (see my CV), papers from other groups, and unpublished data from our group.

### **3. Department of Mathematics Talk**

#### **Title: Using Bayesian estimation to solve diabetes and glucose physiology problems**

This talk will be divided in two parts. First, I will present a computational method based on Bayesian inference to estimate glucose fluxes during the meal tolerance test that employs glucose isotope tracers (input estimation problem that is ill-conditioned). I will then present some of the clinical applications of this method, more specifically, to understand 1) absorption patterns of meal-related glucose appearance in adolescents after slowly and fastly absorbed meals; 2) glucose metabolism in pregnant women during different trimesters.

The second part of the talk will cover the development of mathematical models of virtual patients with individualized parameters to test artificial pancreas systems in computer-simulation environments. Clinical trials are integral part of the development process but are time-consuming, resource demanding, and costly. Pre-clinical testing in computer-simulation environments accelerates development and facilitates optimization of control algorithms. However, mathematical models of virtual patients need to be driven by real data and need to capture realistic higher order and time-varying dynamics, as well as intra- and inter-patient variability. To this end, I will present two methods within the Bayesian framework (utilising Markov chain Monte Carlo methods) to model the gluco-regulatory system, insulin and glucagon absorption kinetics, and sensor dynamics.

This talk will be partially based on [6, 7, 9, 13, 16, 20, 21] (see my CV), papers from other groups, and unpublished data from our group.

#### **Inviting two students from Arizona State University to Montreal**

In my departmental lectures at the Division of Endocrinology and the Department of Mathematics, I will present two paid summer internships to one medical school student and one senior mathematics undergraduate student to be conducted at McGill University/Montreal Institute of Clinical Research within our research program. Each internship will be accompanied by \$3500 that will allow the students to pay for travel expenses (~\$700), accommodation (\$500 per month), and some living expenses. I will personally fund these two internships from the Origins Project Postdoctoral Prize Lectureship.