# Toward an artificial pancreas: Math modeling and diabetes control

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October 4, 2012—Diabetes mellitus is a chronic disease in which individuals exhibit high levels of sugar in the blood, either due to insufficient production of insulin—the hormone that allows glucose to be absorbed by body cells—or the body's lack of response to insulin. Type 1 diabetes occurs due to loss or dysfunction of β-cells of the pancreas, the organ that produces insulin. Type 2 diabetes is caused by a defective glucose-insulin regulatory system. The most common control for diabetes is by subcutaneous injection of insulin analogues through insulin pumps.

In a paper published today in the *SIAM Journal on Applied Mathematics*, authors Mingzhan Huang, Jiaxu Li, Xinyu Song, and Hongjian Guo propose novel mathematical models for injection of insulin in type 1 and type 2 diabetes. The models simulate injections of insulin in the manner of insulin pumps, which deliver periodic impulses in diabetes patients.

Management of diabetes by insulin pumps usually follows an open-loop approach in which blood glucose can be periodically monitored by an individual using a glucose meter, and then adjusted by either eating a carbohydrate in cases of low blood glucose or administering a dose of insulin in cases of high blood sugar. While this is important to ensure that diabetes patients have sufficient insulin, it carries the risk of hypoglycemia, which is caused by excess insulin leading to excessive glucose absorption, resulting in low blood sugar. In addition, this approach requires diabetics to follow stringent regimens with regard to diet and insulin injections.

Research is now focused on a closed-loop approach, where a medical device will provide automatic glucose-responsive insulin administration. Closed-loop systems achieve this by real-time feedback between glucose levels and insulin delivery, approximating the endocrine functionality of a healthy pancreas, hence, also called the artificial pancreas. Early clinical trials of the artificial pancreas have shown positive results. This type of system will greatly improve the lifestyles of diabetes patients, obviating the need for manual injections, and making diet control slightly less stringent. The key factor here is the control algorithm, which manages insulin delivery based on glucose levels while accounting for measurement errors and kinetic delays. However, development of an artificial pancreas is impeded due to lack of reliable predictive models and methods for accurate glucose monitoring, in addition to inefficient control algorithms.

In this paper, differential equation models are used to simulate injections of insulin in both open and closed-loop systems. Algorithms are carefully designed to determine the time and dose of injections based on physiology and metabolism of insulin secretion, designed to prevent episodes of hyper and hypoglycemia. The models are then qualitatively and numerically assessed by injections of insulin analogues in the environment of both type 1 and type 2 diabetes.

The open loop model incorporates uniform injection of insulin at periodic intervals, where the frequency and dose of injection are chosen based on set parameters. "In open-loop control, the model analysis reveals that a smaller dose with higher delivery frequency is more effective, which confirms that continuous subcutaneous insulin injection (CSII), which is currently used clinically, is efficient," explains senior author Hongjian Guo.

The closed-loop model proposes injection of insulin when blood glucose level passes a certain threshold value using automatic feedback from a glucose monitoring system. "The model analysis for closed-loop control asserts that a larger dose is preferred with a careful consideration toward avoiding hypoglycemic episodes," Guo says. This is helpful in cases where patients may retain some ability to secrete small amounts of insulin; excessive insulin delivery would be prevented here as signaled by low glucose levels.

The paper thus demonstrates that insulin delivery can be modeled based on both periodic (open loop) and state-dependent (closed loop) impulses.

"Efficient and effective algorithms could be developed based on this model and embedded in the closed-loop control of artificial pancreas, which determine the dose and the timing for insulin delivery," says Guo. "Validation is extremely important in the design of an artificial pancreas. [Software] for validating the designs could be developed based on these models with an appropriate simulation of glucose input functions."

Future work involves achieving greater sensitivity by factoring specific aspects of body physiology into the artificial pancreas software, and using patient statistics to fine-tune parameters used in its algorithm. "We continue to improve the models by incorporating physiological time delays and mechanical delays in the system, and estimating model parameters with competent statistical methods."

**More information:** Modeling Impulsive Injections of Insulin: Towards Artificial Pancreas, Mingzhan Huang, Jiaxu Li, Xinyu Song, and Hongjian Guo, SIAM Journal on Applied Mathematics, 72(5), 1524–1548 (Online publish date: October 4, 2012)
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