

Emerging Technologies In Diabetes Research

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FDA Approves Computer Simulator to Model Diabetes, Test Artificial Pancreas Algorithms

In early January, 2008, the FDA approved an *in silico* model of diabetes as a pre-clinical testing tool for closed-loop research at the seven JDRF Artificial Pancreas Consortium sites. Functioning as a computer simulator of type 1 diabetes, the software program is housed at the Jaeb Center for Health Research in Tampa, FL, the consortium's coordinating center; each group will also have a fully functional but scaled-down version of the simulator for local use.

Among its benefits: The simulator will facilitate the development of new control algorithms—the computer programs that interpret continuous glucose sensor data and instruct the pump to dose the proper amount of insulin—by enabling consortium researchers to test and refine artificial pancreas algorithms quickly; it will allow for computer-based algorithm comparisons; and it will eliminate the need for animal testing, allowing investigators to focus instead on in-hospital human clinical trials, which will save significant investments of time or money. Because the simulator is now FDA-approved, the process of receiving regulatory approval for human trials of closed-loop systems will also be faster and more clearly defined.

On a broader scale, because the simulator is equipped with a wide array of tools for precise fine-tuning, it should help to bring promising algorithms closer to perfection—a necessary criterion for seamless communication between continuous glucose monitors (CGMs) and insulin pumps, and ultimately, the development and possible commercialization of a closed-loop artificial pancreas.

JDRF launched the Artificial Pancreas Project (APP) in late 2005 to expedite the availability of this rapidly emerging technology for people with type 1 diabetes. The Artificial Pancreas Consortium, one of the two research initiatives of the APP, includes top diabetes researchers, mathematicians, and engineers from around the world who

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In Brief: Updates from the Artificial Pancreas Project

For a wealth of articles and other updates about emerging technologies, visit JDRF's Artificial Pancreas Project Web site at www.jdrf.org/artificialpancreas.

A Third CGM Now FDA-Approved

The Food and Drug Administration recently approved a 5-day real-time continuous glucose monitor from Abbott Diabetes Care. Called the Freestyle Navigator, the device displays blood glucose values every minute, including the direction and rate of change, and will alarm up to 30 minutes before the occurrence of a low or high glucose target. “Continuous glucose monitors offer a major breakthrough in diabetes care management,” said Aaron Kowalski, PhD, research director of the JDRF Artificial Pancreas Project. “More choices are better for patients, and a competitive marketplace will encourage investment in new and even better generations of these products.”

Enrollment Complete for JDRF's Continuous Glucose Sensor Trial

In December, researchers completed the enrollment of 450 patients in the JDRF Continuous Glucose Sensor Clinical Trial. Taking place at ten sites across the U.S., the trial is the largest and first independent clinical study to measure how well blood sugar can be controlled using continuous glucose monitors compared with the more conventional fingerstick method. ❖

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are developing sophisticated computer programs that “close the loop” and automatically control glucose levels in a variety of circumstances and types of patients.

Dynamic duo

The story of the development of the artificial pancreas computer simulator begins with Dr. Claudio Cobelli of the University of Padova in Italy. An internationally recognized leader in the field, Dr. Cobelli’s pioneering work in the mathematical modeling of glucose metabolism began over 30 years ago and laid the foundation from which he and the other APP investigators built the *in silico* (or computer-based) platform for developing the artificial pancreas. One of his metabolic models, called the Meal Simulation Model, described in a recent issue of the journal *IEEE Transactions On Biomedical Engineering*, is in fact an early predecessor of the closed-loop metabolic simulator now approved by the FDA; both are fundamentally complex systems built on extensive clinical data collected over the past decade.

Dr. Boris Kovatchev, principal investigator of a consortium team at the University of Virginia in

Charlottesville, took the lead for the consortium in developing and obtaining approval for the simulator, and has been working closely with Dr. Cobelli for many years. Dr. Kovatchev has always stressed the importance of *in silico* testing, calling it “the flight simulator of the artificial pancreas,” and of making computer tests as close to real-world situations as possible.

Using the simulator to develop the artificial pancreas, he explains, is analogous to methods used to develop the Boeing 777 jetliner, which was the first airplane to be 100% digitally designed in a computer simulation environment. Employing computer-aided design, engineers conducted virtual test runs, launching and landing the plane before actual ground and flight tests began, saving time, money, and (possibly) lives in the process.

An interactive program driven by algorithms

As its name suggests, the computer simulator provides an *in silico* environment for developing the algorithm component of the artificial pancreas, the programming language of mathematical equations and variables that will “interpret” a person’s metabolic state and (in a true closed-loop system) relay this information from the glucose monitor to the

Using the Computer Simulator to Develop An Artificial Pancreas



Members of the Artificial Pancreas Consortium can now use an FDA-approved computer model of diabetes for driving and evaluating their research. The computer simulator, illustrated here, is a comprehensive software program designed to facilitate the development of safe and effective control algorithms—the programming language of mathematical equations and variables that will allow seamless communication between continuous glucose monitors and insulin pumps, the essential step to creating a true closed-loop artificial pancreas.

Tests of each algorithm will be run on the computer “against an *in silico* patient population that approximates—as closely as currently possible—the variability of the real population of people with diabetes,” says Dr. Kovatchev, a lead consortium researcher. This would include the whole range of variables that people with diabetes currently have to calculate on their own, from current blood sugar levels, to the direction it’s trending, to what and how recently they have eaten, to the impact of exercise and one’s individual sensitivity to insulin. As a result, the *in silico* experiments will accurately, efficiently, and safely capture the sensitivity of the algorithms before they are considered for testing in real patients, either in hospital-based clinical settings, or eventually, in everyday environments such as overnight tests at home or day tests for children in school.

Why is the development of an artificial pancreas a priority for JDRF? Research shows that most people with type 1 diabetes could significantly improve their blood sugar control. Thus the development of devices that facilitate tighter control of blood sugar would have immediate health benefits for people with diabetes, particularly in avoiding dangerously low blood sugars, or hypoglycemia. Such devices would also reduce the risk of developing diabetic complications, and would aid in the effectiveness of other cure therapeutics, such as beta cell replacement or regeneration. ♦

pump for automatic insulin delivery, the right amount at the right time. It is the algorithm that will enable the artificial pancreas to function as an autonomous system, much as a healthy pancreas does in people without diabetes. These algorithms will recognize or predict, for example, changes in blood glucose after a meal or in response to stress or exercise, and deliver an appropriate insulin dose to correct sugar imbalances, ensuring that individuals stay within their target range.

But formulating an algorithm “to capture and quantify the variability in the life of a person with diabetes” is no easy feat, as there is no typical person, explains Dr. Roman Hovorka, consortium leader at Cambridge University in England, who began researching artificial pancreas technologies in 2000.

THE new simulator has key design advantages that address this challenge. To begin, the computer simulation environment—the nuts-and-bolts structure of the new simulator—has three important and principal components, what Drs. Cobelli, Kovatchev, and the other contributing consortium researchers call “modular blocks”:

- The simulated subjects, representing virtual type 1 patients who have been programmed into the simulator and in whom the algorithms will be tested. This part of the model represents a patient’s physiologic response to a meal, and thus factors in the roles of the liver, gastrointestinal tract, and fat and muscle in response to changing glucose levels. Because individuals with type 1 diabetes do not produce insulin, insulin secretion is not included in the model.

- A simulated sensor, akin to the CGM, which will replicate calibration errors relating to delays in glucose movement from the bloodstream to the interstitial fluid where the sensor takes its reading; and also monitor sensitivity in measuring glucose levels.

- And a simulated insulin pump, which will register delivery of insulin. This part of simulation is particularly important because subcutaneously administered insulin, in real patients, shows significant delay in reaching the bloodstream, as well as significant variability in the delay from person-to-person.

The algorithm itself, representing a kind of portable, or independent, fourth modular block, is actually “plugged” into the simulator by the researchers, enabling “plug-and-play” capabilities. All four components—not just the algorithm—can be improved and upgraded, with researchers able to add new silicon subjects, sensors, and insulin delivery systems.

In addition to its design, the computer simulator brings a new and noteworthy degree of comprehensiveness. Tests of each algorithm will be run on “silicon” subjects, sensors, and pumps that were constructed using large amounts of data accumulated over many years. Such data on human metabolism, sensor accuracy, and between-subject variability on the subcutaneous transport of insulin were not available to earlier diabetes models, which were generally based on population averages and on the variance of a few parameters, and as a result, their application was largely limited to simulations of the “average person.”

In contrast, the new simulator is based on the distributions (and variance) of 26 key metabolic parameters determined from elaborate studies that included more than 350 people. This level of detail allows the safety of a control algorithm to be tested against an *in silico* patient population that approximates—as closely as currently possible—the variability of the real population of people with diabetes. An algorithm run through such a system would be deemed safe for the vast majority of patients, including those who are lighter in weight or susceptible to hypoglycemia.

However, the true strength of the simulator, according to its designers, is the inclusion of a large number and broad range of validated *in silico* subjects with type 1 diabetes—300 in total, including 100 children, 100 adolescents, and 100 adults. This virtual population was selected to cover the full range of human metabolic variability, and even to go beyond it, ensuring comprehensive testing of any closed-loop control algorithm that is run through the program. For example, the simulator can account for body weight ranging from 60-pound “children” to over 260-pound “adults,” as well as virtual patients who are very insulin sensitive (taking only 20 units of insulin per day) or extremely insulin resistant (taking over 100 insulin units per day, which most typically occurs in adolescence). As a result, the *in silico* experiments will accurately capture the sensitivity of the algorithms across a multitude of settings.

So as researchers refine and reprogram their algorithms to account for a broader range of patients and real-life scenarios, they will be able to use the new simulation model to test the responses of these algorithms to any number of catastrophic possibilities, including extreme scenarios that cannot be tested *in vivo*, such as a complete discharge of the entire pump reservoir—they can subject their virtual patients to these risks in order to prevent and cope with serious events in real people.

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Practically speaking

How exactly do consortium members use the simulator to evaluate their algorithms? Although the central system is located at Jaeb, each consortium site has a fully functional, but smaller version of the simulator that includes 30 *in silico* subjects, 10 in each of the age groups. Site members plug their algorithm into their local simulator by uploading and embedding it into the simulator platform—in computer terminology, they are replacing one of the modular blocks described earlier, in this case the interface representing the algorithm. The consortium researchers are expected to perform local test simulations on prospective algorithms prior to sending them to Jaeb for full review.

Before running the simulation, the researchers need to create or select a number of clinical scenarios. These choices range from the length of the simulation to the types and numbers of virtual subjects, the number of carbohydrates consumed in a single meal, and the insulin bolus required before breakfast, lunch, or a snack. Ultimately, the simulator produces a number of outcome measures—in the form of tables, charts, and graphs—that allow the researcher to judge the value of the algorithm. For instance, the simulation will indicate how long the virtual patients were able to stay within the target blood sugar range of 70-180 mg/dL, and it will generate an indicator of hypoglycemia called the low blood glucose index.

To send an algorithm to Jaeb, the researchers use a dedicated upload interface on the JDRF Artificial Pancreas Study Web site. Dr. Marc Breton, for example, who works with Dr. Kovatchev at the University of Virginia, recently used this interface to formally submit the UVa algorithm, which Jaeb has validated. The results were submitted to the FDA, and in April 2008 the Agency granted an Investigational Device Exemption (IDE) for a clinical trial of closed-loop control at UVa, largely based on the *in silico* testing. The total time between approval of the simulator and approval of the IDE: just 3 months—this versus the several years that would have been required with animal trials.

Consortium coordinators at Jaeb store the submitted files on their server and have a corresponding study database that logs the date, time, and submitter's name. Maintaining a central simulator at Jaeb will ultimately enable the researchers to share validation data on the various closed-loop systems, accelerating research on the artificial pancreas through collaboration.

Artificial pancreas research now a global effort

Recent international meetings dedicated to artificial pancreas technology have underscored just how much JDRF funding has galvanized the international research community to tackle the challenges of an artificial pancreas. Today, only two years since the APP consortium was first launched, dozens of top researchers around the world are focusing on developing advanced treatments and technologies for diabetes.

At both the January AIDPIT meeting in Innsbruck, Austria, and the February ATTD conference in Prague, Czechoslovakia, there was much discussion of the progress underway and praise for JDRF leadership. At the AIDPIT meeting (Study Group on Artificial Insulin Delivery, Pancreas and Islet Transplantation), the announcement of the FDA approval of artificial pancreas computer simulator was praised by Dr. Cobelli as “one of the most significant accomplishments of my career,” and justifiably so, given the likely impact the simulator will have on improving patients' lives, even in the short-term.

Dr. Aaron Kowalski, research director of the APP program at JDRF, recently presented at the ATTD conference (the 1st International Conference on Advanced Technologies & Treatments for Diabetes), sponsored in part by JDRF. Along with several JDRF-funded researchers, private sector representatives also attended the meetings and expressed great enthusiasm for progress in the artificial pancreas field, as well as increased interest in the commercialization pathway for an artificial pancreas. A good sign that all this hard work is paying off. ❖

JDRF has launched the Artificial Pancreas Project to accelerate the availability of an artificial pancreas to people with diabetes, one of the foundation's cure therapeutic pathways. The overall goal of the project is to accelerate the development, regulatory approval, health insurance coverage, and clinical acceptance of continuous glucose monitoring and artificial pancreas technology.

The long term goal is for broad patient access and a thriving competitive market for these devices and products.

For regular updates to the Artificial Pancreas Project, please visit www.jdrf.org/artificialpancreas.