In the fight to control glucose levels, this control algorithm comes out on top

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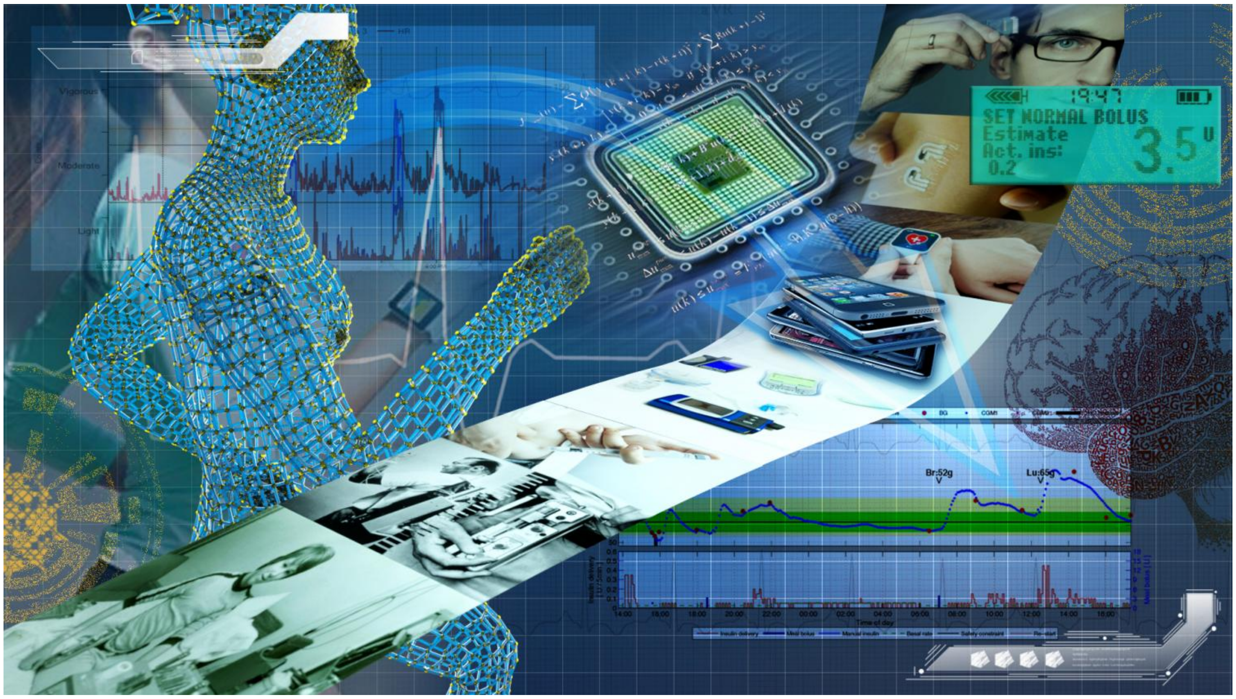

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The so-called artificial pancreas—an automated insulin delivery system for people with type 1 diabetes mellitus—uses an advanced control algorithm to regulate how much insulin a pump should deliver and when. Regulating glucose is challenging because levels respond to a wide-array of variables, including food, physical activity, sleep, stress, hormones, metabolism and more.

For years, researchers have been trying to find the best control algorithm to account for and control for all these variables. Over the years, two primary control strategies emerged as the front-runners—model predictive control (MPC) and proportional integral derivative (PID). There has been a long-running debate in the field over which of these controls works better.

Now, researchers from the Harvard John A. Paulson School of Engineering and Applied Sciences and the William Sansum Diabetes Center have conducted the first head-to-head randomized crossover evaluation of the two controls under comparable clinical conditions. The team found that MPC outperformed PID on the primary outcome of the study, as well as on several secondary outcomes.

The research was presented by Frank Doyle, Dean of the Harvard Paulson School of Engineering and Applied Sciences and senior author of the study at the American Diabetes Association 2016 meeting in New Orleans and published in the journal *Diabetes Care*.

"This research won't put an end to the debate because both controls worked well," said Eyal Dassau, Senior Research Fellow in Biomedical Engineering at SEAS, and co-author of the paper. "But we showed that there are scenarios in which MPC is superior, due to the flexibility of that design. This is the first real head-to-head clinical study that compares the two lead controllers in identical conditions with the same population in a randomized crossover study."

"What is remarkable here is that we used a very basic formulation of MPC, and it still outperformed PID," said Doyle. "We have much more sophisticated versions of the algorithm that have been tested on hundreds of subjects and are in the early stages of commercial development. It is a remarkable flexible and powerful algorithm."

Doyle and Dassau were collaborators at the University of California, Santa Barbara before joining Harvard in the fall of 2015.

An artificial pancreas system controlled with a PID system is reactive, like a home thermostat adjusting temperature. But MPC is proactive, allowing the system to think multiple steps ahead, predicting when the body may need more or less insulin and planning in advance.

The clinical study consisted of 30 adults with type 1 diabetes. They were randomly assigned either a PID or MPC control for the first round of the study and then switched for the second. Every participant had the same food to eat and the same schedule for eating. The researchers observed how the system responded to announced meals, when insulin is manually administered before a meal; unannounced meals, to simulate when people forget to increase insulin before eating; how the system controlled insulin during before and after breakfast, when insulin resistance increases due to hormones; and overnight control.

The researchers monitored the glucose levels of the participants in real time, at five minute intervals.

The team found that while both controls worked, MPC kept participants within the safe glucose range 74 percent of the time, while PID kept them in range 64 percent of the time including an unannounced meal. The mean glucose values for each subject were also statistically lower for MPC compared to PID.

Being able to predict those highs and lows and provide optimal insulin delivery is a big part of MPC's success, said Dassau.

"With MPC, we have a vision into the future and can make course corrections before something bad happens like hypoglycemia," he said. "The model can identify a drift and course correct gradually without causing a crash landing. PID on its own does not have that prediction capability."

The next steps are to conduct longer, outpatient studies to learn how to adapt the system to long-term changes in stress, activity level, weight gain or loss, etc. The ultimate goal is to create a system that can adapt to all of these changes with minimal patient involvement.

"Diabetes is a unique disease in that patients are very involved in their own therapy and are required to put a lot of trust in an automated system," Dassau said. "Our goal is to improve that trust and make it so that users can spend less time on diabetes."

More information: Jordan E. Pinsker et al. Randomized Crossover Comparison of Personalized MPC and PID Control Algorithms for the Artificial Pancreas, *Diabetes Care* (2016). DOI: 10.2337/dc15-2344

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