Mathematical model could lead to better treatment for diabetes

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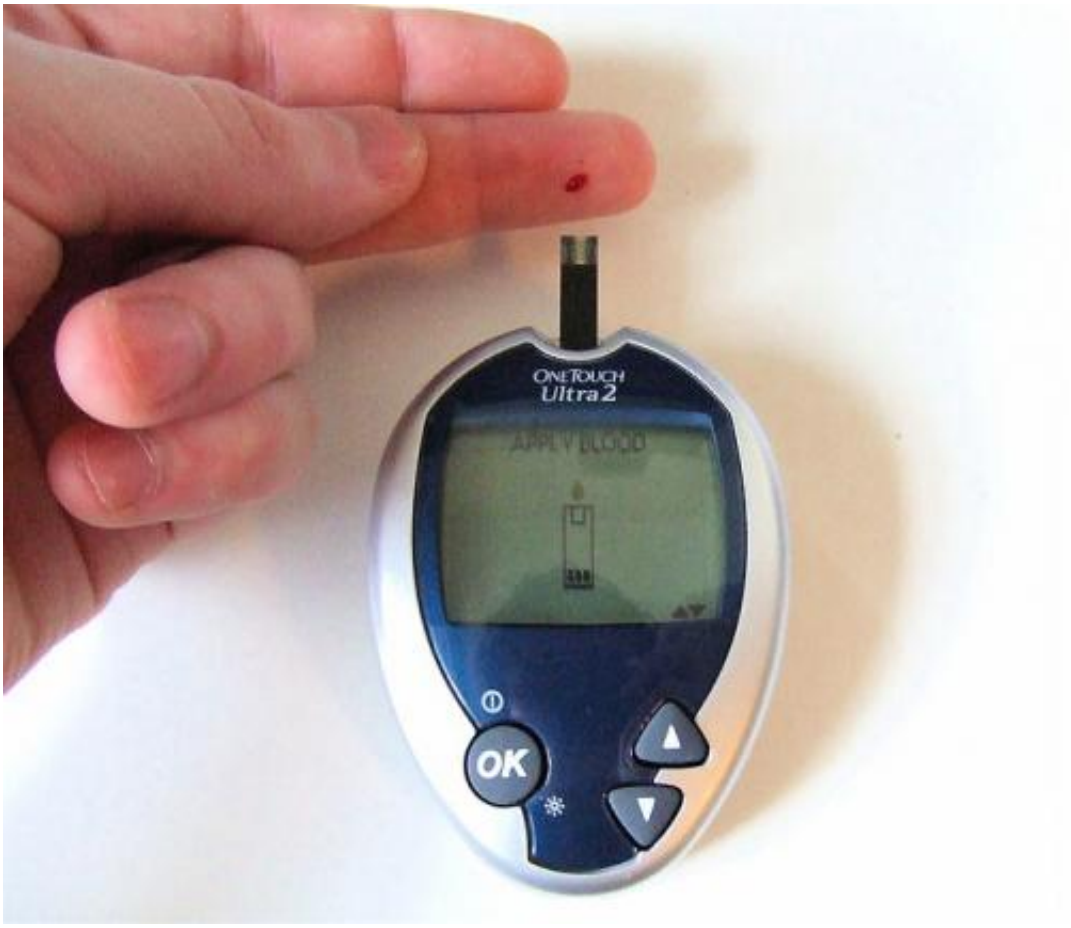

Blood glucose monitoring. Credit: Wikipedia

One promising new strategy to treat diabetes is to give patients insulin that circulates in their bloodstream, staying dormant until activated by

rising blood sugar levels. However, no glucose-responsive insulins (GRIs) have been approved for human use, and the only candidate that entered the clinical trial stage was discontinued after it failed to show effectiveness in humans.

MIT researchers have now developed a mathematical model that can predict the behavior of different kinds of GRIs in both humans and in rodents. They believe this model could be used to design GRIs that are more likely to be effective in humans, and to avoid drug designs less likely to succeed in costly clinical trials.

"There are GRIs that will fail in humans but will show success in animals, and our models can predict this," says Michael Strano, the Carbon P. Dubbs Professor of Chemical Engineering at MIT. "In theory, for the animal system that diabetes researchers typically employ, we can immediately predict how the results will translate to humans."

Strano is the senior author of the study, which appears today in the journal *Diabetes*. MIT graduate student Jing Fan Yang is the lead author of the paper. Other MIT authors include postdoc Xun Gong and graduate student Naveed Bakh. Michael Weiss, a professor of biochemistry and molecular biology at Indiana University School of Medicine, and Kelley Carr, Nelson Phillips, Faramarz Ismail-Beigi of Case Western Reserve University are also authors of the paper.

Optimal design

Patients with diabetes typically have to measure their blood sugar throughout the day and inject themselves with insulin when their blood sugar gets too high. As a potential alternative, many diabetes researchers are now working to develop glucose-responsive insulin, which could be injected just once a day and would spring into action whenever blood sugar levels rise.

Scientists have used a variety of strategies to design such drugs. For instance, insulin might be carried by a polymer particle that dissolves when glucose is present, releasing the drug. Or, insulin could be modified with molecules that can bind to glucose and trigger insulin activation. In this paper, the MIT team focused on a GRI that is coated with molecules called PBA, which can bind to glucose and activate the insulin.

The new study builds on a mathematical model that Strano's lab first developed in 2017. The model is essentially a set of equations that describes how glucose and insulin behave in different compartments of the human body, such as blood vessels, muscle, and fatty tissue. This model can predict how a given GRI will affect blood sugar in different parts of the body, based on chemical features such as how tightly it binds to glucose and how rapidly the insulin is activated.

"For any glucose-responsive insulin, we can turn it into mathematical equations, and then we can insert that into our model and make very clear predictions about how it will perform in humans," Strano says.

Although this model offered helpful guidance in developing GRIs, the researchers realized that it would be much more useful if it could also work on data from tests in animals. They decided to adapt the model so that it could predict how rodents, whose endocrine and metabolic responses are very different from those of humans, would respond to GRIs.

"A lot of experimental work is done in rodents, but it's known that there are lots of imperfections with using rodents. Some are now quite wittily referring to this situation as 'lost in [clinical] translation,'" Yang says.

"This paper is pioneering in that we've taken our model of the human endocrine system and we've linked it to an animal model," adds Strano.

To achieve that, the researchers determined the most important differences between humans and rodents in how they process glucose and insulin, which allowed them to adapt the model to interpret data from rodents.

Using these two variants of the model, the researchers were able to predict the GRI features that would be needed for the PBA-modified GRI to work well in humans and rodents. They found that about 13 percent of the possible GRIs would work well in both rodents and humans, while 14 percent were predicted to work in humans but not rodents, and 12 percent would work in rodents but not humans.

"We used our model to test every point in the range of potential candidates," Gong says. "There exists an optimal design, and we found where that optimal design overlaps between humans and rodents."

Analyzing failure

This model can also be adapted to predict the behavior of other types of GRIs. To demonstrate that, the researchers created equations that represent the chemical features of a glucose-responsive insulin that Merck tested from 2014 to 2016, which ultimately did not succeed in patients. They now plan to test whether their model would have predicted the drug's failure.

"That trial was based on a lot of promising animal data, but when it got to humans it failed. The question is whether this failure could have been prevented," Strano says. "We've already turned it into a mathematical representation and now our tool can try to figure out why it failed."

Strano's lab is also collaborating with Weiss to design and test new GRIs based on the results from the model. Doing this type of modeling during the drug development stage could help to reduce the number of animal

experiments needed to test many possible variants of a proposed GRI.

This kind of model, which the researchers are making available to anyone who wants to use it, could also be applied to other medicines designed to respond to conditions within a patient's body.

"You can envision new kinds of medicines, one day, that will go in the body and modulate their potency as needed based on the real-time patient response," Strano says. "If we get GRIs to work, this could be a model for the pharmaceutical industry, where a drug is delivered and its potency is constantly modulated in response to some therapeutic endpoint, such as levels of cholesterol or fibrinogen."

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