BRINGING GLUCOSE MONITORING TO NEW LEVELS THROUGH INTEGRATED SENSOR DESIGN

Researchers and designers at Roche Diagnostics are developing glucose sensors with greater measurement accuracy for diabetic care, aided by multiphysics simulation.

By **LEXI CARVER**

CLOSE METABOLIC CONTROL through glucose monitoring is a well-known way for persons with diabetes to maintain good health and avoid medical complications. The current generation of glucose monitors relies on electrochemical methods to facilitate unprecedented measurement accuracy, and has given diabetics a reliable way to control their diet and insulin intake.

However, the chemical reactions that take place on the sensing strips used in glucose monitors are sensitive to environmental conditions and chemical interferences. Sensors are shipped worldwide, stored under uncertain conditions, and needed by users with different levels of knowledge and experience. Robust design is crucial for enabling sensors to survive these environments, deliver accurate results, and detect conditions that would cause errors. Now multiphysics simulation is used alongside experiments and calculations, enabling scientists to understand the chemical, electrical, and biological phenomena interacting in these systems so they can optimize their design and measurement methods.

» GAINING GROUND WITH A NEW KIND OF SENSOR

ENGINEERS AT ROCHE DIABETES CARE, a worldwide leader in diabetes diagnostic products and services, are currently pursuing a better understanding of the electrochemistry in their existing devices and are designing new sensing methods to provide more accurate monitoring. Like other amperometric biosensors, their glucometers (an example is shown in Figure 1) measure the electric current that results when a voltage is applied to an electrode system. The resulting current is proportional to the glucose levels in an electrolyte solution (such as a blood sample combined with a chemical reagent).

FIGURE 1: Photograph of an ACCU-CHEK Aviva® and ACCU-CHEK Nano® created at Roche Diagnostics.

A set of gold traces lie on each glucose test strip, running from the electrode system in the strip to electrical contacts that insert into the glucose meter (see Figure 2). The reagent, which consists of a glucose-reactive enzyme and a very stable chemical referred to as a proto-mediator, is deposited on these electrodes during manufacturing and then dried. A capillary channel constructed over the electrode system receives a blood sample that rehydrates the reagent, causing it to react with glucose in the blood. "The initial reaction of glucose with the enzyme converts the proto-mediator to a reactive, low-potential mediator, which carries out the rest of the reaction," explains Harvey Buck, principal scientist at Roche Diagnostics Operations, Inc.

» SIMULATION UNVEILS CHEMICAL AND ELECTRICAL MYSTERIES

THE CURRENT RESPONSE to a DC voltage applied at the electrodes during the reaction predicts glucose concentration in a blood sample, providing crucial information that tells a patient what action to take to correct their blood sugar levels. But configuration and manufacturing of the test strip affect this response accuracy. Using two COMSOL Multiphysics® software simulations, the Roche team was able to study a new test strip design—one of several they are investigating—and isolate the chemical reactions from the electrical, mechanical, and temperature conditions so that they could analyze the voltage response.

The isolated system contains many parameters and coupled variables, such as concentrations of different chemical species. The reagent system has so many complex interactions between the chemicals and their reactions that it was difficult to predict the response to different measurement methods or interfering substances. So the team made the simplifying assumption that mass transport of chemicals only occurs in a very thin layer above the electrode, thin

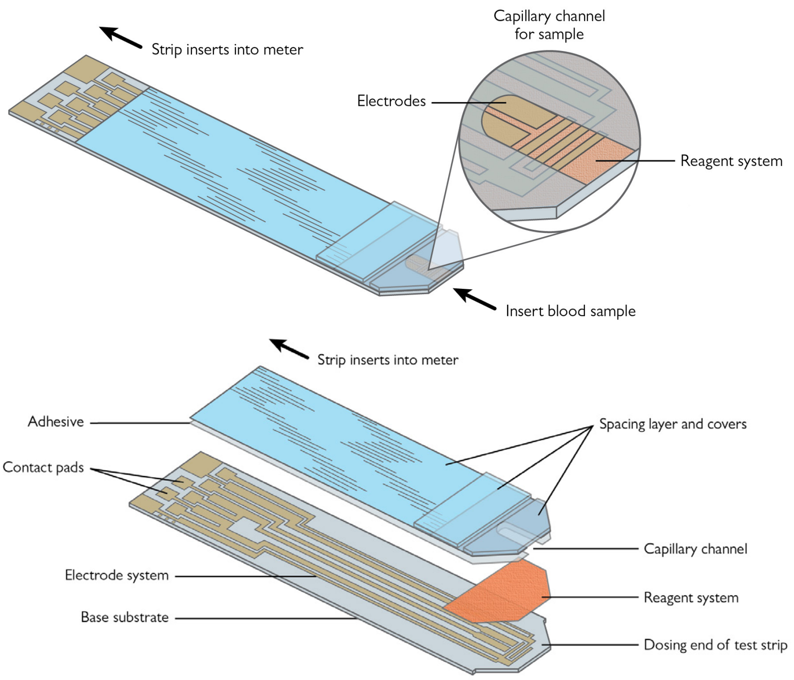

FIGURE 2: Schematic of test strip components. The chemical reaction occurs right on top of the electrodes. Adhesives and spacing layers form the curve of the capillary channel and bind together the electrodes, reagent system, and top and bottom covers.

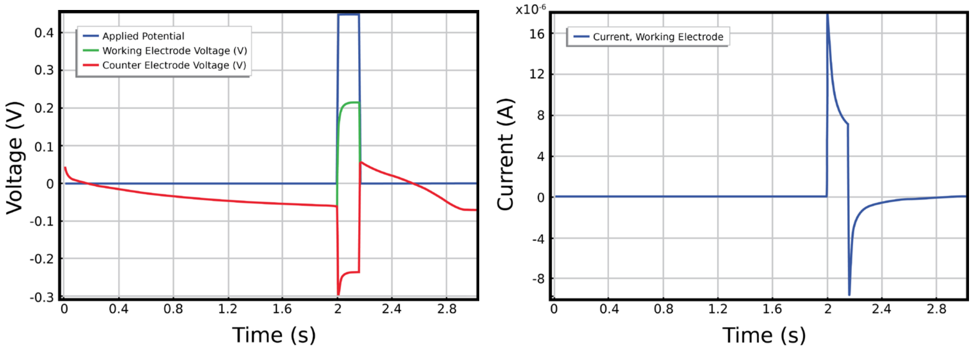

FIGURE 3: Simulation results showing the applied potential difference and the working and counter electrode potentials in the Roche sensor (left), as well as the current response to a potential difference step (right). The current response is proportional to the glucose concentration in the sample. The working and counter electrode potentials (green and red, respectively) are not measurable and are only available through the simulation.

enough for the reactivity to be considered uniform in the direction perpendicular to the surface. "We built a one-dimensional model that lets us understand and predict the responses, which required a combination of Michaelis Menten enzyme kinetics and mixed Butler-Volmer electrode kinetics," Buck comments.

Having established rates for the different reactions, the relevant equations were then easy to implement in the software. By restricting the model to one dimension, it was possible to predict the sensor response to different DC potential profiles with reasonable solution times (see Figure 3).

But the DC current is also affected by temperature and red blood cell fraction in the sample (called hematocrit), so prior to the DC measurement, an AC signal is applied to obtain impedance information used to compensate for these effects (see Figure 4). These are combined with the DC measurements in a mathematical algorithm, giving the sensor the information needed to make a truly accurate glucose prediction.

The capabilities of COMSOL® software proved particularly valuable for interpreting these complex measurements. "We quickly found during our modeling process that when you try to apply a large potential step to create diffusion-limited flux at an electrode, you risk causing unrealistically high potential calculations," says Buck. "In COMSOL it's very easy to use a log transform of the concentration variables, which really simplified the analysis process."

"The impedance measurements are very sensitive to the sample and not very sensitive to the reagent," Buck continues. "The electrode arrangement to enable impedance measurement is an integral part of the sensor design, and has a great influence on the measurement sensitivity." Buck's team built a second model of the cell to solve the electrical problem, this time in 3D. "The sample conductivity in the cell serves as a proxy for hematocrit variation. We're able to investigate different electrode configurations and materials, and predict the sensitivity of the

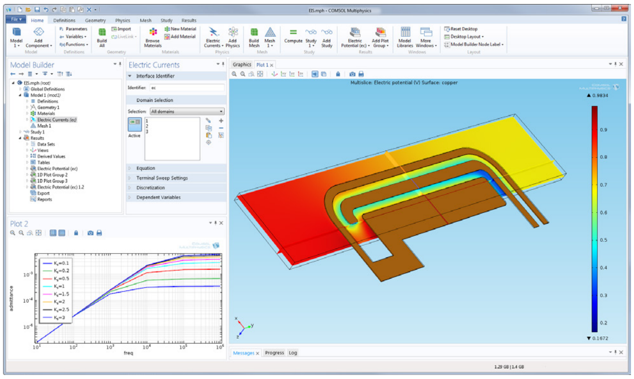

FIGURE 4: Buck's 3D COMSOL simulation showing the admittance response for different conductivities, plotted with a log scale (lower left) and a plot of the electric potential in the sensor measurement zone (right). The gold electrodes contact the electrolyte at a surface impedance interface.

> *"We're able to investigate different electrode configurations and materials, and predict the sensitivity of the impedance measurements to hematocrit as well as to other mechanical properties of the sensor, such as capillary height and spacer placement."*
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> **—HARVEY BUCK, PRINCIPAL SCIENTIST, ROCHE DIAGNOSTICS**

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The electrodes are fabricated from sputtered metal films whose resistance significantly affects the impedance measurements and potential distribution. It's impossible to measure the potential drop across the electrodes or within the electrolyte in the measurement cell without physically disturbing the system, but it is relatively easy to simulate it.

Relying on the COMSOL results for guidance, Buck adjusted the shape, length, and spacing of the working and counter electrodes until he had optimized the electrode design for impedance measurements. Ultimately, he was able to maximize the electrode sensitivity to hematocrit levels while minimizing sensitivity to manufacturing tolerances—thereby ensuring an accurate impedance measurement for the DC signal compensation. This paved the way for the new configuration to move toward production.

» *APPROACHING NEW HORIZONS FOR GLUCOSE MONITORING*

THROUGH THE CHEMICAL and electrical response correction modeled in COMSOL, the researchers at Roche have gained greater insight into their new sensor design and are delivering glucose monitors that correct the DC signal for more accurate measurements. Their innovative system, including its built-in sensing capabilities, sets a new standard for biosensing devices. Simulation allowed them to investigate parameters that were impossible to measure experimentally, make informed design decisions, and optimize their electrode configuration. Their continued research and modeling work is leading to the production of these new sensors and, ultimately, better care for persons with diabetes. ◎

Harvey Buck, principal scientist, Roche Diagnostics.

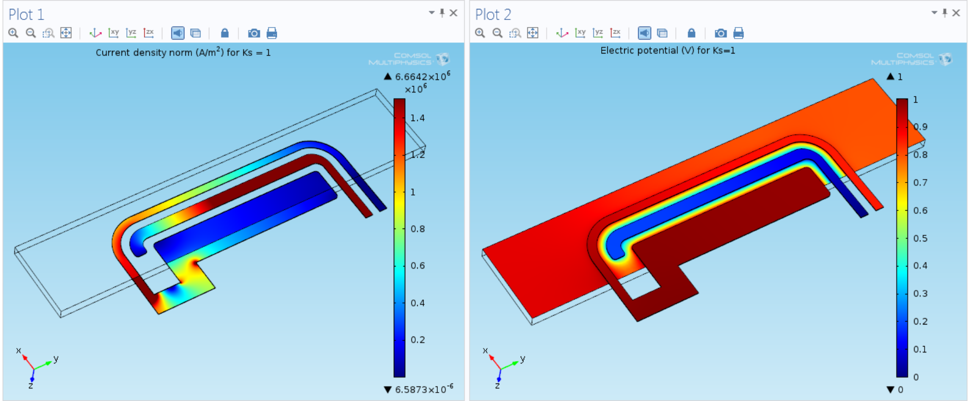

FIGURE 5: COMSOL simulation results showing the current distribution (left) and electric potential (right) in the electrodes and electrolyte.