Modeling The Electrochemistry of Blood Glucose Test Strips

Lifescan Scotland Ltd. uses multiphysics for product design and optimization.

BY GARY DAGASTINE

Self-monitoring of blood glucose levels is vital to effective diabetes control, and so every day, diabetics around the world share the same routine: They place a drop of their blood on a test strip and insert the strip into a meter to measure their glucose level.

But few of them probably stop to think that the humble little plastic test strip that makes self-monitoring possible is actually a highly engineered sensor. It must meet not only commercial goals for accuracy, ease of use, manufacturability, and cost, but increasingly stringent regulatory standards for medical products as well.

Lifescan Scotland Ltd. designs and manufactures blood glucose monitoring kits for the global market. Part of the Johnson & Johnson family of companies, Lifescan Scotland's research, development, and production facility in Inverness is regarded as a world center of excellence for those working in the field of diabetes.

The company's product range includes the popular OneTouch® brand of blood glucose monitoring systems and the specialized test strips that work with them, as well as diabetes management software, control solutions, and lancing devices (see Figure 1).

For about three years, Lifescan Scotland researchers have used COMSOL Multiphysics to characterize existing and new biosensor designs.

How a Complex Electrochemical Sensor Works

Lifescan Scotland's test strips comprise a plastic substrate, two carbon-based electrodes (called working and counter electrodes, respectively), a thin dry reagent layer, and a capillary volume where the blood is placed.

Conceptually, the blood mixes with and hydrates the dry reagent, producing an enzymatic reaction that generates a chemical product. The amount of this

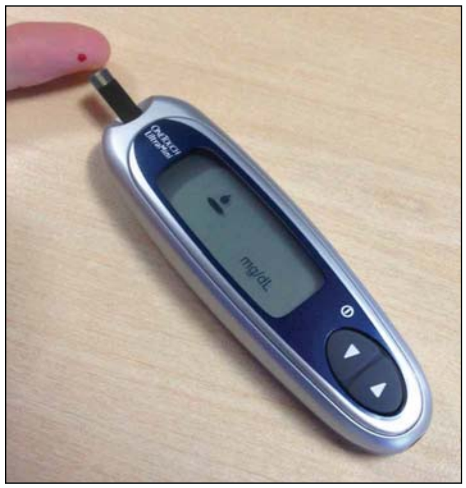


FIGURE 1: A test being performed with the OneTouch® strip and meter.

product is proportional to the amount of glucose in the blood.

Then, when the strip is inserted into a meter, the battery-powered device polarizes the strip's working electrode. This sets in motion an oxidation process that generates a transient electrical signal, whose strength is proportional to the amount of the chemical product oxidized. The meter then applies an algorithm to convert the signal strength into a numerical value for the user.

Beyond Analytical Solutions

Historically, researchers at Lifescan Scotland relied upon analytical methods for product design. "We solved Partial Differential Equations (PDEs) using simplified assumptions of geometries, reagents, and boundary conditions," said Stephen Mackintosh, senior scientist. "Research Fellows Manuel Alvarez-Icaza, Steve Blythe, and Marco Cardosi built up many of these early modeling approaches. Our later work extended these models to include multiple chemical species, chemical interactions, and full electrochemistry."

However, although this approach does yield general solutions that encapsulate the main variables, it's not optimum in state-of-the-art product design because simplified assumptions ignore critical detailed chemical interactions.

"Our goals are to develop test strips that yield faster results, to reduce manufacturing costs, and to increase accuracy to meet ever-greater regulatory demands," Mackintosh said. "Finite and/or complex geometries are required to describe such systems, and in these cases, numerical models are more useful than analytical constructs.

"I began this progression by building more complex simulations using generic numerical PDE solvers. These could compute multiple species interactions very quickly, and worked well, but some electrochemistry components were still missing, and the underlying code was difficult to maintain," he said.

The underlying physics is complex, often incorporating Fick's laws of mass diffusion coupled with both Michaelis-Menten-based descriptions of enzyme-catalyzed chemical reaction kinetics, and Butler-Volmer expressions to understand concentration-dependent potential changes in addition to the battery-supplied potential of the meter.

Mass diffusion is a particularly important consideration. "There are many diffusing species in our simulations, with glucose just one example," Mackintosh said. "The tricky thing is, their diffusion coefficients may vary in subtle and complex ways depending on the specific properties of the blood sample (see Figure 2).

"Thus, we have to consider such things as the concentration of a generated product, the characteristic limiting rates of enzyme-substrate reactions, current density, concentration of oxidized species, and temperature. This would be impossible to do with precision using legacy analytical methods," he said.

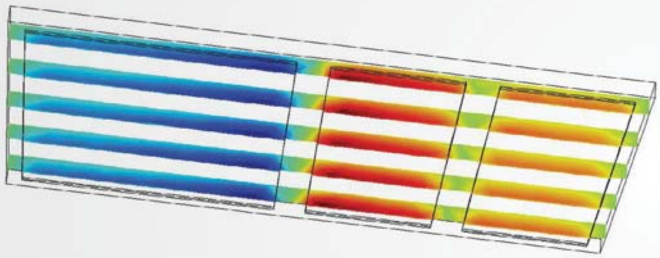


FIGURE 2: 3D slice plot, showing the concentration of a diffusing blood species in a simplified strip chamber, with both working and counter electrodes.

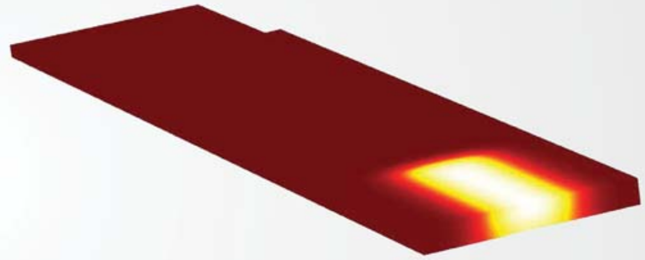


FIGURE 3: Study of the dissipation of heat from a drop of blood applied to a test strip (temperature distribution is shown).

Benefitting from the Multiphysics Approach

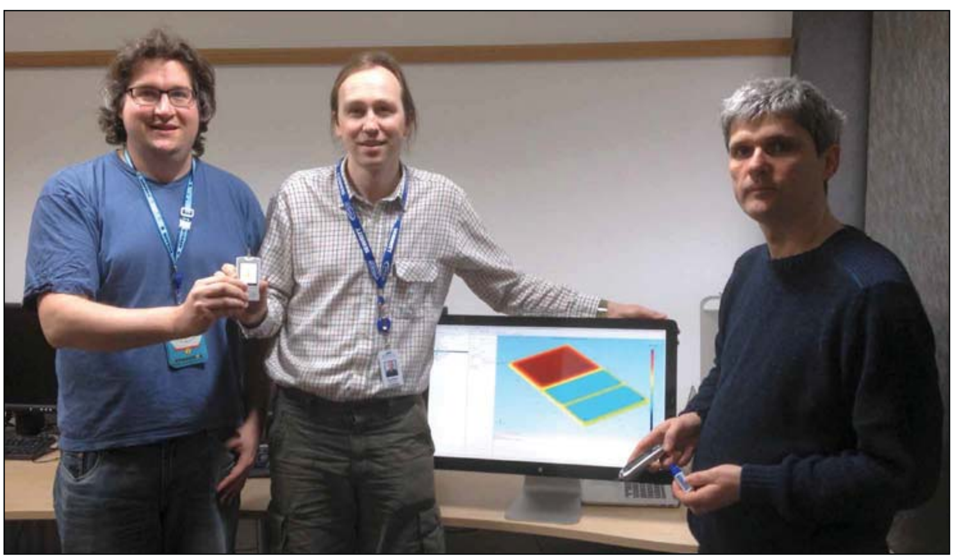
COMSOL Multiphysics has helped Mackintosh, a mathematician, develop powerful working models. "Other scientists in the R&D group provided valuable scientific background to these models, in particular Staff Scientist Jamie Rodgers, whose electrochemical expertise was invaluable," Mackintosh said.

COMSOL Multiphysics has several modules that extend its capabilities. The modules Mackintosh and the modeling and simulation team use most often are Heat Transfer to study temperature distribution (see Figure 3), and Batteries & Fuel Cells to facilitate development of detailed electrochemical reactions. These modules are then easily coupled to other capabilities included in COMSOL Multiphysics: Transport of Diluted Species to study mass diffusion, and PDE Interfaces to explore user-defined boundary conditions.

The team has automated mesh generation via the software's physics-controlled mesh setting, with extra refinement nodes added near each electrode-electrolyte boundary. Mackintosh said they also are considering use of the Microfluidics Module to extend their models to study such processes as the hydrophilic filling of the blood chamber from the applied blood drop.

Based on the success of this work, the use of COMSOL Multiphysics is being extended throughout the Inverness lab, and Senior Algorithm Engineer Adam Craggs is spearheading the required IT infrastructure. So that users without modeling experience can access these powerful tools, Craggs is implementing LiveLink™ *for* MATLAB® to create specialized graphical user interfaces (GUIs).

On the computing side, meanwhile, Craggs has taken advantage of COMSOL Client/Server mode to solve large problems more quickly by implementing a rack of Apple Mac Pro® computers to share the load of running the models.



Members of Lifescan Scotland's Research and Development group. From left are Adam Craggs, Senior Algorithm Engineer; Stephen Mackintosh, Senior Scientist; and Jamie Rodgers, Staff Scientist.

Developing Better Products

Mackintosh said COMSOL Multiphysics has aided with cost-effective optimization of device chemistry and geometry. Outputs such as the correlation between analyte concentration and current signal, at different time periods and with alternate layouts, along with the detailed concentration gradients the software has produced, have increased understanding of signal features and the impact of design changes, he said.

"We've used COMSOL Multiphysics to help develop and refine a range of blood glucose sensors that have enabled rapid model-based prototyping of alternative chamber geometries and/or reagent compositions," he said. "In fact, some of the output from our models is used to map the sensitivity of our products to manufacturing changes, an aid to future product development.

"Our simulation results are in good agreement with experimental work using existing systems and prototypes," Mackintosh said. "Of course, such models can never be used to make decisions on the safety or efficacy of medical devices released to the public, but they are a useful tool in the design and optimization of future products." ■