Computer Simulation Saves Many Years of Testing in Development of First Continuous Glucose Monitor

The GlucoWatch developed by Cygnus

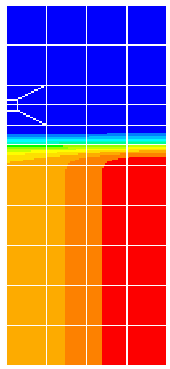
Computer simulation reduced the need for many years of physical testing in the development of a painless, bloodless and continuous glucose monitor. The monitor, which is in development, measures glucose levels through skin contact, eliminating the need for diabetic patients to prick their fingers to obtain blood. Computational fluid dynamics (CFD) was used to simulate critical functionality that extracts glucose molecules through intact skin and measures its level in the blood. The ability to evaluate different designs without building prototypes drastically reduced the amount of time needed to bring the glucose monitor to market.

Several million Americans with diabetes need to measure blood glucose levels to enable them to adjust their diet and use insulin to avoid severe complications. Currently, diabetic patients are required to stab their fingers with a lancet, draw blood, place a drop of blood on a glucose reagent strip, then place the strip in an instrument that provides a blood glucose reading. Studies show that diabetic patients test their blood glucose levels an average of half as often as recommended, largely due to the pain and disruption of daily life associated with this finger stab method.

Cygnus Inc., (Redwood City, California) is developing a monitoring device called the GlucoWatch that is worn like a wristwatch. The GlucoWatch is designed to extract and measure glucose levels and trends while eliminating the need for the patient to stab their fingers to obtain blood samples. Studies have shown that frequent evaluation of blood glucose leading to multiple insulin injections results in reductions in diabetes-related complications of up to 70%. Complications arising from diabetes cost the U.S. health care system in excess of $45 billion in 1992.

The GlucoWatch extracts glucose molecules through intact skin utilizing a proprietary process called electroosmosis that uses low levels of electric current. Glucose molecules are collected in a small disposable pad that adheres to the skin. This pad also contains an enzyme specific to glucose. The collected glucose triggers an electro-chemical reaction with a reagent in the pad, generating an electrical current. A sensor measures the current and an integrated circuit equates it to a concentration of glucose in the patient's blood.

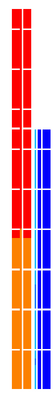
Insuring repeatable measurements was the toughest design challenge after the basic technology had been proven. It was recognized, even before the designprocess started, that simulation was essential to validating the accuracy of the device within the company's time to market goals. One critical area targeted for simulation was determining the amount of enzyme required to generate a current consistent with the glucose concentration. Another was determining the timing sequence of the iontophoretic and sensor electrodes used to extract and measure the amount of glucose passing through the skin. Simulation also helped maintain the uniformity of electrical fields in order to maintain stable glucose extraction rates.



Glucose concentration profile in GlucoPad at the end of the sensing interval.

Cygnus scientists evaluated a number of CFD codes before selecting Nekton CFD software from Fluent, Inc., Lebanon, NH. The primary reason for selecting Nekton is its versatility. CFD software was originally developed to simulate fluid flow which is almost nonexistent in this problem. What is important in this application is the ability to track the reactions and diffusion of several species of chemicals as well as electrical fields on the electrodes and at the gel-skin interface. Nekton makes it easy to access the mathematics required for heat transfer, mass transfer, and electrical fields required in this problem. Nekton provides for the simulation of 10 chemical species. Another advantage of Nekton in this problem is that it uses spectral elements that require about 1/5 the number of cells as a finite element CFD code while achieving equivalent accuracy. Spectral elements are a high-order, weighted residual technique that combines the advantages of low-order finite element methods with the accuracy and rapid convergence of high-order techniques. It's also worth mentioning that, despite the complexity of this analysis, with heat transfer, mass transfer and chemical reactions all occurring at the same time, no difficulty was found in convergence of the models in two or three dimensions.

It was considered essential that the amount of enzyme supplied be sufficient to obtain diffusion control of the reaction. In diffusion control the reaction is controlled by how fast the glucose molecules can diffuse to the enzyme as opposed to kinetic control where the reaction is controlled by the amount of enzyme. Diffusion control is less sensitive to the amount of enzyme present and to temperature fluctuations, resulting in higher accuracy of sensor readings. In order to insure this condition, Cygnus researchers evaluated designs under conditions with a wide range of different concentrations of enzyme to make sure that the amount of enzyme did not affect the measurement results. The ability to vary the pad temperature made it possible to rerun the analysis at different temperatures to insure that measurement accuracy was not affected by temperature.



Voltage distribution at electrode-GlucoPad interface, skin-GlucoPad interface and throughout GlucoPad during iontophoresis.

Timing of the electrode activation is another critical issue. Two types of electrodes are used in the electroosmosis process. The iontophoretic electrode is used to apply an electric field to extract the glucose from beneath the skin. An additional sensing electrode is used to measure the electric current that is produced when glucose is detected. Both electrodes are cycled on and off for certain periods of time. The length of these time periods is critical because it's important that all glucose is completely reacted before the next iteration begins so that each iteration starts from the same baseline. "Nekton was used to perform a series of 72 iterations representing an entire day's usage of the product," says Ron Kurnik, Ph.D., a staff scientist at Cygnus. "Each iteration started with the conditions that the previous iteration finished with in order to be sure that timing does not affect the measurements. An example would be to run the iontophoretic electrode for 15 minutes to collect glucose, then run the sensing electrode for 5 minutes to react the glucose that had been collected." he says. The sequence of iterations was run without intervention using a UNIX shell script.

Valuable insights were provided by studies configured to yield the electrical fields on the skin and electrodes. Uniformity of the field on the gel-skin interface and on the gel-electrode interface was the goal. These studies were useful in configuring the electrode geometry and the thickness and resistivity of the gel to maintain uniformity of voltage and current distributions on the skin surface to promote a constant level of extraction.

These analyses provided dramatic time savings. The results provided quantitative measurements of mass transfer, heat transfer, chemical reactions and electrical fields at every point in the model. "The ability of the software to display all of this data within a few graphic charts made it possible to assimilate the results of each iteration within a few minutes," says Kurnik. Viewing the results of the analysis, engineers generally gained a far better understanding of the operation of device than could have been obtained with physical experiments.

According to Kurnik, in some cases, analysis answered problems that would have been difficult or impossible to resolve by experimental methods. It's almost impossible to map out a current distribution across an electrode. The electrode is too small to accept more than a few point sensors. With CFD, on the other hand, it's possible to obtain precise estimates at any point of interest. CFD is also able to provide perfect conditions that are difficult or impossible to achieve in the laboratory. For example, it's inevitable that some other species in addition to glucose will come across the skin in the electroosmosis process that might affect experimental results. The effect of these additional species on the sensor response can be estimated using the passive scalars built into the Nekton code.

It's important to note that Cygnus is careful to always validate analytical models by comparing the results to experiments. This validation process is important because it eliminates the possibility that inaccurate assumptions or boundary conditions in the model will cause misleading outputs. Once the basic model has been validated, it can safely be modified to evaluate a wide range of different design alternatives with complete confidence.

After the design of the GlucoWatch is finalized, clinical trials will begin. Beyond that, Cygnus plans to develop improved versions of this products as well as other devices designed to measure other substances from the blood using different enzymes. The basic technology of the GlucoWatch may also be used in the future to deliver drugs through the skin. Analysis will continue to play a crucial role in the development of future generations of the GlucoWatch and spinoff products.