Easy and Accurate Measurement of Blood Viscosity with Breakthrough MEMS-Based Device

Simulation-led design has put Microvisk on track to take advantage of the huge home healthcare market when it launches a hand held device that allows individuals to monitor their own blood viscosity quickly, easily and reliably.

BY JENNIFER HAND

The viscosity of blood is widely regarded as an indicator of general health. When a blood vessel is damaged or broken loss of blood needs to be minimized so a series of reactions (known as the clotting cascade) begins and a blood clot is formed. A number of medical conditions adversely affect this process and in these cases patients are often prescribed an anti-coagulant such as warfarin. Health management for many of these individuals involves the weekly monitoring of blood clotting time to ensure that drug dosage is appropriate.

Existing hand held devices work by inducing a chemical reaction which is picked up by electrodes coated with compounds, a technology that has not fundamentally changed in many years. In contrast, Microvisk has developed a radical new technique that stems from futuristic research on microtechnology and harnesses the power of Micro Electronic Mechanical Systems (MEMS).

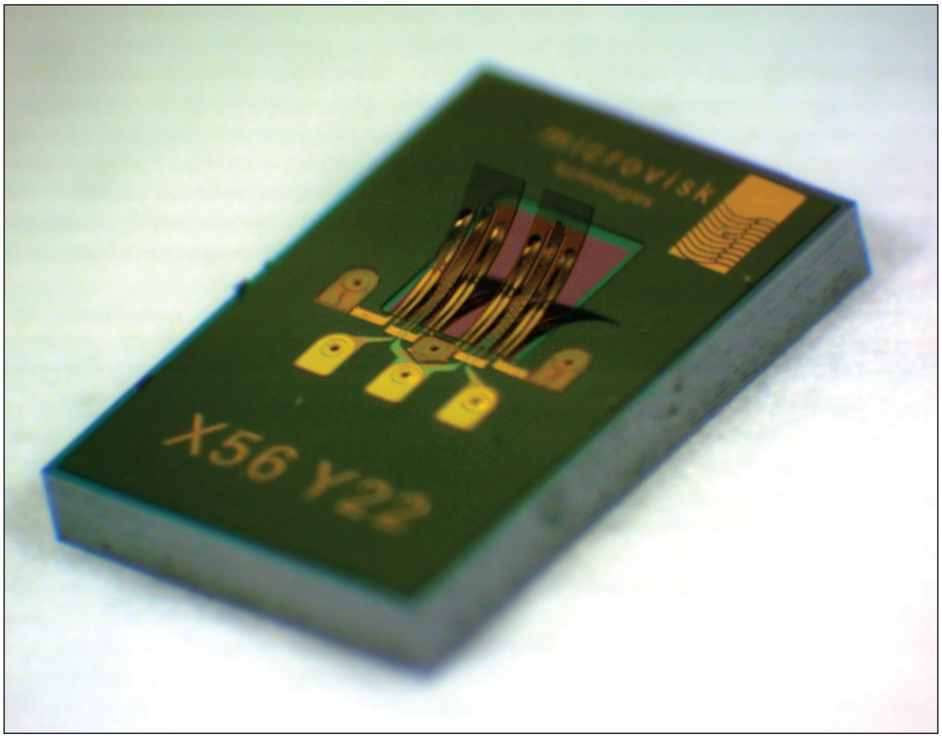

Figure 1. Microvisk's MEMS-based micro-cantilever device.

A Completely Different Architecture

Microvisk's MEMS-based micro-cantilever devices are produced on a wafer-scale, where thousands of identical microchips are processed together as flat structures on the surface of silicon wafers. Only at the final stage of production are the micro-cantilevers released to deflect above the supporting surface, forming truly 3D microstructures (Figure 1). Such highly deformable and flexible micro-cantilevers, controlled by CMOS (Complementary metal-oxide-semiconductor) type signals, form the heart of Microvisk's unique fluid micro-probe utilized in determining the rheometric properties of minute (nano-litre volume) samples. When a current is passed through the structure each layer deflects in a different way (Figure 2). As one structural layer expands more, another expands less, which leads to each cantilever moving up and down in response to immersion in a gas or in a liquid such as blood. The speed of blood clotting and its rheometric changes associated with the clotting process can therefore be monitored in a one-stage process based on physics rather than chemistry.

Dr. Slava Djakov, inventor and Sensor Development Director of Microvisk, explains why Microvisk's approach is unique. "Other cantilever designs typically used in Atomic Force Microscopy (AFM) applications or in biological research for probing and assessing DNA, protein and aptamer bindings with drugs or antibodies, usually utilize crystalline silicon (cSi) rigid cantilevers. Because of their rigidity, cSi and similar structures are very delicate, brittle and offer restricted movement. Although cSi cantilevers can be very sensitive, through actuation in resonant mode, the restricted mobility impedes performance once these micro-cantilevers or similar structures such as micro-bridges or membranes are immersed in liquids. Through the clever choice of polymer materials we enabled the free end of the cantilever to deflect a significantly long way up from its resting position, which makes it extremely efficient and accurate in its response. We can probe for certain parameters, for example the viscosity and visco-

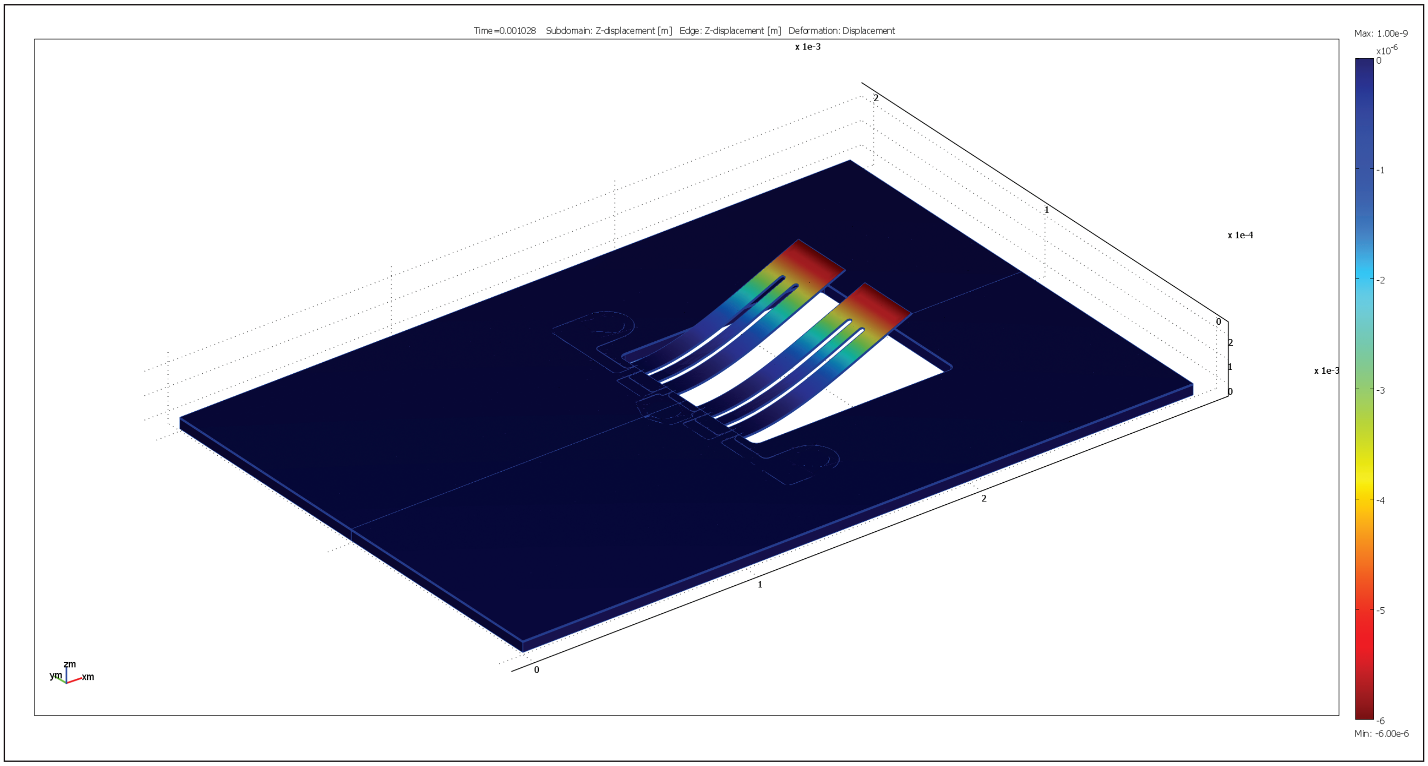

Figure 2. COMSOL model showing deflection of the micro-cantilevers.

elastic properties of blood, even at very small, sub micro-liter volumes."

By 2004, when the company was founded and patents were applied for, Microvisk's research team was quietly confident about the strength of the technology and its potential for use by 'consumers' in the convenience of their own homes. The MEMS solution could be incorporated in a hand held device (Figure 3) and the testing process was more robust than existing methods. The sample of blood required was tiny and accuracy was greatly improved. As chemicals were not needed to drive the test there was no shelf life issue and no requirement for strict storage controls before, during and after testing.

Signals, Statistics and Synergy

The very sophistication of the technology was also the challenge. "This solution is not so much about how the cantilever moves up and down," comments Dr Djakov (Figure 4). "It is more about a holistic approach to integration, packaging and signal processing. The big questions in MEMS-based microchip design, once the concept is proven, are how likely are the chips to perform and what are the set points? While the standard test interrogates material electronically, we also need to consider mechanical response and reproducibility and reliability aspects such as cycling times and performance deterioration."

This calls for an approach combining both mechanics and statics of beams systems with the thermal and electric properties of structural materials at hand. Complexity is further increased when a current is applied to the MEMS structures immersed in and interacting with fluids. A current not only changes electrostatic fields, it also alters mechanical structures and creates thermal effects. Dr. Djakov reports that when the research began there was no suitable modeling option and initially the team was unable to conduct multiple analyses of the MEMS. Then as multiphysics simulation software began to appear the company was restrained by its small size and limited financing. "We had to rely on past experience, basic know how and gut feeling. Determining the design was a long and tedious process involving laboratory experiments and real life tests."

In 2009 he received the go ahead from the Microvisk board and management to make the investment required to adopt COMSOL Multiphysics®. "They were focusing on experiments only at first but now acknowledge that it was an excellent move to complement the design flow with simulation. COMSOL Multiphysics addresses all the physical properties of a design. This is not easy as we are dealing with a lot of different parameters: not only are we looking at individual materi-

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Figure 3. Model of hand held device.

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als which have their own unique thermal and electric properties, we also have to analyse them when they are tangled together. Which materials are the most critical and how will they behave in the presence of fluid?"

COMSOL Multiphysics enables Microvisk's researchers to see the microchips mechanically, thermally (Figure 5) and electro–statically. They can also analyze micro fluids and their properties and how these interface with the chips and moving cantilevers. "By linking all the physical properties of the design COMSOL has sped up the whole process of iteration, reduced prototyping and shortened development time. We no longer need to solve one problem, then another and plot a graph after each step," says Dr. Djakov.

Previously, data was collected from a number of prototyping variants of test strips then it had to be analyzed, understood and verified. One iteration typically assessed 20 different design options plus the manufacturing and assembly implications of each. Through modeling with COMSOL Multiphysics Microvisk was able to start picking out the most promising options and confirming simulation results with laboratory testing. After only fifteen months the company had completed two major design iterations and a number of optimization refinements and Dr. Djakov estimates that it had saved four to five months of development time. "Of course it is not as though we would sit and wait for four or five months but scientists would be put on the spot to make quick decisions, perhaps without the time and resources to satisfy all their queries. COMSOL Multiphysics enables us to look at much broader possibilities and decide to investigate two or three much further. This means that we achieve a better end product at the same time as cutting development time."

Not only has COMSOL Multiphysics enabled design optimization, it has improved the way that the development team communicates with Microvisk's investors. Models are easily presented to the board and progress is marked using color maps and video.

Responding to Regulatory Requirements

With medical diagnostic equipment there are stringent requirements, for example, there is a time limit on blood sample testing. Blood clotting begins as soon as a finger prick is made so the process needs to be quick. Dr. Djakov is confident that Microvisk has the best possible design. "COMSOL Multiphysics has, for example, enabled us to create a very good solution for the performance of the micro capillary channel that feeds fluid samples onto the microchips." The whole cantilever is immersed immediately and so the test can begin, with just a quarter of the volume required by existing test devices. This means less pain for the patient. In addition there is no need to take the blood sample to the microchip; and no need to drip blood onto a certain part of a device. When the device is held against a pricked finger for two seconds the micro capillary draws in the right amount of blood and the result is available 30 seconds later. The patient is in complete control.

A Small Investment; a Huge Potential Return

Point of care testing and home use figure highly in the health care strategy of developed countries. The market is still emerging and according to Dr. Djakov the potential for home blood testing is similar to that of glucose testing by patients diagnosed with diabetes, a market in which 160 companies are now established.

Microvisk plans to launch the new device in the last quarter of 2011 and is al-

Figure 4. Dr. Slava Djakov, Sensor Development Director of Microvisk.

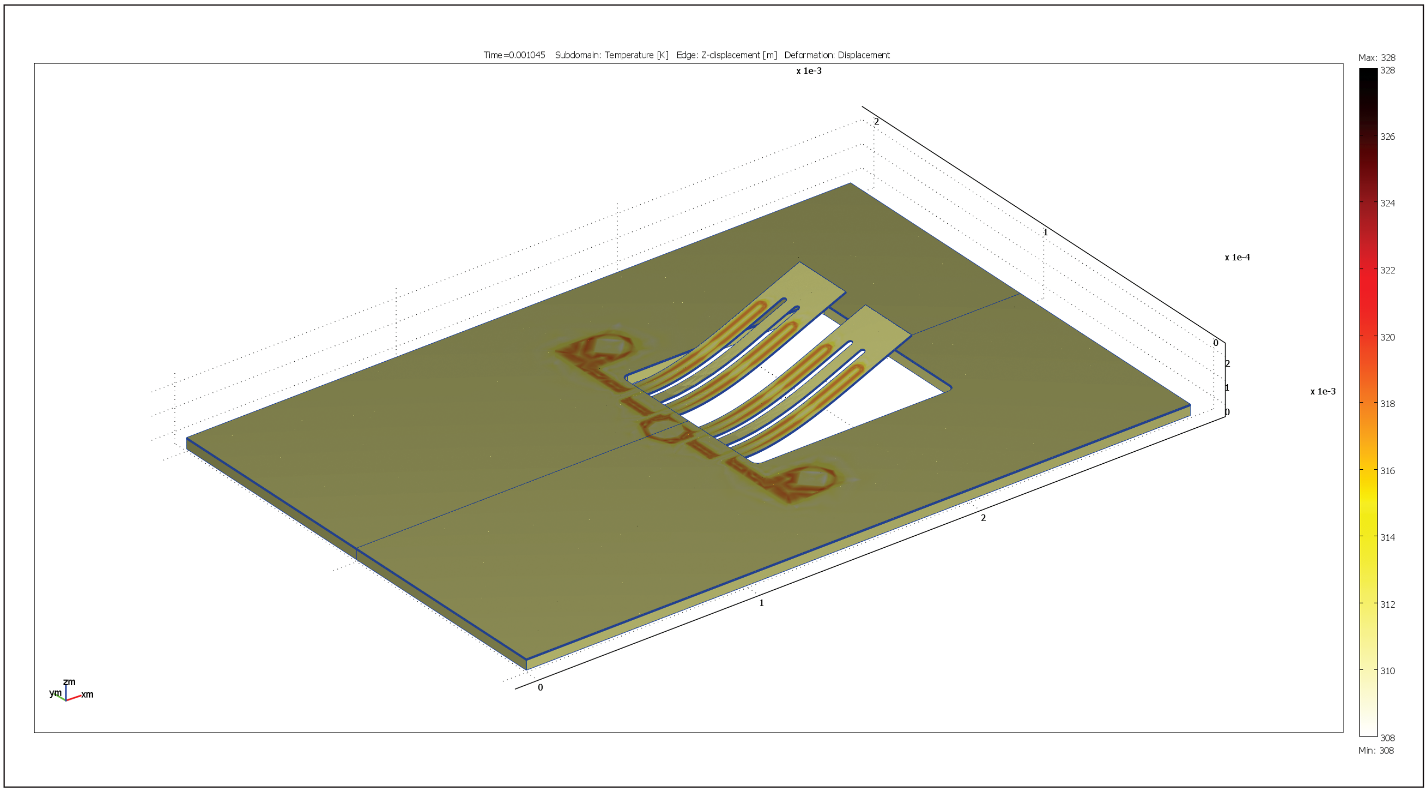

Figure 5. The COMSOL model shows accurate thermal deflection.

ready working on various add-on features.

"Once we launch we will be able to scale up very, very quickly, produce millions of microchips per month and do so cheaply. We know experts are getting very excited because they recognize that changes in blood are all driven by changes in viscosity. In due course there is nothing to prevent our microchips from performing several tests at once, our technology is already capable of handling a number of tests on one sample of blood."

With such a large market opportunity, accompanied by low technical risk and a strong intellectual property portfolio the company expects to break even just one year after the launch of the product. "In terms of development we are right on track," confirms Dr. Djakov. "The situation would be very different without COMSOL Multiphysics, which is giving us exactly what we need. Holistic modeling of our technology has made verification of the design much easier for my team. COMSOL Multiphysics and its MEMS module cost only £14,000 yet it has proved to be the best software for us." ■

Summary

- Microvisk is developing a hand held Point of Care and Home Use test for patients who are using anti-coagulant treatments.
- These devices conduct the internationally recognized Prothrombin Time/International Normalized Ratio test by using a drop of the patient's whole blood taken by a finger prick.
- The devices are simple to use with a clear display and large buttons. They are comfortable in the hand and the Home Use device is a discreet size.
- Microvisk's technology takes a different approach to other devices and tests currently on the market, which use optical analysis or chemical reactions.
- Microvisk uses Micro Electro Mechanical Sensors (MEMS) on a disposable strip which incorporates a small cantilever to measure viscosity.
- As the devices use a small volume of whole blood the test is less intrusive and removes the need for a laboratory.
- The Prothrombin Time / INR test works by introducing Tissue Factor to begin a reaction known as the Clotting Cascade. This changes blood from a free flowing solution to a gel-like substance and it is this change that the sensors monitor and detect.