Shrinking medical labs onto tiny chips

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According to Dongqing Li, just about anything you can do in a medical lab, he can do faster, cheaper and better with a device that fits nicely in the palm of your hand.

"With lab-on-a-chip technology, you don't have to take the hospital with you," says Li, who is the H. Fort Flowers professor of engineering at Vanderbilt University.

His ultimate goal is to create miniature medical laboratories the size of a business card capable of on-the-scene diagnosis of diseases and rapid detection of biochemical warfare agents. He would like to put these devices directly in the hands of emergency medical technicians, police officers, security personnel and hazardous waste materials assessors.

An international leader in the emerging field of microfluidics, Li has developed a series of micro-scale devices that can analyze DNA, proteins and cells with fully integrated systems that have been miniaturized until they fit on the surface of a computer chip. These systems contain tiny channels, pumps, mixers, reactors, detectors and fluid controllers that store, transport, sort, separate and analyze tiny biological samples.

Li's "lab-on-a-chip" devices are more than just impressive gadgets. They are the cutting edge of a biochip industry, which is projected by Multimedia Research Group to grow into a $5 billion per year market by 2010. Today, commercial lab chips are being used in a variety of pharmaceutical and research settings. Li's latest creations are designed to

work in the hospital floor to identify bacteria, viruses and cancers more rapidly and reliably than current laboratory procedures.

One of his devices, for example, detects bacteria, viruses and cancers using fluorescence and a miniature laser multiplex system that can carry several signals over a single beam of light. A second is designed to separate white blood cells and DNA from a single drop of blood. Li is also working on special "immunoassay chips" that can detect the presence of various disease agents based on the reactions between antigens and antibodies. (Antigens are foreign substances introduced into the body that stimulate the immune system to special protective proteins called antibodies.)

In one of his newest designs, Li is working with Spyros A. Kalams, associate professor of medicine at the Vanderbilt Medical Center, to develop a hand-held detector of the HIV virus, as part of the National Institute of Biomedical Imaging and Bioengineering's Quantum Projects that support research into novel technologies for diagnosing, treating, managing and preventing disease.

"I tell medical researchers that if they will give me the details of a laboratory process, we can build a lab-on-a-chip that will not only replicate, but will also improve the process," Li says.

Creating tiny labs on chips is not a one-size-fits-all operation. Each laboratory process must be painstakingly recreated at miniature scale, using and respecting the laws of physics that can make or break reactions at the molecular and cellular level.

Flowing and Growing

Li's general field of research is microfluidics, which applies chemistry, engineering, physics and biotechnology to understand fluid behavior at

the micro and meso scales.

"Microfluidics refers to the study of flow, mass transfer and heat transfer in microchannel systems," Li says. "Precise manipulation of liquids is the key to the operation and performance of lab-on-a-chip technology."

Getting particles, molecules and cells in fluids to go where you want them to go, at the right speed and proper temperature, requires a complex juggling of thermal and electrokinetic forces. Electrokinetic forces are produced by the build-up of static electricity at the interface between particles and liquids. Although these forces don't have a significant effect on the behavior of liquids at larger scales, at the microscale they play a governing role and so make fluid control at the micro-scale very different.

Li and his associates are studying these forces, incorporating them in their designs, predicting their performance using computer simulations and testing their predictions in new chip designs.

"There are currently two basic methods of molecular analysis in use in medical laboratories: genetics assessment and immunoassay," Li explains. As a result, replicating these two methods on a chip will allow the researchers to replace dozens of medical laboratory procedures. To duplicate the two basic methods, Li is developing a variety of lab-on-a-chip technologies that can preterits samples, separate particles, grow DNA, open up cells, mix and deliver chemical reagents. These include:

Real-time PCR lab-on-a-chip technology to detect bacteria, viruses and cancers using fluorescence and miniature laser multiplex system. This portable device will be able to complete tests within 30 minutes, compared with 4-6 hours required by conventional lab tests.

Immunoassay lab-on-a-chip to detect bacteria, viruses and cancers based on antigen-antibody reactions. This technology will be helpful in situations where quick field analysis is needed, such as in forensics and medical emergencies.

Dielectrophoresis lab-on-a-chip for detecting cancer cells and bacteria based on response to a non-uniform AC field. This technology dramatically reduces the complexity of biomedical diagnostics and tests.

Blood sample preparation lab chip that can crack cells to extract DNA. Whereas most lab-on-a-chip devices require samples that are pretreated in conventional laboratories, this device can separate the white blood cells from a single drop of blood, lyse the cells, and extract and amplify the DNA.

Cellular lab-on-a-chip for single-cell analysis. This device will count cells, separate a single cell from a population of cells, put individual cells in micro-chambers, deliver reagents to the selected cells and then study its response under controlled conditions.

Miniaturizing the processes in full-size laboratories requires an extraordinary degree of precision. "First we must have optimum design parameters. From that we can develop concise protocols and build them into the chips. Each application is different," Li says.

The combination of high levels of complexity and very little room for error makes lab-on-a-chip technology quite a challenge — one reason the field is still in an early stage of development .

"Most lab-on-a-chip technology is still in the proof-of-concept stage," Li says. "More fundamental research on microfluidic transport processes is required for further development of this promising technology."

From Design to Reality

To test their lab-on-a-chip designs, Li and his associates fabricate working lab chips using "soft photolithography," a process that uses light to produce molds with microscopic features that are needed to cast lab chips.

The process begins with creation of a two-dimensional "photomask" that is clear in locations where the lab chip will be indented, such as microchannels and reservoirs, and is opaque everywhere else. Next, a glass plate is coated with a thin layer of a fluid called photoresist, which hardens when exposed to light. The mask is placed over the plate and exposed to light. In the places that the light shines through the mask, the photoresist hardens, leaving a raised pattern on its surface when the plate is chemically washed.

Finally, the plate is coated with a film of polydimethylsiloxane, a soft plastic that solidifies and peels off to provide the foundation of the new chip. Electrical components are added in separate steps.

Most lab-on-a-chip designs rely on fluid pressure to move materials around. Li, however, has developed a flow control system that uses the precise application of electrical fields and the natural behavior of solutions containing molecules, cells and particles.

Li's method relies on an effect called electro-osmosis, a natural phenomenon by which particles, molecules and cells in fluids attach to the charged surfaces of the microchannels. By placing computer-controlled electrodes at strategic locations along these tiny channels, Li has found that he can control the movement of particles by a process called electrophoresis, which acts on the positively charged particles that line the sides of the channels. As they move, these particles bump up against particles in the middle of the channel and propel them along, too.

The engineer has also applied a related process, called dielectrophoresis, to separate different-sized particles. A strong electrode is coupled with a weak electrode, producing a non-uniform electrical field focused on a specific point. As they are carried down a channel, particles align with the field. Because larger particles generate more charge they are more strongly affected. Li leverages the difference to push large particles in one direction and small particles in another.

For DNA testing, Li and his associates have developed a chip capable of producing a real-time polymerase chain reaction, a key technique in genetic research. PCR uses a special enzyme to produce millions of copies of specific regions of DNA molecules. Once the DNA has been amplified by this process, sufficient quantities are present so the sequence can be identified.

Throughout all these processes, the temperature in the microchannels must be controlled precisely to produce the desired reactions. The researchers achieve this by using a combination of computer-controlled resistant heaters that line the channels, as well as by passing electrical currents through the fluid, which produces heat through an effect called Joule heating.

The progress of the reactions that take place on the chip are monitored by laser sensors that detect the presence of fluorescent molecules attached to cells and proteins or the special optical characteristics of the particles involved. On any given chip, hundreds of different reactions and analyses can be performed at the same time through hundreds of parallel microchannels.

Source: By Vivian F. Cooper, Vanderbilt University