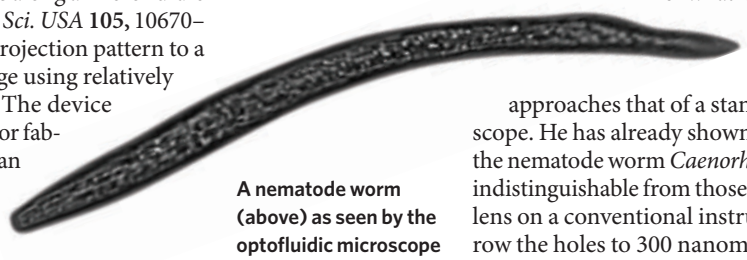
MICROSCOPE FOR THE MASSES

Blurry specks in the eye seem an unlikely source of inspiration for a revolutionary microscope. But 'floaters' — tiny debris that floats inside the eyeball — led Changhuei Yang at the California Institute of Technology in Pasadena to devise a microscope so small, cheap and mass-producible that it could, according to its inventor, transform the way that microscopy is done.

The human eye registers floaters when bright light casts the shadow of debris directly onto the retina. On the tiny 'optofluidic' microscope that Yang and his colleagues invented, the sample casts a shadow directly on to an array of commercial light sensors as it floats along a microfluidic channel (X. Cui *et al. Proc. Natl Acad. Sci. USA* **105,** 10670–10675; 2008). The sensors feed the projection pattern to a computer, which constructs an image using relatively simple image-processing software. The device itself is assembled using semiconductor fabrication techniques and is smaller than an American dime. When mounted into a device with a USB port so that it can transfer information to a computer, it is still just 3 centimetres square.



X. CUI *ET AL.*

A nematode worm (above) as seen by the optofluidic microscope (shown en masse and slightly larger than life, opposite, and in schematic below).

Yang says that his microscopes, which could cost as little as US$10 apiece, could have the same revolutionary impact on science that the integrated circuit has had on the electronics industry. "When people were building transistors individually, it was still a pretty expensive proposition to build circuits out of them," he says. "But the move to build integrated circuits moved the semiconductor industry forwards because you could build things comparably cheaply with high functionality. If we can start to put 10–100 microscopes on a single chip and link a bunch of them up to operate in parallel to do high-throughput processing of a large number of samples, this opens up the opportunity to do experiments you might not otherwise do."

With cheap, high-throughput imaging, researchers could perform drug assays, genomic or proteomic screens and rapidly observe the outcome of hundreds or thousands of manipulations on the shape or behaviour of living cells. "It's very clever work," says Charles DiMarzio, director of the Optical Science Laboratory at Northeastern University in Boston, Massachusetts. "This is a way of making a [high-power] microscope that is very low cost, maybe even disposable, and that's something that we haven't had before."

Yang recognized that it would be difficult to shrink the lens and other delicate optics in a high-end instrument — so his 'direct projection' technique did away with lenses altogether. Other scientists have worked out similar techniques before, but they couldn't resolve anything smaller than 5 micrometres, because that's as small as the pixels on most digital light-sensing chips get. Yang coated the sensing chips with a thin layer of metal, than punched 500-nanometre holes into the metal to create apertures that are smaller than a pixel and that are patterned along the path of the microfluidic channel (see graphic). As the sample floats along, the chip captures repeated but staggered snapshots of what is passing overhead.

With 500-nanometre holes, Yang's optofluidic microscope has a resolution that approaches that of a standard laboratory light microscope. He has already shown that it can capture images of the nematode worm *Caenorhabditis elegans* that are almost indistinguishable from those collected with a 20× objective lens on a conventional instrument. He is working to narrow the holes to 300 nanometres, a resolution capable of distinguishing the finer details of cells.

Besides transforming research microscopy, Yang's microscope could boost low-cost science and medicine in developing nations. The scope is rugged, works with sunlight, needs only the amount of computational power found in an iPod and, Yang wrote in his paper last July, might be "a boon for a health worker who needs to travel from village to village". That statement struck home for Ricardo Leitão, a postdoctoral fellow at New York University School of Medicine, who is founding a non-profit group called Tek4Dev — Science & Technology for Sustainable Development — which is putting together a tool kit to enable 'telemedicine' (using networks such as the Internet to facilitate clinical care) in poor countries. Leitão wrote to Yang on the day the paper was published to propose a collaboration. Yang, Leitão and Ana Rodriguez, a malaria researcher also at New York University, are now testing the microscope's ability to diagnose malaria-infected red blood cells based on their shape and those of the parasites inside them. Microscopy is still the standard method for diagnosing malaria, but microscopes can be few and far between in malaria-endemic areas. "Having a diagnostic tool as powerful as Yang's integrated with our hardware and 'tele' ability would be of tremendous clinical value," says Leitão.

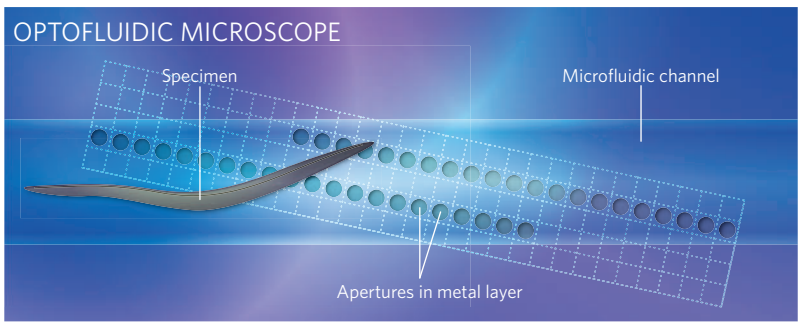
Yang admits that by trying to do more with less, he is thinking differently from many of his peers. "In the field of biomicroscopy, there is a very strong drive towards building more sophisticated microscopes, giving you ever better resolution," he says. "But I think there's another axis to pursue, which is if you're actually building this in a comparably low-cost fashion, it can create experimental formats that are currently not doable using a traditional microscope or any other high-end microscope that other research groups are pursuing."

What is certain is that by making microscopes exceedingly small, Yang has actually been thinking very, very big. ■

Erika Check Hayden

See also page 629 and online at http://tinyurl.com/microspecial.

X. CUI *ET AL.*



G. MARSHALL