Artificial intelligence helps detect subtle differences in mutant worms

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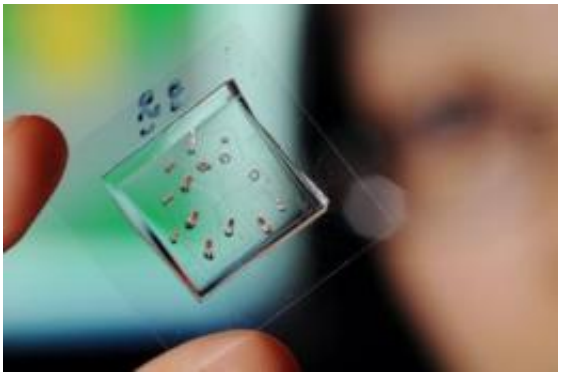

Georgia Tech associate professor Hang Lu holds a microfluidic chip that is part of a system that uses artificial intelligence and cutting-edge image processing to automatically examine large number of nematodes used for genetic research. Credit: Georgia Tech Photo: Gary Meek

Research into the genetic factors behind certain disease mechanisms, illness progression and response to new drugs is frequently carried out using tiny multi-cellular animals such as nematodes, fruit flies or zebra fish.

Often, progress relies on the microscopic visual examination of many individual animals to detect mutants worthy of further study.

Now, scientists have demonstrated an automated system that uses artificial intelligence and cutting-edge image processing to rapidly

examine large numbers of individual Caenorhabditis elegans, a species of nematode widely used in biological research. Beyond replacing existing manual examination steps using microfluidics and automated hardware, the system's ability to detect subtle differences from worm-to-worm – without human intervention – can identify genetic mutations that might not have been detected otherwise.

By allowing thousands of worms to be examined autonomously in a fraction of the time required for conventional manual screening, the technique could change the way that high throughput genetic screening is carried out using *C. elegans*.

Details of the research were scheduled to be reported August 19th in the advance online publication of the journal *Nature Methods*. The research has been supported by the National Institutes of Health (NIH), the National Science Foundation (NSF) and the Alfred P. Sloan Foundation.

"While humans are very good at pattern recognition, computers are much better than humans at detecting subtle differences, such as small changes in the location of dots or slight variations in the brightness of an image," said Hang Lu, the project's lead researcher and an associate professor in the School of Chemical & Biomolecular Engineering at the Georgia Institute of Technology. "This technique found differences that would have been almost impossible to pick out by hand."

Lu's research team is studying genes that affect the formation and development of synapses in the worms, work that could have implications for understanding human brain development. The researchers use a model in which synapses of specific neurons are labeled by a fluorescent protein. Their research involves creating mutations in the genomes of thousands of worms and examining the resulting changes in the synapses. Mutant worms identified in this way are studied further to help understand what genes may have caused the

changes in the synapses.

One aspect the researchers are studying is why synapses form in the wrong locations, or are of the wrong sizes or types. The differences between the mutants and the normal or "wild type" worms indicate inappropriate developmental patterns caused by the genetic mutations.

Because of the large number of possible genes involved in these developmental processes, the researchers must examine thousands of worms – perhaps as many as 100,000 – to exhaust the search. Lu and her research group had earlier developed a microfluidic "worm sorter" that speeds up the process of examining worms under a microscope, but until now, there were two options for detecting the mutants: a human had to look at each animal, or a simple heuristic algorithm was used to make the sorting decision. Neither option is objective or adaptable to new problems.

Lu's system, an optimized version of earlier work by her group, uses a camera to record three-dimensional images of each worm as it passes through the sorter. The system compares each image set against what it has been taught the "wild type" worms should look like. Worms that are even subtly different from normal can be sorted out for further study.

"We feed the program wild-type images, and it teaches itself to recognize what differentiates the wild type. It uses this information to determine what a mutant type may look like – which is information we didn't provide to the system – and sorts the worms based on that," explained Matthew Crane, a graduate student who performed the work. "We don't have to show the computer every possible mutant, and that is very powerful. And the computer never gets bored."

While the system was designed to sort *C. elegans* for a specific research project, Lu believes the machine learning technology – which is

borrowed from computer science – could be applied to other areas of biology that use model genetic organisms. The system's hardware and software are currently being used in several other laboratories beyond Georgia Tech.

"Our automated technique can be generalized to anything that relies on detecting a morphometric – or shape, size or brightness difference," Lu said. "We can apply this to anything that can be detected visually, and we think this could be expanded to studying many other problems related to learning, memory, neuro-degeneration and neural developmental diseases that this worm can be used to model."

Individual *C. elegans* are less than a millimeter long and thinner than a strand of hair, but have 302 neurons with well-defined synapses. While research using single cells can be simpler to do, studies using the worms are good in vivo models for many important processes relevant to human health.

Other researchers who contributed to this paper include student Jeffrey Stirman from Georgia Tech's interdisciplinary program in bioengineering, Professor James Rehg from Georgia Tech's School of Interactive Computing, and three researchers from the Department of Biology at Stanford University's Howard Hughes Medical Institute: Chan-Yen Ou, Peri Kurshan, and Professor Kang Shen.

The autonomous processing facilitated by the new system could allow researchers to examine more animals more rapidly, potentially opening up areas of study that are not feasible today.

"We are hoping that the technology will really change the approach people can take to this kind of research," said Lu. "We expect that this approach will enable people to do much larger scale experiments that can push the science forward beyond looking what individual mutations are

doing in a specific situation."

More information: Autonomous screening of C. elegans identifies genes implicated in synaptogenesis, *Nature Methods* DOI: 10.1038/NMETH.2141

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