Microfluidic device rapidly orients hundreds of embryos for high-throughput experiments

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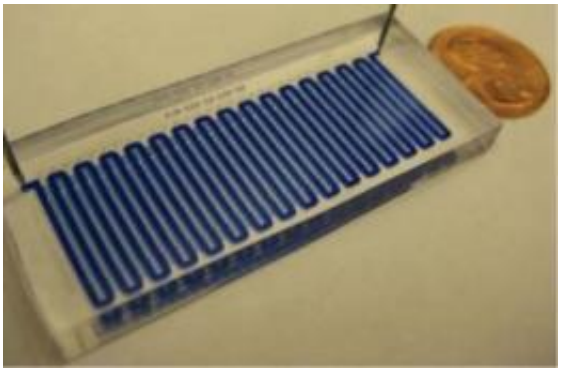


This is a photograph of a penny next to the microfluidic device designed by Hang Lu, an associate professor in the Georgia Tech School of Chemical & Biomolecular Engineering, to automatically orient hundreds of embryos to prepare them for research. Credit: Georgia Tech/Hang Lu

Researchers have developed a microfluidic device that automatically orients hundreds of fruit fly and other embryos to prepare them for research. The device could facilitate the study of such issues as how organisms develop their complex structures from single cells -- one of the most fascinating aspects of biology.

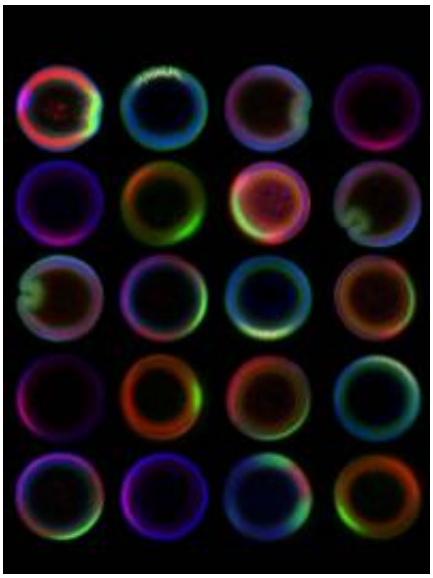
Scientists know that among an embryo's first major developments is the establishment of its dorsoventral axis, which runs from its back to its belly. Determining how this axis development unfolds -- specifically the presence and location of proteins during the process -- requires the

ability to simultaneously monitor large numbers of embryos with different genetic backgrounds at several time points.

"Collecting and analyzing the signaling and transcriptional patterns of the dorsoventral axis typically requires manual manipulation of individual embryos to stand them on their ends, making it difficult to conduct high-throughput experiments that can achieve statistically significant results," said Hang Lu, an associate professor in the Georgia Tech School of Chemical & Biomolecular Engineering.

To enable large-scale quantitative analyses of protein positional information along the dorsoventral axis, Lu designed a microfluidic device that reliably and robustly orients several hundred embryos in just a few minutes.

Details of the device design and results from proof-of-concept experiments with fruit fly embryos were published in the Dec. 26 advance online edition of the journal *Nature Methods*. This project was supported by the National Science Foundation, the National Institutes of Health, the Alfred P. Sloan Foundation and the DuPont Young Professor program.



These are *Drosophila* embryos in dorsoventral cross-sectional views stained for a variety of morphogens. This view of embryos would have been difficult to obtain without the use of the microfluidic device. Credit: Georgia Tech/Hang Lu

Lu designed and fabricated the device with the help of Kwanghun Chung and Emily Gong, who worked on the project as Georgia Tech graduate and undergraduate students, respectively. Fabricated from polydimethylsiloxane (PDMS), the compact device is the size of a microscope slide and contains approximately 700 traps for embryos, which are shaped like grains of rice but smaller in size.

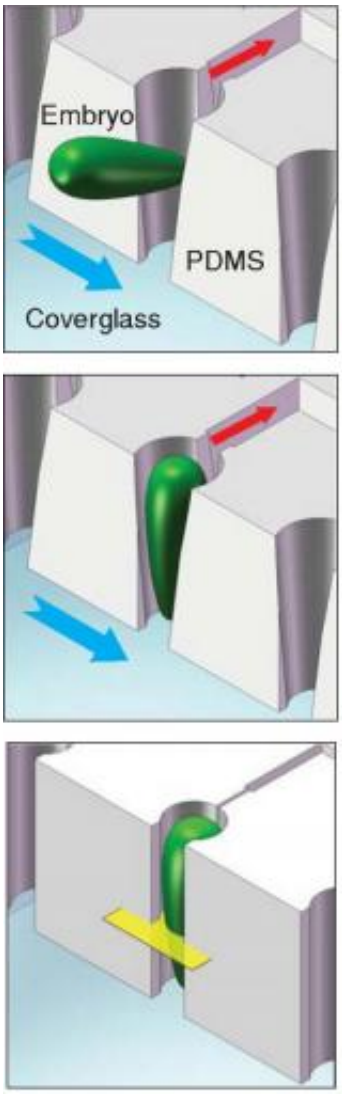
In operation, fluid flows through an "S"-shaped channel wide enough for embryos of any orientation to move easily through it. The fluid efficiently directs the embryos toward the traps, while sweeping out extra and improperly trapped embryos.

"The flow pattern significantly increased the frequency at which embryos contacted the traps and were loaded into them," explained Lu. "Experimentally, we found on average 90 percent of the embryos

became trapped in the device, which will be valuable for studies that only have a small number of embryos available."

When an embryo approaches an empty trap, it experiences non-uniform pressure and shear from the surrounding fluid. The resulting force flips the embryo vertically and inserts it into the cylindrical trap in an upright position, with its dorsoventral axis parallel to the ground. The embryo is then secured inside the trap, without any need for user intervention or control. The lock-in feature allows the device to be disconnected from the rest of the hardware and transported for imaging or storage with the embryos enclosed.

"At one point, we mailed a microfluidic embryo trap array device full of trapped fruit fly embryos to our collaborators at Princeton University, and upon arrival, the embryos were still upright in their locked traps," said Lu.



These schematic diagrams show the embryo trapping process: (top) the cross-flow guides an embryo into the cylindrical trap; (middle) the flow around the embryo orients it vertically; (bottom) the trap contracts after loading is finished and secures the embryo inside the trap. The yellow plane represents the focal plane where images are obtained. Credit: Georgia Tech/Hang Lu

To demonstrate the device's capabilities, Lu collaborated with Stanislav Shvartsman, an associate professor in the Department of Chemical and Biological Engineering at Princeton University, and his graduate student Yoosik Kim. The Princeton researchers used the device to quantify

gradients of signaling molecules called morphogens in fixed embryos and also used it to monitor nuclear divisions in live embryos.

In one experiment, the Princeton researchers determined the spatial extent of the distribution of Dorsal, a transcription factor that initiates the dorsal-to-ventral patterning of the *Drosophila* embryo. They also demonstrated that this gradient could be quantitatively compared between wild-type and mutant embryos.

"The trap array device provided a significant increase in the number of fixed and live embryos we could image simultaneously and allowed us to accurately resolve issues of interest to developmental biologists today," explained Lu.

In the future, scientists should be able to adapt the microfluidic device for studies of pattern formation and morphogenesis in other model organisms, such as zebrafish or worm embryos. Results of those studies will be important to the scientific community because many genes controlling development are similar in worms, fruit flies and mammals.

Provided by Georgia Institute of Technology