Massive effort yields image-based cell sorting technology

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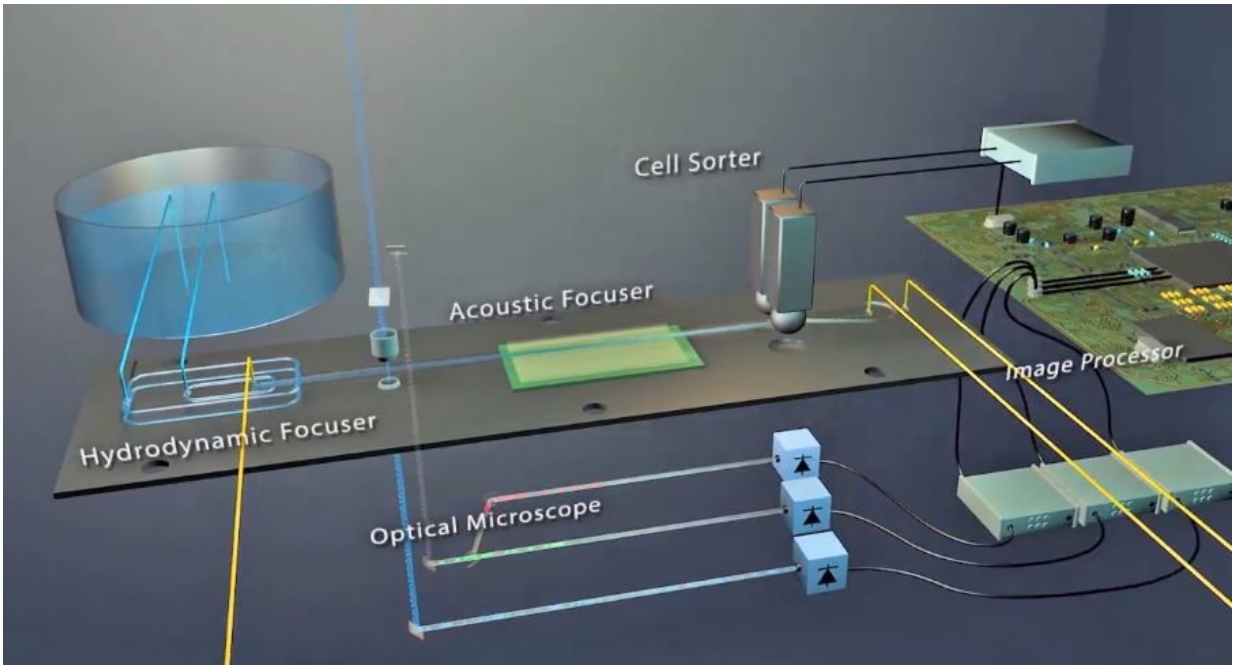

Invented over 50 years ago, flow cytometry-based cell sorting has become a widely used tool in biology labs for physically isolating cells based on their global surface marker expression profiles. But on August 27 in the journal *Cell*, an international, multi-institutional team of researchers unveil the next evolution in this critical process, "Image-Activated Cell Sorting", or IACS for short.

IACS is an intelligent machine that integrates optical, microfluidic, electrical, computational, and mechanical technology to sort cells based not only on their global phenotypic profiles but also on their spatial and morphological properties using an image-driven approach. The researchers will launch an open innovation platform where users can suggest ideas, submit interesting samples, and test them at the machine built at the University of Tokyo. Separately, a startup, CYBO, Inc, will turn the intelligent IACS technology into a commercial product.

"We aim to extend flow cytometry's capability from 1D intensities to 2-D pictures to sort cells with unique spatial architectures of biomolecules. This will allow addressing new fundamental biological questions like "how is cellular architecture molecularly connected with physiological function?" says senior author Keisuke Goda, a physical chemist at the University of Tokyo. "We envision the developed tool to be broadly applicable in the study of what genes affect the spatial localization of various molecules within cells."

To make IACS a reality, the researchers needed to achieve a balance between speed and accuracy. With a combined force of over 50 experts from 26 institutions including the University of Tokyo, Nagoya University, Kyoto University, RIKEN, UCLA, and Columbia University, Goda and his colleagues identified a method to isolate target cells in real time without interruptions while using deep learning to rapidly process high-resolution data. It took 2 years to design, 2 years to develop the subsystems, and another 2 years to integrate them and test the platform on microalgae and blood cell samples. Goda, a former researcher in the LIGO (Laser Interferometer Gravitational-Wave Observatory) group that was awarded the Nobel Prize in physics last year, took the LIGO strategy for leading the team to build the highly interdisciplinary, complex machine.

As with all flow cytometers, a tube containing a sample of suspended

cells is placed at the injection port to be introduced in to the IACS system. During the run, the cells are imaged as they pass one by one under a microscope lens; data is collected in real time and used to construct a sort decision whereby cells that meet the criteria are physically separated from those that do not. When finished, two tubes containing the sorted and remaining parts of the sample are collected, inspected under an optical microscope, and evaluated for yield and purity. Unlike flow cytometry, cells can be sorted from large heterogeneous populations based on spatial and morphometric parameter such as intracellular protein localization and cell-cell interaction as demonstrated by Goda and colleagues.

"The platform enables image acquisition, image processing, decision making, and actuation, all within 32 milliseconds even with deep learning algorithms, and hence realizes real-time image-based intelligent cell search and sorting at an unprecedented rate of about 100 cells per second," Goda says. "The intelligent IACS technology is highly versatile, can handle various types and sizes of cells in diverse fields ranging from microbiology to hematology, and holds promise for making machine-based discoveries in biological, pharmaceutical, and medical sciences."

At the moment the platform is optimized for analyzing individual cells and cannot handle larger biological objects such as cell spheroids, organoids, tissue fragments, and whole organisms. However, the researchers are planning to modify the microfluidic channels and optical system to make this possible in the future. And because the system is so large and complex, it is not easy to build in outside labs. In the short term, the researchers will use the open innovation platform to assist anyone interested in using the tool.

More information: *Cell*, Nitta et al.: "Intelligent Image-Activated Cell Sorting" www.cell.com/cell/fulltext/S0092-8674(18)31044-4 , DOI: 10.1016/j.cell.2018.08.028

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