Machine learning tracks moving cells

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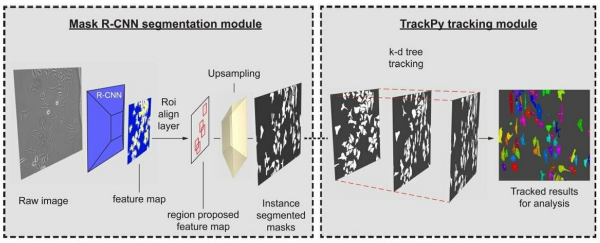

Usiigaci, a software developed by the Micro/Bio/Nanofluidics Unit, allows users to easily segment, track and analyze the migration of label-free cells. The tool can be used as an all-in-one solution to quantify cell migration, or can be employed as three separate applications (ie for segmentation, tracking, and data analysis, respectively). Using the machine learning infrastructure known as a “neural network,” the system allows users to train it on different data sets and analyzes images as a simplified human brain would. Credit: Okinawa Institute of Science and Technology

Both developing babies and elderly adults share a common characteristic: the many cells making up their bodies are always on the move. As we humans commute to work, cells migrate through the body to get their jobs done. Biologists have long struggled to quantify the movement and changing morphology of cells through time, but now, scientists at the Okinawa Institute of Science and Technology Graduate University (OIST) have devised an elegant tool to do just that.

Using machine learning, the researchers designed a software to analyze microscopic snapshots of migrating cells. They named the software Usiigaci, a Ryukyuan word that refers to tracing the outlines of objects, as the innovative tool detects the changing outlines of individual cells. Usiigaci, described in a paper published March 13, 2019 in *SoftwareX*, is now available online for anyone to use, along with a video tutorial explaining the software.

In the womb, a baby's cells migrate to precise locations so that each arm, leg, and organ grows in its proper place. Our immune cells race through the body to mend wounds after injury. Cancerous cells metastasize by traveling through the body, spreading tumors to new tissues. To test the efficacy of new medicines, drug developers track the movement of cells before and after treatment. The Usiigaci software finds applications in all these areas of study and more.

"This is an all-in-one solution to get us from raw images to quantitative data on cell migration," said Hsieh-Fu Tsai, first author of the study. Tsai is a graduate student and a Japan Society for the Promotion of Science (JSPS) DC1 research fellow in the OIST Micro/Bio/Nanofluidics Unit, led by Prof. Amy Shen. "Our software is at least 100 times faster than manual methods, which are currently the gold-standard for these types of experiments because computers are not yet powerful enough."

"We're hoping this software can become quite useful for the scientific community," said Prof. Amy Shen, principal investigator of the unit and senior author of the study. "For any biological study or drug screening that requires you to track cellular responses to different stimuli, you can use this software."

Machine Learning Makes Usiigaci Adaptable

In order to observe cells under the microscope, scientists often steep them in dye or tweak their genes to make them glow in eye-popping colors. But coloring cells alters their movement, which in turn skews the experimental results. Some scientists attempt to study cell migration without the help of fluorescent tags, using so-called "label-free" methods, but end up running into a different problem; Label-free cells blend into the background of microscopic images, making them incredibly difficult to analyze with existing computer software.

Usiigaci hops this hurdle by allowing scientists to train the software over time. Biologists act as teachers, providing the software new images to

study so that it can come to recognize one cell from the next. A fast learner, the program quickly adapts to new sets of data and can easily track the movement of single cells, even if they're crammed together like commuters on the Tokyo metro.

"Most software...cannot tell cells in high-density apart; basically, they're segmenting into a glob," said Tsai. "With our software, we can segment correctly even if cells are touching. We can actually do single-cell tracking throughout the entire experiment." Usiigaci is currently the fastest software capable of tracking the movement of label-free cells at single-cell resolution on a personal laptop.

Software Mimics the Human Brain

The researchers designed Usiigaci to process images as if it were a simplified human brain. The strategy enables the software to trace the outlines of individual cells, monitor their movement moment to moment, and transform that information into crunchable numbers.

The program is built around a machine learning infrastructure known as a "convolutional neural network." roughly based on how brain cells work together to process incoming information from the outside world. When our eyes capture light from the environment, they call on neurons to analyze those signals and figure out what we're looking at and where it is in space. The neurons first sketch out the scene in broad strokes then pass the information on to the next set of cells, progressively rendering the image in more and more detail. Neural networks work similarly, except each "neuron" is a collection of code rather than a physical cell.

This design grants Usiigaci its accuracy and adaptability. Looking forward, the researchers aim to develop neural networks to identify different components within cells, rather than just their outlines. With these tools in hand, scientists could easily assess whether a cell is healthy or diseased, young or old, derived from one genetic lineage or another. Like Usiigaci, these programs would have utility in fundamental biology, biotechnology research and beyond.

More information: Hsieh-Fu Tsai et al. Usiigaci: Instance-aware cell tracking in stain-free phase contrast microscopy enabled by machine learning, *SoftwareX* (2019). DOI: 10.1016/j.softx.2019.02.007

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