Scientists teach computers how to analyze brain cells

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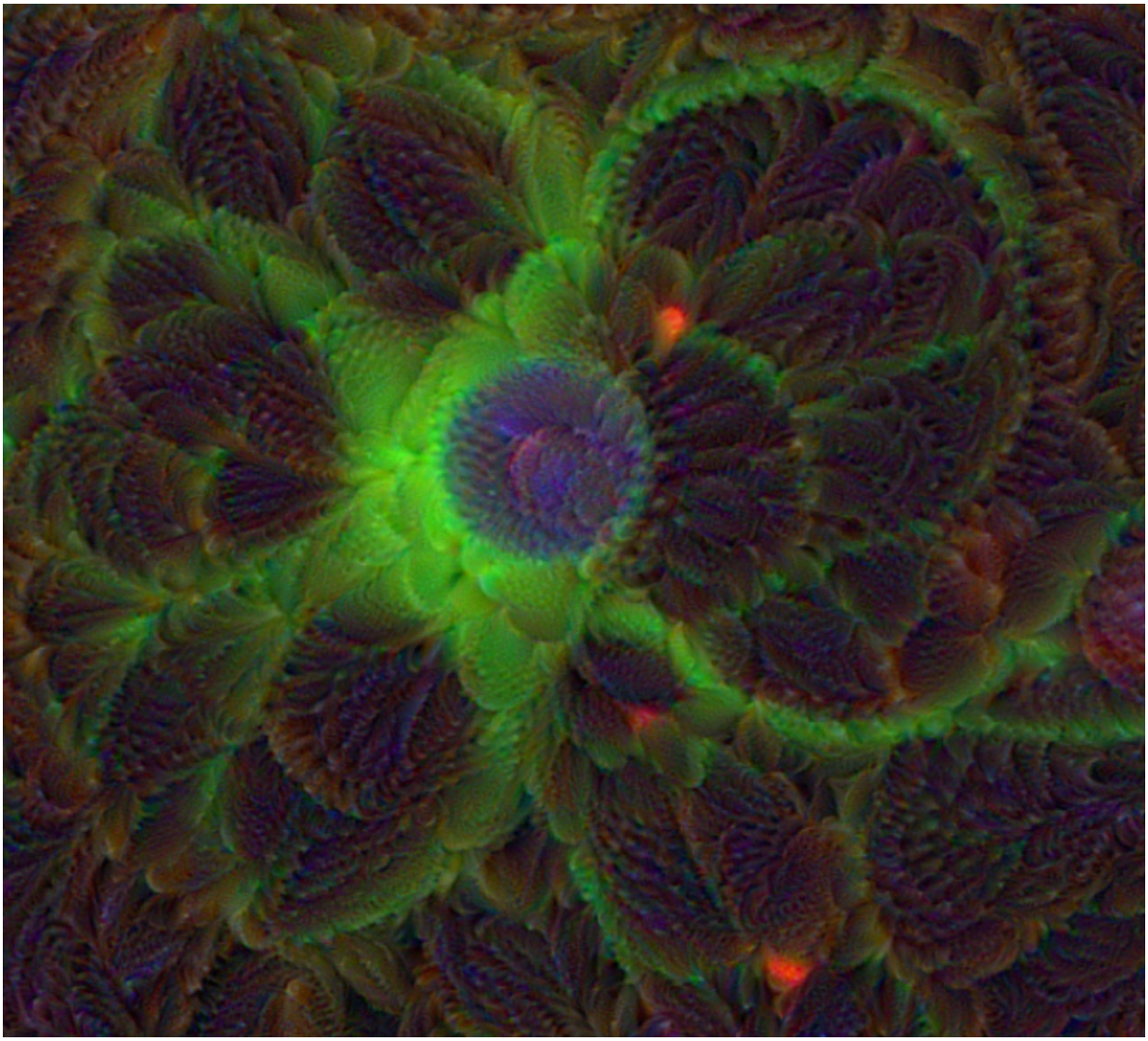

Researchers trained a computer program to analyze brain cells. This image shows the program 'thinking,' as it considers what cellular structures to identify. Credit:

Dr. Finkbeiner, Gladstone Institutes and UCSF.

In the early days of neuroscience research, scientists painstakingly stained brain cells and drew by hand what they saw in a microscope. Fast forward to 2018 and machines may be able to learn how to do that work. According to a new study in *Cell*, it may be possible to teach machines how to pick out features in neurons and other cells that have not been stained or undergone other damaging treatments. The study was partially funded by the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

"This approach has the potential to revolutionize biomedical research," said Margaret Sutherland, Ph.D., program director at the NINDS. "Researchers are now generating extraordinary amounts of data. For neuroscientists, this means that training machines to help analyze this information can help speed up our understanding of how the cells of the brain are put together and in applications related to drug development."

A dish, or culture, of neuronal cells appears uniform to the naked eye and the different, individual cells in it cannot be seen. Ever since the late nineteenth century when pioneering neuroscientists, Santiago Ramon y Cajal and Camillo Golgi, drew the earliest maps of the nervous system, scientists have been developing dyes and staining methods to help distinguish the structures in the brain, including different types of cells and their state of health. However, many of these methods involve harsh chemicals that fix, or freeze, cells in an unnatural state or damage living cells after multiple stains have been applied. The traditional techniques also limit the details scientists can observe.

A team led by Steven Finkbeiner, M.D., Ph.D., director and senior investigator at the Gladstone Institutes in San Francisco, and professor of

neurology and physiology at the University of California, San Francisco, explored whether computers could be trained to identify structures in unstained cells.

"Every day our lab had been creating hundreds of images, much more than we could look at and analyze ourselves. One day, a couple of researchers from Google knocked on our door to see if they could help us," said Dr. Finkbeiner, the senior author of the study.

The researchers used a method called Deep Learning, which relies on principles of machine learning, a type of artificial intelligence in which machines can learn from data and make decisions. Facial recognition software is an example of machine learning.

Using Deep Learning, Dr. Finkbeiner's team trained a computer program to analyze brain cells by showing it stained and unstained images. Then, to test whether the program had learned anything, the researchers challenged it with new unlabeled images.

After the first round of training, the program identified where cells were located in the culture dish by learning to spot a cell's nucleus, a round structure that contains genetic information and serves as the cell's command center. During additional experiments, Dr. Finkbeiner's group increased the complexity of the features the program was looking for and successfully trained it to distinguish dead cells from living cells, as well as to identify specific types of brain cells. In addition, the program learned to differentiate between axons and dendrites, which are two specific types of extensions on neurons. According to the results, the program was successful in predicting structures in unlabeled tissue.

"Deep Learning takes an algorithm, or a set of rules, and structures it in layers, identifying simple features from parts of the image, and then passes the information to other layers that recognize increasingly

complex features, such as patterns and structures. This is reminiscent of how our brain processes visual information," said Dr. Finkbeiner. "Deep Learning methods are able to uncover much more information than can be seen with the human eye."

Dr. Finkbeiner and his team noted that the main drawback to using this technology is that the training datasets need to be very large, ideally around 15,000 images. In addition, there may be a risk to overtraining the programs, that they become so specialized they can only identify structures in a particular set of images or in images generated in a particular way, and not make predictions about more general images, which could limit the use of this technology.

Dr. Finkbeiner and his colleagues plan to apply these methods to disease-focused research.

"Now that we showed that this technology works, we can start using it in disease research. Deep Learning may spot something in cells that could help predict clinical outcomes and can help us screen potential treatments," said Dr. Finkbeiner.

More research is needed to refine the technology and make it more widely available.

More information: Christiansen E. et al. In silico labeling: Predicting fluorescent labels in unlabeled images. *Cell*. April 12, 2018.

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