Artificial intelligence digitally stains tissue samples used in pathology, saving labor, time and cost

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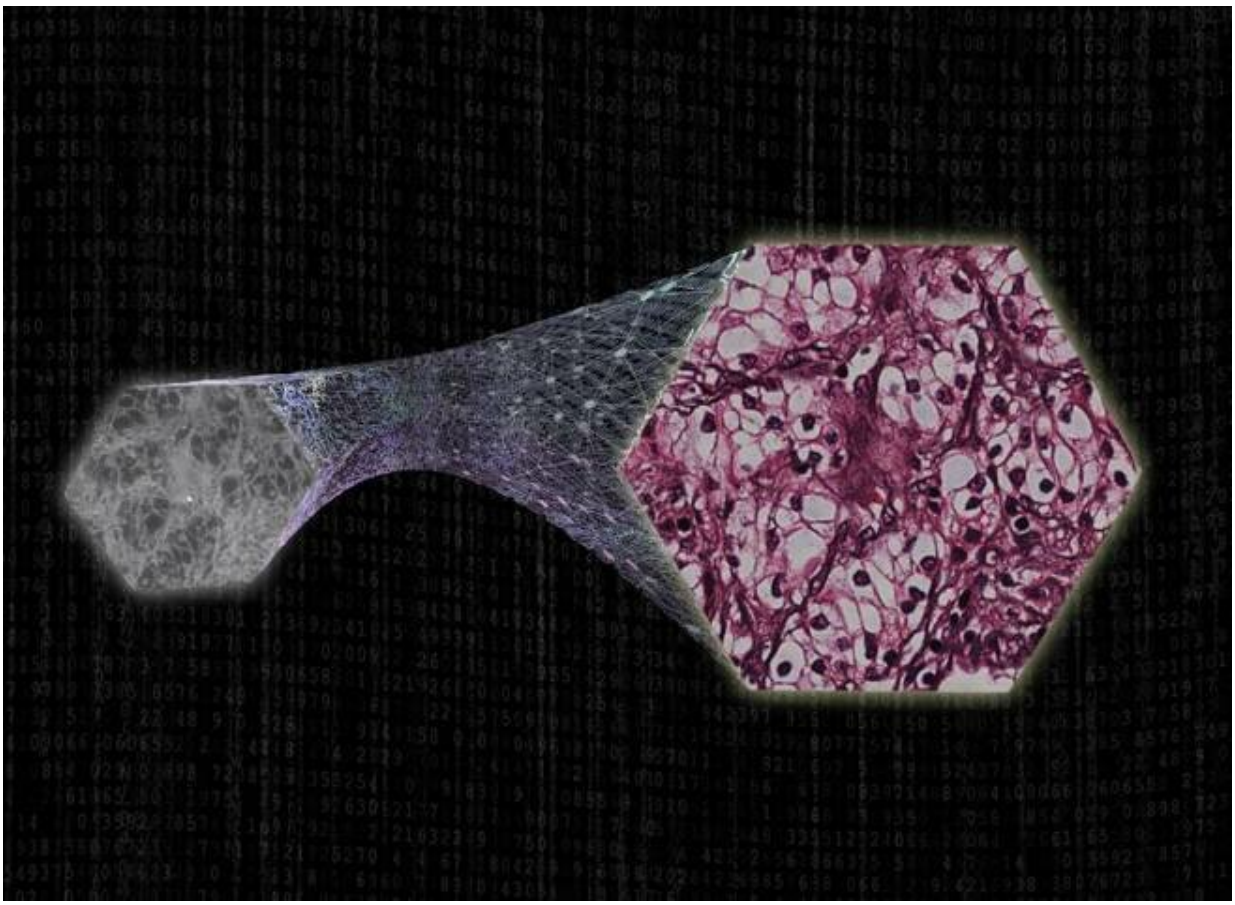

Deep learning enables virtual staining of label-free tissues from a single autofluorescence image. Credit: UCLA Engineering Institute for Technology Advancement

Histopathology is one of the main methods used for diagnosis of disease. Following a medical screening process, a patient can undergo a biopsy, in which a piece of tissue is removed for further inspection and diagnostic analysis. This tissue specimen is then sliced into thin sections that are on the order of a few millionths of a meter in thickness. These thin sections of tissue contain at the microscopic scale the diagnostic information regarding the patient's condition. However, they exhibit almost no contrast under standard light microscopy. To reveal these microscopic features embedded inside tissue and bring visible contrast for inspection by a pathologist, various tissue staining methods have been created in pathology dating back to more than 150 years ago. These tissue staining procedures use different types of colored dyes that specifically label micro-scale structures in tissue, forming colorful images of specimens, which have been widely used as a gold standard diagnostic method in modern medicine.

However, this standard process of staining a tissue specimen is laborious, costly and requires a dedicated laboratory infrastructure, chemical reagents, as well as trained personnel (histotechnologists). Furthermore, currently used staining methods do not preserve tissue samples, which is a limitation since advanced molecular analysis of the tissue sample cannot be easily performed after the initial staining process.

Researchers at UCLA have developed a deep learning-based method to take a microscopic image of naturally present fluorescent compounds in unstained tissue sections and digitally transform this "auto-fluorescence" image into an equivalent image of the same tissue, as if it was taken after the standard tissue staining process. Stated differently, this deep learning-based method virtually stains unlabeled tissue samples, replacing the manual and laborious processing and staining steps that are normally performed by histotechnologists or medical personnel, saving labor, cost and time by substituting most of the tasks performed a histotechnologist with a trained neural network.

The success of this new virtual staining method was demonstrated for different stains and human tissue types, including sections of salivary gland, thyroid, kidney, liver and lung. The efficacy of the virtual staining process was independently evaluated by a panel of board-certified pathologists, who were blinded to the origin of the examined images such that the pathologists did not know which images were actually stained by an expert technician and which images were virtually stained by a neural network. The conclusion of this blinded study revealed no clinically significant difference in the staining quality and the medical diagnoses resulting from the two sets of images. This virtual staining process powered by deep learning will significantly reduce cost and sample preparation time, while also saving expert labor. Since it only requires a standard fluorescence microscope and a simple computer (such as a laptop), it is especially transformative for pathology needs in resource-limited settings and developing countries.

This research was published in *Nature Biomedical Engineering*, and was led by Dr. Aydogan Ozcan, the Chancellor's Professor of electrical and computer engineering at UCLA, and an associate director of the California NanoSystems Institute (CNSI), Dr. Yair Rivenson, an adjunct Professor of electrical and computer engineering at UCLA, along with UCLA graduate students, Hongda Wang, Kevin de Haan and Zhensong Wei. Clinical validation of this virtual staining method was directed by Dr. W. Dean Wallace from the Department of Pathology and Laboratory Medicine at the David Geffen School of Medicine at UCLA.

"This technology has the potential to fundamentally change the clinical histopathology workflow, by making tissue staining process extremely fast and simple, without the need for expert technicians or an advanced medical laboratory." said Dr. Rivenson. "This powerful AI-based virtual staining framework can also be used in surgery rooms to rapidly assess tumor margins, providing highly-needed and critical guidance for surgeons during an operation", added Dr. Ozcan.

Another major impact of this virtual staining method is the standardization of the entire staining process since a trained neural network also eliminates the staining variability observed among technicians and medical laboratories, which can cause misdiagnoses and misclassification of biopsies.

More information: Yair Rivenson et al. Virtual histological staining of unlabelled tissue-autofluorescence images via deep learning, *Nature Biomedical Engineering* (2019). DOI: 10.1038/s41551-019-0362-y

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