MICROSCOPY

Microscopes are coming for your job

Advances in microscopy, computer vision and open source software are converging to usher in a new era of microscopes that control themselves.

Henry Pinkard and Laura Waller

Unlike the control of the earliest microscopes, which required scientists adjusting knobs and moving samples by hand, the control of modern microscopes has been mostly automated. However, most of this automation is used to adjust motorized components according to experimental settings that are still predefined by a human being. The field of adaptive microscopy (also known as 'reactive', 'feedback', 'smart' or 'intelligent' microscopy) takes automation to the next level: using an algorithm to interpret images and decide which experiments to run next.

In this issue of *Nature Methods*, Alvelid et al[1]. and Mahecic et al[2]. provide new examples in this growing field. Like past studies in adaptive fluorescence microscopy[3–5], their techniques switch experimental parameters in response to the detection of rare, interesting biological processes. Using this approach, Alvelid et al. perform time-lapse imaging of neurons in the hippocampus and, in response to calcium fluxes indicating firing neurons, switch from imaging a large area using widefield microscopy to a small area at high resolution using stimulated emission depletion (STED) microscopy. This enables visualization of the dynamics of synaptic proteins with 30-nm resolution.

Similarly, Mahecic et al. use structured illumination microscopy (SIM) to capture images of bacteria or mitochondria at high spatial resolution and low temporal resolution, with a neural network processing the images in real time. Upon detecting that the bacteria or mitochondria are dividing, they increase temporal resolution to capture detailed time lapses of these rare events unfolding.

Adaptive super-resolution fluorescence microscopy techniques such as STED and SIM are especially powerful because they subject cells to potentially damaging, high-intensity illumination light. Selectively applying them at their full capabilities at the right times and locations enables the capture of a larger number of rare events. The automation of this process enables the

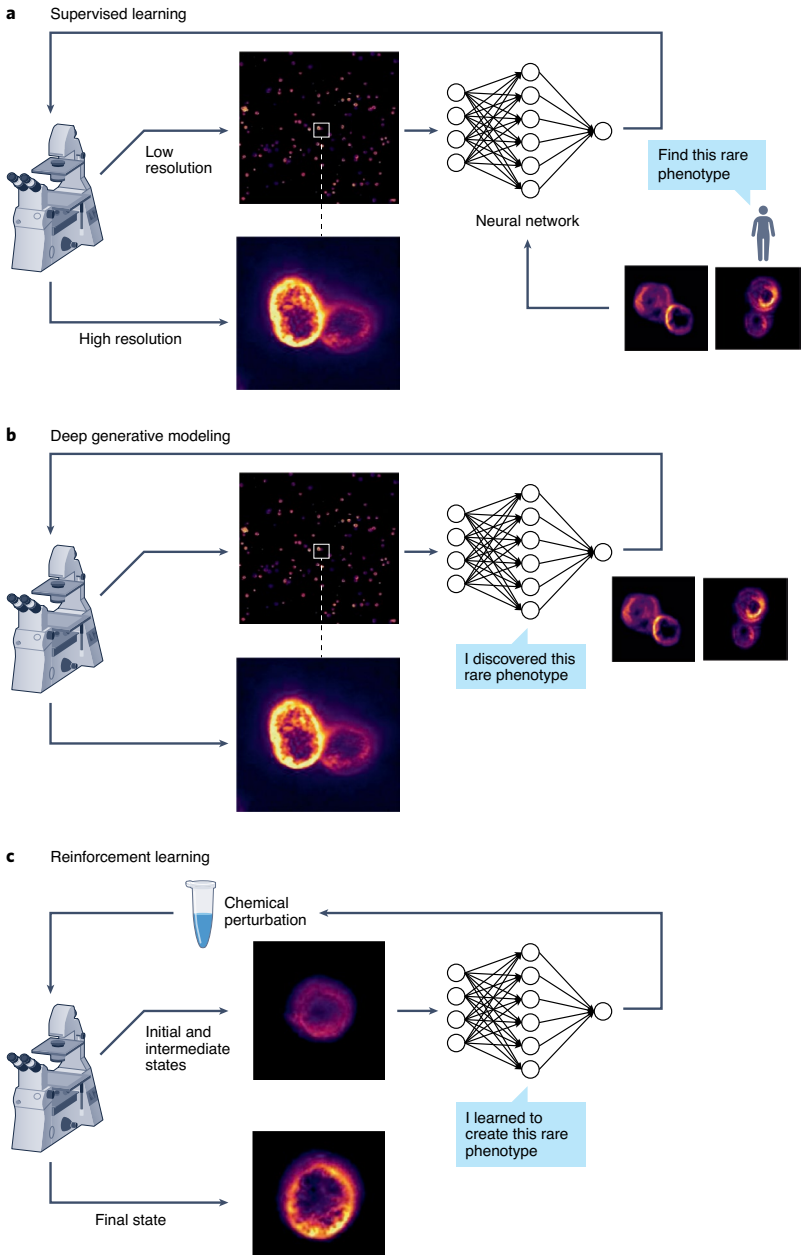

Fig. 1 | Adaptive microscopy using supervised learning, generative modeling, and reinforcement learning. a, Using supervised deep learning, a human labels examples of a rare phenotype, and a neural network locates similar cells and controls the microscope to image them at higher resolution. **b**, Using deep generative modeling, the neural network can itself discover which phenotypes are rare and image them at higher resolution. **c**, Using deep reinforcement learning, the neural network learns how to chemically perturb cells to produce a particular phenotype.

capture of events that manual human control would not be able to capture in real time.

One can imagine similar techniques being applied to other applications of super-resolution microscopy. The barrier to entry has been lowered by the widespread availability of open-source software for adaptive control of microscopes. Representative examples include Pycro-Manager[6], AutoScanJ[7] and MicroMator[8]. Furthermore, the ease of developing algorithms for adaptive microscopy experiments will benefit from the power of deep neural networks. Neural networks possess the ability to learn functions from training data. This means adaptive microscopy techniques no longer require the careful design of customized image processing algorithms that determine what and where to image; instead, labeling some representative examples is sufficient to teach the microscope to start looking for more instances of a particular phenotype. In addition, neural networks can be executed quickly — on the order of milliseconds — such that real-time adaptation of imaging parameters is possible. The days of researchers 'babysitting' experiments may be numbered.

But the possibilities don't stop there. In contrast to 'supervised' approaches, where instances of the pattern of interest must be explicitly provided (Fig. 1a), deep neural networks can be used as 'unsupervised' probabilistic models (called 'deep generative modes') that learn the distribution of a particular type of images. This means that by feeding a neural network a large amount of unlabeled data, it can learn to model the inherent biological heterogeneity: which images are rare, which are common, and the shared characteristics over which they vary. This could be deployed to make adaptive microscopes that themselves discover which phenotypes are surprising and proceed to gather more detailed information on them (Fig. 1b). And because computers are often better at pattern-matching than people, they may be able to make new discoveries that were previously overlooked by their human counterparts.

Deep reinforcement learning algorithms are another promising neural network-based controller for adaptive microscopes. They learn not just patterns in images, but also strategies to take actions based on these patterns. They gained attention in recent years for their ability to beat expert human players at games such as chess and go, and they have potentially powerful biological applications as well. For example, one can imagine agents that automatically learn to optimize cell culture conditions or use existing optical tools that manipulate intracellular signaling[9] or transcription[10] to better understand biological processes or control them to create biological products (Fig. 1c).

These possibilities entail challenges in collecting, storing and processing image data. Computers that control microscopes will need to be equipped with (or connected over a network to) hardware such as graphics processing units (GPUs) that can execute neural networks efficiently. In addition, research has shown that deep neural network performance scales with both the amount of computation and the amount of data, and experiments on the largest current computers show there is still room for improvement by increasing both. As a result, individual labs may not be able access state-of-the-art performance without mechanisms for sharing resources.

In addition, neural networks are only as good as the data fed to them. They are quite capable of picking up and even amplifying human biases in the training data provided to them. If they are entrusted to decide what data to capture and what experiments to do, these biases must be measured and appropriately mitigated.

In spite of these challenges, adaptive microscopy looks to have a bright future: the ingredients are ready, many possibilities remain to be explored, and the potential for new tools at researchers' fingertips is tantalizing. Microscopes may indeed be coming for your job — but they're also giving you a promotion. ❐

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Competing interests

H.P. is the founder of and L.W. is a scientific advisor to Photomics Inc., which develops microscopy technology and open-source software.