THE AUTHOR FILE

Na Ji

How joy and wide-ranging curiosity leads to neurobiology tools for new types of questions.

I'm basically a microscopist who wants to be a neurobiologist," says Na Ji from the University of California, Berkeley (UCB). It makes her happy when neurobiology colleagues tell her she is already one of them. Ji designs and develops tools for experimental neurobiologists that do not require a physics PhD to operate and maintain them, she says.

As an undergraduate in China she studied chemical physics, in which tools from physics are used to assess chemical systems. She continued this work for her PhD research at UCB's chemistry department, where she spent much time in the physics department. Her advisor Yuen-Ron Shen encouraged lab members to explore widely for their postgraduate training. "He was just an excellent, excellent advisor," says Ji. She set out to build on her long-standing interest in the brain, which, she says, is also a puzzle on a metaphysical and philosophical level. Her brain had taken her to a deep understanding of the behavior of inanimate objects, such as the way atoms and molecules vibrate and rotate. Yet she knew little about the brain itself, which, feels like "the ultimate mystery" that helps us understand "who we are." Ji decided on a postdoctoral fellowship at the Howard Hughes Medical Institute's Janelia Research Campus, where she also became a group leader. She joined the Berkeley faculty in 2016 and splits her time between the physics and molecular and cell biology departments. She realizes she has always wanted to apply knowledge from one field in another. "I'm just very curious about things, like anything," she says and it drives her inter- and cross-disciplinary activities. "It's not something I have to strive for, it's just something that I really enjoy to be doing," she says. She reads voraciously about, among other subjects, pop culture, politics and history.

In one of two new papers¹, Ji and her team developed a way to image to a depth of 600 micrometers in vivo in a mouse's brain and capture all inputs along the neuron's length — the entire dendritic tree. With conventional imaging this would have involved a big stack of serially imaged cross-sections. But the team set up a Bessel beam module to work with a mesoscope, a two-photon fluorescence microscope with a five-millimeter-diameter field of view that was developed in Karel Svoboda's lab at Janelia. A Bessel beam is a laser beam with a narrow focal volume that yields high resolution in *x* and *y* dimensions.

Na Ji. Credit: E. Betzig

Because the Bessel beam's excitation focus can be extended to 100 micrometers, one can excite fluorescence all along that depth. What would have needed 300 images with standard imaging takes around six images for the same length. "We just scan the Bessel focus at 100-micron steps and we can cover this whole dendritic tree," she says. This paper, she hopes, can be a door-opener for neurobiologists to let them ask new types of questions related to single-neuron computation in a behaving mouse. The Bessel module is easy to set up and has been licensed to Thorlabs, she says. Her team was also able to image thousands of GABAergic neurons in a mouse that was awake and resting. "We can monitor them at the same time over four cortical regions," she says. "Even when the brain is 'resting', there's lots of activity," she says. A resting animal's brain shows waves of neural activity. "It's just mesmerizing."

The other paper² involves technology developed by Kevin Tsia, an electrical engineer from the University of Hong Kong, and the voltage indicator ASAP3 from Michael Lin's lab at Stanford University. Ji and the team developed an all-optical passive laser scanner that uses Tsia's free-space angular-chirp-enhanced delay (FACED), which is a super-fast imaging technique that can keep pace with cells zooming through microfluidic channels, enabling healthy cells to be told from malignant. Two-photon microscopy-based calcium imaging is how researchers capture events in the one to two seconds after a neuron fires. What this misses are the subthreshold events that led up to the firing, says Ji. The firing — the actual electrical signal — lasts only around one

millisecond, and imaging at the classic 30 frames per second is too slow for that signal.

The FACED module adapted for fluorescence let the team image at 3,000 frames per second and capture voltage signals 345 micrometers deep in the brain of an awake mouse. "You can get a lot more information than the calcium imaging can give you," says Ji. The FACED module is a little like the Infinity Room by the Japanese artist Yayoi Kusama, says Ji, in which light is bounced around a mirror-lined room. The result is a dizzying array of nested reflections. To image 80 focal points, Ji and her colleagues built a kind of miniaturized Infinity Room to bounce light around a cylinder with two parallel mirrors. They stimulated each focal point in rapid succession, with a two-nanosecond delay between each so the team could distinguish fluorescent signals.

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"Na Ji is a fantastic addition to the neuroscience community," says Maria Feller, a UCB neuroscientist. Ji focuses on novel imaging techniques to directly study the functional nervous system in vivo for neurobiology questions of her own, and she willingly shares the technologies with colleagues who work on many kinds of neuroscience questions. "She is the ideal colleague — brilliant, friendly and scientifically curious," says Feller. Ji fully embraces running a lab that bridges physics and biology, teaches advanced microscopy courses to graduate students and physics to undergraduates, and sits on committees to help create more interdisciplinary programs. "I am both proud and humble to have her as a friend and a colleague," she says. □

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References

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