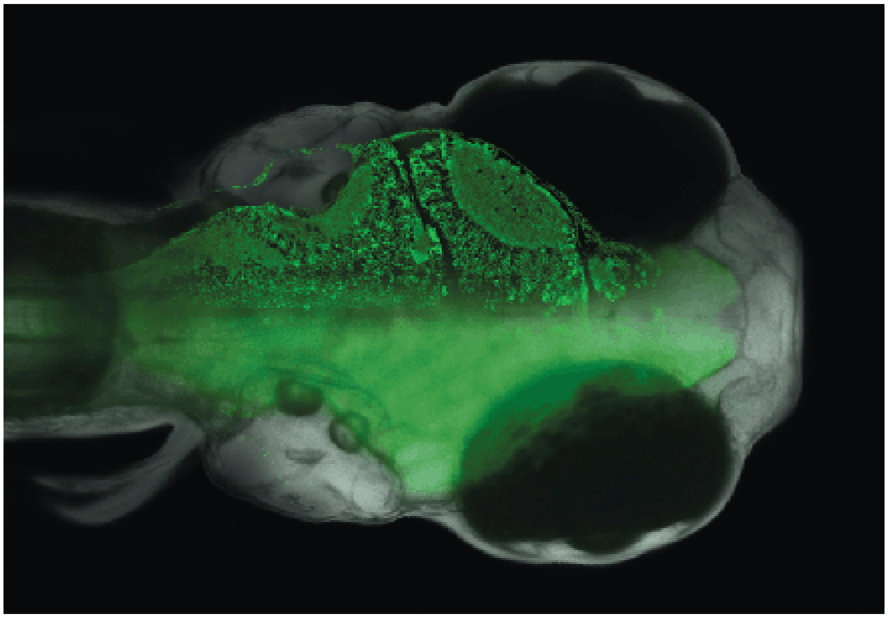
BRAIN project meets physics

by **Emily Underwood** from *Science* 30 May 2014: Vol. 344 no. 6187 pp. 954-955 doi: 10.1126/science.344.6187.954 (http://www.sciencemag.org/content/344/6187/954.summary)



Neuroscientists were over the moon in April 2013 when President Barack Obama announced a bold new initiative to study the human brain in action. But in their heady excitement, some may have forgotten to check the math in their first proposals. At least, that's the contention of a group of physicists, engineers, and neuroscientists meeting this week in Arlington, Virginia, to discuss which ideas are likely to succeed and which may fall flat.

Key to the success of the roughly $100 million Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is crafting new tools or methods to measure neural activity either from inside or outside the brain. Unfortunately, some ideas "violated either a physical law or some very significant engineering constraint or biological constraint," says neurophysicist Partha Mitra of Cold Spring Harbor Laboratory in New York, who helped organize the meeting, sponsored by the National Science Foundation.

The goal is to have a realistic discussion of what the physical limits are, he says, so "scientists who want to make devices will not make crazy proposals," or, "if a proposal is crazy, one could recognize it as such" and look for other ways to make the idea work.

One such "fanciful" idea is to build nanosized radios that could snuggle up to individual neurons to record and transmit information about their activity, says physicist Peter Littlewood, director of Argonne National Laboratory in Lemont, Illinois. But any radio small enough to be injected into the brain without causing significant harm would not be able to transmit any information out through tissue and bone, he says. Make the devices any more powerful, he adds, and they'd likely cook the surrounding brain. Another aspiration that is likely doomed is to get microscopes that probe the brain with pulses of light to penetrate much further than they already do, Mitra says. A little more than 1 mm is possible, he adds, but even 1 cm is "out of the question, since the signal to background [noise] ratio decreases exponentially with depth."

But physicists and engineers shouldn't simply shoot down outlandish proposals—or gripe about the intrinsic messiness of the brain's biology. They should model themselves as "fancy technicians" who can help develop revolutionary tools, Littlewood says. There are precedents for such collaboration, he notes: He, Mitra, and their colleagues at Bell Labs, for example, helped develop functional magnetic resonance imaging in the 1990s.

One area where physical scientists can help today is in fashioning small, strong, conductive wires that can record from many different neurons simultaneously, says neuro physicist David Kleinfeld of the University of California, San Diego. For decades, neuro scientists have relied largely on electrodes fashioned from fragile glass pipettes. But only a small number of these sensors will fit in a given brain region without disrupting connections between cells or killing them outright. Biophysicist Timothy Harris at the Janelia Farm Research Campus in Ashburn, Virginia, and others have had some success at making much smaller ones for fish and fly brains—some, made of silicon, are roughly 3 microns wide, about 25 times thinner than a human hair.

These probes are by no means the tiniest possible—polymer-coated carbon nanotubes, for example, can be 0.1 microns or smaller across and are highly conductive. Such thin wires tend to be very short and too flexible to get into the brain easily, however—when pushed, they simply buckle. One question Harris plans to pose at the meeting is whether the probes could be magnetized, then pulled, rather than pushed, into the brain with a powerful magnet. Ultimately, researchers hope to measure neural activity inside the brain without poking wires into living tissue, and there, too, physics can help. Harris has his eye on light-sheet microscopy, which shines a plane of light across a living brain tissue, illuminating neurons engineered to fluoresce green or red when they are flooded by calcium during neuronal firing. Last year, neuroscientist Misha Ahrens and colleagues at Janelia Farm used this technique to produce the first "real" whole-brain activity map of a zebrafish larva, Harris says.

A larval zebrafish brain is 1000 times smaller than a mouse brain, however. It is also conveniently transparent, while mouse and human brain tissue scatter and blur light. Using the same optical techniques that astronomers employ to discern very faint or close-together stars with a telescope, researchers such as physicist Na Ji, also at Janelia Farm, have discovered ways to distinguish between hard-to-see neurons in murky brain tissue.

In preparation for the meeting, Mitra has brushed off an old copy of Principles of Optics by Emil Wolf and Max Born, one of the most venerable and difficult physics tomes. Getting back to basics, he hopes, will help him and his BRAIN project colleagues determine which rules must be followed to the letter, and which might be cleverly circumvented.