Podcast Interview: Jeff Lichtman

**PNAS:** I’m your host Prashant Nair and welcome again to Science Sessions. With the Obama administration’s investment in the BRAIN initiative and advances in biological imaging that allow researchers to peer closely into the workings of the mammalian brain, the decade of big neuroscience might well be upon us. At the forefront of efforts aimed at gaining a near-comprehensive view of the brain is Harvard University neuroscientist Jeff Lichtman. For years, Lichtman has been working on an ambitious project aimed at creating a high-resolution wiring diagram of the mouse brain from thinly sliced sections that are visualized using a suite of techniques. Such a diagram, sometimes called the connectome, would not only allow researchers to understand how neurons are connected with one another, but also offer a fine-grained view of individual synaptic vesicles in the brain – a formidable challenge, considering that each such vesicle, which enables neuronal communication, is no more than about 40 nanometers wide. Lichtman explains his technique for creating the connectome.

**Lichtman:** We have spent the last 4 years or so developing technologies; their main goal is to take what is traditionally the strength of electron microscopy, which is very high resolution, and marry it to the strength of other kinds of techniques that give you large areas or volumes. If you get high resolution, you sacrifice volume, and if you get a lot of area or volume, you sacrifice resolution, and so trying to get both at the same time – a lot of area and a lot of resolution – is challenging. So where are we? So at the moment, cutting-edge for us is imaging about a terabyte of information a day. That’s going with a single machine that’s running about 20 million pixels per second. But there’s some costs; it doesn’t run 24 hours a day, because there’s moments when we have to move the stage or add new wafers. So we’re generating actually a throughput that’s closer to 15 million pixels a second, which gives us about a terabyte a day.

**PNAS:** At that rate, says Lichtman, it would take up to 50 years to generate 1 cubic millimeter of data – approximately equivalent to a single voxel of fMRI data.

**Lichtman:** One way you go faster is if you had a thousand machines like that. You cut your tape up into a thousand pieces, and each machine is running simultaneously, that could give you a speed up of 1000. As you can imagine, that would be a very expensive solution. Another solution would be to get machines that go even faster. We just acquired a machine that goes 40 million pixels a second, which is 25 years for a cubic millimeter instead of 50. So that’s going to help, and because we have three machines now running – one running slower still – we would be able to generate more data. But I think, ultimately, we’re hoping for machines like this one that Zeiss is making that is like having 61 scanning electron microscopes; instead of 61 separate machines that one machine has 61 simultaneous beams. And we hope that gives us a regime where we might break through to a billion pixels a second, and then we’ll be doing terabytes
instead of in a day, in an hour. It would be multiple terabytes; that is a scary thought, but I think one has to go there if one really wants to do a whole mouse brain.

**PNAS:** A single voxel of an fMRI image might compress information pertaining to millions of synapses. By turning to such automated, high-resolution techniques, Lichtman hopes to glean details at the cellular level. But what might these details reveal about the brain?

**Lichtman:** The questions of how nerve cells of a particular kind distribute their synapses among target cells of a particular kind, where you could no longer leverage molecular differences between nerve cells. And that is the area I think where one is going to see a lot of the effects of learning. The quantitative relationships of which neurons of a class are making strong connections and which aren’t on particular targets can be revealed with this kind of technology and would be harder to reveal with stains that stain a class of nerve cells one color and another class of nerve cells another color.

**PNAS:** With the deluge of data that such an endeavor is likely to generate, even if it were possible to annotate all the data in a meaningful way, Lichtman says mining the data would be a massive challenge. Another concern is the utility of the so-called reference connectome – analogous to the reference human genome. Because the connectome is a dynamic structure, researchers realize that no single connectome might be entirely representative of a species.

**Lichtman:** Everyone’s connectome is unique, and so what could you possibly learn? You can’t even do one cubic millimeter, you’re going to do a hundred people? You’ve got not even an n of 1. I think this a very fair concern – except that there is, almost certainly, in connectomes, as there is in almost all other biological phenomena, organizational principles that are true even though the specific instantiations are different. And you know, you look at a game like American football, every game is completely different from every other game. But once you understand one game, then all the games fall into a subset. And chess is another example, every game’s different, but the rules are very simple. And I imagine the same thing would be true that whatever allows information about the world to get instantiated in our brains, there can’t be a million ways that happens, because once it gets in, it’s just action potentials causing cells to respond to input, whether it comes in through the ears or comes in through the eyes. So I have the feeling the learning rules for perception – whether it’s visual or auditory or tactile – are probably very similar, and therefore the cellular motifs, the way cells are connected may have some commonalities.

**PNAS:** Given the scale of the challenge, Lichtman says that such a brain mapping initiative would need collaboration at a level similar to that seen in the Human Genome Project. That level of collaboration, he says, is just beginning to happen in neurobiology. You can find more podcasts at pnas.org