Podcast Interview: Christof Koch

PNAS: I'm Brian Doctrow, and welcome again to Science Sessions.

The cerebral cortex—the outermost layer of the largest part of the mammalian brain— is the source of such high-level functions as thought, rationality, intelligence, language, and consciousness. Christof Koch, the President and Chief Scientific Officer of the Allen Brain Science Institute, considers the cortex to be the most complex piece of organized matter in the universe. Because of its complexity, much about how the cortex gives rise to such high-level functions is not well understood. In July 2016, as part of the Sackler Colloquium on Drawing Causal Inferences from Big Data, Koch published a paper in PNAS about Project MindScope, a 10-year project of the Allen Institute. Project MindScope is aimed at gaining a fine-grained understanding of a model cortical system—the mouse visual cortex. I spoke with Koch at the World Conference of Science Journalists in October 2017. He described MindScope's approach to studying cortical function.

Koch: We are studying it using a diversity of different techniques, but all in the same type of animal, at the same age, using the same coordinate system. We're really trying to get sort of a holistic view, using the best technologies and techniques we have right now, of this piece of biological brain matter.

PNAS: One of the major obstacles to understanding cortical function has been a lack of systematic knowledge of the neurons that compose it.

Koch: We're like chemistry before the periodic table, we don't know how many different types of neurons there are. So, it was recognized early on there are, particularly in cortex, there are spiny cells, and there are aspiny cells; there are basket cells and pyramidal cells. But now we find out, well, there's not just one pyramidal cell, there are maybe 30 different types of pyramidal cells. There are probably now at least a thousand different cell types. They have different electrical behavior, they express different genes, they go to different parts of the brain, their morphology—the way they look differs. And so, one thing we're trying to get is just a complete census of all these different cell types and their characteristics.

PNAS: However, it can be a challenge just to decide whether two given neurons should be considered the same type.

Koch: We use their shape, particularly the input shape—the dendritic shape—the shape of the output wire—the axon—where it projects to, what type of neuron it connects to. Then, the electrical behavior of the neurons and the genes they express. And what hasn't happened yet with us or in the field in general, trying to take all of these and trying to align them. So, is it true once you study all these properties that there's a clear picture that you have discrete buckets of neurons? In chemistry we know a carbon is always a carbon. There's no ambiguity about it. Is that true for a neuron? Is a pyramidal cell in the lower part of layer five always a pyramidal cell in lower five? Or depending on learning, or plasticity, or development, can it shift? And how many of these buckets are there? How do these types change in development? How do they change across evolution? Those are all open questions that we and the field as a whole is trying to answer.

PNAS: A key component of MindScope is the development of computational models that can simulate cortical activity, from the level of individual neurons, to networks of neurons, to the entire primary visual cortex.

Koch: Ultimately, it's a piece of physics, and we can model, at the mechanistic level, the electrical activity, how it propagates, and charge conservation. The nice thing about computer models is, you can't cheat—you can't just say "well, I don't know." Because then your computer model isn't going to work. You have to put in something. So, it forces you—it confronts you—with what you know and what you don't know. It informs you what is really important that you do need to know. And finally, it tells you, once you're successful, "yeah, this is not a bad model. We've captured certain aspects of reality." And that's one way you can say, "I've understood something."

PNAS: One of the things that distinguishes the work of the Allen Institute, including Project MindScope, from traditional neuroscience research is its large-scale collaborative nature.

Koch: We follow the motto, "if you want to go fast, go alone. If you want to go far, go together." MindScope involves, I think I counted the last time 100 people, roughly. That's a very large team compared to your typical lab of 10 or 15 people. So, it has some unique challenges, in the sociology of science: how you motivate your people, how you harness their creativity and brilliance and ambition and drive but harness them to this overall sense of mission. It's not easy. On the other hand, we know physics has done this: the astronomical, the high-energy community in physics has done this very successfully. It's come somewhat to molecular biology with the Human Genome Project and now the ENCODE project. We're trying to learn from that experience and apply it to this younger, less mature science.

PNAS: I asked Koch what kind of progress MindScope had made so far, and what he hopes it will accomplish in the future.

Koch: We've made a huge amount of progress in understanding the different cell types. Ultimately it should lead to a better understanding of what is unique about cortex? What is the similarity and difference across different visual cortical areas? Is it the same basic operation that's being performed in one part of cortex as another, or is there some systematic variability? And finally, if there is such a canonical operation, what is the canonical operation? Understanding how all those cell types wire together to give rise, ultimately, to the flickering activity of 50,000 cells, let's say, in this cubic millimeter of cortex—we're still a ways away from that. To really understand, how does it all get put together that results in the behavior of the animal or the person—that is *the* great challenge of neuroscience.

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