Neuroscience's grand question: A new model to understand neural self-regulation

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When your car needs a new spark plug, you take it to a shop where it sits, out of commission, until the repair is finished. But what if your car could replace its own spark plug while speeding down the Mass Pike?

Of course, cars can't do that, but our nervous system does the equivalent, rebuilding itself continually while maintaining full function.

Neurons live for many years but their components, the proteins and molecules that make up the cell are continually being replaced. How this continuous rebuilding takes place without affecting our ability to think, remember, learn or otherwise experience the world is one of neuroscience's biggest questions.

And it's one that has long intrigued Eve Marder, the Victor and Gwendolyn Beinfield Professor of Neuroscience. As reported in *Neuron* on May 21, Marder's lab has built a new theoretical model to understand how cells monitor and self-regulate their properties in the face of continual turnover of cellular components.

Ion channels, the molecular gates on the surface of cells, determine neuronal properties needed to regulate everything from the size and speed of limb movement to how sensory information is processed. Different combinations of types of ion channels are found in each kind of neuron. Receptors are the molecular 'microphones' that enable neurons to communicate with each other.

Receptors and ion channels are constantly turning over, so cells need to regulate the rate at which they are replaced in a way that avoids disrupting normal nervous system function. Scientists have considered the idea of a 'factory' or 'default' setting for the numbers of ion channels and receptors in each neuron. But this idea seems implausible because there is so much change in a neuron's environment over the course of its life.

If there is no factory setting, then neurons need an internal gauge to monitor electrical activity and adjust ion channel expression accordingly, the team asserts. Because a single neuron is always part of a larger circuit, it also needs to do this while maintaining homeostasis across the nervous system.

The Marder lab built a new theoretical model of ion channel regulation based on the concept of an internal monitoring system. The team, comprised of postdoctoral fellow Timothy O'Leary, lab technician Alex Williams, Alessio Franci, of the University of Liege in Belgium, and Marder, discovered that cells don't need to measure every detail of activity to keep the system functioning. In fact, too much detail can derail the process.

"Certain target properties can contradict each other," O'Leary says. "You would not set your air conditioning to 64 degrees and your heat to 77 degrees. One might win over the other but they would be continually fighting each other and you would end up paying a big energy bill."

The team also learned that cells can have similar properties but different ion channel expression rates—like cellular homophones, they sound alike but look very different.

The model showed that the very internal monitoring system designed to control runaway electrical activity can actually lead to neuronal

hyperexcitability, the basis of seizures. Even if set points are maintained in single neurons, overall homeostasis in the system can be lost.

The study represents an important advance in understanding the most complex machinery ever built—the human brain. And it may lead to entirely different therapeutic strategies for treating diseases, O'Leary says. "To understand and cure some diseases, we need to pick apart and understand how biological systems control their internal properties when they are in a normal healthy state, and this model could help researchers do that."

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