NEUROSCIENCE

Brains gone wild

Analyzing brain signals from freely moving rodents in the wild is possible using a wireless neural recording system.

Monitoring the activity of multiple neurons in awake, behaving rodents is now a common technique in neurobiology laboratories. In some setups, animals wear a headpiece that contains multiple electrodes, and neuronal signals are then transmitted to a computer via a long, multistranded cable. This technology has increased our understanding of how brain function relates to behavior. But the necessary wires can also constrain the range of behaviors studied and hold back experimenters from exploring the animal's natural ways in the wild.

Brains have adapted, through millions of years of evolution, to interact with the natural world. Sensory systems, such as vision or audition, are likely to respond very differently to natural, complex stimuli compared to simplified ones. Studying the brain's responses to an animal's behavior in the laboratory, one invariably misses the many rich experiences that await the animal outdoors.

Photograph of a rat carrying the wireless system outdoors. Image courtesy of M. Meister.

So why not remove the wires that tether the animal to the computer and design a wireless neural recording system? This question had lingered in Markus Meister's head for a number of years, but the job of running his laboratory at Harvard University never seemed to leave him enough time to delve into it. It was not until he spent a sabbatical year at California Institute of Technology that he found the time and the right collaborators to design the system and make it work.

To build their wireless neural recording device, Meister and his colleagues combined three components originally designed for different purposes: a tetrode microdrive, for chronic positioning of electrodes in the brain; an integrated circuit for high channel-count neural recordings; and a radio-frequency wireless transmitter. The device takes up to 64 analog voltage signals from neurons in the brain and muliplexes them into one signal that appears in a temporally interleaved fashion, one after the other. Then that signal is transmitted by analog FM radio to a receiver. This is in striking contrast to other wireless neural recording devices that exist and are based on digital transmission. Meister's group found that analog transmission requires less power and hardware and results in a device that is lighter in weight and has the capacity to transmit signals over longer ranges and record from more neurons.

SYNTHETIC BIOLOGY

BACTERIA'S PUPPETEERS

Gene expression in bacteria can be modulated in response to unnatural amino acids with engineered transcriptional systems.

Human-designed cells are becoming more of a reality every day. But engineering a microbe—for example, that mobilizes metal better than its natural counterparts, cleans water or hunts down and kills a tumor—is still a challenging task. Cells are extremely complicated, and the high uncertainty surrounding them slows down the design process.

According to Adam Arkin at the University of California, Berkeley, at the start of cellular engineering one needs to build standardized sets or parts that can control a particular function in a cell. Ideally one would have many of these control devices that respond to different inputs and that can be used together in a combinatorial fashion.

Researchers in Arkin's laboratory are interested in both the evolutionary and human-manufactured design of cells. "We have one part of the lab that tries to reverse-engineer how cells work and another where we try to exploit what we learn for engineering new function in cells," he explains.

His group has recently become interested in the engineering of transcriptional controllers for bacteria. Bacteria control the expression of some of their genes through the use of 5′ transcriptional regulation units called *cis*-regulatory leader peptides. In these systems, first described by coauthor Charles Yanofsky, translation of the leader peptide by the ribosome determines whether the RNA polymerase will efficiently transcribe downstream genes. Arkin and postdoctoral fellow, Chang Liu, identified *cis*-regulatory leader-peptide elements as a new way to achieve transcriptional regulation units. By engineering this mechanism, the group created transcriptional switches that respond to genetically encoded unnatural amino acids.

Unnatural amino acids are commonly used for protein bioengineering, but the group decided to adapt them as a signaling framework. They hypothesized that by introducing blank codons that do not encode natural amino acids into a leader-peptide sequence, they could prevent its proper translation and therefore affect transcription of downstream genes. If they then introduced the necessary machinery to load these blank codons with unnatural amino acids into the cell, they could make the translation of the leader peptide dependent on the presence of these small molecules. As a result, the group built two classes of genetic switches: transcriptional 'off' switches in which the addition of specific unnatural amino acids inhibit transcription of desired downstream genes and transcriptional 'on' switches that act the opposite way.

One of the exciting capabilities of this system is its modularity and the possibility of making combinatorial logics with it. "It

The resulting device weighs around 50 grams and allows high-quality signal recordings to be obtained within a 60-meter range. It can be carried by a medium-sized rat, part of it on the rat's head and part of it as a backpack. Meister's group tested the device by making neural recordings from the primary visual cortex of the rat under diverse experimental conditions. First, they monitored neural activity in the laboratory in a medium-size arena in which they exposed the rats to standardized illumination schemes. Then, they took the rats to a nearby field where the rats were exposed to a rich variety of natural light stimuli and contrasts, and recorded the activity of the rats' neurons while the animals were fully engaged in tasks involving all their senses.

Meister thinks that performing indoor and outdoor recordings in the same rats will be very informative. "Eventually we have to check whether all the things that we learn under laboratory conditions when we try to isolate one sensory modality and study only that, extrapolate to a case where the animal is actually fully engaged," he says.

With this technology, one can catch on to the brain's waves as an animal builds a nest of leaves, travels through a tunnel or runs away from a predator. These studies have the potential to generate a whole set of new data and refine our knowledge of brain function. One day, maybe soon, we might even be able to peek into the brain of a bird and follow its tune as it flies away.

Erika Pastrana

RESEARCH PAPERS

Szuts T.A. *et al.* A wireless multi-channel neural amplifier for freely moving animals. *Nat. Neurosci.* **14**, 263–269 (2011).

works as if we are building railroad switches; you can add an arbitrary number of individual switches that respond to a given unnatural amino acid, each of which controls whether the train continues moving in one direction or not, and the movement of the train integrates the decisions made at each switch," explains Liu. A second advantage is that this system relies on components engineered for expanded genetic codes and as such, the number of unnatural amino acid–induced switches that could be made is large and quickly expanding.

In this work the group used the system to control the expression of GFP in *Escherichia coli*, but this system's potential for more sophisticated applications, such as engineering therapeutic bacteria, is an ongoing effort that Arkin's group is pursuing with the help of collaborators. Notably, other organisms such as yeast or humans also use *cis*-regulatory leader-peptides to control gene expression. Although several adaptations will be needed to translate this tool to eukaryotes, the group is actively at work on this as well.

Once again, this type of research teaches us how the knowledge obtained from basic science studies—here aimed at understanding how microbes control transcription to survive in the world—can be imaginatively put into practice for the building of tools that will one day be of practical value to humans.

Erika Pastrana

RESEARCH PAPERS

Liu, C.C. *et al.* Regulation of transcription by unnatural amino acids. *Nat. Biotechnol.* **29**, 164–168 (2011).

NEWS IN BRIEF

MICROSCOPY

Advances in label-free chemical imaging

Stimulated Raman scattering is a label-free biomedical imaging technique based on vibrational spectroscopy. In its original implementation, narrow-band laser beams had been used to excite a single Raman-active mode, but molecules with overlapping Raman bands could not be distinguished. Freudiger *et al.* now introduce spectrally tailored excitation-stimulated Raman scattering (STE-SRS) microscopy, which applies collective excitation of selected vibrational frequencies to allow specific molecules to be imaged, even when interfering species are present.

Freudiger, C.W. *et al. Nat. Photonics* **5**, 103–109 (2011).

BIOPHYSICS

Transient time-resolved FRET

The integration of structural and kinetic data is necessary to understand protein function. Nesmelov *et al.* describe transient time-resolved fluorescence resonance energy transfer (dubbed $(TR)^2$FRET), a method that allows structural kinetics to be resolved on a sub-millisecond timescale, based on the use of a fluorescence instrument with a pulsed laser and direct waveform recording. They applied the method to investigate the real-time structural kinetics of the motor protein myosin.

Nesmelov, Y.E. *et al. Proc. Natl. Acad. Sci. USA* **108**, 1891–1896 (2011).

GENOMICS

De novo assembly of large genomes

Massively parallel DNA sequencing technologies have revolutionized genomics, but a continuing challenge has been the assembly of high-quality, large mammalian genomes from these short-read technologies. Gnerre *et al.* describe an algorithm and software package called ALLPATHS-LG, optimized for *de novo* assembly of large genomes. The quality of human and mouse genome assembly with ALLPATHS-LG is comparable to that of traditional capillary-based sequencing, but at a much lower overall cost.

Gnerre, S. *et al. Proc. Natl. Acad. Sci. USA* **108**, 1513–1518 (2011).

STRUCTURAL BIOLOGY

A method to measure water-protein interactions

Hydration water molecules that specifically interact with the protein surface can have an important role in protein dynamics and function, but the extremely short residence times of water molecules make them difficult to study. Nucci *et al.* describe a way around this. Using ubiquitin as an example, they tightly confine the protein in a reverse micelle, which slows down the water dynamics and allows site-resolved water-protein interactions to be detected by nuclear magnetic resonance spectroscopy.

Nucci, N.V. *et al. Nat. Struct. Mol. Biol.* **18**, 245–249 (2011).

IMAGING

Imaging organic-inorganic interfaces in the tooth

Gordon and Joester show that atom probe tomography (APT), a widely used technique in materials research, may be applied to generate three-dimensional chemical maps of organic fibers embedded in biominerals, such as in a marine mollusk tooth. APT is uniquely suited to detecting chemical and structural heterogeneity with its high spatial resolution and sensitivity for all elements.

Gordon, L.M. & Joester, D. *Nature* **469**, 194–197 (2011).