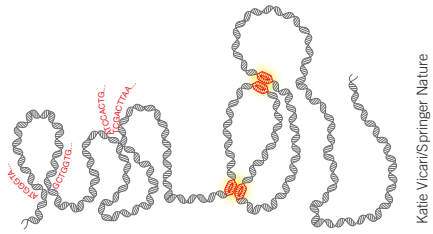
Towards a dynamic 3D genome

Sequencing and imaging bring unique aspects to genome architecture.

The plethora of methods for probing a genome's 3D architecture all share the same principle: jointly isolate and sequence genomic regions that are distant from one another in linear space but in close proximity in 3D. Methods differ in whether they probe interactions genome wide, such as Hi-C, or around specific loci, such as 3C and 4C. Some approaches enrich for genomic loci that interact with a certain protein, such as ChIA-PETs or the recent Hi-ChIP (*Nat. Methods* **13**, 919–922, 2016); others work with sparse input material, such as the recent single-cell Hi-C (*Nature*, **502**, 6469, 2013; *Nat. Methods* **14**, 263–266, 2017). In addition to these techniques, which rely on cross-linking interacting loci, the year 2017 also saw a ligation-free method, genome architecture mapping (*Nature* **543**, 519–524, 2017).



Combining imaging and sequencing for a better 3D genome.

In all these methods, sequence-based contact frequencies are converted into contact maps, which generate important insights into chromatin architecture. But a strictly molecular readout cannot visualize interactions, let alone follow chromatin dynamics in live cells.

The assumption that imaging methods, such as fluorescence *in situ* hybridization (FISH), can validate 3C methods is not always accurate. Contact frequency, determined by 3C methods, and spatial distance, viewed by FISH, measure different aspects of genome organization. Also, FISH views an order of magnitude fewer interactions than those probed by 3C, thus it misses rare events. Reconciling these data to obtain a unified chromosome model is an outstanding challenge (*Nat. Methods* **14**, 673–678, 2017).

To go beyond static FISH images, CRISPR-based methods for viewing chromatin dynamics in living cells have recently emerged (e.g., *Nat. Commun.* **8**, 14725, 2017). These methods have been largely restricted to repeat regions, but with continued progress they will become sensitive enough to follow multiple, unique, nonrepetitive loci.

Each approach adds essential information, and integrating all the data is likely to yield the best answers. Researchers want to simultaneously achieve a high-resolution view of regions interacting in real time and know the sequences of these regions. This is particularly important, as progress is being made to manipulate genome structure at will (e.g., *Nat. Commun.* **8**, 15993, 2017). Combining molecular and imaging readouts will deepen our understanding of the effects of wild-type or altered genome architectures on biological processes.

Nicole Rusk

Transformative electrophysiology

Increases in throughput push electrophysiology into a new era.

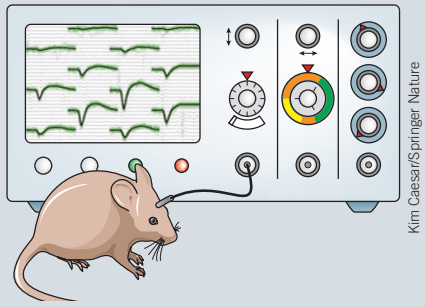
Electrophysiology has been widely used to record neuronal activity in the brain. Patch–clamp recordings can provide insight into the properties of individual neurons, while extracellular recordings assess the activity of several neurons. However, both technologies are limited in their throughput, and the advent of optical recording technologies has threatened to send this technology to the back burner.

Patch–clamp recordings are difficult to perform, but automation could facilitate such approaches. In particular, image-guided patch–clamp robots could increase the throughput for recordings from targeted neurons (*Neuron* **95**, 1037–1047, 2017; *Neuron* **95**, 1048–1055, 2017), although these robots' potential is yet to be explored.

The Neuropixels probe (*Nature* **551**, 232–236, 2017) combines the advantages of both optical and electrical recording technologies, namely the high temporal resolution of the classical microelectrode probes with the high neuronal coverage of optical recordings. With its 960 recording sites, 384 of which can be used simultaneously, the Neuropixels probe exceeds the capabilities of previous state-of-the-art technology by an order of magnitude and enables high-quality recordings from hundreds of units in the rodent brain while maintaining a small footprint. The probes are scheduled to become available to the research community at large in mid-2018.

Currently, the Neuropixels probe is optimized for electrophysiological recordings in rodents, but further development will hopefully extend its capabilities to other systems, increase the number of recorded units via multishank probes, and add optical stimulation capabilities for optogenetic experiments.

The Neuropixels probe may transform neuroscience research, as it can gather data at the resolution of single units across multiple brain areas in behaving animals. It will facilitate studies that are designed to understand how neurons that are distributed in different areas in the brain work together. Furthermore, its compact and lightweight design enables long-term recordings in freely moving animals.



A renaissance of electrophysiology. Reproduced in part from Jun, J.J. *et al.*, *Nature* **8**, 232–236, 2017.

Once the Neuropixels and robotic patch-clamping technologies become accessible to the community, it will be exciting to see how they will inspire scientists to ask questions that could not be addressed previously. Will they reverse the trend from assessing neuronal activity by optical means, and trigger an electrophysiology renaissance?

Nina Vogt