probe was capable of penetrating cells and reading the electrical potential directly from within.

Additional work remains to develop this new synthetic nanoFET probe into a routine tool. The group is now working on designs that would allow researchers to manipulate it in a more traditional way, similarly to a patch-clamp micropipette. Gaining further control of the *z*-position of the probe and improving the optics used to guide the device will also greatly increase the utility of the system.

Work is underway to poke neurons with these nanoFET probes in acute brain slices, and the group hopes to use them soon in organisms *in vivo*. An exciting future application of this probe will be measuring membrane potentials directly from cellular organelles, something no other technology can currently do. As FETs can also be used for biochemical detection in cells, these probes could be adapted to simultaneously perform different types of intracellular measurements.

Lieber and his group are also interested in using the nanoFET probes as part of a scaffold to build biological tissue. "One dream is to merge arrays of these 3D nanoFETs with stem cells to drive and probe the differentiation, or with neural tissue for subsequent reimplantation so that one could have a seamless electrical interface in and out of the brain," he explains.

Lieber emphasizes that the most important next step will be to develop these nanoprobes in a format that makes them easily accessible to researchers. Now that the technology is here, biologists will surely be eager to peek into their favorite cells at the nanoscale.

Erika Pastrana

RESEARCH PAPERS
Tian, B. *et al.* Three-dimensional, flexible nanoscale field-effect transistors as localized bioprobes. *Science* **329**, 830–834 (2010).

Surprisingly, the HapMap team also found that the rate of accumulation of rare variants in each individual did not flatten even after 700 people had been analyzed, supporting the idea that much larger sequencing efforts are called for to truly understand human genetic diversity.

Such sequencing efforts are underway in the 1000 Genomes Project, which aims to provide an extensive catalog of human genetic variation drawn from sequence data of thousands of people from 20 populations. Gibbs sees HapMap 3 as a forerunner for the 1000 Genomes Project, as it shows that deep sequencing uncovers variants that are hidden to array analysis; he quips that an appropriate summary of HapMap 3 could be, "Look what a good idea it is to sequence all these people."

Although HapMap 3 offers important insights into the variation in the human genome, a true data explosion will arise out of the 1000 Genomes project. These data will inform the design of new GWAS that may lead to a better understanding of the contribution of rare variants to complex traits.

Nicole Rusk

RESEARCH PAPERS
The International HapMap 3 Consortium. Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52–58 (2010).

NEWS IN BRIEF

STEM CELLS

p53 knockout rats

Transgenic technologies for rats have lagged behind those developed for mice. Tong *et al.* now describe the generation of *p53* (*Tp53*) knockout rats. They disrupted the p53 gene in germline-competent rat embryonic stem cells via homologous recombination and then introduced the cells into early-stage embryos to generate the knockout rat. This technology will permit the creation of a variety of gene-knockout rat strains for studying human disease.

Tong, C. *et al. Nature* **467**, 211–213 (2010).

PROTEOMICS

The aggregating proteome

Protein aggregation occurs in neurodegenerative disorders such as Alzheimer's and Huntington's disease, but little is known about age-related protein aggregation in the absence of disease. David *et al.* performed a systematic proteomics analysis to address this question, using quantitative mass spectrometry to compare the insoluble fraction of proteins left after extracting all soluble proteins in young versus old roundworms. They found that hundreds of proteins become more insoluble in aging worms.

David, D.C. *et al. PLoS Biol.* **8**, e1000450 (2010).

SIGNAL TRANSDUCTION

An integrated view of GPCR signaling

G protein–coupled receptor (GPCR) signaling is typically measured by quantifying second messengers via fluorescence, but such assays do not reveal the integrated cellular response. Schröder *et al.* now demonstrate that a label-free, polarized light–based technology to monitor the dynamic mass redistribution (DMR) of molecules in the cell can be used to obtain a more complete view of GPCR signaling. This DMR assay allowed them to probe complex signaling patterns and map them to individual G-protein pathways.

Schröder, R. *et al. Nat. Biotechnol.* **28**, 943–949 (2010).

LAB ON A CHIP

Multiplexing in the billions

In high-throughput suspension bioassays, a barcoding system is necessary for keeping track of different analytes. This can be done by attaching the analyte to a microparticle that is either spectroscopically encoded (by color) or graphically encoded (by pattern). Lee *et al.* now report a method combining spectroscopic and graphical encoding to generate potentially billions of unique magnetic microparticles carrying up to ten spatially separate colored barcodes, which can be decoded by ordinary microscopes.

Lee, H. *et al. Nat. Mater.* **9**, 745–749 (2010).

BIOPHYSICS

Scanning ultrafast electron microscopy

Scanning electron microscopy (SEM) can be used to obtain three-dimensional–like images of surfaces. Ultrafast electron microscopy allows imaging in both space and time at very high resolution. Yang *et al.* now combine these modalties to develop scanning ultrafast electron microscopy (SUEM), a four-dimensional imaging technique with nanometer and sub-picosecond spatiotemporal resolution. They show that SUEM can be used to rapidly obtain three-dimensional pictures of biological specimens, including an ant's setae and an erythrocyte.

Yang, D.-S. *et al. Proc. Natl. Acad. Sci. USA* **107**, 14993–14998 (2010).