

chips by increasing surface area and dropping the number of transistors.

Ion Torrent Systems, the company founded by Rothberg and now part of Life Technologies, made this technology commercially available in the form of their Personal Genome Machine late last year. In the current work, they show that it is capable of whole-genome sequencing. They first produced robust sequence data for three bacterial genomes at five- to tenfold coverage. Accuracy lagged somewhat behind that of other methods for the first 50 bp, but was greater for sequences over 100 bp. One limitation was single-base repeats, for which data accuracy drops the longer they are. Using one thousand 1.2-million-sensor chips, the researchers produced a low-coverage personal genome sequence of Gordon Moore, author of the eponymous law, which states that the number of transistors on an integrated circuit will double every two years. Although the results were roughly comparable to those for the same genome sequenced at low coverage on a different platform, ion sequencing is currently best suited to small genomes and diagnostic detection of variants in targeted stretches of DNA.

As a young technology, accuracy and sequence yield are expected to improve. In addition to their own tweaks, Rothberg is banking that innovations in CMOS chip fabrication will also drive improvements. As he puts it, “the publication used a factory built using technology from 1995, but we can use accumulated Moore’s law and time travel by making our next chips in a 2005 factory.” He expects it will be possible to make a 1-billion-sensor chip capable of rapidly sequencing personal genomes in the near future.

**Tal Nawy**

#### RESEARCH PAPERS

Rothberg, J.M. *et al.* An integrated semiconductor device enabling non-optical genome sequencing. *Nature* **475**, 348–352 (2011).

lipid mixing and from full fusion, so we know the nature of the events,” says Brunger. Also, in contrast to ensemble measurements, in which single vesicles are not observed and which is how reconstituted systems have been monitored in the past, this allows one to effectively distinguish between fusing vesicles and those that may burst or leak accidentally.

Notably, the reconstituted system showed rapid full vesicle fusion upon injection of calcium and could recapitulate known *in vivo* effects of mutant synaptotagmin and complexin. As *in vivo*, the system behaves cooperatively as calcium concentration is increased, though the levels of calcium that trigger fusion are one to two orders of magnitude higher than those *in vivo*. The minimal system is most probably lacking components needed to perfectly mimic the situation in the cell. It is, however, undoubtedly an excellent starting point to quantitatively study the functions of additional players in neurotransmitter release.

Brunger and colleagues hope to reach a complete mechanistic understanding of synaptic vesicle fusion at the single-molecule level. “We want,” says Brunger, “to make movies of this process, and this system is a major stepping stone to this goal.”

**Natalie de Souza**

#### RESEARCH PAPERS

Kyoung M. *et al.* *In vitro* system capable of differentiating fast Ca<sup>2+</sup>-triggered content mixing from lipid exchange for mechanistic studies of neurotransmitter release. *Proc. Natl. Acad. Sci. USA* **108**, 304–313 (2011).

#### GENETICS

##### Large-scale genome editing in *Escherichia coli*

Isaacs *et al.* achieve large-scale genome editing in *E. coli* by stitching together smaller-scale viable intermediates. They started by using multiplex automated engineering to produce strains with mutations in different sections of the chromosome. Through a clever combination of integrated resistance markers and a conjugation-initiating gene, their hierarchical conjugative assembly genome engineering approach allowed them to seamlessly convert all stop codons from TAG to TAA.

Isaacs, F.J. *et al.* *Science* **333**, 348–353 (2011).

#### CHEMISTRY

##### Clickable, stable fluorophores

Perylene tetracarboxylic acid diimides (perylene diimides, PDIs) are stable fluorophores with high quantum yields, making them promising for single-molecule studies. To make these compounds water-soluble for use in biological experiments, Yang *et al.* report encapsulating PDIs in polyglycerol dendrons. They also introduced a single azide group as a ‘click’ chemistry handle. The resulting PDI-cored dendrimers were used in labeling proteins on the surface of live bacterial and mammalian cells.

Yang, S.K. *et al.* *J. Am. Chem. Soc.* **133**, 9964–9967 (2011).

#### NEUROSCIENCE

##### Optogenetic tools for social disorders

Behavioral problems in psychiatric disorders such as autism and schizophrenia have been hypothesized to arise from an elevated cellular excitation to inhibition balance in neural microcircuitry. Yizhar *et al.* now test this E-I by using optogenetic tools to elevate the cellular E-I balance in the medial prefrontal cortex of freely moving mice. This resulted in social and cognition impairments, and could be ameliorated by elevating the inhibitory cell activity, lending support to the hypothesis.

Yizhar, O. *et al.* *Nature* advance online publication 27 July 2011.

#### STRUCTURAL BIOLOGY

##### High-resolution structures from low-resolution data

Electron crystallography is a powerful method for obtaining structural information about membrane proteins from two-dimensional crystals. A challenge, however, is collecting image data that can provide experimental phase information to solve structures at high resolution. Wisedchaisri and Gonen describe a way around this by obtaining phase information from low-resolution images using a fragment-based phase-extension method. This allowed them to solve the high-resolution structures of aquaporin-4, bacteriorhodopsin and aquaporin-0.

Wisedchaisri, G. & Gonen, T. *Structure* **19**, 976–987 (2011).

#### SYNTHETIC BIOLOGY

##### RNA scaffolds for biosynthesis in bugs

There is great interest in engineering synthetic pathways in bacteria to produce useful compounds, drugs and biofuels. Delebecque *et al.* describe the engineering of RNA modules into scaffolds to spatially organize bacterial proteins involved in the hydrogen production pathway. They captured the proteins [FeFe]-hydrogenase and ferredoxin onto a scaffold with RNA aptamer binding domains. As a result of scaffolding, they observed a 48-fold increase in hydrogen production.

Delebecque, C.J. *et al.* *Science* **333**, 470–474 (2011).