METHODS IN BRIEF

GENOMICS

Population mixing to finish the genome

A decade after the completion of the Human Genome Project, it may be surprising that the location of nearly 30 million base pairs of euchromatic DNA—the form associated with active gene expression—is still not known. Genetic mapping uses inheritance in families or linkage disequilibrium in populations to estimate the positions of long and short blocks of genetic information, respectively. To fill in gaps at a scale between these extremes, Genovese *et al*. use genotyping data from African American individuals, an admixed population that integrated genomic fragments from ancestral African and European populations after their historical isolation. The authors placed 4 megabases of unmapped sequence by showing that sequence variation that could be traced to one of the ancestral populations matched the pattern of variation at specific regions of the genome.

Genovese, G. *et al*. *Nat. Genet.* advance online publication (24 February 2013).

NANOBIOTECHNOLOGY

Nanopore-based protein sequencing

Nanopore-based DNA sequencing is well on its way to becoming a practical technique. Such an approach could also be adapted to sequence proteins. Before a bench-top protein sequencer can be made, however, several methodological challenges must be overcome. In new work, Nivala *et al*. address two of these challenges: how to unfold the protein to allow it to go through the pore, and how to ensure that it goes through the pore processively and unidirectionally. The researchers created a system using the α-hemolysin pore with the unfoldase ClpX positioned on the *trans* side of the pore. They designed a polyanionic tag (for the protein of interest) that is captured and threaded through the pore when a voltage is applied; ClpX then recognizes a targeting motif on the C terminus of the tag and, fueled by ATP hydrolysis, unfolds and pulls the protein of interest through the pore.

Nivala, J. *et al*. *Nat. Biotechnol.* **31**, 247–250 (2013).

IMAGING

Particle imaging beyond the quantum limit

Laser-based particle tracking enables high-precision biological studies. Often it is used in combination with optical tweezers to trap a molecule and study its dynamics. The sensitivity of optical tracking experiments such as these is limited by noise because of the uncertainty in the number of photons, or shot noise. Increasing the intensity of the light can help but is not an ideal approach when dealing with biological specimens that can be damaged by high light levels. Taylor *et al*. report the use of a 'nonclassical' form of light called 'squeezed' light, which enabled tracking lipid granules in yeast cells with higher sensitivity by surpassing the quantum-noise limit. This approach provides a way to improve measurement sensitivity without increasing the risk of optical damage to the sample

Taylor, M.A. *et al*. *Nat. Photonics* **7**, 229–233 (2013).

BIOINFORMATICS

Rare variants run in the family

Identifying which variants are real among next-generation sequencing data is a challenge. Filtering strategies can remove a large fraction of false variant calls that are due to sequencing and alignment errors, but they also tend to remove true rare variants that are important for genetic studies. Peng *et al*. use sequencing data from families to increase the sensitivity for detecting rare variants. Their family-based sequencing program, or FamSeq, uses raw sequence data from all family members jointly to determine the level of support for each variant. This Bayesian network approach uses Mendelian transmission information and reduces false negatives by up to 33% in extended HapMap pedigrees.

Peng, G. *et al*. *Proc. Natl. Acad. Sci. USA* **110**, 3985–3990 (2013).