METHODS IN BRIEF

SINGLE MOLECULE

Improved 3D single-molecule imaging

Single-molecule imaging allows scientists to probe the conformation, dynamics, and activities of biological molecules. However, the axial resolution of single-molecule setups is typically lower than the lateral resolution, making isotropic 3D measurements challenging. Wang *et al.* addressed this challenge by using interferometry to gain information about a fluorophore's position in the *z*-dimension, thereby developing multicolor single-molecule interferometric super-resolution microscopy. The team validated the method using dsDNA rulers and demonstrated the power of the approach by examining nuclear pore complex proteins in mammalian cells. To demonstrate the full versatility of the approach, the researchers studied the transcription cycle of the *Escherichia coli* RNA polymerase with good spatiotemporal resolution.

Wang, G. *et al. Cell* **167**, 1839–1852.e21 (2016).

CHEMICAL BIOLOGY

Cell-based fragment screening

Much of the human proteome is considered 'undruggable'—that is, it has been difficult to identify ligands to inhibit most of its proteins. New inhibitors can be found by phenotype-based screening of libraries of small molecules in cells, but the major challenge is pinpointing a ligand's target(s). Parker *et al.* describe the combination of fragment-based screening with quantitative chemical proteomics. They use low-molecular-weight simple compounds, referred to as fragments, to find low-affinity interactions; the fragment hits serve as starting points for developing more potent inhibitors. To identify fragment targets with certainty, they created a reagent consisting of the fragment, photoreactive crosslinker, and a chemical handle for screening and capturing target proteins, which can then be identified by mass spectrometry. In applying their method, the authors identified ligands for the protein PGRMC2, which promotes adipocyte differentiation.

Parker, C.G. *et al. Cell* **168**, 527–541.e29 (2017).

BIOPHYSICS

Biomechanical properties measured *in vivo*

The viscoelastic properties of cells have been studied extensively, and measuring these properties in tissues or organisms has now become possible as well. Doubrovinski *et al.* and Serwane *et al.* inject ferrofluidic droplets (which can be manipulated with a magnetic field) into their subjects and manipulate the droplets using external magnets. In the former study, the researchers dragged the droplets through cellularizing *Drosophila* embryos and inferred the viscoelastic properties of different regions based on the movement of the droplets. These measurements showed that the actin cytoskeleton confers elasticity to the cellular cortex, while the cytoplasm behaves in a viscous fashion. In Serwane *et al.*, the researchers monitored the deformation of the droplets upon application of a magnetic field and found that viscoelasticity varies throughout the zebrafish tailbud.

Doubrovinski, K. *et al. Proc. Natl. Acad. Sci. USA* **114**, 1051–1056 (2017).

Serwane, F. *et al. Nat. Methods* **14**, 181–186 (2017).

MICROSCOPY

Faster Bayesian localization microscopy

Typical single-molecule localization microscopy methods provide high-resolution images at the cost of speed, because many thousands of image frames are required to generate an image. Widefield-based super-resolution methods, such as Bayesian analysis of blinking and bleaching (3B), improve temporal resolution by using orders of magnitude fewer, densely labeled frames. Despite its potential, 3B utilization has been hindered by the time and computational cost of processing the data. Xu *et al.* have addressed this problem by developing single molecule-guided Bayesian localization microscopy (SIMBA), which achieves more efficient image processing. The new algorithms used in SIMBA also reduce image artifacts that can arise during 3B. The researchers used their method to generate high-quality images of labeled structures in fixed and live mammalian cells.

Xu, F. *et al. Cell Res.* http://dx.doi.org/10.1038/cr.2015.160 (2016).