MICROSCOPY

Extending Fourier ring correlation

Koho, S. et al. *Nat. Commun.* **10**, 3103 (2019).
Descloux, A. et al. *Nat. Methods* https://doi.org/10.1038/s41592-019-0515-7 (2019).

The Fourier ring correlation (FRC) and related Fourier shell correlation methods have widely been used for analyzing resolution in cryoelectron microscopy. More recently, the FRC has been used as a metric to assess image resolution in fluorescence microscopy, especially localization microscopy. Koho et al. now extend the FRC beyond an estimate of image resolution, for image restoration. The researchers show how the FRC can aid image de-noising and can be used to estimate the point-spread-function of a microscope to enable blind linear and non-linear image deconvolution. The authors also show how the FRC can be used to estimate image resolution from a single image, rather than two images that are conventionally required. Estimating image resolution from a single image is also achieved by Descloux et al. in this issue. *RS*

https://doi.org/10.1038/s41592-019-0561-1

GENOMICS

Improving HDR

Chen, S. et al. *Cell Rep.* **27**, 3780–3789 (2019).

The mouse has proved its mettle as a model organism to test gene function in vivo and to model disease. But, despite its popularity, it is still not trivial to create a transgenic mouse with large insertions or to swap an endogenous gene with a transgene. To streamline this process, Chen et al. have combined the CRISPR system with adeno-associated virus (AAV)-mediated delivery of donor DNA in a method they call CRISPR–READI. Mouse embryos are transduced with an AAV harboring the donor DNA; the Cas9–sgRNA complex, targeting the insertion site, is then delivered into the mouse embryos via electroporation. The treated embryos are implanted back into a mouse and the offspring is tested for editing. The authors see up to 48% homology-directed recombination (HDR). They insert transgenes of over 3 kb, only limited by the AAV packaging capacity of 4.9 kb. It will be interesting to explore the ability of CRISPR–READI to generate multiplexed gene insertions. *NR*

https://doi.org/10.1038/s41592-019-0562-0

SOFTWARE

Machine intelligence rules in molecular design

Button, A. et al. *Nat. Machine Intell.* **1**, 307–315 (2019).

Discovery of drug-like compounds is often limited by the associated synthetic challenges. Button et al. described a machine-intelligence-based method termed DINGOS, which is trained on known reaction data from chemical patent literature as well as structural information of reactants and products. To generate compounds bearing desired physiochemical properties and structural similarity to an input structure, the algorithm chooses appropriate building blocks and optimizes pre-encoded rules for synthesis as well as modification of the intermediate compounds. The method was tested for de novo design of four approved drugs, and the suggested synthetic routes were found to be appropriate for the desired structures. Successful experimental validation of these compounds suggests that machine-learning models are capable of capturing chemical knowledge and suggesting feasible synthetic reactions. *AS*

https://doi.org/10.1038/s41592-019-0563-z

MICROSCOPY

A large-scale, high-resolution microscope

Fan, J. et al. *Nat. Phot.* http://doi.org/c88b (2019).

Imaging of large fields-of-view typically requires making a trade-off in resolution. Fan et al. have built a one-photon microscope that overcomes this bottleneck. They project the imaged surface onto a curved intermediate, which they then divide into 35 sectors. These sectors are then imaged with an array of 35 sCMOS cameras. This design avoids the geometric aberrations that typically require correction in mesoscale microscopes. This real-time, ultra-large-scale high-resolution (RUSH) macroscope can image a field of view of 10×12 mm^2 with a resolution of 1.3 µm or better. The researchers use their RUSH macroscope to image cultured cardiomyocytes or neurons, monitor calcium dynamics in human brain slices, and visualize leukocytes in the awake mouse brain. They achieve cellular and subcellular resolution at video rate, despite light scattering that is associated with wide-field imaging approaches. *NV*

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