https://doi.org/10.1038/s41592-022-01721-x

Year in review 2022

As 2022 draws to a close, we highlight some of our favorite papers that we published this year in *Nature Methods*.

2022 has been a year of transition. COVID-19 is still with us, but many parts of the world have seen some semblance of normalcy return. Researchers are mostly back in labs full-time, in-person conferences have largely resumed, and laboratory supply chain kinks are being worked out — all crucial for allowing scientific research to continue to advance. We are thrilled that the methods development community chose to submit and publish so many strong papers with us in the past year. Here we highlight some of our team's favorites from 2022.

One exciting area where we saw strong advances was in single-cell multimodal omics analysis. The method ISSACC-seq, developed by Jin, Chen and colleagues, allows profiling of transcriptome and chromatin accessibility in single cells. It is compatible with both flow cytometry and droplet-based microfluidics systems, and its cost-effectiveness is promising for carrying out high-throughput studies. NEAT-seq from the Greenleaf lab enables profiling three modalities — the transcriptome, chromatin accessibility and nuclear protein abundance — in single cells, facilitating studies of the influence of epigenetic regulators, such as transcription factors and chromatin modifiers, on the epigenetic and transcriptional status of cells. On the computational side, ScBasset from Yuan and Kelley offers a sequence-based deep learning method for analyzing single-cell ATAC-seq and multiomics datasets, facilitating the identification of transcription factors that regulate cell states. For further reading about single-cell multimodal omics, see the Technology Feature from our February issue.

In metagenomics, we published the results of the CAMI II challenge, the Critical Assessment of Metagenome Interpretation. This was a large, community-driven study led by McHardy and colleagues to assess the performance of computational methods for analyzing complex metagenomics datasets. Such benchmarking studies are important for helping researchers assess which tools or methods might best suit their needs.

In proteomics, we were pleased to see technical developments aimed at increasing our understanding of protein function on a broad scale, particularly the role of post-translational modifications. Cravatt, Kemper and colleagues developed a chemical proteomics approach to profile changes in cysteine reactivity in response to proximal serine and threonine phosphorylation events. Work from Lemeer and colleagues showed that phosphorylation of histidine residues in human proteins may not be as prevalent as previously thought. For further reading about the proteomics field's increasing focus on function, read the Technology Feature from our September issue.

We were impressed by continuing advances in cryo-electron microscopy (cryo-EM) throughout 2022. An intriguing paper from Sasche, Lazić and colleagues demonstrated that scanning transmission electron microscopy (STEM), commonly used in materials science, could be applied in integrated differential phase contrast (iDPC) mode to determine near-atomic-resolution structures of biological molecules. iDPC-STEM is more dose efficient and enables higher contrast than the typical cryo-EM approach, so this method appears promising.

Microscopy continued to be a key area for us, with many exciting papers published this year. A standout paper from Fiolka and colleagues combined light-sheet microscopy and structured illumination microscopy (SIM), addressing a long-standing goal in the imaging field. This method allows researchers to perform three-dimensional SIM of subcellular structures at twice the standard resolution, with excellent optical sectioning and at high speeds. Smart microscopy technology also advanced further toward the goal of taking humans out of the image acquisition decision-making process. Manley, Mahecic and colleagues and Testa and colleagues each developed deep-learning-based approaches that capture images at low resolution until an event of interest is identified, at which point the algorithm automatically switches to faster, high-resolution imaging to monitor the event in greater detail. We also published several tools for analyzing microscopy data, exemplified by PyImageJ, an anxiously awaited tool from Eliceiri and colleagues that modernizes ImageJ (probably the most widely used image analysis program in the world) by enabling its integration with Python-based routines.

In neuroscience, we were pleased to see strong advances in tracking methods to analyze animal behavior, particularly for the challenge of studying social interactions in groups of animals. Murthy and colleagues developed SLEAP (social LEAP estimates animal poses) and Mathis, Mathis and colleagues described DeepLabCut. Some standout work in the area of connectomics included an update from Kornfeld and colleagues of the popular tool SyConn2, a toolkit for automated extraction of connectomic information from volume electron microscopy data. This tool was applied to reconstruct neural circuits in the brain of a larval zebrafish in a Resource by Baier and colleagues. And Misic and colleagues developed neuromaps, a toolbox for comparing molecular, electrophysiological, structural and fMRI-based brain maps. This platform helps address the general challenge in neuroscience of integrating diverse datasets from different modalities to synthesize new knowledge.

Finally, immunology is a field where we have recently been focusing more attention. One interesting paper from Birnbaum and colleagues reported a method for analyzing immune receptor repertoires using a screening approach. In this method, libraries of VSV-G lentivirus mutants expressing ligands are combined with target cells expressing receptor libraries. Specific interactions lead to infection of the target cell, as read out by flow cytometry followed by sequencing. In another beautiful study, Fan and colleagues developed a mouse model engrafted with human thymus organoids that generate functional T cells, which should be relevant for studying disorders of the human immune system.

As we close in on the start of 2023, we look forward to seeing yet more methodological advances in these and the many other areas of interest to *Nature Methods*. Stay tuned for our January 2023 issue, where we will unveil our 2022 Method of the Year and highlight some other areas that are intriguing us in the Methods to Watch section.

Published online: 2 December 2022