We present methods and areas worth watching in the coming years.

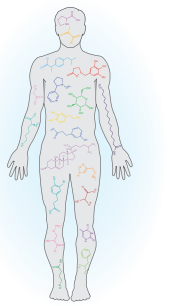
Global metabolomics

The ability to measure the metabolome on a global scale lags behind other omics techniques.

The genome, the transcriptome, and the proteome have gotten the lion's share of attention in the recent past. To truly understand biological mechanisms, however, researchers must also consider lipids, glycans, and the compendium of the thousands of small molecules (both endogenous and exogenous)—referred to as the metabolome—that serve as the substrates and products of biochemical reactions and play crucial roles in biological regulation.

There are many technical challenges when it comes to the untargeted discovery and quantification of small molecules. Given the diverse chemistries of metabolites, no single analysis method offers a 'one-size-fits-all' solution. The metabolome is also subject to very rapid changes, making it hard to accurately capture biological timepoints of interest.

Mass spectrometry is a highly sensitive technology that can potentially be used for broad analysis of metabolites in a biological sample. However, a major challenge remains: the identification of metabolites from a mass spectrum. Current public mass spectral libraries of chemical structures represent just a fraction of the expected diversity of metabolites across kingdoms. The field is in need of better computational tools for spectral identification, statistical validation of results, data management, and biological interpretation. And while it is common in other omics fields to make raw data publicly available, this culture shift has not yet happened in metabolomics, despite the availability of several resources where researchers can archive their data. Data sharing would spur the development of novel data analysis algorithms and help build spectral libraries, benefitting the field as a whole.



Metabolites play crucial biological roles; methods are needed for their study.

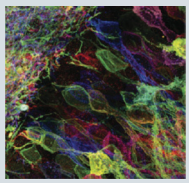
Metabolomics is an essential component of systems biology, and studies of metabolism abound in fields ranging from agriculture to the study of human disease. We look forward to seeing future user-friendly methodological developments that will drive this technique forward and help it become an integral part of a biologist's toolbox. **Allison Doerr**

Expansion microscopy

The changing face of super-resolution imaging

Super-resolution microscopy methods are maturing and are becoming more widely used for scientific discovery. However, most methods remain technically challenging and involve sophisticated hardware and/or software tools. In 2014, Ed Boyden's group at the Massachusetts Institute of Technology introduced expansion microscopy (ExM) for generating super-resolution images (*Science* **347**, 543–548, 2014). The concept behind ExM is remarkably straightforward. Labels are affixed to targets of interest within a sample, and then the sample is expanded to roughly four times its original size and imaged with conventional microscopes. One can divide the resolution obtained in these diffraction-limited images by the fold expansion, and thus achieve an approximately four-fold improvement in resolution.

Although the original method served to deliver super-resolution images into the hands of anyone with a conventional microscope, ExM's versatility was limited by technical details like the need for special labeling probes. However, several improvements to the original ExM method were published in 2016 that enhanced its general applicability. Three papers published within months of each other introduced changes to the original protocol that made ExM compatible with conventional probes, such as commercially available labeled antibodies and endogenous fluorescent proteins (*Nat. Methods* **13**, 485–488, 2016; *Nat. Biotechnol.* **34**, 987–992, 2016; *Nat. Biotechnol.* **34**, 973–981, 2016). In addition, the method has been extended to allow for fluorescence *in situ* hybridization (FISH) of RNA, enabling improved quantitative single-molecule FISH (smFISH) measurements in tissues (*Nat. Methods* **13**, 679–684, 2016).



Primate neurons imaged after expansion. Adapted with permission from *Nat. Biotechnol.* **34**, 973–981 (2016).

Even more breakthroughs are likely on the horizon. Obvious questions, such as whether and how ExM can be combined with conventional super-resolution microscopy, beg to be investigated. In addition, ExM's application to important research in biology, like exploring the connectome, may be dramatically advanced. An added advantage of ExM is that large or dense samples are not only expanded but also optically cleared in the same procedure, removing some problems associated with imaging such specimens. We look forward to seeing the bigger picture with these techniques. **Rita Strack**