Voices in methods development

To mark the 15th anniversary of *Nature Methods*, we asked scientists from across diverse fields of basic biology research for their views on the most exciting and essential methodological challenges that their communities are poised to tackle in the near future.

Credit: Andrew LaNoue

Polina Anikeeva: Neural engineering has benefitted from decades of innovation in micro- and nano-electronics, photonics, materials science, chemistry and synthetic biology. Our current ability to integrate these fields with each other and with neuroscience, however, pales in comparison with the scale and complexity of neuronal signaling. Understanding the nervous system in the context of health and disease will demand a paradigm shift, from refinement of individual device components to integration of multiple signaling capabilities, to address the richness of communication within neural circuits. Such a paradigm shift highlights the need for fluid exchange of ideas between the fields and demands understanding of fundamental physical principles at the core of each technology.

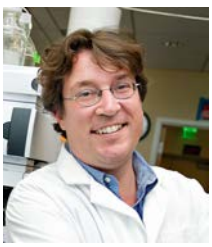
Credit: Justin Knight

Edward Boyden: Over the last few decades, we have seen the invention of new technologies for imaging brain activity, controlling brain activity, and mapping the molecular composition and wiring of the brain. An important methodological challenge will be to optimize these technologies and incorporate them into a single workflow, so that scientists can systematically investigate how the molecular composition and wiring of the brain yields its emergent dynamics, which in turn generates behavior and pathology. For example, experimental workflows that enable imaging activity throughout a brain circuit, then perturbing its dynamics, and finally mapping the molecules and wiring throughout, may yield new insights into the mechanisms underlying complex brain functions and dysfunctions.

Clifford Brangwynne: We have a detailed understanding of the conditions under which distinct states of non-living matter form, codified in phase diagrams that reflect underlying thermodynamic driving forces. Can we achieve a similar quantitative understanding of liquid–liquid phase separation within living cells? To truly understand intracellular self-assembly, and its functional and pathological dysregulation in devastating diseases, the answer needs to be yes. New technologies are needed to probe and engineer intracellular phase behavior, and should interface with deep proteomics, metabolomics and genomics readouts of biological function. These technologies will also elucidate non-equilibrium driving forces within the complex intracellular milieu, and provide the foundation for a rigorous understanding of living matter.

Credit: Matt Staley, HHMI/Janelia

Ibrahim I. Cissé: To detect a single fluorescent molecule, it must either be dilute or one must turn off any other nearby fluorescent molecule. Although the ability to localize individual fluorophores is advantageous and has led to development of super-resolution fluorescence microscopy, an implication of needing sparse fluorescent molecules is the concentration limit of a few nano-molar or less that it imposes. Practically, this means that, at molecular resolution, live-cell fluorescent microscopes only capture the more strongly interacting biomolecules, and are blind to most assemblies of weaker affinities. However, the growing appreciation for biomolecular condensates and in vivo phase transitions will likely force us to come up with clever ways to unveil the blind spots of in vivo single-molecule microscopy.

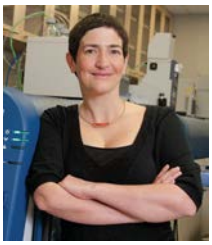


Oliver Fiehn: Metabolomics has become an integral cornerstone of biological research. Biological interpretations rely on accurate identification of metabolites. Yet, currently, compound annotations lack confidence scoring; this needs to change! Data reports should become more harmonized, with cloud processing for large data sets and kits of internal standards to assess metabolite levels. Even in-depth untargeted discovery assays should become cheaper and use fast-turnaround standardized protocols. Data needs to become findable, accessible, interoperable and re-usable for large-scale analyses. Metabolome atlases of compound levels in organs and cells are needed to compare individual studies against animal models and human population health data. Eventually, the community should tackle the biggest bottleneck: interpreting metabolomics data sets by extending database queries towards automatic literature text mining.

Credit: Mary Zhu

Petra Fromme: Biological processes are highly dynamic, but most biomolecular structure determination approaches only show a static picture. X-ray-free electron lasers (XFELs) have revolutionized structural biology with femtosecond pulses: structures can be determined before destruction takes place, enabling the discovery of the dynamics of biomolecular reactions 'on the fly'. However, access to XFELs is limited, with only five facilities in the world. Compact XFELs, which aim to shrink XFELs from 1 mile to 30 feet, could bring XFEL technology to the laboratory scale, opening the field to the broad scientific community. Combined with ultrafast spectroscopy, this will enable the

determination of the dynamics of molecular and electronic structural transitions simultaneously, in real time, in the future.



Credit: Annie Tong, Sinai Health System

Anne-Claude Gingras: Proteomics research is currently undergoing a burst of exciting technical developments, in terms of improving throughput, quantification and the ability to analyze very small samples by mass spectrometry. These improvements are already being applied to profile protein abundance, but they can also be employed in functional proteomics. Coupled with, for example, CRISPR technologies and advances in protein labeling and crosslinking techniques, advanced proteomics methods will provide fine details of cellular organization, as well as of changes in the association, localization and functions of proteins following perturbations. This will require the acquisition of multi-faceted datasets, and one of the next challenges will be to develop tools to facilitate their visualization and re-use by the broader scientific community.

Credit: Anna Greene

Casey S. Greene: We are generating data at an unprecedented scale and at levels of resolution ranging from environmental sensors to molecular profiling of individual cells. It can be tempting to search through large-scale datasets to identify results that support existing notions. A near-term challenge is to develop techniques that integrate data to illuminate under-studied processes or reveal relationships that are at odds with our expectations. Uniting machine learning methods with representations of biomedical knowledge that account for the complexity of living systems will be critical to designing computational techniques that can overturn our existing understanding and sidestep confirmation bias in this era of abundant data.

Edith Heard: Thanks to revolutionary chromosome conformation capture and imaging technologies, we are attaining an unprecedented understanding of genome architecture. The structures of many of the protein complexes that sculpt, read

Credit: Institut Curie

or duplicate the genome have been characterized at the atomic level, and the CRIPSR–Cas9 genetic engineering revolution has helped dissect their functions. These technologies provide profound insights into how genome structure relates to genome regulation and gene expression. The main technological challenge today is to follow the dynamics of genome folding and function over time in living cells, integrating imaging and genomic data. We also have to address the behavior and role of the repetitive portion of the genome, which may dictate many of its architectural and regulatory features. The repeat fraction of the genome has been somewhat of a blind spot for the analysis of genome architecture, yet it may contain key architectural and regulatory features.

Stefan W. Hell: Now that the ultimate resolution limit in fluorescence microscopy—that is, 3D resolution of the size scale of a molecule—has been reached with MINFLUX, we should seriously think beyond fluorescence. Coming up with molecular signals that are as specific as fluorescence but do not require labeling with reporter molecules; that would be something.

Credit: Eileen Barroso

Elizabeth Hillman: The latest microscopes are revealing the inner workings of living organisms like never before: dynamics of motion, high-speed signaling, connectivity, and molecular and genetic identity, all in the context of function. Seeing is believing, and what used to be inferred can now be directly observed. However, better ways to extract quantitative information from these datasets are urgently needed. Brilliant biologists with novel specimens need both new expertise and accessible analysis tools to move beyond beautiful visualizations to find patterns, trends and answers. Artificial intelligence will surely help, but deeper interdisciplinary training of our next generation of life scientists will also be essential.

Grant Jay Jensen: The history of cell biology has been punctuated by major advances in imaging technology. Cryo-EM imaging methods have recently enjoyed an amazing 'resolution revolution'. In the future, the range of samples that can be imaged will expand to both much smaller and much larger targets. For imaging macromolecules, electrons have profound advantages over X-rays in that they can be focused to high resolution, revealing phases as well as amplitudes. Because of this, and because imaging in 3D is better than 2D, the way of the future will be to image macromolecules using cryo-electron tomography. Eventually, this will be true across scales and context from crystals of small purified proteins to enormous macromolecular complexes inside tissues, but there are formidable technical challenges to be overcome in sample preparation, instrumentation and analysis.

Rachel Karchin: Cancer researchers are working with high-dimensional data: genomic, transcriptomic, proteomic and epigenomic, from bulk sequencing to single-cell sequencing of tens of thousands of cells. New imaging technologies will provide 2D and 3D views of the cancer cells and their environments. Longitudinal studies will make it possible to model the dynamics of these changes in many dimensions. We imagine it will be feasible to associate the dynamics of omics measurements and imaging with clinical outcomes for a large population of patients, when machine-readable electronic medical records are adopted on a large scale. To support clinical decision making, we will need algorithms that can handle high-dimensional data and that provide interpretable results.

Laura L. Kiessling: The surface of every cell is coated with glycans (glycoproteins, glycolipids and polysaccharides) that serve as the 'face' of the cell, reflecting its identity and state. In humans, glycans are critical for distinguishing foreign from self (for example,

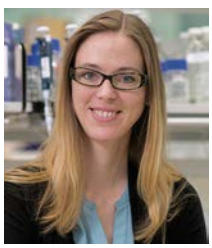
microbial versus human cells) and diseased from healthy cells. Still, we cannot yet determine a cell's glycome. We must develop technologies that sensitively and accurately identify and sequence glycans. New methods to elucidate the relationship between genomic data and cell-surface glycans could transform our understanding of human health and disease. Such tools would also illuminate the basis for cell interactions in tissues, host–microorganism interactions and mixed biological communities.

Benjamin P. Kleinstiver: The unrelenting growth of the 'CRISPR toolbox' has fundamentally altered the type and scale of biological questions that the research and therapeutic communities can ask. Our ability to edit DNA sequences in virtually any organism has given humanity the technologies necessary to study life and potentially cure disease. We eagerly await answers from the first CRISPR-containing human clinical trials that utilize genome editing to augment immune-oncology and to treat inherited genetic diseases of the eye, blood, muscle and liver. Pending results that may motivate further tweaks and improvements to the technologies, the community may not need to ask what we cannot do with CRISPR for much longer, but instead might more seriously contemplate what we should not do.

Credit: David Ahntholz

Rob Knight: The metagenomics community is poised to make three major advances. First, an accumulation of reference genomes (especially metagenome-assembled genomes) will make reference-mapping increasingly feasible for a wide range of environments, allowing easier estimation of which genomes are in each environment, and at what abundance, from cheap, short-read data. Second, an integration of genomic with chemical data (for example, short-chain fatty acids and other metabolites), especially in perturbation experiments, will greatly accelerate our understanding of which microorganisms produced which molecules. Third, improved tools for spatial mapping will enable visual analytics and deep learning of microorganism–molecule interactions, and improve our understanding of how microorganisms and their products exchange between hosts and environments.

Philipp Kukura: Single-molecule methods have had a significant impact on the life sciences, ranging from imaging and structure determination to DNA sequencing. A central challenge for the field is applicability: transforming techniques used by specialists answering specific questions into those that are universally usable. There is something genuinely unique about being able to watch single molecules come together in space and time: the resulting images and movies directly reveal the mechanisms we draw when we try to conceptualise complex biomolecular processes. Key will be to connect the universality of our diagrams with the applicability of our technologies to enable the next generation of breakthroughs in the life sciences.



Credit: MRC Laboratory of Molecular Biology

Madeline A. Lancaster: The human brain, one of the final frontiers of exploration, still remains largely a mystery. How does such an otherwise indiscriminate lump of protoplasm carry out advanced human cognition? Brain organoids (models of the developing human brain) are now allowing us to embark on a new age of discovery in neuroscience. The next 5–10 years will see a rapid succession of human neurological conditions modelled with this highly relevant and tractable system. In the long run, advancements in vascularisation and functional connectivity will push this technology further, and have the potential to answer an age-old question: what makes us human?

Nicholas Loman: Recent advances in nanopore sequencing, combined with re-discovery of classical DNA extraction techniques and the gentlest of pipetting, have permitted ultra-long reads (over 100 kb and up to 2.3 megabases) to be generated from cell lines. This technique recently permitted the first telomere-to-telomere assembly of a human chromosome. The next big challenge is to make this approach applicable to human clinical samples containing much smaller amounts of DNA, and to find creative bioinformatics approaches that rapidly generate robust de novo genome assemblies and enable clinical interpretation both for human genomes and the microbiome! We are trying to tackle these problems as part of a global collaboration, so please join our Long Read Club.

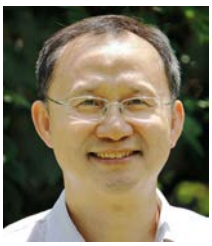
Credit: Matthew Staley, Janelia Research Campus

Loren Looger: Much progress has been made in the activation or silencing of genetically defined populations of cells with light, drugs, heat and sound. Methods for the control of specific proteins lag far behind. Ideally, techniques would: be at the protein, not nucleic acid, level; be essentially instantaneous and easily reversible; function on endogenous, not over-expressed, protein; not disrupt function in the unstimulated state; and work in living animals and plants. For instance, the instantaneous, reversible ablation of a single transcription factor or receptor in genetically defined cells (or sub-cellular compartments) would reveal its contributions to cellular function and animal behavior in unprecedented detail.

Credit: Markus Marcetic

Emma Lundberg: Measuring the expression of biomolecules in space and time at the single cell level will deepen our understanding of cell identity. Such studies of RNAs, proteins, lipids and metabolites are becoming increasingly feasible with advanced imaging, sequencing and mass spectrometry platforms. Exciting

methodological challenges include the development of computational models of cells that integrate molecular and spatial information, and can represent cells as the dynamic and complex systems they are. Such single cell omics methods and computational cellular models have the potential to revolutionize our understanding of the normal states of human cells and trajectories into disease. By tuning the models to represent any cellular state, we should be able to infer the concerted changes that allow cells to perform their functions.



Qingming Luo: Our knowledge of neuroscience is based on comprehensive identification and characterization of distinct neurons and neuronal circuits. Obtaining brain-wide mammalian brain atlases at single-neuron resolution with identified neuron morphology and entire neuronal circuits containing long projections is still challenging and requires the development of wide-field imaging techniques with high throughput and high voxel resolution, as well as intelligent high-throughput mass data processing techniques. Once we retrieve the entire set of projections of specific neuronal circuits as well as the affiliated functionally defined brain areas (which we call brainsmatics), it will be exciting to unravel mysteries such as the mechanisms of consciousness, dreams and cognition. Those discoveries will benefit our understanding of and development of therapy strategies for neurological disorders.

Credit: RIKEN CBS

Atsushi Miyawaki: The introduction of functional probes may lead to either the up- or down-regulation of downstream intracellular signaling, and may perturb the cells we observe. Moreover, even with knock-in methods for probe introduction, a substantial amount of light or chemicals are absorbed by cells labeled with fluorescent or bioluminescent probes, respectively. Quantitative bio-imaging is expected to provide a methodological framework for simulating observation-dependent perturbation. Once we accept the idea that 'seeing is perturbing', the visualization process will be regarded as a reaction towards objects, and our research efforts will lead us closer to real understanding. It is time to evaluate the assets of bio-imaging for their potential and limitations to truly benefit from this relatively new technology.

Eugene W. Myers Jr: In genome sequencing, improvements in technology and computer algorithms will soon allow us to perfectly sequence a complex, multi-gigabase genome de novo at a modest price point, US$1,000 or less. This will herald an unprecedented exploration of ecosystems and the evolution of life. Many technical and methodological challenges must first be solved. In microscopy, microscopes are becoming increasingly programmable, and 'smart' devices and computational methods such as deep neural nets are enabling us to see further and more clearly into biological samples. A key challenge is to fully harness the power of adaptive optics, particularly in devices and samples where the use of fiducial markers and explicit measurement of the wave front are not possible.

Garry P. Nolan: Single-cell phenotyping is moving towards generating tissue atlases and trekking inward towards establishing a 3D map of a cell's constituents, simultaneously driving algorithmic development that enables mere humans to understand biology. The limitations of current marker technologies, including antibodies, chemical tags and gene fusions, beg the question of how do we measure everything? Inevitably, we need every atom's position and identity, and from that atom cloud reconstruct the identities and positions of all cellular constituents. We are developing the concepts behind such an instrument to determine the positions of every atom in situ at sub-Ångstrom resolution. The field has spent so much time inferring, indirectly, a cell's interior structure; why not just take a picture?

Paola Picotti: Proteomics can measure changes in the abundances of proteins for almost complete proteomes. However,

Credit: Kaska Nowak

a variety of molecular events can profoundly alter protein function without affecting protein levels. A key challenge for the future will be to find ways to simultaneously monitor all these events and thus provide a comprehensive picture of protein states. Protein structures integrate molecular cues such as chemical modification, conformational change, interaction with other molecules and cleavage, which all affect protein function. I propose that detecting protein structural changes on a global scale by mass spectrometry will provide novel ways to comprehensively detect protein functional changes, capture physiological and pathological alterations, and generate mechanistic hypotheses.

Wolf Reik: We are witnessing an enormous revolution in single-cell genomics, which is being applied to millions of cells and giving rise to a new anatomy of the human body through the Human Cell Atlas and Human Developmental Biology initiatives. But there are many more layers of molecular information we can capture now and in the future in single cells, combining the transcriptome with DNA modifications and chromatin accessibility, histone marks and perhaps the proteome as well. An integration of time as a dimension in these measurements would be particularly exciting. Powerful machine-learning algorithms will connect these layers together and will be able to detect cell fate decisions, or cell fate change in disease, at an unprecedented level of precision. Eventually, single-cell editing may allow pathological changes in cell fate to be corrected, although this may take a little while yet.

Markus Sauer: Super-resolution microscopy methods can provide spatial resolution that is well below the diffraction-limit of light microscopy, but they do not yet provide the molecular resolution

required to understand how a cell functions and which mechanisms occur in the case of a dysfunction or disease. I anticipate that within the next years, combinations of methods such as expansion and super-resolution microscopy, supported by the development of intelligent dyes and labeling methods with minimal linkage error, will provide imaging of organelles and protein complexes with one to two nanometer resolution. By harnessing these tools, the future will allow us to decipher how nature encodes function at the molecular level.

Credit: Juliana Sohn

Alex K. Shalek: Single-cell RNA-seq has transformed our ability to dissect cellular systems, enabling transcriptome-wide identification of cellular components and their molecular signatures. Yet, we still need to do more, such as: faithfully capture cell states at scale to decipher critical molecular attributes; comprehensively appreciate what a 'transcriptional snapshot' can actually tell us about a cell's past, present and future within a tissue; and systematically uncover the value derived from collecting and integrating additional data (for example, spatial position, dynamics, other omics, existing single-cell datasets, reference gene signatures and perturbations). Equally important, we must also empower global participation in the generation and analysis of these data to achieve broad mechanistic insights into human health and disease.

Jay Shendure: This is a very exciting time for high-throughput functional genomic screens. The growing CRISPR toolset is enabling increasingly versatile experiments, for example, expanding the 'targetable genome' to noncoding regions. In my view, the primary challenge of the moment lies with expanding the range of phenotypes that are compatible with such screens beyond the typical 'growth rate' experiments. This includes, but is not limited to, whole transcriptional or epigenetic profiling, as well as imaging-based phenotyping, in association with each perturbation. Further challenges include achieving comprehensive pairwise interaction screens and moving functional genomic screens in vivo. Encouraging proof-of-concepts have recently been described for at least some of these goals.

Credit: Ivana Dimitrova

Nikolai Slavov: Recently, mass-spectrometry methods have increased the specificity and throughput of quantifying proteins in single mammalian cells: we can now quantify thousands of proteins across hundreds of single cells. I am confident that soon we will extend these methods to quantifying metabolites, post-translational modifications, and the dynamics and spatial distributions of proteins and their complexes. Ultimately, the accuracy, completeness and throughput of these measurements will provide data for transitioning from descriptive classification of single cells to quantitative models of regulatory protein interactions. I believe these data and models will enable systematic inference of direct causal mechanisms that underpin biological functions.

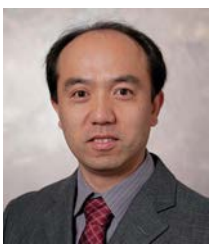
Amos Tanay: Epigenomics is moving toward single-cell resolution and is already facilitating unprecedentedly sharp descriptive analysis of multiple epigenetic scales, ranging from DNA methylation, through decorated nucleosomes, up to chromosomal topologies. But epigenetics regulates genes by changing their physical contexts rather than turning them on and off in a digital fashion. Understanding all its scales and layers, therefore, requires truly quantitative models that are based on millions of single-cell epigenomic profiles. Such models must go significantly beyond black-box machine-learning predictions. We will have to learn to use the new data to develop principled and interpretable tools, with a clear multi-scale biophysical basis that can match the multi-scale biology of the genome and its regulation.

Olga Troyanskaya: With the broad availability of whole genome sequencing, the promise of precision medicine relies on the comprehensive interpretation of these genomes. Recently, deep learning models enabled the prediction of regulatory effects

Credit: Ruth Dannenfelser

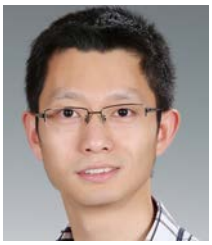
for many genetic variants. In the next decade, the challenge will be to integrate regulatory and coding variant effects across the whole genome to holistically predict phenotypic consequences for patients. This requires advances in modeling approaches as well as improved algorithmic efficiency, scalability and model interpretation. Critically, all progress relies on continued generation and sharing of experimental and clinical data. Integrative whole genome interpretation will deepen our understanding of genetics and can transform our ability to precisely diagnose and treat diverse diseases.

David van Valen: The intersection of deep learning and biology is a very exciting space, particularly for those of us who work with biological images, as these methods are starting to provide robust solutions to long-standing problems such as image restoration, image segmentation and object tracking. To me, the most exciting aspect of this area is seeing the creative ways biologists are incorporating deep learning throughout their experimental designs and analytics pipelines. As deep learning methods become more commonplace, I think we are going to see a drastic increase in the pace of biological discovery.

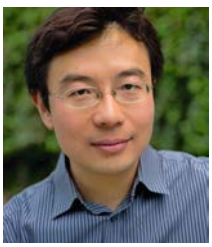


Hong-Wei Wang: Cryo-EM uses transmission electron microscopy to study frozen-hydrated specimens at liquid nitrogen temperature to reveal the structures of macromolecules or cellular organelles in their relatively close-to-native states. The recent hardware and software breakthroughs in cryo-EM technology have transformed structural biology to a new phase, where macromolecule structure can be more robustly elucidated at near-atomic resolution. Instrumentation and computational developments

of cryo-EM methods in the next decade will aim to solve structures at resolutions close to 1 Ångstrom, deciphering the dynamic conformational landscapes of macromolecules during reactions, revealing high-resolution molecular structures in situ, and directly correlating structures with functions in a broader cellular context.



Chengqi Yi: Epitranscriptomic sequencing technologies that enable transcriptome-wide mapping of RNA modifications have added valuable knowledge about the role and regulation of RNA. Yet, there is an unmet biological need to quantify the absolute stoichiometry of the epitranscriptome. In addition, robust and sensitive methods that are highly reproducible and can serve as the gold standard of detection are still lacking for the majority of RNA modifications. Tools to specifically manipulate epitranscriptomic marks in spatially and temporally controlled manners are also urgently needed. Future challenges and exciting opportunities include epitranscriptome analysis at the single-cell and single-molecule level, and in situ via the combination of sequencing and imaging.



Credit: Seth Kroll

Peng Yin: DNA nanotechnology enables precise engineering of nanostrucures with user-prescribed structural and dynamic properties, and has recently advanced diverse bioimaging approaches by providing enhanced resolution, signal amplification and multiplexing abilities, as well as methods in biosensing and single-molecule biophysics. More sophisticated nanodevices that perform in situ analysis of the molecular environment to generate real-time signal or action, or to encode spatial temporal features in DNA records, are particularly exciting for future development. Dare we even imagine molecular robots that survey an otherwise inaccessible molecular landscape, in a similar spirit as Web crawlers that index the internet or Mars rovers that inspect the planetary surface?

Credit: David Glover

Magdalena Zernicka-Goetz: One of the most interesting challenges in my field would be to uncover the principles by which the embryo builds itself so that we can create embryo models from cultured stem cells. Such models, if successful, would provide powerful tools to understand the complexity of intrinsic interactions between the cells that are essential for the embryo-building process, with its distinct organs, as well as uncover how developmental defects arise and how we can prevent them. Of course, such research has to be bounded and guided by ethical considerations.

Xiaowei Zhuang: With recent advances in imaging and genomics technologies, it is truly exciting to envision the possibility of two previously seemingly unreachable goals. The first is to generate a full census and atlas of cells for living organisms, including human beings. Although the scale may seem daunting — a human is made of tens of trillions of cells — the rapid development of single-cell omics methods, including image-based single-cell transcriptomics, will allow this goal to be achieved in the foreseeable future. The second is to generate a full molecular architecture of the cell. The advent of super-resolution imaging and genomic-scale imaging has led us closer to realizing this ambition, though major challenges still lie ahead, making this a longer-term goal. ❐

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Published online: 27 September 2019
https://doi.org/10.1038/s41592-019-0585-6