World view

By Edith Heard

Molecular biologists: let's reconnect with nature

A New Year's resolution for bench scientists is to step out of the lab to study how life really works.

Charles Darwin's voyage on HMS *Beagle* led to a treasure trove of observations: the behaviour of cuttlefish, a parasitic ichneumon wasp feasting inside live caterpillars, fossils of extinct giant sloths and 'mastodons'. The result, of course, was his theory of natural selection.

Darwin needed the complex natural world to inspire his theory. Today's molecular biologists usually focus on specific organisms in isolation and in carefully controlled environments that have as few variables as possible. To be sure, this has yielded impressive discoveries: RNA vaccines against COVID-19, bioluminescence to monitor tumours, genomic sequencing to produce better crops, and more.

Molecular biologists, myself included, study the world at the smallest of scales: chromosomes, subcellular structures, proteins, metabolites. But, too often, this focus and our well-controlled labs deprive us of the fullest picture. We miss the range of genetic variation and how that mediates physiological and behavioural responses to environmental fluctuations, in individuals as well as in populations of organisms and across ecosystems. How Darwin's 'struggle for life' happens has been largely unexplored at the molecular level. In my view, molecular and cellular biologists must go back out into the world to study life in its natural context.

This year, the European Molecular Biology Laboratory (EMBL), of which I am director-general, is launching a programme called Molecules to Ecosystems that will pursue new ways of doing exactly this. For example, we will collaborate with ecologists, zoologists, environmental scientists and epidemiologists. And we plan to launch mobile labs with state-of-the-art molecular technologies to explore land–water interfaces across Europe — areas that harbour pollutants and pockets of antimicrobial resistance.

Molecular biologists are used to multidisciplinarity: we deploy X-ray physics and cryo-electron microscopy to study DNA, RNA and protein structures; chemistry to understand metabolic pathways; and informatics to analyse variation, including genomes and their epigenetic modifications. We can measure metabolites at the single-cell level, and we use fluorescence to identify cell organelles and macromolecules in multicellular systems. These data integrate genetic variation with phenotypic variation in individual cells, revealing associations that show how microbes (and other cells) function in different conditions.

For example, in oceanic plankton, some hosts of symbiotic microalgae trigger expansion of symbiont photosynthetic machinery to increase carbon production, which boosts ecological success in nutrient-poor waters. The ability to culture free-living symbionts mimicking the host microhabitat, and understand how their metabolism and morphology shift, could prompt fresh thinking around carbon fixation.

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Technological advances will also allow researchers to explore organisms from volcanic coasts to the ocean depths. Sampling at sites that vary in pH, pollution, nutrients and salinity will offer insights into biodiversity and how natural and human-made changes influence it. Metabolic pathways are often at the heart of environmentally induced change. Such work can and should inspire metabolomics analysis to assess how toxins work, or prompt high-throughput biological imaging to catalogue morphological effects.

All of this means applying tools of basic research — in the wild and in the lab — to decipher molecular mechanisms that underlie organisms' variability and survival. Collaborative research at EMBL includes how nutrition affects a sea anemone's phenotype, the potential impact of nitrogen-fixing microbes called diazotrophs on oceans, and how antibiotics and other drugs alter the gut microbiome and human health.

Exploring 'life in context' is more urgent than ever, because that context is changing quickly. In 2009, US synthetic biologist James Collins pointed out a tragedy of timing: the first generation of scientists with the tools to address the dimensions of biodiversity on Earth might also be the last with the opportunity to do so.

Multidisciplinary collaboration enhances everyone's research. For instance, the artificial-intelligence system AlphaFold, which predicts 3D protein structures from amino-acid sequences, was the fruit of work involving structural biologists and deep-learning specialists. It gives researchers a head start on any problem involving protein structures. Likewise, cooperative efforts between machine-learning experts, biologists and clinicians are building tools to guide customized treatments for cancers.

Such successes mean that all scientists should work together to scrutinize genetic and environmental variation, and how human changes to the planet affect it. Molecular biologists can contribute to solving global challenges such as dealing with a changing climate, polluted water supplies and unsustainable food systems. For example, greater molecular understanding of microbial communities or crops could inspire alternative food sources, or biomaterials from fungal mycelium could replace conventional materials that contribute to carbon emissions.

Gaining insights about how organisms function under different conditions requires us to move beyond our usual comfort zone of lab research — and to look at areas such as arid soils and polluted rivers and cities, where there is a real 'struggle for life'. These crucial sites need to be tackled.

As 2022 rolls in, I would like to ask every scientist reading this to consider how to interrogate the changing natural context in their research.

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