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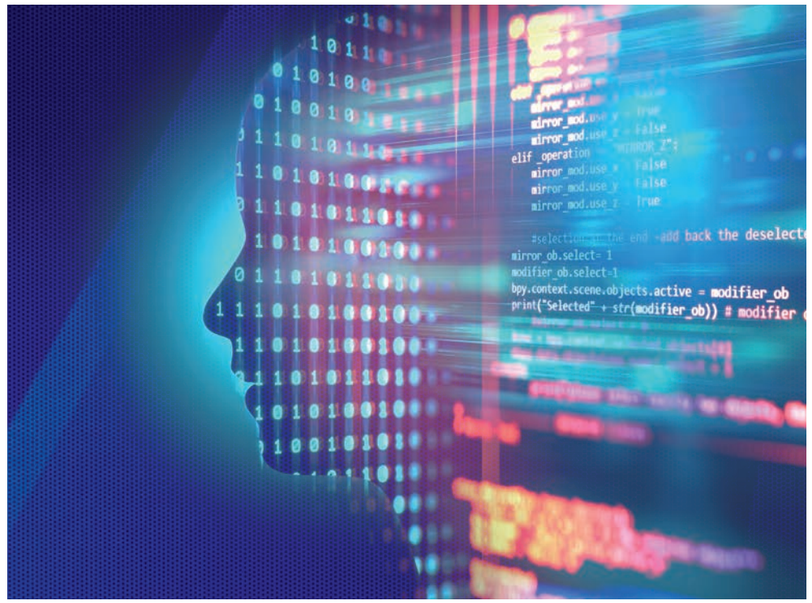
UNRAVELLING COMPLEX BIOLOGY THROUGH BIG DATA AND AI

The combination of big data with DEVELOPMENTS IN ARTIFICIAL INTELLIGENCE is allowing researchers to tackle problems in the life sciences and medicine on a new level.

Biology is mind-bogglingly complex. Even simple biological systems are made up of a huge number of components that interact with one another in complicated ways. Furthermore, systems vary in both space and time. And because cells have so much variation, averaging is often not a helpful way for analysing or understanding them.

But technology is now reaching a point where it can begin to unravel such complexity and reveal insights in topics ranging from brain and microbiome science, to the uncovering of targets for new drugs. In very broad strokes, the amassing of huge datasets is allowing researchers to gain fuller, more accurate pictures of complex biological systems, while artificial intelligence (AI) is helping them extract salient information from those massive datasets.



▲ Artificial intelligence is being used to decipher the great complexity of the workings of the human brain.

This transformative combination is poised to revolutionize how research is conducted in the life sciences. Until now, research has been mainly driven by hypotheses, with researchers proposing a hypothesis and then checking to see if it is supported by experiments. But with the ability to generate and analyse such a plethora of data, researchers can now uncover mechanisms by scouring the data alone, without making any prior assumptions.

Both big data and AI were key themes underpinning the Uehara International Symposium 2023 held in Tokyo, Japan, on 5–7 June 2023. The symposium is held every three years and is sponsored by the Uehara Memorial Foundation (see box, overleaf). This year's symposium was centred on the theme of 'Big Data-Driven Approaches with AI in Life Sciences', and featured presentations by 18 Uehara research grant recipients and 10 international experts.

MASSIVE DATASETS

Technology is revolutionizing the way scientists collect data, with researchers now routinely collecting amounts of data that were unthinkable a decade ago. Many of the symposium speakers described the ways this data is collected.

For example, Takeharu Nagai and his team at Osaka University in Japan have developed an automated trans-scale-scope system that has a very wide field of view of about several square centimetres (roughly a thousand times that of conventional microscopes) but can still resolve single cells. This allows it to image more than 1,000,000 cells at a time, enabling it to spot minor populations of cells that have an oversized influence on an organism.

For instance, there might be only one circulating tumour cell per billion blood cells in the bloodstream, but it can go on to cause cancer to spread to new organs and eventually lead to the death of the organism. Such outliers get overlooked in conventional analysis, which by necessity focuses on average descriptions of phenomena. Nagai explained that his trans-scale-scope is paving the way to go from ensemble average analysis to individual analysis.

Ibrahim Cissé of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, Germany, is extending microscopy in the opposite direction — to image the extremely small.

▲ 1. Speakers at the Uehara International Symposium 2023, held in Japan, included Kozo Kaibuchi of Fujita Health University in Aichi;
2. Takeharu Nagai at Osaka University;
3. Ibrahim Cissé of the Max Planck Institute of Immunobiology and Epigenetics in Freiburg, Germany;
4. Ross King at the University of Cambridge, UK;
5. and Maryann Martone of the University of California San Diego, US.

His team has developed a super-resolution microscopy technique that can image single molecules, allowing it to observe transcription of DNA in the nucleus of living cells. In particular, the team is interested in how genes get switched on in living cells. Conventional techniques are unable to explore this question, but using their microscope, Cissé's team has found evidence that defies the textbook view of how DNA is transcribed, namely that the proximity of clusters of mediator and RNA polymerase II is correlated with enhanced mRNA bursting in living cells.

ROBOT RESEARCHERS

Robot scientists — robots that design and conduct experiments — are another example of an emerging technology that is helping researchers amass big data. A pioneer in this area, Ross King of the University of Cambridge in the UK and his team are currently working on a third generation of robot scientists with the goal of accelerating the pace of research 1,000 times over.

Robot scientists do more than automate data collection; they use AI to form hypotheses and test them experimentally. King is a co-organizer of the Nobel Turing Challenge, which has the ambitious goal of developing robot scientists capable of making Nobel-prize-worthy discoveries by 2050.

King and his team are looking to apply robot scientists to design drugs for tropical diseases such as malaria, a neglected area because pharmaceutical companies don't stand to make large profits from new drugs. By employing intelligent screening, the robot scientist 'Eve' has identified an existing antimicrobial drug that could be repositioned for treating malaria.

UNRAVELLING THE BRAIN

If biological systems in general are complex, the human brain takes that complexity to a whole new level, consisting of about 86 billion neurons that form interrelated networks and circuits. Despite decades of neuroscience studies, we still possess only a rudimentary understanding of how the human brain functions and what goes wrong in neurological disorders. But this complexity makes neuroscience especially ripe to benefit from big data and AI. Indeed, there is a fascinating two-way interplay between AI and neuroscience, where new discoveries about the brain inspire the development of deep-learning techniques, while advances in deep learning can lead to insights into how the brain processes information.

It doesn't do much good to generate big datasets if they are difficult to use or in a format that is difficult to share. Maryann Martone, professor emeritus at the University of California San Diego spoke about the importance of making neuroscience data shareable, AI ready and FAIR (findable, accessible, interoperable and reusable).

She noted that while neuroscience was slow off the starting blocks in this area, it has subsequently made great strides. This is especially important with many national neuroscience initiatives reaching their ten-year mark and making their data freely available. Concluding her talk with question "Are we FAIR yet?", Martone noted that more still needs to be done in this area, and she predicted that neuroscience will soon enter an era analogous to that in genetics, where data is more accessible and shareable.

A team led by Kozo Kaibuchi, director of the International Center for Brain Science at Fujita Health University in Aichi prefecture, Japan, is seeking to elucidate the neuronal signals that regulate emotion and memory, which is important for developing new drugs for treating psychiatric disorders, such as schizophrenia and dementia, as well as work out exactly how existing drugs work.

This a formidable task due to the many different cell types present in the brain and the different signals they use to communicate within cells. By applying a novel imaging technique for mapping phosphorylation — a key means of communication — in the whole brain, the team is deciphering the signalling pathways of antipsychotic drugs. Their technique shortens the time needed to image a whole brain from about a month to about a week.

Masanori Sakaguchi of the University of Tsukuba and his team are exploring the question of how brain waves generated during sleep are formed. Despite their scarcity, neurons formed in adults are known to play important roles in memory, but what role they play during sleep had been unknown. To their surprise, Sakaguchi's team found that as few as ten adult-born neurons in the hippocampus

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are needed for memory consolidation during rapid eye movement (REM) sleep. When they silenced these neurons in mice, memory consolidation that occurs during REM sleep was impaired.

A NEW ERA IN MEDICINE

There is a lot of excitement about how big data and AI will transform medicine, helping to develop tailored treatments and ushering in an era of personalized medicine.

The 100 trillion or so microbes that inhabit our guts are increasingly being recognized as playing key roles in both health and disease. Indeed, as Rob Knight of the University of California San Diego pointed out in his talk, nine of the ten main causes of death in the United States have strong links to the microbiome. His group is seeking to realize precision medicine by applying big-data approaches to the microbiome.

They can predict biological age from stool samples to within 12 years, making it possible to compare people's microbiome ages. The microbiome can also be used to predict health into the long-term future. Knight's group is also exploring its influence on neurological disorders such as schizophrenia and Alzheimer's disease. He closed his talk by raising the possibility of developing a "CrapGPT" app in the future that can recommend a diet to improve an individual's health based on stool samples.

Also on the topic of microbiome, Seiya Imoto of the University of Tokyo in Japan discussed the possibility of using viruses known as bacteriophages to take out specific gut microbes. While the vast majority of gut microbes are beneficial to our health, producing valuable enzymes that the human body cannot make by itself, a few microbial species are detrimental to health. For example, the bacterium *Helicobacter pylori* has been implicated in stomach ulcers and gastric cancer.

NEW DRUGS

Antibiotics have broad spectra and tend to eliminate microbes indiscriminately. Interventions are needed that can selectively bad actors. Imoto's team is using AI to explore the possibility of bacteriophages for realizing this. They have identified several antimicrobial substances that phages produce that act against *Clostridioides difficile*, an intestinal bacterium that causes intractable diseases. This information could lead to the development of new drugs for treating those diseases.

Marnix Medema of Wageningen University & Research in the Netherlands is also applying AI to big data in order to discover natural products that have therapeutic effects. Metabolites produced by plants, fungi and microbes are a largely untapped resource for new therapeutics, with only about 3% having been experimentally characterized. Medema's team is using AI to accelerate the discovery of therapeutic natural products by using it to predict the biological activities and macromolecular targets of small molecules.

The symposium provided a tantalizing glimpse into just some of the exciting ways that big data and AI are set to transform research in the life sciences and medicine. It's clear that in the coming years the combination is going to provide answers into complex problems that have been out of our reach. ■

THE UEHARA MEMORIAL FOUNDATION

The Uehara Memorial Foundation was established in 1985 as part of the celebration of the 70th anniversary of the Japanese drug manufacturing company Taisho Pharmaceutical. Named after a former president and chairman of the company Shokichi Uehara (1897–1983), the foundation supports research in the life sciences through an annual prize, grants and symposiums.

The Uehara Prize is awarded to two Japanese researchers each year who have made notable achievements in the life science field. The Uehara Memorial Foundation has provided more than 11,200 grants with a total value of JPY 35.8 billion (US$250 million). About one third of these are for Japanese researchers who study abroad.

The Uehara International Symposium is held in Tokyo, Japan, every three years. It runs over three days and brings together Uehara research grant recipients as well as invited international experts. Registration for the symposium is free. In addition to the symposium, there is a 'Meet the Expert' session that allows young in-person participants to talk freely with some of the symposium speakers.

▲ Left to right: Haruhisa Inoue, Maryann Martone, Rob Knight, Xaq Pitkow and Ryo Sasaki discussing the use of big data and artificial intelligence in life science research at the Uehara International Symposium 2023.

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