MEETING REPORT

Modelling natural and synthetic biological networks*

Richard Feynman's blackboard, on the day he died, had a few interesting phrases written on it as part of his preparation for the next lecture. One of them read 'What I cannot create, I do not understand'[1]. The complexity of structures and functions observed in living systems that we see around us, and the enormous amount of information generated about their parts/components (molecules, cells, tissues) have inspired biologists, engineers, physicists, chemists and mathematicians to design and create these forms and functions. But as the level of organization with multiple scales increases, the more formidable it becomes. We are still trying to understand the logic of the large networks of biochemical pathways, and the design principles that regulate cellular functions. One of the approaches taken is the new multi-disciplinary area of 'synthetic biology' that deals with the 'design and construction of new biological parts, devices, and systems, and the re-design of existing, natural biological systems for useful purposes'[2]. In India, the initial rise has been slow, with isolated groups in different academic institutions working on developing small genetic circuits that perform the desired functions as predicted by their mathematical models. Over the past few years, several engineering and biology departments with interdisciplinary objectives have been working in this area, and have moved from engineering 'toy circuits' towards applying the synthetic biology tools to understand large-scale metabolism.

In an attempt to bring experimental biologists and mathematical modellers to the same platform to consolidate, a meeting was organized. The speakers and participants were from different science and engineering departments. To begin with, Chetan Gadgil (CSIR-NCL) laid the basis for the meeting's theme of mathematical modelling. He focused on the role of computation and simulation as critical aspects of generating novel biological hypothesis, especially in data-heavy aspects of biology. Somdatta Sinha (IISER Mohali) outlined her work done in collaboration with experimentalists, on theoretical predictions and experimental testing of operon design principles with delay feedback loops[3]. Her work neatly showcased how simple control mechanisms, such as feedback mechanisms in the form of end-product inhibition and allosteric activation, can regulate functional stability and sensitivity in microbial systems.

Even though synthetic engineering of gene–protein networks built using existing genetic components has been pioneered by studies to show novel behaviour, a more applied aspect of this engineering approach has also been to metabolically shunt intermediates into producing novel chemical entities. One such approach was highlighted by Anu Raghunathan (CSIR-NCL), who showcased the work of CSIR-NCL on biologically engineering bacteria using metabolic engineering and synthetic biology approaches, to produce biodegradable plastics like poly lactic acid and drug molecules like violacein. Though the need to understand natural networks is of critical importance, the full potential of synthetic biology remains unknown if we only engineer those systems about which we already know quite a bit (e.g. λ-phage, lac-operon and others). In this context, Ganesh Vishwanathan (IIT Bombay) described the steps needed to algorithmically construct pathways from biological measurements and the tools to validate them[4]. From biochemical networks to cellular functions, Pranay Goel (IISER Pune) took the participants through the mathematical biology of excitability in the insulin-secreting pancreatic beta cells in the Islets of Langerhans. Using a small-world network of beta cells, his team has found that a sparsely interconnected network-of-networks can surprisingly explain new experimental observations[5]. Such talks clearly point towards the need for building and analysing multi-scale models to understand the functional dynamics of cells/tissues.

The importance of regulation in cellular processes during development was emphasized by Sandip Kar (IIT Bombay), during discussion of his work on neural stem cell differentiation[6]. His work used a nonlinear dynamics approach to explain the role of bone morphogenetic protein-2 in cell fate determination using a deterministic model. Such models, validated through experiments, have potential in therapeutic regimes that can minimize neurodegenerative diseases involving gliogenesis. In contrast, a structural approach to synthetic biology was pointed out by Shaunak Sen (IIT Delhi) with the design principles of RNA sensors for temperature[7], that may have applications in large volume reactor control. The nature of high throughput datasets in the field of bacterial metabolism[8] was discussed by Rachna Chaba (IISER Mohali), who combined her experimental work on fatty acid metabolism and indicated the potential avenues for mathematical modelling of such datasets.

The meeting ended with a structured discussion on effective collaborations between theoreticians and experimentalists, as well as some questions on the utility and future of synthetic biology in India. The participants weighed the value of the 'design-test-build-analyse' paradigm in synthetic biology and whether it was feasible and with caveats of pre-existing principles, the participants agreed that it was useful for certain kinds of genetic systems. It was agreed that such an interdisciplinary activity requires active collaboration among modellers, engineers and biologists. The pertinent question now is – what are the limits to what can be done with biological components? Can it be applied to solve real-world problems, such as in gene therapy? Synthetically designed transcription factors to control a disease have been successfully tried in mice[9]. The hope is that in the next few years synthetic biology will be able to deliver more applications.

Along with enthusiastic participation from research students, an undergraduate team that is preparing for the iGEM 2017 (international Genetically Engineered

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Machines; http://igem.org) contest from IISER Pune was also notable by its presence. For the past few years, several student-teams from India are participating in the iGEM, an international competition where teams of students use standard, interchangeable parts to build genetically engineered biological systems to solve real-world challenges. In the midst of the busy schedule of the meeting, participants also visited the famed Karla Caves. The carving of these Buddhist caves is thought to have begun in 200 BCE and completed in 500 CE. However, for some of us it also struck a chord of the similarity between the complex biological networks, for which we are seeking to make design plans, and these ancient caves whose design plans are all but lost. Thankfully however, as the meeting highlighted, discovering the 'plan' from biological networks is a more tractable problem, if we can develop mathematical models and test them experimentally.

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OPINION

An expedition from 'time-pass research' to innovative research

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Human society is under severe threat from the problems triggered by natural as well as human-mediated activities. Providing solutions to these emerging problems by the conventional way of thinking is largely insufficient to meet these challenges. Therefore, innovative research is mandatory to efficiently tackle them. The problems faced by developing countries, particularly India, are different from those of the developed nations. At this juncture, it is highly expected from Indian researches to find suitable solutions through innovative research. Being the fastest growing economy in the world, the Government of India (GoI) supports many of these nonconventional research ideas which can be witnessed through many of its recent programmes. The 'High Risk High Reward' programme initiated by the Department of Science and Technology, New Delhi, addresses and funds research activities that are conceptually new and risky, mainly to promote new hypotheses and scientific breakthroughs. Another initiative by the Ministry of Human Resource Development (GoI), 'Impacting Research Innovation and Technology' (IMPRINT-India) is in place to link the gap prevailing between the science and technological institutions and to find innovative solutions to the problems faced by humans. A fund of Rs 1000 crores has been allocated for this programme. Though presently university researchers like us are unable to participate as Principal Investigators in this programme, we hope to be included in the future. The latest budget announcement stated that 10 universities in our country will be given Rs 500 crores each to upgrade their status to world-class institutions. The University Grants Commission (UGC), New Delhi plays a vital role in providing favourable atmosphere for taking up research activities. The Information and Library Network (INFLIBNET) takes care of providing most of the journals and books to researchers through the internet. Many central funding agencies generously support the development of infrastructure facilities in the institutions. All these programmes clearly convey the message that financial assistance is not a constraint to pursue innovative research in India.

Apart from the infrastructure facilities, researchers need an original and worthwhile research idea. Most of the present generation scientists think that research happens somewhere in the air-conditioned laboratories with uninterrupted internet access and sophisticated equipments. The information available to address a research problem is not necessarily restricted within the concrete walls of a laboratory. If we recall the history of scientific discovery, we will notice that most of the findings arose from keen observations. One of the best examples is that of C. V. Raman, who conceived the path-breaking discovery by intently observing the scattering of the sunlight by water molecules in his leisure hours, while travelling back on a ship from England. This critical observational skill is essential for innovative research. Once we cultivate the skill to identify innovative ideas, such ideas will keep us engaged lifelong. This might be the reason why many scientists could discover more than one significant research finding in their lifetime in different fields.

Marvin Herndon[1] stated that science is evolving by replacing less precise knowledge with more precise understanding. However, most researchers are now satisfied with the 'less precise knowledge' and keep themselves from thinking out of the box. When I happened to see a large number of honey bees foraging on disposed paper cups in a dust bin of a coffee shop, it provoked me to