SysMO: back to the future

Ian Booth explains how SysMO — the largest and most ambitious systems biology programme to date — might help to revolutionize microbiology.

“What a trifling difference must often determine which shall survive, and which perish” (Charles Darwin, Letter to Asa Gray, 5 September 1857).

Darwin's comment to Asa Gray, 150 years ago, is a clarion call to systems biologists today, particularly those using microbial systems. Microbial research has always had a significant quantitative element. Whether investigating growth, survival or productivity, there has always been a degree of accountancy in the analysis. From this tendency have come concepts such as Y_{ATP} , — an attempt to measure the yield of bacterial growth that is possible per mole of ATP, which is generated by metabolism — probably one of the most fundamental accounting methods that is required for understanding biological systems¹. In bacteria, understanding the gene–protein relationship, the organization of metabolic pathways and, crucially for systems biology, the organization of control circuits, is already possible owing to the ease of genetic manipulation. With so much achieved in the first 50 years of molecular microbiology, what need is there for systems biology, let alone systems microbiology?

The answer lies in Darwin's quote. The precise quantitative relationships between gene expression and cell function have been glossed over by all but a few. The immediate predecessor of systems biology, the flux control theory (FCT), sought to place metabolism, enzyme levels, metabolite pools and the resulting net enzyme activity in the context of the cell phenotype². Systems biology aims to move from the FCT to the high-level predictive-modelling of biological systems. It was therefore appropriate that the SysMO (Systems Biology of Microorganisms) initiative, a trans European systems microbiology programme, was launched in Edinburgh, (10–11 May 2007), where Henrik (Henry) Kacser, one of the original proponents of FCT, carried out his research.

Although there are many definitions of systems biology, the common approach is to derive simple principles from complex datasets and combine them with our knowledge of the properties of the elements that comprise the system, to provide insights into the logic of living systems. As Guespin-Michel suggested “the properties of the whole do not arise from those of the parts and yet the whole is only constituted by its parts” (REF. 3). Also hopefully more than the sum of its parts, SysMO represents the

collaborative efforts of the research funding organizations of six European partners — the United Kingdom, Austria, Germany, Norway, Spain and the Netherlands — and generated a €28 million fund to invest in eleven systems microbiology projects drawn from 91 laboratories. In addition, a further seven laboratories from three countries — the Czech Republic, France and Switzerland — joined the programme in the later stages of its formation.

SysMO is the largest and most ambitious systems biology programme formed to date. By bringing together European microbiologists, systems biologists, engineers and physicists, the programme has the potential to vastly increase the number of young scientists that are involved in systems microbiology. The research programmes combine studies on *Escherichia coli*, *Pseudomonas*, *Bacillus*, *Sulfolobus*, *Clostridium* and *Streptomyces* species, as well as lactic acid bacteria and yeast. Projects range from high-level integrative proteomics and array-led analyses of whole-organism biology, to the investigation of responses to specific nutritional changes and the analysis of ionic homeostasis. The goal of SysMO is to record and describe the dynamic molecular processes going on in unicellular microorganisms in a comprehensive way and to present these processes in the form of computerized mathematical models.

One major ambition of the programme is to establish structures for distributing and sharing data and models across projects and national boundaries, and to establish a framework that similar programmes can use and improve on in the future: this is possibly the greatest impact that the programme will have on the development of systems biology. Ultimately, we must be able to explain, not just describe, the peculiar individual behaviours of cells that arise from stochastic biochemical processes. This has significant end points not just for intellectual debate but also for understanding why some pathogens always persist in hostile environments, despite human interventions. Systems-based approaches offer a genuine hope of improving our understanding of stochastic cell behaviours and, through this, creating a cleaner, safer world.

1. Neijssel, O. M. & Teixeira de Mattos, M. J. The energetics of bacterial growth: a reassessment. *Mol. Microbiol.* **13**, 172–182 (1994).
2. Dykhuizen, D. E., Dean, A. M. & Hartl, D. L. Metabolic flux and fitness. *Genetics* **115**, 25–31 (1987).
3. Guespin-Michel, J. F. *et al.* Epigenesis and dynamic similarity in two regulatory networks in *Pseudomonas aeruginosa*. *Acta Biotheor.* **52**, 379–390 (2004).

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