Cellular metabolism is a complex network of chemical processes that convert nutrients into energy and molecules for survival. Advances in experimental and mathematical techniques are paving the way for quantitative descriptions of how metabolism regulates itself and of how it can be artificially controlled for biotechnology. Dr Diego A. Oyarzún (University of Edinburgh) uses computational models to understand metabolism, and to exploit it in cutting-edge synthetic biology and healthcare technologies.

A HISTORICAL VIEW OF LIFE

Systems biology is a multidisciplinary field of research that applies mathematical and computational approaches to model complex biological systems. It has gained substantial importance in the last two decades as a powerful set of methods to study the interactions between the components of a biological system (like, for instance, proteins and metabolites in cells) and to define how these interactions determine the function of the system, its behavior, and its response to external perturbations. At its core, systems biology attempts to describe an emergent property of a biological system by integrating information about the interactions among its constituents. At variance with traditional reductionist approaches, which focus on the definition and identifying the elementary constituents of large interacting systems, systems biology aims to provide a rigorous framework for the interpretation of a system’s function and behaviour from the quantitative observation of multiple components simultaneously and from the integration of these data with mathematical models.

QUANTITATIVE MODELS OF CELLULAR METABOLISM

For decades, cellular metabolism has been largely seen as a process isolated from the rest of the cellular machinery. This traditional view has been challenged in recent years, in light of a number of studies that highlight the interplay between metabolism and other cellular functions. For example, it is now established that metabolic regulation plays an important role in disease. Conditions such as cardiovascular diseases and cancer have for instance been linked to metabolic misregulation, and pathogens can exploit their own metabolic regulation systems to evade drug treatments.

ENGINEERING AND SYNTHETIC BIOLOGY

Dr Oyarzún’s research applies computational modelling to unravel the complexity of the metabolic machinery in cells and to understand the principles of how its function can adapt to changing environments. His approach is based on the integration of mathematics, engineering and biology and aims to provide a quantitative description of how life, as an emergent property of a complex biological network, sustains itself in diverse situations and under a variety of external stimuli. This knowledge can be exploited to make predictions on how genetic modifications influence the cell response, which can then in turn be used to control the cell behaviour and adapt it to serve human purposes, for instance to produce new therapeutic drugs.

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The novelty of Dr Oyarzún’s approach to metabolism is the use of mathematics to achieve what is virtually impossible to obtain from purely experimental approaches: a separation between the intertwined roles of regulatory architecture and regulatory parameters that control metabolism. The goal of this effort is to develop an understanding of how microbes self-adapt their metabolism to ensure their survival.

BIOTECHNOLOGY

Modelling cellular metabolism and its regulation is an ambitious and far-reaching programme from a basic science perspective, but it can also provide a basis for developing metabolic pathways for use in biotechnology. Metabolic pathways are the raw materials for synthesis of new molecules required for their survival and reproduction. Depending on the availability of nutrients, bacteria need to adjust their metabolism. This is accomplished through a complex network of feedback mechanisms that detect changes in nutrients and modify metabolism accordingly. In order to shed light onto this intriguing feedback effect and to understand how bacteria self-adapt to changing environments, Dr Oyarzún has been pioneering the use of control theory, a discipline borrowed from the engineering world, whose objective is to develop algorithms to robustly control dynamical processes found in virtually every technology, from manufacturing to aircraft control and communication systems. He applies this approach to understand how different regulatory architectures found in nature enable microbes to survive environmental shocks. The novelty of Dr Oyarzún’s approach to metabolism is the use of mathematics to achieve what is virtually impossible to obtain from purely experimental approaches: a separation between the intertwined roles of regulatory architecture and regulatory parameters that control metabolism. The goal of this effort is to develop an understanding of how microbes self-adapt their metabolism to ensure their survival.
have important implications in rapidly developing fields like biotechnology. One of the current crucial challenges in biotechnology is how to achieve robust, predictable and economically sustainable processes for a variety of targets, like the synthesis of therapeutic drugs, the development of new materials and the production of food. The quantitative biology approaches developed by Dr Oyarzún and his collaborators are providing a key contribution towards achieving this goal. In particular, the availability of robust and quantitative models of cell metabolism can pave the way for the design of artificial biological systems, in which cell metabolism is reprogrammed to deliver custom functionalities. Promising applications of this technique are in microbial cell factories, which exploit microorganisms to produce therapeutic drugs and a variety of other chemicals.

MATHS AND MEDICINE: PRECISION HEALTHCARE

The mathematical approaches developed by Dr Oyarzún can have far reaching impact even outside basic science and biotechnology. Precision medicine, whose holy grail is to deliver the right medicine, to the right patient medicine, whose holy grail is to deliver science and biotechnology. Precision medicine is how to achieve the full potential of such molecular data. Another big challenge is the lack of methods to integrate various layers of data, such as metabolomics, proteomic and transcriptomic, into tractable models. With the current big data revolution in biology, there is huge potential for machine learning and artificial intelligence to bridge this gap, so that we can harness the full potential of such molecular data. Another big challenge is the role of heterogeneity. Even genetically identical cells display different metabolic phenotypes, which not only negatively affects performance of engineered cell factories, but is also thought to play key roles in bacterial responses to antibiotics, one of the most pressing challenges in global health.

The ability to develop quantitative and predictive models of cell metabolism, especially in bacteria, is an extremely ambitious and sought after goal. What do you think are the fields that will benefit most from your work in the short term and what are the major remaining challenges for the application of the approaches you are developing to the field of biotechnology?

The most direct benefits are in synthetic biology and metabolic engineering. Our work is paving the way for computer-aided design of cell factories, much like the way things are done in other engineering disciplines. A major challenge is the lack of methods to integrate various layers of data, such as metabolomics, proteomic and transcriptomic, into tractable models. With the current big data revolution in biology, there is huge potential for machine learning and artificial intelligence to bridge this gap, so that we can harness the full potential of such molecular data. Another big challenge is the role of heterogeneity. Even genetically identical cells display different metabolic phenotypes, which not only negatively affects performance of engineered cell factories, but is also thought to play key roles in bacterial responses to antibiotics, one of the most pressing challenges in global health.

Microbial metabolism can be controlled through genetic engineering to produce therapeutic drugs.