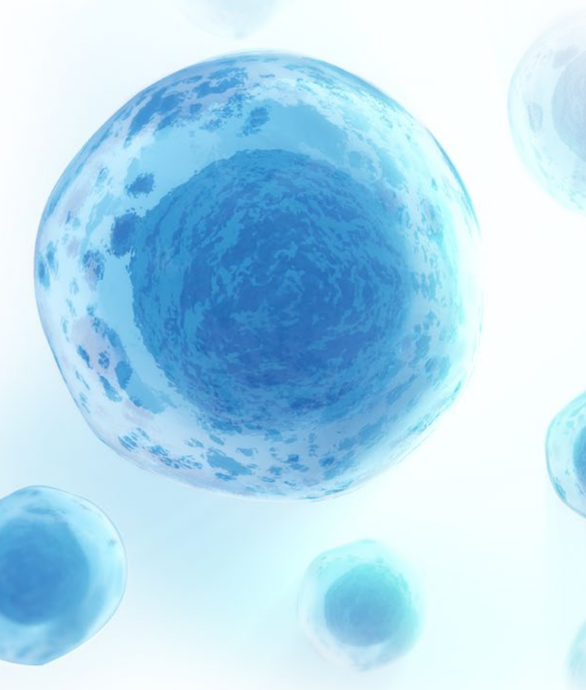
The mathematics of life:

Metabolic control in living cells

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.



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At its most fundamental level, life is chemistry. Billions of chemical reactions occur simultaneously in living cells every second, which can involve complicated macromolecules like proteins and DNA, as well as smaller and more mobile molecules that are free to roam within the cell and even cell membranes. These chemical reactions do not happen in isolation: in order for a cell to survive, thrive and reproduce, a high degree of control of how and when individual reactions take place is essential.

Cellular metabolism is an extremely complex and robust network, in which individual subunits (proteins and metabolites) interact to keep the whole network working and to guarantee survival in unfavourable environmental conditions. Understanding the details of this enormously complicated machinery appears to be well beyond the grasp of traditional analytical approaches, but this is set to change.

A HOLISTIC 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 behaviour 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 defining 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.

Dr Oyarzún has been pioneering the application of systems biology to metabolic regulation in living cells. His work aims to understand the interplay between metabolism and gene regulation in natural systems. This is a cellular control strategy that is widely conserved across species and enables robust homeostatic adaptations to fluctuating environments. Various metabolic control systems can be addressed, in order to elucidate the role of the regulatory architecture on metabolic phenotypes, including pathways relevant for next-generation antibiotics and synthetic biology.

The long term ambition of this work is to develop a predictive theory of how complex regulatory networks shape the metabolic response of cells to the environment. Such a theory is the key to understand how cells self-regulate in response to external perturbations, including for instance the effects of pathogens or antibiotic treatments.

Computational models allow a detailed understanding of metabolic networks in cells, which can be exploited for cutting-edge synthetic biology and healthcare technologies.

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Dr Oyarzún's research uses ideas from control engineering and automation to study living systems.

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Interactions between theory and experiments can reveal the fundamental rules of biological processes.

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.

One of Dr Oyarzún's interests concerns the mechanisms of metabolic regulation in bacteria. Bacteria use their metabolism to consume nutrients from their environment, which provides energy and raw materials for synthesis of new molecules required for their survival and reproduction. Depending on the conditions of their environment, in particular on the availability of nutrients, bacteria need to adjust their metabolism. This is accomplished through a complex web 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 the problem is in 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.

Metabolism is an incredibly complex network of chemical reactions essential for the survival of cells.

BIOTECHNOLOGY

Modelling cellular metabolism and its regulation is an ambitious and far reaching programme from a basic science perspective, but it can also 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.

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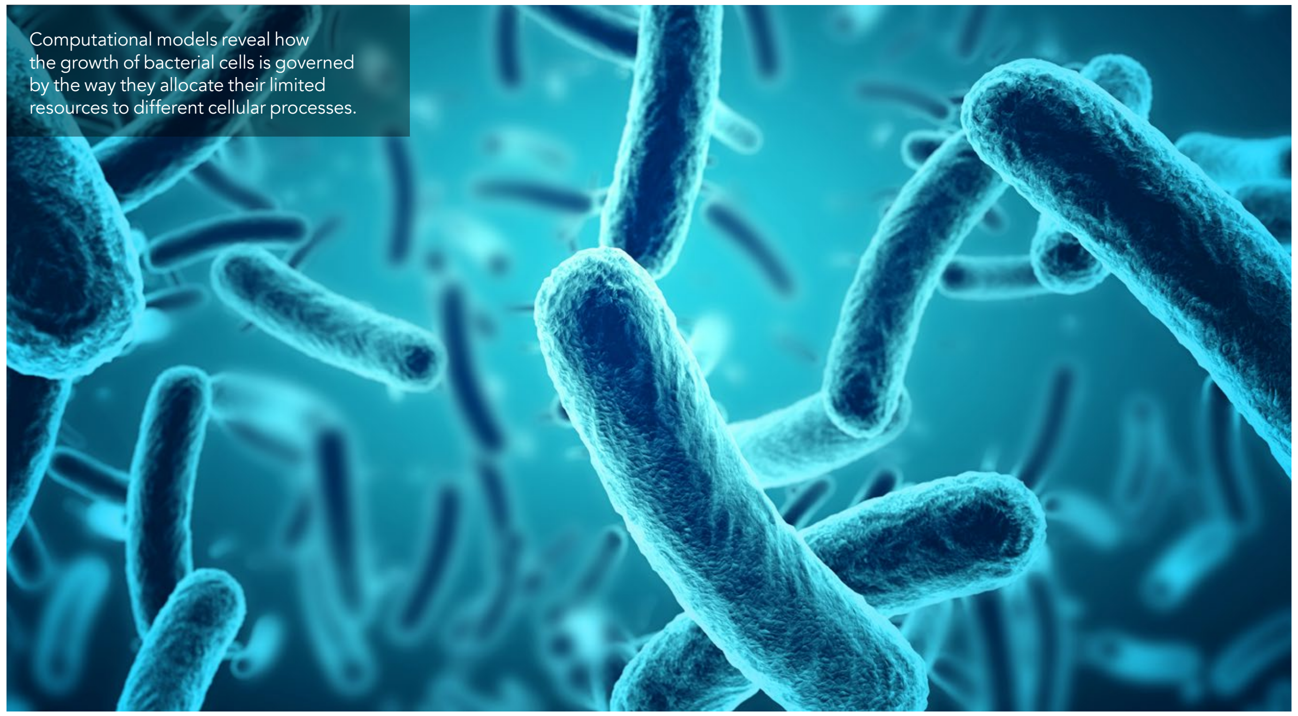
Microbial metabolism can be controlled through genetic engineering to produce therapeutic drugs.

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 and at the right time, is one field that is likely to benefit greatly from approaches based on the integration of system biology, mathematics and engineering. Progresses in screening technologies (like DNA sequencing) and image analysis algorithms now offer physicians the ability to distinguish between healthy and diseased individuals and to identify stages in disease progression. In this context, Dr Oyarzún has been exploring the application of tools from network theory to analyse cancer omics datasets and identify biomarkers and new drug targets. This is part of the multiple efforts devoted to developing the new mathematical tools for data integration and analysis that may transform precision medicine into a mainstream tool for wide segments of the world's populations.



Computational models reveal how the growth of bacterial cells is governed by the way they allocate their limited resources to different cellular processes.

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Behind the Research

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Research Objectives

Dr Oyarzún's group develops computational methods to analyse biological networks in living cells. His team uses mathematics to understand the function of natural networks, as well as to design novel biomolecular systems for Biotechnology and Healthcare.

Detail

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Bio
Dr Oyarzún leads the Biomolecular Control Group at the University of Edinburgh, with a joint appointment at the School of Informatics and School of Biological Sciences. Previously he was a Research Fellow in Biomathematics at Imperial College London and a Marie Curie Fellow at INRIA Sophia Antipolis. He obtained his PhD in 2010 from the Hamilton Institute, Maynooth University, Ireland. In 2016, Dr Oyarzún was appointed Global Future Council Fellow by the World Economic Forum and in 2017 he was selected as one of the 100 Young Global Changers by the Think 20 Summit, mandated by the G20 presidency.

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Personal Response

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. "