

Impact Objectives

- Develop new engineering methods and tools
- Apply them to solve foundational and applied problems in synthetic biology

Engineering biology

Dr Guy-Bart Stan leads a diverse research group of scientists and engineers working on introducing control engineering in synthetic biology. Here, he introduces himself and his team, outlines the nature of their work, and highlights the importance of working across disciplines and with industry



To begin, can you share a little about your own research interests and background?

I am fascinated by the possibility of engineering biology in a way akin to what has happened for highly complex physical systems in other engineering fields, such as aeronautics, information technology or advanced robotics. I started my career as an electronic engineer. I then spent some time as an applied mathematician, with a PhD focused on complex systems. After a stint at Philips Applied Technologies in Belgium, where I worked as Senior Digital Signal Processing Engineer, I returned to academic research, first as a Postdoctoral Research Associate in the Control Group of the Department of Engineering at the University of Cambridge, and then as Principal Investigator and permanent member of staff in the Department of Bioengineering at Imperial College London. My return to academia was motivated by my urge to apply my systems and control engineering knowledge to one of the biggest engineering challenges of our time: biology.

You head the Control Engineering Synthetic Biology group at Imperial College London. What are its key aims?

One of our chief aims is obtaining a thorough understanding of the dynamics

and regulatory mechanisms governing genetic circuits in order to describe their operation in terms of rigorous mathematical and computational models as is done for example in electronics for complex circuits. We then use these models to rigorously analyse, design, optimise and implement novel biological systems in living cells (e.g. gene regulatory networks, metabolic pathways, whole-cell biosensors, biomolecular feedback systems). We are also interested in characterising and predicting the interactions between cells and the engineered genetic systems they host.

Can you talk a little about the interdisciplinary nature of your research and why this is an important approach?

Our group is composed of researchers with expertise ranging from biological sciences, such as molecular biology and biochemistry, to engineering, computer science and applied mathematics. Each researcher brings a unique perspective and a different skillset on how to approach the scientific questions and bioengineering challenges we are facing. This mix of educational backgrounds and problem-solving skills produces a very stimulating and creative environment for everyone, which allows us to undertake complex and ambitious multidisciplinary projects.

Do you collaborate with industry in your work? How do you ensure the outcomes have practical application?

Our group strives to engage with industry to understand which technological innovations will have the most practical and beneficial impact on society. As an example, we are currently running a project for the optimised production of high-value recombinant proteins in bacterial hosts for which the initial project formulation was pieced together after consultation with a leading UK-based synthetic biology company.

Finally, how do you disseminate and share the results from your work?

One of the most effective methods of sharing the group's work is through scientific collaborations and publications. We collaborate with different research groups wherever possible. This is not only vital for strengthening our interdisciplinarity, but also helps in opening our research to the wider scientific community, either through joint projects, publications, or academic/general audience events. We also maintain a strong presence at broad audience events; this in turn helps people from a variety of backgrounds to become familiar with our research. For example, one talk was at the Mathematical Biosciences Institute at Ohio State University, USA, in October 2017, where we presented our recent efforts to engineer living *E. coli* cells that exhibit improved robustness and performance during synthetic network operations (you can watch the talk at: <https://mbi.osu.edu/video/player/?id=4377>).



Designing and controlling synthetic biology systems

*In the Centre for Synthetic Biology at Imperial College London, the **Control Engineering Synthetic Biology group** is working to produce solutions to some of the most important challenges of our time*

In essence, synthetic biology aims to engineer biology. Similar to how classic engineering disciplines such as mechanical and electrical engineering employ knowledge from maths and physics to rationally design, model and build mechanical and electronic systems, synthetic biology aims to rationally design and implement novel biological systems in living cells. As such, its development and progression rely on researchers from a wide range of disciplines coming together in an effort to solve some of the most important challenges facing the world today. The Stan group is working at the frontier between control engineering and synthetic biology to create new bioengineering methods and tools that will help the development of applications in the medical, pharma, energy, bio-remediation and bio-production sectors.

The importance of synthetic biology is illustrated by the significant increase in investments the field receives from around the world. In the USA in 2016, more than \$1 billion was invested in synthetic biology companies, of which there were more than 400 (rising from 88 in 2001). Meanwhile, in the UK, there has been significant investment in the field by the public research councils. It is hoped that, by pooling a community of experts from many different disciplines, the potential of this relatively new field can be realised sooner rather than later – thereby accelerating growth across many sectors of the bioeconomy, such as the pharmaceutical, healthcare, chemical, energy and food sectors.

BIOTECHNICAL SYSTEMS

It is with the above in mind that the Control Engineering Synthetic Biology group was established. Led by Dr Guy-Bart Stan and based at Imperial College London, UK, the group's research focuses on exploring the modelling, analysis and design of biotechnical systems, and developing engineering methods that will enable the design, control, optimisation and easy implementation of novel biological systems in living cells.

The work of the group falls within three major categories. First, they want to understand the dynamics and regulatory mechanisms that govern genetic expression by describing their operation through rigorous mathematical and computational models. Second, they want to characterise and predict the interactions between cells and the engineered genetic networks they host. And third, they are expanding current state-of-the-art results in biocontrol theory to facilitate the design and experimental realisation of predictable, controllable and robust genetic systems.

However, given the relative youth of the field and its inherent complexity, the group's aims are not without their challenges. 'Some of the most important barriers are due to stochastic gene expression, cross talks between native and non-native genetic parts, and burden due to limited shared cellular resources,' explains Stan. 'In our work we are addressing these challenges by designing and

implementing novel control mechanisms that aim to automatically regulate the behaviour of a genetic system to meet our design objectives.' These novel control mechanisms can be thought of as similar to a thermostat; just as a thermostat can detect discrepancies between the desired temperature and the actual temperature, a genetic control mechanism can be designed to sense the deviation between the desired and actual levels of a protein of interest. From there, the system can automatically downregulate or upregulate its expression to minimise the error.

Another major challenge centres around the pressing need for mathematical and computational tools to describe and design synthetic genetic regulatory networks that need to operate within a specific context. 'While biological organisms have evolved networks of impressive complexity, we are trying to identify and parametrise only what is essential to adequately capture the behaviour of a given system through abstract models,' explains Stan. 'We use these coarse-grained models to capture rigorously observed biological phenomena and dynamic behaviours and, based on their mathematical analysis, to optimise our designs.'

TOOLS, TECHNOLOGIES, FRAMEWORKS

Many of the projects that are currently ongoing within the group's laboratory are laying the groundwork for the future of biological engineering by the development of genetic tools, foundational technologies and

Through our collaborations, we develop cutting-edge biomolecular engineering methods and tools necessary to come up with solutions to the current challenges faced by the synthetic biology community

conceptual frameworks. One project is focused on the development of predictable and robust design methods for the engineering of complex genetic systems (such as robust genetic oscillators whose oscillation properties, such as amplitude and frequency, can be independently controlled). Another project is centred on developing breakthrough technologies that will take synthetic biology to the next level by engineering biological functions and dynamic behaviours at the multicellular level. And yet another is concerned with creating whole-cell mathematical models that will improve the predictability of genetic designs by considering the interplay between synthetic circuits and their host cells.

In addition, the group is also conducting research that focuses on the practical applications of synthetic biology – such as the investigation of methodologies that optimise the production of valuable recombinant proteins in bacterial cells, and the combination of 3D printing and synthetic biology to create novel 3D biosynthetic printing methods for manufacturing applications.

NOVEL POSSIBILITIES

Given that the group's vision is to bring systems and control engineering principles to the field of biology, it follows that they actively collaborate with multiple research groups, both within Imperial College London and around the world. 'Building relationships with academic groups gives us the chance to use engineering concepts and develop novel bioengineering methods aimed at efficiently building more reliable, robust and predictable systems,' explains Stan. 'Through our collaborations, we develop cutting-edge biomolecular engineering methods and tools necessary to come up with solutions to the current challenges faced by the synthetic biology community.'

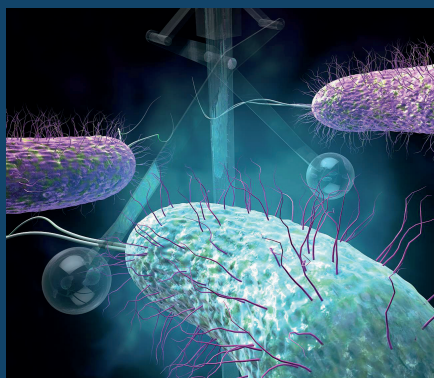


Image courtesy of Ella Maru Studio

The complexity of living organisms realising the goals of the group as outlined above requires a multitude of expertises to come together and work harmoniously. This is why the members of the group come from various backgrounds like life sciences, engineering, maths and chemistry. The emergent outcome of this interdisciplinary mix is what generates novel possibilities for engineering biology in ways that could not be imagined before.

The group also collaborates with undergraduate-led research teams to great success. The International Genetically Engineered Machine (iGEM) competition is the largest undergraduate synthetic biology competition globally, with more than 300 teams from around the world showcasing innovative ideas and projects covering a diverse range of societal challenges. In 2016, Imperial's iGEM team, led by Stan, pursued a foundational project tackling some of the current core challenges facing the synthetic biology community, and ultimately emerged victorious. 'The undergraduate students identified a problem – namely that researchers in our Centre for Synthetic Biology had difficulties maintaining stable co-cultures – and proposed a solution, called 'E.colibrium' (http://2016.igem.org/Team:Imperial_College), that involved creating a circuit that could maintain two bacterial populations at a specific ratio,' recalls Stan. 'Our lab now continues to develop this idea of expanding synthetic biology to microbial consortia and we are currently looking into different ways of building stable co-cultures and synthetic ecosystems for a multitude of applications.'

OPTIMISING ENGINEERED BIOLOGICAL SYSTEMS

As it stands, synthetic biologists spend significant amounts of time and resources growing cell cultures and carefully engineering them to perform desired tasks. This can often be a painstaking process, where systematic and exhaustive testing of numerous variables is required because of the lack of predictive models which would allow them to accelerate and systematically explore the design space. By bringing together biological and biomolecular engineering, rigorous characterisation and quantification of biology, and theoretical and computational modelling, the Control Engineering Synthetic Biology group strives to accelerate the design-build-test-learn cycle for the realisation of optimally engineered biological systems.

Project Insights

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