

INTRODUCTION

Synthetic biology: history, challenges and prospects

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Synthetic biology is an emerging field that seeks to employ engineering principles to reprogramme living systems. Biological systems are characterized by highly complex genetic and cellular networks that are locked together by dynamic, parallel and nonlinear feedback interactions that give rise to properties of self-organization, repair and reproduction. These evolved systems pose formidable challenges to rational engineering approaches. Yet, they are capable of assembling functional structures that are many orders of magnitude more complex than the most sophisticated man-made artefacts, and they do this in a renewable fashion, and cheaply.

A formidable array of biochemical, biophysical and genetic techniques have been assembled for the description of biological systems, and this has given us methods for the comprehensive description of an organism's genome, gene expression patterns and metabolic activities. New imaging techniques allow us to monitor activities within living organisms and to precisely reconstruct cellular architecture. In addition, advances in the technology of DNA synthesis and assembly have allowed the copying and reconstruction of an entire chromosome (Gibson *et al.* 2008). This has raised the prospect of wholesale reprogramming of biological systems, or creation of new organisms. Unfortunately, the capacity for DNA synthesis has far outstripped our ability to design new or modified genetic systems on a similar scale.

While recombinant DNA technology has advanced at a rapid pace over the last 35 years, the cloning and assembly of synthetic DNA sequences remains a largely bespoke affair. The field is in a situation similar to mechanical engineering in the early 1800s and microelectronics in the early 1950s, when rapid progress required the adoption of standardized interchangeable parts and modular construction methods. Engineers

were then free to reap the benefits of abstraction and decoupling to accelerate the design process, and aid the development of new parts and subsystems. These issues are even more pressing for the design of living systems. We have now seen the establishment of the first standards for assembly of DNA-based biological circuits, pioneered by Knight (2003). A Registry of Standard Biological Parts (<http://partsregistry.org>) has been established at MIT as part of the international Genetically Engineered Machine competition (<http://www.igem.org>). OpenWetWare (<http://openwetware.org>) is facilitating the web-based exchange of standard protocols, and the BioBricks Foundation (<http://bbf.openwetware.org>) is a community-driven effort to establish a legal framework for the sharing and use of standardized parts. In addition, work in systems biology has provided a wide range of software tools for the description and design of genetic circuits.

This issue contains a collection of articles that cover efforts to establish improved software and biological tools for the design and assembly of synthetic DNA-based programmes. Matsuoka *et al.* (2009) describe important initiatives to standardize design schematics and representation of DNA-encoded functions in biological engineering. The use of quantitative models is a key element in the design and analysis of synthetic systems, and Endler *et al.* (2009) provide an overview of the model creation process and software tools in common use.

Phillips & Cardelli (2009) present a programming language for the design and simulation of DNA computers based on strand displacement, while Pedersen & Phillips (2009) introduce a formal language for genetic engineering of cells, which allows synthetic systems to be described at the level of logical interactions between DNA-encoded genes and proteins and which addresses the composability of the systems in terms of parts. Bentley (2009) describes methods for improving simulations of biological systems, and introduces an interaction-based language, systemic computation, which

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enables individual-based expression and modelling of biological systems.

Welch *et al.* (2009) apply their considerable experience in DNA synthesis to provide a discussion of the main constraints for the design of synthetic genes and outline rules for the optimization of gene expression. Suárez & Jaramillo (2009) describe progress in computational design of synthetic proteins and future challenges for the generation of novel parts for synthetic biology. Gulati *et al.* (2009) introduce microfluidics technology as a foundational technology for synthetic biology with important applications in fabrication and testing of synthetic systems.

Like all engineering disciplines, synthetic biology is motivated by application to solve specific problems. Here, both computational and biological approaches are highly focused towards developing design methods and tools for applications ranging from the implementation of *in vitro* systems to micro-organisms for biofuel production. Hold & Panke (2009) suggest that determining design parameters for enzymatic reaction networks such as glycolysis may be more easily investigated through *in vitro* systems rather than working with the complexity of living systems. Network design simplified by the reduction/specification of constituents and time invariance afford system manipulations amenable to chemical and mathematical analysis. Simpson *et al.* (2009) discuss a similar reductionist approach in the analogy between electronic CMOS and transcriptional logic gates. These biological logic gates may be assembled for 'amorphous computation' where the outcome could be pattern formation. Through the use of RNA hairpins and the design parameters therein, mutually inhibitory hairpin promoters can be constructed and paired to form a bistable latch. These and other types of logic gates, if immobilized on a two-dimensional surface with RNA polymerase and nucleoside triphosphates could interact, resulting in robust pattern formation. The modularity of RNA-based logic gates/switches is also seen in other gene regulatory and biosynthesis systems. Boyle & Silver (2009) promote the exploitation of natural diversity for the construction of synthetic devices because natural systems have evolved to be robust. Examples include phosphorylation-based signalling cascades, polyketide synthase 'assembly lines' and intercellular quorum sensing. French (2009) extends the notion of exploiting natural systems to consider how co-opting natural systems could be used for the design of 'ideal biofuel producing microorganisms'. The problems of biomass degradation, biofuel product formation and solvent tolerance are reviewed in this context.

Stepping back from the exciting possibilities that synthetic biology promises, even projects that appear to be inherently beneficial such as biofuel production have regulatory, ethical, social and political issues associated with them. Yearley (2009) reminds us that along with the benefits of synthetic biology is the need for ongoing review of regulatory standards and a continued, vigorous ethical and social debate. In this context, he argues that the use of the predominant bioethics framework may be too limited as this form

of principlism is non-political, and is hence not suitable for addressing ecological/environmental issues or 'how to check the power of the mighty'.

Studies in basic science have provided the well-characterized biological components that are raw materials for standard modular parts. Numerical tools that have been developed in the study of natural systems are forming the basis for new computational tools for design. These principles are beginning to provide a conceptual and practical framework for the systematic engineering of biological systems. This will allow approaches that are routine in other fields of engineering, and cause a fundamental and growing shift in our approach to biology.

This synthetic biology approach is arising as a result of the collision between science and engineering. It is especially appropriate that this special issue is co-sponsored by the Royal Society and the Institution of Engineering and Technology. As well as representing the twin disciplines of science and technology, the two institutions have provided strong support and guidance for the emerging field. Synthetic biology shows great potential for the engineering of complex biological systems required for improved production of biomass, fuels, food, polymers and drugs, and we hope that this collection of articles provides an insight into thinking about current challenges in the field, and prospects for future progress.

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