SYNTHETIC BIOLOGY

Genetically engineered microbes and viruses have the potential to transform chemical production, therapeutics development, and our entire economy to be more efficient and sustainable. A barrier to realising this vision is the fact that all genetic engineering design choices are currently driven by a fear of breaking the system in unanticipated ways. For example, the totally synthetic *Mycoplasma* genome created by Craig Venter’s group contained few changes from the natural sequence. There is currently a disconnect between the explosive growth in our ability to write synthetic DNA of any sequence we desire, and our ability to rationally design functional genetic systems.

The Jaschke lab uses bacteriophage, viruses that infect bacteria, as model systems to learn how to design and build synthetic genomes. We aim to redesign natural genomes to be modular and easier to understand and reuse while maintaining the original functionality of their natural ancestors. Bacteriophages are ideal models because they can be thought of as self-contained genetic 'programs' that run within a constant cellular 'operating system' that, like computer software, can be debugged if not working as designed. Bacteriophages also share many lifecycle characteristics of self-replicating cellular systems, such as DNA replication and temporal regulation of gene expression.

Our group draws on a wide range of cutting edge techniques from synthetic biology such as synthetic DNA design, standardisation, and manipulation to produce novel bacteriophage genomes. We study the new viruses that we create using both traditional techniques from microbiology such as plate-based plaque assays (pictured above, right), but are also developing, in collaboration with groups in the United States, novel microfluidic approaches to scaling down and automating phage lifecycle measurements.

PROJECT 1: DEEP CHARACTERISATION OF A HIGHLY ENGINEERED BACTERIOPHAGE

The phage øX174 has been part of many firsts in science, from being the first DNA genome sequenced in 1977 (Nature 1977, 265: 687-695), to the first synthetic genome ‘booted up’ by Craig Venter in 2003 (PNAS 2003, 100: 15440-5), to the first bacteriophage genome accessioned by MoMA1. The genome of øX174 is interesting from many perspectives, but one feature that has puzzled and intrigued scientists over the years is the fact that many of its genes are overlapped with each other. This creates a genome with highly compressed information analogous to what happens when music gets compressed into an MP3 file. Several years ago the genome of øX174 was redesigned to fully decompress (separate) all the overlapped genes from each other. The resulting virus was shown to be functional but not studied any further2. The decompressed øX174 phage will be analysed using microbiological methods to determine viral lifecycle characteristics, while molecular techniques will be used to determine how RNA and protein expression is altered from the naturally occuring wild-type øX174 phage.
PROJECT 2: REFINING THE GENOME OF A HIGHLY ENGINEERED BACTERIOPHAGE USING EVOLUTION

This project will aim to improve lifecycle characteristics, such as growth rate, of the fully decompressed synthetic øX174 genome. Our approach will be to use evolution to refine the genome through iterative rounds of natural selection followed by sequencing and analysis to understand how the observed genome changes result in a faster growth phenotype. Evolution is a unique property of biological systems that sets them apart from the raw material of other engineering fields (Nature 2005, 438: 449-453). Synthetic biology has yet to fully recognize the utility of evolution in shaping engineered genomes. This project will complement recent work from our group that has shown that a øX174 genome containing hundreds of silent point mutations can be improved through an evolutionary process3.

PROJECT 3: ENGINEERING START CODON FLEXIBILITY WITHIN NATURAL AND SYNTHETIC BACTERIOPHAGE GENOMES

The vast majority of all known genes, across all known species, use the three DNA letters ATG as their first (start) codon. Recently in an experimental survey of all 64 possible codons it was found that there may be as many as 15 codons, that under certain conditions, will function as the start codon for a gene4. This project will explore the possibility of recoding all the genes of an organism to use non-canonical start codons. This work will aim to reveal the total functional start codon sequence space available for bioengineering. In this project, both the wild type øX174 genome as well as the fully decompressed øX174 genome will have the start codon for each known gene swapped out for a series of non-canonical codons shown to have activity. Genomes will be constructed and evaluated in high-throughput screens to identify codon combinations that result in viable phage. Results of this work will contribute to our understanding of how natural genomes are 'designed' by natural selection as well as lead to better understanding of additional ways to tune protein expression from artificial genetic systems.

Selected publications


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