biotechnologists. Importantly, the approach taken by the authors allowed them to circumvent an important problem: *E. coli* codon usage. This is optimized for *in vivo* conditions, but is for some reason inefficient *in vitro*, so they tinkered with the codon usage at the oligo-design stage to maximize translation efficiency.

Tian *et al.* elegantly show how technical obstacles can be overcome on the way to synthetic biology. As more and more hypotheses line up to be tested, the push for advances in this field is likely to increase.

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References and links

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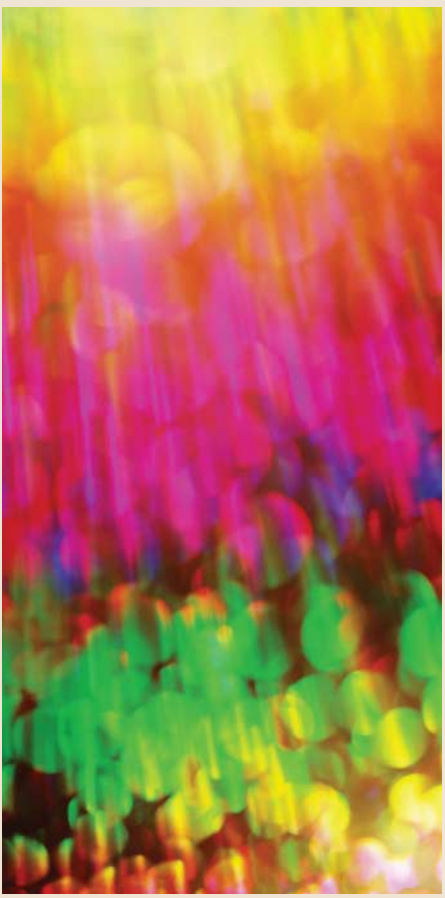
FURTHER READING Shendure, J. *et al.* Advanced sequencing technologies: methods and goals. *Nature Rev. Genet.* **5**, 335–344 (2004)

WEB SITE

George Church's laboratory: http://arep.med.harvard.edu/



GENE REGULATION

Wading in upstream

Figuring out how gene expression has evolved can take some serious detective work. Because regulatory sequences are short and are surrounded by unconserved, non-coding DNA, spotting similar elements in different species by sequence alignment is often impossible, especially in distantly related organisms. In a recent paper, Audrey Gasch and colleagues describe a new approach to this problem and apply it to the evolution of gene expression in fungi.

The authors predicted that groups of genes that are co-expressed under specific conditions are likely to be controlled by similar regulatory elements and that this could be used as a starting point to identify related elements in different species. On this basis, they first identified groups of *Saccharomyces cerevisiae* genes that were predicted to be co-regulated owing to similar functions or expression patterns. Examining upstream regions revealed 42 different elements that are involved in the co-regulation of different sets of these genes.

The next step was to see whether similar regulatory elements regulate the expression of the corresponding genes in other species. *Saccharomyces cerevisiae* belongs to a group of fungi known as the ascomycetes that are thought to have existed for 500 million to 1 billion years. The authors used a modified BLAST search to identify the orthologues of co-regulated *S. cerevisiae* genes in 13 other ascomycete species and looked at which regulatory elements were present in their upstream regions. In species closely related to *S. cerevisiae*, most of the regulatory elements were conserved in the corresponding groups of orthologous genes. For example, in *Saccharomyces kluyveri* and *Saccharomyces castelli*, this proportion was 50–75%. Even in *Candida albicans* — which is thought to have diverged from *S. cerevisiae* ~200 million years ago — more than a third of the same elements were identified in orthologous gene groups, indicating that *cis*-regulatory elements can be conserved over large evolutionary distances.

Gasch and colleagues also found evidence for evolutionary changes in gene regulation. For example, although there are many cases in which regulatory sequences are conserved, there are also orthologous groups of co-regulated genes that might rely on distinct sets of regulatory elements in different species, with these differences being more pronounced between more distantly related species.

An example of evolutionary change that the authors examined in more detail was the control of gene expression by the transcription factor Rpn4, which regulates proteasomal genes in *S. cerevisiae*. One binding site for this protein was identified as a conserved *cis*-regulatory element in all of the hemiascomycetes, a group that includes *S. cerevisiae*.

However, in another group — the euascomycetes — a distinct element was identified. Comparison of an Rpn4 protein from three species revealed that the binding specificities are different between fungi, with each binding to elements identified in the corresponding species. So, the *cis*-regulatory elements that are involved seem to have co-evolved with the Rpn4 protein to produce species-specific regulatory interactions.

The evolutionary distances covered in this study are far greater than would have been possible through sequence alignment, providing the opportunity to explore the evolution of gene regulation in unprecedented detail. As more complete genome sequences of related sequences become available, similar studies should become possible across a range of taxonomic groups, leading to a greater understanding of the mechanisms that have shaped organismal diversity.

Louisa Flintoft

References and links

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WEB SITES

Audrey Gasch's laboratory: http://www.genetics.wisc.edu/faculty/profile.php?id=159

Michael Eisen's laboratory: http://rana.lbl.gov/