Title: Re-write the yeast genome for customised biosynthesis control

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Synthetic genomics is a field in synthetic biology aiming to assemble whole genomic DNAs while manipulating the genome content into a customised way. Saccharomyces cerevisiae yeast, a model organism with its whole genome sequence determined and well understood, is a good candidate for genome de novo redesign and synthesis. Here, we demonstrate the feasibility of defragmenting a yeast genome and the benefits of co-regulating a synthetic cluster that can be exploited for genome optimisation. We generated two functional synthetic chromosome clusters by genetically re-locating the genes associated with histidine and tryptophan biosynthesis. A master regulation switch was engineered to achieve the targeted and efficient co-regulation of the gene expression in the synthetic cluster. We also applied the Synthetic Chromosome Rearrangement and Modification by LoxP-mediated Evolution (SCRaMbLE) system to induce dynamic changes to optimise the cluster function and study the evolutionary choice of gene layout under different selection pressure. By relocating and clustering genes in the yeast genome, we get a better understanding of the rules underlying the natural eukaryotic genome organisation and so improve our ability to design and build custom synthetic genomes in the future.