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LEARNING WHAT TO WRITE: APPLYING DNA SYNTHESIS AND SEQUENCING TECHNOLOGIES TO IMPROVE STRAIN DESIGN AND CONSTRUCTION

The era of genome engineering has arrived. Synthetic DNA technologies can now generate sufficient DNA to construct tens of thousands of genes in parallel; enough to synthesize several complete microbial genomes at the same time. Genome sequencing has advanced to the point where so synthesized artificial genomes could be completely sequenced in < 1 day for about $1000 using a benchtop sequencer. These technologies were used in the creation of the first synthetic genome, which was successfully applied in the construction of the first viable cell (species?) controlled by a man-made genome. Such genome-construction technology was first applied to the copying of existing genomes. Future applications will seek to develop artificial genomes that will be designed to encode industrially relevant functions; such as production of biofuels, sustainable chemicals, pharmaceuticals, industrial enzymes, etc. Such applications will require that we are able to not only identify genes encoding functions that enable such applications but also combinations of such genes that result in optimal organism performance. The size of combinatorial mutation space, however, is well beyond what can possibly be searched in laboratory timescales. Developing new methods and approaches that enable the efficient search for such genes and gene combinations is a major focus of our research efforts. We envision this process as requiring three key steps, i) the mapping of genetic modifications onto a trait of interest, ii) the analysis of mapping data to assign relevance to each genetic modification, and iii) the exhaustive searching of combinations of the most relevant subset of genetic modifications to identify combinations that optimize expression of the desired trait. We have developed several methods relevant for each of these steps. This presentation will describe such methods and their most recent application to improve a range of traits relevant to sustainable fuels and chemicals production.