Modular 5′-UTR hexamers for context-independent tuning of protein expression in eukaryotes - DTU Orbit (16/12/2018)

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Functional characterization of regulatory DNA elements in broad genetic contexts is a prerequisite for forward engineering of biological systems. Translation initiation site (TIS) sequences are attractive to use for regulating gene activity and metabolic pathway fluxes because the genetic changes are minimal. However, limited knowledge is available on tuning gene outputs by varying TISs in different genetic and environmental contexts. Here, we created TIS hexamer libraries in baker's yeast Saccharomyces cerevisiae directly 5′ end of a reporter gene in various promoter contexts and measured gene activity distributions for each library. Next, selected TIS sequences, resulted in almost 10-fold changes in reporter outputs, were experimentally characterized in various environmental and genetic contexts in both yeast and mammalian cells. From our analyses, we observed strong linear correlations ($R^2 = 0.75–0.98$) between all pairwise combinations of TIS order and gene activity. Finally, our analysis enabled the identification of a TIS with almost 50% stronger output than a commonly used TIS for protein expression in mammalian cells, and selected TISs were also used to tune gene activities in yeast at a metabolic branch point in order to prototype fitness and carotenoid production landscapes. Taken together, the characterized TISs support reliable context-independent forward engineering of translation initiation in eukaryotes.
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