How innovations originate remains a central challenge in evolutionary biology. Innovation in metabolism allows the utilization of new nutrients, and arises through the integration of new metabolic reactions into the network. In many cases, metabolic innovations depend on the simultaneous acquisition of multiple reactions that provide little or no benefit individually. It has been argued that such complex innovations may arise through the non-adaptive exploration of phenotype space, but it remains unclear if such processes are widespread and fast enough to explain the metabolic diversity observed.

Here, we investigate how complex metabolic evolution can instead arise through purely adaptive processes. We traced \textit{in silico} how bacterial metabolic networks can evolve across hundreds of different nutrient conditions. The analysis revealed that the \textit{Escherichia coli} network can generally utilize novel nutrients through the addition of just one to three metabolic reactions, but the endosymbiont Buchnera has to acquire 80 reactions on average. We also demonstrate that temporally varying nutrient conditions can accelerate the adaptive expansion of metabolic networks: novel environments serve as stepping stones towards the establishment of more complex pathways. Contingent gain of metabolic genes on the bacterial tree of life and results of a short-term laboratory evolutionary study in the same species provided empirical support for the scenario.

We conclude that complex innovations in metabolic networks can evolve through a series of adaptive steps without the need to invoke non-adaptive processes.

\textbf{MPA_32}

\textbf{TDPS - Turnover dependent phenotypic simulation: a quantitative constraint-based simulation method that accommodates all main strain design strategies}

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Constraint-based modelling methodologies can expedite the strain engineering process by helping in the search for interesting genetic modification targets. Although the search for gene knock-outs is fairly established with \textit{in silico} methodologies, most computational strain design methods still model gene up/down-regulations by forcing the corresponding flux values to pre-calculated levels without considering the availability of resources.

We have developed a new simulation method, Turnover Dependent Phenotypic Simulation (TDPS), which was designed with the goal of simulating quantitatively the phenotype of strains with diverse genetic modifications in a resource conscious manner. Besides gene deletions and down-regulations, TDPS can also simulate the up-regulation of metabolic reactions as well as the introduction of heterologous genes or the activation of “dormant” reactions. In TDPS the flux values through modified metabolic reactions are modelled by taking into consideration the availability of precursor metabolites in the network, which is accomplished by assuming that the production turnover of a metabolite can be used as an indication of its abundance. The developed method is based on a MILP formulation that manipulates the fractions of metabolite turnovers consumed by the modified reactions. Furthermore, TDPS also integrates a new objective function that promotes network rigidity in order to predict the flux phenotype of modified strains. TDPS was validated using metabolically engineered \textit{S. cerevisiae} strains available in the literature by comparing the simulated and experimental production yields of the target metabolite.