

176. Predicting *Clostridium ljungdahlii* Cellular Phenotypes Through a Metabolic and Gene-Expression Model

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Project Goals: This project will substantially enhance our knowledge about chemolithoautotrophs and their potential for advanced biocommodity production by detailing the interconnectivity of metabolism, energy conservation, and regulation of *Clostridium ljungdahlii* through sequencing and modelling. As a result, we will have next-gen modeling capability as well as methods to utilize next-gen models (also known as metabolic and gene-expression models, abbreviated ME-models) for the design of tunable systems that produce biocommodities from inexpensive sources.

Clostridium ljungdahlii is emerging as an acetogenic model organism to be developed into a new chassis for strain designed chemical production as well as a platform for gaining in-depth knowledge about acetogens. There are many attractive features that endorse *C. ljungdahlii* for strain design, including its ability to grow either heterotrophically on a variety of sugars or autotrophically on carbon monoxide (CO), or carbon dioxide (CO₂) and hydrogen (H₂), as well as mixtures of those gases (i.e. syngas). Metabolism of syngas by acetogenic microorganisms produces multi-carbon organics, an ability that may be engineered to produce biocommodities.

C. ljungdahlii's known metabolic and energy pathways were reconstructed in the form of a constraint-based metabolic model (M-model). Furthermore, we have also reconstructed the macromolecular synthesis machinery (E-matrix) through sequence homology and literature curation of over 100 genes. Integration of the E-matrix into the M-model produced a predictive genome-scale ME-model for *C. ljungdahlii*. This ME-model serves as a theoretical baseline to understand and predict the metabolic, transcriptomic, and proteomic responses to environmental or genetic perturbations. For example, the ME-model predicts dramatic phenotypic differences in autotrophic and heterotrophic growth conditions. Unlike traditional approaches, the ME-model also accounts for critical factors and properties of candidate pathways (e.g., cost of enzymes, protein complex stoichiometry, codon usage, cofactor dependency and prosthetic group-usage), which will be of utmost importance for tuning expression of non-native pathways for biocommodity production.

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