Methanogenic archaea and the global carbon cycle: a systems biology approach to the study of *Methanosarcina* species

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Project Goals: Our initial goal is to sequence the genomes of approximately forty strains that span the taxonomic scale within the Order *Methanosarcinales*. These strains include isolates with thoroughly characterized physiology, biochemistry and genetics from both marine and freshwater environments. Strains from additional well-studied and important ecosystems will be isolated and examined at later stages of the project. Our ultimate goal is to incorporate the observed regulatory and metabolic networks into integrated, multi-scale models that accurately and quantitatively predict the role of methanogenic organisms in the global carbon cycle under dynamic environmental conditions.

Methanogenesis is responsible for a significant fraction of the global carbon cycle and plays an essential role in the biosphere. In many anaerobic environments, turnover of organic matter is completely dependent on methanogenic archaea. Although a great deal is known about the physiology and metabolism of these organisms, our ability to incorporate methanogens into carbon cycle models remains in the "black box" stage. To address this issue we are developing systems level models that capture the metabolic and regulatory networks of *Methanosarcina* species, which are among the most experimentally tractable of the methane-producing archaea. One of the initial successes of the first year of funding was to develop a genome-scale model of *Methanosarcina acetivorans* metabolism.

Methanosarcina acetivorans strain C2A is a marine methanogenic archaeon notable for its substrate utilization, genetic tractability, and novel energy conservation mechanisms. To help probe the phenotypic implications of this organism's unique metabolism, we have constructed and manually curated a genome-scale metabolic model of *M. acetivorans*, iMB745, which accounts for 745 of the 4540 predicted protein coding genes (16%) in the *M. acetivorans* genome. The reconstruction effort has identified key knowledge gaps and differences in peripheral and central metabolism between methanogenic species. Using flux balance analysis, the model quantitatively predicts wild type phenotypes and is 96% accurate in knockout lethality predictions compared to currently available experimental data. The model was used to probe the mechanisms and energetics of byproduct formation and growth on carbon monoxide, and the nature of the reaction catalyzed by the soluble heterodisulfide reductase HdrABC in *M. acetivorans*. The genome-scale model provides quantitative and qualitative hypotheses that can be used to help iteratively guide additional experiments to further the state of knowledge about methanogenesis.

References

Benedict, M.N, Gonnerman, M.C, Metcalf, W.W., and Price, N.D., 2011. Genome-scale metabolic reconstruction and hypothesis tesing in the methanogenic archaeon *Methanosarcina acetivorans* C2A. *Journal of Bacteriology*. Epub ahead of print.

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