The Genome-Scale Metabolic Extreme Pathway Structure in *Haemophilus influenzae* and *Helicobacter pylori* Show Differing Degrees of Network Redundancy

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ABSTRACT

Genome-scale metabolic networks can be characterized by a set of systemically independent and unique extreme pathways [1]. These extreme pathways span a convex, high-dimensional space that circumscribes all potential steady state flux distributions achievable by the defined metabolic network. Genome-scale extreme pathways associated with the production of non-essential amino acids in *Haemophilus influenzae* and *Helicobacter pylori* were computed. They offer valuable insight into the structure of its metabolic network. Three key results were obtained for *H. influenzae*. First, there were multiple internal flux maps corresponding to externally indistinguishable states. It was shown that there was an average of 37 internal states per unique exchange flux vector when the network was used to produce a single amino acid while allowing carbon dioxide and acetate as carbon sinks. With the inclusion of succinate as an additional output, this ratio increased to 52, a 40% increase. Second, an analysis of the carbon fates illustrated that the extreme pathways were non-uniformly distributed across the carbon fate spectrum. In the detailed case study, 45% of the distinct carbon fate values associated with lysine production represented 85% of the extreme pathways. Third, this distribution fell between distinct systemic constraints. For lysine production, the carbon fate values that represented 85% of the pathways described above corresponded to only 2 distinct stoichiometric ratios of 1:1 and 4:1 between carbon dioxide and acetate. Results for *H. pylori* showed two significant characteristics. First, there was an average of 2 internal states per unique exchange flux vector for amino acid production in *H. pylori*, an order of magnitude less than *H. influenzae* under similar conditions. Second, the *H. pylori* stoichiometric network illustrated a significant robustness and preference for high ammonia secretion, necessary for its survival in the human gastric environment. The present study analyzed single outputs and small sets of outputs from two organisms, but it provides a start to genome-scale extreme pathways studies. These emergent system-level characterizations show the significance of metabolic extreme pathway analysis at the genome-scale.

REFERENCES

[1] Schilling, C. H., D. Letscher, et al. (2000). Theory for the Systemic Definition of Metabolic Pathways and their use in Interpreting Metabolic Function from a Pathway-Oriented Perspective. *J. Theoret. Biol*. **203**: 229-248.