

## Evolution of Bacterial Genomic Networks

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Gain and loss of genes are genomic macro-mutations. In order to understand the selective forces leading to their fixation, it is necessary to analyze these mutations in a systemic context. We chose *E. coli* as our model system, as it is one of the best studied cellular systems, and because of the availability of experimentally verified simulation methods for its metabolic network.

How and why did *E. coli*'s metabolic network change in the course of evolution? We first compared the role of gene duplications and horizontal gene transfer in feeding network growth, showing that in *E. coli* (as opposed to the eukaryote *S. cerevisiae*) network growth was almost entirely driven by horizontal gene transfer. Flux balance analysis demonstrated that metabolic genes that are frequently gained or lost among the relatives of *E. coli* contribute to fitness only in specific environments. Accordingly, genes gained in the evolutionary history of the metabolic network are located at or near its interface with the environment.

To model individual network changes in response to specific environmental conditions, we had to further simplify our system, focusing on reductive evolution in endosymbionts (where gene gain appears to be negligible). Depending on the randomly chosen order of gene deletions, simulations led to highly variable minimal networks, sharing on average only about 50% of their reactions. Minimal networks were about twice as large as predicted based on single gene deletion studies. Observed gene content in the endosymbionts *Buchnera* and *Wigglesworthia* was predicted by this method with over 80% accuracy.

What other forces affect the fixation and integration of horizontally transferred genes in a new host? While 20-24% of the nodes in the protein interaction network have been gained by horizontal gene transfer during the last 100 million years, most horizontally transferred genes have few physical and regulatory links. Further, co-regulation of physically interacting proteins is drastically diminished if one partner was recently transferred into *E. coli*, and is gradually rebuilt during evolution. While dependence on interaction partners impedes horizontal gene flow, new interactions can evolve after successful integration and are fine-tuned over evolutionary time.

### References:

Nature Genetics **37**: 1372-1375 (2005)

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