

→ Asymmetric relationships between metabolic reactions shape genome evolution

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→ Summary

Often, dependency relations between proteins are asymmetric: one protein (A) depends for its function on another, second protein (B), but that second protein does not depend on the first.

Stoichiometric modelling of complete metabolisms suggests that most of the reaction pairs with coupled fluxes are asymmetrically rather than symmetrically coupled: 82% in *S. cerevisiae* and 67% in *E. coli*.

This asymmetry in the coupling of fluxes is reflected in the expression of the catalyzing enzymes, the impact of their gene's knock-outs and the evolution of gene content.

Figure 1 | Examples of asymmetric relations between reactions. Nodes represent metabolites, edges reactions. For a reaction pair $A \rightarrow B$, if reaction A is active also reaction B carries a flux. Conversely, B can be active without A because of alternative converging or diverging fluxes (--->).

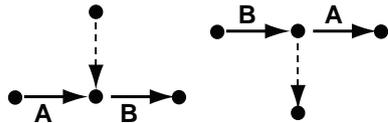


Figure 2 | Analysis outline. As activity of reaction A is not necessary for reaction B, A could be considered "dispensable". Various other genomic data can be interpreted in terms of dispensability: "dispensable" genes are not expressed in a condition, do not affect growth when knocked-out or are absent from a species' genome.

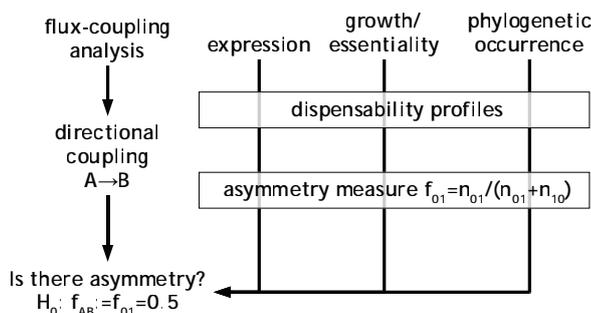
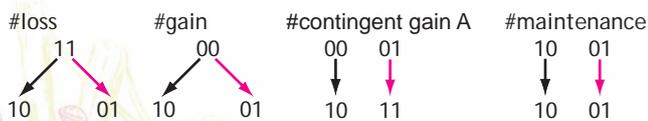


Figure 3 | Four measures of asymmetry extracted from the parsimony reconstruction of ancestral gene content (STRING database & PAUP). The type of change across branches that is more expected in asymmetric pairs $A \rightarrow B$ is denoted in pink. E.g. "contingent gain A": If A's function depends on B, then A should be gained if B is already present but not if B is absent.



→ Results

Figure 4 | Asymmetry in various genomic data sets is consistent with model predictions. All asymmetry values are significantly larger than the random expectation (two-sided, one-sample Wilcoxon test; McNemar test).

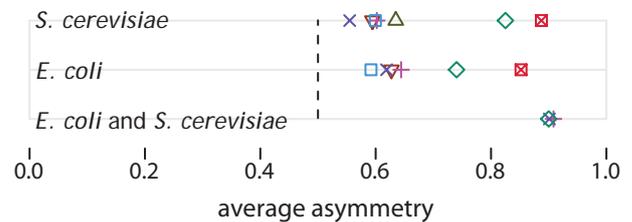


Figure 5 | Strength of asymmetry is independent of network distance.

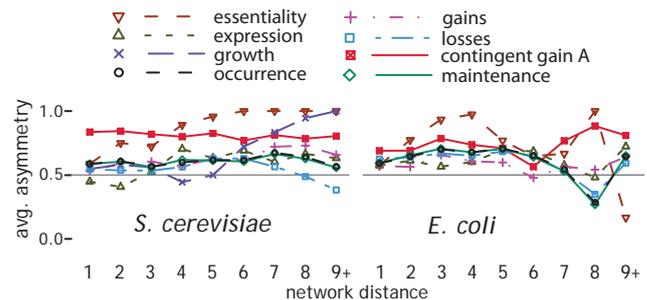
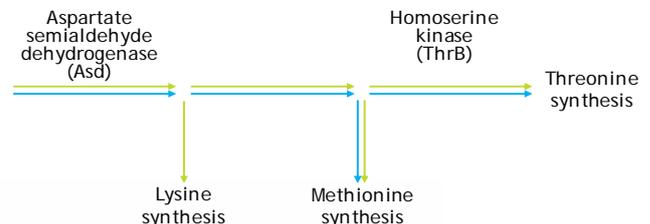


Figure 6 | The asymmetric relationship [ThrB → Asd] conserved between *E. coli* and *S. cerevisiae* is reflected in their phylogenetic distributions: *thrB* is almost never present in a genome without *asd* because ThrB's activity depends on Asd, but not vice versa.



<i>asd</i> \ <i>thrB</i>	present	absent
present	184	129
absent	1	59

Thermophilum pendens
Crenarcheote that feeds on peptides

→ Conclusions

Genomic data contain not only information about whether proteins interact but also about the characteristics of the interaction. Asymmetric patterns could be used to predict characteristics of known and new functional relations.

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