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Protein Cost and Metabolic Network Structure Underlie Different Modes of Metabolic Efficiency

When growth rate increases, many unicellular organisms shift from an energetically efficient to an energetically inefficient metabolic pathway to break down glucose. An example is baker's yeast *Saccharomyces cerivisiae*, which ferments glucose to ethanol if the glucose concentration is high, even in aerobic environments that allow for more efficient catabolism of glucose [1]. Recently, a new explanation for this paradoxical behaviour has been proposed: because cells can only pack a limited volume of metabolic enzymes, inefficient metabolism can maximise the growth rate of the cell, because efficient metabolic pathways require more enzymes than inefficient pathways [2,3]. Indeed, Vazquez *et al.* [2] explained the concurrent use of the efficient and inefficient pathway by *Escherichia coli* in this way. However, it is unknown why, at high growth rates, some microbes only use efficient metabolism, while others only use inefficient metabolism and again others use both concurrently.

Here we apply Vazquez' method on genome-scale metabolic models of three organisms that use different modes of inefficient metabolism, *E. coli*, *S. cerevisiae* and *Lactococcus lactis*: *E. coli* does not downregulate its efficient pathway at high growth rates, while *S. cerevisiae* and *L. lactis* do. The Vazquez method incorporates a protein cost for each reaction in the genome-scale metabolic network. This cost is proportional to enzyme volume divided by enzyme turnover number (k_{cat}). Because these protein costs are not known for each reaction individually, we created 1000 networks, each with protein costs for each reaction drawn randomly from an experimentally-obtained distribution. For only a subset of these networks inefficient metabolism is the optimal strategy. This allowed us to study the protein costs of this inefficient subset in more detail.

We found that for cells with low glycolytic protein cost, inefficient metabolism is the optimal strategy, in all these organisms. Furthermore, for *S. cerevisiae* and *L. lactis* optimal growth yield is bimodally distributed over these 1000 networks: metabolism is either efficient or inefficient. In contrast, for *E. coli* we observed that optimal growth yield varies continuously over these 1000 networks. This could explain why *S. cerevisiae* and *L. lactis* truly switch off efficient metabolism, while *E. coli* uses inefficient and efficient metabolism concurrently. We show that differences in metabolic network structure underlie this qualitative difference between *E. coli* on the one hand and *S. cerevisiae* and *L. lactis* on the other hand. Concluding, protein costs determine whether inefficient metabolism is optimal, while the metabolic network structure determines the mode of inefficient metabolism.

References

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