

Quantitative prediction of genome-wide resource allocation in bacteria

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Predicting resource allocation between cell processes is the primary step towards decoding the evolutionary constraints governing bacterial growth under various conditions¹. Quantitative prediction at genome-scale remains a computational challenge as current methods are limited by the tractability of the underlying problem² or by simplifying hypotheses.

In this talk, we present the constraint-based modeling method Resource Balance Analysis (RBA). By considering the bacterial cell as a self-replicating system, the RBA method intrinsically captures the bottleneck due to resource sharing between all biological processes as a non-smooth convex feasibility problem that is efficiently solved through the resolution of an equivalent Linear Programming (LP) optimization problem. The optimal cellular configuration can be computed under the objective of growth rate maximization by solving a sequence of LPs^{3,4}. The refinement of the underlying mathematical description of cell processes compared to well-established constraint-based methods like Flux Balance Analysis⁵ entails inevitably an increased number of parameters in the model^{4,6,7}. By combining physiological and large-scale datasets (growth rate, fluxome, and absolute protein abundances), we successfully calibrated RBA for the Gram-positive model bacterium *Bacillus subtilis* and showed that RBA accurately predicts the resource allocation for a wide range of growth conditions⁸. During the calibration process, the apparent catalytic rates of active metabolic enzymes are estimated and most of them are linearly decreasing with decreasing growth rate. The regulation of most cellular processes is consistent with the objective of growth rate maximization except for a few suboptimal processes which likely integrate more complex objectives such as coping with stressful conditions and survival. We also illustrate how calibrated RBA enables the prediction of complex strategies like managing the uptake of nutrients (carbon and/or amino acid sources) in complex medium. Altogether, RBA offers new opportunities to investigate design principles in prokaryotes and to exploit them for future biotechnological applications.

References

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