rbatools - a programming interface to cellular resource allocation modelling with *Resource Balance Analysis*

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Motivation

Optimised allocation of resources underlies an organism's fitness and facilitates success in competition. *Resource Balance Analysis* (*RBA*), as a computational framework, enables the analysis of an organism's growth-optimal configurations in various environments, at genome-scale[1]. The available tool *RBApy* enables the construction of RBA-models on genome scale and the determination of medium-specific growth-optimal cellular configurations (metabolic fluxes and the abundance of macromolecular machineries)[2]. Since the *RBA*-formalism facilitates a comprehensive representation of cellular resource allocation; a flexible programming interface to the framework allows the implementation of custom workflows to simulate and analyse various aspects of resource allocation and modify genome scale *RBA* models and exports simulation results to various formats.

Conclusions

rbatools utilises the flexible formulation of *RBA* to provide a user friendly interface to the modelling of cellular resource allocation in *Python,* with predefined or custom algorithms. The method was exemplified by evaluating the fitness cost of over-/under expression of individual genes or quantification of the feasible uncertainty of metabolic fluxes and machinery levels at different growth rates.**

References

[1] A. Goelzer, V. Fromion, and G. Scorletti, "Cell design in bacteria as a convex optimization problem" Automatica, vol. 47, 2011.

[2] A. Bulović, S. Fischer, F. Golib, W. Liebermeister, C. Poirier, L. Tournier, E. Klipp, V. Fromion, A. Goelzer. Automated generation of bacterial resource allocation models. Metabolic Engineering, vol. 55, 2019.

Summary

rbatools has been developed as a programming interface around *RBApy[2]*, facilitating the flexible implementation of analyses on cellular resource allocation, beyond the representation of growth-optimal cellular configurations. The tool utilises the flexible formulation of *RBA,* as constraint-based linear problem, to alter and extend the model's scope and structure by the addition and modification of user-defined constraints on cellular growth and maintenance. The internal model representation database allows to access information on model structure and components, complemented with external annotations, and to export this information to tabular formats (*SBtab* or *CSV*). Fundamental methods allow to programatically vary model parameters, set environmental conditions such as medium-composition and growth rate, define cellular objectives, solve the specific *RBA* problem and export simulation results to various formats (e.g *SBtab*, *JSON* or *CSV* and inputs to *Escher*- and *Proteomaps* for visualisation). Implemented algorithms include finding the environment-specific optimal growth rate, specific feasible ranges of model variables, applying and evaluating the effect of gene knock-outs. Exemplary applications (results to the right) were obtained with an existing *E. coli RBA* model[2], during the development process.

Information on *RBA* and existing models can be found on the website rba.inrae.fr
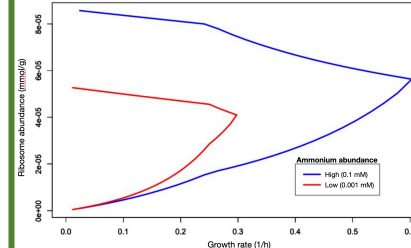
Usage concept of *rbatools*
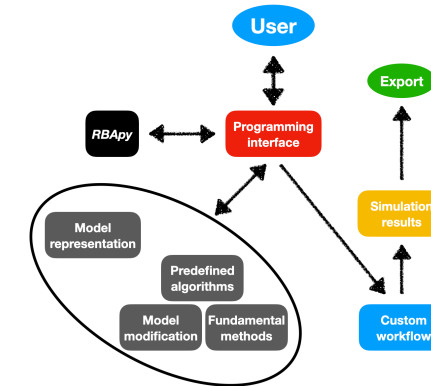
The user utilises the of the functionality of *rbatools* and *RBApy[2]* via the programming interface to develop custom simulation- and analysis workflows with predefined or custom algorithms. The simulation results can then be exported for analysis or visualisation.
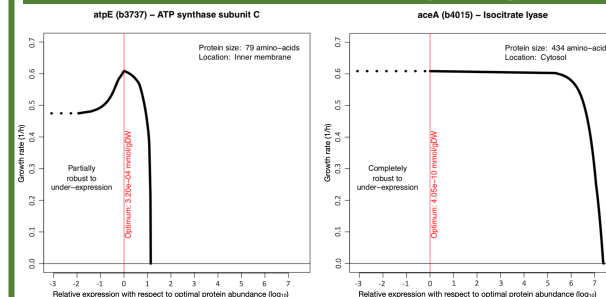
Feasible variability of ribosome levels

Feasible ranges for the abundance of ribosomes, over various growth rates with low and high nitrogen availabilities in *E. coli*. Tolerance to variability decreases with growth rate and converges to the optimal value at the maximum.

Fitness and uncertainty in gene expression

Relative abundance of two proteins with different metabolic function in *E. coli* and its effect on growth rate. TCA-cycle gene *aceA* is less sensitive to expression uncertainty and rewiring of metabolism can recover fitness. While the cost of over expression of the *ATP synthase* subunit *atpE* is less able to be compensated and under expression results in different metabolic modes with lower relative fitness.