Exploring the gap between dynamic and constraint-based models of metabolism

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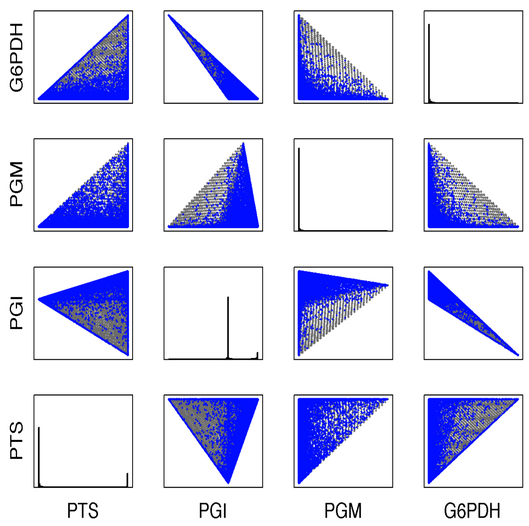
Introduction

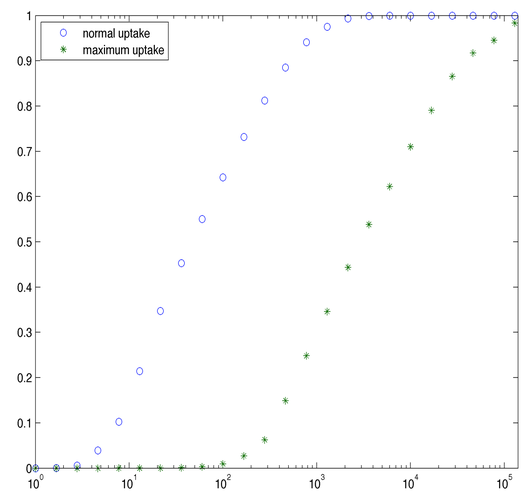
Systems Biology provides new approaches for metabolic engineering through the development of models and methods for simulation and optimization of microbial strains. Nowadays, two main different modeling frameworks coexist. The construction of dynamic models with detailed kinetic rate laws has been limited to central pathways due to the amount of experimental data required for parameter estimation [1]. On the other hand, genome-scale stoichiometric reconstructions have been used in the formulation of constraint-based models that define a space of solutions for the steady-state flux distribution [2]. In this work, we explore the gap between these two kinds of models by comparing the dynamic and constraint-based formulations of the central carbon metabolism of *E. coli* [1].

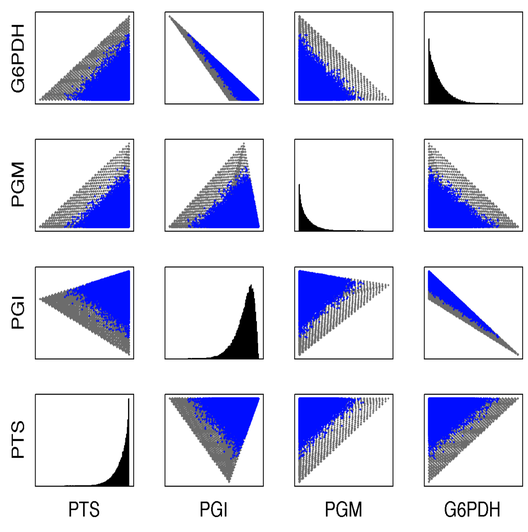
Results and Discussion

- Random sampling by Monte Carlo methods [3] is the common approach for sampling the solution space of constraint-based models (figure: blue sample and diagonal).
- However our new sampling approach, based on the geometric properties of this space (known as the flux cone), reveals its shape more clearly (figure: grey sample).

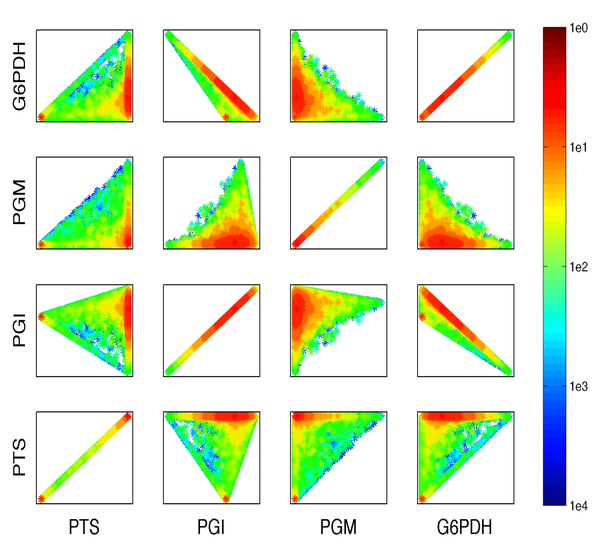


- Limiting the range of variation of the kinetic parameters (1 to 10^4-fold) constrains the range of variation of the steady-state solution of the dynamic model.
- In this case, a 100-fold variation range (figure: green sample) is sufficient to cover almost completely the solution space of the constraint-based model.



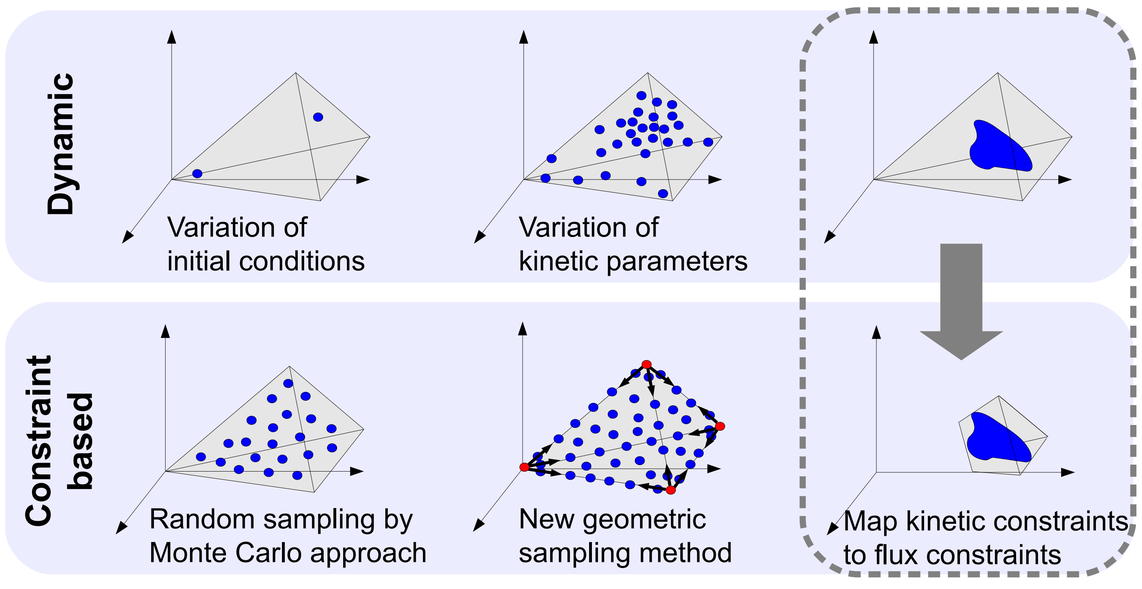


- Sampling the kinetic parameters of the dynamic model shows that its steady-state solution (figure: blue sample) moves within the solution space defined by the constraint-based model (figure: grey sample).
- Despite the areas of different probability (figure: diagonal), the whole space is reachable by fine-tuning the kinetic parameters of the dynamic model.



- Kinetic constraints of the dynamic model can be mapped into flux constraints. The relative volume of the solution space was estimated as a function of the parameter variation ranges (figure: blue circles).
- The volume of the solution space depends on the glucose uptake rate. At the maximum rate, the impact of the constraints becomes more significant (figure: green stars).

Methods



Conclusions

Dynamic and constraint-based modeling represent bottom-up and top-down approaches from Systems Biology. The gap between these two frameworks can be explored at their common domain, the steady-state flux distribution. We take advantage of the availability of dynamic models, even if incomplete, in order to generate flux constraints that can be applied into constraint-based models. The resulting reduction in the volume of the solution space can increase the accuracy of current simulation methods. The recent application of both kinds of models to gene regulatory and signaling networks shows that this gap will continue to have an impact in the integration of biological networks.

References

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Acknowledgments

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