

Metabolic Pathway Analysis in Studying Evolution of Metabolism and the Emergence of Network Properties

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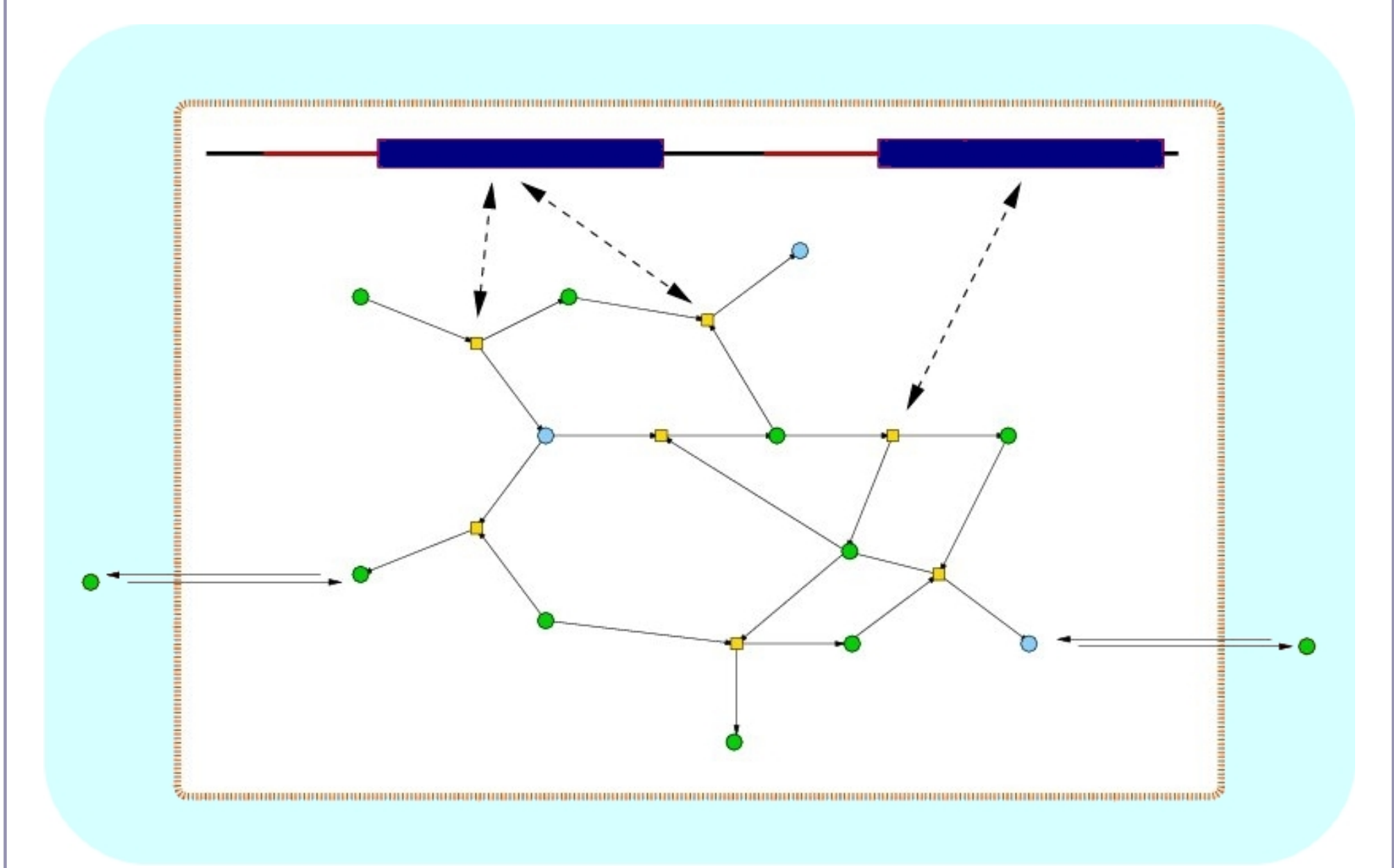


Introduction

The emergence and evolution of metabolism, its parts -metabolites and enzymes-, as well as its properties on the network level, is an intriguing and still open question. We introduce an improved metabolic pathway analysis tool for the application in a simulated evolution of metabolisms. During the evolutionary process the tool is used to define a realistic selection criteria -optimal metabolic yield- for the metabolisms, leading to networks with properties as observed in their real-world counterparts (e.g. small world property). Further it is used to analyze less well understood properties of the resulting networks, such as robustness or modularity, to make predictions about their origin and development. It can also be used as a stand-alone tool for the enumeration of elementary modes and the subsequent computation of minimal cut-sets, in a very memory efficient way.

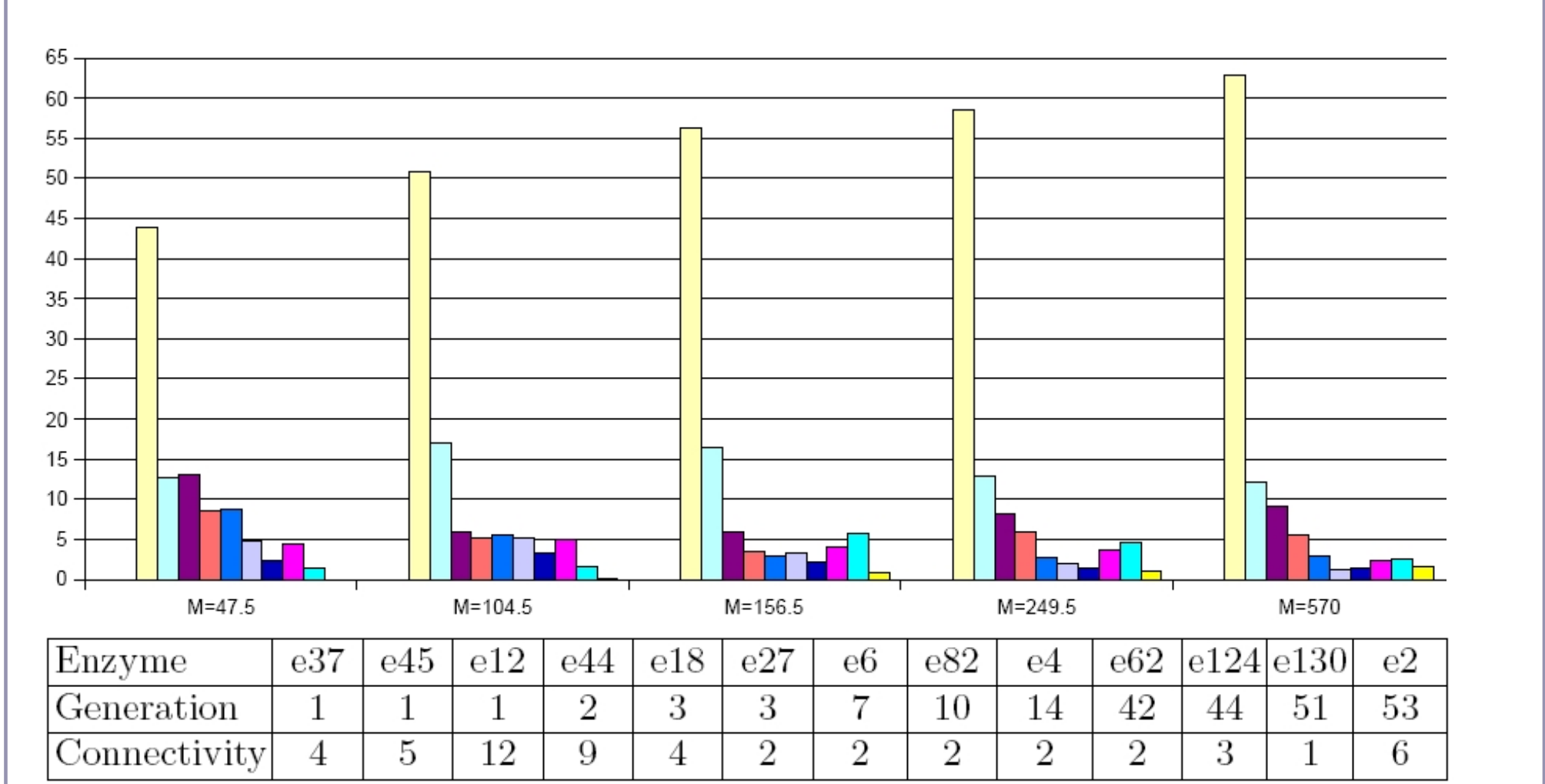
Simulation

Initially, a population of cells containing a genome and a metabolism are added to the simulation. Enzymes look for reactants, produce new metabolites and thus build up the metabolic reaction network.



Selection is based on the optimal metabolic yield of an individual, which is derived from metabolic pathway analysis.

Results (Simulation)



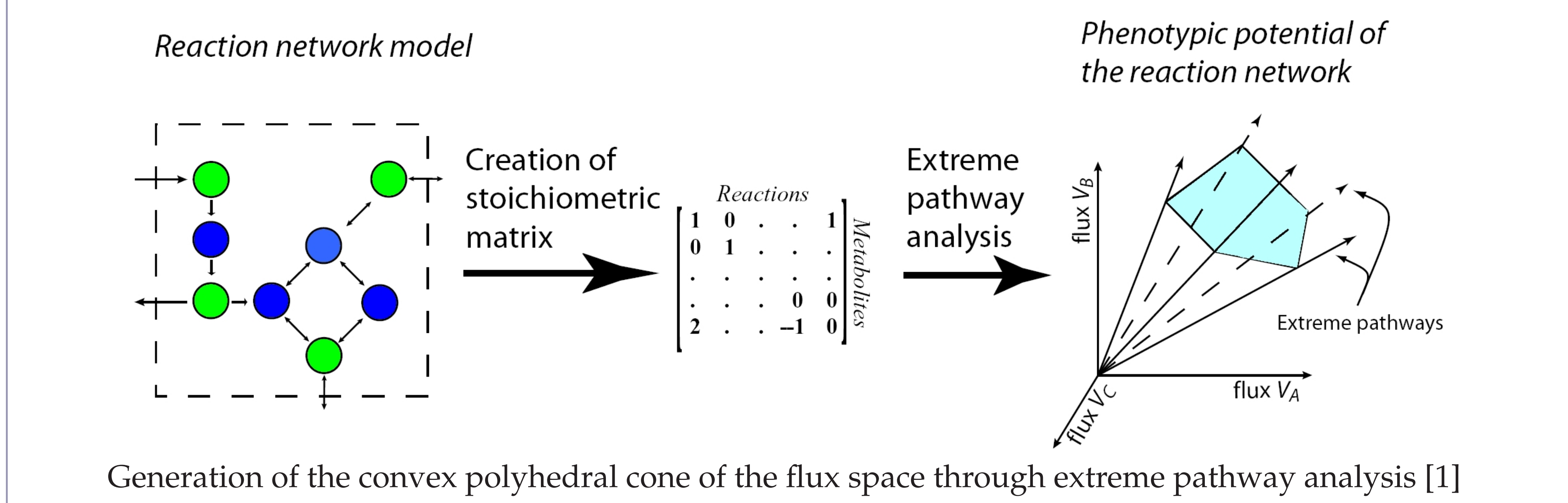
The histogram shows the distribution of metabolite-connectivities for groups of networks of different sizes. The connectivities in our networks follow the power law as is expected in real-world metabolisms. Looking at the connectivity and generation time of enzymes (table), we make the observation that highly connected enzymes occur in the first generations, later more specific enzymes enter, compliant with the biological expectation.

References

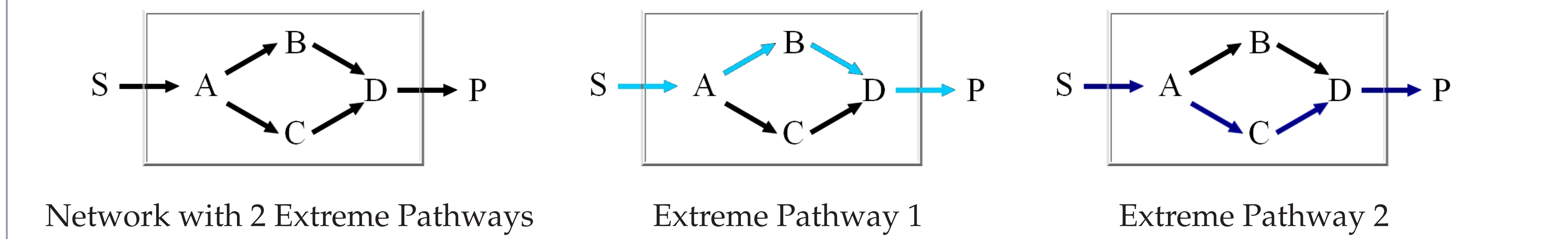
[1] B. O. Palsson Systems Biology: Properties of R. N.
[2] U. U. Haus, S. Lamt, T. Stephen. Computing Knock-Out Strategies in Metabolic Networks In *J Comp Biol* 2008
[3] T. Wilhelm, J. Behre, S. Schuster. Analysis of structural robustness of metabolic networks In *IEE PSB* 2004

Metabolic Pathway Analysis

Metabolic pathway analysis is the calculation and analysis of the pathway distribution of a steady-state metabolic network to gain insights about its structure, functionality and properties. The calculation starts with the formation of the stoichiometric matrix presentation of the network and delivers the extreme pathways, spanning the entire steady state flux space, as the final result.



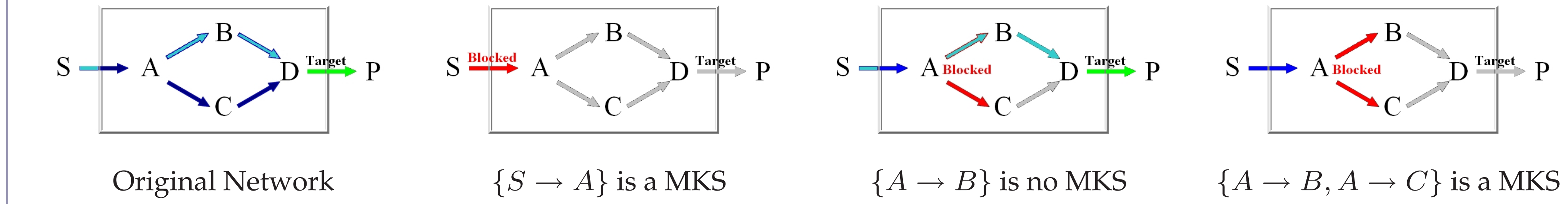
Extreme Pathways are the set of essential pathways through which all other possible pathways of the metabolic network can be generated, they are also minimal in the sense that they do not consist of smaller pathways.



We calculate the set of extreme pathways with an improved binary Null-space approach. The computation time of the existing approach is dependent on the row-ordering. We integrated a new way to order the rows to reduce the number of candidate pathways.

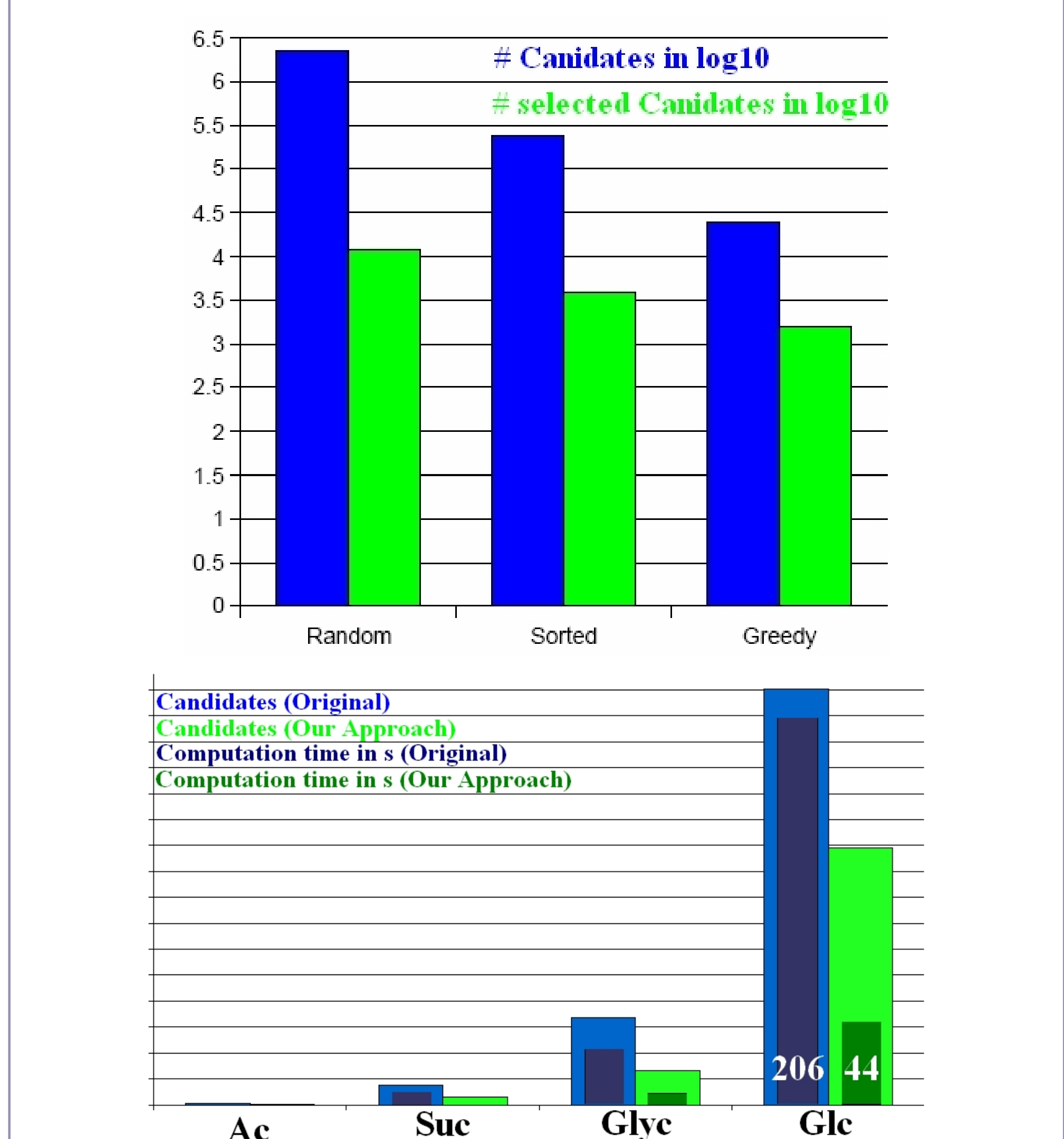
Minimal Knockout Sets

Minimal knockout sets are sets of reactions that need to be removed in order to disable the function of a certain target reaction, this means that there may not be any extreme pathway containing this target reaction.



For the computation of the minimum knockout sets we implemented an improved depth-first version of Berge's algorithm which avoids the costly superset removal.

Results (MPA + MKS)



Our new row-ordering produces an order of magnitude fewer candidates (left), thus is more memory efficient. The new MKS approach is faster than the original [2] and needs less memory due to its depth-first procedure.

Experiments (Robustness)

