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Extensions to Kinetic Flux Profiling to determine the distribution of fluxes in the central carbon metabolism of Arabidopsis thaliana

Determining the stationary and transient behaviors of metabolic networks is tightly coupled with quantitative descriptions of metabolic states, characterized by the distribution of reaction fluxes and metabolite concentrations. Despite recent progress in methods for estimating the flux distributions in a metabolic network based on ^{13}C labeled metabolomics data, the existing approaches ultimately rely on precise stoichiometry, atomic mappings, and availability of data for all metabolites participating the analyzed biochemical reactions. Kinetic Flux Profiling (KPF) is a recently proposed method for determining reaction fluxes based on the washout of the unlabeled fraction of a metabolite pool and is described mass-action-like differential equation model [1,2]. However, without substantial assumptions, KPF is applicable only to linear pathways.

Here we propose an extension of KPF based on simulated annealing that allows analysis of branched and circular pathways. Our approach does not rely on atomic maps, and can efficiently utilize the time-resolved distribution of isotopomers to determine the fluxes in an experimentally studied metabolic network. With the proposed approach, we quantify the flux distribution of the central carbon metabolism of Arabidopsis thaliana based on the time-resolved isotopomoer data over 60 minutes for 16 metabolites together with information about their subcellular localization. We investigate the robustness of the findings due to partial data inclusion with respect to both metabolites and different time scales. In addition, we demonstrate that our method together with the employed data can be used to discriminate between different models of the underlying metabolic network.

References

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