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Efficient reaction deletion algorithms for redesign of constraint-based metabolic networks for metabolite production with weak coupling

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概要：Metabolic engineering strategies enabling the production of specific target metabolites by host strains can be identified in silico through the use of metabolic network analysis such as flux balance analysis. This type of metabolic redesign is based on the computation of reactions that should be deleted from the original network representing the metabolism of the host strain to enable the production of the target metabolites while still ensuring its growth (the concept of growth coupling). In this context, it is important to develop algorithms that enable this growth-coupled reaction deletions identification for any metabolic network topologies and any potential target metabolites. A recent method that ensures the target metabolite production even when the cell growth is not maximized (strong coupling) has been shown to be able to identify such computational redesign for nearly all metabolites included in the genome-scale metabolic models of *Escherichia coli* and *Saccharomyces cerevisiae* when cultivated under aerobic conditions. However, this approach enables the computational redesign of *S. cerevisiae* for only 3.9% of all metabolites if under anaerobic conditions. Therefore, it is necessary to develop algorithms able to perform for various culture conditions. The author developed an algorithm, CubeProd, that could calculate the reaction deletions that achieve the coupling of growth and production under the condition that the cell growth is maximized (weak coupling) for 91.3% metabolites in genome-scale models of *S. cerevisiae* under anaerobic conditions. In CubeProd, the solution space was divided into small sub-spaces by the constraints on cell growth, target production, and the absolute sum of fluxes, and the reaction deletion strategies that achieve weak coupling were efficiently determined. While the weak coupling-based methods assume the cell growth maximization, the strong coupling-based methods do not assume it. Computational experiments showed that the proposed algorithm is efficient also for aerobic conditions and *E. coli*. The developed software, CubeProd, implemented in MATLAB, and the obtained reaction deletion strategies are freely available on https://sunflower.kuicr.kyoto-u.ac.jp/~tamura/software.

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