110e A General Hybrid Optimization Framework for the Optimal Modulation of Enzyme Levels Using Large-Scale Kinetic Models of Bacterial Metabolism

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The intrinsic complexity of cellular systems has necessitated the use of various modeling approaches to address specific problems of cellular organization and function. To this end, we have developed a general optimization framework to identify which enzyme level should be modulated up or down in response to overproduction requirements using large-scale mechanistic models of bacterial systems. The framework is demonstrated on a kinetic model of carbon metabolism of *Escherichia coli* for serine biosynthesis (Chassagnole et al. 2002). An efficient hybrid *deterministic/stochastic* solution strategy is devised to solve the resulting general mixed integer nonlinear problem (MINLP) problems. Specifically, a customized simulated annealing algorithm is used to identify which enzyme levels to change while gradient-based algorithms (i.e., SQP) are employed to identify the corresponding optimal enzyme levels. Computational results show that by optimally manipulating relatively *small* enzyme sets, a substantial increase in serine production can be achieved. For example, the modulation of only three enzymes results in a flux increase which matches approximately 50% of the best predictions obtained by manipulating all the thirty enzymes in the model. Importantly, by manipulating ten enzymes the organism's maximum overproduction capability is reached. To get quantitative insights into how successive small enzyme sets can be chosen, flux control coefficients (FCCs) (Kacser and Burns 1973) are calculated to compare FCC-based predictions with global optimization results. The proposed approach thus provides a versatile tool for the elucidation of controlling enzymes with implications in biotechnology.

References

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