

Maintaining optimal network functions in dynamic environments

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Microorganisms continuously face dynamics in their environment. Fitness depends to a large extent on their ability to give rise to adequate adaptation, involving altered gene expression profiles and protein activities. The accumulation of adaptive mutations in molecular network provides yet another set of perturbations that cells have to cope with. So in order to maintain high fitness, cells have to regulate themselves to keep some of their network functions robust while delicately changing others. I will present an approach to deal with the optimal regulation of metabolic networks despite changes in levels of external nutrients and intracellular regulators.

If a metabolic network is supposed to operate at an optimal state, say optimal flux, then it should be regulated upon an environmental change in such a way that it attains again an optimal state. This typically requires a (signalling and) gene network that senses changes from the optimal state and brings about a compensatory change in expression levels of metabolic enzymes. I will show that the structure of such an optimal-regulation gene network can be predicted from a kinetic model of the metabolic network alone. It turns out that a set of gene networks can achieve optimal steering of the same metabolic network model. The gene network that performs best can then be selected on the basis of additional objective functions, possibly including additional gene and metabolic network functions. Thus, gene networks that achieve optimal steering retain some level of flexibility: some parameter combinations of the gene network are fixed to achieve optimality (note that this approach works for any input-output relationship, *e.g.* not necessary optimal input-output) whereas others are free to changes within bounds.