

Title: Optimal control for long-term behavior of dynamic biological networks

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Abstract: Searching the optimal gene or enzyme manipulation *in silico* in a biological network in order to modify the long-term behavior of the network to achieve a desired state is an important problem. Because the search space for the optimal gene or enzyme manipulation problem increases exponentially with the size of a network, the *in vivo* experiment through try-and-error becomes so time-consuming as to be impractical. Therefore, a computational model is needed to approach the solution more efficiently. In the problem, biological networks include gene regulatory and metabolic networks in a cell. The long-term behavior of a modified biological network has to be either a stable steady state or a stable periodic orbit for maintaining cell homeostasis. The approach to the problem can be applied to, for instance, drug development to suppress the proliferation of tumor cells or cancer cells by manipulating its upstream genes.

Dynamical system models are often used to represent biological networks. An integer programming, based on dynamical systems, is formulated to define the optimal gene or enzyme manipulation problem. The integer programming is constructed with side effect constraints and an objective function which measures the long-term behavior of a dynamical system. The values of parameters of a dynamical system, which change as genes or enzymes are manipulated, are considered the decision variables. An effective and efficient algorithm is developed for the integer programming. The algorithm uses the continuation method in the bifurcation theory to evaluate the objective function and a branch-and-bound algorithm as the optimal strategy. The algorithm approaches an optimal solution to a cell cycle modeling problem which minimizes the concentration of maturation promoting factor of a cell cycle model, a protein to trigger the mechanism of a cycle, during cell growth by altering some parameters with zero. After applying the optimal solution to the model, the cycle is forced to exit as the concentration of maturation promoting factor is closed to zero during cell growth.