Module Decomposition and Integration Optimizes Gene Regulatory and Metabolic Networks

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1. Introduction

Major objectives of systems biology are to build molecular interaction networks and to predict or understand their dynamics at the molecular interaction level. Mathematical simulation plays an important role. A problem is how to determine the values of many kinetic parameters for mathematical models. An increase in the size of networks makes the optimization problems difficult. To circumvent these problems, we propose a novel evolutionary optimization method based on module decomposition and integration. A large-scale dynamic model is decomposed into functional modules. After optimizing each module, the modules are integrated together.

2. Method and Results

2.1 Ammonia Assimilation System

*E. coli* absolutely needs ammonia for synthesizing glutamine and glutamate. Glutamine and glutamate are synthesized through glutamine synthetase (GS), glutamate synthase, and glutamate dehydrogenase by adding ammonia to 2-ketoglutarate that is an intermediate of the TCA cycle. Among them GS plays a major role in the ammonia assimilation. The feedback loops are conventionally decomposed into two major loops for controlling the activity and synthesis of GS. The former module consists of UTase/UR, PII, GlnK, PI, and GS; the latter consists of UTase/UR, PII, GlnK, NRI, NRII, and GS.

2.2 Decomposition and Integration

By using CADLIVE, we built a dynamic model from the ammonia assimilation network [1,2]. To estimate kinetic parameter values by genetic algorithms (GAs) efficiently, the ammonia assimilation system is decomposed into two functional modules of "GS activity-controlling module" and "GS synthesis-controlling module". The fitness function is defined by using the N/C ratio, which indicates the ratio of the glutamine concentration to the 2-ketoglutarate one. An appropriate value of the N/C ratio is the target for optimization. First, each module is optimized separately by using GAs. In the first step, it is not necessary to explore the exact parameter solution showing a high fitness value. In the second step, these modules are integrated to optimize the full model. It is necessary to provide initial values to the kinetic parameters common to both the modules. Here, the initial values of those parameters were provided by (1) the arithmetic average values for the activity-controlling and synthesis-controlling modules, (2) the geometrical average values for the activity-controlling and synthesis-controlling modules, (3) the values of the activity-controlling module, (4) the values for the synthesis-controlling module. As a reference (5), we consider the case where the entire system is optimized without decomposing into the modules.

2.4 Decomposition and integration

After the decomposed modules were optimized separately, merging multiple parameter solutions from each module creates various initial populations for GAs. The overlapped parameters of both the modules are merged by four methods of (1-4). A high fitness value was obtained for (1), (2) and (4). In particular, the (4) method showed the best transition of the fitness with respect to generations. In (3), the transition of the fitness was not increased, indicating that the search of the integrated modules failed. It suggests that GS
synthesis-controlling module plays a major role in the full model. Since the GS synthesis-controlling module contains a positive feedback loop, the fitness value is very sensitive to changes in kinetic parameters. In the (5), the search range of a parameter was too wide to optimize the full model. The module decomposition is necessary for optimization of the ammonia assimilation system.

2.5 Variety of solution of ammonia assimilation system

In this method, it is important to search all possible parameter solutions that satisfy the specific N/C ratio. The number of search parameters is large compared with the objective function (fitness). We expect various parameter solutions to be obtained, if our method performs a global search. To check it, we picked four sets from final solutions of the full system and showed the parameter spectra in Fig. 1. Unexpectedly, the parameter spectra are relatively similar. Here, we discuss the reason why we cannot get a broad spectrum of parameters. One of the reasons is that parameter sensitivity of the GS synthesis-controlling module is very high. When the changes in some parameters of it are large, the fitness value rapidly decreases. We locally searched the space around the initial population derived for the GS synthesis-controlling module. On the other hand, variation was seen in parameter solutions of the GS activity-controlling module, but such variations were not seen in the final solution. The initial populations of the optimized GS synthesis-controlling module may govern our search. The important thing is to find multiple parameter solutions so that the subsequent search can explore a global parameter space. In the next step, it is necessary to expand the search range of the GS synthesis-controlling module and to obtain various parameter solutions.

3. Discussion

We understand that the variation in the initial populations derived from each module is critical for exploring multiple solutions in a global parameter space. A benchmark function was designed to verify our idea as follows:

$$F=\sum_{i=1}^{n}(x_i - x_{ref})^2, \ 0 < x_i < 1.$$  

The full model with $n = 3$ is decomposed into two modules: One is built from $i = 1, 2$, and the other is from $i = 2, 3$. The variable of $x_2$ is the parameter common to both modules. Multiple modules with various parameter solutions were integrated to optimize the full model. By preparing various initial populations, multiple solutions were obtained. Decomposing a dynamic model into functional modules is effective for fast optimization. Next, we will apply this improved method to the full model of the ammonia assimilation system.

References
