

Project Title:

Evolutionary parameter optimization of a circadian oscillator

Name :Craig Jolley

Affiliation :Center Director's Strategic Program Laboratory for Systems Biology,
RIKEN Center for Developmental Biology (CDB),Kobe Institute

At its most basic level, the mammalian circadian clock comprises a complex network of clock genes which are connected by interlocking positive and negative feedback loops. The literature contains several examples of highly detailed mathematical models of the clock, but recent experimental results obtained in our laboratory suggest that these theoretical treatments omit several features that are essential to realistically describe the function of the clock network.

Over the last several months, we have been developing a simplified model of the mammalian circadian clock consisting of two activators and three repressors that we feel captures the most essential features of the complete clock system. One intrinsic difficulty with mathematical models in biology, however, is the determination of the correct parameters for the reaction rate constants and binding affinities.

We have developed an evolutionary algorithm for the estimation of model parameters. Evolutionary algorithms begin with a population of solutions and a fitness function that quantifies their agreement with the experimental data. At each step in the refinement process, members of this population are randomly "bred" in a manner that leads to "offspring" that inherit parameter values from either parent; these offspring are then added to the population and only the fittest members are retained for the next iteration.

The computing power provided by RICC was essential in evaluating the performance of our evolutionary algorithm. We found that the ability of the algorithm to correctly fit the experimental data was strongly dependent on the precise fitness function used, and that our fitness function did not weight the different contributions to the fit optimally.

As a result, we've taken some time to step back and re-evaluate our approach. This has led to substantial improvements in the speed and accuracy of our calculations that will allow us to use computing resources more efficiently in the future. At the moment, it is not entirely clear whether an evolutionary

optimization approach will be the best way to move forward with this project. Our current plan is to try fitting our improved model with more conventional optimization approaches (Powell, quasi-Newton, simulated annealing, etc.) and return to the evolutionary approach only if these prove to be unsatisfactory.

We hope to complete the parameter estimation phase of this project sometime in the spring of 2012. In the event that we decide to return to the evolutionary approach and high-performance computing facilities become necessary for this project, we will submit a Quick Use application at that time.