# The Search for Robust Topologies of Oscillatory Gene Regulatory Networks by Evolutionary Computation


Kazuki Komiya
Dept. of Electrical Engineering and Information Systems,
Graduate School of Engineering,
University of Tokyo, Japan.
komiya@iba.t.u-tokyo.ac.jp

Nasimul Noman
Dept. of Information and Communication Engineering,
Graduate School of Information Science and Technology,
University of Tokyo, Japan.
noman@iba.t.u-tokyo.ac.jp

Hitoshi Iba
Dept. of Information and Communication Engineering,
Graduate School of Information Science and Technology,
University of Tokyo, Japan.
iba@iba.t.u-tokyo.ac.jp



## ABSTRACT

Synthetic biology has yielded many successful basic modules inspired by electronic devices over the last ten years. However, there has been very limited success in designing higher order modules by assembling these simpler devices. The lack of robustness in these devices, fails them to work as successful parts in larger system in general. In this paper, we propose a evolutionary search method to construct a robust topology of gene regulatory network in which the concentrations of genes oscillate like a repressilator. This kind of oscillating network works as a “clock” in the biological system and has been in the center of attraction for long. However, the issue of robustness of the designed network remained less attended. Our genetic algorithm evolves oscillating gene regulatory network with a topology superior to other existing topologies in terms of robustness.



## Categories and Subject Descriptors

J.3 [**Life and Medical Sciences**]: Biology and Genetics; I.2.8 [**Problem Solving, Control Methods, and Search**]: Heuristic methods

## General Terms

Design, Algorithms

## Keywords

Synthetic Biology, Robustness, Genetic Algorithm, Repressilator


## 1. INTRODUCTION

The ultimate goal of synthetic biology is the rational construction of biological systems based on engineering principles. Towards this goal, this emerging field has produced many lower level modules such as bistable switch [3], oscillator [2], logic gates [1] and so on. Although these relatively simple and basic modules have been successfully designed, unpredictable side-effects have been experienced while implementing higher order modules by assembling them [4].Consequently, the designer has to go through the painful trial-and-error modifications, mutating the constituents modules, until he finds the appropriate one.

One of the primary reasons behind the collapse of these modules to acts as constituent parts is that these devices exhibit their intended behavior in precise environmental condition. Because of the lack of their robustness, these lower order devices fail to act interoperably in the design of higher level modules. Therefore, the design of robust modules, capable of working independent of their surrounding environment, is utmost important. Towards this goal, this work propose to use genetic algorithm (GA) to evolve robust topology of gene regulatory networks (GRN). As the target behavior of the network we use the oscillating dynamics because of the existence of many synthetic oscillatory circuits [2, 6].

## 2. METHOD

In this work, we used one of the ODE based models called Artificial Gene Network (AGN) [5] to represent and simulate GRNs. The general structure of the mathematical formulation of AGN is given by

$$\begin{aligned}
\frac{dG_i}{dt} &= s(G_1, K, G_n) - b(G_i) \\
s_i(G_1, K, G_n) &= V_i \cdot \prod_j \left( \frac{Ki_j^{n_j}}{I_j^{n_j} + Ki_j^{n_j}} \right) \\
&\quad \cdot \prod_k \left( 1 + \frac{A_k^{n_k}}{A_k^{n_k} + Ka_k^{n_k}} \right) \\
b_i(G_i) &= U_i \cdot G_i
\end{aligned}$$

where $G_i$ represents the mRNA of gene $i$, $A_k$ and $I_j$ represent activators and inhibitors respectively, $V_i$ is the basal rate of transcription. The constants $Ki_j$ and $Ka_k$ represent concentrations at which the effect of the inhibitor or activator is half of its saturating value and $n_j$ and $n_k$ regulate the sigmoidicity of the curve. The number of activators ($k$) and inhibitors ($j$) depend on the topology of the network.

Our aim is to search for GRN topology that can exhibit oscillation in different environmental condition. Therefore, instead of targeting any particular oscillating behavior, under a specific parameter setting, we aim to achieve oscillation under different parameter settings. We select some predefined points in the parameter space and examine a particular


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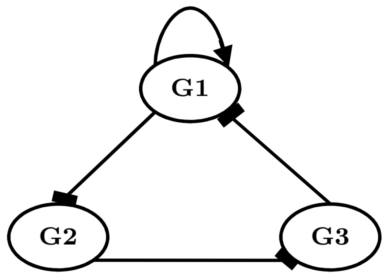


**Figure 1: The evolved network**

GRN topology in each of these points for oscillation. The more points a GRN topology oscillates in, the more robust the topology is. We also penalize a GRN topology based on the number of interactions in order to achieve a sparse architecture. Integrating these two criteria we designed the following fitness function for evaluating the robustness of a GRN topology.

$$fitness = \frac{(\#\ of\ parameters\ where\ GRN\ oscillates)}{(\#\ of\ parameters)} - w\frac{(\#\ of\ connections\ in\ GRN)}{(\#\ of\ mRNA)^2}$$

where $w$ is weight factor of the penalty term. In our experiments, we set $w = 0.01$ when GRN oscillates with at least one of the predefined parameters, $w = 0.0$ when GRN doesn't oscillate at all. By changing the weight factor in this way we prevent that models with lower connections get undesirable high fitness.

In order to search the oscillating GRN, we used a Genetic Algorithm (GA) because of their robust and reliable performance in complex problems. Our GA searches for the robust topology of GRN starting from a random population of individuals. We encode the topology of a GRN as directed graph using relational matrix. Each individual of GA represents a GRN model characterizing the type of relation among the genes using a trinary matrix (+1: activation, –1: inhibition, 0: no-interaction). After random initialization the individuals are evaluated using the fitness function explained earlier. Based on their fitness, some individuals are selected for reproduction using tournament selection. The next generation of individuals are created using two-point crossover and mutation operation from the selected parent individuals. Our GA also implements the elitist strategy and introduces some random individual in every new generation. This process of selection, reproduction and replacement is iterated generation after generation until the termination criteria is satisfied.

# 3. EXPERIMENTAL RESULT

In our experiment we kept the AGN parameters $K_i = 1.0$, $K_a = 1.0$, $n_k = 1.5$ and $n_j = 1.5$ fixed and varied only $V_i$ and $U_i$ within [0.001, 10.0]. We chose 25 different points on the search space of $\{V_i, U_i\}$ and evaluated each GRN topology at these points to calculate their fitness (robustness). Our GA was run for 100 generations with a population size of 50. We performed our evolutionary search with a fixed number of genes (seven).

**Table 1: Comparison of the robustness of GRN topologies**

| Topology | # of Parameters | Successes | Trials | Successes/Trials |
|---|---|---|---|---|
| Elowitz | 12 | 100 | 6743 | 0.0148 |
| Striker | 18 | 24 | 10000 | 0.0024 |
| **Evolved** | 14 | 100 | 4524 | 0.0221 |

The GRN topology showed in Figure 1 is one of the representative structures that the GA evolved. The figure does not show those nodes which have no connection with others. This network topology was successful in generating excellent oscillating response. The structure was very similar to the original design by Elowitz *et al.* [2] but with an additional self activation arc at G1.

We contrasted the evolved topology with the original repressilator designed by Elowitzh *et al.* [2] and the robust tunable oscillator designed by Striker *et al.* [6]. In order to compare their robustness we represented these topologies with AGN model and simulated them using random parameters to see whether they oscillate with that parameter sets. We repeated the random sampling until the number of success reached to 100 or the number of trial reached to 10000. The calculated robustness of the GRN topologies are compared in Table 1. These results show that the evolved topology has much higher probability of oscillation and is about 10 times robust compared to the existing ones.

# 4. CONCLUSION

In this work we showed that a simple genetic algorithm was successful to evolve a network structure which is very robust in generating oscillatory dynamics in presence of environmental perturbation. The robustness of the network was measured based on the number of different parameter sets in which they can exhibit oscillation. Comparing the evolved network topology with the existing oscillators' topologies, it was found more robust.

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