Evolving genetic regulatory networks

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***Short Abstract* — To understand how living organisms work it is necessary to analyse their genetic regulatory networks (GRNs). Because of the complexity of GRNs, modeling and simulation techniques are used to aid our understanding, but the application of these techniques is hampered by lack of qualitative and quantitaive data. Therefore, we apply evolutionary algorithms to evolve artificial GRNs with prespecified dynamics, with the aim of studying the relationship between GRN structure and function.**

***Keywords* — GRNs, evolutionary algorithm, selection, mutation, modeling, simulation.**

I. Purpose

GENETIC regulatory networks (GRNs), which describe the regulation of gene expression by gene products, and are ultimately responsible for development of single cells into complex organisms. Most GRNs are large and complex, and it is necessary to use modeling and simulation to gauge their dynamics and to gain additional insights (overview in [1]). However, the available information on GRNs found in living cells is generally far from complete, and the predictive power of GRN models based on this information is restricted. Therefore, we have developed a method for creating artificial GRNs (aGRNs) that exhibit a required functionality. Our aim is to analyse and compare the dynamics of these aGRNs, and – if possible - extract general principles on structure-function relations in GRNs.

II. Methods

To evolve aGRNs, we use an evolutionary algorithms (EAs) [2]. EAs are appropriate to find 'good' (not necessarily the 'best') solutions to problems with a large search space. They use populations of individuals ('genomes'), in which each individual represents one potential solution within the search space, and is assigned a fitness value that measures its quality. The population is changed over several generations by keeping only the best individuals (selection), and creating new ones using randomized processes such as mutation and recombination (cross-over).

Our EA [3] uses binary genomes consisting of a fixed number of 'genes', each with a several regulatory regions, and one region that specifies the 'gene product' ('proteins'). In the associated network model, genes and proteins are represented as nodes; their interaction as edges. Gene 'transcription and translation' results in an increase in the level of its protein product, and is regulated by the current level of other proteins that can interact with its regulatory region. Protein-gene interactions may be activatory or inhibitory, and their effect may be additive or multiplicative. The response of one or more 'output genes' is compared with a target response, and their likeness determines the fitness of the genome.

Network evolution starts off with a first generation of randomly generated genomes. Once the response of each individual genome has been tested and assessed, the best-performing, as well as some randomly chosen less well performing ones are subjected to mutation and crossover operations to create a new generation of networks.

A mutation in a gene product region results in the production of a different protein; mutations and crossover in regulatory regions result in changes in the way the protein levels are regulated by other proteins. Moreover, mutations may also affect certain parameters, such as rate constants.

This approach is somewhat similar to that used by Deckard et al. [4] and Paladugu et al. [5], who use random graphs to evolve 'metabolic' networks that produce basic mathematical functions, or show bistability or oscillatory behaviour.

III. Results and Conclusion

Knabe et al. [3] have already successfully evolved aGRNs whose response to an incoming oscillating signal is similar to that of a biological circadian clock. These networks, which consist of fewer than 10 genes, are capable of differentiation [6], and we are trying to develop methods that identify common elements in networks that exhibit similar behaviour.

We are currently focusing on the development of a user-friendly integrated environment, named NetBuilder' [7], which can be used to model and evolve aGRNs, draw the associated networks (according to the Petri-net formalism), simulate their behaviour and plot the results, and (in the future) subject the structure and dynamics of the evolved networks to various analyses.

With this evolutionary approach we hope to be able to generate networks that are more realistic than the Boolean networks analysed by Kaufman [8] to provide more insights in the requirements for robustness, distinct steady states, and other basic network properties.

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