

Title: Toward Automated Selection of Parts for Genetic Regulatory Networks

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Work sponsored by DARPA I20 under contract HR0011-10-C-0168; the views and conclusions contained in this document are those of the authors and not DARPA or the U.S. Government.

Design automation is an important enabling technology for synthetic biological systems. Encoding design expertise in software will make engineering more complex systems tractable, increase the accessibility of synthetic biology to new practitioners, and increase system reliability by reducing the number of undetected design errors.

A top-down design approach will let practitioners design organisms using higher level descriptions. These descriptions will be mapped to a composition of primitive motifs, producing an "abstract" genetic regulatory network: one which defines relationships between parts, but leaves the actual identities of those parts unspecified. To realize this network, one must solve the part selection problem: mapping abstract features to a collection of particular standardized biological parts that preserve the relationships between features prescribed by the network. Prior work has demonstrated the design of abstract GRNs from high level programs (Beal, et al., 2010) and automated assembly of DNA sequences from standardized biological parts such as BioBricks (Densmore et al., 2010). But, a critical gap exists in the actual selection of particular biological parts to implement the design.

Our solution is a two-level approach to the part matching problem: finding topological and quantitative solutions. The topological solution focuses on finding compatible parts that have the same regulatory relationship as defined in the abstract GRN. The quantitative solution focuses on choice of specific parts within the family such that the chemical concentration levels are compatible with each other to ensure a robust system.

We have formulated the topological solution as a special case of the subgraph isomorphism problem, which is known to be NP-complete (Garey and Johnson, 1979). In this formulation, we are given parts grouped into families and relationships between families. For example, it is given that variants of the TetR regulatory protein form a family, and this family has a repression relationship with the family of pTet

promoter variants. A topological solution assigns each element of a GRN to a family compatible with these relationships and with non-interference requirements, using search algorithms and heuristics.

In the quantitative solution, we pick particular parts from each family. We use a Hill equation model of chemical dynamics to represent the I/O relationship between each promoter and its regulators. Using these models, we predict the noise margins and interoperability range of each regulatory interaction, using a generalized version of electronic digital noise rejection via the static discipline. Parts are chosen subject to two constraints: obedience to the generalized static discipline in their interactions with adjacent parts, and heuristically to maximize the minimum noise margin over all interactions in the system.

Using the Hill equation models and a differential equation simulation in MATLAB, we have verified that systems constructed of parts with chemical dynamics obeying these constraints do produce overall system behavior in accordance with the higher level design. Preliminary results indicate that, with an appropriate choice of heuristics, this approach to part selection is likely to be computationally tractable for a large family of parts and designs.