Quantifying evolvability in small biological networks

Andrew Mugler[1], Etay Ziv[2], Ilya Nemenman[3], and Chris H. Wiggins[4]

***Short Abstract* — We introduce a quantitative measure of the capacity of a small biological network to evolve. We apply our measure to the stochastic description of the experimental setup of Guet [1], treating chemical inducers as functional inputs and the expression of a reporter gene as the functional output. We take an information-theoretic approach, allowing the system to set parameters that optimize signal processing ability, thus enumerating each network's highest-fidelity functions. We find that, while all networks studied are highly evolvable by our measure—meaning that change in function has little dependence on change in parameters—evolvability is nonetheless correlated with certain topological features.**

***Keywords* — evolvability, linear noise approximation, systems biology, nonparametric statistics, synthetic biology.**

I. Purpose

A driving question in systems biology in recent years has been the extent to which the topology of a biological network constrains or guides its function. Several recent analyses have argued that a network can perform multiple functions via changes in its biochemical parameters, even when its topology is held fixed [2-4]. Conceptually, a more evolvable network is able to access a higher variety of its functions with only minimal changes in its parameters. We introduce a measure of evolvability that quantifies this concept, and we compare this measure across a set of network topologies.

II. Model and methods

Following the experimental setup of Guet et al. [1], we model a set of small transcriptional regulatory networks in which each gene is regulated by only one transcription factor. The efficacy of these transcription factors is itself influenced by small molecules (e.g. aTc and IPTG in the experiment), whose presence or absence defines the input states to the network, while the steady-state concentration of a particular "reporter" gene defines the output.

The dynamics are specified by standard Hill kinetics, with the additional feature that the effective abundance of the transcription factor is mollified by a scaling factor when the associated small molecule is present. The resulting deterministic dynamical system yields fixed points that determine probability distributions (centered at these fixed points) by employing the linear noise approximation (as is well-studied in the systems biology literature [5]). The set of distributions corresponding to each input state constitutes the function performed by the network at a particular setting of the system parameters.

We numerically find local optima (with respect to parameters) of the mutual information between input and output, thus identifying points in parameter space that yield the highest-fidelity functions. From the set of pair-wise parameter distances and corresponding function "distances" between all points, we define a measure of evolvability. Our measure is nonparametric and thus invariant to monotonic changes the definitions of parameter and function distance.

III. Findings

We find that all networks studied are highly evolvable. Specifically, all networks share the somewhat unintuitive feature that functional change has little dependence on distance traveled in parameter space.

Even within this regime of high evolvability, however, the ranking of networks by their evolvability scores is robust to sampling error, meaning that networks significantly differ from each other in their capacity to evolve. Furthermore, statistically significant correlations emerge between networks' evolvability and certain topological features. These correlations, and their robustness to the free parameters in the analysis, will be discussed.

References

[1] Guet CC, Elowitz MB, Hsing W, Leibler S (2002) Combinatorial synthesis of genetic networks. *Science* **296**, 1466-1470.

[2] Wall ME, Dunlop MJ, Hlavecek WS (2005) Multiple functions of a feed-forward loop gene circuit. *Mol Biol* **349**, 501-514.

[3] Ziv E, Nemenman I, Wiggins CH (2007) Optimal signal processing in small stochastic biochemical networks. *PLoS One* **2**, e1077.

[4] Voigt CA, Wolf DM, Arkin AP (2005) The *Bacillus subtilis sin* operon: an evolvable network motif. *Genetics* **169**, 1187-1202.

[5] Kaufman BB, van Oudenaarden A (2007) Stochastic gene expression: from single molecules to the proteome. *Curr Opin Genet Dev* **17**, 107-112.

Acknowledgements: This work was funded by NSF grant ECS-0425850. IN was supported by the LANL/LDRD program.

[1] Department of Physics, Columbia University. E-mail: ajm2121@columbia.edu.

[2] College of Physicians and Surgeons, Columbia University

[3]Computer, Computational, and Statistical Sciences Division, Center for Nonlinear Studies, Los Alamos National Laboratory

[4]Department of Applied Physics and Applied Mathematics, Center for Computational Biology and Bioinformatics, Columbia University.