Automatic design of functional genetic networks

Javier Carrera[1], Guillermo Rodrigo[1] and Alfonso Jaramillo[2,*]

[1] Universidad Politecnica de Valencia, Camino de Vera s/n, 46022 Valencia, Spain

[2] Ecole Polytechnique, Route de Saclay, 91128 Palaiseau, France

[*] alfonso.jaramillo@polytechnique.edu: contact author email address

Biological systems are composed of protein networks with unknown functions that are difficult to unveil by reverse-engineering. On the other hand, the use of forward-engineering techniques allows to generate new networks with targeted behaviors that are useful to understand the design principles underlying complex networks [1]. Genetic circuits sharing the same topology could behave very differently depending on their kinetic parameters [2]. Furthermore, the addition of new interactions could change the circuit dynamics in unexpected ways. Using an automated evolutionary design procedure, based on combinatorial optimization [3], we explore the degree of complexity that can be obtained using a restricted set of transcription factors. We have designed genetic circuits having a prescribed time-response and a degree of robustness under stochastic perturbations. Thus, we explore the space of all possible transcriptional regulation networks to find the optimal circuit with specified behavior [4]. We apply our methodology to the design of transcriptional networks having desired Boolean logic functions or oscillatory behavior (see Fig. 1). This allows us to study the evolution of genetic networks, where we propose a scenario for their evolution based on a selection for dynamical function [5]. In addition, we discuss the decomposability of regulatory networks in terms of genetic devices, and the evolution mechanism of circadian clocks [6].

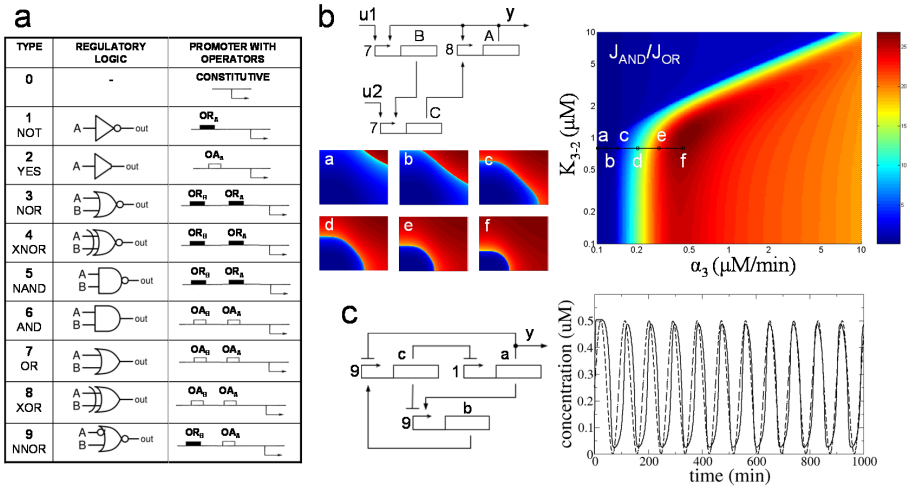

Figure 1: (a) List of promoters considered in our study. (b) Design of a functional circuit with logical behavior OR. However, this circuit can behave as AND too depending on its parameters. On bottom, contour plots showing the evolution from an AND to an OR behavior. We plot the output y versus the concentration of the two inputs ($u1$ and $u2$) for different values of the transcription-translation rate of gene C (α_3): a) $0.10\mu M/min$, b) $0.12\mu M/min$, c) $0.15\mu M/min$, d) $0.20\mu M/min$, e) $0.30\mu M/min$, and f) $0.45\mu M/min$, keeping the repression coefficient of $u2$ (K_{3-2}) $= 0.80\mu M$. On the left, representation of J_{AND}/J_{OR} (where J_D is the score of the device D) versus α_3 and K_{3-2}. (c) Oscillatory circuit and its dynamics. The solid line shows the network dynamics, whereas the dashed line shows the targeted behavior. We only evaluated the score in the regions around the maxima and minima.

References

[1] Hasty, J., McMillen, D., and Collins, J. J. (2002) *Nature*, **420**, 224-230.

[2] Guet, C. C., Elowitz, M. B., Hsing, W., and Leibler, S. (2002) *Science*, **296**, 1466-1470.

[3] Kirkpatrick, S., Gelatt, C. D., and Vecchi, M. P. (1983) *Science*, **220**, 671-680.

[4] Francois, P. and Hakim, V. (2004) *Proc. Natl. Acad. Sci. USA*, **101**, 580-585.

[5] Dekel, E. and Alon, U. (2005) *Nature*, **436**, 588-592.

[6] Dunlap, J. C. (1999) *Cell*, **96**, 271-290.