Promiscuity of function, changing environments, and molecular evolution

Pablo Catalán[1,2], Susanna Manrubia[1,3], and José A. Cuesta[1,2,4,5]
[1]Grupo Interdisciplinar de Sistemas Complejos (GISC)
[2]Departamento de Matemáticas, Univesidad Carlos III de Madrid
[3]Centro Nacional de Biotecnología (CNB-CSIC), Cantoblanco, Madrid
[4]Instituto de Biocomputación y Física de Sistemas Complejos (BIFI), Universidad de Zaragoza
[5]UC3M-BS Institute of Financial Big Data (IFiBiD), Universidad Carlos III de Madrid

Enzymes used to be known for their great specificity. It has thus come as a surprise to find out that they perform regulatory or metabolic tasks other than their main function. The finding is so widespread that is has been termed *molecular promiscuity*. Evolution is known to make use of any available resource —in particular for reusing existing elements. However, the evolutionary consequences of this promiscuity are not yet fully understood.

Biomolecules that perform tasks in the cell (proteins, ribozymes…) are characterised by a *genotype* (the sequence of aminoacid or bases) and a *phenotype* (the function they perform). Promiscuity amounts to exhibiting several phenotypes for a given genotype. This genetic plasticity turns out to be very useful when environmental changes ensue, for a molecule may be well adapted to the new environment without having to undergo any mutation. Further mutations may improve the new function that the molecule performs in this new environment.

However, the effect of rapidly changing environments is unclear. On the one hand, if changes are sporadic, molecules have enough time to transform the promiscuous function into a well adapted one by successive mutations. On the other hand, if changes are fast, molecules adopt promiscuous genotypes rejecting mutations by purifying selection, thus being adapted to all environements simultaneously. In both cases molecules thrive. What is unclear is what happens between these two limits.

In order to provide an answer to this issue we have made up a model in which a population of molecules "moves" across two fitness landscapes through point mutations. The two landscapes are negatively correlated (a genotype that has a high fitness in one landscape tends to have a low fitness in the other and viceversa), and each generation there is a probability p that the current landscape is replaced by the other one. If $p = 1$ changes occur every generation. In the limit $p \to 0$ environments hardly change. These are the two limits described above. Figure 1**a** illustrates these landscapes.

We performed 500 realisations of this evolutionary process for a set of values of p and compute the average lifetime of the population until it becomes extinct. Figure 1**b** plots this average lifetime as a function of p. The most remarkable feature of this plot is the fact that lifetimes are shorter for intermediate values of p than for the two limiting cases described above.

The explanation of this effect goes as follows. As p decreases from 1 the population has more time to spread among neighbouring (in mutational terms) genotypes before an environmental change occurs, so that when this eventually happens many individuals suddenly become unfit. This severely hinders the growth of the population. As p decreases even more, two effects start competing: on the one hand the wider spread of the population puts it at a higher risk upon an environmental change; on the other hand, since environmental changes are more rare it also has more time to recover, thus improving its chances of surviving.

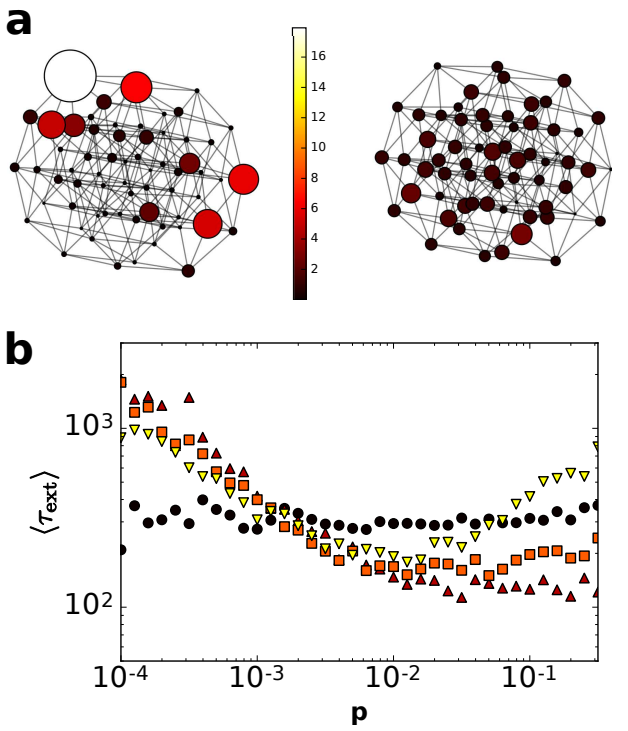

Figure 1: **a.** Experimental landscapes of Ref. [1]. Size and colour of the nodes represent fitness. Edges join genotypes one point mutation away. **b.** Average lifetimes for the simulations of our population model on these two landscapes as a function of p, the probability of an evironmental change, for mutation rates: $\mu = 0.5$ (black circles), 0.1 (red triangles), 0.05 (orange squares) and 0.01 (yellow triangles).

This finding may have important consequences in health care. It is well known that bacteria are steadily becoming resistant to antibiotics, to the extent that we are exhausting our resources to fight them. If every antibiotic is interpreted as a different environment for the bacteria, our results suggest that a wise strategy against bacterial infections would be to alternate between two or more antibiotics with a suitable frequency. Recent experimental studies show that sequential therapy can be highly effective in controlling bacterial populations [2].

[1] De Vos, M. G., Dawid, A., Sunderlikova, V., & Tans, S. J. PNAS **112**, 14906-14911 (2015).

[2] Fuentes-Hernandez, A., Plucain, J., Gori, F., Pena-Miller, R., Reding, C., Jansen, G., Schulenburg, H., Gudelj, I. and Beardmore, R. PLoS Biol, **13**, e1002104 (2015).