Gene regulation in natural systems is optimized for specific dynamic regimens

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***Short Abstract*—When an antibiotic resistance mechanism is mobilized to a new host living under different environmental conditions, its regulation needs to evolve from a configuration optimized for the old environment to a new one. Predicting changes in the regulation of drug responses during adaptation to new ecological challenges remains challenging. We modeled the molecular-level interactions involved in antibiotic responses with a dynamical systems approach and determined the optimized regulatory architectures that emerged in response to specific selective pressures through *in silico* evolution. We were able to predict shifts in the regulation of antibiotic resistance that optimize the response to new environmental conditions.**

***Key Words* — antibiotic responses, *in silico* evolution, gene regulation.**

DYNAMICS OF DRUG RESPONSES ARE CRUCIAL FOR CELL SURVIVAL

Most antibiotic compounds and their respective resistance mechanisms evolved in the soil. However, recent use of clinical antibiotics has transported this bacterial arms race to clinical environments, where cells are thought to be exposed more rapidly to much higher drug concentrations than in the soil, posing a significantly stronger selective pressure [1].

Most resistance mechanisms have evolved regulation that repress gene expression in the absence of drug to mitigate the fitness burden of expressing resistance when drug is absent. When facing abrupt increases in drug concentration, the cell needs to induce the responses efficiently to ensure optimal levels of expression are reached, at the risk of compromising the survival of the cell. Therefore, regulation of drug responses is optimized for the specific dynamics of the cell's environment, and the short-term evolution of cell responses happens primarily through mutations in regulatory pathways [2, 3]. Although much is known about the dynamics of cell responses, we still lack a quantitative understanding of how different regulatory strategies evolved in natural systems for specific dynamical regimens.

IN SILICO EVOLUTION OF DRUG RESPONSES

We model the dynamics of drug responses focusing on the tetracycline resistance *tet* operon, a well-characterized classical example of drug-induced resistance mechanisms. We use differential equations to describe the relevant biochemical interactions involved in the response and translate the selective pressures of the environment into a set of costs associated with key concentrations of the molecular components during the response (initial, maximum, and final). We then simulate the system for different regulatory architectures upon sudden drug exposure, with increasing drug concentrations. We use an iterative procedure to optimize a set of parameters set of parameters describing the regulation of the response (binding affinities of promoters and repressor binding sites) according to the cost function. By comparing the optimal cost for each configuration, we determine the disposition of regulatory elements that optimized regulation in each specific dynamical environment.

Trade-off between strength of repression and speed of response. Constitutive expression of high levels of the response repressor ensures very low levels of expression of resistance in the absence of drug, at the expense of longer activation times. This architecture is favored in environments where contact with the drug is rare. A self-regulated repressor results in slightly higher expression of resistance in the absence of drug but allows a faster response. This architecture is favored in more rapidly changing environments with higher drug levels.

Sudden exposure to very high drug doses favors loss of regulation. When the drug concentration in the environment shifts too quickly, there is not enough time for cells to induce their responses. Therefore, constitutive expression of resistance is favored over regulated responses, despite the burden of unnecessary expression in the absence of drug.

CONCLUSION

The spread of antibiotic-resistance mechanisms requires the evolution of regulatory features that optimize costs and benefits in the host's environment. Understanding how gene regulation of resistance mechanisms evolves in response to new ecological challenges is essential to predict and possibly halt the spread of antibiotic resistance to the clinic.

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