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(I) Noise, Networks, and Population Dynamics in the Evolution of Drug Resistance

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Drug resistance is a global health threat that is undermining the advances of modern medicine. Non-genetic forms of drug resistance have been established over the last two decades to play an important role in drug resistance. However, the interplay between non-genetic and genetic forms of drug resistance is largely unknown, as are the evolutionary dynamics in fluctuating drug conditions.

Recently, we have shown using deterministic models and stochastic simulations that non-genetic drug resistance enhances the survival of a cell population undergoing drug treatment, while hindering the genetic evolution of drug resistance due to competition between non-genetically and genetically resistant subpopulations. This effect is enhanced in fluctuating drug conditions compared to constant drug conditions.

We are testing these predictions in evolution experiments on genetically engineered yeast harbouring synthetic drug resistance gene circuits. Synthetic resistance gene circuits are well characterized, mimic natural gene networks, and allow gene expression mean and "noise"(i.e., cell-to-cell variability among genetically identical cells) to be precisely controlled and quantified. Preliminary results from these evolution experiments in fluctuating drug conditions demonstrate that gene expression evolves to optimize growth rates, and, counterintuitively, that expression noise levels are reduced in fluctuating compared to constant drug conditions.

Overall, these investigations on quantitative model systems are enhancing our fundamental understanding of drug resistance evolution, which is essential to prolong and extend our armamentarium against drug-resistant infections.

Keyword-1

Drug resistance

Keyword-2

Gene networks and noise

Keyword-3

Population dynamics

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