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Drug interactions between translation-inhibiting antibiotics

Wednesday 23 September 2020 14:00 (40 minutes)

Antibiotics that interfere with translation, when combined, interact in diverse and difficult-to-predict ways. We explain these interactions by "translation bottlenecks": points in the translation cycle where antibiotics block ribosomal progression. To elucidate the underlying mechanisms of drug interactions between translation inhibitors, we generate translation bottlenecks genetically using inducible control of translation factors that regulate well-defined translation cycle steps. These perturbations accurately mimic antibiotic action and drug interactions, supporting that the interplay of different translation bottlenecks causes these interactions. We further show that growth laws, combined with drug uptake and binding kinetics, enable the direct prediction of a large fraction of observed interactions, yet fail to predict suppression. However, varying two translation bottlenecks simultaneously supports that dense traffic of ribosomes and competition for translation factors account for the previously unexplained suppression. These results highlight the importance of "continuous epistasis"in bacterial physiology.

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