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RESEARCH ARTICLE

Antibiotic-induced population fluctuations and stochastic clearance of bacteria

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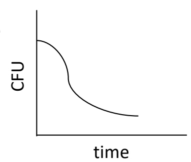
Deterministic models of population dynamics successfully predict **large** to **small** kill curves under antibiotic treatment.



Due to **experimental detection limits**, these models have never been tested on **small** to **zero** kill curves.

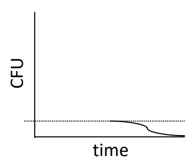
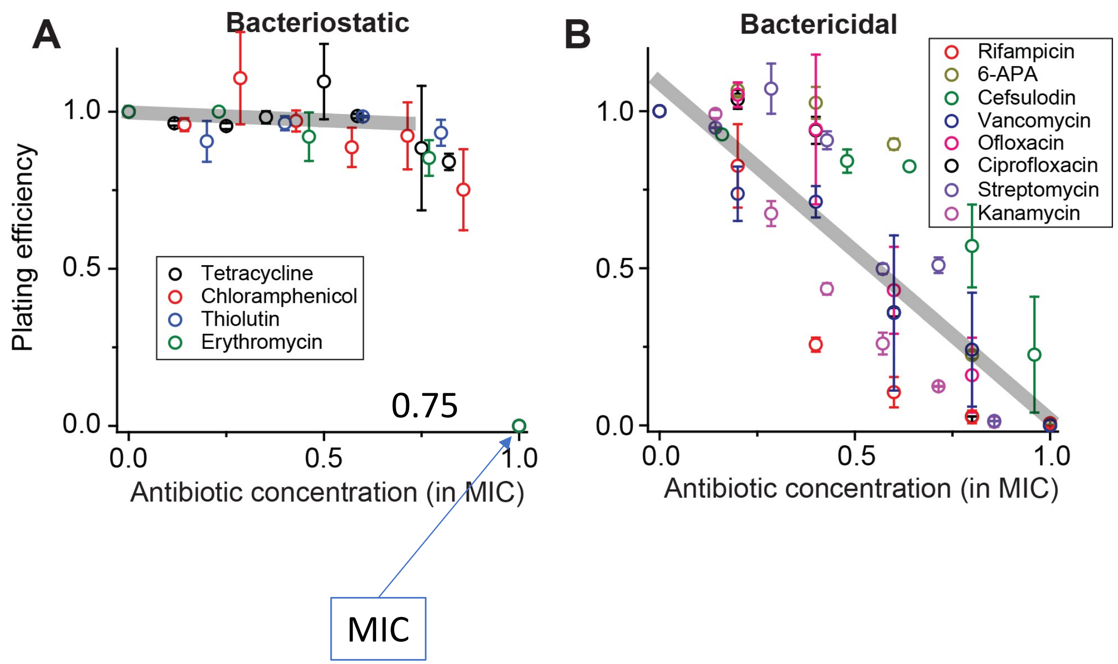


Figure 1: Bacteriostatic deterministic, but bactericidal not



E. coli dynamics by plating efficiency: $\frac{CFU_{abx}}{CFU_{nodrug}}$

Figure 2: Homogeneous growth with static drugs

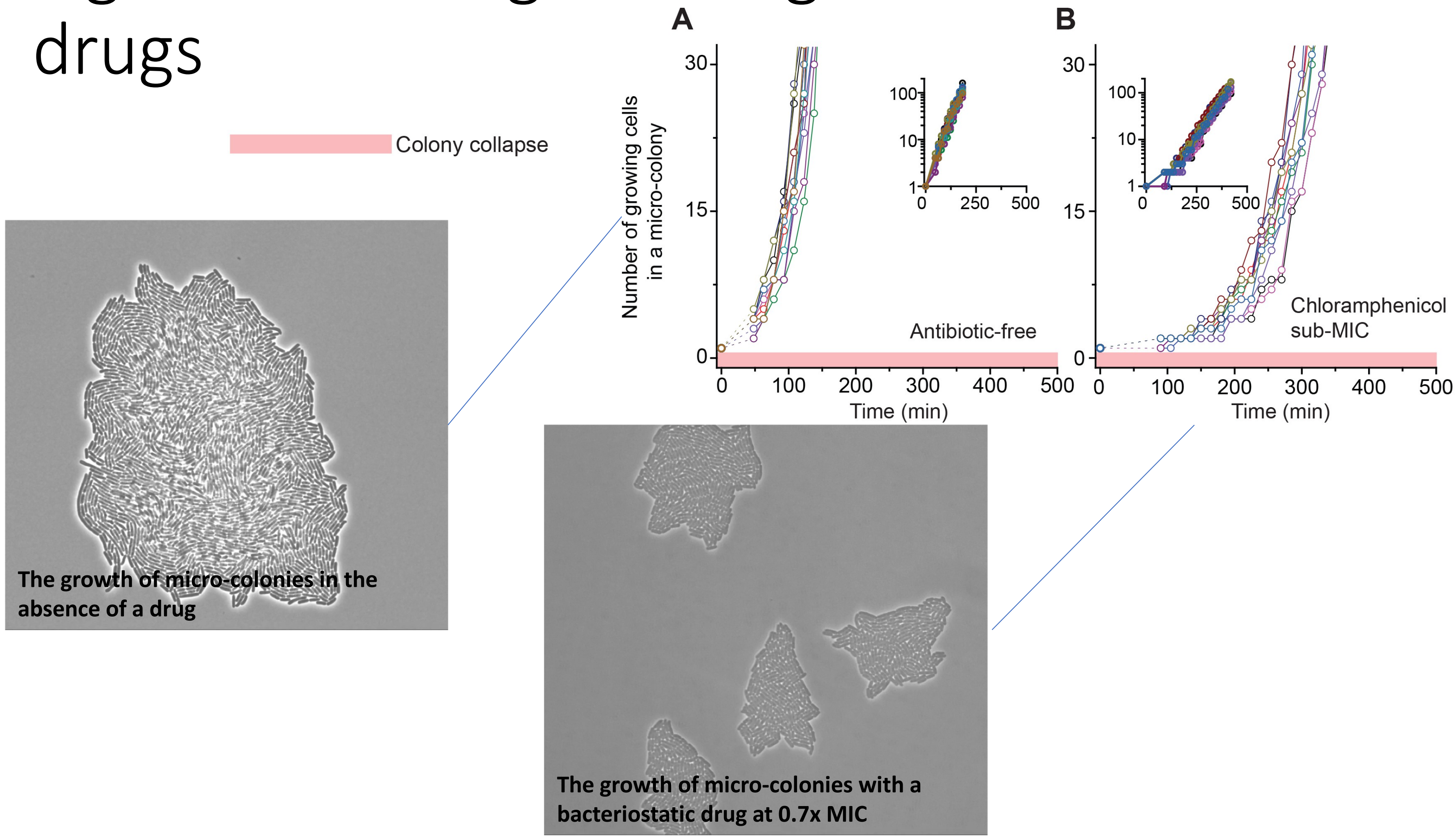
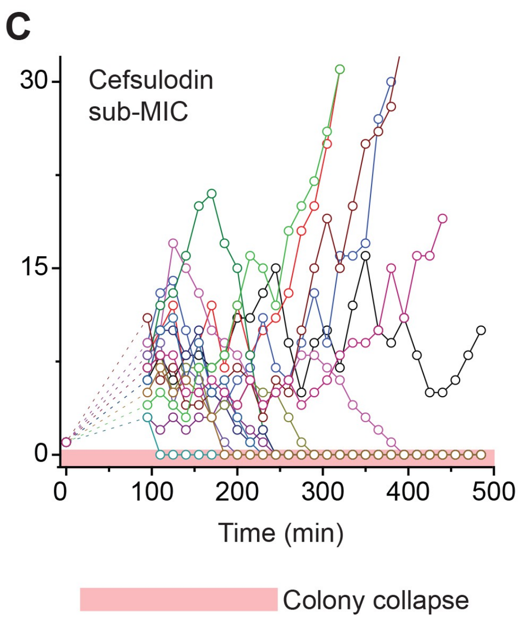
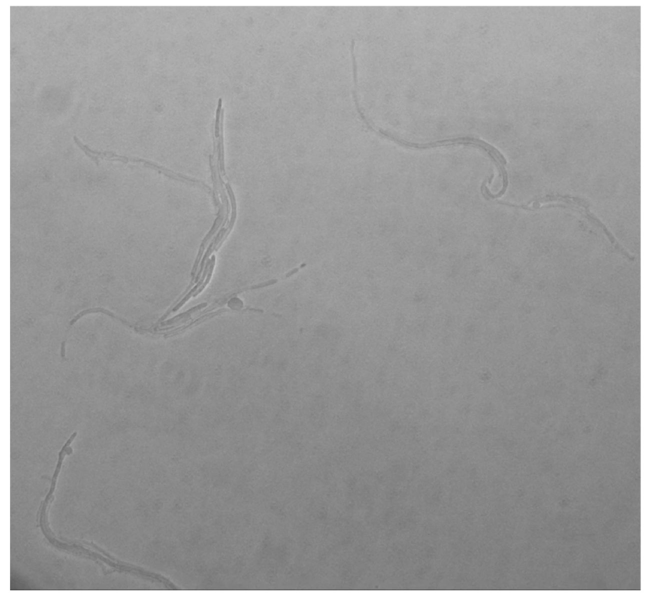


Figure 2: Stochastic fluctuations in population size with cidal drugs





The growth of micro-colonies with a bactericidal drug at 0.8x MIC

Figure 2: Probabilistic model and cidal data agree

Works for bacteriostatic abx
Also works for large to small pop size

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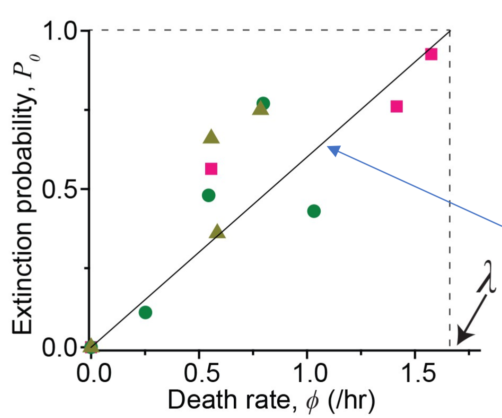


A deterministic model of population dynamics

If cells replicate at rate, λ, and die at rate, ϕ, a general deterministic model of population growth can be described by

$$\frac{dn}{dt} = \lambda \cdot n - \phi \cdot n, \quad \text{(A1)}$$

where n is the number of cells in the population. Its solution is

$$n(t) = n(0) \cdot e^{(\lambda - \phi) \cdot t}. \quad \text{(A2)}$$

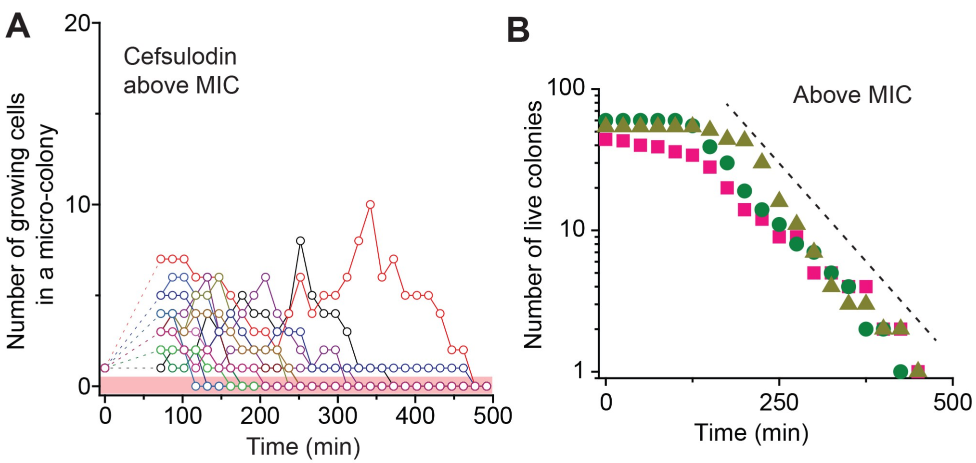
Previous studies modeled the population dynamics of bacteria exposed to antibiotics using this solution; e.g., see (***Regoes et al., 2004***; ***Czock et al., 2009***). At drug concentrations below the MIC (sub-MIC), growth rate is higher than death rate ($\lambda > \phi$); thus, a bacterial population grows. When the drug concentration reaches the MIC, growth rate and death rate are equal ($\lambda = \phi$); thus, the population size is maintained. At drugs concentrations above the MIC, growth rate is lower than death rate ($\lambda < \phi$); thus, a bacterial population declines.

Found clearance of cells (small to zero) within a population can only be predicted probabilistically,

$$\dot{P}_n = \lambda(n-1)P_{n-1} - (\lambda + \phi)nP_n + \phi(n+1)P_{n+1}, \quad \text{(1)}$$

The solution, $P_0 = \Phi/\lambda$, is shown in black, while experimental data agreement is shown in colored points.

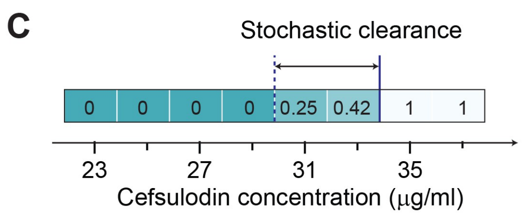
Figure 3: experimental data (above MIC) agree with model

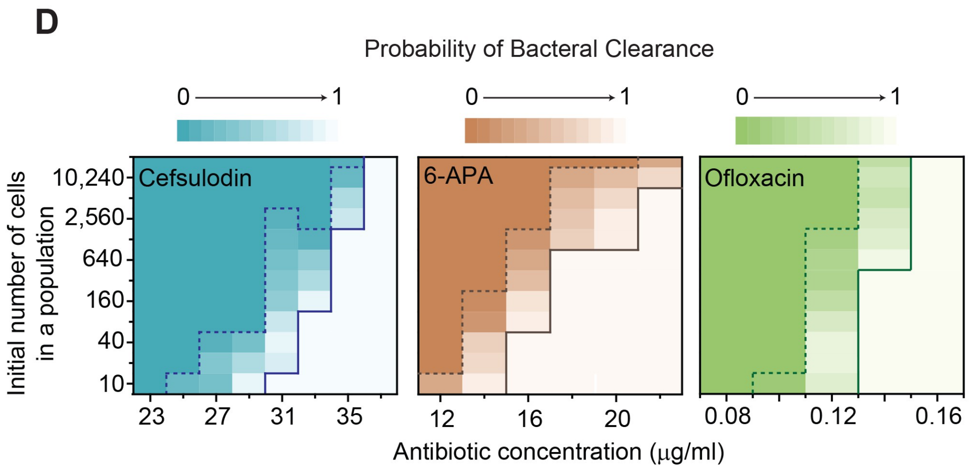


Fluctuating extinction times

Linear log plot means exponential decay

Figure 3: sub-MIC cidal drugs can cause stochastic extinction





Suggests that as you decrease growth rate, λ, you increase the extinction probability, P_0

Figure 4: used static drugs to decrease λ and increase P_0

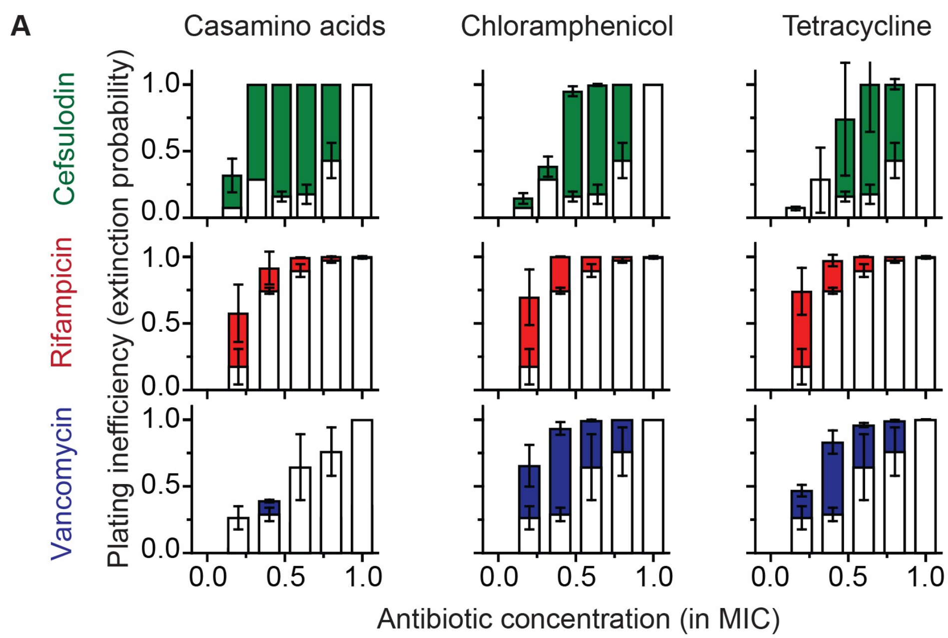


Figure 4: true for RESISTANT strains as well

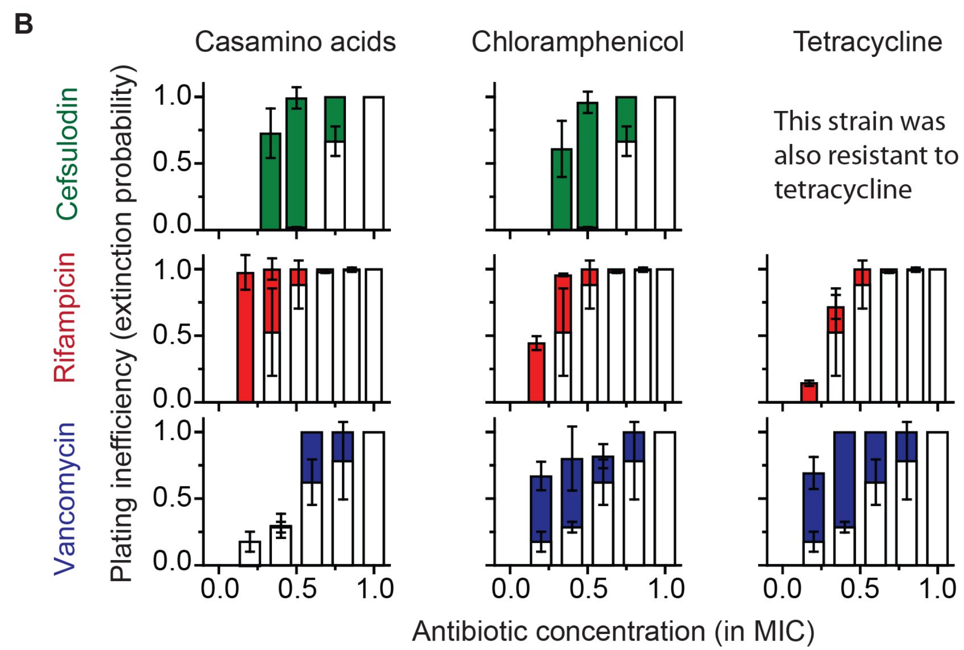


Figure 1, S1: not due to heritable resistance

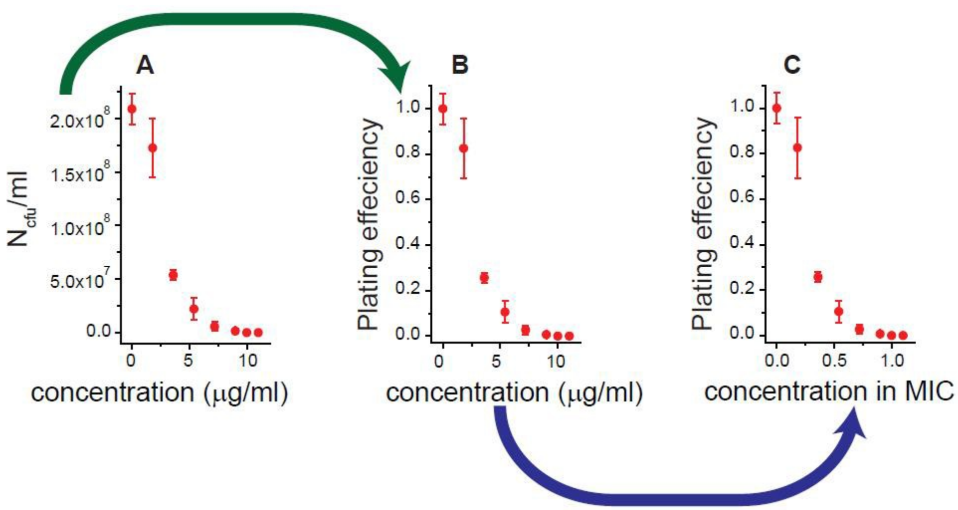


Fig S1, Rifampicin