# Privatization of public goods governs evolutionary dynamics of combination antibacterial treatment

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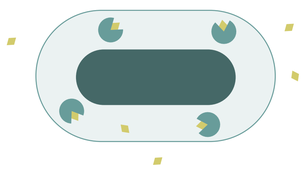
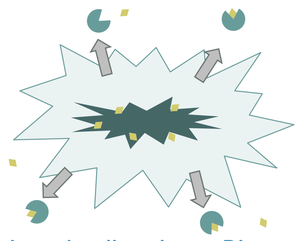
## Motivation

- β-lactams are the most commonly prescribed antibiotic class
- β-lactamase (Bla) enzymes are the typical resistance mechanism
- A combination of β-lactams and Bla inhibitors can re-sensitize Bla-producing bacteria. However, Bla-mediated antibiotic degradation is partially cooperative. This leads to complex population dynamics among coexisting sensitive and resistant populations[1, 2].

Periplasmic location of Bla **privately** protects resistant cells from death



Antibiotic degradation **publicly** benefits non-producing neighbors



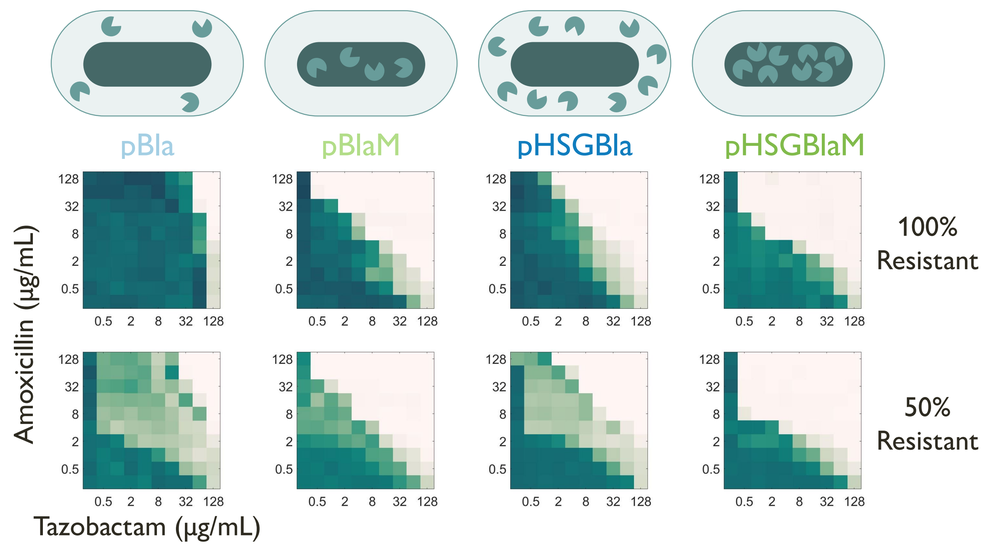
Lysed cells release Bla to extracellular environment

We ask the following questions:

- Which properties of the bacterial strain, antibiotic, inhibitor, and dose govern the response to combination therapy?
- How can we use this to guide combination treatment design?

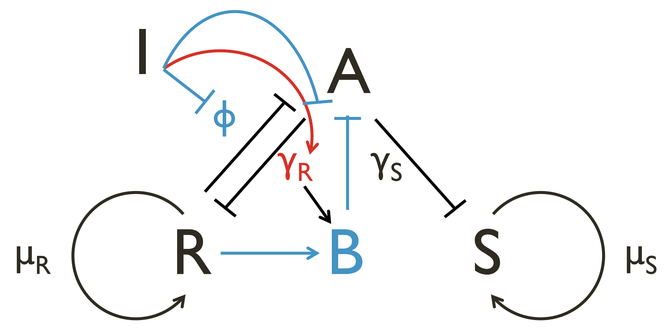
## Characterizing dose responses in synthetic strains

- Bla localized to the periplasm provides both public and private benefits, while Bla localized to the cytoplasm requires cell lysis for release and is a more public good
- Our strains express either periplasmic (Bla) or cytoplasmic (BlaM) β-lactamase at low (10) or high (500) copy number



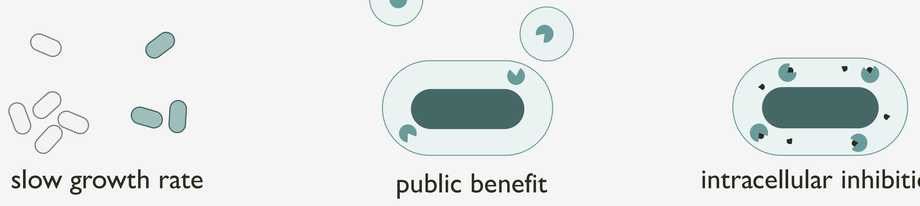

- OD600 shows that burden and privatization impact survival and mixed population dynamics. How does this affect resistance?

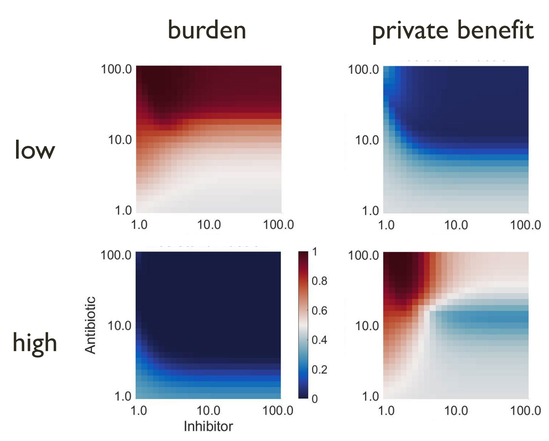
## Modeling evolutionary dynamics in mixed populations




- R – resistant cells
- S – sensitive cells
- A – antibiotic
- B – extracellular Bla
- μ – growth rate ($\mu_R < \mu_S$)
- γ – antibiotic-induced lysis ($\gamma_R < \gamma_S$)
- Φ – degradation by intracellular Bla
- I – inhibitor (affects public and private benefits)

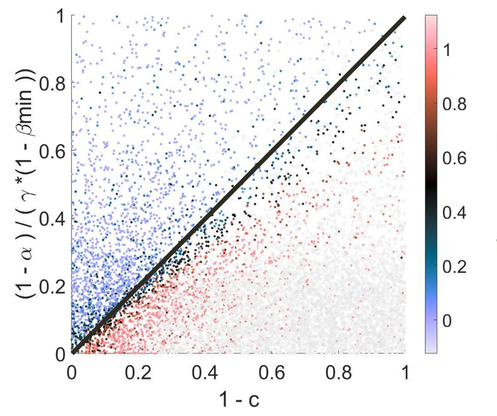
Factors favoring selection against resistance



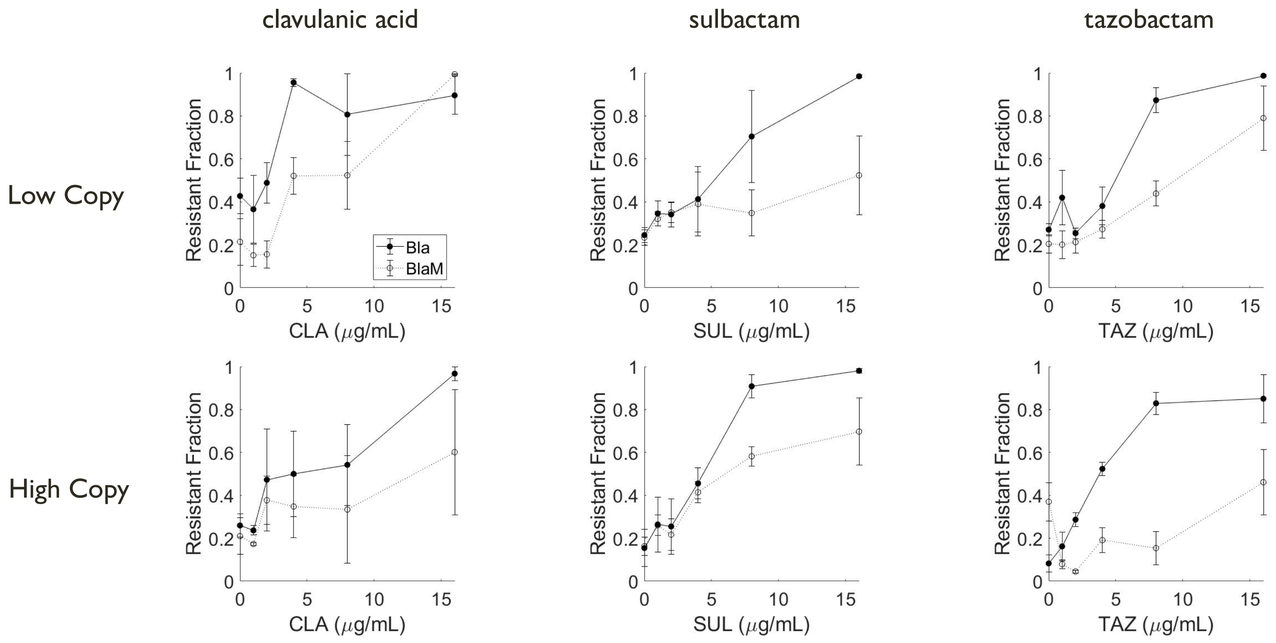

The effects of burden and privatization on cell survival in simulation are analogous to experimental results. However, simulations show that **similar cell density** patterns can obscure dramatic **differences in resistance** selection.

The simplified **criterion** below, based on the key governing factors, **predicts the evolutionary responses** of simulated strains with randomized parameters



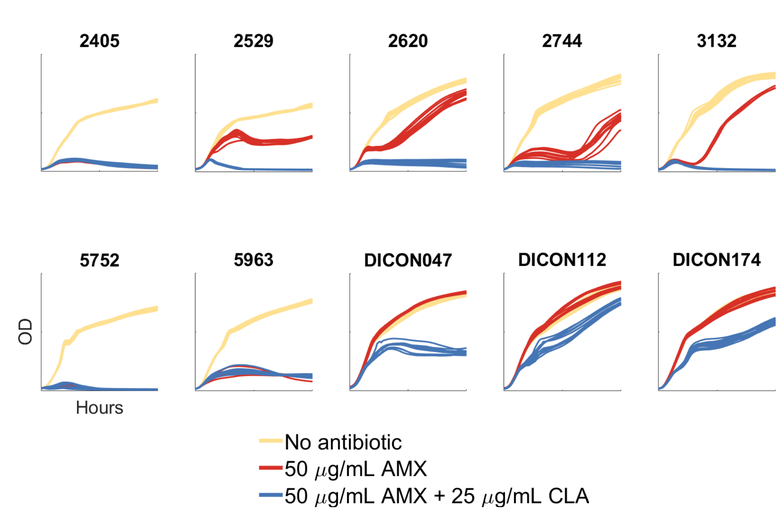

$$(1 - intracellular\ inhibition) > \frac{1 - burden}{maximum\ lysis\ rate(1 - private\ benefit)}$$

## Privatization increases resistance




- Cytoplasmic Bla results in lower resistance than periplasmic Bla, a finding maintained over different copy numbers and inhibitors
- Copy number may increase both burden and private benefit, muddying its effect on resistance
- Limited impact of naturally differing intracellular inhibitor effect[3]

## Implications and future directions




- Characterization of clinical isolates can identify strains with high private benefit for which resistance selection is likely
- Flexibility in antibiotic to inhibitor ratio may allow optimization based on minimizing resistance
- Adjuvants could be developed to increase intracellular inhibition

References: [1] Yurtsev, E. A. et al. *Mol. Syst. Biol.* 2013 [2] Allen, R., Brown, S. *mBio* 2019 [3] Farmer, T. H. et al. *FEMS Microbiol. Lett.* 1999
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