

Eco-Evolutionary Dynamics of Cooperative Antimicrobial Resistance:

Spatial organisation, private benefits and horizontal gene transfer

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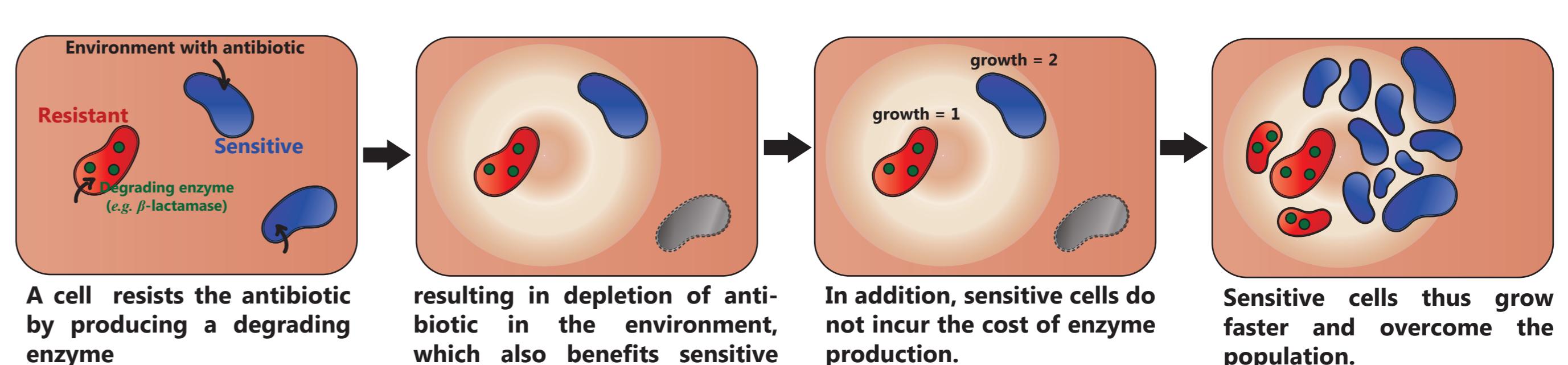


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Motivation

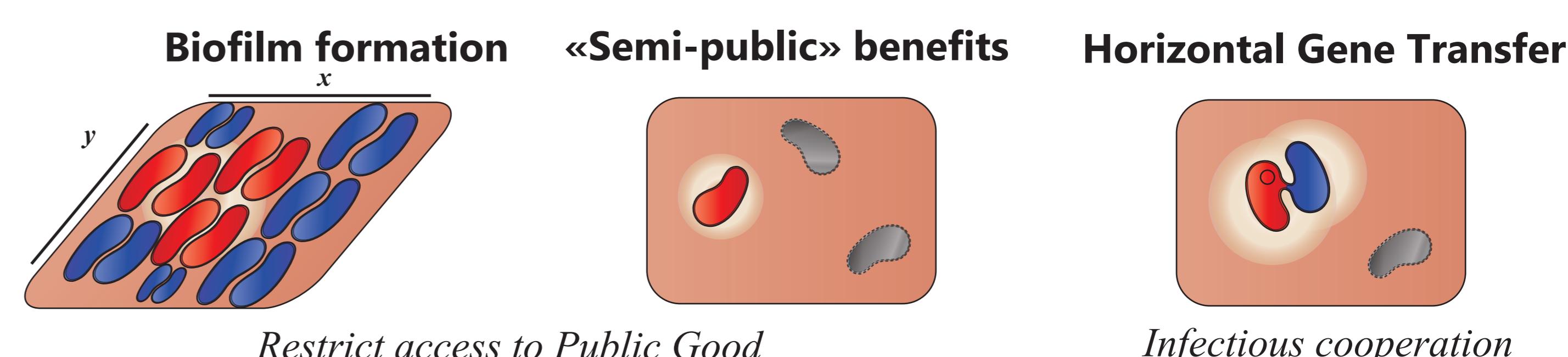
- AMR is a huge public health and environmental issue and is on the rise
- The most common mechanism for AMR is the secretion of antibiotic-degrading enzymes
- Evolutionary theory says this is an unstable strategy because cheating non-producers can readily evolve to reap the benefits of the enzymes while avoiding paying the cost of production; if cheaters win, the prevalence of AMR should decrease
- What, then, maintains high levels of AMR in the face of exploitation by cheaters?
- Spatial structure (e.g. biofilm formation) and semi-public benefits (e.g. reduced diffusivity) can restrict access to the public good and thus enable cooperator to avoid exploitation. Horizontal gene transfer renders cooperation «infectious», seeding the population with new cooperators
- However, we do not know their relative importance for the maintenance of AMR and how spatial structure mediates their importance. Thus, we need to study them within a coherent modeling framework in which we can manipulate each of these factors to compare their impact on AMR dynamics.

A Cheater - Cooperator problem



This «exploitation» results in population collapse

How to maintain resistance = how to avoid exploitation?

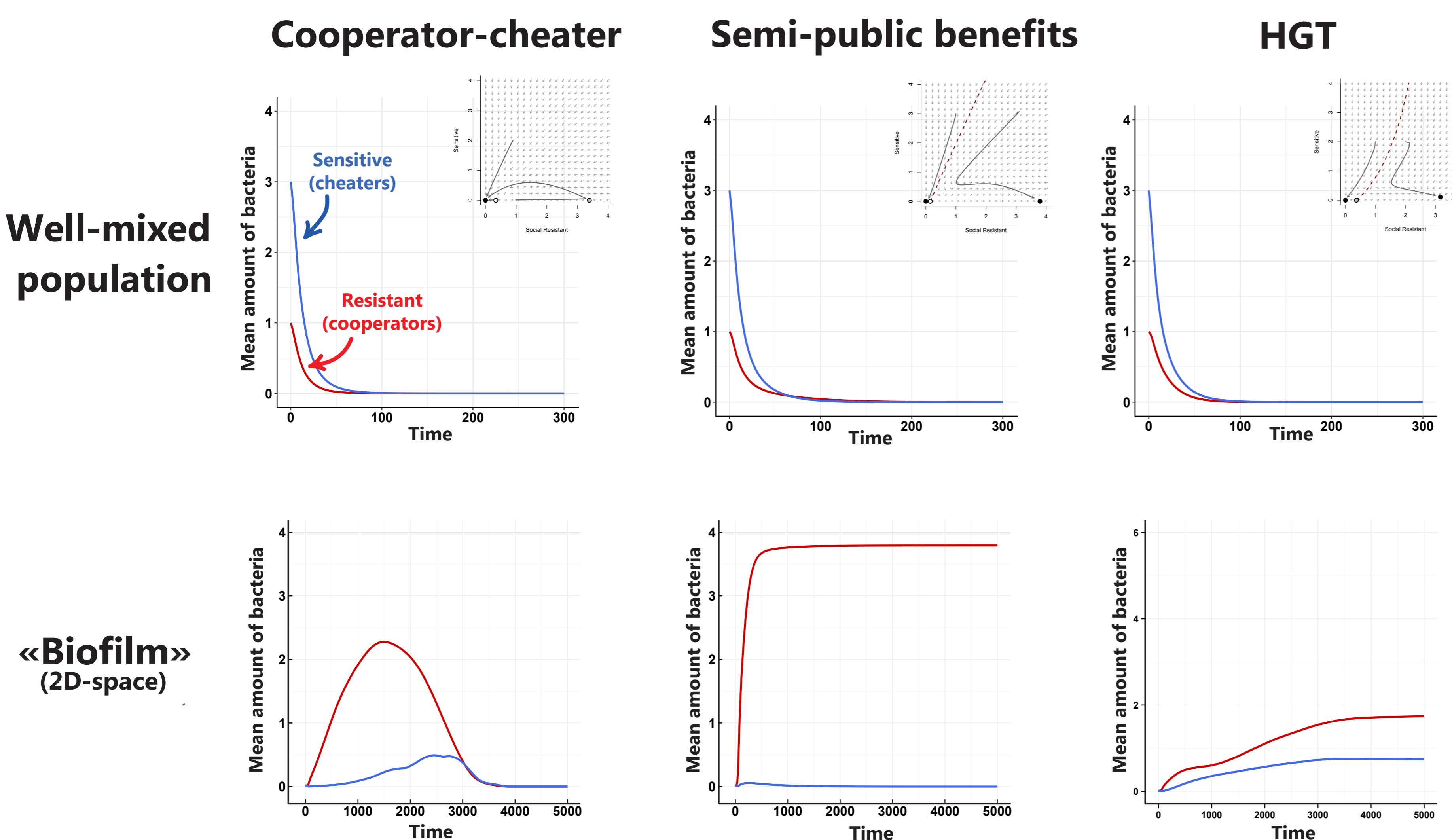


Restrict access to Public Good

Infectious cooperation

1. Different mechanisms induce a rich spatio-temporal dynamic with various stable states

We model the dynamics of an antibiotic, nutrients and cells growth. Cells grow logistically as a function of their nutrient consumption. Sensitive cells allocate all nutrient intake to growth. Resistant cells allocate part of this intake to enzyme production (*i.e.* cost of resistance). The antibiotic kills cells as a function of its concentration, which decreases upon degradation by the enzyme. **Given identical initial conditions, we compare the temporal dynamic and the long term equilibrium for each model** (simple cooperator-cheater, semi public benefits, HGT) **in a well-mixed or a spatially explicit population.**



The Model

Differential equations model describing the dynamic of Antibiotic (A), Nutrients (H), Sensitive bacteria (S) and Resistant bacteria (R).

$$\begin{aligned} \frac{dA}{dt} &= a - dA - bRA && \text{Degradation by Resistant} \\ \frac{dH}{dt} &= n - fH - gHS - gHR && \text{Consumption} \\ \frac{dS}{dt} &= gHS - mS - cAS + \alpha R - \beta RS && \begin{array}{l} \text{Growth} \\ \text{Plasmid loss} \\ \text{Conjugation} \end{array} \\ \frac{dR}{dt} &= g(1-e)HR - mR - c(1-j)AR - \alpha R + \beta RS && \begin{array}{l} \text{Cost of resistance} \\ \text{Amount of private benefits} \end{array} \end{aligned}$$

Turned into Partial Differential Equation model describing the dynamic in time and space, considering the diffusion of nutrients, antibiotic and bacteria in space with:

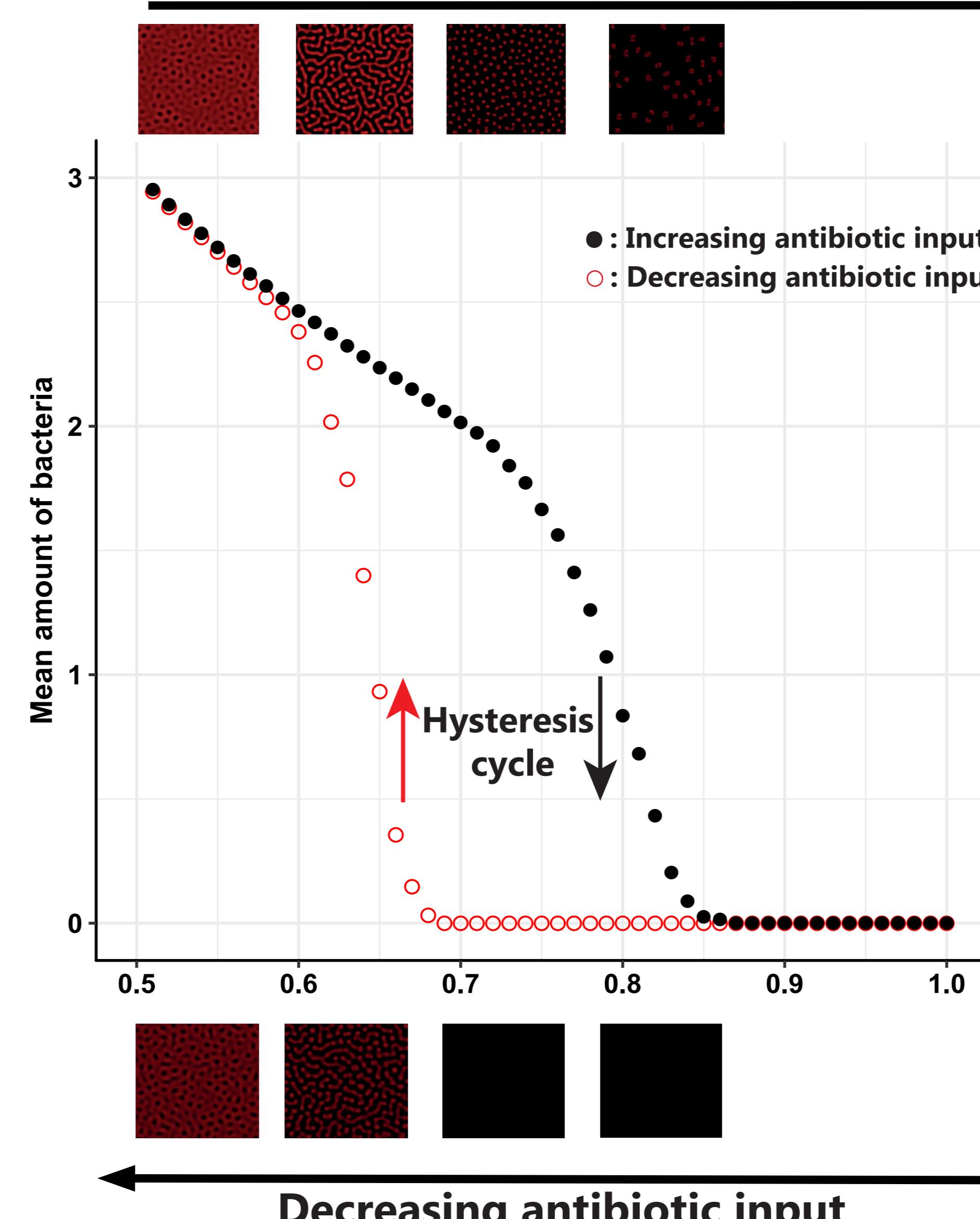
$$Diff_S = Diff_R < Diff_A < Diff_H$$

2. Space matters

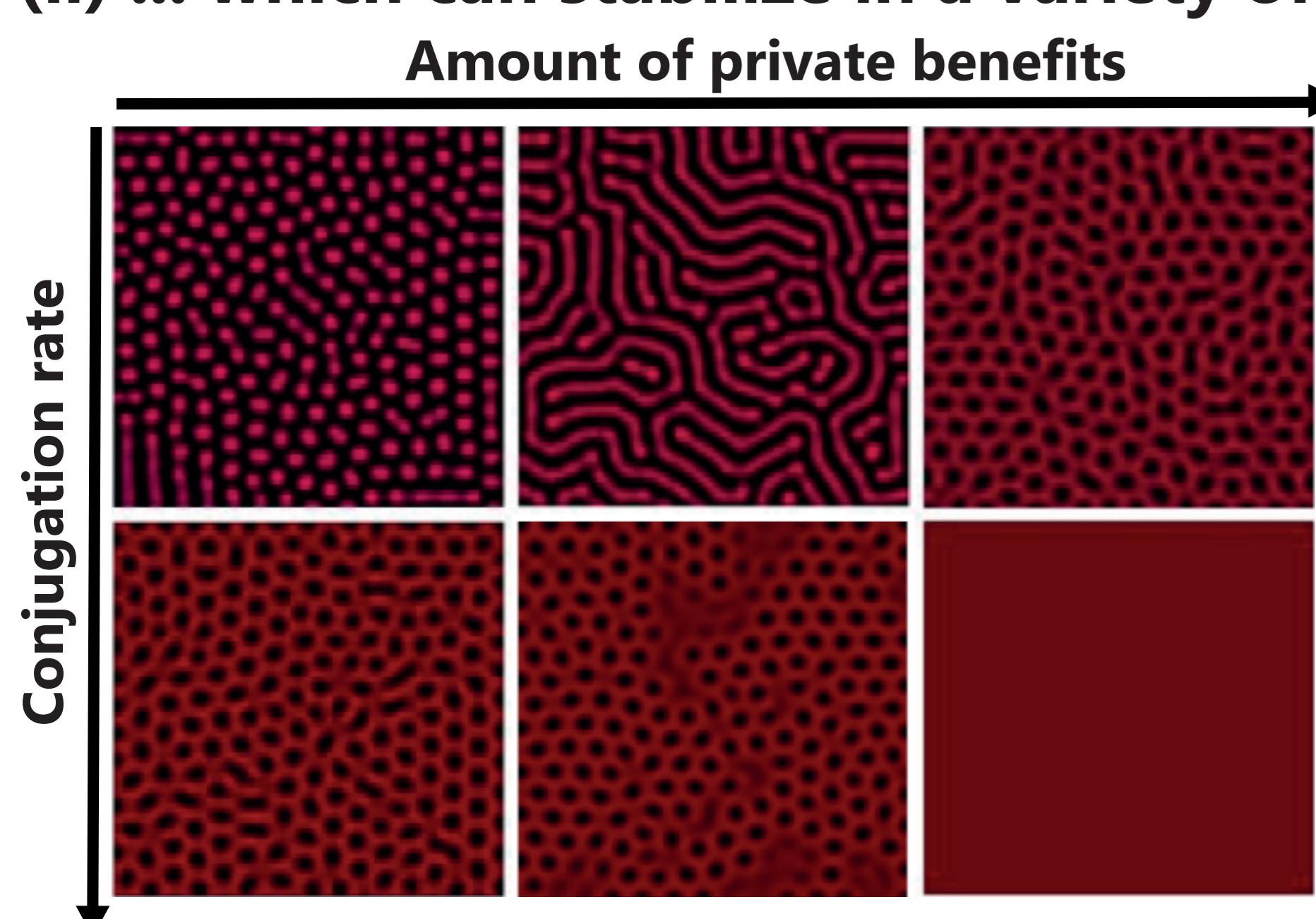
(i) Formation of regular spatial patterns...

(iii) ... and increase population level resistance

Increasing antibiotic input



(ii) ... which can stabilize in a variety of shapes



Conclusion and perspectives

The cooperative nature of AMR through degrading enzyme results in very complex eco-evolutionary dynamics.

The consequences of various mechanisms at different levels (individuals, population) must be understood to fully capture the dynamic of this type of resistance.

Spatial dynamics are particularly important to take into account (*e.g.* investigate biofilm formation during infections).

In particular, patterns formation may participate to increased population level resistance.

We plan on integrating these results into epidemiological models to assess the consequences of these mechanisms in the context of cooperative AMR at larger scale.

We also plan to test experimentally this model predictions and the formation of spatially organised patterns in biofilms.