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Eco-evolutionary dynamics in a switching antimicrobial environment

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Introduction

Antimicrobial resistance (AMR) is responsible for **~1 million deaths per year** with this reaching **10 million deaths per year by 2050** [1], **costing $100 trillion USD** via a loss in global production.

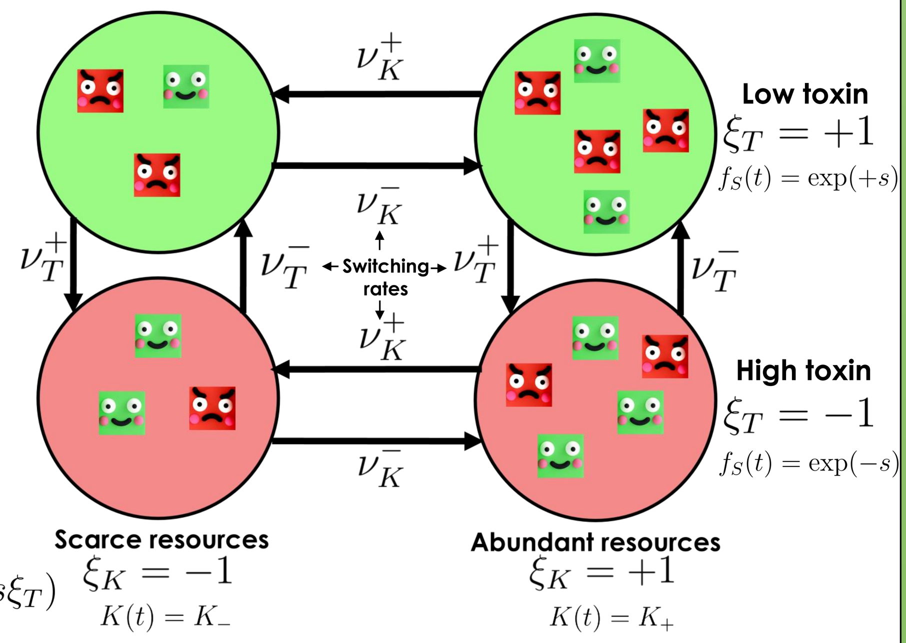
AMR: resistant bacteria pay a **metabolic cost** to be **resistant** but **are protected** if antimicrobial is present; sensitive bacteria pay **no cost** but **are affected** by the antimicrobial.

Demographic fluctuations (birth / death events) and **environmental changes** are vital to understand AMR, but they are rarely considered together. Their **eco-evolutionary dynamics** remain unsolved.

In which cases do resistant bacteria dominate, die out, or coexist with sensitive strains?

Model

Well-mixed population of N bacteria, containing N_R resistant bacteria and N_S sensitive bacteria with birth & death rates $T^{\pm}_{R/S}$. The system experiences **instantaneous random environmental switches** in resource availability and toxicity.



Resistant bacteria – fitness: $f_R = 1$

Sensitive bacteria – fitness: $f_S(t) = \exp(s\xi_T)$

Carrying capacity: $K(t) = K_0[1 + \gamma\xi_K(t)]$

Births & deaths

$$N_{R/S} \xrightarrow{T^+_{R/S} = \frac{f_{R/S}}{\bar{f}(t)} N_{R/S}} N_{R/S} + 1$$

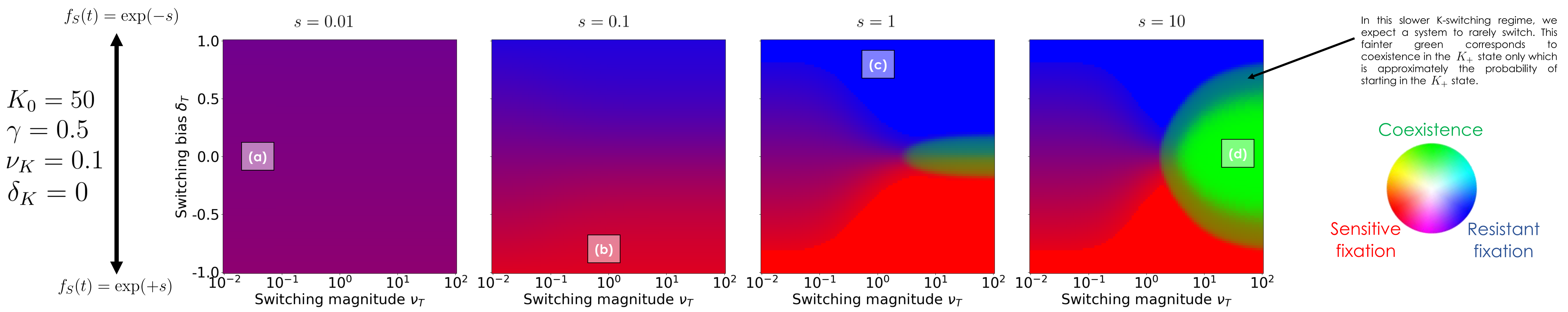
$$N_{R/S} \xrightarrow{T^-_{R/S} = \frac{N}{K(t)} N_{R/S}} N_{R/S} - 1$$

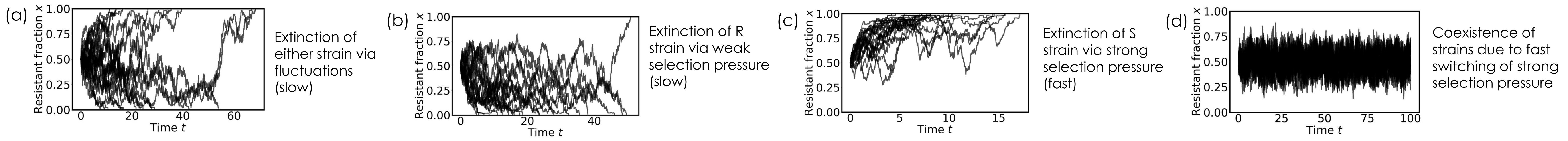
Definitions

$s > 0$: selection strength
$x \equiv N_R/N$: resistant fraction of population
$\bar{f}(t) \equiv x + (1-x)\exp(s\xi_T)$: average fitness
$\nu_\alpha \equiv (\nu_\alpha^+ + \nu_\alpha^-)/2$: switching magnitude $\alpha \in \{T, K\}$
$\delta_\alpha \equiv (\nu_\alpha^+ - \nu_\alpha^-)/2\nu_\alpha$: switching bias $\alpha \in \{T, K\}$
$K_0 \equiv (K_+ + K_-)/2$: carrying capacity magnitude
$\gamma \equiv (K_+ - K_-)/2K_0 > 0$: carrying capacity bias

Increased selection pressure promotes coexistence in fast-switching environments

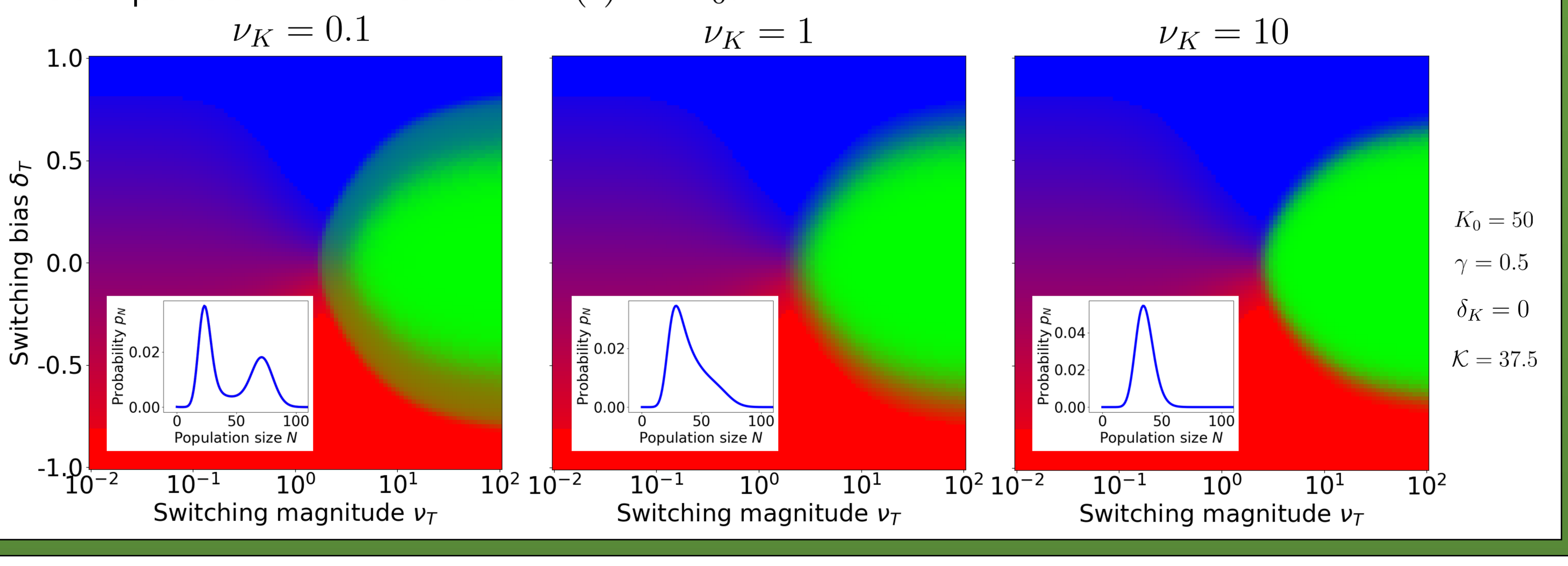
This switching environment can lead either to **dominance of a strain** or **coexistence of the two strains** ($\tau > 2K_+$[2]).





Switching of carrying capacity impacts size of coexistence region

Carrying capacity switching impacts the population size distribution. As ν_K increases, the carrying capacity takes an effective value given by $\mathcal{K} = K_0(1-\gamma^2)/(1-\gamma\delta_K)$[3] instead of the stationary K_0 . Hence, the size of the coexistence regime decreases for $\delta_K < \gamma$ and increases for $\delta_K > \gamma$. Since $\gamma > 0$, in the symmetric case, $\delta_K = 0$, the region always decreases compared with the case $K(t) = K_0$.

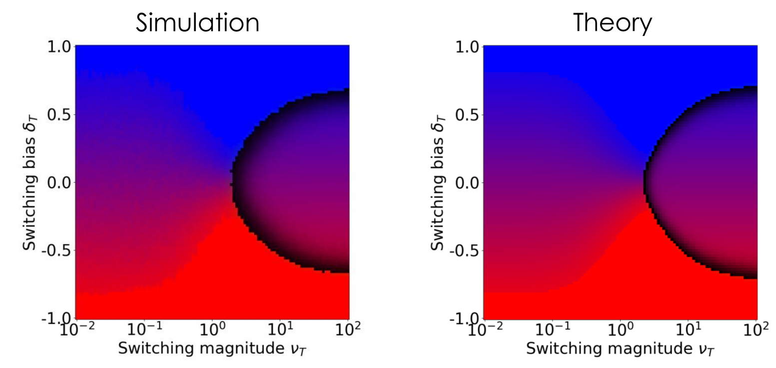


Composition of coexistence is predicted well by a PDMP approximation

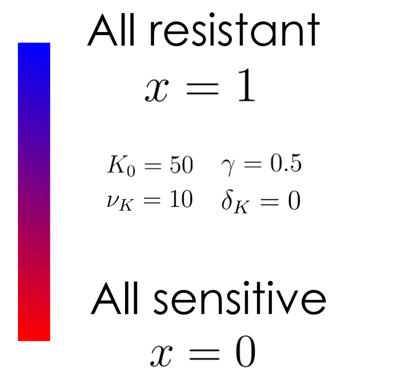
If we neglect demographic fluctuations, but maintain the stochastic switching of the environment, we find that x follows a piecewise deterministic Markov process. We can solve this for the quasi- stationary distribution of x and find that the modal value of this distribution is given by

$$x_{\text{mode}} = \frac{1}{2} + \frac{\delta_T}{2} \frac{\nu_T \sinh(s)}{\nu_T(\cosh(s) - 1) - 1}$$

This result matches excellently to simulations where both $K(t)$ and $f_S(t)$ fluctuate and so allows for an accurate prediction of the composition of the system with a simple expression.



The colours in the semi-circular coexistence region (previously green) now denote composition at coexistence as given by the colour bar on the right. Additionally, the brighter a point is, the higher its coexistence probability.



Conclusions

- For large enough s and ν_T a long-lived coexistence is permitted. The size of this coexistence region increases with increasing s.
- Increasing ν_K can either increase or decrease the size of the coexistence regime compared to the $K(t) = K_0$ case depending on δ_K and γ.
- When there is long-lived coexistence, the composition of this state can be accurately predicted by the modal value of the PDMP distribution of x .

Switches in toxicity and resource availability can lead to either dominance of a strain or coexistence of the strains. The coexistence region is impacted non-trivially by the switches. The composition of a coexistence state can be accurately predicted with a PDMP approximation.

References

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