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, costing $100 trillion USD** via a loss in global production [1].

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

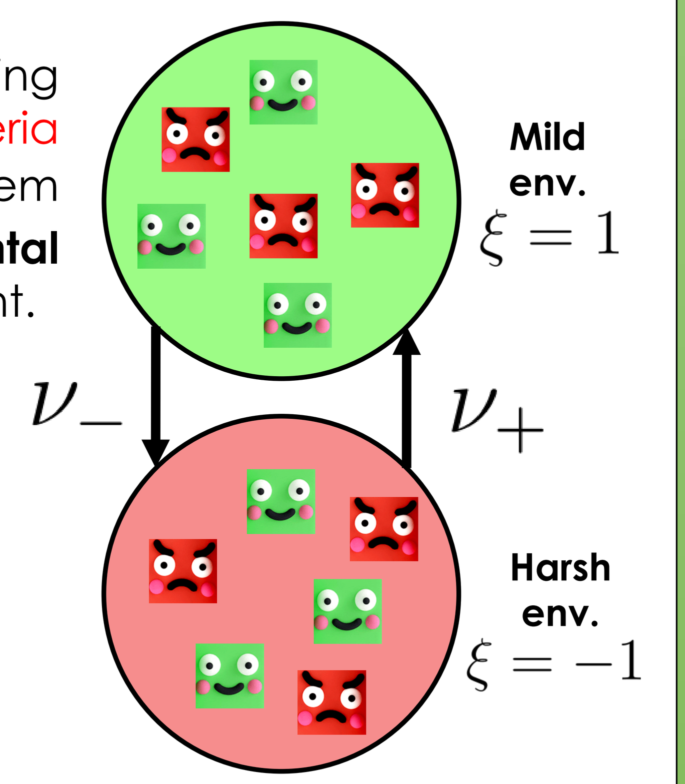
Well-mixed population of N bacteria, containing N_R resistant bacteria and N_S sensitive bacteria with birth & death rates $T^{\pm}_{R/S}$. The system experiences **instantaneous random environmental switches** between a mild and harsh environment.

$$N_{R/S} \xrightarrow{T^{+}_{R/S}=\frac{f_{R/S}}{\overline{f}}N_{R/S}} N_{R/S}+1$$

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

s: selection strength of sensitive bacteria ($s > 0$)
K: carrying capacity
ξ: environmental state (-1 ≡ harsh, +1 ≡ mild)
$\nu_{+/-}$: switching rate from ξ = -1 to 1 / ξ = 1 to -1
x: resistant fraction in system $x \equiv N_R/N$

Useful definitions
ν: switching magnitude $\nu \equiv (\nu_+ + \nu_-)/2$
δ: switching bias $\delta \equiv (\nu_+ - \nu_-)/2\nu$
$\Rightarrow \nu_\pm = (1 \pm \delta)\nu$



Resistant bacteria – fitness: $f_R = 1$
Sensitive bacteria – fitness: $f_S = \exp(\xi s)$
Average fitness: $\overline{f} = x + (1-x)\exp(\xi s)$

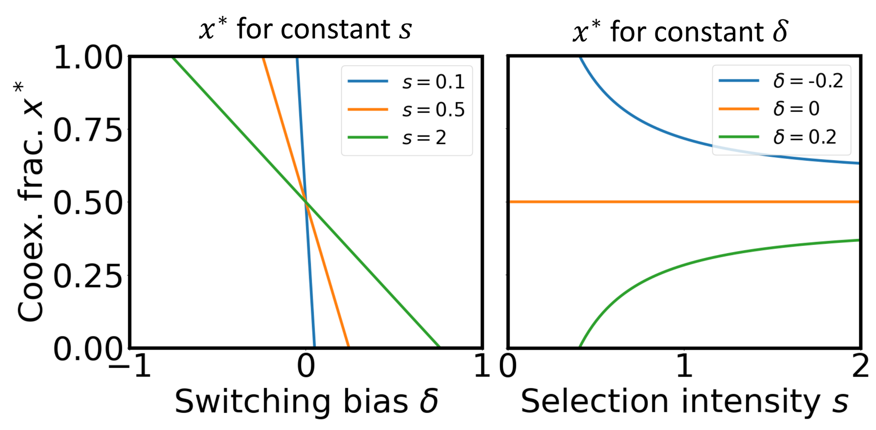
Large populations in fast-switching environments coexist

For large N, the equations for total pop. and composition x follow [2]:

$$\dot{N} = N\left(1 - \frac{N}{K}\right), \quad \boxed{\dot{x} = x(1-x)\left(\frac{1-\exp(\xi s)}{x + (1-x)\exp(\xi s)}\right)}$$

Stable fixed point: $x^* = \frac{(1-\delta)\exp(s) - (1+\delta)}{2(\exp(s)-1)}$

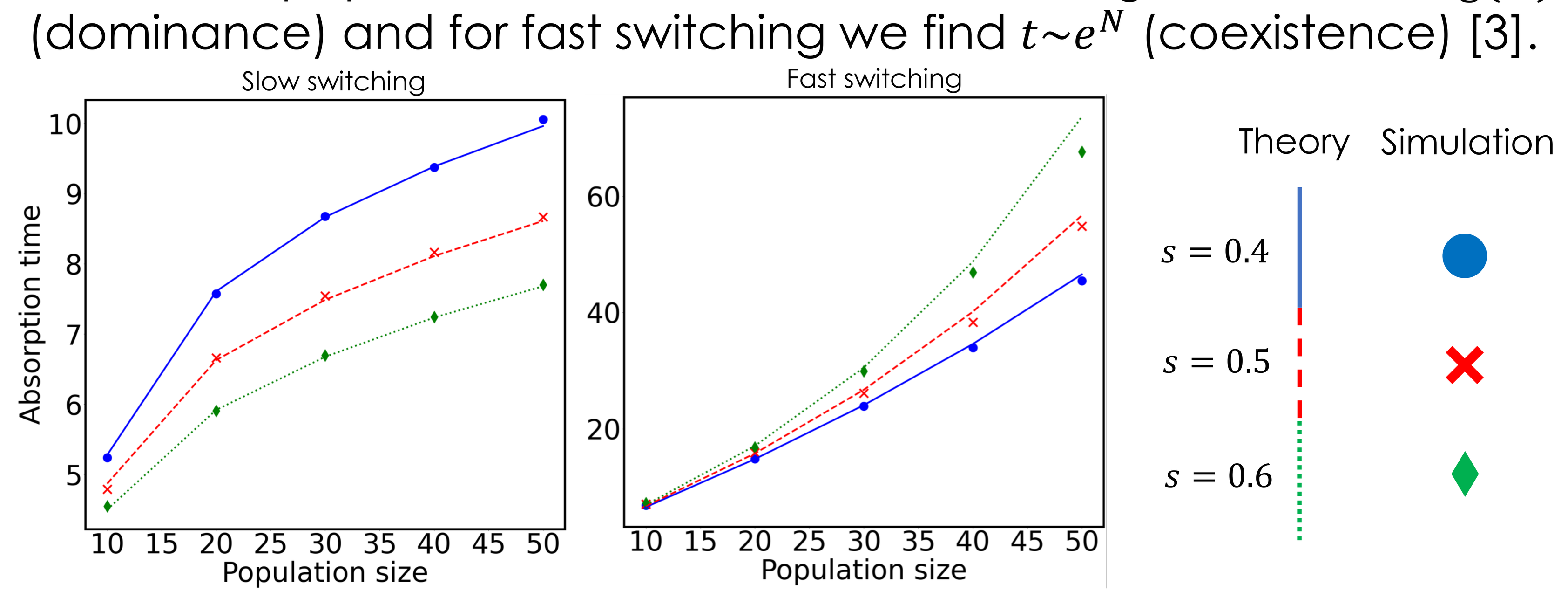
Fast-switching limit (large number of switches between birth / death events) $\nu \gg T^{\pm}_{R/S}$



Crucially, this fixed point **does not exist in a static environment**. It appears only when the environment switches rapidly.

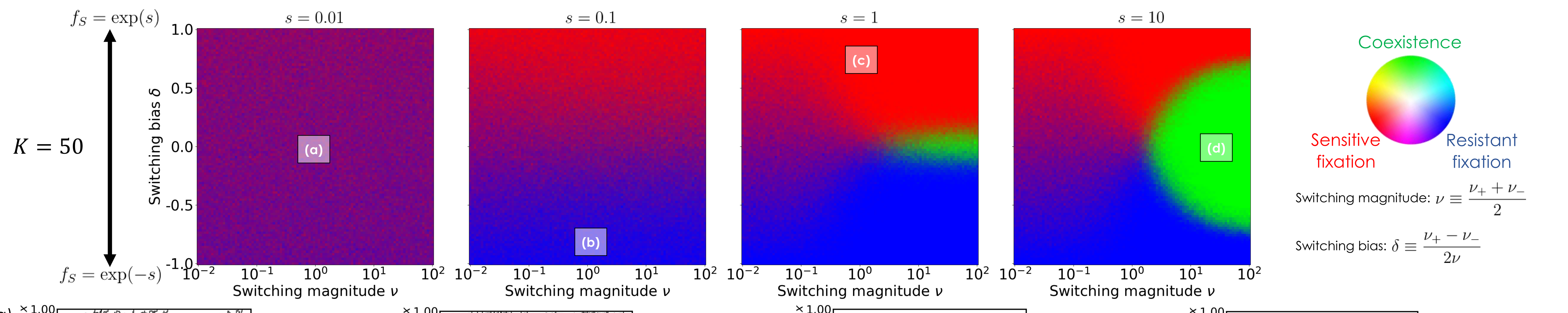
Small populations in fast-switching environments can coexist for a long time

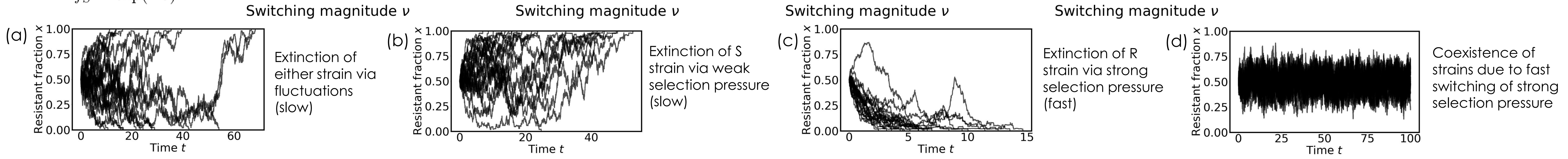
For small N, demographic fluctuations about the coexistence point will cause fixation of either strain after some time t (absorption time). We approximate the system with an effective Moran process of a fixed population size N. For slow switching we find $t \sim \log(N)$ (dominance) and for fast switching we find $t \sim e^N$ (coexistence) [3].



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** ($t > 2K$).





Conclusions

- Fast switching in large populations permits a stable coexistence point.
- In small populations the time taken to fixation either scales like $t \sim \log(N)$ (dominance) or $t \sim e^N$ (coexistence) depending on the switching.
- Increasing the selection pressure in these populations increases the size of the coexistence regime in parameter space.
- Have also found that allowing K to switch between values results in similar separate regimes.

Environmental switching can promote coexistence of resistant and sensitive strains where one strain dominates in a static environment.

References

[1] - J. O'Neill, report,Government of the United Kingdom, May 2016
[2] - K. Wienand, E. Frey, and M. Mobilia, Physical Review Letters, vol. 119, p. 158301, Oct. 2017.
[3] - J. Cremer, T. Reichenbach, and E. Frey, New Journal of Physics, vol. 11, p. 093029, Sept. 2009.

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