

Coexistence of Competing Microbial Strains under Twofold Environmental Variability and Demographic Fluctuations

Asker, Matthew^{1*}; Hernández-Navarro, Lluís¹; Rucklidge, Alastair M.¹ and Mobilia, Mauro¹

¹Department of Applied Mathematics, School of Mathematics, University of Leeds, Leeds LS2 9JT, United Kingdom;

*mmmwa@leeds.ac.uk

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.

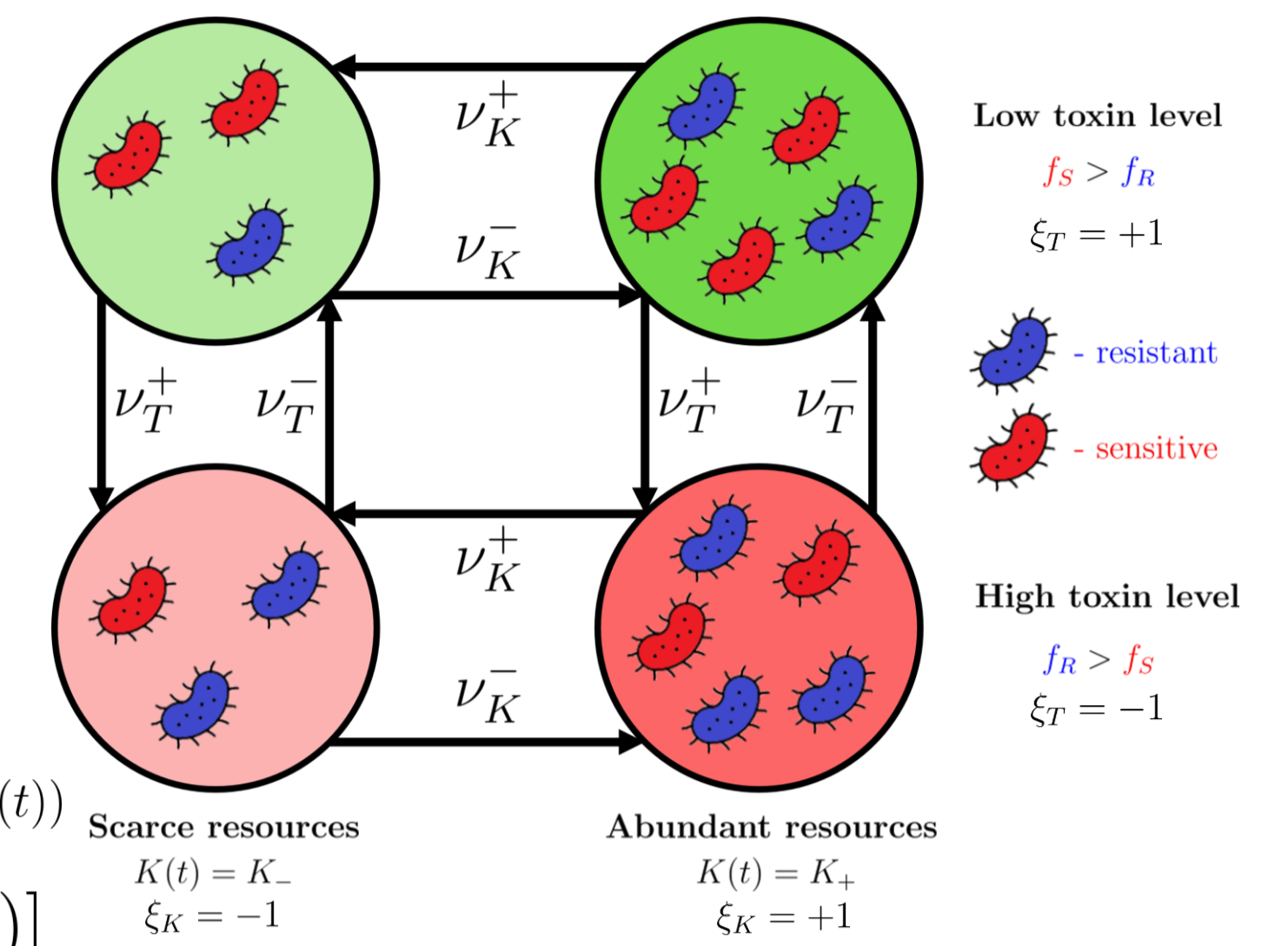
AMR: resistant bacteria pay a **metabolic cost** to be **resistant** but **are protected** if antimicrobial is present; sensitive bacteria pay **no cost** but **are affected** by the antimicrobial.

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 $T_{R/S}^\pm$. The system experiences **instantaneous random environmental switches** in resource availability and toxicity.



Resistant bacteria – fitness: $f_R = 1$

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

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

Births & deaths

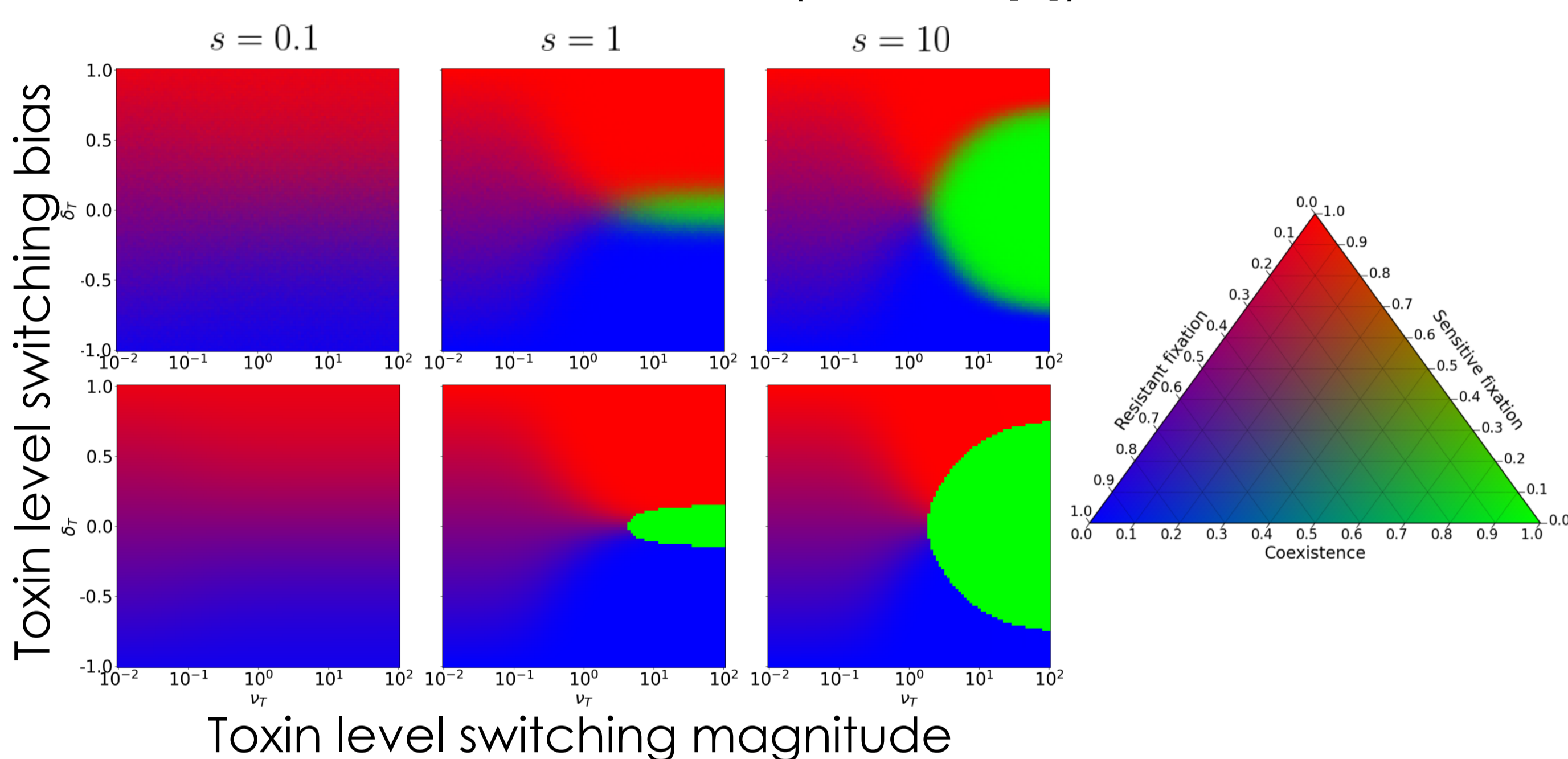
$$N_{R/S} \xrightarrow{T_{R/S}^+ = \frac{f_{R/S}}{\bar{f}(t)} N_{R/S}} N_{R/S} + 1$$

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

Definitions
 ξ_α : environmental state $\alpha \in \{T, K\}$
 $s > 0$: 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 $\alpha \in \{T, K\}$
 $K_0 \equiv (K_+ + K_-)/2$: static carrying capacity
 $\gamma \equiv (K_+ - K_-)/2K_0 > 0$: pop. bottleneck strength

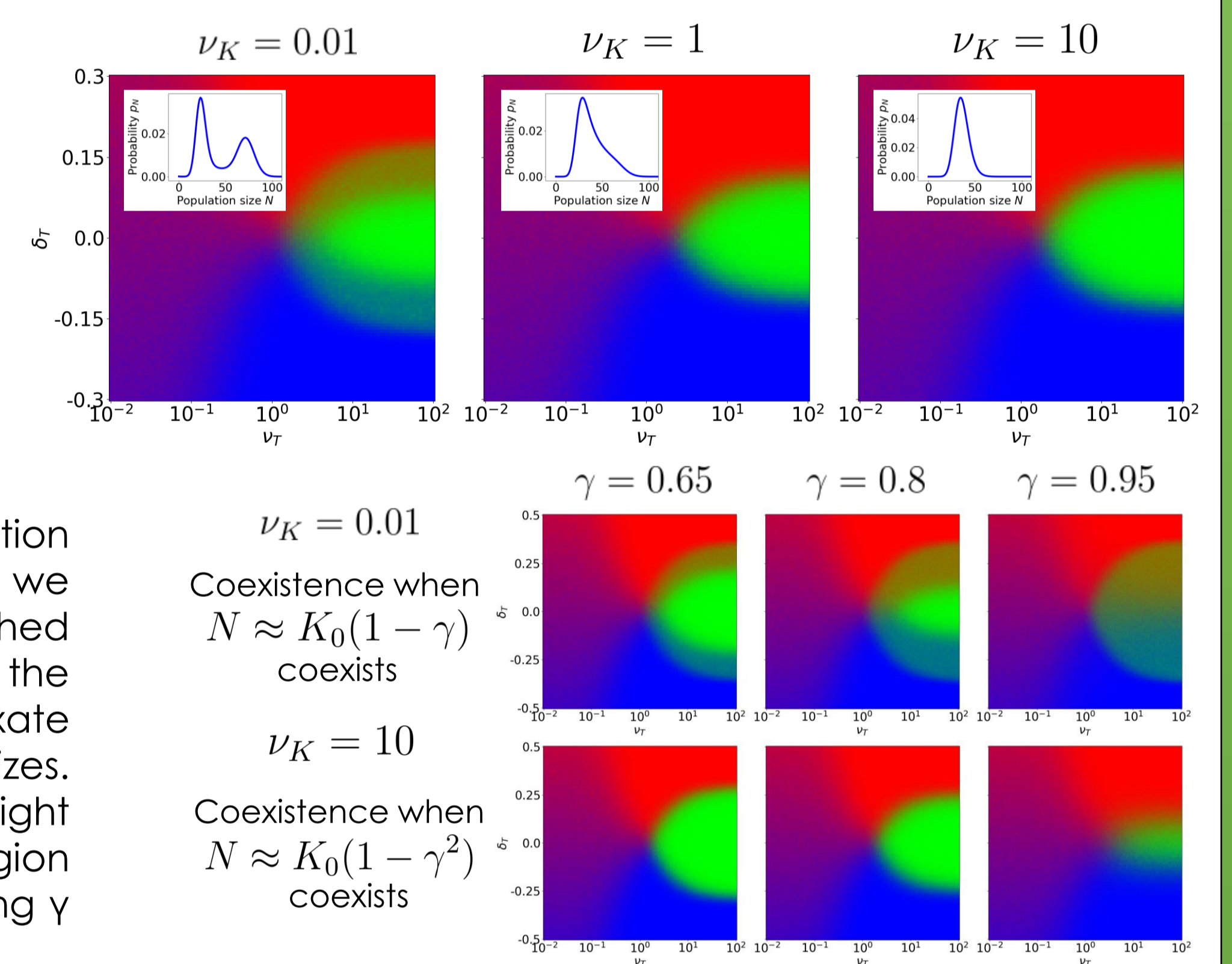
Increased selection pressure promotes coexistence for fast toxin level switching

We start by considering toxin switching only. We see that the switching environment can lead either to **dominance of a strain** or **coexistence of the two strains** ($\tau > 2\langle N \rangle$ [2]).



Carrying capacity switching can promote or jeopardise coexistence

For small switching rates in the carrying capacity, the pop. size distribution is bimodal around the two values. As ν_K increases, it becomes unimodal around an effective value between the two and the coexistence region increases in size.



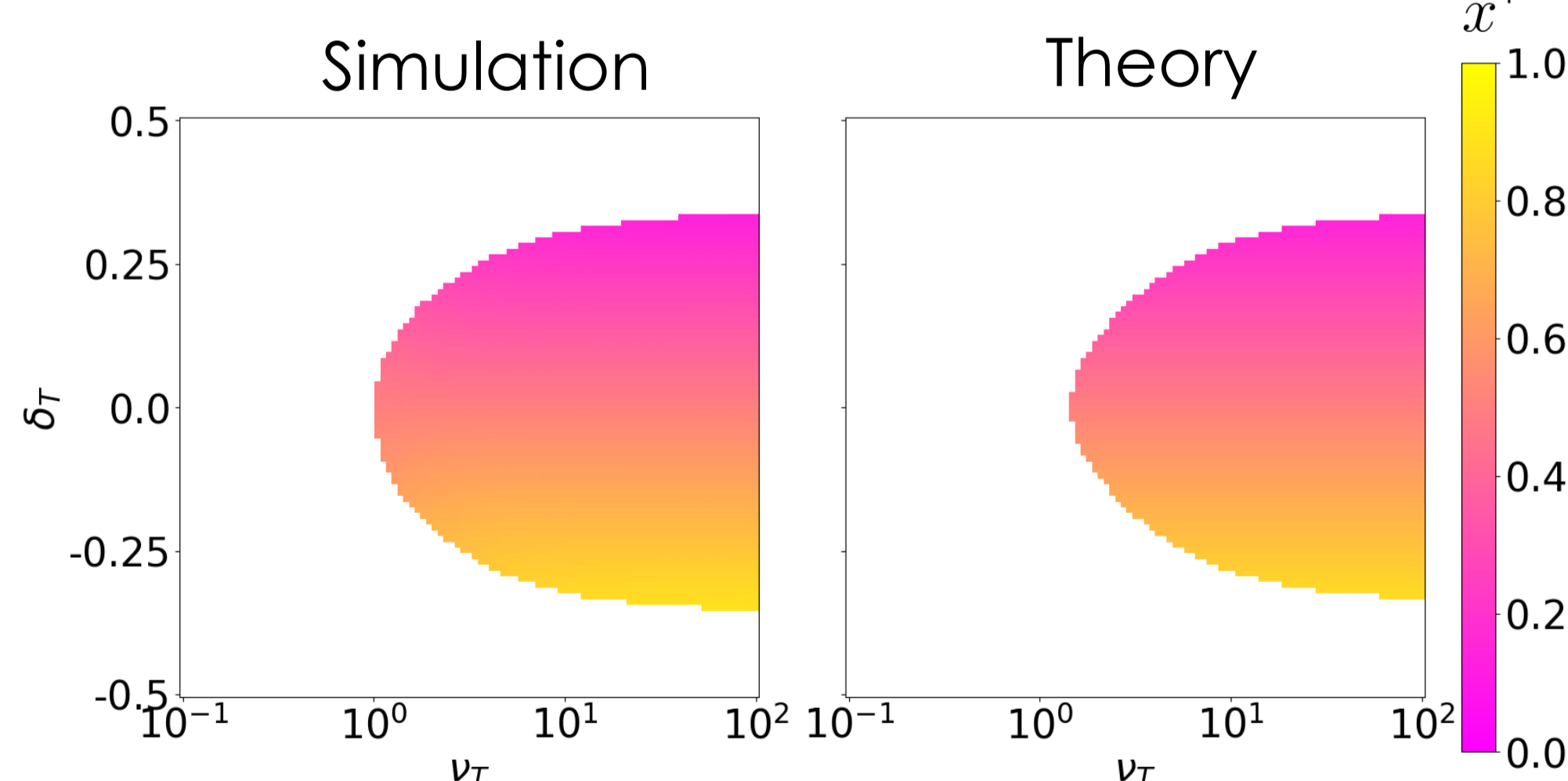
As the strength of population bottlenecks, γ , increases, we see coexistence is diminished for small and large ν_K , as the system finds it easier to fixate at the smaller population sizes. We also see that the bright green coexistence region decays slower for increasing γ when the switching is fast.

Mean-field dynamics with fast toxin switching predicts coexistence composition

By considering the mean-field equations for x in the fast-switching limit, we find an emergent coexistence fixed point,

$$x^* = \frac{1}{2} - \frac{\delta_T}{2} \coth \frac{s}{2}$$

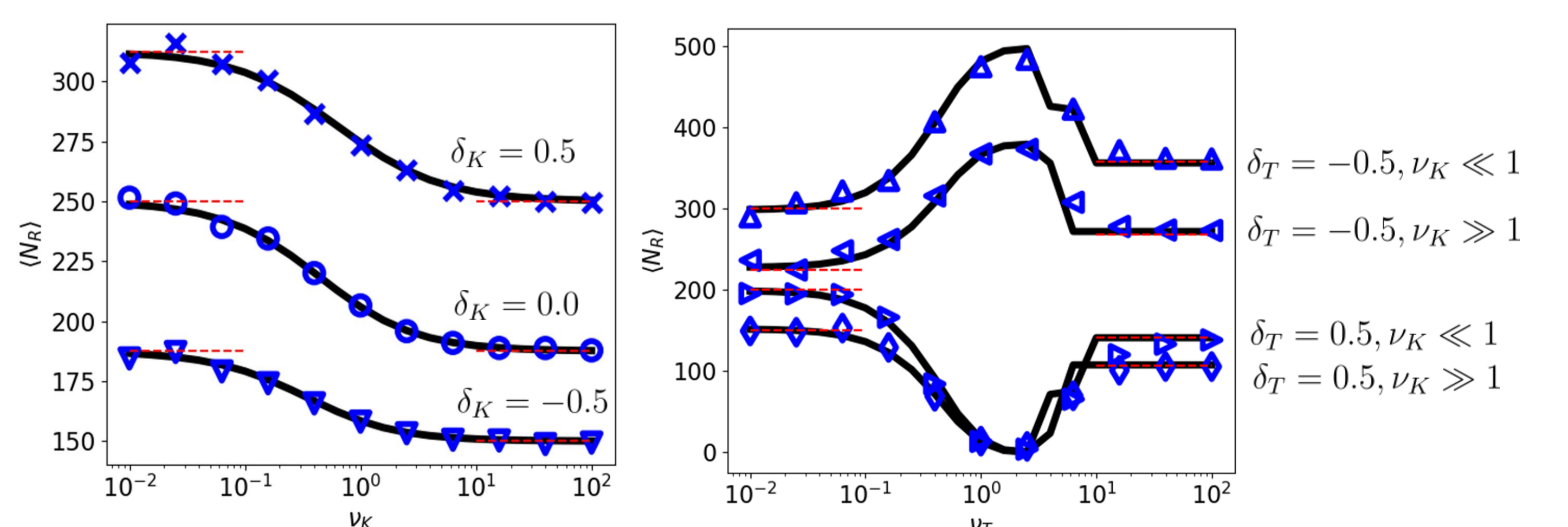
This predicts very well the composition of the system, given that the system coexists.



Abundance of resistant bacteria depends non-linearly on switching rate

Since the pop. size and composition are decoupled, we find results for the average values independently and combine to find the behaviour of abundances for resistant bacteria.

$$\langle N_R \rangle \approx \langle N \rangle \langle x \rangle$$



Conclusions

- For large enough selection strength and toxin switching magnitude, a long-lived coexistence is permitted.
- Increasing resource switching magnitude increases the size of the coexistence regime, while increasing the strength of population bottlenecks decreases it.
- When there is long-lived coexistence, the composition can be accurately predicted by the mean-field value in the limit of fast toxin switching.
- Resistant bacteria abundance decreases with faster resource switching and varies non-linearly with toxin switching magnitude.

Fluctuating environments can change population evolution radically. We have found that long-lived coexistence emerges for sufficient toxin level variation, while variability in the resource level can oppose coexistence due to population bottlenecks which increase the strength of demographic fluctuations. In considering twofold environmental variations, we have shown that these can have qualitative effects on the population evolution.

References

- [1] - J. O'Neill, report, Government of the United Kingdom, May 2016.
 [2] - J. Cremer, T. Reichenbach, and E. Frey, New Journal of Physics, vol. 11, p. 093029, Sept. 2009.

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