Eco-evolutionary dynamics of cooperative antimicrobial resistance in time-varying environments with spatial structure

Lluís Hernández-Navarro, Matthew Asker,
Kenneth Distefano, Alastair M. Rucklidge,
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ANR meeting 28-29/11/24

UKRI Engineering and Physical Sciences Research Council

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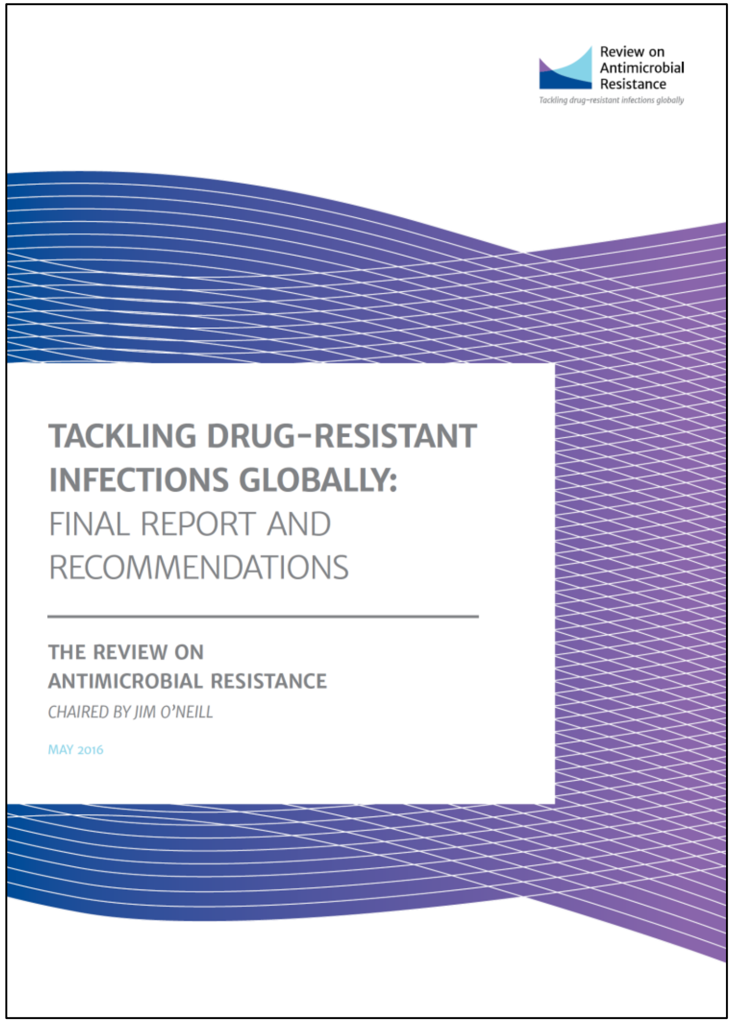
Some context on AntiMicrobial Resistance (AMR)



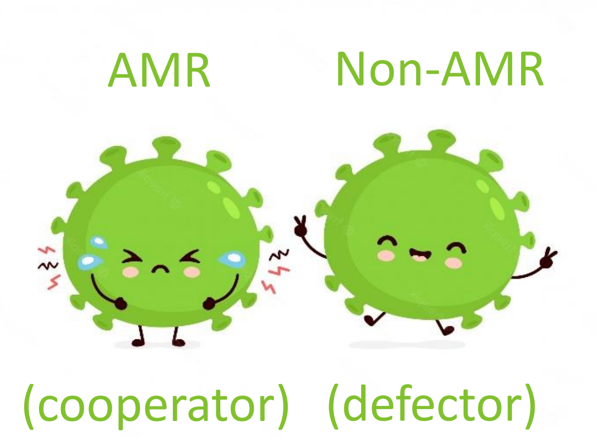
- 10^6 deaths/year

- 20 billion $ US health excess costs

- 10^7 deaths/year by 2050 (more than cancer)

J. O'Neill, *Tackling drug-resistant infections globally: final report and recommendations*, Review on Antimicrobial Resistance (2016)

AMR: <u>**cooperative (Public Good)**</u> and comes with an <u>**extra metabolic cost**</u>



Microorganisms live in ecologically **dynamic environments.**

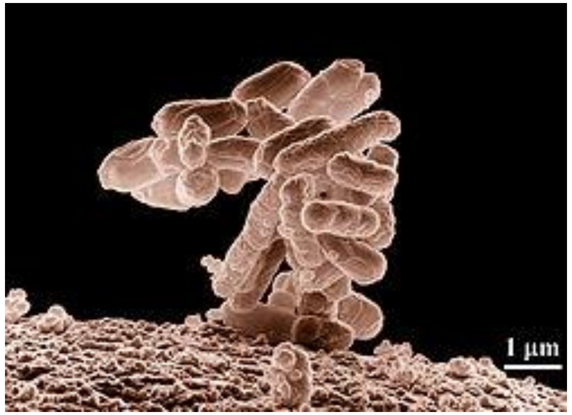
Main question(s)

In dynamic environments, when do resistant and sensitive strains coexist?

Otherwise, which strain dominates?

Model

(inspired by experiments with E. Coli, ampicillin, and pSEVA121 at ICL)



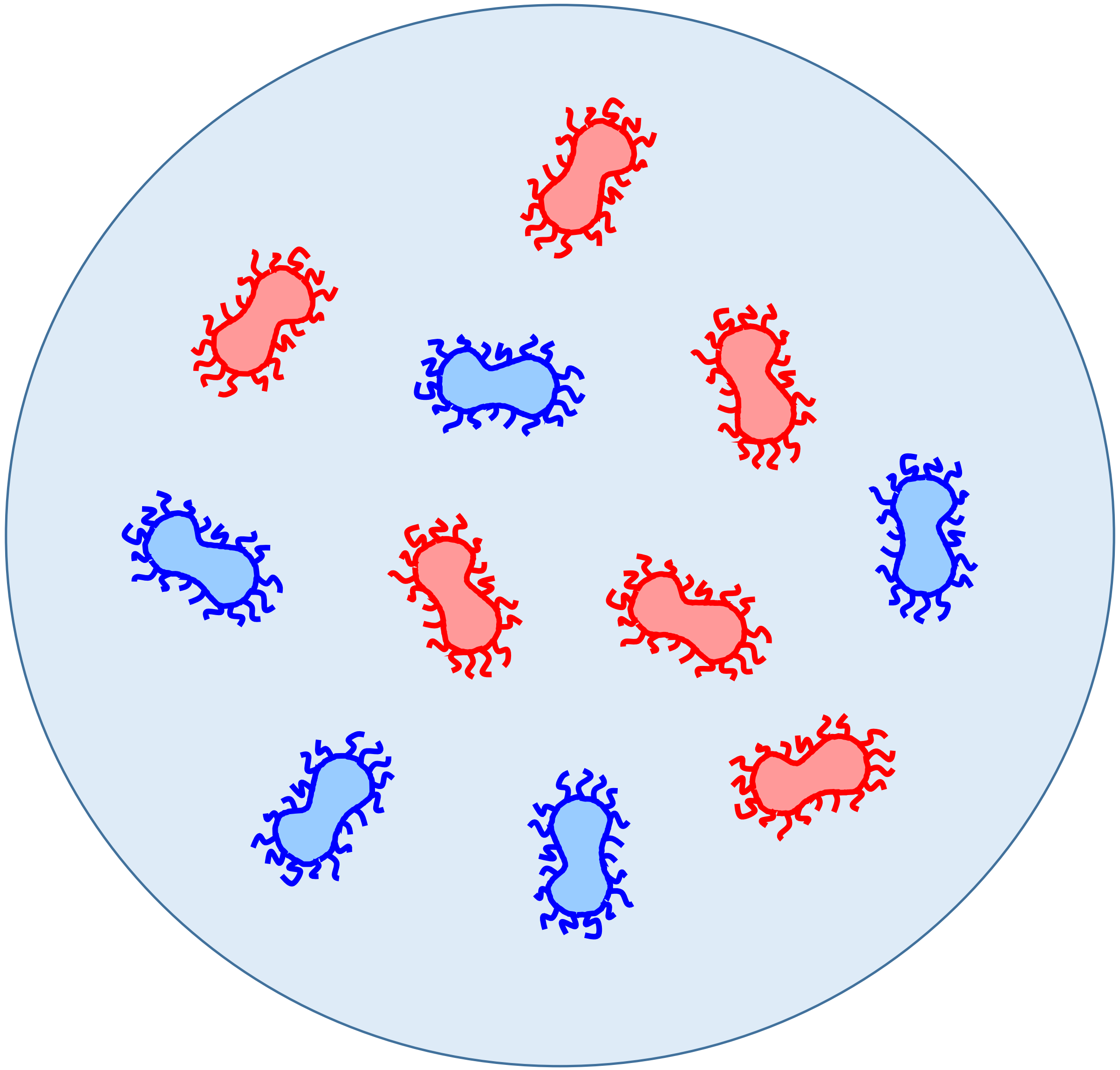
E. Coli

Imperial College London

PhD candidate
Said Muñoz Montero

Prof. José Jiménez

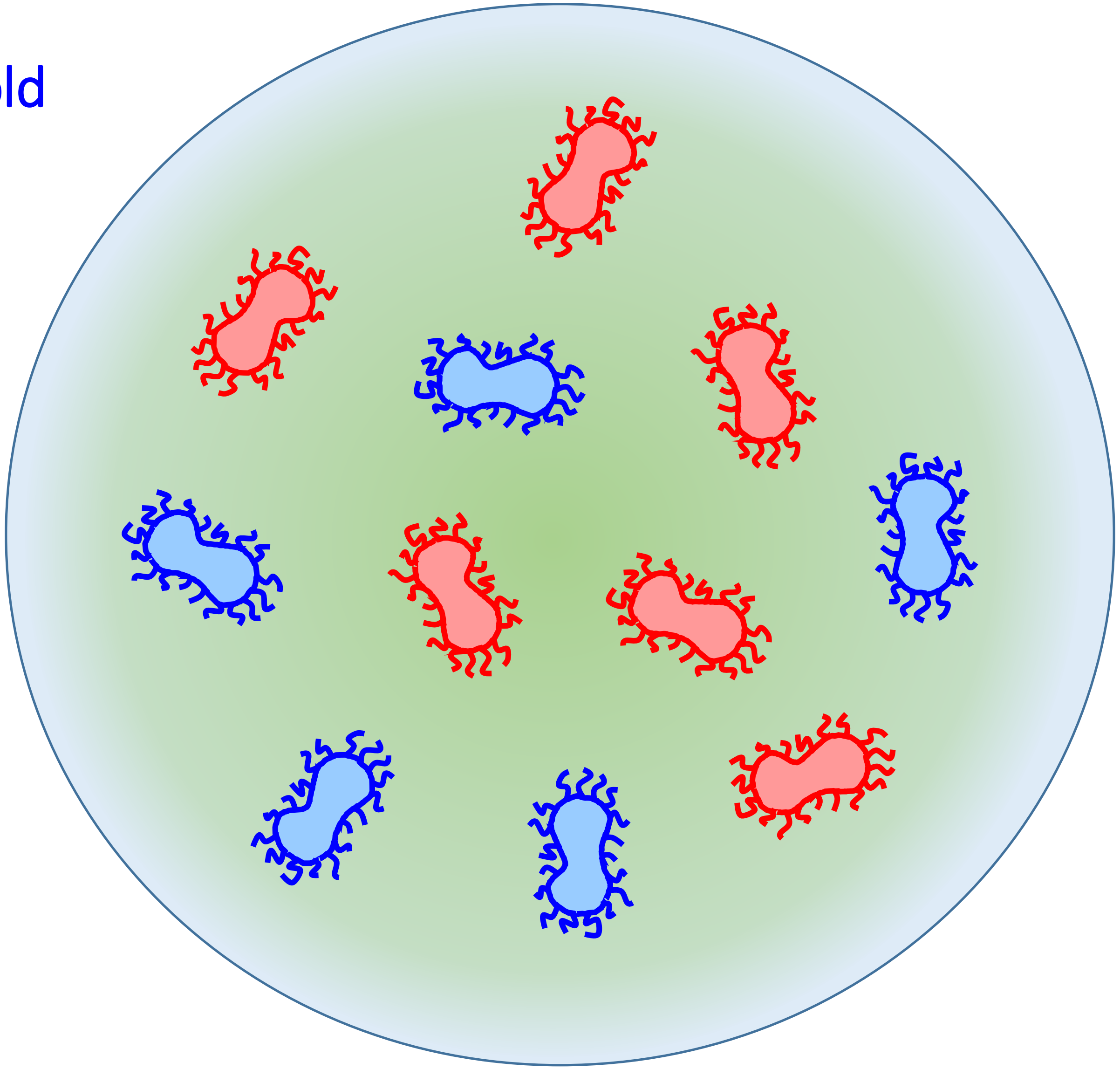
$$N = N_R + N_S$$



$$N = N_R + N_S$$

$$N_R \geq N_{Threshold}$$

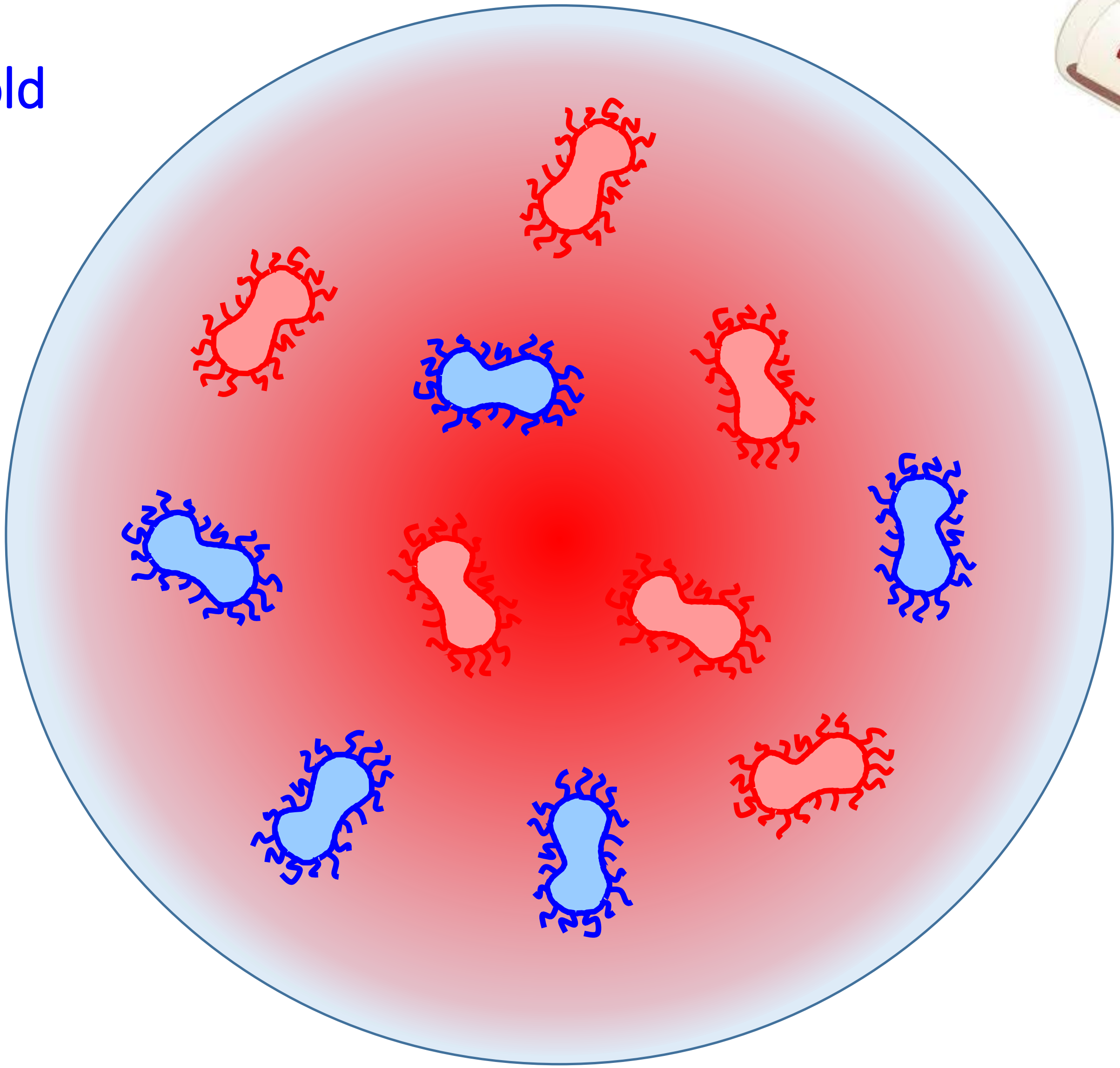
Cooperation:
Public Good (PG)



$$N = N_R + N_S$$

$$N_R \geq N_{Threshold}$$

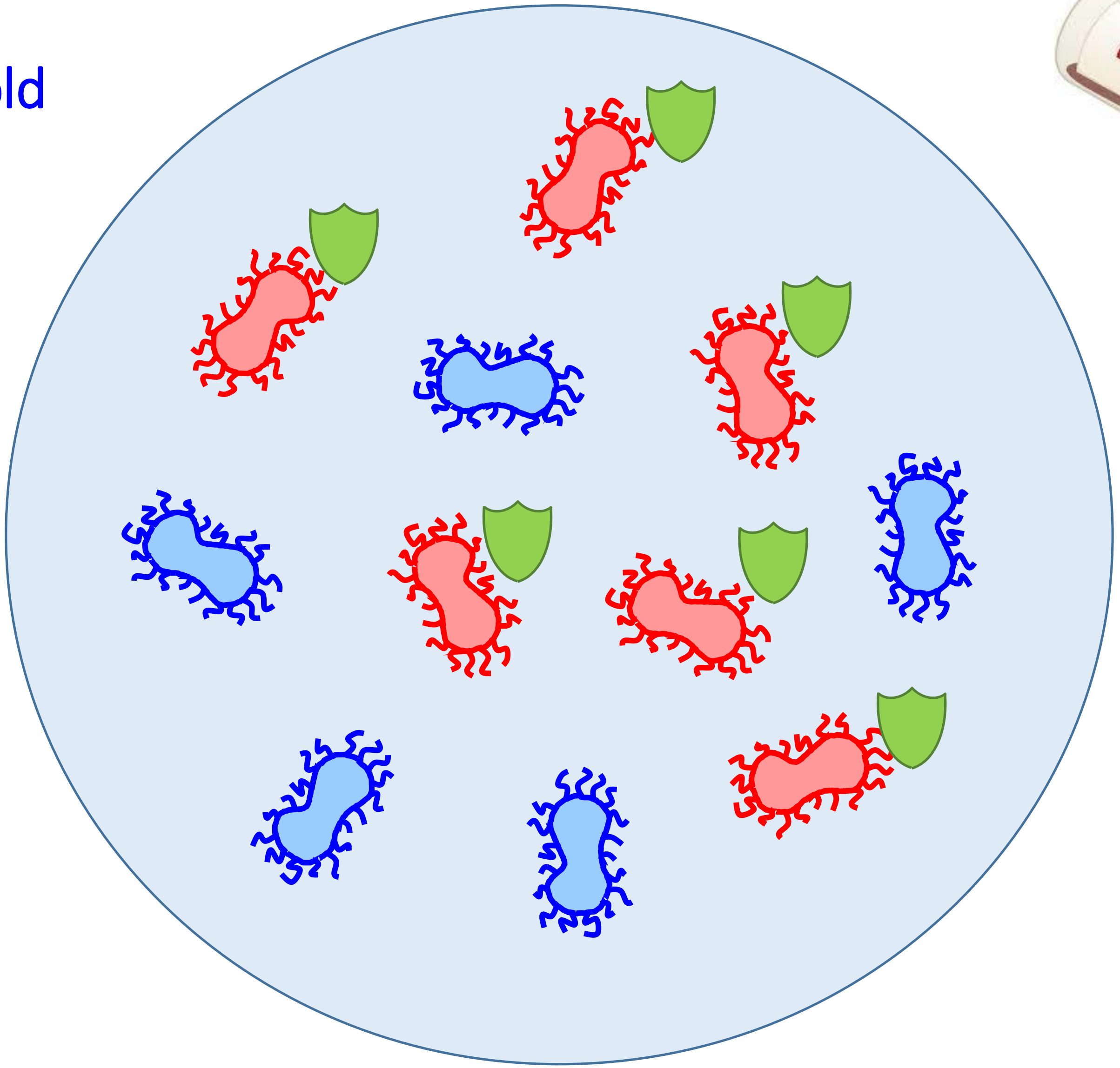
Antimicrobial drug



$$N = N_R + N_S$$

$$N_R \geq N_{Threshold}$$

Public Good protects **S** at the expense of **R** metabolism

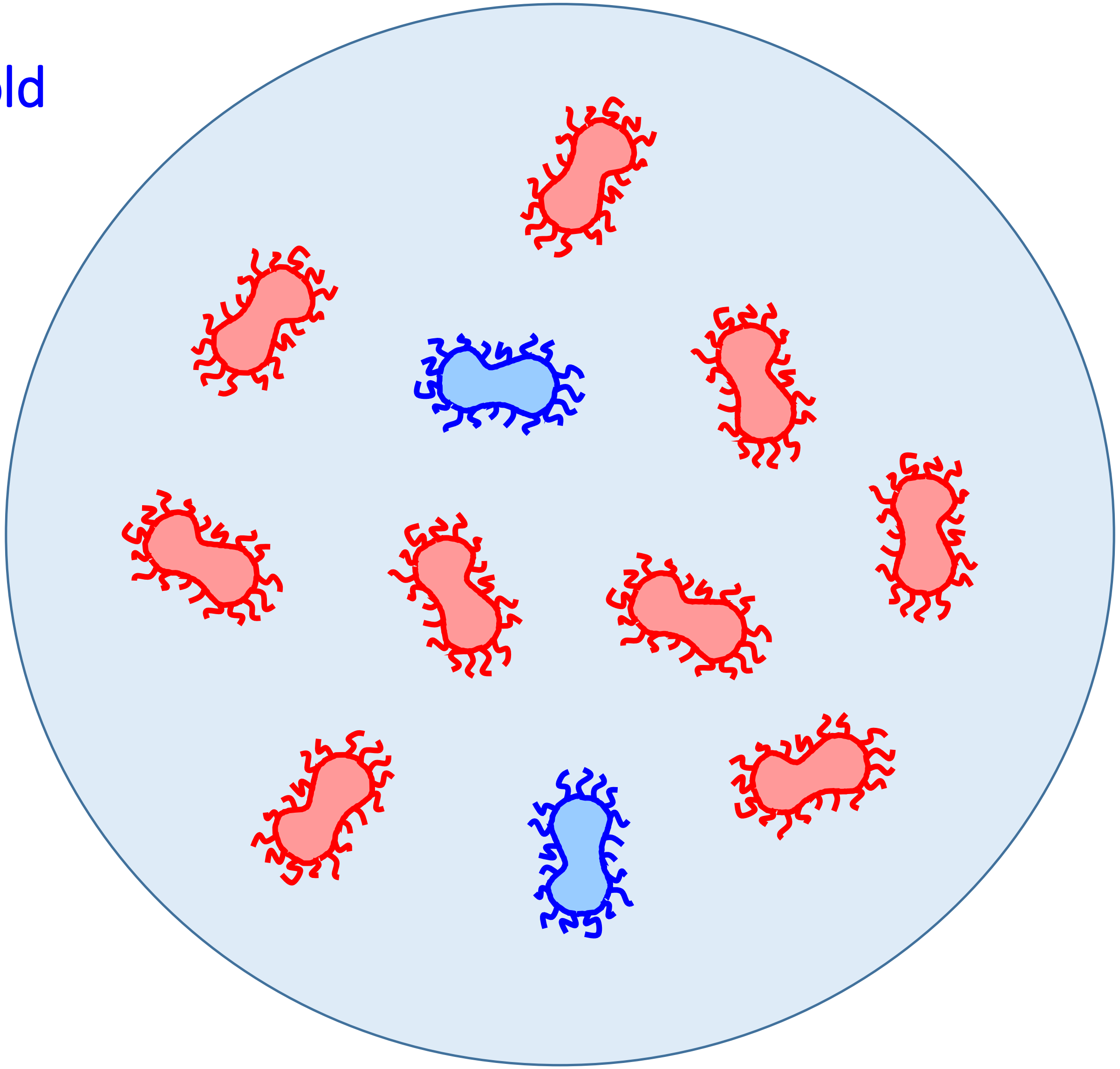


S take advantage!

But if $N_R < N_{threshold}$ …

$$N = N_R + N_S$$

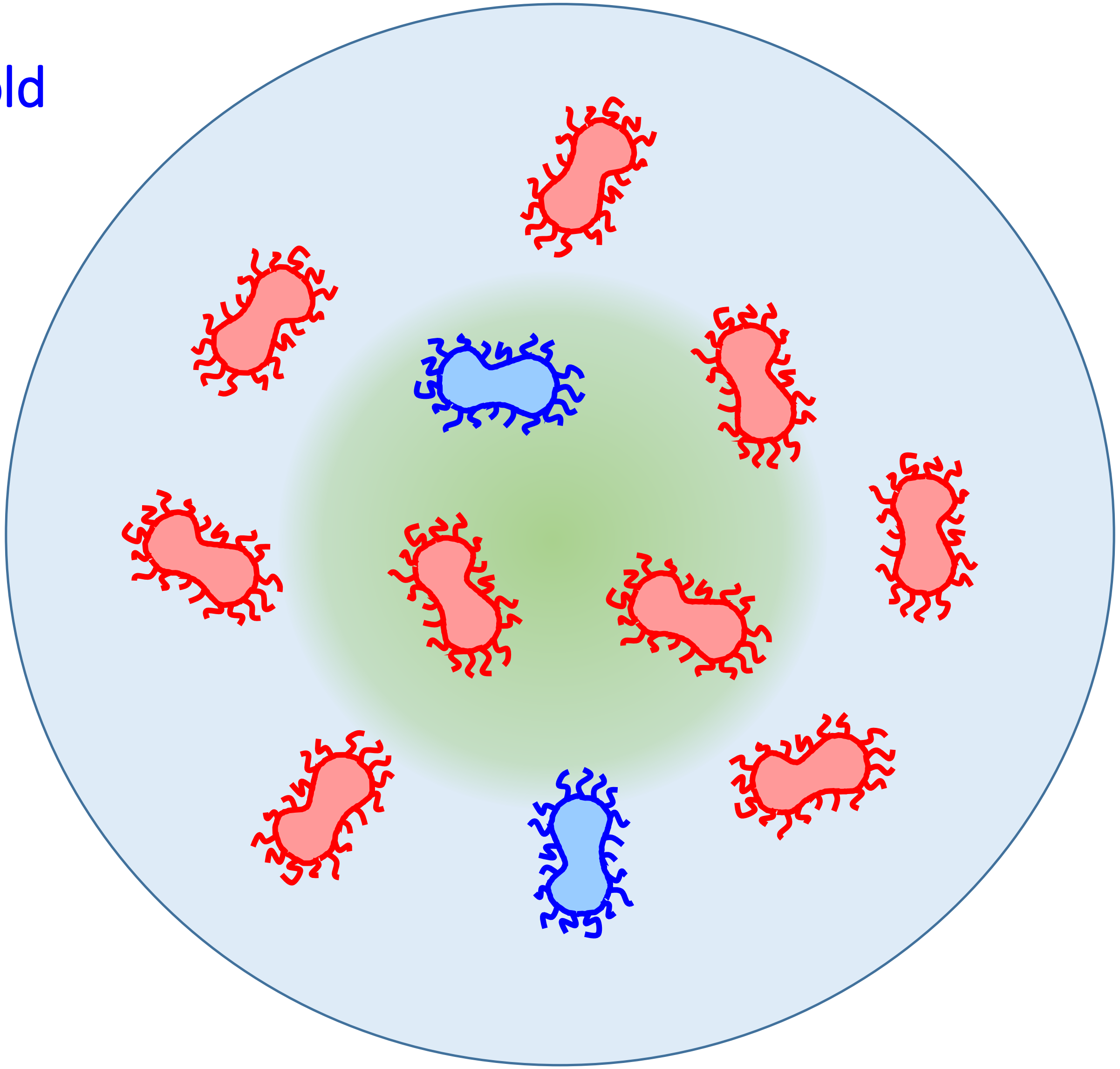
$$N_R < N_{Threshold}$$



$$N = N_R + N_S$$

$$N_R < N_{Threshold}$$

Not enough **R**
for Public Good

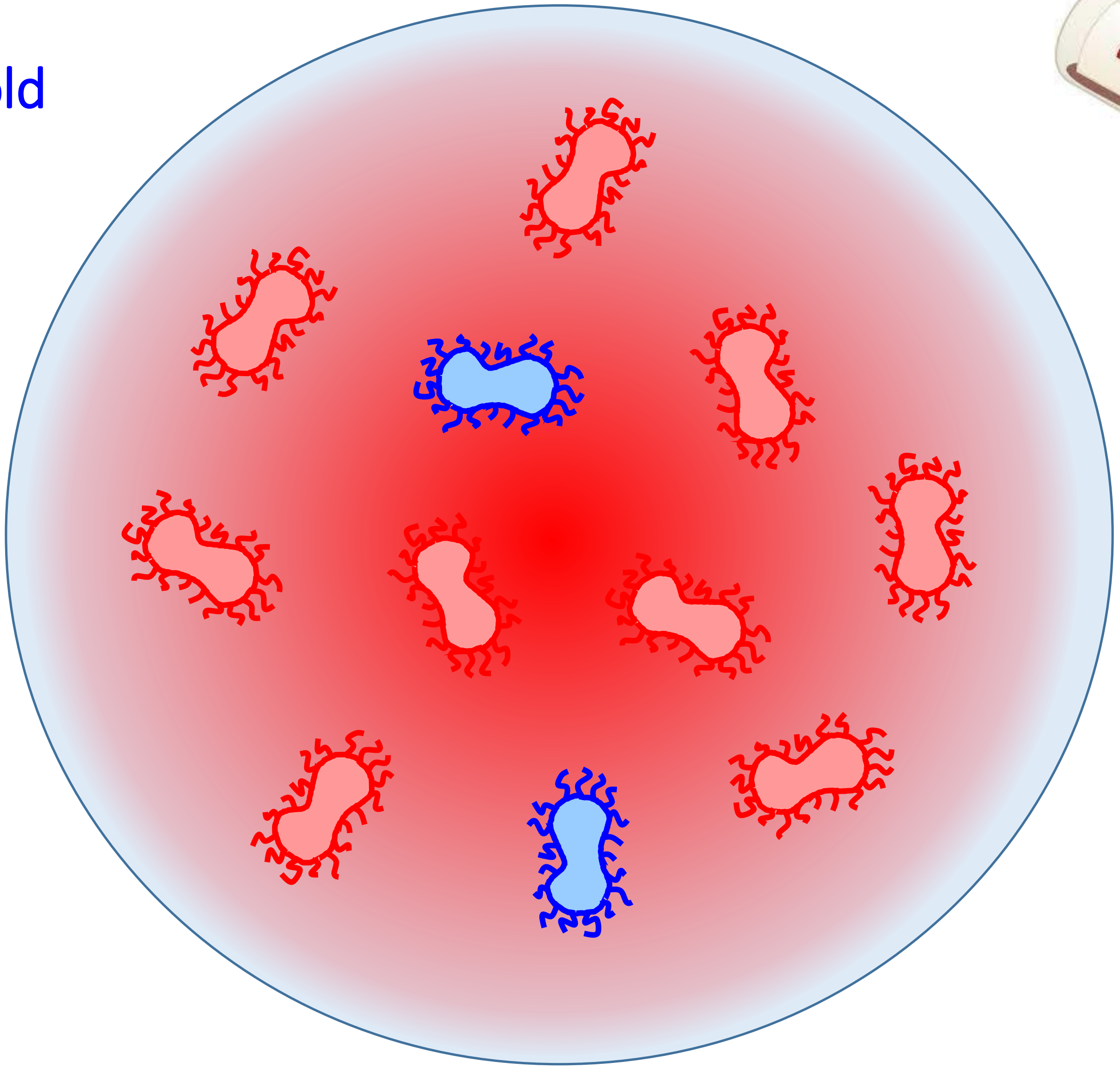


$$N = N_R + N_S$$

$$N_R < N_{Threshold}$$

Not enough **R**
for Public Good

Antimicrobial
drug affects **S**



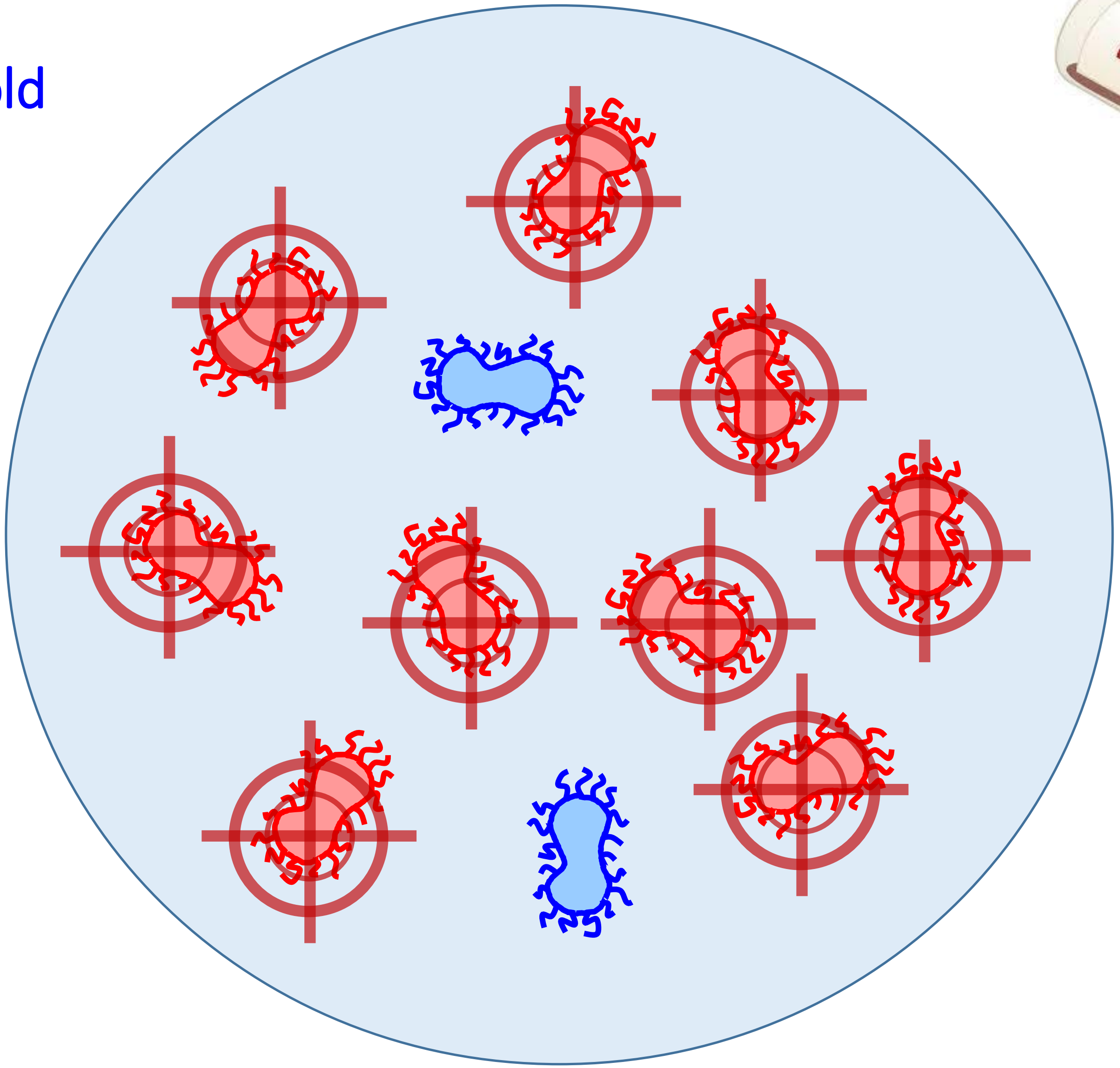
$N = N_R + N_S$

$N_R < N_{Threshold}$

Not enough **R** for Public Good

Antimicrobial drug affects **S**

R take advantage!



Birth rate per capita $\propto$ f_{R} or f_{S}

$$f_R = 1 - s$$

$$0 < s \leq 1$$

(s: AMR extra metabolic cost)

$$f_S = \begin{cases} 1 - a & \text{if } N_{\mathrm{R}} < N_{\mathrm{th}} \\ 1 & \text{if } N_{\mathrm{R}} \geq N_{\mathrm{th}} \end{cases}$$

$$s < a \leq 1$$

(a: biostatic drug impact)

Death rate per capita = $\dfrac{N}{K}$

K is the (constant) carrying capacity

Transition rates

$$N_{C/D} \xrightarrow{T^{+}_{C/D} = \frac{f_{C/D}}{\langle f \rangle} N_{C/D}} N_{C/D} + 1$$

$$N_{C/D} \xrightarrow{T^{-}_{C/D} = \frac{N}{K(t)} N_{C/D}} N_{C/D} - 1,$$

Mean Field (neglect fluctuations)

Wienand, K., Frey, E., & Mobilia, M. (2017), PRL, 119(15), 158301.

Mean Field (neglect fluctuations)

$$\dot{N} = N\left(1 - \frac{N}{K}\right)$$

- **Stable point at N = K**

Wienand, K., Frey, E., & Mobilia, M. (2017), PRL, 119(15), 158301.

Mean Field (neglect fluctuations)

$x \equiv N_R/N$

$$\dot{N} = N\left(1 - \frac{N}{K}\right)$$

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Wienand, K., Frey, E., & Mobilia, M. (2017), PRL, 119(15), 158301.

Mean Field (neglect fluctuations)

$x \equiv N_R/N$

$$\dot{N} = N\left(1 - \frac{N}{K}\right)$$

$$\dot{x} \propto \begin{cases} (a-s)\cdot x(1-x) & 0 \leq x < x_{th} \\ -s\cdot x(1-x) & x_{th} \leq x \leq 1 \end{cases}$$

- **Stable point at N = K**

Equilibrium at $x = x_{th} \equiv N_{th}/N$

(coexistence)

Wienand, K., Frey, E., & Mobilia, M. (2017), PRL, 119(15), 158301.

Mean Field (neglect fluctuations)

$x \equiv N_R/N$

Big populations in static environments:

Stable coexistence at $N_R = N_{th}$ and $N_S = K - N_{th}$

- **Stable point at $N = K$**

- **Equilibrium at $x = N_{th}/N$**

  (coexistence)

Wienand, K., Frey, E., & Mobilia, M. (2017), PRL, 119(15), 158301.

Beyond Mean Field:

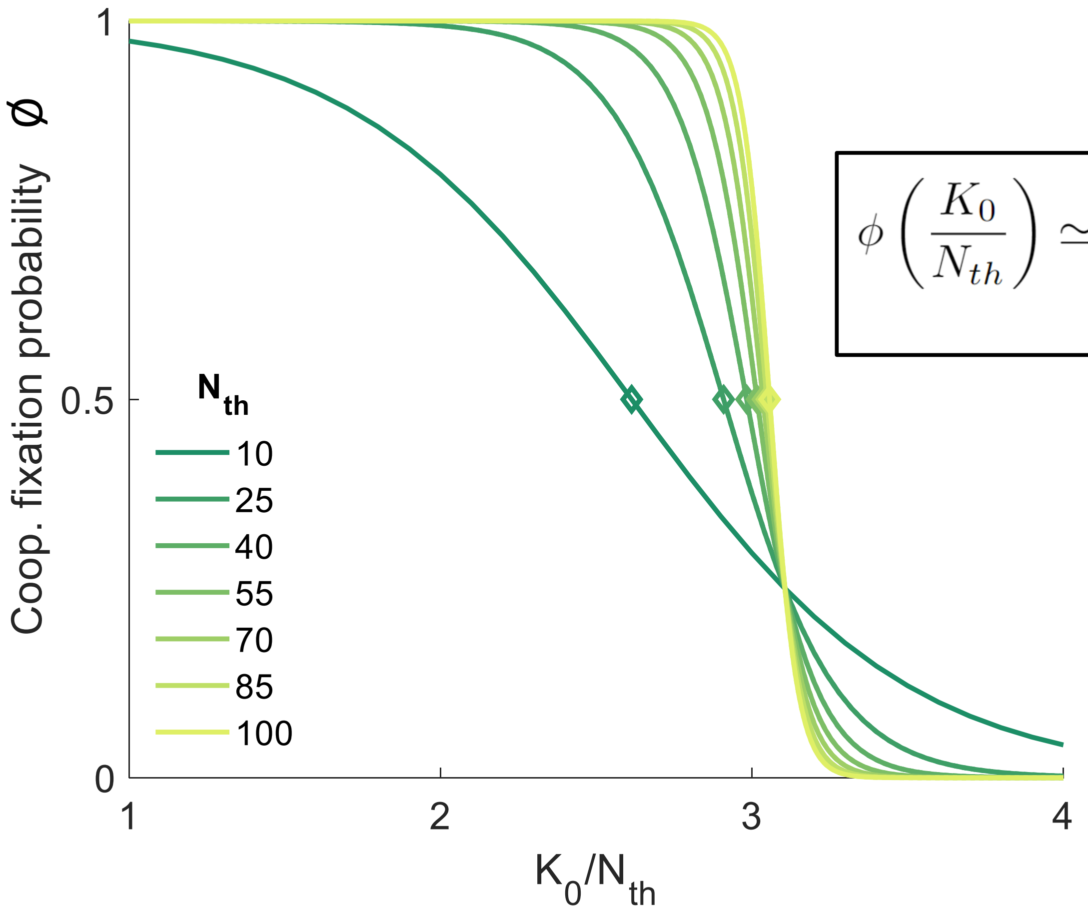
Role of demographic (x) fluctuations

Beyond Mean Field:

Role of demographic (x) fluctuations

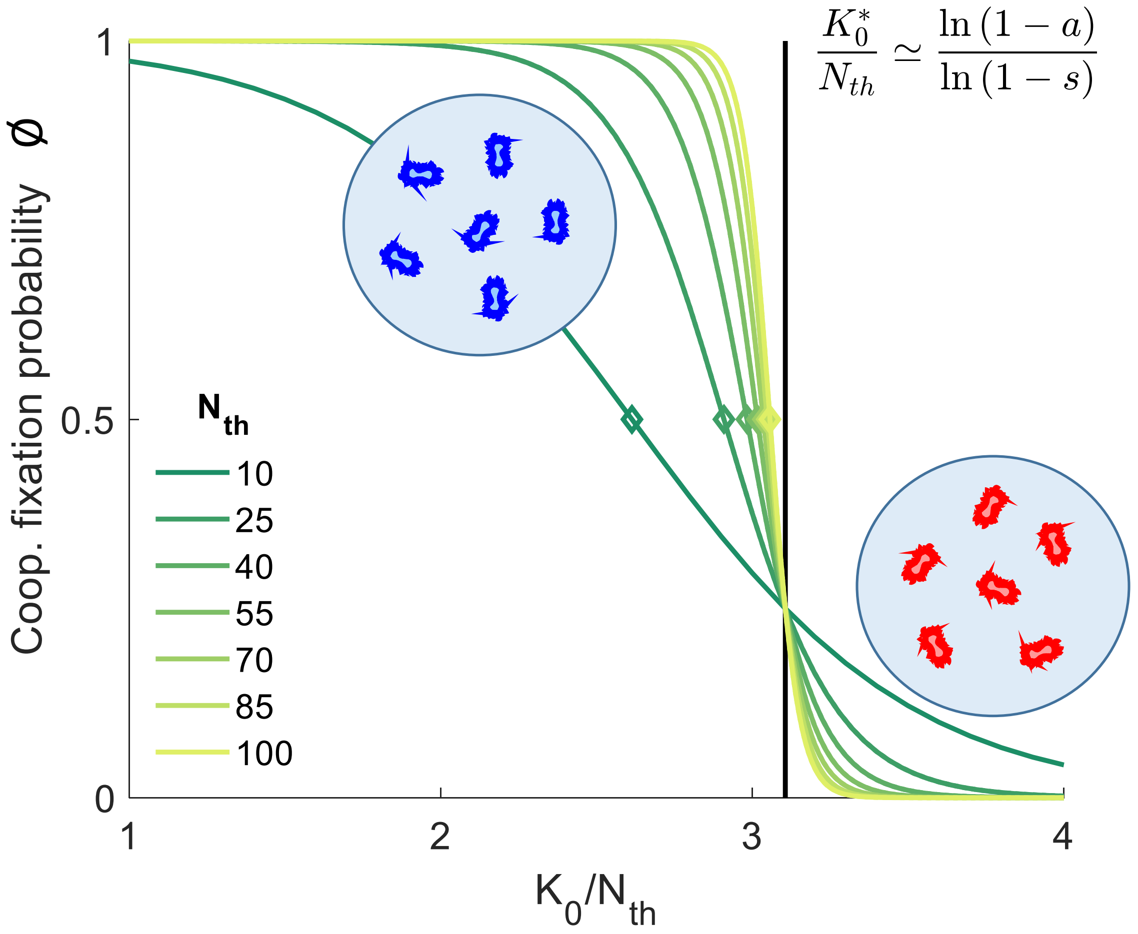
Assume Moran process (fixed $N=K_0$)

Fixation probability

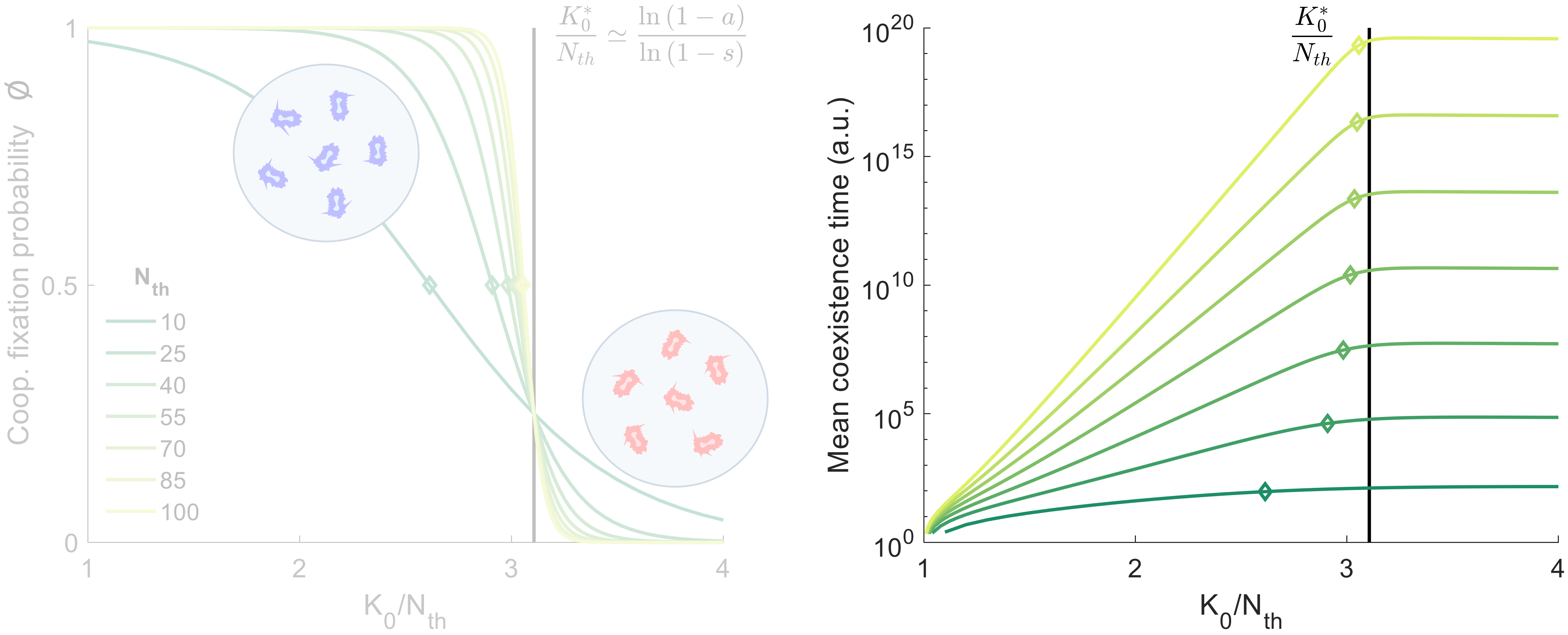


$$\phi\left(\frac{K_0}{N_{th}}\right) \simeq \frac{1}{1+(1-s)^{-N_{th}\left[\frac{K_0}{N_{th}}-\frac{K_0^*}{N_{th}}\right]}} \quad \text{with} \quad \frac{K_0^*}{N_{th}} = \frac{\ln(1-a)}{\ln(1-s)} + \mathcal{O}\left(N_{th}^{-1}\right)$$

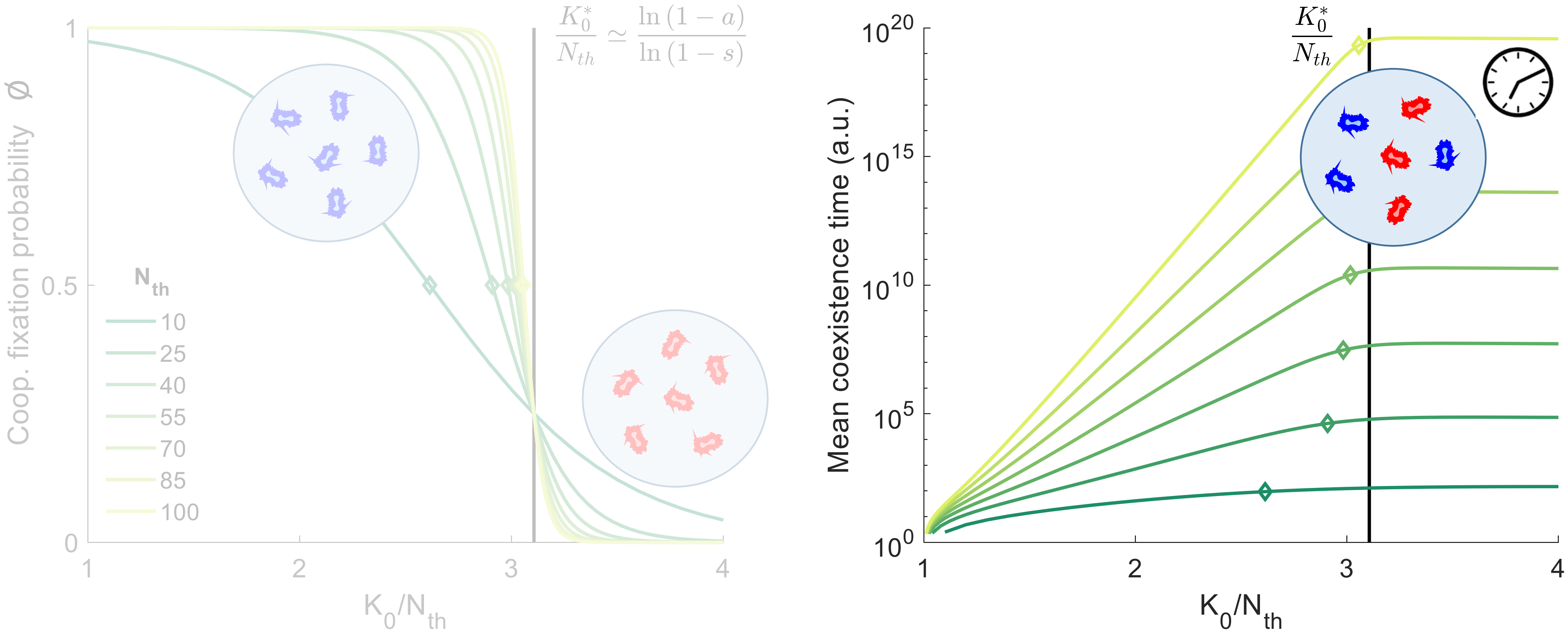
Fixation probability



Coexistence time



Coexistence time



Small populations in static environments:

AMR is doomed to survive!

Does AMR survive in dynamic environments as well?

Eco-Evolutionary dynamics: beyond static environments

Before: demographic fluctuations only

Now: demographic + environmental fluctuations
(N changes driven by K(t))

INTERFACE

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Research

Coupled environmental and demographic fluctuations shape the evolution of cooperative antimicrobial resistance

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Eco-evolutionary dynamics of cooperative antimicrobial resistance in a population of fluctuating volume and size

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Abstract
Antimicrobial resistance to drugs (AMR), a global threat to human and animal health, is often regarded as resulting from cooperative behaviour. Moreover, microbes generally evolve in volatile environments that, together with demographic fluctuations (birth and death events), drastically alter population size and strain survival. Motivated by the need to better understand the evolution of AMR, we study a population of time-varying size consisting of two competing strains, one drug-resistant and one drug-sensitive, subject to demographic and environmental variability. This is modelled by a binary carrying capacity

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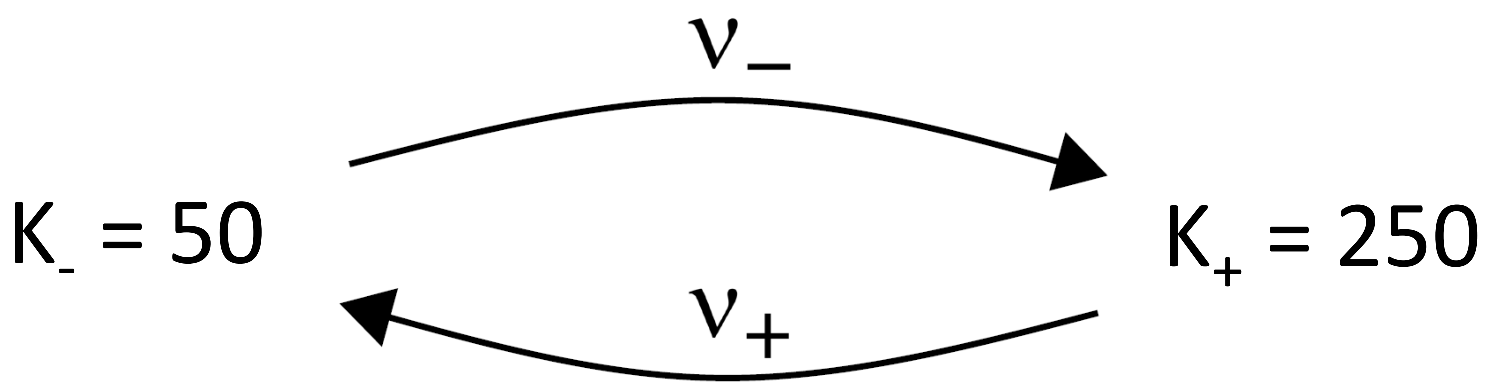
Switching carrying capacity



Mean switching rate

$$\nu \equiv \frac{\nu_- + \nu_+}{2}$$

Environmental bias

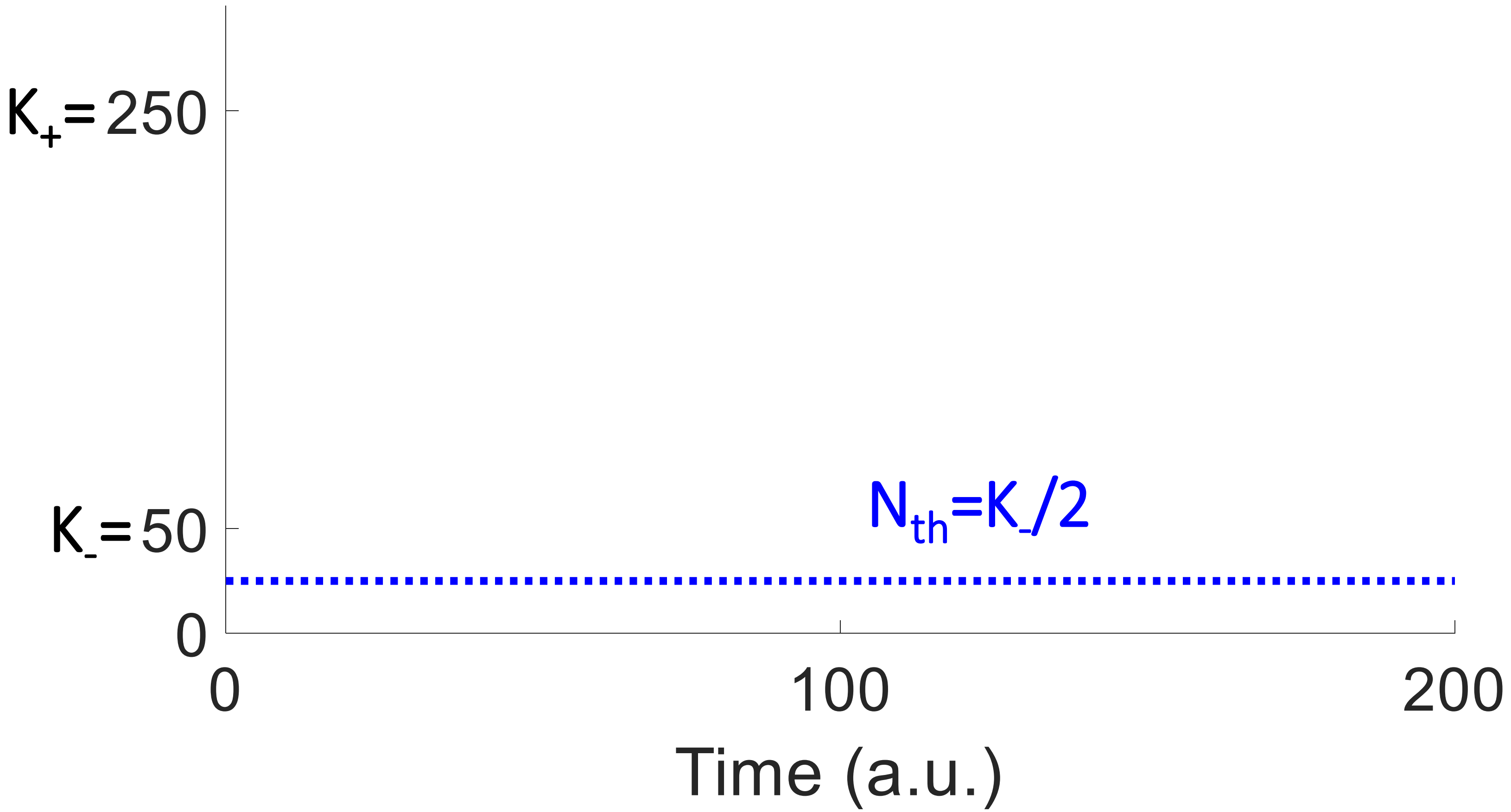
$$\delta \equiv \frac{\nu_- - \nu_+}{2\nu}$$

Master equation in dynamic environments

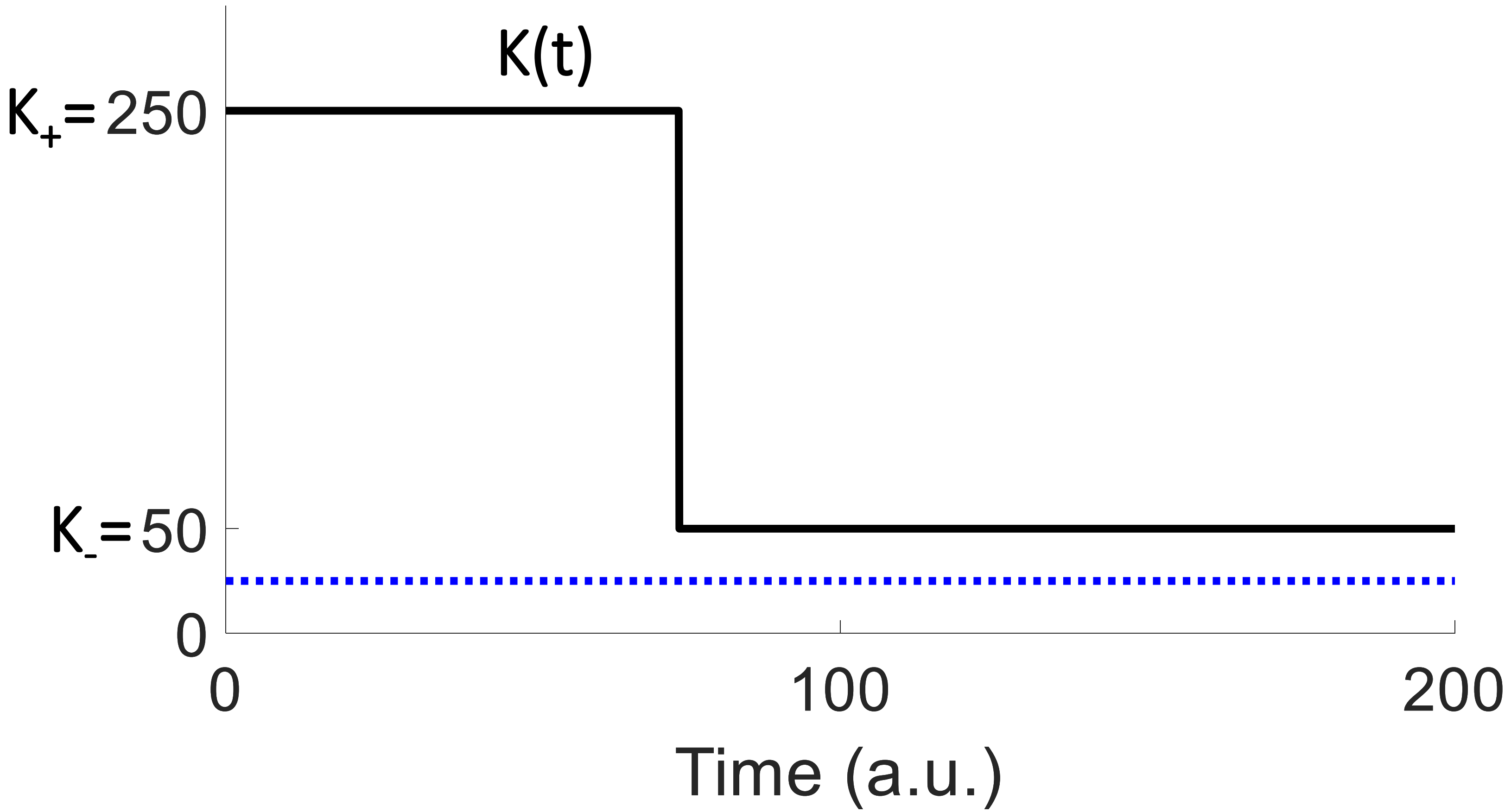
$$\frac{\partial P(N_C, N_D, \xi, t)}{\partial t} = \left(\mathbb{E}_C^- - 1\right)\left[T_C^+ P(N_C, N_D, \xi, t)\right] + \left(\mathbb{E}_D^- - 1\right)\left[T_D^+ P(N_C, N_D, \xi, t)\right]$$
$$+ \left(\mathbb{E}_C^+ - 1\right)\left[T_C^- P(N_C, N_D, \xi, t)\right] + \left(\mathbb{E}_D^+ - 1\right)\left[T_D^- P(N_C, N_D, \xi, t)\right]$$
$$+ \nu_{-\xi} P(N_C, N_D, -\xi, t) - \nu_\xi P(N_C, N_D, \xi, t)$$

$$\mathbb{E}_{C/D}^{\pm} f(N_{C/D}, N_{C/D}, t) = f(N_{C/D} \pm 1, N_{D/C}, t)$$

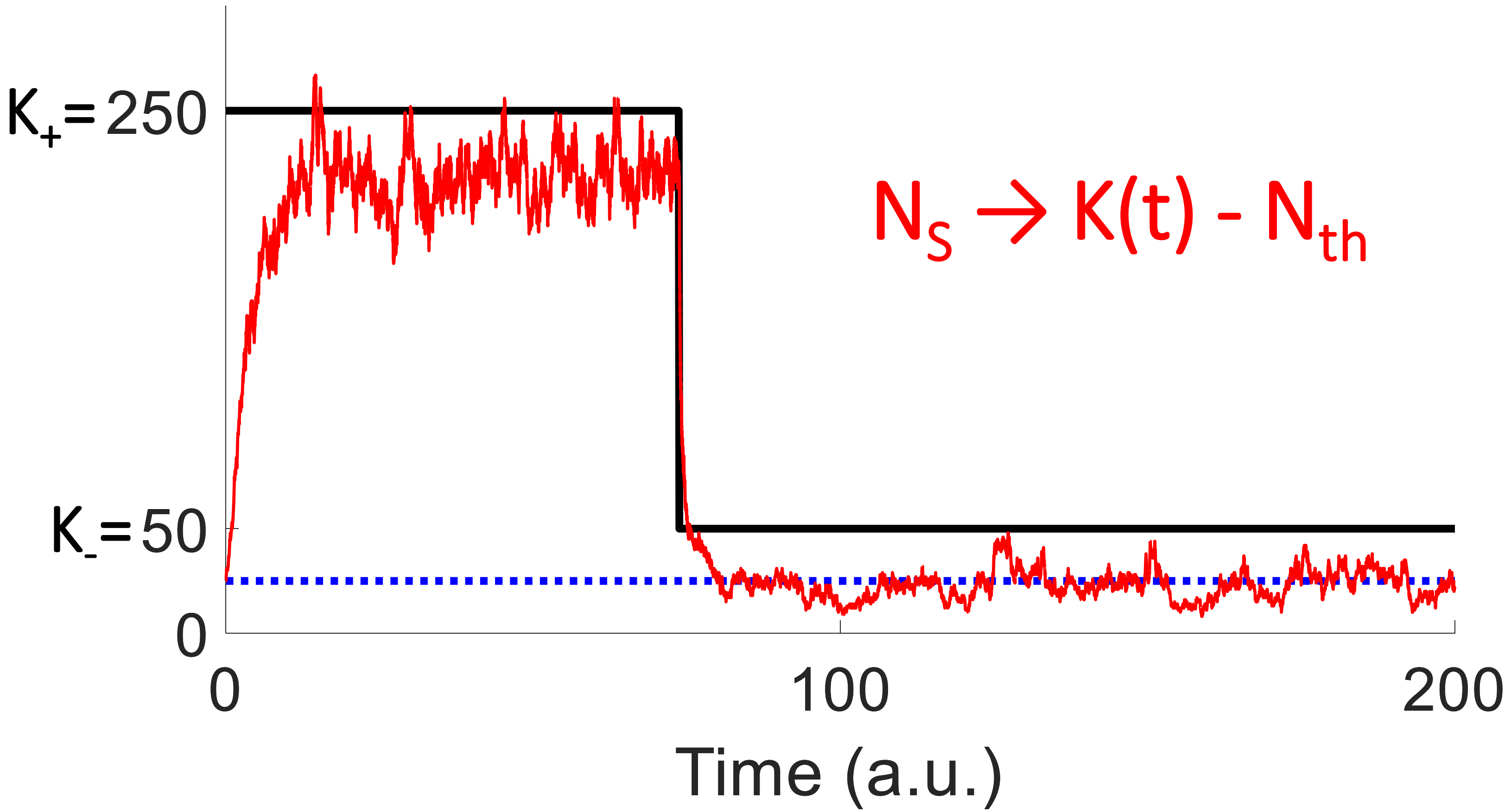
$s = 0.2 \quad a = 0.5 \quad N_{th}=K_-/2$



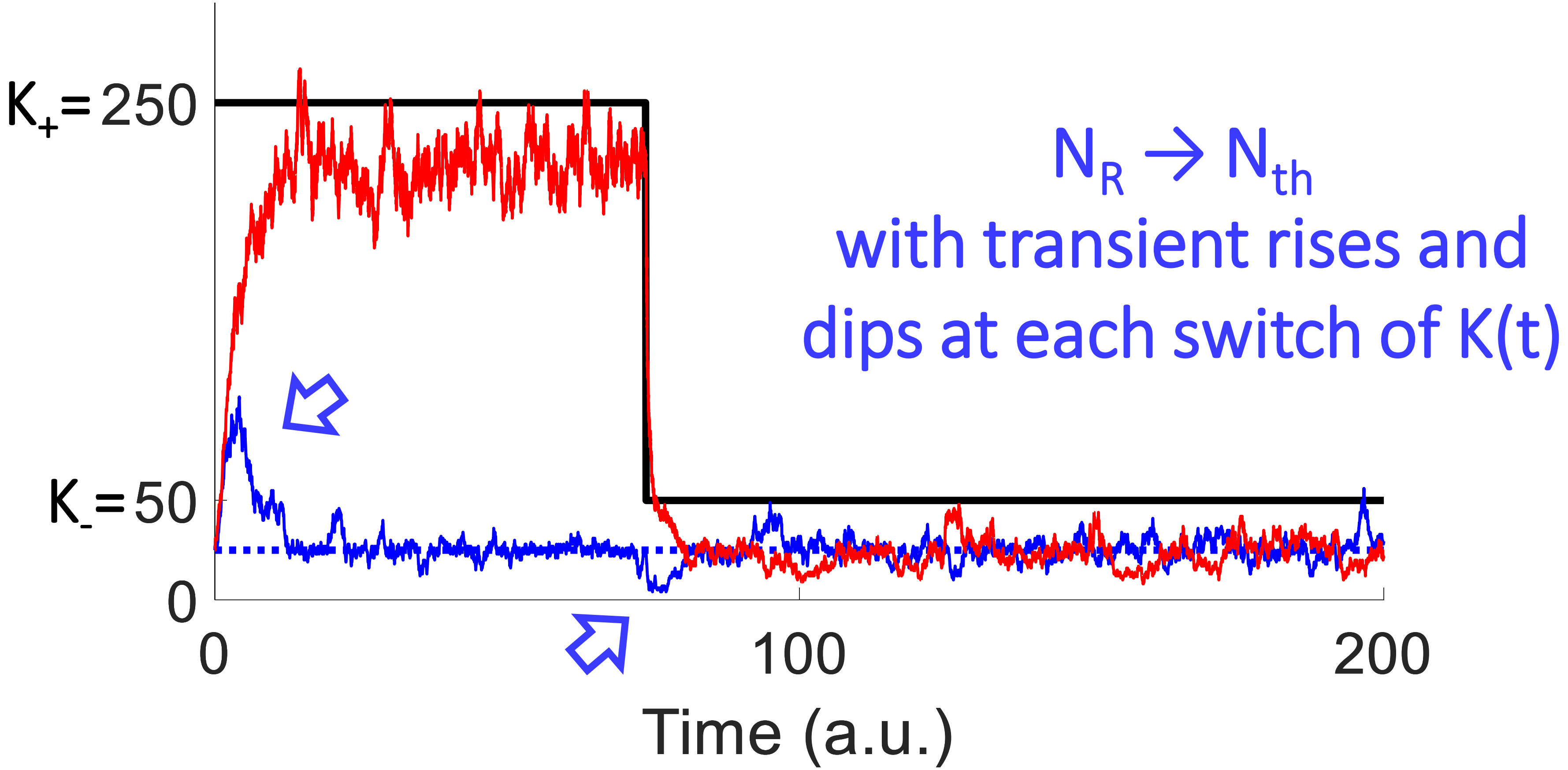
Trajectories in dynamic environments



Trajectories in dynamic environments



Trajectories in dynamic environments



Trajectories in dynamic environments

Remember static environments:

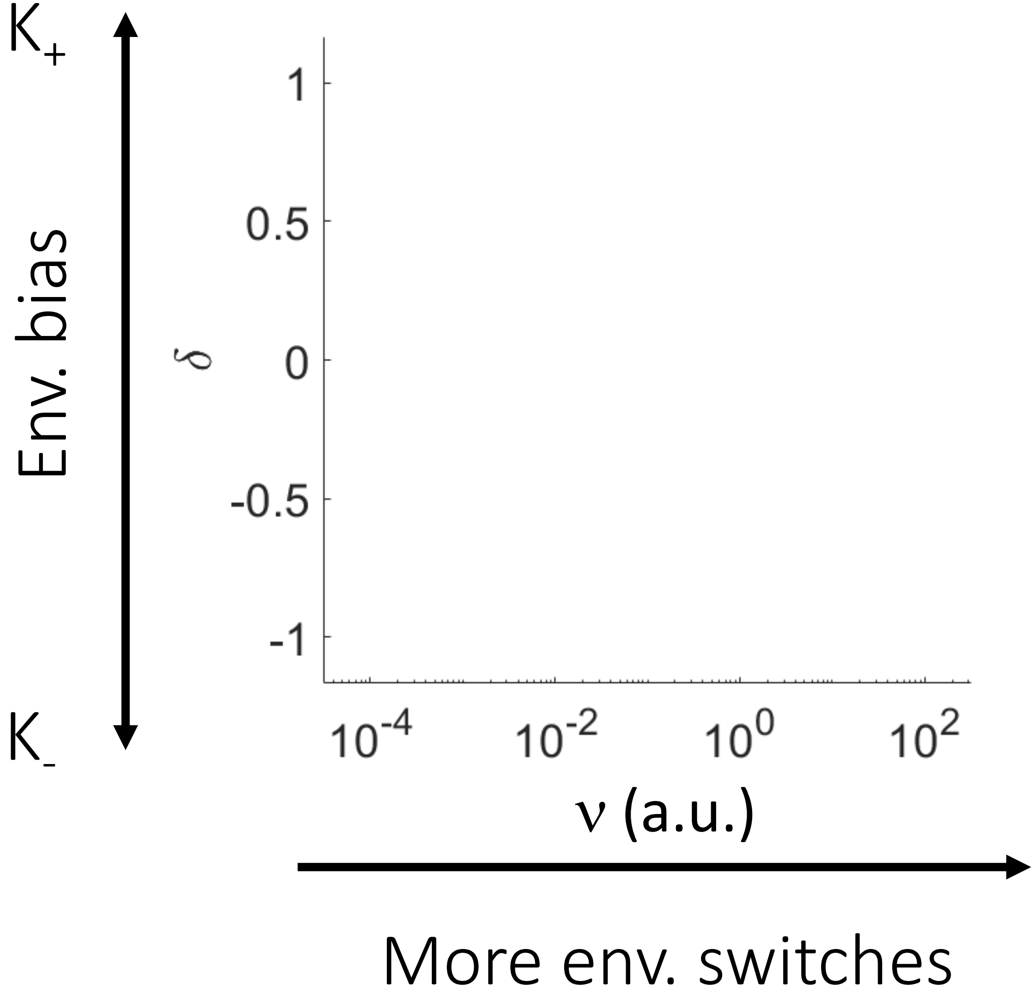
Resistant microbes fixate for K_-

Sensitive cells fixate for K_+

↑

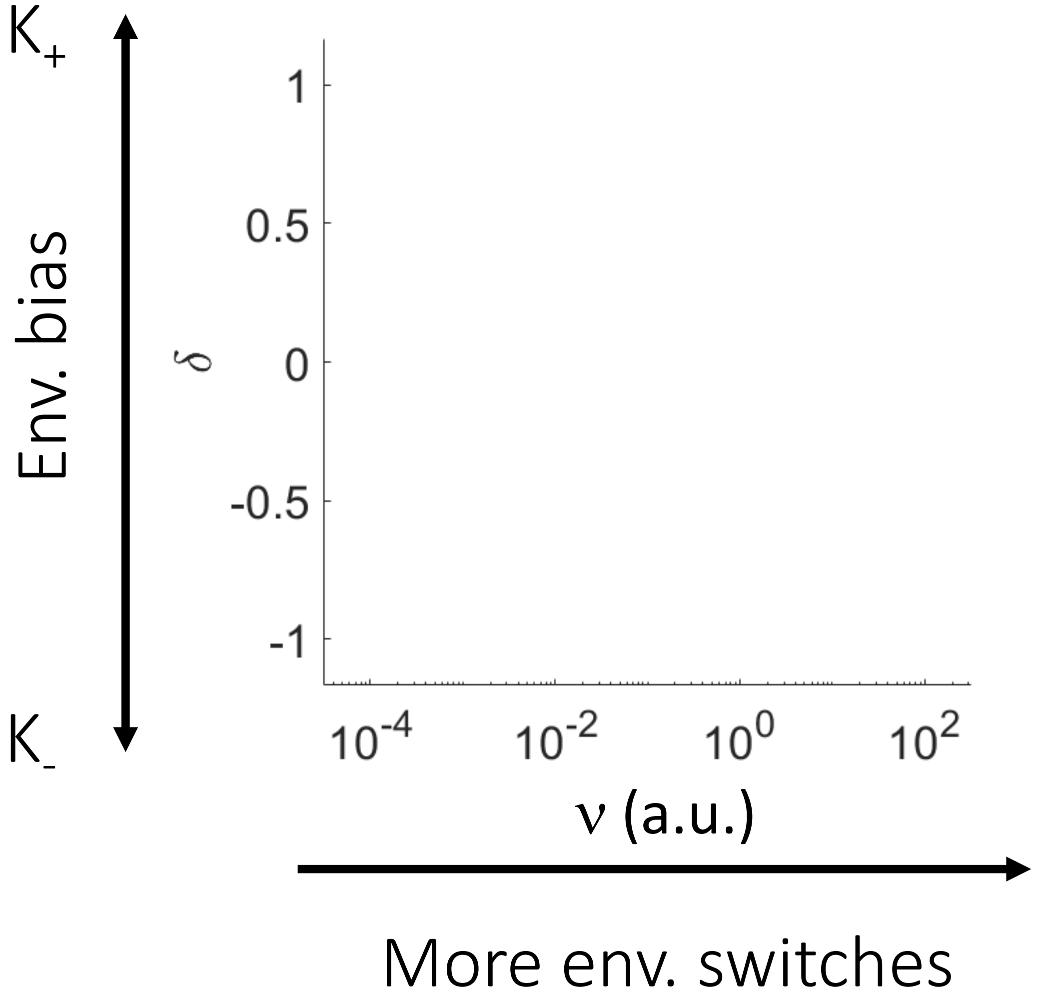
But fixation takes exponentially longer the higher K

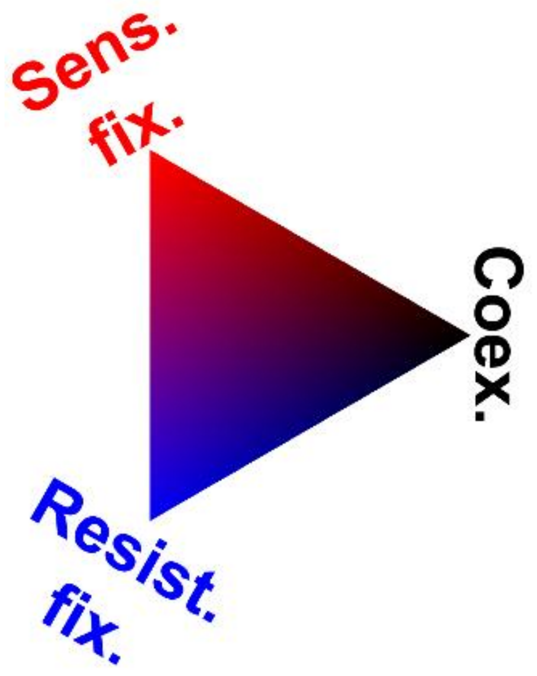
$s = 0.1$ $a = 0.25$ $K_{-}=120$ $K_{+}=1000$



Fixation in dynamic environments?

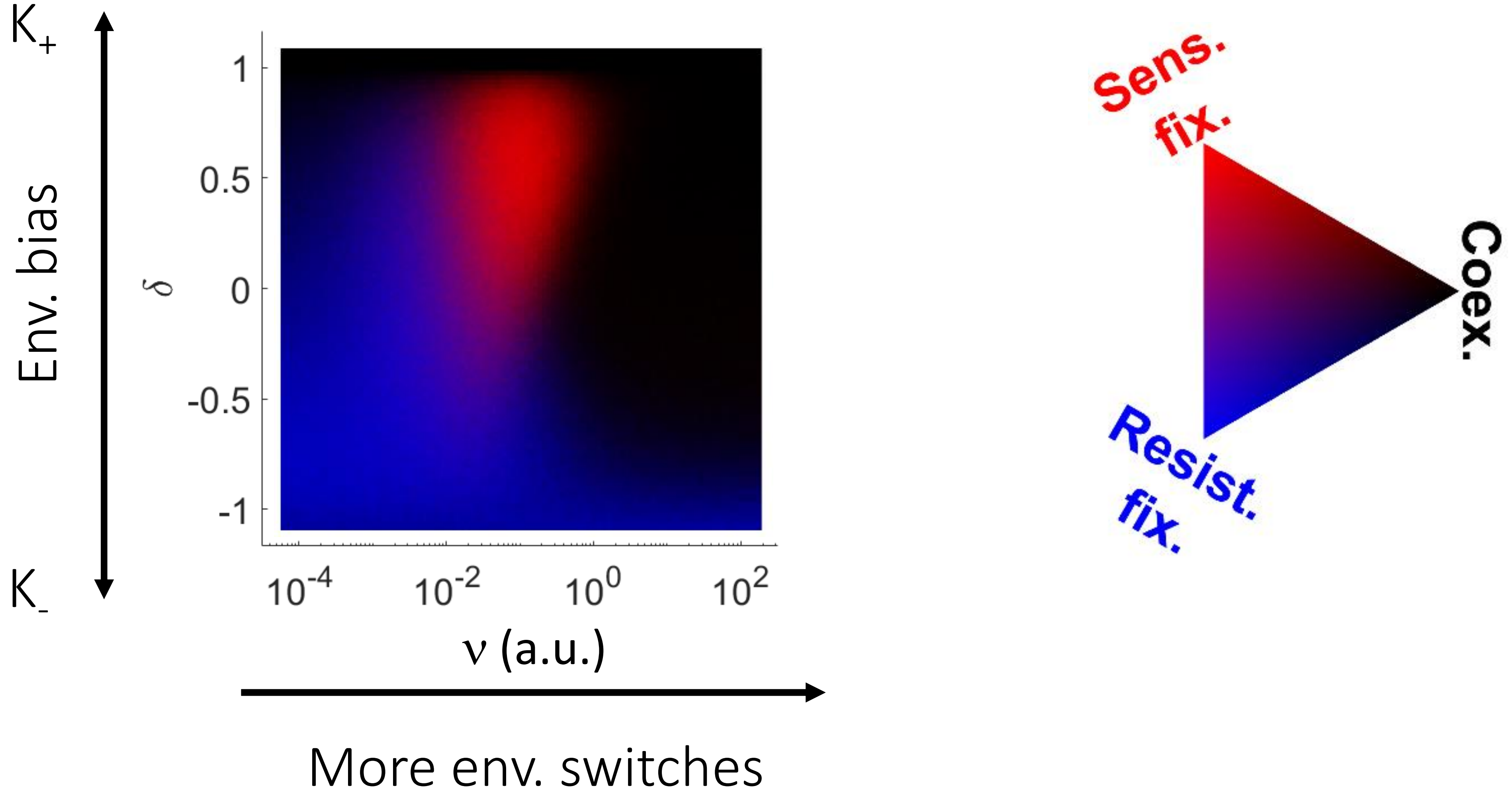
$s = 0.1$ $a = 0.25$ $K_-=120$ $K_+=1000$



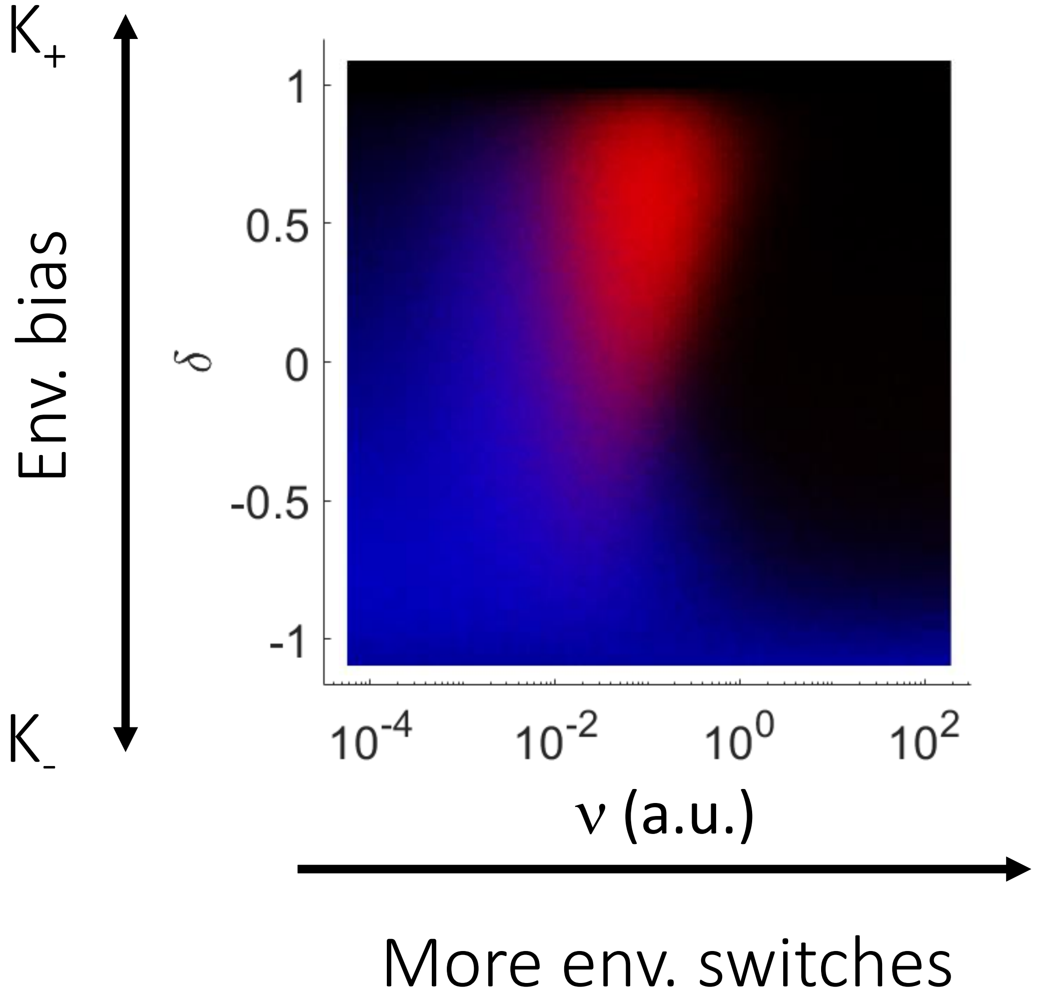


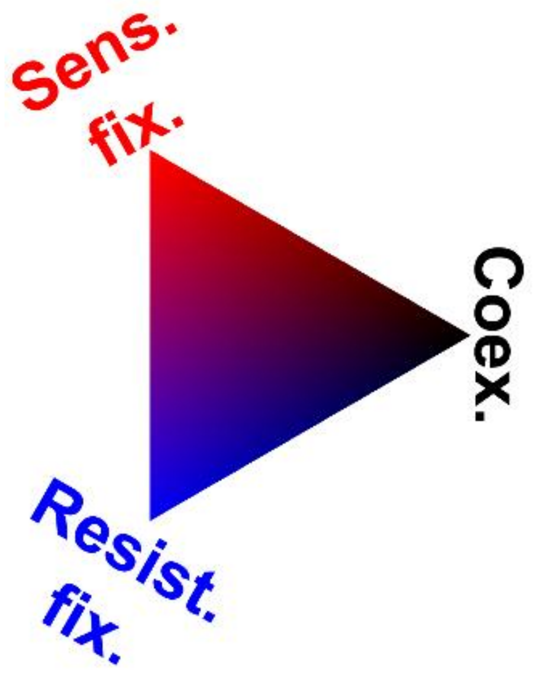
s = 0.1 a = 0.25 K_-=120 K_+=1000

N_{th}=80

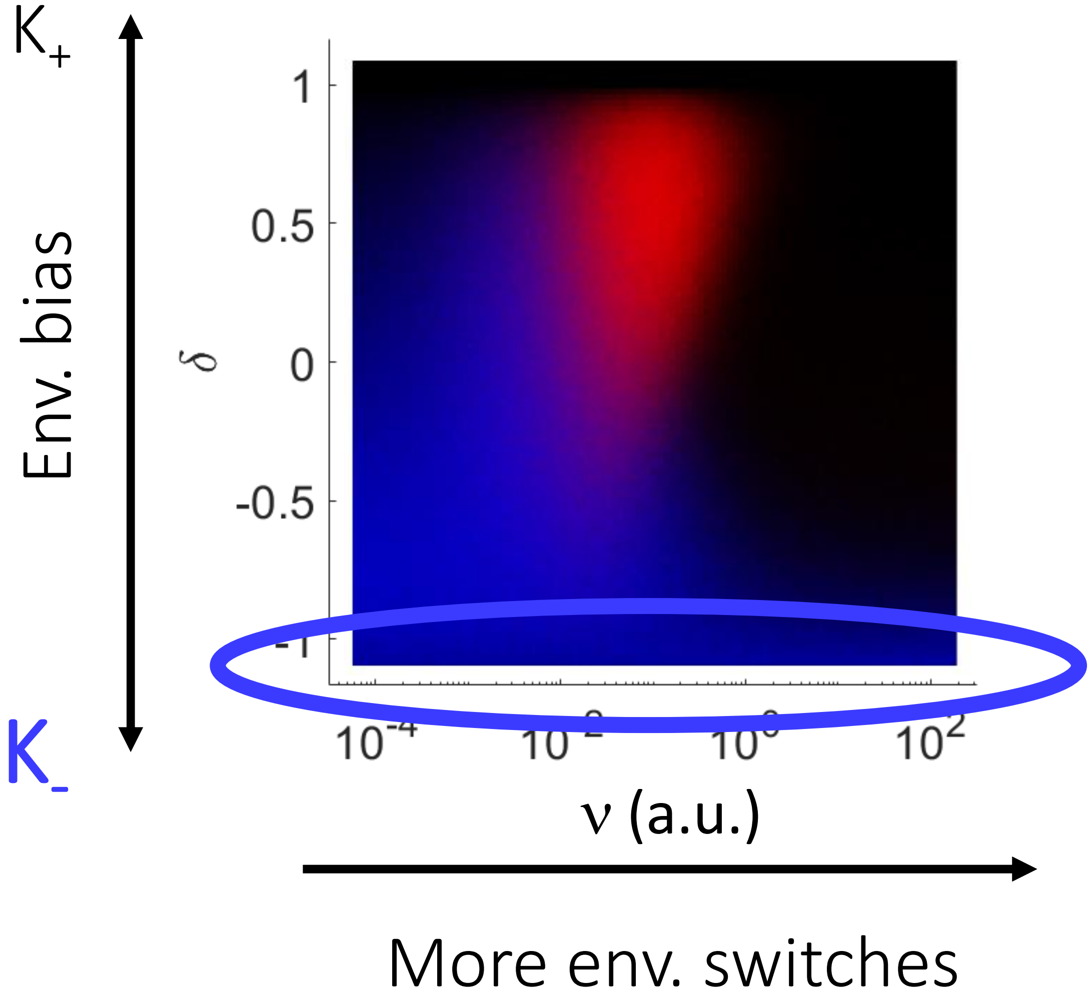


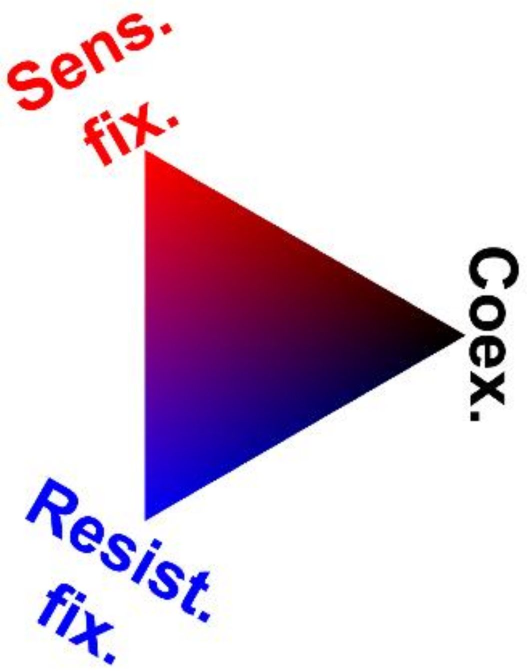
$s = 0.1$ $a = 0.25$ $K_- = 120$ $K_+ = 1000$ $N_{th} = 80$

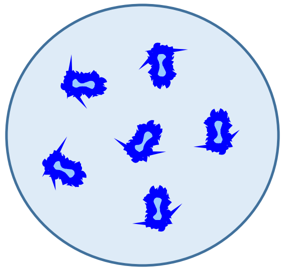




$s = 0.1$ $a = 0.25$ $K_- = 120$ $K_+ = 1000$ $N_{th} = 80$

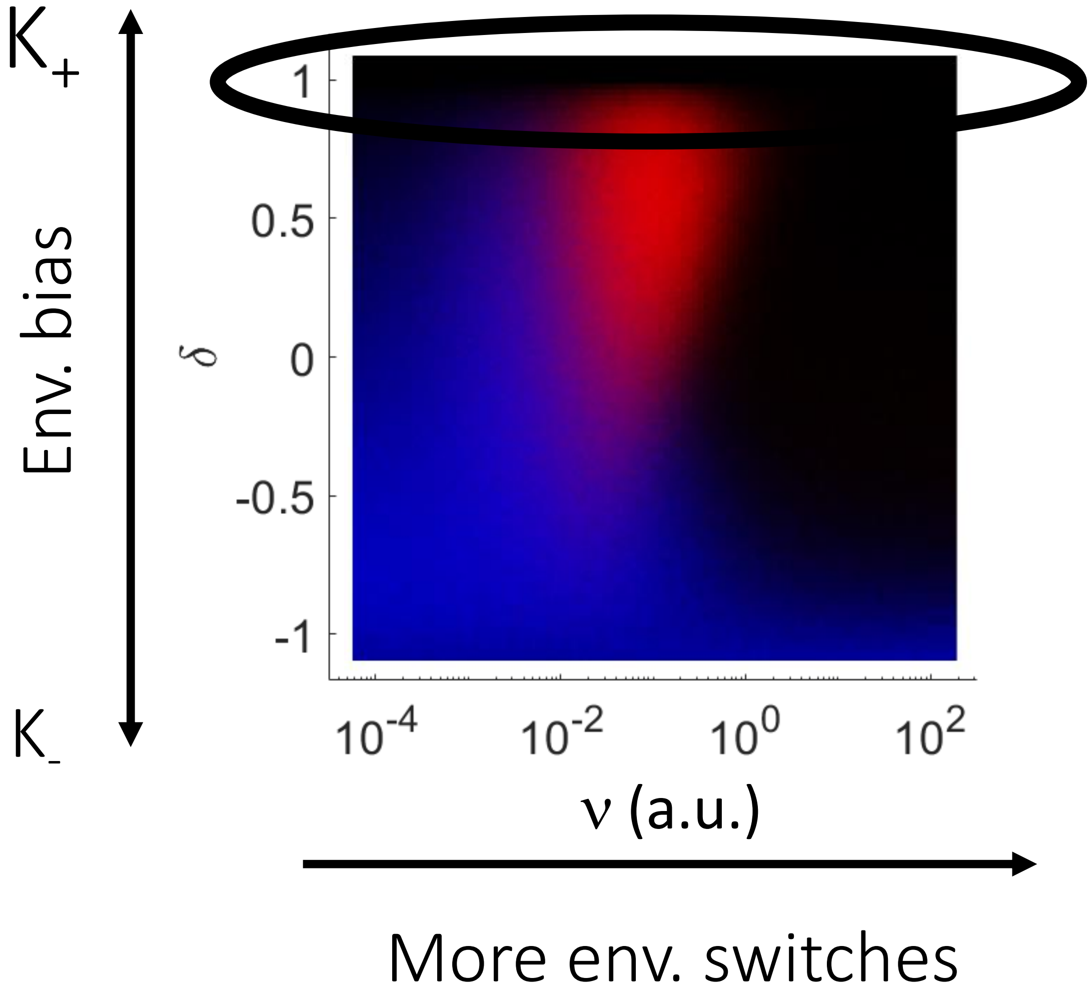


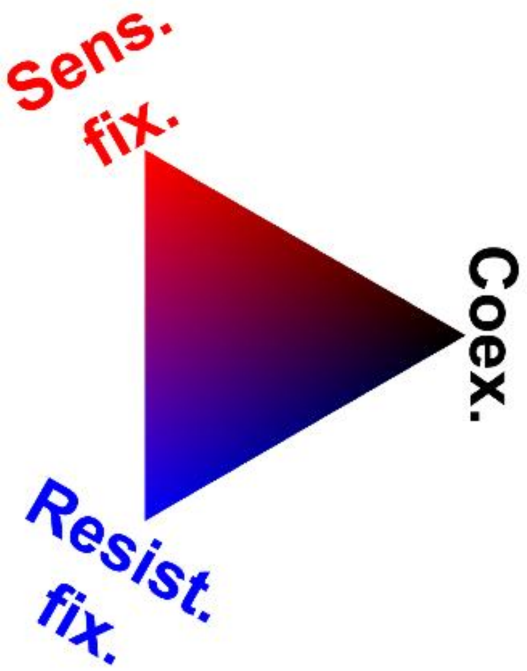


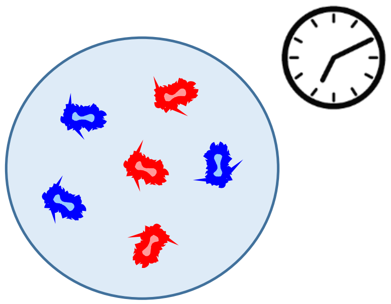


Resistant coop. fixate for K_-

s = 0.1   a = 0.25 K_-=120 K_+=1000 N_{th}=80

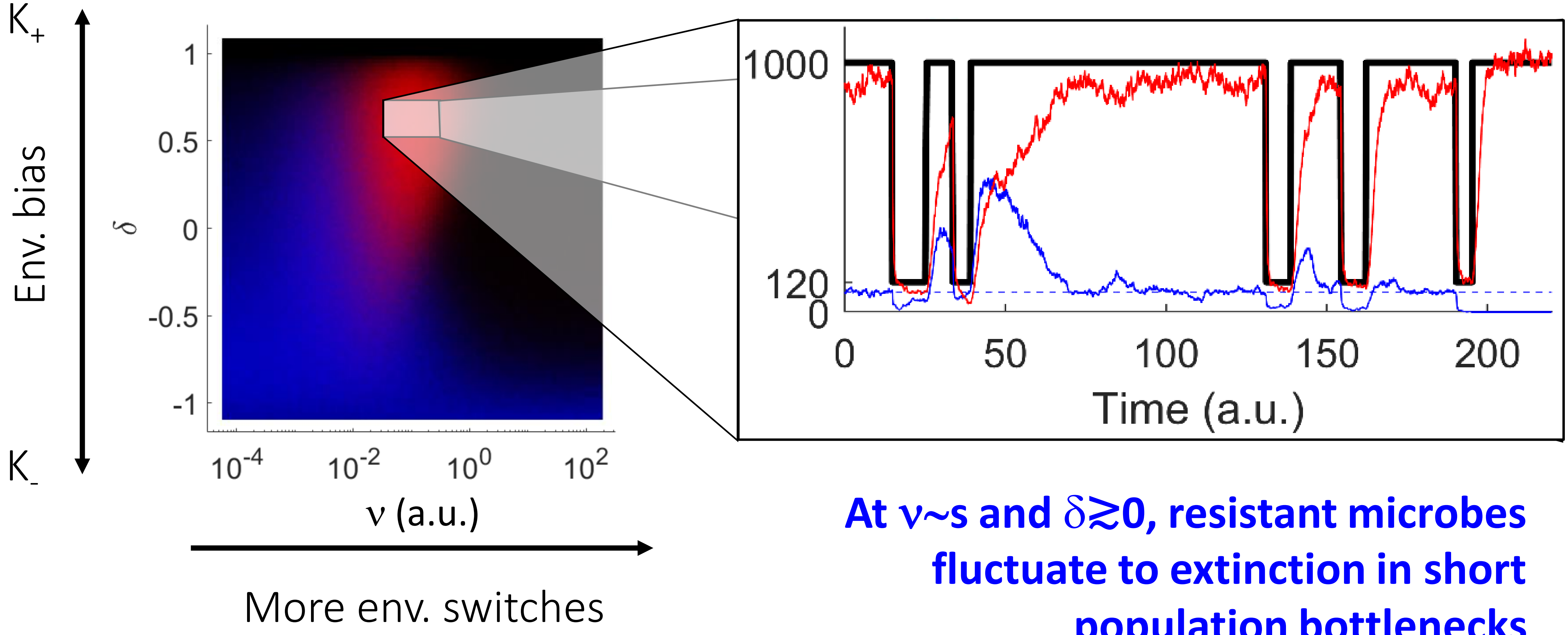






Long term coexistence for K_+

s = 0.1   a = 0.25 K_-=120 K_+=1000 N_{th}=80

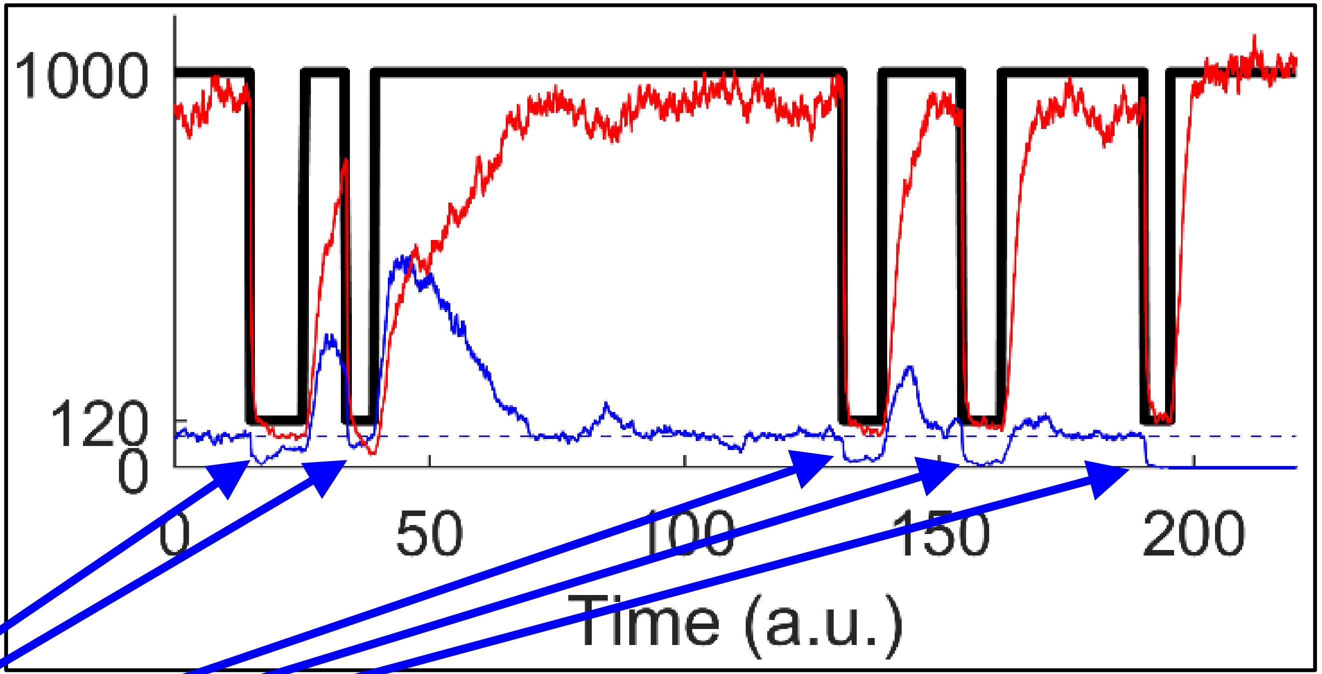


At ν~s and δ≳0, resistant microbes fluctuate to extinction in short population bottlenecks

$K_-=120$ $K_+=1000$ $N_{th}=80$

If N_R^{dip} is small enough, then demographic noise is strong enough to drive *R* to extinction

$$\left(mean\left(N_R^{dip}\right) \sim std\left(N_R^{dip}\right)\right)$$



$$N_R^{dip} \approx \frac{N_{th} K_-}{K_+}$$

$K_- = 120$ $K_+ = 1000$ $N_{th} = 80$

If N_R^{dip} is small enough, then demographic noise is strong enough to drive *R* to extinction $\left(N_R^{dip} \sim \sqrt{N_R^{dip}}\right)$

$$\left(N_R^{dip} \approx 10 \sim \sqrt{N_R^{dip}} \approx 3\right)$$

$$N_R^{dip} \approx \frac{N_{th} K_-}{K_+}$$

This fluctuation-driven mechanism works for realistically big microbial populations too!

(e.g., try $\mathrm{N_{th}} = 10^6$**,** $\mathrm{K_-} = 2 \cdot 10^6$**, and** $\mathrm{K_+} = 10^{12}$**)**

$$N_R^{dip} \approx \frac{N_{th} K_-}{K_+}$$

Take-home message(s)

In static environments:

- AMR fixates when public drug-inactivation requires a high proportion of resistant microbes $(N_{th} \approx K)$.
- AMR becomes extinct when public drug-inactivation requires a small R fraction $(N_{th} \ll K)$, **but it usually takes very long**.

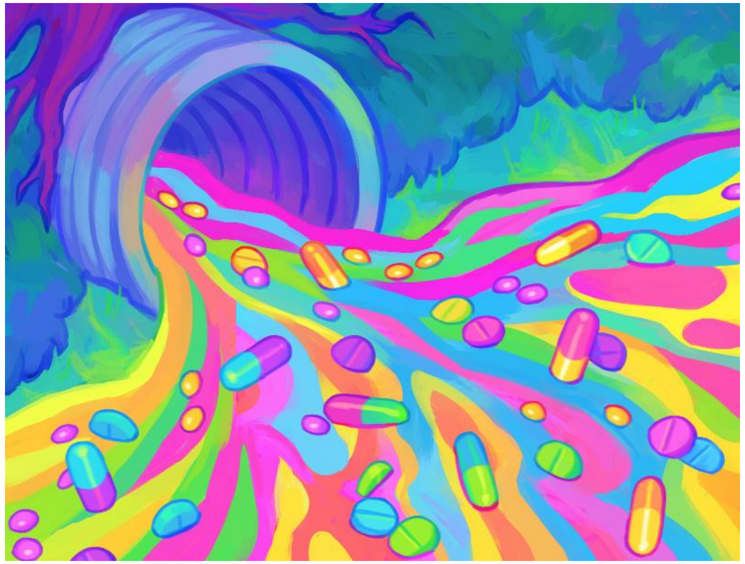
In switching environments:

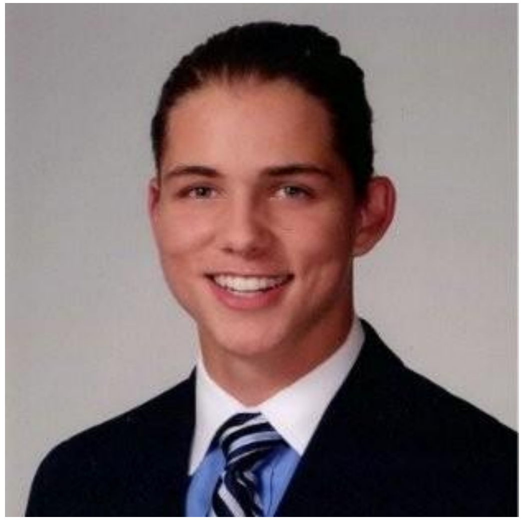
- Intermediate switching frequencies $(\nu \sim s)$ enforce and speed up the eradication of AMR through transient dips (if $\frac{N_{th} K_-}{K_+} \lesssim O(1)$).

AMR in environments with

<u>spatial structure</u>

(farms, sewerage, hospitals…)





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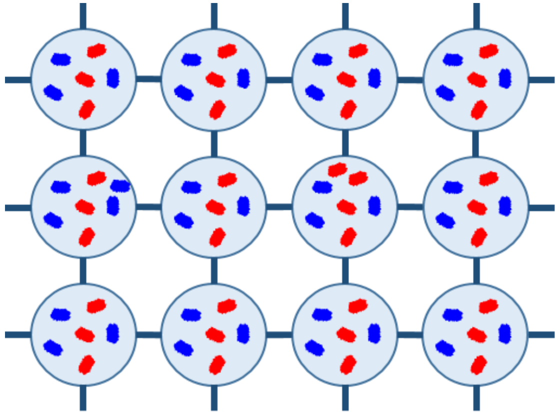
Prof. Mauro Mobilia

AMR fixates/survives in well-mixed, static environments and…



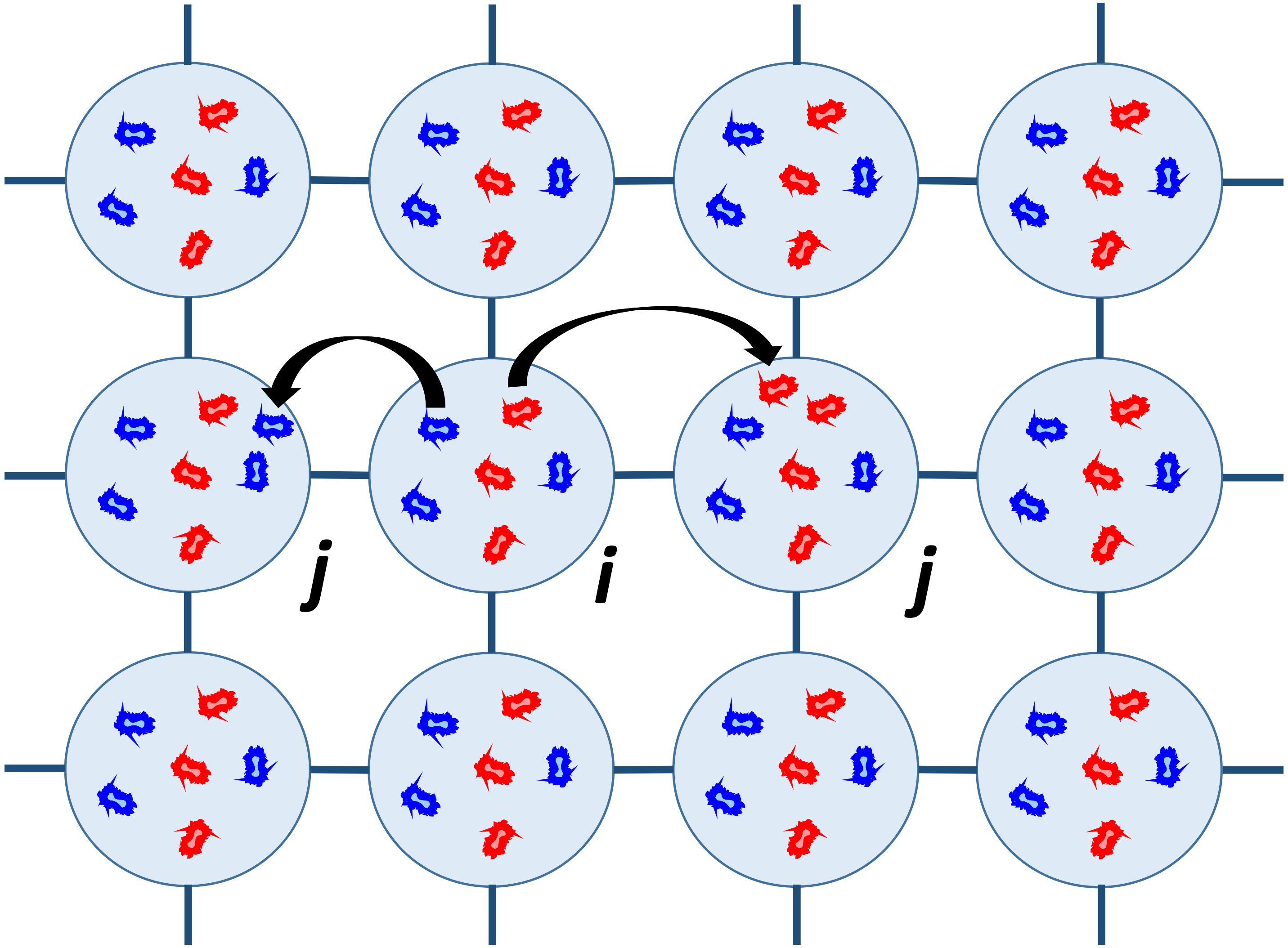
…AMR can be eradicated in dynamic environments but…

…can AMR be eradicated when the environment has spatial structure?

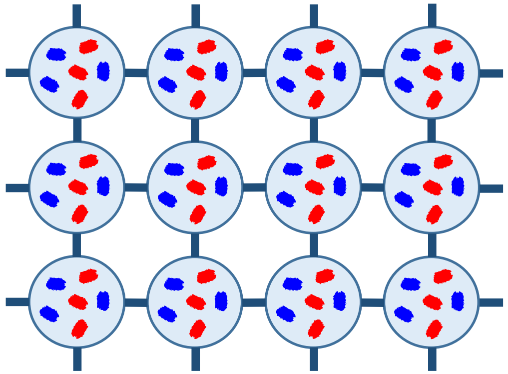
2D periodic square lattice of L x L (gamo)demes

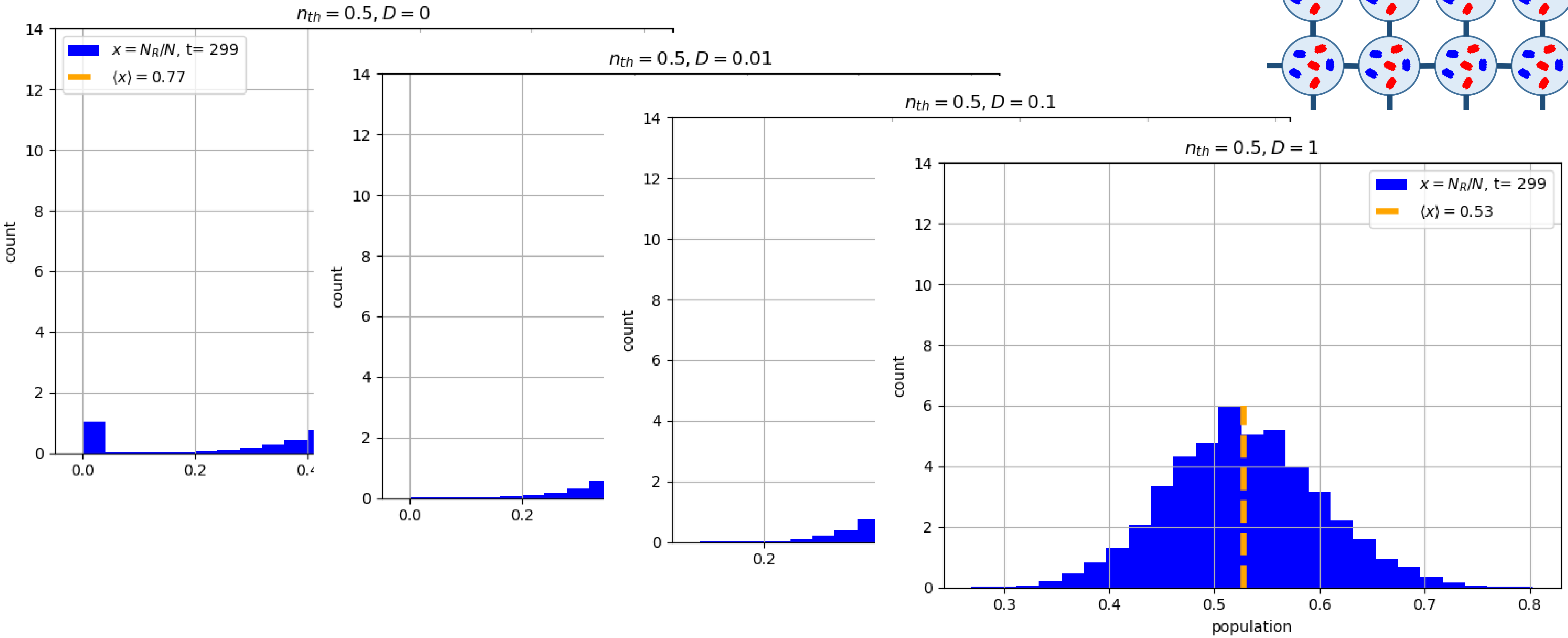
Emigration from deme ***i*** to a nearest neighbour random deme (*j*) at per capita rate:

$$\mathbf{D \cdot N_i/K(t)}$$



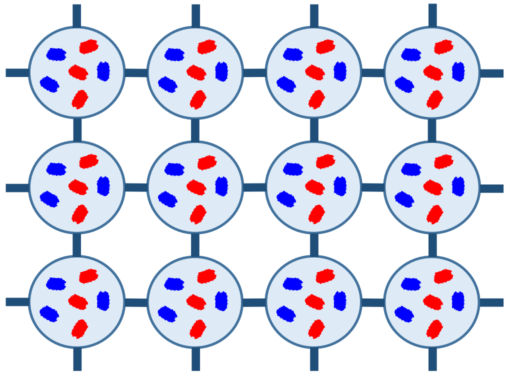
Square Lattice: Static environment



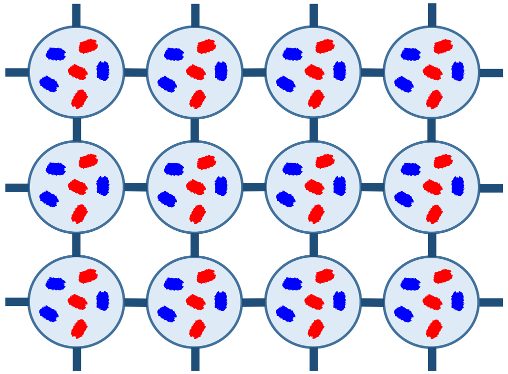


Spatial migration enforces and shapes strain coexistence

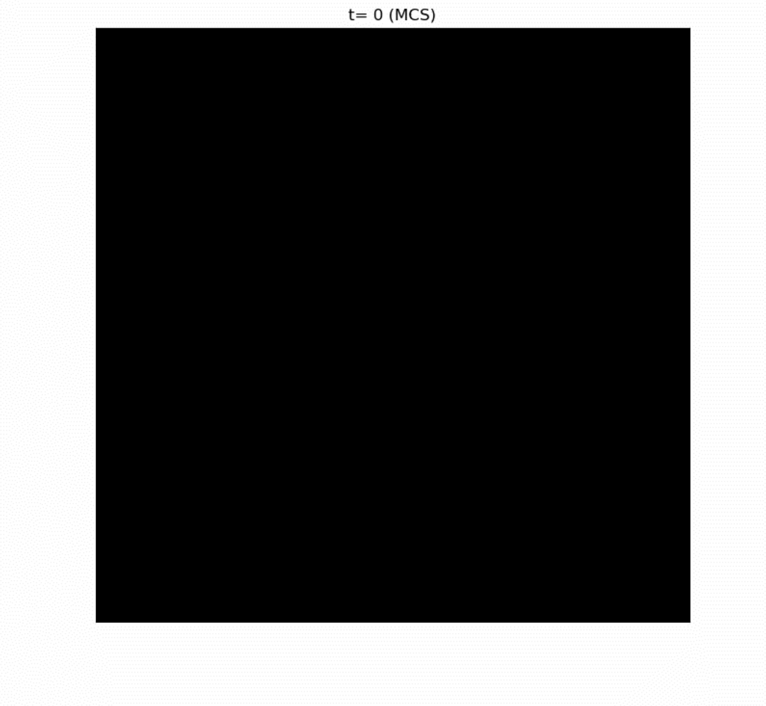
Can we eradicate R?



Can we eradicate R?



L x L = 20 x 20

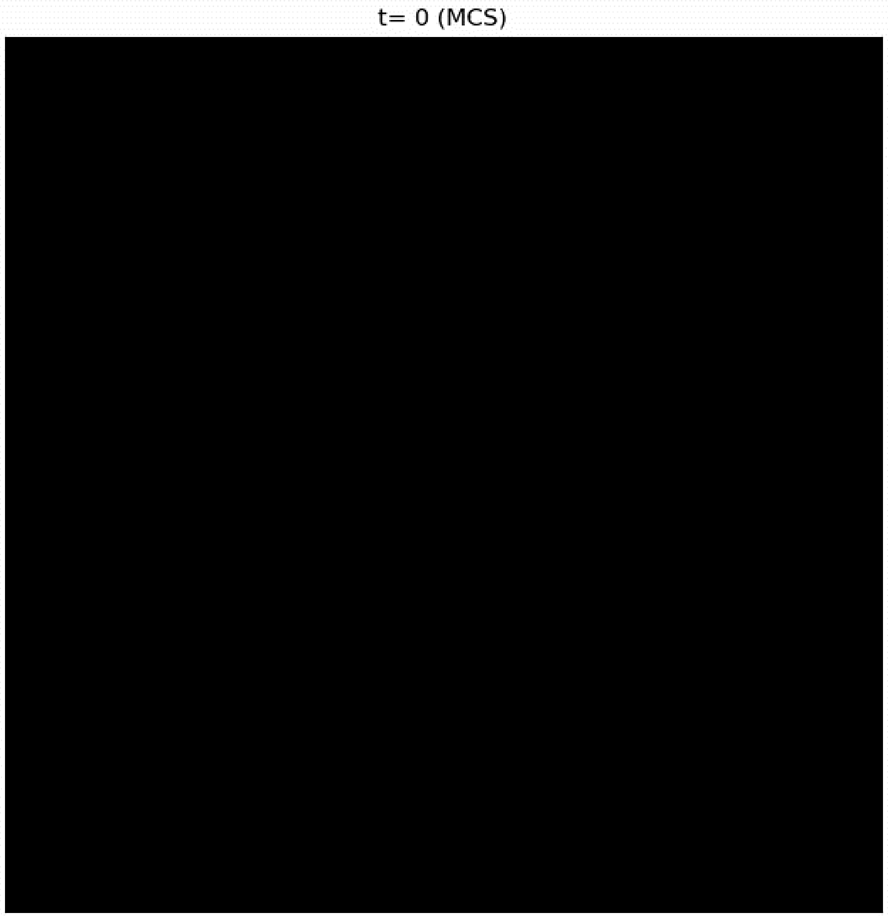


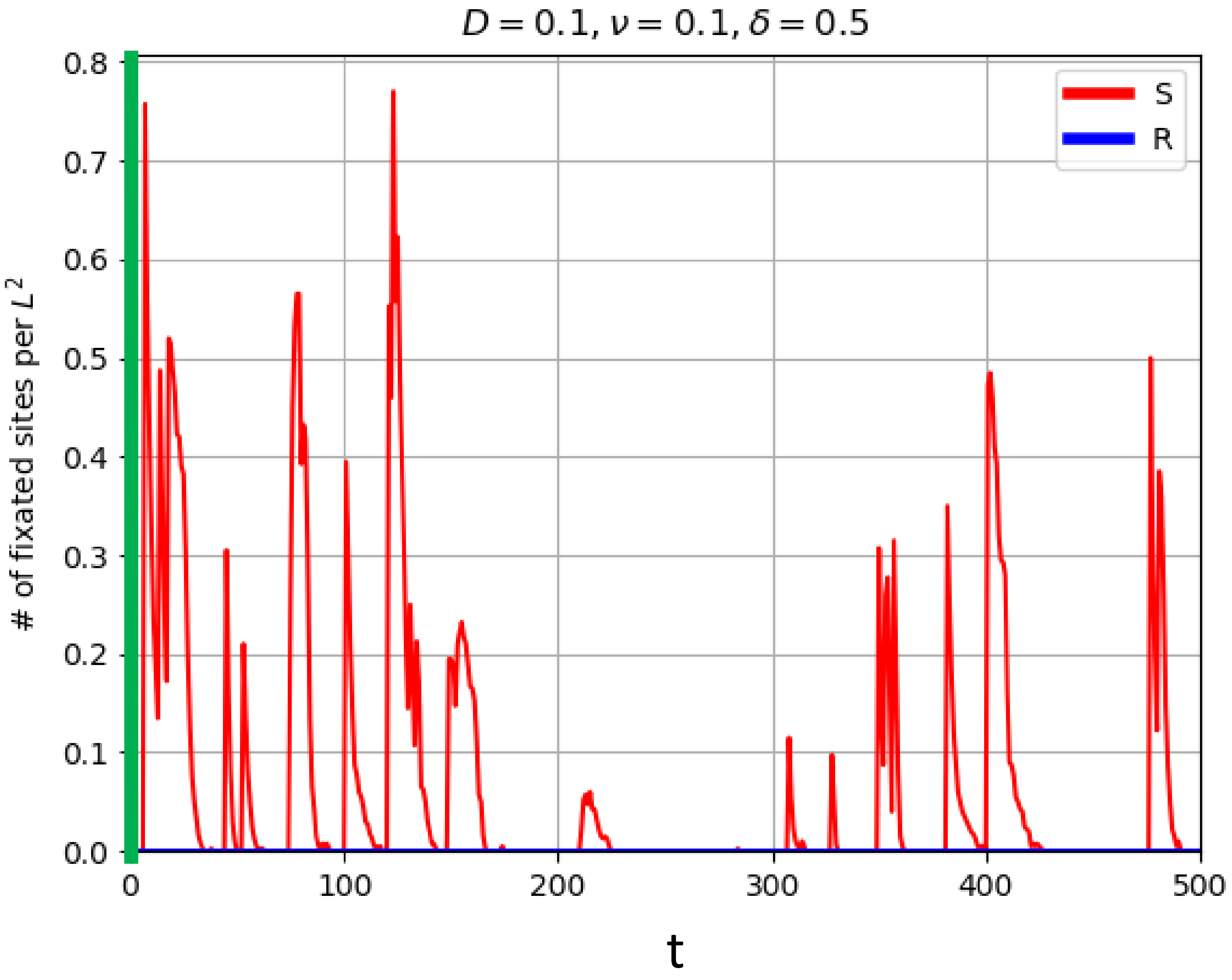
Frequent Population bottlenecks with **high migration rate (D=0.1)**

■ Site with R and S cells

■ Site with no R cells

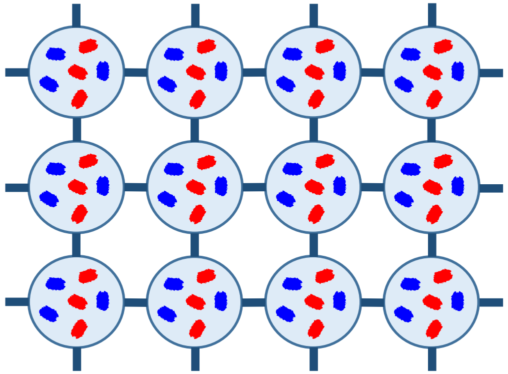
High migration rate (D=0.1)



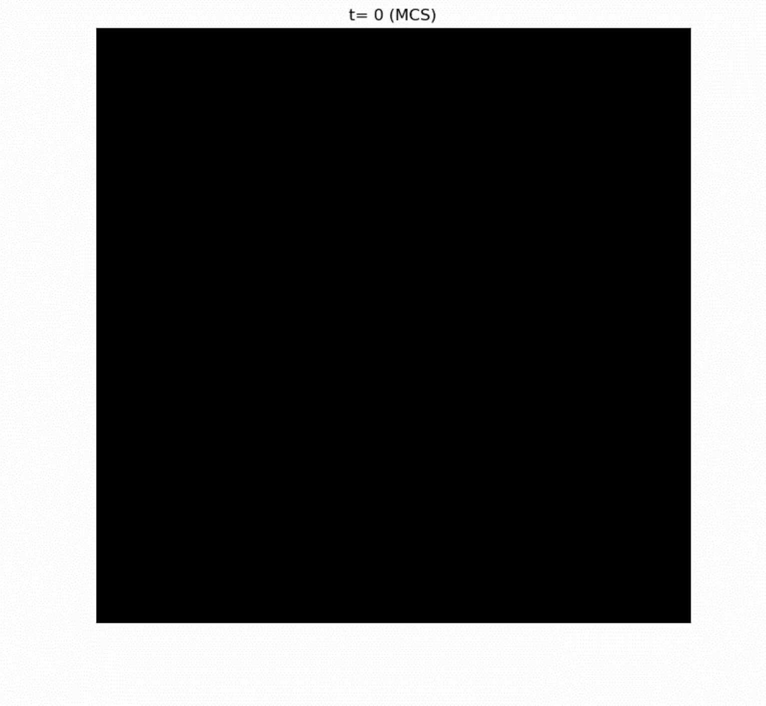


Spatial migration enforces strain coexistence, but…

Can we eradicate R?



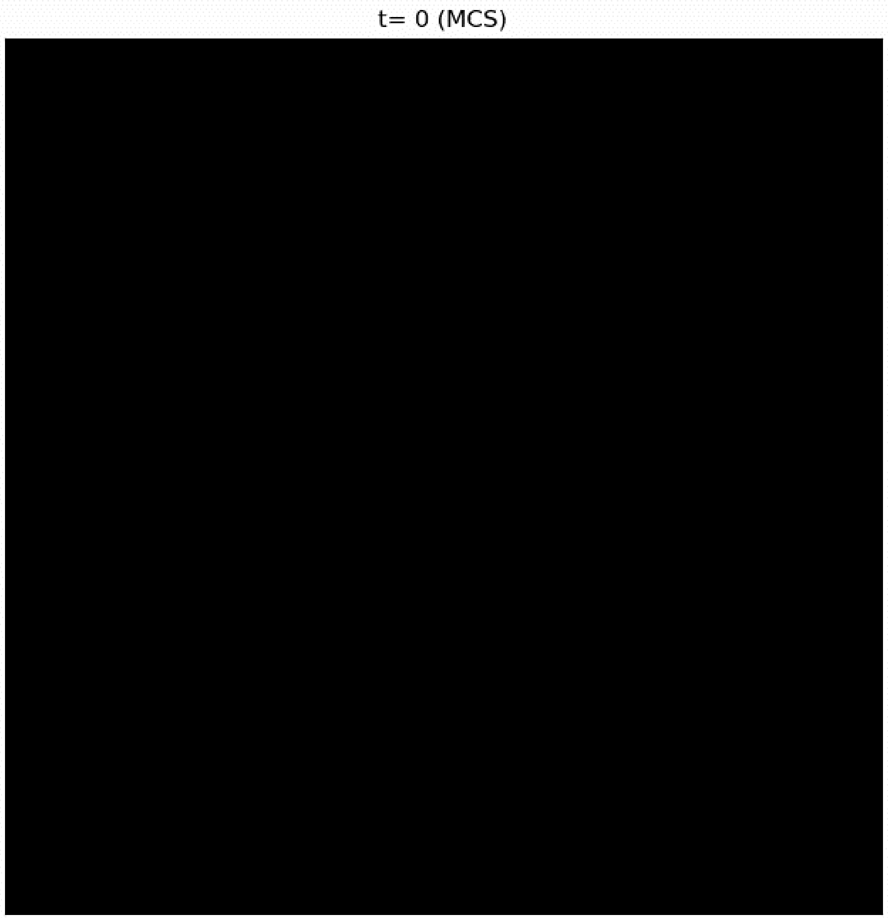
L x L = 20 x 20

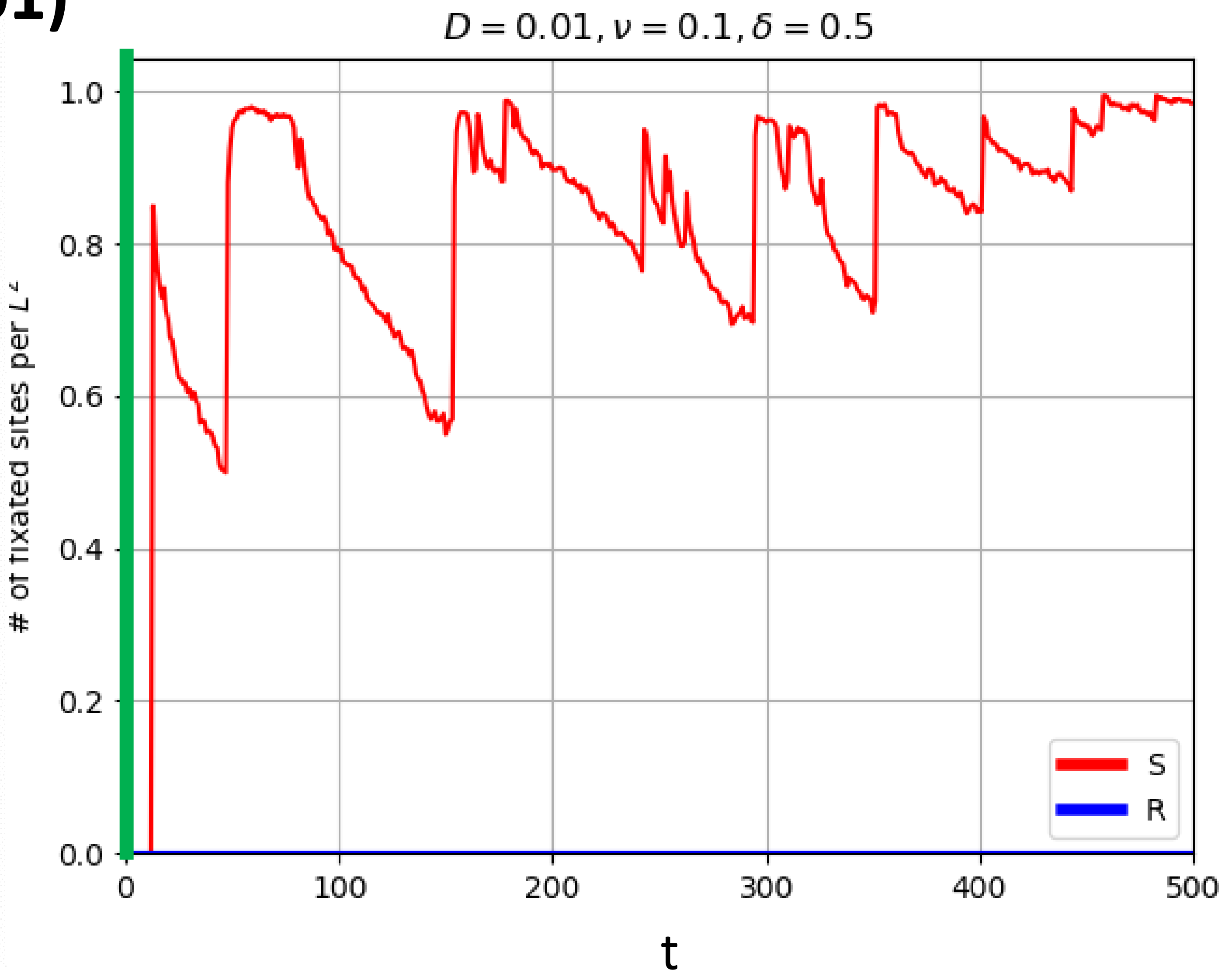


Frequent Population bottlenecks with **lower migration rate (D=0.01)**

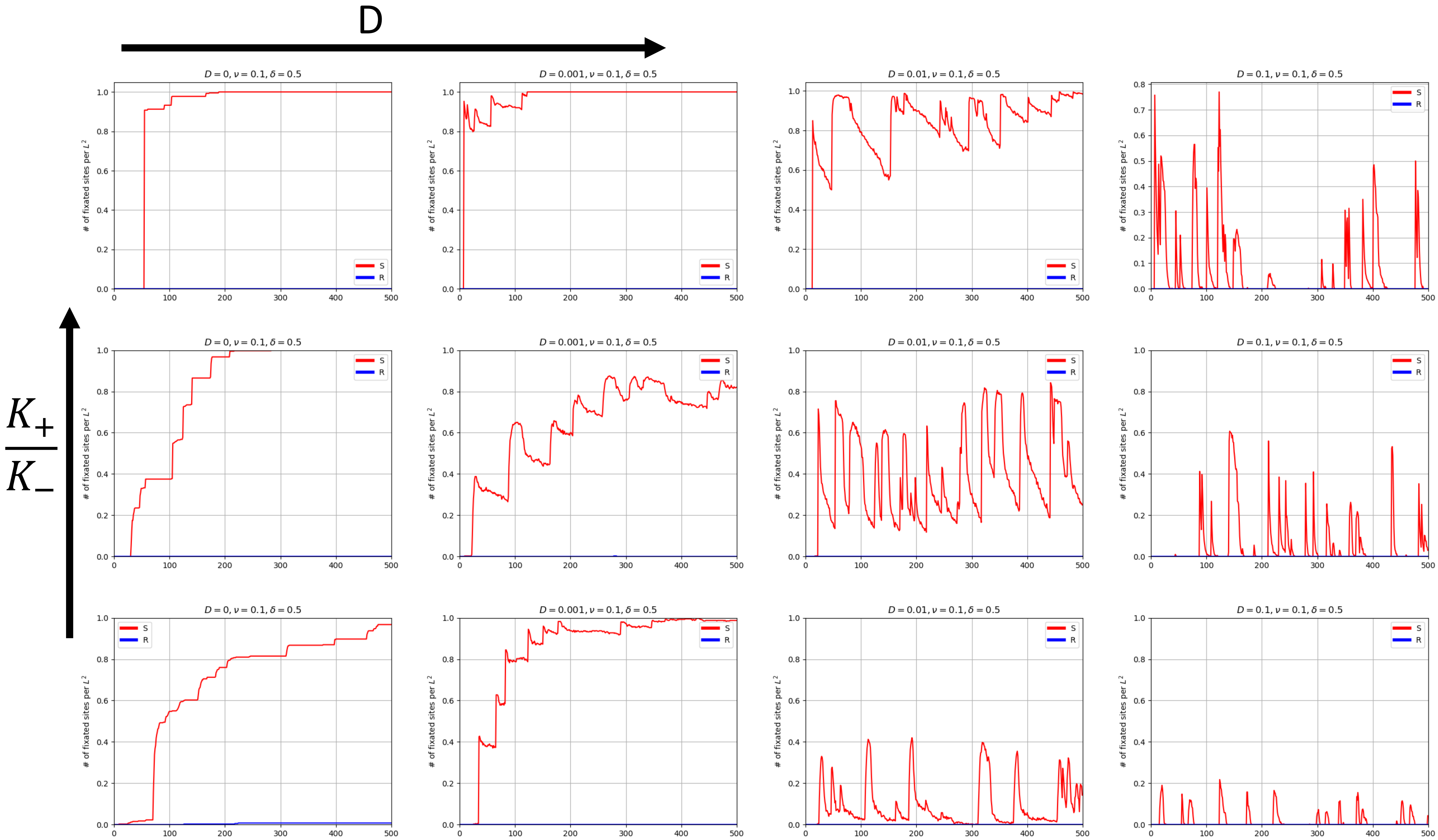
...AMR can still be eradicated with strong bottlenecks and/or slow migration!

Lower migration rate (D=0.01)

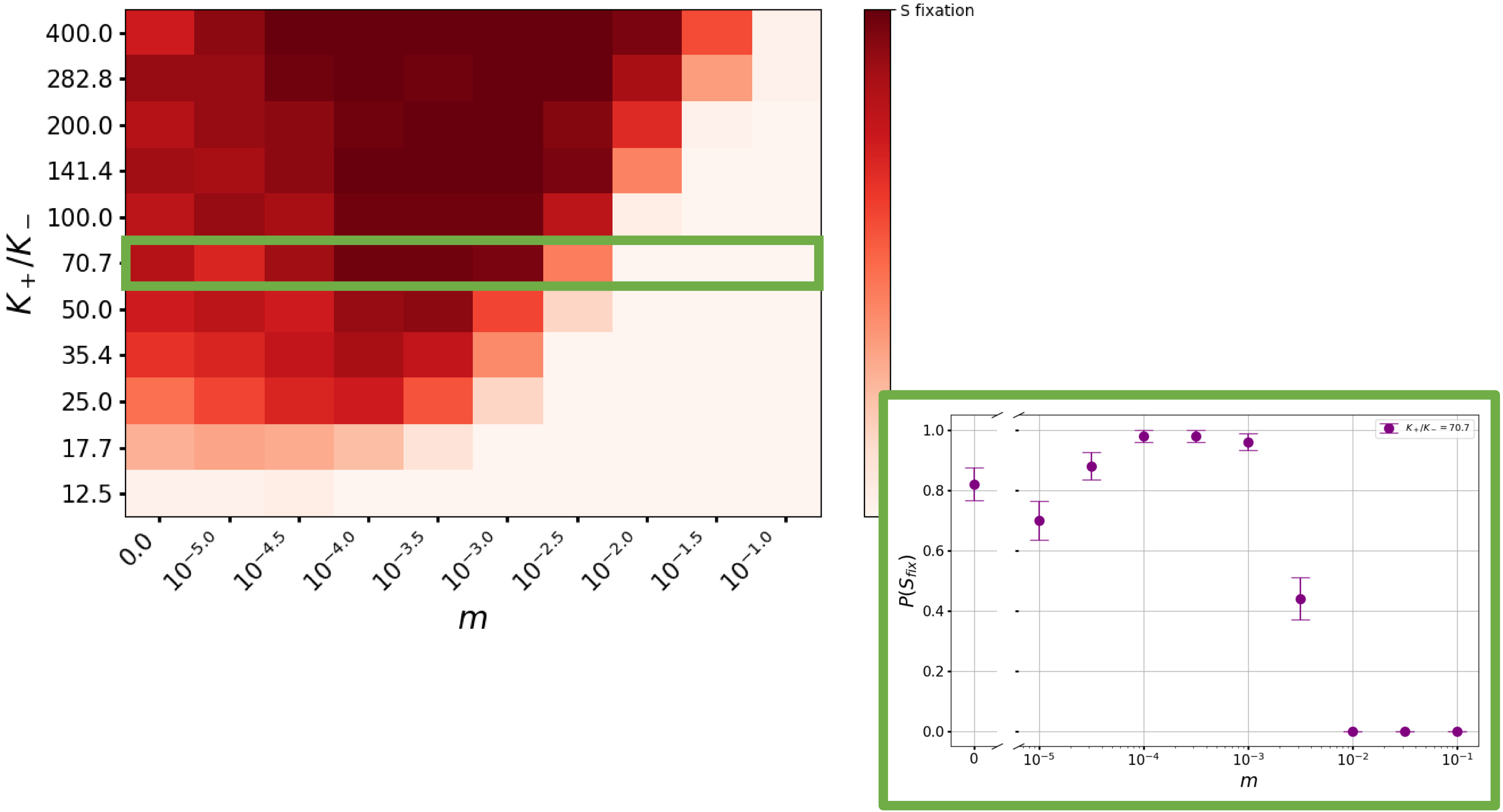




...AMR can still be eradicated!



D
K_+ / K_-
$D = 0, \nu = 0.1, \delta = 0.5$
$D = 0.001, \nu = 0.1, \delta = 0.5$
$D = 0.01, \nu = 0.1, \delta = 0.5$
$D = 0.1, \nu = 0.1, \delta = 0.5$
# of fixated sites per L^2
S
R



S fixation
400.0
282.8
200.0
141.4
100.0
70.7
50.0
35.4
25.0
17.7
12.5
K_+/K_-
0.0
$10^{-5.0}$
$10^{-4.5}$
$10^{-4.0}$
$10^{-3.5}$
$10^{-3.0}$
$10^{-2.5}$
$10^{-2.0}$
$10^{-1.5}$
$10^{-1.0}$
m
$K_+/K_- = 70.7$
$P(S_{fix})$
1.0
0.8
0.6
0.4
0.2
0.0
0
10^{-5}
10^{-4}
10^{-3}
10^{-2}
10^{-1}
m

‘Spatial’ take-home message(s)

- Faster migration hinders the eradication of AMR.
- But strong population bottlenecks can still eradicate AMR.
- And slow-but-non-zero enhances AMR eradication.

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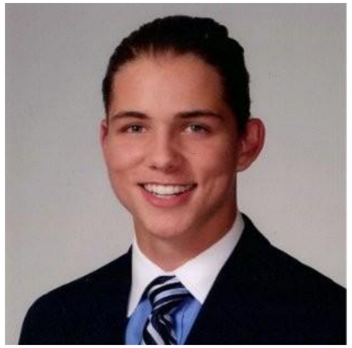

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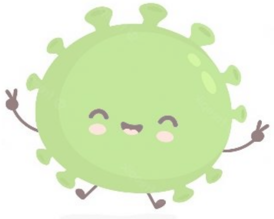
Merci beaucoup!



Questions?

Coupled Environmental and Demographic Fluctuations Shape the Evolution of Cooperative Antimicrobial Resistance; Hernández-Navarro, L., Asker, M., Rucklidge, A.M., & Mobilia, M.; J. R. Soc. Interface (2023)