The Role of Microbial Communities in Shaping Antibiotic Resistance (and vice versa)

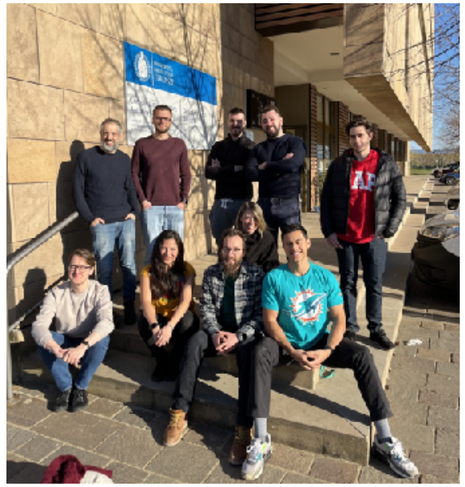
Marco Fondi, Dep. of Biology, University of Florence



Scuola di Genetica 'Mario Polsinelli' 2026







Florence computational biology group

What we study:

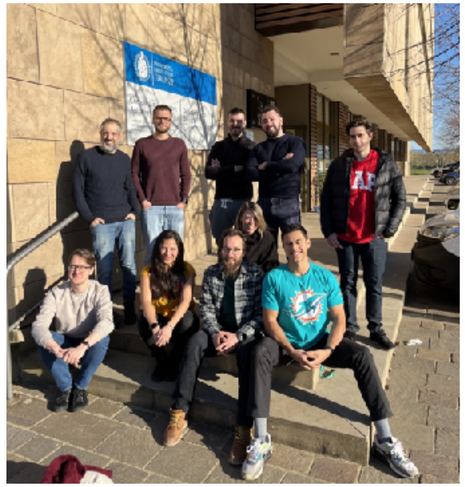
- Cell-to-cell communication, i.e. Quorum Sensing
- Microbial metabolism
- Microbial communities dynamics

What we use:

- Genome-scale metabolic modeling
- NGS data analysis
- Dynamic and stochastic modelling of microbial communities







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It takes two to tango

It takes a community *to* tackle AMR

The world is heading toward an **antimicrobial resistance (AMR) catastrophe** that no single therapeutic class can avert alone.

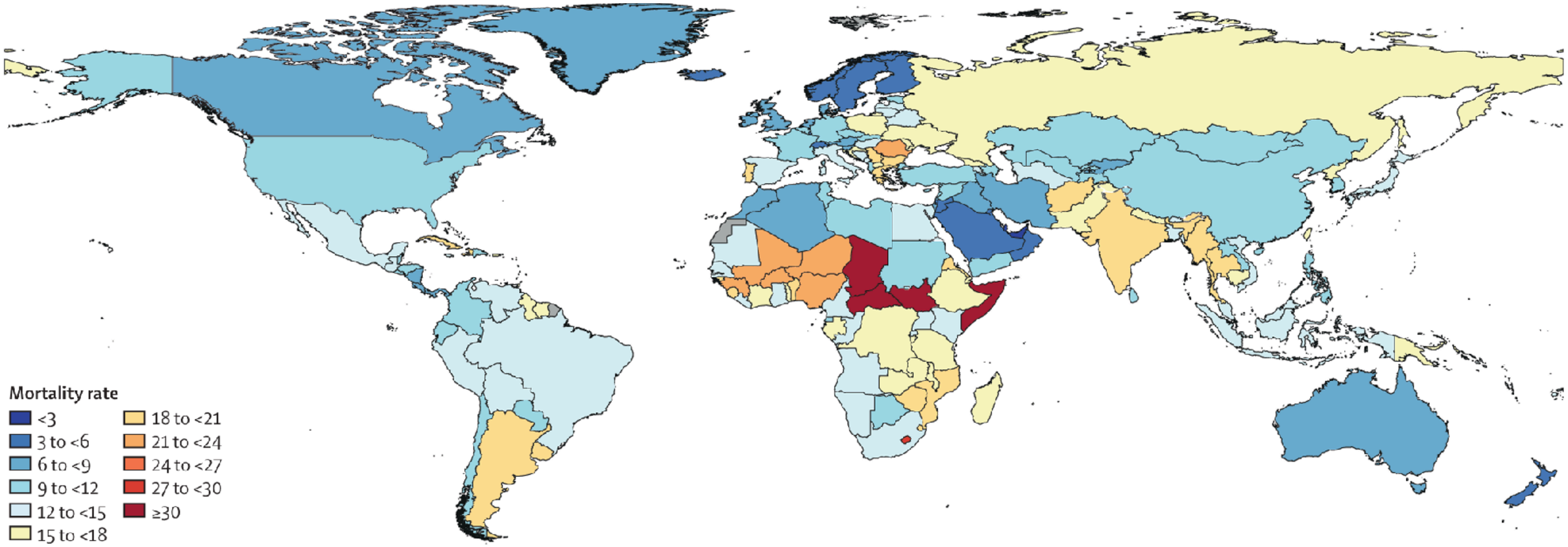
The most comprehensive epidemiological analysis to date estimates that drug-resistant bacterial infections will directly cause 39 million deaths between 2025 and 2050 — **three every minute** — and will be indirectly associated with a further 169 million deaths over the same period

Lancet 2024; 404: 1199–226

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

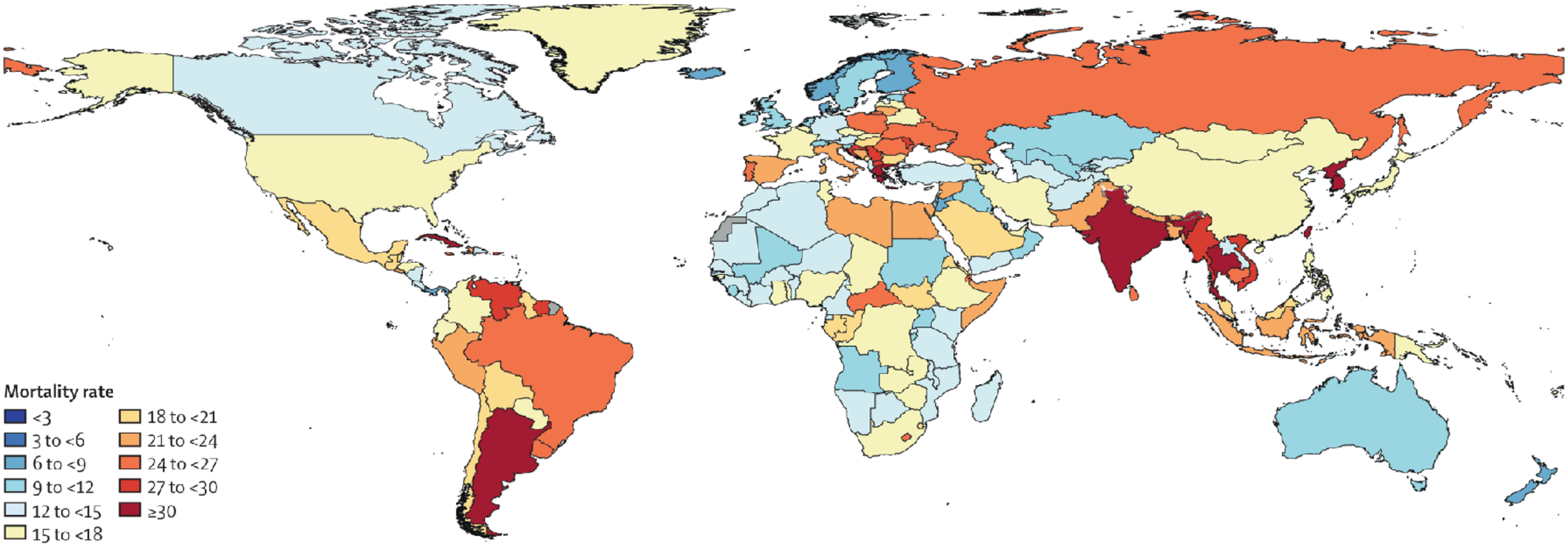
GBD 2021 Antimicrobial Resistance Collaborators*

Death rate attributable to AMR, all ages, 2021

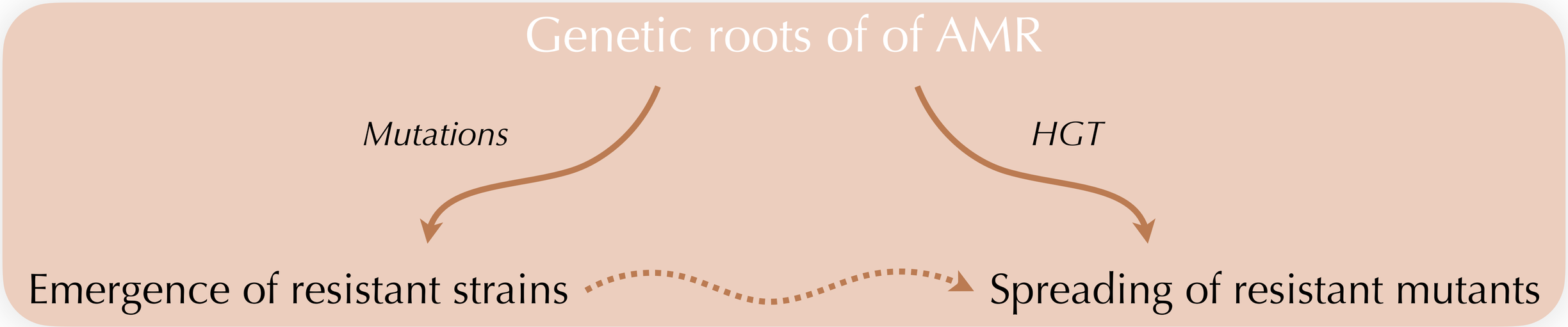


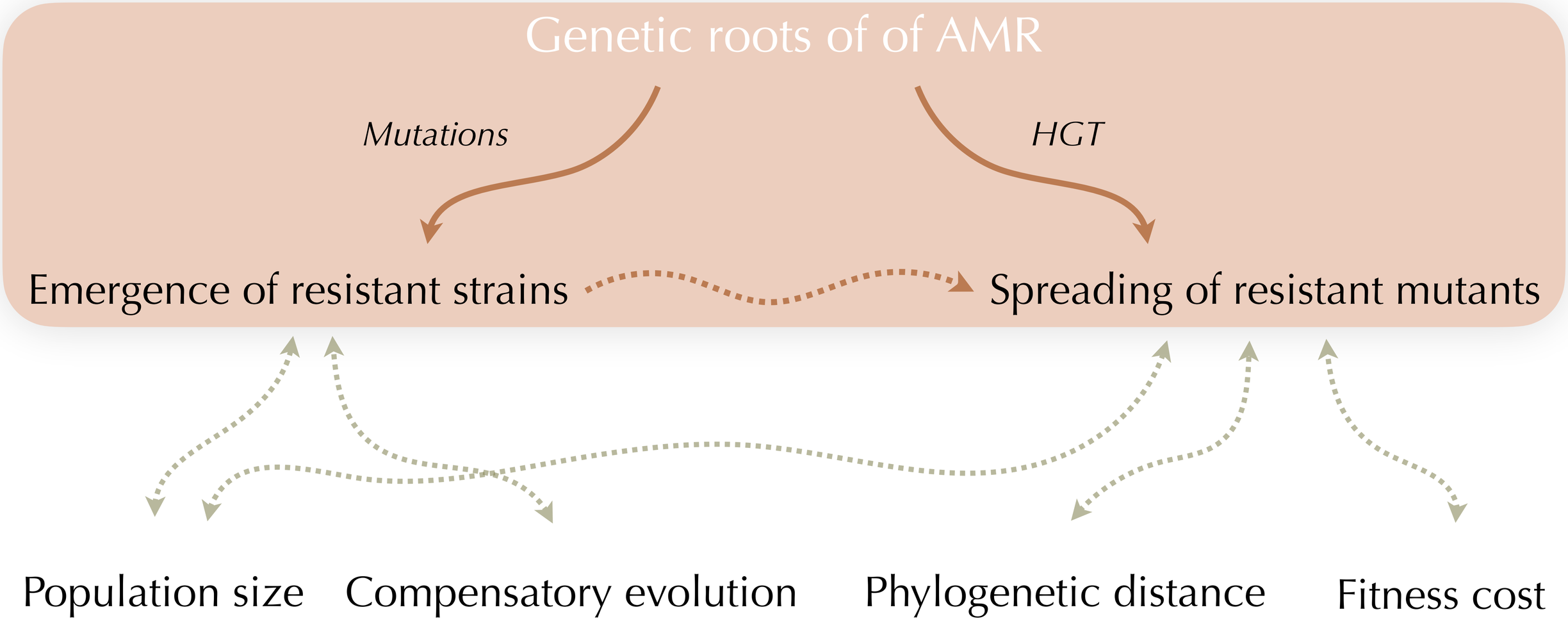
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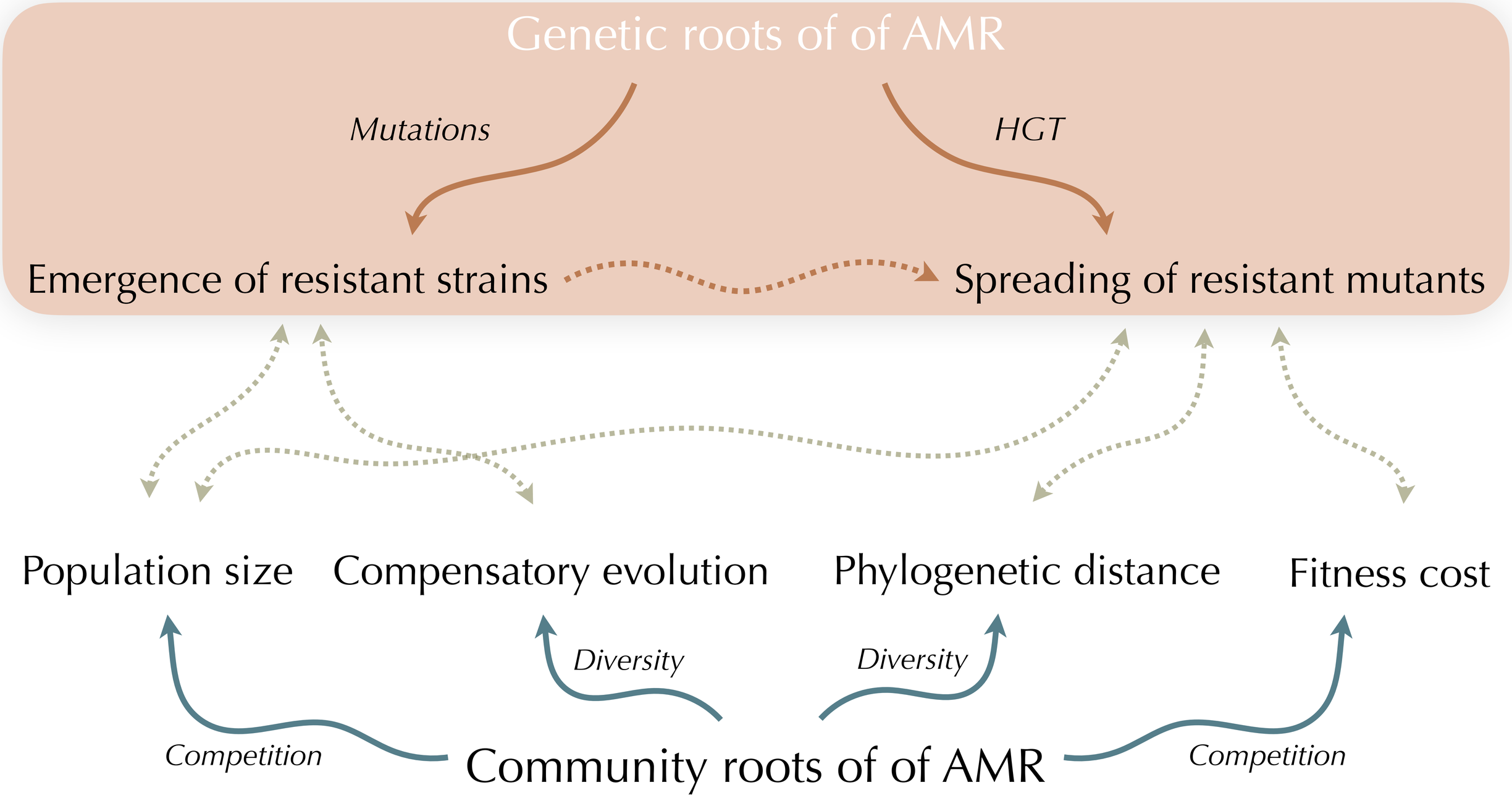
Death rate attributable to AMR, all ages, 2050

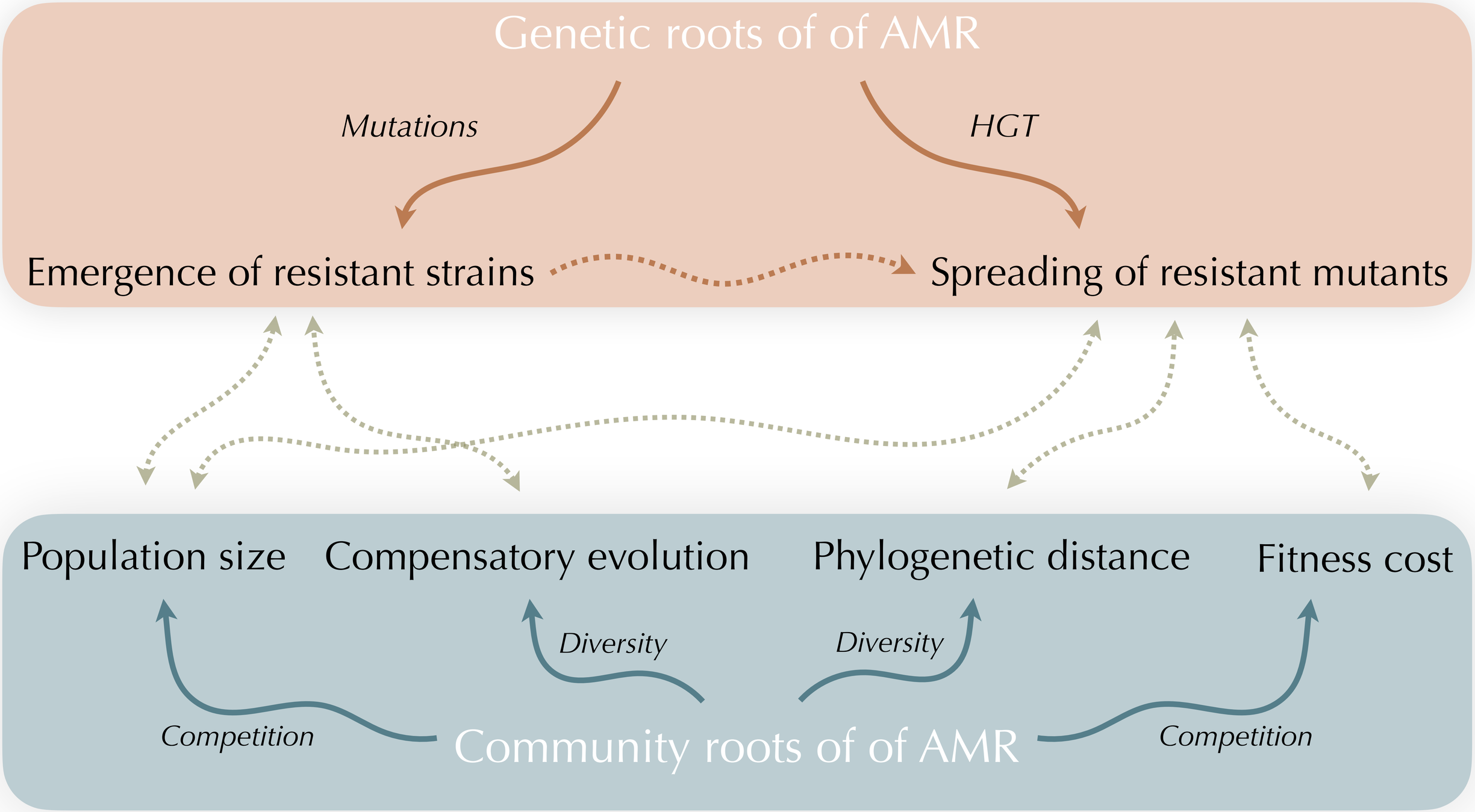


Lancet 2024; 404: 1199–226


Genetic roots of of AMR
Mutations
HGT
Emergence of resistant strains
Spreading of resistant mutants


Genetic roots of of AMR
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Compensatory evolution
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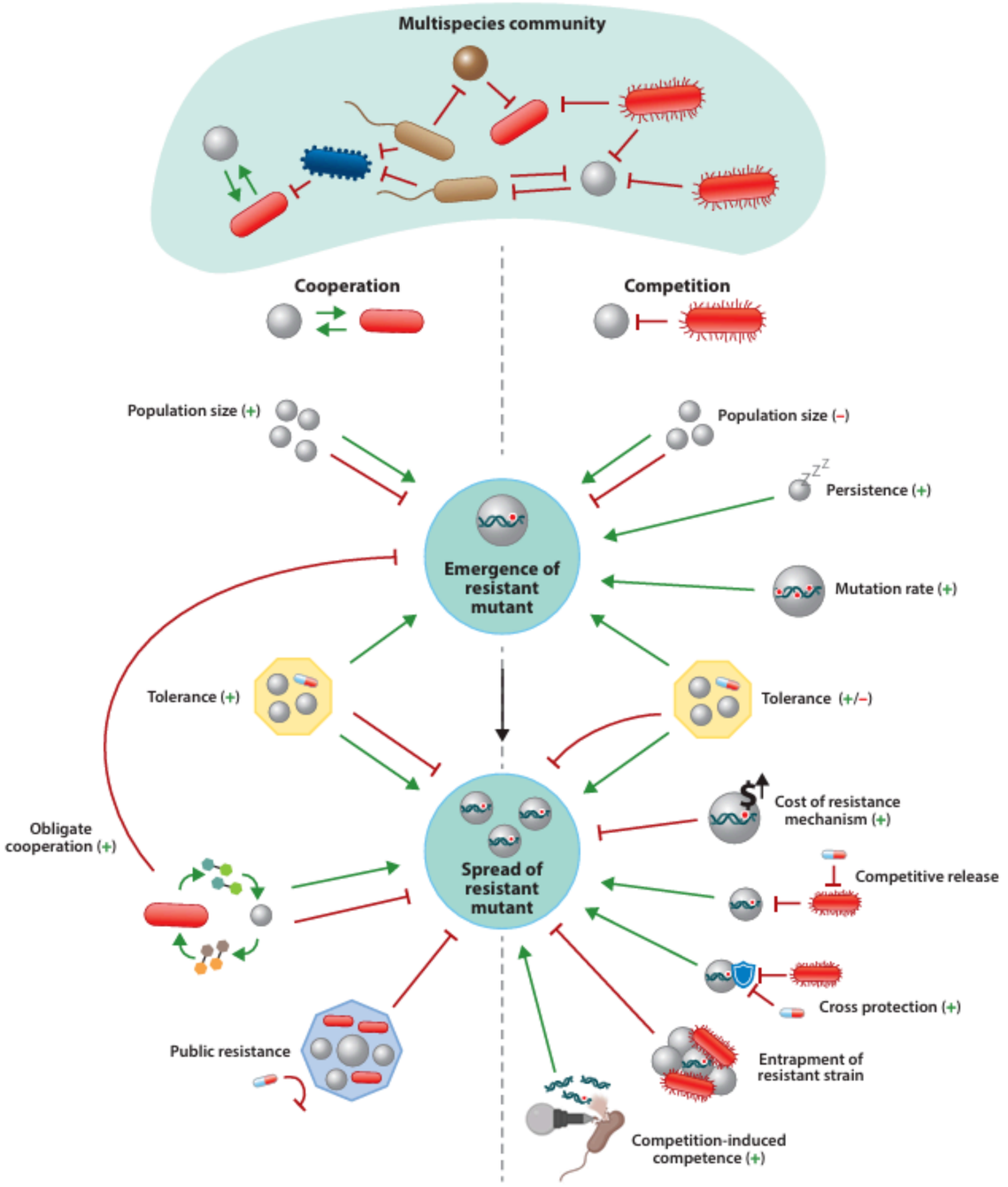
The classic parameters of resistance genetics are not community-independent. The microbial community is not the background against which resistance evolves. It is an active determinant of resistance dynamics.

Research question

Does the microbiota structure hamper/facilitate/is neutral to the emergence and spread of AMR and/or related phenotypes?

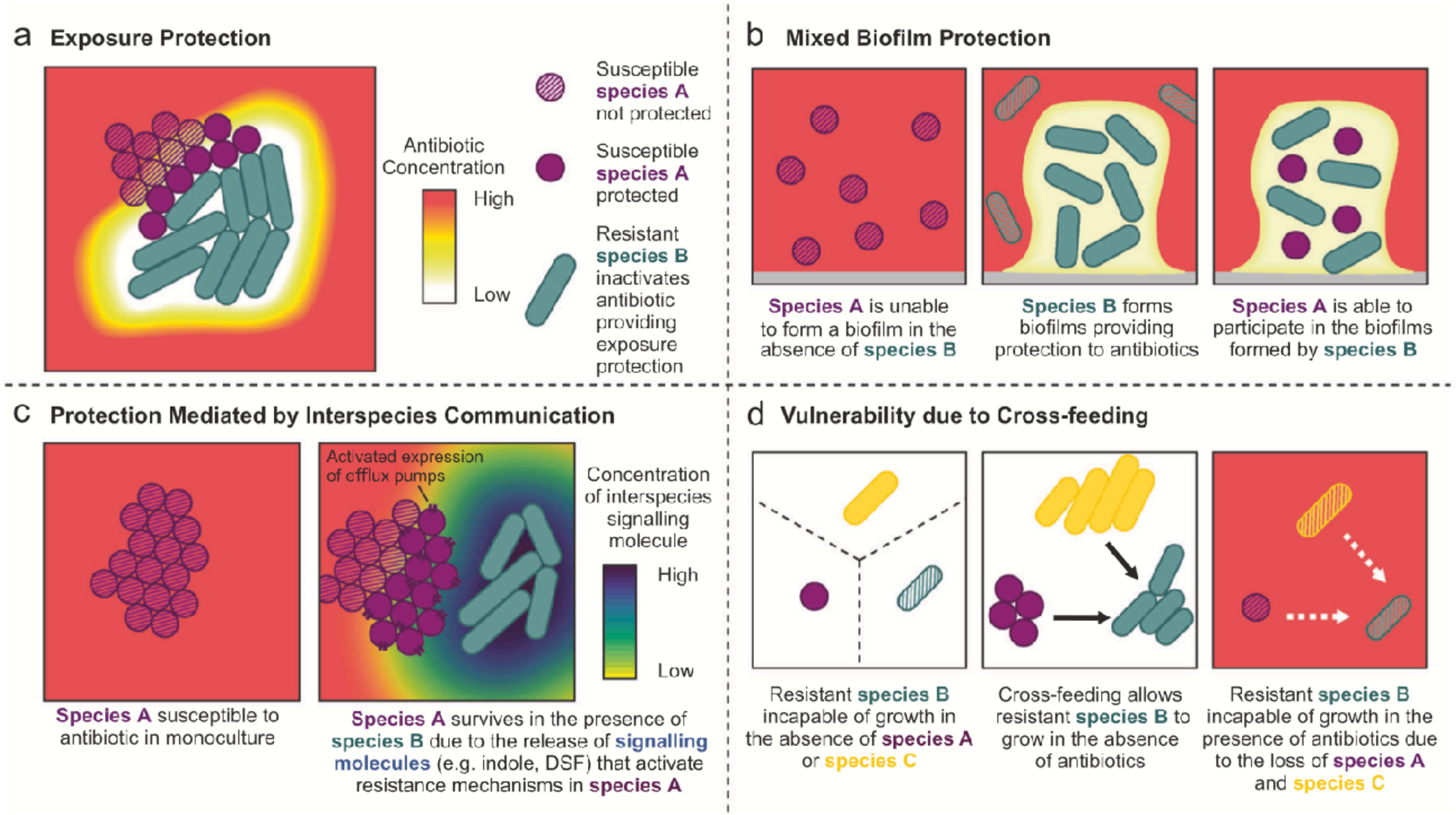
Overall, the relative contributions of these various mechanisms are expected to be highly case specific and will depend on, among other factors, the community composition and structure, resource availability, the resistance mechanism, and the antibiotic treatment.

How can we study all this?



De Wit et al. 2022 Annual Review of Microbiology

The response of bacteria to antimicrobials is significantly affected by the presence of other interacting microbes.



Bottery et al. 2020, ISME J

Negative interactions rule the system

Competition, Not Cooperation, Dominates Interactions among Culturable Microbial Species

Kevin R. Foster[1,*] and Thomas Bell[2,*]
[1]Department of Zoology and Oxford Centre for Integrative Systems Biology, University of Oxford, Oxford OX1 3PS, UK
[2]Division of Ecology and Evolution, Imperial College London, Silwood Park Campus, Ascot SL5 7PY, UK

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Nope, positive interactions are common

SCIENCE ADVANCES | RESEARCH ARTICLE

ENVIRONMENTAL STUDIES

Positive interactions are common among culturable bacteria

Jared Kehe[1,2]†, Anthony Ortiz[3,4], Anthony Kulesa[1,2]‡, Jeff Gore[3,4], Paul C. Blainey[1,2,5]*, Jonathan Friedman[6]*

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Negative interactions contrast AMR

The ISME Journal (2019) 13:2927–2937
https://doi.org/10.1038/s41396-019-0483-z

ISME

ARTICLE

Selection for antimicrobial resistance is reduced when embedded in a natural microbial community

Uli Klümper[1,2] · Mario Recker[3] · Lihong Zhang[2] · Xiaole Yin[4] · Tong Zhang[4] · Angus Buckling[1] · William H. Gaze[2]

Received: 28 February 2019 / Revised: 22 July 2019 / Accepted: 23 July 2019 / Published online: 5 August 2019
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ENVIRONMENTAL STUDIES

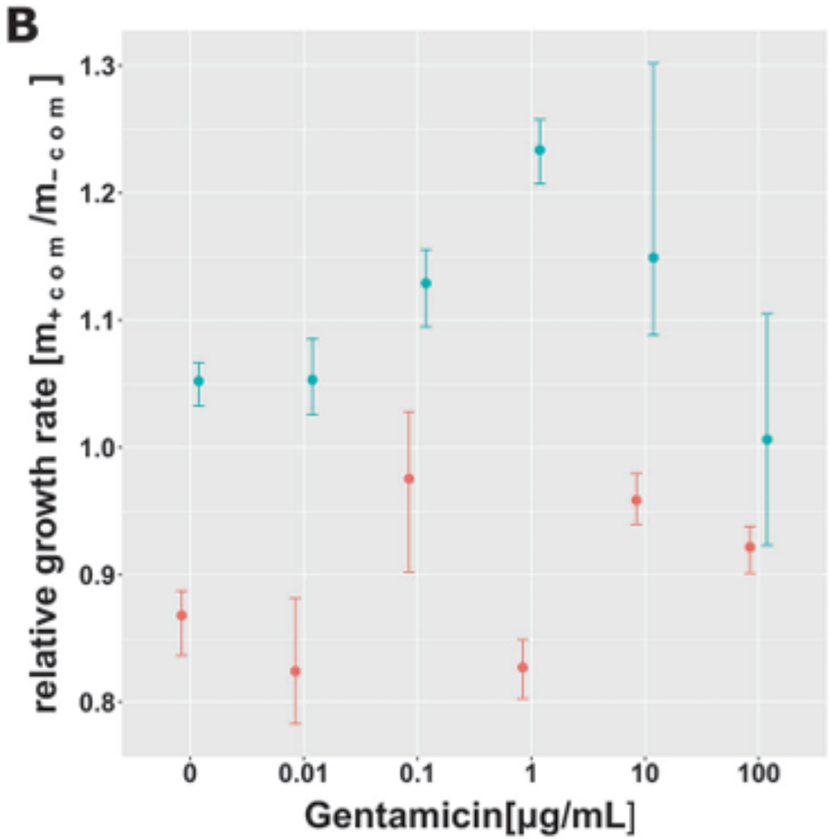
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Selection for antimicrobial resistance is reduced when embedded in a natural microbial community

43-fold increase in MSC in the presence of the community

The community increased the fitness costs reflected by reduced growth rates that are associated with resistance in the absence of antibiotics.



susceptible
mutant

Klümper et al. 2019, ISME J

Negative interactions rule the system

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Nope, negative interactions facilitate AMR

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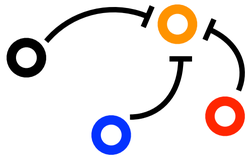
MICROBIAL ECOLOGY
October 2023 Volume 89 Issue 10 e01155-23
https://doi.org/10.1128/aem.01155-23

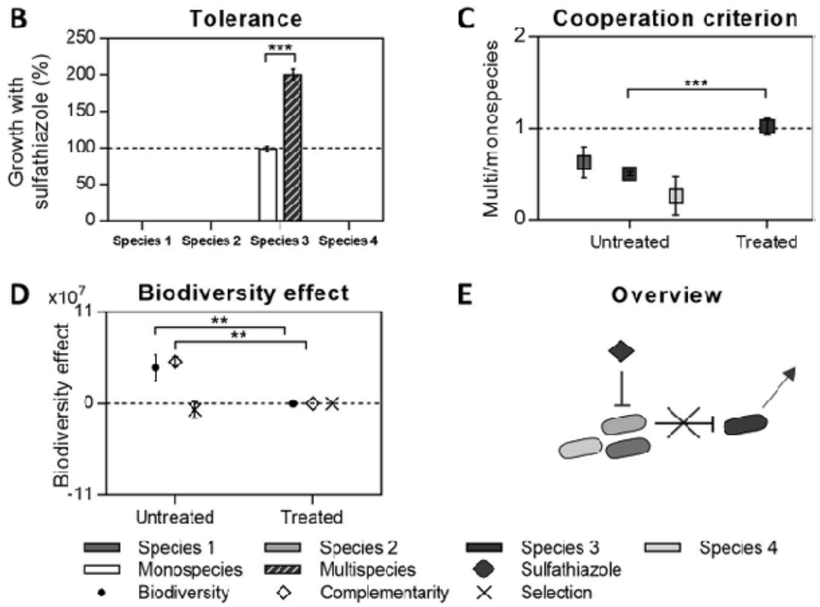
Competitive interactions facilitate resistance development against antimicrobials

Luka Svet[1], Ilse Parijs[1], Simon Isphording[2], Bram Lories[1], Kathleen Marchal[2], Hans P. Steenackers[1]

Competitive interactions facilitate resistance development against antimicrobials.

Tolerance → Resistance

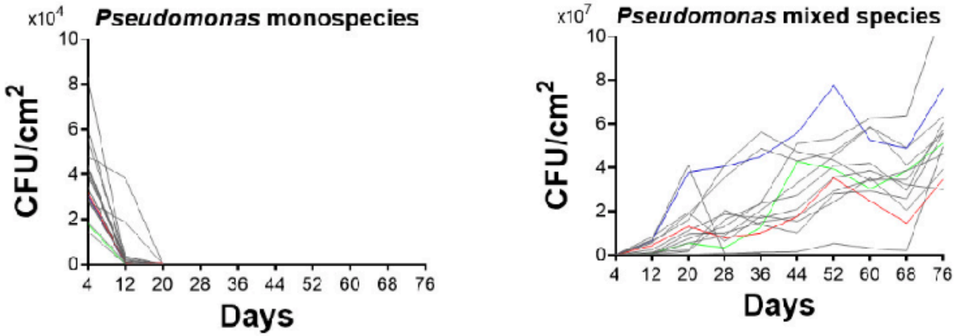






vs.





Antimicrobial treatment reduced the level of competition and therefore caused a subset of species to bloom. The result was a lower percentage inhibition of these species in the multispecies biofilm compared to the mono-culture biofilms (increased tolerance).

Hans and Steenackers 2018, ISME J

The enhanced tolerance in duo-species conditions could expand the number of viable mutants, i.e., certain mutations might only provide sufficient resistance and enable growth in duo-species conditions.

Svet et al. 2023, Appl Environ Microbiol

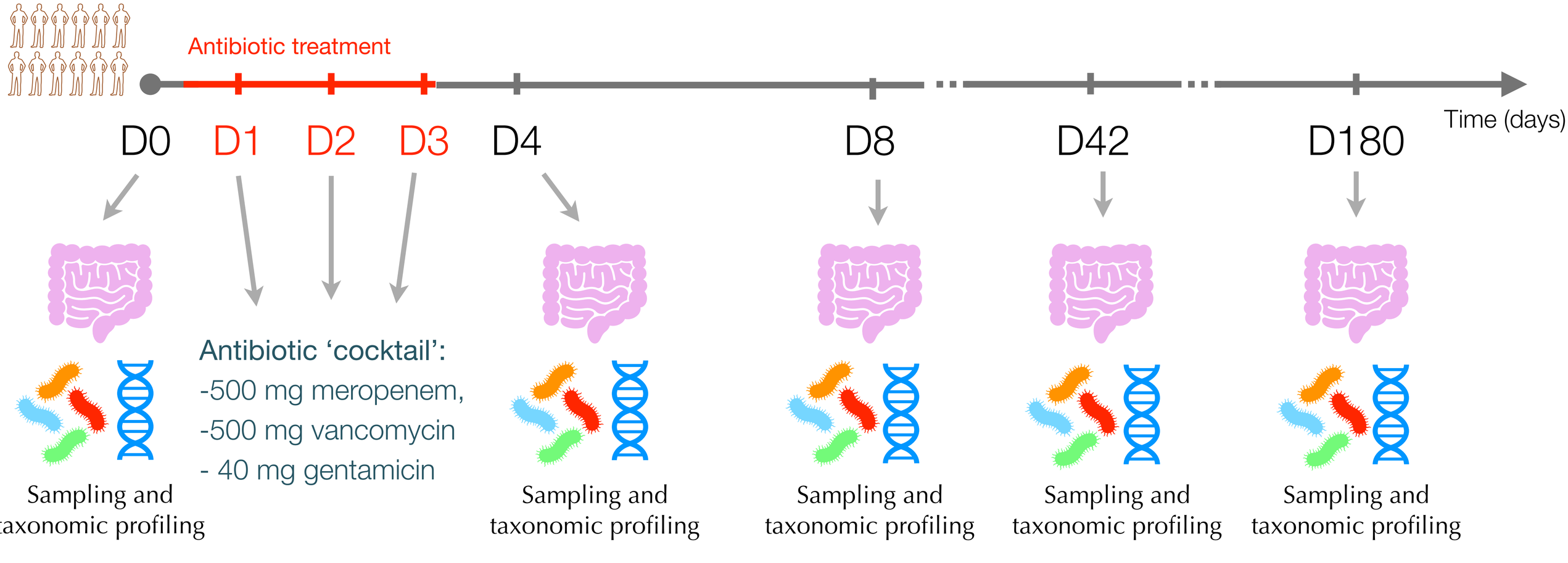
nature microbiology ARTICLES
https://doi.org/10.1038/s41564-018-0257-9

Recovery of gut microbiota of healthy adults following antibiotic exposure

Albert Palleja[1,2,23], Kristian H. Mikkelsen[3,23], Sofia K. Forslund[4,5,6,7,8,23], Alireza Kashani[1,9], Kristine H. Allin[1,10], Trine Nielsen[1], Tue H. Hansen[1], Suisha Liang[11,12], Qiang Feng[11,12], Chenchen Zhang[11,12], Paul Theodor Pyl[1], Luis Pedro Coelho[8], Huanming Yang[11,12,13], Jian Wang[11,12,13], Athanasios Typas[8,14], Morten F. Nielsen[3], Henrik Bjorn Nielsen[2], Peer Bork[5,8,15,16], Jun Wang[17,18,19,20], Tina Vilsbøll[3], Torben Hansen[1,21], Filip K. Knop[1,3,22*], Manimozhiyan Arumugam[1*] and Oluf Pedersen[1*]

Gut microbiota in 12 healthy men over a 6-month period following a 4-day intervention with a cocktail of 3 last-resort antibiotics

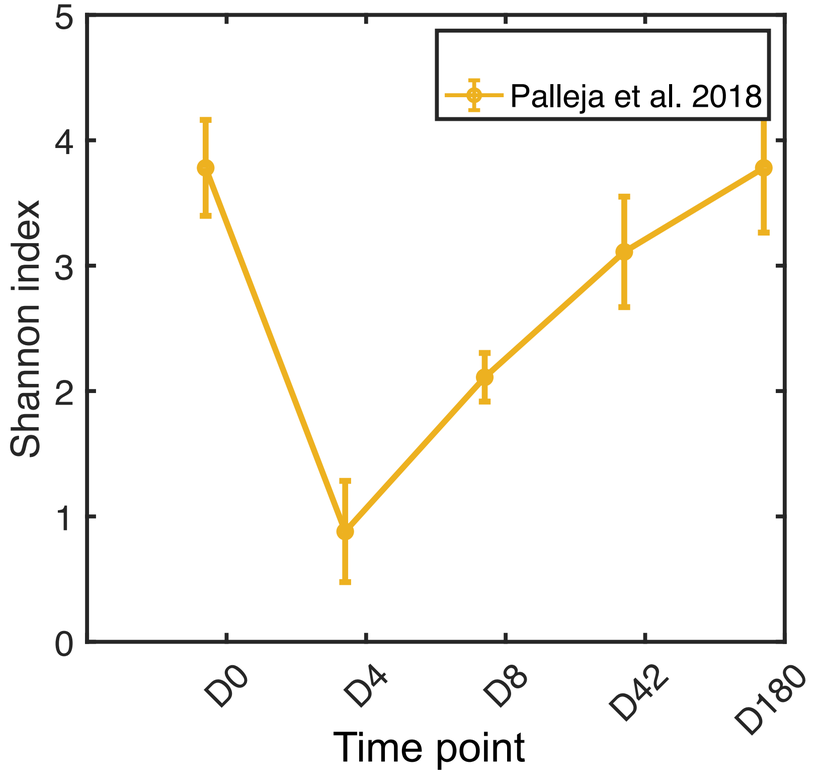
Palleja et al. 2018, Nat. Mic.



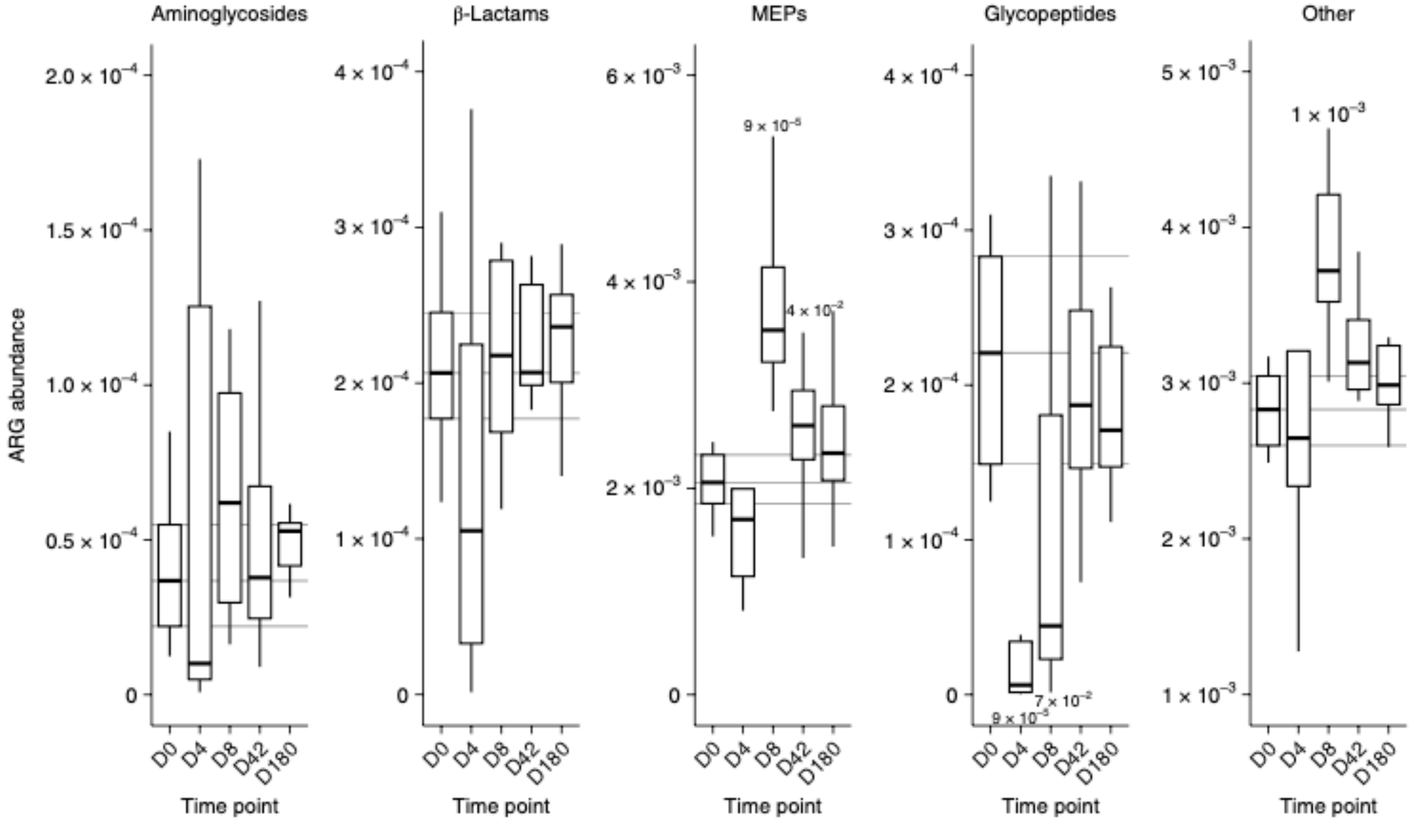
Main outcomes

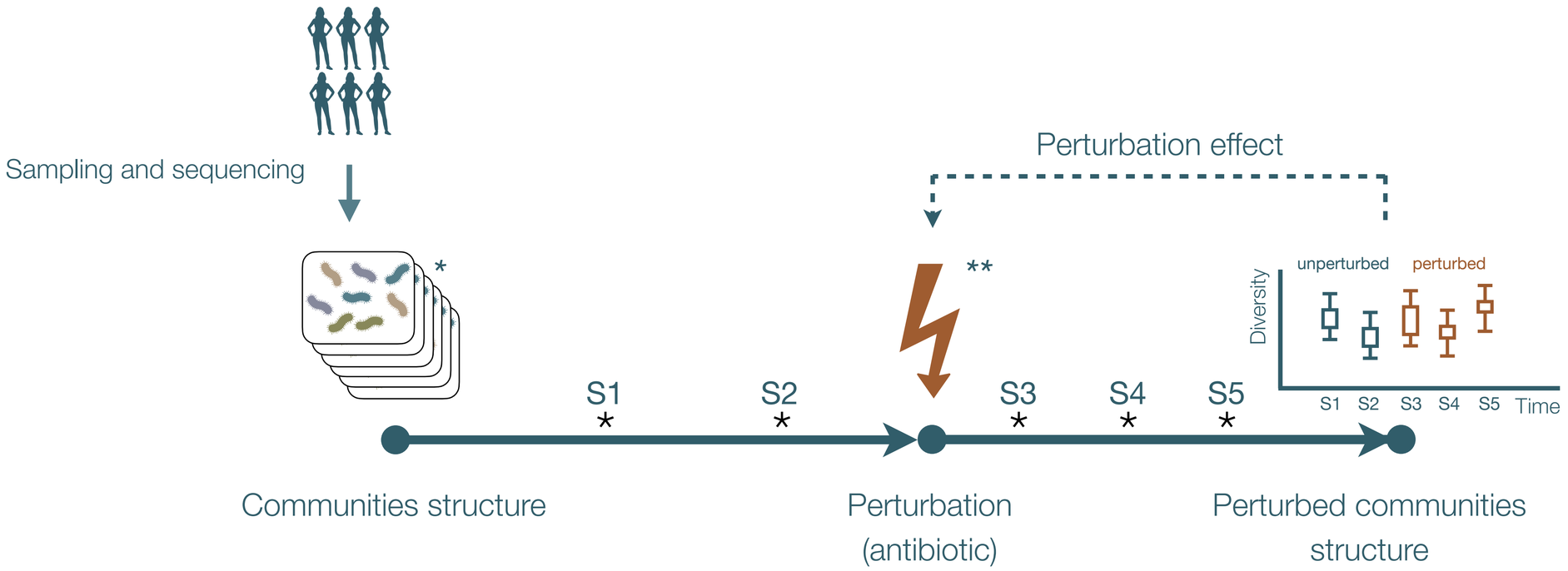
1. Microbial diversity

Initial richness = 140

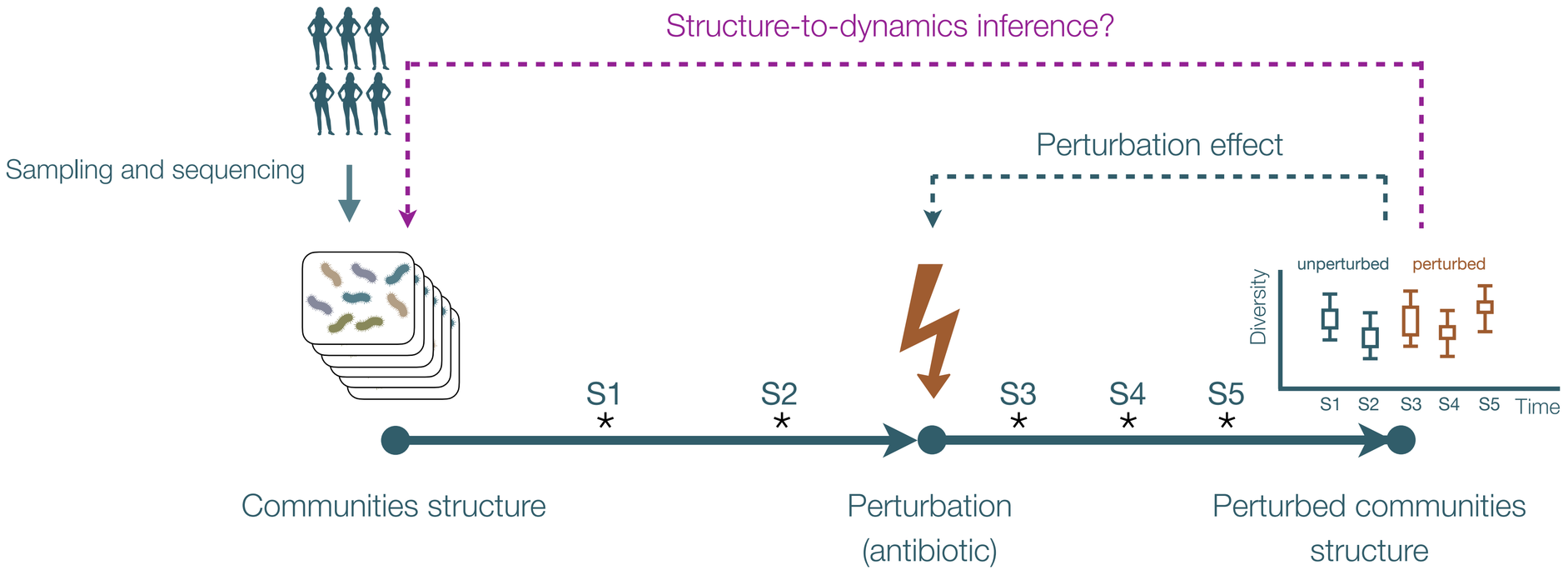


2. Resistome dynamics

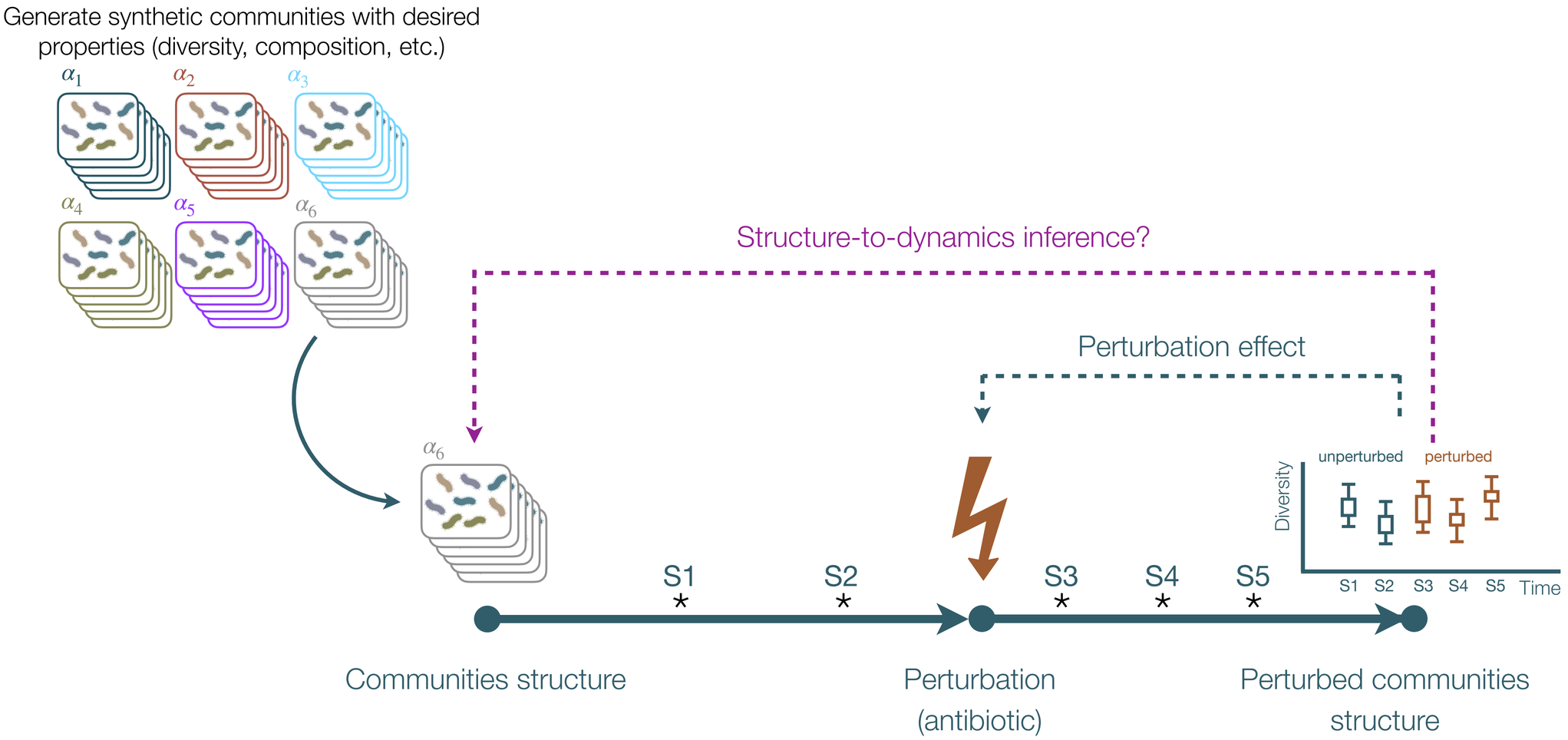


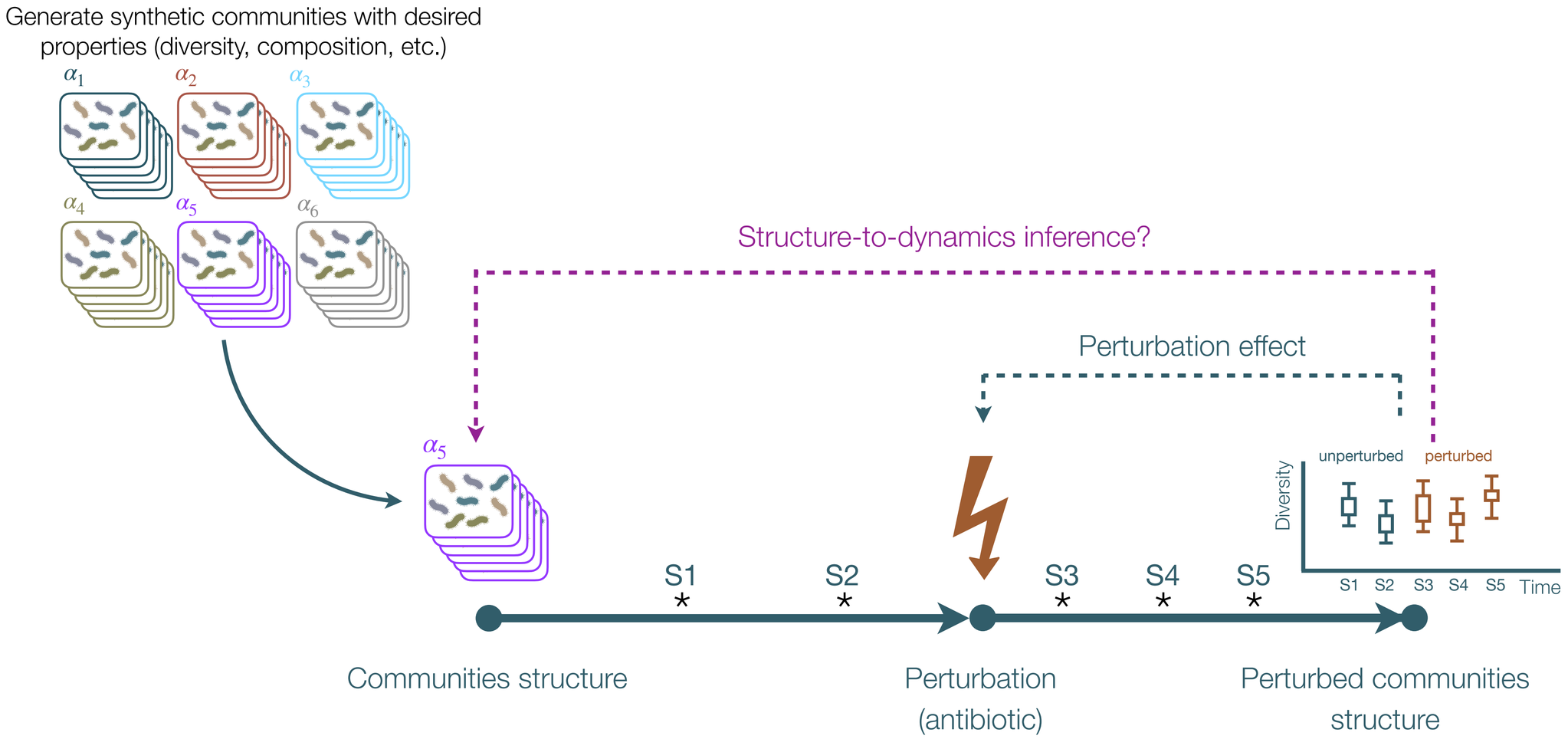


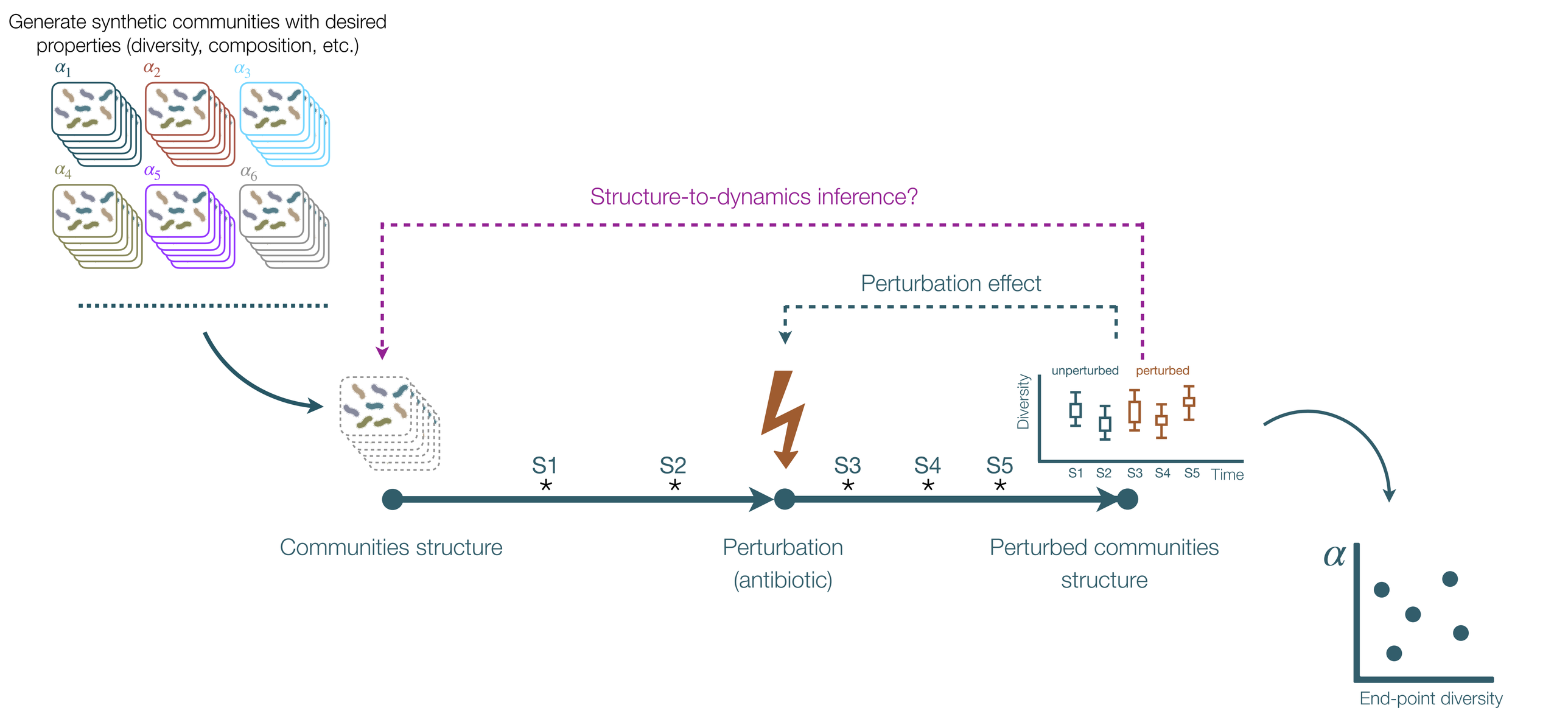
*How this * community responds to this ** perturbation.*



Which are the characteristics that impact the most the response to this perturbation?


Generate synthetic communities with desired properties (diversity, composition, etc.)
α_1
α_2
α_3
α_4
α_5
α_6
Structure-to-dynamics inference?
Perturbation effect
α_6
S1
S2
S3
S4
S5
unperturbed
perturbed
Diversity
S1 S2 S3 S4 S5 Time
Communities structure
Perturbation (antibiotic)
Perturbed communities structure


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S2
S3
S4
S5
Communities structure
Perturbation (antibiotic)
Perturbed communities structure
α
End-point diversity

To do this, we need two things:

1. A way to generate communities with desired properties
2. A way to simulate their dynamics and the emergence/spreading of AMR.

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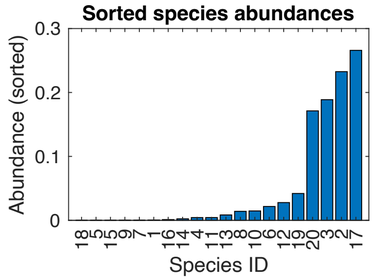
1. A way to generate communities with desired properties
2. A way to simulate their dynamics and the emergence/spreading of AMR.

Parametric synthetic community framework: Microbial interactions are not derived from the structure and the time course of the community. The structure of the community is defined first and the the interactions are HGT rates are derived from it (Dirichlet function).

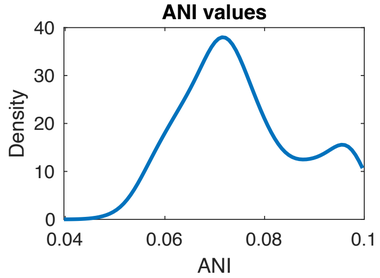
1. Fix a given diversity index (e.g. Shannon)

$$H'$$

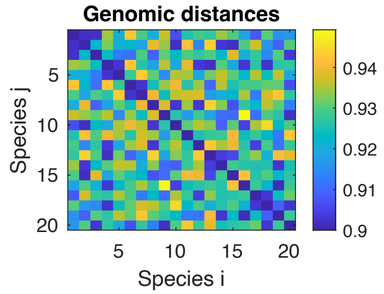
2. Find the species distribution that satisfies that diversity index (Dirichlet distribution*)



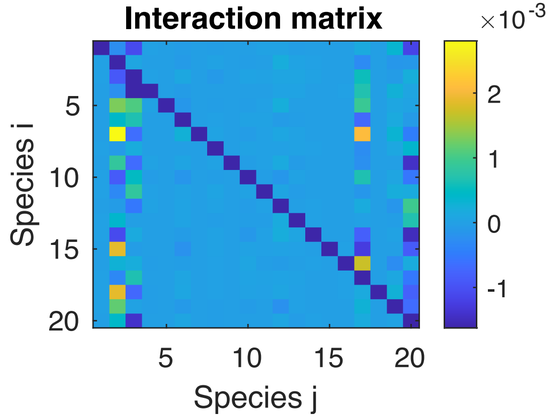
3. Compute ANI distribution (within a given interval)



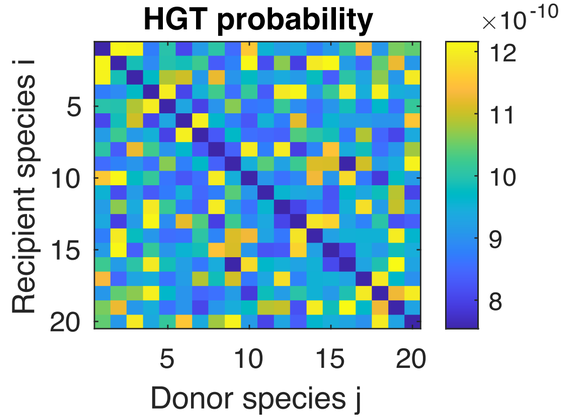
4. Compute genomic distances



5. Output n. 1



6. Output n. 2



* The Dirichlet distribution:multivariate generalization of the beta distribution.

The Dirichlet distribution of order with parameters

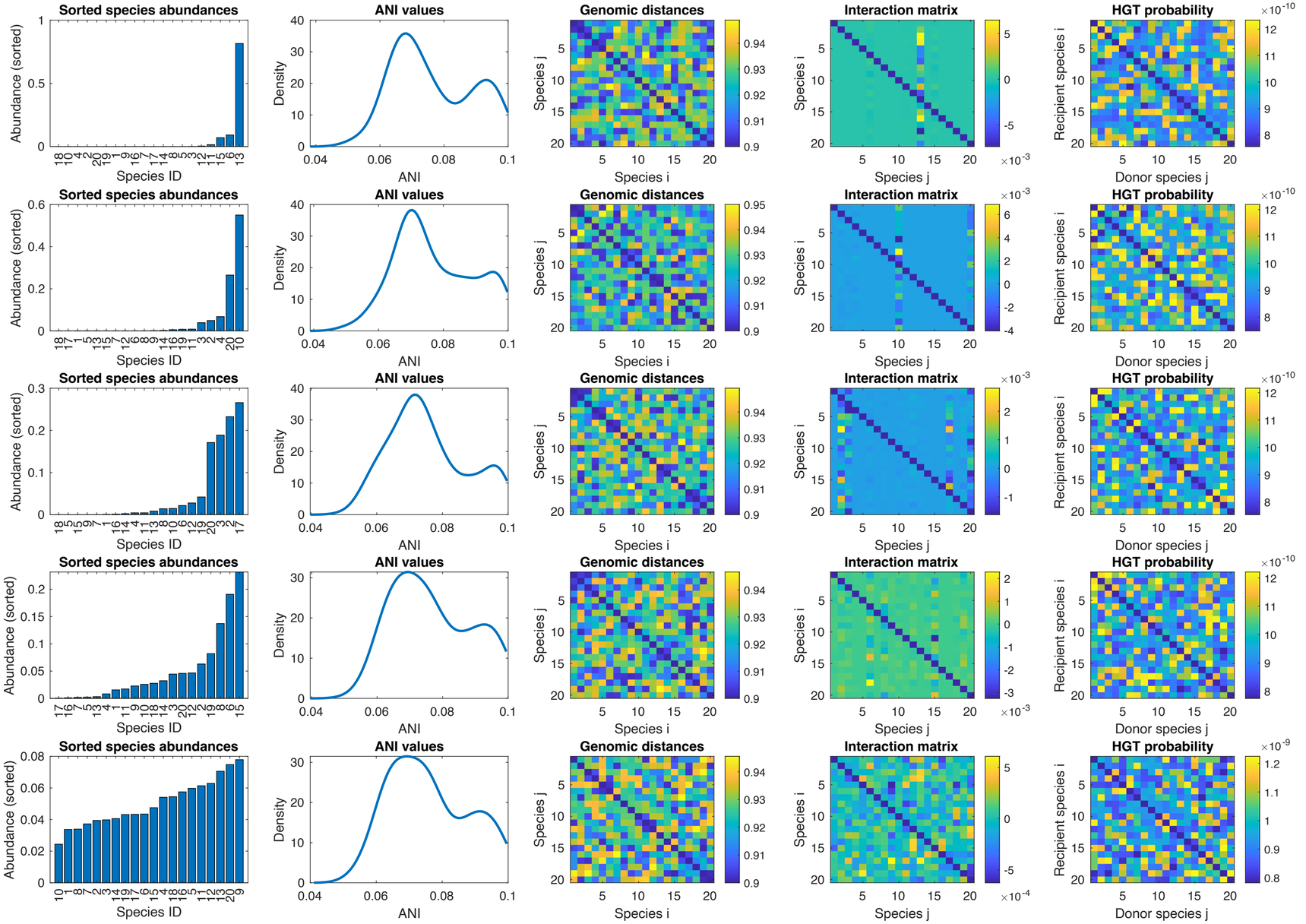
$$\alpha_1, \ldots, \alpha_K$$

(with K>2) has a probability density function given by

$$f(x_1, \ldots, x_K; \alpha_1, \ldots, \alpha_K) = \frac{1}{\mathrm{B}(\boldsymbol{\alpha})} \prod_{i=1}^{K} x_i^{\alpha_i - 1}$$

Parametric synthetic community framework, *in practice*

Community diversity



To do this, we need two things:

1. A way to generate communities with desired properties
2. A way to simulate their dynamics and the emergence/spreading of AMR.

Generalized Lotka-Volterra model

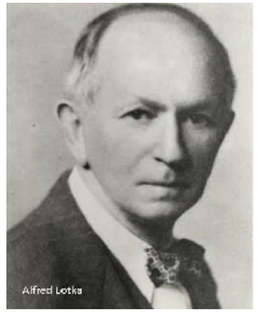
$$\frac{dx_i(t)}{dt} = x_i(t)\left(r_i + \sum_j A_{ij} x_j(t) \right)$$

Generalized Lotka-Volterra model

$$\frac{dx_i(t)}{dt} = x_i(t)\left(r_i + \sum_j A_{ij} x_j(t) \right)$$

ANALYTICAL NOTE ON CERTAIN RHYTHMIC RELATIONS IN ORGANIC SYSTEMS

By Alfred J. Lotka

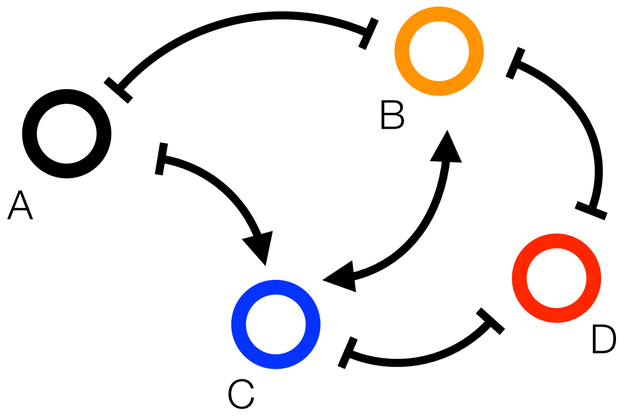


Fluctuations in the Abundance of a Species considered Mathematically.[1]

By Prof. Vito Volterra, For. Mem. R.S., President of the R. Accademia dei Lincei.



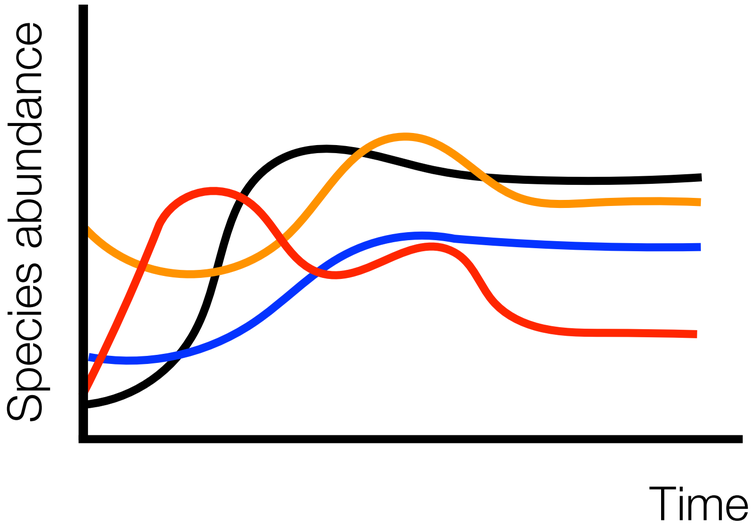
$$\frac{dx_i(t)}{dt} = x_i(t)\left(r_i + \sum_j A_{ij}x_j(t)\right)$$



	A	B	C	D
A	-1	-0.6	0.3	0
B	-0.5	-1	0.1	-1
C	-0.4	0.2	-1	-0.7
D	0	-0.5	-0.5	-1

Sample interaction matrix

Dynamic prediction





RESEARCH ARTICLE

When does a Lotka-Volterra model represent microbial interactions? Insights from *in vitro* nasal bacterial communities

Dedrick et al. 2023, mSystems

Scaling up the models: replicating *in silico* complex communities dynamics

$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i \eta_i x_{S,i}$$

$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i \eta_i x_{S,i}$$

Scaling up the models: replicating *in silico* complex communities dynamics

$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i \eta_i x_{S,i}$$

$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i \eta_i x_{S,i}$$

AMR evolution

HGT *Mutation*

Scaling up the models: replicating *in silico* complex communities dynamics

pharmacokinetic model

$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i \eta_i x_{S,i}$$

$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i \eta_i x_{S,i}$$

$$d_{ABX} = \frac{E_{max} * C_{abx}}{EC_{50} + C_{abx}};$$

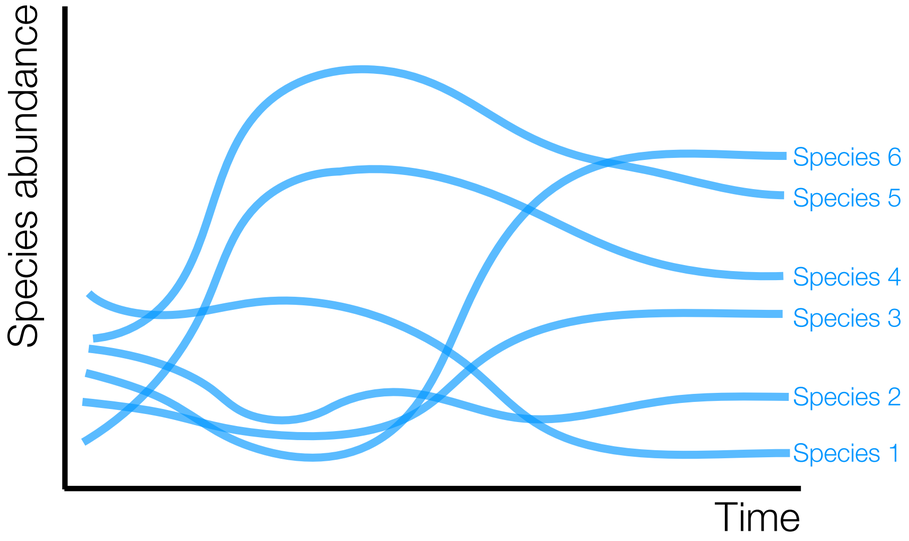
Accounting for [antibiotic] and killing rate

$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i \eta_i x_{S,i}$$

AMR evolution

HGT

Mutation



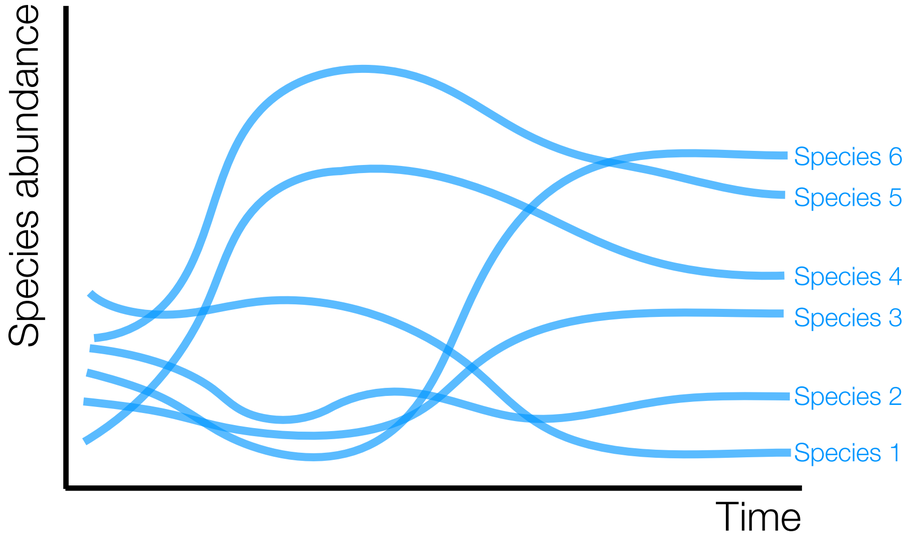
AMR evolution

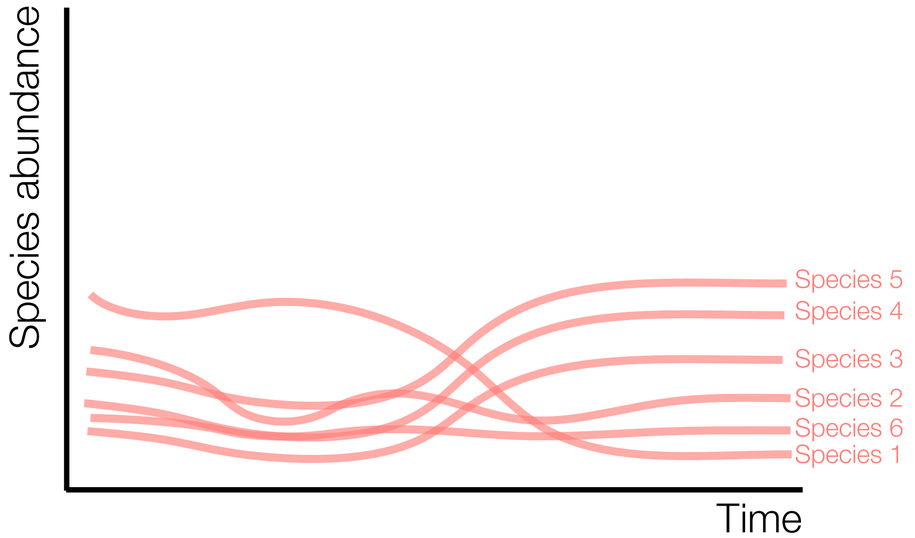
$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i\eta_i x_{S,i}$$

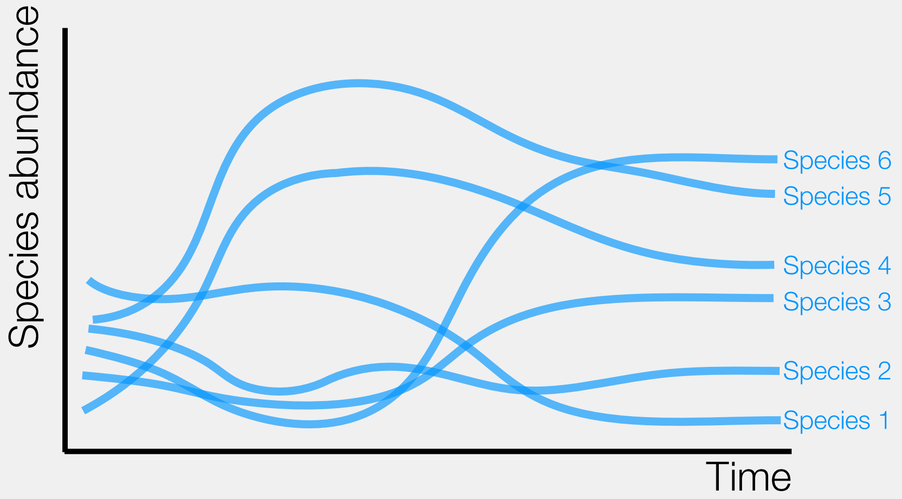
$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i\eta_i x_{S,i}$$

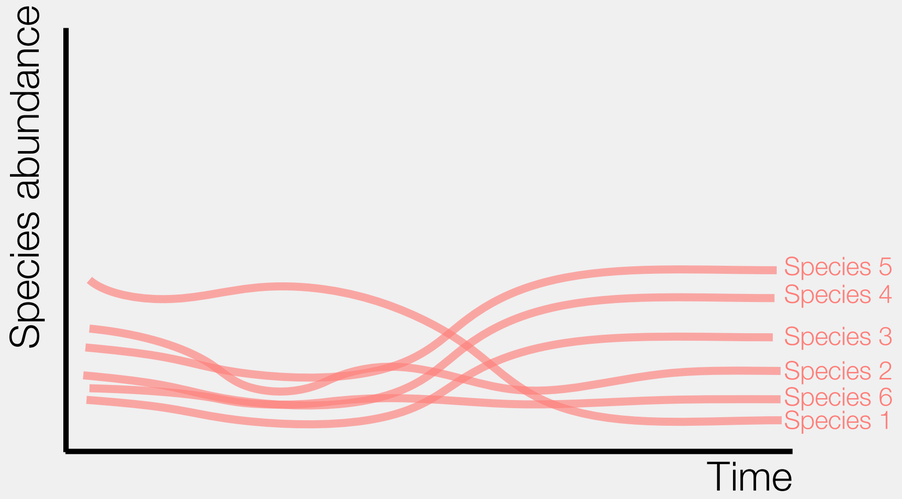
HGT

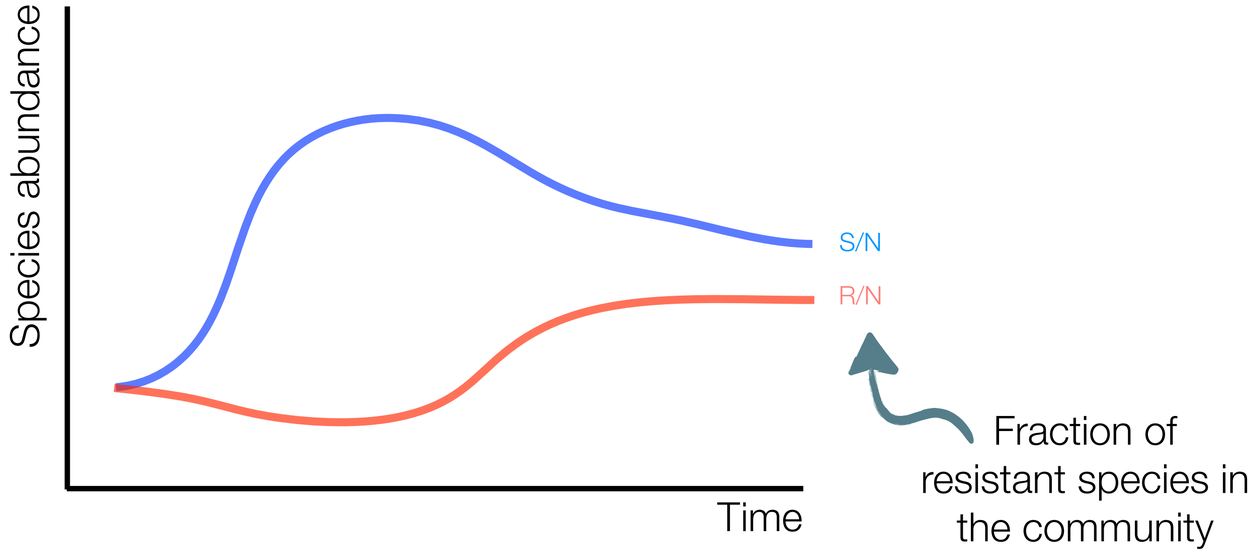
Mutation

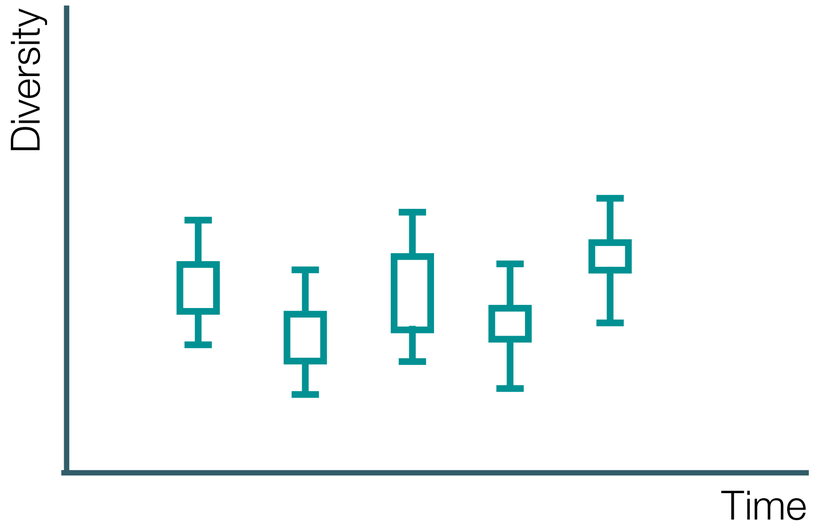




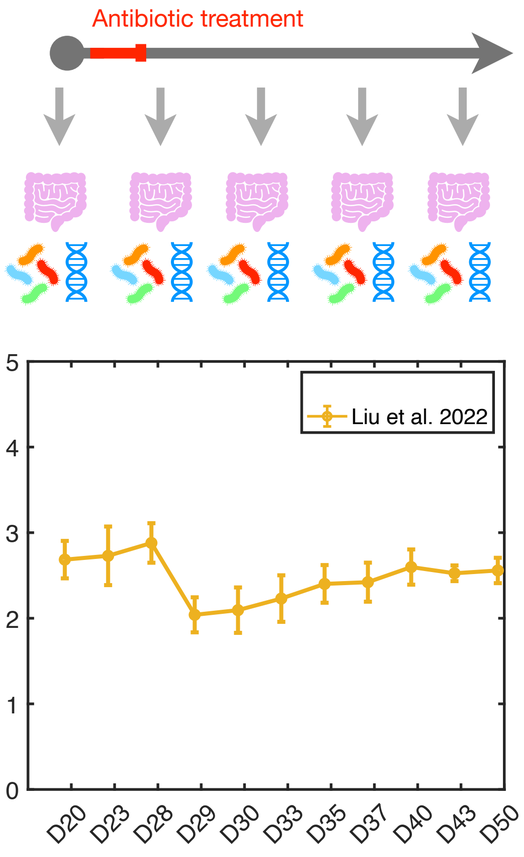

Species abundance
Species 6
Species 5
Species 4
Species 3
Species 2
Species 1
Time


Species abundance
Species 5
Species 4
Species 3
Species 2
Species 6
Species 1
Time

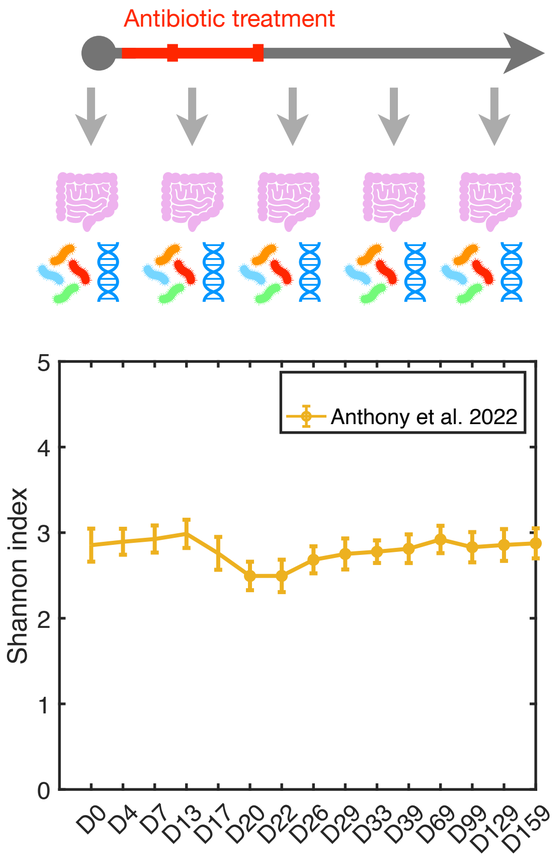

Species abundance
S/N
R/N
Time
Fraction of resistant species in the community


Diversity
Time

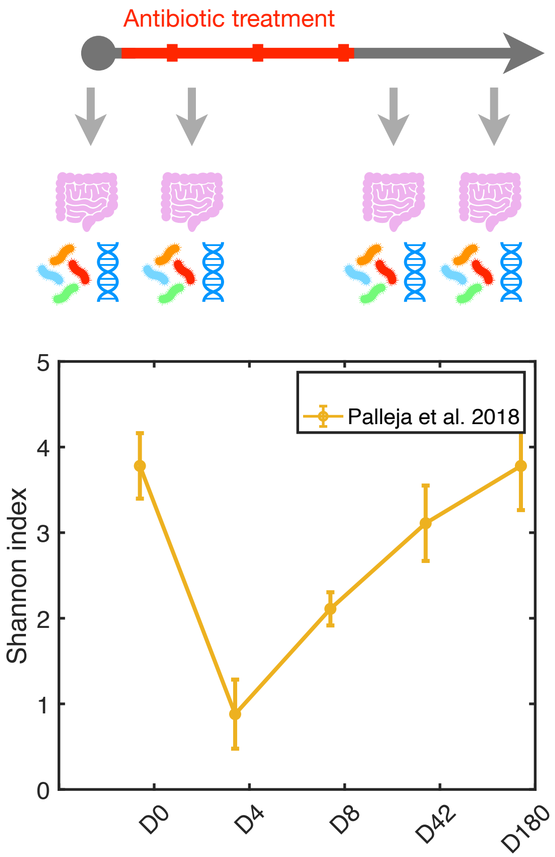
Study-case 1, Liu et al. 2022



Study-case 2, Anthony et al. 2022

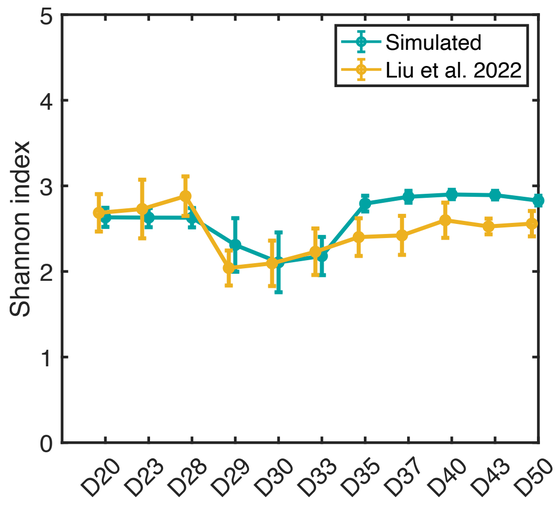


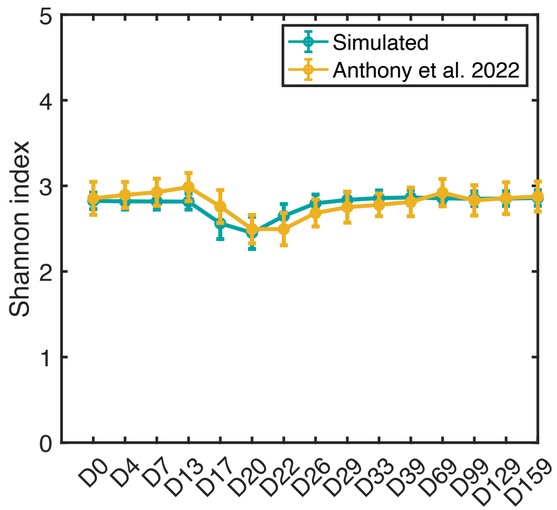
Study-case 3, Palleja et al. 2018

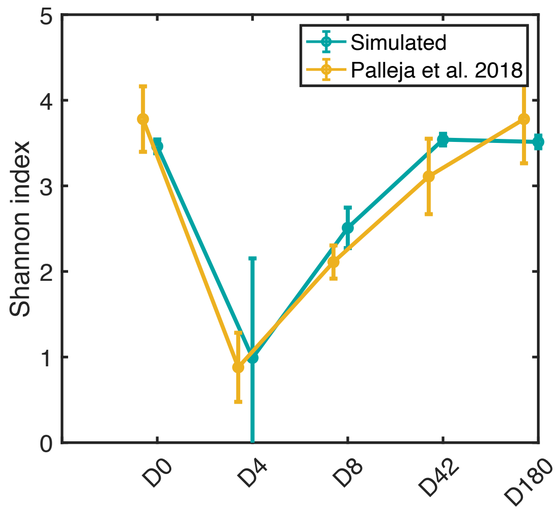


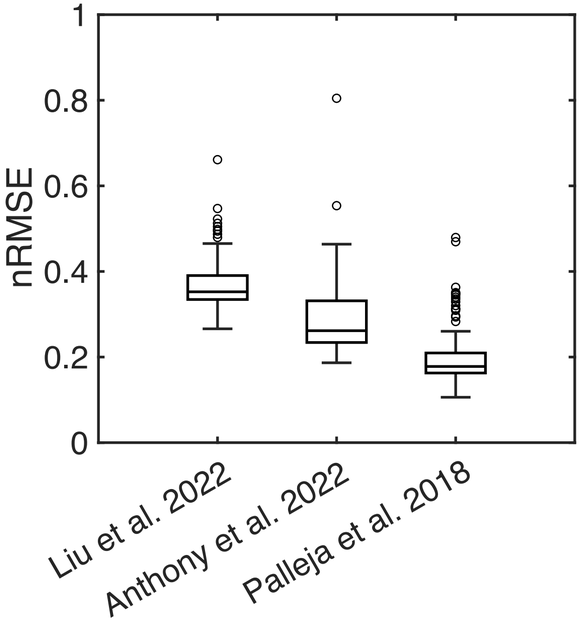
Model fit with real data

Model fit with real data







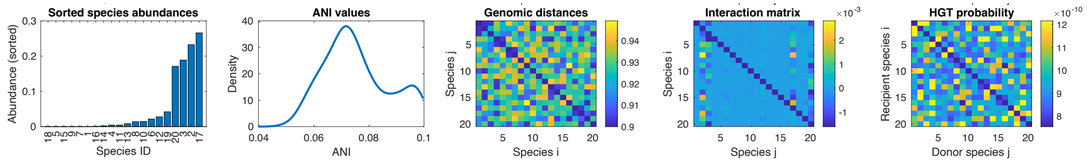


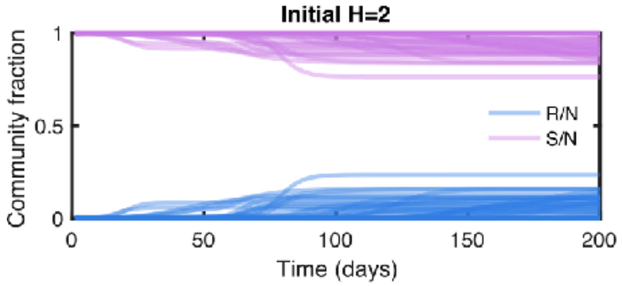
Simulations highlights:

- same n. of species as in the study
- same n. of antibiotics doses
- same sampling points
- same simulation length

Parametric synthetic community framework

1. Set up the communities

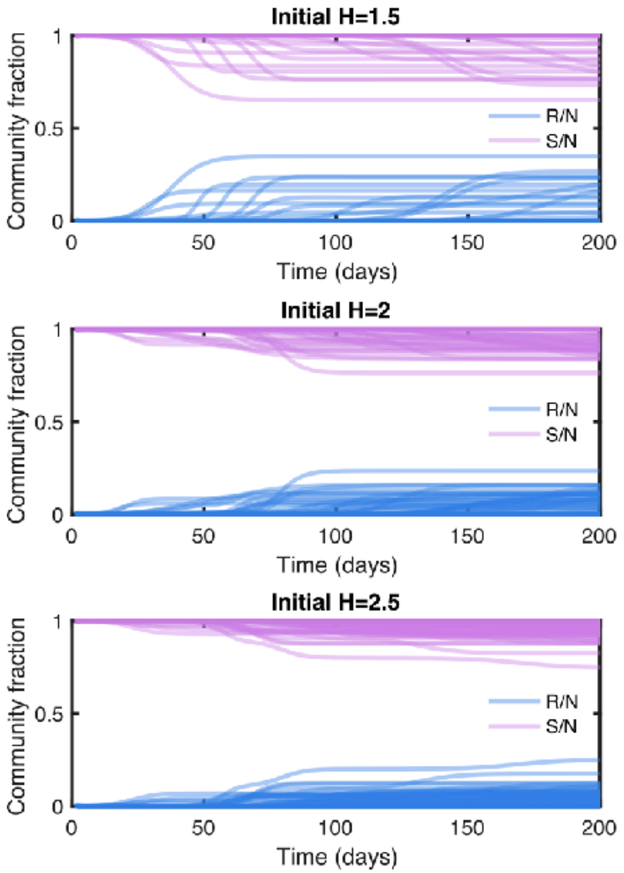


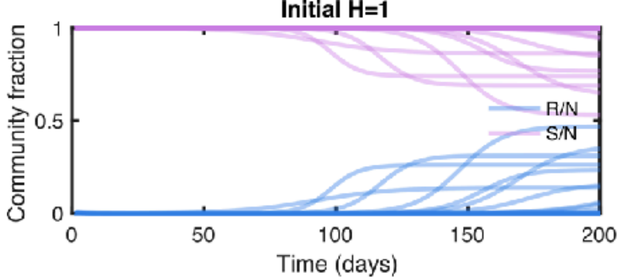


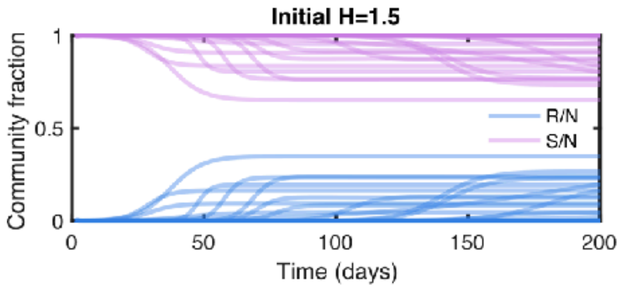
2. Run the model for each of them

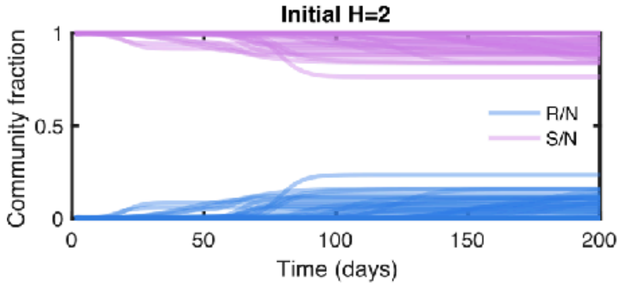
$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i \eta_i x_{S,i}$$

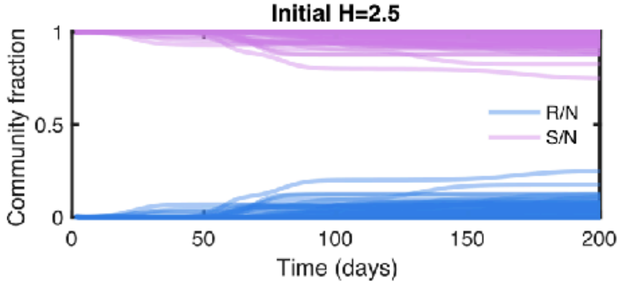
$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i \eta_i x_{S,i}$$

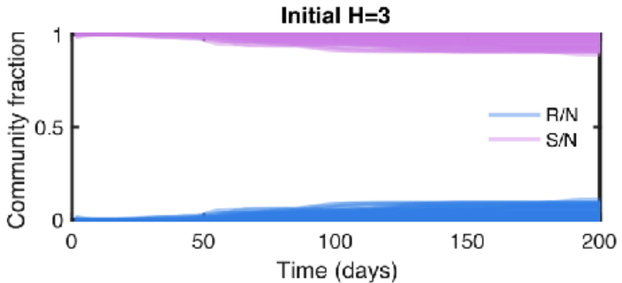

Initial H=1.5
Community fraction
Time (days)
R/N
S/N
Initial H=2
Community fraction
Time (days)
R/N
S/N
Initial H=2.5
Community fraction
Time (days)
R/N
S/N

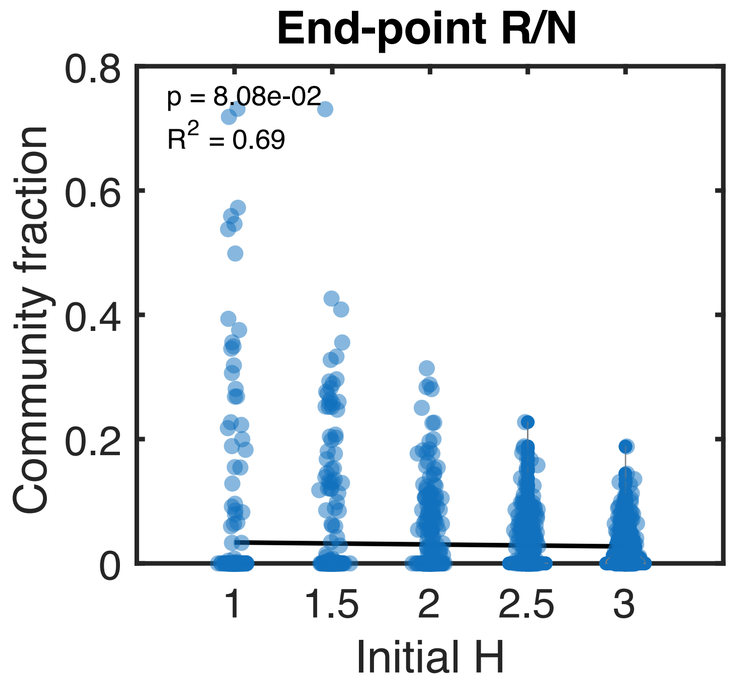

Initial H=1
Community fraction
Time (days)
R/N
S/N

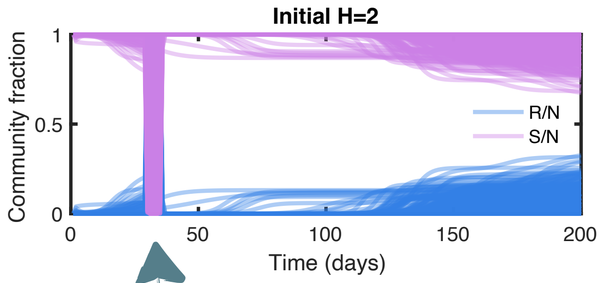

Initial H=1.5
Community fraction
Time (days)
R/N
S/N


Initial H=2
Community fraction
Time (days)
R/N
S/N

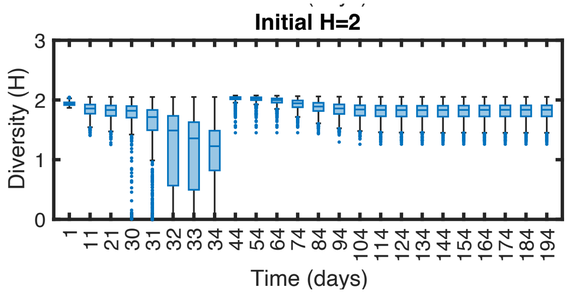

Initial H=2.5
Community fraction
Time (days)
R/N
S/N

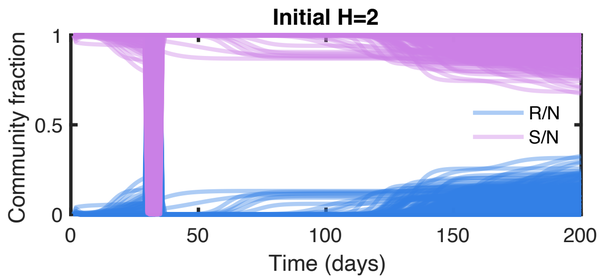

Initial H=3
Community fraction
Time (days)
R/N
S/N

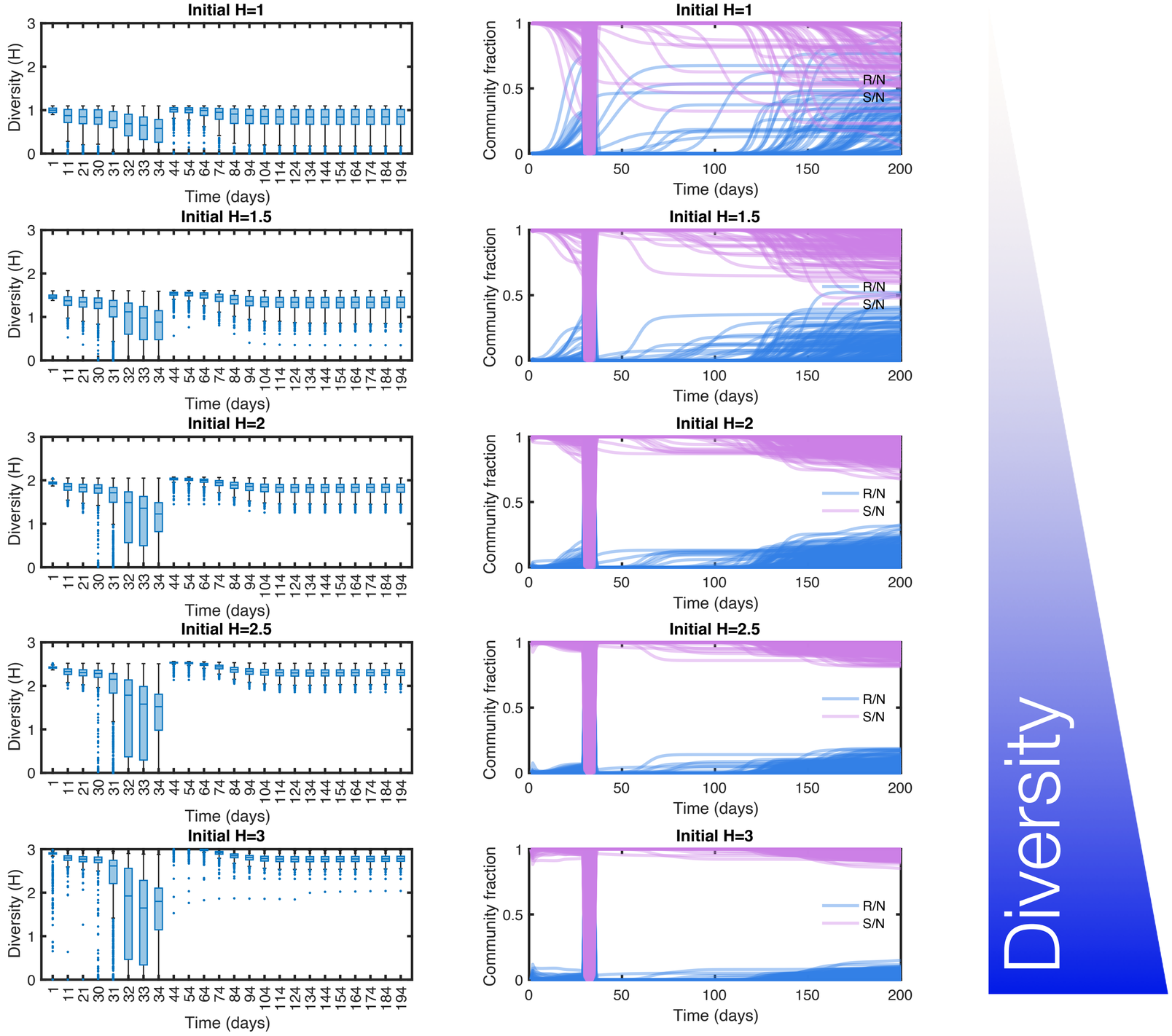

End-point R/N
p = 8.08e-02
R2 = 0.69
Community fraction
Initial H

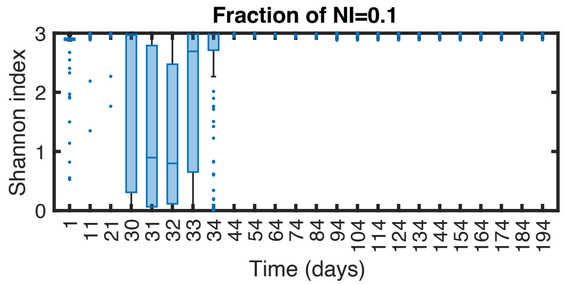


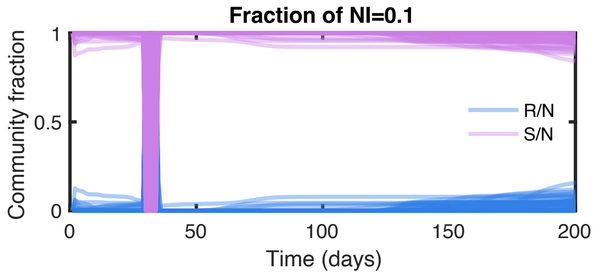
Antibiotics exposure

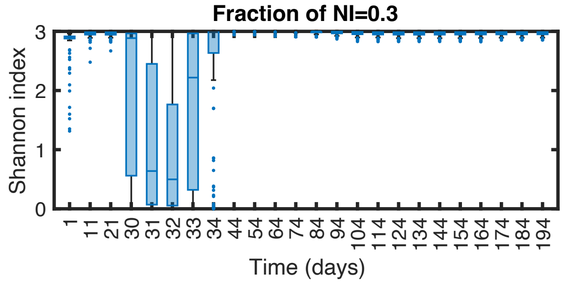

Initial H=2
Diversity (H)
0
1
2
3
1
11
21
30
31
32
33
34
44
54
64
74
84
94
104
114
124
134
144
154
164
174
184
194
Time (days)

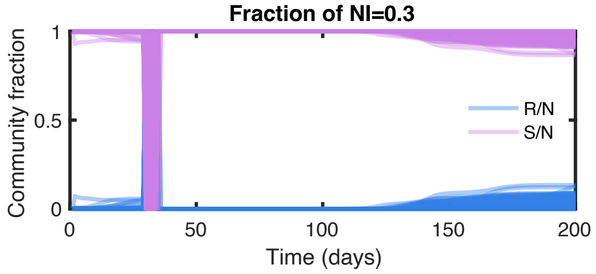

Initial H=2
Community fraction
0
0.5
1
R/N
S/N
0
50
100
150
200
Time (days)

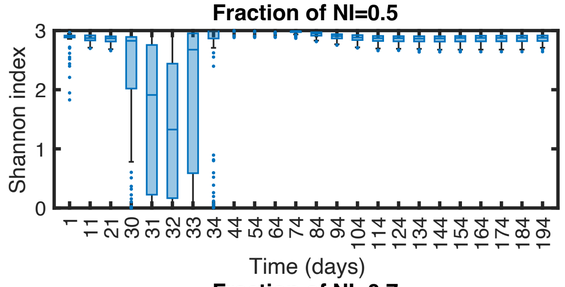

Initial H=1
Diversity (H)
Time (days)
Community fraction
R/N
S/N
Initial H=1.5
Initial H=2
Initial H=2.5
Initial H=3
Diversity

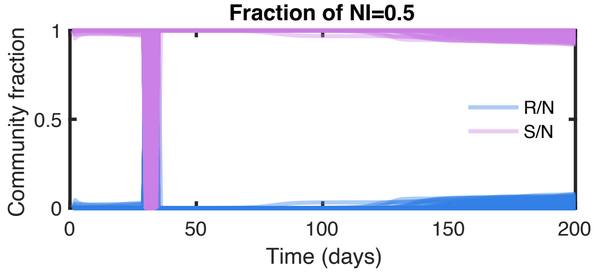


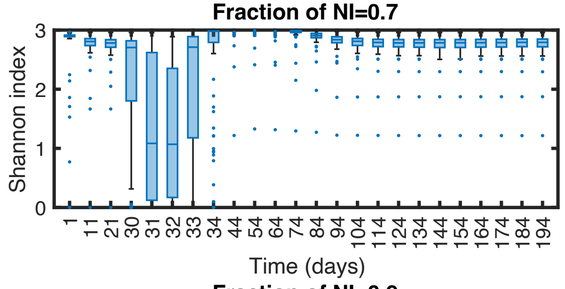


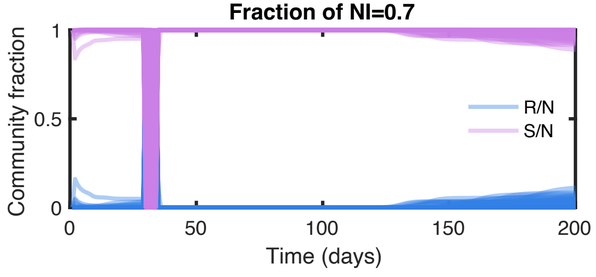


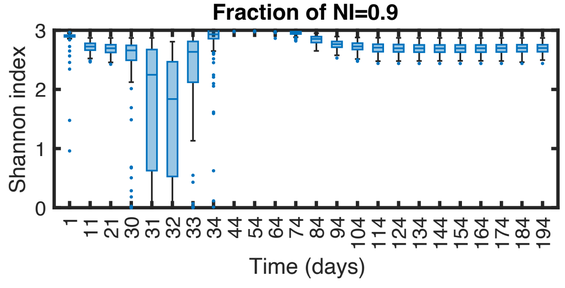


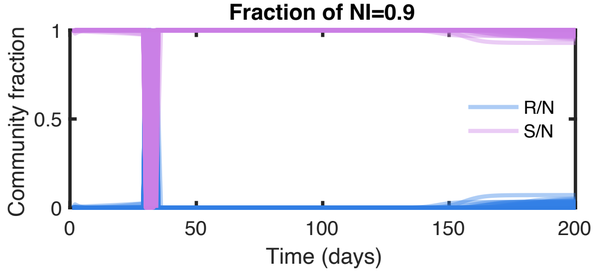








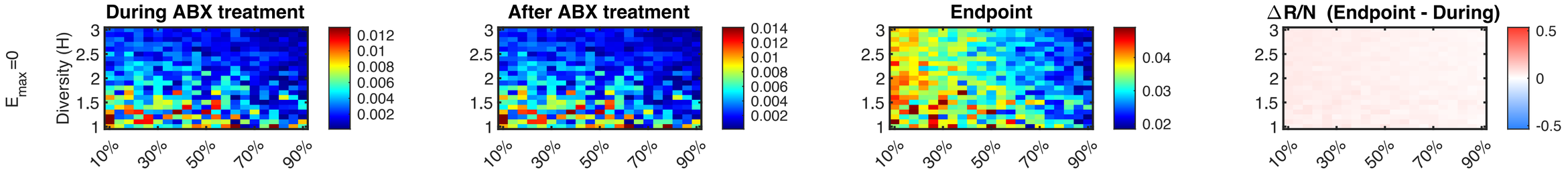


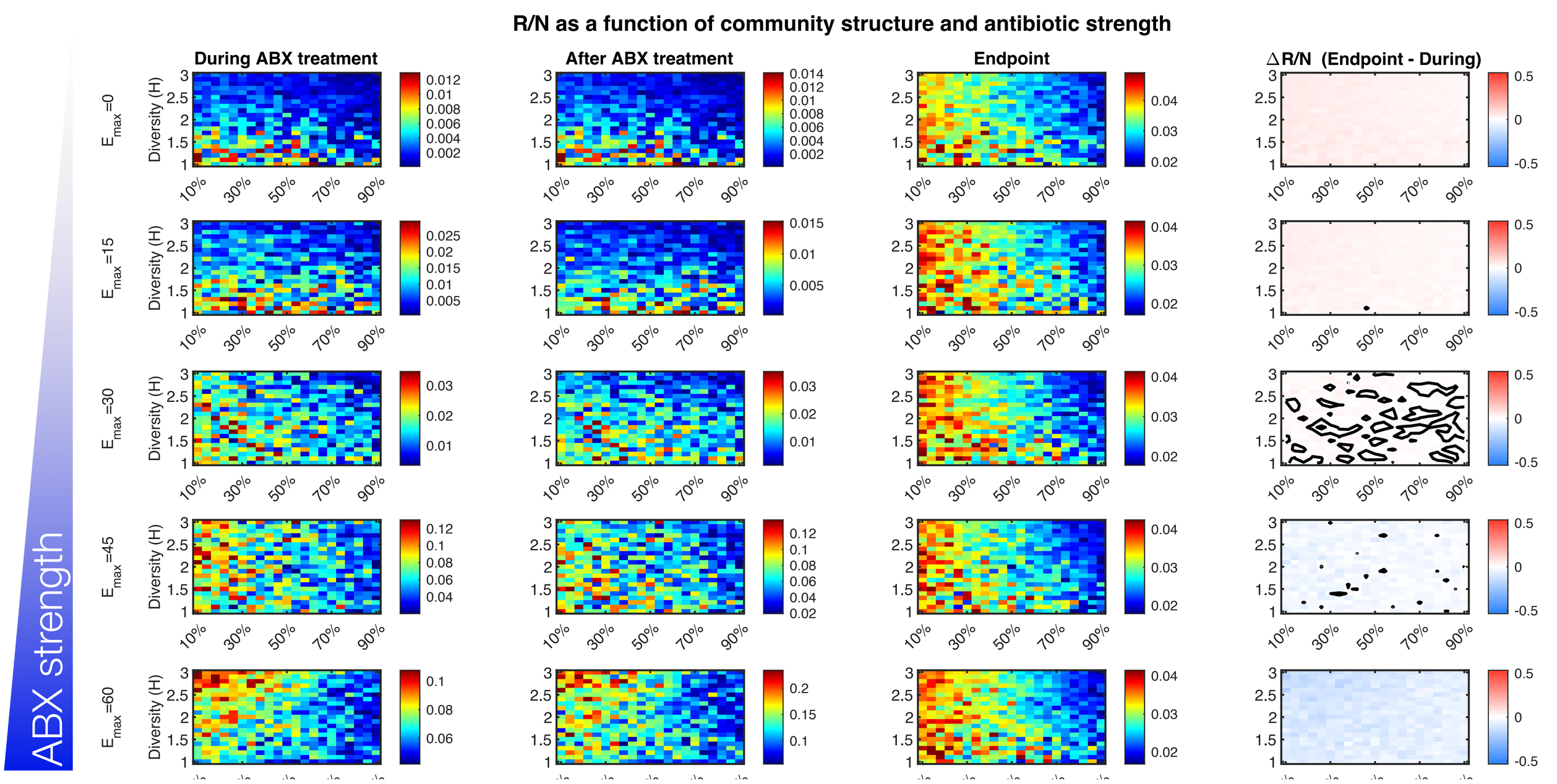


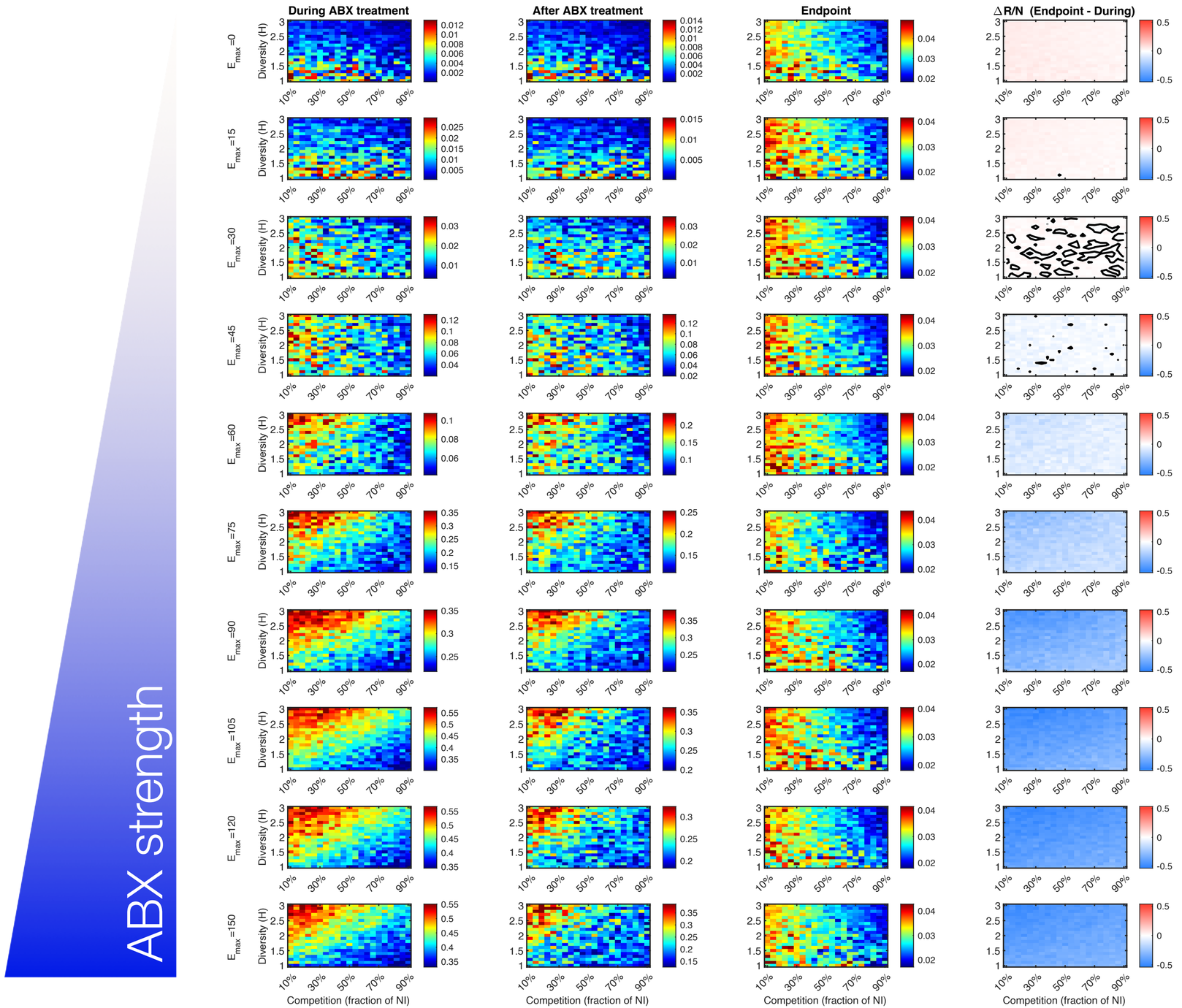
Competition

Community structure seems to affect the emergence, spreading and maintenance of AMR. Does this depend on the antibiotic treatment?

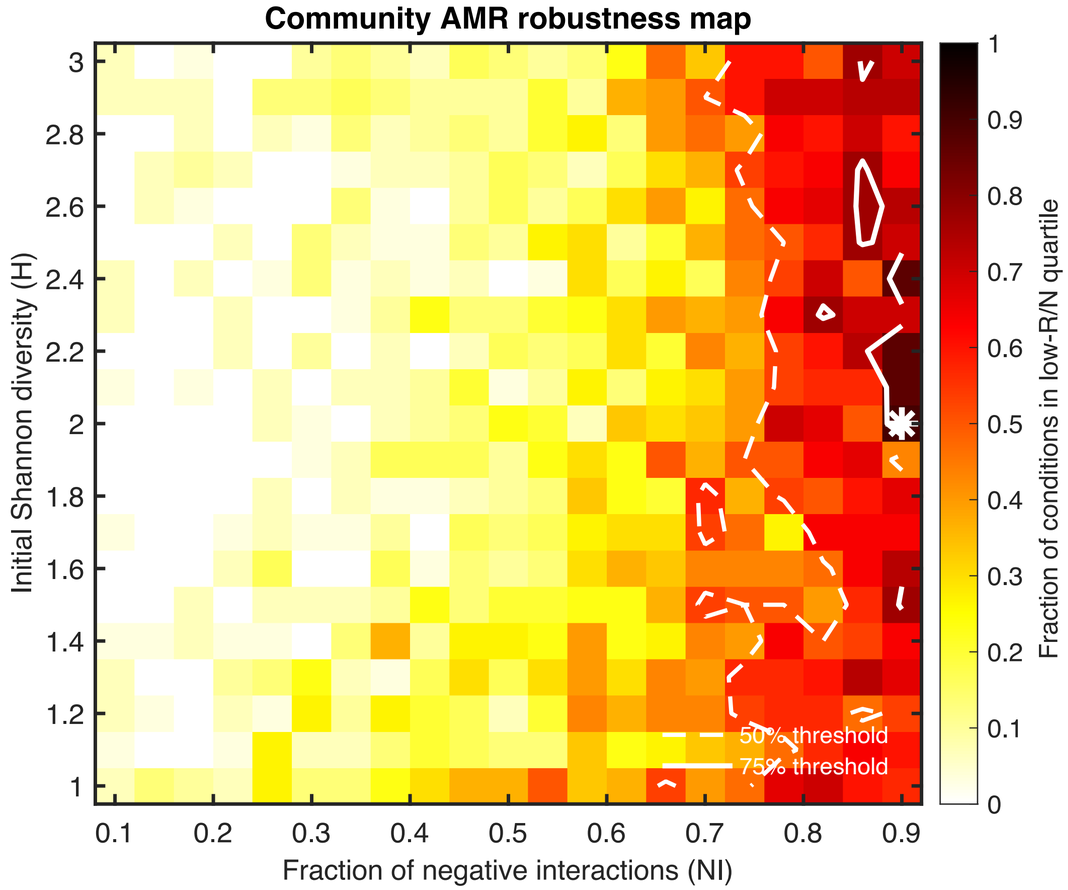
R/N as a function of community structure and antibiotic strength




R/N as a function of community structure and antibiotic strength
During ABX treatment
After ABX treatment
Endpoint
△R/N (Endpoint - During)
ABX strength
E_{max}=0
E_{max}=15
E_{max}=30
E_{max}=45
E_{max}=60
Diversity (H)
10%
30%
50%
70%
90%


R/N as a function of community structure and antibiotic strength
During ABX treatment
After ABX treatment
Endpoint
ΔR/N (Endpoint - During)
ABX strength
Emax=0
Emax=15
Emax=30
Emax=45
Emax=60
Emax=75
Emax=90
Emax=105
Emax=120
Emax=150
Diversity (H)
Competition (fraction of NI)
10%
30%
50%
70%
90%

How should a microbiota be to contrast the emergence and spreading gf AMR most of the times?



Take home messages

Microbial community dynamic modeling is a solid alternative to classical sample and sequence approaches.

When augmented with other features (pharmacokinetics and evolution), gLV models can provide reliable predictions on coarse-grained metrics like Shannon diversity

Negative interactions, not diversity, seem to play a major role in determining the faith of AMR in a microbial community and, in particular, to reduce it on the short term.

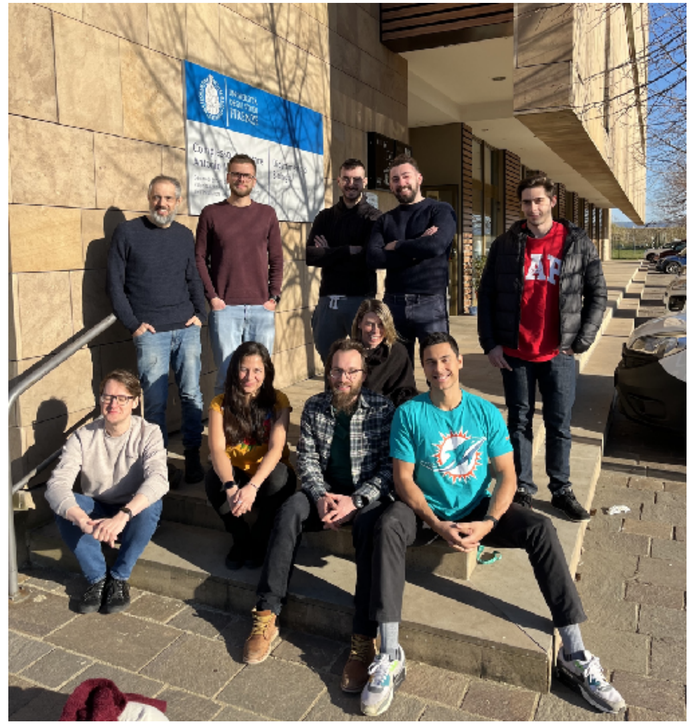
Microbiota-based predictions on the emergence, spreading and maintenance of AMR can inform on the optimal antibiotic dose to optimize the treatment.

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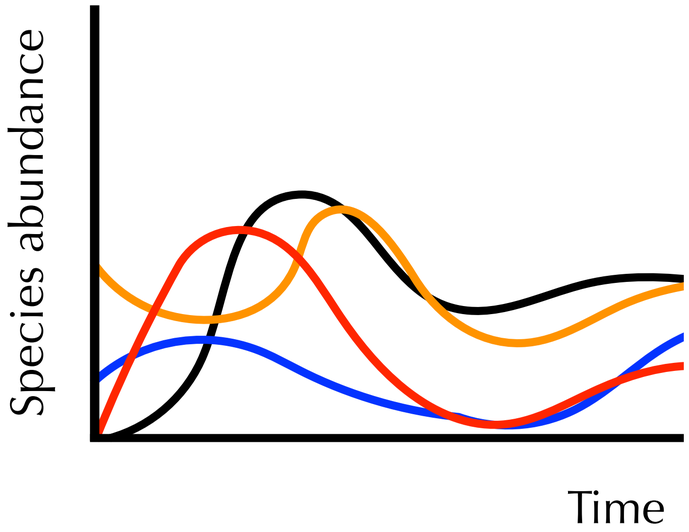
Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

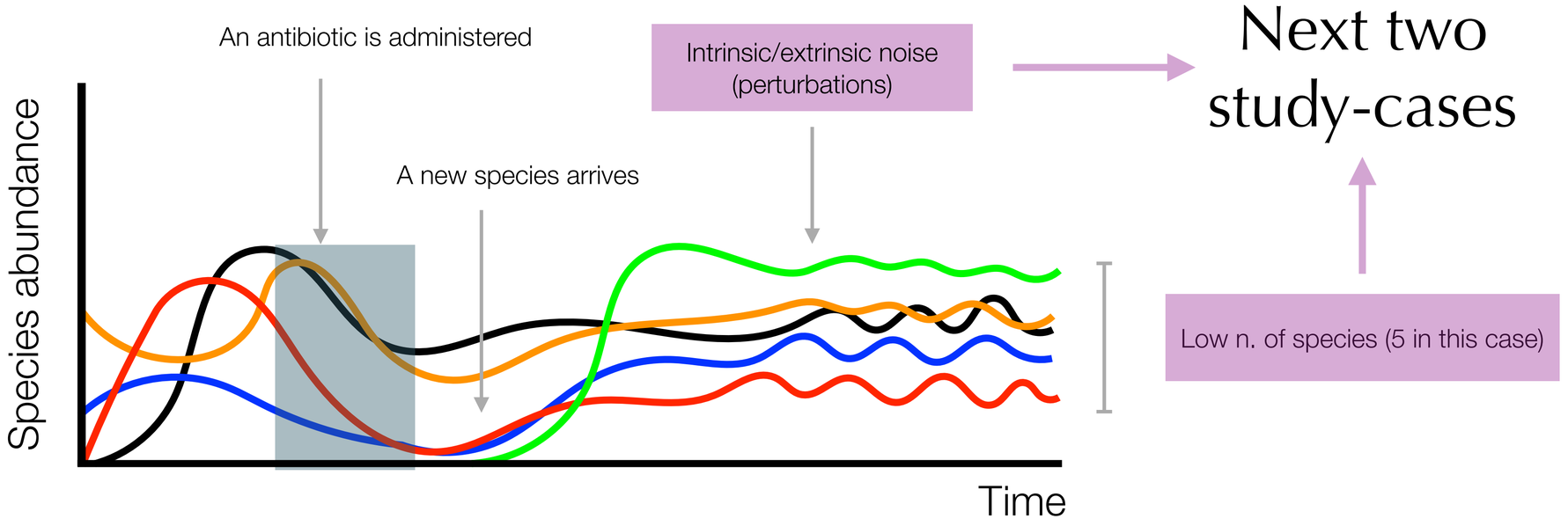
UNIVERSITÀ DEGLI STUDI FIRENZE
BIO DIPARTIMENTO DI BIOLOGIA
Da un secolo, oltre.

EMBO

PRIN
PROGETTI DI RICERCA DI RILEVANTE INTERESSE NAZIONALE

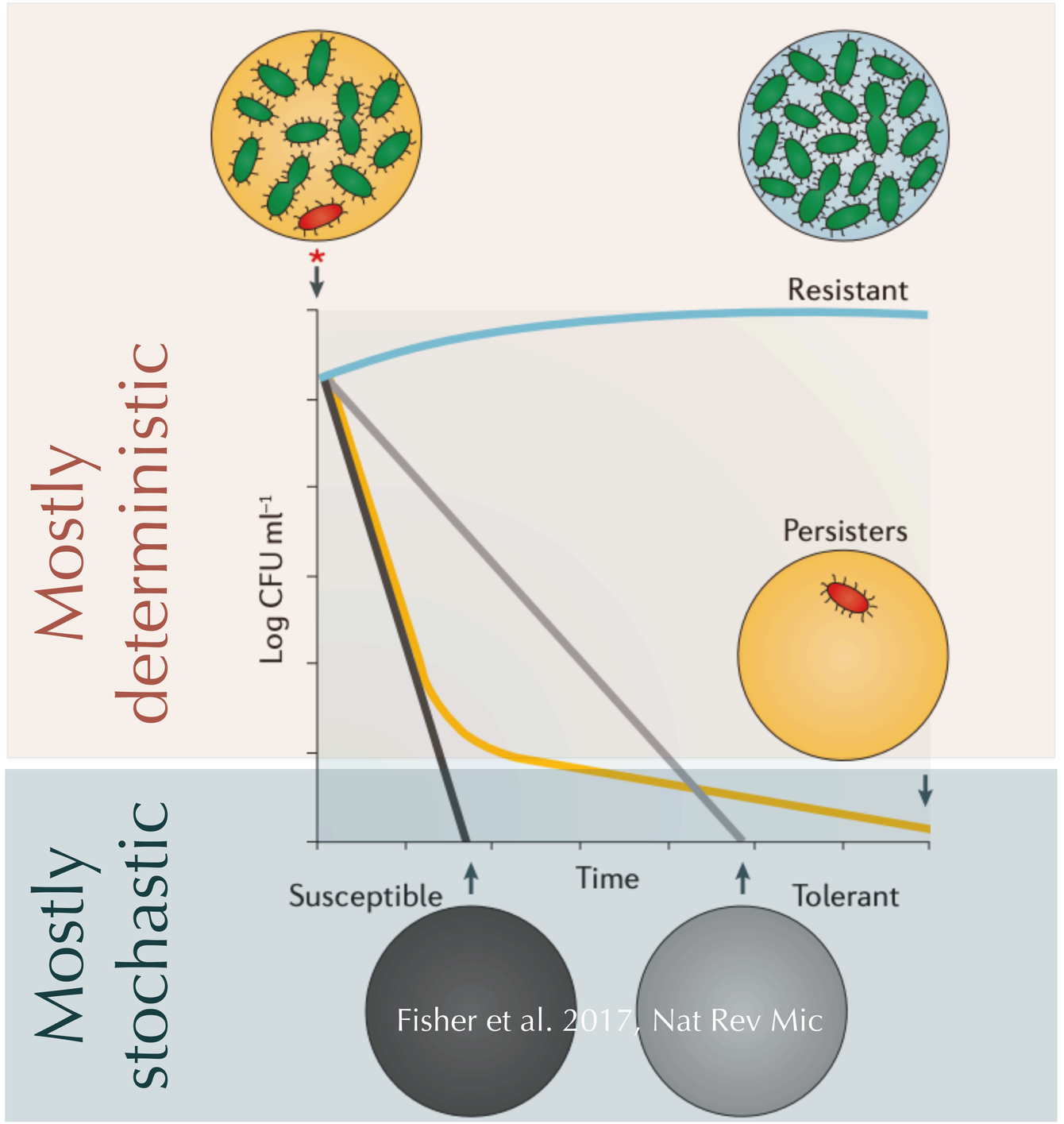
GIDA


Species abundance
Time

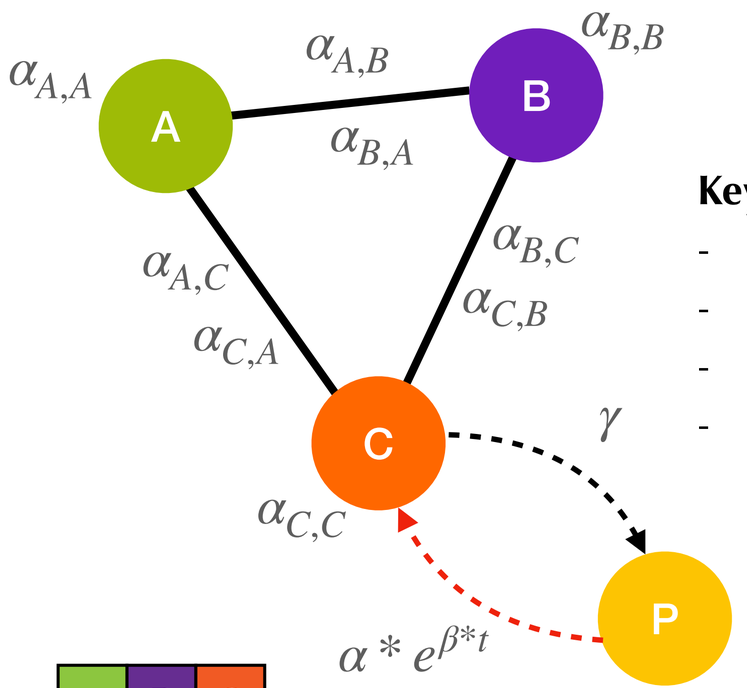

An antibiotic is administered
Intrinsic/extrinsic noise
(perturbations)
A new species arrives
Species abundance
Time
Next two
study-cases
Low n. of species (5 in this case)

Case-study n. 1

Key concept: Microbe-microbe interactions represent an additional factor affecting the mode, tempo and success of persisters awakening.



The model: a simple model of 3 interacting species.
Persisters are a subpopulation of species C and are formed stochastically



	A	B	C
A	-0.57	-0.34	-0.60
B	-0.61	-0.90	-0.13
C	-0.24	-0.35	-0.27

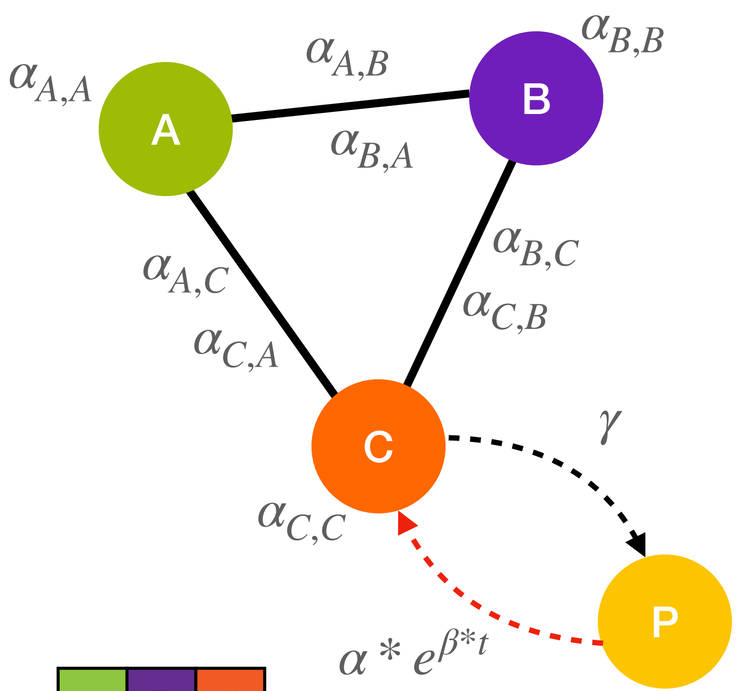
Key assumptions:

- C is the focal species
- P are persisters cells stochastically generated from C
- P cells resuscitate following ABX treatment (rate according to Fang and Allison 2023)
- A and B are not sensitive to the ABX, C is.

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

The model: a simple model of 3 interacting species.
Persisters are a subpopulation of species C and are formed stochastically

Chemical equations



	A	B	C
A	-0.57	-0.34	-0.60
B	-0.61	-0.90	-0.13
C	-0.24	-0.35	-0.27

$$x_i \xrightarrow{\mu_i} 2x_i$$

$$x_i \xrightarrow{\delta} \varnothing$$

$$x_i + x_j \xrightarrow{\alpha_{i,j}} 2x_i + x_j$$

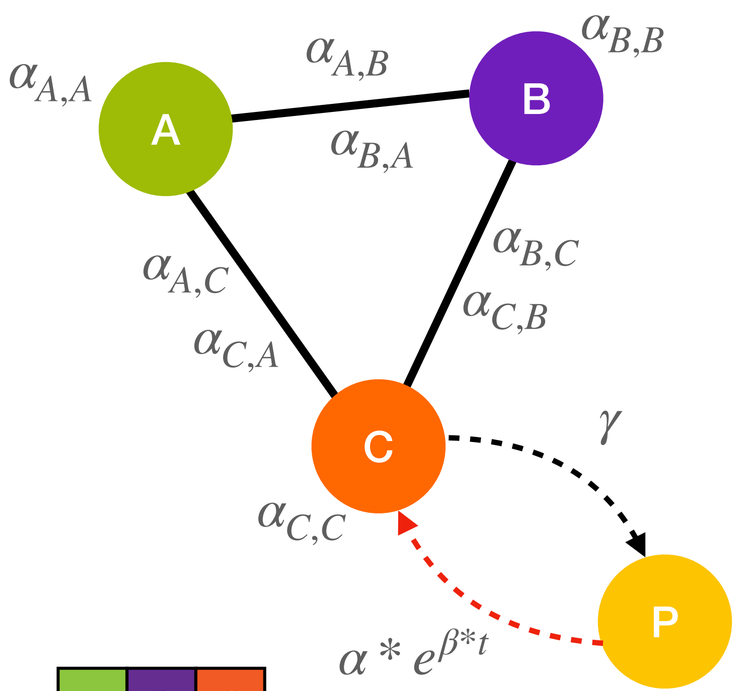
$$C \xrightarrow{\gamma} P$$

$$C \xrightarrow{\xi} \varnothing$$

$$P \xrightarrow{\alpha * e^{\beta * t}} C$$

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

The model: a simple model of 4 interacting species.
Persisters are a subpopulation of species C and are formed stochastically



	A	B	C
A	-0.57	-0.34	-0.60
B	-0.61	-0.90	-0.13
C	-0.24	-0.35	-0.27

Chemical equations

$$x_i \xrightarrow{\mu_i} 2x_i$$

$$x_i \xrightarrow{\delta} \varnothing$$

$$x_i + x_j \xrightarrow{\alpha_{i,j}} 2x_i + x_j$$

$$C \xrightarrow{\gamma} P$$

$$C \xrightarrow{\xi} \varnothing$$

$$P \xrightarrow{\alpha * e^{\beta * t}} C$$

Deterministic model

$$\dot{A} = \mu_A A + \alpha_{A,B} AB + \alpha_{C,A} AC + \alpha_{A,A} A^2 - \delta A$$

$$\dot{B} = \mu_B B + \alpha_{B,A} BA + \alpha_{C,B} BC + \alpha_{B,B} B^2 - \delta B$$

$$\dot{C} = \mu_C C + \alpha_{A,C} CA + \alpha_{B,C} CB + \alpha_{C,C} C^2 - \delta C - \gamma C$$

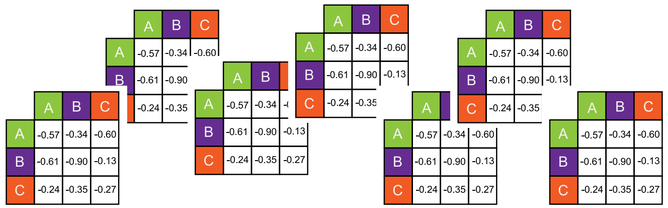
$$\dot{P} = \gamma C - \delta P$$

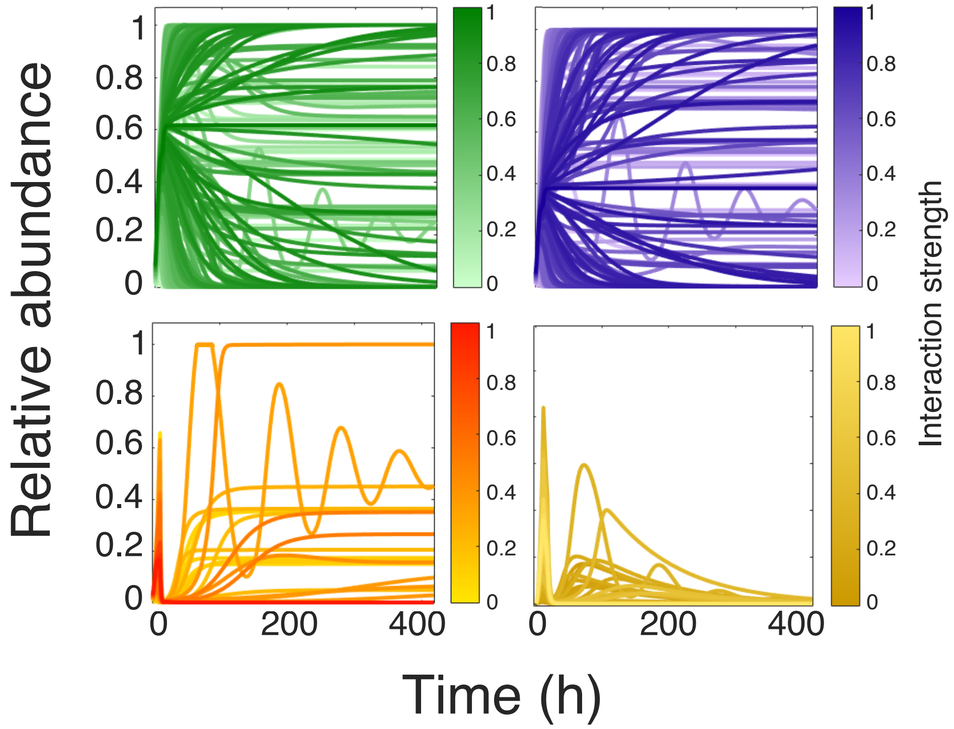
$$\dot{C} = \mu_C C + \alpha_{A,C} CA + \alpha_{B,C} CB + \alpha_{C,C} C^2 - \delta C - \gamma C - \xi C$$

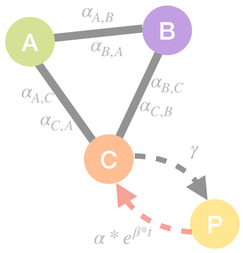
$$\dot{C} = \alpha_{res} e^{\beta t} P + \rho \mu_C C + \alpha_{A,C} CA + \alpha_{B,C} CB + \alpha_{C,C} C^2 - \delta C - \gamma C$$

$$\dot{P} = \gamma C - \delta P - \alpha_{res} e^{\beta t} P$$

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.



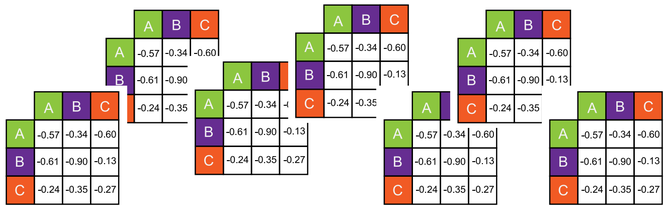


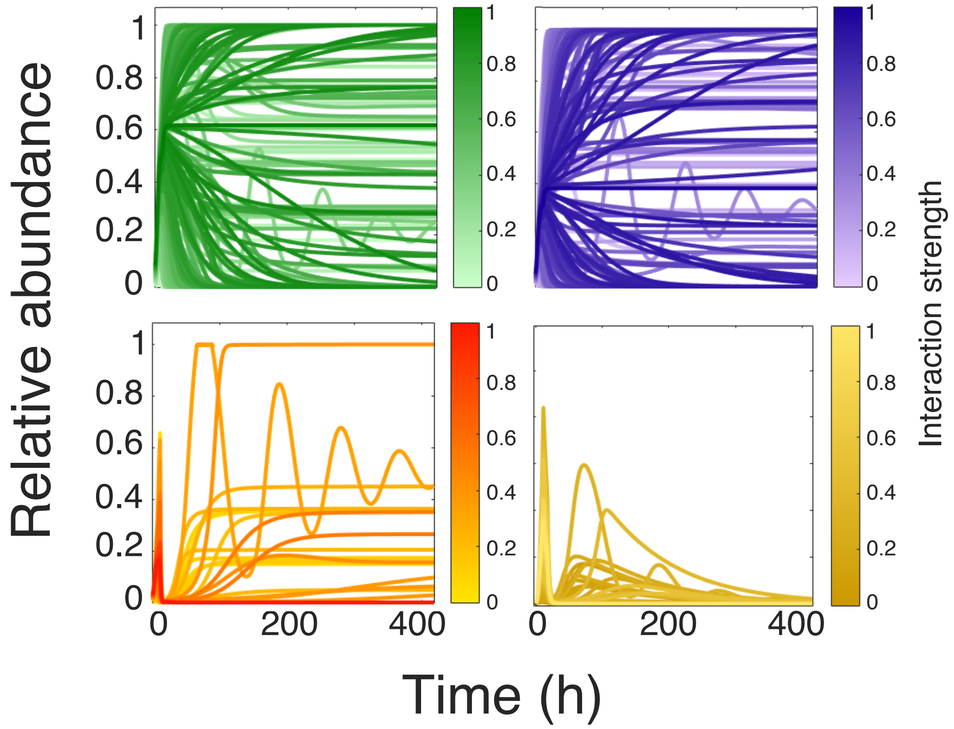


Different interaction matrices

Different end-points

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

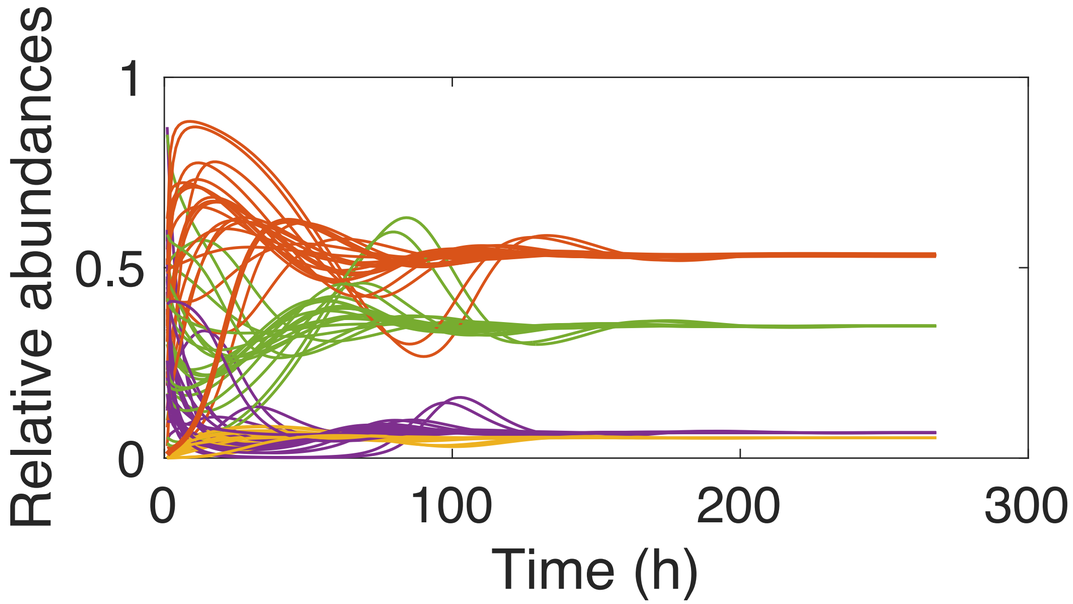




Different interaction matrices

Different end-points

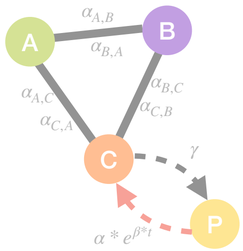
	A	B	C
A	-0.57	-0.34	-0.60
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C	-0.24	-0.35	-0.27



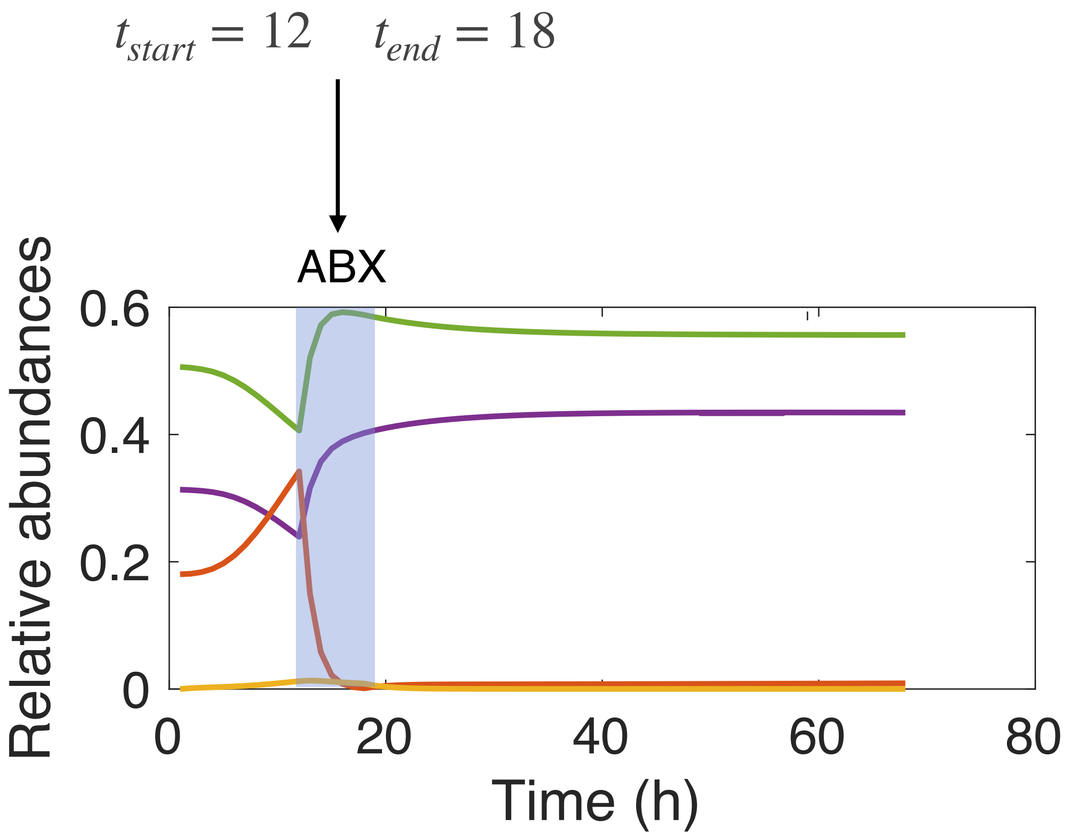
Same interaction matrices

Different initial-points

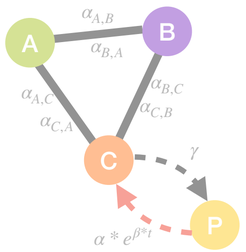
Same end-point



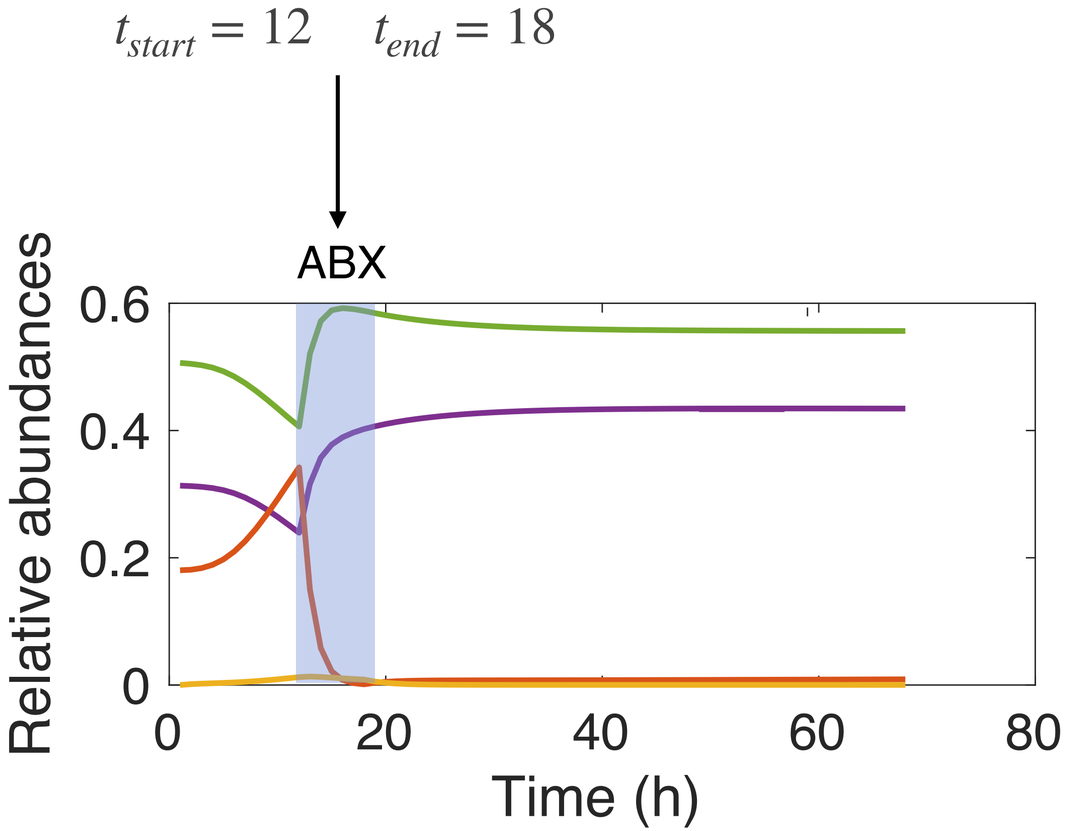
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

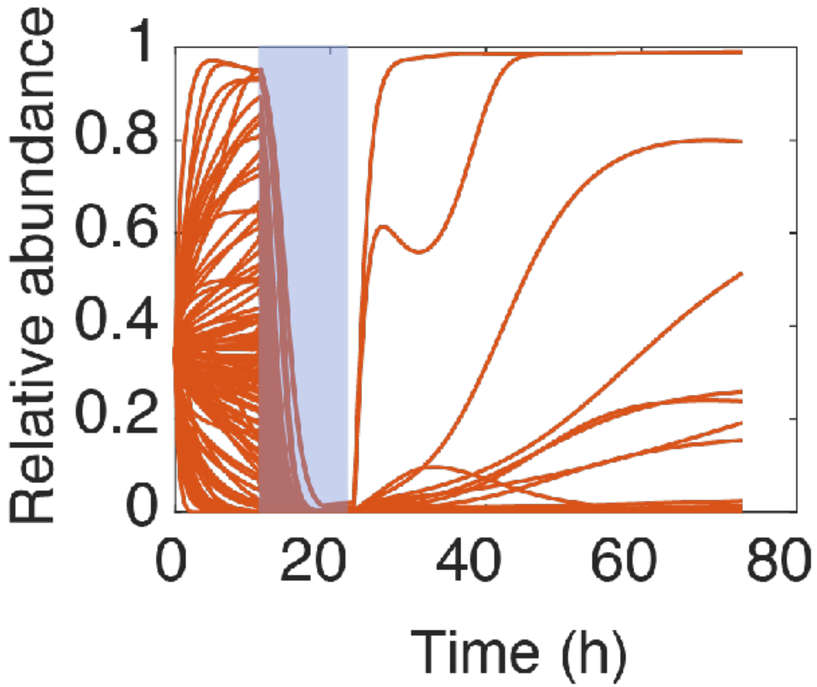


Species *C* reaches a very low level of abundance

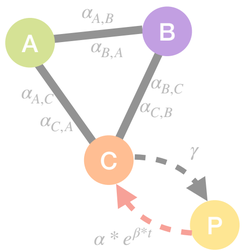


Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

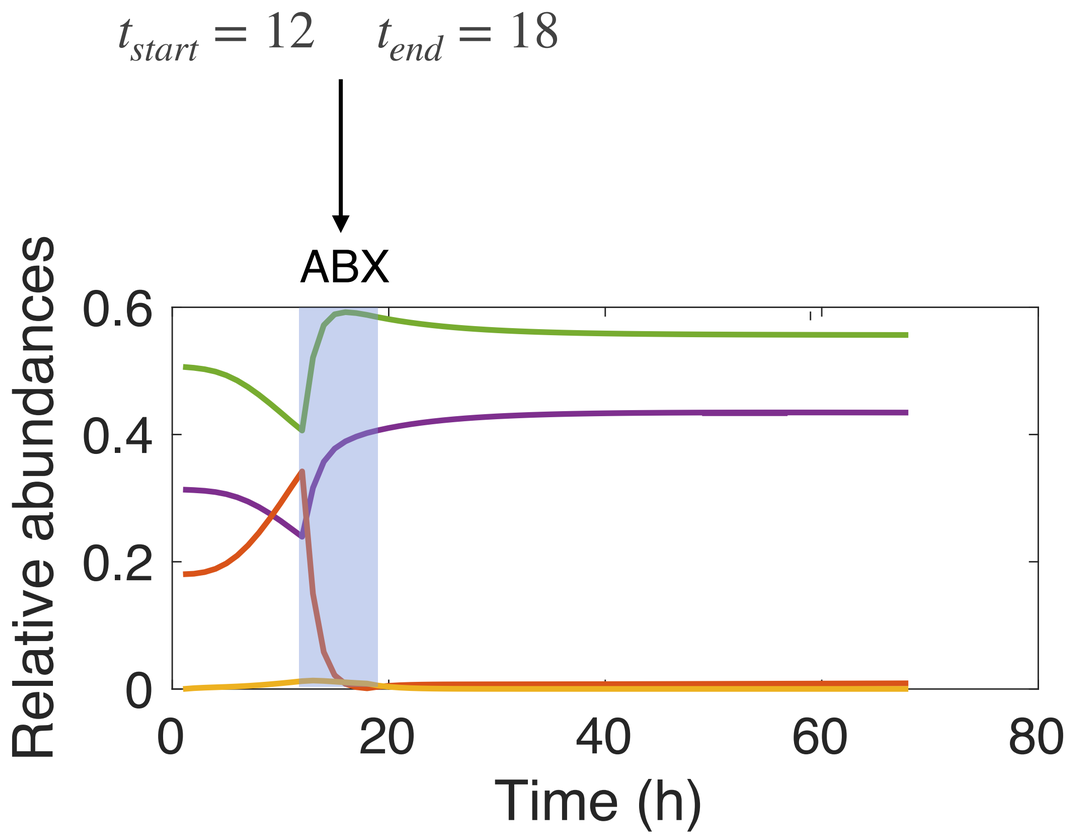




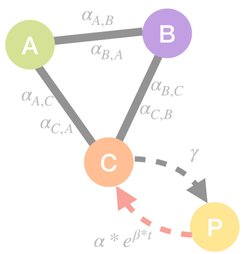
Species *C* reaches a very low level of abundance



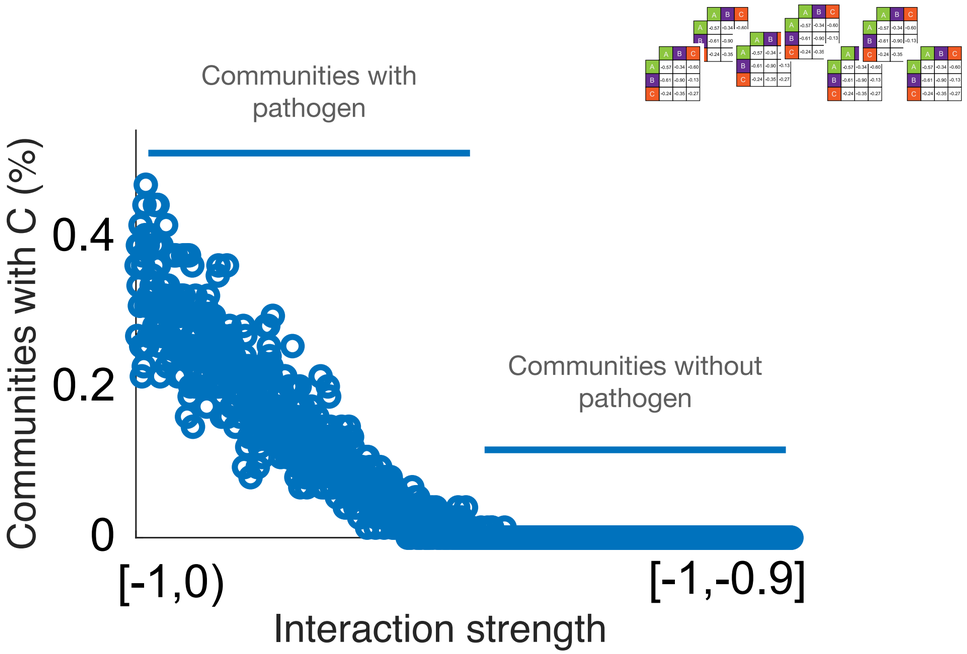
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.



Species *C* reaches a very low level of abundance



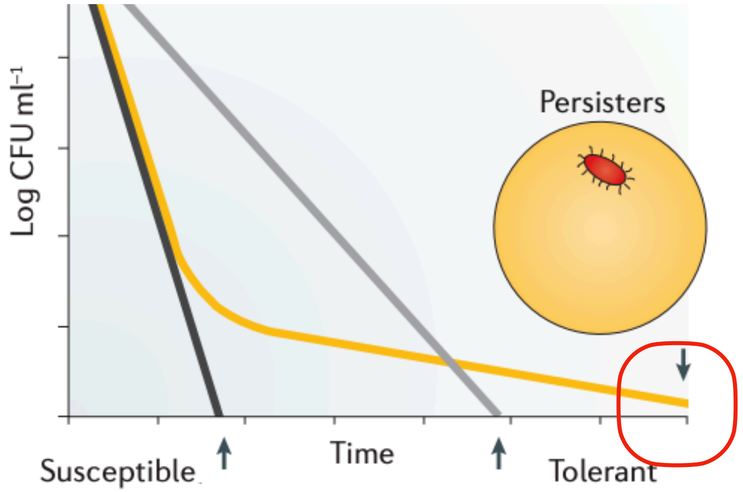
Testing many (i.e. 10^5) interaction matrices

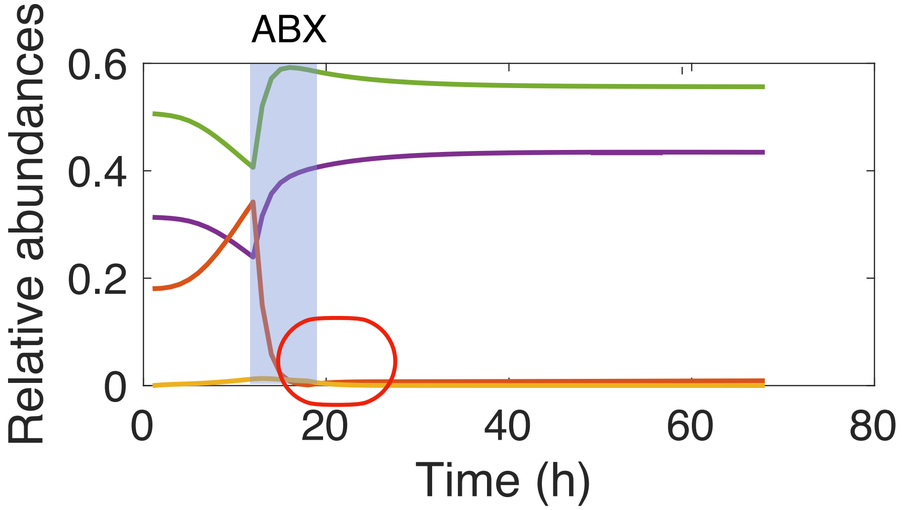


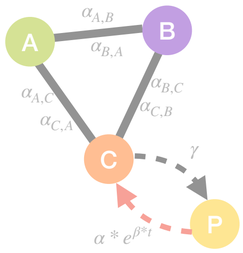
Ecological interactions may determine persisters resuscitation

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Can random fluctuations counteract the effect of social interaction?

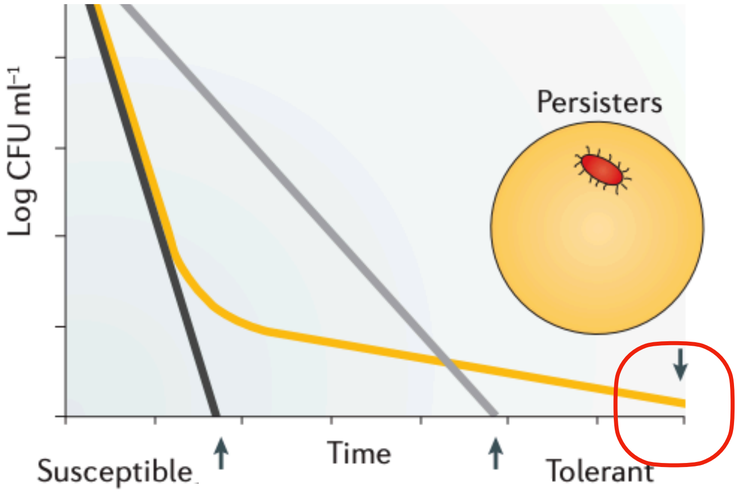


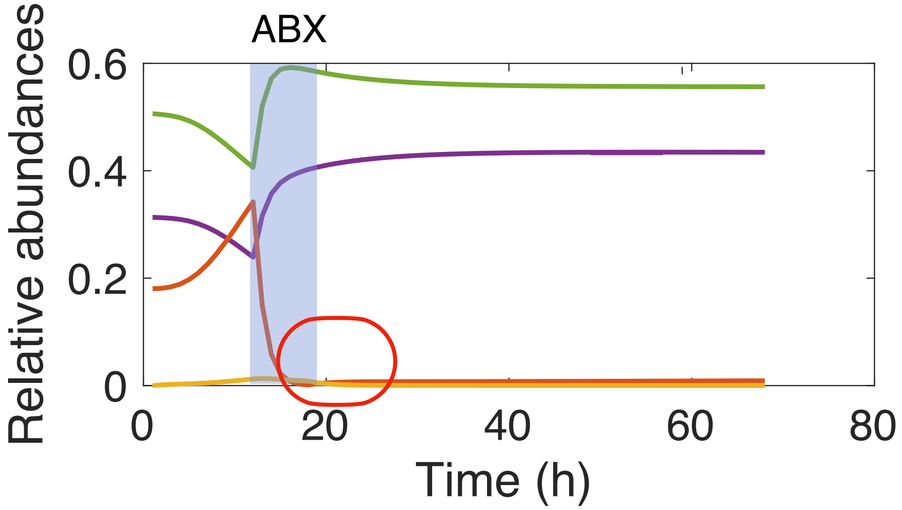


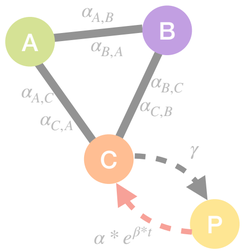


Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Can random fluctuations counteract the effect of social interaction?







General Master Equation

$$\frac{d}{dt}P(x,t) = \sum_{y \neq x} T(x\,|\,y)P(y,t) - T(y\,|\,x)P(x,t)$$

$$T_1(n_A + 1\,|\,n_A) = \mu_A \cdot n_A$$

$$T_2(n_B + 1\,|\,n_B) = \mu_B \cdot n_B$$

$$T_3(n_C + 1\,|\,n_C) = \mu_C \cdot n_C$$

$$T_4(n_A - 1\,|\,n_A, n_B) = \frac{\alpha_{B,A}}{V} \cdot n_A \cdot n_B$$

$$T_5(n_A - 1\,|\,n_A, n_C) = \frac{\alpha_{C,A}}{V} \cdot n_A \cdot n_C$$

$$T_6(n_B - 1\,|\,n_B, n_A) = \frac{\alpha_{A,B}}{V} \cdot n_B \cdot n_A$$

$$T_7(n_B - 1\,|\,n_B, n_C) = \frac{\alpha_{C,B}}{V} \cdot n_B \cdot n_C$$

$$T_8(n_C - 1\,|\,n_C, n_A) = \frac{\alpha_{A,C}}{V} \cdot n_C \cdot n_A$$

$$T_9(n_C - 1\,|\,n_C, n_B) = \frac{\alpha_{B,C}}{V} \cdot n_C \cdot n_B$$

$$T_{10}(n_C - 1, n_P + 1\,|\,n_C, n_P) = \gamma \cdot n_C$$

$$T_{11}(n_A - 1\,|\,n_A) = \delta \cdot n_A$$

$$T_{12}(n_B - 1\,|\,n_B) = \delta \cdot n_B$$

$$T_{13}(n_C - 1\,|\,n_C) = \delta \cdot n_C$$

$$T_{14}(n_C - 1\,|\,n_C) = \xi \cdot n_C$$

$$T_{15}(n_P - 1\,|\,n_P) = \delta \cdot n_P$$

$$T_{16}(n_C + 1, n_P - 1\,|\,n_C, n_P) = \alpha_{res} e^{\beta t} \cdot n_P$$

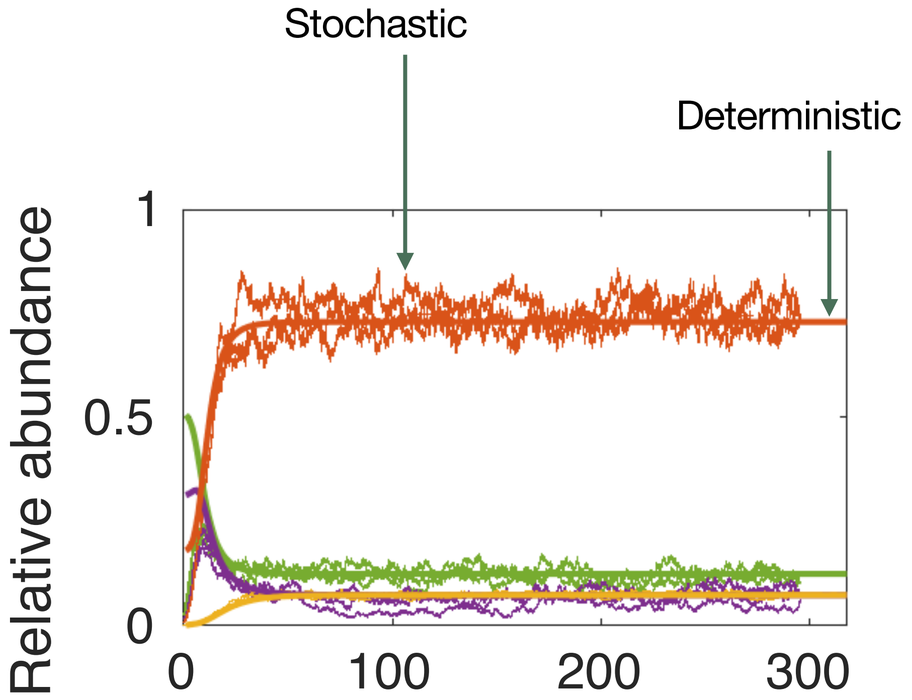
$$T_{17}(n_A - 1\,|\,n_A) = \frac{\alpha_{A,A}}{V} \cdot n_A \cdot (n_A - 1)$$

$$T_{18}(n_B - 1\,|\,n_B) = \frac{\alpha_{B,B}}{V} \cdot n_B \cdot (n_B - 1)$$

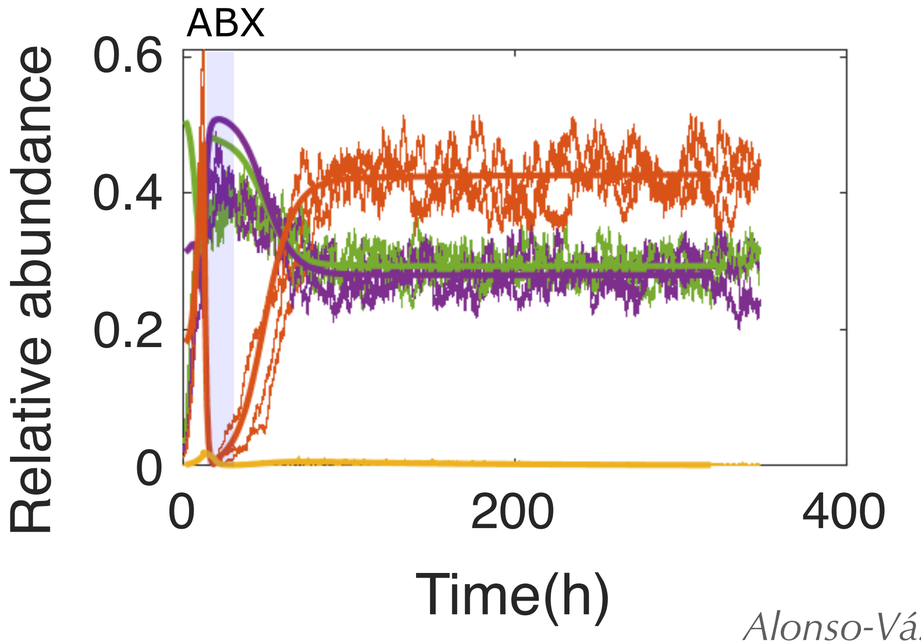
$$T_{19}(n_C - 1\,|\,n_C) = \frac{\alpha_{C,C}}{V} \cdot n_C \cdot (n_C - 1)$$

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Models benchmark



Without antibiotics



With antibiotics

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Can the pathogen reappear in the community only because of the fluctuations?

1. Explored 10^5 interaction matrices

	A	B	C
A	-0.57	-0.34	-0.60
B	-0.61	-0.90	-0.13
C	-0.24	-0.35	-0.27

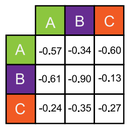
2. Kept matrices (i.e. communities) where species C < 1% in the deterministic model

3. Simulated stochastically 100 communities for each

Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

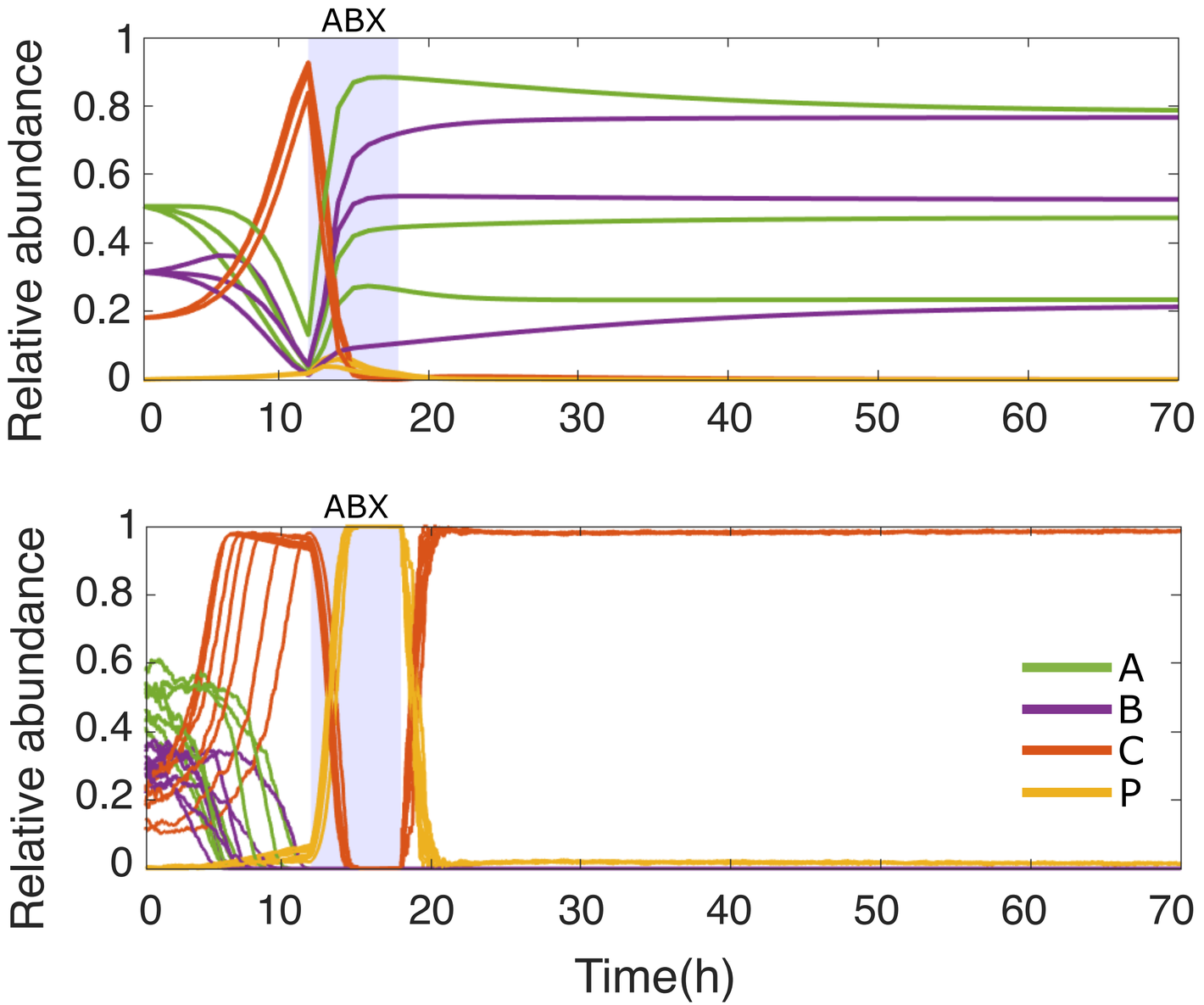
Can the pathogen reappear in the community only because of the fluctuations?

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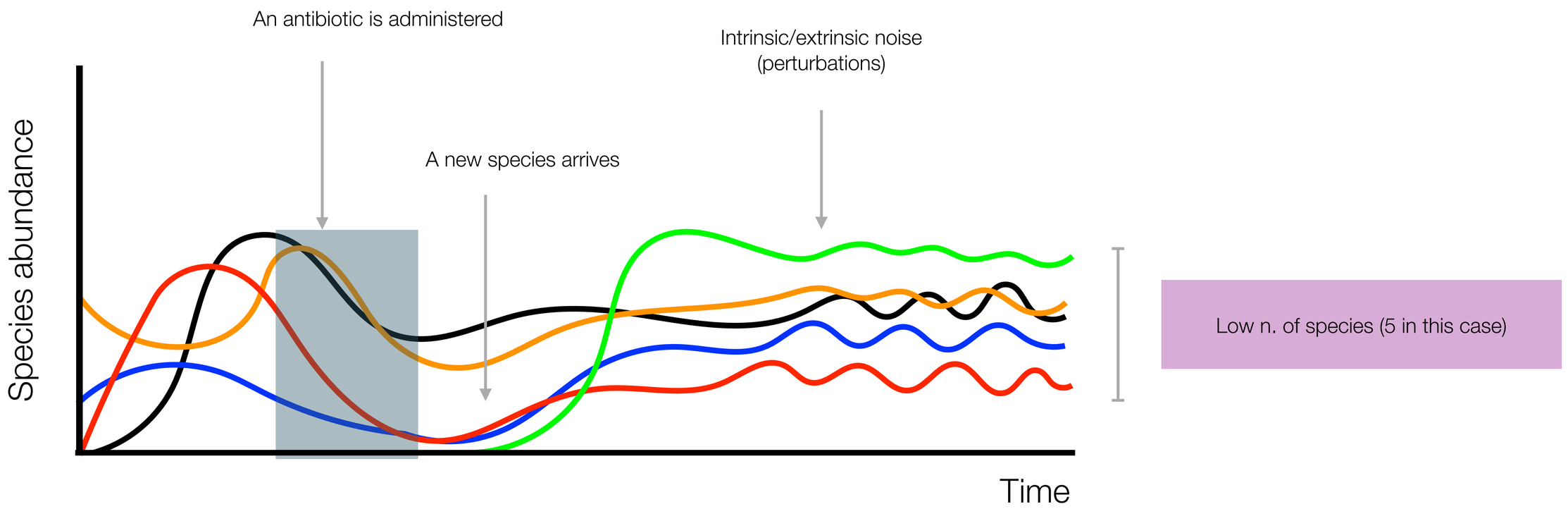
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Conclusions 1/2

In some cases, **the pathogen species could resuscitate** and eventually **dominate** the community following ABX treatment, a scenario that **was never observed** using the deterministic model but that is known to occur seldom during real microbial infections eradication.

Our findings **highlight the role of population size fluctuations** (and hence the cellular mechanisms that account for them) in determining the success of microbial infections and, more in general, in the resilience of microbial populations following a stressful perturbation.

Link to the paper


An antibiotic is administered
Intrinsic/extrinsic noise
(perturbations)
A new species arrives
Species abundance
Time
Low n. of species (5 in this case)

Scaling up the models: replicating *in silico* complex communities dynamics

$$\frac{dx_{i_R}(t)}{dt} = x_{i_R}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_R}} + d_{ABX})x_{i_R}(t) + \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} + \mu_i\eta_i x_{S,i}$$

$$\frac{dx_{i_S}(t)}{dt} = x_{i_S}(t)\left(r_i + \sum_j A_{ij}x_j(t)\right) - (d_{x_{i_S}} + d_{ABX})x_{i_S}(t) - \sum_{j=1}^{n} P_{HGT,ij}\, x_{j_R}\, x_{i_S} - \mu_i\eta_i x_{S,i}$$

AMR evolution

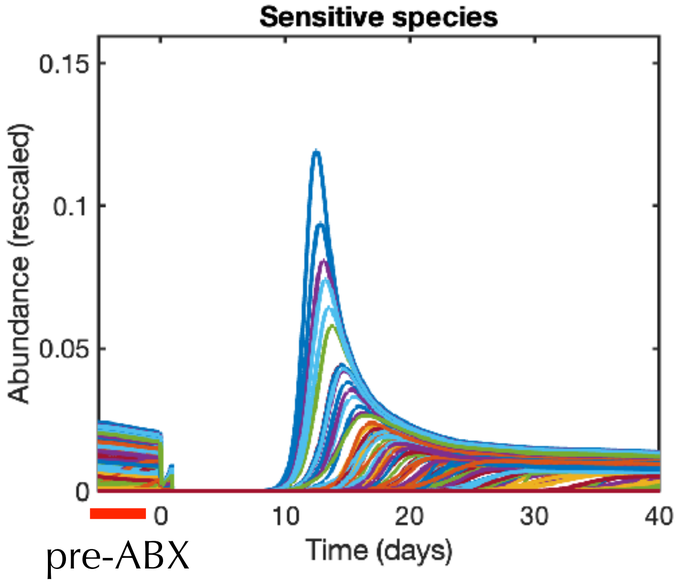
HGT *Mutation*

Model parameters and assumptions

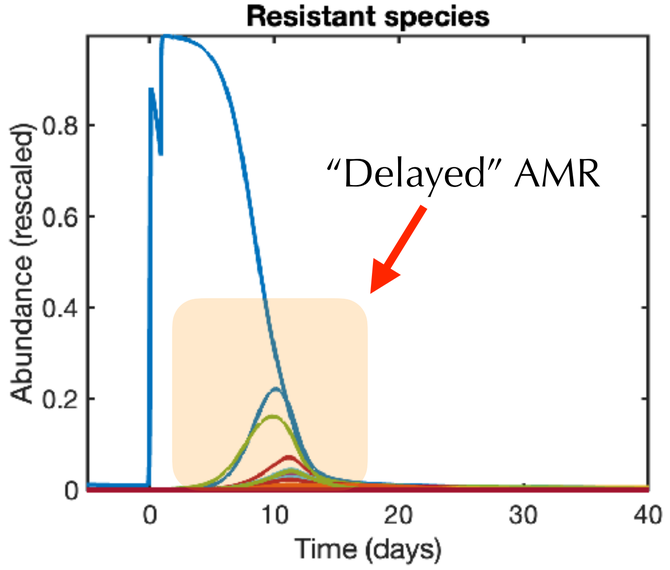
- n. species = 140
- mutation rate = 10^{-7}
- HGT rate = 10^{-7}
- ABX = as in Palleja et al. 2018
- random noise introduced for mutation, growth and ABX killing rates

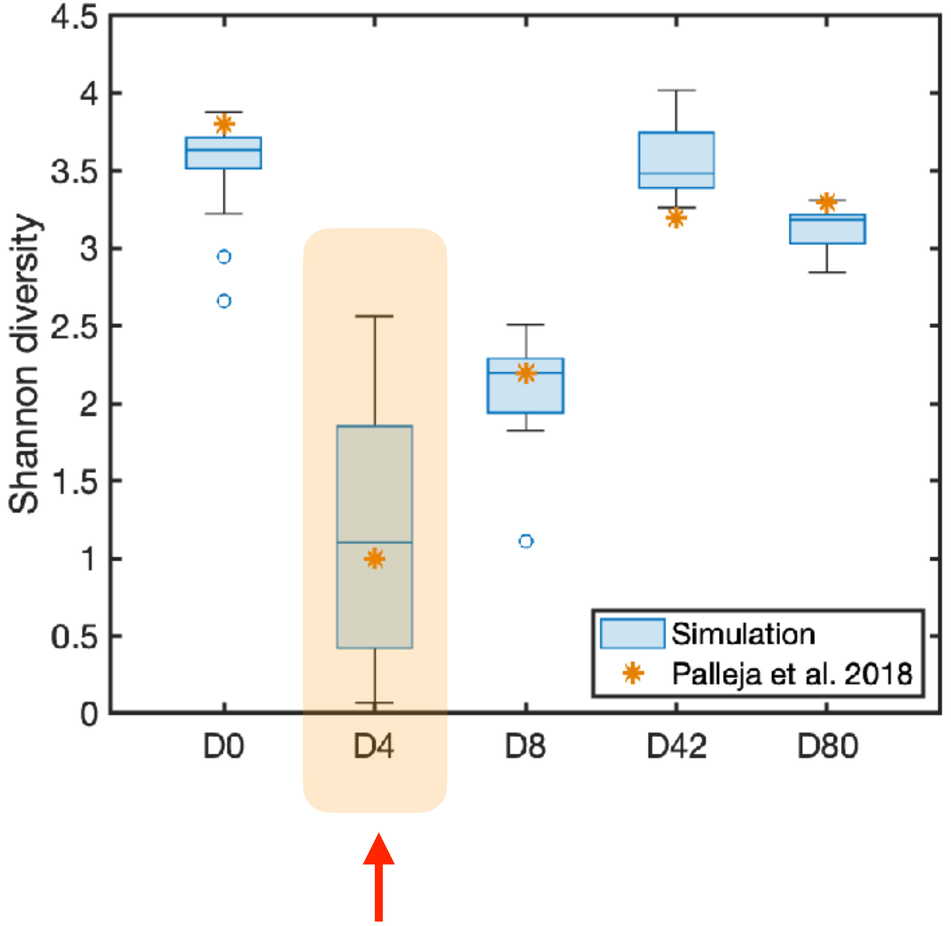
Introducing a reverse ecology approach

Community dynamics, including mutations and HGT of AMR



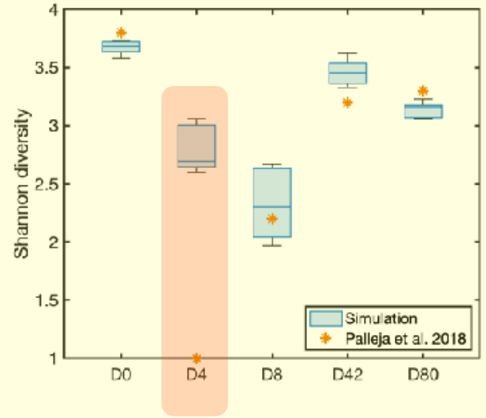
pre-ABX equilibrium





Microbial diversity matched

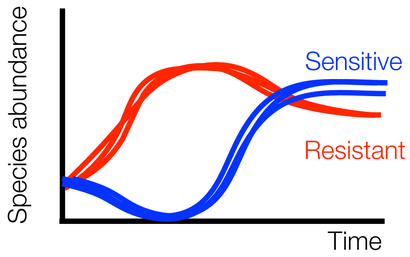
No AMR evo and spreading considered

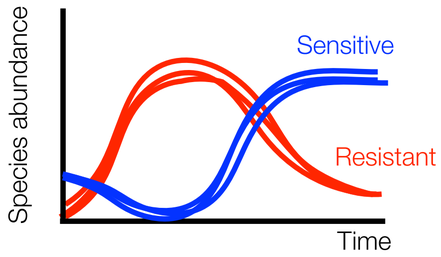


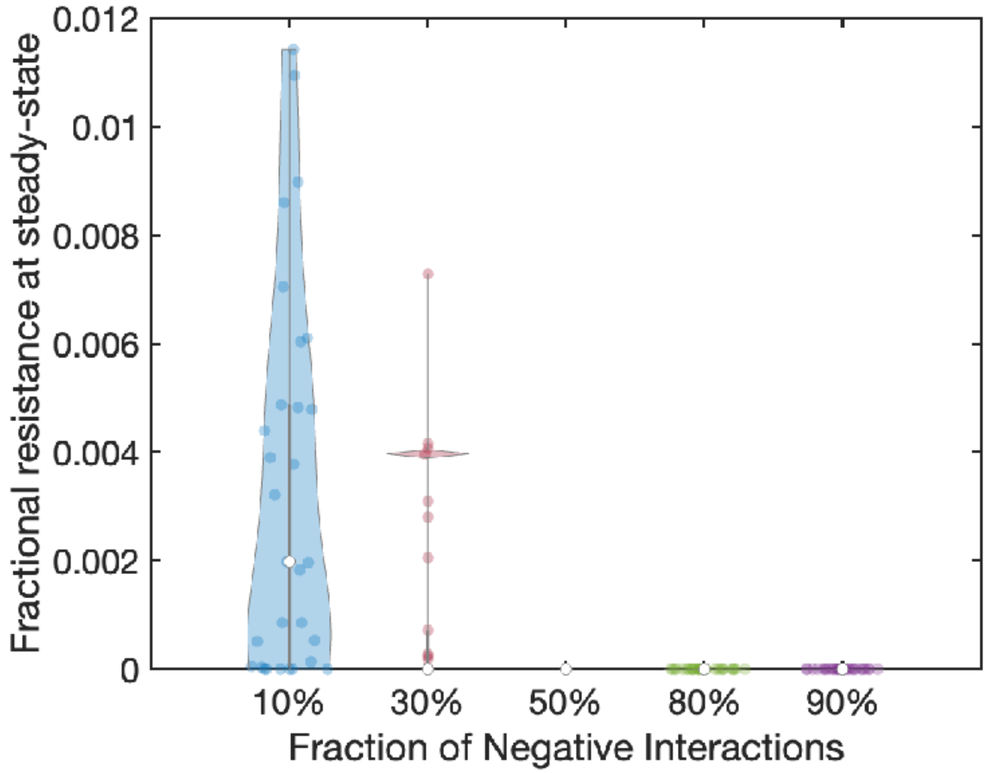

```
mutation_rate = 1e-7;
HGTrate  =1e-5;
```

The impact of interactions on the control of AMR

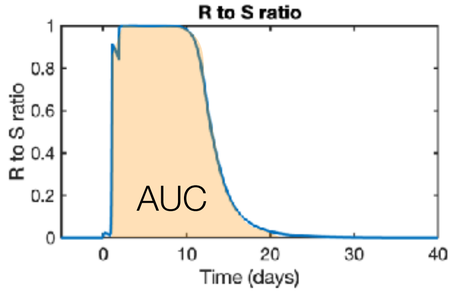
Resistant species at community steady-state

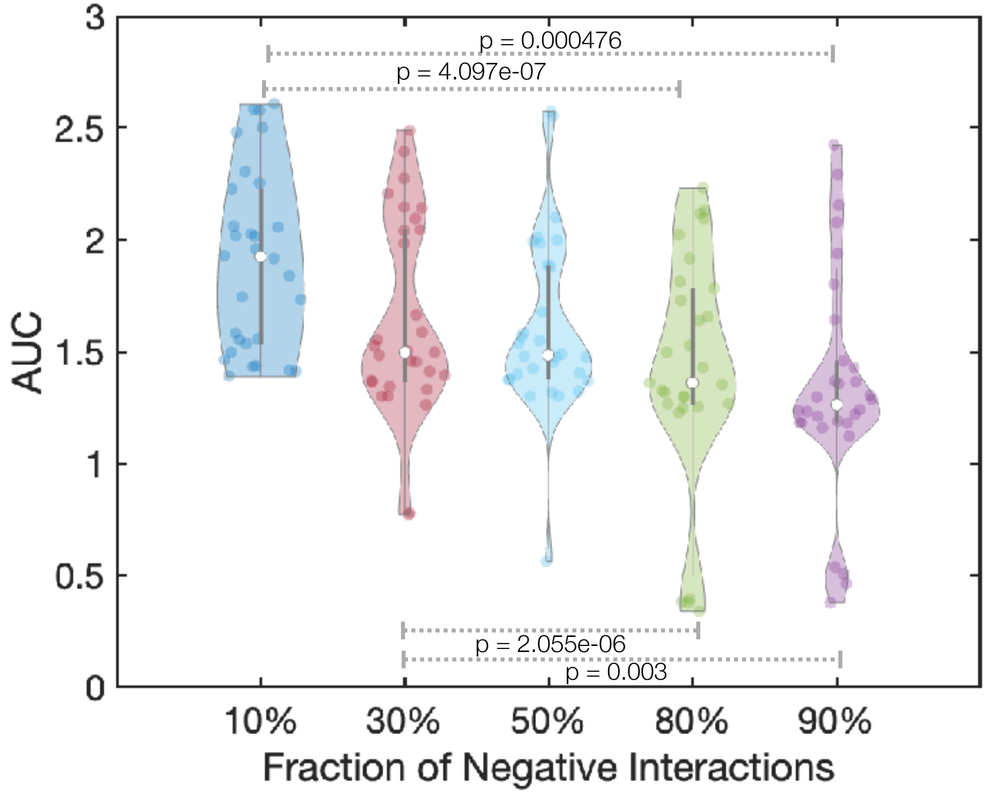






Area Under the resistant to rensitive Curve





Conclusions 2/2

Microbial community dynamic modeling can be expanded to “real size” communities and reproduce realistic dynamics.

Using a “reverse ecology” approach, we can test the impact of diversity (and related features such as HGT) on key aspects such as AMR evolution and spreading, under different scenarios.

More in general…

We stress the i) necessity of experimental data (e.g. abundance data and/or evolutionary rates) to parametrize the models and ii) the need for including microbial interactions (i.e. the microbiota composition and structure) when considering the possible outcomes of antimicrobial strategies.

Treatment optimization strategies could be designed based on parametrized and personalized microbial community models.