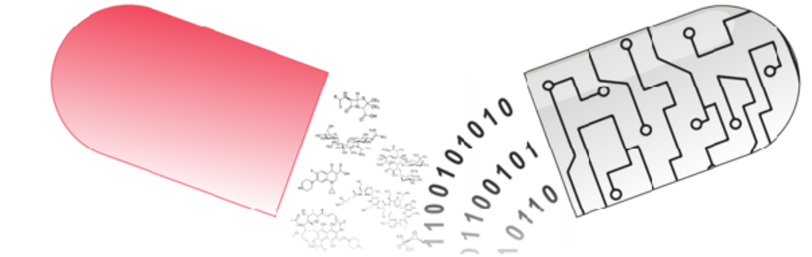
Modelling the emergence and spreading of antimicrobial resistance in microbial communities

Marco Fondi, Dep. of Biology, University of Florence



ICAComP

2nd International Conference on Antimicrobial Computational Pharmacology

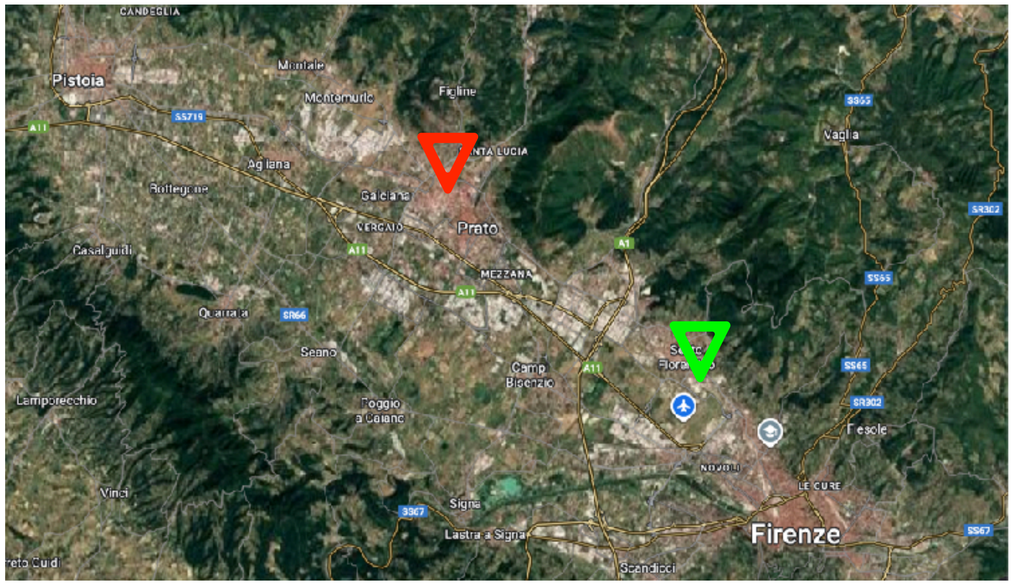
15-17 October 2025 | Prato, Italy



Florence
computational
biology group

What we study:

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

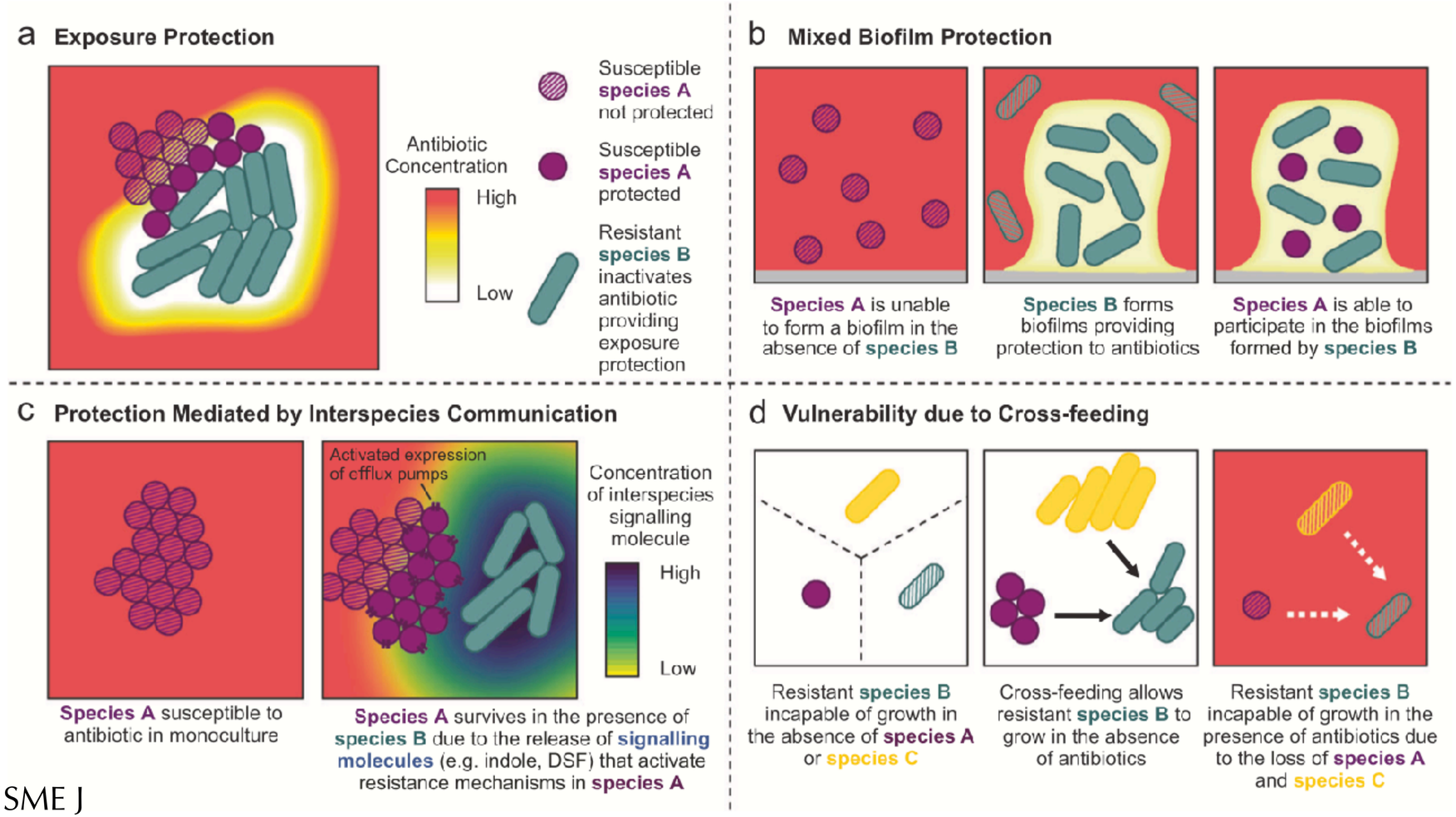


What we use:

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

Aim of the talk: to introduce and discuss a further level of complexity for ICAComP people (you are welcome).

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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Nope, positive interactions are common

SCIENCE ADVANCES | RESEARCH ARTICLE

ENVIRONMENTAL STUDIES

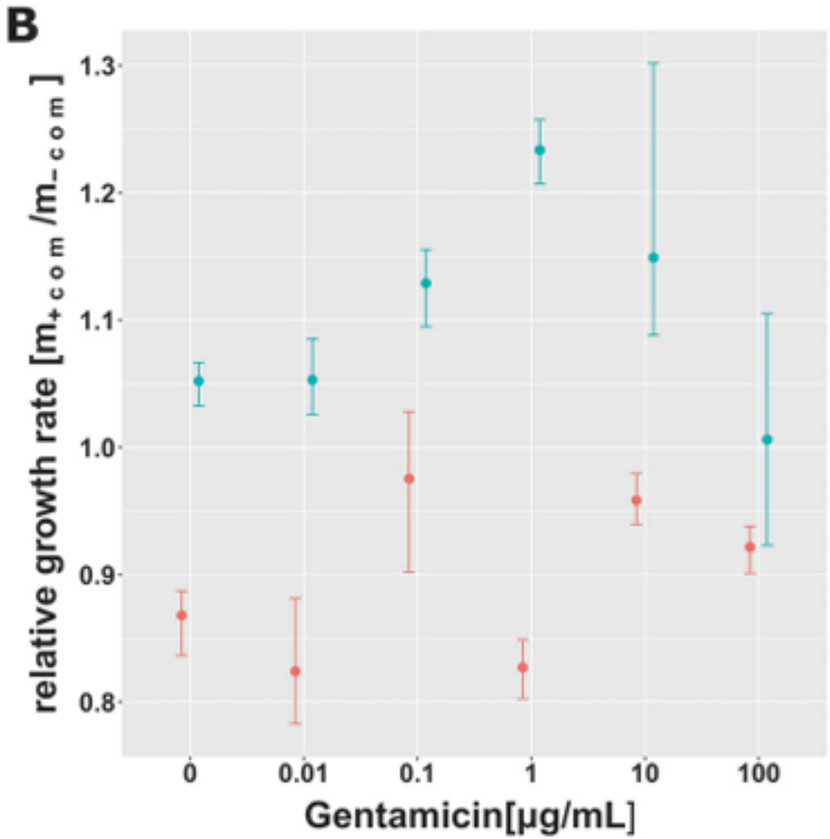
Positive interactions are common among culturable bacteria

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]*

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

Competition, Not Cooperation, Dominates Interactions among Culturable Microbial Species

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SCIENCE ADVANCES | RESEARCH ARTICLE

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Positive interactions are common among culturable bacteria

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Nope, negative interactions facilitate AMR

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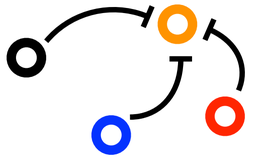
MICROBIAL ECOLOGY
October 2023 Volume 89 Issue 10 e01155-23
https://doi.org/10.1128/aem.01155-23

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]

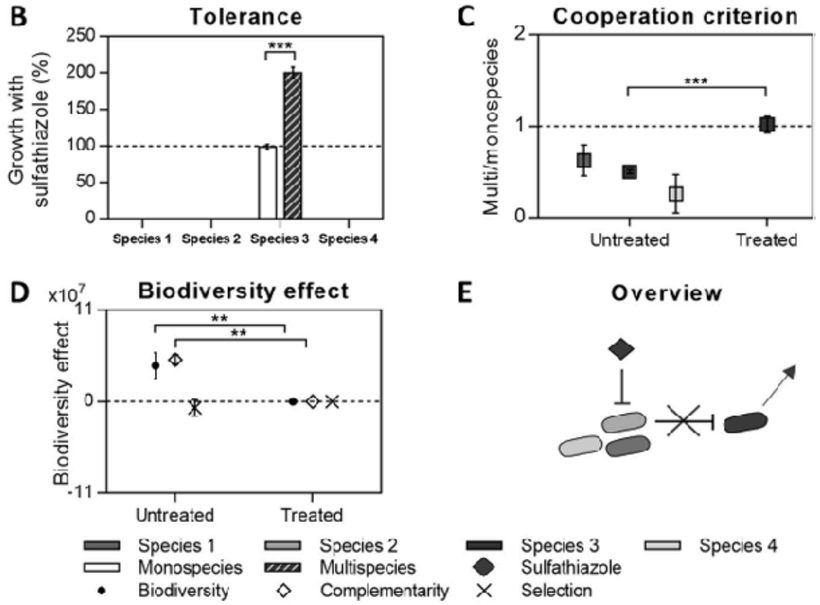
Competitive interactions facilitate resistance development against antimicrobials.

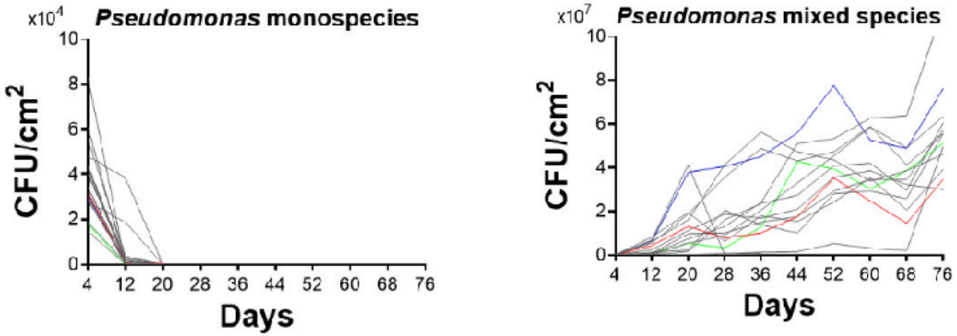
Tolerance → Resistance



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

Microbial communities and AMR: friends or foes?

Do microbial communities hamper or facilitate the emergence and spread of AMR and/or related phenotypes?

Emergence of resistant strains

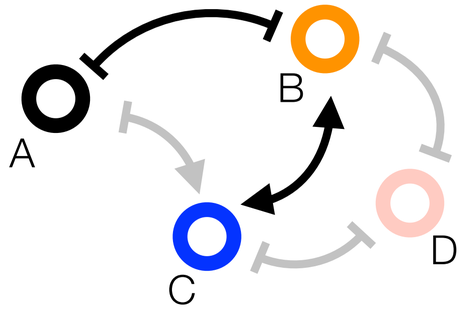
Spreading of resistant mutants

Population size

Fitness cost, HGT

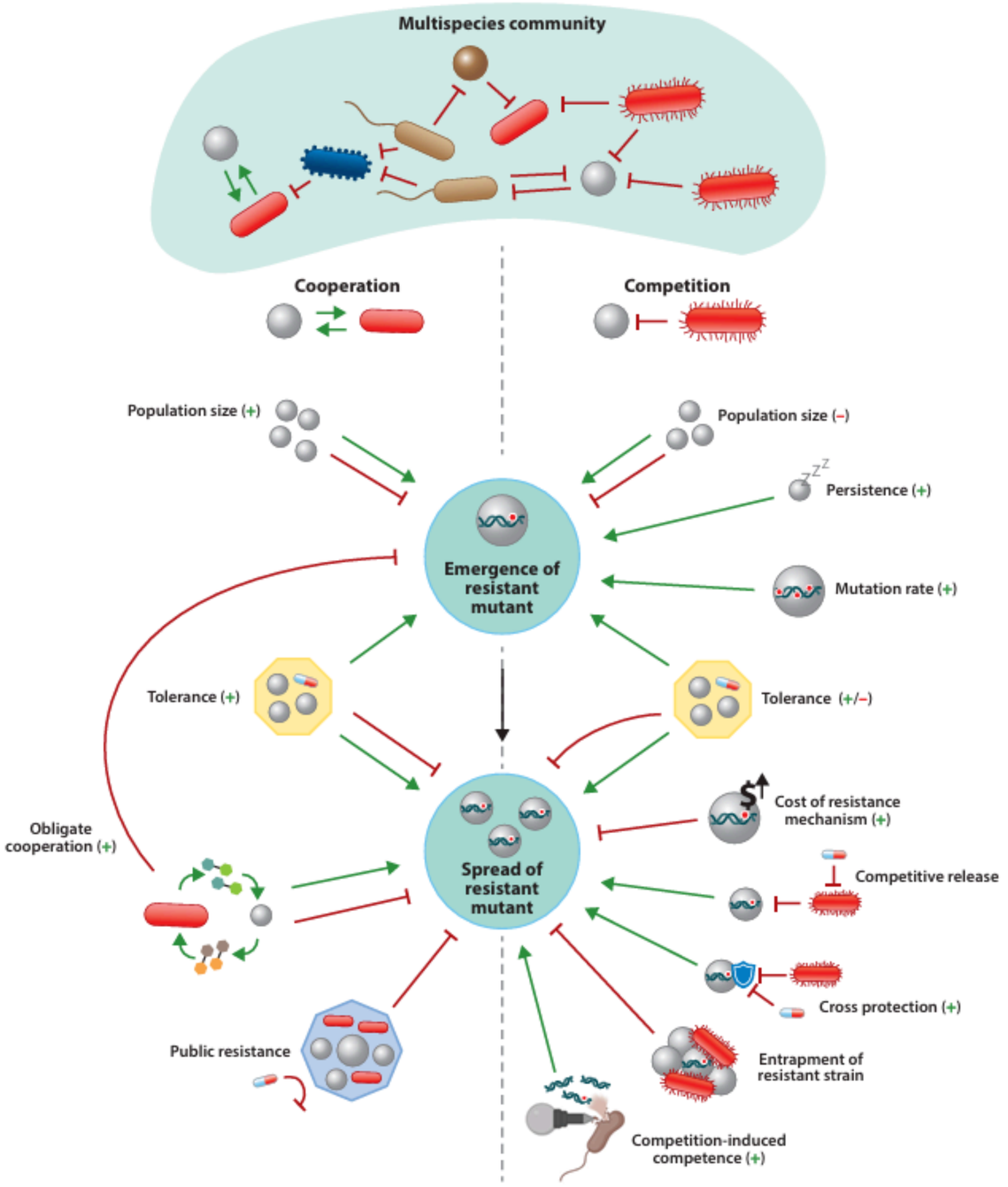
Microbial interactions

Effect on resistance-related phenotypes
(e.g. tolerance and persistence)

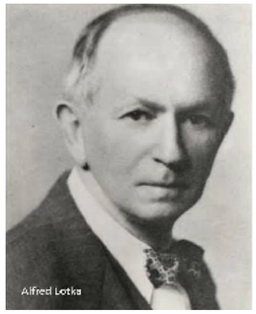


Overall, the relative contributions of these various mechanisms are expected to be highly case specific and will depend on, among other factors, the **community composition and structure**, **resource availability, the resistance mechanism, and the antibiotic treatment**.

How can we study all this?



De Wit et al. 2022 Annual Review of Microbiology



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



ANALYTICAL NOTE ON CERTAIN RHYTHMIC RELATIONS IN ORGANIC SYSTEMS

By Alfred J. Lotka

Brooklyn, N. Y.

Communicated by R. Pearl, May 20, 1920

Periodic phenomena play an important rôle in nature, both organic and inorganic.

In chemical reactions rhythmic effects have been observed experimentally, and have also been shown, by the writer[1] and others,[2] to follow, under certain conditions, from the laws of chemical dynamics.

However, in the cases hitherto considered on the basis of chemical dynamics, the oscillations were found to be of the damped kind, and therefore, only transitory (unlike certain experimentally observed periodic reactions). Furthermore, in a much more general investigation by the writer, covering the kinetics not only of chemical but also of biological systems, it appeared, from the nature of the solution obtained, improbable[3] that undamped, permanent oscillations would arise in the absence of geometrical, structural causes, in the very comprehensive class of systems considered. For it seemed that the occurrence of such permanent oscillations, the occurrence of purely imaginary exponents in the exponential series solution presented, would demand peculiar and very specific relations between the characteristic constants of the systems undergoing transformation; whereas in nature these constants would, presumably, stand in random relation.

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.

A CONSIDERATION of biological associations, or of the mutual interactions between two or more species associated together, has led me to certain mathematical results which may be set forth as follows.

The first case I have considered is that of two associated species, of which one, finding sufficient food in its environment, would multiply indefinitely when left to itself, while the other would perish for lack of nourishment if left alone; but the second feeds upon the first, and so the two species can co-exist together.

The proportional rate of increase of the eaten species diminishes as the number of individuals of the eating species increases, while the augmentation of the eating species increases with the increase of the number of individuals of the eaten species. Having determined the laws of this increase and diminution, it is possible to establish two differential equations of the first order, non-linear, which can be integrated. The integrals reveal the fact that the numbers of individuals of the two species are periodic functions of the time, with equal periods but with different phases, so that each species goes through a cycle relative to the other during a period, a process which may be called the 'fluctuation of the two species.' Figs. 1 and 2 give representations of different possible cycles, corresponding to different initial values of the number of individuals of the two species: ordinates representing the eating, and abscissæ the eaten species.

The co-ordinates of a point on a cycle are the concurrent values of the numbers of individuals of the two species, those of the central point ½ being the mean values; and the following laws have been deduced from integration of the differential equations which represent the fluctuation:

I. The fluctuation of the two species is periodic, the period depending only on the coefficients of increase and of destruction of the two species, and on the initial numbers of the individuals of the two species.

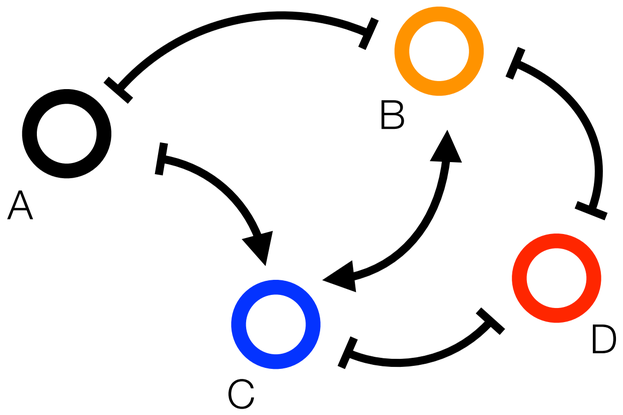
II. The average numbers of the two species tend to constant values, whatever the initial numbers may have been, so long as the coefficients of increase or of destruction of the two species and also the coefficients of protection and attack remain constant. (Laws I. and II. are illustrated in Fig. 2.)

III. If we try to destroy individuals of both species uniformly and proportionately to their number, the average number of individuals of the *eaten* species grows and the average number of the eating species diminishes (see Fig. 1). But increased protection of

[1] V. Volterra.—Variazioni e fluttuazioni del numero di individui in specie animali conviventi.—*Memorie della R. Accademia dei Lincei* (Cl. di Sci. Fis. etc.), ser. 6, vol. ii. fasc. 3, 85 pp., 1926.

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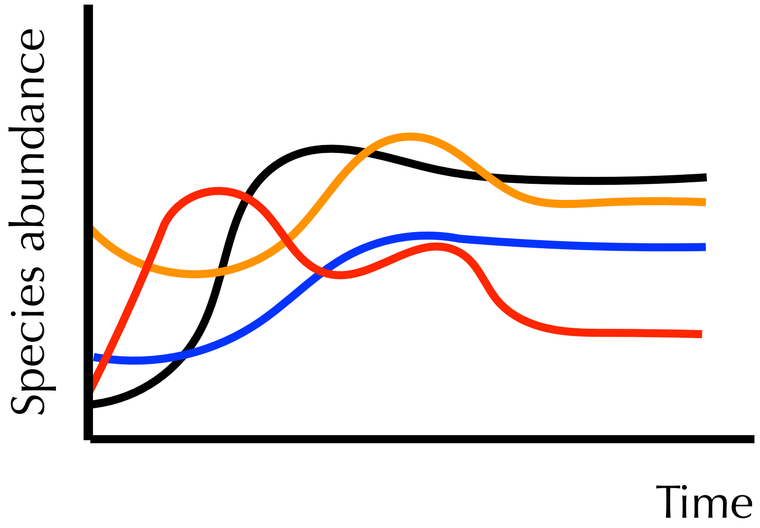
$$\frac{dx_i(t)}{dt} = x_i(t)\left(r_i + \sum_j A_{ij}x_j(t)\right)$$



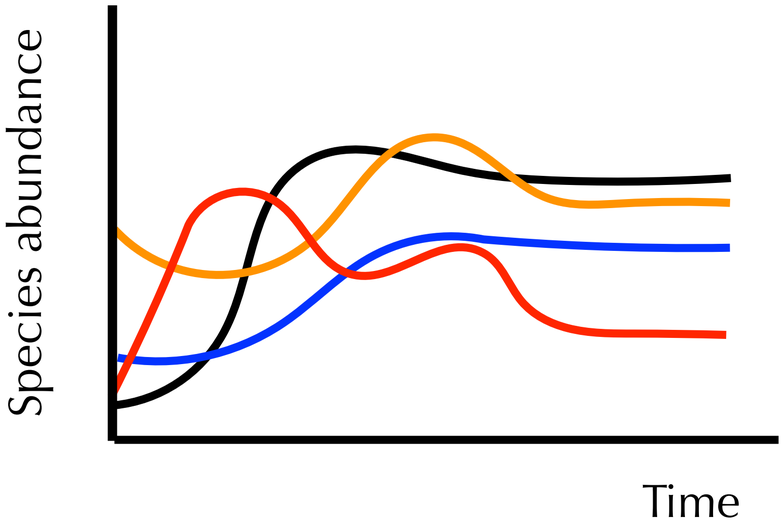
	A	B	C	D
A	-1	-0.6	0.3	0
B	-0.5	-1	0.1	-1
C	-0.4	0.2	-1	-0.7
D	0	-0.5	-0.5	-1

Sample interaction matrix

Dynamics prediction



Dynamics prediction



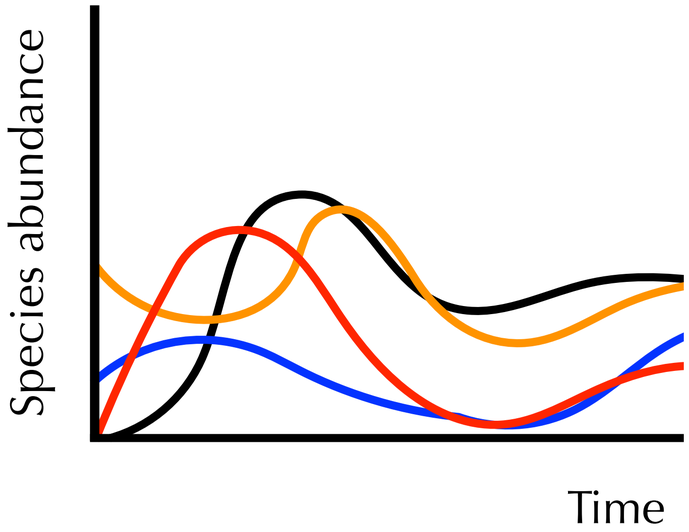
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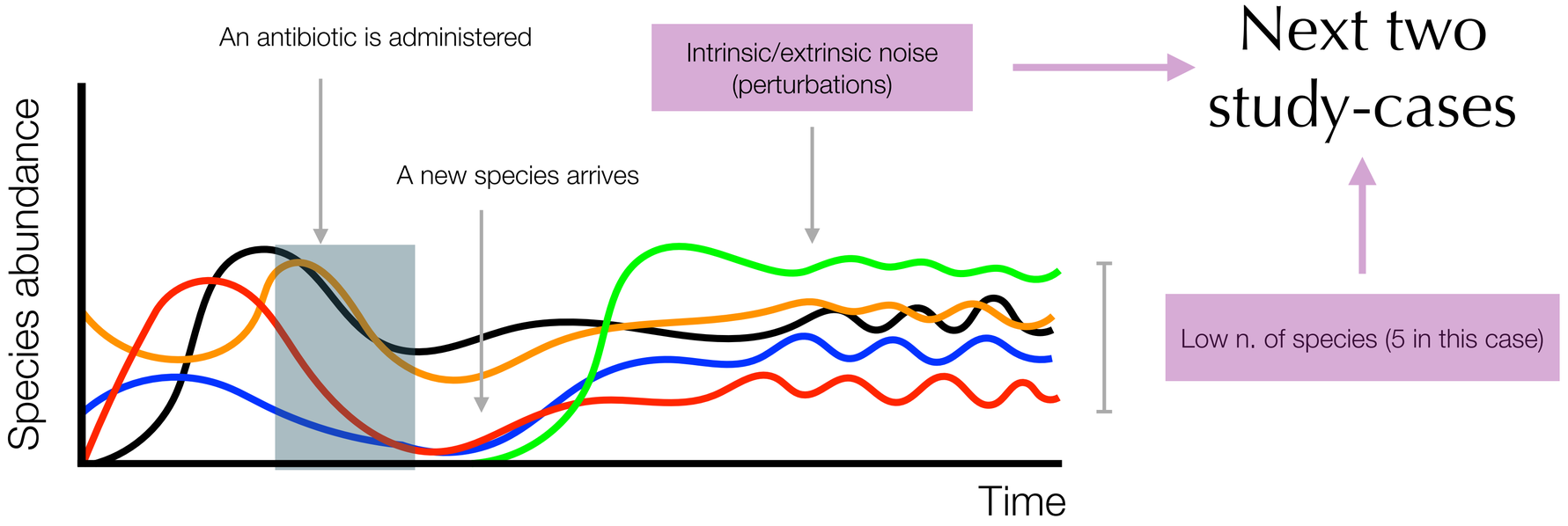
RESEARCH ARTICLE
May/June 2023 Volume 8 Issue 3 e00757-22
https://doi.org/10.1128/msystems.00757-22

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

The commonly used generalized Lotka-Volterra model can represent interactions among microbes well when the environment is complex (with many interaction mediators) and low-nutrient.

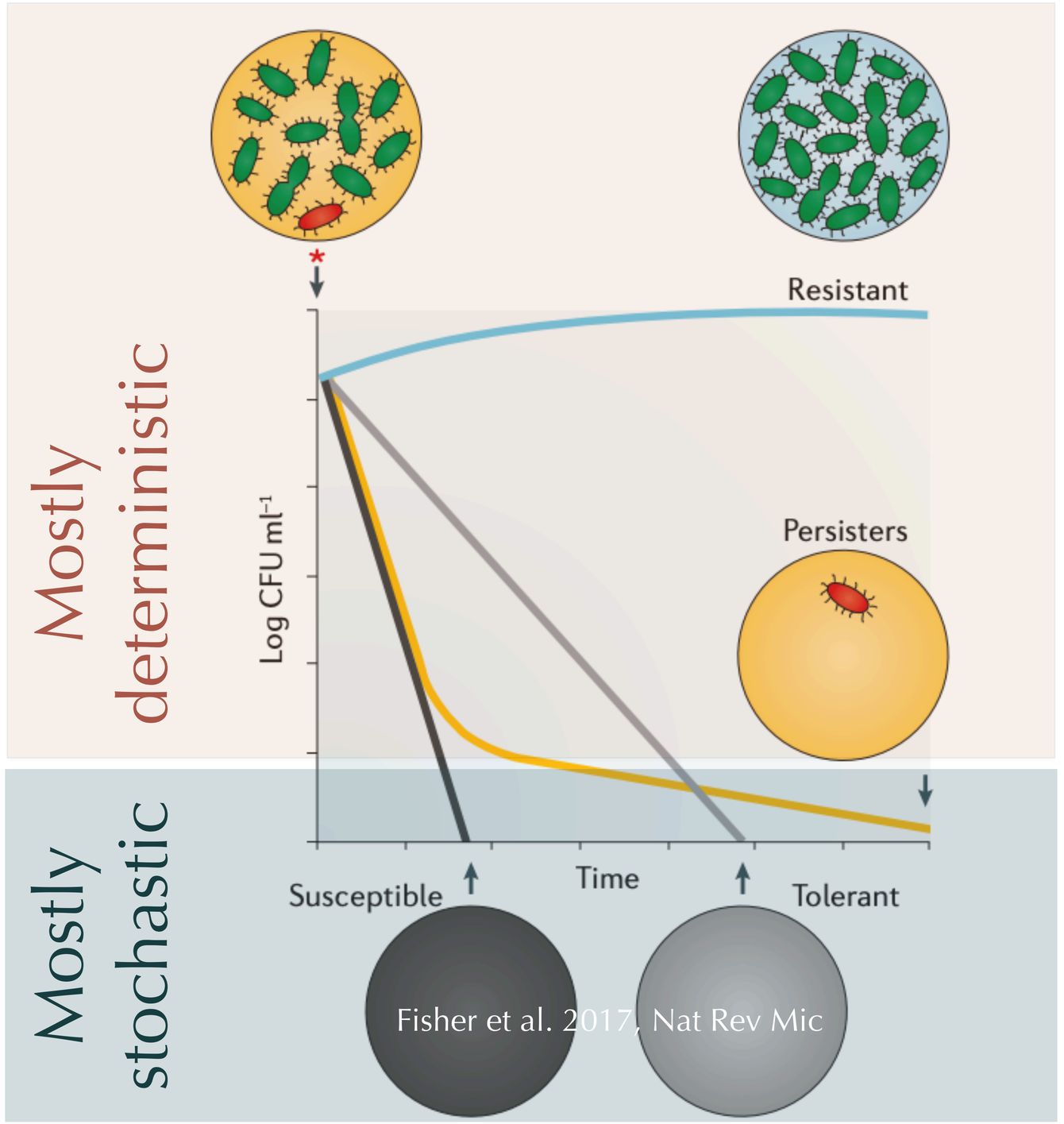
Dedrick et al. 2023, mSystems


Species abundance
Time

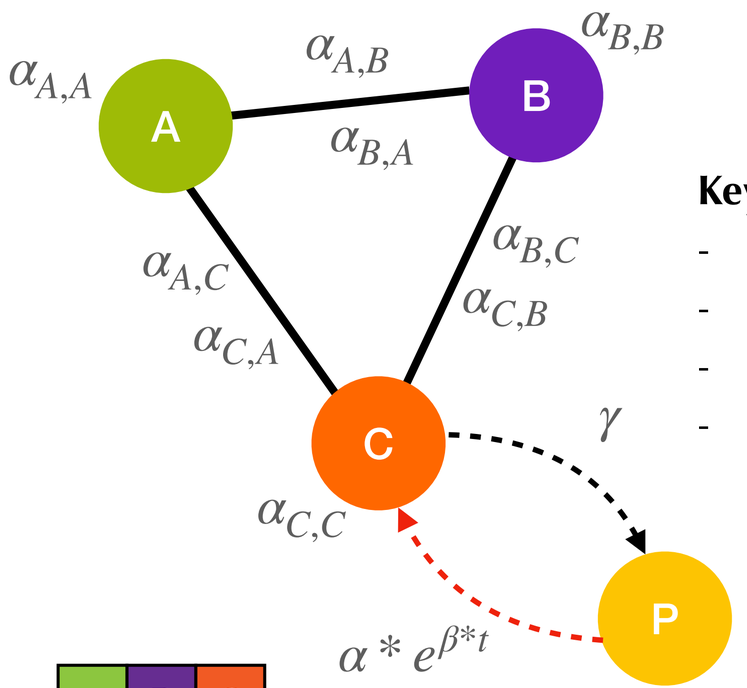

An antibiotic is administered
Intrinsic/extrinsic noise
(perturbations)
A new species arrives
Species abundance
Time
Next two
study-cases
Low n. of species (5 in this case)

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

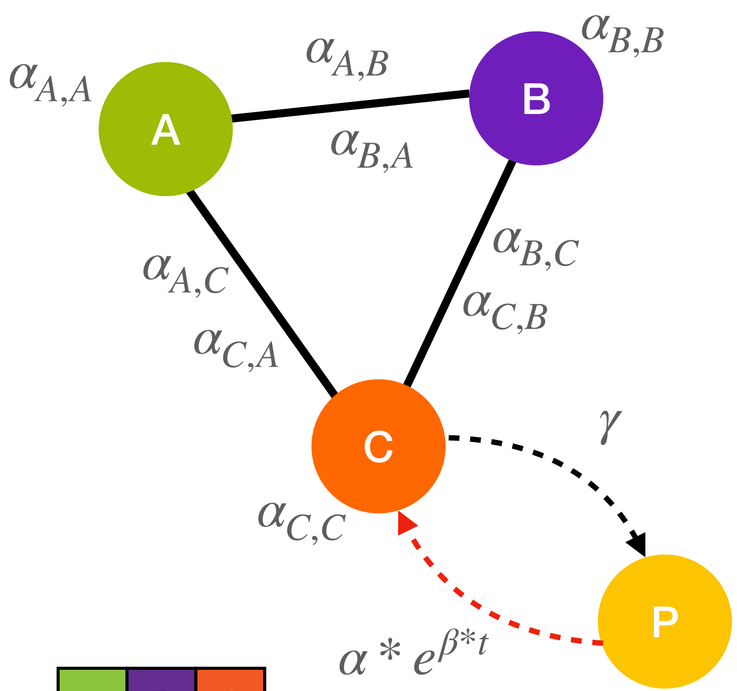
Key assumptions:

- 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

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

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

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

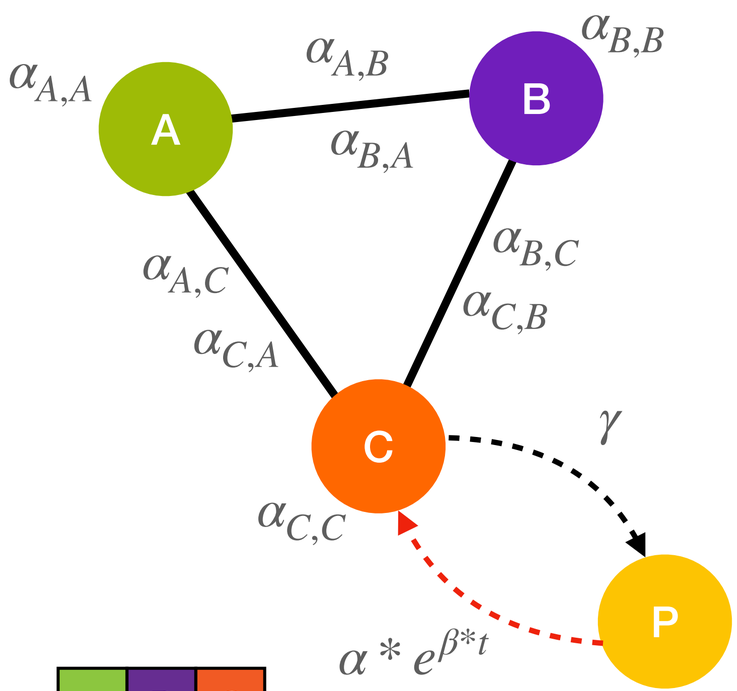
$$C \xrightarrow{\gamma} P$$

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

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

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

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

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

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

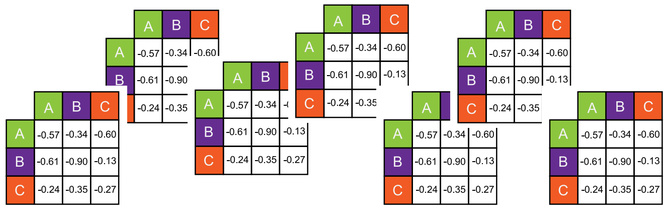
$$\dot{P} = \gamma C - \delta P$$

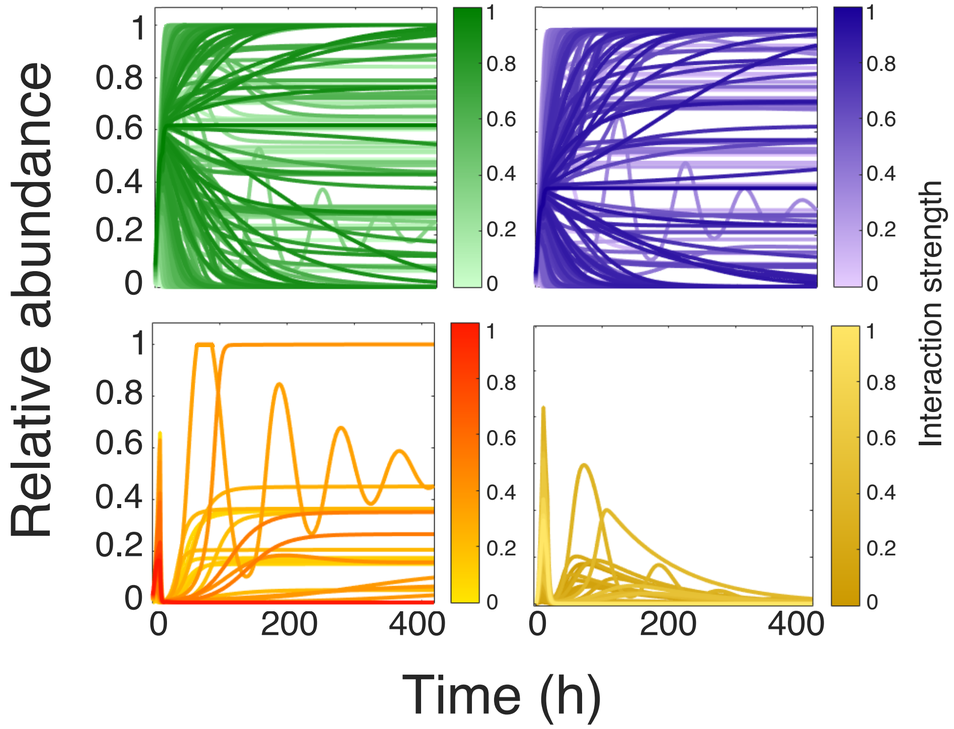
$$\dot{C} = \mu_C C + \alpha_{A,C} CA + \alpha_{B,C} CB + \alpha_{C,C} C^2 - \delta C - \gamma C - \xi C$$

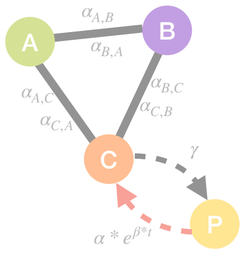
$$\dot{C} = \alpha_{res} e^{\beta t} P + \rho \mu_C C + \alpha_{A,C} CA + \alpha_{B,C} CB + \alpha_{C,C} C^2 - \delta C - \gamma C$$

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

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



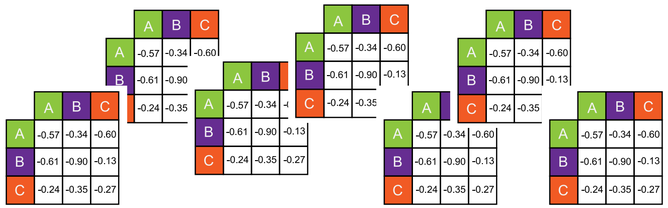


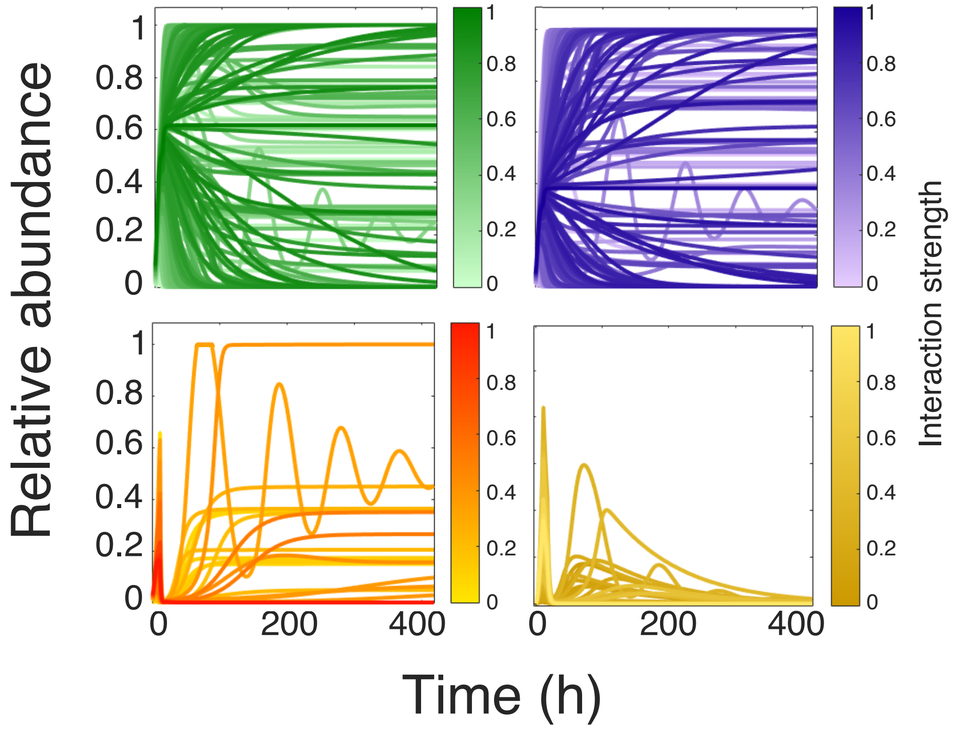


Different interaction matrices

Different end-points

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

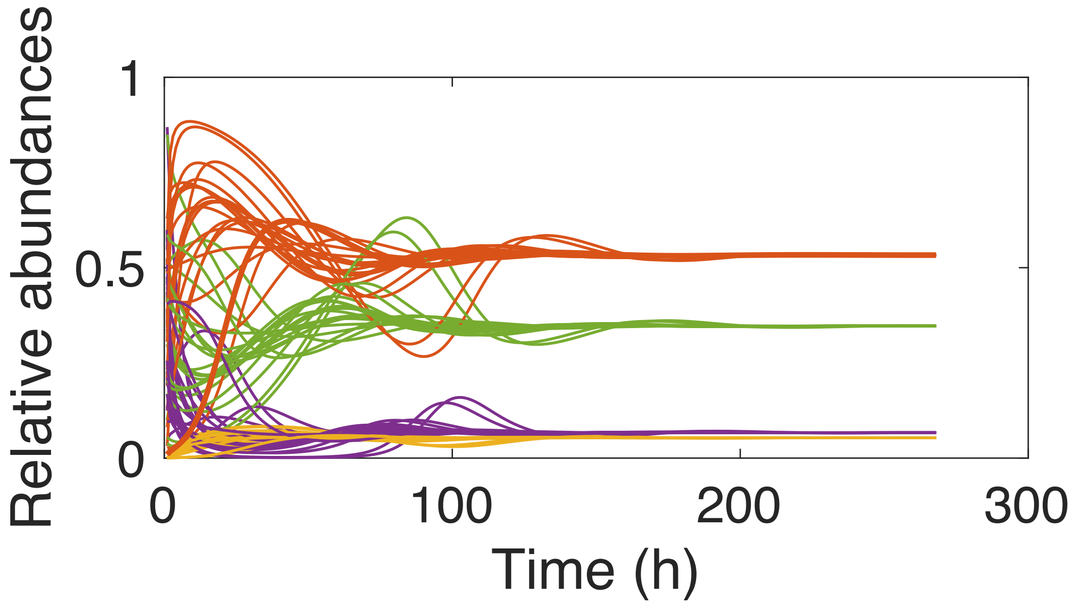




Different interaction matrices

Different end-points

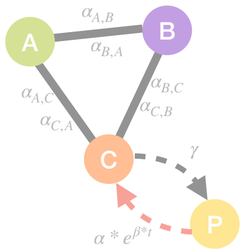
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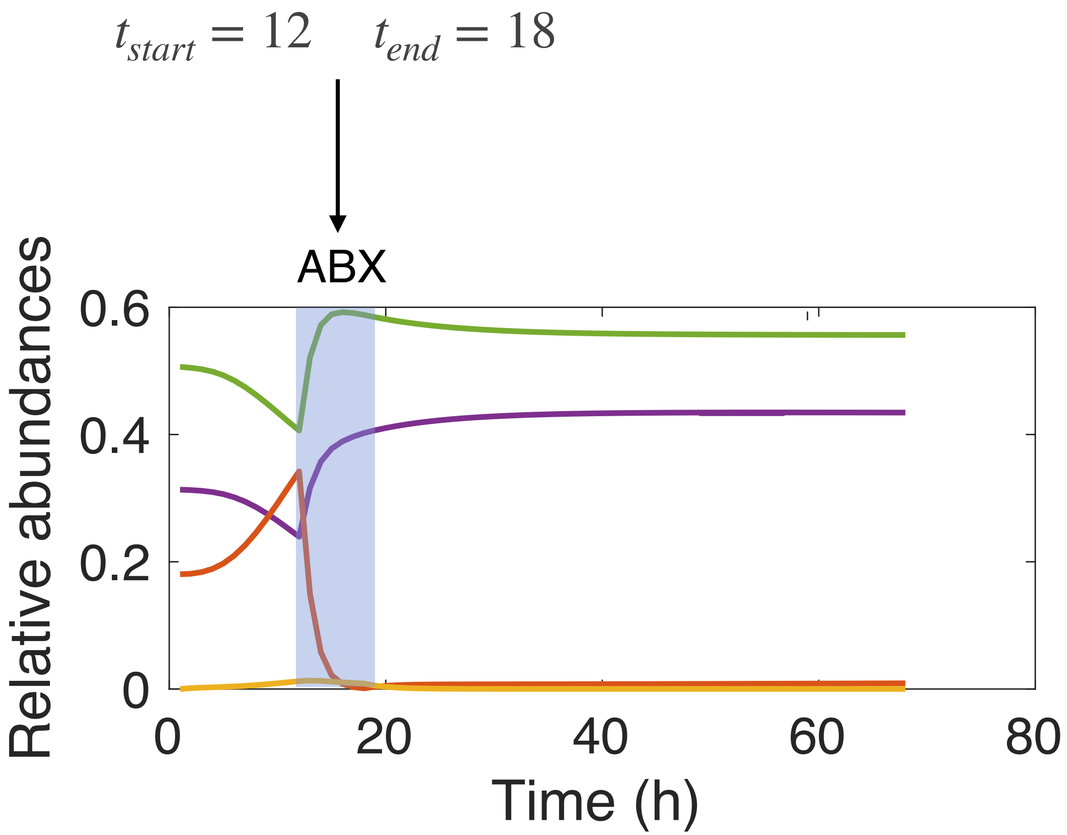
Same interaction matrices

Different initial-points

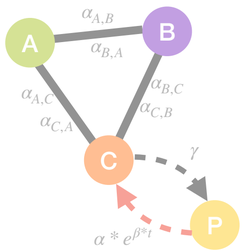
Same end-point



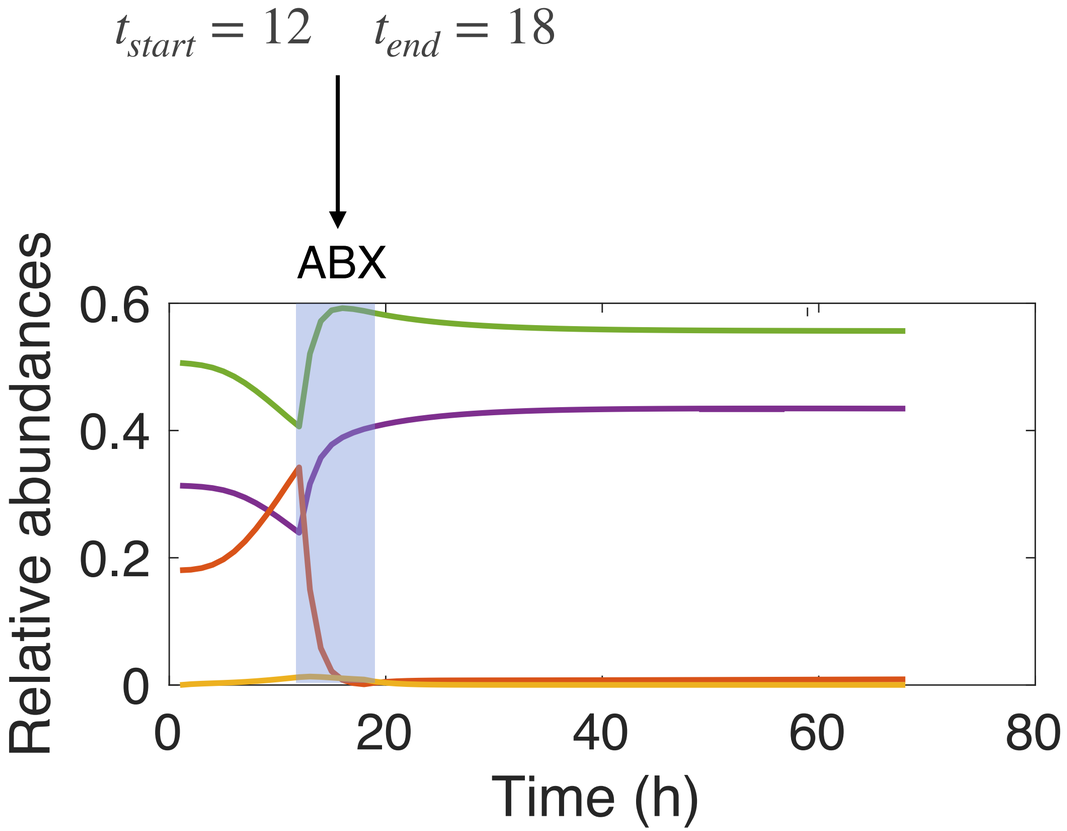
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

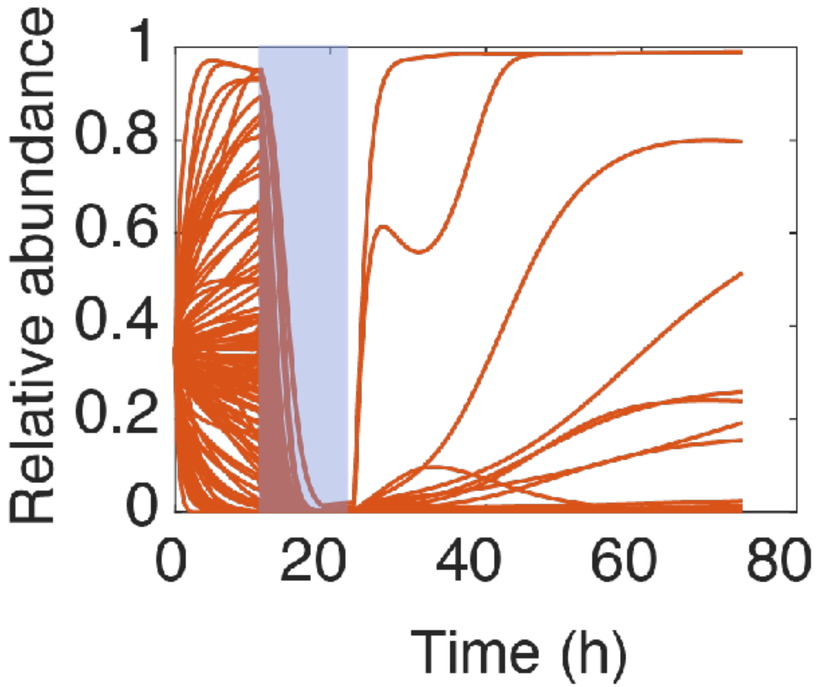


Species *C* reaches a very low level of abundance

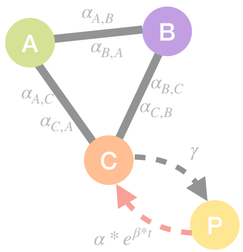


Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

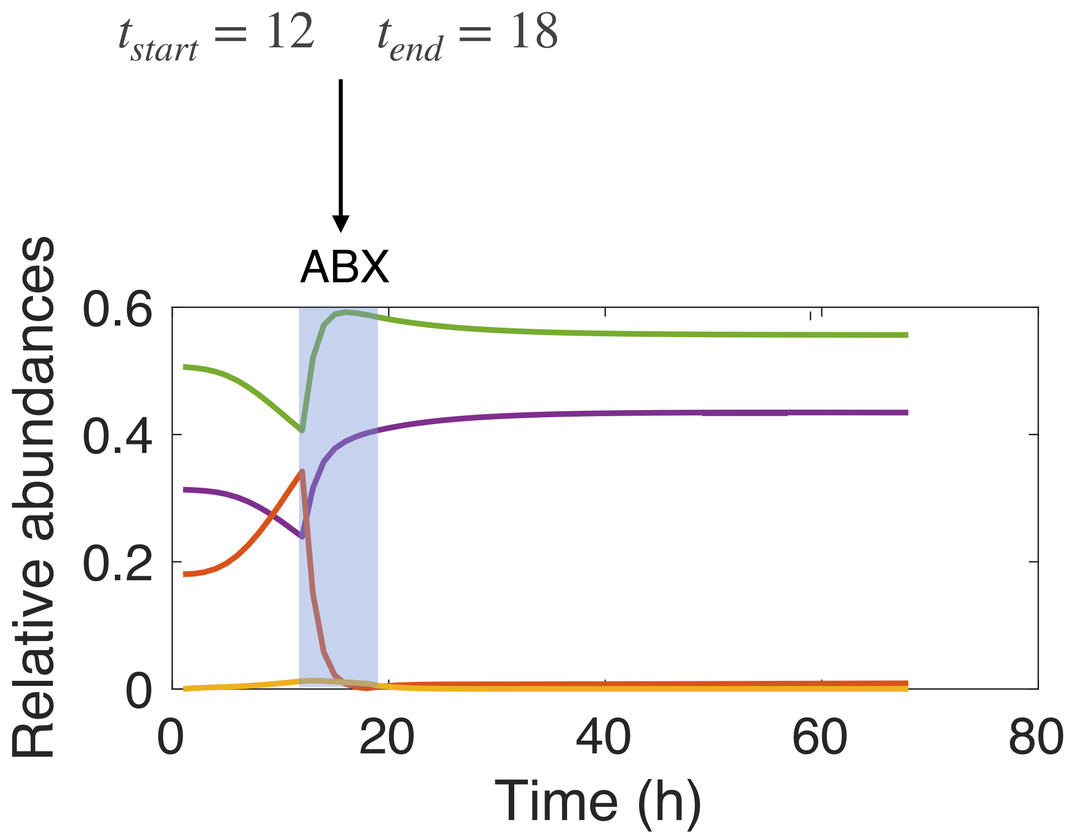




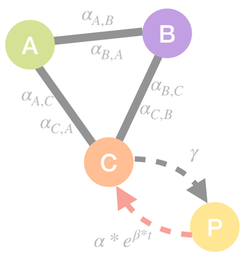
Species *C* reaches a very low level of abundance



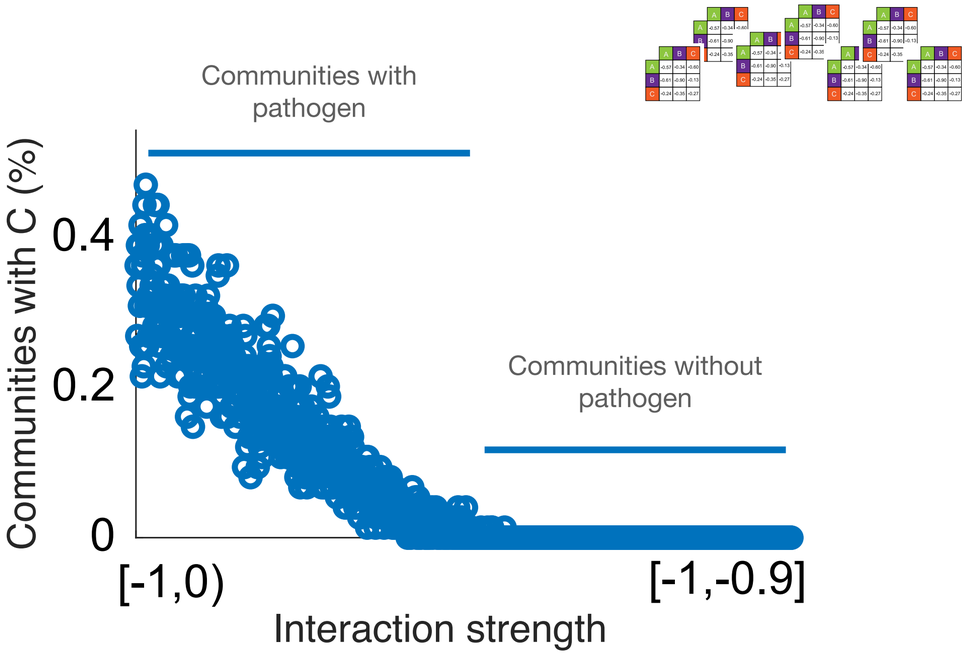
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.



Species *C* reaches a very low level of abundance



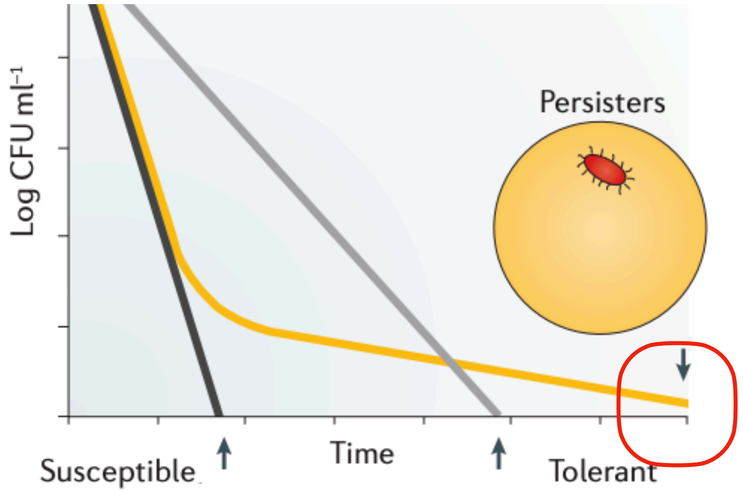
Testing many (i.e. 10^5) interaction matrices

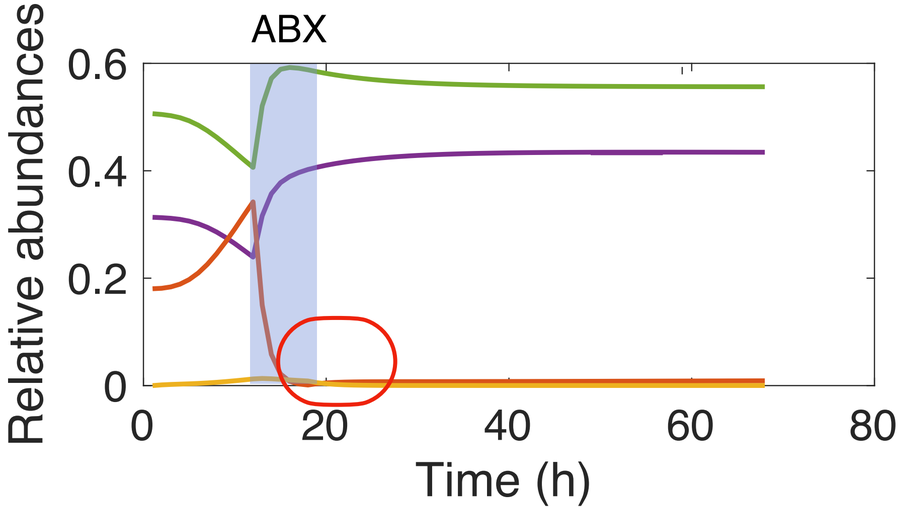


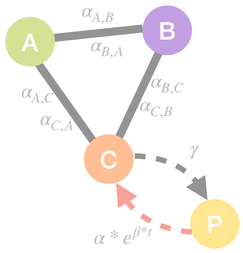
Ecological interactions may determine persisters resuscitation

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

Can random fluctuations counteract the effect of social interaction?

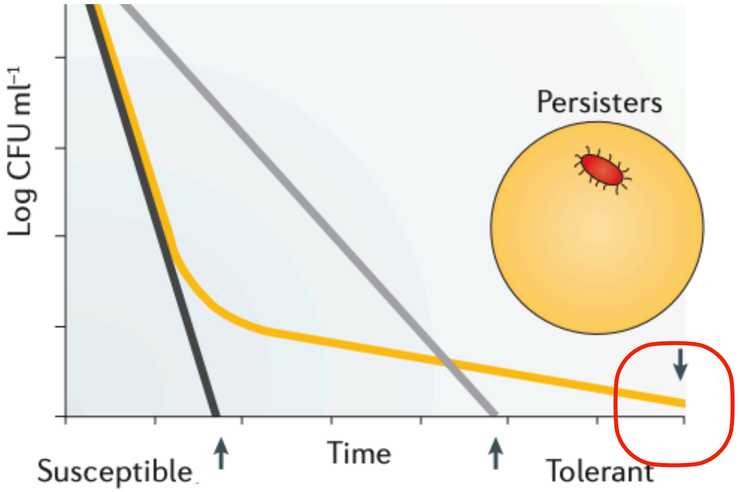


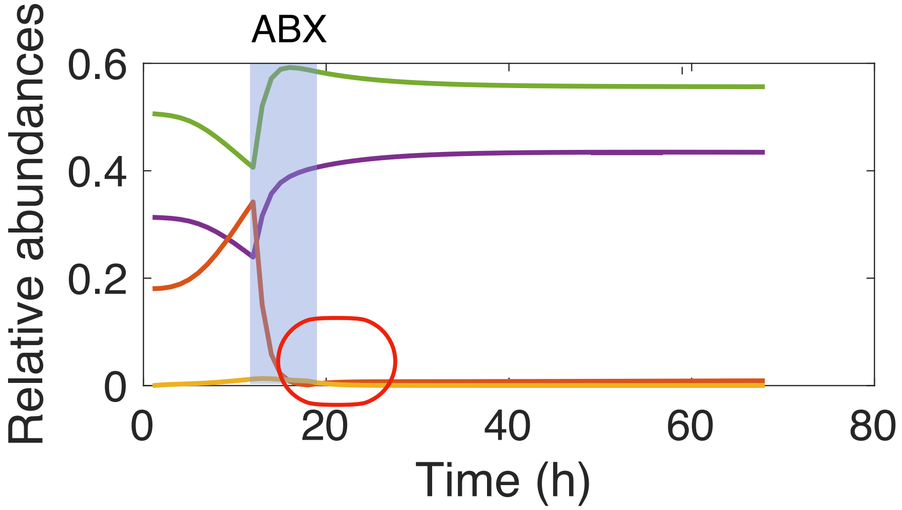


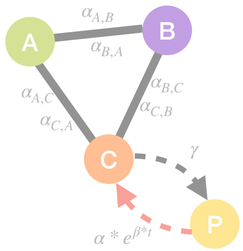


Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

Can random fluctuations counteract the effect of social interaction?







General Master Equation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

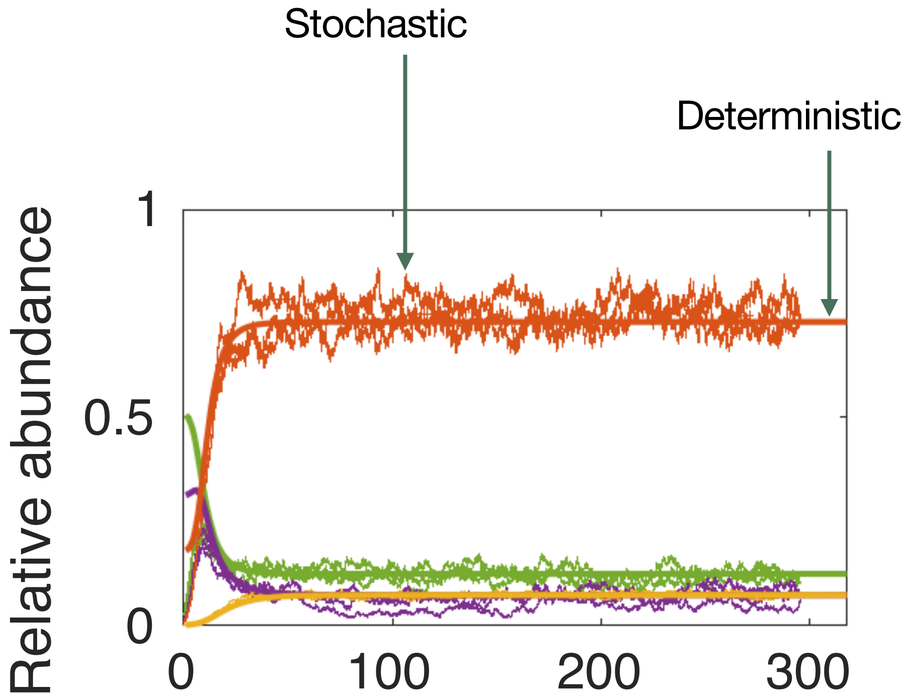
$$T_{17}(n_A - 1\,|\,n_A) = \frac{\alpha_{A,A}}{V} \cdot n_A \cdot (n_A - 1)$$

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

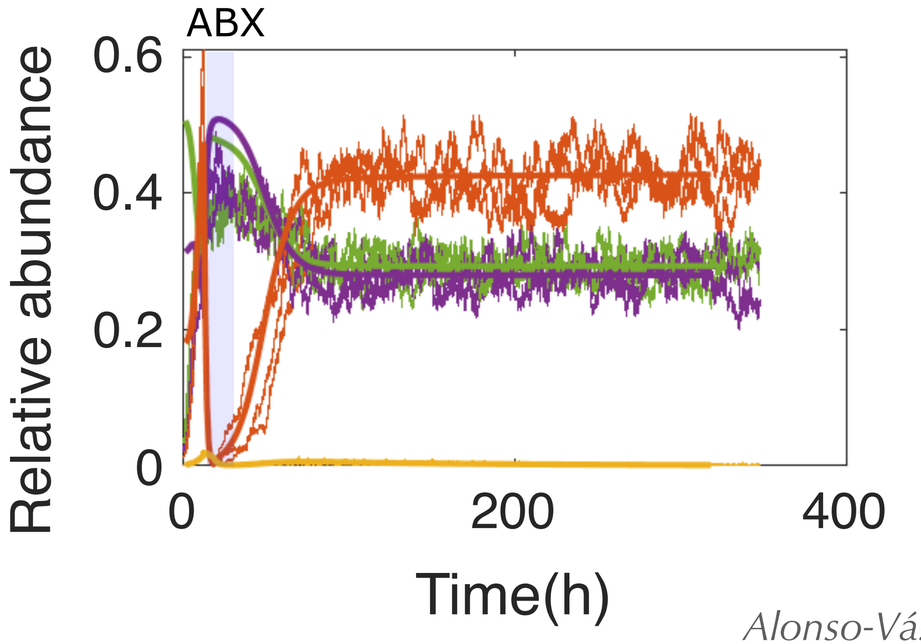
$$T_{19}(n_C - 1\,|\,n_C) = \frac{\alpha_{C,C}}{V} \cdot n_C \cdot (n_C - 1)$$

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.

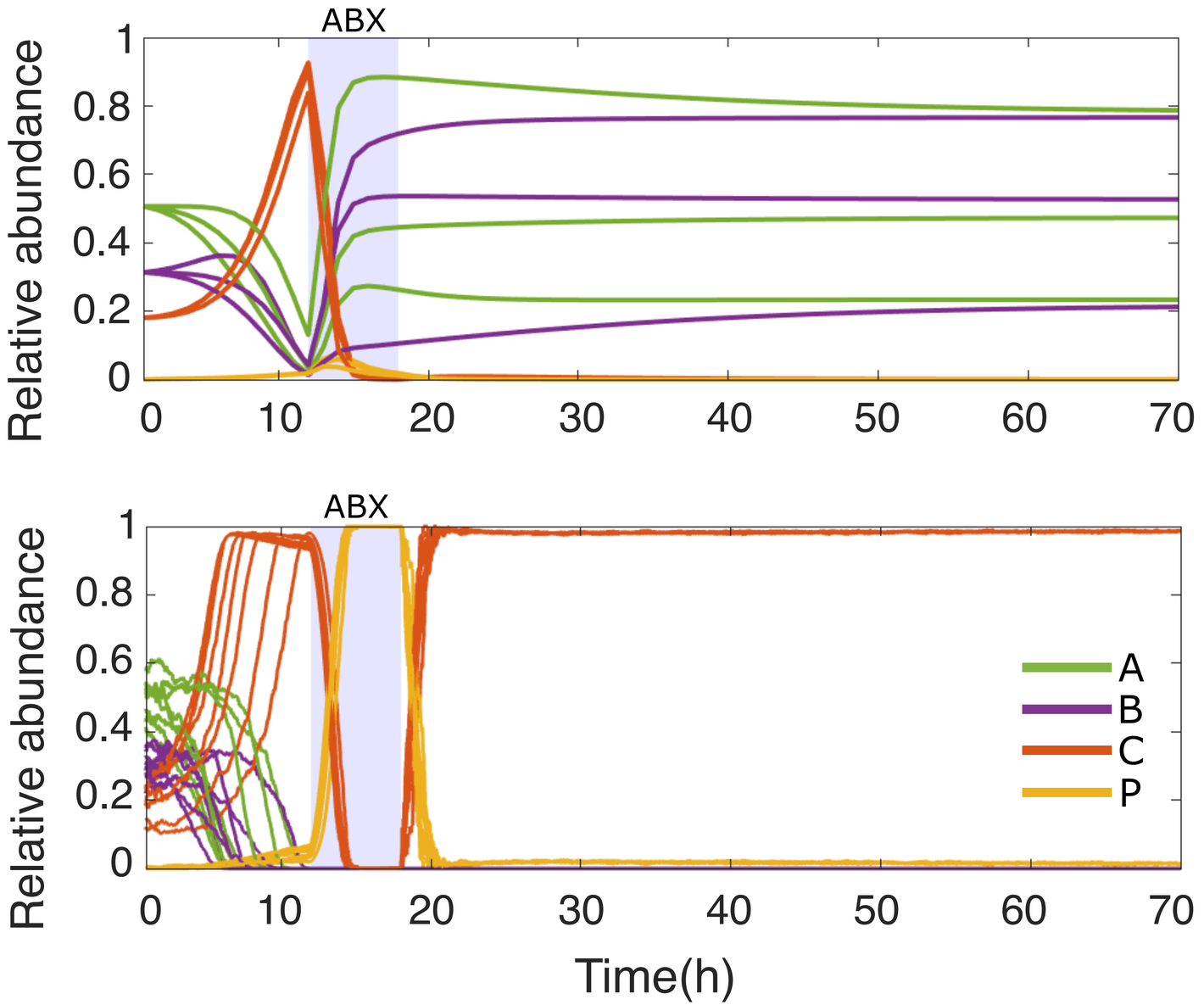
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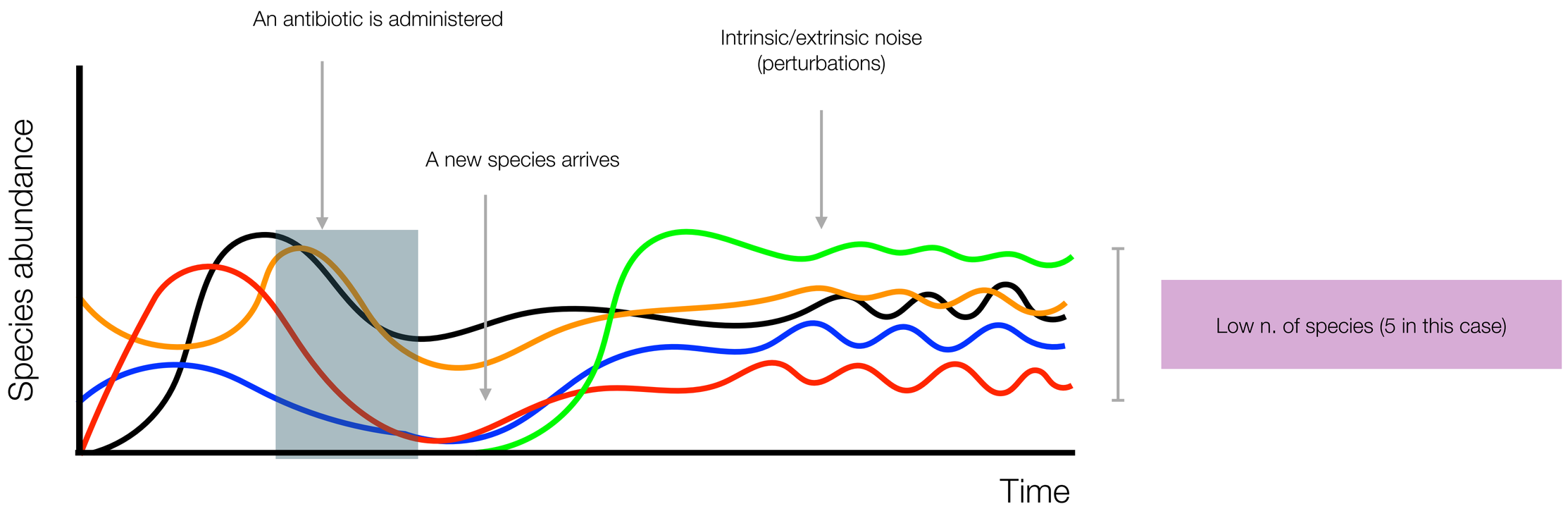
Alonso-Vásquez et al. 2025, Comput. Struct. Biotechnol. J.

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)

Case-study n. 2

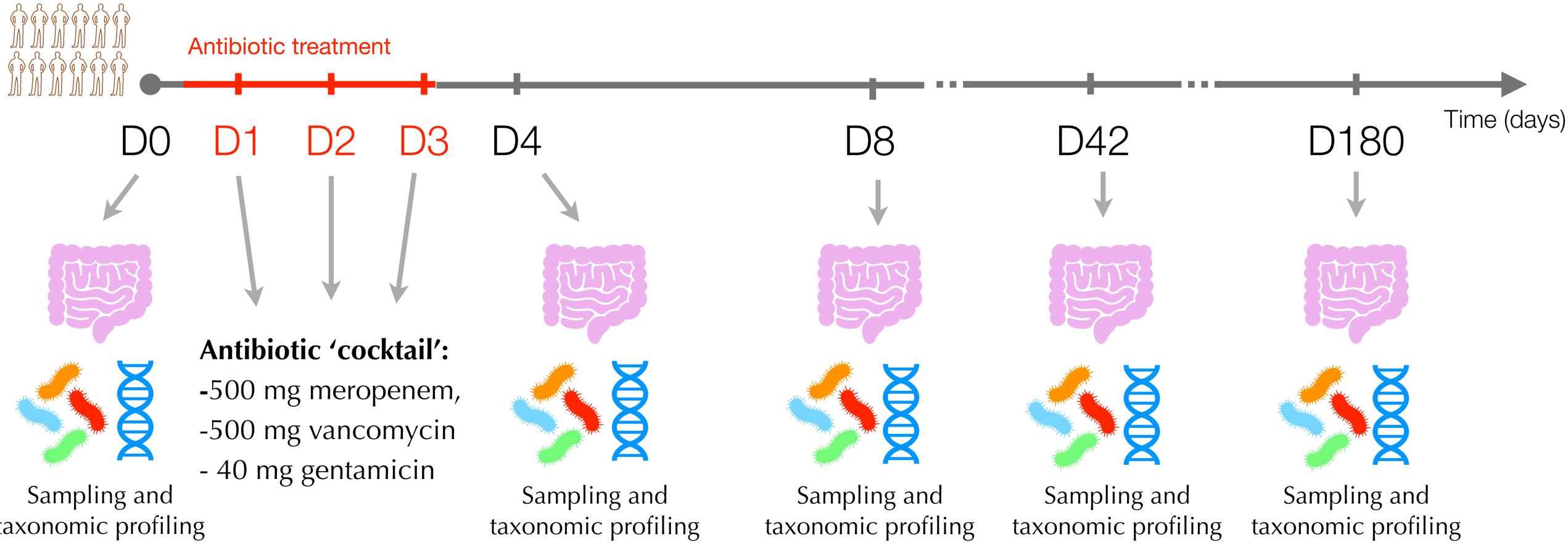
nature microbiology ARTICLES
https://doi.org/10.1038/s41564-018-0257-9

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

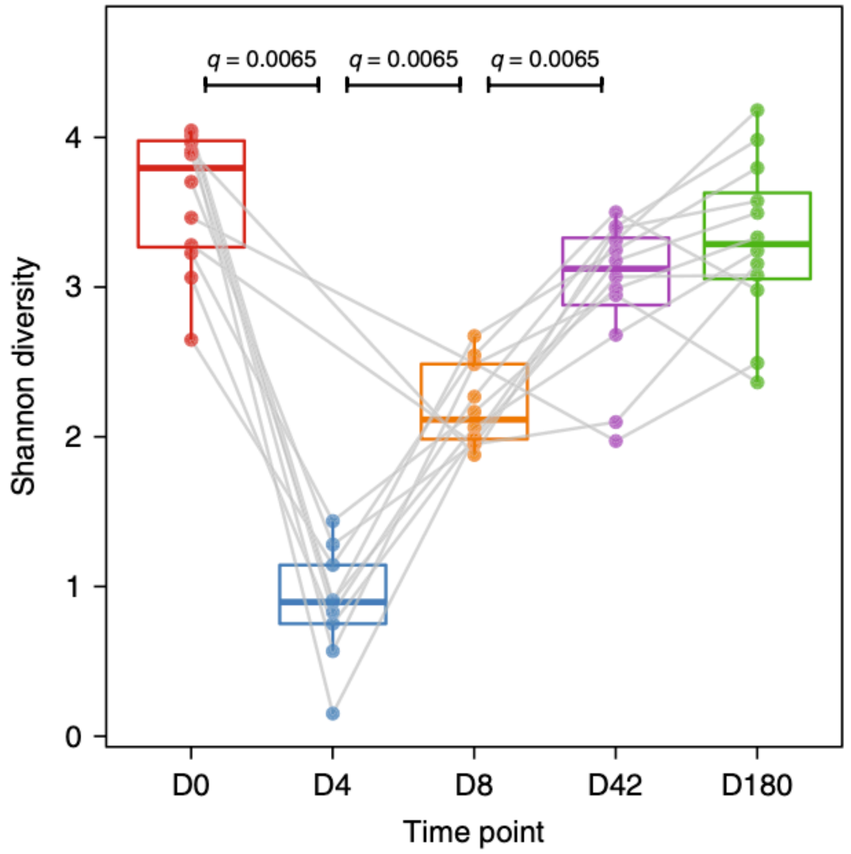
Palleja et al. 2018, Nat. Mic.



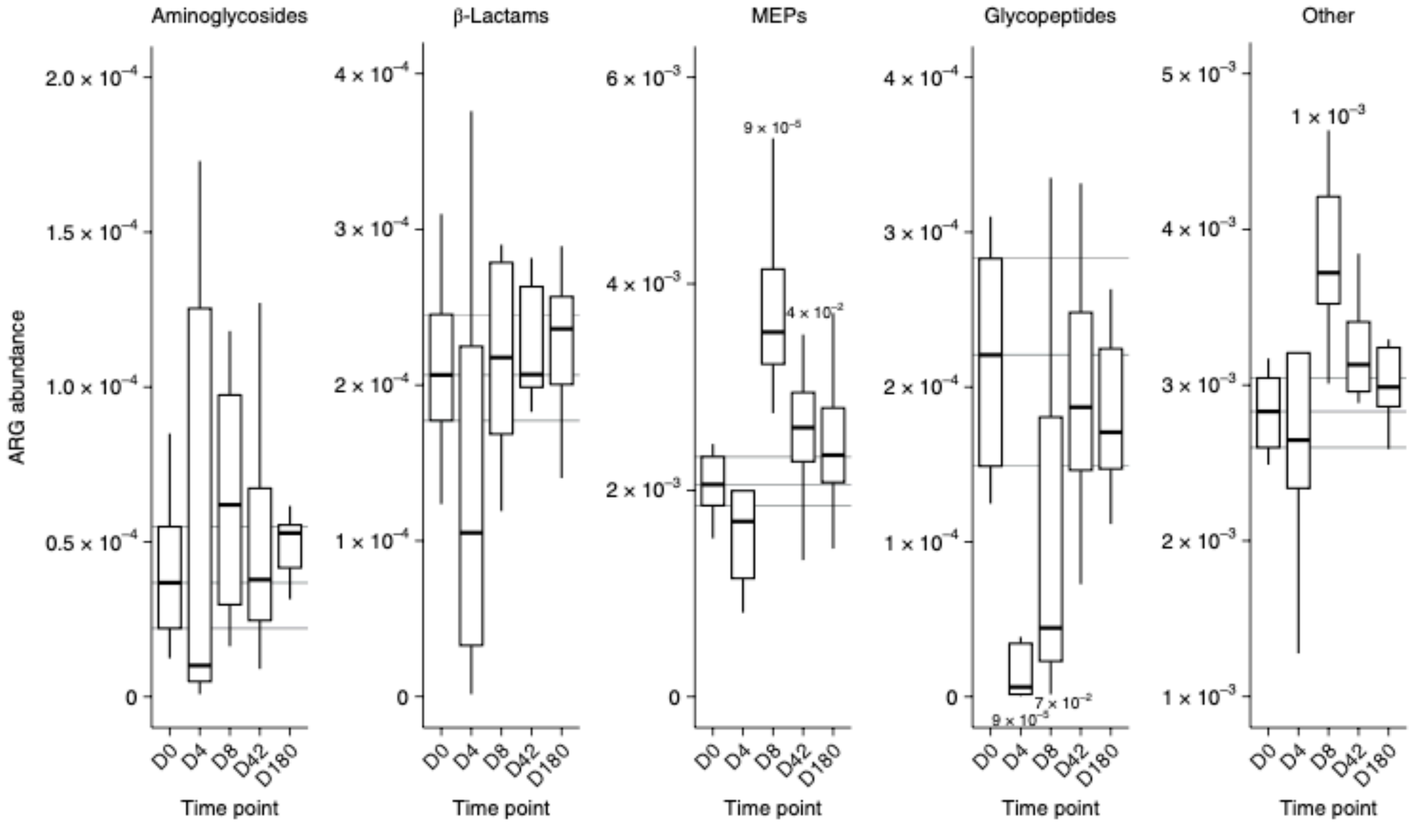
Main outcomes (in our opinion)

1. Microbial diversity

Initial richness = 140



2. Resistome dynamics (delay)



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

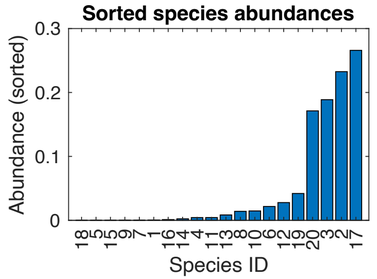
Introducing a reverse ecology approach

“Reverse ecology” approach: 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).

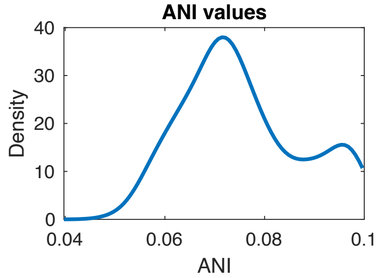
1. Fix a given diversity index (e.g. Shannon)

$$H'$$

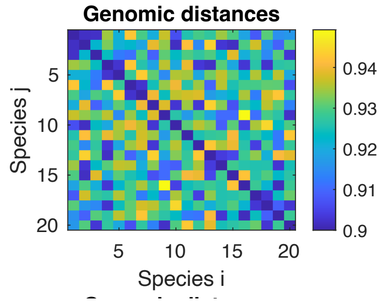
2. Find the species distribution that satisfies that diversity index (Dirichlet distribution*)



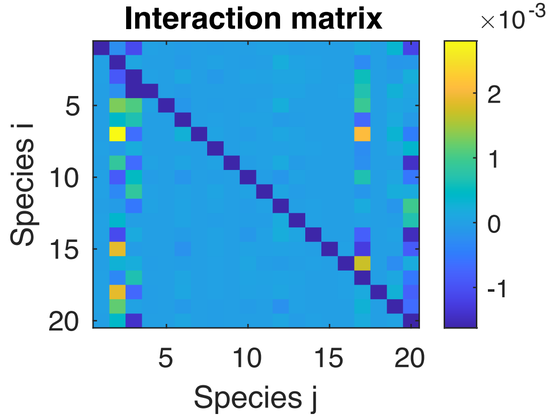
3. Compute ANI distribution (within a given interval)



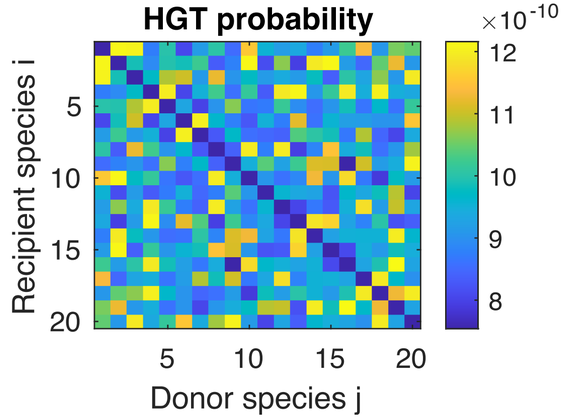
4. Compute genomic distances



5. Output n. 1



6. Output n. 2



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

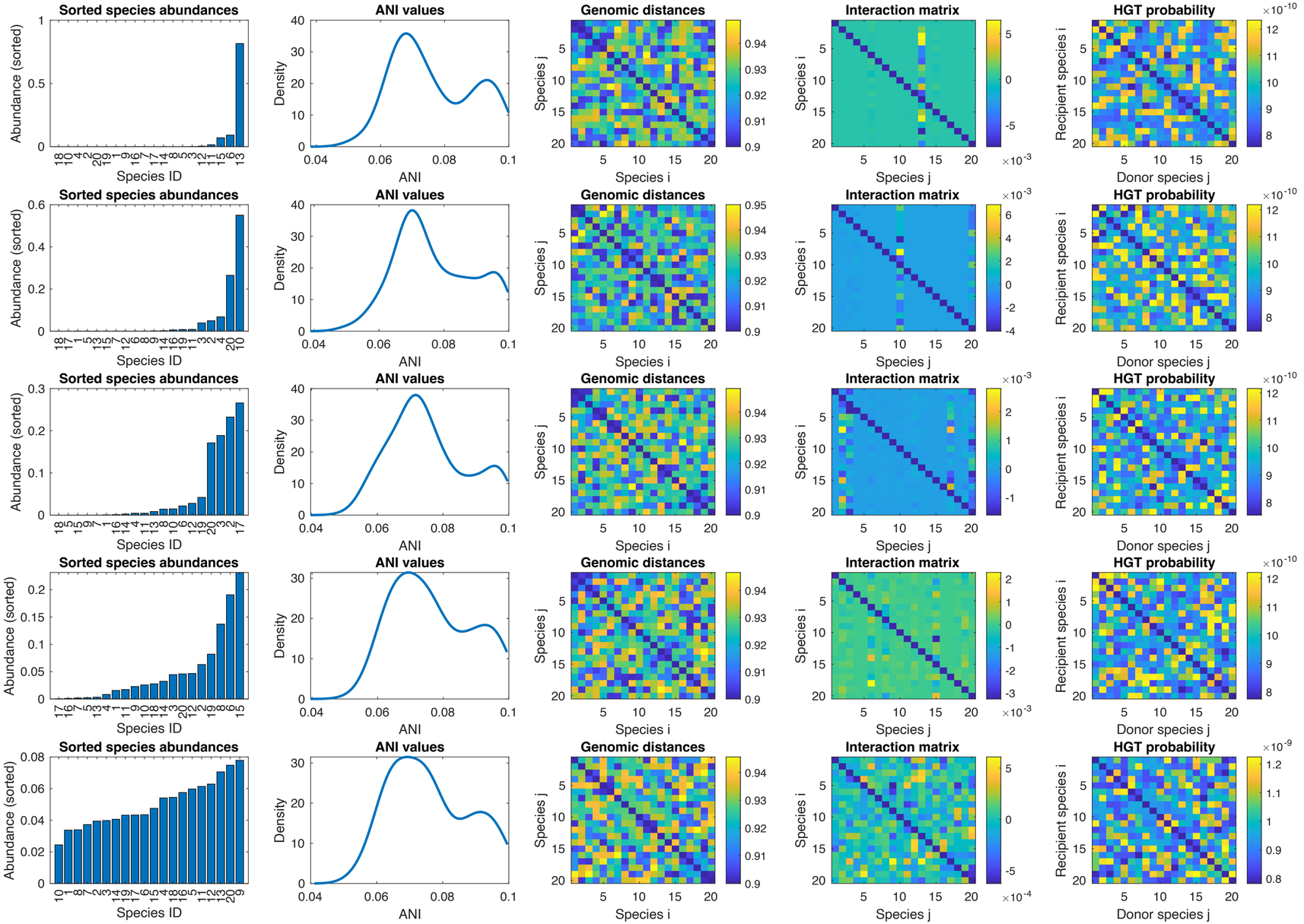
The Dirichlet distribution of order with parameters

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

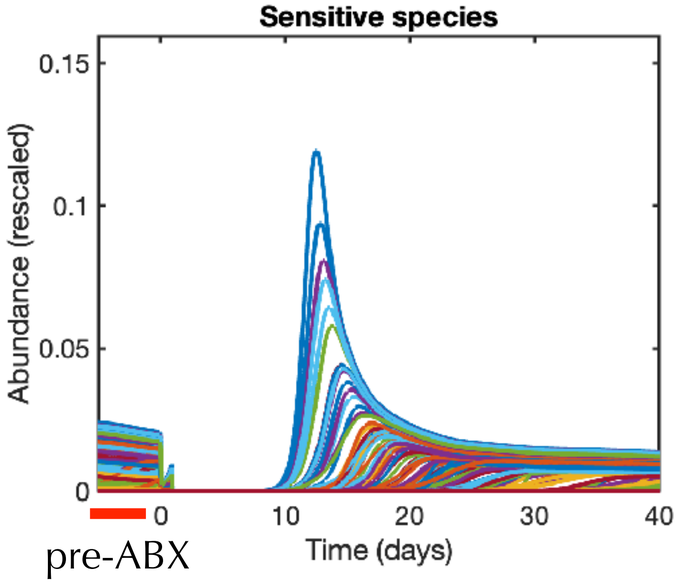
(with K>2) has a probability density function given by

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

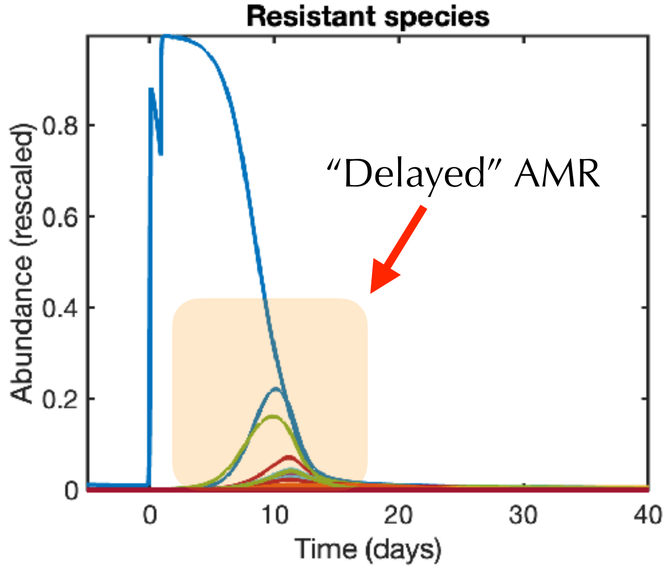
Community diversity

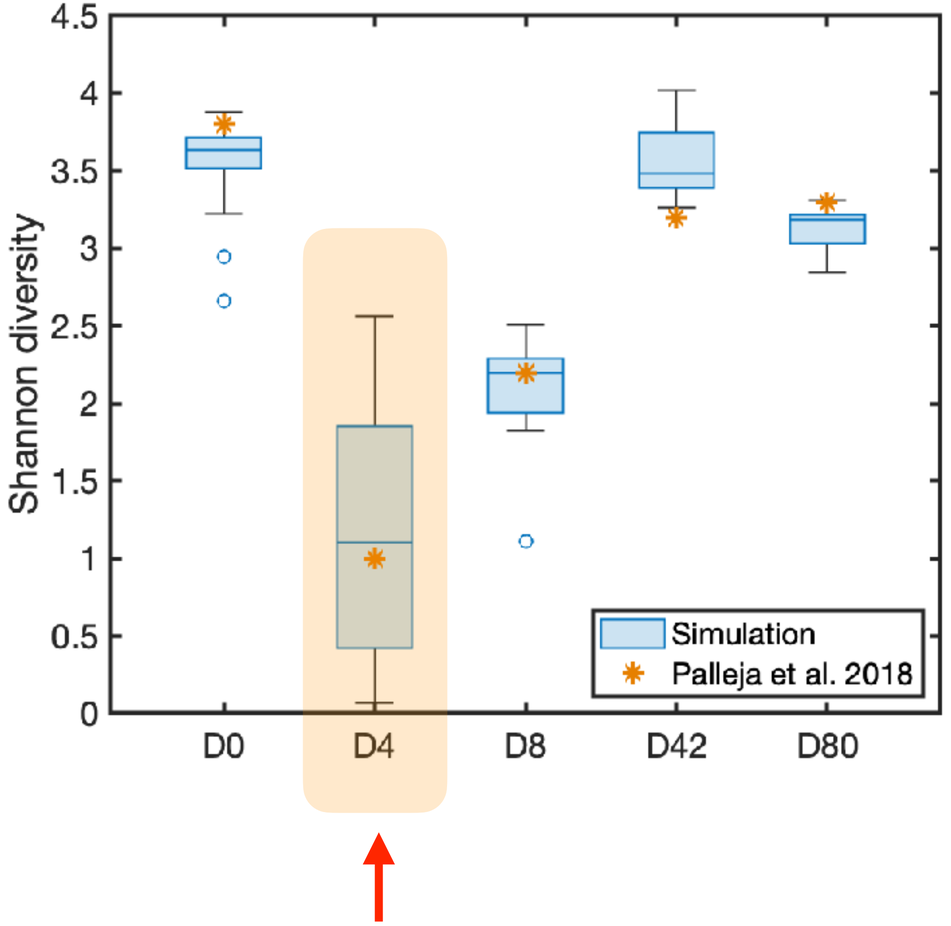


Community dynamics, including mutations and HGT of AMR



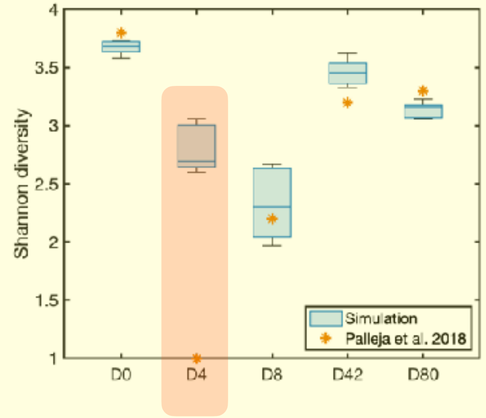
pre-ABX equilibrium





Microbial diversity matched

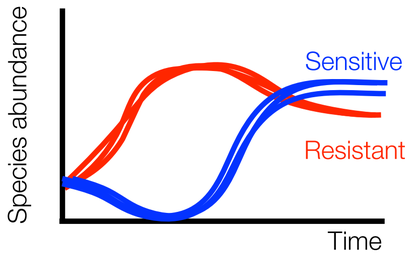
No AMR evo and spreading considered

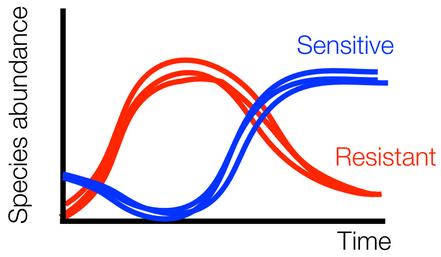


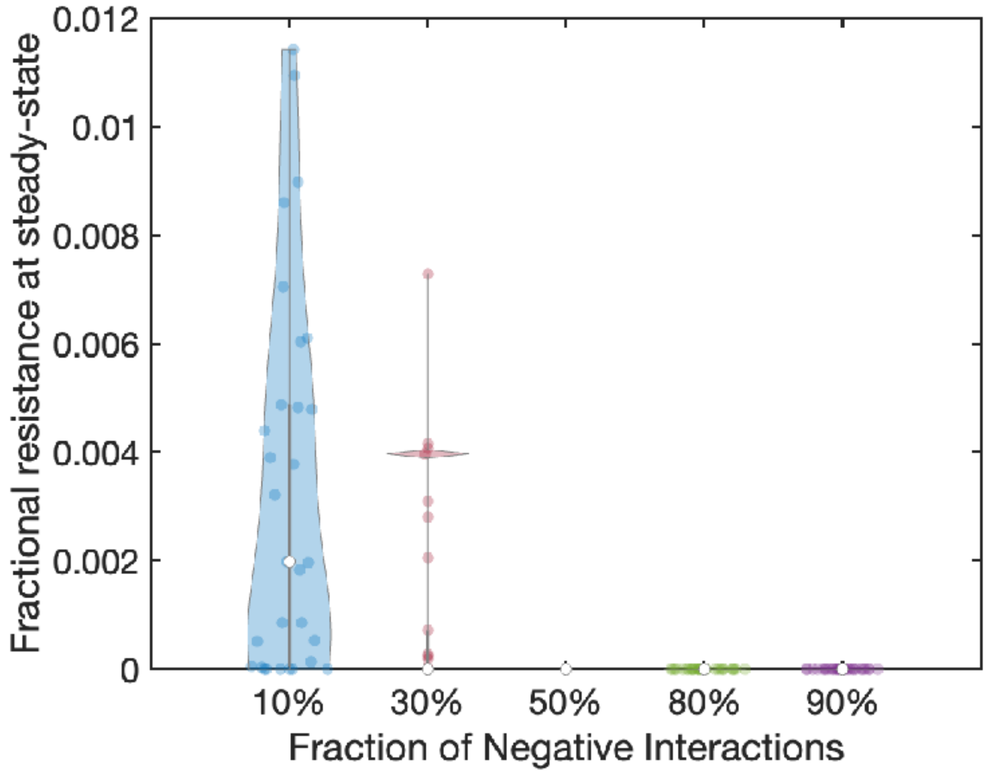

```
mutation_rate = 1e-7;
HGTrate  =1e-5;
```

The impact of interactions on the control of AMR

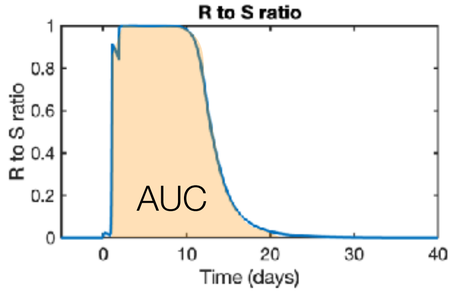
Resistant species at community steady-state

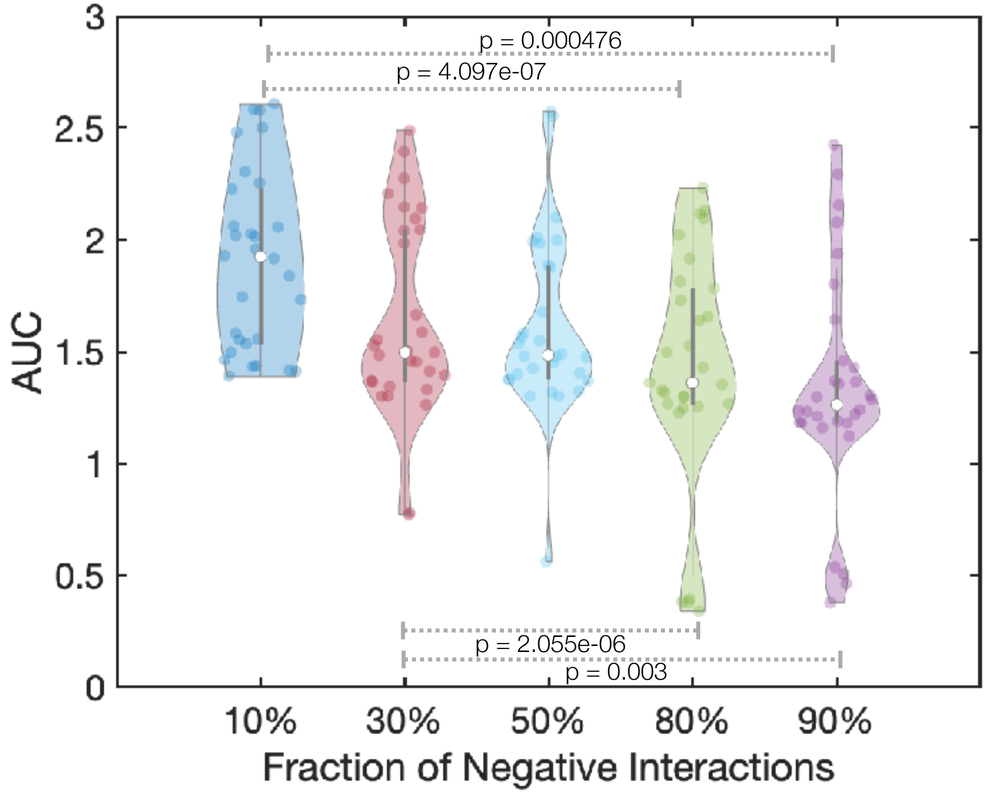






Area Under the resistant to rensitive Curve





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…

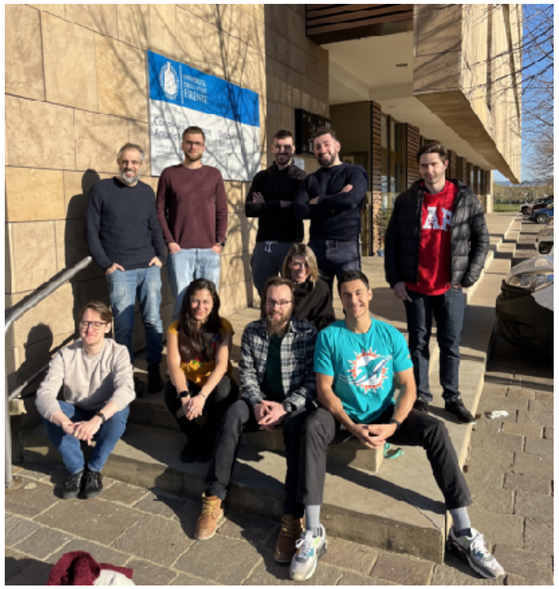
We stress the i) necessity of experimental data (e.g. abundance data and/or evolutionary rates) to parametrize the models and ii) the need for including microbial interactions (i.e. the microbiota composition and structure) when considering the possible outcomes of antimicrobial strategies.

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

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Silvia Buroni (UNIPV)
Matteo Brilli (UNIMI)

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