Population dynamics of infection diseases

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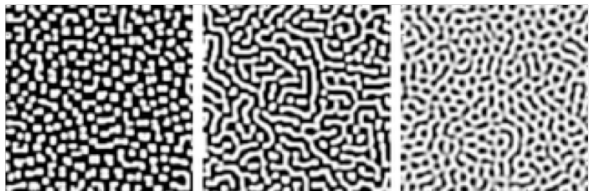
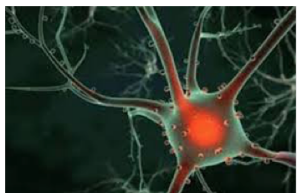
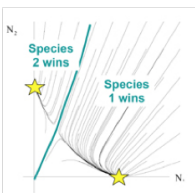
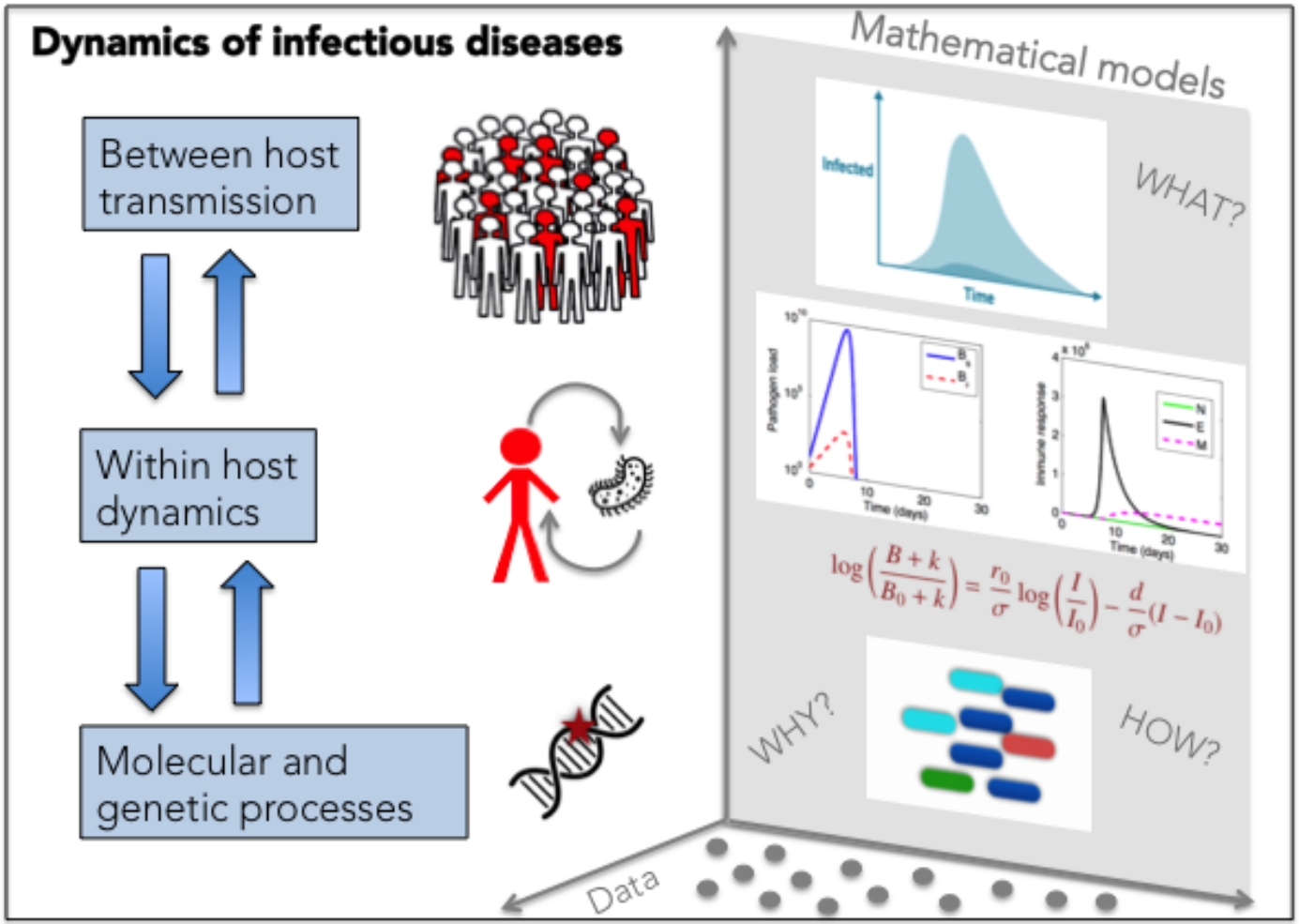
Mathematical biology

An interdisciplinary field where Mathematics (Algebra, Calculus, Analysis, Probability and Statistics) is used to study analyze and explain quantitatively and theoretically biological phenomena and processes in life sciences and medicine.

Cell organization, Ecology and ecosystems, Evolution and biodiversity, Genome organization and expression, Growth and development, Immune system, pathogens and host defenses, Integrative approaches to organism function and disease, Molecular structure and function, Neurobiology and behavior, New technology and industrial biotechnology, Plant biology and agriculture...

Mathematics for infectious disease ecology and evolution



I. Dynamics and control of infectious diseases

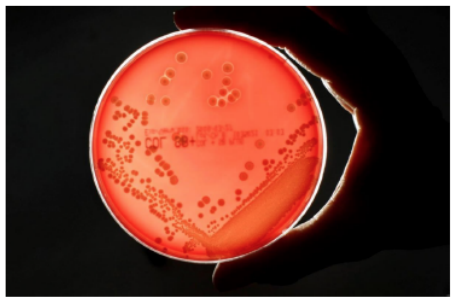
- **Pathogen diversity, evolution and control in antibiotic resistance**
- **Patient diversity, personalized medicine and disease trajectory prediction**

SAÚDE

A matemática pode ajudar a travar as resistências aos antibióticos?

Investigadores do Instituto Gulbenkian de Ciência desenvolveram novo modelo matemático que pode ajudar a medicina a lidar com as infecções resistentes a antibióticos. Entre outras variáveis importantes nesta equação está a resposta do sistema imunitário de cada doente.

Andrea Cunha Freitas · 27 de Abril de 2016, 7:41



Na lista das resistências a antibióticos, uma das situações mais preocupantes é a infecção pela bactéria MRSA (*Staphylococcus aureus* resistentes à meticilina). REUTERS/FABRIZIO BENSCH

PLOS | COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Integrating Antimicrobial Therapy with Host Immunity to Fight Drug-Resistant Infections: Classical vs. Adaptive Treatment

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Abstract

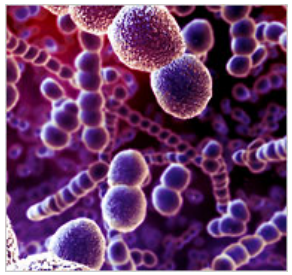
Antimicrobial resistance of infectious agents is a growing problem worldwide. To prevent the continuing selection and spread of drug resistance, rational design of antibiotic treatments is needed, and the question of aggressive vs. moderate therapies is currently heatedly debated. Host immunity is an important, but often-overlooked factor in the clearance of drug-resistant infections. In this work, we compare aggressive and moderate antibiotic treatment, accounting for host immunity effects. We use mathematical modelling of within-host infection dynamics to study the interplay between pathogen-dependent host immune responses and antibiotic treatment. We compare classical (fixed dose and duration) and adaptive (coupled to pathogen load) treatment regimes, exploring systematically infection outcomes such as time to clearance, immunopathology, host immunization, and selection of resistant bacteria. Our analysis and simulations uncover effective treatment strategies that promote synergy between the host immune system and the antimicrobial drug in clearing infection. Both in classical and adaptive treatment, we quantify how treatment timing and the strength of the immune response determine the success of moderate therapies. We explain key parameters and dimensions, where an adaptive regime differs from classical treatment, bringing new insight into the ongoing debate of resistance management. Emphasizing the sensitivity of treatment outcomes to the balance between external antibiotic intervention and endogenous natural defenses, our study calls for more empirical attention to host immunity processes.

Author Summary

The evolution and spread of antimicrobial resistance is a major global problem, and a cause of substantial human mortality. As the discovery of new antibiotics does not follow the rate at which new resistances develop, a more judicial use of available drugs is needed. Here we develop a mathematical model of within-host infection dynamics that combines the effects of pathogen clearance by the host immune system and by the antibiotics. Computer simulations and mathematical analysis are used to evaluate treatment protocols in

II. More generally, complexity and dynamics in ecosystems






- Which forces shape ecosystems?
- How is biodiversity generated and maintained?
- What are the fundamental principles for stability and resilience?

Control and management of diseases

Interplay between extrinsic and intrinsic factors

Aggressive vs. moderate interventions

Personalized medicine vs. public/system health

Phenomena across multiple scales

Deterministic forces vs. stochasticity

Biodiversity in multi-type microbial ecosystems

- In **dengue, influenza, malaria, TB, pneumococcus,** the questions of what generates and shapes diversity are a very important public health issue:

- Antigenic variants
- Antibiotic resistance
- Virulence
- Growth and transmission traits
- Vaccine escape mutants, etc.

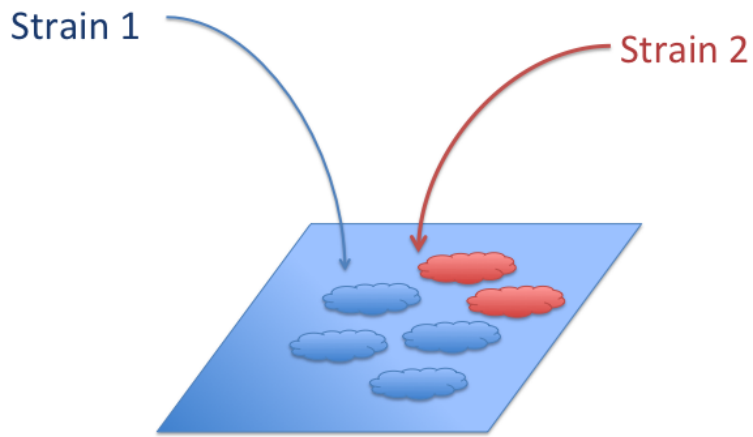
MULTIPLE TRAITS FOR ECOLOGY and EVOLUTION

Which variants coexist and via which mechanisms?

- We need good, mechanistic, computationally efficient mathematical models

How does collective coexistence arise from micro-scale pairwise interactions?

Co-colonization as a route to coexistence

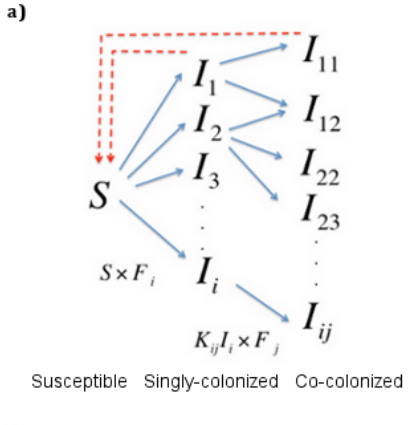


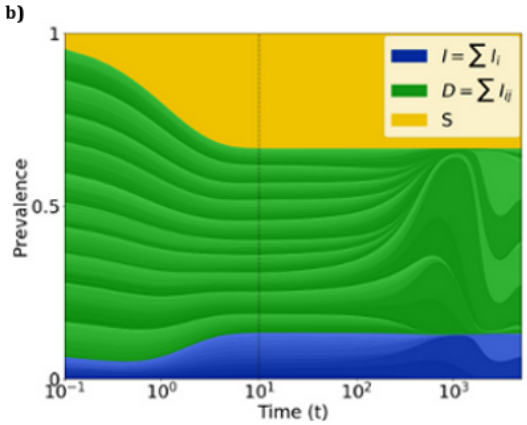
$K_{ij} < 1$: competition $i \to j$

$K_{ij} \geq 1$: facilitation $i \to j$

Co-colonization epidemiological model with N strains

in collaboration with Dr. Sten Madec, University of Tours, France





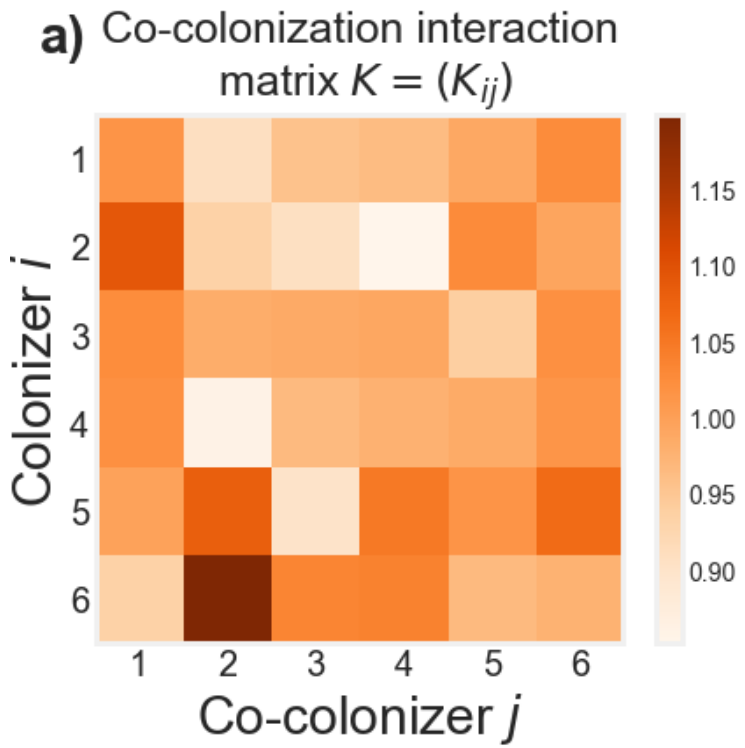
$N + N(N-1)/2$ equations for population structure

Can we simplify?
What is the ecological backbone of epidemiological dynamics?

$$\text{The model: } \begin{cases} \dot{S} = m(1-S) - S\sum_{j=1}^{N} F_j, \\ \dot{I}_i = F_i S - m I_i - I_i \sum_j K_{ij} F_j, \quad 1 \le i \le N \\ \dot{I}_{ij} = I_i K_{ij} F_j - m I_{ij}, \qquad 1 \le i,j \le N \end{cases} \tag{1}$$

where $F_i = \beta\left(I_i + \sum_{j=1}^{N} \frac{1}{2}(I_{ij} + I_{ji})\right)$ gives the force of infection of strain i, and $m = \gamma + r$ is the net clearance plus natural mortality rate.

The co-colonization interaction matrix K_{ij} $(N \times N)$



Since we model N closely-related strains, the K_{ij} are sufficiently close:

$$K_{ij} = k + \varepsilon\alpha_{ij}, \text{ where } 0 \leq \varepsilon << 1.$$

We want to apply time-scale separation to simplify the ODE system

Represent the dynamics in variables that change in two (or more) time scales:

$$\frac{dx}{dt} = f(x, y) \quad \text{FAST VARIABLE}$$
$$\frac{dy}{dt} = \varepsilon g(x, y) \quad \text{SLOW VARIABLE}$$

with the small parameter $0 < \varepsilon \ll 1$.

Challenge: figure out which are the **fast** variables and which are the **slow** variables in our co-colonization model. And how do they change?

Madec & Gjini, Bull Math Biol. 2020 Oct 29;82(11):142

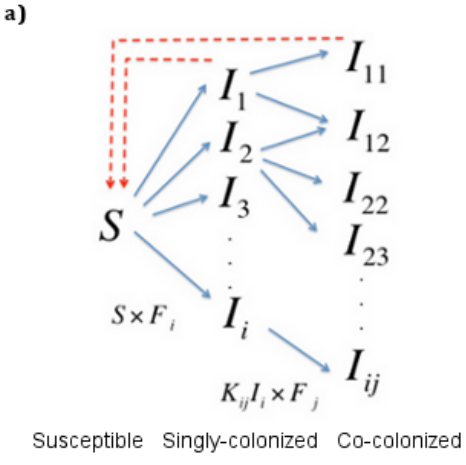
Re-write the ODE system in a more convenient form

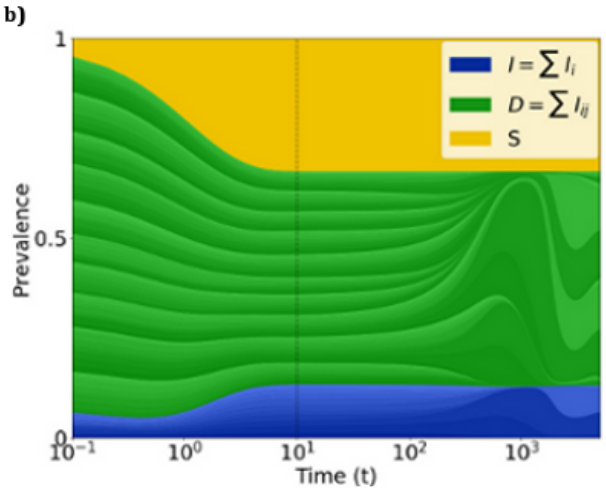
$$\text{Define } J_i = I_i + \sum_{j=1}^{N} \frac{1}{2}(I_{ij} + I_{ji}) \text{ and } T = \sum_i I_i + \sum_i I_{ii} + \sum_{i \neq j} I_{ij}. \quad (2)$$

as the **prevalence of strain** i in the population, and the **total prevalence** of all strains. $T = \sum_i J_i$ and the forces of infection are: $F_i = \beta J_i$. Now, the system reads :

$$\begin{cases} \dot{S} = m(1 - S) - \beta S T, \\ \dot{T} = \beta S T - m T, \\ \dot{I} = m(\mathbf{T} - I) - \beta k T I - \varepsilon\beta \sum_{i=1}^{N}\sum_{j=1}^{N} I_i \alpha_{ij} J_j \\ \dot{I}_i = m(J_i - I_i) - \beta k \mathbf{T} I_i - \varepsilon\beta I_i \sum_{j=1}^{N} \alpha_{ij} J_j \\ \dot{J}_i = \frac{\beta k}{2}(I J_i - I_i \mathbf{T}) + \frac{\varepsilon\beta}{2} \sum_{j=1}^{N} (I_j \alpha_{ji} J_i - I_i \alpha_{ij} J_j) \\ I_{ij} = \frac{\beta}{m} I_i (k + \varepsilon\alpha_{ij}) J_j \end{cases} \quad (3)$$

FAST+ SLOW dynamics, made explicit





$R_0 = \frac{\beta}{m}$ (Basic reproduction number)

$K_{ij} = k + \varepsilon \alpha_{ij}$

On a fast time scale, strains behave as neutral ($\varepsilon = 0$)

A conservation law for global quantities:

susceptibles prevalence $S(t) \to \mathbf{S} := \frac{1}{R_0}$,

carriage prevalence $T(t) \to \mathbf{T} := 1 - \frac{1}{R_0}$,

single colonization $I(t) \to \frac{\mathbf{T}}{1 + R_0 k \mathbf{T}}$ and $\mathbf{D} = \mathbf{T} - \mathbf{I}$ (co-colonization)

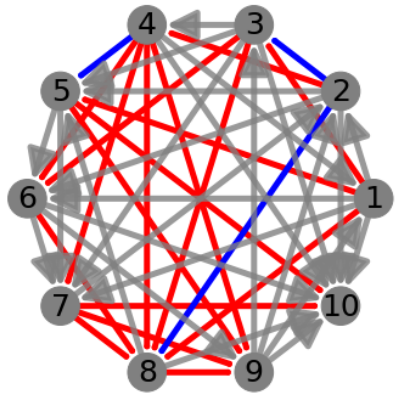
Slow dynamics (on the time-scale $\tau = \varepsilon t$)

Let λ_i^j be the growth rate of strain i when introduced at the endemic equilibrium of strain j alone. In our model, **pairwise invasion fitness** [1] is:

$$\lambda_i^j = \alpha_{ji} - \alpha_{jj} - \mu(\alpha_{ij} - \alpha_{ji}) \tag{4}$$

The λ_{ij} define the **edges** of an invasion network between N strains. Each edge between i and j depends on the signs of $(\lambda_i^j\ ,\ \lambda_j^i)$:

- $(+,+)$: **stable coexistence** of i and j;
- $(-,-)$: **bistability** of i-only and j-only;
- $(+,-)$: i-**wins** competitive exclusion;
- $(-,+)$: j-**wins** competitive exclusion.

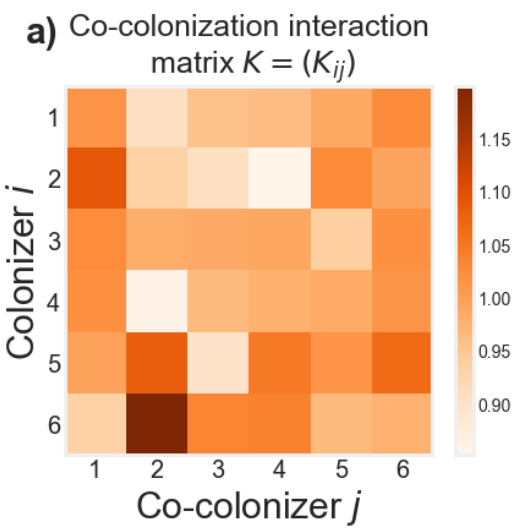


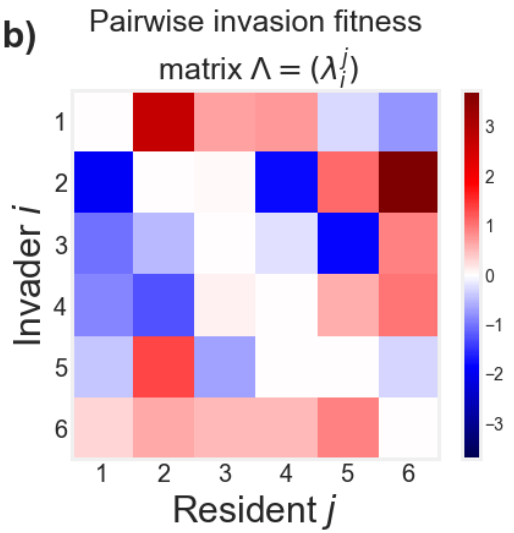
Slow dynamics: an N-dimensional replicator equation for strain frequencies:

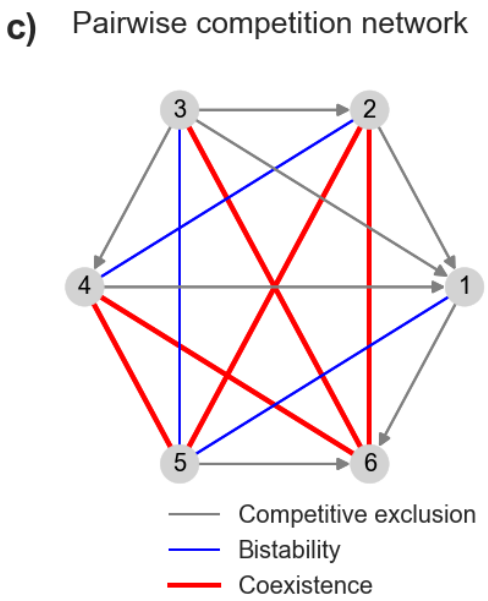
$$\frac{dz_i}{d\tau} = \Theta z_i \cdot \left(\sum_{j \neq i} \lambda_i^j z_j - \sum_{k,j} (\lambda_j^k + \lambda_k^j) z_j z_k \right) \tag{5}$$

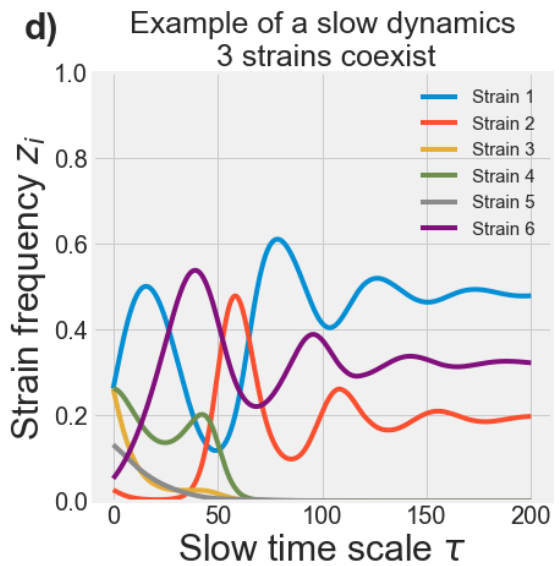
[1] Adaptive dynamics: (Geritz et al., 1998; Meszena et al., 2005)

An example of dynamics for $N = 6$

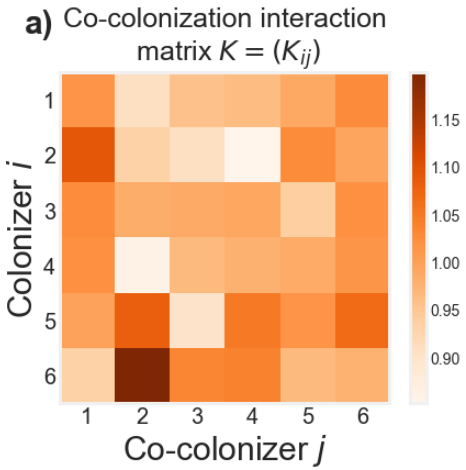


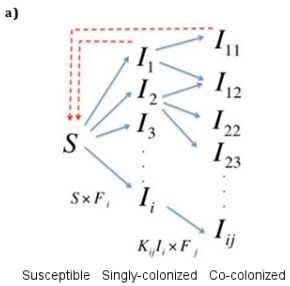


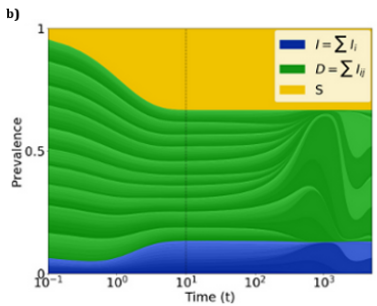




From strain frequencies (z_i) back to population structure







- Define $k = \frac{\sum_{i,j} K_{ij}}{N^2}$ (Mean),
- Define $\varepsilon = \sqrt{\frac{\sum_{i,j}(K_{ij}-k)^2}{N^2}}$, (Std.)
- Obtain $\alpha_{ij} = \frac{K_{ij}-k}{\varepsilon}$.

- Solve the replicator equation for frequencies z_i...
- Obtain epidemiological variables

$$S(t) = \mathbf{S} := \frac{1}{R_0}, \quad T(t) = \mathbf{T} := 1 - \frac{1}{R_0}, \quad \mathbf{I}(t) := \frac{\mathbf{T}}{1 + R_0 k \mathbf{T}}, \mathbf{D}(t) = \mathbf{T} - \mathbf{I}$$

$$I_i(t) := \mathbf{I} z_i(\tau), \quad I_{ij}(t) = \mathbf{D} z_i(\tau) z_j(\tau).$$

Complexity- stability-diversity in N type coexistence

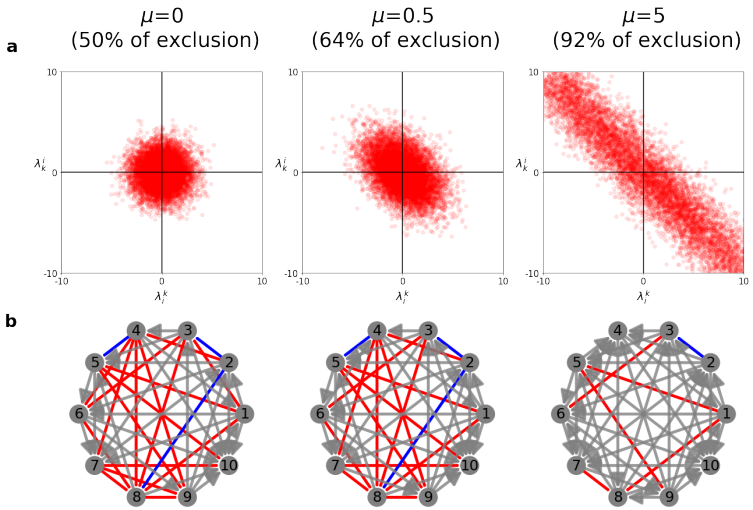
The **ratio of single to co-colonization**

$$\mu = \frac{\mathbf{I}}{\mathbf{D}} = \frac{1}{(R_0 - 1)k}$$

is key to qualitative shifts in coexistence between multiple strains:

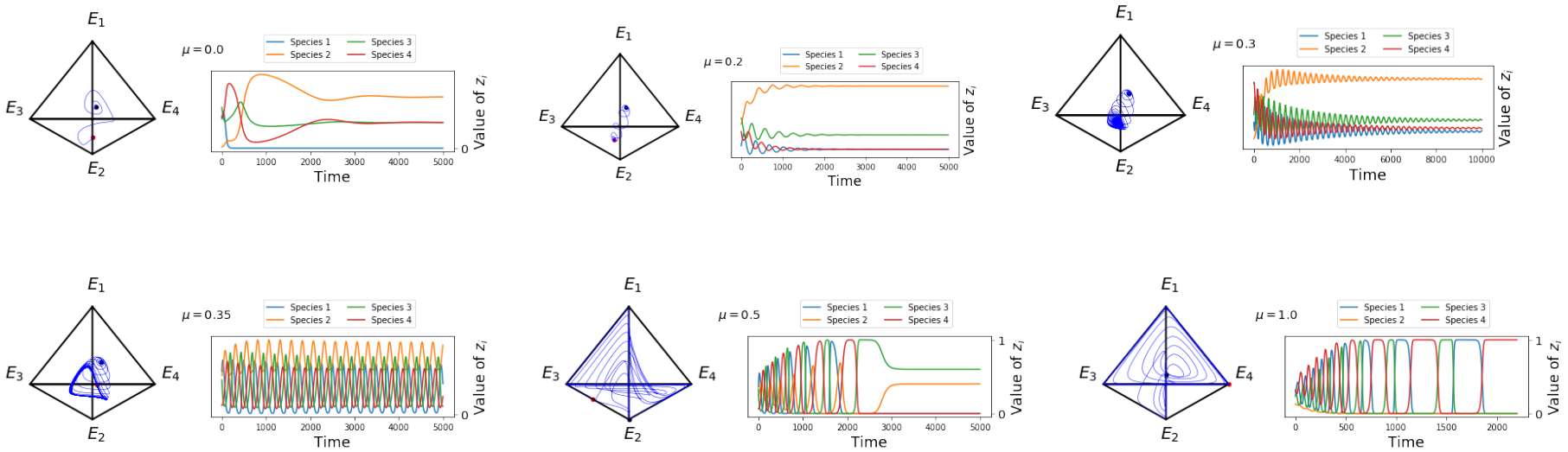
$$\lambda_i^j = \alpha_{ji} - \alpha_{jj} - \mu(\alpha_{ij} - \alpha_{ji})$$

Amplifies the importance of asymmetry in between-strain interactions for net competitive outcome of each pair:

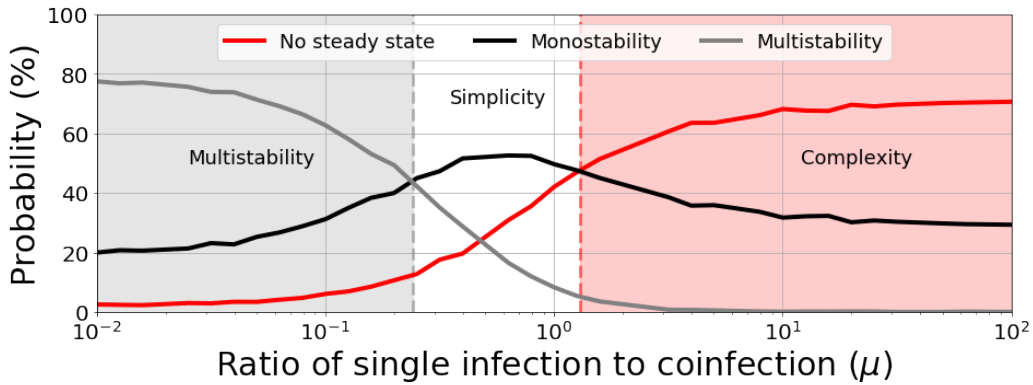


Dynamics shift qualitatively with global ratio μ

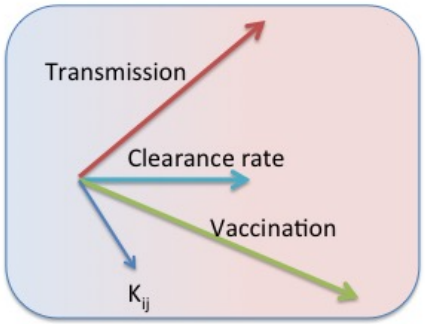
Example ($N = 4$) high transmission (R_0) $\rightarrow$ low transmission (R_0): Very different coexistence dynamics!



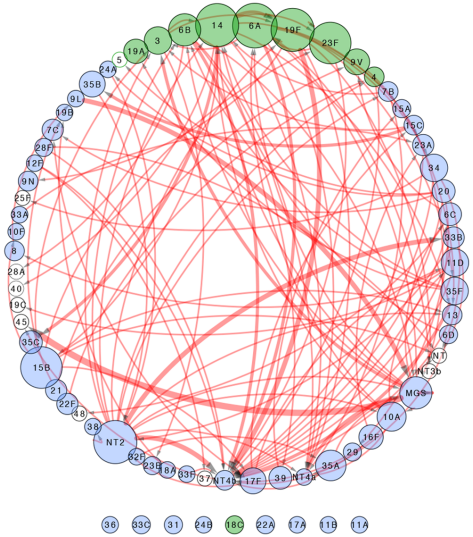
Generally, increasing the ratio μ, increases dynamic complexity



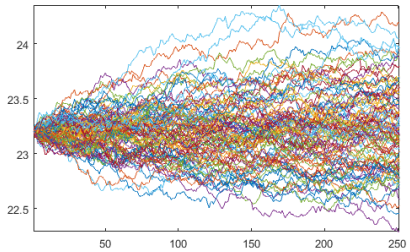
Model extensions, tools and applications



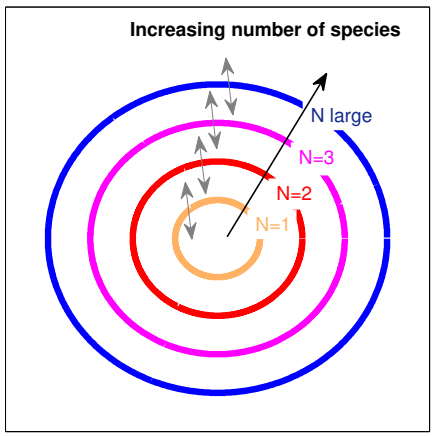
Diversity in other traits



Links with data

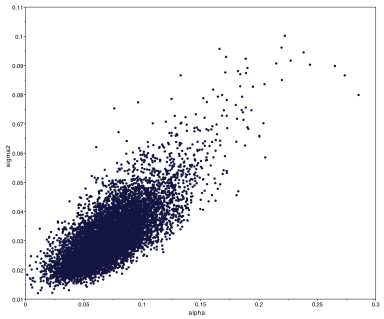


Stochasticity



Community assembly

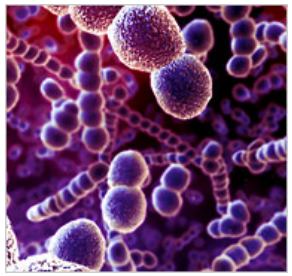
Host contact structure



Parameter inference

Come to join this exciting project!






- **A new path for modeling and understanding** N-species colonization dynamics under cooperation and competition in co-colonization
- **Framework general** for epidemiology, ecology, evolution (SIS 'prototype')
- **Replicator dynamics** in ecological networks: more attention, huge potential
- **Collective dynamics from pairwise outcomes**
- Model reduction has many computational and analytical advantages
- **Many applications** to microbiota, antibiotic resistance, vaccination
- Multi-strain system $\rightarrow$ **multi-type contagion**, opinion dynamics, social evolution

Acknowledgement

Main collaborator in this project:

Sten Madec, Institut Denis Poisson, University of Tours, France

PhD student Thi Minh Thao Le, graduated in 2021, University of Tours, France






Students who have joined (IST, Lisbon):

- Ermanda Dekaj (MSc), - verify **stress-gradient hypothesis in pneumococcus** using global epidemiological data (https://arxiv.org/pdf/2205.12629.pdf)
- Tomas Freire, - **stochastic model version** and now links of replicator dynamics with microbiota data (MSc and PhD)
- Miguel Maroco (MSc) - **2-patch SIS coinfection model for 2 strains**
- Joao Galvao (fellowship) -**theoretical study of special cases of the replicator**

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