Mechanistic Modeling of Microbial Interactions: A Simplicity-Realism Trade-off

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Acknowledgment

Experiments


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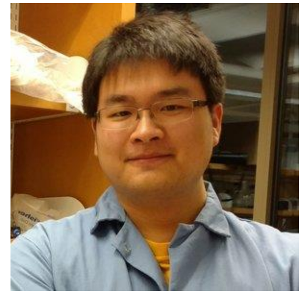
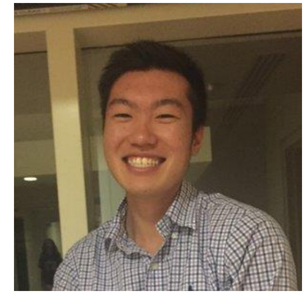

Kevin Chen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Simulations


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Why are we interested in microbial communities?

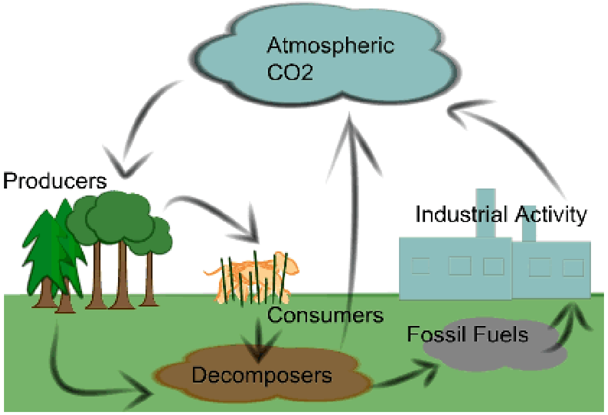
Microbial communities: assemblies of interacting microbes

Why important? Impact on health, industry, and environment

Chronic wound infections

Waste treatment

Ecosystem carbon cycling



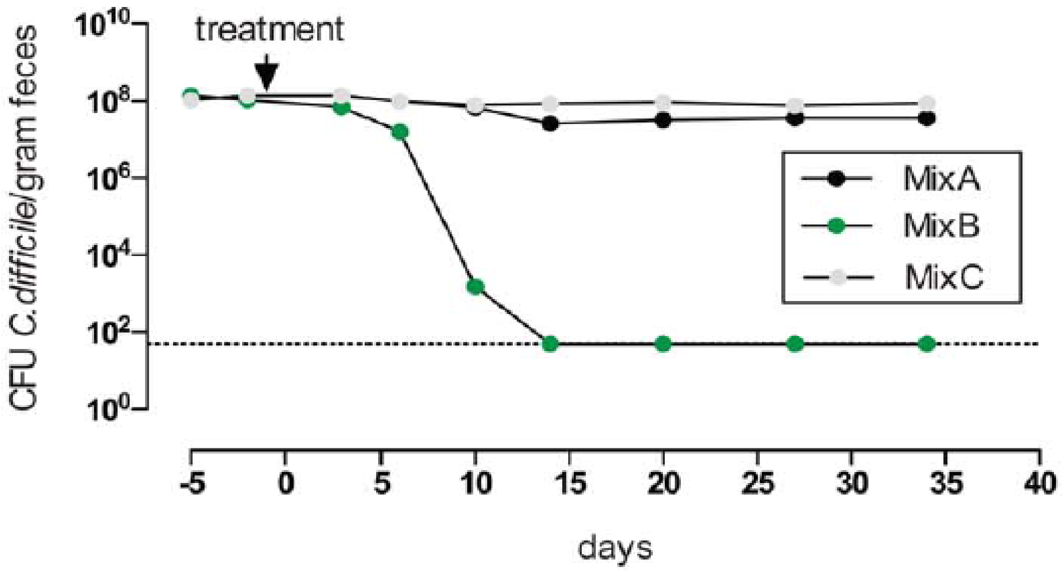
Long-term objective: <u>control</u>

- Eradicating harmful communities
- Maintaining useful communities

Communities can exhibit functions not achievable by any of the individual species

Example: Gut community can resist pathogens

- Constructed six-species community treats *C. diff* infection in mice
- No treatment with any of the single species (or other subsets)



Lawley et al, *PLOS Pathogens* (2012)

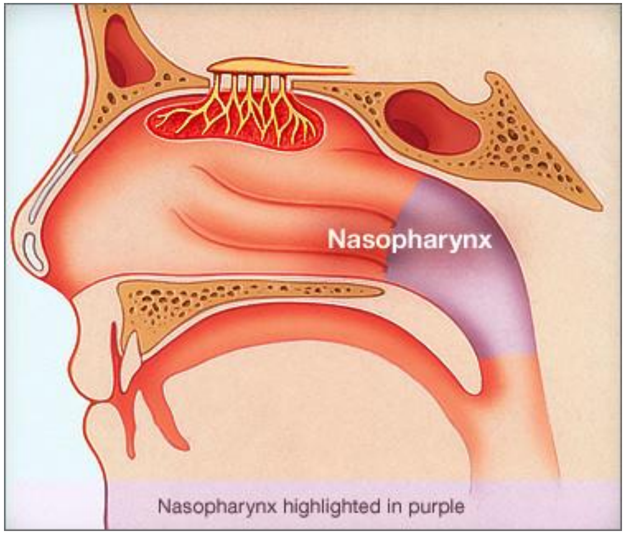
Controlling communities requires a better understanding of underlying processes

Example: nasal microbiota can prevent pathobiont colonization

- *Staph. aureus* present in ~30% of population (often not harmful)
- *S. aureus* carrier vs non-carrier states not dependent on host genes
- Possibly other harmless microbiota residents determine colonization
- Self-infection is the primary cause in hospitalized patients
- Use of antibiotics is not an effective solution

Goal (to decrease the chance of infection):

- What are the processes that shape nasal microbiota?
- What strategy can convert carrier-type to non-carrier-type?



Brugger, Bomar, & Lemon, *PLOS Pathogens* (2016)

Objective

Understanding the basic processes that shape microbial communities (using simple models)

with the goal of

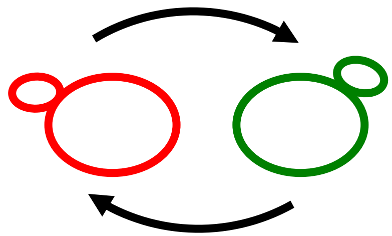
devising strategies to control communities

Approaches for studying microbial communities

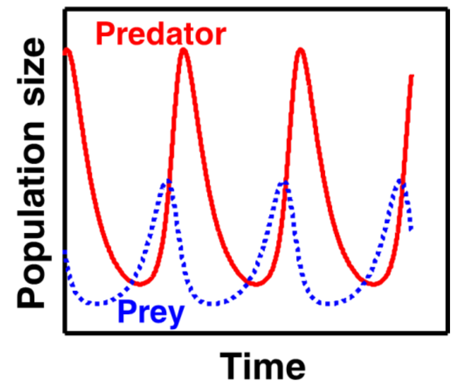
Transparency
Control

Natural

Engineered



Simulated

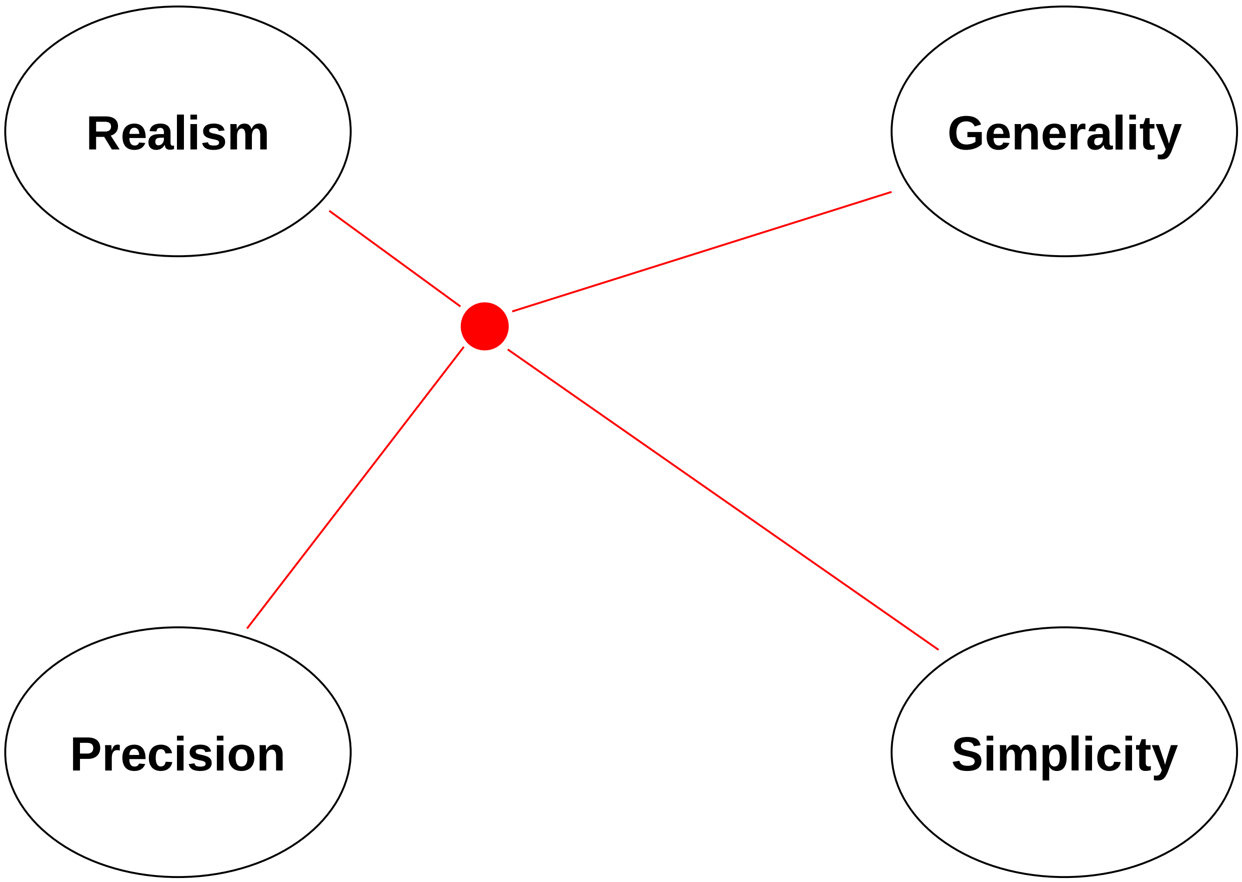


Realism
Complexity

Informing models to make them more realistic, without sacrificing transparency/control

Trade-off in building a model

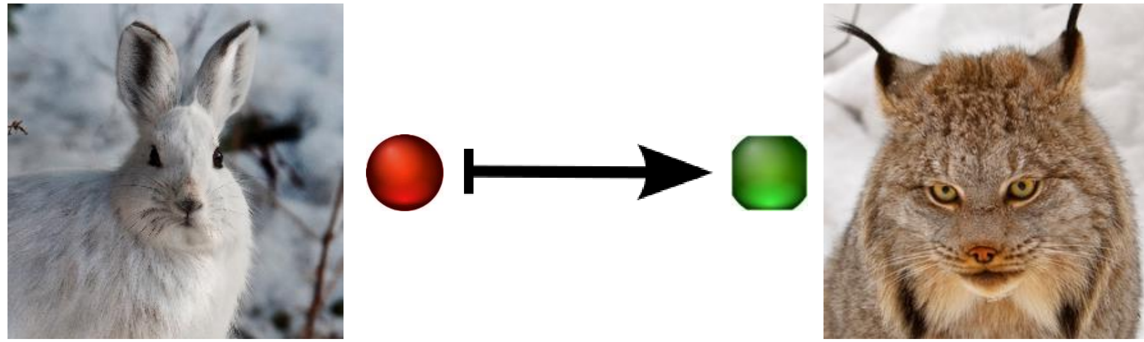
Modified from Levins 1966, *Strategy of model building in population biology*

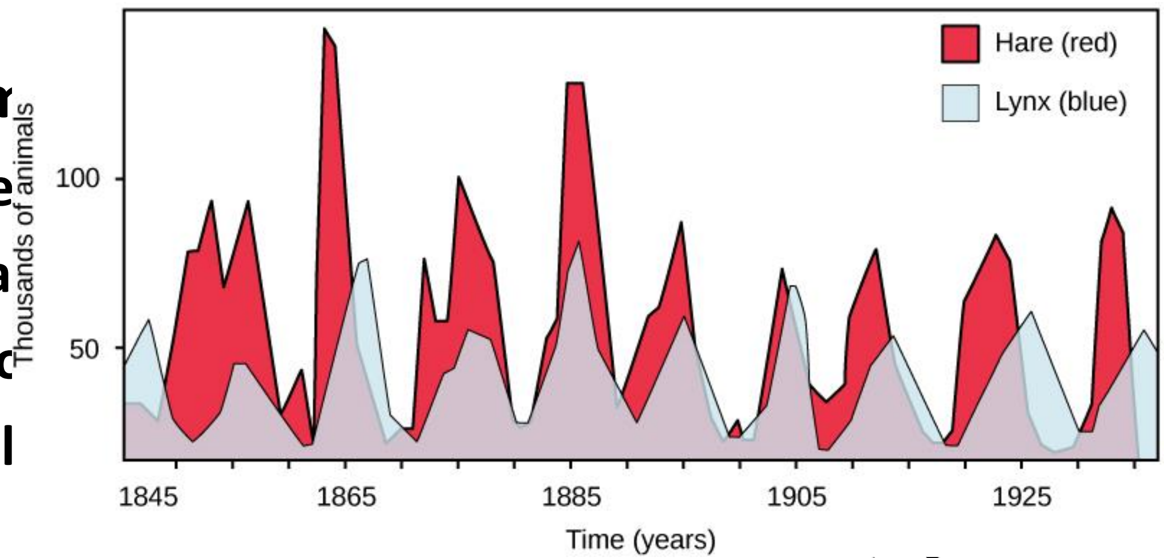


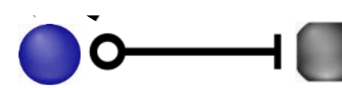
Pairwise fitness models are most commonly used

Modeling interactions as net fitness effects, regardless of mechanisms

e.g. Lotka-Volterra







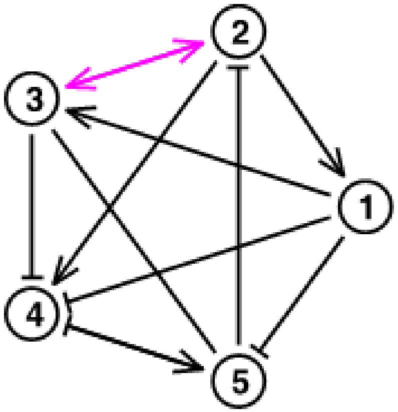
Advantages of pairwise m

- No need to know inte
- Easy to estimate para
- Some empirical suppc
- Easy to extend to mul

Is pairwise modeling applicable to microbial communities?

Lotka-Volterra modeling of microbial communities

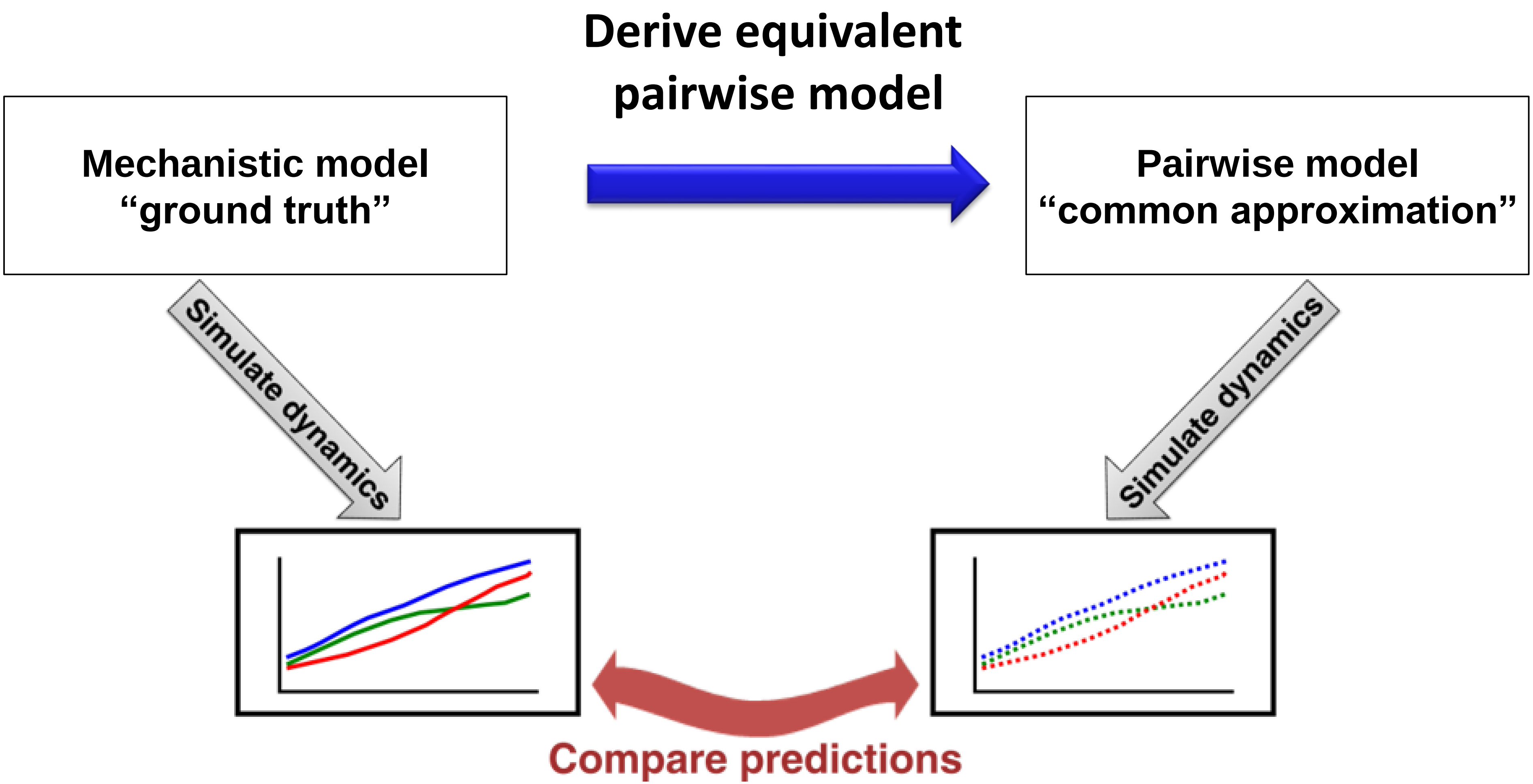
- Intrinsic assumptions
  - Pairwise interactions can be properly modeled
  - Interactions are independent



- Many interactions among species are mediated through chemicals
  - Beneficial metabolic exchanges
  - Inhibiting metabolic byproducts, toxins, and antibiotics

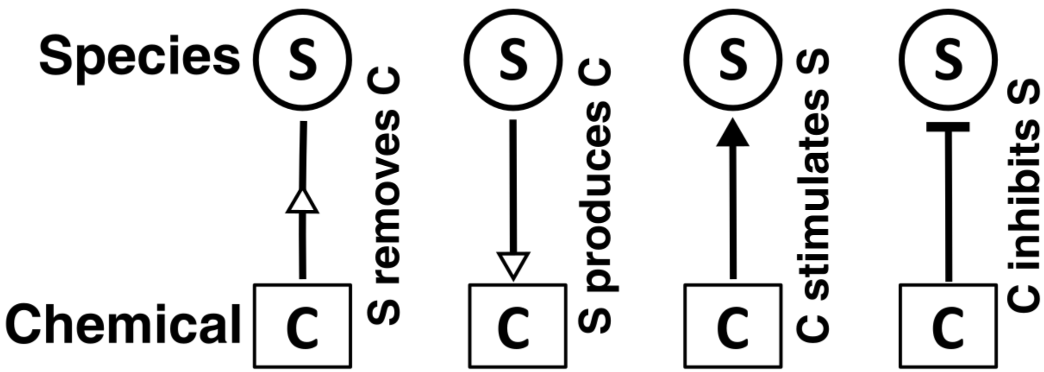
→ How do LV models handle interactions mediated through chemicals?

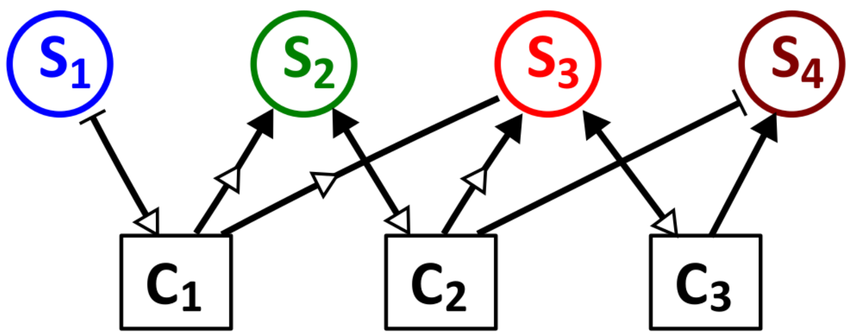
Comparing predictions: pairwise versus mechanistic



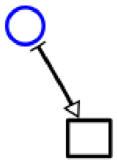
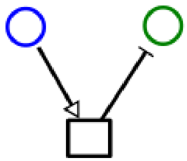
Mediator-explicit (ME) modeling

Explicitly incorporating chemical mediators of interactions in the model





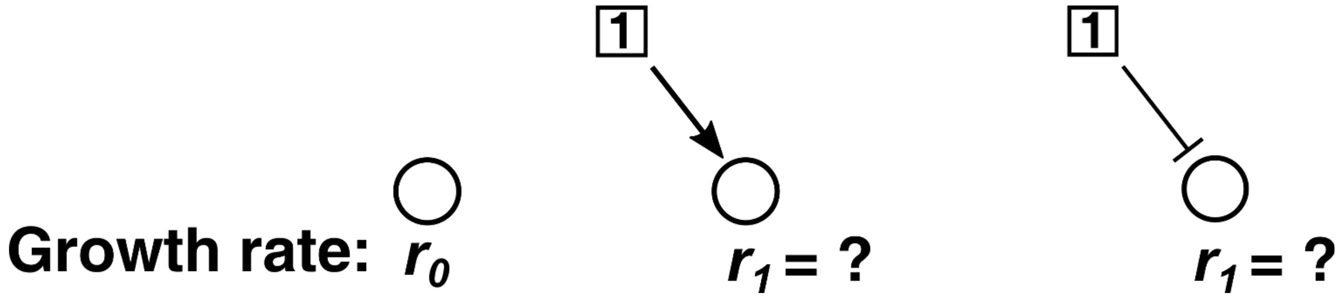
Examples of interactions among microbial species

Interaction			
Intrapopulation	**Interpopulation**	**Type**	**Example**
		**Target cell not degrading its inhibitor**	**Accumulation of end-products such as acetate (Kato et al. 2005) or ethanol (Gause 1934a)**

Assumptions of the mediator-explicit model

How to model the effect of individual mediators?

- Measure cell's response to sample mediators



- Our "guinea pig": *E. coli* MG1655 or environmental isolates *Brevibacillus agri* and *Pseudoxanthomonas taiwanensis*
- Choice of mediators:
  - Facilitators: carbon sources (e.g. glycerol); amino acids
  - Inhibitors: antibiotics (e.g. gentamicin); fermentation products (e.g. acetic acid)
- Read-out: growth rate in exponential phase

Modeling the effect of growth facilitators

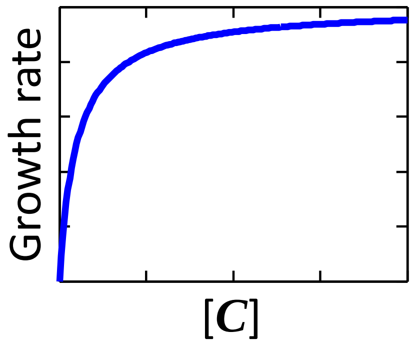
Assumptions:

- Single limiting resource, C
- Michaelis-Menten uptake of resources
- Cells divide after acquiring enough of the limited resource

$$\frac{\Delta S}{\Delta t} = \frac{(uptake\ rate\ per\ cell)\times(cell\ \#)}{amount\ required\ to\ build\ a\ cell} = \frac{v_M C/(C+K)}{\alpha} S$$

Or

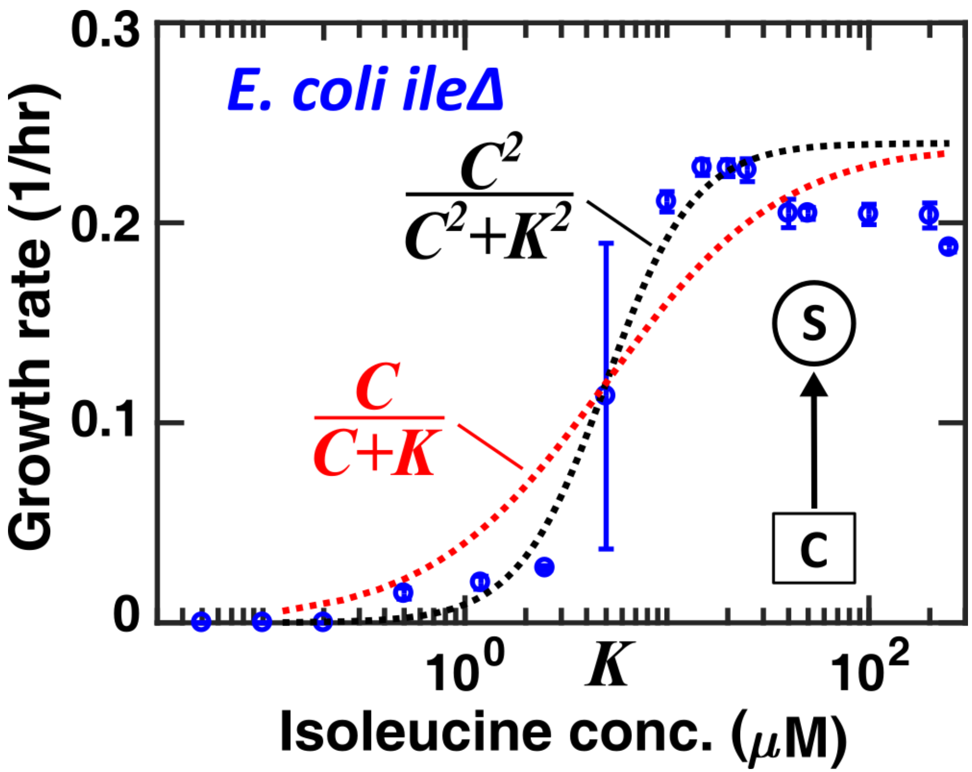
$$\frac{dS}{dt} = r_M \frac{C}{C+K} S$$



Experimental test of the effect of single facilitators

Isoleucine facilitation (for isoleucine auxotrophic *E. coli*)

- Measured exponential growth rate at different concentrations



- Data suggests transition is often steeper:

$$\frac{dS}{dt} = r_M \frac{C^n}{C^n + K^n} S \;\; ; n > 1$$

Modeling the effect of growth inhibitors

Assumptions:

- Cell-inhibitor random encounter in a well-mixed environment
- Upon encounter, cells die with a fixed probability, p_d
- Motivated by ecological models of prey-predators, chance of encounter per unit time is proportional to SC (S: cell density, C: inhibitor conc.)

Change in population size in unit time

= cells born – cells dead due to inhibitorencounter

$$\frac{\Delta S}{\Delta t} = r_0 S - p_d r_e S C$$

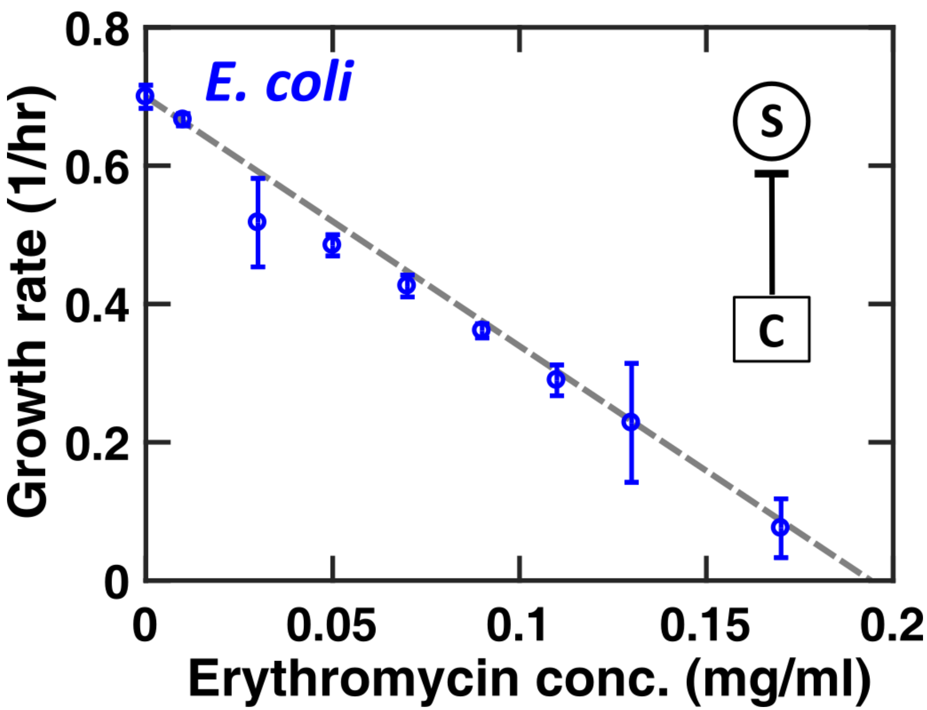
Or

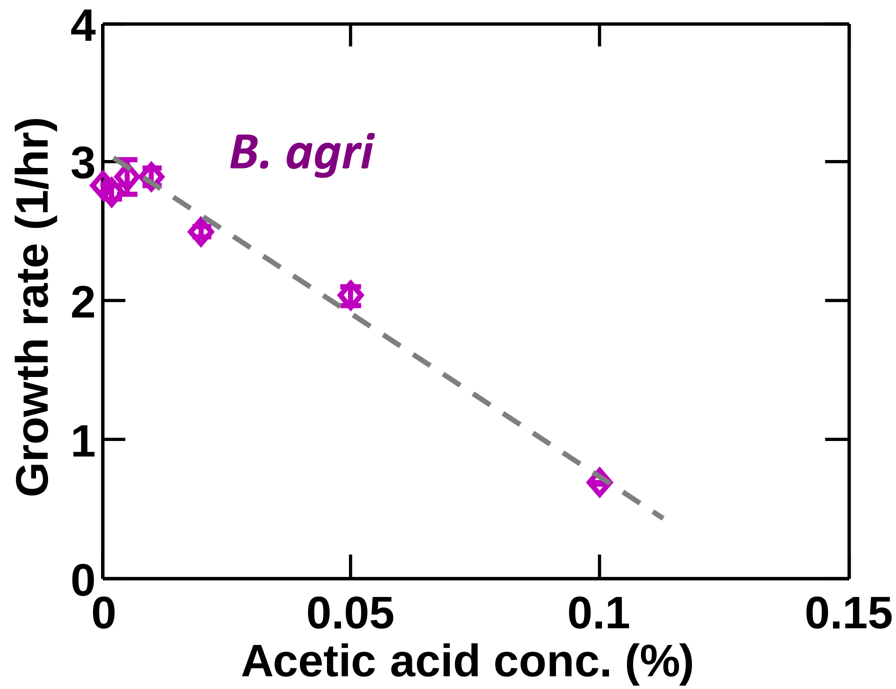
$$\frac{dS}{dt} = \left(r_0 - \eta C\right) S$$

Experimental test of the effect of single inhibitors

Acetic acid and erythromycin inhibition

- Measured exponential growth rate at different concentrations



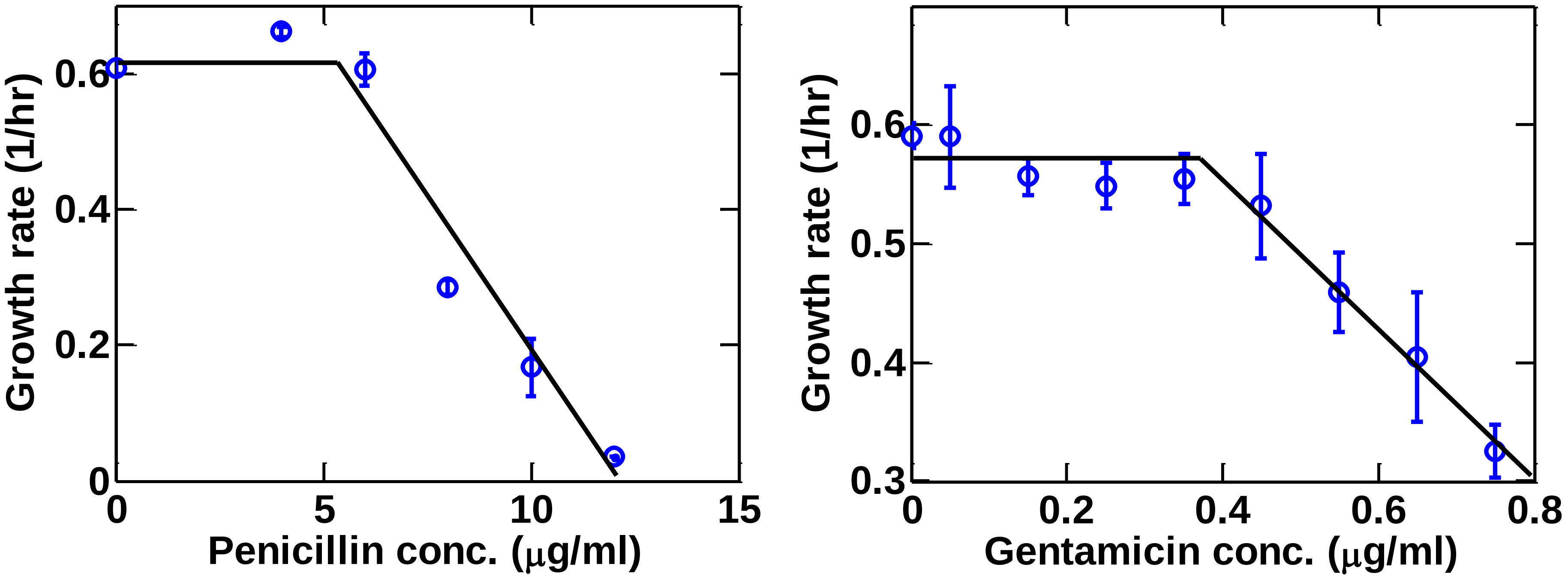


- In many cases:

$$\frac{dS}{dt} = \left(r_0 - \eta C\right) S$$

Experimental test of the effect of single inhibitors

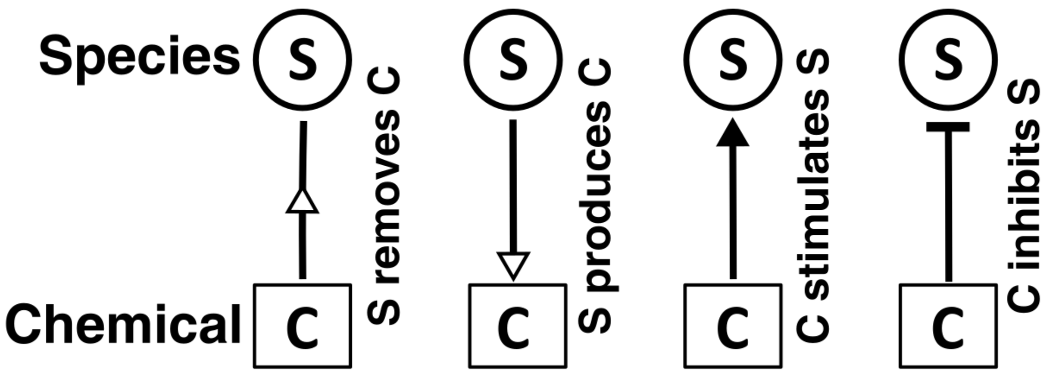
With some antibiotics, inhibition is effective beyond a threshold conc.

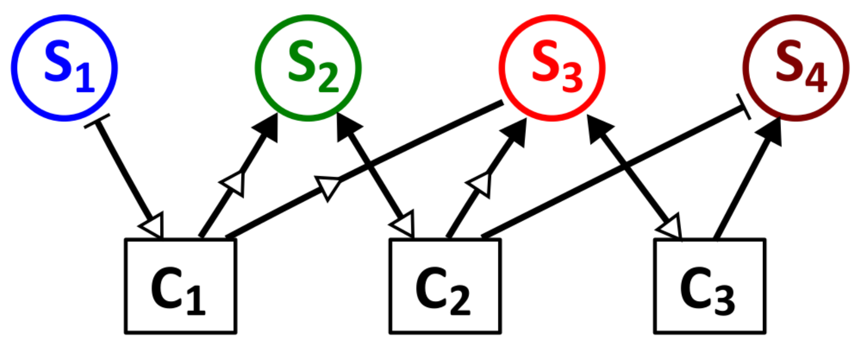


$$\frac{dS}{dt} = \begin{cases} r_0 S & ; \quad C \le C_{th} \\ r_0 S - \eta S (C - C_{th}) & ; \quad C > C_{th} \end{cases}$$

Mediator-explicit (ME) modeling

Explicitly incorporating chemical mediators of interactions in the model

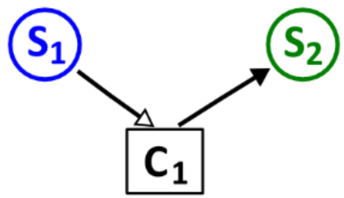




LV does not capture chemical mediated interactions

Can the canonical LV model represent all microbial interactions?

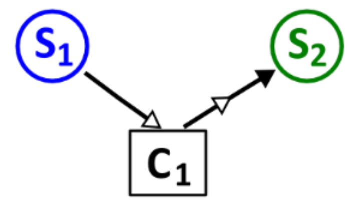
Reusable



$$\frac{dS_2}{dt} = r_{20}\, S_2 + r_{21} \frac{S_1}{S_1 + K_{21}} S_2$$

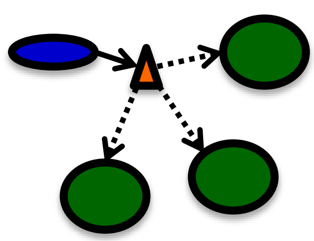
Saturable LV model

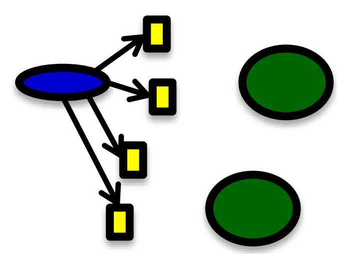
Consumable



$$\frac{dS_2}{dt} \approx r_{20}\, S_2 + r_{S_2 C_1} \frac{S_1}{\omega S_1 + \psi S_2} S_2$$

Divided influence model

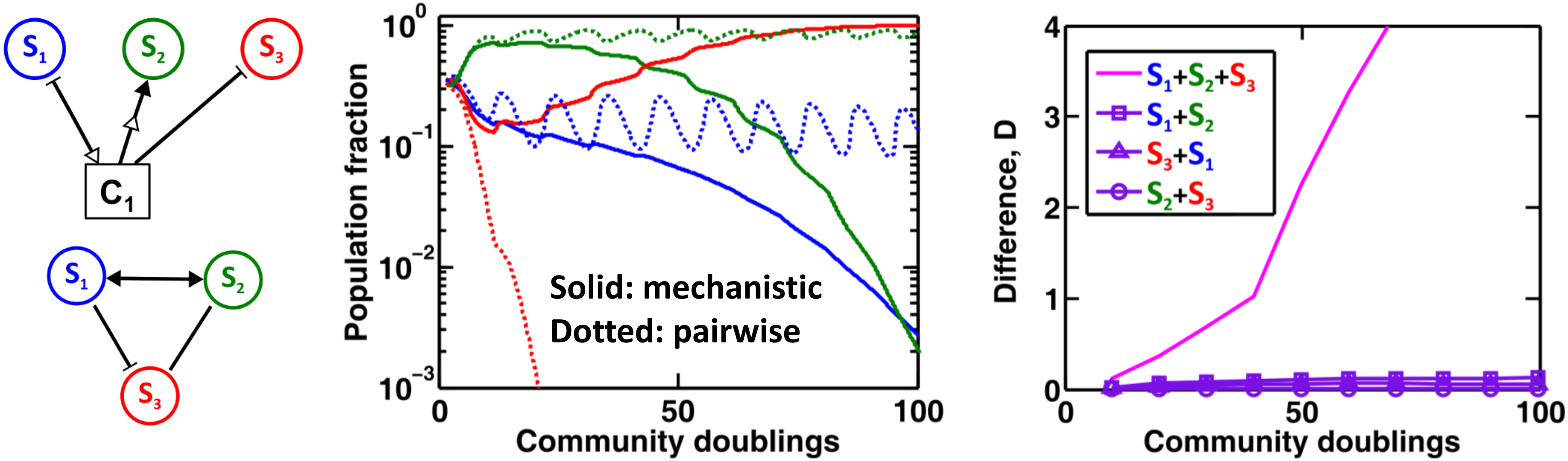




Momeni, Xie, and Shou, *eLife* 2017.

LV does not capture chemical mediated interactions

Can the model be extended beyond two-species communities?



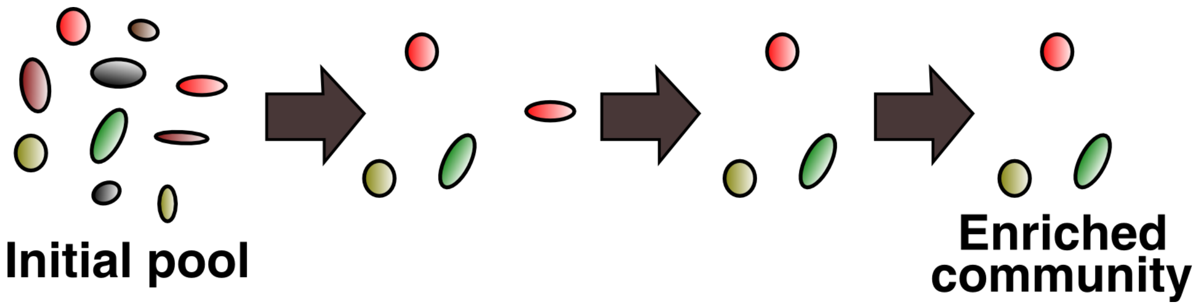
Momeni, Xie, and Shou, *eLife* 2017.

Coexistence of species in microbial communities

How does the interaction network among species lead to their coexistence?

Insights from common features of simulated coexistence

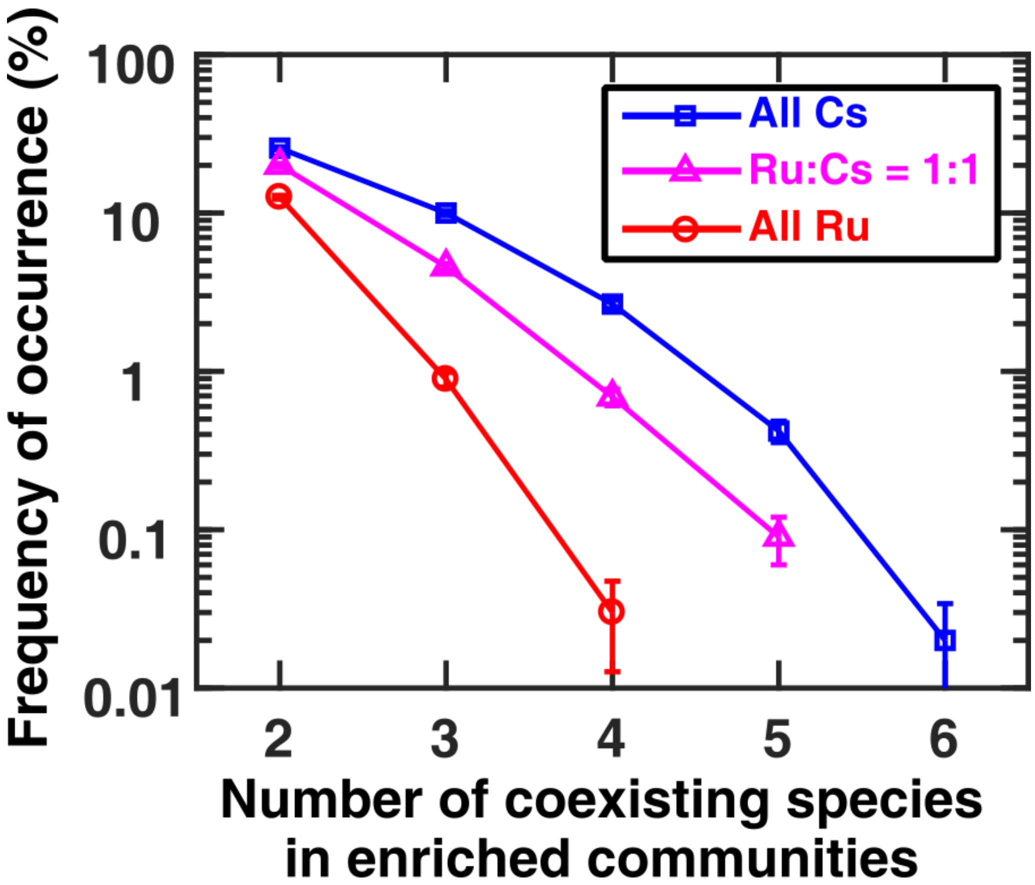
- Procedure:
  1. Simulate the enrichment process to get coexisting species (~200 gen.)



  2. Repeat, using other parameters of the initial pool (randomly) to make an ensemble of communities that show species coexistence
  3. Look for commonalities in network properties of coexisting species

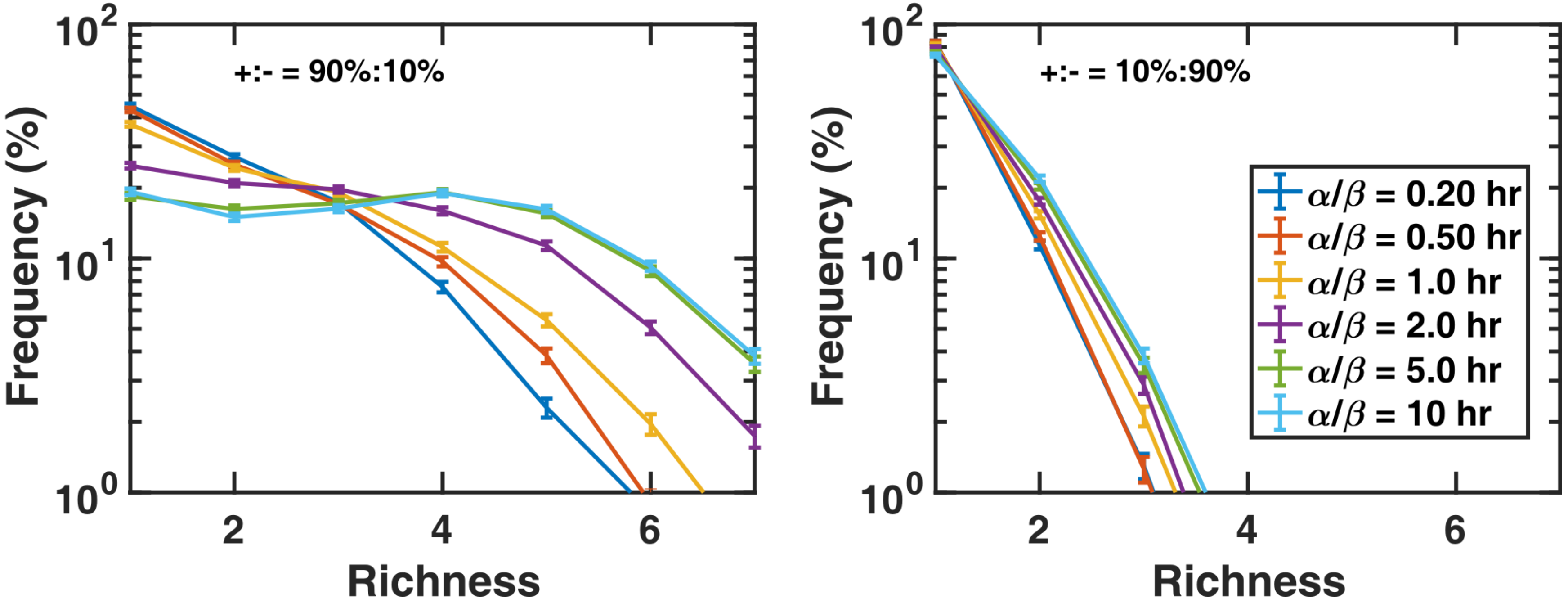
Interaction mechanisms affect coexistence outcomes

- Comparing the same network of interactions with either consumable or reusable mediators



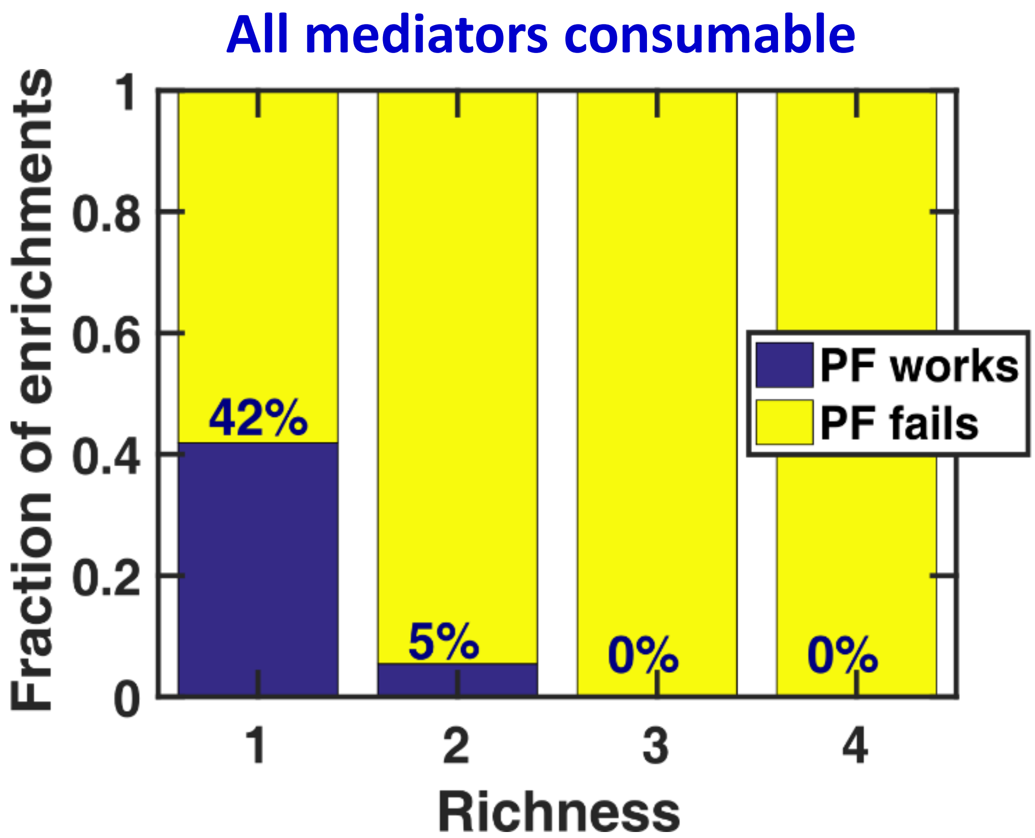
Interaction mechanisms affect coexistence outcomes

- Consumption/degradation of mediators by cells has a pronounced impact on coexistence



LV model fails to accurately predict coexistence

- Comparing coexistence predictions between a reference mediator-explicit model and a corresponding pairwise model

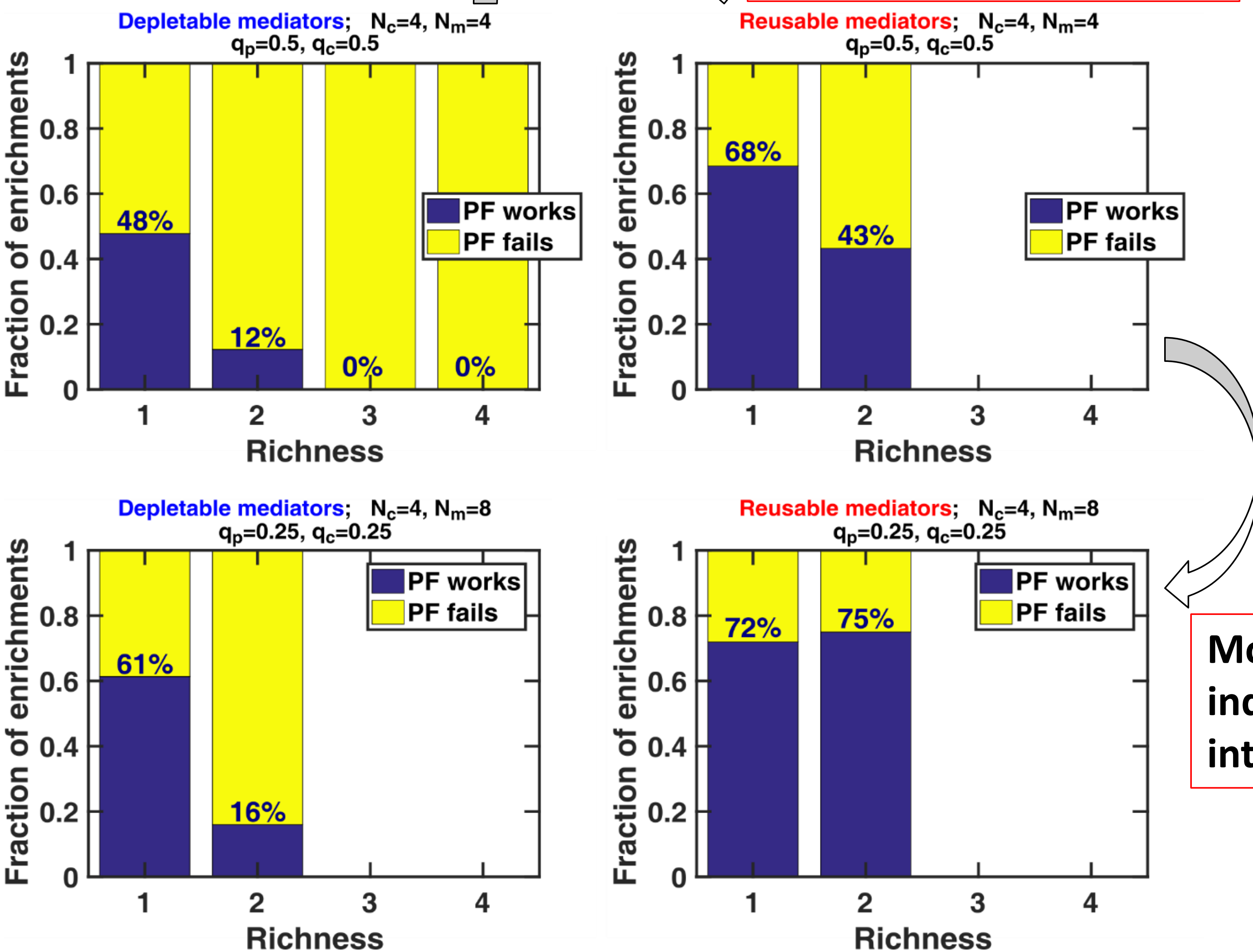


- Are there conditions under which LV works well?

LV model predicts coexistence under certain conditions

What matters?

More reusable mediators



More independent interactions

Summary

- A mediator-explicit model resolves some of the issues of pairwise Lotka-Volterra models, allowing a more realistic study of coexistence
- Interaction mechanisms (e.g. mediation through a reusable or a consumable chemical) seem to be important for coexistence predictions; thus motivating more mechanistic studies of interactions
- Pairwise LV models fail to predict coexistence when
  - Diverse interactions cannot be represented by a single LV equation
  - Interactions are not independent because of shared mediators
- What to do then?

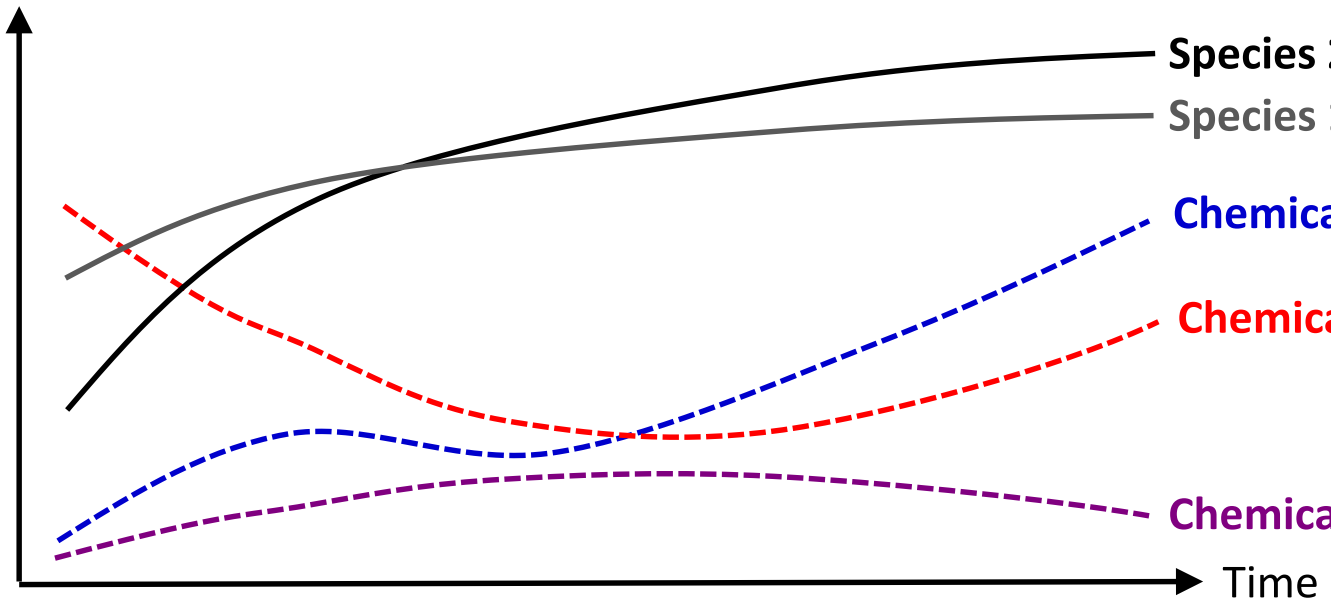
Characterizing chemical-mediated interactions

Q1. Are there general equations that would adequately capture common chemical-mediated interactions?

Q2. How often are mediators shared (and interactions are interdependent)?

→ Systematically surveying chemical-mediated interactions

- Chemical profiling (colorimetric/fluorimetric assays, MS, NMR, etc.)
- **Challenge:** unclear *a priori* what chemicals are influential



Coordinating the efforts to model microbial interactions

1. **Database of microbe-microbe interactions**
   - Ongoing (to be made public soon)

2. **Accessible user interface for simulating known mechanisms**
   - Engaging both theorists and experimentalists

3. **Aggregation of raw interaction assay data (species + chemicals)**
   - What is the proper format?

Thank you!

Questions?

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