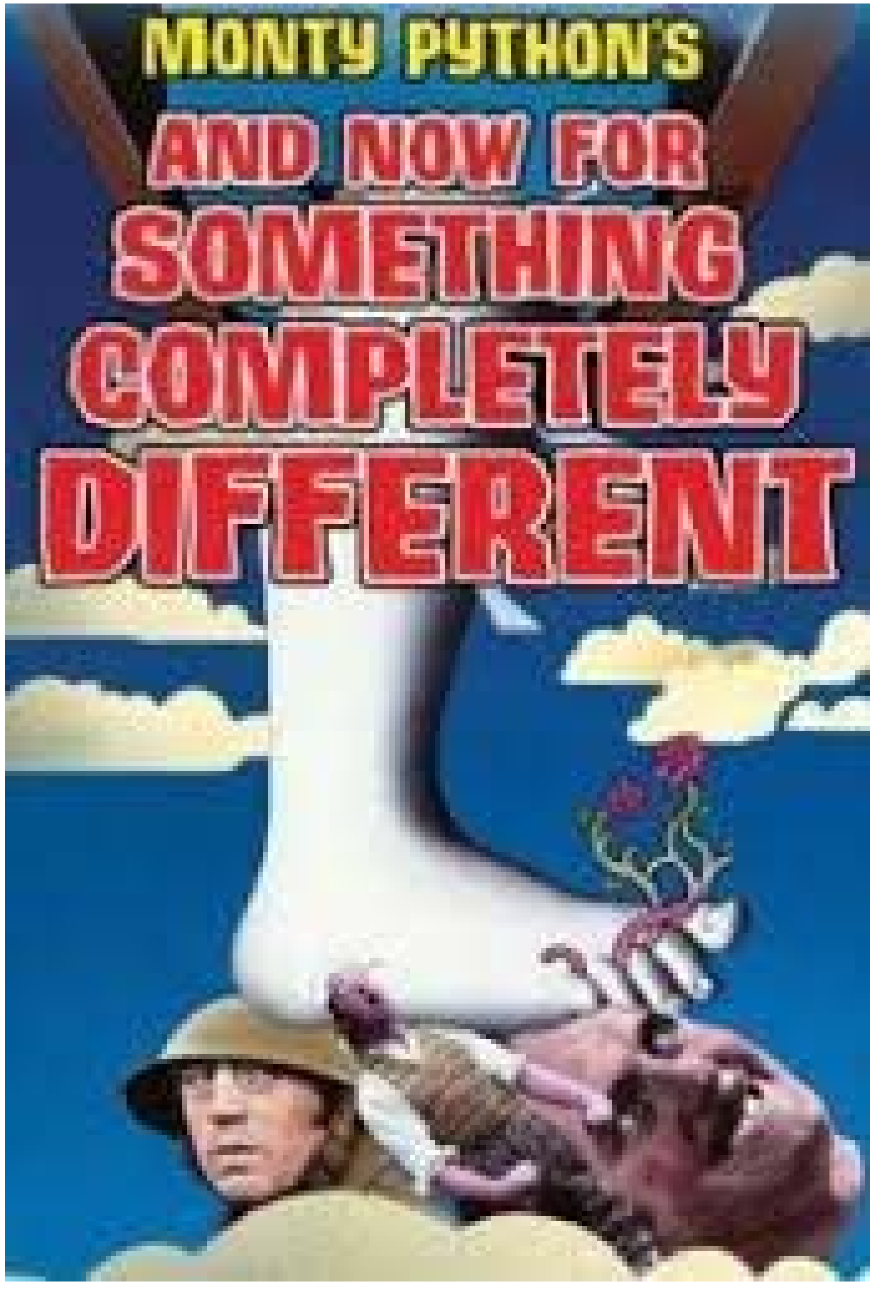
MONTY PYTHON'S
AND NOW FOR
SOMETHING
COMPLETELY
DIFFERENT

What's love got to do with it? Stable marriage in microbial ecosystems

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Carl R. Woese Institute for Genomic Biology,

University of Illinois at Urbana-Champaign

Microbial ecosystems are everywhere & they are important

- They affect our health: human microbiome impact obesity, allergies, GE problems, and may even mess with neural processes (gut-brain axis)
- They feed us: soil microbiome and plant rhizosphere help plants grow, decompose waste
- They help us breathe: Phototrophs in the ocean generate >50% of oxygen. Affect climate by modulating carbon sink

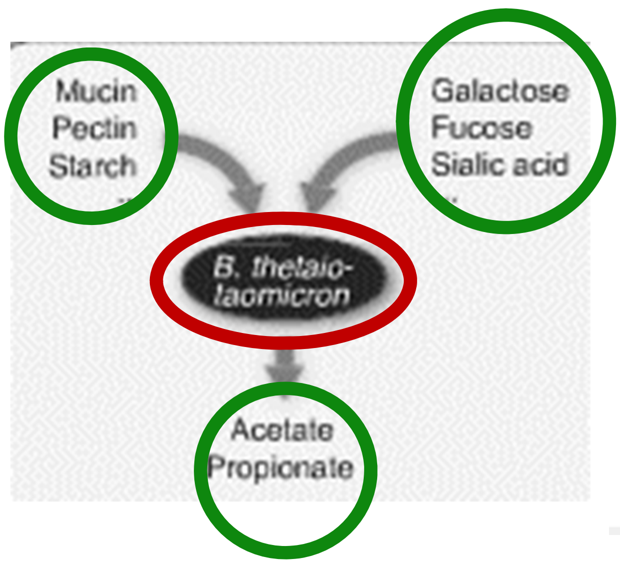
What we would like to understand?

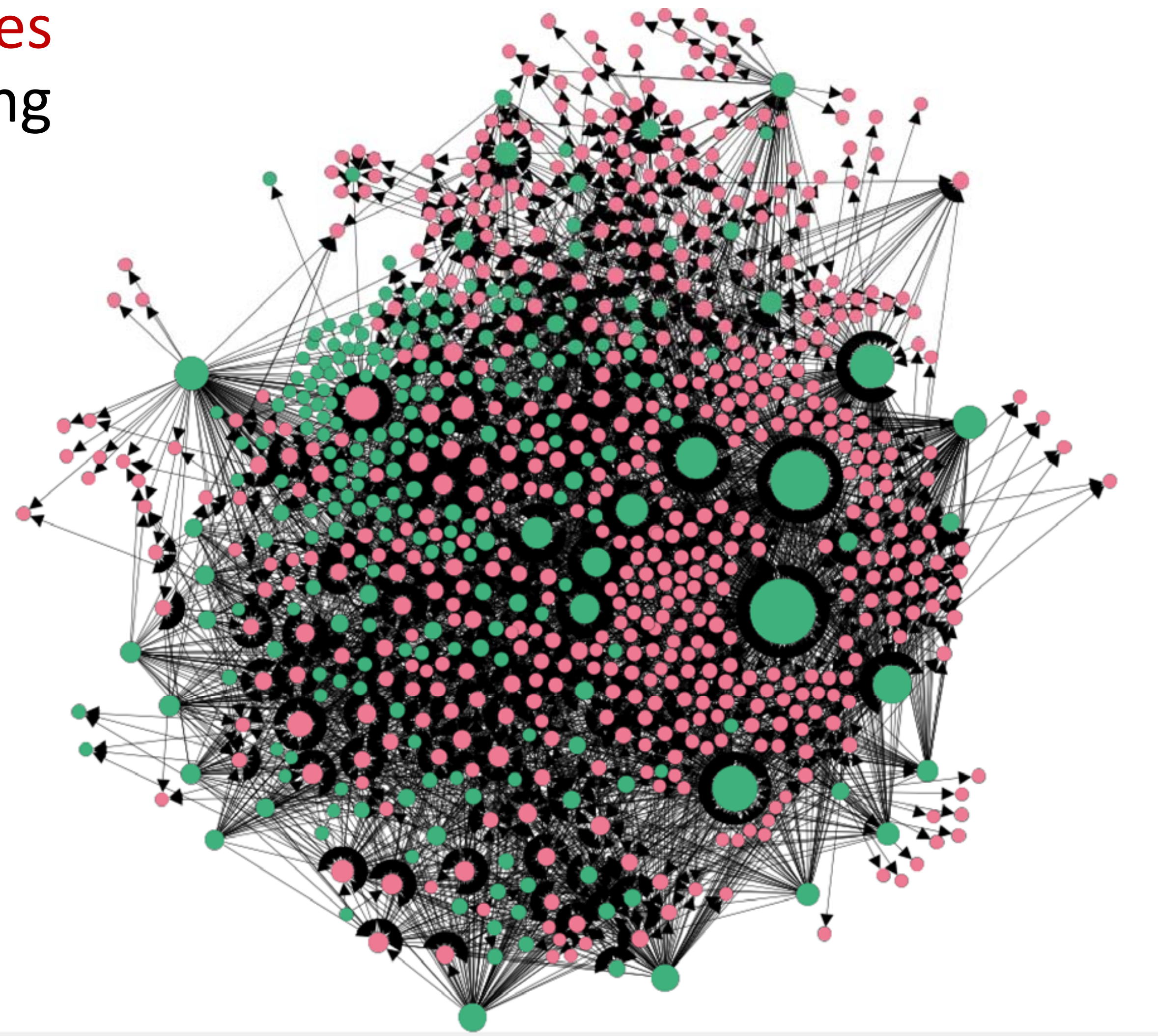
- **Diversity**: how 100s of species can coexist?
  - How to reconcile this with **competitive exclusion principle** due to Darwinian competition?
- **(Multi)stability**: how many stable states an ecosystem has? How to control them?
  - How **robust** are **stable states** with respect to **environmental fluctuations** and new species **invasions**?
  - How can we **control** and manipulate these states and cause **transitions** between them?
- **Reproducibility**: how different is species composition of ecosystems in similar environments?
  - What distinguishes **core species** from variable **peripheral species**?
  - Why **U-shaped distribution** of species **prevalence**?

Metabolic interactions in human gut microbiome are complex

570 human gut microbes
consuming and excreting
244 metabolites.

Data from Sung et al.
Nature Comm, **8**
15393 (2017).





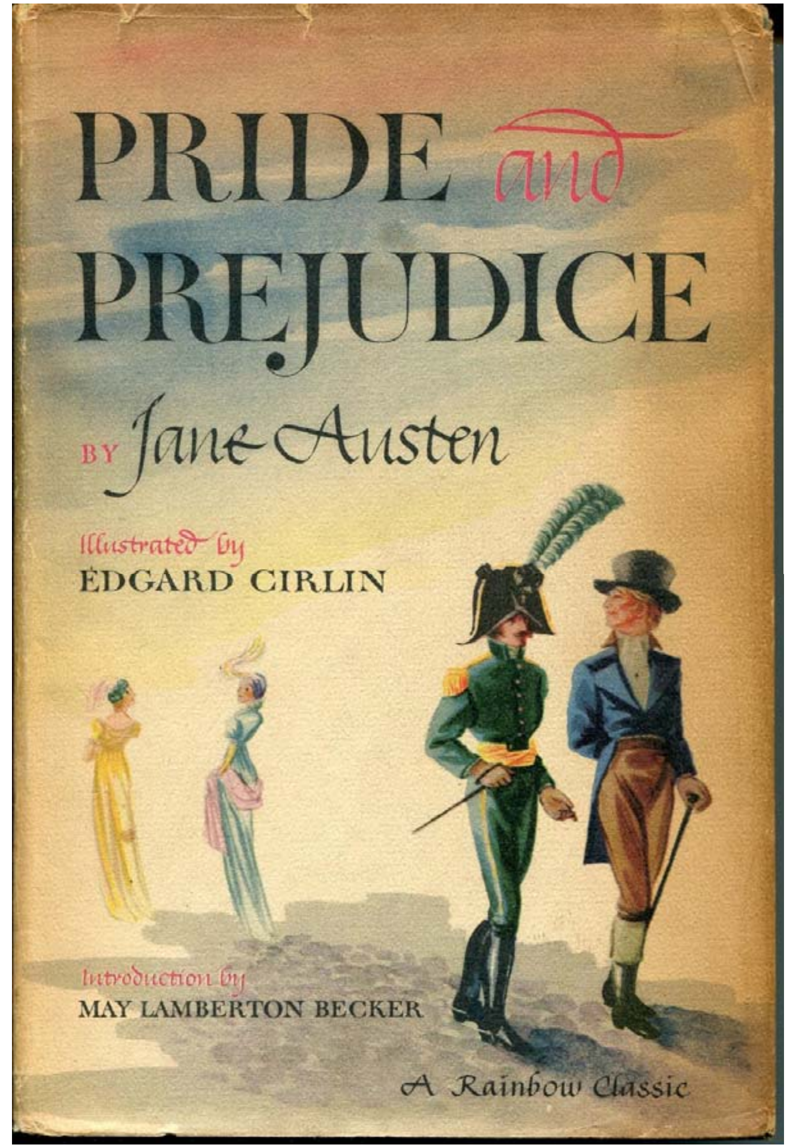
Network is just the skeleton of a model

- OR-gate or AND-gate on inputs ?
  Expected to have AND-gate on essential resources C, N, P, S, Fe….
  - **Model 1**: many C and N resources and microbes with AND-gate.
    Manuscript in preparation.
    For realization in autocatalytic polymers see:
    Tkachenko AV, Maslov S (2017),
    bioRxiv 204826; https://doi.org/10.1101/204826
- If OR-gate: are nutrients used all-at-once or one-at-a-time?
  - **Model 2**: microbes utilize their nutrients one-at-a-time
    Goyal A, Dubinkina V, Maslov S, ISME (2018),
    bioRxiv 235374 (2017); https://doi.org/10.1101/235374
- What inputs generate what byproducts?
  - **Model 3**: single carbon source but many trophic levels. Microbes in higher levels live off byproducts of microbes in lower levels
    Goyal A, Maslov S (2018) Cover of Phys. Rev. Letters, Editor's selection,
    Faculty of 1000 https://doi.org/10.1103/PhysRevLett.120.158102

Multiple states and their control in the "Stable Marriage" approach

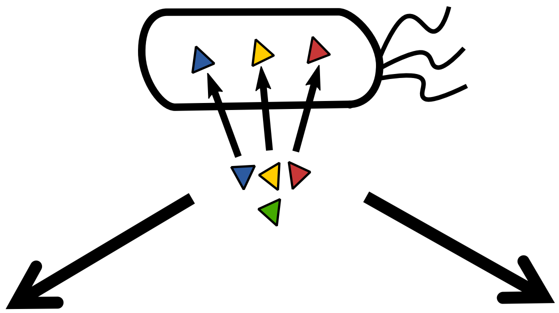
(Model 2)

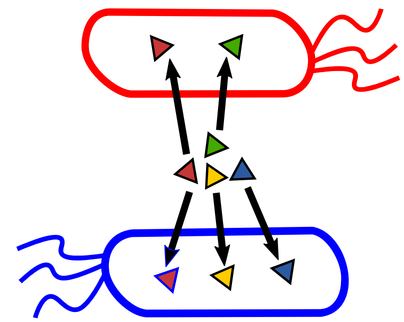
Goyal A, Dubinkina V, Maslov S, ISME Journal (2018)



How each microbe uses nutrients?

How microbes divide nutrients?





One nutrient at a time: diauxie

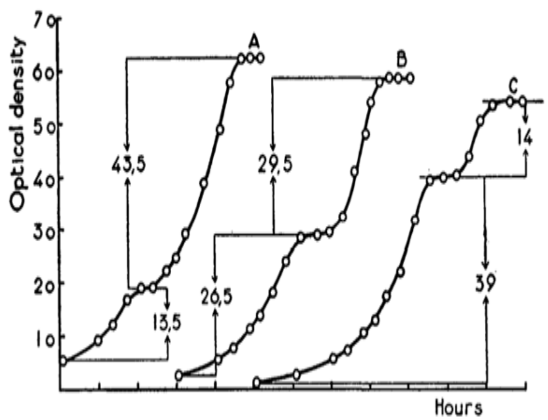


FIG. 9.—Diauxie. Growth of *E. coli* in synthetic medium with glucose+sorbitol as carbon source.

Known since Monod (1949)

Co-utilization:

Assumed in most models since MacArthur (1969)

Microbe's preferences towards metabolites are encoded in its regulatory network. Preferences of even closely related microbes could be quite different from each other (for Bacteroides see Tuncil et al, mBIo 2017

Competitive exclusion:

If two or more microbes compete for the same resource, the microbe with the strongest affinity wins

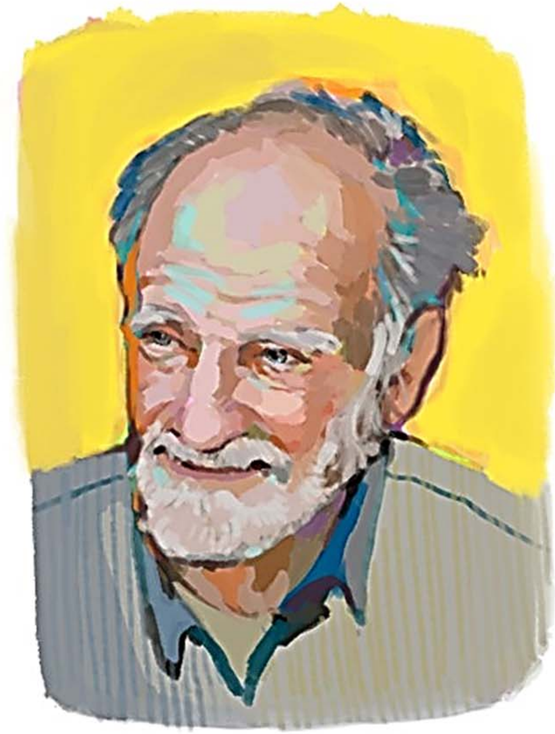
Monogamous marriage of microbes to resources

- Each microbe uses one resource at a time (diauxic shift) and each resource is used by no more than one microbe (competitive exclusion)
- Marital bliss is based on only **two ranked lists**: microbes' order of preferences towards resources and resources' "preferences" = microbes' competitive abilities for this resource.
- To predict steady states **no need to know** the detailed biochemical parameters[1]

[1] To describe the catabolic repression in **just one microbe** people used models with up to **282 variables** and up to **476 parameters**

Stable Marriage Problem

David Gale (1921-2008)
PROFESSOR, UC BERKELEY

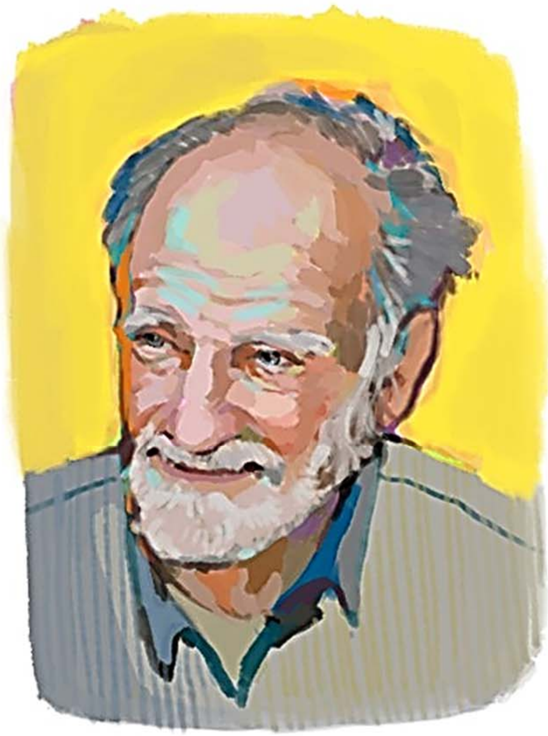


Lloyd Shapley
PROFESSOR EMERITUS, UCLA

D. Gale & L. S. Shapley, College Admissions and the Stability of Marriage
The American Mathematical Monthly, 69, 9-15 (1962)

Nobel Prize in Economics 2012
"for the theory of **stable allocations**…"

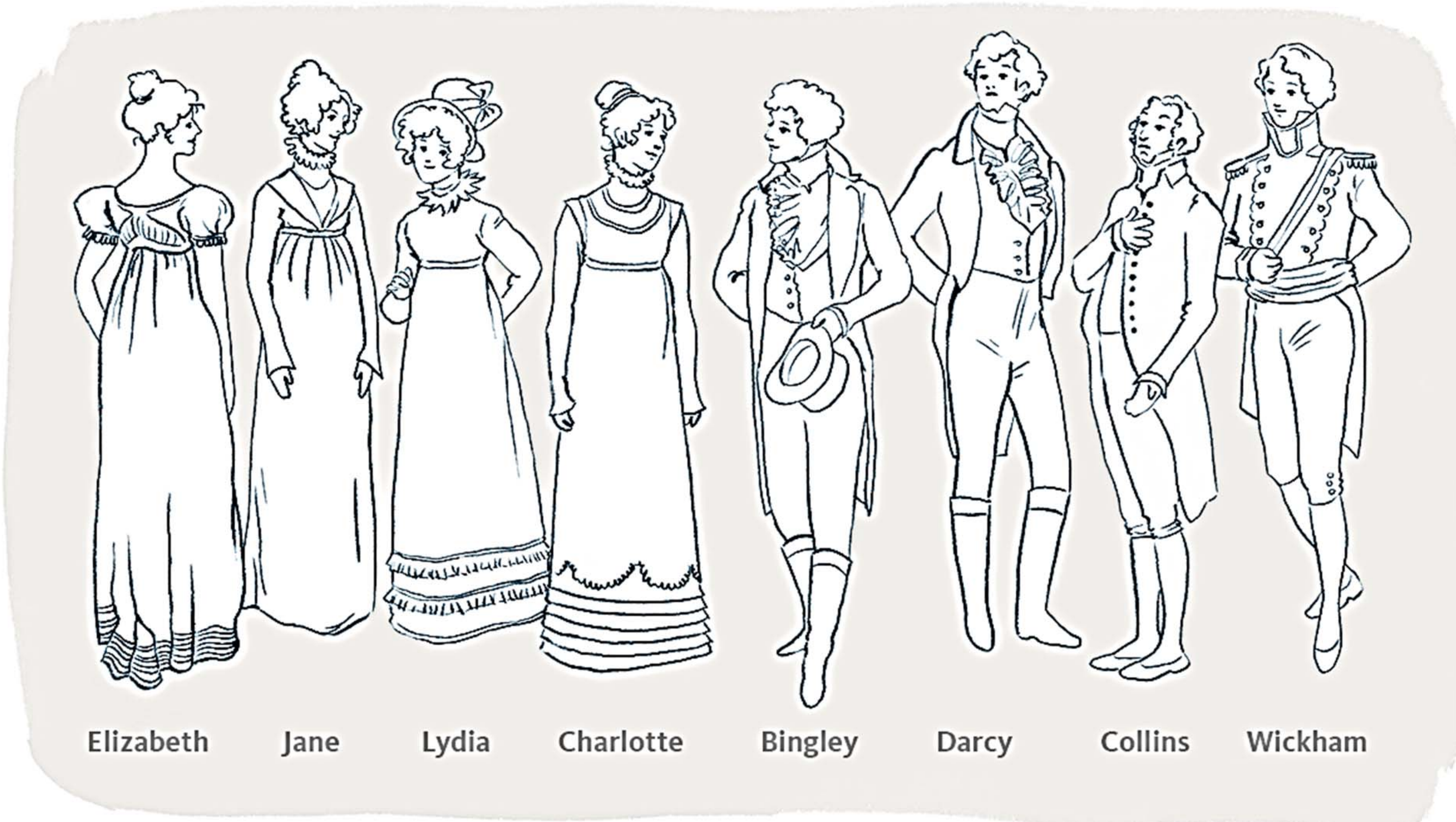
Alvin Roth
PROFESSOR, STANFORD



Lloyd Shapley
PROFESSOR EMERITUS, UCLA

https://medium.com/@UofCalifornia/how-a-matchmaking-algorithm-saved-lives-2a65ac448698

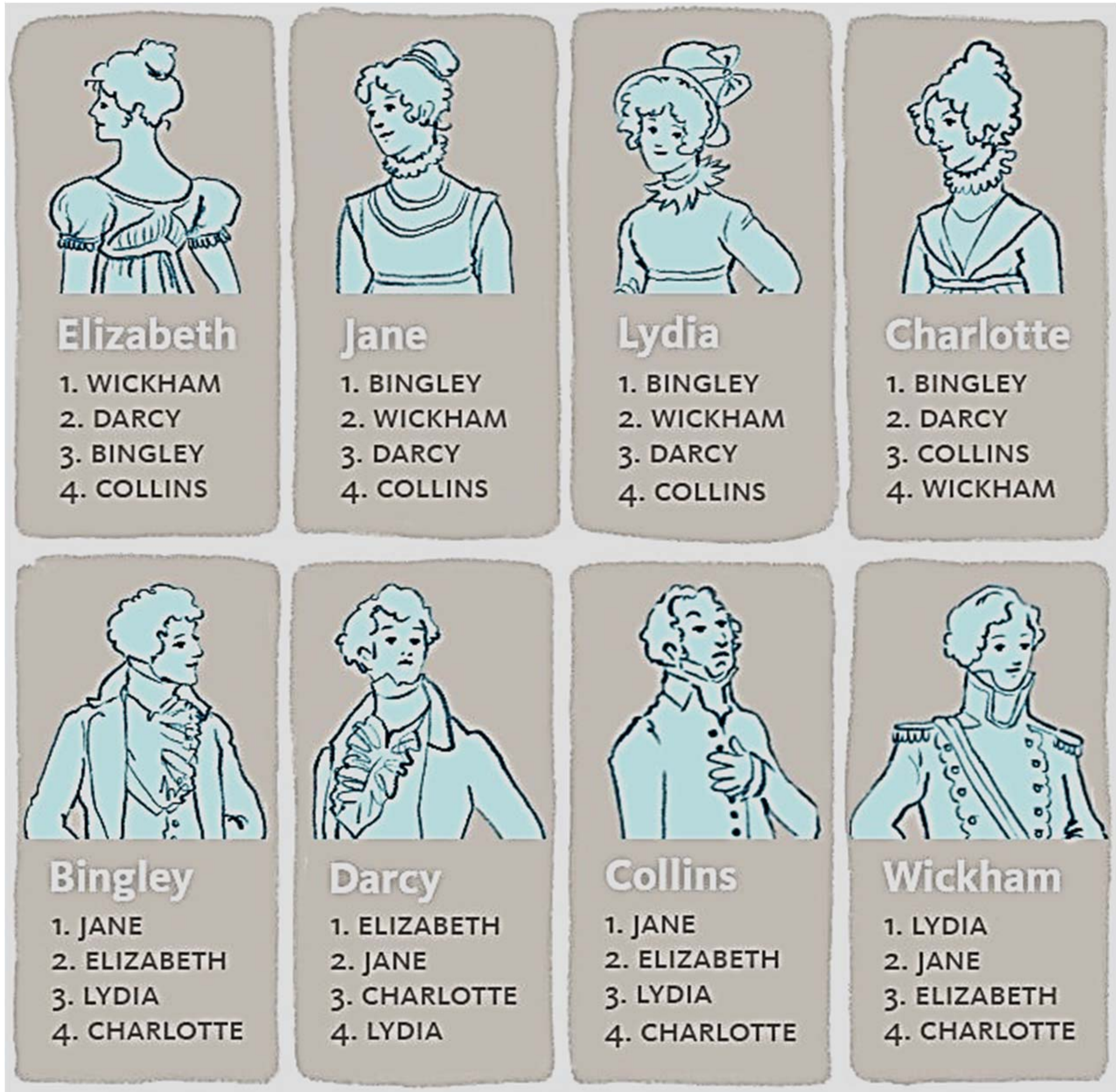
Consider a group of men and women who all know each other



https://medium.com/@UofCalifornia/how-a-matchmaking-algorithm-saved-lives-2a65ac448698

Inspired by Jane Austin's "Pride and Prejudice"

They rank each other as potential partners



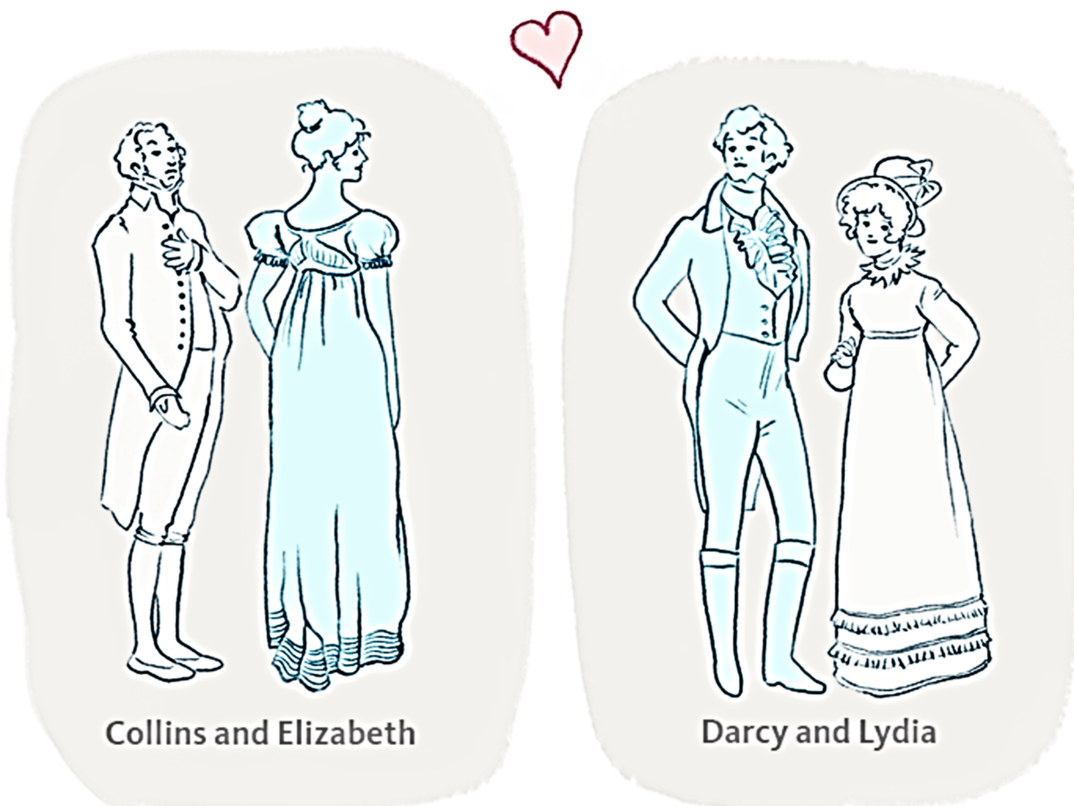
https://medium.com/@UofCalifornia/how-a-matchmaking-algorithm-saved-lives-2a65ac448698

And ultimately get married to each other

https://medium.com/@UofCalifornia/how-a-matchmaking-algorithm-saved-lives-2a65ac448698

Is this marriage stable?

An unstable marriage has at least one "blocking pair"
each preferring the other to his/her spouse



An unstable match:
ELIZABETH AND DARCY LIKE EACH OTHER BETTER THAN THEIR PARTNERS

https://medium.com/@UofCalifornia/how-a-matchmaking-algorithm-saved-lives-2a65ac448698

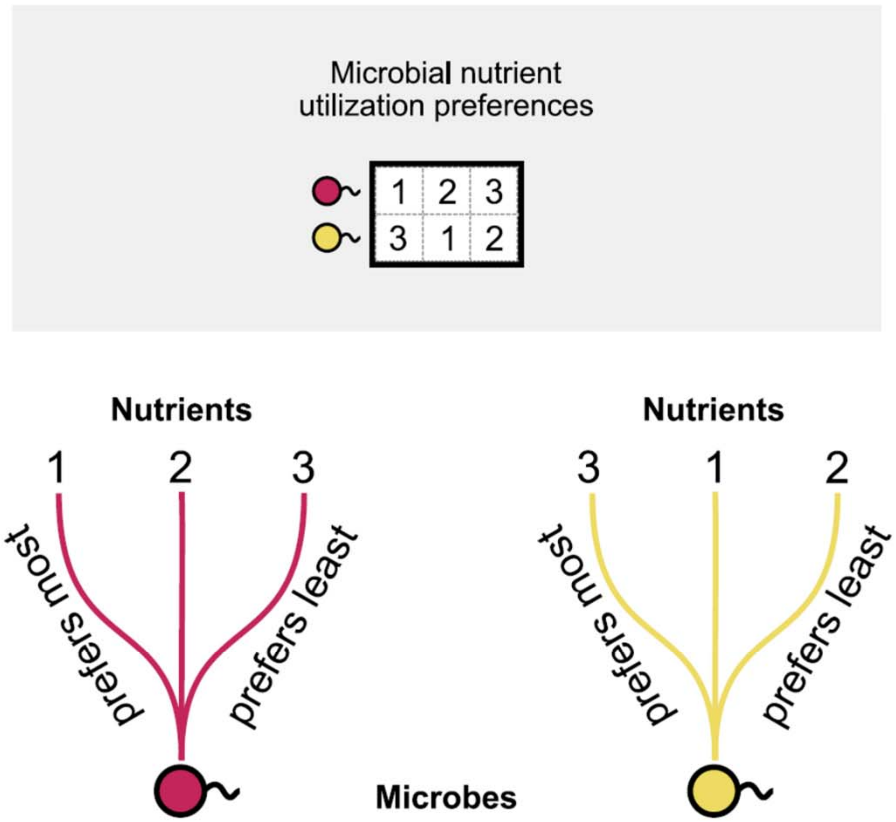
Is there a stable marriage?

How to find it?

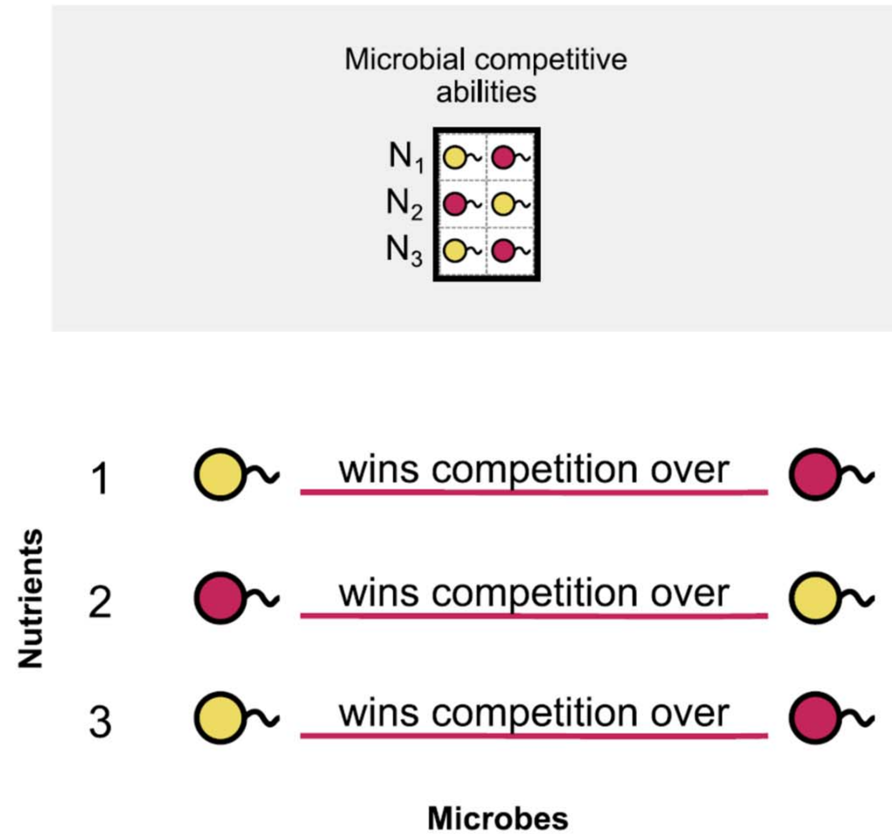
Gale-Shapely or men-proposing algorithm

- On the first day every man proposes to the top woman on his list
- If a woman receives more than one proposal, she is getting engaged with the top proposer according to her list and dismisses the rest of suitors
- Next day each among dismissed men propose to the second woman on his list, and so on….
- It is proven that the resulting set of marriages is **stable**
- Every man gets **the best** woman he can have in a stable marriage
- Every woman gets **the worst** man she can have in a stable marriage
- Women-proposing algorithm → usually another stable state
- **All stable states** can be found from the men-optimal one by women initiating divorces and men going down their lists

Marriage model in microbes

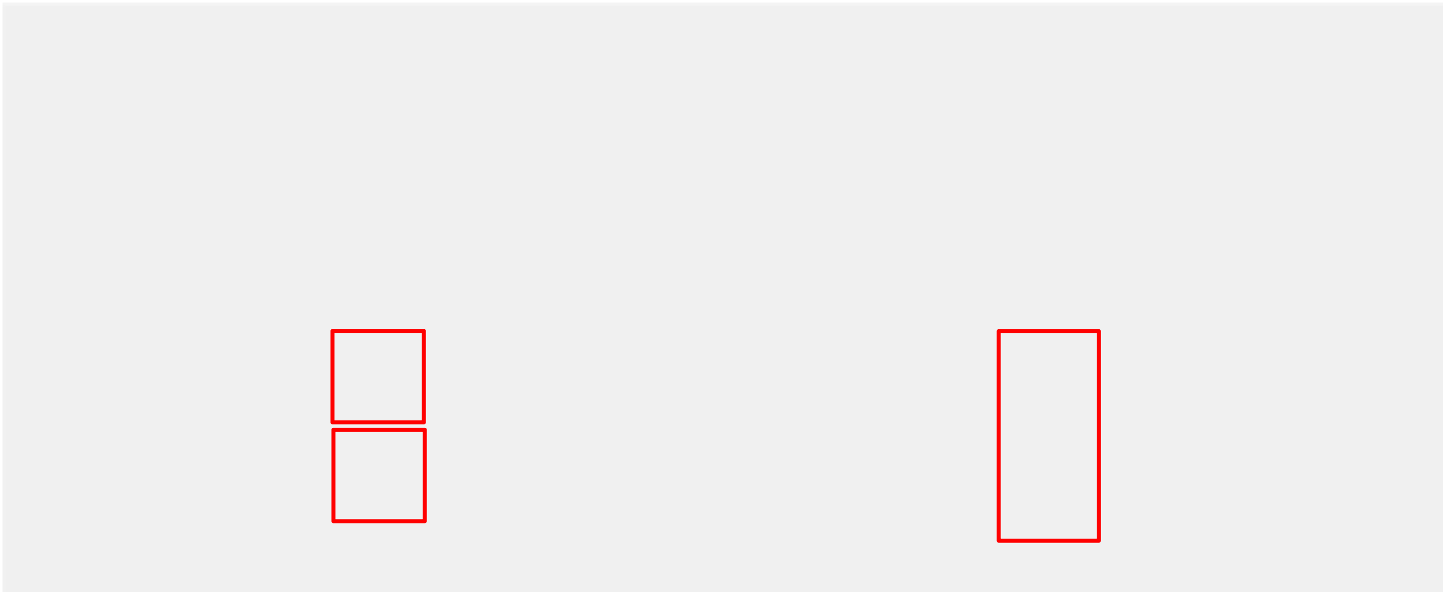


Nutrient preferences

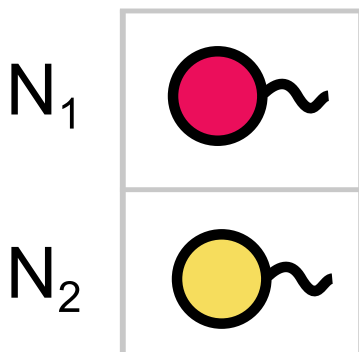


Competitive abilities

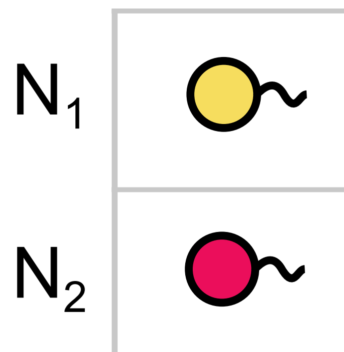
Microbial love ~~triangle~~ square



Microbe-optimal
stable state 1

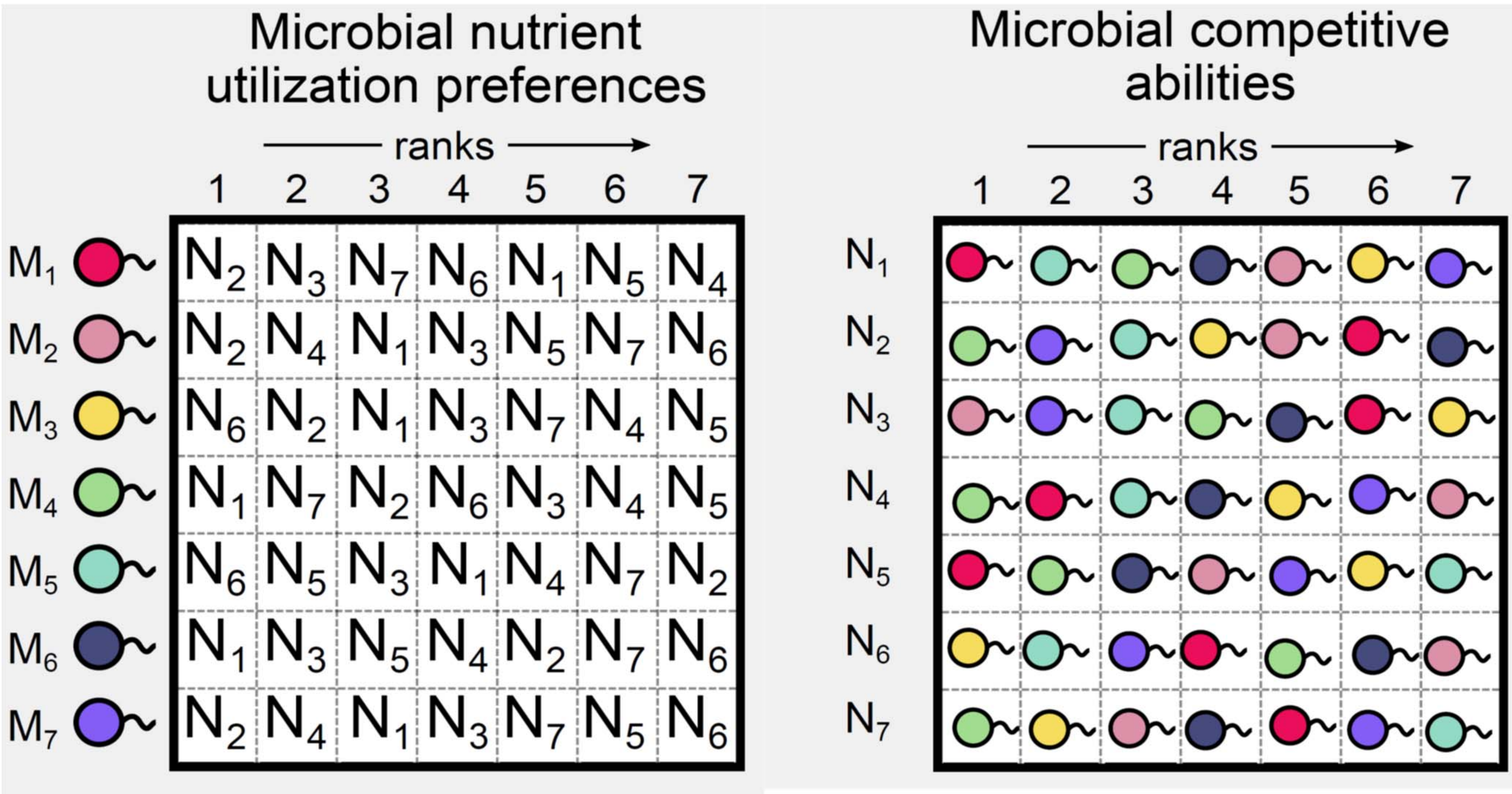


Nutrient-optimal
stable state 2



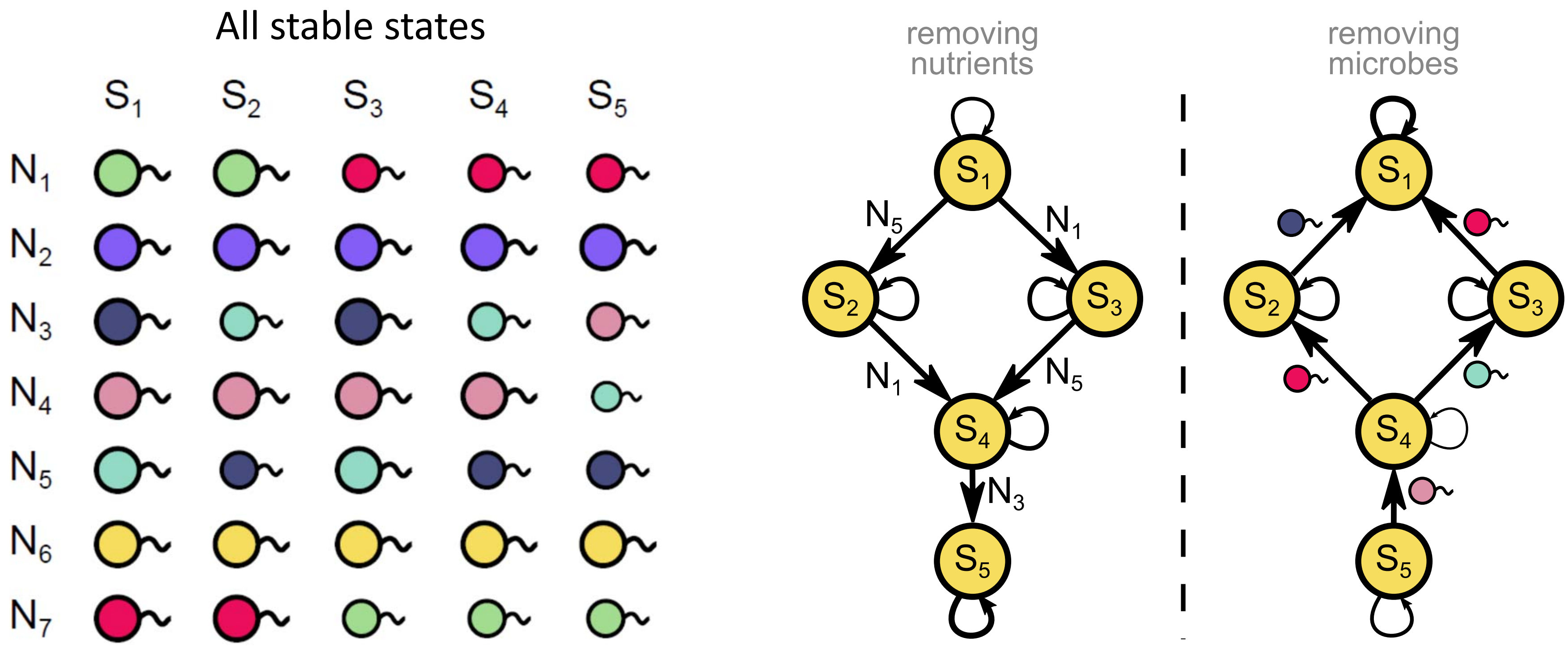
Goyal A, Dubinkina V, Maslov S (2017), ISME in press, bioRxiv: https://doi.org/10.1101/235374

Example: 7 microbes, 7 nutrients



Goyal A, Dubinkina V, Maslov S (2017), ISME in press, bioRxiv: https://doi.org/10.1101/235374

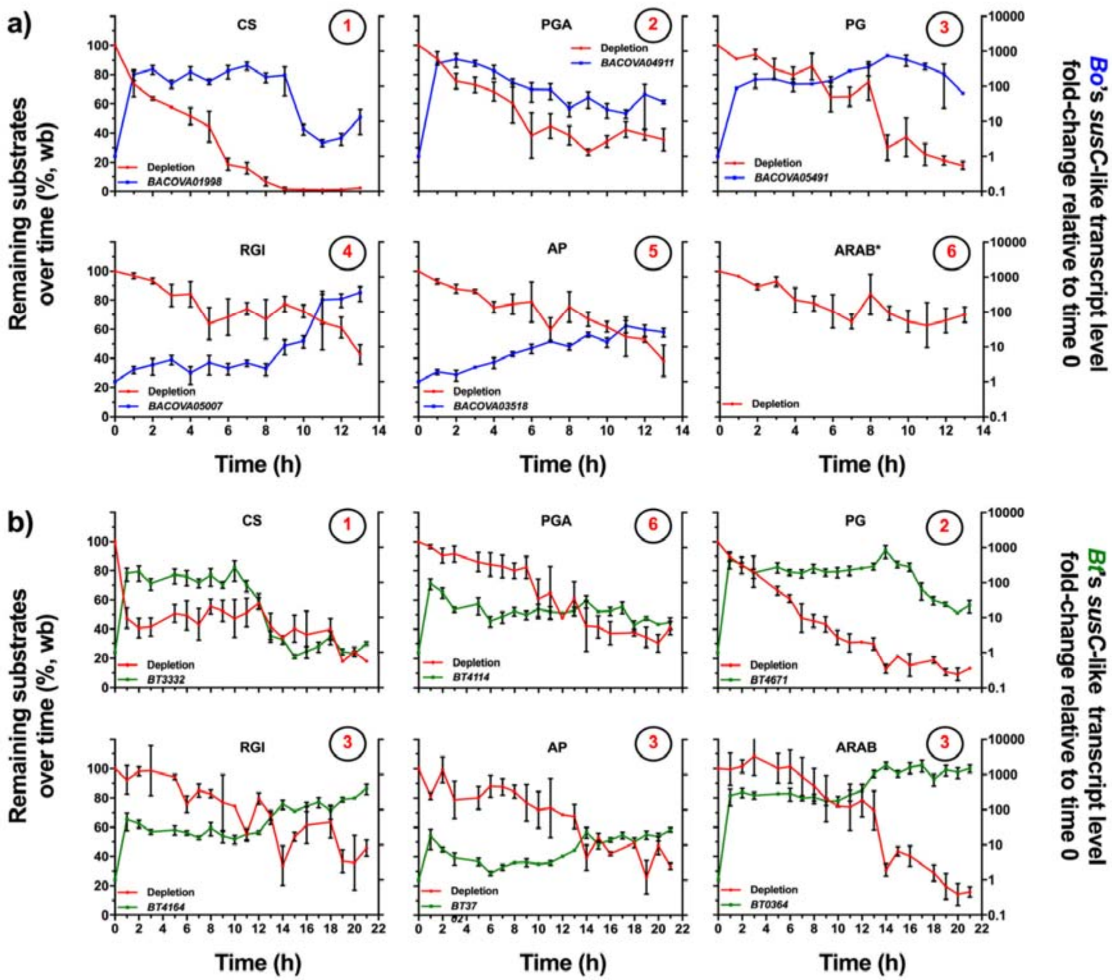
Hierarchy of stable states



- Random lists: ~(N/e)*log N stable states
- # of stable states can be made exponentially large for really messed up lists
- Correlated lists between men-men, women-women, or men-women reduce the # of stable states

Goyal A, Dubinkina V, Maslov S (2017), ISME in press, bioRxiv: https://doi.org/10.1101/235374

Closely related Bacteroides species in human gut have different preferences towards polysaccharides

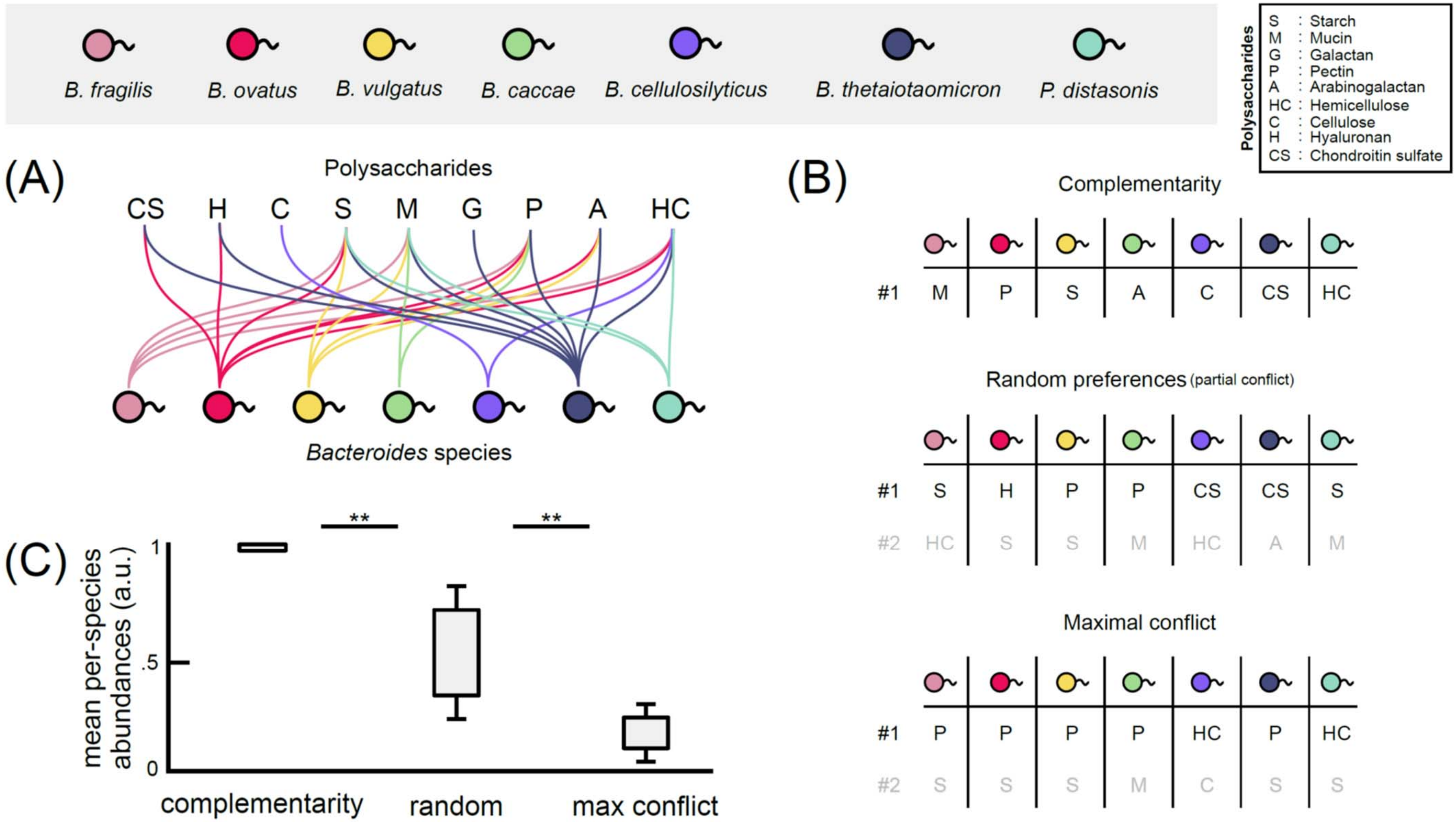


Bacteroides ovatum consuming different polysaccharides: arabinan (ARAB), pectic galactan (PG), rhamnogalacturonan I (RGI), chondroitin sulfate (CS), polygalacturonic acid (PGA), amylopectin (AP)

Bacteroides thetaiotaomicron consuming different polysaccharides: arabinan (ARAB), pectic galactan (PG), rhamnogalacturonan I (RGI), chondroitin sulfate (CS), polygalacturonic acid (PGA), amylopectin (AP)

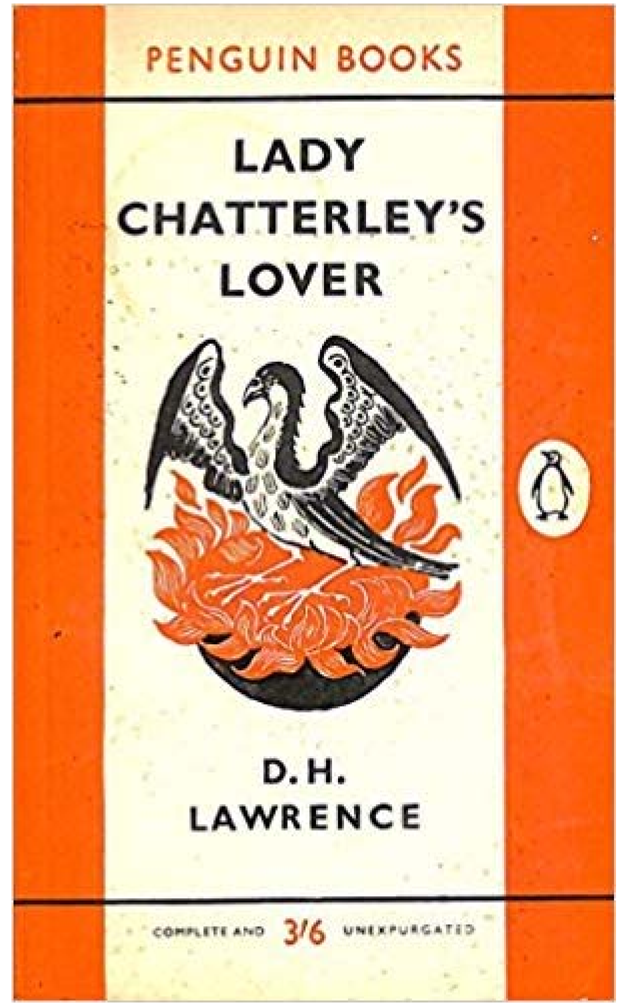
Tuncil, Y. et al. (Eric Martens @ U Michigan) Reciprocal Prioritization to Dietary Glycans by Gut Bacteria in a Competitive Environment Promotes Stable Coexistence. Mbio 8, e01068–17 (2017).

Stable Marriage: 7 Bacteroides species using 9 dietary glycans



On spouses and lovers

(Model 1)



Multiple essential resources

- Life needs many nutrients to grow: C, N, P, etc.
- Growth is limited by the most scarce resource
- Our assumptions: K carbon and M nitrogen types of resources (metabolites)
- S species each using just one pair c_i and n_j
- Liebeg's growth law: $$\frac{dB_\alpha}{dt} = B_\alpha \left(\min(\lambda_\alpha^{(c)} c_i, \lambda_\alpha^{(n)} n_j) - \delta \right)$$
- Conservation laws:

$$\frac{dc_i}{dt} = \phi_i^{(c)} - \delta \cdot c_i - \\ - \sum_{\text{all } \alpha \text{ using } c_i} B_\alpha \min(\lambda_\alpha^{(c)} c_i, \lambda_\alpha^{(n)} n_j)/Y_\alpha^{(c)};$$

Similar for n_j

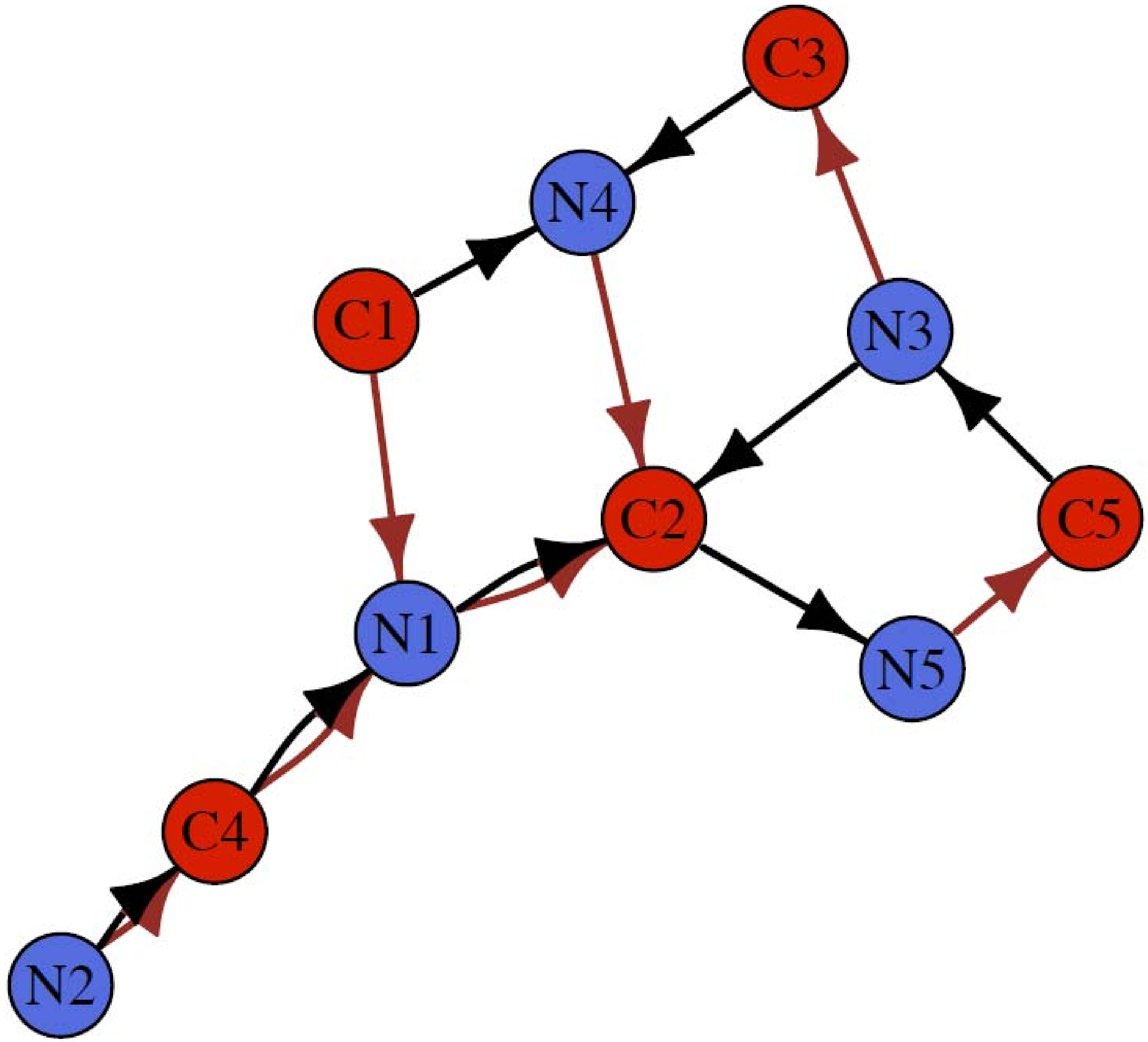
Modified competitive exclusion principle

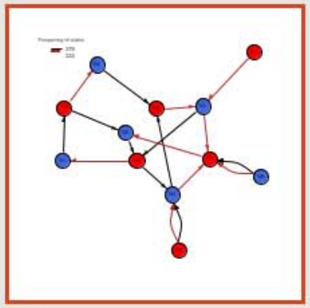
$$\frac{dB_\alpha}{dt} = B_\alpha \left(\min(\lambda_\alpha^{(c)} c_i, \lambda_\alpha^{(n)} n_j) - \delta \right)$$

- Each nutrient (c_i or n_j) can have no more than one species limited by it.
  - No more than K+M species (out of S>KM) survive.
- Each nutrient can have any number of species using it in a non-limiting fashion
  - All non-limited species have to have better λ than the (unique) species limited by the resource.

Modified exclusion rule = marriage

- Related to the marriage model: microbes are marriages between C and N resources
- Each nutrient has no more than one spouse (only marriages between C and N are allowed)
- Each nutrient can have as many lovers at it wants. But lovers have to be better than its spouse (if any)
- Twisted part: marriages are not reciprocal: Your spouse views you as a lover
- If C, N, P, S,… – marriage with more than 2 sexes


C3
N4
C1
N3
C2
C5
N1
N5
C4
N2



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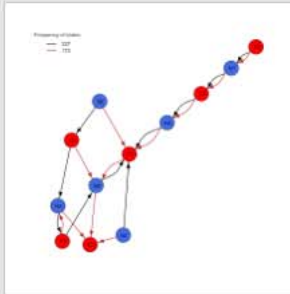

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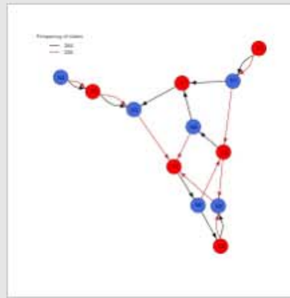

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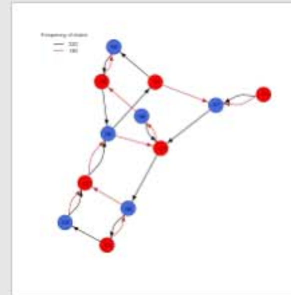

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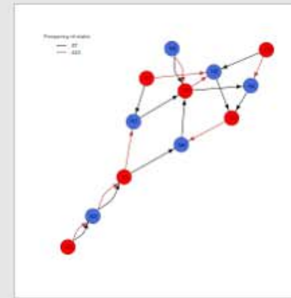

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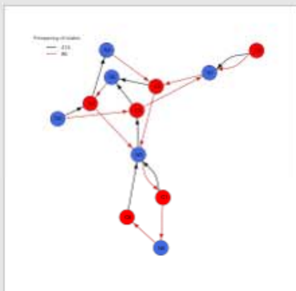

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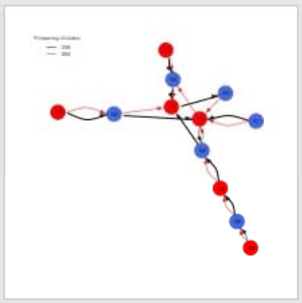

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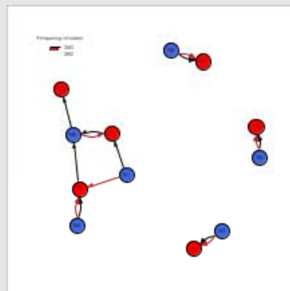

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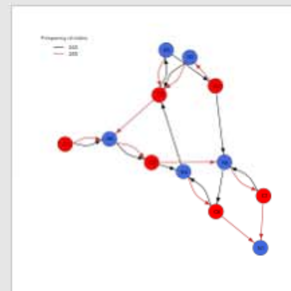

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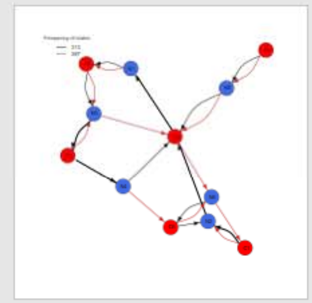

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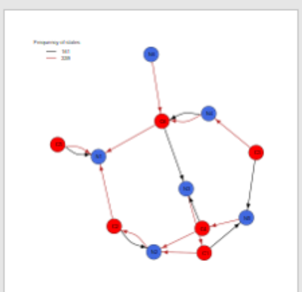

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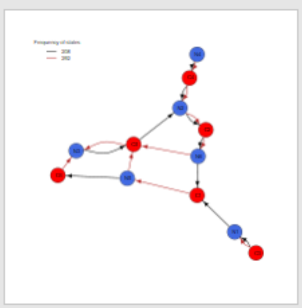

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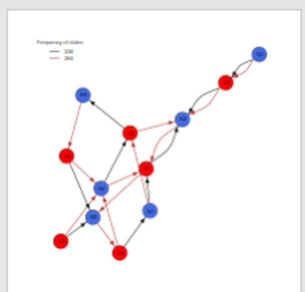

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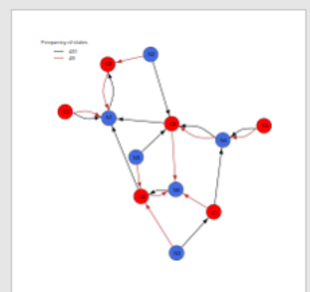

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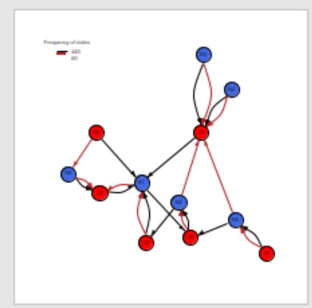

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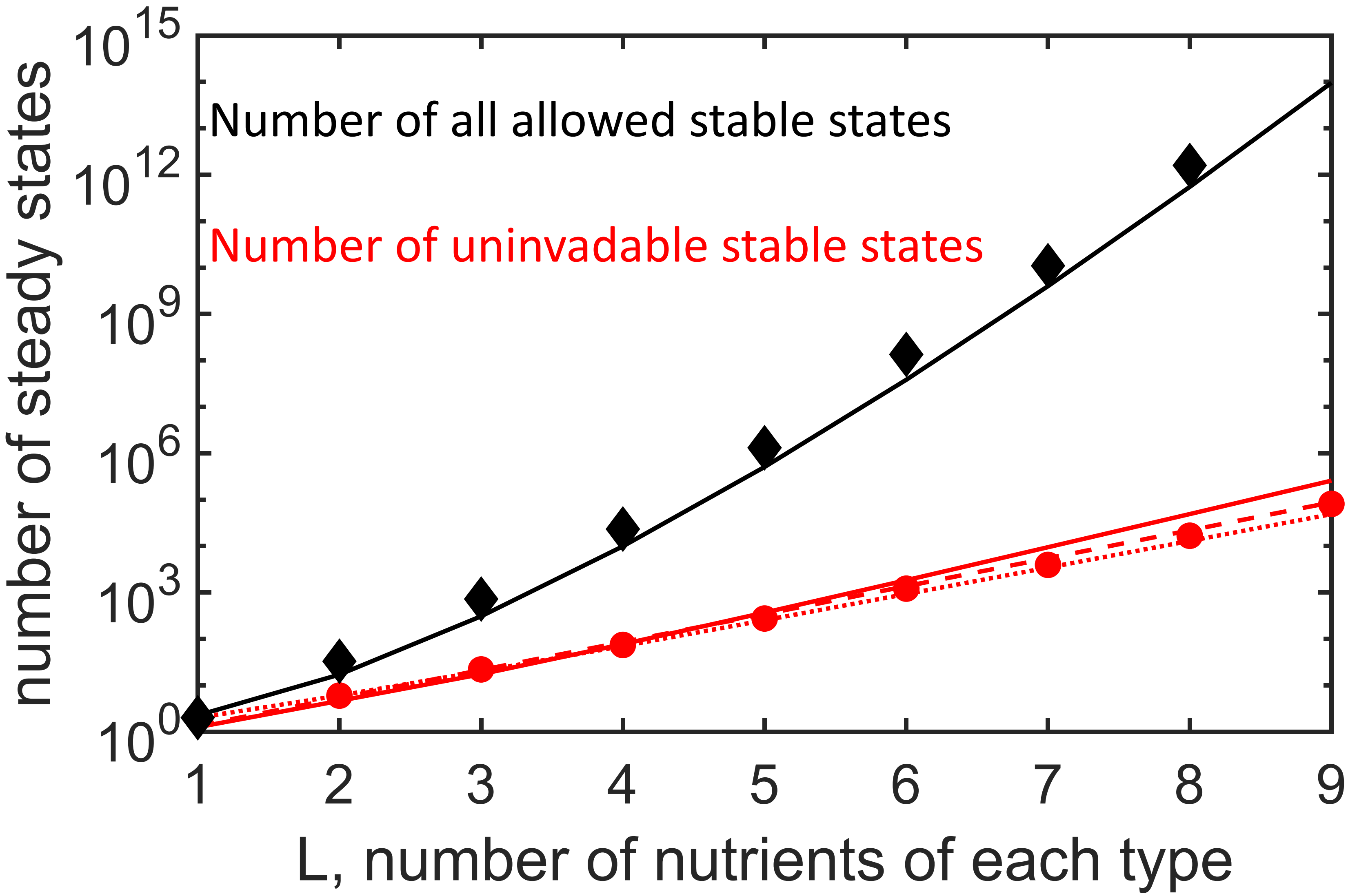
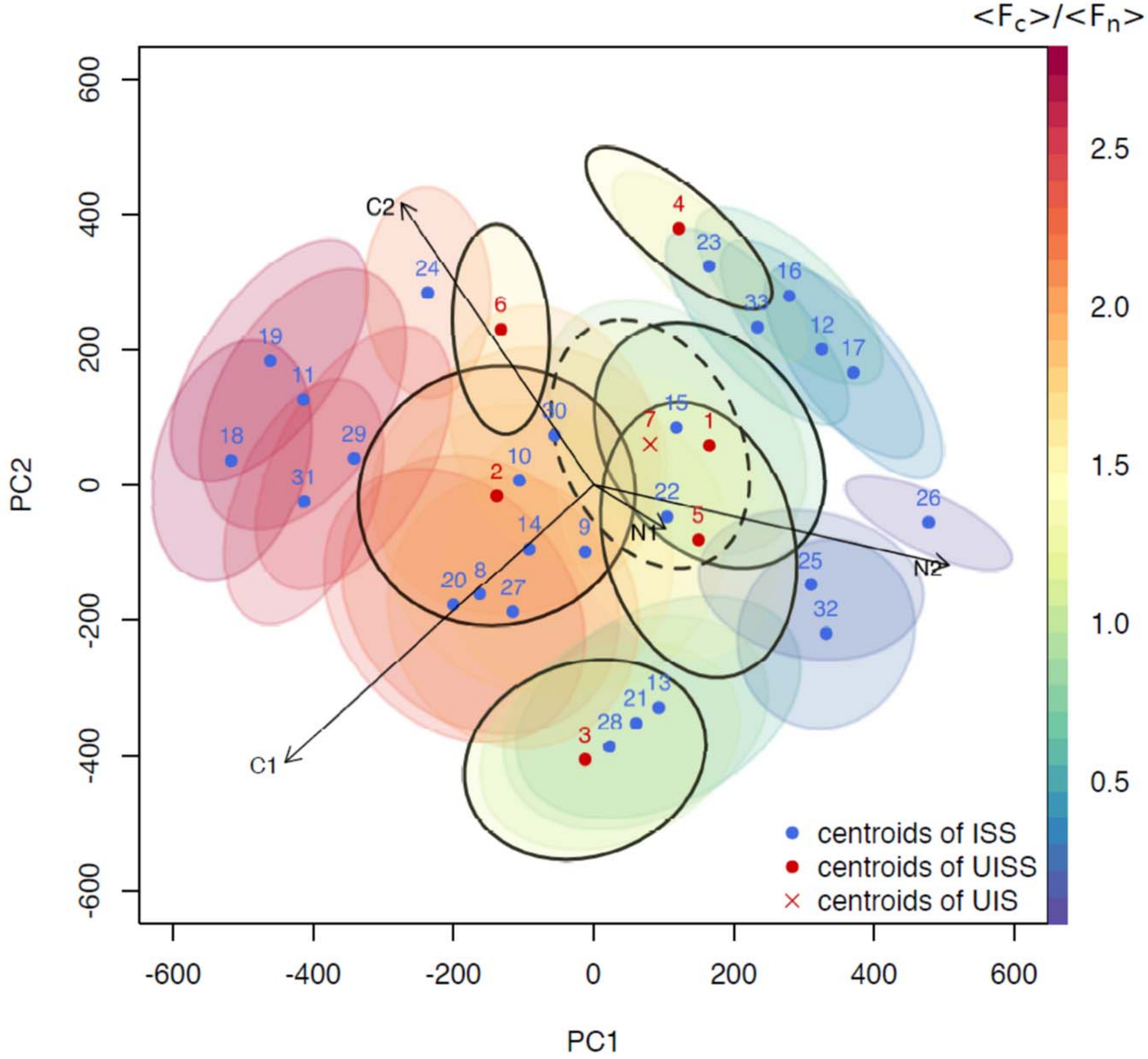
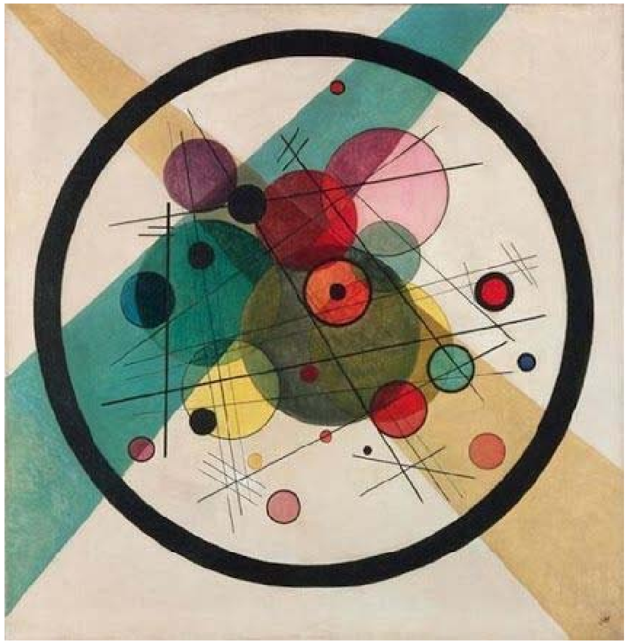
Exponentially many univadable stable states:
80,000 UIS for 9C x 9N and 81 species system



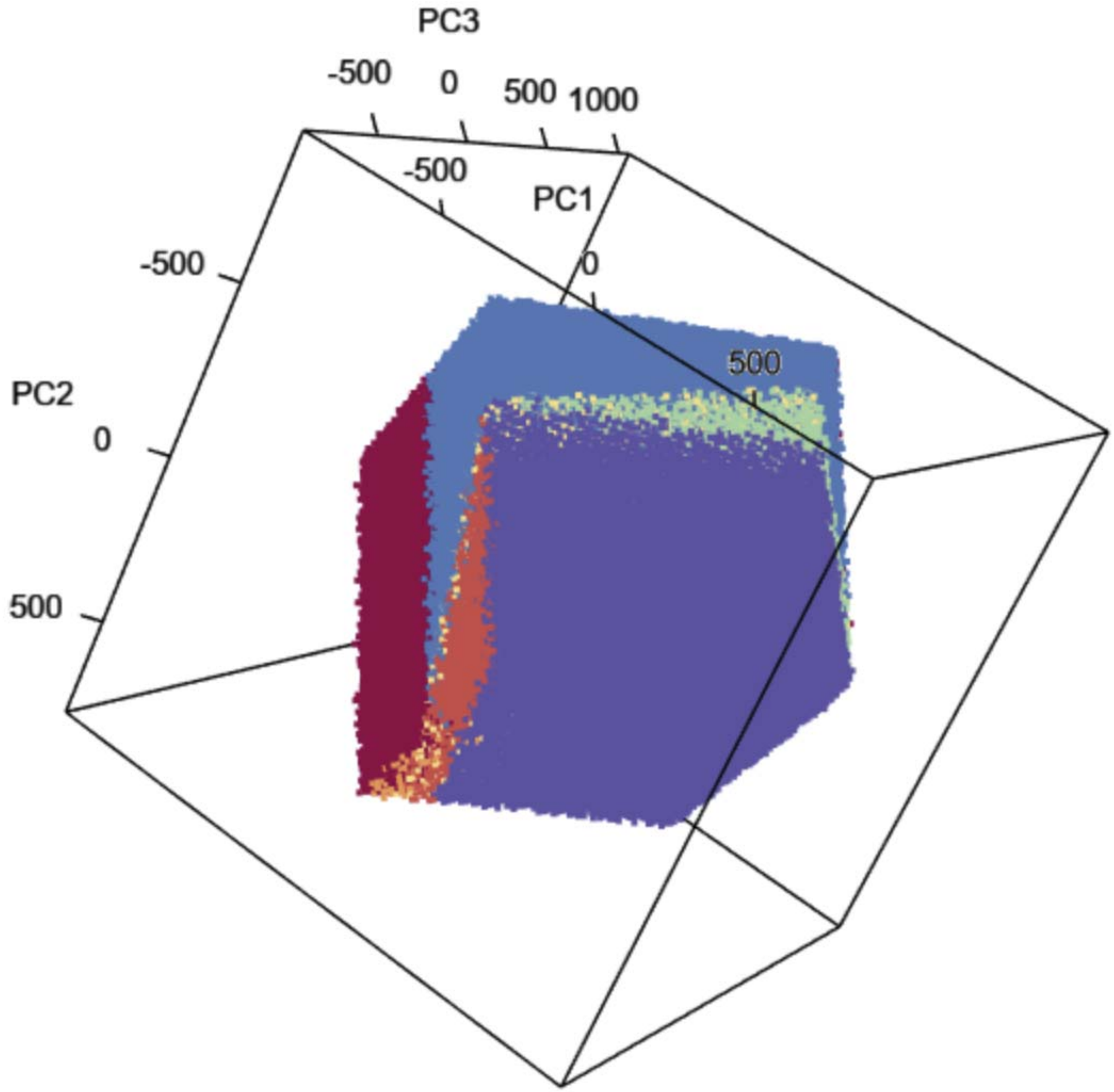
Each state has a region of carbon and nitrogen fluxes, where it is allowed.



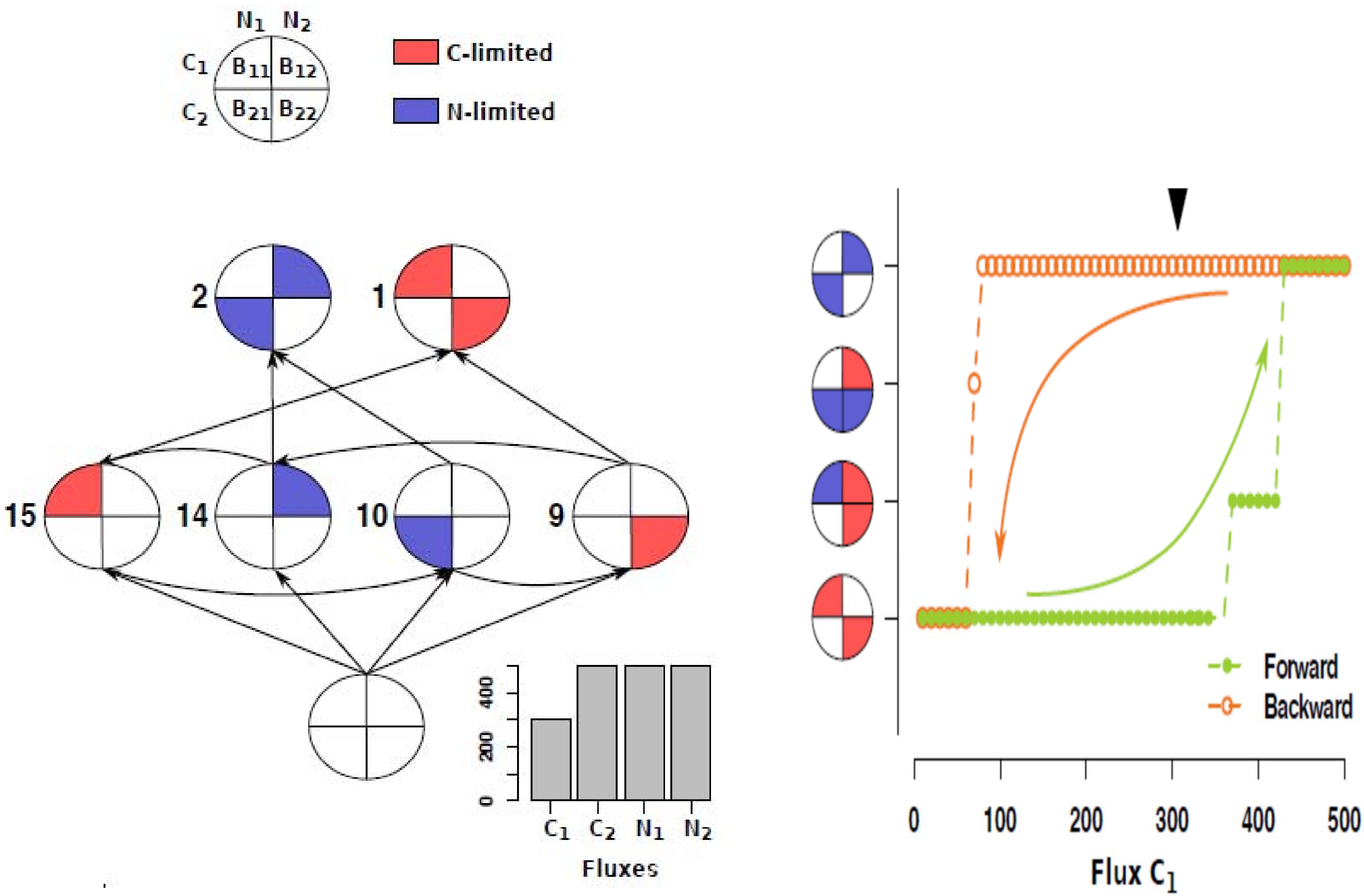


Wassily Kandinsky (Russian, later French, Circles in a Circle, 1923

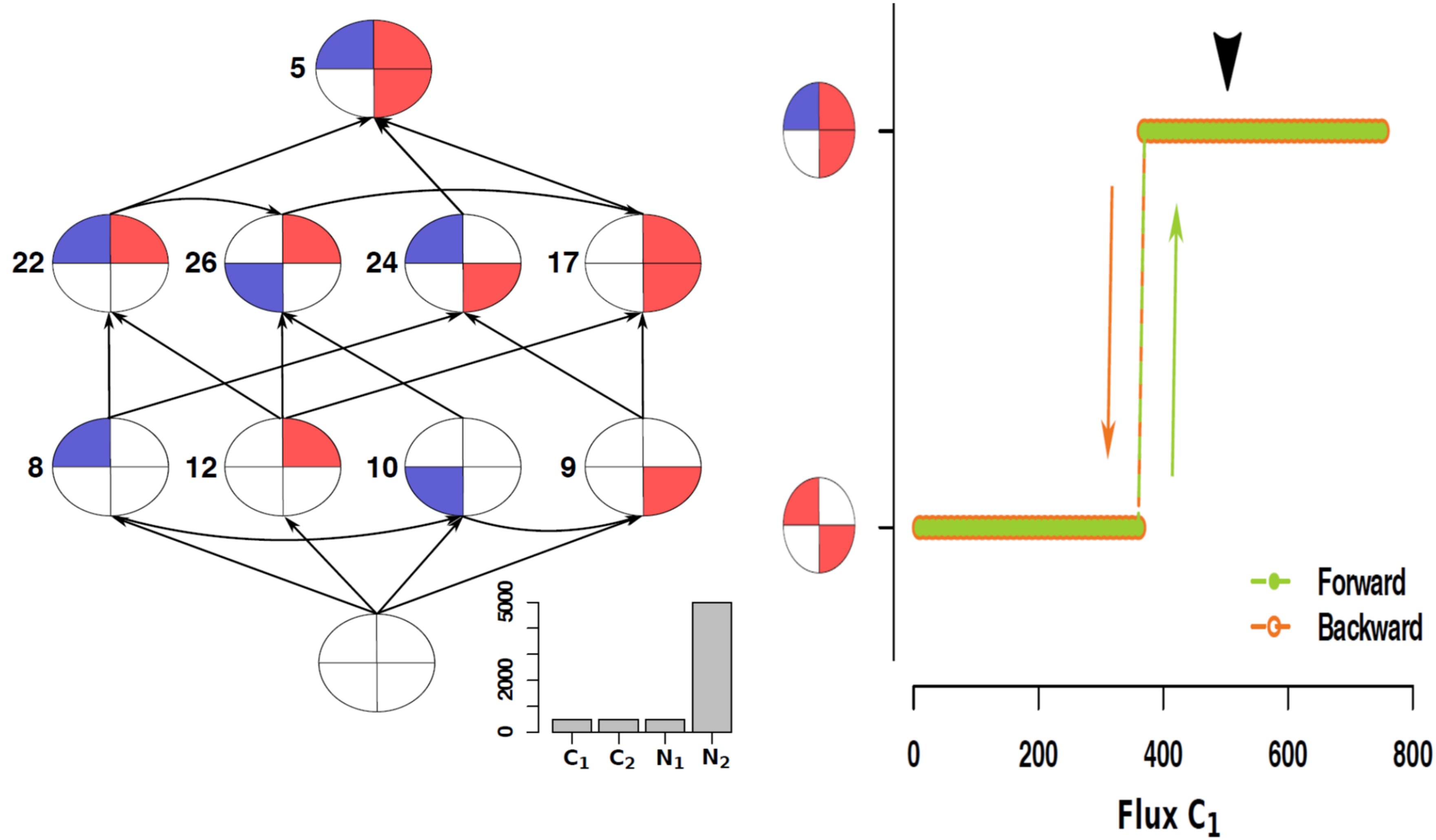
And now a cubistic version



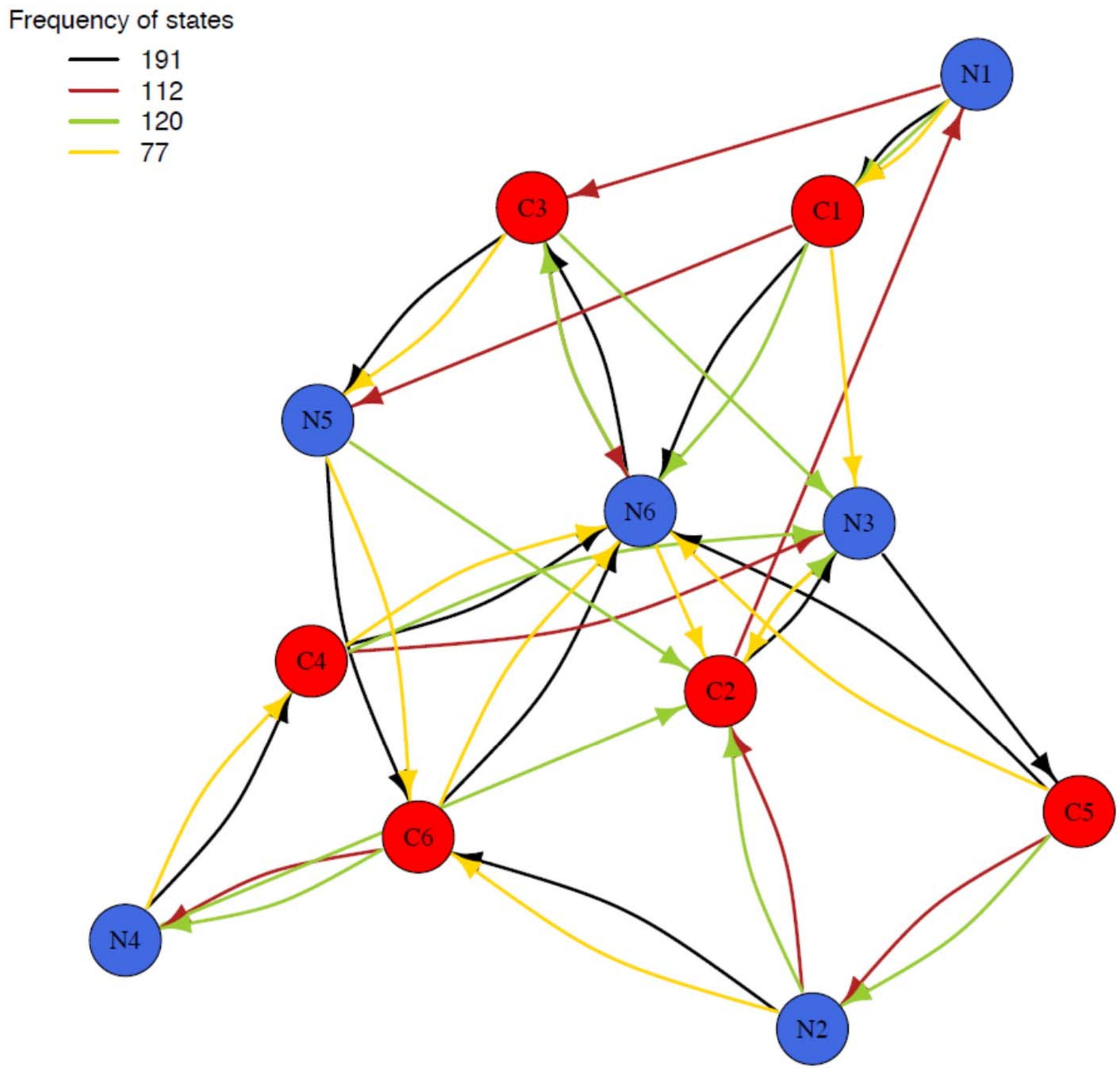
Bistability of 2 states for given fluxes



Monostability: 1 state is allowed for given fluxes



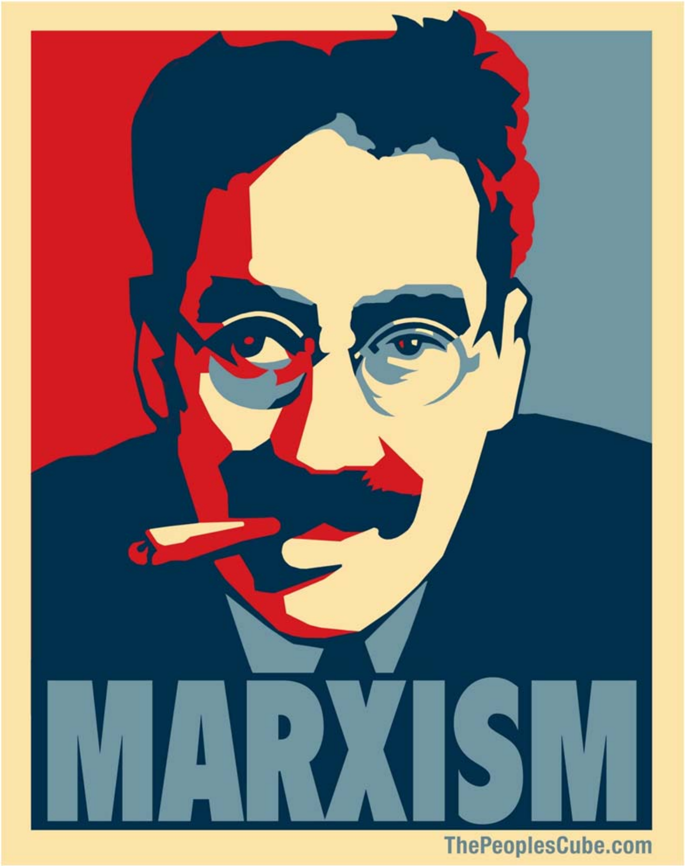
Multistability: 3,4,… states allowed for given fluxes



6C-6N
36 species

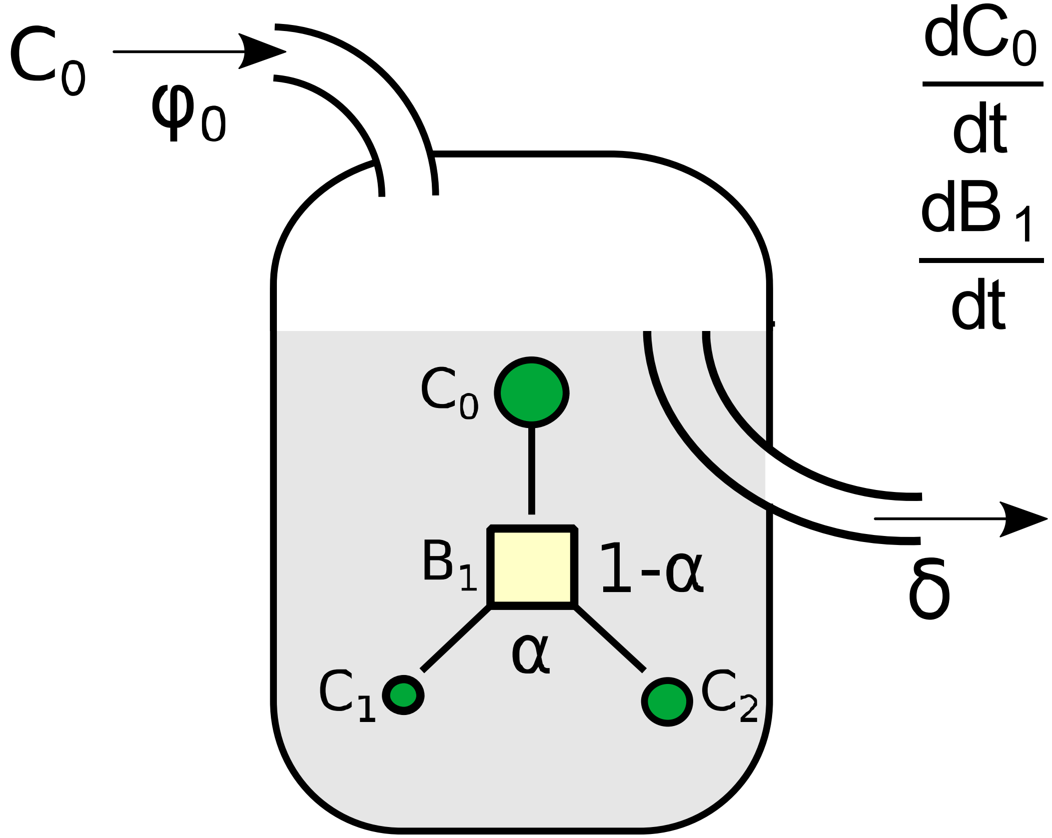
THOSE ARE MY PRINCIPLES, AND IF YOU DON'T LIKE THEM... WELL, I HAVE OTHERS.

GROUCHO MARX



Many microbes could co-exist on
few resources
if they can use each other's
metabolic byproducts
(cross-feeding)

Model assumptions



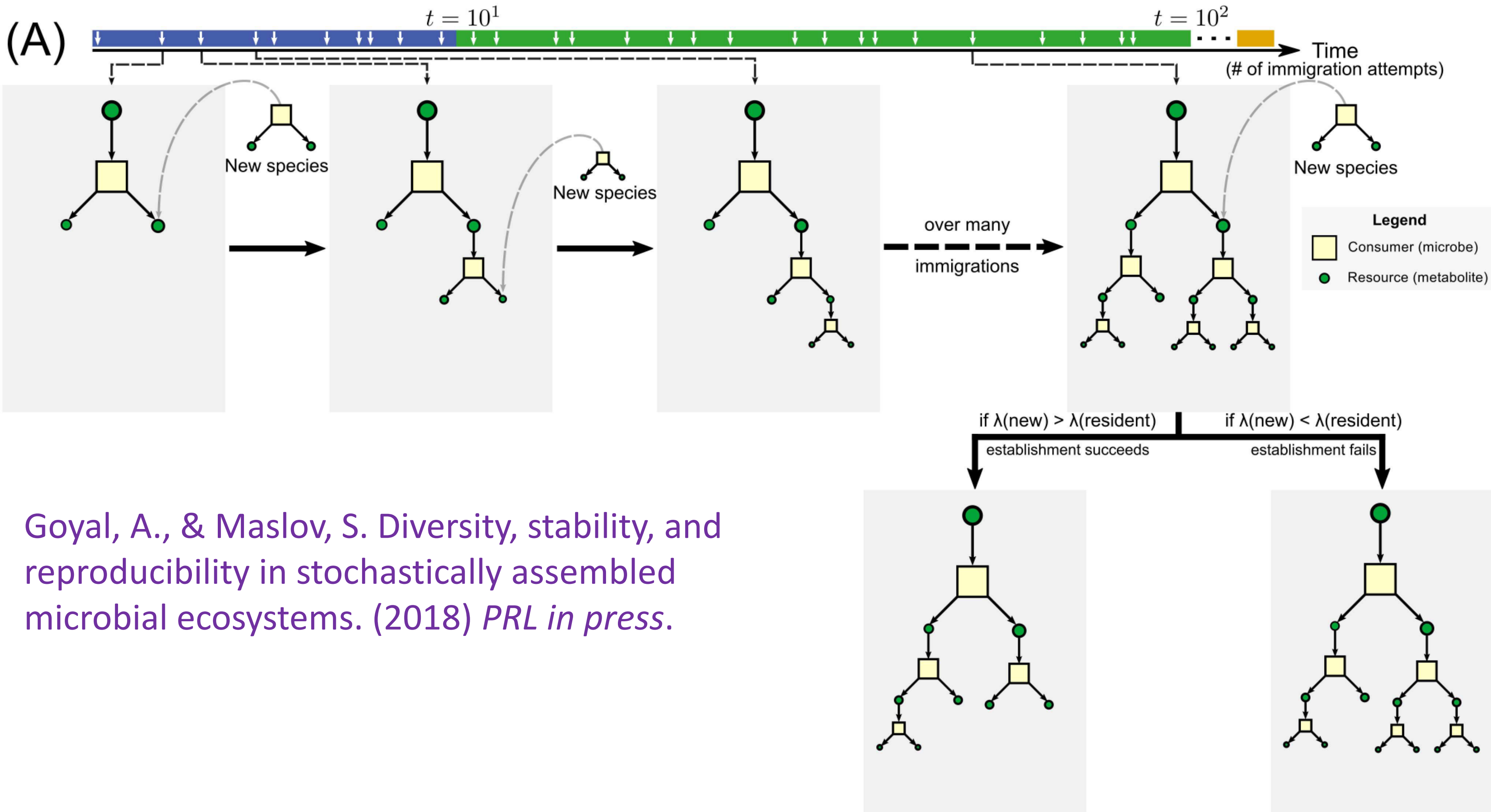
$$\frac{dC_0}{dt} = \varphi_0 - \frac{\lambda_1 C_0 B_1}{Y} - \delta \cdot C_0,$$

$$\frac{dB_1}{dt} = \lambda_1 C_0 B_1 - \delta \cdot B_1,$$

- Each microbe uses one resource C_i
- Fraction $1\text{-}\alpha$ goes to to biomass (Yield, $Y=1\text{-}\alpha$)
- Fraction α - converted to β=2 byproducts

- If two species want to use the same nutrient, one with a larger competitive ability λ_i wins

Community assembly process



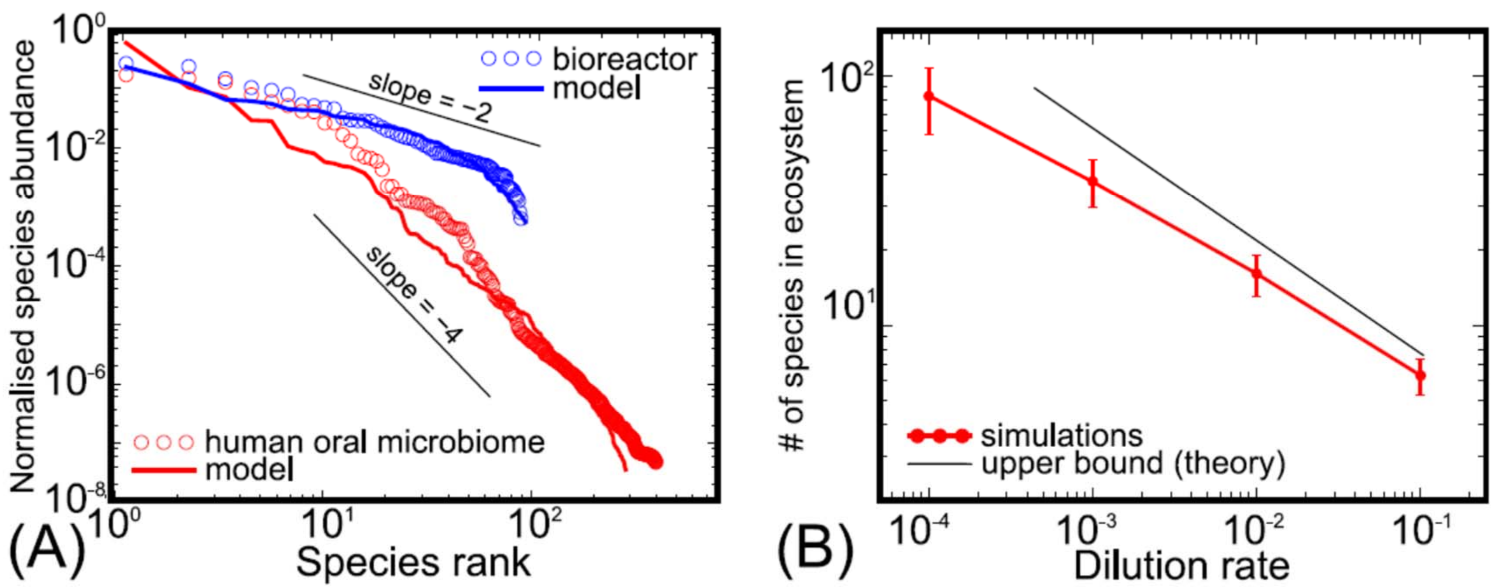
Goyal, A., & Maslov, S. Diversity, stability, and reproducibility in stochastically assembled microbial ecosystems. (2018) *PRL in press*.

- Power law abundance (*b*) distribution

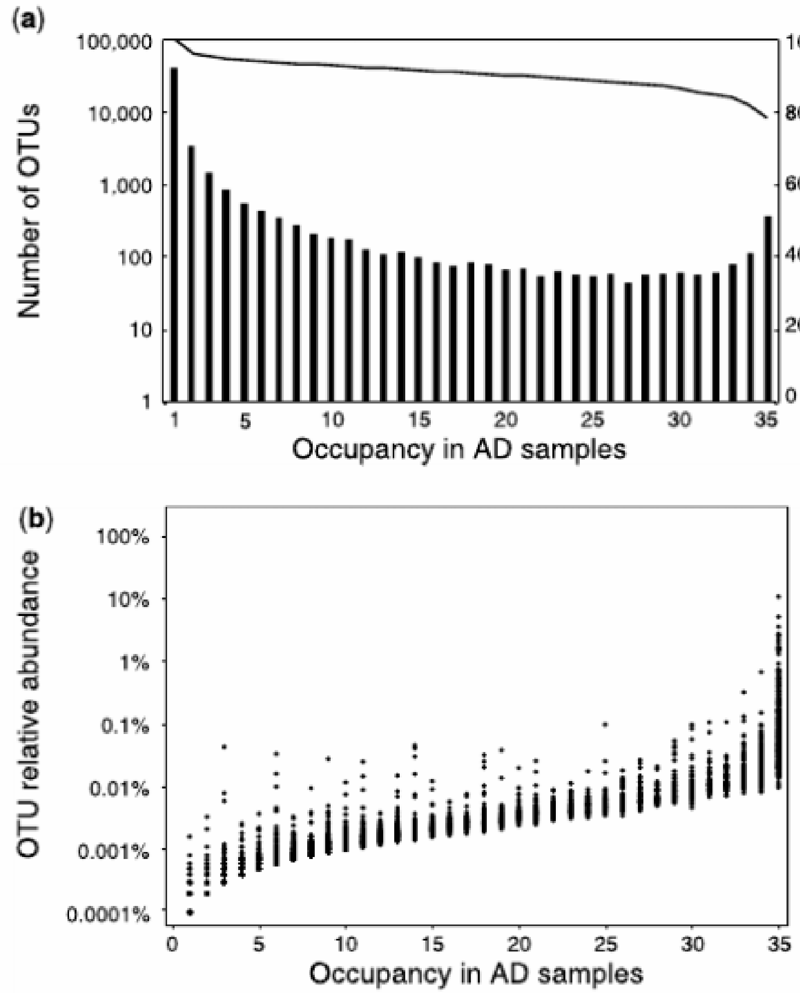
$$\mathcal{N}(B=b) \sim b^{-\left(1+\frac{\log\beta}{|\log\alpha|+\log(\alpha+\beta)}\right)}$$

- Maximal number of species increases with decreasing dilution rate

$$\mathcal{N}_{\max}(\delta) \sim \delta^{-\left(\frac{2\log\beta}{|\log\alpha|+\log(\alpha+\beta)}\right)}.$$



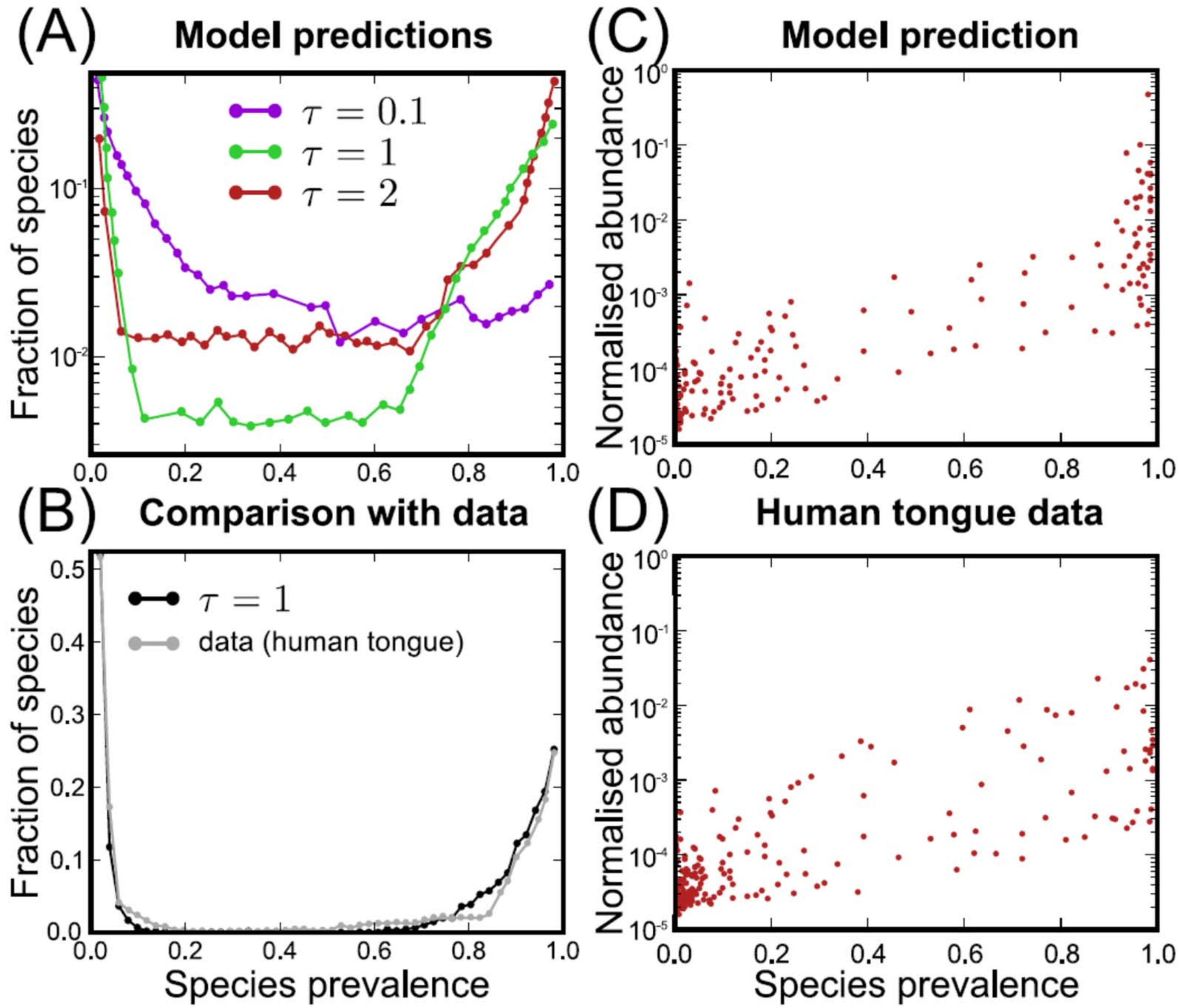
Species reproducibility has U-shaped distribution & is correlated with abundance



Anaerobic Digesters in full-scale water reclamation plant at Chicago, Illinois

Mei R, Narihiro T, Nobu M, Kuroda K, Liu W-T (2016) Sci Reports 6:34090.

U-shaped prevalence distribution



Collaborators

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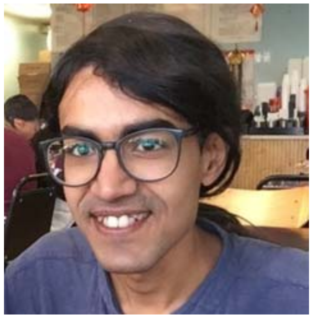

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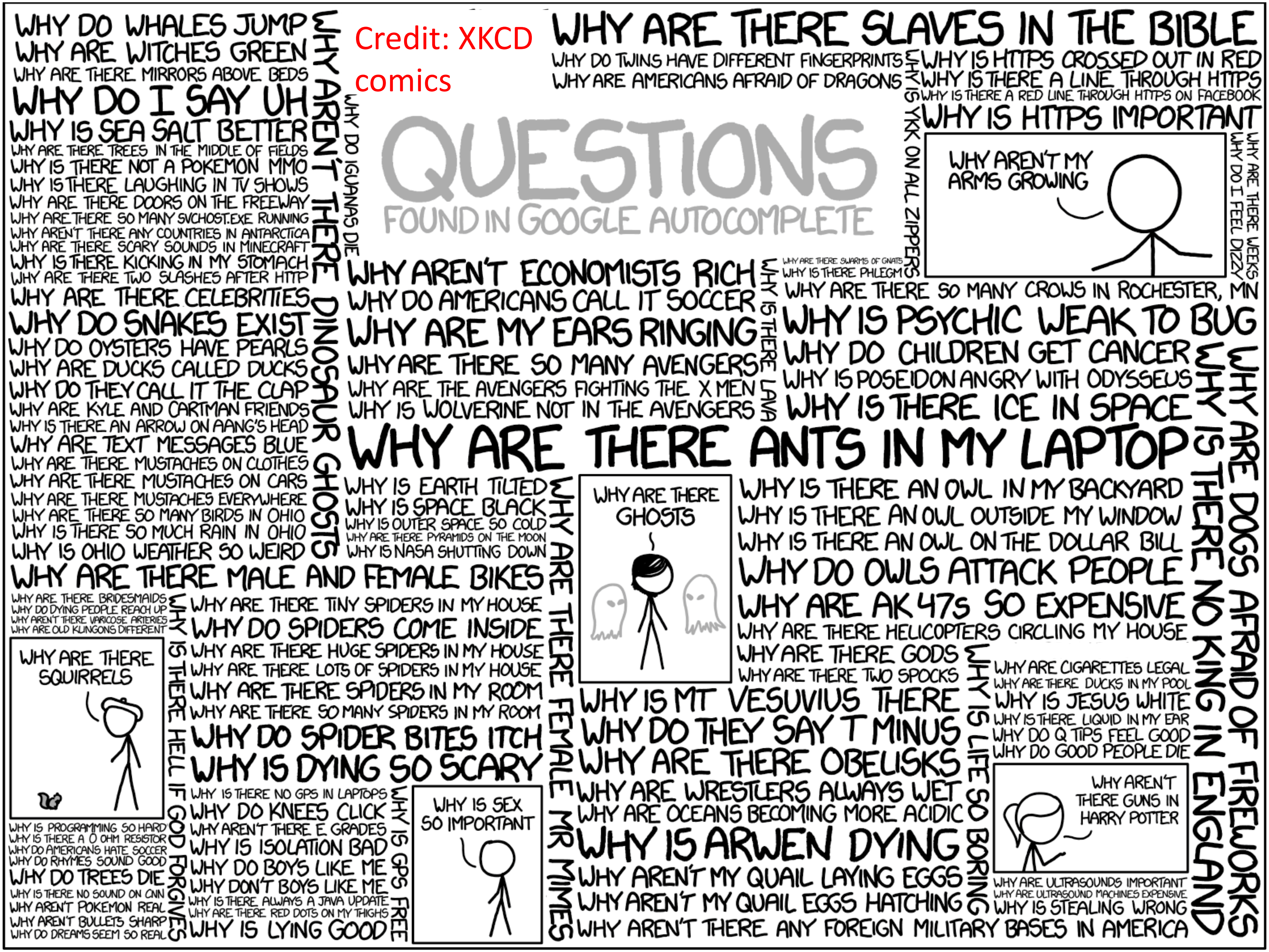

Credit: XKCD comics