

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

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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



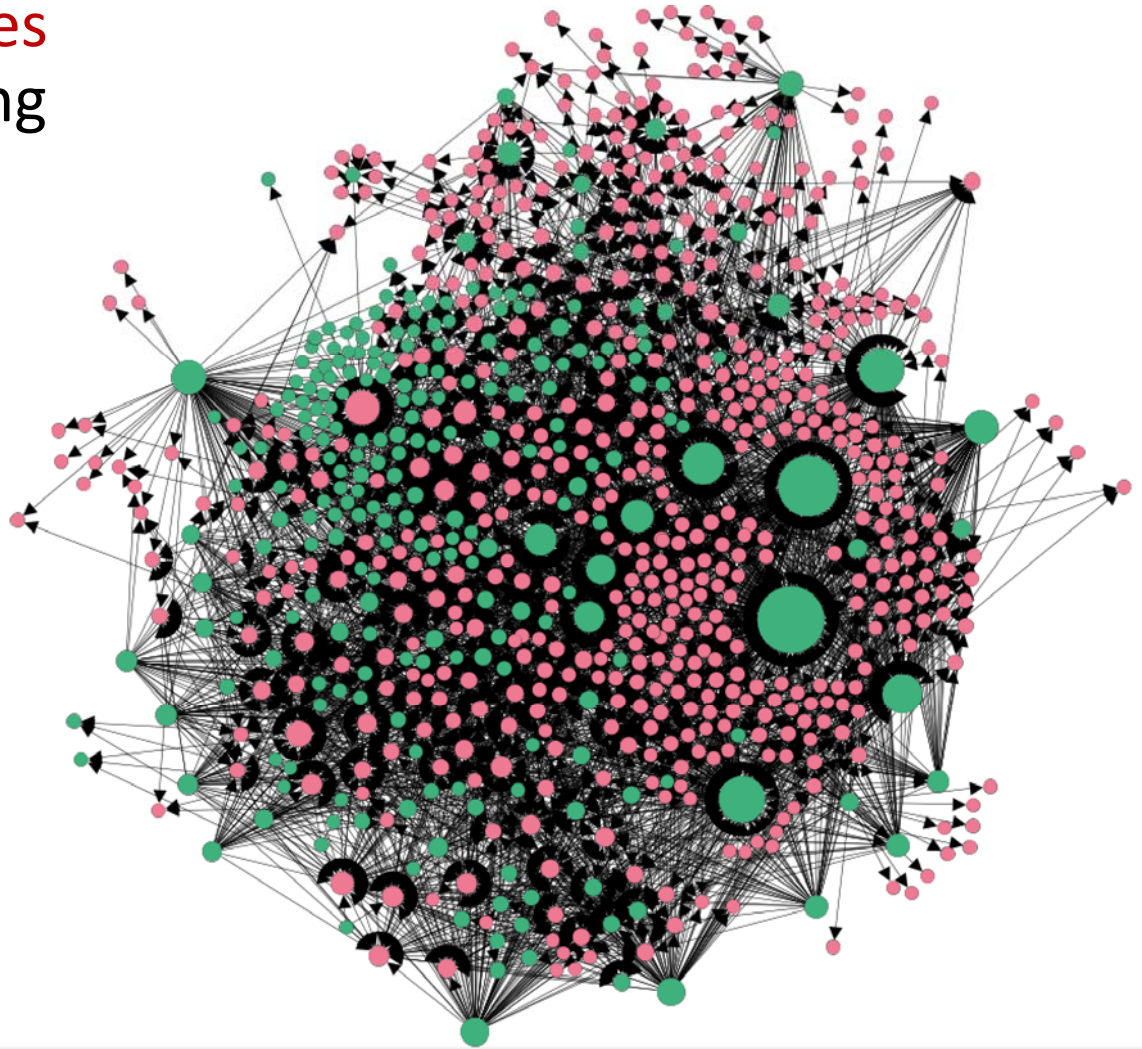
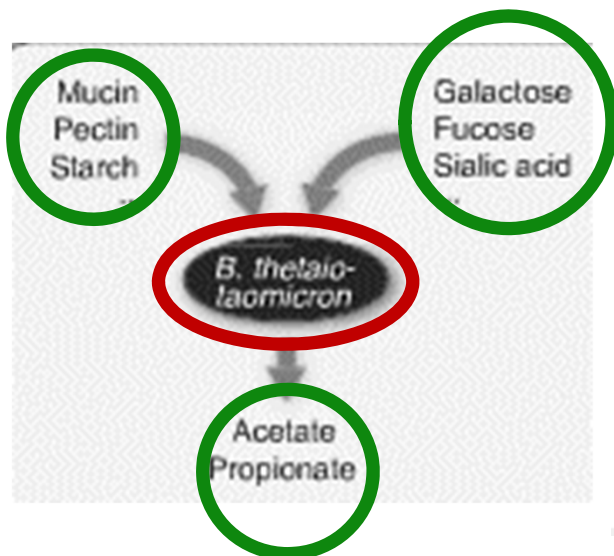
What we would like to understand?

- **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).



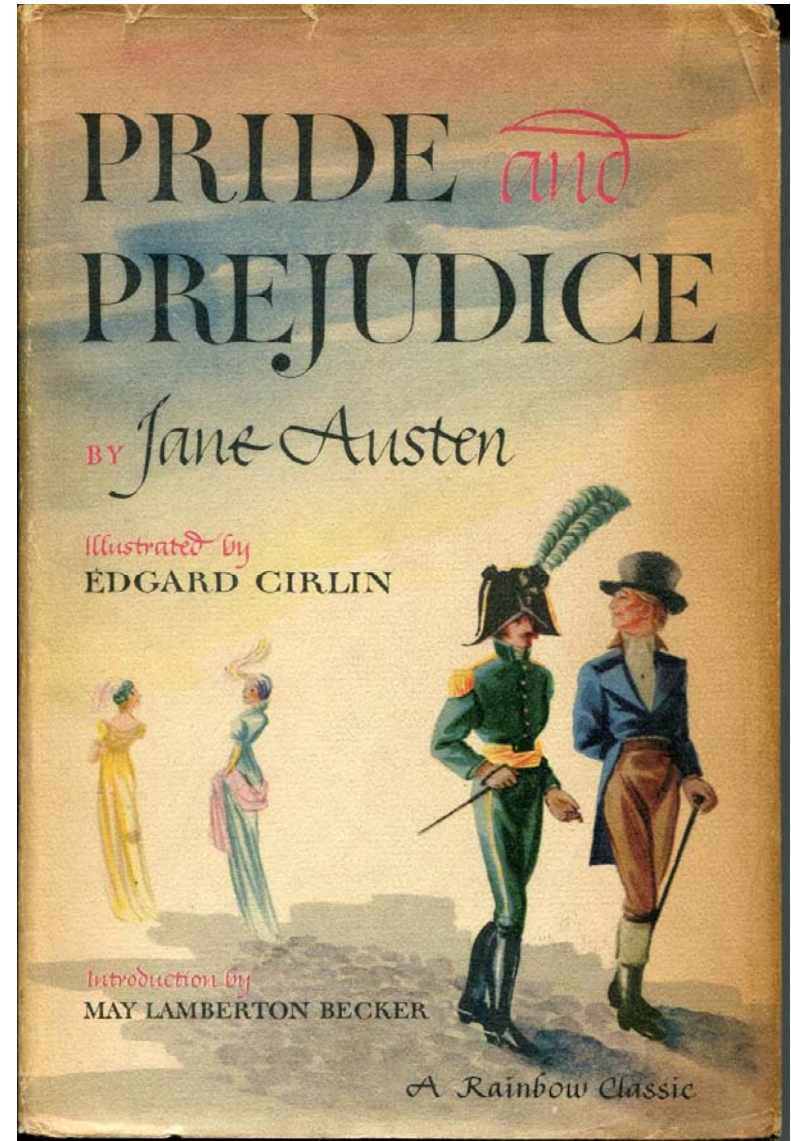
Network is just the skeleton of a model

- 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>

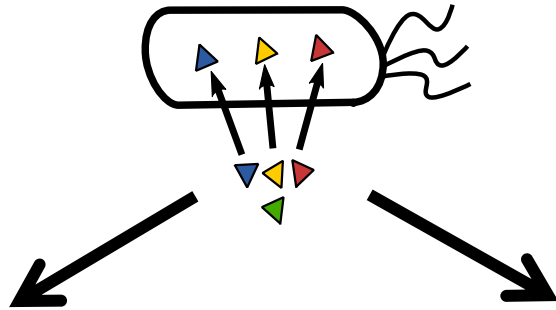
Multiple states and
their control
in the
“Stable Marriage”
approach

(Model 2)

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



How each microbe uses nutrients?



One nutrient at a time: diauxie

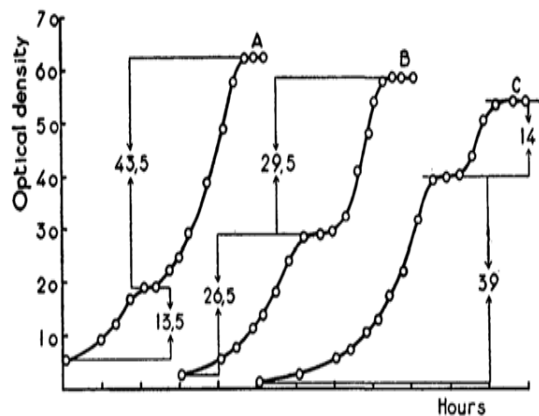


FIG. 9.—Diauxie. Growth of *E. coli* in synthetic medium with glucose+sorbitol as carbon source.

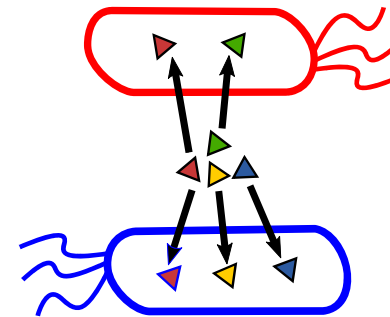
Known since Monod (1949)

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)

How microbes divide nutrients?



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



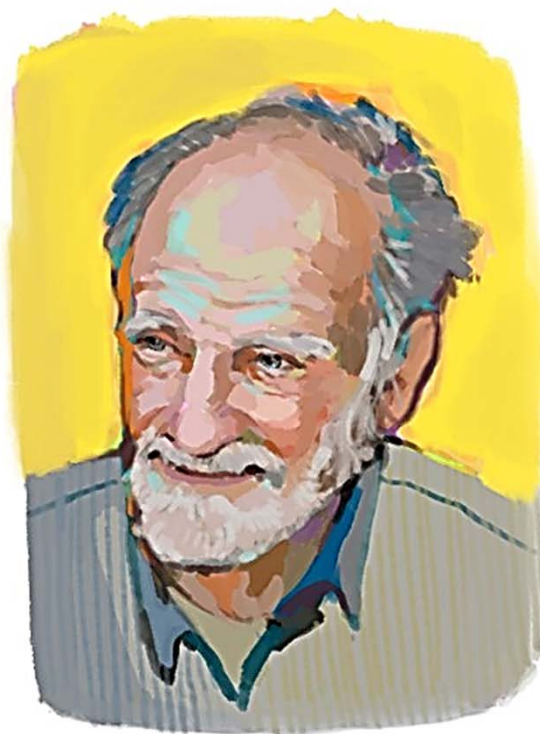
- Each **microbe** uses one resource at a time (diauxic shift) and **each resource** is used by no more than one microbe (competitive exclusion)
- Marital bliss is based on only two ranked lists: **microbes' order of preferences towards resources** and resources' "preferences" = **microbes' competitive abilities** for this resource.
- To **predict steady states** no need to know the detailed biochemical parameters¹

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

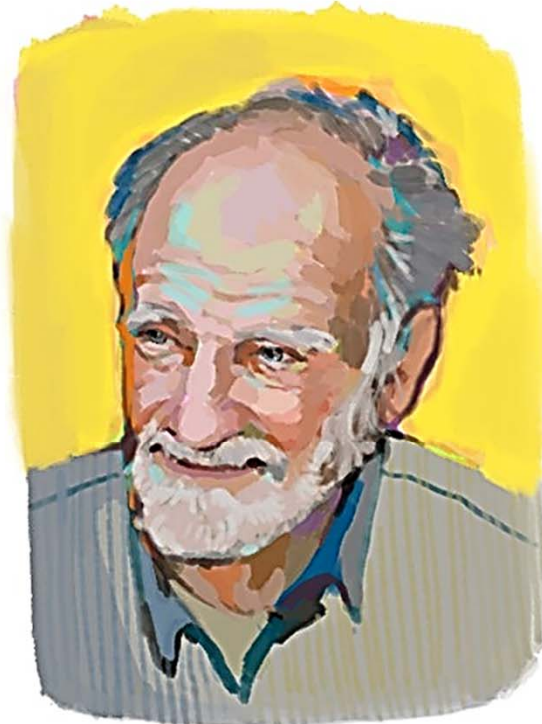
D. Gale & L. S. Shapley, College Admissions and the Stability of Marriage
The American Mathematical Monthly, 69, 9-15 (1962)

Nobel Prize in Economics 2012

"for the theory of stable allocations..."



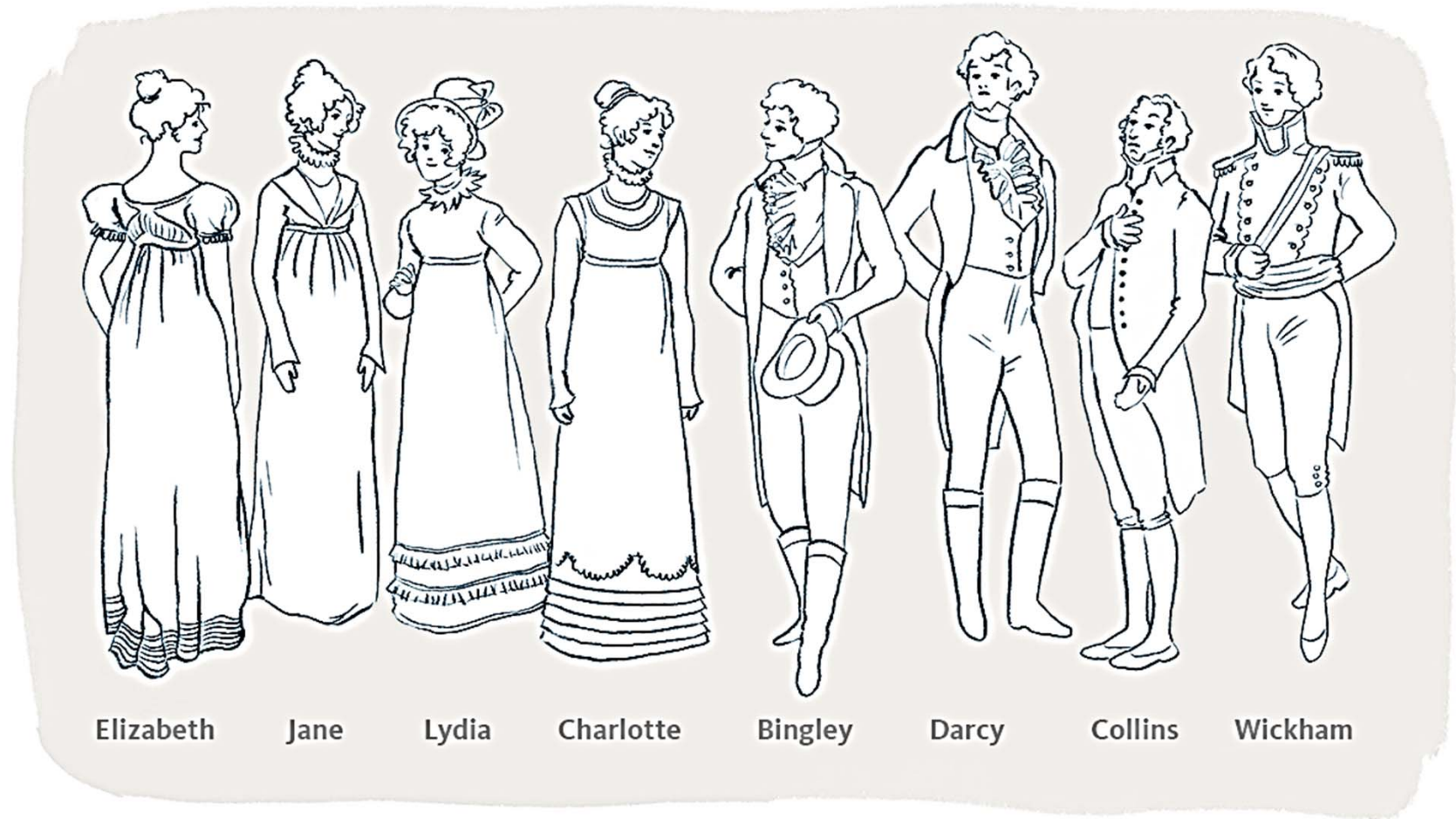
Alvin Roth
PROFESSOR, STANFORD



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 Austen's "Pride and Prejudice"

They rank each other as potential partners

| | | | |
|---|--|---|---|
|  <p>Elizabeth</p> <ol style="list-style-type: none">1. WICKHAM2. DARCY3. BINGLEY4. COLLINS |  <p>Jane</p> <ol style="list-style-type: none">1. BINGLEY2. WICKHAM3. DARCY4. COLLINS |  <p>Lydia</p> <ol style="list-style-type: none">1. BINGLEY2. WICKHAM3. DARCY4. COLLINS |  <p>Charlotte</p> <ol style="list-style-type: none">1. BINGLEY2. DARCY3. COLLINS4. WICKHAM |
|  <p>Bingley</p> <ol style="list-style-type: none">1. JANE2. ELIZABETH3. LYDIA4. CHARLOTTE |  <p>Darcy</p> <ol style="list-style-type: none">1. ELIZABETH2. JANE3. CHARLOTTE4. LYDIA |  <p>Collins</p> <ol style="list-style-type: none">1. JANE2. ELIZABETH3. LYDIA4. CHARLOTTE |  <p>Wickham</p> <ol style="list-style-type: none">1. LYDIA2. JANE3. ELIZABETH4. CHARLOTTE |

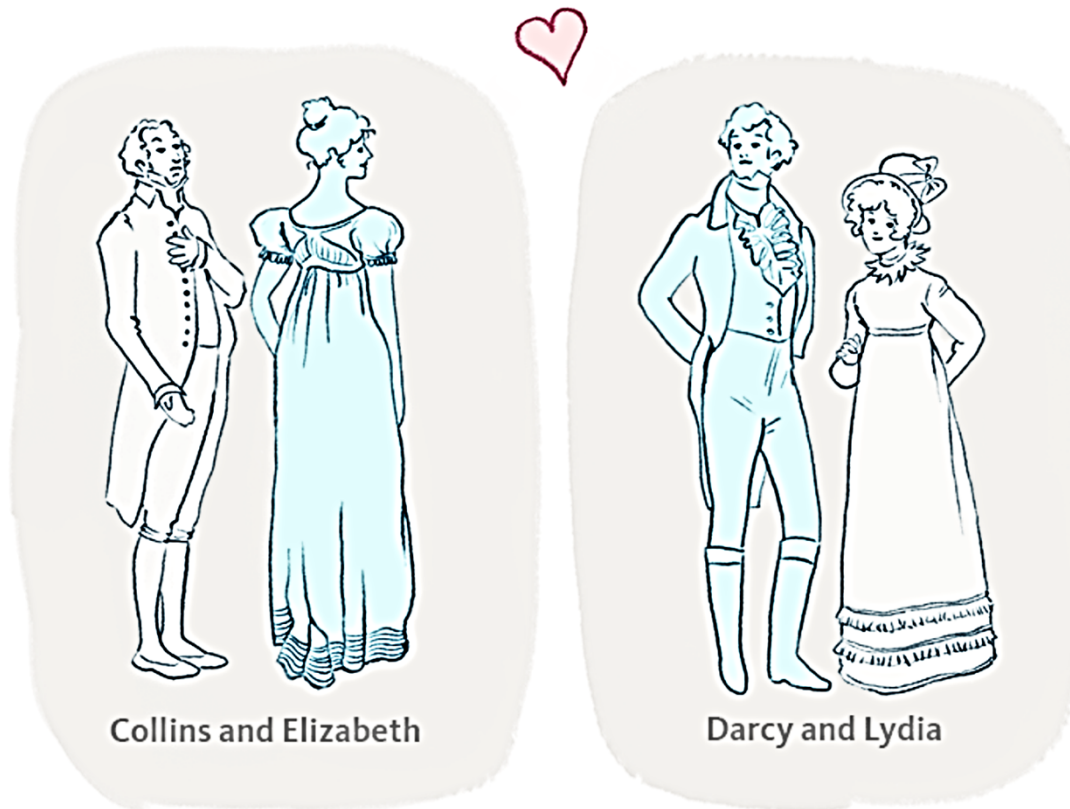
And ultimately get married to each other



<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



Collins and Elizabeth

Darcy and Lydia

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?

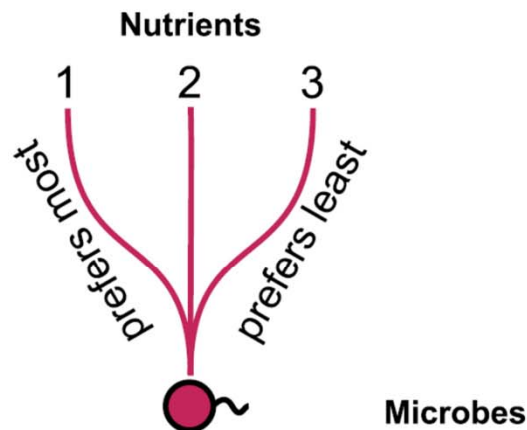
Gale-Shapely or men-proposing algorithm

- 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

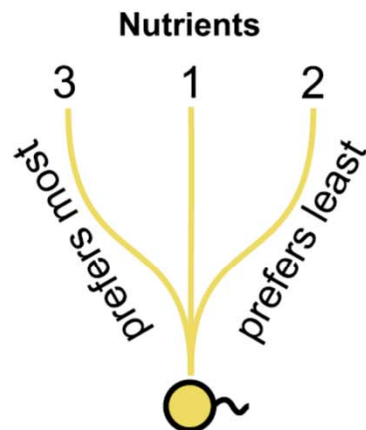
Marriage model in microbes

Microbial nutrient utilization preferences







| | | | |
|---|---|---|---|
|  | 1 | 2 | 3 |
|  | 3 | 1 | 2 |

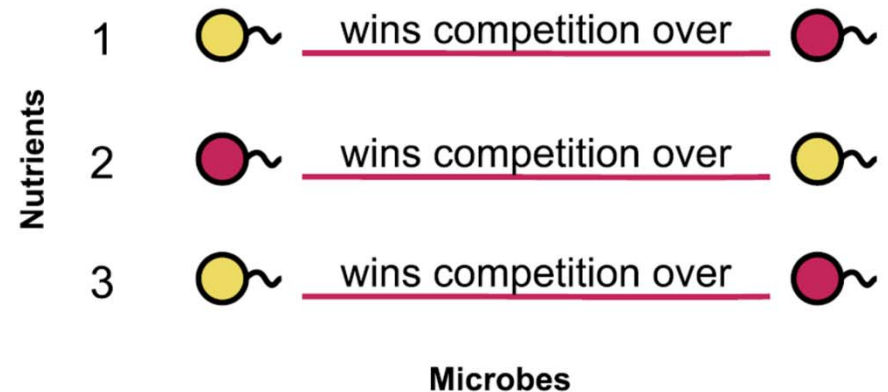


Nutrient preferences



Microbial competitive abilities

| | | |
|-------|---|---|
| N_1 |  |  |
| N_2 |  |  |
| N_3 |  |  |

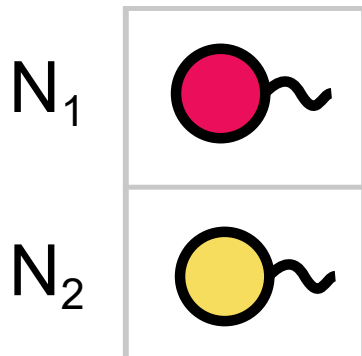


Competitive abilities

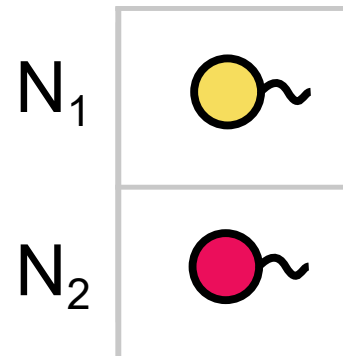
Microbial love ~~triangle~~ square



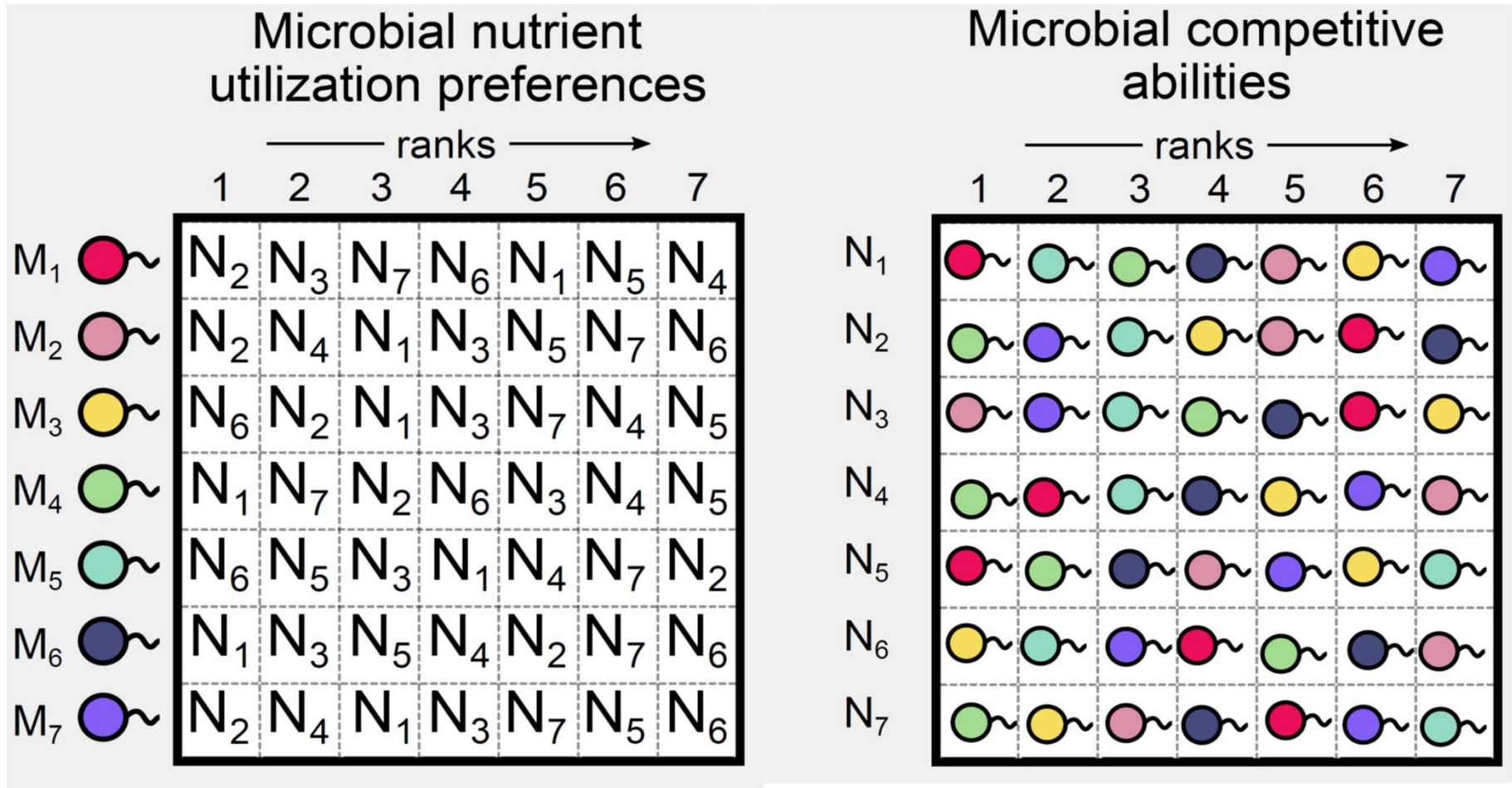
Microbe-optimal
stable state 1



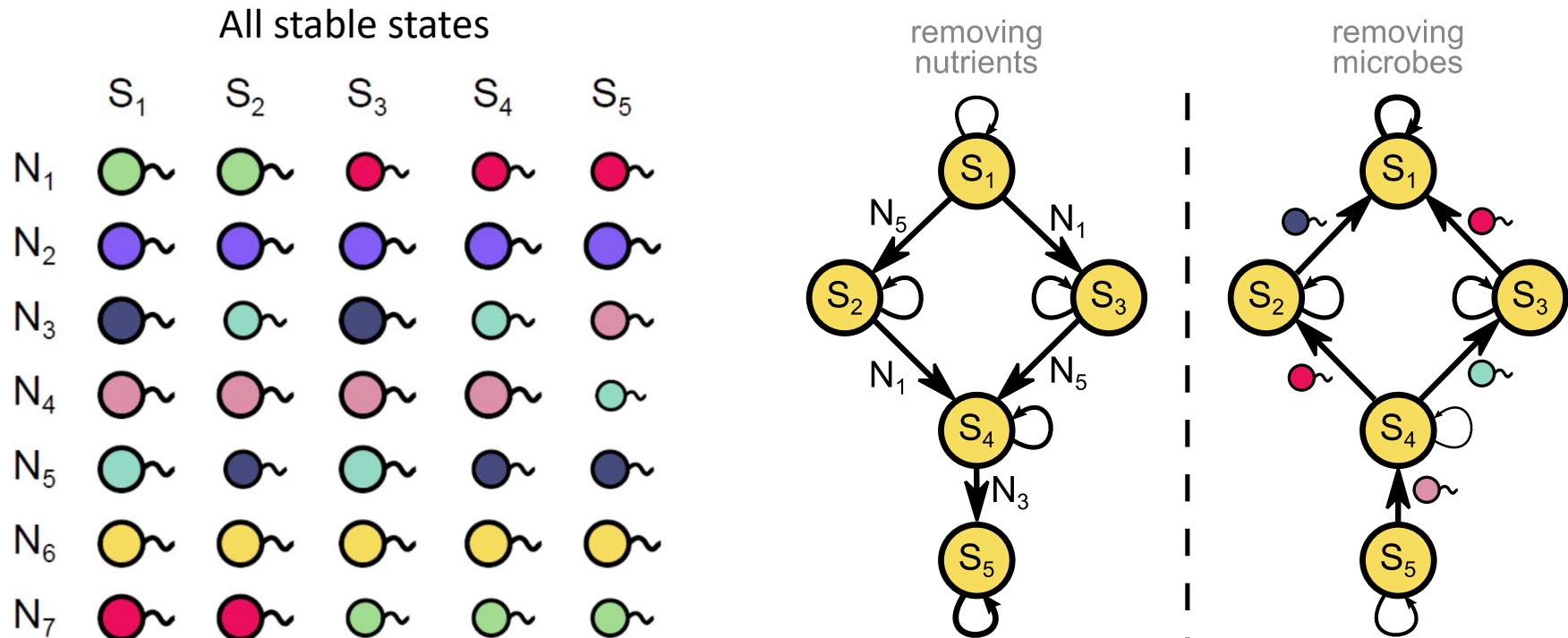
Nutrient-optimal
stable state 2



Example: 7 microbes, 7 nutrients

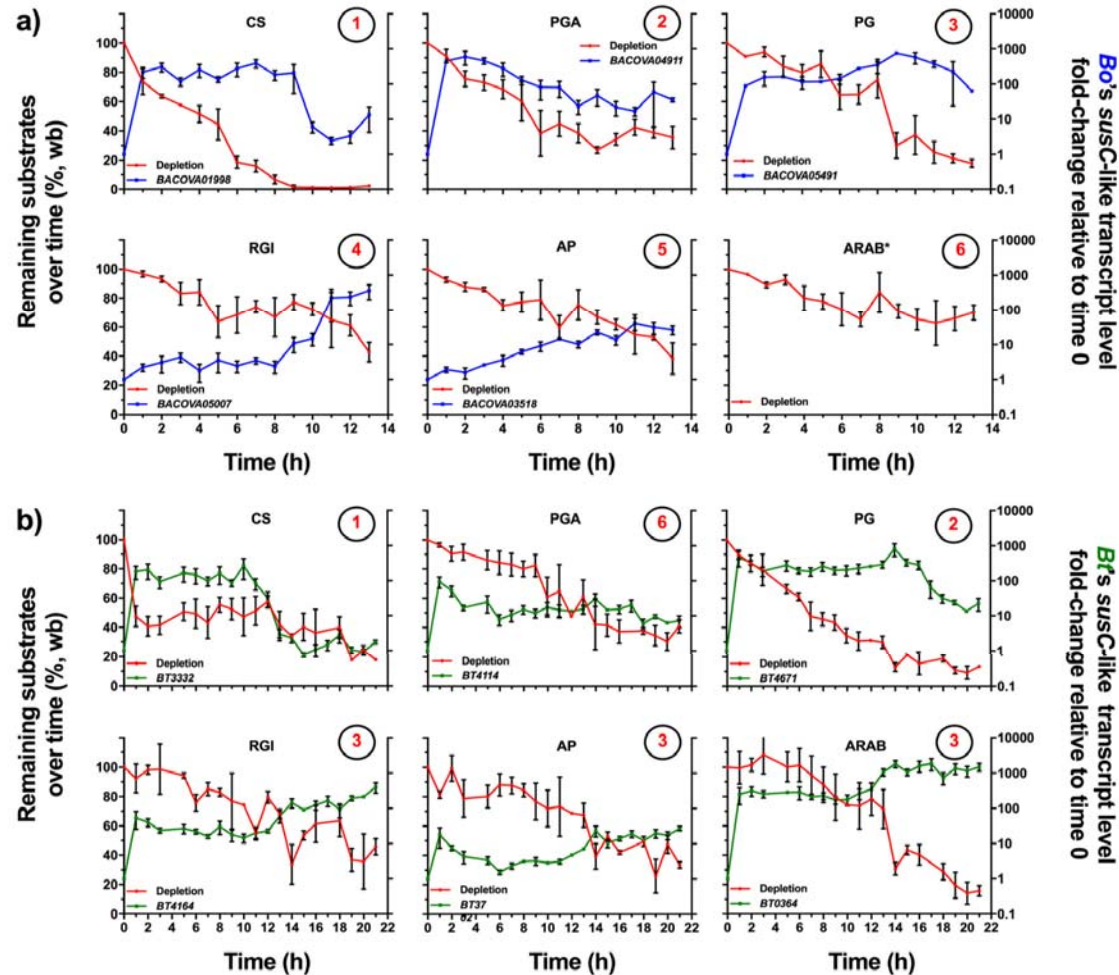


Hierarchy of stable states



- Random lists: $\sim(N/e) \cdot \log N$ 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

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

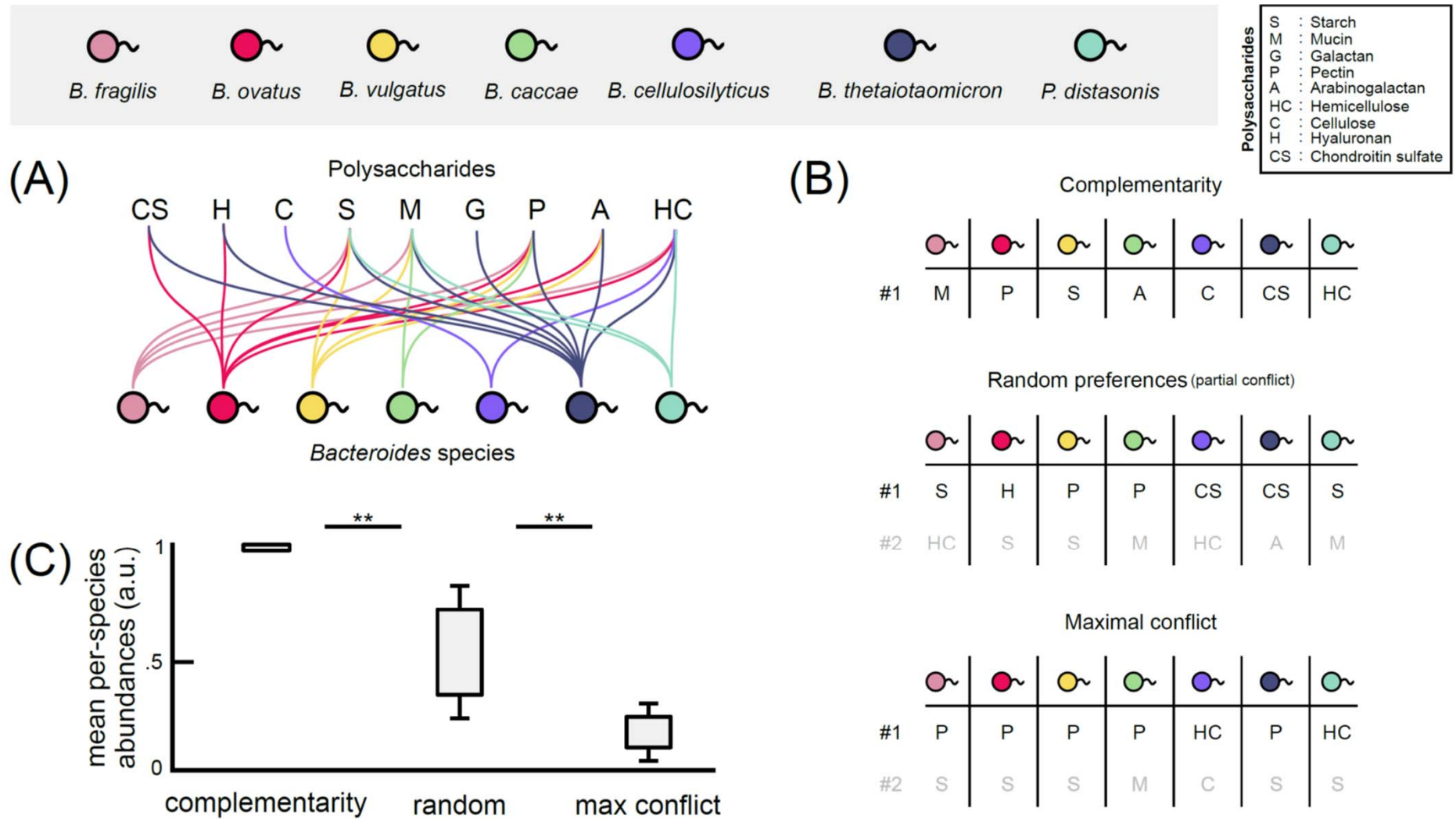


Bacteroides ovatum
consuming different
polysaccharides:
arabinan (ARAB),
pectic galactan (PG),
rhamnogalacturonan I (RGI),
chondroitin sulfate (CS),
polygalacturonic acid (PGA),
amylopectin (AP)

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

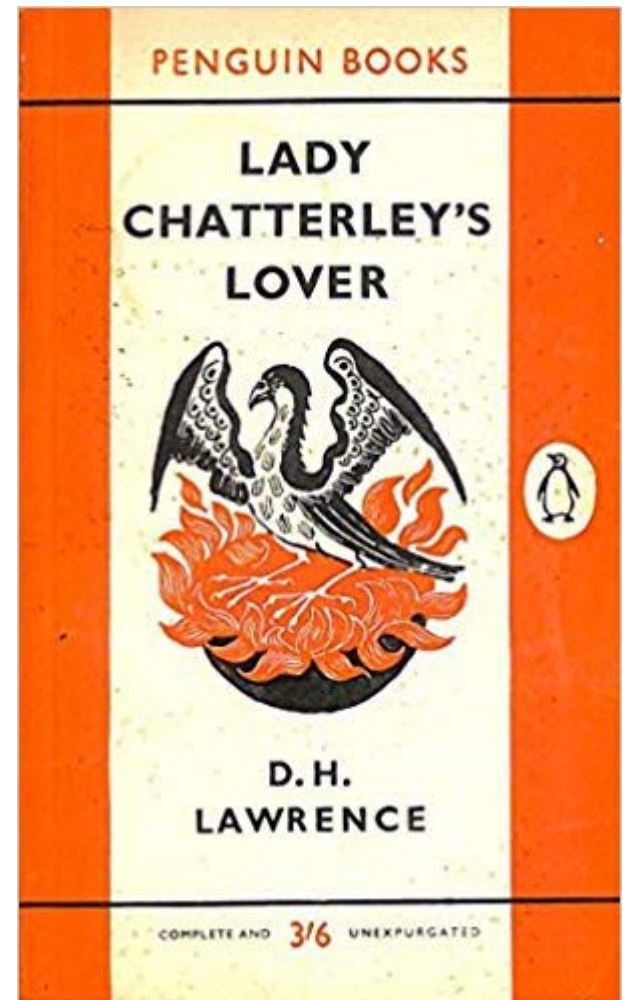
Tuncil, Y. et al. (Eric Martens @ U Michigan) Reciprocal Prioritization to Dietary Glycans by Gut Bacteria in a Competitive Environment Promotes Stable Coexistence. *Mbio* 8, e01068–17 (2017).

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:

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

Similar
for n_j

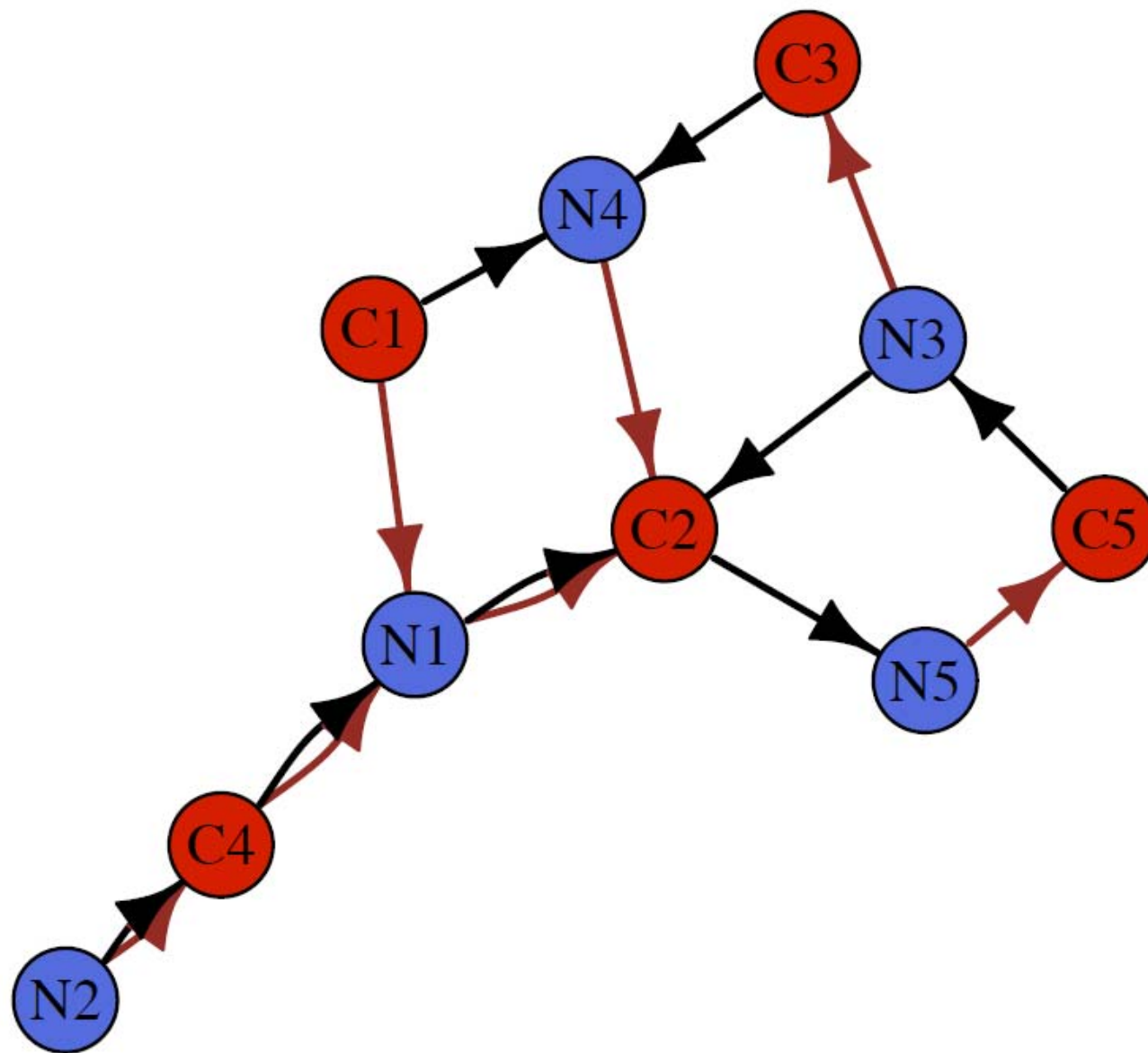
Modified competitive exclusion principle

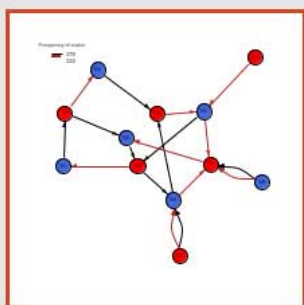
$$\frac{dB_{\alpha}}{dt} = B_{\alpha} \left(\min(\lambda_{\alpha}^{(c)} c_i, \lambda_{\alpha}^{(n)} n_j) - \delta \right)$$

- 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.

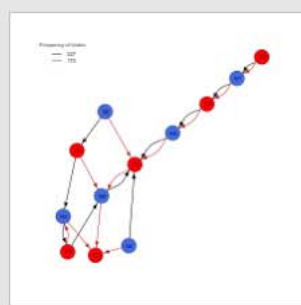
Modified exclusion rule = marriage

- 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

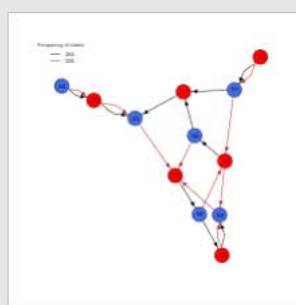




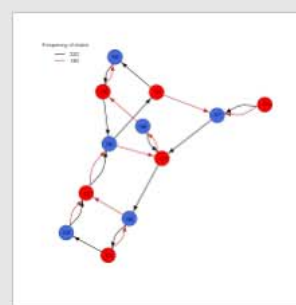
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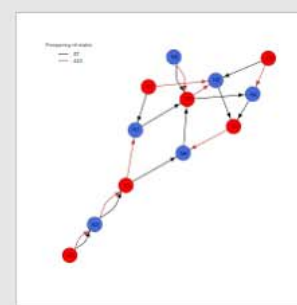
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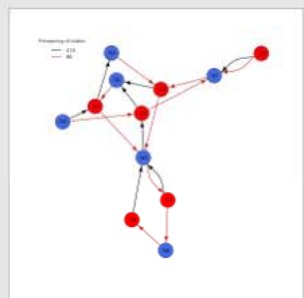
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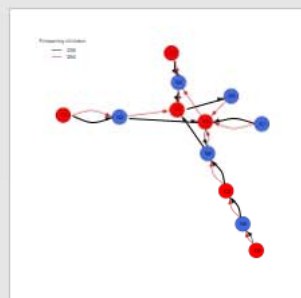
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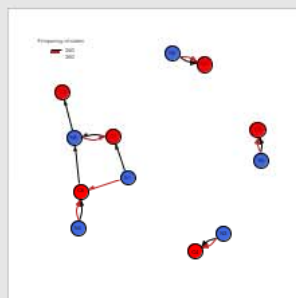
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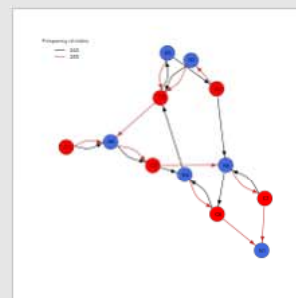
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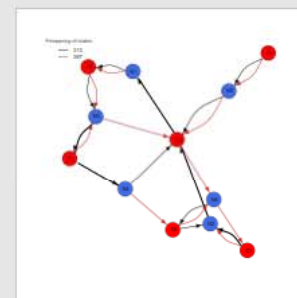
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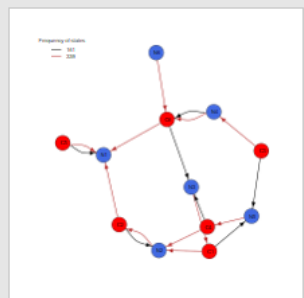
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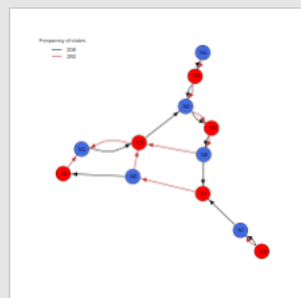
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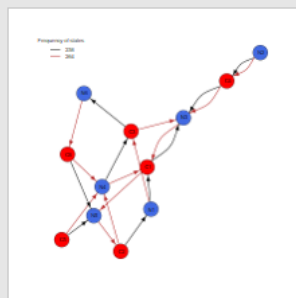
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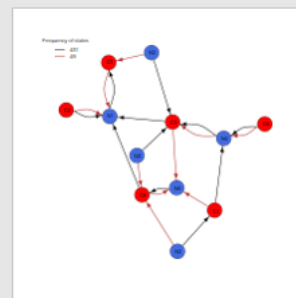
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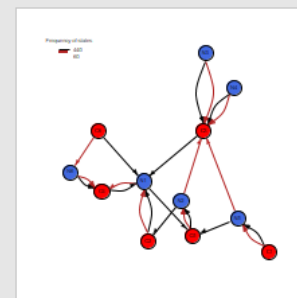
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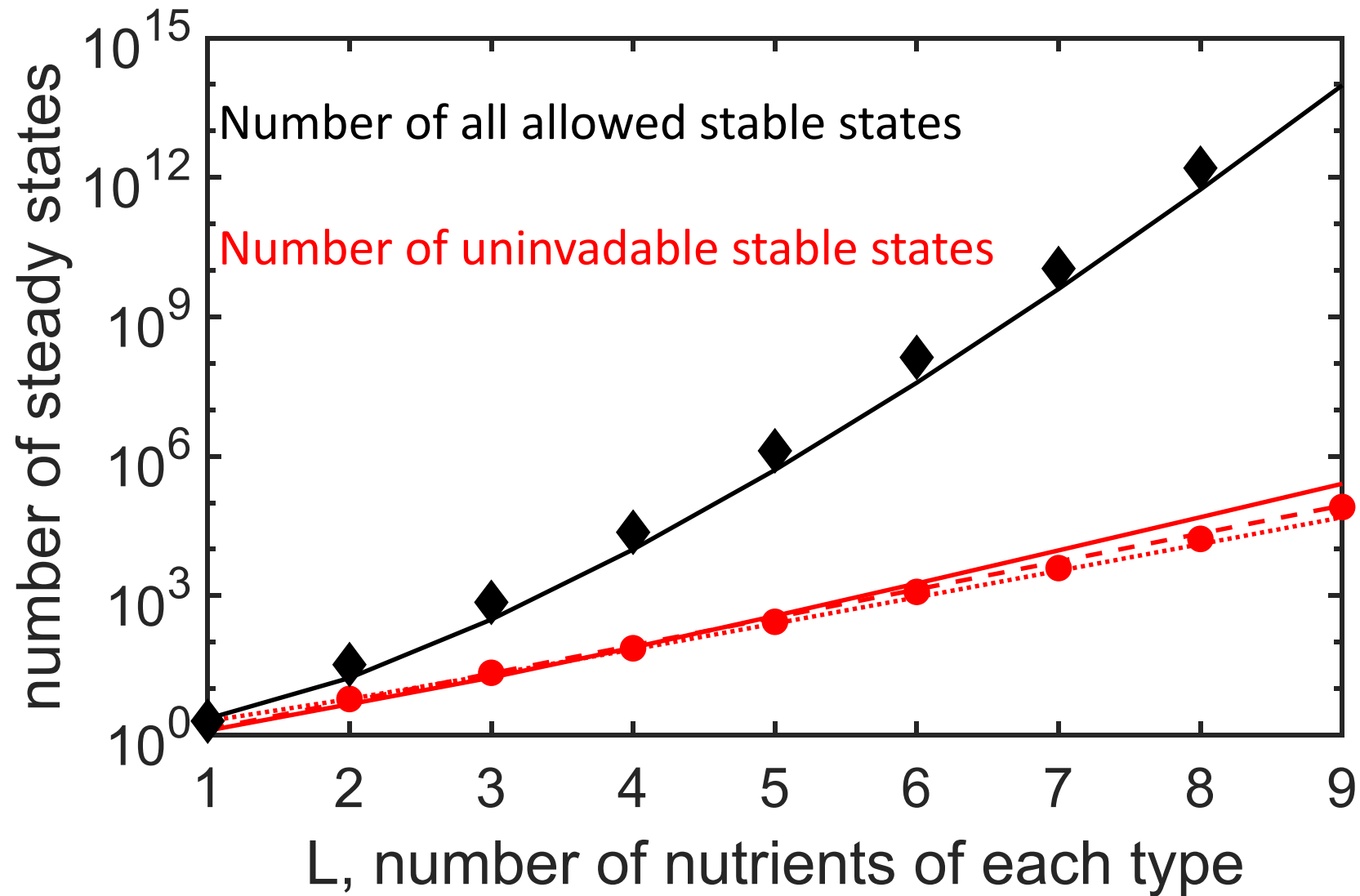


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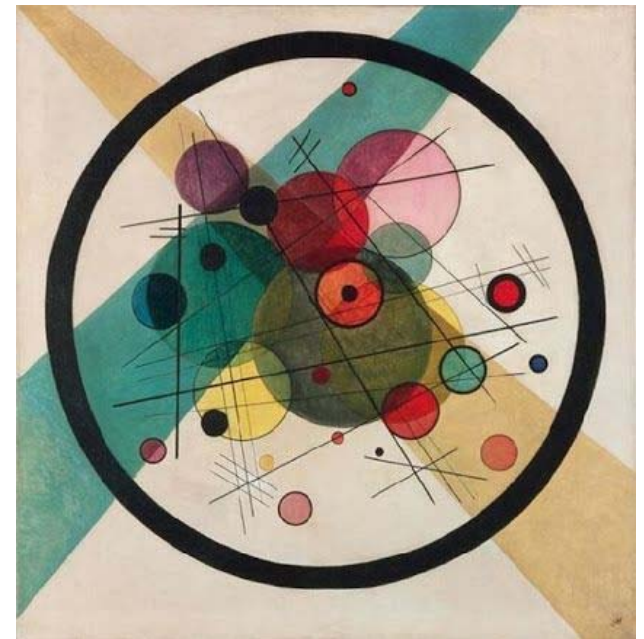
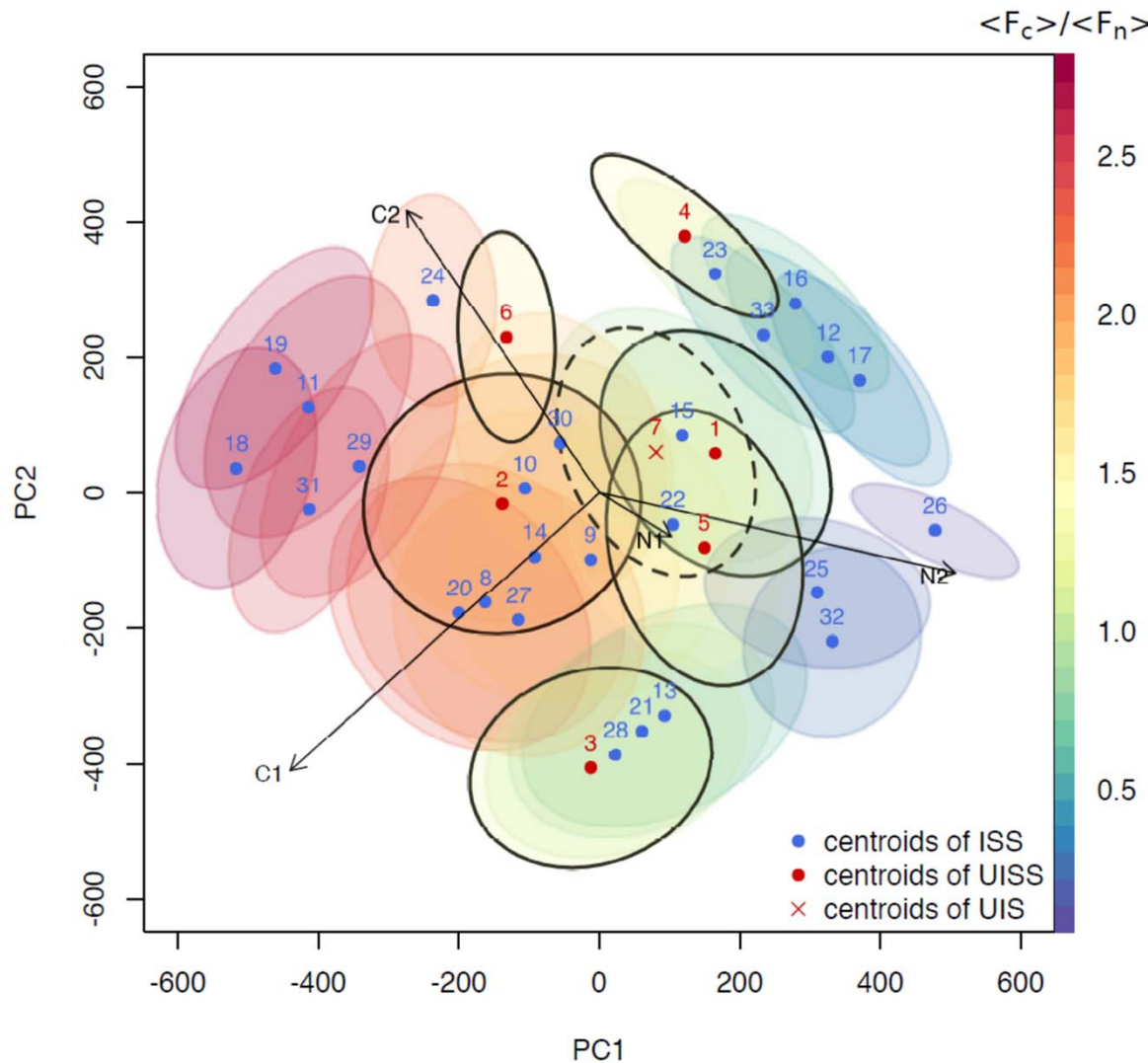


21

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

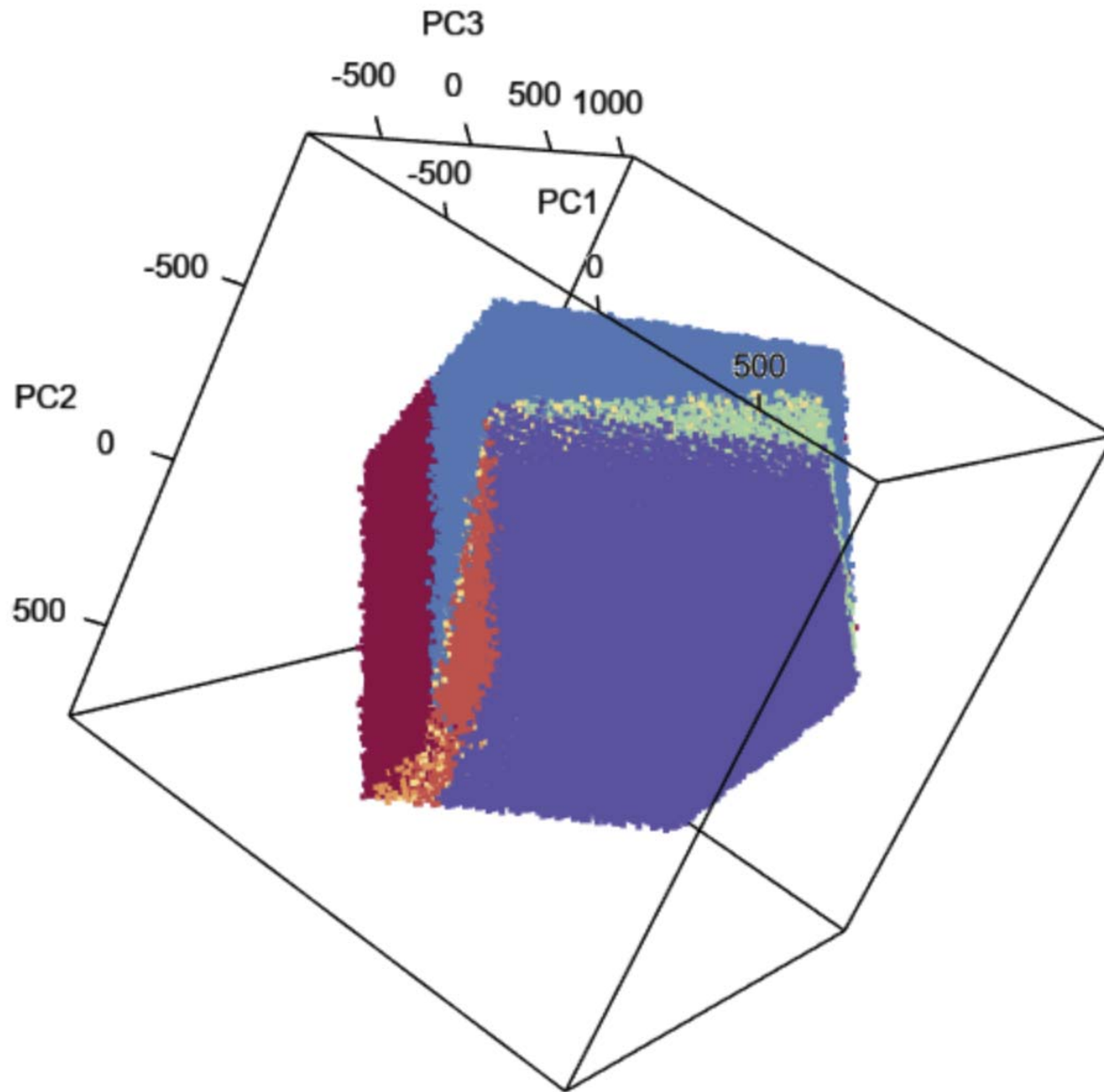


Each state has a **region of carbon and nitrogen fluxes**, where it is **allowed**.

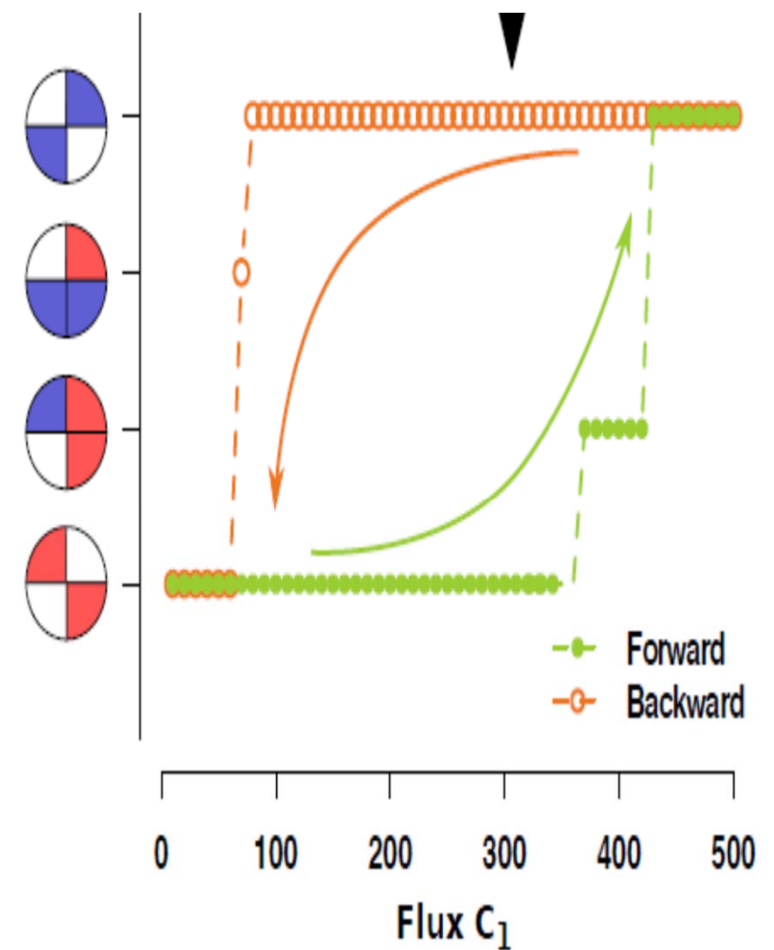
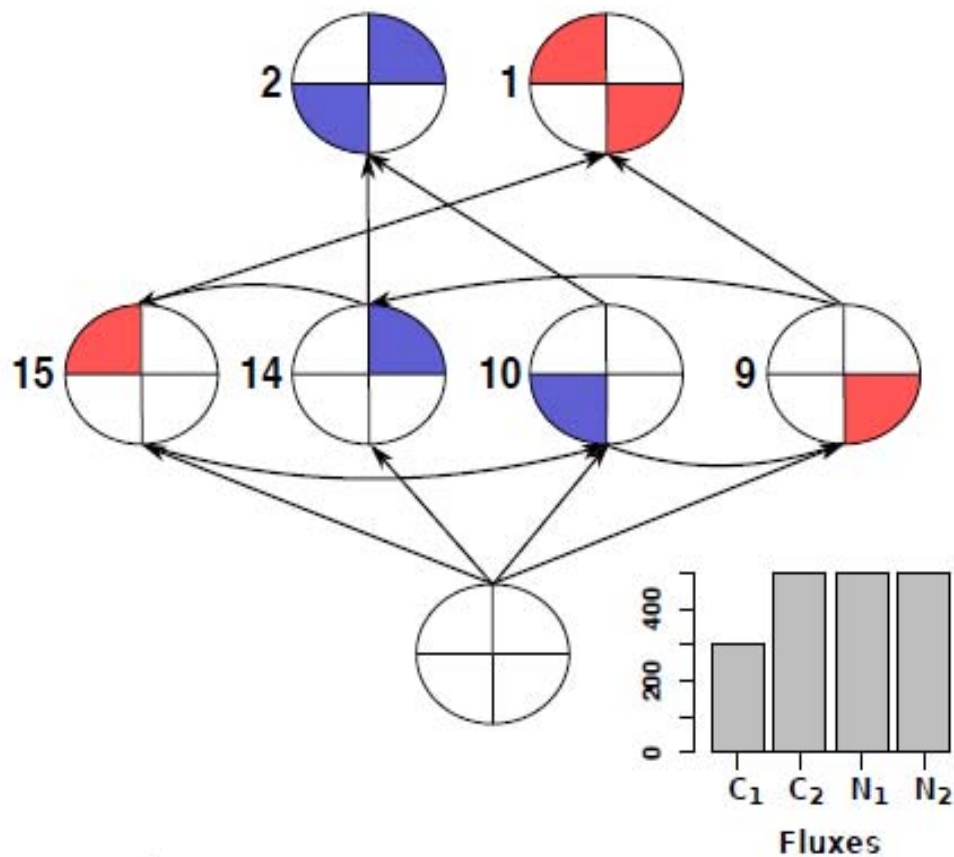
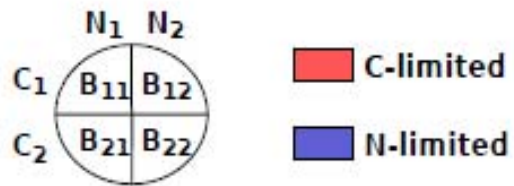


Wassily Kandinsky (Russian, later French, *Circles in a Circle*, 1923

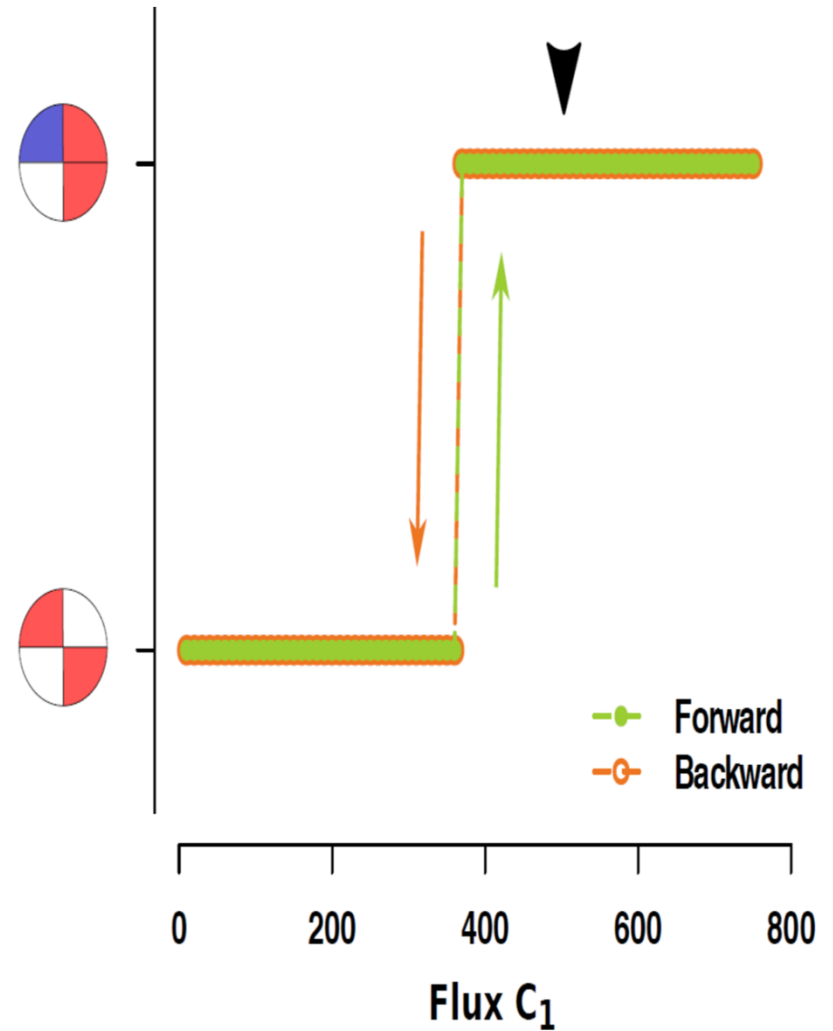
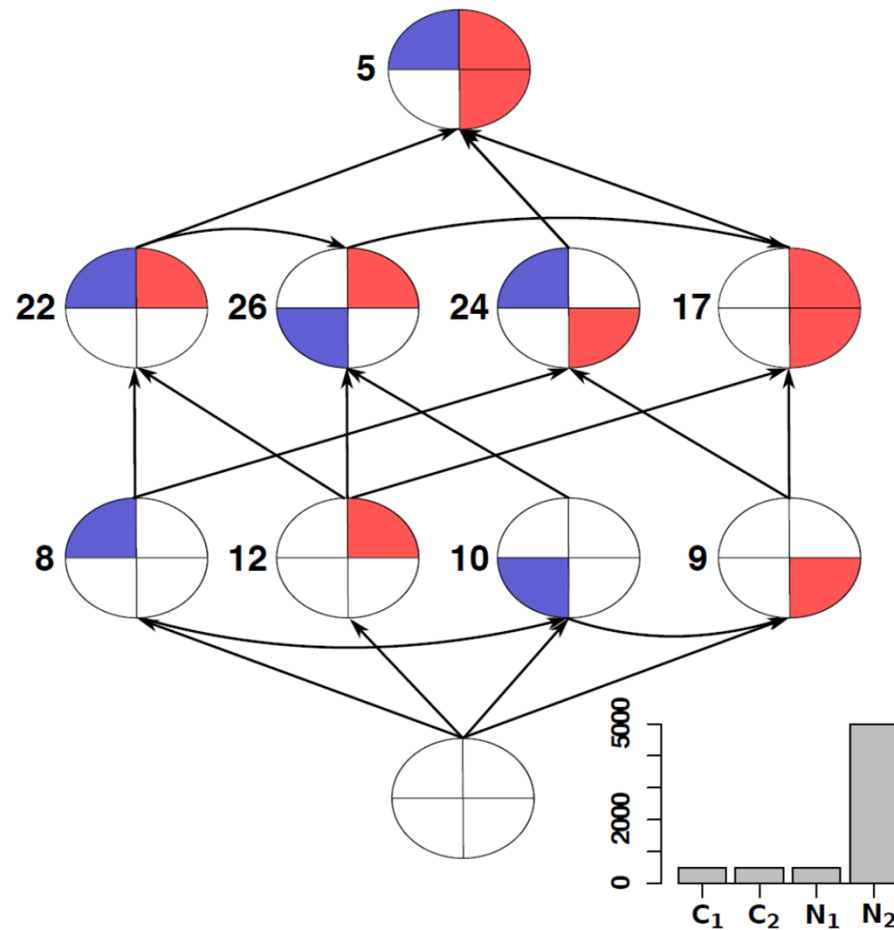
And now a cubistic version



Bistability of 2 states for given fluxes

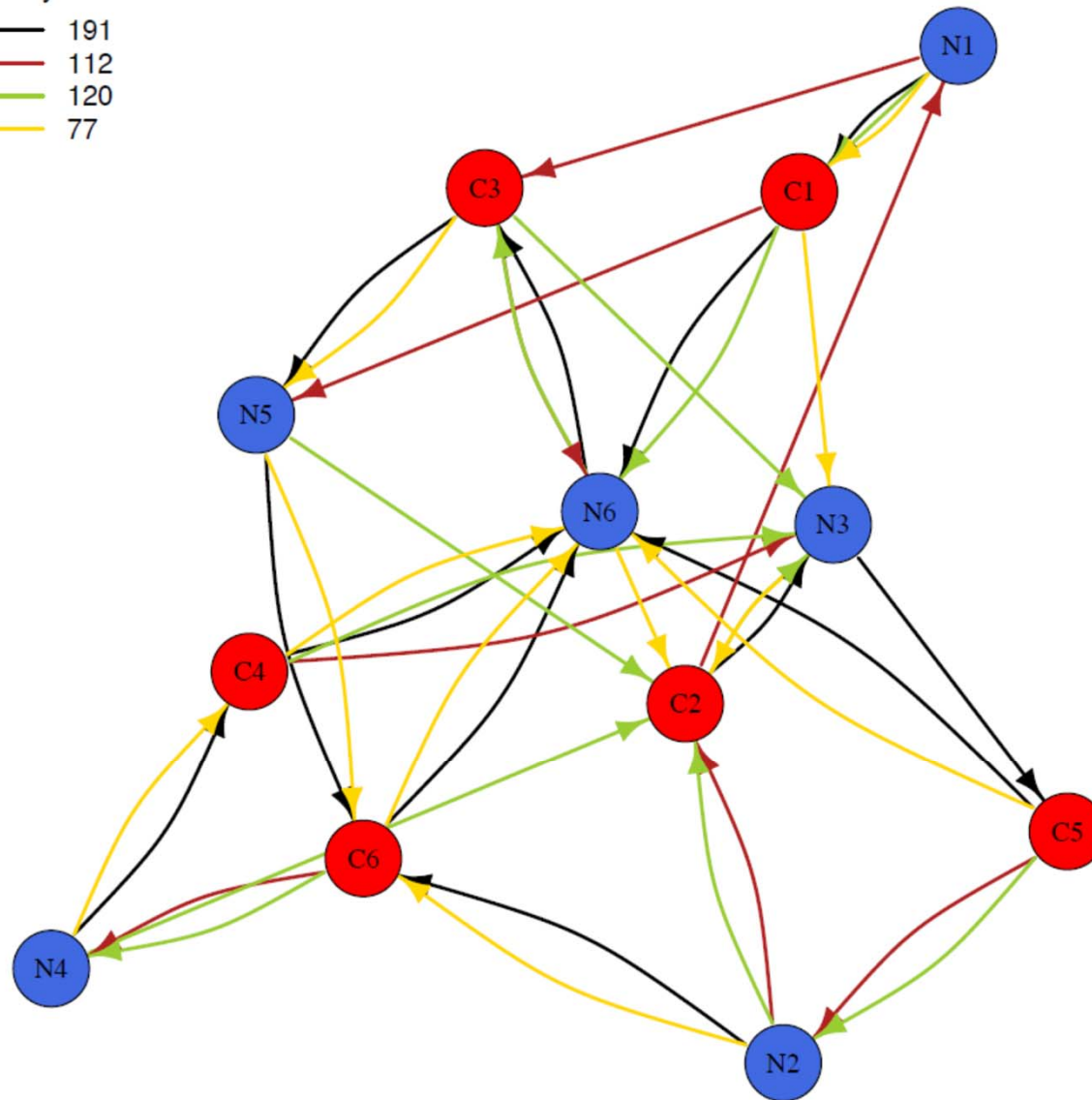


Monostability: 1 state is allowed for given fluxes



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

Frequency of states



6C-6N
36 species

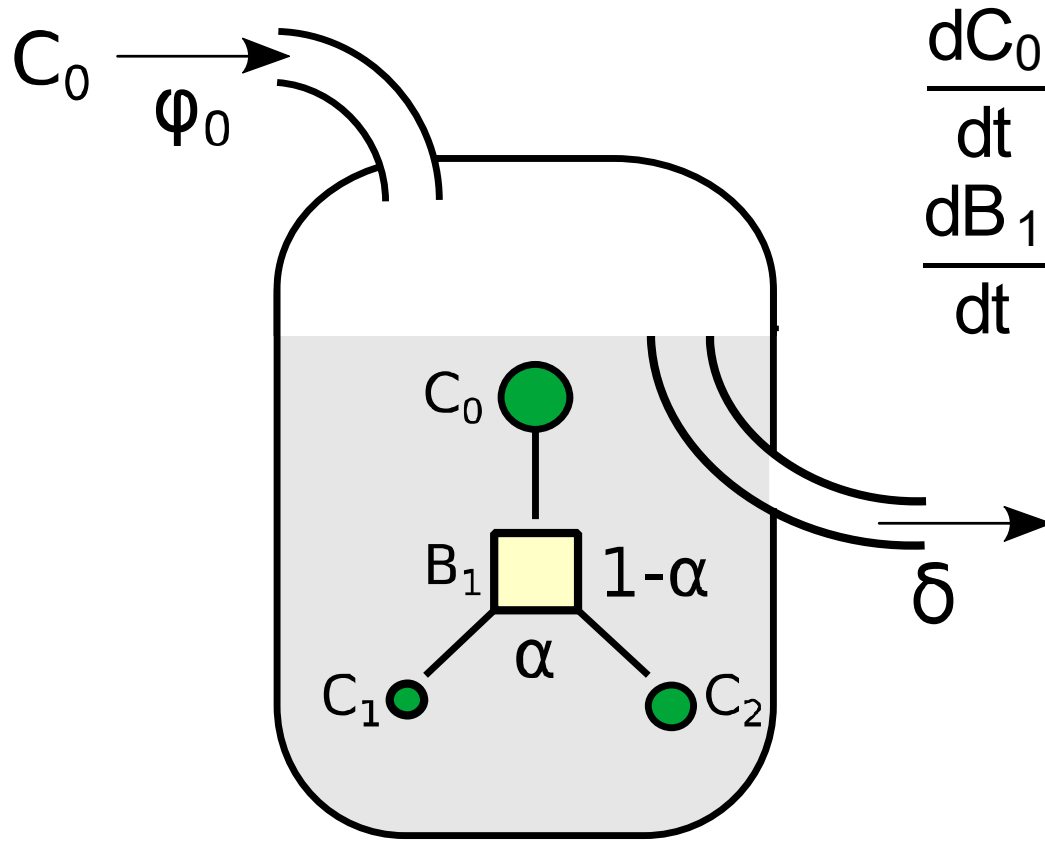
**THOSE ARE MY PRINCIPLES, AND IF YOU DON'T
LIKE THEM... WELL, I HAVE OTHERS.**

GROUCHO MARX



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

Model assumptions

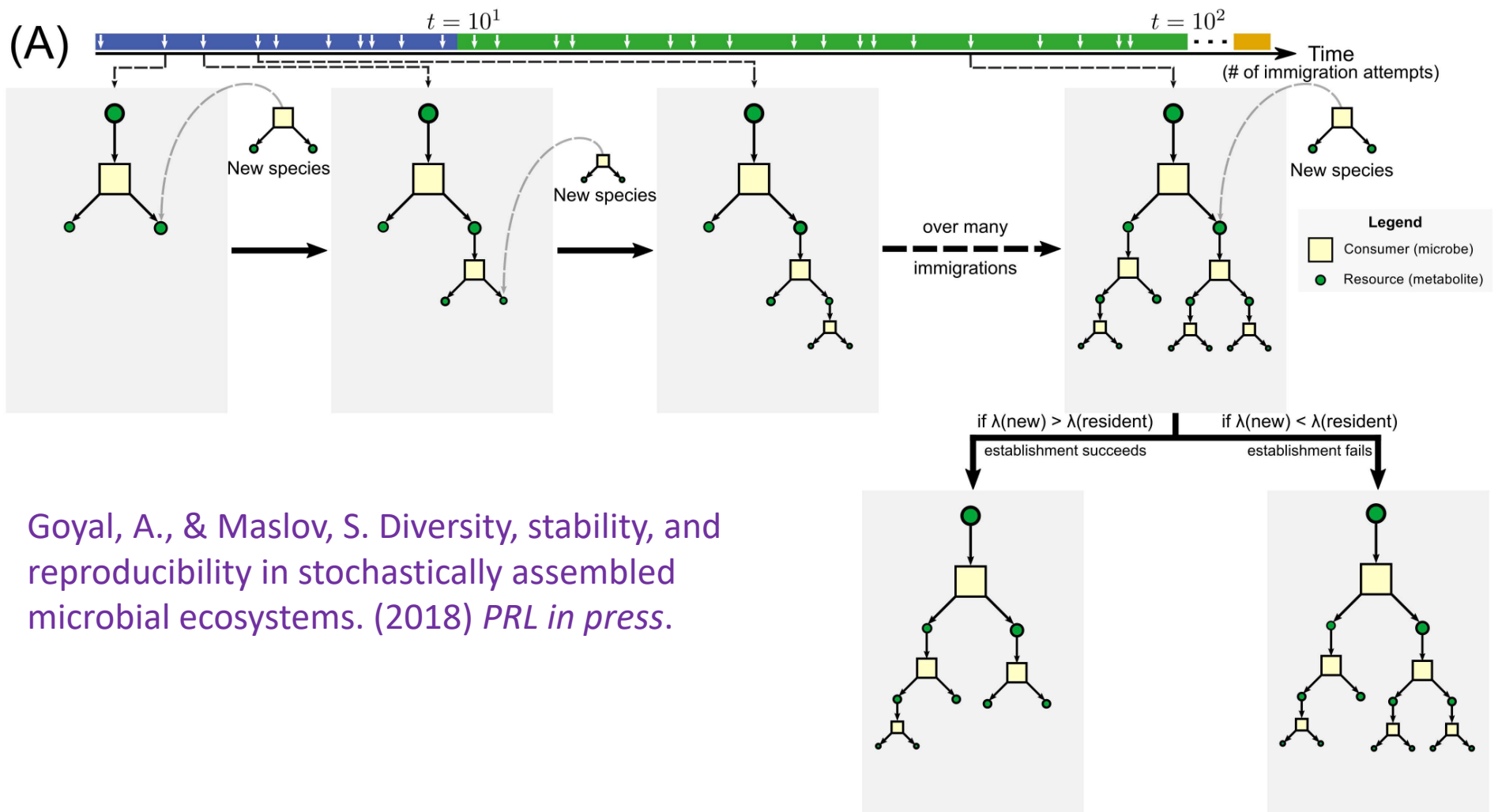


$$\frac{dC_0}{dt} = \varphi_0 - \frac{\lambda_1 C_0 B_1}{Y} - \delta \cdot C_0,$$

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

- Each microbe uses one resource C_i
- Fraction $1-\alpha$ goes to biomass (Yield, $Y=1-\alpha$)
- Fraction α - converted to $\beta=2$ byproducts
- If two species want to use the same nutrient, one with a larger competitive ability λ_i wins

Community assembly process



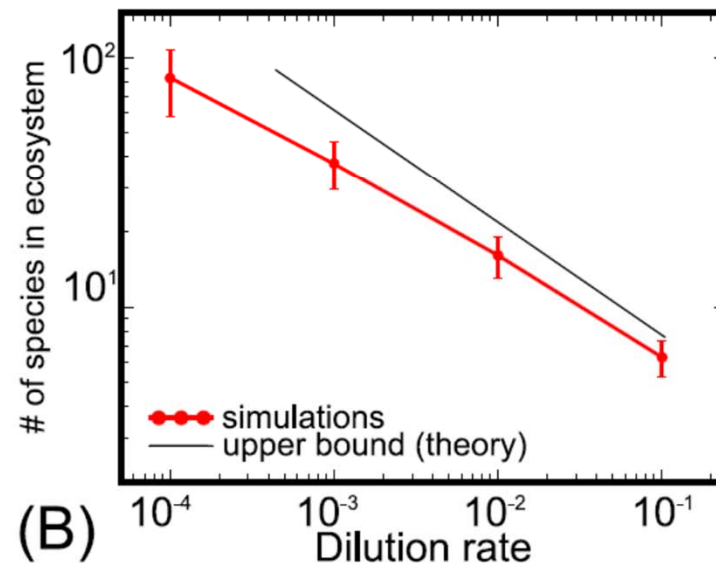
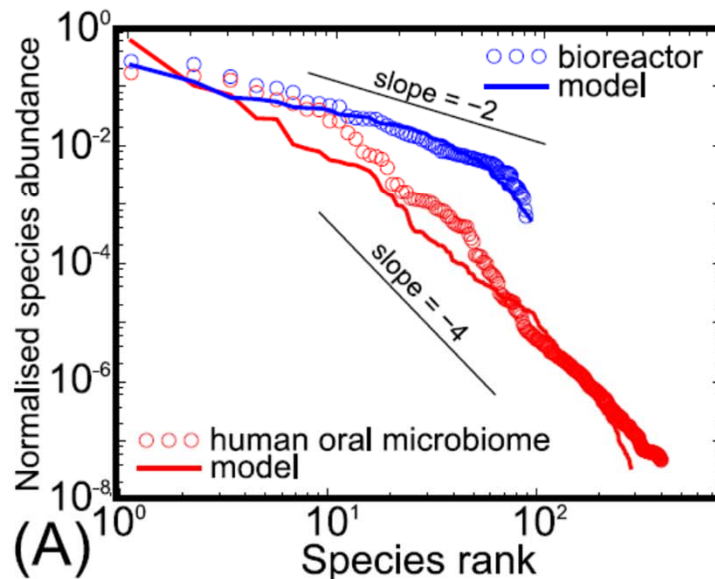
Goyal, A., & Maslov, S. Diversity, stability, and reproducibility in stochastically assembled microbial ecosystems. (2018) *PRL in press*.

- Power law abundance (b) distribution

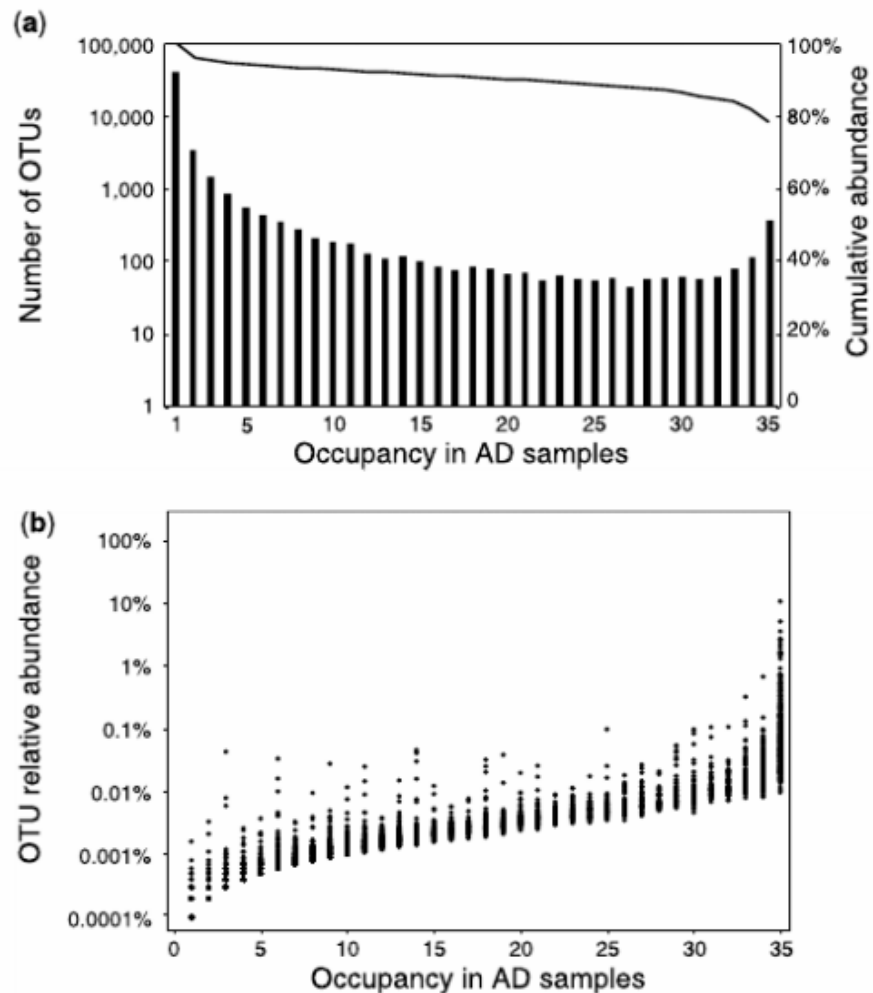
$$\mathcal{N}(B = b) \sim b^{-\left(1 + \frac{\log \beta}{|\log \alpha| + \log(\alpha + \beta)}\right)}$$

- Maximal number of species increases with decreasing dilution rate

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



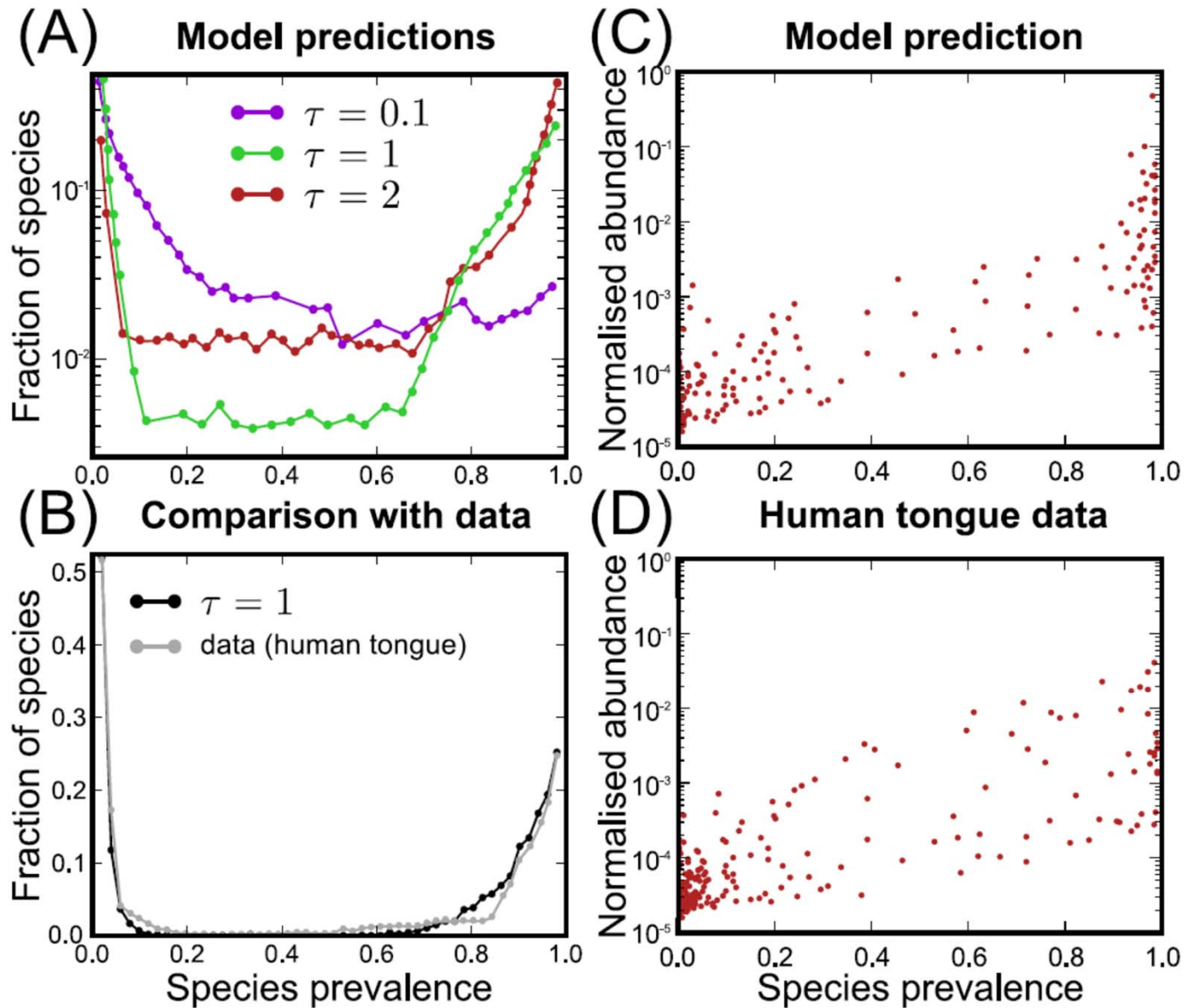
Species reproducibility has U-shaped distribution & is correlated with abundance



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

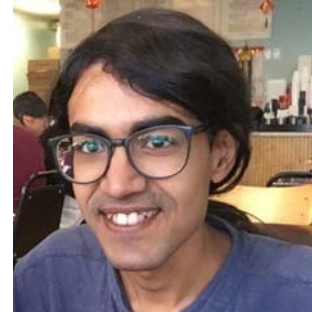
Mei R, Narihiro T, Nobu M, Kuroda K, Liu W-T (2016) Sci Reports 6:34090.

U-shaped prevalence distribution



Collaborators

- Akshit Goyal,
PhD student, Simons
Centre, NCBS, Bangalore, India



- Veronika Dubinkina,
PhD student, UIUC



- Parth Pratim
postdoc, UIUC



- Yulya Fridman
researcher, Kurchatov
Institute, Moscow



WHY ARE THERE SLAVES IN THE BIBLE

WHY DO TWINS HAVE DIFFERENT FINGERPRINTS
WHY ARE AMERICANS AFRAID OF DRAGONS
WHY IS HTTPS CROSSED OUT IN RED
WHY IS THERE A LINE THROUGH HTTPS
WHY IS THERE A RED LINE THROUGH HTTPS ON FACEBOOK
WHY IS HTTPS IMPORTANT

Credit: XKCD
comics

QUESTIONS FOUND IN GOOGLE AUTOCOMPLETE



WHY ARE THERE WEEKS IN MAY DO I FEEL DIZZY

WHY DO WHALES JUMP
WHY ARE WITCHES GREEN
WHY ARE THERE MIRRORS ABOVE BEDS
WHY DO I SAY UH
WHY IS SEA SALT BETTER
WHY ARE THERE TREES IN THE MIDDLE OF FIELDS
WHY IS THERE NOT A POKEMON MMO
WHY IS THERE LAUGHING IN TV SHOWS
WHY ARE THERE DOORS ON THE FREEWAY
WHY ARE THERE SO MANY SVCHOST.EXE RUNNING
WHY AREN'T THERE ANY COUNTRIES IN ANTARCTICA
WHY ARE THERE SCARY SOUNDS IN MINECRAFT
WHY IS THERE KICKING IN MY STOMACH
WHY ARE THERE TWO SLASHES AFTER HTTP
WHY ARE THERE CELEBRITIES
WHY DO SNAKES EXIST
WHY DO OYSTERS HAVE PEARLS
WHY ARE DUCKS CALLED DUCKS
WHY DO THEY CALL IT THE CLAP
WHY ARE KYLE AND CARTMAN FRIENDS
WHY IS THERE AN ARROW ON AANG'S HEAD
WHY ARE TEXT MESSAGES BLUE
WHY ARE THERE MUSTACHES ON CLOTHES
WHY ARE THERE MUSTACHES ON CARS
WHY ARE THERE MUSTACHES EVERYWHERE
WHY ARE THERE SO MANY BIRDS IN OHIO
WHY IS THERE SO MUCH RAIN IN OHIO
WHY IS OHIO WEATHER SO WEIRD
WHY ARE THERE MALE AND FEMALE BIKES

WHY ARE THERE BRIDESMAIDS
WHY DO DYING PEOPLE REACH UP
WHY AREN'T THERE VARIOUS PRIETIES
WHY ARE OLD KLINGONS DIFFERENT



WHY IS PROGRAMMING SO HARD
WHY IS THERE A 0 OHM RESISTOR
WHY DO AMERICANS HATE SOCCER
WHY DO RHYMES SOUND GOOD
WHY DO TREES DIE
WHY IS THERE NO SOUND ON CNN
WHY AREN'T POKEMON REAL
WHY AREN'T BULLETS SHARP
WHY DO DREAMS SEEM SO REAL

WHY AREN'T ECONOMISTS RICH
WHY DO AMERICANS CALL IT SOCCER
WHY ARE MY EARS RINGING
WHY ARE THERE SO MANY AVENGERS
WHY ARE THE AVENGERS FIGHTING THE X MEN
WHY IS WOLVERINE NOT IN THE AVENGERS

WHY ARE THERE ANTS IN MY LAPTOP

WHY IS EARTH TILTED
WHY IS SPACE BLACK
WHY IS OUTER SPACE SO COLD
WHY ARE THERE PYRAMIDS ON THE MOON
WHY IS NASA SHUTTING DOWN



WHY IS THERE AN OWL IN MY BACKYARD
WHY IS THERE AN OWL OUTSIDE MY WINDOW
WHY IS THERE AN OWL ON THE DOLLAR BILL
WHY DO OWLS ATTACK PEOPLE
WHY ARE AK 47s SO EXPENSIVE
WHY ARE THERE HELICOPTERS CIRCLING MY HOUSE
WHY ARE THERE GODS
WHY ARE THERE TWO SPOCKS

WHY ARE THERE TINY SPIDERS IN MY HOUSE
WHY DO SPIDERS COME INSIDE
WHY ARE THERE HUGE SPIDERS IN MY HOUSE
WHY ARE THERE LOTS OF SPIDERS IN MY HOUSE
WHY ARE THERE SPIDERS IN MY ROOM
WHY ARE THERE SO MANY SPIDERS IN MY ROOM
WHY DO SPIDER BITES ITCH
WHY IS DYING SO SCARY

WHY IS THERE NO GPS IN LAPTOPS
WHY DO KNEES CLICK
WHY AREN'T THERE E GRADES
WHY IS ISOLATION BAD
WHY DO BOYS LIKE ME
WHY DON'T BOYS LIKE ME
WHY IS THERE ALWAYS A JAVA UPDATE
WHY ARE THERE RED DOTS ON MY THIGHS
WHY IS LYING GOOD



WHY IS MT VESUVIUS THERE
WHY DO THEY SAY T MINUS
WHY ARE THERE OBELISKS
WHY ARE WRESTLERS ALWAYS WET
WHY ARE OCEANS BECOMING MORE ACIDIC
WHY IS ARWEN DYING
WHY AREN'T MY QUAIL LAYING EGGS
WHY AREN'T MY QUAIL EGGS HATCHING
WHY AREN'T THERE ANY FOREIGN MILITARY BASES IN AMERICA

WHY ARE CIGARETTES LEGAL
WHY ARE THERE DUCKS IN MY POOL
WHY IS JESUS WHITE
WHY IS THERE LIQUID IN MY EAR
WHY DO Q TIPS FEEL GOOD
WHY DO GOOD PEOPLE DIE



WHY ARE ULTRASOUNDS IMPORTANT
WHY ARE ULTRASOUND MACHINES EXPENSIVE
WHY IS STEALING WRONG

WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND