

Microbial community assembly and competition in boom-and-bust environments

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Astrology → **Astronomy**

Nostradamus → Brahe → Kepler, Newton

Biology → **Bionomy**

Terrence Hwa[©]

Ecology → **Economy**

Physiology → **Physiognomy**

Slow progress in models predicting microbial community assembly

- I started modeling microbial communities 8 years ago, hoping to make predictions
- Growth is described by Monod equation:

$$g(R) = \frac{g_{max} R}{R + K}$$

- For steady state in a chemostat $R \ll K$ so

$$g(R) = \frac{g_{max}}{K} R$$

chemostats are to study oligotrophs not copiotrophs

- But K varies a lot between strains, depends on growth history, and is hard to measure!

TABLE 2. Kinetic constants and their temperature dependencies for *E. coli* grown with glucose as the sole source of carbon and energy

<i>E. coli</i> strain	<i>T</i> (°C)	<i>K_s</i> (μg liter ⁻¹)	μ _{max} (h ⁻¹)	Cultivation method	Reference
ML 30	40	34 ^a	0.75	Chemostat	135
H	37	4,000	0.94	Batch	166
B/r Thy ⁻	37	180	1.04	Batch	260
ML 308	37	3,400	0.75	Batch	125
B/r CM6	37	540	NR ^c	Batch	19
K-12	37	7,160	0.76	Batch	52
ML 308	37	107	0.54	Chemostat	129
		2,340	1.23	Batch	
ML 30	37	53	0.80	Chemostat	224
		72	0.92		
ML 30	37	33 ^a	0.76	Chemostat	34
B/r Thy ⁻	30	180	NR	Batch	260
NR ^c	30	77,000–99,000	0.92–1.05	Chemostat	222
ML 30G	30	68 ^b	0.78	Batch	226
		12,600			
ML 30	28.4	33 ^a	0.54	Chemostat	34
O-124	26	2,400	0.55	Batch	49
OUMI7020	20	8,460 ^b	0.55	Batch	109
		46,800			
NR ^c	20	8,000	0.65	Chemostat	111
ML 30	17.4	33 ^a	0.19	Chemostat	34

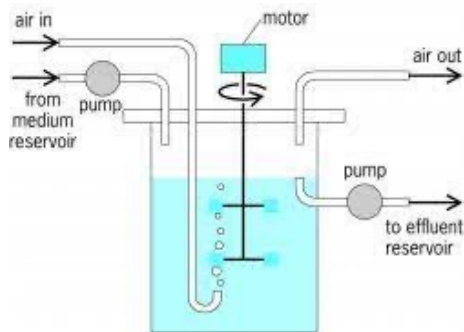
Karin Kovárová-Kovar
Thomas Egli

Growth Kinetics of
Suspended Microbial
Cells: From Single-
Substrate-Controlled
Growth to Mixed-
Substrate Kinetics.

Microbiol Mol Biol Rev
62, 646–666 (1998)

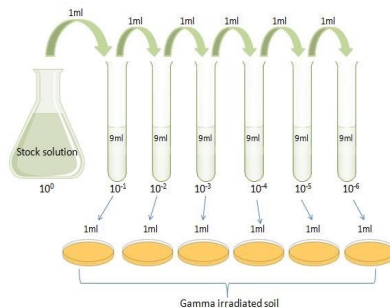
Microbial community dynamics is often **not in steady state** but **boom-and-bust**

We model this
(**chemostat**)



Many real ecosystems are dominated by **copiotrophs** not **oligotrophs**
(e.g., **algal blooms**)

But in the lab we do this
(**serial dilution/passage = batch growth**)



Boom-and-bust model parameters are **easy to measure**

To model batch growth
one needs to know:

- The **maximum growth rate** $g_i^{(\max)}$ on each resource
- The **lag times** τ_{ij} and dilution factor $D > 1$
- The **resource hierarchy** or **co-utilization ratio**

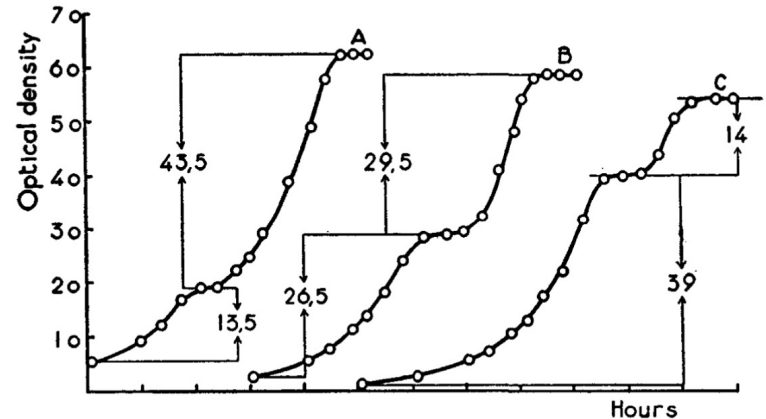


FIG. 9.—Diauxie. Growth of *E. coli* in synthetic medium with glucose+sorbitol as carbon source.

The figures between arrows indicate total growth corresponding to each cycle.

(a) Glucose 50 $\mu\text{g.}$ per ml.; sorbitol 150 $\mu\text{g.}$ per ml.

(b) Glucose 100 $\mu\text{g.}$ per ml.; sorbitol 100 $\mu\text{g.}$ per ml.

(c) Glucose 150 $\mu\text{g.}$ per ml.; sorbitol 50 $\mu\text{g.}$ per ml.

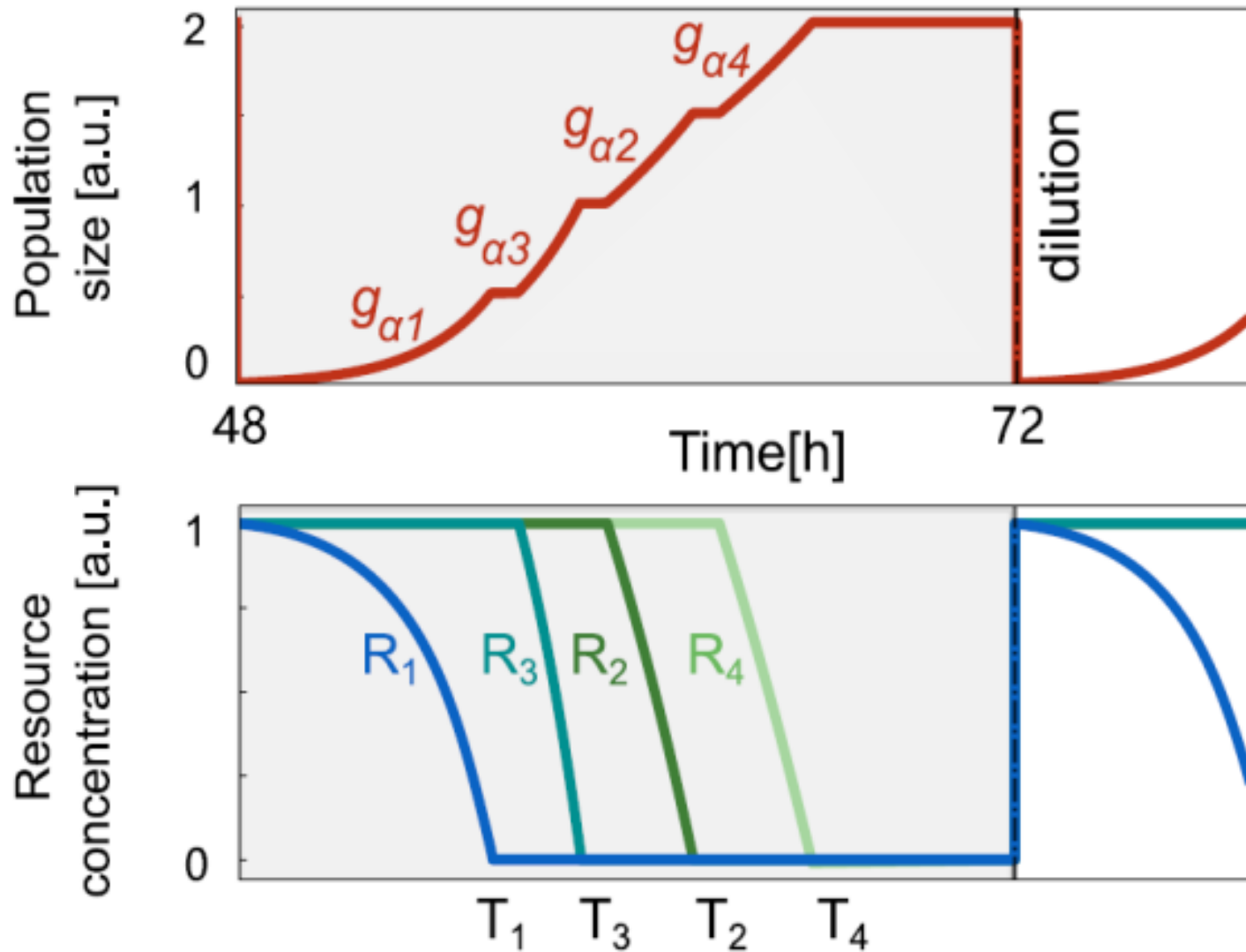
Total growth corresponding to first cycle is proportional to glucose concentration. Total growth of second cycle is proportional to sorbitol concentration (11).

Monod (1949) *The Growth of Bacterial Cultures. Annual Reviews in Microbiology*

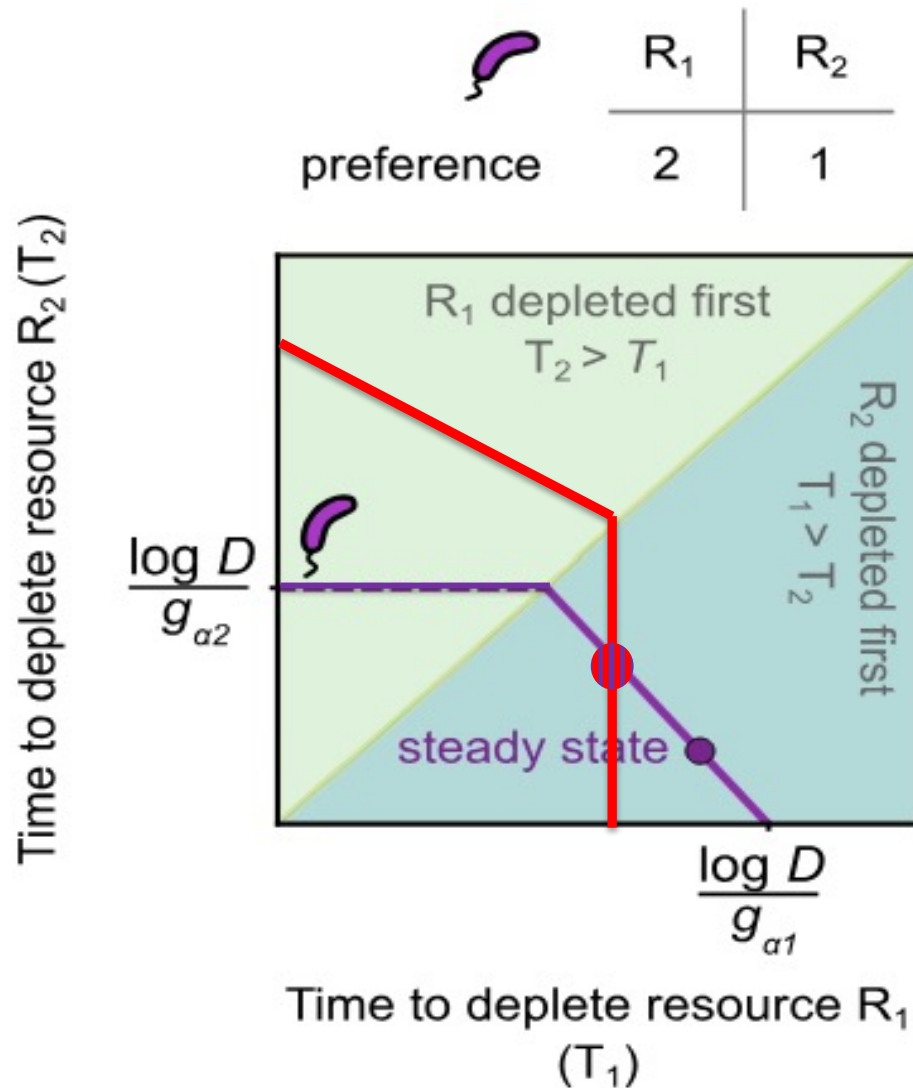
Use case scenario

- Your experimentalist friend has a favorite **set of n_S species: the “dream team”**
- He needs to keep **all species alive** in a serial passage (dilution) experiment
- We can provide the following services:
 - Determine if these species **can in principle stably coexist** on a given set of **n_R resources**
 - Design the **resource ratio $R_1: R_2: R_3$** for this community to successfully assemble
 - **Bonus.** Tune the resource ratio for a desired species abundance ratio **$N_1: N_2: N_3$**

The boom phase is defined
by resource depletion times T_i

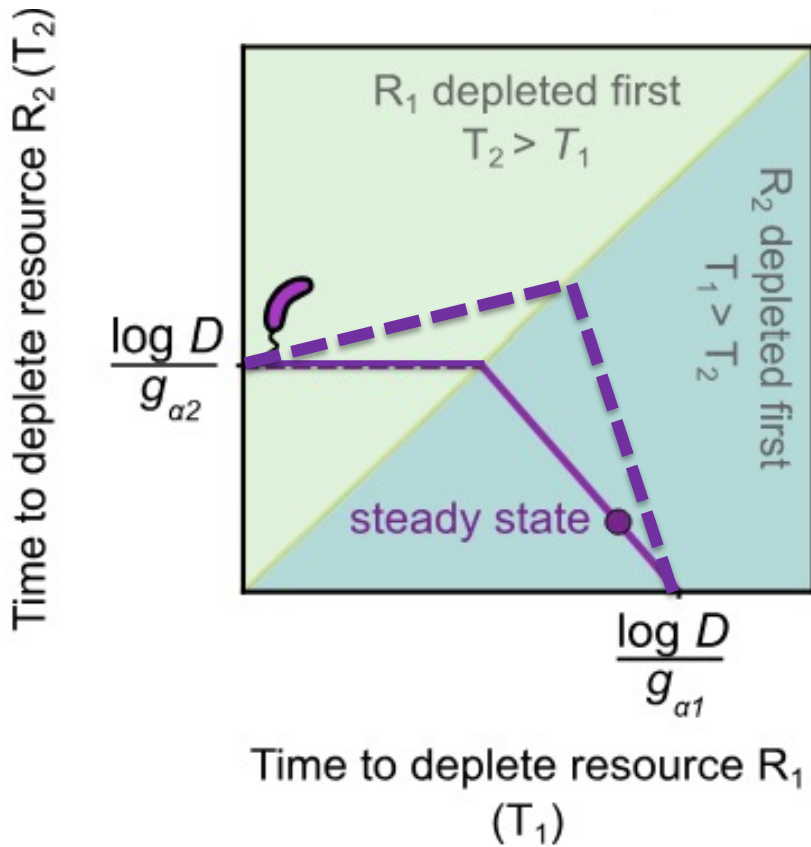


How to generalize Tilman's graphical method of from chemostats to serial dilution?

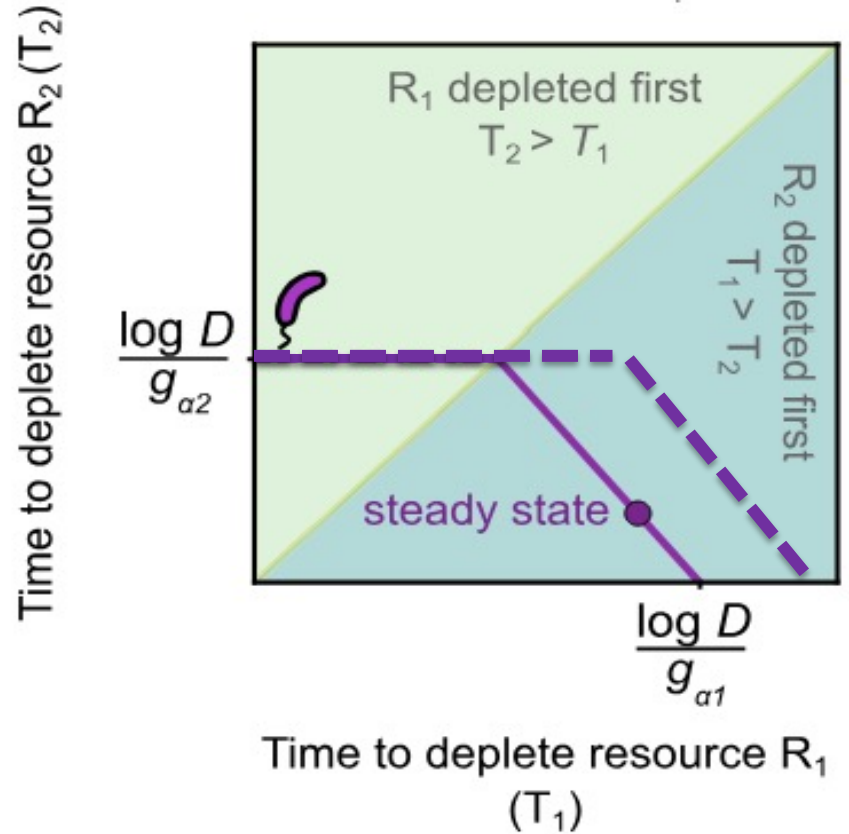


$$\exp(g_2 T_2) = D$$

$$T_2 = \log D / g_2$$

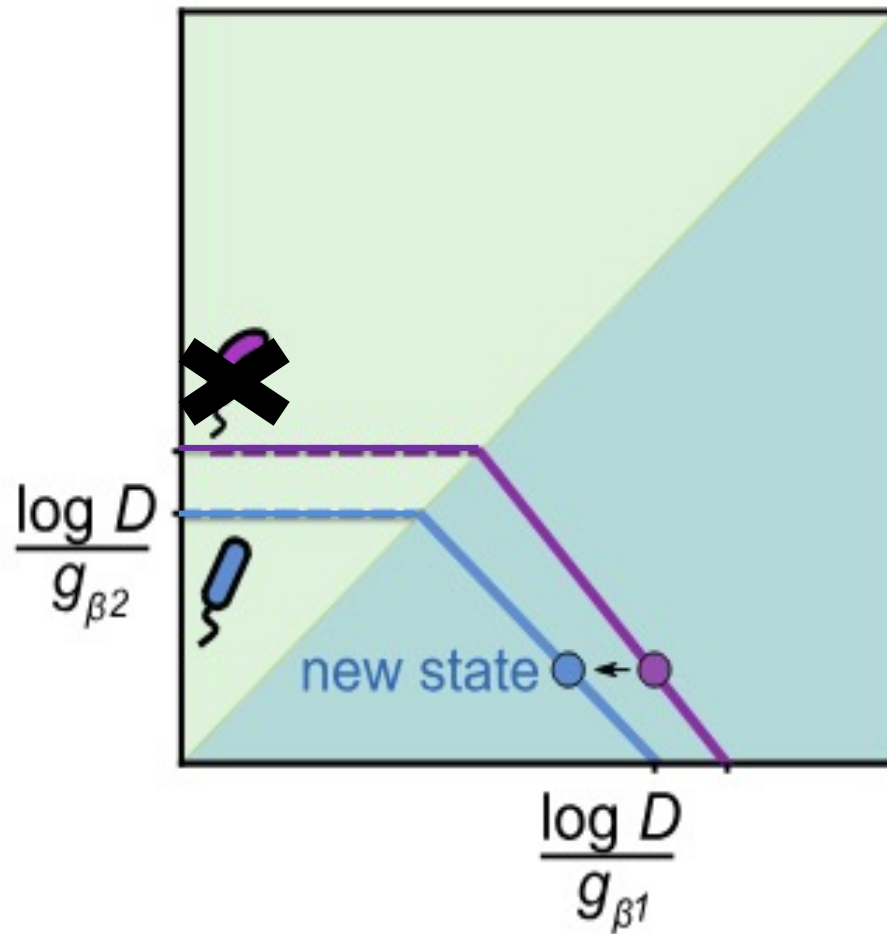


can be generalized
for co-utilization

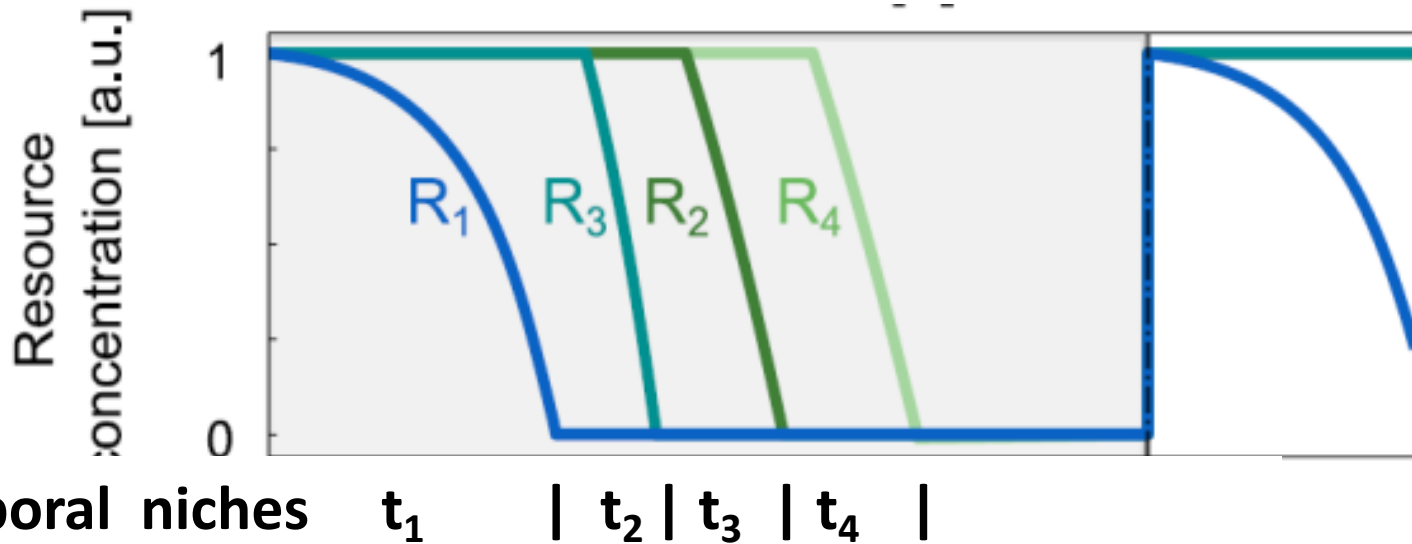


can be generalized
for lags

Feasibility: can these species in principle coexist? **These two cannot**



Change from resource depletion times to duration of temporal niches



- For **n resources** there are **$2^n - 1$ possible temporal niches**
- **Resource depletion order** (e.g., $T_1 < T_3 < T_2 \dots < T_n$ shown) determines which **n temporal niches** ($t_1, t_2, t_3, \dots, t_n$) are realized
- **To test feasibility**, one needs to go through **all of n! possible depletion orders**

Feasibility of the steady state

- $G_{\alpha i}$ is the growth rate of bug α in niche i
- Fix the depletion order $T_1 < T_3 < T_2 \dots < T_n$
- **Without lags:** $\sum_i G_{\alpha i} t_i = \log D$
- **With lags:** $\sum_i G_{\alpha i} (t_i - \tau_{\alpha i}) = \log D$
- $\sum_i G_{\alpha i} t_i = \log D + \sum_i G_{\alpha i} \tau_{\alpha i} = \log D_\alpha$

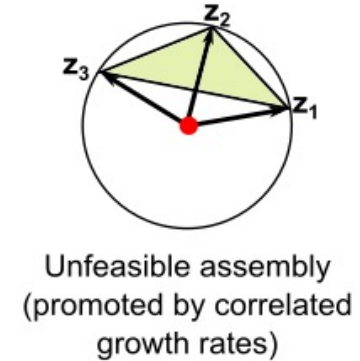
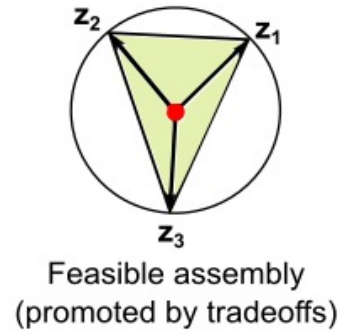
can be **formally solved** as

$$\mathbf{t}_i = \hat{G}^{-1} \cdot \overrightarrow{\log D}_\alpha$$

- The steady state is **feasible** if all $t_i > 0$
- $|\det(G)|$ = **stability** against **variations in lags**
- We separately test for **dynamical stability**

Feasibility of a random community with identical hierarchies

$$\vec{z}_i = \begin{bmatrix} z_{\alpha i} \\ z_{\beta i} \\ z_{\gamma i} \end{bmatrix} \sim \begin{bmatrix} g_{\alpha i} \\ g_{\beta i} \\ g_{\gamma i} \end{bmatrix} - \begin{bmatrix} \mu_{\alpha i} \\ \mu_{\beta i} \\ \mu_{\gamma i} \end{bmatrix}$$



$$P_{\text{feasible}}(n_S, n_R) = 1 - \left(\frac{1}{2}\right)^{n_R-1} \cdot \sum_{j=0}^{n_S-2} \binom{n_R-1}{j}$$

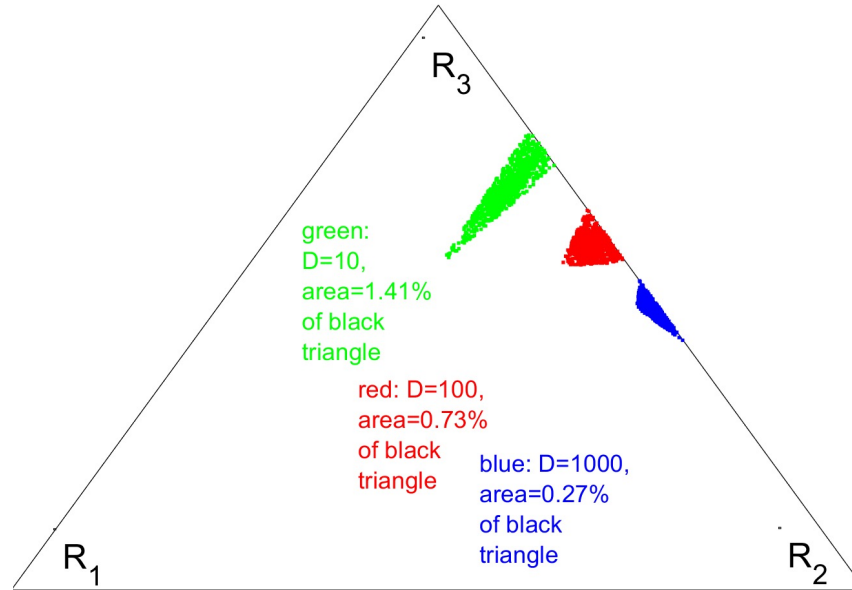
$$P_{\text{feasible}}(n_S, n_S) = \left(\frac{1}{2}\right)^{n_S-1}$$

$P_{\text{feasible}} \sim 0.5$ when $n_R = 2n_S$

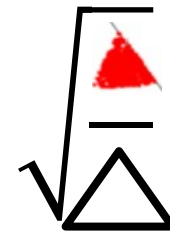
Tradeoffs promote the likelihood of assembly (see Posfai et al PRL 2017)

Supebugs suppress the likelihood of assembly (*V. natriegens* will win)

At what resource concentration ratios is this coexistence possible?



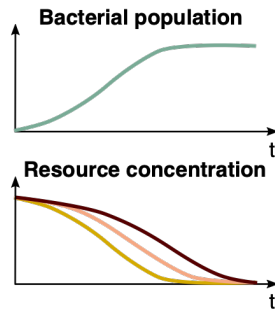
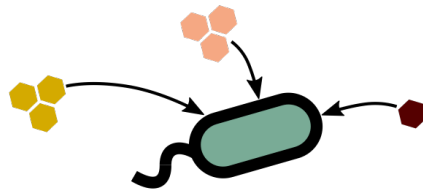
Normalized structural stability=



Can we use our
engineered assembly methods to
compare the success of
different metabolic strategies
in **real-life ecosystems?**

Microbial metabolic strategies

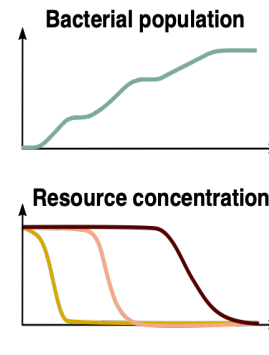
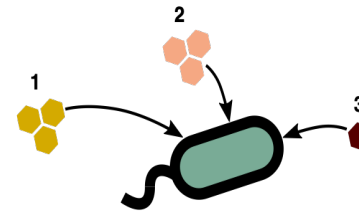
Cointilization of substitutable resources



MacArthur model, 1960s

See recent papers from
Mehta, O'Dwyer, Tikhonov,
Wingreen labs, and many others

Sequential utilization of substitutable resources



There is no standard model
for communities

We developed the methods:
Maslov lab 2018, 2021,
Gore lab, 2023



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Current Opinion in
Microbiology

Hierarchical and simultaneous utilization of carbon substrates: mechanistic insights, physiological roles, and ecological consequences

Hiroyuki Okano¹, Rutger Hermsen² and Terence Hwa¹



Bacteria grown on a mixture of carbon substrates exhibit two utilization patterns: hierarchical utilization (HU) and simultaneous utilization (SU). How and why cells adopt these different behaviors remains poorly understood despite decades of research. Recent studies address various open

underlying these utilization patterns. Here we review recent experimental and modeling studies that have provided fresh insights into this classical topic.

Hierarchical utilization (HU) refers to cases in which the

- **Regulatory mechanisms:** known well in model organisms. But may need 282 variables/476 parameters to describe
- **Physiological role:** understood through proteome allocation → growth optimization. But species **do not always optimize** proteome allocation
- **Ecological consequences:** poorly understood

How do we choose growth rates in our model?

- $g_i^{(max)} \rightarrow \lambda_i$

we follow the notation from [Hermsen et al. MSB \(2015\)](#)

- $\frac{\lambda_i}{1-\lambda_i/\lambda_c} = N(0.5, 0.1), \lambda_c = 1$

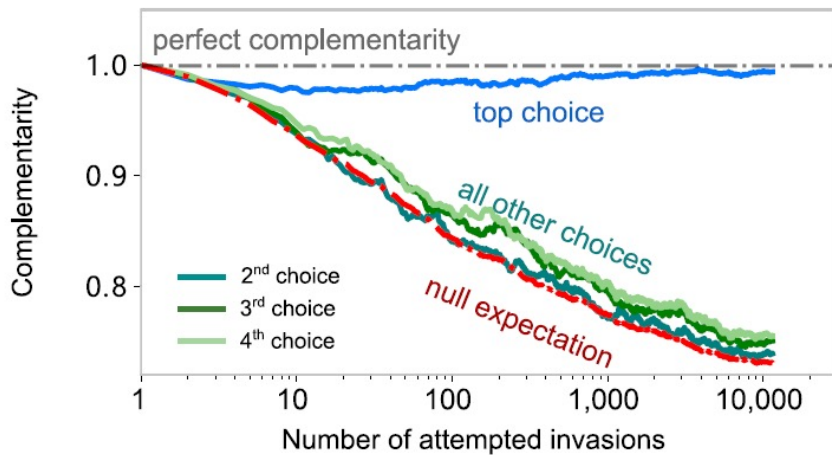
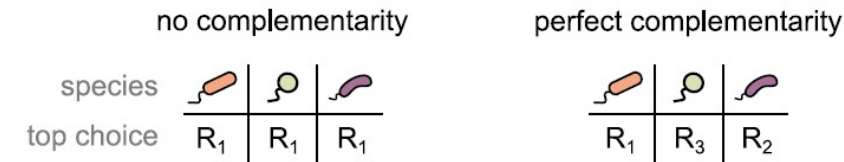
- $\lambda_{ij} = \frac{\lambda_i + \lambda_j - 2\lambda_i\lambda_j/\lambda_c}{1 - \lambda_i\lambda_j/\lambda_c^2}$ for co-utilizing species

Metabolic strategies we compare

- **“Smart” sequential utilization:**
 - resource hierarchy matches that of growth rates
- **Random sequential utilization:**
 - resource hierarchy is not correlated with growth rates
- **“Top smart” sequential utilization:**
 - top resource has the fastest growth rate. Other resources
 - random hierarchy (inspired by [Z Wang, et al Nat Comm 2021](#))
- **Co-utilization strategy:**
 - proteome equally allocated among the remaining resources. Growth rate – average among growth rates on these resources


Mature communities have complementary resource preferences and no “anomalous species”

Complementarity for top choice resource: **emerges**

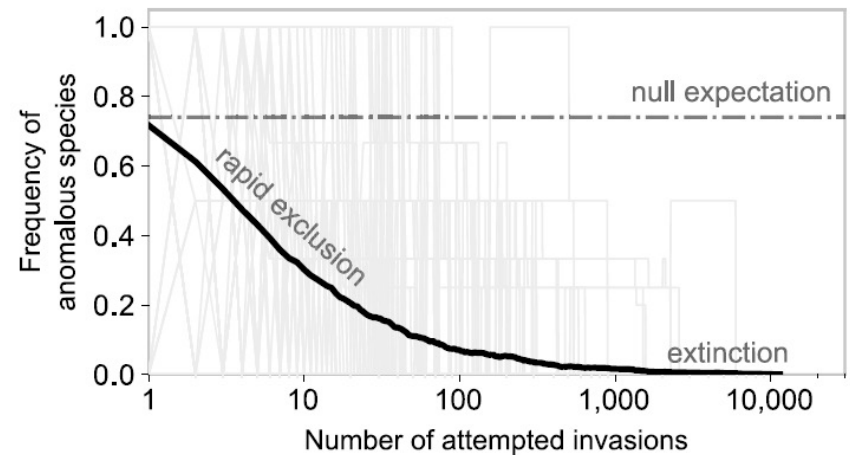


**Only top resource is
complementary**

Frequency of anomalous species: **decreases**

		R_1	R_2	R_3
preference		1	2	3
growth rate		0.2	0.1	0.5

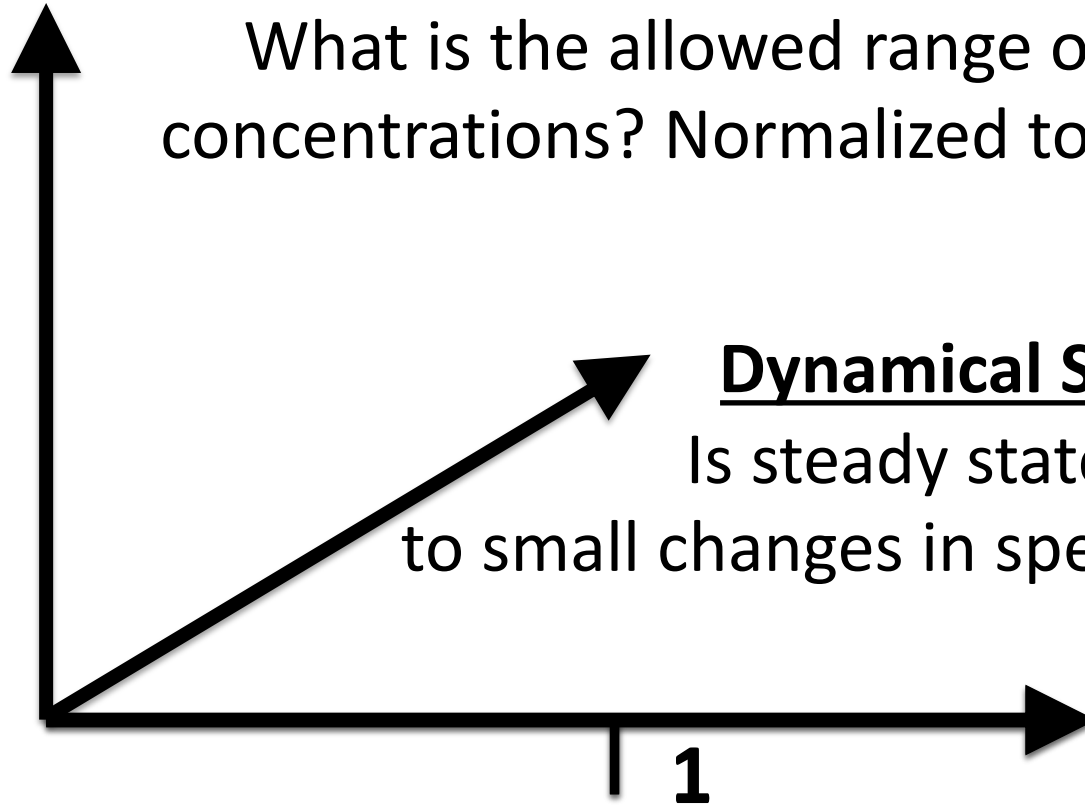
← highest growth
not on top choice



**Anomalous species = top preference
is not the fastest growth resource**

Structural stability

What is the allowed range of resource concentrations? Normalized to a single ratio



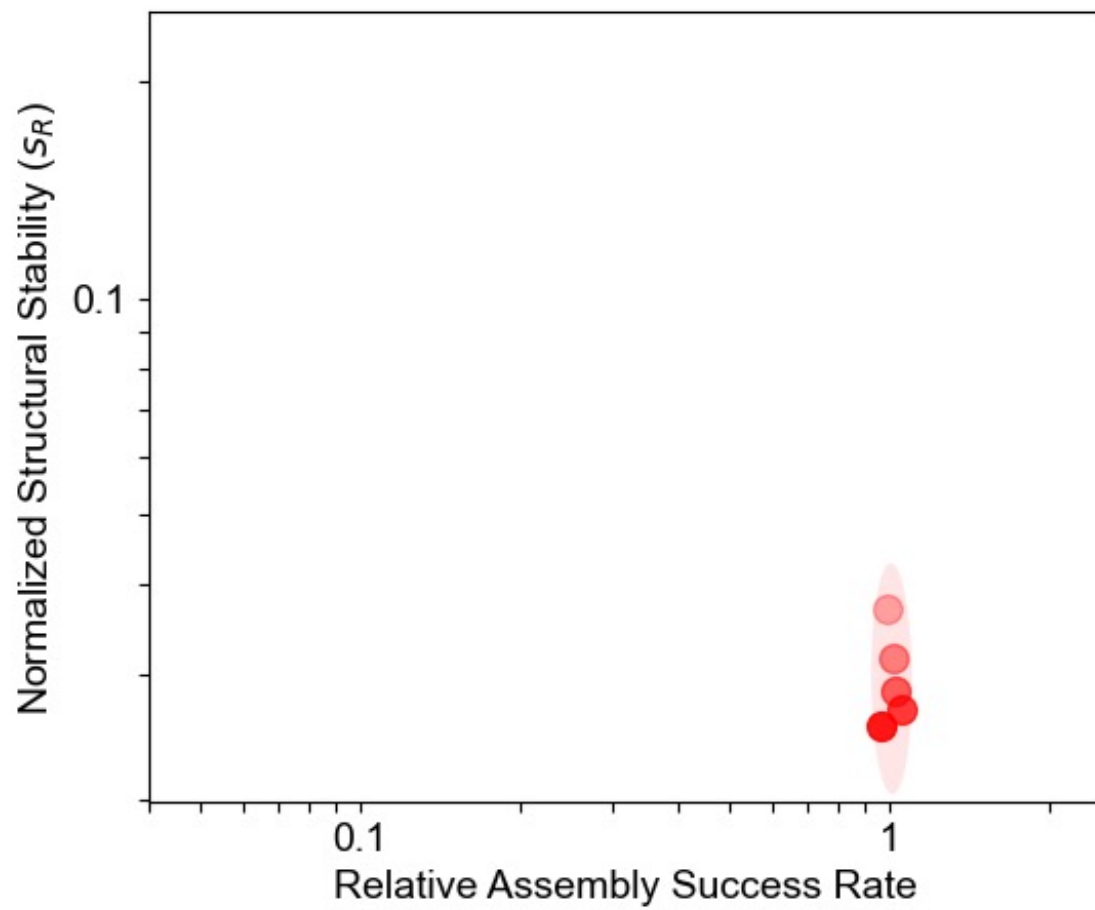
Dynamical Stability

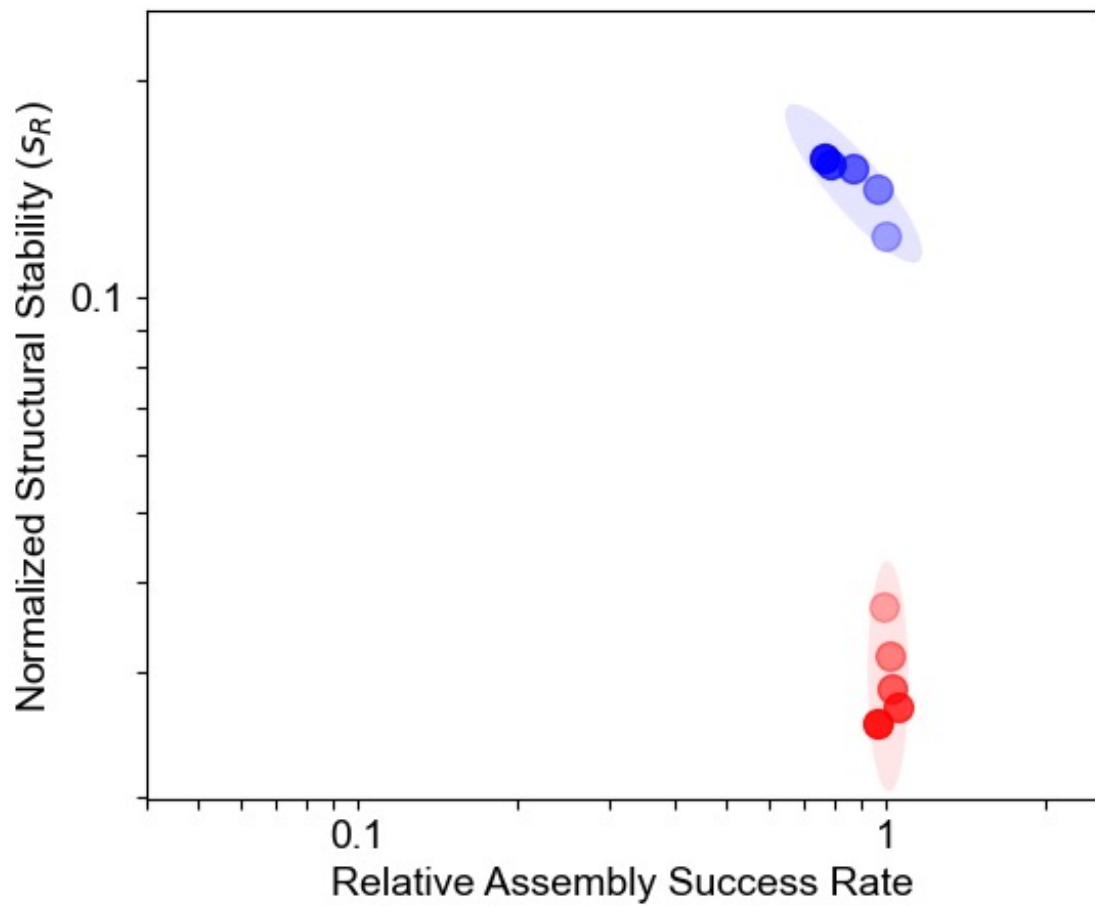
Is steady state stable to small changes in species abundances

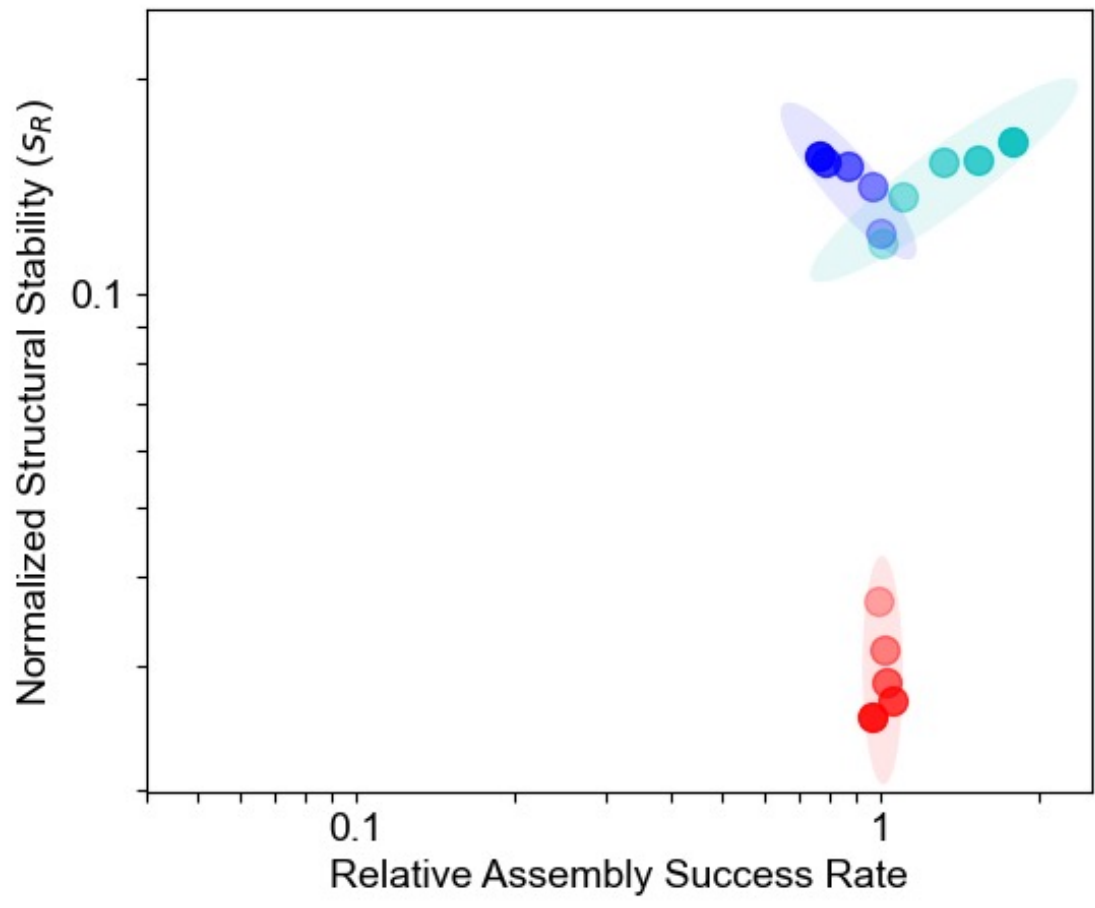
Feasibility Dynamical Stability

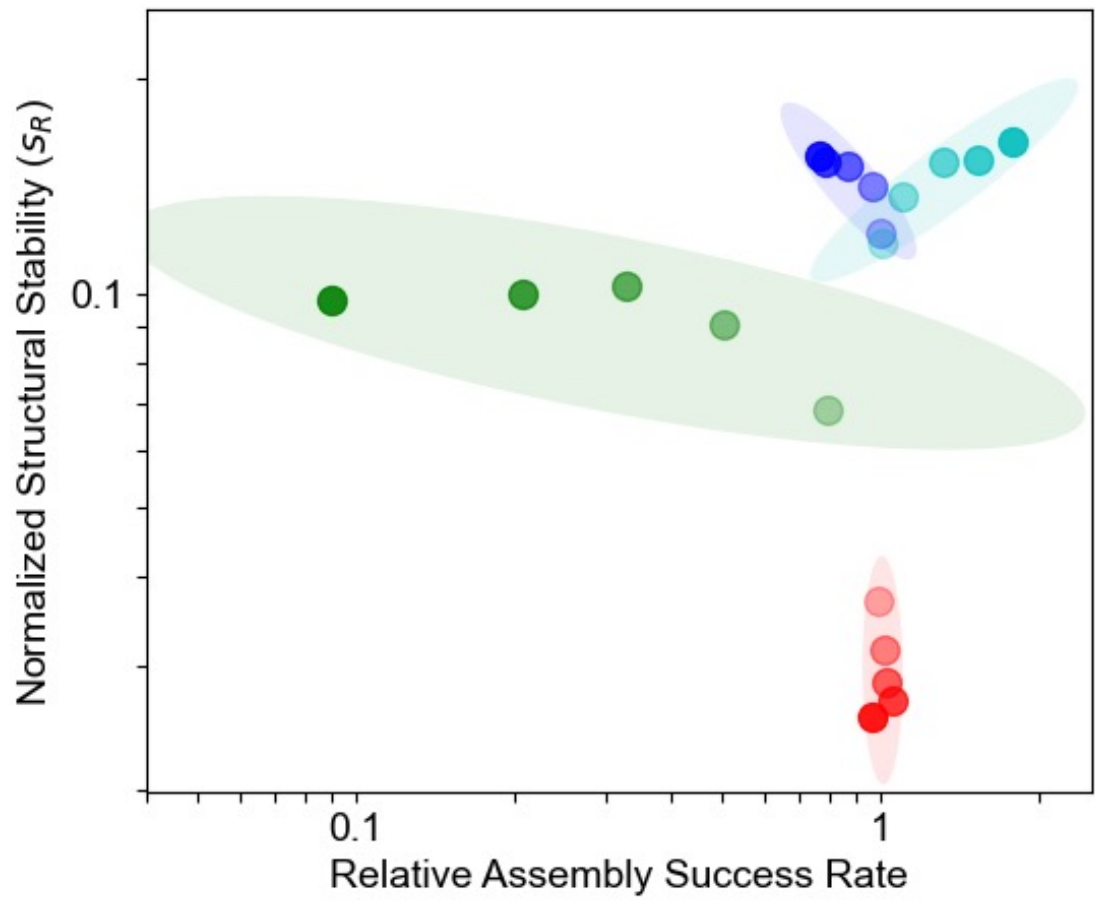
How likely is it that the "dream team" can be stably assembled?

Normalized to random: $\frac{1}{2^{n_s-1}} \rightarrow 1$

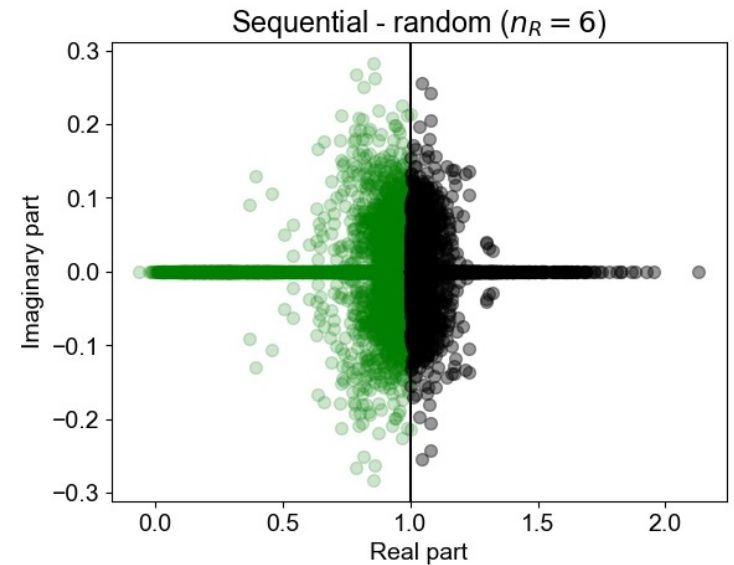
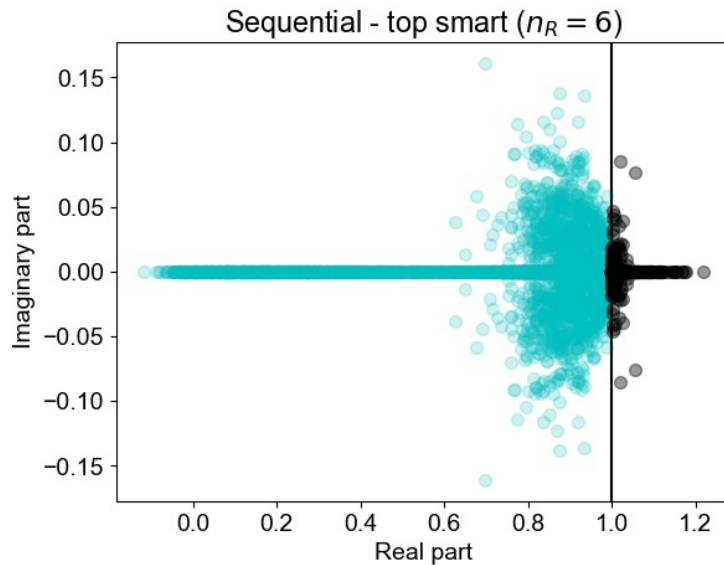
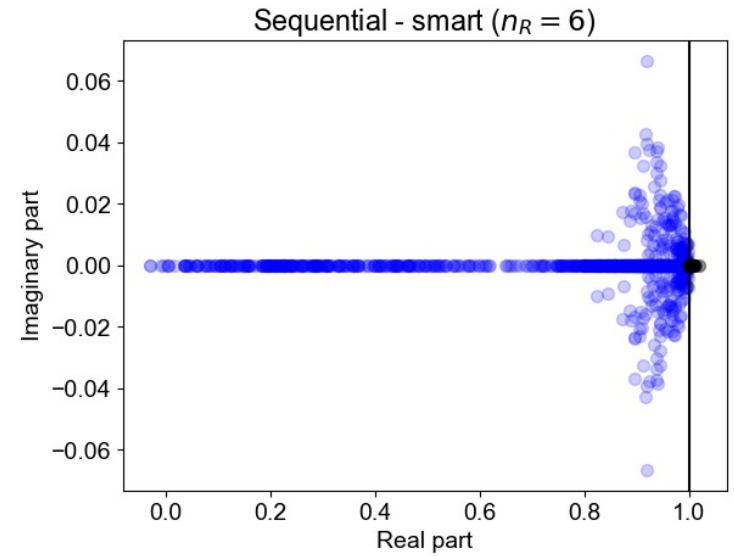
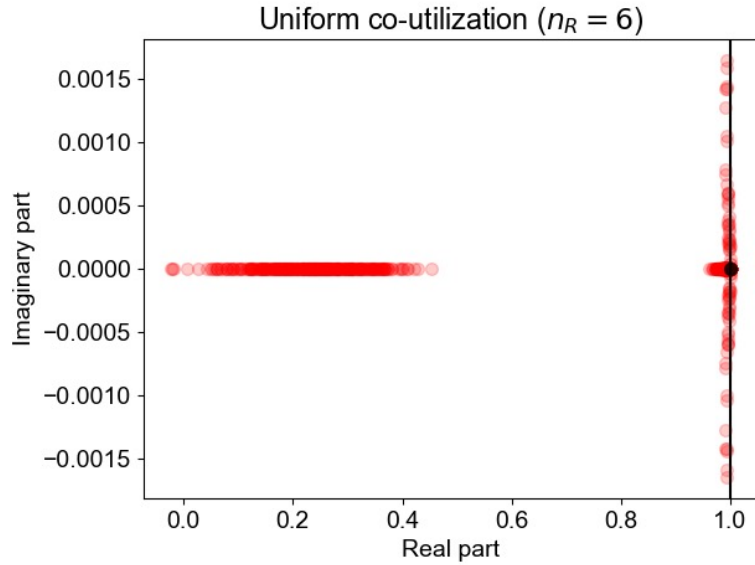






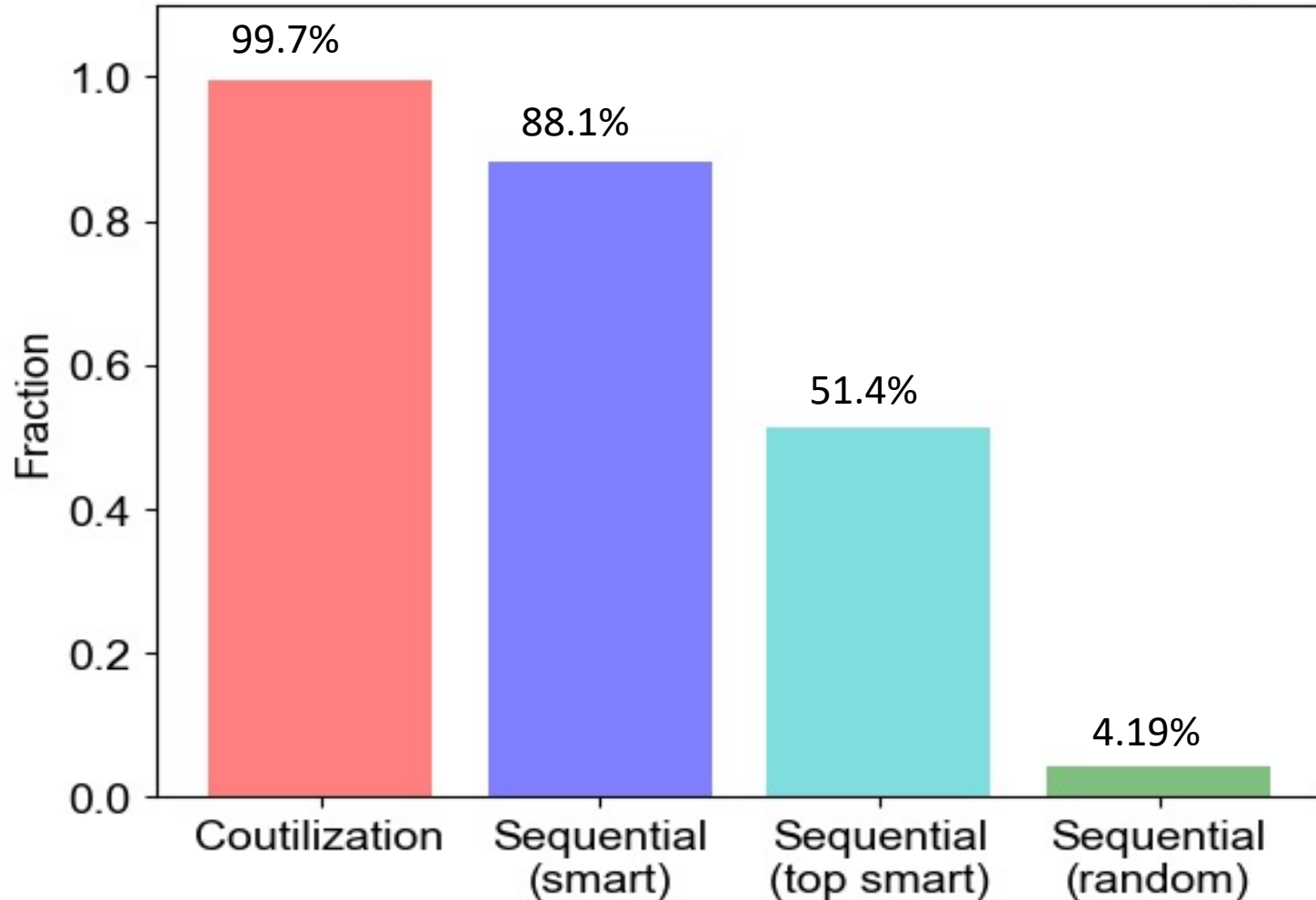


Dynamical stability spectra

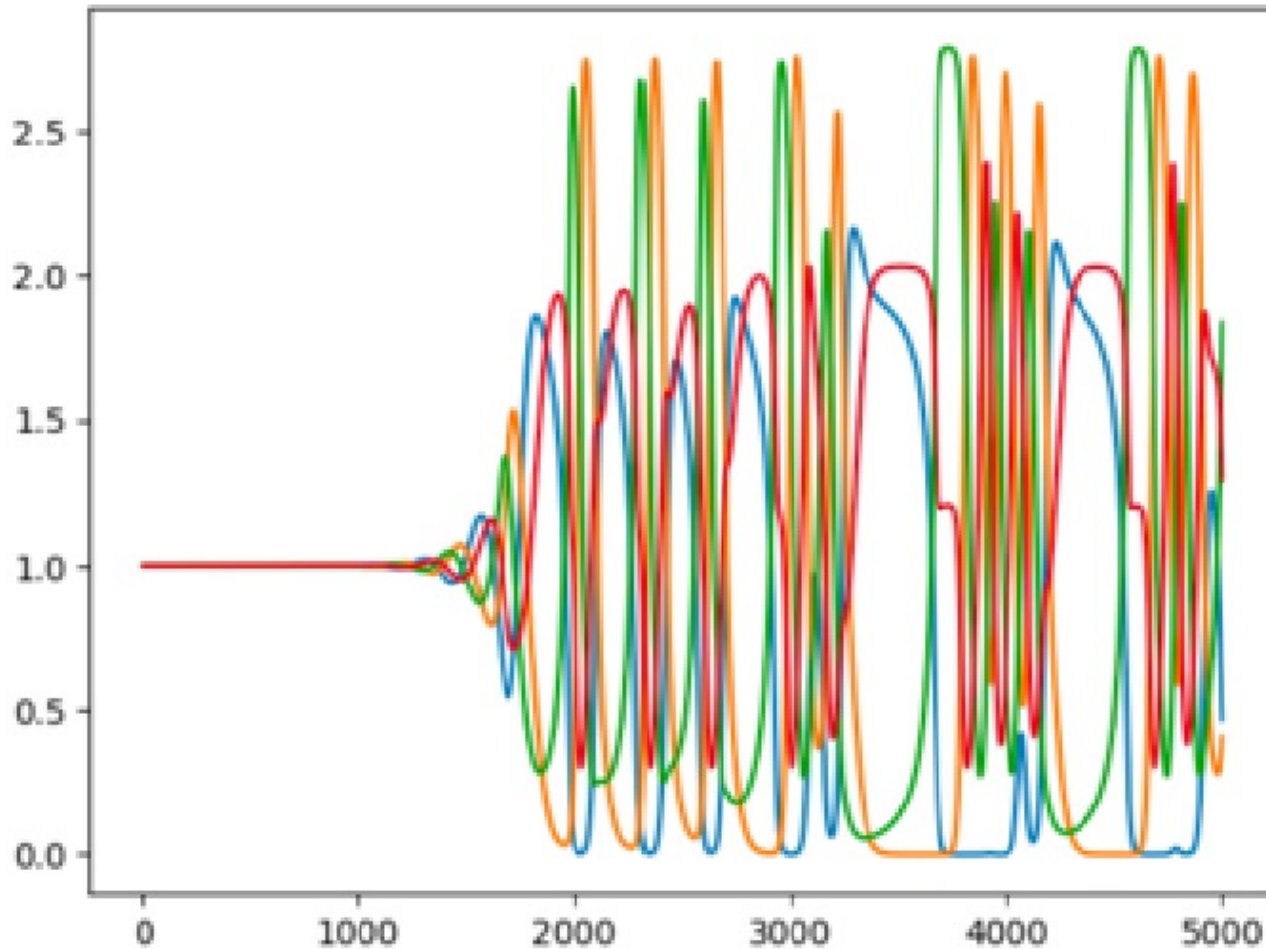


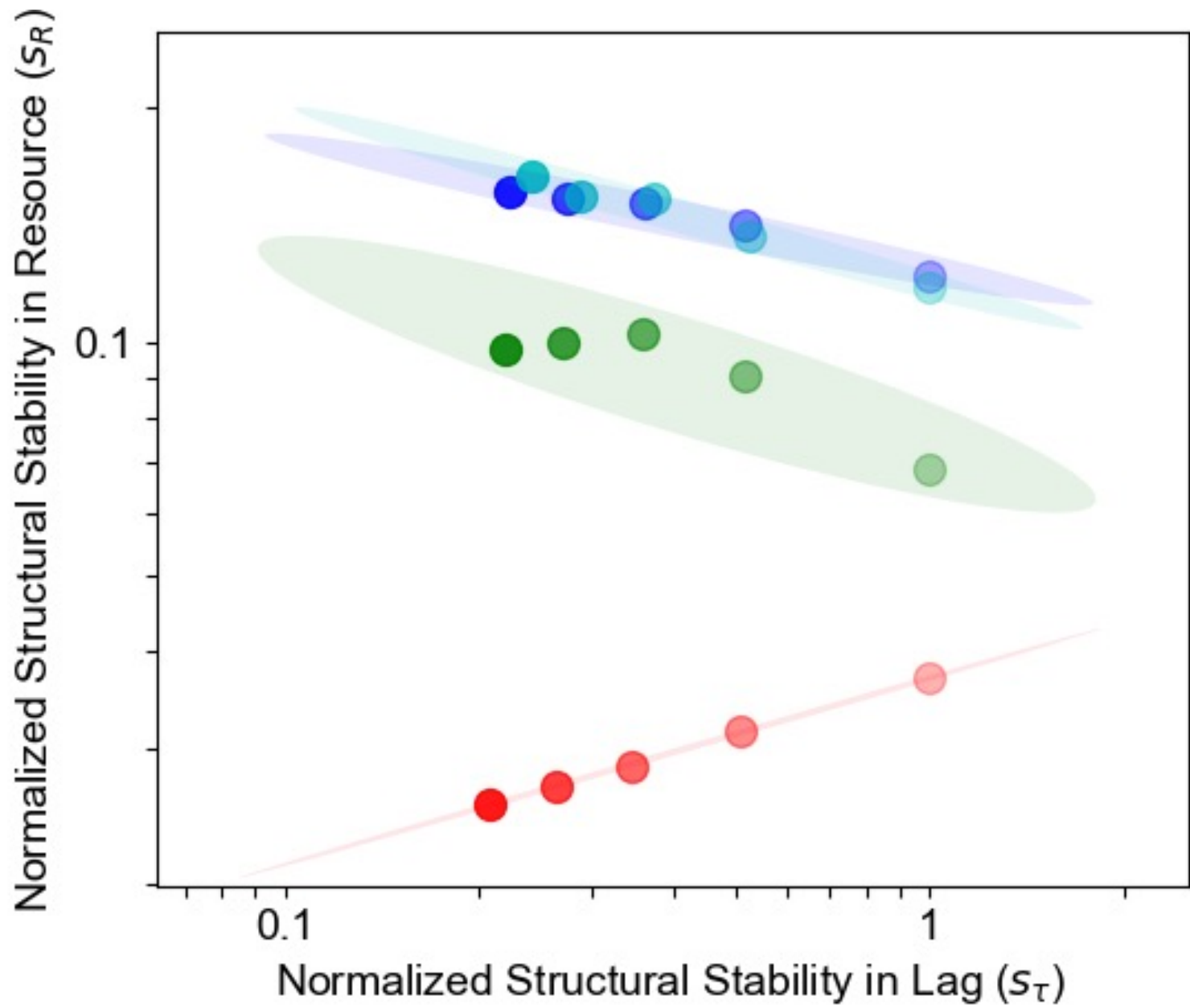
Dynamical stability fraction

Fraction of feasible states that are stable at $n_R = 6$



Chaotic solutions are possible
but rare: <1 out of 10,000

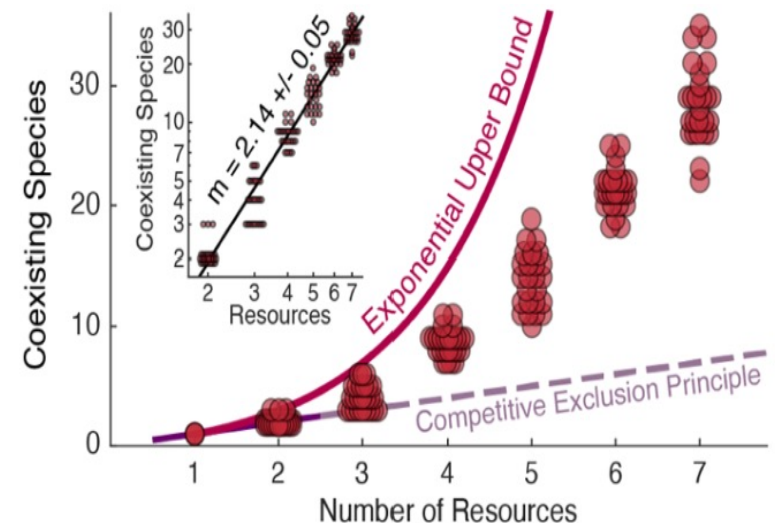




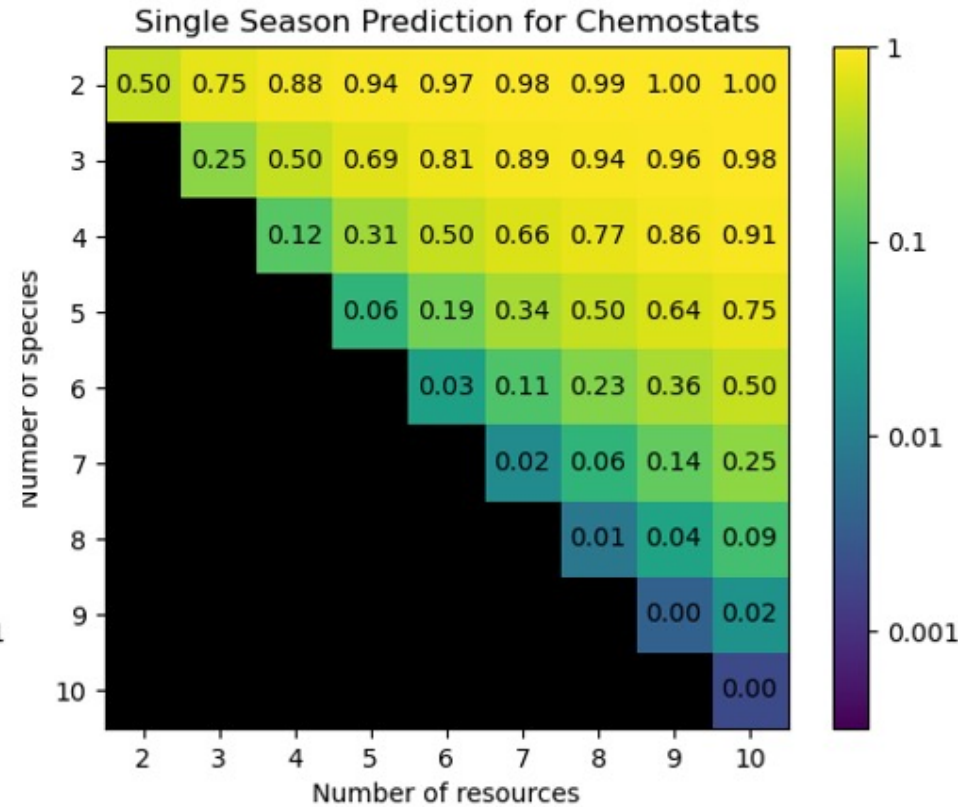
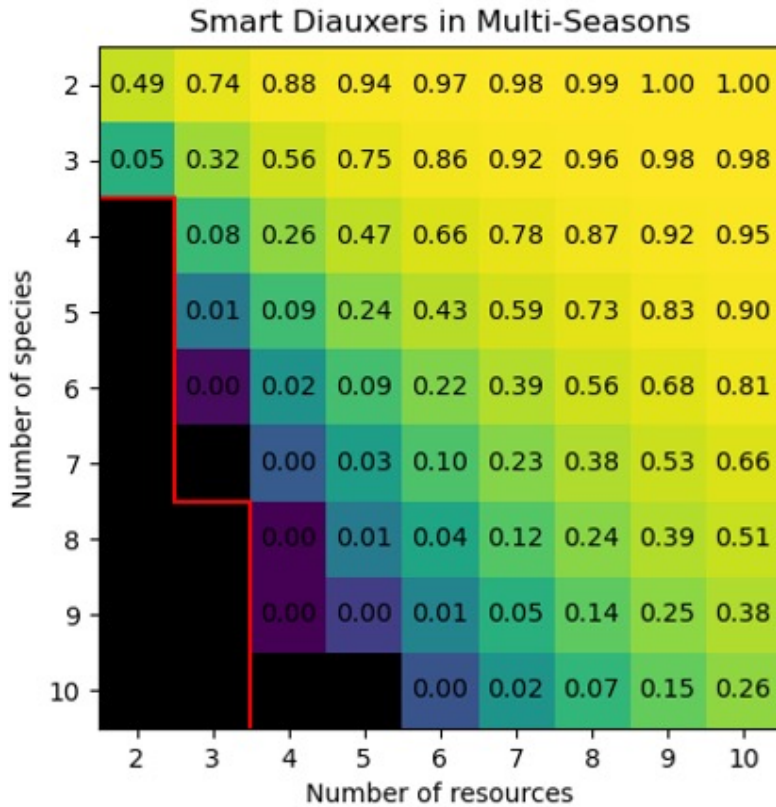
What if the **number of resources**
you have access to **is too low?**

Robots to the rescue!

- Blox Bloxham et al., bioRxiv (2023):
 - In principle: $n_{species} \leq 2^{n_{resources}} - 1$
 - In practice in randomly fluctuating environments:
 $n_{species} \sim (n_{resources})^2$
- We can beat it by using robots to add **prescribed different nutrient ratios at different cycles**



Success rates of assemblies for smart diauxers



Z Wang, A Goyal, Y. Fu, Y. Fridman, S Maslov, in preparation

Take home messages and open questions

- **We can engineer resource ratios** for a given set of species to co-exist in **boom-and-bust environments**
 - **Bonus 1**: we can make **any desired** relative species abundances
 - **Bonus 2**: we can break the competitive exclusion principle: $n_{species} \leq n_{resources}$ potentially going up to $n_{species} = 2^{n_{resources}} - 1$
- **We can compare different metabolic strategies to each other.** Next steps:
 - **Ecology and evolution** of the **optimal tradeoff** between **shorter lags** and **reduced growth rate** due to pre-allocated enzymes
 - Include **crossfeeding diauxie** (glucose-acetate)
 - Can we explain deviations from optimal hierarchy by the success of the **top smart sequential strategy?**

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

Credit: XKCD
comics

QUESTIONS FOUND IN GOOGLE AUTOCOMPLETE

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 VARIOUSE ARIERIES
WHY ARE OLD KLINGONS DIFFERENT

WHY AREN'T THERE ANY COUNTRIES IN ANTARCTICA
WHY DO IGUANAS DIE
WHY ARE THERE DINOSAUR GHOSTS
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 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 ARE THERE GHOSTS

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 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 AREN'T MY ARMS GROWING



WHY AREN'T THERE GUNS IN HARRY POTTER

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
WHY ARE THERE WEIBS
WHY DO I FEEL DIZZY
WHY ARE THERE SO MANY CROWS IN ROCHESTER,
WHY IS PSYCHIC WEAK TO BUG
WHY DO CHILDREN GET CANCER
WHY IS POSEIDON ANGRY WITH ODYSSEUS
WHY IS THERE ICE IN SPACE
WHY ARE DOGS AFRAID OF FIREWORKS
WHY IS THERE NO KING IN ENGLAND
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 IS LIFE SO BORING
WHY ARE ULTRASOUNDS IMPORTANT
WHY ARE ULTRASOUND MACHINES EXPENSIVE
WHY IS STEALING WRONG