מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

Compositional Lipid Assemblies as Evolving Protocells

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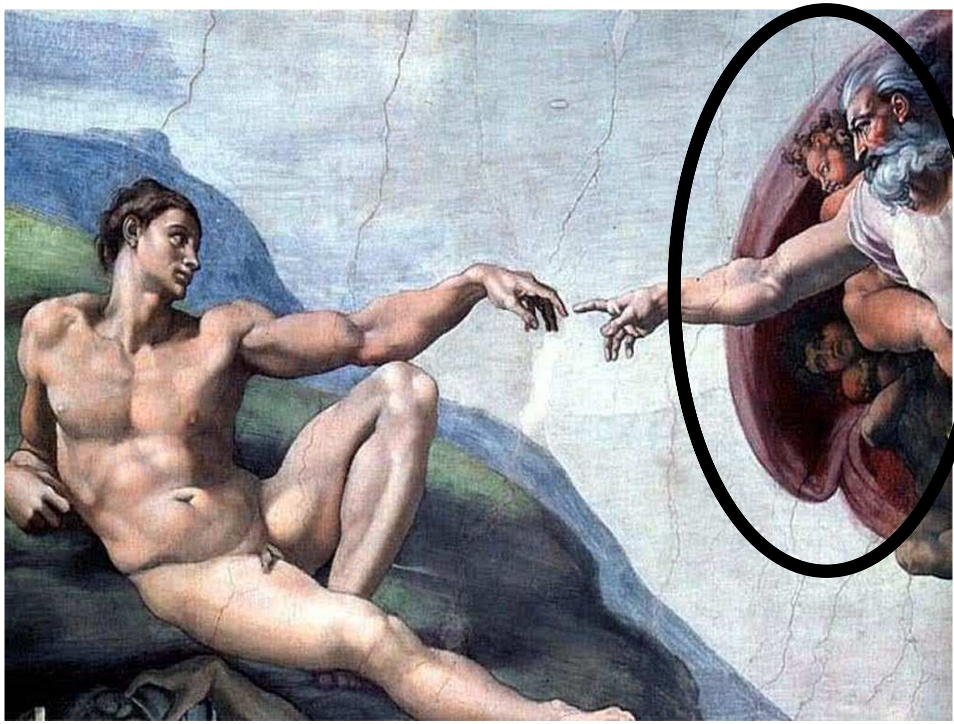
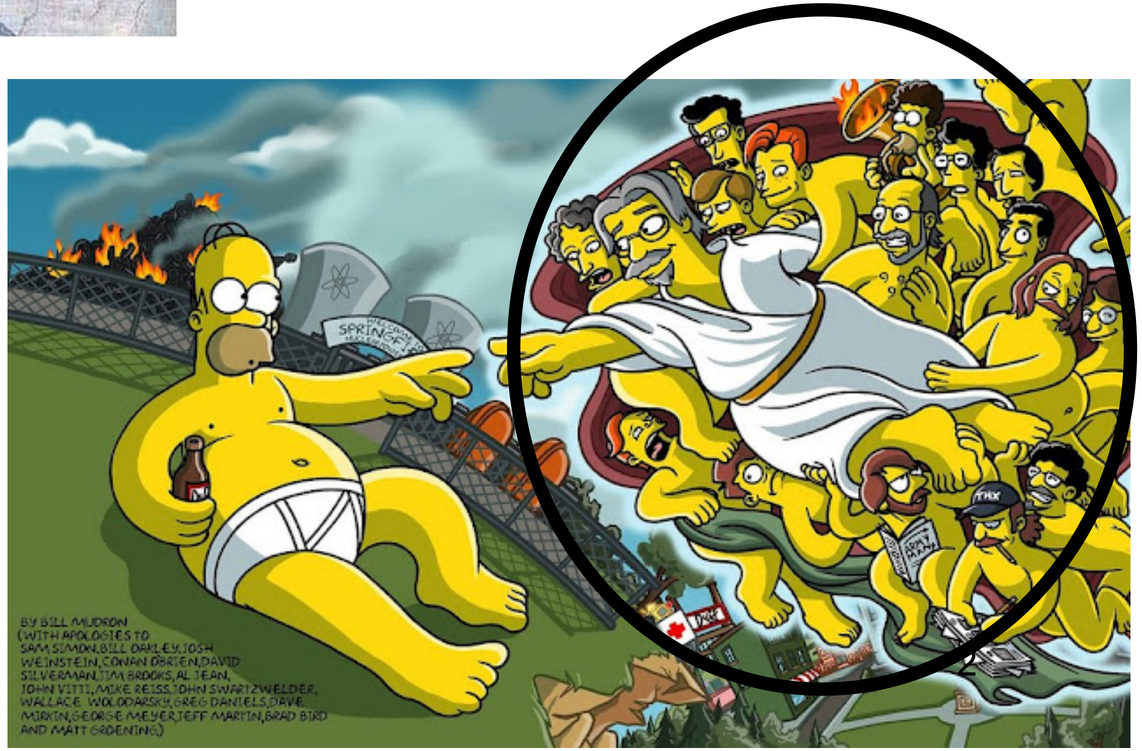
Origin of life workshop, ELSI, June 2013

ELSI EARTH-LIFE SCIENCE INSTITUTE
地球生命研究所



Life .....

... is complex



“Prebiotic Soup”

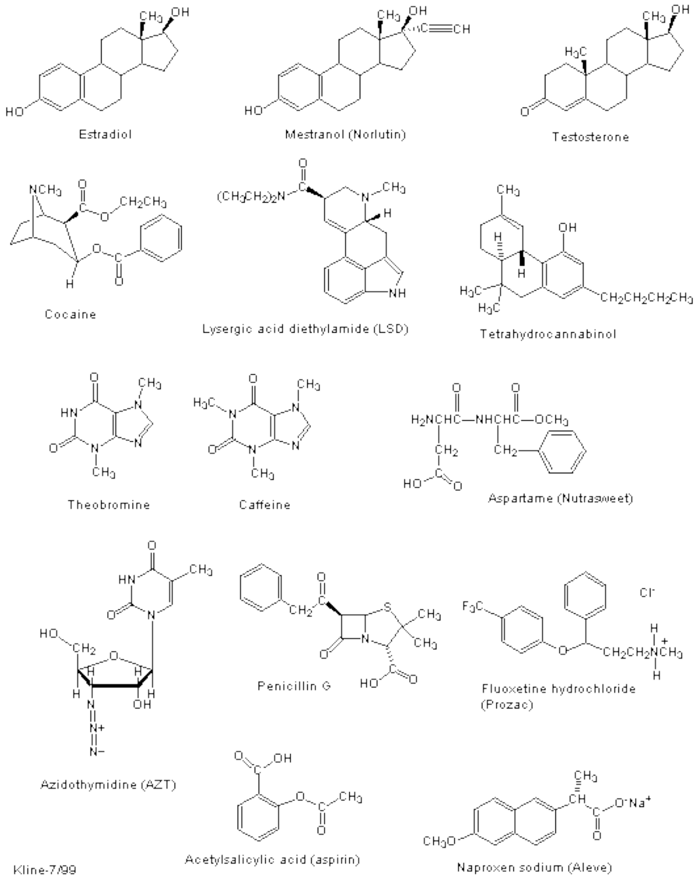
~4,000,000,000 years ago

The emergence of the first cell-like entity, the ***Protocell***.

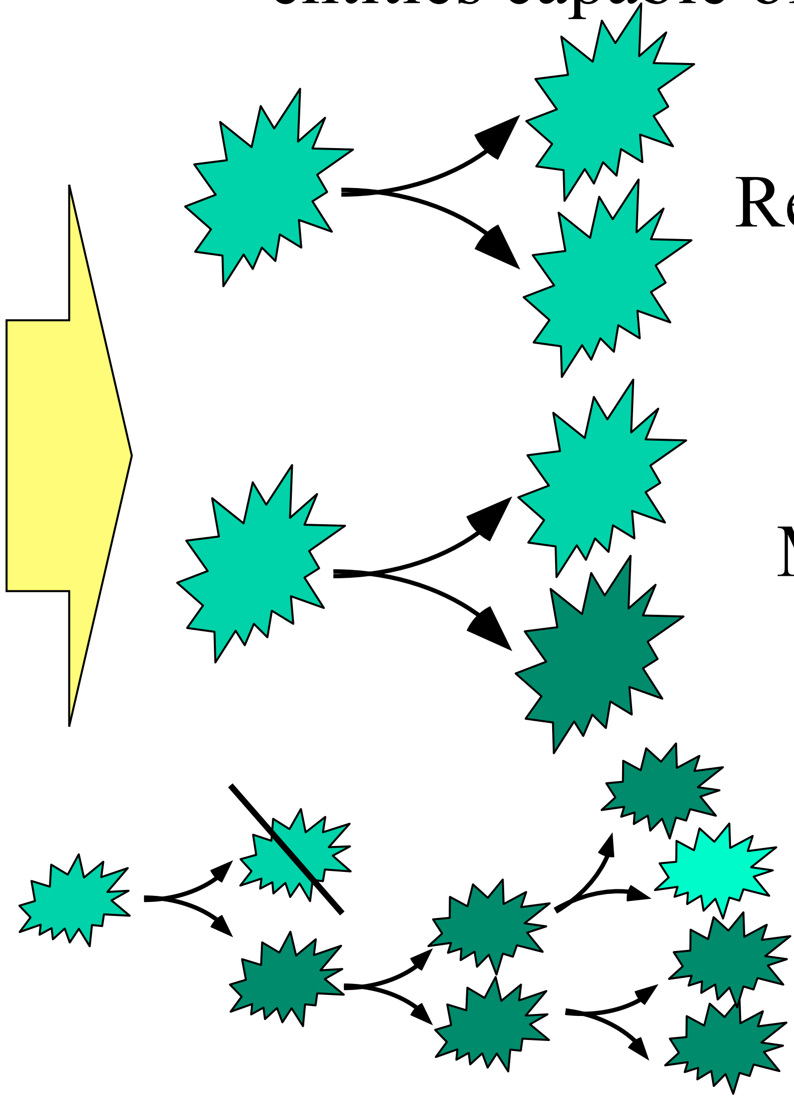
Life is a self-sustaining system capable of undergoing Darwinian evolution.

The problem

Organic molecules



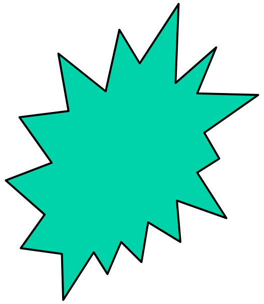
More complex chemical entities capable of:



Replication

Mutation

Selection & Evolution

What is  ?

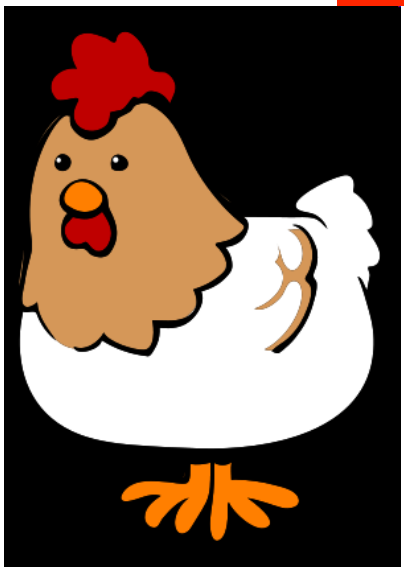
Occam's razor – simple

Life requires **information**.

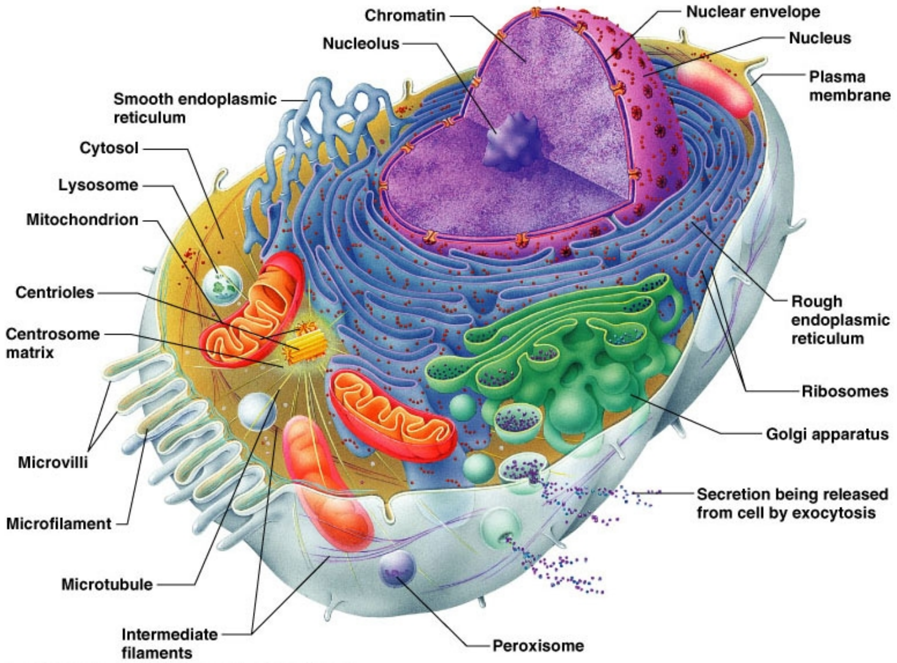
Information undergoes evolution.

Which came first: chicken or egg?

Chicken + Egg = Chegg ☺



The Cell as a Complex Network



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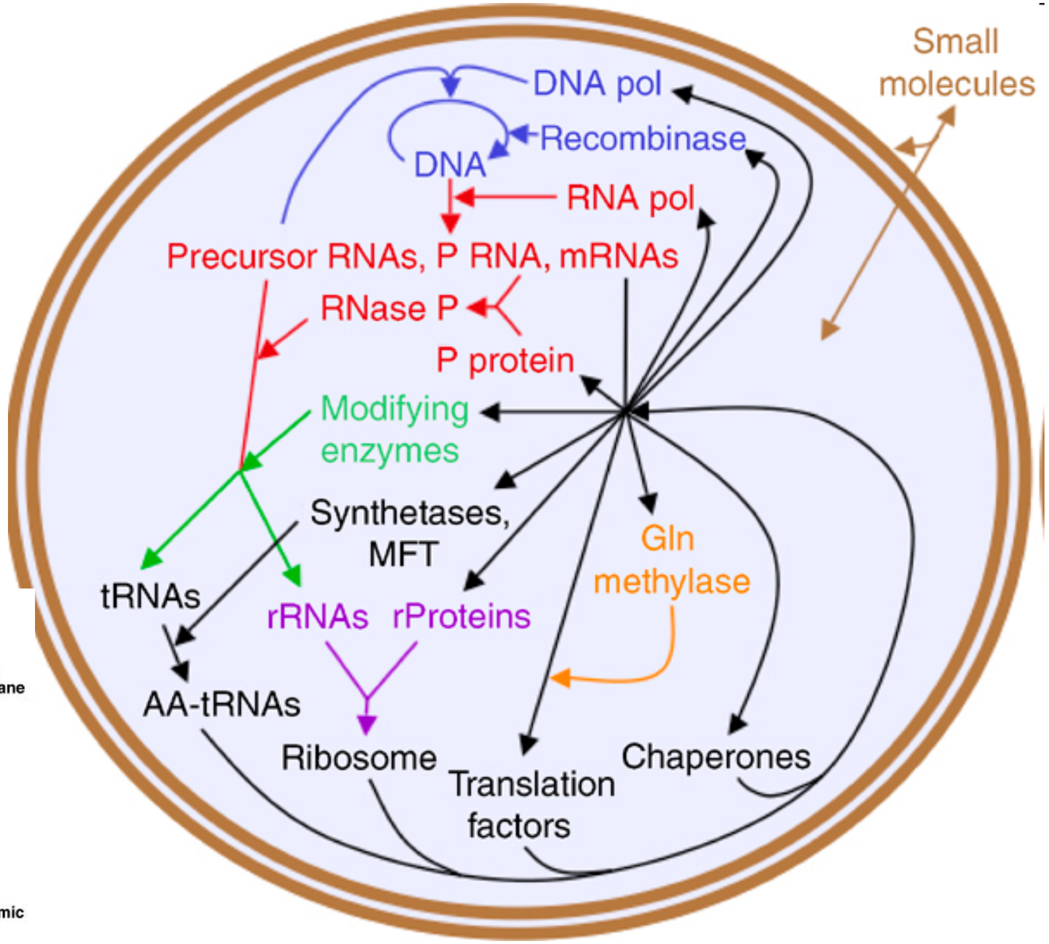
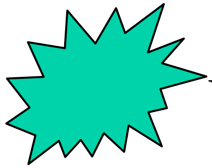


RNA World / Replicator-First

Altman and Cech – self-cleaving Ribozyme (Nobel prize in Chemistry, 1989).

Could  **be a ribozyme?**

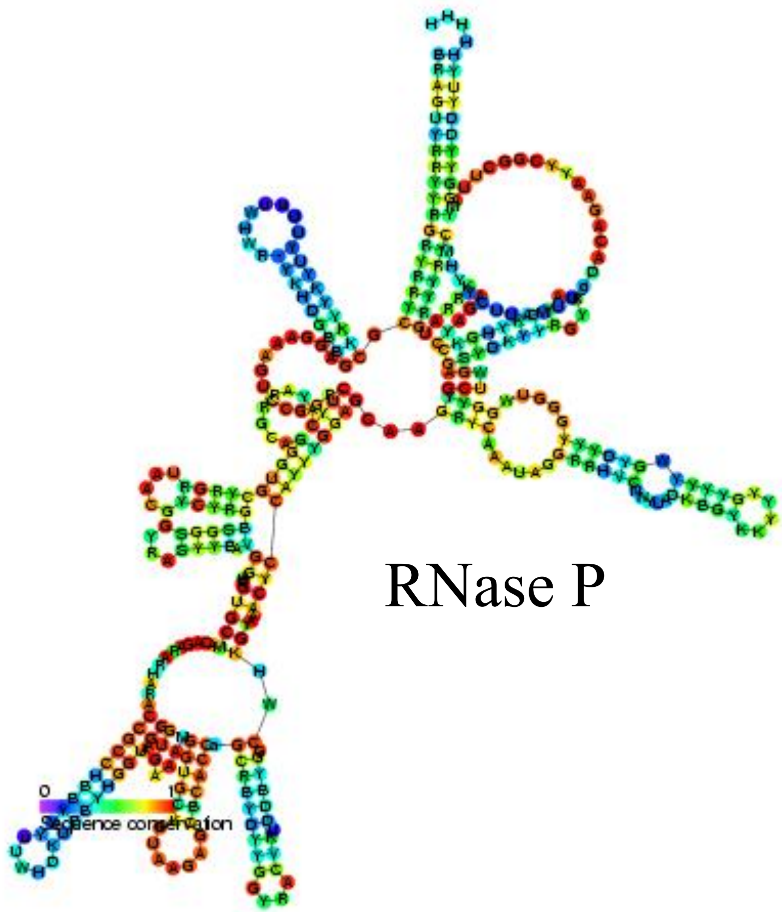
Strongly dependents on covalent

bonds

• Difficult to form

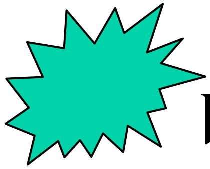
• Mutation = breaking and remaking

two covalent bonds



RNase P

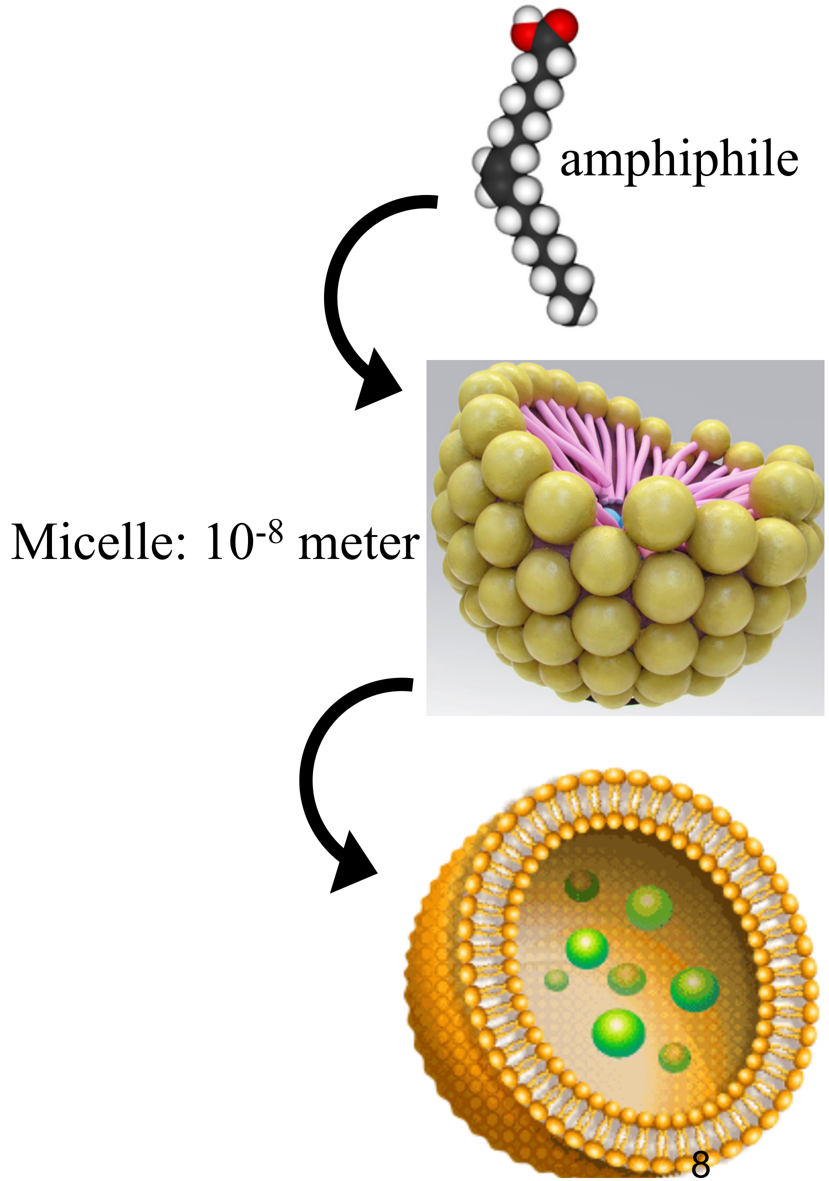
The Lipid World

Could  **be a Micelle?**

Held together by non-covalent bonds.

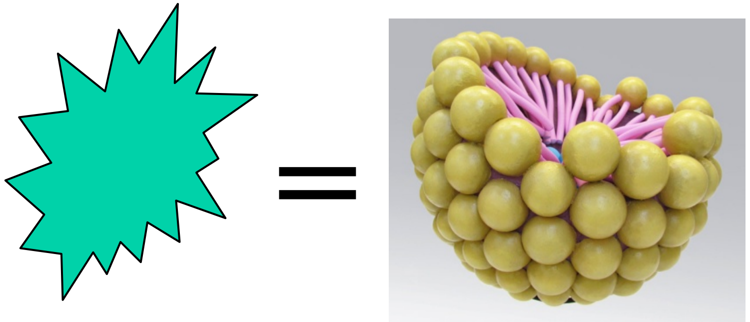
- Forms spontaneously
- Mutation = “random access” lipid entry/exit

Much simpler!

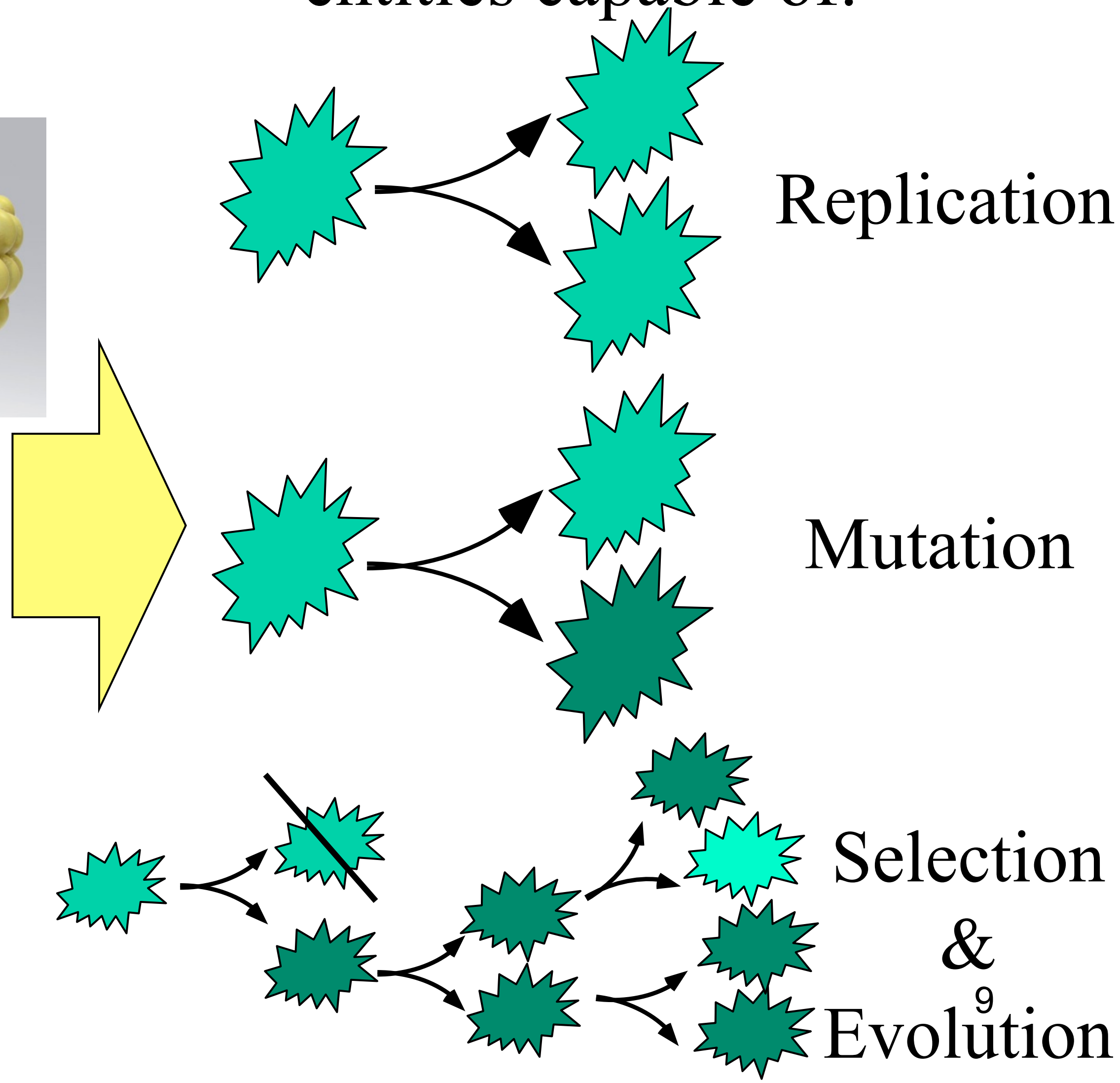


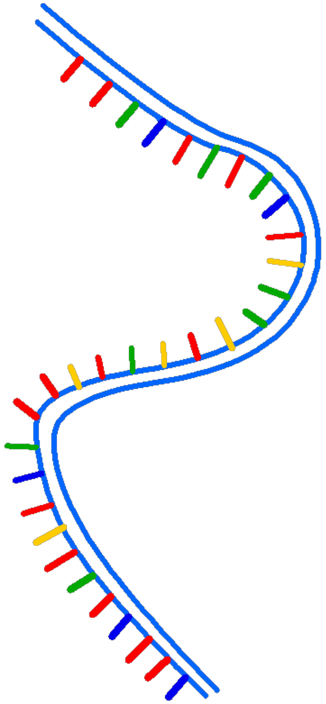
The Lipid World

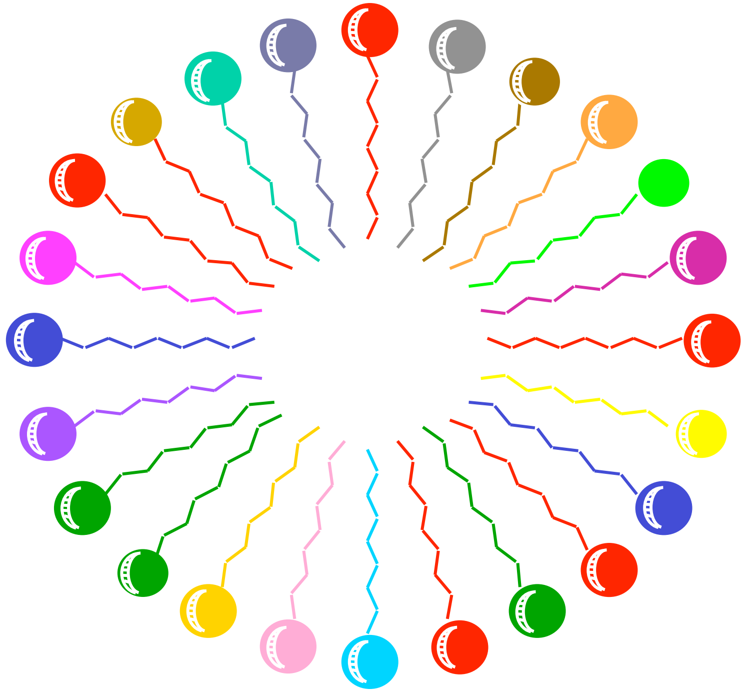
More complex chemical entities capable of:



“Deliver” all of that?





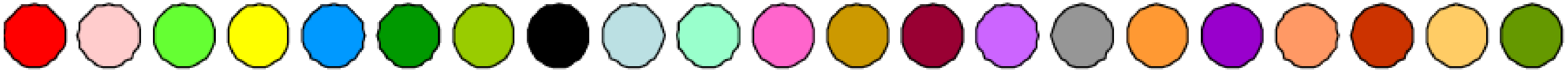


DNA / RNA / Polymers → **<u>Sequence</u>**

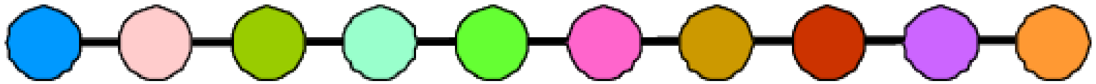
Assemblies / Clusters / Vesicles / Membranes → **<u>Composition</u>**

Segre and Lancet, EMBO Reports 1 (2000)

Sequential vs. Compositional Information

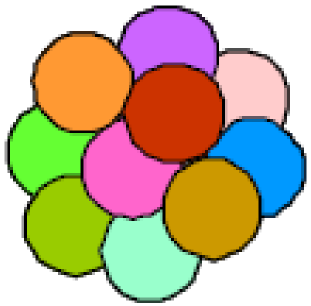


Alphabet: 20 amino acids



10-letters long polymer

$$\log_2\left(20^{10}\right) \approx 43 \text{ bits}$$

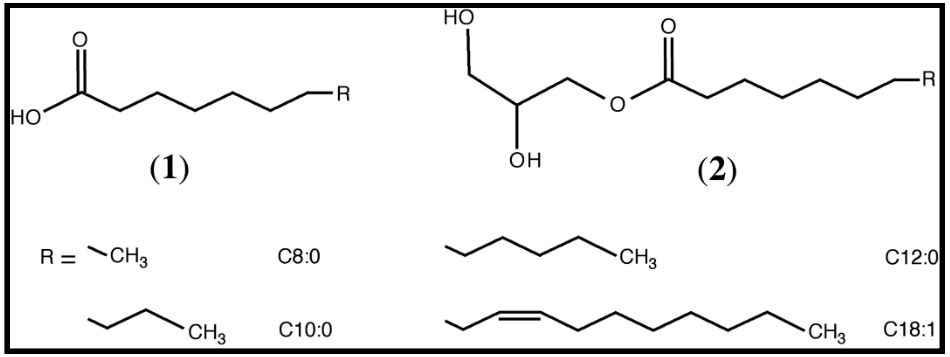


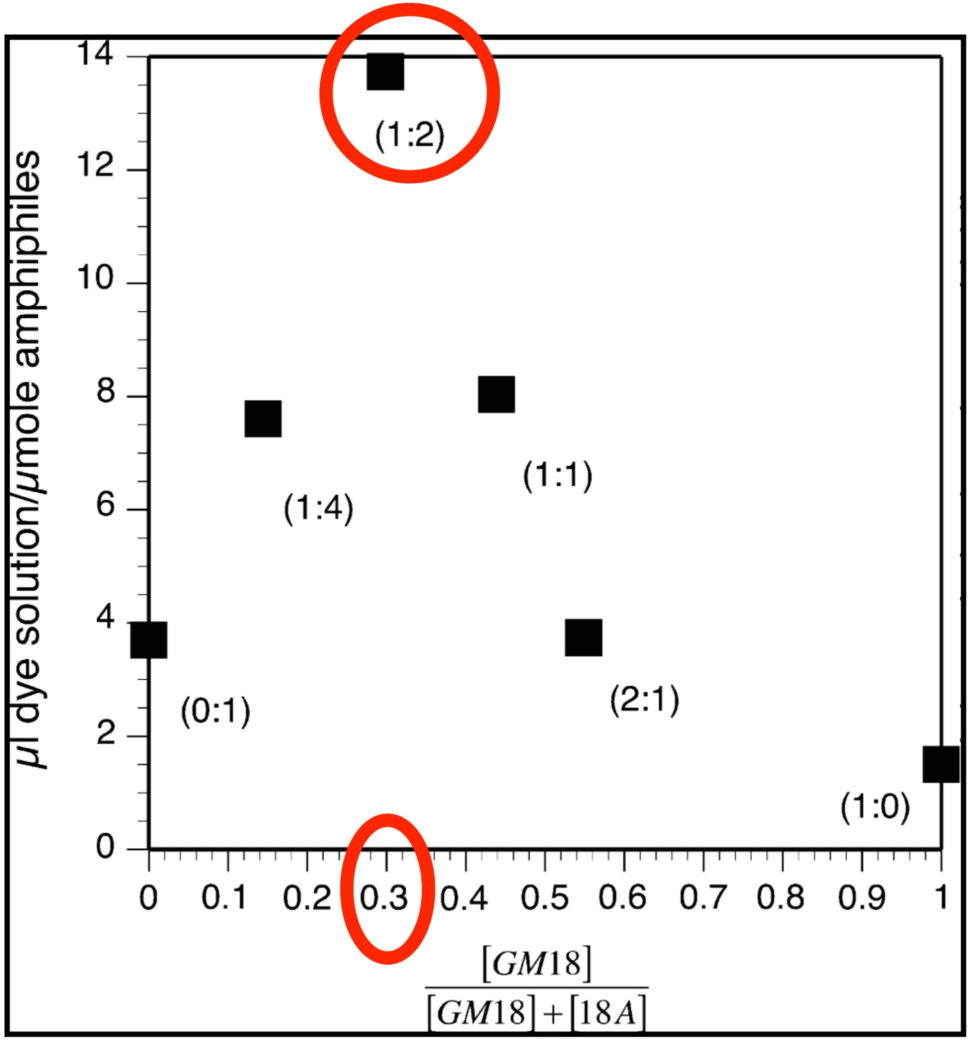
10 molecules assembly

$$\log_2\left(\frac{(20+10-1)!}{10!}\right) \approx 27 \text{ bits}$$

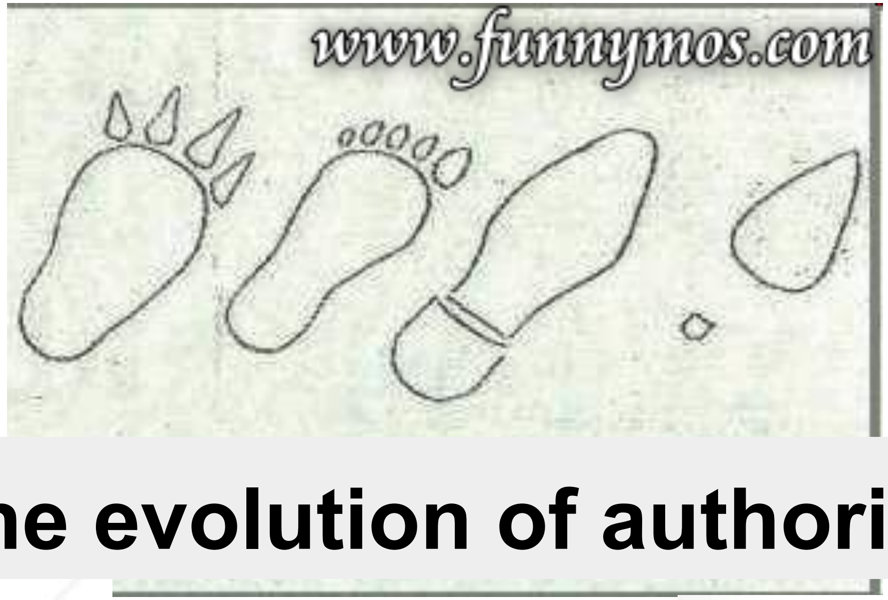
Composition effect vesicle encapsulation-efficiency

Phenotype



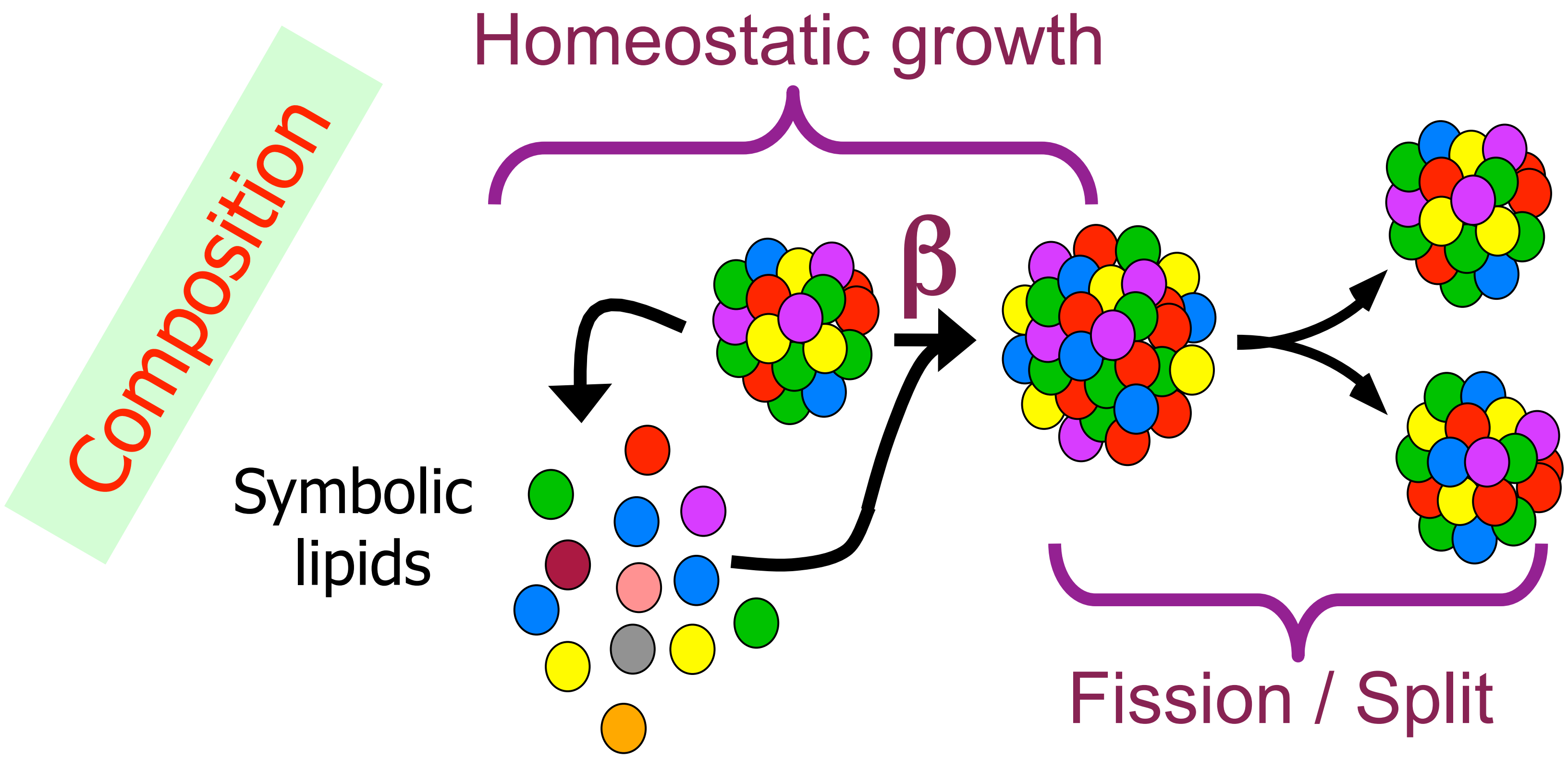


Maurer et al, Astrobiology 9 (2009)



The evolution of authority

GARD model (Graded Autocatalysis Replication Domain)



$$\frac{dn_i}{dt} = \left(k_f \rho_i N - k_b n_i\right)\left(1 + \sum_{j=1}^{N_G} \beta_{ij} \frac{n_j}{N}\right) \qquad \left(i = 1..N_G\right)$$

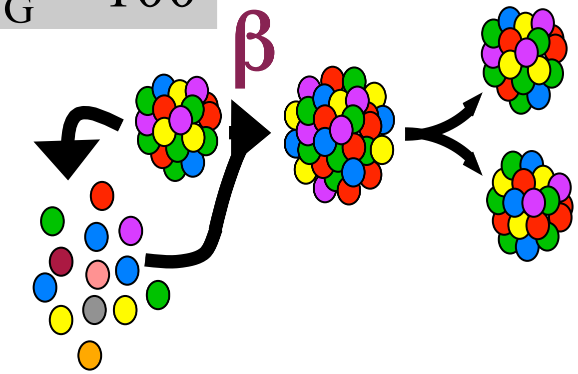
Rate enhancement

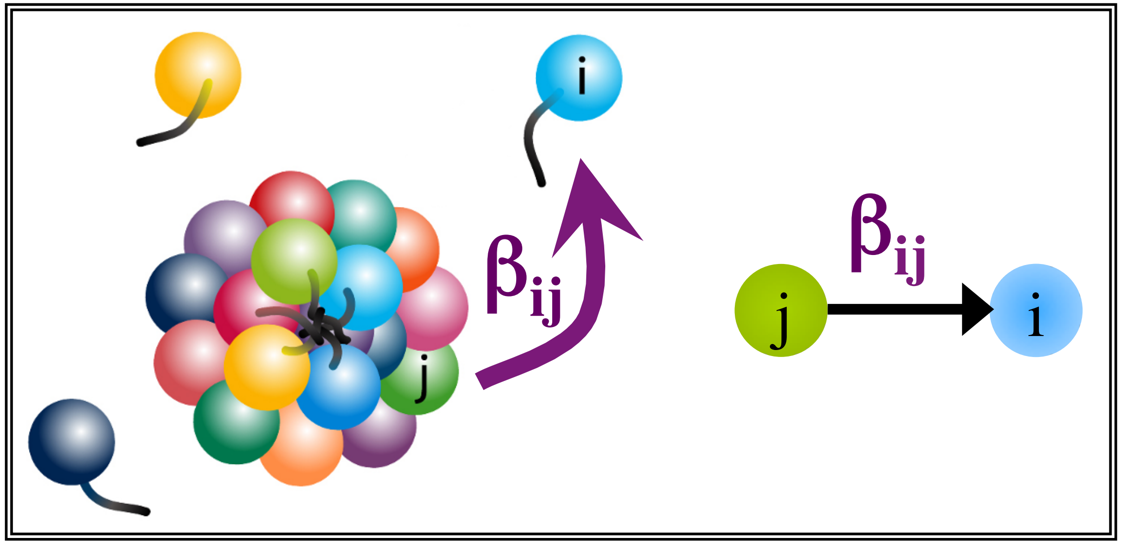
Molecular repertoire

Segre, Ben-Eli and Lancet, Proc. Natl. Acad. Sci. 97 (2000)

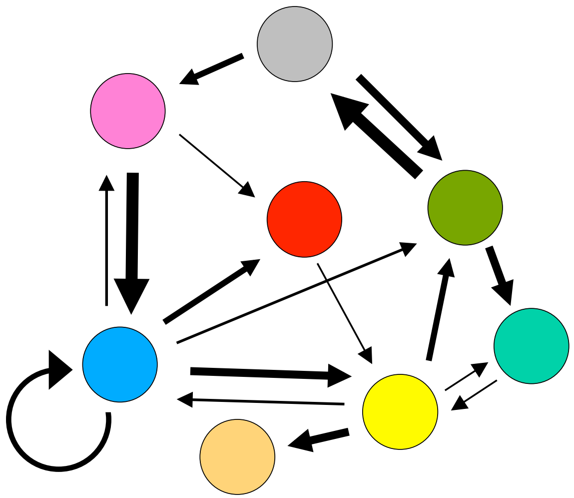
β ; Catalytic Network (environmental chemistry)

$N_G = 100$





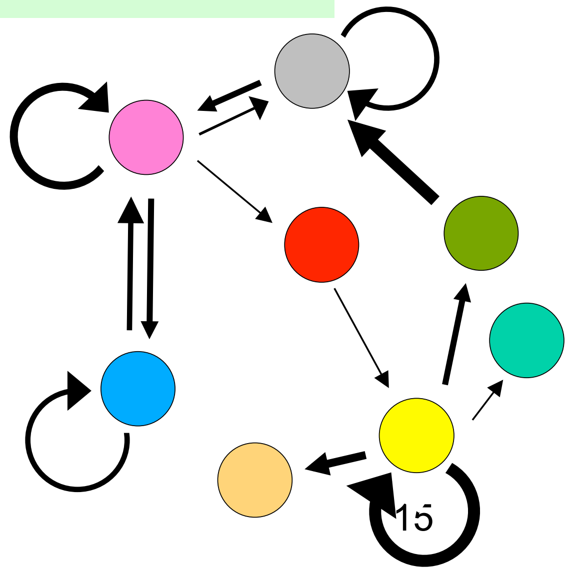
More mutualistic



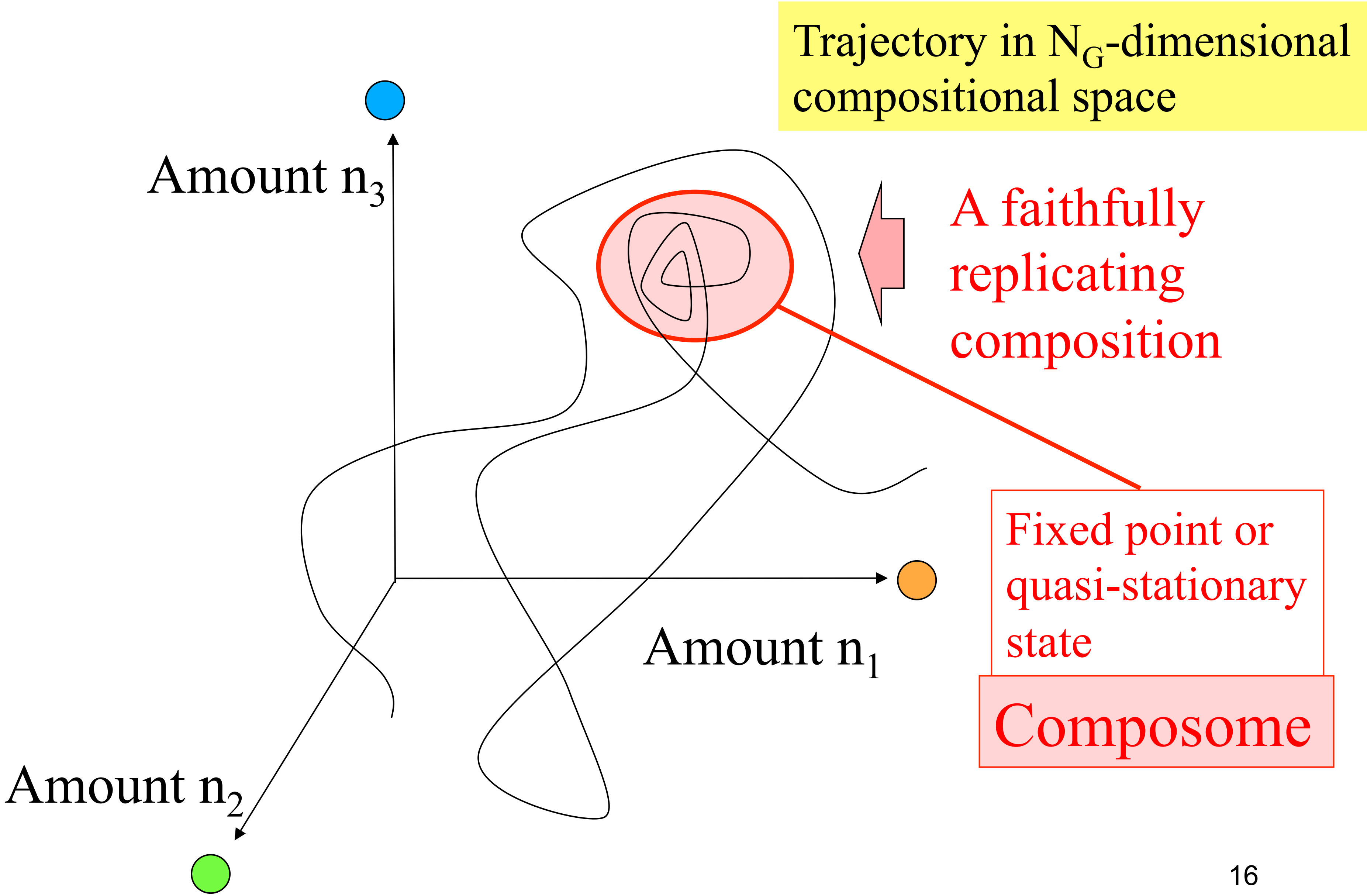
*Self-catalysis is the chemical manifestation of self-replication [Orgel, Nature 358 (1992)]

Dyson, Gánti, Kauffman, Varela

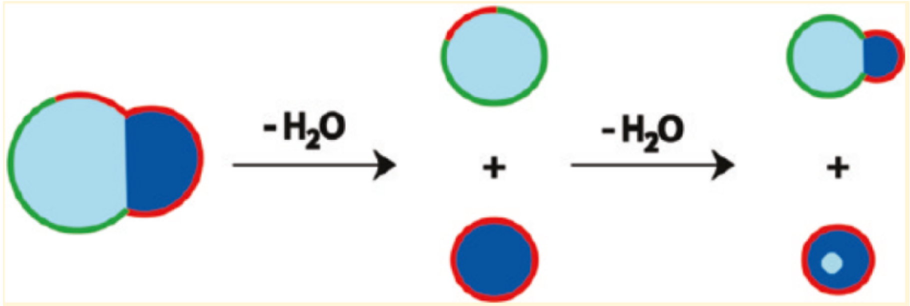
More selfish



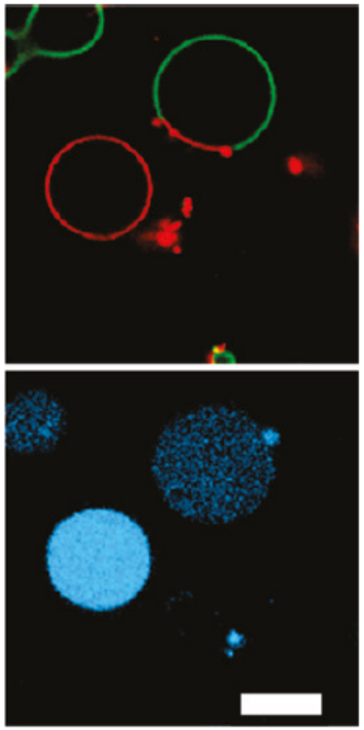
GARD Dynamics



Experimental Vesicle Heredity



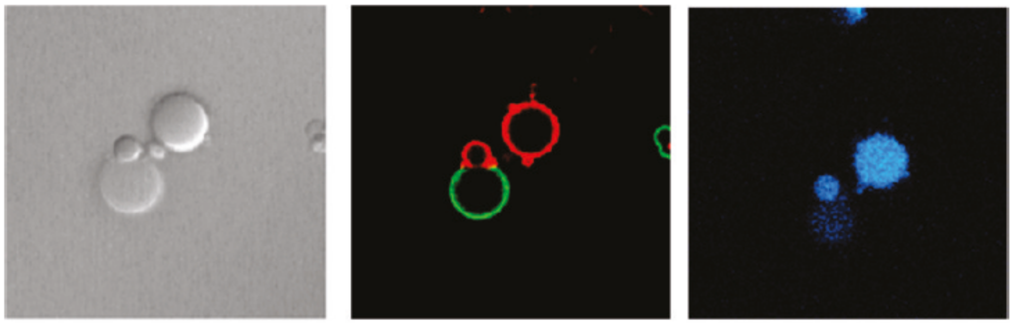
First generation



10^{-6} meter

Membrane composition was inherited by daughter vesicle, and affected daughter fission.

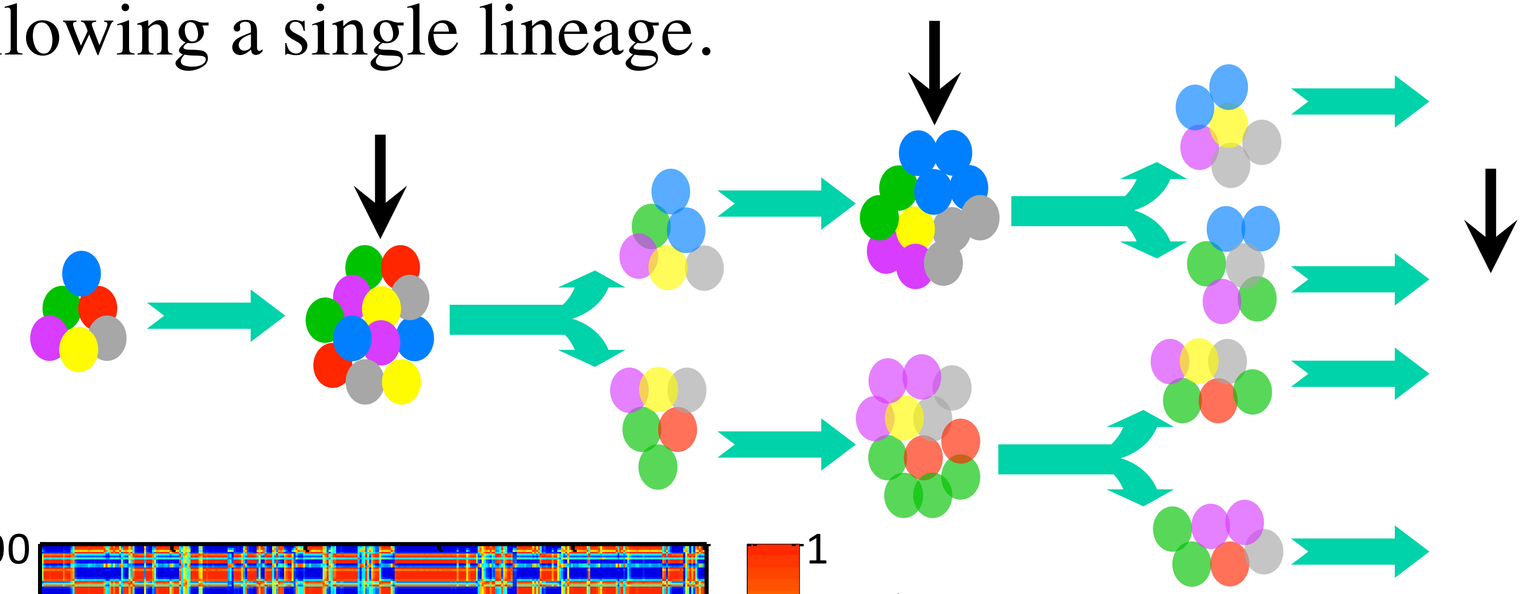
Second generation

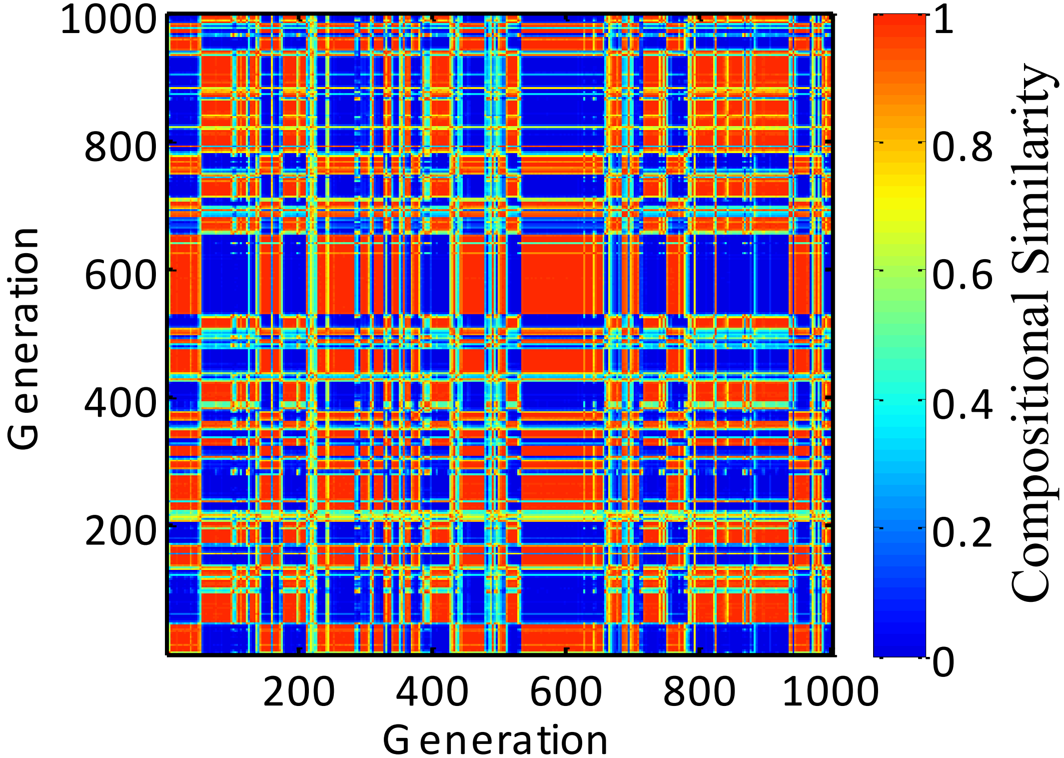


Andes-Koback and Keating, JACS 133 (2011)

Example of GARD Similarity 'Carpet'

Following a single lineage.

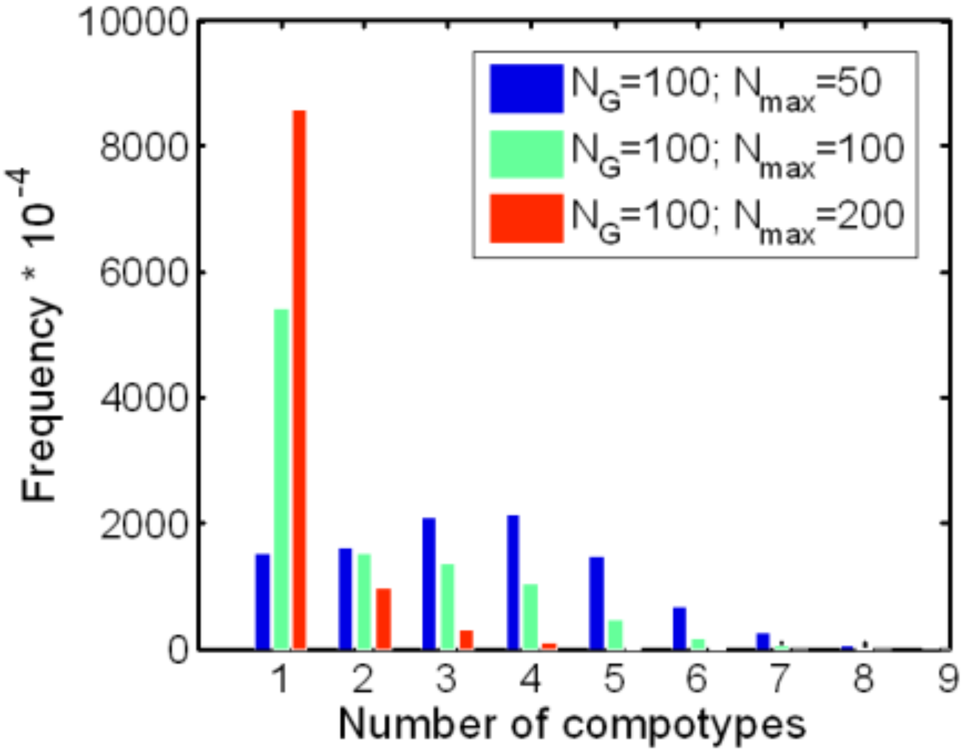




Compotype, a cluster of similar composomes (**quasi species**)

$$H(\chi,\delta) = \frac{\overline{n}^{\chi} \cdot \overline{n}^{\delta}}{\left|\overline{n}^{\chi}\right| \cdot \left|\overline{n}^{\delta}\right|}$$

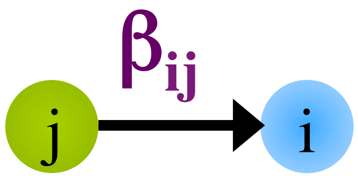
GARD Simulations Show Multiple Compotypes



Different β networks give rise to different dynamics.

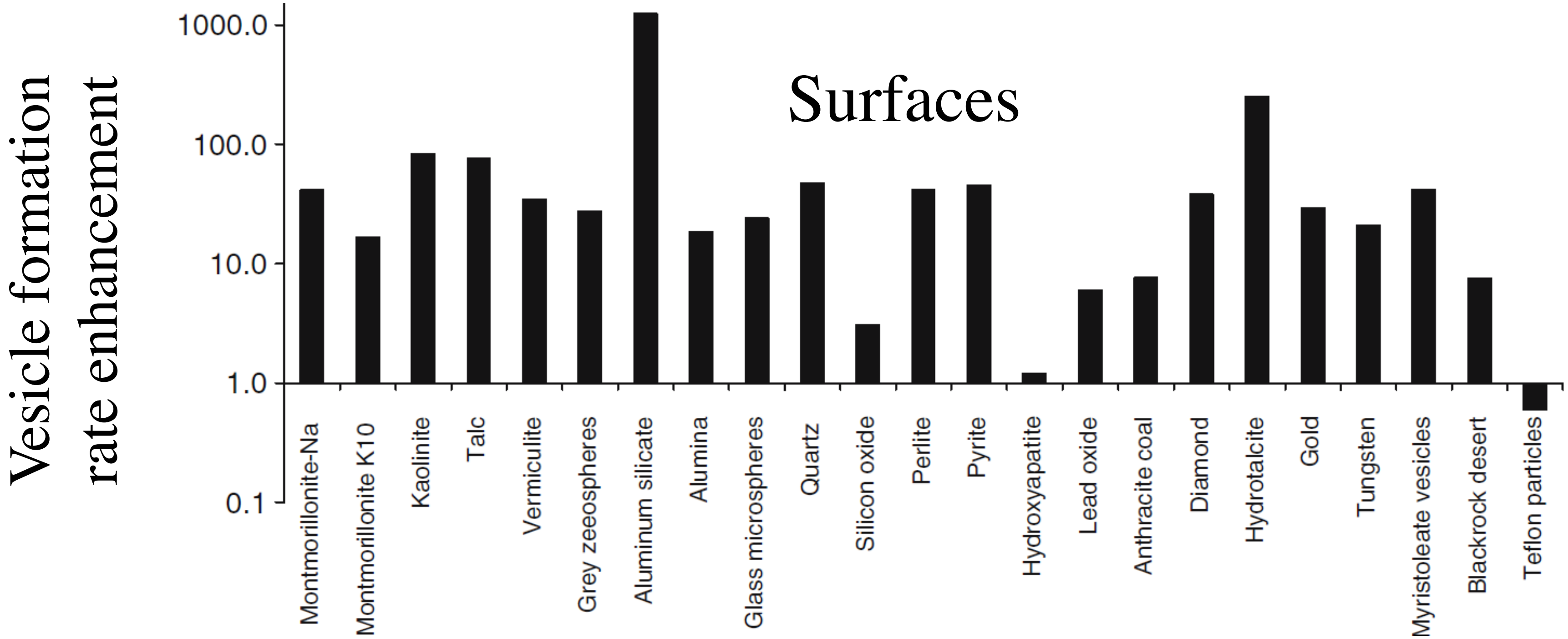
Number of compotypes: range 1-7, average ~2.

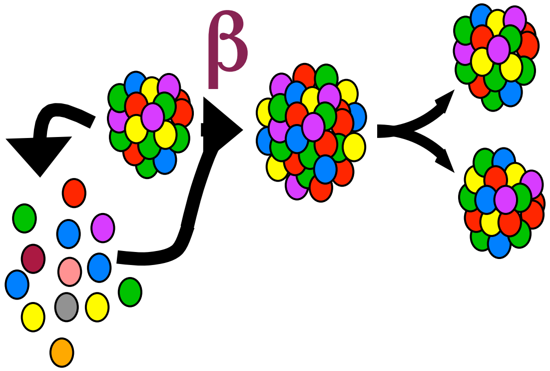
β's ↔ environmental chemistries

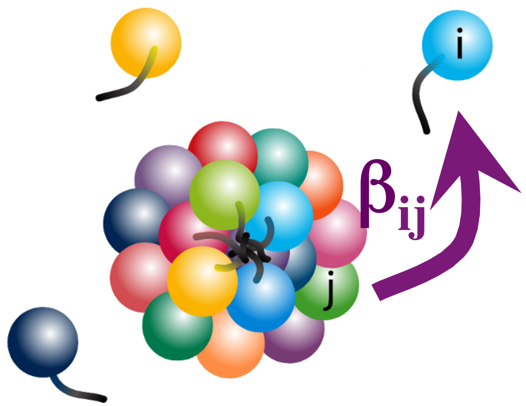


values are drawn from a <u>lognormal</u> distribution ('graded network')

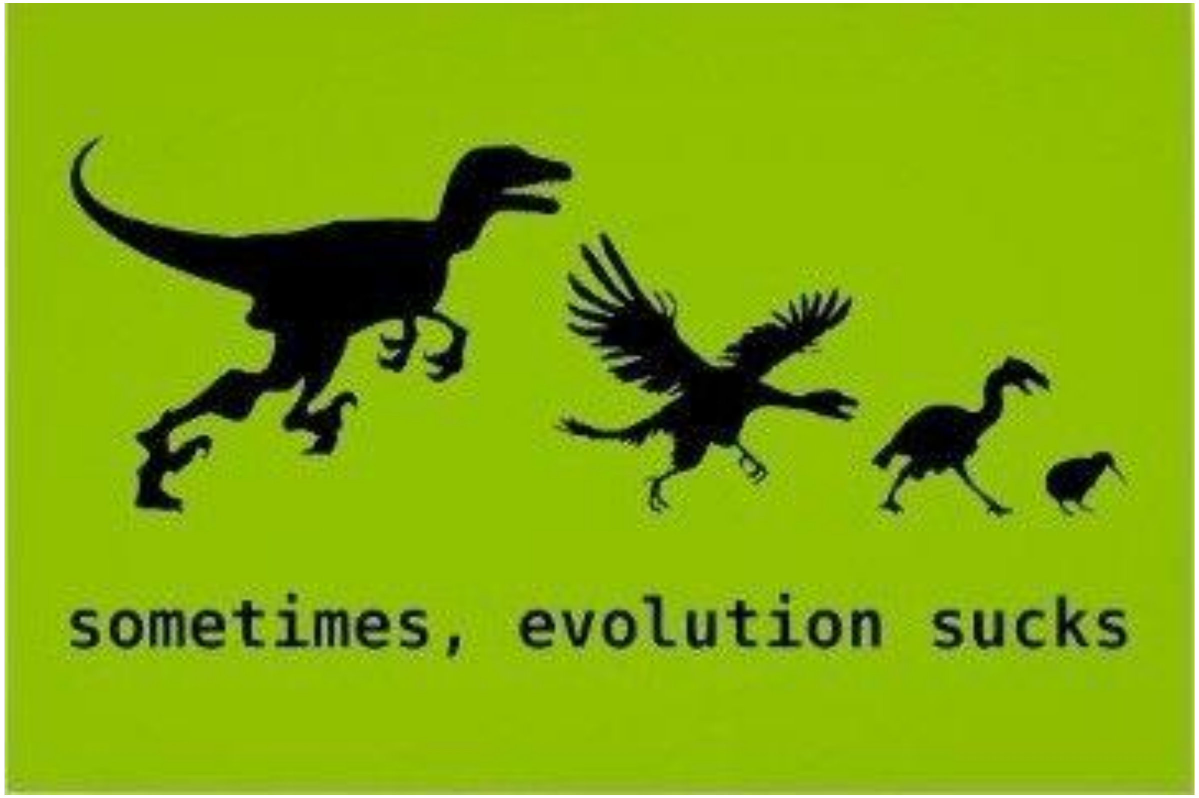
β's ↔ environmental chemistries







Hanczyc, Mansy and Szostak, Orig. Life. Evol. Biosph. (2007)


sometimes, evolution sucks

Selection in GARD

- Can a network of chemical reactions undergo Darwinian evolution?
- Are metabolism first & lipid world even worth to consider as protocells?

Selection of GARD assemblies towards a target compotype.

1) Identify most frequent compotype (= target).
2) Rerun the same simulation while modifying the β_{ij} values at each generation, biasing the growth rate towards the target.

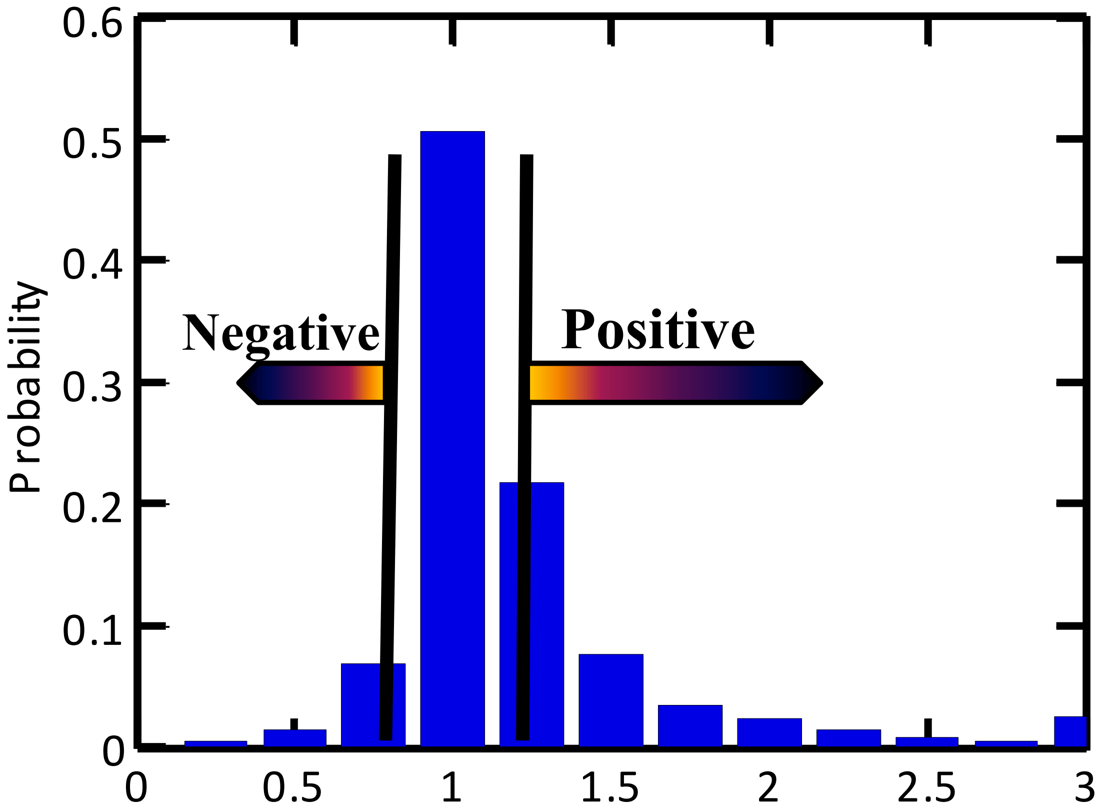
$$\beta'_{ij} = \begin{Bmatrix} \beta_{ij} & i \text{ or } j \notin Current \\ 1.1H\beta_{ij} & i \text{ and } j \in Current \end{Bmatrix}$$

H: compositional similarity between **current** and **target**.

$$Selection\ Excess = \frac{\text{Target frequency after}}{\text{Target frequency before}}$$

Based on: Vasas, Szathmary and Santos, Proc. Natl. Acad. Sci. 107 (2010).

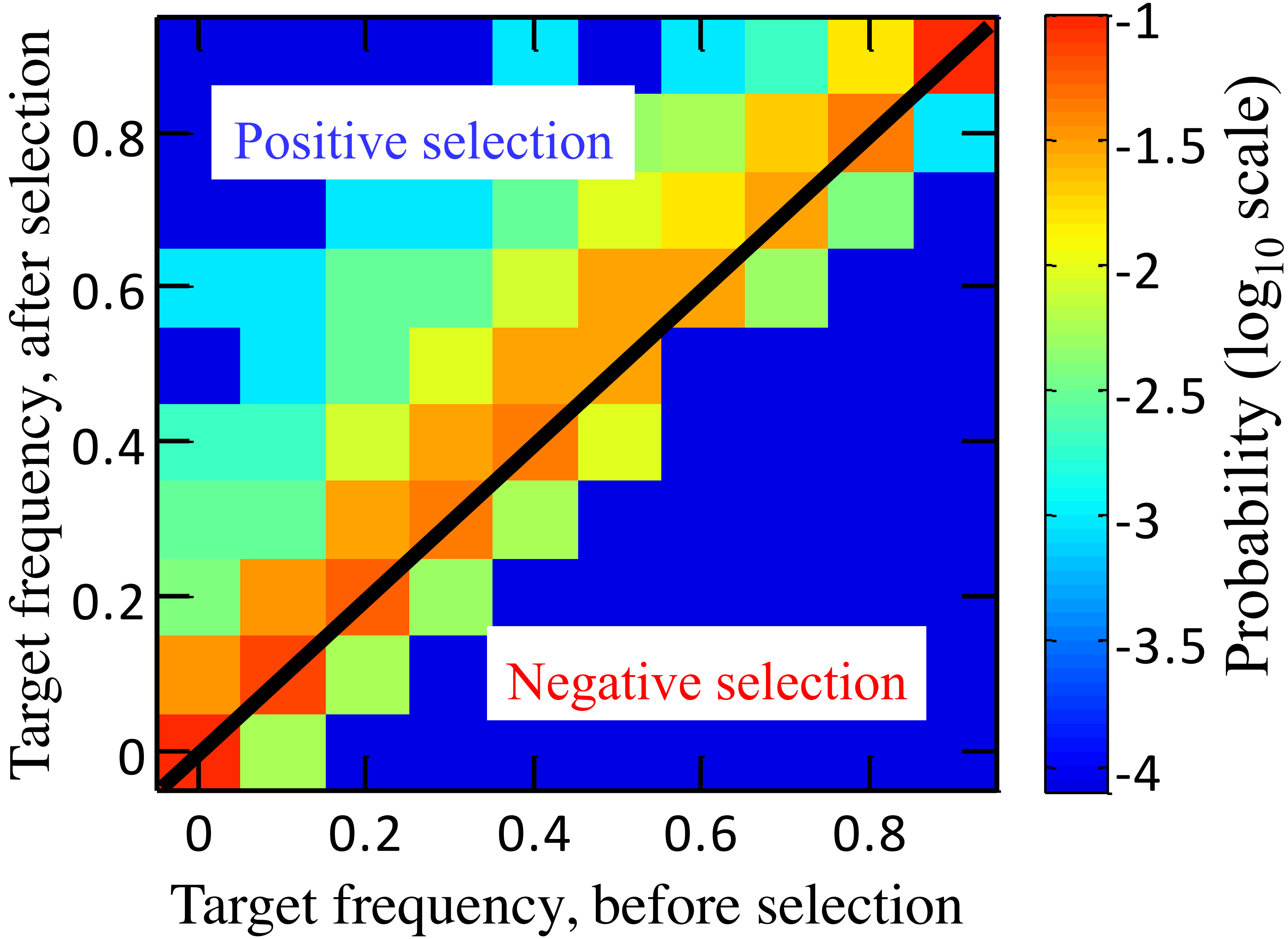
Selection in GARD



$$Selection\ Excess = \frac{\text{Target frequency after}}{\text{Target frequency before}}$$

Markovitch and Lancet, Artificial Life 18:3 (2012).

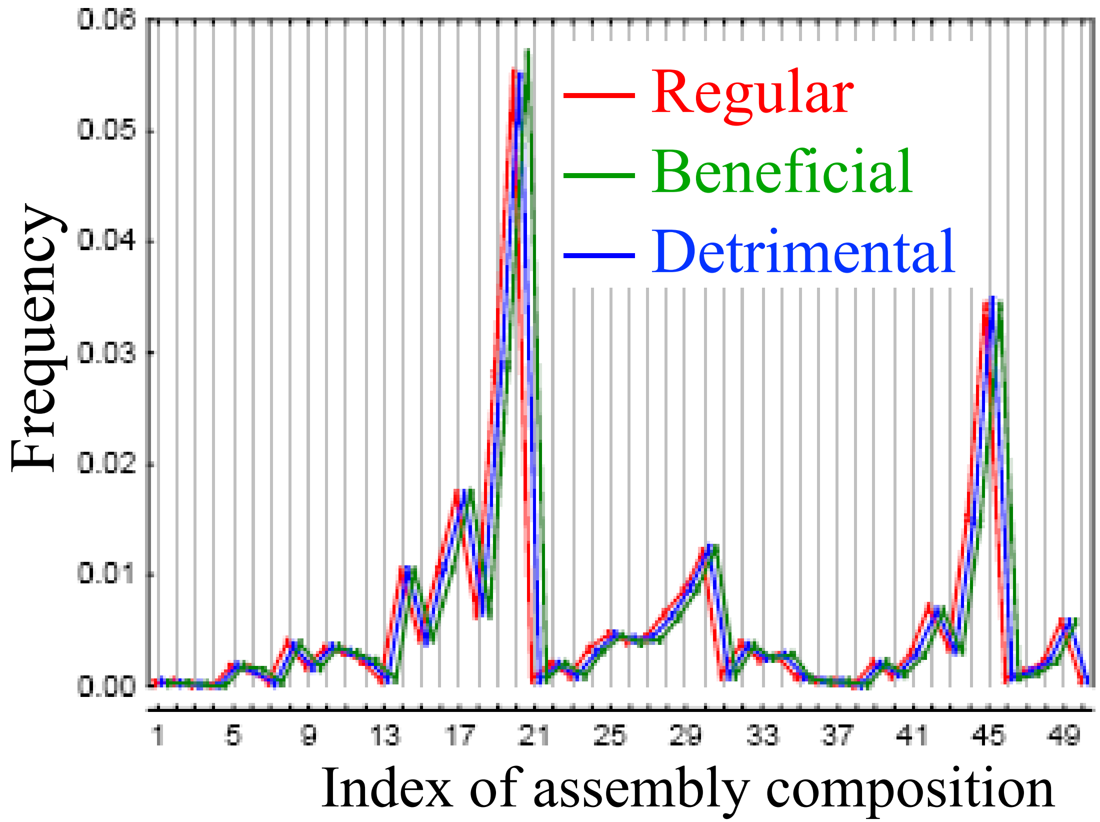
Selection in GARD



Markovitch and Lancet, Artificial Life 18:3 (2012).

Lack of selectivity in GARD? *NO.*

Vasas, Szathmary & Santos, PNAS 107, 1470-1475 (2010): Imposing Darwinian selection in GARD has, at most, negligible effect…



Their weak points:

(1) Target is not a composome.

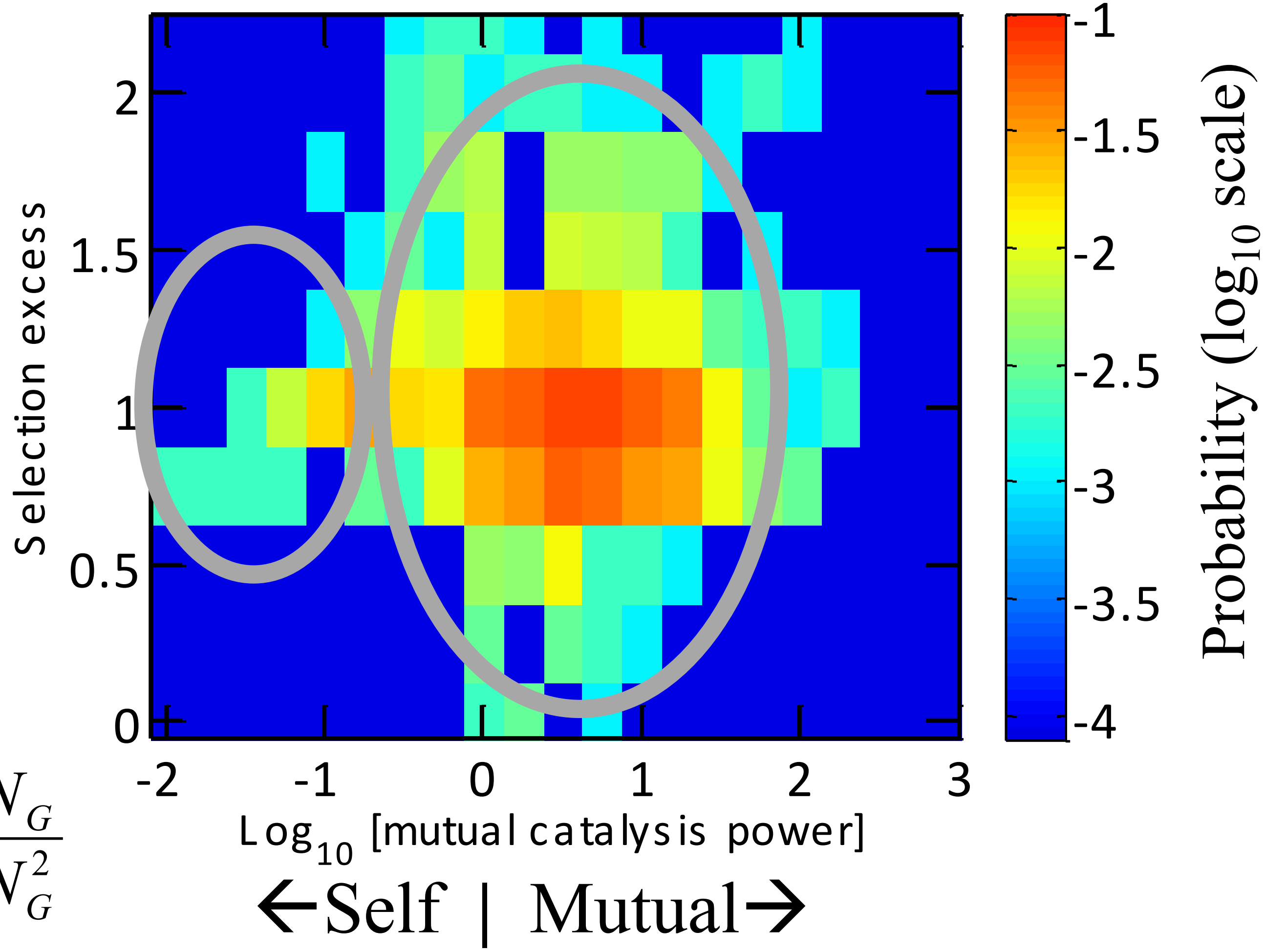
(2) Only a single simulation performed.

(3) Small repertoire (N_G=10) and assembly size (N_{max}=6).

(4) Arbitrary fitness threshold.

How the β network effects selection ?

→ Too much self-catalysis is not good → 'Dead-End'.



$$p_{mc} = \frac{\sum_{i=1}^{N_G}\sum_{j=1}^{N_G}\beta_{ij}}{\sum_{q=1}^{N_G}\beta_{qq}} \cdot \frac{N_G}{N_G^2}$$

Markovitch and Lancet, Artificial Life 18:3 (2012).

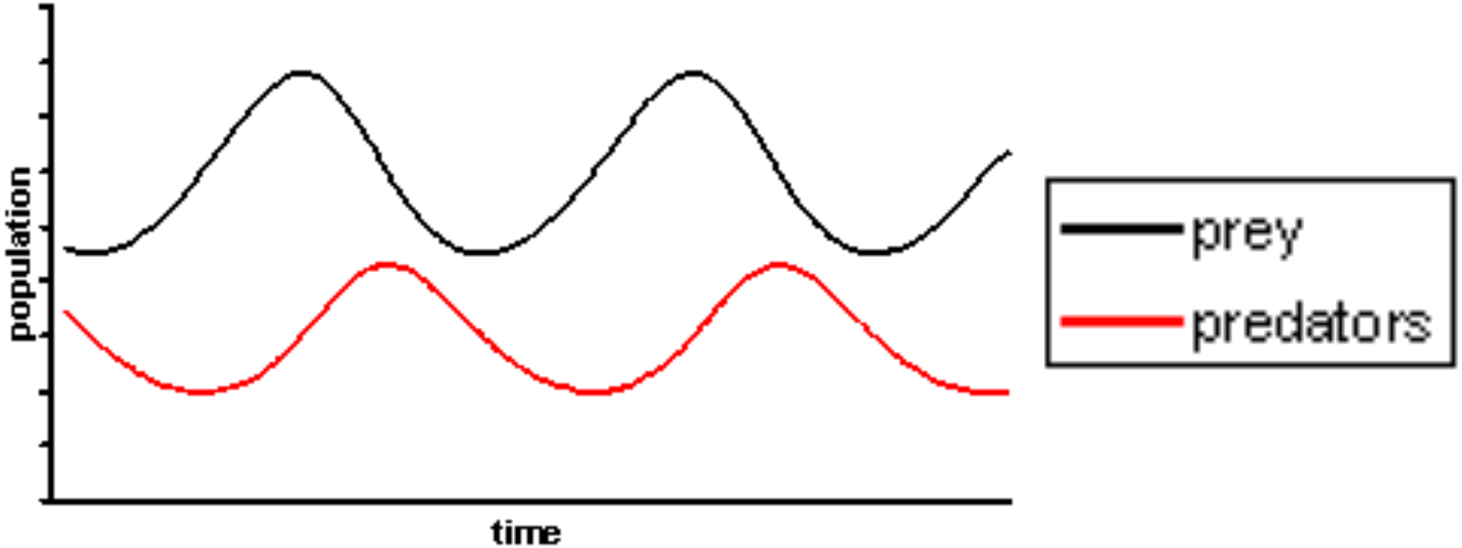
Self *vs.* Mutual catalysis

Experimental hints that excess mutual catalysis is required for effective evolvability:

- In an abstract chemistry model, if self-replication is inhibited then self-maintaining organizations arise [Fontana & Buss, PNAS (1994); see also Szathmary, Proceedings: Biological Sciences (1995)].
- RNA fragments (of *Azoarcus group I ribozyme*) that are mutually interacting outcompete selfish yet efficient individual fragments [Vaidya & Lehman Nature (2011)].
- A particular ribozyme (R3C) is capable of only 2 slow doublings, yet a conversion into two cross-replicating ribozymes allows for many fast doublings [Lincoln & Joyce, Science (2009)].
- A mutualistic network of replicating peptides is adaptable to physiochemical conditions (pH, salt) [Dadon et al, Angew. Chem. Int. Ed. (2008)].
- Mutualism is also needed for effective contagion [Ugander et al, Proc. Natl. Acad. Sci (2012)].

Ecology

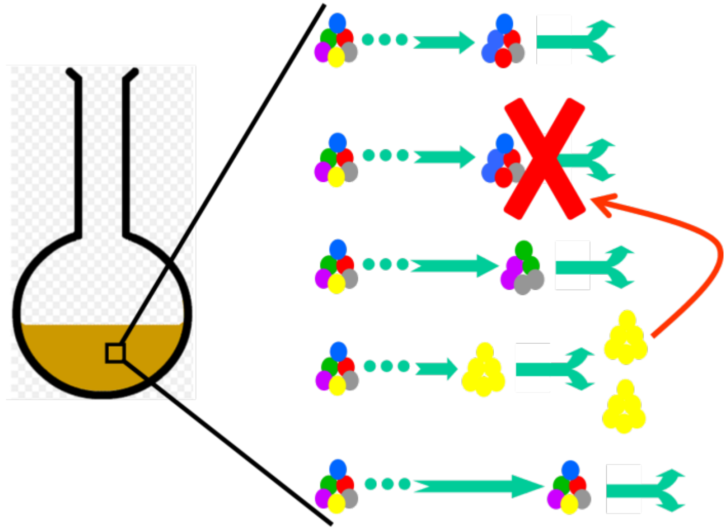
- Predator–Prey
- r–K relations

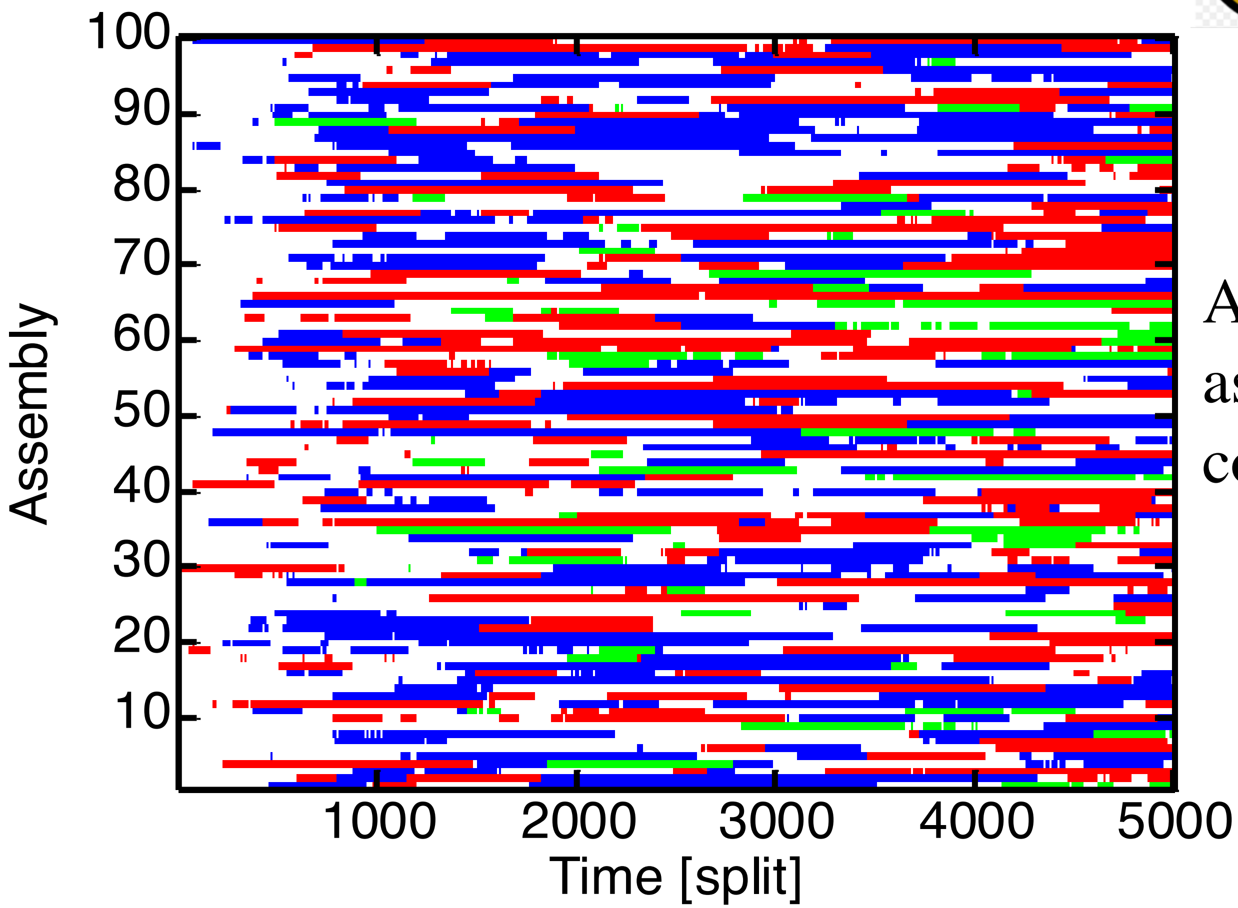


- Lotka & Volterra
- MacArthur
- Malthus & Verhulst

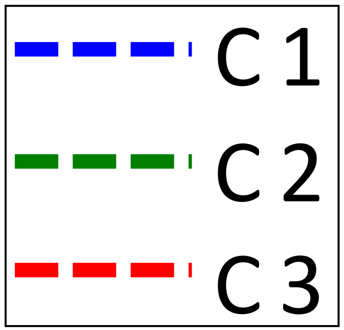
Population Dynamics in GARD

Fixed population size.

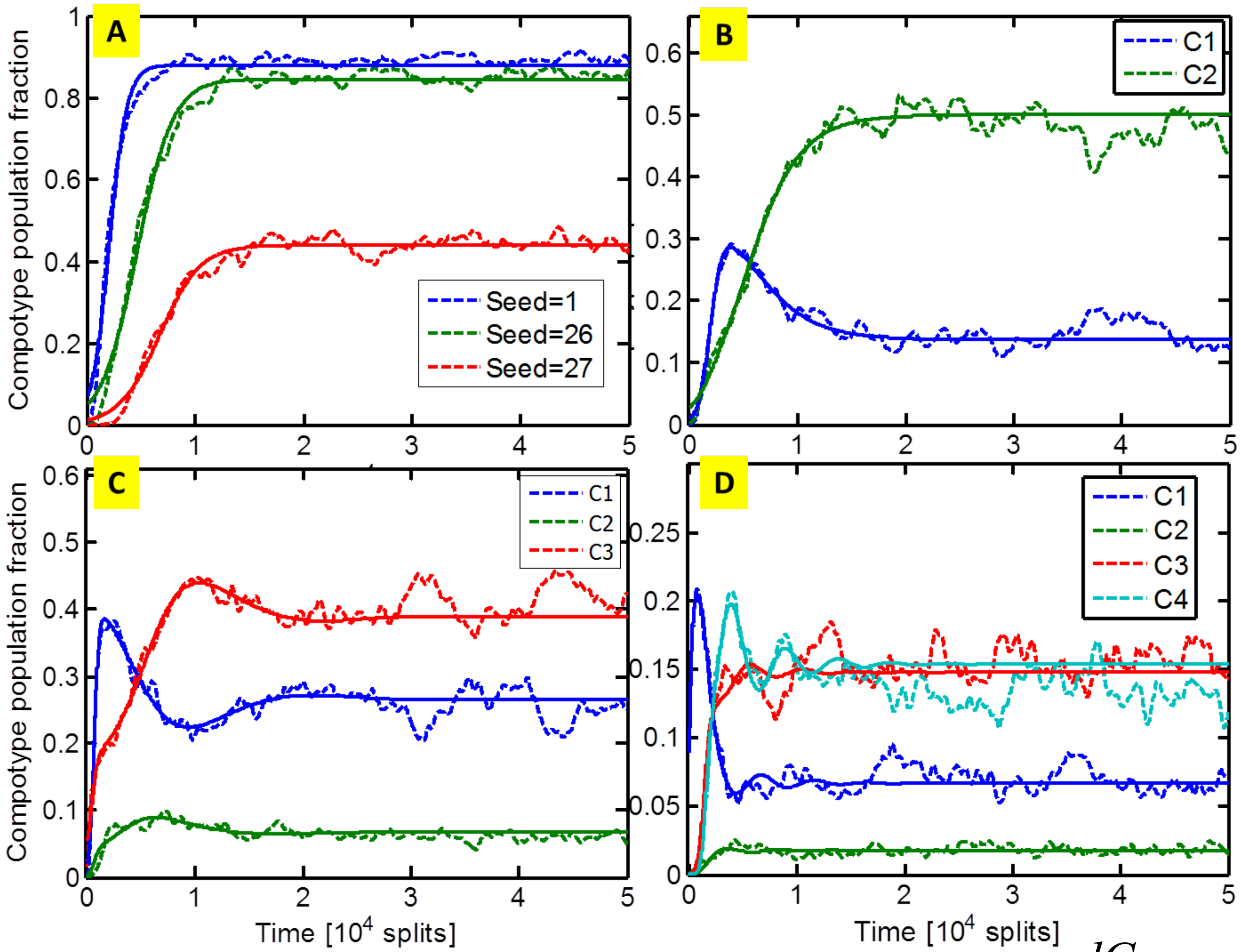




At each time point, each assembly is colored by its compotype.



Population Dynamics in GARD

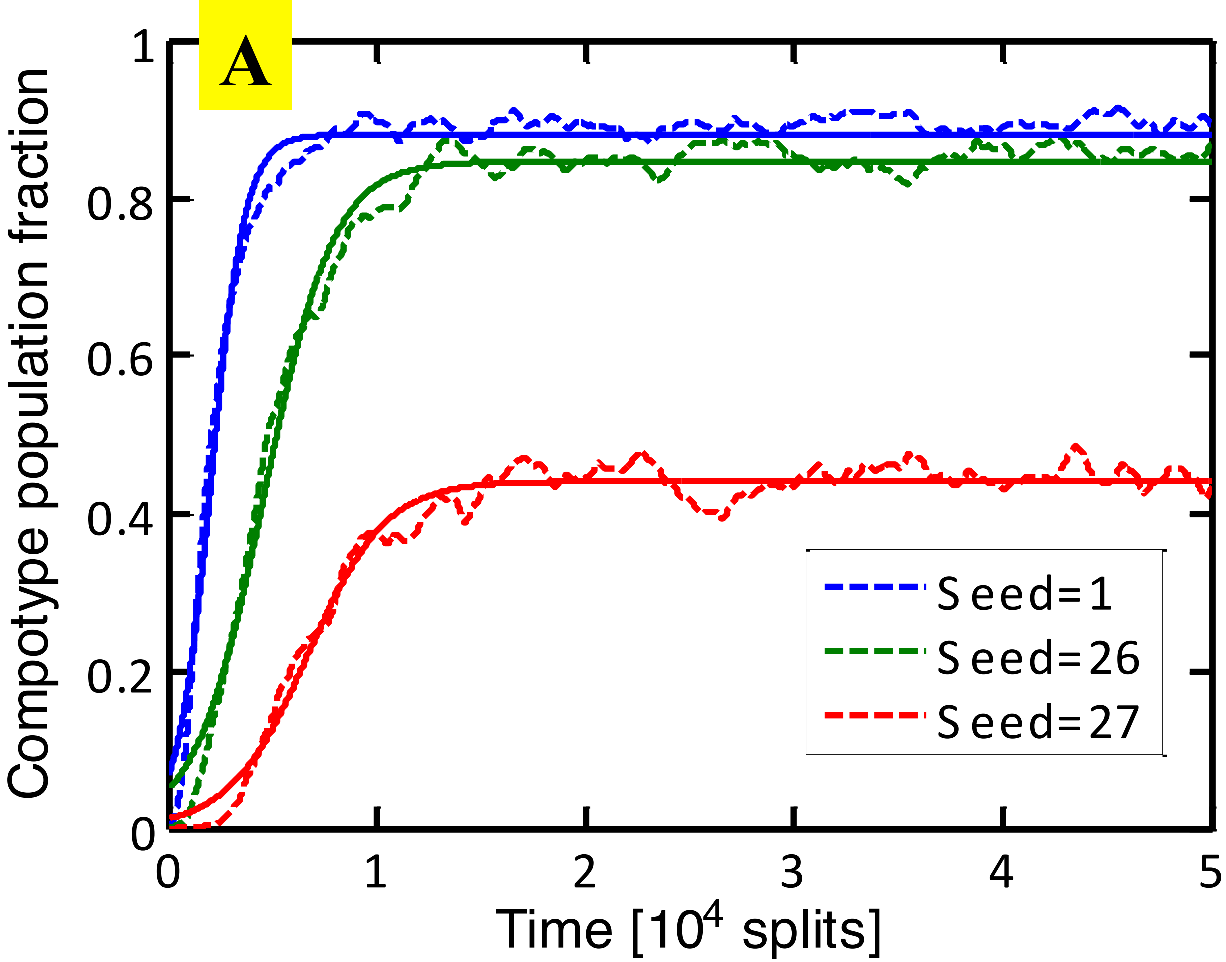


Logistic growth:

$$\frac{dC_i}{dt} = r_i C_i \left(1 - \frac{C_i + \sum_{j=1, j \neq i}^{N_C} \alpha_{ij} C_j}{K_i} \right)$$

Species = compotypes

Population Dynamics in GARD



3 examples with single compotype (different β).

Why plateau doesn't reach 1.0 ?

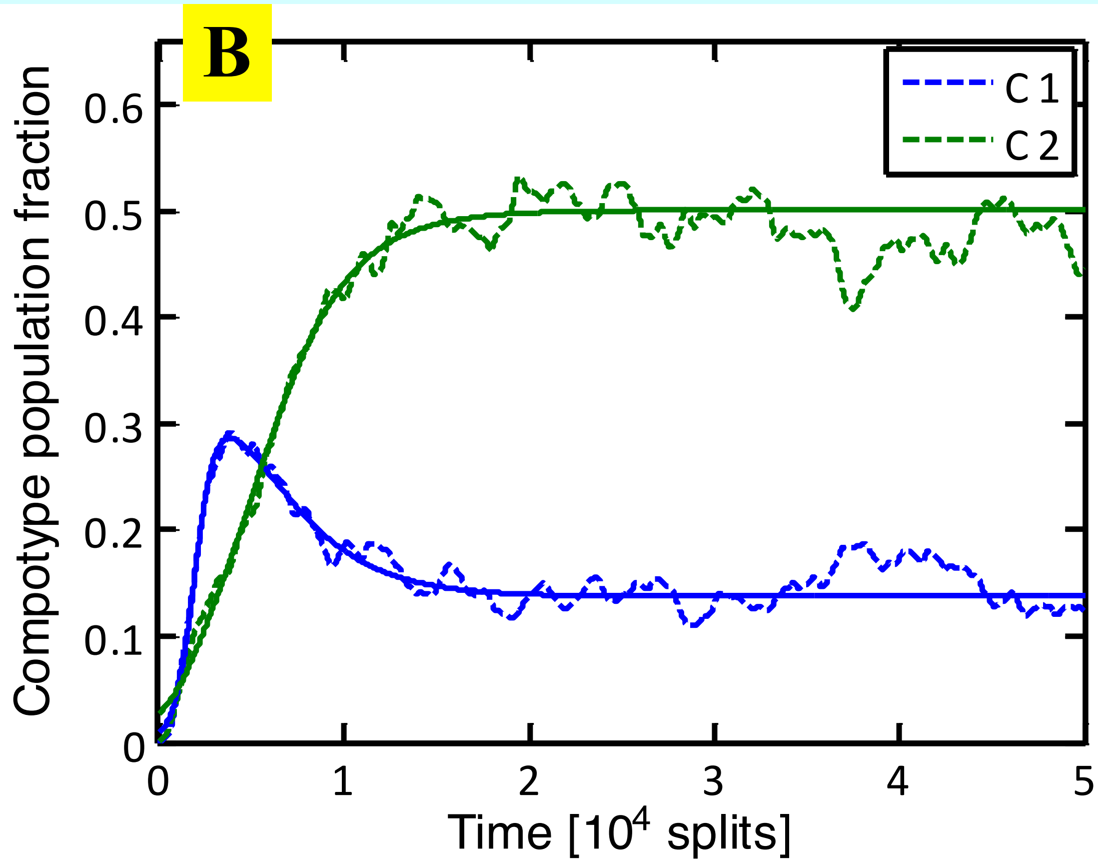
Species = compotypes

Logistic growth:

$$\frac{dC_i}{dt} = r_i C_i \left(1 - \frac{C_i + \sum_{j=1, j\neq i}^{N_C} \alpha_{ij} C_j}{K_i} \right)$$

Population Dynamics in GARD

"**Takeover**" of a fast-rising compotype by a slower one.

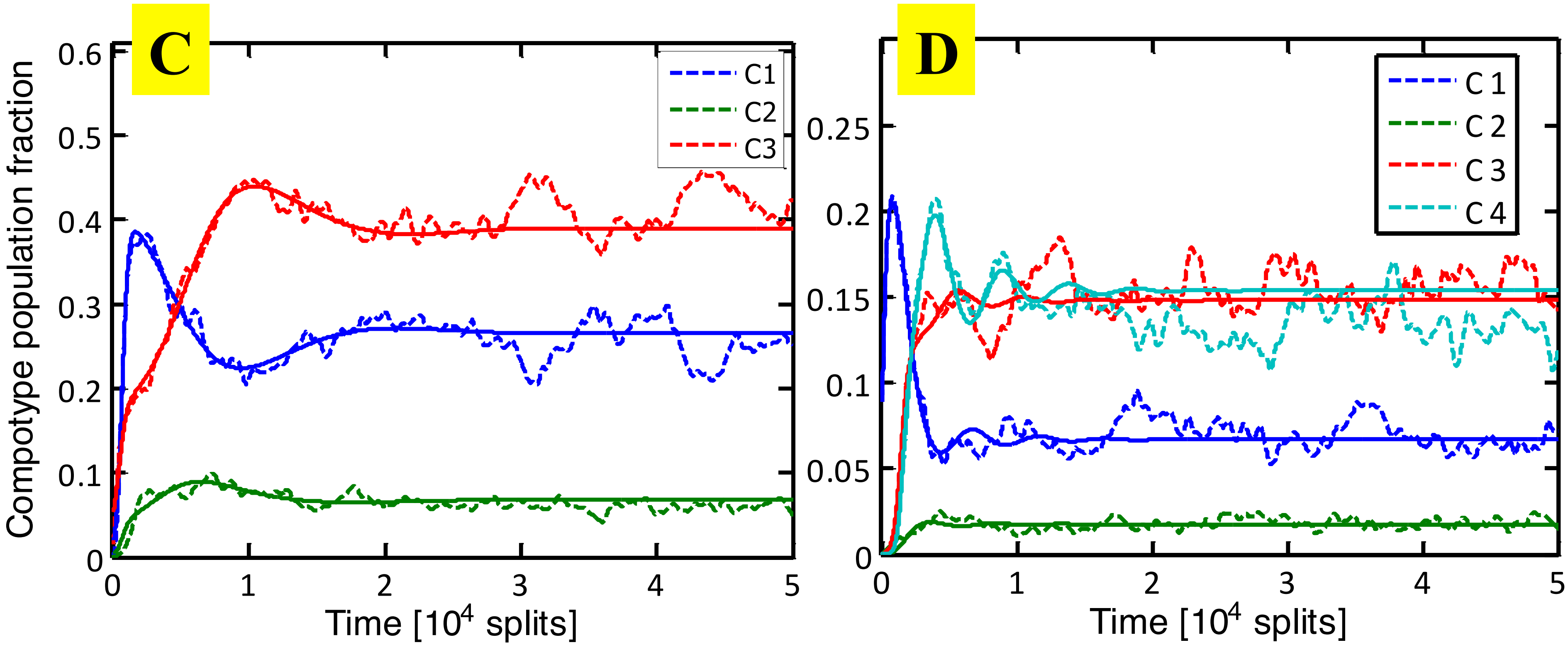


Logistic growth:

$$\frac{dC_i}{dt} = r_i C_i \left(1 - \frac{C_i + \sum_{j=1, j\neq i}^{N_C} \alpha_{ij} C_j}{K_i} \right)$$

Species = compotypes

Population Dynamics in GARD



Intricate food-web (αij values).

Species = compotypes

Logistic growth:

$$\frac{dC_i}{dt} = r_i C_i \left(1 - \frac{C_i + \sum_{j=1, j \neq i}^{N_C} \alpha_{ij} C_j}{K_i} \right)$$

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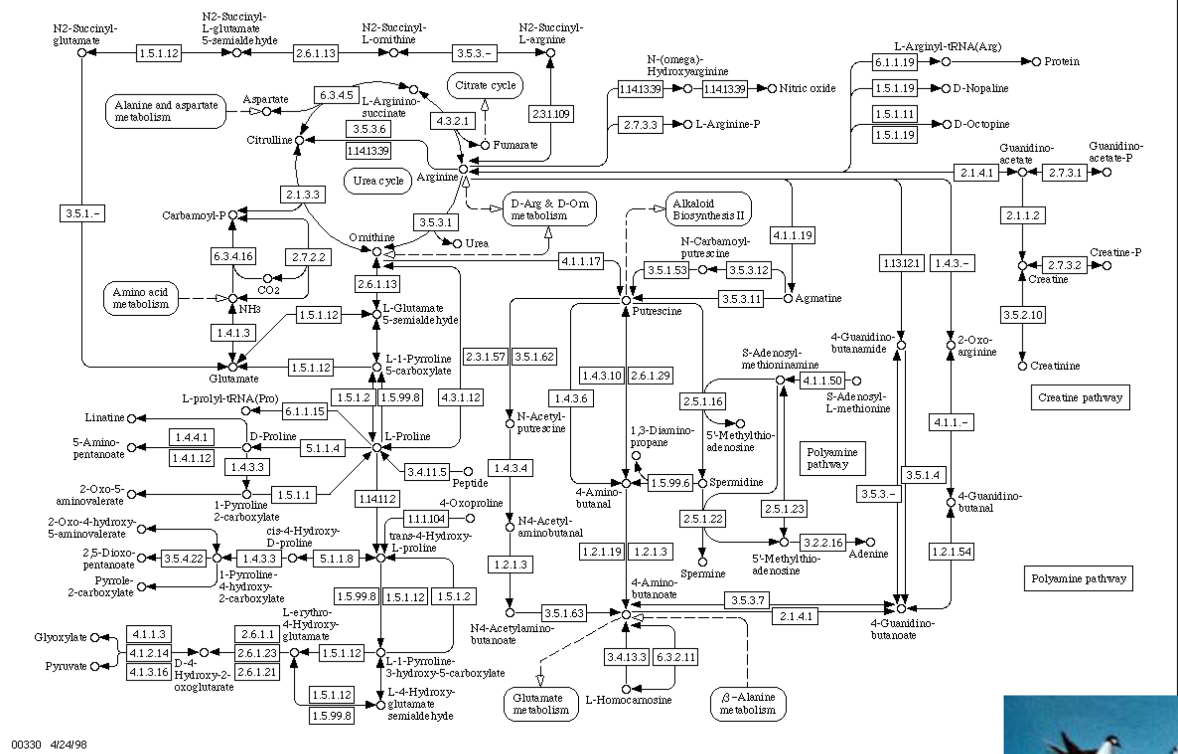
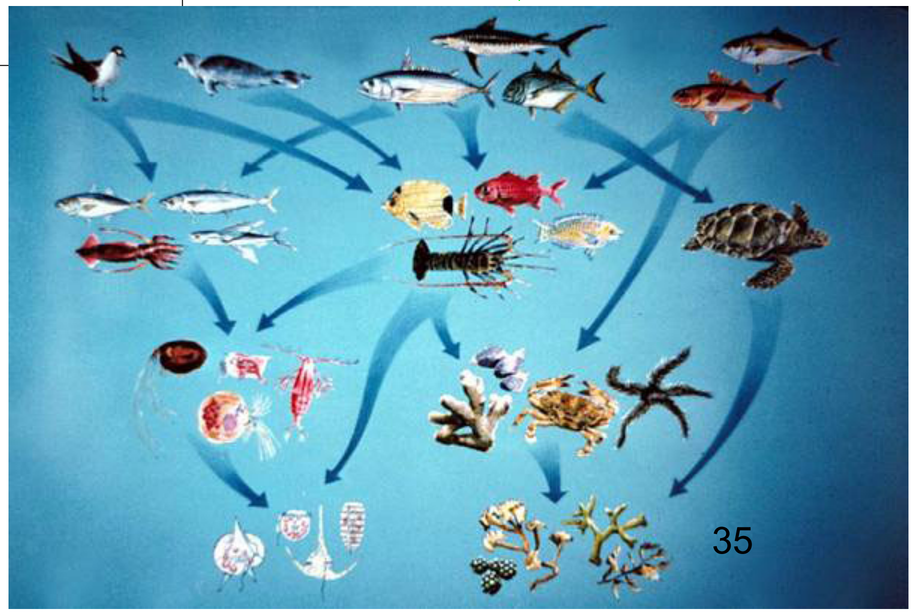
Metabolism





Prebiotic Ecology

From molecules to Ecosystem

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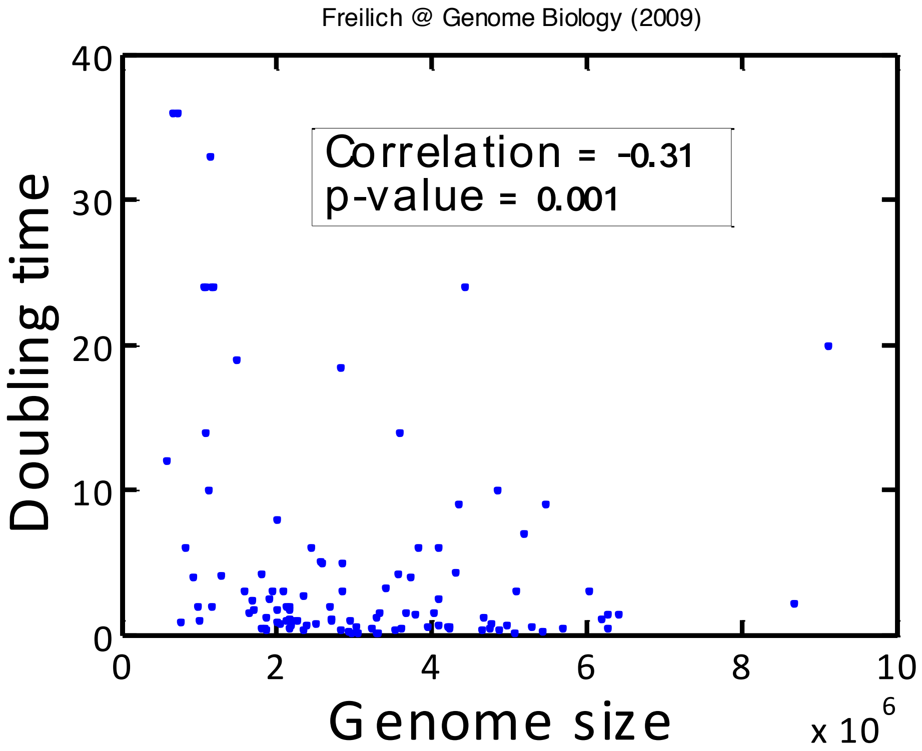
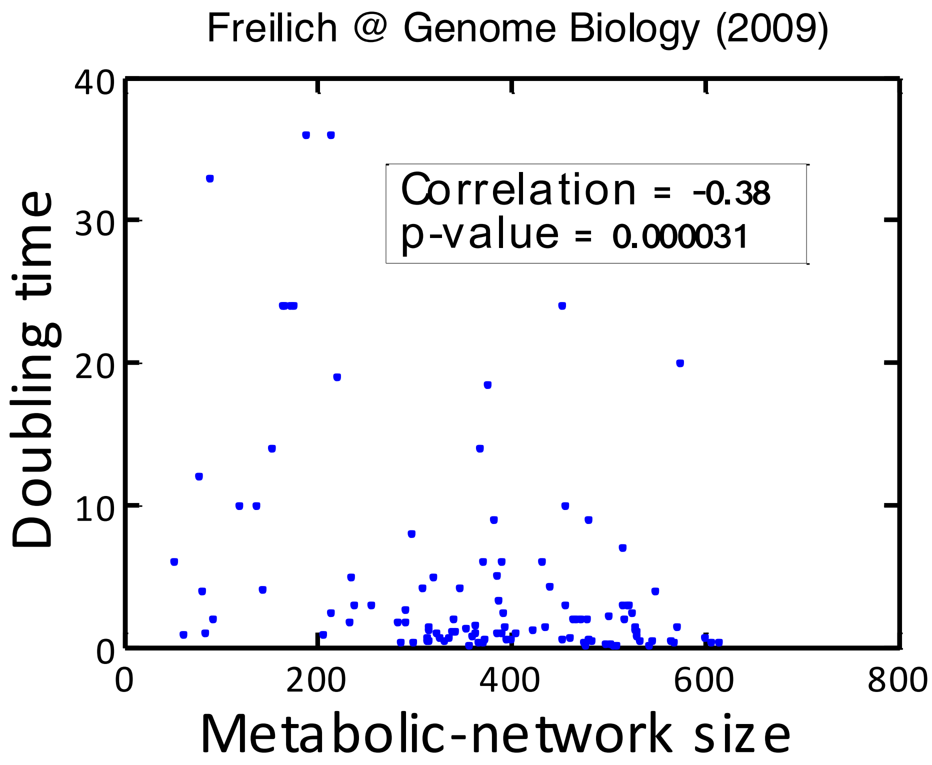
GARD’s Ecology

Based on experimental data of 111 bacteria.





Freilich et al, Genome Biology (2009)

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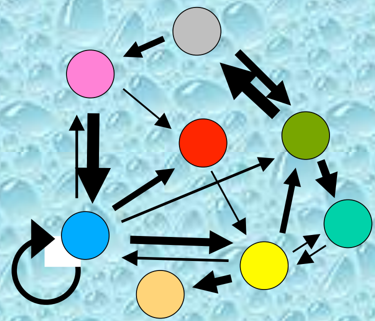
Lipid-world & GARD model: compositional assemblies

- ➢ **NOT JUST CONTAINER !**

Compotypes (clusters of faithfully replicating compositions)

- ➢ **Darwinian <u>selection</u>**

Mutual catalysis is required for effective evolvability



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מכון ויצמן למדע
WEIZMANN INSTITUTE OF SCIENCE

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Doron Lancet.

Raphael Zidovetzki (U. California Riverside, USA).

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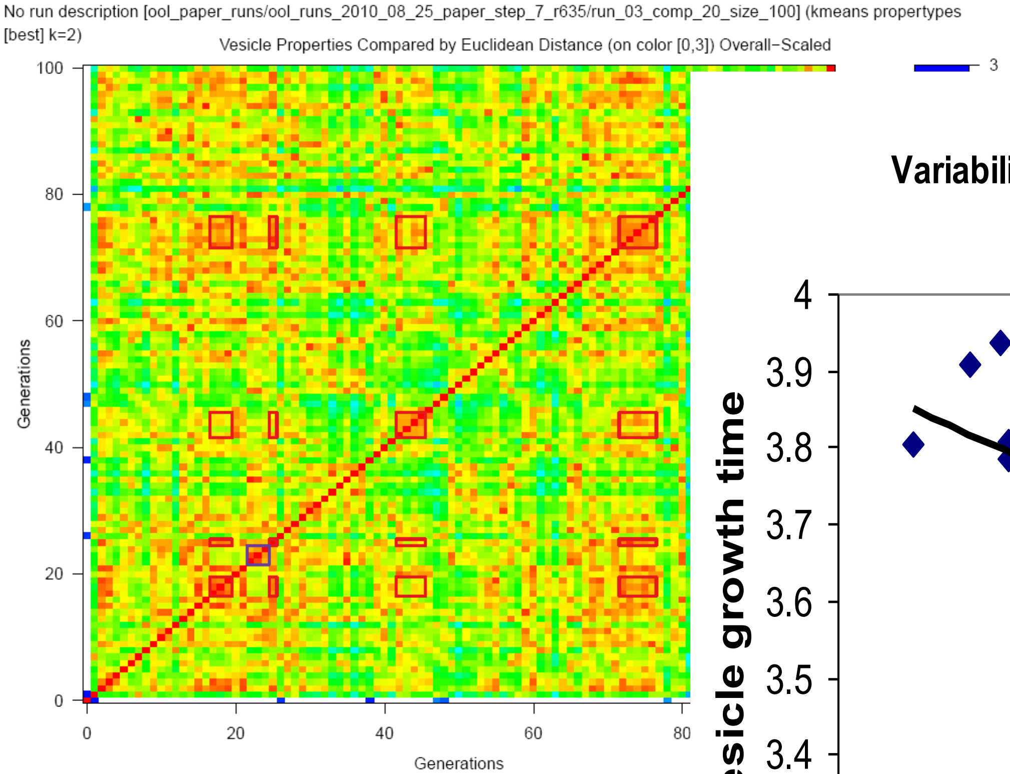
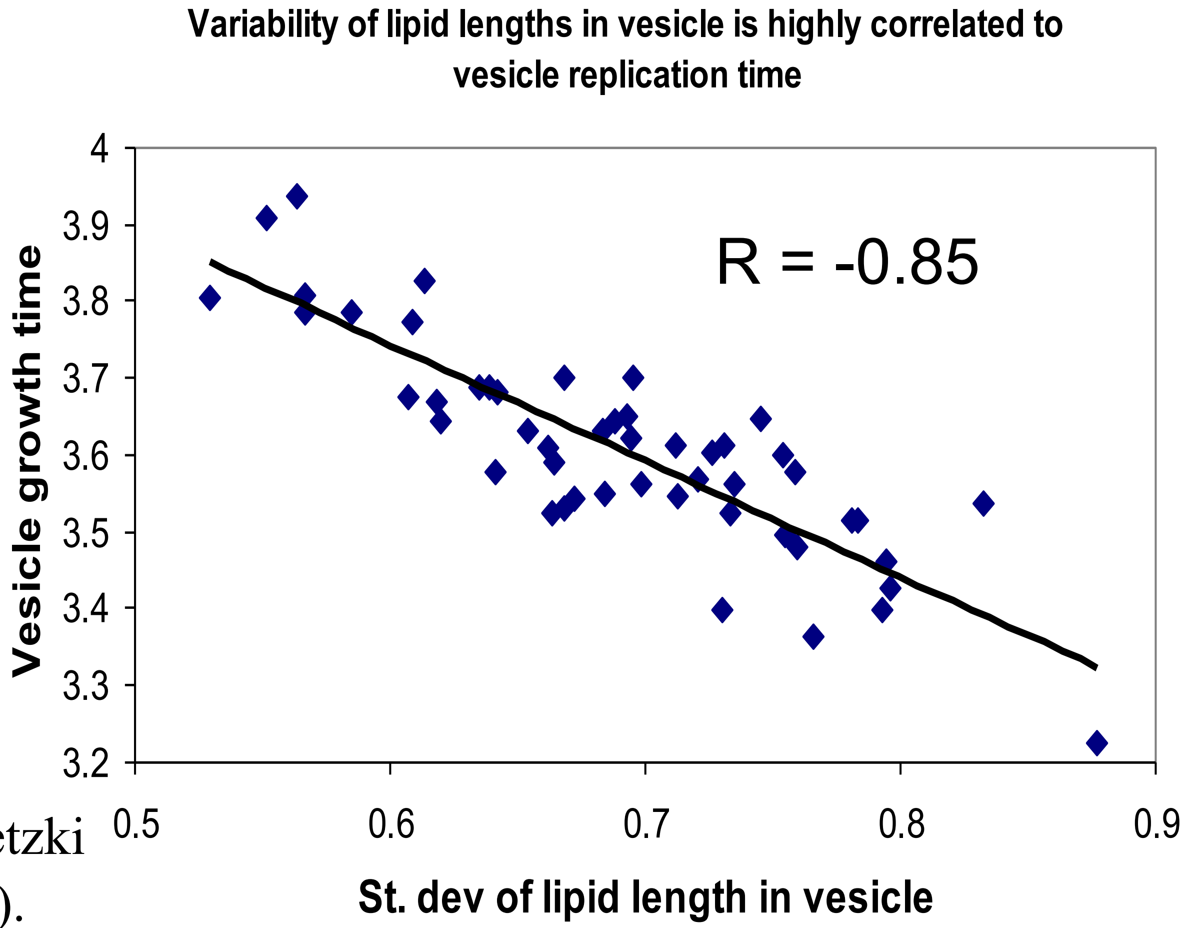
*** E.U. FP7 “MATCHIT”**

Real GARD – Raphael Zidovetzki, U. California Riverside

Real lipids: phosphate-idyl-(serine / amine / choline), sphingo-myelin and cholesterol.

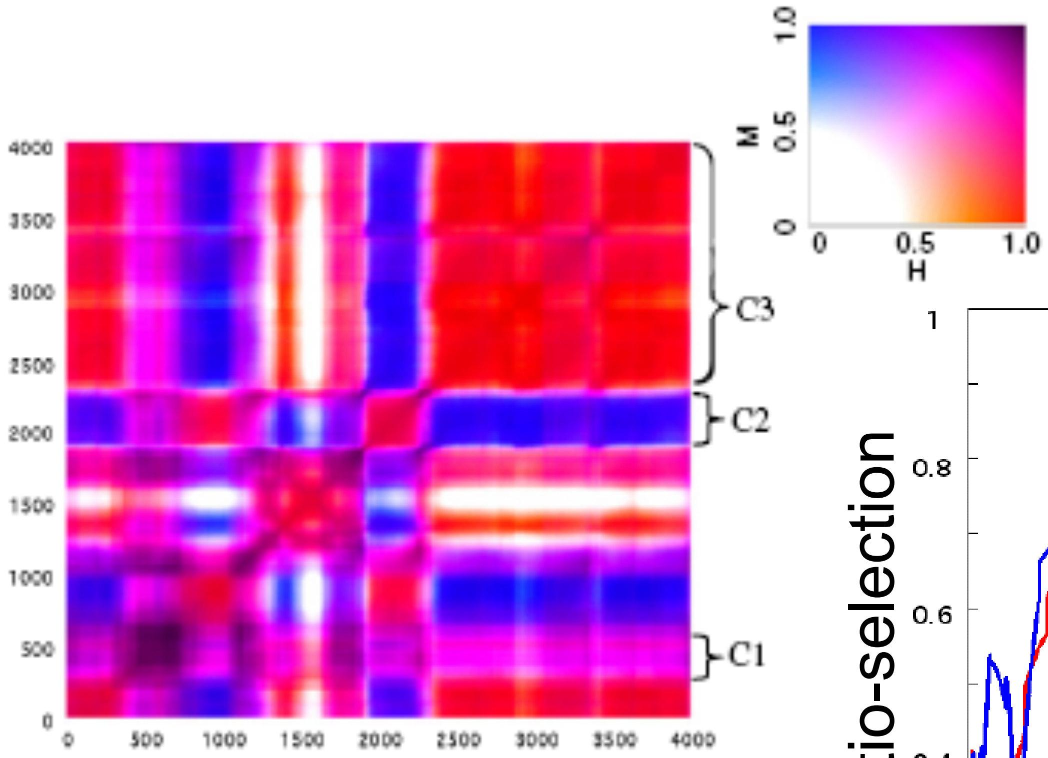
Actual physical properties (charge, length, unsaturation).

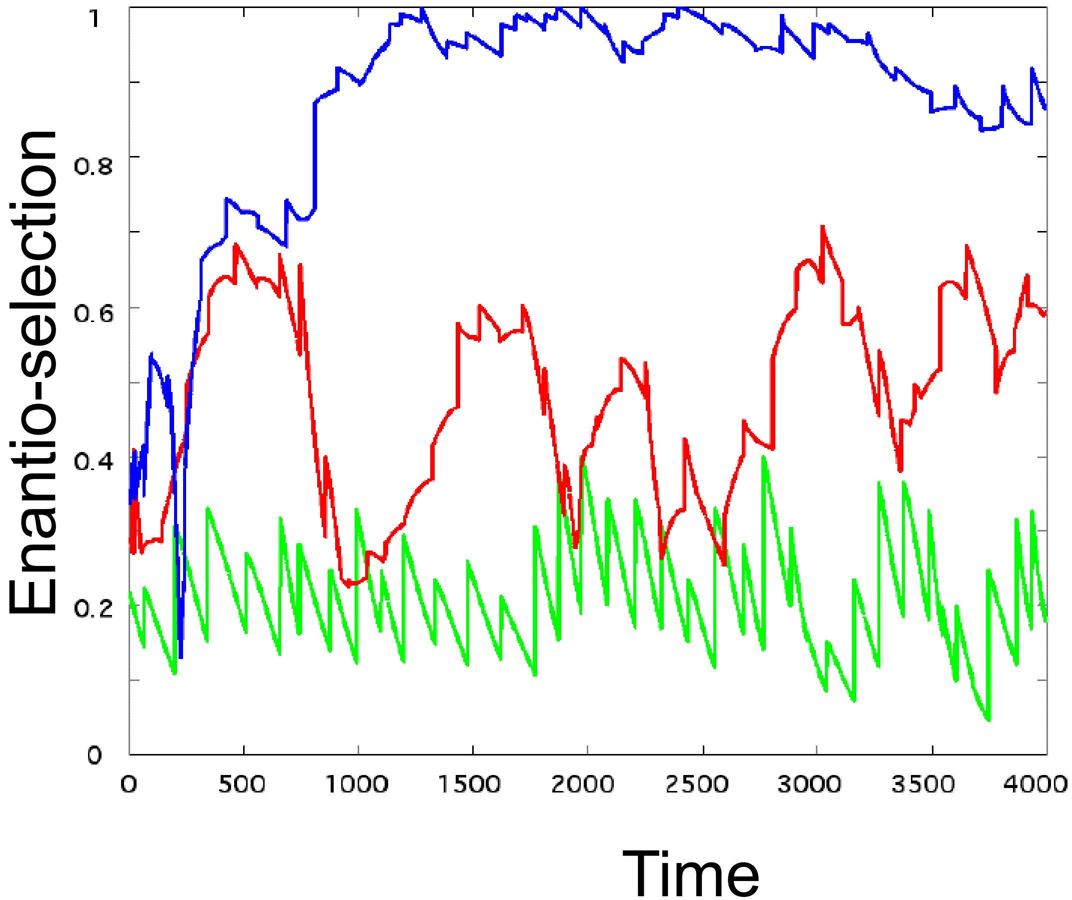




Armstrong, Markovitch, Zidovetzki and Lancet, Phys. Biol. 8 (2011).

Chiral GARD – origins of biochirality

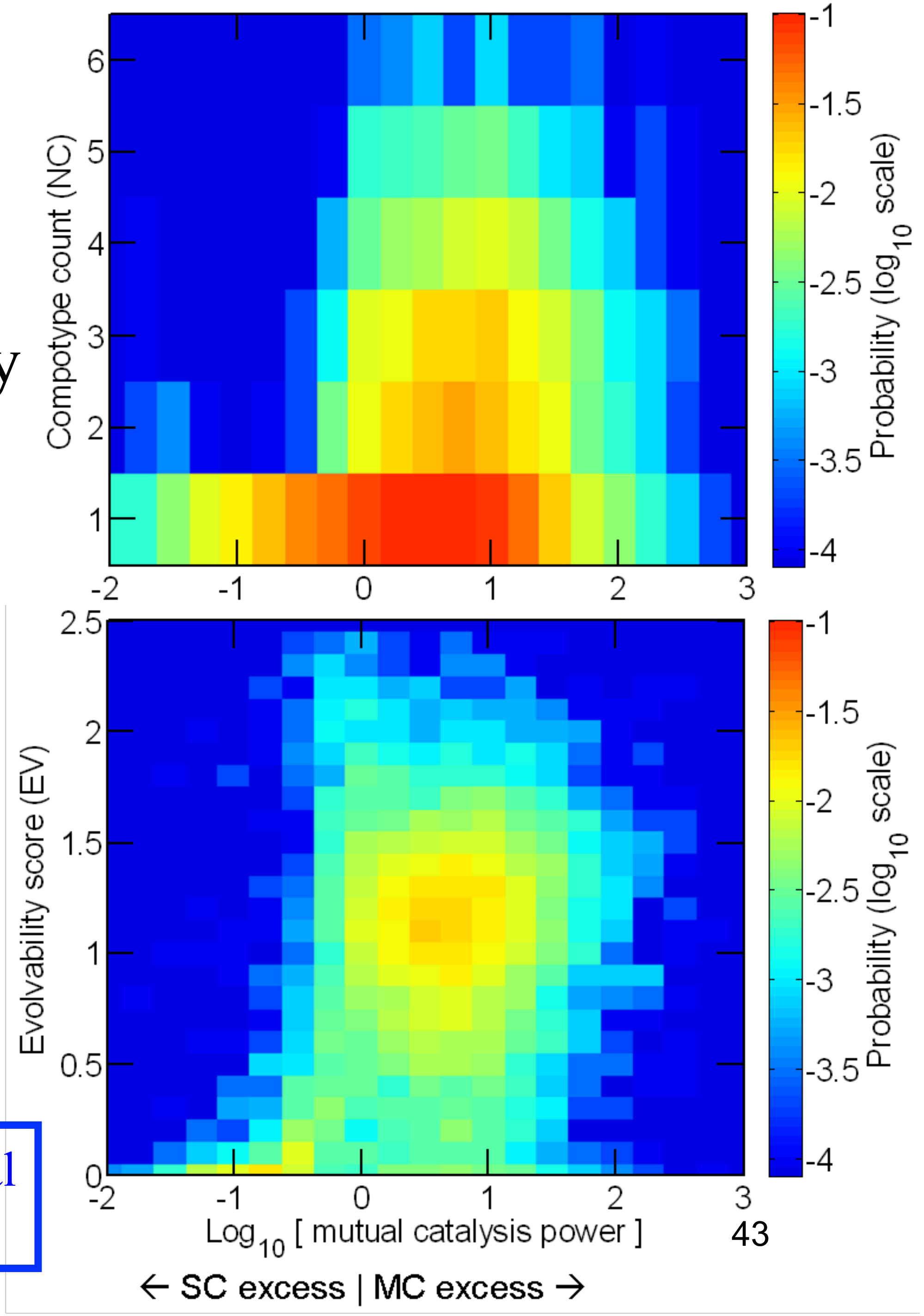




Biology Direct 5 (2010)

Same behavior in other evolutionary parameters

Compotype diversity



<u>Evolvability Score:</u>

$$ES = \tau(1 - H_0)$$

$1/\tau$ ~ compositional mutation rate.

Compositional diversity