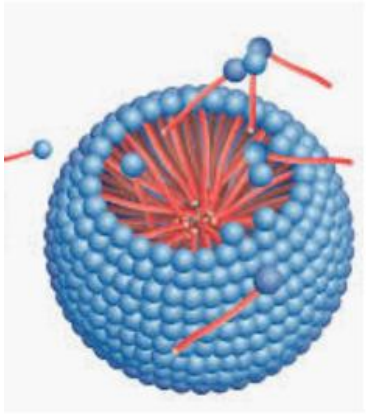
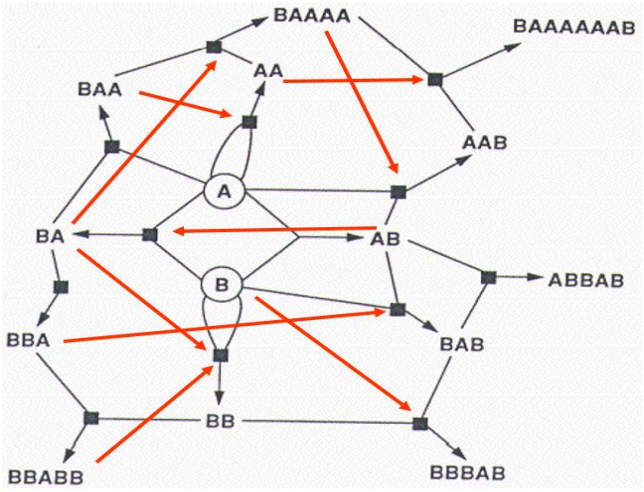
Life began with catalytic reproducing micelles

Doron Lancet, Dept Molecular Genetics
Weizmann Institute of Science
Rehovot, Israel

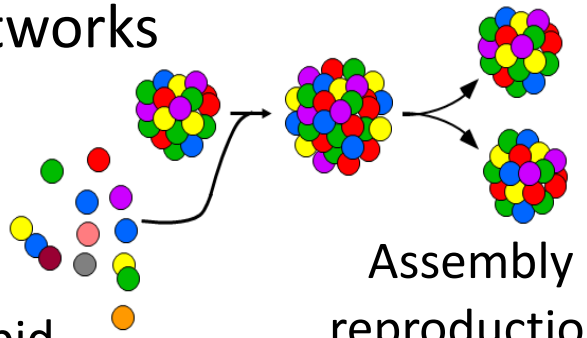
Micelle



Autocatalytic set



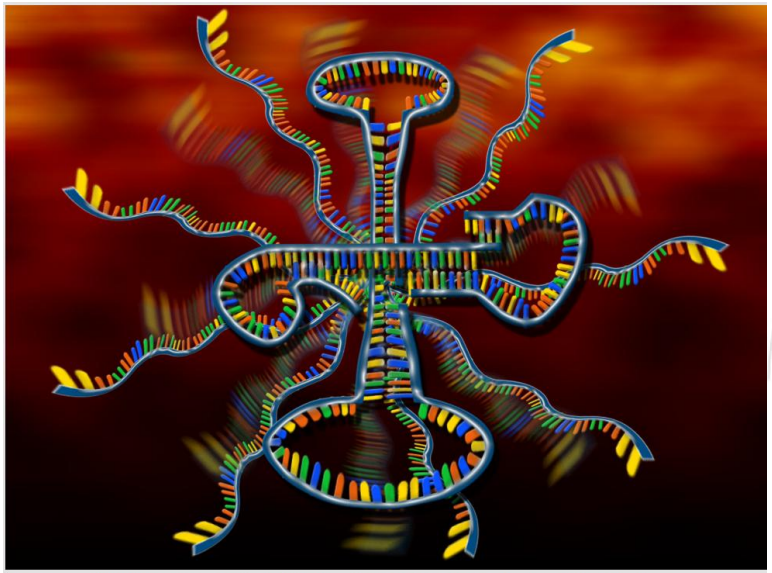
Lipid
Catalytic
networks



Lipid
monomers

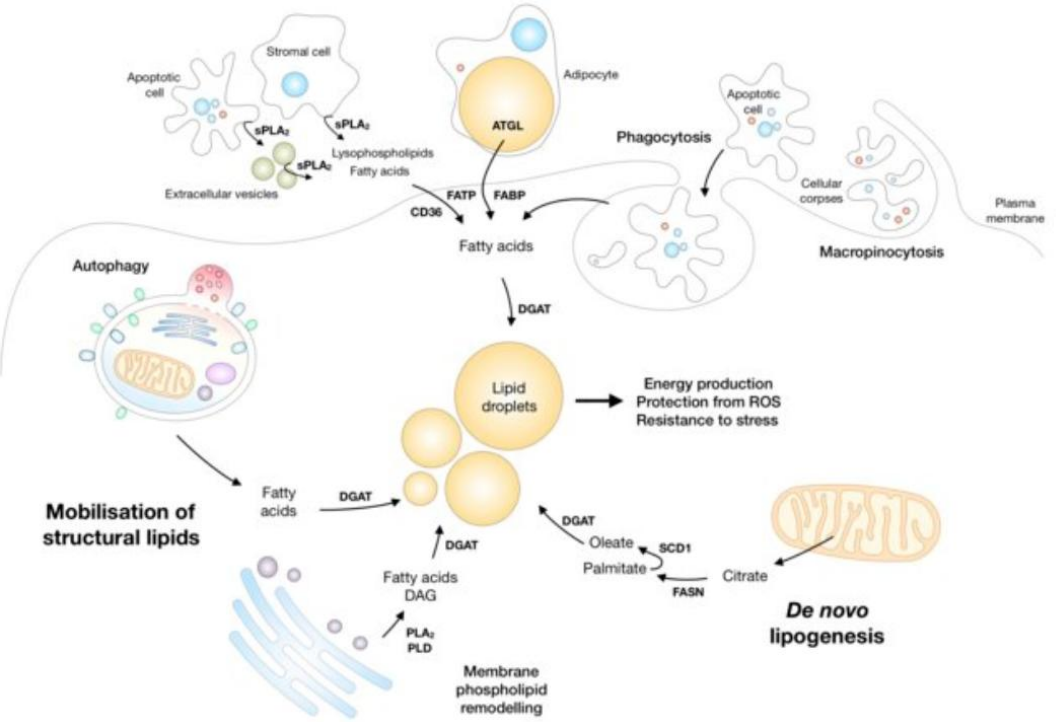
Assembly
reproduction

RNA World



An artist's rendering of a Ribonucleic Acid (RNA) molecule.Credit: Nicolle Rager Fuller, National Science Foundation

Lipid World



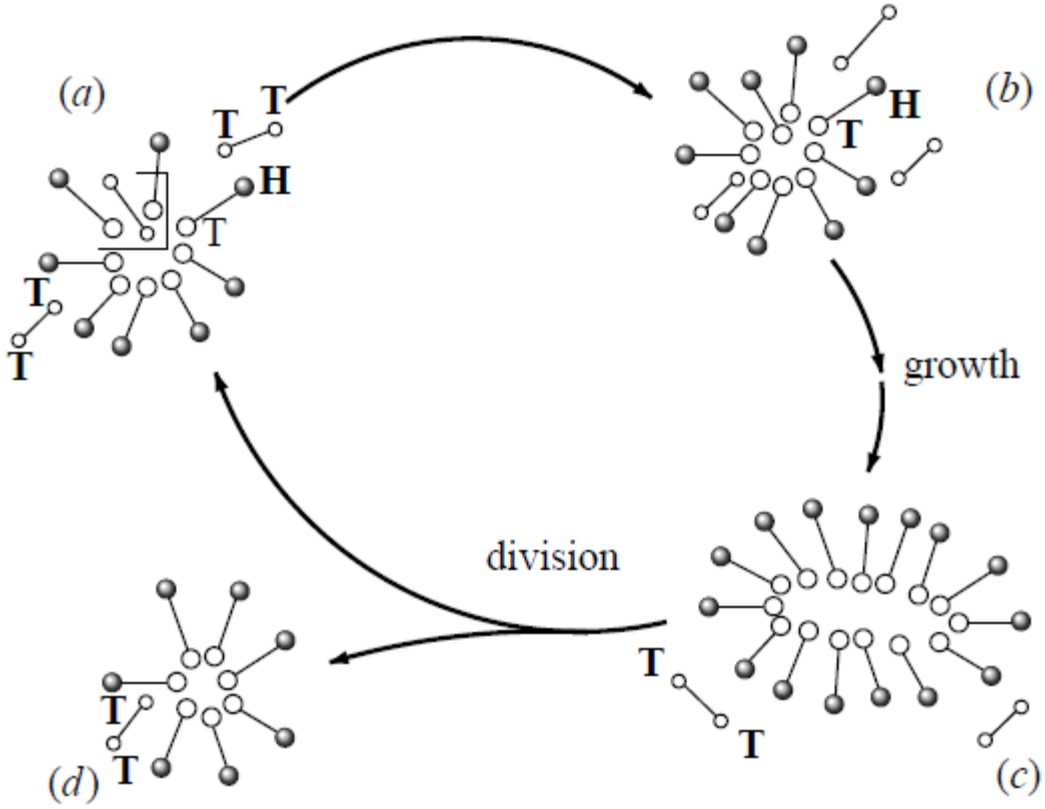
Although the classical view of a living protocell assumes that it includes information-carrying molecules as an essential ingredient, a dividing cell-like structure can be built from a metabolism–container coupled system only.

Fellermann, Sole 2007

The basic model of nanocell replication

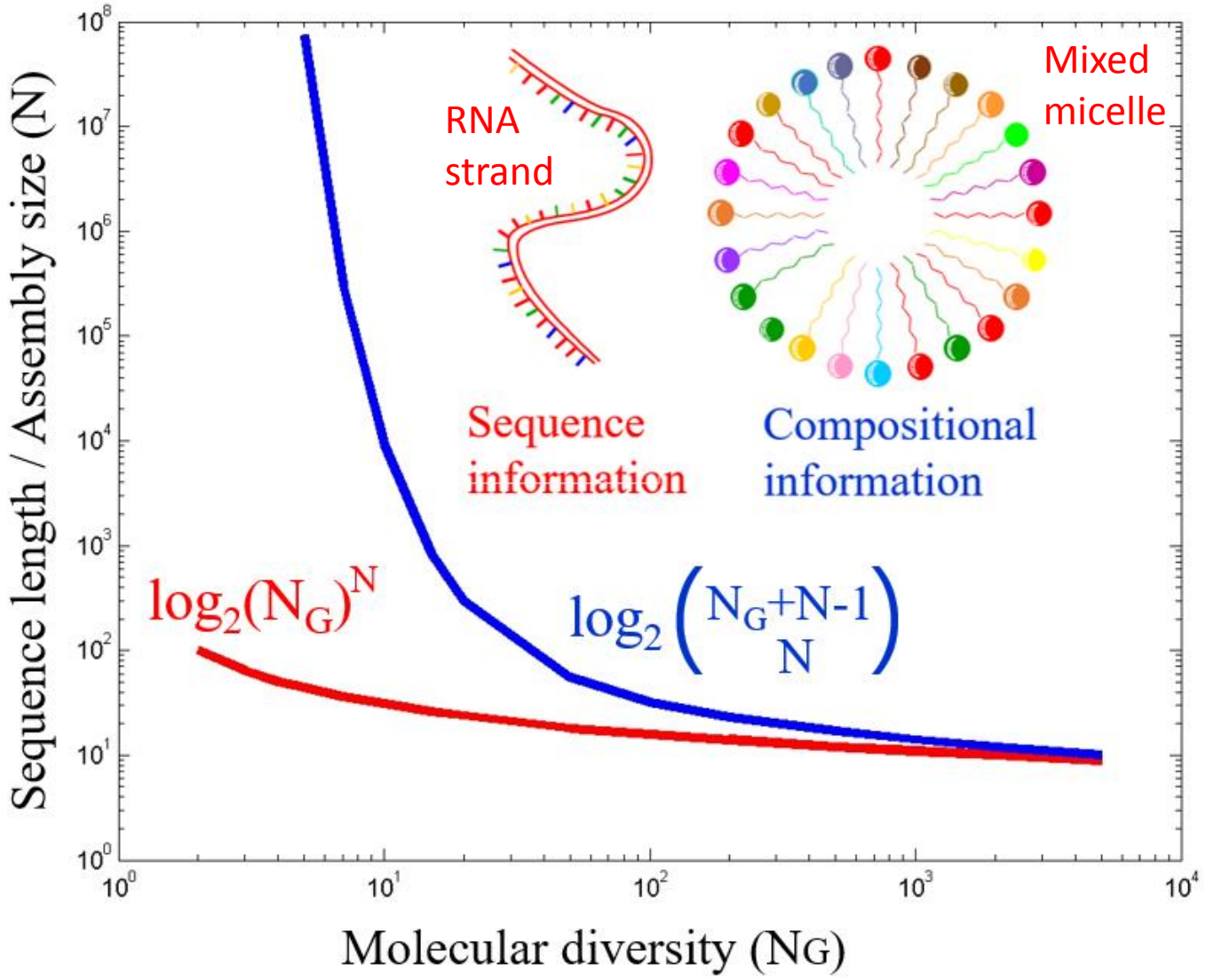
Dissipative Particle Dyneamics simulations

Fellermann, Sole 2007

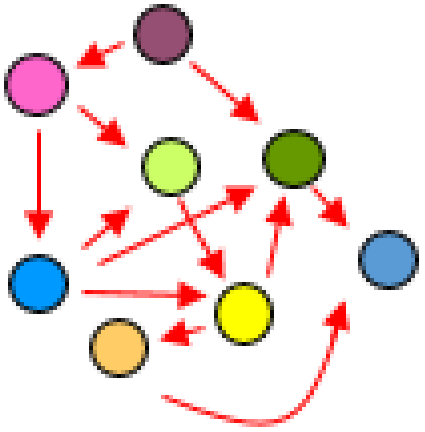


These micellar systems can be considered to be simpler in organization than biopolymers because they **lack any genetic information that could be passed from one generation to the next**….under the umbrella of Oparin's views of life origins (Oparin 1936)

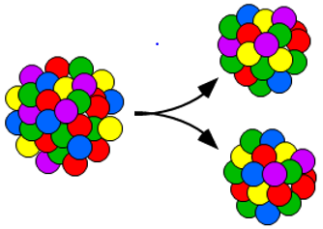
Compositional information: an alternative type of transmittable biological information

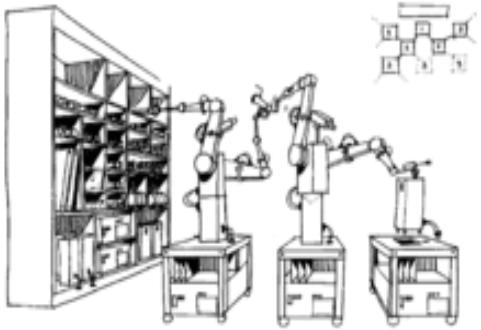


Reproduction criteria



This network has **catalytic closure**
But is this sufficient to ensure micellar reproduction?





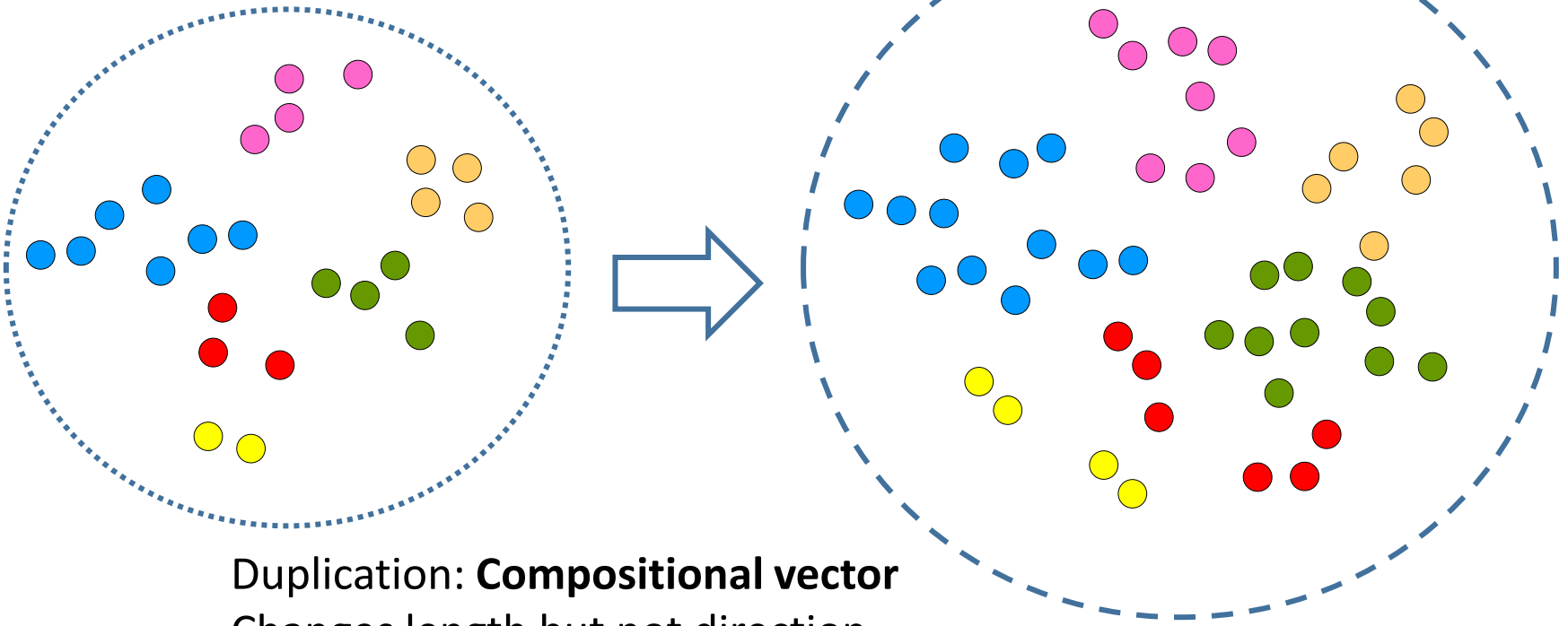
Rami Pugatch PNAS 2015

The Cell as an Autocatalytic Cycle

- Cell model essentially identical to the von Neumann's **self-replicating machine**
- **"Closure" is reached** when each processing unit is **present in duplicate**

Duplication = Concentration-preserving

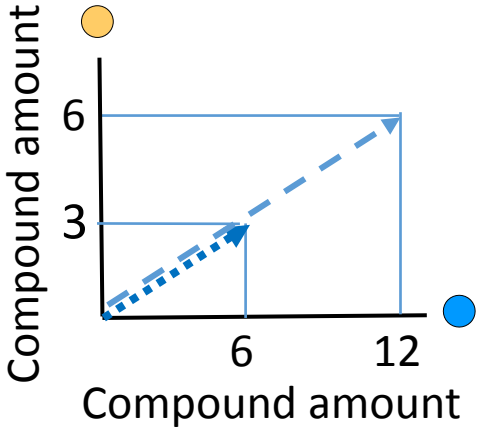
homeostatic growth



Duplication: **Compositional vector**

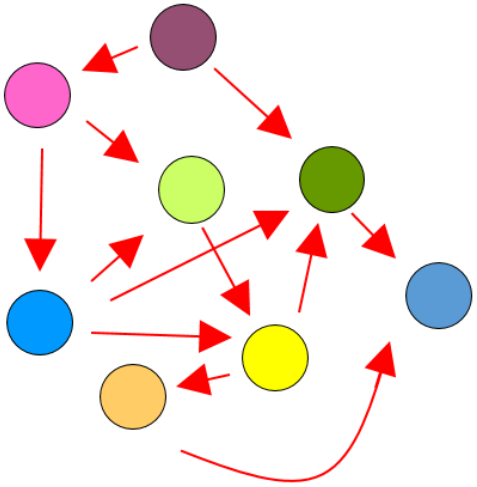
Changes length but not direction

4
3
6
3
5
2

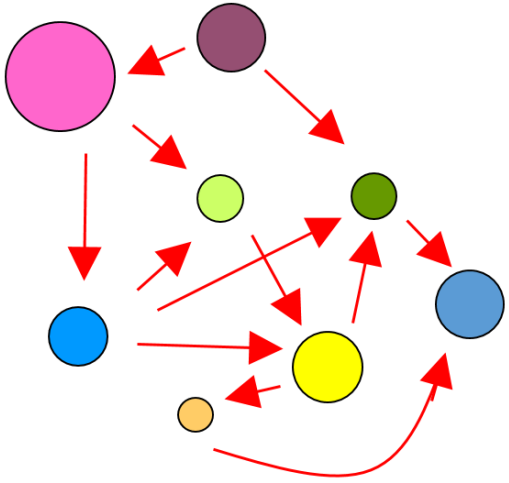


8
6
12
6
10
4

Modifying the descriptors of autocatalytic set (1)

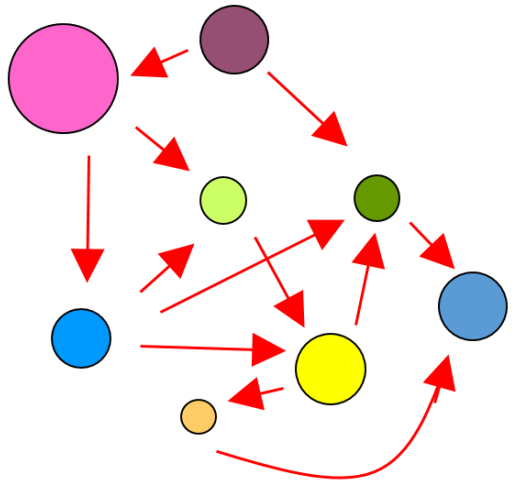


Catalytic arrows only cannot capture assembly composition

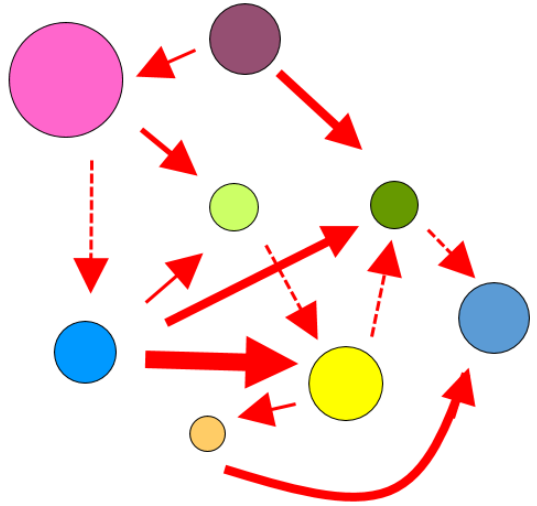


Add the amounts of compounds (shown here as circle size)

Modifying the descriptors of autocatalytic set (2)

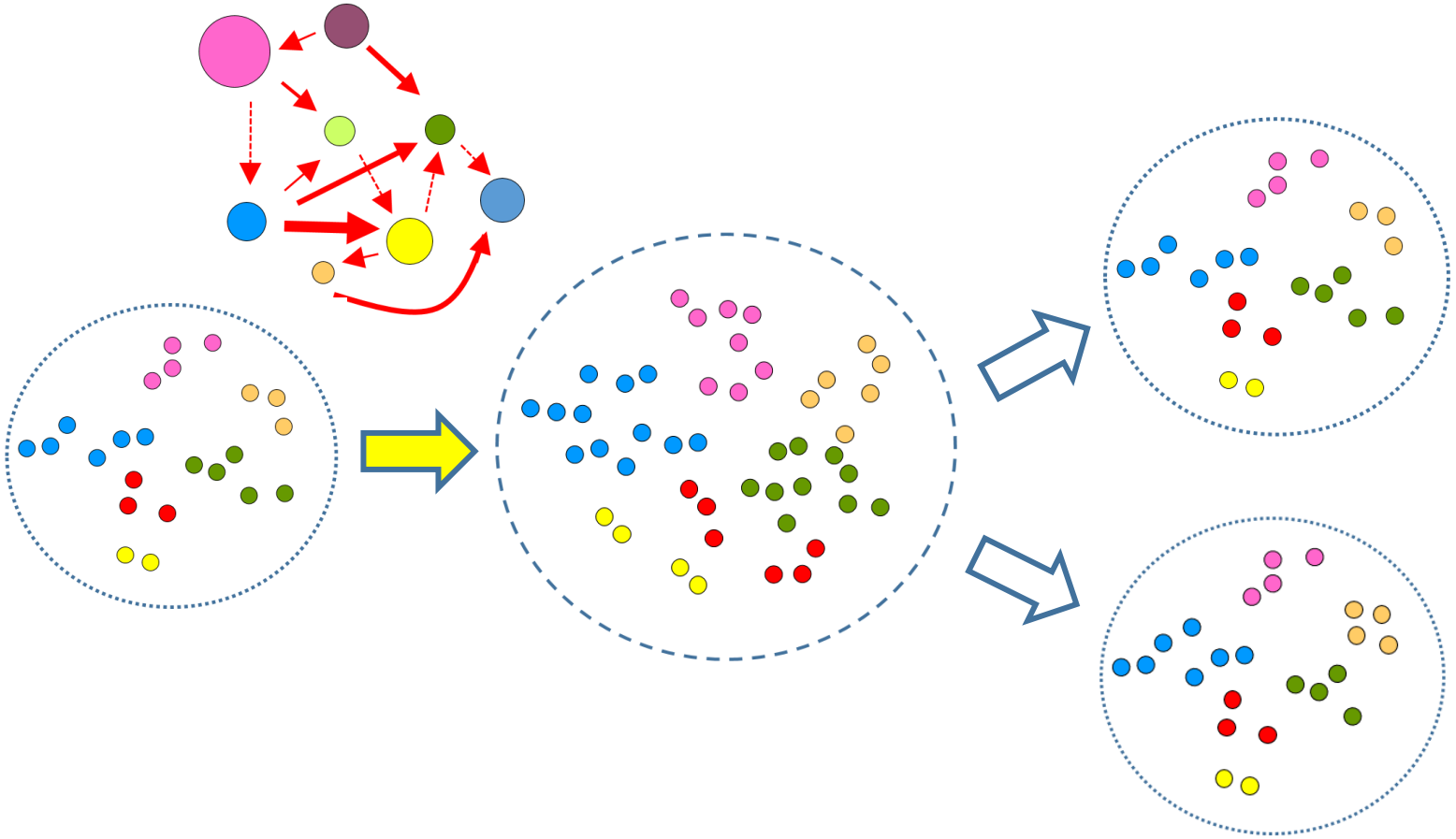


Yes/no catalytic arrows cannot capture assembly dynamics leading to homeostatic growth



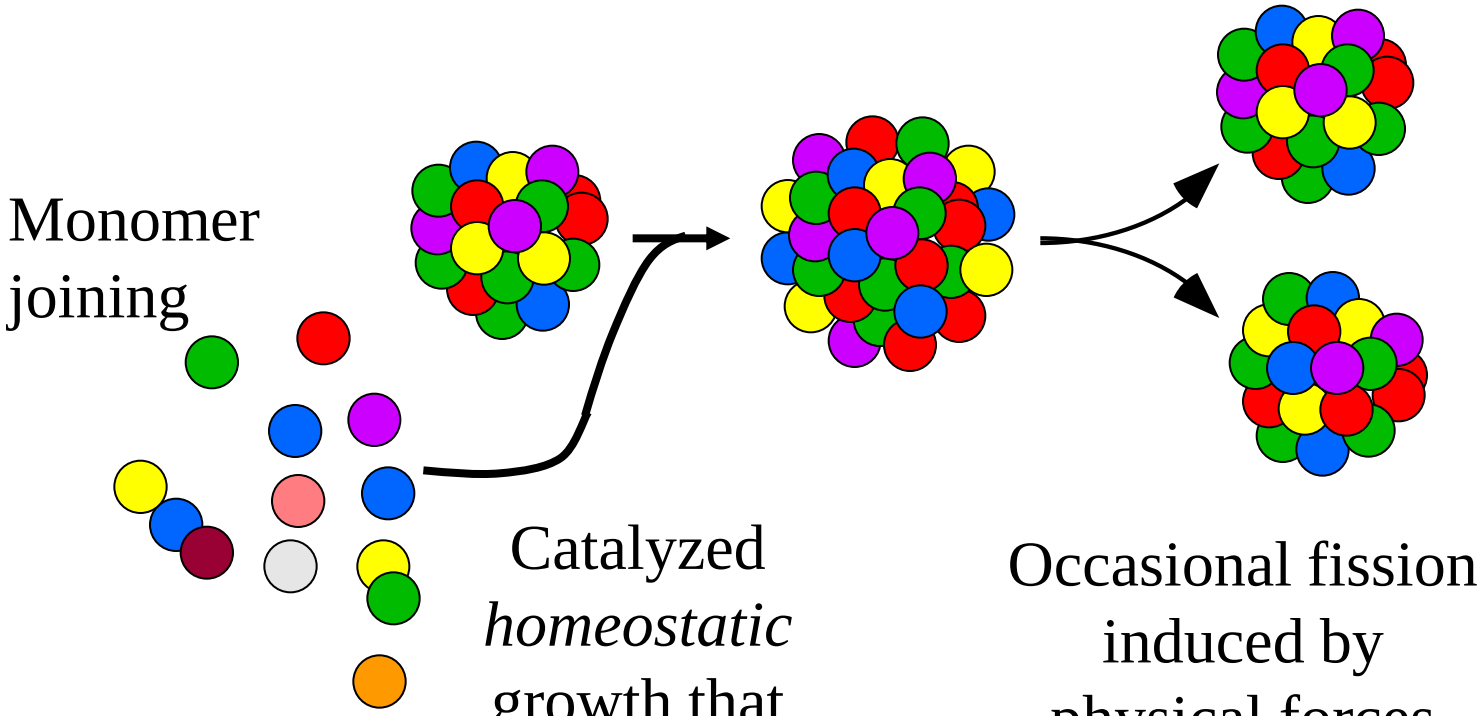
Add intensity of catalysis - Weighted network

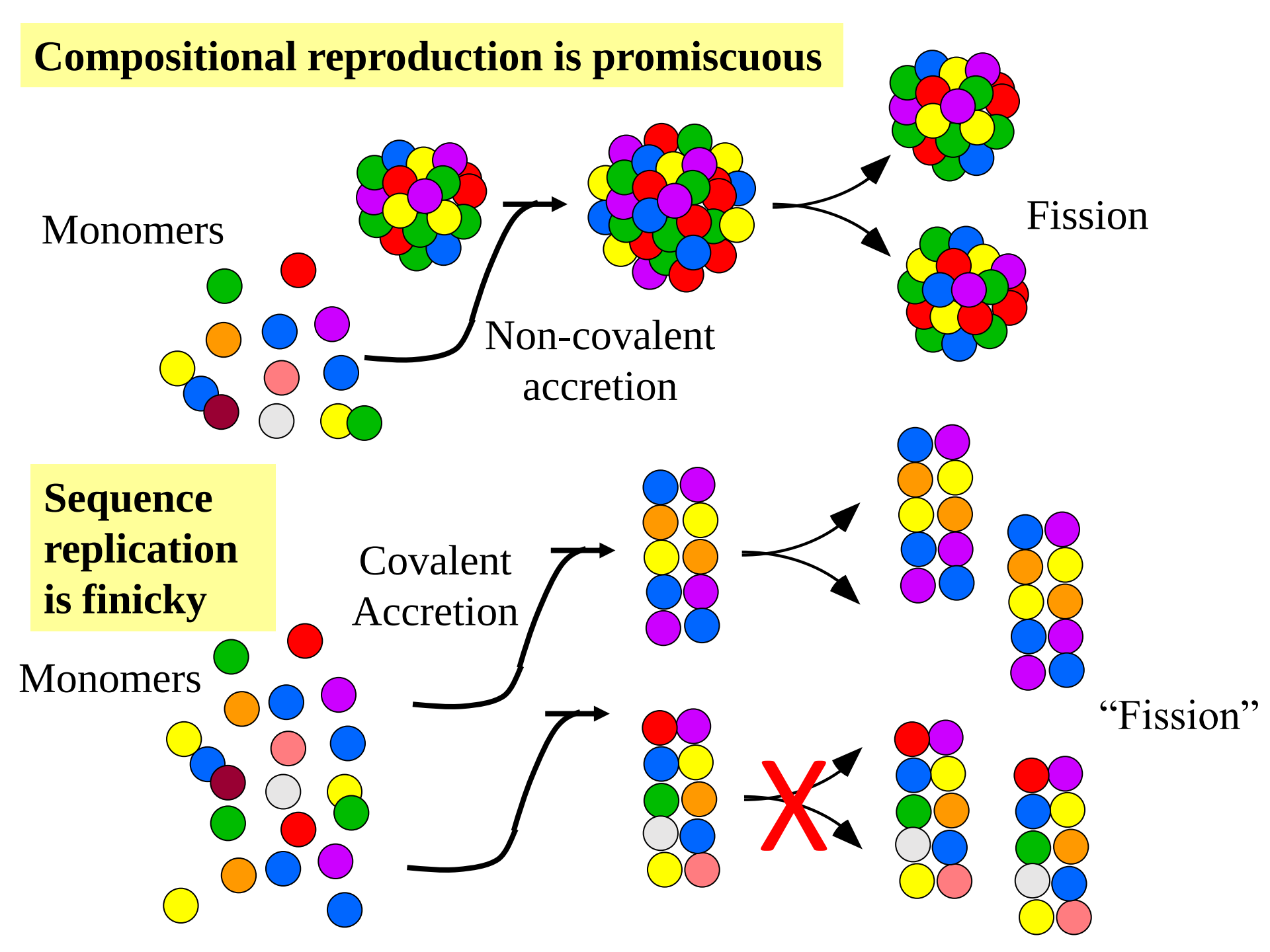
The essence of assembly reproduction is homeostatic growth governed by a catalytic network



Fission in early life is merely a boring **statistical partitioning**

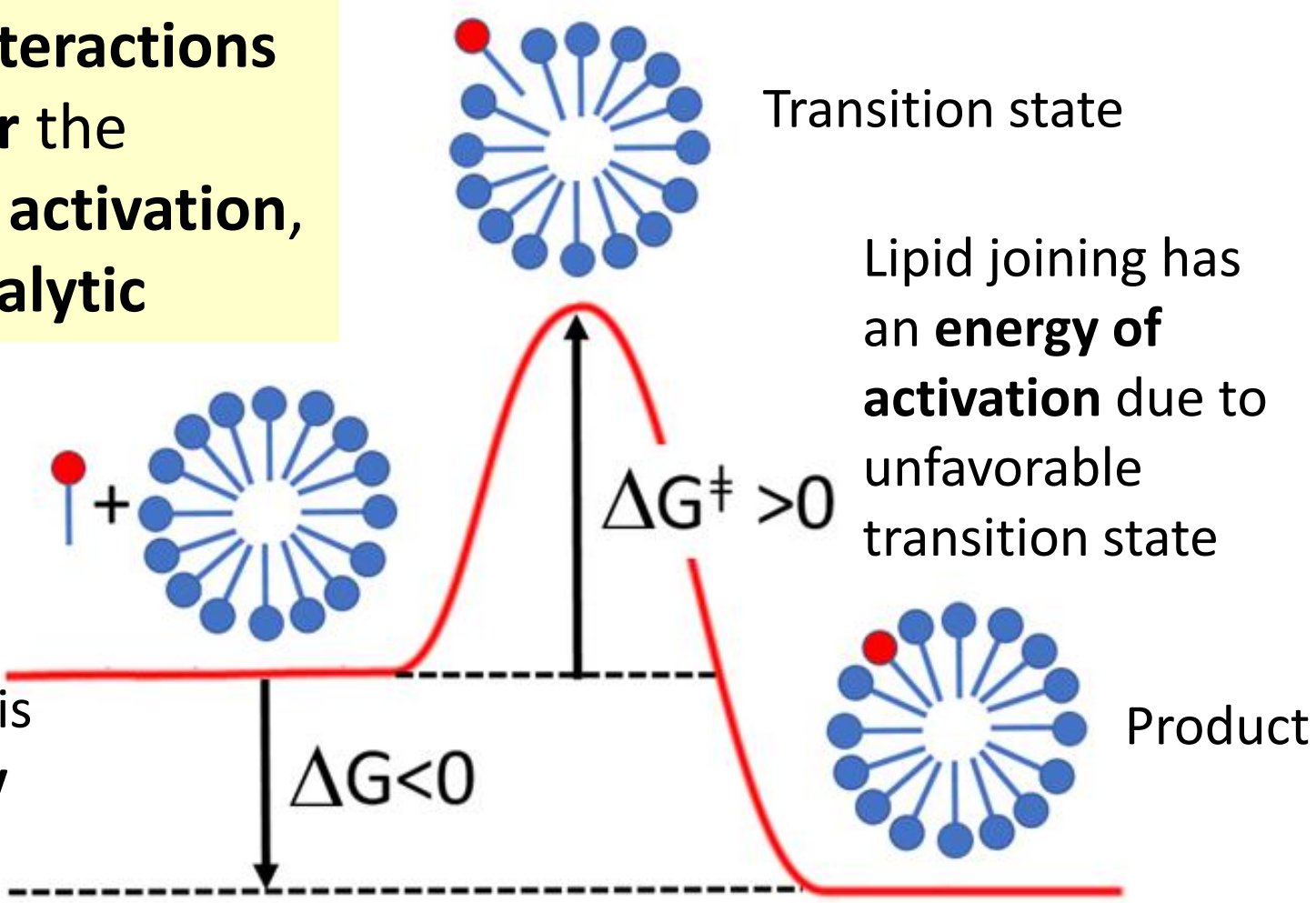
Lipid World: Compositional information may be transmitted to progeny




Compositional reproduction is promiscuous
Monomers
Non-covalent
accretion
Fission
Sequence
replication
is finicky
Covalent
Accretion
Monomers
“Fission”

May lipid entry to a micelle involve catalysis?

Mutual **interactions** may **lower** the **energy of activation**, i.e. be **catalytic**

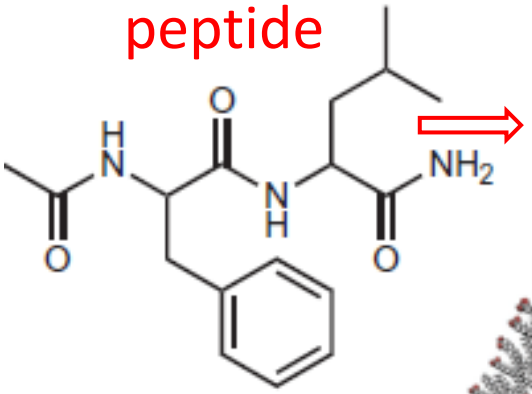


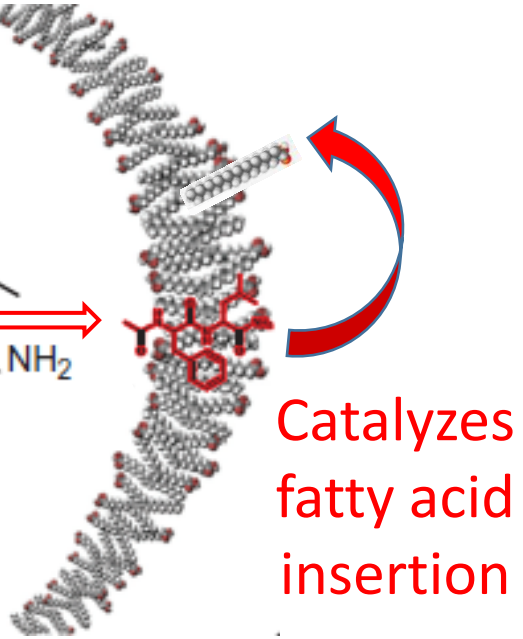
Experimental example of catalyzed non-covalent reaction in lipid assembly

Adamala, Szostak

Nature Chemistry 2013

Membrane -integrated peptide

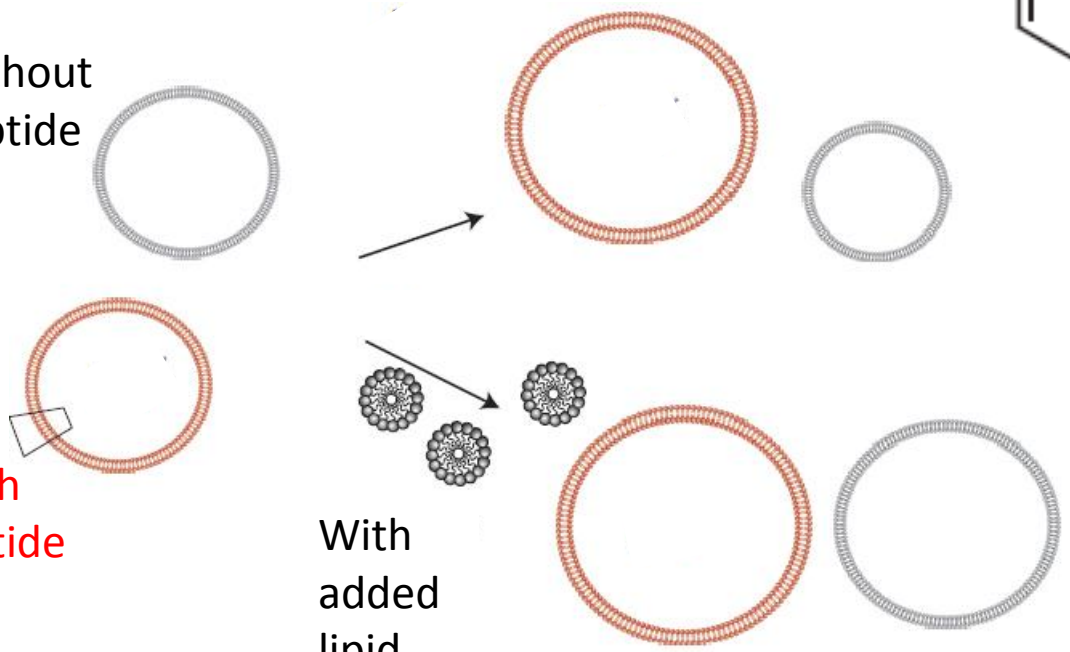




Catalyzes fatty acid insertion

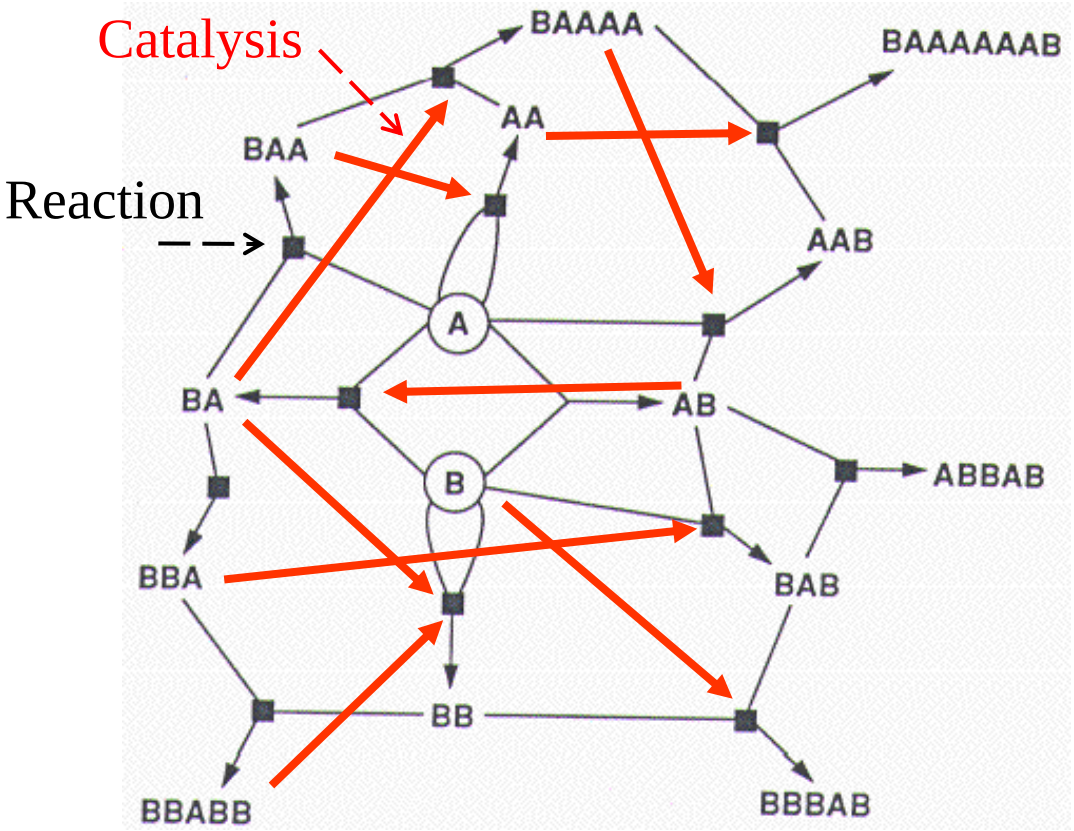
Without peptide

With peptide



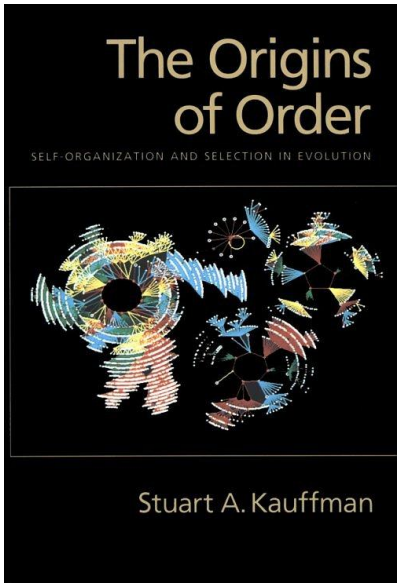
With added lipid micelles

Mutually catalytic networks (Autocatalytic sets): Prebiotic assembly reproduction without RNA



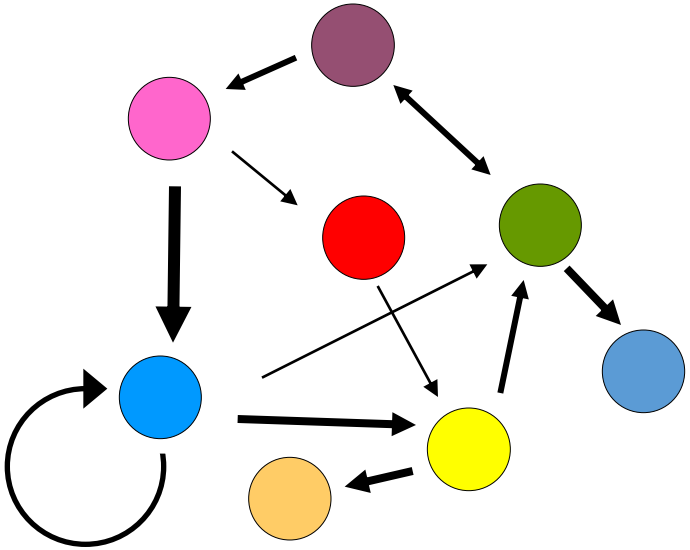
A, B are monomeric “foodset”

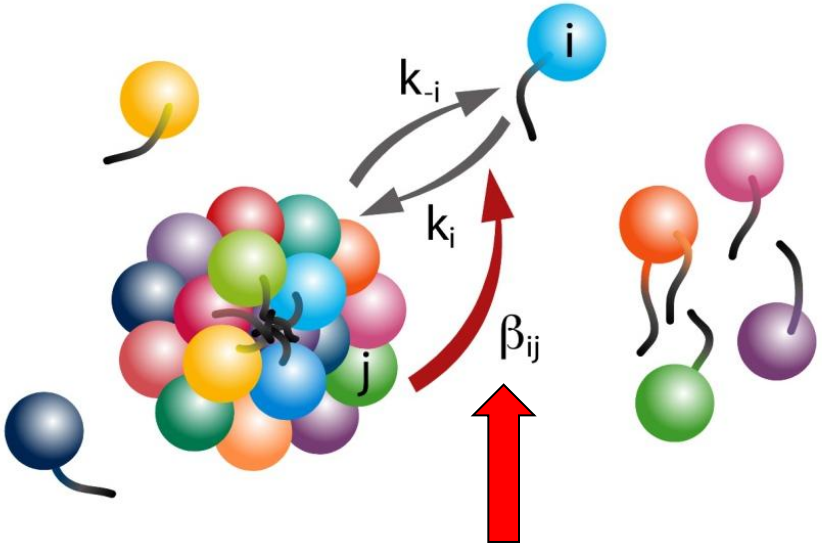
Stuart Kauffman



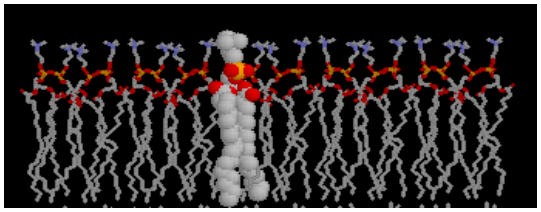
1993 Book

GARD assembly is a non-covalent mutually-catalytic networks





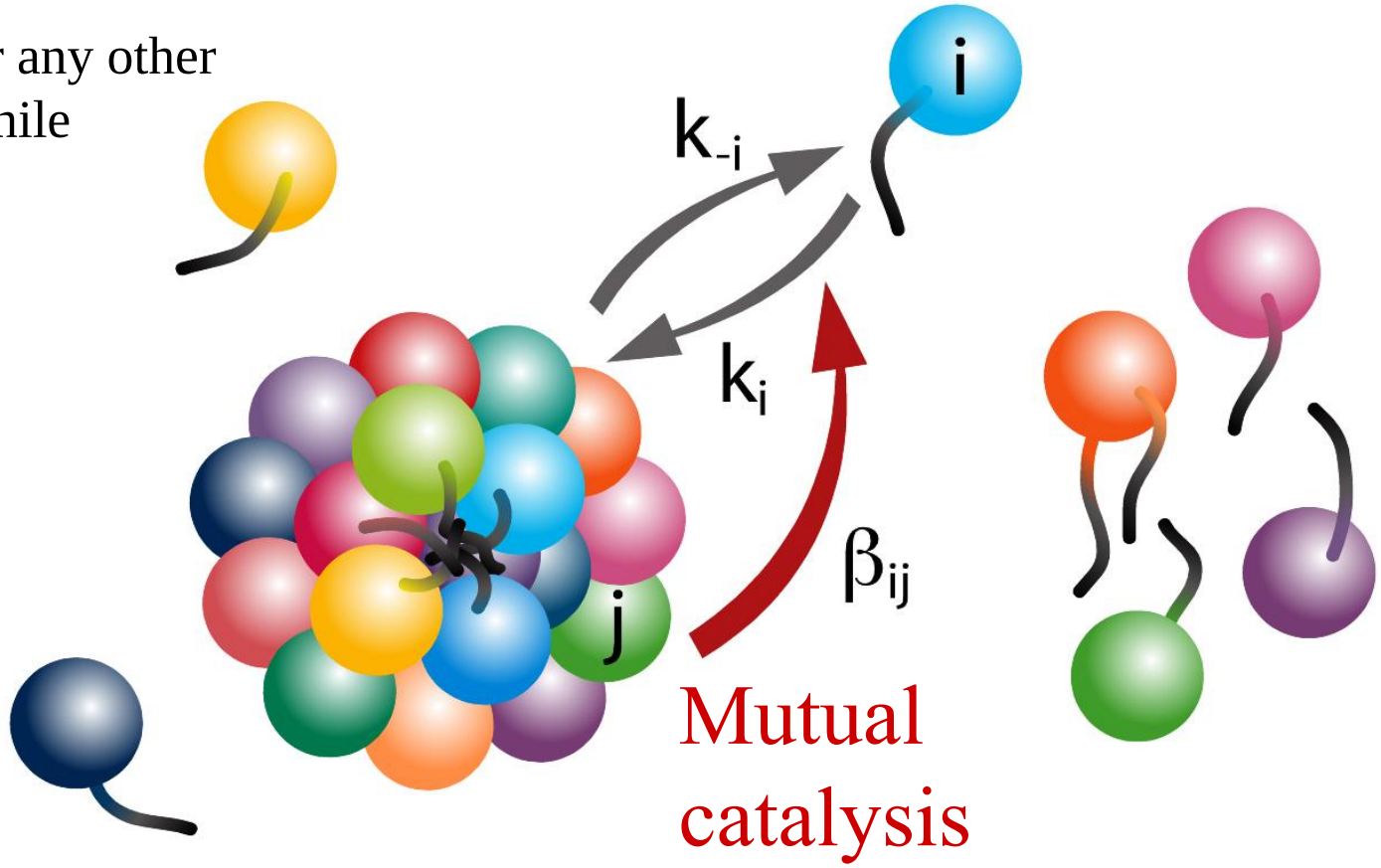
Catalyzed lipid insertion



Network represented by the β_{ij} matrix of **graded** catalytic factors

GARD: the Graded Autocatalysis Replication Domain model

Lipid or any other amphiphile



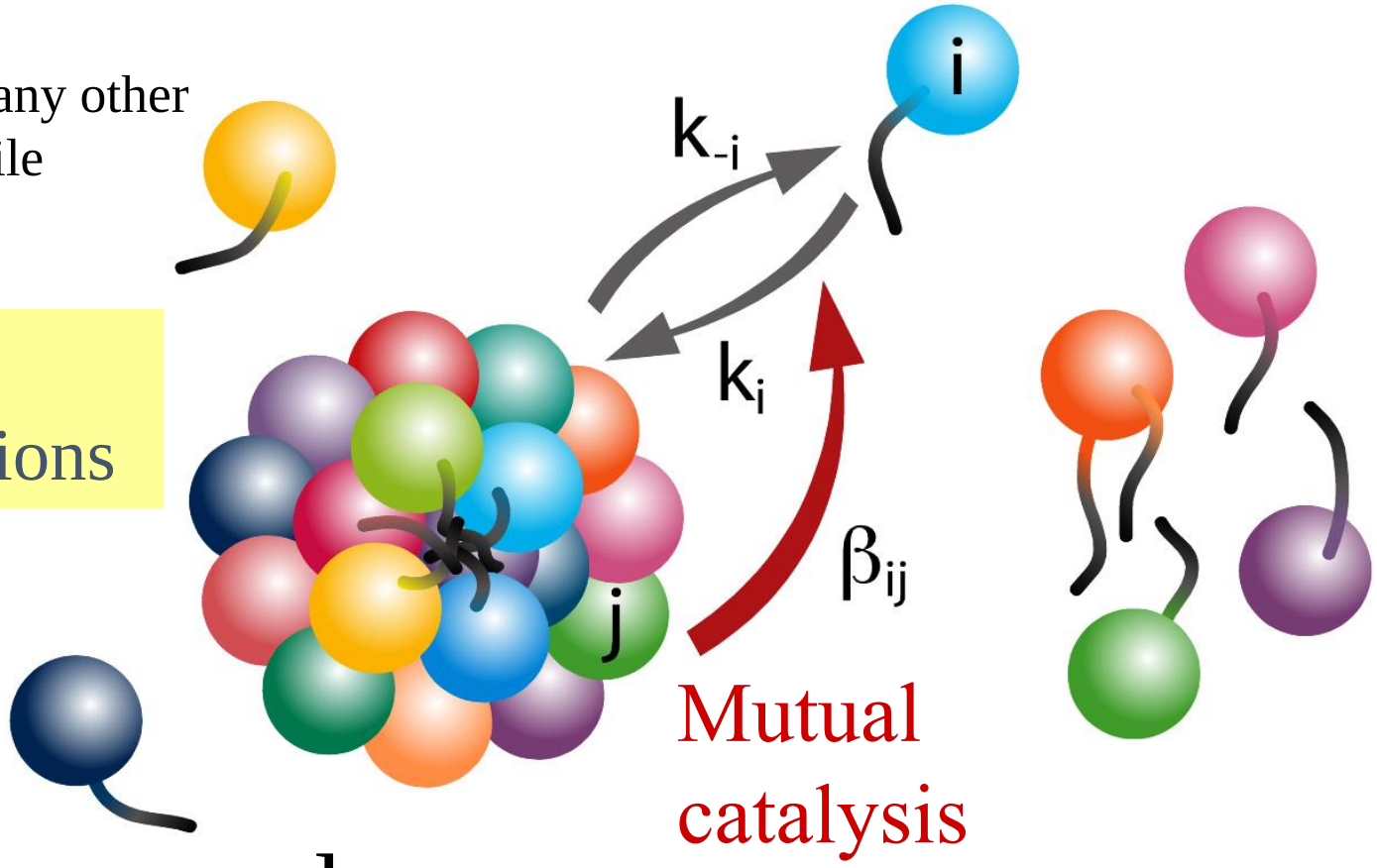
Segre et al PNAS 2000

Lancet et al., J Royal Soc Interface 2018

GARD: the Graded Autocatalysis Replication Domain model

Lipid or any other amphiphile

GARD simulations

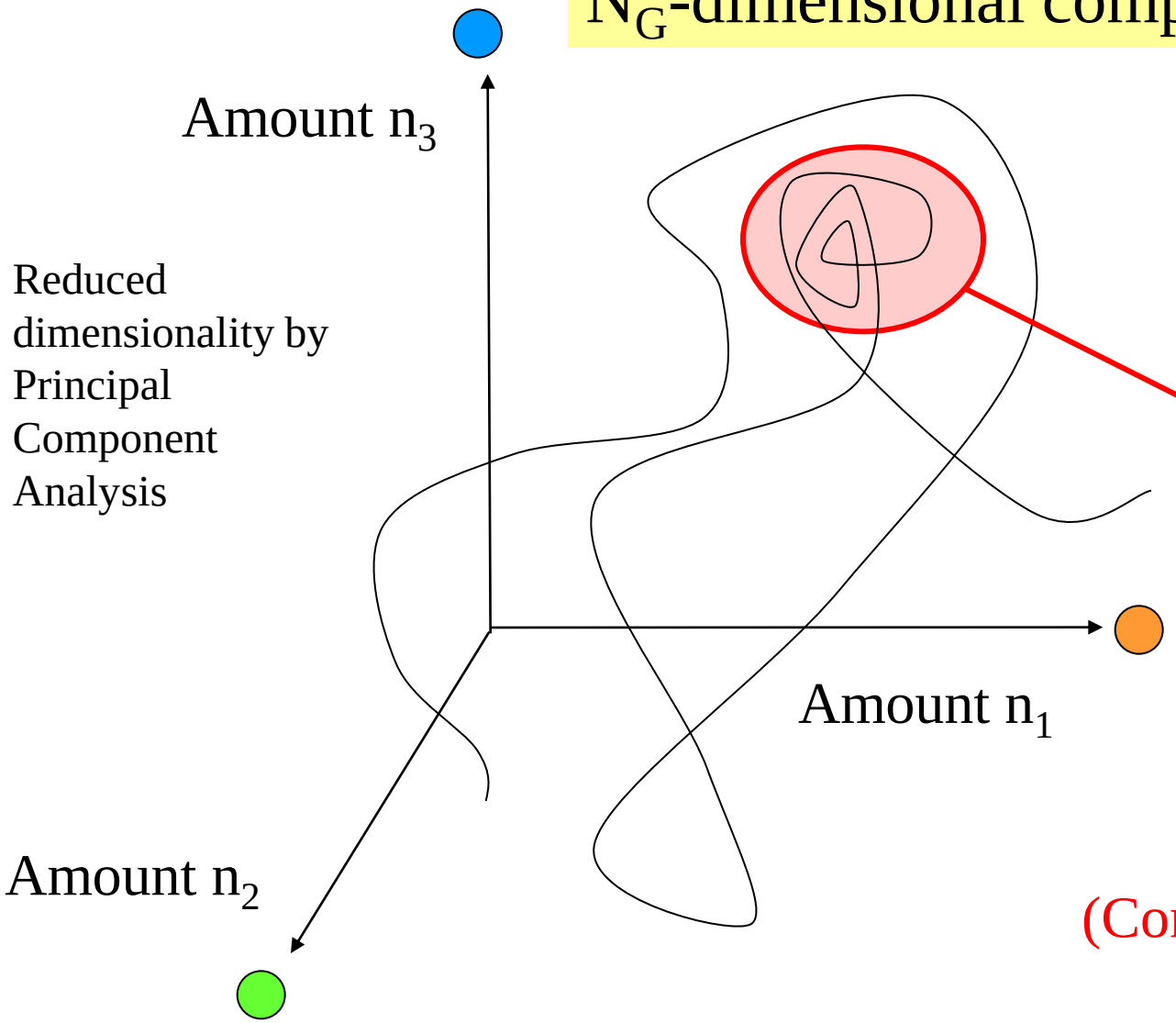


Differential equation set

$$\frac{dn_i}{dt} = (k_i\rho_i - k_{-i}n_i)(1 + \Sigma\beta_{ji}n_j)$$

Stochastic chemistry simulations (Gillespie Comput. Phys., 1976. **22**: p. 403)

GARD dynamics: Trajectory in a N_G-dimensional compositional space

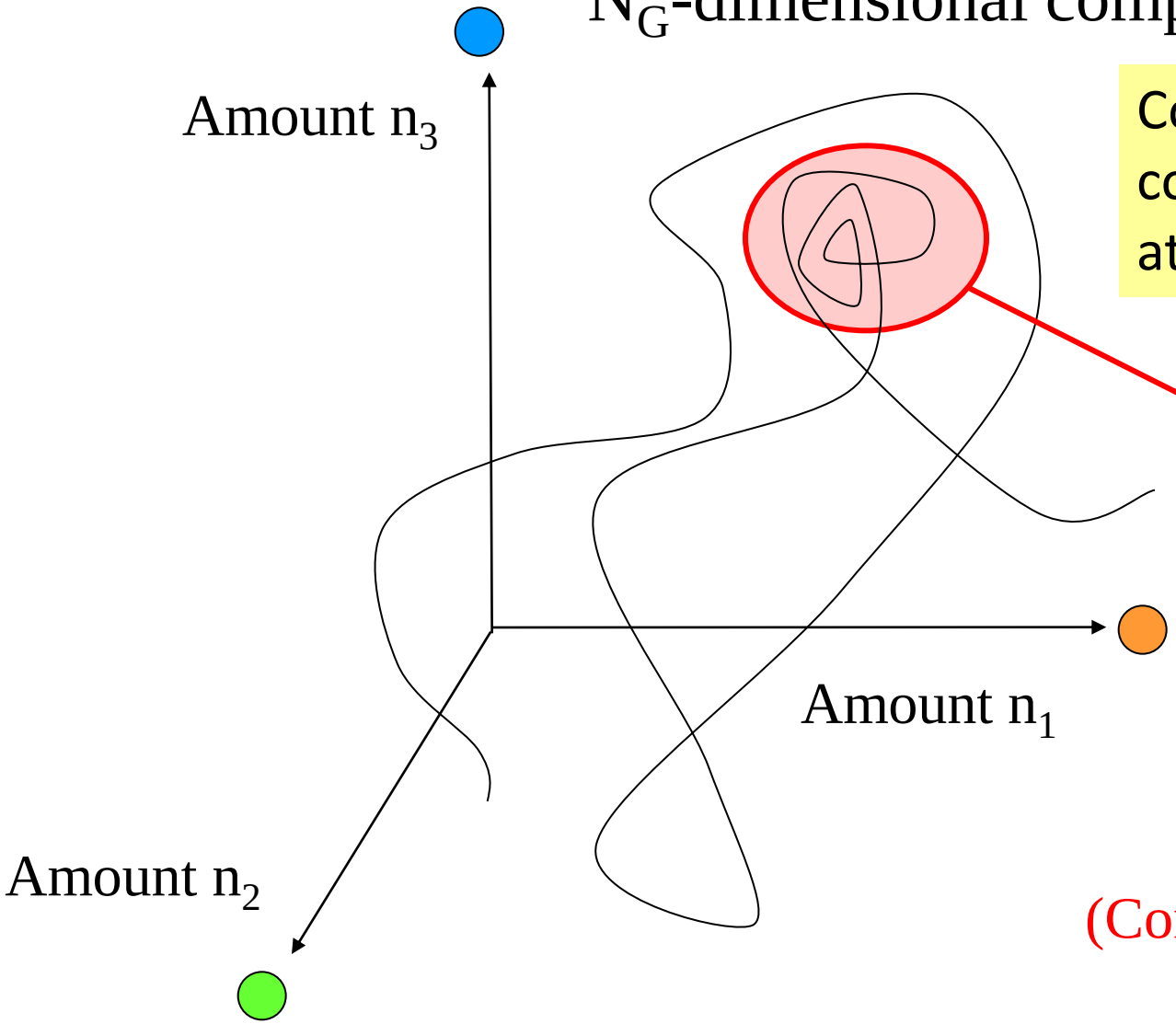


Fixed point or quasi-stationary state

Composome

(Compositional genome)

GARD dynamics: Trajectory in a N_G-dimensional compositional space



Composome is a compositional attractor!

Lancet et al
J Royal Soc Interface '18

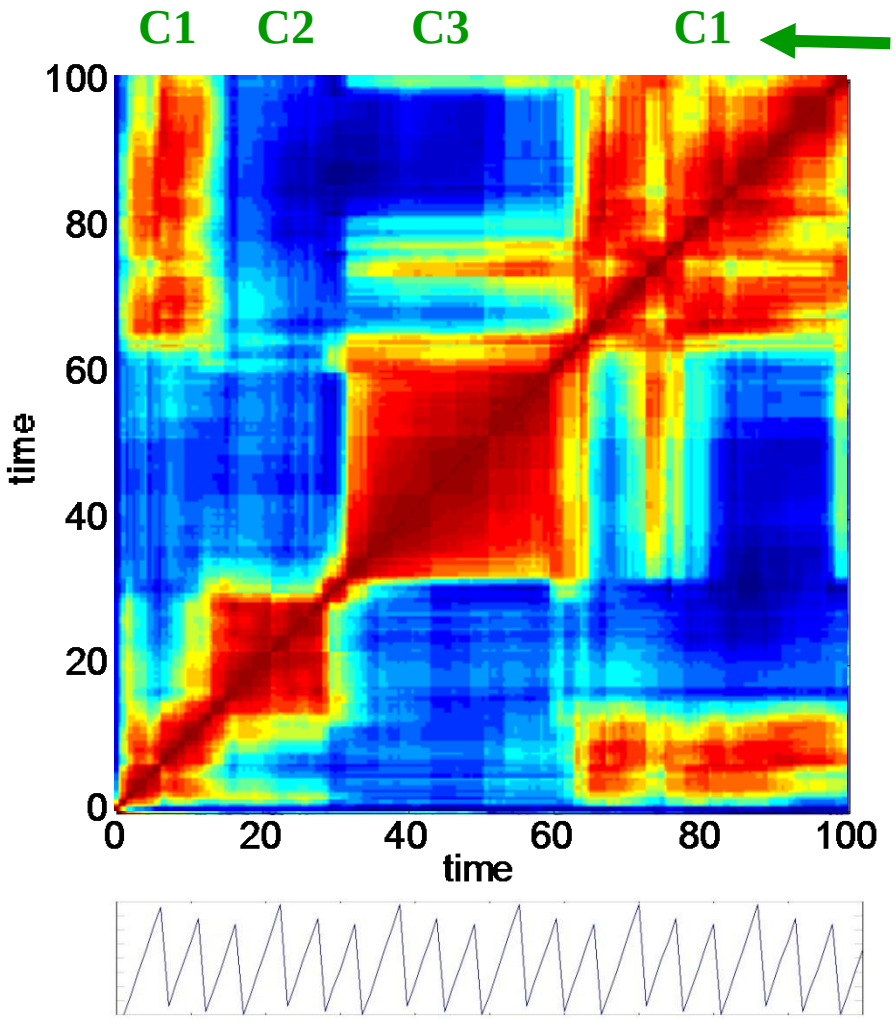
Fixed point or quasi-stationary state

Composome

(Compositional genome)

GARD: Multiple stationary states

GARD correlation "carpet"



Composomes: (quasi-stationary states)

Compositional similarity metric

$$H(\mathbf{n},\mathbf{n}') = \frac{\mathbf{n}}{|\mathbf{n}|} \cdot \frac{\mathbf{n}'}{|\mathbf{n}'|}$$

H=1 H=0

Growth-split cycles

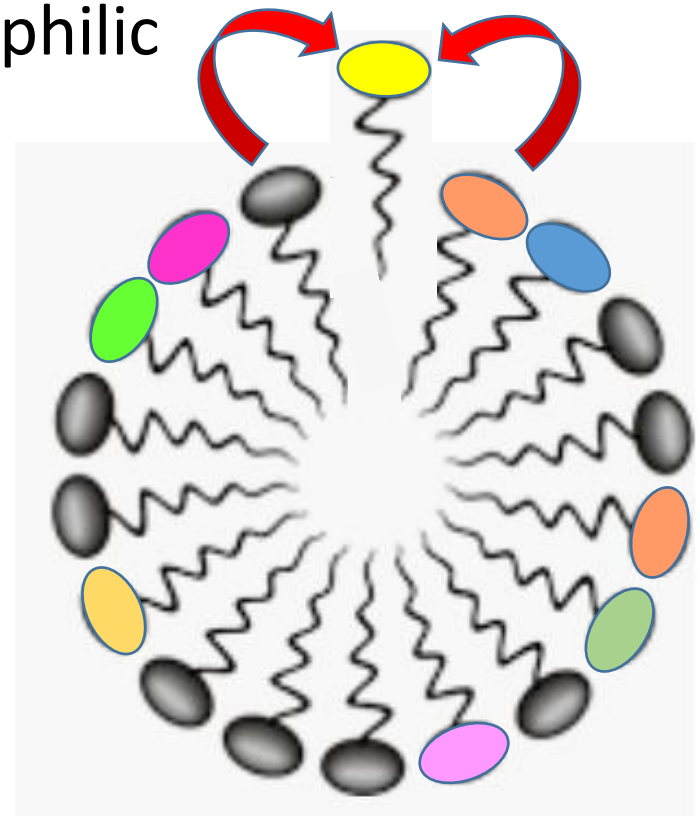
Micellar beginning: The first molecular reproducer?

- All network molecules are amphiphilic
- Entry-exit reactions only
- Reactions catalyzed by neighbors
- All compounds are food
  (complete heterotrophy)

Heterogeneous Lipid micelles:
Best **prebiotic catalytic network?**

- **Compositional information**
- **Small size** affords diversity
- Effectively Harbors **mutually**
- **Ensemble catalysis (~enzyme!)**
- Can **grow and split** → progeny

Joint Catalysis



Mixed Lipid micelle

Containment is advantageous to **covalent** catalytic networks

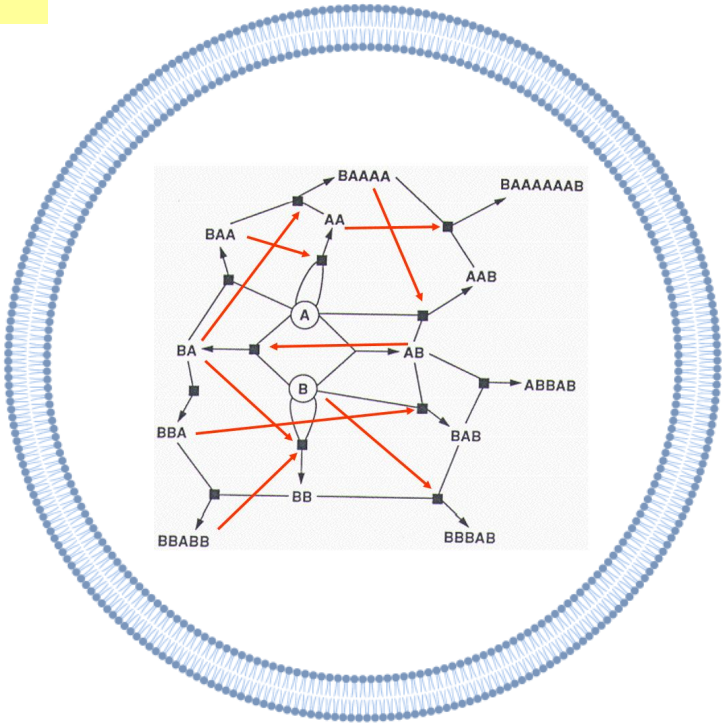
Enhances concentrations by adsorption

Crowds molecules - speeds up rates

Promotes network growth and diversity

Protects against parasitic reactions

Supports inter-compartmental competition



Prebiotic network evolution: six key parameters

Nghe, Hordijk, Kauffman, Walker, …, Lehman

Mol. BioSyst., 2015,

.

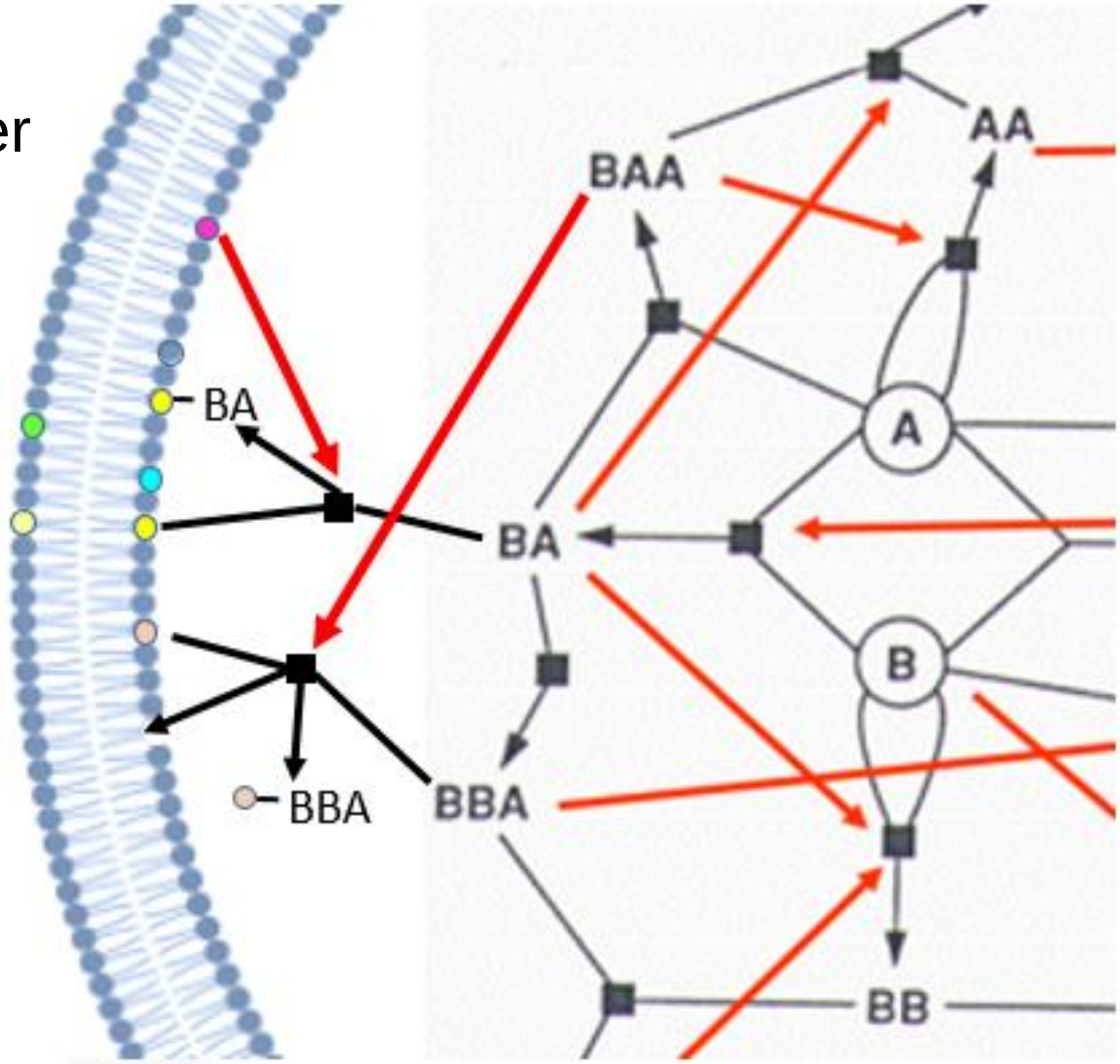
But the membrane components need to be part of the network!

Metabolism–container coupled system

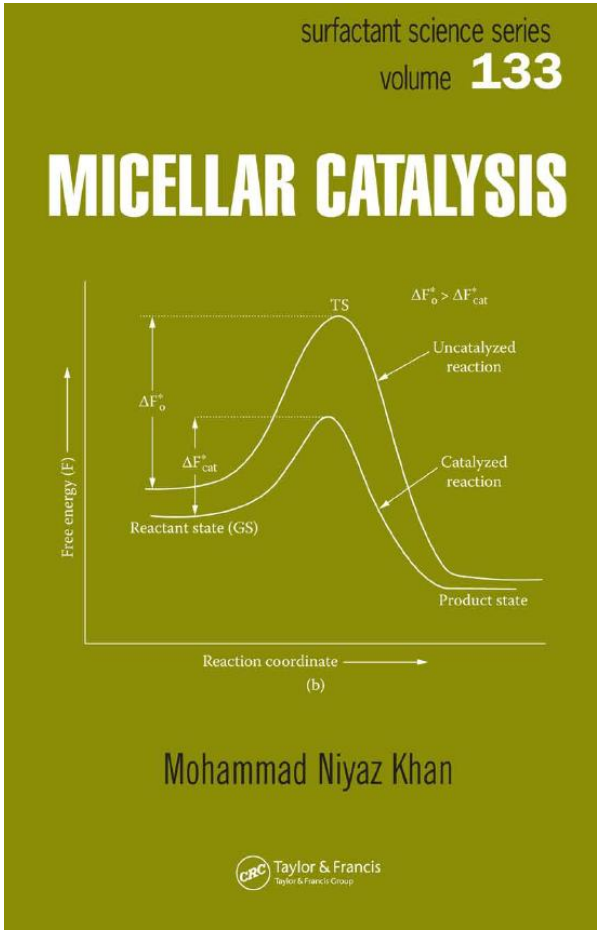
Fellermann, Sole 2007

Roberto Serra's Synchronization

Serra and Villani
Modelling Protocells, 2017



Micellar covalent catalysis amply documented



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-09751-4 OPEN

Bridging the gap between transition metal- and bio-catalysis via aqueous micellar catalysis

Margery Cortes-Clerget[1], Nnamdi Akporji[1], Jianguang Zhou[2], Feng Gao[2], Pengfei Guo[2], Michael Parmentier[3], Fabrice Gallou[3], Jean-Yves Berthon[4] & Bruce H. Lipshutz[1]

J. Am. Chem. Soc. **1998,** *120,* 9517−9525

Million-Fold Acceleration of a Diels−Alder Reaction due to Combined Lewis Acid and Micellar Catalysis in Water

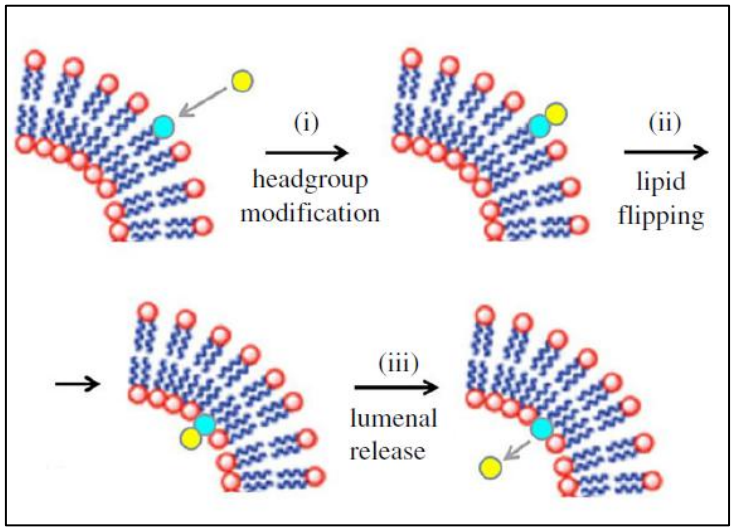
Sijbren Otto,† Jan B. F. N. Engberts,*,† and Jan C. T. Kwak‡

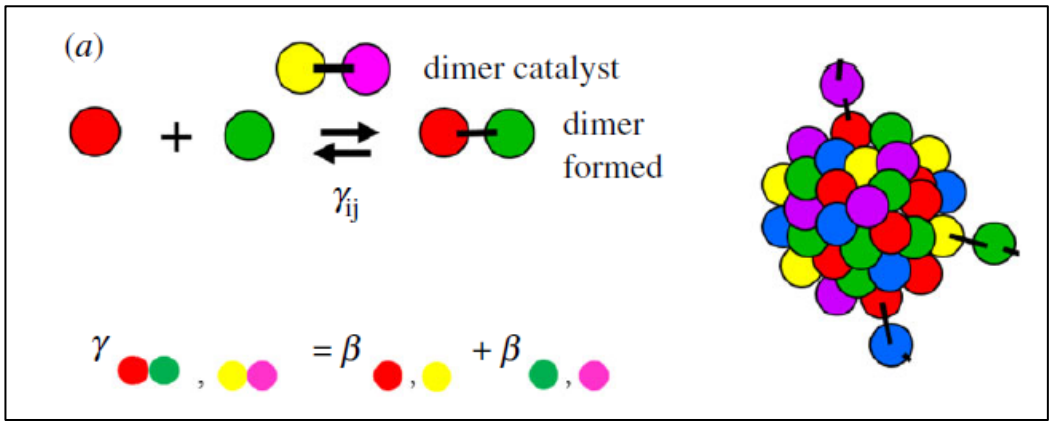
Catalysis by Micelles, Membranes and other Aqueous Aggregates as Models of Enzyme Action

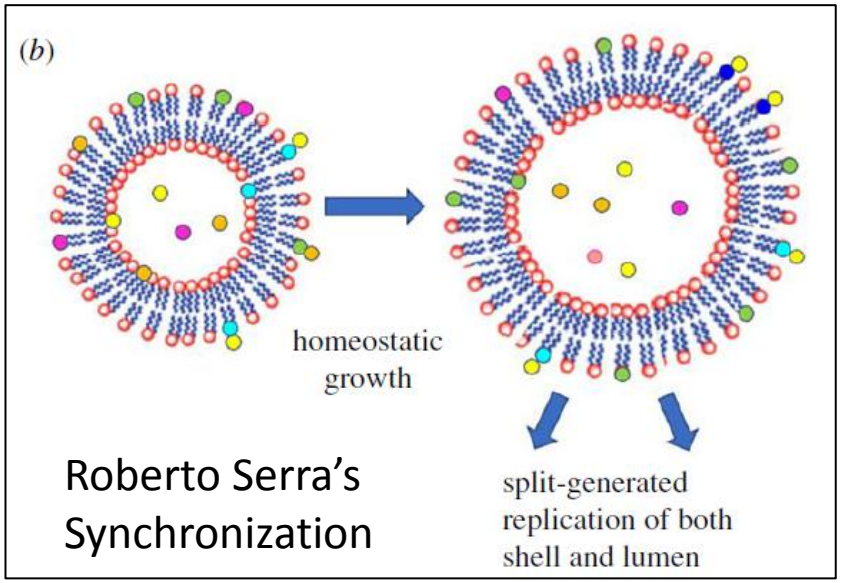
TOYOKI KUNITAKE and SEIJI SHINKAI Book 1980

How GARD becomes more and more life-like via Metabolic-GARD

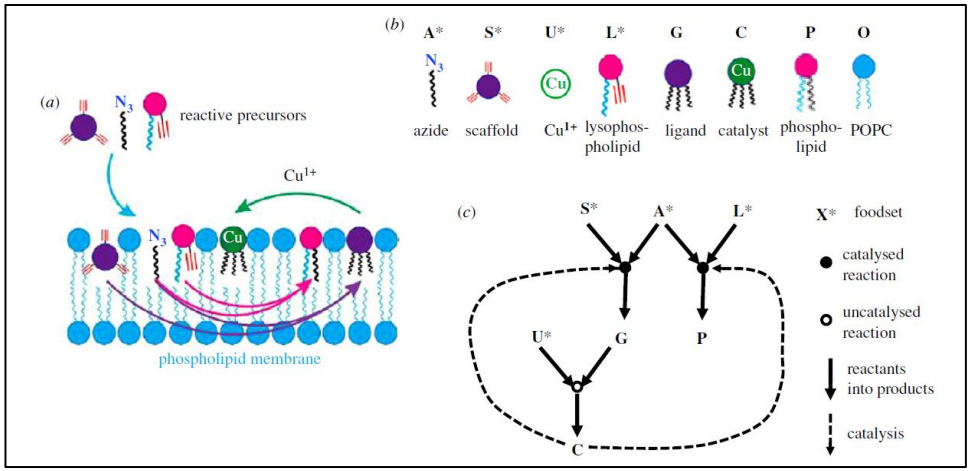
Lancet et al., J Royal Soc Interface 2018







Roberto Serra's Synchronization



Neal Devaraj
Lipid catalytic networks

Autocatalytic set

Present

Rafael Zidovetzki (UC Riverside)

Amit Kahana

Lior Segev

Christian Mayer (Essen DE)

Past:

Omer Markovitch

Tzachi Pilpel

Daniel Segrè

David Deamer (UC Santa Cruz)

Natalio Krasnogoer (Newcastle)

Renan Gross

Aron Inger

Hamutal Arbel

Ran Kafri

Barak Shenhav

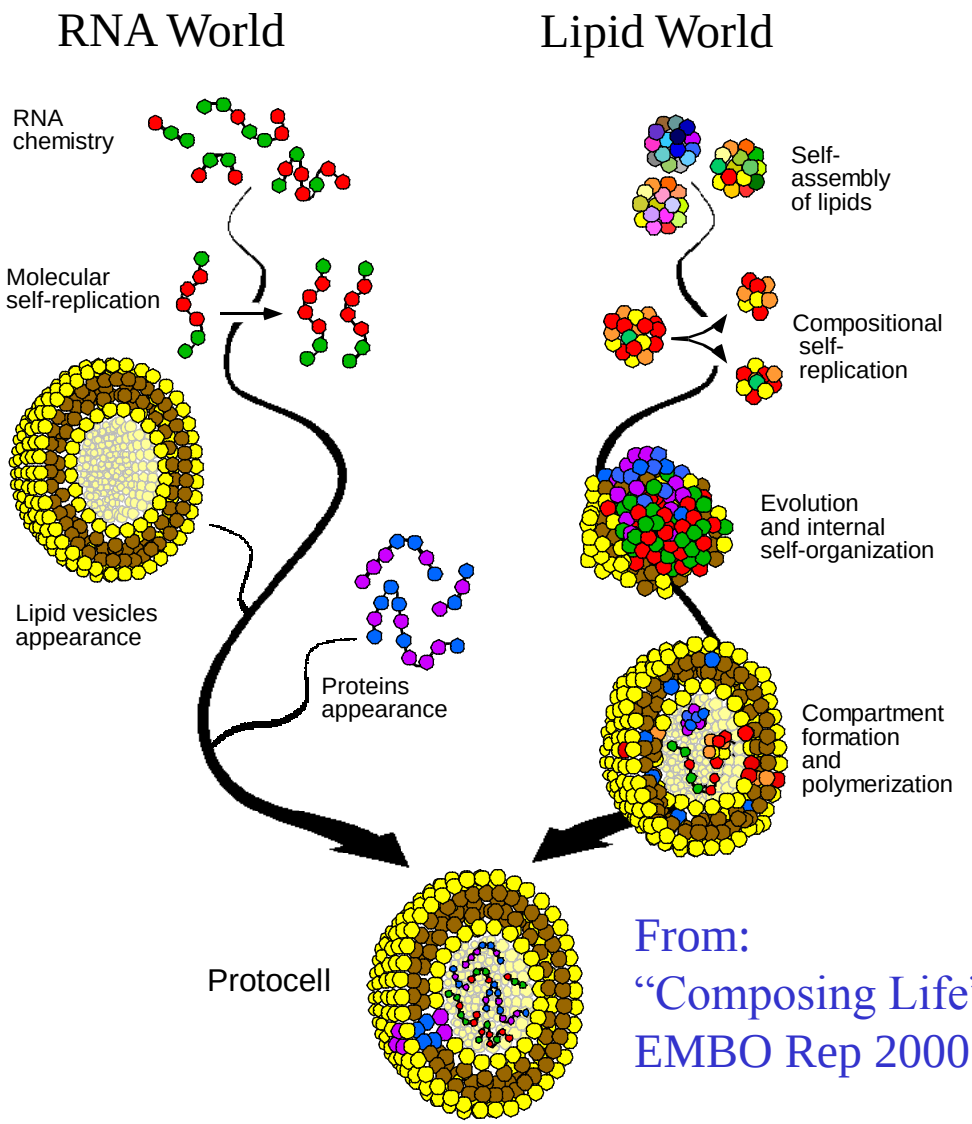
Ariel Solomon

Arren Bar-Even

Dafna Ben-Eli

Daniel Sorek

Itzhak Fouxon



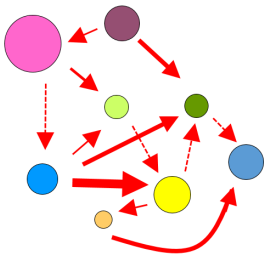
From:
"Composing Life"
EMBO Rep 2000

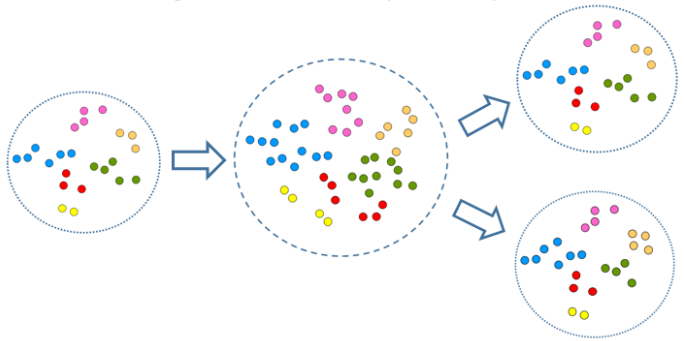
Comprehensive review in: Lancet et al.
J Royal Soc Interface 2018

How can we find out whether a given mutually catalytic assembly will grow homeostatically?

1) Use explicit **kinetic equations** for the **time-dependence** of every compound's **concentrations**
2) Seek a **realistic prediction** for the distribution of catalytic power for every molecular pair*
3) **Computer-simulate** the **time-dependence** dynamics of the **compositional vector**.
4) Ask whether and **under what conditions** will **homeostatic growth** arise, hence **reproduction**

**RAF typically has single probability and single catalytic power*





ECLT Sep19 abstract Lancet

Life began with catalytic reproducing micelles

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Studying the very early stages of life's emergence is conceptually similar and relevant to ECLT's long term goals, which address technologies with life-like properties including self-organization, adaptability and the capacity to evolve. In this respect, we are now studying an origin scenario in which life may have been seeded by lipid micelles. The key to such Origin scenario is the pursuit of a model in which reproduction takes place without RNA. The only viable path to pre-RNA reproduction behavior is mutually catalytic network of small molecules. We show evidence that the best material embodiment for such networks is lipid micelles. This is because there is substantial literature on catalytic capacities of lipid molecules in micellar aggregates, including in industrial contexts [1]. Some papers go as far as claiming that micelles resemble globular proteins in their structure and catalytic power [2]. Not less important, a realistic chemical platform for the emergence and function of mutually catalytic networks is a lipid assembly in which fluidity and reduced dimensionality offers excellent opportunity for effective all-against-all interactions [3]. Finally, our work over the last two decades has laid the foundation for showing, via realistic physicochemical computer simulations, that assemblies made of prebiotically-copious lipids [4] are capable of attaining self-reproduction with adaptive mutations, and a robust potential to evolve [3,5,6]. This allows us to delineate a rigorous, Molecular-Dynamics-testable evolutionary chemistry path [7] towards more genuine life-like characteristics such as complexification in the direction of vesicular structures with aqueous metabolic content, as well as an ascent to polypeptide-mediated catalysis, and to replicating polynucleotides that instruct protein synthesis [3].