ILASOL 2018

And yet GARD evolves!

11Apr18
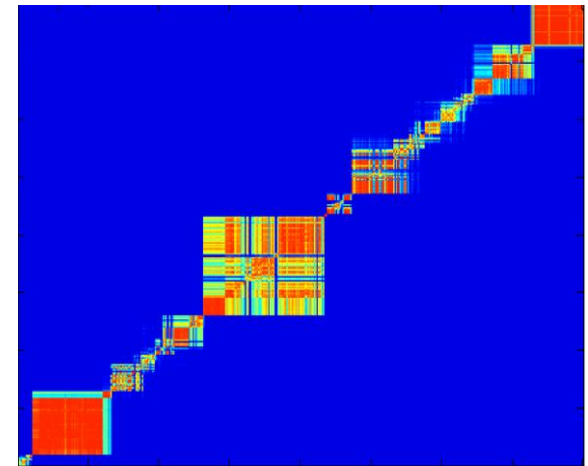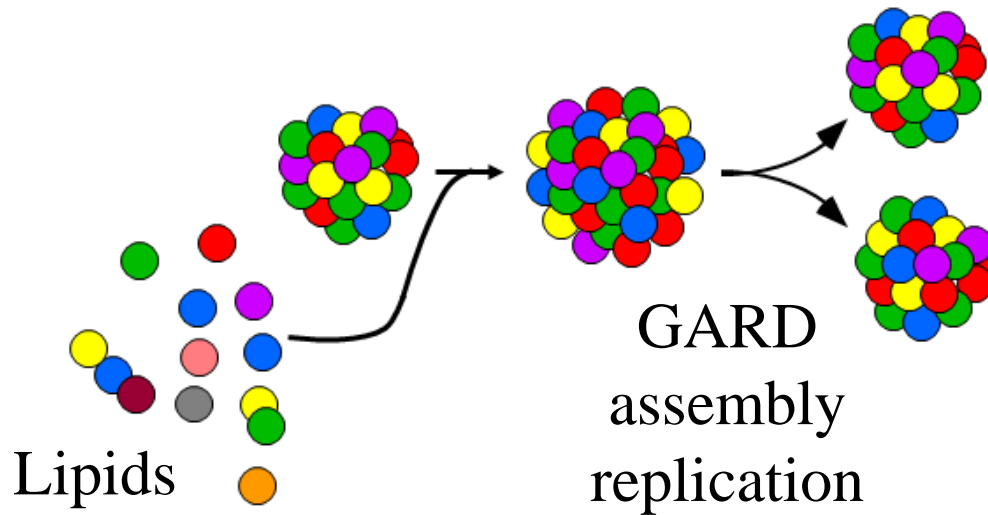
Doron Lancet
Dept. Molecular Genetics
Weizmann Institute of Science, Israel

Eppur si muove
And yet it moves

Lipids

GARD
assembly
replication

GARD
Evolution

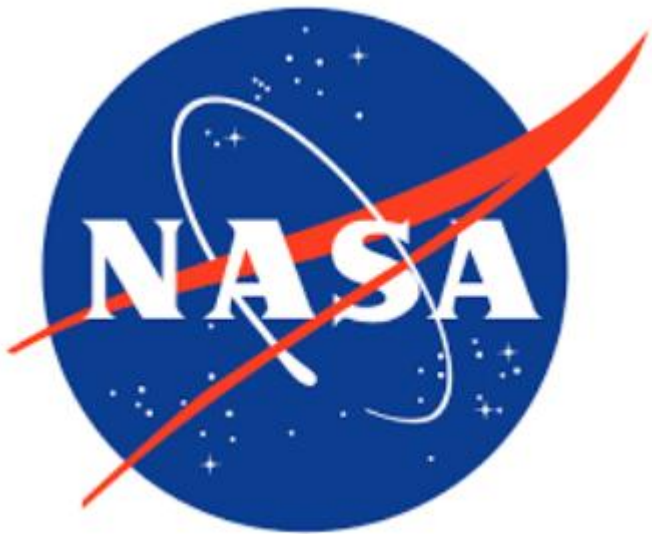NASA defined life broadly as
"A self-sustaining* chemical system
capable of Darwinian evolution."

*Homeostatic, replicating

Steven A. Benner, "Defining Life" **Astrobiology** 10 (10) 16 Dec 2010
Special Collection of Essays: What is Life?

NASA defined life broadly as
"A self-sustaining chemical system
capable of Darwinian evolution."

The open question :
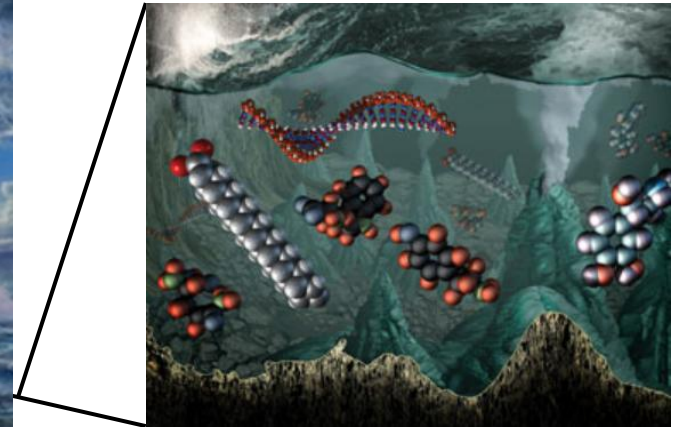What was the earliest
evolving replicator

"RNA World" in the primordial ocean

Late bombardment

Cool down a bit

Is there an alternative replicator?

Idée fixe

An idea that dominates one's mind, especially for a prolonged period
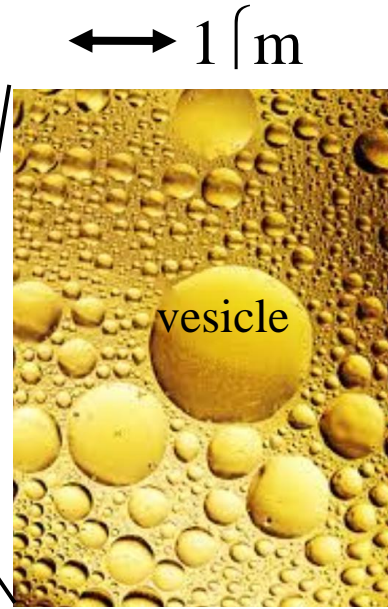
Examples from Origin of Life research

- RNA is the only informational replicator

- Lipids can only make compartments

- Enzymes, ribozymes and minerals are the only catalysts
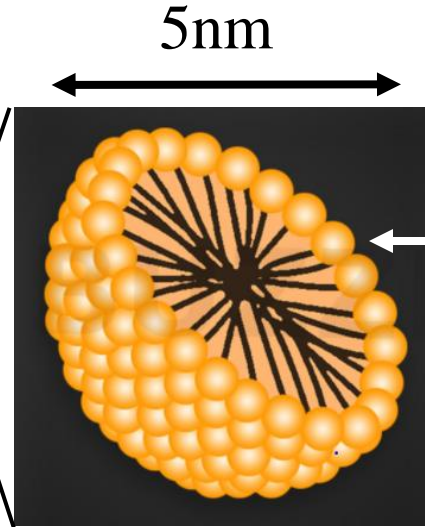
- Metabolic networks cannot evolve

The alternative replicator may be a lipid micelle
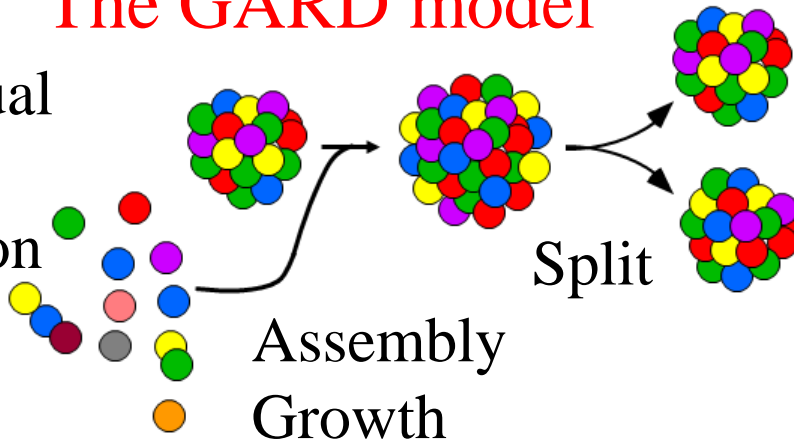

1 μm

5nm

vesicle

Lipid Micelles

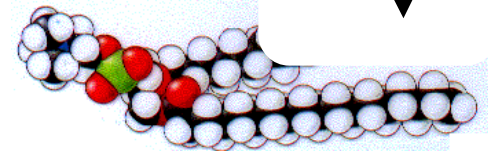Late bombardment

Lipid structures

Lipid World

The GARD model

Individual
Lipid
Accretion

Split

Assembly
Growth

Lipid molecule

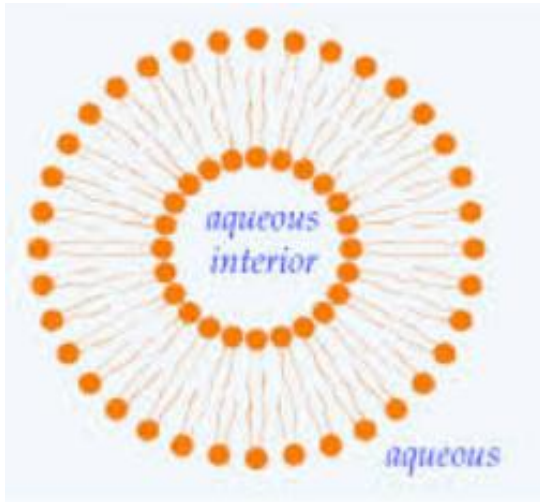Hydrophilic head

Hydrophobic chain(s)

Lipids come from space

Meteorite extract forms lipid vesicles

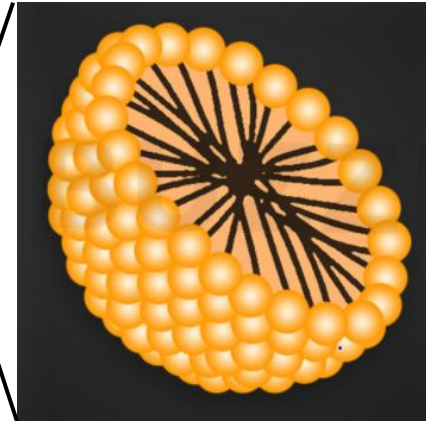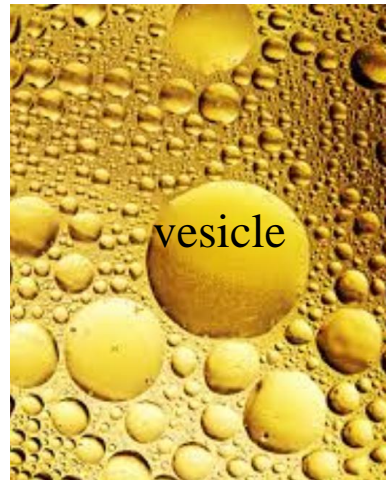The Murchison chondritic (carbonaceous) meteorite
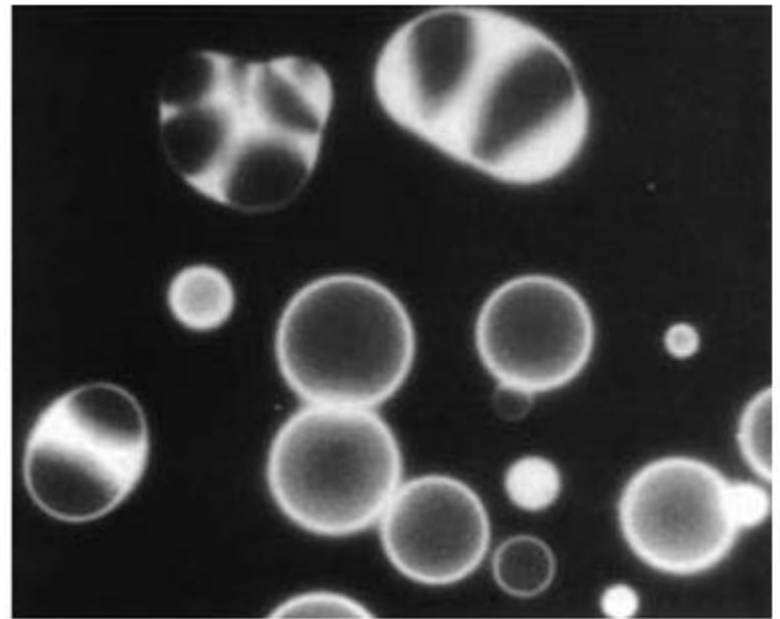
David Deamer and colleagues

Lipid structure advantages for Life's origin

Lipid Vesicle

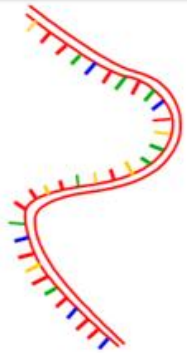vesicle

Lipid Micelles

Lipid structures:

- Form *spontaneously* from dilute solutions
- Fluidic – allow easy *exchange* and *interaction*
- Heat *resistant* (early planetary emergence)
- Opportunistic (*any available* lipids work)
- May harbor significant *catalysis*
- Undergo facile *fission* (splitting)
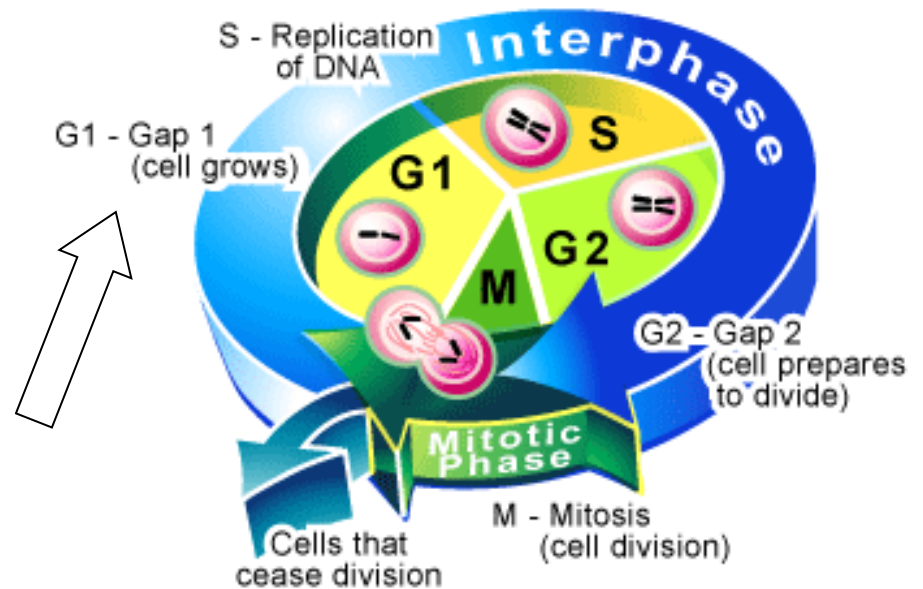- May encompass aqueous *volume* (vesicles)
- Harbors *compositional* information

Compositional information is metabolicaly copied at G-phase prior to cell division
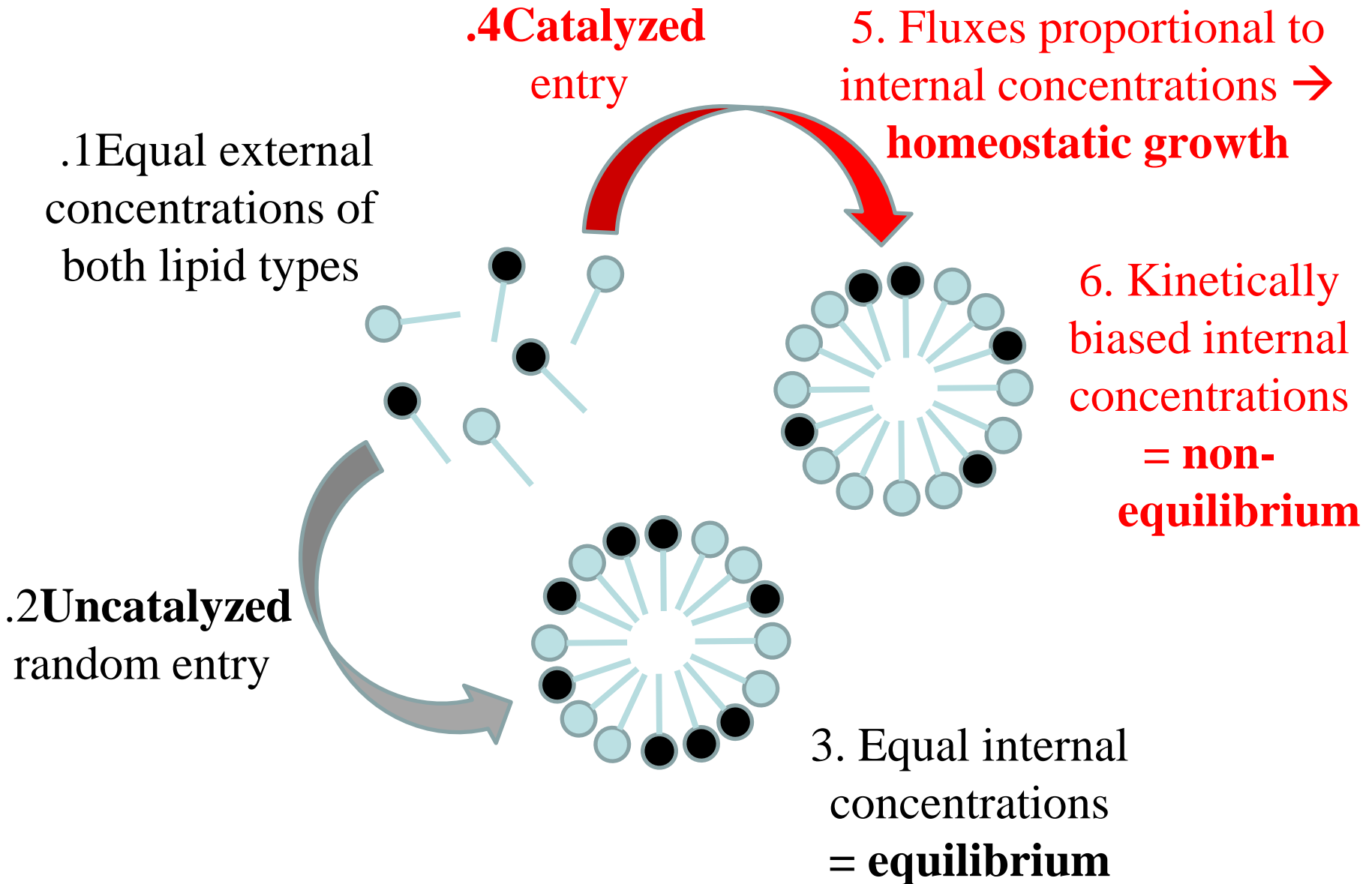

Sequence information

Compositional information

S - Replication of DNA

Interphase

G1 - Gap 1 (cell grows)

G1

S

G2

M

G2 - Gap 2 (cell prepares to divide)

Mitotic Phase

Cells that cease division

M - Mitosis (cell division)

The kinetic principles of compositional preservation

.1Equal external concentrations of both lipid types

.4Catalyzed entry

5. Fluxes proportional to internal concentrations → **homeostatic growth**

6. Kinetically biased internal concentrations = **non-equilibrium**

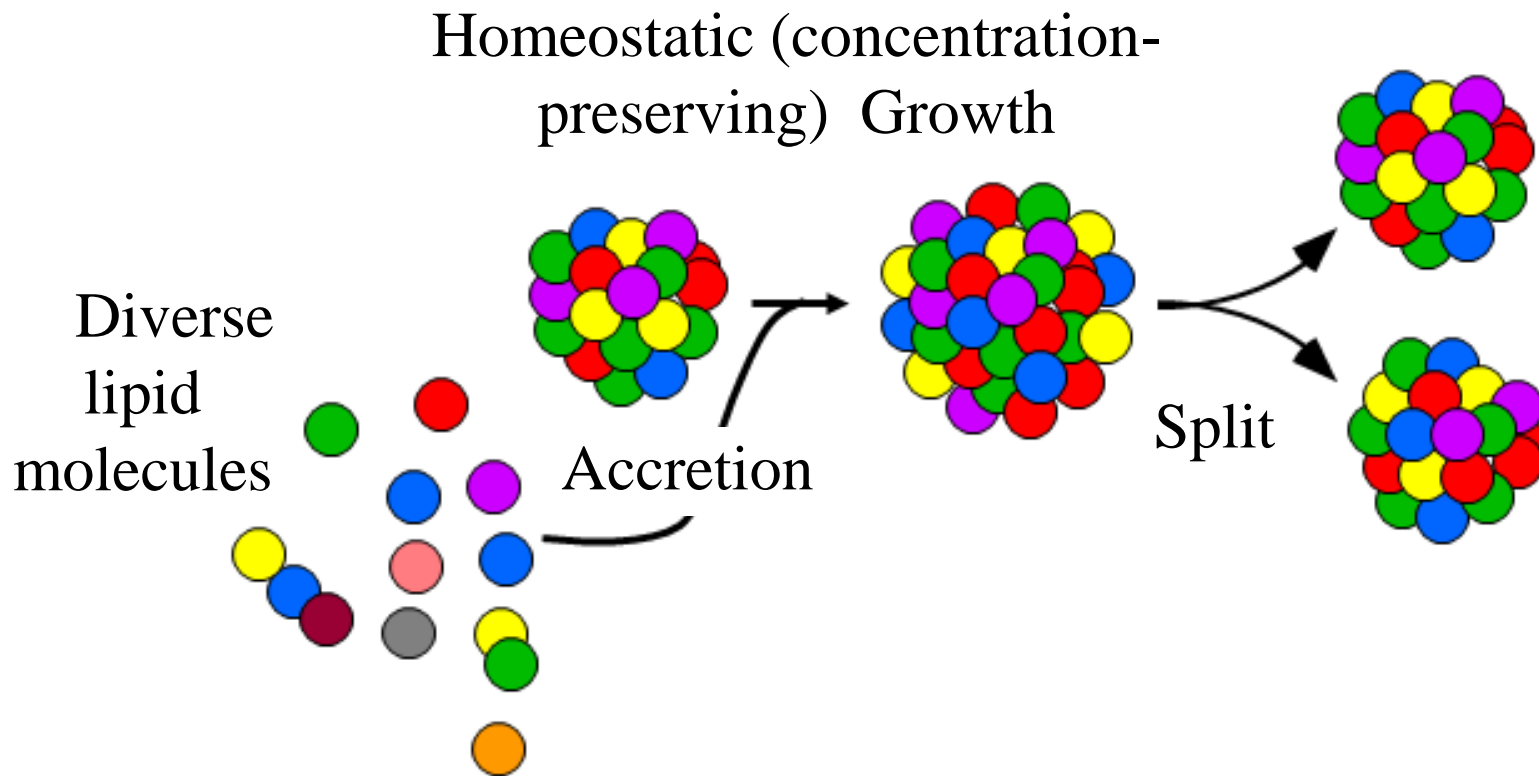**.2Uncatalyzed** random entry

3. Equal internal concentrations = **equilibrium**

Kinetically-controlled of compositional **replication**

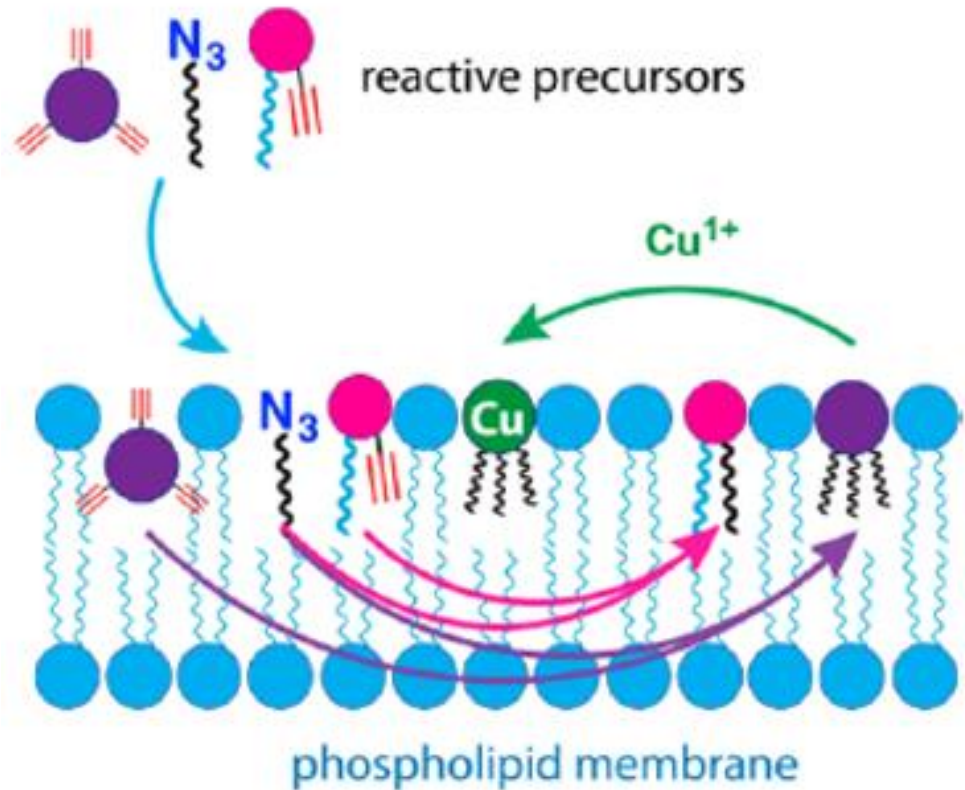**Kinetically biased non- equilibrium composition prevails along repeated splits**

Catalyzed entry

Growth+ fission

Growth+ fission
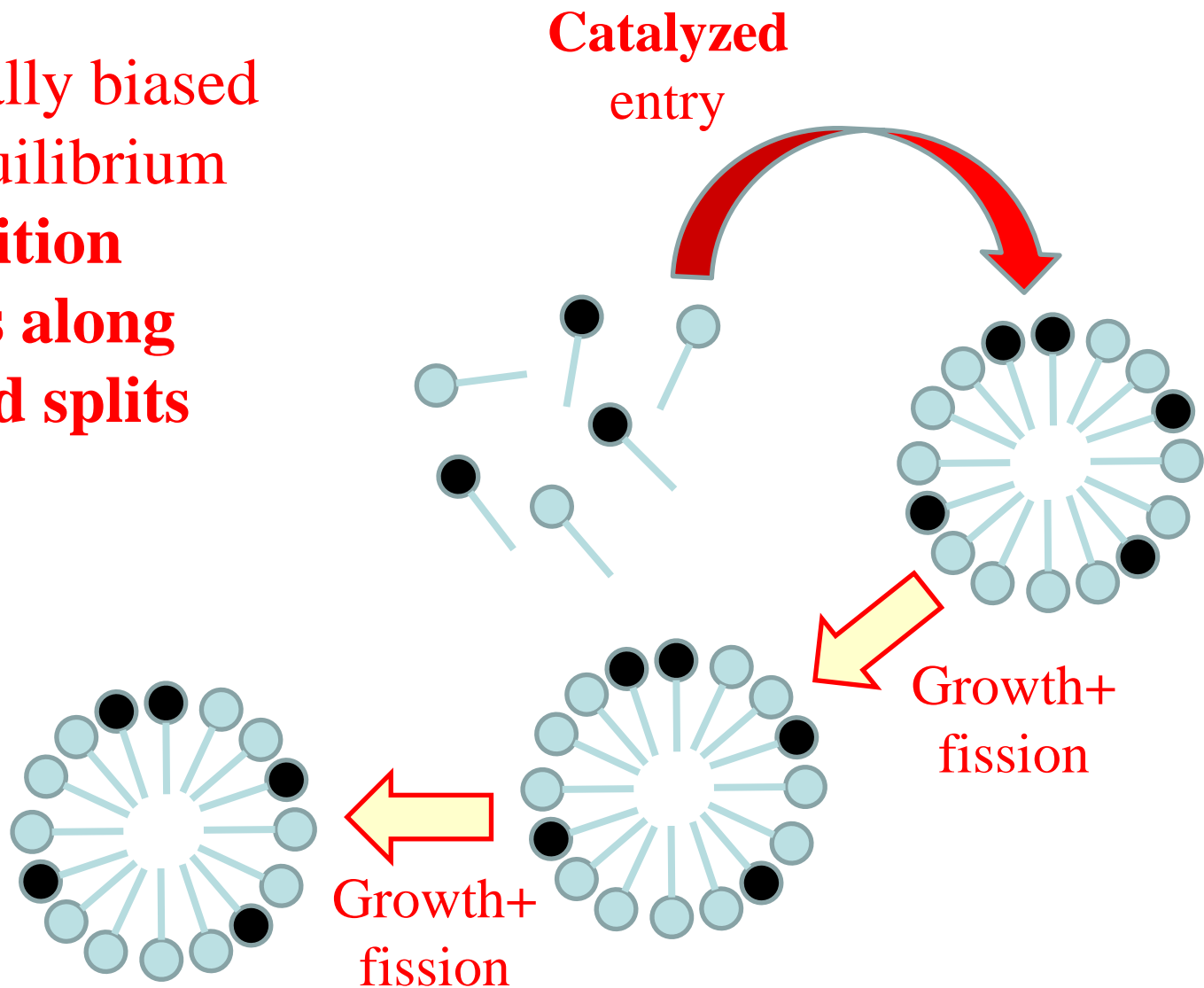
GARD: the Graded Autocatalysis Replication Domain model

Homeostatic (concentration-preserving) Growth

Diverse lipid molecules

Accretion

Split

Experimental evidence for such a process

Example showing → lipid-exerted non-enzymatic catalysis

reactive precursors

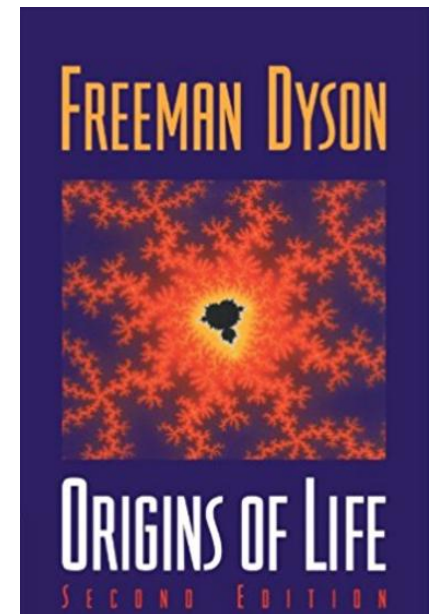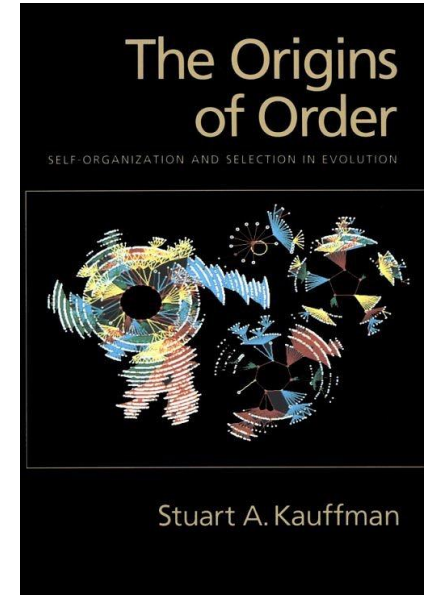phospholipid membrane

Self-reproducing catalyst drives repeated phospholipid synthesis and membrane growth
Neal K. Devaraj and colleagues, PNAS 2015
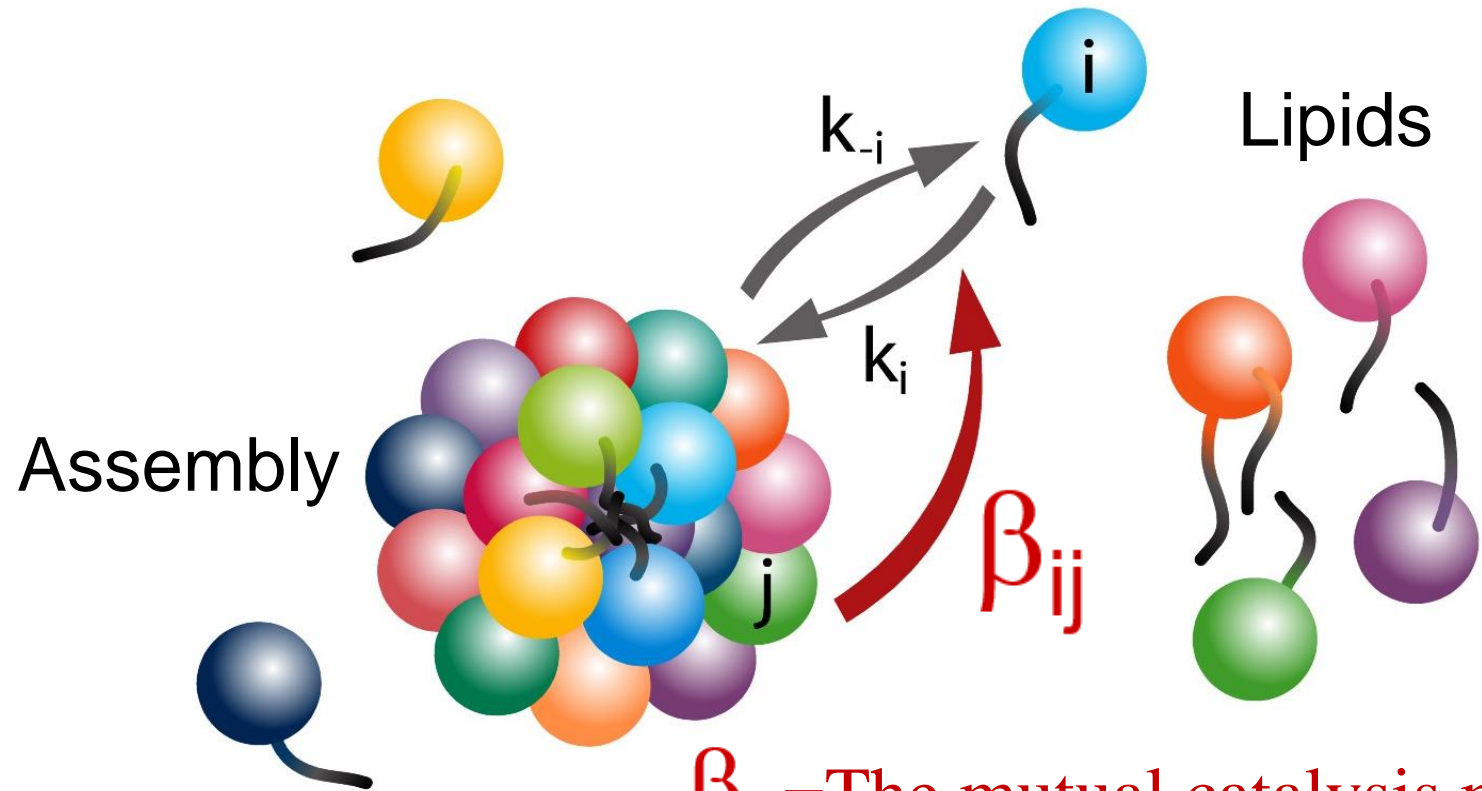
Mutually catalytic networks - Kauffman and Dyson
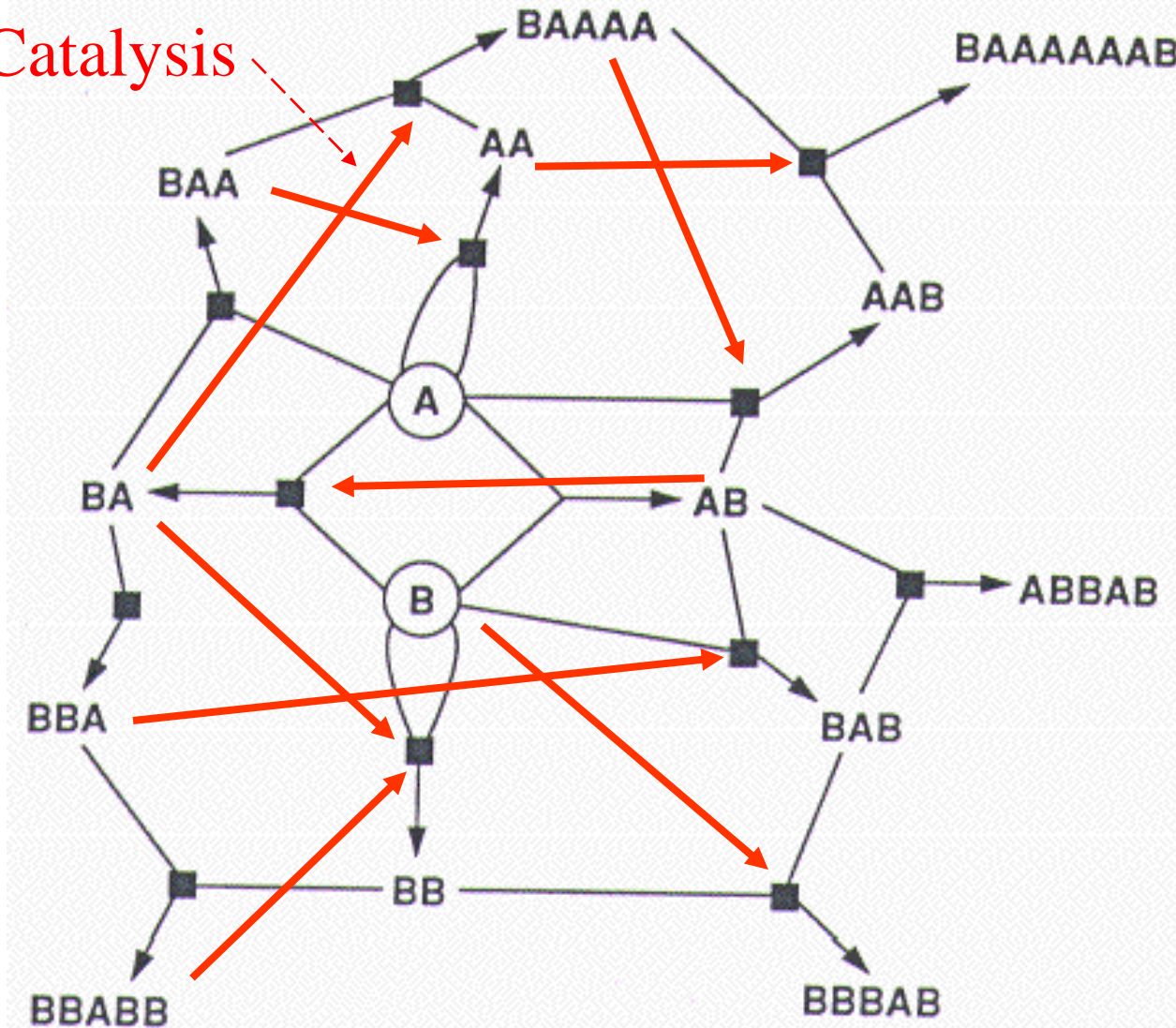
A, B are "foodset" (monomers(

The GARD world: not a theoretical model!

Lipids

Assembly

k_{-i}

k_i

i

j

β_{ij}

β_{ij} = The mutual catalysis matrix
Based on experimental data

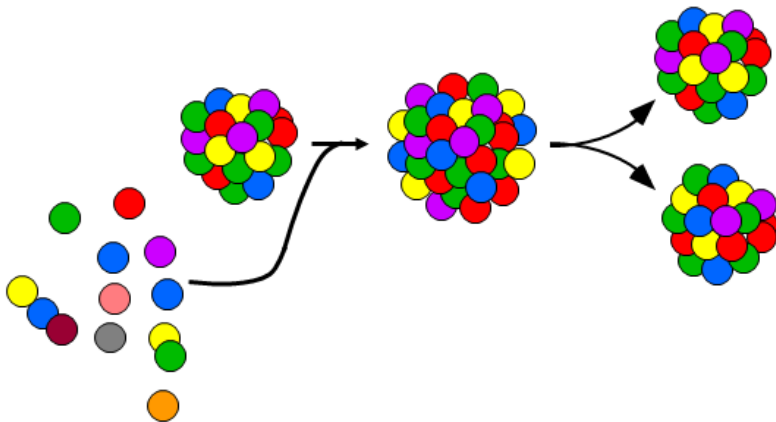Chemical kinetics equations

$$\frac{dn_i}{dt} = (k_i \cdot \rho_i N - k_{-i} n_i)\left(1 + \frac{1}{N}\sum_{j=1}^{N_G} \beta_{ij} n_j\right)$$

Computer-simulated by a Gillespie Algorithm

GARD simulations:

- ®$_{ij}$ are **given by the chemistry** of the participating lipids.
- **Simulations portray** the **internal concentrations** at which **replication** Takes place.

The red "cloud" is a position in compositional space at which concentrations remain unchanged across many growth-split cycles: Replicating "Composome"
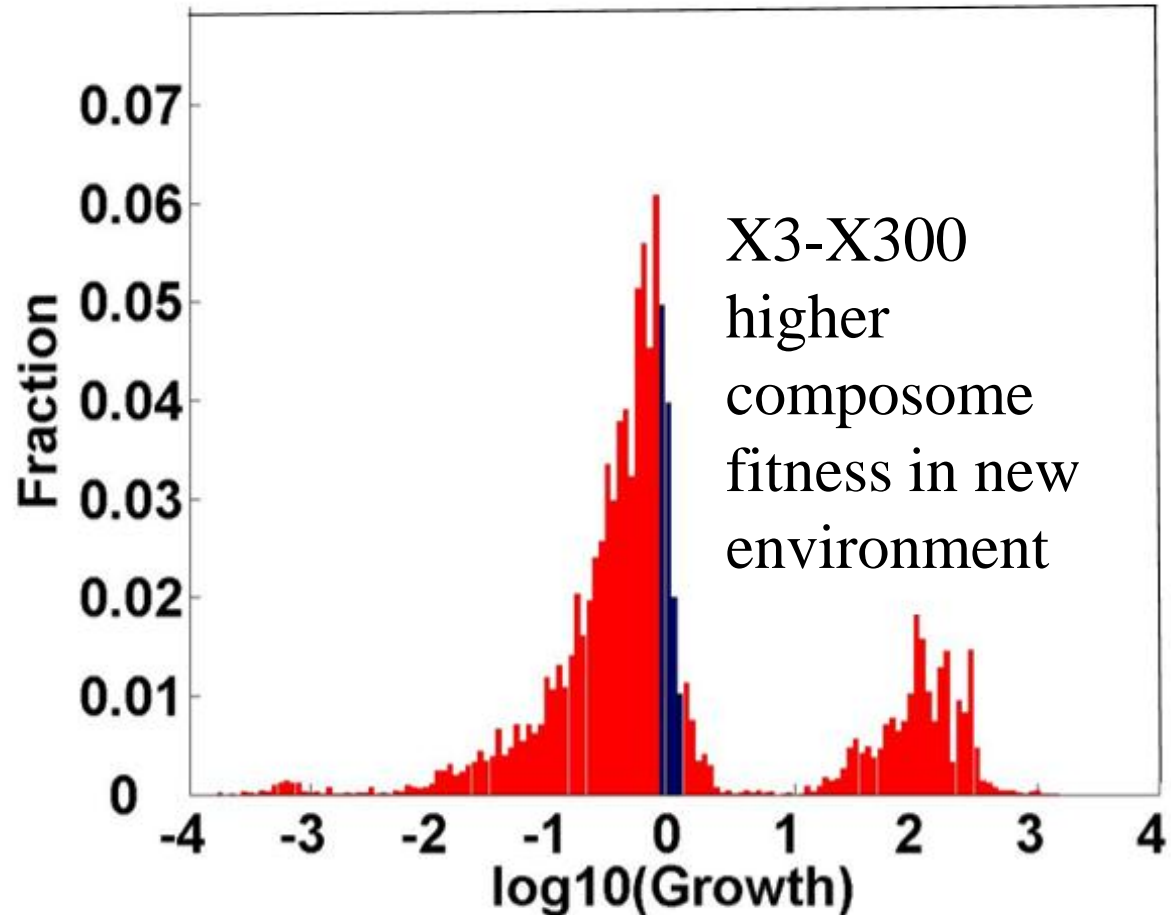
Composome = attractor

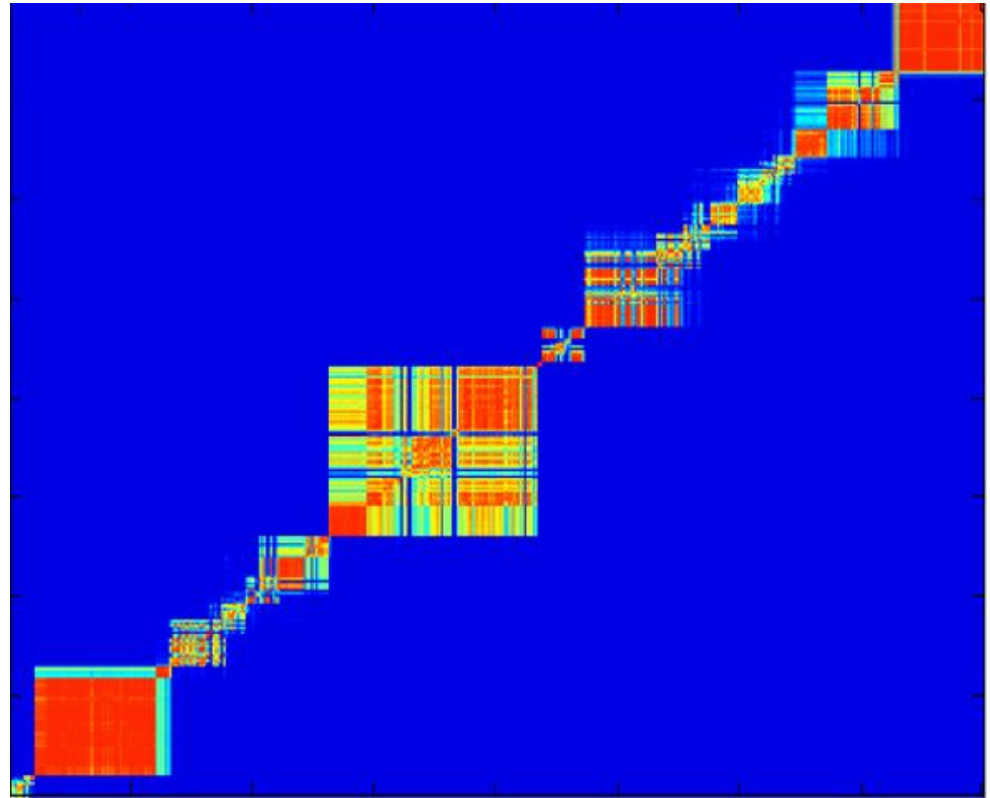

Trajectory in compositional space, axes are concdentrations
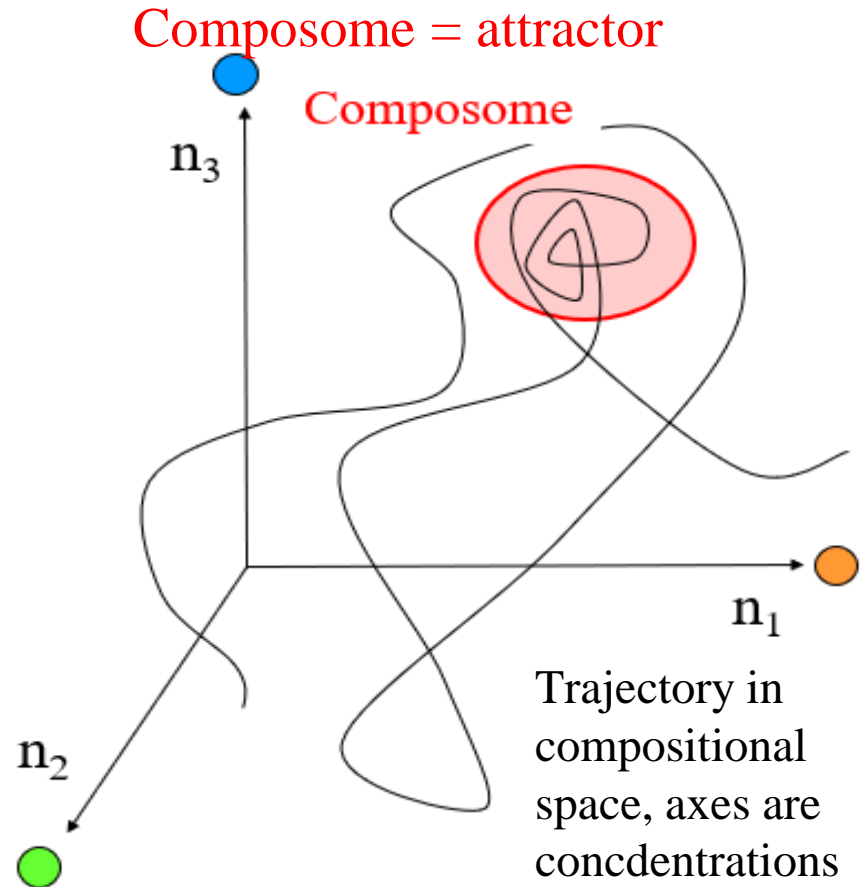
Carpet

And yet GARD composomes **evolve!**

Computer simulation with 5,000 repeats of single compound removal from environment

X3-X300 higher composome fitness in new environment

Open-ended evolution in response to continuous environmental chemical changes
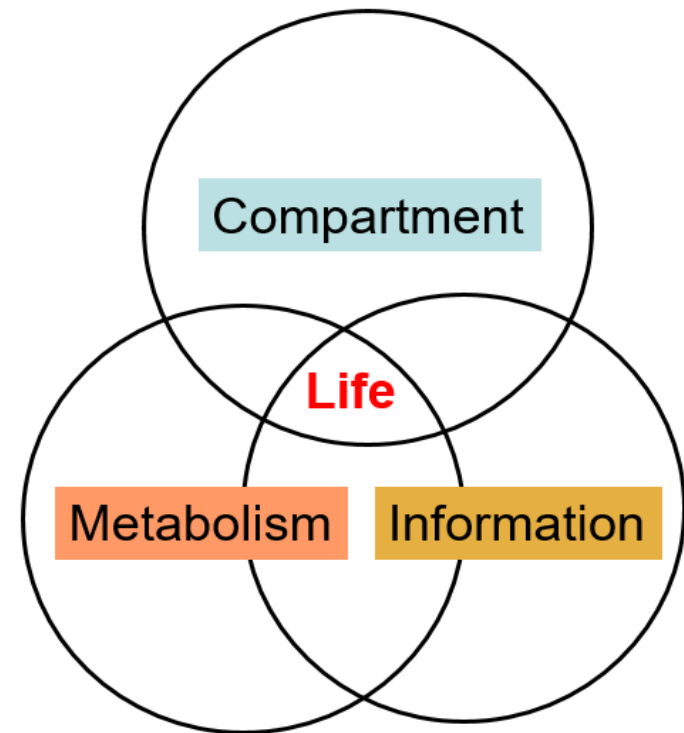

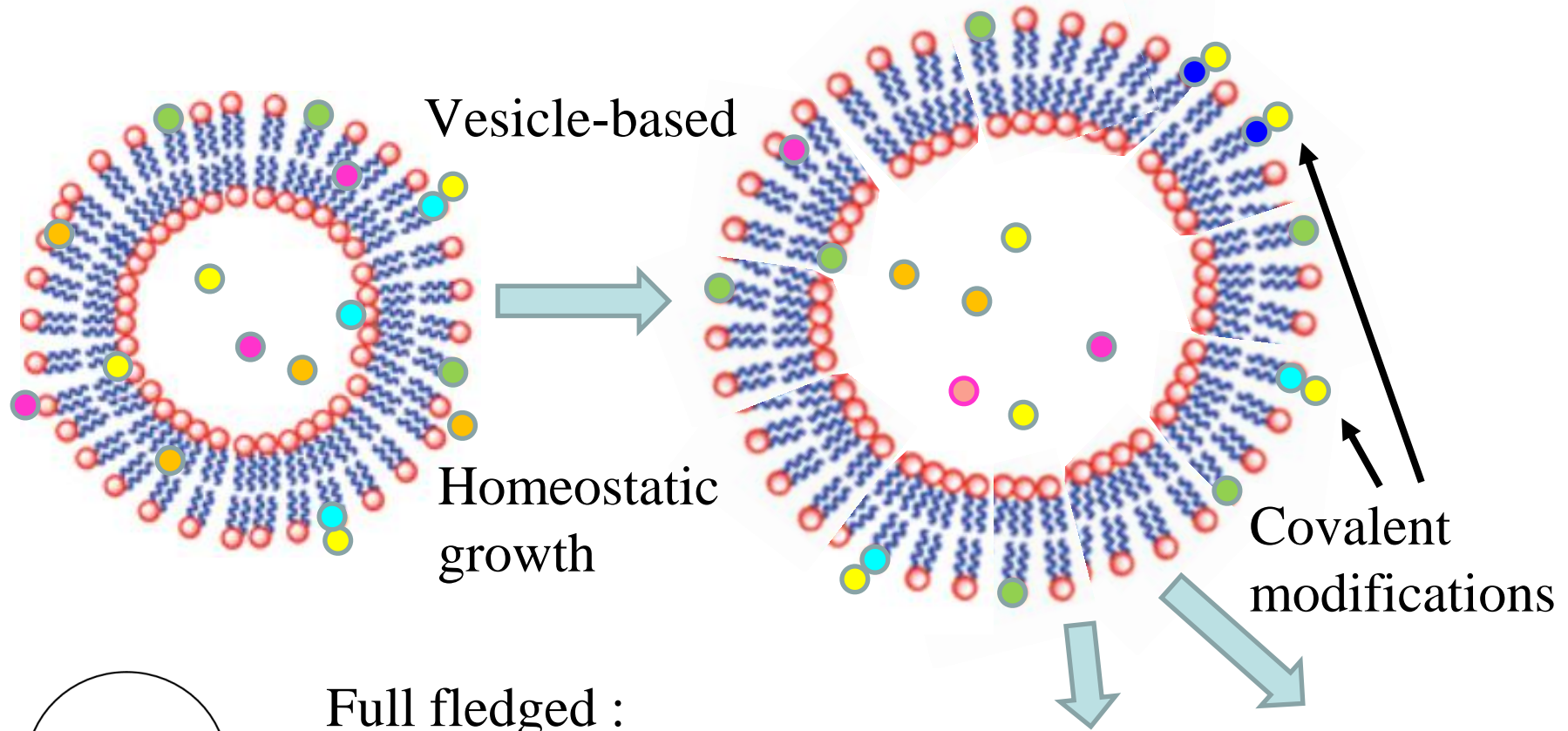Newly emerging composomes along the time axis
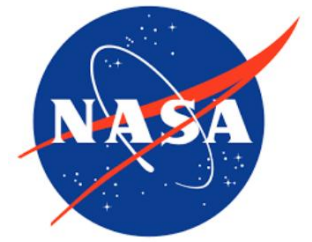
NASA definition for Life
"A self-sustaining chemical system capable of Darwinian evolution."

GARD lipid composomes:

1) Fulfill the NASA
     definition of life
2) Embody all 3 "pillars"
     of life

New Metabolic GARD, adds covalent chemistry

Vesicle-based

Homeostatic growth

Covalent modifications

Full fledged :
(1 Vesicular compartment
(2 Covalent metabolism
(3 compositional information copying

Split-effected replication of both shell and lumen

Compartment

Life

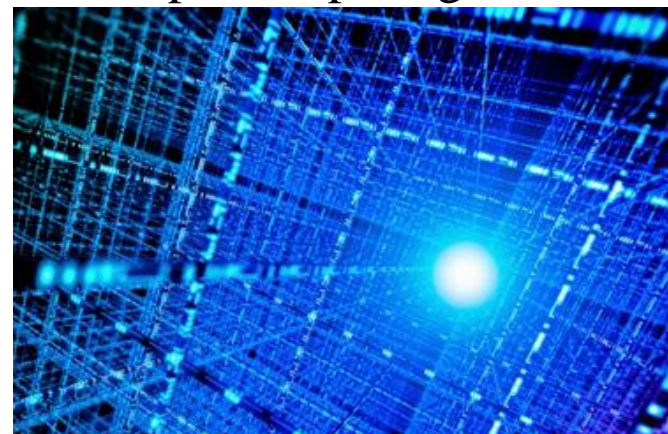Metabolism   Information
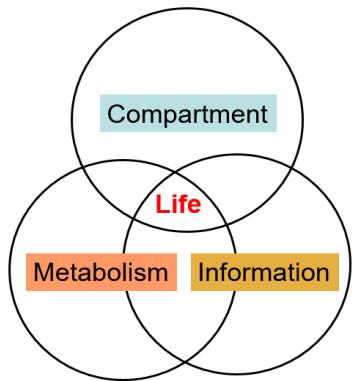
Futuristic computer Simulations of M-GARD

The *In-silico* Chemistry of 2028 are predicted* to provide accurate simulations of protein folding, enzyme specificity, hence also M-GARD open-ended evolution
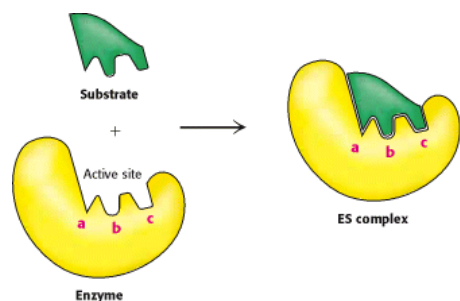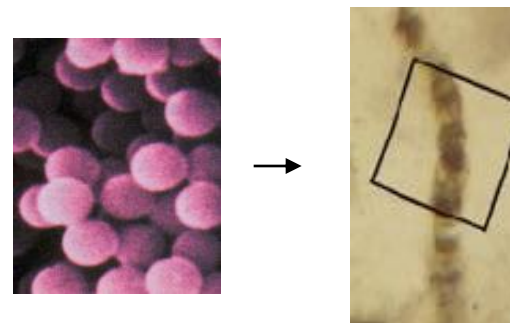

Supercomputing

*Borhani, Shaw
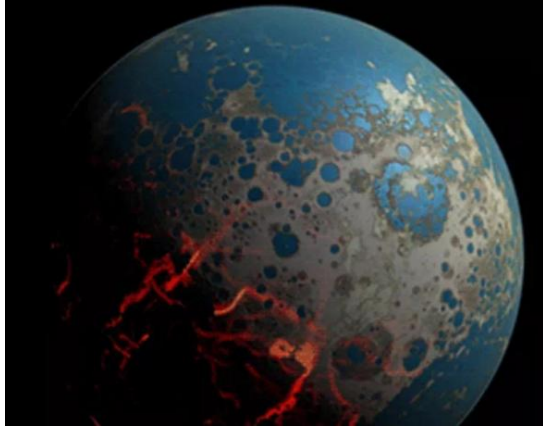The future of molecular dynamics simulations, *J computer-aided molec design* **26**, 15-26, .2012
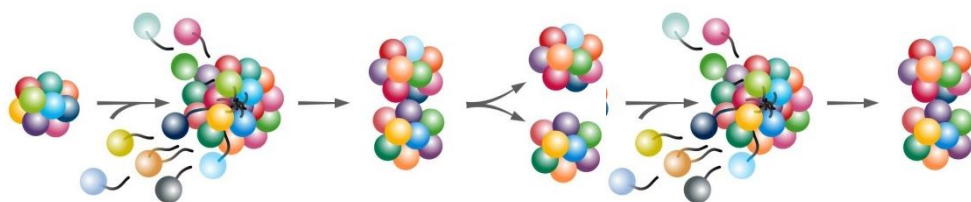
Quantum computing

GARD affords an estimate of life's probability

Area of 1/50 of earth surface = 10^7 km^2
Volume of top 10 meter = 10^{14} m^3
Replicator of 10nm at 10^{-5} by volume 10^{-19} m^3
Total GARD-type replicators = 10^{33}

Molecular repertoire N_G =100
F choose micelle size N=36 (a small micelle) Total
Number of GARD combinations ~10^{33}
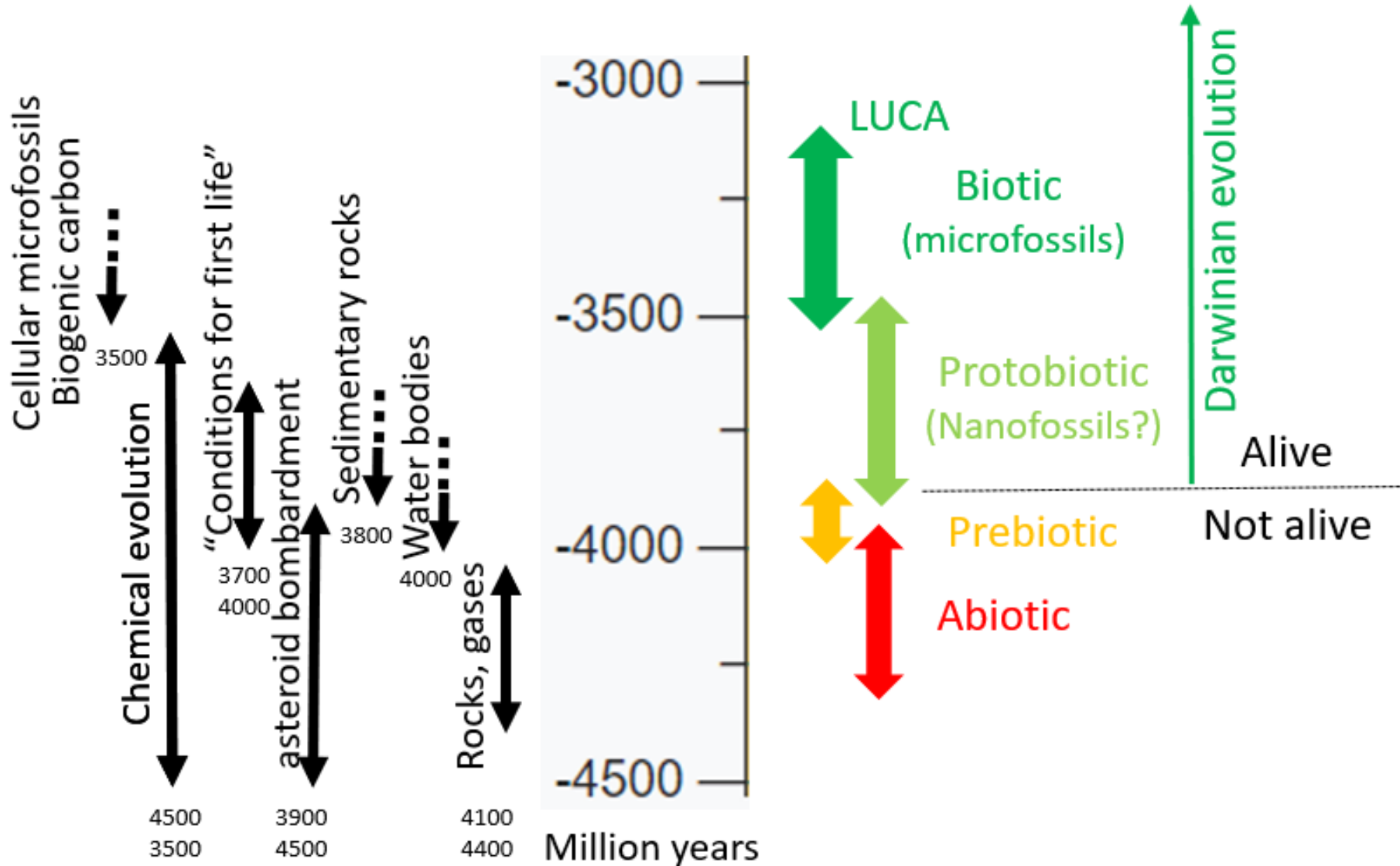based on the compositional information
formula: $\binom{N_G+N-1}{N}$

Thus, **all possible compositions** were present
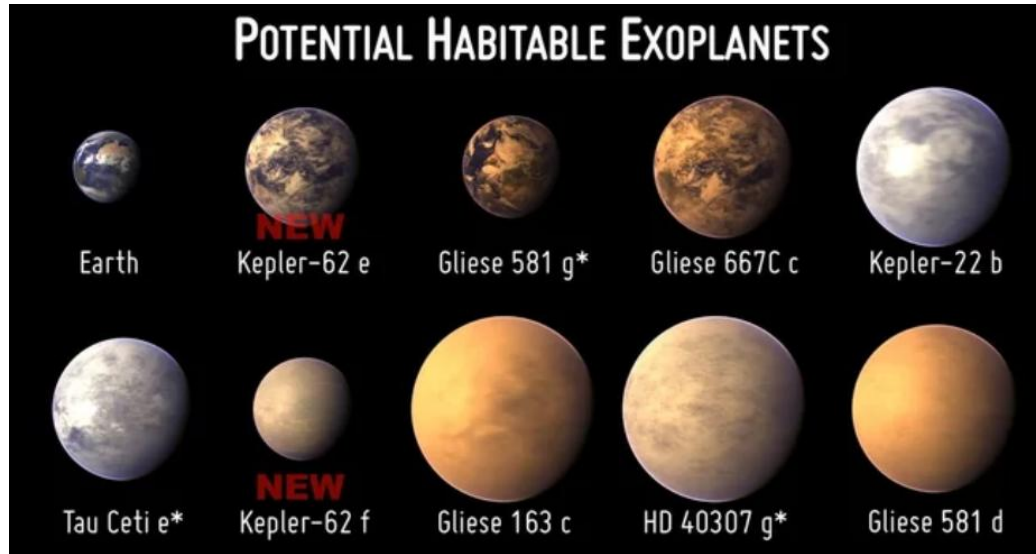**Including** the **best replicator** for the parameter set

Life is probable!

Planetary time-line suggested by GARD predictions
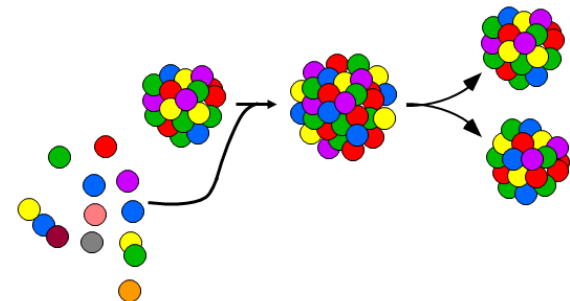
Search for life on extrasolar planets

POTENTIAL HABITABLE EXOPLANETS

Earth | Kepler-62 e | Gliese 581 g* | Gliese 667C c | Kepler-22 b
Tau Ceti e* | Kepler-62 f | Gliese 163 c | HD 40307 g* | Gliese 581 d

This?

Or that?

Search for life on extrasolar planets

This?

Or that?

POTENTIAL HABITABLE EXOPLANETS

Earth — Kepler-62 e (NEW) — Gliese 581 g* — Gliese 667C c — Kepler-22 b

Tau Ceti e* — Kepler-62 f (NEW) — Gliese 163 c — HD 40307 g* — Gliese 581 d

Martian meteorite
ALH84001

1 μm
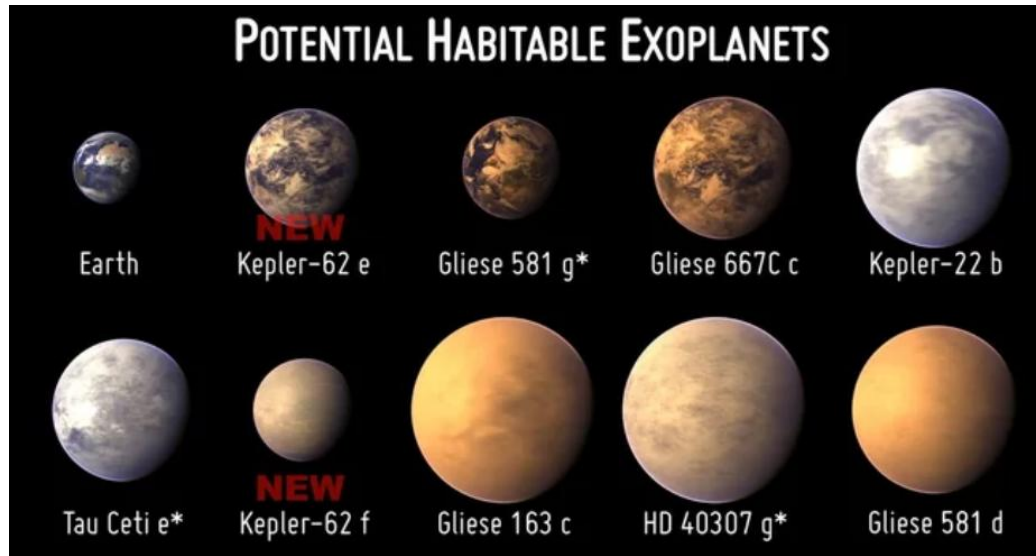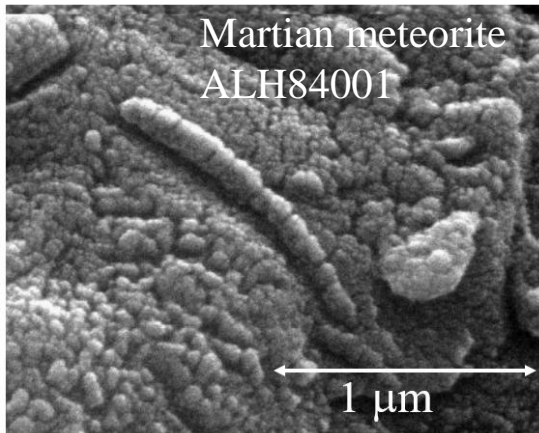
GARDobes from Mars?

Perhaps not too small…

McKay et al. Science 1996

End of talk on beginning of life

Does lipid entry to a micelle require catalysis?
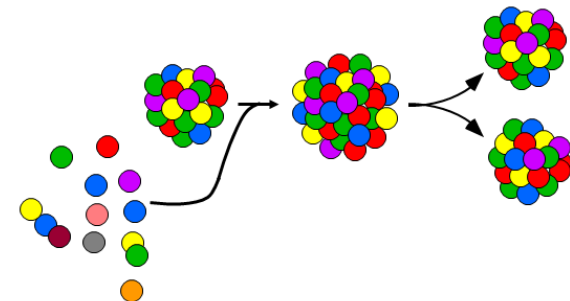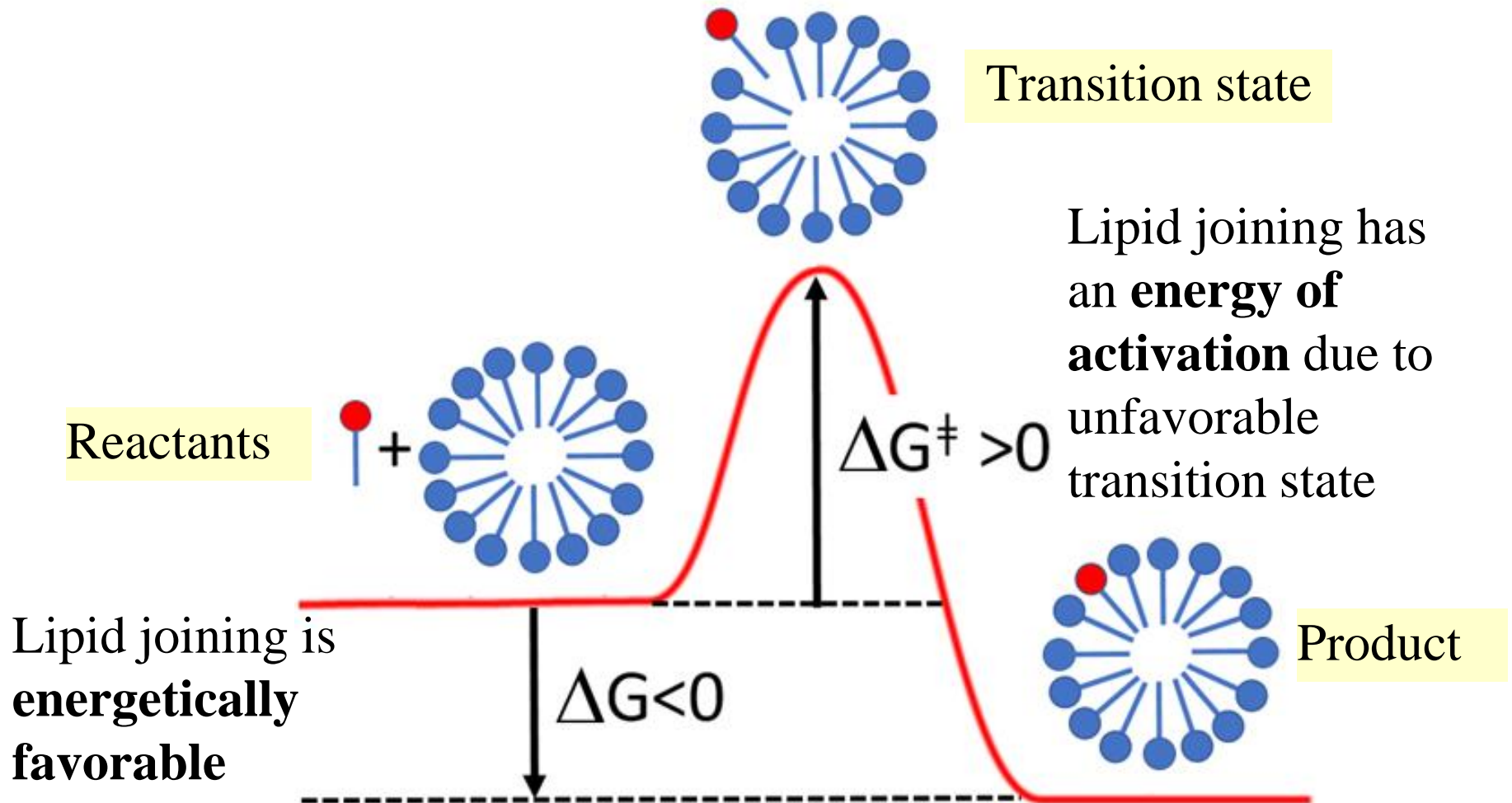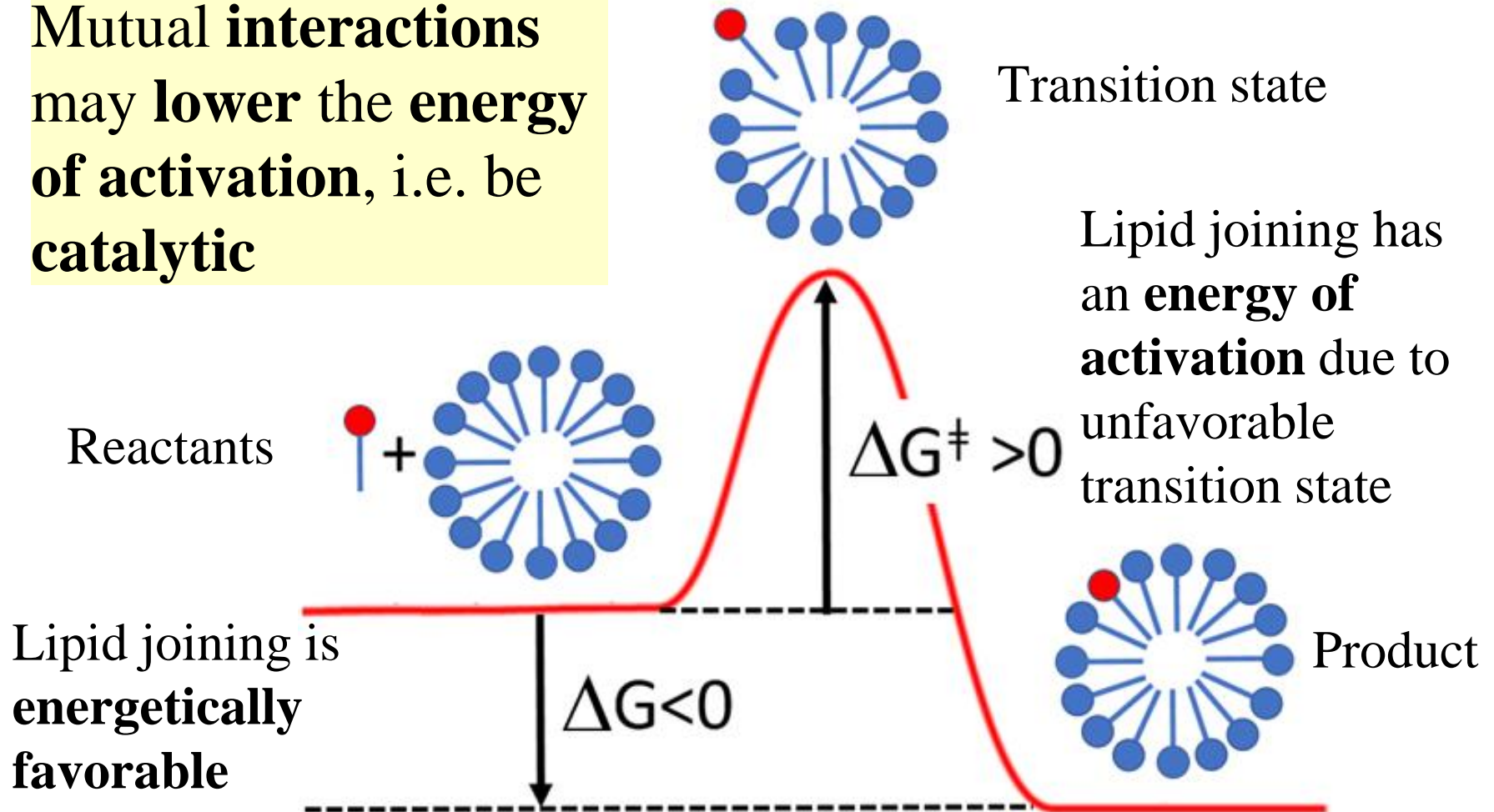## Lipid joining free energy diagram

Transition state

Lipid joining has an **energy of activation** due to unfavorable transition state

Reactants

$\Delta G^{\ddagger} > 0$

Product

Lipid joining is **energetically favorable**

$\Delta G < 0$

Does lipid entry to a micelle require catalysis?
Lipid joining free energy diagram

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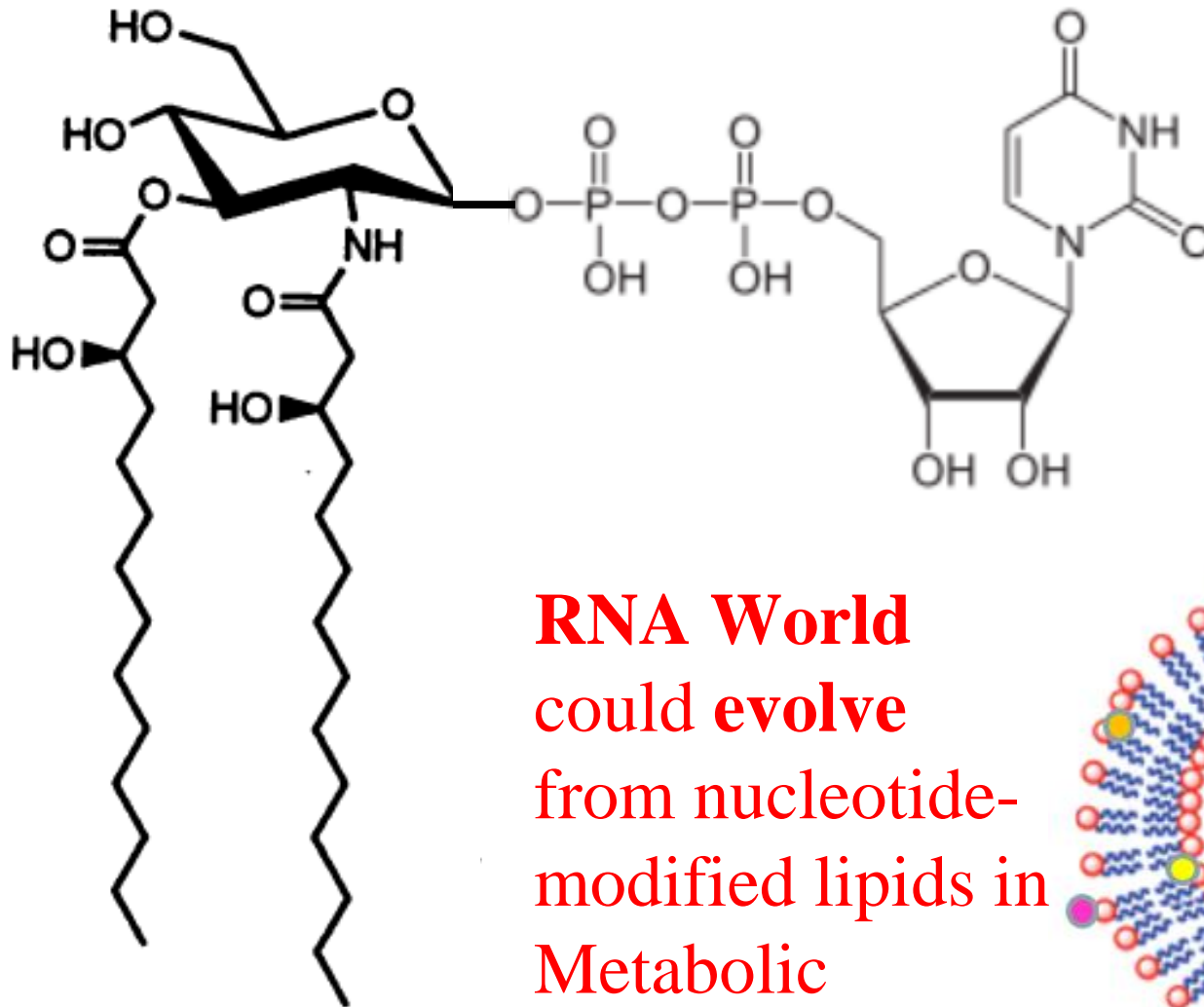
Transition state

Lipid joining has an **energy of activation** due to unfavorable transition state

Reactants

$\Delta G^{\ddagger} > 0$

Lipid joining is **energetically favorable**

$\Delta G < 0$

Product

An interaction strength **distribution** is obtained from **experimental biomolecules** such as **antibodies** and hormone **receptors**, is used in GARD computer simulations

Real

Random Ligand library

Receptor

Receptor Affinity Distribution (RAD) model

probability

Affinity

GARD

Catalytic events in a diverse molecular repertoire

Substrate

Catalyst

β_{ij}
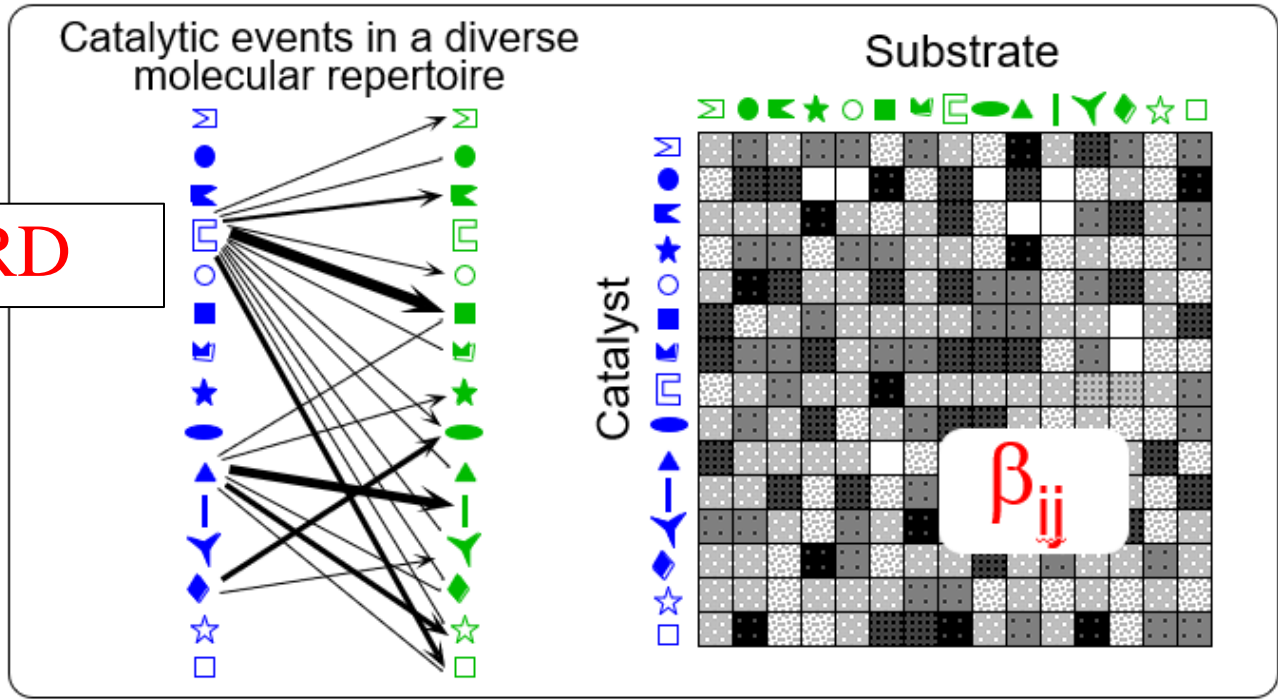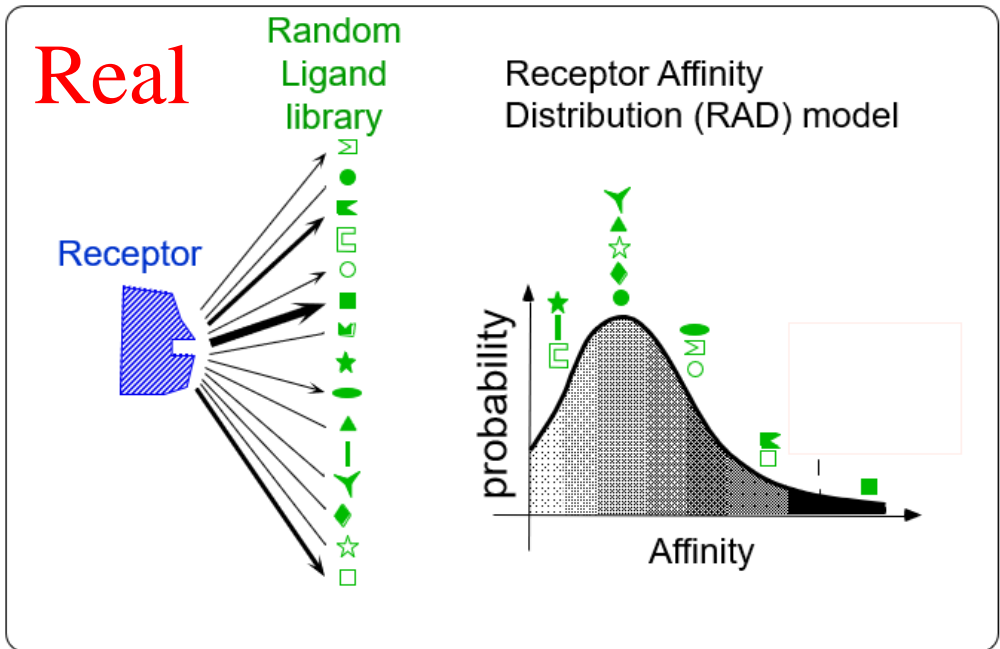
UDP-2,3-diacylglucosamine
A bacterial nucleotide-lipid

RNA World could **evolve** from nucleotide-modified lipids in Metabolic GARD

Christian R. H. Raetz, Journal of Bacteriology, 1993, 5745-5753