



Dept. of Logic and Philosophy of Science (IAS Research Group)
Biophysics Research Unit (CSIC-UPV/EHU)

**Taking a strong ‘bottom-up’ approach to the
origins of life:
How far can prebiotically plausible molecules go?**

Kepa Ruiz-Mirazo

CERN, Geneva
20 May 2011



«The idea that biological organization is fully determined by molecular structures is popular, seductive, potent and true up to a point -- yet fundamentally wrong... It disregards the fact that the cell as a whole is required to create the proper environment for self-assembly to proceed.»

[F. Harold 2003]

LIFE

very complex molecules (DNA, RNA, proteins, sugars, lipids,...)

very complex organization
(‘genetically-instructed’ cellular metabolisms)

A universal definition of
‘minimal life’

[Ruiz-Mirazo et al. 2004, *Origins of Life Evol. Biosph.*]

[Reprinted (2010): *Anthology -- CUP*]

‘autonomy’

‘open-ended evolution’



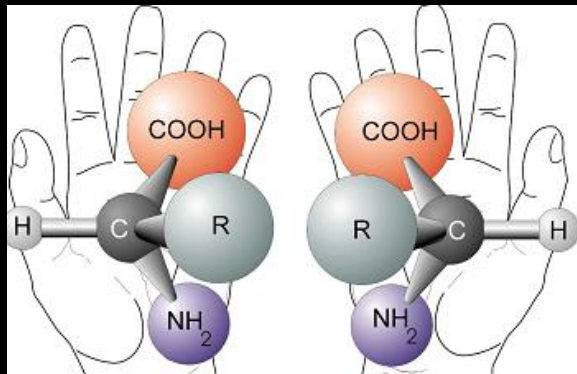
**CAPACITY FOR
‘SELF-CONSTRUCTION’
(metabolism)**

**POTENTIAL FOR
‘INDEFINITE GROWTH OF COMPLEXITY’
(‘Darwinian’ evolution)**

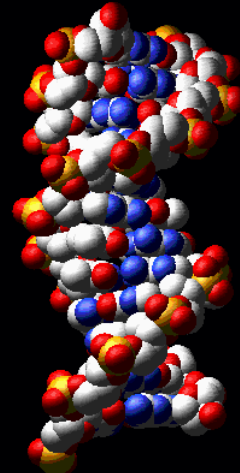
LIFE: SYSTEM PROPERTY ! → ORIGINS: SYSTEMIC APPROACH!!

Universal biochemical features

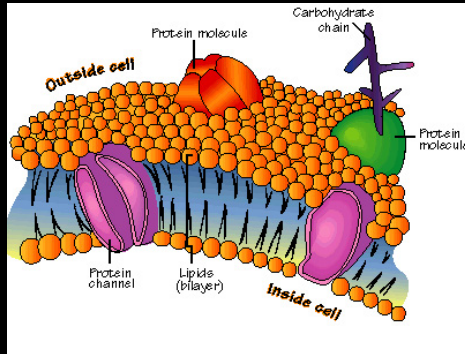
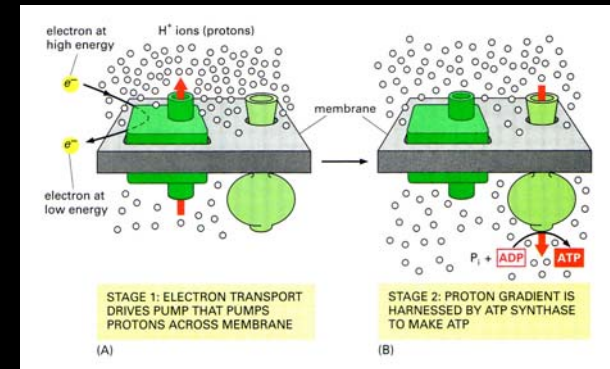
Homochirality



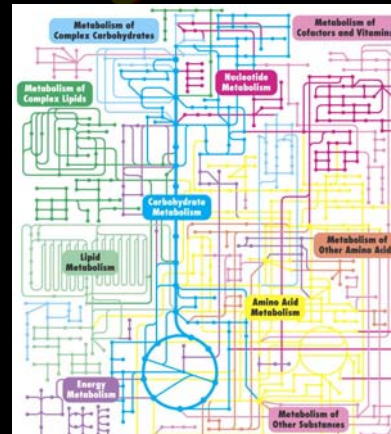
DNA
as the genetic material



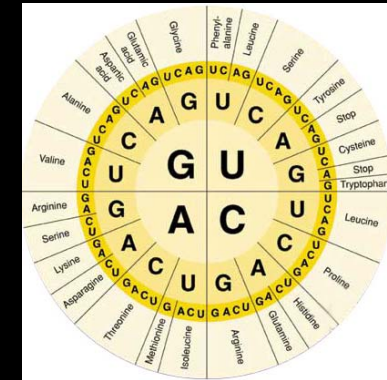
Energy currencies



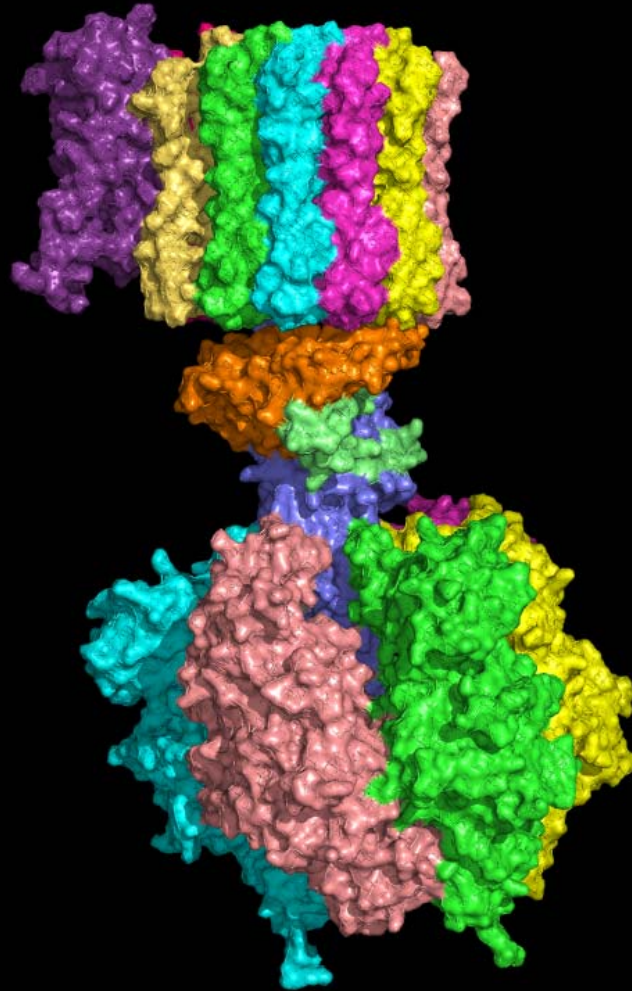
Cellular boundary



Common
coenzymes and metabolic
intermediaries



Genetic code

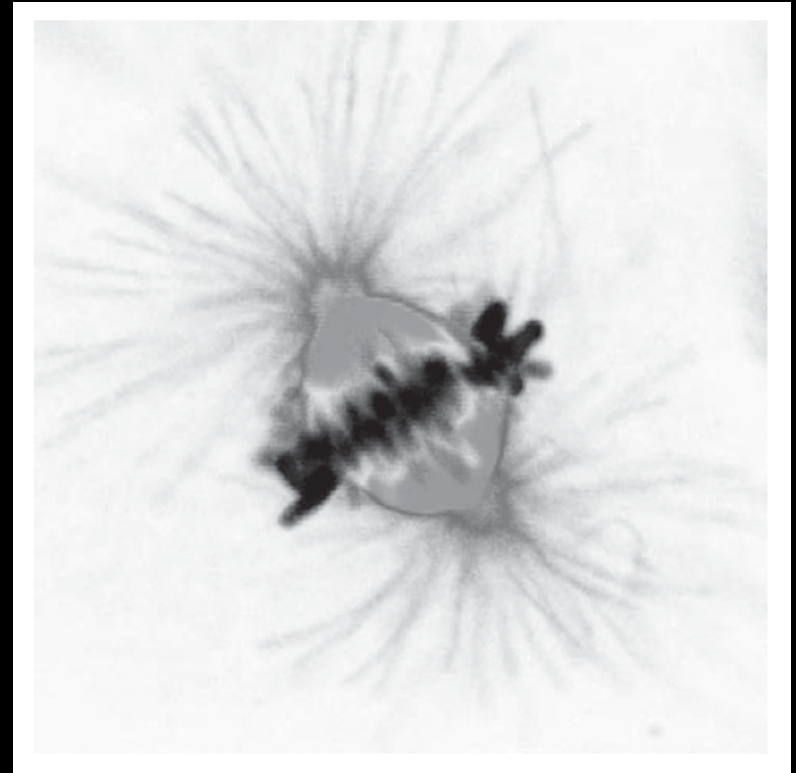
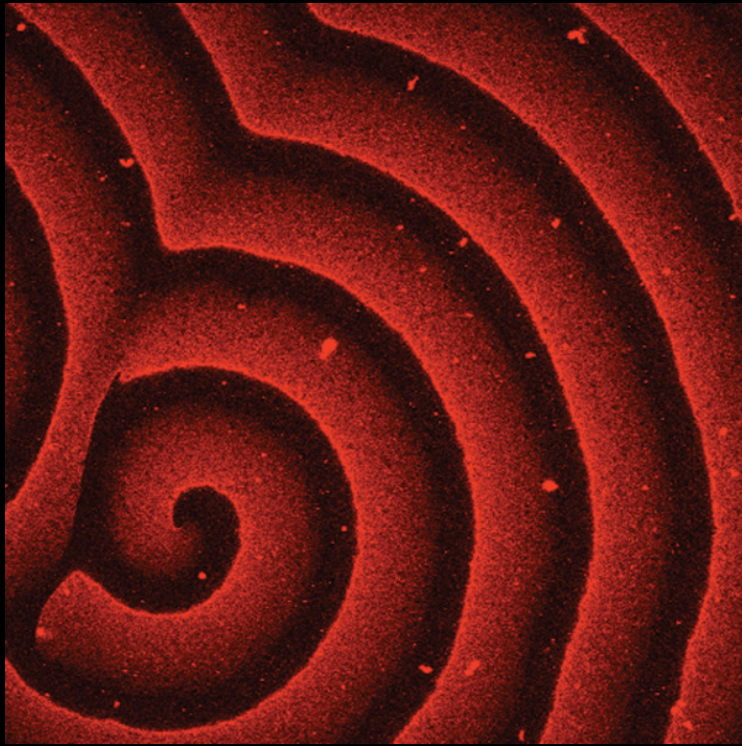


ATP Synthase

[INSERT: 'grt video of atp synthase']

Universal biophysical/biochemical features

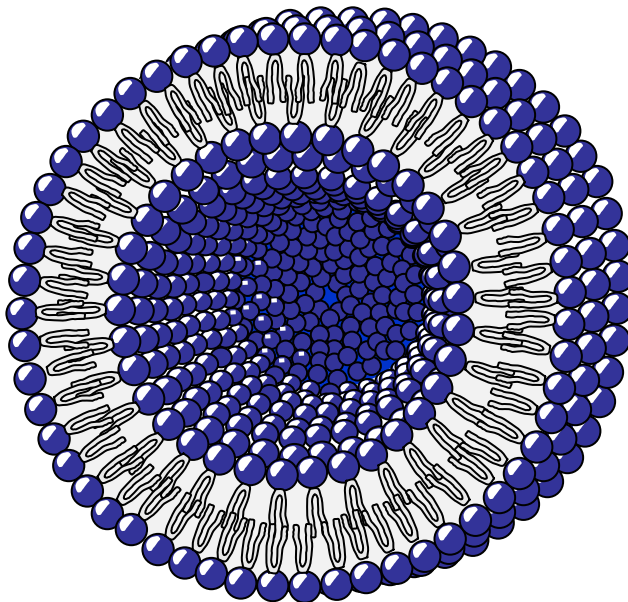
SELF-ORGANIZATION & SELF-ASSEMBLY (!)



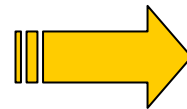


MAIN BOTTOM-UP PROBLEMS TO BE ADDRESSED:

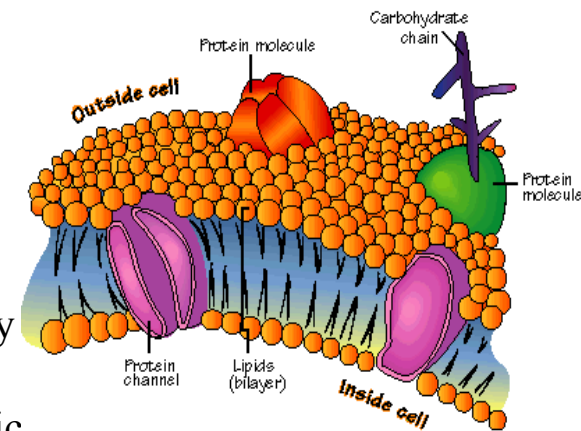
- MINIMAL CONCENTRATION THRESHOLDS
(*BOUNDARIES: PROTOCELLULARITY*)
- KINETIC CONTROL: ORIGIN AND DEVELOPMENT OF CATALYSIS
(*OLIGOMERIZATION, ANABOLIC AUTOCATALYSIS, ORGANOCATALYSIS!*)
- PROCESS SYNCHRONIZATION + INTEGRATION SUPERSYSTEMS
(*e.g., chemical oscillations with division cycles*)
- CONTROL ON MATTER AND ENERGY FLOW:
(*TRANSDUCTION + ENDERGONIC-EXERGONIC COUPLINGS*)



'co-evolution'

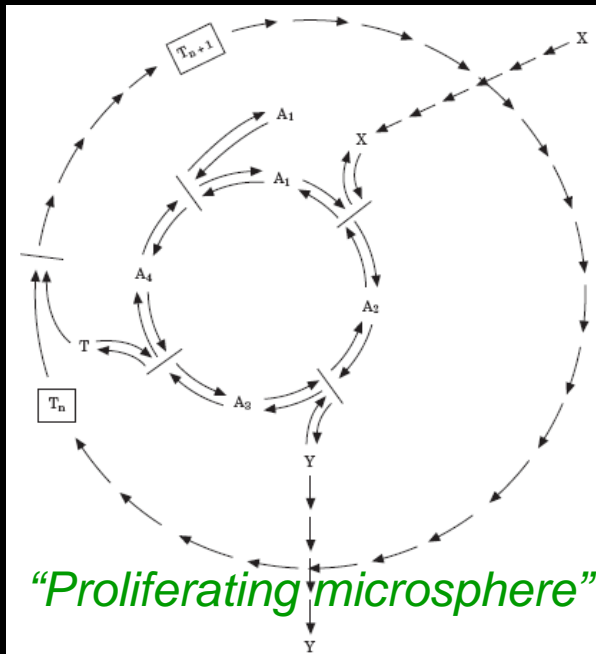


between boundary
(scaffolding)
and protometabolic
reactions

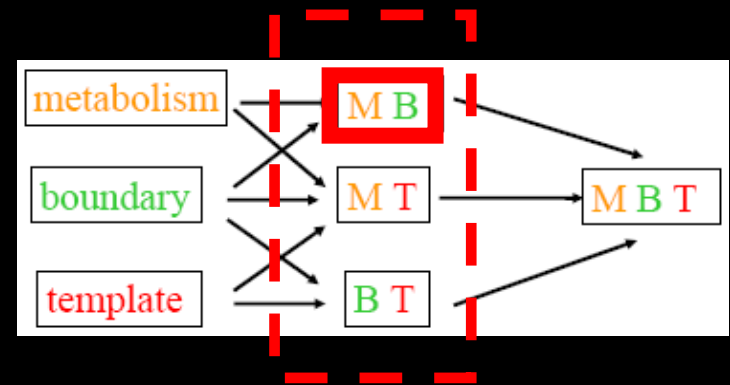


FORGET (temporarily) ABOUT COMPLEX BIOMOLECULES
(e.g.: DNA, RNA, PROTEINS,...):

CAN WE DO INTERESTING ‘SYSTEMS CHEMISTRY’ WITH
MUCH SIMPLER (and prebiotically plausible) MOLECULES ?
(e.g., fatty acids, amphiphiles/surfactants, alcohols, aminoacids, short peptides...)



(Gánti 1975; 2002)



Infrabiological systems

(Szathmáry et al., 2005)

ORIGINS OF LIFE

[Ruiz-Mirazo et al. (2004) OLEB 34: 323-346]

INFORMATION

INCREASE IN
MOLECULAR AND
ORGANIZATIONAL
COMPLEXITY

FUNCTION

minimal living systems
(autonomy + open-ended evolution):
'TWO/THREE-POLYMER WORLD'
(RNA-protein/DNA-RNA-protein)

'hereditary autonomous'
systems
'ONE-POLYMER (RNA)
WORLD'

third major bottleneck:
phenotype-genotype decoupling
(catalysis /// template activity)
'translation' mechanisms
and genetic code

'basic autonomous'
systems
'OLIGOMER (peptides)
WORLD'

second major 'bottleneck':
'template-replication' mechanisms

first major bottleneck: 'proto-bioenergetic' mechanisms



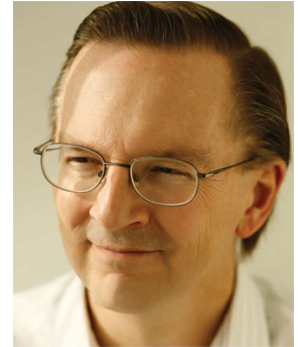
If so, apart from self-organisation and self-assembly...

Are there any other “driving forces”?

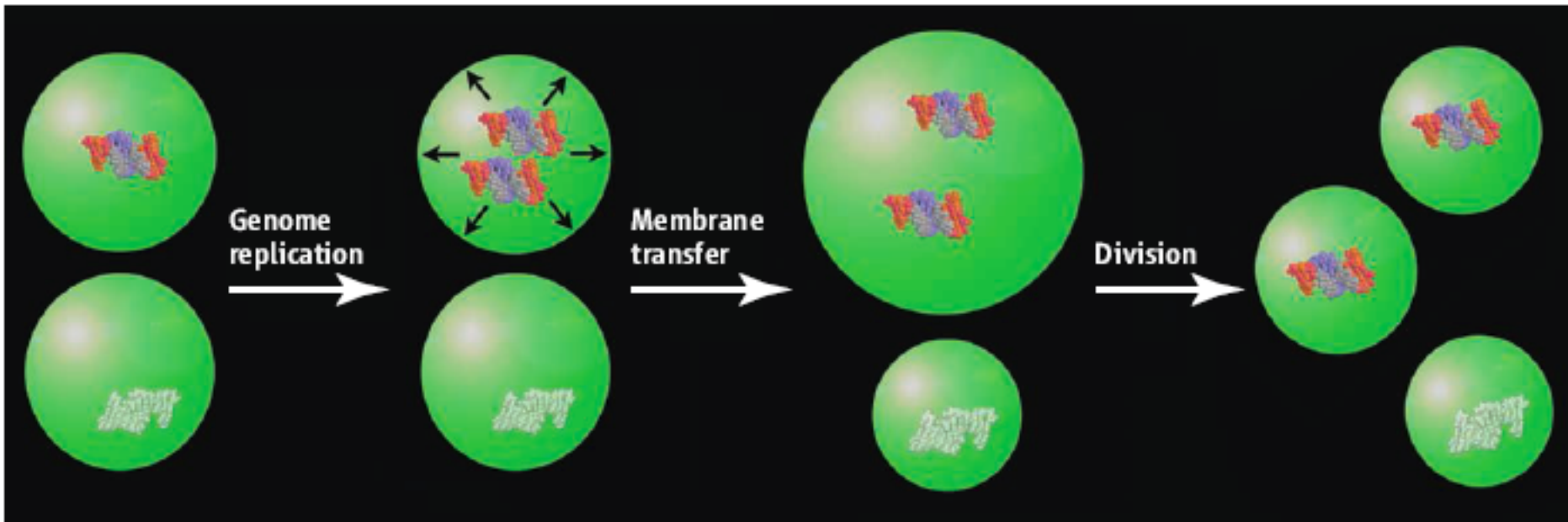
...when proper Darwinian evolution
(i.e., involving replication of modular templates)
is still on its way...

The Emergence of Competition Between Model Protocells

Irene A. Chen,^{1,2} Richard W. Roberts,³ Jack W. Szostak^{1*}



The transition from independent molecular entities to cellular structures with integrated behaviors was a crucial aspect of the origin of life. We show that simple physical principles can mediate a coordinated interaction between genome and compartment boundary, independent of any genomic functions beyond self-replication. RNA, encapsulated in fatty acid vesicles, exerts an osmotic pressure on the vesicle membrane that drives the uptake of additional membrane components, leading to membrane growth at the expense of relaxed vesicles, which shrink. Thus, more efficient RNA replication could cause faster cell growth, leading to the emergence of Darwinian evolution at the cellular level.



The emergence of cellular behavior. Competition emerges as protocells containing replicating genomes steal membrane from protocells containing inactive molecules.

Physical effects underlying the transition from primitive to modern cell membranes

Itay Budin^{a,b} and Jack W. Szostak^{a,b,1}

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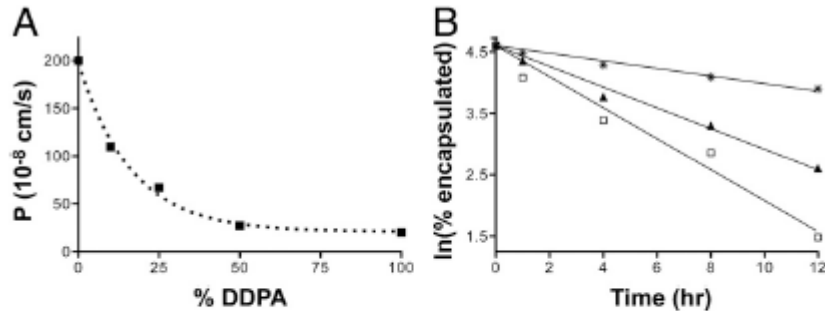


Fig. 4. Phospholipids inhibit solute permeation through fatty-acid-based membranes. (A) Permeability of C10 membranes (4:1:1 DA:DOH:GMD) to ribose as a function of DDPA content as measured by a stopped-flow relaxation assay. (B) Leakage of encapsulated ImpdA from C10 vesicles as measured by scintillation counting of dialysis buffer aliquots. Membrane compositions: \square , 4:1:1 DA:DOH:GMD; \blacktriangle , 4:1:1 DA:DOH:GMD with 25 mol % DDPA; and $*$, DDPA.

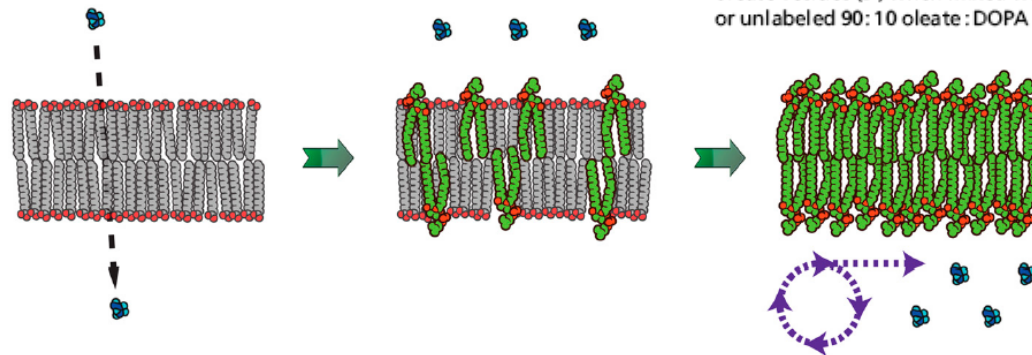


Fig. 5. Schematic for membrane-driven cellular evolution. The gradual transition from highly permeable primitive membranes (Left) to phospholipid membranes (Right) is driven by the selective growth advantage provided by increasing phospholipid content in the membrane. In turn, this transition in membrane composition imposes a selective pressure for the emergence of internalized metabolism to counter the reduced permeability of diacyl lipid membranes.

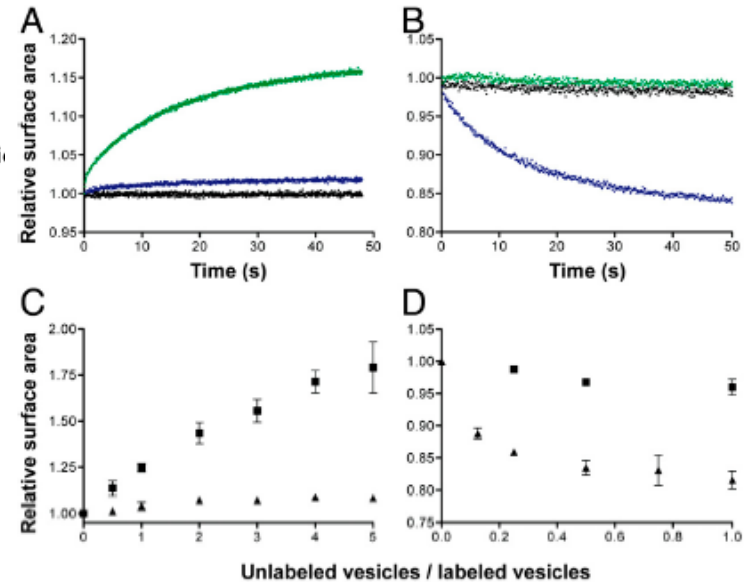


Fig. 1. Phospholipids drive competition between fatty acid vesicles. (A and B) Competition between vesicles was monitored by a FRET-based real-time surface area assay. Growth of FRET-labeled 90:10 oleate:DOPA vesicles (A) and shrinkage of FRET-dye labeled oleate vesicles (B) when mixed 1:1 with buffer (black), unlabeled oleate vesicles (green), or unlabeled 90:10 oleate:DOPA vesicles (blue). (C and D) The dependence of vesicle growth or shrinkage on vesicle stoichiometry. Final growth after equilibrium of FRET-labeled 90:10 oleate:DOPA vesicles (C) and shrinkage of FRET-labeled oleate vesicles (D) when mixed with varying amounts of unlabeled oleate (\blacksquare) or unlabeled 90:10 oleate:DOPA (\blacktriangle) vesicles. Error bars indicate SEM ($N = 3$).

Template-directed synthesis of a genetic polymer in a model protocell

Sheref S. Mansy¹, Jason P. Schrum¹, Mathangi Krishnamurthy¹, Sylvia Tobé¹, Douglas A. Treco¹ & Jack W. Szostak¹

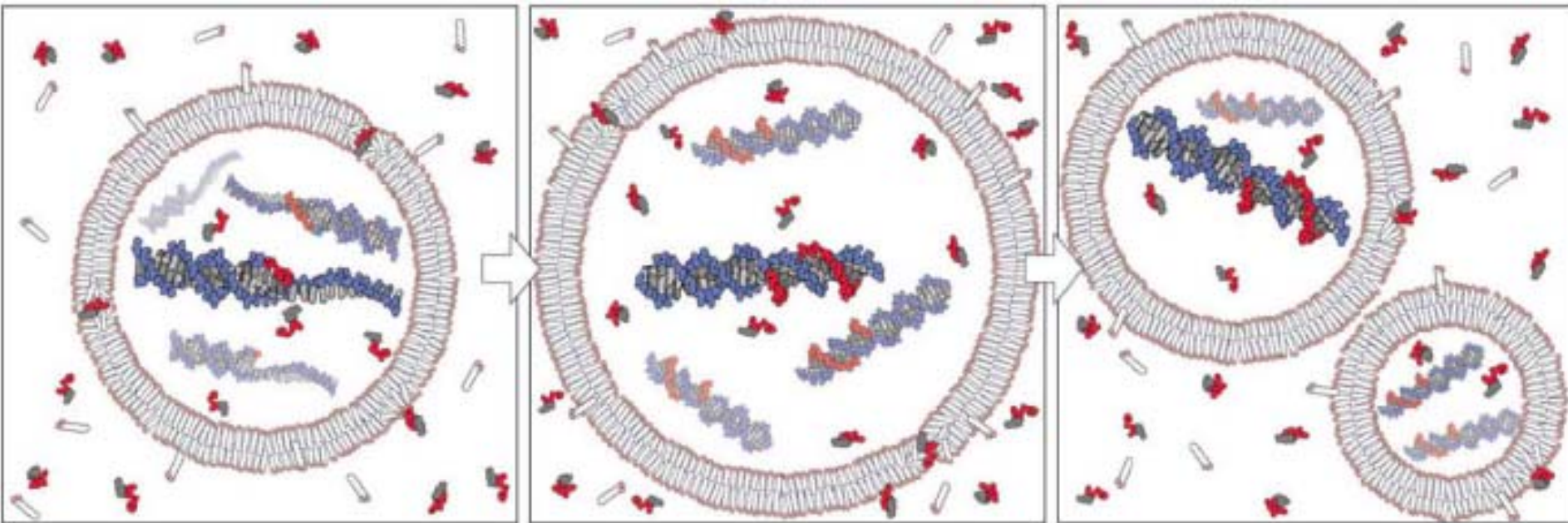


Figure 1 | Conceptual model of a heterotrophic protocell. Growth of the protocell membrane results from the incorporation of environmentally supplied amphiphiles, whereas division may be driven by intrinsic or extrinsic physical forces. Externally supplied activated nucleotides permeate

across the protocell membrane and act as substrates for the non-enzymatic copying of internal templates. Complete template replication followed by random segregation of the replicated genetic material leads to the formation of daughter protocells.

BOTTOM-UP APPROACH: MINIMAL 'lipid-peptide' CELL

(Pre-biopolymer) scenario with:

- SELF-ASSEMBLING VESICLES

made of fatty acids, amphiphiles/surfactants, alcohols, mixtures,...

evidence from: (a) external sources [Deamer 1986, 1997; Dworkin et al. 2001]

(b) abiotic (Fischer-Tropsch) synthesis [Nooner et al. 1976;

Allen & Ponnampereuma 1967; Rushdi & Simoneit 2001]

- SHORT PEPTIDE CHAINS (rudimentary channels/carriers and catalysts)

made of: Ala, Gly, Asp, Glu, Ser, Val...

evidence from: (a) external sources [Pizzarello et al. 2006; Bernstein et al. 2002]

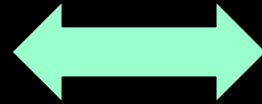
(b) abiotic (Strecker, SIPF,...) synthesis [Miller 1953; Rode 1999]

+ [• VARIOUS 'COENZYME-LIKE' COMPOUNDS (e⁻ carriers, pigments...)

• PAHs: PHOTOCHEMICALLY ACTIVE and MEMBRANE STABILIZING!

• PRIMITIVE ENERGY TRANSDUCTION MECHANISMS ?
('chemical and chemiosmotic' -- energy currency precursors)

DEVELOPMENT OF
LIPIDIC
COMPARTMENTS



PRODUCTION OF
MOLEC. COMPLEXITY
(e.g., POLYPEPTIDES)

- avoid diffusion
- adequate scaffolding to anchor transduction mechanisms
- catalytic effect (hydrophobic phase)

- osmotic control/regulation
- accessibility of simple molecules
- constructive use of conc. gradients

[Skulachev, V.P. 1992; Harold F. M., 1986]

Why postpone the appearance of compartments when they seem to be pivotal for the material-energetic implementation of a complex reaction system ??
(+later on: only makes integration problems worse!)



‘COMPARTIMENTALIST VIEW’: Morowitz, Deamer, Luisi, Szostak, Monnard...

'Autopoietic vesicles' (Pier Luigi Luisi)



Luisi (2003) "Autopoiesis: a review and a reappraisal" *Naturwissenschaften* 90:49-59

THE MINIMAL AUTOPOIETIC SYSTEM

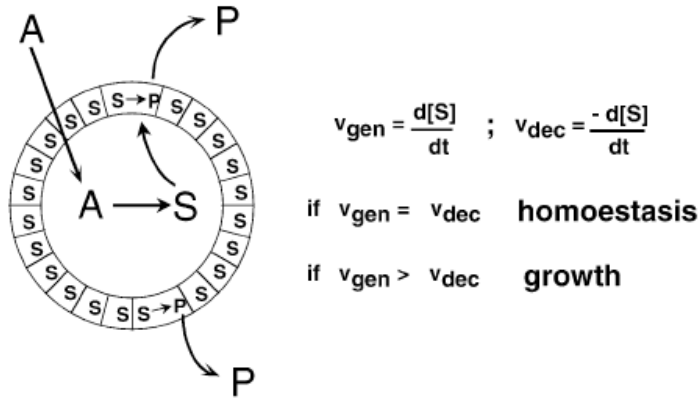


Fig. 4 The minimal autopoietic system. This system is characterized by two competitive reactions, one that builds the component of the boundary, and another one that destroys it. According to the relative value of these two velocity constants, the system can be in homeostasis, or grow, or die

a simple experimental model of chemical homeostasis

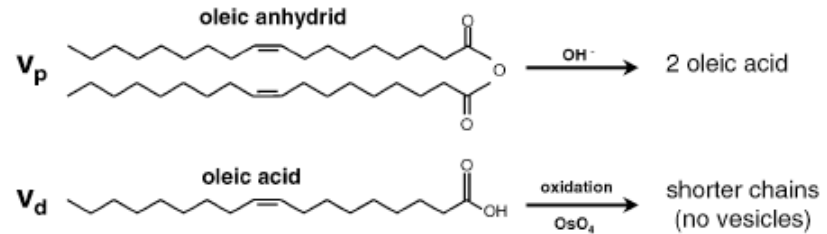
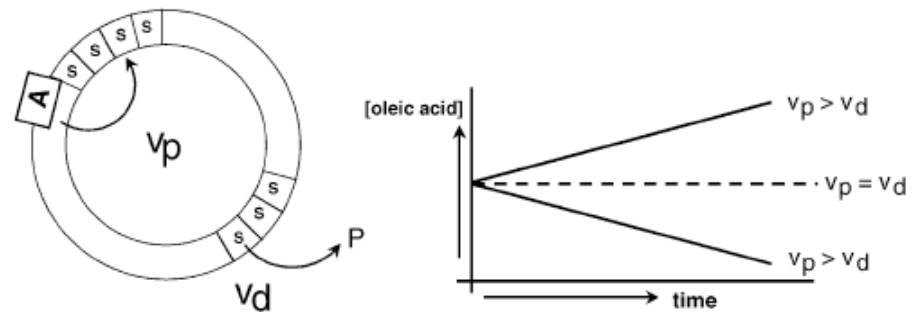


Fig. 8 The experimental implementation of the autopoietic model of Fig. 3 with two competitive reactions. Here, one reaction forms new oleate surfactant from the hydrolysis of the anhydride, and one reaction destroys oleate via oxidation of the double bond. Depending upon whether the two velocities are equal or not, different pathways for the systems are obtained—homeostasis (which corresponds to an autopoietic self-maintenance system), growth and self-reproduction, or decay and death (Zepik et al. 2001)

The Influence of Environmental Conditions, Lipid Composition, and Phase Behavior on the Origin of Cell Membranes

Jacquelyn A. Thomas • F. R. Rana

OPEN QUESTIONS (difficulties):

- high cac?
- pH dependence?
- sensitivity to salts?
- capacity to hold gradients?
- fatty acids or isoprenoids?

TABLE 2. ENCAPSULATION TRENDS OF CF OR tRNA
IN MIXED AND PURE SYSTEMS

System	CF	tRNA
8A	–	–
GM8/8A	–	–
10A	–	–
GM10/10A	–/+	+
12A	–/+	+
GM12/12A	+	+
18A	+	+
GM18/18A	+	+

(–) indicates no encapsulation; (–/+) indicates a leakage from the vesicles within 1 h; (+) indicates encapsulation was detectable after 1 h. All experiments were performed at room temperature, except for 12A (lauric acid), which was at 32°C.



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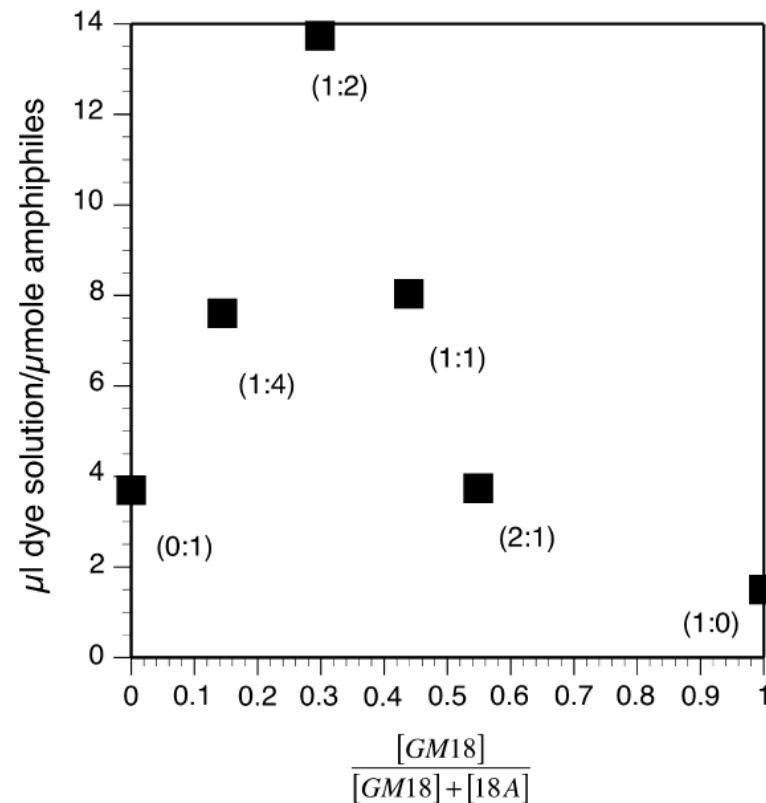
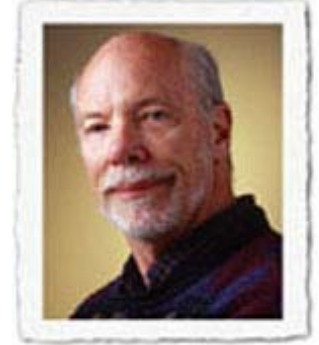


FIG. 2. Effect of the mixed bilayer composition (ratio of GM18 to 18A) on the encapsulation of pyranine. Ratio of [GM18] to [18A] is shown in parentheses; pH = 9.0.

Chemical Evolution of Amphiphiles: Glycerol Monoacyl Derivatives Stabilize Plausible Prebiotic Membranes

S.E. Maurer,^{1,2,3} D.W. Deamer,² J.M. Boncella,³ and P.-A. Monnard^{1,3}



Stability of Model Membranes in Extreme Environments

Trishool Namani • David W. Deamer

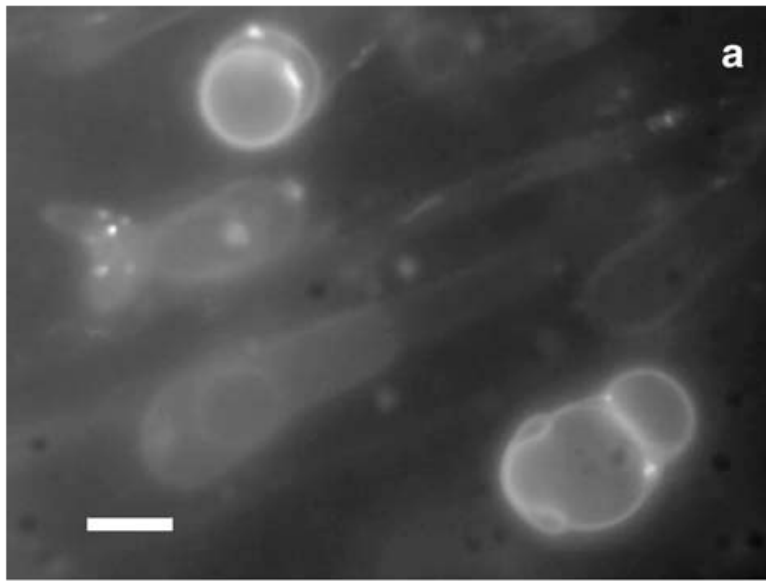


Fig. 5 Epifluorescence micrograph of decylamine/decanoic acid (25 mM each) vesicles in presence of **a** 0.1 M $MgCl_2$, **b** 0.1 M $CaCl_2$ and **c** sea salts 40 g/l. All the vesicles were prepared in 0.1 M borate at pH 2. The scale bars indicate 5 μm

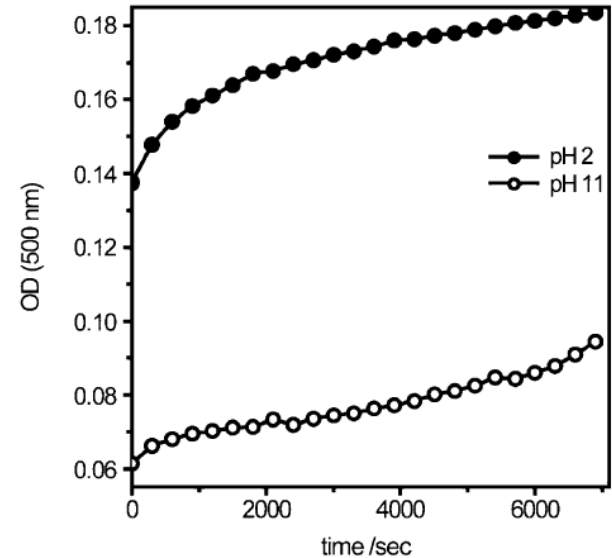


Fig. 7 The stability of decylamine (10 mM) and decanoic (10 mM) acid vesicles at pH 11 and pH 3 was monitored as turbidity changes over time, using absorbance at 500 nm to measure turbidity. Open circles correspond to vesicles at pH 11 and the closed circles correspond to pH 2. The vesicles were sonicated for 15 min in a bath sonicator before measuring the absorbance



MAIN SOLUTION to the problems:

continue experimental work

1) using MIXTURES!

(of ffaa, alcohols, other surfactants, etc.)

2) trying different CHEMISTRIES (reaction networks)
in those 'messy', heterogeneous conditions

General features of our simulation platform

- 1.- A flexible (object-oriented/C++) computational environment to simulate the dynamics of *chemically reacting* cellular systems
(e.g., minimal proto-metabolic cells, biological cells,...)
- 2.- *Stochastic kinetics (Gillespie method)*: tool to explore all possible dynamic behaviours
(including critical transitions at low population numbers,
role of noise, fluctuations,...)
- 3.- *Realistic* but not aiming to mimic nature (goal: to inform/complement *in vitro* models)
 - 3a. Not spatially-explicit, but vol/surf constraints calculated from molec. prop.
 - 3b. Water molecules not included, but buffering or osmotic effects into account
- 4.- *Heterogeneous* conditions (beyond the ‘well-stirred tank flow reactor’ hypothesis)
 - 4a. Various reactive domains/phases
 - 4b. Cell population dynamics
 - 4c. Transport processes between the different reactive domains
(‘molecular diffusion’, ‘gradient diffusion’, ‘aggregation process’,...)

[crucial point: coupling between transport and internal –or boundary– reaction proc.]

ENVIRONMENT: a computational platform to stochastically simulate reacting and self-reproducing lipid compartments

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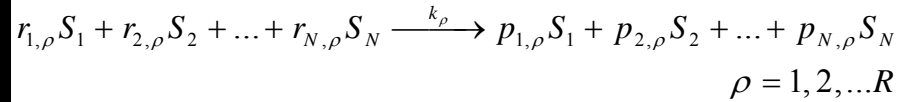
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Stochastic Kinetics (I)

Given a homogeneous, well-stirred, chemically reacting system, where N species S_n ($n=1,2,\dots,N$) can be transformed according to R different elementary reactions:



its time evolution is described in terms of the numbers of reactant molecules and requires solving the so-called *Master Equation*:

$$\frac{\partial P(\mathbf{X}, t | \mathbf{X}_0, t_0)}{\partial t} = \sum_{\Delta \mathbf{X}} \left[a(\mathbf{X} - \Delta \mathbf{X}, t) w(\Delta \mathbf{X}, | \mathbf{X} - \Delta \mathbf{X}, t) P(\mathbf{X} - \Delta \mathbf{X}, t | \mathbf{X}_0, t_0) \right] - a(\mathbf{X}, t) P(\mathbf{X}, t | \mathbf{X}_0, t_0)$$

that gives the rate of change of the probability density function $P(\mathbf{X}, t | \mathbf{X}_0, t_0)$.

Where:

$P(\mathbf{X}, t | \mathbf{X}_0, t_0) dt \equiv$ probability that the system will be in the state \mathbf{X} at time $t' \in [t, t+dt]$, if it was in \mathbf{X}_0 at the beginning.

$$a(\mathbf{X}) = \sum_{\rho=1}^R k_\rho \frac{\prod_j^N x_j (x_j - 1) \dots (x_j + 1 - r_{j,\rho})}{\Omega \left(\sum_j^N r_{j,\rho} \right)^{-1}}$$

$a(\mathbf{X}, t) dt \equiv$ probability that the process will jump away from state \mathbf{X} in the next infinitesimal time interval $[t, t+dt]$, given $\mathbf{X}(t)=\mathbf{X}$.

$$w(\Delta \mathbf{X}_\mu | \mathbf{X}) = \frac{\frac{k_\mu}{\Omega \left(\sum_j^N r_{j,\mu} \right)^{-1}} \prod_j^N x_j (x_j - 1) \dots (x_j - r_{j,\mu})}{a(\mathbf{X})}$$

$w(\Delta \mathbf{X} | \mathbf{X}, t) dt \equiv$ probability that the system, upon jumping away from state \mathbf{X} at time t , will land in state $\mathbf{X} + \Delta \mathbf{X}$.

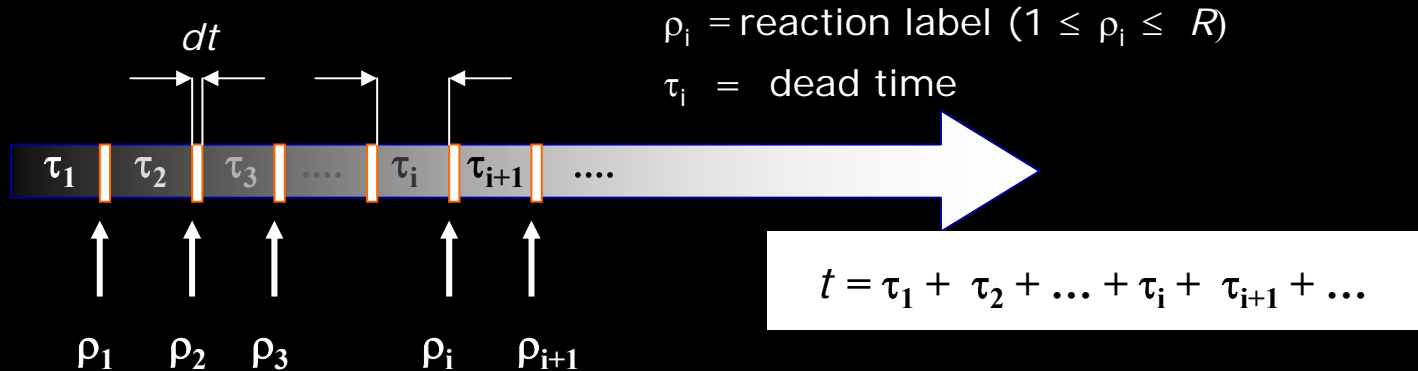
$\mathbf{X} = \|\mathbf{x}_1, \mathbf{x}_2, \mathbf{x}_3, \dots, \mathbf{x}_N\|$ ($x_j \equiv$ number of molecules of the j^{th} species)
 $k_\rho \equiv$ kinetic constant of the ρ -th reaction ; $\Omega = N_A V$ (\equiv scale factor)

Stochastic Kinetics (II)

• The Master Equation is very hard to solve analytically, but **Gillespie** introduced a Monte Carlo **method** to simulate the stochastic time evolution of a chemically reacting system.

• This approach allows to study reacting systems with very low molecular populations, as well as micro-dispersed. It is also possible to generalize it to deal with **heterogeneous cases** (complex organization!).

G's M: the stochastic time evolution of a reacting system can be seen as sequence of finite time intervals t_i , where nothing occurs (*dead times*), followed by an infinitesimal time interval dt where one of the possible reactions takes place:



It can be shown that by drawing two random number n_1 and n_2 uniformly distributed in the range $[0, 1]$ the following formulae can be used:

a) to stochastically simulate the dead time:

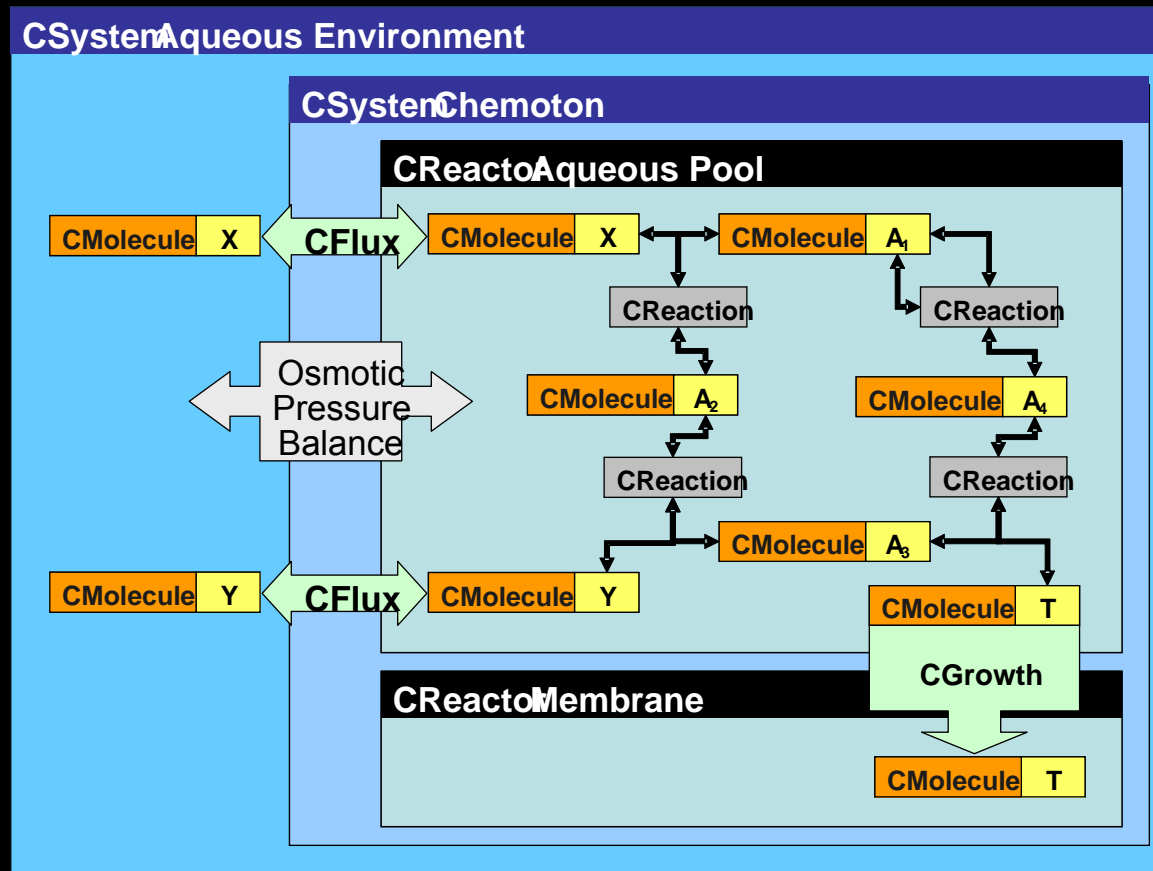
$$\tau = \frac{1}{a(\mathbf{x})} \ln\left(\frac{1}{n_1}\right)$$

b) to draw the next reaction:

$$\sum_{\mu=1}^{\rho-1} w(\Delta \mathbf{x}_{\mu} | \mathbf{x}) \leq n_2 a(\mathbf{x}) < \sum_{\mu=1}^{\rho} w(\Delta \mathbf{x}_{\mu} | \mathbf{x})$$

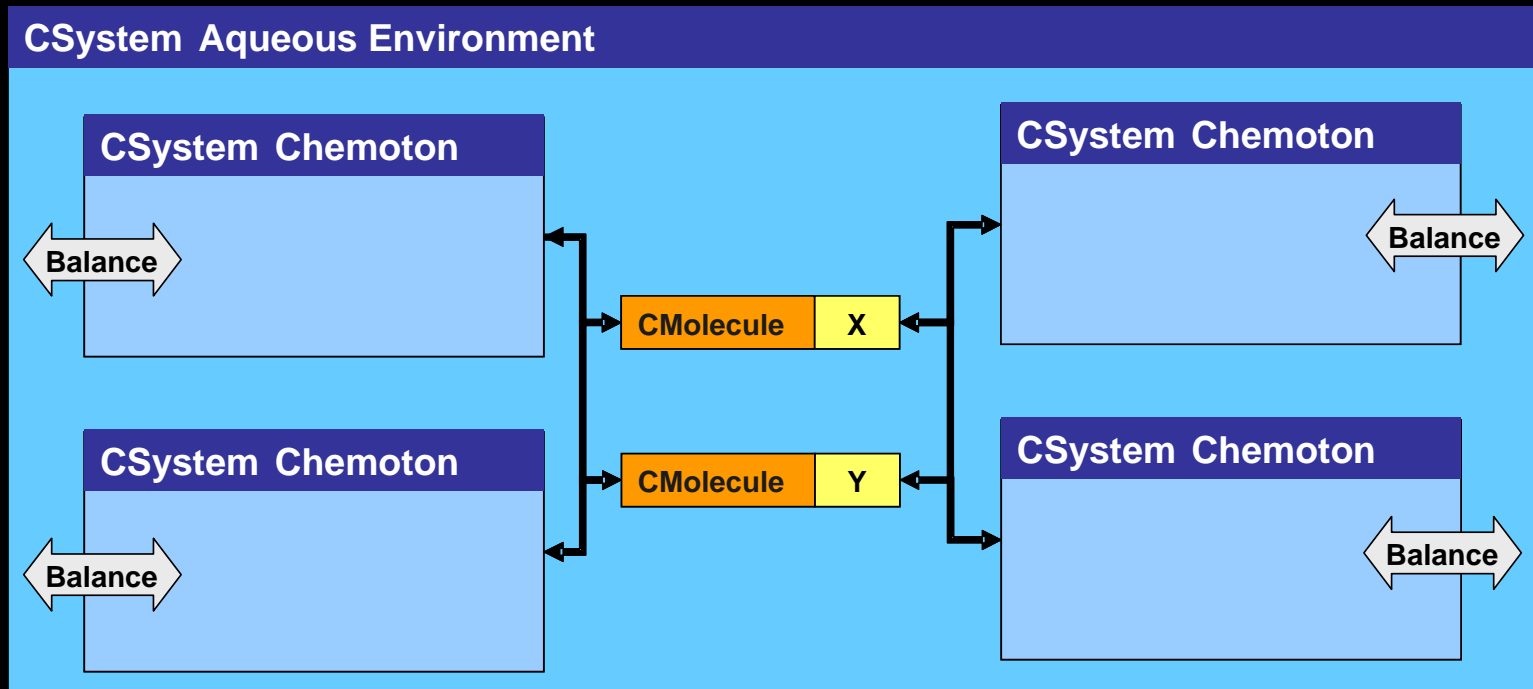
A new object-oriented computational environment to simulate complex chemically reacting systems (minimal proto-metabolic cells)

The object-oriented paradigm allows a one-to-one correspondence between objects in the real world and the abstract objects -or classes- in the code. In this case, the C++ classes *CSystem*, *CReactor*, *CMolecule*, *CFlux* and *CReaction* cooperate all together to perform the stochastic time evolution of a reacting system (minimal cell model) according to the master equation.



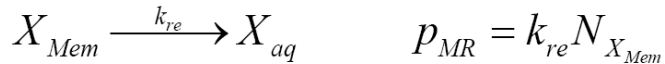
A new object-oriented computational environment (II)

The hierarchical structure of this programming language gives the possibility to build up quite easily increasing levels of complexity in the system (e.g., from a single reactor, in which self-maintenance or growth dynamics can be analysed, to a population of them, in which competitive behaviour and selective evolution could arise).



MOLECULAR_DIFFUSION

Membrane Release Density Probability

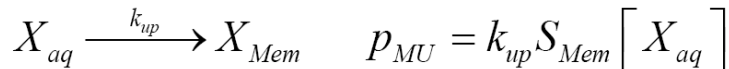


$N_{X_{Mem}}$ \equiv Number of X molecules in membrane [molecules]

k_{re} \equiv release constant [s^{-1}]

MEMBRANE_MOLECULAR_UPTAKE

Membrane Uptake Density Probability



S \equiv Membrane area [dm^2]

$[X_{aq}]$ \equiv aqueous concentration of X molecules [$mole/dm^3$]

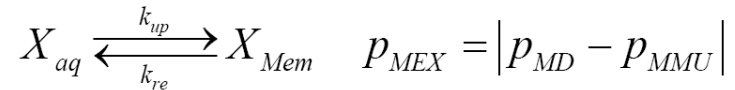
k_{up} \equiv uptake constant [$mole^{-1}s^{-1}dm$]

$$w_{L/C \rightarrow \mu}^J = k_{in} [x_{i,E/C}] S_{\mu} \exp\left(\frac{1-\phi}{\phi}\right)$$

MEMBRANE_MOLECULAR_EXCHANGE

Reaction

Density Probability



$$p_{MMU} = k_{up} S_{Mem} [X_{aq}]$$

$$p_{MD} = k_{re} N_{X_{Mem}}$$

The flux direction depends on the relative values of p_{MD} and p_{MMU} .

S \equiv Membrane area [dm^2]

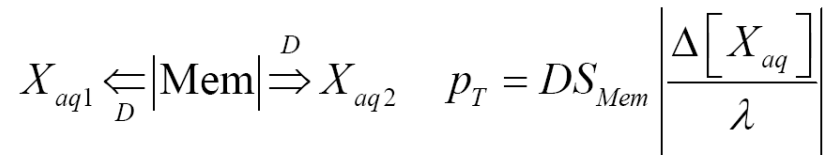
$[X_{aq}]$ \equiv aqueous concentration of X molecules [$mole/dm^3$]

$N_{X_{Mem}}$ \equiv Number of X molecules in the membrane [molecules]

MEMBRANE_TRANSPORT

Reaction

Density Probability



$$\Delta [X_{aq}] = [X_{aq1}] - [X_{aq2}]$$

S \equiv Membrane area [dm^2]

$[X_{aq}]$ \equiv aqueous concentration of X species [$mole/dm^3$]

λ \equiv Membrane thickness is fixed [$4.0e-8$ dm]

D \equiv Diffusion constant [$mole^{-1}s^{-1}dm^2$]

Our protocell model: main features/assumptions

[Mavelli & Ruiz-Mirazo: *Phil Trans. B* (2007)]

1) Realistic diffusion processes (passive transport) across the membrane, considering free flow of water

Overall isotonic condition:

$$C_{Total} = \frac{\sum_i^{Internal\ species} n_i}{N_A V_{Core}} = \frac{\sum_j^{External\ species} n_j}{N_A V_{Env}}$$

so:

$$V = \frac{\sum_i^{internal\ species} n_i}{\sum_j^{external\ species} n_j} V_{Env}$$

2) Conditions for division or an eventual 'osmotic crisis'

$$\sqrt[3]{36\pi V^2} = S_{sphere} < S < 2S_{sphere(V/2)} = 2\sqrt[3]{9\pi V^2}$$

• If: $S \leq \sqrt[3]{36\pi V^2}$ then: **OSMOTIC BURST!**

• When (or before): $S = 2\sqrt[3]{9\pi V^2}$ then: **DIVISION!**

Initially spherical



pre-division state



$$\Phi = S / \sqrt[3]{36\pi V^2}$$

$$1 \leq \Phi \leq \sqrt[3]{2}$$

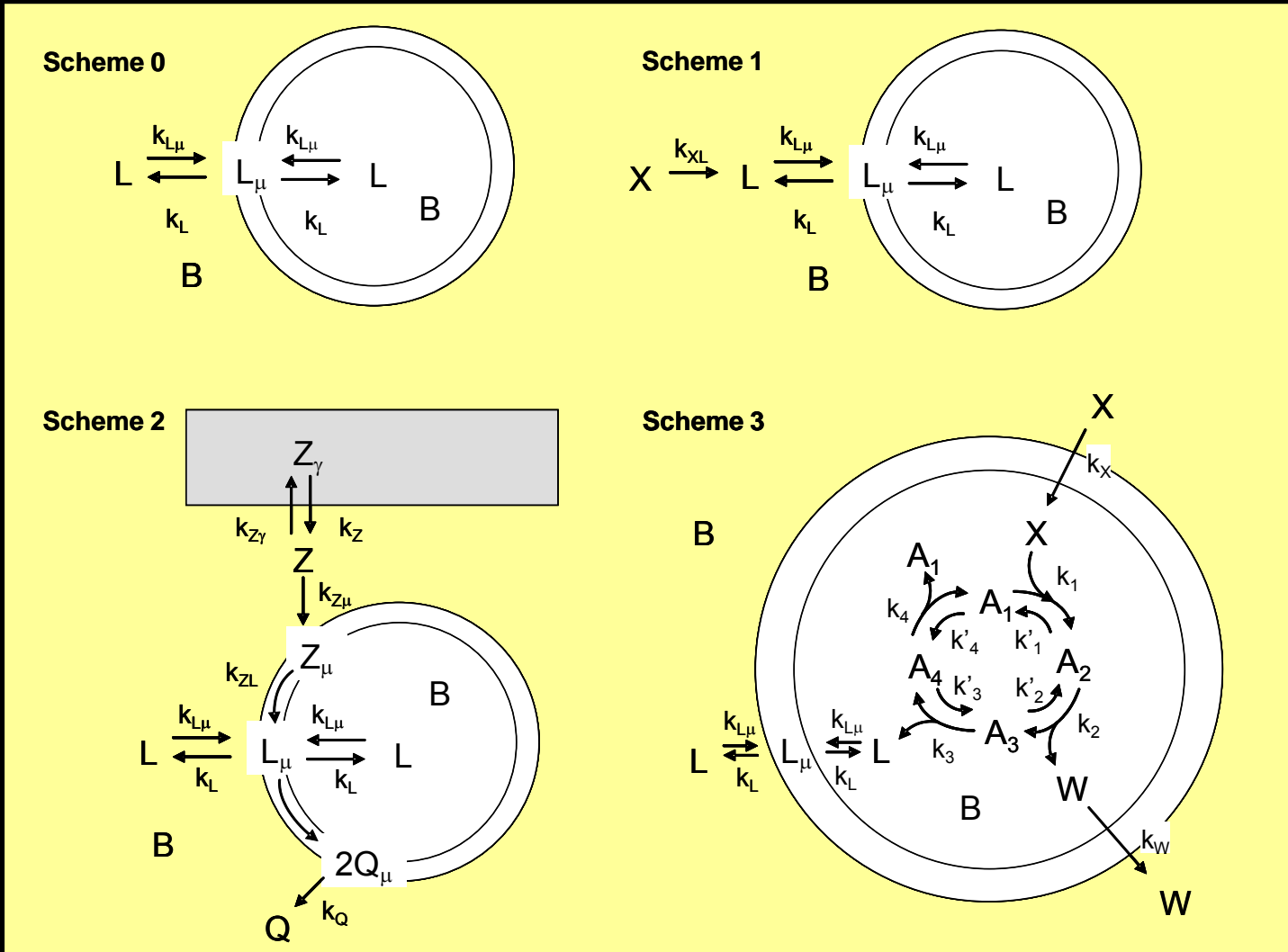
$$1 - \varepsilon \leq \Phi \leq (1 + \eta) \sqrt[3]{2}$$

$$(\varepsilon = \eta = 0.1)$$

$$0.9 \leq \Phi \leq 1.386$$

Minimal cell models

[Mavelli & Ruiz-Mirazo: *Phil Trans. B* (2007)]



Eq. condition: $k_{L\mu}[L]_{aq} S = k_L n_{L,mem}$

$$S \approx \alpha_L n_{L,mem} / 2$$

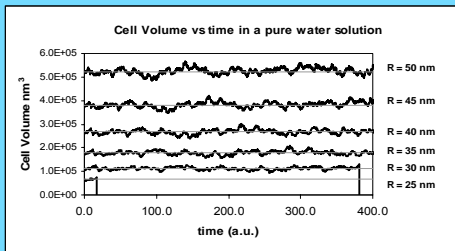
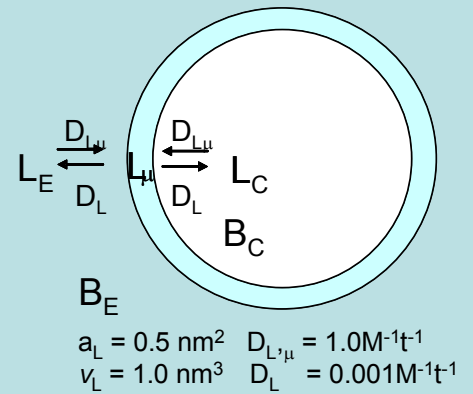
$$k_{L\mu} = 1.0 M^{-1}t^{-1} ; k_L = 0.001 t^{-1}$$

$$[L]_{aq} = \frac{k_L}{k_{L\mu}} \frac{2}{\alpha_L}$$

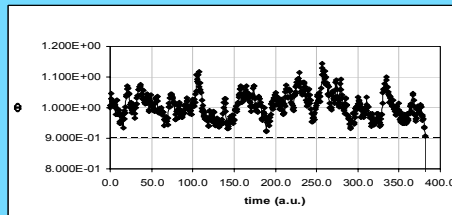
$$[L]_{eq} = 0.004 M$$

'Empty cell' dynamics

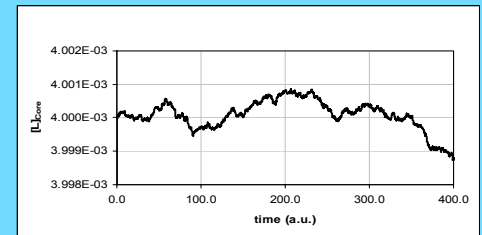
Spherical membranes with different radius (R) in a pure water solution continuously exchanging lipids L with the internal core and the external environment. As a consequence, the volume fluctuates around the initial spherical value $4/3\pi R^3$. In fact, these fluctuations bring small structures ($R \leq 30$) to collapse due to an osmotic crisis.



Stability of spherical membranes with different radius (R) in a pure water solution

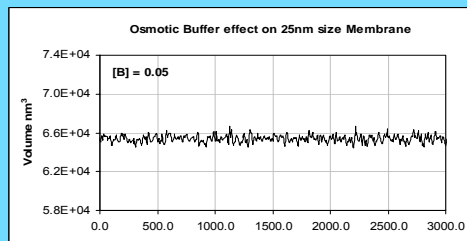


Φ stability factor reported against time for an initial spherical membrane of 30 nm radius. Φ fluctuates around 1.0 (i.e., the value of a perfect sphere).

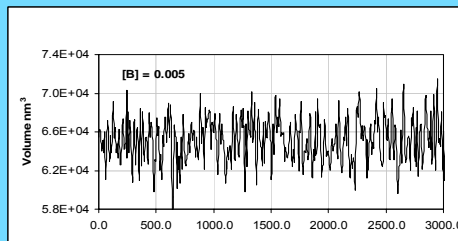


Cell water pool lipid concentration against time for a 50 nm radius membrane: $[L]_C$ fluctuates around the equilibrium value 0.004M.

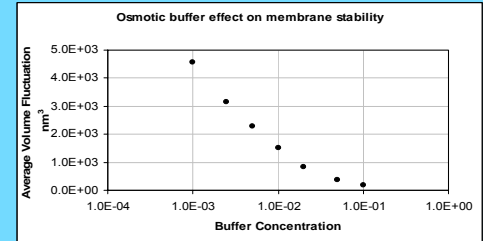
In the presence of an osmotic buffer B , the fluctuations of the core volume decrease as the buffer concentration increases and this enlarges size range for cell stability.



Osmotic buffer effect on the core volume fluctuations: $[B]_E = [B]_C = 0.05M$.



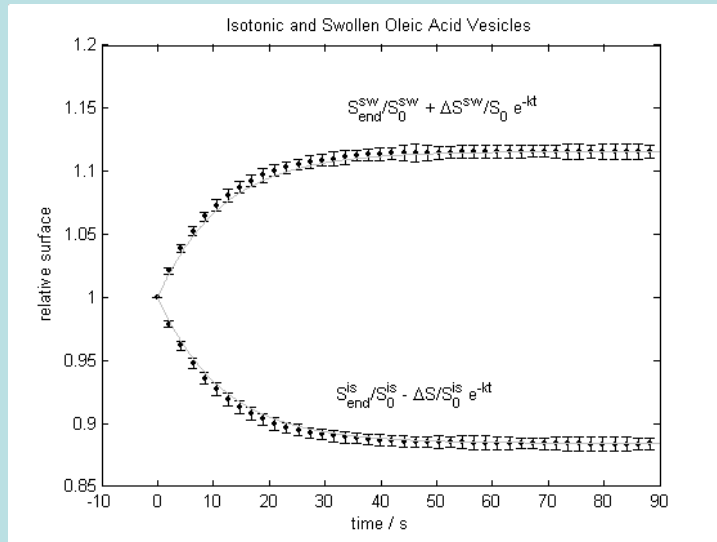
Osmotic buffer effect on the core volume fluctuations: $[B]_E = [B]_C = 0.005M$.



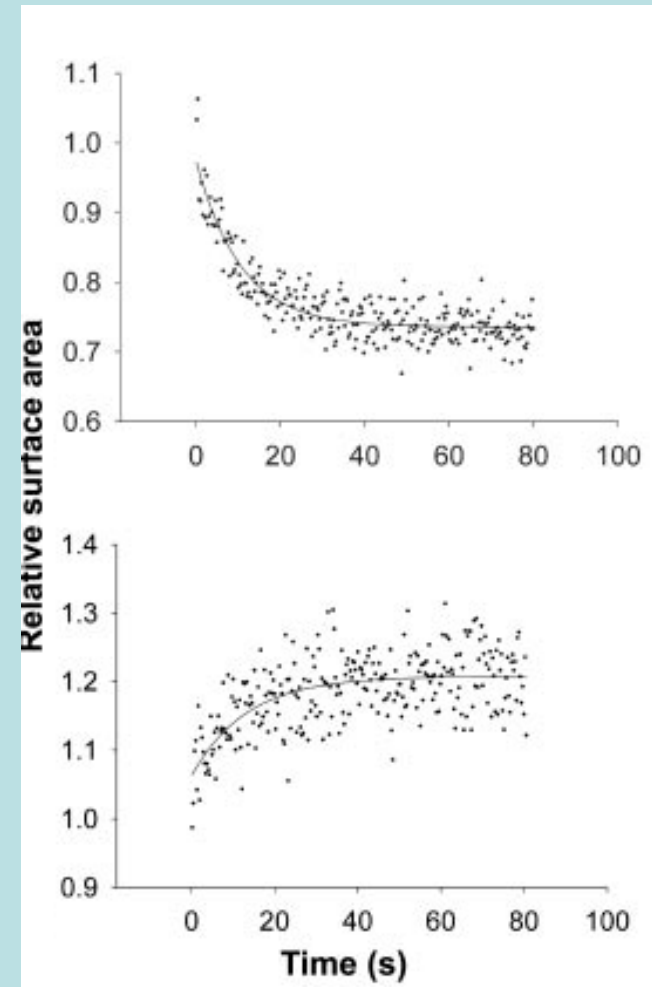
The average volume fluctuations are reported against buffer concentration

Reproducing real experimental data: swollen vs. deflated protocell competition dynamics

[Mavelli & Ruiz-Mirazo (2008): *BIOCOMP'08 Proceedings*]

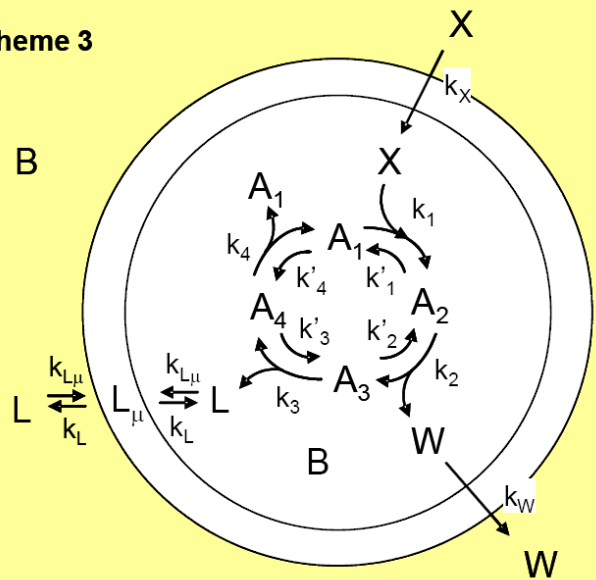


Parameters	Oleic Acid	POPC
k_{in}	$7.6 \cdot 10^3 \text{s}^{-1} \text{M}^{-1} \text{nm}^{-2}$	$7.6 \cdot 10^3 \text{s}^{-1} \text{M}^{-1} \text{nm}^{-2}$
k_{out}	$7.6 \cdot 10^{-2} \text{s}^{-1}$	$7.6 \cdot 10^{-7} \text{s}^{-1}$
$[L]_{Eq} (\phi=1)$	$6.667 \cdot 10^{-5} \text{M}$	$2.857 \cdot 10^{-10} \text{M}$
α	0.3 nm^2	0.7 nm^2
v	0.6 nm^3	1.3 nm^3
ε	0.21	0.59



[Chen et al. (2004): *Science* 305]

Scheme 3

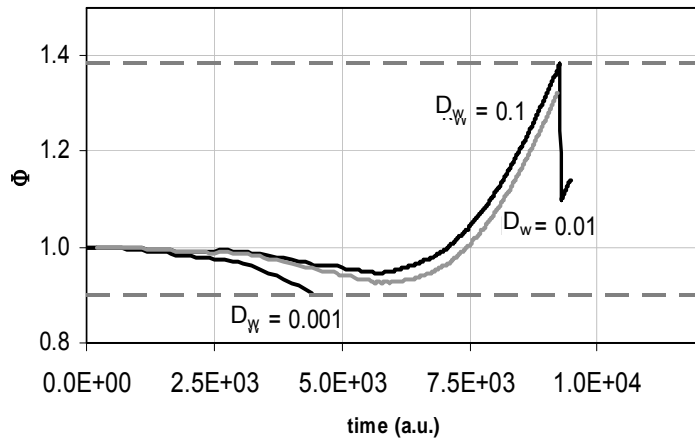


A 'proliferating microsphere'?

[Ganti T. 1975; 2002]

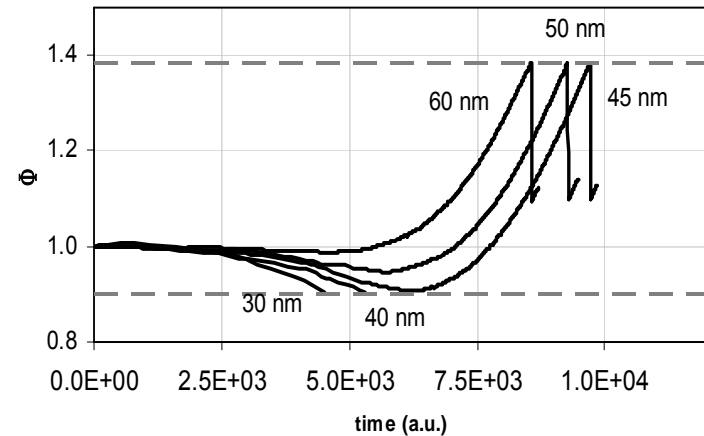
[Mavelli & Ruiz-Mirazo: Phil Trans. B (2007)]

Proto-Chemotons with different capability of throw out waste



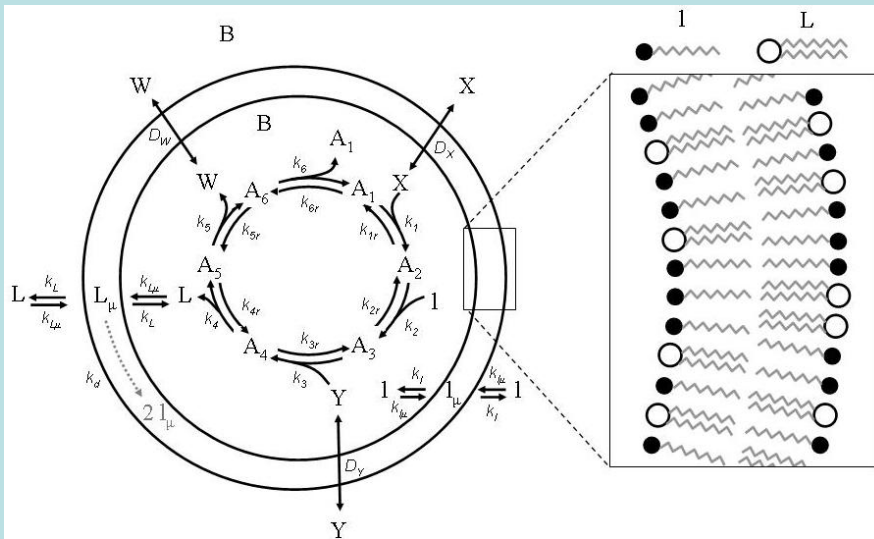
The permeability coefficient to waste results to be a fundamental parameter to guarantee the stability of the cell.

Proto-Chemotons with different initial radius

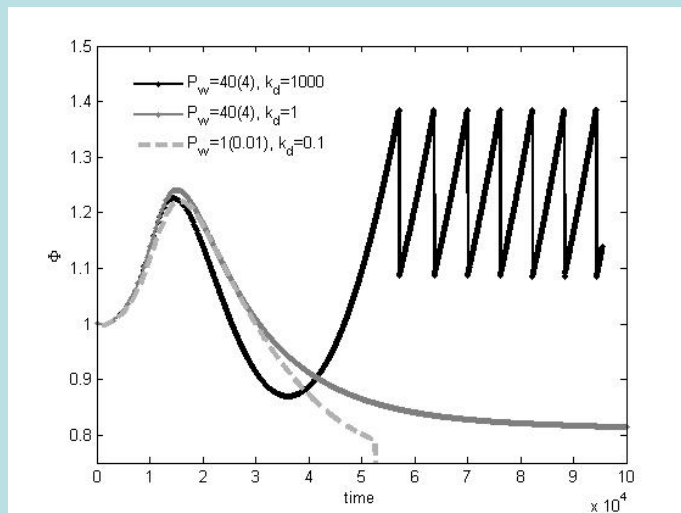
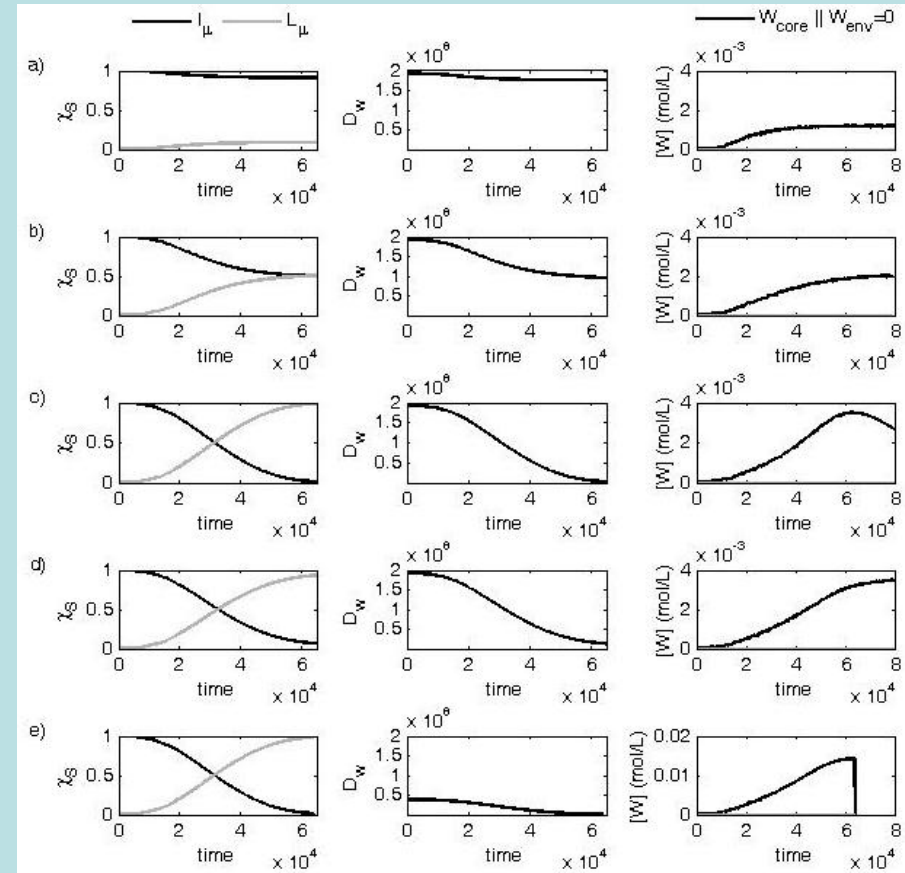


A critical size was found to overcome an eventual osmotic crisis. As much bigger is the size as higher are the stability and growth rate

Two-lipid membranes: FROM 'SELF-ASSEMBLY' TO 'SELF-PRODUCTION'



$k_i = 10, k_{tr} = 0.1, \text{ for } i=\{1-6\}; k_{\mu L} = k_{L\mu} = 7.6 \times 10^{19} \text{ s}^{-1} \text{ M}^{-1} \text{ dm}^2;$
 $k_1 = 4.56 \text{ s}^{-1}; k_L = 7.6 \times 10^{-2} \text{ s}^{-1}$
 $D_x = D_y = 4.62 \times 10^8 \text{ dm}^2 \text{ s}^{-1} \text{ mole}^{-1}; D_w^I = 1.93 \times 10^8 \text{ dm}^2 \text{ s}^{-1} \text{ mole}^{-1}; D_w^L = 5.40 \times 10^5 \text{ dm}^2 \text{ s}^{-1} \text{ mole}^{-1}$
 $[X]_{env} = [Y]_{env} = 0.001 \text{ M (constant)}; [W]_{env} = 0 \text{ (constant)}$
 $[I]_{env} = [I]_{core} = 4 \text{ mM}; [A_i]_{core} = 0.002 \text{ M}; [B] = 0.2 \text{ M (other initial concentrations set to zero)}$



[Piedrafita et al. 2009 ECAL Proc.]

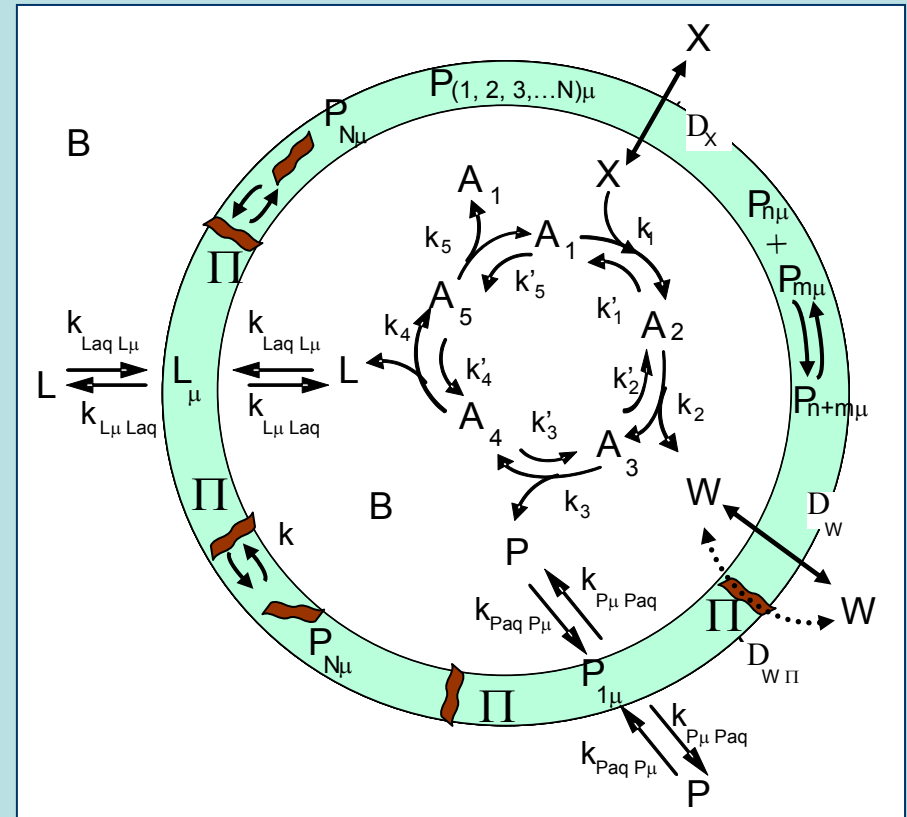
[Ruiz-Mirazo et al. 2010 AEMB, Springer Series]

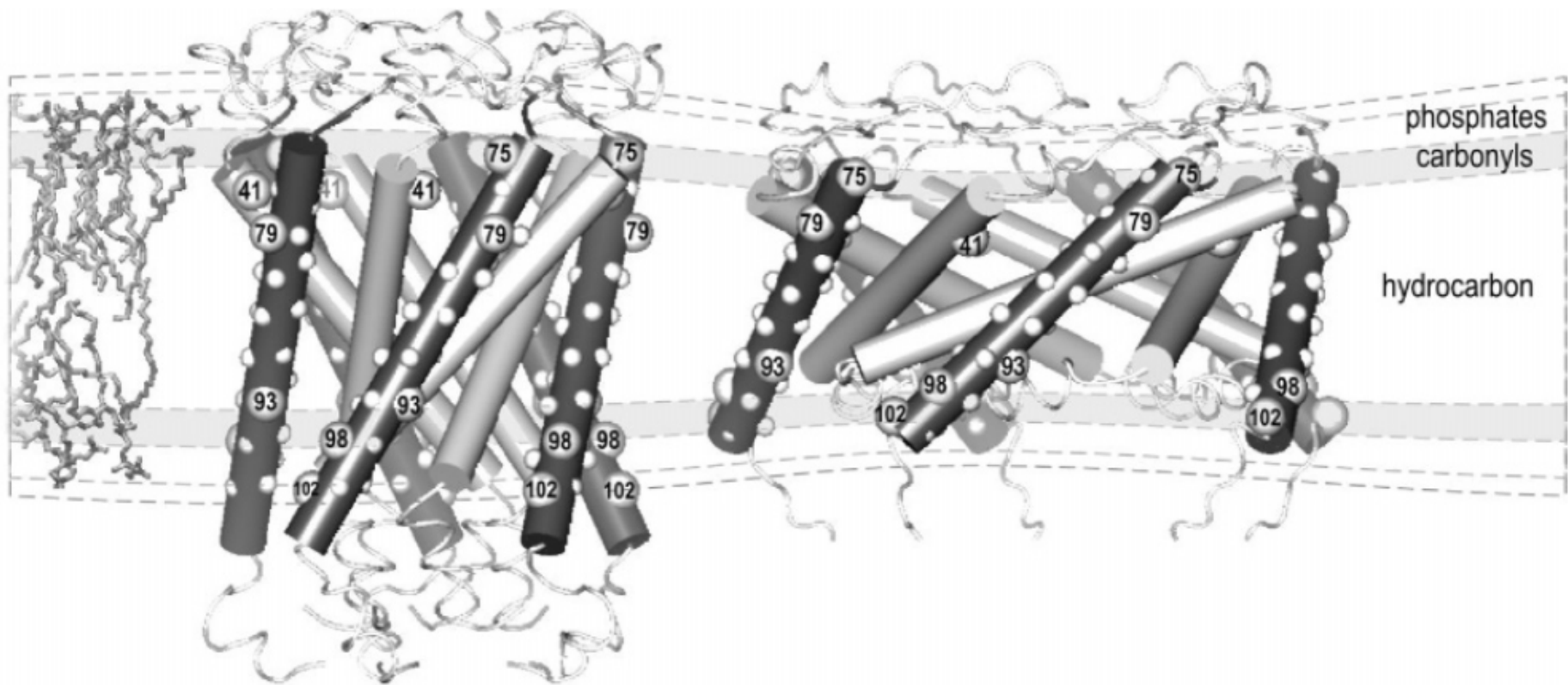
Modelling minimal self-(re-)producing 'lipid-peptide' cells (+ osmotic regulation)

[Ruiz-Mirazo & Mavelli (2008): *BioSystems* 91(2)]

[Ruiz-Mirazo & Mavelli (2007): *ECAL Proceedings*]

Cell Metabolic Network	
$A_1 + X \xrightleftharpoons[k_{2,1}]{k_{1,2}} A_2$	
$A_2 \xrightleftharpoons[k_{3,2}]{k_{2,3}} A_3 + W$	$k_{2,3} = k_{3,4} = k_{4,5} = k_{5,1} = 1.0$ $k_{3,2} = k_{4,3} = k_{5,4} = k_{1,5} = 0.1$ $k_{2,1} = 0.1$ $k_{1,2} = 1.0$
$A_3 \xrightleftharpoons[k_{4,3}]{k_{3,4}} A_4 + P$	
$A_4 \xrightleftharpoons[k_{5,4}]{k_{4,5}} A_5 + L$	
$A_5 \xrightleftharpoons[k_{1,5}]{k_{5,1}} 2A_1$	
Membrane Molecular Uptake and Release	
$(P_1)_{in} \xrightleftharpoons[k_{P_{\mu}P_{aq}}]{k_{P_{aq}P_{\mu}}} (P_1)_{\mu} \xrightleftharpoons[k_{P_{aq}P_{\mu}}]{k_{P_{\mu}P_{aq}}} (P_1)_{out}$	$k_{L_{aq}L_{\mu}} = 1.0 \quad k_{L_{\mu}L_{aq}} = 10^{-3}$ $k_{P_{aq}P_{\mu}} = 1.0 \quad k_{P_{\mu}P_{aq}} = 10^{-4}$
$(L)_{in} \xrightleftharpoons[k_{L_{\mu}L_{aq}}]{k_{L_{aq}L_{\mu}}} (L)_{\mu} \xrightleftharpoons[k_{L_{aq}L_{\mu}}]{k_{L_{\mu}L_{aq}}} (L)_{out}$	
Membrane Reactions	
$P_n + P_m \xrightleftharpoons[k_{B(n,m)}]{k_{G(n,m)}} P_{n+m}$	$k_{G/B}(n,m) = \begin{cases} 0 & \text{if } n+m > 20 \\ k_{G/B} & \text{if } n+m \leq 20 \end{cases}$ $k_G = 100 \quad k_B = 0.1$
$P_{20} \xrightleftharpoons[k_{\Pi P}]{k_{P\Pi}} \Pi$	$k_{P\Pi} = 100 \quad k_{\Pi P} = 50$
Molecular Transport Processes	
$(X)_{Env} \xrightleftharpoons{D_X} (X)_{Core}$	$D_X = 40$ $D_W = 4$ $D_{W\Pi} = 400$
$(W)_{Env} \xrightleftharpoons{D_W} (W)_{Core}$	
$(W)_{Env} \xrightleftharpoons[(\Phi < 1)]{D_{W\Pi}(\Pi)_{\mu}} (W)_{Core}$	





Coevolution of metabolic networks and membranes: the scenario of progressive sequestration

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DOI 10.1002/bies.200800226

Problems and paradigms

Peptide-dominated membranes preceding the genetic takeover by RNA: latest thinking on a classic controversy

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TIBS-654; No of Pages 10

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Review

Cell
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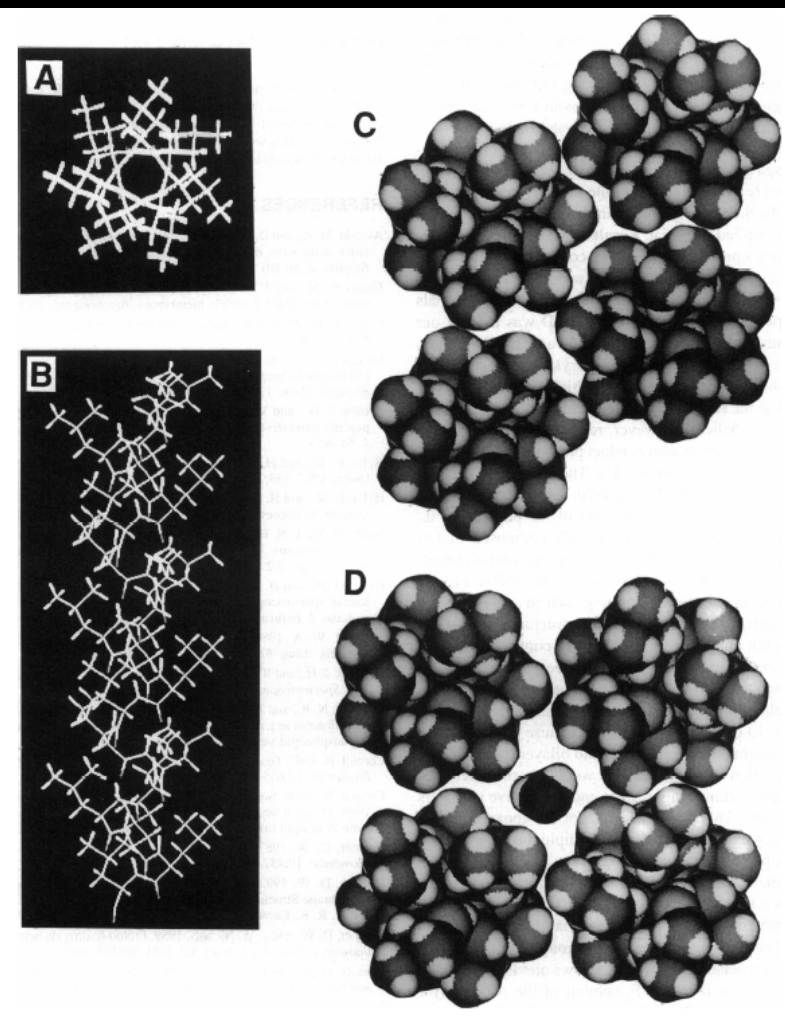
Co-evolution of primordial membranes and membrane proteins

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α -Helical Hydrophobic Polypeptides Form Proton-Selective Channels in Lipid Bilayers

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ABSTRACT Proton translocation is important in membrane-mediated processes such as ATP-dependent proton pumps, ATP synthesis, bacteriorhodopsin, and cytochrome oxidase function. The fundamental mechanism, however, is poorly understood. To test the theoretical possibility that bundles of hydrophobic α -helices could provide a low energy pathway for ion translocation through the lipid bilayer, polyamino acids were incorporated into extruded liposomes and planar lipid membranes, and proton translocation was measured. Liposomes with incorporated long-chain poly-L-alanine or poly-L-leucine were found to have proton permeability coefficients 5 to 7 times greater than control liposomes, whereas short-chain polyamino acids had relatively little effect. Potassium permeability was not increased markedly by any of the polyamino acids tested. Analytical thin layer chro-

FIGURE 13 Computer-generated α -helical aggregates. Polyleucine α -helices (20 residues) were produced with MacIcmdad software (Molecular Applications Group, Stanford University, Stanford CA). The backbone structure is shown from above in 13 A, and in side view in 13 B. CPK space-filling versions of the top view were then fitted to show the 3a structure (13 C), described by Furois-Corbin and Pullman (1986), which excludes water, and the 4a structure (13 D), which may include a chain of water molecules. Certain pentameric aggregates (not shown) have ample room to provide an aqueous channel. The bundles of α -helices shown here are for illustration only. No attempt was made to find energy-optimized structures.

Review

The Origin and Early Evolution of Membrane Channels

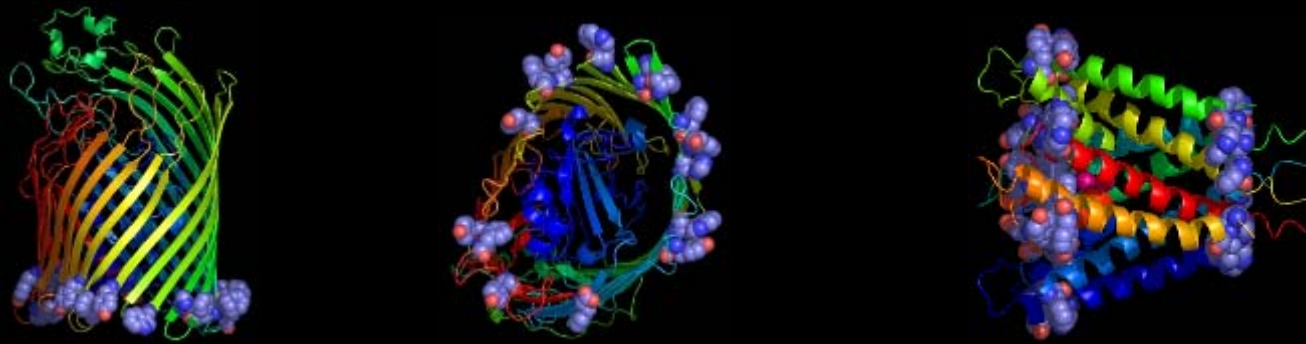
ANDREW POHORILLE,^{1,2} KARL SCHWEIGHOFER,^{1,3} and MICHAEL A. WILSON^{1,2}

ABSTRACT

The origin and early evolution of ion channels are considered from the point of view that the transmembrane segments of membrane proteins are structurally quite simple and do not require specific sequences to fold. We argue that the transport of solute species, especially ions, required an early evolution of efficient transport mechanisms, and that the emergence of simple ion channels was protobiologically plausible. We also argue that, despite their simple structure, such channels could possess properties that, at the first sight, appear to require markedly greater complexity. These properties can be subtly modulated by local modifications to the sequence rather than global changes in molecular architecture. In order to address the evolution and development of ion channels, we focus on identifying those protein domains that are commonly associated with ion channel proteins and are conserved throughout the three main domains of life (Eukarya, Bacteria, and Archaea). We discuss the potassium-sodium-calcium superfamily of voltage-gated ion channels, mechanosensitive channels, porins, and ABC-transporters and argue that these families of membrane channels have sufficiently universal architectures that they can readily adapt to the diverse functional demands arising during evolution. **Key Words:** Ion channels–Ion transport–Folding of membrane proteins–Protocells. *Astrobiology* 5, 1–17.

Aromatic residues of actual membrane proteins:

typically located in the transition zone between the low dielectric lipid interior and the polar lipid head groups



www.dur.ac.uk/.../science/peptide_lipid/pl.html



Thank you!