Dynamics of and ancient RNA world: impasses and challenges

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Albert Eschenmoser:

The best minds in chemistry should move to origin of life research!

You will probably never know how it *happened*, but we might well agree upon how it *could have happened*

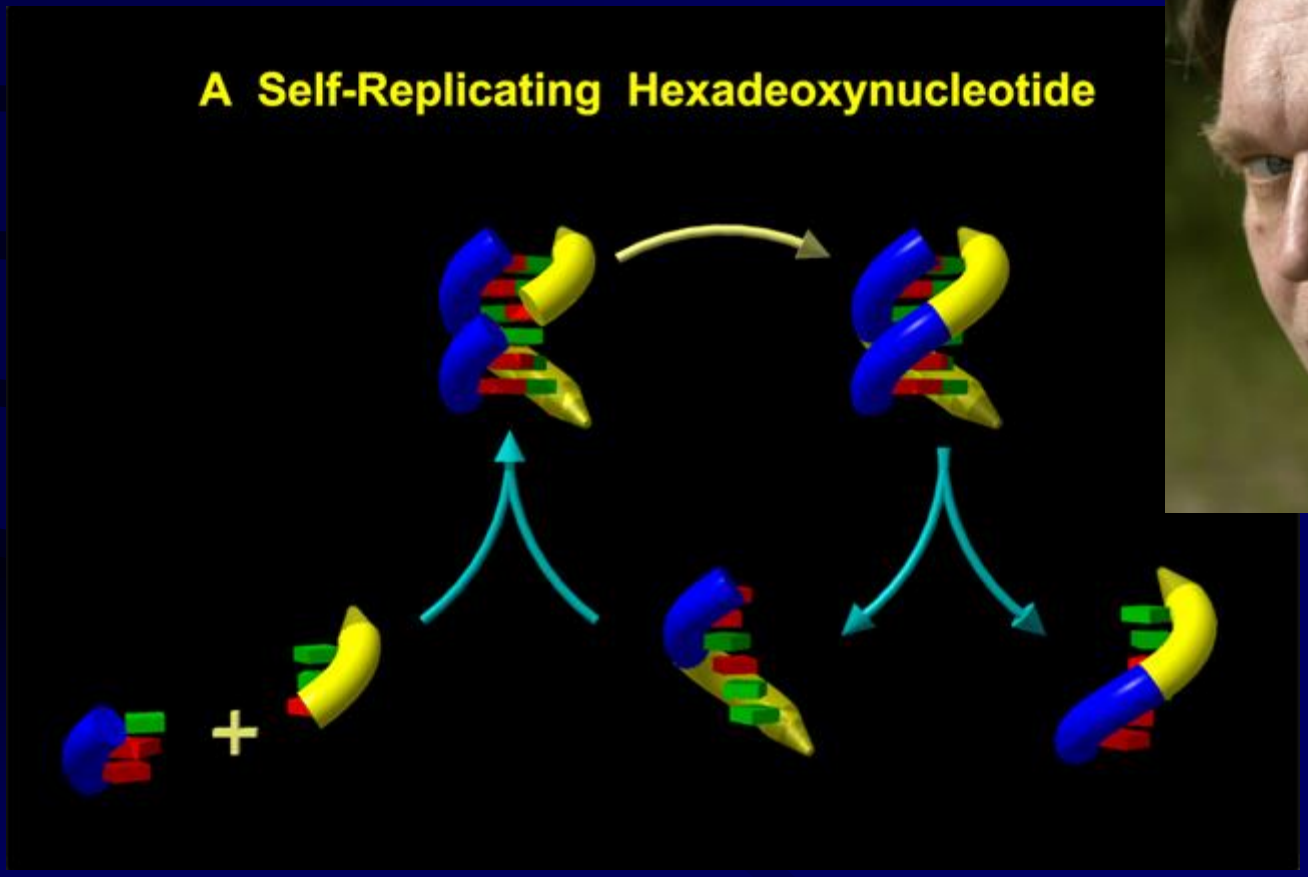
The centrality of autocatalysis

- Replication from a chemical point of view always rests on autocatalysis
- The basic form is

  $A + X \rightarrow 2\ A + Y$

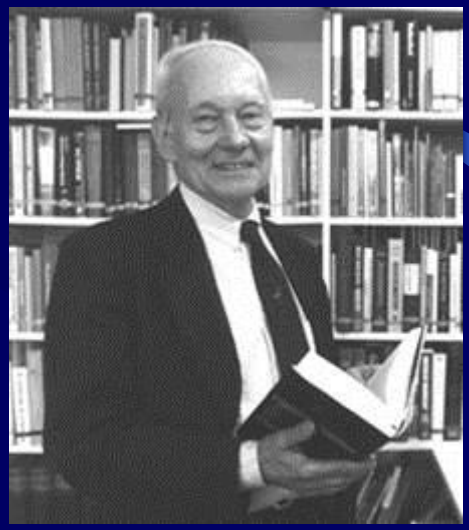
- very important for biology
- Much more general than DNA

Von Kiedrowski's replicator

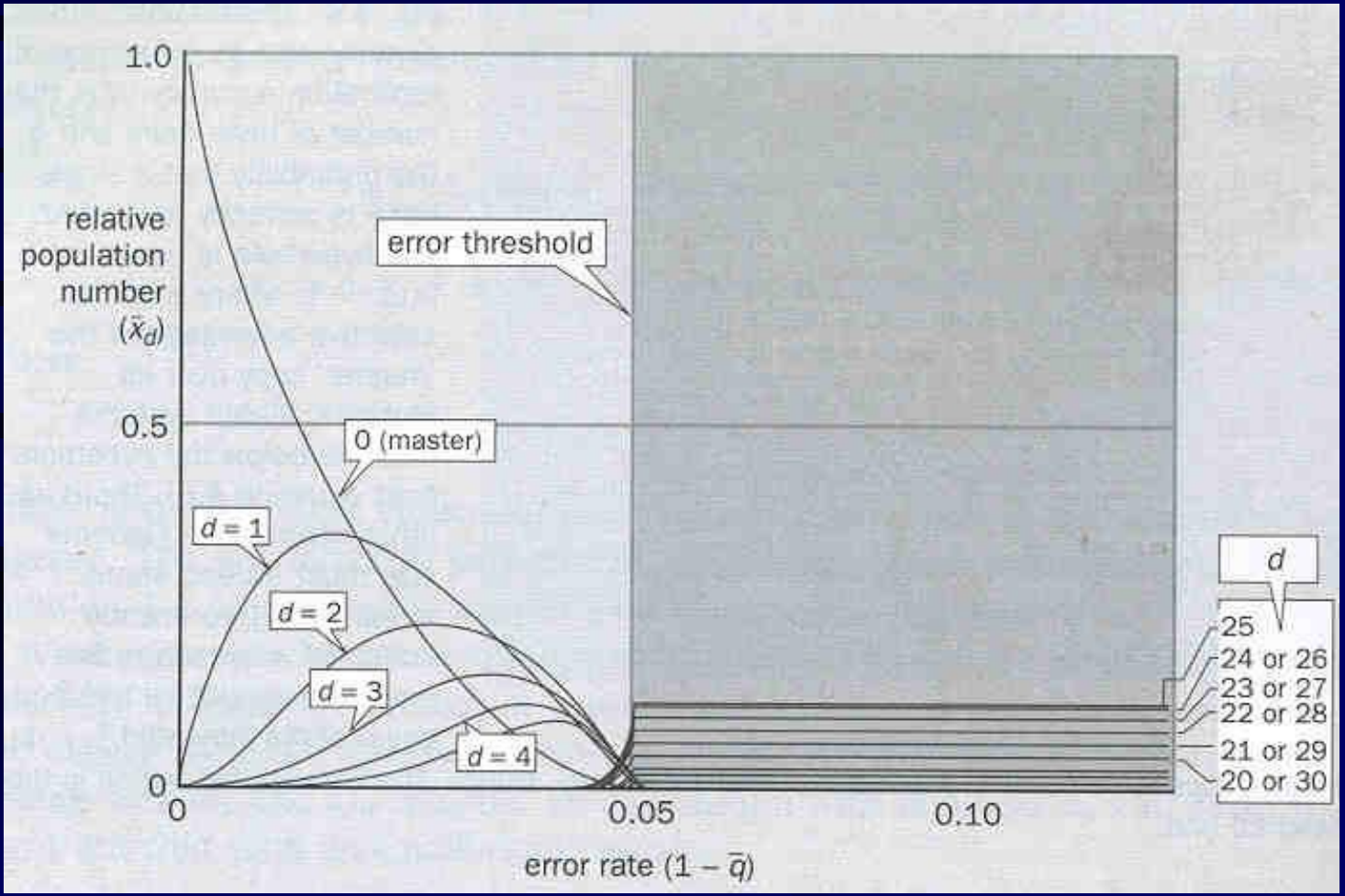


A crucial insight: Eigen's paradox (1971)

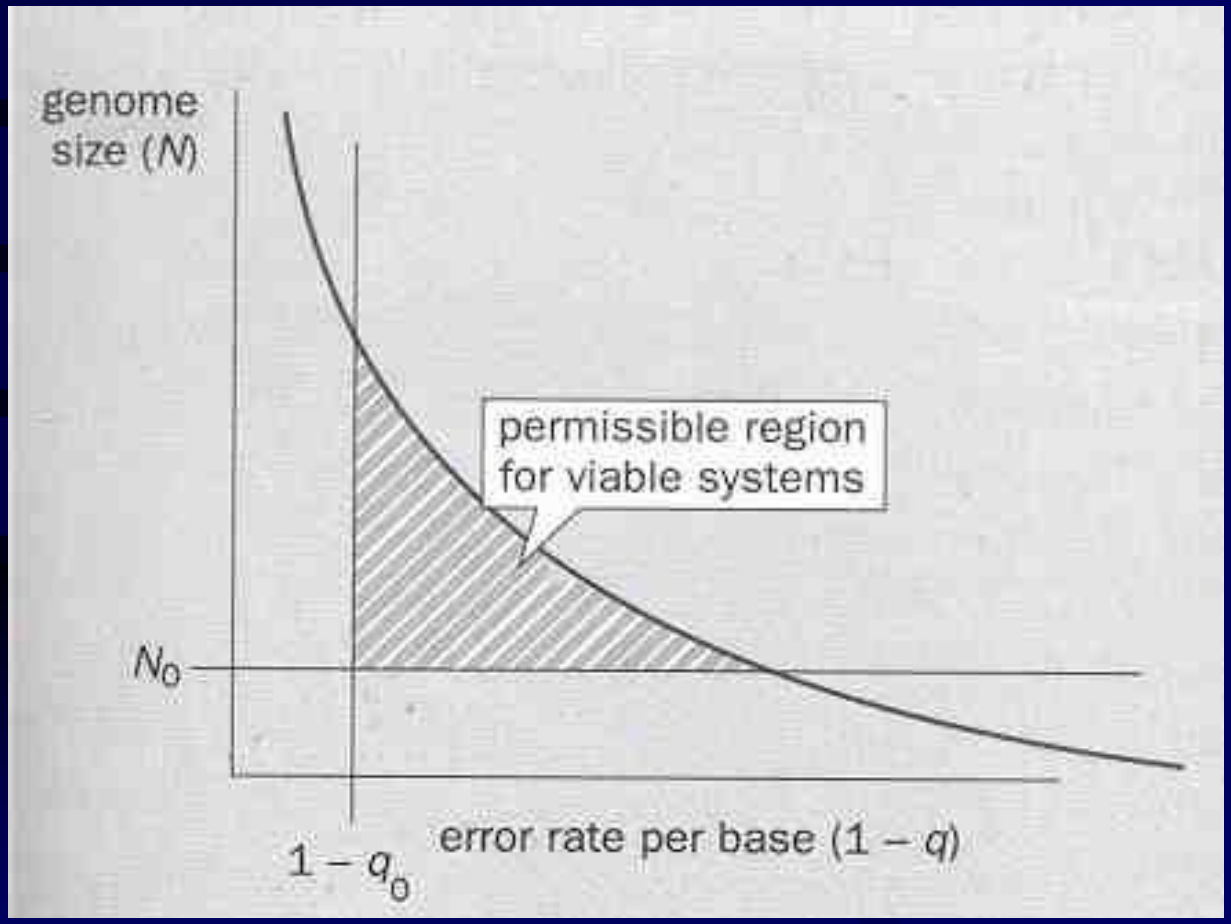
- Early replication must have been error-prone
- Error threshold sets the limit of maximal genome size to <100 nucleotides
- Not enough for several genes
- Unlinked genes will compete
- Genome collapses
- Resolution???



The error threshold:

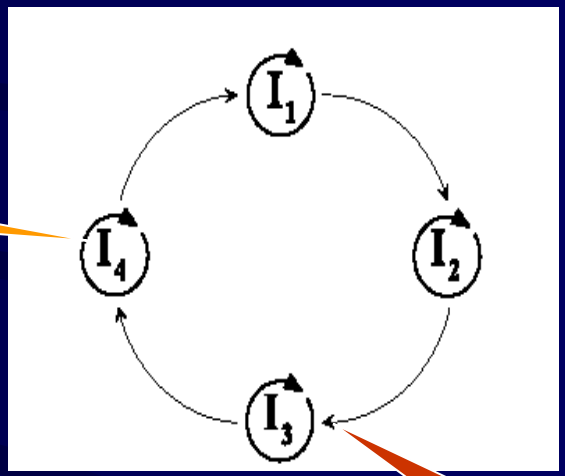


The maximal length of a genome is inversely proportional to the error rate:



Molecular hypercycle (Eigen, 1971)

autocatalysis



heterocatalytic aid

Catalysis of a catalytic replication cycle: SECOND-order autocatalysis!!!

Szathmáry *Journal of Systems Chemistry* 2013, **4**:1
http://www.jsystchem.com/content/4/1/1

JOURNAL OF SYSTEMS CHEMISTRY

COMMENTARY Open Access

On the propagation of a conceptual error concerning hypercycles and cooperation

Eörs Szathmáry[1,2,3]

$$\mathrm{I}_2 + \mathrm{R}_1 \xrightarrow{k_1} \mathrm{I}_1 + \mathrm{I}_2$$

$$\mathrm{I}_1 + \mathrm{R}_2 \xrightarrow{k_2} \mathrm{I}_2 + \mathrm{I}_1.$$

"The three-membered cycle shown here resembles a hypercycle as envisioned previously but without hyperbolic growth."

"Vaidya *et al*. show that variants of such RNA fragments can assemble and act on one another to form cooperative self-assembly cycles very much like the proposed hypercycles, in which ribozyme 1 aids assembly of ribozyme 2; 2 aids 3; and 3 aids 1"

$$\mathrm{I}_1 + \mathrm{I}_2 + \mathrm{R}_1 \xrightarrow{k_1} 2\mathrm{I}_1 + \mathrm{I}_2$$

$$\mathrm{I}_2 + \mathrm{I}_1 + \mathrm{R}_2 \xrightarrow{k_2} 2\mathrm{I}_2 + \mathrm{I}_1,$$

An interesting suggestion to overcome the replicase problem (Ellington)

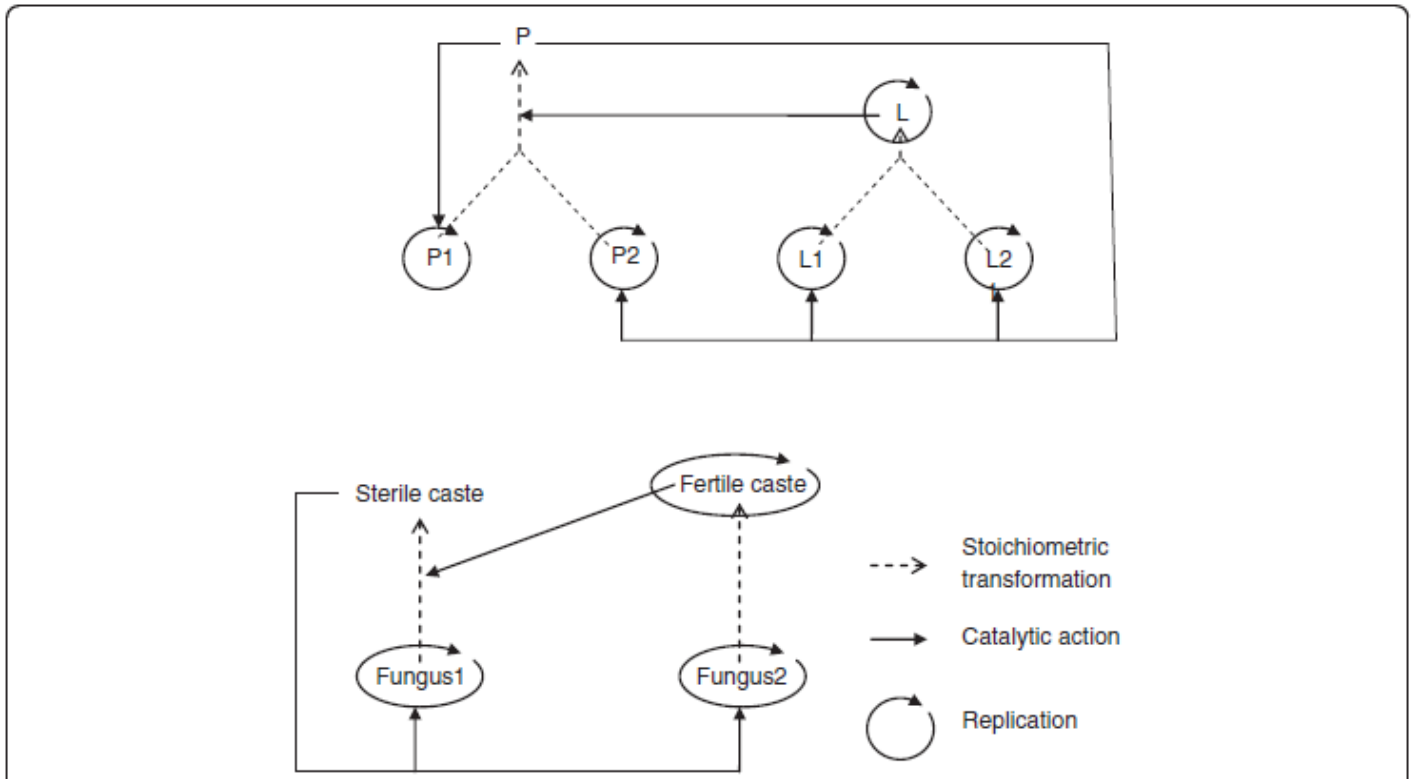
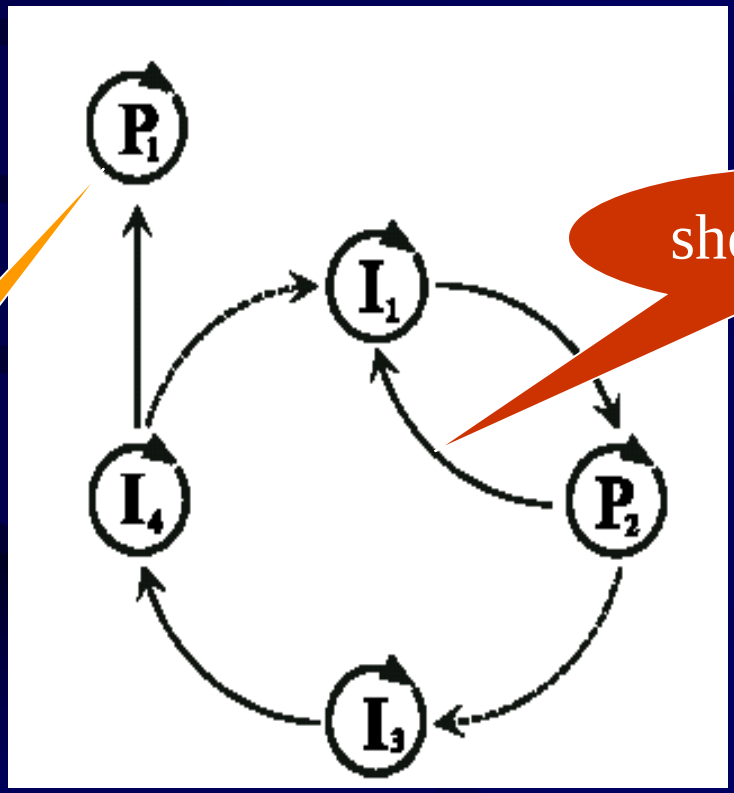


Figure 1 A non-hypercyclic molecular network [24] with multiple 'trophic levels' (*top*) and a possible biological analogue (*bottom*). P1 and P2: replicating oligomers as building blocks of polymerase P. L1 and L2: replicating oligomers as building blocks of ligase L.

Parasites in the hypercycle (JMS)



short circuit

parasite

Without a solution we would not be here...

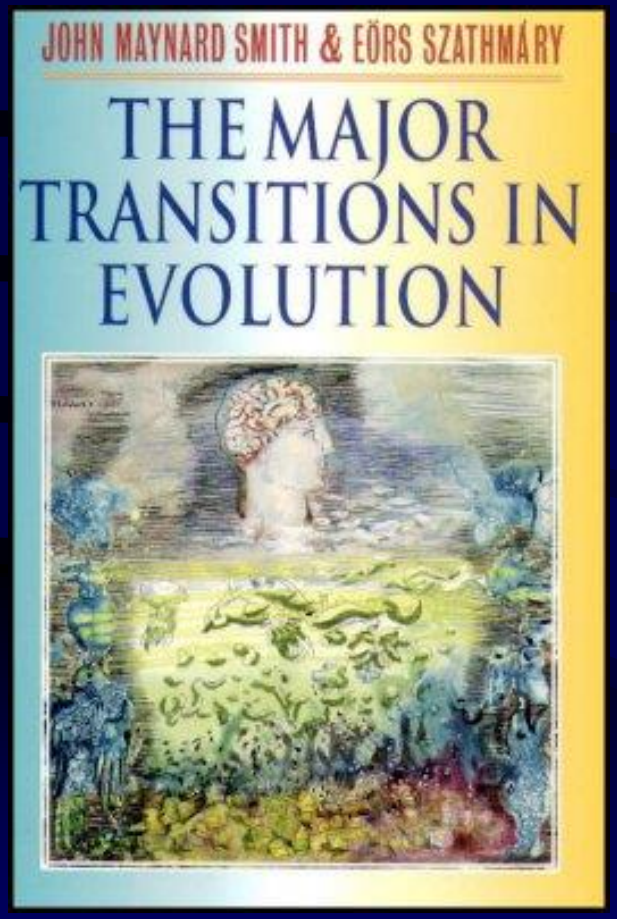


Table 1. The major transitions in evolution

Before	*After*
Replicating molecules	Populations of molecules in protocells
Independently replicating genes	Chromosomes
RNA as gene and enzyme	DNA genes, protein enzymes
Bacterial cells (prokaryotes)	Cells with nuclei and organelles (eukaryotes)
Asexual clones	Sexual populations
Single-celled organisms	Animals, plants and fungi
Solitary individuals	Colonies with non-reproductive castes
Prelinguistic societies	Human societies with language

Reproduced from Maynard Smith J and Szathmáry E (1999) *The Origins of Life. From the Birth of Life to the Origin of Language.* Oxford: Oxford University Press.

A forgotten mechanism

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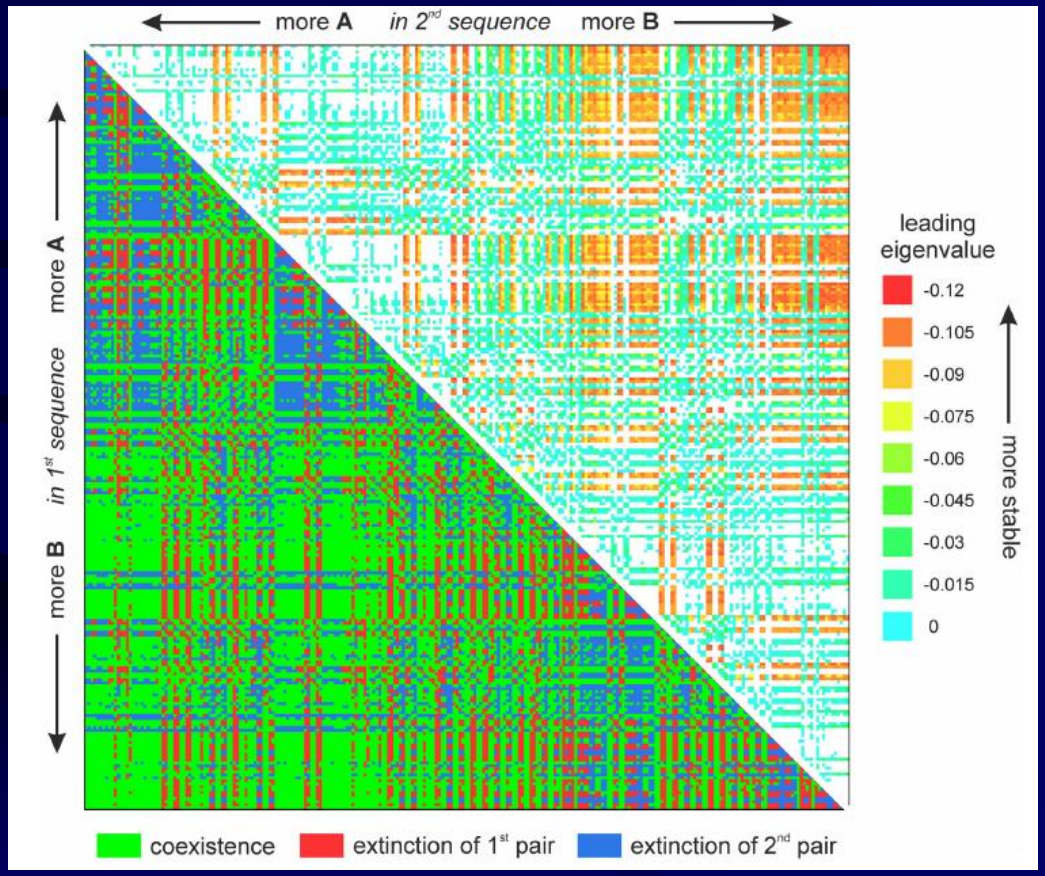
PLOS | COMPUTATIONAL BIOLOGY

Gause's Principle and the Effect of Resource Partitioning on the Dynamical Coexistence of Replicating Templates

András Szilágyi[1,2,3], István Zachar[3], Eörs Szathmáry[1,2,3]*

- The dynamical theory of competing templates has not yet taken the effect of sequences explicitly into account. One might think that complementary sequences have very limited competition only.
- We show that, despite interesting sequence effects, competing template replicators yield to Gause's principle of competitive exclusion so that the number of stably coexisting template species cannot exceed the number of nucleotide species on which they grow, although one of the findings is that plus and minus strands together count as one species.
- Thus up to four different templates/ribozymes can constitute the first steps to an early, segmented genome: we suggest that other mechanisms build on this baseline mechanism.

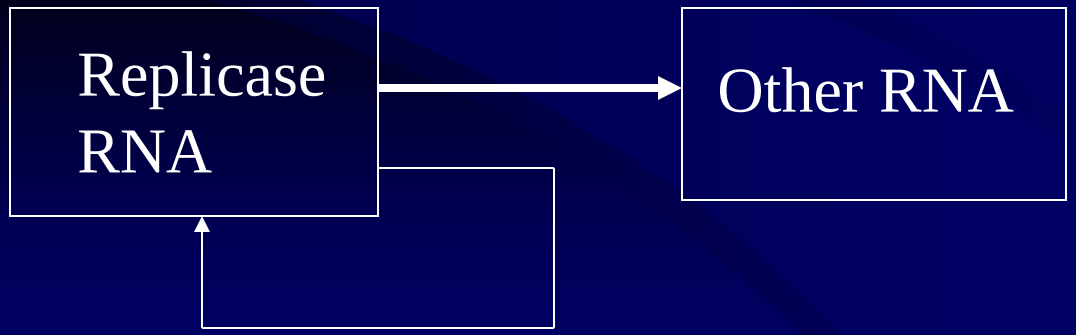
Sequence-dependent outcome of competition



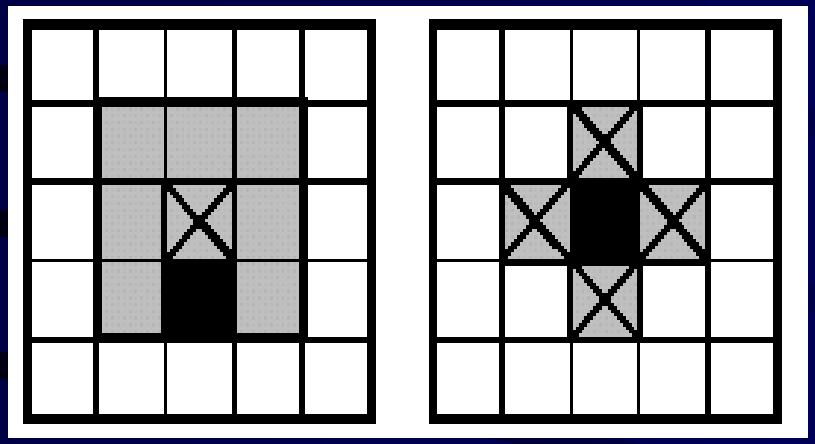
***In silico* simulations reveal that replicators with limited dispersal evolve towards higher efficiency and fidelity**

Péter Szabó*†, István Scheuring*, Tamás Czárán* & Eörs Szathmáry*‡

Nature **420,** 360-363 (2002).



A cellular automaton simulation



Metabolic Replication

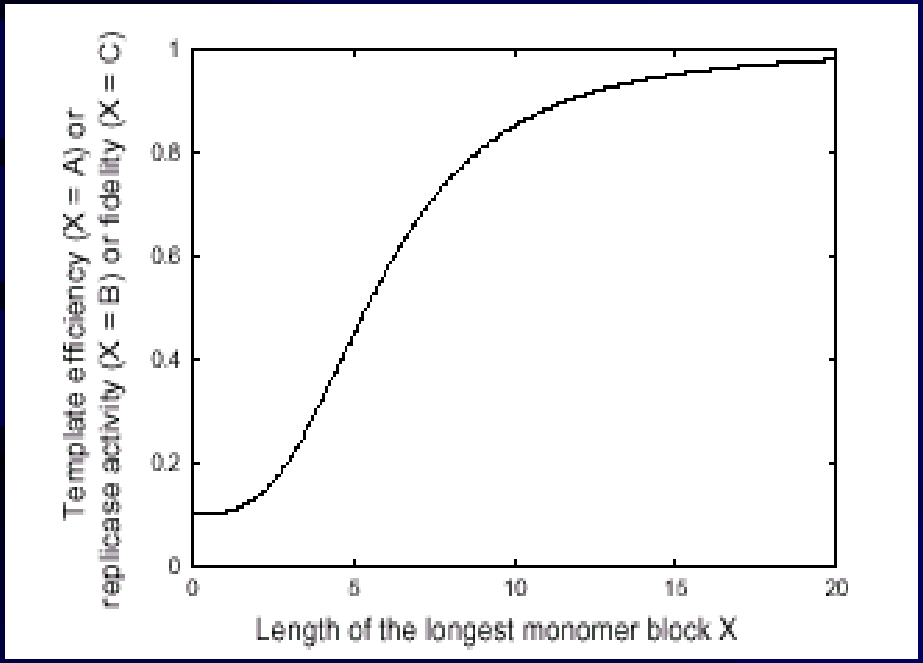
Grey sites: neighbourhood

Black: empty site

X: potential mothers

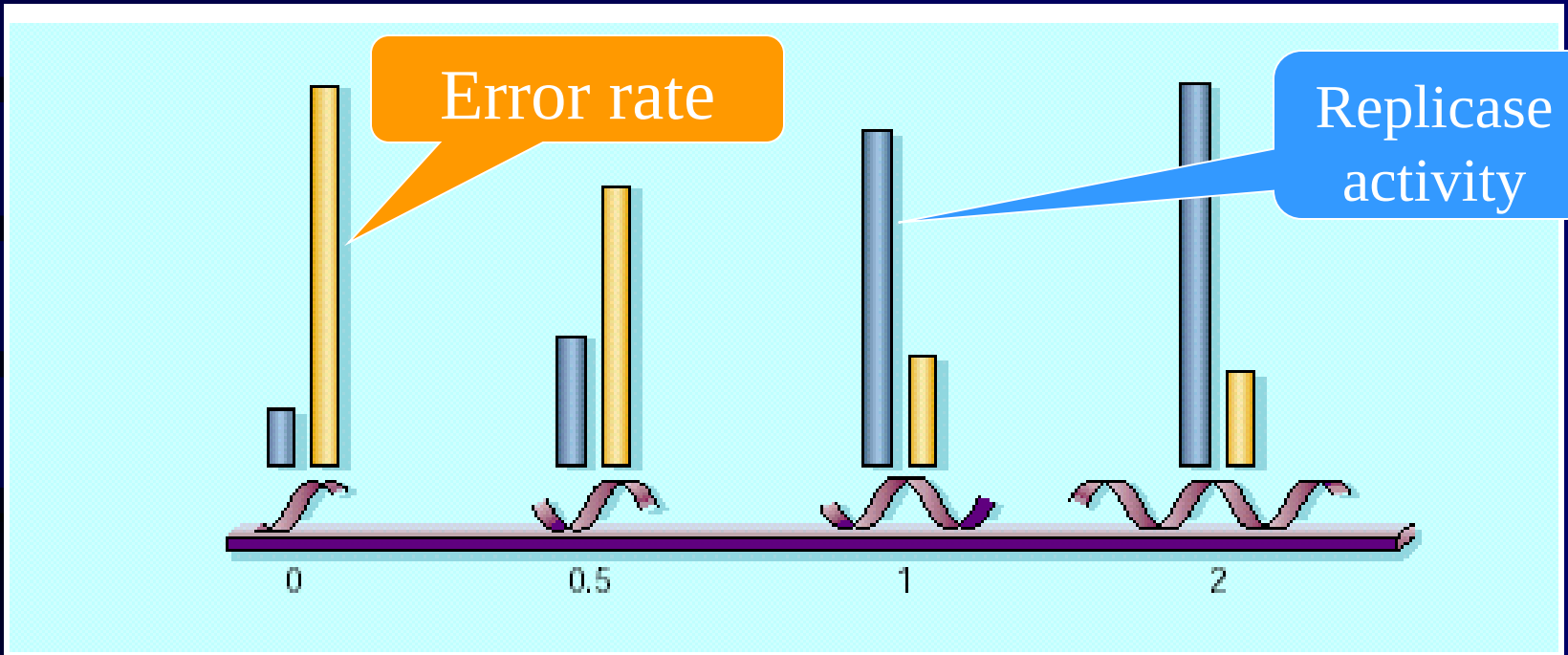
- Reaction: template replication
- Diffusion (Toffoli-Margolus algorithm)
- Metabolic neighbourhood respected

Maximum as a function of molecule length



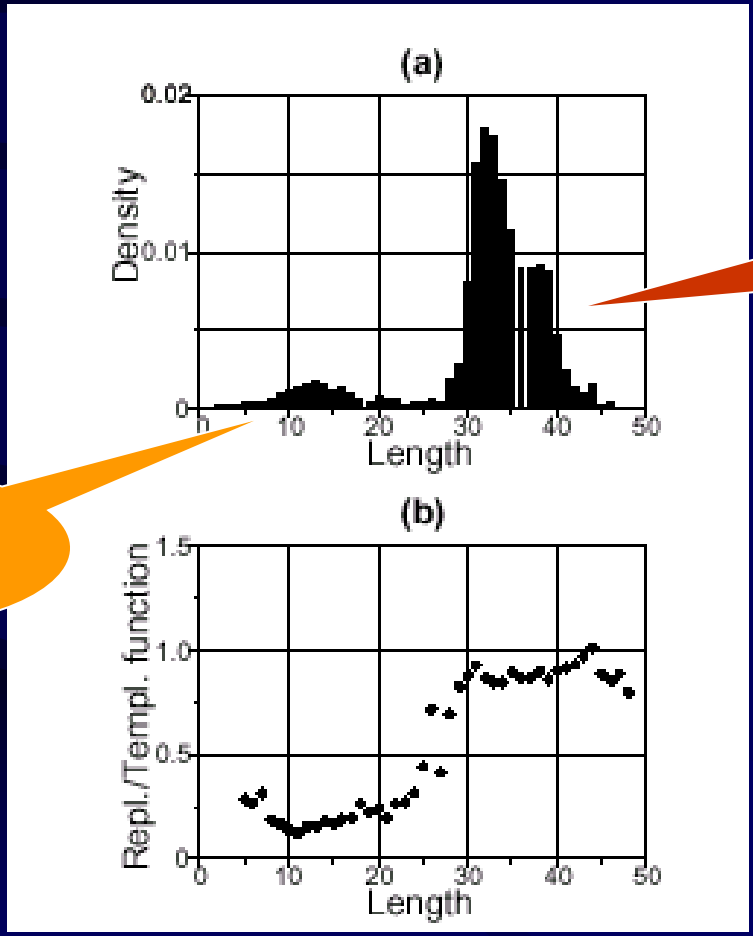
- Target and replicase efficiency
- Copying fidelity
- Trade-off among all three traits: worst case

Evolving population



- Molecules interact with their neighbours
- Have limited diffusion on the surface

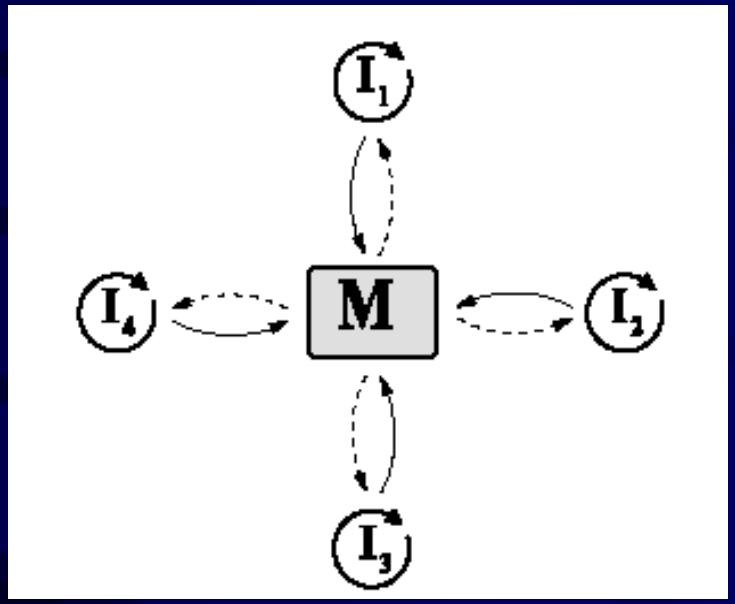
‘Stationary’ population



efficient replicases

parasites

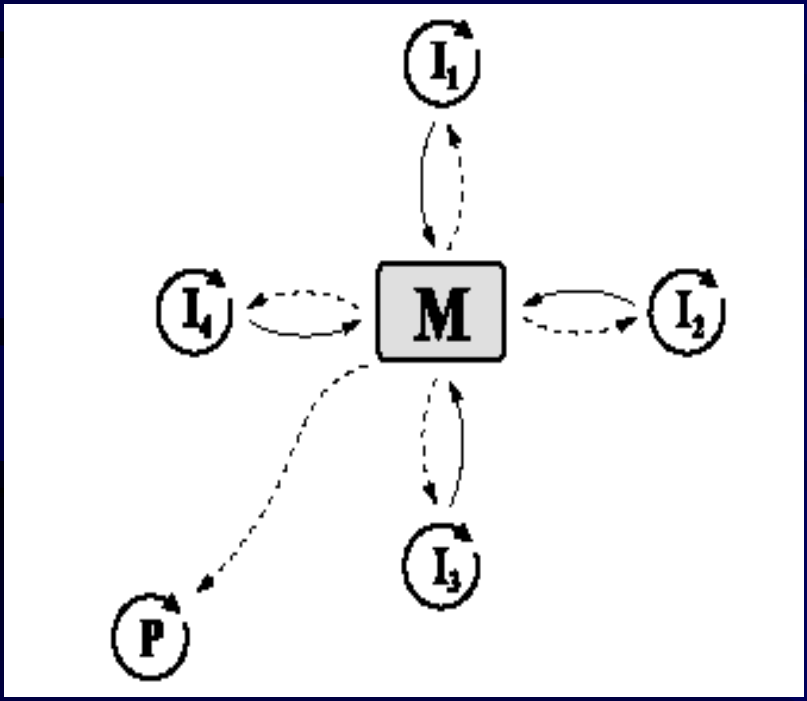
A ‘metabolic’ system on the surface (2000)



$$\frac{dx_i}{dt} = x_i[k_i M(\mathbf{x}) - \phi(\mathbf{x})].$$

$$M(\mathbf{x}) = \left[\prod_{i=1}^{n} x_i\right]^{1/n}$$

Parasite on metabolism

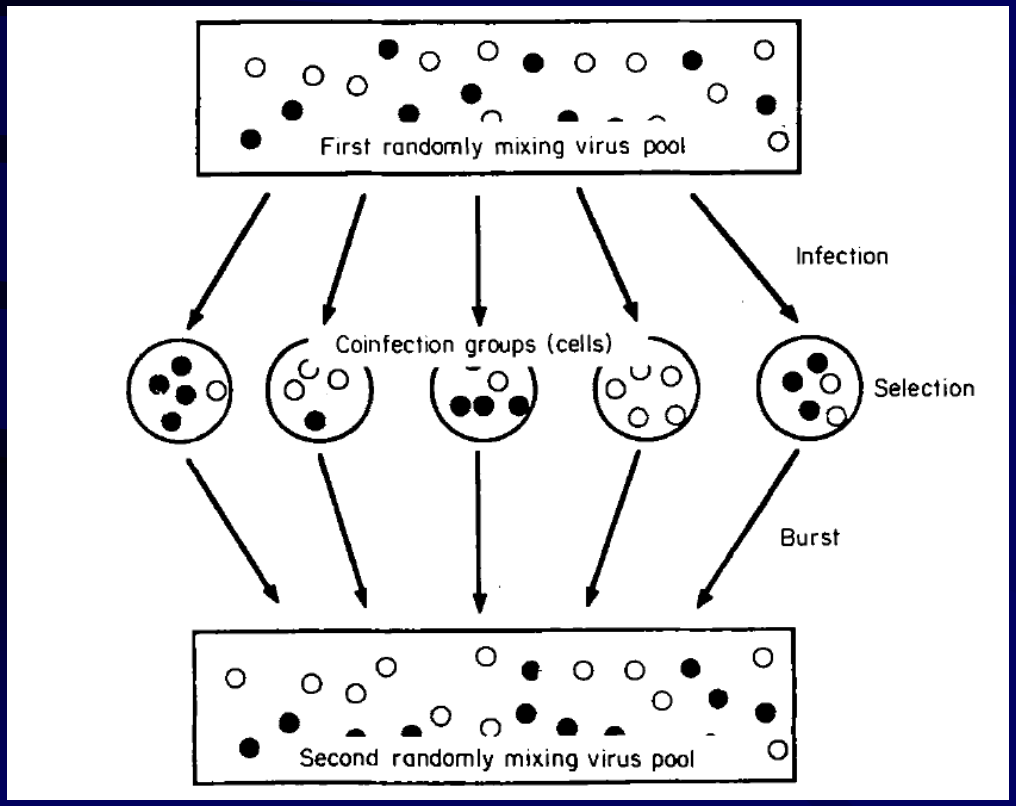


- Parasites do not kill the system
- Can be selected for to perform useful function

J. theor. Biol. (1992) **159**, 99–109

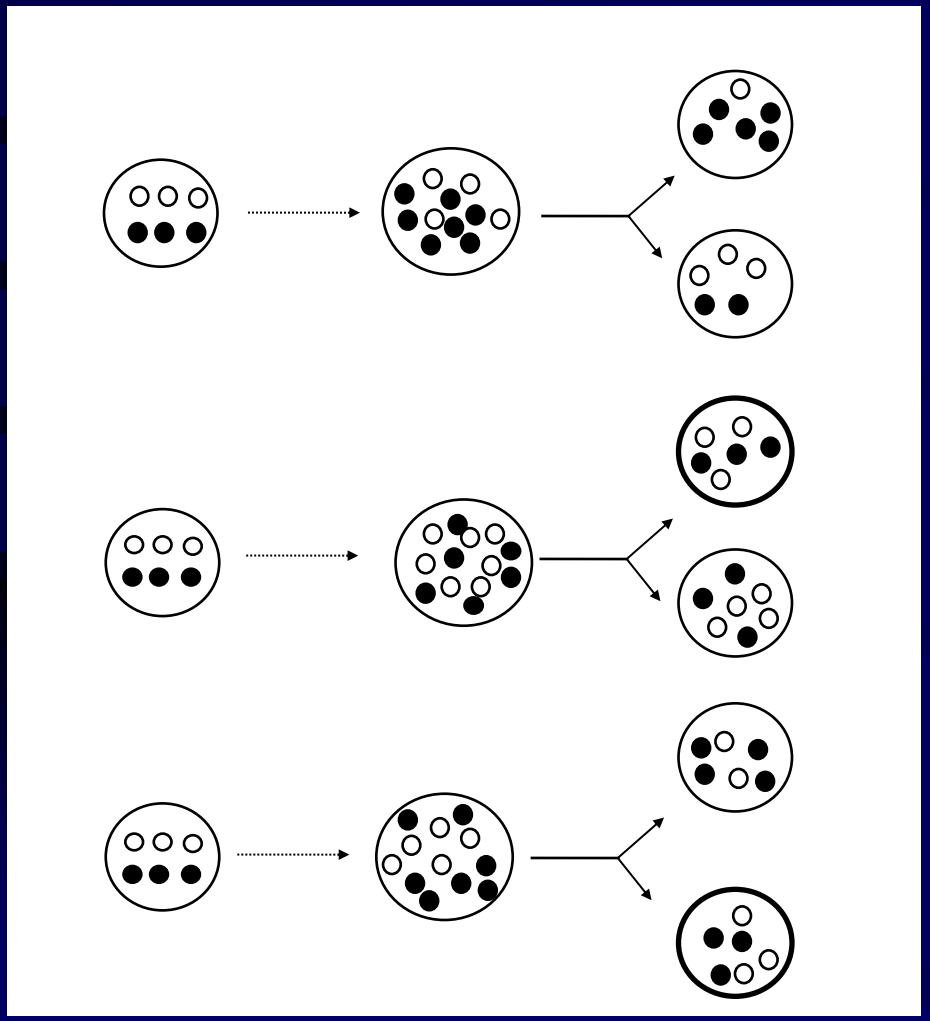
Viral Sex, Levels of Selection, and the Origin of Life

EÖRS SZATHMÁRY†



The structured deme framework for defective interfering particles and coviruses

The stochastic corrector model for compartmentation



Szathmáry, E. & Demeter L. (1987) Group selection of early replicators and the origin of life. *J. theor Biol.* **128,** 463-486.

Grey, D., Hutson, V. & Szathmáry, E. (1995) A re-examination of the stochastic corrector model. *Proc. R. Soc. Lond.* B **262,** 29-35.

An interesting twist

Szilágyi *et al. Biology Direct* 2012, **7**:38
http://www.biology-direct.com/content/7/1/38

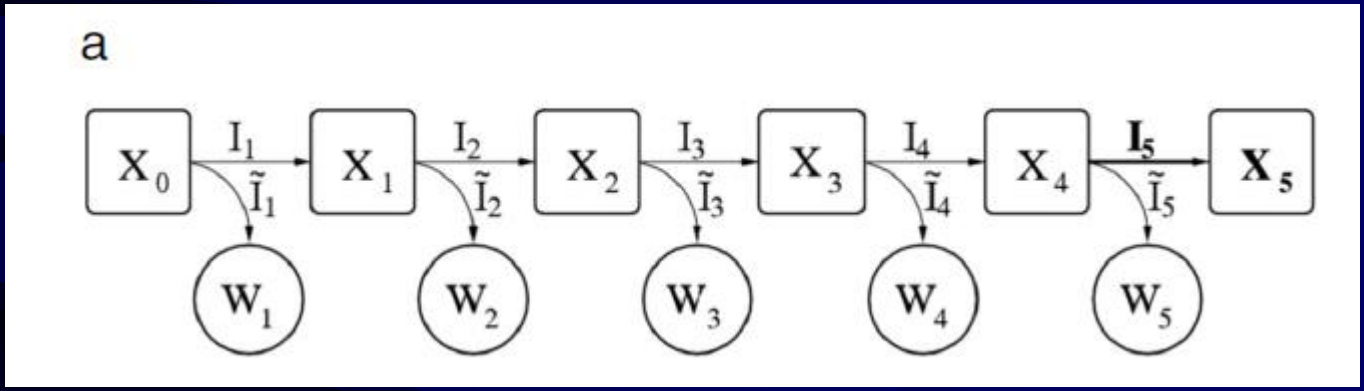
BIOLOGY DIRECT

RESEARCH **Open Access**

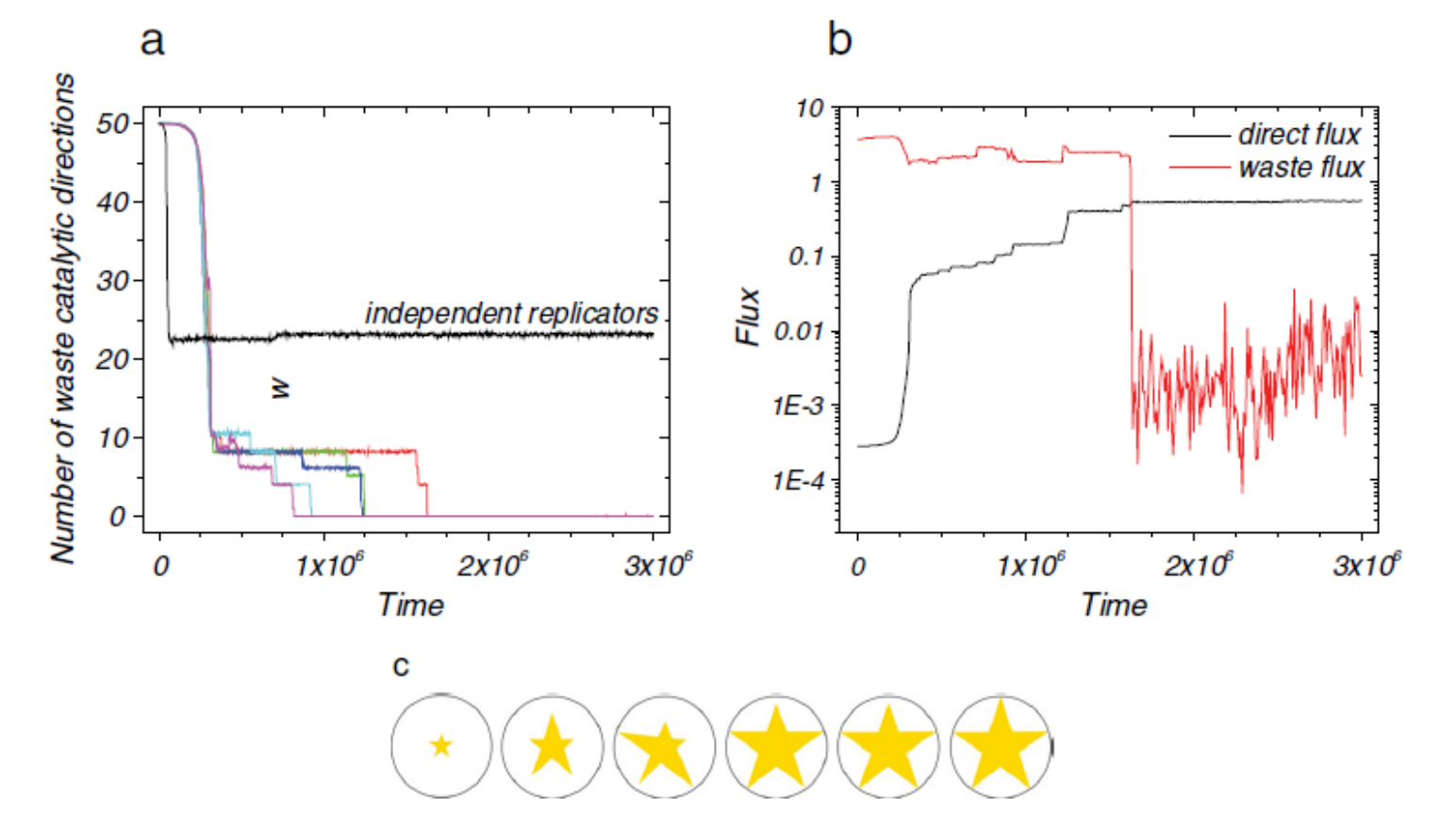
Early evolution of efficient enzymes and genome organization

András Szilágyi[1,2], Ádám Kun[1,2,3] and Eörs Szathmáry[1,2,3*]

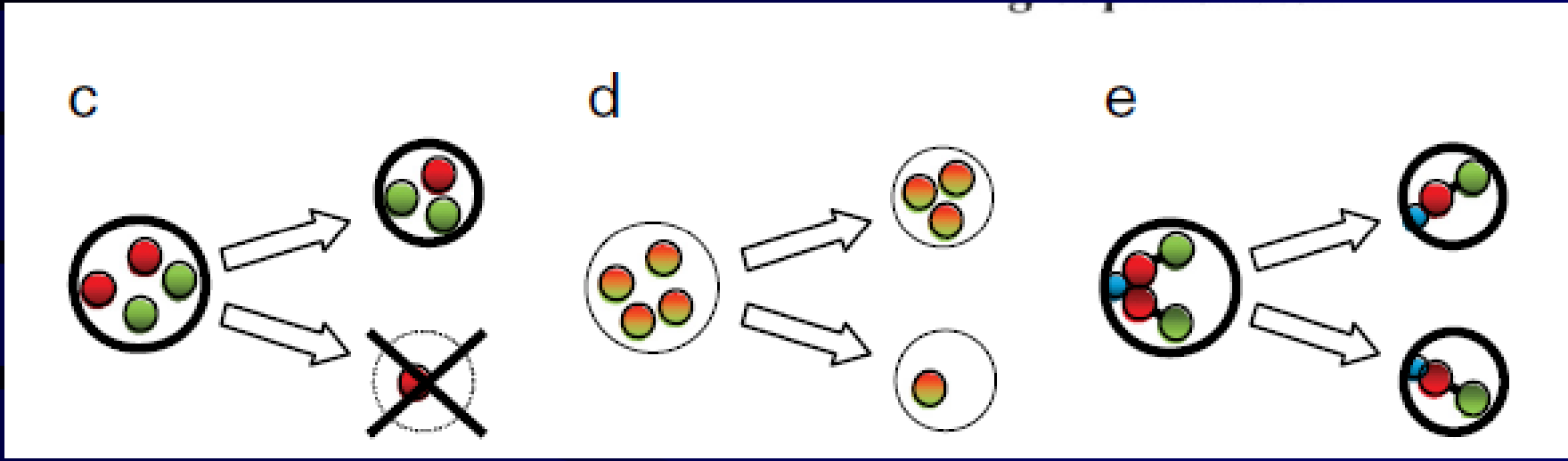
Evolution of enzymes in a biochemical pathway



Evolution of waste production



...but only with chromosomes!



- Specific enzymes generate a high assortment load
- Generalist enzymes reduce this load
- Chromosomes reduce the load and *allow for* the evolution of highly specific enzymes