

Mathematical Biology and Dynamical Systems. Lecture 3.

J. Tomás Lázaro

Departament de Matemàtiques, Universitat Politècnica de Catalunya

IRP DYN³BIO Advanced Course,
Centre de Recerca Matemàtica, September 6-10, 2021.

A principle of natural self-organisation [3]



Figure: Manfred Eigen and Peter Schuster. Font: Wikipedia.

The diversity of species is the outcome of a huge branching process of evolution, based on an enormous number of single steps of replication and mutation.

It involves competition, isolation, creation of niches and, in the case of mild constraints, mutualism and symbiosis.

Which are the **necessary** prerequisites a molecular system has to fulfill to be a feasible evolutionary self-organisation? (Eigen-Schuster 1977)

- It must be based on dynamical criteria: the distribution of present competitors should decide which species is selected.
- Open to changes where more favourable structures appear.

Necessary properties suggested by Eigen and Schuster:

- **Metabolism**: both formation and degradation of molecular species have to be independent of each other and spontaneous, driven by positive affinity.
- **Self-reproduction**: they must have the ability of self-replication (**autocatalysis**).
- **Mutability**: it is certainly required for evolution. However, fidelity of this process is limited.

The **simplest** system modelling such requirements can be described by the following system of ordinary differential equations:

$$\dot{x}_i = (A_i q_i - D_i) x_i + \sum_{k \neq i} w_{ik} x_k + \Phi_i(x), \quad i = 1, 2, \dots, n. \quad (1)$$

where $x = (x_1, x_2, \dots, x_n)$ denotes population of species (or its concentration/density).

In this model we observe:

- **Metabolism**. Given by the term $(A_i q_i - D_i)$, with $A_i q_i$ indicates **spontaneous formation** and D_i **decomposition**.
- **Self-reproduction**. Given by $(A_i q_i - D_i)x_i$
- **Mutability**. Given by the terms $q_i \in [0, 1]$. It denotes the fraction of reproductions providing an exact copy of the population i .
The term w_{ik} represents the probability that an erroneous replication of species (or "template") k gives rise to a an element of species i . So, the sum $\sum_{k \neq i} w_{ik} x_k$ collects all these contributions.
- The term corresponding to error in copying species i , i.e., $A_i(1 - q_i)x_i$ needs to be also taken into account.

- The functions Φ_i , usually called **individual flow** or **transport term** describe any supply or removal of species i do not come from the previous points.
- In many cases, the overall population $x_1 + x_2 + \dots + x_n$ is assumed to be constant (i.e., $\sum_k x_k$ is a first integral).

The hypercycle [3]

- It is a cycle of connected, self-replicating macromolecules.
- All molecules are linked such that each of them catalyses the creation of its successor. The last one catalyses the first one and closes the cycle.
- Each macromolecule can, on its turn, autocatalyses itself.
- It constitutes a higher level of organisation.
- It combines competition and cooperation.

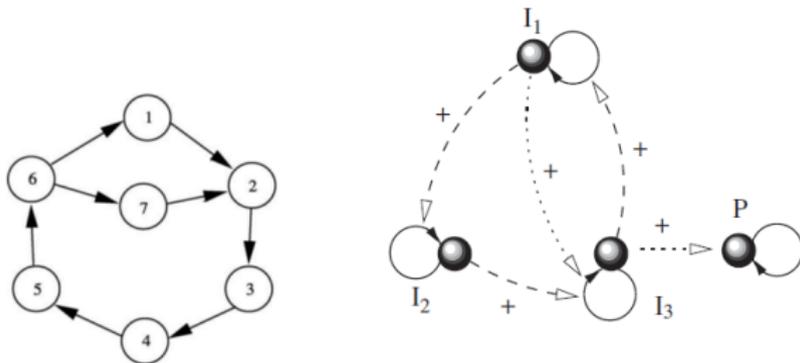


Figure: Examples of hypercycles: Kim-Jeong 2005 and Sardañés-Solé 2007.

Quasispecies

Another related crucial concept introduced by Eigen and Schuster (1977) in [3] is the one of [quasispecies](#).

“A single species is not an independent entity because of the presence of couplings. Conservation of the total population number forces all species into mutual competition, while mutations still allow for some cooperation, especially among closely related species.”

So, according to Nowak (1992) [1]:

“A [quasispecies](#) is a well-defined distribution of mutants that is generated by a mutation-selection process. Selection does not act on a single mutant but on the quasispecies as a whole.”

- Let consider l_1, l_2, \dots, l_n different variants or templates of a 'master' species.
- Let f_1, f_2, \dots, f_n define their corresponding replication rates (sometimes named also fitness).

In the absence of mutations, the variant with highest replication rate dominates and leads to a homogeneous population with such variant.

However, replication is not error free.

- Sol let us denote by q_{ij} the probability of erroneous replication of template I_j resulting in the production of template I_i :

$$I_j \xrightarrow{q_{ij}} I_i.$$

- By extension, we can define q_{jj} the probability of error-free replication of template I_j .
- Hence, we have the so-called **mutation matrix**:

$$Q = \begin{pmatrix} q_{11} & q_{12} & \dots & q_{1n} \\ q_{21} & q_{22} & \dots & q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ q_{n1} & q_{n2} & \dots & q_{nn} \end{pmatrix}.$$

Notice that all $q_{ij} \in [0, 1]$ and the sum of each column is 1, i.e.

$$\sum_{i=1}^n q_{ij} = 1, \quad j = 1, 2, \dots, n.$$

Q is called a **Markov matrix** (by columns) or an **stochastic matrix**.

Mutation scheme

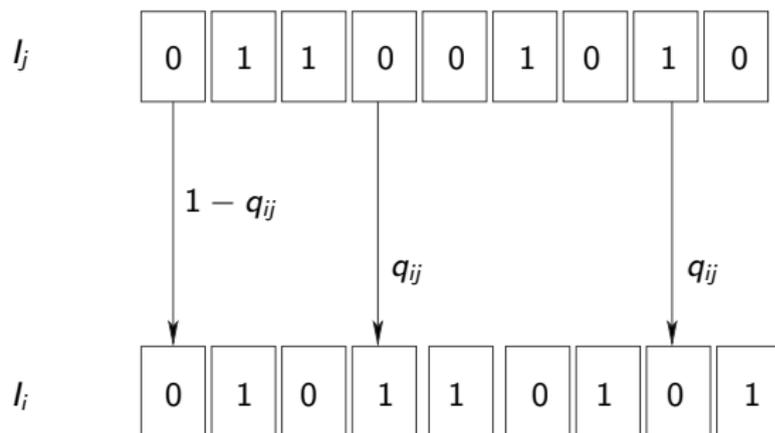


Figure: Mutation scheme from sequences x_j to x_i .

- Therefore, if x_1, x_2, \dots, x_n denote the population sizes of the variants l_1, l_2, \dots, l_n , respectively, we have that they satisfy

$$\dot{x}_i = f_1 q_{i1} x_1 + f_2 q_{i2} x_2 + \dots + f_n q_{in} x_n = \sum_{j=1}^n f_j q_{ij} x_j, \quad i = 1, 2, \dots, n.$$

- In this context, the population will no longer consist on the fastest growing sequence (the 'dominant') but of a whole ensemble of mutants with different replication rates. Moreover, evolution acts on them as a whole. This is the concept of **quasispecies** introduced by Eigen and Schuster [3].
- The frequency of a given population x_j does not only depend on its fitness f_j but also on its replication-fidelity and on the mutation errors of other variants. According to Nowak, **Evolution** could be thought as the interaction between **mutation** and **selection**.

- In a more general setting the differential equation modelling the evolution of $x = (x_1, x_2, \dots, x_n)$ can be written as

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \vdots \\ \dot{x}_n \end{pmatrix} = \begin{pmatrix} f_1 q_{11} & f_2 q_{12} & \dots & f_n q_{1n} \\ f_1 q_{21} & f_2 q_{22} & \dots & f_n q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ f_1 q_{n1} & f_2 q_{n2} & \dots & f_n q_{nn} \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix} - \varphi(x) \begin{pmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{pmatrix},$$

where $\varphi : \mathbb{R}^n \rightarrow \mathbb{R}$ is often given by

$$\varphi(x) = \frac{\sum_{j=1}^n f_j x_j}{\sum_{j=1}^n x_j}$$

or, simply,

$$\varphi(x) = \sum_{j=1}^n f_j x_j$$

if the total population has been normalised to 1, that is, $\sum_{j=1}^n x_j = 1$ (and so x_j 's represent densities).

- In short,

$$\dot{x} = QDx - \varphi(x)x,$$

with

$$Q = \begin{pmatrix} q_{11} & q_{12} & \dots & q_{1n} \\ q_{21} & q_{22} & \dots & q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ q_{n1} & q_{n2} & \dots & q_{nn} \end{pmatrix}, \quad D = \begin{pmatrix} f_1 & & & \\ & f_2 & & \\ & & \ddots & \\ & & & f_n \end{pmatrix}$$

and

$$\sum_{j=1}^n x_j = 1, \quad \varphi(x) = \sum_{j=1}^n f_j x_j.$$

- The matrix QD has all its entries ≥ 0 .

The Perron-Frobenius theorem

- We say that a matrix $A = (a_{ij})_{ij}$ is **positive** if $a_{ij} > 0$ for all $i, j = 1, 2, \dots, n$. We denote it by $A > 0$.
- We say that $A = (a_{ij})_{ij}$ is **non-negative** if $a_{ij} \geq 0$ for all $i, j = 1, 2, \dots, n$. We denote it by $A \geq 0$.

Theorem (Perron, 1907)

Let $A > 0$ be a square matrix. Then,

- *There exists a positive, real, simple eigenvalue $\lambda > 0$ of A such that for any other eigenvalue μ of A we have that $|\mu| < \lambda$. This eigenvalue λ is called **Perron** or **Perron-Frobenius eigenvalue**.*
- *There exists an eigenvector u of λ with all its components positive: $Au = \lambda u$. Respectively, there exists a left-eigenvector v with all its components positive of eigenvalue λ : $v^T A = \lambda v^T$.*
- *There is no other eigenvector with these properties except positive multiples of u and v .*

We say that a matrix A is **irreducible** if it has no non-trivial invariant subspaces. Equivalently, **there is no** permutation matrix P such that

$$PAP^{-1} = \begin{pmatrix} E & F \\ 0 & G \end{pmatrix}$$

an upper block-triangular matrix.

Theorem (Frobenius, 1908-1912)

Let $A \geq 0$ be a square matrix. Assume that A is *irreducible*, Then

- There exists a real, simple, eigenvalue $\lambda > 0$ of A , called the *Perron–Frobenius eigenvalue*.
- A has a right eigenvector u of eigenvalue λ whose components are all positive. Likewise, A has a left eigenvector v with eigenvalue λ (i.e. $v^\top A = \lambda v^\top$) whose components are all positive.
The only eigenvectors whose components are all positive are those associated with the eigenvalue λ .
- The matrix A has exactly h (where h is called the *period*) complex eigenvalues with modulus λ . They are of the form $\mu = \lambda \xi_h$ with ξ_h a h -th root of unity (i.e., $\xi_h^h = 1$).
- If we define $\omega = 2\pi/h$ then the matrix A is similar to $e^{i\omega} A$. Consequently the spectrum of A is invariant under multiplication by $e^{i\omega}$ (a rotation of the complex plane by the angle ω).

Markov matrices

- We say that a square matrix \mathcal{M} is a **Markov matrix** (by columns) if the sum of the elements of any column is always equal to 1. They are also called **stochastic matrices**.
- Similarly, we say that $u = (u_1, u_2, \dots, u_n)$ is an **stochastic vector** if $u_j \geq 0$ $\forall j = 1, 2, \dots, n$ and $\sum_{j=1}^n u_j = 1$.
- Observe that if \mathcal{M} is Markov then it is $\mathcal{M} \geq 0$.

Markov matrices have very nice properties. Indeed, let assume that \mathcal{M} is a Markov matrix. Then,

- If v is a stochastic vector then $\mathcal{M}v$ is a stochastic vector.
- If \mathcal{M}' is another Markov matrix then the product $\mathcal{M}\mathcal{M}'$ is also Markov.
- $\lambda = 1$ is always an eigenvalue of \mathcal{M} and $u_* = (1, 1, 1, \dots, 1)$ is a (left) eigenvector.
- If $\mu \in \text{Spec } \mathcal{M}$ is an eigenvalue of \mathcal{M} then $|\mu| \leq 1$.

- Markov matrices are ubiquitous (Game theory, Probability Theory, Economics, Computer Science, Population Genetics, etc). They are also the base of the original [PageRank](#) algorithm of Google (Larry Page and Sergey Brin, 1996).
- In our case,

$$\dot{x} = QDx - \varphi(x)x,$$

we have that Q is Markov and $D \geq 0$.

Error threshold, error catastrophe or critical mutation rate

Let us consider the following toy model, where sequences are formed by 0 and 1. It is based in the one suggested by M. Nowak in [1].

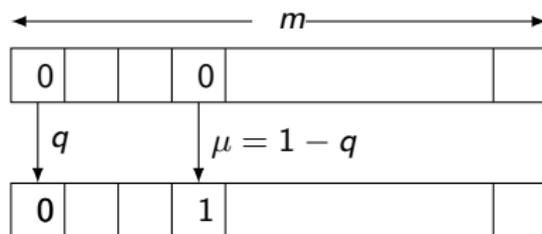


Figure: Example of mutation: q is the probability of no-mutation while $\mu = 1 - q$ is the probability that a 0-digit mutates into a 1-digit.

Assume that m is the length of the sequences, q the error-free probability and $\mu = 1 - q$ the probability of mutation. We take x_1 as the size of the **master sequence** population and x_2 the **mutant** population.

In terms of differential equations

$$\begin{aligned}\dot{x}_1 &= a_1 Q x_1 \\ \dot{x}_2 &= a_1(1 - Q)x_1 + a_2 x_2,\end{aligned}\tag{2}$$

where $Q = q^m$ and $a_1, a_2 > 0$.

- We consider $x_2(t)/x_1(t)$ and differentiate it with respect to time

$$\frac{d}{dt} \left(\frac{x_2}{x_1} \right) = \frac{\dot{x}_2}{x_1} - \frac{\dot{x}_1 x_2}{x_1^2} = a_1(1 - Q) + (a_2 - a_1 Q) \frac{x_2}{x_1}.$$

- If we define $w = x_2/x_1$ the previous equation becomes the lineal ode

$$\dot{w} = a_1(1 - Q) + (a_2 - a_1 Q)w,$$

whose general solution is given by

$$w(t) = \frac{a_1(1 - Q)}{a_1 Q - a_2} + c e^{(a_2 - a_1 Q)t},$$

$c \in \mathbb{R}$ a constant depending on the initial condition at $t = 0$, provided that $a_1 Q - a_2 \neq 0$. In the case that $a_2 = a_1 Q$ the ode is trivial and has general solution

$$w(t) = a_1(1 - Q)t + c, \quad c \in \mathbb{R}.$$

So, if $a_2 = a_1 Q$, we have that

$$\frac{x_1(t)}{x_2(t)} = \frac{1}{a_1(1-Q)t + \frac{x_2(0)}{x_1(0)}} \rightarrow 0 \quad \text{if } t \rightarrow +\infty,$$

that is, **mutant population dominates** the total population. Keep in mind that, since $\dot{x}_1 = a_1 Q x_1$, master population always grows with no restriction:

$$x_1(t) = x_1(0)e^{a_1 Q t}.$$

Assume now that $a_2 - a_1 Q \neq 0$. Then, the general solution is

$$\frac{x_2(t)}{x_1(t)} = \frac{a_1(1-Q)}{a_1 - a_2 Q} + ce^{(a_2 - a_1 Q)t}$$

or, equivalently,

$$\frac{x_1(t)}{x_2(t)} = \frac{1}{\frac{a_1(1-Q)}{a_1 - a_2 Q} + ce^{(a_2 - a_1 Q)t}}.$$

And the following cases hold:

- 1 If $a_2 - a_1 Q > 0$, that is, $a_2 > a_1 Q$, we get that $\exp((a_2 - a_1 Q)t) \rightarrow +\infty$ as $t \rightarrow +\infty$ and, therefore,

$$\frac{x_1(t)}{x_2(t)} \rightarrow 0, \quad t \rightarrow +\infty.$$

As before, mutant populations largely dominates.

- ② If $a_2 - a_1 Q < 0$, i.e., $a_2 < a_1 Q$ (and, in particular, $a_2 < a_1$) one has $\exp((a_2 - a_1 Q)t) \rightarrow 0$ as $t \rightarrow +\infty$ and, consequently

$$\frac{x_1(t)}{x_2(t)} \longrightarrow \frac{a_1 Q - a_2}{a_1(1 - Q)}, \quad t \longrightarrow +\infty.$$

Therefore, master sequence population x_1 becomes, for large time, comparable in size with the mutant population x_2 provided that $a_2 - a_1 Q < 0$, that is

$$Q > \frac{a_2}{a_1} \Leftrightarrow q^m > \frac{a_2}{a_1} \Leftrightarrow q > \left(\frac{a_2}{a_1}\right)^{1/m} \Leftrightarrow \mu = 1 - q < 1 - \left(\frac{a_2}{a_1}\right)^{1/m}.$$

In other words, it is needed that $a_2 < a_1 Q$ and the mutation probability μ to be smaller than the **critical mutation rate**

$$\mu_{\text{critical}} := 1 - \left(\frac{a_2}{a_1}\right)^{1/m}.$$

This critical value μ_{critical} depends on the sequences length m and satisfies that

$$\mu_{\text{critical}} \longrightarrow 0 \quad \text{as} \quad m \longrightarrow +\infty.$$

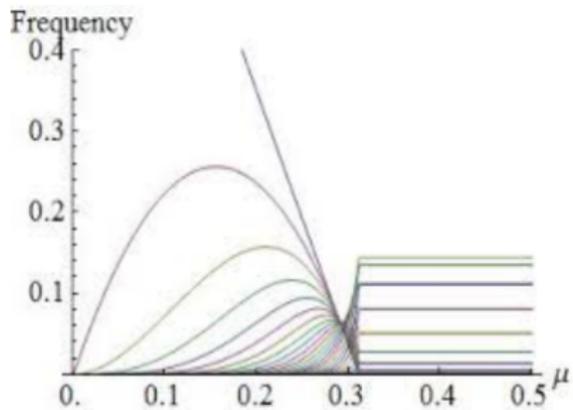


Figure: Example of catastrophe error in a population formed by a master sequence and a group of mutants.

Hypercycles, the Eigen's paradox and the origin of life

- The size of replicating molecules is limited by the accuracy of replication: **error threshold** or **critical mutation rate**.
- Quasispecies, in particular, suffer this error threshold.
- The concept of error threshold is crucial to understand the so-called **Eigen's paradox**:
"No possible mechanisms of error correction without large information contents and no possible large information contents without error correction mechanisms."

In other words: we can imagine the first self-replicating molecules as consisting of strings of base pairs or digits. Therefore,

- The error threshold limits the size of these molecules to a few hundreds pairs.
- Living cells handle this difficulty by encoding enzymes which repair error in mutations.
- However, the size of a replicating molecule to encode their own error correcting enzymes must be much bigger than several hundreds and certainly thousands of these pair bases.

So, how evolution could overcome this paradox? [Hypercycles?](#)

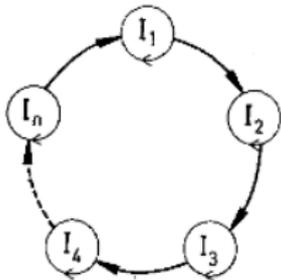


Figure: Example of a (catalytic) hypercycle [3].

- Hypercycles theory, suggested by Eigen and Schuster, was initially (and still is) very criticized since:
- Hypercycles are sensitive to catalytic parasites (P) and to short-circuits (inner cycles). See Figure 7 below).
- It is difficult to find stable hypercycles of large size.
- However, recent experiments (Vayda et al, 2012) have proved advantages of cooperative network among fragments of self-assembling ribozymes over self-replicating cycles.

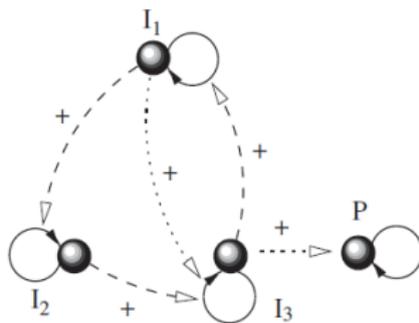
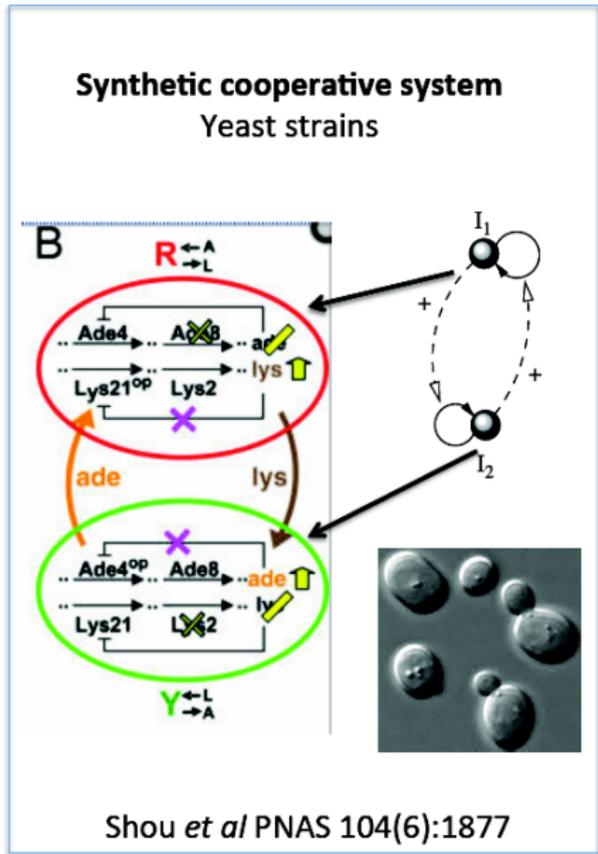
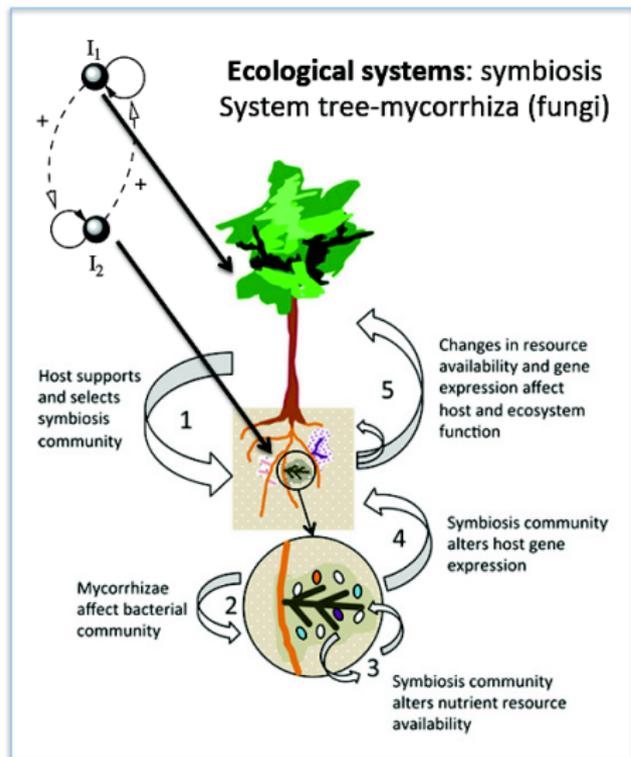


Figure: Example of hypercycle with a shortcircuit and a parasite.

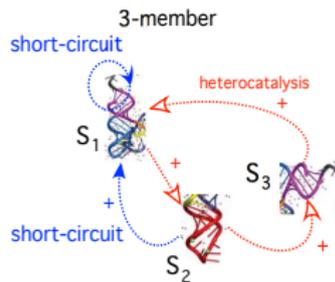
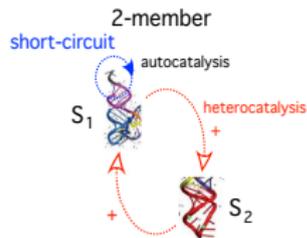
Hypercycles with shortcircuits and parasites

Some examples

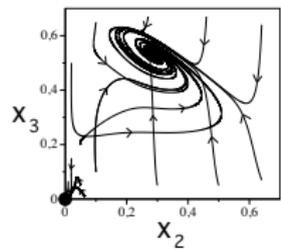
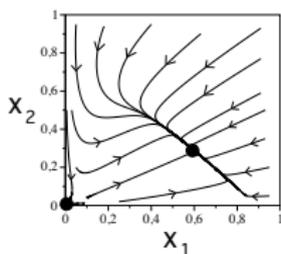


The model

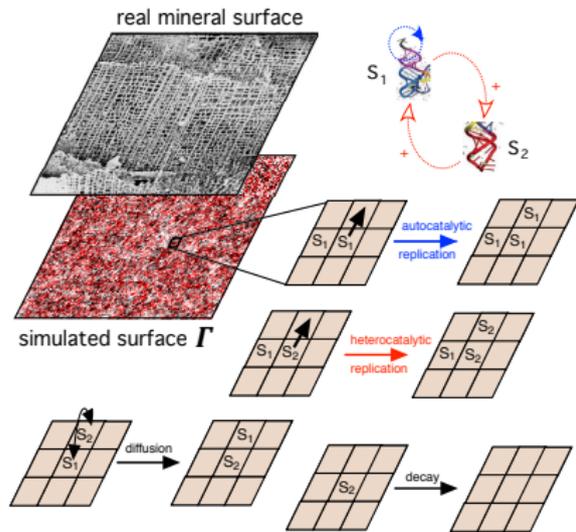
(a) Hypercycles



(b) Mean field dynamics



(c) Spatial dynamics



The mean field model

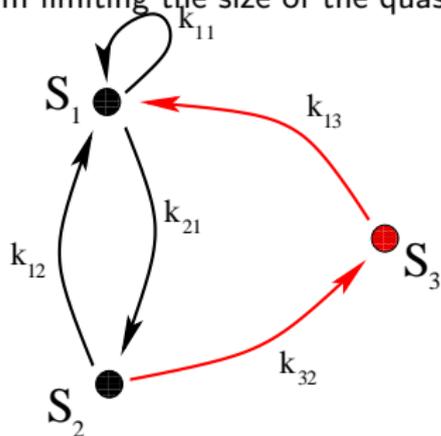
$$\dot{x}_1 = x_1 (k_{11}x_1 + k_{12}x_2 + k_{13}x_3) \theta(x) - \varepsilon x_1,$$

$$\dot{x}_2 = x_2 (k_{21}x_1) \theta(x) - \varepsilon x_2,$$

$$\dot{x}_3 = x_3 (k_{32}x_2) \theta(x) - \varepsilon x_3,$$

where $\theta(x) = 1 - (x_1 + x_2 + x_3)$ is a constraint term limiting the size of the quasispecies forming the hypercycle.

- x_i denote population numbers.
- All $k_{ij} > 0$ and $\varepsilon > 0$.



We reduce our study to

$$\Omega = \{x_1 \geq 0, x_2 \geq 0, x_3 \geq 0 \mid x_1 + x_2 + x_3 \leq 1\}$$

since:

- It is the domain of biological meaning.
- Solutions cross transversally any plane $\{x_1 + x_2 + x_3 \leq \delta\}$ inwards for all $\delta \geq 1 \implies \Omega$ contains the long-term behaviour and the interesting dynamics.

Sardanyés-L-Guillamon-Fontich, Physica D, 2017.

- Equilibrium points of the three different types:
 - ▶ Type $P = (x_1, 0, 0)$ \longrightarrow Only the autocatalytic replicator S_1 survives.
 - ▶ Type $Q = (x_1, x_2, 0)$ \longrightarrow The hypercycle replicators S_1 and S_2 coexist.
 - ▶ Type $R = (x_1, x_2, x_3)$ \longrightarrow The three replicator species survive.
- Invariant lines.
- Bifurcations of the equilibrium points.
- Non-existence of periodic orbits.

Equilibrium points

Parameters governing the existence of the equilibrium points:

$$\alpha_2 := \frac{k_{21} - k_{11}}{k_{12}}, \quad \alpha_3 := \frac{k_{21}}{k_{32}}, \quad \beta_3 := \frac{k_{12}}{k_{13}} \left(\frac{k_{21} - k_{11}}{k_{12}} - \frac{k_{21}}{k_{32}} \right)$$

$$\mu_2 := 1 + \alpha_2, \quad \mu_3 := 1 + \alpha_3 + \beta_3,$$

$$\varepsilon_1 := \frac{k_{11}}{4}, \quad \varepsilon_2 := \frac{k_{21}}{4\mu_2}, \quad \varepsilon_3 := \frac{k_{21}}{4\mu_3}.$$

Equilibrium points

Equilibrium points of type $(x_1, 0, 0)$ exist if and only if $\varepsilon \leq \varepsilon_1$:

$$\begin{cases} P^\pm = (p_1^\pm, 0, 0) & \text{if } 0 < \varepsilon < \varepsilon_1, \\ P^0 = (p_1^0, 0, 0) & \text{if } \varepsilon = \varepsilon_1, \end{cases}$$

where $p_1^{\pm,0}$ are the two solutions of $\xi^2 - \xi + \varepsilon/k_{11} = 0$, that is,

$$p_1^\pm = \frac{1}{2} \left(1 \pm \sqrt{1 - \frac{\varepsilon}{\varepsilon_1}} \right), \quad \text{and} \quad p_1^0 = \frac{1}{2}.$$

Equilibrium points

Equilibrium points of the form $(x_1, x_2, 0)$ exist in Ω if and only if $\varepsilon \leq \varepsilon_2$ and $\alpha_2 \geq 0$:

$$\begin{cases} Q^\pm = (q_1^\pm, q_2^\pm, 0) & \text{if } 0 < \varepsilon < \varepsilon_2, \\ Q^0 = (q_1^0, q_2^0, 0) & \text{if } \varepsilon = \varepsilon_2, \end{cases}$$

where q_1^\pm are the two solutions of $\mu_2 \xi^2 - \xi + \varepsilon/k_{21} = 0$ and $q_2^{\pm,0} = \alpha_2 q_1^{\pm,0}$.

- If $\alpha_2 = 0 \Rightarrow \varepsilon_2 = \varepsilon_1$ and therefore $Q^\pm = P^\pm$ and $Q^0 = P^0$.
- If $\alpha_2 < 0$ there are no fixed points of this type in Ω .

Remind that $\alpha_2 = \frac{k_{21} - k_{11}}{k_{12}}$.

Equilibrium points

Equilibrium points of the form (x_1, x_2, x_3) exist in Ω if and only if $\beta_3 \geq 0$:

$$\begin{cases} R^\pm = (r_1^\pm, r_2^\pm, r_3^\pm) & \text{if } 0 < \varepsilon < \varepsilon_3 \\ R^0 = (r_1^0, r_2^0, r_3^0) & \text{if } \varepsilon = \varepsilon_3, \end{cases}$$

where r_1^\pm are the two solutions of $\mu_3 \xi^2 - \xi + \varepsilon/k_{21} = 0$, and

$$r_2^{\pm,0} = \alpha_3 r_1^{\pm,0}, \quad r_3^{\pm,0} = \beta_3 r_1^{\pm,0}.$$

- If $\beta_3 = 0 \Rightarrow \varepsilon_3 = \varepsilon_2$ and therefore $R^\pm = Q^\pm$ and $R^0 = Q^0$.
- If $\beta_3 < 0$ there are no fixed points of this type in Ω .

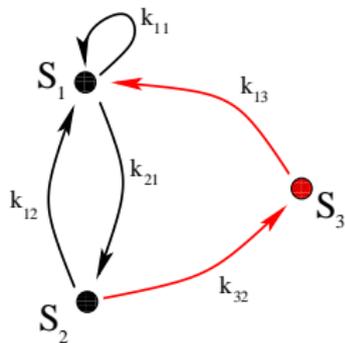
Remind that $\alpha_3 = \frac{k_{21}}{k_{32}} > 0$ and $\beta_3 = \frac{k_{12}}{k_{13}} \left(\frac{k_{21} - k_{11}}{k_{12}} - \frac{k_{21}}{k_{32}} \right)$

Equilibrium points

Summarising:

- $P^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_1$, where $\varepsilon_1 = k_{11}/4$.
- $Q^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_2$ and $k_{21} \geq k_{11}$ (equiv. $\alpha_2 \geq 0$).
- $R^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_3$ and $\frac{k_{11}}{k_{21}} + \frac{k_{12}}{k_{32}} \leq 1$ (equiv. $\beta_3 \geq 0$).

Notice that $\beta_3 \geq 0 \Rightarrow \alpha_2 \geq 0$.



Equilibrium points

Summarising:

- $P^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_1$, where $\varepsilon_1 = k_{11}/4$.
- $Q^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_2$ and $k_{21} \geq k_{11}$ (equiv. $\alpha_2 \geq 0$).
- $R^{\pm,0}$ exist if $0 < \varepsilon \leq \varepsilon_3$ and $\frac{k_{11}}{k_{21}} + \frac{k_{12}}{k_{32}} \leq 1$ (equiv. $\beta_3 \geq 0$).

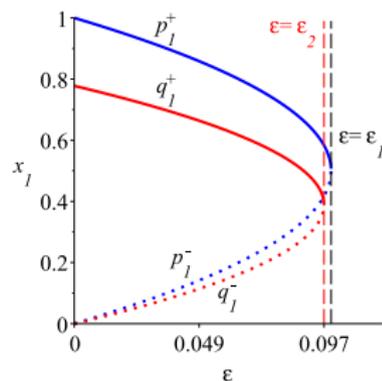
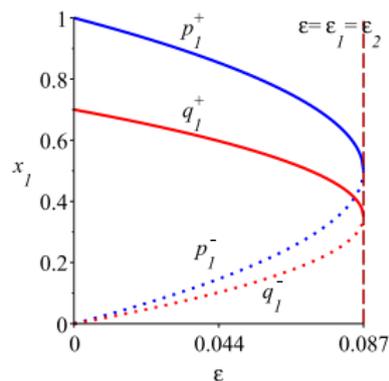
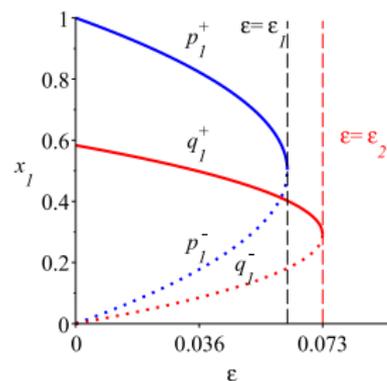
Notice that $\beta_3 \geq 0 \Rightarrow \alpha_2 \geq 0$.

Remark:

- $\alpha_2 = 0 \Rightarrow Q^{\pm,0} = P^{\pm,0}$.
- $\beta_3 = 0 \Rightarrow R^{\pm,0} = Q^{\pm,0}$.

Equilibrium points

Evolution of the first coordinate of the fixed points P^\pm, Q^\pm when varying ε from 0 to $\varepsilon_1, \varepsilon_2$.



Invariant lines

Our system has the following invariant lines through the origin:

- $L_1 = \langle v_1 \rangle = \langle (1, 0, 0) \rangle$
- $L_2 = \langle v_2 \rangle = \langle (1, \alpha_2, 0) \rangle$
- $L_3 = \langle v_3 \rangle = \langle (1, \alpha_3, \beta_3) \rangle$
- $L_j = \langle v_j \rangle$, $j = 4, 5$, with $v_4 = (0, 1, 0)$ and $v_5 = (0, 0, 1)$.
- $L_6 = \langle v_6 \rangle = \langle (1, 0, \beta_6) \rangle$ and $\beta_6 = -k_{11}/k_{13} < 0$.

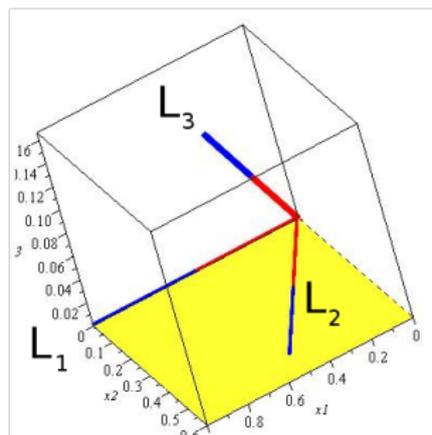
Moreover:

- Each equilibrium point is on one of these lines.
- L_2 intersects $\Omega \setminus \{0\} \Leftrightarrow \alpha_2 \geq 0$. If $\alpha_2 = 0$ then $L_2 = L_1$.
- L_3 intersects $\Omega \setminus \{0\} \Leftrightarrow \beta_3 \geq 0$. If $\beta_3 = 0$ then $L_3 = L_2$.
- If $\alpha_2 = \beta_3 = 0$ then $L_1 = L_2 = L_3$.
- L_6 never intersects $\Omega \setminus \{0\}$.

Invariant lines

Our system has the following invariant lines through the origin:

- $L_1 = \langle v_1 \rangle = \langle (1, 0, 0) \rangle$
- $L_2 = \langle v_2 \rangle = \langle (1, \alpha_2, 0) \rangle$
- $L_3 = \langle v_3 \rangle = \langle (1, \alpha_3, \beta_3) \rangle$
- $L_j = \langle v_j \rangle, j = 4, 5$, with $v_4 = (0, 1, 0)$ and $v_5 = (0, 0, 1)$.
- $L_6 = \langle v_6 \rangle = \langle (1, 0, \beta_6) \rangle$ and $\beta_6 = -k_{11}/k_{13} < 0$.



Linear stability at the equilibrium points

$\lambda_j^{\pm,0}$, $j = 1, 2, 3$ denote the eigenvalues at the points $P^{\pm,0}$, $Q^{\pm,0}$, $R^{\pm,0}$.

Linear stability at the equilibrium points

Points $P^{\pm,0}$:

- $v_1 = (1, 0, 0)$ is always eigenvector (they all are on line L_1)
- All eigenvalues are real.
- $\lambda_3^{\pm,0} = -\varepsilon < 0$
- One has

	λ_1	λ_2	λ_3
P^+	-	$\text{sgn}(\alpha_2)$	-
P^-	+	$\text{sgn}(\alpha_2)$	-
P^0	0	$\text{sgn}(\alpha_2)$	-

- Remind that $\alpha_2 \geq 0 \rightarrow$ existence of $Q^{\pm,0}$
- And $\alpha_2 \geq 0 \Leftrightarrow k_{21} \geq k_{11}$.

Linear stability at the equilibrium points

Points $Q^{\pm,0}$:

- $v_2 = (1, \alpha_2, 0)$ is always eigenvector (they are all on line L_2)
- All eigenvalues are real.
- $\lambda_3^{\pm,0} = -\alpha_2 \varepsilon < 0$ ($\alpha_2 > 0$ for $Q^{\pm,0}$ to exist)
- One has

	λ_1	λ_2	λ_3
Q^+	$\text{sgn}(\beta_3)$	-	-
Q^-	$\text{sgn}(\beta_3)$	+	-
Q^0	$\text{sgn}(\beta_3)$	0	-

- Remind that $\beta_3 \geq 0 \rightarrow$ existence of $R^{\pm,0}$
- And $\beta_3 \geq 0 \iff \frac{k_{11}}{k_{21}} + \frac{k_{12}}{k_{32}} \leq 1$.

Linear stability at the equilibrium points

Points $R^{\pm,0}$:

- $v_3 = (1, \alpha_3, \beta_3)$ is always eigenvector (they are all on line L_3)
- $\lambda_1^{\pm,0}$ is always real. Indeed,

$$\lambda_1^+ < 0, \quad \lambda_1^0 = 0, \quad \lambda_1^- > 0.$$

- Let us define

$$\Delta = \left(1 - \frac{k_{11}}{k_{21}}\right)^2 - 4 \left(1 - \frac{k_{12}}{k_{32}}\right).$$

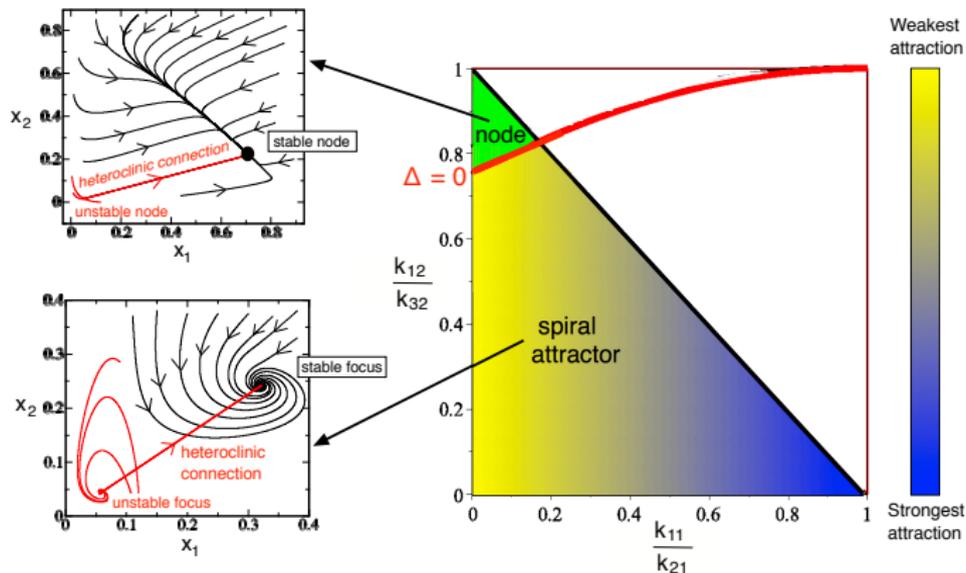
Then,

- ▶ If $\Delta \geq 0$ then $\lambda_{2,3}^{\pm,0} < 0$.
- ▶ If $\Delta < 0$ then λ_2, λ_3 complex conjugate with $\text{Re } \lambda_{2,3}^{\pm,0} < 0 \rightarrow$ spirals.

Remind that $\beta_3 = 0 \implies R^{\pm,0} = Q^{\pm,0}$.

Linear stability at the equilibrium points

Points $R^{\pm,0}$:



Bifurcations

- We focus on 2-member hypercycle, the smallest dimension with all the interesting bifurcations.
- Two types:

- ▶ **Saddle-node**: when ε overcomes the thresholds $\varepsilon_1, \varepsilon_2$, i.e.

$$P^\pm \rightarrow P^0, \quad Q^\pm \rightarrow Q^0.$$

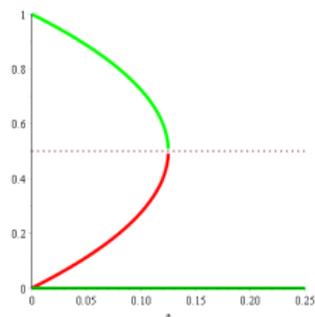
- ▶ **Transcritical**: when one equilibrium leaves/enters region Ω (and switch their stability).

Bifurcations

- We illustrate these bifurcations on the plane (ε, k_{21}) .
 ε =degradation, k_{21} =catalysis from S_1 to S_2 .
- We have three cases: $k_{11} < k_{12}$, $k_{11} = k_{12}$, and $k_{11} > k_{12}$.
- Remark: $\text{sgn}(k_{12} - k_{11}) = \text{sgn}(\varepsilon_2 - \varepsilon_1)$.

Bifurcations

- $\varepsilon = \varepsilon_1$: collision of P^+ and $P^- \rightarrow$ saddle-node.



- $k_{21} = k_{11}$: appearance of $Q^\pm \rightarrow$ transcritical.
- $\varepsilon = \varepsilon_2(k_{21})$, where

$$\varepsilon_2(k_{21}) = \frac{k_{21}k_{12}}{4(k_{21} + k_{12} - k_{11})}.$$

Collision of Q^+ and $Q^- \rightarrow$ saddle-node.

Bifurcations

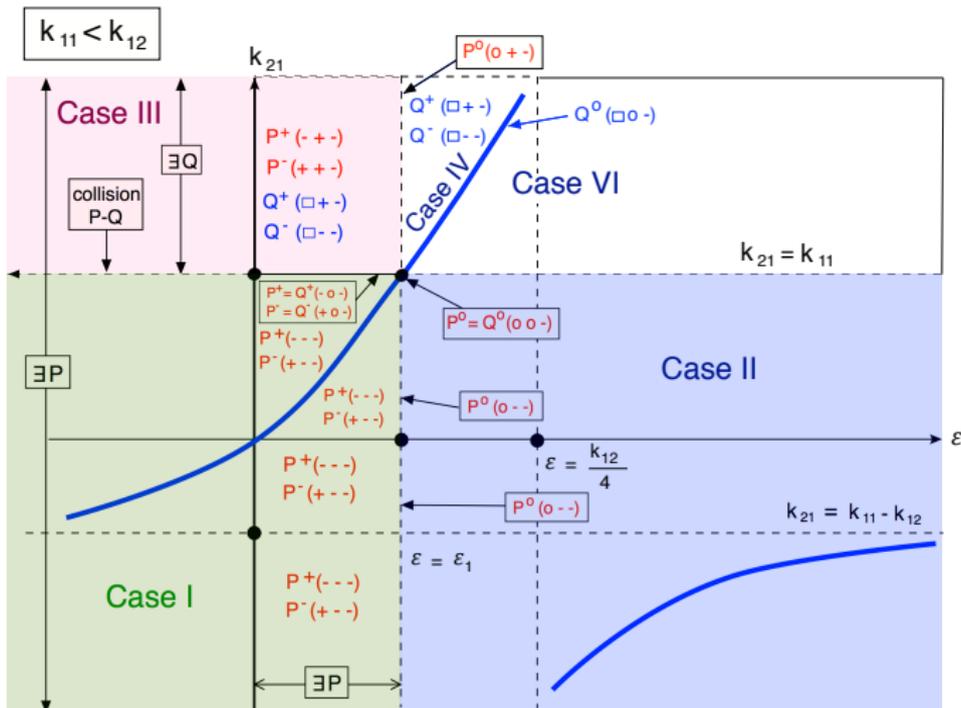


Figure: Case $k_{11} < k_{12}$

Bifurcations

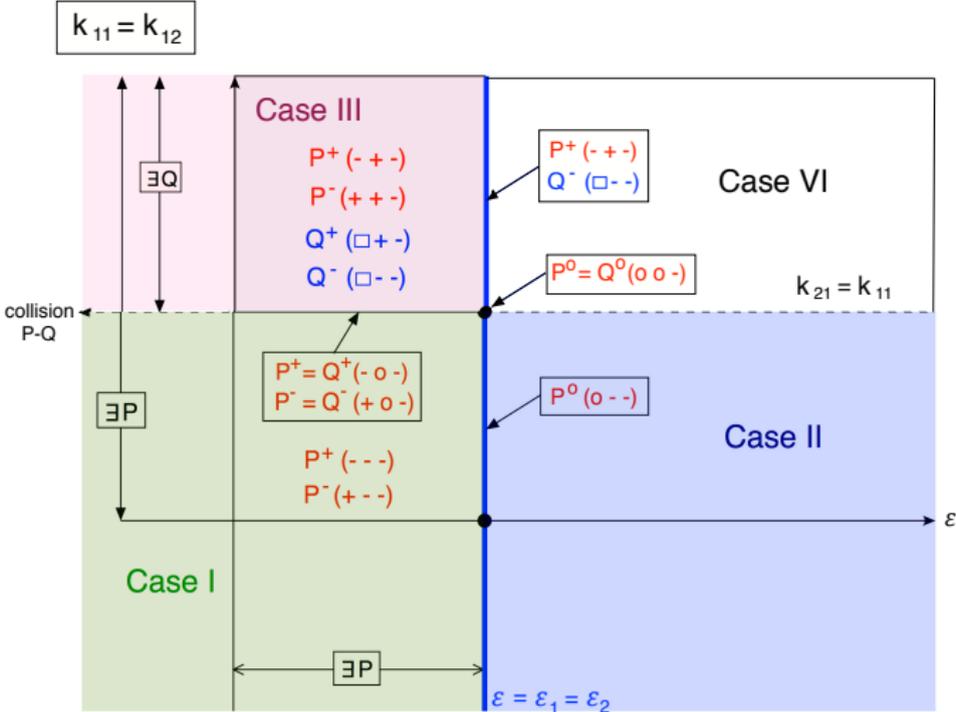


Figure: Case $k_{11} = k_{12}$

Bifurcations

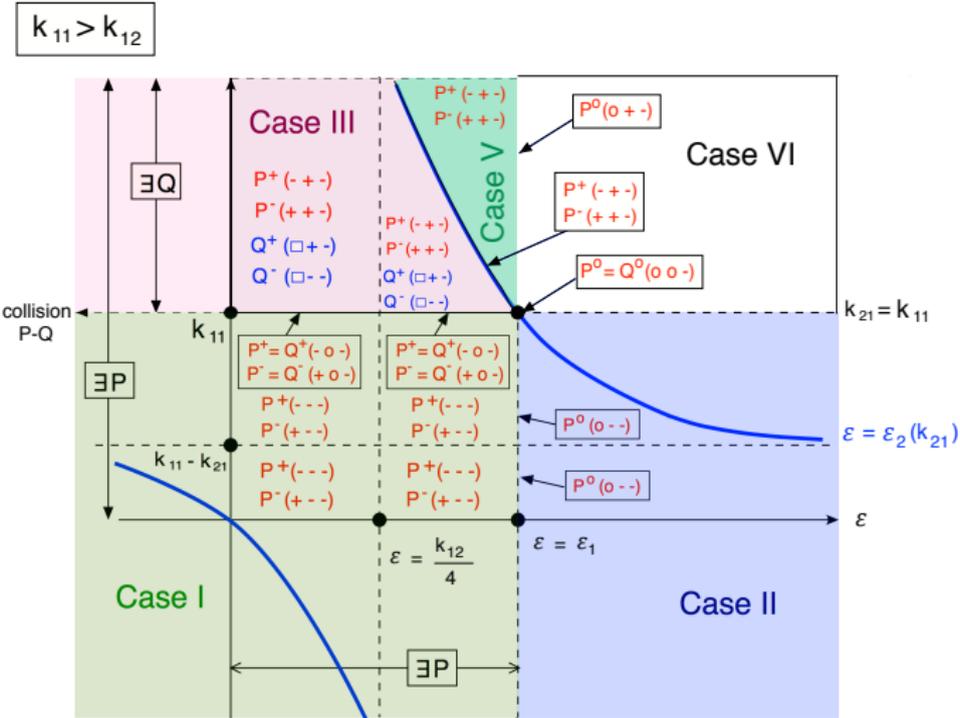


Figure: Case $k_{11} > k_{12}$

Bifurcations

Case	$k_{21} - k_{11}$	ε	P^-	P^+	Q^-	Q^+
I	< 0	$\varepsilon < \varepsilon_1$	Saddle	Attractor	\nexists	\nexists
II	< 0	$\varepsilon > \varepsilon_1$	\nexists	\nexists	\nexists	\nexists
III	> 0	$\varepsilon < \min\{\varepsilon_1, \varepsilon_2\}$	Saddle	Saddle	Saddle	Attractor
IV	> 0	$\varepsilon_1 < \varepsilon < \varepsilon_2$	\nexists	\nexists	Saddle	Attractor
V	> 0	$\varepsilon_2 < \varepsilon < \varepsilon_1$	Saddle	Saddle	\nexists	\nexists
VI	> 0	$\varepsilon > \max\{\varepsilon_1, \varepsilon_2\}$	\nexists	\nexists	\nexists	\nexists

Table: Existence and stability of equilibria in Ω in the planar case.

Non-existence of periodic orbits

- **2-member hypercycle:** No p.o. by a Poincaré-Hopf argument.
- **3-member hypercycle:** We divide Ω in several subdomains and consider suitable Poincaré section. Numerical evidence of non-existence of p.o.

Stochastic spatial dynamics

- Assembly of complex biomolecules in a 3D-environment is implausible (Parsons-Lee-Smith'98).
- Mineral surfaces (honey-combed feldspar) could offer suitable organized environment and protection from dispersion and hydrolysis.
- Use of **Cellular automata** (CA) to investigate spatial dynamics of hypercycles (Boerlijst-Hogeweg'91, Sardanyés-Solé'07, Scheuring et al.'03, Attolini-Stadler'06).

Building our Cellular Automata

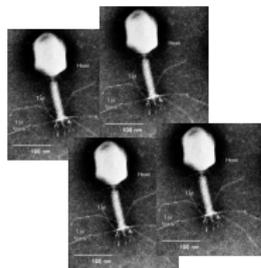
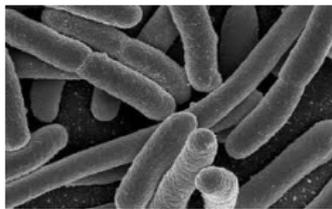
- We consider a $L \times L$ lattice $\rightarrow L^2$ cells. Typically $L = 200$.
- Each cell can contain: S_0 (void), S_1 , S_2 (2-member) or also S_3 (3-member hypercycle).
- We will run our CA for $\tau = 5 \cdot 10^3, 10^5, 18 \cdot 10^4, \dots$
- Number of simulations to get an averaged result: 10.
- **Normalized population of replicators:**

$$N_i = \frac{1}{L^2} \sum_j^L \sum_\ell^L S_i(j, \ell), \quad i = 1, \dots, \nu,$$

with $\nu = 2$ or $\nu = 3$ (2 or 3-member hypercycle).

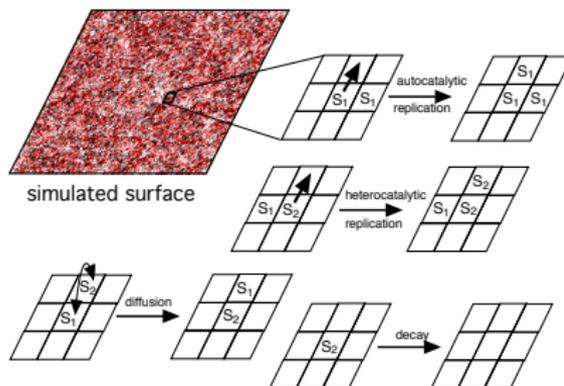
- Initial conditions: equidistribution, i.e., $N_{0,1,2} = 1/3$ for 2-member and $N_{0,1,2,3} = 1/4$ for 4-member.

Stochastic spatial dynamics



Hypercube amb bit strings

with interactions



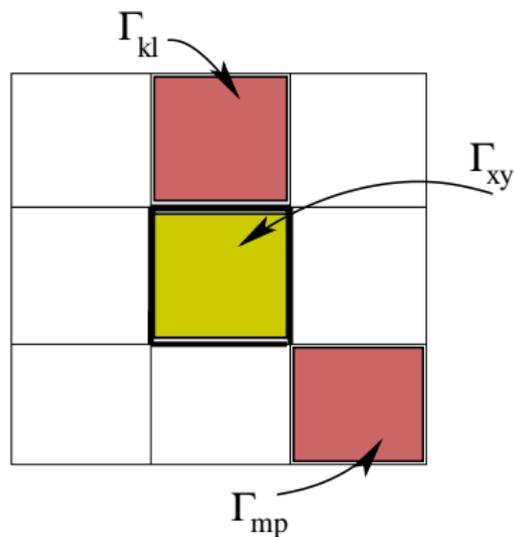
Cellular Automata: rules

- At each generation τ we take a cell Γ_{xy} of the lattice and follow these three steps:
 - 1 Catalytic replication.
 - 2 Degradation.
 - 3 Diffusion.
- This choice of Γ_{xy} is done L^2 times each generation \Rightarrow in average each cell is affected in each generation.

Cellular Automata: rules

1.- Catalytic replication.

Taken Γ_{xy} , we choose random two cells Γ_{kl} and Γ_{mp} from its Moore domain (8-nearest nghbs).

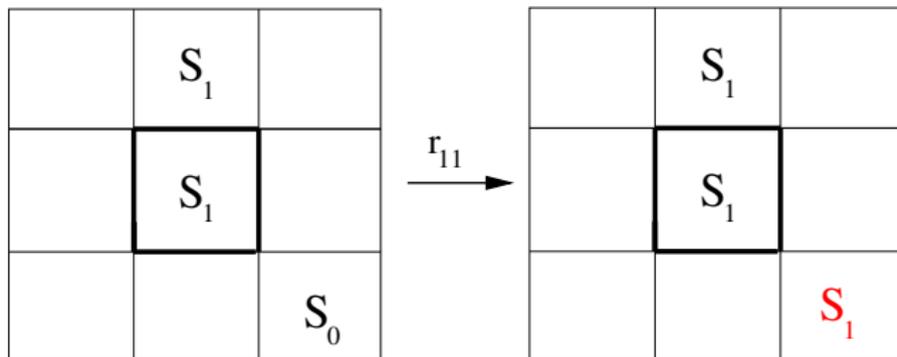


Cellular Automata: rules

1.- Catalytic replication.

Taken Γ_{xy} , we choose random two cells Γ_{kl} and Γ_{mp} from its Moore domain (8-nearest nghbs).

a) Autocatalytic replication

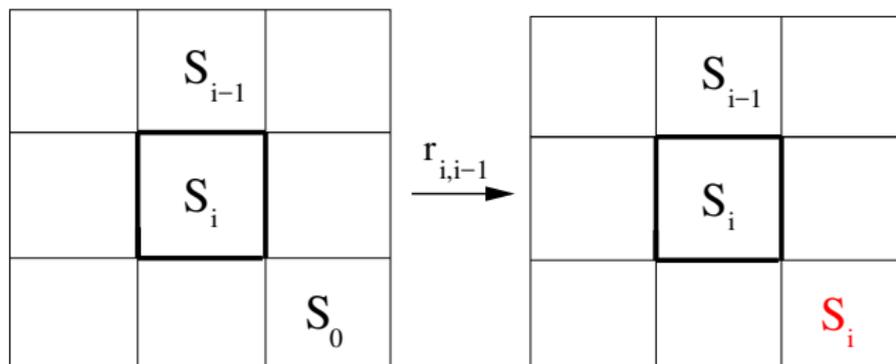


Cellular Automata: rules

1.- Catalytic replication.

Taken Γ_{xy} , we choose random two cells Γ_{kl} and Γ_{mp} from its Moore domain (8-nearest nghbs).

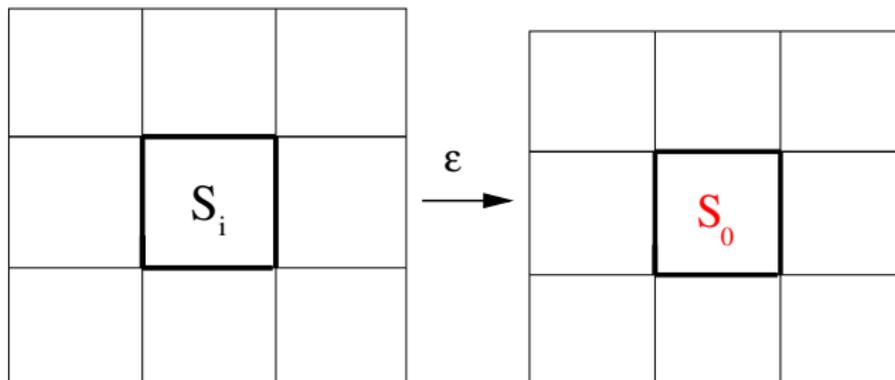
b) Heterocatalytic replication



$i \neq 0, 1$ and cyclic ordering: $S_\nu \rightarrow S_1 \rightarrow S_2 \rightarrow \dots \rightarrow S_\nu$.

Cellular Automata: rules

2.- Degradation.



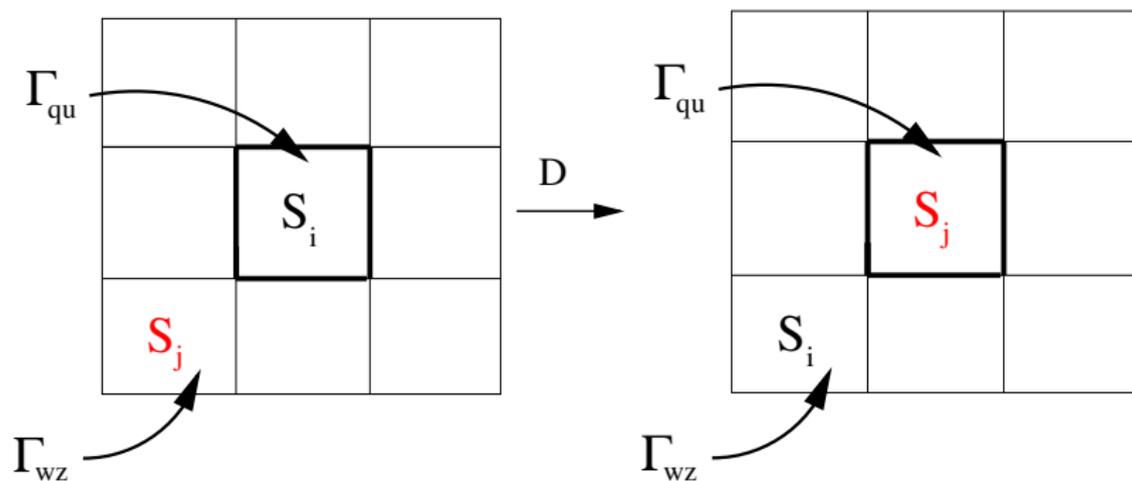
for $i \neq 0$.

Cellular Automata: rules

3.- Diffusion.

It is always applied after catalytic replication + degradation.

We choose random cell Γ_{qu} and after, from its Moore domain, a random Γ_{wz} .



with fixed $D \in [0, 1]$.

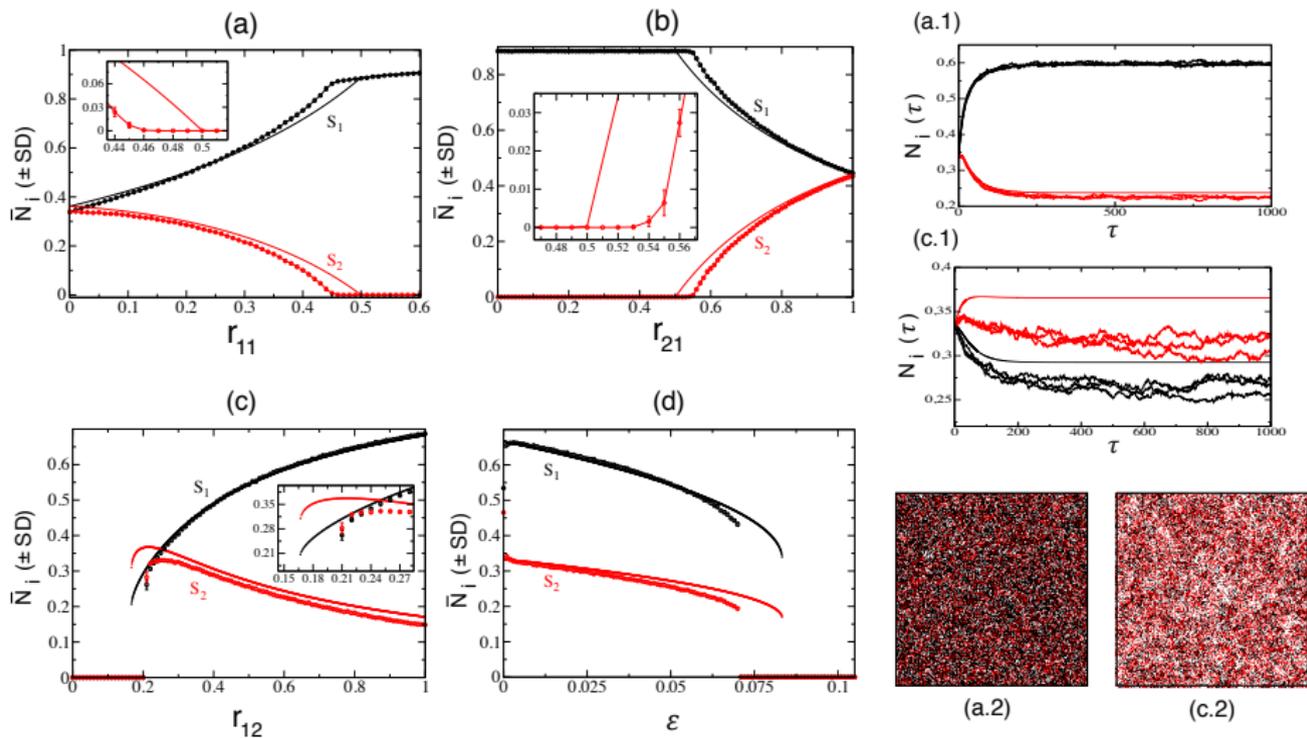


Figure: Spatial and temporal dynamics for a 2-member hypercycle with shortcircuit. Circles denote averaging over 10 independent replicas at $\tau = 5000$ time generations. Thick lines represent the mean field predictions. Bottom-right: final spatial distributions for cases (a.1) and (c.1), respectively.

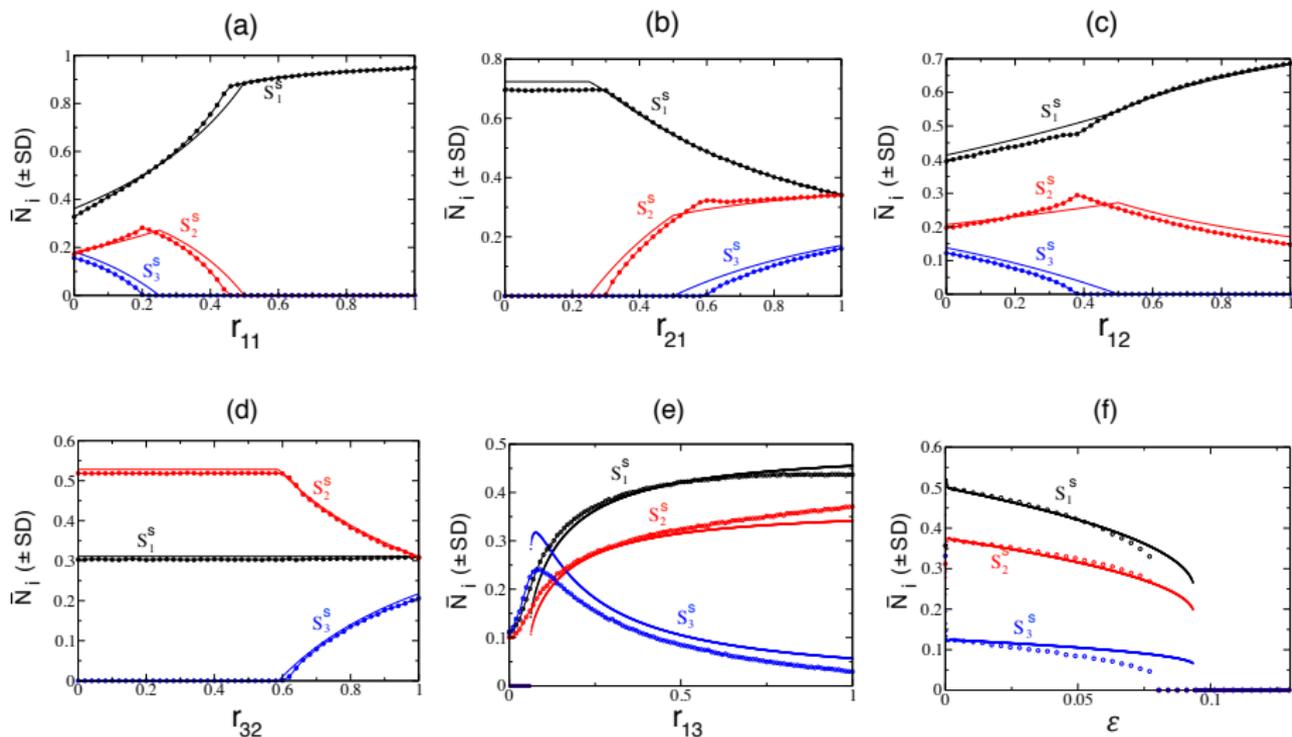


Figure: Dependence of the population equilibria (stable states, $S_{1,2,3}^s$) on the model probabilities for the three-member hypercycle with two short-circuits. Values: 10 independent replicas at $\tau = 5000$ time generations, $D = 0.25$ (circles). (a) $r_{12,21,13} = 0.5$ and $r_{32} = 1$. (b) $r_{11} = 0.25$, $r_{12,13} = 0.5$ and $r_{32} = 1$. (c) $r_{11} = 0.25$, $r_{21} = 0.5$, $r_{32} = 1$, and $r_{13} = 0.75$. (d) $r_{11} = 0.15$, $r_{12,13} = 0.5$, and $r_{21} = 1$. (e) $r_{11} = 0.25$, $r_{12} = 0.5$, $r_{21} = 0.75$, and $r_{32} = 1$. In (a-e) $\varepsilon = 0.05$. (f) $r_{11} = 0.25$, $r_{12,13} = 0.5$, $r_{21} = 0.75$, and $r_{32} = 1$. The solid lines correspond to the predictions of the mean field model. Populations S_1 and S_2 are represented in black and red, respectively, while S_3 population values are indicated in blue.

Some references



Martin N. Nowack

What is a quasispecies? *Trends Ecol Evol.*, 1992 Apr;7(4):118-21. doi:
[10.1016/0169-5347\(92\)90145-2](https://doi.org/10.1016/0169-5347(92)90145-2)



M. Eigen

Selforganization of Matter and the Evolution of Biological Macromolecules
Naturwissenschaften 58, 465–523 (1971).



M. Eigen and P. Schuster

A principle of natural self-organization. *Naturwissenschaften* 64, 541–565 (1977).