Some Mathematical Challenges from Life Sciences

Part II

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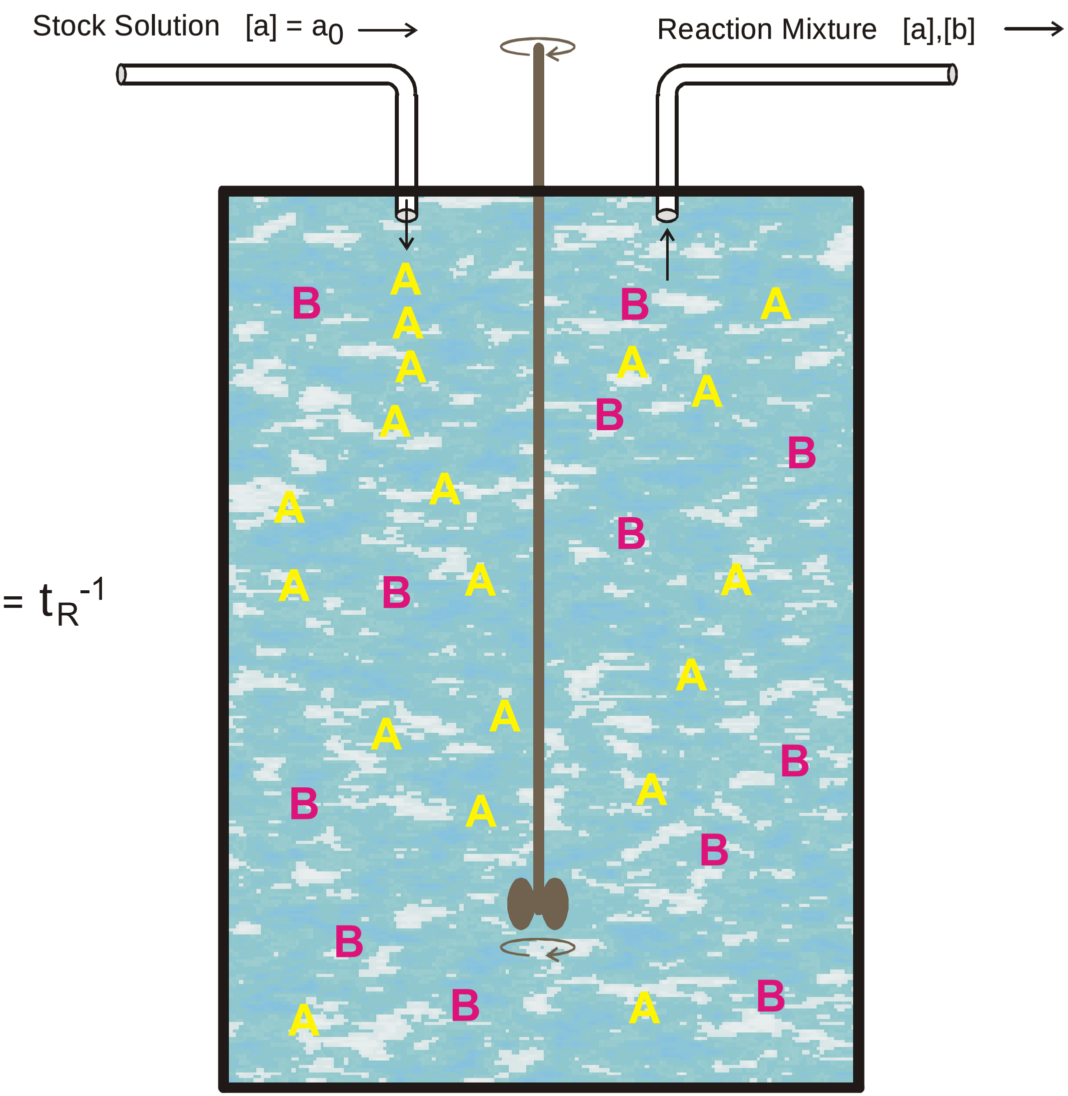
Web-Page for further information:

http://www.tbi.univie.ac.at/~pks

1. Mathematics and the life sciences in the 21st century

2. **Selection dynamics**

3. RNA evolution *in silico* and optimization of structure and properties

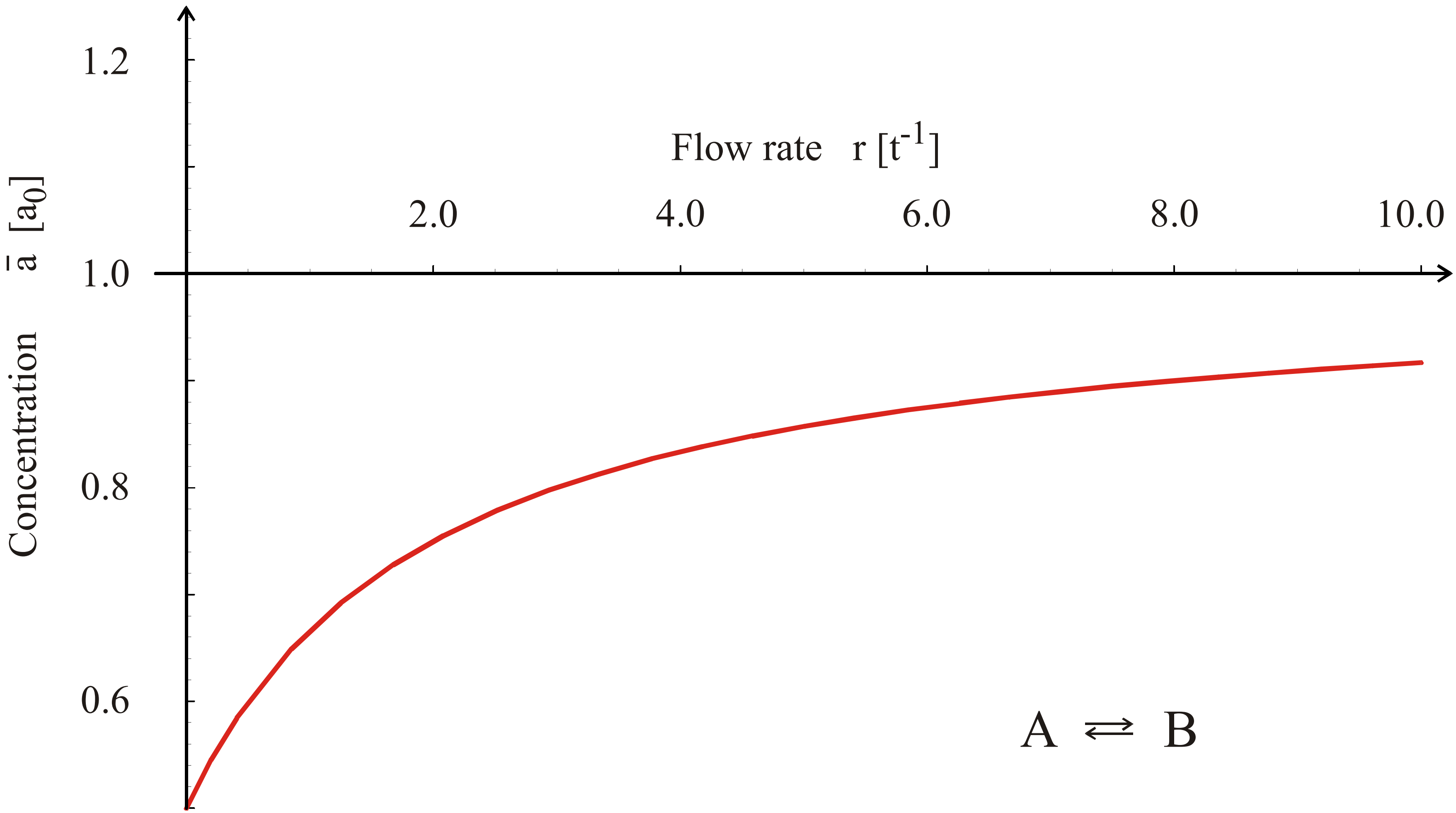


Flow rate $r = t_R^{-1}$

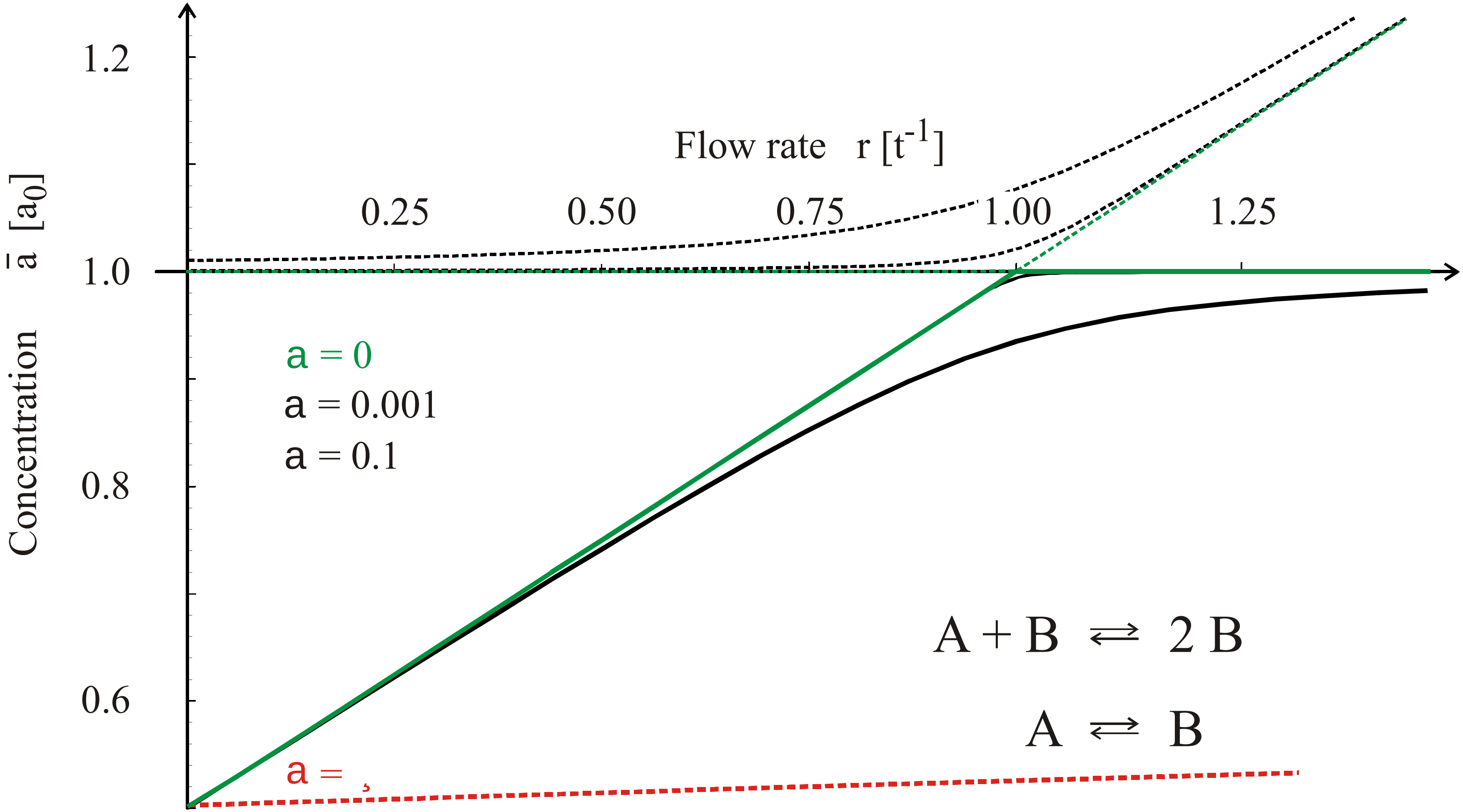
A Á B

B Á A

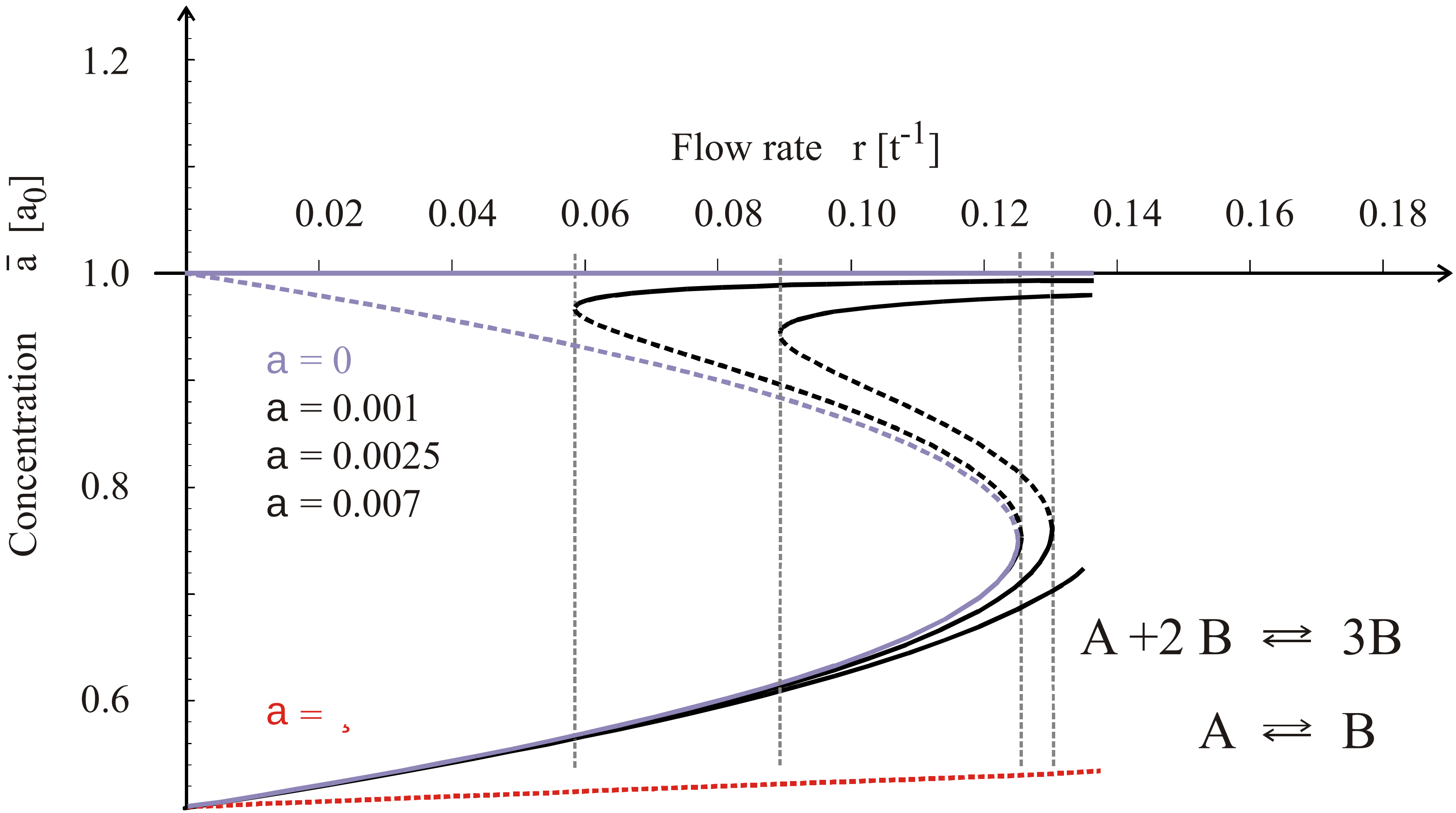
Reactions in the continuously stirred tank reactor (CSTR)



Reversible first order reaction in the flow reactor



Autocatalytic second order and uncatalyzed reaction in the flow reactor



Autocatalytic third order and uncatalyzed reaction in the flow reactor

Autocatalytic third order reactions

Direct, $A + 2X \rightarrow 3X$, or hidden in the reaction mechanism (Belousow-Zhabotinskii reaction).

→ Multiple steady states

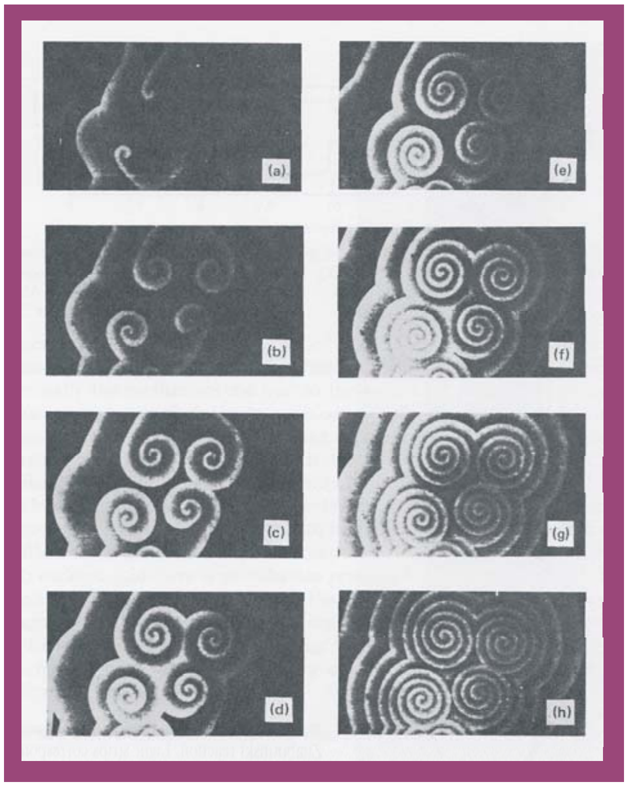
→ Oscillations in homogeneous solution

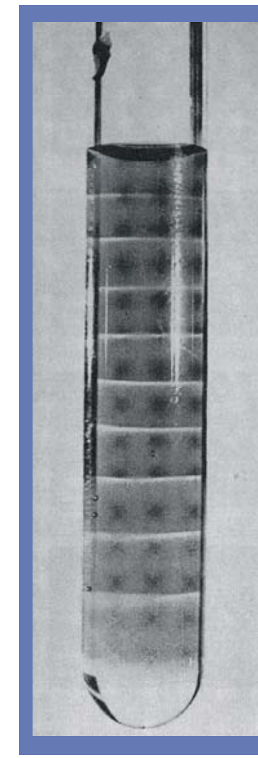
→ Deterministic chaos

→ Turing patterns

→ Spatiotemporal patterns (spirals)

→ Deterministic chaos in space and time





Pattern formation in autocatalytic third order reactions

G.Nicolis, I.Prigogine. *Self-Organization in Nonequilibrium Systems. From Dissipative Structures to Order through Fluctuations*. John Wiley, New York 1977

Autocatalytic second order reactions

Direct, $\mathbf{A + I \rightarrow 2\,I}$, or hidden in the reaction mechanism

→ Chemical self-enhancement

→ Combustion and chemistry of flames

→ **Selection of laser modes**

→ **Selection of molecular species competing for common sources**

Autocatalytic second order reactions are the basis of selection processes.

The autocatalytic step is formally equivalent to replication or reproduction.

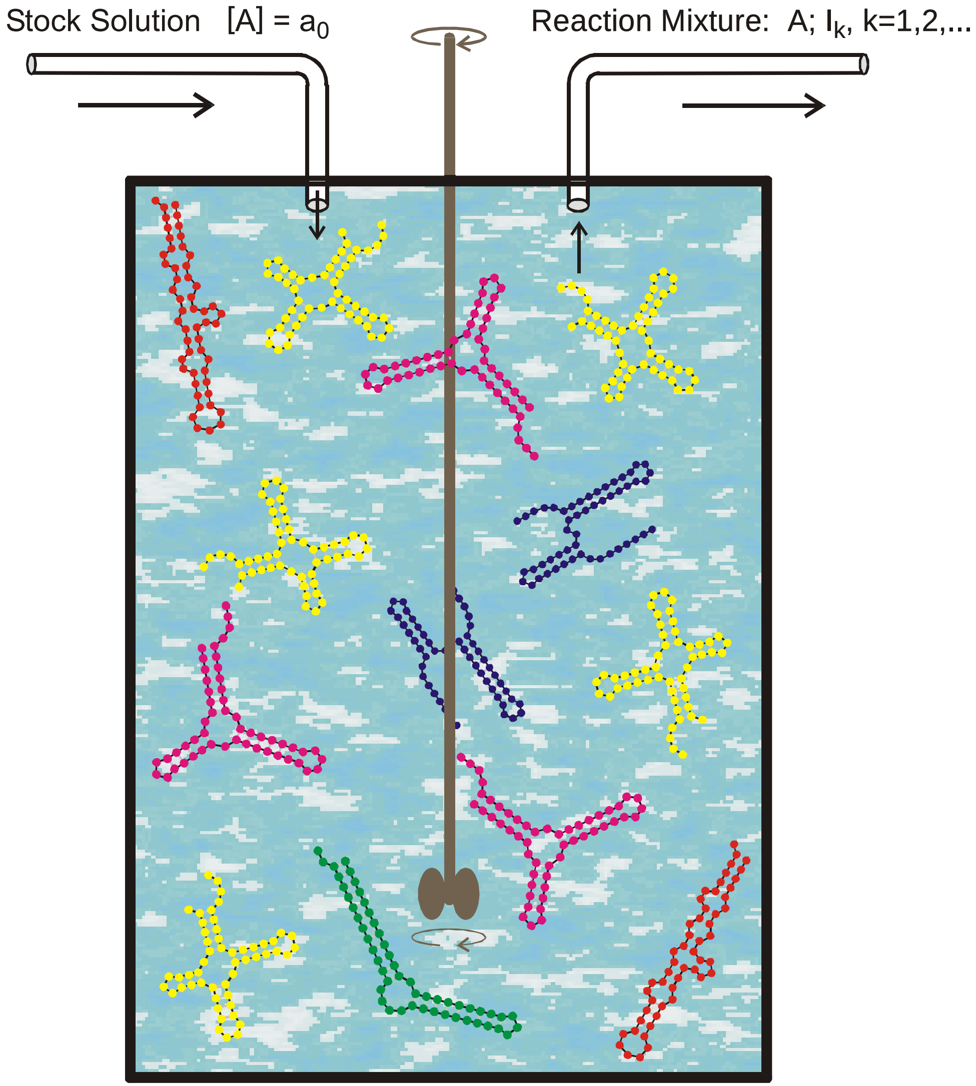
$$A + I_1 \underset{d_1}{\overset{k_1}{\rightleftharpoons}} 2\, I_1$$

$$A + I_2 \underset{d_2}{\overset{k_2}{\rightleftharpoons}} 2\, I_2$$

$$A + I_3 \underset{d_3}{\overset{k_3}{\rightleftharpoons}} 2\, I_3$$

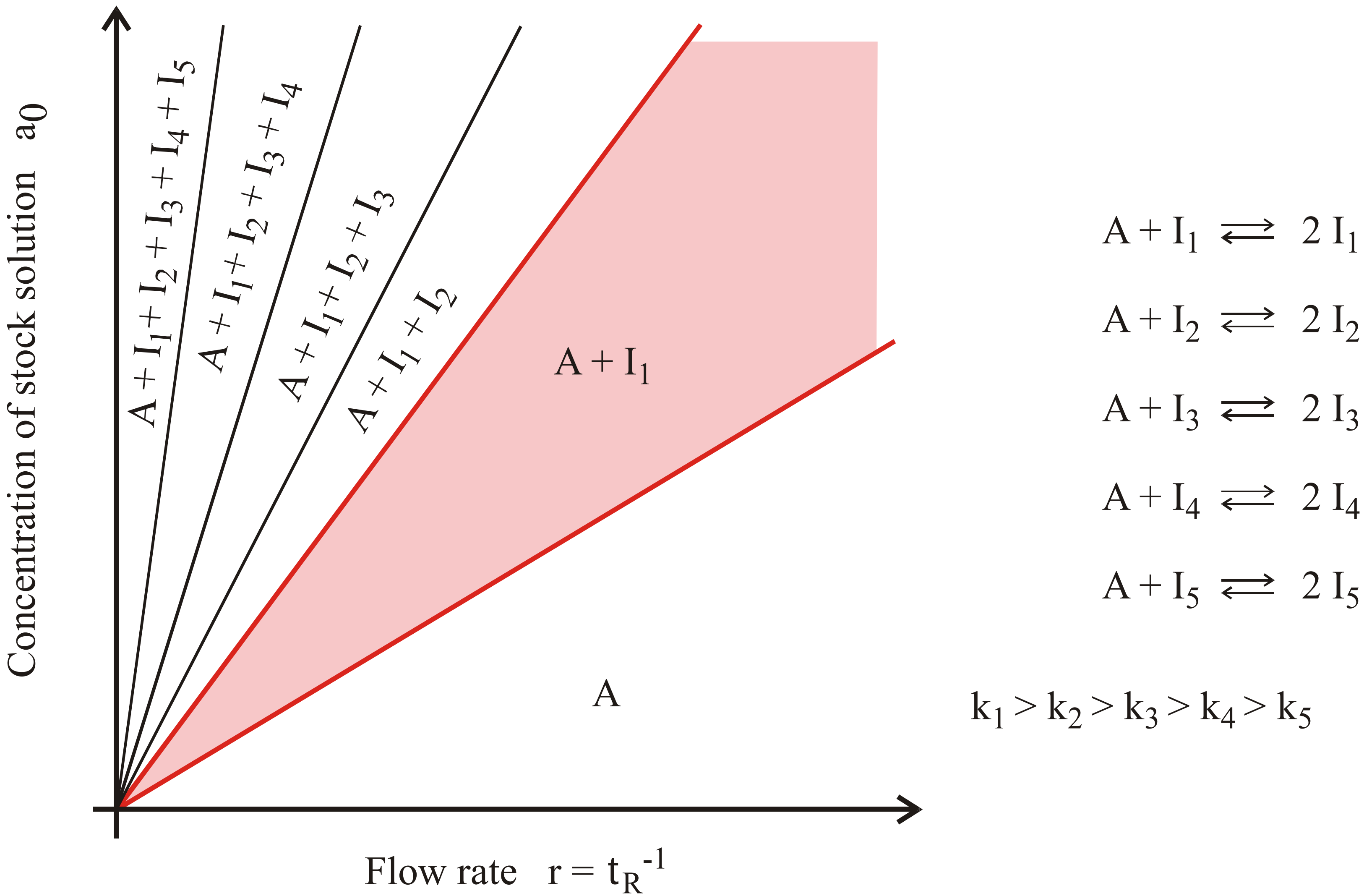
$$A + I_4 \underset{d_4}{\overset{k_4}{\rightleftharpoons}} 2\, I_4$$

$$A + I_5 \underset{d_5}{\overset{k_5}{\rightleftharpoons}} 2\, I_5$$

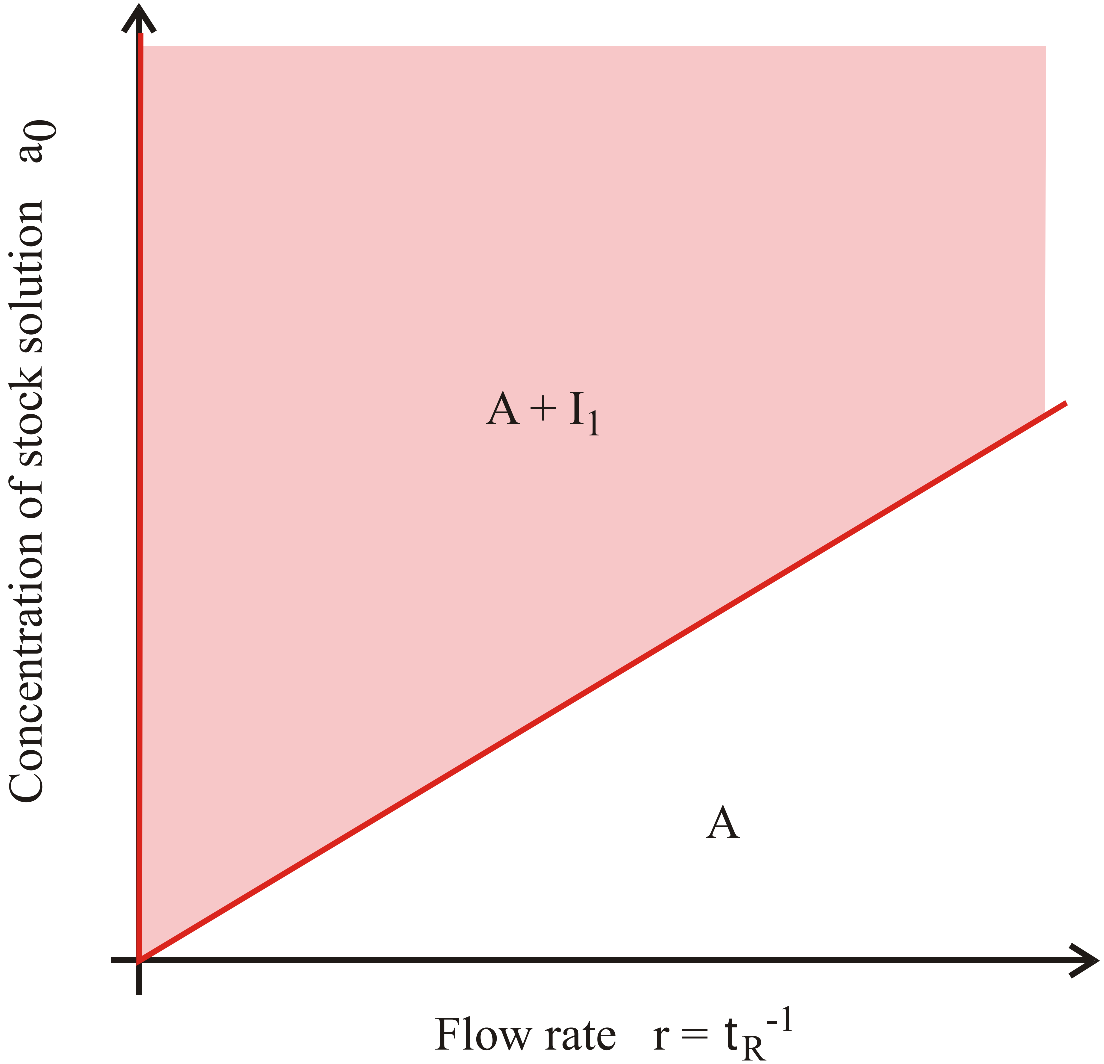


Replication in the flow reactor

P.Schuster & K.Sigmund, Dynamics of evolutionary optimization, *Ber.Bunsenges.Phys.Chem.* **89**: 668-682 (1985)



Selection in the flow reactor: Reversible replication reactions



$A + I_1 \longrightarrow 2\,I_1$

$A + I_2 \longrightarrow 2\,I_2$

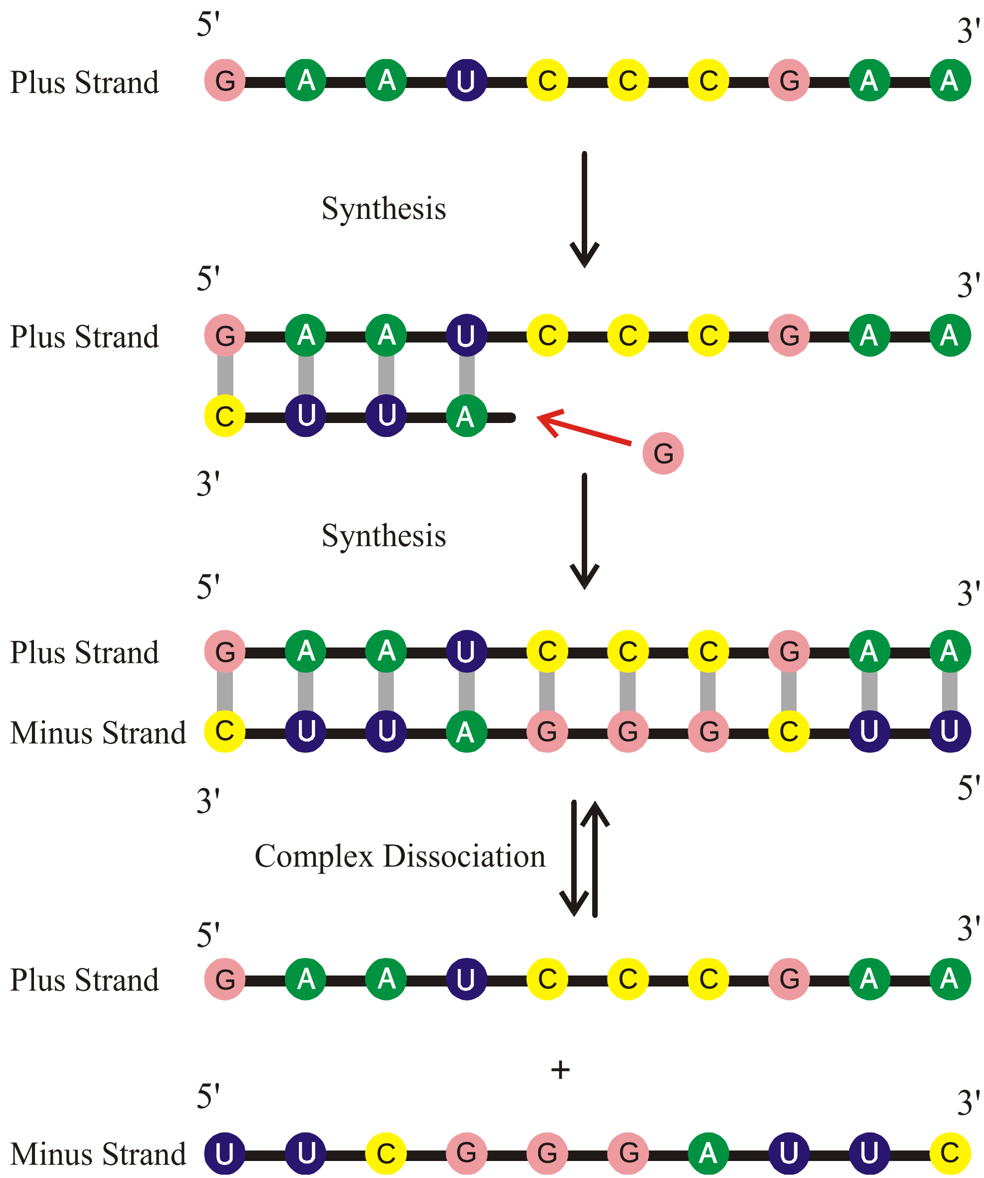
$A + I_3 \longrightarrow 2\,I_3$

$A + I_4 \longrightarrow 2\,I_4$

$A + I_5 \longrightarrow 2\,I_5$

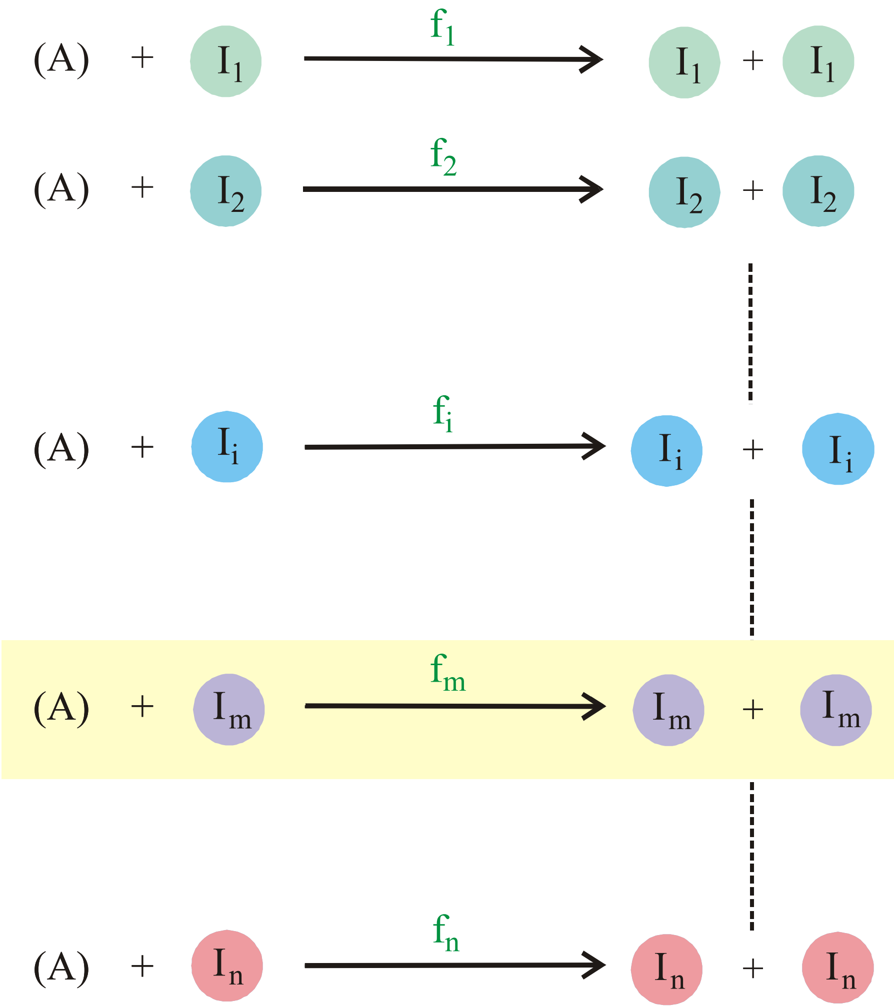
$k_1 > k_2 > k_3 > k_4 > k_5$

Selection in the flow reactor: Irreversible replication reactions



Complementary replication as the simplest copying mechanism of RNA Complementarity is determined by Watson-Crick base pairs:

G Í C and A=U



$$dx_i / dt = f_i x_i - x_i \Phi = x_i (f_i - \Phi)$$

$\Phi = \Sigma_j f_j x_j$; $\Sigma_j x_j = 1$; $i,j = 1,2,\ldots,n$

$[I_i] = x_i \geq 0$; $i = 1,2,\ldots,n$;

$[A] = a = \text{constant}$

$$f_m = \max \{f_j; j=1,2,\ldots,n\}$$

$x_m(t) \to 1$ for $t \to \infty$

Reproduction of organisms **or replication** of molecules as the basis of selection

Selection equation: $[\mathrm{I}_i] = x_i$ Æ 0 , $f_i > 0$

$$\frac{dx_i}{dt} = x_i\left(f_i - \phi\right), \quad i = 1,2,\cdots,n; \quad \sum\nolimits_{i=1}^{n} x_i = 1; \quad \phi = \sum\nolimits_{j=1}^{n} f_j x_j = \overline{f}$$

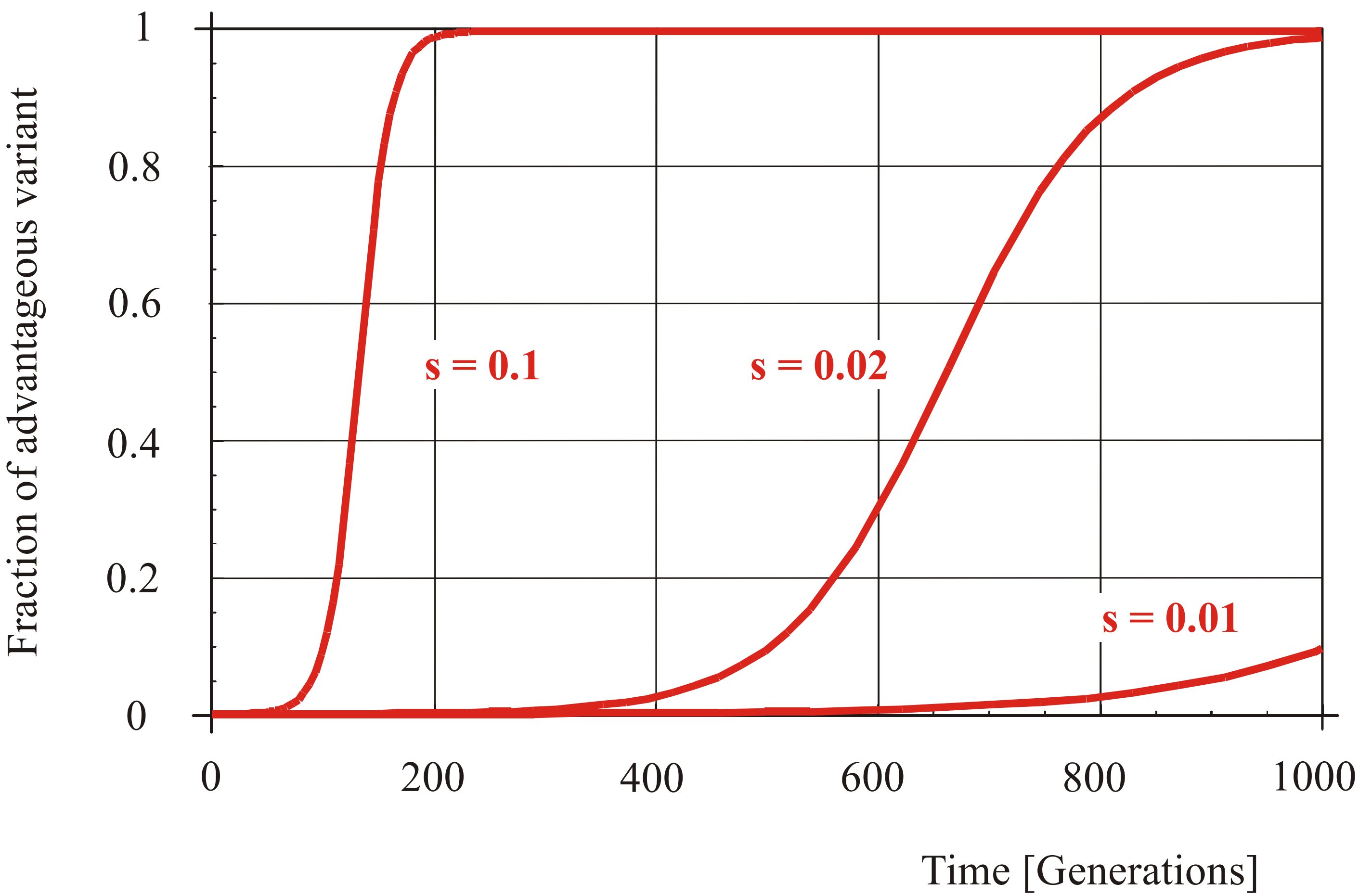
Mean fitness or dilution flux, ϕ (t), is a **non-decreasing function** of time,

$$\frac{d\phi}{dt} = \sum_{i=1}^{n} f_i \frac{dx_i}{dt} = \overline{f^{\,2}} - \left(\overline{f}\right)^2 = \mathrm{var}\{f\} \geq 0$$

Solutions are obtained by integrating factor transformation

$$x_i(t) = \frac{x_i(0)\cdot \exp\left(f_i t\right)}{\sum\nolimits_{j=1}^{n} x_j(0)\cdot \exp\left(f_j t\right)}; \quad i = 1,2,\cdots,n$$

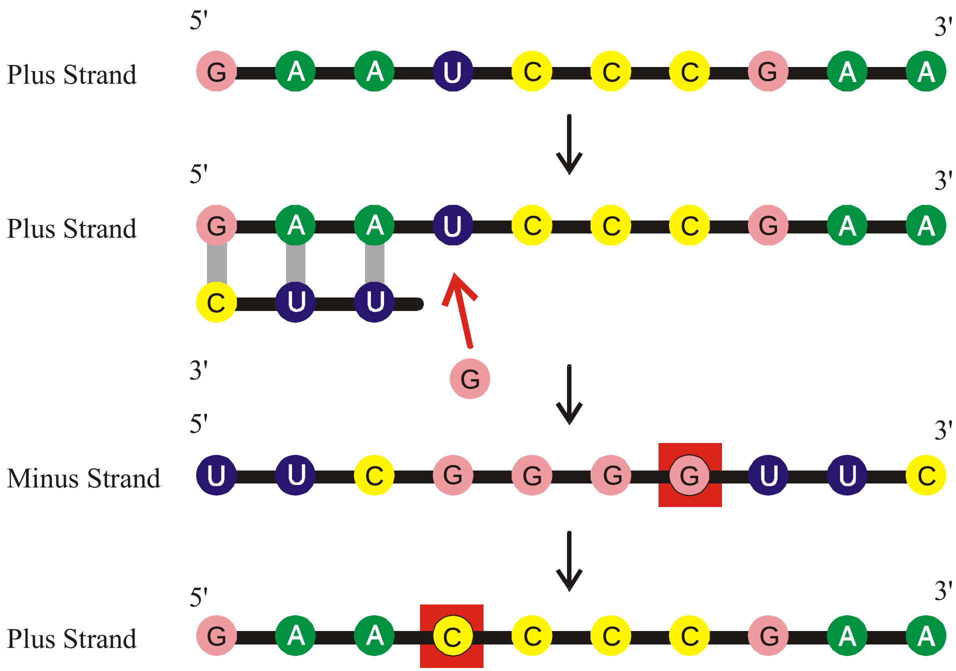
$\mathbf{s} = (f_2 - f_1) / f_1;\ f_2 > f_1;\ x_1(0) = 1 - 1/N;\ x_2(0) = 1/N$



Selection of advantageous mutants in populations of N = 10 000 individuals

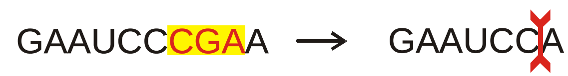
Changes in RNA sequences originate from replication errors called **mutations**.

Mutations occur uncorrelated to their consequences in the selection process and are, therefore, commonly characterized as **random elements** of evolution.



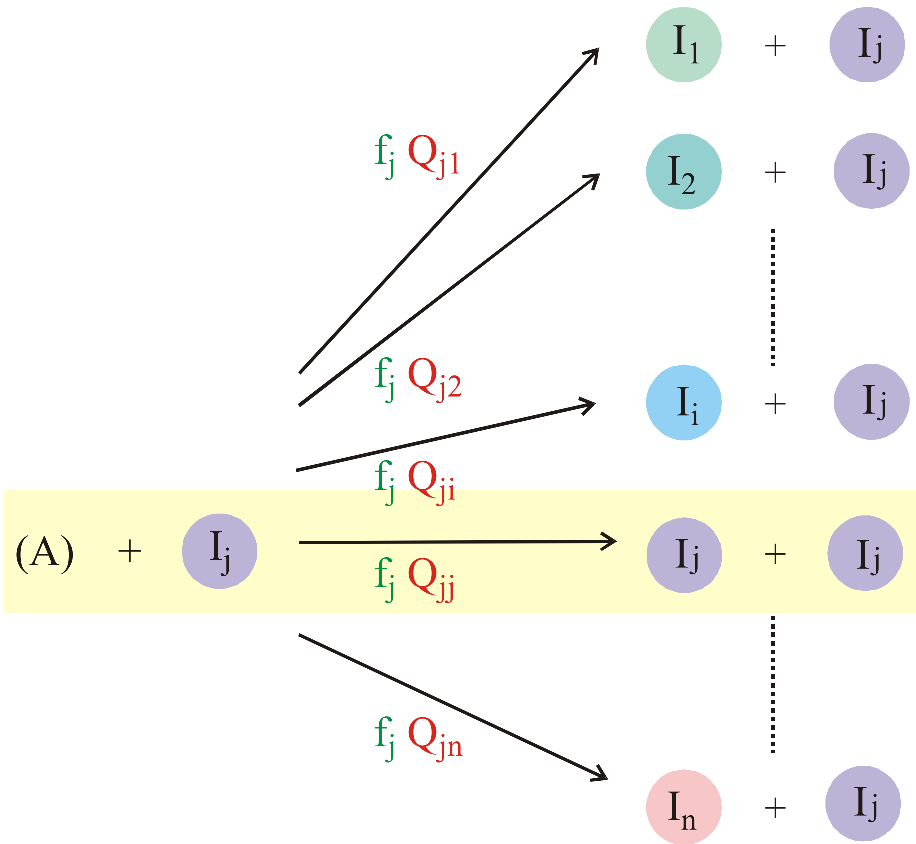
Point Mutation

Insertion



Deletion

The origins of changes in RNA sequences are **replication errors** called **mutations**.



$$dx_i \,/\, dt = \Sigma_j \, f_j Q_{ji} \, x_j - x_i \, \Phi$$

$\Phi = \Sigma_j \, f_j \, x_i$; $\Sigma_j \, x_j = 1$; $\Sigma_i \, Q_{ij} = 1$

$[I_i] = x_i$ Æ 0 ; $i = 1,2,\ldots,n$;

$[A] = a =$ constant

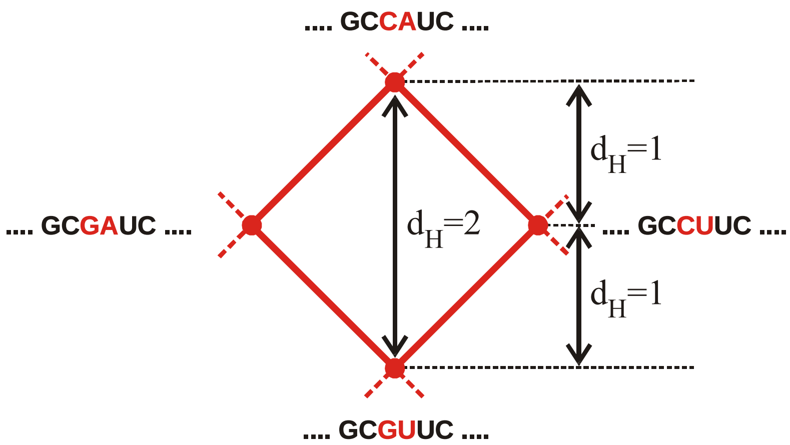
$$Q_{ij} = (1-p)^{\ell - d(i,j)} \, p^{d(i,j)}$$

p .... Error rate per digit

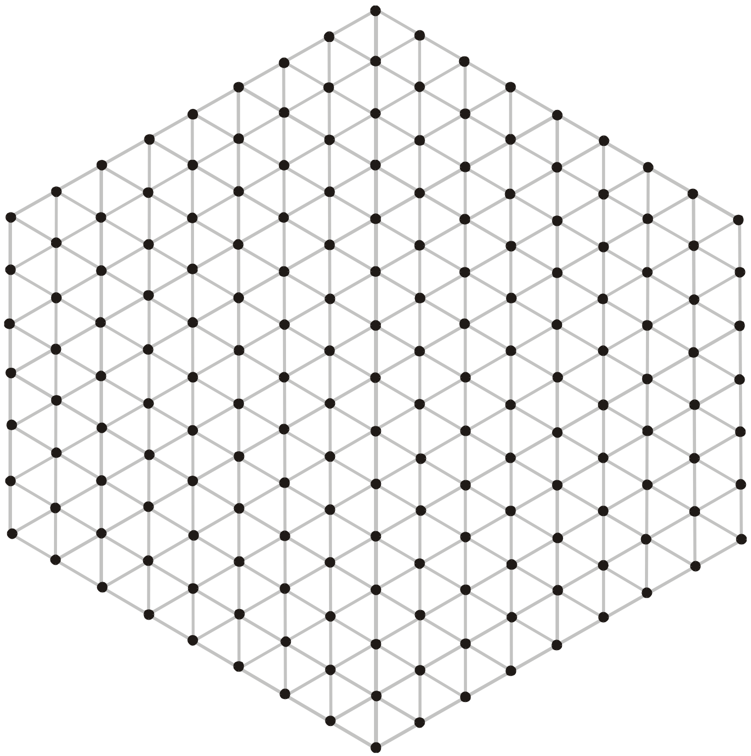
ℓ .... Chain length of the polynucleotide

d(i,j) .... Hamming distance between I_i and I_j

Chemical kinetics of replication and mutation as parallel reactions



City-block distance in sequence space



2D Sketch of sequence space

Single point mutations as moves in sequence space

Mutation-selection equation: $[\mathrm{I}_i] = x_i$ Æ $0,\ f_i > 0,\ Q_{ij}$ Æ 0

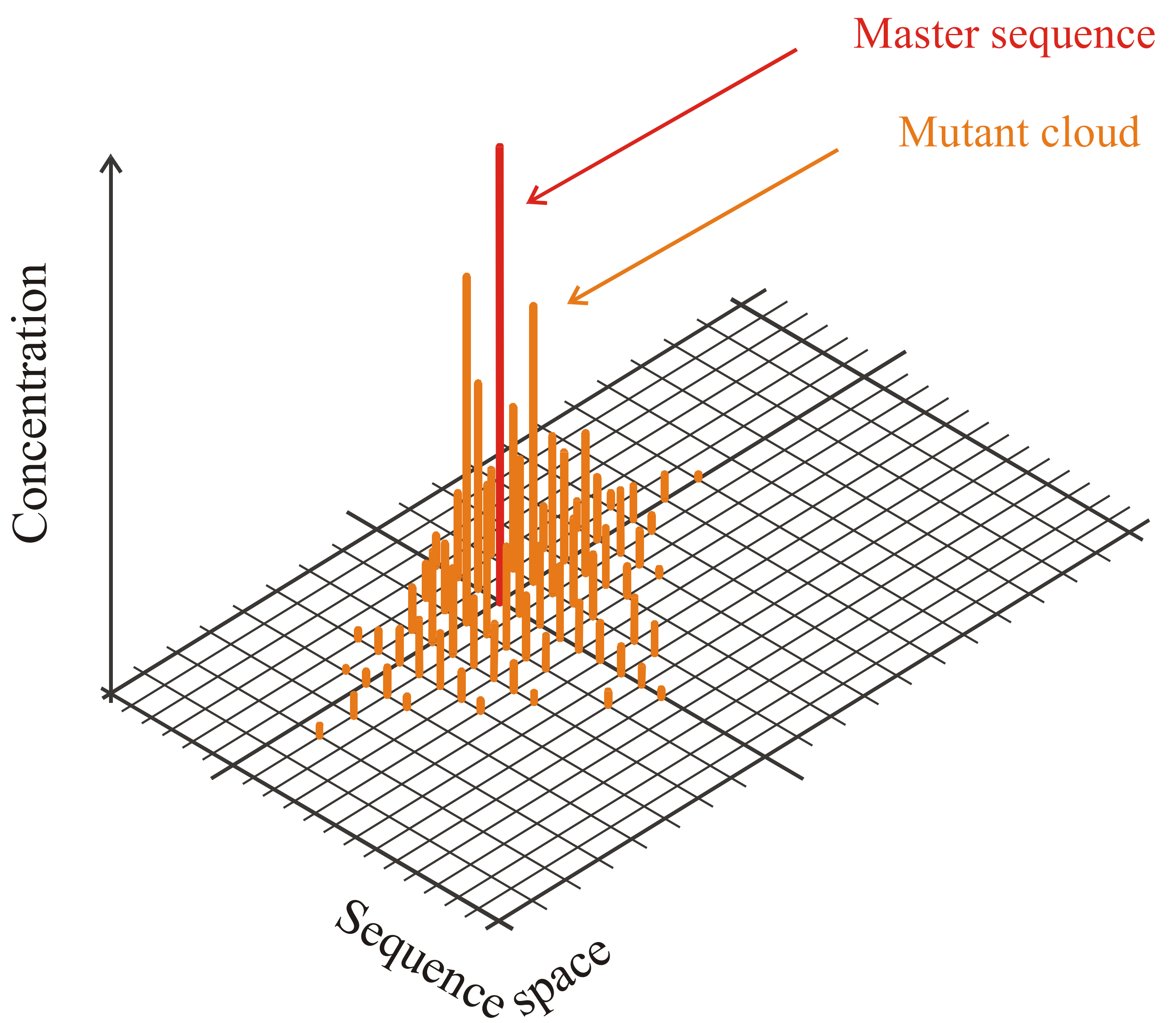
$$\frac{dx_i}{dt} = \sum_{j=1}^{n} f_j Q_{ji}\, x_j - x_i\, \phi\,, \quad i=1,2,\cdots,n\,; \quad \sum_{i=1}^{n} x_i = 1; \quad \phi = \sum_{j=1}^{n} f_j\, x_j = \overline{f}$$

Solutions are obtained after integrating factor transformation by means of an eigenvalue problem

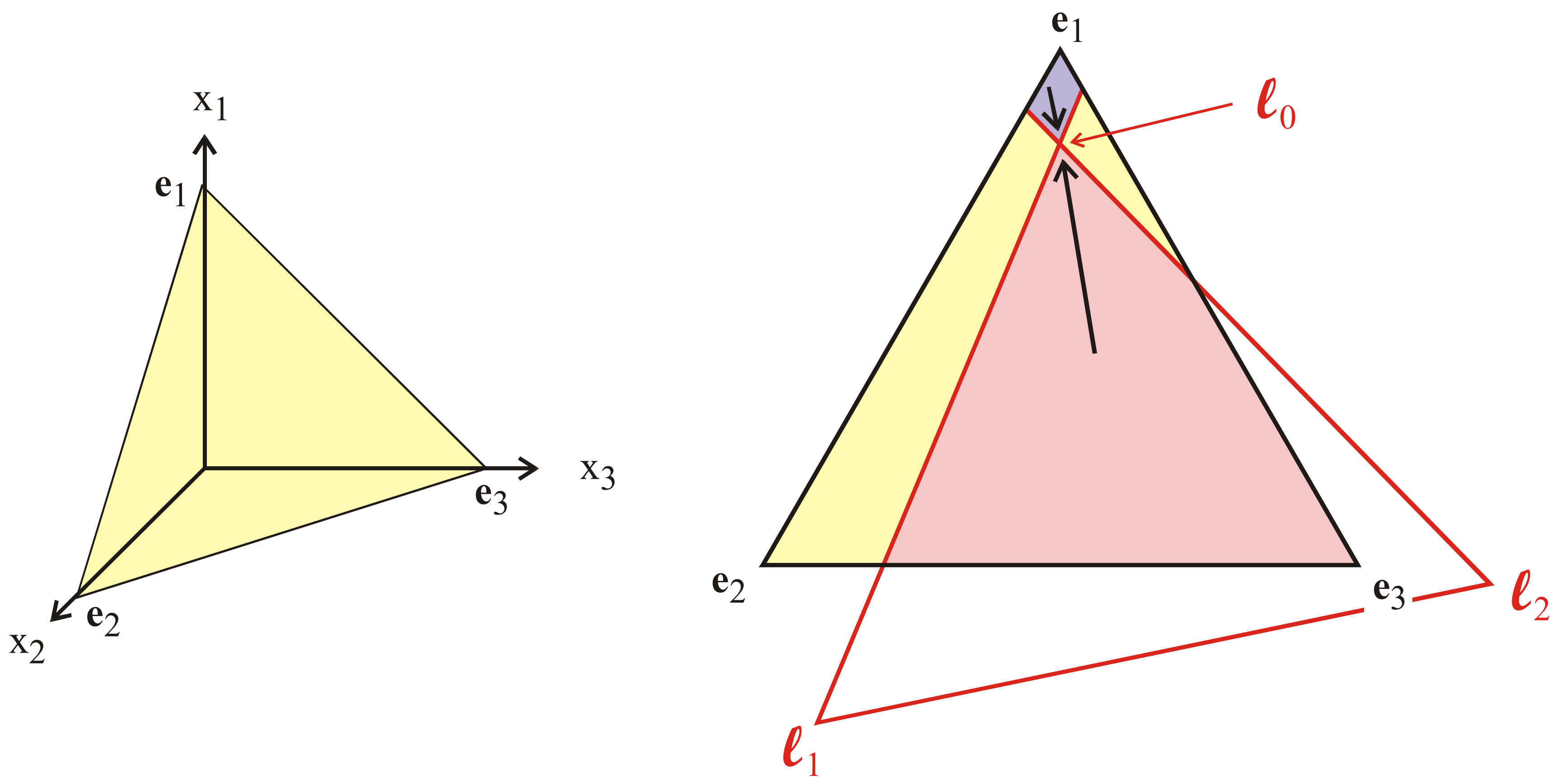
$$x_i(t) = \frac{\sum_{k=0}^{n-1} \ell_{ik} \cdot c_k(0) \cdot \exp(\lambda_k t)}{\sum_{j=1}^{n} \sum_{k=0}^{n-1} \ell_{jk} \cdot c_k(0) \cdot \exp(\lambda_k t)}; \quad i=1,2,\cdots,n\,; \quad c_k(0) = \sum_{i=1}^{n} h_{ki}\, x_i(0)$$

$$W \div \{ f_i Q_{ij};\, i,j=1,2,\cdots,n \};\ L = \{ \ell_{ij};\, i,j=1,2,\cdots,n \};\ L^{-1} = H = \{ h_{ij};\ i,j=1,2,\cdots,n \}$$

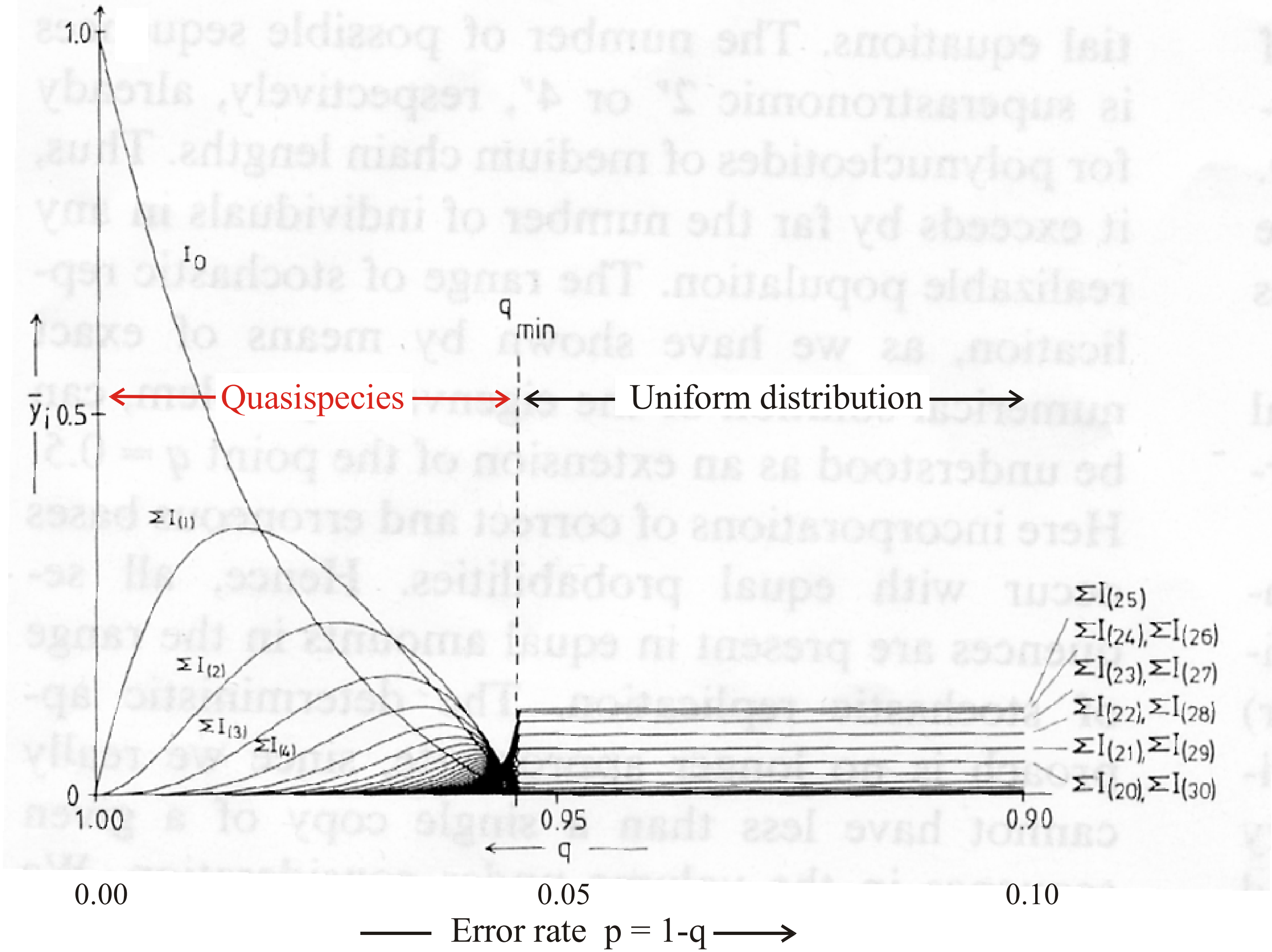
$$L^{-1} \cdot W \cdot L \quad = \quad \Lambda \quad = \quad \{ \lambda_k;\, k=0,1,\cdots,n-1 \}$$



The molecular quasispecies in sequence space



The quasispecies on the concentration simplex $\mathbb{S}_3 = \left\{ x_i \geq 0,\ i = 1, 2, 3;\ \sum_{i=1}^{3} x_i = 1 \right\}$



Quasispecies as a function of the replication accuracy q