Populations in Reality

Quasispecies truncated by integer particle numbers

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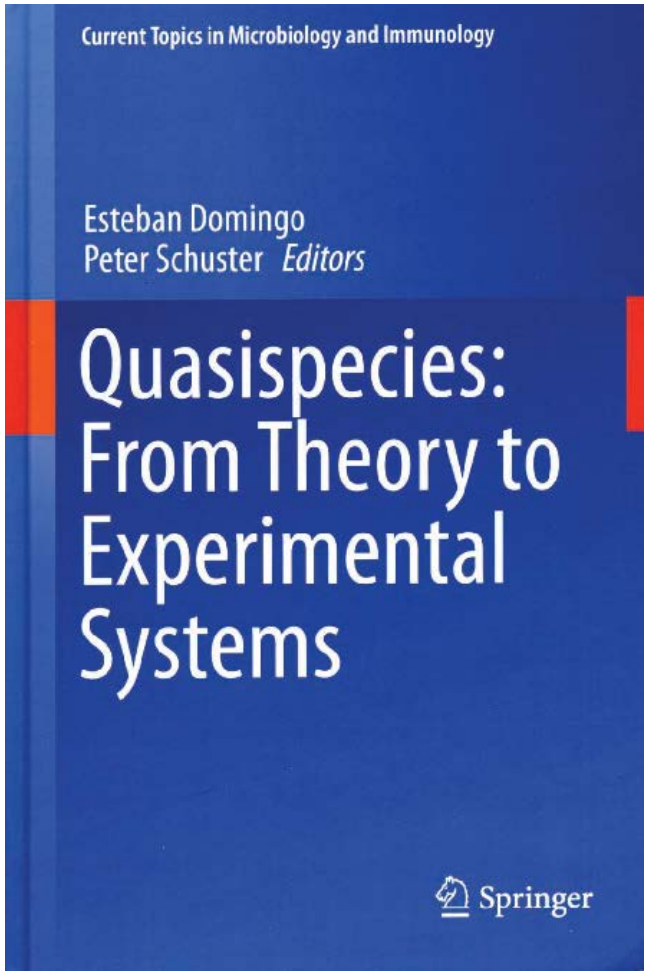
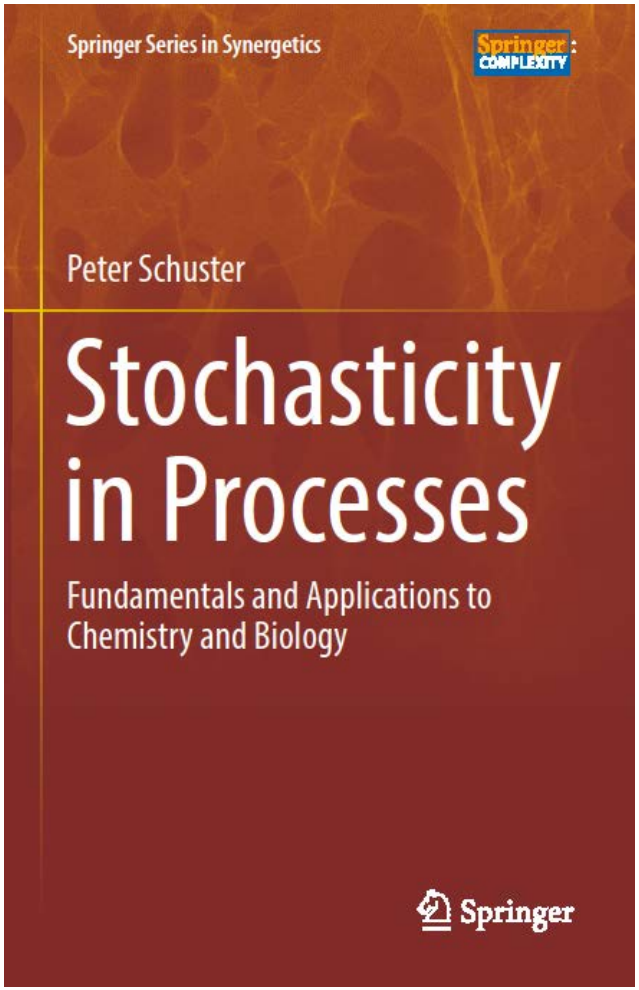
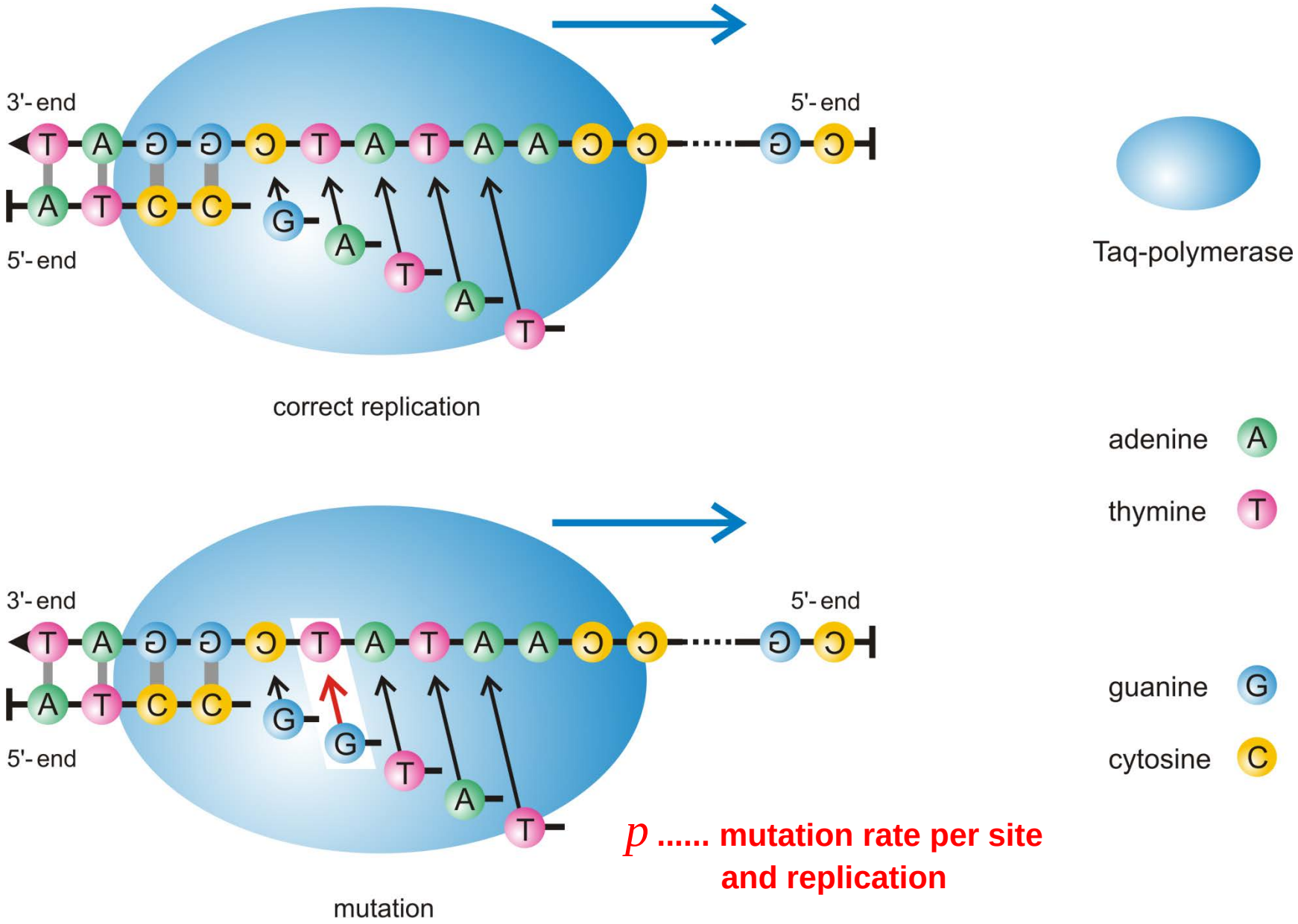
Joint Seminar TBI - KLI

Wien, 27.09.2017

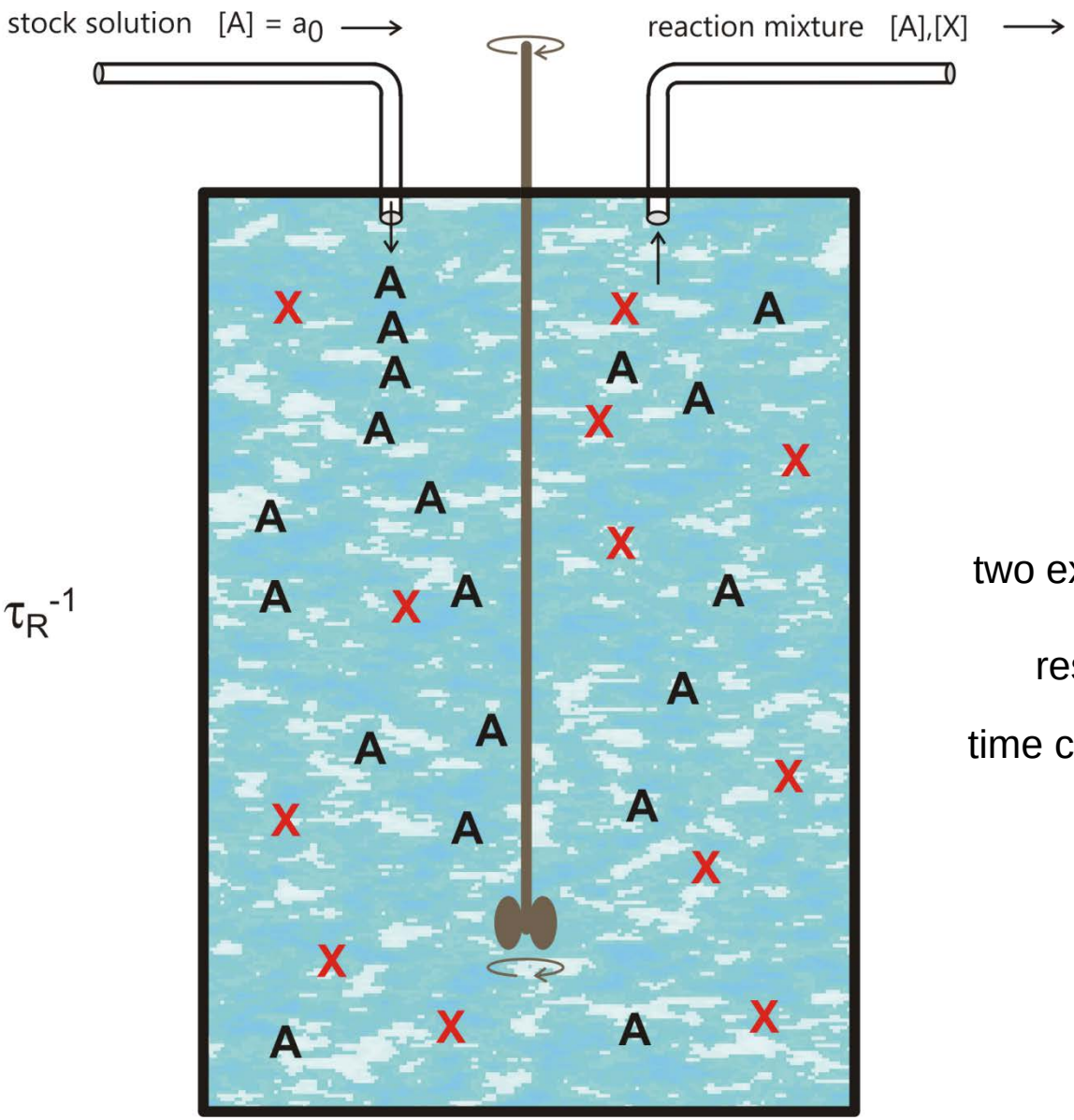
Web-Page for further information:
http://www.tbi.univie.ac.at/~pks







DNA replication and mutation



flow rate $r = \tau_R^{-1}$

two external parameters:

resources **A** … a_0

time constraint … $\tau_R = r^{-1}$

The continuously fed stirred tank reactor (CFSTR)

quasispecies in the flow reactor

$$
\begin{aligned}
* &\xrightarrow{a_0\, r} \mathbf{A}\ , \\
\mathbf{A} + \mathbf{X}_i &\xrightarrow{k_i\, Q_{ji}} \mathbf{X}_i + \mathbf{X}_j\ ;\quad i,j = 1,\ldots,n\ , \\
\mathbf{A} &\xrightarrow{r} \varnothing\ ,\quad \text{and} \\
\mathbf{X}_i &\xrightarrow{r} \varnothing\ ;\ i = 1,\ldots,n
\end{aligned}
$$

$$
[\mathbf{A}] \;=\; a \quad \text{and} \quad [\mathbf{X}_j] \;=\; x_j\ ;\quad j = 1,\ldots,n
$$

$$
\begin{aligned}
\frac{\mathrm{d}a}{\mathrm{d}t} &= -\,a\left(\sum_{j=1}^{n} k_j\, x_j \;+\; r\right) \;+\; a_0\, r \\
\frac{\mathrm{d}x_j}{\mathrm{d}t} &= \left(\sum_{i=1} Q_{ji} k_i\, x_i\right) a \;-\; x_j\, r\ ;\ j = 1,\ldots,n
\end{aligned}
$$

stationary solutions: (i) $\overline{a} = \overline{c}_0,\ \overline{x}_j = 0\,;\ c_0 = \sum_{j=1}^{n} x_j;\ j = 1,\ldots,n$

$$
\text{(ii)}\ \left(\sum_{i=1}^{n} Q_{ji} k_i\, \overline{x}_i\right) \overline{a} \;-\; \overline{x}_j\, r \;=\; 0\,;\ j = 1,\ldots,n
$$

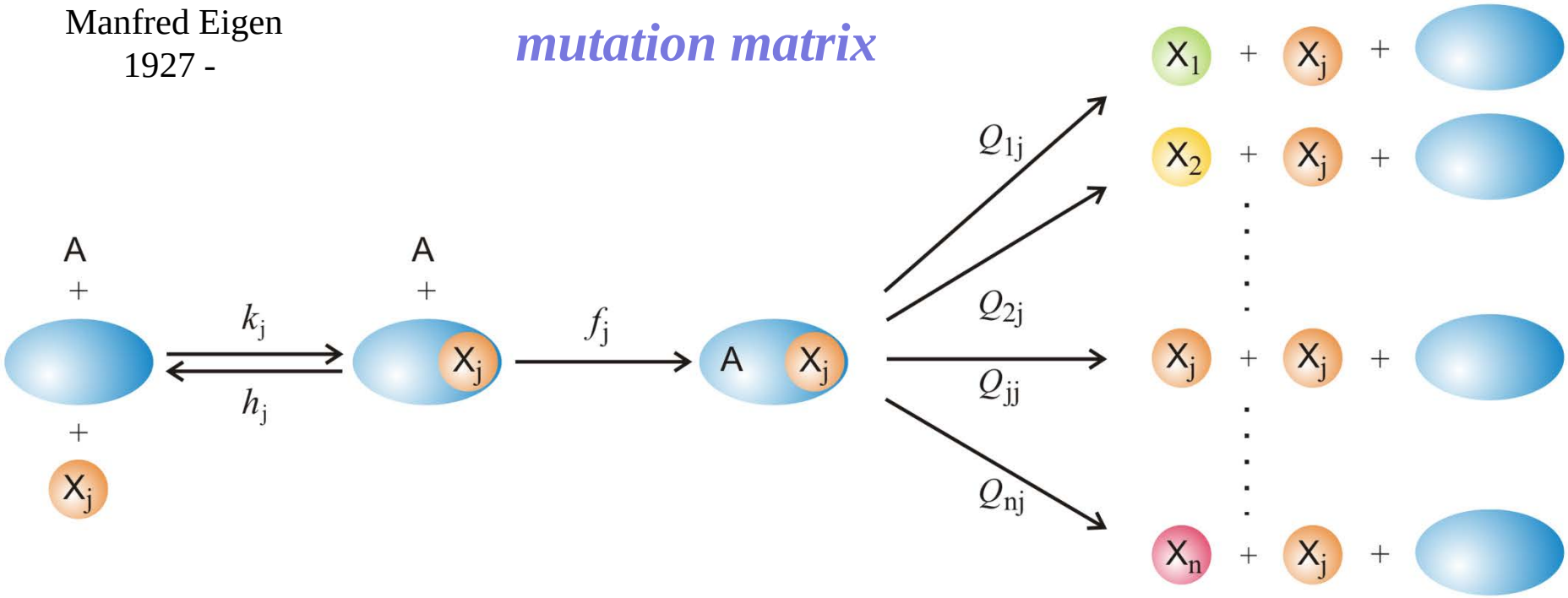
Manfred Eigen
1927 -

$$\frac{dx_j}{dt} = \sum_{i=1}^{n} W_{ji}\, x_i - x_j\, \Phi\,; \quad j = 1, 2, \ldots, n$$

$$W_{ji} = Q_{ji} \cdot f_i\,, \quad \sum_{i=1}^{n} x_i = 1, \quad \Phi = \sum_{i=1}^{n} f_i\, x_i$$

fitness landscape

mutation matrix



Mutation and (correct) replication as parallel chemical reactions

M. Eigen. 1971. *Naturwissenschaften* 58:465,
M. Eigen & P. Schuster.1977-78. *Naturwissenschaften* 64:541, 65:7 und 65:341

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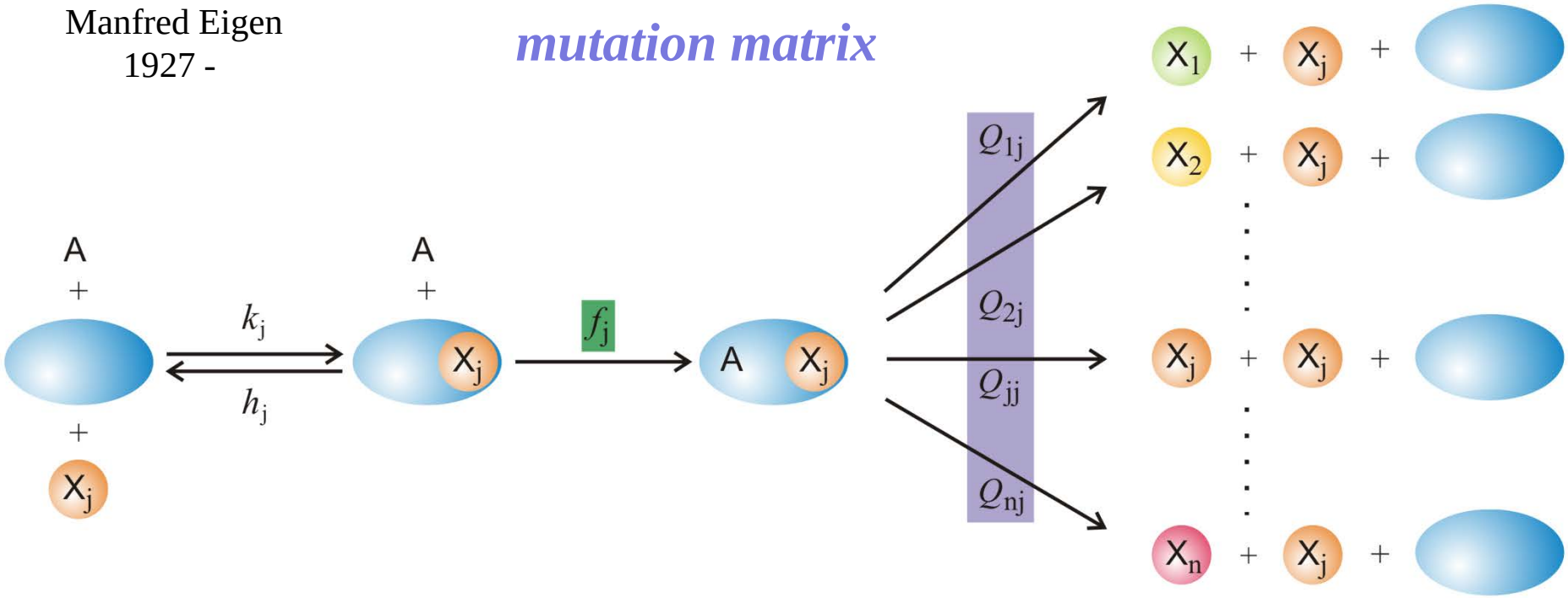

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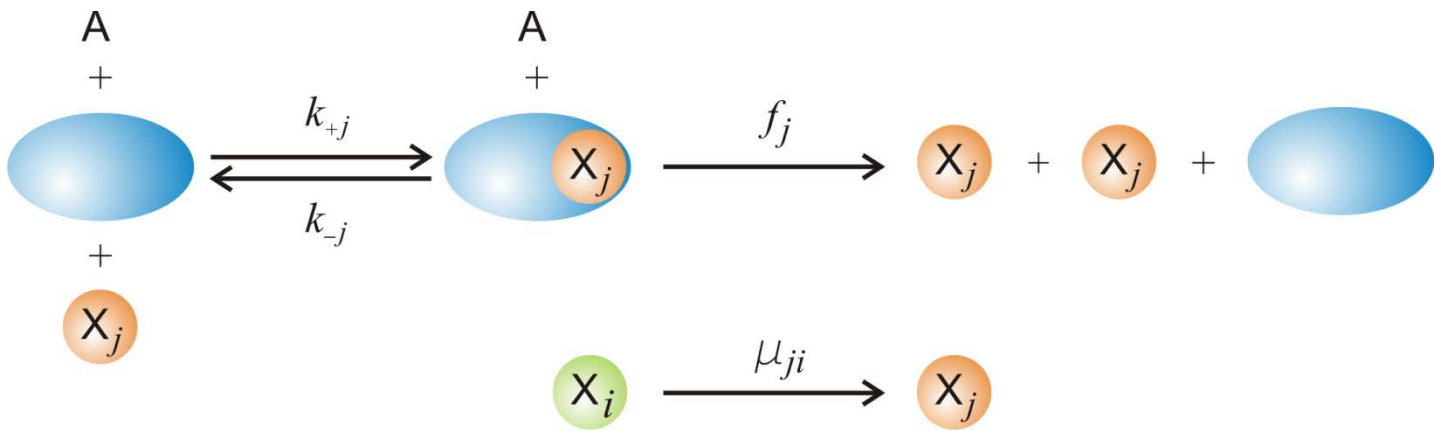


$$\frac{\mathrm{d}x_j}{\mathrm{dt}} = \left(f_j - \overline{f(t)}\right) x_j + \sum_{j=1}^{N} \mu_{ji}\, x_j \quad \text{or} \quad \frac{\mathrm{d}\mathbf{x}}{\mathrm{dt}} = \left(\mathrm{F} + \boldsymbol{\mu} - \overline{f(t)}\right) \mathbf{x}$$

paramuse – paralell mutation and selection model:

Ellen Baake, Michael Baake, Holger Wagner. 2001. *Ising quantum chain is equivalent to a model of biological evolution.* Phys.Rev.Letters 78:559-562.

James F. Crow and Motoo Kimura. 1970. *An introduction into population genetics theory*. Harper & Row, New York. Reprinted at the Blackburn Press, Cladwell, NJ, 2009, p.265.

The Crow-Kimura model of replication and mutation

$$\mathrm{Q} = \begin{pmatrix} q^3 & p & p & p & p^2 & p^2 & p^2 & p^3 \\ p & q^3 & p^2 & p^2 & p & p & p^3 & p^2 \\ p & p^2 & q^3 & p^2 & p & p^3 & p & p^2 \\ p & p^2 & p^2 & q^3 & p^3 & p & p & p^2 \\ p^2 & p & p & p^3 & q^3 & p^2 & p^2 & p \\ p^2 & p & p^3 & p & p^2 & q^3 & p^2 & p \\ p^2 & p^3 & p & p & p^2 & p^2 & q^3 & p \\ p^3 & p^2 & p^2 & p^2 & p & p & p & q^3 \end{pmatrix}$$

$$\mu = \begin{pmatrix} -3\gamma & \gamma & \gamma & \gamma & 0 & 0 & 0 & 0 \\ \gamma & -3\gamma & 0 & 0 & \gamma & \gamma & 0 & 0 \\ \gamma & 0 & -3\gamma & 0 & \gamma & 0 & \gamma & 0 \\ \gamma & 0 & 0 & -3\gamma & 0 & \gamma & \gamma & 0 \\ 0 & \gamma & \gamma & 0 & -3\gamma & 0 & 0 & \gamma \\ 0 & \gamma & 0 & \gamma & 0 & -3\gamma & 0 & \gamma \\ 0 & 0 & \gamma & \gamma & 0 & 0 & -3\gamma & \gamma \\ 0 & 0 & 0 & 0 & \gamma & \gamma & \gamma & -3\gamma \end{pmatrix}$$

$$q^3 = (1-p)^3$$

$$\mathrm{Q}: \sum_{i=1}^{N} Q_{ij} = 1;\ j = 1, \ldots, N$$

$$\mu: \sum_{i=1}^{N} \mu_{ij} = 0;\ j = 1, \ldots, N$$

$$\mathrm{W} = \mathrm{Q} \cdot \mathrm{F}$$

$$\mathrm{W} = \boldsymbol{\mu} + \mathrm{F}$$

The mutation matrix in the quasispecies and the Crow-Kimura model

Integrating factor transformation: $$z_j(t) \;=\; x_j(t)\,\cdot\,\exp\left(\int_0^t \overline{f}(\tau)\,\mathrm{d}\tau\right)\;;\; j=1,\ldots,N$$

Eigenvalue problem: $$\Lambda \;=\; \mathrm{H}\cdot\mathrm{W}\cdot\mathrm{H}^{-1} \;=\; \mathrm{H}\cdot\mathrm{W}\cdot\mathrm{B}$$

$$\Lambda = \{\Lambda_{ii}=\lambda_i \;\; i=1,\ldots,N\}\,,\;\; \mathrm{H}=\{h_{ij}\}\,,\;\; \mathrm{H}^{-1}=\mathrm{B}=\{b_{ij}\}$$

$$\mathrm{H}\cdot\mathrm{W} \;=\; \Lambda\cdot\mathrm{H}\,,\;\; \mathbf{h}_k=(h_{ki},\; i=1,\ldots,N) \text{ and}$$

$$\mathrm{W}\cdot\mathrm{B} \;=\; \mathrm{B}\cdot\Lambda\,,\;\; \mathbf{b}_j=(b_{ij},\; i=1,\ldots,N)^{\mathrm{t}}$$

Solution:

$$x_j(t) \;=\; \frac{\sum_{k=1}^N b_{jk}\,\sum_{l=1}^N h_{kl}\,x_l(0)\,\exp(\lambda_k\,t)}{\sum_{i=1}^N\sum_{k=1}^N b_{ik}\,\sum_{l=1}^N h_{kl}\,x_l(0)\,\exp(\lambda_k\,t)} \;=$$

$$=\; \frac{\sum_{k=1}^N b_{jk}\,\beta_k(0)\,\exp(\lambda_k\,t)}{\sum_{i=1}^N\sum_{k=1}^N b_{ik}\,\beta_k(0)\,\exp(\lambda_k\,t)} \quad \text{with} \quad \beta_k(0) \;=\; \sum_{l=1}^N h_{kl}\,x_l(0)$$

Solution of the quasispecies equation

Largest eigenvalue λ_1 and corresponding eigenvector $\mathbf{b}_1$:

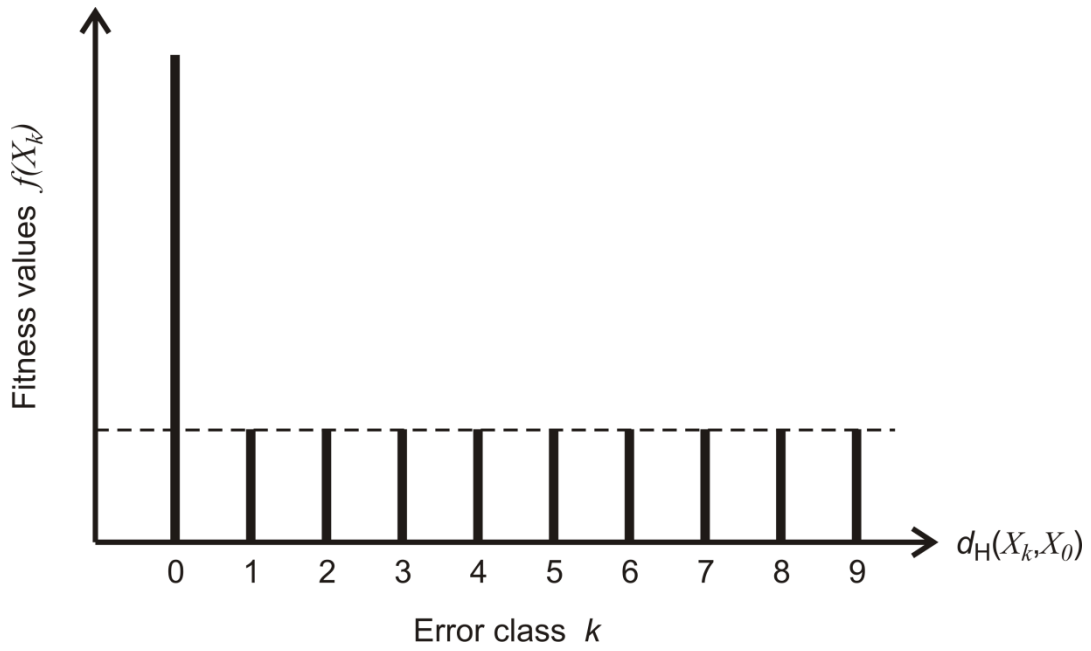
$$x_j(t) \approx \frac{b_{j1}\,\beta_1(0)\,\exp(\lambda_1\,t)}{\sum_{i=1}^{N} b_{i1}\,\beta_1(0)\,\exp(\lambda_1\,t)} = \frac{b_{j1}}{\sum_{i=1}^{N} b_{i1}} = \overline{x}_j \quad \text{for large } t$$

master sequence: X_m at concentration $\overline{x}_m$

mutant cloud: X_j at concentration $\overline{x}_j$; $j=1,\ldots,N$; $j\neq m$

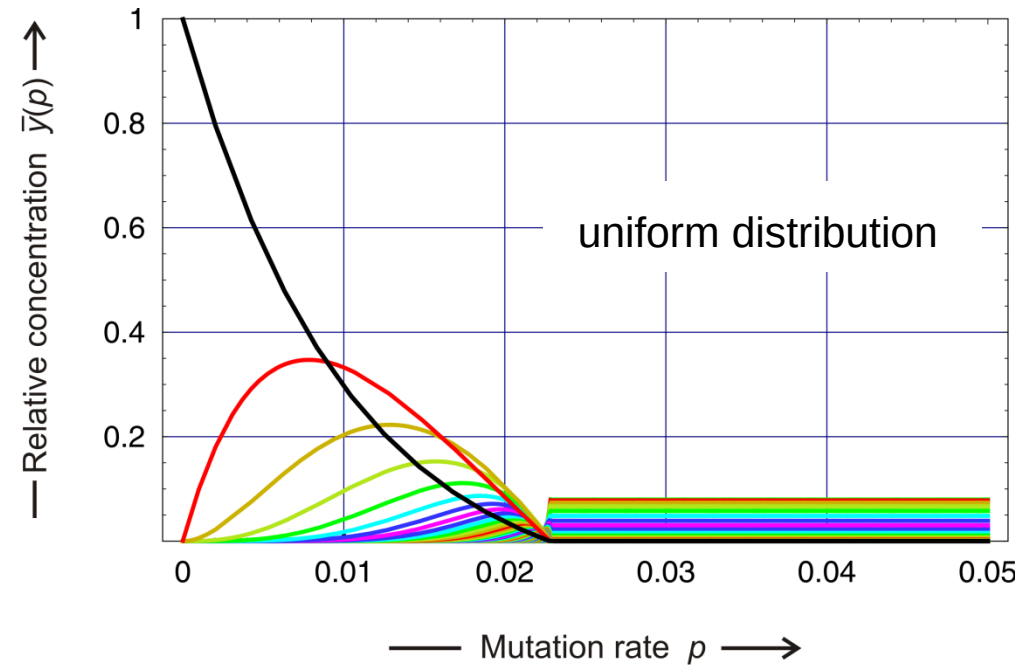
Stationary solution of the quasispecies equation

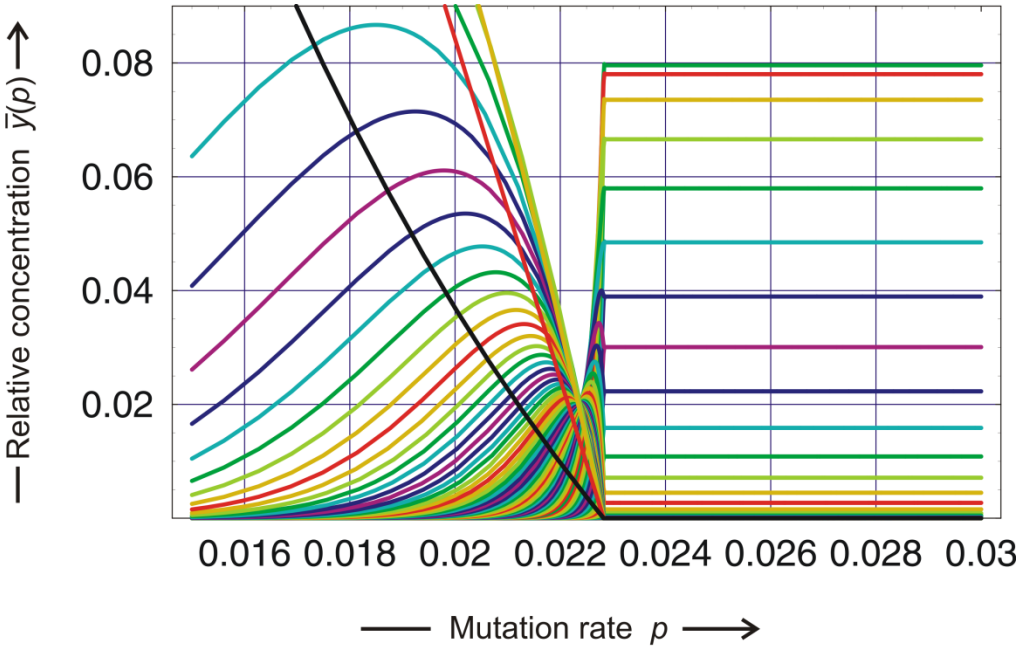
single peak landscape



A simple model fitness landscapes

$l = 100$, $f_m = 10$, $f = 1$,
$\sigma_m = 10$





error threshold on the
single peak landscape

phenomenological approach (Eigen, M., Naturwissenschaften 1971)

(i) zero mutational backflow (non consistently applied)

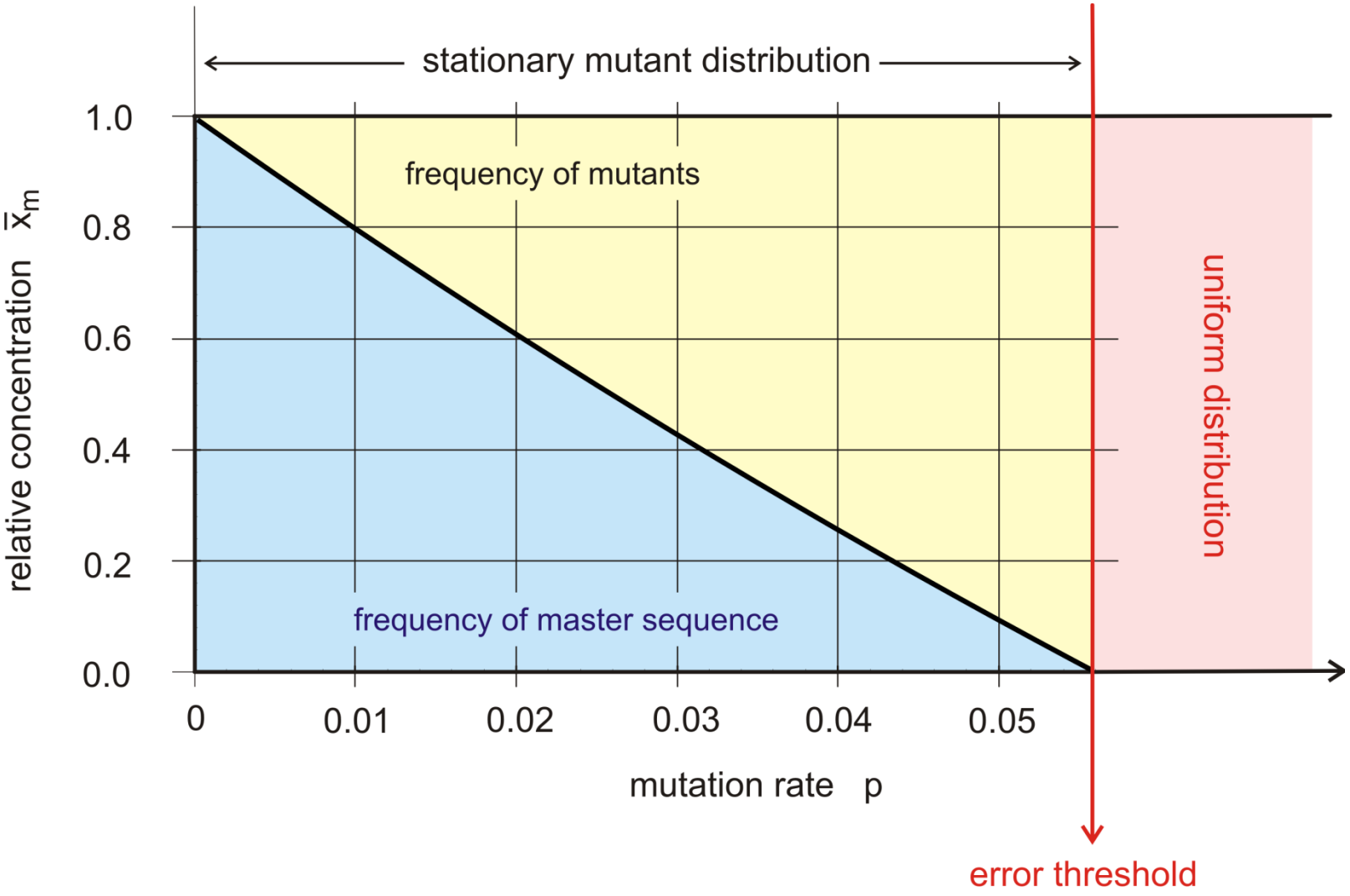
(ii) uniform error rate: p is independent of nature and position of nucleotide

$$Q_{ij} = \varepsilon^{d_{ij}^{(H)}} Q \text{ with } \varepsilon = \frac{p}{1-p} \text{ and } Q = (1-p)^l$$

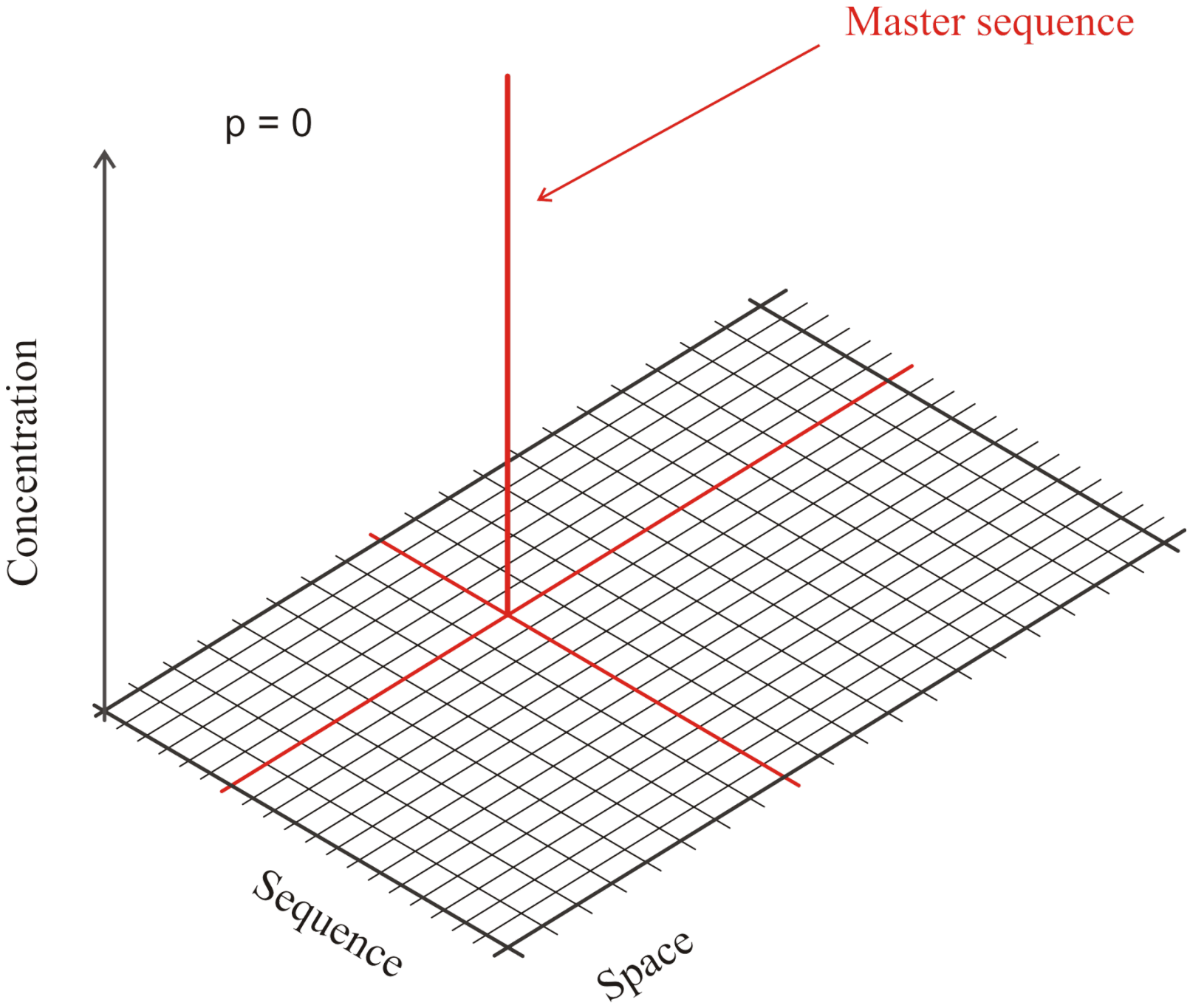
and $d_{ij}^{(H)}$ is the Hamming distance between $\mathbf{X}_i$ and $\mathbf{X}_j$.

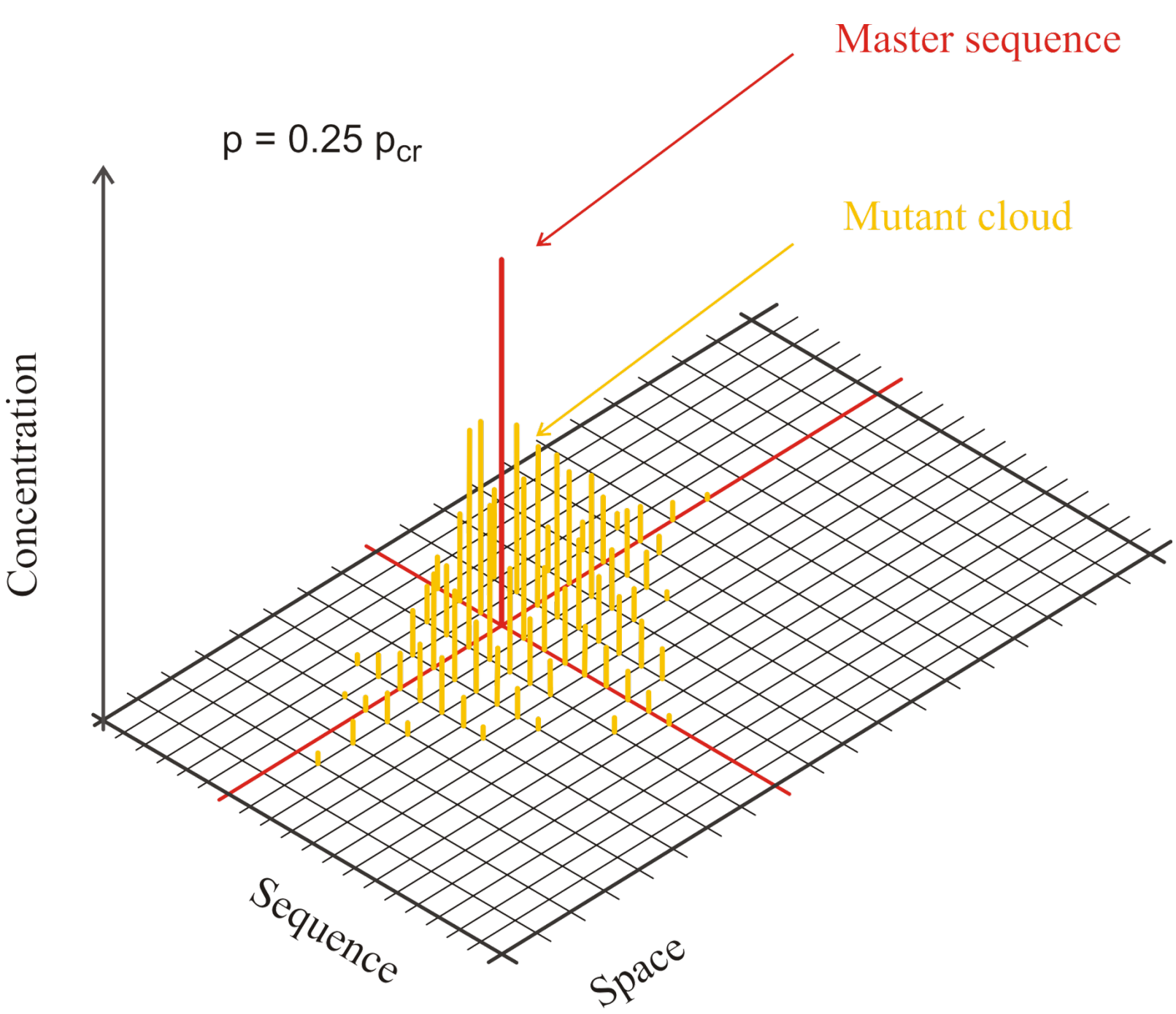
(iii) single peak landscape: $f_m = f_0$, $f_j = f \ \forall\ j \neq m$

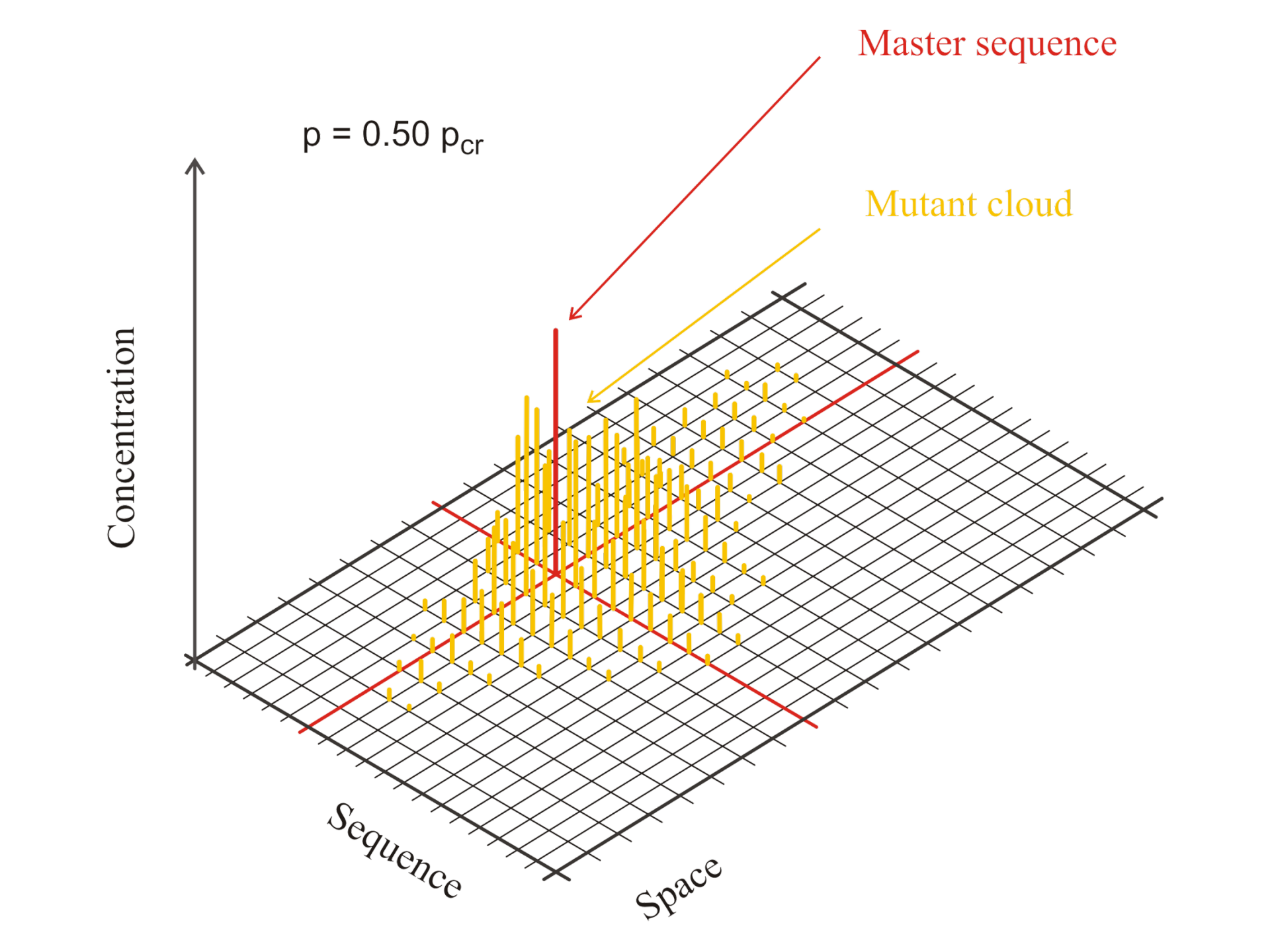
phenomenological approximation to the quasispecies equation

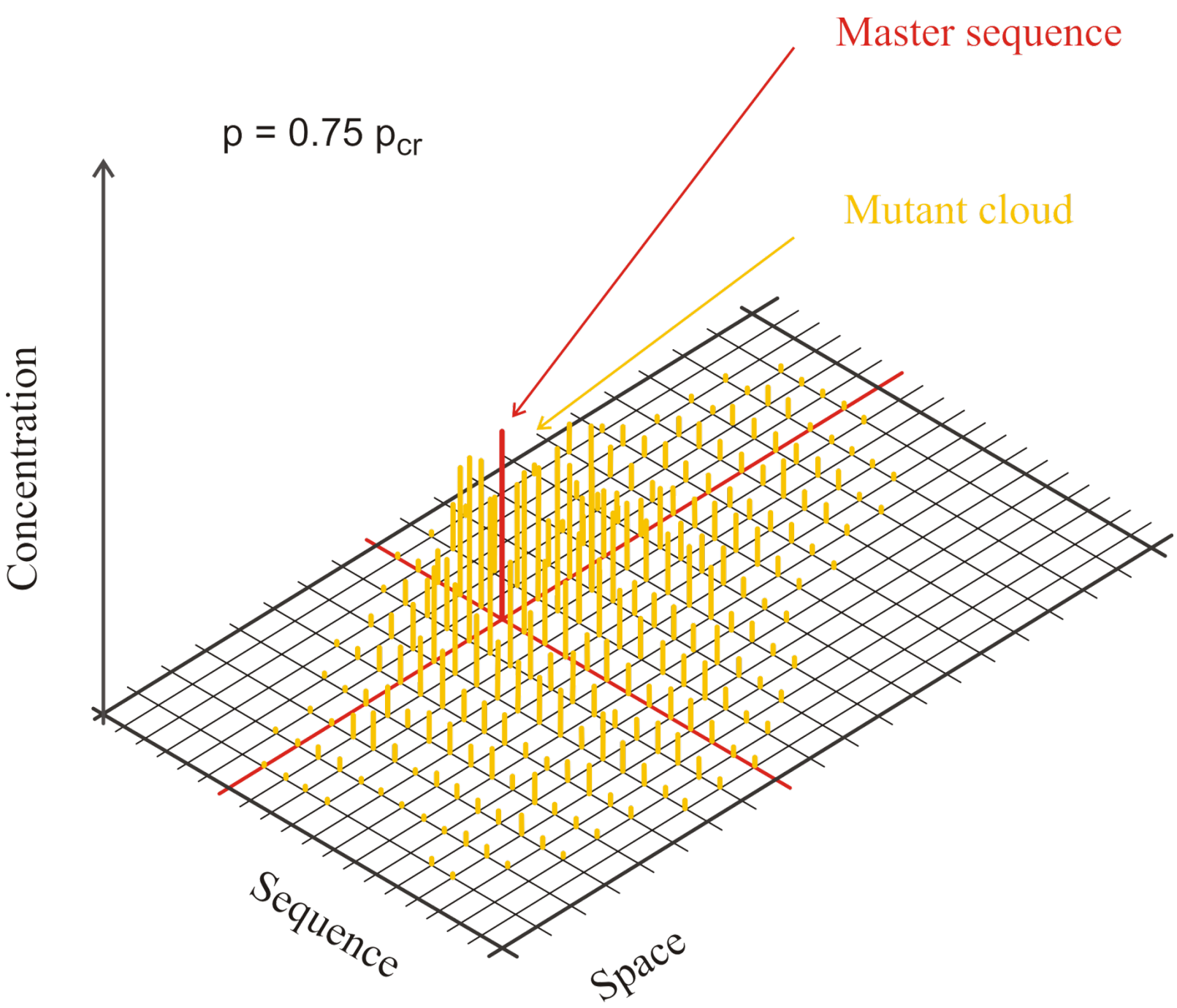


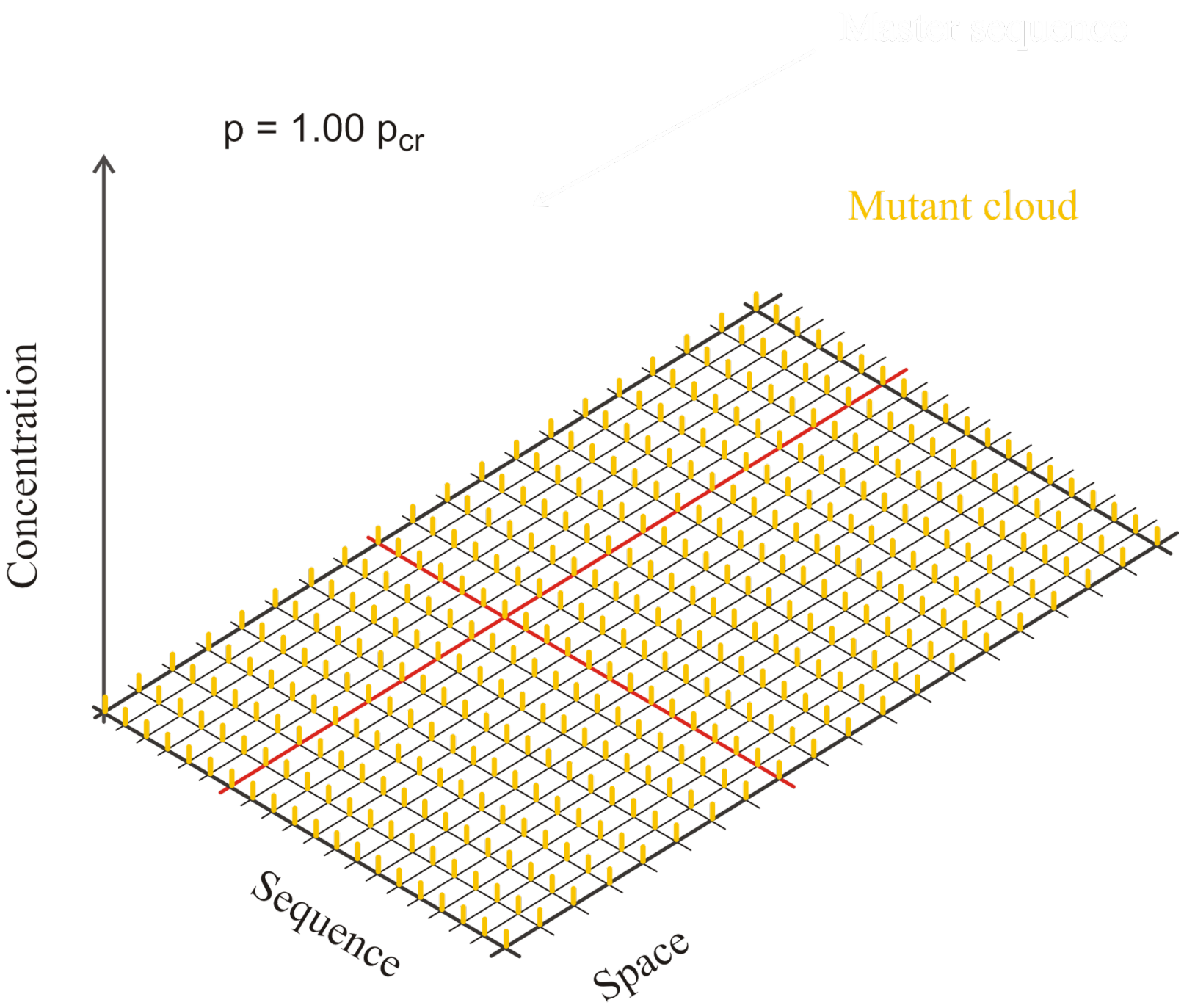
The error threshold in replication and mutation


Master sequence
p = 0
Concentration
Sequence
Space


Master sequence
p = 0.25 p_cr
Mutant cloud
Concentration
Sequence
Space


Master sequence
p = 0.50 p_cr
Mutant cloud
Concentration
Sequence
Space


Master sequence
p = 0.75 p_cr
Mutant cloud
Concentration
Sequence
Space


Master sequence
p = 1.00 p_cr
Mutant cloud
Concentration
Sequence
Space

$$\Pi(t) = x_1(t)\mathbf{X}_1 \oplus x_2(t)\mathbf{X}_2 \oplus \ldots \oplus x_n(t)\mathbf{X}_n$$

$$\lim_{t\to\infty} \Pi(t) = \overline{\Upsilon} = \overline{x}_1\mathbf{X}_1 \oplus \overline{x}_2\mathbf{X}_2 \oplus \ldots \oplus \overline{x}_n\mathbf{X}_n$$

continuous quasispecies

$$\widetilde{\Upsilon} = \overline{\eta}_1\mathbf{Y}_1 \oplus \overline{\eta}_2\mathbf{Y}_2 \oplus \ldots \oplus \overline{\eta}_n\mathbf{Y}_n \quad \text{with} \quad \overline{\eta}_i = \begin{cases} \lfloor \overline{x}_i \rfloor & \text{if } \overline{x}_i \geq 1 \\ 0 & \text{if } \overline{x}_i < 1 \end{cases}$$

discrete quasispecies

$$\widehat{x}_m = \frac{Q - \sigma_m^{-1}}{1 - \sigma_m^{-1}}\,\widehat{c}_0 \quad \text{and}$$

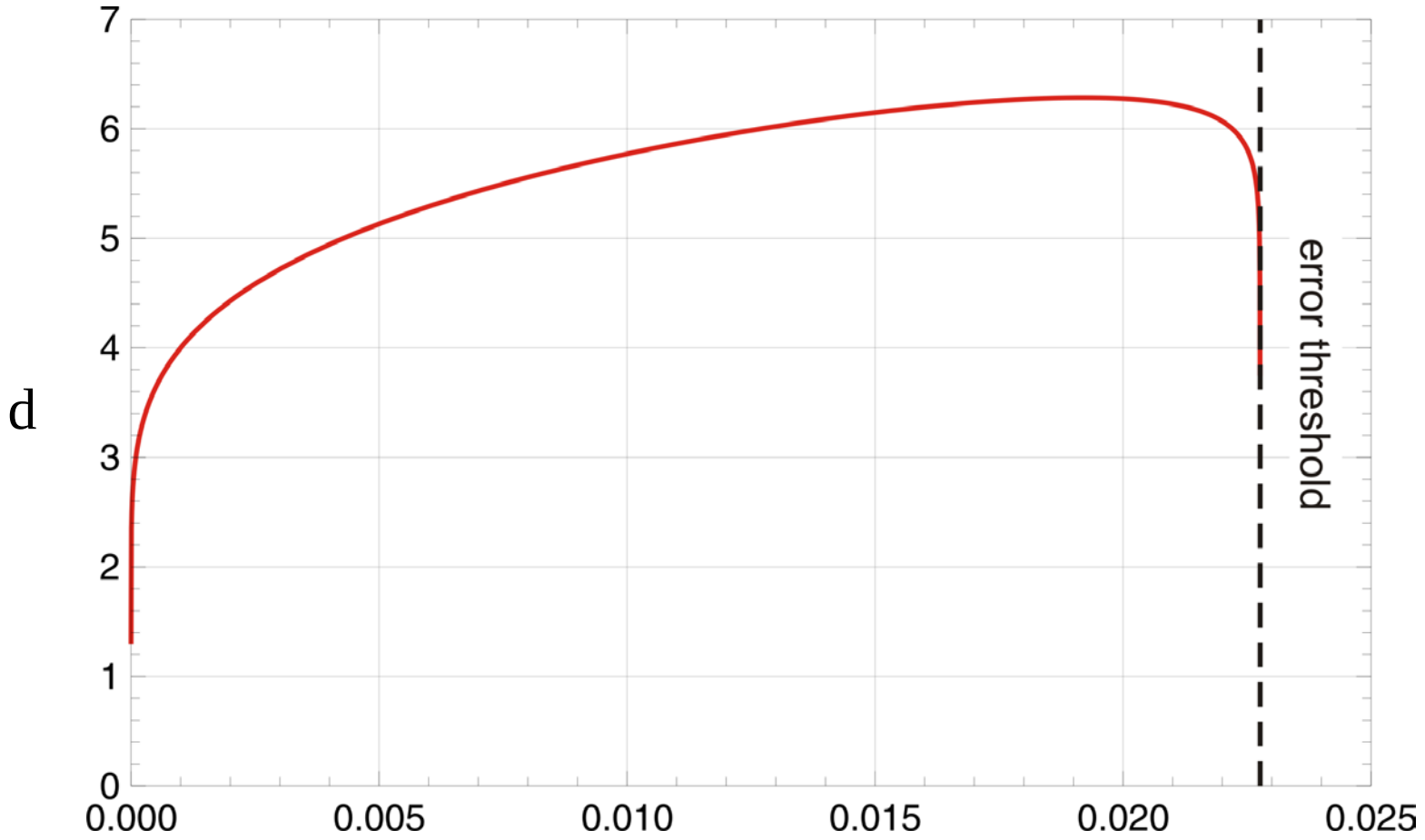
$$\widehat{x}_j = \varepsilon^{d_{mj}^{(H)}}\,\frac{Q - \sigma_m^{-1}}{(1 - \sigma_m^{-1})^2}\,\widehat{c}_0\,, \quad j \neq m$$

phenomenological approximation

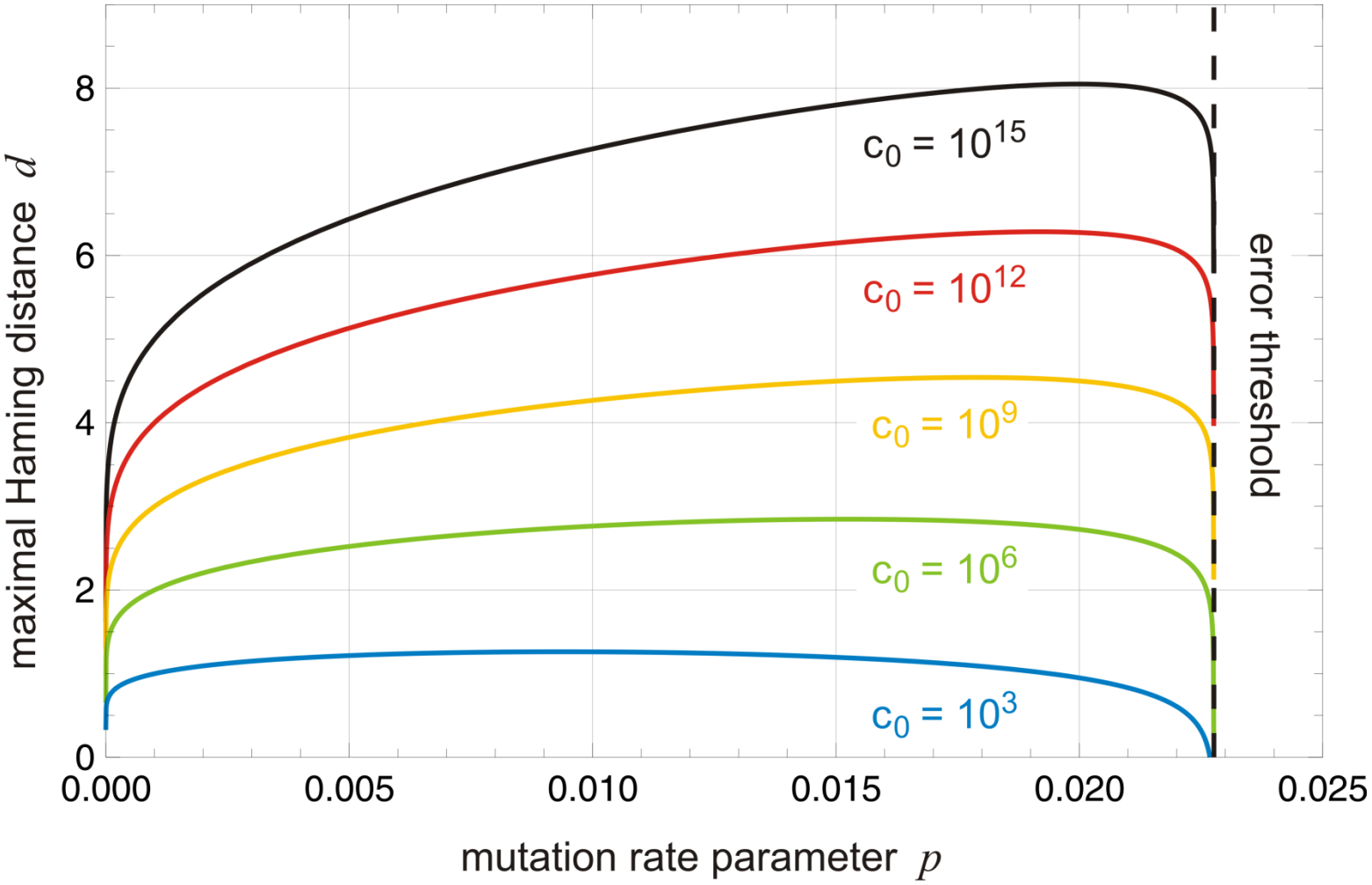
$$\hat{x}_j \geq k \implies d \leq \frac{1}{\log \varepsilon}\,\log \frac{k(1 - \sigma_m^{-1})^2}{(Q - \sigma_m^{-1})\widehat{c}_0}$$

discreteness condition

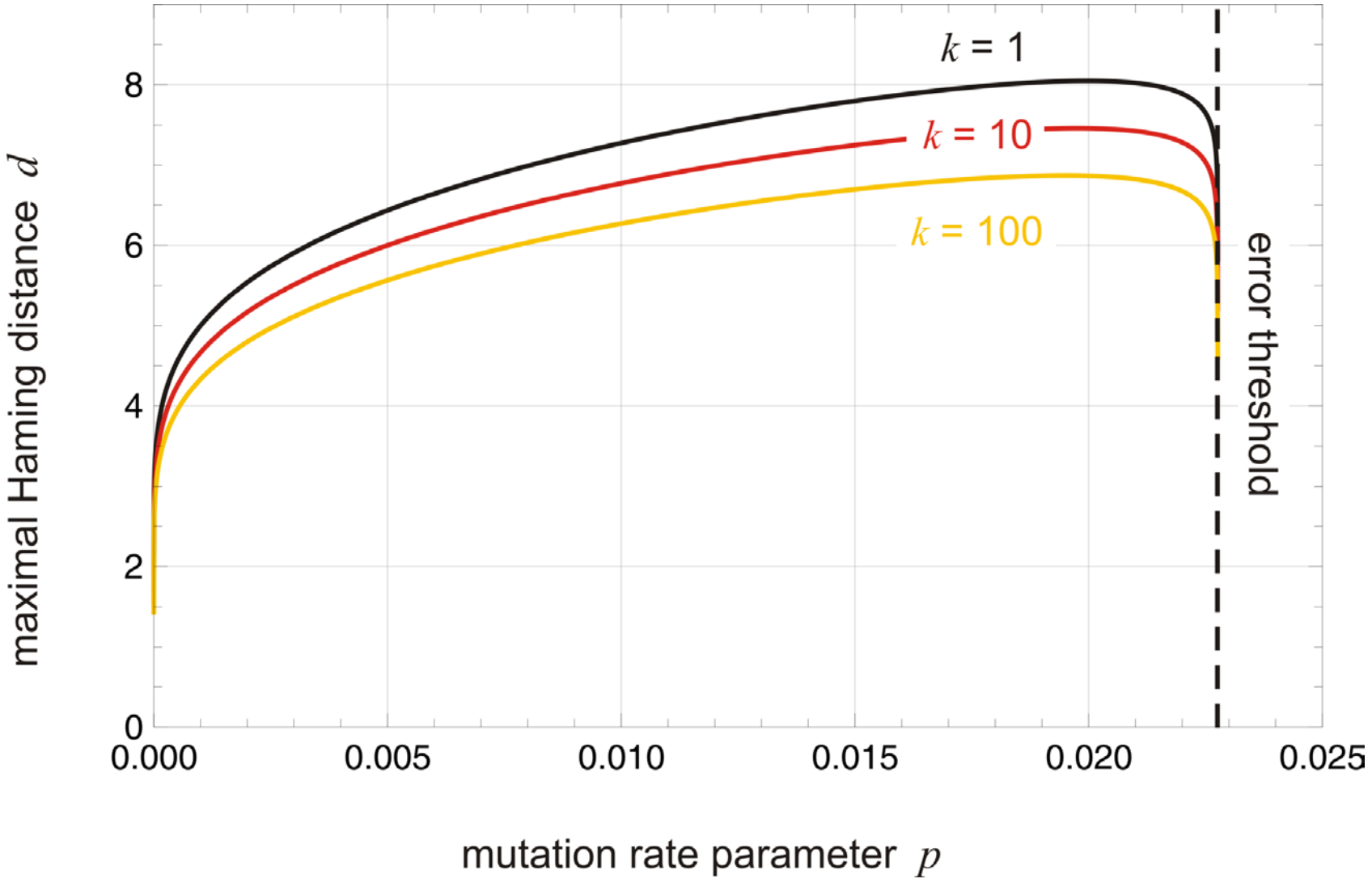
width of the discrete quasispecies: 2d



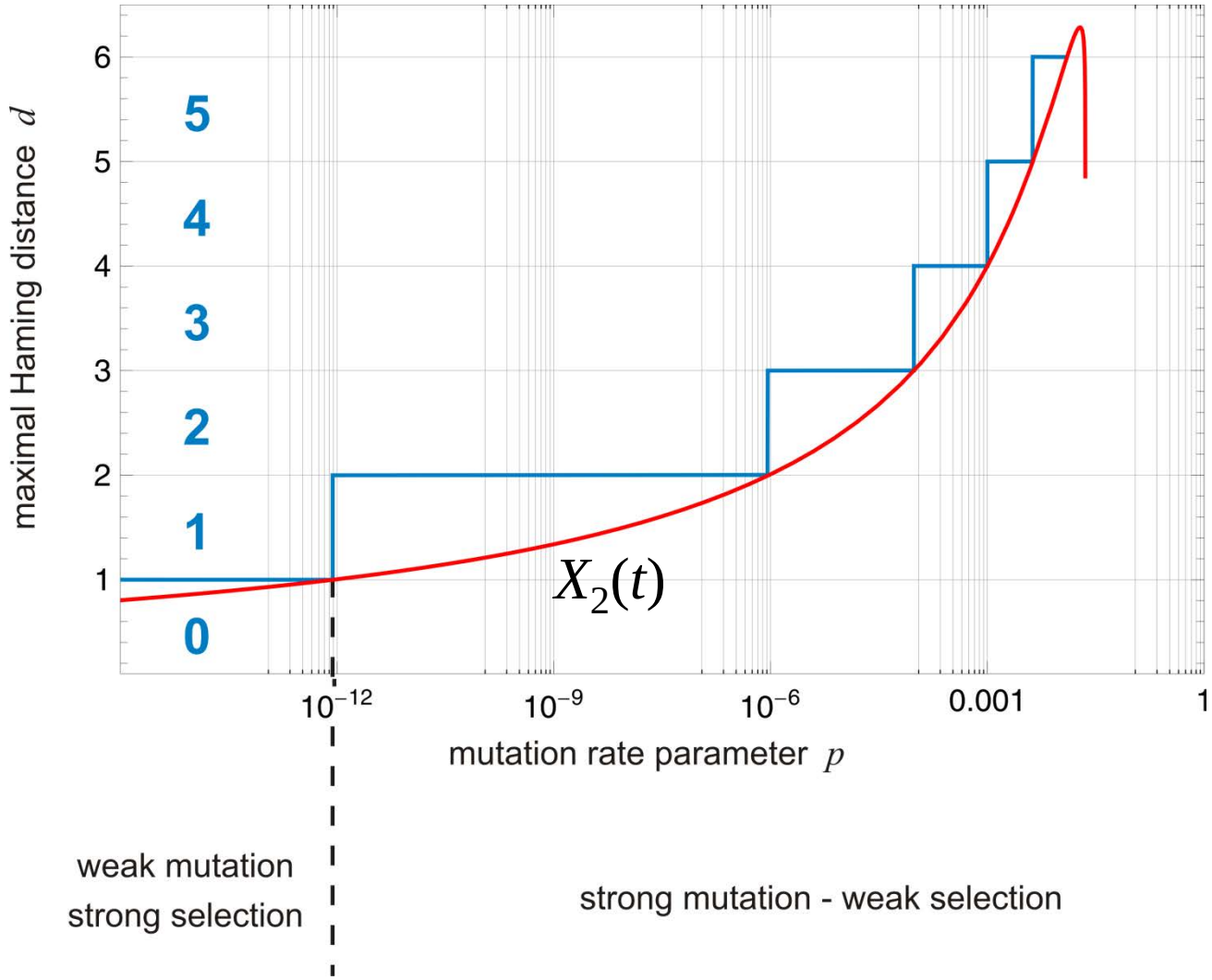
discrete quasispecies: $c_0 = 10^{12}$, $l = 100$, $k = 1$



discrete quasispecies: $l = 100$, $k = 1$



discrete quasispecies: $c_0 = 10^{12}$, $l = 100$



width of the discrete quasispecies

$$P_m(t) = \text{Prob}\Big(A(t) = m\Big) \quad \text{and} \quad P_{s_i}(t) = \text{Prob}\Big(X_i(t) = s_i\Big)$$

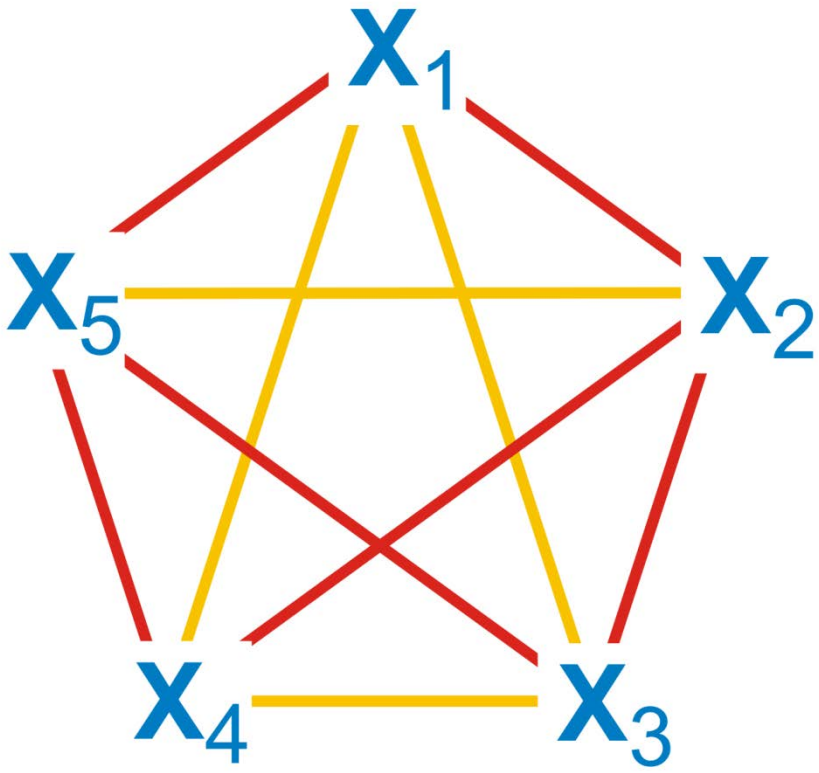
$$\mathbf{m} = (m, s_1, \ldots, s_n)$$

$$\begin{aligned}
\frac{\mathrm{d}P_{\mathbf{m}}}{\mathrm{dt}} &= a_0 r\Big(P_{(\mathbf{m};m-1)} - P_{\mathbf{m}}\Big) + r\Big((m+1)P_{(\mathbf{m};m+1)} - mP_{\mathbf{m}}\Big) + \\
&\quad + r\sum_{i=1}^{n}\Big((s_i+1)P_{(\mathbf{m};s_i+1)} - s_i P_{\mathbf{m}}\Big) + \\
&\quad + \sum_{i=1}^{n} Q_{ii}k_i\Big((m+1)(s_i-1)P_{(\mathbf{m};m+1,s_i-1)} - m\,s_i P_{\mathbf{m}}\Big) + \\
&\quad + \sum_{i=1}^{n}\sum_{j=1,j\neq i}^{n} Q_{ij}k_j\,s_j\Big((m+1)P_{(\mathbf{m};m+1,s_i-1)} - mP_{\mathbf{m}}\Big)
\end{aligned}$$

$$\mathbf{m} = (m, s_1, \ldots, s_n)$$

$$\begin{aligned}
\mathbf{m}' &= (m \pm 1, s_1, \ldots, s_n) \equiv (\mathbf{m}; m \pm 1) \quad \text{or} \\
\mathbf{m}' &= (m, s_1, \ldots, s_k \pm 1, \ldots, s_n) \equiv (\mathbf{m}; s_k \pm 1)
\end{aligned}$$

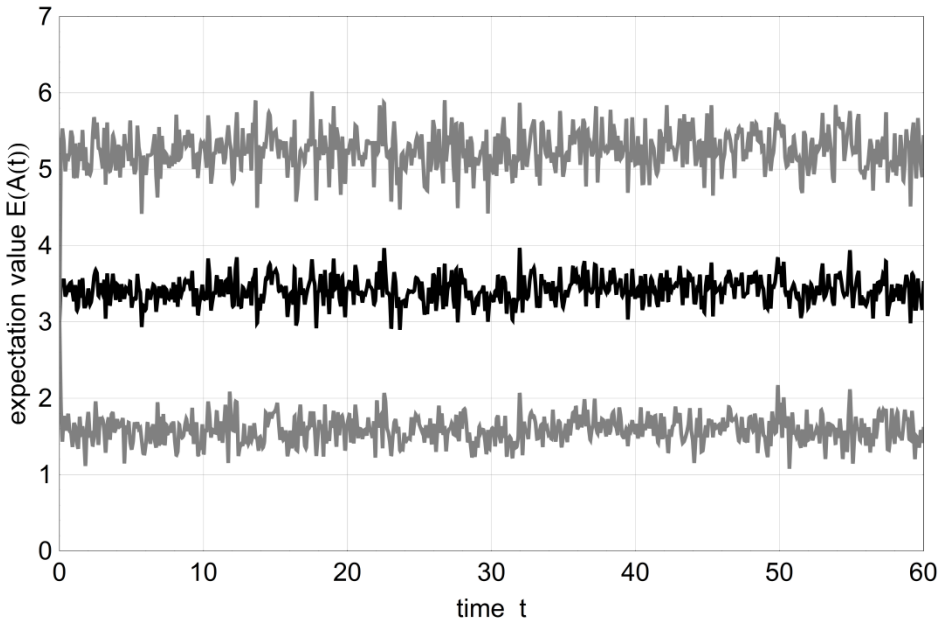
jumps: $S_{\mathbf{m}} \rightarrow S_{\mathbf{m}'}$ and $S_{\mathbf{m}'} \rightarrow S_{\mathbf{m}}$



mutation scheme *pentagram* for n = 5

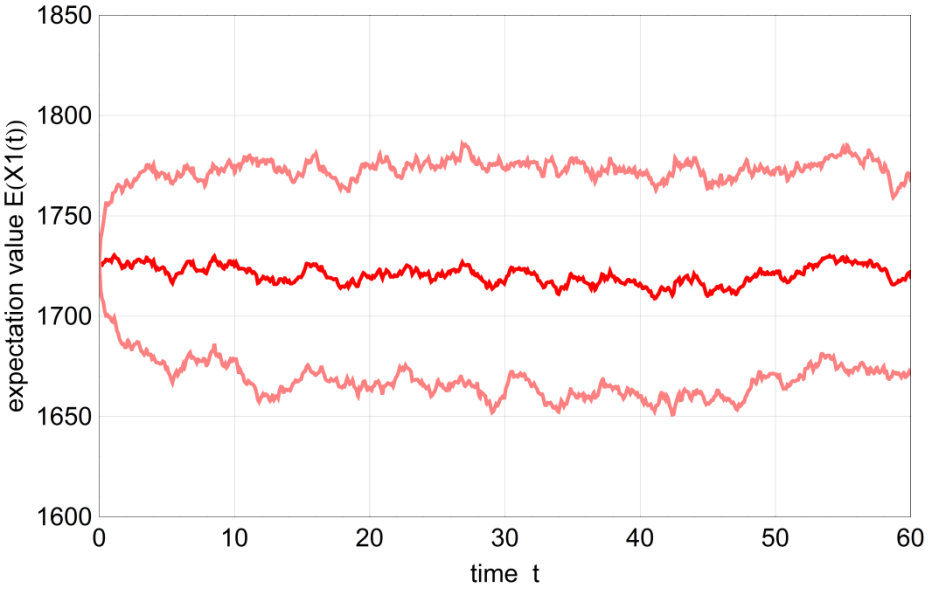
statistics of 100 trajectories:

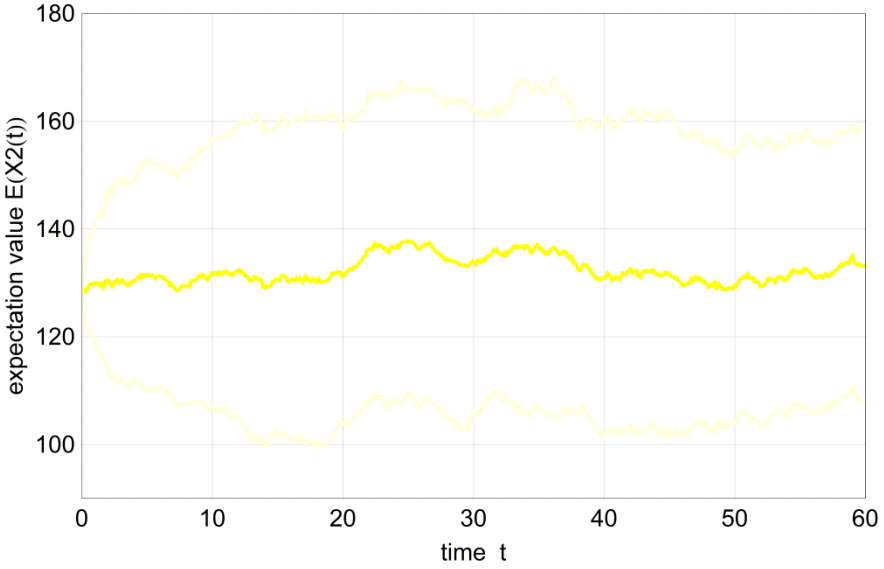
N = 2000, k = 5, p = 0.0124;
flow reactor: r = 0.5;
$k_1 = 0.150$, $k_2 = k_5 = 0.0125$,
$k_3 = k_4 = 0.100$

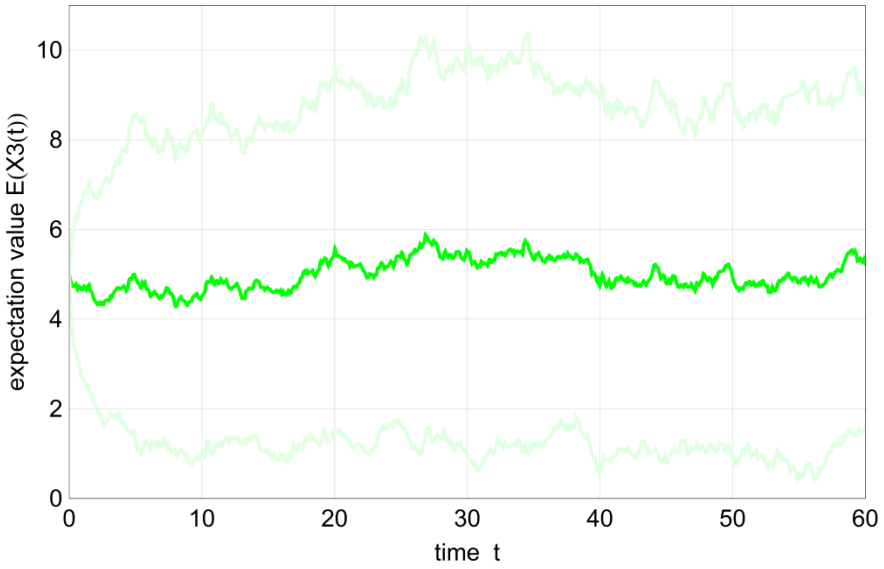


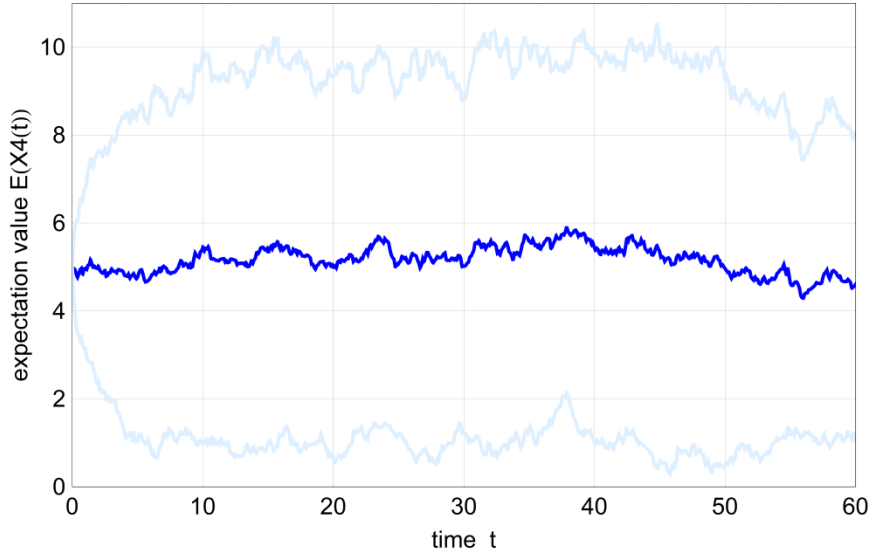
one standard deviation band:

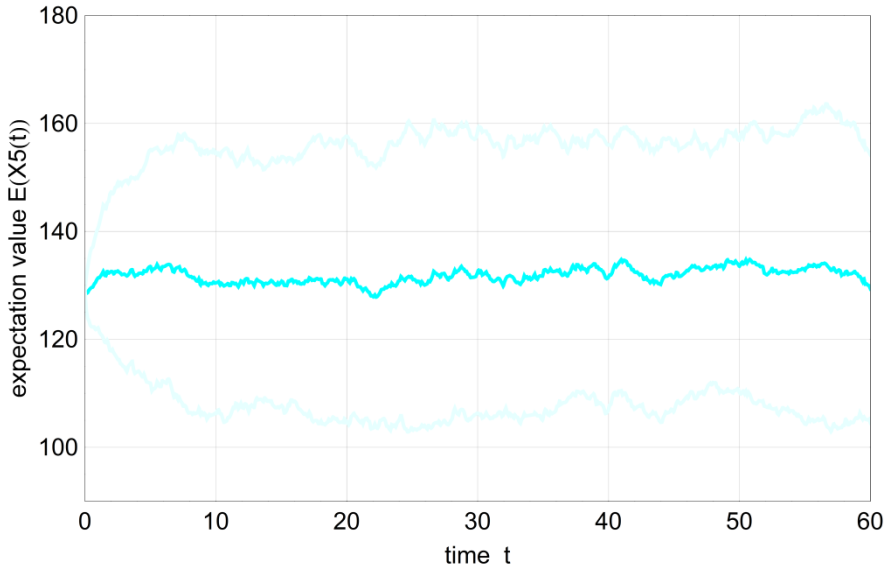
resource A, master sequence X_1







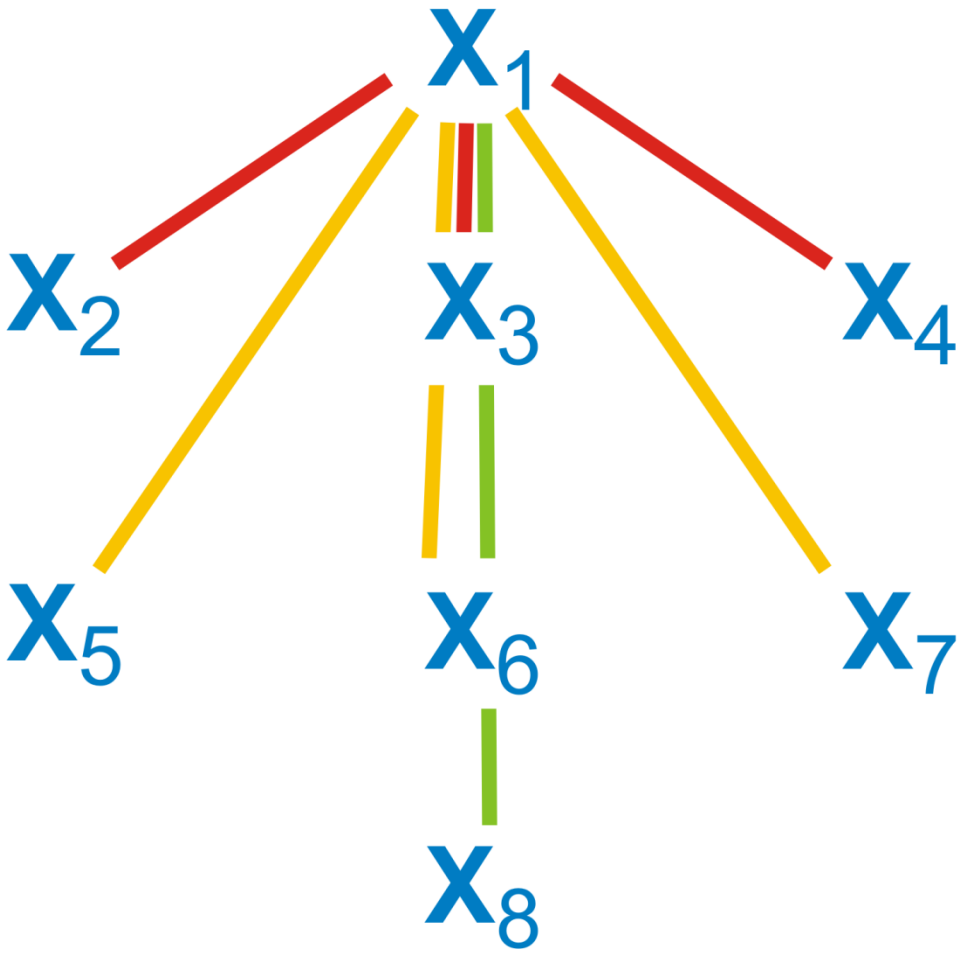




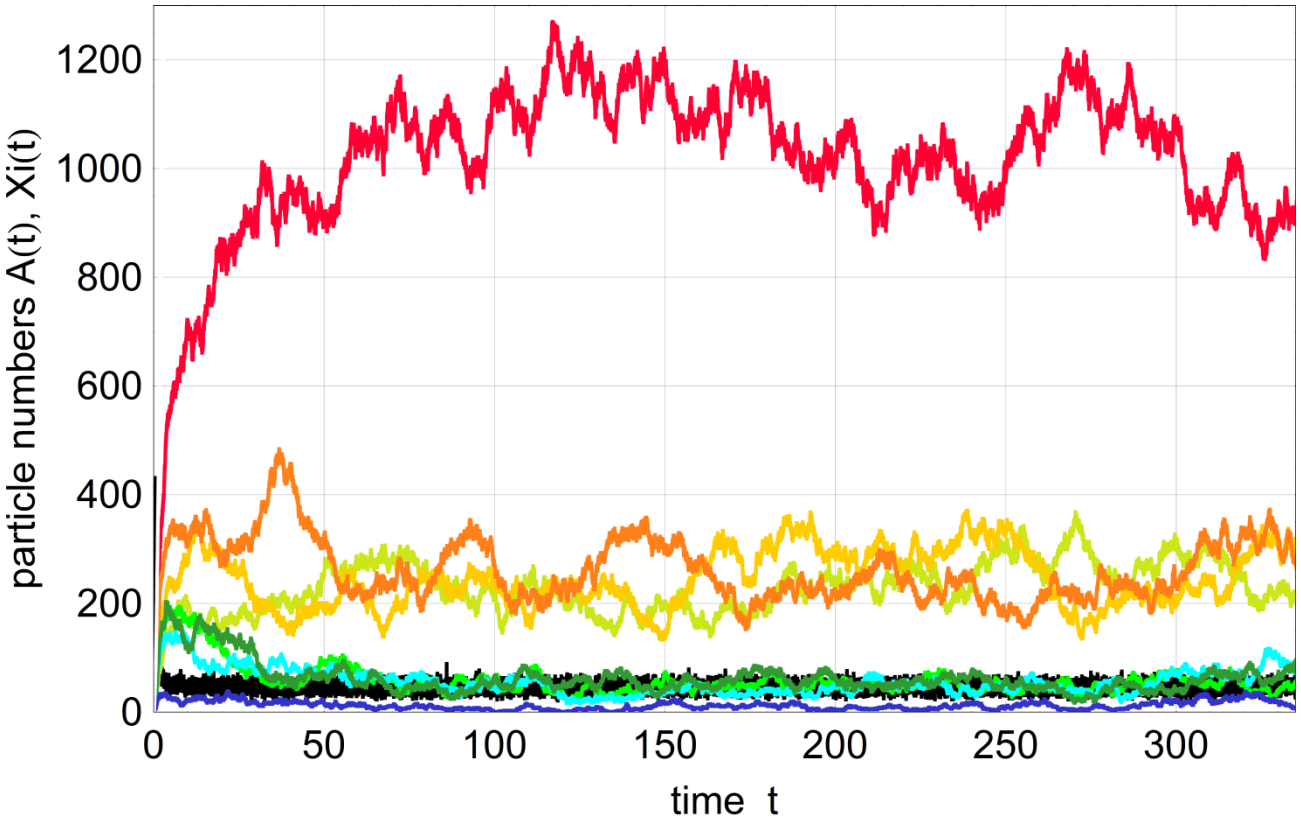
one standard deviation bands: mutants

	deterministic	expectation E	standard dev. σ	√E
$A(t)$	3.413	3.424	1.843	1.850
$X_1(t)$	1727.9	1720	54.68	41.47
$X_2(t)$	129.31	133.2	27.69	11.54
$X_3(t)$	5.0298	5.132	3.945	2.265
$X_4(t)$	5.0298	5.200	4.215	2.280
$X_5(t)$	129.31	132.1	25.59	11.49

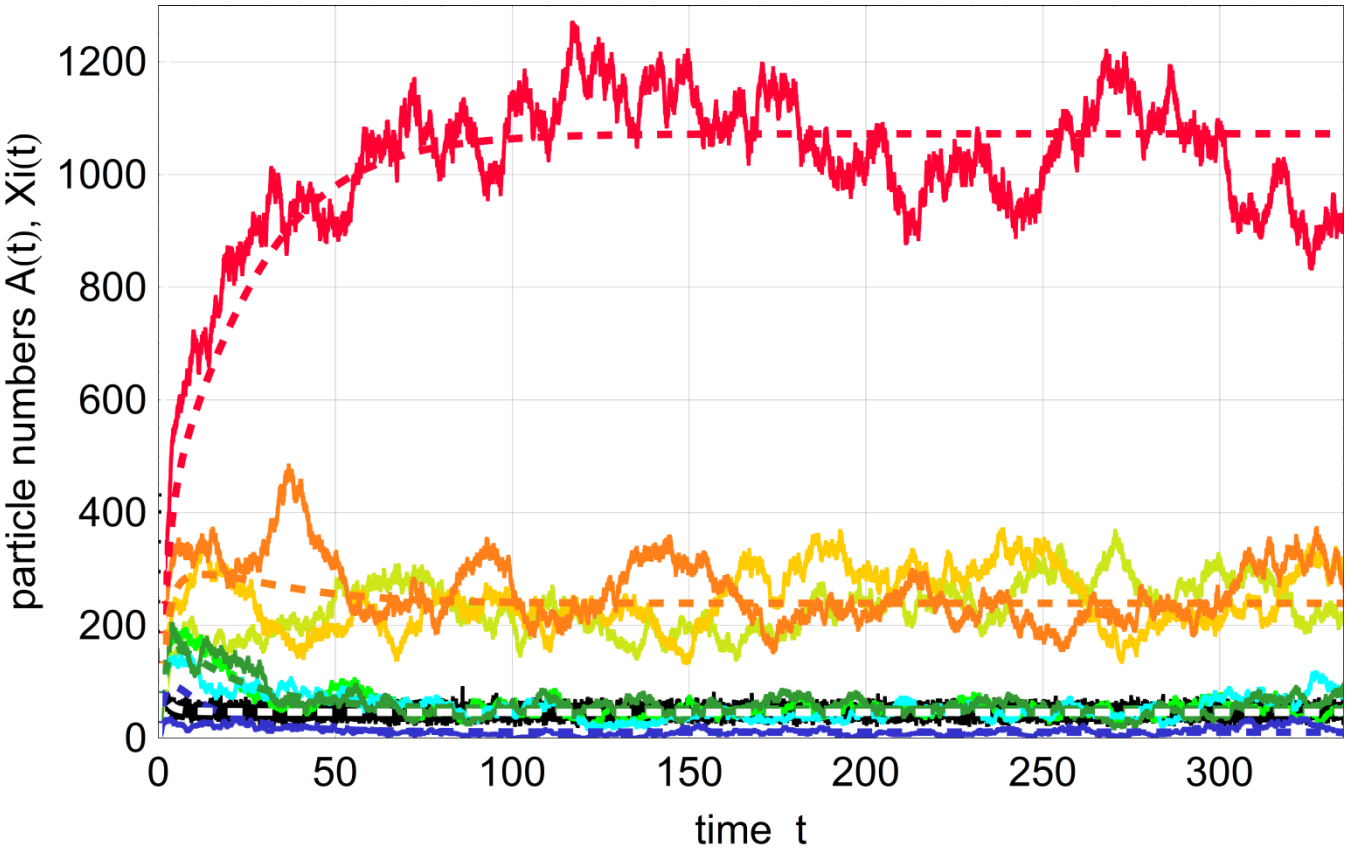
N = 2000, k = 5, p = 0.0124; flow reactor: r = 0.5; $k_1 = 0.150$, $k_2 = k_5 = 0.125$, $k_3 = k_4 = 0.100$



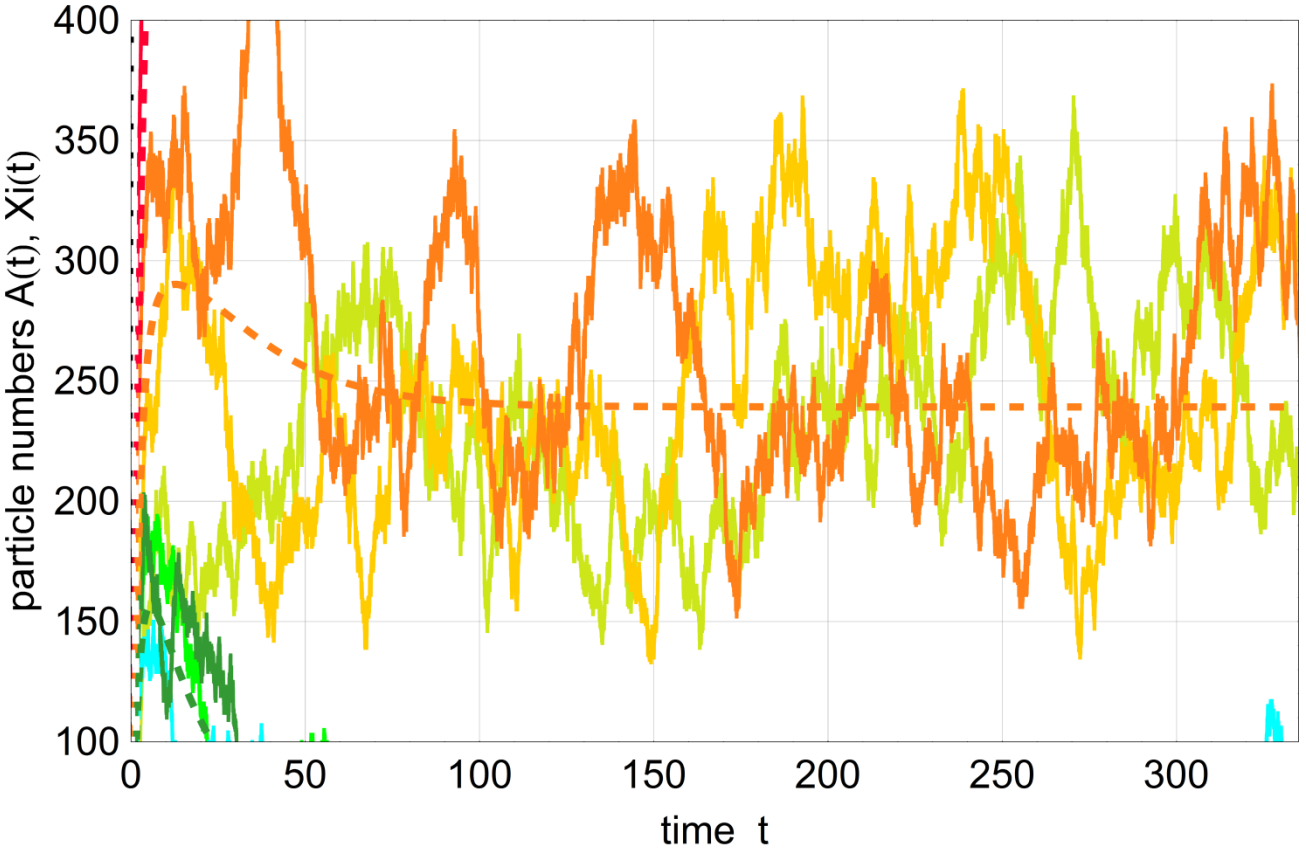
mutation scheme *sequence space* for $l = 3$ ($n = 8$)



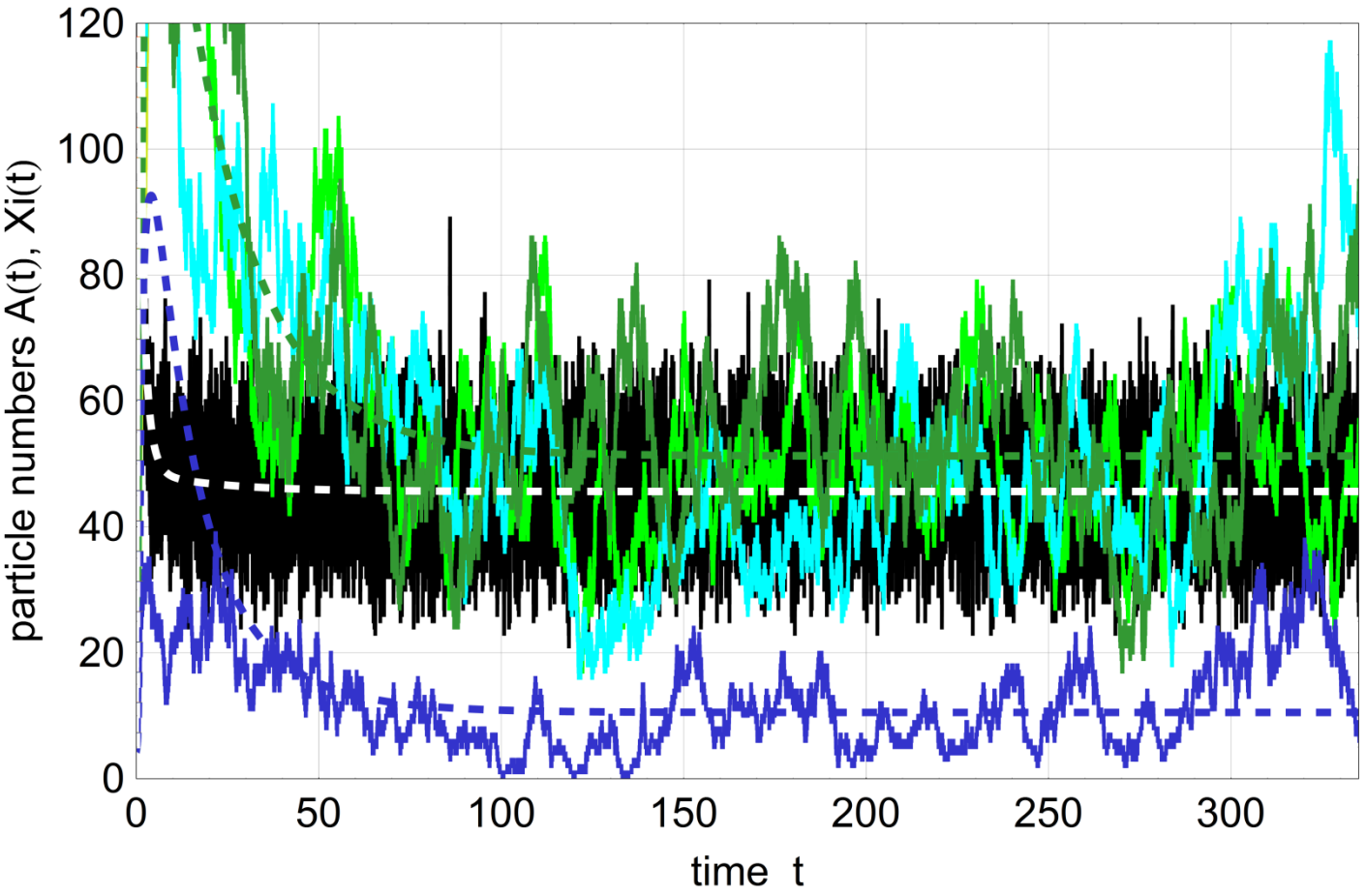
Gillespie simulation of stochastic quasispecies $l = 3$



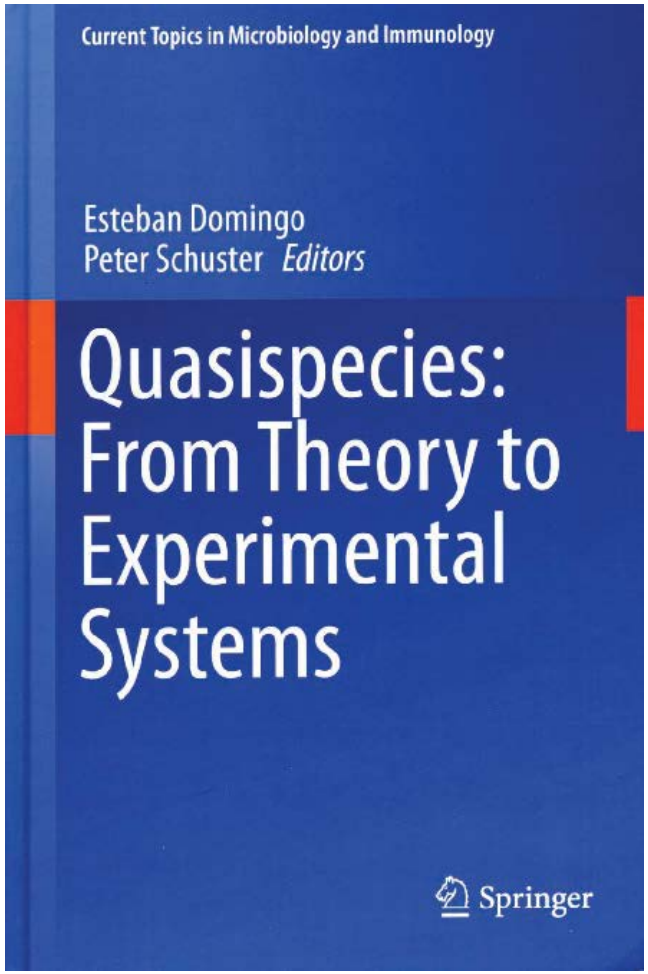
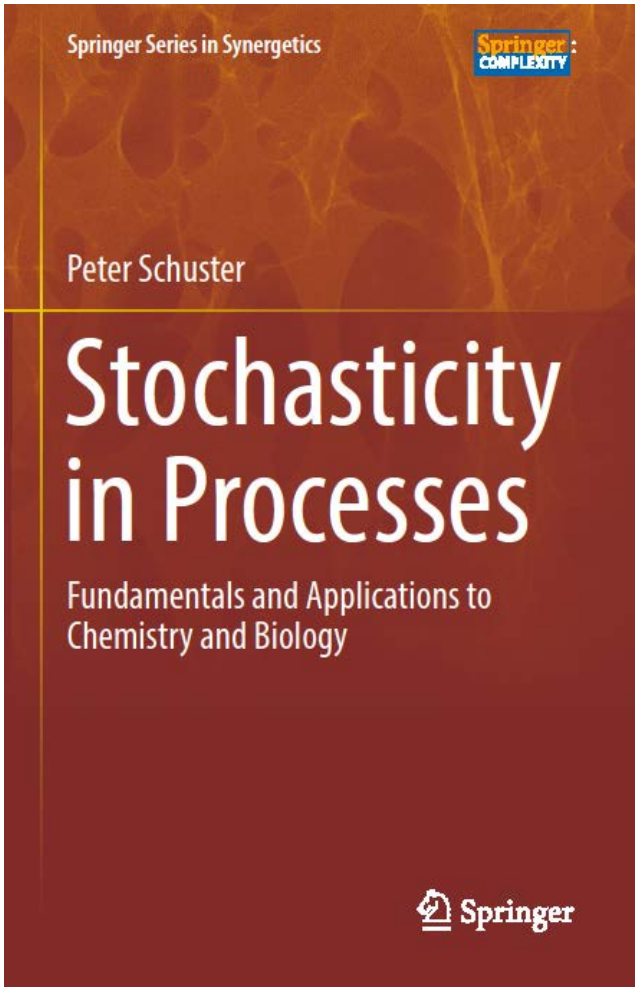
comparison with deterministic solution



comparison with deterministic solution



comparison with deterministic solution

Thank you for your attention!

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