Does it pay to be consistent?

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Biomathematik Seminar

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Web-Page for further information:

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

1. Quasispecies and Crow-Kimura model
2. Mutation flow analysis
3. Zero backflow and phenomenological approach
4. Error thresholds on model landscapes
5. Error thresholds on realistic landscapes

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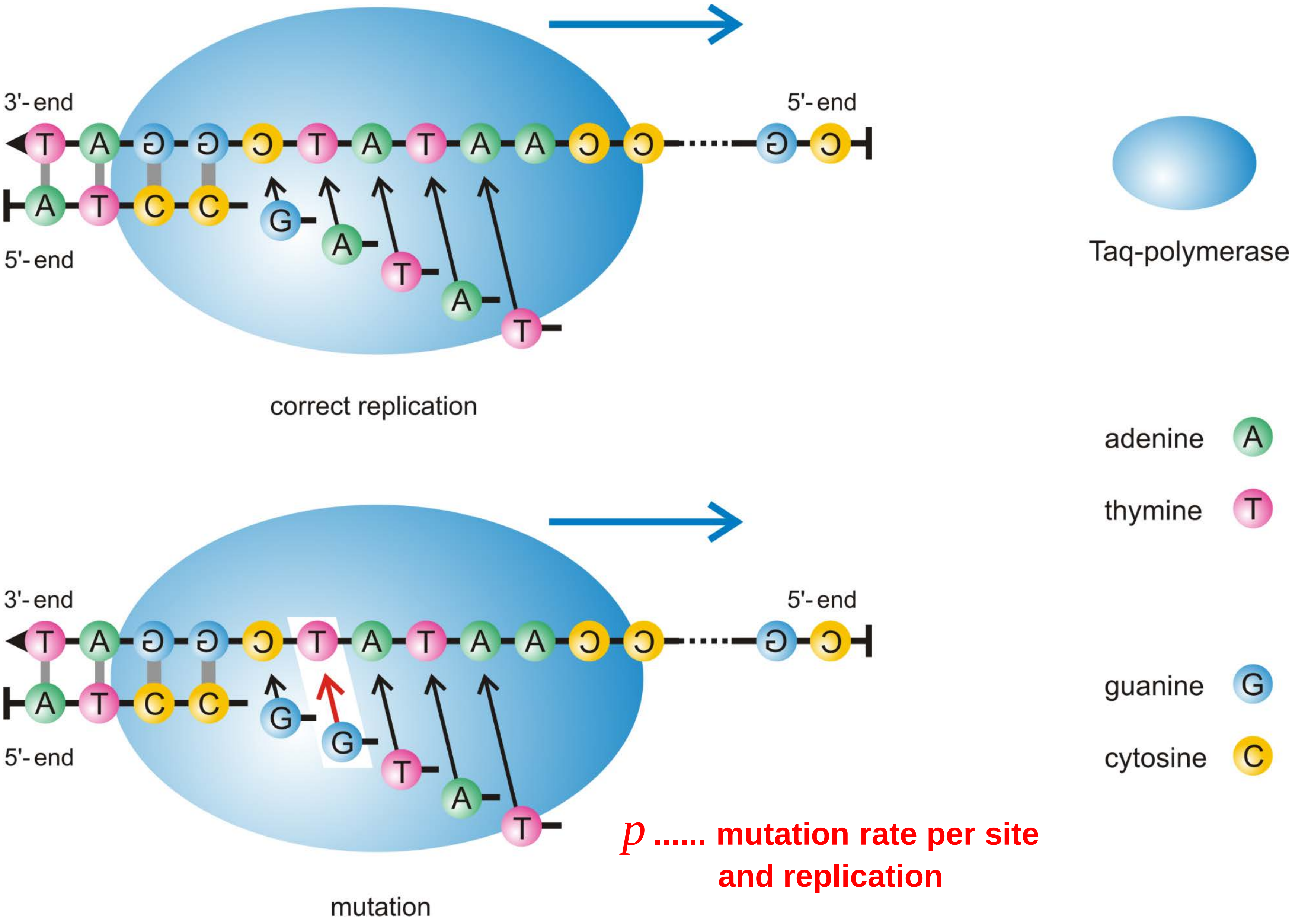


p ...... **mutation rate per site and replication**

DNA replication and mutation

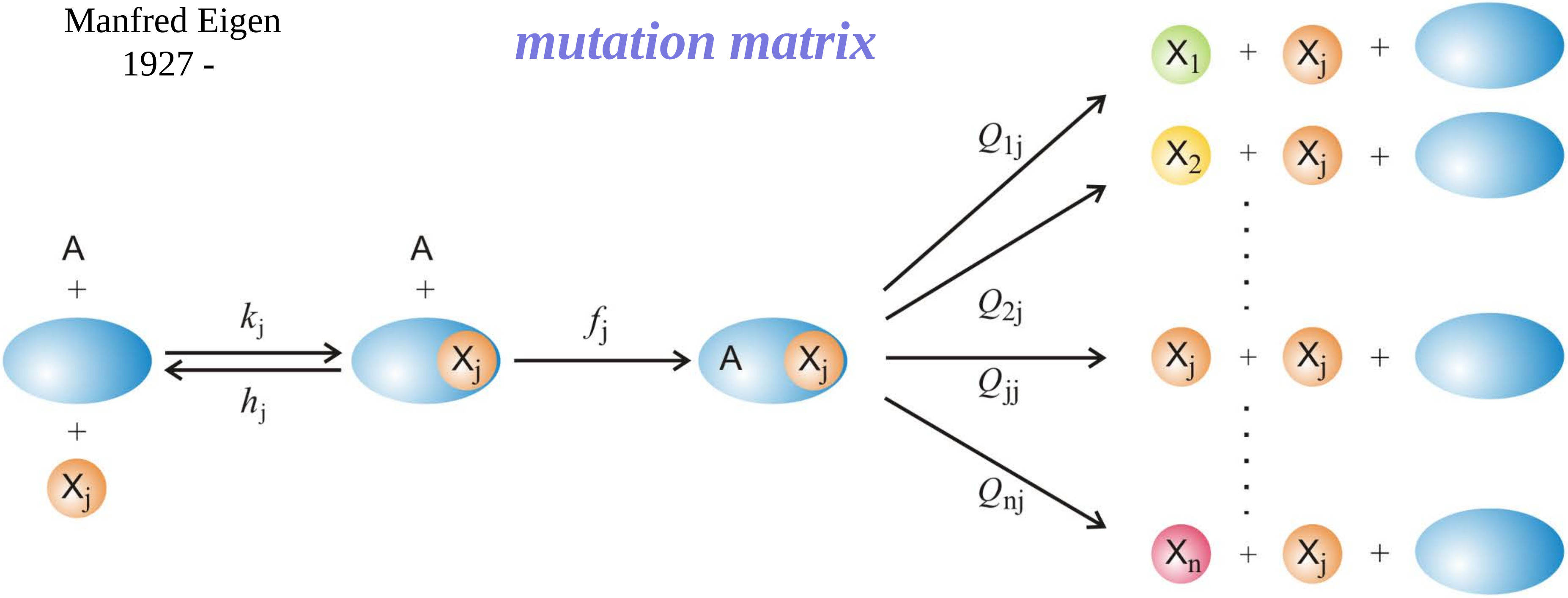
Manfred Eigen
1927 -

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

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

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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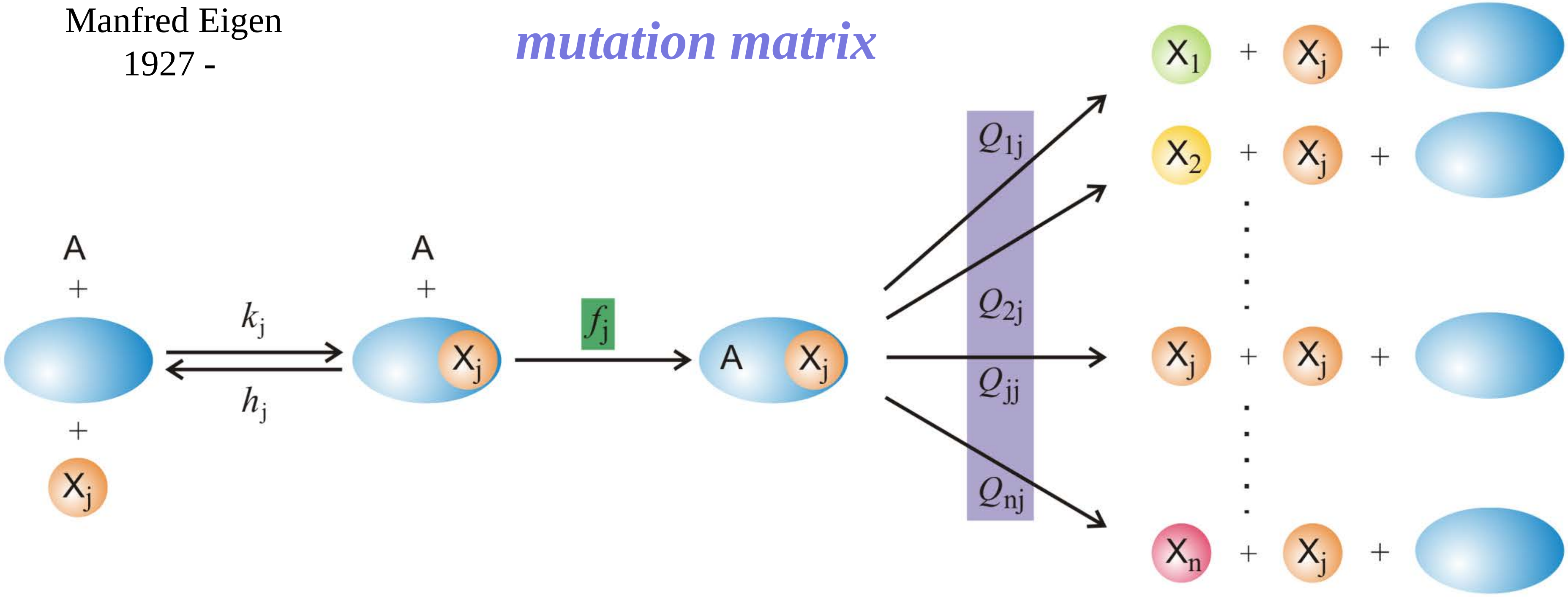

Mutation and (correct) replication as parallel chemical reactions

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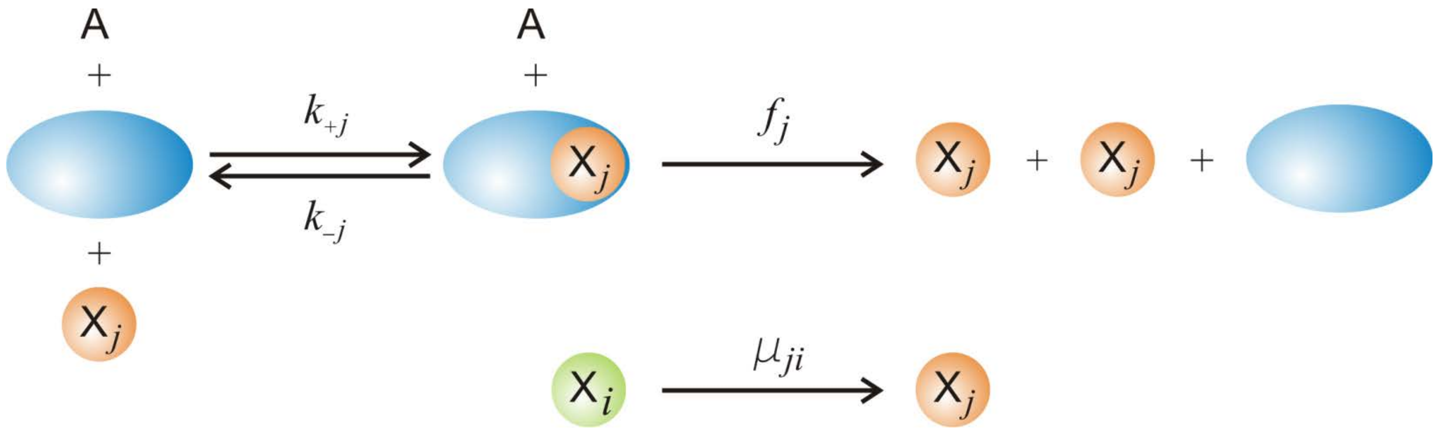


$$\frac{\mathrm{d}x_j}{\mathrm{d}t} = \left(f_j - \overline{f(t)}\right) x_j + \sum_{j=1}^{N} \mu_{ji}\, x_j \quad \text{or} \quad \frac{\mathrm{d}\mathbf{x}}{\mathrm{d}t} = \left(\mathrm{F} + \boldsymbol{\mu} - \overline{f(t)}\right) \mathbf{x}$$

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

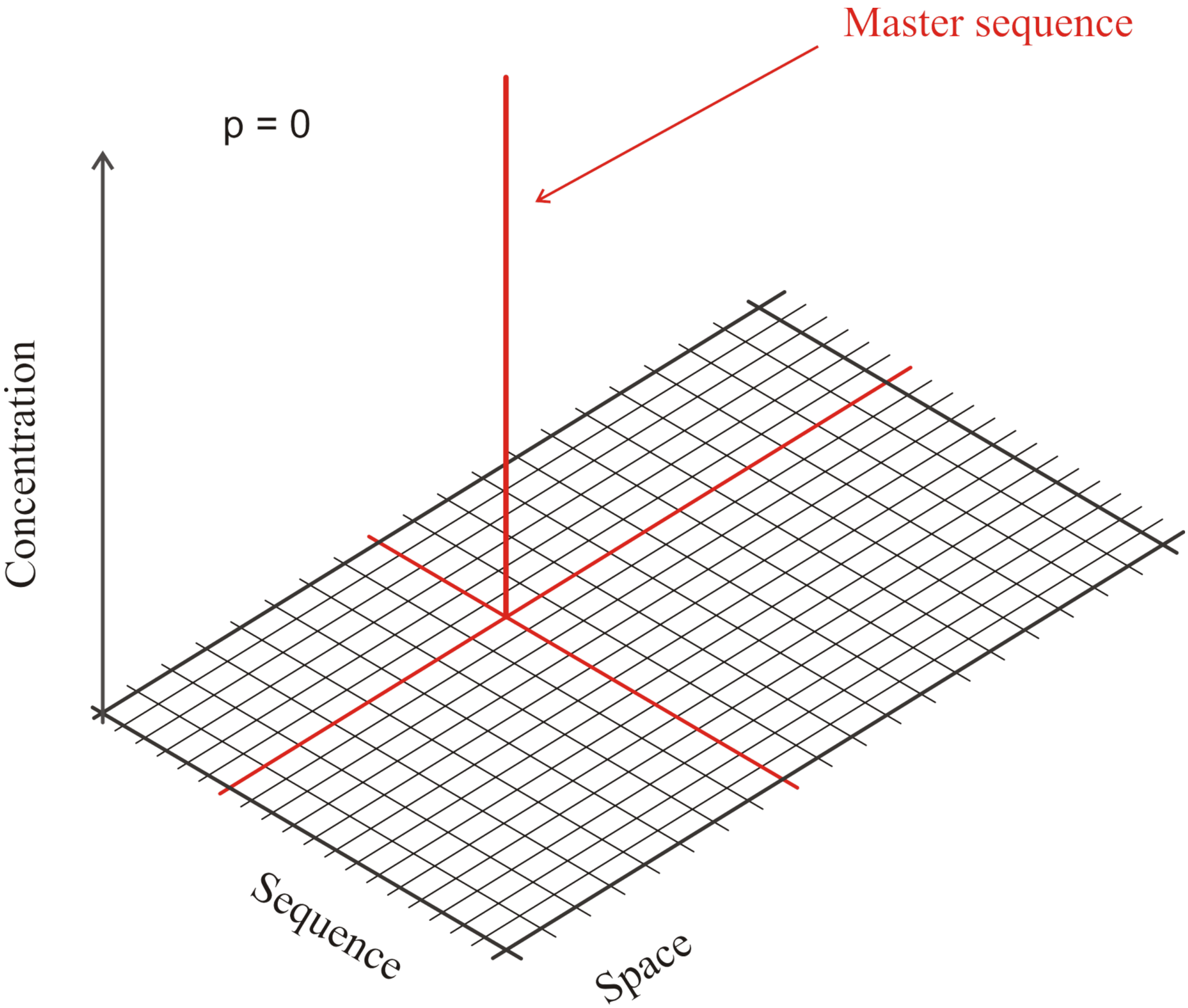
Largest eigenvalue λ_1 and corresponding eigenvector $\mathbf{b}_1$:

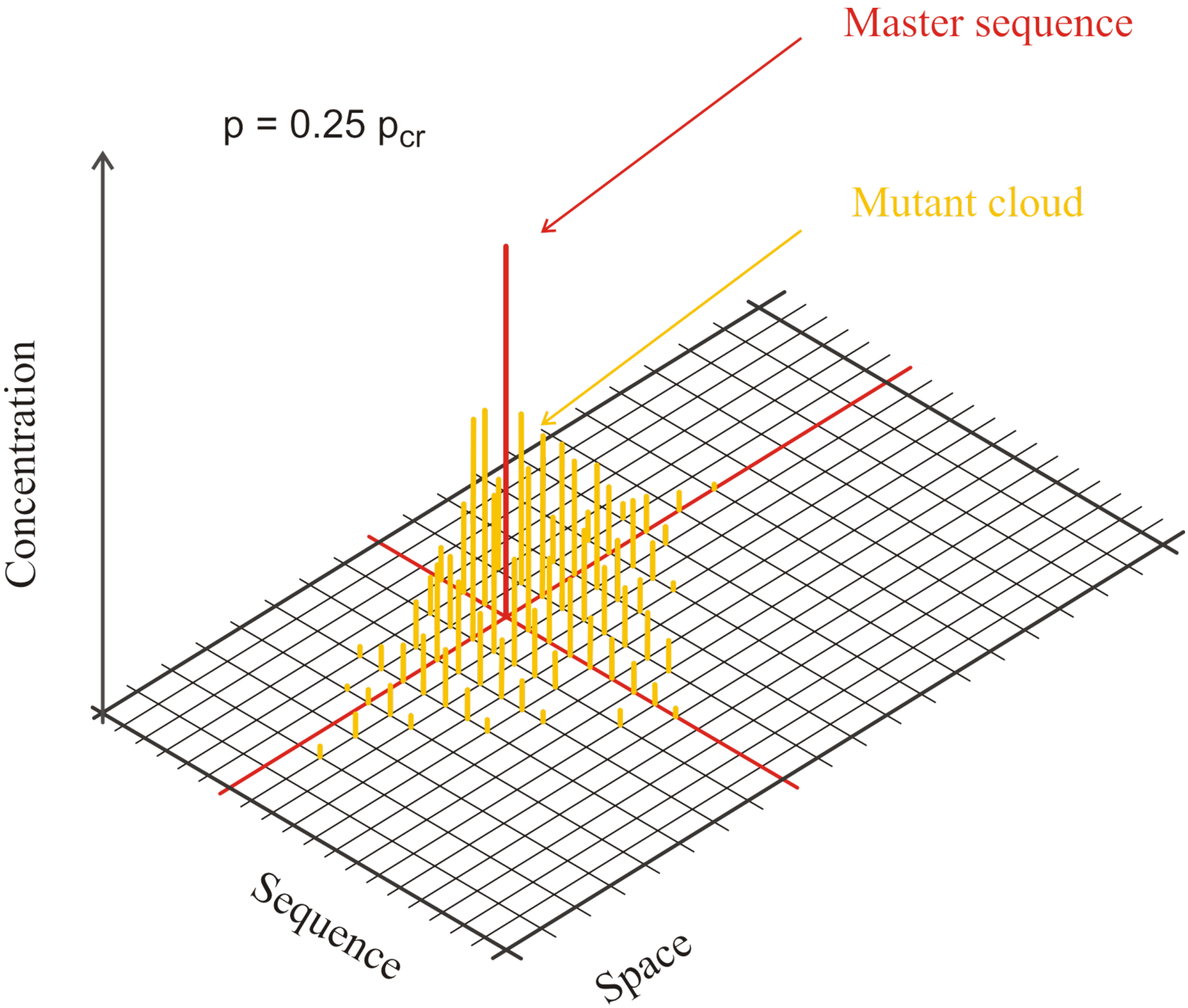
$$x_j(t) \approx \frac{b_{j1}\,\beta_1(0)\,\exp(\lambda_1\,t)}{\sum_{i=1}^{N} b_{i1}\,\beta_1(0)\,\exp(\lambda_1\,t)} = \frac{b_{j1}}{\sum_{i=1}^{N} b_{i1}} = \bar{x}_j \quad \text{for large } t$$

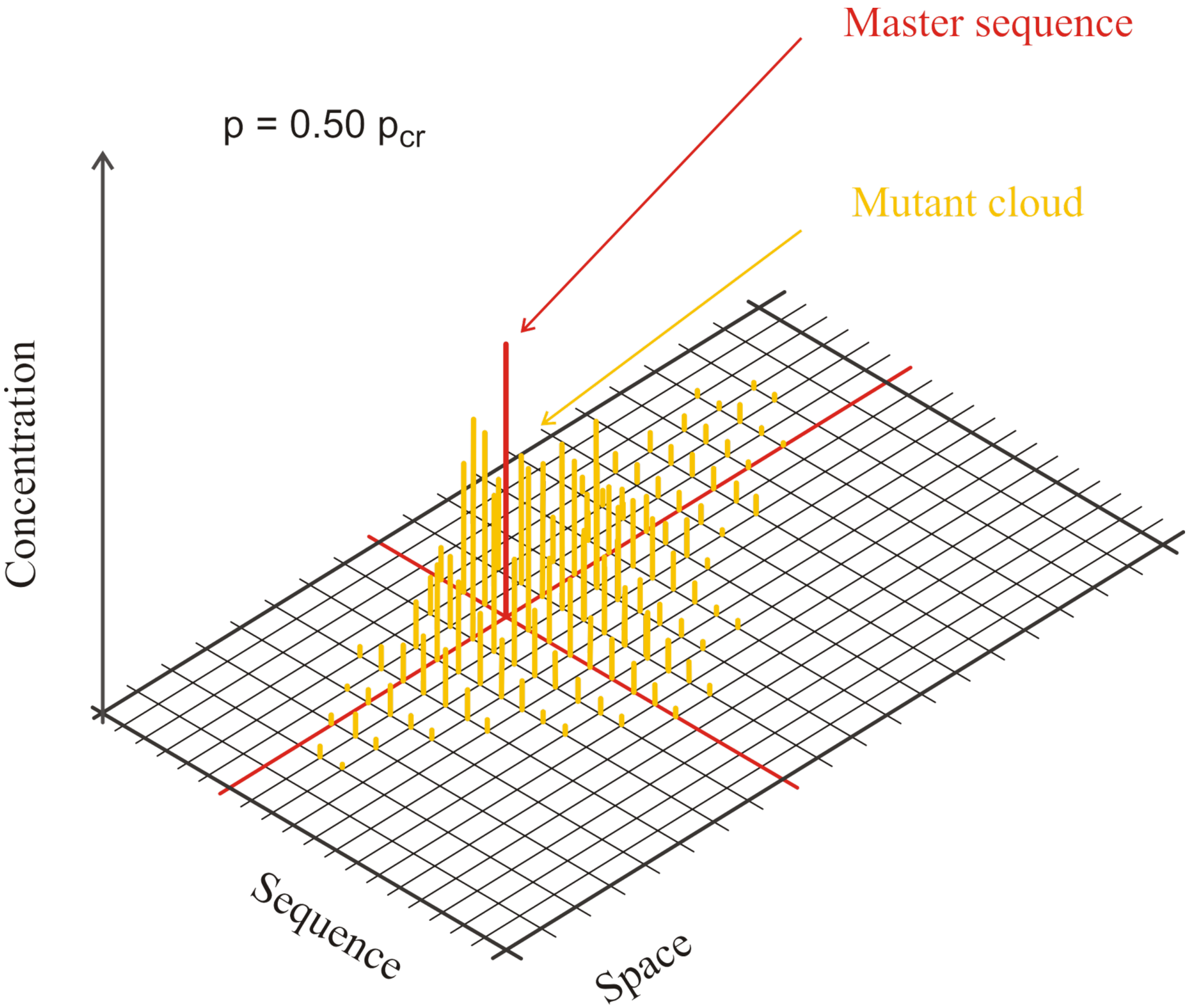
master sequence: X_m at concentration $\bar{x}_m$

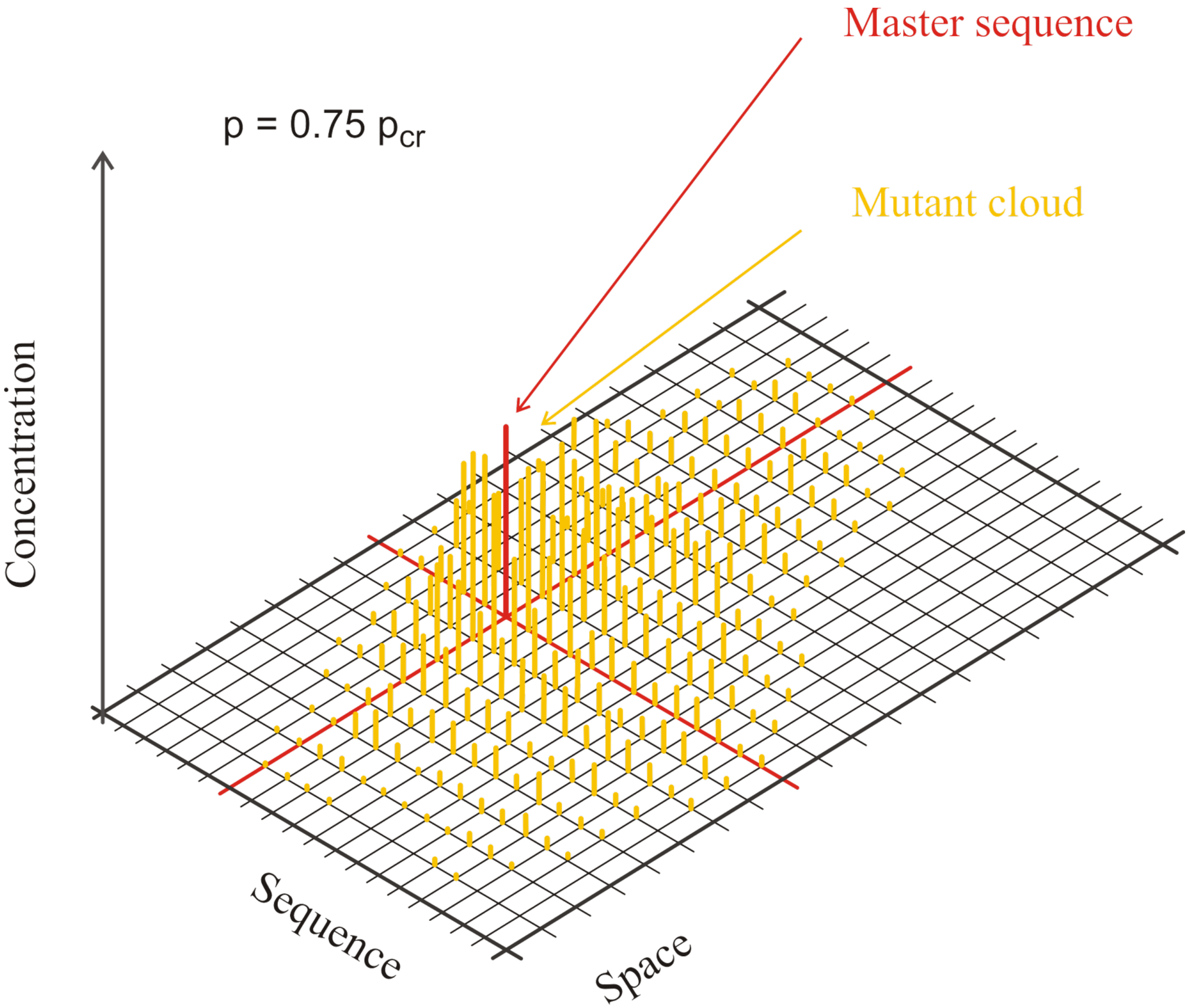
mutant cloud: X_j at concentration $\bar{x}_j\,;\; j=1,\ldots,N;\; j\neq m$

Stationary solution of the quasispecies equation

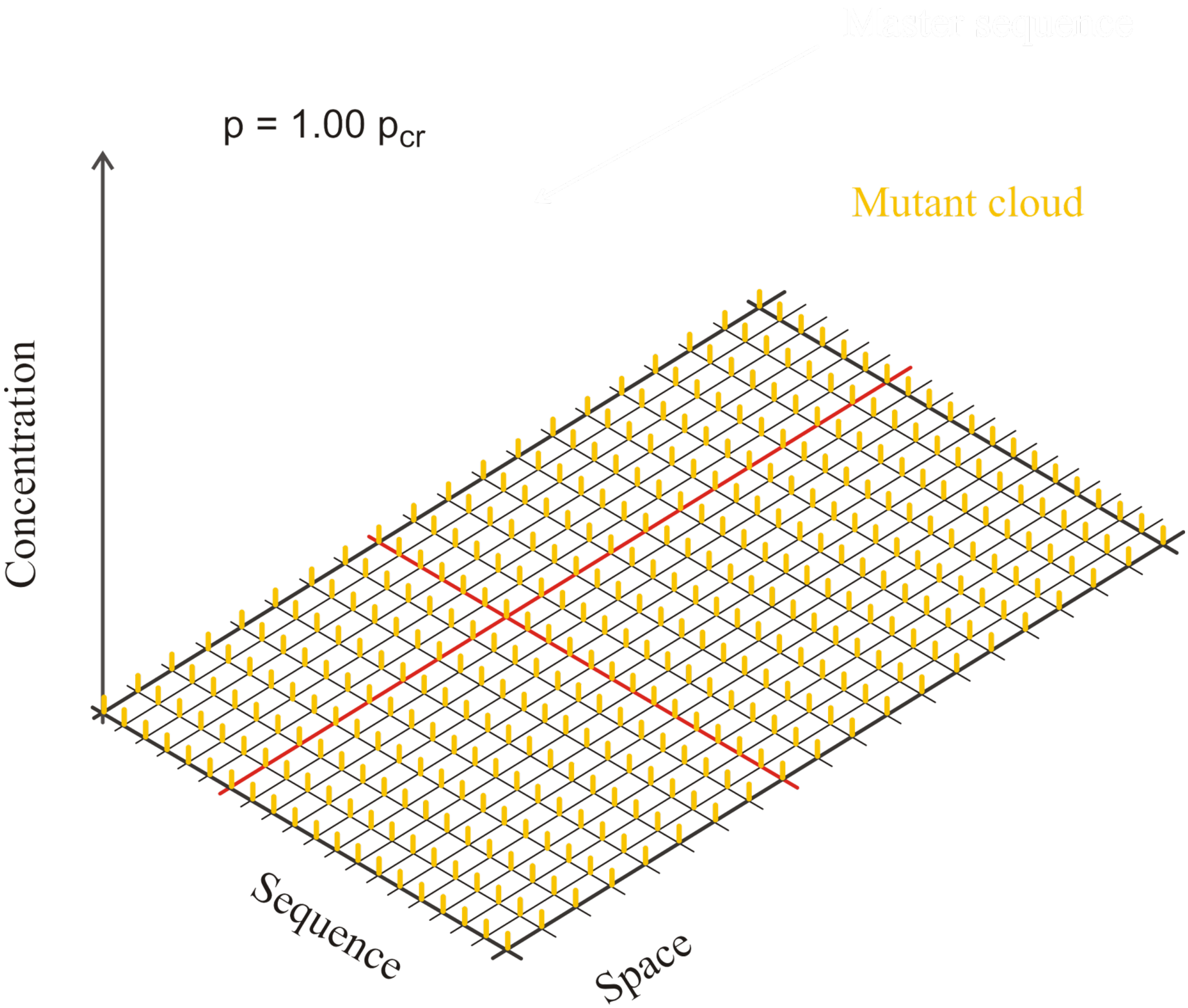

Master sequence
p = 0
Concentration
Sequence
Space


Master sequence
p = 0.25 p_{cr}
Mutant cloud
Concentration
Sequence
Space

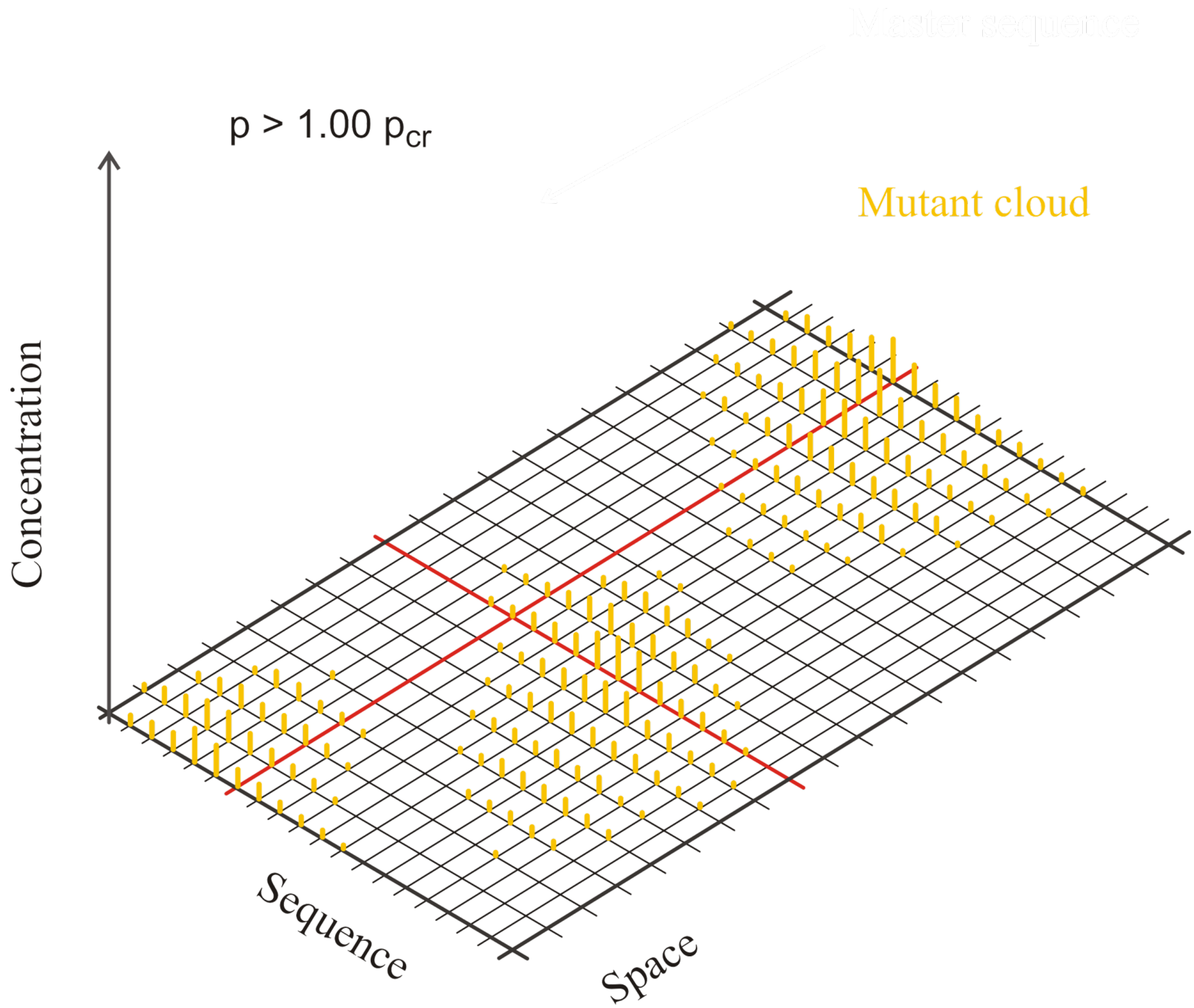

Master sequence
Mutant cloud
p = 0.50 p_{cr}
Concentration
Sequence
Space


Master sequence
Mutant cloud
p = 0.75 p$_{cr}$
Concentration
Sequence
Space

$p = 1.00\ p_{cr}$


Master sequence
Mutant cloud
Concentration
Sequence
Space

$p > 1.00\ p_{cr}$


Master sequence
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Concentration
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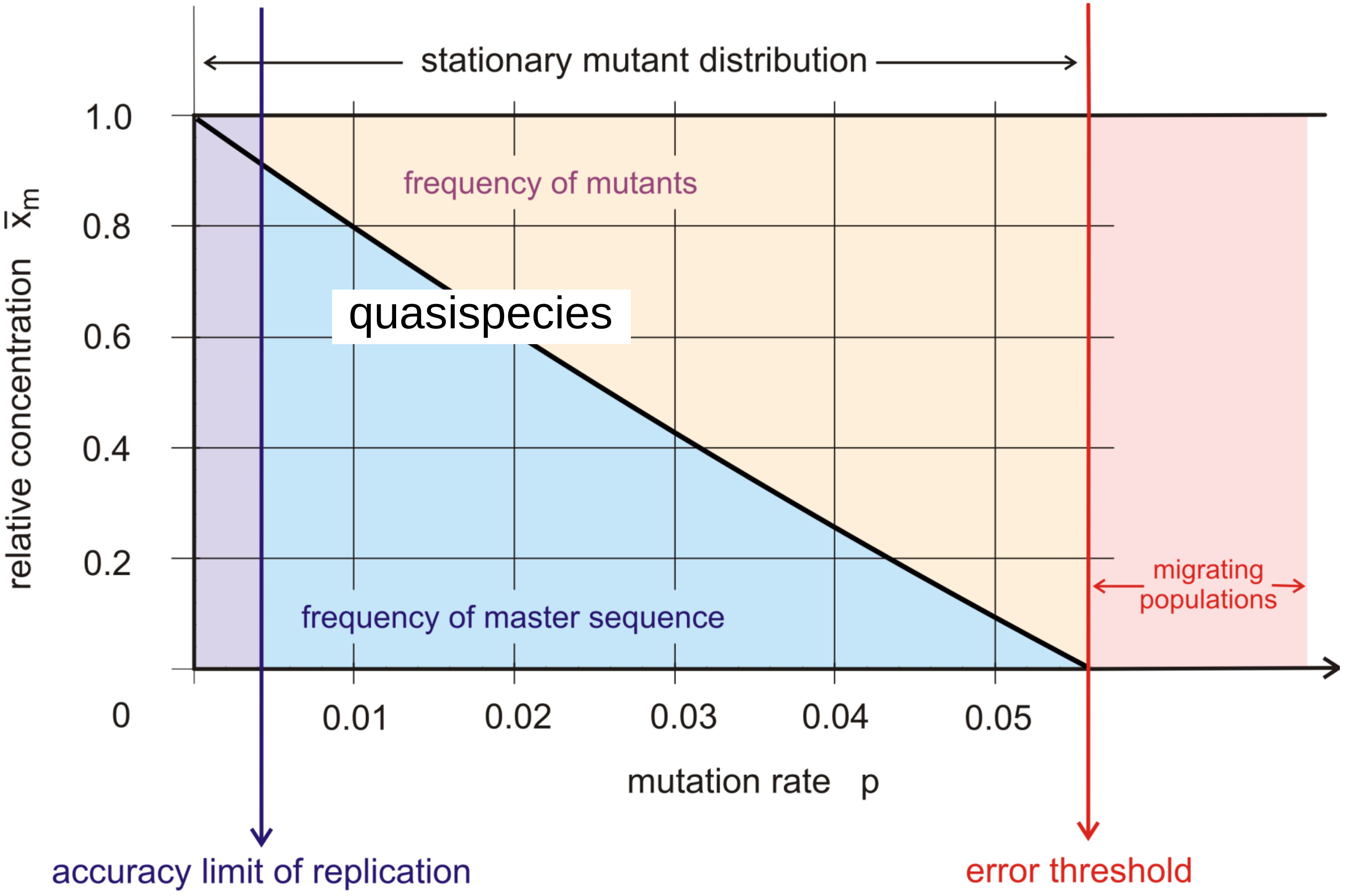
Space



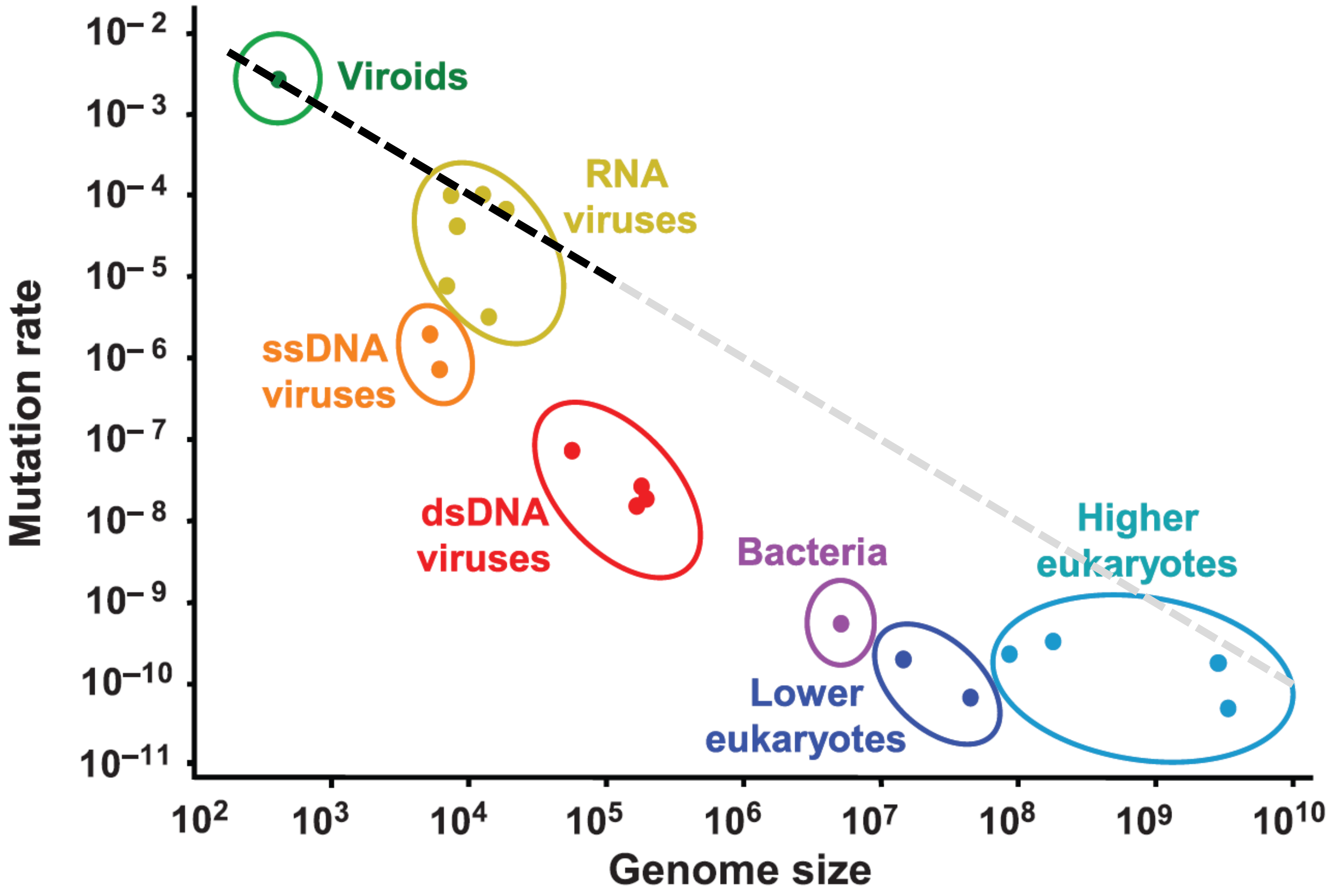
The error threshold in replication and mutation

$$p_{\max} \approx \frac{\ln \sigma}{l}$$ ……… antiviral strategies

$$l_{\max} \approx \frac{\ln \sigma}{p}$$ ……… prebiotic chemistry

M. Eigen. 1971. Self-organization of matter and the evolution of biological macromolecules. *Naturwissenschaften* 58:465-523

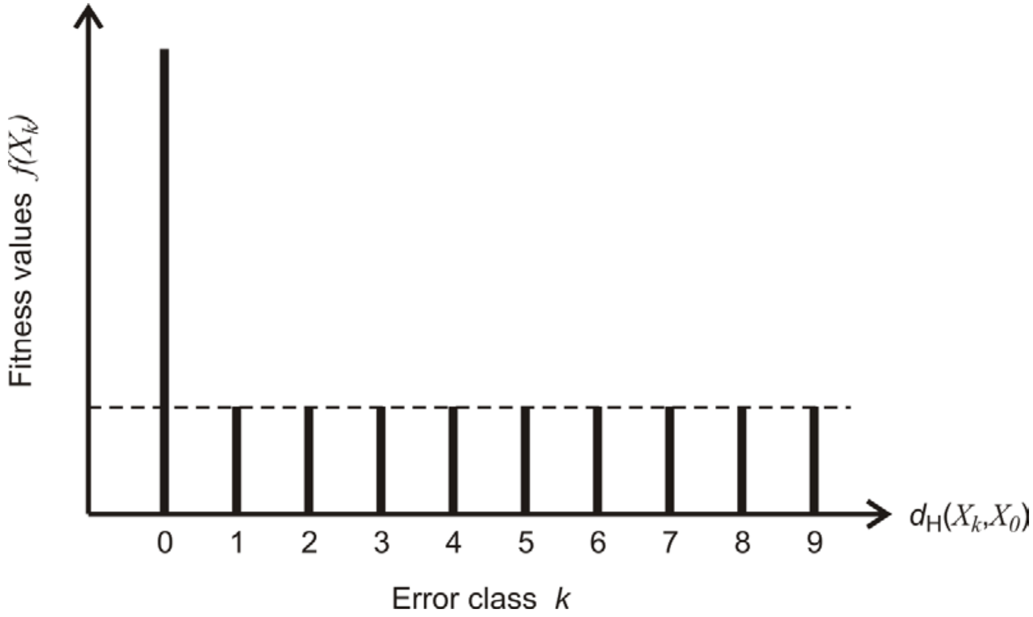
The error threshold



Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. 2009, Extremely high mutation rate of a hammerhead viroid. Science 323:1308.

Mutation rate and genome size

single peak fitness landscape



$$Q_{ij}(p) \;=\; (1-p)^{l-\mathrm{d}_{ij}^{\mathrm{H}}}\, p^{\mathrm{d}_{ij}^{\mathrm{H}}} \;=\; (1-p)^{l}\, \varepsilon^{\mathrm{d}_{ij}^{\mathrm{H}}} \;\; \text{with} \;\; \varepsilon \;=\; \frac{p}{1-p}$$

uniform error rate model

Approximations for handling realistic chain lengths

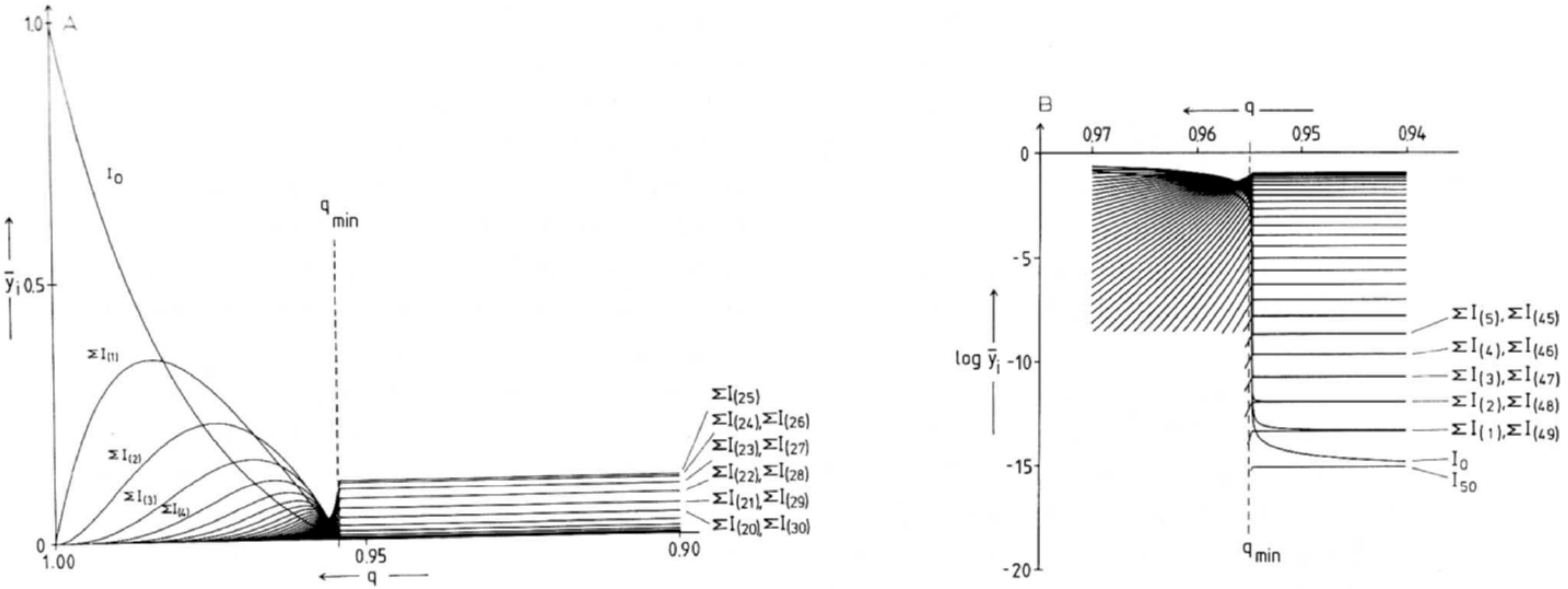
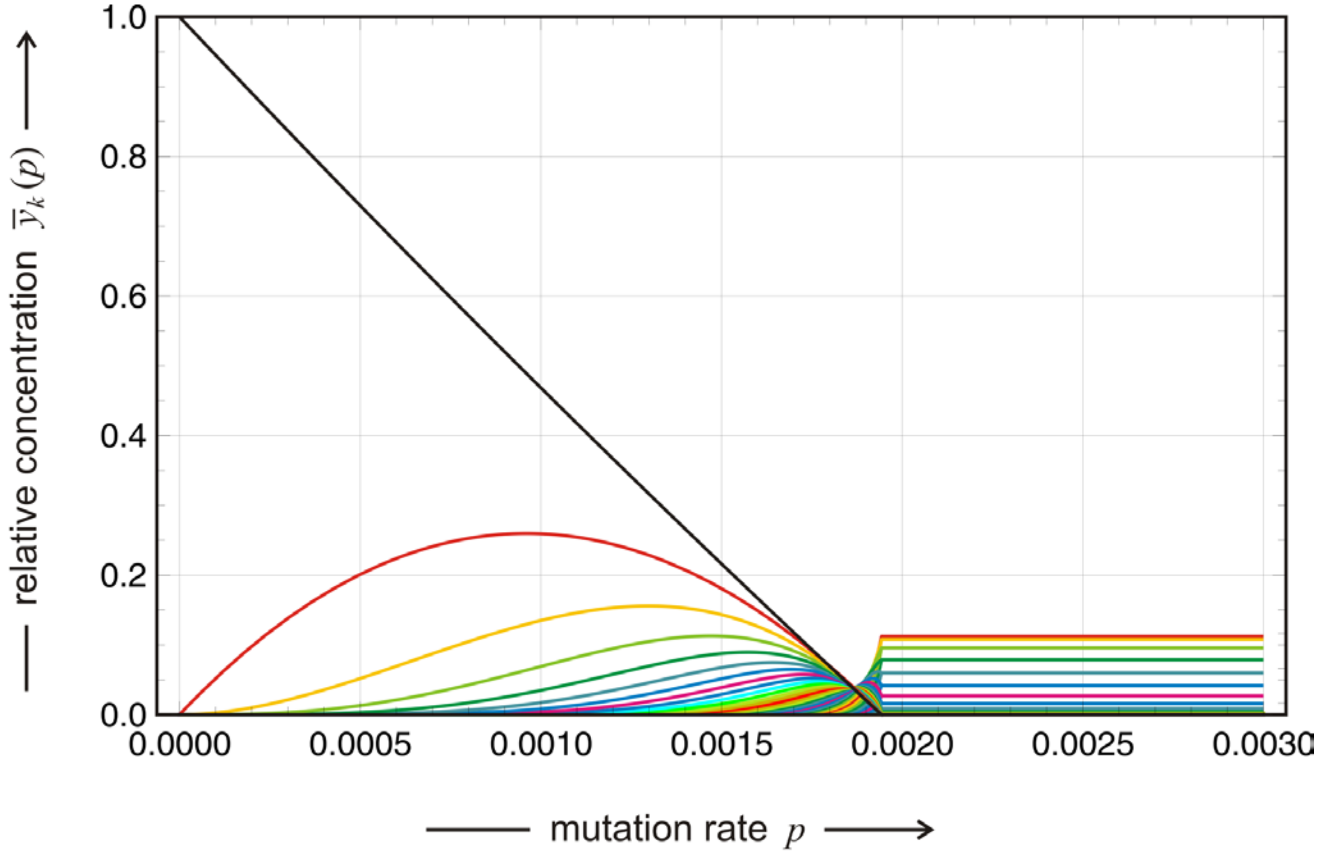


Fig. 10. Distribution of mutant classes as a function of the single-digit accuracy q for $\nu = 50$. Note the sharpness of the transition from direct to stochastic replication around $q_{\min}$. This is seen best on the logarithmic plot. In the domain of stochastic replication individual concentrations become exceedingly small: $\bar{\xi}_i = 8.9 \times 10^{-16}$, $i = 0, \ldots 2^{50} - 1$. For basic definitions and numerical values see fig. 7.

Jörg Swetina, Peter Schuster. 1982. Self-replication with errors. A model for polynucleotide replication. Biophys. Chem. 16, 329-345

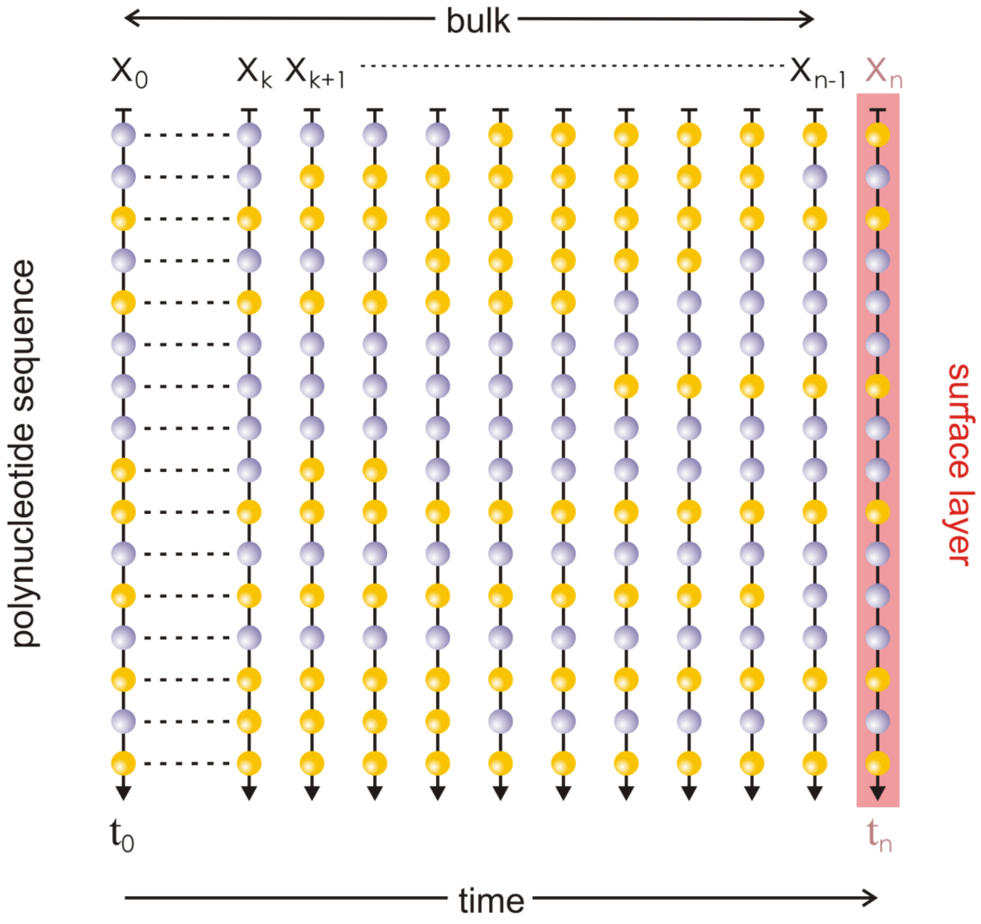
The error threshold



$l = 50$, $f_0 = 1.1$, $f_n = 1.0$, $p_{cr} = 0.001904$

Jörg Swetina, Peter Schuster. 1982. Self-replication with errors. A model for polynucleotide replication. Biophys.Chem. 16, 329-345.

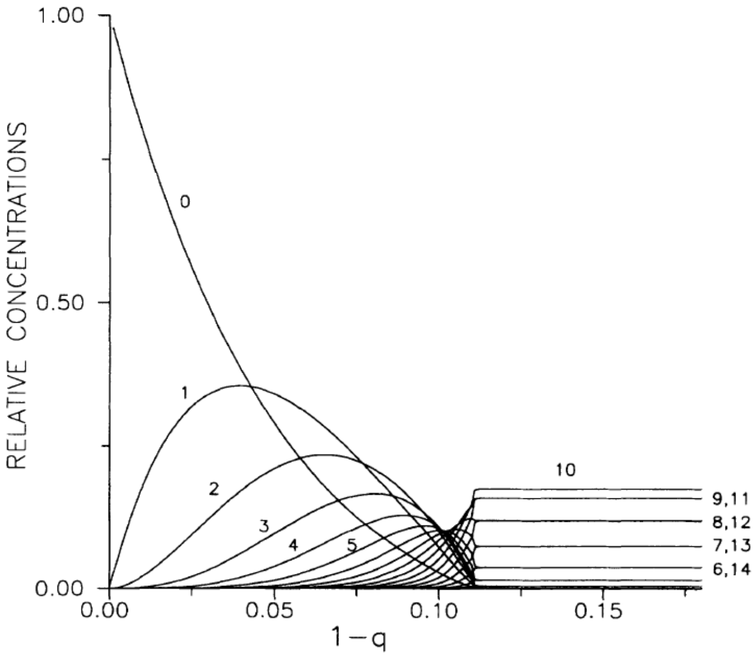
Quasispecies and error threshold



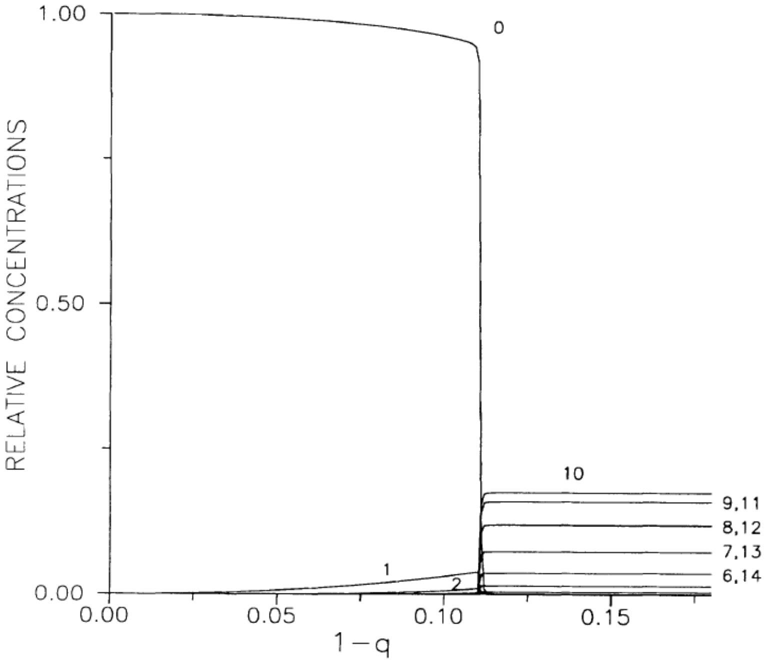
Ira Leuthäusser. 1987. Statistical mechanics of Eigen‘s evolution model. J.Statist.Phys.48, 343-360

Pedro Tarazona. 1992. Error thresholds for molecular quasispecies as phase transitions: From simple landscapes to spin-glass models. Phys.Rev.A 45, 6038-6050.

Quasispecies and statistical mechanics of spin systems



distribution on the surface layer



bulk distribution

stationary distribution on the single peak landscape

Pedro Tarazona. 1992. Error thresholds for molecular quasispecies as phase transitions:
From simple landscapes to spin-glass models. Phys.Rev.A 45, 6038-6050.

Quasispecies and statistical mechanics of spin systems

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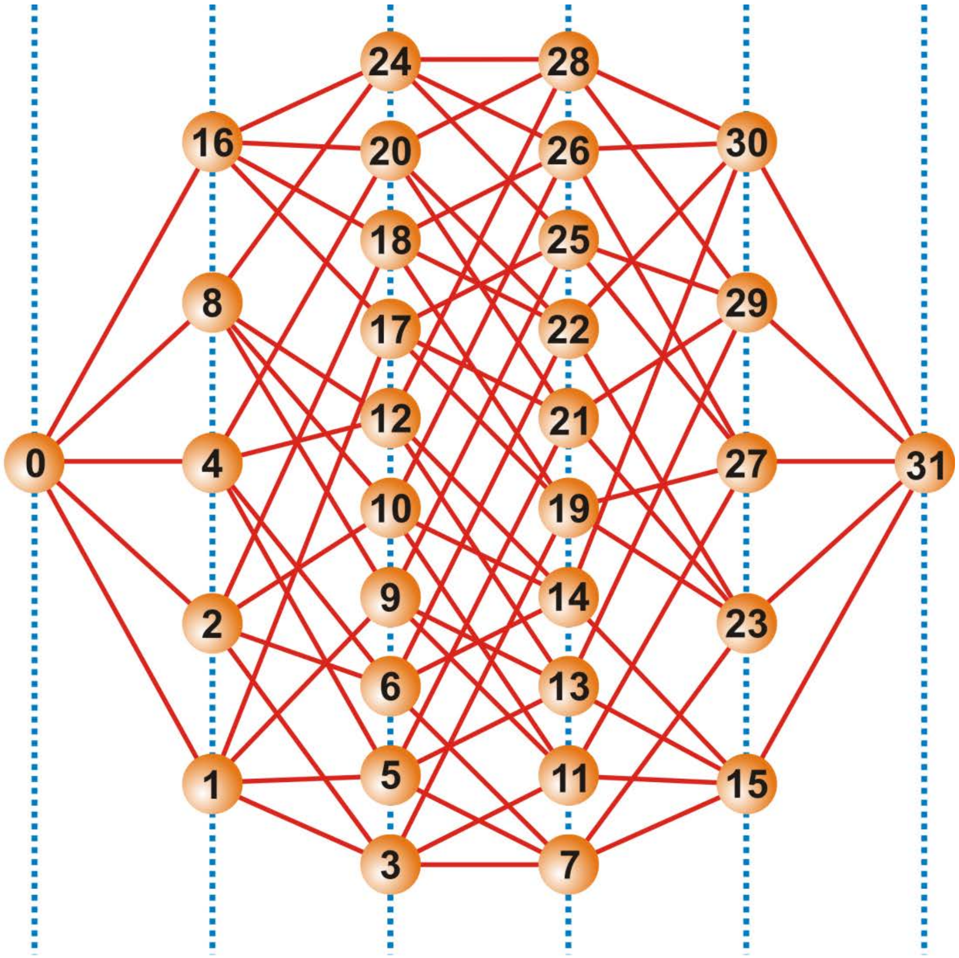
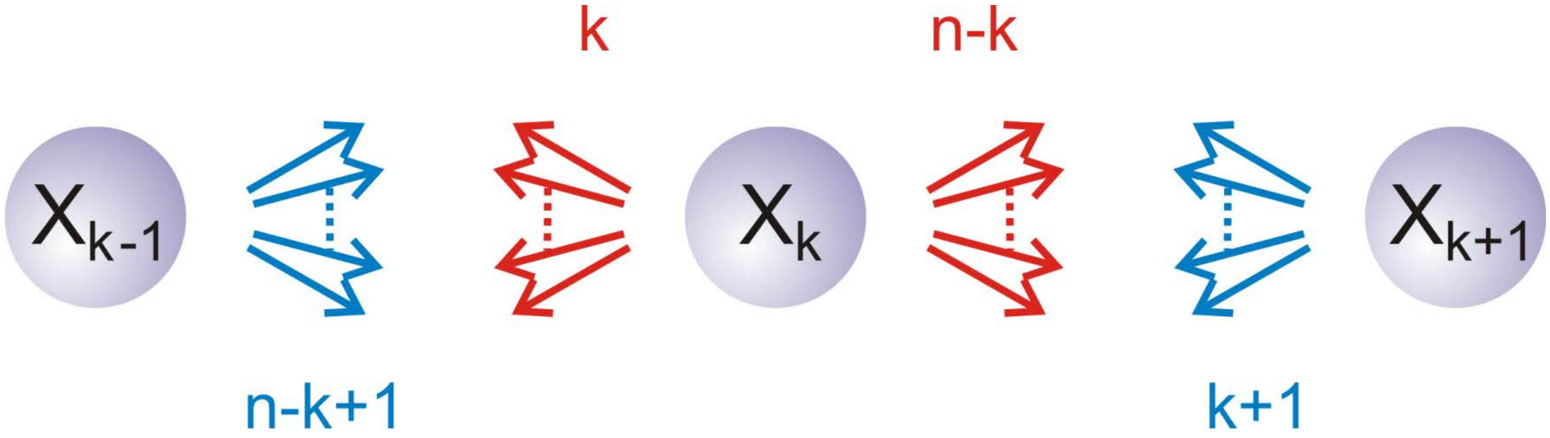


mutant classes	0	1	2	3	4	5
number of sequences	1	5	10	10	5	1

The space of binary sequences

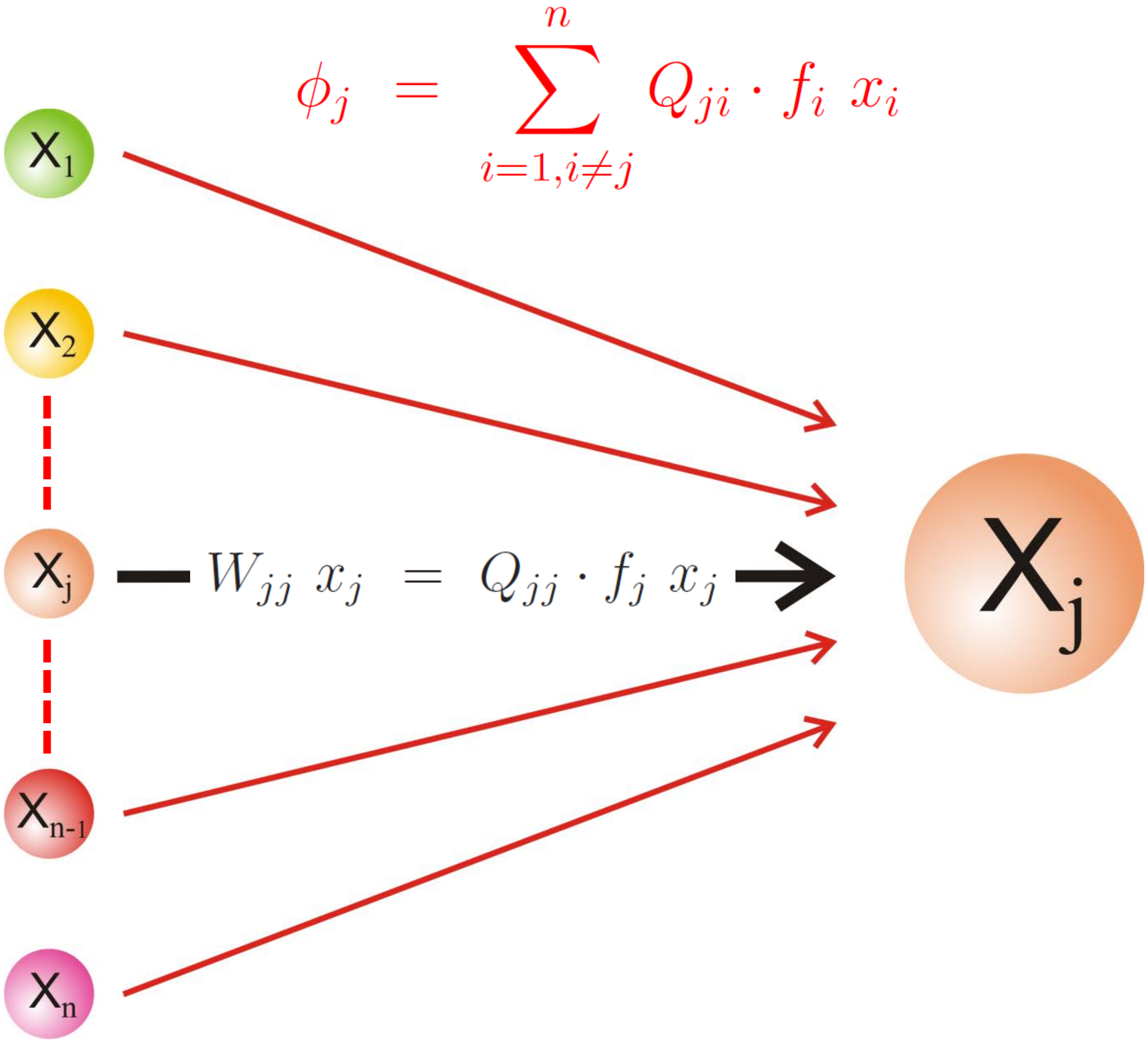


Neighbor distribution on binary sequence spaces

$$\varphi_{ji} = Q_{ji} \cdot f_i \, x_i \, ; \; Q_{ji} \approx (1-p)^{l-\mathrm{d}^{\mathrm{H}}_{ji}} \cdot p^{\mathrm{d}^{\mathrm{H}}_{ji}}$$

$$\phi_j = \sum_{i=1, i \neq j}^{n} \varphi_{ji} = \sum_{i=1, i \neq j}^{n} Q_{ji} \cdot f_i \, x_i$$

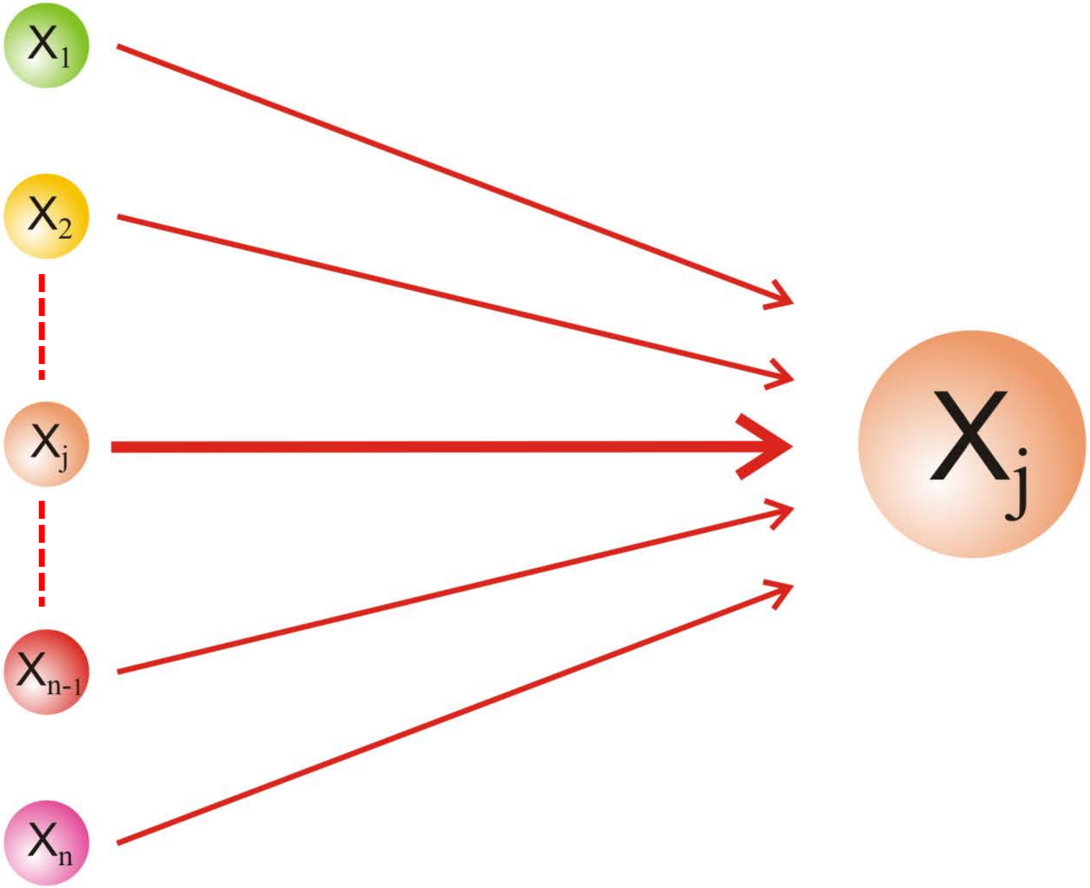
Mutation flow component and mutation flow



$$\phi_j = \sum_{i=1, i\neq j}^{n} Q_{ji} \cdot f_i \, x_i$$

$$W_{jj} \, x_j = Q_{jj} \cdot f_j \, x_j$$

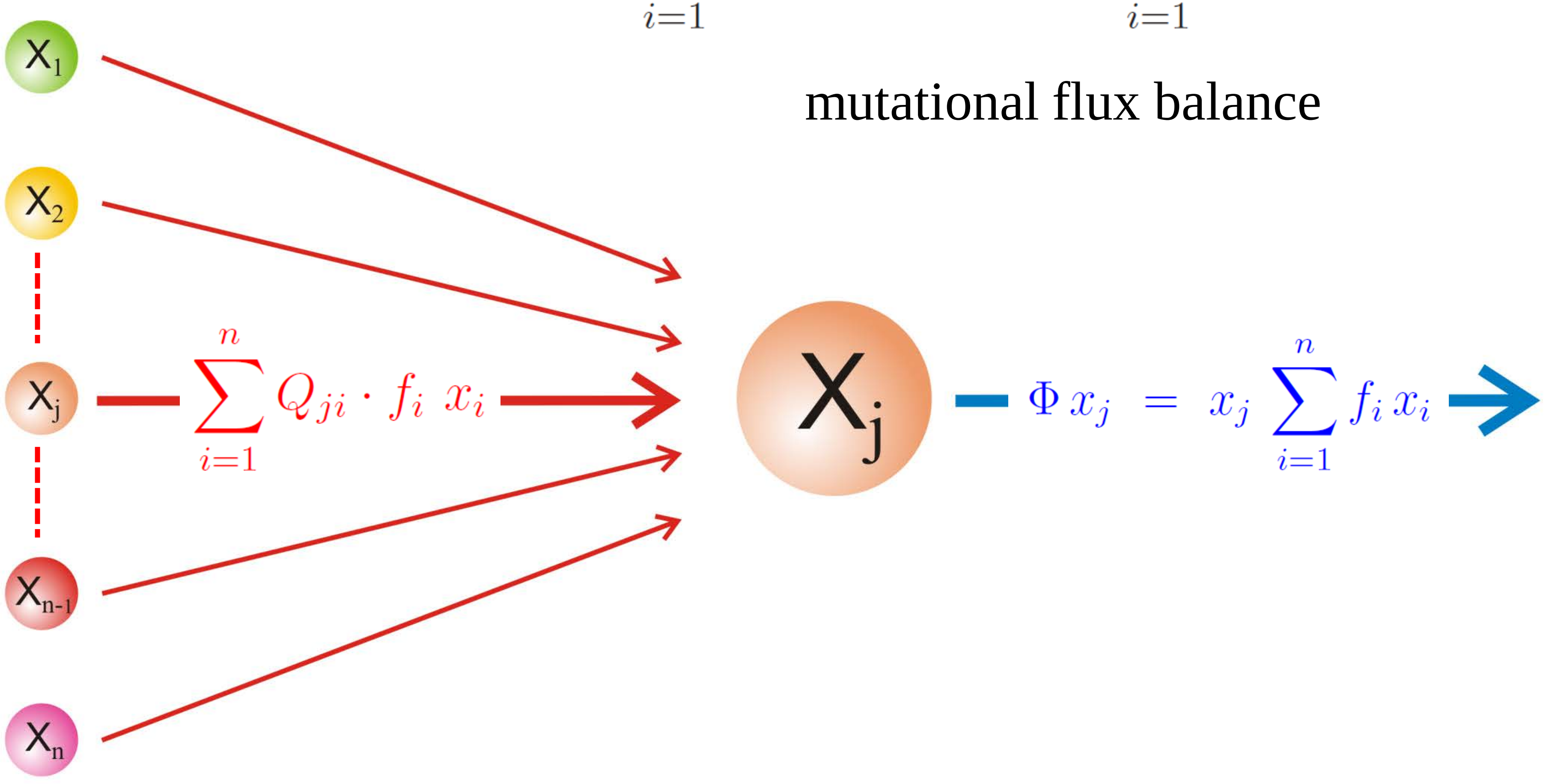
Definition of the mutation flow



Mutational flux balance and quasispecies

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

mutational flux balance



$$\sum_{i=1}^{n} Q_{ji} \cdot f_i \; x_i$$

$$\Phi \, x_j \;=\; x_j \sum_{i=1}^{n} f_i \, x_i$$

Mutational flux balance and quasispecies

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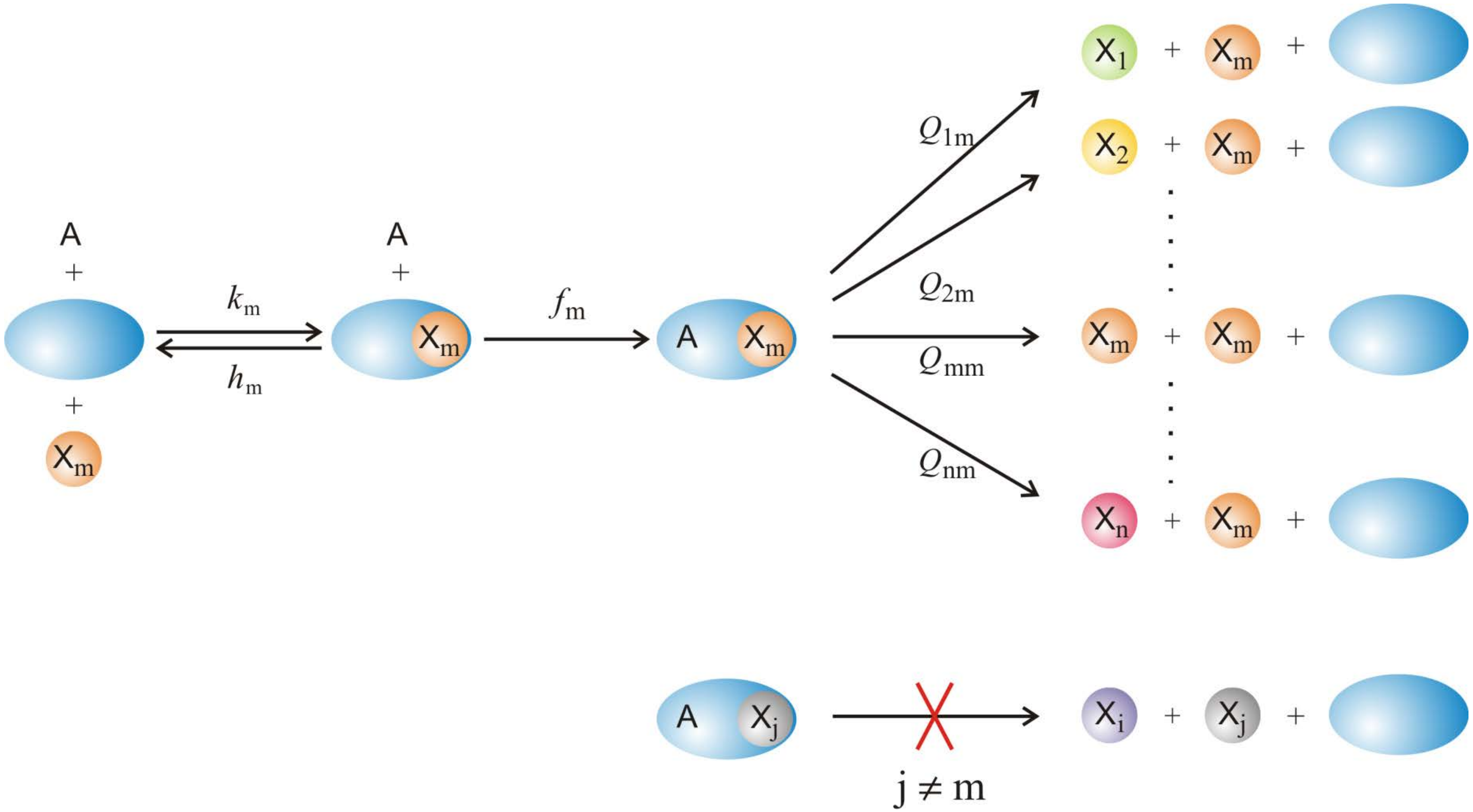


Zero mutation backflow

$$\frac{\mathrm{d}x_m^{(0)}}{\mathrm{dt}} = (W_{mm} - \phi)\, x_m^{(0)} = (Q_{mm}\, f_m - \phi)\, x_m^{(0)}$$

$$\phi = \sum_{i=1}^{N} Q_{ii}\, f_i\, x_i^{(0)} + f_m\, x_m^{(0)} \sum_{j=1, j\neq m}^{n} Q_{jm}$$

single peak, uniform error: $\phi = f_0\, x_m^{(0)} + Q\, f\, (1 - x_m^{(0)})$

$$\frac{\mathrm{d}x_j^{(0)}}{\mathrm{dt}} = (W_{jj} - \phi)\, x_j^{(0)} + W_{jm}\, x_m^{(0)} =$$

$$= (Q_{jj}\, f_j - \phi)\, x_j^{(0)} + Q_{jm}\, f_m\, x_m^{(0)}$$

Kinetic equations of the zero backflow approximation

$$\bar{x}_m^{(0)} = \frac{Q\,(1 - \sigma_m^{-1})}{1 - Q\,\sigma_m^{-1}}$$

$Q = (1-p)^l$ and $\sigma_m = f_m \,/\, \bar{f}_{-m} = f_m \,/\, f$

$$\bar{x}_j^{(0)} = \frac{Q\,\varepsilon^{d_{jm}}}{1 - Q\,\sigma_m^{-1}}\,,\ j = 1, \ldots, n,\ j \neq m$$

Solutions of the zero backflow approximation

$$Q_{mm}\, f_m\, \hat{c} \;-\; f_m\, \hat{x}_m^{(0)} \;-\; \overline{f}_{-m}\, (\hat{c} - \hat{x}_m^{(0)}) \;=\; 0$$

single peak, uniform error

$$\hat{x}_m^{(0)} \;=\; \frac{Q f_m - f}{f_m - f} \;=\; \frac{Q - \sigma_m^{-1}}{1 - \sigma_m^{-1}}\; \hat{c}^{(0)}$$

$$\hat{x}_j^{(0)} \;=\; \frac{\varepsilon^{\mathrm{d}^{\mathrm{H}}_{jm}} (Q - \sigma_m^{-1})}{(1 - \sigma_m^{-1})^{2}}$$; $j = 1, \ldots, N$

$$\hat{c}^{(0)} \;=\; \frac{(1 - Q\sigma_m^{-1})(Q - \sigma_m^{-1})}{Q(1 - \sigma_m^{-1})^2}$$

The phenomenological approach (Eigen, 1971)

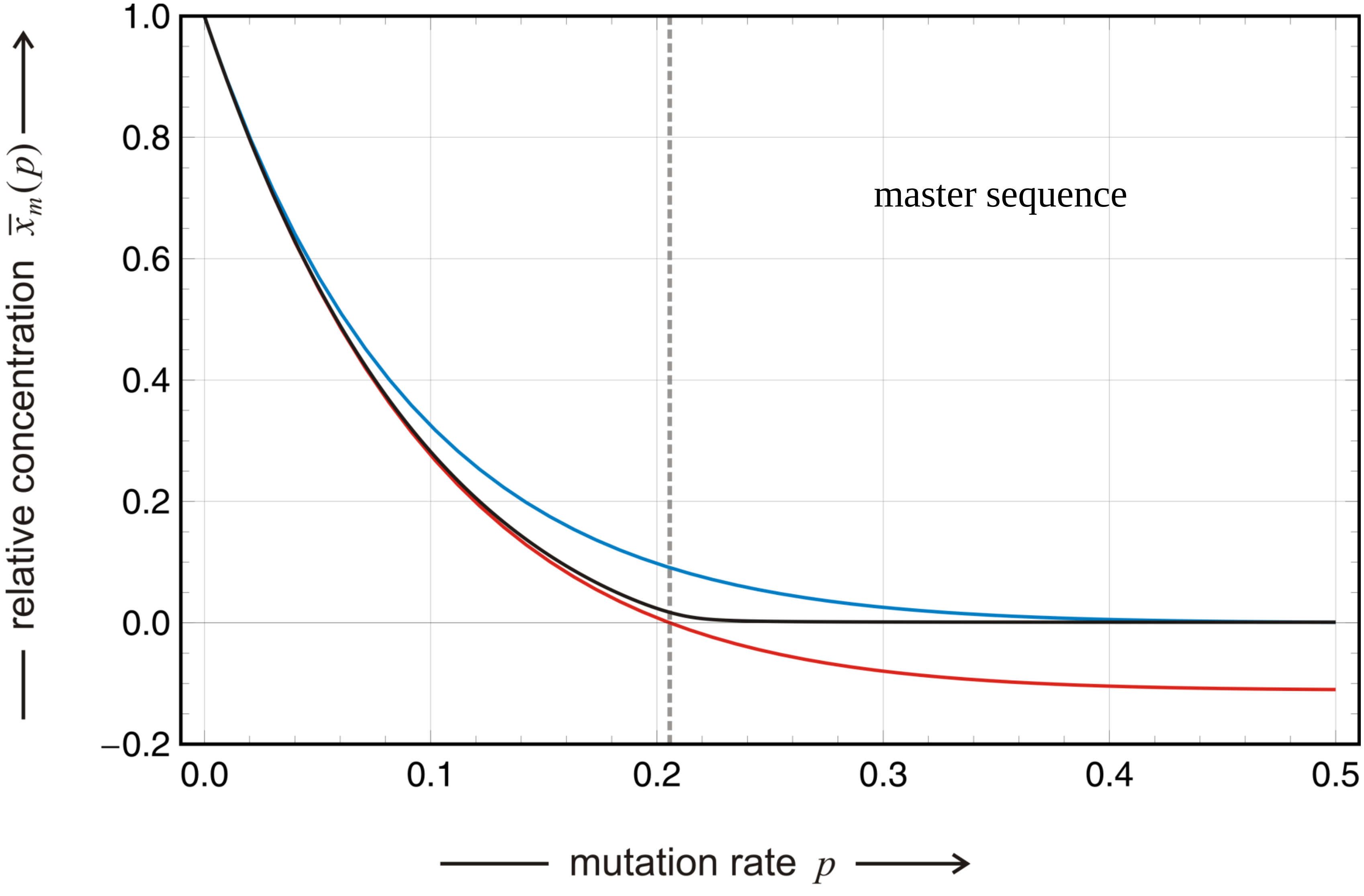
$$\hat{x}_m^{(0)}(p) \;=\; \frac{Q(p) \;-\; \sigma_m^{-1}}{1 \;-\; \sigma_m^{-1}}$$

$$\hat{x}_m^{(0)}(p_{cr}) = 0 \quad \Longrightarrow \quad Q(p_{cr}) \;=\; \sigma^{-1}$$

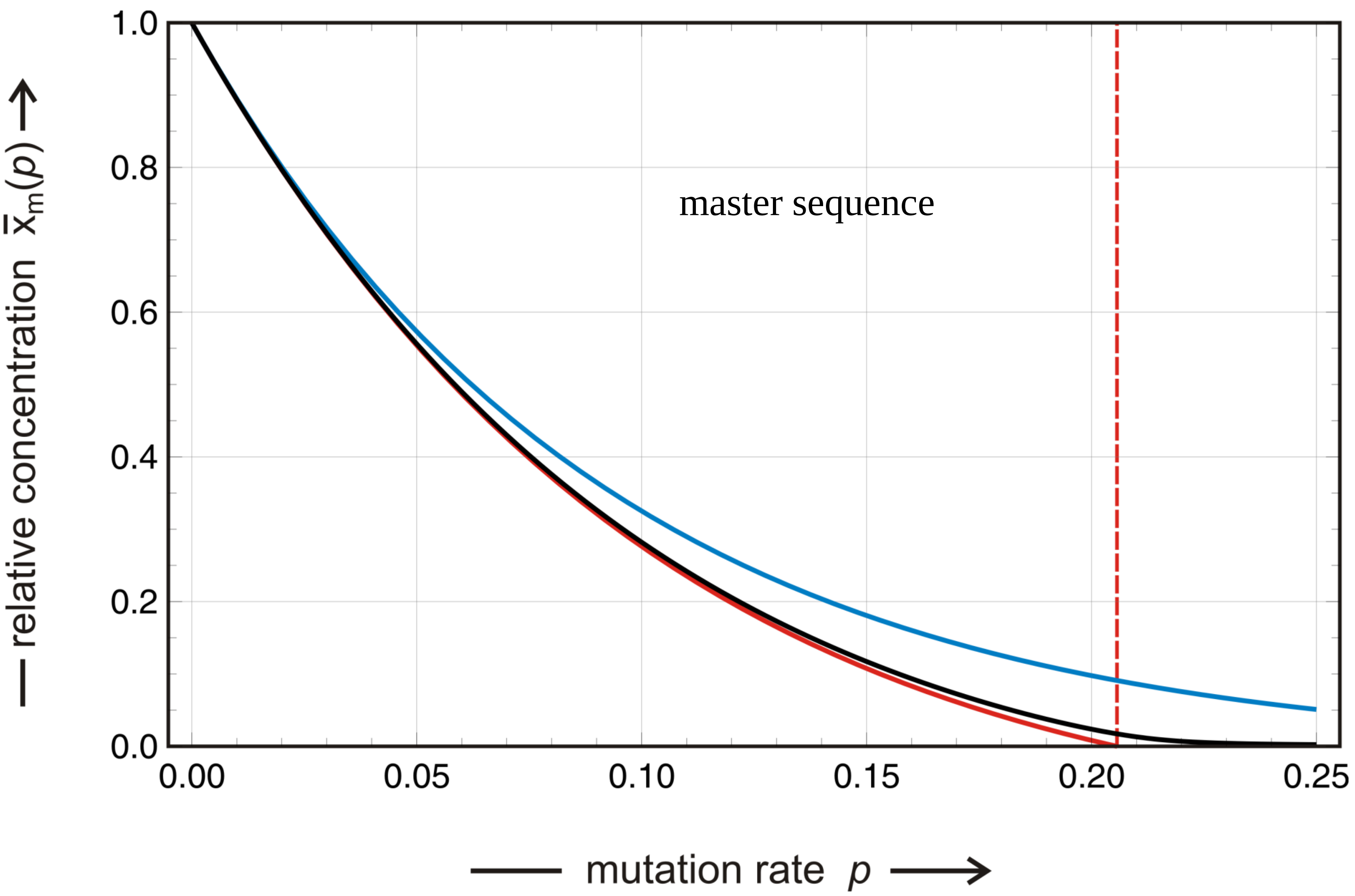
l constant: $p_{cr} \equiv p_{\max}$ or p constant: $p_{cr} \rightarrow l_{\max}$

$$p_{\max} \;\approx\; \frac{\ln \sigma}{l} \qquad \text{or} \qquad l_{\max} \;\approx\; \frac{\ln \sigma}{p}$$

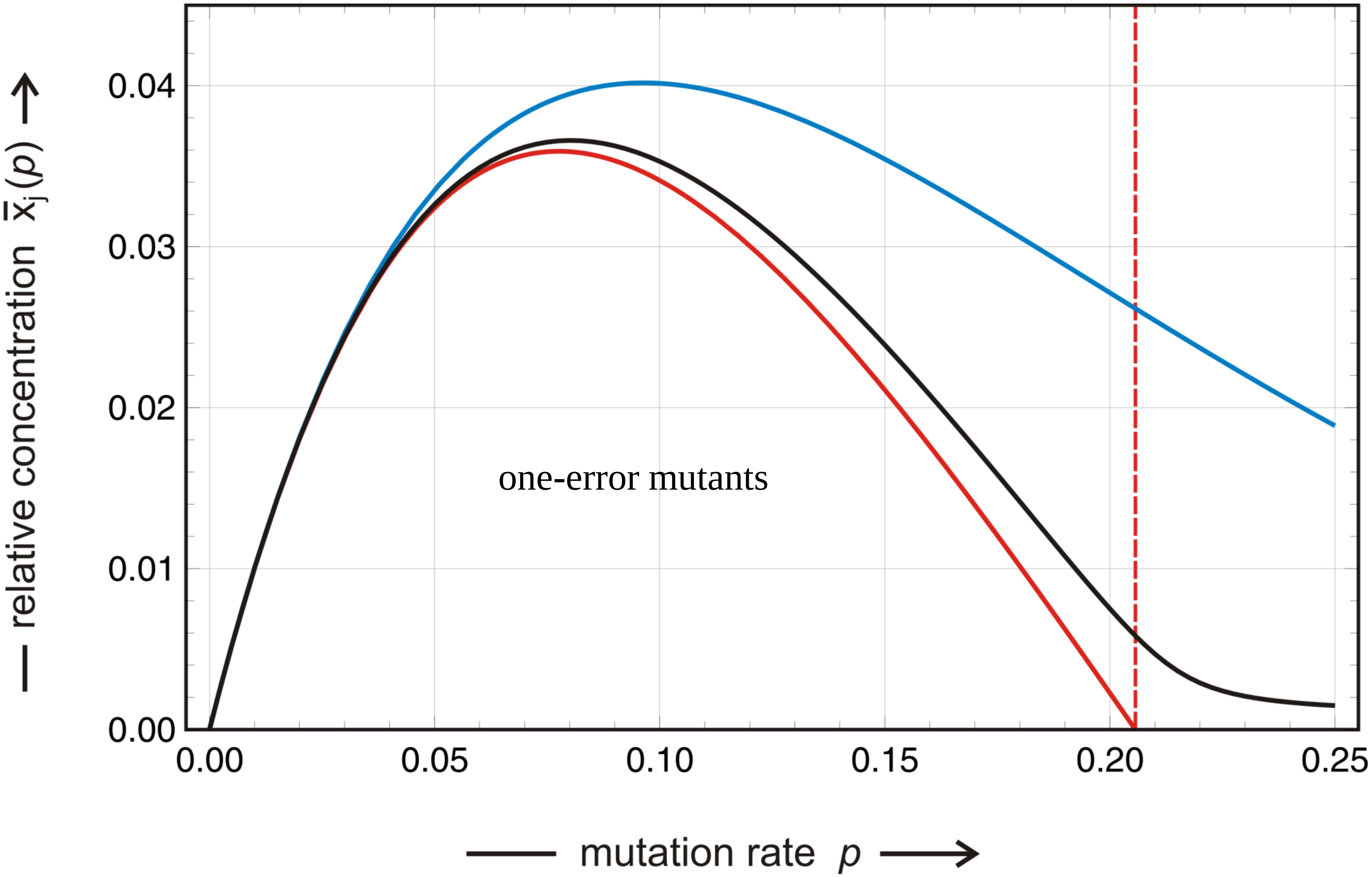
The phenomenological approach (Eigen, 1971)



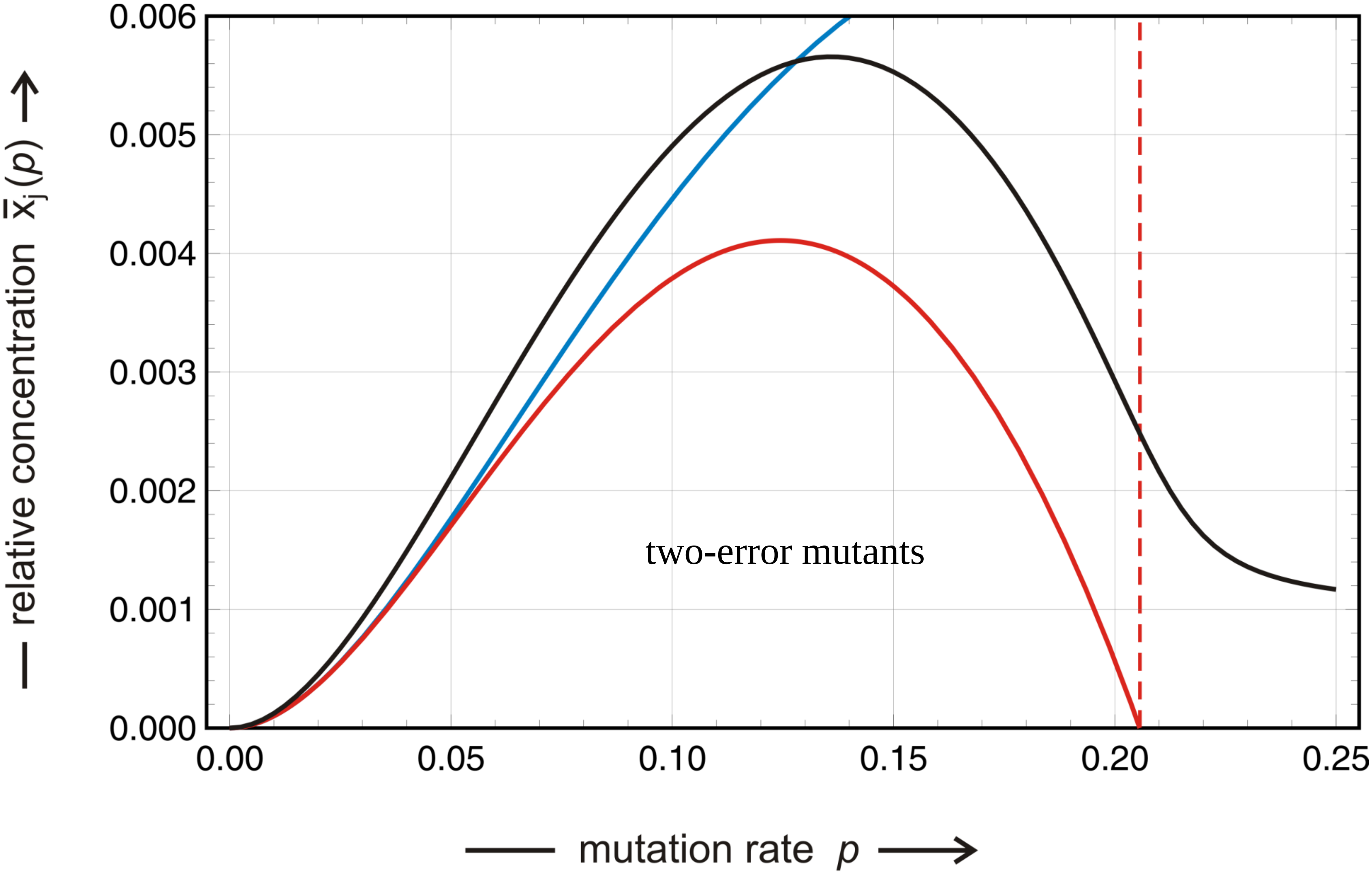
Comparison of exact, zero backflow and phenomenological solutions



Comparison of exact, zero backflow and phenomenological solutions



Comparison of exact, zero backflow and phenomenological solutions



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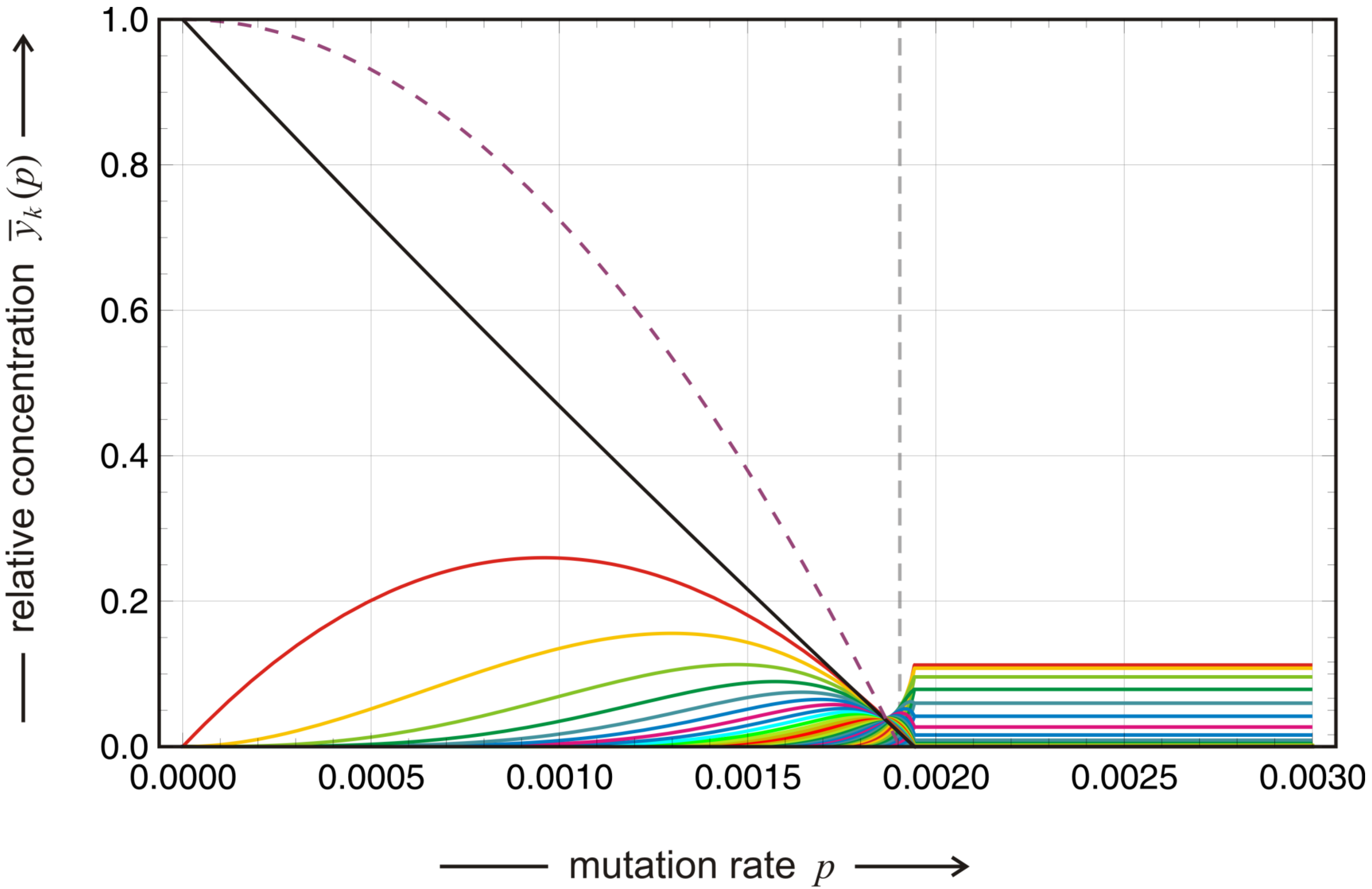
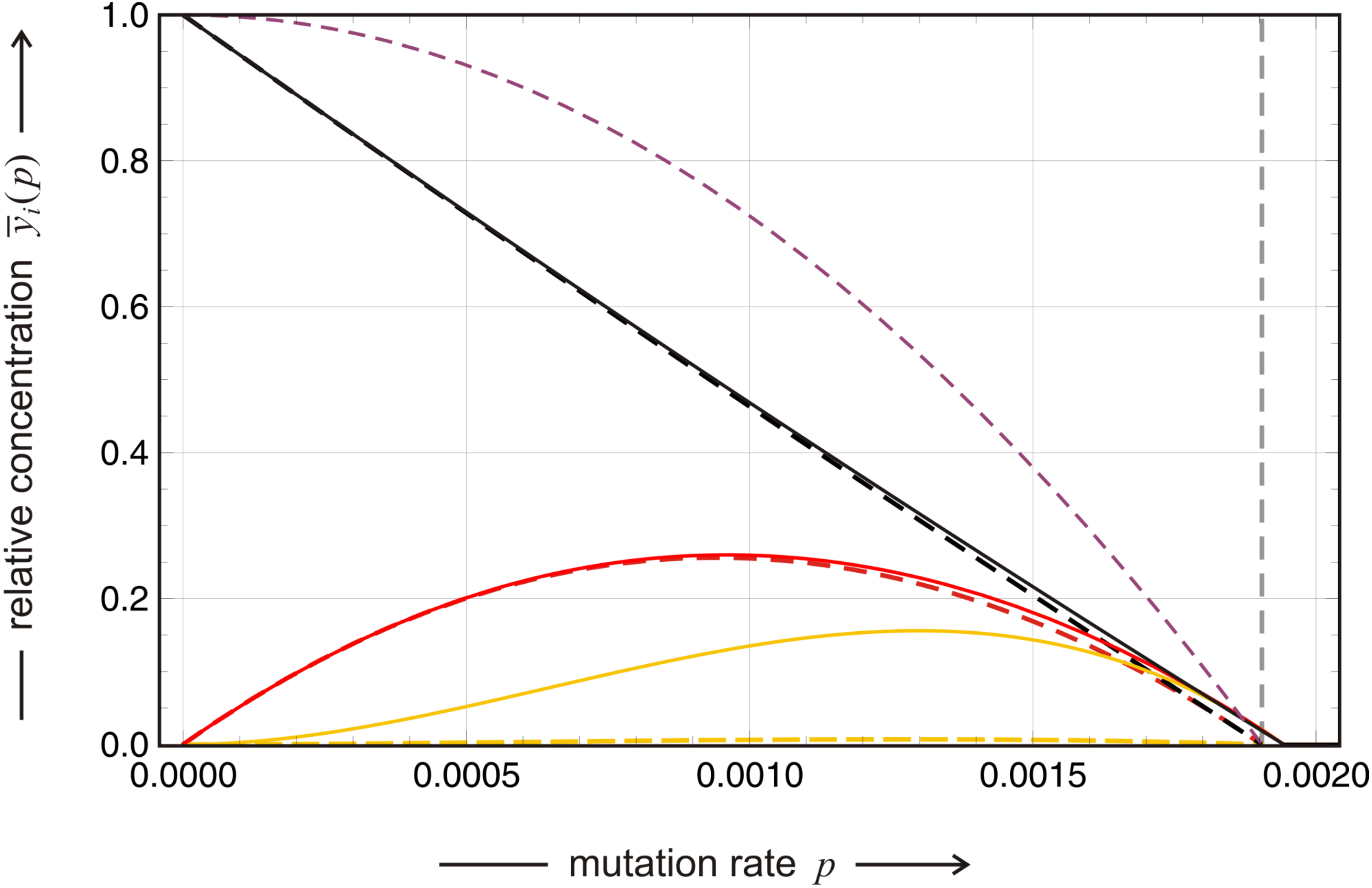


Error threshold in the exact and in the phenomenological solution



Error threshold in the exact and in the phenomenological solution

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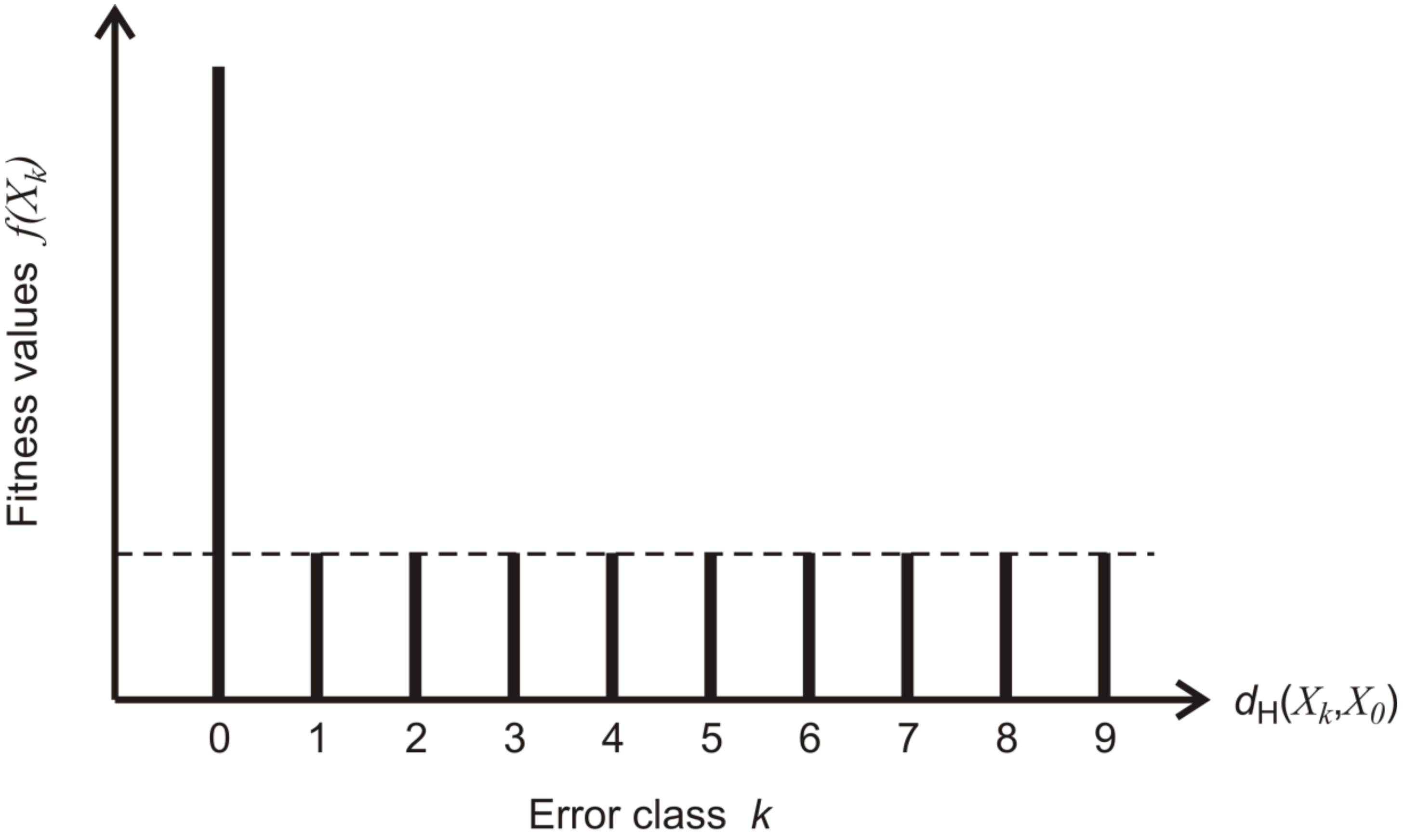
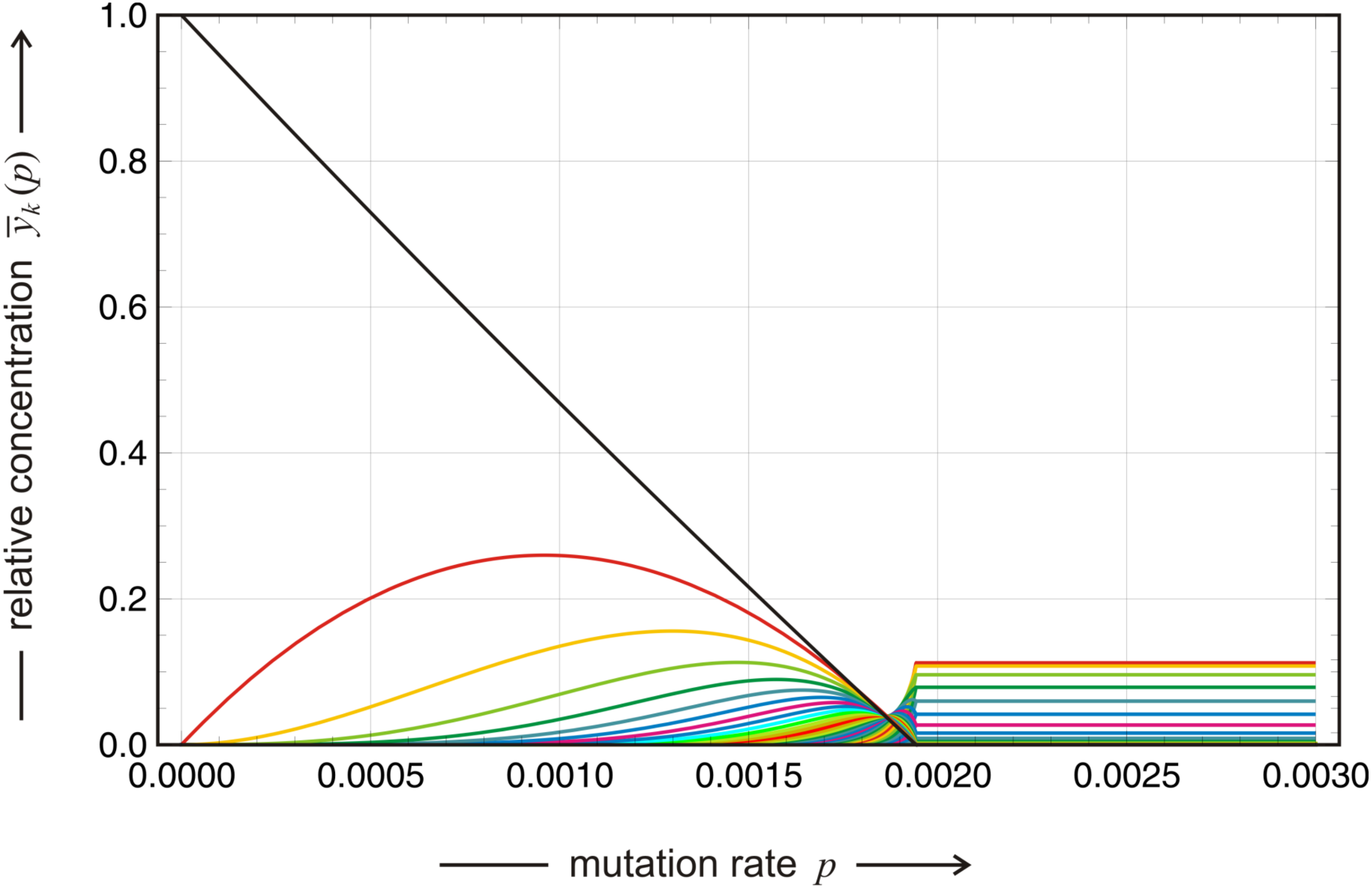


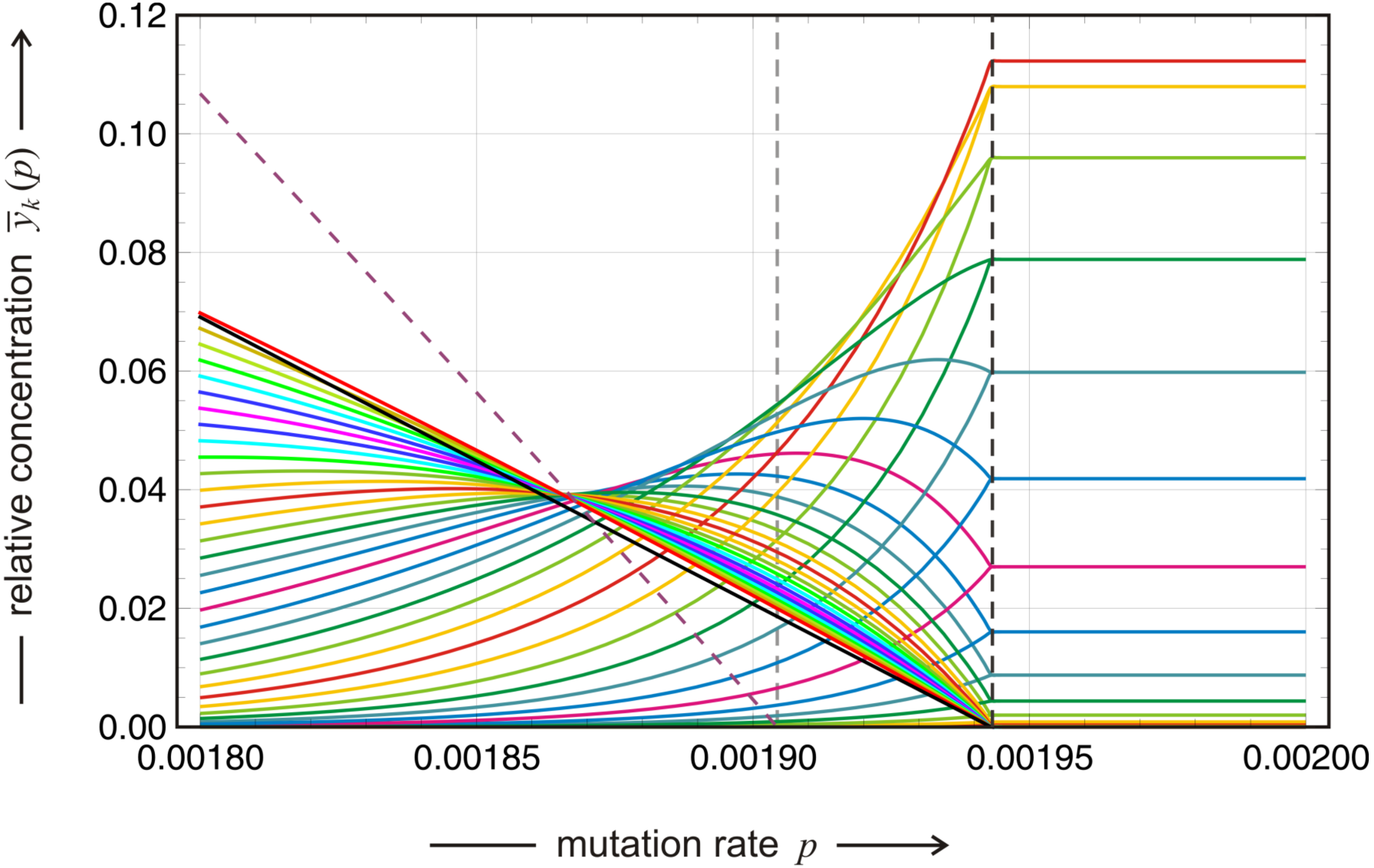
Single peak landscape

Model fitness landscapes



$l = 50$, $f_0 = 1.1$, $f_\mathrm{n} = 1.0$, $p_\mathrm{cr} = 0.001904$

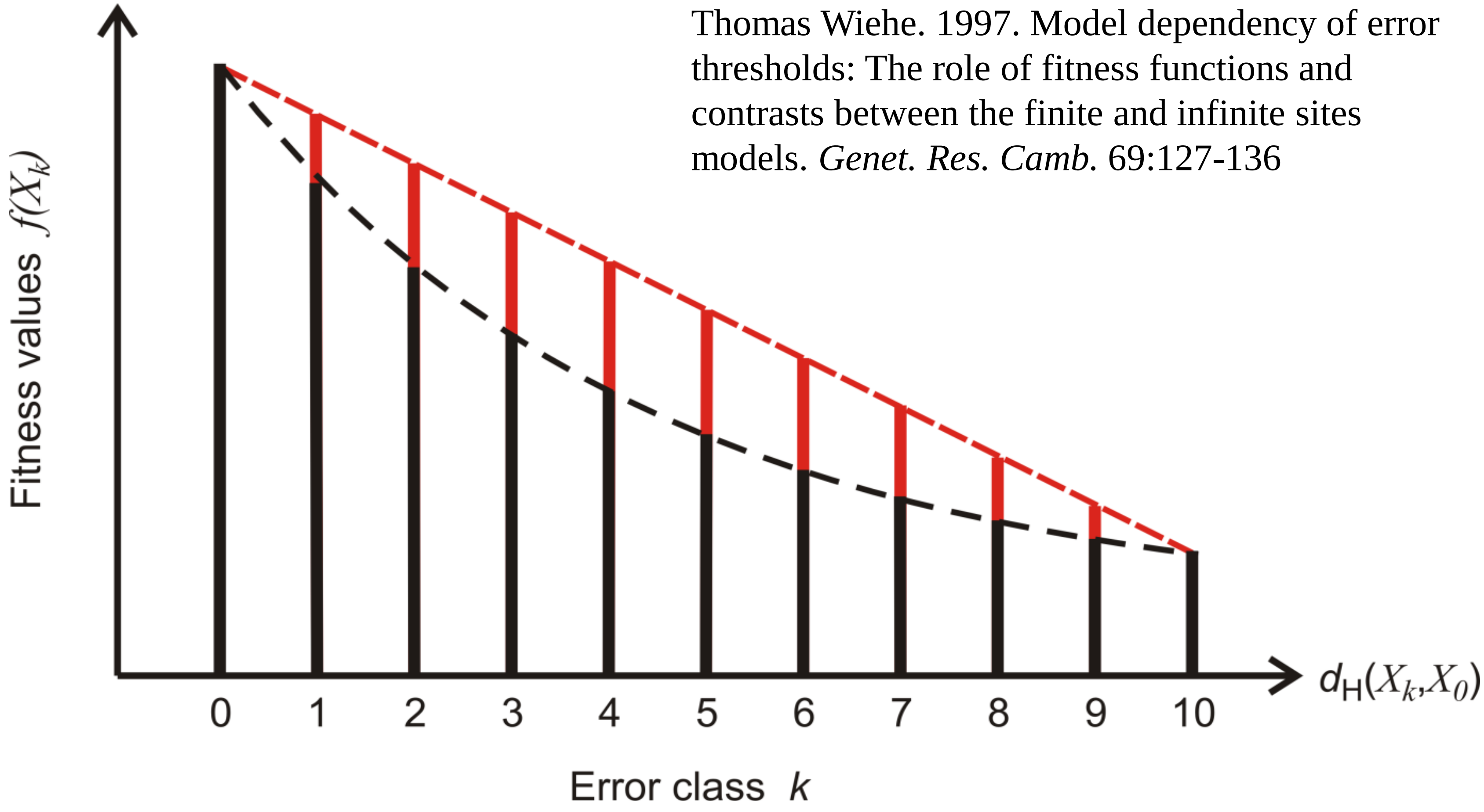
Quasispecies and error threshold



$l = 50$, $f_0 = 1.1$, $f_n = 1.0$, $p_{cr} = 0.001904$

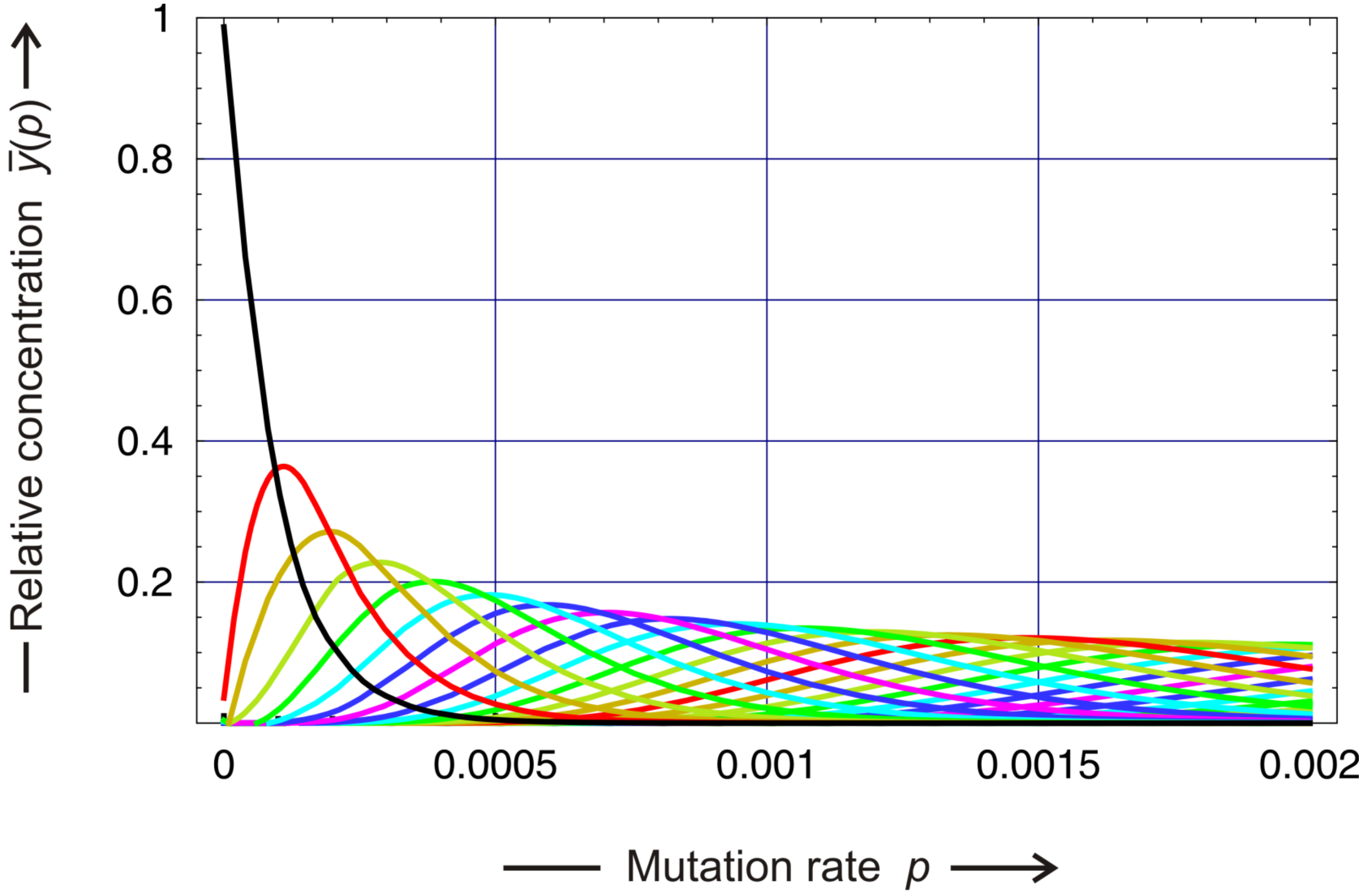
Quasispecies and error threshold exact and in the phenomenological approach

Thomas Wiehe. 1997. Model dependency of error thresholds: The role of fitness functions and contrasts between the finite and infinite sites models. *Genet. Res. Camb.* 69:127-136



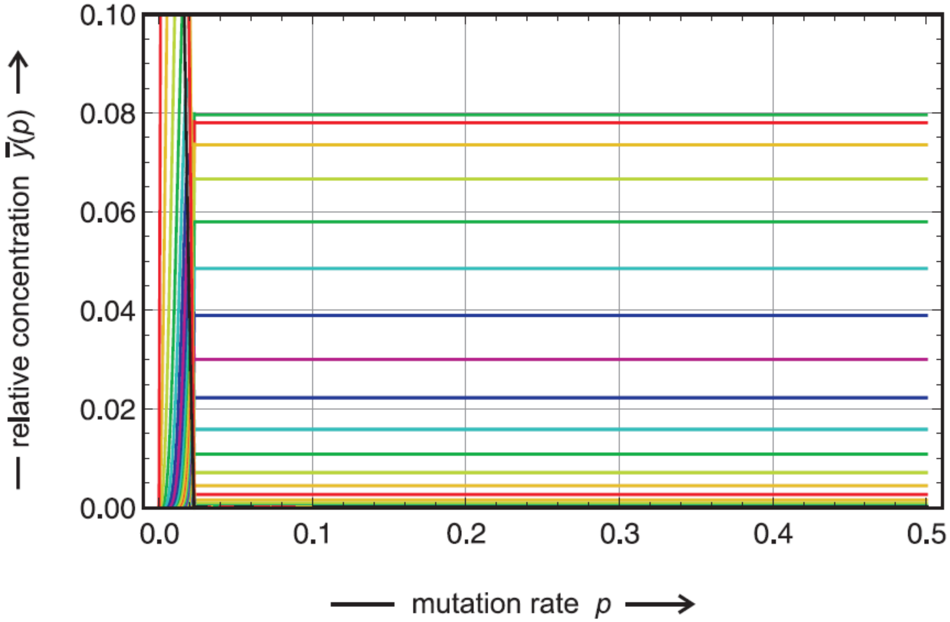
Linear and multiplicative fitness

Model fitness landscapes



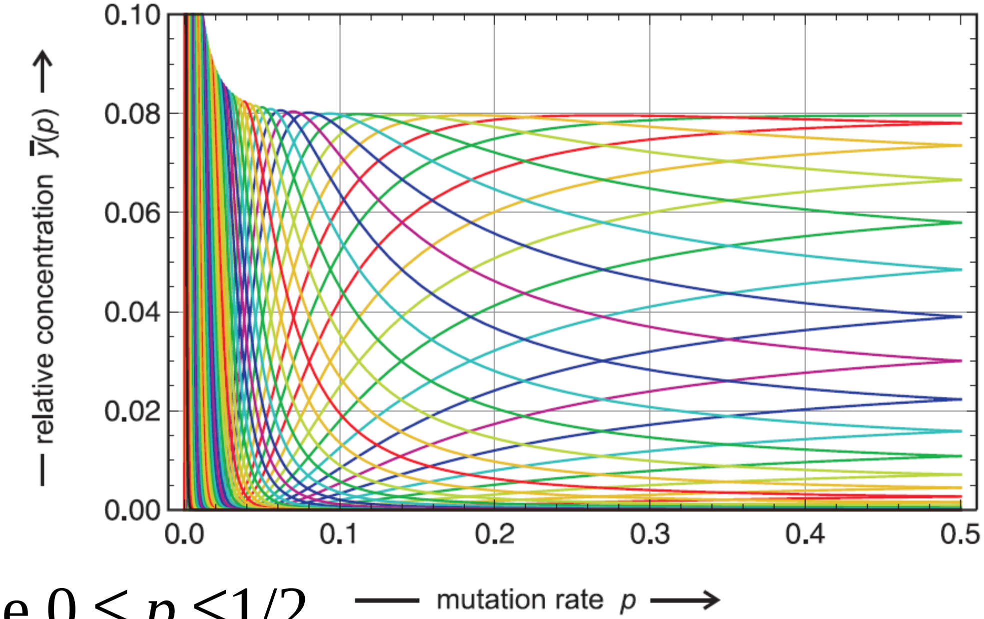
The linear fitness landscape does not show an error threshold single peak landscape

$l = 100, f_0 = 10, f = 1.0, p_{cr} = 0.02276$



multiplicative landscape

$l = 100, f_0 = 10, f = 0.009472$



Quasispecies in the entire range $0 \leq p \leq 1/2$

level crossing of master sequence: $\bar{x}_m\left(p_{\mathrm{tr}}^{(\vartheta)}\right) = \vartheta$

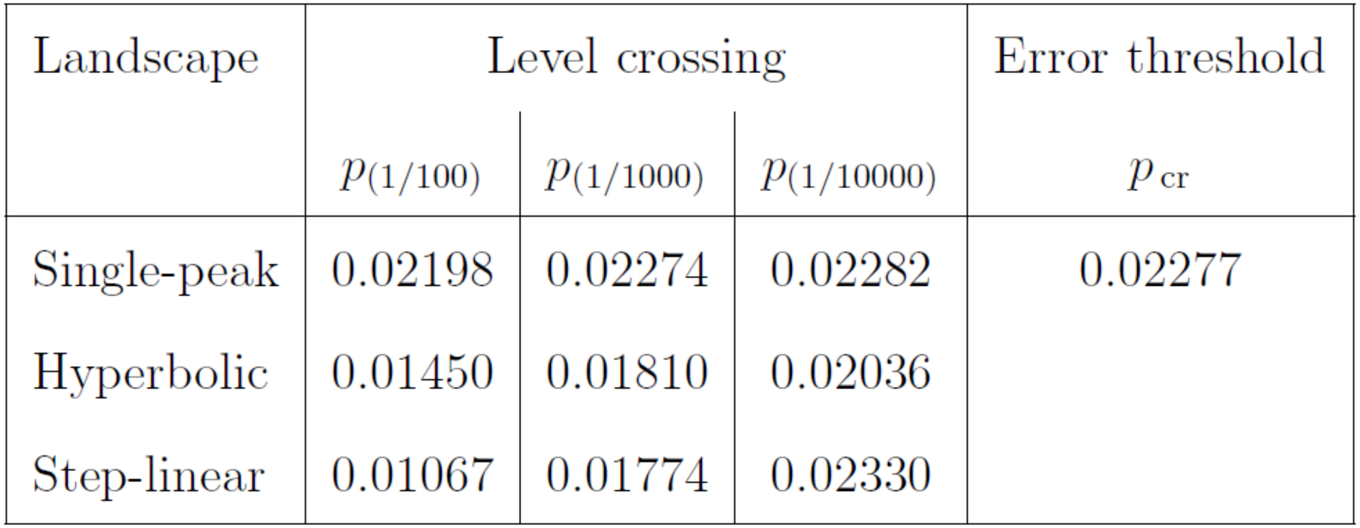
complementary class merging: $\Delta_k = \left|\bar{y}_k - \bar{y}_{l-k}\right|$

$$\left(\Delta_k\right)_{\mathrm{cr}} = \theta; \quad \left(p_{\mathrm{mg}}^{(\theta)}\right)_k; \, k = 0, \ldots, \left\lfloor \frac{l}{2} \right\rfloor$$

width of the transition $\Delta p_{\mathrm{mg}}^{(\theta)} = \max\left(p_{\mathrm{mg}}^{(\theta)}\right)_k - \min\left(p_{\mathrm{mg}}^{(\theta)}\right)_k; \, k = 0, \ldots, \left\lfloor \frac{l}{2} \right\rfloor$

$$p_{\mathrm{tr}}^{(\vartheta)} \approx \left(p_{\mathrm{mg}}^{(\theta)}\right)_0 \ \text{ for } \ \vartheta = \theta$$

Quantitative analysis of error thresholds



Landscape	Level crossing			Error threshold
	$p_{(1/100)}$	$p_{(1/1000)}$	$p_{(1/10000)}$	p_{cr}
Single-peak	0.02198	0.02274	0.02282	0.02277
Hyperbolic	0.01450	0.01810	0.02036	
Step-linear	0.01067	0.01774	0.02330	

$l = 100$, $f_0 = 10.0$, $f_n = 1.0$, $p_{cr} = 0.0227628$

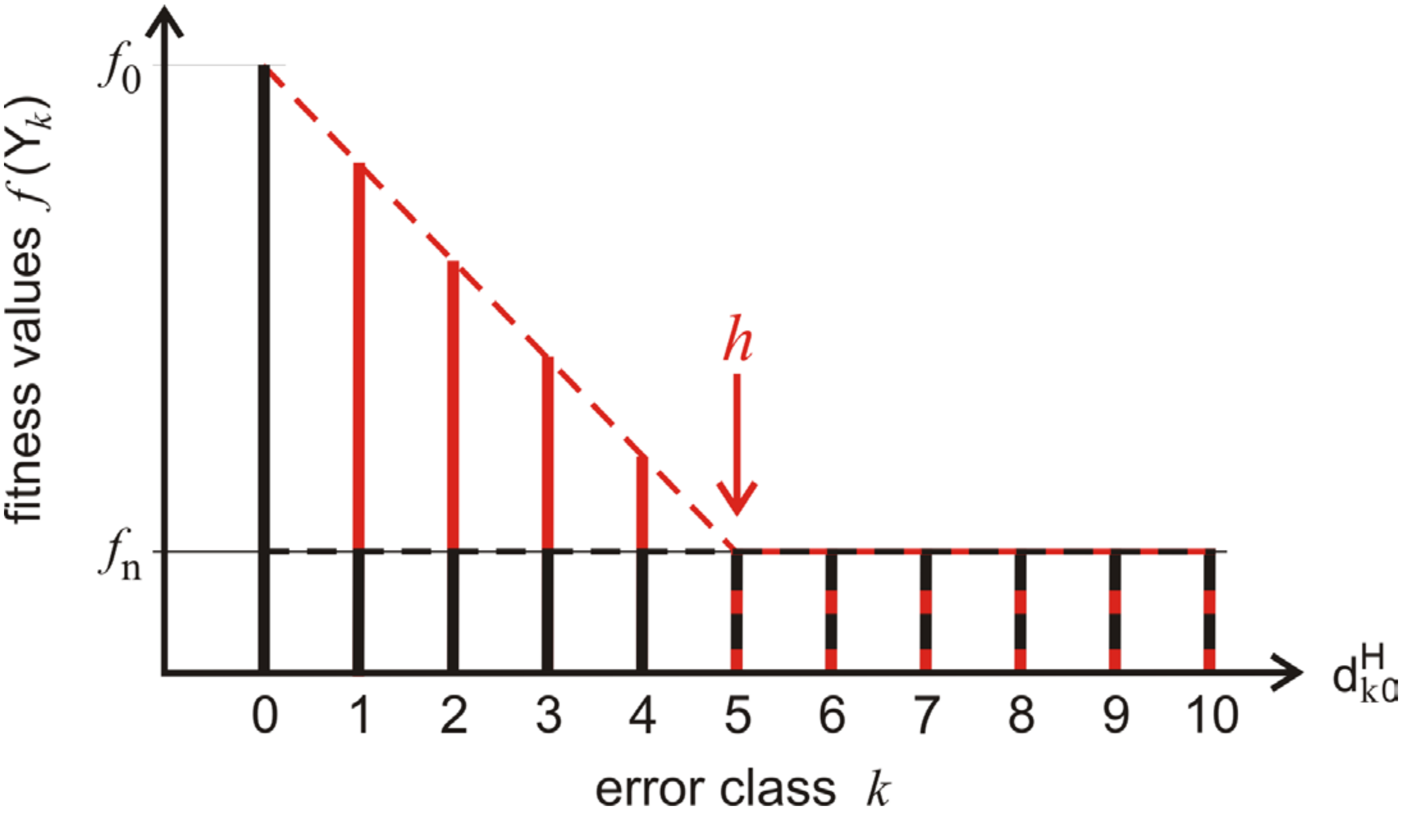
Level crossing on model landscapes

$(p_{\text{mg}}^{(0.01)})_k$	Additive landscape f_k (3a)		Single peak landscape f_k (3d)	
k	$\nu = 10$	$\nu = 20$	$\nu = 10$	$\nu = 20$
0	0.01630	0.002552	0.01164	0.004969
1	0.06791	0.004363	0.01210	0.004977
2	0.17233	0.007967	0.01261	0.004983
3	0.24174	0.012590	0.01282	0.004990
4	0.22508	0.027993	0.01230	0.004997
5	- - -	0.064427	- - -	0.005005
6	- - -	0.113894	- - -	0.005011
7	- - -	0.153431	- - -	0.005013
8	- - -	0.162072	- - -	0.005009
9	- - -	0.120962	- - -	0.004990
$\Delta p_{\text{mg}}^{(0.01)}$	0.22544	0.15952	0.00118	0.000045
$p_{\text{tr}}^{(0.01)}$	0.01634	0.002552	0.01175	0.004969

additive: $l = 20$ (10), $f_0 = 1.1$, $f_n = 0.9$

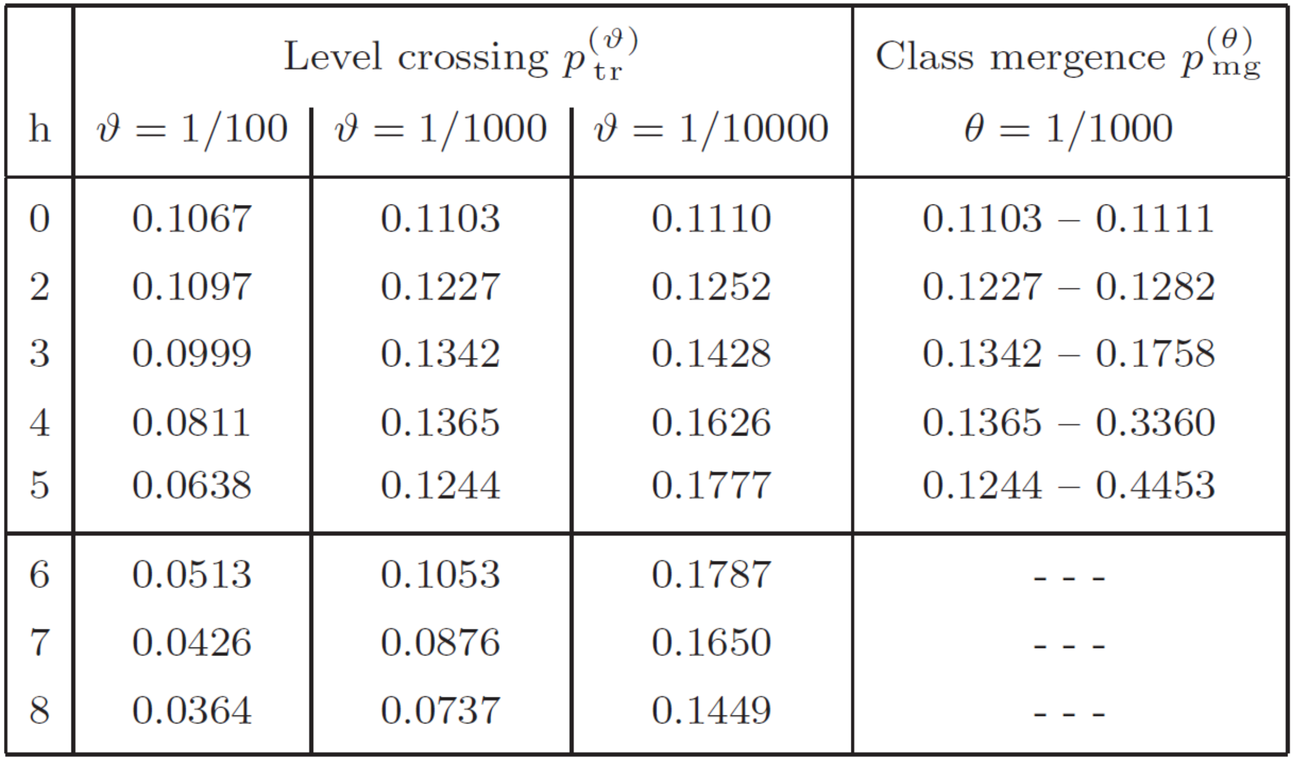
single peak: $l = 20$ (10), $f_0 = 1.1$, $f_n = 1.0$, $p_{\text{cr}} = 0.0047542$ (0.0094857)

Complementary class mergence on model landscapes



step-linear landscape

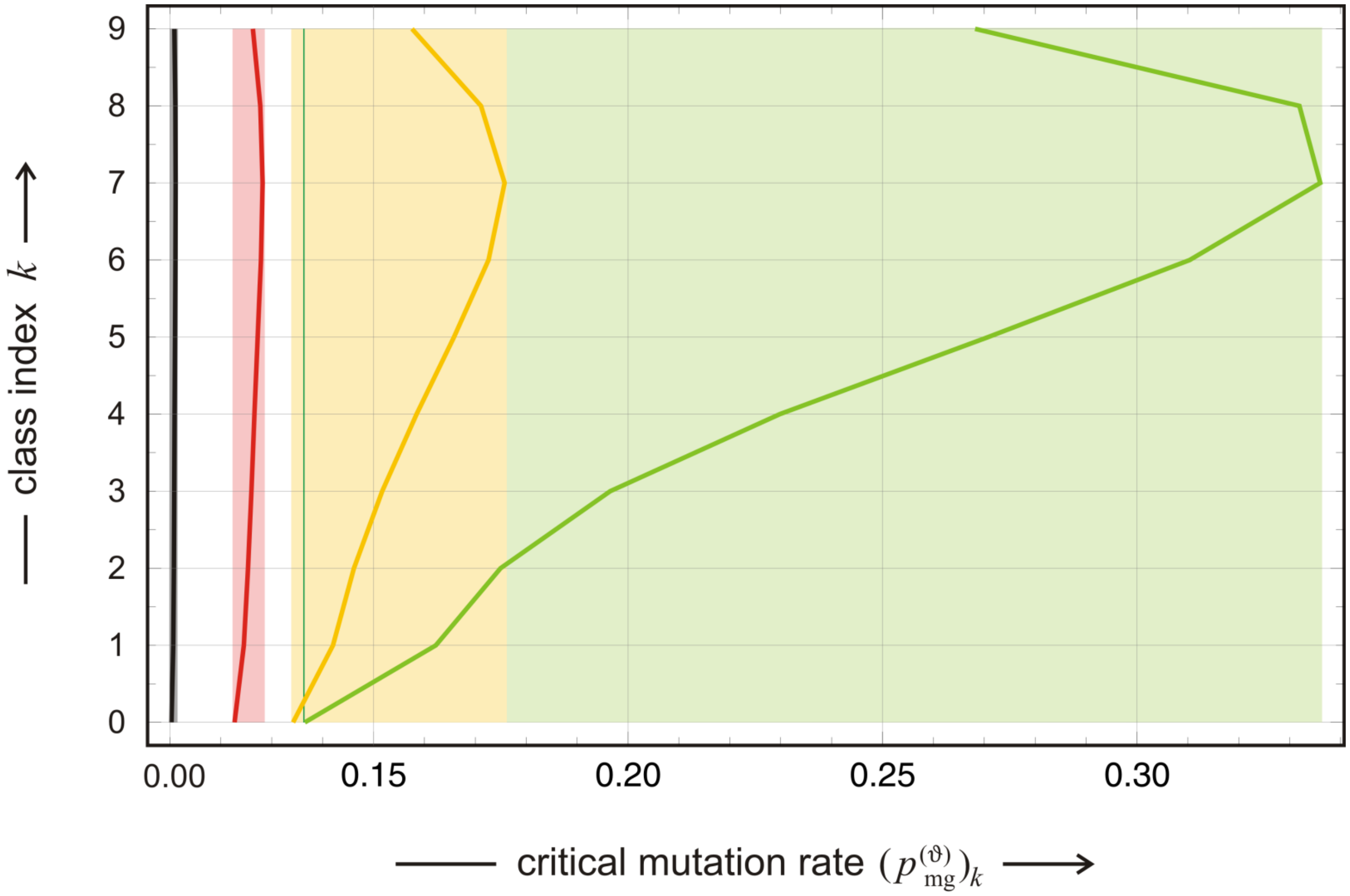
Model fitness landscapes



h	Level crossing $p_{\mathrm{tr}}^{(\vartheta)}$			Class mergence $p_{\mathrm{mg}}^{(\theta)}$
	$\vartheta = 1/100$	$\vartheta = 1/1000$	$\vartheta = 1/10000$	$\theta = 1/1000$
0	0.1067	0.1103	0.1110	0.1103 – 0.1111
2	0.1097	0.1227	0.1252	0.1227 – 0.1282
3	0.0999	0.1342	0.1428	0.1342 – 0.1758
4	0.0811	0.1365	0.1626	0.1365 – 0.3360
5	0.0638	0.1244	0.1777	0.1244 – 0.4453
6	0.0513	0.1053	0.1787	- - -
7	0.0426	0.0876	0.1650	- - -
8	0.0364	0.0737	0.1449	- - -

$l = 20$, $f_0 = 10.0$, $f_{\mathrm{n}} = 1.0$, $p_{\mathrm{cr}} = 0.108749$

Level crossing on model landscapes



h = 0,1 , h = 2 , h = 3 , h = 4

Width of the error threshold on the steplinear landscape

1. Quasispecies and Crow-Kimura model
2. Mutation flow analysis
3. Zero backflow and phenomenological approach
4. Error thresholds on model landscapes
5. Error thresholds on realistic landscapes

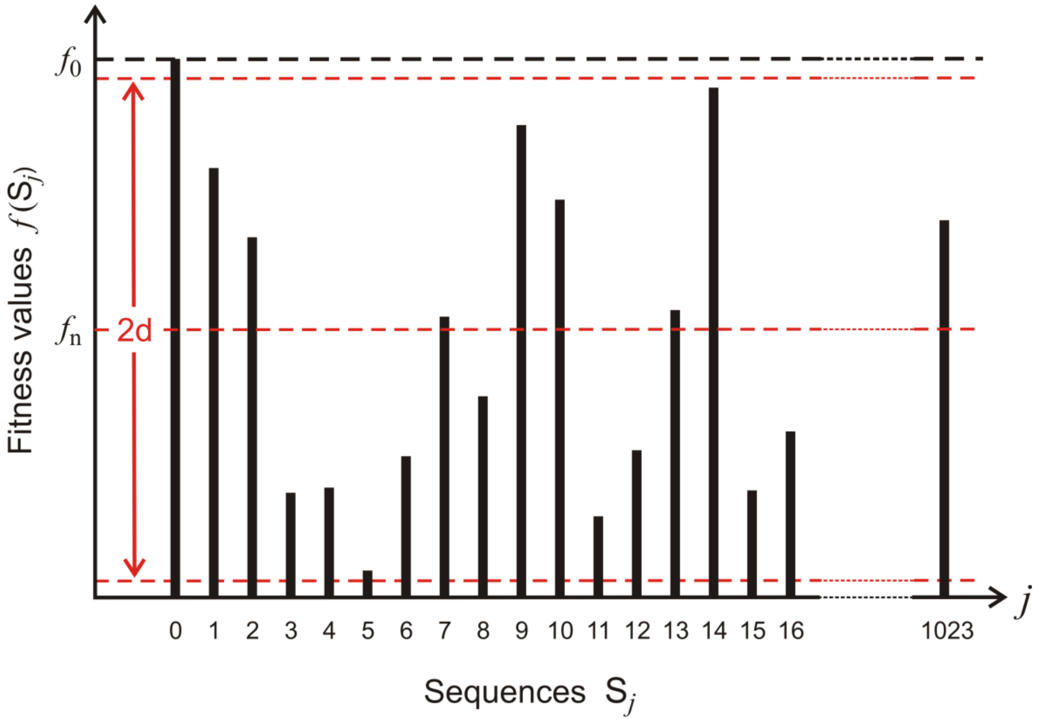
$$f(S_j) = f_n + 2d\,(f_0 - f_n)\left(\eta_j^{(s)} - 0.5\right)$$

$$j = 1, 2, \ldots, N\,;\; j \neq m$$

η … random number

s … seeds

„realistic" landscape



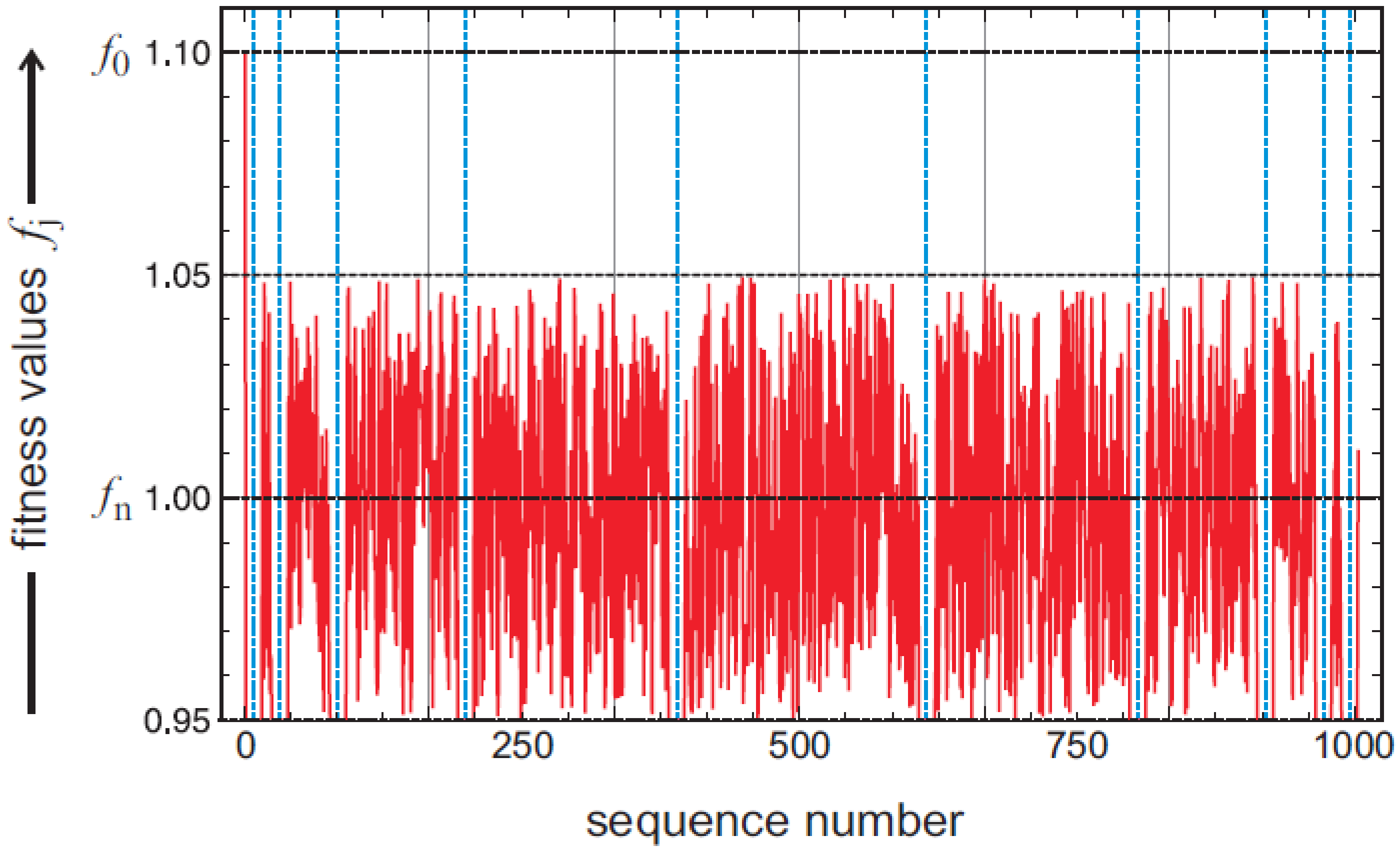
"experimental computer biology":

(i) choose seeds, e.g., s ∈ {000, … , 999},

(ii) compute landscape, $f(S_j)$, $j = 1, \ldots, N$,

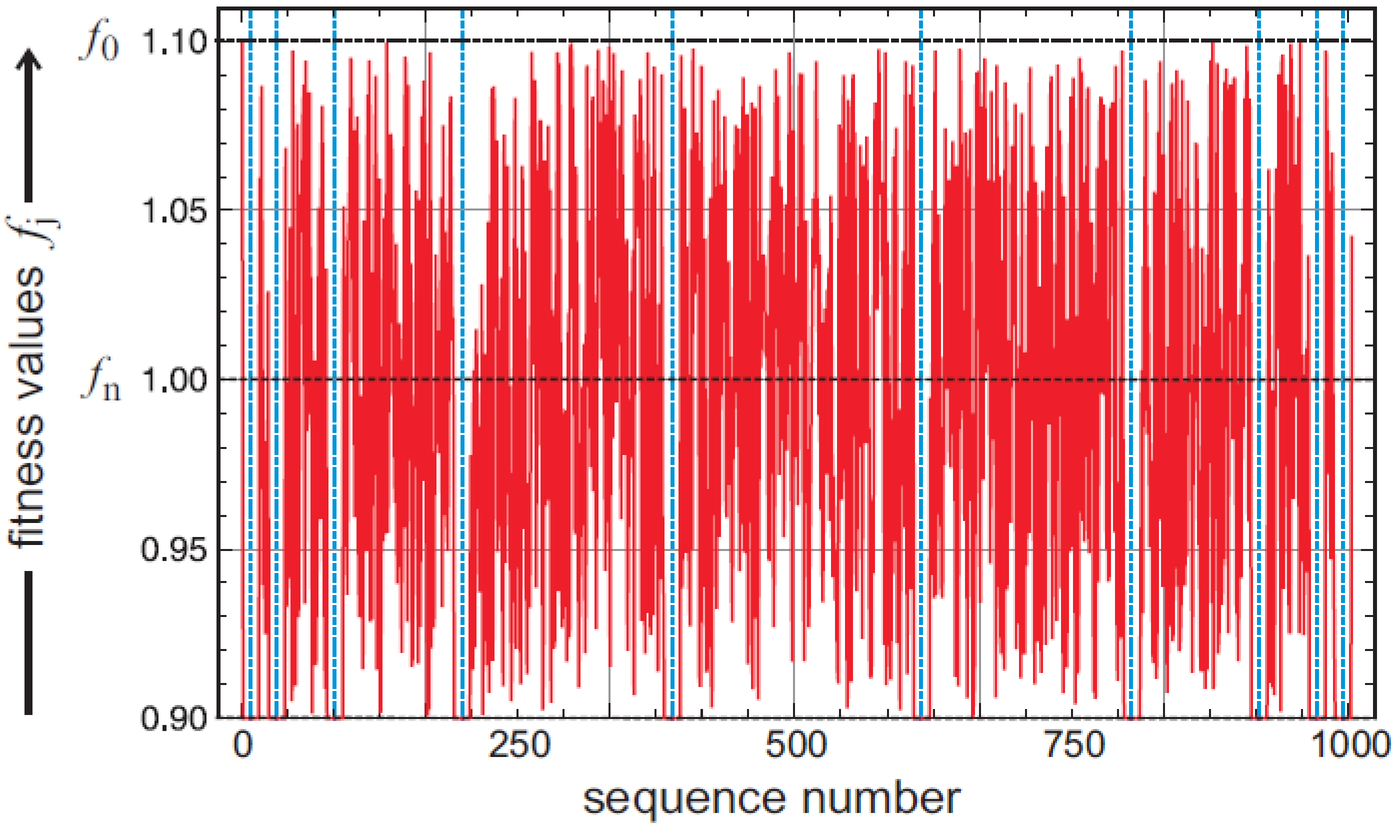
(iii) compute and analyze quasispecies, $\Upsilon(p,d)$

Rugged fitness landscapes over individual binary sequences with n = 10



$\mathcal{L}$(10,2,1.1,1.0; 0.0, d = 0.5, 919)

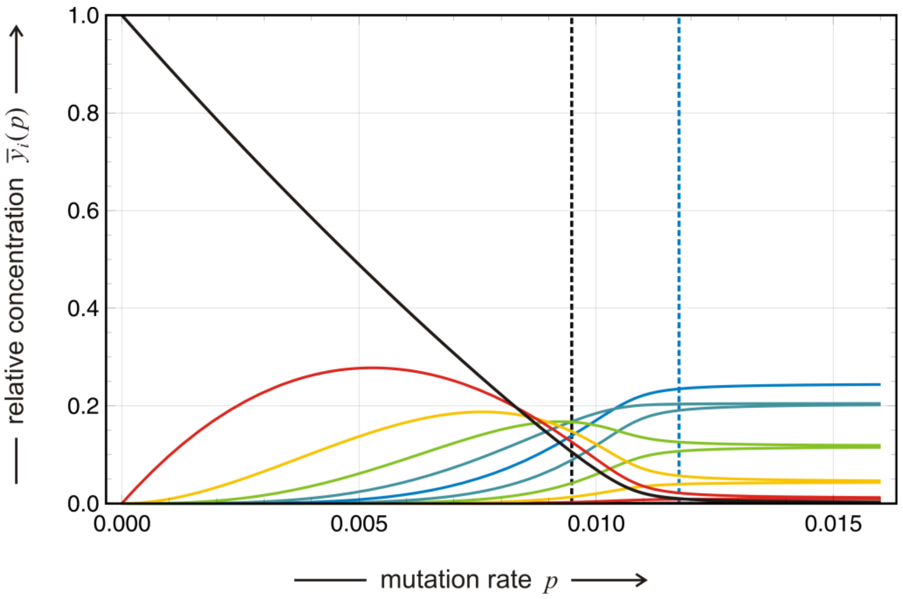
„Realistic“ random landscape



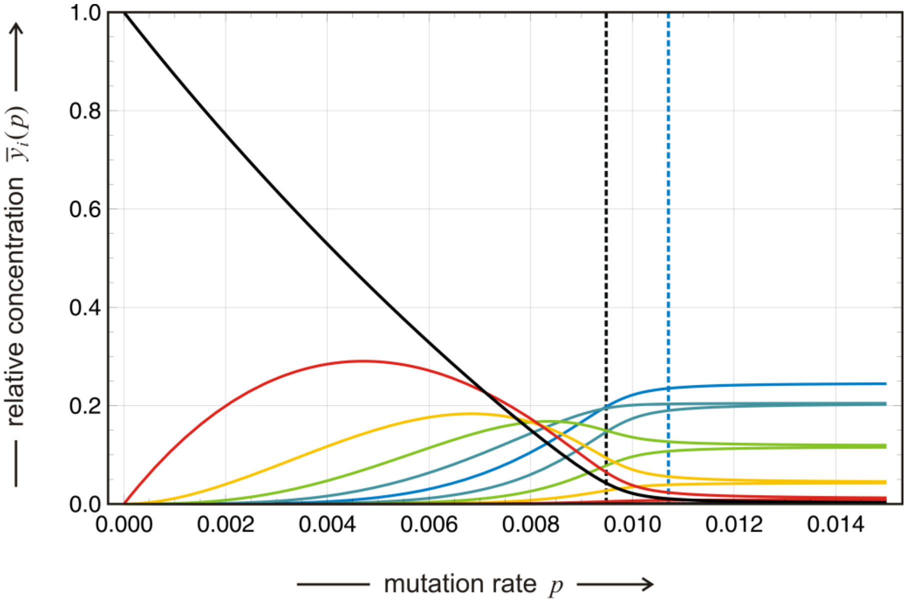
$\mathcal{L}(10,2,1.1,1.0;\ 0.0,\ d = 1.0,\ 637)$

„Realistic“ random landscape

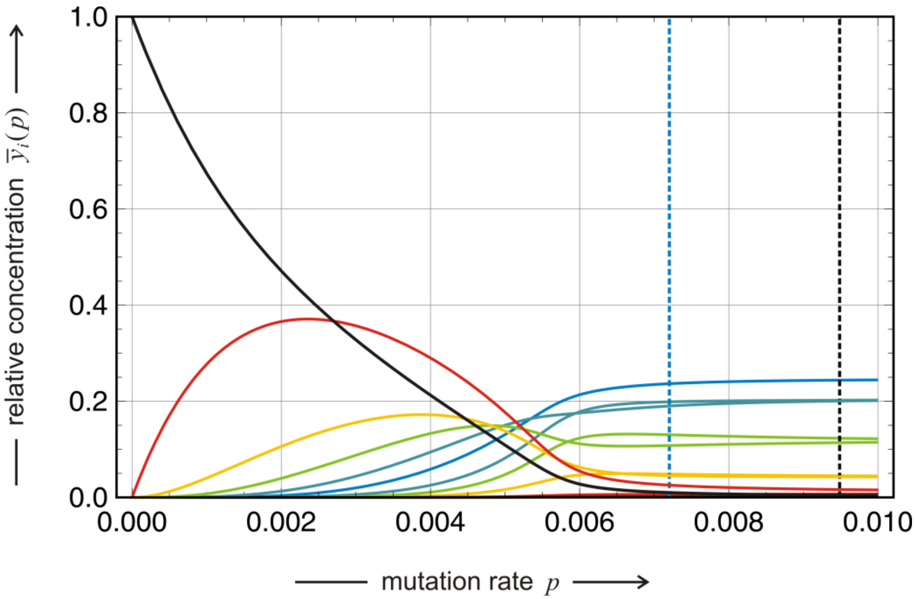
d = 0.000



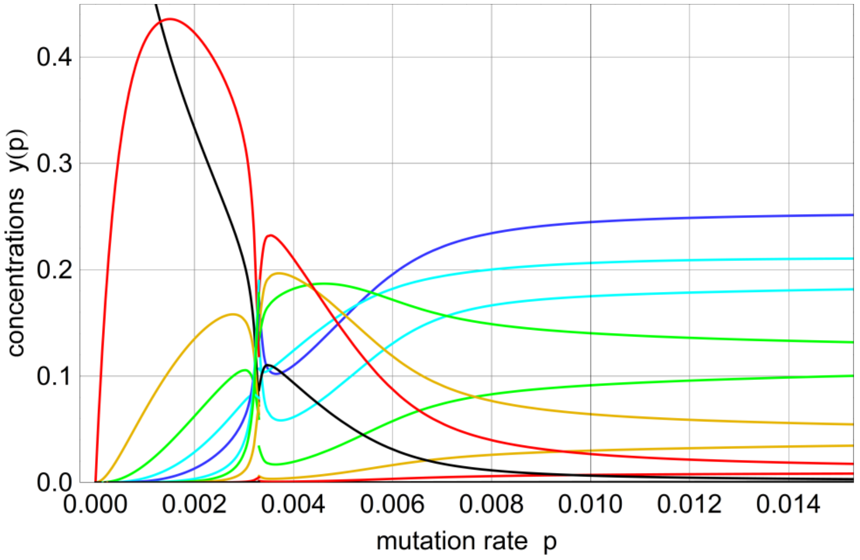
d = 0.500



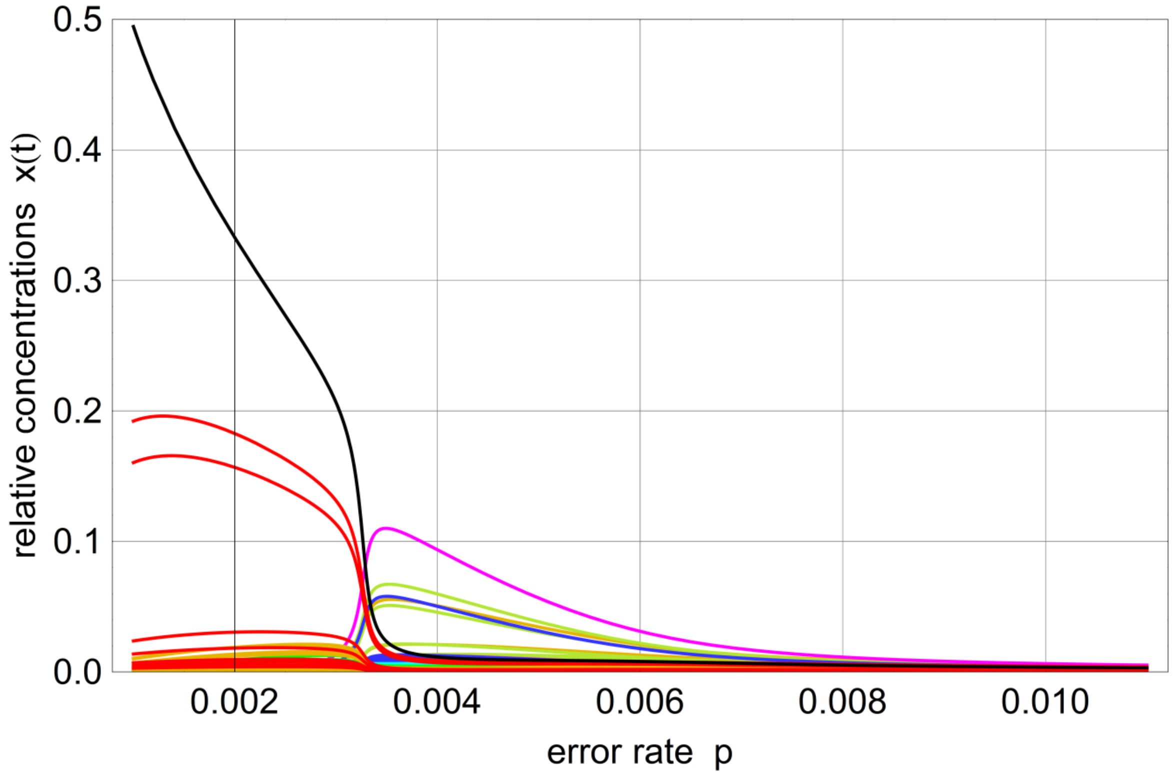
Quasispecies and error threshold on $\mathcal{L}$(10,2,1.1,1.0;0.0,d,023) d = 0.950



d = 1.000

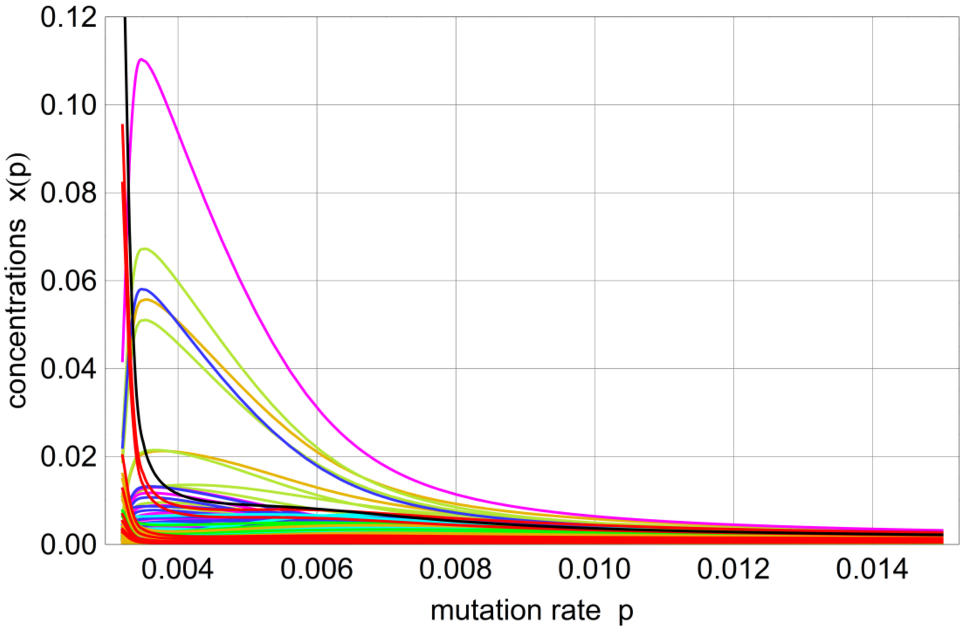


Quasispecies and error threshold on $\mathcal{L}(10,2,1.1,1.0;0.0,d,023)$

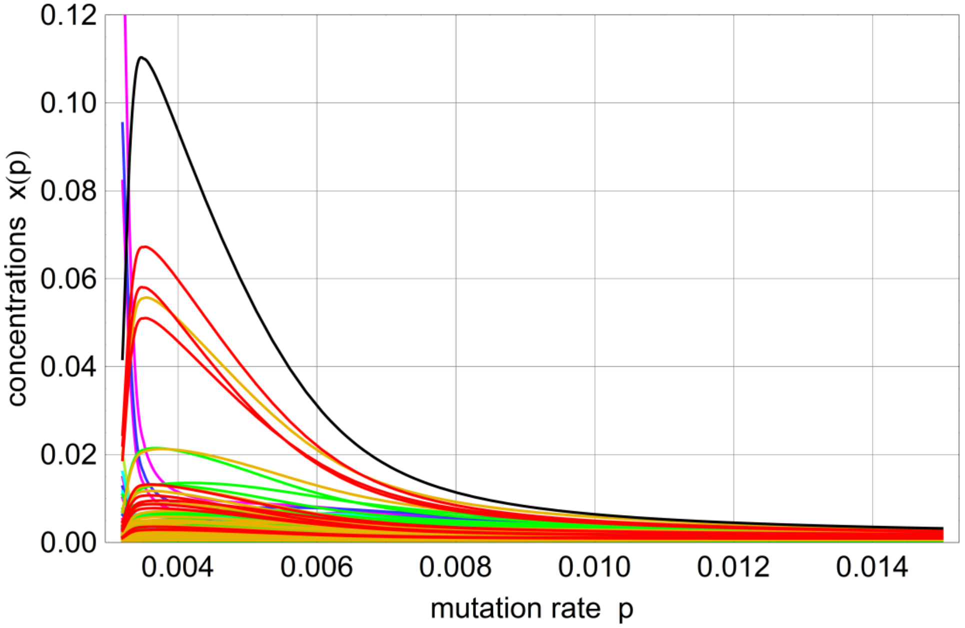


Quasispecies transition on $\mathcal{L}(10,2,1.1,1.0;0.0,1.000,023)$

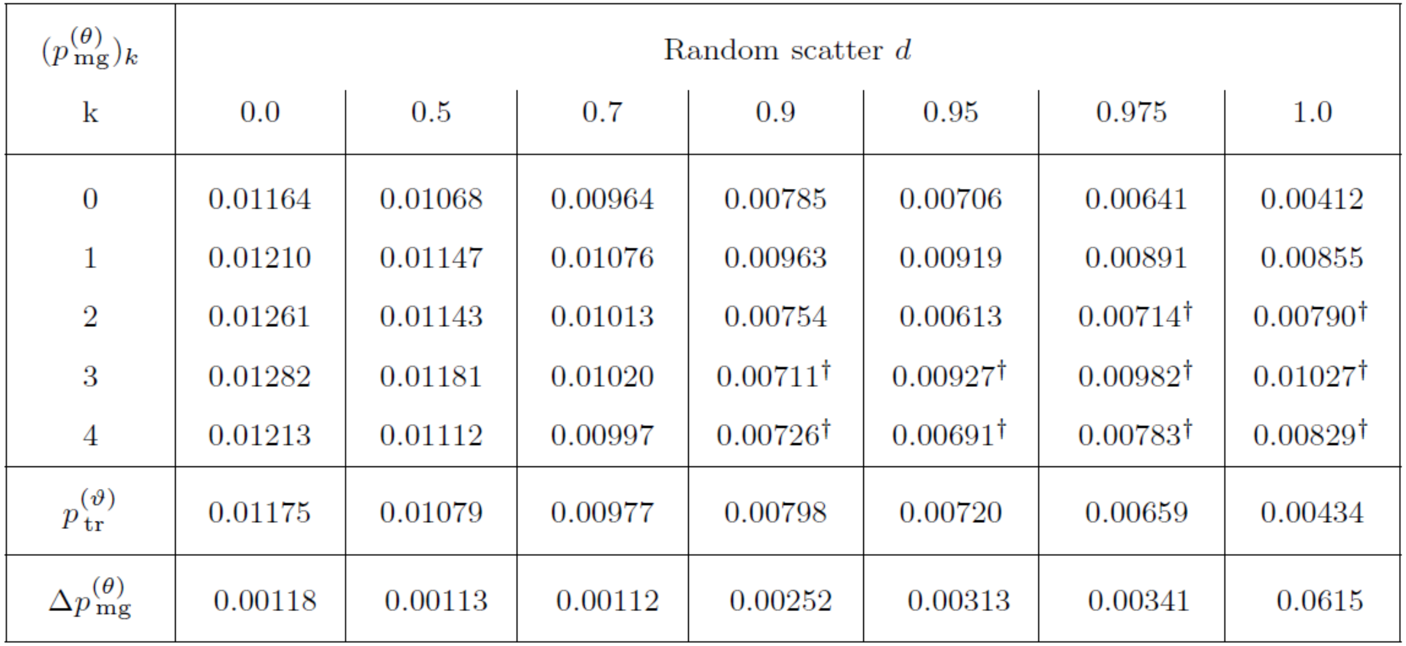
centered around X_{000}



centered around X_{911}



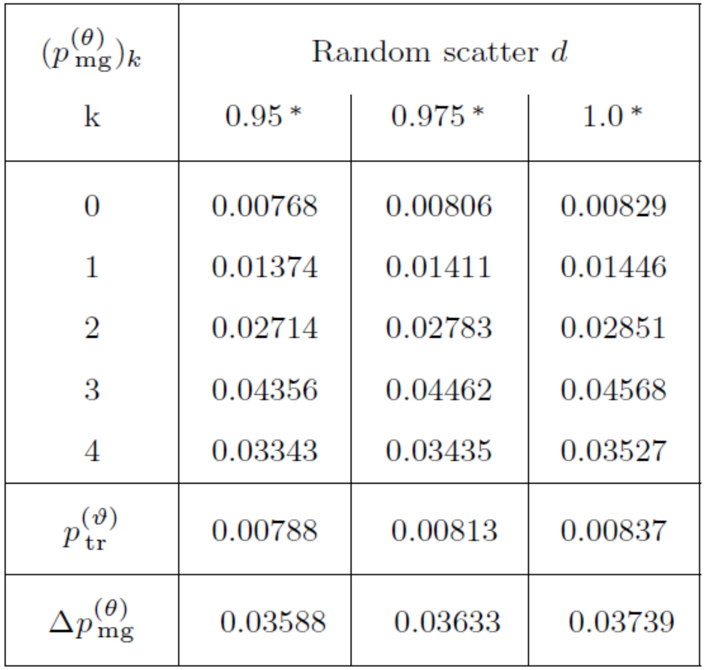
Quasispecies transition on $\mathcal{L}(10,2,1.1,1.0;0.0,d,023)$



$(p_{\mathrm{mg}}^{(\theta)})_k$	Random scatter d						
k	0.0	0.5	0.7	0.9	0.95	0.975	1.0
0	0.01164	0.01068	0.00964	0.00785	0.00706	0.00641	0.00412
1	0.01210	0.01147	0.01076	0.00963	0.00919	0.00891	0.00855
2	0.01261	0.01143	0.01013	0.00754	0.00613	$0.00714^{\dagger}$	$0.00790^{\dagger}$
3	0.01282	0.01181	0.01020	$0.00711^{\dagger}$	$0.00927^{\dagger}$	$0.00982^{\dagger}$	$0.01027^{\dagger}$
4	0.01213	0.01112	0.00997	$0.00726^{\dagger}$	$0.00691^{\dagger}$	$0.00783^{\dagger}$	$0.00829^{\dagger}$
$p_{\mathrm{tr}}^{(\vartheta)}$	0.01175	0.01079	0.00977	0.00798	0.00720	0.00659	0.00434
$\Delta p_{\mathrm{mg}}^{(\theta)}$	0.00118	0.00113	0.00112	0.00252	0.00313	0.00341	0.0615

$\mathcal{L}\,(10\,,\,2\,,1.1\,,\,1.0\,;\,0.0\,,\,d\,\,,\,023)$:

$p_{\mathrm{cr}} = 0.009486\,;\;\theta = \vartheta = 0.01$



$(p_{\mathrm{mg}}^{(\theta)})_k$	Random scatter d		
k	0.95 *	0.975 *	1.0 *
0	0.00768	0.00806	0.00829
1	0.01374	0.01411	0.01446
2	0.02714	0.02783	0.02851
3	0.04356	0.04462	0.04568
4	0.03343	0.03435	0.03527
$p_{\mathrm{tr}}^{(\vartheta)}$	0.00788	0.00813	0.00837
$\Delta p_{\mathrm{mg}}^{(\theta)}$	0.03588	0.03633	0.03739

Level crossing and complementary class merging for quasispecies with transition

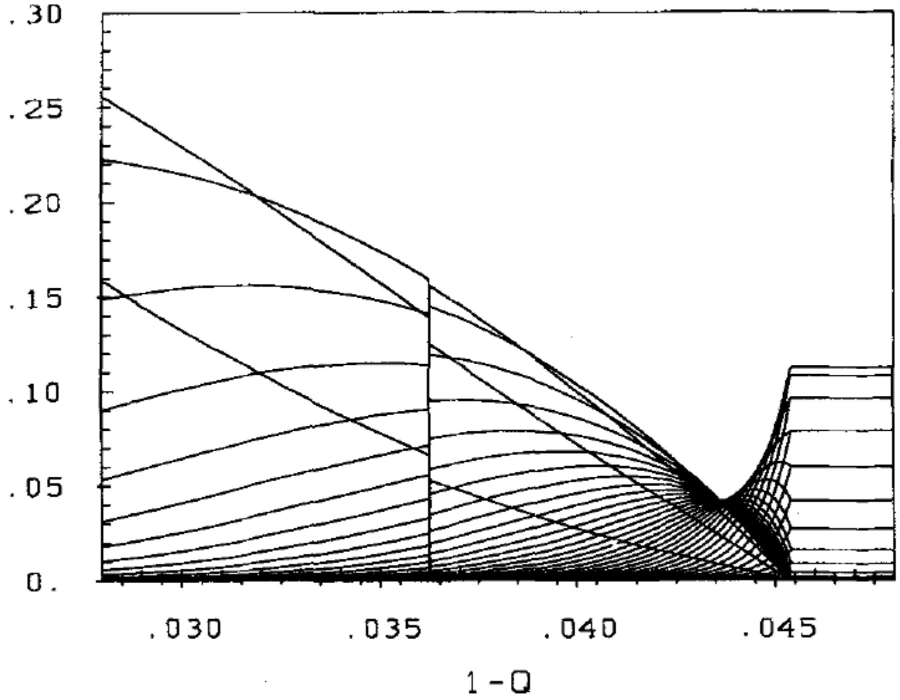
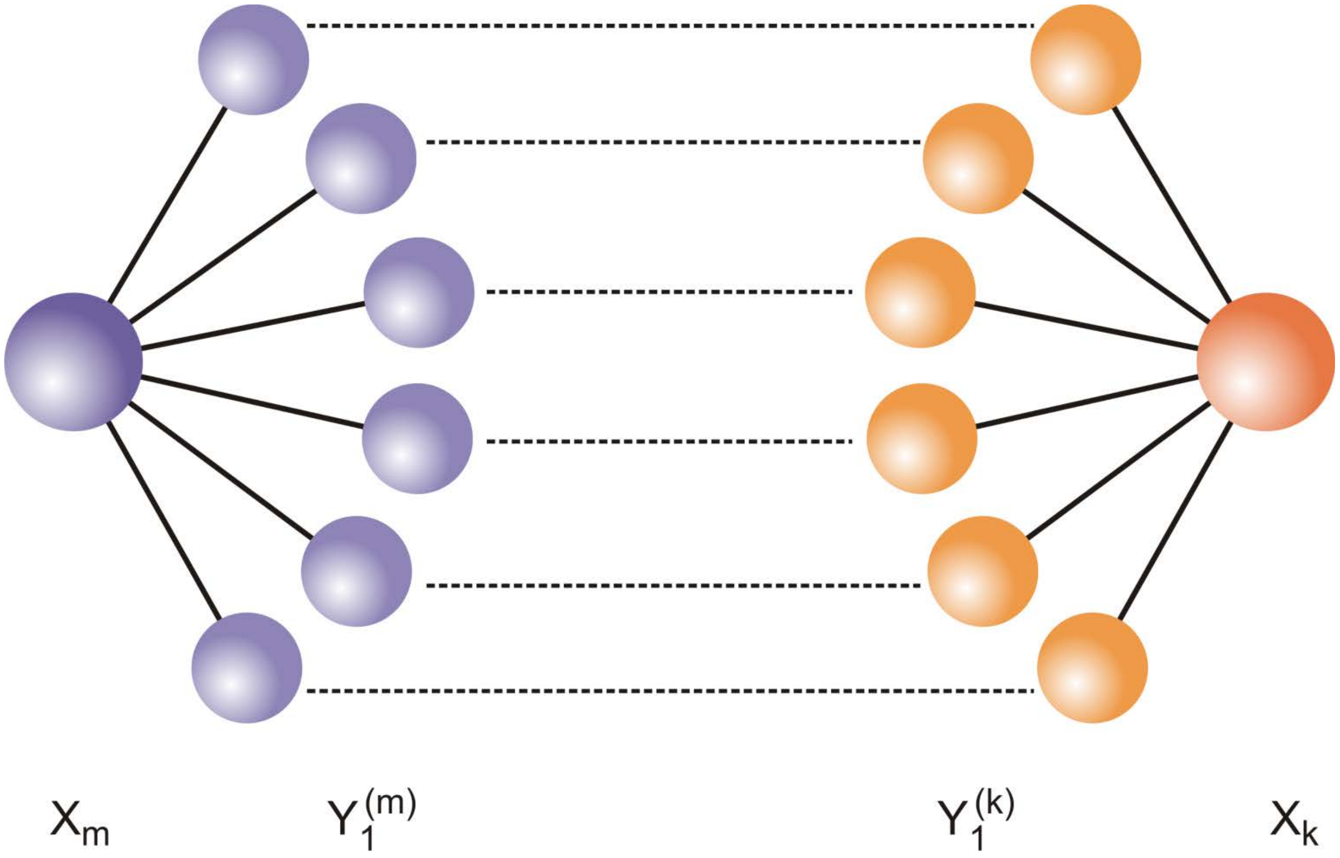


Figure 11. Almost degenerate quasispecies. For a system of chain length $\nu=50$ the relative concentrations of the 51 mutant classes (=sum over the relative concentrations of species lying in that class) are shown in the accurate replication region $0.028 \leqslant 1-q \leqslant 0,048$. Notice the extremely sharp transition at $1-q_{tr}=0.0362$ ($q_{tr}=0.9638$) when the new master sequence and its nearest neighbours become dominant. At $1-q=0.0454$ one observes the usual error threshold. The selective values in this example are: $A_{(0)}=10$ (=zero error mutant); $A_{(50)}=9.9$ (=fifty error mutant); $A_{(49)}=$ (forty nine error mutant class); all other $A_i=1$.

Peter Schuster, Jörg Swetina. 1988. Stationary mutant distributions and evolutionary optimization. Bull.Math.Biol. 50, 635-660

Transition between quasispecies



Transition between quasispecies $\Upsilon_m \Leftrightarrow \Upsilon_k$

$$\text{Transition } \Upsilon_m \Leftrightarrow \Upsilon_m\text{:} \quad \overline{x}_m = \overline{x}_k = \overline{x}$$

$$\sum_{i=1}^{n} Q_{mi} \cdot f_i x_i = \overline{x}_m \, \Phi = \overline{x}_k \, \Phi = \sum_{i=1}^{n} Q_{ki} \cdot f_i x_i$$

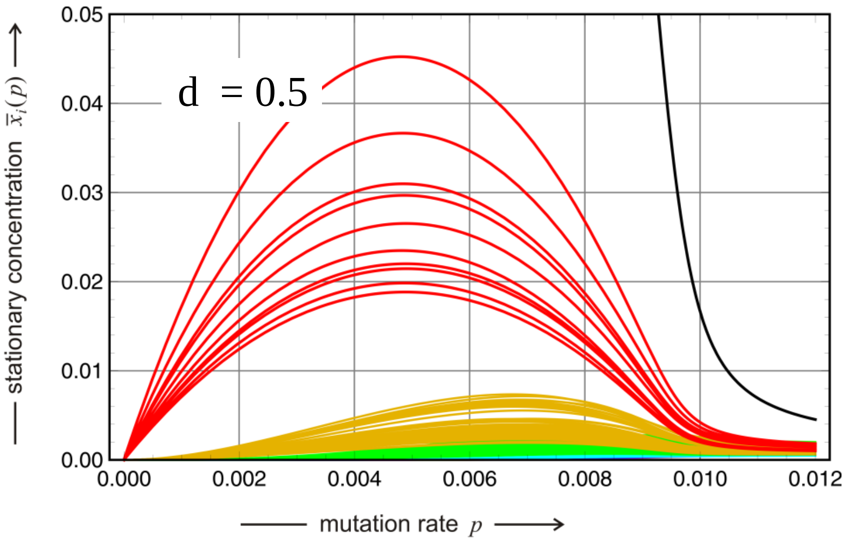
$$\overline{x} \left(Q_{mm} f_m - Q_{kk} f_k \right) = - \left(\phi_m - \phi_k \right)$$

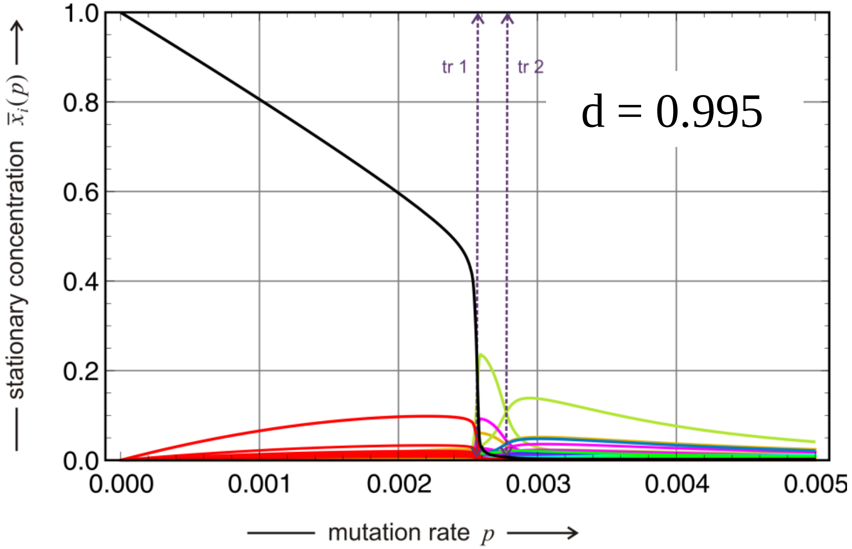
$$Q_{mm} = Q_{kk} \approx (1-p)^l \, , \quad \varepsilon = \frac{p}{1-p} \, , \quad \varepsilon_{\mathrm{tr}} = \frac{p_{\mathrm{tr}}}{1-p_{\mathrm{tr}}}$$

$$\overline{x} \, (f_m - f_k)(1 - \varepsilon^{d_{mk}}) = - \, \varepsilon_{\mathrm{tr}} \left(f_m^{(1)} \overline{y}_m^{(1)} - f_k^{(1)} \overline{y}_k^{(1)} \right)$$

$$\varepsilon_{\mathrm{tr}} = \frac{(f_m - f_k)\bar{x}}{f_k^{(1)} \overline{y}_k^{(1)} - f_m^{(1)} \overline{y}_m^{(1)}}$$

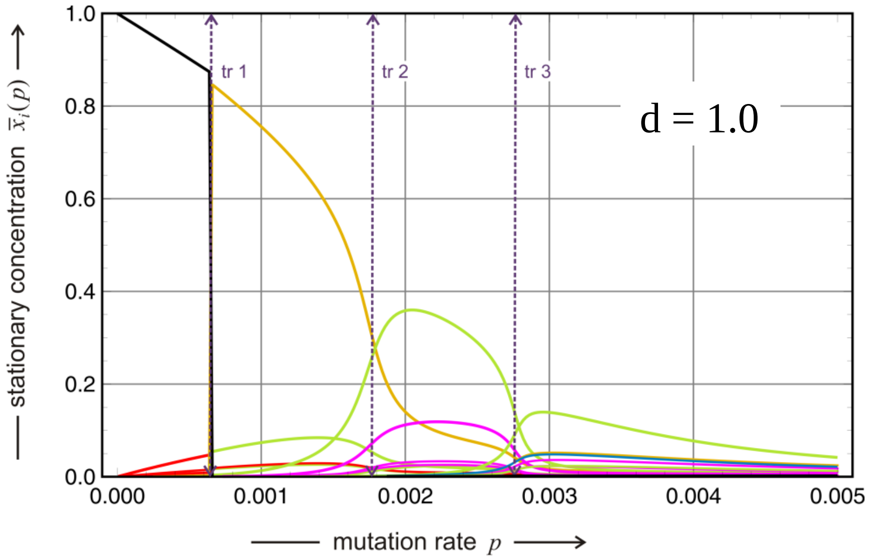
Transitions between quasispecies





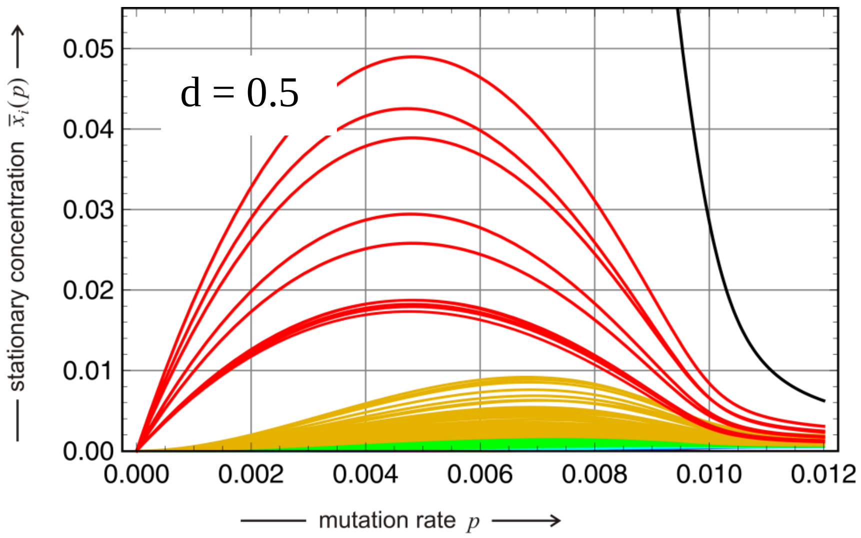
Choice of random scatter:

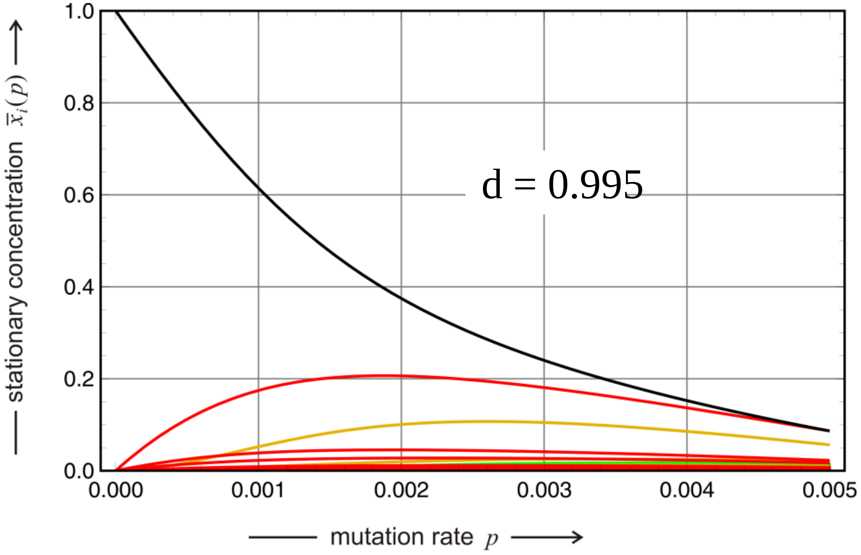
s = 637



Error threshold on realistic landscapes

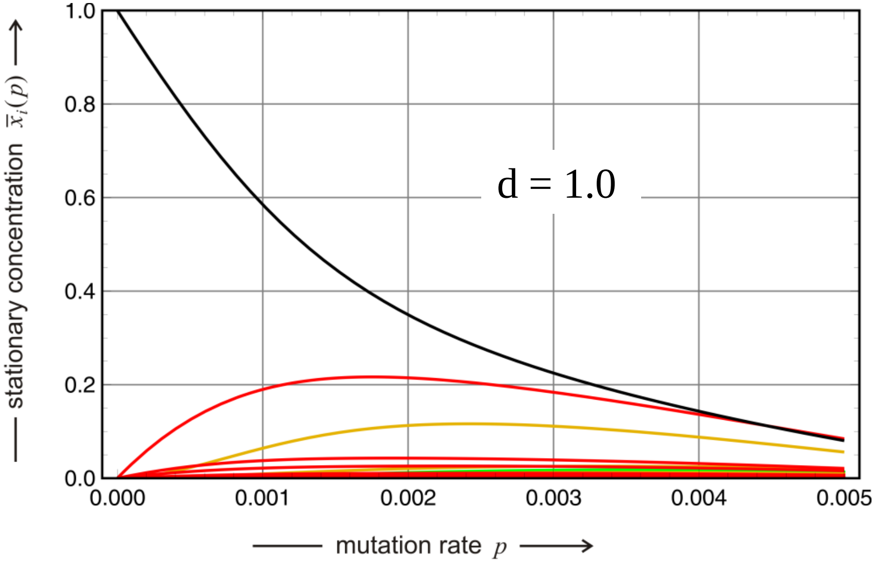
n = 10, f_0 = 1.1, f_n = 1.0, s = 637





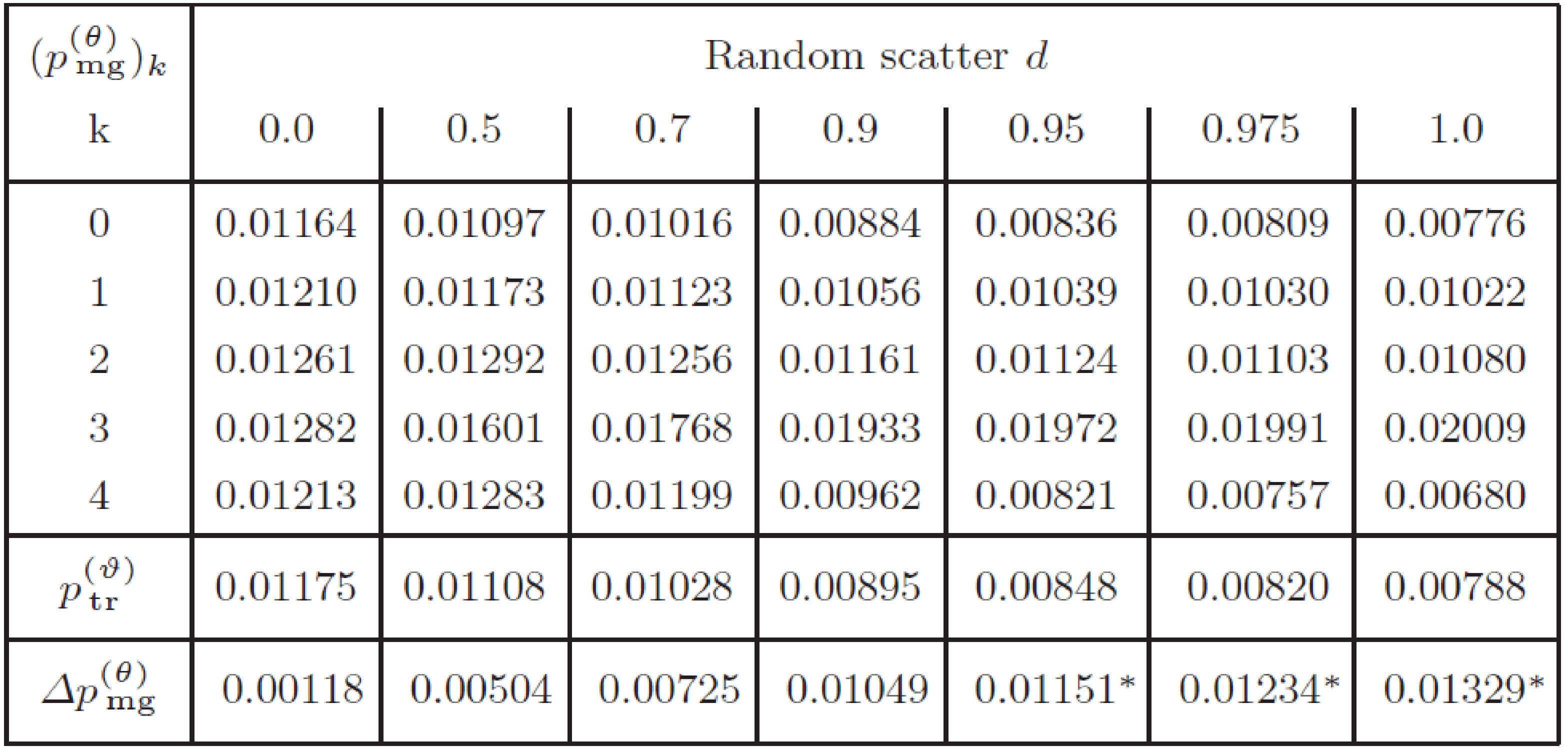
Choice of random scatter:

s = 919



Error threshold on realistic landscapes

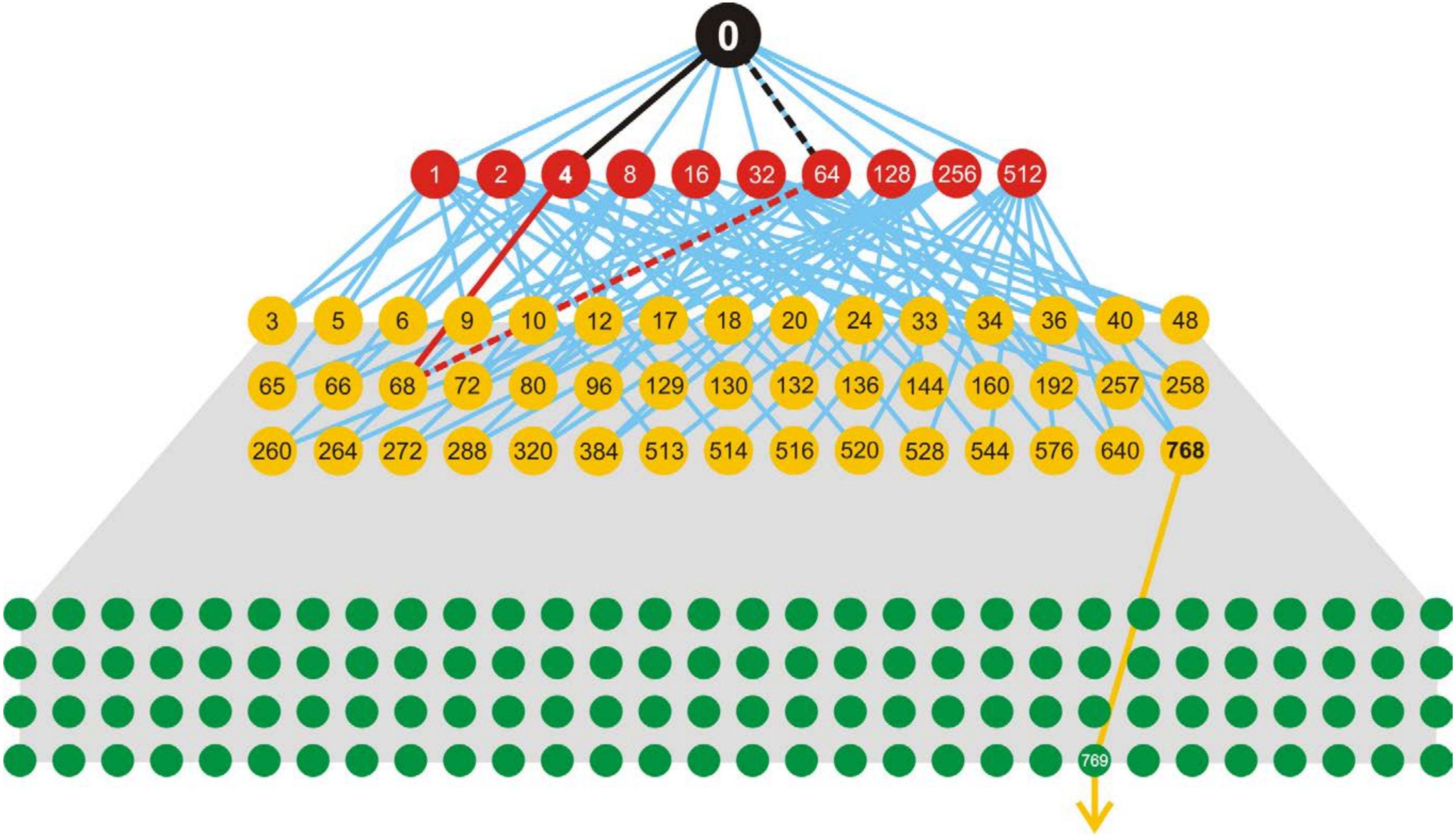
n = 10, $f_0 = 1.1$, $f_n = 1.0$, s = 919



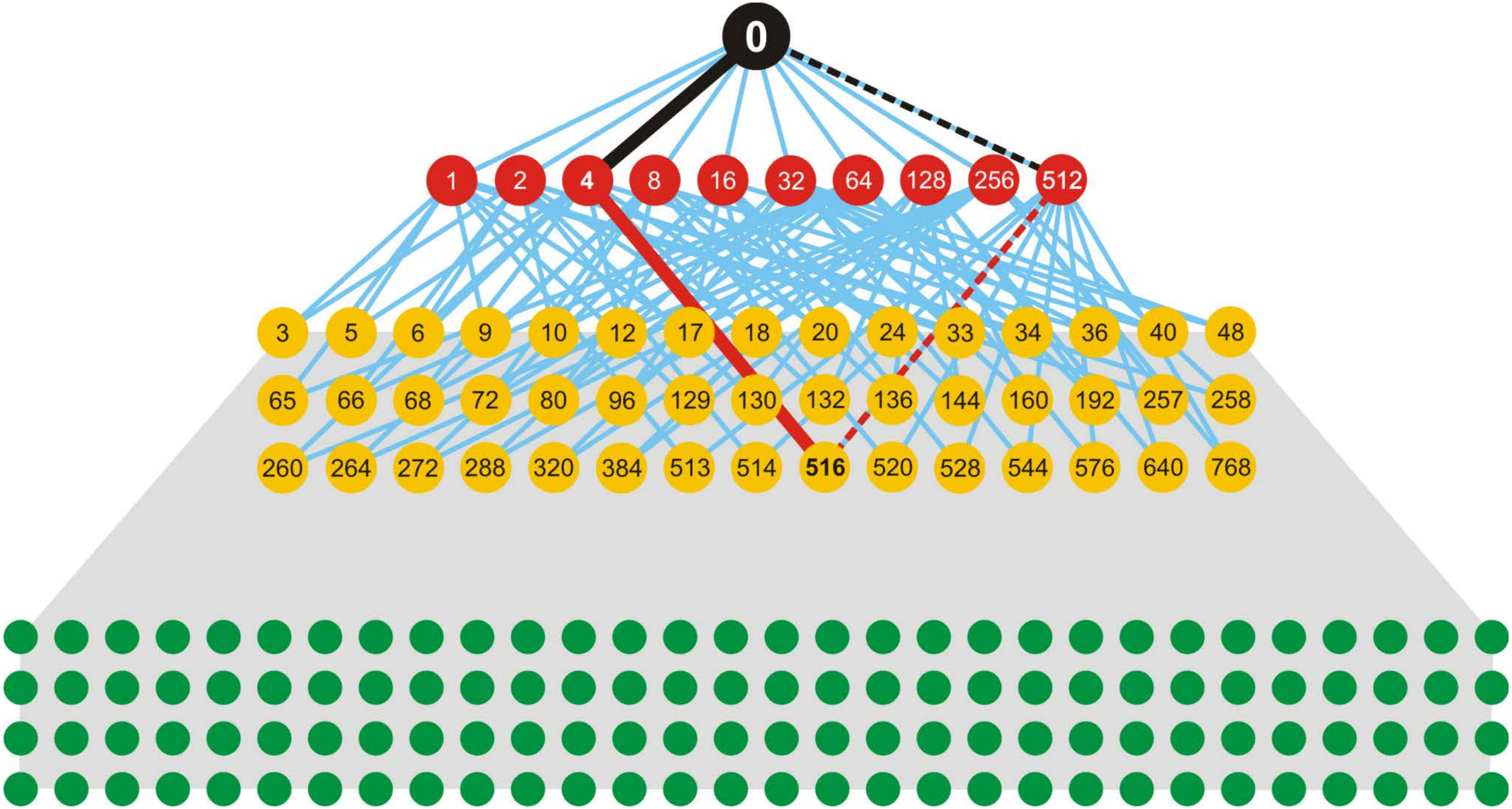
$(p^{(\theta)}_{\mathrm{mg}})_k$	Random scatter d						
k	0.0	0.5	0.7	0.9	0.95	0.975	1.0
0	0.01164	0.01097	0.01016	0.00884	0.00836	0.00809	0.00776
1	0.01210	0.01173	0.01123	0.01056	0.01039	0.01030	0.01022
2	0.01261	0.01292	0.01256	0.01161	0.01124	0.01103	0.01080
3	0.01282	0.01601	0.01768	0.01933	0.01972	0.01991	0.02009
4	0.01213	0.01283	0.01199	0.00962	0.00821	0.00757	0.00680
$p^{(\vartheta)}_{\mathrm{tr}}$	0.01175	0.01108	0.01028	0.00895	0.00848	0.00820	0.00788
$\Delta p^{(\theta)}_{\mathrm{mg}}$	0.00118	0.00504	0.00725	0.01049	0.01151*	0.01234*	0.01329*

$$\mathcal{L}(10\,,\,2\,,1.1\,,\,1.0\,;\,0.0\,,\,d\,\,,\,919) : p_{\mathrm{cr}} = 0.009486\,;\,\theta\,=\,\vartheta = 0.01$$

Level crossing and compelementary class merging for strong quasispecies



Determination of the dominant mutation flow: $d = 1.0$, $s = 637$



Determination of the dominant mutation flow: $d = 1.0$, $s = 919$

Predictions of the strong quasispecies concept

1. A strong quasispecies is dominated by a **clan** of mutationally coupled closely related sequences.

2. A four-membered clan consists of the **master sequence** being the fittest sequence, its **fittest one error mutant**, the **fittest two-error mutant** that **has to lie in the one-error neighborhood of the fittest one-error mutant**, and the **fourth sequence** completing the mutationally coupled quartet.

3. A strong quasispecies is stable against changes in the mutation rate and hence provides an evolutionary advantage over conventional quasispecies.

Thank you for your attention!

Web-Page for further information:

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