

Web-Page for further information:

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

1926 Kaiser Wilhelm-Institut für
Anthropologie

1953 MPI für vergleichende Erb-
biologie und Erbpathologie



*Happy birthday Max Planck-Institute for Molecular
Genetics*

*and to a successful continuation with outstanding
cutting-edge science*

1. Prologue
2. Landscapes and evolutionary dynamics
3. Realistic landscapes and mutant clans
4. Neutrality in evolutionary dynamics
5. Concluding remarks and perspectives

1. Prologue

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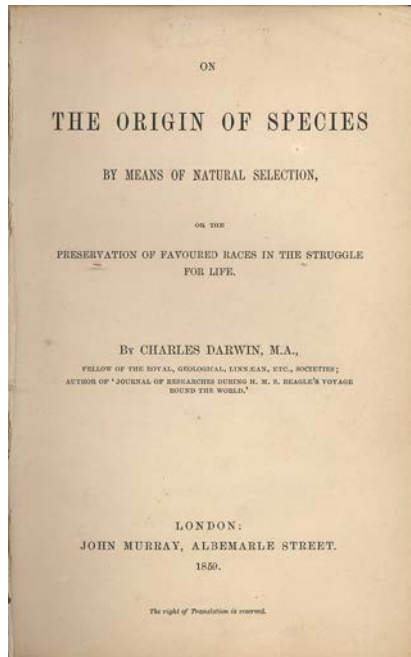


Charles Darwin,
1809 - 1882



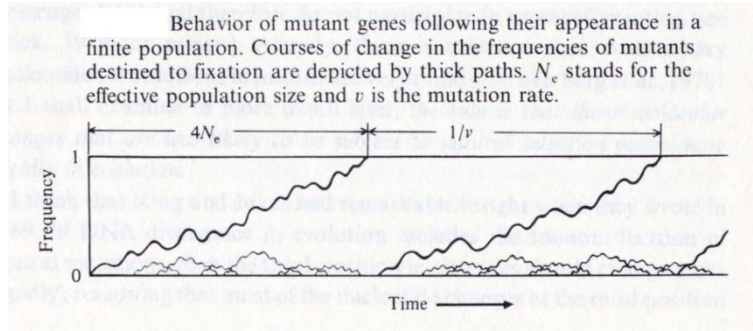


Charles Darwin,
1809 - 1882



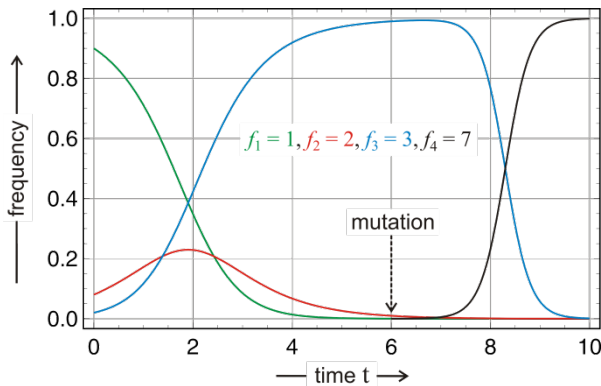


Charles Darwin,
1809 - 1882



Sewall Wright,
1889 - 1988

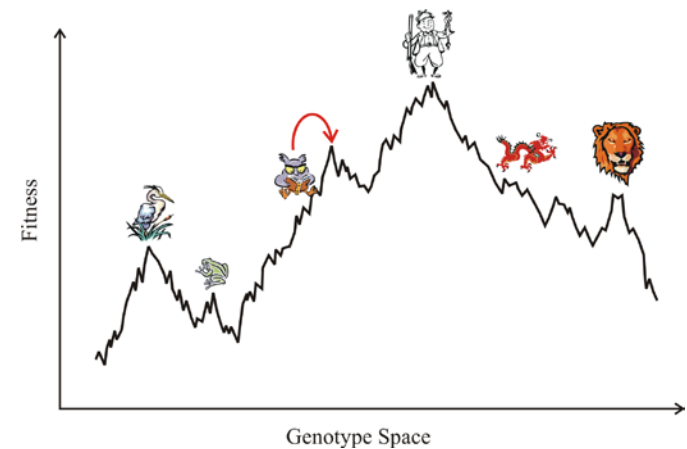
random drift



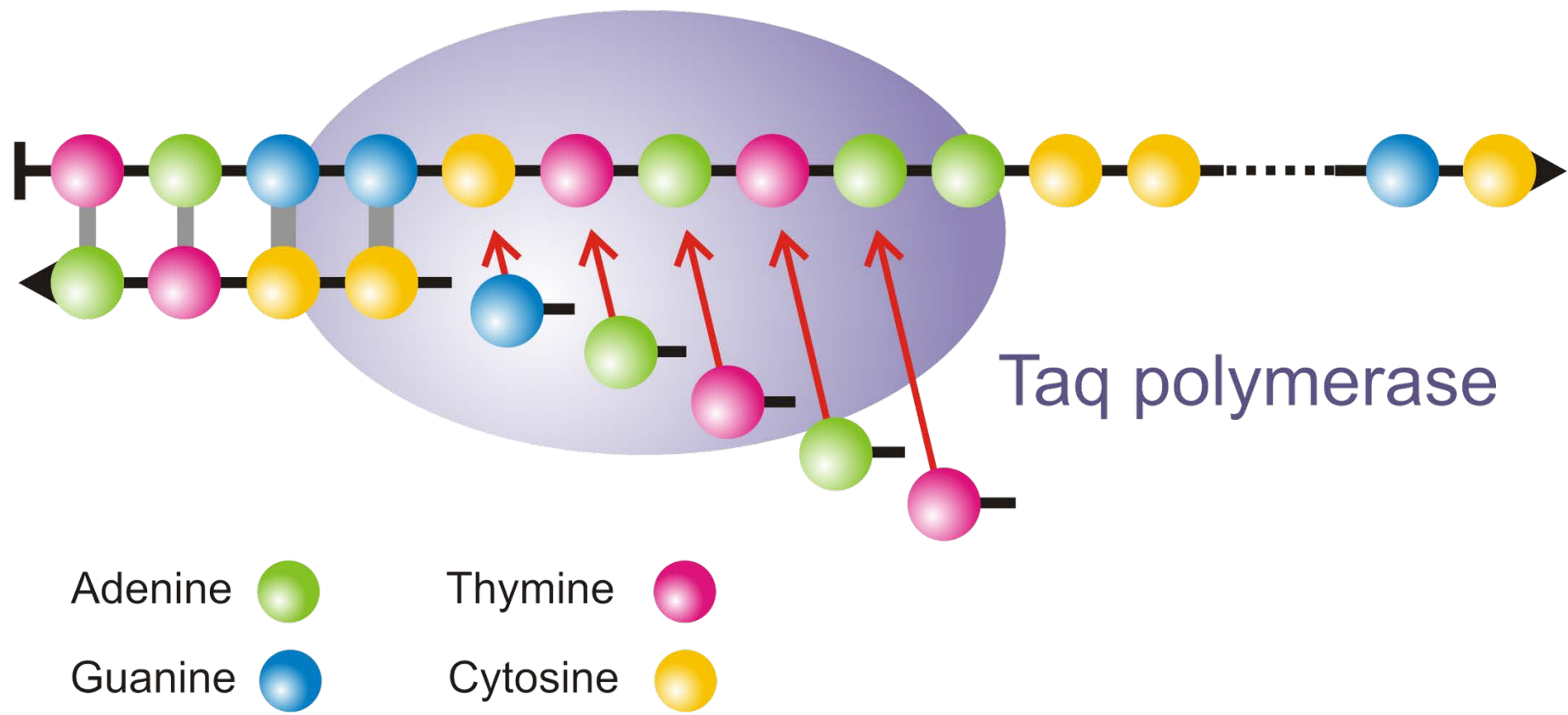
survival of the fittest



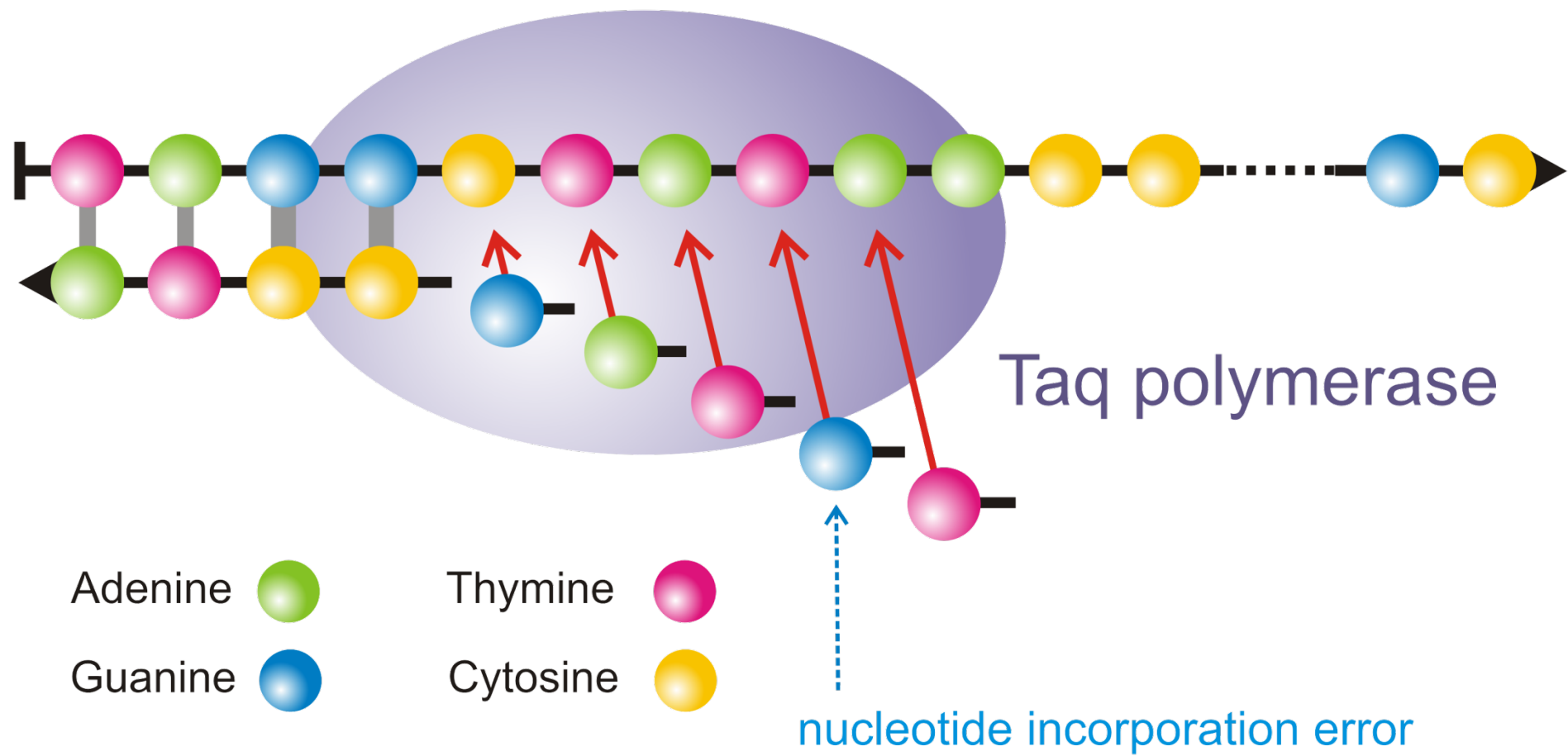
Motoo Kimura,
1924 - 1994



fitness landscape



The logic of DNA (or RNA) replication and mutation



p mutation rate per site and replication

The logic of DNA (or RNA) replication and mutation

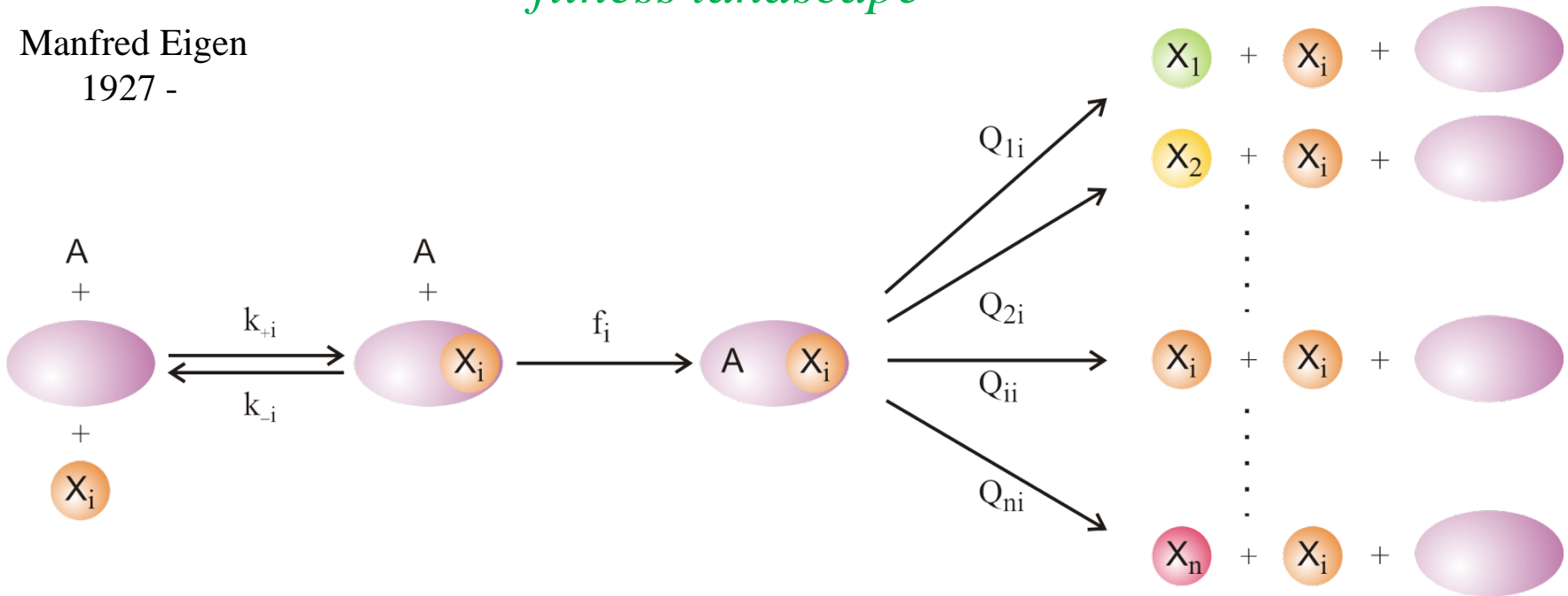


Manfred Eigen
1927 -

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

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

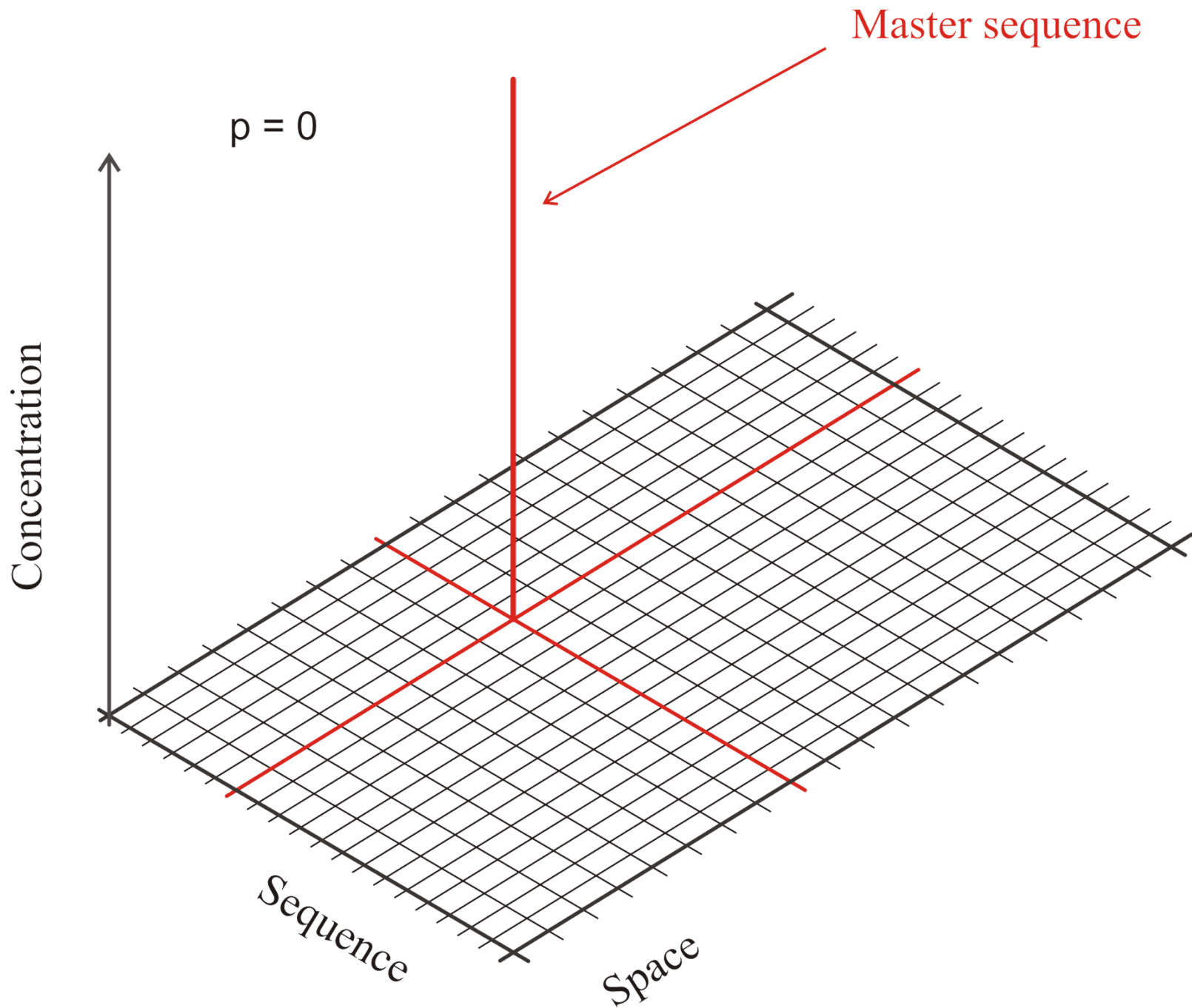
fitness landscape

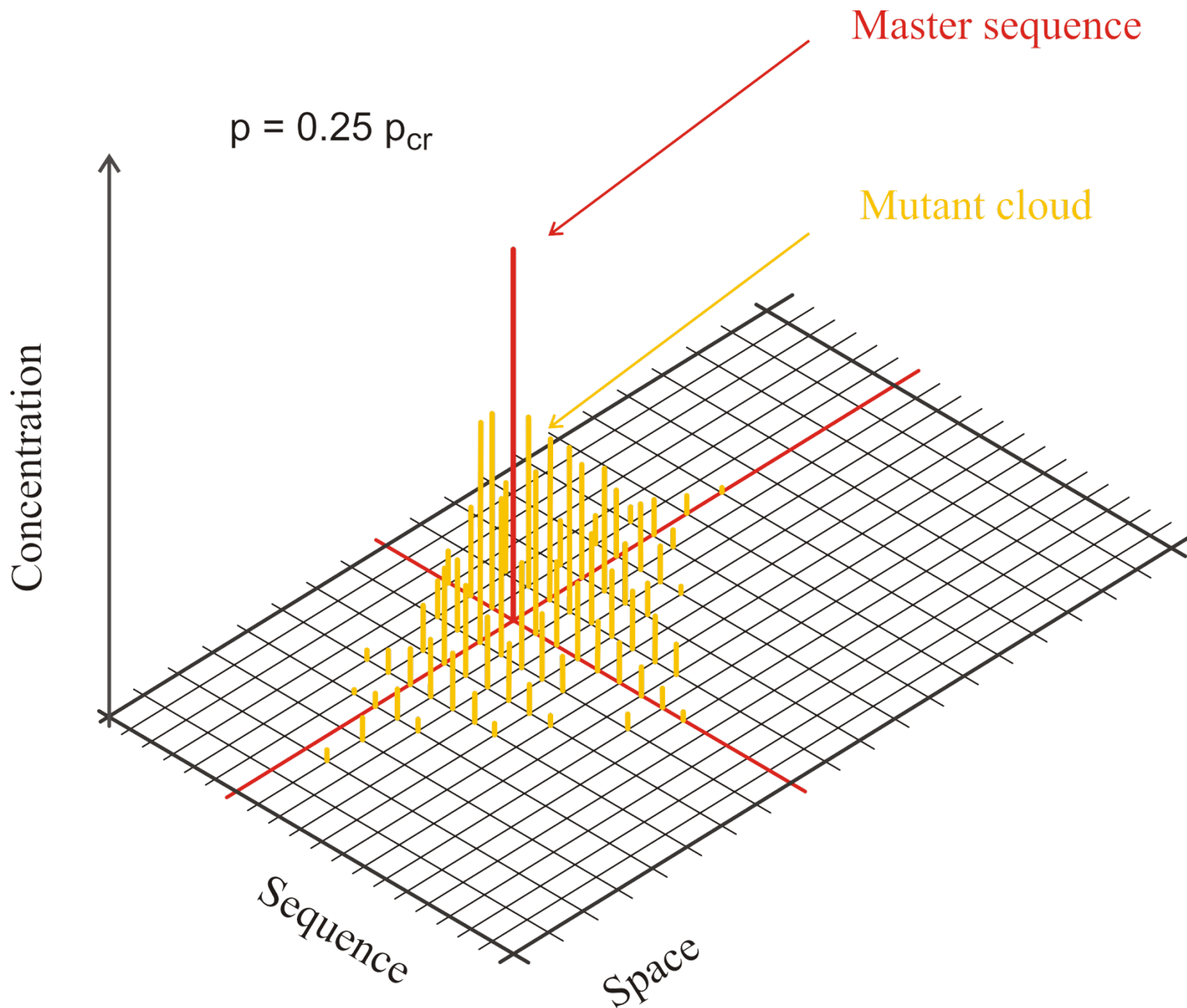


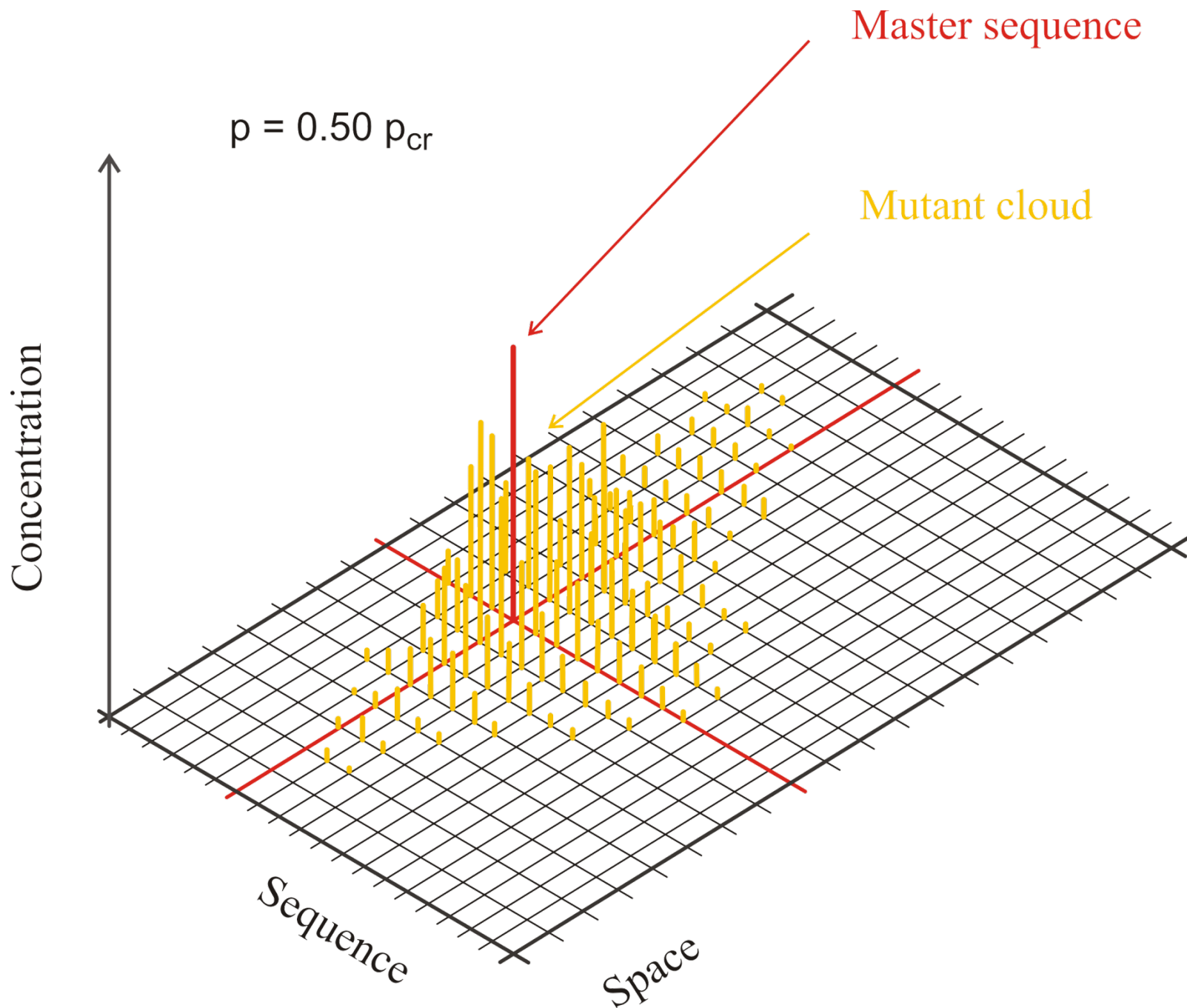
Mutation and (correct) replication as parallel chemical reactions

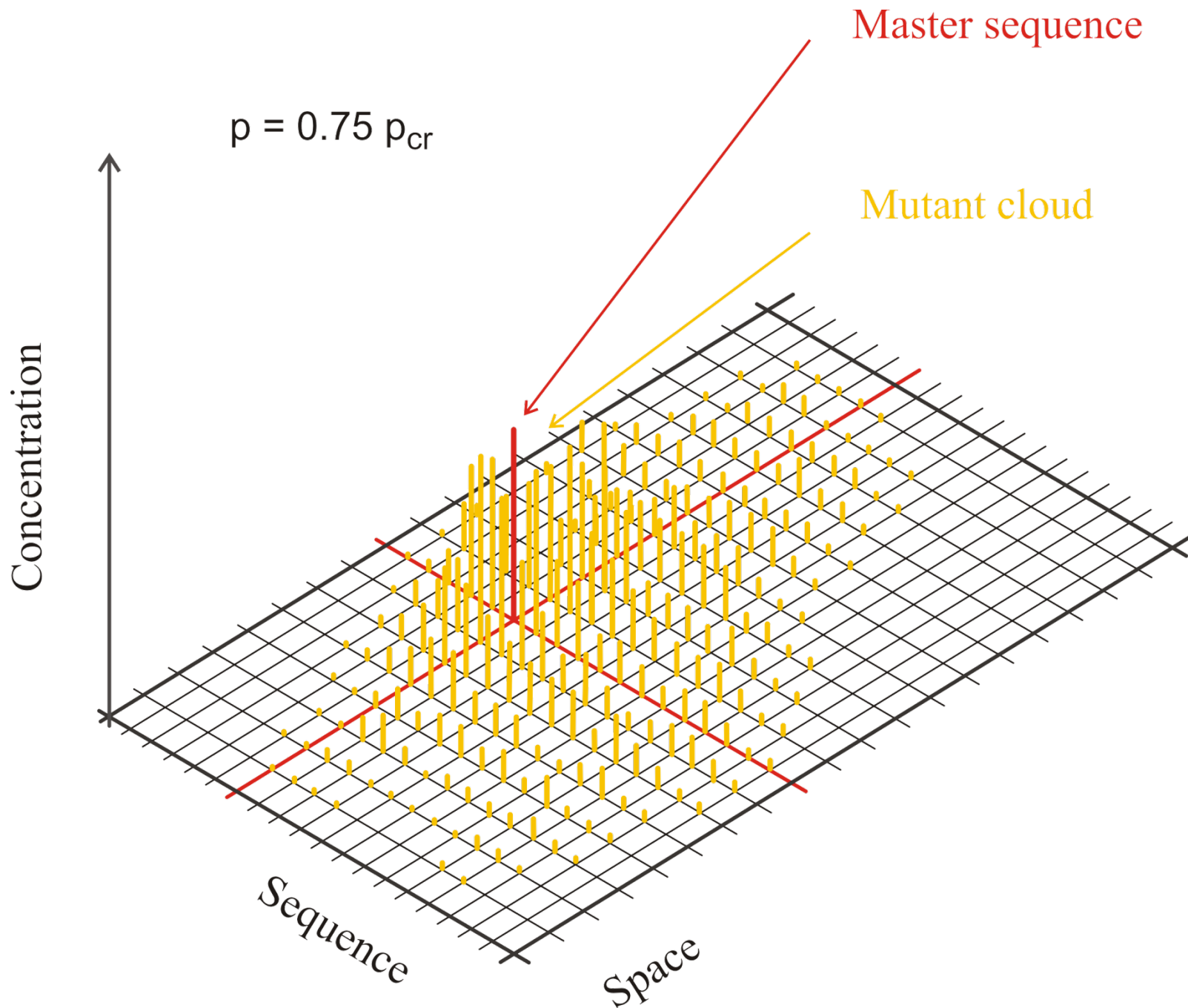
M. Eigen. 1971. *Naturwissenschaften* 58:465,

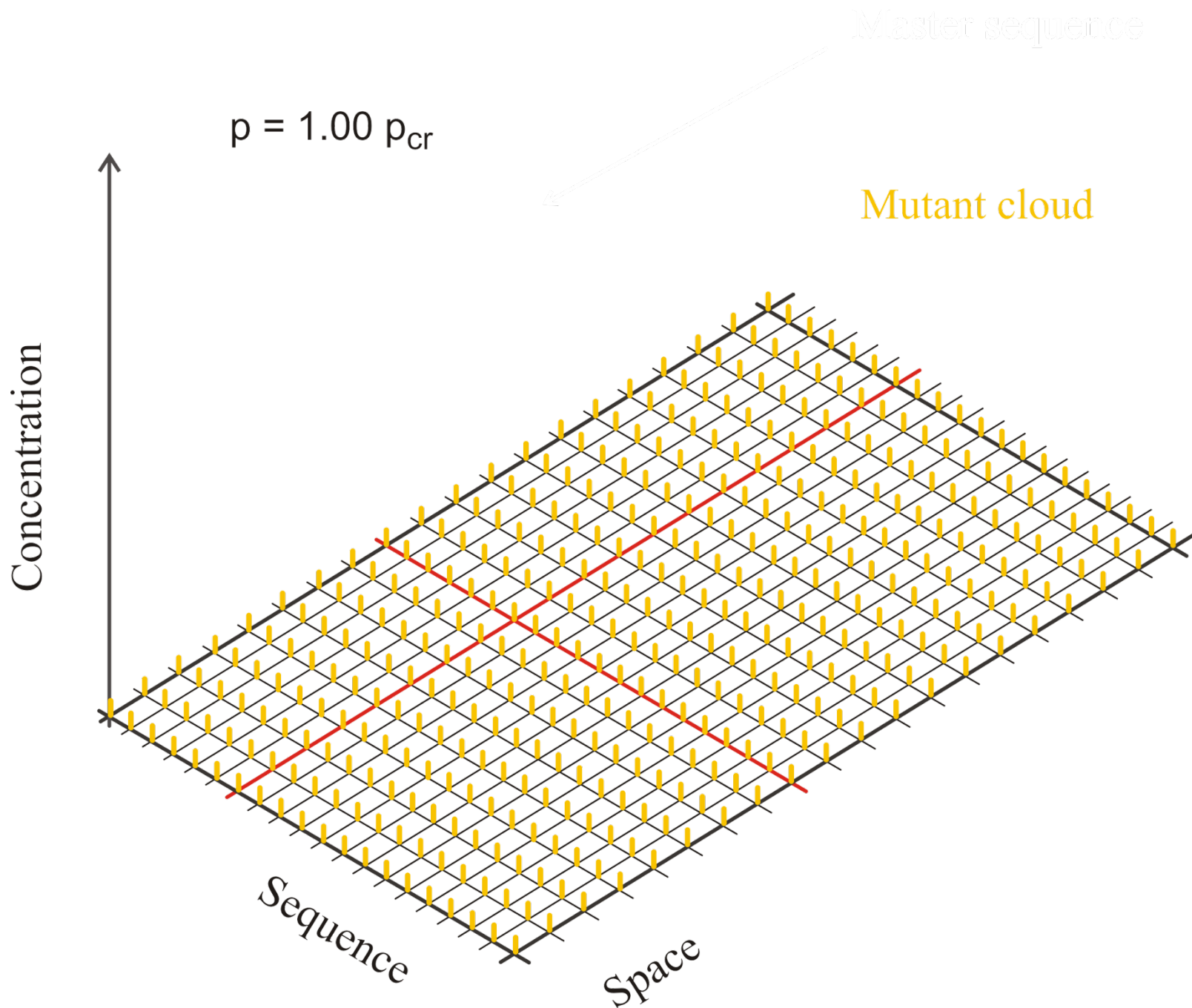
M. Eigen & P. Schuster. 1977. *Naturwissenschaften* 64:541, 65:7 und 65:341

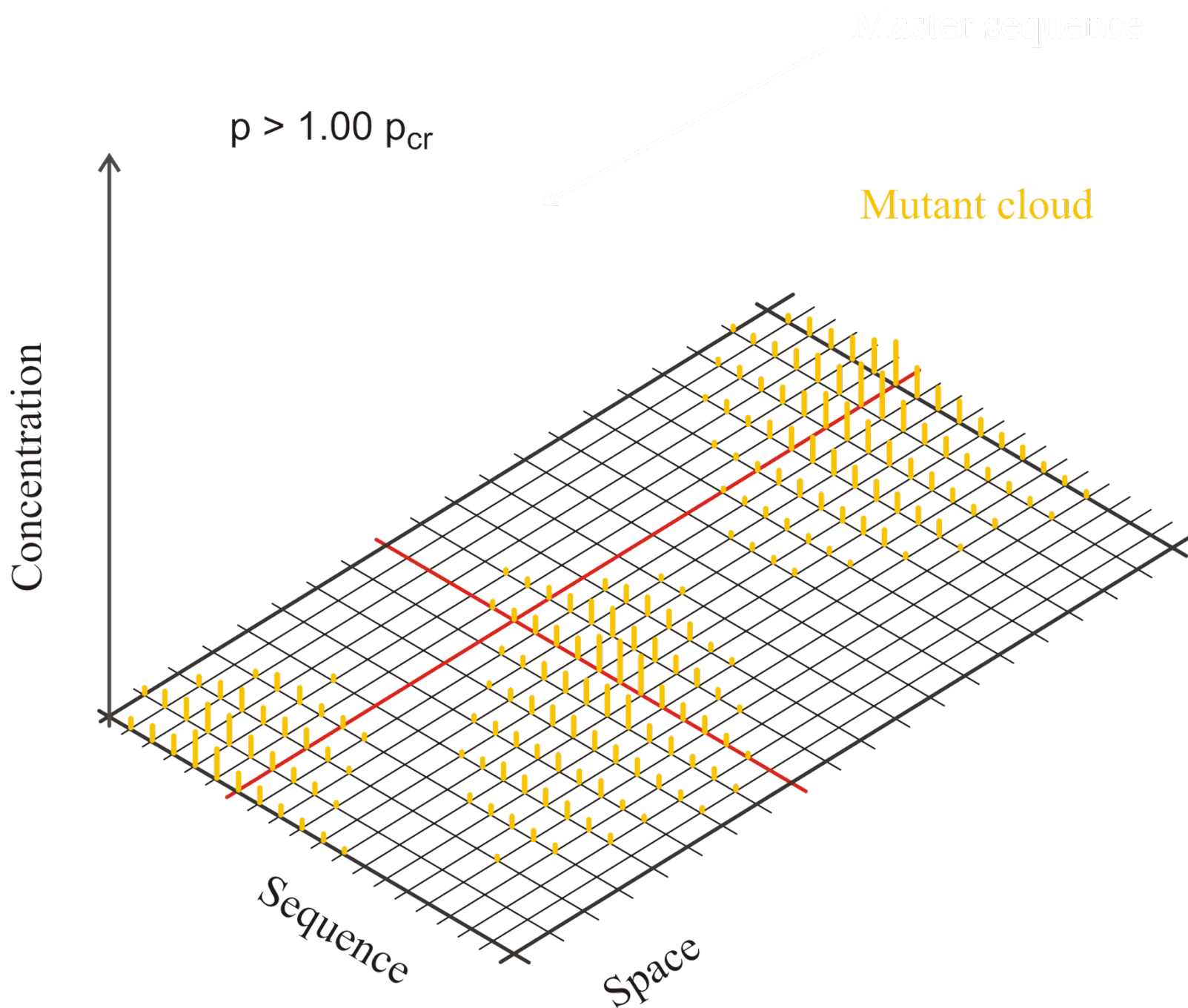


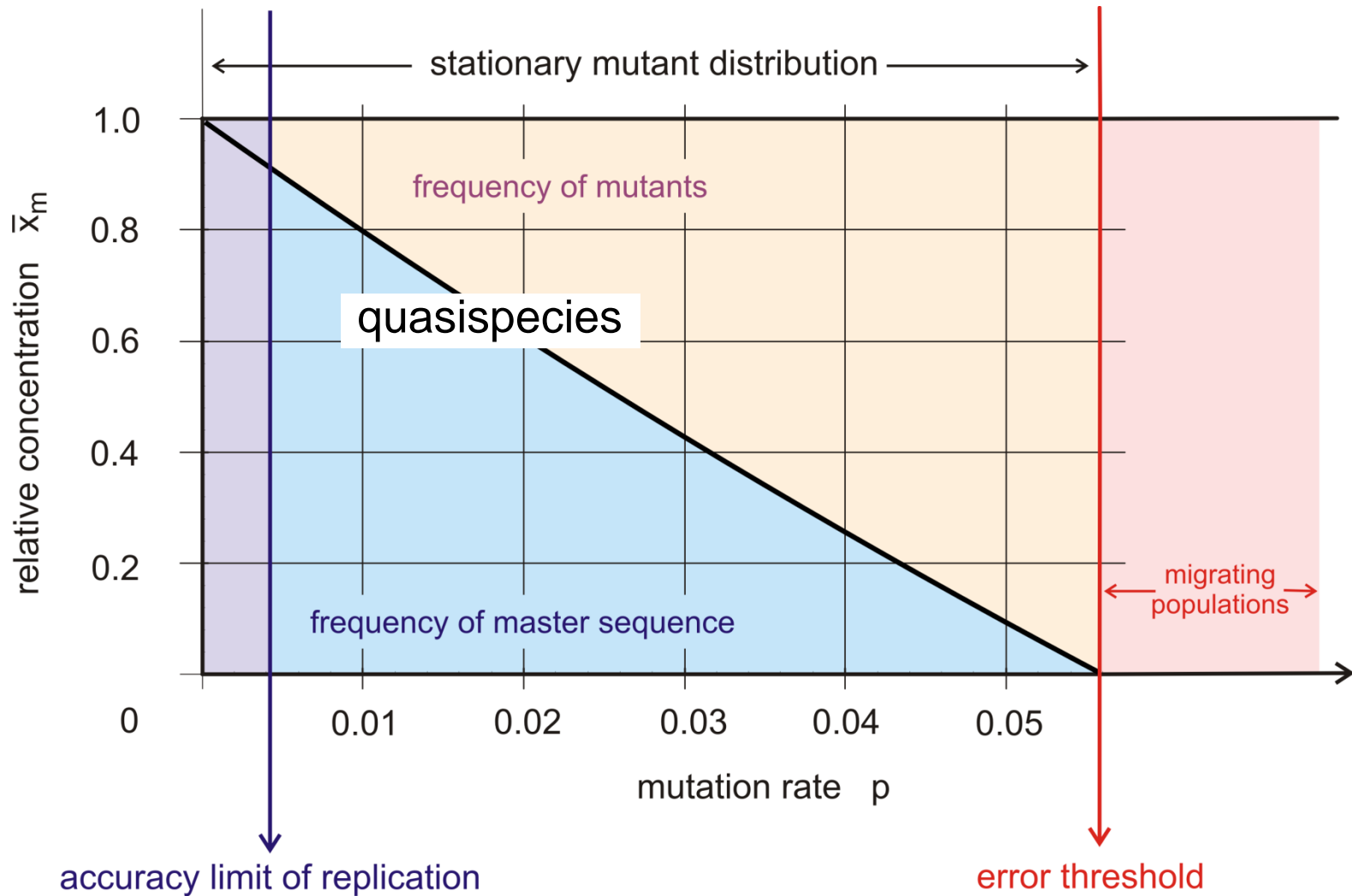




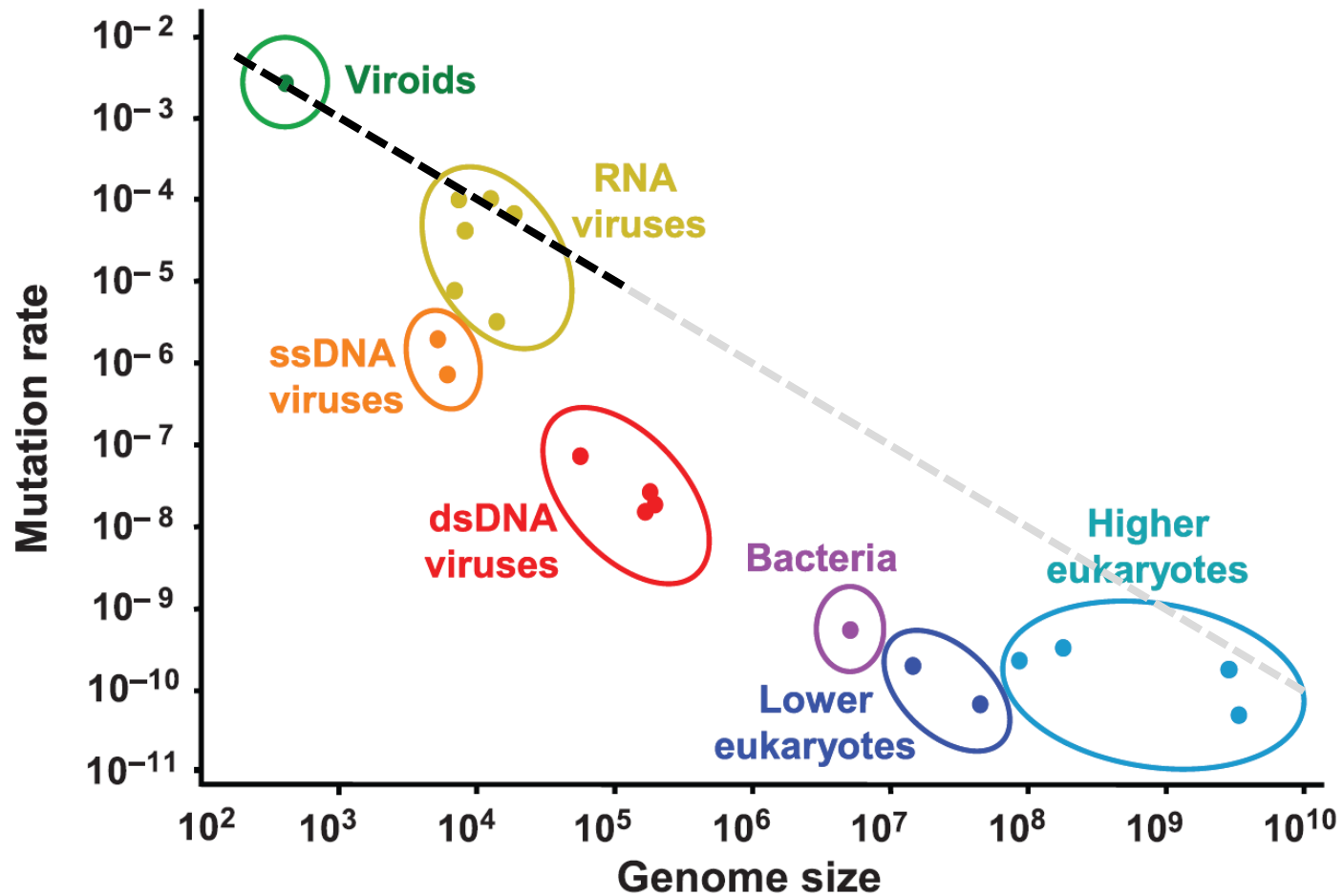








The error threshold in replication and mutation

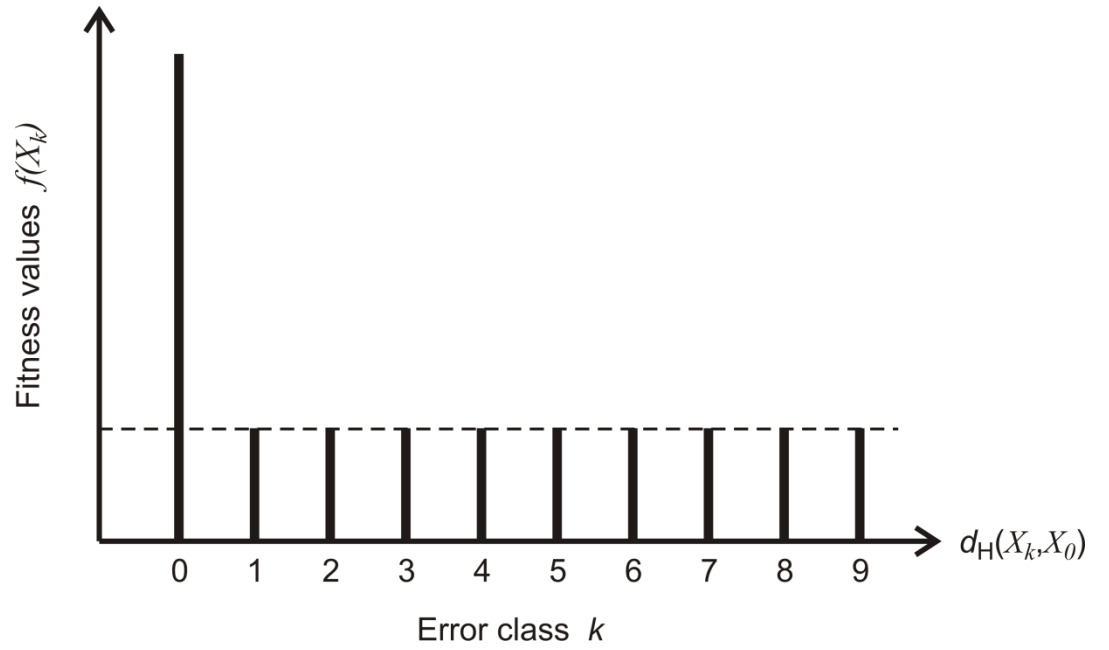


Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. 2009. Extremely high mutation rate of a hammerhead viroid. *Science* 323:1308.

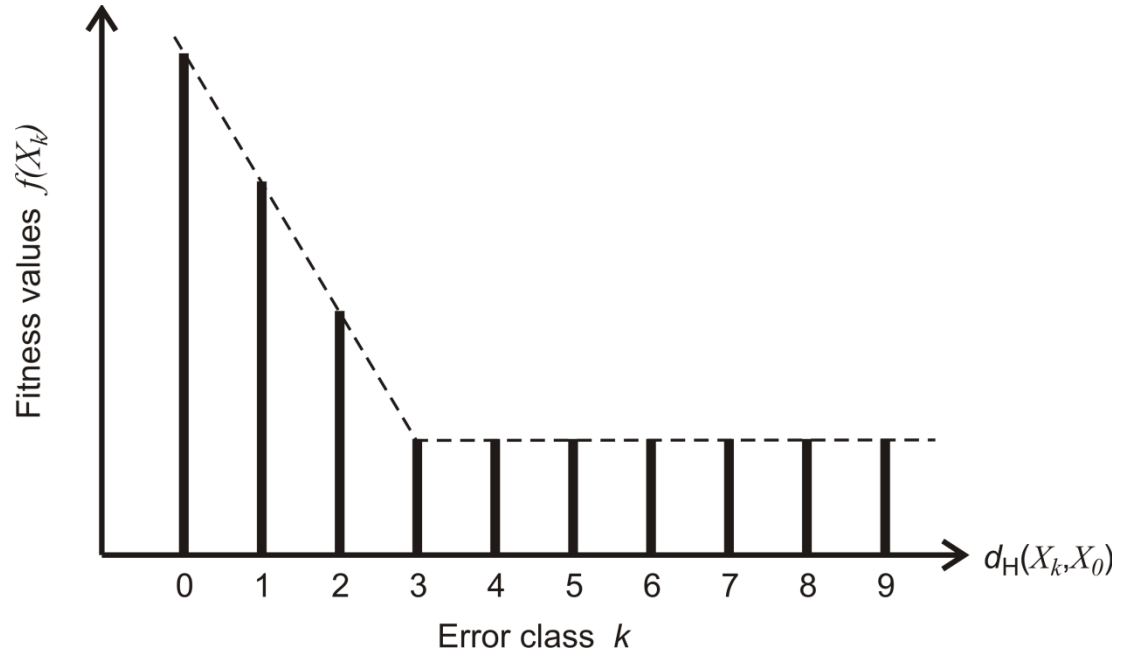
Mutation rate and genome size

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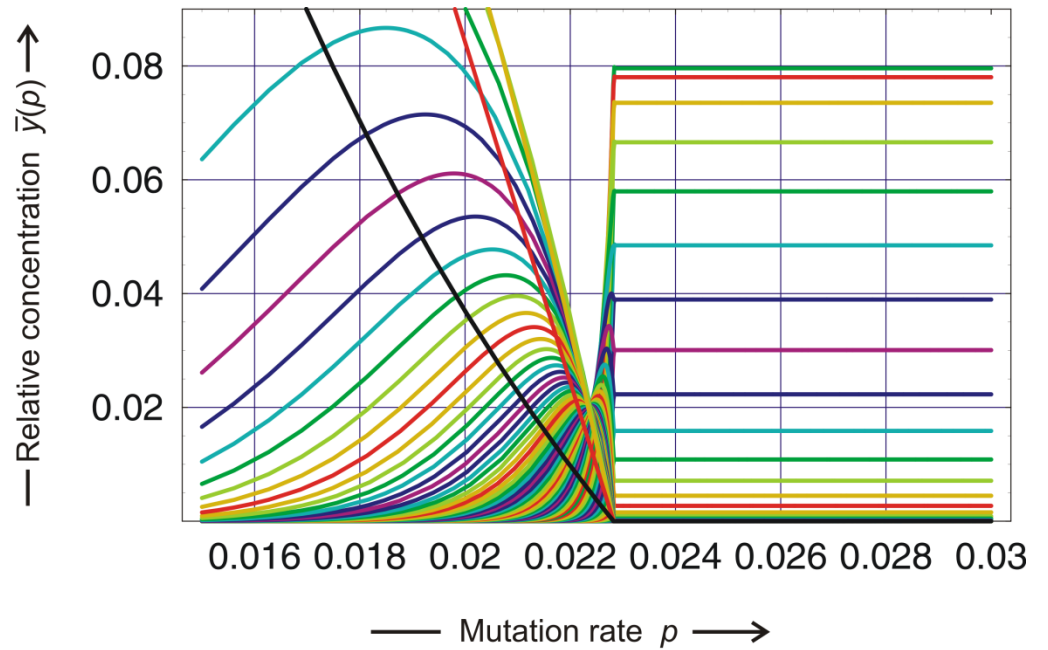
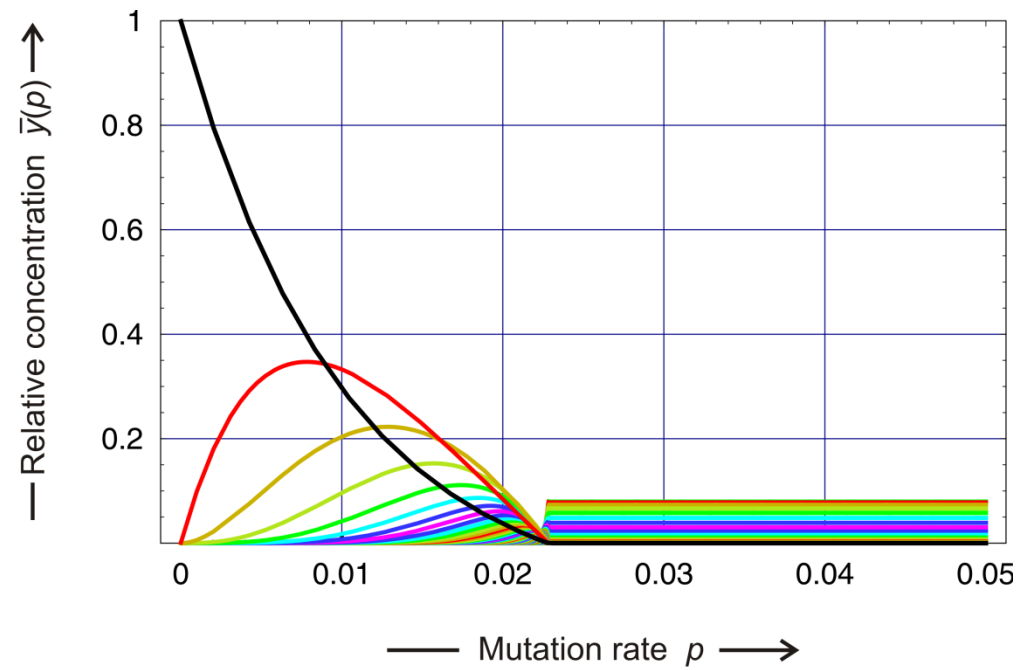
single peak landscape



step linear landscape



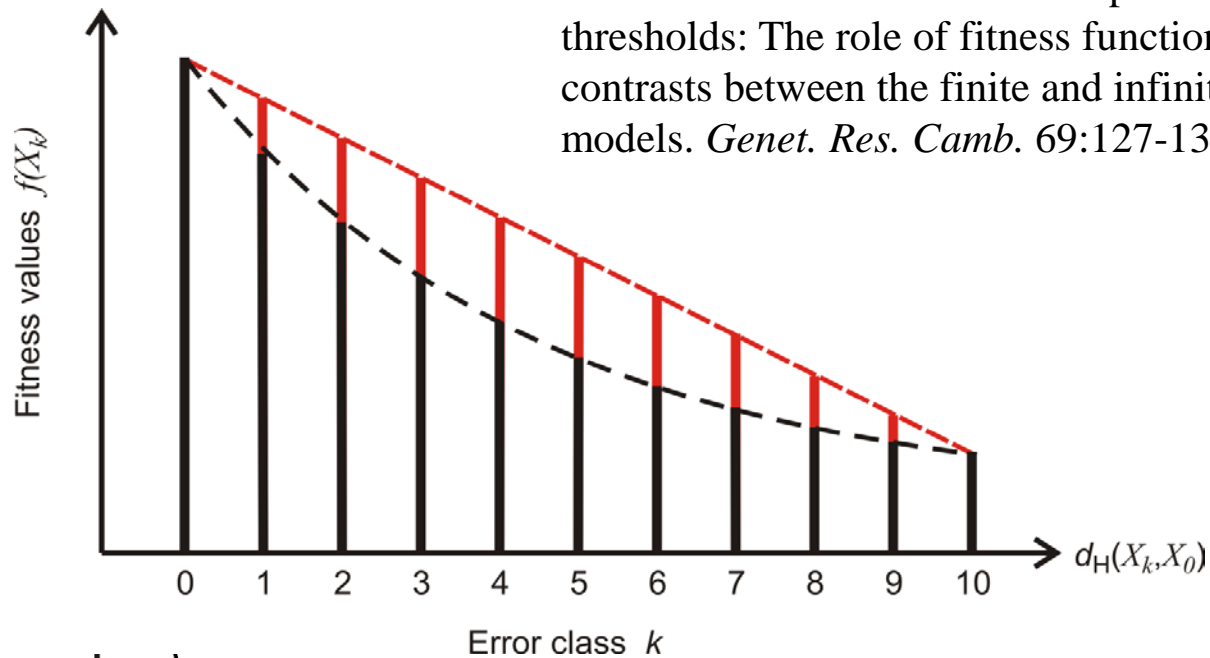
Model fitness landscapes I



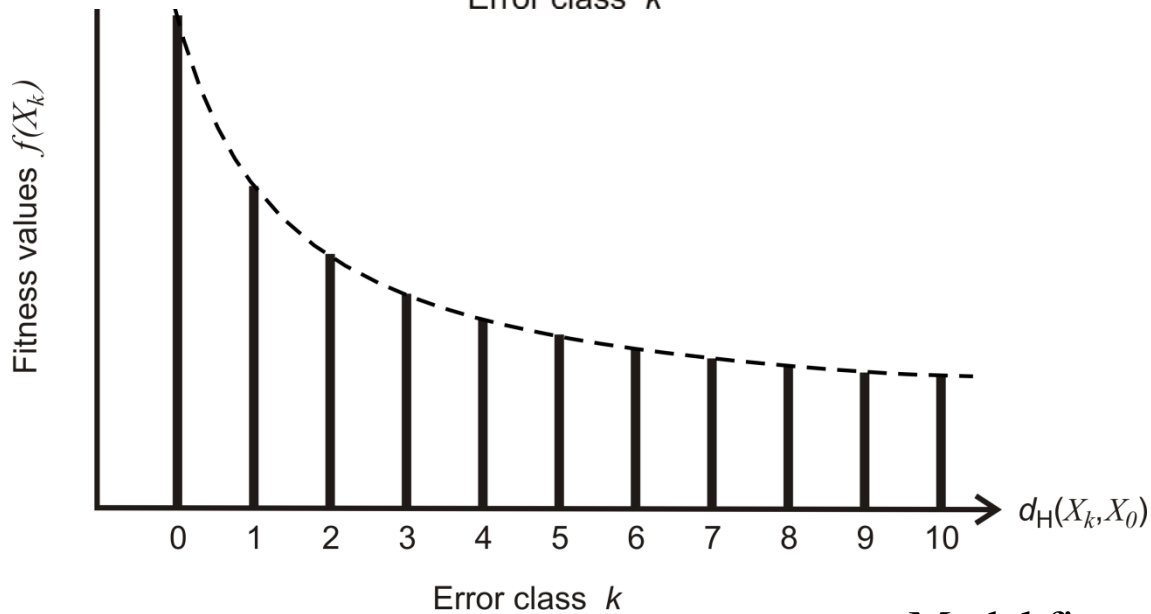
Error threshold on the single peak landscape

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

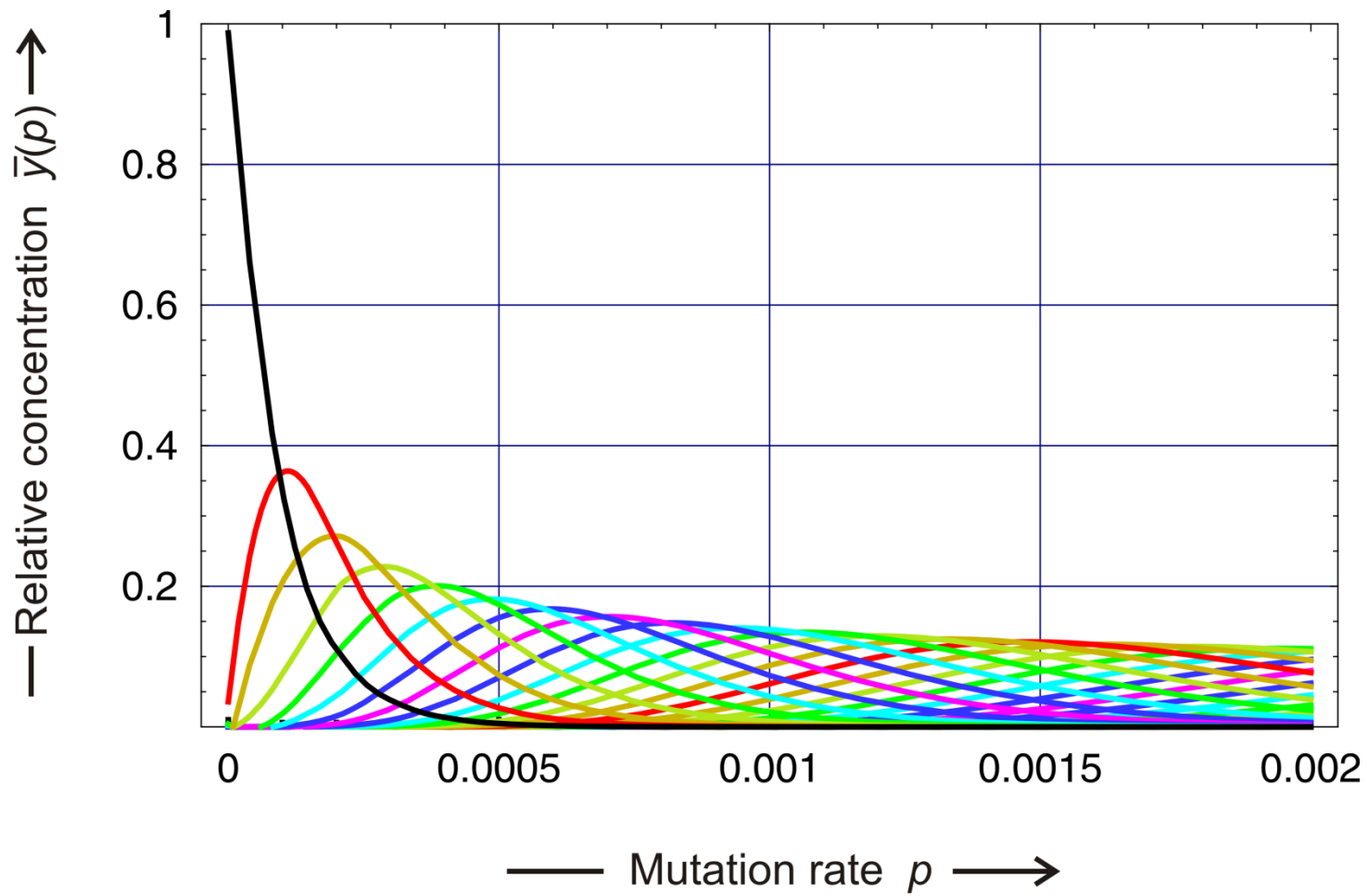
linear and
multiplicative



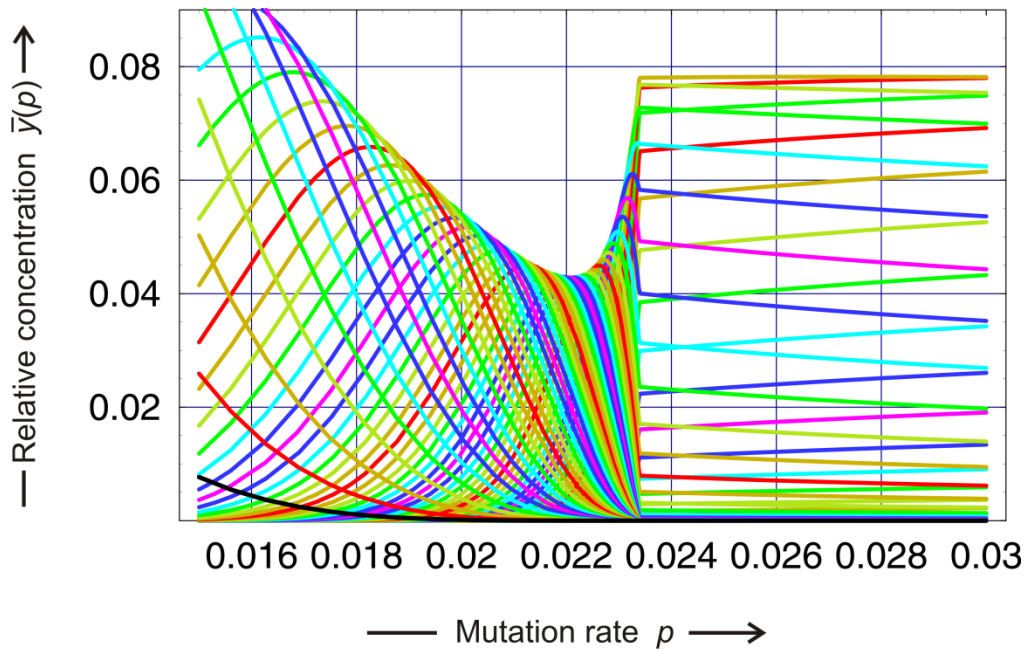
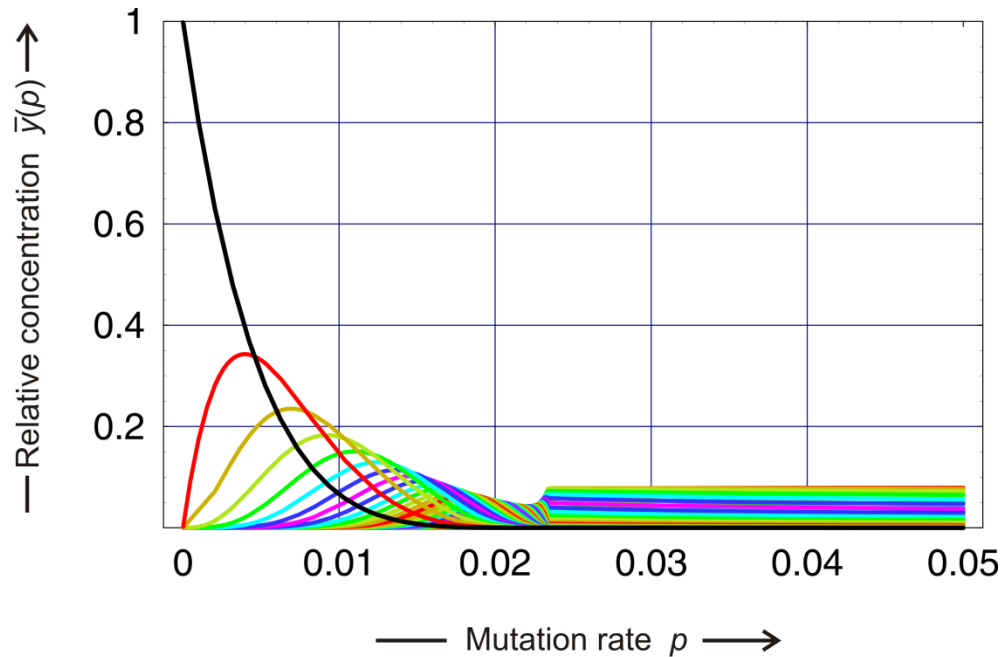
hyperbolic



Model fitness landscapes II

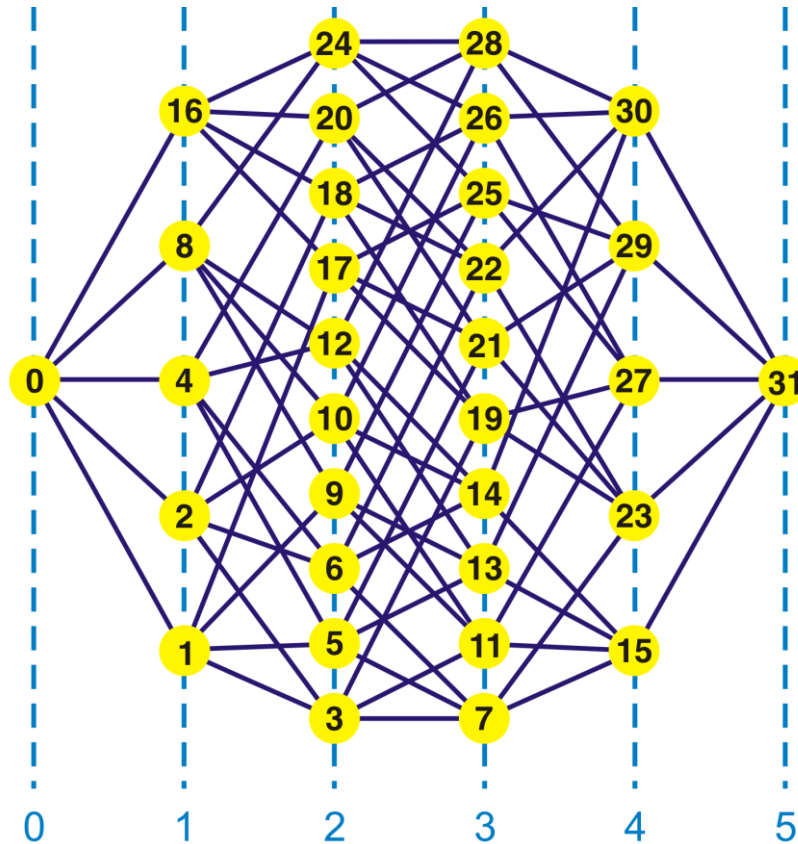


The linear fitness landscape shows no error threshold



Error threshold on the
 hyperbolic landscape

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Mutant classes

sequences

0	1	2	3	4	5
1	5	10	10	5	1

Binary sequences are encoded by their decimal equivalents:

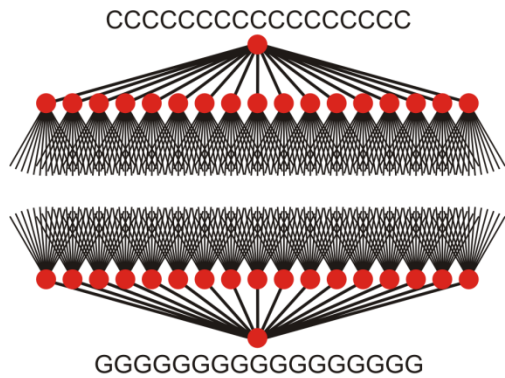
C = 0 and **G** = 1, for example,

"0" \equiv 00000 = **CCCCC**,

"14" \equiv 01110 = **CGGGC**,

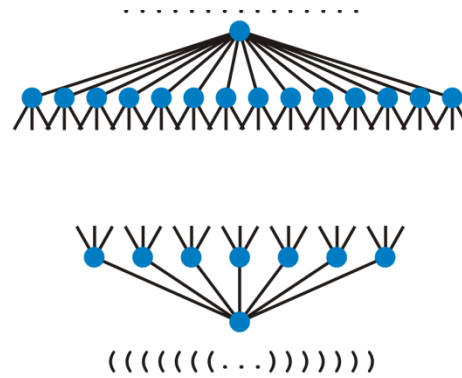
"29" \equiv 11101 = **GGGCG**, etc.

\mathcal{Q}_5 : the space of binary sequences of chain length $l = 5$



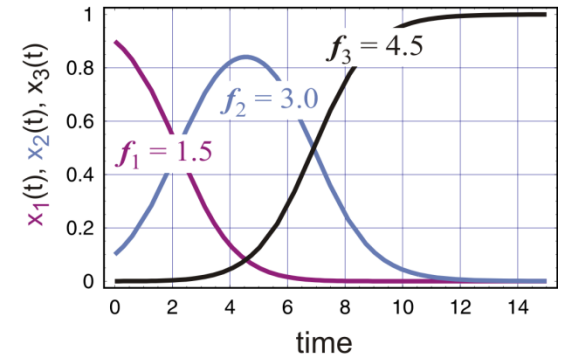
sequence space

\mathcal{Q}



shape space

\mathcal{S}



parameter space

\mathbb{R}_+

$$\Phi: (\mathcal{Q}, d_H) \Rightarrow (\mathcal{S}, d_S)$$

$$\Psi: (\mathcal{S}, d_S) \Rightarrow \mathbb{R}_+$$

X



$S = \Phi(X)$



$f = \Psi(S)$

sequence

structure

function

genotype

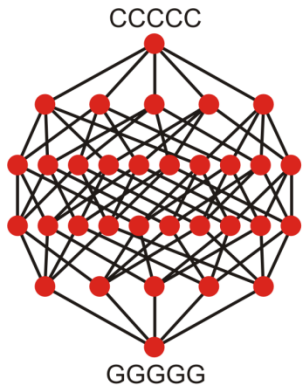


phenotype

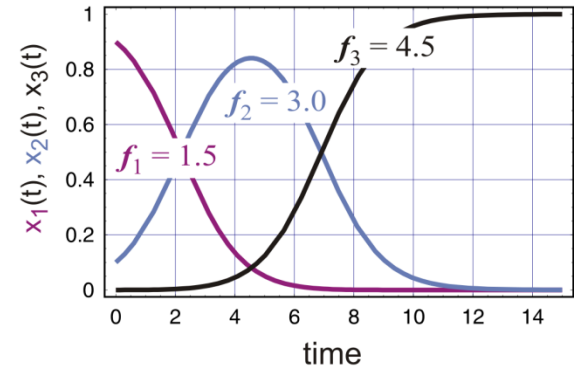


selection

Evolution as a global phenomenon in genotype space



sequence space



parameter space

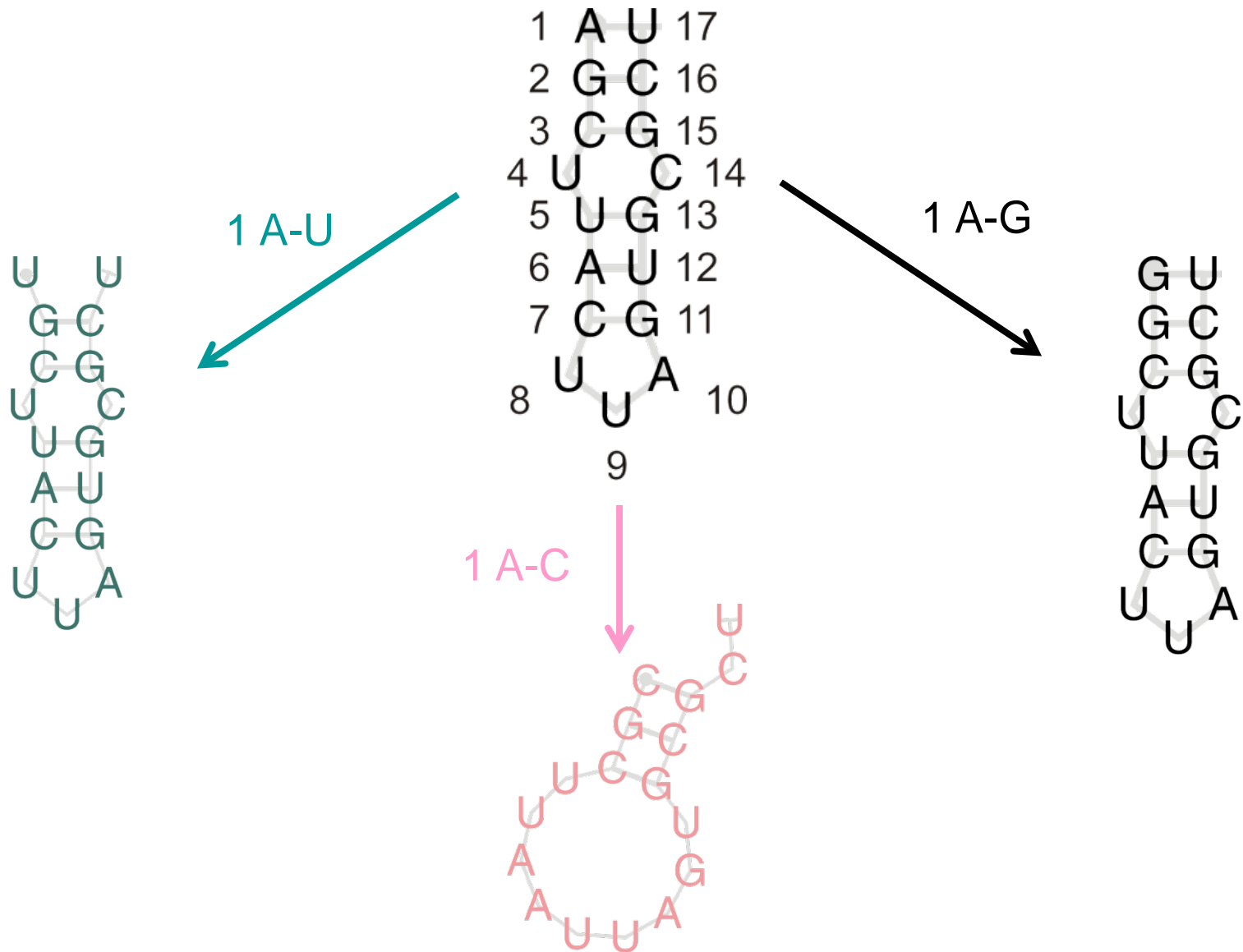
S
sequence

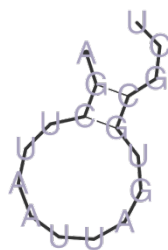
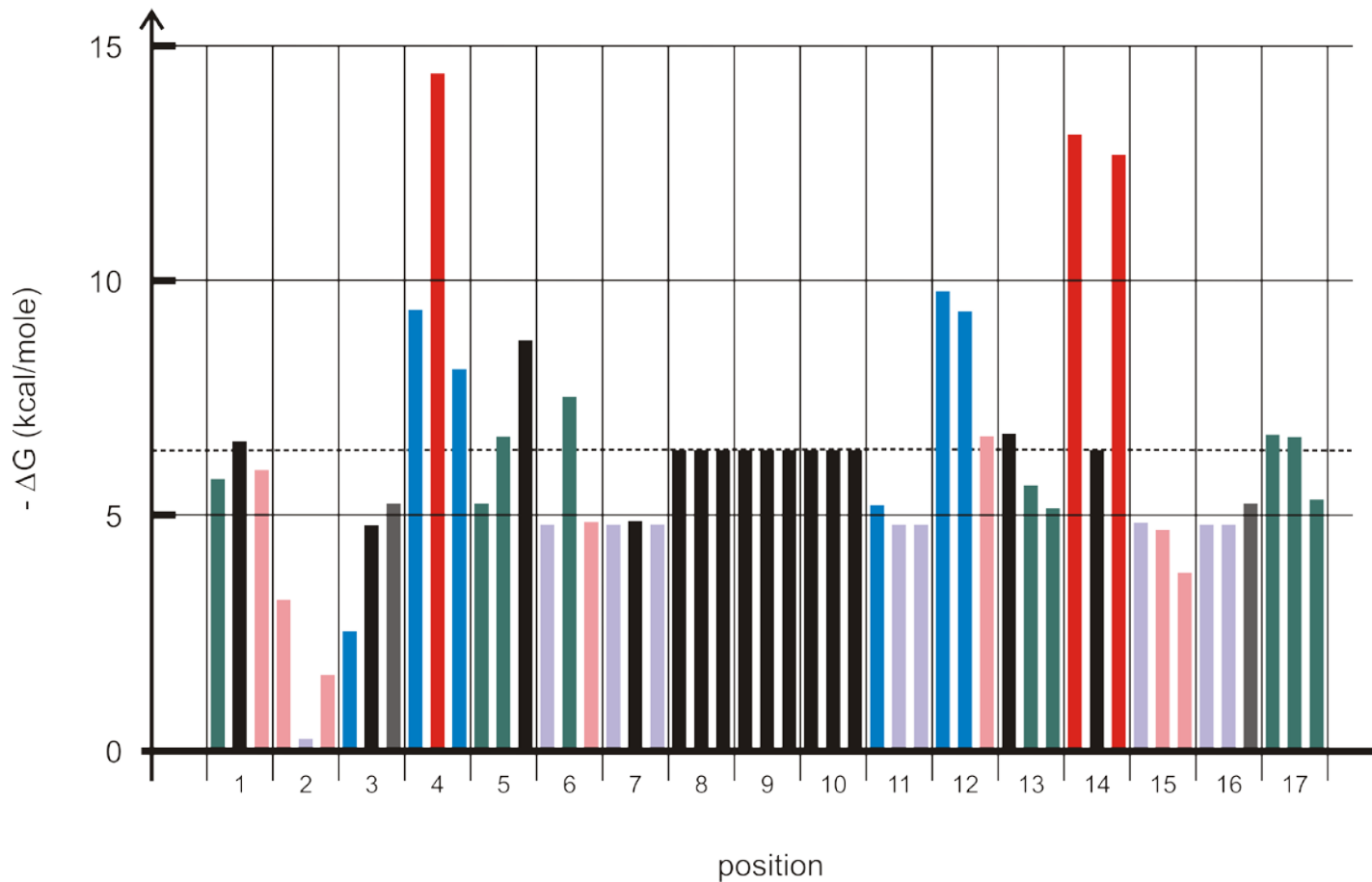
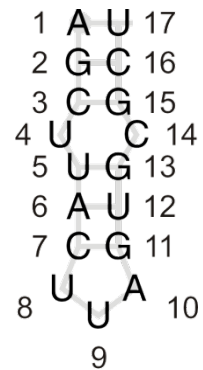


$f = \Psi(Y)$
function

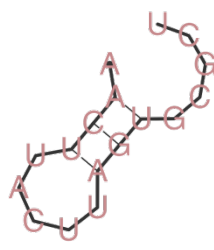
The simplified model

AGCUUAACUUAGUCGCU

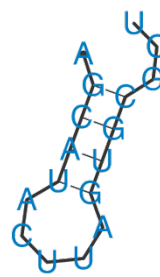




9



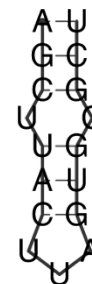
7



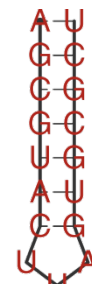
6



9

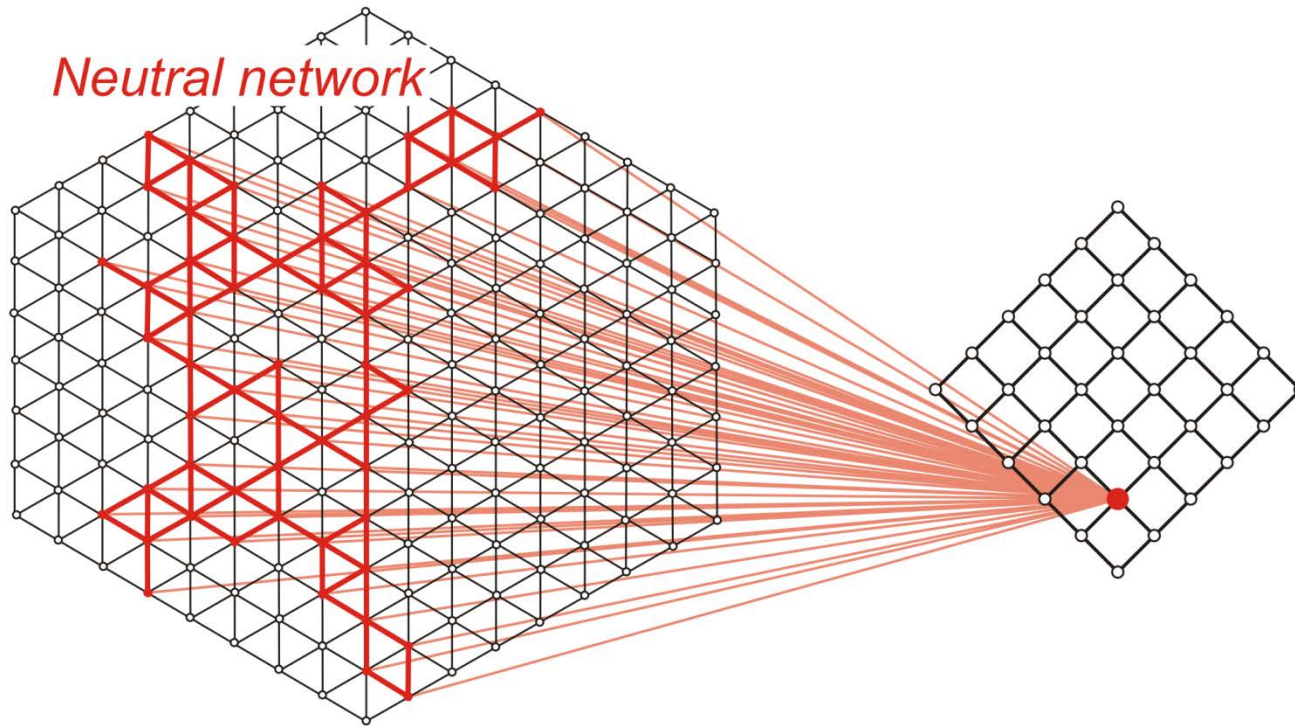


15



3

structures



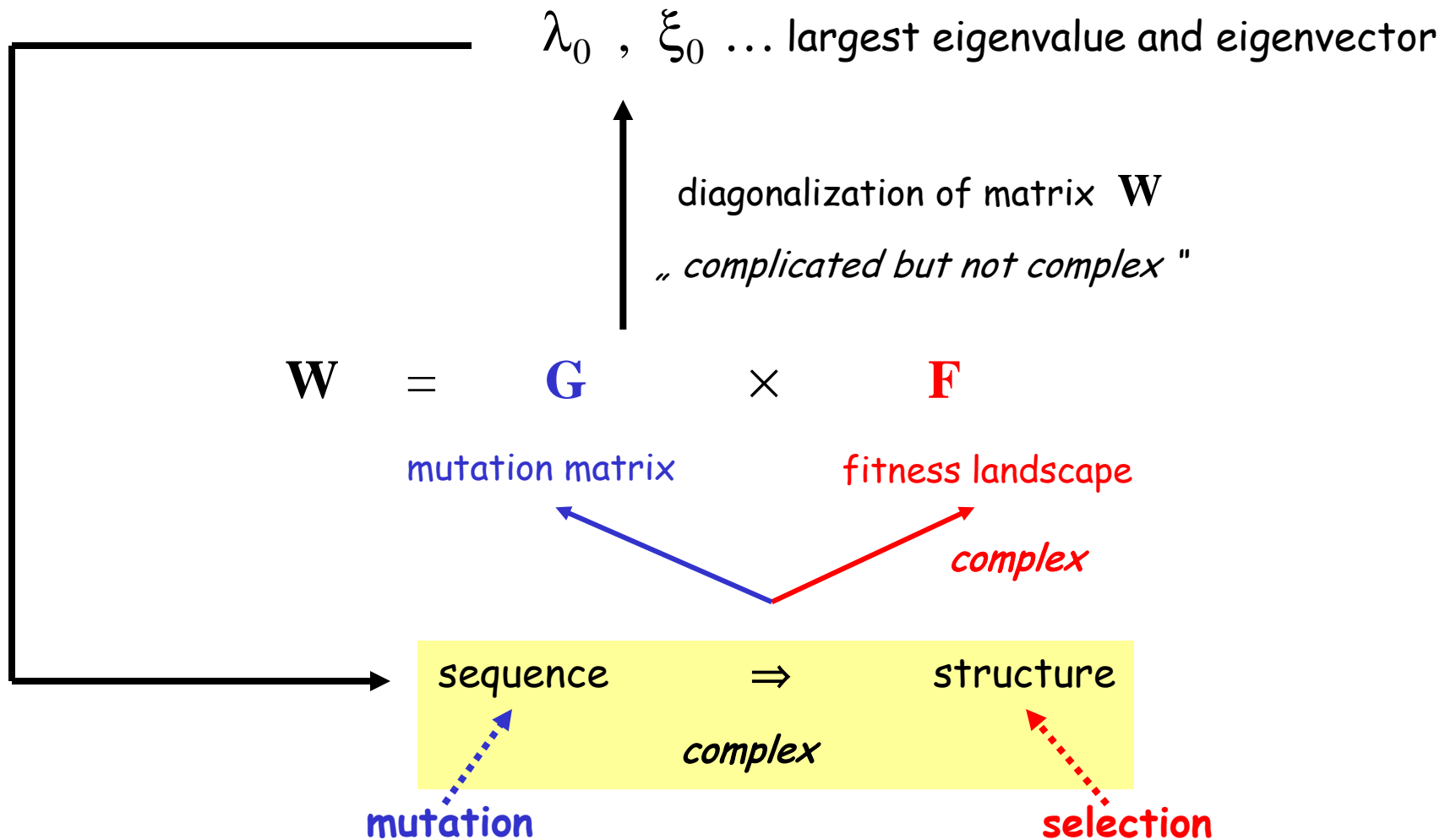
Sequence space

Structure space

many genotypes

⇒

one phenotype



Complexity in molecular evolution

Fitness landscapes became experimentally accessible!

Protein landscapes: Yuuki Hayashi, Takuyo Aita, Hitoshi Toyota, Yuzuru Husimi, Itaru Urabe, Tetsuya Yomo. 2006. Experimental rugged fitness landscape in protein sequence space. *PLoS One* 1:e96.

RNA landscapes: Sven Klussman, Ed. 2005. The aptamer handbook. Wiley-VCh, Weinheim (Bergstraße), DE.

Jason N. Pitt, Adrian Ferré-D'Amaré. 2010. Rapid construction of empirical RNA fitness landscapes. *Science* 330:376-379.

RNA viruses: Esteban Domingo, Colin R. Parrish, John J. Holland, Eds. 2007. Origin and evolution of viruses. Second edition. Elsevier, San Diego, CA.

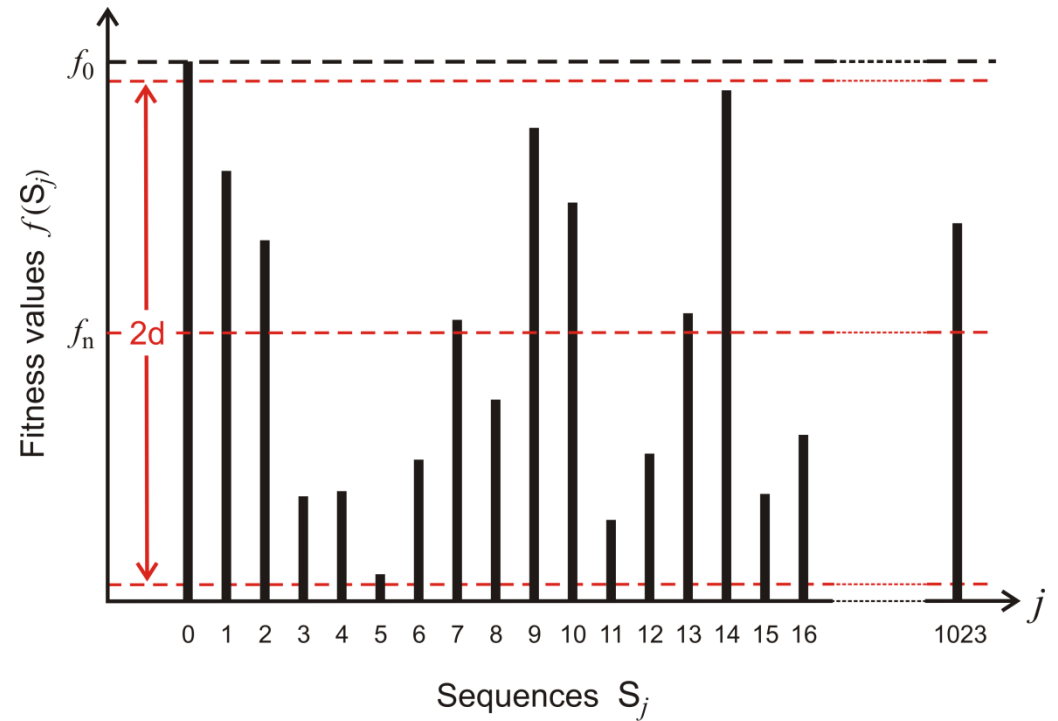
Retroviruses: Roger D. Kouyos, Gabriel E. Leventhal, Trevor Hinkley, Mojgan Haddad, Jeannette M. Whitcomb, Christos J. Petropoulos, Sebastian Bonhoeffer. 2012. Exploring the complexity of the HIV-I fitness landscape. *PLoS Genetics* 8:e1002551

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

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

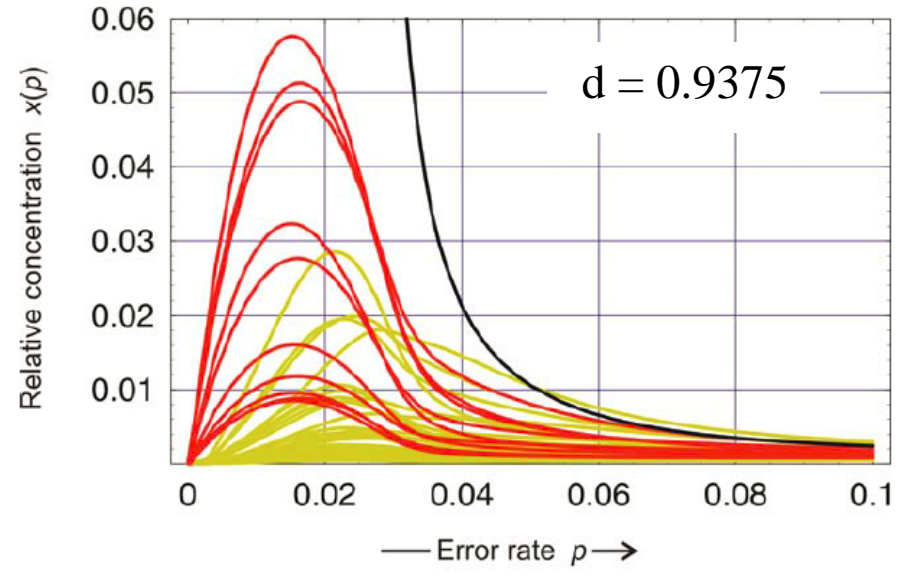
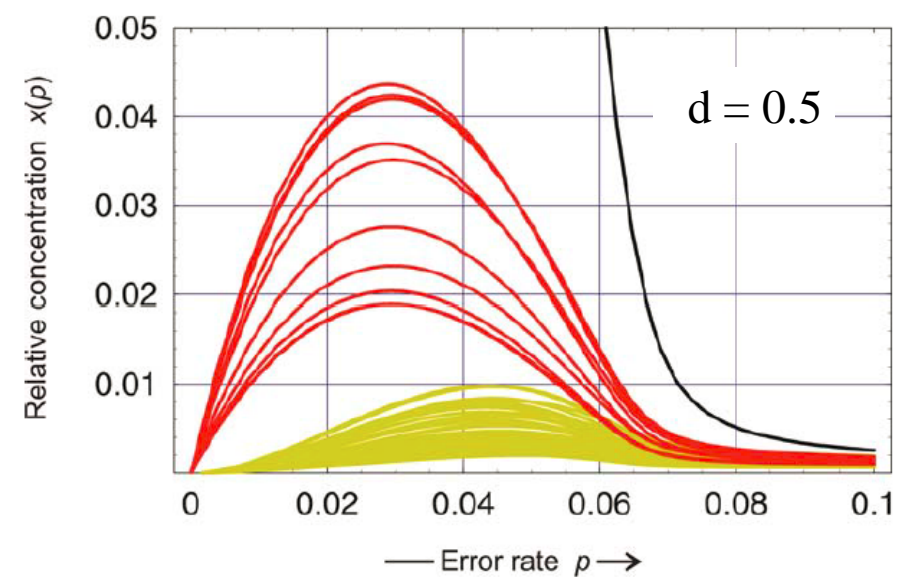
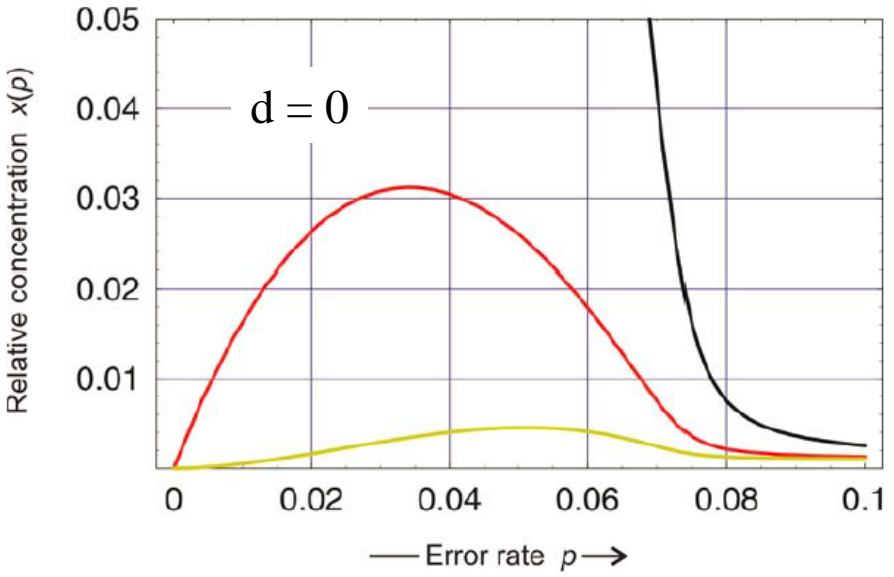
η ... random number

s ... seeds



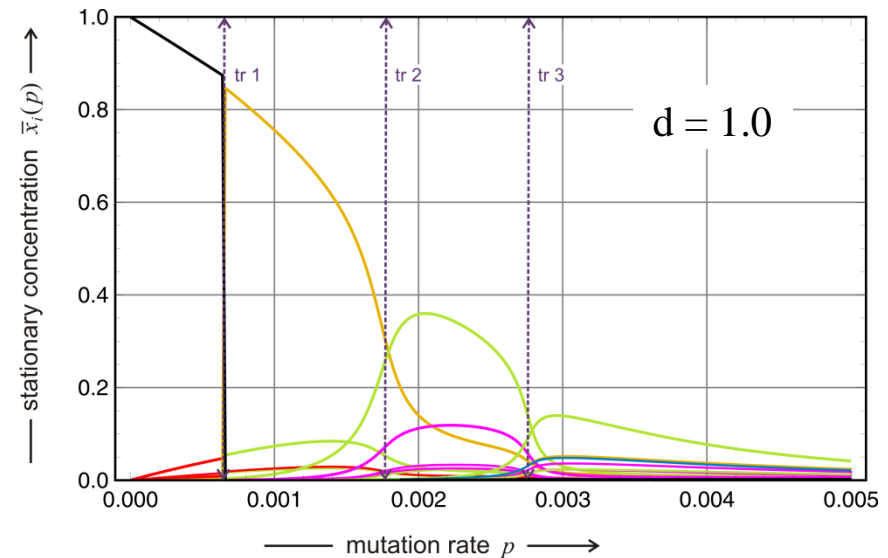
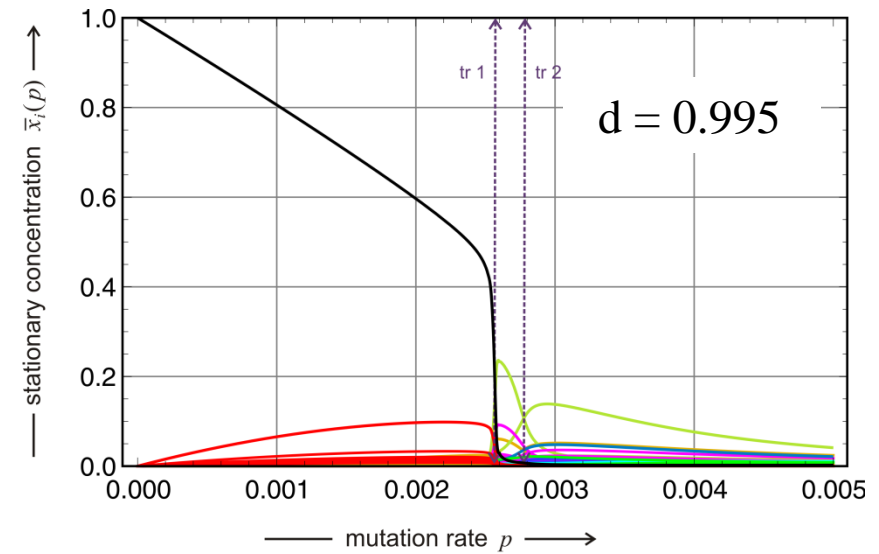
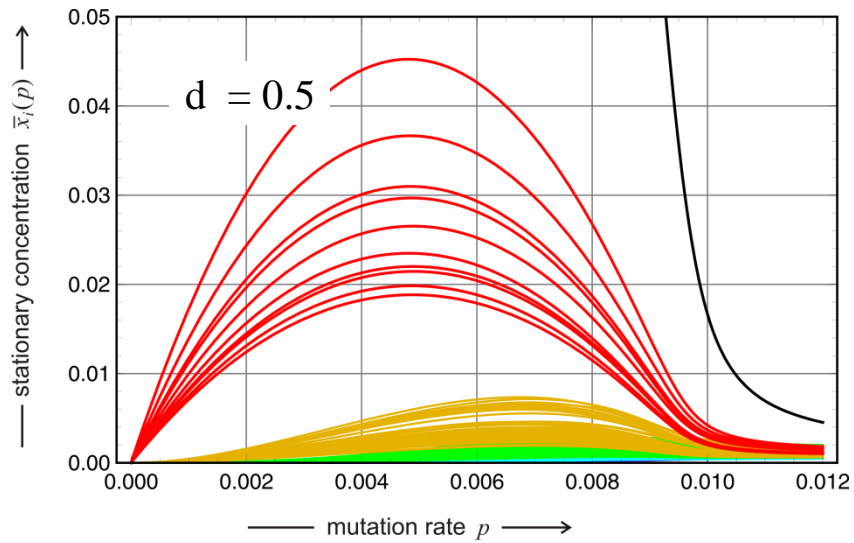
„realistic“ landscape

Rugged fitness landscapes over individual binary sequences with $n = 10$



Quasispecies with increasing random scatter d

Error threshold: Individual sequences
 $n = 10, \sigma = 2, s = 491$ and $d = 0, 0.5, 0.9375$

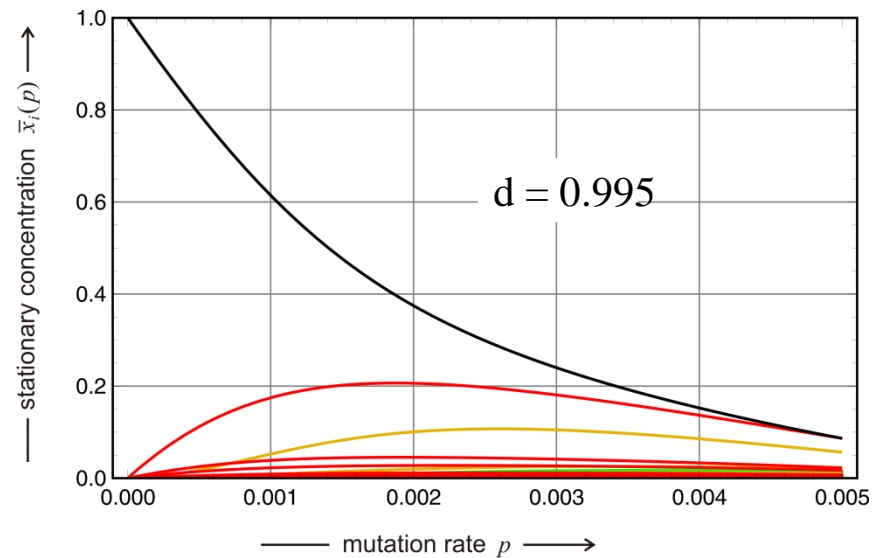
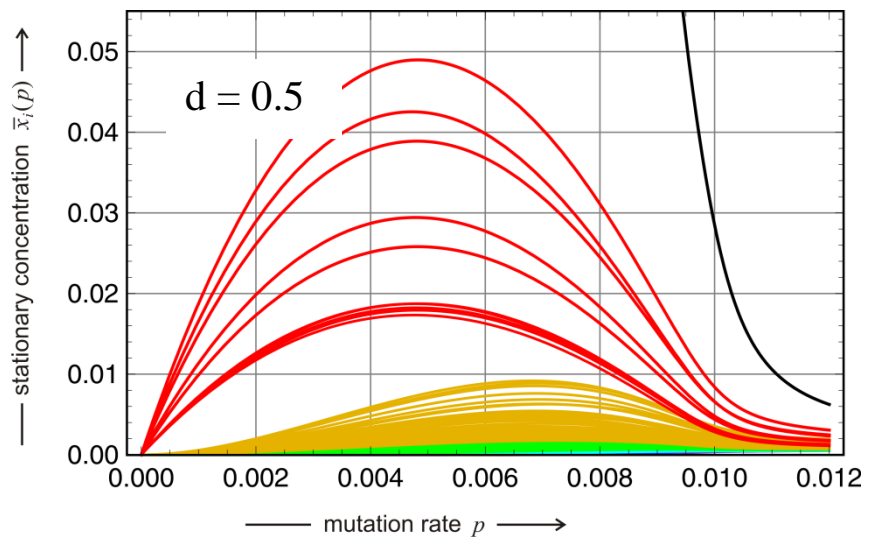


Choice of random scatter:

$$s = 637$$

Error threshold on ,realistic‘ landscapes

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

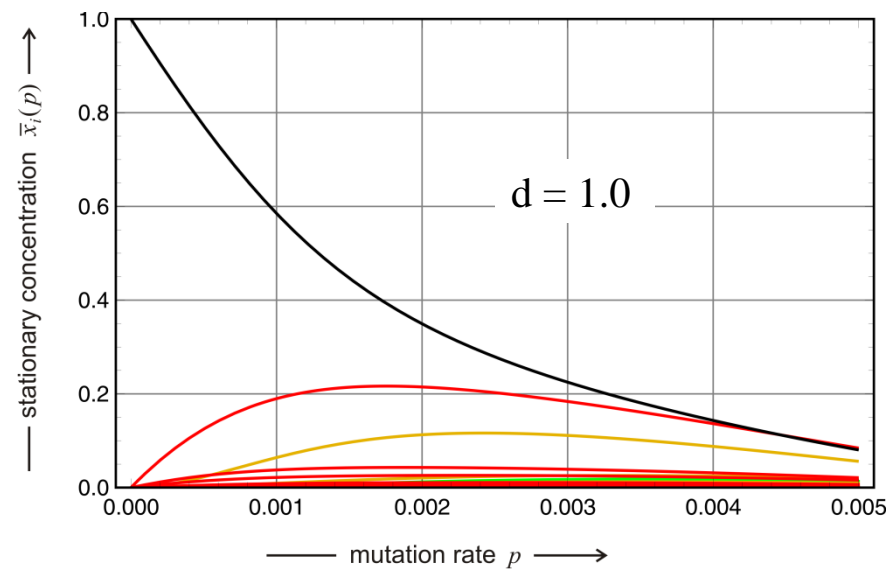


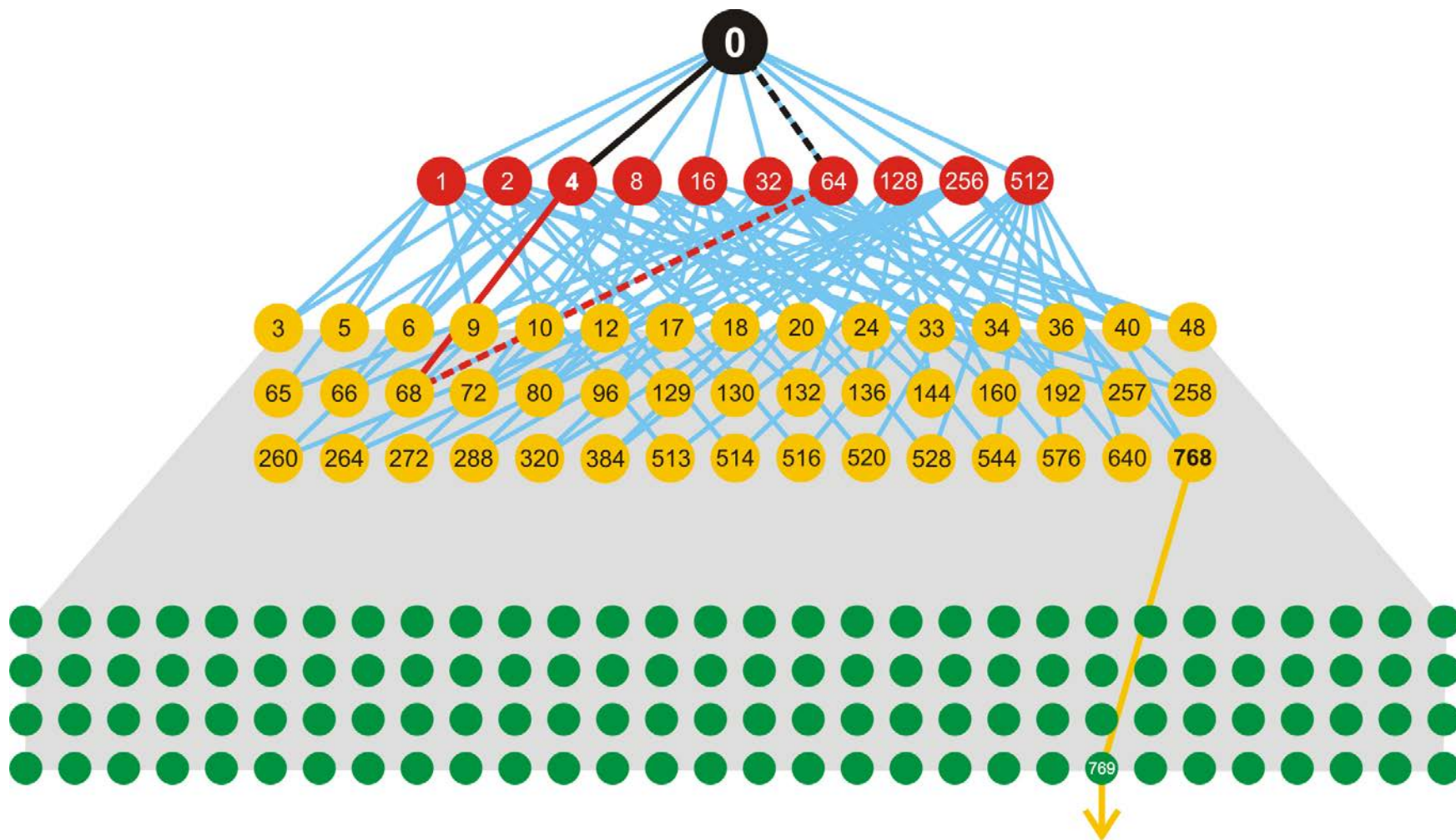
Choice of random scatter:

$$s = 919$$

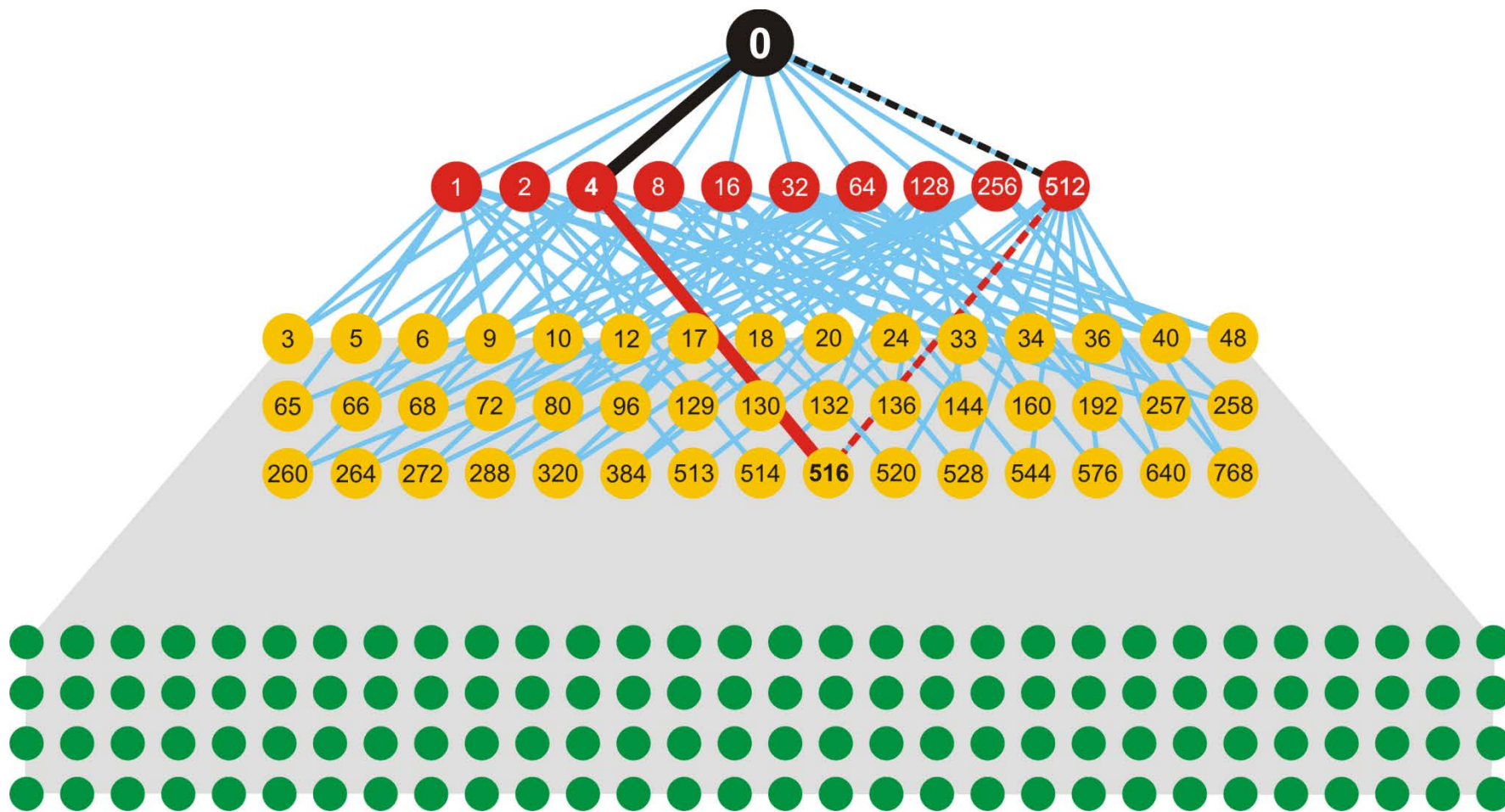
Error threshold on ,realistic‘ landscapes

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





Determination of the dominant mutation flow: $d = 1$, $s = 613$



Determination of the dominant mutation flow: $d = 1$, $s = 919$

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.

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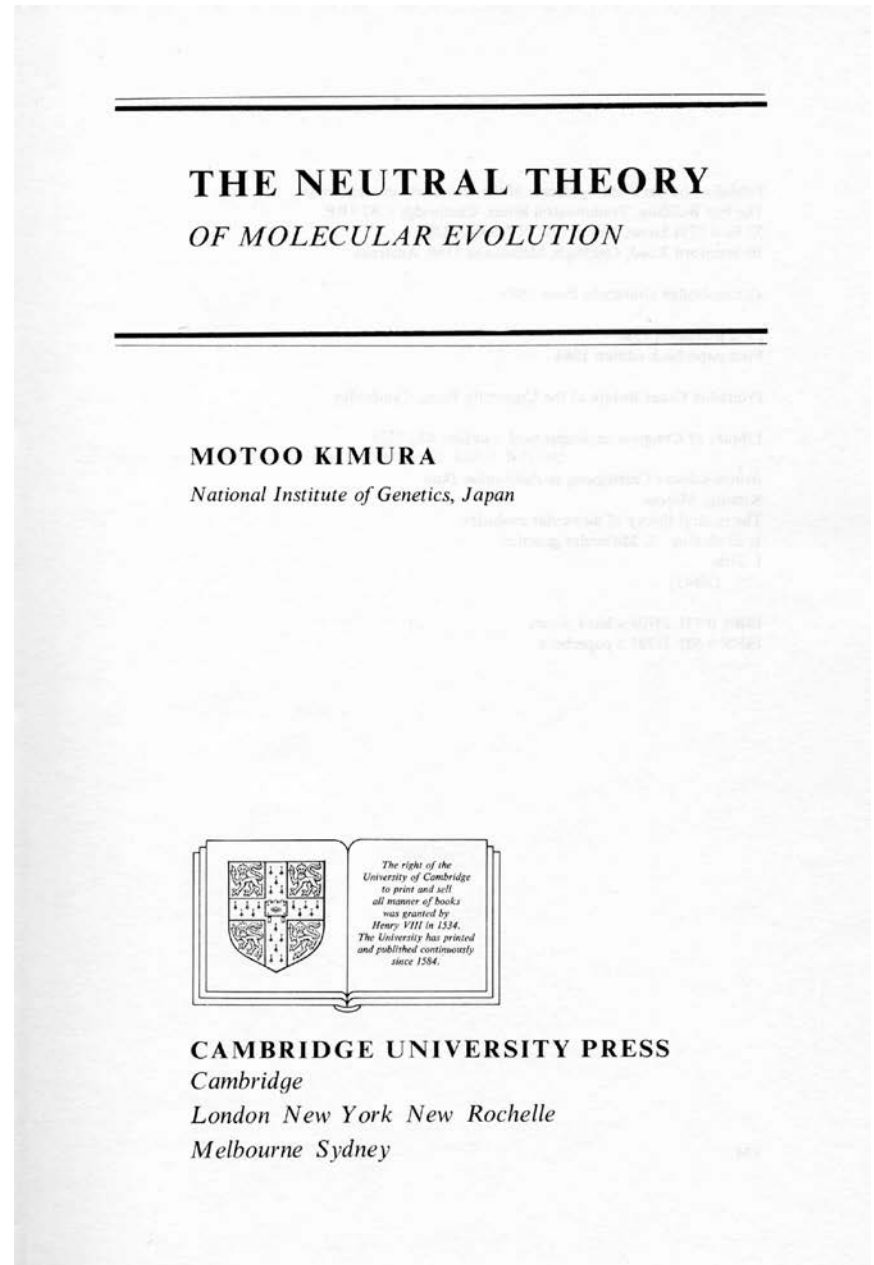


Motoo Kimura, 1924 - 1994

Motoo Kimura's population genetics of neutral evolution.

Evolutionary rate at the molecular level.
Nature **217**: 624-626, 1955.

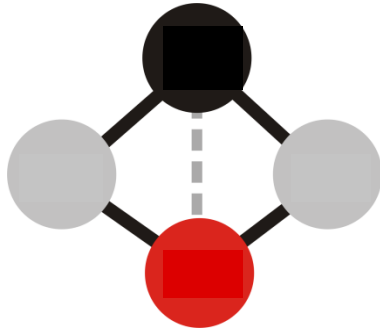
The Neutral Theory of Molecular Evolution.
Cambridge University Press. Cambridge,
UK, 1983.





$$d_H = 1$$

$$\lim_{p \rightarrow 0} x_1(p) = x_2(p) = 0.5$$



$$d_H = 2$$

$$\lim_{p \rightarrow 0} x_1(p) = \alpha / (1 + \alpha)$$

$$\lim_{p \rightarrow 0} x_2(p) = 1 / (1 + \alpha)$$

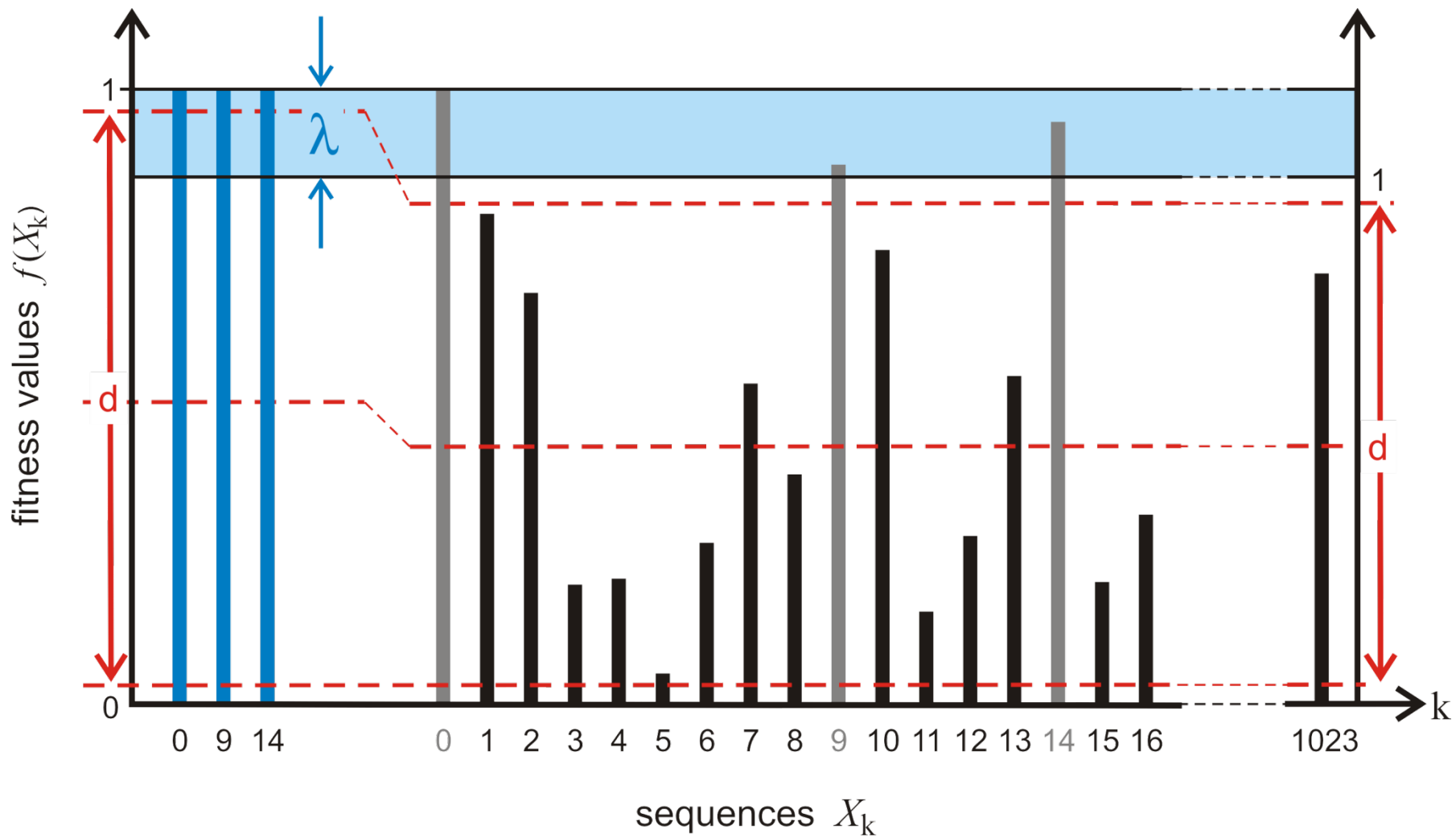
$$d_H \geq 3$$

$$\lim_{p \rightarrow 0} x_1(p) = 1, \lim_{p \rightarrow 0} x_2(p) = 0 \text{ or}$$

$$\lim_{p \rightarrow 0} x_1(p) = 0, \lim_{p \rightarrow 0} x_2(p) = 1$$

Pairs of neutral sequences in replication networks

Random fixation in the sense of Motoo Kimura

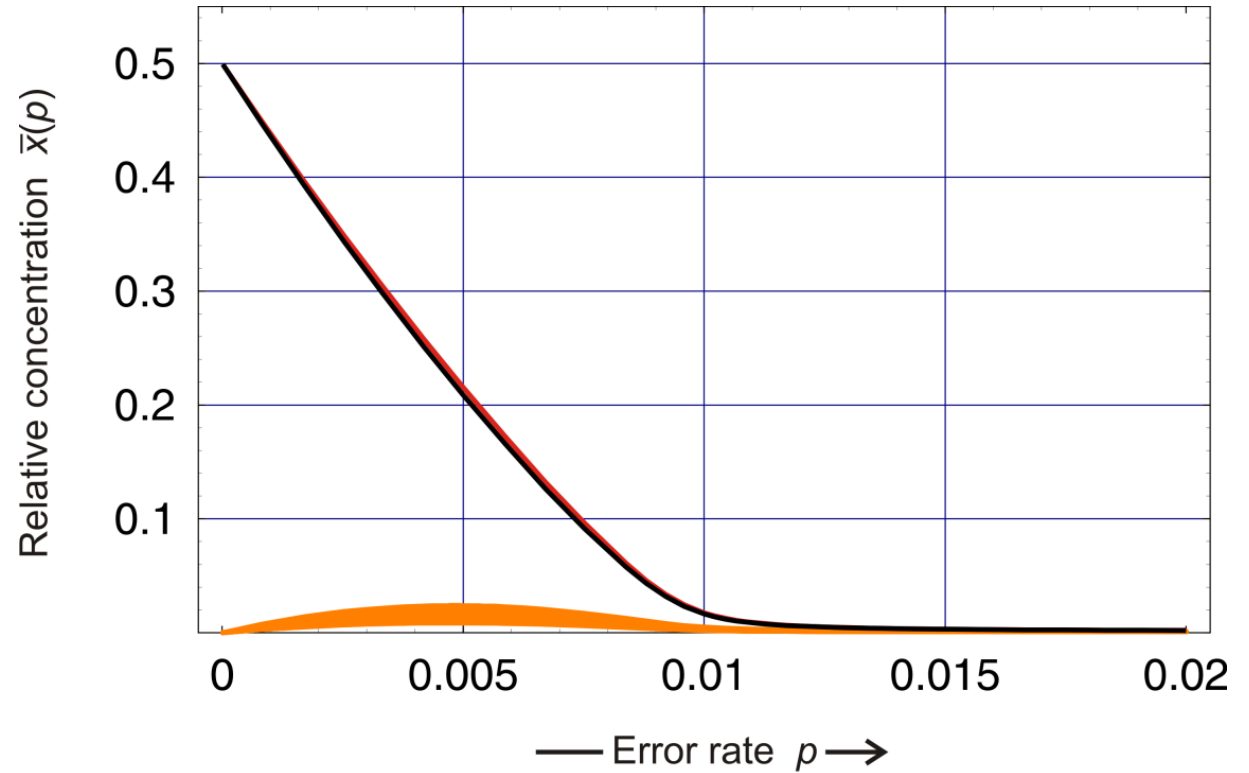


A fitness landscape including neutrality



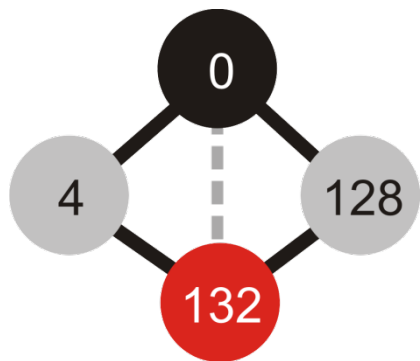
neutral network

$\lambda = 0.01$, $s = 367$



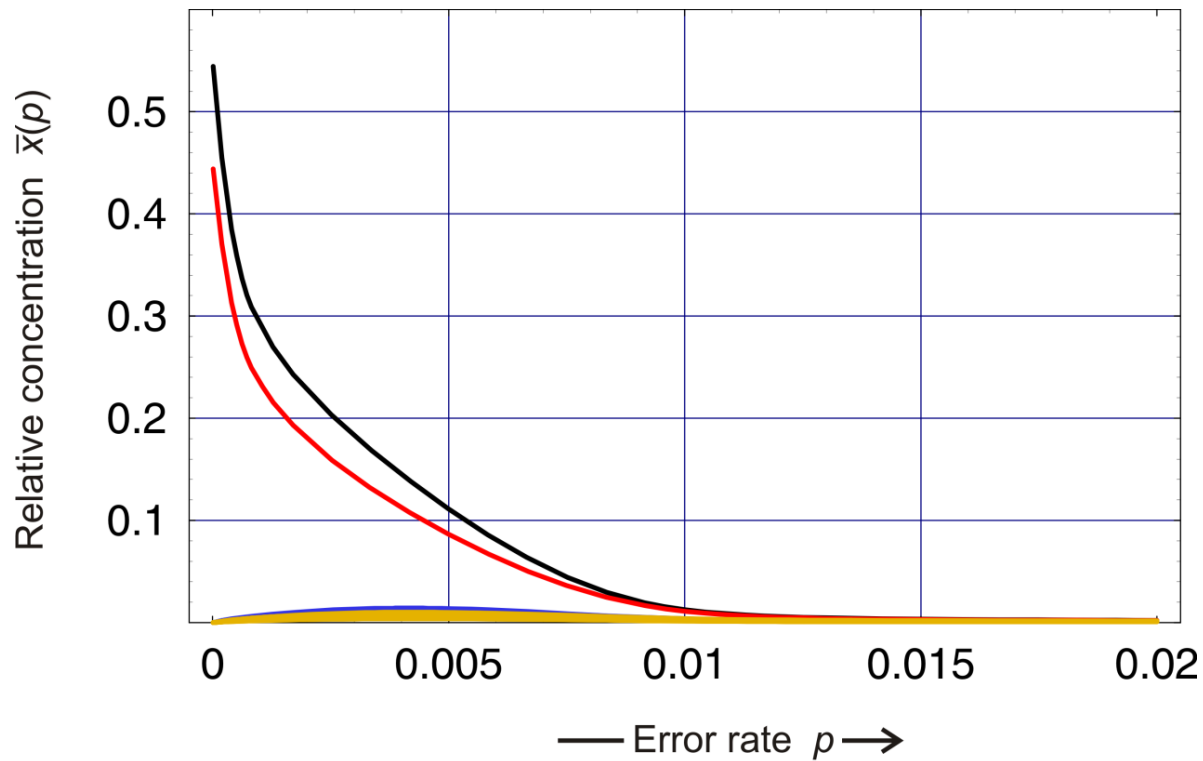
Neutral network: Individual sequences

$n = 10$, $\sigma = 1.1$, $d = 1.0$



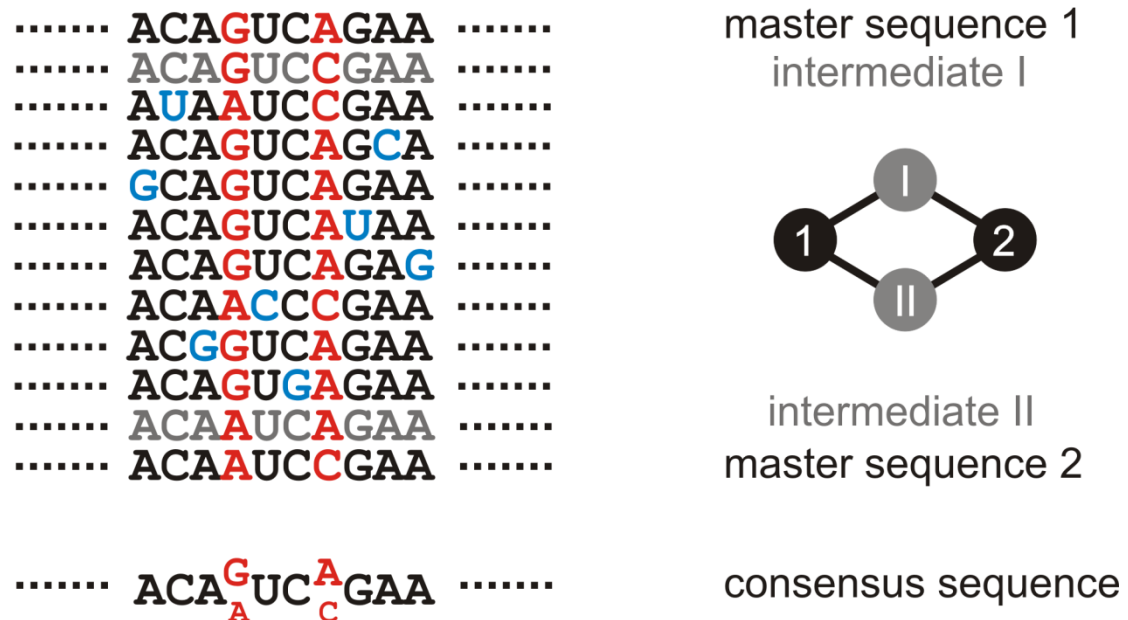
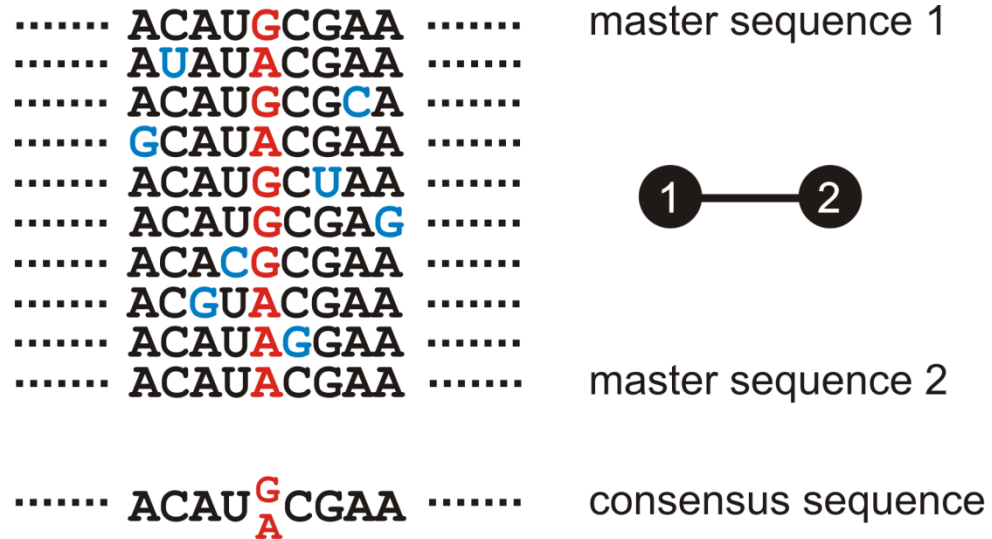
neutral network

$\lambda = 0.01, s = 877$

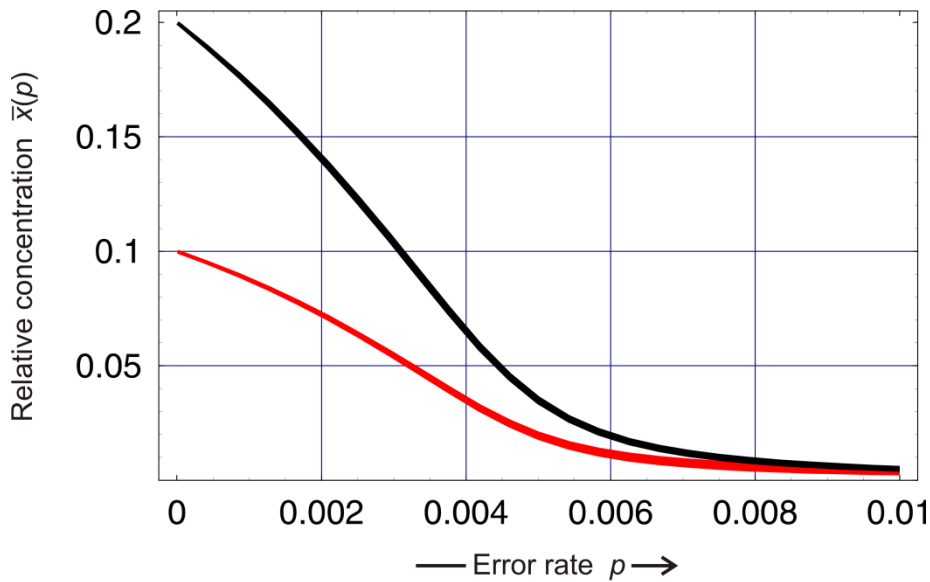


Neutral network: Individual sequences

$n = 10, \sigma = 1.1, d = 1.0$



Consensus sequences of a quasispecies of two strongly coupled sequences of Hamming distance $d_H(X_i, X_j) = 1$ and 2.



Perturbation matrix W

$$W = \begin{pmatrix} f & 0 & \varepsilon & 0 & 0 & 0 & 0 \\ 0 & f & \varepsilon & 0 & 0 & 0 & 0 \\ \varepsilon & \varepsilon & f & \varepsilon & 0 & 0 & 0 \\ 0 & 0 & \varepsilon & f & \varepsilon & 0 & 0 \\ 0 & 0 & 0 & \varepsilon & f & \varepsilon & \varepsilon \\ 0 & 0 & 0 & 0 & \varepsilon & f & 0 \\ 0 & 0 & 0 & 0 & \varepsilon & 0 & f \end{pmatrix}$$

Eigenvalues of W

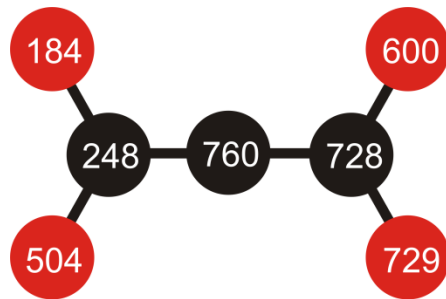
$$\lambda_0 = f + 2\varepsilon,$$

$$\lambda_1 = f + \sqrt{2}\varepsilon,$$

$$\lambda_{2,3,4} = f,$$

$$\lambda_5 = f - \sqrt{2}\varepsilon,$$

$$\lambda_6 = f - 2\varepsilon.$$



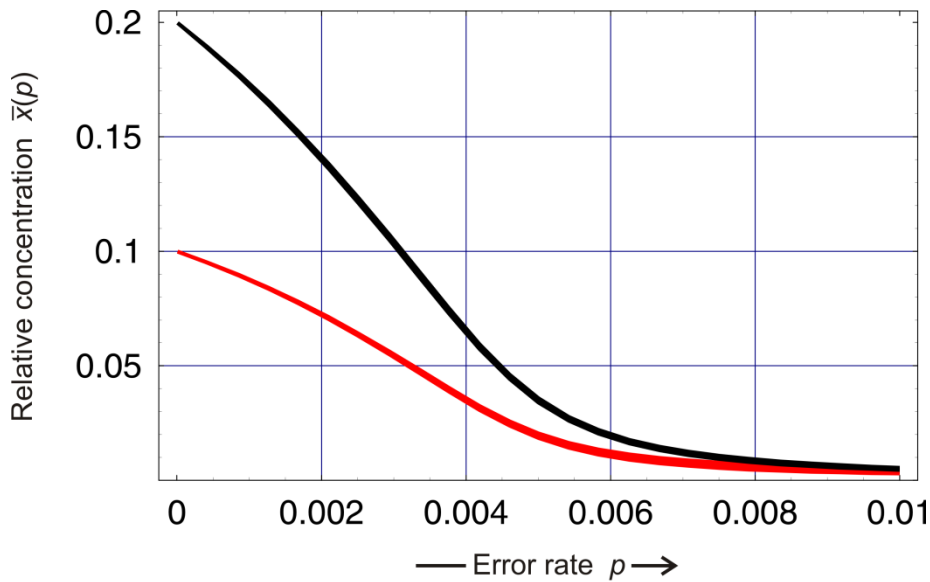
Neutral network

$$\lambda = 0.10, s = 229$$

Largest eigenvector of W

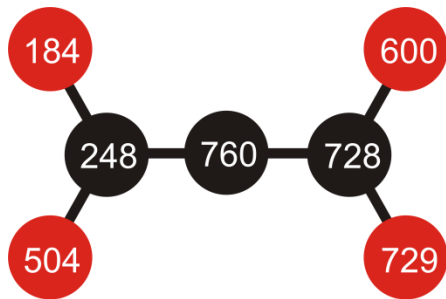
$$\xi_0 = (0.1, 0.1, 0.2, 0.2, 0.2, 0.1, 0.1).$$

Neutral networks with increasing λ : $\lambda = 0.10, s = 229$



Perturbation matrix W

$$W = \begin{pmatrix} f & 0 & \varepsilon & 0 & 0 & 0 & 0 \\ 0 & f & \varepsilon & 0 & 0 & 0 & 0 \\ \varepsilon & \varepsilon & f & \varepsilon & 0 & 0 & 0 \\ 0 & 0 & \varepsilon & f & \varepsilon & 0 & 0 \\ 0 & 0 & 0 & \varepsilon & f & \varepsilon & \varepsilon \\ 0 & 0 & 0 & 0 & \varepsilon & f & 0 \\ 0 & 0 & 0 & 0 & \varepsilon & 0 & f \end{pmatrix}$$



Neutral network

$$\lambda = 0.10, s = 229$$

Adjacency matrix

Largest eigenvector of W

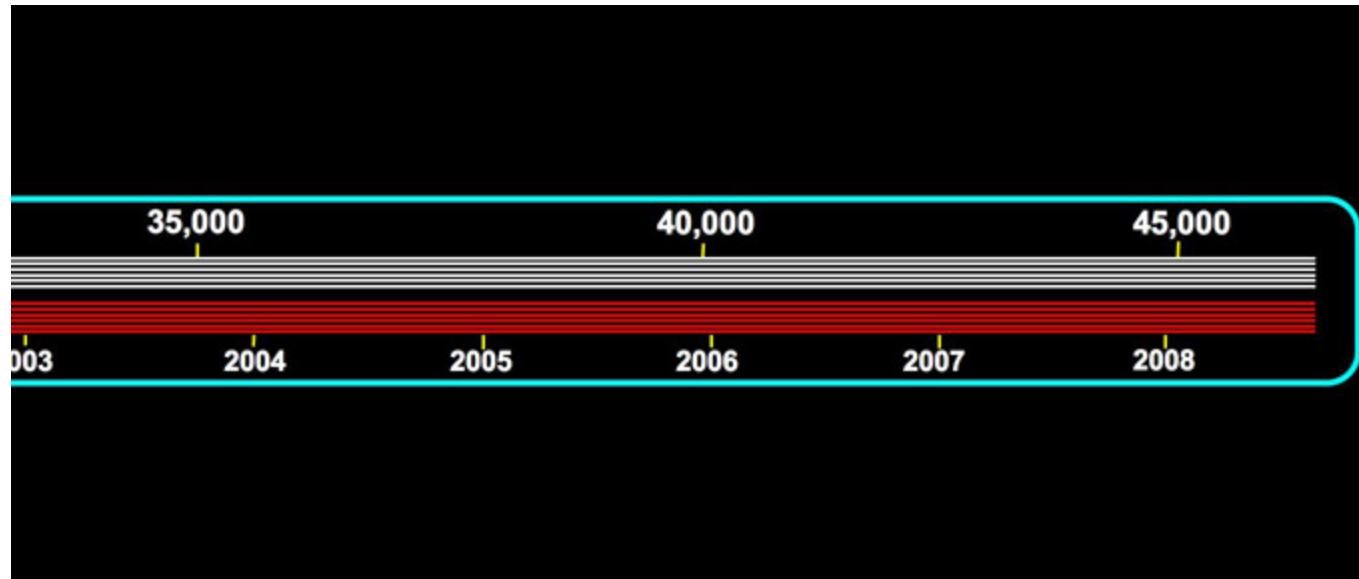
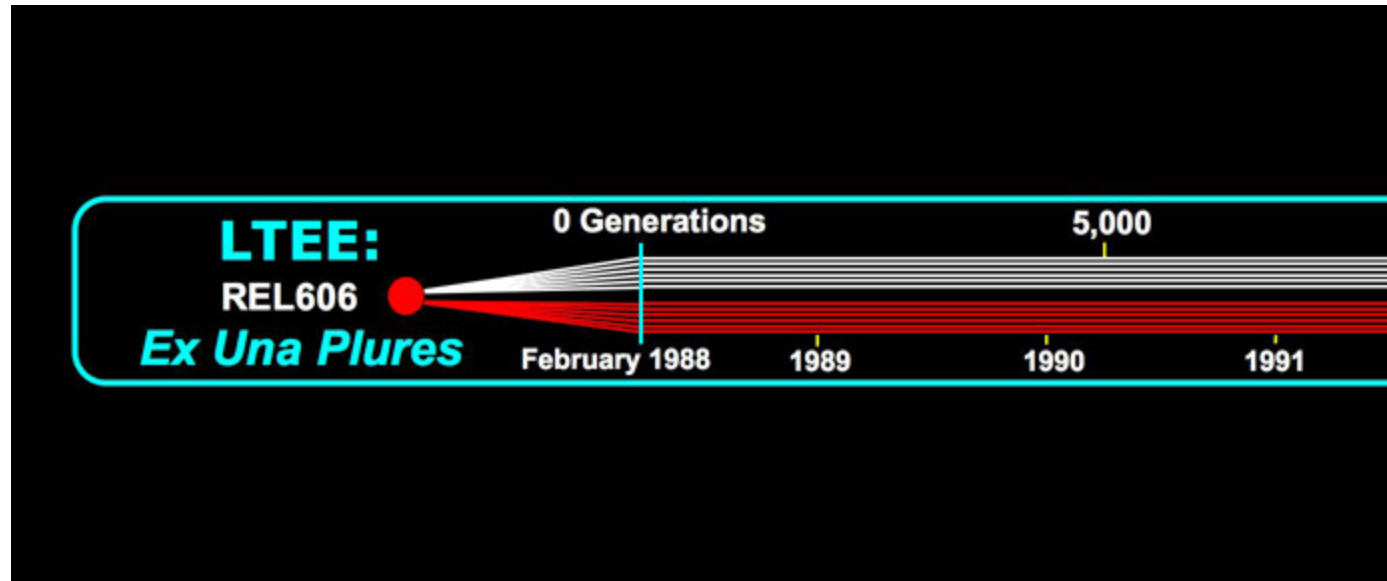
$$\xi_0 = (0.1, 0.1, 0.2, 0.2, 0.2, 0.1, 0.1)$$

Neutral networks with increasing λ : $\lambda = 0.10, s = 229$

1. Prologue
2. Landscapes and evolutionary dynamics
3. Realistic landscapes and mutant clans
4. Neutrality in evolutionary dynamics
5. **Concluding remarks and perspectives**

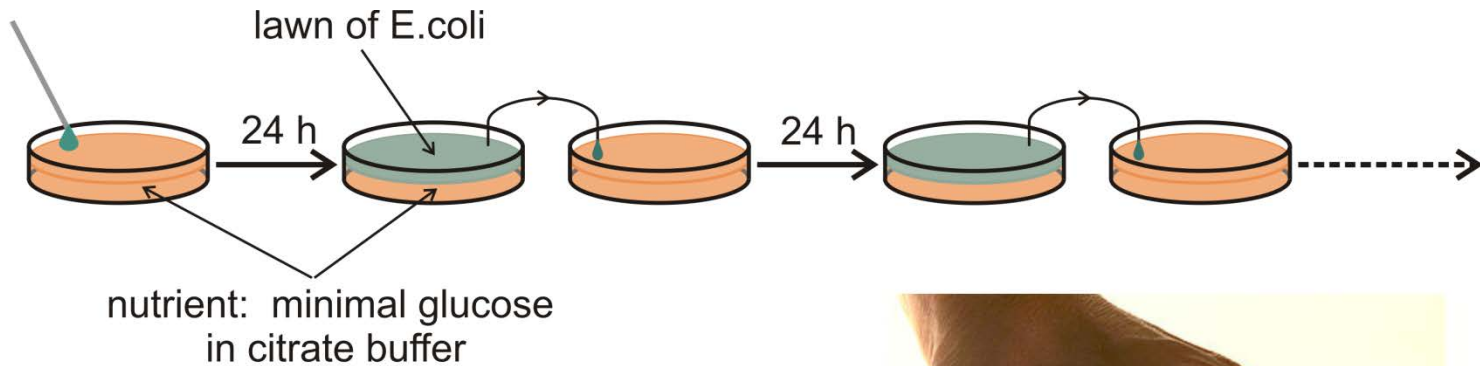


Richard Lenski, 1956 -



Bacterial evolution under controlled conditions: A twenty years experiment.

Richard Lenski, University of Michigan, East Lansing



medium supports $\approx 5 \times 10^8$ bacteria

1 day ≈ 6.67 generations

1 month ≈ 200 generations

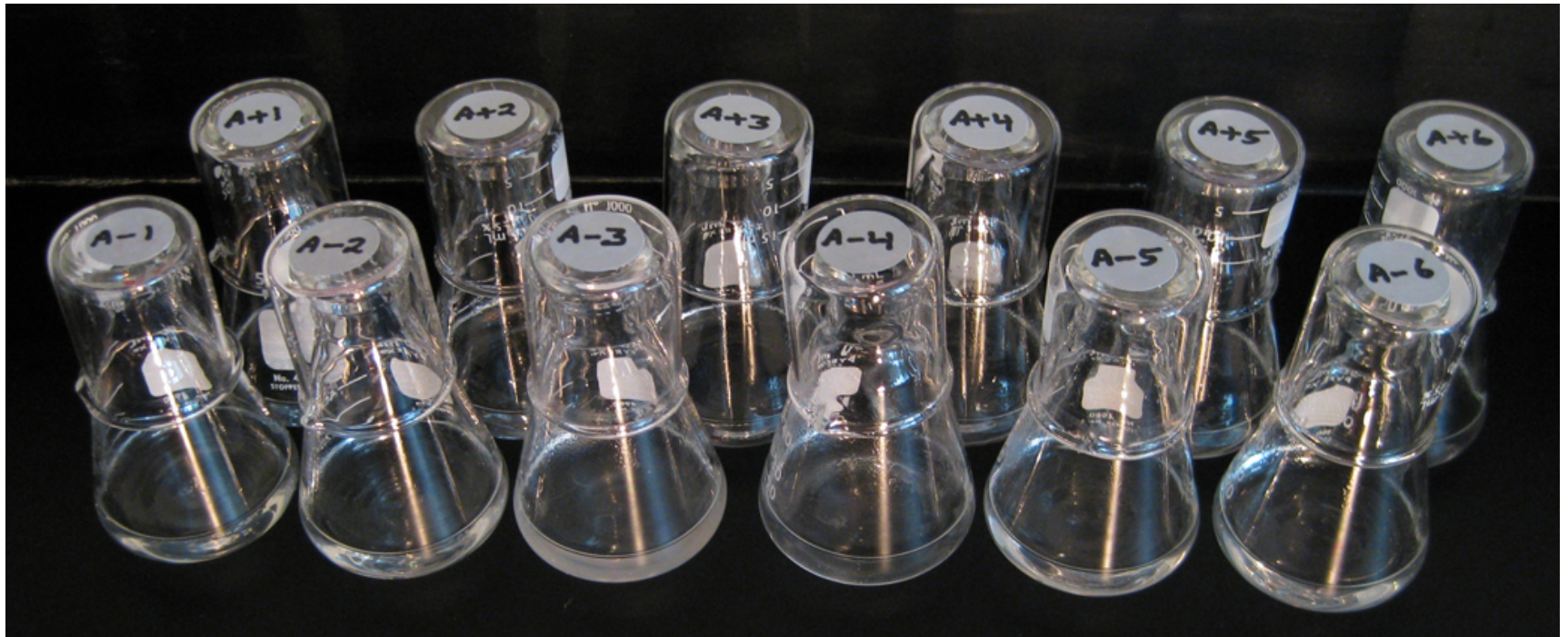
1 year ≈ 2400 generations

Serial transfer of bacterial cultures in Petri dishes



Bacterial evolution under controlled conditions: A twenty years experiment.

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The twelve populations of Richard Lenski's long time evolution experiment

Perspectives of molecular evolution

1. Populations with high and low mutation rates are described within the same model based on the quasispecies concept.
2. Accurate predictions on *in vitro* evolution and virus evolution can be made wherever fitness parameters are available.
3. The modeling approach can be extended in qualitative terms to other prokaryotic and eukaryotic populations provided enough data are available.
4. The mechanism of reproduction can be extended to more complex mechanisms like sexual reproduction and reproduction including epigenetic effects.

Acknowledgement of support

Fonds zur Förderung der wissenschaftlichen Forschung (FWF)
Projects No. 09942, 10578, 11065, 13093
13887, and 14898

Wiener Wissenschafts-, Forschungs- und Technologiefonds (WWTF)
Project No. Mat05

Jubiläumsfonds der Österreichischen Nationalbank
Project No. Nat-7813

European Commission: Contracts No. 98-0189, 12835 (NEST)

Austrian Genome Research Program – GEN-AU: Bioinformatics
Network (BIN)

Österreichische Akademie der Wissenschaften

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