Happy birthday Manuel !

Good health, enjoy science

and

ad multos annos !

Present Day Biology Seen in the Looking Glass of the Physics of Complex Systems

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„A Week of Science“ at Instituto Pluridisciplinar, UCM

In honor of Manuel G. Velarde

Madrid, 15.09.2011

Web-Page for further information:

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

Nothing in biology makes sense
except in the light of evolution.

Theodosius Dobzhansky. 1973.
Am.Biol.Teach. **35**:125-129.

1. Darwin and evolutionary optimization
2. Evolution as an exercise in chemical kinetics
3. Sequences and structures in biopolymers
4. Evolution on simple model landscapes
5. Evolution on realistic landscapes
6. Neutrality in evolution
7. Perspectives

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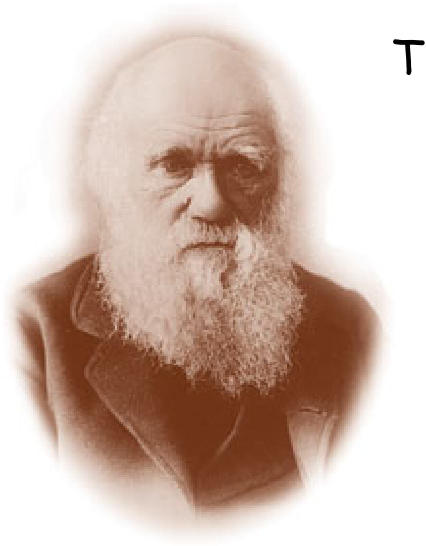


Three necessary conditions for Darwinian evolution are:

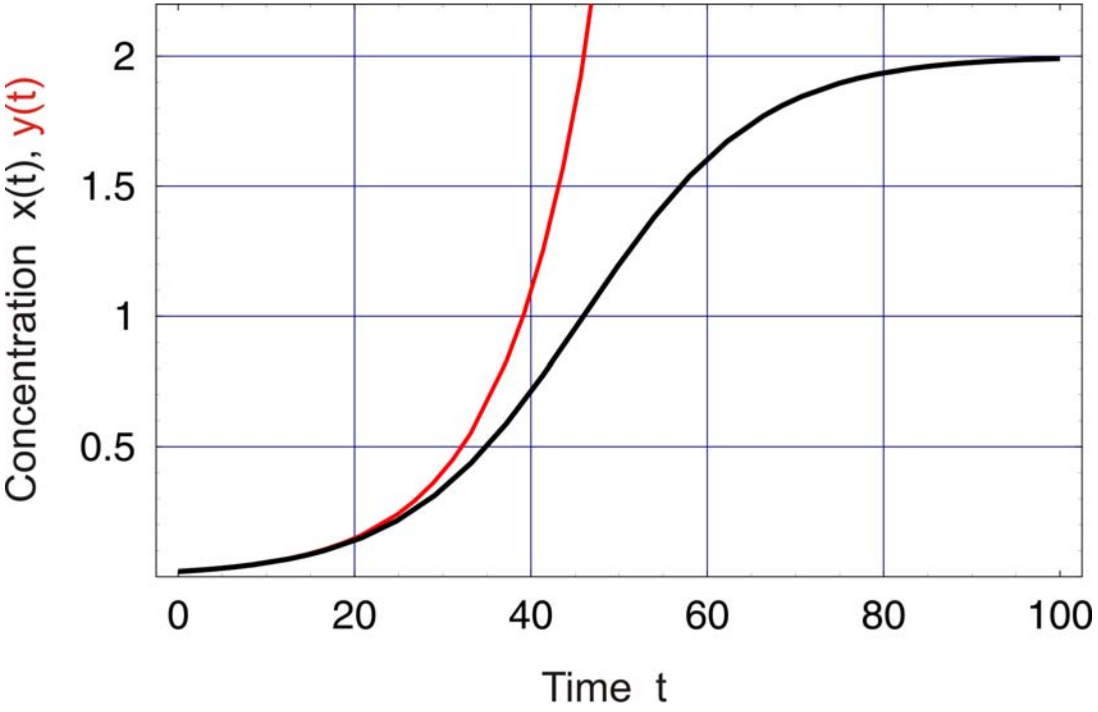
1. **Multiplication,**
2. **Variation**, and
3. **Selection**.

Biologists distinguish the **genotype** – the genetic information – and the **phenotype** – the organisms and all its properties. The **genotype** is unfolded in development and yields the **phenotype**.

Variation operates on the **genotype** – through mutation and recombination – whereas the **phenotype** is the target of **selection**. Without human intervention **natural selection** is based on the number of fertile progeny in forthcoming generations that is called **fitness**.

Pierre-François Verhulst,
1804-1849

$$\frac{dx}{dt} = r\,x\left(1-\frac{x}{C}\right), \quad x(t) = \frac{x(0)\,C}{x(0)+\big(C-x(0)\big)e^{-rt}}$$



The logistic equation, 1828

$$\frac{dx}{dt} = r\,x\left(1-\frac{x}{C}\right) \quad \Longrightarrow \quad \frac{dx}{dt} = r\,x - \frac{x}{C}\,r\,x$$

$$\Phi(t) \equiv r\,x\,,\; C=1: \quad \frac{dx}{dt} = x\,(r - \Phi)$$

Population: $\mathsf{X}_1, \mathsf{X}_2, \ldots \mathsf{X}_N\,;\ [\mathsf{X}_i] = x_i$

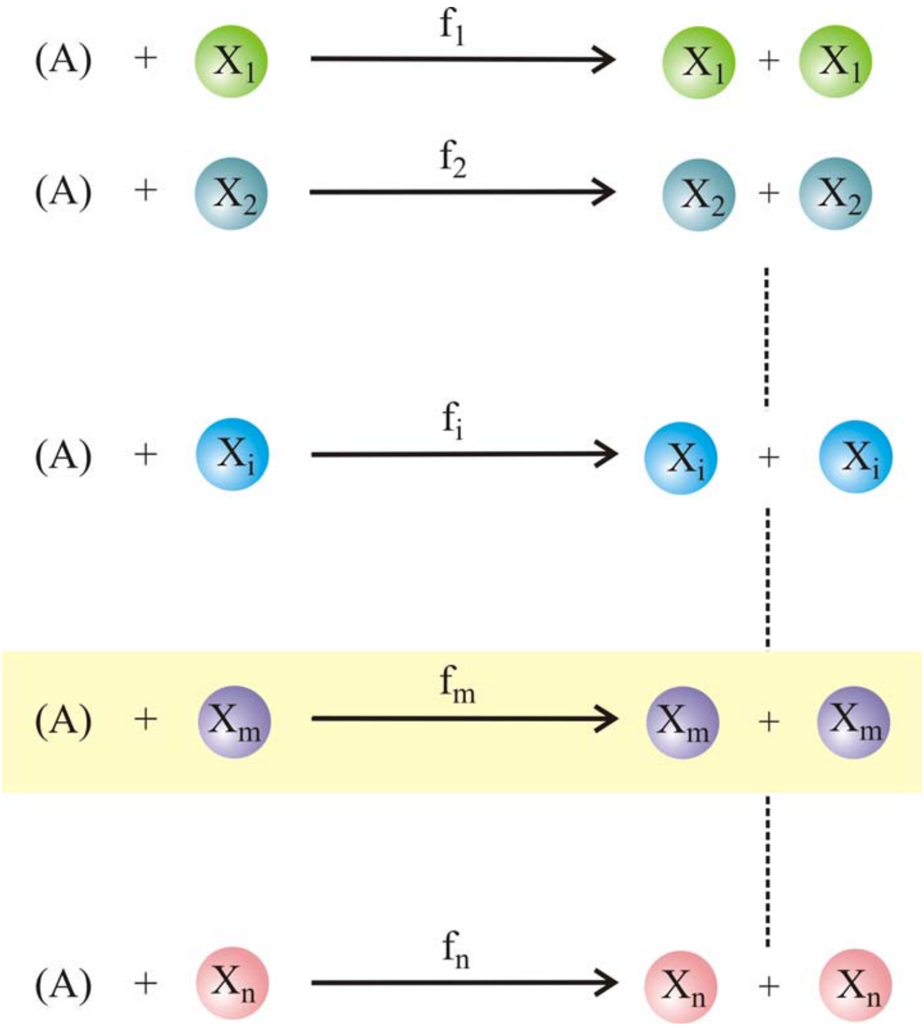
Stationary population: $\sum_{i=1}^{N} x_i = C = 1$

$$\frac{\mathrm{d}x_j}{\mathrm{dt}} = x_j\left(f_j - \sum_{i=1}^{n} f_i\,x_i\right) = x_j\left(f_j - \Phi\right)\,; \quad \Phi = \sum_{i=1}^{n} f_i\,x_i$$

Darwin

$$\frac{\mathrm{d}\Phi}{\mathrm{dt}} = 2\left(< f^{2} > - < \bar{f} >^{2}\right) = 2\ \mathrm{var}\,\{f\} \geq 0$$

Generalization of the logistic equation to *n* variables yields selection



$$x_j(t) = N_j(t) \Big/ \sum_{i=1}^{n} N_i(t)$$

$$f_m = \max\left\{f_j;\ j=1,2,\dots,n\right\}$$

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

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

Selection equation: $[\mathrm{X}_i] = x_i \geq 0\,,\; f_i \geq 0$

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

mean fitness or dilution flux, $\phi(\mathrm{t})$, is a **non-decreasing function** of time,

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

solutions are obtained by integrating factor transformation

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

The mean reproduction rate or mean fitness, $\phi(\mathrm{t})$, is optimized in populations.

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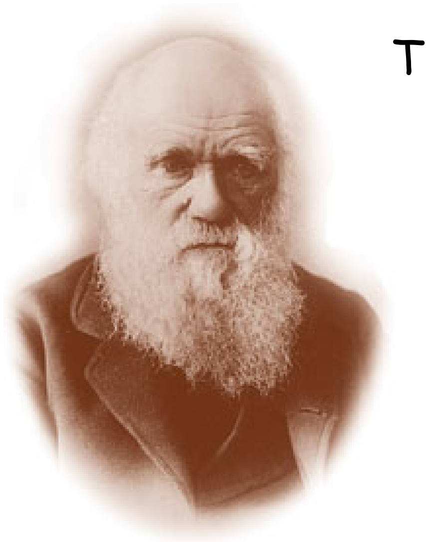


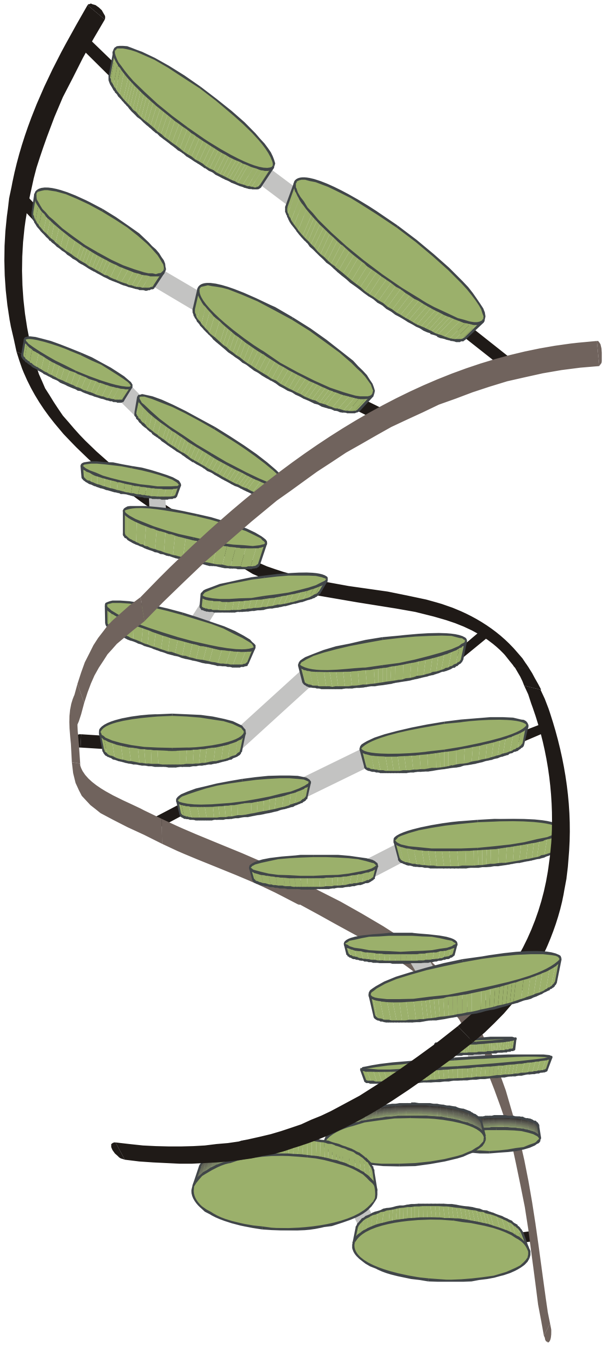
Charles Darwin, 1809-1882

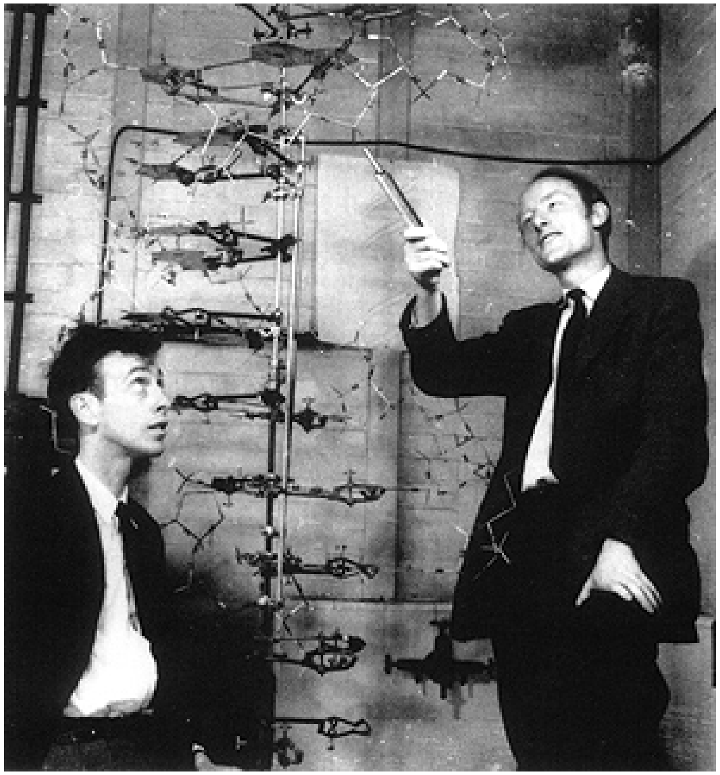
Three necessary conditions for Darwinian evolution are:

1. **Multiplication,**
2. **Variation**, and
3. **Selection.**

All three conditions are fulfilled not only by cellular organisms but also by **nucleic acid molecules** – **DNA** or **RNA** – **in** suitable **cell-free experimental assays**:

Darwinian evolution in the test tube



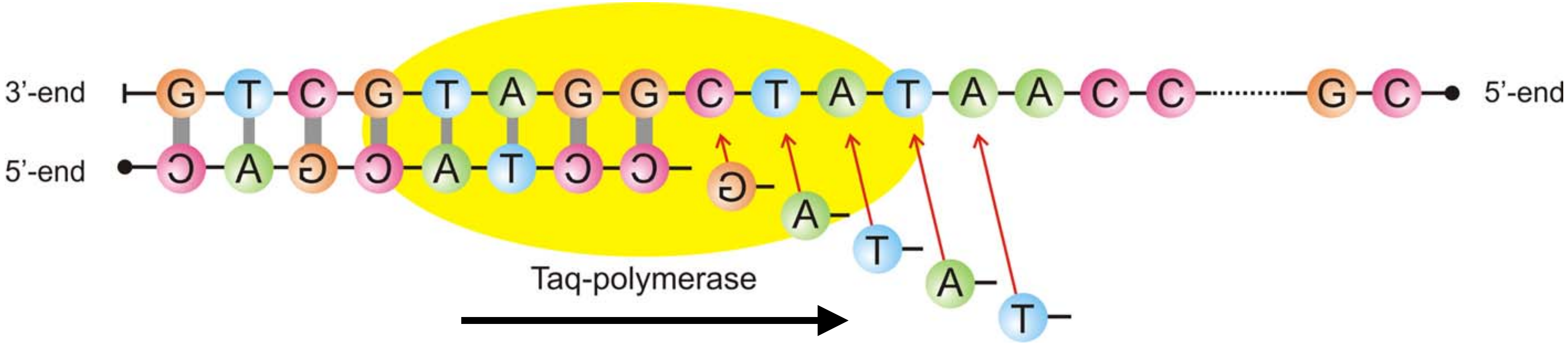


James D. Watson, 1928-, and Francis H.C. Crick, 1916-2004

Nobel prize 1962

1953 – 2003 fifty years double helix

The three-dimensional structure of a
short double helical stack of B-DNA

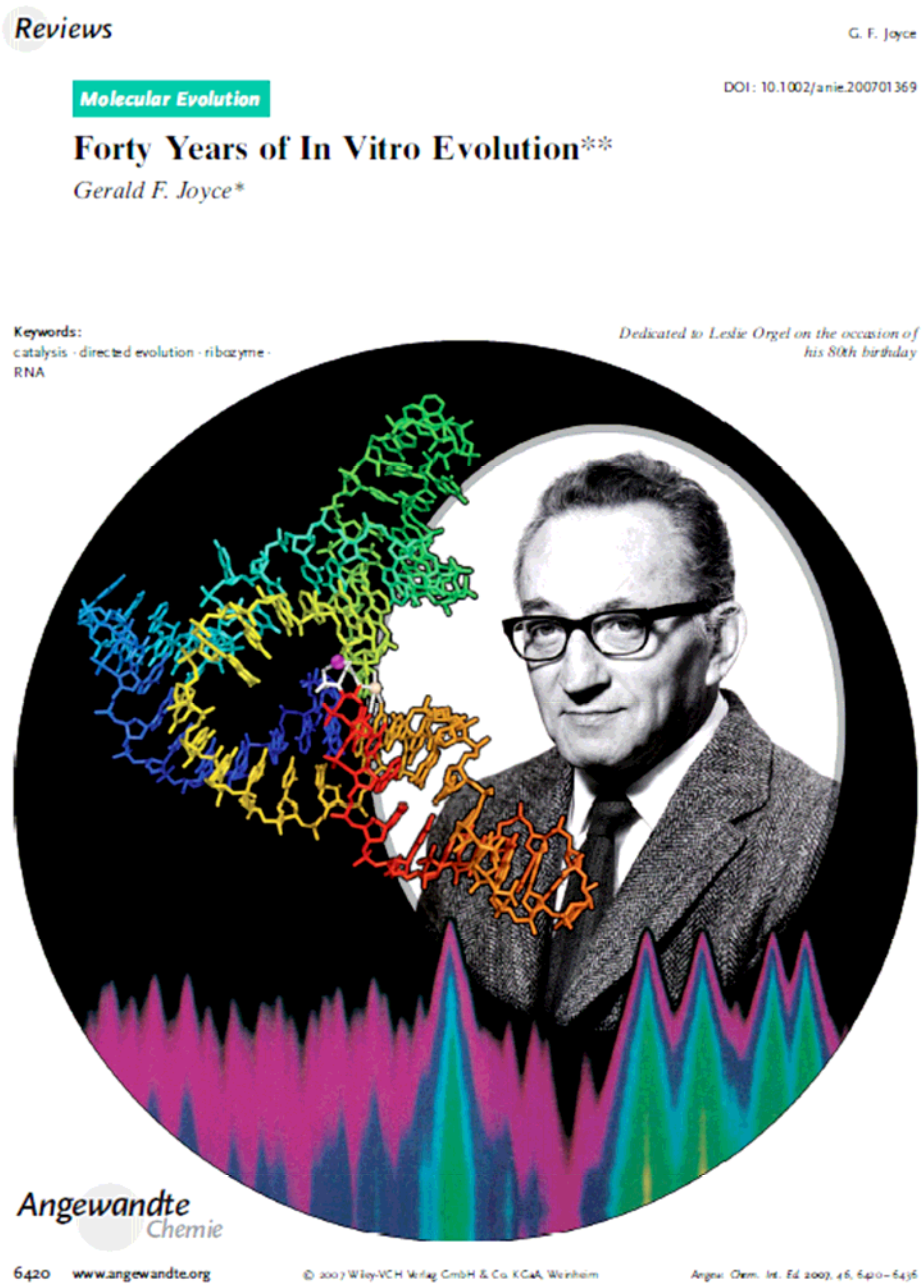


Accuracy of replication: $Q = q_1 \cdot q_2 \cdot q_3 \cdot \ldots \cdot q_n$

Template induced nucleic acid synthesis proceeds from 5'-end to 3'-end

Evolution in the test tube:

G.F. Joyce, *Angew.Chem.Int.Ed.* **46** (2007), 6420-6436



Reviews

G. F. Joyce

DOI: 10.1002/anie.200701369

Molecular Evolution

Forty Years of In Vitro Evolution**

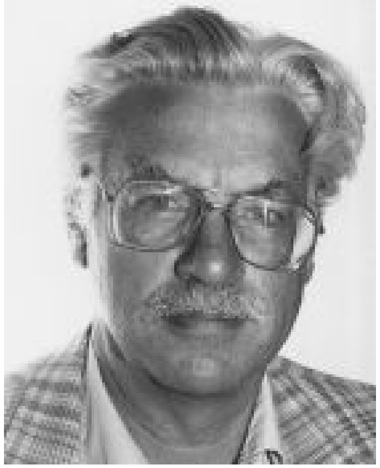
*Gerald F. Joyce**

Keywords:
catalysis · directed evolution · ribozyme · RNA

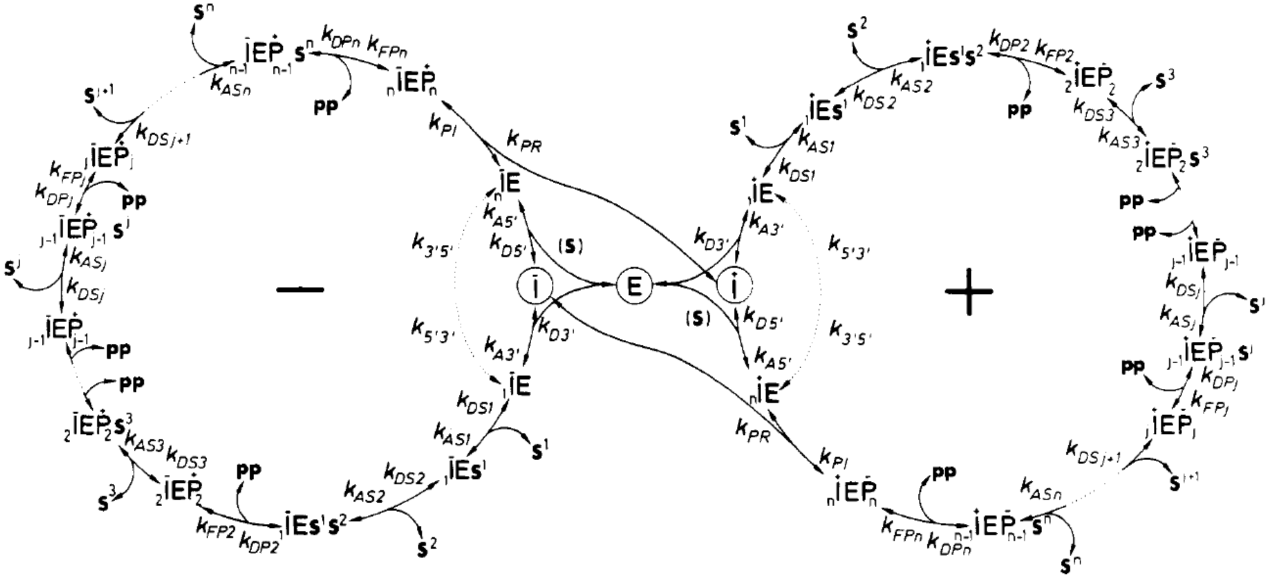
Dedicated to Leslie Orgel on the occasion of his 80th birthday

6420 www.angewandte.org

Angew. Chem. Int. Ed. 2007, 46, 6420 – 6436

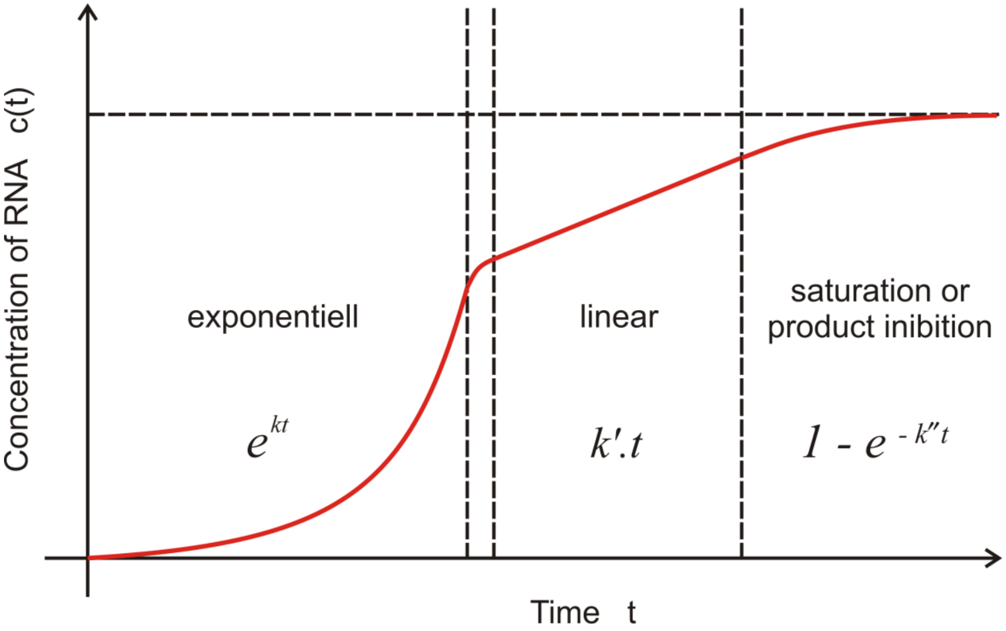


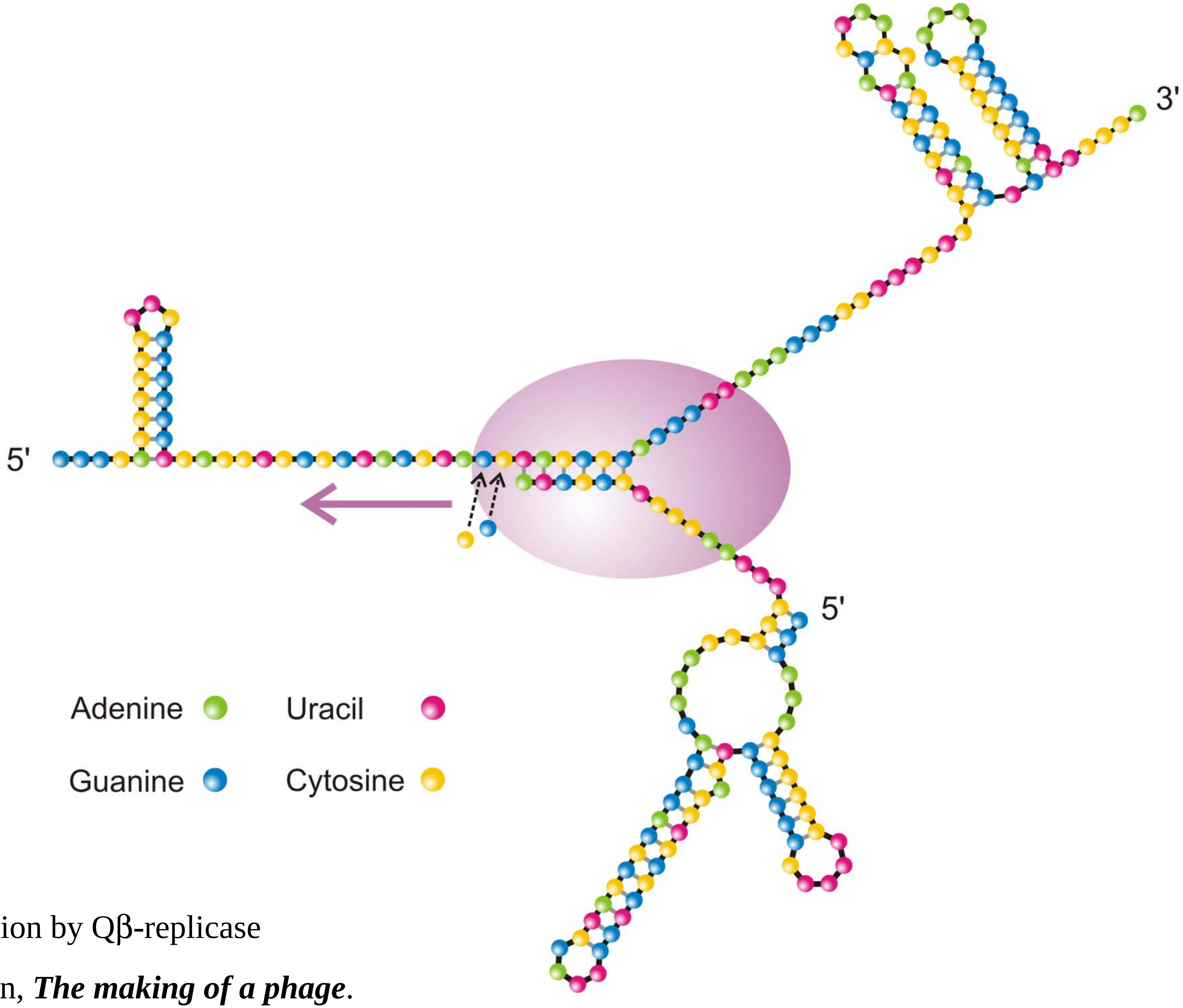
Christof K. Biebricher,
1941-2009



Kinetics of RNA replication

C.K. Biebricher, M. Eigen, W.C. Gardiner, Jr.
Biochemistry **22**:2544-2559, 1983





RNA replication by Qβ-replicase

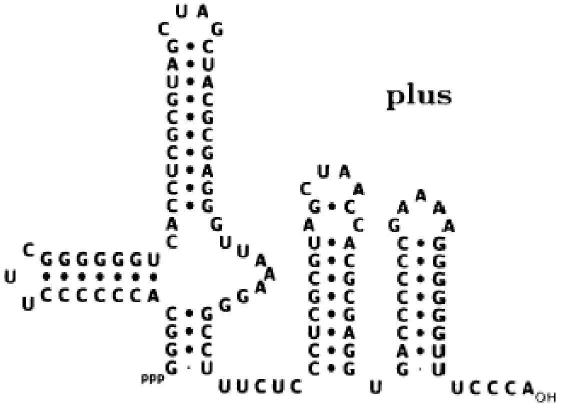
C. Weissmann, ***The making of a phage***.
FEBS Letters **40** (1974), S10-S18

plus SV-11 (115 b)

minus

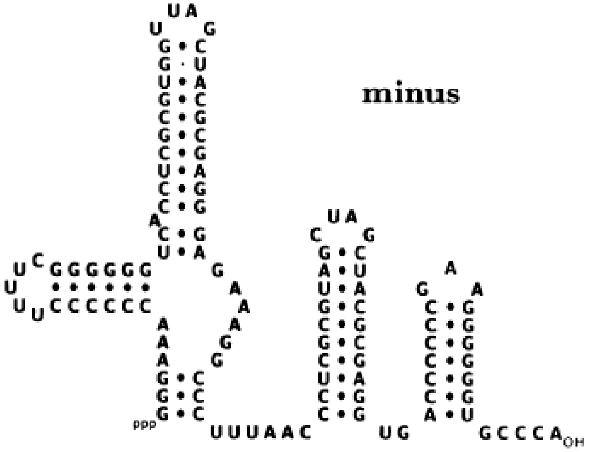
stable

does not replicate!



plus

SV-11 (115 b)



minus

metastable

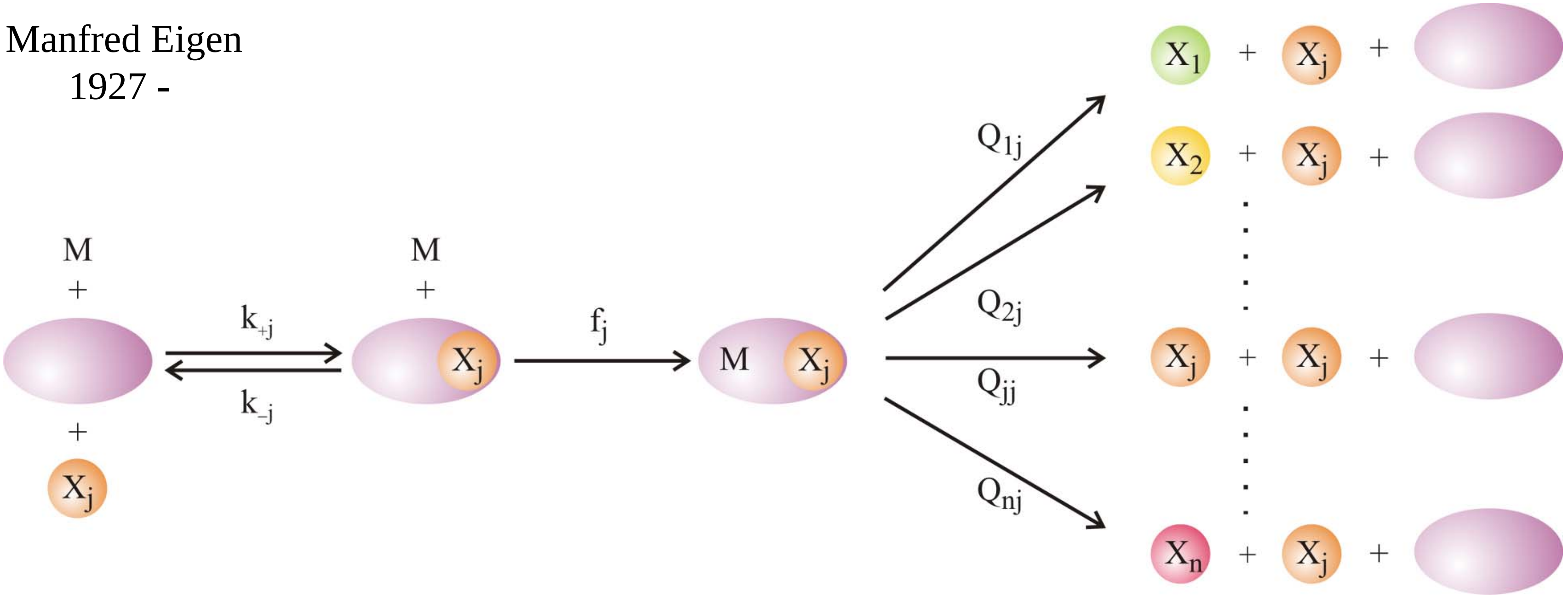
replicates!

C.K. Biebricher, R. Luce. 1992. *In vitro* recombination and terminal recombination of RNA by Qβ replicase. *The EMBO Journal* 11:5129-5135.

Manfred Eigen
1927 -

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

$$\Phi = \sum_{i=1}^{n} f_i\, x_i \Big/ \sum_{i=1}^{n} x_i$$



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

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

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

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

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

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

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

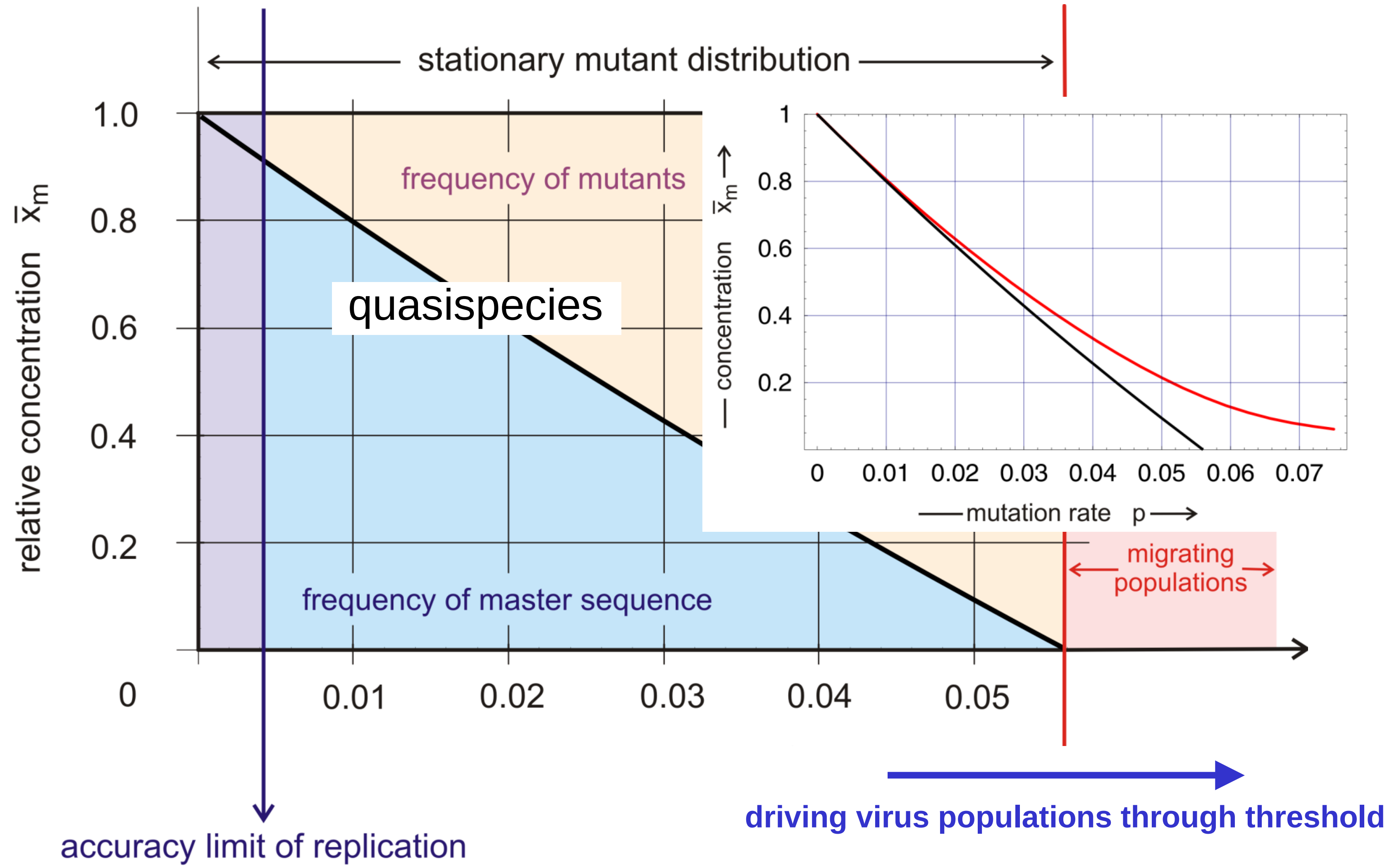
$$\frac{\mathrm{d}x_m^{(0)}}{\mathrm{dt}} = x_m^{(0)}\left(Q_{mm} f_m - \phi(t)\right) = 0 \quad \text{and} \quad \phi(t) = Q_{mm} f_m$$

$$\bar{x}_m^{(0)} = \frac{Q_{mm} - \sigma_m^{-1}}{1 - \sigma_m^{-1}} = \frac{1}{\sigma_m - 1}\left(\sigma_m (1-p)^n - 1\right)$$

$$\bar{x}_m^{(0)} = 0 \quad \Rightarrow \quad (1-p)^n = \sigma_m^{-1} \quad \text{and} \quad p_{\mathrm{cr}} \approx 1 - (\sigma_m)^{-1/n}$$

$$\sigma_m = \frac{f_m}{\bar{f}_{-m}} \quad \text{and} \quad \bar{f}_{-m} = \frac{1}{(1-x_m)} \sum_{i=1, i\neq m}^{N} x_i f_i$$

The ‚no-mutational-backflow‘ or zeroth order approximation



The error threshold in replication and mutation

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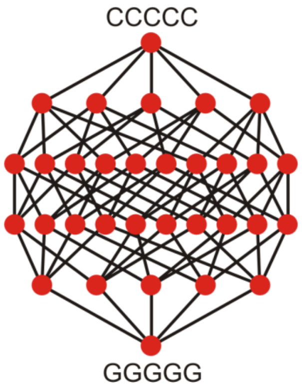
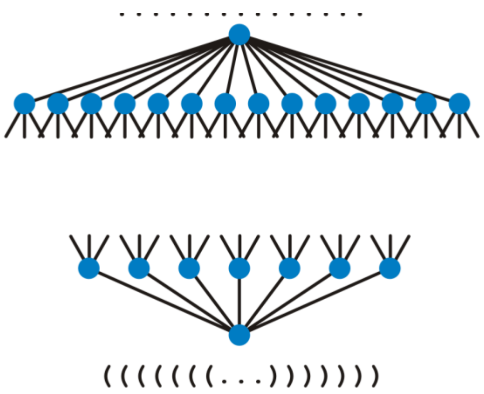
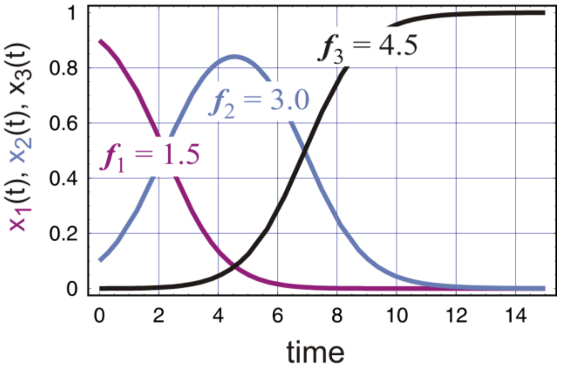


sequence space



shape space



parameter space

$\Phi: (\mathcal{Q}, d_{\mathrm{H}}) \Rightarrow (\mathcal{Y}, d_{\mathrm{Y}})$ $\Psi: (\mathcal{Y}, d_{\mathrm{Y}}) \Rightarrow \mathbf{R}^1$

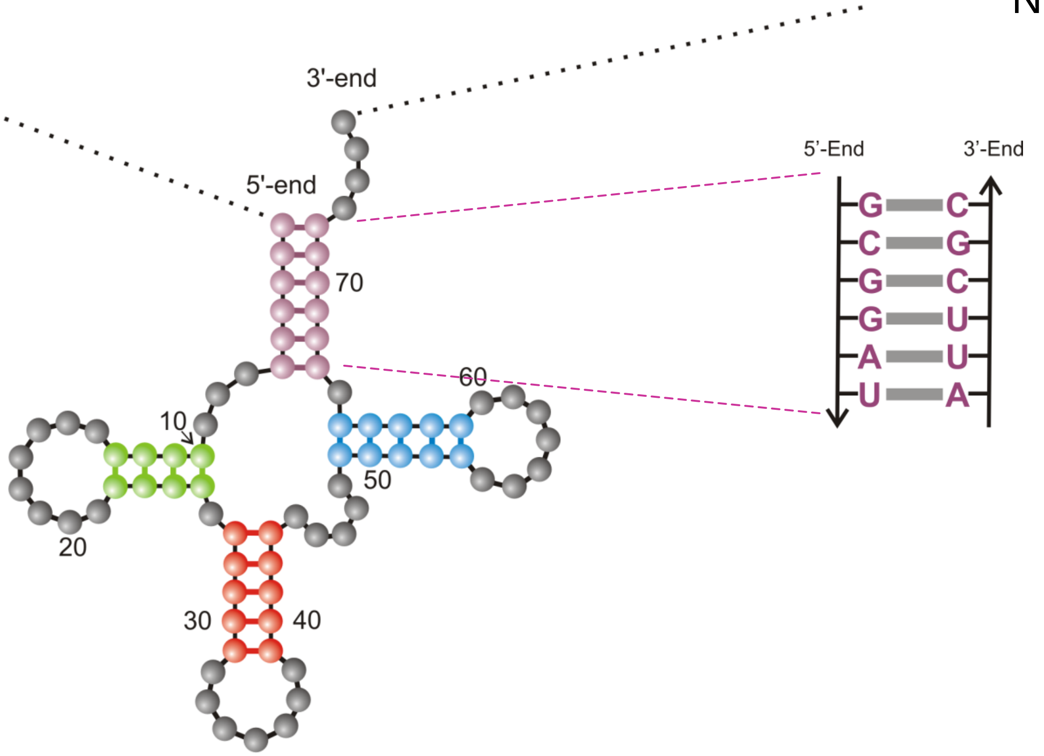
$$\mathrm{S} \longrightarrow \mathrm{Y} = \Phi(\mathrm{S}) \longrightarrow f = \Psi(\mathrm{Y})$$

sequence structure function

The paradigm of structural biology

Sequence 5'-End GCGGAUUUAGCUCAGDDGGGAGAGCMCCAGACUGAAYAUCUGGAGMUCCUGUGTPCGAUCCACAGAAUUCGCACCA 3'-End $N = 4^n$

Secondary structure

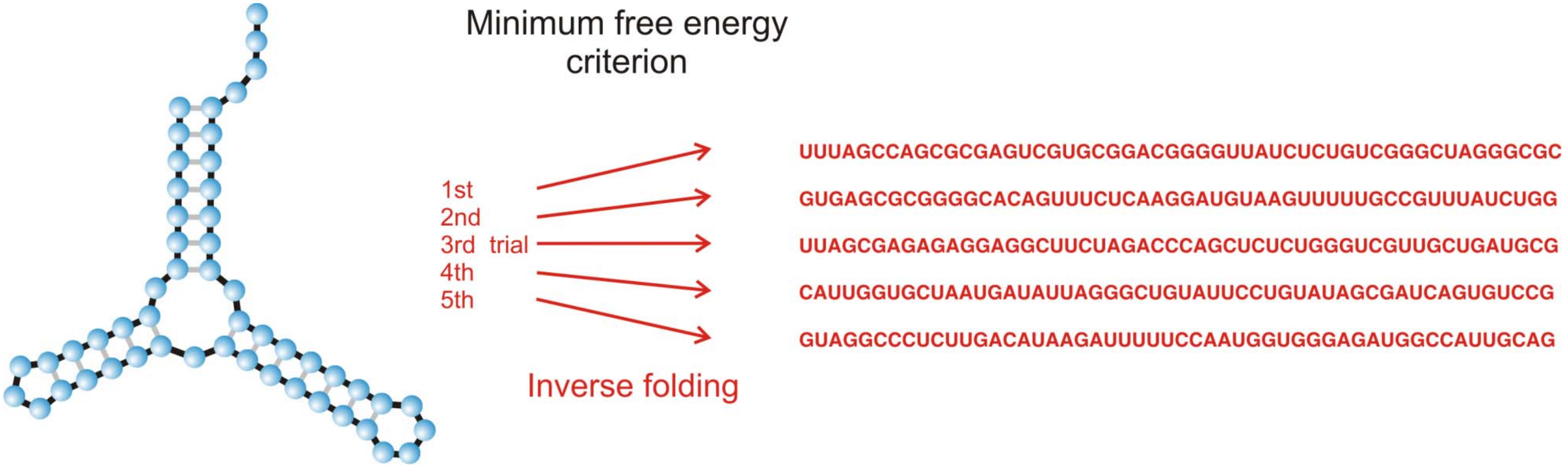


Symbolic notation 5'-End ((((((···((((········))))·(((((·······)))))·····(((((·······)))))·))))))···· 3'-End $N_S < 3^n$

Criterion: Minimum free energy (mfe)

Rules: _ (_) _ ∈ {**AU**,**CG**,**GC**,**GU**,**UA**,**UG**}

A symbolic notation of RNA secondary structure that is equivalent to the conventional graphs



Minimum free energy criterion

1st
2nd
3rd trial
4th
5th

UUUAGCCAGCGCGAGUCGUGCGGACGGGGUUAUCUCUGUCGGGCUAGGGCGC

GUGAGCGCGGGGCACAGUUUCUCAAGGAUGUAAGUUUUUGCCGUUUAUCUGG

UUAGCGAGAGAGGAGGCUUCUAGACCCAGCUCUCUGGGUCGUUGCUGAUGCG

CAUUGGUGCUAAUGAUAUUAGGGCUGUAUUCCUGUAUAGCGAUCAGUGUCCG

GUAGGCCCUCUUGACAUAAGAUUUUUCCAAUGGUGGGAGAUGGCCAUUGCAG

Inverse folding

The **inverse folding algorithm** searches for sequences that form a given RNA secondary structure under the minimum free energy criterion.

space of genotypes: $\mathcal{Q} = \{S_1, S_2, S_3, \ldots, S_N\}$

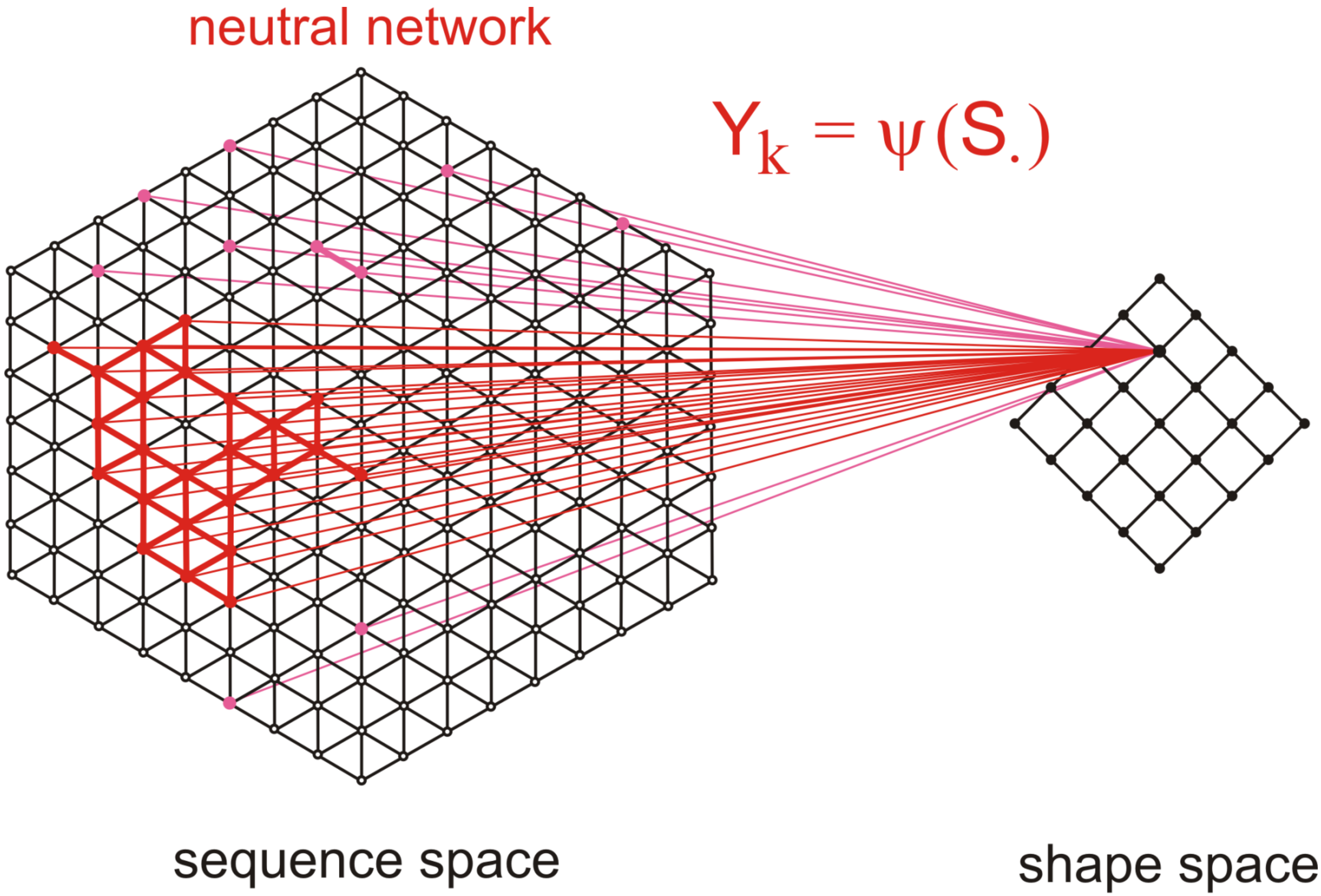
space of phenotypes: $\mathcal{Y} = \{Y_1, Y_2, Y_3, \ldots, Y_M\}$

$$N >> M$$

$$\Phi(S_j) = Y_k$$

$$G_k = \Phi^{-1}(Y_k) \equiv \{S_j \mid \Phi(S_j) = Y_k\}$$

Inversion of genotype-phenotype mapping



Neutral networks in sequence space

$$G_k = \psi^{-1}(Y_k) \equiv \{ S_j \mid \psi(S_j) = Y_k \}$$

$$\lambda_j = 12 / 27 = 0.444 \, , \quad \bar{\lambda}_k = \frac{\sum_{j \in G_k} \lambda_j(k)}{|G_k|}$$

Connectivity threshold: $\lambda_{cr} = 1 - \kappa^{-1/(\kappa-1)}$

$\bar{\lambda}_k > \lambda_{cr}$ . . . . network G_k is **connected**

$\bar{\lambda}_k < \lambda_{cr}$ . . . . network G_k is **not connected**

The parameter κ is the size of the alphabet underlying the strings in sequence space

κ	λ_{cr}	
2	0.5	GC, DU
3	0.423	AUG
4	0.370	AUGC

Degree of neutrality of neutral networks and the connectivity threshold

Realistic fitness landscapes

1. Ruggedness: nearby lying genotypes may unfold into very different phenotypes

2. Neutrality: many different genotypes give rise to phenotypes with identical selection behavior

λ_0 , ξ_0 … largest eigenvalue and eigenvector

diagonalization of matrix **W**

„ complicated but not complex "

$$\mathbf{W} = \mathbf{G} \times \mathbf{F}$$

mutation matrix

fitness landscape

(complex)

„ complex "

sequence ⇒ structure

„ complex "

mutation

selection

Complexity in molecular evolution

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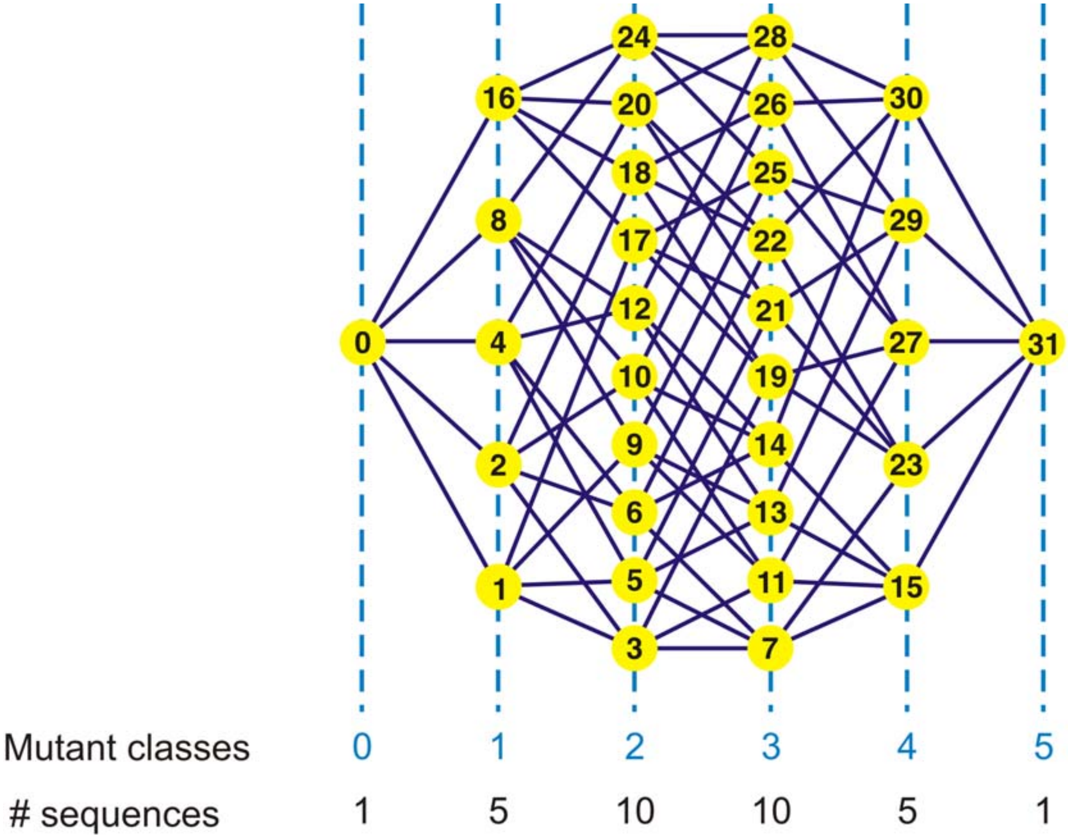
Make things as simple as possible,
but not simpler !

Albert Einstein

Albert Einstein‘s razor, precise refence is unknown.



Binary sequences are encoded by their decimal equivalents:

C = 0 and G = 1, for example,

"0" ≡ 00000 = CCCCC,

"14" ≡ 01110 = CGGGC,

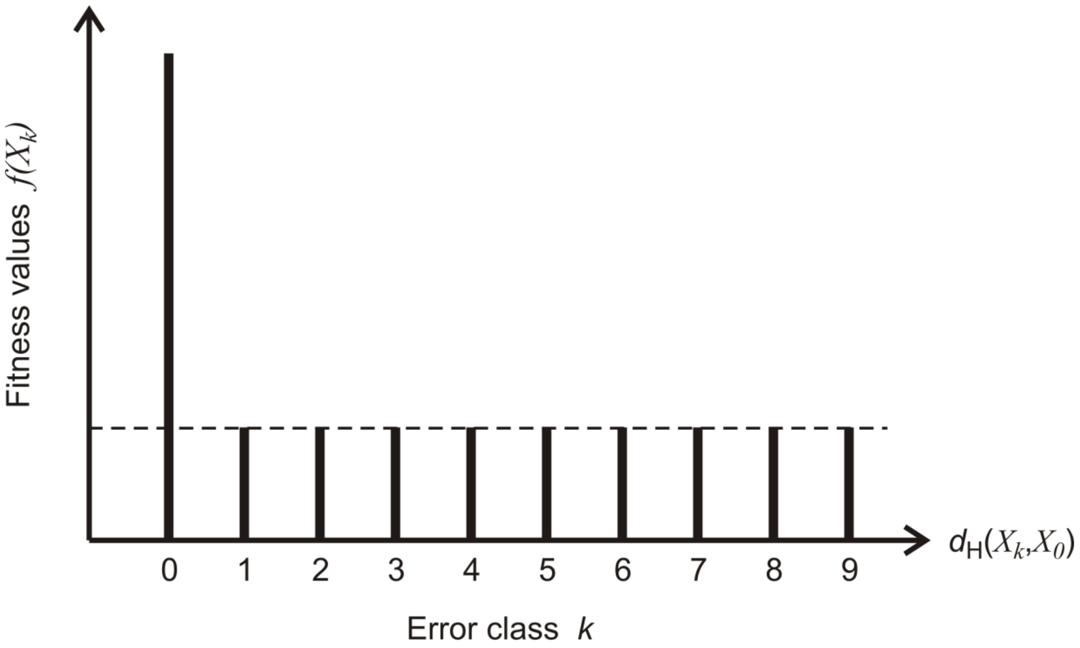
"29" ≡ 11101 = GGGCG, etc.

Concentrations of entire error classes: $[\Gamma_k] = y_k(p)\,,\ k = 0, 1, \ldots, n$

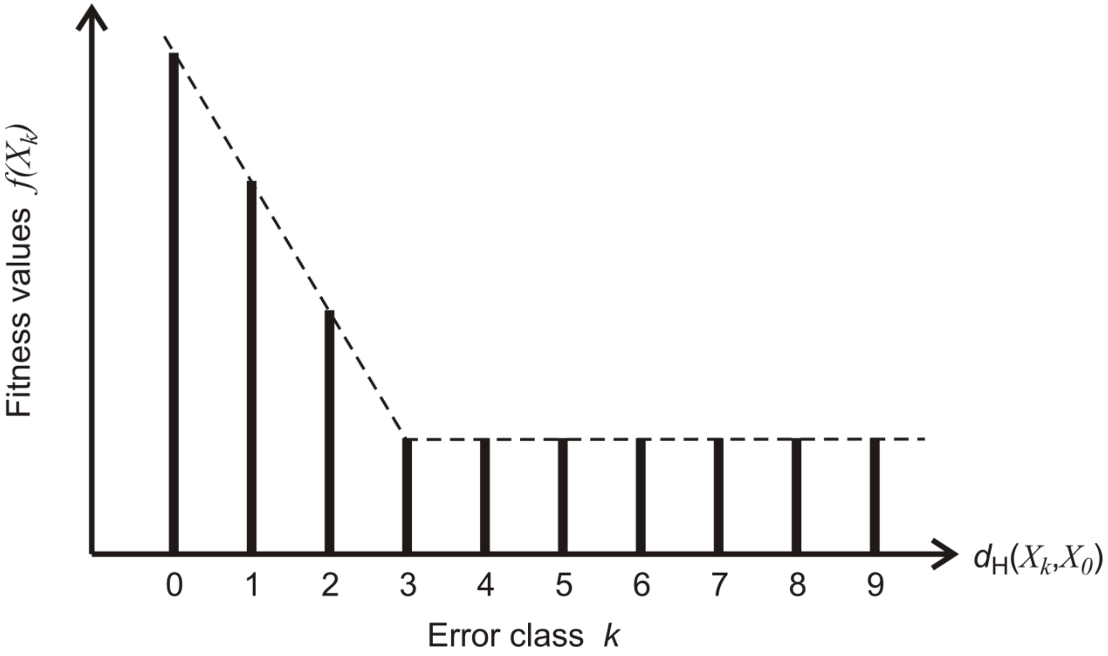
$$y_k(p) = \sum_{i=1,\ d_{\mathrm{H}}(\mathsf{X}_i,\mathsf{X}_k)=k}^{N} x_i(p)\ , \quad |\Gamma_k| = \binom{n}{k}$$

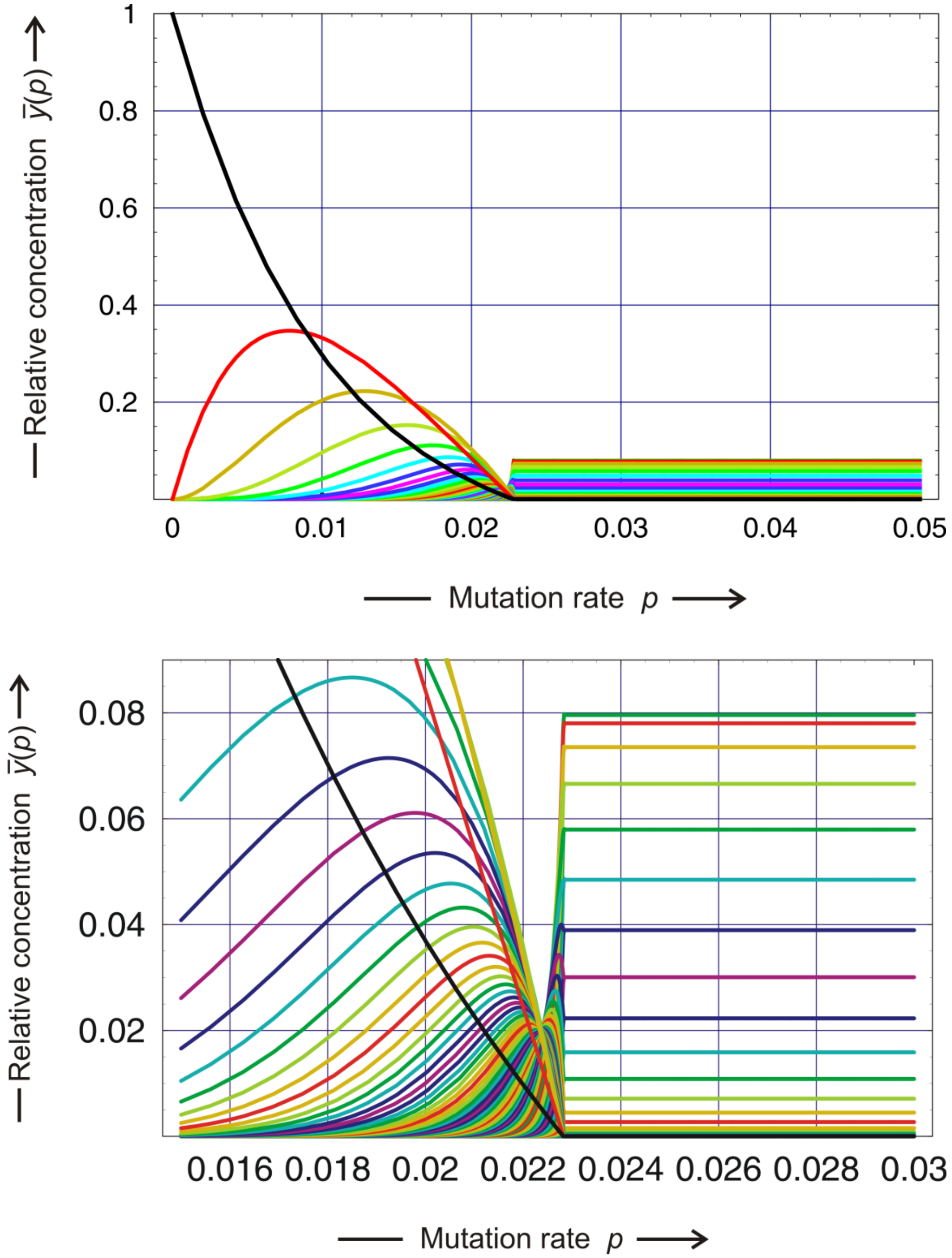
Model fitness landscapes I

single peak landscape

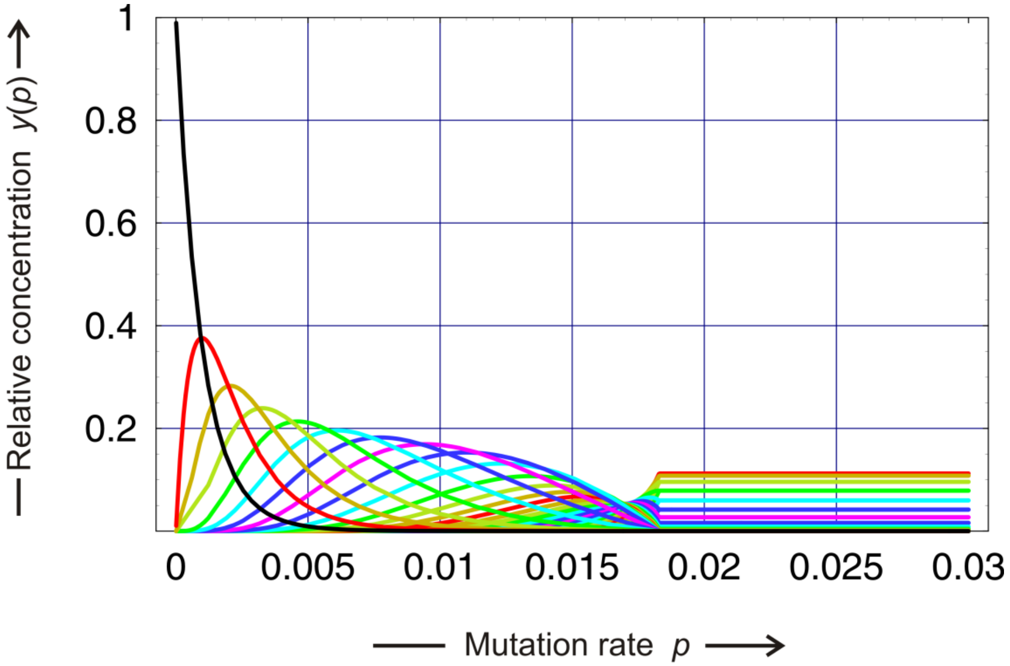


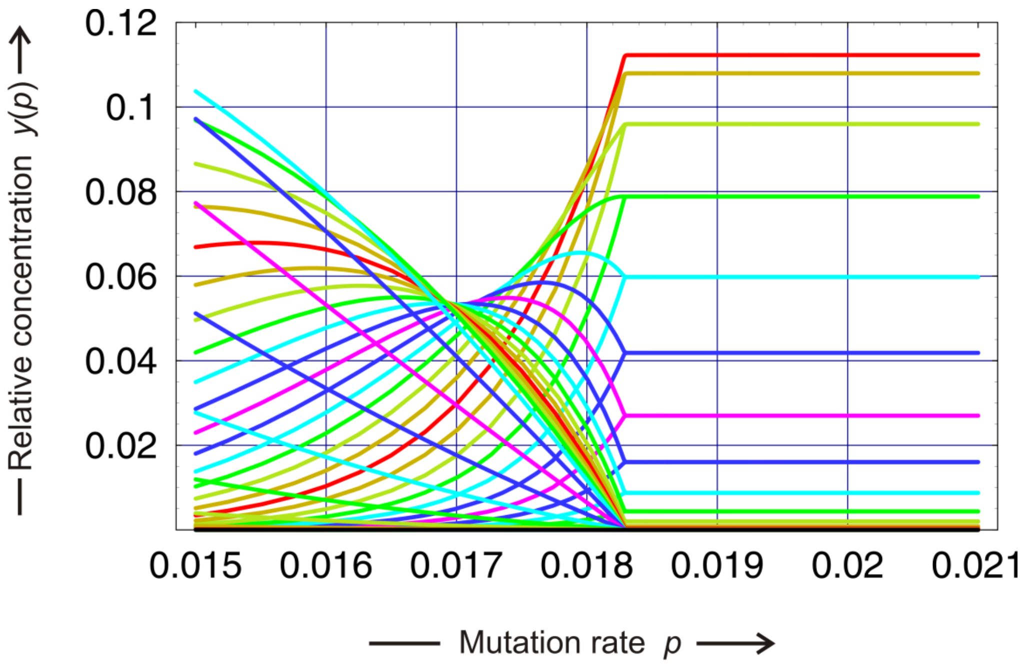
step linear landscape





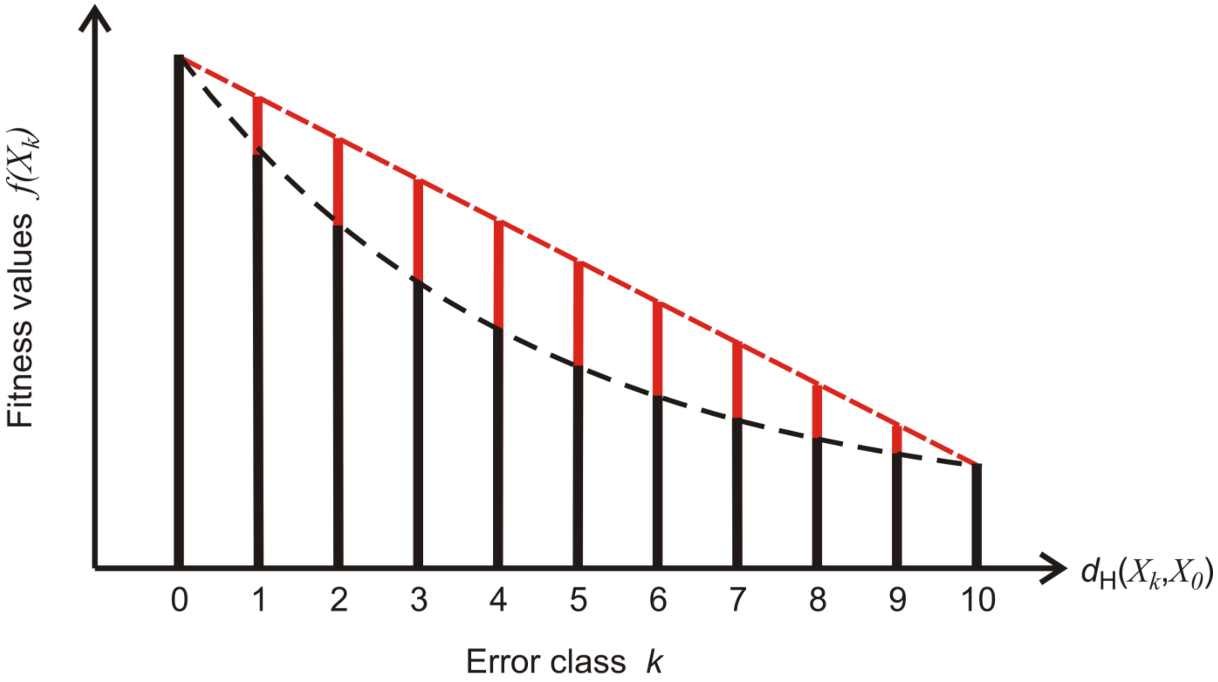
Error threshold on the single peak landscape



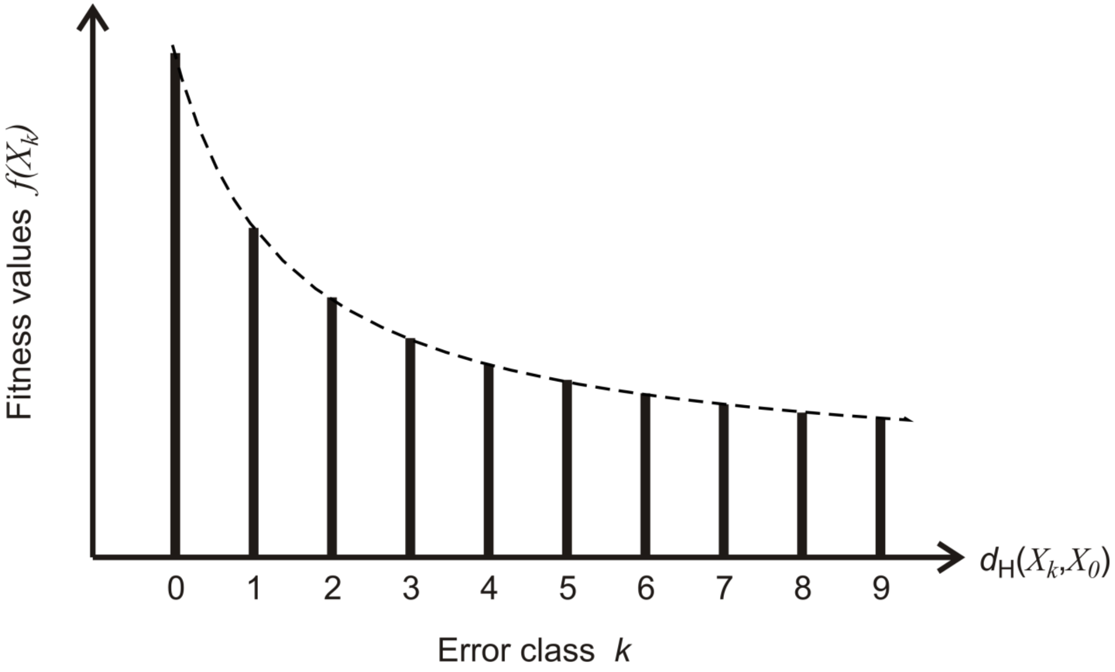


Error threshold on the step linear landscape

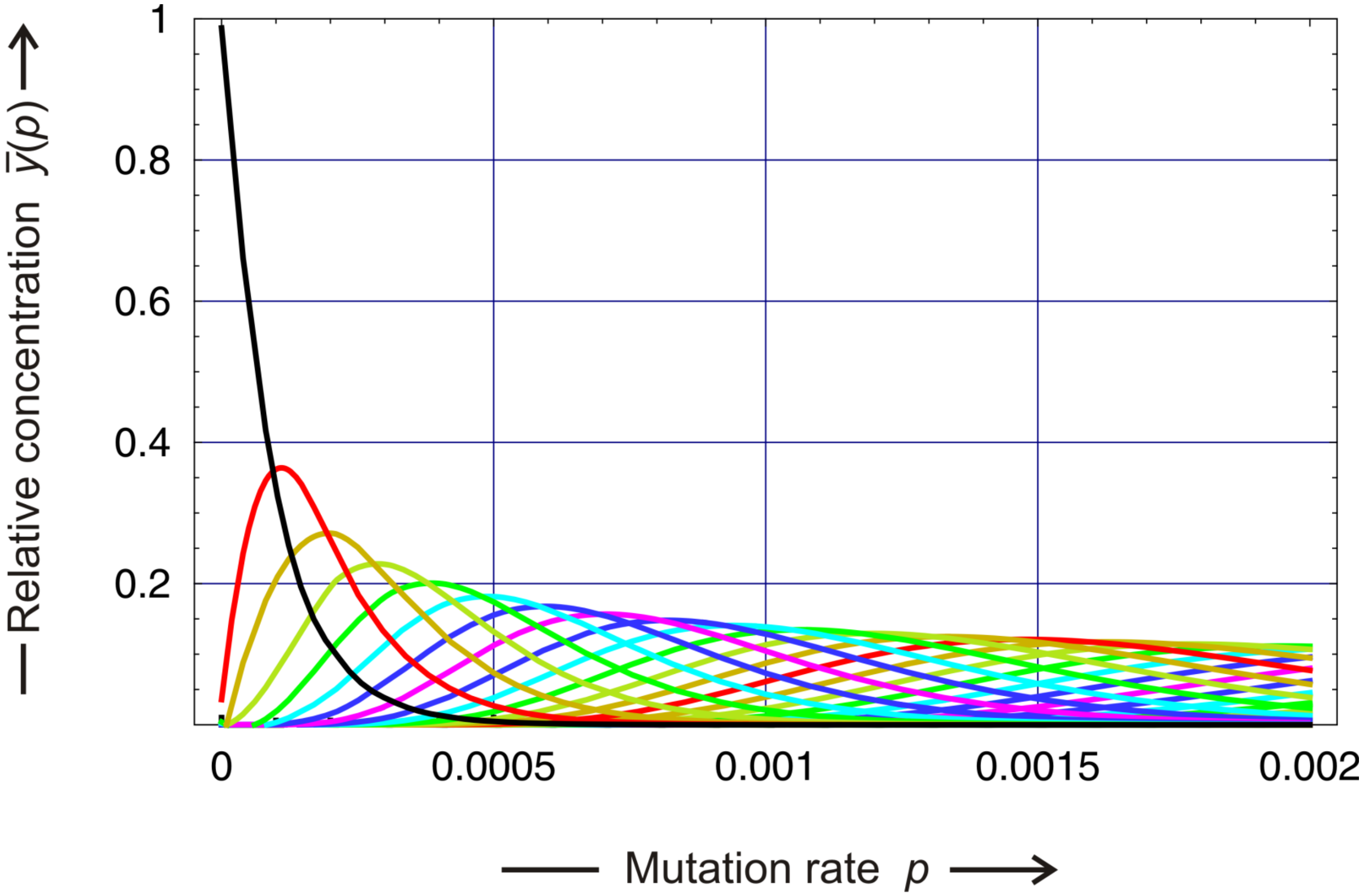
linear and
multiplicative



hyperbolic



Model fitness landscapes II



The linear fitness landscape shows no error threshold

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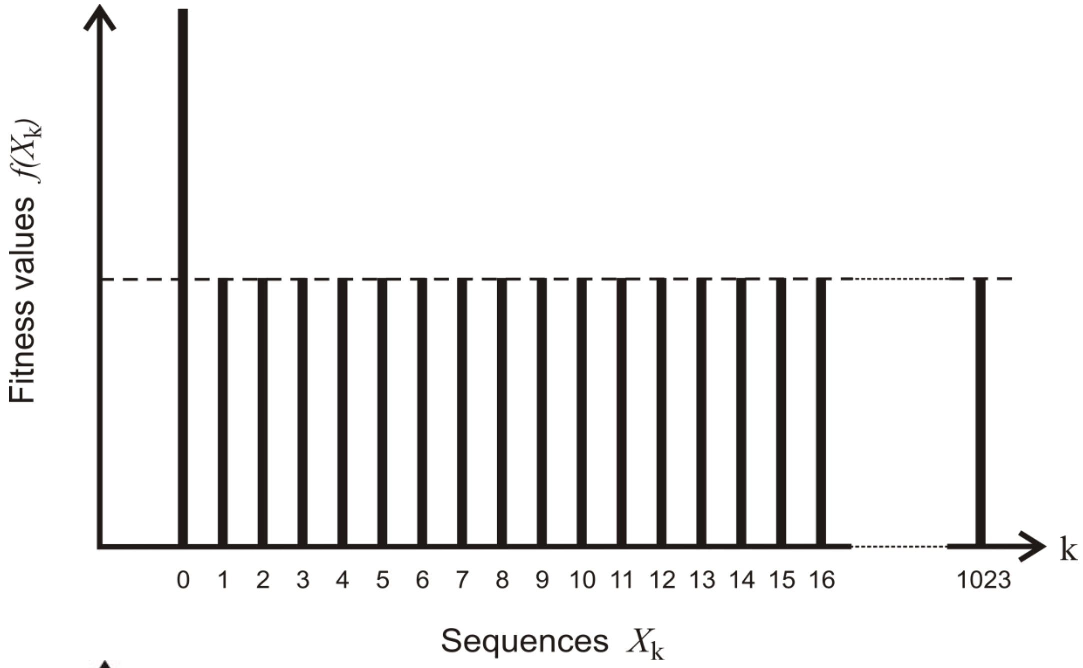
single peak landscape

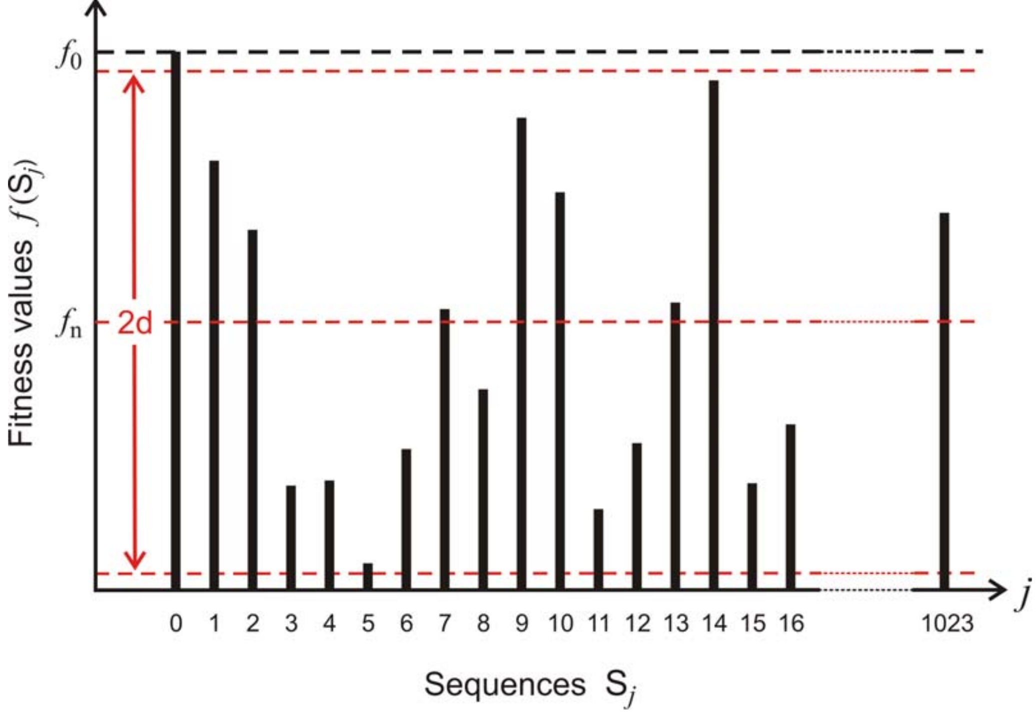


$$f(\mathsf{S}_j) \;=\; f_n \;+\; 2\,d\,(f_0 - f_n)\left(\eta_j^{(s)} - 0.5\right)$$

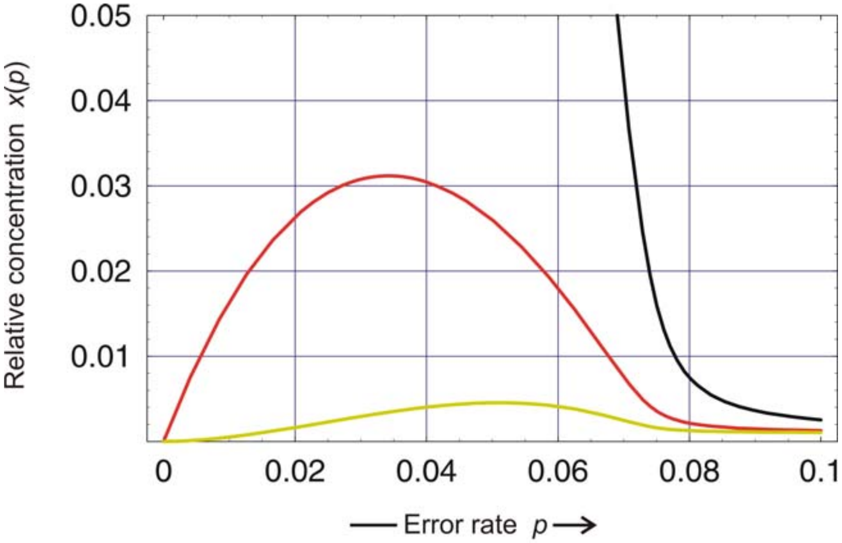
$j = 1, 2, \ldots, N\,;\;\; j \neq m\,,$

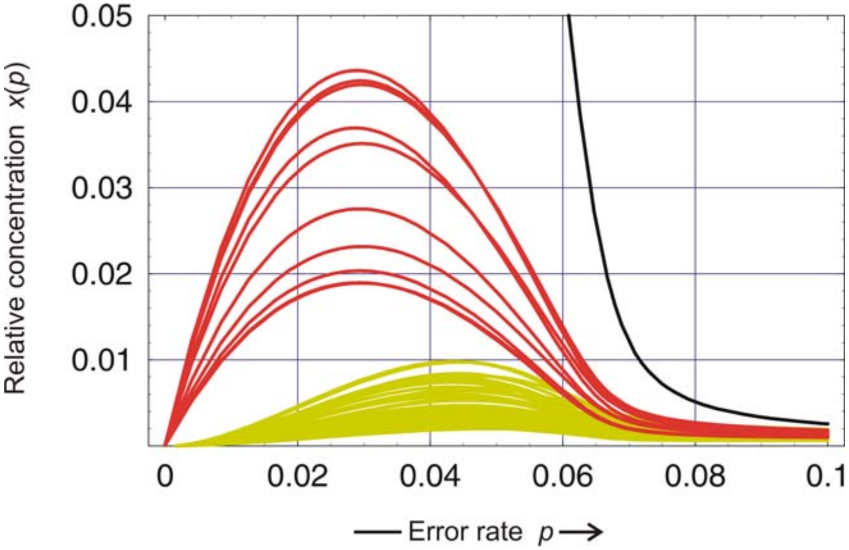
η … random number ; s … seeds

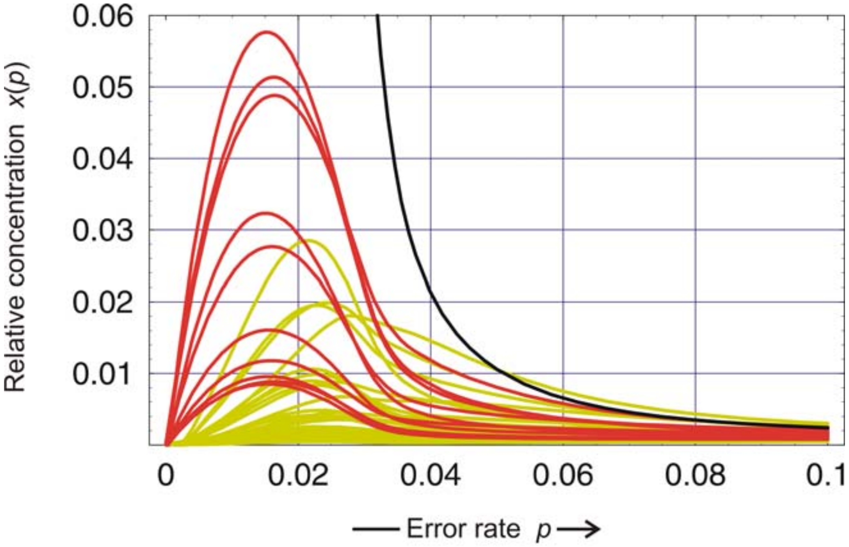
„realistic“ landscape



Rugged fitness landscapes
over individual binary sequences
with n = 10



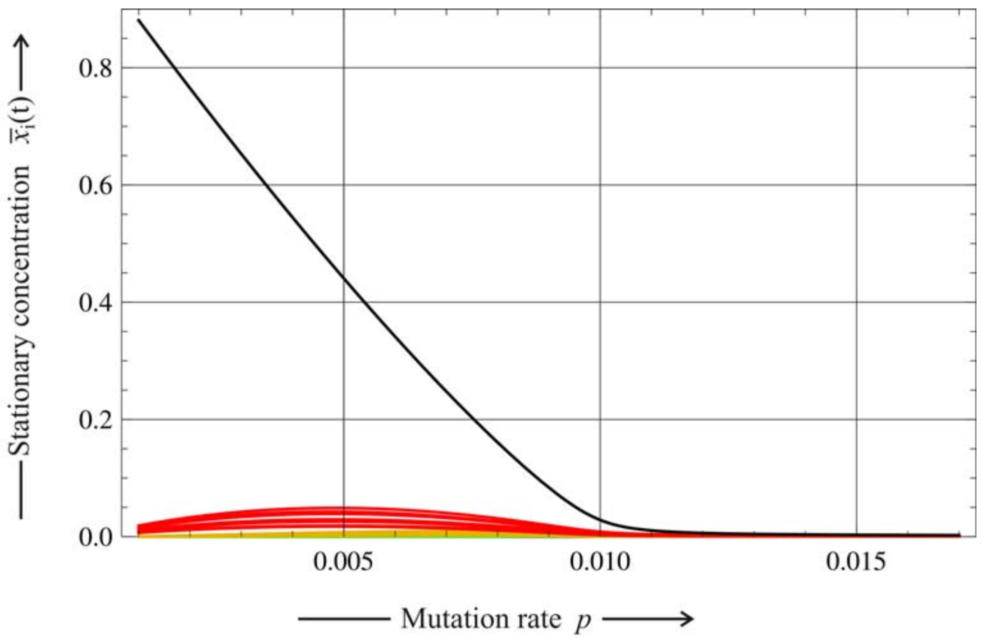




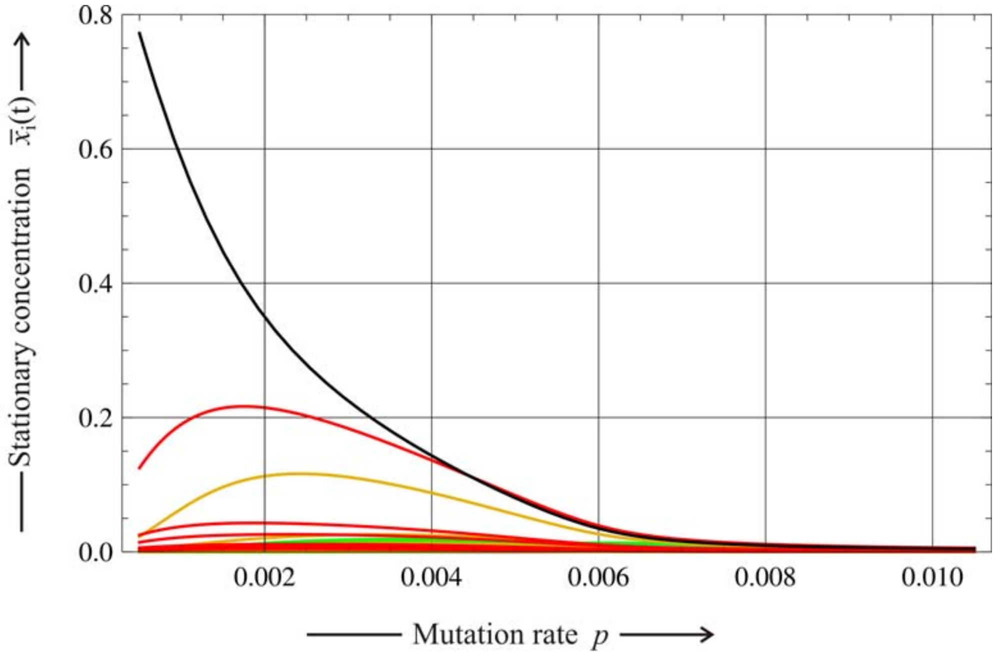
Error threshold: Individual sequences

n = 10, σ = 2, s = 491 and d = 0, 0.5, 0.9375

d = 0.5



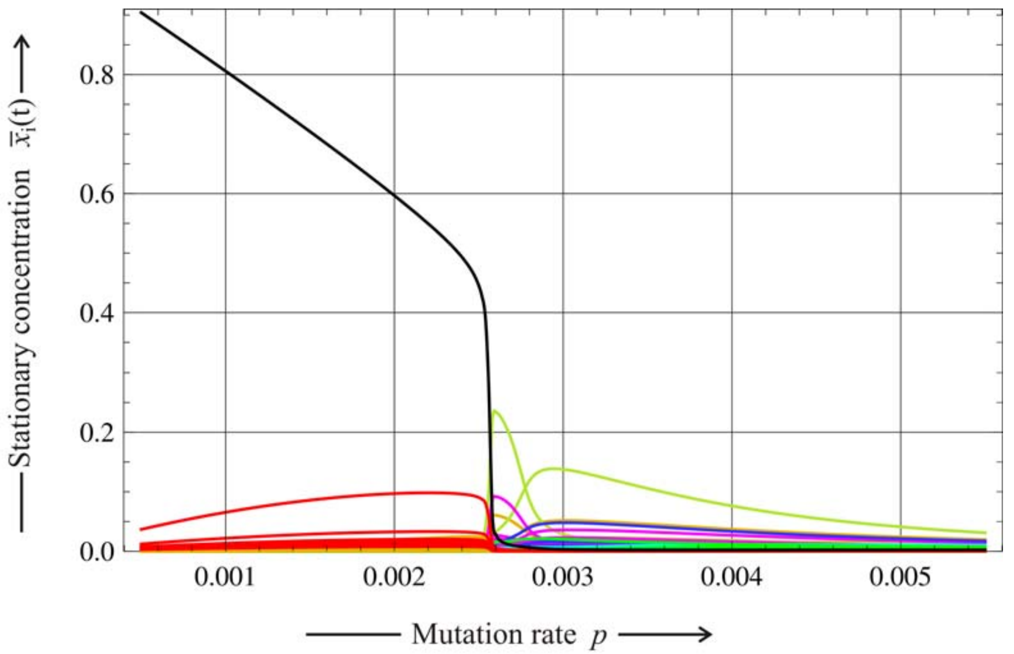
d = 1.0



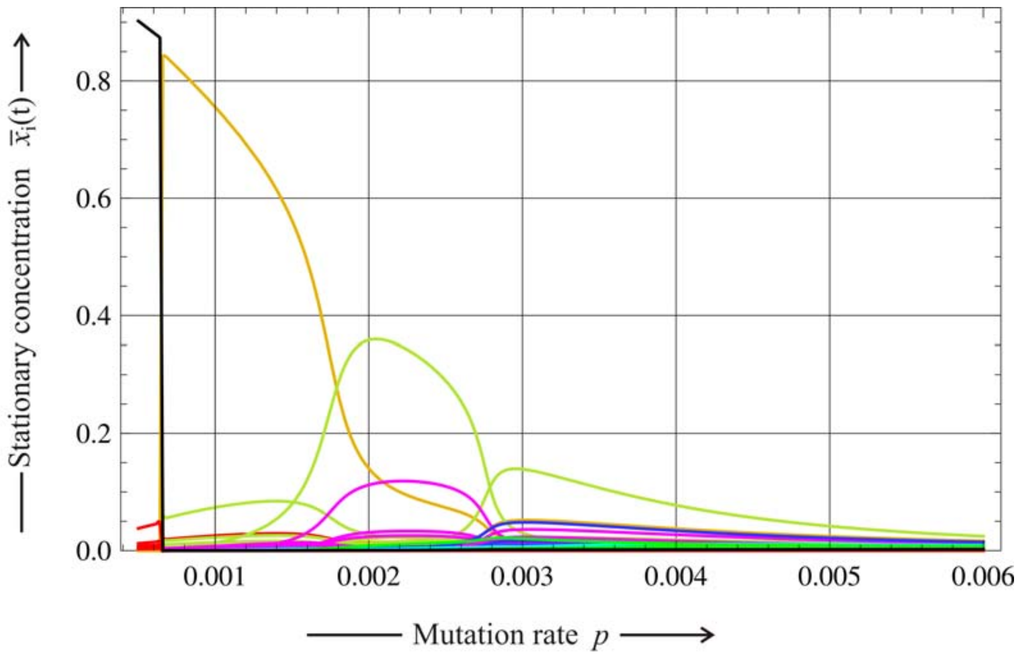
Case I: Strong quasispecies

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

d = 0.995



d = 1.0



Case III: multiple transitions

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

1. Darwin and evolutionary optimization
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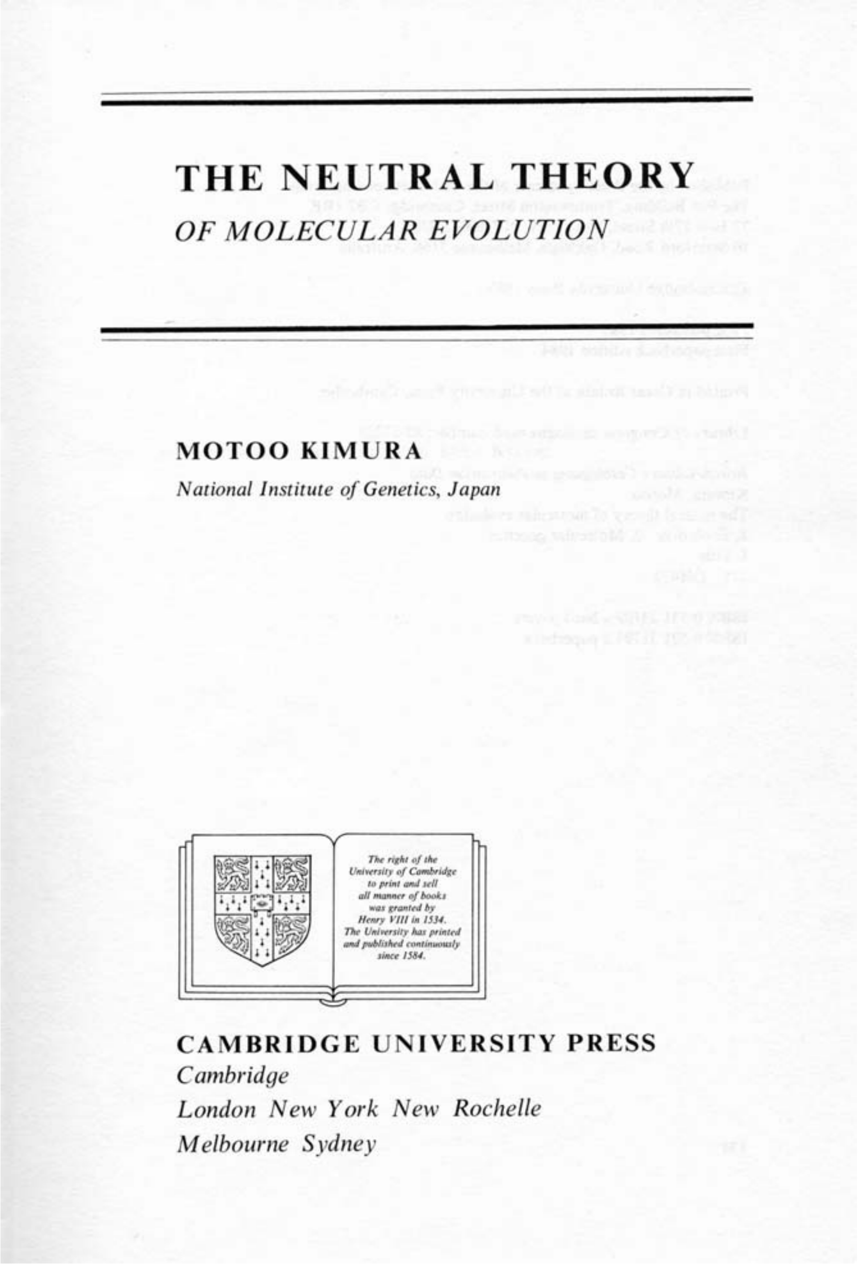
4. Evolution on simple model landscapes
5. Evolution on realistic landscapes
6. **Neutrality in evolution**
7. Perspectives


MOTOO KIMURA

Motoo Kimuras 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.


THE NEUTRAL THEORY
OF MOLECULAR EVOLUTION

MOTOO KIMURA
National Institute of Genetics, Japan

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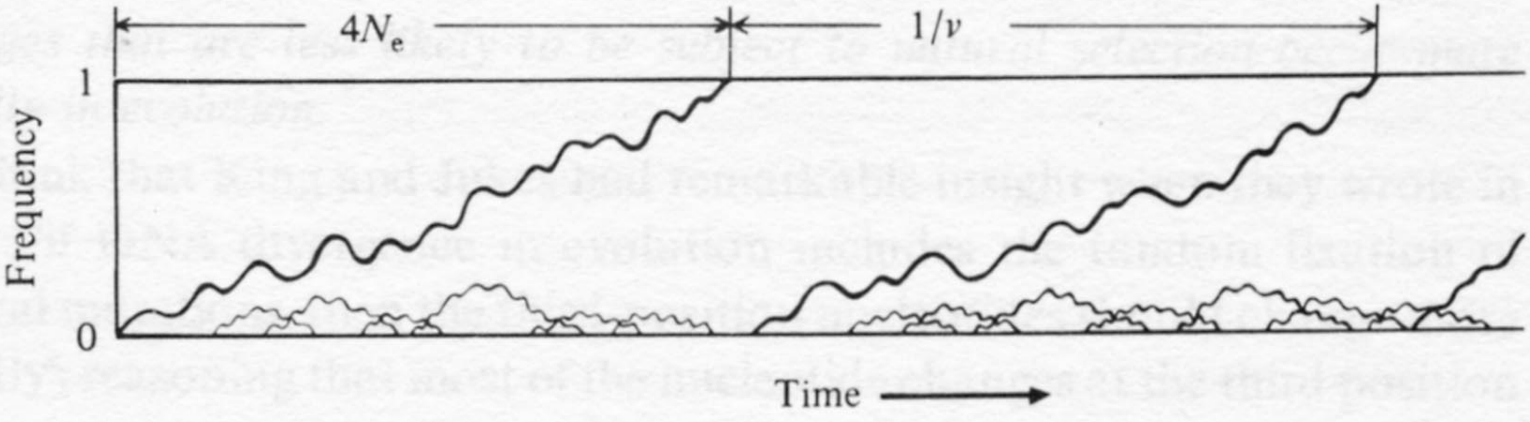
Fig. 3.1. Behavior of mutant genes following their appearance in a finite population. Courses of change in the frequencies of mutants destined to fixation are depicted by thick paths. N_e stands for the effective population size and v is the mutation rate.

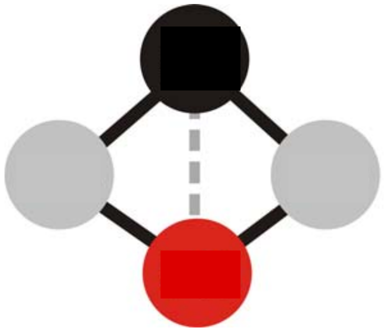


Motoo Kimura

Is the Kimura scenario correct for frequent mutations?

$d_H = 1$

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



$d_H = 2$

$$\lim_{p\to 0} x_1(p) = a$$

$$\lim_{p\to 0} x_2(p) = 1 - a$$

$d_H \geq 3$

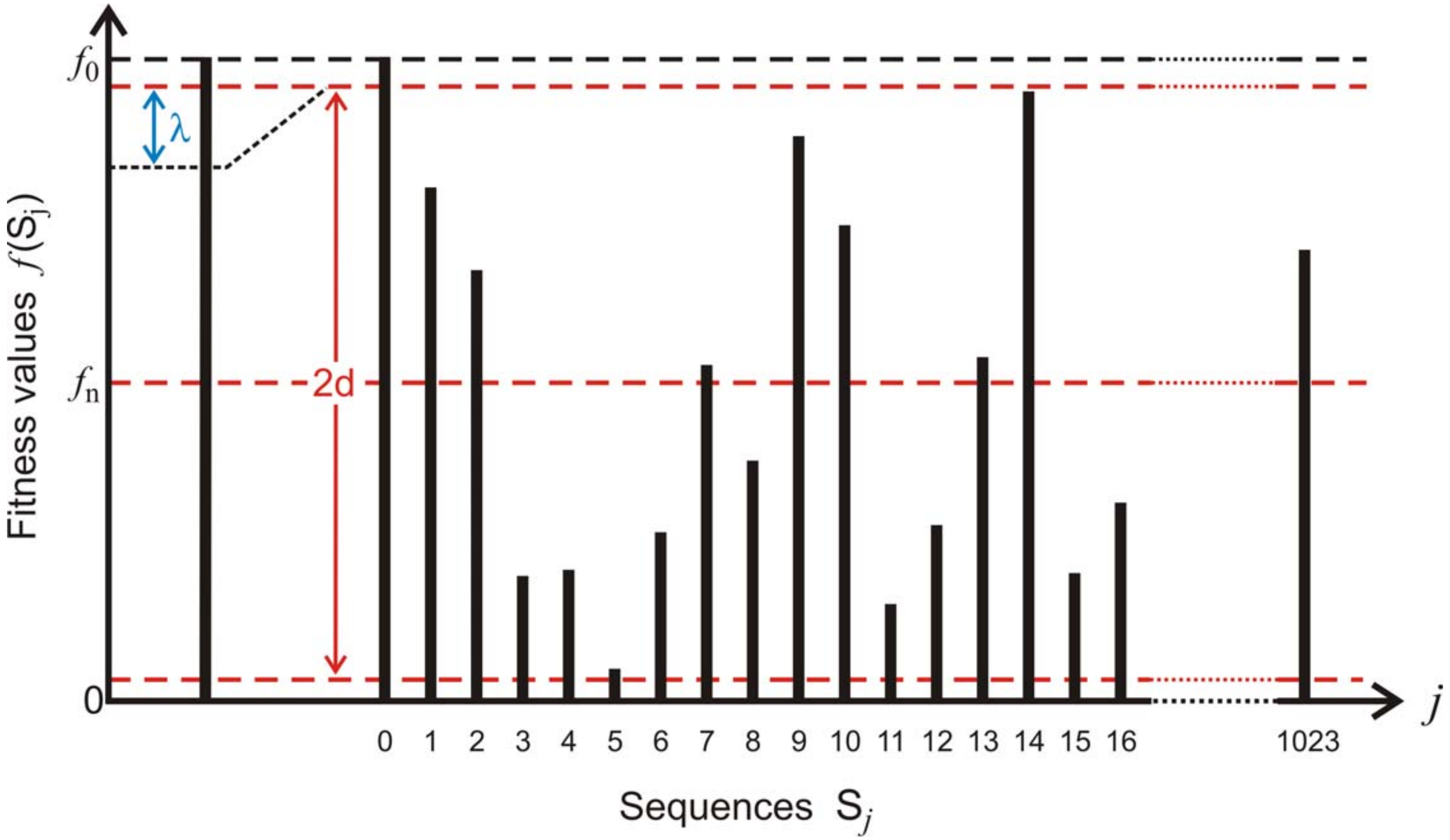
$$\lim_{p\to 0} x_1(p) = 1, \lim_{p\to 0} x_2(p) = 0 \quad \text{or}$$

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

Pairs of neutral sequences in replication networks

Random fixation in the
sense of Motoo Kimura

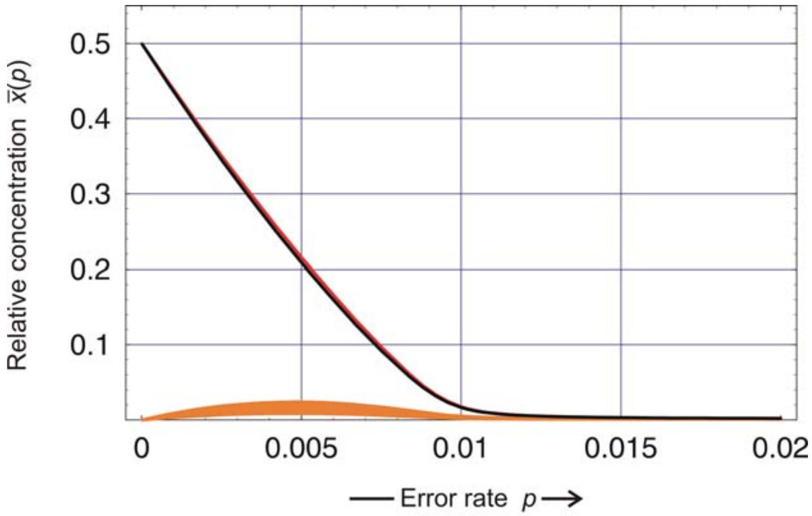
P. Schuster, J. Swetina. 1988. Bull. Math. Biol. 50:635-650

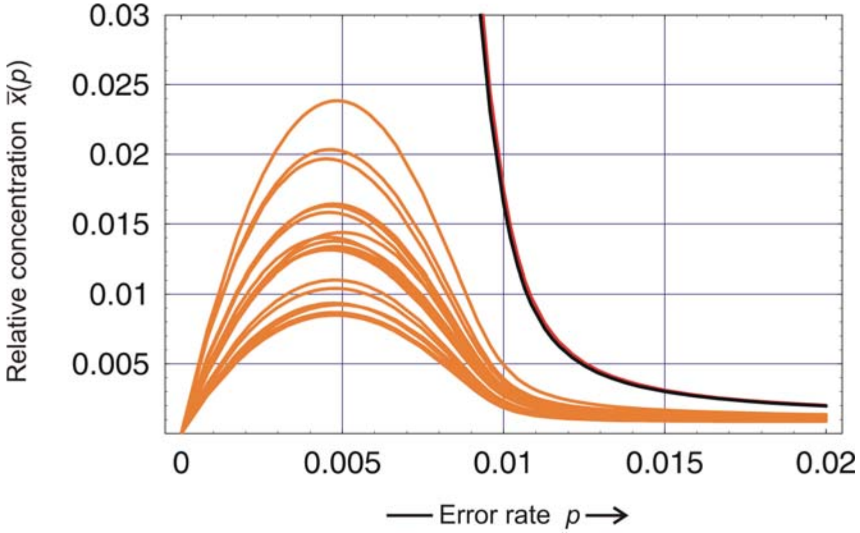


$$f(\mathsf{S}_j) \;=\; \begin{cases} f_0 & \text{if } \eta_j(s) \,\geq\, 1-\lambda\,, \\ f_n \,+\, \frac{2\,d}{1-\lambda}\,(f_0 - f_n)\left(\eta_j^{(s)} - 0.5\right) & \text{if } \eta_j(s) \,\leq\, 1-\lambda\,, \end{cases}$$

$$j = 1, 2, \ldots, N\,;\;\; j \neq m\,;\;\; \eta \;\ldots\; \text{random number}\,;\;\; s \;\ldots\; \text{seeds}$$

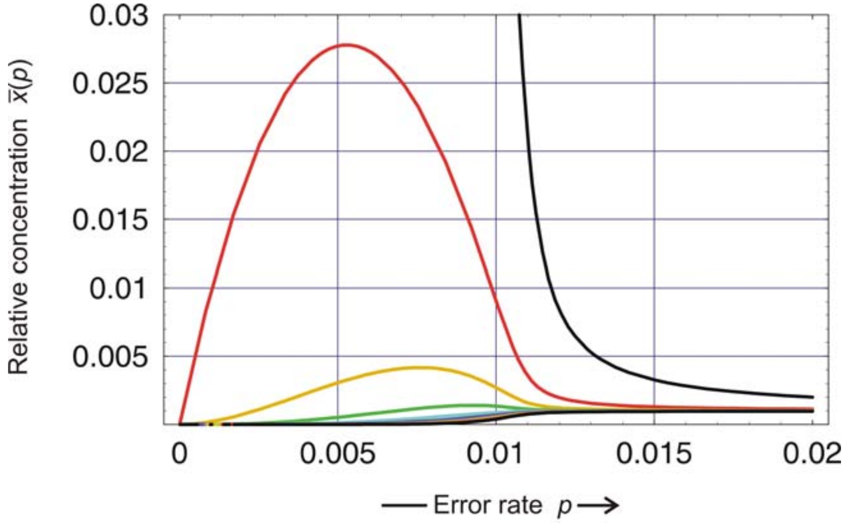
A fitness landscape including neutrality





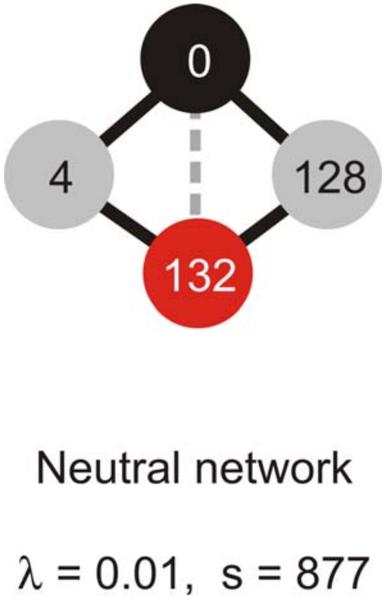
Neutral network

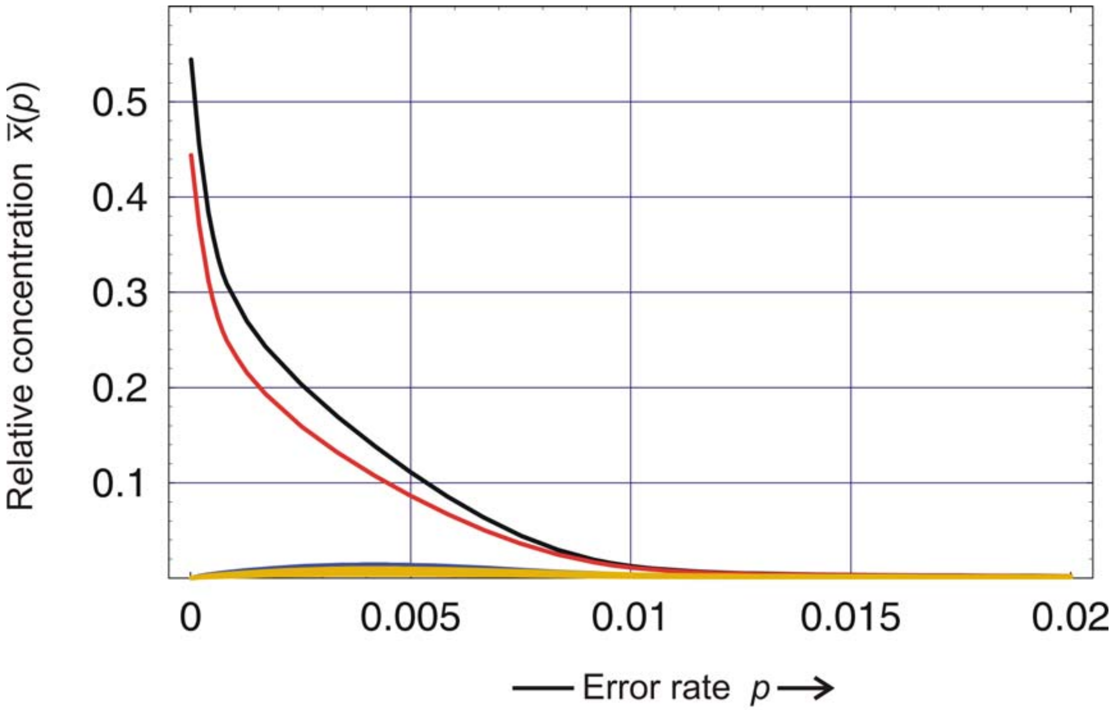
$\lambda = 0.01$, $s = 367$



Neutral network: Individual sequences

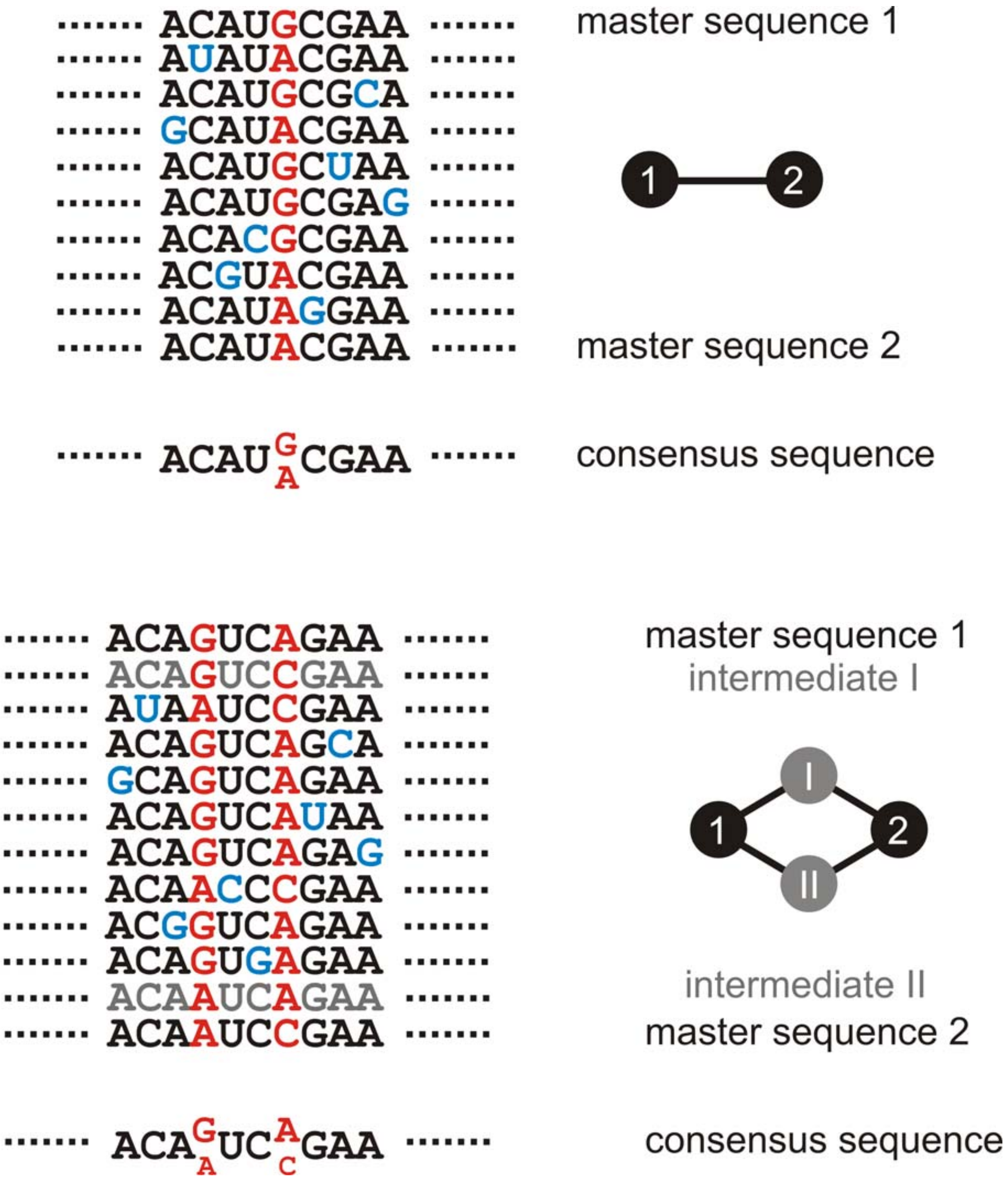
$n = 10$, $\sigma = 1.1$, $d = 0.5$





Neutral network: Individual sequences

$n = 10, \sigma = 1.1, d = 0.5$



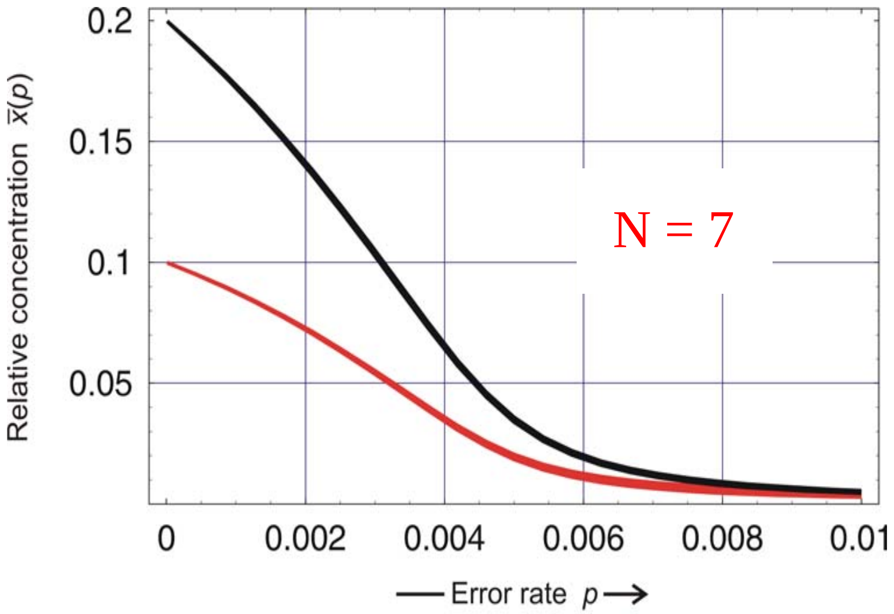
ACAUGCGAA master sequence 1
AUAUACGAA
ACAUGCGCA
GCAUACGAA
ACAUGCUAA
ACAUGCGAG
ACACGCGAA
ACGUACGAA
ACAUAGGAA
ACAUACGAA master sequence 2

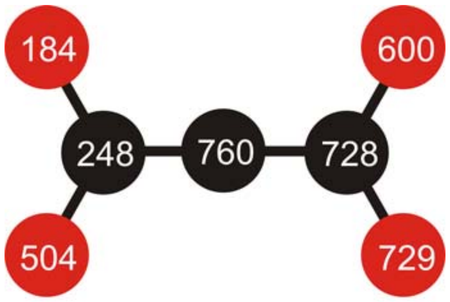
$\mathrm{ACAU}^{G}_{A}\mathrm{CGAA}$ consensus sequence

ACAGUCAGAA master sequence 1
ACAGUCCGAA intermediate I
AUAAUCCGAA
ACAGUCAGCA
GCAGUCAGAA
ACAGUCAUAA
ACAGUCAGAG
ACAACCCGAA
ACGGUCAGAA
ACAGUGAGAA
ACAAUCAGAA intermediate II
ACAAUCCGAA master sequence 2

$\mathrm{ACA}^{G}_{A}\mathrm{UC}^{A}_{C}\mathrm{GAA}$ consensus sequence

Consensus sequence of a quasispecies with strongly coupled sequences of Hamming distance $d_H(X_{i,},X_j) = 1$ and 2.





Neutral network

λ = 0.10, s = 229

Selection-mutation matrix W

$$W = \begin{pmatrix} f & O(\varepsilon^2) & \varepsilon & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) \\ O(\varepsilon^2) & f & \varepsilon & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) \\ \varepsilon & \varepsilon & f & \varepsilon & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) \\ O(\varepsilon^2) & O(\varepsilon^2) & \varepsilon & f & \varepsilon & O(\varepsilon^2) & O(\varepsilon^2) \\ O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & \varepsilon & f & \varepsilon & \varepsilon \\ O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & \varepsilon & f & O(\varepsilon^2) \\ O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & O(\varepsilon^2) & \varepsilon & O(\varepsilon^2) & f \end{pmatrix}$$

Adjacency matrix A

$$A = \begin{pmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}$$

Eigenvalues of W and A

$$\begin{aligned} \lambda_0 &= f + 2\varepsilon\,, & \lambda_0 &= 2\,, \\ \lambda_1 &= f + \sqrt{2}\,\varepsilon\,, & \lambda_1 &= \sqrt{2}\,, \\ \lambda_{2,3,4} &= f\,, & \lambda_{2,3,4} &= 0\,, \\ \lambda_5 &= f - \sqrt{2}\,\varepsilon\,, & \lambda_5 &= -\sqrt{2}\,, \\ \lambda_6 &= f - 2\varepsilon\,, & \lambda_6 &= -2\,. \end{aligned}$$

Largest eigenvector of W and A

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

Computation of sequences in the core of a neutral network

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7. **Perspectives**

(i) Fitness landscapes for the evolution of molecules are obtainable by standard techniques of physics and chemistry.

(ii) Fitness landscapes for evolution of viroids and viruses under controlled conditions are accessible in principle.

(iii) Systems biology can be carried out for especially small bacteria and an extension to bacteria of normal size is to be expected for the near future.

(iv) The computational approach for selection on known fitness landscapes – ODEs or stochastic processes – is standard.

(v) The efficient description of migration and splitting of populations in sequence space requires new mathematical techniques.

Consideration of multistep and nonlinear replication mechanisms as well as accounting for epigenetic phenomena is readily possible within the molecular approach.

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