30. Jubiläums Winterseminar

Peter Schuster

Institut für Theoretische Chemie, Universität Wien, Austria

and

The Santa Fe Institute, Santa Fe, New Mexico, USA

30. TBI Winter Seminar

Bled, 20.02.2015

Web-Page for further information:

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

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TBI Winter-Seminar

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Kärntner Artilleriebund

Barbarahaus, Turracher Höhe 176

S E M I N A R

Mathematische Methoden in der Theoretischen Chemie

25.-30.März 1984

Barbarahaus

Turracher Höhe 176, 9565 Ebene Reichenau

Montag, 26.3.1984

P.Schuster, Stochastische Prozesse in der Chemie - die Anwendbarkeit von Master-, Langevin- und Fokker-Planck-Gleichungen

K.Sigmund, Stochastische und deterministische Analyse der Selektionsgleichung

W.Fontana, Replikation als stochastischer Prozeß

Dienstag, 27.3.1984

B.Gassner, Lösung einer Mastergleichung für die fehlerhafte, molekulare Replikation mit Hilfe der Erzeugenden-Funktion

J.Hofbauer, Bifurkationstheorie und Anwendungen auf nicht-lineare Reaktionsmechanismen

F.Kemler, Stochastische und deterministische Analyse von dynamischen Systemen mit Autokatalyse höherer Ordnung

Mittwoch, 28.3.1984

H.P.Kauffmann, Inkohärente Energiewanderung zwischen identischen Chromophoren - Stochastische Variable und transientes Verhalten

O.Steinhauser, Molekulare Dynamik im Feld von stochastischen Kräften - eine molekulare Analyse der Brown'schen Bewegung

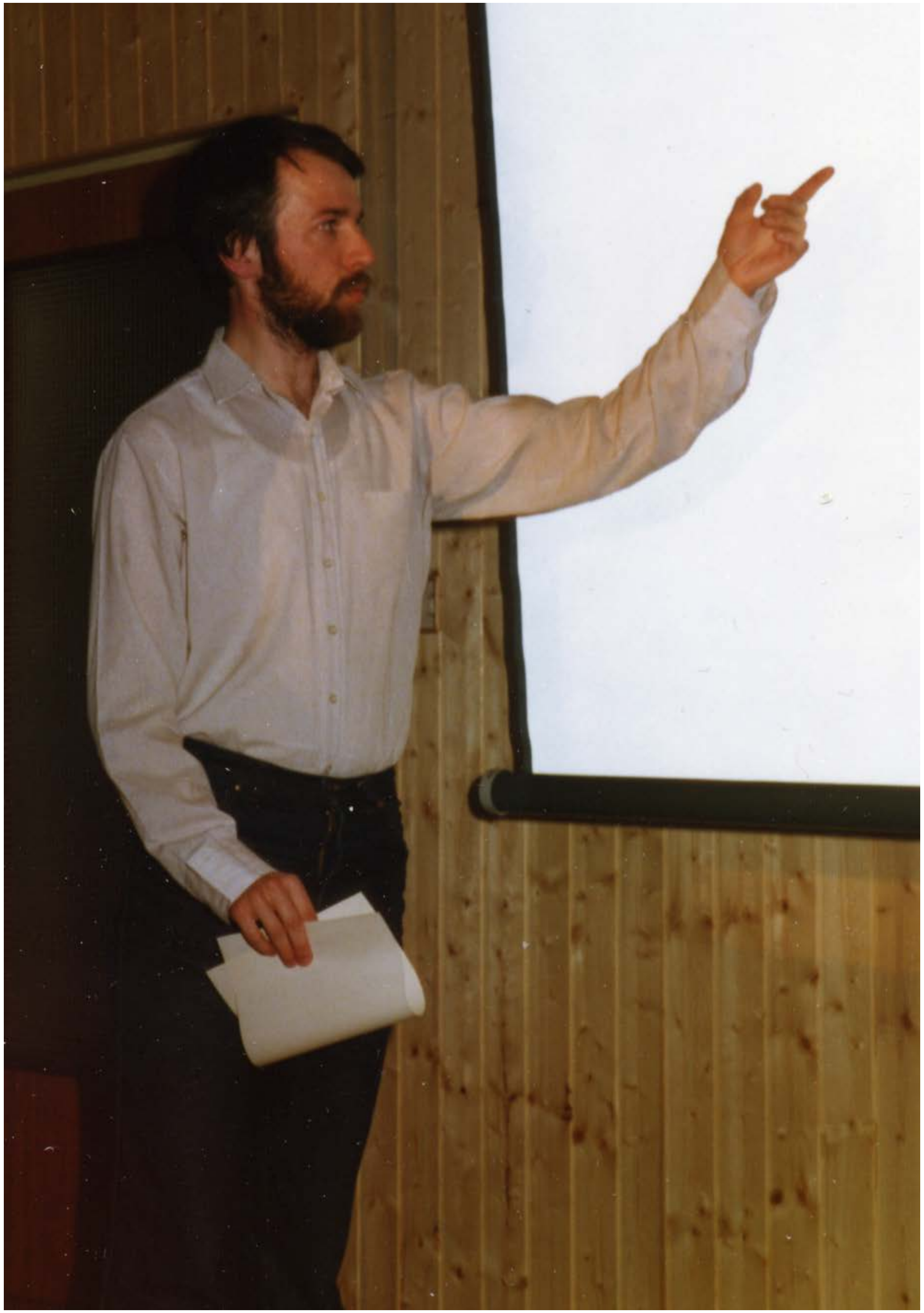
A.Beyer, Proteindynamik

Donnerstag, 29.3.1984

J.Swetina, Über das asymptotische Verhalten von Eigenfunktionen von 1-Teilchen Schrödingeroperatoren

M.Hoffmann-Ostenhof,
Asymptotisches Verhalten von Eigenfunktionen von n-Teilchen Schödingeroperatoren in Zusammenhang mit dem Spektrum des Operators

T.Hoffmann-Ostenhof,
Über Triplettzustände von atomaren Systemen mit 2 Elektronen




COUSCOUS
SIPA

S E M I N A R

Mathematische Methoden in der Theoretischen Chemie

Reaktions-Diffusionsgleichung

24.-30.März 1985

Barbarahaus

Turracher Höhe 176, 9565 Ebene Reichenau

Sonntag,24.3.1985

P.Schuster, Die Reaktions-Diffusionsgleichung und einige Anwendungen in Chemie und Biologie (mit Film)

Montag, 25.3.1985

T.Hoffmann-Ostenhof, Elliptische Differentialgleichungen

M.Hoffmann-Ostenhof, Parabolische Differentialgleichungen

J.Swetina, Vergleichssätze für Reaktions-Diffusionsgleichungen

Dienstag,26.3.1985

H.Muthsam, Zur numerischen Behandlung partieller Differentialgleichungen

R.Bürger und W.Fontana, Populationsgenetik und Diffusion (M.Kimuras "Neutrale Theorie"

Mittwoch,27.3.1985

K.Sigmund, Topologische Methoden für Reaktions-Diffusionssysteme

J.Hofbauer, Methoden der Bifurkationstheorie für partielle Differentialgleichungen

J.Hofbauer, "Travelling Waves"

Donnerstag,28.3.1985

T.Hoffmann-Ostenhof, Regularitätseigenschaften und Eigenschaften der Nullstellen von Lösungen 2-dimensionaler Schrödingergleichungen in der Nähe von unendlich

K.Sigmund, Stabile und instabile Mannigfaltigkeiten für Reaktions-Diffusionsgleichungen

H.Kauffmann, Zeitabhängige Diffusion in excitonischen Transportvorgängen

B.Rupp, Pilzgifte und Giftpilze


adidas

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Auftraggeber-Konto-Nr. (bei Verwendung als Überweisungsauftrag)
Empfänger
Kameradschaft des
Kärntner Artilleriebund
Konto-Nr. 1oo-285754 bei Bank für Kärnten und Steiermark Aktiengesellschaft KLAGENFURT
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Hinweise für den Einzahler
Seminar Theoret. Chemie
Barbarahaus, 24.-30.3.85
AUFTRAGSBESTÄTIGUNG
Quittung 27. FEB. 85
LESEZONE – BITTE UNBEDINGT VON BE

Pro

Herrn
Leutnant Knapp
Kärntner Artillerie Bund
Barbarahaus-Verwaltung
Windischkaserne
A-9020 Klagenfurt

Sehr geehrter Herr Leutnant!

Haben Sie vielen Dank für Ihr Schreiben vom 18.9.1984. Wir freuen uns sehr, daß Sie uns das Barbarahaus auch für 1985 zur Verfügung stellen können.
Wir sind mit den von Ihnen genannten Konditionen einverstanden und betrachten von uns aus die Reservierung als endgültig.

Mit bestem Dank für Ihre Mühe und freundlichen Grüßen

Ihr

(Peter Schuster)

PS: Wir werden uns selbstverständlich große Mühe geben, alle Einzelheiten der Heizordnung genau zu beachten!

The Landscape Paradigm in Evolution

History, State of the Art, and Perspectives

Peter Schuster

Institut für Theoretische Chemie, Universität Wien, Austria
and
The Santa Fe Institute, Santa Fe, New Mexico, USA

32. TBI Winter Seminar

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Santa Fe Institute Preprint Series # 12-06-006

1. Prologue
2. Quasispecies and paramuse model
3. Landscapes
4. Mutation flows and mutant clans
5. Neutrality in evolutionary dynamics
6. Concluding remarks and perspectives

1. **Prologue**
2. Quasispecies and paramuse model
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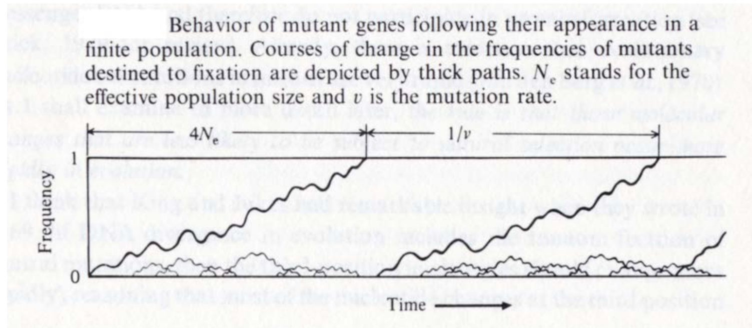
Charles Darwin,
1809 - 1882

survival of the fittest

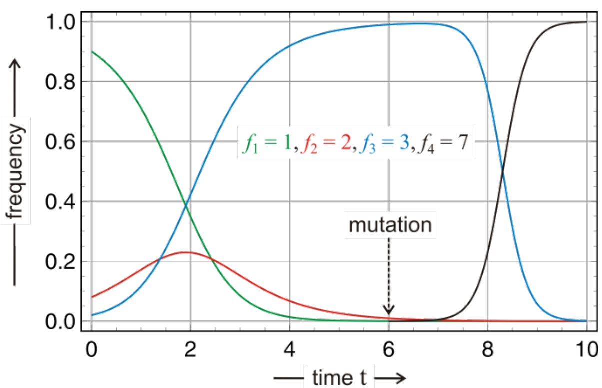
Charles Darwin,
1809 - 1882


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.

survival of the survivor

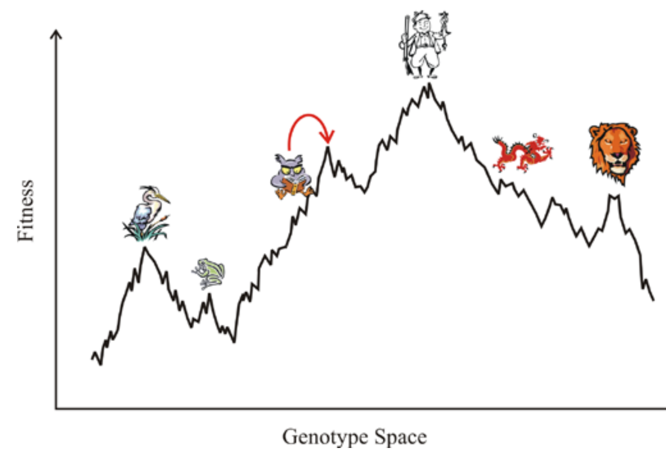
„random drift"

Sewall Wright,
1889 - 1988



survival of the fittest

Motoo Kimura,
1924 - 1994



fitness landscape

J. Wynne McCoy (1979). The Origin of the „Adaptive Landscape“ Concept. The American Naturalist 113: 610-613.

The contribution is by one Armand Janet of Toulon, France, "former naval engineer" and delegate from the "Sociètè de Spéléologie." It would be hard to find a more unlikely source for an important addition to Darwin's theory. The originality of Janet's solution to the puzzling lack of intermediate forms in the fossil record is even more striking when we discover that, of the many other prominent French zoologists attending the same congress, none participated in the section on evolution. In fact, it appears Janet's paper may be the only original theoretical contribution to Darwinian theory to come out of France before 1900.

Armand Janet (1895). Condsidérations méchanique sur l‘évolution et le problème des espéces. In Comptes Rendue des 3me Congrès International de Zoologie, pages 136-145. Leyden, NL.

The concept of an „adaptive landscape“

Sewall Wright, 1889 - 1988

+ …….. wild type

a .... alternative allele on locus A

:

:

:

abcde … alternative alleles on all five loci

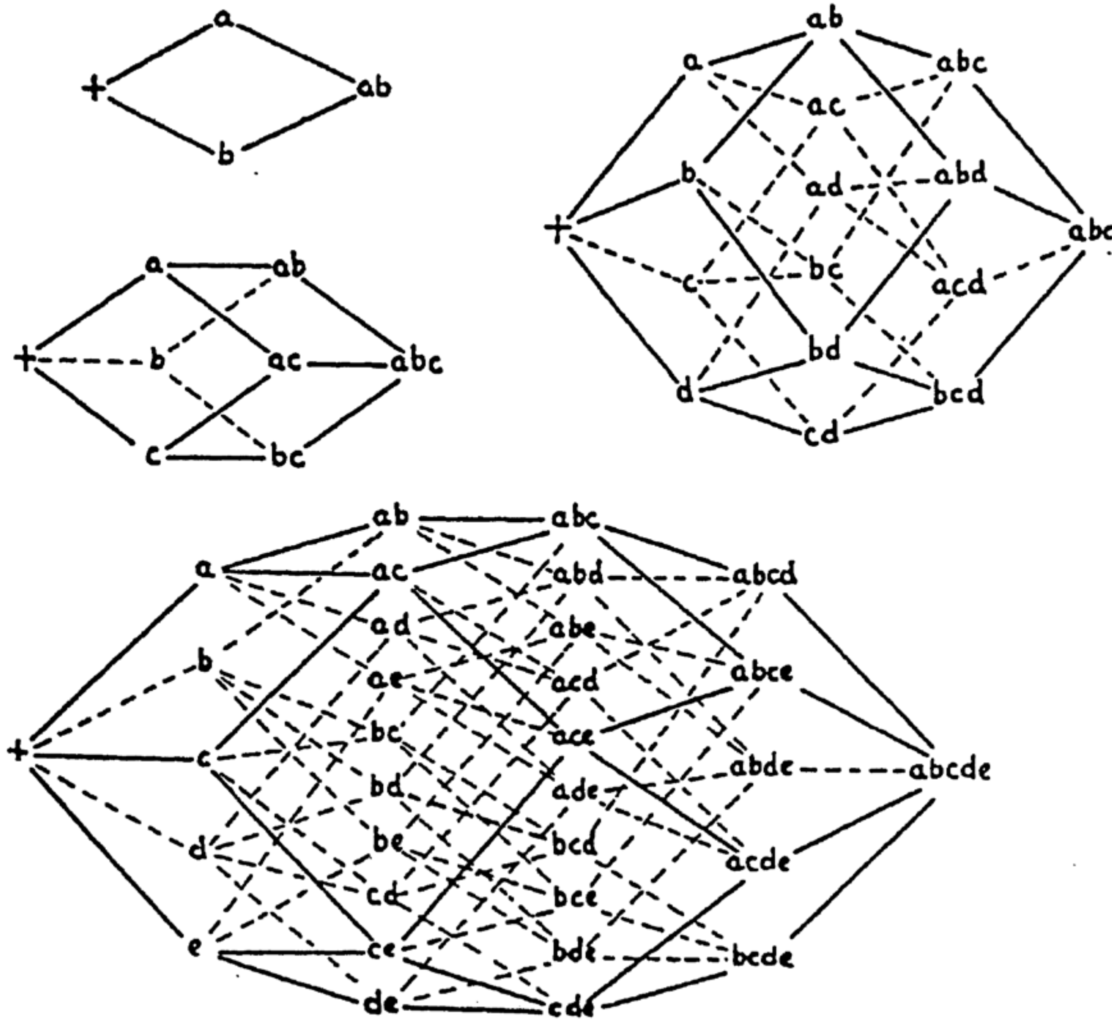


FIG. 1.—The combinations of from 2 to 5 paired allelomorphs.

The multiplicity of gene replacements with two alleles on each locus

Sewall Wright. 1988. Surfaces of selective value revisited. American Naturalist 131:115-123

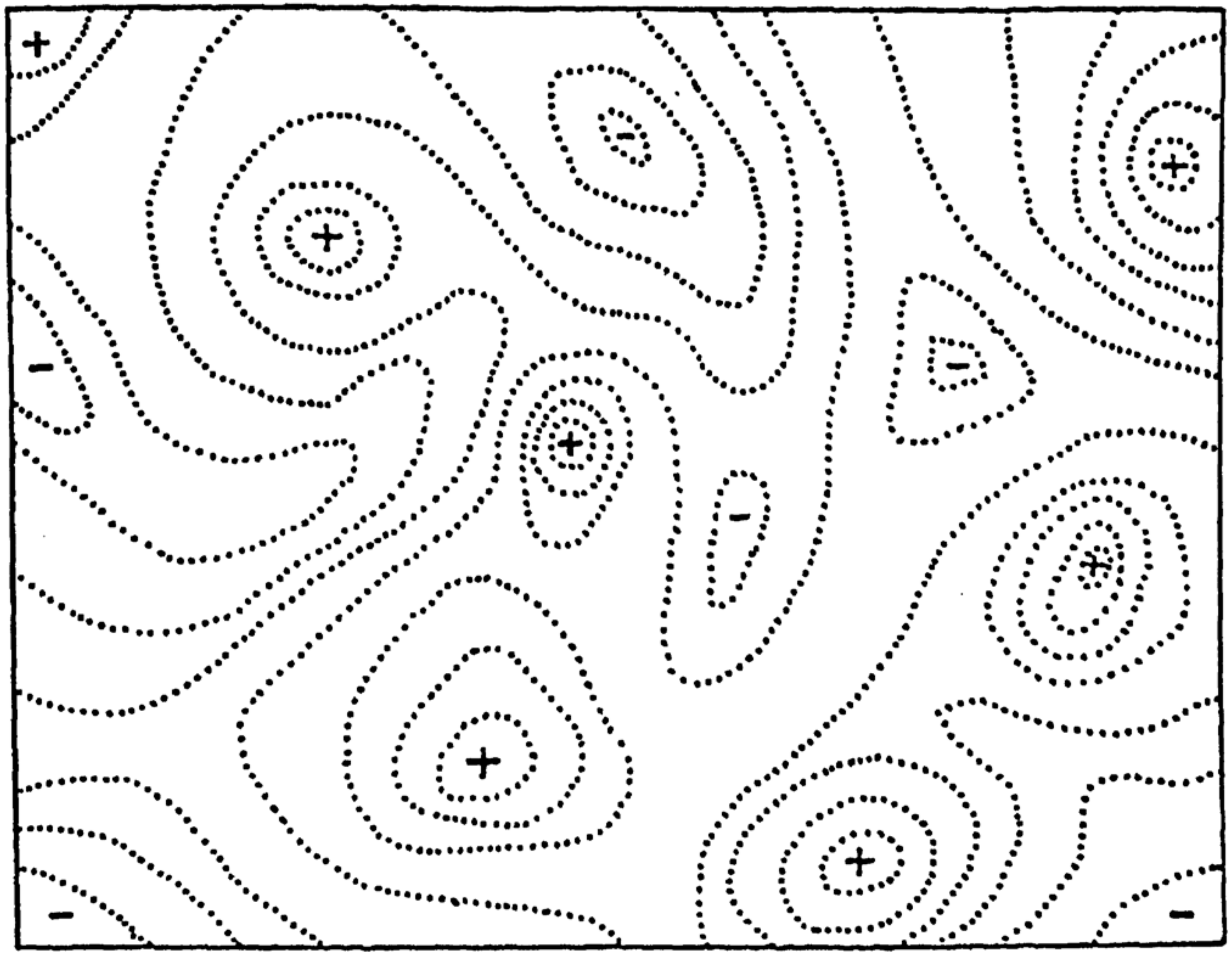
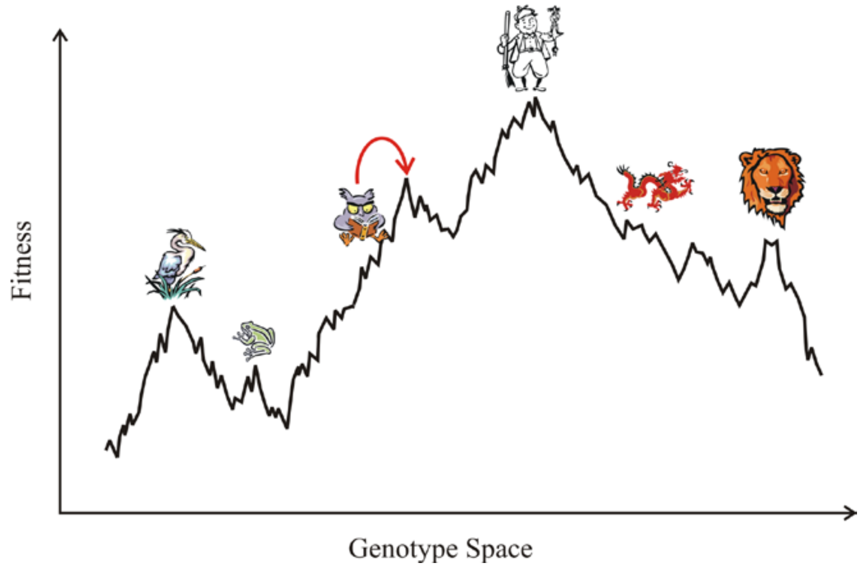


FIG. 2.—Diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands. Dotted lines represent contours with respect to adaptiveness.

Evolution is hill climbing of populations or subpopulations

Sewall Wright. 1988. Surfaces of selective value revisited. American Naturalist 131:115-123



phase (i): fitness decreases

phase (ii): fitness increases

phase (iii): fitness increases

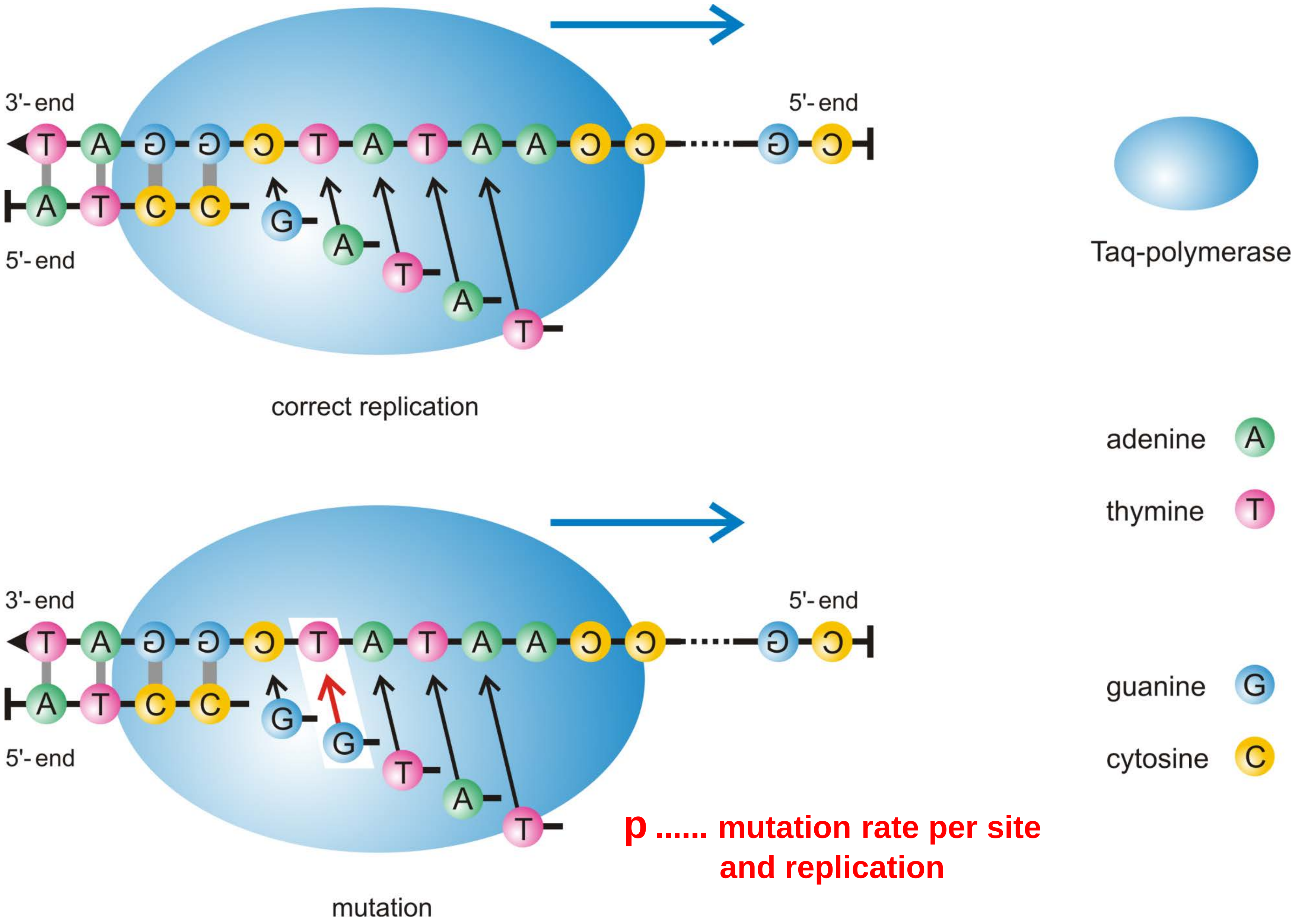
Evolution in three phases:

(i) random genetic drift and partitioning of the global population into subpopulations,

(ii) adaptive selection within subpopulations, and

(iii) adaptive selection between subpopuolations.

Sewall Wright's shifting balance model of evolution



DNA replication and mutation

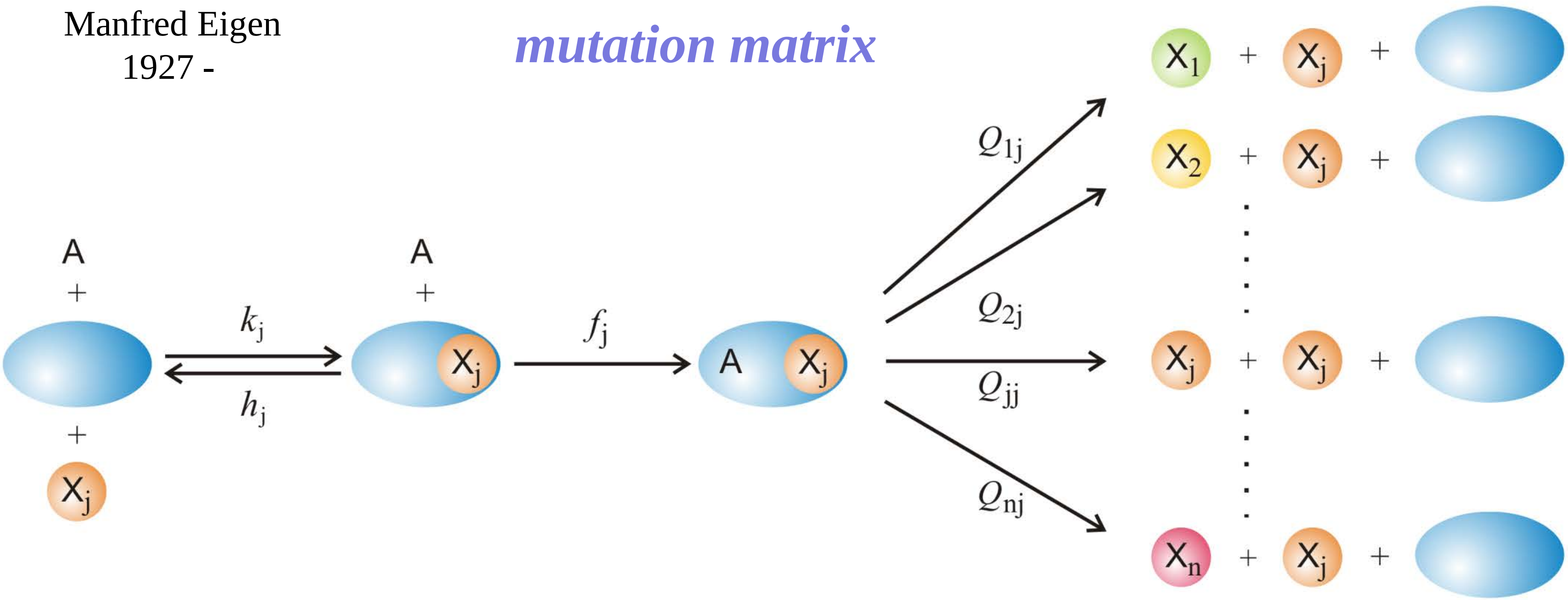
Manfred Eigen
1927 -

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

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

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

Manfred Eigen
1927 -

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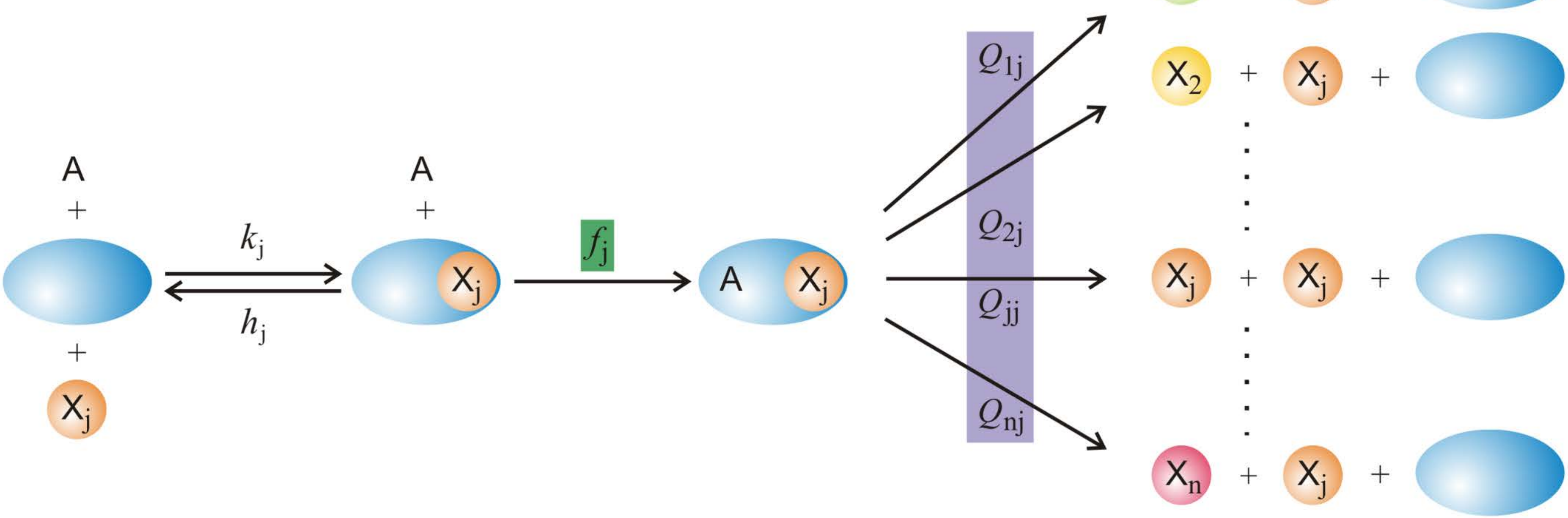
fitness landscape

mutation matrix



Mutation and (correct) replication as parallel chemical reactions

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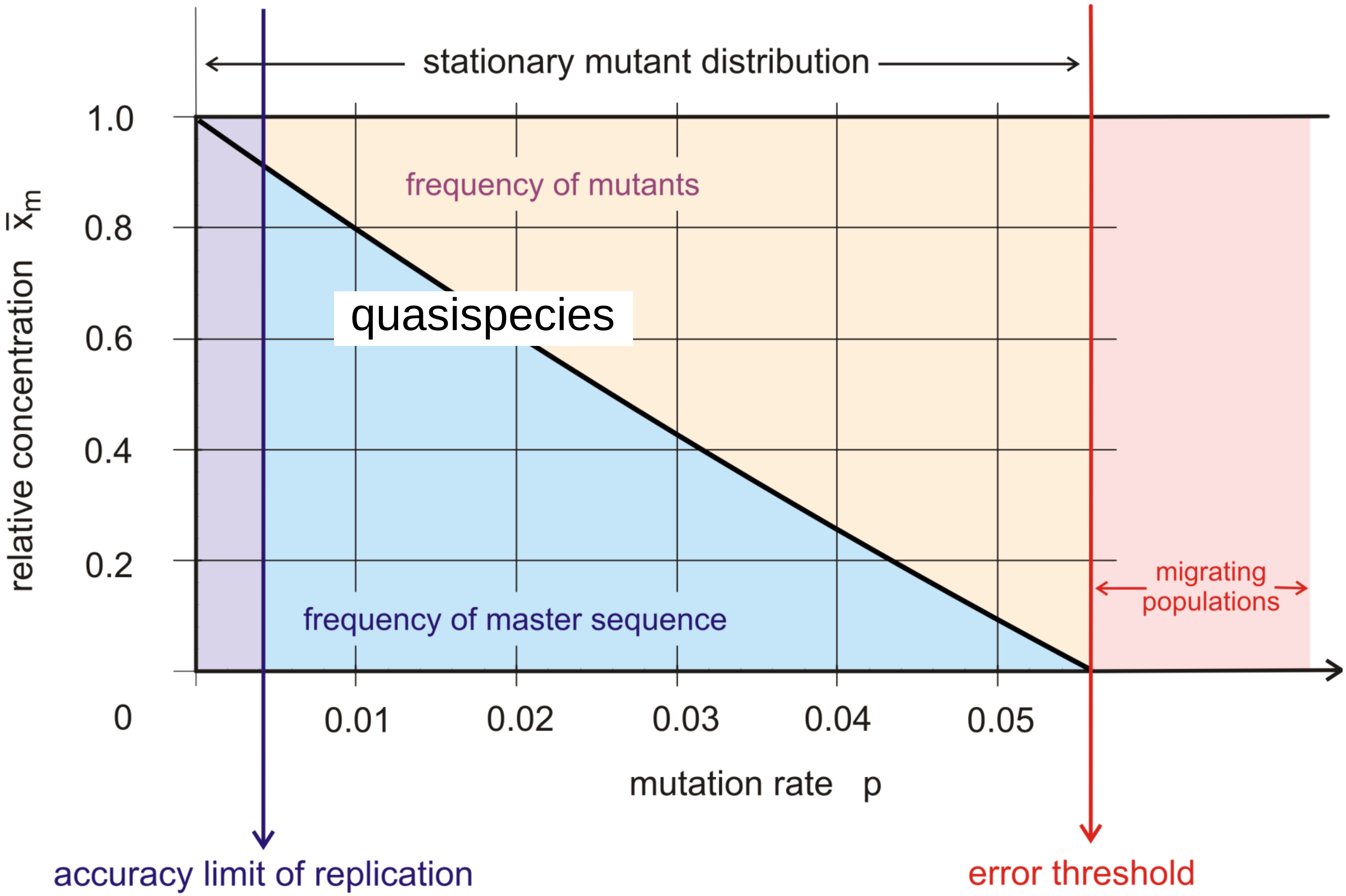
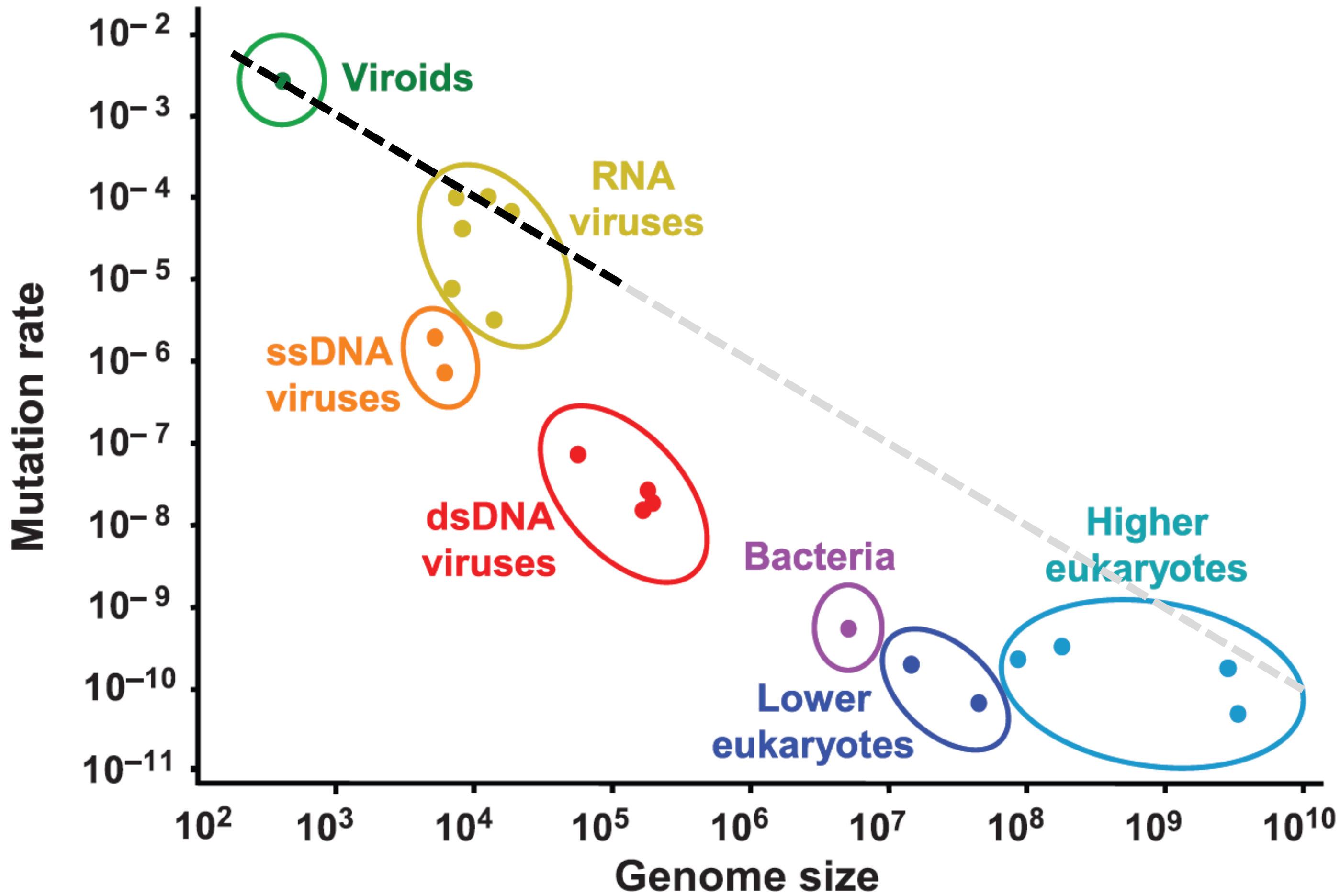


The error threshold in replication and mutation



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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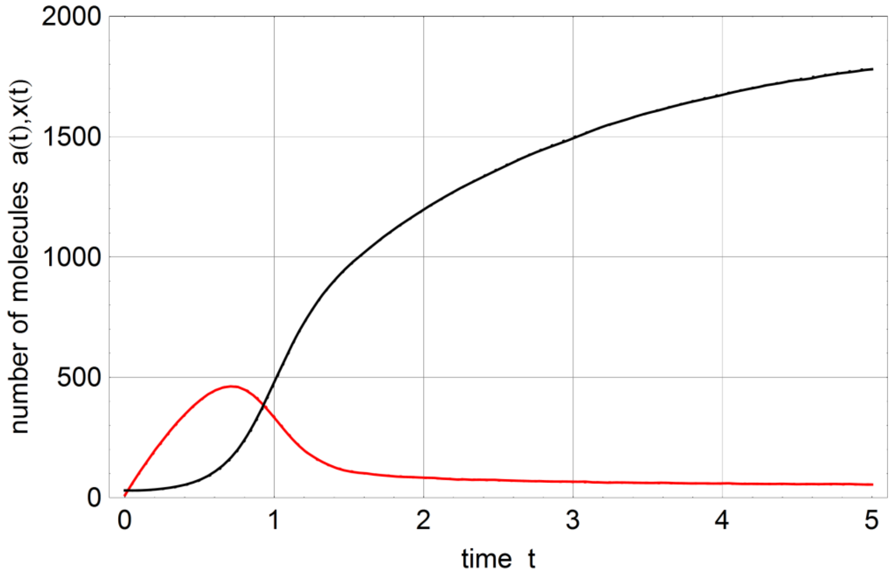
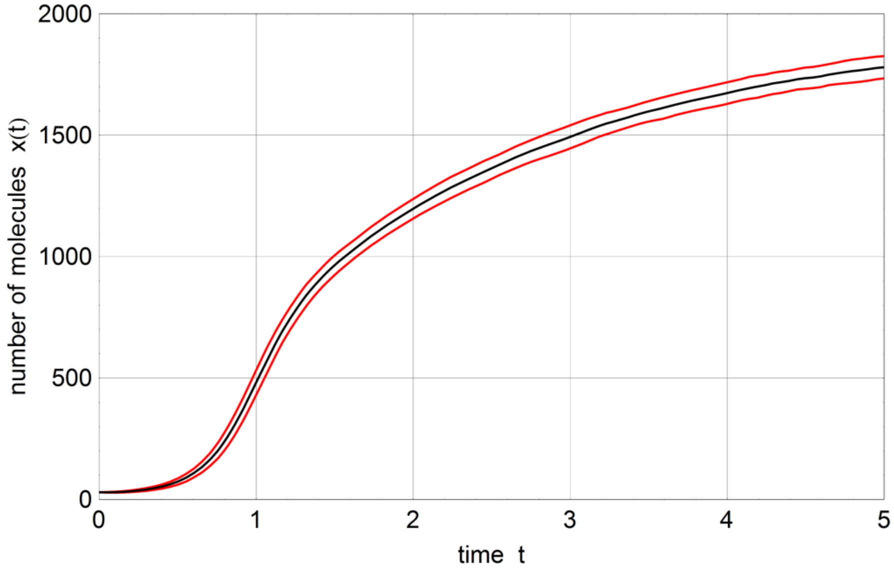
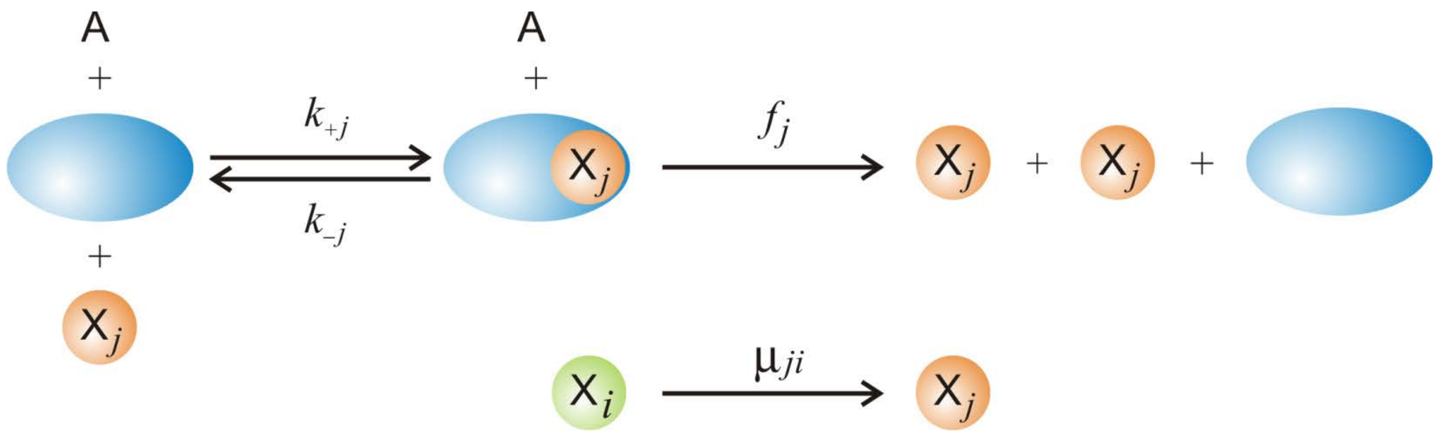
A , X



E ± σ

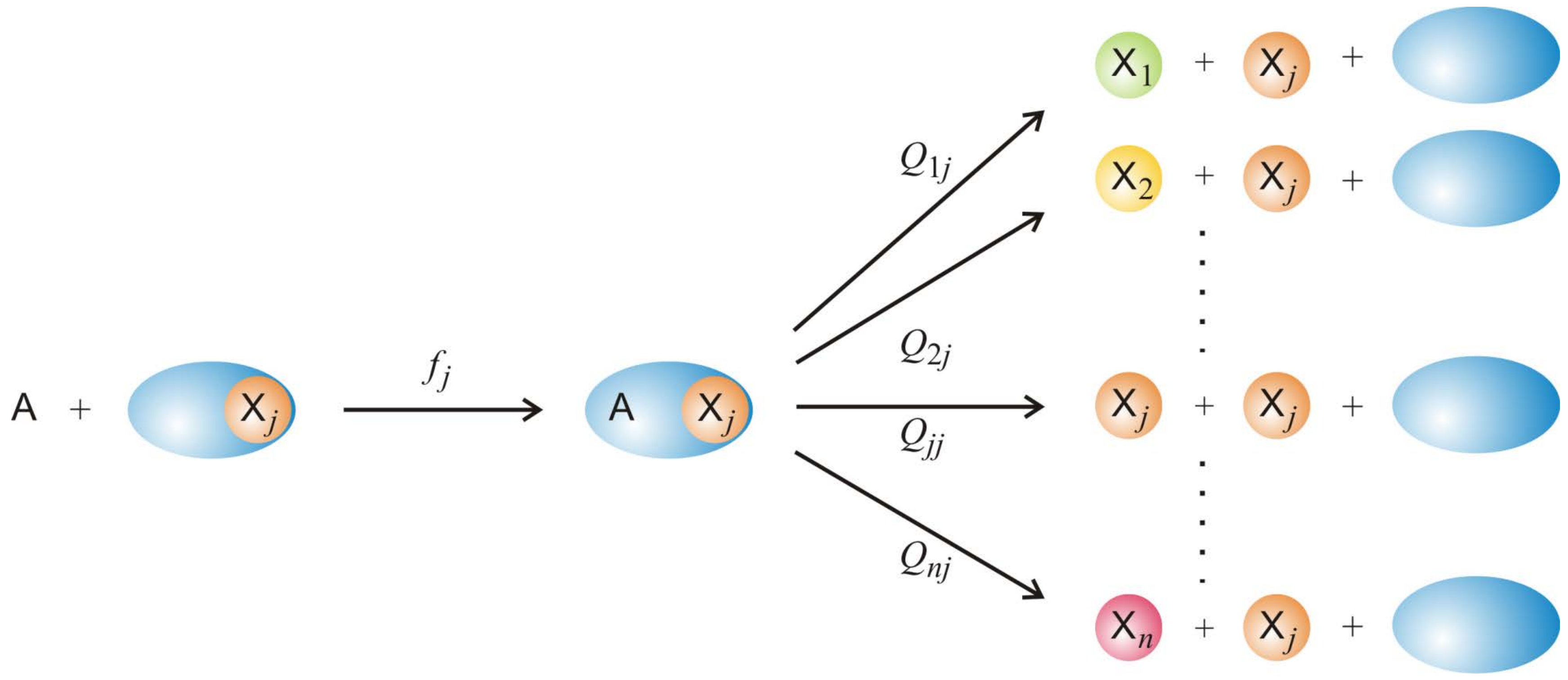


Autocatalysis A + X → 2 X in the flow reactor



$$W = r + \mu$$

The paramuse or Crow-Kimura model of reproduction and mutation



$$W = Q \cdot F$$

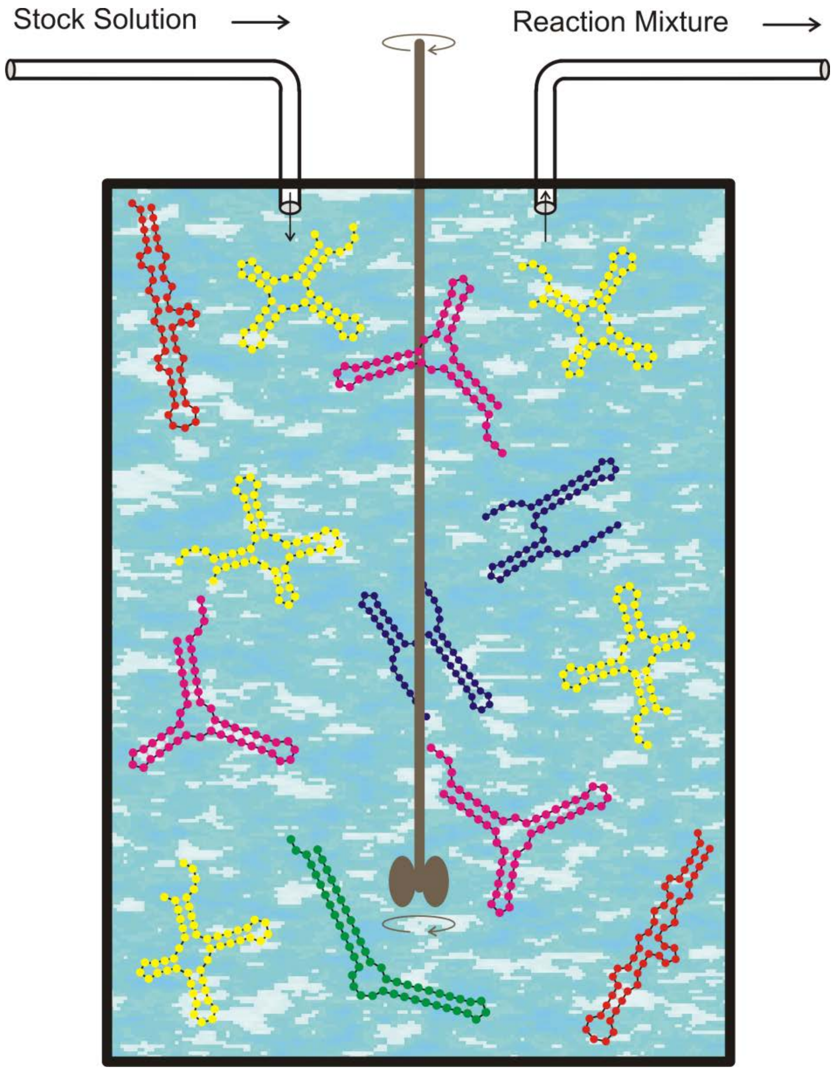
The quasispecies model of reproduction and mutation

$$* \rightarrow A$$

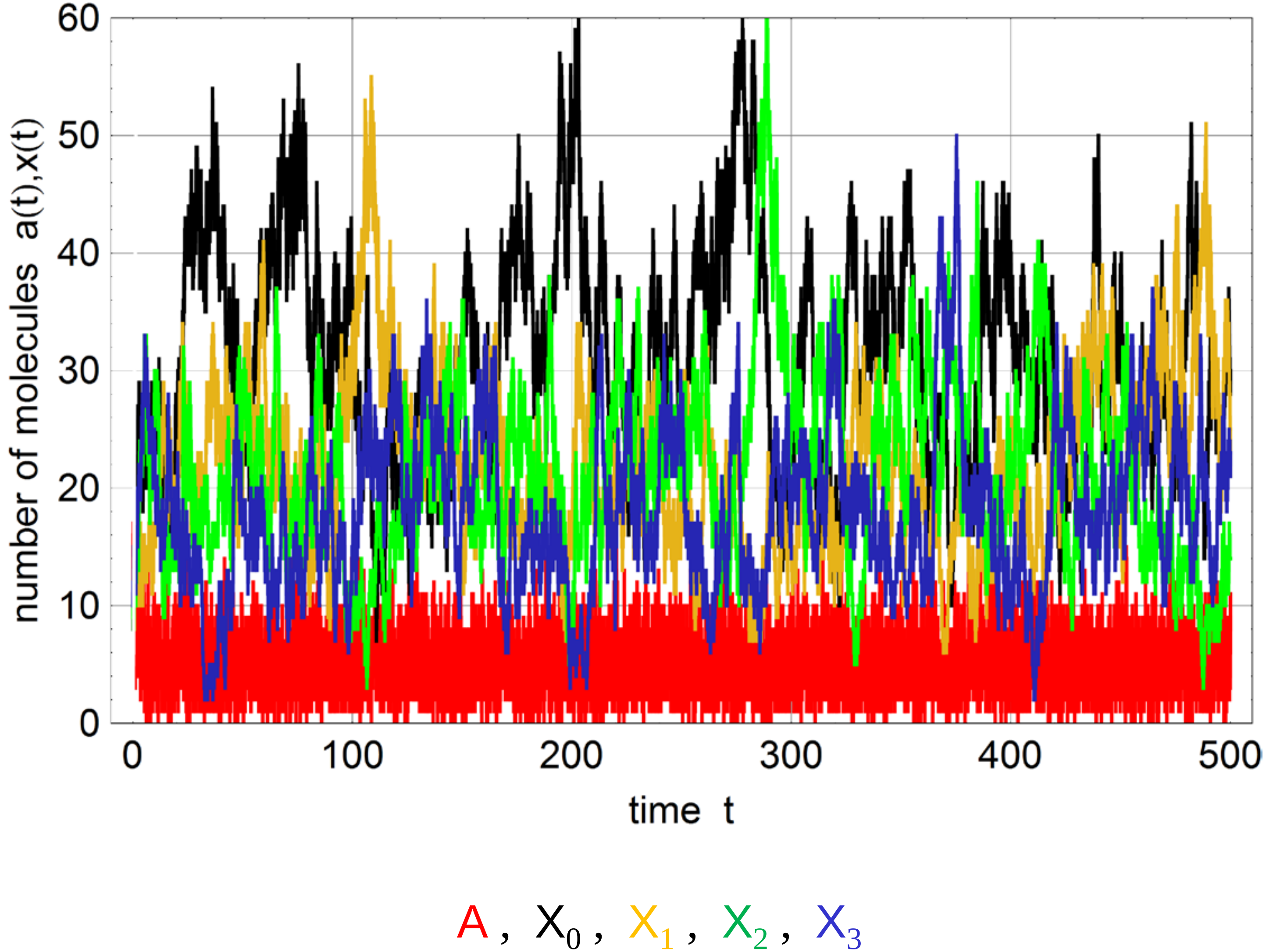
$$X_i \rightarrow X_j + X_i$$

$$A \rightarrow \varnothing$$

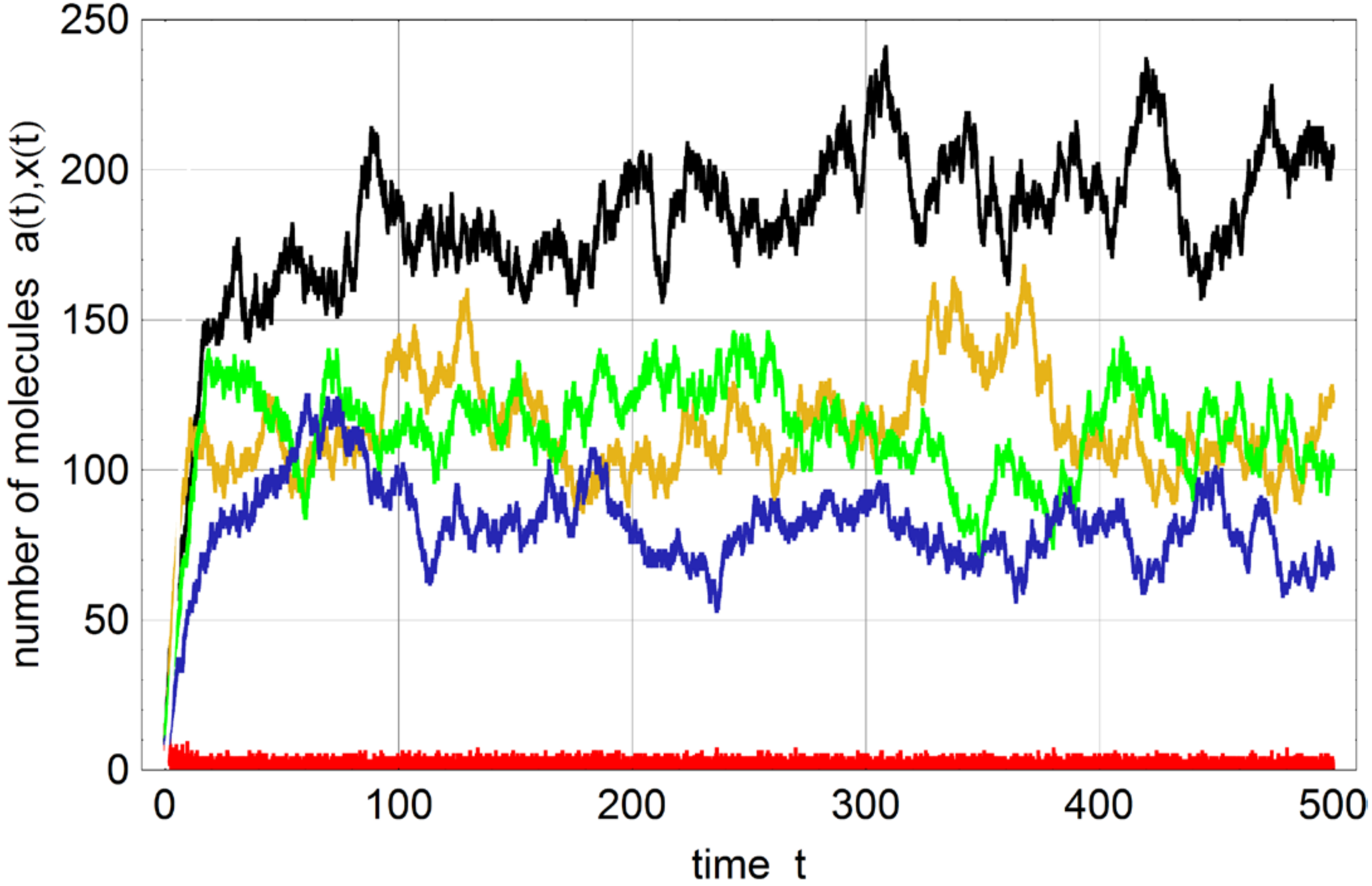
$$X_j \rightarrow \varnothing$$



Quasispecies formation in the flow reactor



Quasispecies formation in the flowreactor

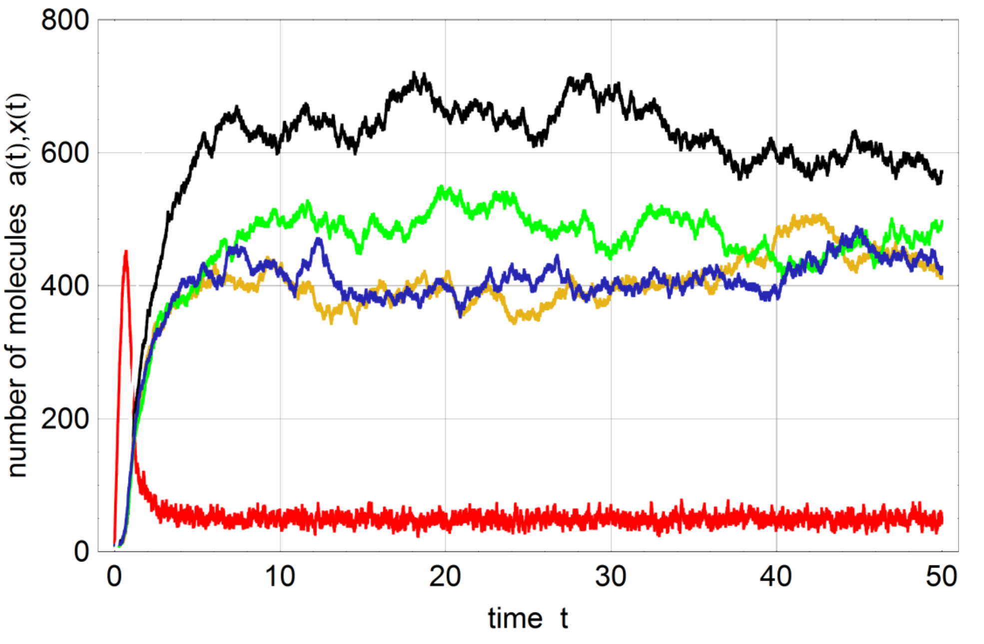


A , X_0 , X_1 , X_2 , X_3

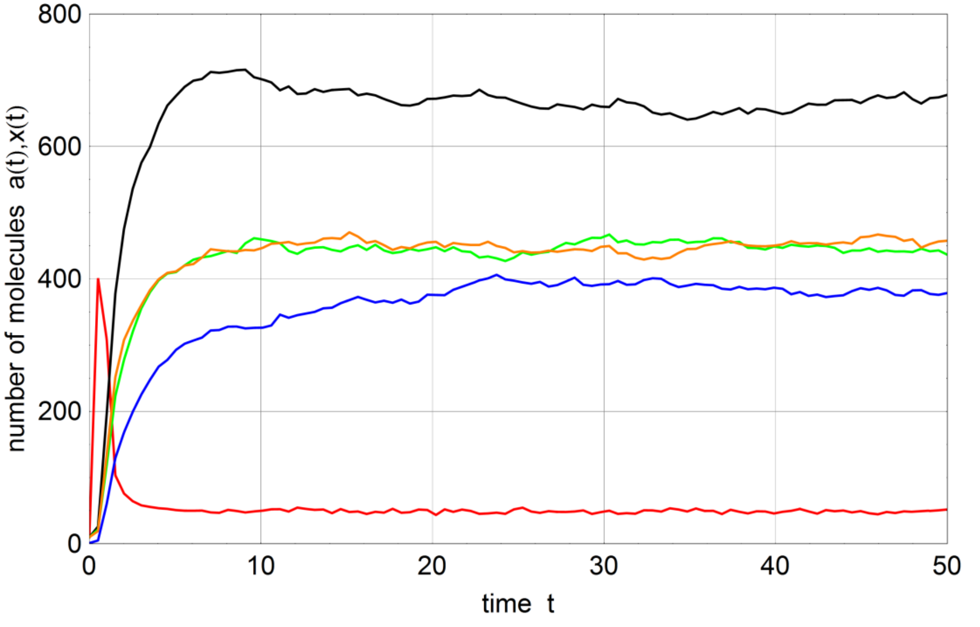
Quasispecies model in the flowreactor

single trajectory

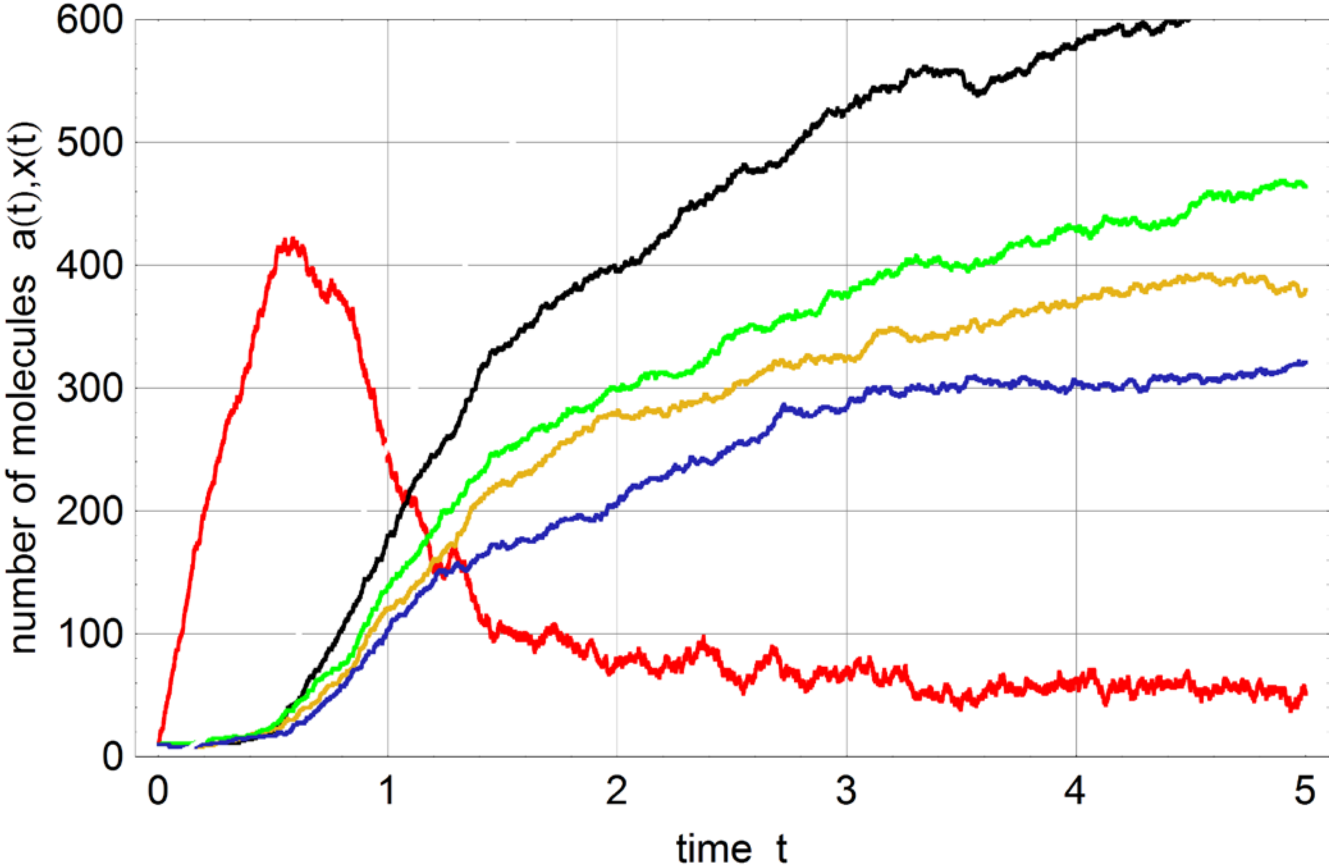
A , X_0 , X_1 , X_2 , X_3



expectation values of 100 trajectories

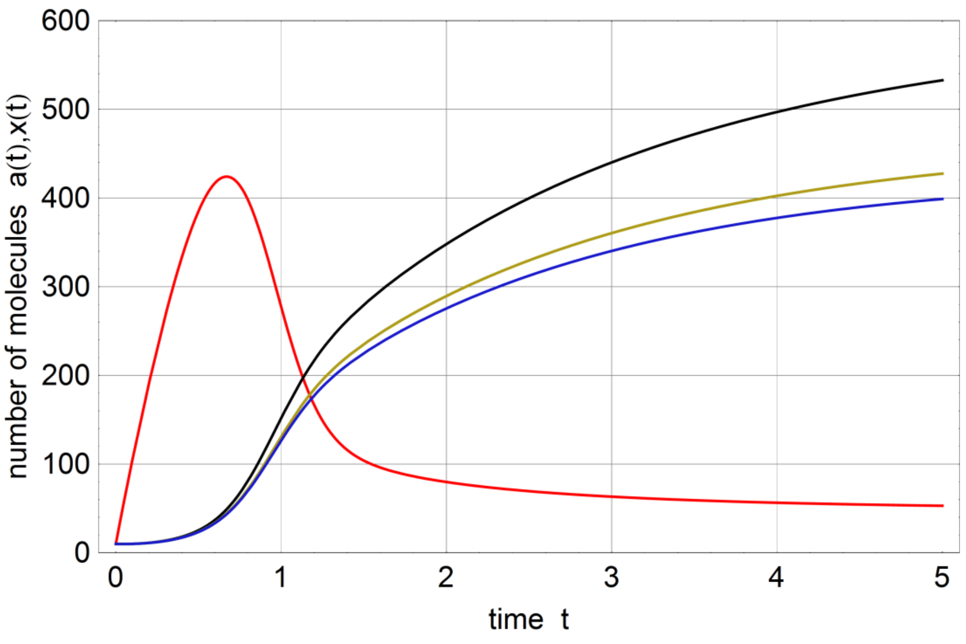


Quasispecies formation in the flow reactor



A , X_0 , X_1 , X_2 , X_3

Quasispecies formation in the flow reactor

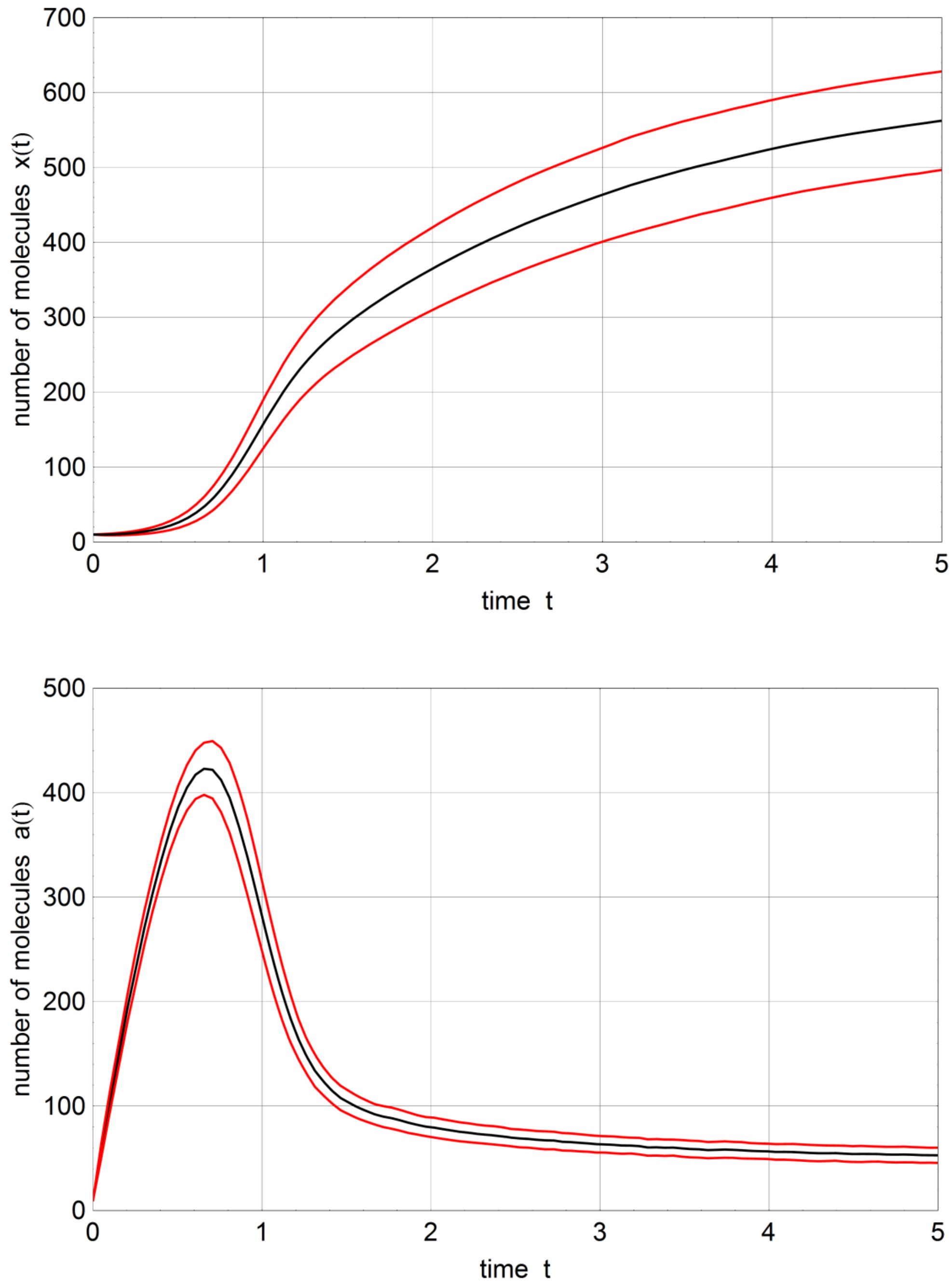


A , X_0 , X_1 , X_2 , X_3

expectation values from 1000 trajectories

Quasispecies formation in the flow reactor

fluctuations: E ± σ



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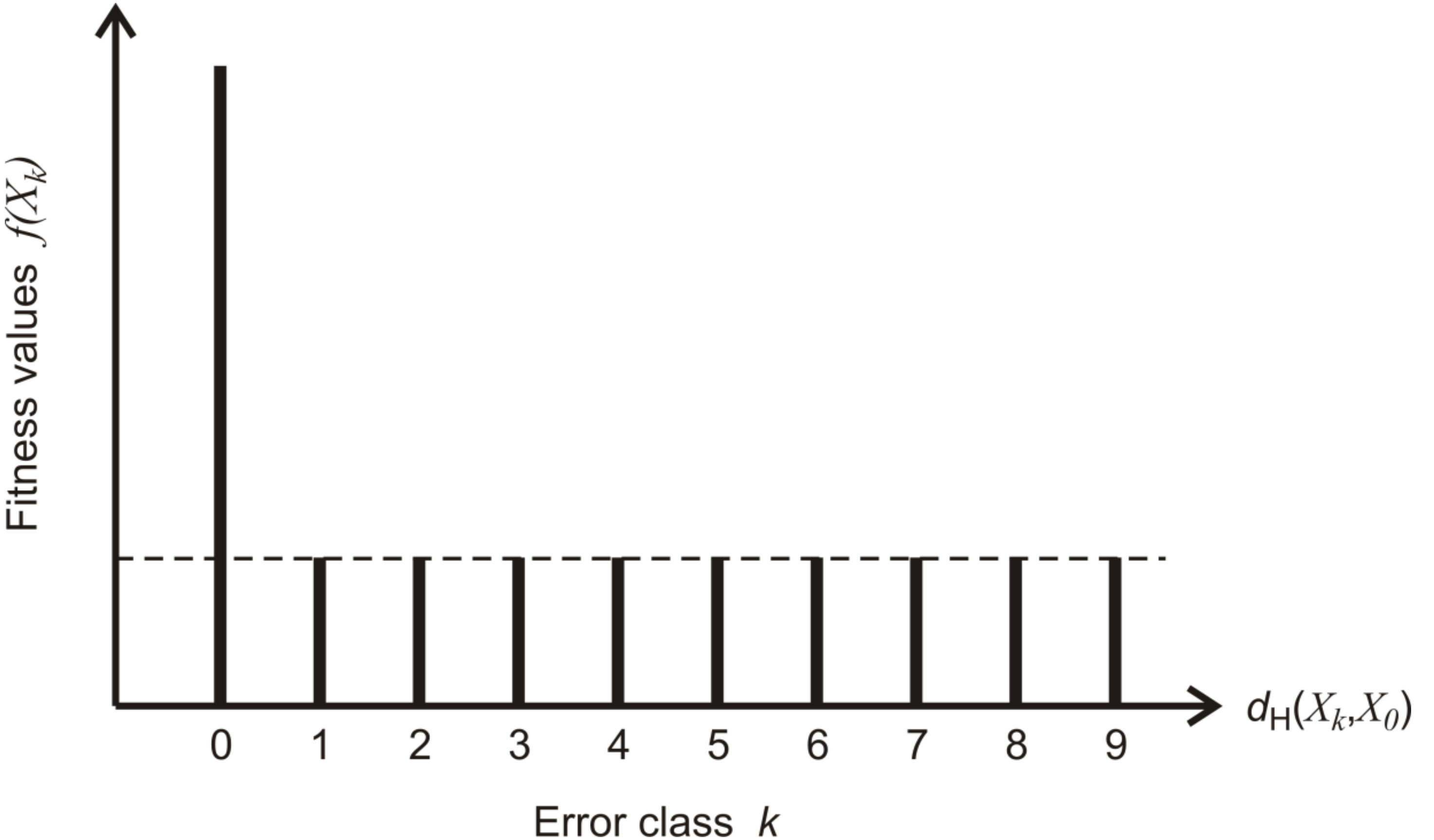
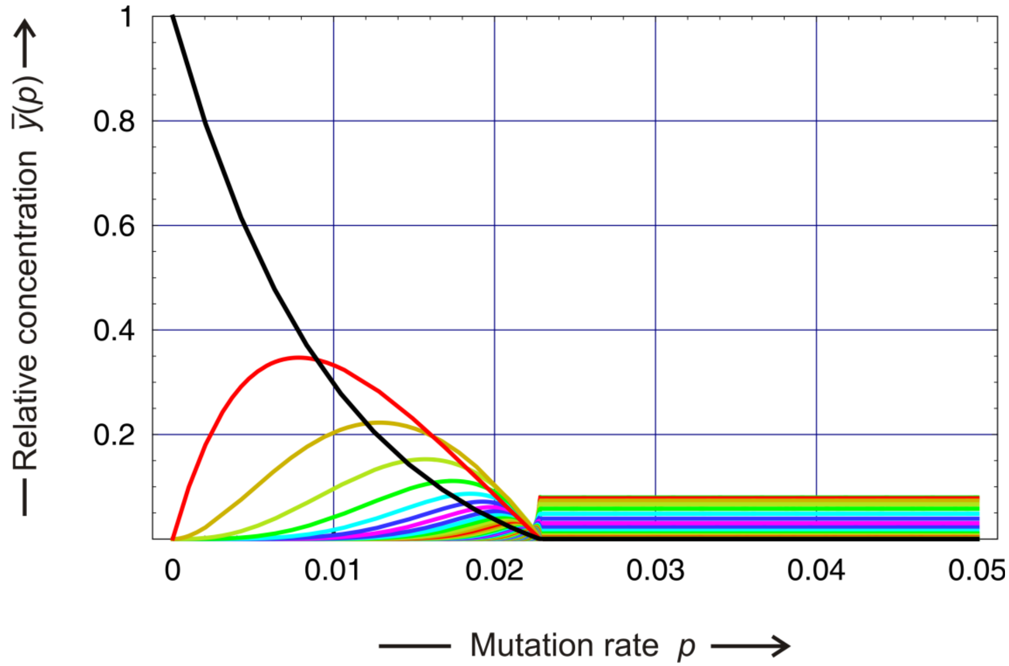
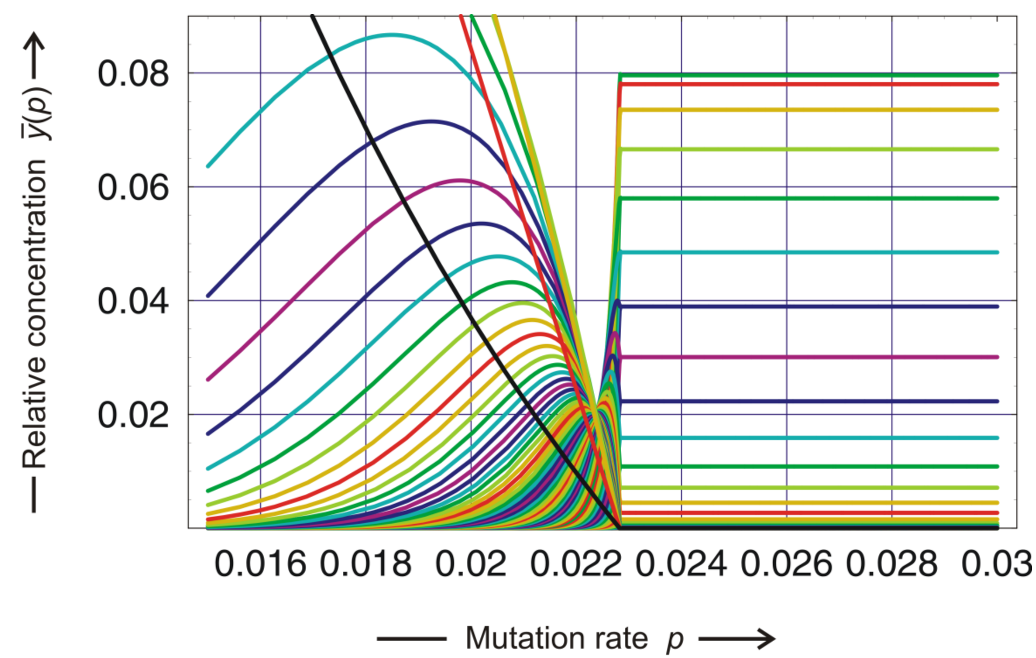


Single peak landscape

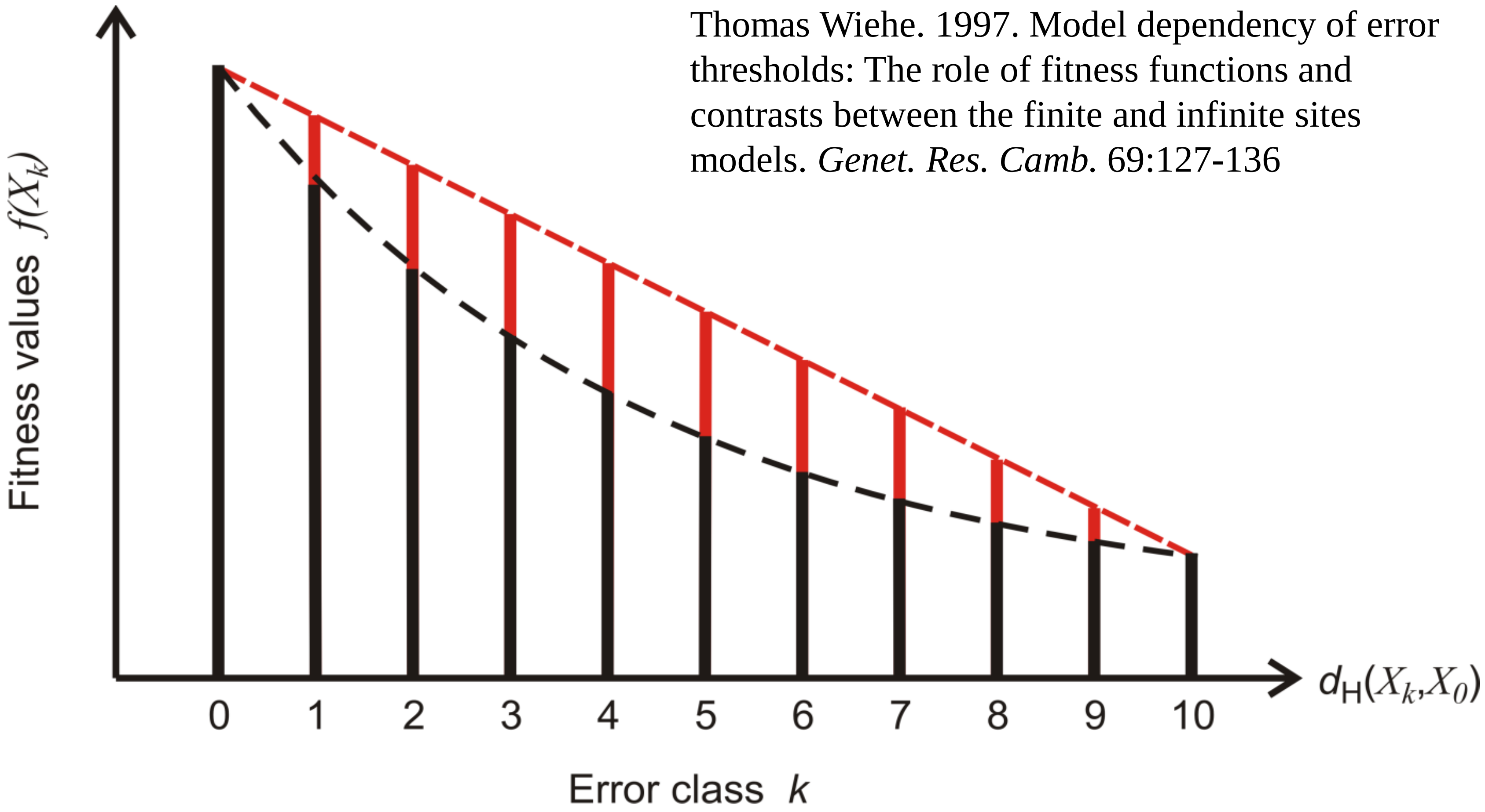
Model fitness landscapes I





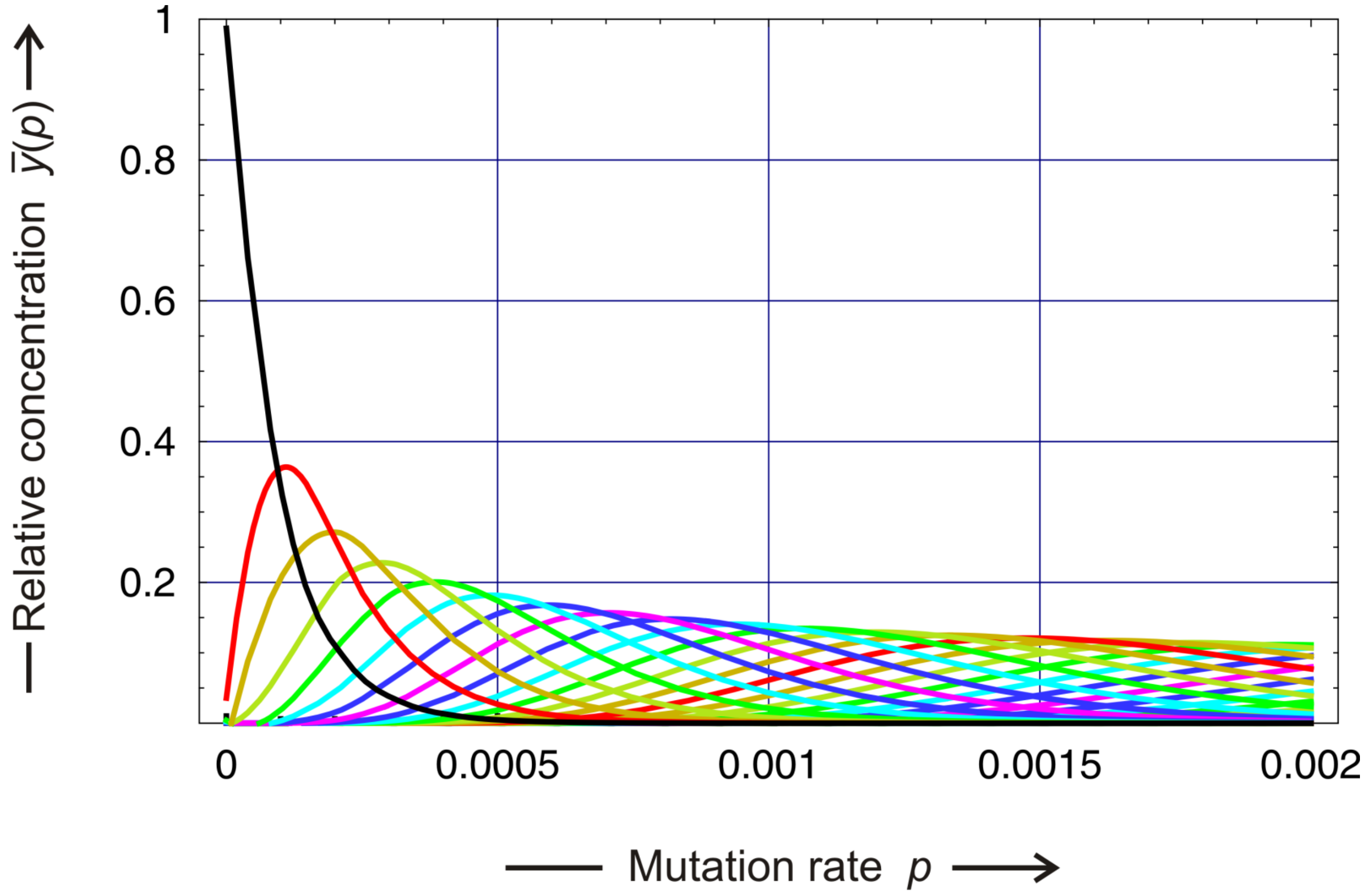
Error threshold on the single peak landscape

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

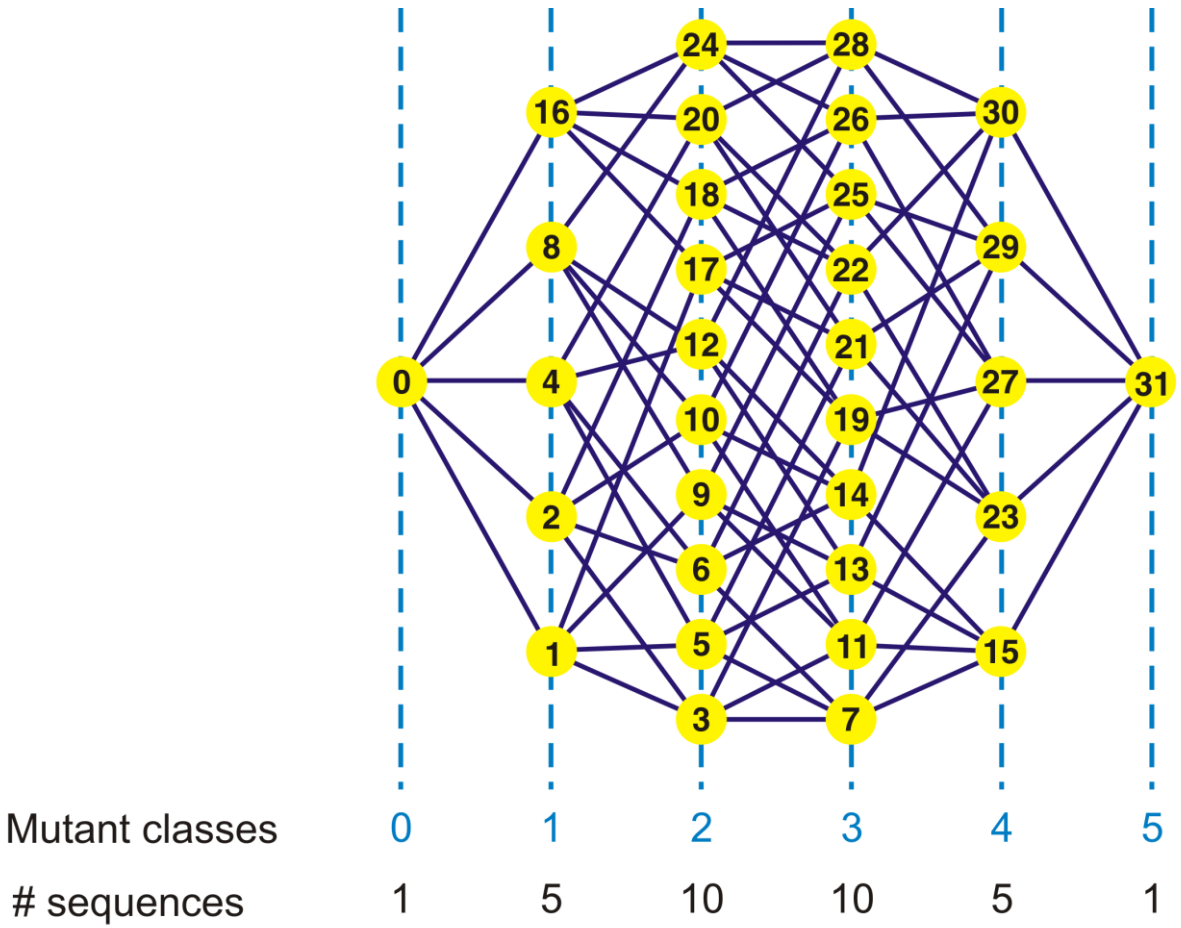


Linear and multiplicative fitness

Model fitness landscapes II



The linear fitness landscape does not show an error threshold



Binary sequences are encoded by their decimal equivalents:

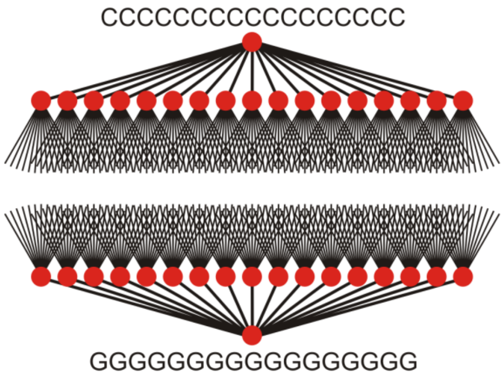
C = 0 and G = 1, for example,

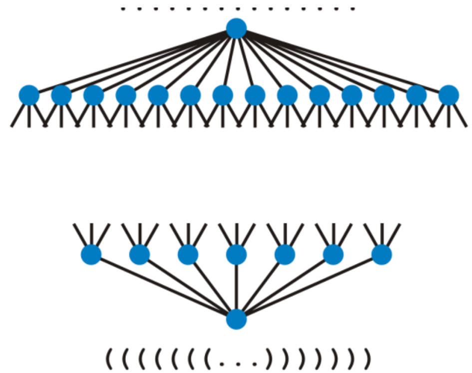
"0" ≡ 00000 = CCCCC,

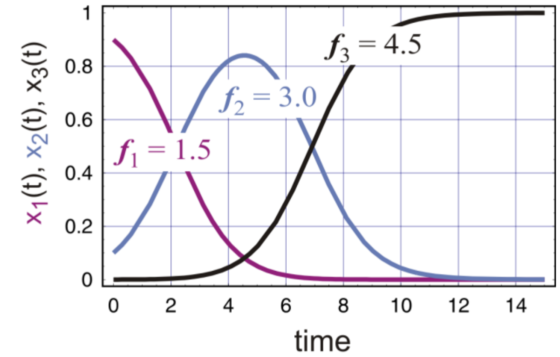
"14" ≡ 01110 = CGGGC,

"29" ≡ 11101 = GGGCG, etc.

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







sequence space	shape space	parameter space
$\mathcal{Q}$	$\mathcal{S}$	$\mathbb{R}_+$

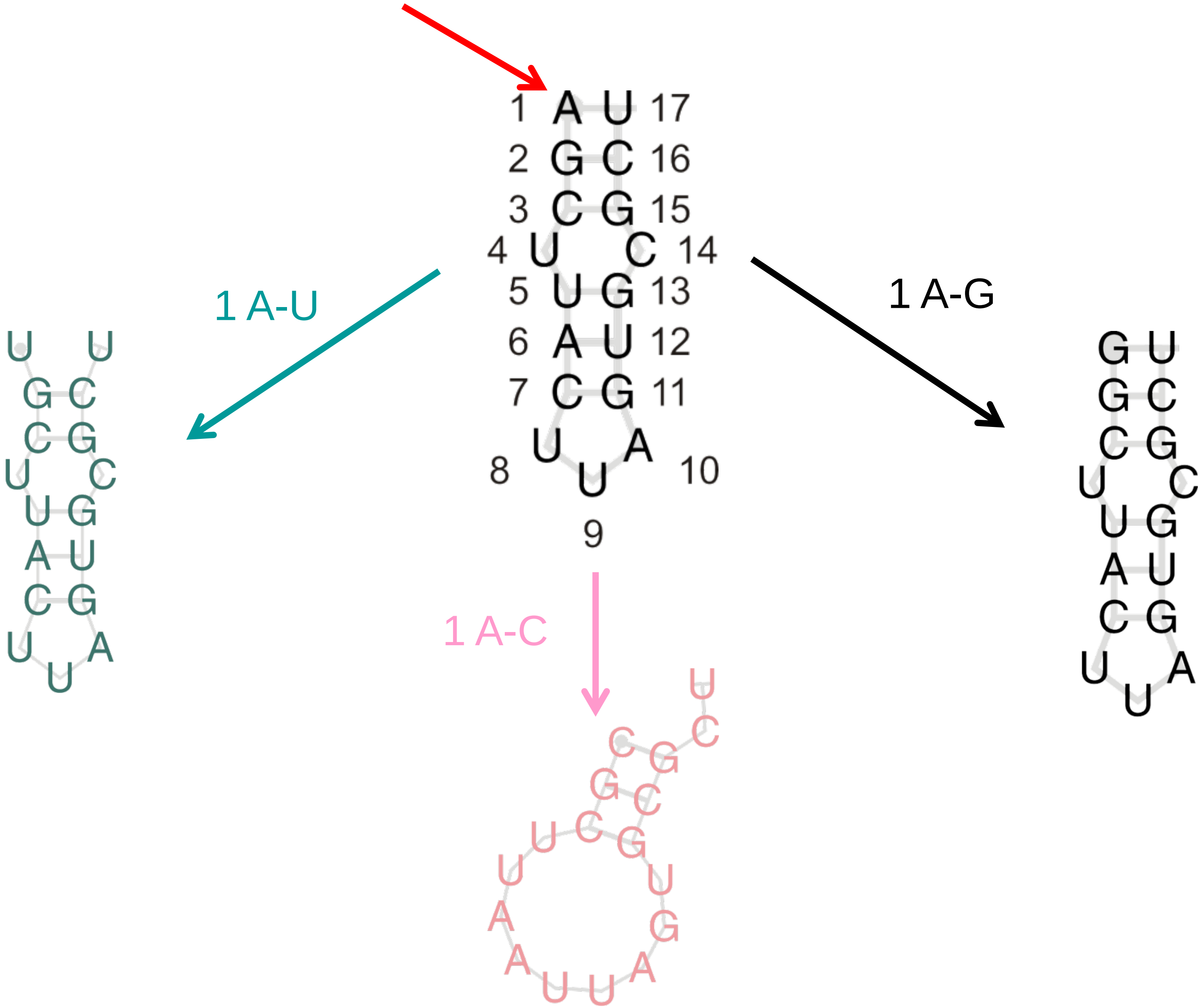
$$\Phi: (\mathcal{Q}, d_H) \Rightarrow (\mathcal{S}, d_S) \qquad \Psi: (\mathcal{S}, d_S) \Rightarrow \mathbb{R}_+$$

$$X \longrightarrow S = \Phi(X) \longrightarrow f = \Psi(S)$$

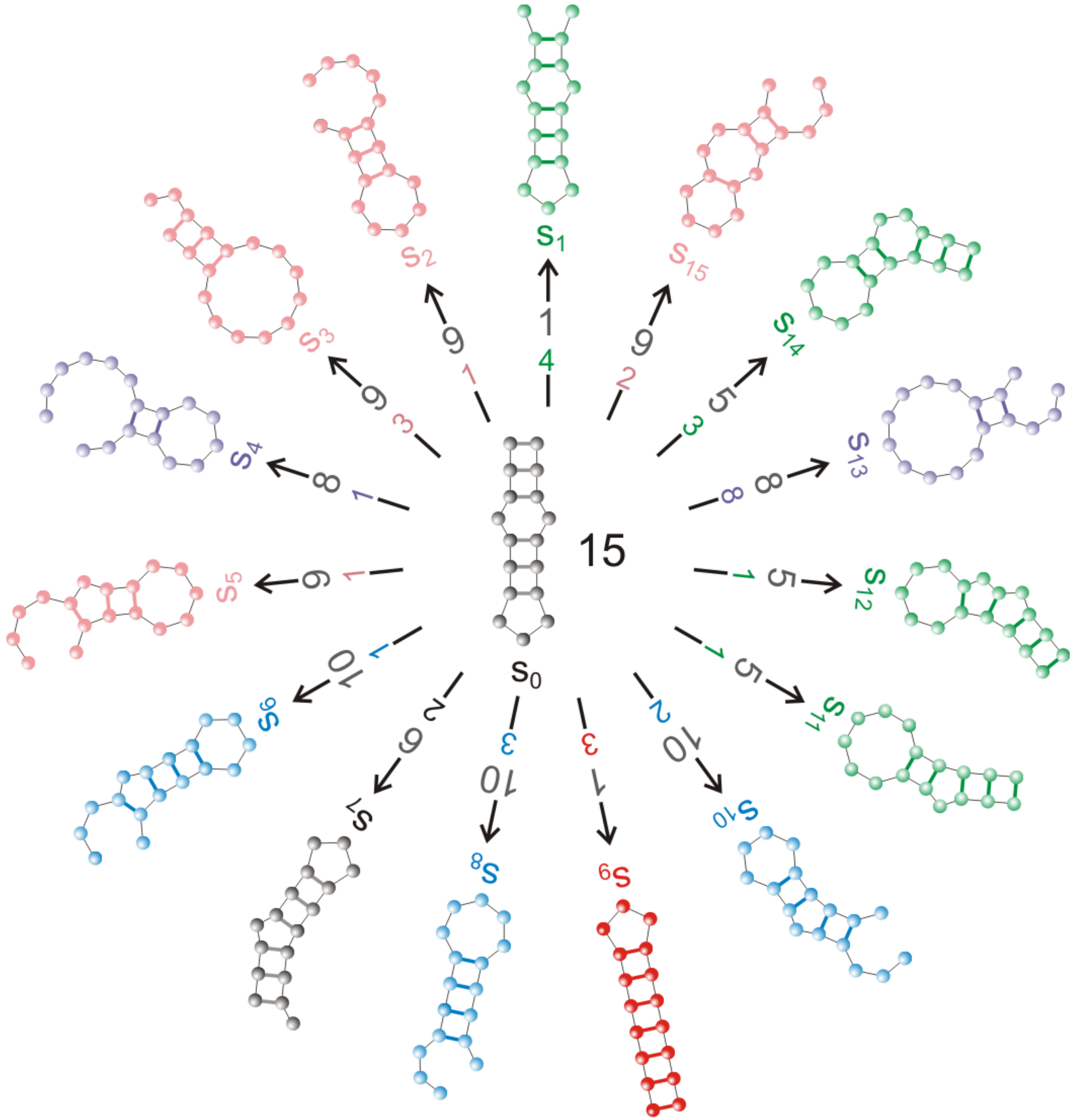
sequence → structure → function

genotype → **phenotype** → **selection**

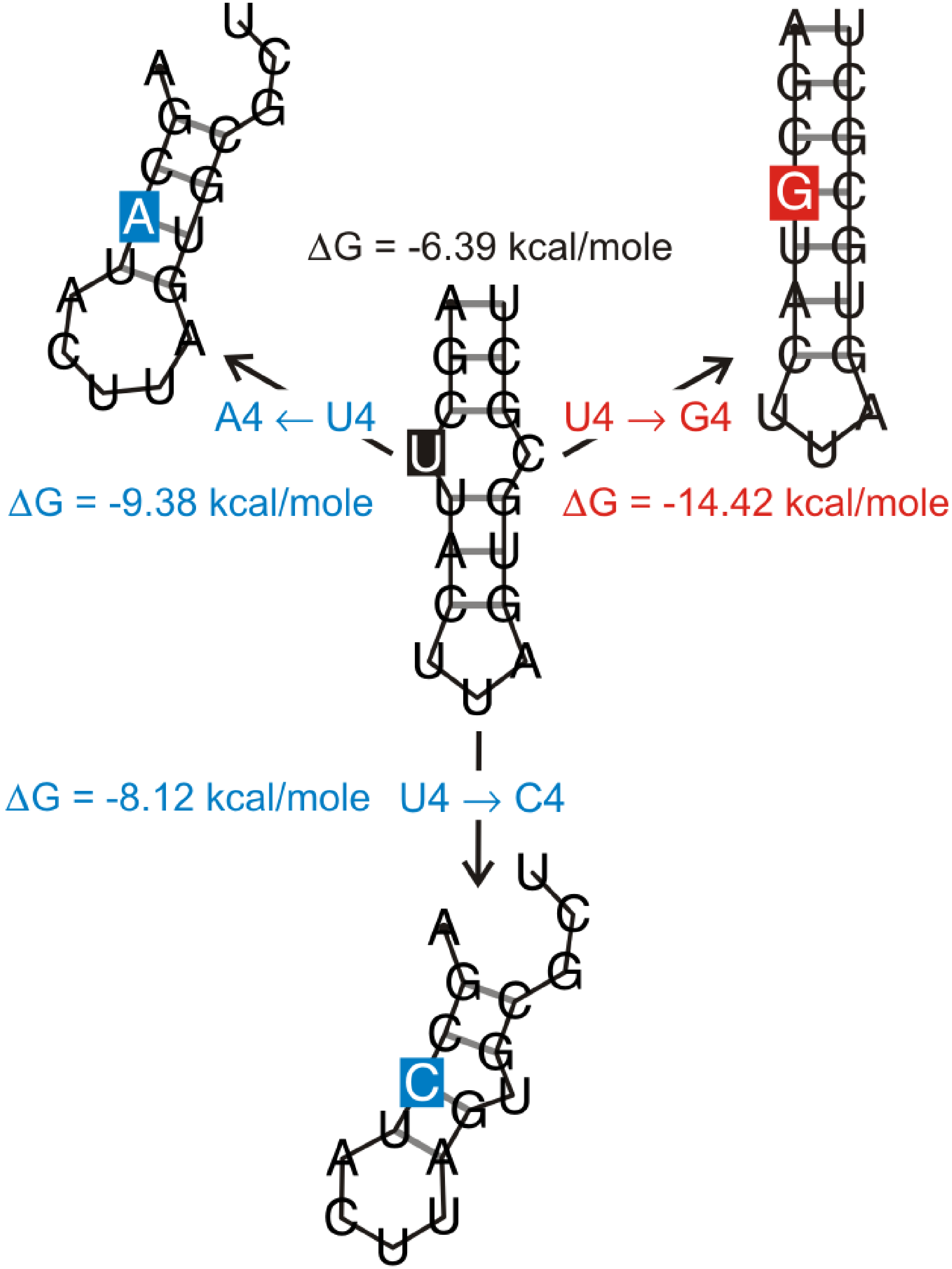
Evolution as a global phenomenon in genotype space

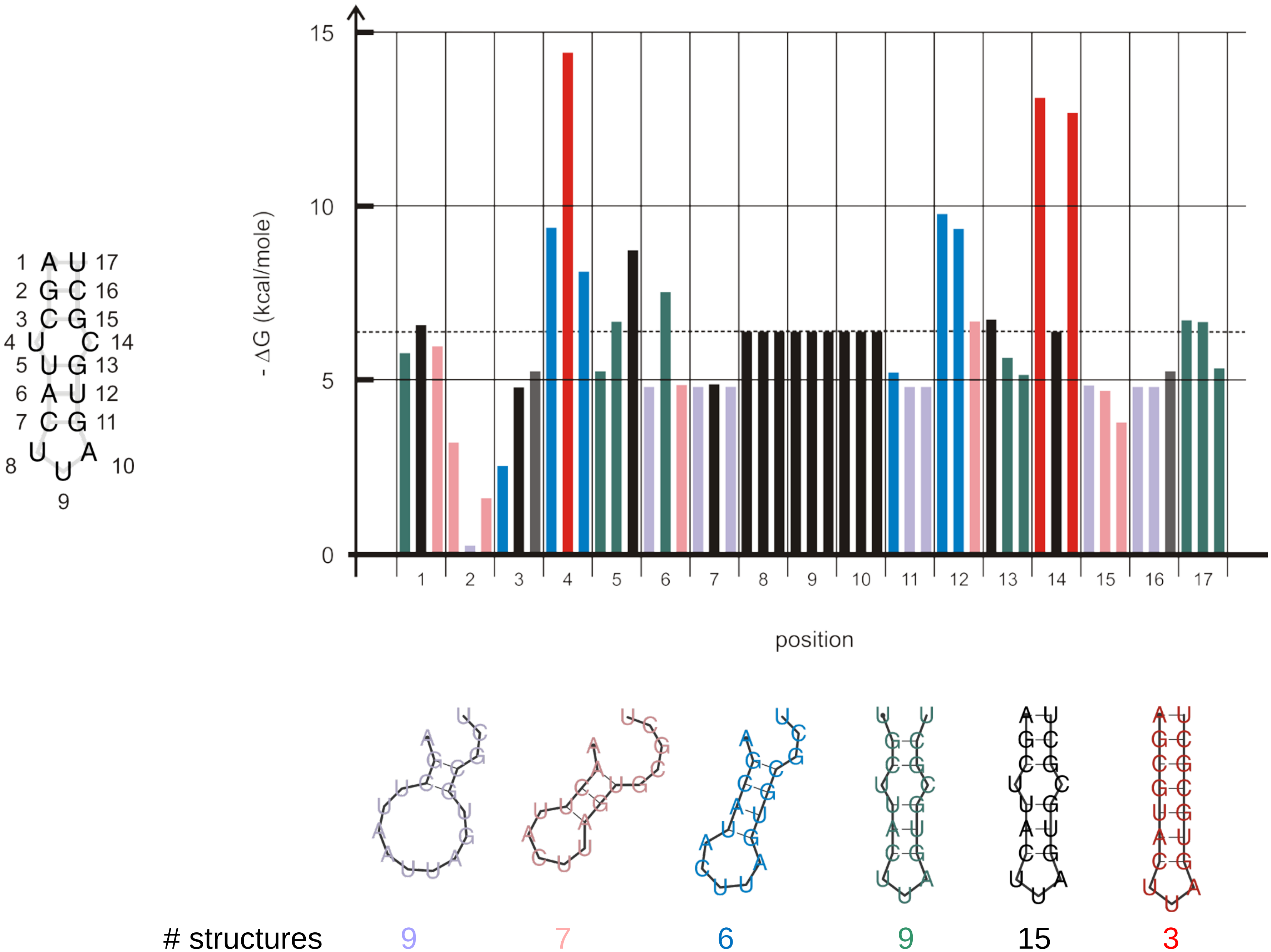


AGCUUAACUUAGUCGCU

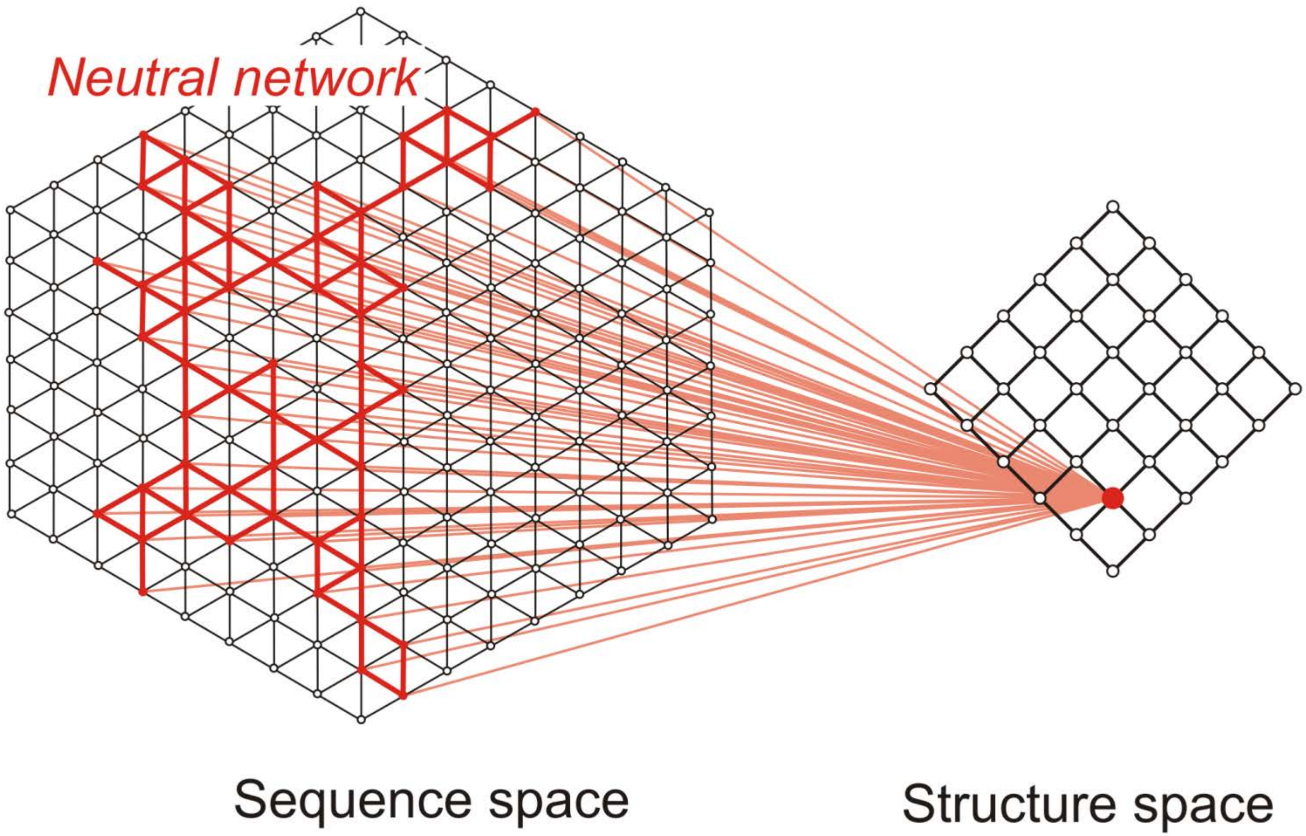


15
S0
S1
S2
S3
S4
S5
S6
S7
S8
S9
S10
S11
S12
S13
S14
S15


ΔG = -6.39 kcal/mole
A4 ← U4
ΔG = -9.38 kcal/mole
U4 → G4
ΔG = -14.42 kcal/mole
ΔG = -8.12 kcal/mole
U4 → C4



1 A U 17
2 G C 16
3 C G 15
4 U C 14
5 U G 13
6 A U 12
7 C G 11
8 U A 10
U
9
15
10
5
0
- ΔG (kcal/mole)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
position
structures
9
7
6
9
15
3



many genotypes ⇒ one phenotype

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. Elesvier, 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

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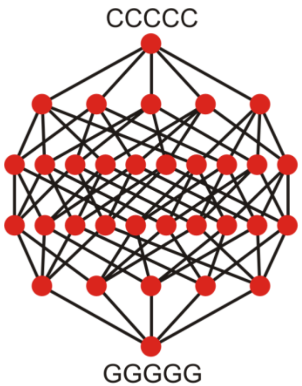
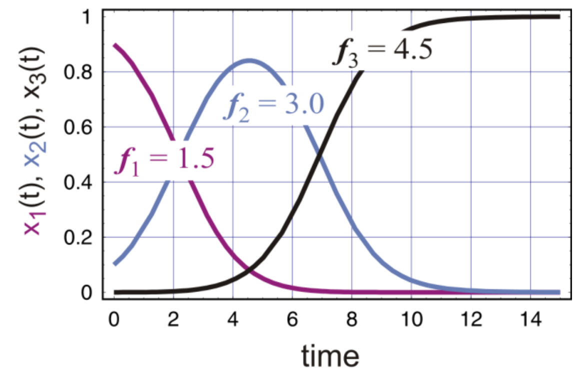


sequence space



parameter space

S

sequence

$$f = \Psi(Y)$$

function

The simplified model

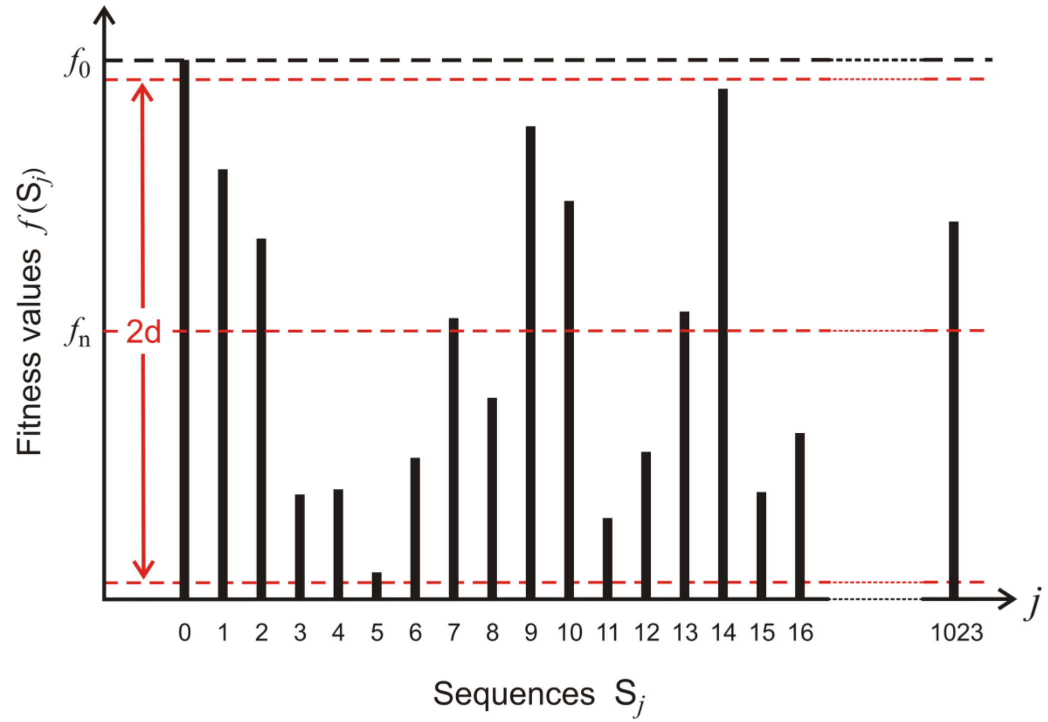
$$f(S_j) = f_n + 2d\,(f_0 - f_n)\left(\eta_j^{(s)} - 0.5\right)$$

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

η … random number

s … seeds

„realistic" landscape



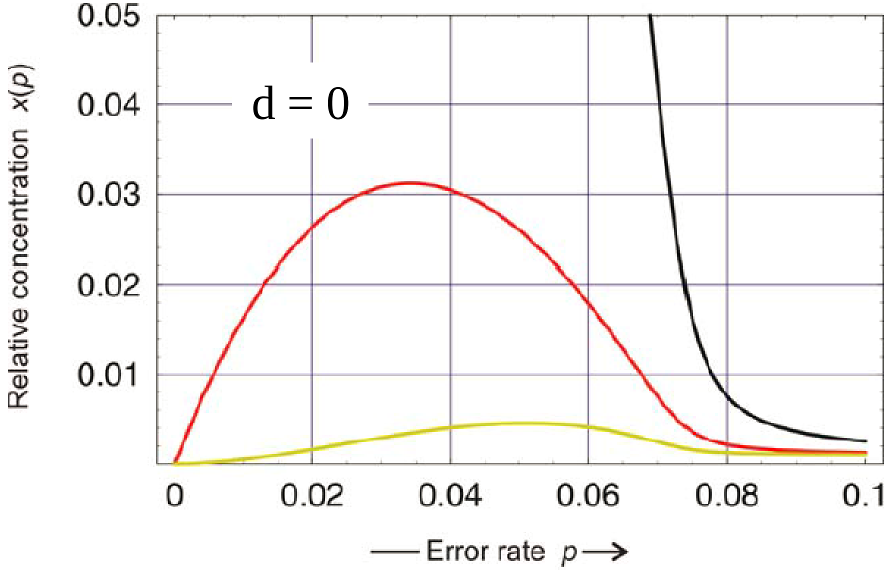
"experimental computer biology":

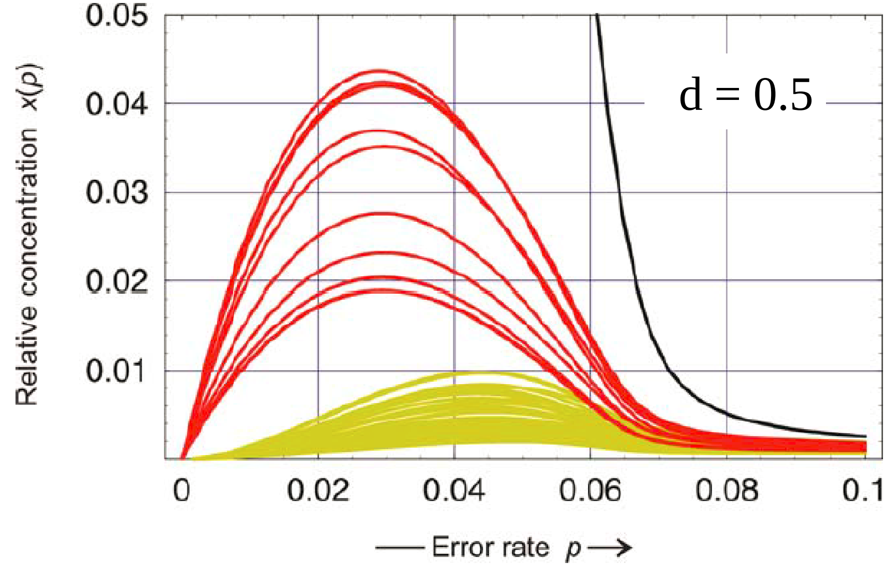
(i) choose seeds, e.g., s ∈ {000, … , 999},

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

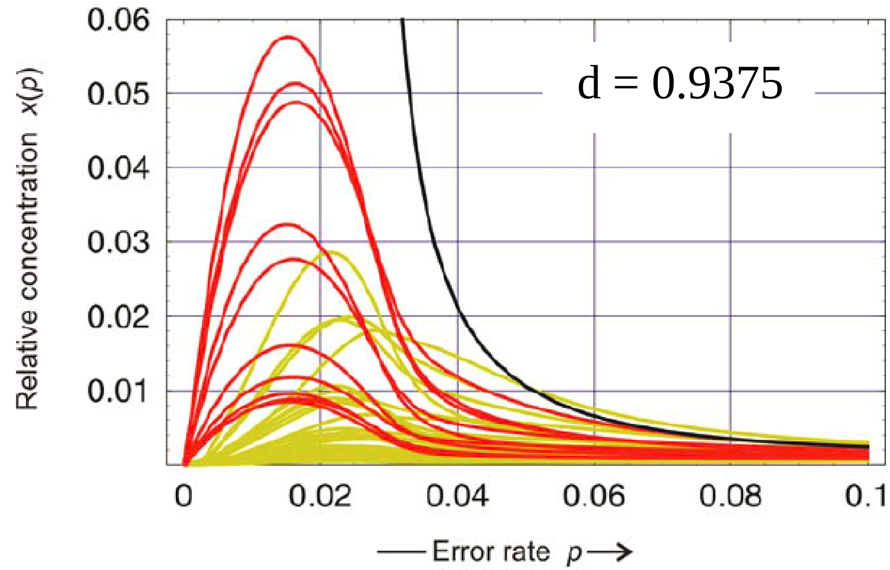
(iii) compute and analyze quasispecies, $\Upsilon(p,d)$

Rugged fitness landscapes over individual binary sequences with n = 10



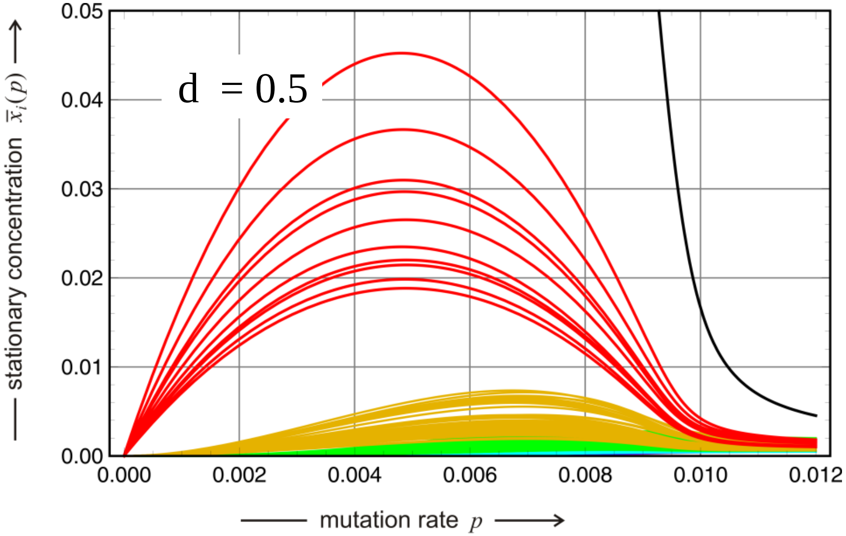


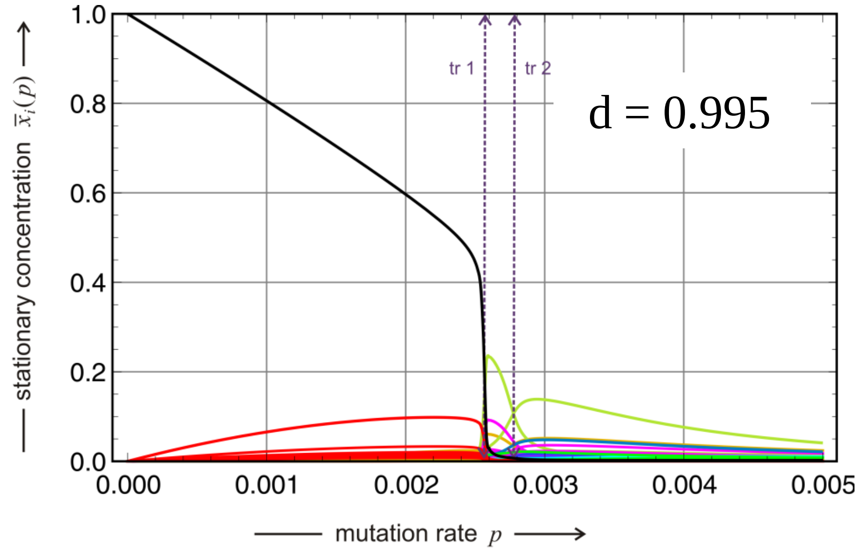
Quasispecies with increasing random scatter *d*



Error threshold: Individual sequences

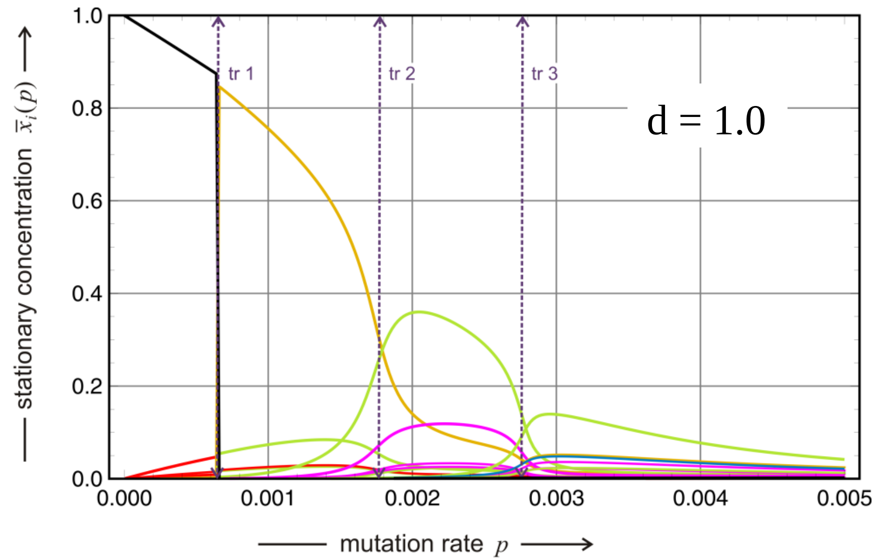
n = 10, σ = 2, s = 491 and d = 0, 0.5, 0.9375





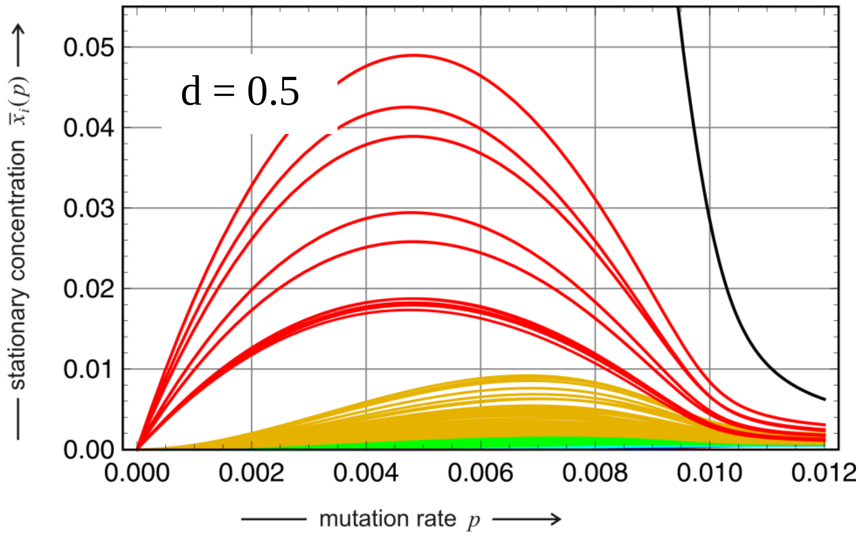
Choice of random scatter:

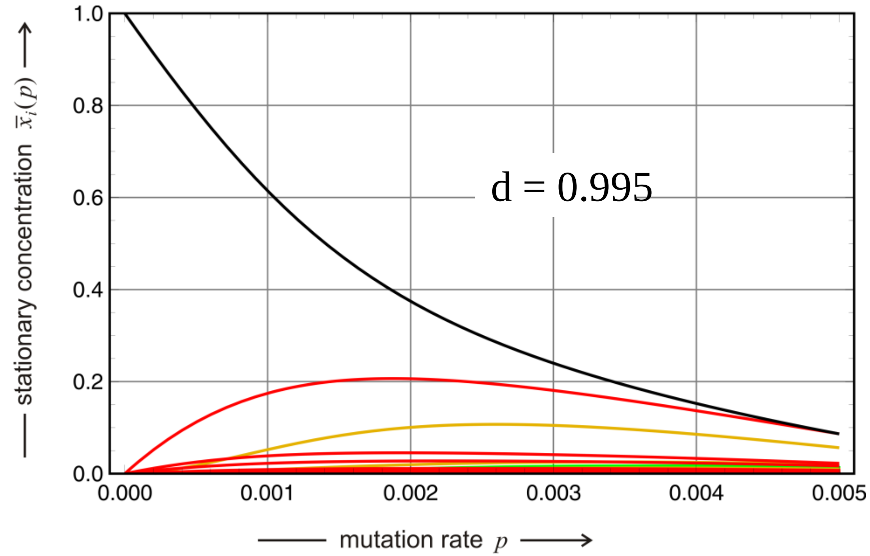
s = 637



Error threshold on ‚realistic‘ landscapes

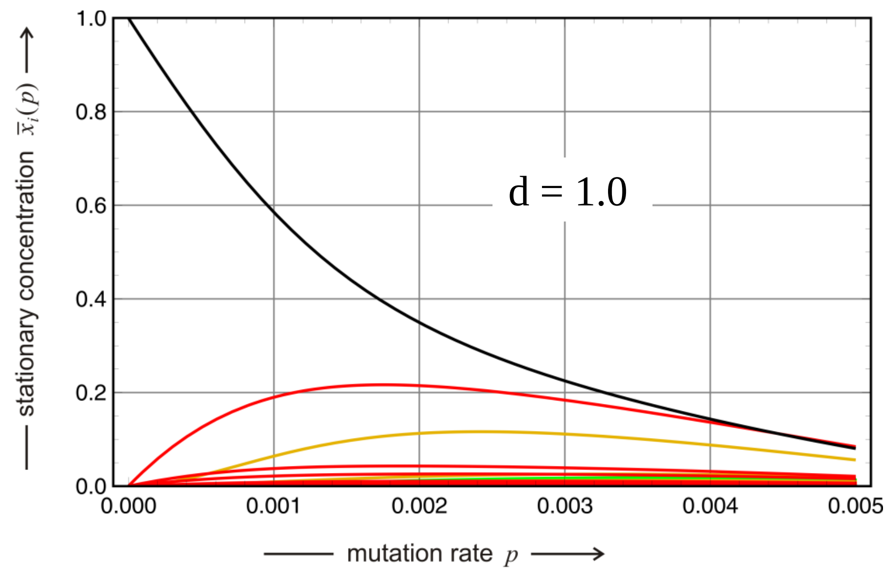
n = 10, f_0 = 1.1, f_n = 1.0, s = 637





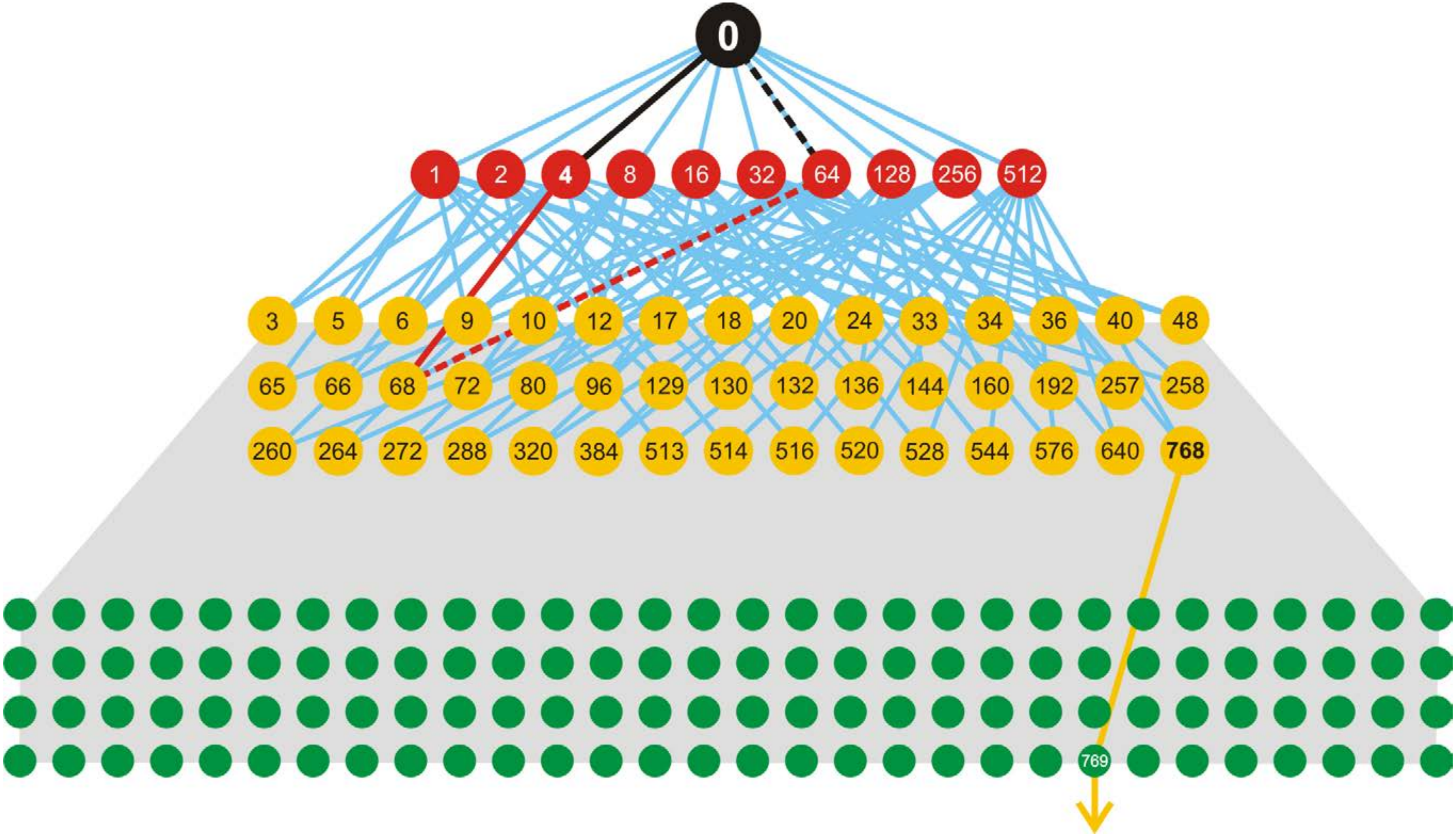
Choice of random scatter:

s = 919

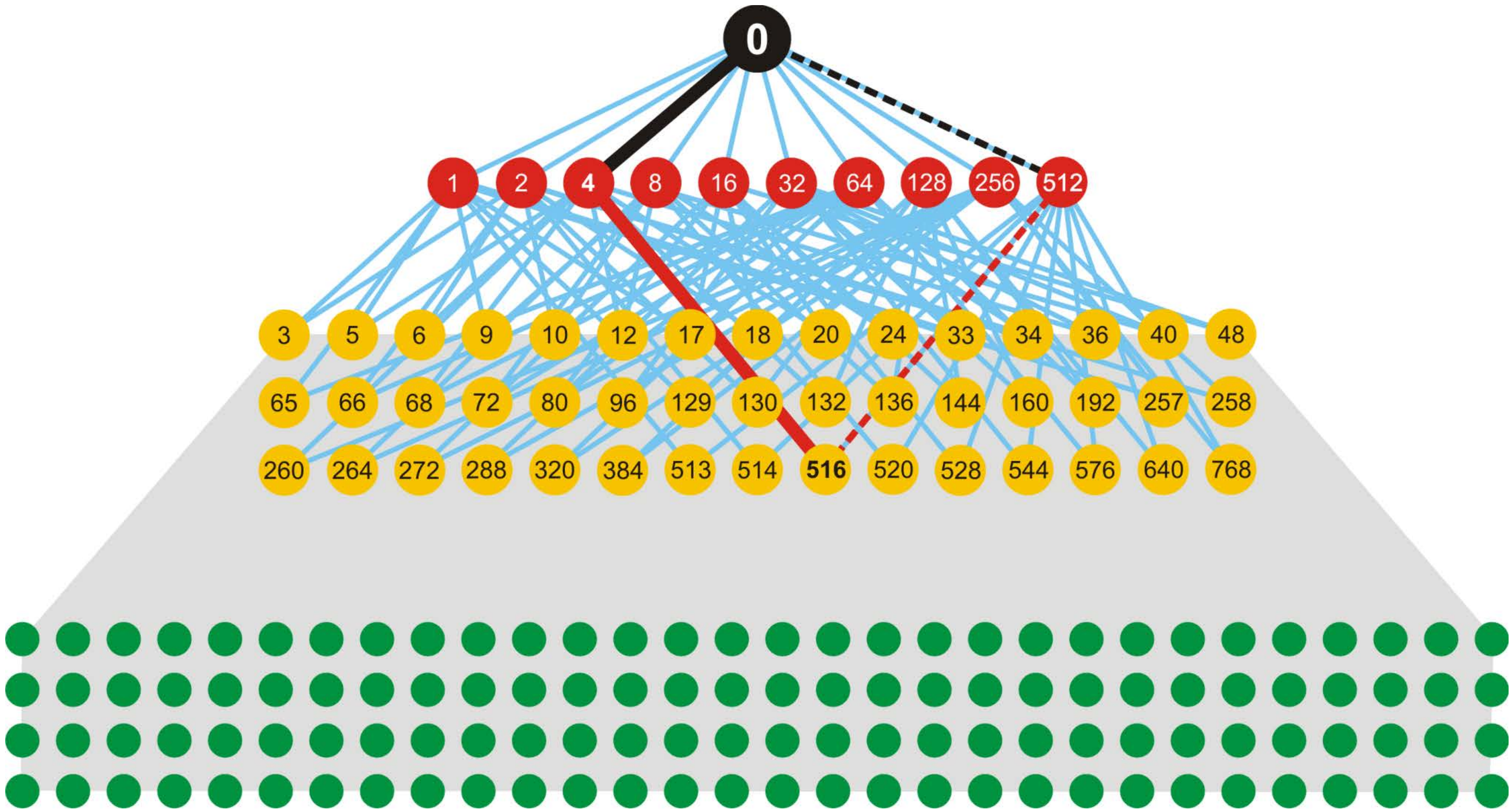


Error threshold on ‚realistic‘ landscapes

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

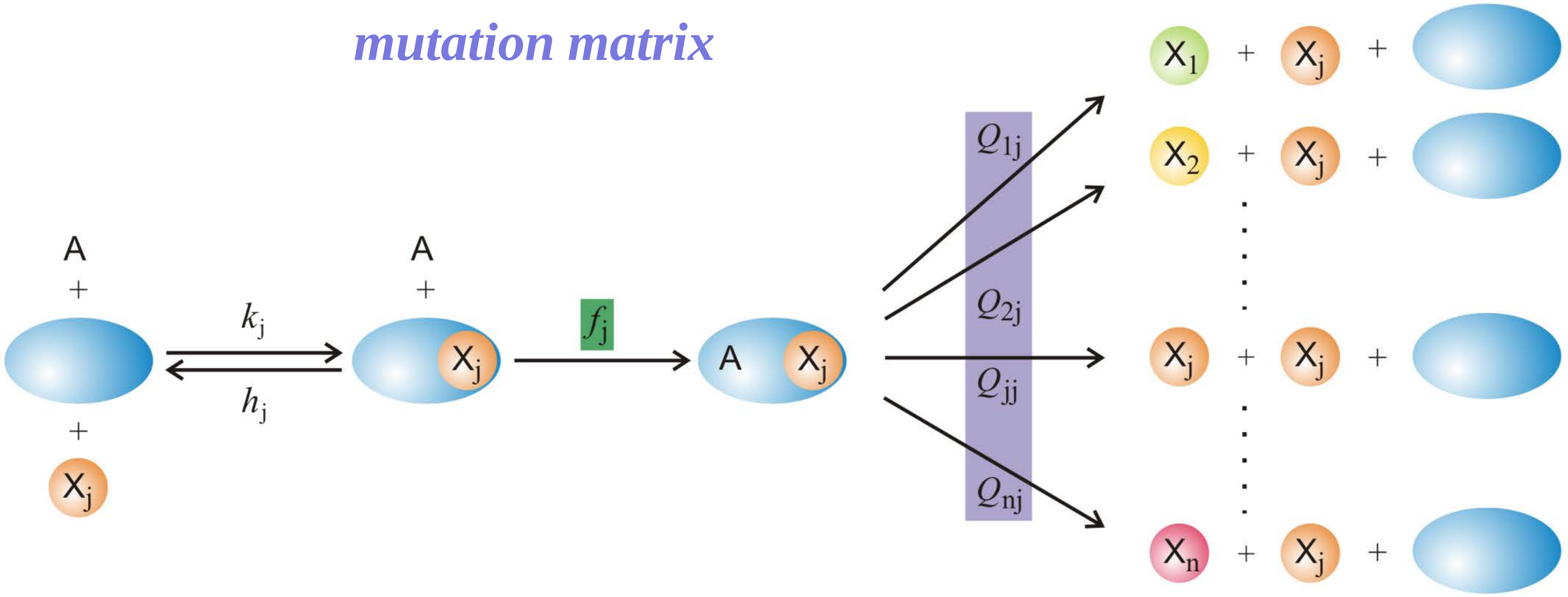
1. A strong quasispecies is dominated by a **clan** of mutationally coupled closely related sequences.

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

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

fitness landscape

mutation matrix

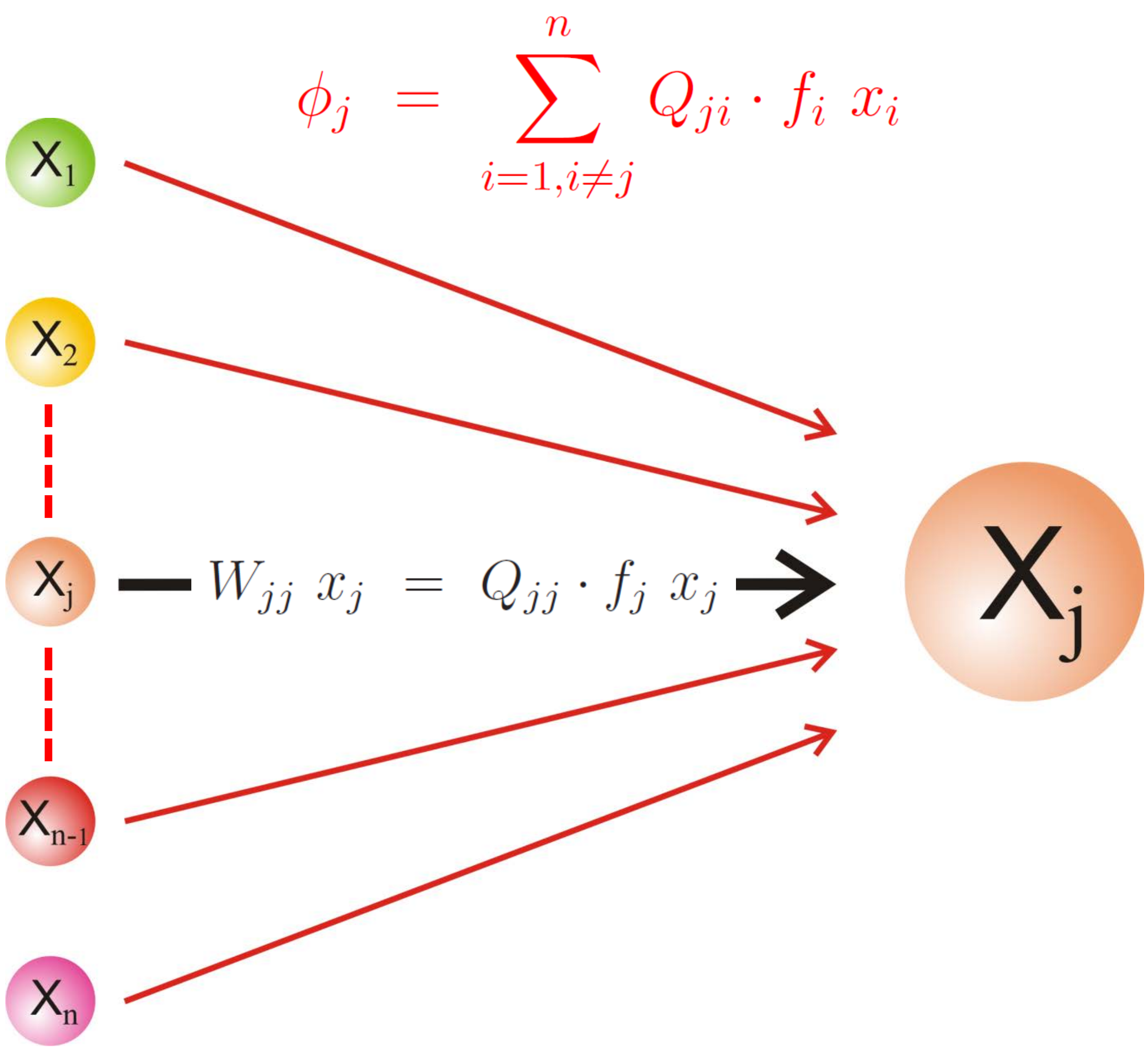


Correct replication and mutation as parallel chemical reactions

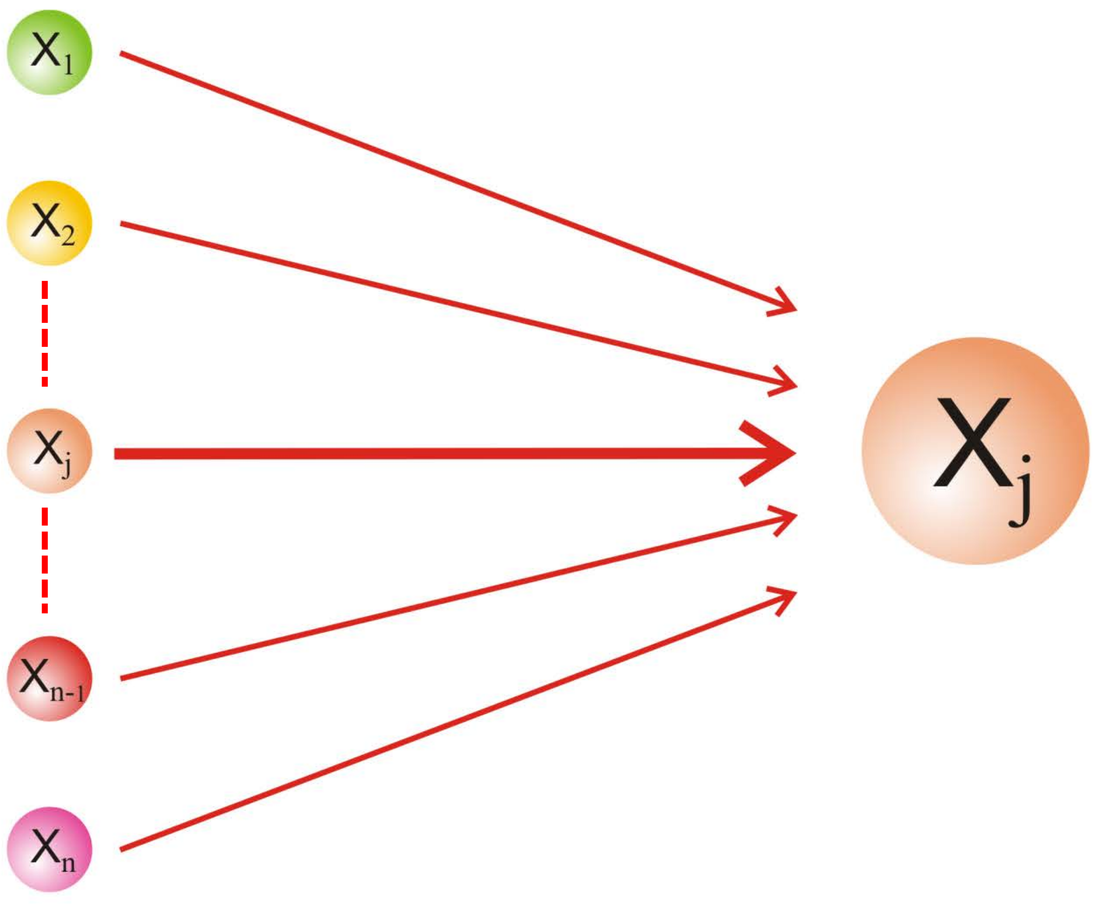
$$\varphi_{ji} = Q_{ji} \cdot f_i \, x_i \, ; \; Q_{ji} \approx (1-p)^{l-\mathrm{d}^{\mathrm{H}}_{ji}} \cdot p^{\mathrm{d}^{\mathrm{H}}_{ji}}$$

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

Mutation flow component and mutation flow



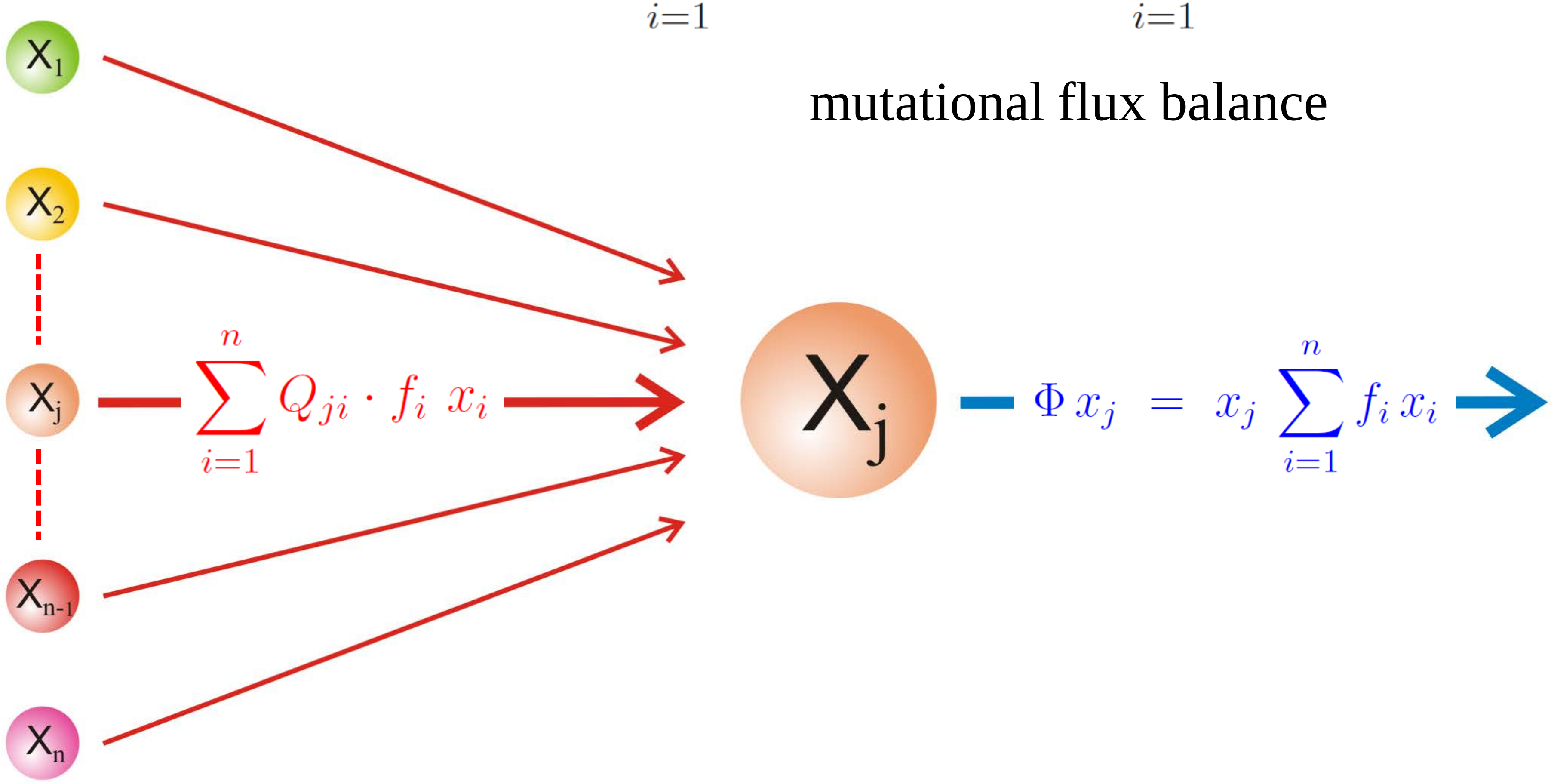
Definition of the mutation flow



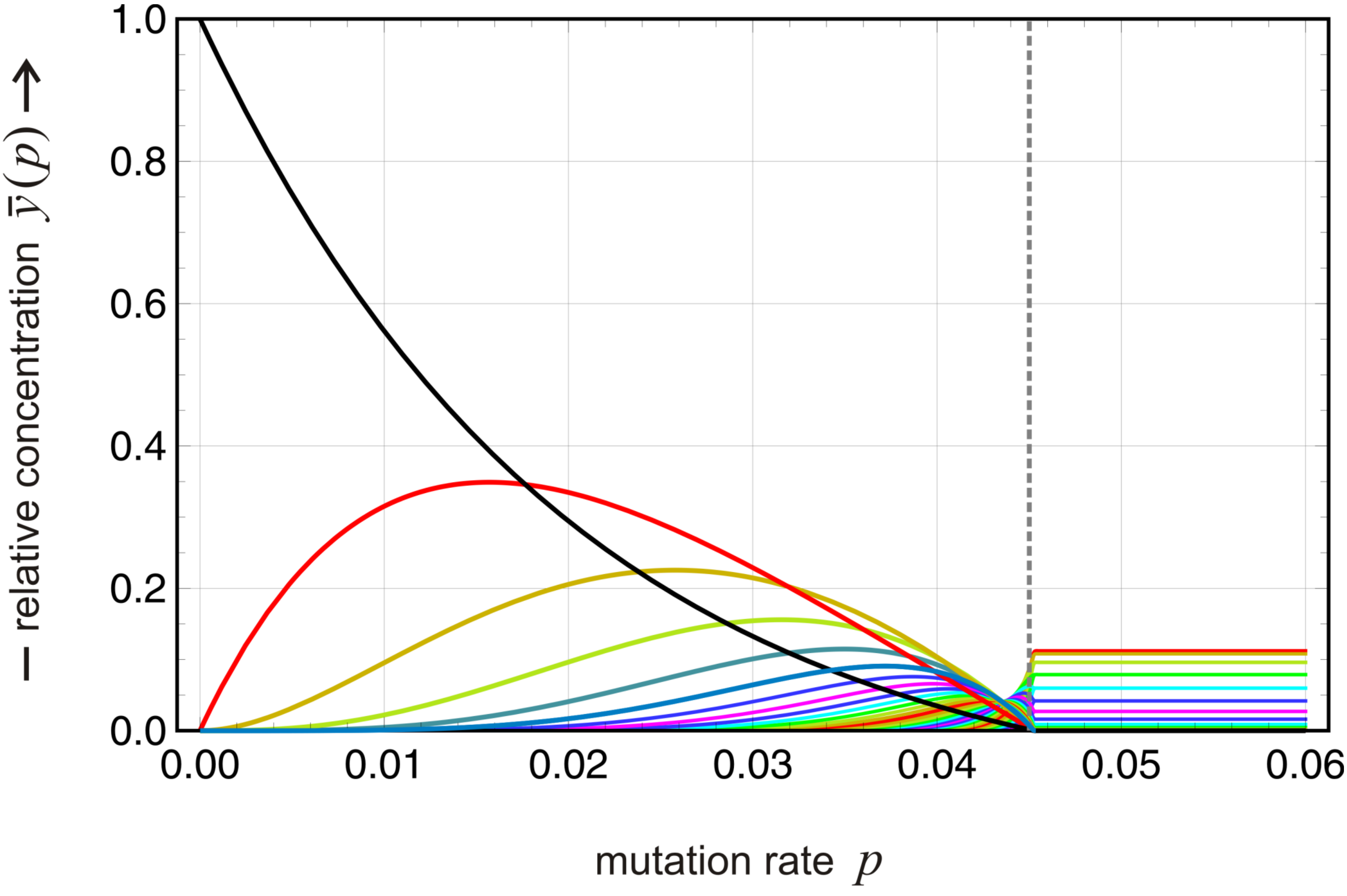
Mutational flux balance and quasispecies

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

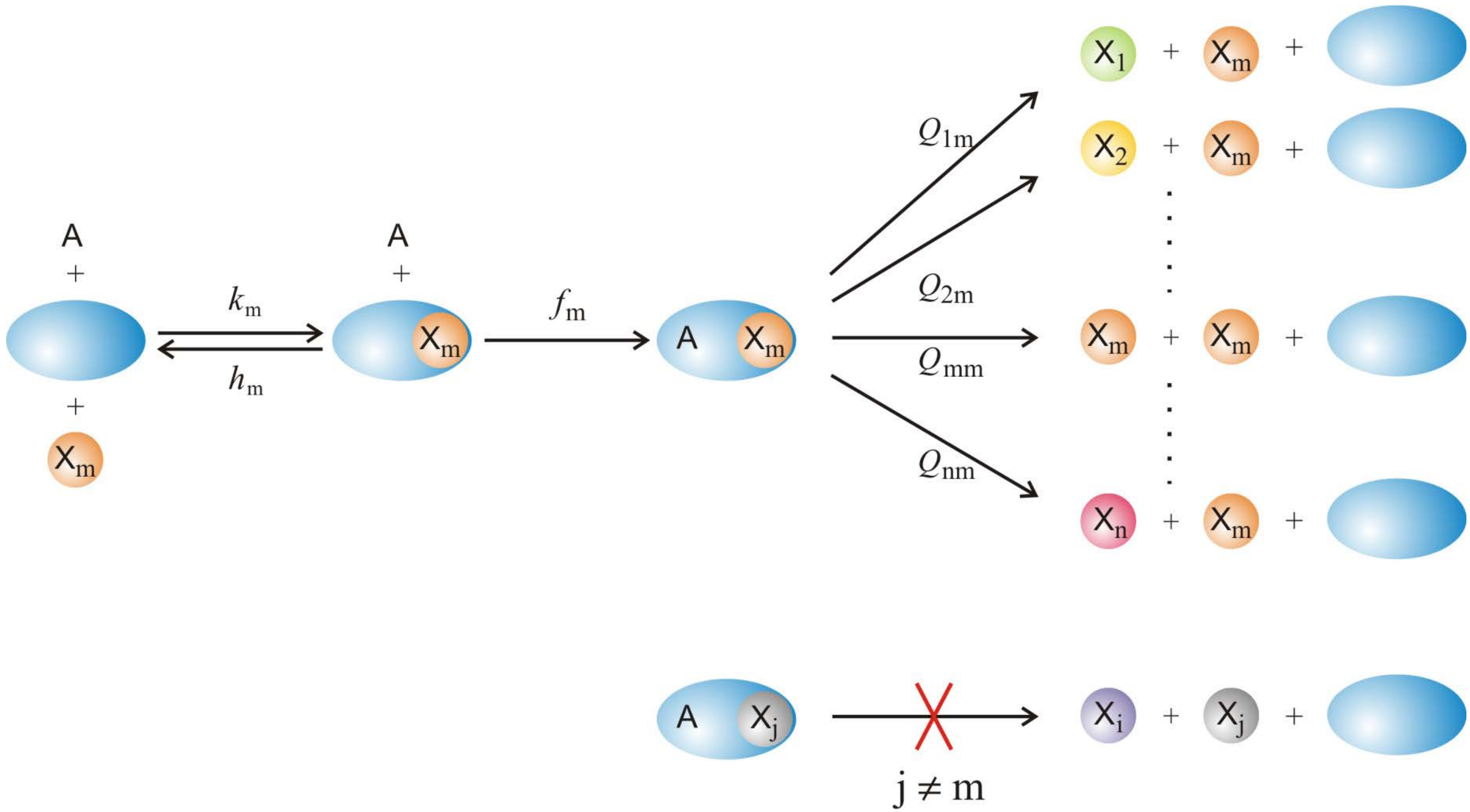
mutational flux balance



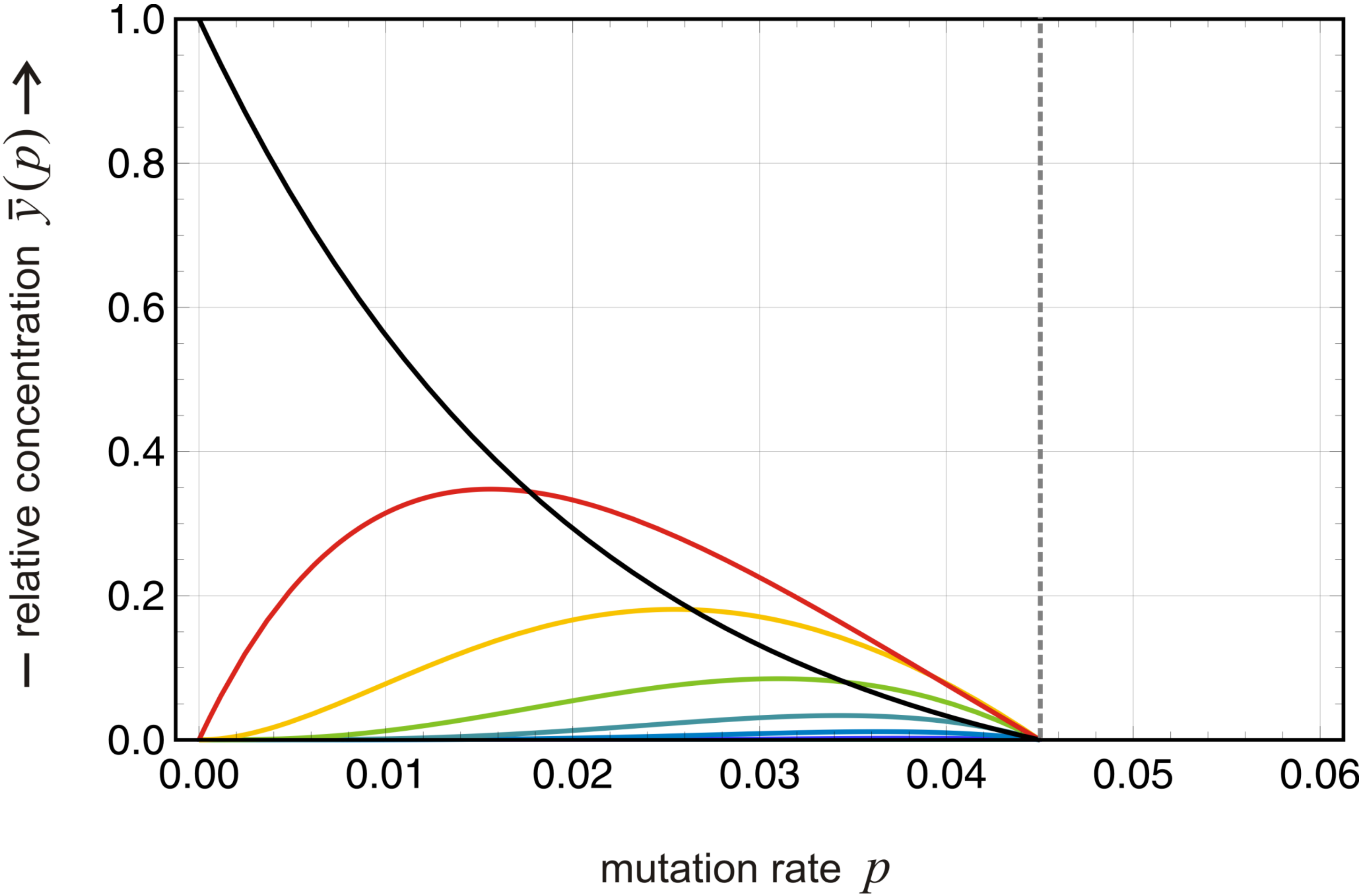
Mutational flux balance and quasispecies



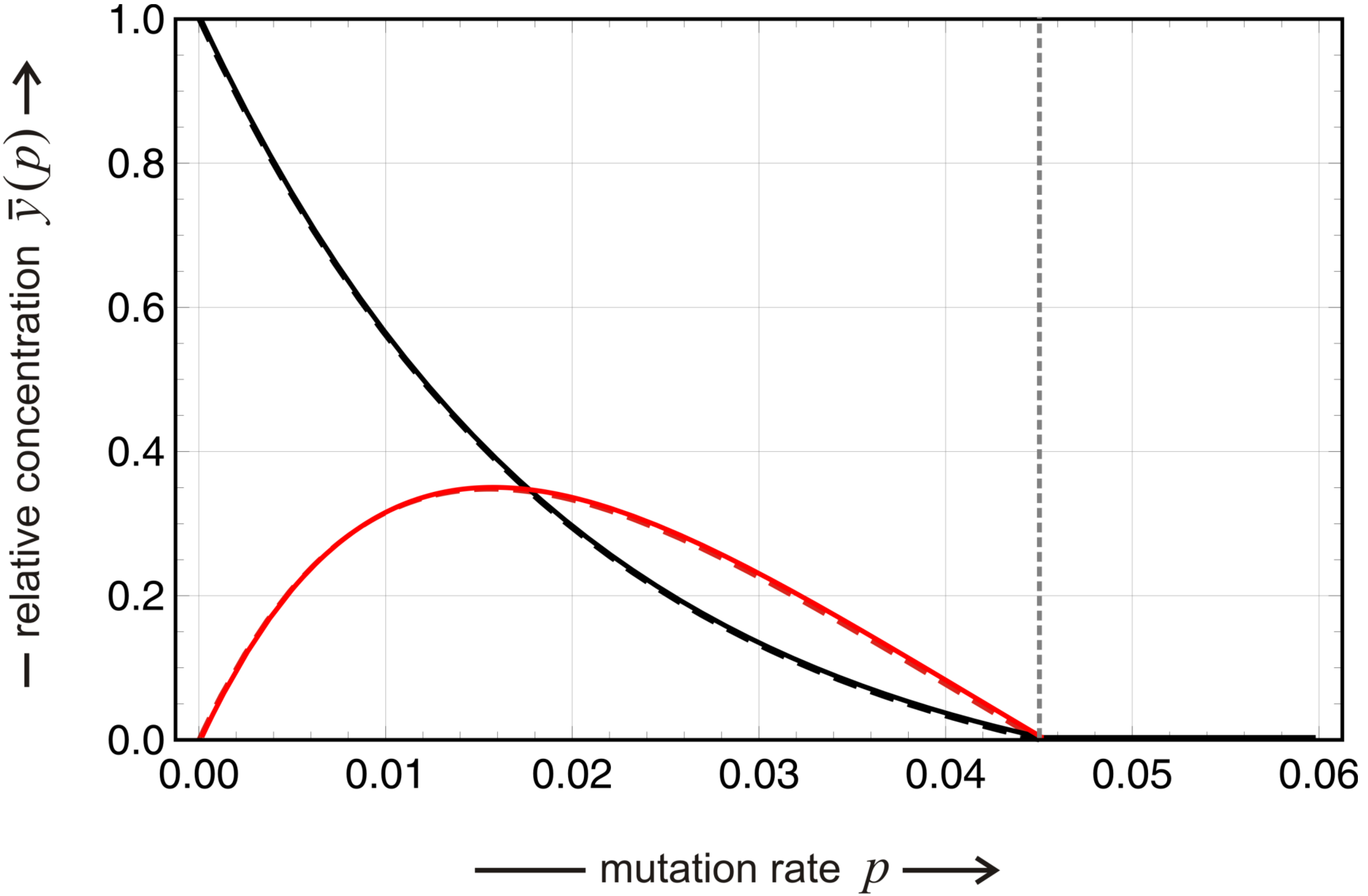
Exact quasispecies: $l = 50$, $f_0 = 10$, $f_j = 1 \; \forall \; j \neq 0$



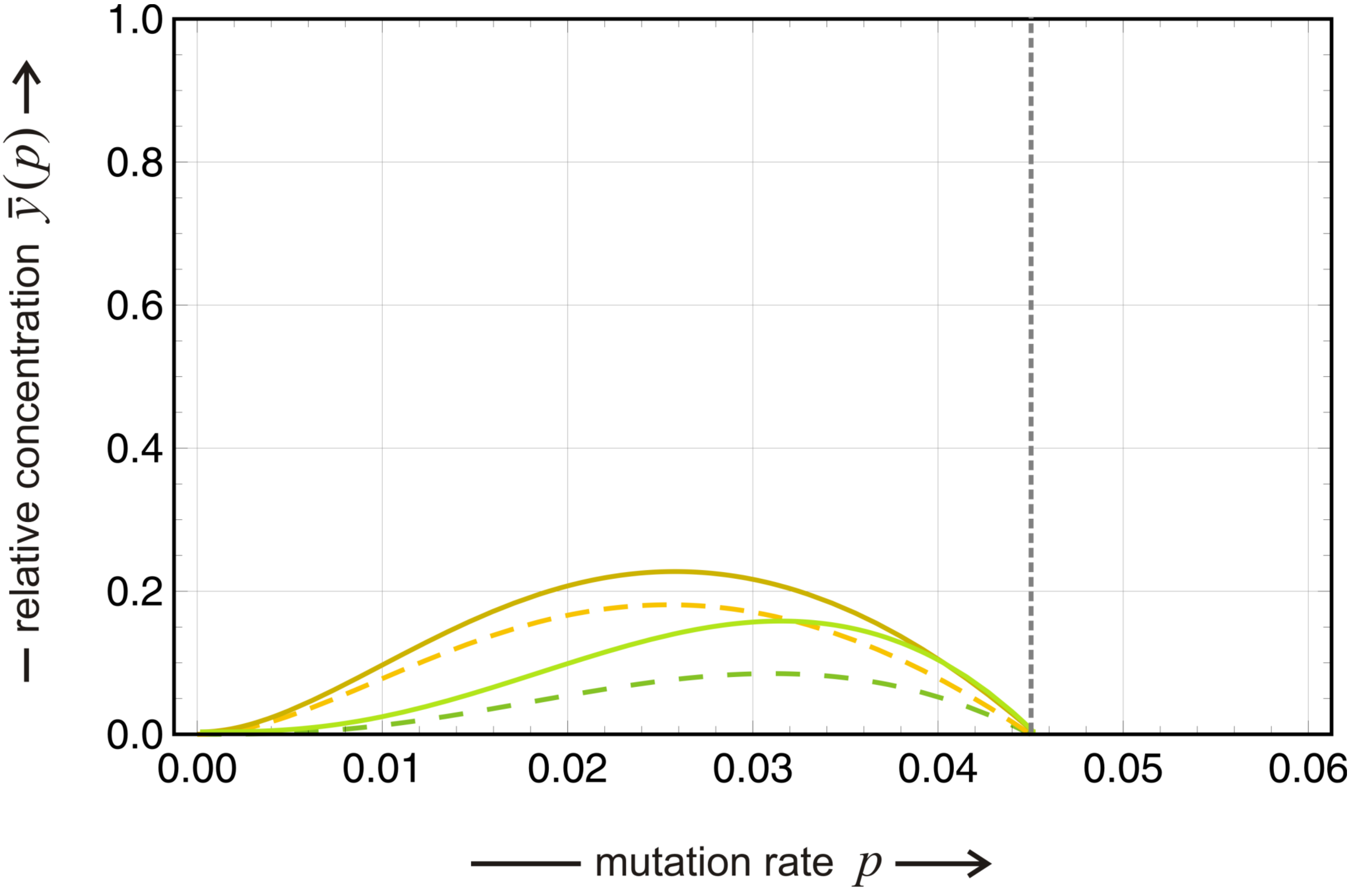
Zero mutation backflow



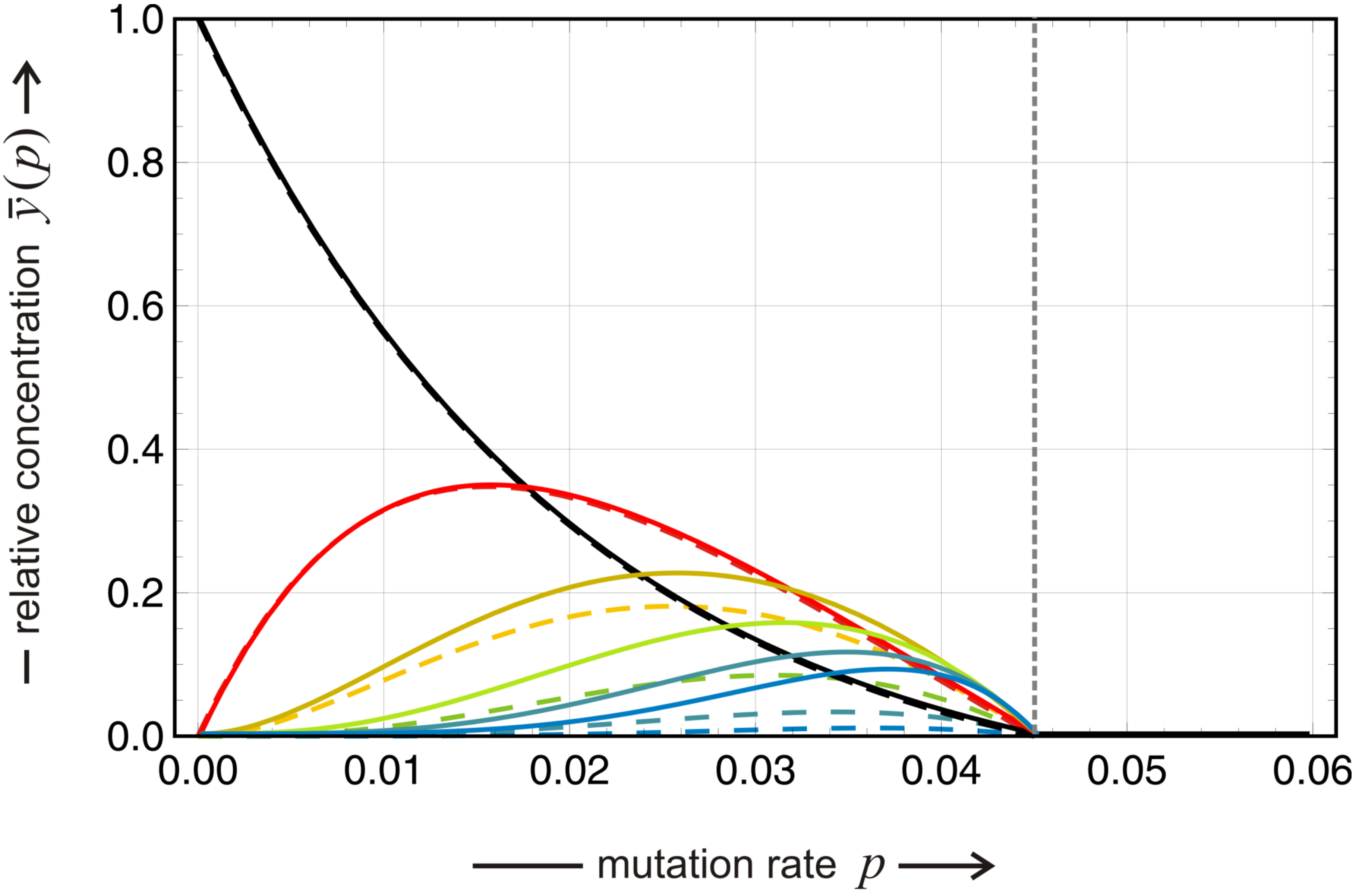
Zero mutation backflow: $l = 50$, $f_0 = 10$, $f_j = 1 \; \forall \; j \neq 0$



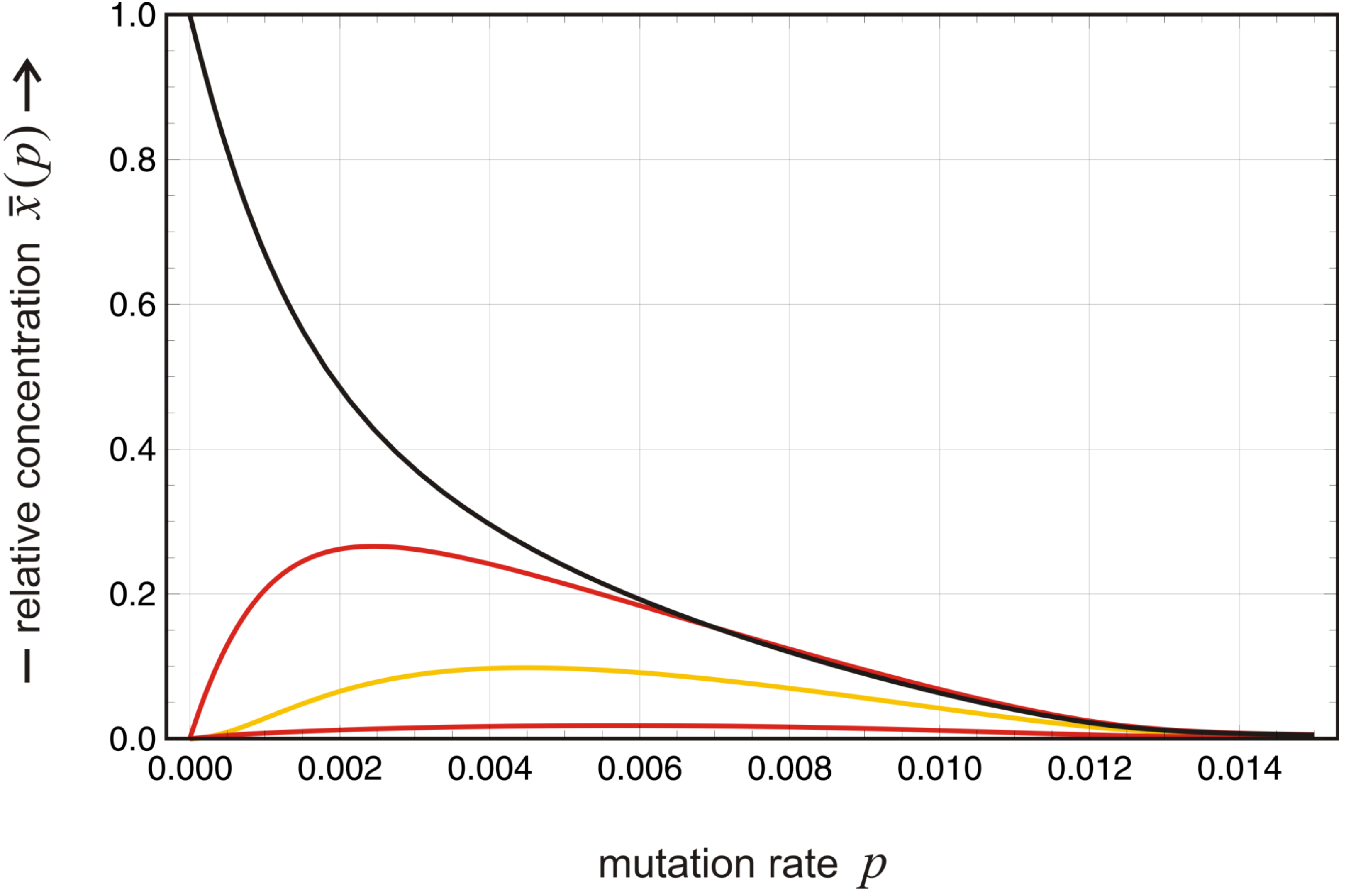
Zero mutation backflow: $l = 50$, $f_0 = 10$, $f_j = 1 \; \forall \; j \neq 0$



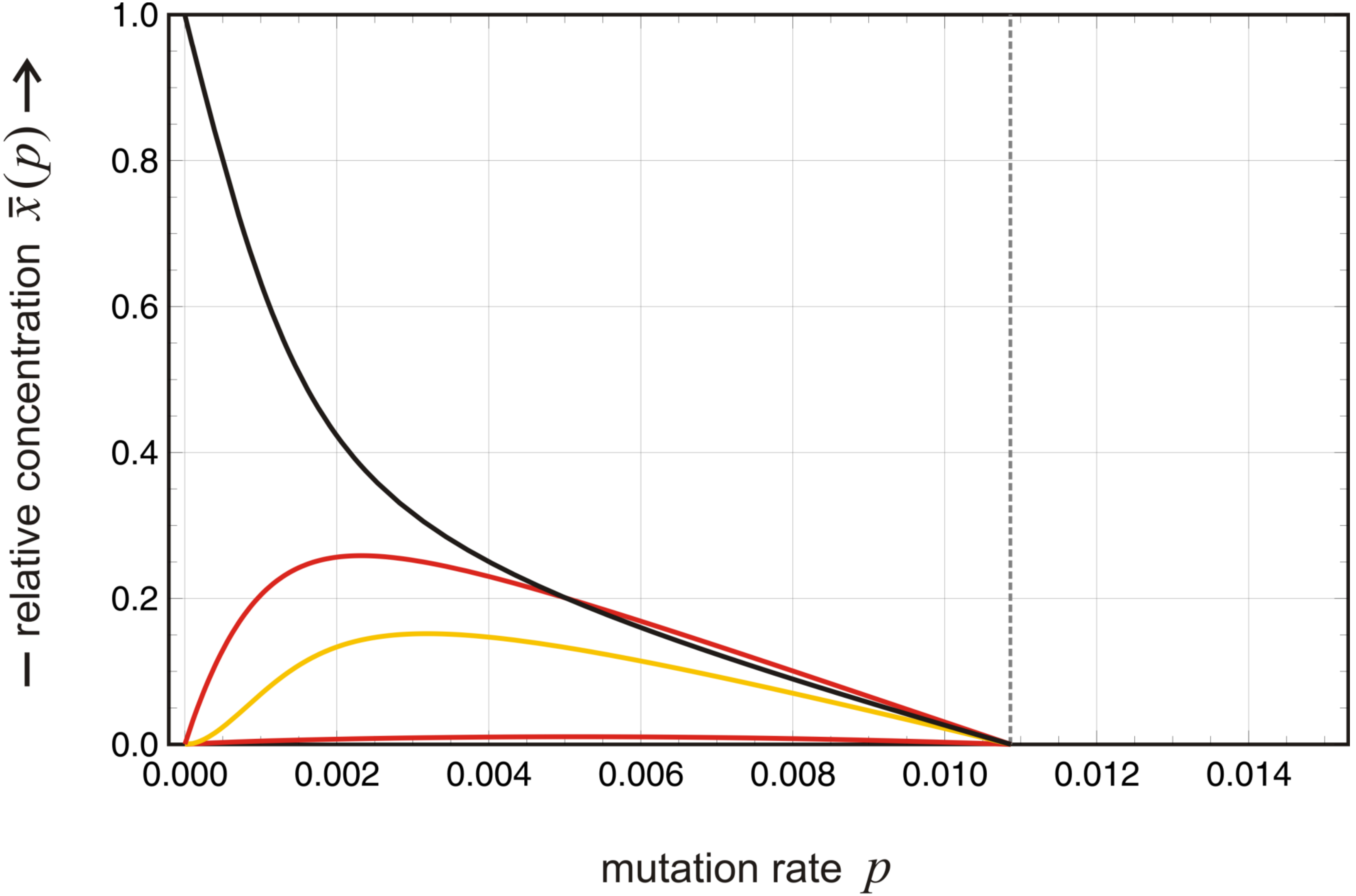
Zero mutation backflow: $l = 50$, $f_0 = 10$, $f_j = 1 \; \forall \; j \neq 0$



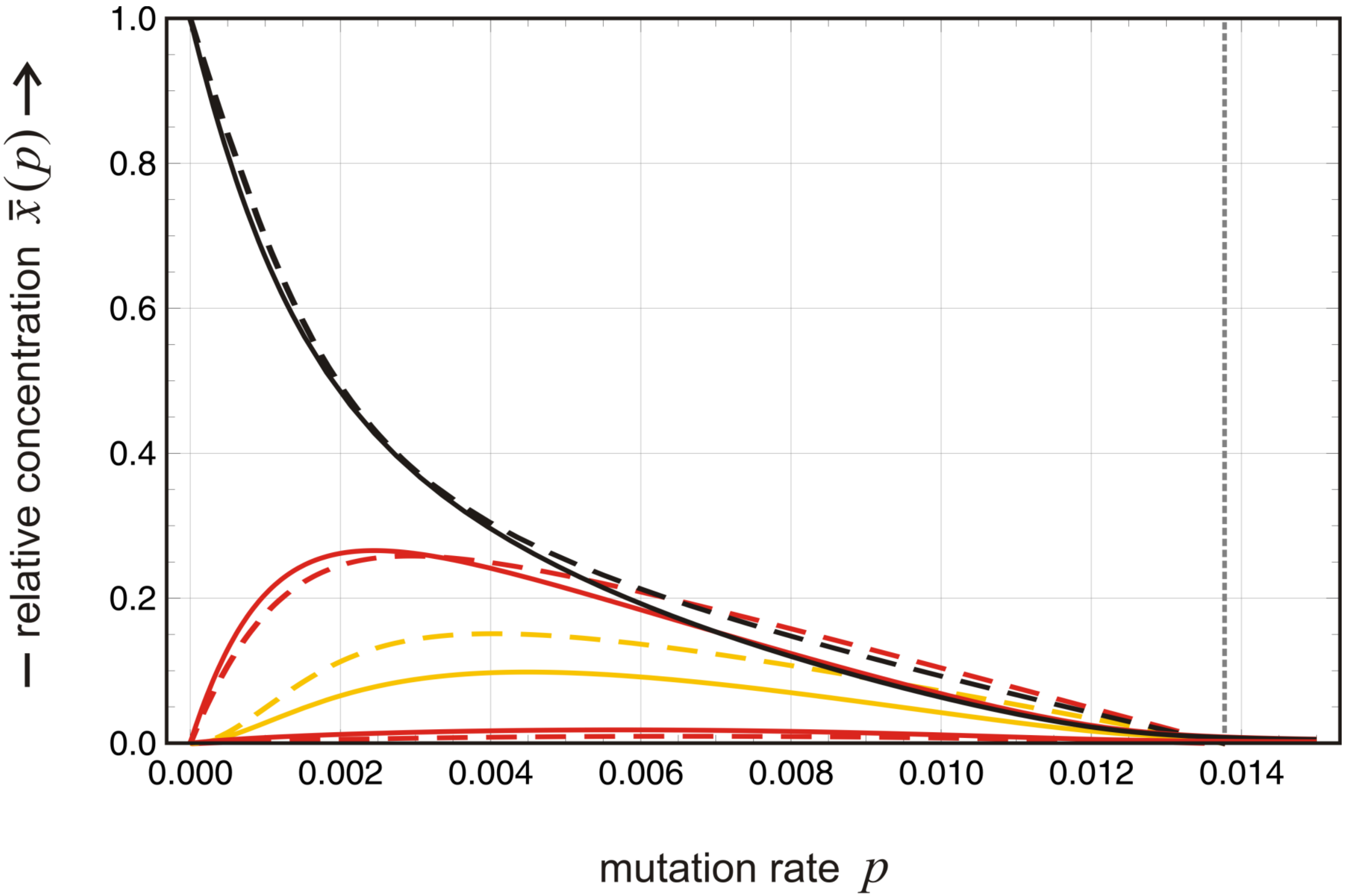
Zero mutation backflow: $l = 50$, $f_0 = 10$, $f_j = 1 \; \forall \; j \neq 0$



Strong quasispecies: l = 10, f_0 = 1.1, f_n = 1.0, d = 1.0, s = 919



Zero mutational backflow: $l = 10$, $f_0 = 1.1$, $f_n = 1.0$, $f_4 = 1.09659$, $f_{516} = 1.09703$



Strong quasispecies: comparison

1. Prologue
2. Quasispecies and paramuse model
3. Landscapes
4. Mutation flows and mutant clans
5. **Neutrality in evolutionary dynamics**
6. Concluding remarks and perspectives

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.

THE NEUTRAL THEORY

OF MOLECULAR EVOLUTION

MOTOO KIMURA

National Institute of Genetics, Japan

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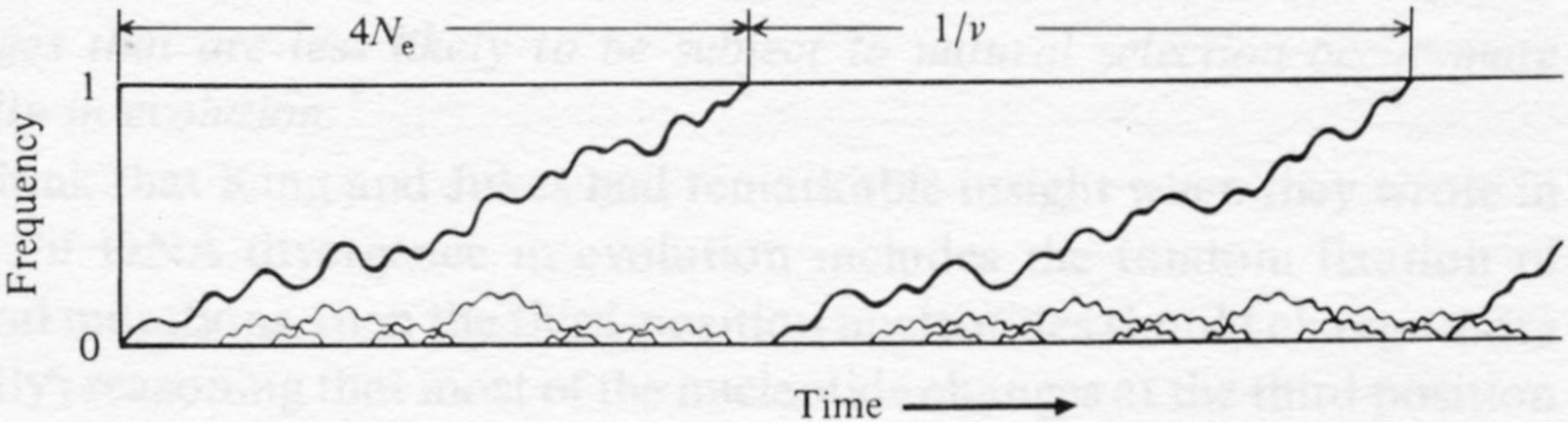
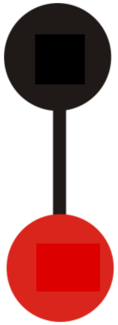
Fig. 3.1. Behavior of mutant genes following their appearance in a finite population. Courses of change in the frequencies of mutants destined to fixation are depicted by thick paths. N_e stands for the effective population size and v is the mutation rate.



The average time of replacement of a dominant genotype in a population is the reciprocal mutation rate, $1/\nu$, and therefore independent of population size.

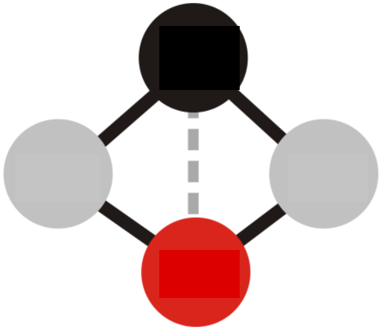
Fixation leads to selection of a single variant in the sense of „survival of the survivor“.

Fixation of mutants in neutral evolution (Motoo Kimura, 1955)



$d_H = 1$

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



$d_H = 2$

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

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

$d_H \geq 3$

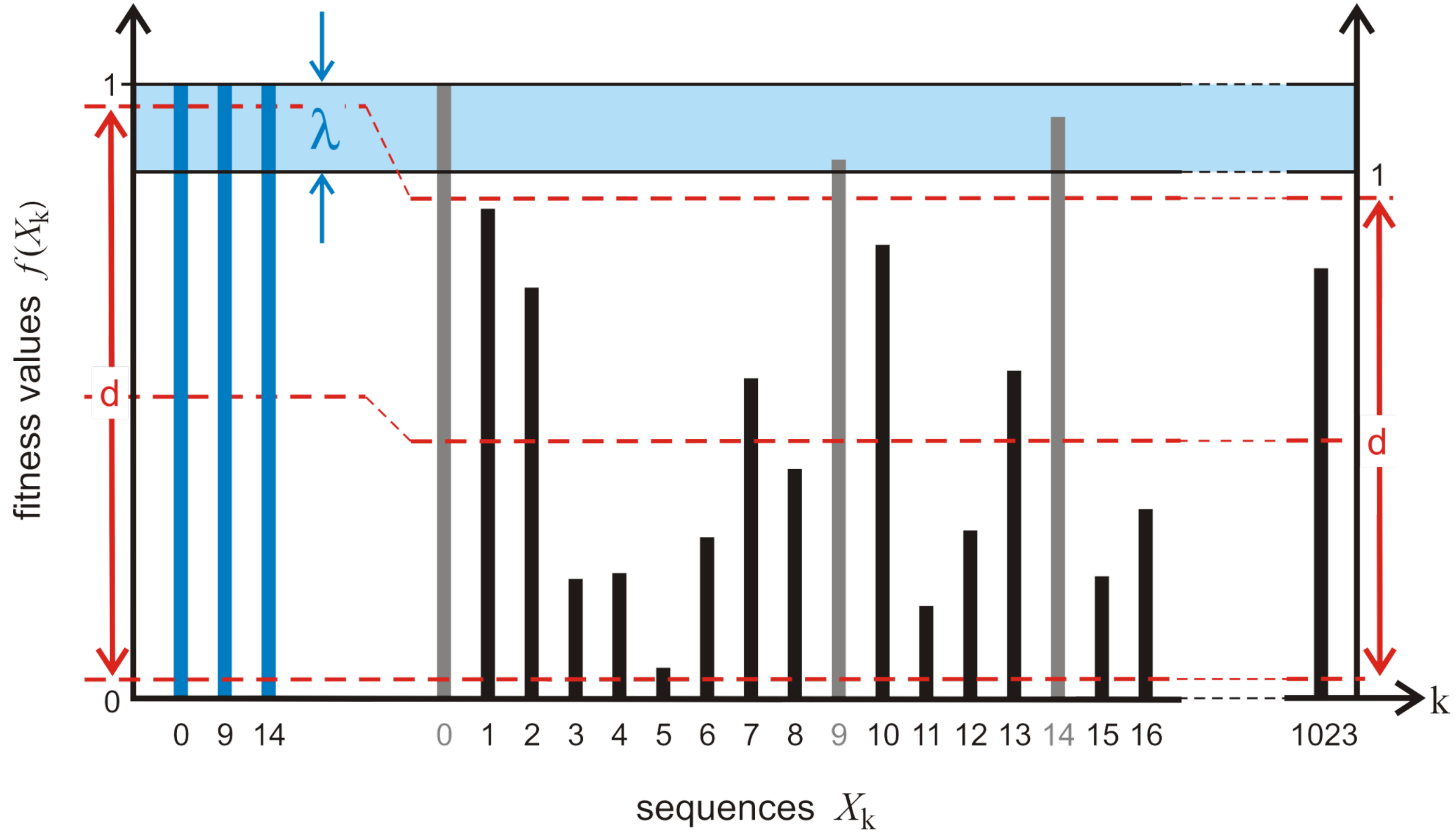
$$\lim_{p\to 0} x_1(p) = 1, \lim_{p\to 0} x_2(p) = 0 \quad \text{or}$$

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

Survival of the survivor or random fixation in the sense of **Motoo Kimura**

Pairs of neutral sequences in replication networks

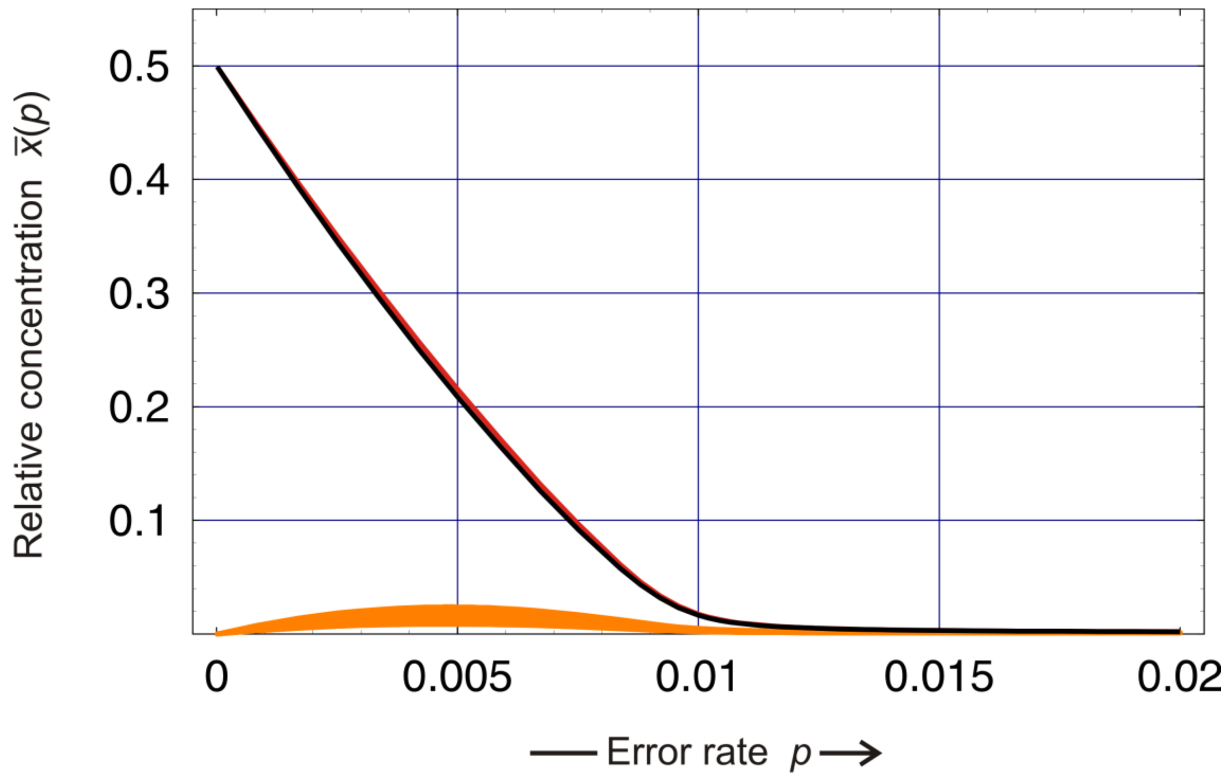
P. Schuster, J. Swetina. 1988. Bull. Math. Biol. 50:635-650



A fitness landscape including neutrality

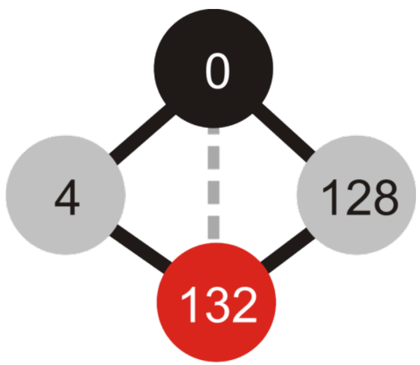
neutral network

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



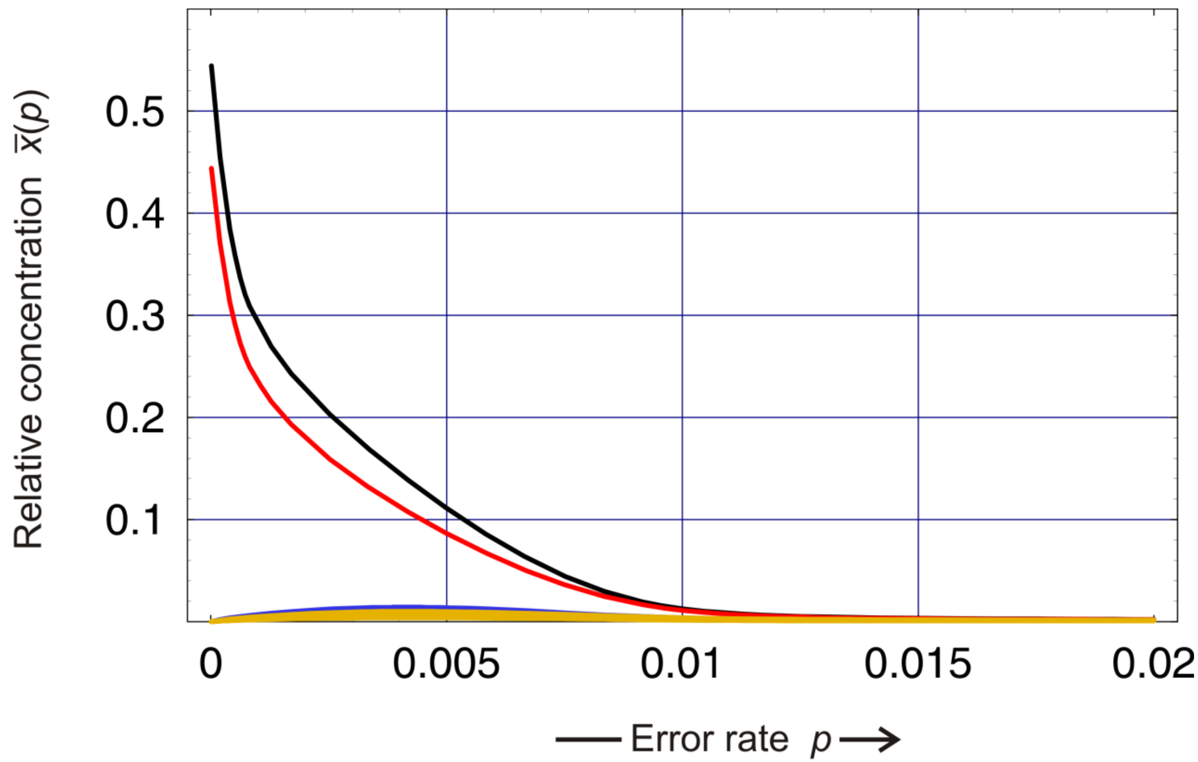
Neutral network: Individual sequences

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



neutral network

$\lambda = 0.01, \; s = 877$



Neutral network: Individual sequences

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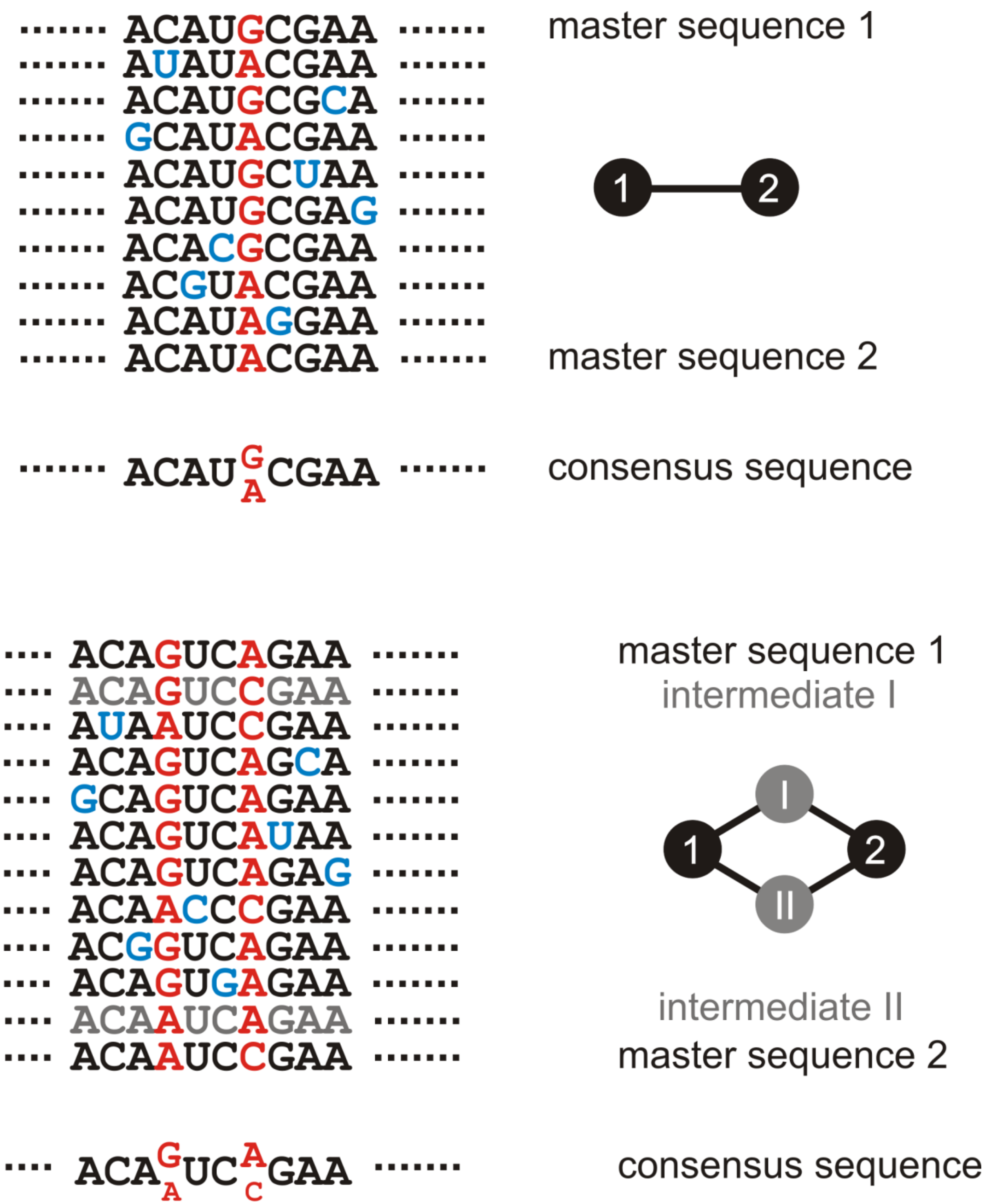
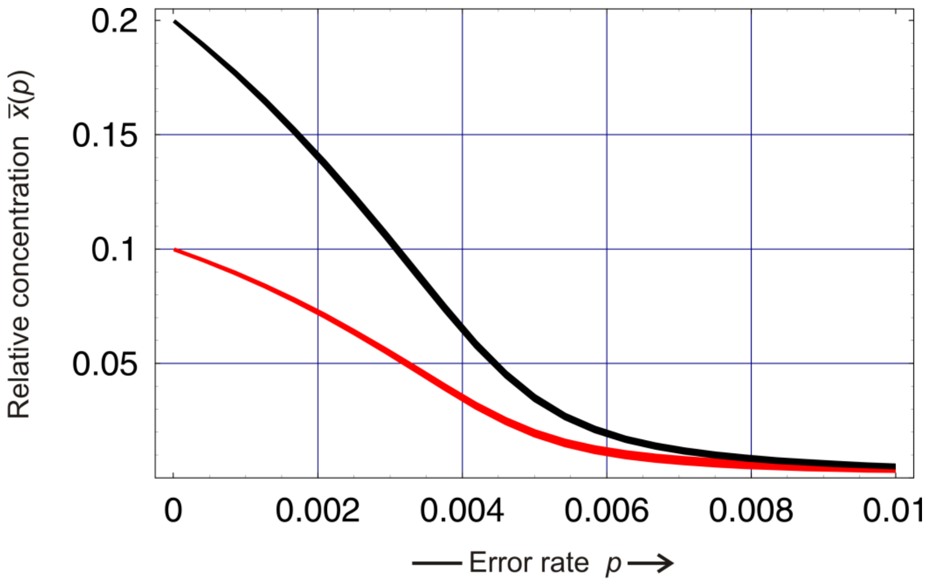
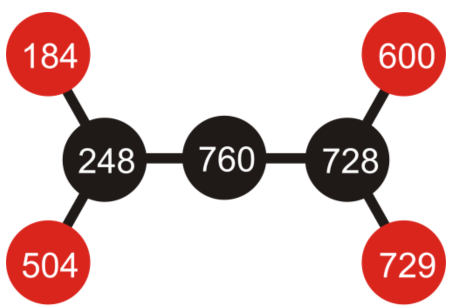


Consensus sequences of a quasispecies of two strongly coupled sequences of Hamming distance $d_H(X_{i,},X_j) = 1$ and 2.



Perturbation matrix W

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



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

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The quasispecies and the error threshold concepts

1. Realistic landscapes combine two seemingly conflicting features: (i) **ruggedness** and (ii) **neutrality**.

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4. Provided certain requirements on the fitness values of one and two error mutants of the master sequence are fulfilled, the populations form especially **stable** or **strong quasispecies**.

5. In strong quasispecies or in the corresponding neutral clusters **clans of sequences** replace the single survivors – deterministic or random.

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.

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