How computation has changed research in chemistry and biology

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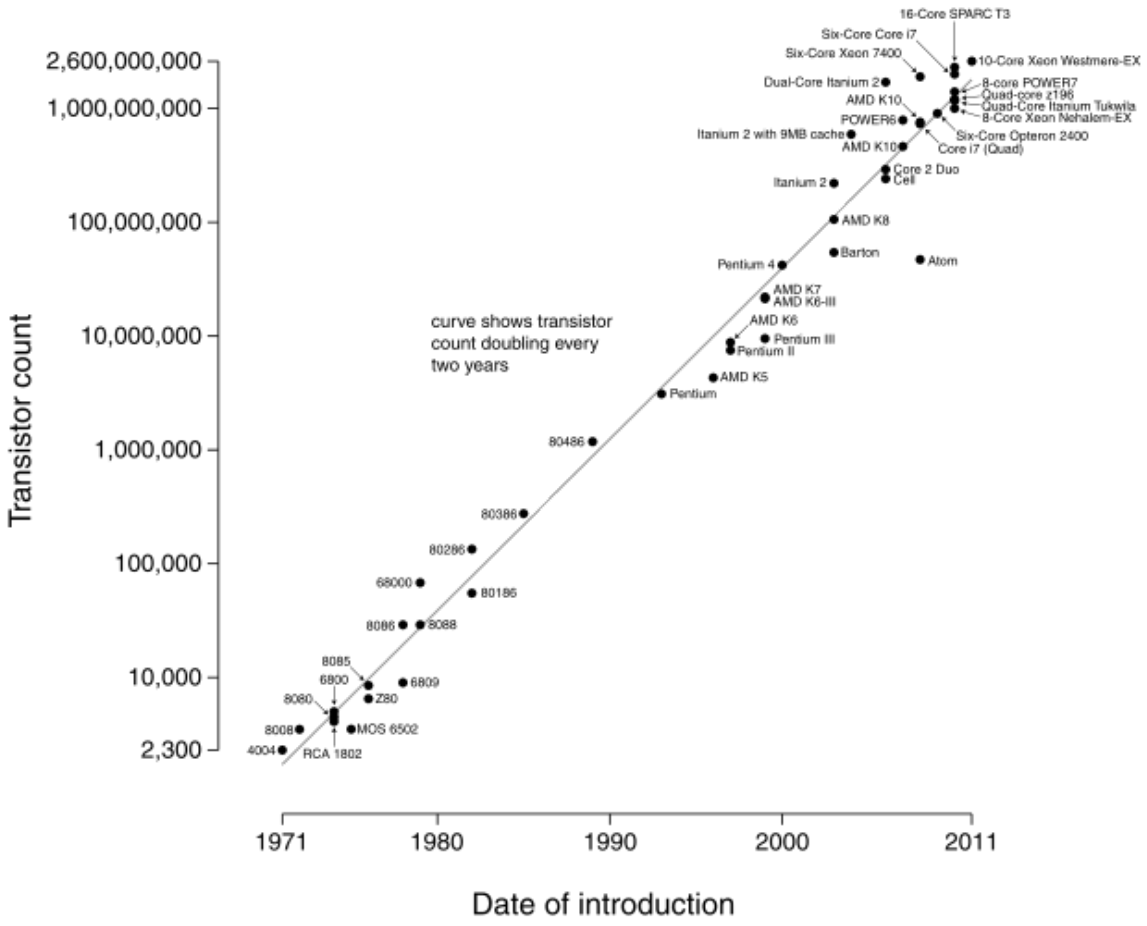
Heidelberg, 21. – 22.02.2013

Web-Page for further information:

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

Some technological revolutions in 20th century science:

1. molecular spectroscopy,
2. micro-technology,
3. electronic computation,
4. molecular revolution in biology,
5. computational quantum chemistry, and
6. holistic chemistry of biological entities.



Gordon E. Moore, 1929 -

The experts look ahead

Cramming more components onto integrated circuits

With unit cost falling as the number of components per circuit rises, by 1975 economics may dictate squeezing as many as 65,000 components on a single silicon chip

By Gordon E. Moore

Director, Research and Development Laboratories, Fairchild Semiconductor division of Fairchild Camera and Instrument Corp.

Exponential increase in hardware power

Electronics **38** (8), 4-7,1965

…. Grötschel, an expert in optimization, observes that a benchmark production planning model solved using linear programming would have taken **82 years to solve in 1988**, using the computers and the linear programming algorithms of the day. Fifteen years later – **in 2003** – the same model could be solved in roughly **1 minute**, an improvement by a factor of roughly **43 million**.

Martin Grötschel, 1948 -

Of this, a factor of roughly **1000** was due to increased **processor speed**, whereas a factor of roughly **43000** was due to improvements in **algortihms** !

Grötschel also cites an algorithmic improvement of roughly **30000** for mixed integer programming between **1991** and **2008**.

PCIT Report to the President, 2010. **Progress in Algorithms Beats Moore's Law**.

J.P. Holdren, E. Lander, H. Varmus. Designing a digital future: Federally funded research and development in networking and information technology. President's council on science and technology, Washington, DC, p.71, 2010

Four selected examples

1. Parameter determination in chemical kinetics
2. Design of ribonucleic acid (RNA) structures
3. Kinetic folding of RNA molecules
4. Modeling evolution

Four selected examples

1. **Parameter determination in chemical kinetics**
2. Design of ribonucleic acid (RNA) structures
3. Kinetic folding of RNA molecules
4. Modeling evolution

L. Michaelis, M. Menten. Die Kinetik der Invertin-Wirkung. *Biochemische Zeitschrift* **49**, 333-369,1913

$$\frac{d[\mathrm{P}]}{dt} = v([\mathrm{S}]) = \frac{v_{\max} \cdot [\mathrm{S}]}{K_{\mathrm{M}} + [\mathrm{S}]}$$

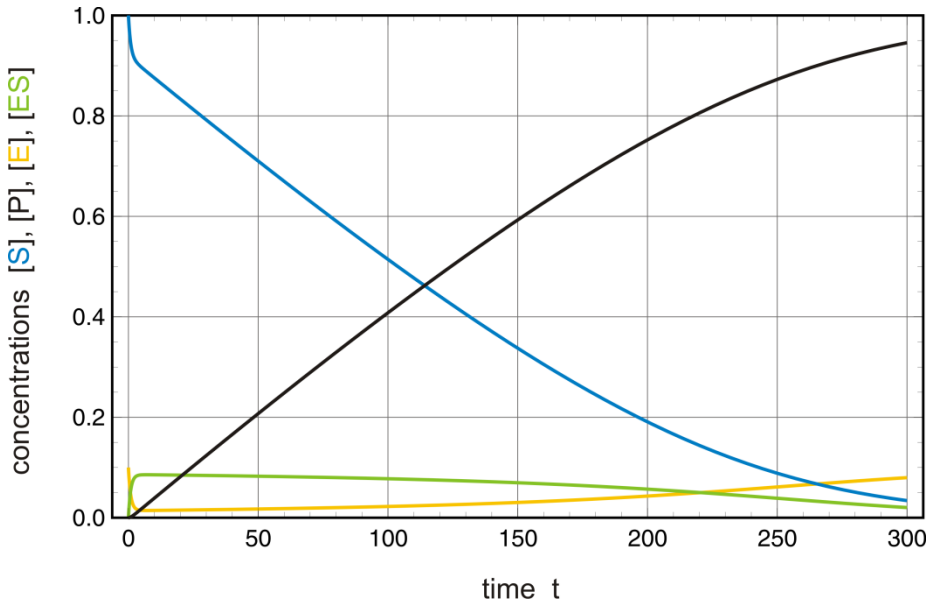
$$\mathrm{S} + \mathrm{E} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} \mathrm{ES} \xrightarrow{k_r} \mathrm{E} + \mathrm{P}$$

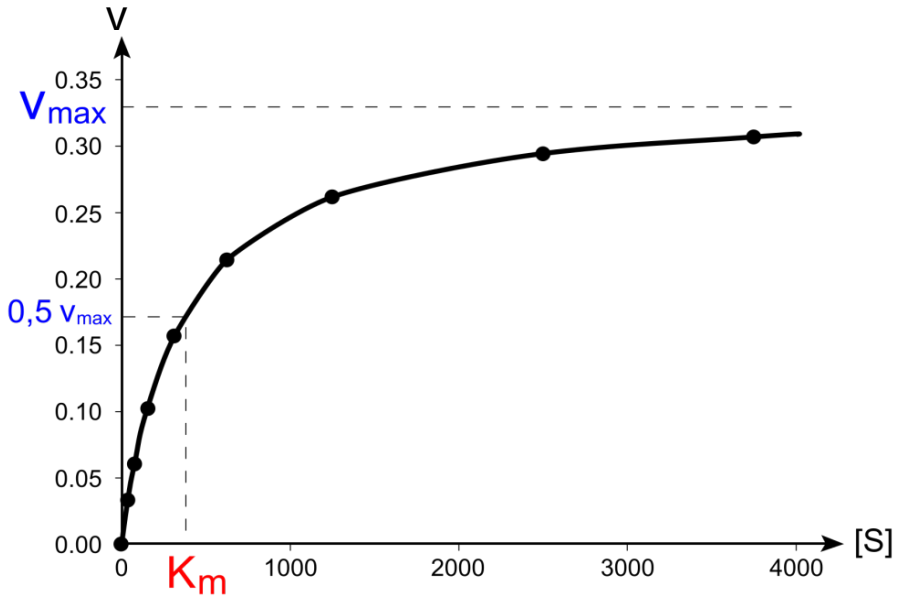
$$K_{\mathrm{M}} = \frac{k_r + k_d}{k_f},$$

basic assumptions: $k_r < k_d$

$[\mathrm{E}]_0 << [\mathrm{S}]_0$

$$v([\mathrm{S}]) = k_r \cdot [\mathrm{ES}] \quad \text{and} \quad v_{\max} = k_r \cdot [\mathrm{E}]_0$$





Michaelis-Menten mechanism of enzyme reactions

Linearization of a hyperbola: $$v([\mathrm{S}]) = \frac{v_{\max} \cdot [\mathrm{S}]}{K_{\mathrm{M}} + [\mathrm{S}]}$$

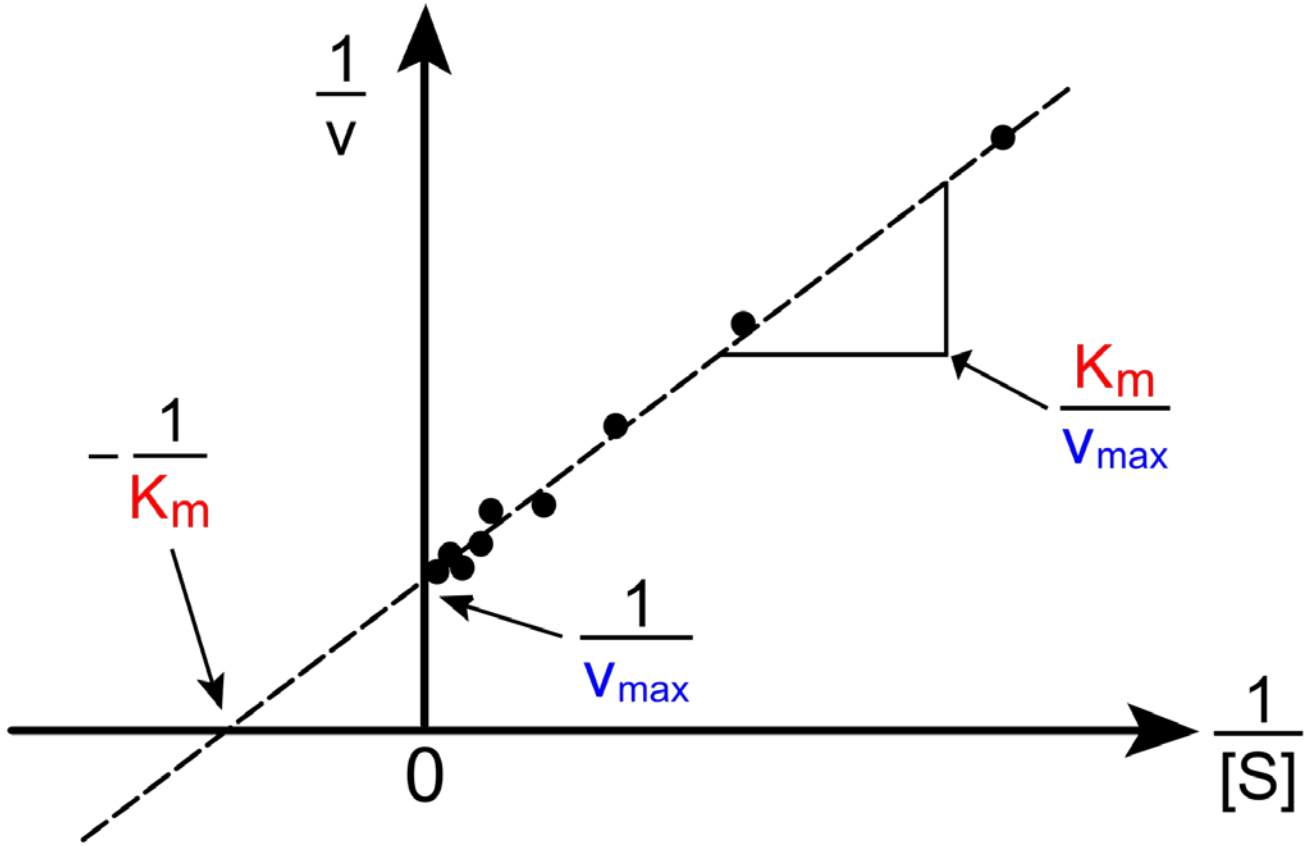
Lineweaver-Burk: $1/v = f(1/[\mathrm{S}])$

Eadie-Hofstee: $v = f(1/[\mathrm{S}])$

Scatchard: $1/[\mathrm{S}] = f(v)$

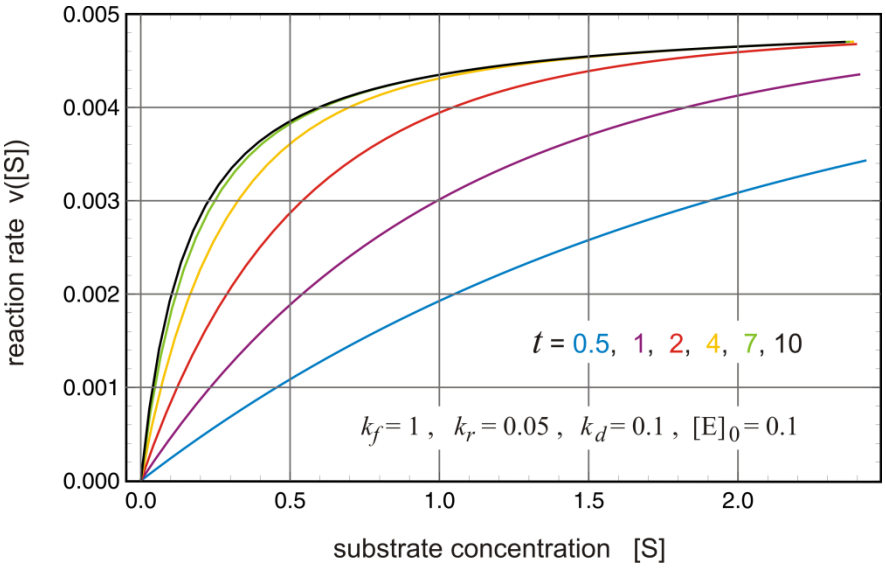
Hanes: $[\mathrm{S}] / v = f([\mathrm{S}])$

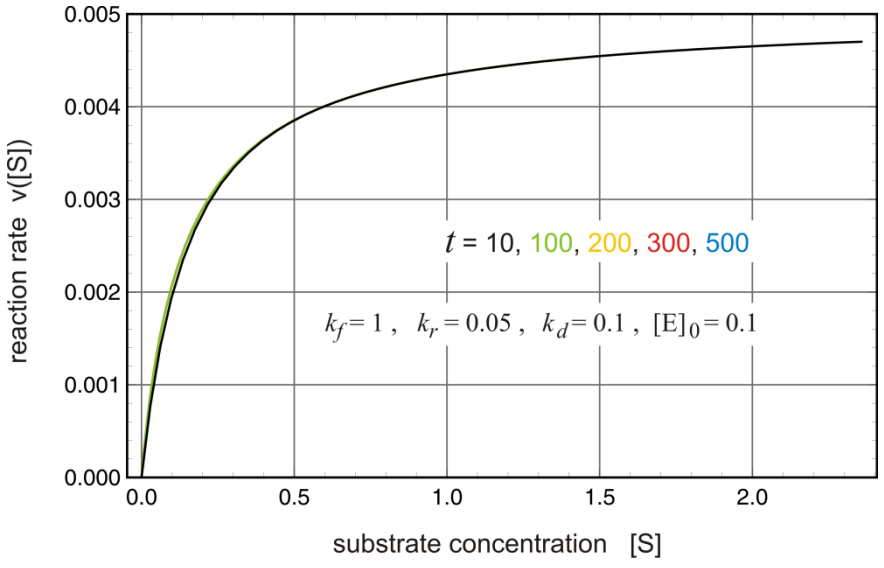
Hill: $\log\left(v/(v_{\max} - v)\right) = f(\log [\mathrm{S}])$

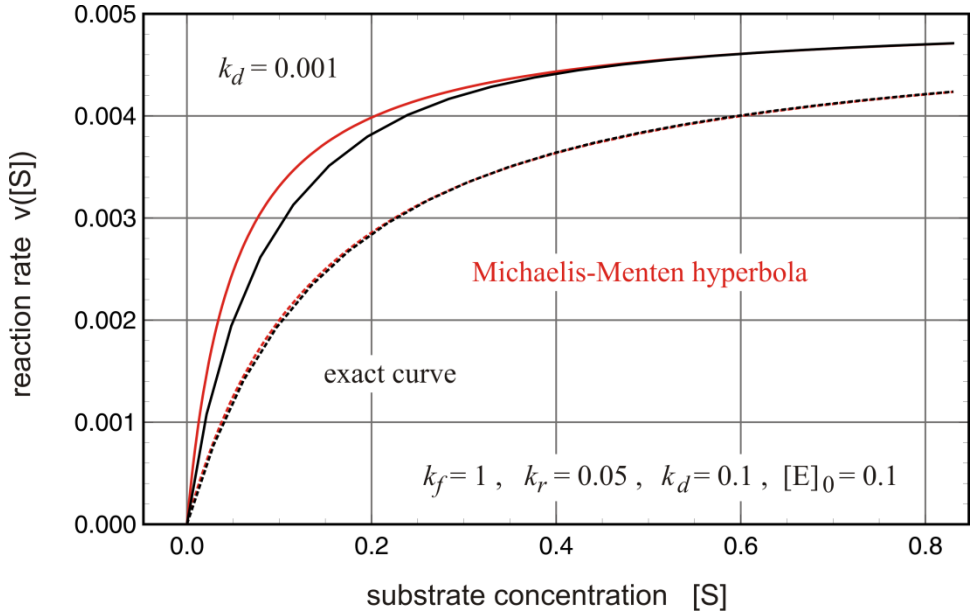


The Lineweaver-Burke plot of Michaelis-Menten kinetics

Source: Wikipedia, “Enzymkinetik”







Validity of the Michaelis-Menten approximation

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

$$\frac{\partial x}{\partial t} = D\,\nabla^2 x + f(x;k)$$

Parameter set

$k_j(\mathrm{T},\mathrm{p},\mathrm{pH},\mathrm{I},\ldots);\ \mathrm{j}=1,2,\ldots,\mathrm{m}$

General conditions : T , p , pH , I , ...

Initial conditions : $x(0)$

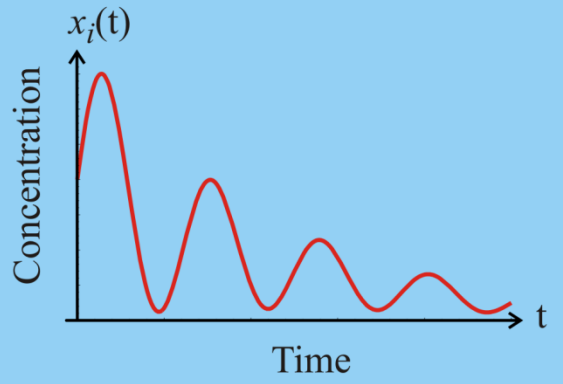
Boundary conditions :

boundary ... S, normal unit vector ... $\hat{u}$

Dirichlet : $x^S = g(r,t)$

Neumann : $\frac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Solution curves: $x(t)$



The forward problem of chemical reaction kinetics

Parameter identification and determination is an ill-posed problem

Inverse problem solution techniques

Kinetic differential equations

$$\frac{dx}{dt} = f(x;k);\ x=(x_1,\ldots,x_n);\ k=(k_1,\ldots,k_m)$$

Reaction diffusion equations

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Dirichlet : $x^S = g(r,t)$

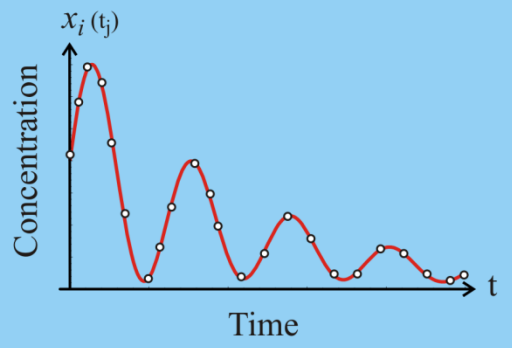
Neumann : $\frac{\partial x}{\partial u} = \hat{u}\cdot\nabla x^S = g(r,t)$

Parameter set

$$k_j(\mathrm{I_G};T,p,pH,I,\ldots);\ j=1,2,\ldots,m$$

Data from measurements

$x\,(t_j);\ j = 1, 2, \ldots, N$



The inverse problem of chemical reaction kinetics

$$F(\vec{q}) = \vec{y}^{\,\delta}$$

$$\left\| \vec{y}^{\,\delta} - F(\vec{q}) \right\|_Y^2 \to \min_{\vec{q} \in Q} \qquad \text{ill-conditioned problem}$$

$$\left\| \vec{y}^{\,\delta} - F(\vec{q}) \right\|_Y^2 + \alpha \mathcal{R}(\vec{q}, \vec{q}_0) \to \min_{\vec{q} \in Q} \quad \text{with} \quad \mathcal{R}(\vec{q}, \vec{q}_0) = \left\| \vec{q} - \vec{q}_0 \right\|_Q^2$$

regularization term $\mathcal{R}$ - here Tikhonov regularization - with q_0 being an initial parameter guess and α the regularization parameter

Parameter identification and determination as an inverse problem

IOP PUBLISHING INVERSE PROBLEMS

Inverse Problems **25** (2009) 123014 (51pp) doi:10.1088/0266-5611/25/12/123014

TOPICAL REVIEW

Inverse problems in systems biology

Heinz W Engl[1], Christoph Flamm[2], Philipp Kügler[3], James Lu[1], Stefan Müller[1] and Peter Schuster[2]

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Received 7 July 2009, in final form 12 November 2009
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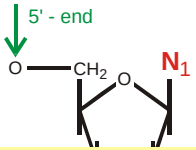
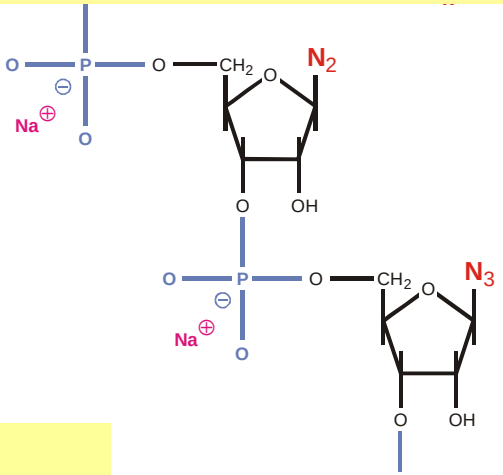
Online at stacks.iop.org/IP/25/123014

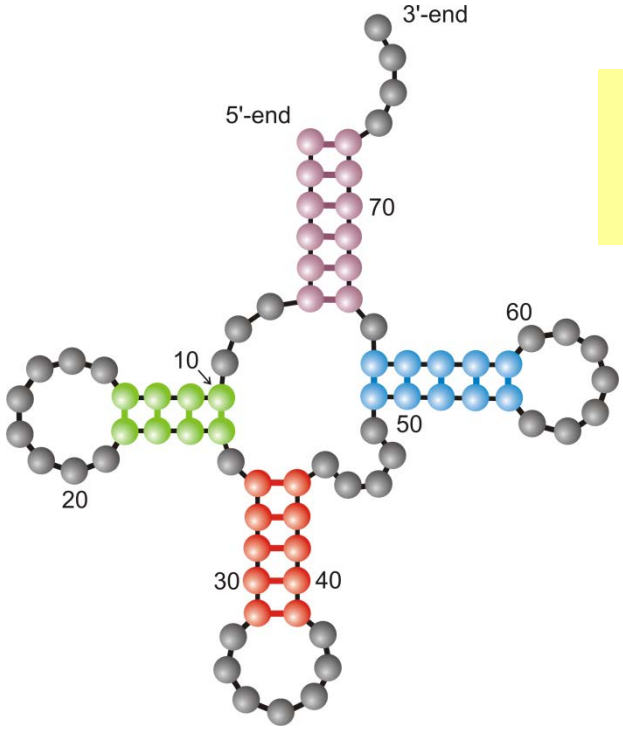
Four selected examples

1. Parameter determination in chemical kinetics
2. Design of ribonucleic acid (RNA) structures
3. Kinetic folding of RNA molecules
4. Modeling evolution



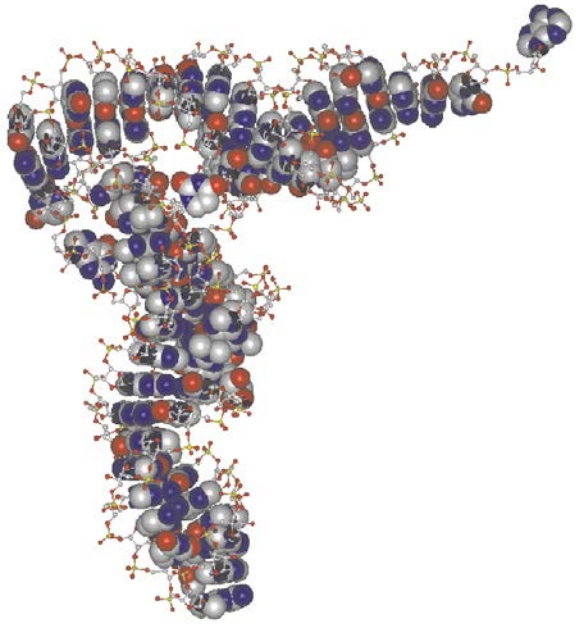
5'-end GCGGAUUUAGCUCAGUUGGGAGAGCGCCAGACUGAAGAUCUGGAGGUCCUGUGUUCGAUCCACAGAAUUCGCACCA 3'-end

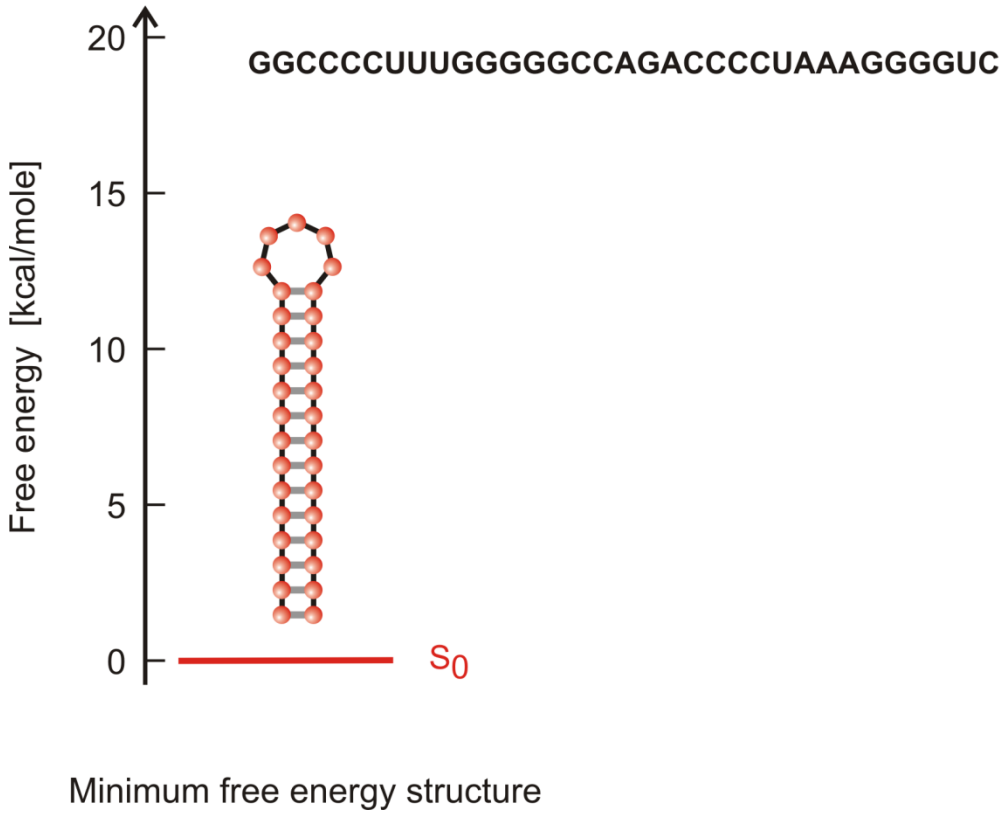




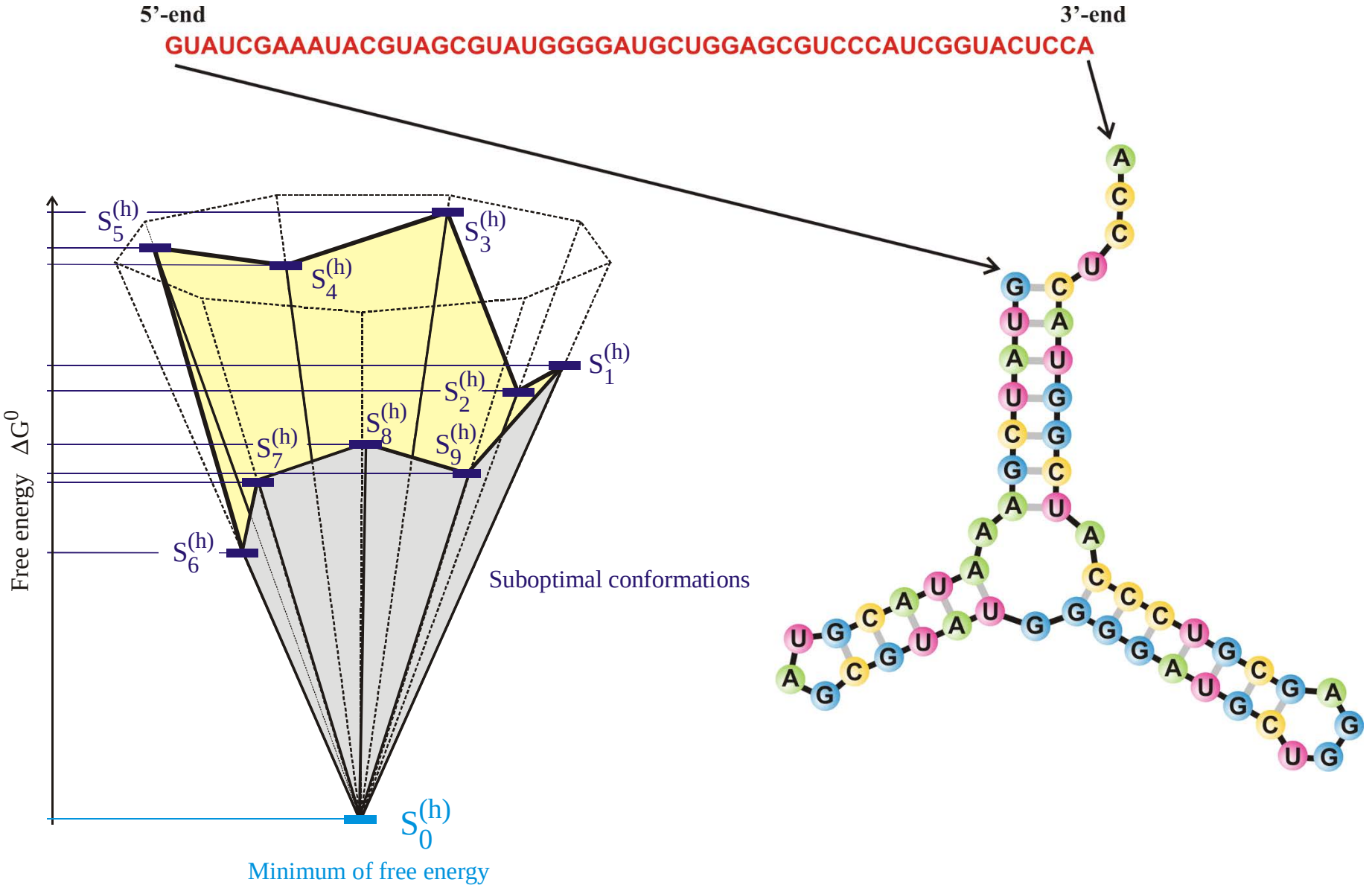
RNA structure

The molecular phenotype





The notion of structure



The minimum free energy structures on a discrete space of conformations

RNA sequence GUAUCGAAAUACGUAGCGUAUGGGGAUGCUGGACGGUCCCAUCGGUACUCCA

linear programming

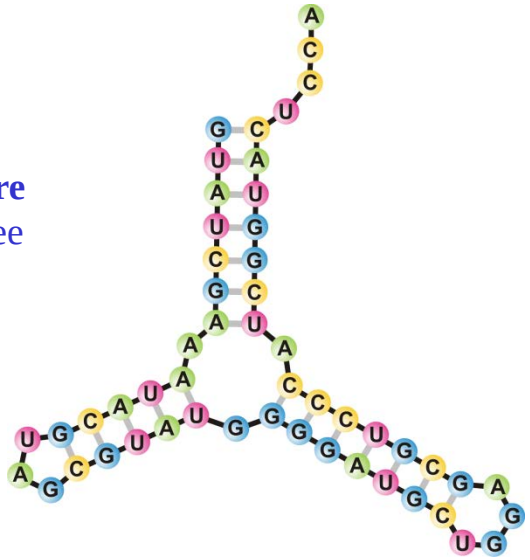
RNA folding:

structural biology, spectroscopy of biomolecules, understanding **molecular function**

biophysical chemistry: thermodynamics and kinetics

empirical parameters

RNA structure of minimal free energy



From RNA sequence to structure

RNA sequence GUAUCGAAAUACGUAGCGUAUGGGGAUGCUGGACGGUCCCAUCGGUACUCCA

Linear programming

RNA folding:

Structural biology, spectroscopy of biomolecules, understanding **molecular function**

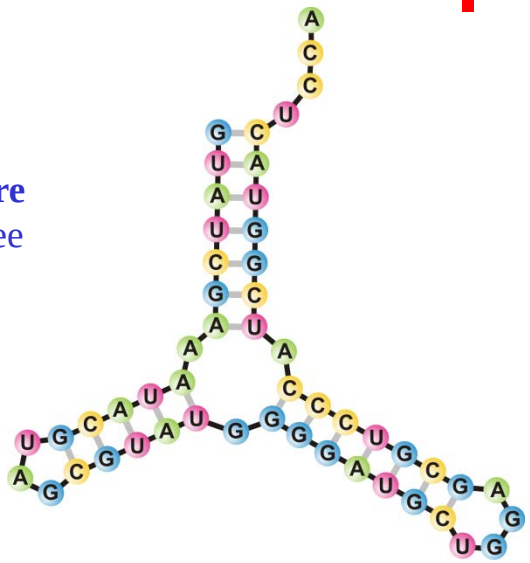
iterative determination of a sequence for the given secondary structure

inverse Folding Algorithm

inverse folding of RNA:

biotechnology, **design of biomolecules** with predefined structures and functions

RNA structure of minimal free energy

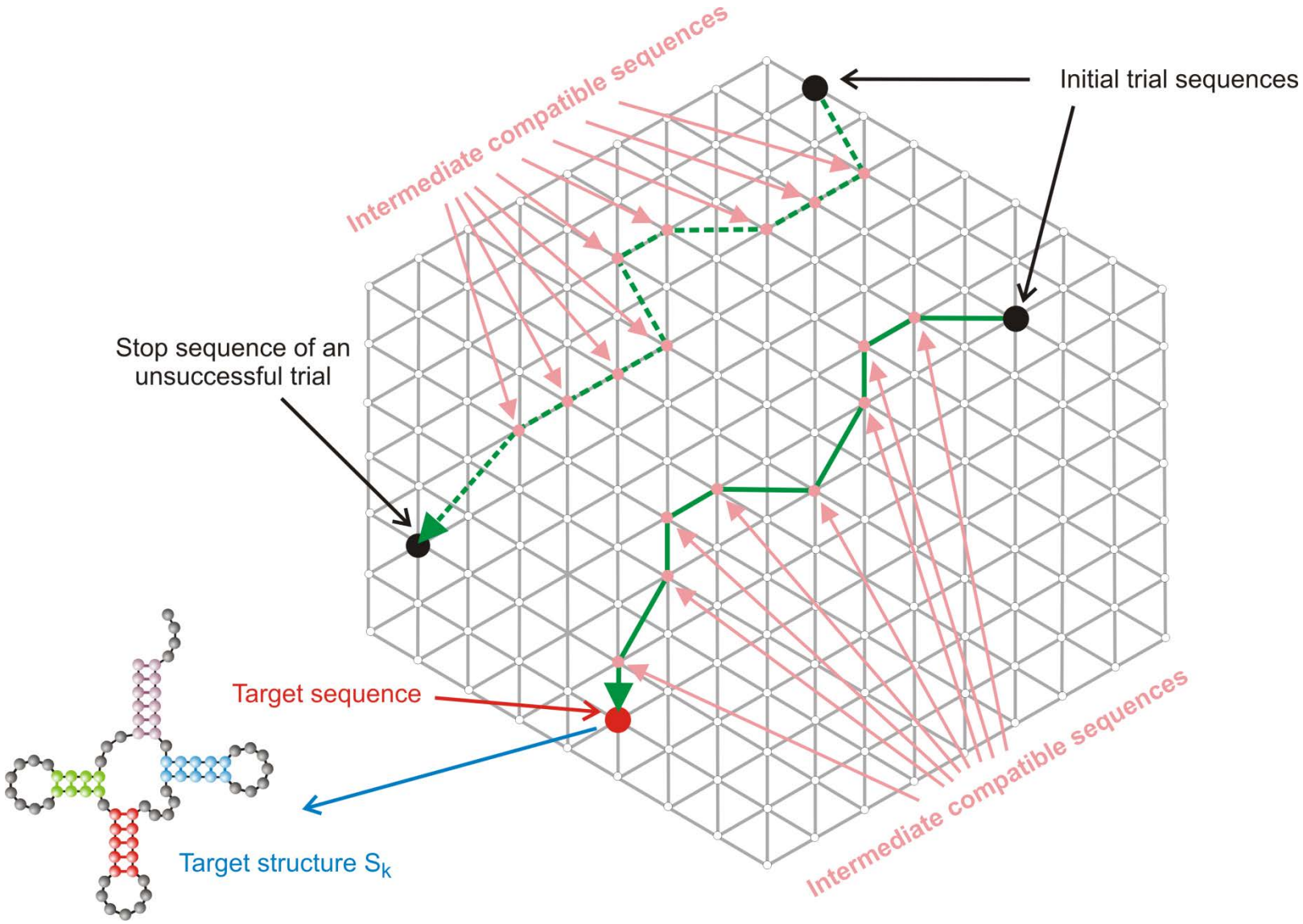


From RNA structure to sequence

ViennaRNA Package:

Ivo L. Hofacker, Walter Fontana, Peter F. Stadler, Sebastian Bonhoeffer, Manfred Tacker, and Peter Schuster.
Fast folding and comparison of RNA secondary structures.
Mh.Chem. **125**:167-188, 1994

Ronny Lorenz, Stephan H. Bernhart, Christian Höner zu Siederissen, Hakim Tafer, Christioh Flamm, Peter F. Stadler, and Ivo L. Hofacker.
ViennaRNA Package 2.0.
Algorithms Mol. Biol. **6**:26, 2011


Intermediate compatible sequences
Initial trial sequences
Stop sequence of an unsuccessful trial
Target sequence
Target structure S_k
Intermediate compatible sequences

Space of genotypes: $\mathcal{I} = \{I_1, I_2, I_3, I_4, \ldots, I_N\}$; Hamming metric

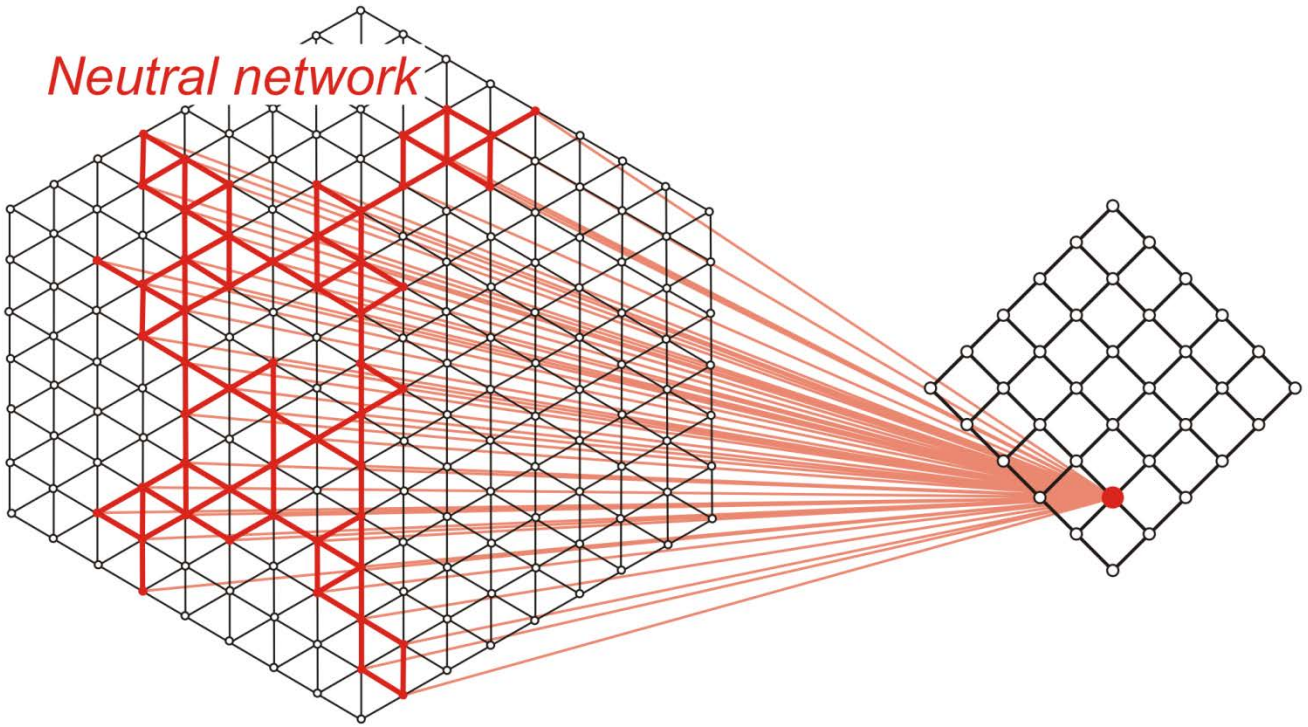
Space of phenotypes: $S = \{S_1, S_2, S_3, S_4, \ldots, S_M\}$; metric (not required)

$$N >> M$$

$$\psi(I_j) = S_k$$

$$\mathbf{G}_k = \psi^{-1}(S_k) \equiv \{ I_j \mid \psi(I_j) = S_k \}$$

A mapping ψ and its inversion



Sequence space

Structure space

many genotypes ⇒ one phenotype

Four selected examples

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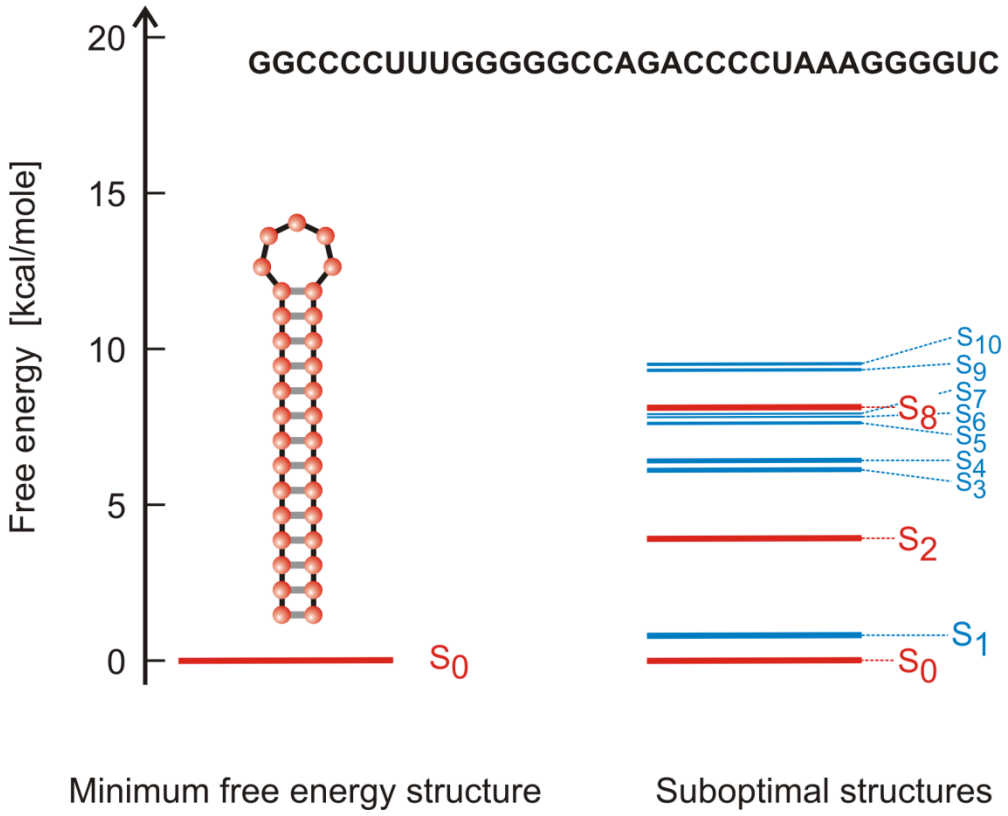
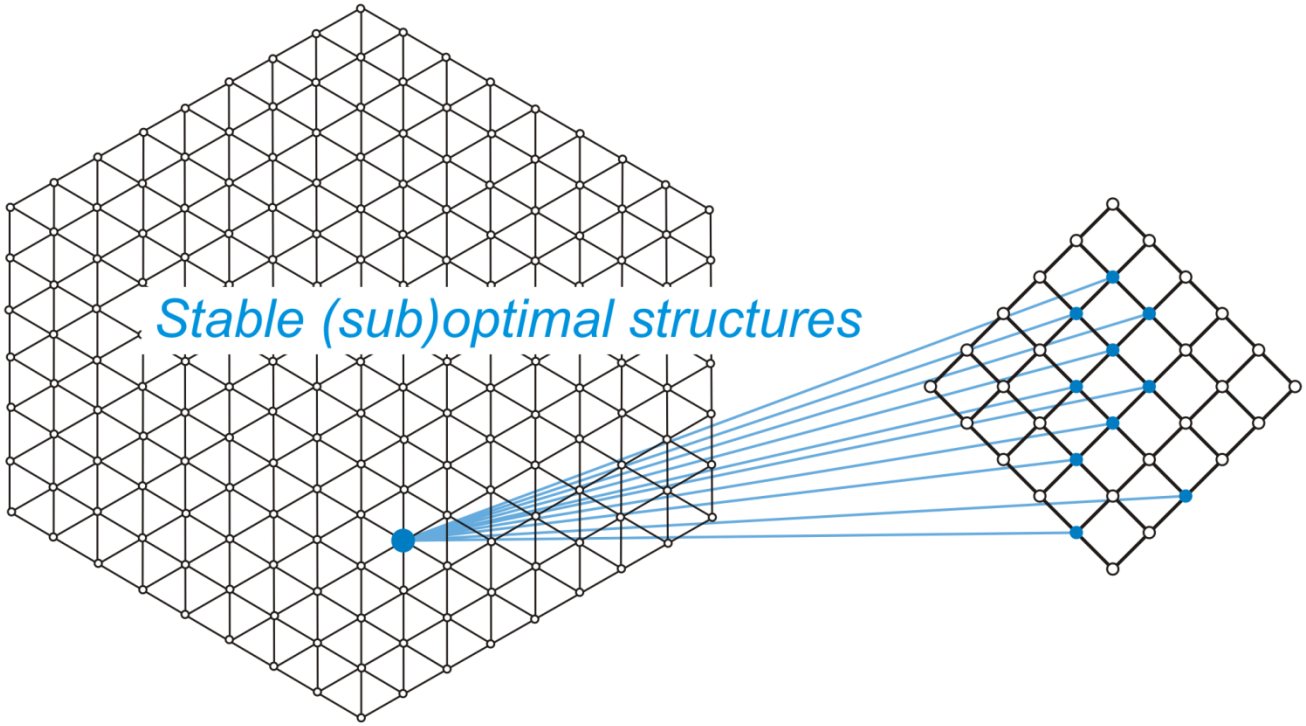
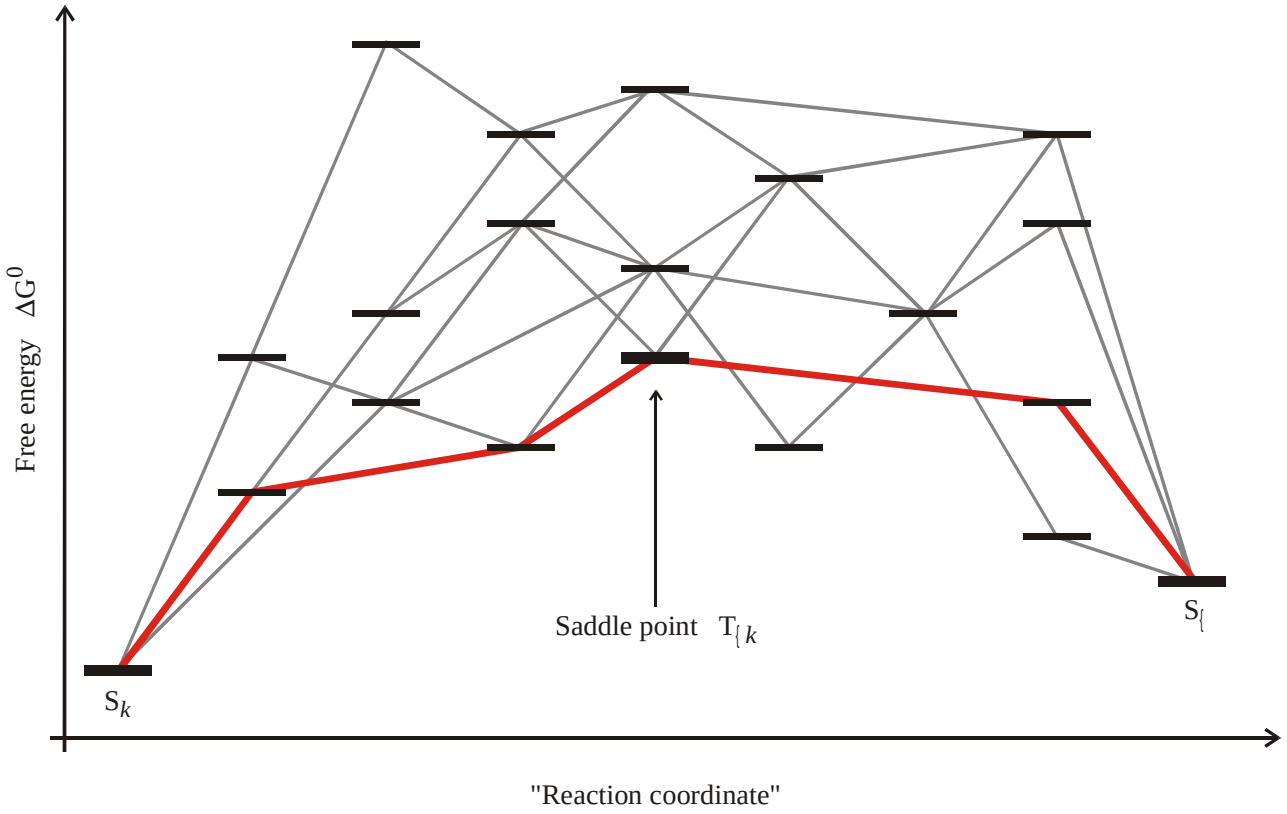
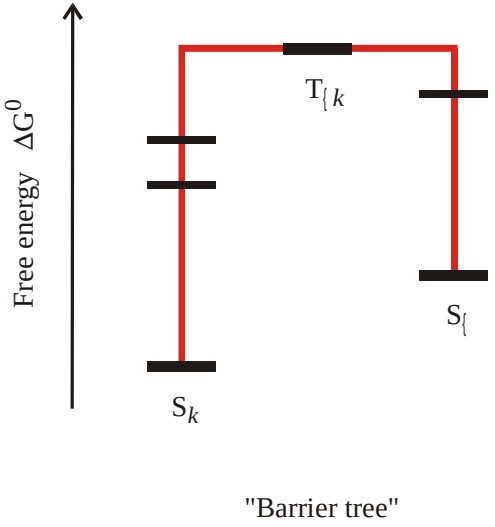
3. **Kinetic folding of RNA molecules**
4. Modeling evolution



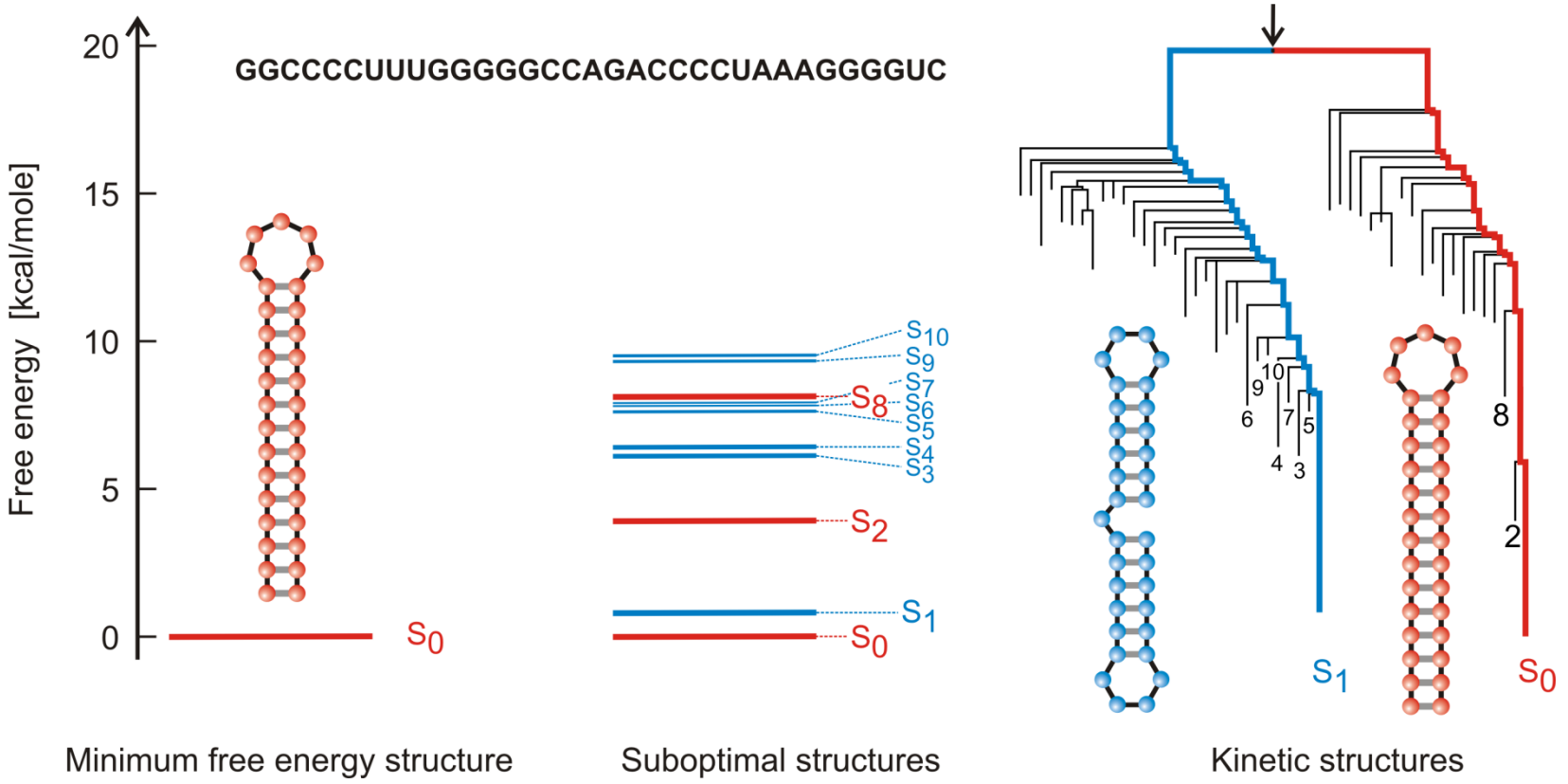
Extension of the notion of structure


Stable (sub)optimal structures
Sequence space
Structure space





Definition of a ‚barrier tree‘



Interconversion of suboptimal structures

INSTITUTE OF PHYSICS PUBLISHING JOURNAL OF PHYSICS A: MATHEMATICAL AND GENERAL

J. Phys. A: Math. Gen. **37** (2004) 4731–4741 PII: S0305-4470(04)73887-1

Efficient computation of RNA folding dynamics

Michael T Wolfinger[1], W Andreas Svrcek-Seiler[1], Christoph Flamm[1], Ivo L Hofacker[1] and Peter F Stadler[2]

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[2] Bioinformatik, Institut für Informatik, Universität Leipzig, D-04103 Leipzig, Germany

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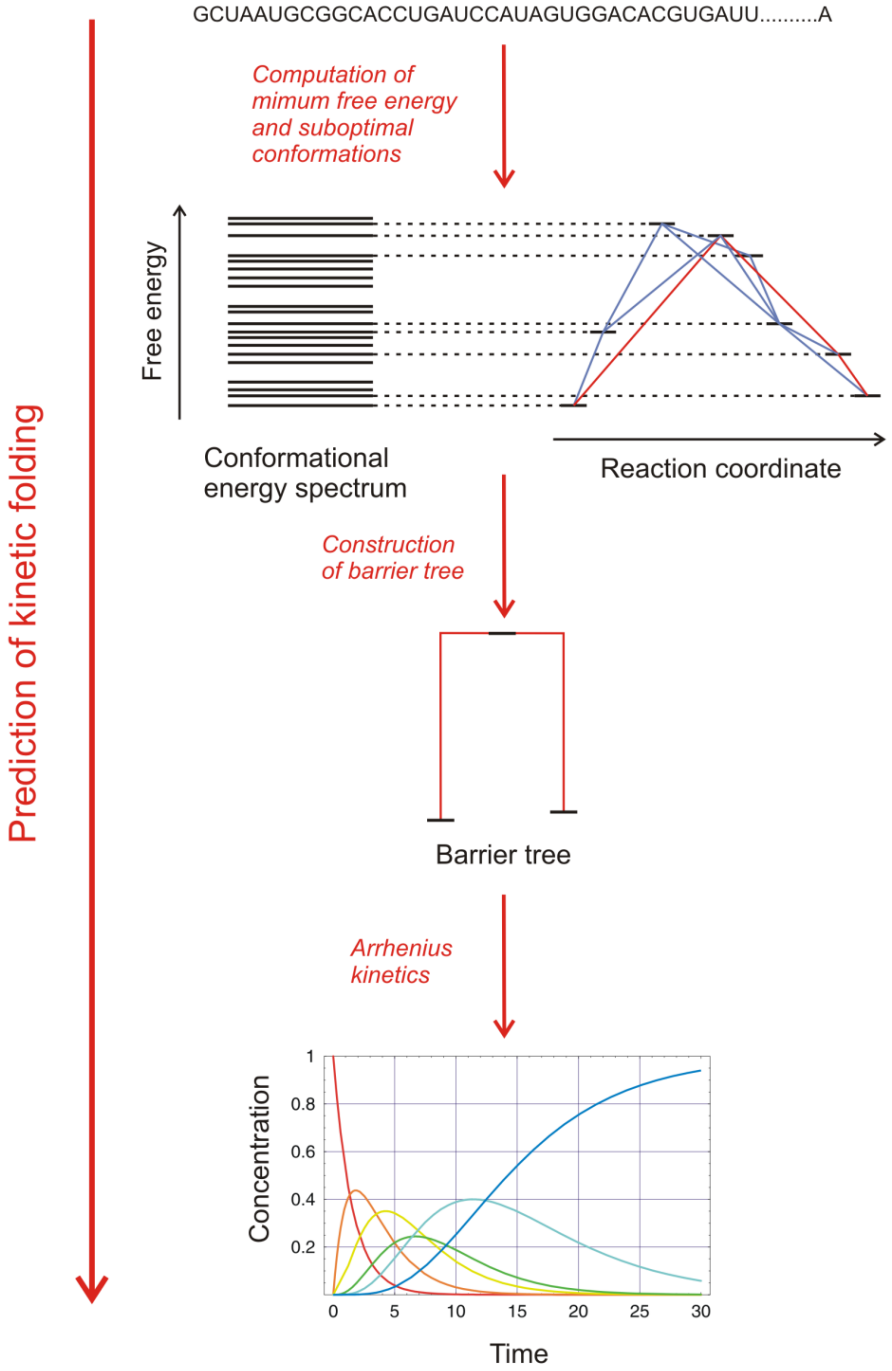
Online at stacks.iop.org/JPhysA/37/4731 (DOI: 10.1088/0305-4470/37/17/005)

Abstract

Barrier trees consisting of local minima and their connecting saddle points imply a natural coarse-graining for the description of the energy landscape of RNA secondary structures. Here we show that, based on this approach, it is possible to predict the folding behaviour of RNA molecules by numerical integration. Comparison with stochastic folding simulations shows reasonable agreement of the resulting folding dynamics and a drastic increase in computational efficiency that makes it possible to investigate the folding dynamics of RNA of at least tRNA size. Our approach is readily applicable to bistable RNA molecules and promises to facilitate studies on the dynamic behaviour of RNA switches.

PACS numbers: 87.14.Gg, 87.15.He, 87.15.Aa, 87.15.Cc



Computation of kinetic folding

3568–3576 Nucleic Acids Research, 2006, Vol. 34, No. 12
doi:10.1093/nar/gkl445

Structural parameters affecting the kinetics of RNA hairpin formation

J. H. A. Nagel, C. Flamm[1], I. L. Hofacker[1], K. Franke[2], M. H. de Smit, P. Schuster[1] and C. W. A. Pleij*

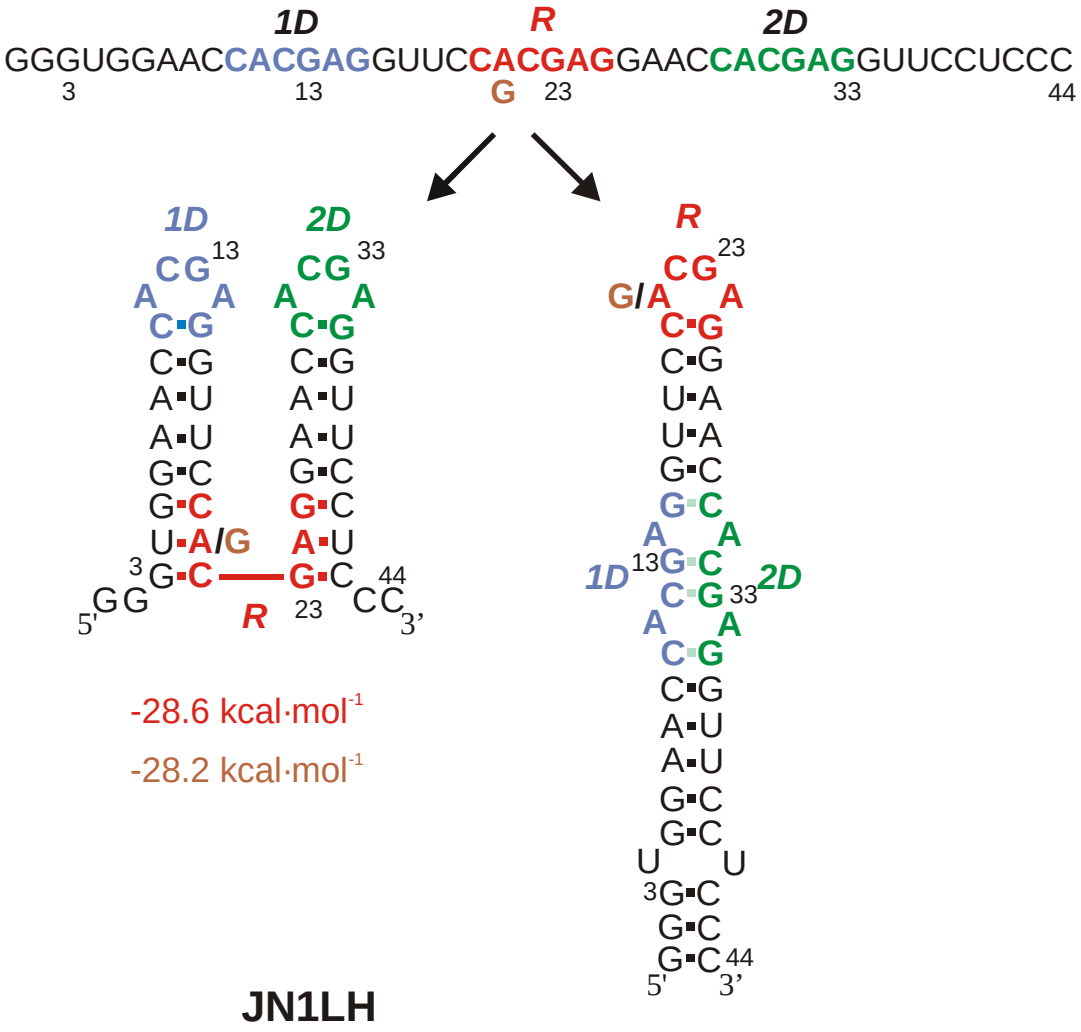
Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University, 2300 RA Leiden, The Netherlands, [1]Institut für Theoretische Chemie und Molekulare Strukturbiologie, Universität Wien, A-1090 Vienna, Austria and [2]IBA NAPS GmbH Rudolf-Wissell-Strasse 28 D-37079 Göttingen, Germany

Received January 28, 2005; Revised and Accepted June 7, 2006

ABSTRACT

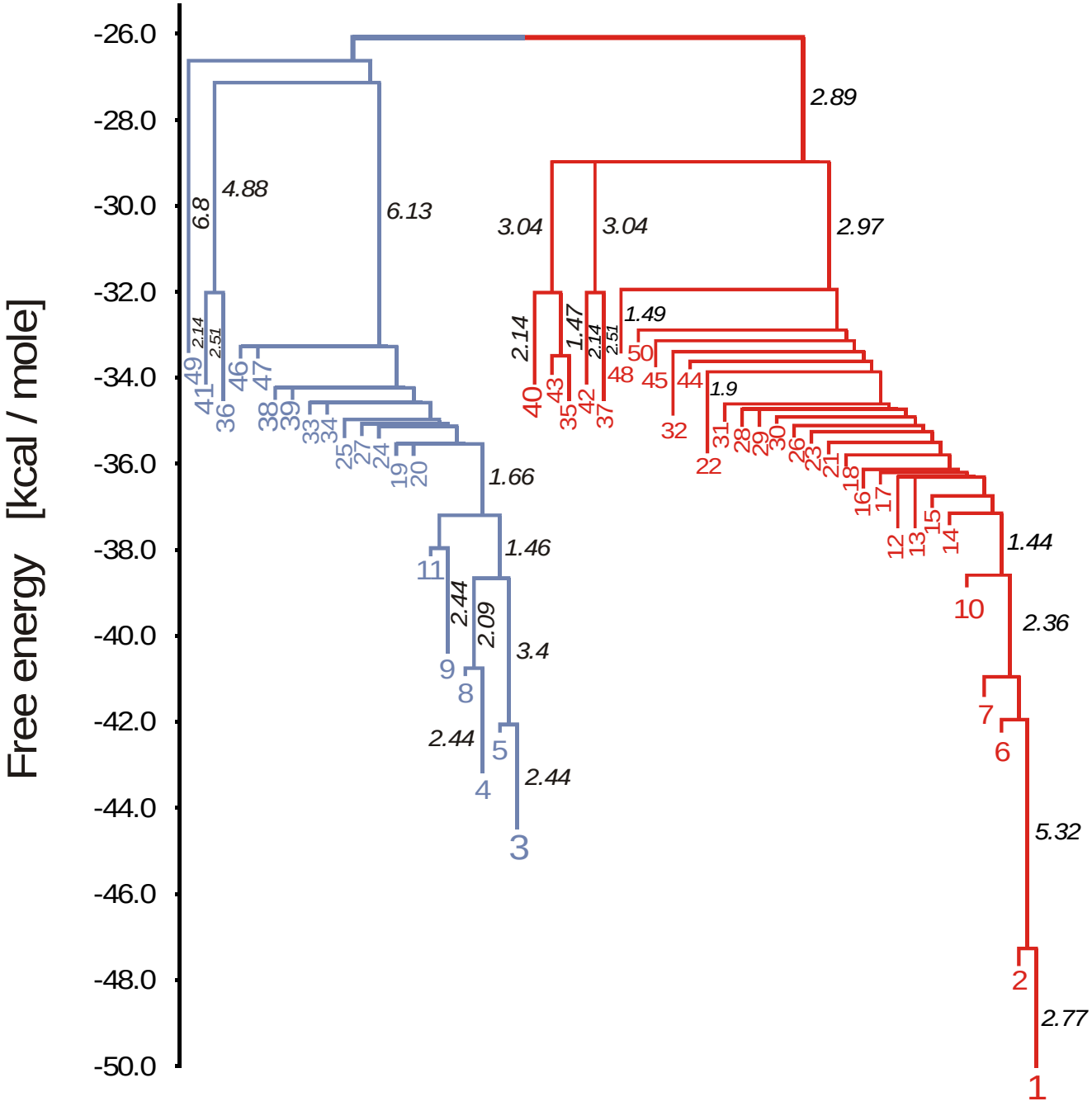
There is little experimental knowledge on the sequence dependent rate of hairpin formation in RNA. We have therefore designed RNA sequences that can fold into either of two mutually exclusive hairpins and have determined the ratio of folding of the two conformations, using structure probing. This folding ratio reflects their respective folding rates. Changing one of the two loop sequences from a purine- to a pyrimidine-rich loop did increase its folding rate, which corresponds well with similar observations in DNA hairpins. However, neither changing one of the loops from a regular non-GNRA tetra-loop into a stable GNRA tetra-loop, nor increasing the loop size from 4 to 6 nt did affect the folding rate. The folding kinetics of these RNAs have also been simulated with the program 'Kinfold'. These simulations were in agreement with the experimental results if the additional stabilization energies for stable tetra-loops were not taken into account. Despite the high stability of the stable tetra-loops, they apparently do not affect folding kinetics of these RNA hairpins. These results show that it is possible to experimentally determine relative folding rates of hairpins and to use these data to improve the computer-assisted simulation of the folding kinetics of stem–loop structures.

An experimental RNA switch



J.H.A. Nagel, C. Flamm, I.L. Hofacker, K. Franke, M.H. de Smit, P. Schuster, and C.W.A. Pleij.

Structural parameters affecting the kinetic competition of RNA hairpin formation. ***Nucleic Acids Res***. **34**:3568-3576 (2006)



J1LH barrier tree

Four selected examples

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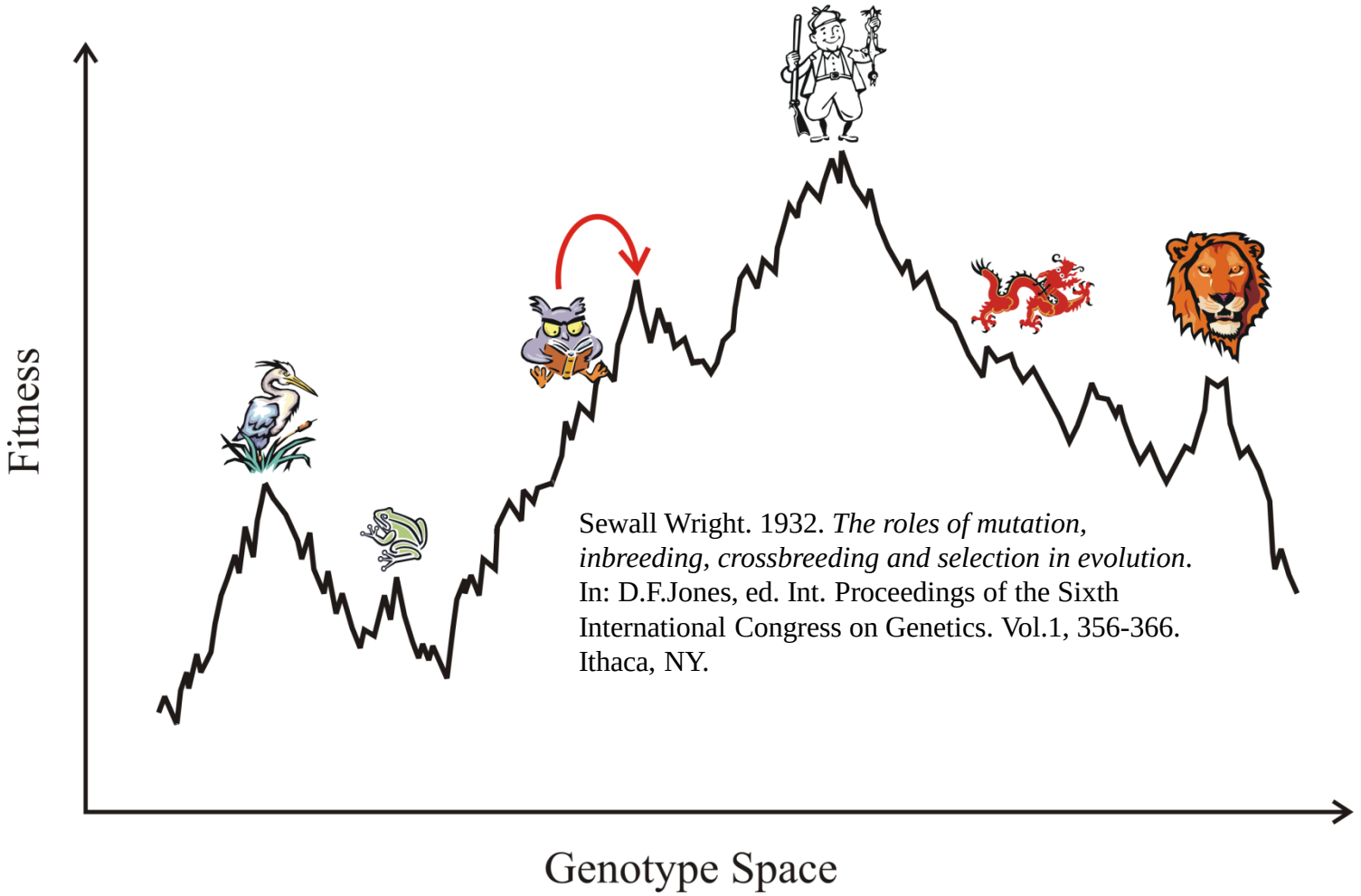
4. **Modeling evolution**



Sewall Wrights fitness landscape as metaphor for Darwinian evolution

Sewall Wright, 1889 - 1988

+ …….. wild type
a ..... alternative allele on locus A
:
:
:
abcde … alternative alleles on all five loci

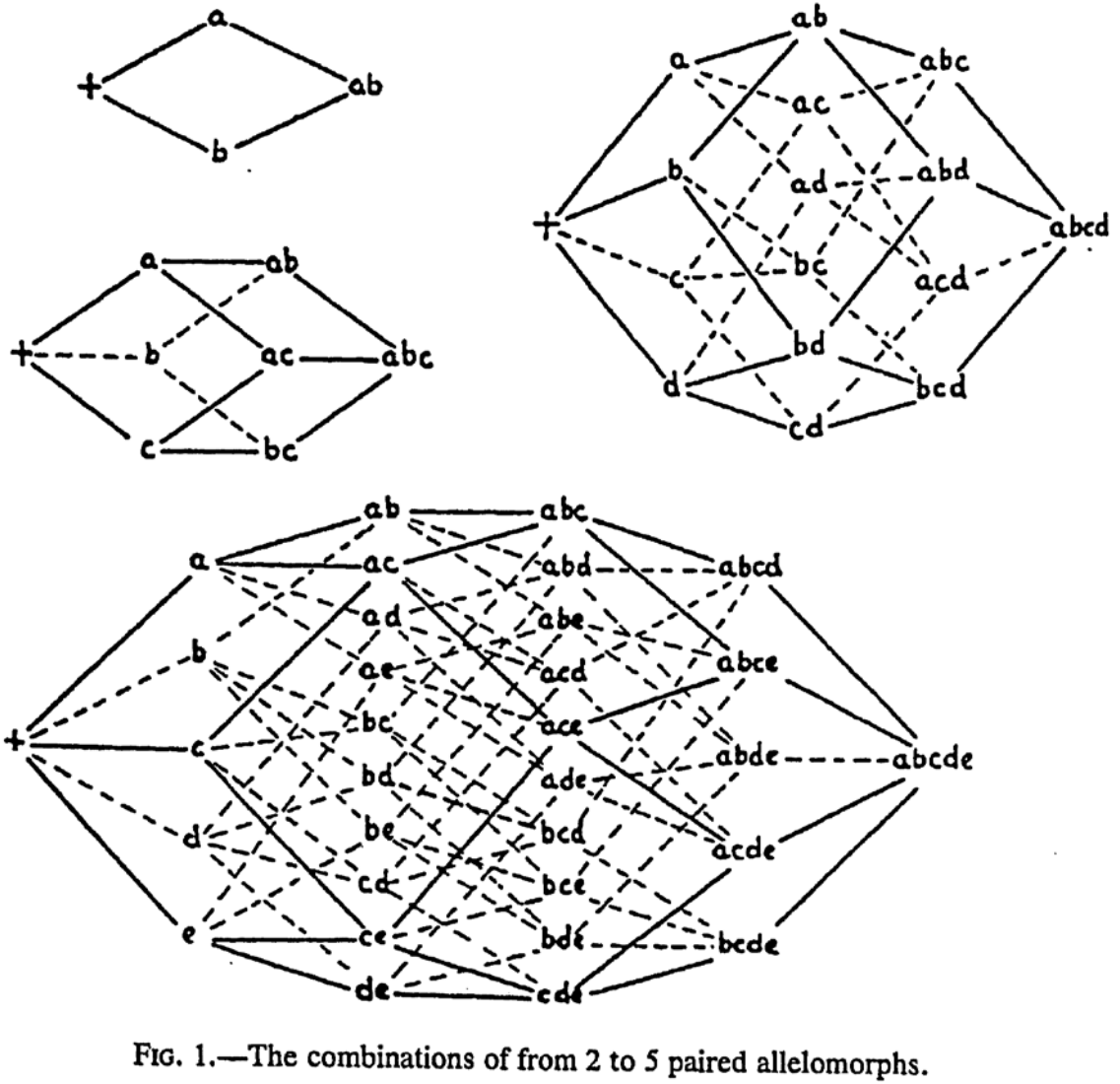


FIG. 1.—The combinations of from 2 to 5 paired allelomorphs.

The multiplicity of gene replacements with two alleles on each locus

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

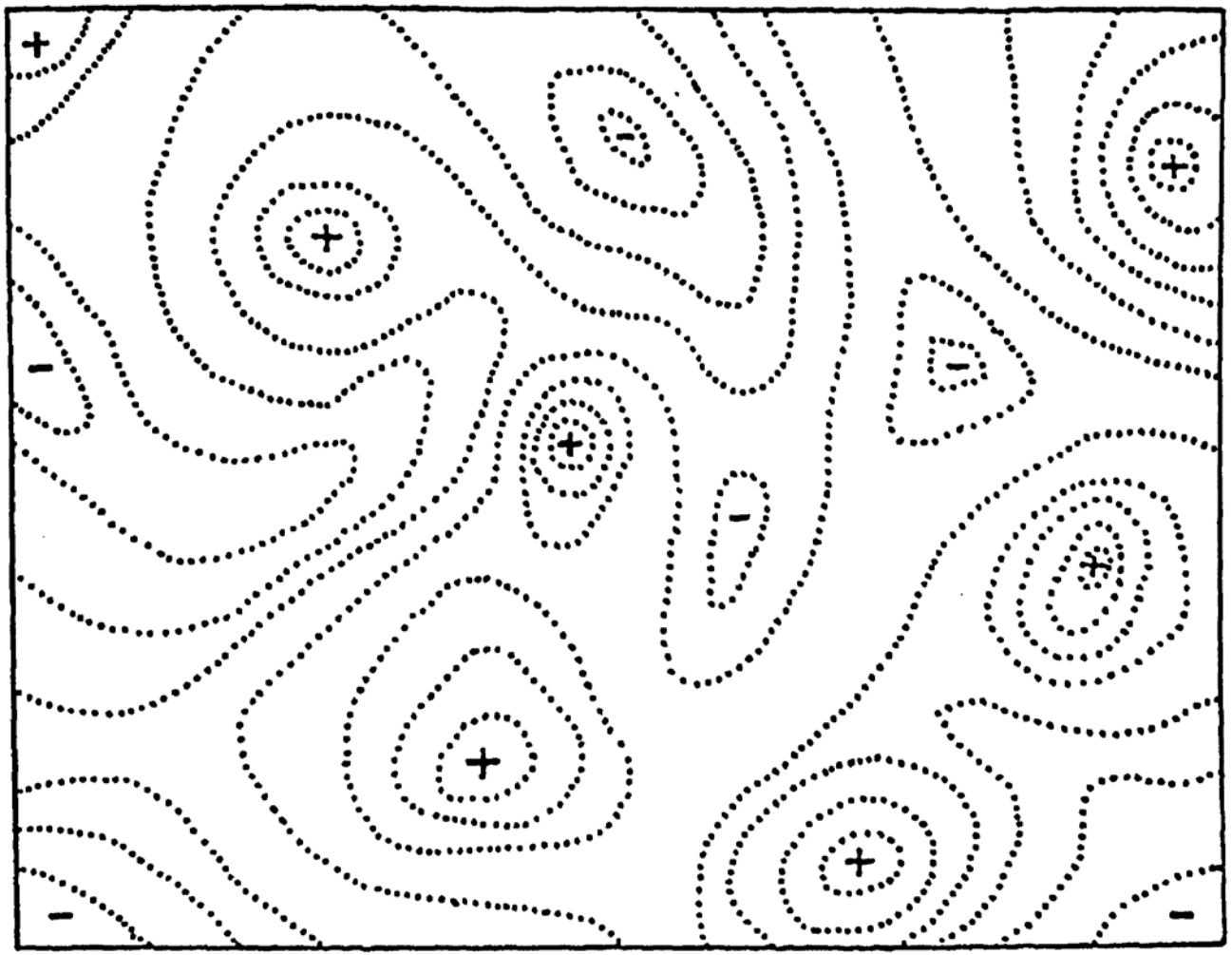
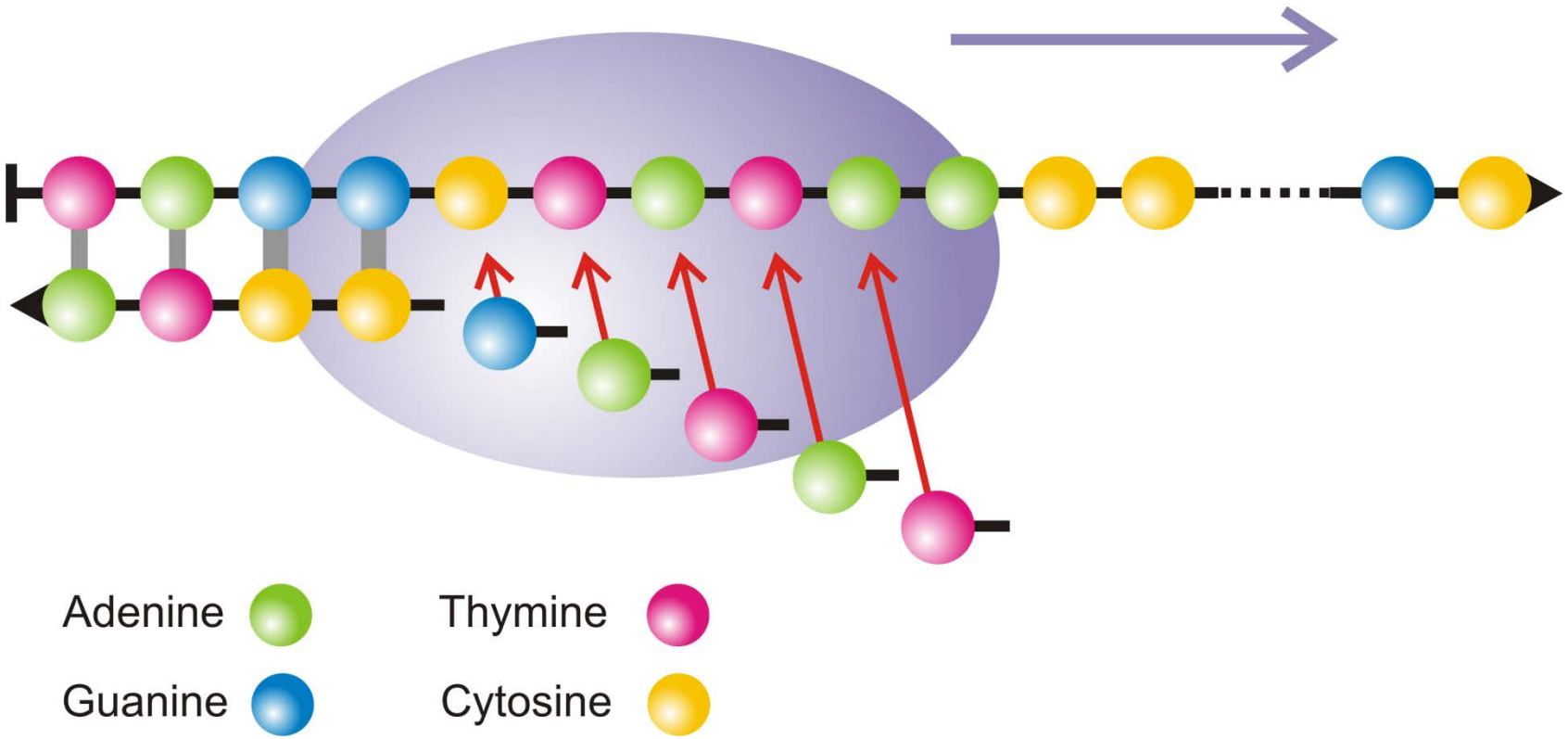


FIG. 2.—Diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands. Dotted lines represent contours with respect to adaptiveness.

Evolution is hill climbing of populations or subpopulations

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



Accuracy of replication: $Q = q_1 \cdot q_2 \cdot q_3 \cdot q_4 \cdot \ldots$

The logics of DNA (or RNA) replication

Sol Spiegelman,
1914 - 1983

Evolution in the test tube:

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

DOI: 10.1002/anie.200701369

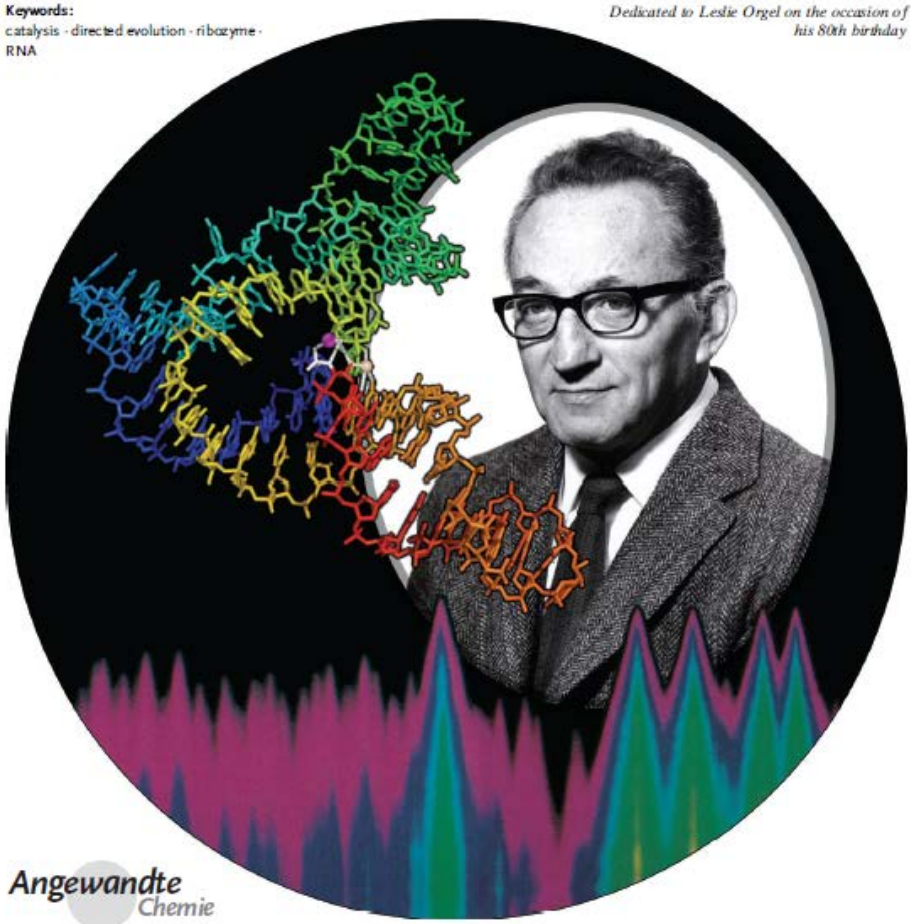
Molecular Evolution

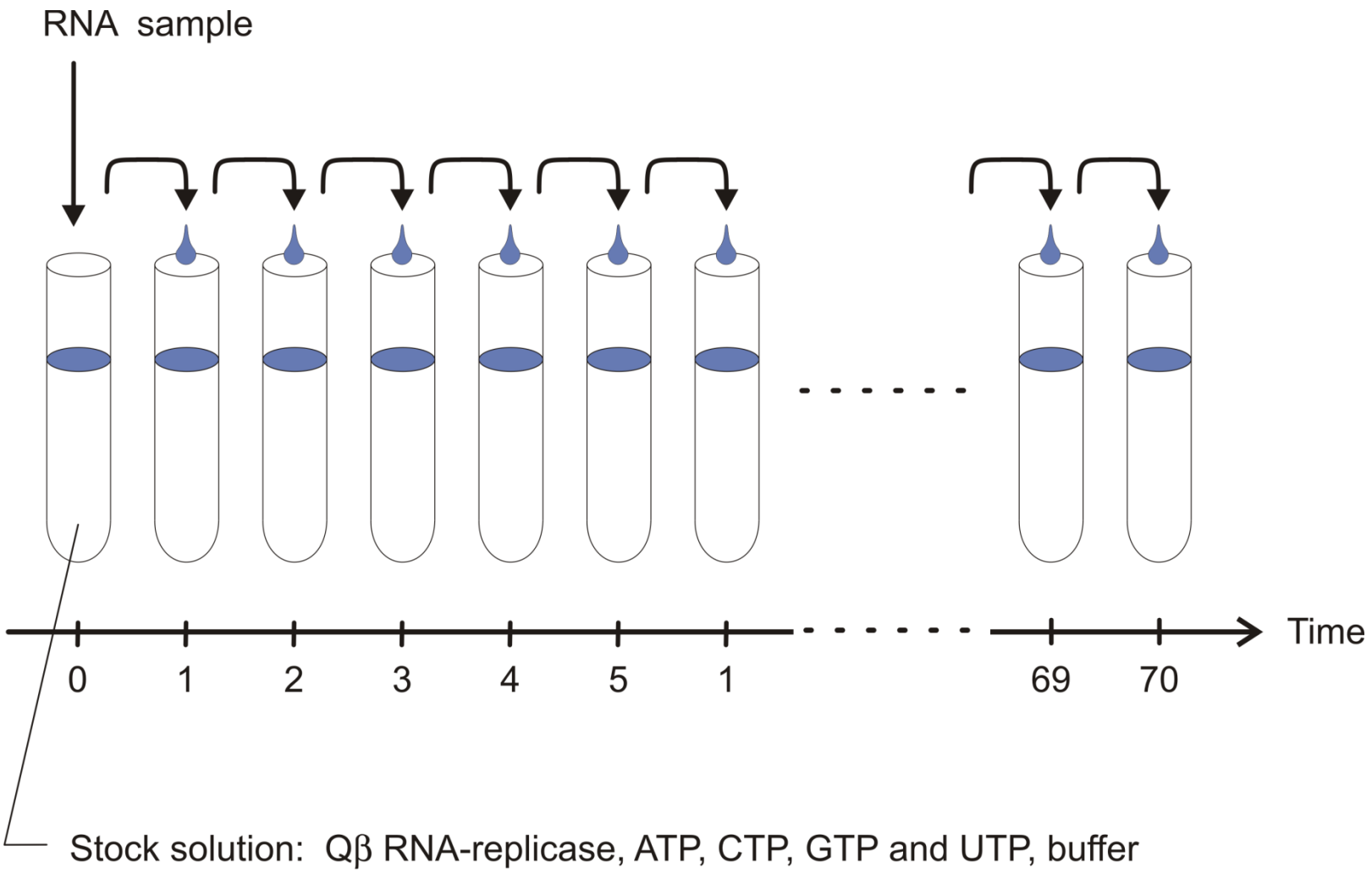
Forty Years of In Vitro Evolution**

*Gerald F. Joyce**

Keywords:
catalysis · directed evolution · ribozyme · RNA

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




RNA sample
Time
0
1
2
3
4
5
1
69
70
Stock solution: Qβ RNA-replicase, ATP, CTP, GTP and UTP, buffer

Reproduction of the original figure of the serial transfer experiment with Qβ RNA

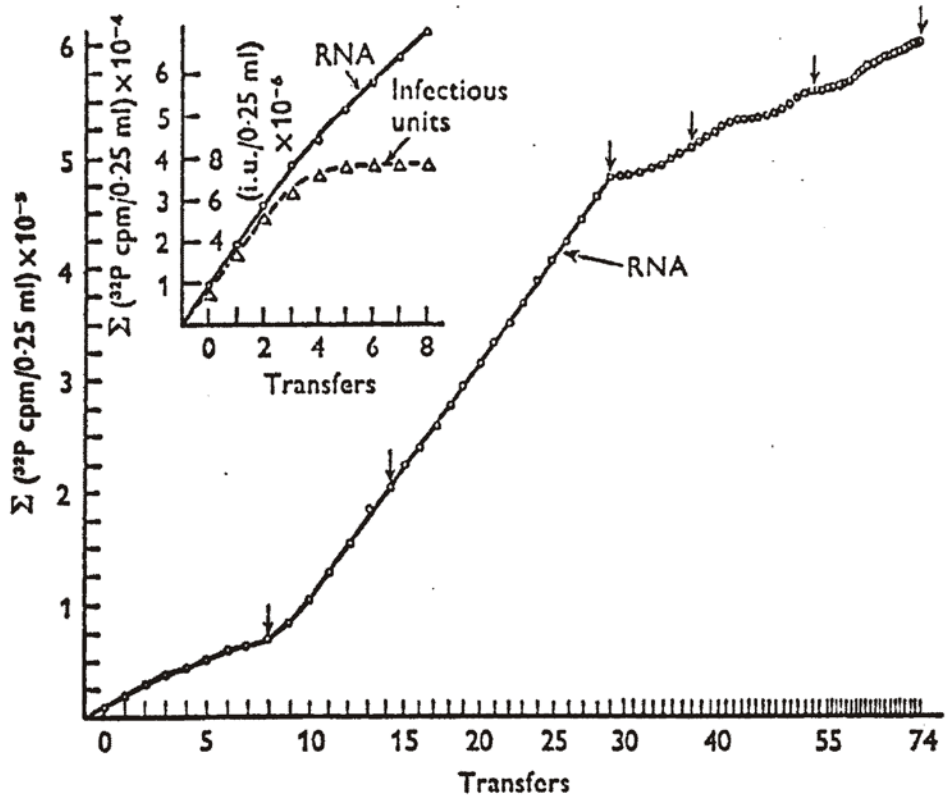
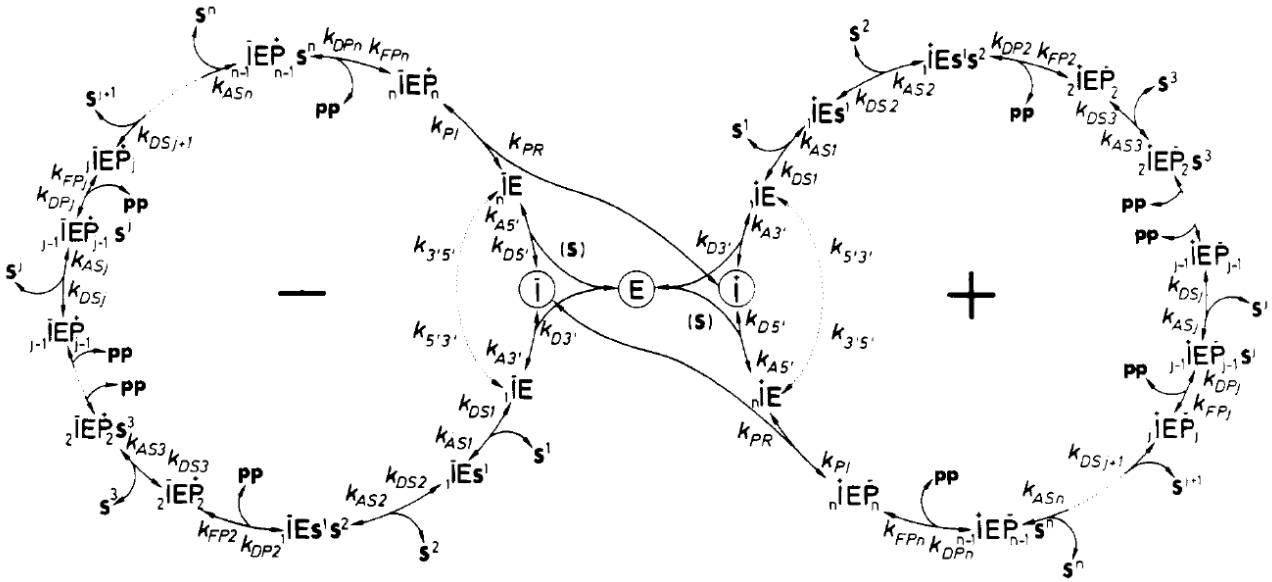
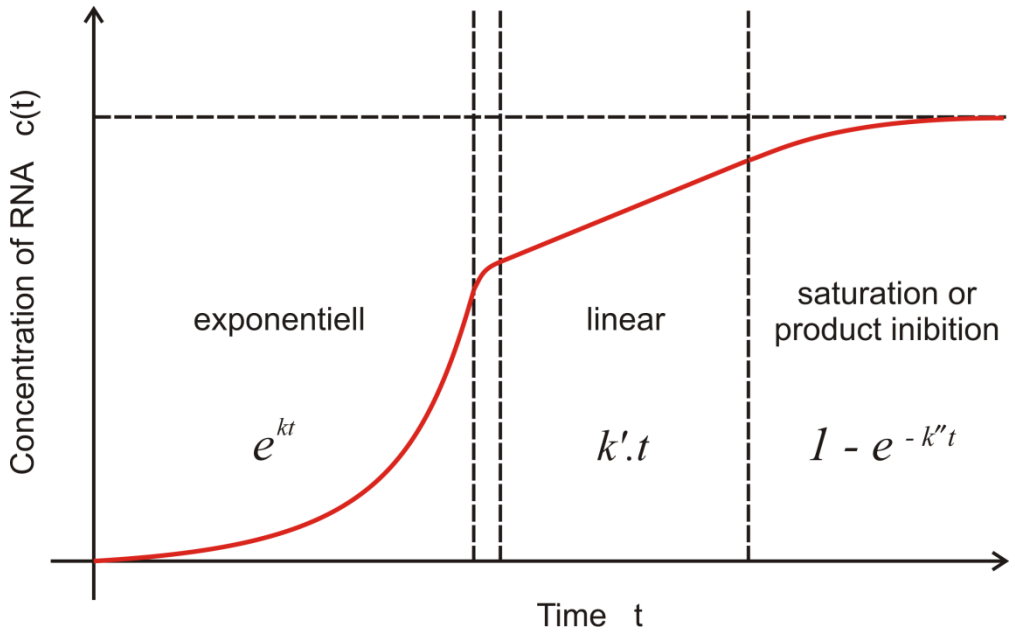


Fig. 9. Serial transfer experiment. Each 0·25 ml standard reaction mixture contained 40 μg of Qβ replicase and ^{32}P-UTP. The first reaction (0 transfer) was initiated by the addition of 0·2 μg ts-1 (temperature-sensitive RNA) and incubated at 35 °C for 20 min, whereupon 0·02 ml was drawn for counting and 0·02 ml was used to prime the second reaction (first transfer), and so on. After the first 13 reactions, the incubation periods were reduced to 15 min (transfers 14–29). Transfers 30–38 were incubated for 10 min. Transfers 39–52 were incubated for 7 min, and transfers 53–74 were incubated for 5 min. The arrows above certain transfers (0, 8, 14, 29, 37, 53, and 73) indicate where 0·001–0·1 ml of product was removed and used to prime reactions for sedimentation analysis on sucrose. The inset examines both infectious and total RNA. The results show that biologically competent RNA ceases to appear after the 4th transfer (Mills *et al.* 1967).

D.R.Mills, R,L,Peterson, S.Spiegelman, *An extracellular Darwinian experiment with a self-duplicating nucleic acid molecule*. Proc.Natl.Acad.Sci.USA **58** (1967), 217-224

Christof K. Biebricher,
1941-2009





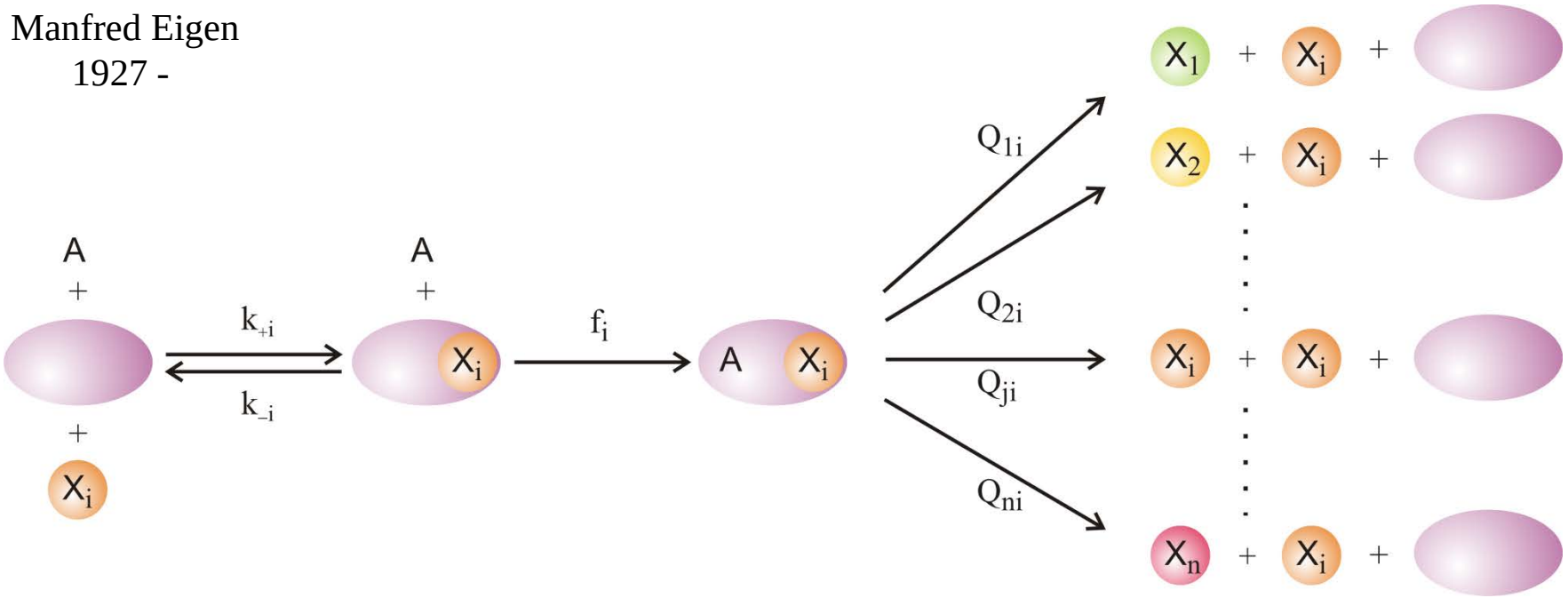
Kinetics of RNA replication

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

Manfred Eigen
1927 -

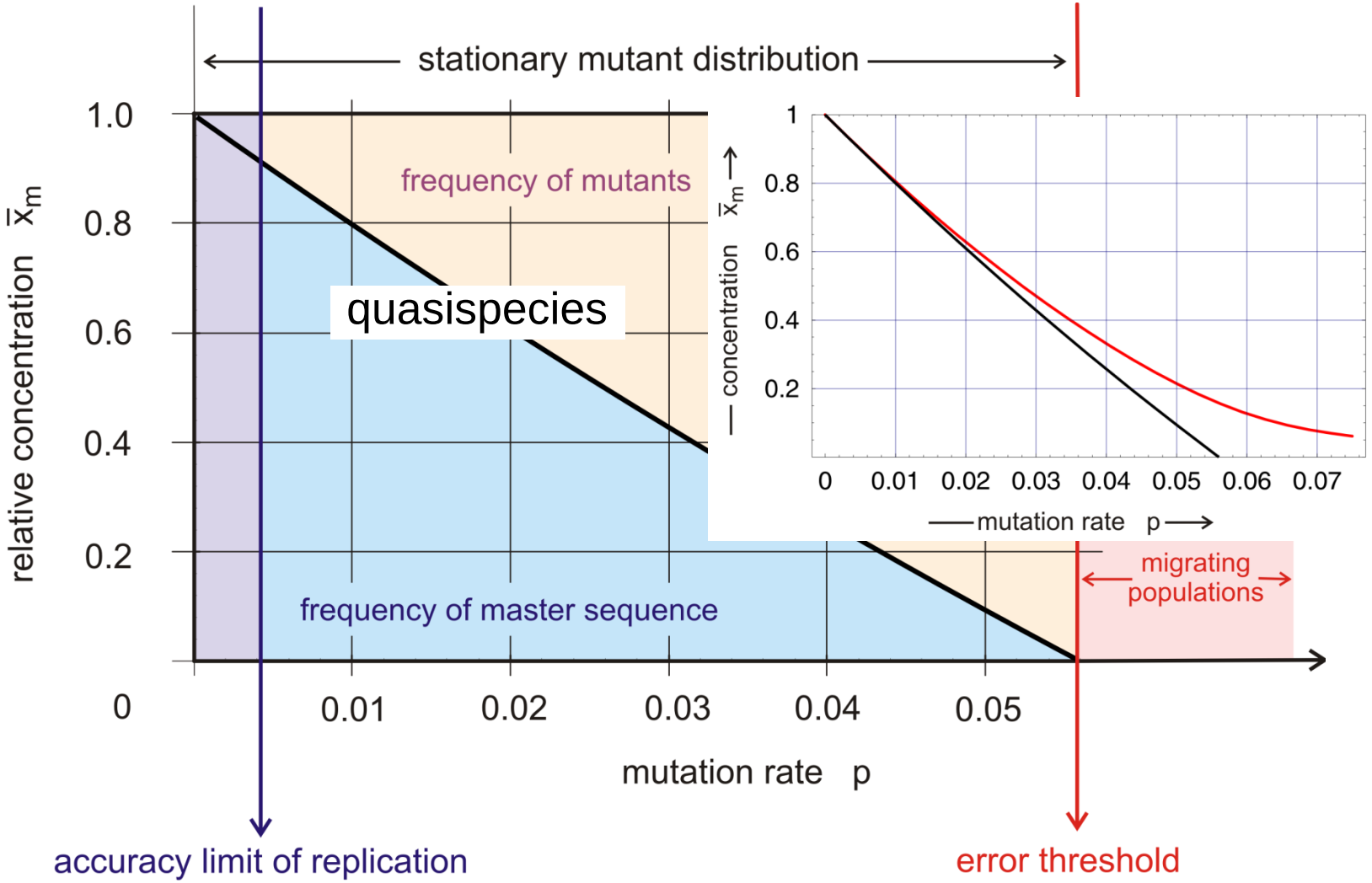
$$\frac{dx_j}{dt} = \sum_{i=1}^{n} W_{ji}\, x_i - x_j\, \Phi\,; \quad j = 1, 2, \ldots, n$$

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

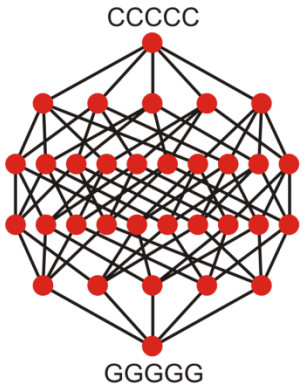


Mutation and (correct) replication as parallel chemical reactions

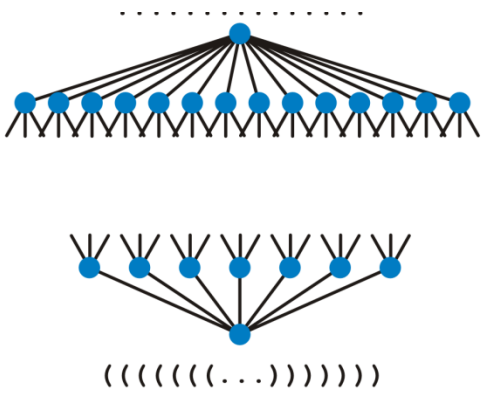
M. Eigen. 1971. *Naturwissenschaften* 58:465,
M. Eigen & P. Schuster.1977. *Naturwissenschaften* 64:541, 65:7 und 65:341



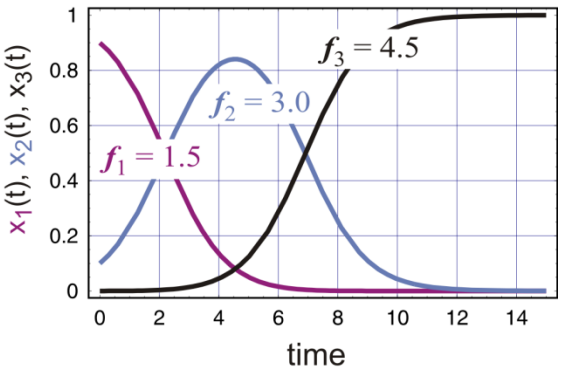
The error threshold in replication and mutation



sequence space



shape space



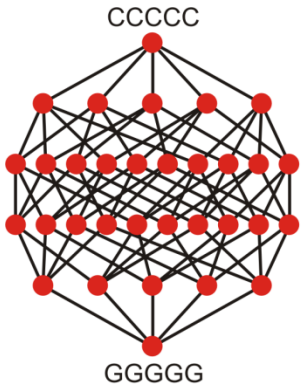
parameter space

$\Phi: (\mathcal{Q}, d_H) \Rightarrow (\mathcal{Y}, d_Y)$ $\quad\quad$ $\Psi: (\mathcal{Y}, d_Y) \Rightarrow \mathbf{R}^1$

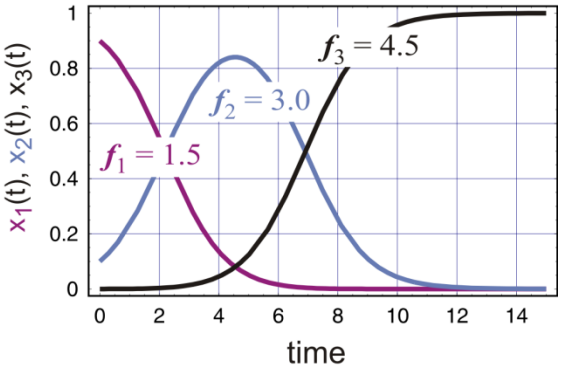
S $\longrightarrow$ Y = Φ(S) $\longrightarrow$ $f = \Psi(Y)$

sequence $\quad$ structure $\quad$ function

The paradigm of structural biology



sequence space



parameter space

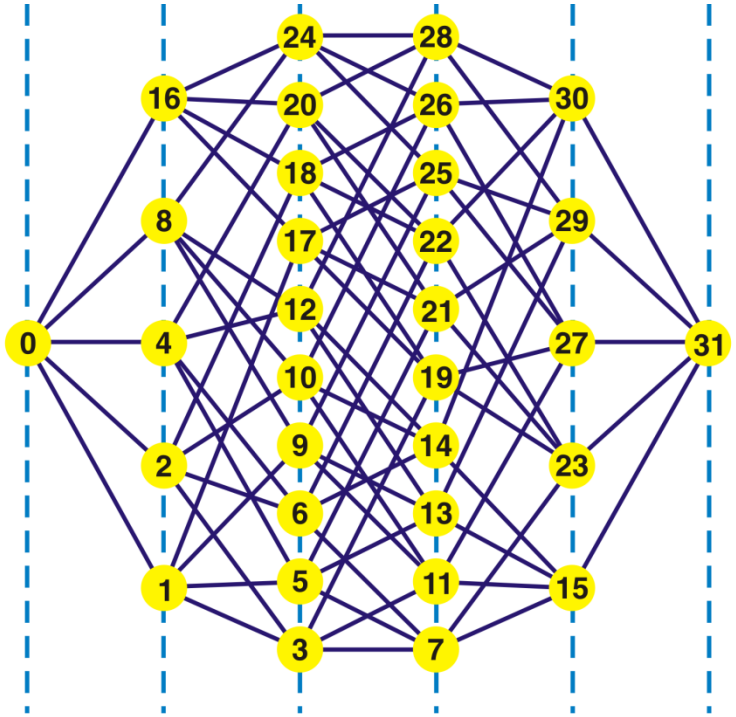
S

sequence

$f = \Psi(Y)$

function

The simplified model



Binary sequences are encoded by their decimal equivalents:

C = 0 and G = 1, for example,

"0" ≡ 00000 = CCCCC,

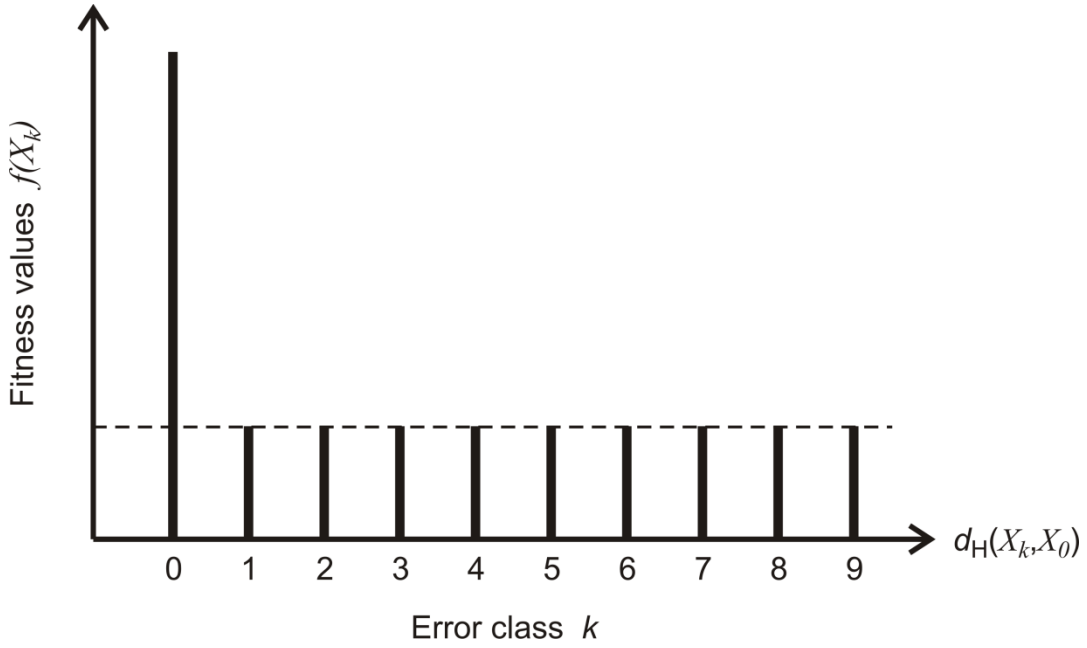
"14" ≡ 01110 = CGGGC,

"29" ≡ 11101 = GGGCG, etc.

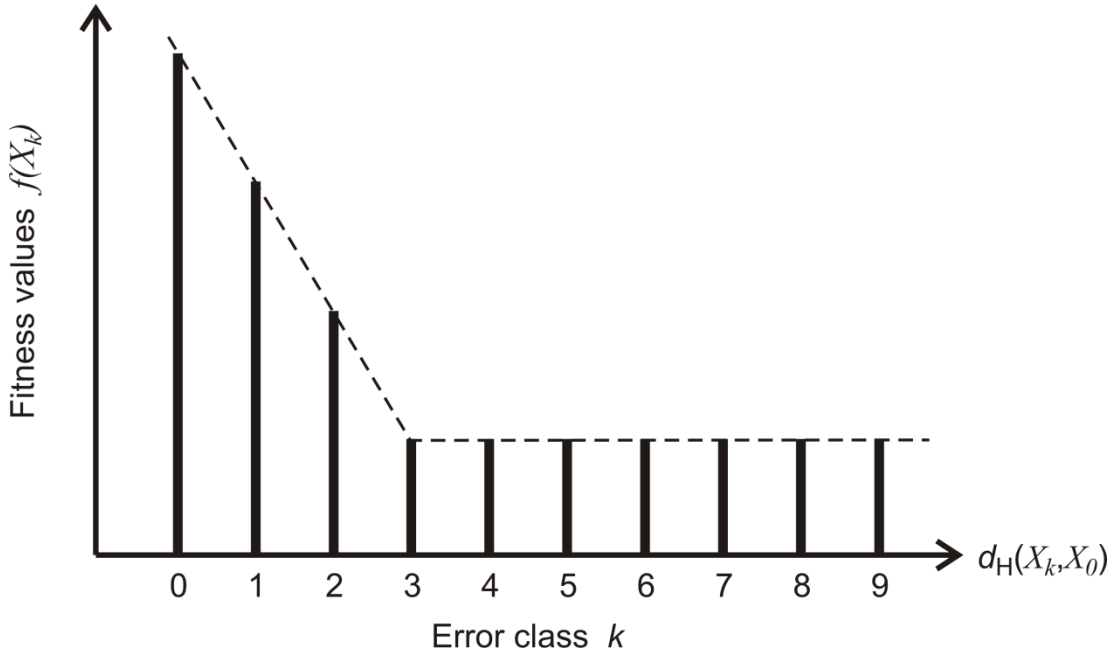
Concentrations of entire error classes: $[\Gamma_k] = y_k(p)\,,\ k = 0, 1, \ldots, n$

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

single peak landscape



step linear landscape



Model fitness landscapes I

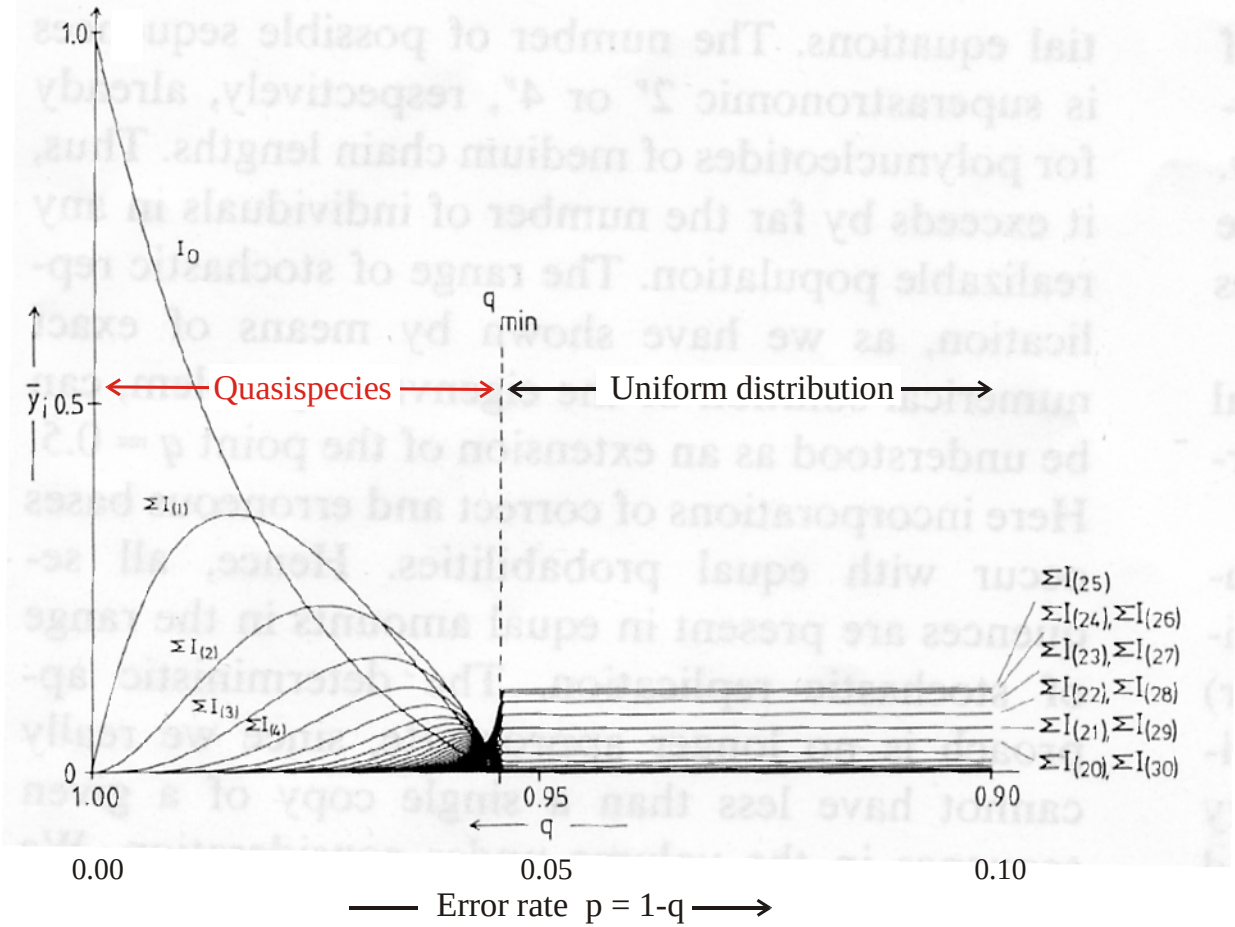
Biophysical Chemistry 16 (1982) 329–345
Elsevier Biomedical Press

SELF-REPLICATION WITH ERRORS

A MODEL FOR POLYNUCLEOTIDE REPLICATION **

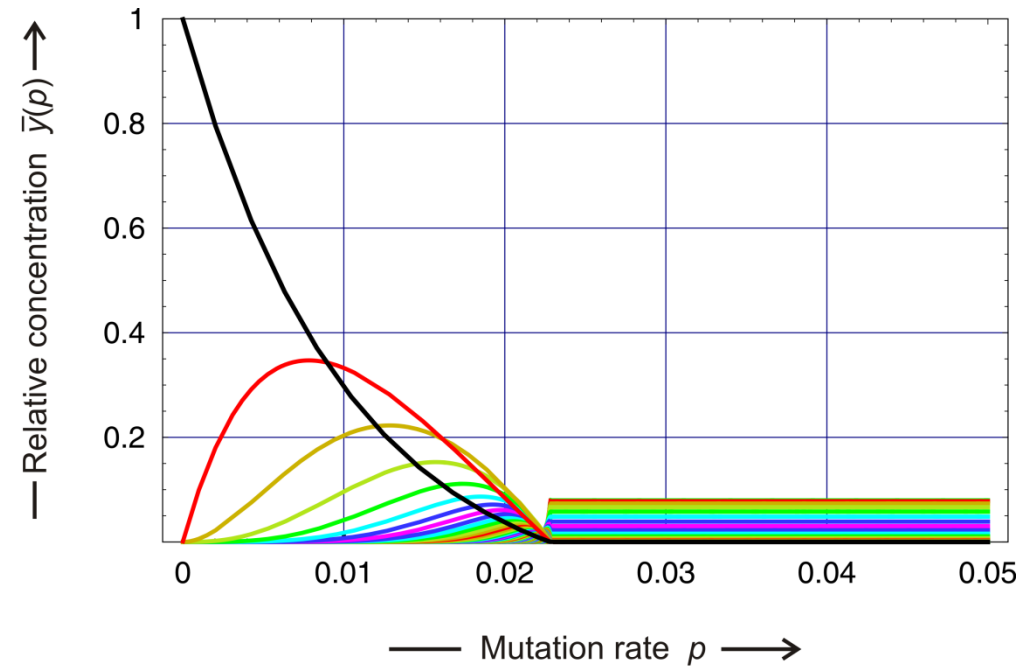
Jörg SWETINA and Peter SCHUSTER *

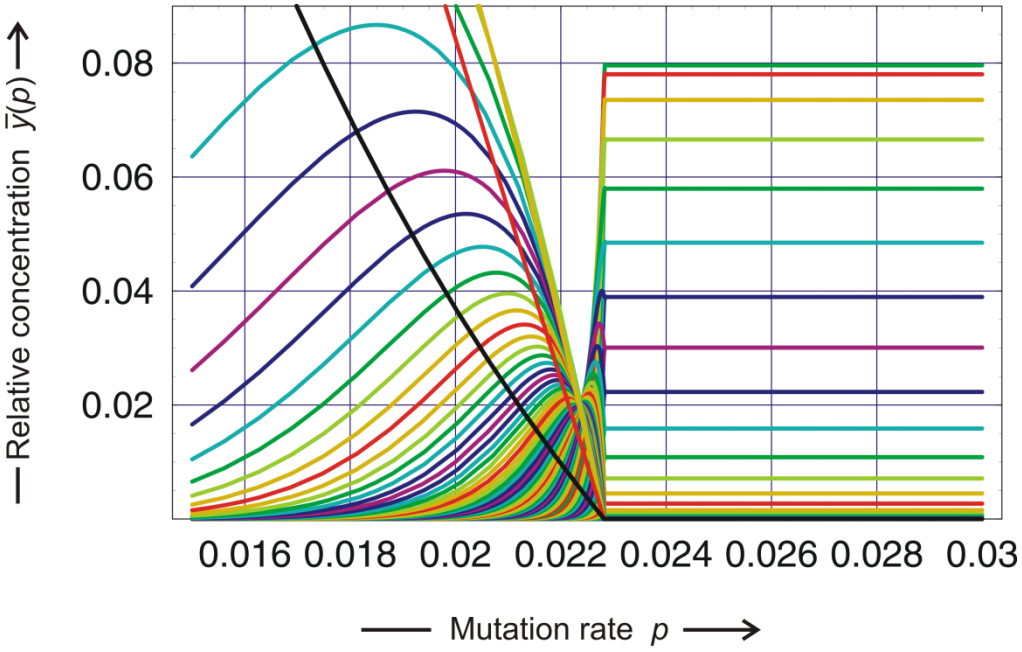
Institut für Theoretische Chemie und Strahlenchemie der Universität, Währingerstraße 17, A-1090 Wien, Austria



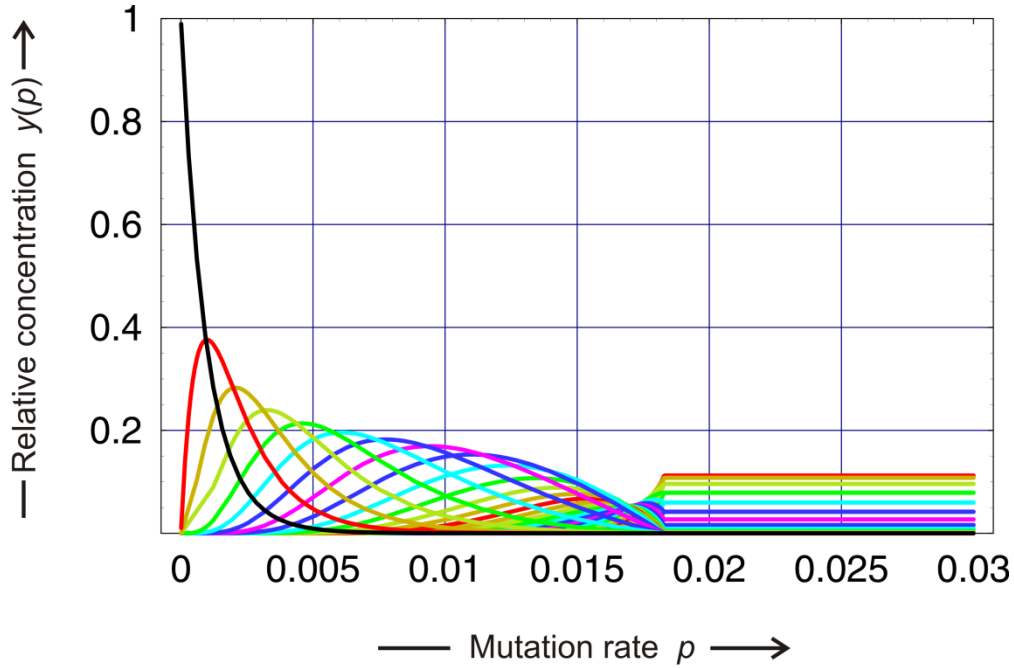
Stationary population or quasispecies as a function of the mutation or error rate *p*

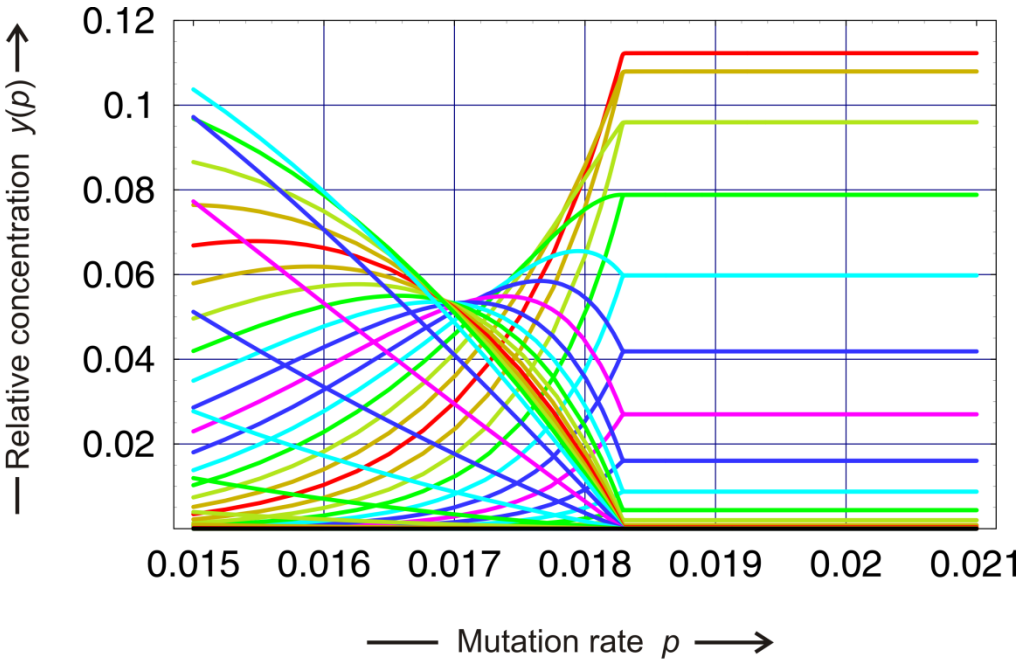
Error threshold on the single peak landscape



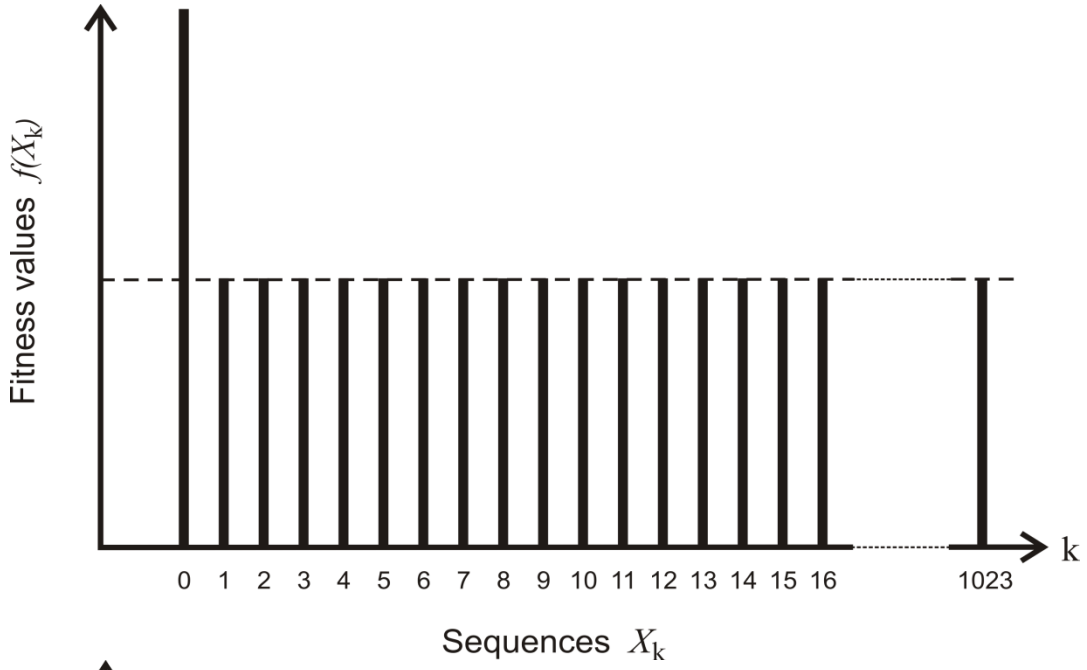


Error threshold on the step linear landscape





single peak landscape

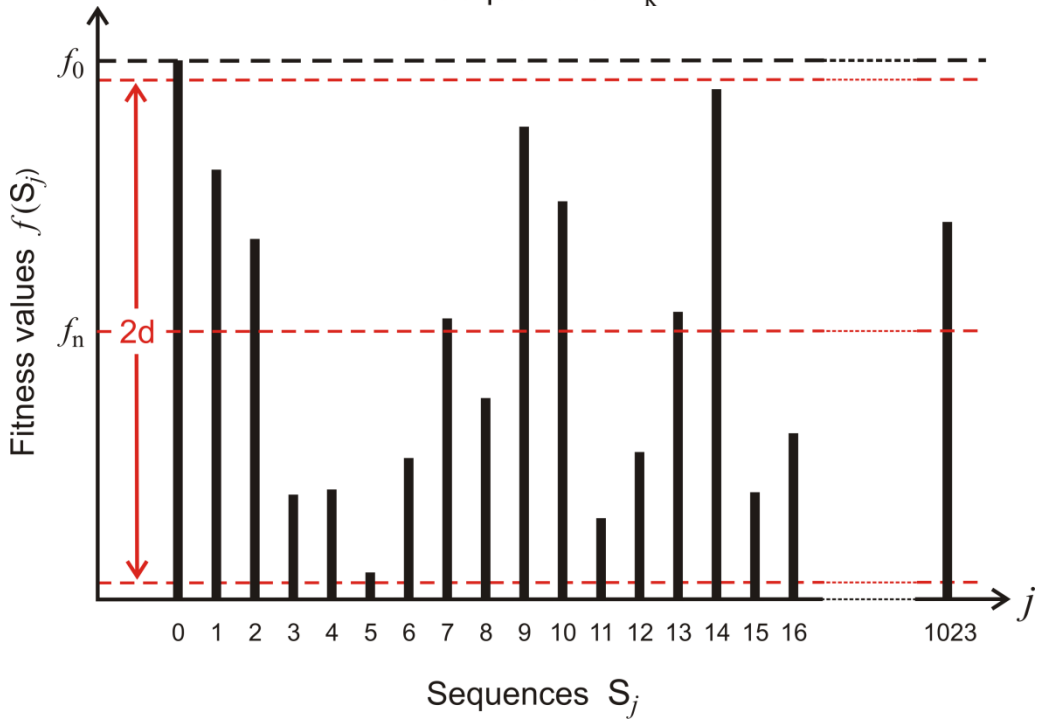


$$f(\mathsf{S}_j) \;=\; f_n \;+\; 2\,d\,(f_0 - f_n)\left(\eta_j^{(s)} - 0.5\right)$$

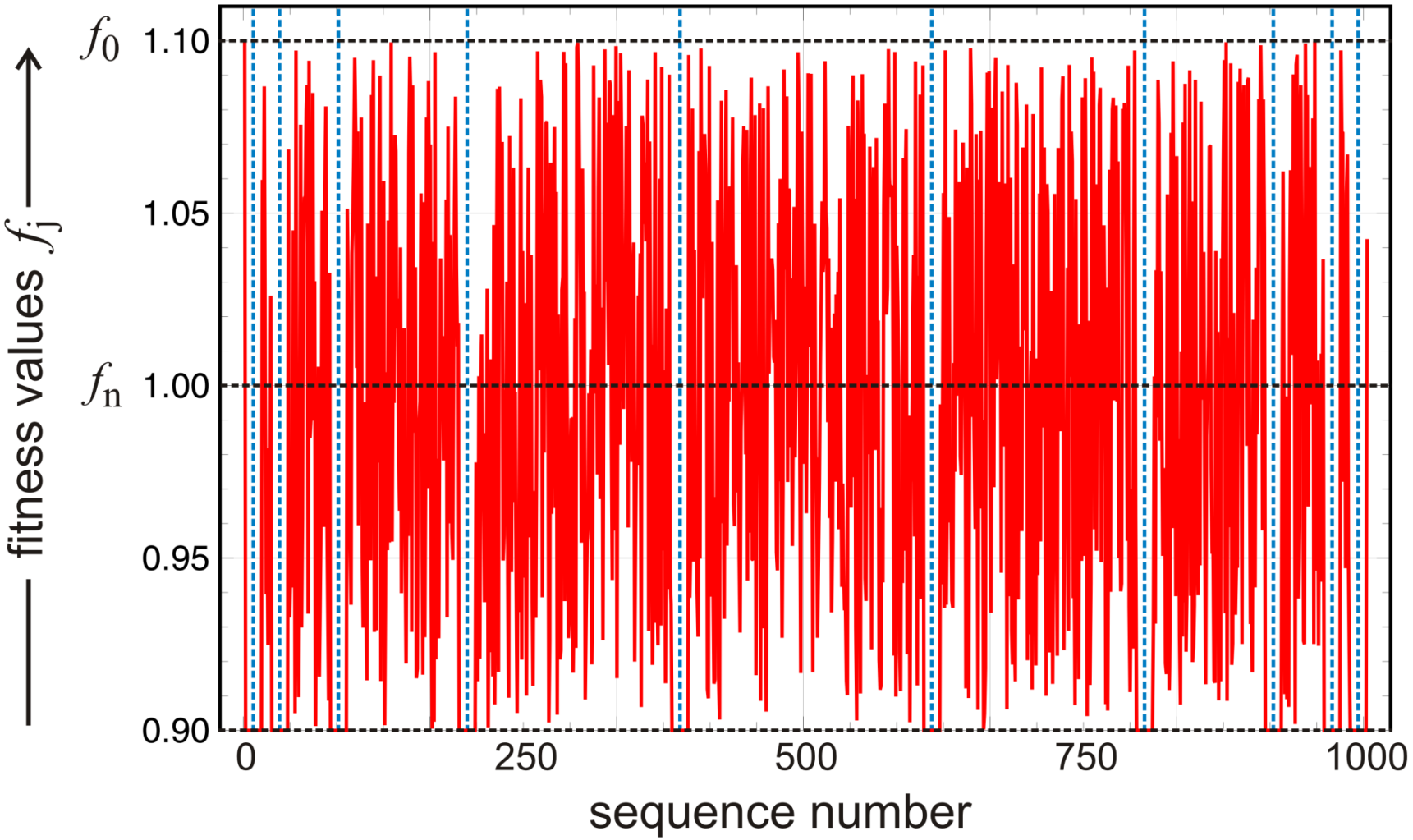
$$j = 1, 2, \ldots, N\,;\; j \neq m\,,$$

η ... random number ; s ... seeds

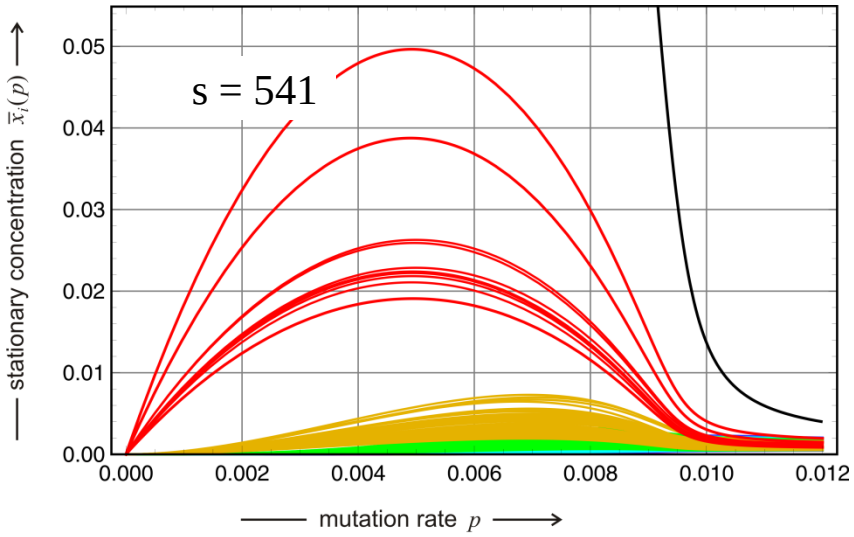
„realistic“ landscape

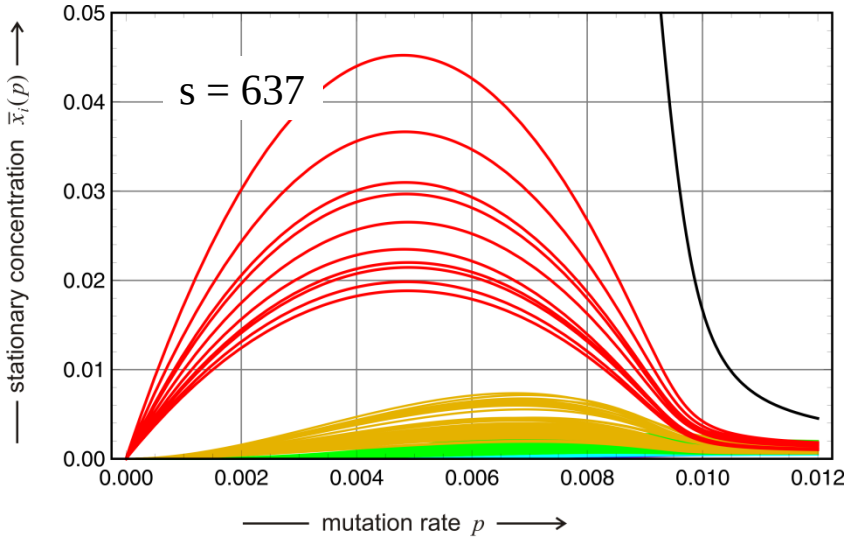


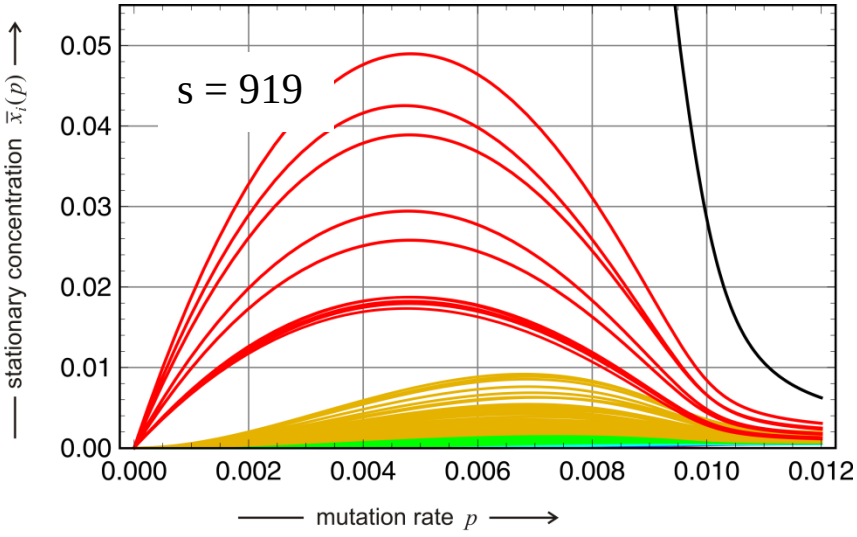
Rugged fitness landscapes
over individual binary sequences
with n = 10



Random distribution of fitness values: d = 1.0 and s = 637

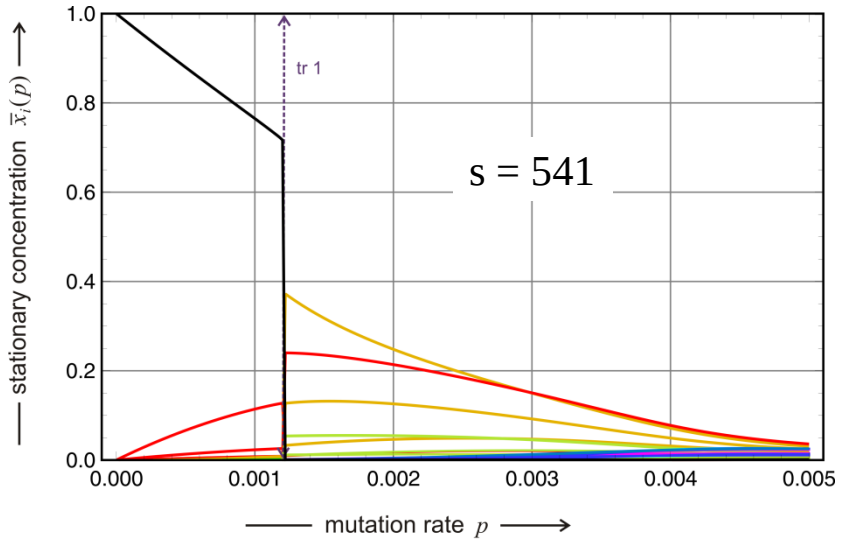


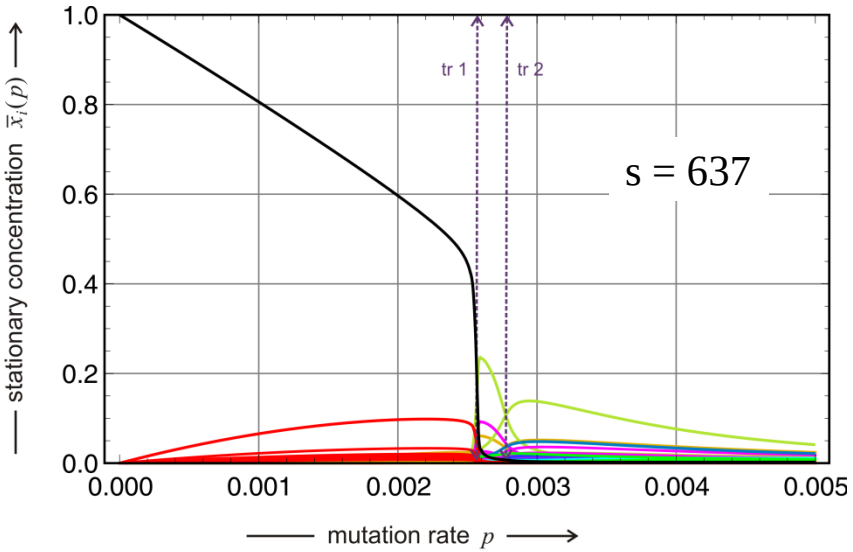


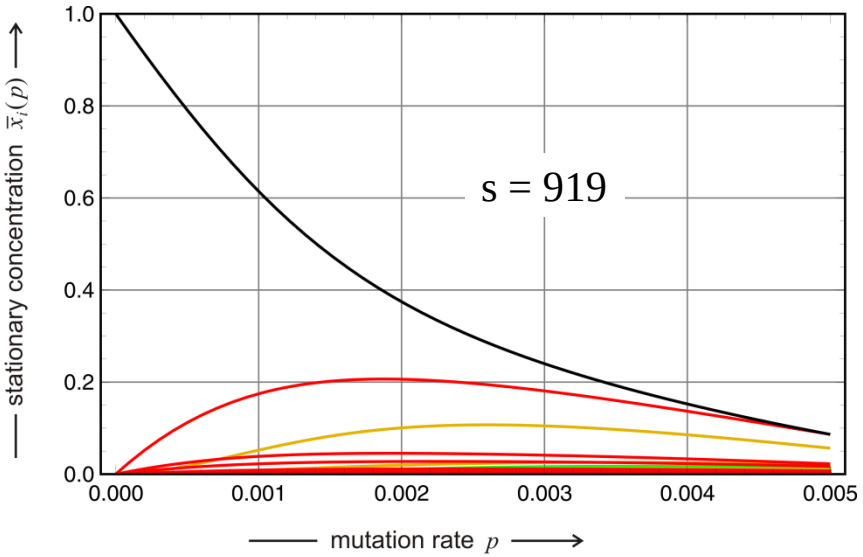


Error threshold on ‚realistic' landscapes

n = 10, $f_0 = 1.1$, $f_n = 1.0$, d = 0.5

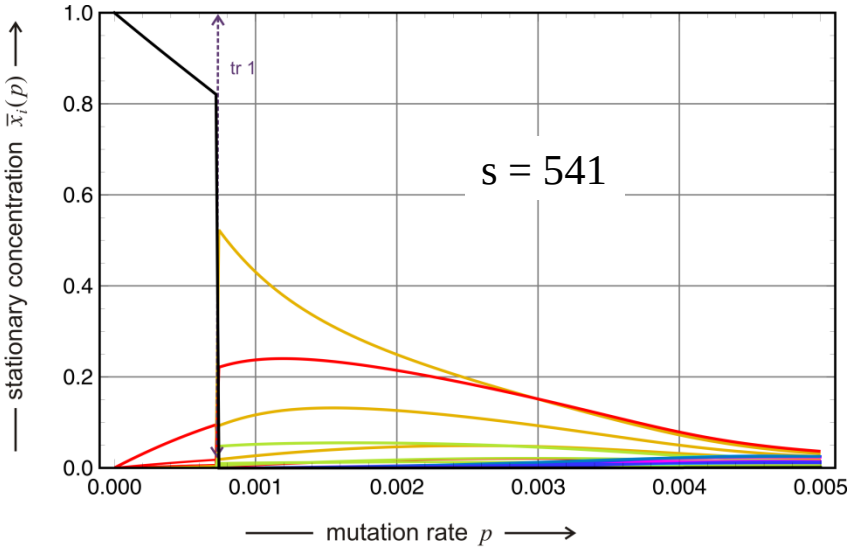


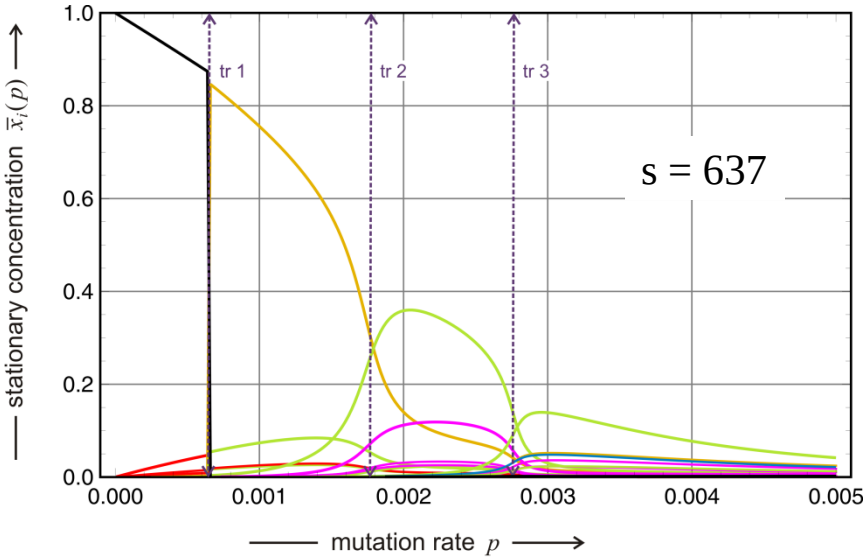


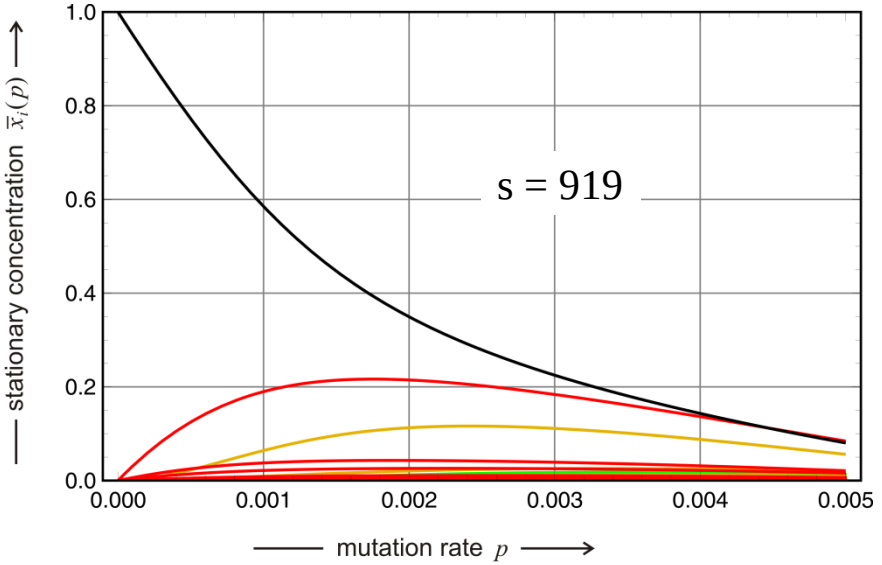


Error threshold on ‚realistic' landscapes

n = 10, $f_0 = 1.1$, $f_n = 1.0$, d = 0.995

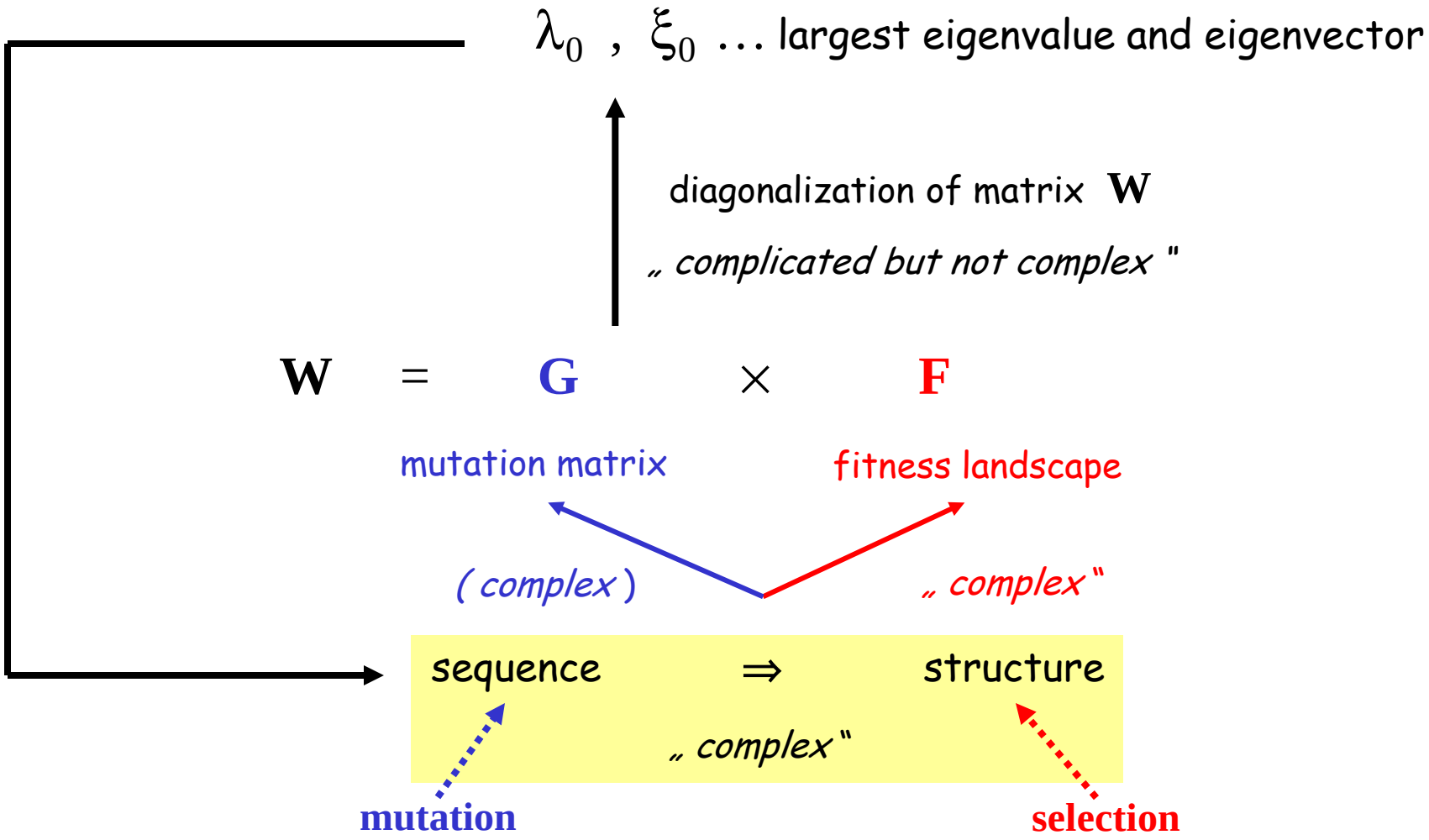






Error threshold on ‚realistic' landscapes

n = 10, $f_0 = 1.1$, $f_n = 1.0$, d = 1.0



Complexity in molecular evolution

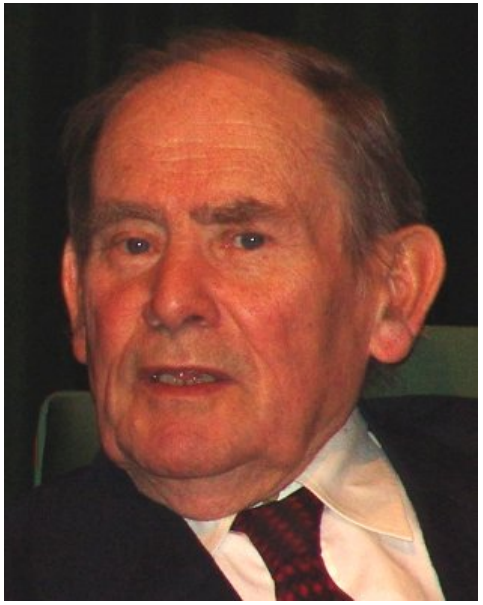
The new biology provides a hitherto unknown challenge for mathematicians, computer scientists, and theorical biologists for mainly two reasons

enormous amount of data and

complexity of structure and dynamics:

…. I was taught in the pregenomic era to be a hunter. I learnt how to identify the wild beasts and how to go out, hunt them down and kill them. We are now urged to be gatherers, to collect everything lying around and put it into storehouses.

Someday, it is assumed, someone will come and sort through the storehouses, discard all the junk, and keep the rare finds. The only difficulty is how to recognize them.



Sydney Brenner, 1927 -

Sydney Brenner. Hunters and gatherers. *The Scientist* **16**(4): 14, 2002

The „big data“ problem in bioinformatics

Theory – mathematics and computation – cannot remove complexity, but it shows what kind of „regular“ behavior can be expected and what experiments have to be done to get a grasp on the irregularities.

Manfred Eigen, 1927 -

Preface to E. Domingo, C.R. Parrish, J.J.Holland, eds. Origin and Evolution of Viruses. Academic Press 2008

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Happy 25th birthday IWR and

ad multos annos.

Thank you for your attention!

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