Wie die Komplexität in die Biologie kommt

Peter Schuster

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

Hermann Haken zum 90. Geburtstag

Technische Universität München, 27.10.2017

Web-Page für weitere Informationen:

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

Happy birthday

ad multos annos

Hermann Haken

Vater der Synergetik

1. Darwinsche Evolution und Mathematik
2. Ein einfaches aber vollständiges Evolutionsmodell
3. Evolution als ein Prozess im Sequenzraum
4. Vom Genotyp zum Phänotyp und zur Fitness
5. Die Strukturbildung bei Biopolymeren
6. Schlussfolgerungen und Ausblick

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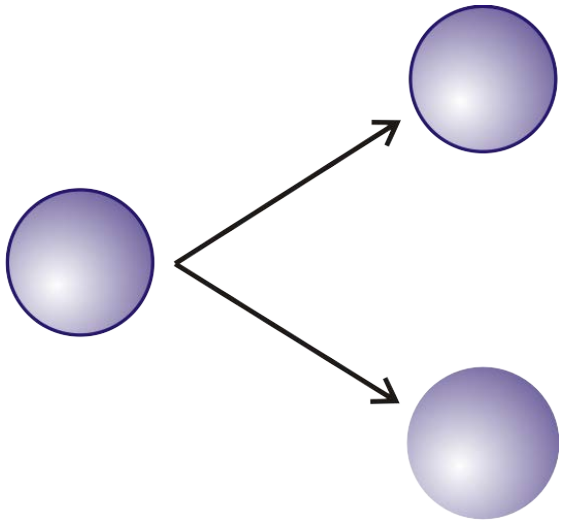


$$(A) + X = 2X$$

$$\frac{dx}{dt} = f\,x \quad \Rightarrow \quad x(t) = x(0)\,e^{f\,t}$$

exponentielles Wachstum

Vermehrung führt auf exponentielles Wachstum

Thomas Robert Malthus

1766 – 1834

Wachstum tierisch-menschlicher Populationen
führt auf eine geometrische Reihe:

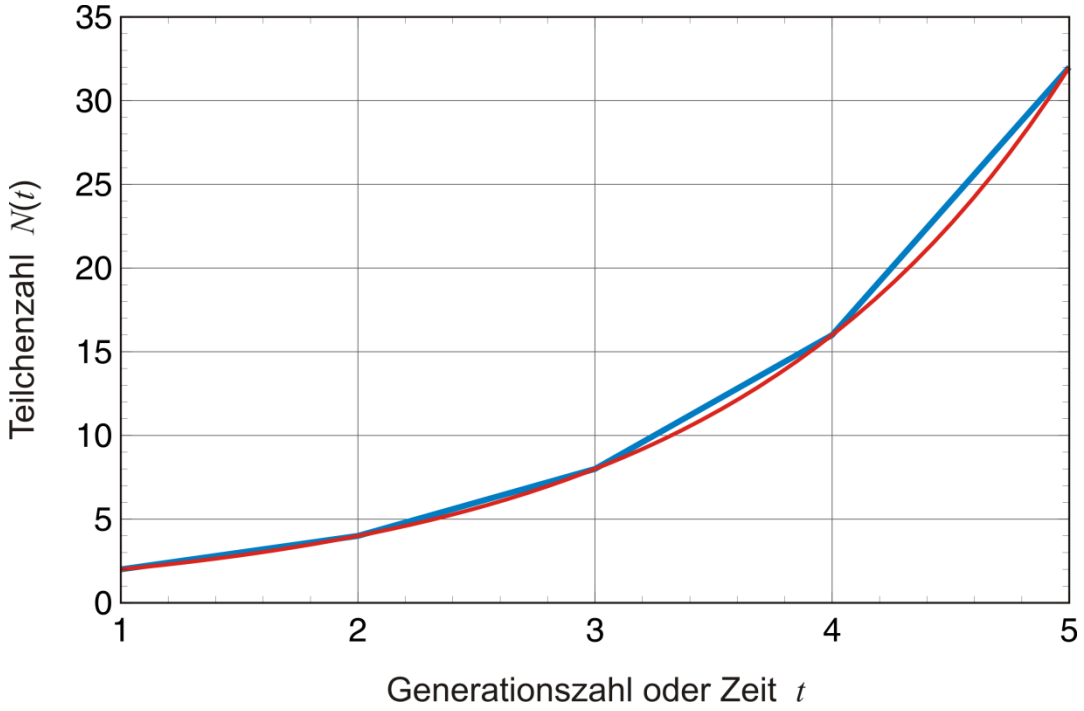
$2 \rightarrow 4 \rightarrow 8 \rightarrow 16 \rightarrow 32 \rightarrow 64 \rightarrow 128 \rightarrow 256 \rightarrow$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = r\,N\,, \quad N(t) = N_0\,\exp(r\,t)$$

Exponentialfuntion

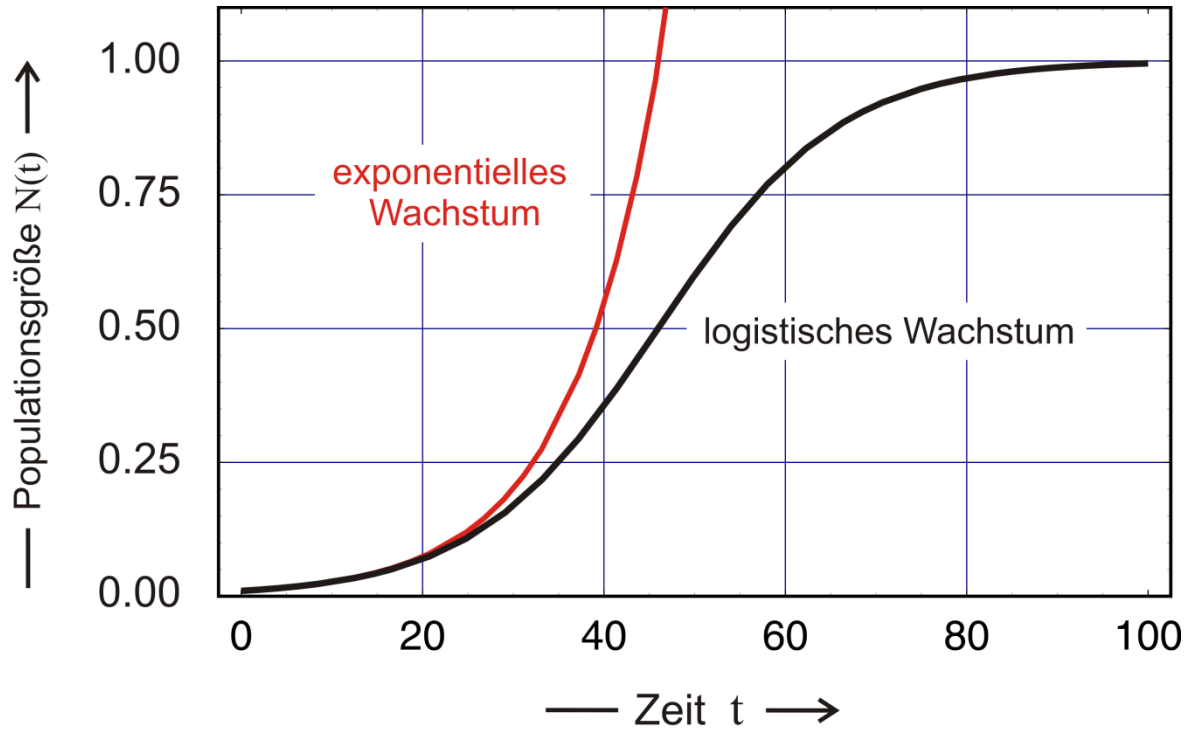
Leonhard Euler

1707 – 1783



Pierre-François Verhulst,
1804-1849

$$\frac{dN}{dt} = r\,N\left(1-\frac{N}{C}\right), \quad N(t) = \frac{N_0\,C}{N_0 + (C - N_0)\exp(-rt)}$$



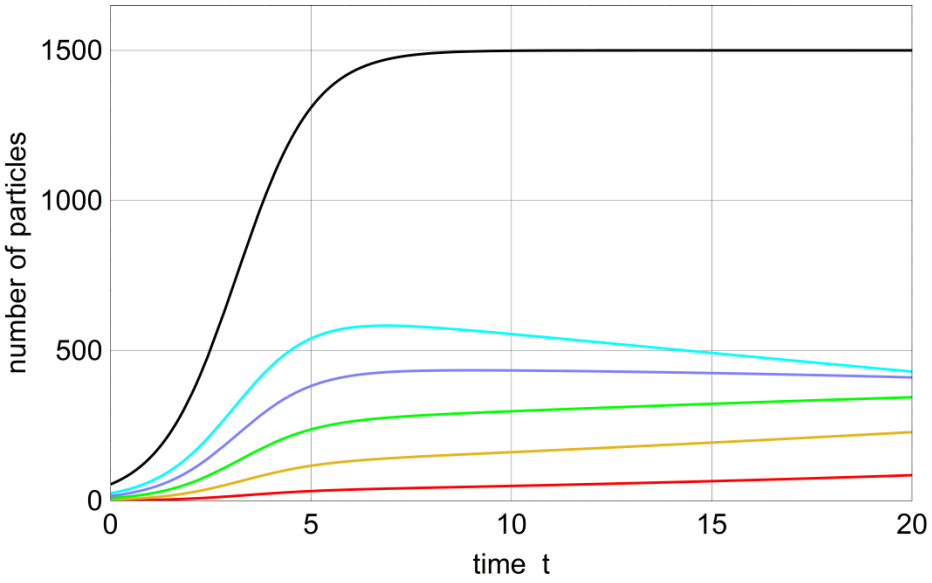
Logistische Gleichung, 1828

$$\Pi = \{X_1, \ldots, X_n\}$$

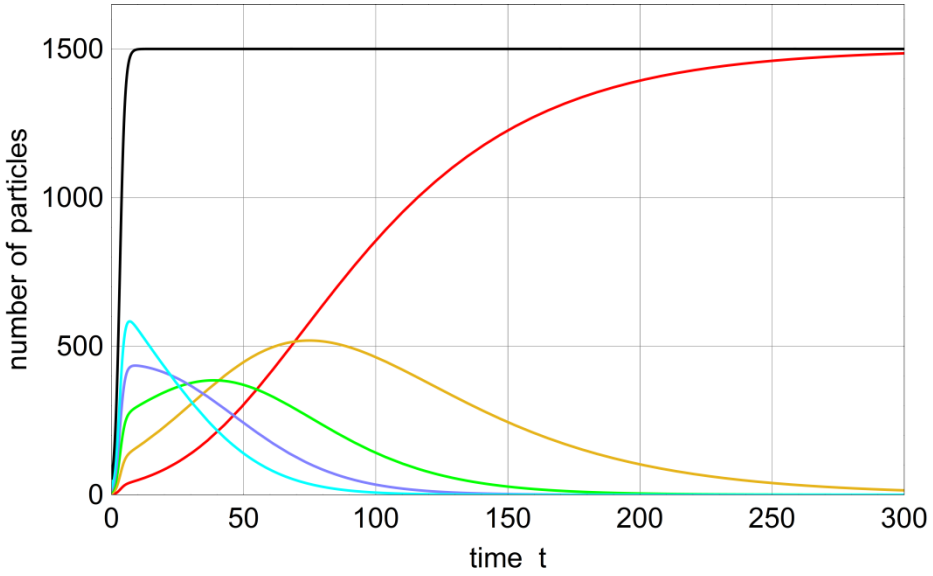
$$\boldsymbol{N}(t) = (N_1(t), \ \ldots \ , N_n(t)) \ ; \quad C(t) = \sum_{j=1}^{n} N_j(t)$$

$$C(t) = \frac{C(0)\,K}{C(0) + \left(K - C(0)\right) e^{-\Phi}}$$

$$\text{with} \quad \Phi = \int_0^t \phi(\tau)\, d\tau \quad \text{and} \quad \phi(t) = \frac{1}{C(t)} \sum_{i=1}^{n} f_i N_i(t)$$



$$x_j(t) = \frac{N_j(t)}{C(t)} = \frac{x_j(0)\, e^{f_j t}}{\sum_{i=1}^{n} x_i(0)\, e^{f_i t}}$$

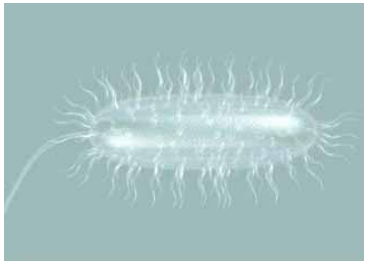


$N(0) = (1,4,9,16,25)$

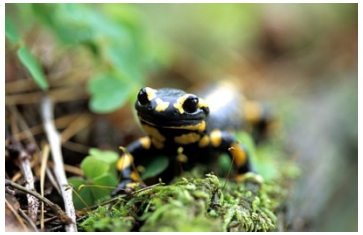
$\boldsymbol{f} = (1.10,1.08,1.06,1.04,1.02)$

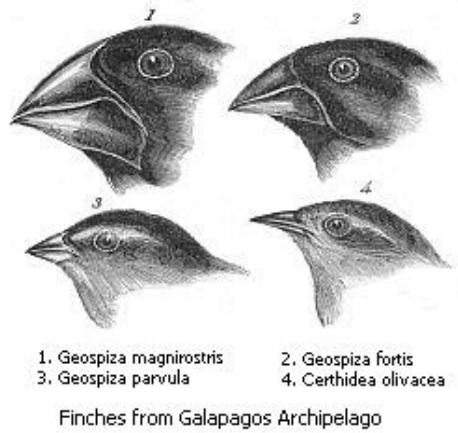
Charles Darwin, 1809 - 1882

Voyage on HMS Beagle, 1831 - 1836

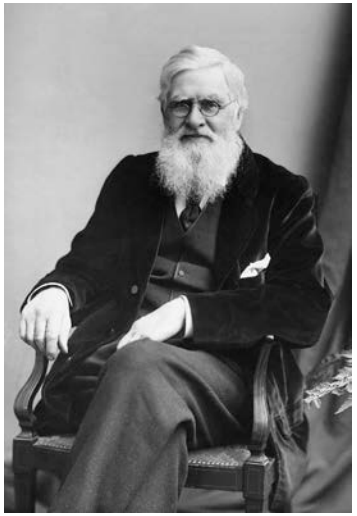


Phänotypen





Finches from Galapagos Archipelago



Alfred Russel Wallace
1823 - 1913

ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

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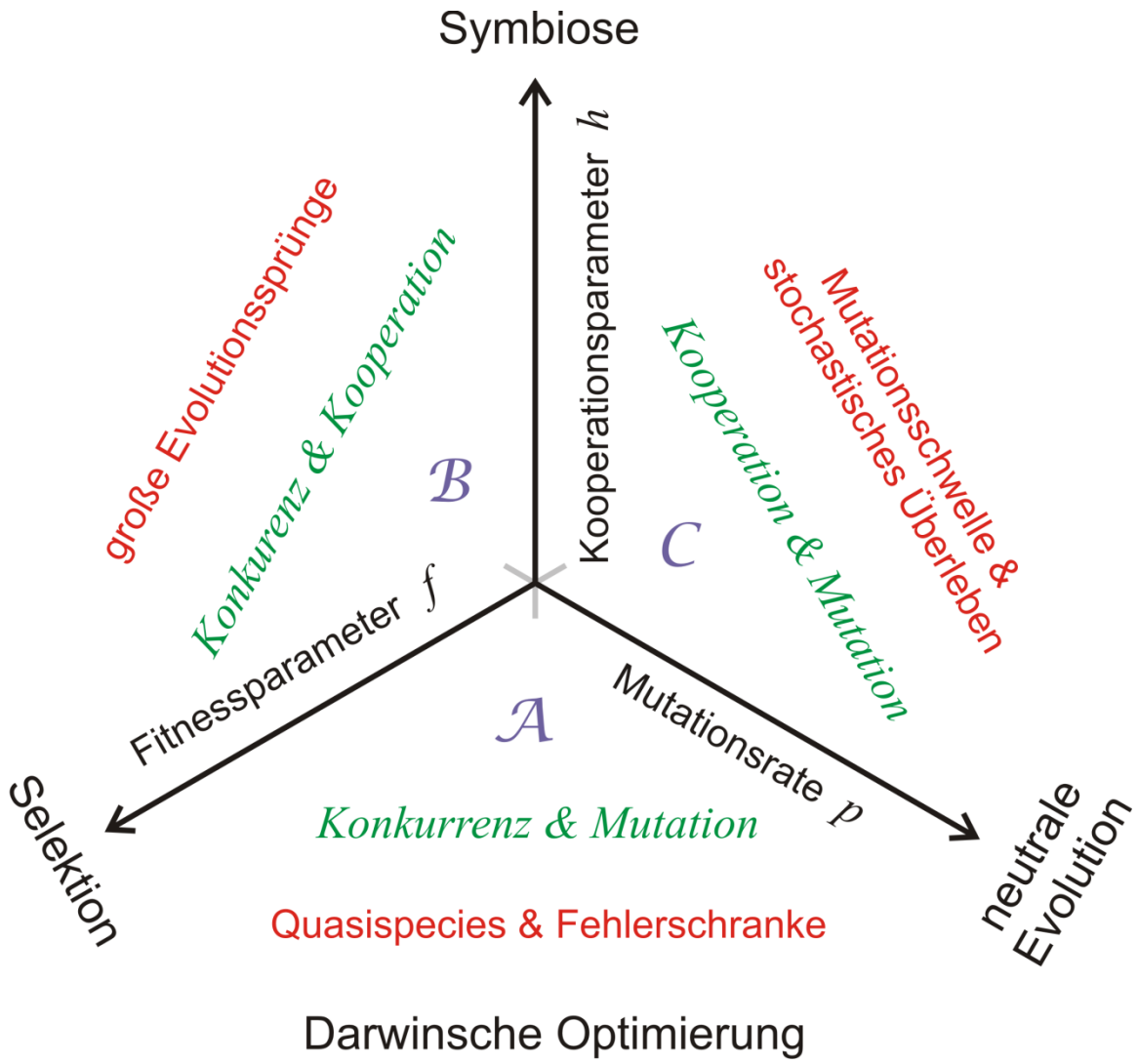
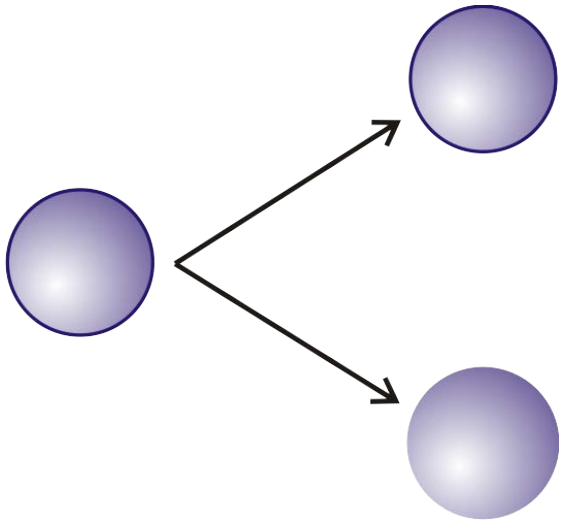


Evolutionsmodell im Parameterraum



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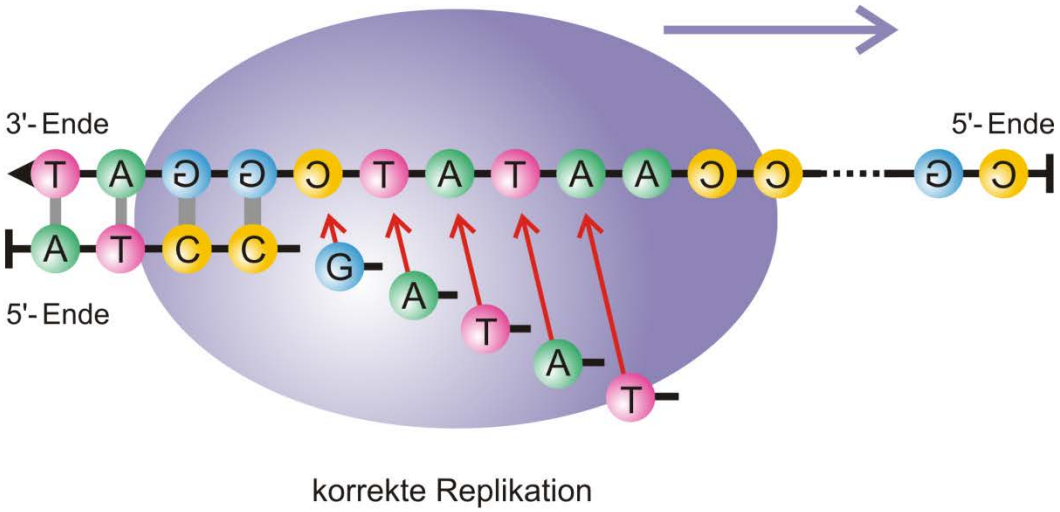
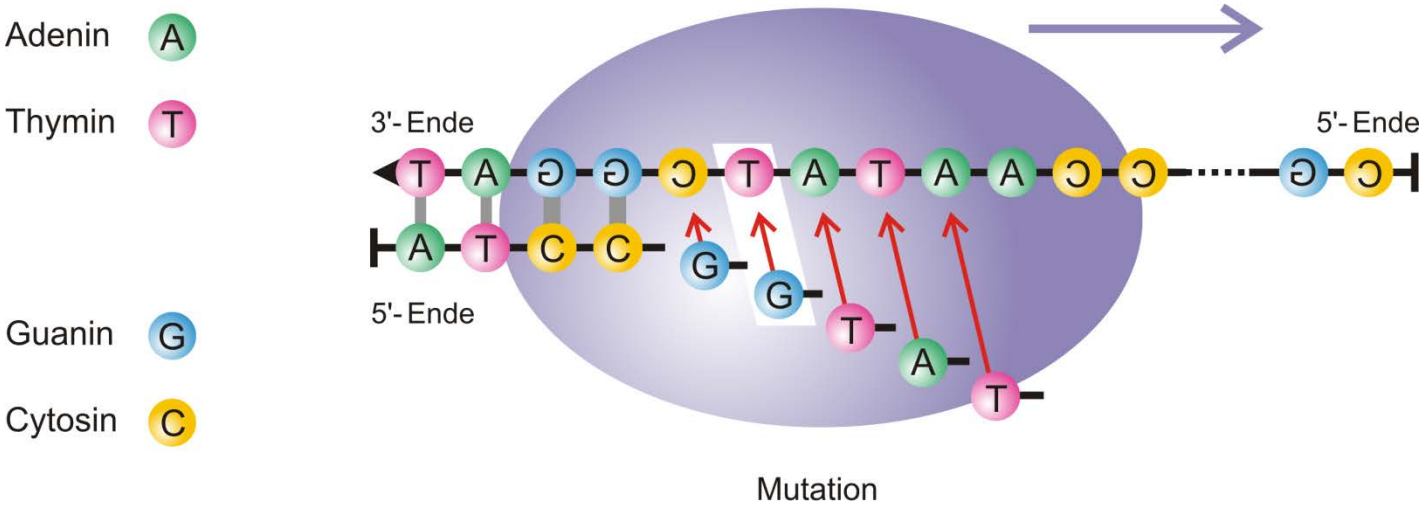
exponentielles Wachstum

Vermehrung führt auf exponentielles Wachstum

Taq-Polymerase





Nukleotideinbaufehler: p … Mutationsrate pro Position und Replikation

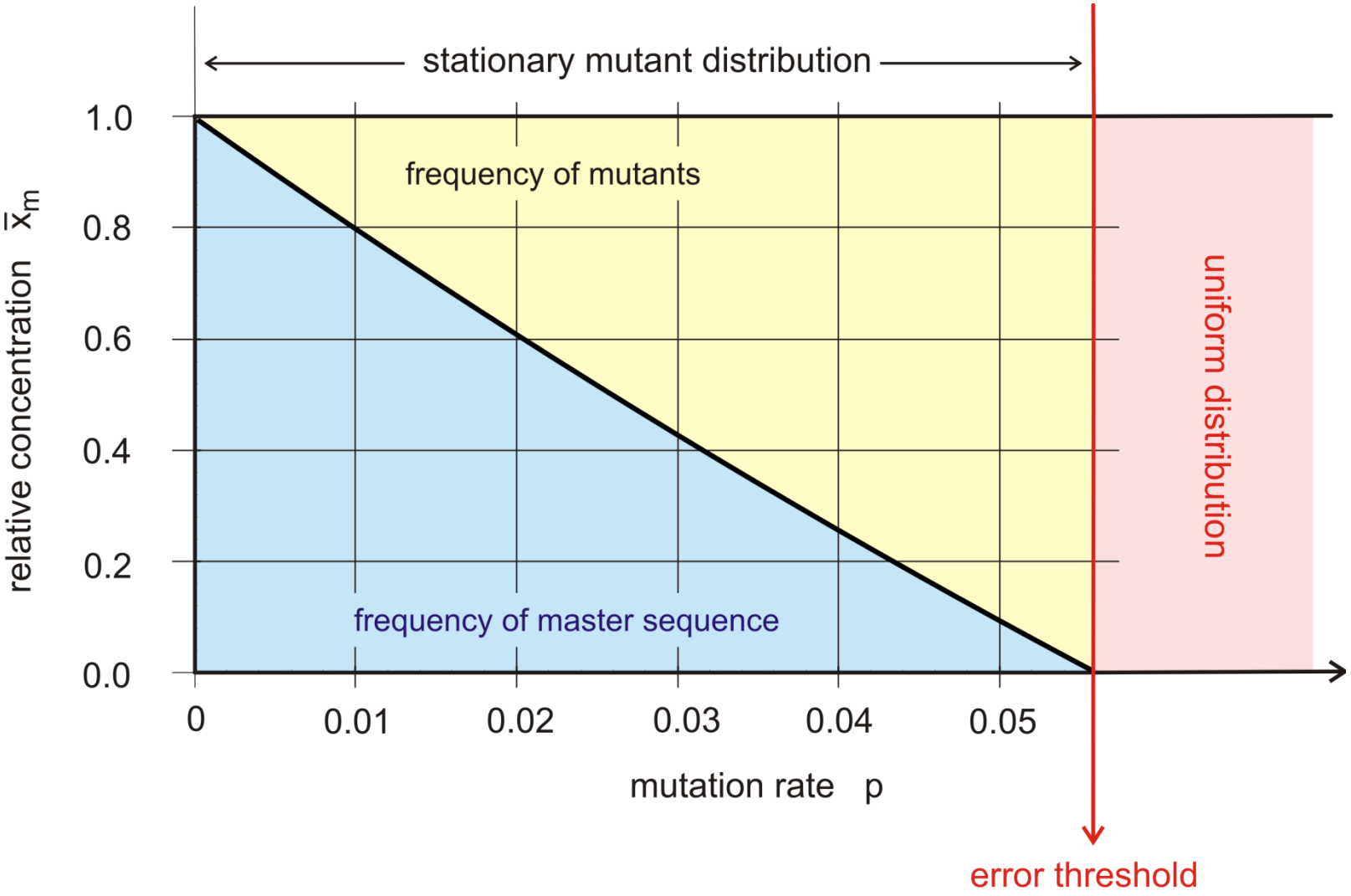
Korrekte Replikation und Punktmutation

$$\frac{dN_j}{dt} = \sum_{i=1}^{n} Q_{ji}\, f_i\, N_i - N_j\, \phi \;\; ; \quad j = 1,2, \ldots , n$$

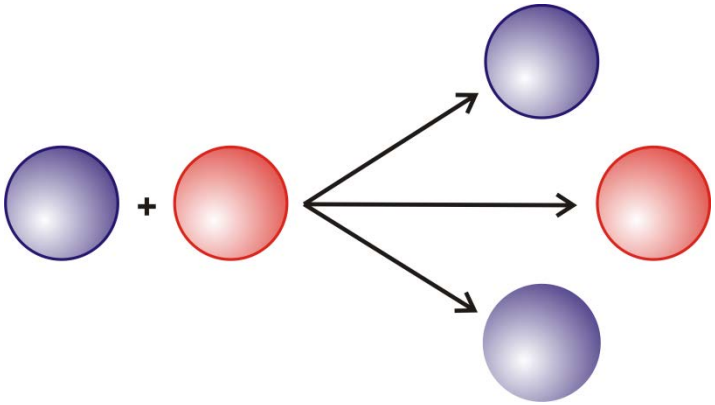
$$Q_{ji} = (1-p)^l\, \varepsilon^{\,d^{(H)}_{X_j X_i}} \;\; ; \quad \varepsilon = \frac{p}{1-p}$$

$$\phi = \frac{1}{C} \sum_{i=1}^{n} f_i\, N_i \;\; \ldots\ldots\ldots \text{ mean fitness}$$

Mutations-Selektionsgleichung (Manfred Eigen 1971)



The error threshold in replication and mutation



(A) + X + Y = 2 X + Y

$$\frac{dx}{dt} = hxy(t) \quad \Rightarrow \quad x(t) = x(0)\,e^{hy(t)t}$$

$$y(t) = x(t) \quad \Rightarrow \quad x(t) = x(0)\frac{1}{1 - x(0)ht}$$

hyperbolisches Wachstum

Katalysierte Vermehrung führt auf hyperbolisches Wachstum

$$\frac{dN_j}{dt} = N_j\left(f_j + h_j N_{j+1} - \phi\right);\ \phi = \frac{1}{C}\sum_{i=1}^{n} N_i\left(f_i + h_i N_{i+1}\right);\ j = 1,\ldots,n;\ i, j \bmod n$$

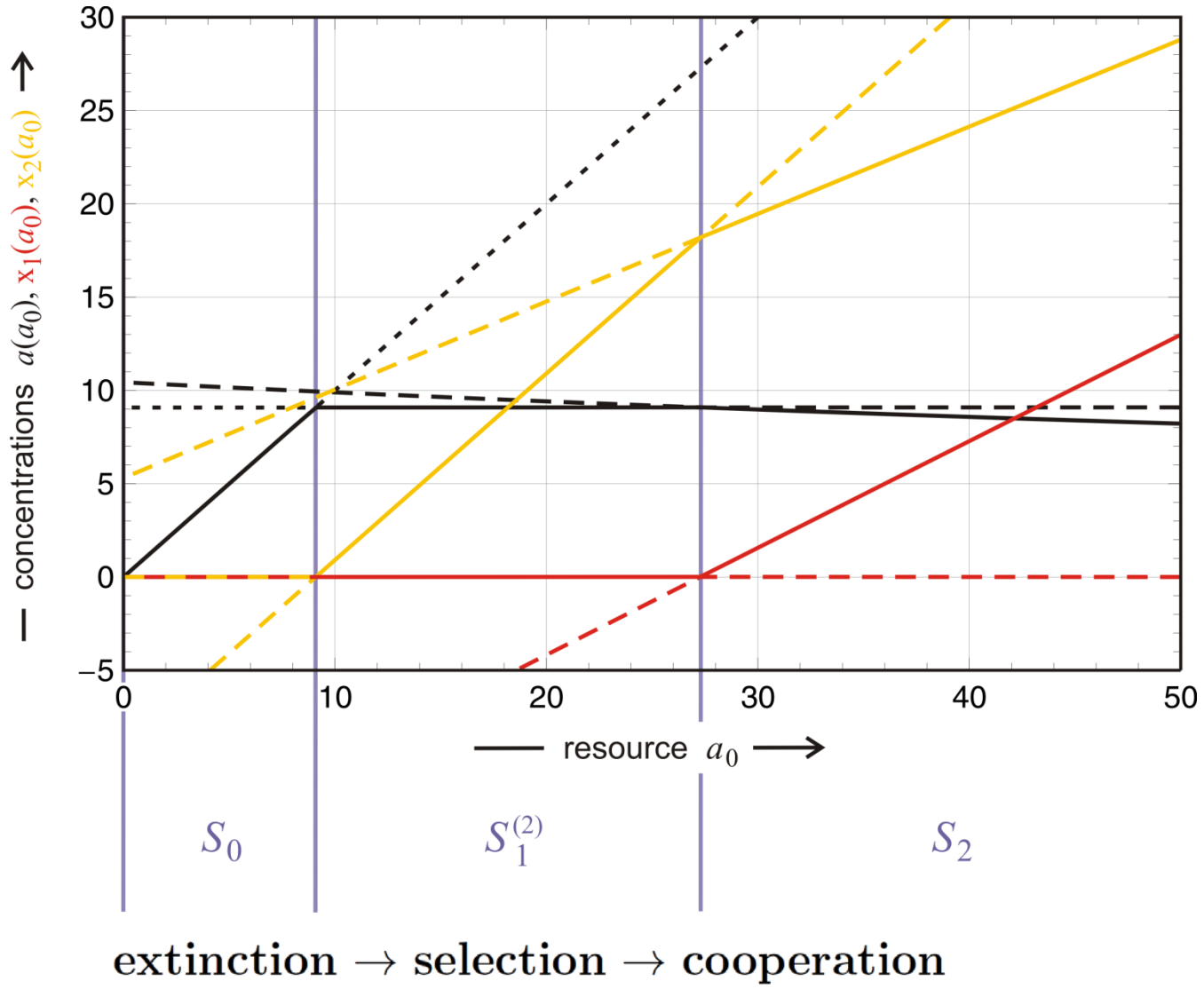
$$\cdots \leftarrow \mathrm{X}_n \leftarrow \mathrm{X}_1 \leftarrow \mathrm{X}_2 \leftarrow \cdots \leftarrow \mathrm{X}_{n-1} \leftarrow \mathrm{X}_n \leftarrow \cdots$$

Hyperzyklus

Extinktion $\leftrightarrow$ Selektion $\leftrightarrow$ Exklusion $\leftrightarrow$ … $\leftrightarrow$ Kooperation

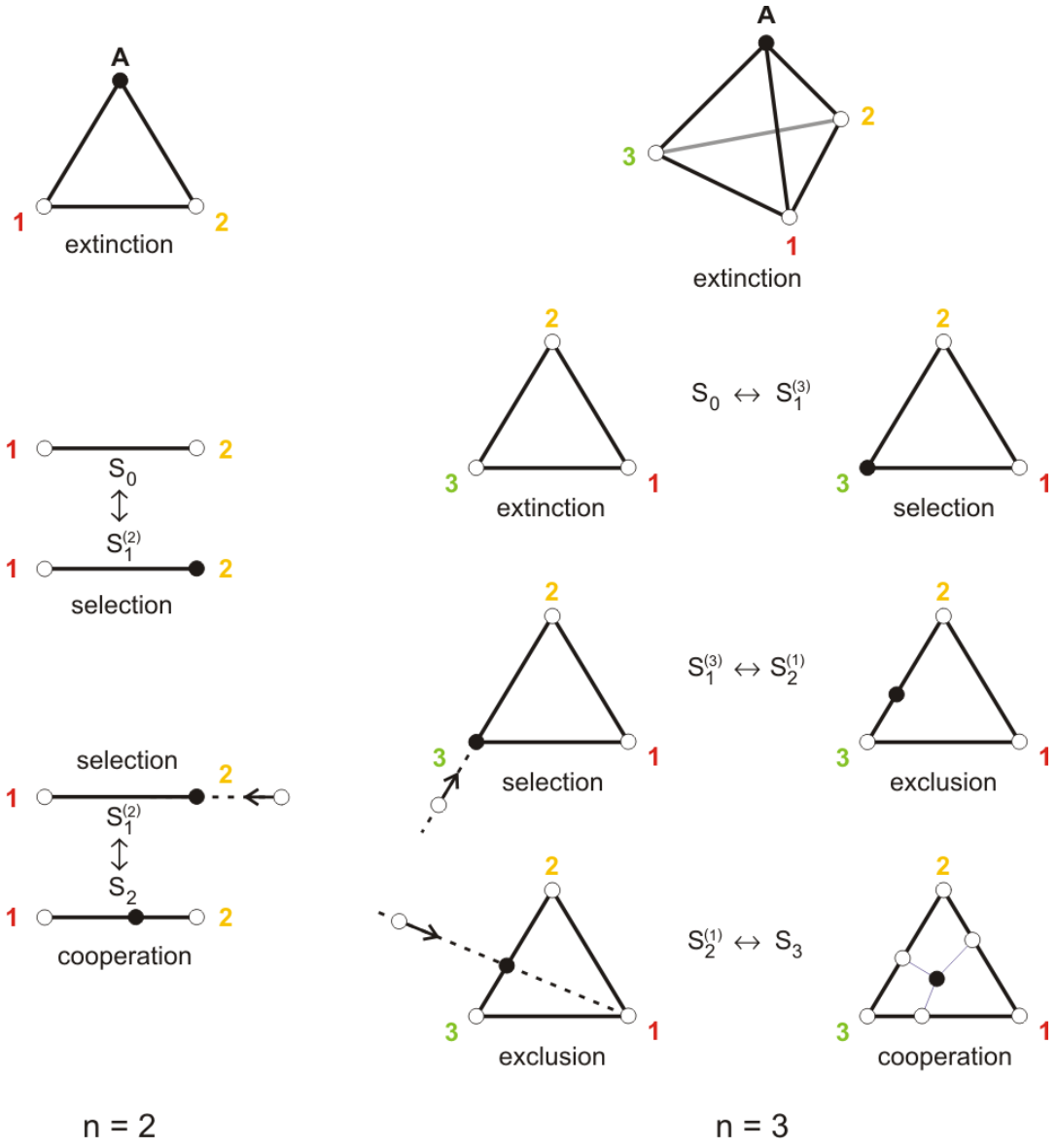
Name	Symbol	Stationary Values				Stability Range
		$\overline{a}$	$\overline{x}_1$	$\overline{x}_2$	$\overline{x}_3$	
extinction	S_0	a_0	0	0	0	$0 \le a_0 \le \frac{r}{k_3}$
selection	$S_1^{(3)}$	$\frac{r}{k_3}$	0	0	$a_0 - \frac{r}{k_3}$	$\frac{r}{k_3} \le a_0 \le \frac{r}{k_3} + \frac{k_3-k_2}{l_2}$
exclusion	$S_2^{(1)}$	$\frac{r}{k_3}$	0	$a_0 - \frac{r}{k_3} - \frac{k_3-k_2}{l_2}$	$\frac{k_3-k_2}{l_2}$	$\frac{r}{k_3} + \frac{k_3-k_2}{l_2} \le a_0 \le \frac{r}{k_3} + \frac{k_3-k_2}{l_2} + \frac{k_3-k_1}{l_1}$
cooperation	S_3	α	$\frac{r-k_3\alpha}{l_3\alpha}$	$\frac{r-k_1\alpha}{l_1\alpha}$	$\frac{r-k_2\alpha}{l_2\alpha}$	$\frac{r}{k_3} + \frac{k_3-k_2}{l_2} + \frac{k_3-k_1}{l_1} \le a_0$

Stationäre Zustände im Selektions-Kooperationssystems mit $n = 3$



Stationäre Zustände im Selektions-Kooperationssystems mit $n = 2$

Bifurkationsdiagramme
im Selektion-Kooperations-
Systemen mit $n = 2$ und $n = 3$



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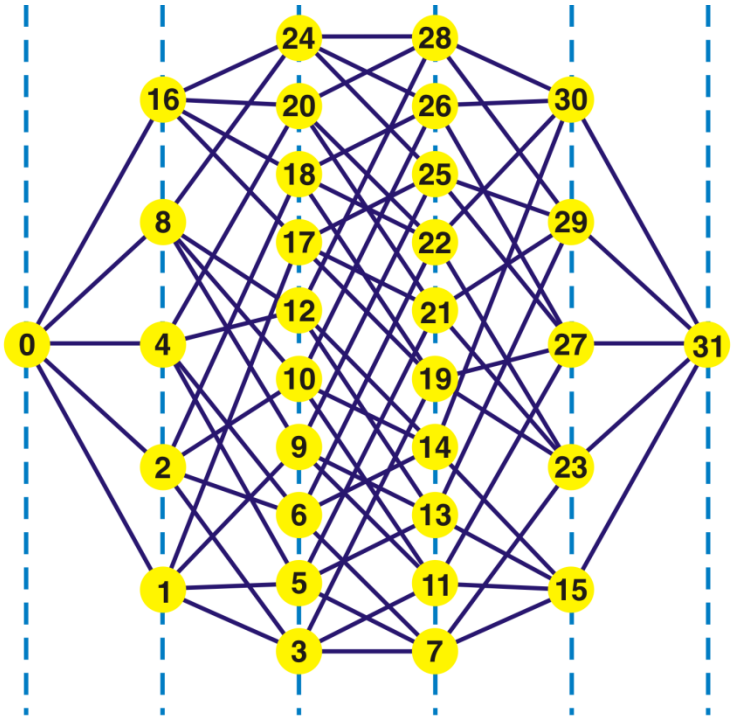


$l = 5$

Binary sequences are encoded by their decimal equivalents:

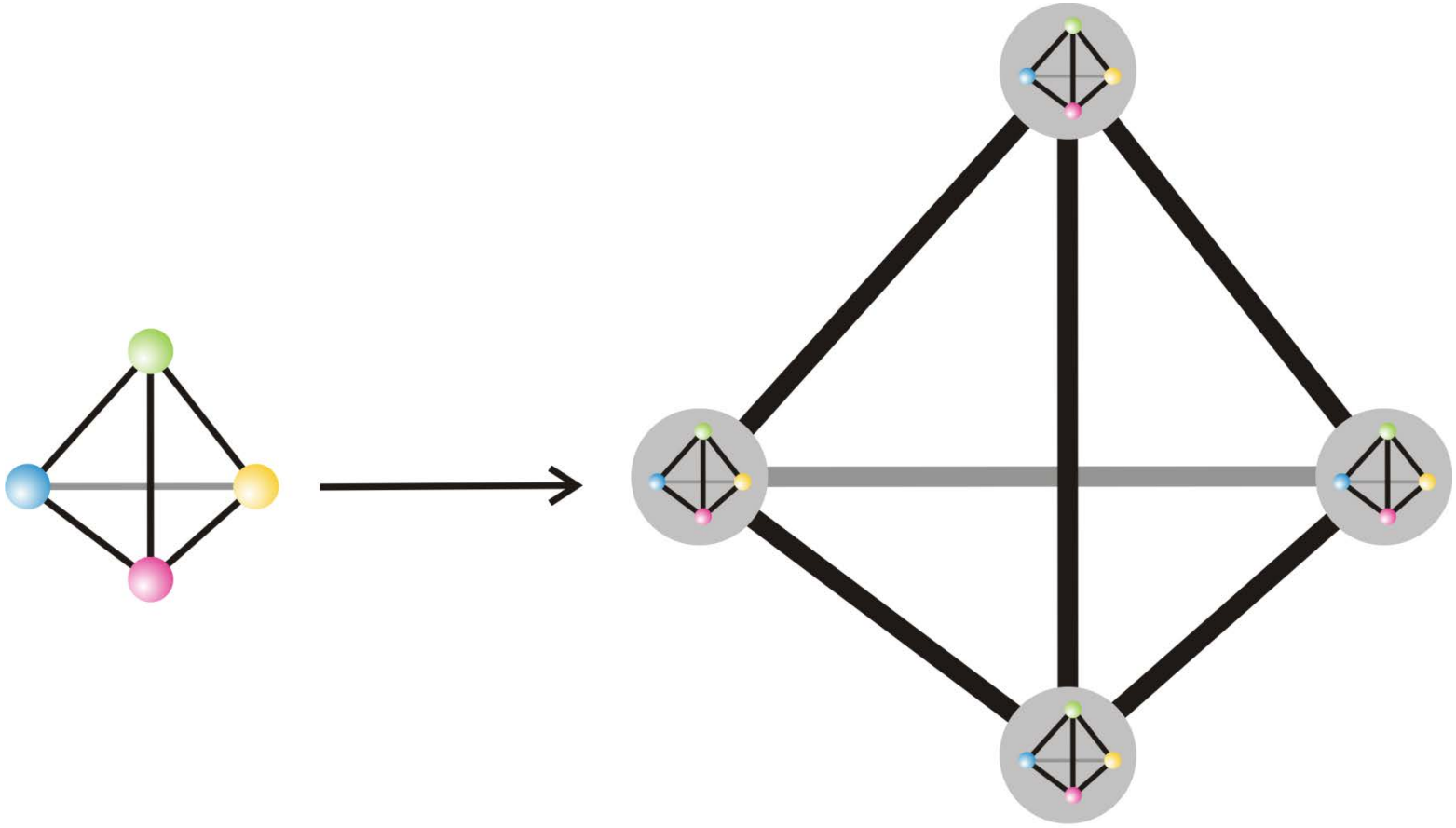
C = 0 and G = 1, for example,

"0" ≡ 00000 = CCCCC,

"14" ≡ 01110 = CGGGC,

"29" ≡ 11101 = GGGCG, etc.

Der Sequenzraum binärer Sequenzen ist ein Hyperwürfel der Dimension l



Konstruktion des Sequenzraumes von Vierbuchstabensequenzen (AUGC)

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Sewall Wright, 1889 - 1988

Fitness

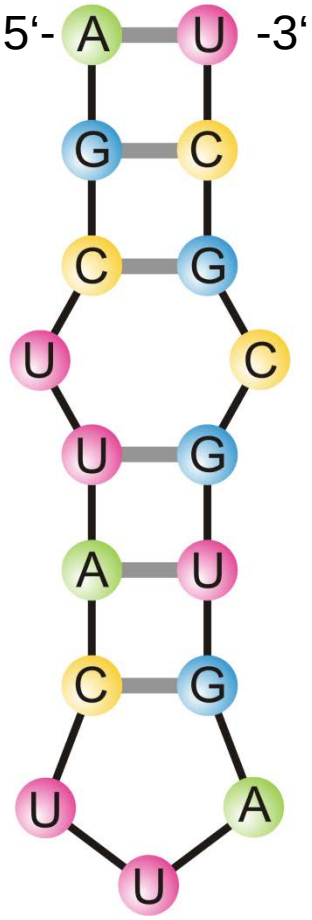
Genotype Space

Sewall Wright. 1932. *The roles of mutation, inbreeding, crossbreeding and selection in evolution*. In: D.F.Jones, ed. Int. Proceedings of the Sixth International Congress on Genetics. Vol.1, 356-366. Ithaca, NY.

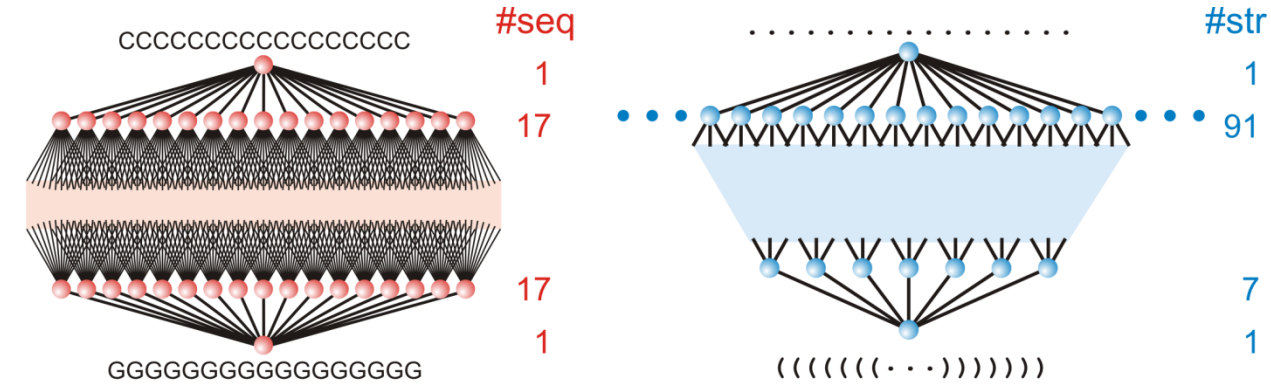
Sewall Wrights fitness landscape as metaphor for Darwinian evolution

5‘- AGCUUACUUAGUGCGCU-3‘

5‘-(((• (((• • •))) •))) -3‘



Die Sekundärstruktur minimaler freier Energie eines kleinen RNA-Moleküls

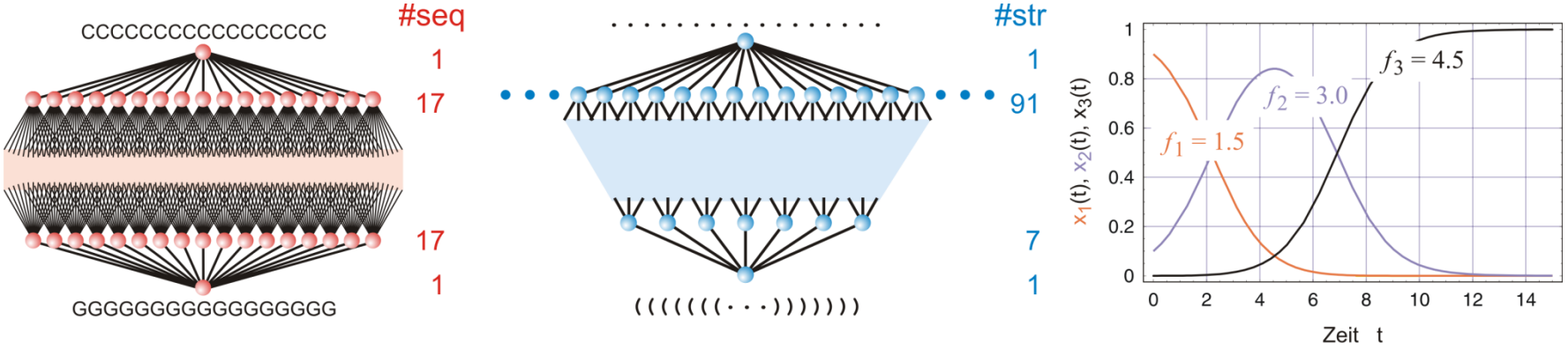


$$X \longrightarrow S = \Phi(X)$$

Sequenz — Struktur

Genotyp ⟶ Phänotyp

Die Ausbildung von RNA-Sekundärstrukturen als Genotyp-Phänotyp Abbildung



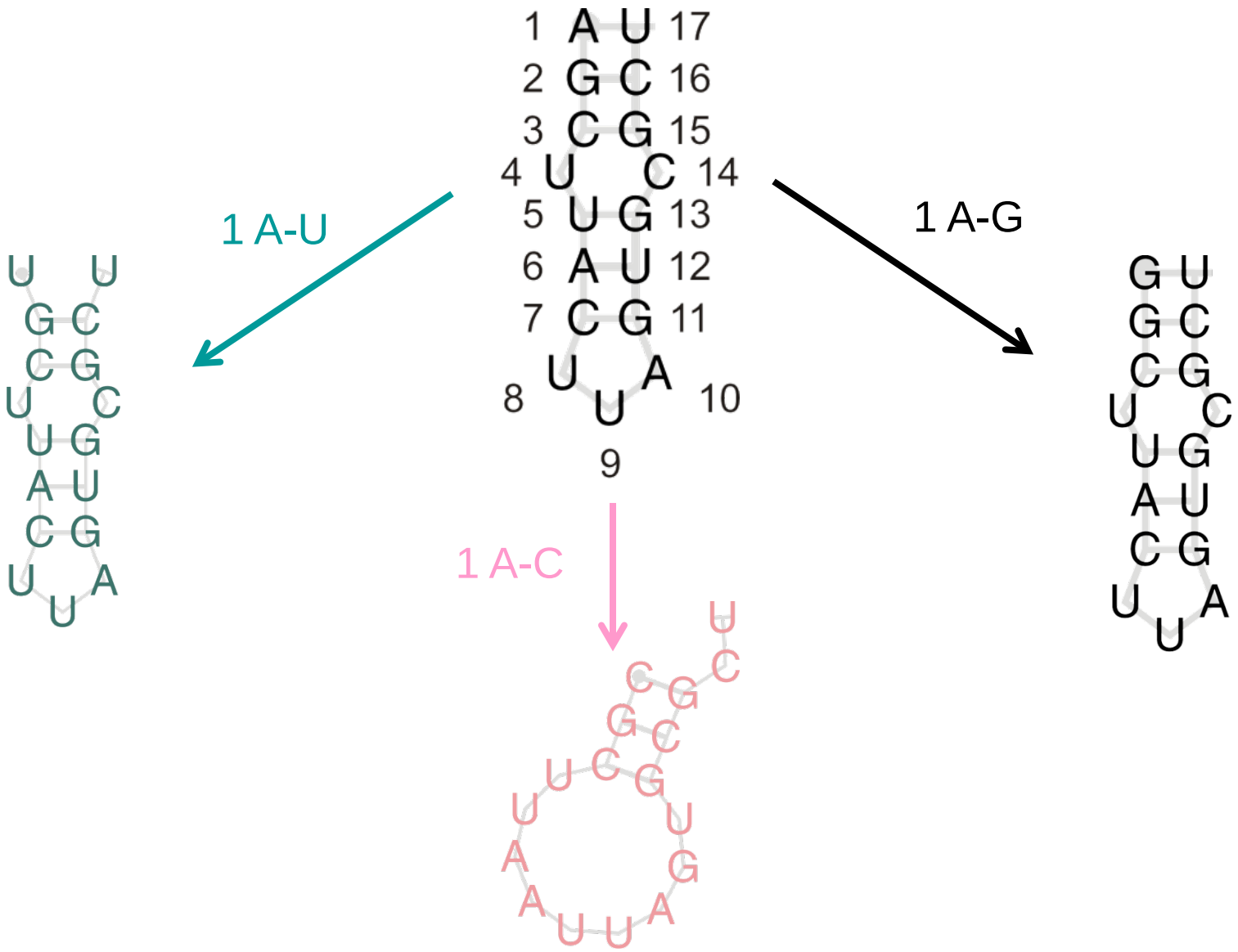
$$X \longrightarrow S = \Phi(X) \longrightarrow f = \Psi(S)$$

Sequenz — Struktur — Fitness

Genotyp → Phänotyp → Selektion

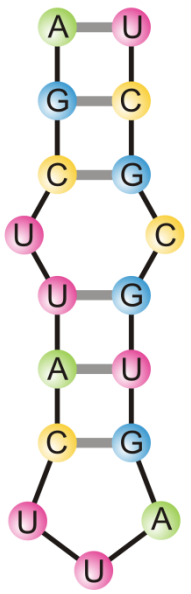
Die Fitness von RNA-Sekundärstrukturen durch Evaluierung der Phänotypen

AGCUUAACUUAGUCGCU

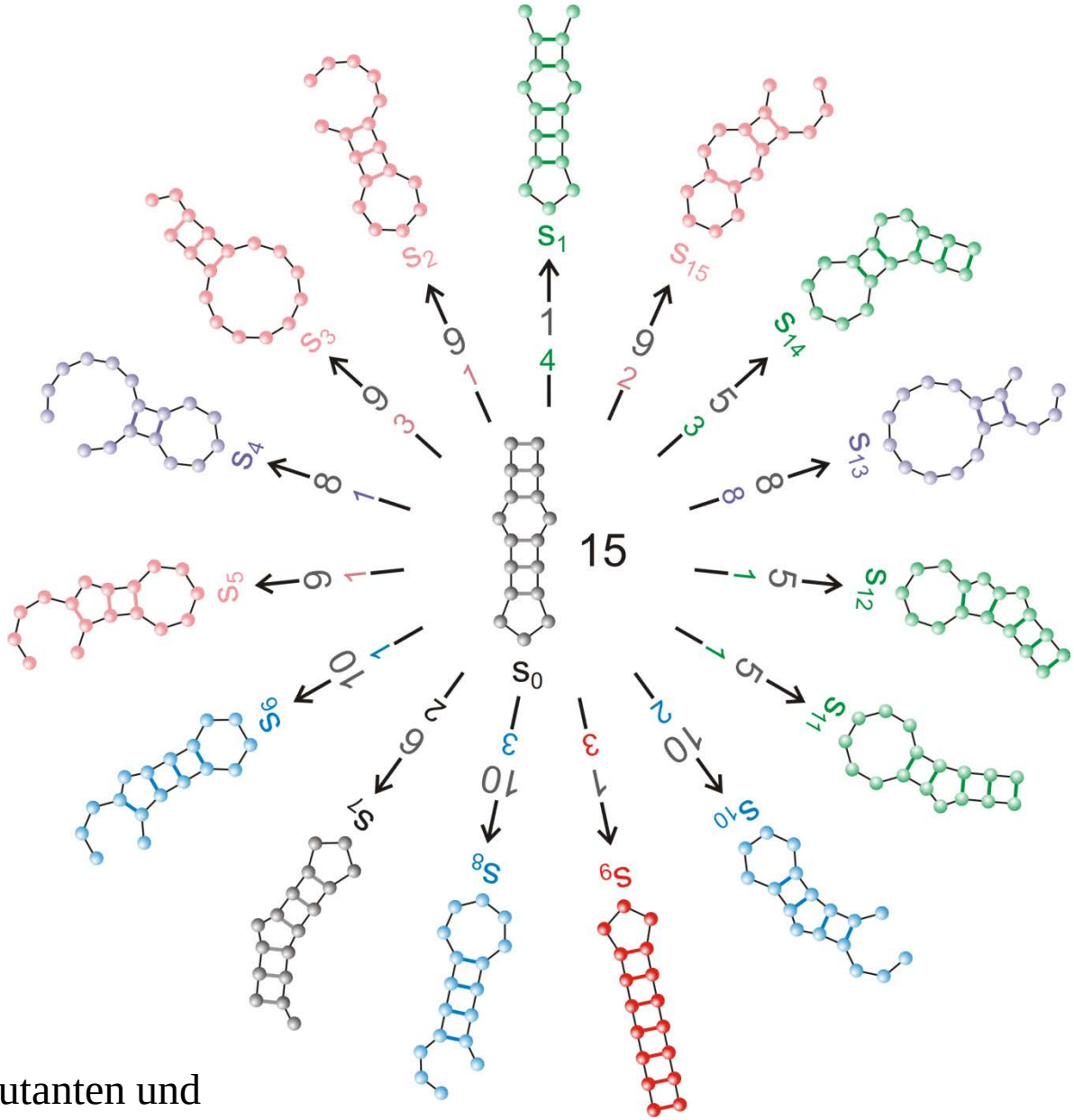


AGCUUACUUAGUGCGCU

(((· (((· · ·))) ·)))

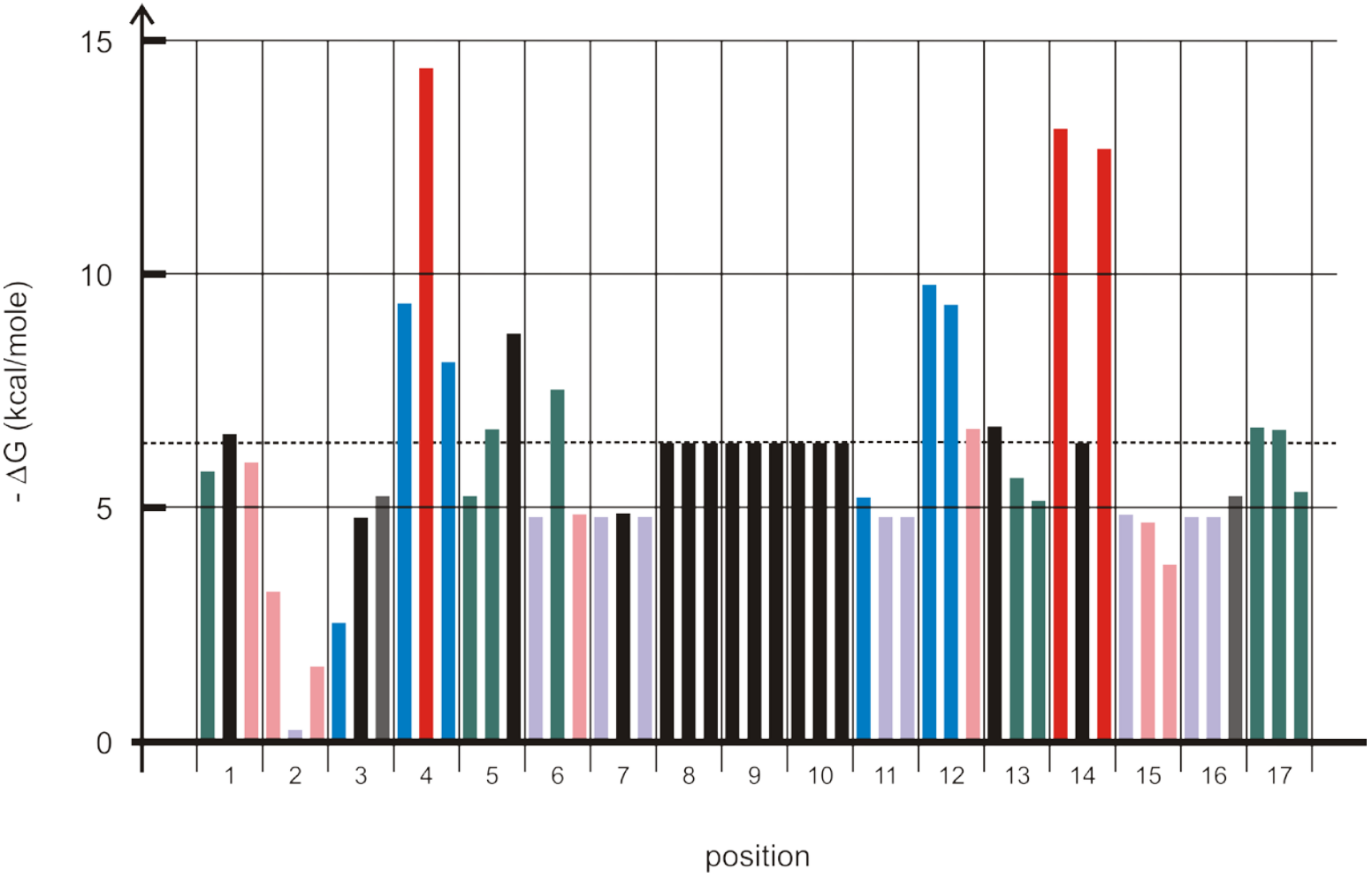


Referenzsequenz

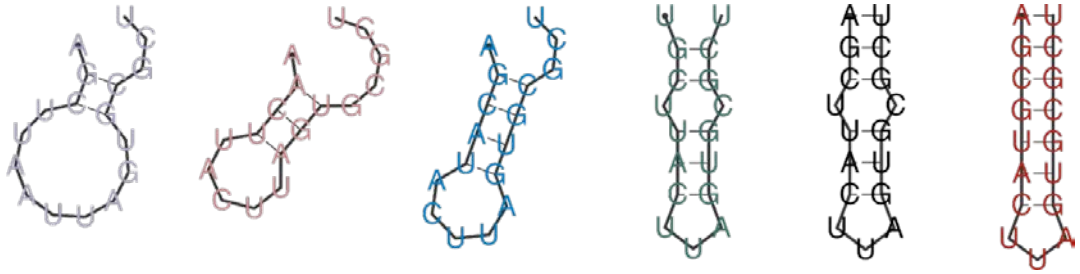


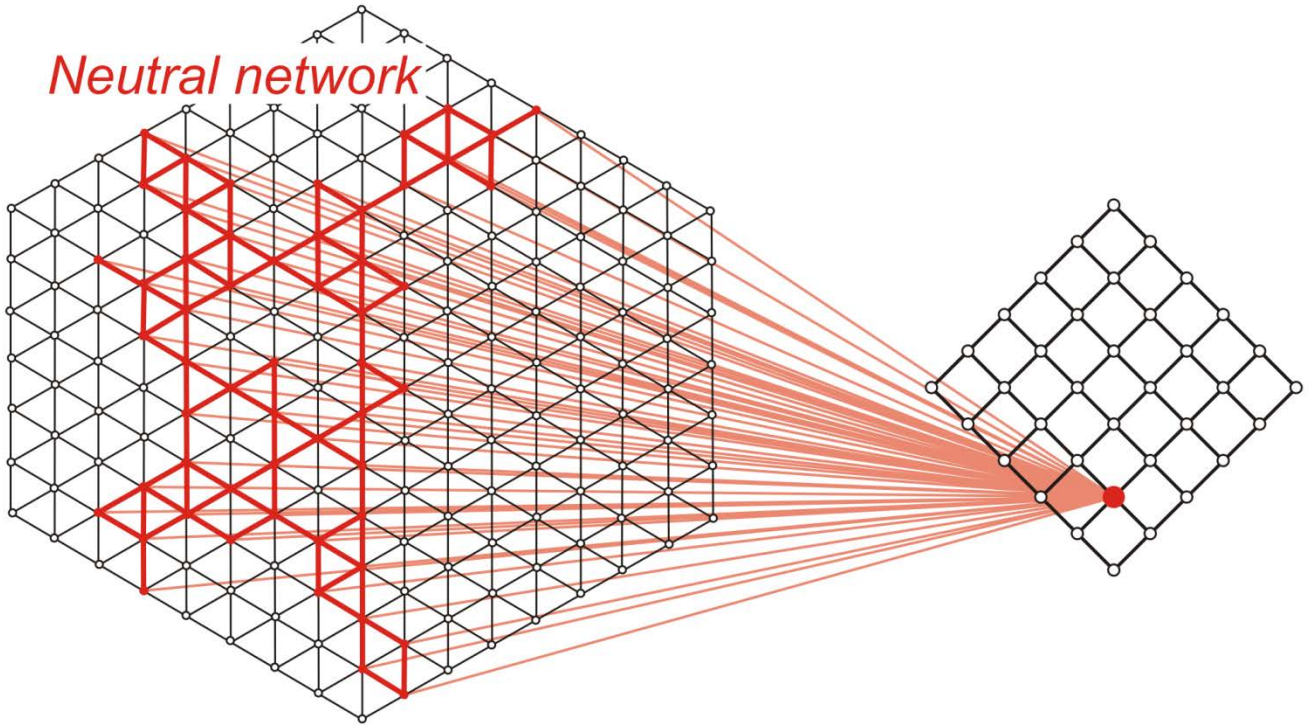
Häufigkeiten der 51 Punktmutanten und Abstände von der Referenzsequenz

Referenz



Freie Faltungsenergien (ΔG_0) der 51 Punktmutanten der Referenzsequenz

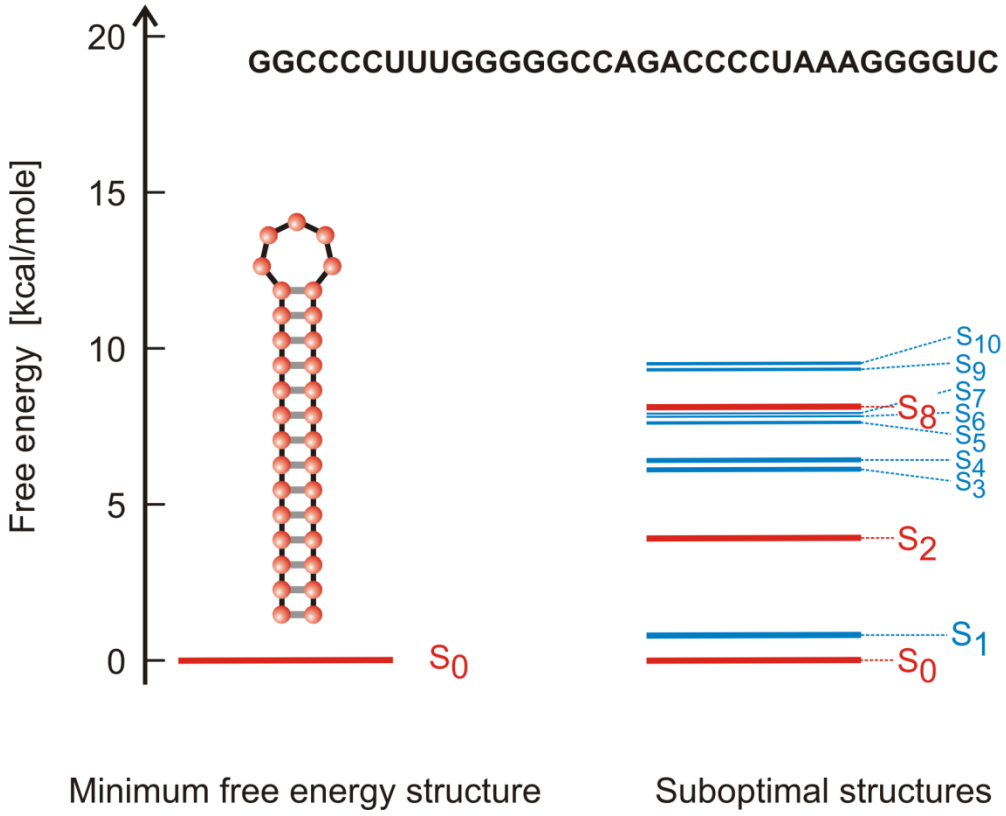




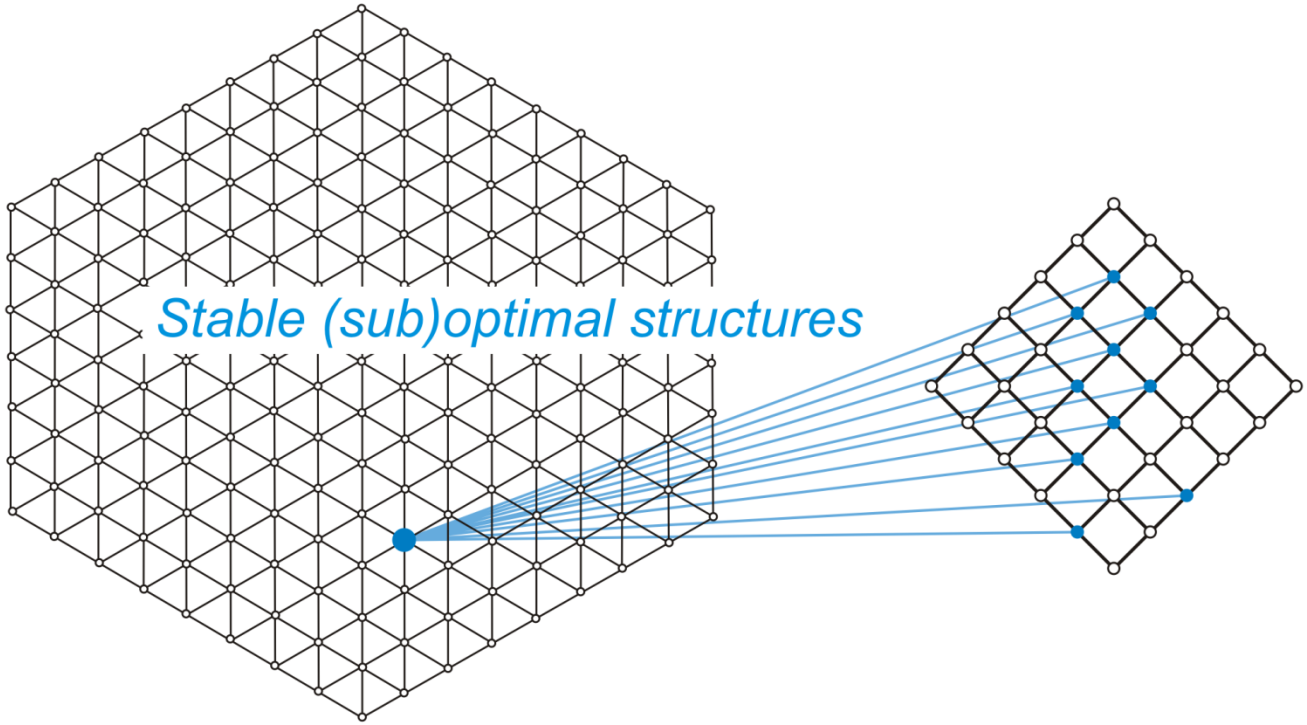
Sequence space

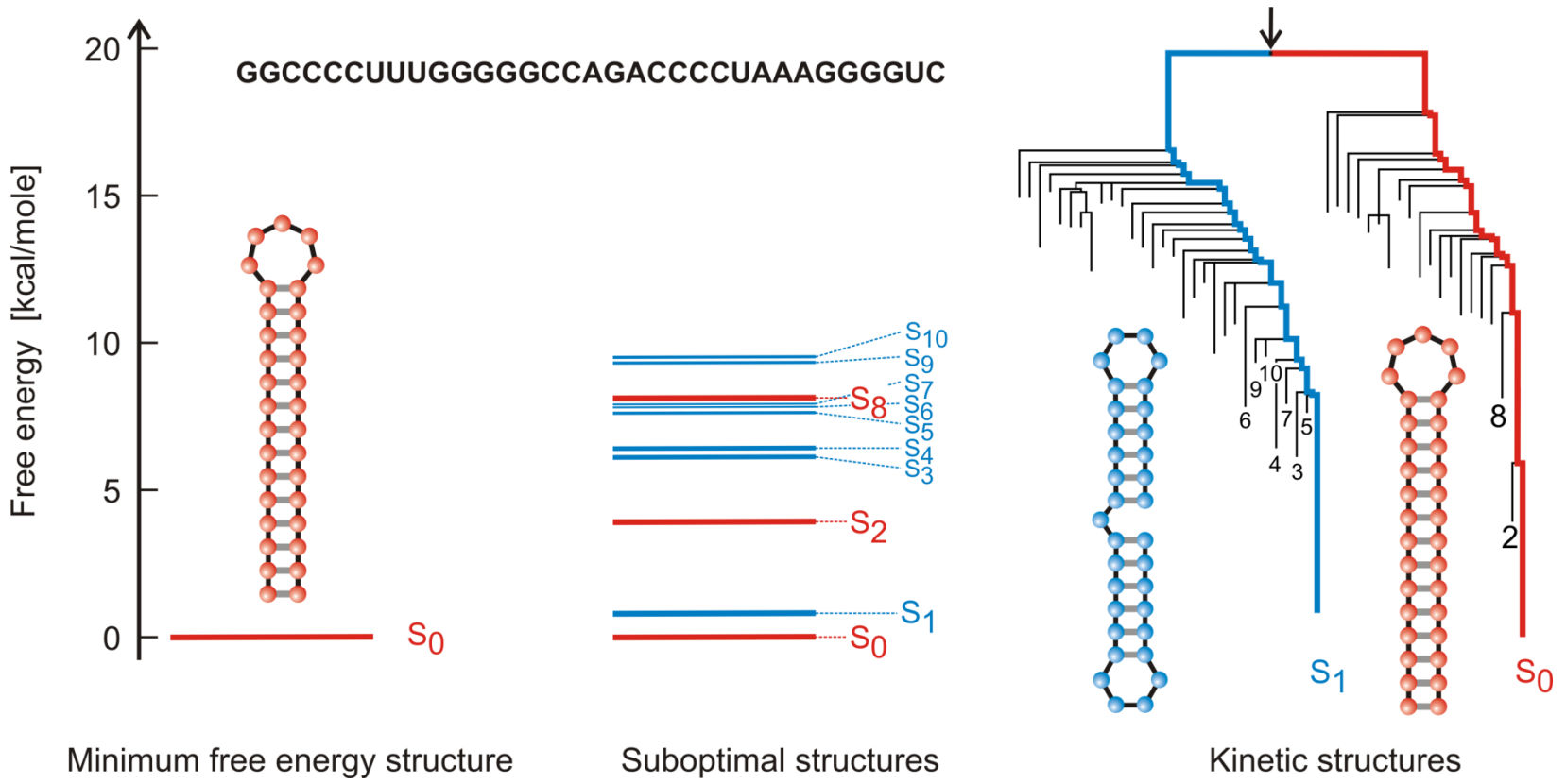
Structure space

many genotypes ⇒ one phenotype



Extension of the notion of structure


Stable (sub)optimal structures
Sequence space
Structure space



Interconversion of suboptimal structures

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

Structural parameters affecting the kinetics of RNA hairpin formation

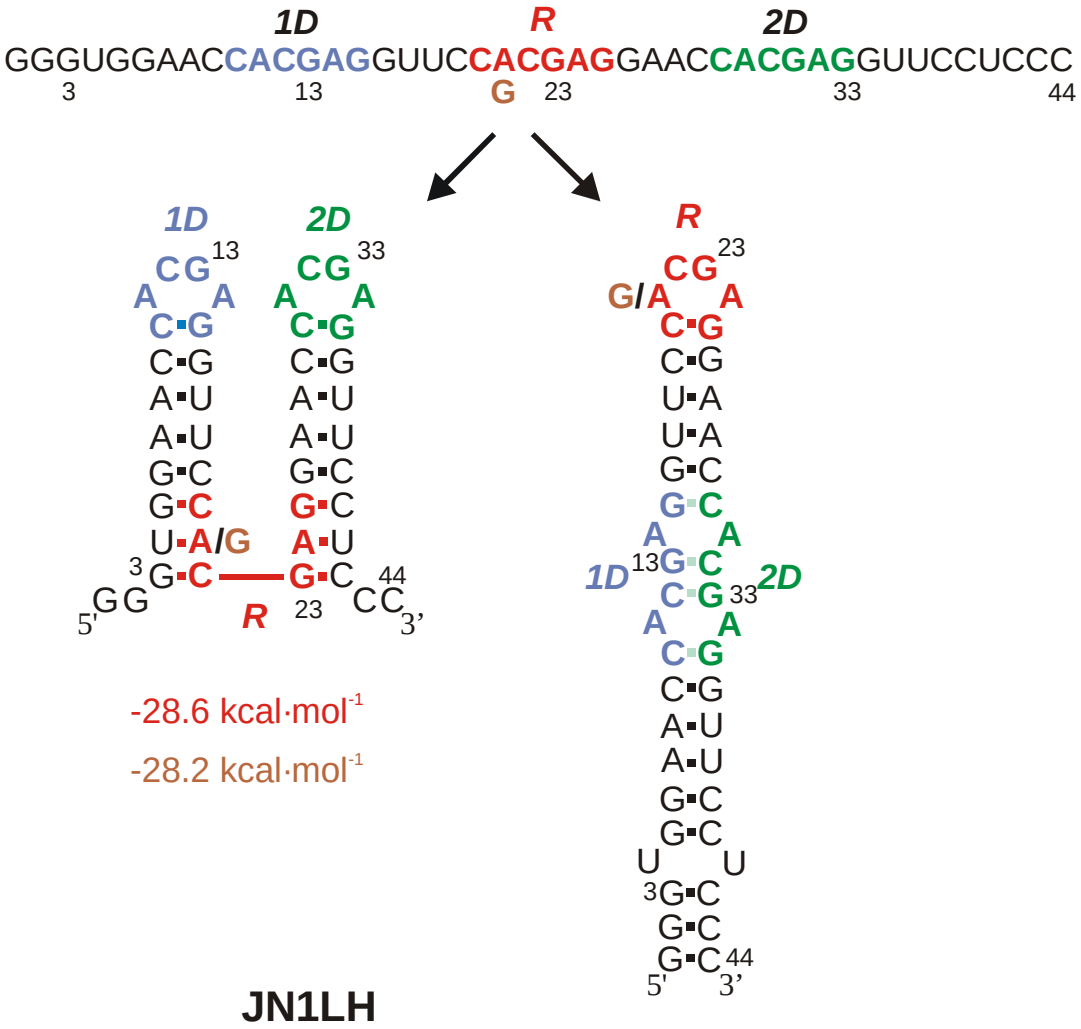
J. H. A. Nagel, C. Flamm[1], I. L. Hofacker[1], K. Franke[2], M. H. de Smit, P. Schuster[1] and C. W. A. Pleij*

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.

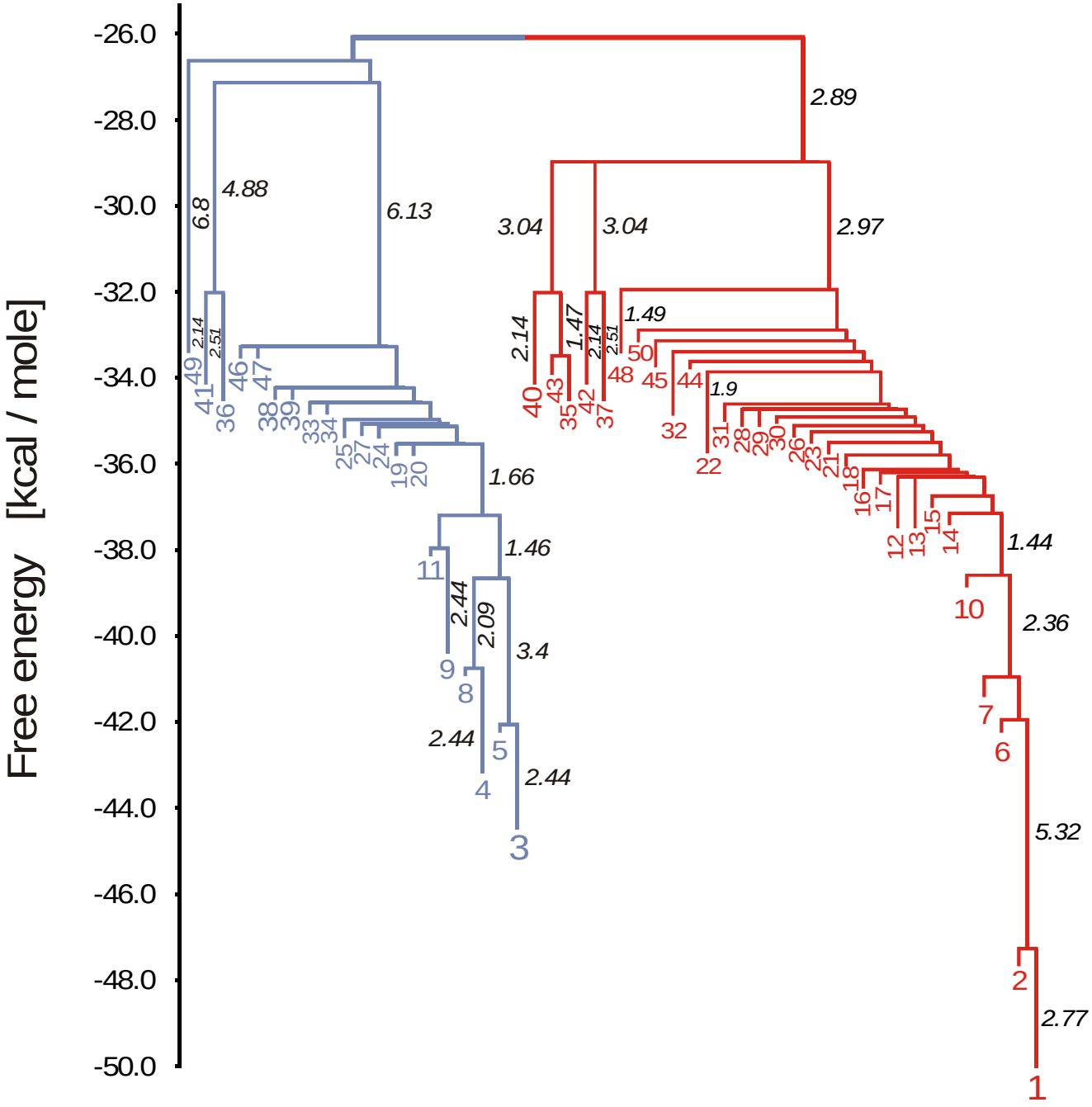


An experimental RNA switch

JN1LH

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

A ribozyme switch

E.A.Schultes, D.B.Bartel, Science **289** (2000), 448-452

minus the background levels observed in the HSP in the control (Sar1-GDP–containing) incubation that prevents COPII vesicle formation. In the microsome control, the level of p115-SNARE associations was less than 0.1%.
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50. GST-SNARE proteins were expressed in bacteria and purified on glutathione-Sepharose beads using standard methods. Immobilized GST-SNARE protein (0.5 μM) was incubated with rat liver cytosol (20 mg) or purified recombinant p115 (0.5 μM) in 1 ml of NS buffer containing 1% BSA for 2 hours at 4°C with rotation. Beads were briefly spun (3000 rpm for 10 s) and sequentially washed three times with NS buffer and three times with NS buffer supplemented with 150 mM NaCl. Bound proteins were eluted three times in 50 μl of 50 mM tris-HCl (pH 8.5), 50 mM reduced glutathione, 150 mM NaCl, and 0.1% Triton X-100 for 15 min at 4°C with intermittent mixing, and elutes were pooled. Proteins were precipitated by MeOH/CH_3Cl and separated by SDS–polyacrylamide gel electrophoresis (PAGE) followed by immunoblotting using p115 mAb 13F12.
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69. We thank G. Waters for p115 cDNA and p115 mAbs; G. Warren for p97 and p47 antibodies; R. Scheller for rbet1, membrin, and sec22 cDNAs; H. Plutner for excellent technical assistance; and P. Tan for help during the initial phase of this work. Supported by NIH grants GM 33301 and GM42336 and National Cancer Institute grant CA58689 (W.E.B.), a NIH National Research Service Award (B.D.M.), and a Wellcome Trust International Traveling Fellowship (B.B.A.).

20 March 2000; accepted 22 May 2000

One Sequence, Two Ribozymes: Implications for the Emergence of New Ribozyme Folds

Erik A. Schultes and David P. Bartel*

We describe a single RNA sequence that can assume either of two ribozyme folds and catalyze the two respective reactions. The two ribozyme folds share no evolutionary history and are completely different, with no base pairs (and probably no hydrogen bonds) in common. Minor variants of this sequence are highly active for one or the other reaction, and can be accessed from prototype ribozymes through a series of neutral mutations. Thus, in the course of evolution, new RNA folds could arise from preexisting folds, without the need to carry inactive intermediate sequences. This raises the possibility that biological RNAs having no structural or functional similarity might share a common ancestry. Furthermore, functional and structural divergence might, in some cases, precede rather than follow gene duplication.

Related protein or RNA sequences with the same folded conformation can often perform very different biochemical functions, indicating that new biochemical functions can arise from preexisting folds. But what evolutionary mechanisms give rise to sequences with new macromolecular folds? When considering the origin of new folds, it is useful to picture, among all sequence possibilities, the distribution of sequences with a particular fold and function. This distribution can range very far in sequence space (*1*). For example, only seven nucleotides are strictly conserved among the group I self-splicing introns, yet secondary (and presumably tertiary) structure within the core of the ribozyme is preserved (*2*). Because these disparate isolates have the same fold and function, it is thought that they descended from a common ancestor through a series of mutational variants that were each functional. Hence, sequence heterogeneity among divergent isolates implies the existence of paths through sequence space that have allowed neutral drift from the ancestral sequence to each isolate. The set of all possible neutral paths composes a "neutral network," connecting in sequence space those widely dispersed sequences sharing a particular fold and activity, such that any sequence on the network can potentially access very distant sequences by neutral mutations (*3–5*).

Theoretical analyses using algorithms for predicting RNA secondary structure have suggested that different neutral networks are interwoven and can approach each other very closely (*3*, *5–8*). Of particular interest is whether ribozyme neutral networks approach each other so closely that they intersect. If so, a single sequence would be capable of folding into two different conformations, would have two different catalytic activities, and could access by neutral drift every sequence on both networks. With intersecting networks, RNAs with novel structures and activities could arise from previously existing ribozymes, without the need to carry nonfunctional sequences as evolutionary intermediates. Here, we explore the proximity of neutral networks experimentally, at the level of RNA function. We describe a close apposition of the neutral networks for the hepatitis delta virus (HDV) self-cleaving ribozyme and the class III self-ligating ribozyme.

In choosing the two ribozymes for this investigation, an important criterion was that they share no evolutionary history that might confound the evolutionary interpretations of our results. Choosing at least one artificial ribozyme ensured independent evolutionary histories. The class III ligase is a synthetic ribozyme isolated previously from a pool of random RNA sequences (*9*). It joins an oligonucleotide substrate to its 5′ terminus. The prototype ligase sequence (Fig. 1A) is a shortened version of the most active class III variant isolated after 10 cycles of in vitro selection and evolution. This minimal construct retains the activity of the full-length isolate (*10*). The HDV ribozyme carries out the site-specific self-cleavage reactions needed during the life cycle of HDV, a satellite virus of hepatitis B with a circular, single-stranded RNA genome (*11*). The prototype HDV construct for our study (Fig. 1B) is a shortened version of the antigenomic HDV ribozyme (*12*), which undergoes self-cleavage at a rate similar to that reported for other antigenomic constructs (*13*, *14*).

The prototype class III and HDV ribozymes have no more than the 25% sequence identity expected by chance and no fortuitous structural similarities that might favor an intersection of their two neutral networks. Nevertheless, sequences can be designed that simultaneously satisfy the base-pairing requirements

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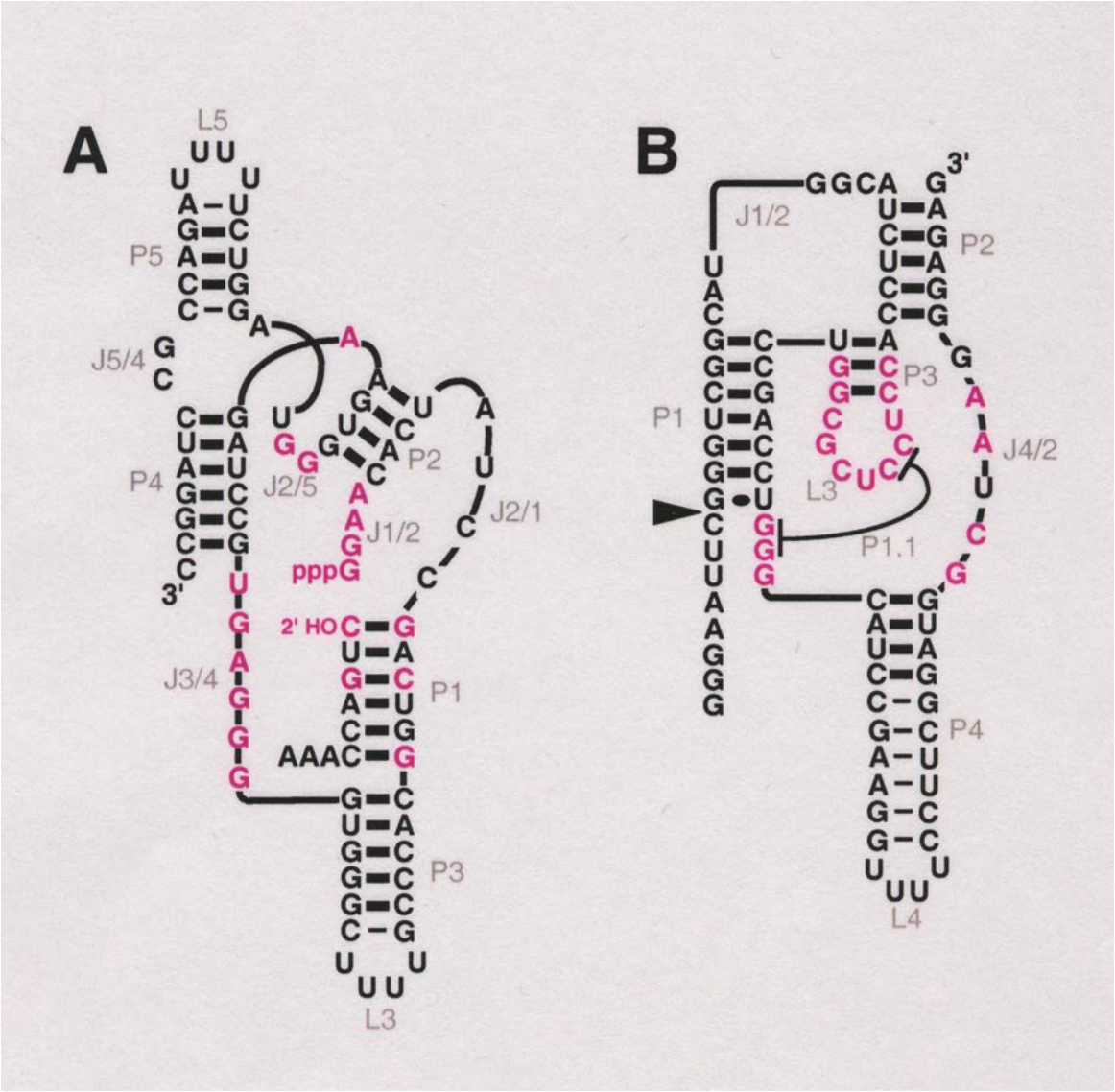
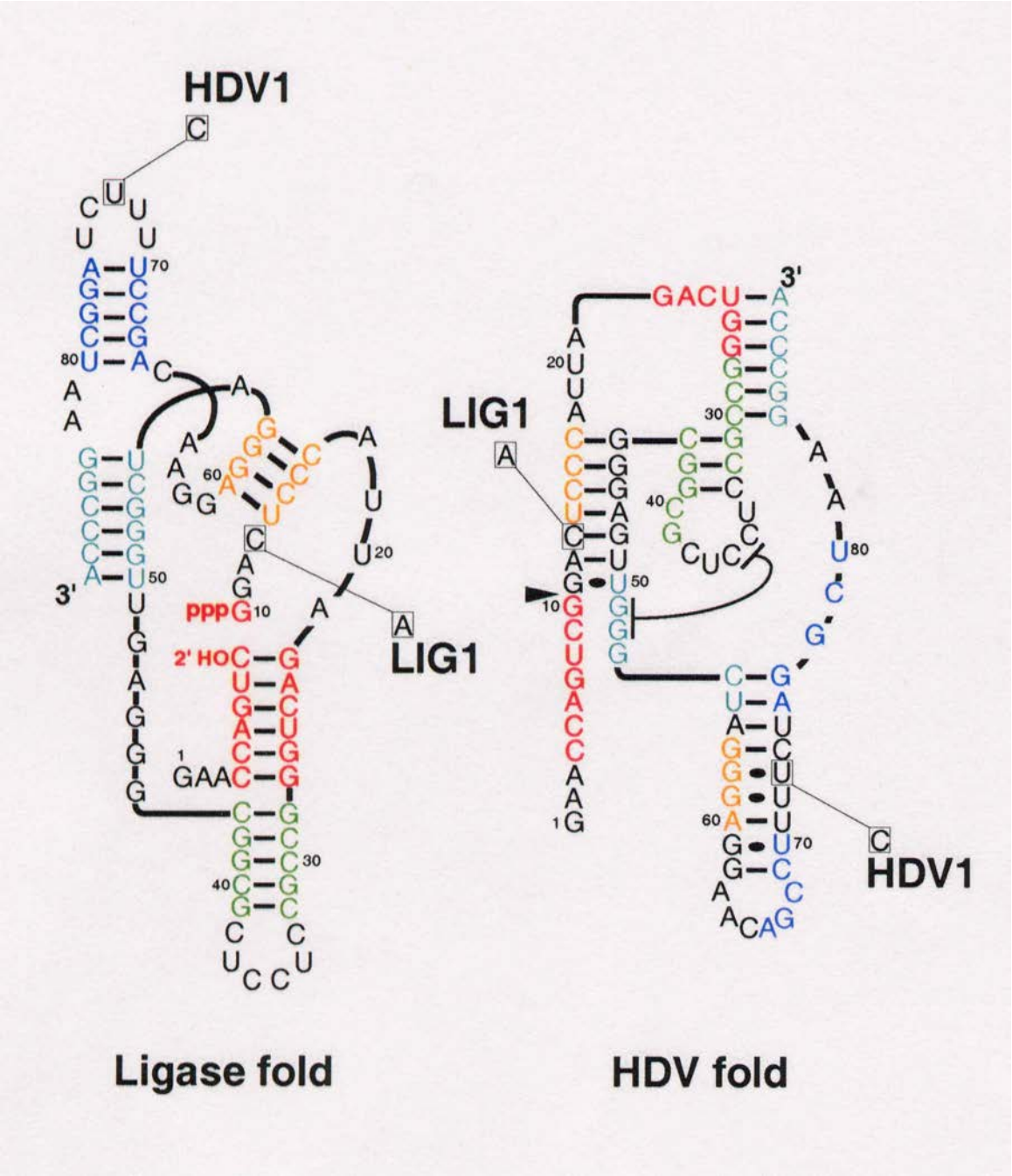
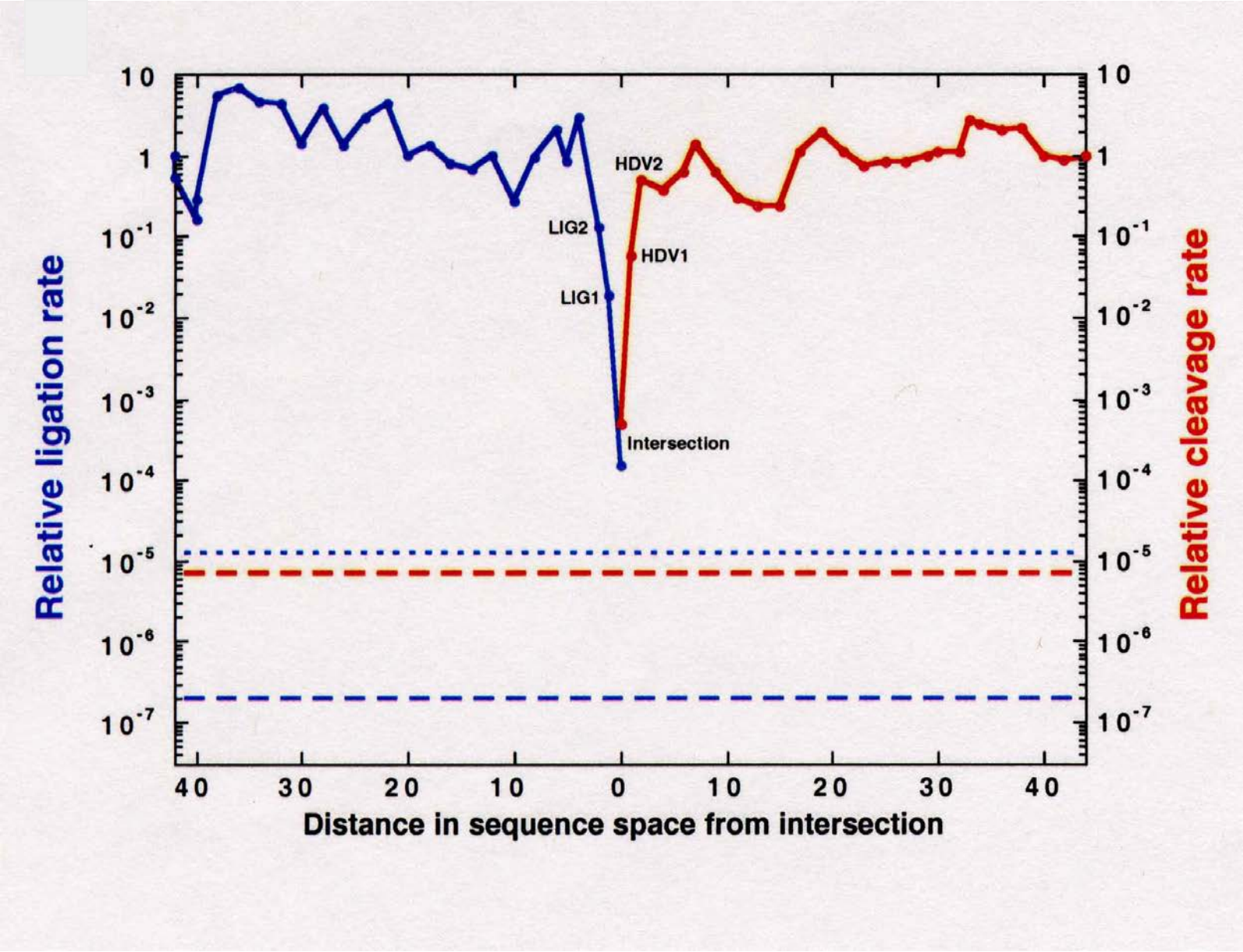


Two ribozymes of chain lengths n = 88 nucleotides: An artificial ligase (**A**) and a natural cleavage ribozyme of hepatitis-δ-virus (**B**)

The sequence at the ***intersection***:

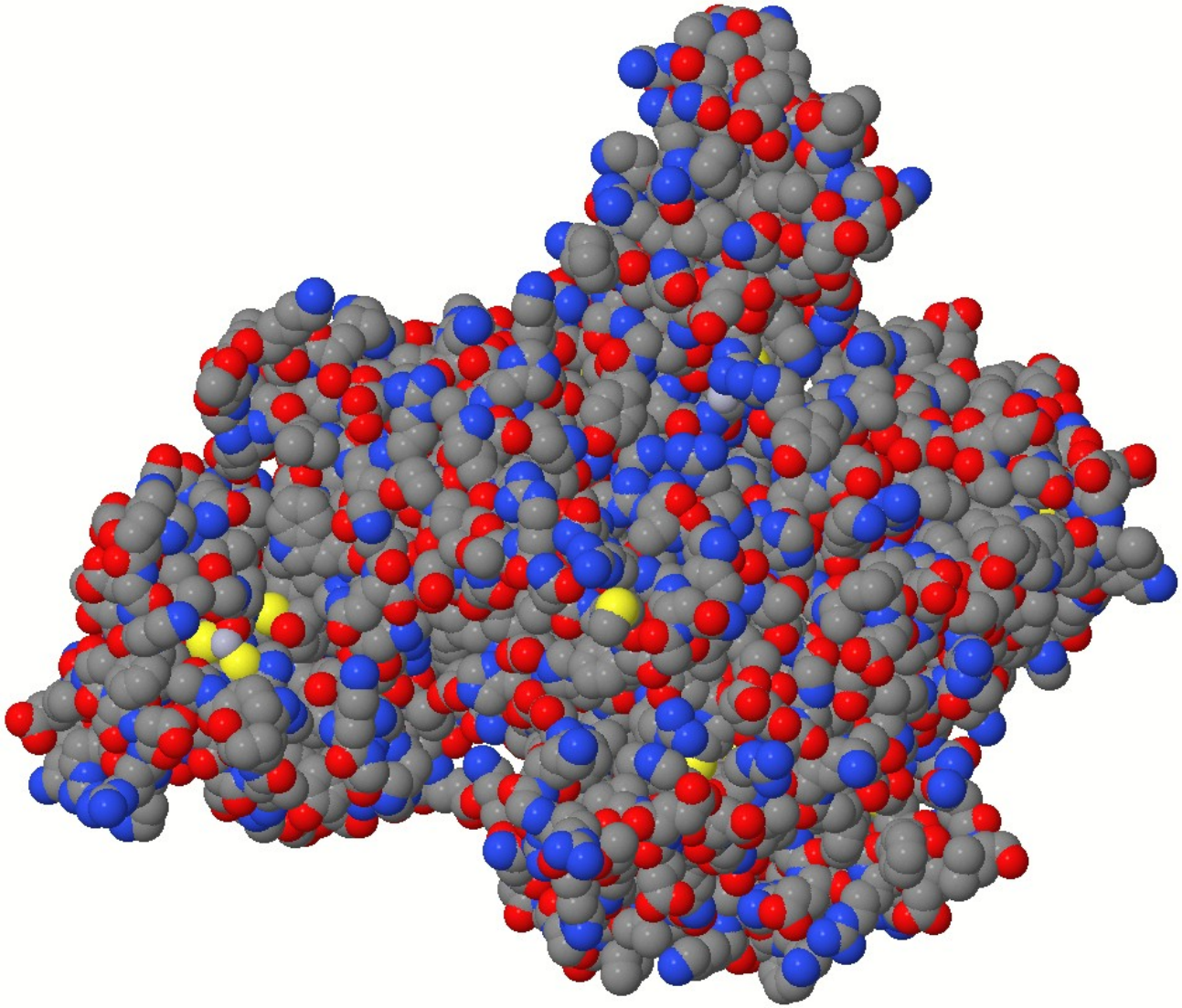
An RNA molecules which is 88 nucleotides long and can form both structures





Two neutral walks through sequence space with conservation of structure and catalytic activity

1. Darwinsche Evolution und Mathematik
2. Ein einfaches aber vollständiges Evolutionsmodell
3. Evolution als ein Prozess im Sequenzraum
4. Vom Genotyp zum Phänotyp und zur Fitness
5. **Die Strukturbildung bei Biopolymeren**
6. Schlussfolgerungen und Ausblick



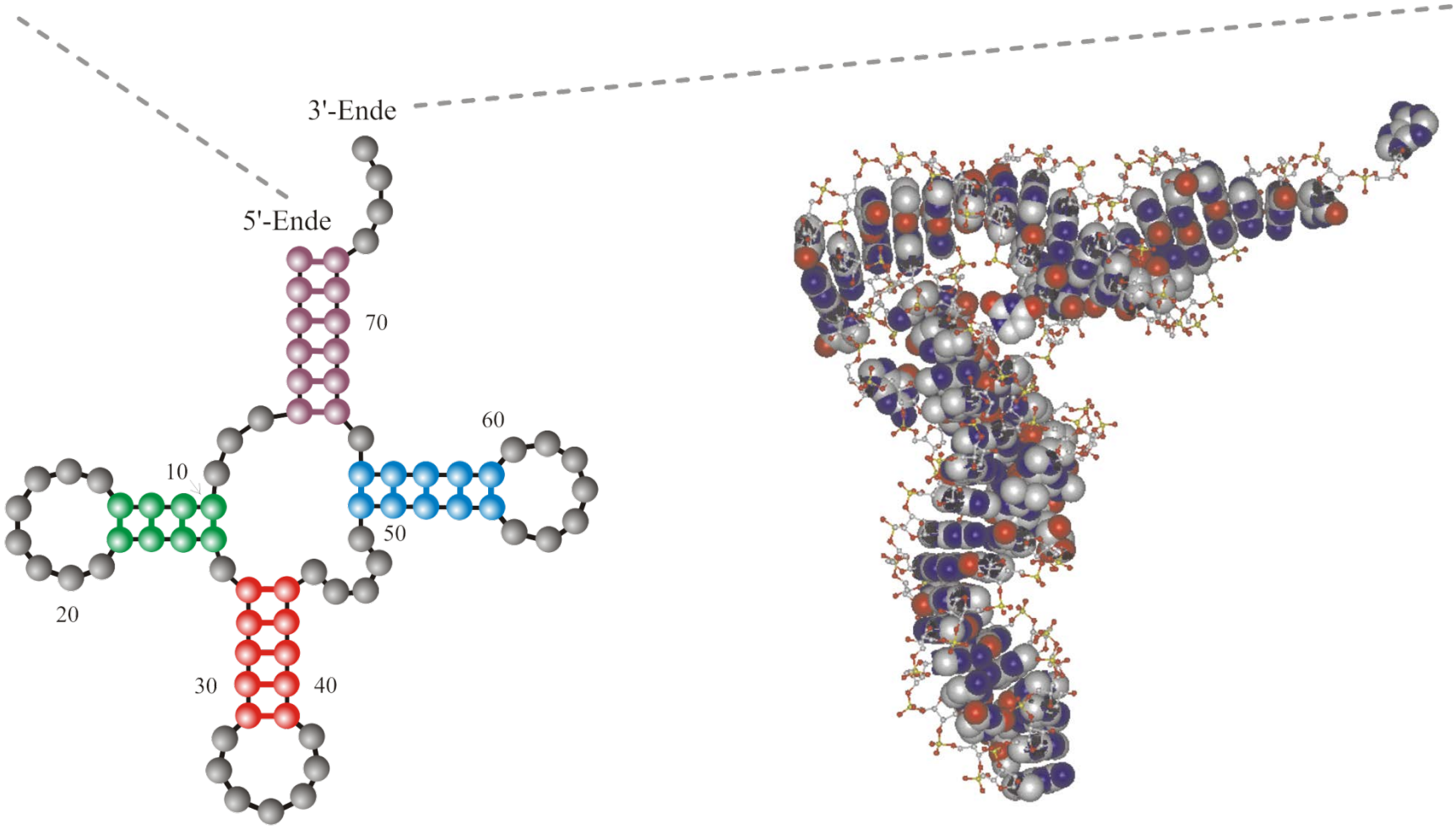
Transkriptionsenzym: DNA → RNA

Sequenz

5'-Ende

3'-Ende

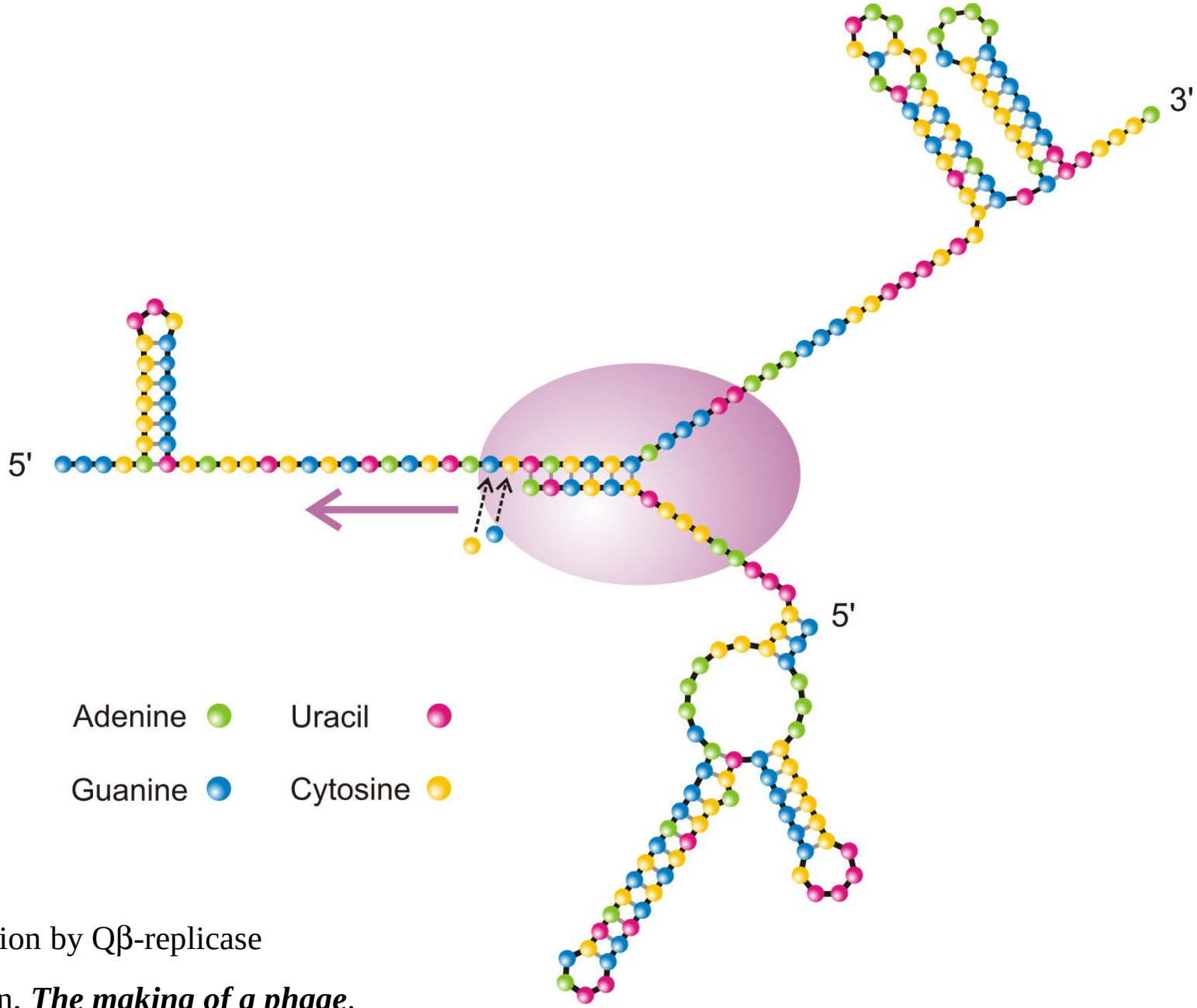
GCGGAUUUAGCUCAGDDGGGAGAGCMCCAGACUGAAYAUCUGGAGMUCCUGUGTPCGAUCCACAGAAUUCGCACCA



Sekundärstruktur

räumliche Struktur

Ribonukleinsäure RNA



RNA replication by Qβ-replicase

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

1. Darwinsche Evolution und Mathematik
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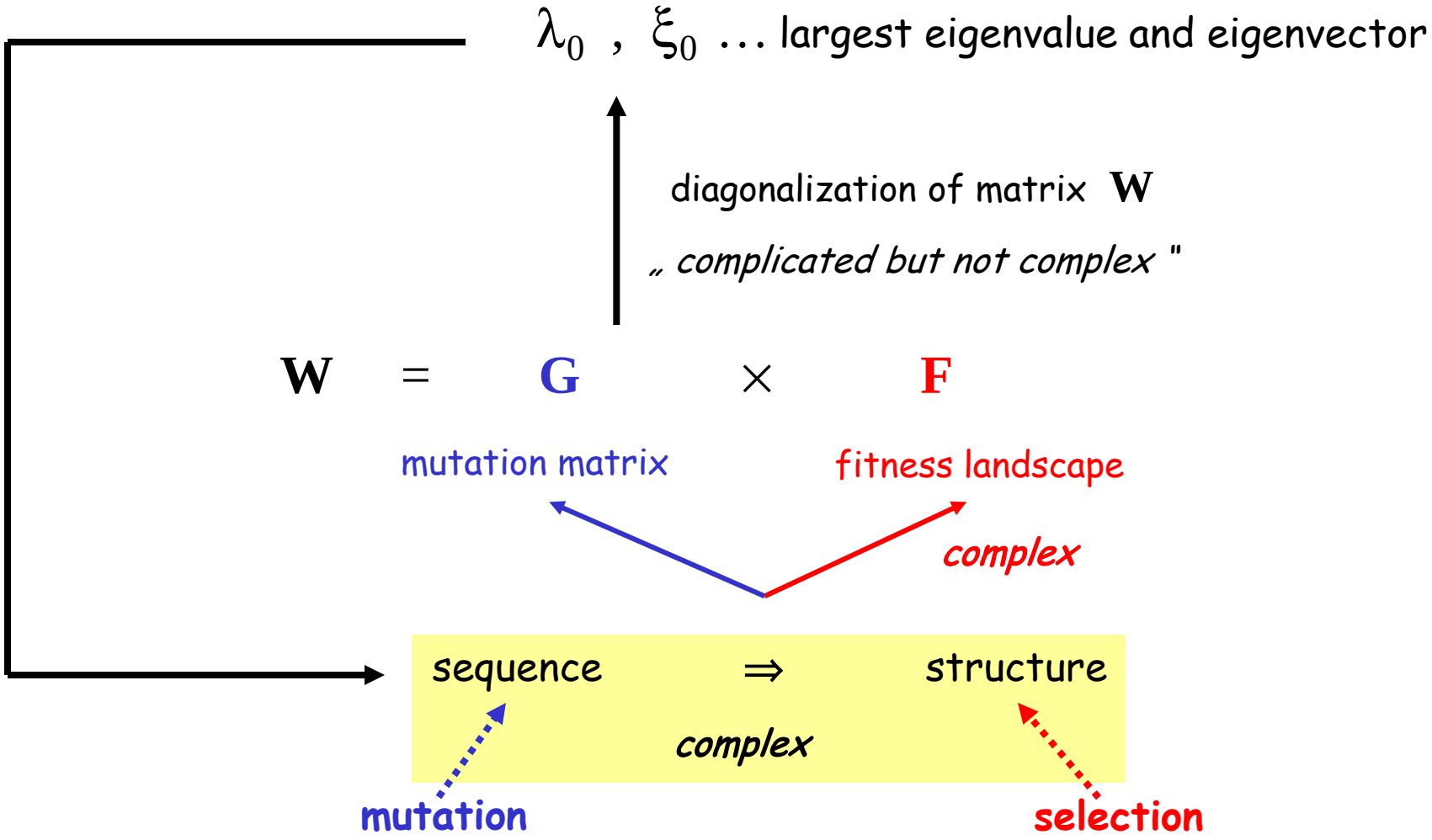


Complexity in molecular evolution

Evolution im Licht der gegenwärtigen Molekulargenetik

1. Die Vorstellungen der konventionellen Genetik müssen hinsichtlich der Genregulation entscheidend erweitert werden.

2. Ein Gen wird im Vielzellerorganismus gewebsspezifisch in mehrere verschiedene Proteine übersetzt.

3. Umwelteinflüsse geben Anlass zu Veränderungen des Genoms, welche einige Generationen lang vererbbar sind.

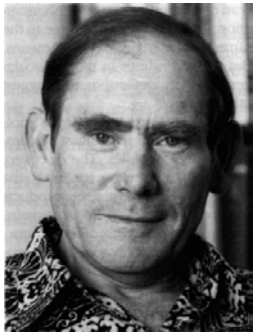
4. Komplexität, Robustheit und Plastizität der Organismen wird erst im Zusammenspiel von Genetik und Epigenetik verstehbar.

Vorteile der molekularen Erforschung des Lebens

1. Komplexe Reproduktionsmechanismen sind erklärbar.

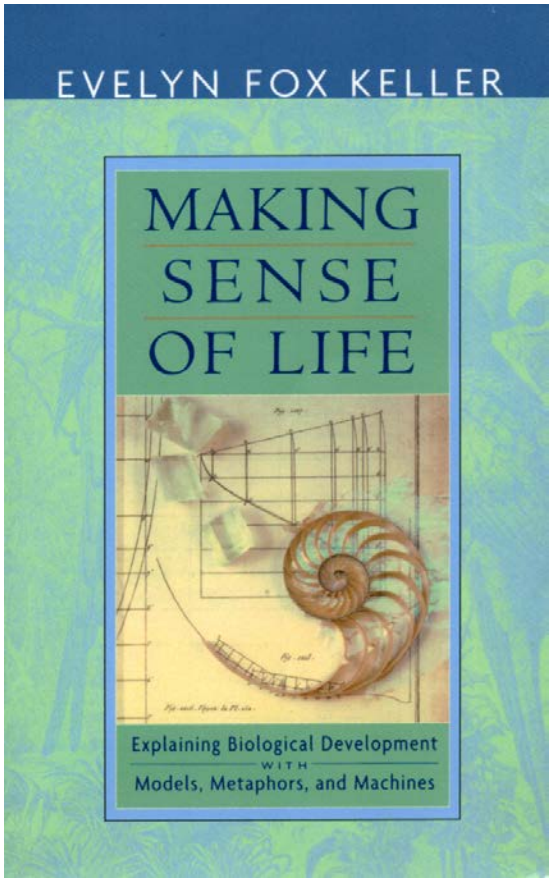
2. Generegulation – basierend auf DNA oder RNA – ist nichts anderes als chemische Kinetik!

3. Epigenetik wird durch die gleichzeitige Betrachtung mehrerer Generationen einfach verstehbar.



Sydney Brenner, 1927 -

What else is epigenetics than a funny form of enzymology ? Each protein, after all, comes from some piece of DNA.



Mathematical Models:
Explaining development
without the help of genes

„Untimely Birth of a
Mathematical Biology“

Evelyn Fox Keller, 1936 –

Fakten müssen der Theorienbildung vorausgehen

Keller, E.F. 2003. Making Sense of Life. Explaining Biological Development with Models, Metaphors, and Machines. Harvard University Press, Cambridge, MA

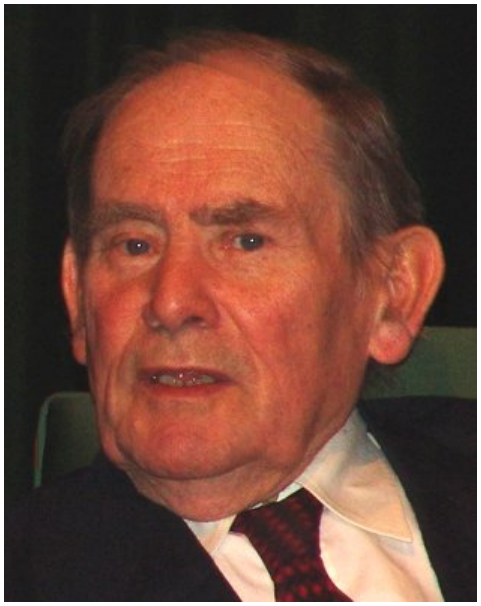
Theory – mathematics and computation – cannot remove complexity, but it shows what kind of „regular“ behavior can be expected and what experiments have to be done to get a grasp on the irregularities.

Manfred Eigen, 1927 -

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

…. 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

Danke für die Aufmerksamkeit!

Web-Page for further information:
http://www.tbi.univie.ac.at/~pks