

Web-Page for further information:

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

1. Evolution - organismisch und molekular
2. Wahrscheinlichkeiten in der Biologie
3. Vermehrung, Mutation und Selektion
4. Molekulares Design
5. Evolution von Molekülen und Optimierung
6. Die Komplexität der Biologie

1. **Evolution - organismisch und molekular**
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Genotype, Genome

Collection of genes

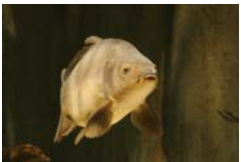
Developmental program

Highly specific environmental conditions

Unfolding of the genotype

Phenotype

Evolution explains the origin of species and their interactions

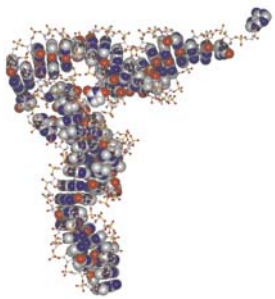


Genotype, Genome

CGGGATTAGCTCAGTTGGGAGAGCGCCAGACTGAAGATCTGGAGGTCCTGTGTTTCGATCCACAGAATTCGCACCA

Quantitative biology

'the new biology is the chemistry of living matter'



evolution of RNA molecules, ribozymes and splicing, the idea of an RNA world, selection of RNA molecules, RNA editing, the ribosome is a ribozyme, small RNAs and RNA switches.

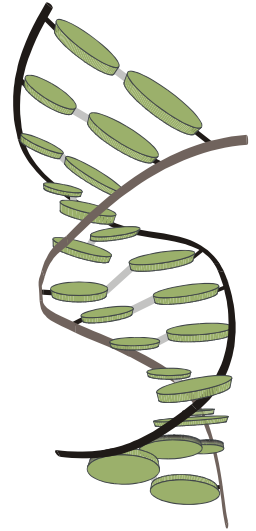
The exciting RNA story

Biochemistry
molecular biology
structural biology
molecular evolution
molecular genetics
systems biology
bioinformatics

Unfolding of the genotype

Phenotype

Highly specific environmental conditions



John Kendrew



Manfred Eigen



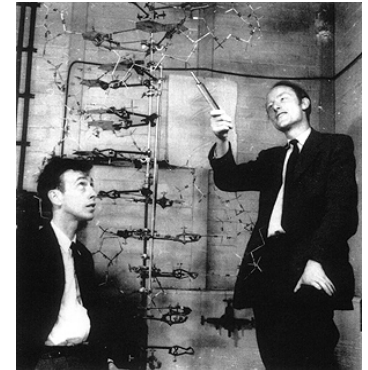
Molecular evolution
Linus Pauling and
Emile Zuckerkandl



Hemoglobin sequence
Gerhard Braunitzer



Max Perutz



James D. Watson und
Francis H.C. Crick



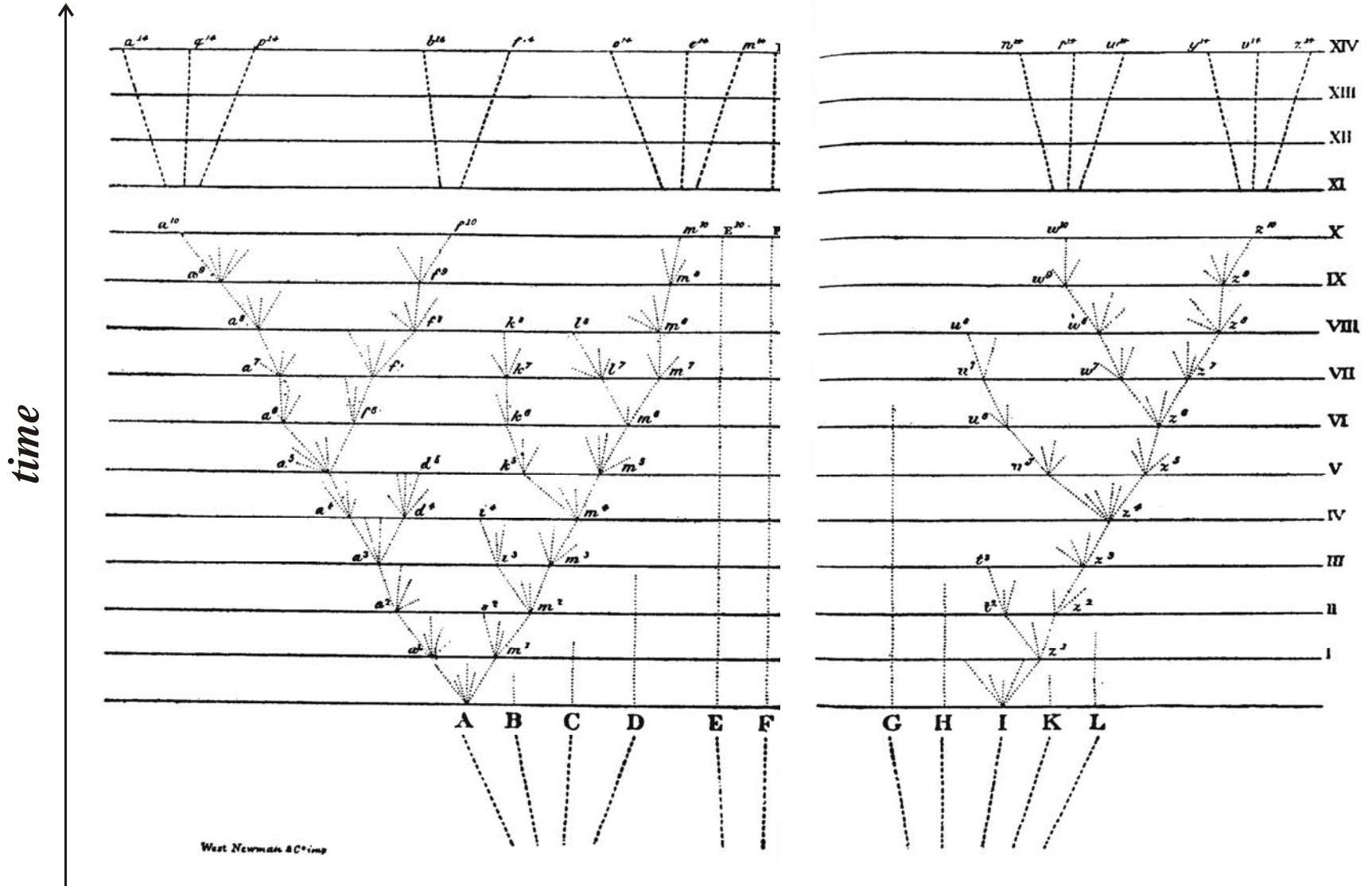
Three necessary conditions for Darwinian evolution are:

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

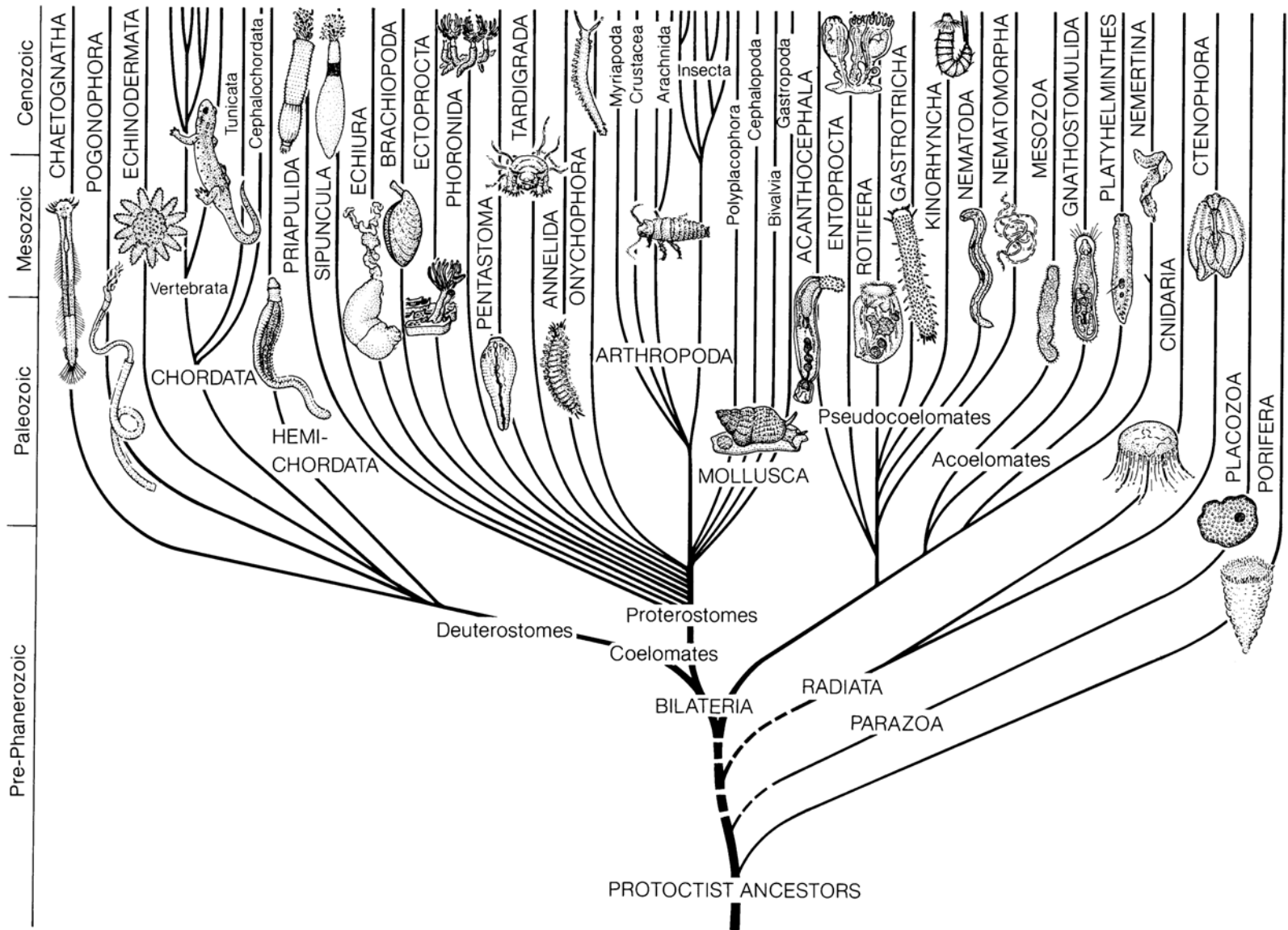
Variation through mutation and recombination operates on the **genotype** whereas the **phenotype** is the target of **selection**.

One important property of the Darwinian scenario is that **variations** in the form of mutations or recombination events occur **uncorrelated** with their **effects on the selection process**.

All conditions can be fulfilled not only by cellular organisms but also by **nucleic acid molecules** in suitable **cell-free experimental assays**.



Charles Darwin, *The Origin of Species*, 6th edition.
 Everyman's Library, Vol.811, Dent London, pp.121-122.



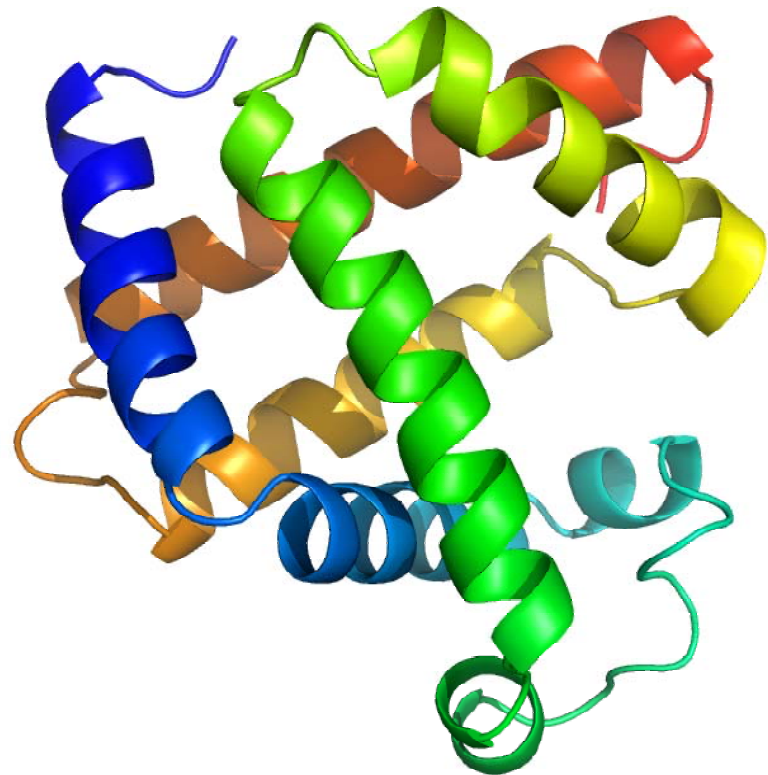
Modern phylogenetic tree: Lynn Margulis, Karlene V. Schwartz. *Five Kingdoms. An Illustrated Guide to the Phyla of Life on Earth*. W.H. Freeman, San Francisco, 1982.

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Kette aus 153 Aminosäureresten mit der Sequenz:

**GLSDGEWQLVLNVWGKVEADIPGHGQEVLIIRLFKGHPEKFDKFKHLK
SEDEMKASEDLKKHGATVLTALGGILKKKGHHEAEIKPLAQSHATKHKIP
VKYLEFISECIIQVLQSKHPGDFGADAQGAMNKALELFRKDMASNYKELG
FQG**

Das Myoglobinmolekül



Eugene Wigner's or Fred Hoyle's argument applied to myoglobin:

All sequences have equal probability and all except one have no survival value or are lethal

GLSDGEWQLVLNVWG FQG

Alphabet size: 20

Chain length: 153 amino acids

Number of possible sequences: $20^{153} = 0.11 \times 10^{200}$

Probability to find the myoglobin sequence:

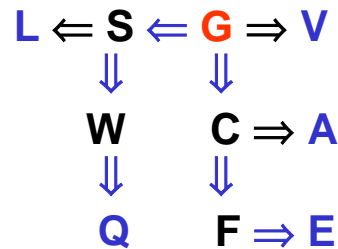
$$20^{-153} = 9 \times 10^{-200} = 0.000\dots009$$



Eugene Wigner's and Fred Hoyle's arguments revisited:

Every single point mutation leads to an improvement and is therefore selected

GLSDGEWQLVLNVWG FQG



Alphabet size: 20

Chain length: 153 amino acids

Length of longest path to myoglobin sequence: $19 \times 153 = 2907$

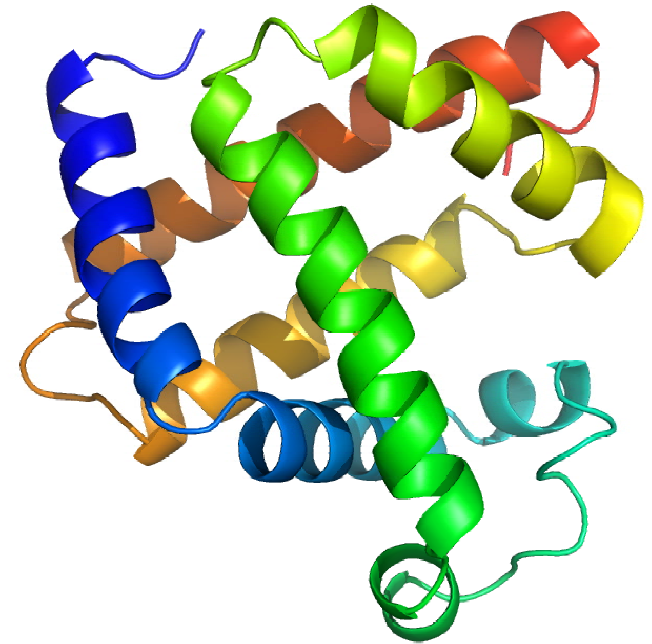
Probability to find the myoglobin sequence: **0.00034**

Das Faltungsproblem des Myoglobinmoleküls:

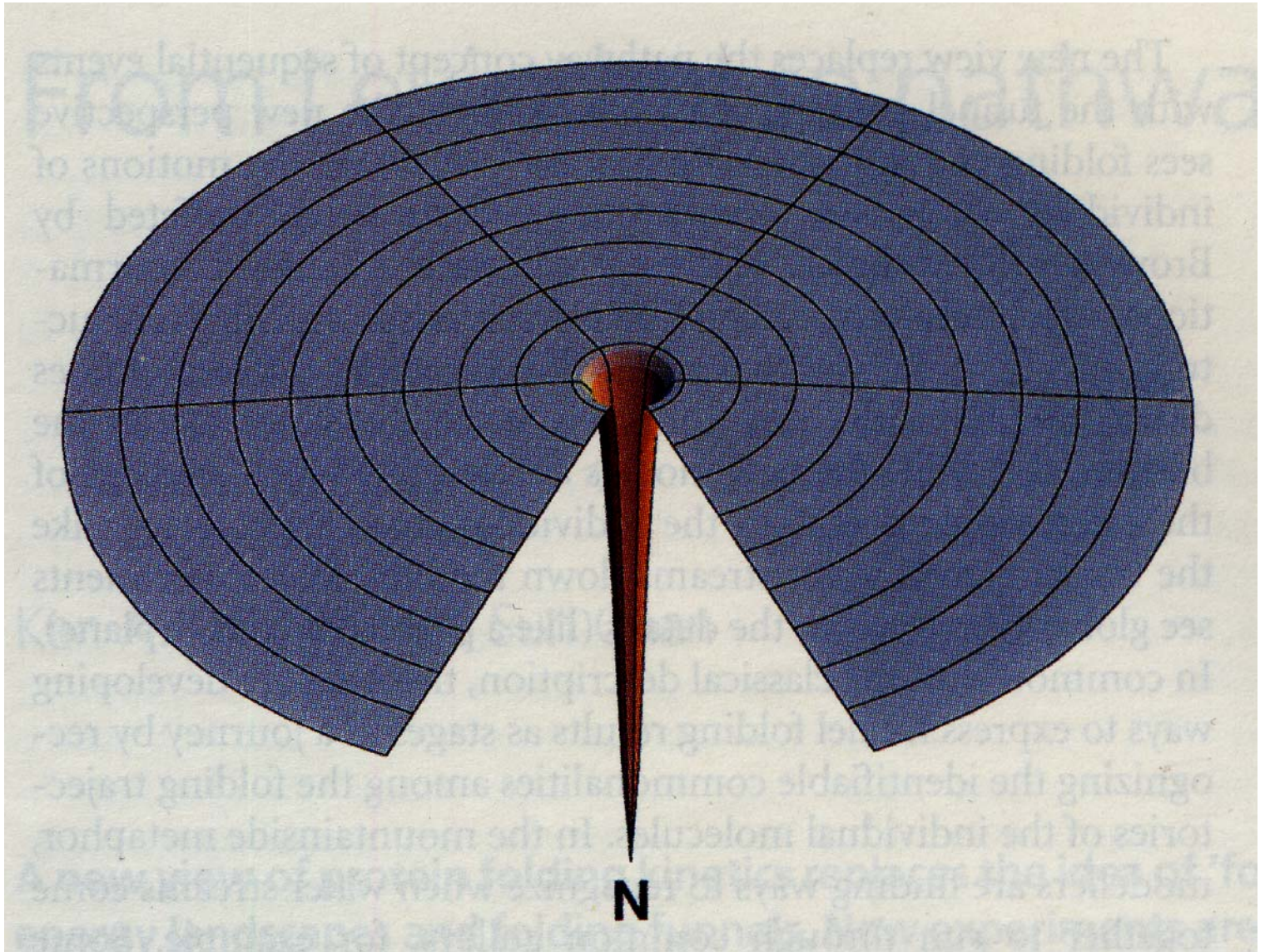
Eine Kette aus 153 Aminosäureresten, von welchen jeder im Mittel 15 verschiedene Konformationen einnimmt, kann in

$$15^{153} = 0.9 \times 10^{180} \text{ Zuständen}$$

vorkommen. Einer davon muss bei der Faltung in die stabile Struktur gefunden werden.



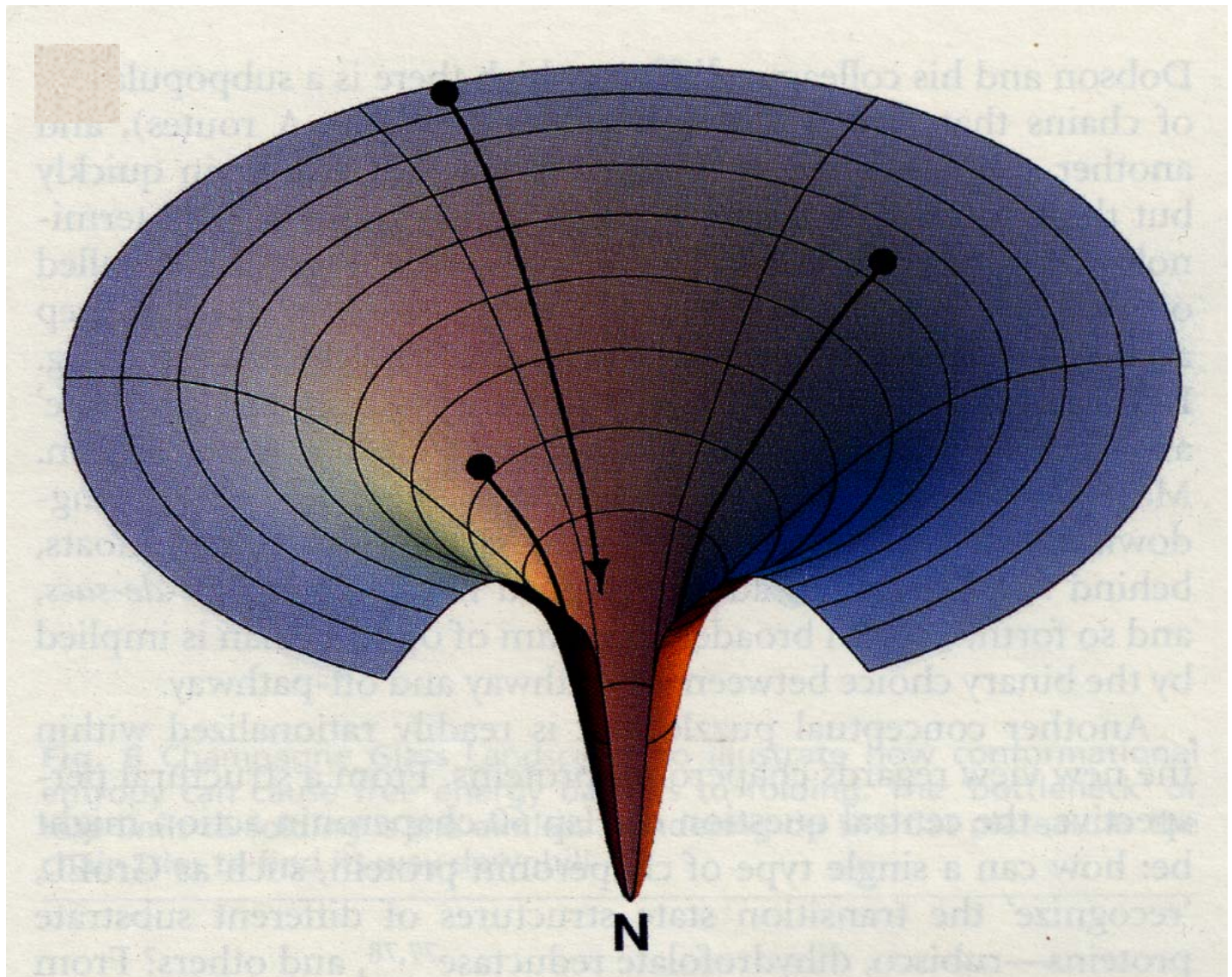
Das Levinthal-Paradoxon der Proteinfaltung



The golf course landscape

Solution to Levinthal's paradox

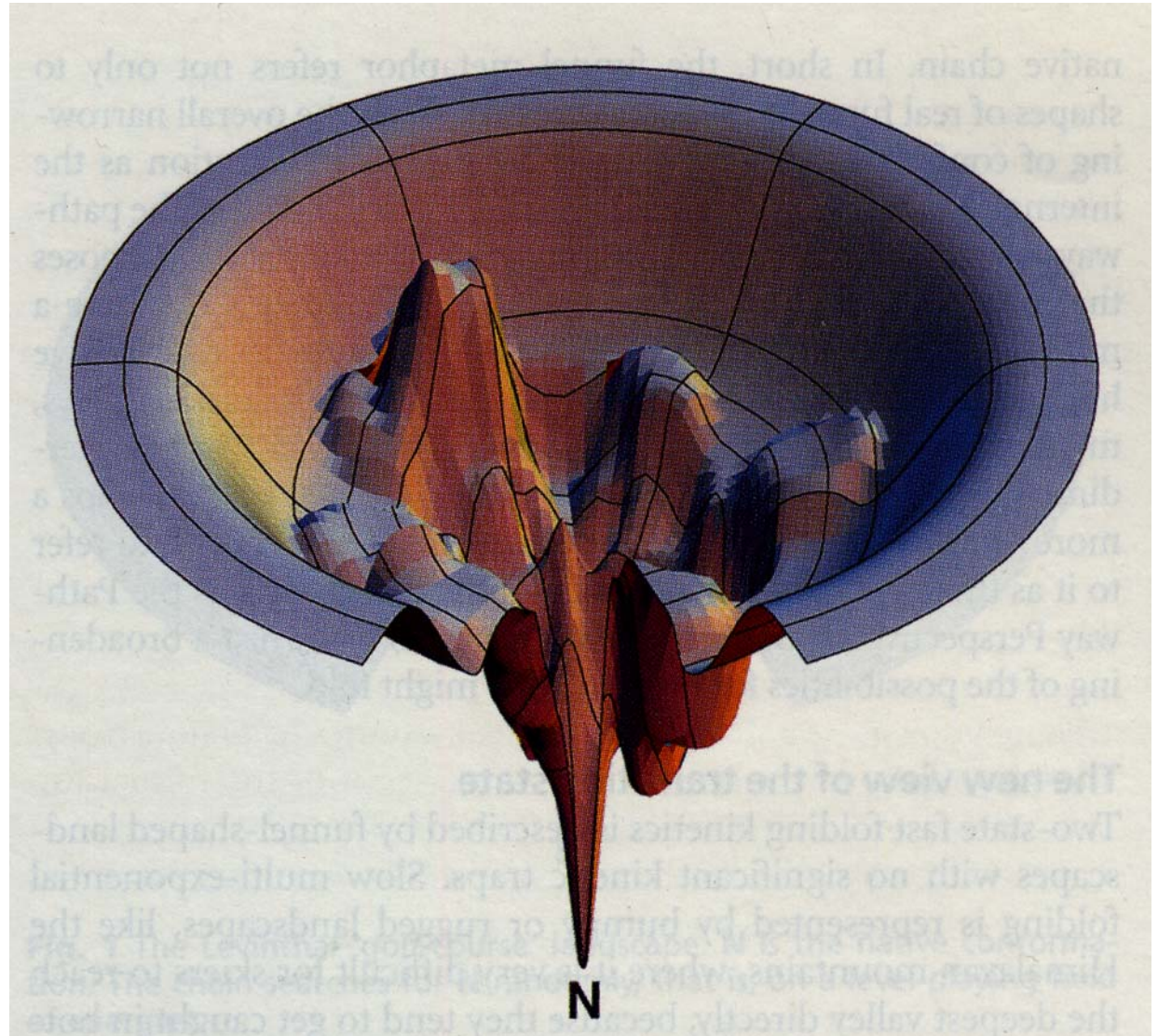
Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19



The funnel landscape

Solution to Levinthal's paradox

Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19

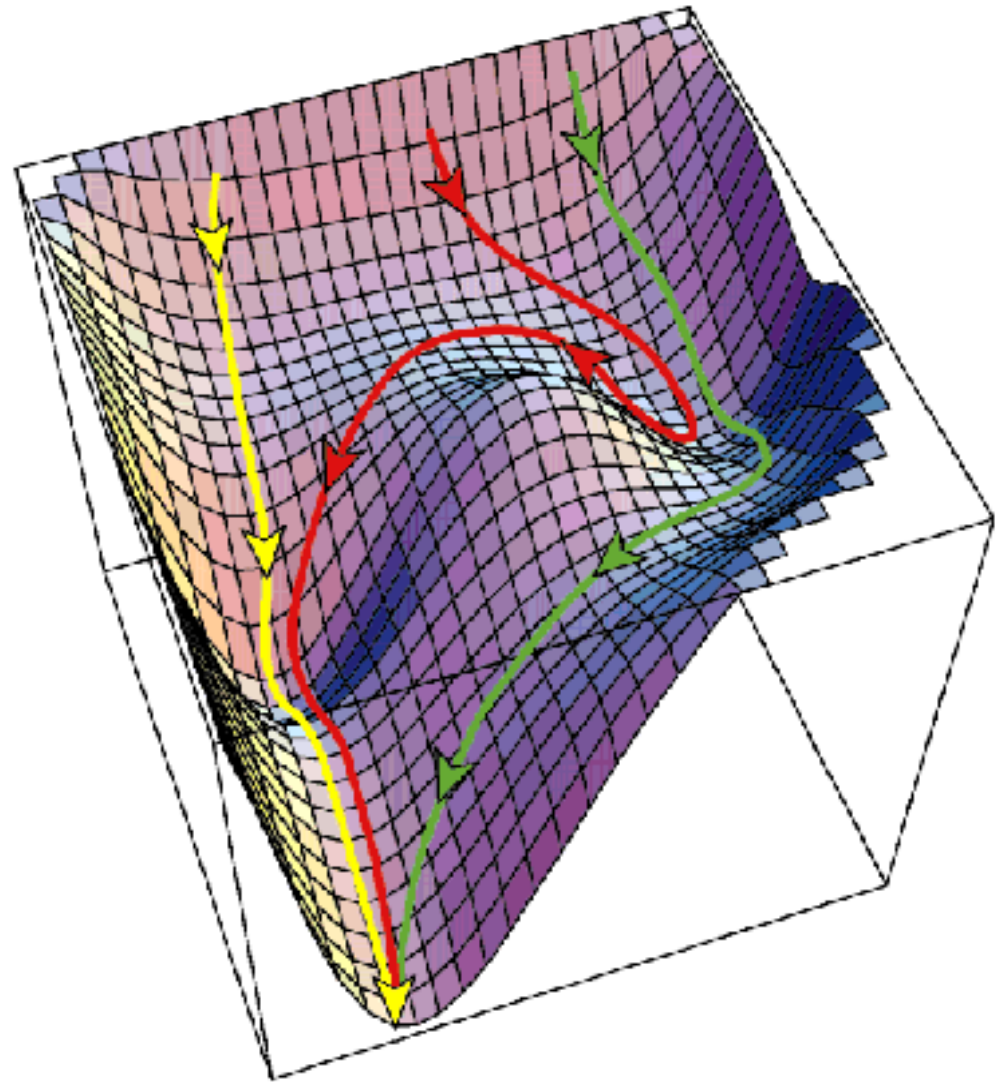


The structured funnel landscape

Solution to Levinthal's paradox

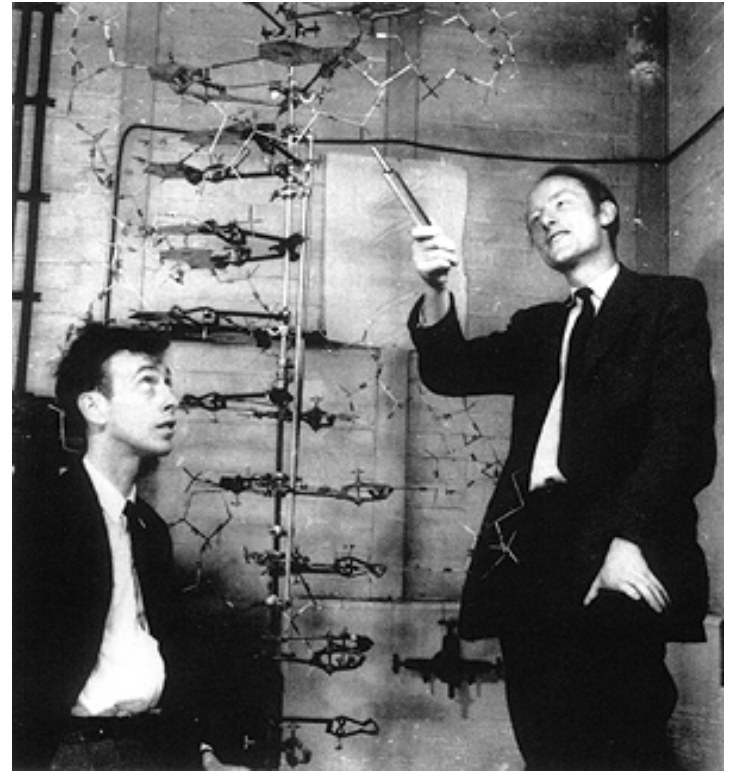
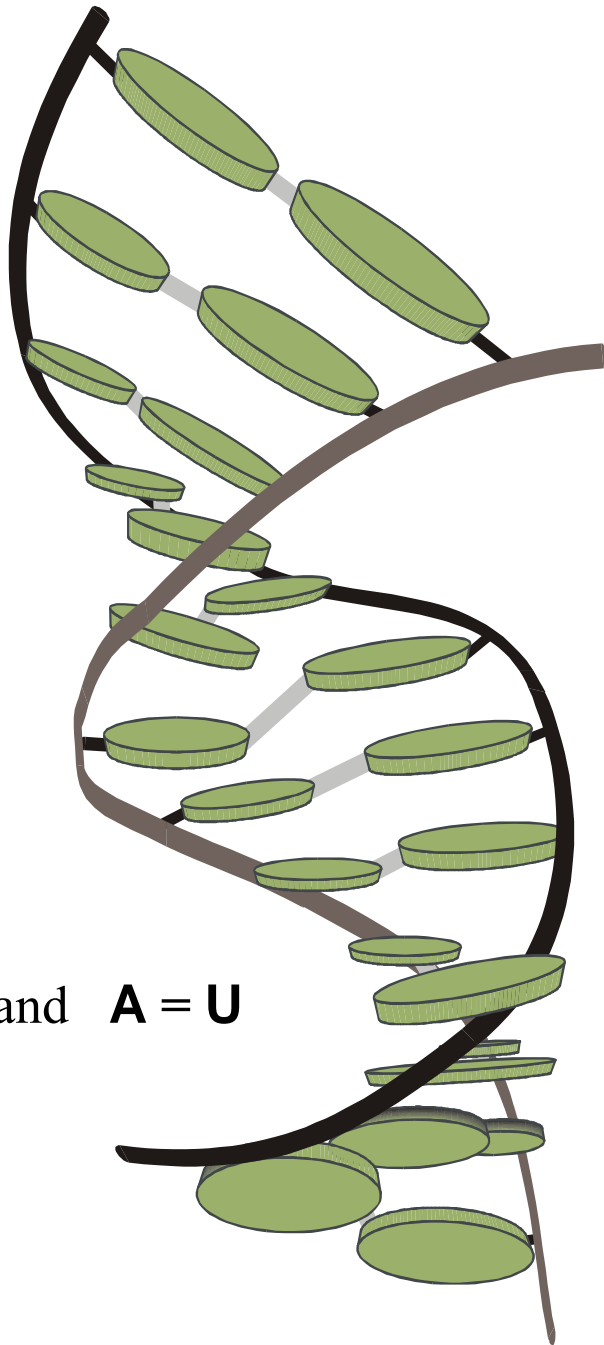
Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19

An “all-roads-lead-to-Rome” landscape



The reconstructed folding landscape
of a real biomolecule: “Lysozyme”

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James D. Watson, 1928- , and Francis Crick, 1916-2004,
Nobel Prize 1962

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

Selforganization of Matter and the Evolution of Biological Macromolecules

MANFRED EIGEN*

Max-Planck-Institut für Biophysikalische Chemie, Karl-Friedrich-Bonhoeffer-Institut, Göttingen-Nikolausberg

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I. Introduction

I.1. „Cause and Effect“

The question about the origin of life often appears as a question about "cause and effect". Physical theories of macroscopic processes usually involve answers to such questions, even if a statistical interpretation is given to the relation between "cause" and "effect". It is mainly due to the nature of this question that many scientists believe that our present physics does not offer any obvious explanation for the existence of life.

* Partly presented at the "Robbins Lectures" at Pomona College, California, in spring 1970.

The Hypercycle

A Principle of Natural Self-Organization

Part A: Emergence of the Hypercycle

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Max-Planck-Institut für biophysikalische Chemie, D-3400 Göttingen

Peter Schuster

Institut für theoretische Chemie und Strahlenchemie der Universität, A-1090 Wien

This paper is the first part of a trilogy, which comprises a detailed study of a special type of functional organization and demonstrates its relevance with respect to the origin and evolution of life. Self-replicating macromolecules, such as RNA or DNA in a suitable environment exhibit a behavior, which we may call Darwinian and which can be formally represented by the concept of the quasi-species. A quasi-species is defined as a given distribution of macromolecular species with closely interrelated sequences, dominated by one or several (hypothesized) master copies. External conditions enforce the selection of the best adapted distribution, automatically referred to as the wild-type. Most important for Darwinian behavior are the criteria for internal stability of the quasi-species. If these criteria are violated, the information stored in the nucleotide sequence of the master copy will disseminate irreversibly leading to an error catastrophe. As a consequence, selection and evolution of RNA or DNA molecules is limited with respect to the amount of information that can be stored in a single replicative unit. An analysis of experimental data regarding RNA and DNA replication at various levels of organization reveals, that a sufficient amount of information for the build up of a translation machinery can be gained only via integration of several different replicative units (reproduction cycles) through reciprocal linkages. A stable functional organization then will arise if the system to a low level of organization and thereby enlarge its information capacity continuously. The Hypercycle appears to be such a form of organization.

Preview on Part B: The Abstract Hypercycle

The mathematical analysis of dynamical systems using methods of differential topology yields the result that there is only one type of mechanism which fulfills the following requirements: The information stored in each single replicative unit (or reproductive cycle) must be maintained, i.e., the respective master copies must compete favorably with their error distributions. Despite their competitive behavior these units must establish a cooperation which includes all functionally integrated species. On the other hand, the cycle as a whole must continue to compete strongly with any other single entity or isolated ensemble which does not contribute to its integrated function. These requirements are crucial for a selection of the best adapted functionally linked ensemble and its evolutive optimization. Only

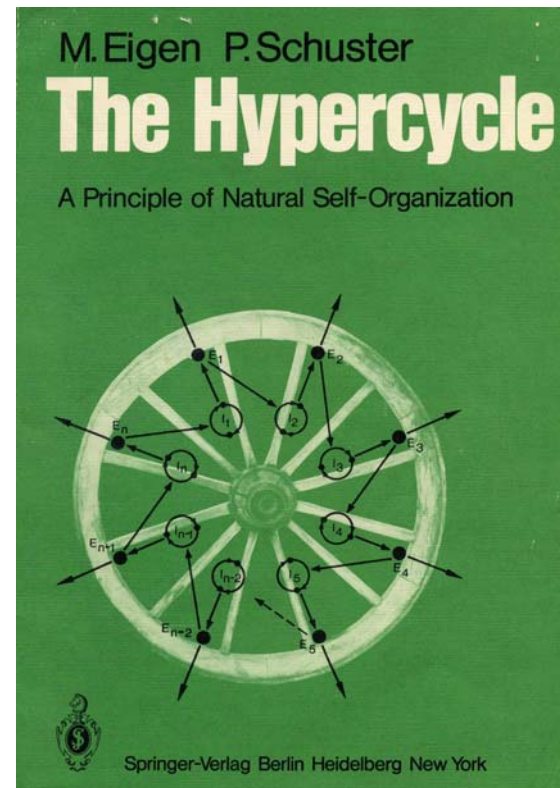
hypercyclic organizations are able to fulfil these requirements. Non-cyclic linkages among the autonomous reproduction cycles, such as chains or branched, one-line networks are devoid of such properties. The mathematical methods used for proving these assertions are fixed-point, Lyapunov and trajectory analysis in high-dimensional phase space, spanned by the concentration coordinates of the cooperating partners. The self-organizing properties of hypercycles are elucidated, using analytical as well as numerical techniques.

Preview on Part C: The Abstract Hypercycle

A realistic model of a hypercycle relevant with respect to the origin of the genetic code and the translation machinery is presented. It includes the following features referring to natural systems: 1) The hypercycle has a sufficiently simple structure to admit an organization with finite probability under prebiotic conditions. 2) It permits a continuous emergence from closely interrelated (in RNA-Shell) precursors, originally being members of a stable RNA quasi-species and having been amplified to a level of higher abundance. 3) The organizational structure and the properties of single functional units of this hypercycle are well reflected in the present genetic code in the translation apparatus of the prokaryotic cell, as well as in certain bacterial viruses.

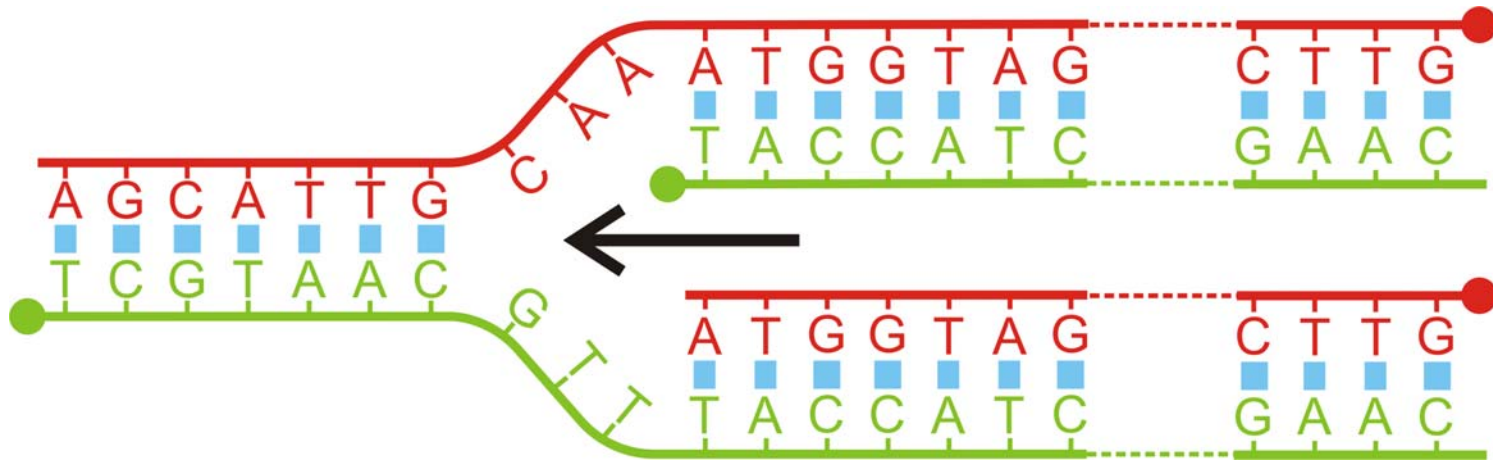
I. The Paradigm of Unity and Diversity in Evolution

Why do millions of species, plants and animals, exist, while there is only one basic molecular machinery of the cell, one universal genetic code and unique chiralities of the macromolecules? The geneticists of our day would not hesitate to give an immediate answer to the first part of this question. Diversity of species is the outcome of the tremendous branching process of evolution with its myriads of single steps of reproduction and mutation. It in-



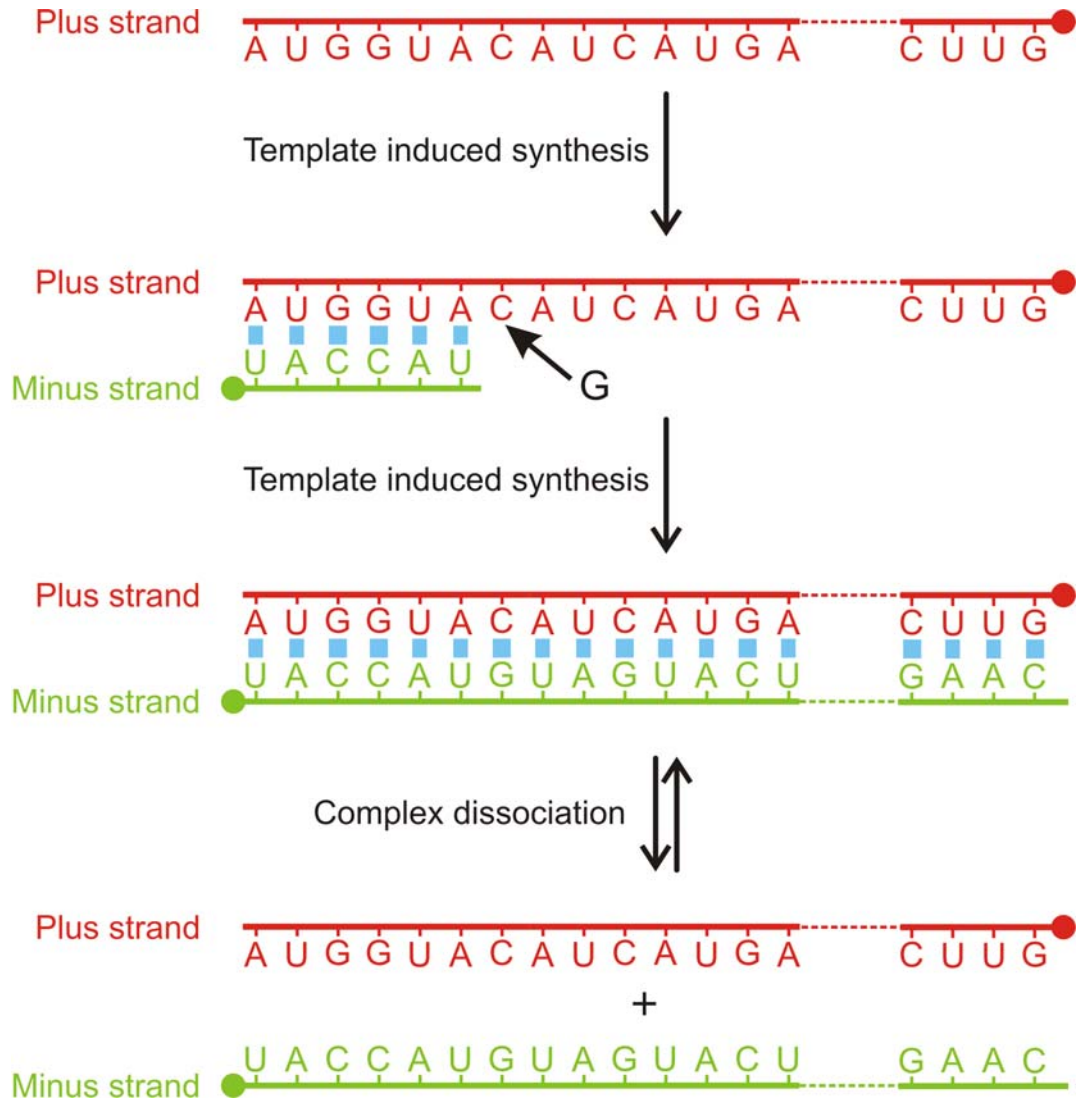
Chemical kinetics of molecular evolution

M. Eigen, P. Schuster, 'The Hypercycle', Springer-Verlag, Berlin 1979



,'Replication fork' in DNA replication

The mechanism of DNA replication is ,semi-conservative'



Complementary replication is the simplest copying mechanism of RNA.

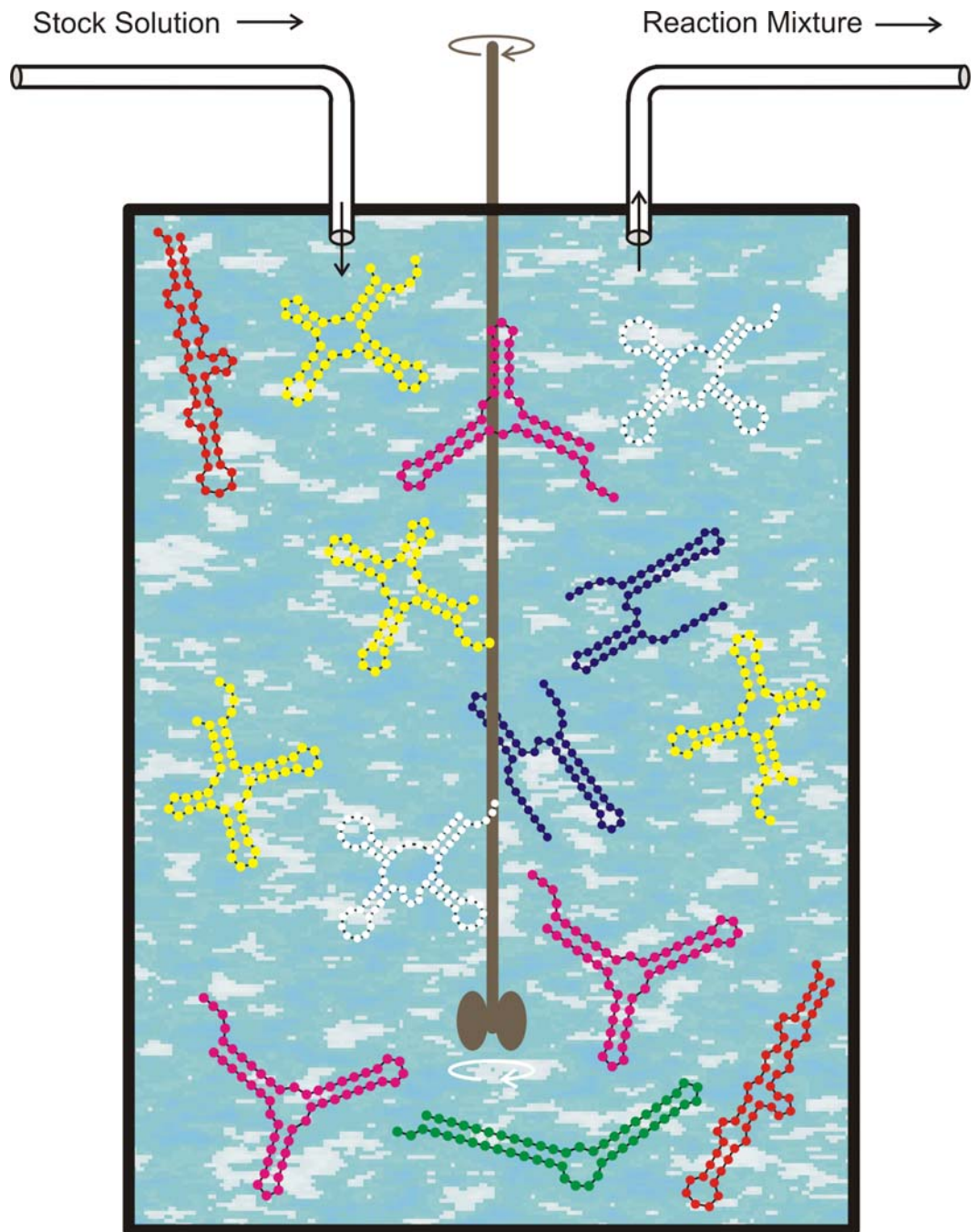
Complementarity is determined by Watson-Crick base pairs:

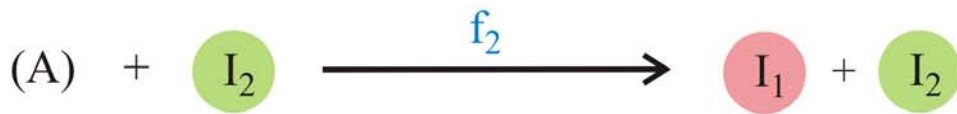
G≡C and **A=U**

Stock solution:

activated monomers, **ATP, CTP, GTP, UTP (TTP)**;
a replicase, an enzyme that performs complementary replication;
buffer solution

The flowreactor is a device for **studies** of evolution *in vitro* and *in silico*.





$$\begin{aligned} dx_1 / dt &= f_2 x_2 - x_1 \Phi \\ dx_2 / dt &= f_1 x_1 - x_2 \Phi \end{aligned}$$

$$\Phi = \sum_i f_i x_i ; \quad \sum_i x_i = 1 ; \quad i=1,2$$

Complementary replication as the simplest molecular mechanism of reproduction

Equation for complementary replication: $[I_i] = x_i \geq 0$, $f_i > 0$; $i=1,2$

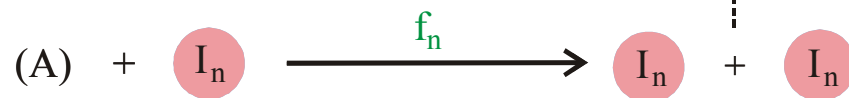
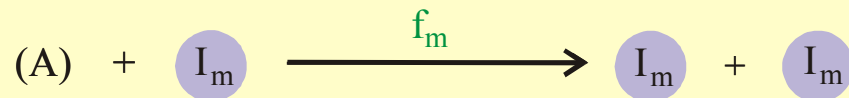
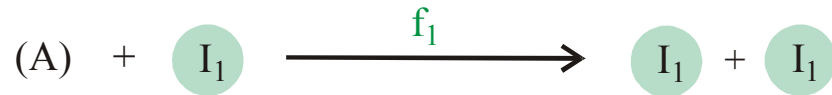
$$\frac{dx_1}{dt} = f_2 x_2 - x_1 \phi, \quad \frac{dx_2}{dt} = f_1 x_1 - x_2 \phi, \quad \phi = f_1 x_1 + f_2 x_2 = \bar{f}$$

Solutions are obtained by integrating factor transformation

$$x_{1,2}(t) = \frac{\sqrt{f_{2,1}} (\gamma_1(0) \cdot \exp(ft) + \gamma_2(0) \cdot \exp(-ft))}{(\sqrt{f_1} + \sqrt{f_2}) \gamma_1(0) \cdot \exp(ft) - (\sqrt{f_1} - \sqrt{f_2}) \gamma_2(0) \cdot \exp(-ft)}$$

$$\gamma_1(0) = \sqrt{f_1} x_1(0) + \sqrt{f_2} x_2(0), \gamma_2(0) = \sqrt{f_1} x_1(0) - \sqrt{f_2} x_2(0), f = \sqrt{f_1 f_2}$$

$$x_1(t) \rightarrow \frac{\sqrt{f_2}}{\sqrt{f_1} + \sqrt{f_2}} \quad \text{and} \quad x_2(t) \rightarrow \frac{\sqrt{f_1}}{\sqrt{f_1} + \sqrt{f_2}} \quad \text{as} \quad \exp(-ft) \rightarrow 0$$



$$dx_i / dt = f_i x_i - x_i \Phi = x_i (f_i - \Phi)$$

$$\Phi = \sum_j f_j x_j ; \quad \sum_j x_j = 1 ; \quad i, j = 1, 2, \dots, n$$

$$[I_i] = x_i \geq 0 ; \quad i = 1, 2, \dots, n ;$$

$$[A] = a = \text{constant}$$

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

$$x_m(t) \rightarrow 1 \text{ for } t \rightarrow \infty$$

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

Selection equation: $[I_i] = x_i \geq 0, f_i > 0$

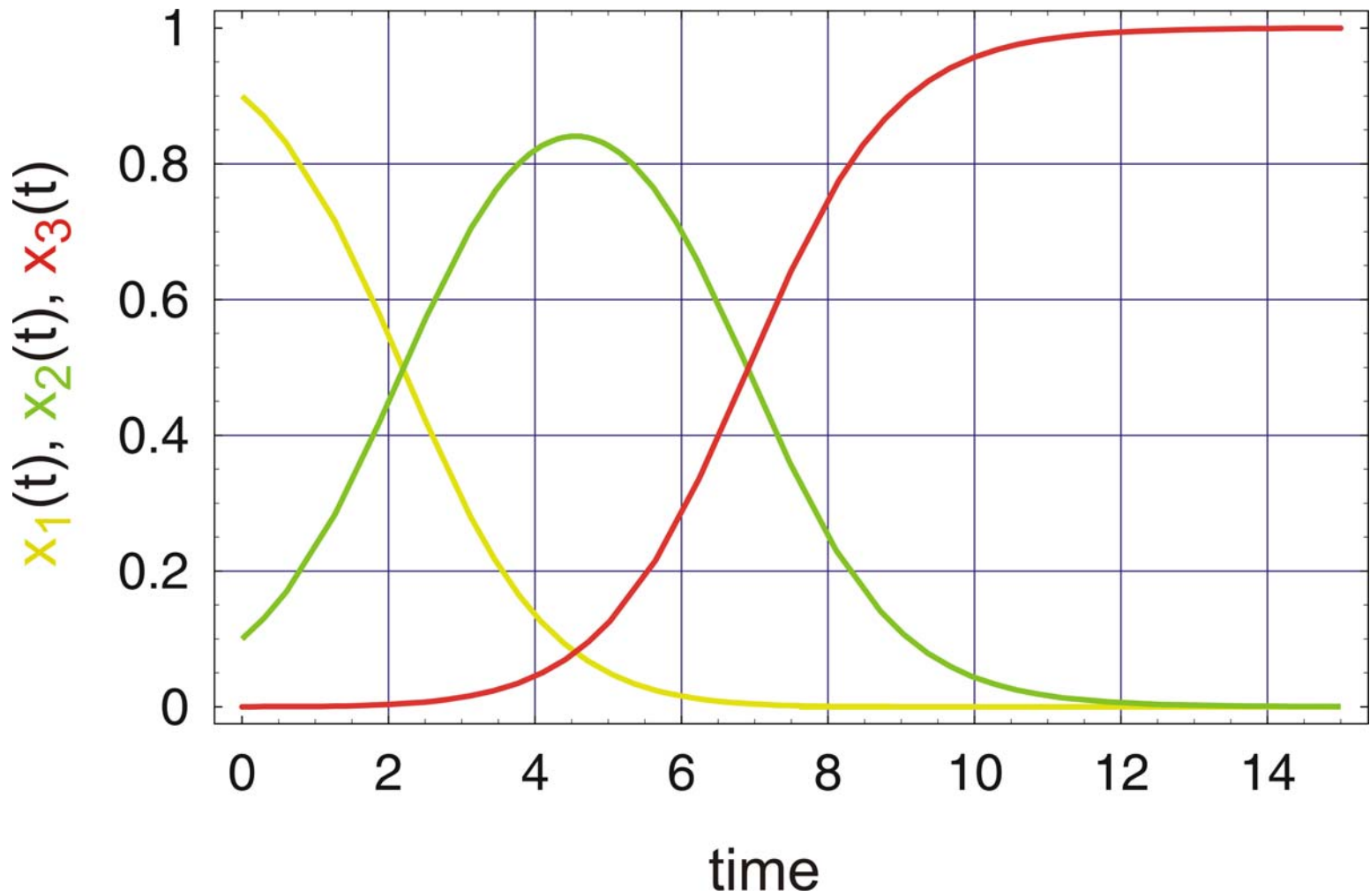
$$\frac{dx_i}{dt} = x_i (f_i - \phi), \quad i=1,2,\dots,n; \quad \sum_{i=1}^n x_i = 1; \quad \phi = \sum_{j=1}^n f_j x_j = \bar{f}$$

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

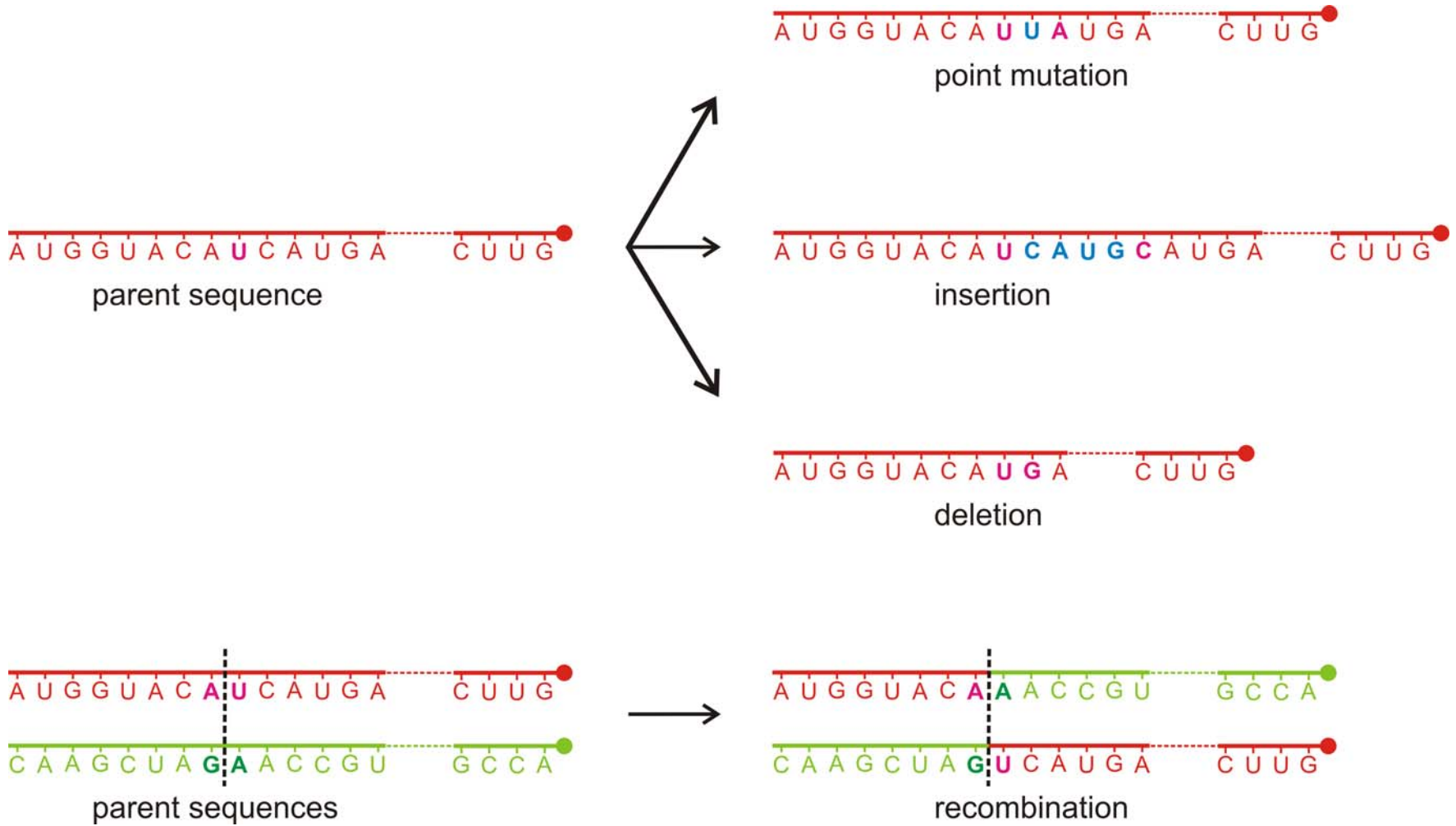
$$\frac{d\phi}{dt} = \sum_{i=1}^n f_i \frac{dx_i}{dt} = \overline{f^2} - (\bar{f})^2 = \text{var}\{f\} \geq 0$$

Solutions are obtained by integrating factor transformation

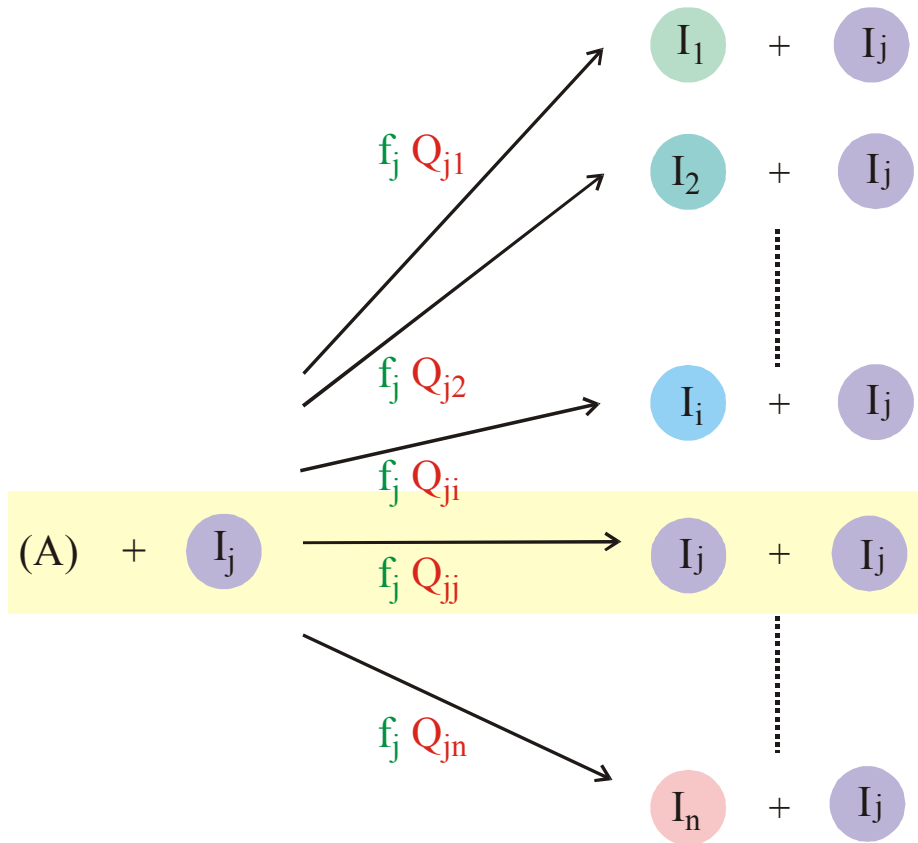
$$x_i(t) = \frac{x_i(0) \cdot \exp(f_i t)}{\sum_{j=1}^n x_j(0) \cdot \exp(f_j t)}; \quad i = 1, 2, \dots, n$$



Selection between three species with $f_1 = 1$, $f_2 = 2$, and $f_3 = 3$



Variation of genotypes through mutation and recombination



$$\frac{dx_i}{dt} = \sum_j f_j Q_{ji} x_j - x_i \Phi$$

$$\Phi = \sum_j f_j x_j ; \quad \sum_j x_j = 1 ; \quad \sum_i Q_{ij} = 1$$

$$[I_i] = x_i \geq 0 ; \quad i = 1, 2, \dots, n ;$$

$$[A] = a = \text{constant}$$

$$Q_{ij} = (1-p)^{\ell-d(i,j)} p^{d(i,j)}$$

p Error rate per digit

ℓ Chain length of the polynucleotide

$d(i,j)$ Hamming distance between I_i and I_j

Chemical kinetics of replication and mutation as parallel reactions

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

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

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

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

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

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

Perron-Frobenius theorem applied to the value matrix W

W is primitive: (i) λ_0 is real and strictly positive

(ii) $\lambda_0 > |\lambda_k|$ for all $k \neq 0$

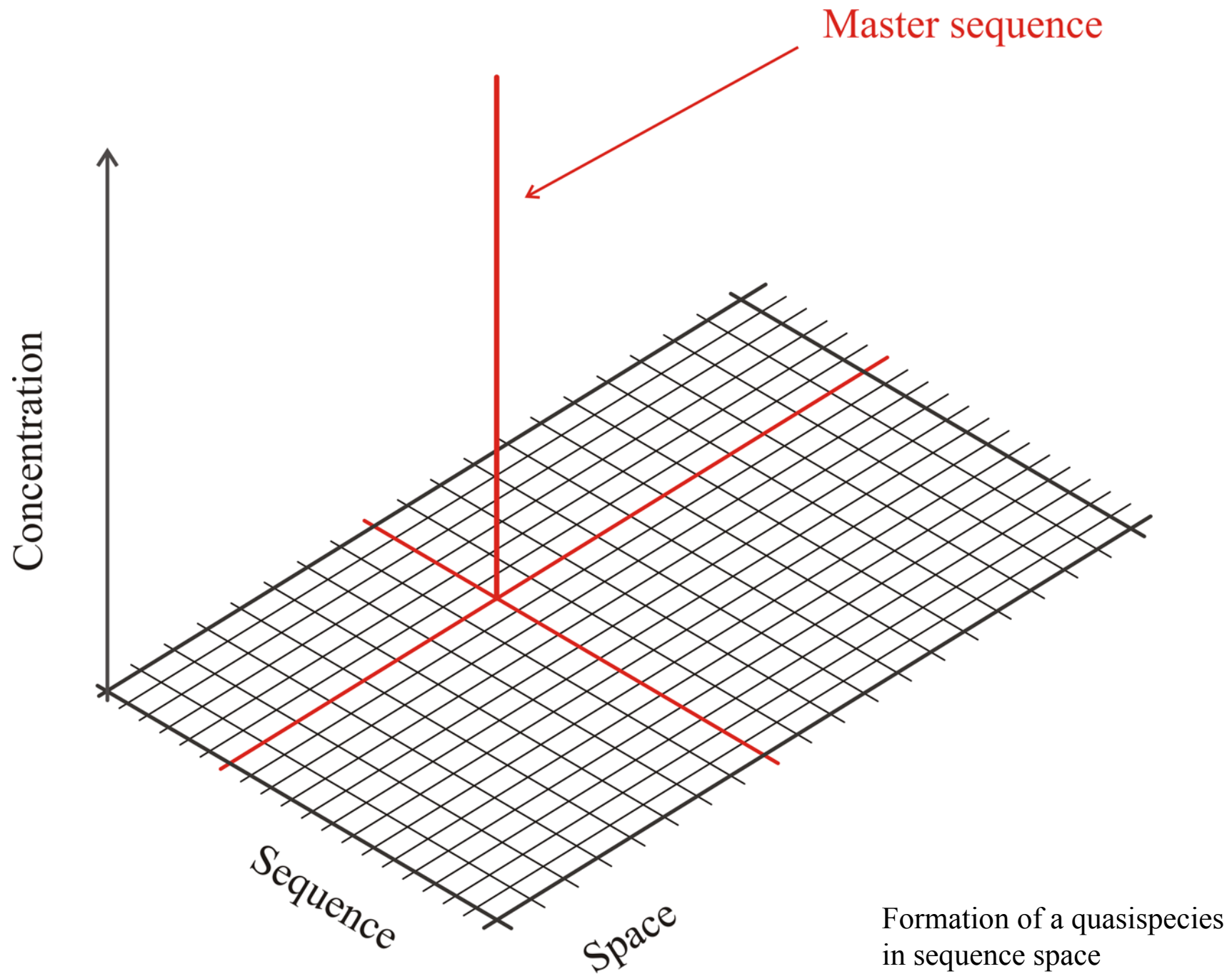
(iii) λ_0 is associated with strictly positive eigenvectors

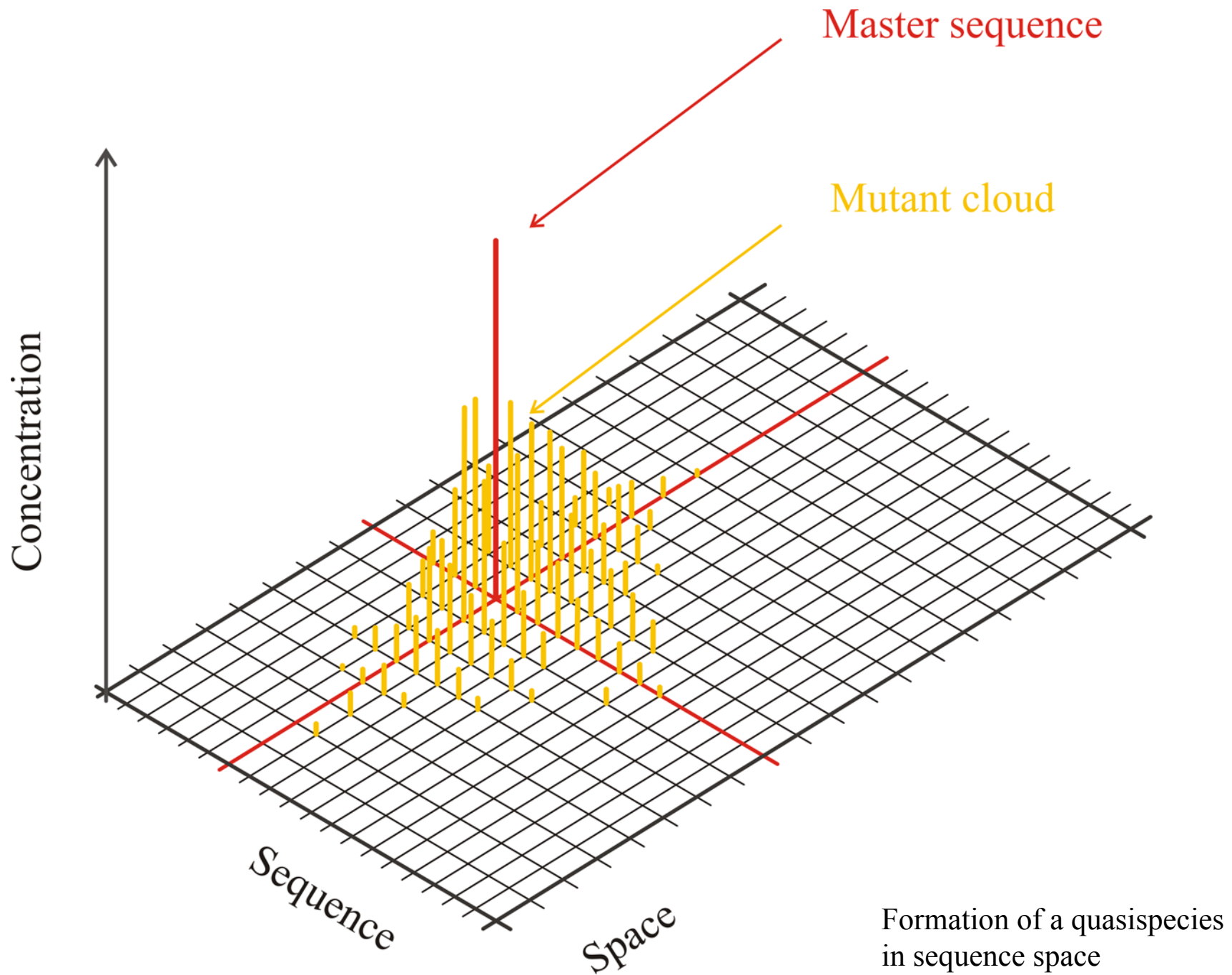
(iv) λ_0 is a simple root of the characteristic equation of W

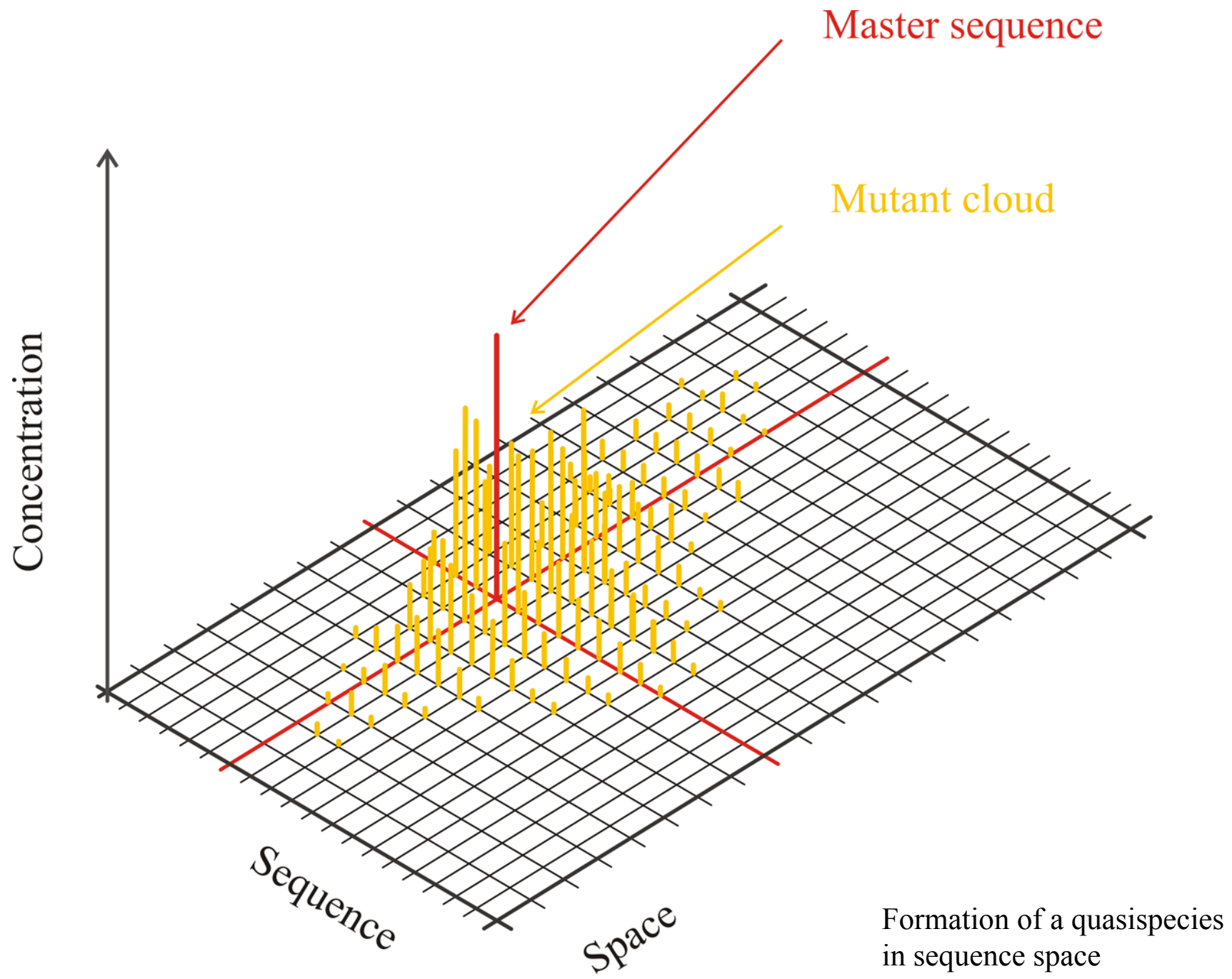
(v-vi) etc.

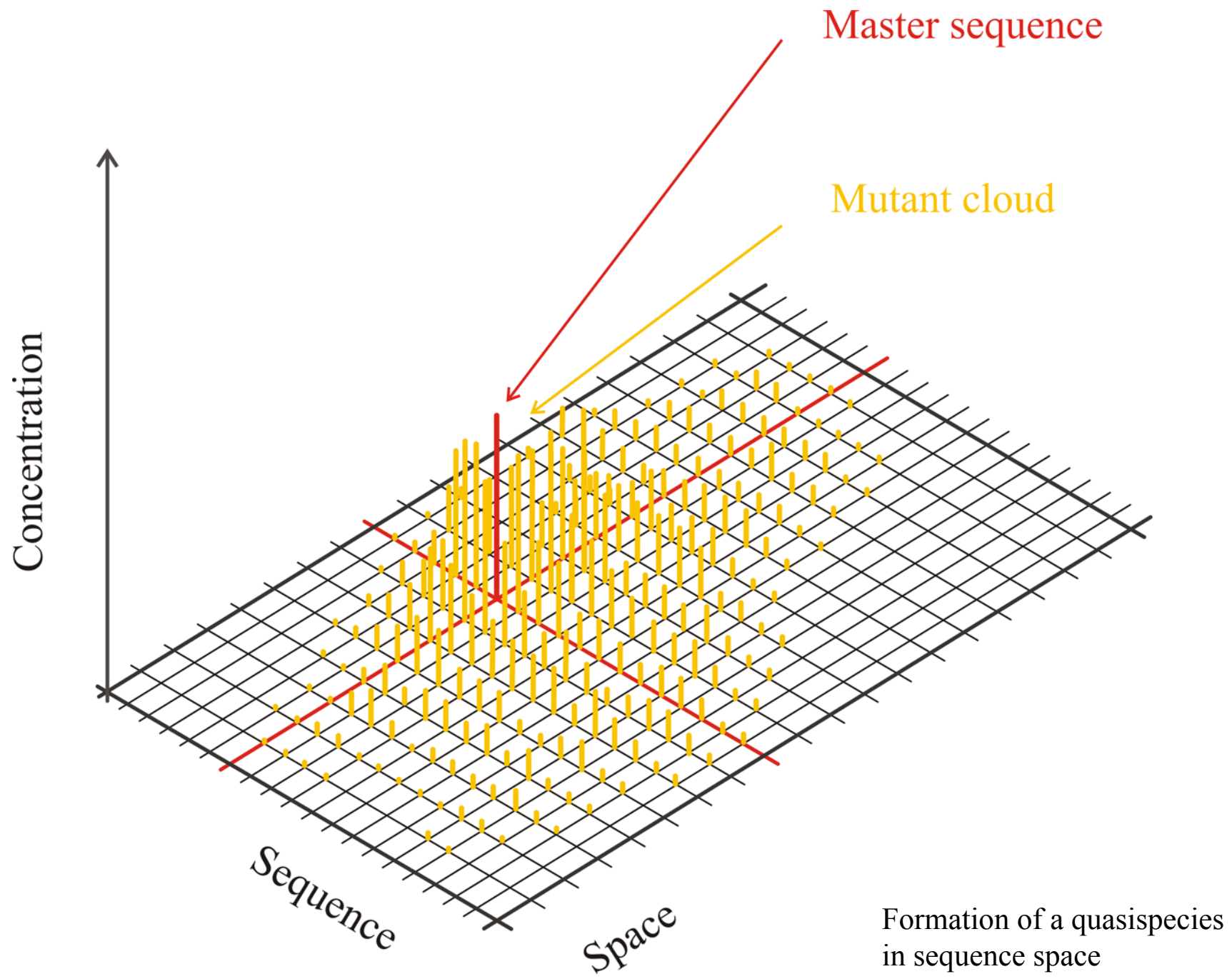
W is irreducible: (i), (iii), (iv), etc. as above

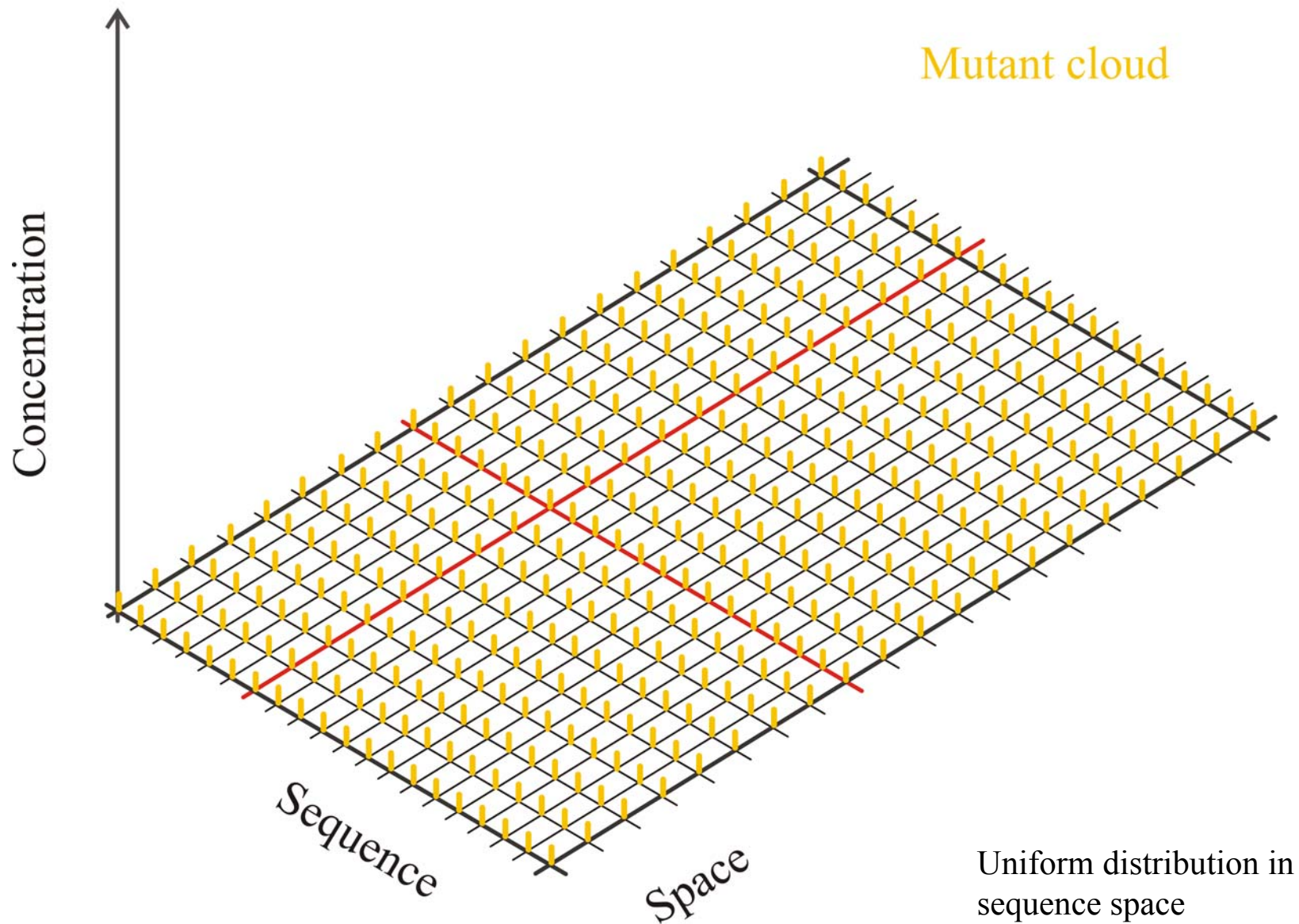
(ii) $\lambda_0 \geq |\lambda_k|$ for all $k \neq 0$











SELF-REPLICATION WITH ERRORS

A MODEL FOR POLYNUCLEOTIDE REPLICATION**

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 Revised manuscript received 23rd August 1982
 Accepted 30th August 1982

Key words: Polynucleotide replication; Quasi-species; Point mutation; Mutant class; Stochastic replication

A model for polynucleotide replication is presented and analyzed by means of perturbation theory. Two basic assumptions allow handling of sequences up to a chain length of $n = 30$ explicitly: point mutations are restricted to a two-digit model and individual sequences are subsumed into mutant classes. Perturbation theory is in excellent agreement with the exact results for long enough sequences ($n > 20$).

1. Introduction

Eigen [8] proposed a formal kinetic equation (eq. 1) which describes self-replication under the constraint of constant total population size:

$$\frac{dx_i}{dt} = x_i \left(\sum_j w_{ij} x_j - \frac{x_i}{c} \phi \right); i = 1, \dots, n \quad (1)$$

By x_i we denote the population number or concentration of the self-replicating element I_i , i.e., $x_i = [I_i]$. The total population size or total concentration $c = \sum_i x_i$ is kept constant by proper adjustment of the constraint $\phi = \sum_i \sum_j w_{ij} x_j x_i$. Characteristically, this constraint has been called 'concomitant organization'. The relative values of diagonal

(w_{ii}) and off-diagonal ($w_{ij}, i \neq j$) rates, as we shall see in detail in section 2, are related to the accuracy of the replication process. The specific properties of eq. 1 are essentially based on the fact that it leads to exponential growth in the absence of constraints ($\phi = 0$) and competitors ($n = 1$).

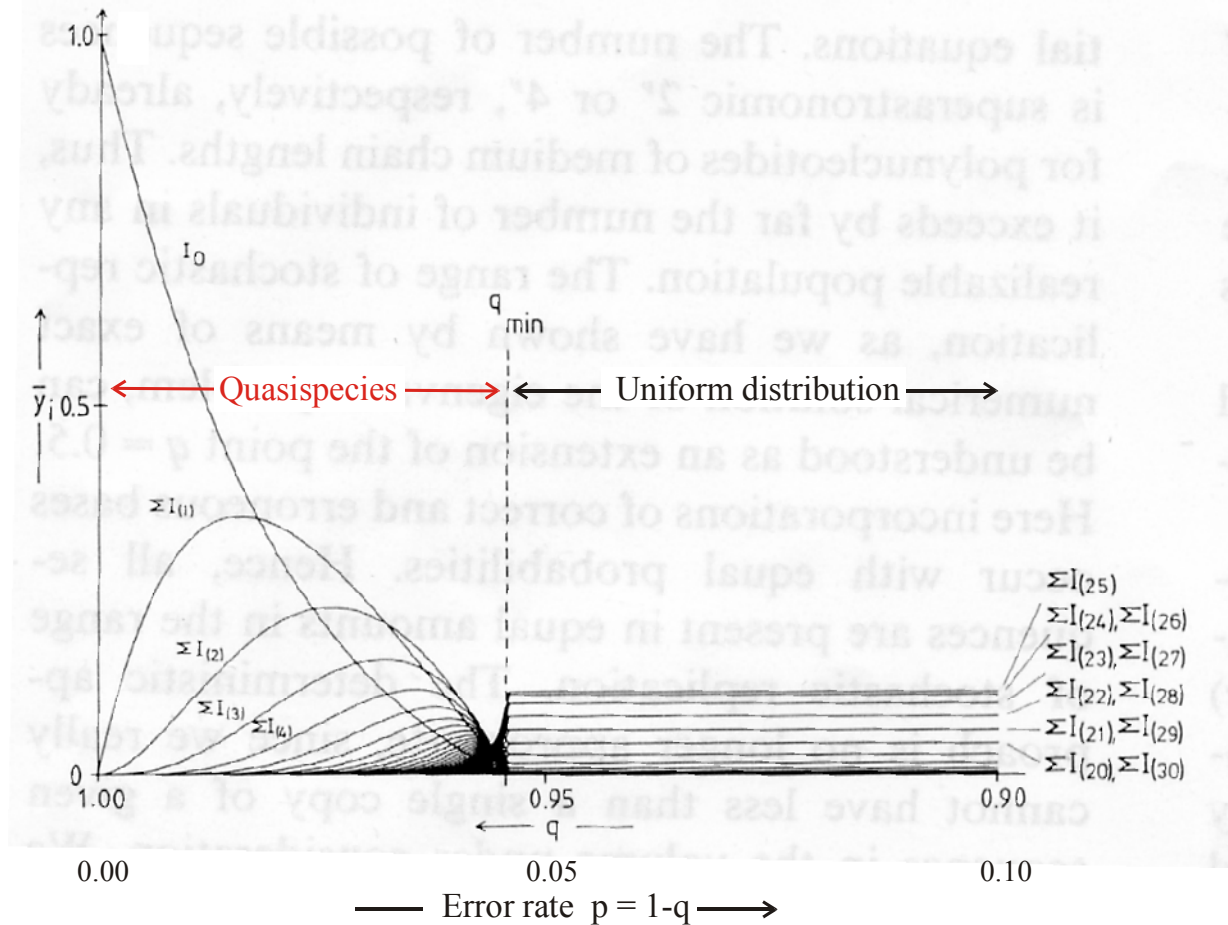
The non-linear differential equation, eq. 1 – the non-linearity is introduced by the definition of ϕ at constant organization – shows a remarkable feature: it leads to selection of a defined ensemble of self-replicating elements above a certain accuracy threshold. This ensemble of a master and its most frequent mutants is a so-called 'quasi-species' [9]. Below this threshold, however, no selection takes place and the frequencies of the individual elements are determined exclusively by their statistical weights.

Rigorous mathematical analysis has been performed on eq. 1 [7,15,24,26]. In particular, it was shown that the non-linearity of eq. 1 can be removed by an appropriate transformation. The eigenvalue problem of the linear differential equation obtained thereby may be solved approximately by the conventional perturbation technique

* Dedicated to the late Professor B.L. Jones who was among the first to do rigorous mathematical analysis on the problems described here.

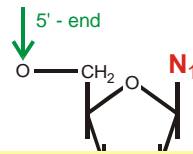
** This paper is considered as part II of Model Studies on RNA replication. Part I is by Gassner and Schuster [14].

† All summations throughout this paper run from 1 to n unless specified differently: $\Sigma_i = \Sigma_{i=1}^n$ and $\Sigma_{i,j} = \Sigma_{i=1}^n + \Sigma_{j=1}^n$, respectively.

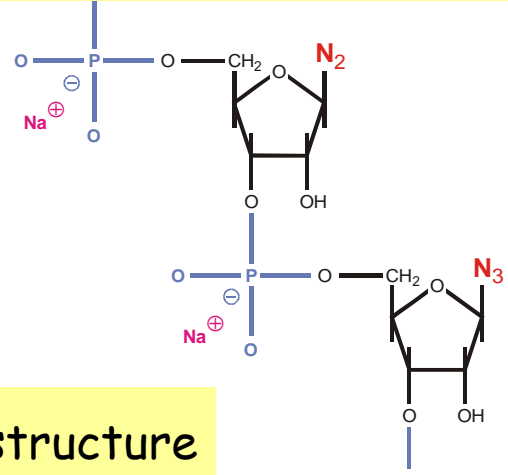


Quasispecies as a function of the replication accuracy q

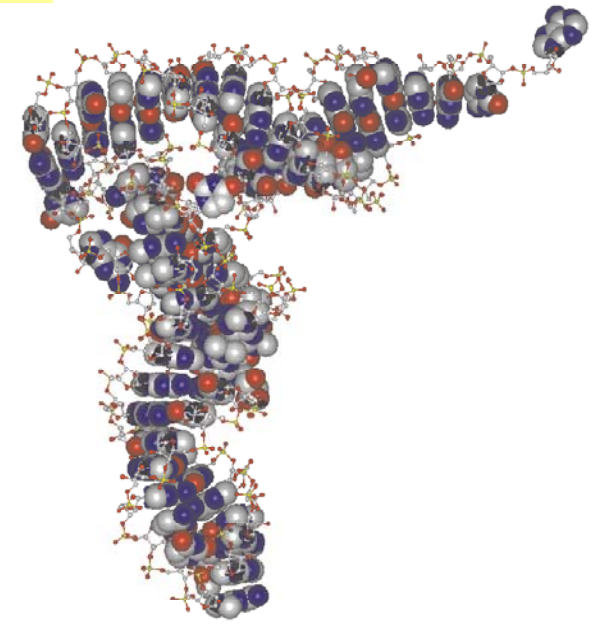
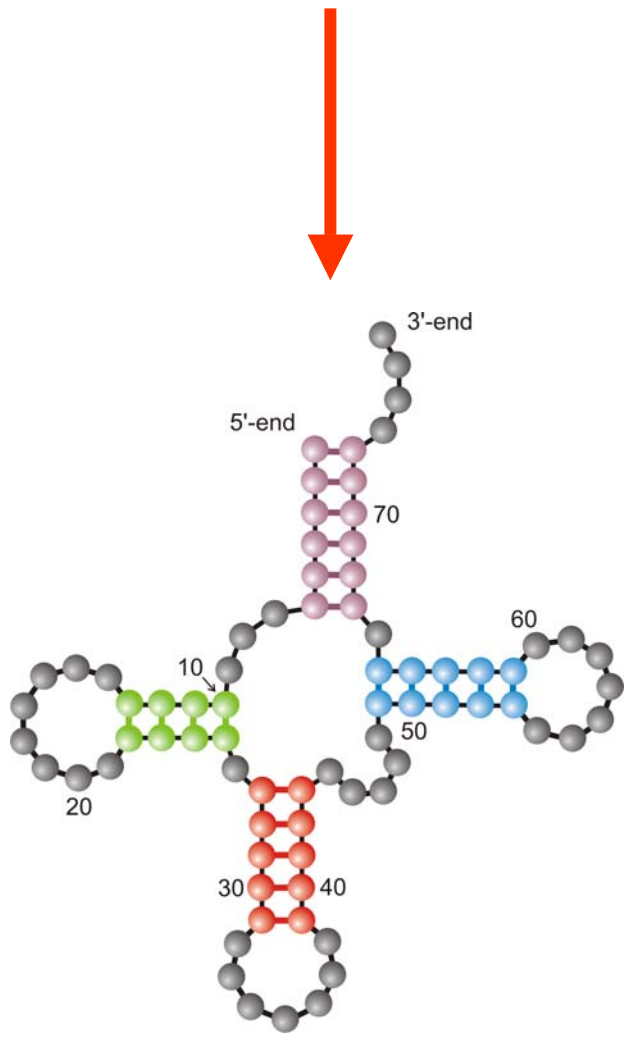
1. Evolution - organismisch und molekular
2. Wahrscheinlichkeiten in der Biologie
3. Vermehrung, Mutation und Selektion
- 4. Molekulares Design**
5. Evolution von Molekülen und Optimierung
6. Die Komplexität der Biologie

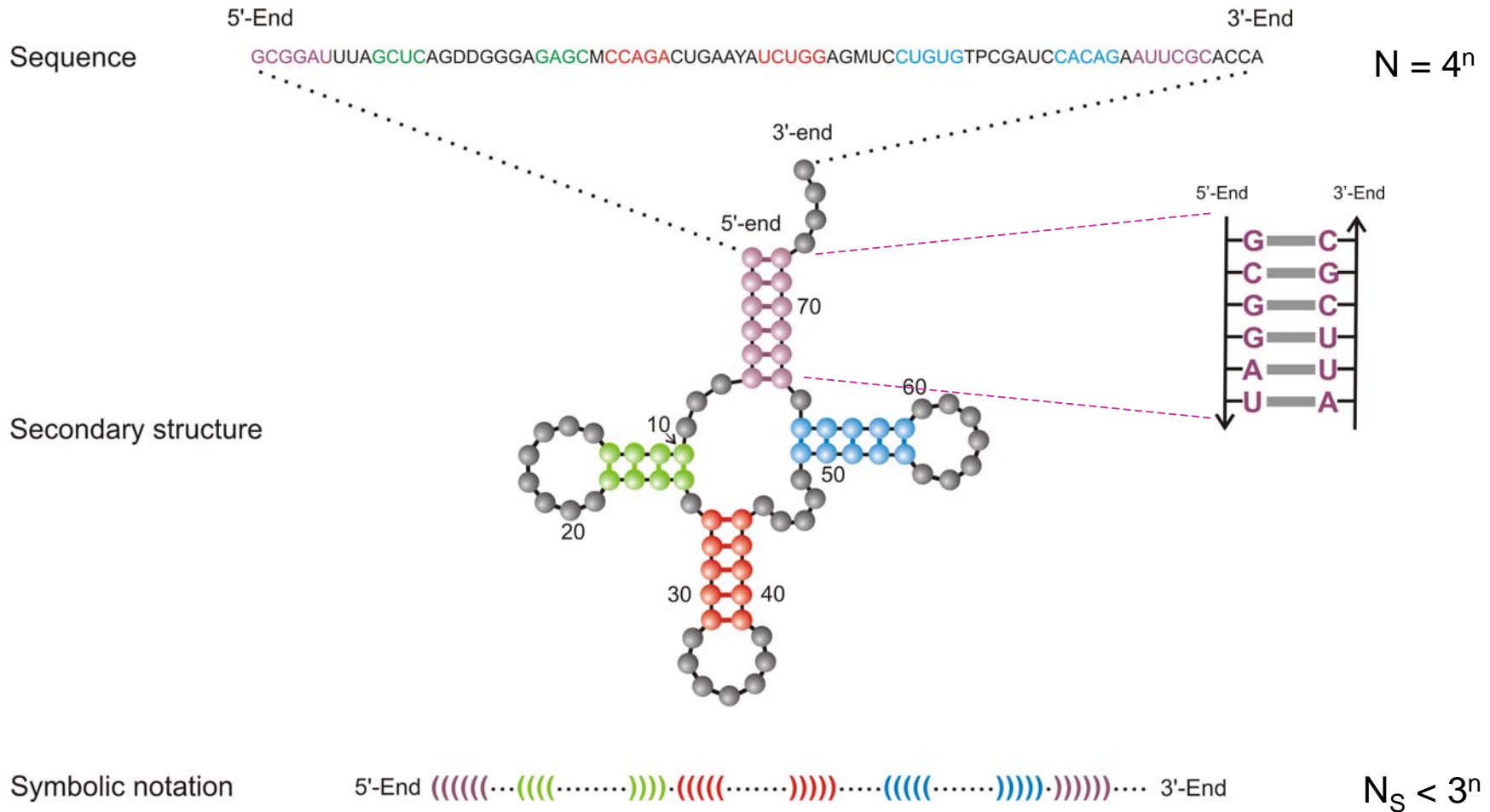


5'-end **GCGGAUUUAGCUC**AGUUGGGAGAG**CGCCAGACUGAAGAUCUGG**AGGUC**CUGUGUUCGAUCCACAGAAUUCGCACCA** 3'-end



Definition of RNA structure



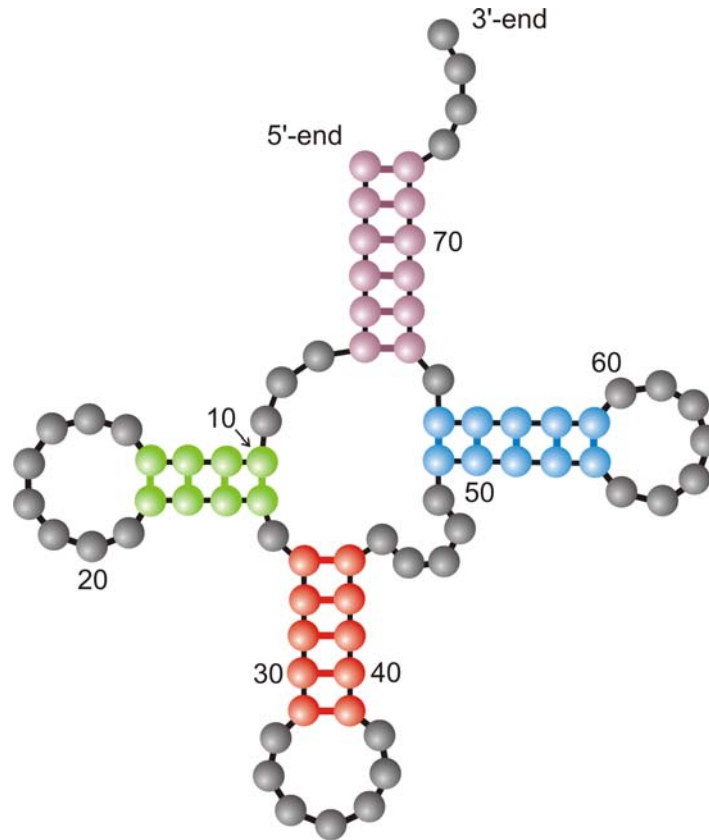


Criterion: Minimum free energy (mfe)

Rules: $_ (_) _ \in \{AU, CG, GC, GU, UA, UG\}$

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

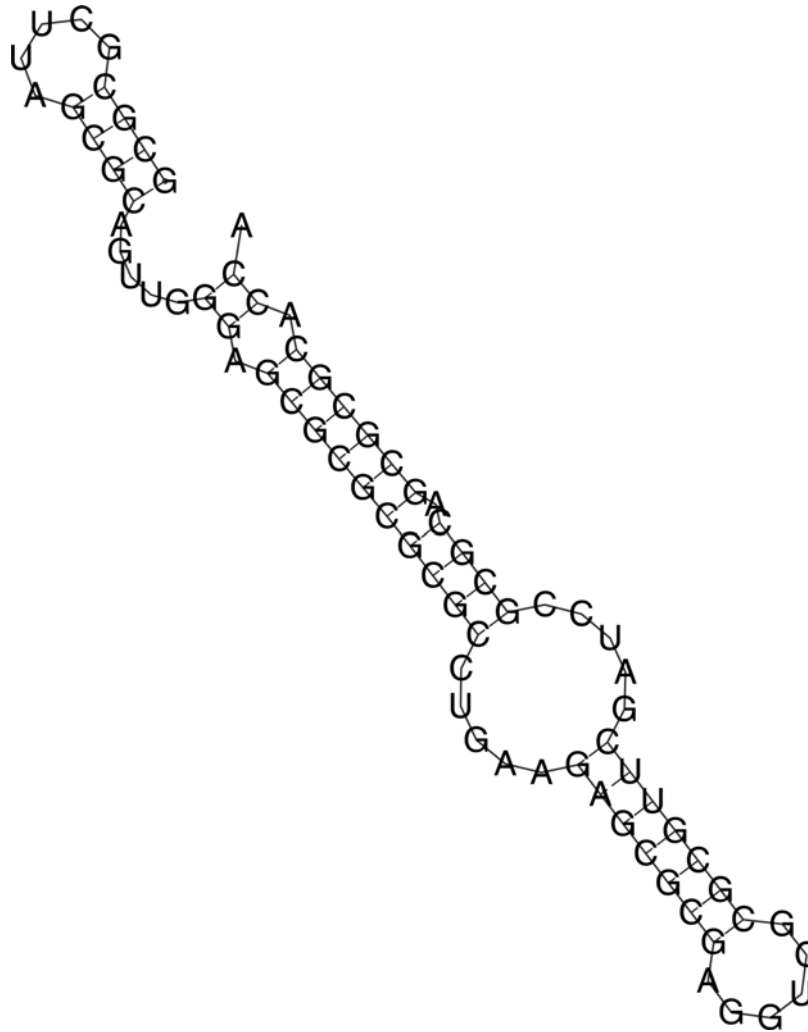
GCGGAU UUA G CUC AG DD GGG A GAG CM CCAGA CUGAAY AUCUGG AGMUC CUGUG TPCGAUC CACAGA AUUCGCACCA



$$\Delta G = -20.20 \text{ kcal/mol}$$

Sequenz und Struktur der Phenylalanyl-transfer-RNA

GCGCGC UUA GCGC AGU UGGG A GCGC GCGCGC CUGAAGA GCGCG AGGUC GCGCG UUCGAUC GCGCA GCGCGC ACCA



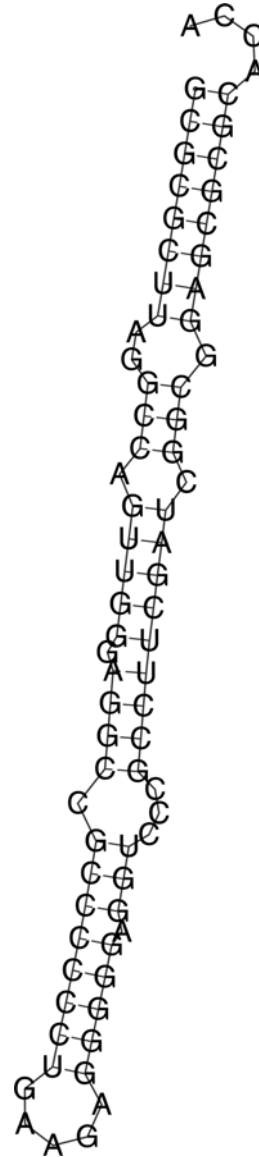
1. Designversuch

$$\Delta G = -43.10 (-36.40) \text{ kcal/mol}$$

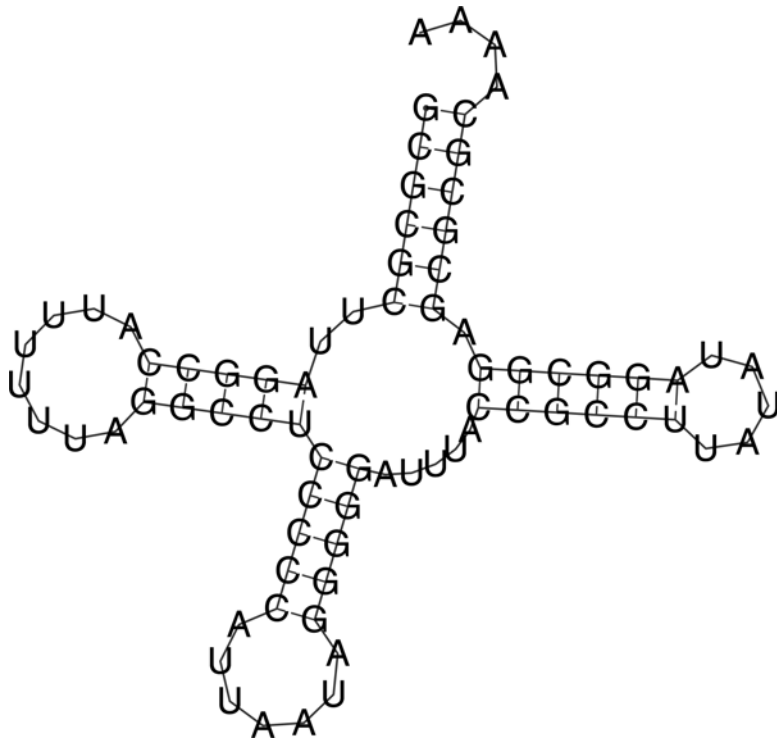
GCGCGCUUAGGCCAGUUGGGAGGCCGCCCCUCUGAAGAAGGGGAGGUCBCGCCUUCGAUCGGCGGAGCGCGCACCA

2. Designversuch

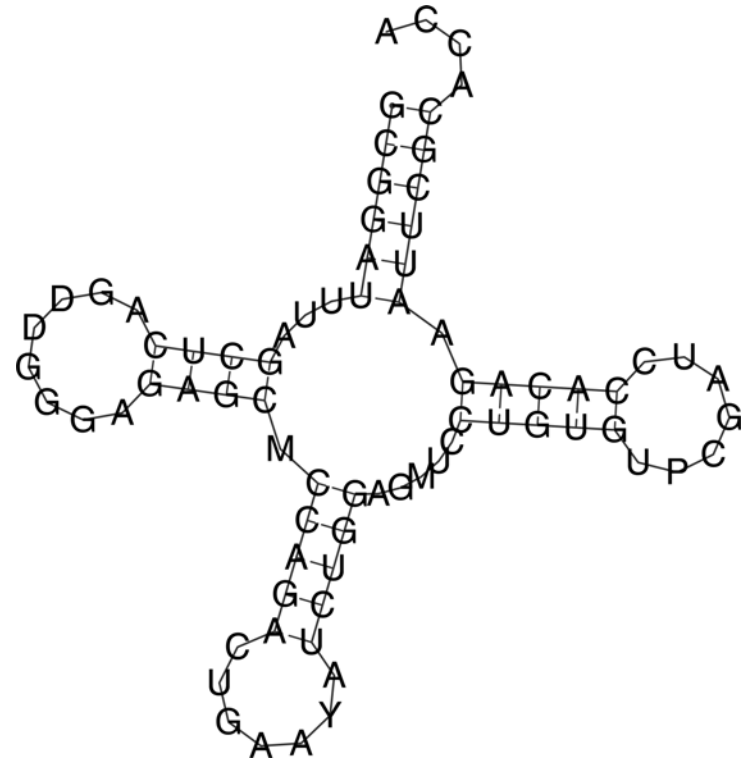
$\Delta G = -45.10$ (-39.40) kcal/mol



GCGCGCUUAGGCCAUUUUUUAGGCCUCCCCCAUUAUAUAGGGGAUUUAACGCCUUAUAUAGGCGGAGCGCGCAAAA



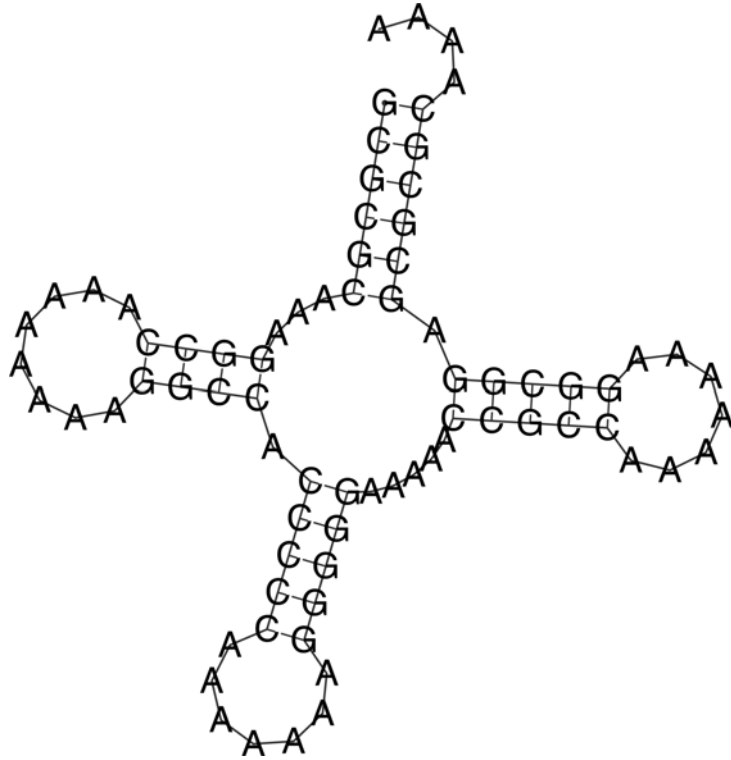
3. Designversuch



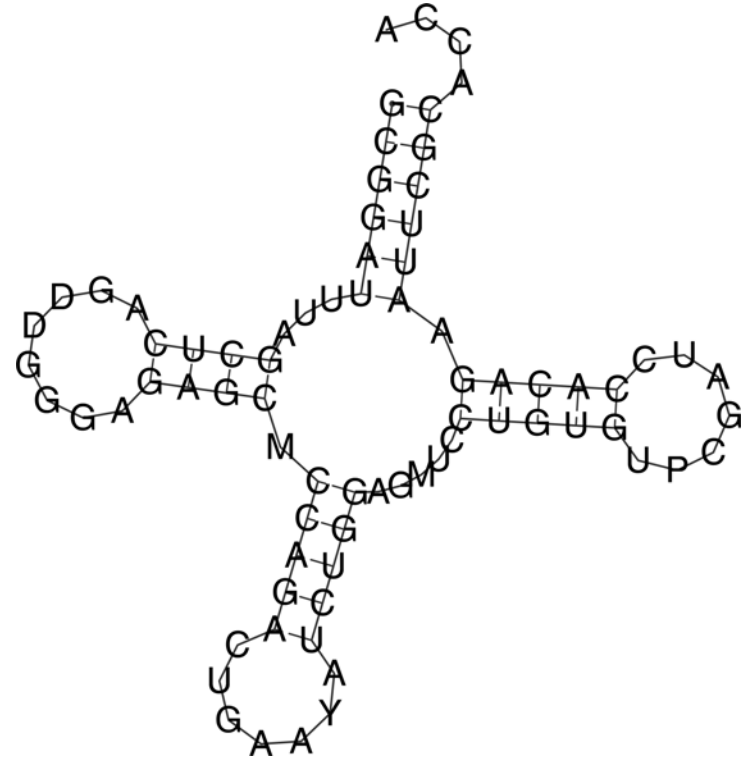
Zielstruktur

$$\Delta G = -41.80 \text{ (-39.90) kcal/mol}$$

GCGCGCAAAAGGCCAAAAAAAAAGGCCACCCCAAAAAAAAAAGGGGAAAAAACCGCCAAAAAAAAAGGCGGAGCGCGCAAAA

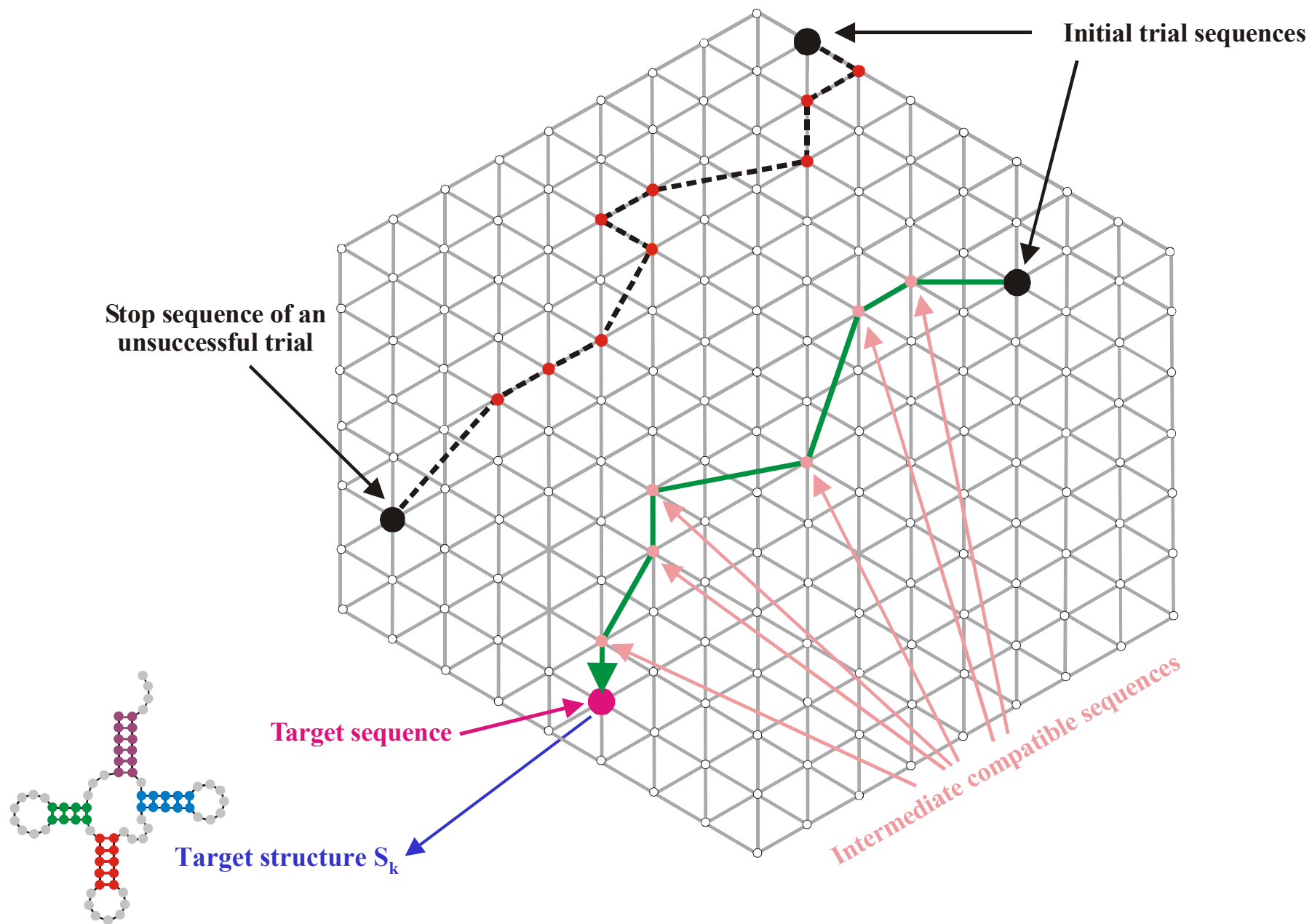


4. Designversuch



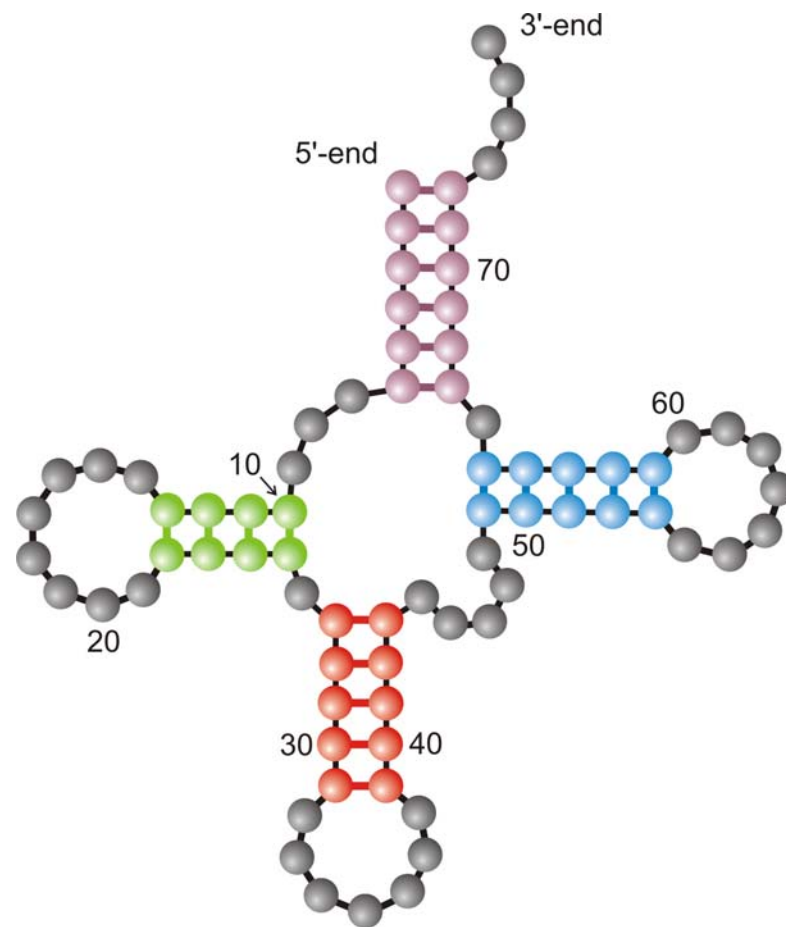
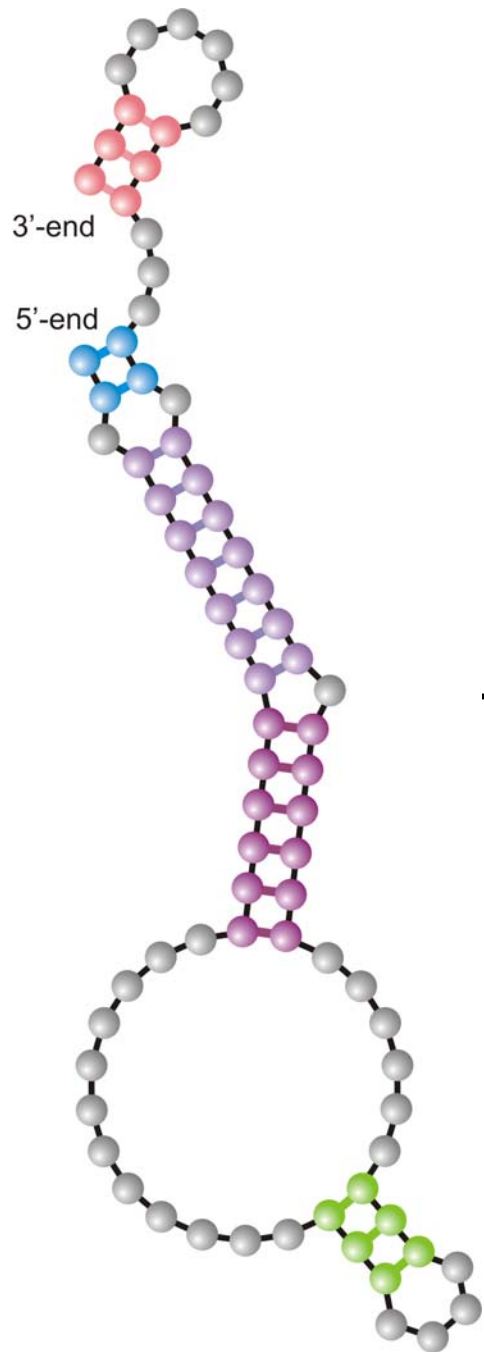
Zielstruktur

$$\Delta G = -40.70 \text{ kcal/mol}$$



Approach to the target structure S_k in the **inverse folding algorithm**

1. Evolution - organismisch und molekular
2. Wahrscheinlichkeiten in der Biologie
3. Vermehrung, Mutation und Selektion
4. Molekulares Design
- 5. Evolution von Molekülen und Optimierung**
6. Die Komplexität der Biologie



Structure of
andomly chosen
initial sequence

Phenylalanyl-tRNA as
target structure

random individuals. The primer pair used for genomic DNA amplification is 5'-TCTCCCTGGATTCT-CATTTA-3' (forward) and 5'-TCTTTGTCTTCTGT-TGCACC-3' (reverse). Reactions were performed in 25 μ l using 1 unit of Taq DNA polymerase with each primer at 0.4 μ M, 200 μ M each dATP, dTTP, dCTP, and dGTP, and PCR buffer [10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM MgCl₂] in a cycle condition of 94°C for 1 min and then 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s followed by 72°C for 6 min. PCR products were purified (Qiagen), digested with Xmn I, and separated in a 2% agarose gel.

32. A nonsense mutation may affect mRNA stability and result in degradation of the transcript [L. Maquat, *Am. J. Hum. Genet.* **59**, 279 (1996)].

33. Data not shown; a dot blot with poly (A)⁺ RNA from 50 human tissues (The Human RNA Master Blot, 7770-1, Clontech Laboratories) was hybridized with a probe from exons 29 to 47 of *MYO15* using the same condition as Northern blot analysis (13).

34. Smith-Magenis syndrome (SMS) is due to deletions of 17p11.2 of various sizes, the smallest of which includes *MYO15* and perhaps 20 other genes [6]; K-S Chen, L. Potocki, J. R. Lupski, *MROD Res. Rev.* **2**, 122 (1996)]. *MYO15* expression is easily detected in the pituitary gland (data not shown). Haploinsufficiency for *MYO15* may explain a portion of the SMS

phenotype such as short stature. Moreover, a few SMS patients have sensorineural hearing loss, possibly because of a point mutation in *MYO15* in trans to the SMS 17p11.2 deletion.

35. R. A. Fiedel, data not shown.

36. K. B. Avraham *et al.*, *Nature Genet.* **11**, 369 (1995); X-Z. Liu *et al.*, *ibid.* **17**, 268 (1997); F. Gibson *et al.*, *Nature* **374**, 62 (1995); D. Weil *et al.*, *ibid.*, p. 60.

37. RNA was extracted from cochlea (membranous labyrinth) obtained from human fetuses at 18 to 22 weeks of development in accordance with guidelines established by the Human Research Committee at the Brigham and Women's Hospital. Only samples without evidence of degradation were pooled for poly (A)⁺ selection over oligo(dT) columns. First-strand cDNA was prepared using an Advantage RT-for-PCR kit (Clontech Laboratories). A portion of the first-strand cDNA (4%) was amplified by PCR with Advantage cDNA polymerase mix (Clontech Laboratories) using human *MYO15*-specific oligonucleotide primers (forward, 5'-GCATGACCTGCGGGTAAT-GCG-3'; reverse, 5'-CTCAAGGCTTCTGGCATGGT-GCTCGCTGGC-3'). Cycling conditions were 40 s at 94°C, 40 s at 66°C (3 cycles), 60°C (5 cycles), and 55°C (29 cycles); and 45 s at 68°C. PCR products were visualized by ethidium bromide staining after fractionation in a 1% agarose gel. A 688-bp PCR

product is expected from amplification of the human *MYO15* cDNA. Amplification of human genomic DNA with this primer pair would result in a 2903-bp fragment.

38. We are grateful to the people of Bengkala, Bali, and the two families from India. We thank J. R. Lupski and K.-S. Chen for providing the human chromosome 17 cosmid library. For technical and computational assistance, we thank N. Dietrich, M. Ferguson, A. Gupta, E. Sorbello, R. Torkzadeh, C. Varner, M. Walker, G. Bouffard, and S. Beckstrom-Stenberg (National Institutes of Health Intramural Sequencing Center). We thank J. T. Hinnant, I. N. Arhya, and S. Winata for assistance in Bali, and T. Barber, S. Sullivan, E. Green, D. Drayna, and J. Battey for helpful comments on this manuscript. Supported by the National Institute on Deafness and Other Communication Disorders (NIDCD) (Z01 DC 00035-01 and Z01 DC 00038-01 to T.B.F. and E.R.W. and R01 DC 03402 to C.G.M.), the National Institute of Child Health and Human Development (R01 HD00428 to S.A.C.) and a National Science Foundation Graduate Research Fellowship to F.J.P. This paper is dedicated to J. B. Snow Jr. on his retirement as the Director of the NIDCD.

9 March 1998; accepted 17 April 1998

Continuity in Evolution: On the Nature of Transitions

Walter Fontana and Peter Schuster

To distinguish continuous from discontinuous evolutionary change, a relation of nearness between phenotypes is needed. Such a relation is based on the probability of one phenotype being accessible from another through changes in the genotype. This nearness relation is exemplified by calculating the shape neighborhood of a transfer RNA secondary structure and provides a characterization of discontinuous shape transformations in RNA. The simulation of replicating and mutating RNA populations under selection shows that sudden adaptive progress coincides mostly, but not always, with discontinuous shape transformations. The nature of these transformations illuminates the key role of neutral genetic drift in their realization.

A much-debated issue in evolutionary biology concerns the extent to which the history of life has proceeded gradually or has been punctuated by discontinuous transitions at the level of phenotypes (1). Our goal is to make the notion of a discontinuous transition more precise and to understand how it arises in a model of evolutionary adaptation.

We focus on the narrow domain of RNA secondary structure, which is currently the simplest computationally tractable, yet realistic phenotype (2). This choice enables the definition and exploration of concepts that may prove useful in a wider context. RNA secondary structures represent a coarse level of analysis compared with the three-dimensional structure at atomic resolution. Yet, secondary structures are empir-

ically well defined and obtain their biophysical and biochemical importance from being a scaffold for the tertiary structure. For the sake of brevity, we shall refer to secondary structures as "shapes." RNA combines in a single molecule both genotype (replicable sequence) and phenotype (selectable shape), making it ideally suited for *in vitro* evolution experiments (3, 4).

To generate evolutionary histories, we used a stochastic continuous time model of an RNA population replicating and mutating in a capacity-constrained flow reactor under selection (5, 6). In the laboratory, a goal might be to find an RNA aptamer binding specifically to a molecule (4). Although in the experiment the evolutionary end product was unknown, we thought of its shape as being specified implicitly by the imposed selection criterion. Because our intent is to study evolutionary histories rather than end products, we defined a target shape in advance and assumed the replication rate of a sequence to be a function of

the similarity between its shape and the target. An actual situation may involve more than one best shape, but this does not affect our conclusions.

An instance representing in its qualitative features all the simulations we performed is shown in Fig. 1A. Starting with identical sequences folding into a random shape, the simulation was stopped when the population became dominated by the target, here a canonical tRNA shape. The black curve traces the average distance to the target (inversely related to fitness) in the population against time. Aside from a short initial phase, the entire history is dominated by steps, that is, flat periods of no apparent adaptive progress, interrupted by sudden approaches toward the target structure (7). However, the dominant shapes in the population not only change at these marked events but undergo several fitness-neutral transformations during the periods of no apparent progress. Although discontinuities in the fitness trace are evident, it is entirely unclear when and on the basis of what the series of successive phenotypes itself can be called continuous or discontinuous.

A set of entities is organized into a (topological) space by assigning to each entity a system of neighborhoods. In the present case, there are two kinds of entities: sequences and shapes, which are related by a thermodynamic folding procedure. The set of possible sequences (of fixed length) is naturally organized into a space because point mutations induce a canonical neighborhood. The neighborhood of a sequence consists of all its one-error mutants. The problem is how to organize the set of possible shapes into a space. The issue arises because, in contrast to sequences, there are

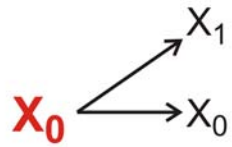
Evolution *in silico*

W. Fontana, P. Schuster,
Science **280** (1998), 1451-1455

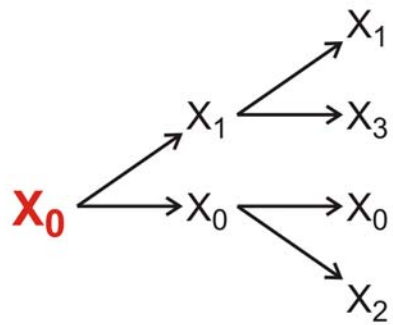
Institut für Theoretische Chemie, Universität Wien, Währingerstrasse 17, A-1090 Wien, Austria, Santa Fe Institute, 1399 Hyde Park Road, Santa Fe, NM 87501, USA, and International Institute for Applied Systems Analysis (IIASA), A-2361 Laxenburg, Austria.

X_0

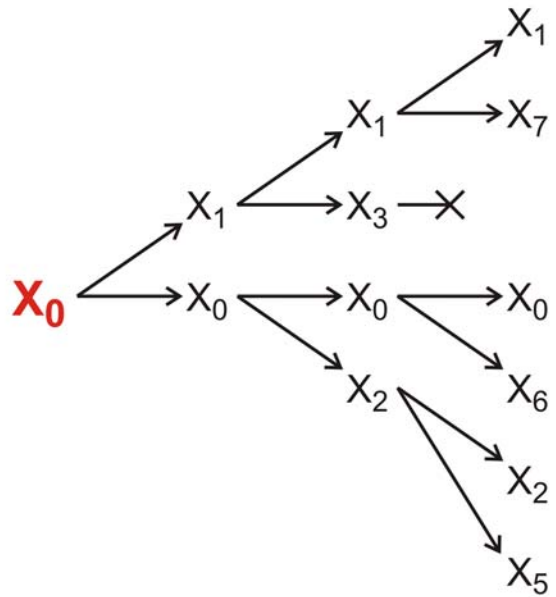
Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



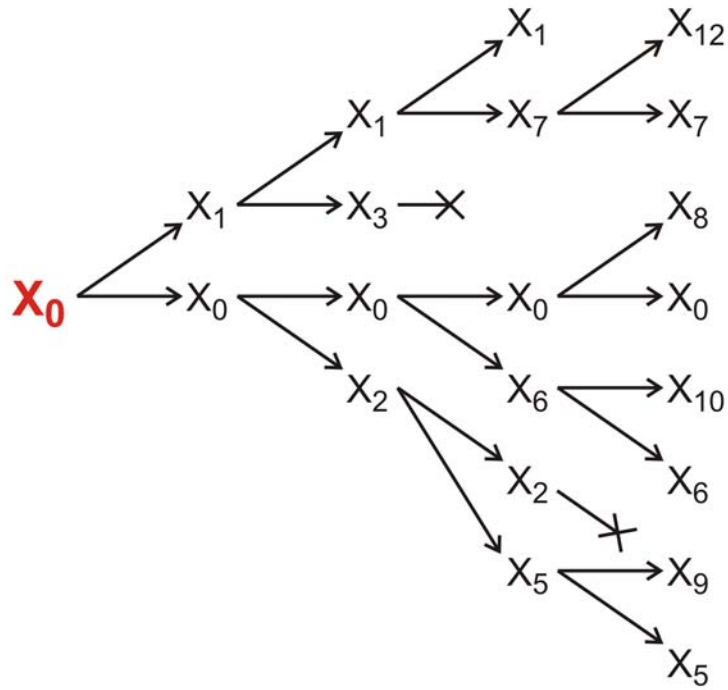
Evolution of RNA molecules as a Markov process and its analysis by means of the relay series



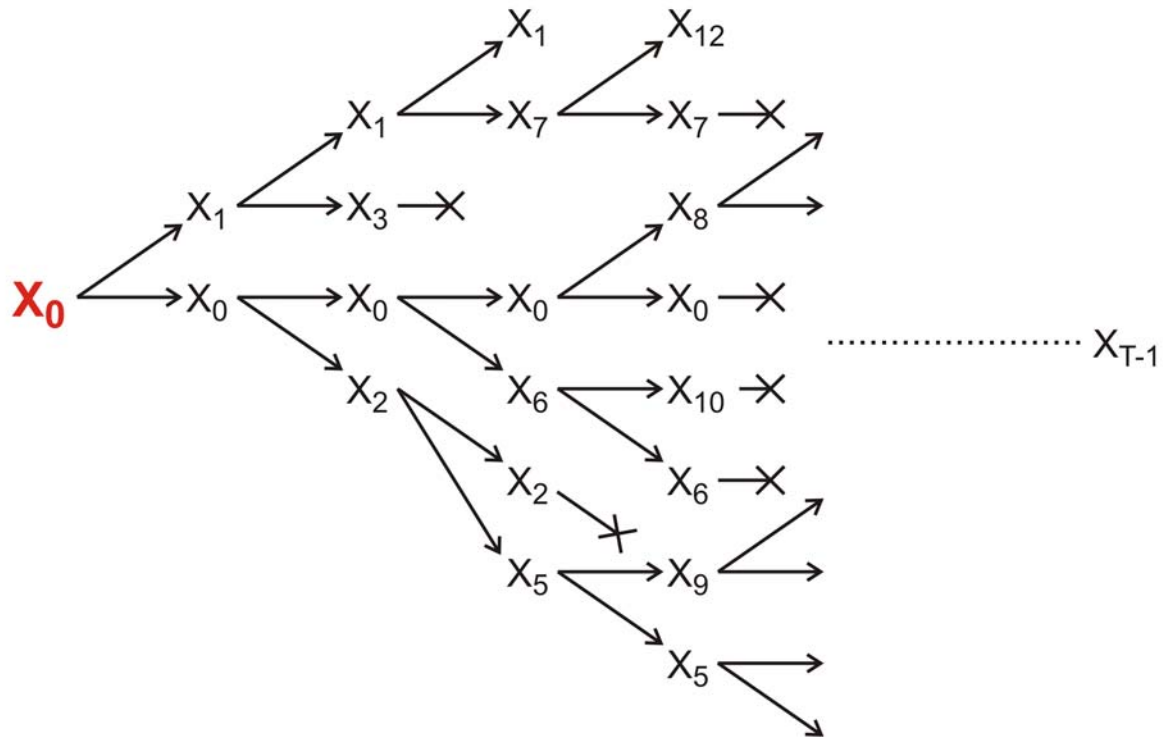
Evolution of RNA molecules as a Markov process and its analysis by means of the relay series



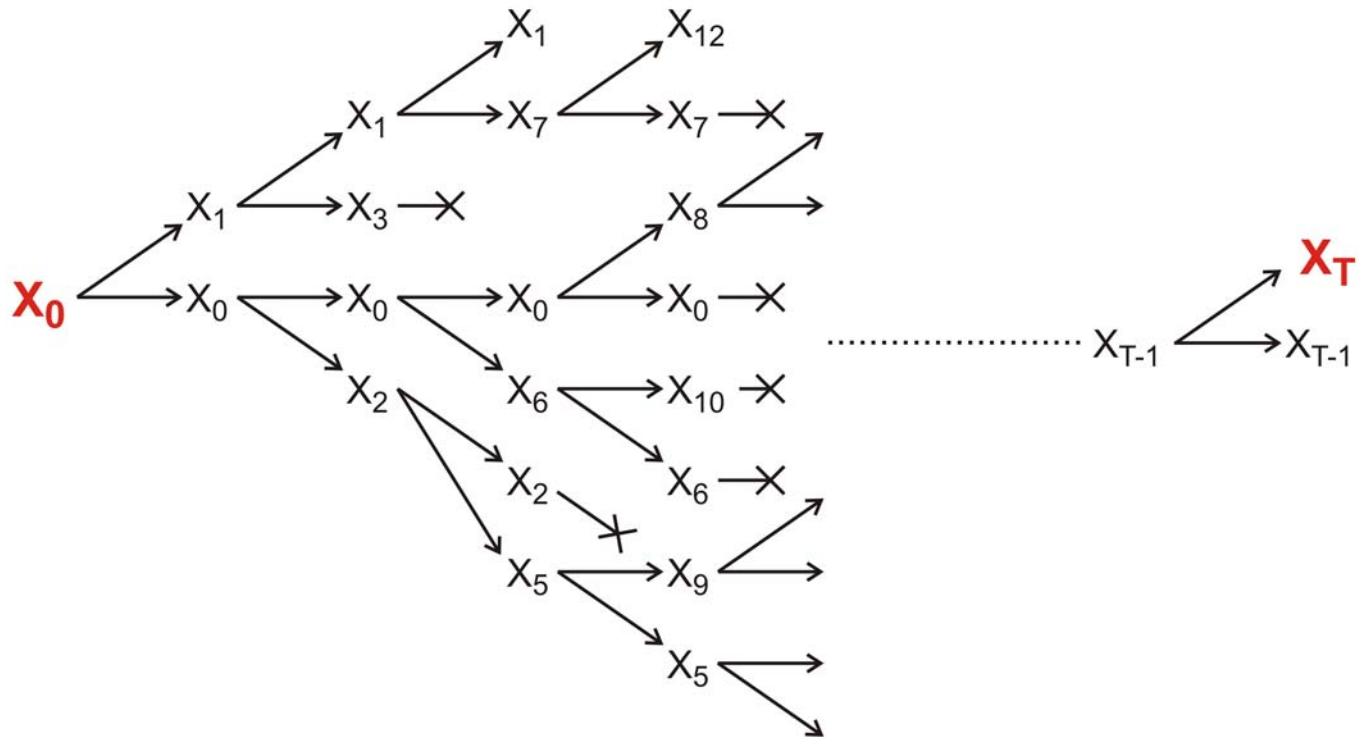
Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



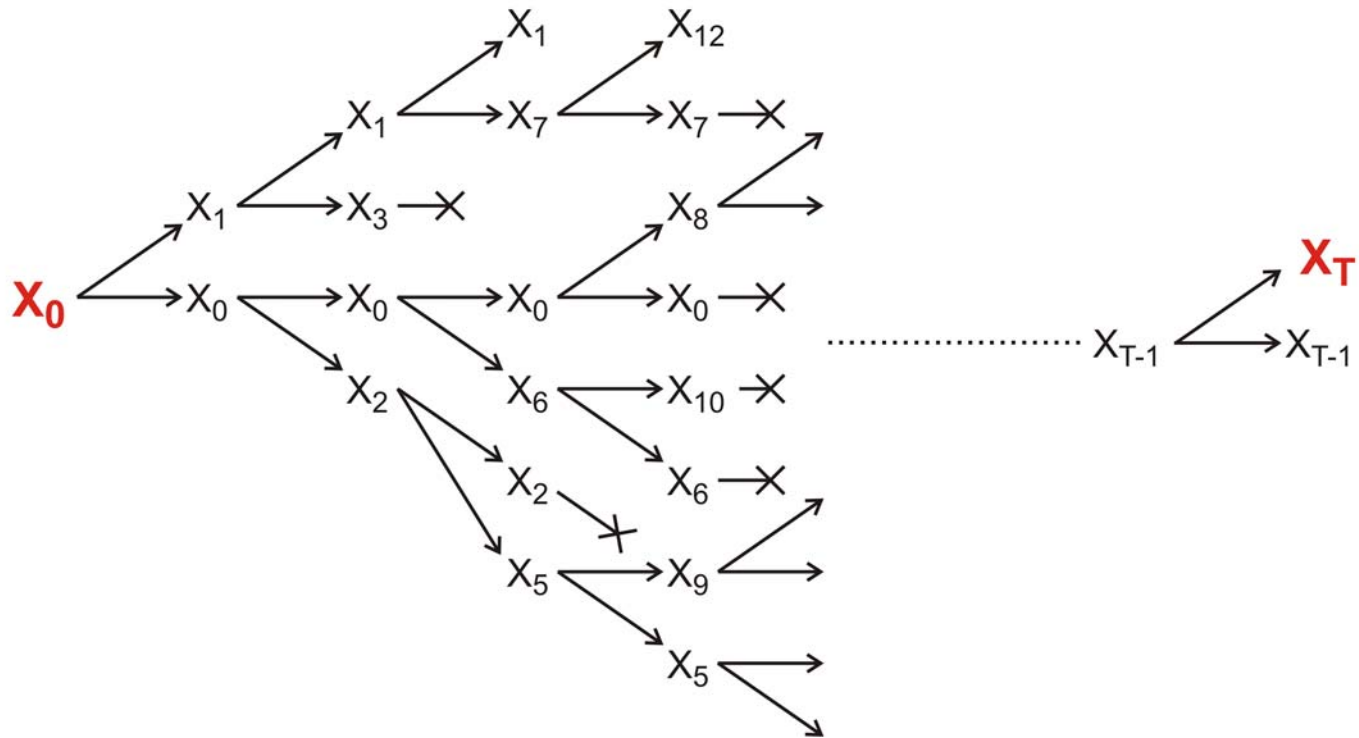
Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



Evolution of RNA molecules as a Markow process and its analysis by means of the relay series

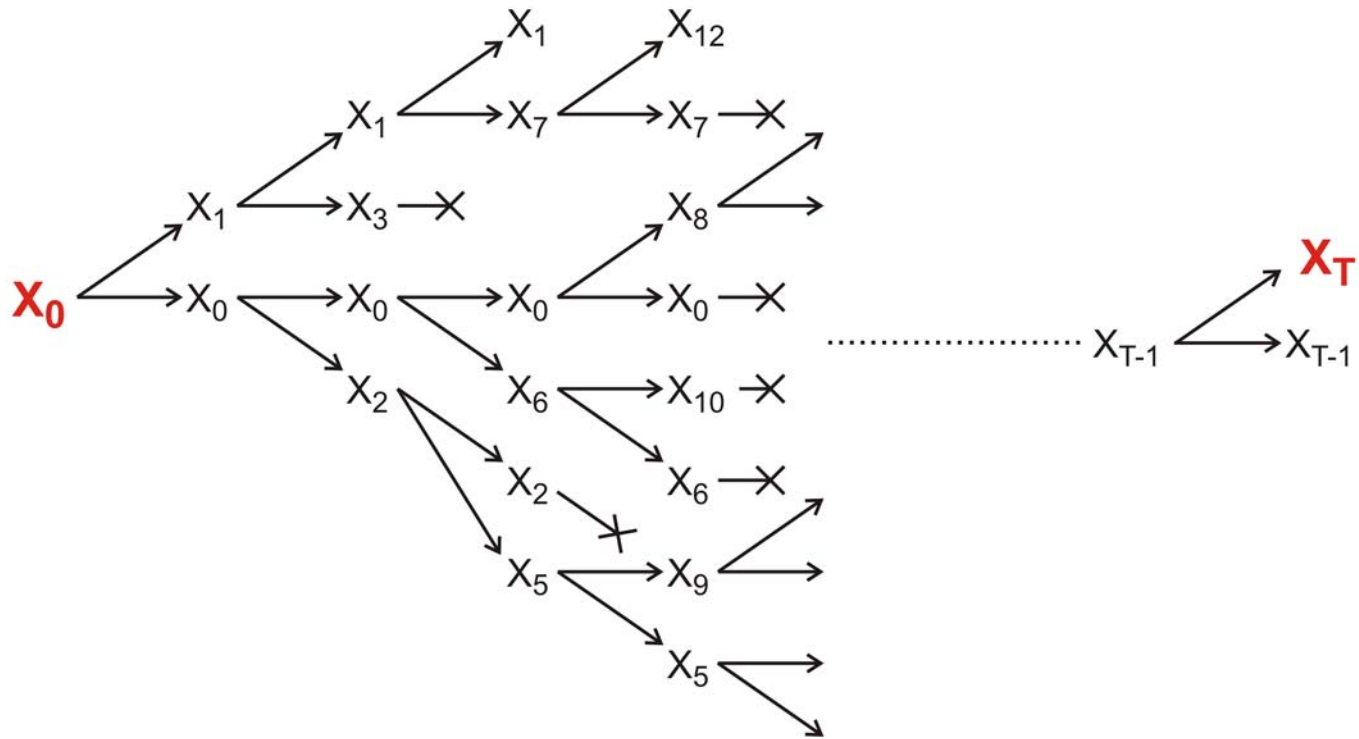


Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



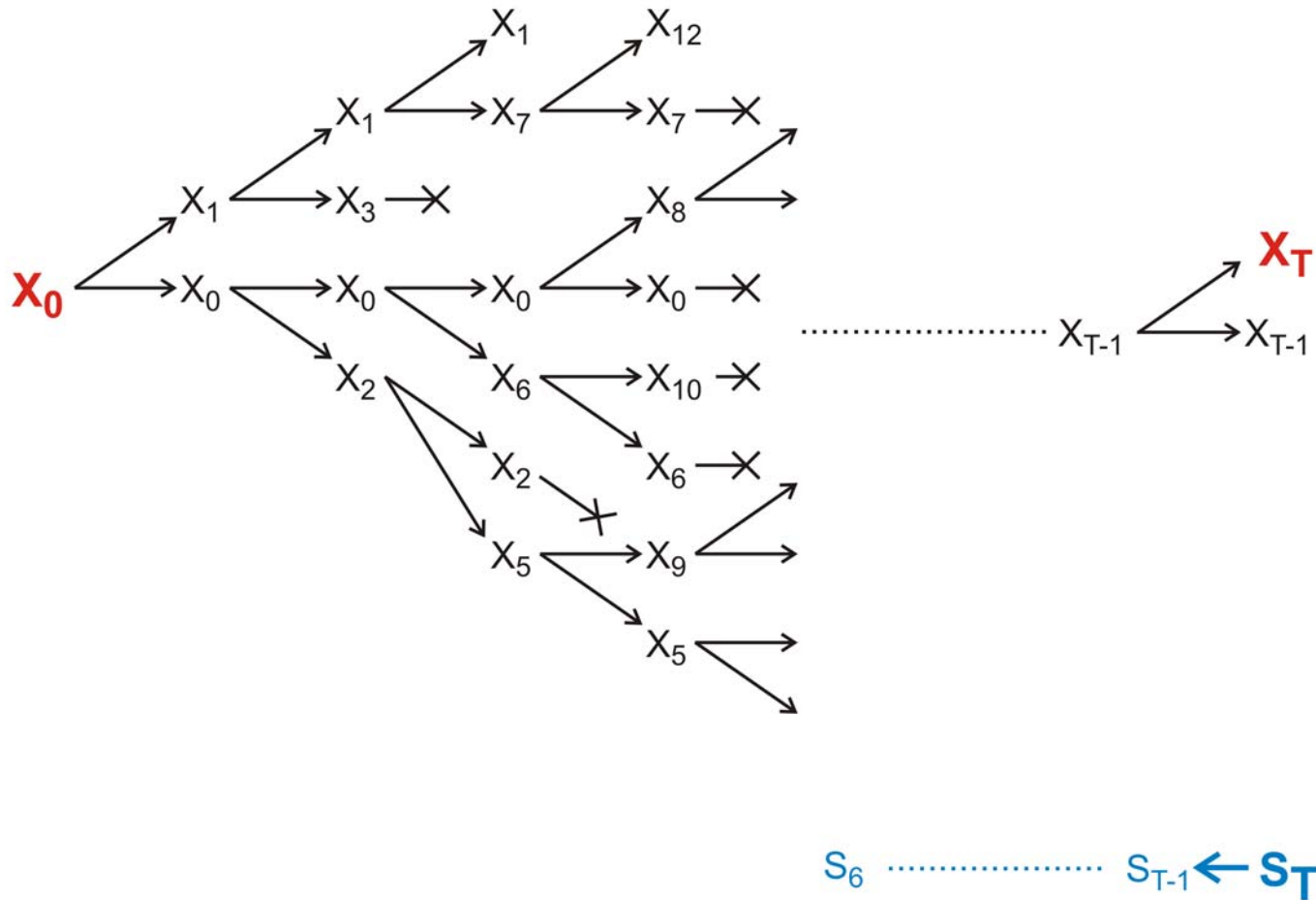
S_T

Evolution of RNA molecules as a Markow process and its analysis by means of the relay series

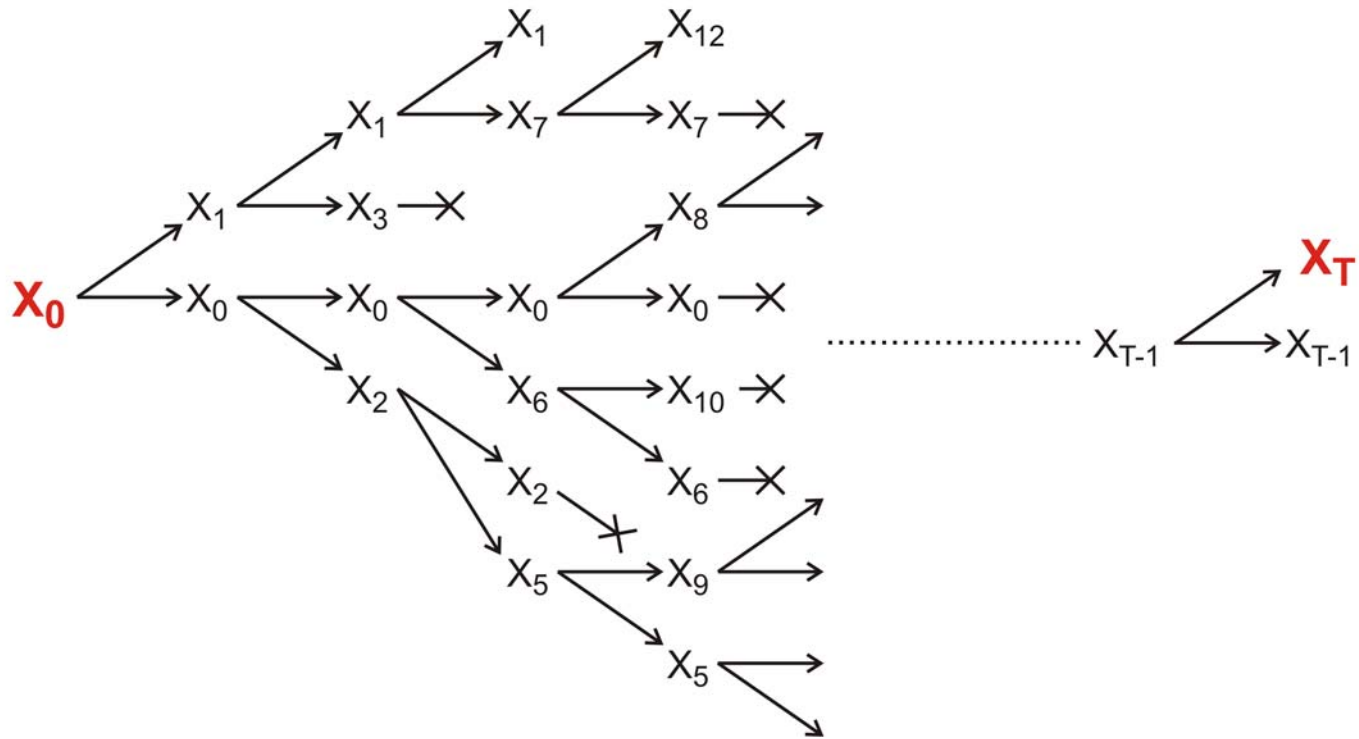


$S_{T-1} \leftarrow S_T$

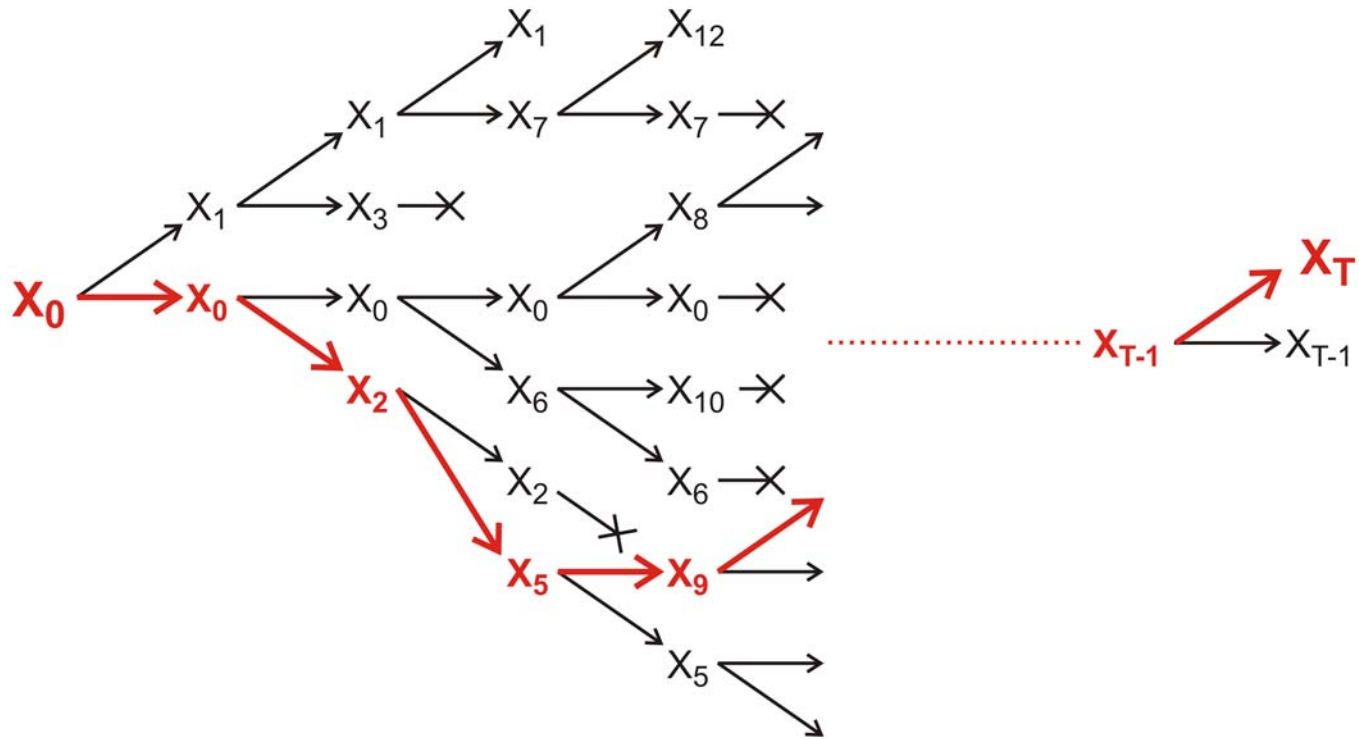
Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



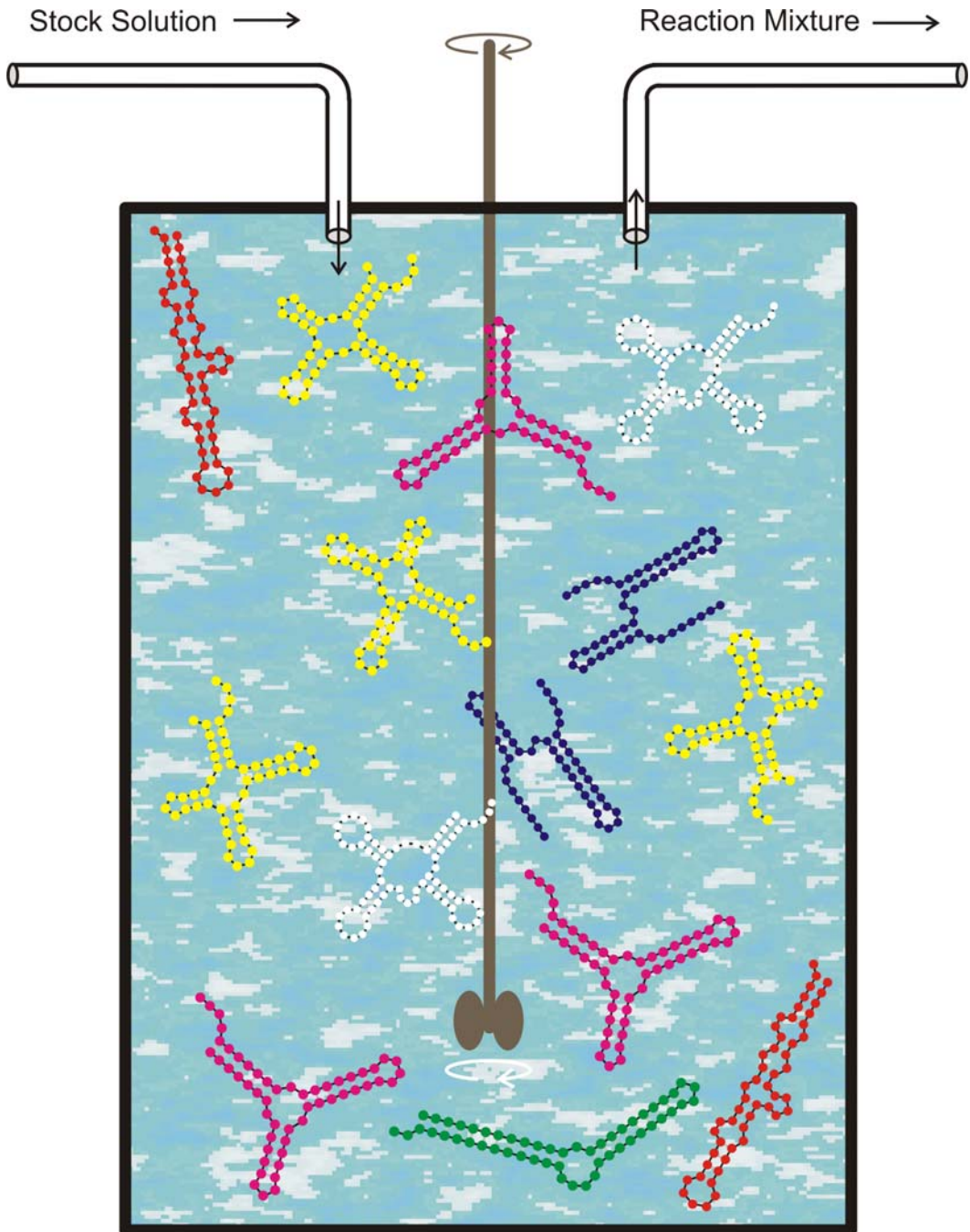
Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



Evolution of RNA molecules as a Markow process and its analysis by means of the relay series



Replication rate constant:

$$f_k = \gamma / [\alpha + \Delta d_S^{(k)}]$$

$$\Delta d_S^{(k)} = d_H(S_k, S_\tau)$$

Selection constraint:

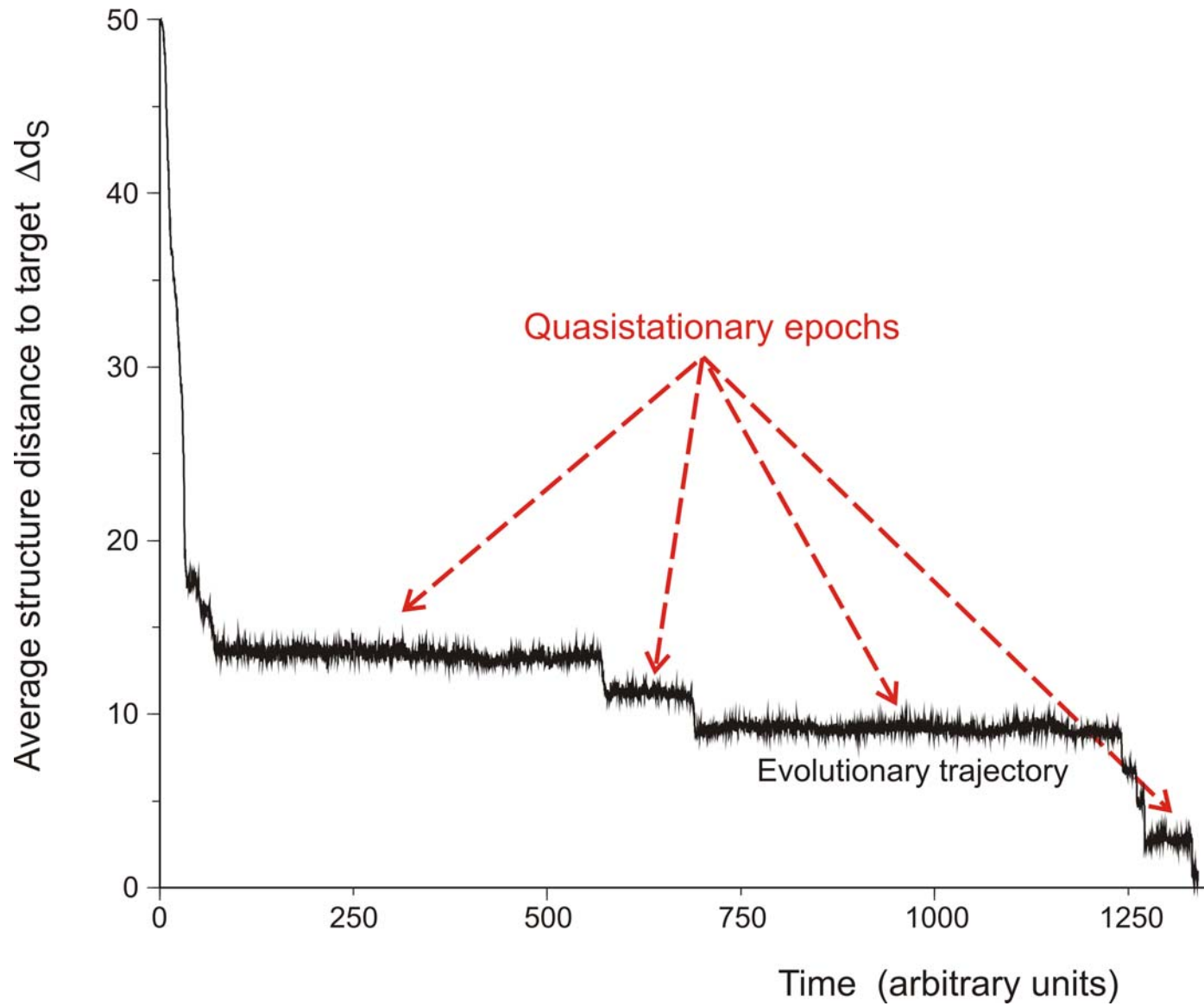
Population size, $N = \#$ RNA molecules, is controlled by the flow

$$N(t) \approx \bar{N} \pm \sqrt{\bar{N}}$$

Mutation rate:

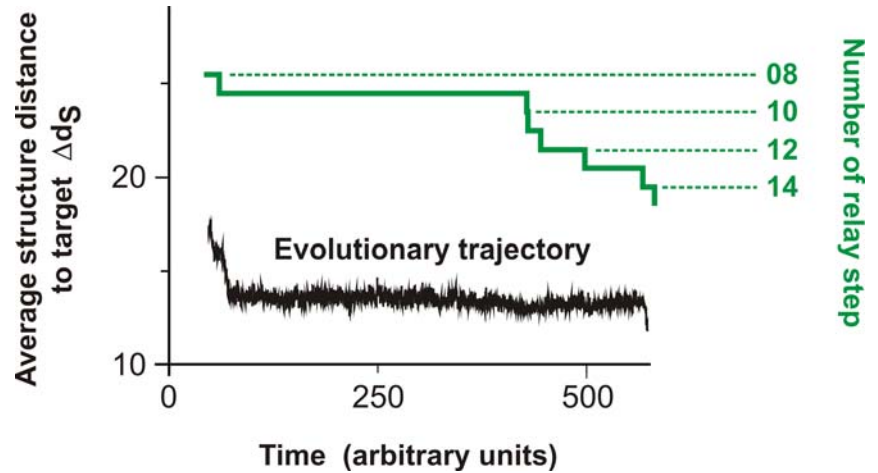
$$p = 0.001 / \text{site} \times \text{replication}$$

The flowreactor as a device for studies of evolution *in vitro* and *in silico*



In silico optimization in the flow reactor: Evolutionary Trajectory

28 neutral point mutations during a long quasi-stationary epoch



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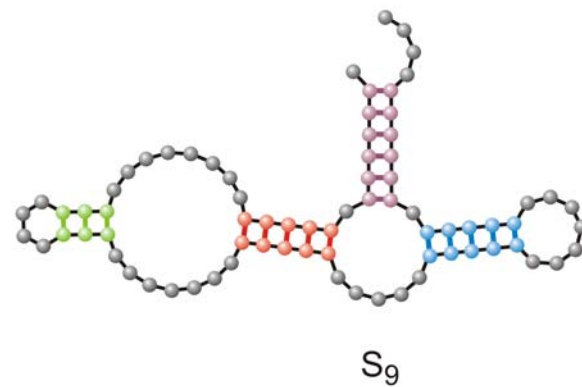
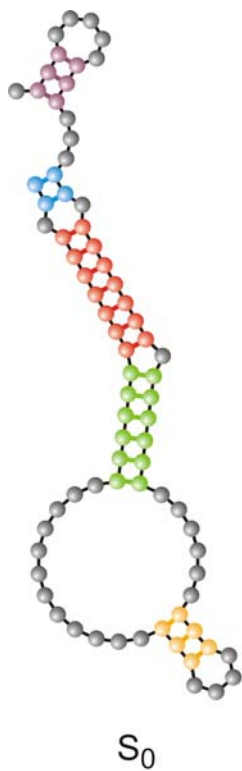
entry  GGUAUGGGCGUUGAAUAGUAGGGUUUAAACCAAUCGGCAACGAUCUCGUGUGCGCAUUUCAUAUCCCGUACAGAA
8      .((((((((((((.....(((.....)))).....)))))).....((((.....)))))))))....
exit   GGUAUGGGCGUUGAAUAUAGGGUUUAAACCAAUCGGCCAACGAUCUCGUGUGCGCAUUUCAUAUCCAUAACAGAA
entry  GGUAUGGGCGUUGAAUAAUAGGGUUUAAACCAAUCGGCCAACGAUCUCGUGUGCGCAUUUCAUAUACCAUACAGAA
9      .(((((((.....(((.....)))).....)))))).....((((.....))))))....
exit   UGGAUGGACGUUGAAUAAACAAGGUAUCGACCAAACAACCAACGAGUAAGUGUGUACGCCCCACACACCGUCCCAAG
entry  UGGAUGGACGUUGAAUAACAAGGUAUCGACCAAACAACCAACGAGUAAGUGUGUACGCCCCACACAGCGUCCCAAG
10     .((((((.....(((.....)))).....)))))).....((((.....))))))....
exit   UGGAUGGACGUUGAAUAAACAAGGUAUCGACCAAACAACCAACGAGUAAGUGUGUACGCCCCACACAGCGUCCCAAG
  
```

Transition inducing point mutations change the molecular structure

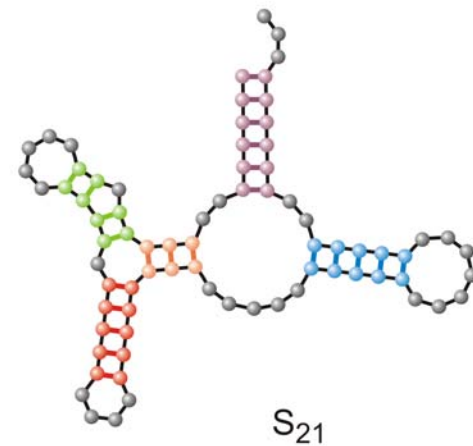
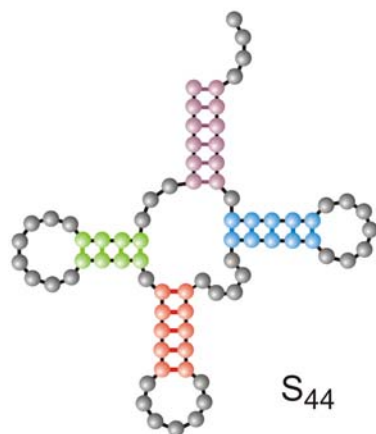
Neutral point mutations leave the molecular structure unchanged

Neutral genotype evolution during phenotypic stasis

Randomly chosen
initial structure



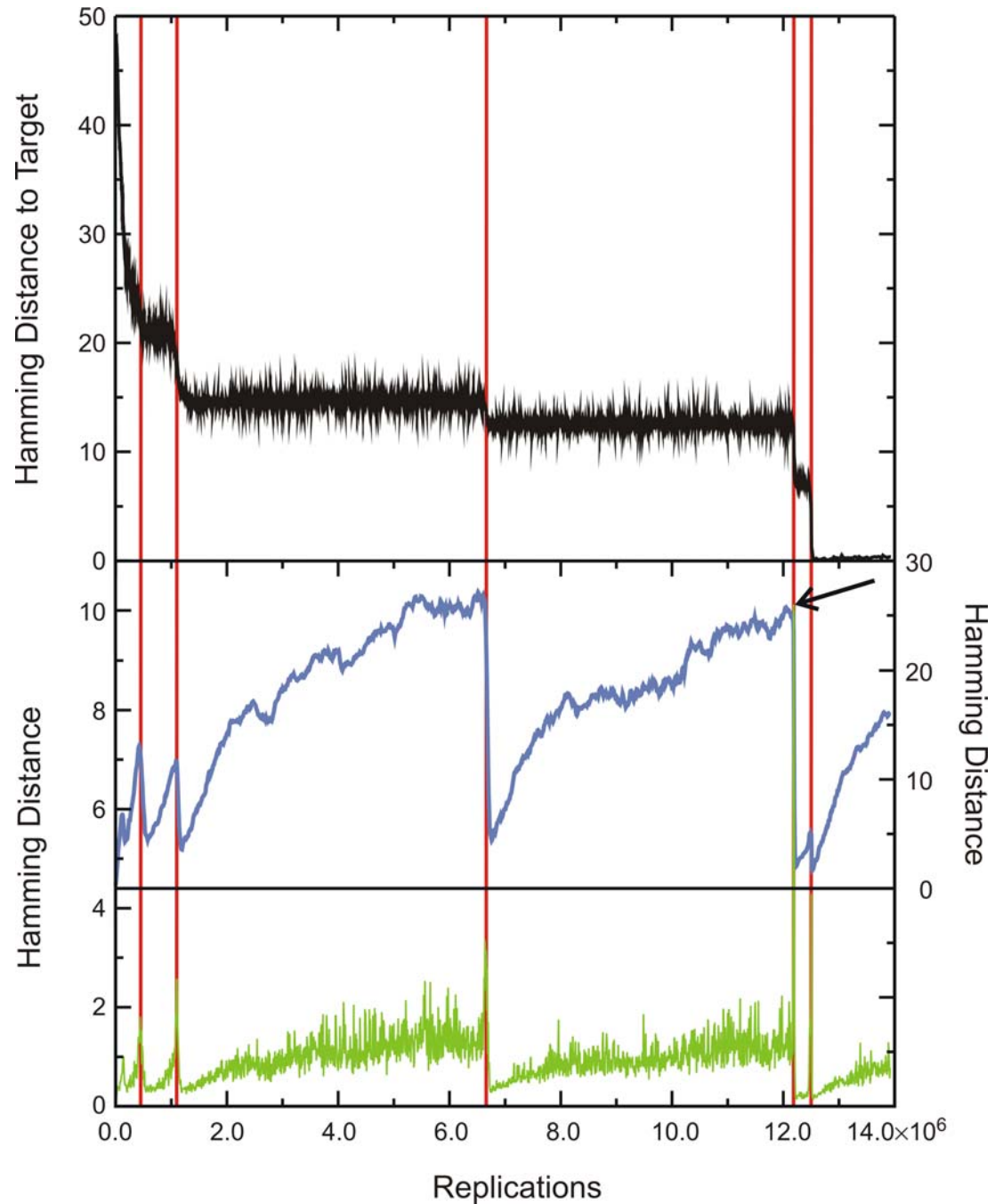
Phenylalanyl-tRNA
as target structure

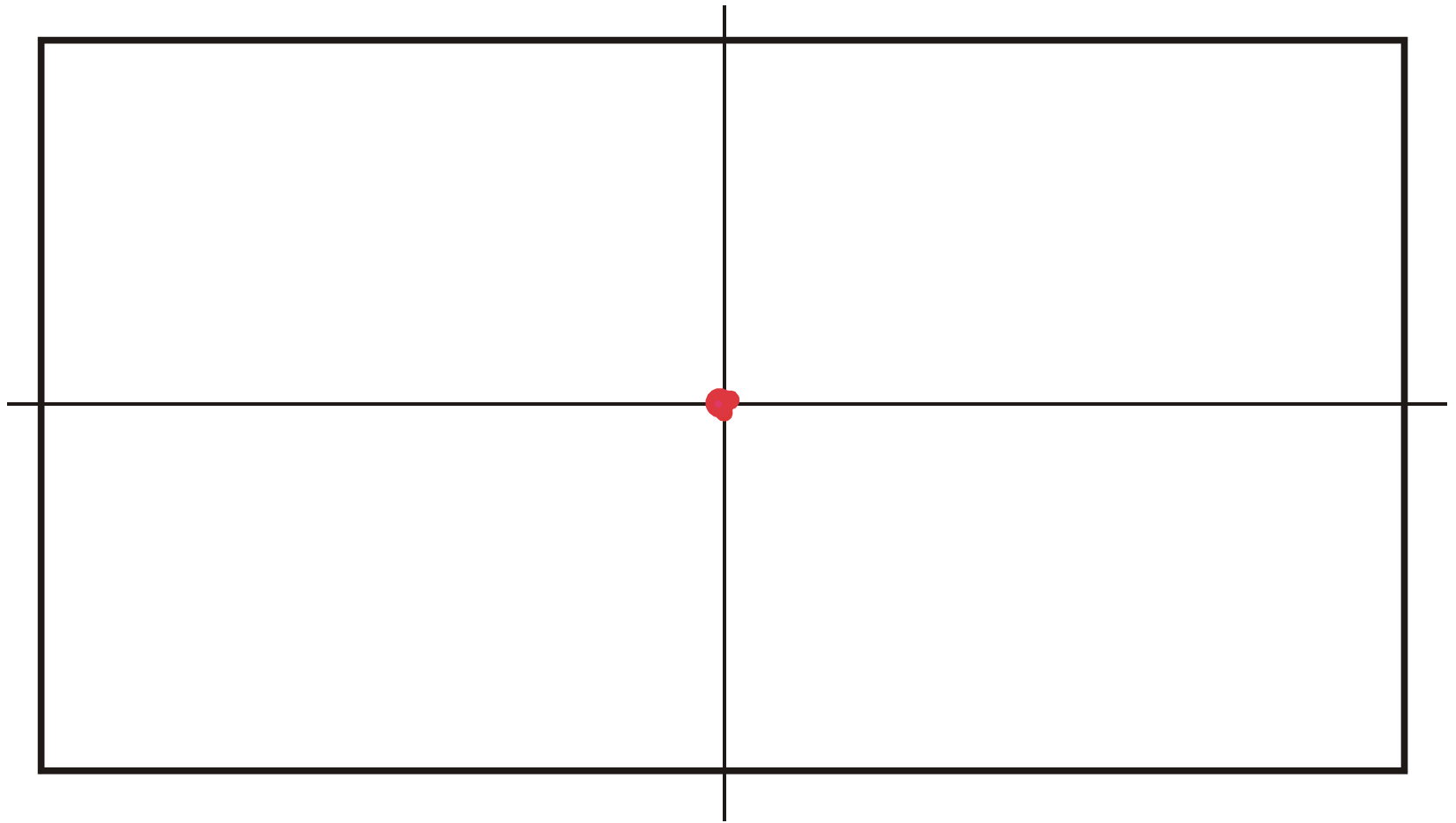


Evolutionary trajectory

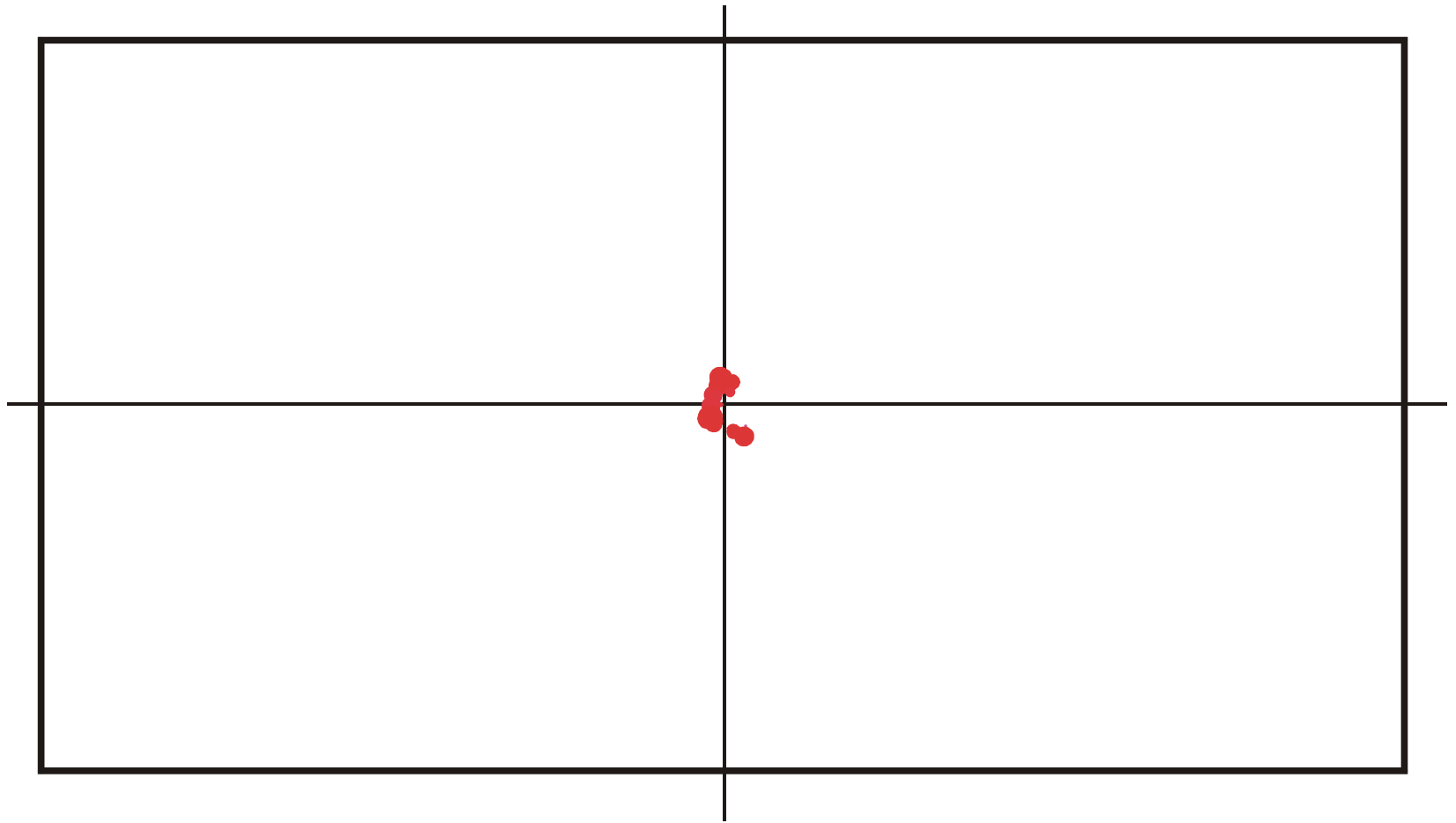
Spreading of the population
on neutral networks

Drift of the population center
in sequence space

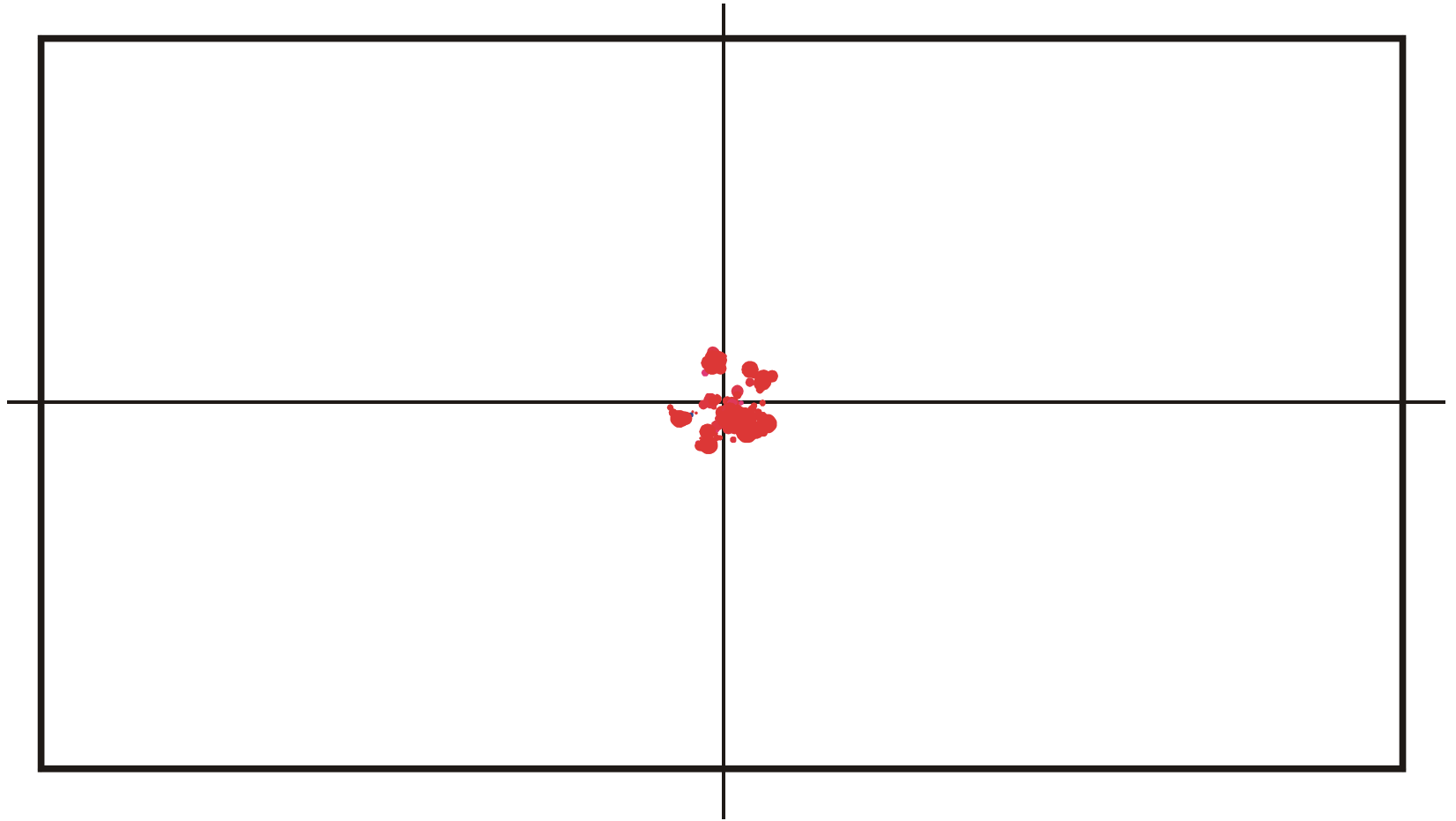




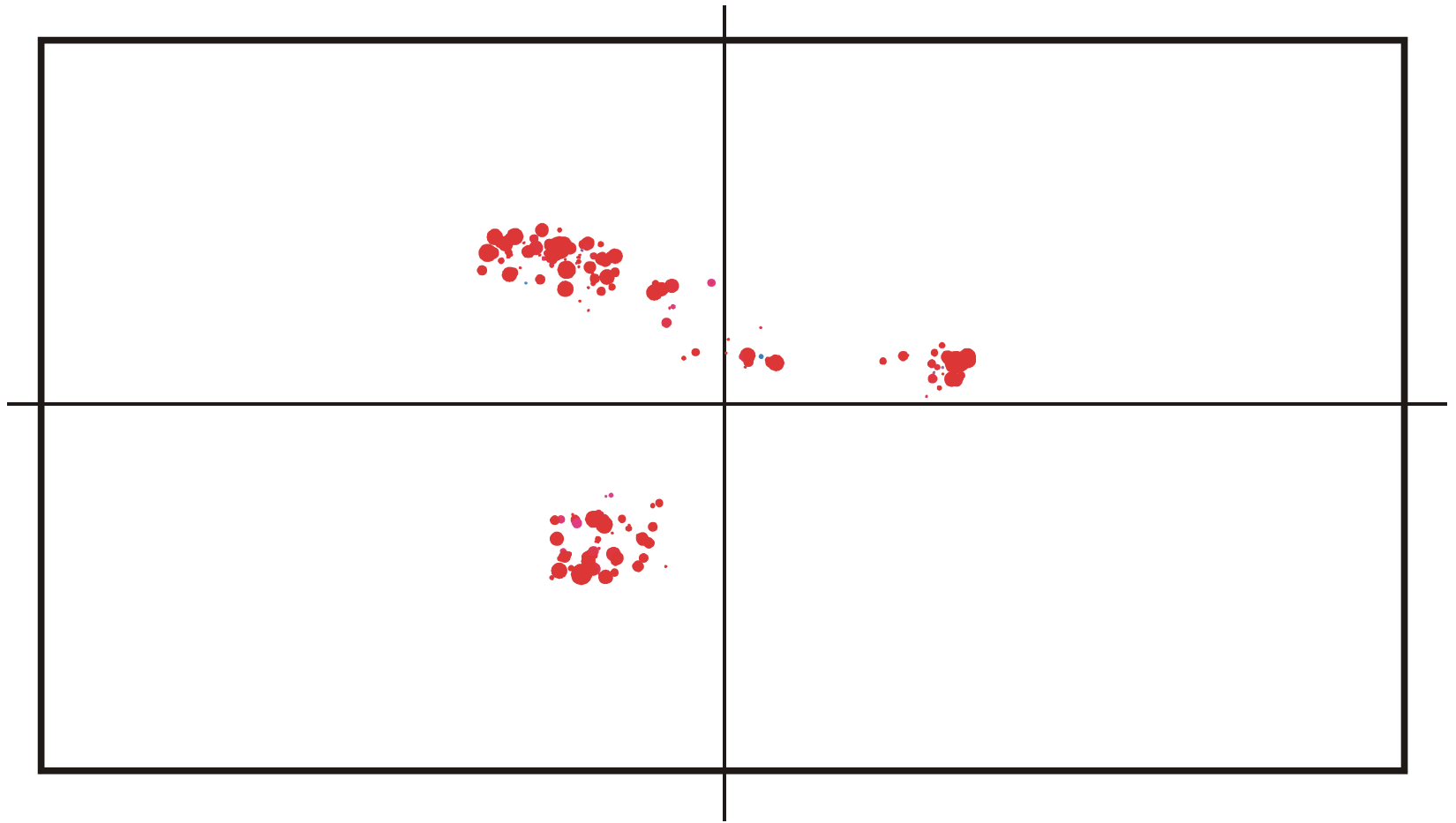
Spreading and evolution of a population on a neutral network: $t = 150$



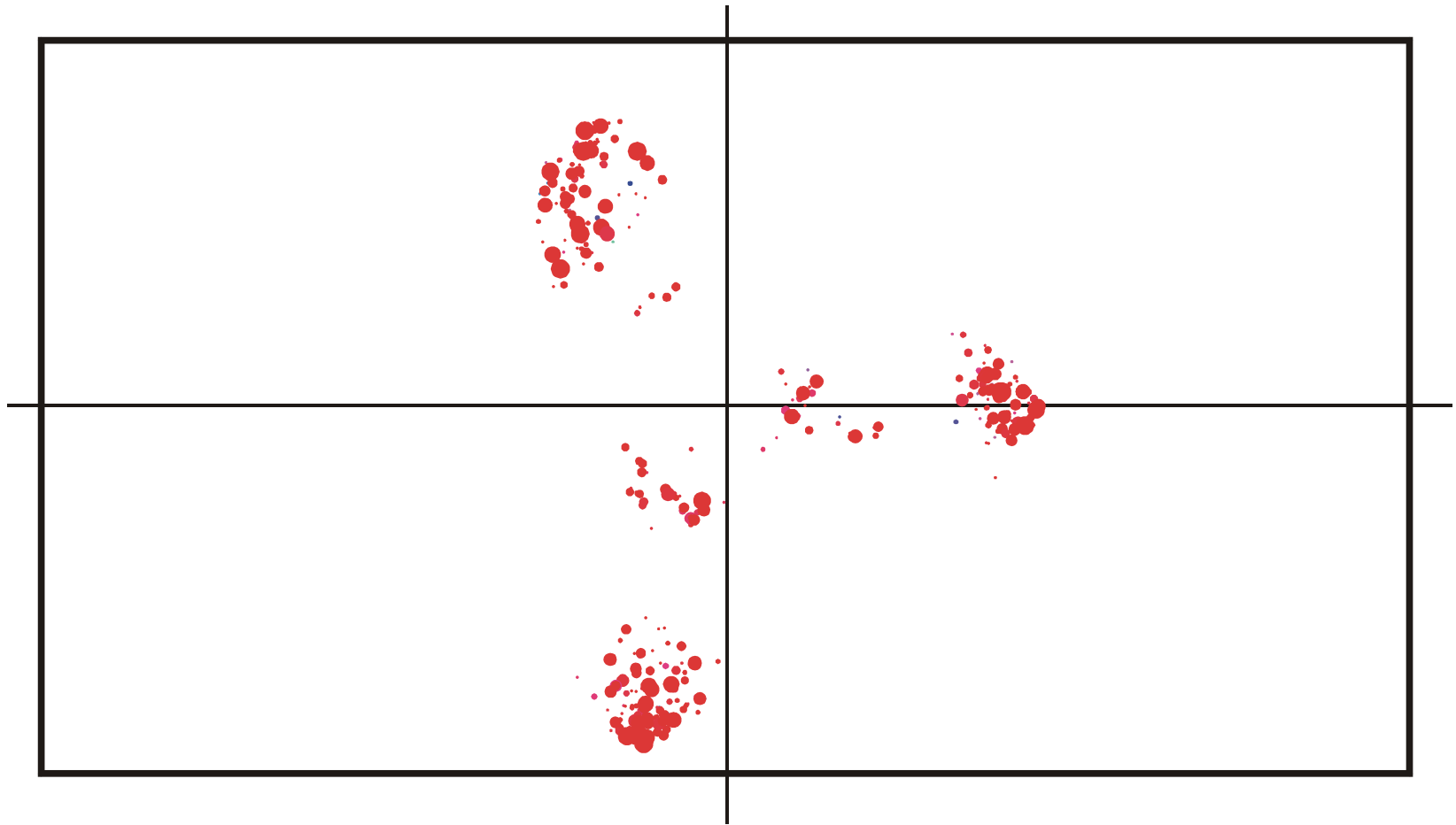
Spreading and evolution of a population on a neutral network : $t = 170$



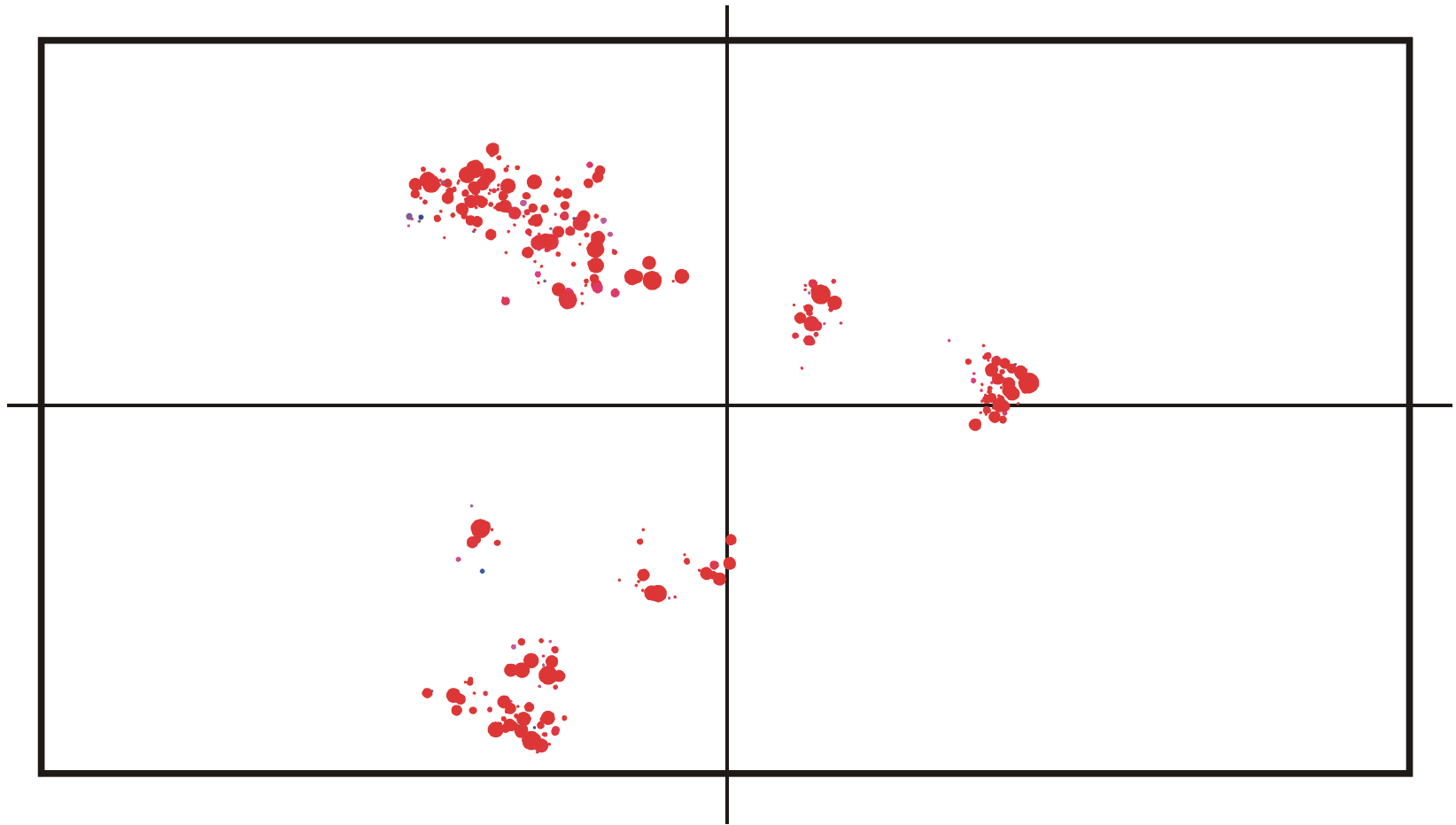
Spreading and evolution of a population on a neutral network : $t = 200$



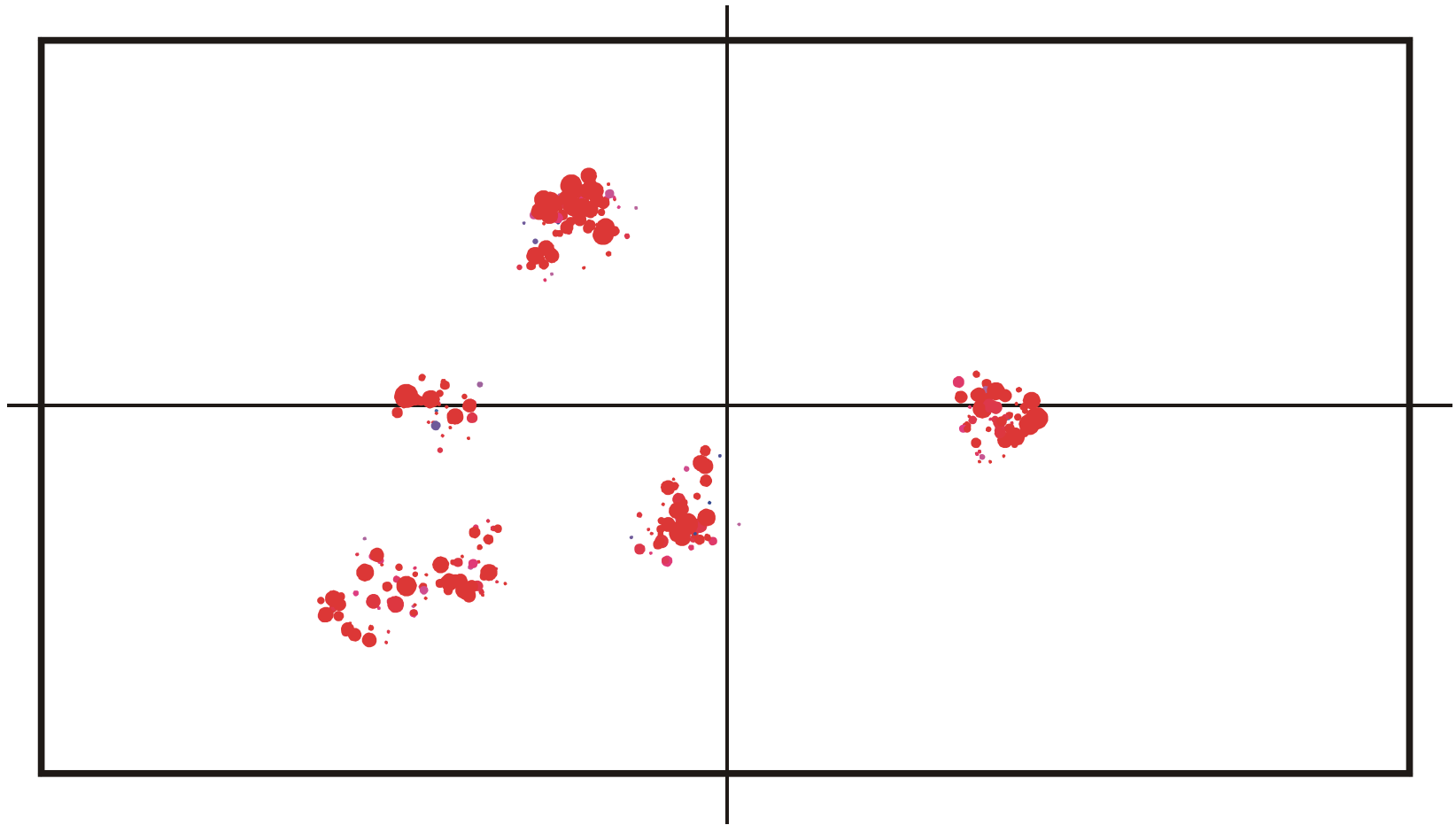
Spreading and evolution of a population on a neutral network : $t = 350$



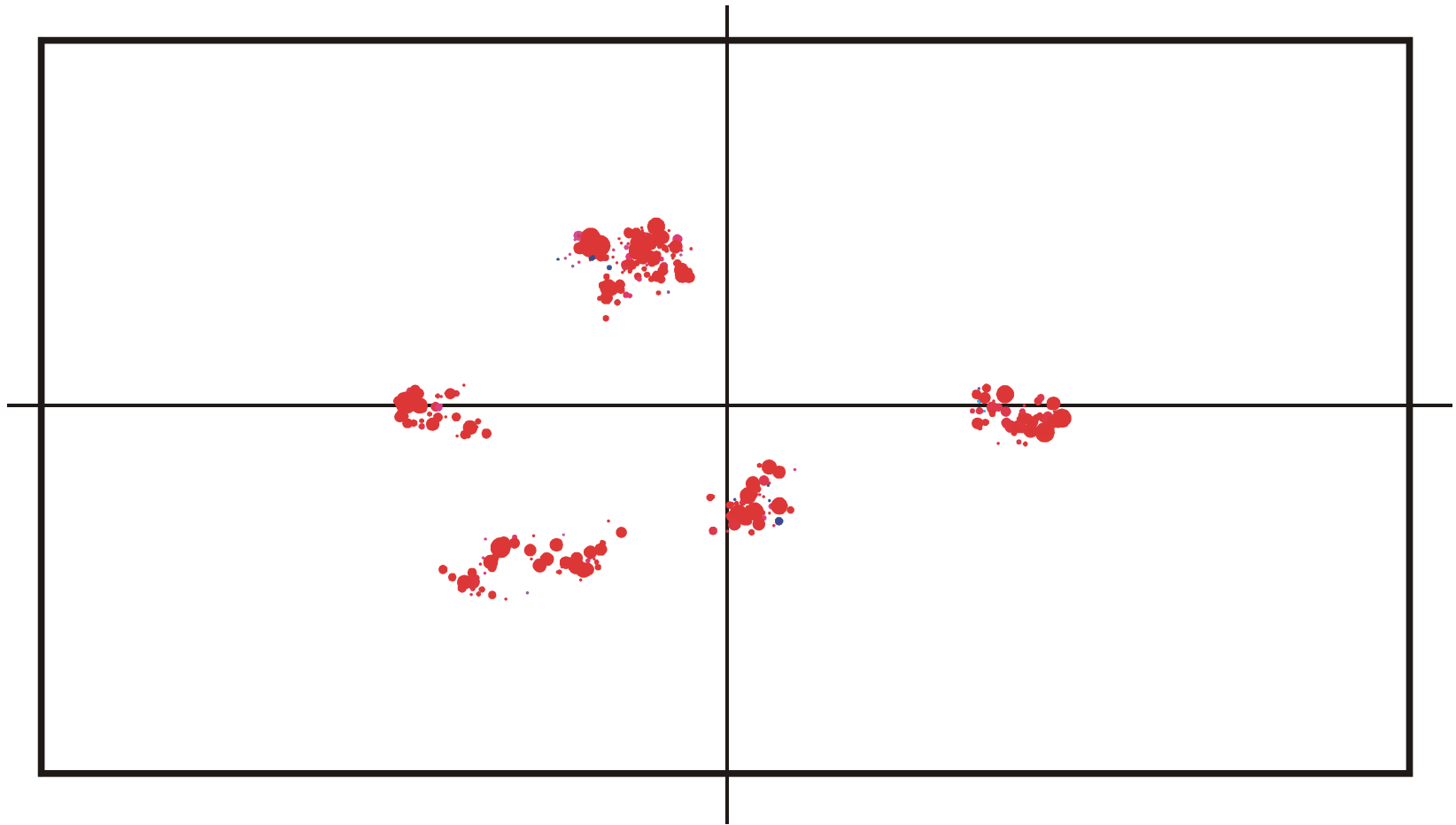
Spreading and evolution of a population on a neutral network : $t = 500$



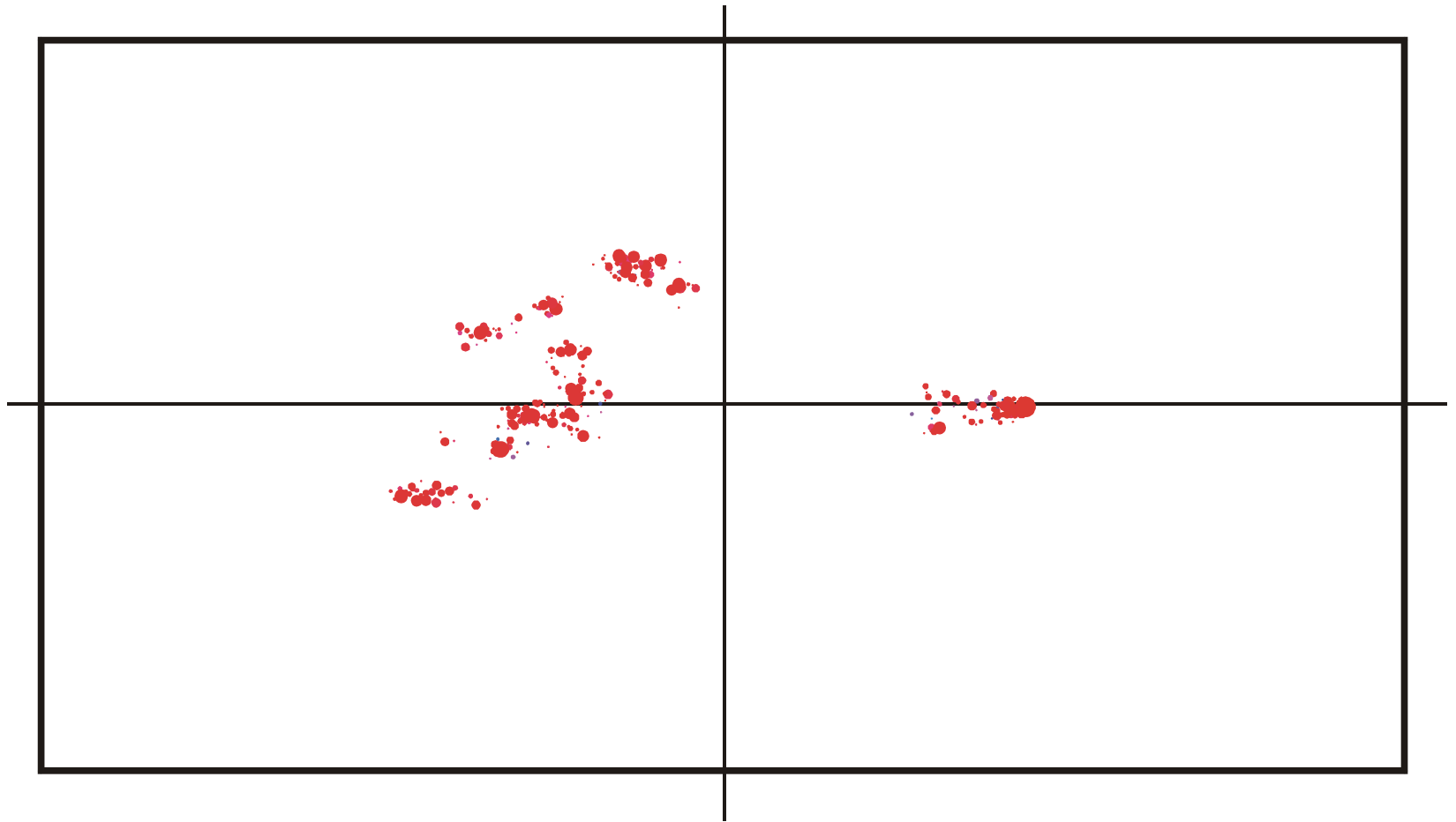
Spreading and evolution of a population on a neutral network : $t = 650$



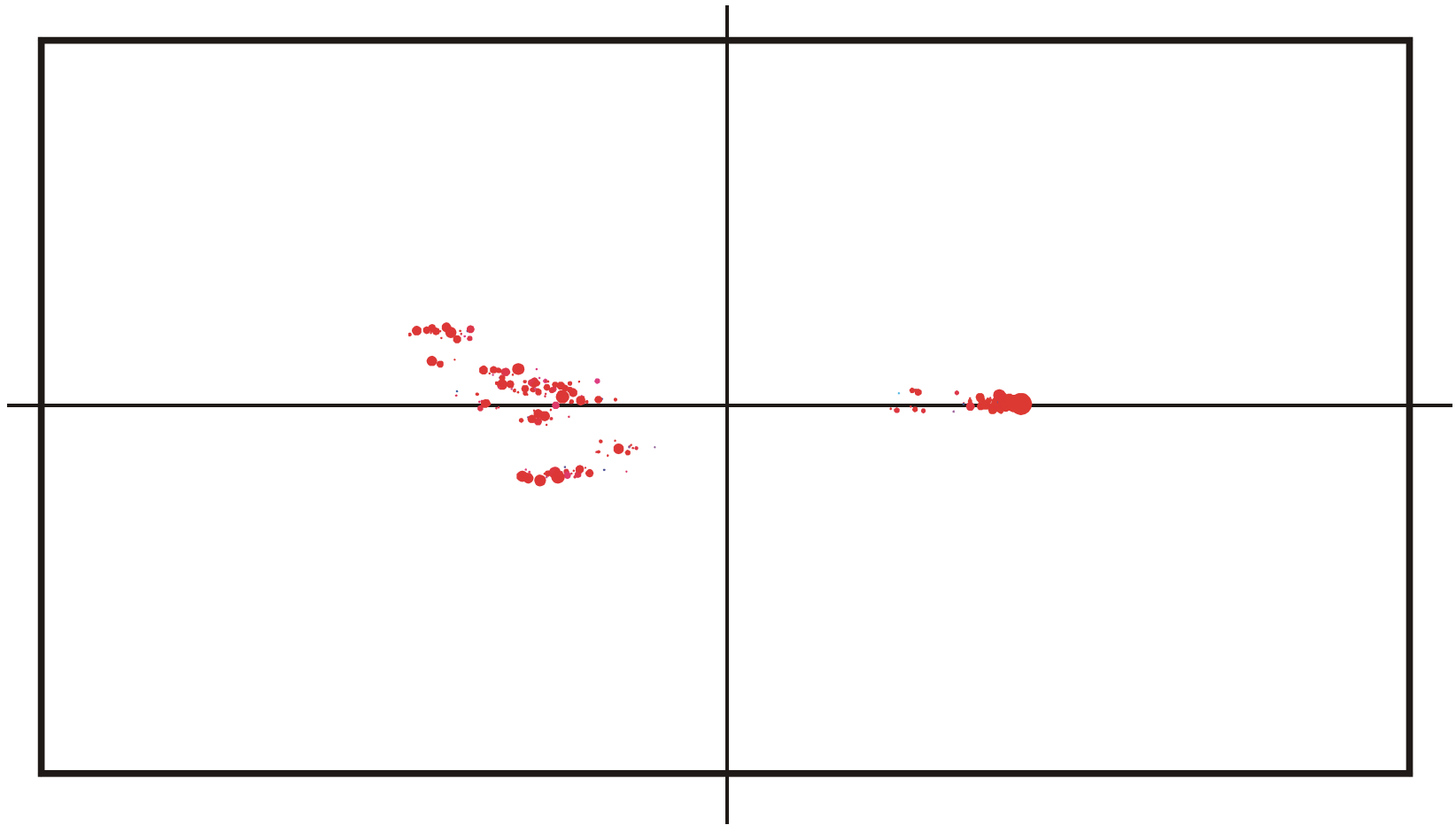
Spreading and evolution of a population on a neutral network : $t = 820$



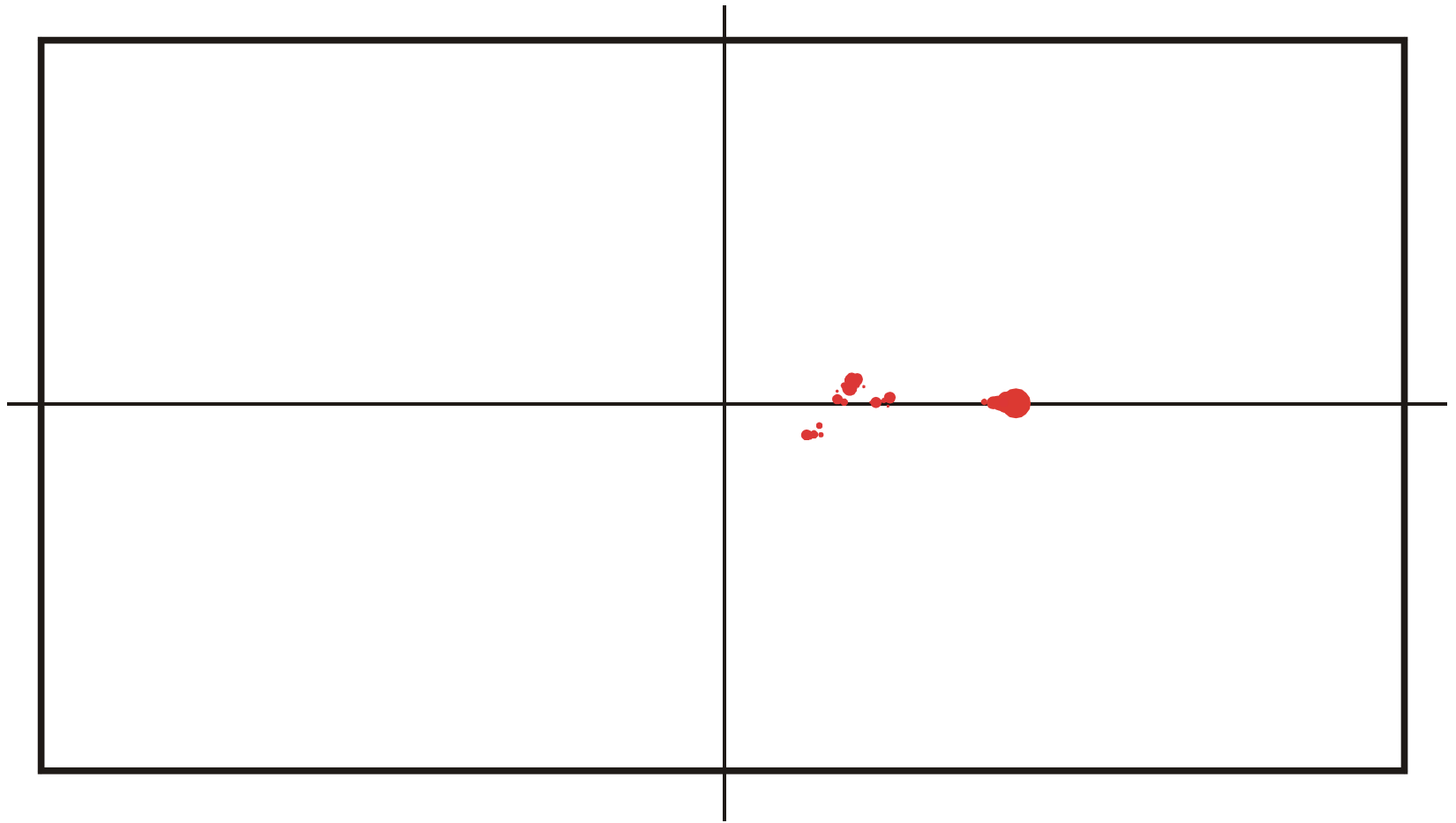
Spreading and evolution of a population on a neutral network : $t = 825$



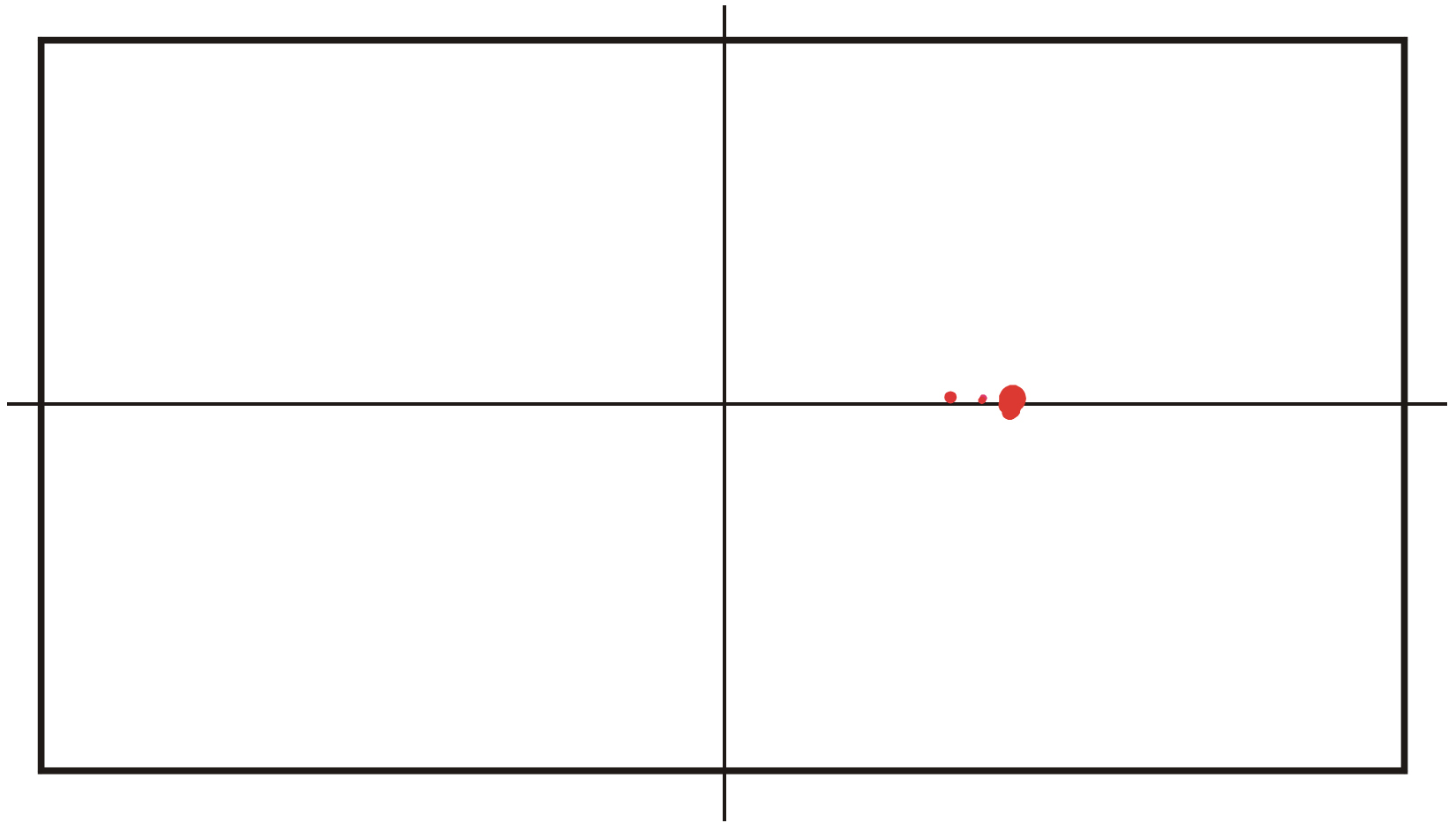
Spreading and evolution of a population on a neutral network : $t = 830$



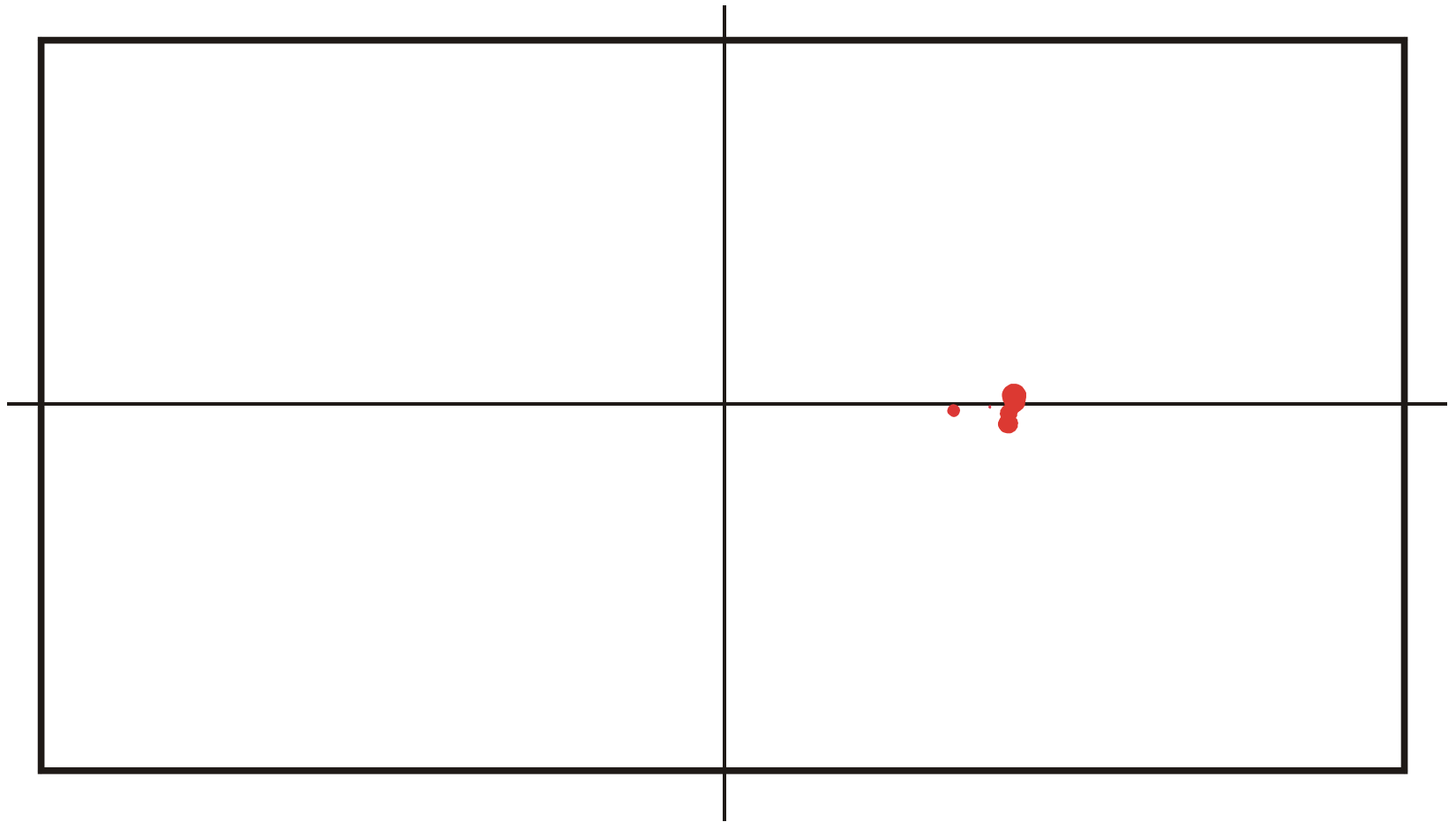
Spreading and evolution of a population on a neutral network : $t = 835$



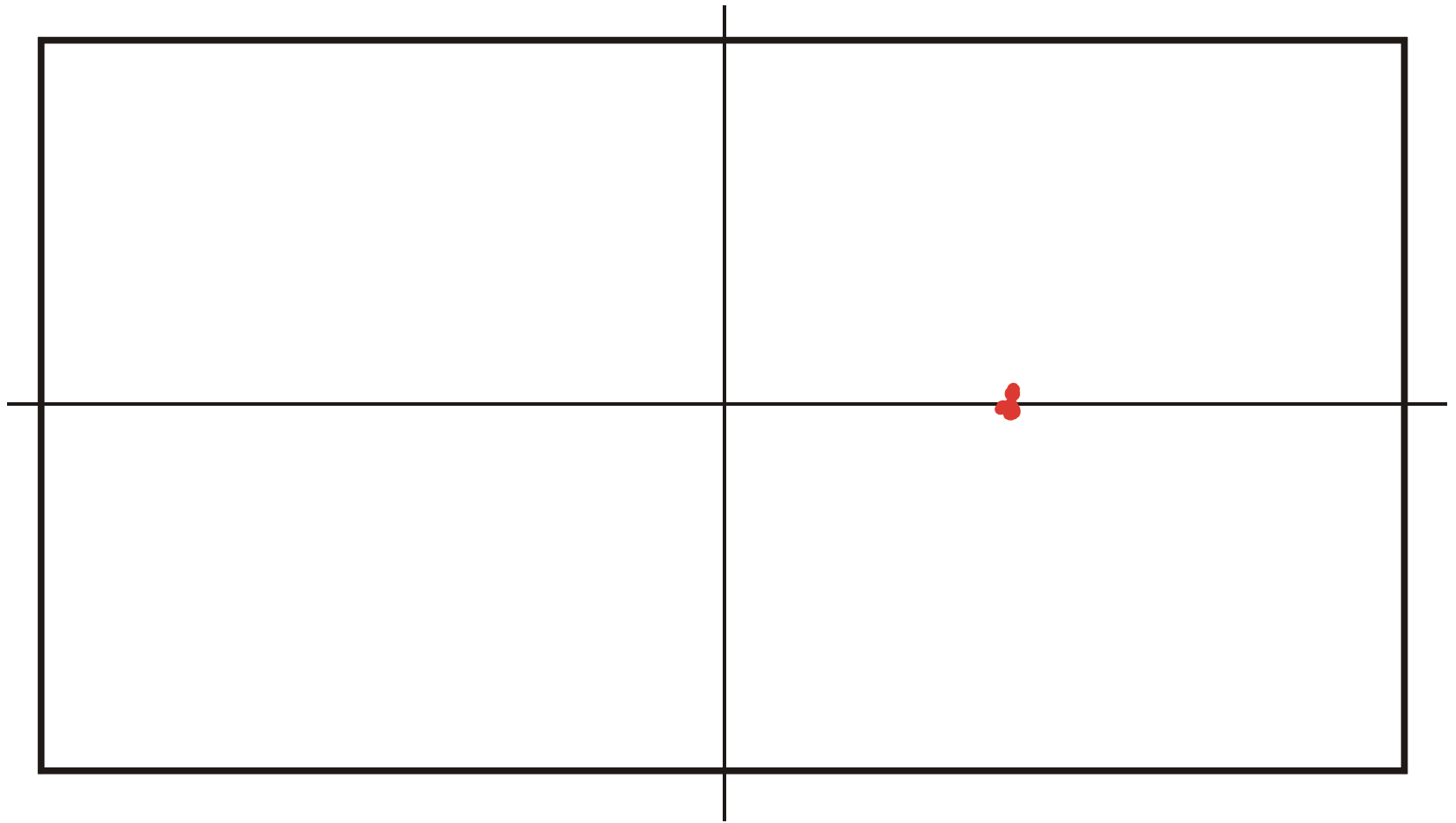
Spreading and evolution of a population on a neutral network : $t = 840$



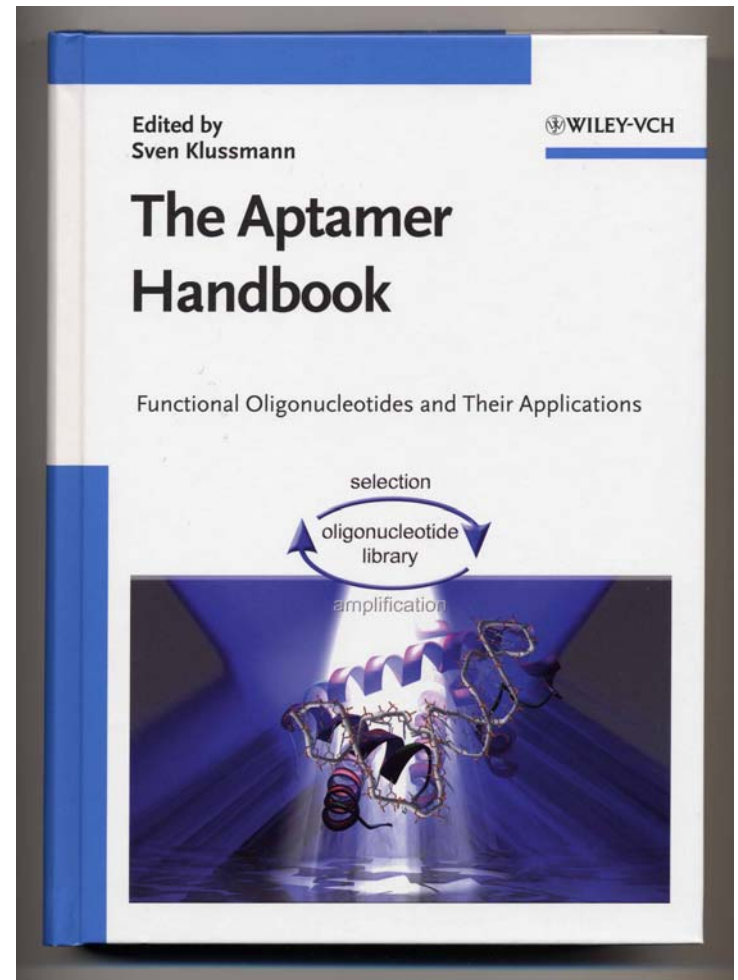
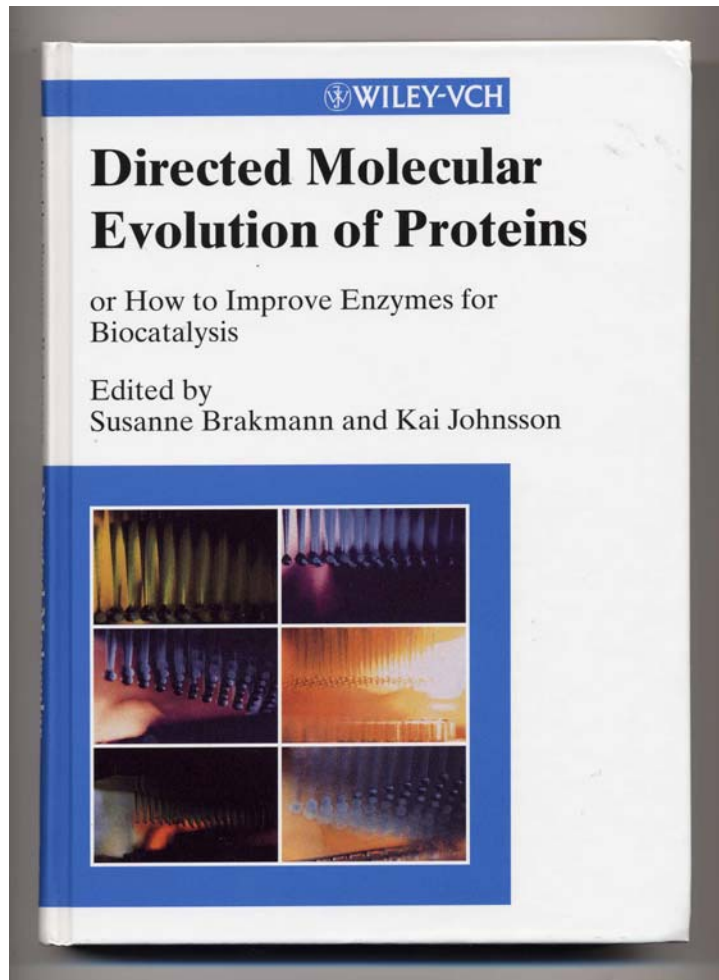
Spreading and evolution of a population on a neutral network : $t = 845$



Spreading and evolution of a population on a neutral network : $t = 850$

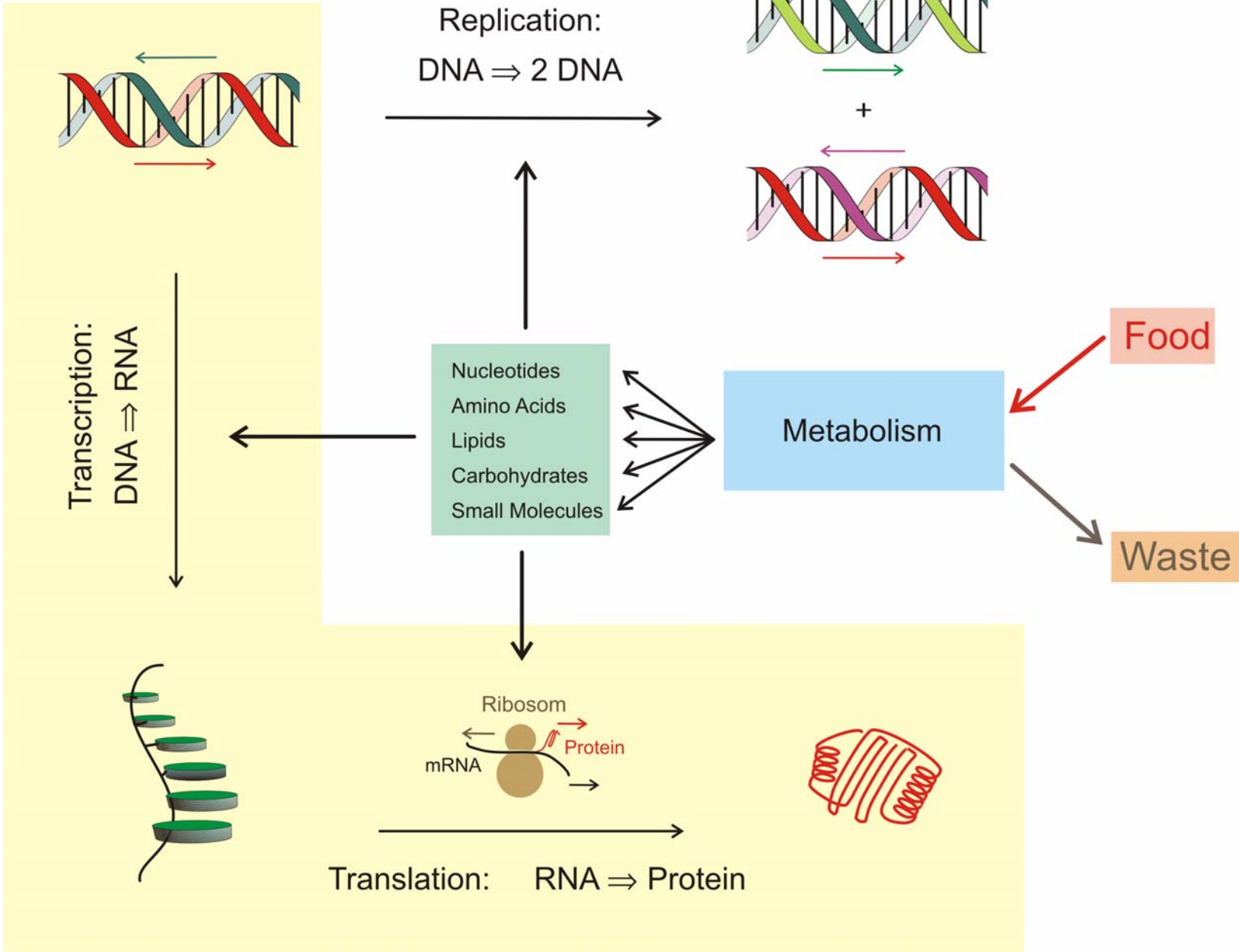


Spreading and evolution of a population on a neutral network : $t = 855$

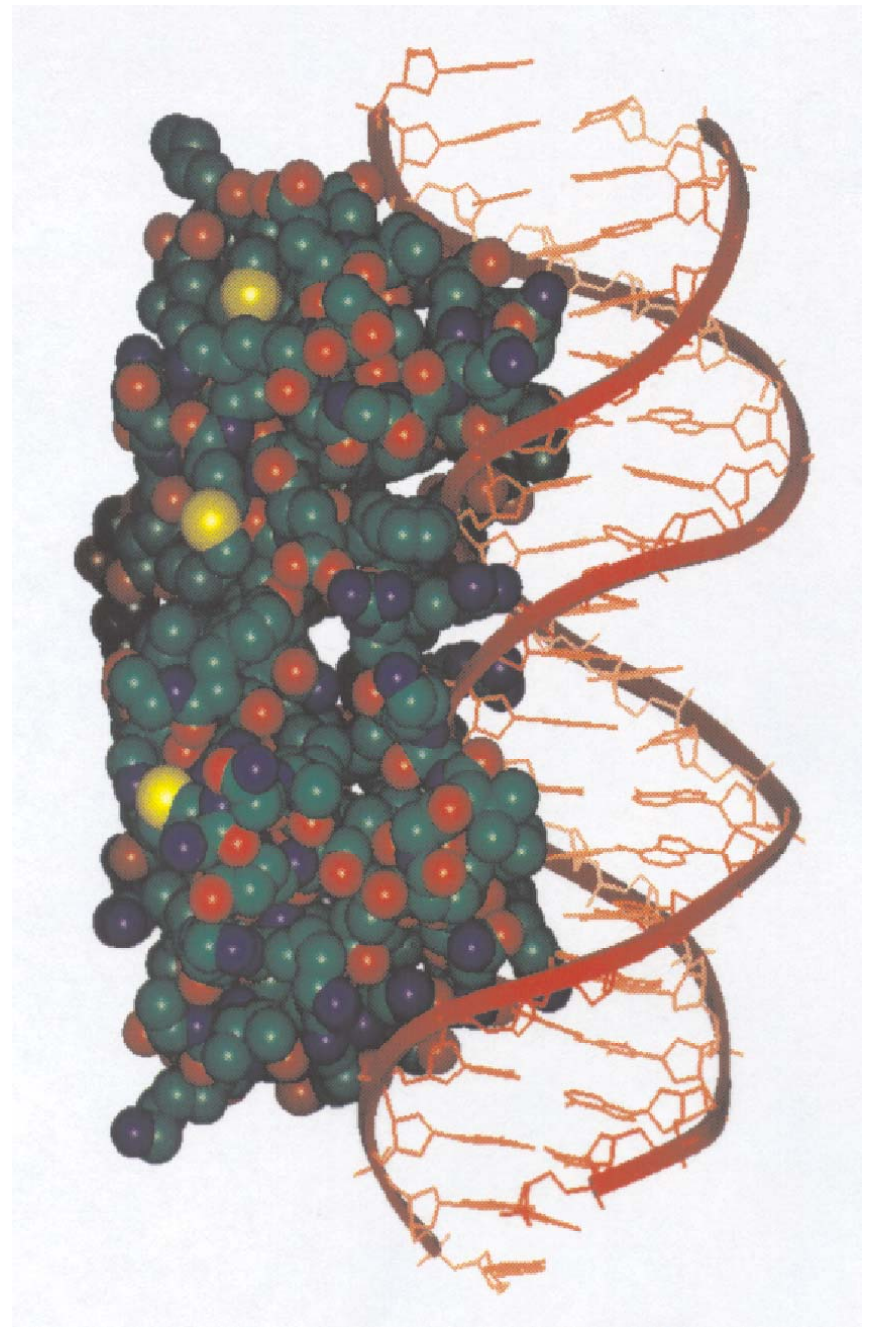


Application of molecular evolution to problems in biotechnology

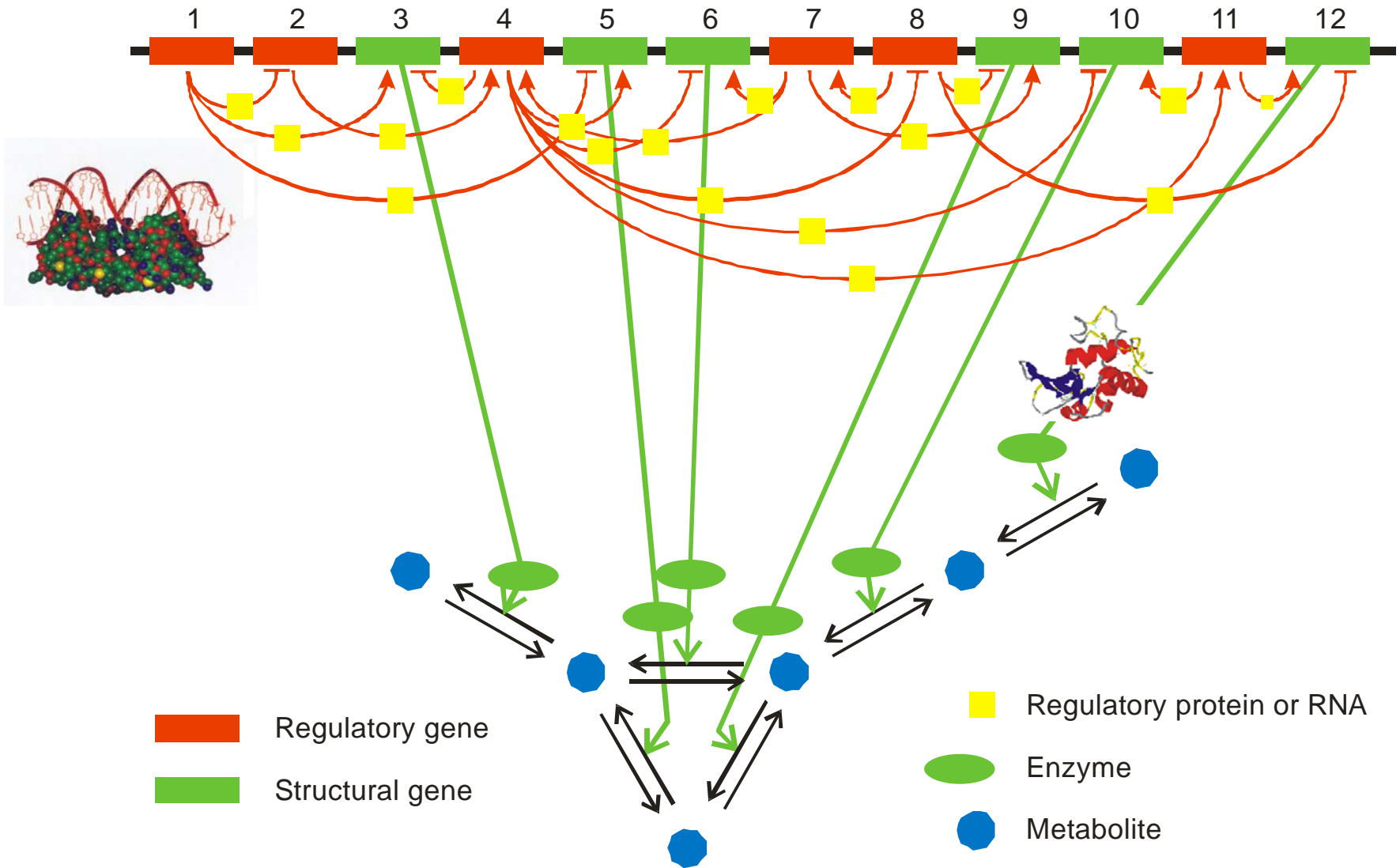
1. Evolution - organismisch und molekular
2. Wahrscheinlichkeiten in der Biologie
3. Vermehrung, Mutation und Selektion
4. Molekulares Design
5. Evolution von Molekülen und Optimierung
6. **Die Komplexität der Biologie**



Three-dimensional structure of the complex between the regulatory protein **cro-repressor** and the binding site on λ -phage **B-DNA**



A model genome with 12 genes



Sketch of a genetic and metabolic network

Dynamic patterns of gene regulation I: Simple two-gene systems

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Abstract

Regulation of gene activities is studied by means of computer assisted mathematical analysis of ordinary differential equations (ODEs) derived from binding equilibria and chemical reaction kinetics. Here, we present results on cross-regulation of two genes through activator and/or repressor binding. Arbitrary (differentiable) binding function can be used but systematic investigations are presented for gene–regulator complexes with integer valued Hill coefficients up to $n = 4$. The dynamics of gene regulation is derived from bifurcation patterns of the underlying systems of kinetic ODEs. In particular, we present analytical expressions for the parameter values at which one-dimensional (transcritical, saddle-node or pitchfork) and/or two-dimensional (Hopf) bifurcations occur. A classification of regulatory states is introduced, which makes use of the sign of a ‘regulatory determinant’ D (being the determinant of the block in the Jacobian matrix that contains the derivatives of the regulator binding functions): (i) systems with $D < 0$, observed, for example, if both proteins are activators or repressors, to give rise to one-dimensional bifurcations only and lead to bistability for $n \geq 2$ and (ii) systems with $D > 0$, found for combinations of activation and repression, sustain a Hopf bifurcation and undamped oscillations for $n > 2$. The influence of basal transcription activity on the bifurcation patterns is described. Binding of multiple subunits can lead to richer dynamics than pure activation or repression states if intermediates between the unbound state and the fully saturated DNA initiate transcription. Then, the regulatory determinant D can adopt both signs, plus and minus.

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Keywords: Basal transcription; Bifurcation analysis; Cooperative binding; Gene regulation; Hill coefficient; Hopf bifurcation

1. Introduction

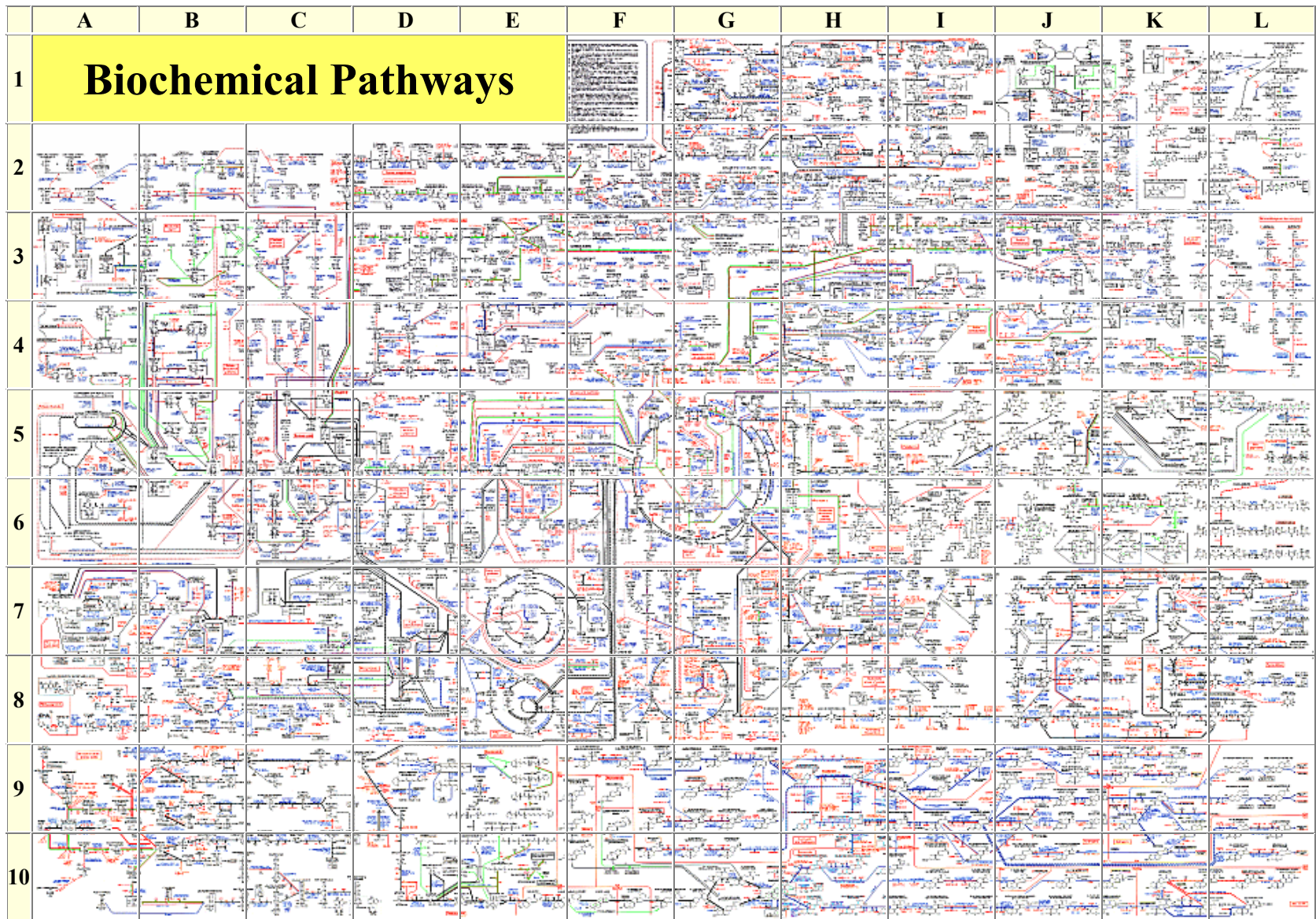
Theoretical work on gene regulation goes back to the 1960s (Monod et al., 1963) soon after the first repressor protein had been discovered (Jacob and Monod, 1961). A little later the first paper on oscillatory states in gene regulation was published (Goodwin, 1965). The interest in gene regulation and its mathematical analysis never ceased (Tiwarei et al., 1974; Tyson and Othmer, 1978; Smith, 1987) and saw a great variety of different attempts to design models of genetic regulatory networks that can be used in systems biology for computer simulation of *genetic* and

metabolic networks.¹ Most models in the literature aim at a minimalist dynamic description which, nevertheless, tries to account for the basic regulatory functions of large networks in the cell in order to provide a better understanding of cellular dynamics. A classic in general regulatory dynamics is the monograph by Thomas and D’Ari (1990). The currently used mathematical methods comprise application of Boolean logic (Thomas and Kaufman, 2001b; Savageau, 2001; Albert and Othmer, 2003), stochastic processes (Hume, 2000) and deterministic dynamic models, examples are Cherry and Adler (2000), Bindschadler and Sneyd (2001) and Kobayashi et al. (2003) and the recent elegant analysis of bistability (Craciun et al.,

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¹Discussion and analysis of combined genetic and metabolic networks has become so frequent and intense that we suggest to use a separate term, *genabolic networks*, for this class of complex dynamical systems.

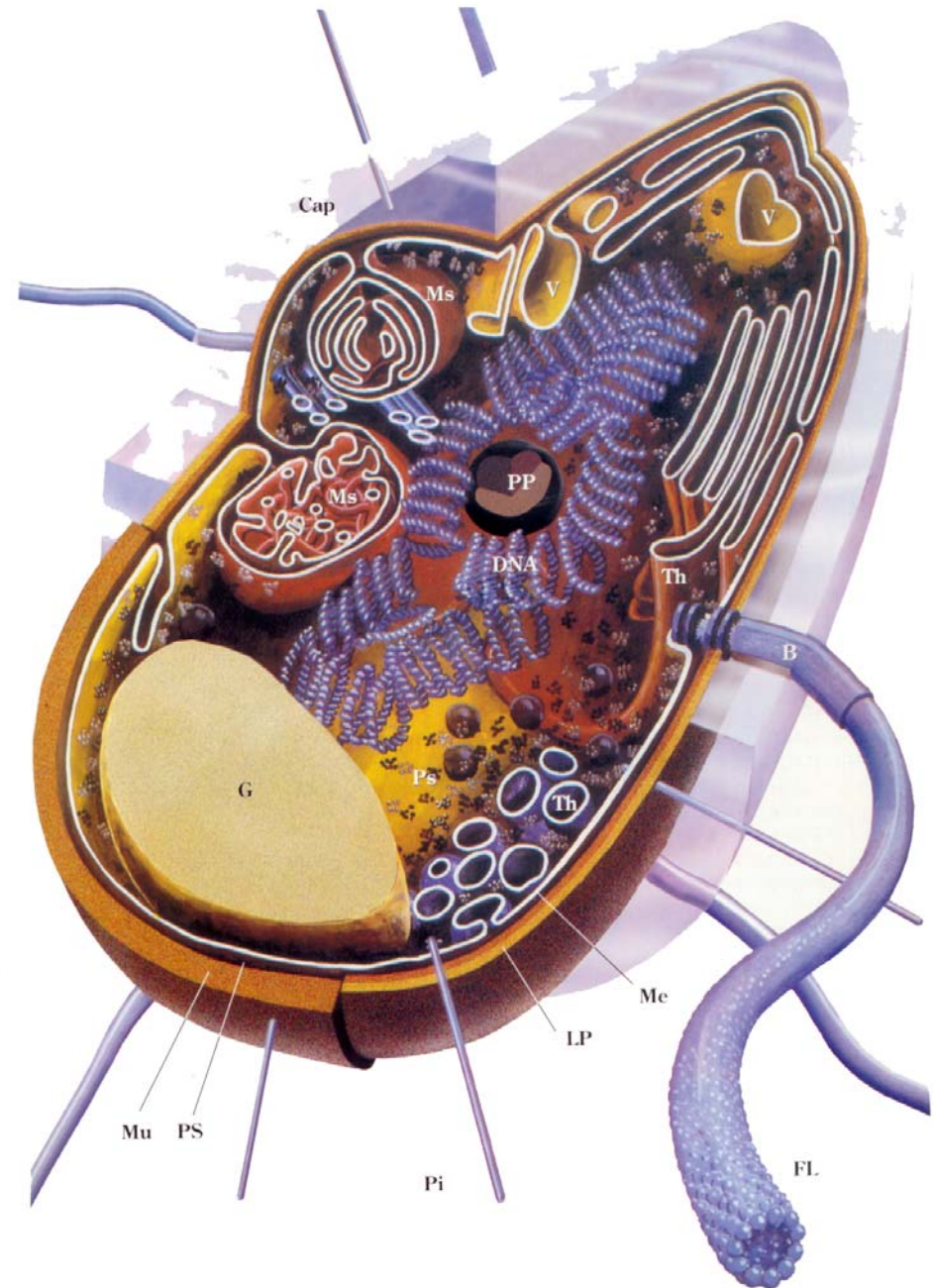


The reaction network of cellular metabolism published by Boehringer-Ingelheim.

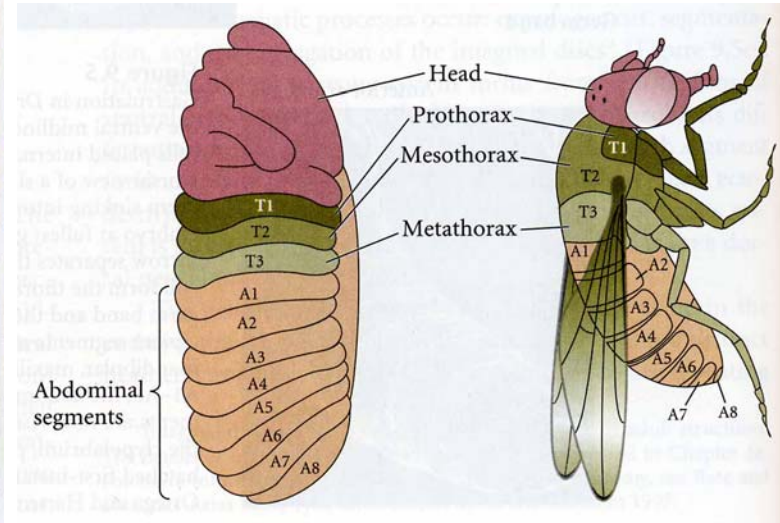
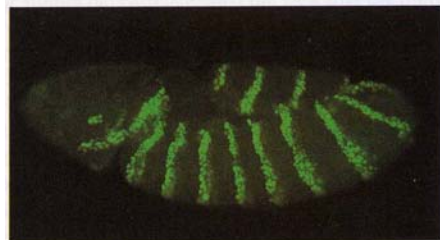
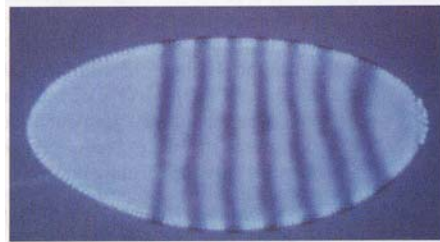
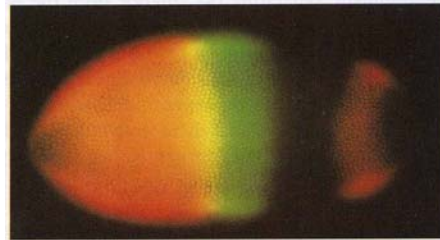
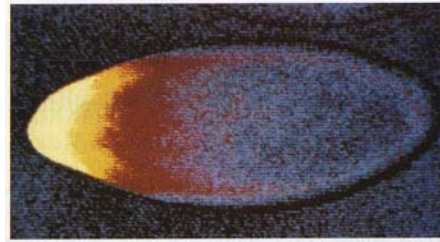
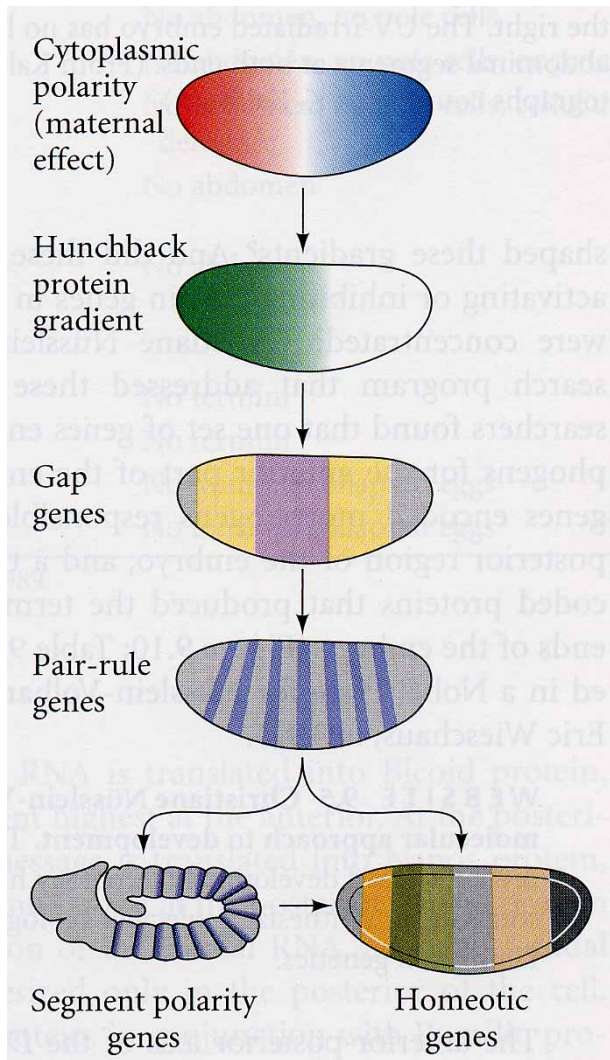
The bacterial cell as an example for the simplest form of autonomous life

The human body:

10^{14} cells = 10^{13} eukaryotic cells +
 $\approx 9 \times 10^{13}$ bacterial (prokaryotic) cells,
and ≈ 200 eukaryotic cell types



The spatial structure of the bacterium *Escherichia coli*



Cascades, $A \Rightarrow B \Rightarrow C \Rightarrow \dots$, and networks of genetic control

Turing pattern resulting from reaction-diffusion equation ?

Intercellular communication creating positional information

Development of the fruit fly *drosophila melanogaster*: Genetics, experiment, and imago

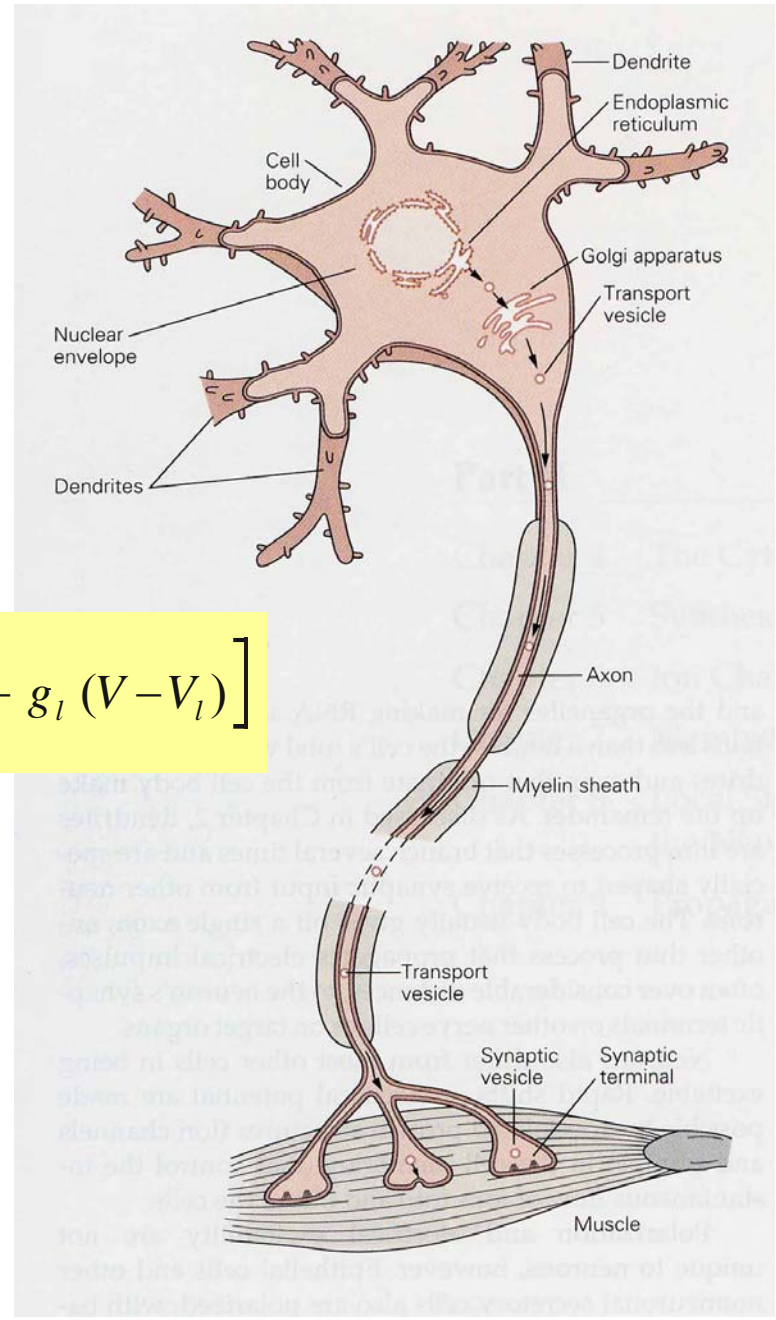
$$\frac{dV}{dt} = \frac{1}{C_M} \left[I - g_{Na} m^3 h (V - V_{Na}) - g_K n^4 (V - V_K) - g_l (V - V_l) \right]$$

$$\frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m$$

$$\frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h$$

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n$$

Hogdkin-Huxley OD equations



A single neuron signaling to a muscle fiber

$$\frac{1}{R} \frac{\partial^2 V}{\partial x^2} = C \frac{\partial V}{\partial t} + [g_{Na} m^3 h (V - V_{Na}) + g_K n^4 (V - V_K) + g_l (V - V_l)] 2\pi r L$$

$$\frac{\partial m}{\partial t} = \alpha_m (1 - m) - \beta_m m$$

$$\frac{\partial h}{\partial t} = \alpha_h (1 - h) - \beta_h h$$

$$\frac{\partial n}{\partial t} = \alpha_n (1 - n) - \beta_n n$$

Hodgkin-Huxley partial differential equations (PDE)

Hodgkin-Huxley equations describing pulse propagation along nerve fibers



ANALYTICAL DYNAMICS OF NEURON PULSE PROPAGATION

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Received July 12, 2005; Revised January 11, 2006

The four-dimensional Hodgkin–Huxley equations describe the propagation in space and time of the action potential $v(z)$ along a neural axon with $z = x + ct$ and c being the pulse speed. The potential $v(z)$, which is parameterized by the temperature, is driven by three gating functions, $m(z)$, $n(z)$ and $h(z)$, each of which obeys formal first order kinetics with rate constants that are represented as nonlinear functions of the potential v . It is shown that this system can be analytically simplified (i) in the number of gating functions and (ii) in the form of associated rate functions while retaining to close approximation quantitative fidelity to computer solutions of the exact equations over the complete temperature range for which stable pulses exist. At a given temperature we record two solutions ($T < T_{\max}$) corresponding to a high-speed and a low-speed branch in speed-temperature plots, $c(T)$, or no solution ($T > T_{\max}$). The pulse is considered as composed of two contiguous parts: (i) a pulse front extending from $v(0) = 0$ to a pulse maximum $v = V_{\max}$, and (ii) a pulse back extending from V_{\max} through a pulse minimum V_{\min} to a final regression back to $v(z \rightarrow \infty) = 0$. An approximate analytic solution is derived for the pulse front, which is predicted to propagate at a speed $c(T) = 1203 \Theta^{\frac{2}{3}} (T^{\circ}\text{C}) \text{ cm/sec}$, $\Theta = 3^{\frac{T-37}{10}}$ in close agreement with computer solution of the exact Hodgkin–Huxley equations for the entire pulse. These results provide the basis for a derivation of two-dimensional differential equation systems for the pulse front and pulse back, which predict the pulse maximum and minimum over the operational temperature range $0 \leq T \leq 25^{\circ}\text{C}$, in close agreement with the exact equations. Most neuron dynamics studies have been based on voltage clamp experiments featuring external current injection in place of self-generating pulse propagation. Since the behaviors of the gating functions are similar, it is suggested that the present approximations might be applicable to such situations as well as to the dynamics of myelinated fibers.

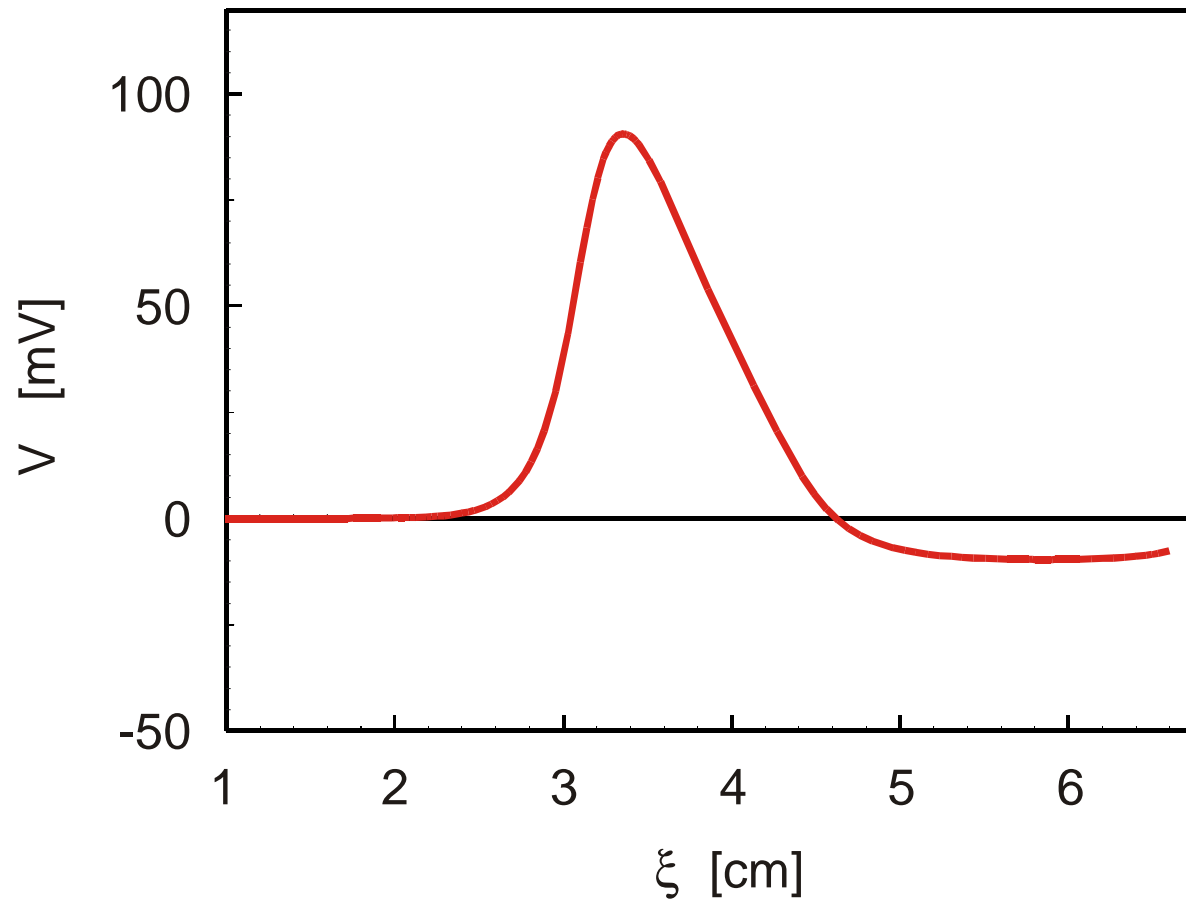
Keywords: Hodgkin–Huxley equations; action potentials; neuron models; nonlinear dynamics; neuron pulse propagation.

1. Neuron Pulse Propagation and the Hodgkin–Huxley Equations

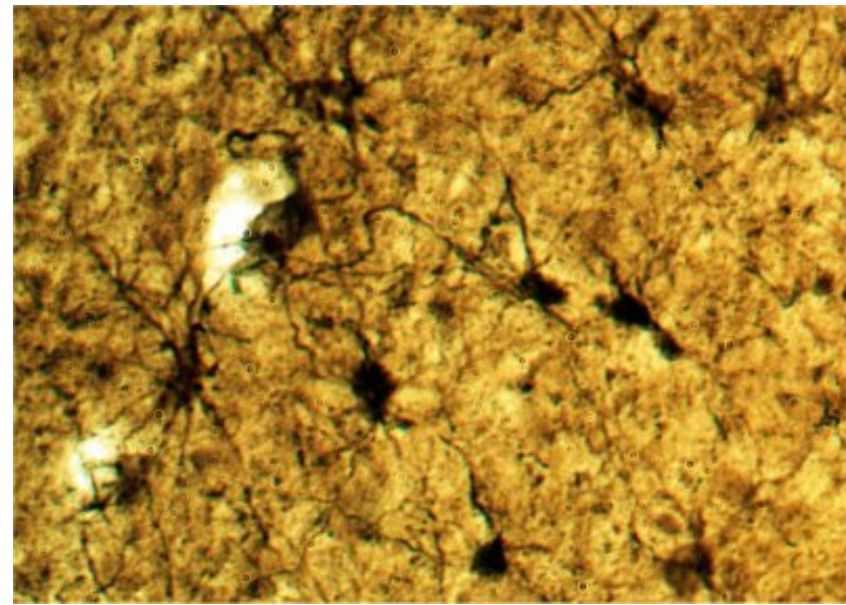
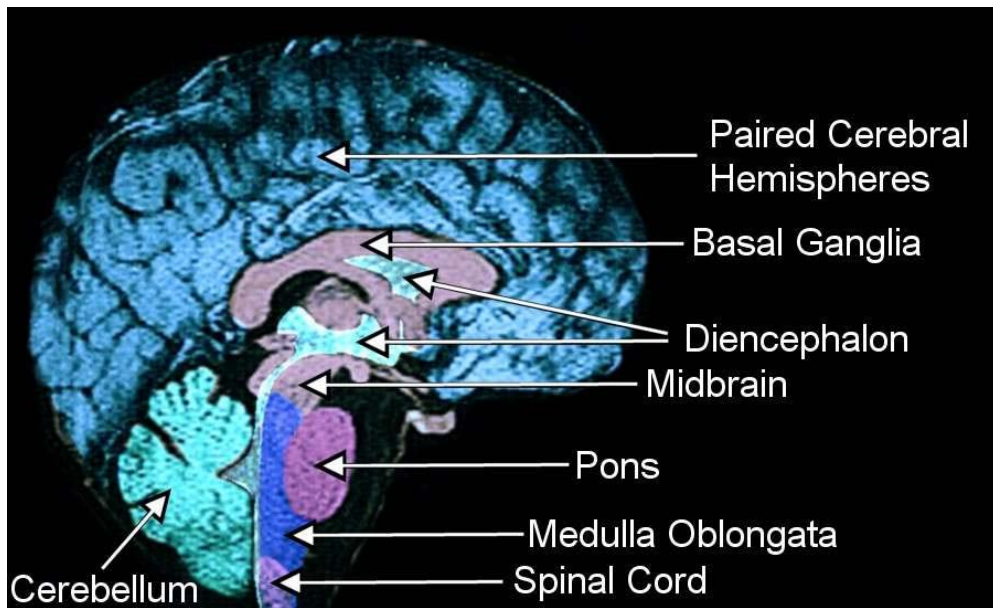
Conductance mechanisms for the propagation of a pulse along an unmyelinated neural axon were encapsulated within a predictive theory by the equations of Hodgkin and Huxley [1952]. These

equations became the prototype for description of neural pulse propagation and provide the basis for all subsequent conduction models of neural behavior. The Hodgkin–Huxley equations relate the propagating action potential v to sodium, potassium and leak conductances I_{Na} , I_{K} , I_{leak} causing the

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$T = 18.5 \text{ C}; \theta = 1873.33 \text{ cm / sec}$



The human brain

10^{11} neurons connected by $\approx 10^{13}$ to 10^{14} synapses



Darwin hatte in folgenden Punkten **nicht recht**:

- Der Darwinsche **Vererbungsmechanismus** war falsch. Mendel hatte die korrekte Lösung.
- Mutation und Rekombination können keine, kleine und große Auswirkungen haben und es besteht kein Grund, dass die biologische Evolution quasikontinuierlich oder anders ausgedrückt **nur in verschwindend kleinen Schritten** erfolgt.
- Im Verlaufe der biologischen Evolution gab es auch **katastrophenartige Ereignisse** terrestrischen und extraterrestrischen Ursprungs.
- Die Komplexität der höheren Lebewesen ist so groß, dass ihre Eigenschaften nicht **voll optimiert** sein können.

Darwins Theorie wurde in folgenden Punkten **voll bestätigt**:

- Das **Auftreten von Varianten** bei der Reproduktion wurde durch die Aufklärung der molekularen Mechanismen von Rekombination und Mutation auf eine solide wissenschaftliche Basis gestellt.
- Das Darwinsche **Prinzip der Optimierung durch Variation und Selektion** in endlichen Populationen gilt nicht nur in der Biologie sondern auch in der unbelebten Welt.
- Die natürliche Entstehung der Arten und die daraus resultierenden **phylogenetischen Stammbäume** wurde durch die Vergleiche der genetischen Informationsträger heute lebender Organismen voll bestätigt.

Das Brettspiel „Mensch ärgere dich nicht“ als ein Beispiel für das Zusammenwirken einer **deterministischen (Regeln)** und einer **zufälligen (Würfel)** Komponente:

Sicher ist, dass **einer** der vier Spieler dadurch gewinnen wird, dass er seine vier Figuren auf die vier vorgesehenen Plätze bringt.

Zufällig ist, **welcher der vier Spieler** das sein wird.

Die **Dauer des Spieles** zeigt eine für stochastische Prozesse typische **Wahrscheinlichkeitsverteilung**.



- Das Referat beschränkte sich auf die heutigen naturwissenschaftlichen Ergebnisse.
- Die Vorstellung der biologischen Evolution ist eine empirisch begründete, naturwissenschaftliche Theorie.
- Die Evolutionstheorie ist in einigen wesentlichen Aussagen experimentell prüfbar und überprüft und baut auf Tatsachen aus mehreren Teildisziplinen auf.
- Die Evolutionstheorie ist daher vom selben Rang wie physikalische Theorien, etwa die Newtonsche Mechanik, die Relativitätstheorie oder die Quantentheorie.
- Wie die meisten naturwissenschaftlichen Theorien kann die biologische Evolutionstheorie nicht alle beobachteten Einzelheiten erklären insbesondere, da die Biologie zur Zeit in einer faszinierenden und raschen Entwicklung steht.
- Die Molekularbiologie führt die biologischen Befunde auf Gesetzmäßigkeiten aus Physik und Chemie zurück, ohne dadurch die Eigenständigkeit der Biologie in Frage zu stellen.

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