

Chance and Randomness in Evolutionary Processes

Peter Schuster

Institut für Theoretische Chemie, Universität Wien, Austria
and

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



Concept of Probability in the Sciences

ESI Wien, 29.– 30.10.2018

Web-Page for further information:

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

1. Is evolution possible ?
2. "Non-probabilities" ?
3. Protein folding - a(n almost) solved example
4. Evolution - The survival of the fittest?
5. Genotype-phenotype mapping and evolution
6. The interplay of adaptation and random drift
7. Natural selection and evolution

1. Is evolution possible ?

2. "Non-probabilities" ?

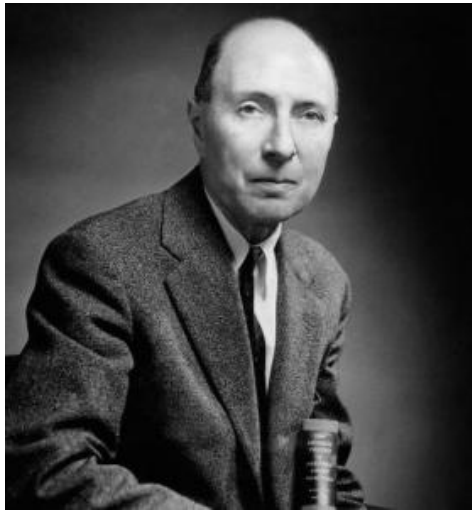
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Eugene P. Wigner
1902-1995

„Assembling elaborate structures
with specific functions through
random events is impossible.“

Statement used
as argument against
Darwinian evolution
and in the context of a
terrestrial origin of life



Fred Hoyle, 1915-2001

The argument is neither correct nor incorrect as long as it is not clearly said what
is meant by **random**?

Three well-known different degrees of randomness are used, e.g.,
(i) in random numbers, (ii) in random walks, and (iii) in targeted random paths.

Eugene Wigner's or Fred Hoyle's argument applied to a bacterium:

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

5'-end **GCGGATTAGCTCAGTTGGGAGAGCGCCAGACTGAAGATCTGGAGGTCCTGTGTTCTGAUCCACAGAATTC.....GCACCA** 3'-end

Alphabet size: 4

Chain length: $\approx 1\,000\,000$ nucleotides

Number of possible genomes: $4^{1\,000\,000}$

Probability to find a given bacterial genome:

$$4^{-1\,000\,000} \approx 10^{-600\,000} = 0.000\ldots001$$

600000
↔

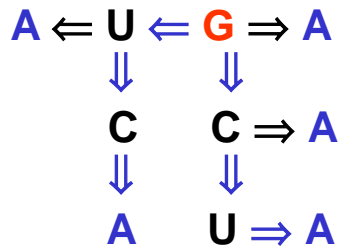
E. Wigner. The probability of the existence of a self-reproducing unit. In: E. Shils, ed. The logic of personal knowledge. Routledge & Kegan Paul, London 1961, pp.231-238

F. Hoyle. The intelligent universe. A new view of creation and evolution. Holt, Rinehart and Winston. New York 1983

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

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

5'-end **GCGGATTTAGCTCAGTTGGGAGAGCGCCAGACTGAAGATCTGGAGGTCCTGTGTTCGAUCCACAGAATTC.....GCACCA** 3'-end



Alphabet size: 4

Chain length: $\approx 1\,000\,000$ nucleotides

Length of longest path to the optimum: $3 \times 10\,000\,000$

Probability to find the optimal bacterial genome:

$$0.333.. \times 10^{-6} = 0.000000333..$$

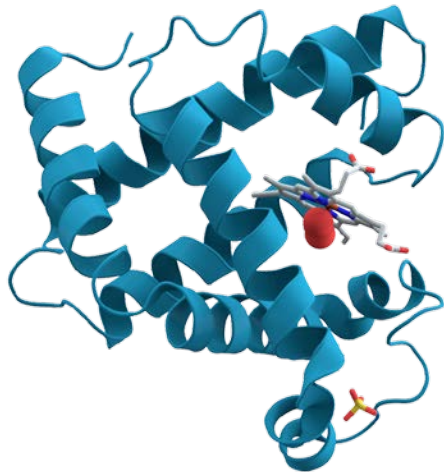
Myoglobin: 153 amino acid residues, MW 17.0 kDalton

amino acid sequence:

GLSDGEWQLV-LNVWGKVEAD-LAGHGQDVLI-RLFKGHPETL-EKFEKFKHLK-TEADMKASED-LKKHGNTVLT-ALGAILKKKG-
-HHDAELKPLA-ESHATKHKIP-IKYLEFISEA-IIHVLHSRHP-AEFGADAEGA-MDKALELFRK-DIAAKYKDLG-FHG

A	ala	alanine	I	ile	isoleucine	R	arg	arginine
C	cys	cysteine	K	lys	lysine	S	ser	serine
D	asp	aspartic acid	L	leu	leucine	T	thr	threonine
E	glu	glutamic acid	M	met	methionine	V	val	valine
F	phe	phenylalanine	N	asn	asparagine	W	trp	tryptophan
G	gly	glycine	P	pro	proline	Y	tyr	tyrosine
H	his	histidine	Q	glu	glutamine			

3D molecular structure:



Alphabet size: 20

Chain length: 153 amino acid residues

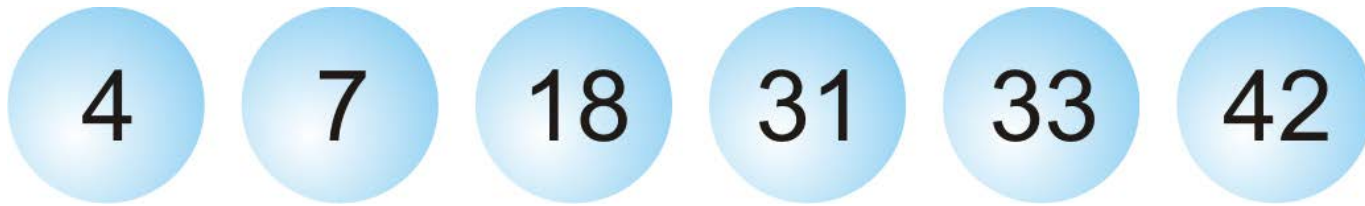
Number of possible sequences: $20^{153} \approx 0.11 \times 10^{200}$

Probability to find the native sequence:

$$20^{-153} \approx 8.8 \times 10^{-200}$$

Myoglobin – a small protein

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Probability: $P_{(6)} = \frac{6}{45} \times \frac{5}{44} \times \frac{4}{43} \times \frac{3}{42} \times \frac{2}{41} \times \frac{1}{40} \cong 1.23 \times 10^{-7}$

$$P_{(6)}^{-1} = 8145060$$

Maximum number of tips: 52.5×10^6 at January 21, 1991

the Austrian lottery „6 out of 45“

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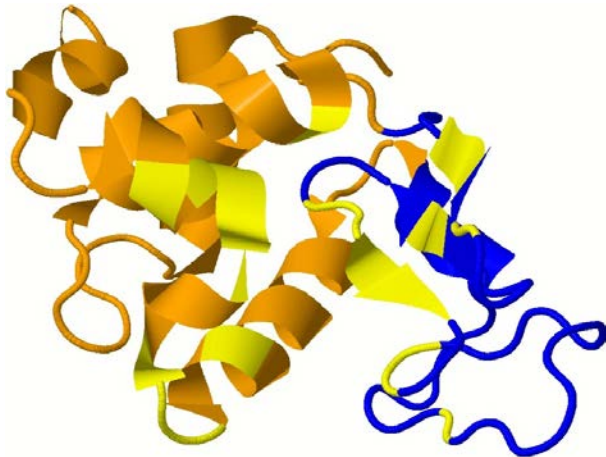
Lysozyme: 129 amino acid residues, MW: 14.4 kDalton

amino acid sequence:

KVFGRCELAA-AMKRHGLDNT-RGYSLGNWVC-AAKFESNFNT-QAYNRNTDGS-TDYGILEINS-RWWCNDGWTP-
-GSRNLCNIPC-SALLSSDITA-SVNCAKKIVS-DGDGMNAYVA-YRNRCKGTDV-QAWIRGCRL

A	ala	alanine	I	ile	isoleucine	R	arg	arginine
C	cys	cysteine	K	lys	lysine	S	ser	serine
D	asp	aspartic acid	L	leu	leucine	T	thr	threonine
E	glu	glutamic acid	M	met	methionine	V	val	valine
F	phe	phenylalanine	N	asn	asparagine	W	trp	tryptophan
G	gly	glycine	P	pro	proline	Y	tyr	tyrosine
H	his	histidine	Q	glu	glutamine			

3D molecular structure:



Conformations per amino acid residue: 3

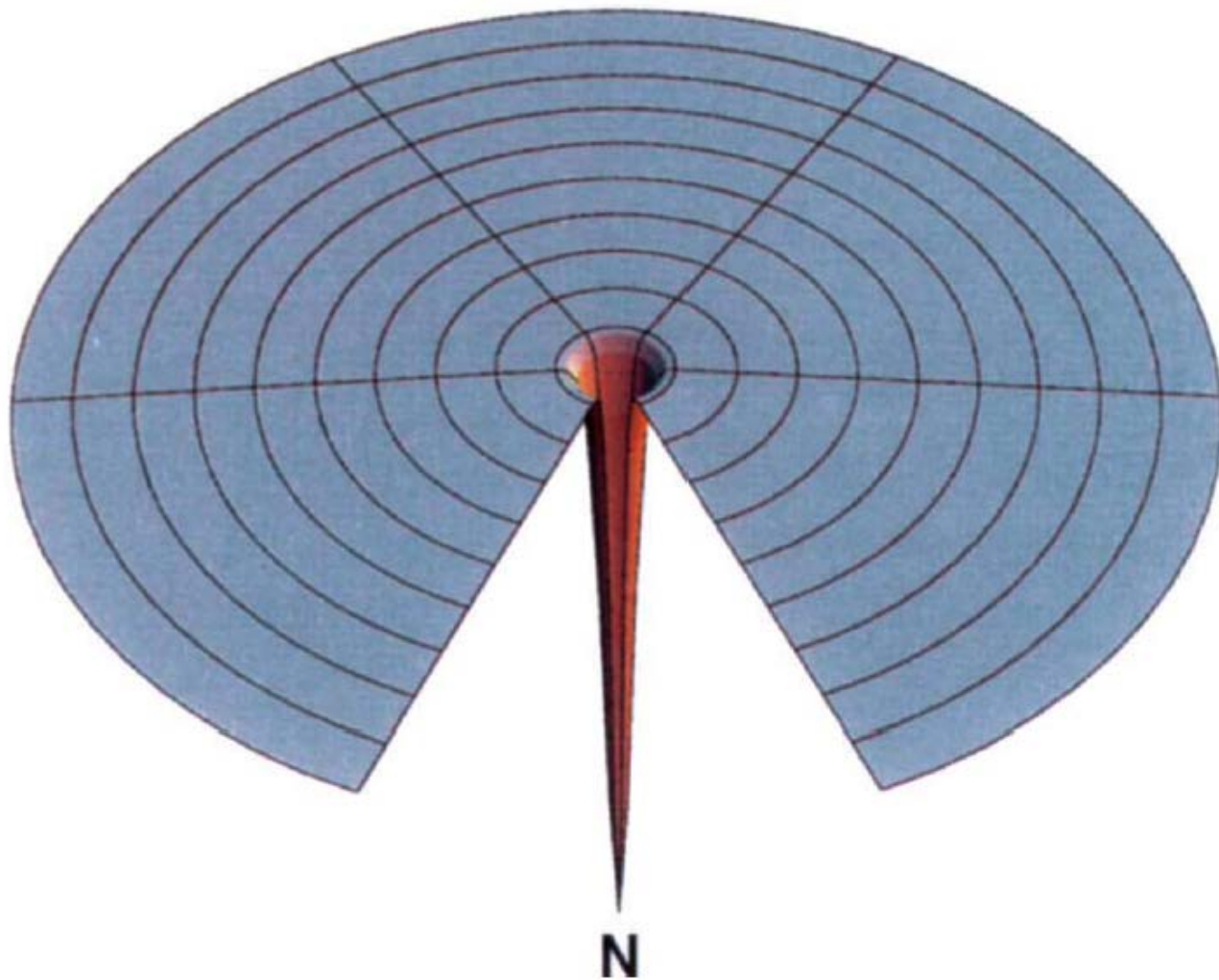
Chain length: 129 amino acid residues

Number of possible conformations: $8^{128} \approx 0.39 \times 10^{116}$

Probability to find the native conformation: $8^{-128} \approx 2.5 \times 10^{-116}$

Testing 10^{13} conformation per second it requires 1.3×10^{95} years to complete the search, **but** proteins of this chain length fold in about a second.

Lysozyme – a small protein

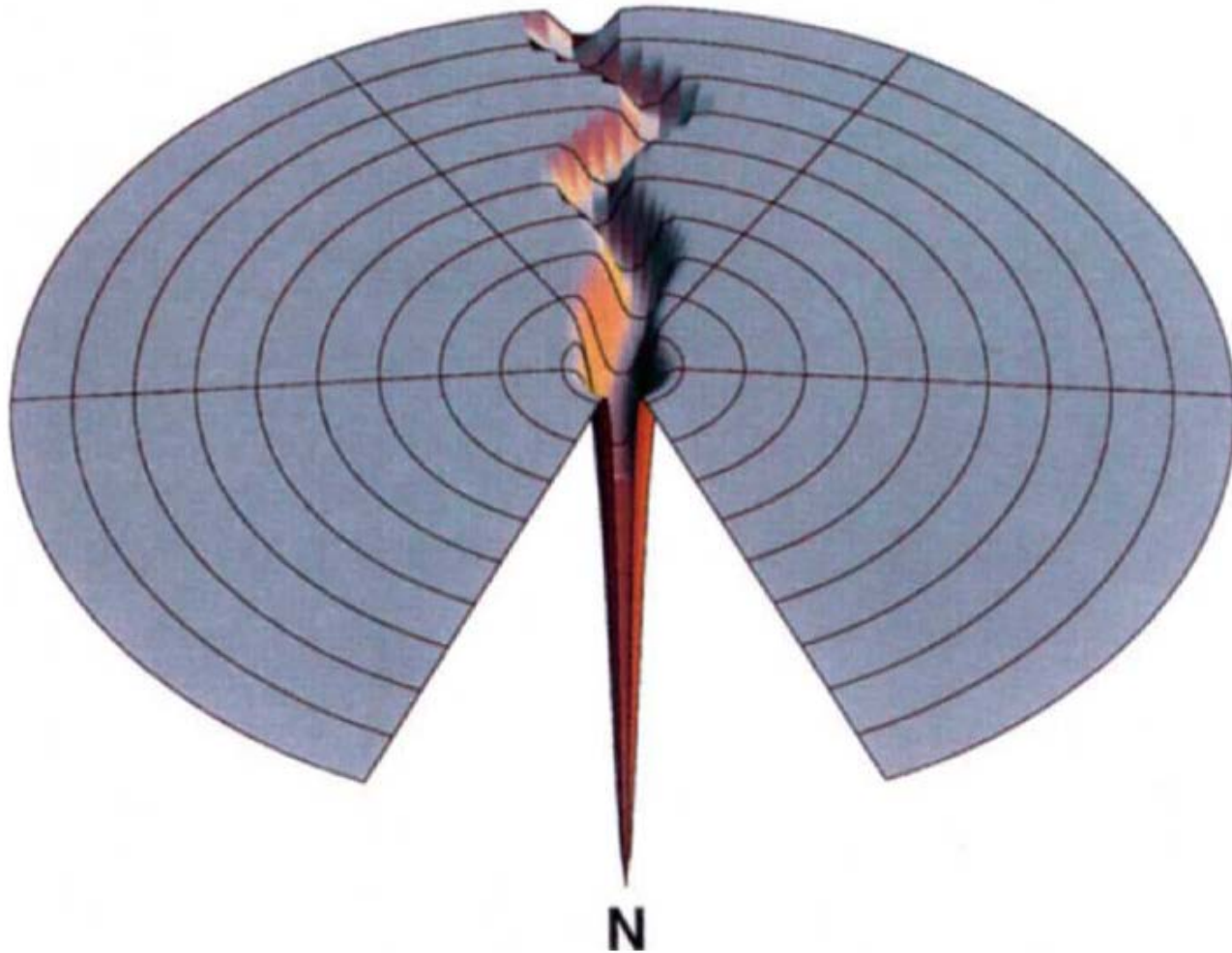


N is the native (folded) state

the golf-course landscape

Levinthal's paradox

Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19, 1997

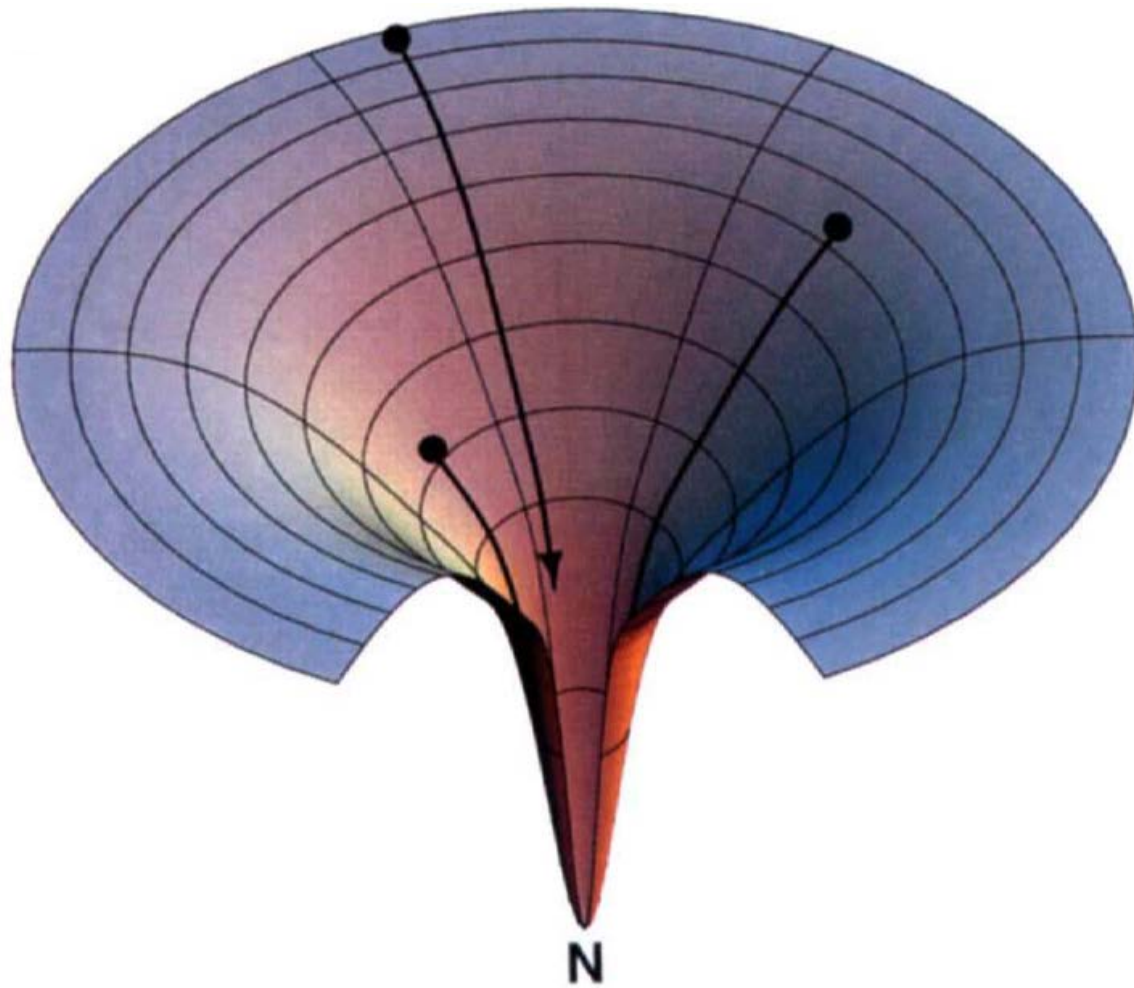


N is the native (folded) state

the “pathway” solution

Levinthal's paradox

Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19, 1997

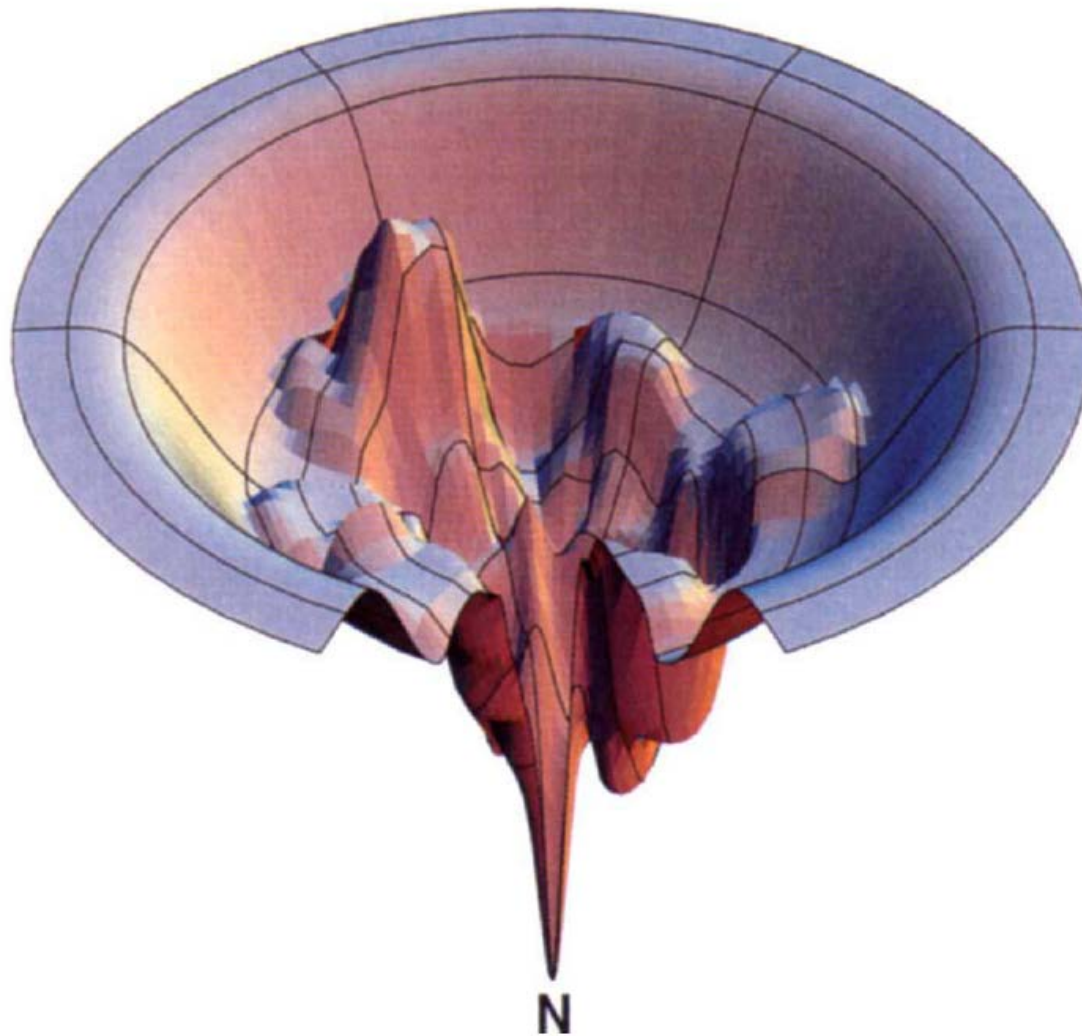


N is the native (folded) state

the funnel landscape

a solution to Levinthal's paradox

Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19, 1997



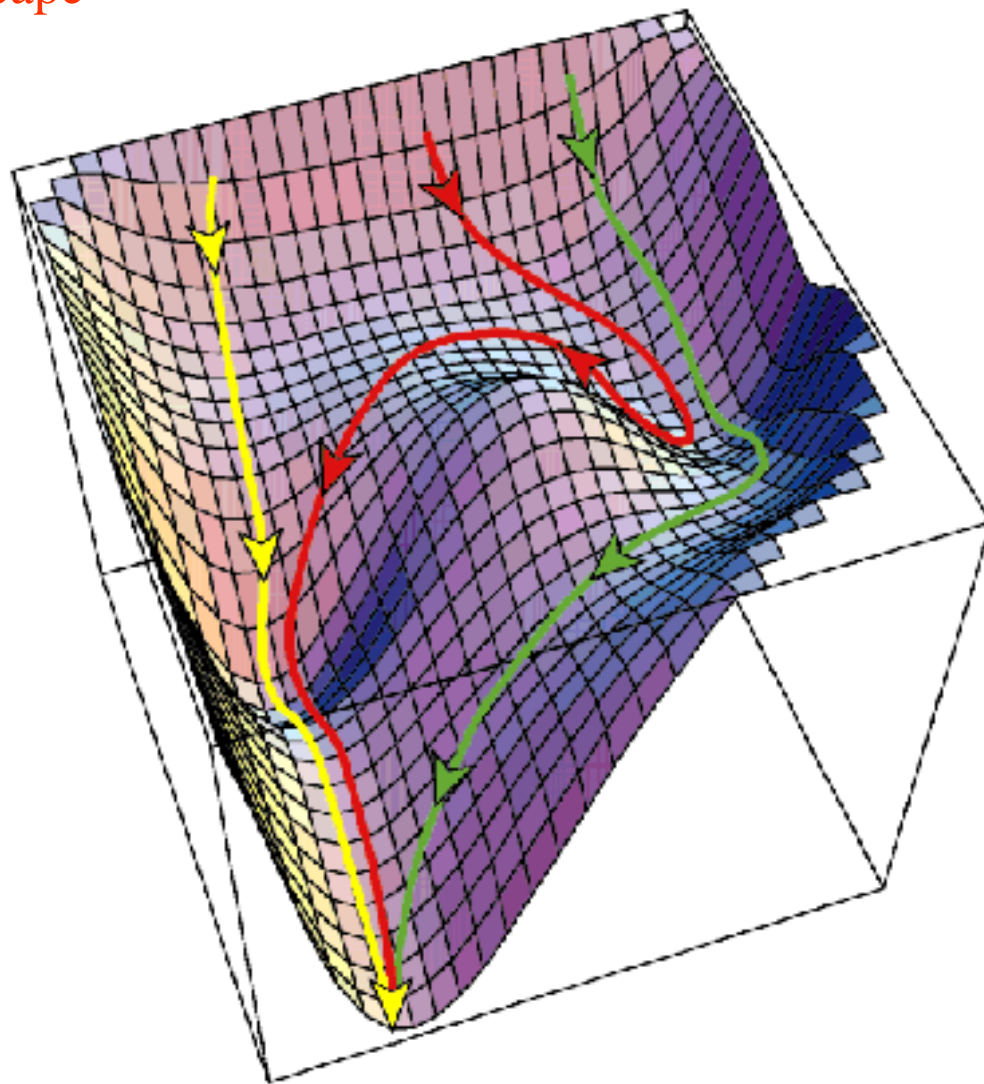
N is the native (folded) state

the structured funnel landscape

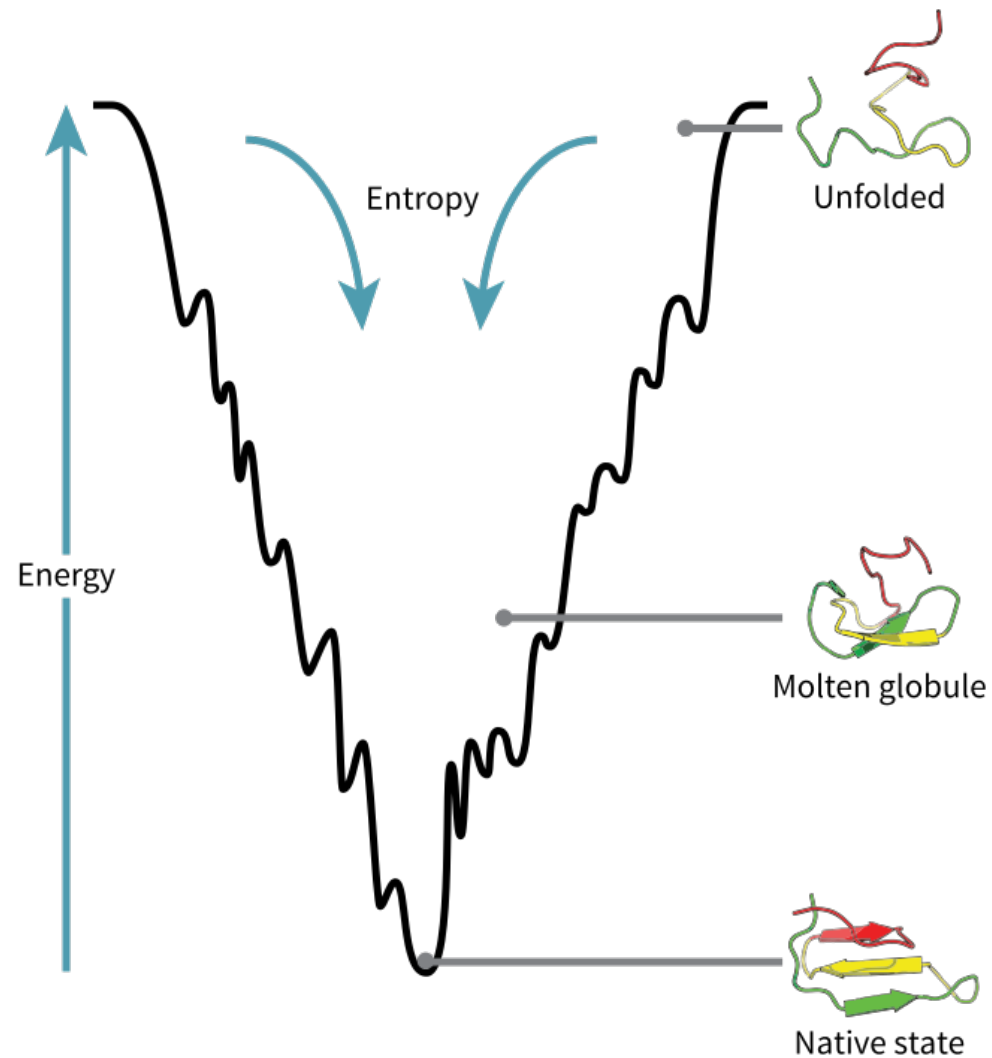
a realistic solution of
Levinthal's paradox

Picture: K.A. Dill, H.S. Chan, Nature Struct. Biol. 4:10-19, 1997

An “all-roads-lead-to-Rome” landscape



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



Statistical mechanics of protein folding

J.D. Bryngelson, J.N. Onuchic, N.D. Socci, P.G. Wolynes. *Proteins* 21:167-195, 1995

But biological landscapes for biopolymer folding or evolution are high dimensional and much more complex than the toy examples shown here.

However, protein and nucleic acid folding landscapes can be investigated by experiment and evolution under controlled laboratory conditions provides insights into the mechanism of biological evolution.

$$\begin{aligned}
U(\vec{R}) = & \sum_{bonds} K_b(b - b_0)^2 + \sum_{angles} K_\theta(\theta - \theta_0)^2 + \sum_{Urey-Bradley} K_{UB}(S - S_0)^2 + \\
& \sum_{dihedrals} K_\phi(1 + \cos(n\phi - \delta)) + \sum_{impropers} K_\omega(\omega - \omega_0)^2 + \\
& \sum_{\substack{non-bonded \\ pairs}} \left\{ \epsilon_{ij}^{min} \left[\left(\frac{R_{ij}^{min}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{ij}^{min}}{r_{ij}} \right)^6 \right] + \frac{q_i q_j}{4\pi\epsilon_0\epsilon r_{ij}} \right\} + \sum_{residues} U_{CMAP}(\phi, \psi)
\end{aligned}$$

Empirical force field for calculations of protein dynamics

CHARMM: B.R. Brooks, ... , M. Karplus. J.Comp.Chem. 30:1545-1614, 2009

The origin of energy landscapes in chemistry is the Born-Oppenheimer approximation of quantum mechanics.

Newtonian dynamics on a molecular energy landscape

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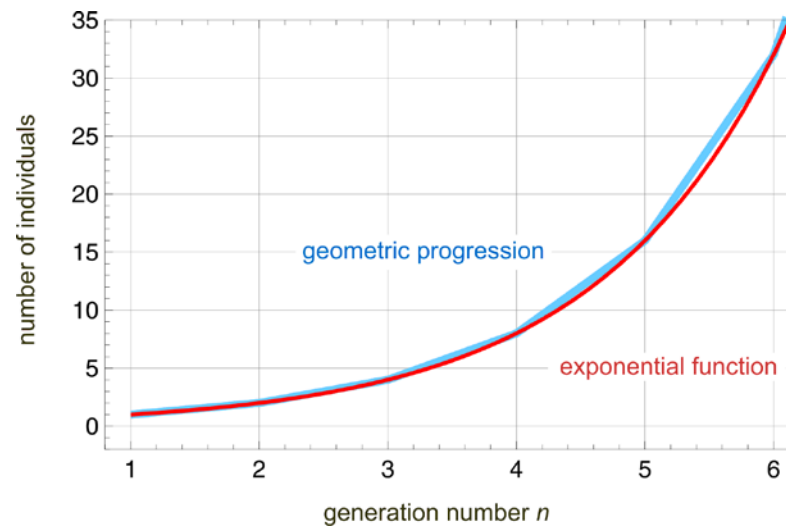
Thomas Robert Malthus,
1766 – 1834

geometric progression



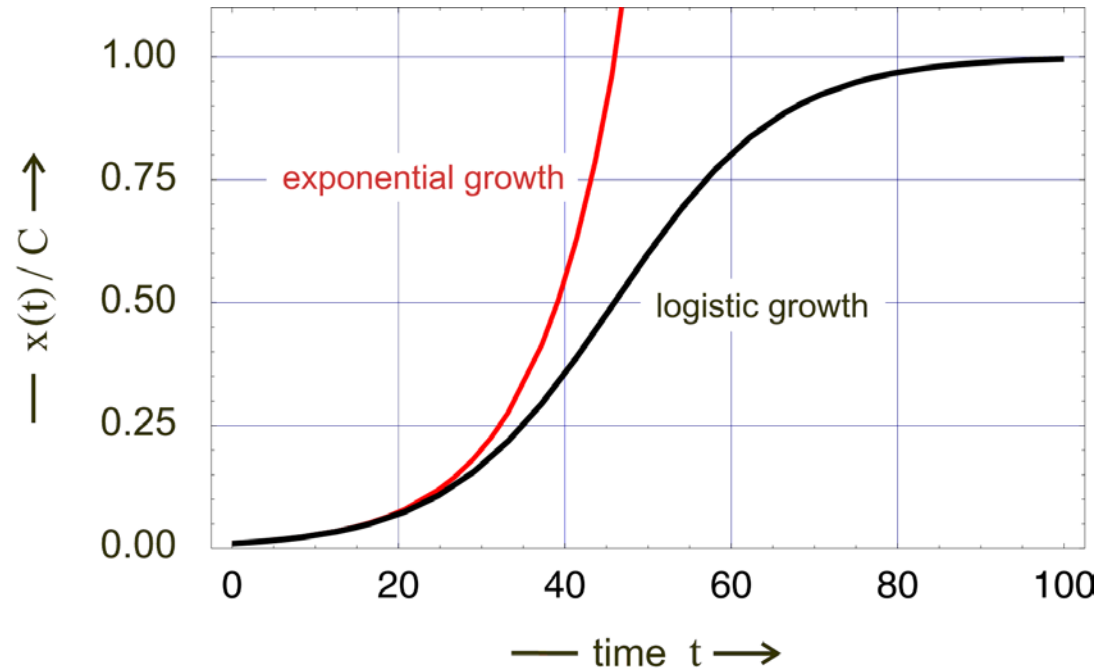
Leonhard Euler,
1717 – 1783

exponential function





Pierre-François Verhulst,
1804-1849



population: $\Pi = \{X\}$

the consequence of finite resources

$$\frac{dx}{dt} = f x \left(1 - \frac{x}{C} \right) \Rightarrow x(t) = \frac{C x_0}{x_0 + (C - x_0) \exp(-f t)}$$

the logistic equation: Verhulst 1838

Verhulst or logistic equation:

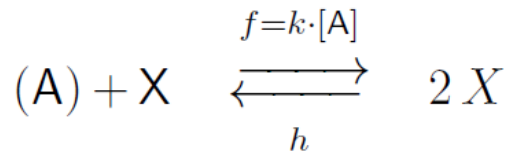
$$\frac{dx}{dt} = f \left(1 - \frac{x}{C}\right) x \quad \text{with} \quad x(0) = x_0$$

$$x(t) = \frac{C x_0}{x_0 + (C - x_0) e^{-r t}}$$

basic structure of the equation:

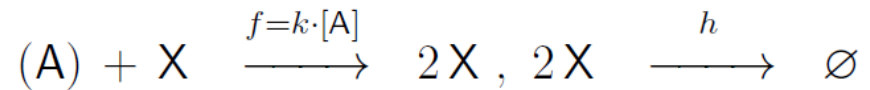
$$\frac{dx}{dt} = \gamma_1 x - \gamma_2 x^2$$

chemical models:



$$\frac{dx}{dt} = f x - h x^2$$

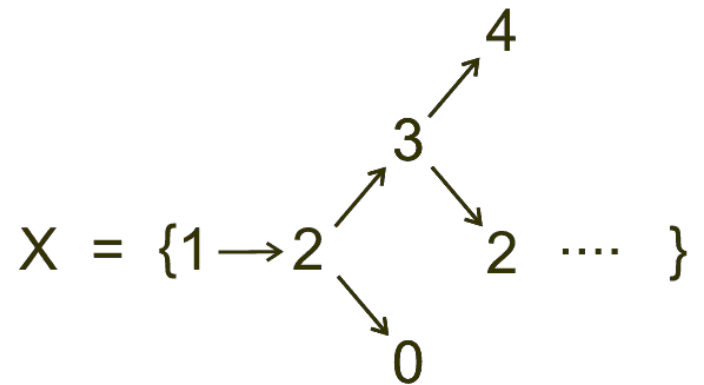
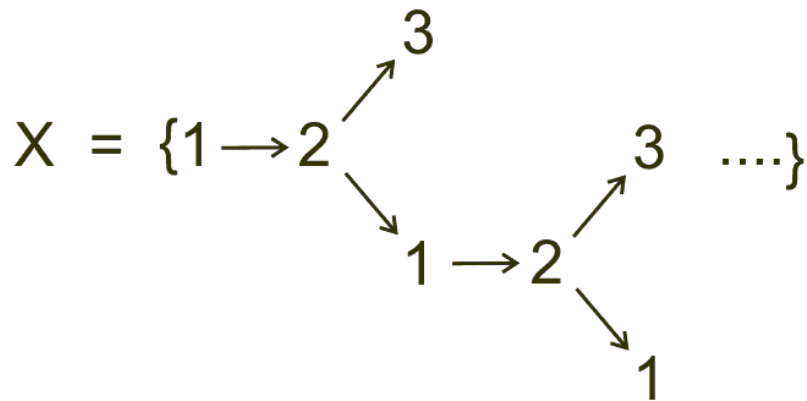
reversible autocatalytic reaction



$$\frac{dx}{dt} = f x - \frac{h}{2} x^2$$

annihilation reaction

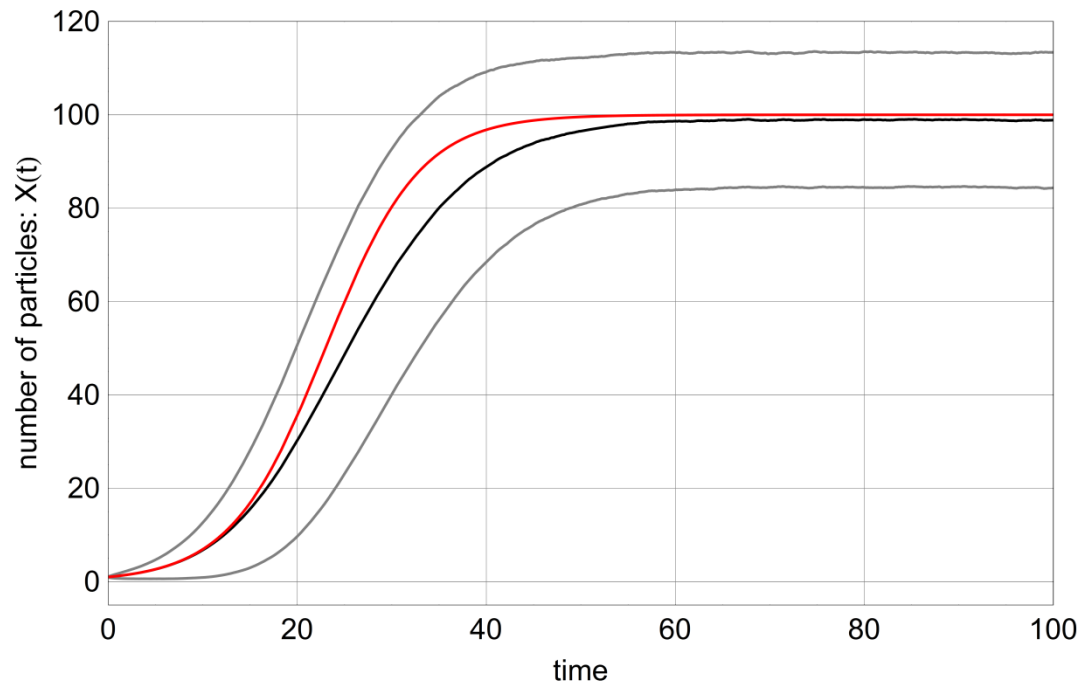
absorbing barrier: $X = 0 \rightarrow dx/dt = 0$



reversible autocatalytic reaction

reflecting barrier

annihilation reaction



logistic growth: $A + X \rightarrow 2X$, $2X \rightarrow \emptyset$, expectation value and **deterministic solution**

extinction in the logistic equation: $N = 100; f = 0.2; h = 0.001$, sample size: 10×10000 .

	X_0									
	1		2		3		4		5	
	X	extinct	X	extinct	X	extinct	X	extinct	X	extinct
numbers	99443	557	99478	522	99988	12	99984	16	99999	1
$E \pm \sigma$	9944.3 ± 7.5	55.7 ± 7.5	9947.8 ± 9.3	52.2 ± 9.3	9998.8 ± 1.0	1.2 ± 1.0	9998.4 ± 0.8	1.6 ± 0.8	9999.9 ± 0.3	0.1 ± 0.3

state of reproduction, S_1 and state of extinction S_0

$$X: \lim_{t \rightarrow \infty} E(X(t)) = C \quad \text{and} \quad \text{extinct: } \lim_{t \rightarrow \infty} X(t) = 0$$

bistability in the logistic equation

$$\frac{dx}{dt} = f x \left(1 - \frac{x}{C} \right) \Rightarrow \frac{dx}{dt} = f x - \frac{x}{C} f x$$

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

$$X_1, X_2, \dots, X_n: [X_i] = x_i; \quad \sum_{i=1}^n x_i = C = 1$$

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

Darwin's natural selection

$$\frac{d\Phi}{dt} = 2 \left(\langle f^2 \rangle - \langle f \rangle^2 \right) = 2 \text{var}\{f\} \geq 0 \quad \text{survival of the fittest}$$

Generalization of the logistic equation to n variables yields selection.

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

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

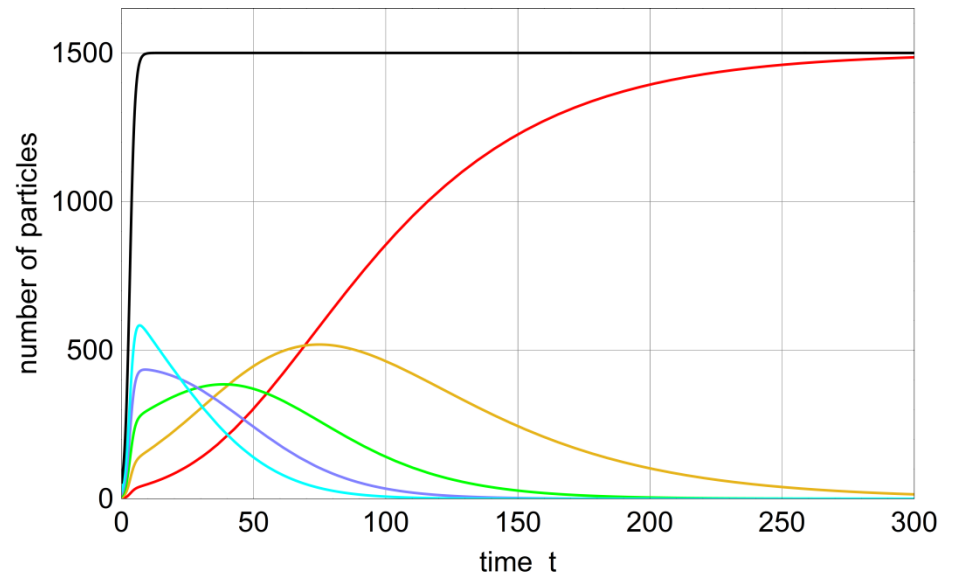
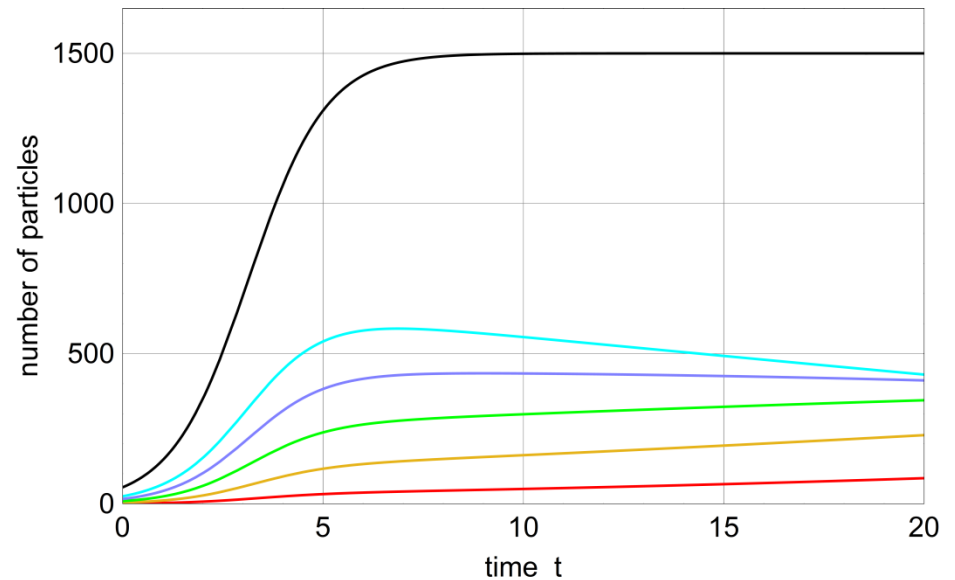
$$C(t) = \frac{C(0)K}{C(0) + (K - C(0))e^{-\Phi}}$$

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

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

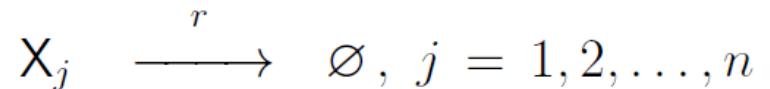
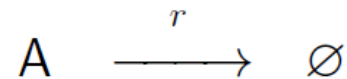
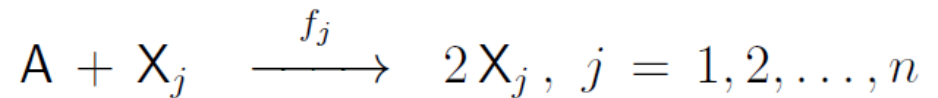
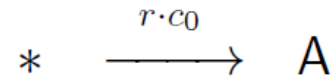
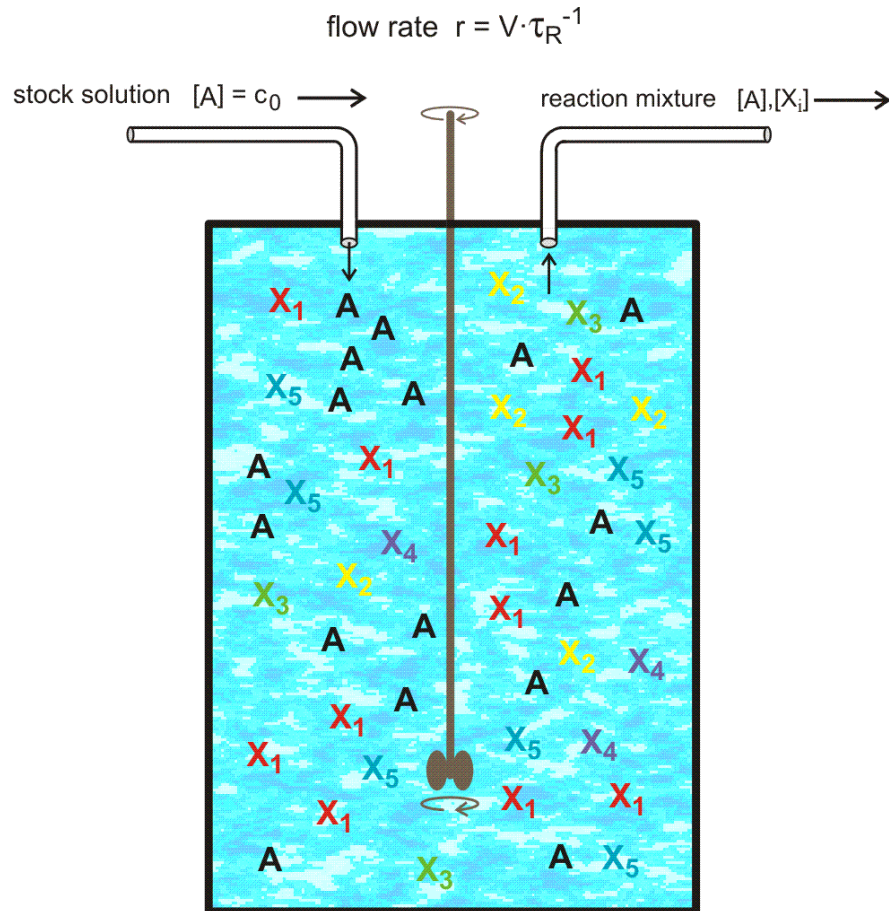
$$N(0) = (1, 4, 9, 16, 25)$$

$$f = (1.10, 1.08, 1.06, 1.04, 1.02)$$



population:

$$\Pi = \{X_1, X_2, X_3, \dots, X_n\}$$



$$\frac{da}{dt} = c_0 r - a \left(\sum_{j=1}^n f_j x_j + r \right)$$

$$\frac{dx}{dt} = x (f_j a - r), \quad j = 1, 2, \dots, n$$

selection in the flow reactor

$$P_m(t) = \text{Prob} \left(A(t) = m \right) \quad \text{and} \quad P_{s_i}(t) = \text{Prob} \left(X_i(t) = s_i \right)$$

$$\begin{aligned} \frac{dP_{\mathbf{m}}}{dt} = & c_0 r \left(P_{(\mathbf{m}; m-1)} - P_{\mathbf{m}} \right) + r \left((m+1) P_{(\mathbf{m}; m+1)} - m P_{\mathbf{m}} \right) + \\ & + r \sum_{i=1}^n \left((s_i + 1) P_{(\mathbf{m}; s_i+1)} - s_i P_{\mathbf{m}} \right) + \\ & + \sum_{i=1}^n f_i \left((m+1)(s_i - 1) P_{(\mathbf{m}; m+1, s_i-1)} - m s_i P_{\mathbf{m}} \right) \end{aligned}$$

$$\begin{aligned} \mathbf{m} &= (m, s_1, \dots, s_n); \quad \mathbf{m}' = (m \pm 1, s_1, \dots, s_n) \equiv (\mathbf{m}; m \pm 1) \quad \text{or} \\ &\mathbf{m}' = (m, s_1, \dots, s_k \pm 1, \dots, s_n) \equiv (\mathbf{m}; s_k \pm 1) \end{aligned}$$

master equation for reproduction and selection in the flow reactor

Analysis of the solutions of chemical master equations through sampling of trajectories. The pioneering work has been done by Andrej Kolmogorov, Willi Feller, Joe Doob, David Kendall, and Maurice Bartlett.

The American physicist Daniel Gillespie revived the Kolmogoriv-Feller formalism and introduced a popular and highly efficient simulation tool for stochastic chemical reactions.



Daniel T. Gillespie, 1938 –

D.T. Gillespie, *Annu.Rev.Phys.Chem.*
58:35-55, 2007

In the limit of an infinite number of trajectories the distribution of the trajectory bundle converges to the probability distribution of the corresponding solution of the master equation.

Gillespie simulation of individual trajectories

Springer Series in Synergetics

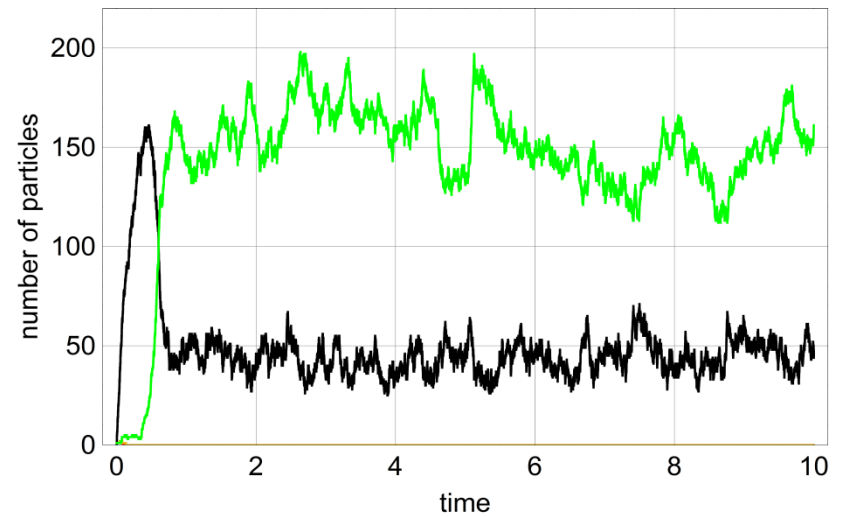
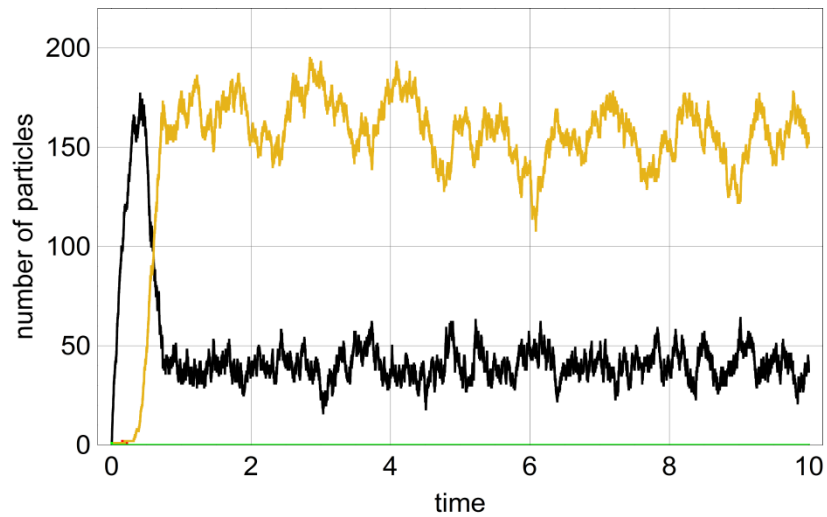
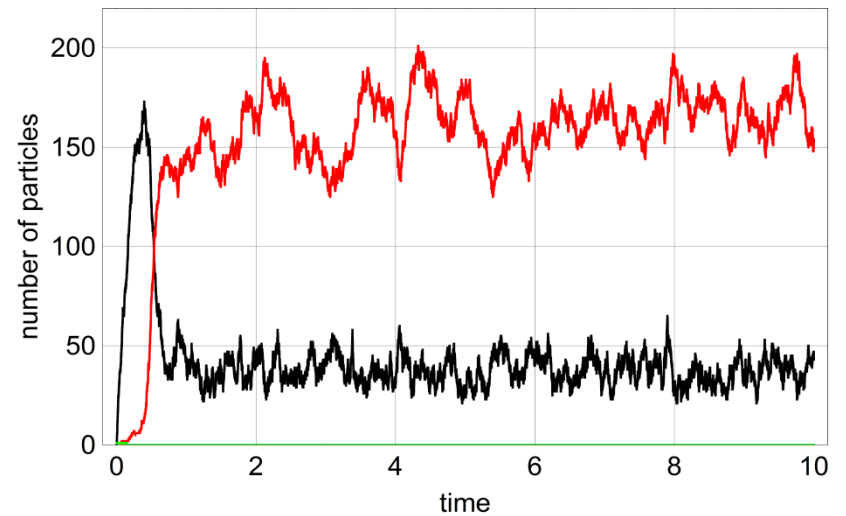
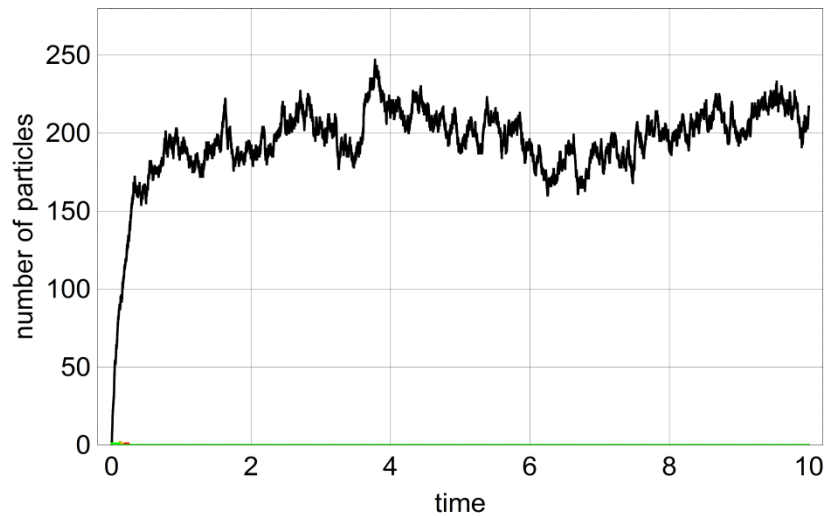
Springer :
COMPLEXITY

Peter Schuster

Stochasticity in Processes

Fundamentals and Applications to
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color code: A , X₁, X₂, X₃

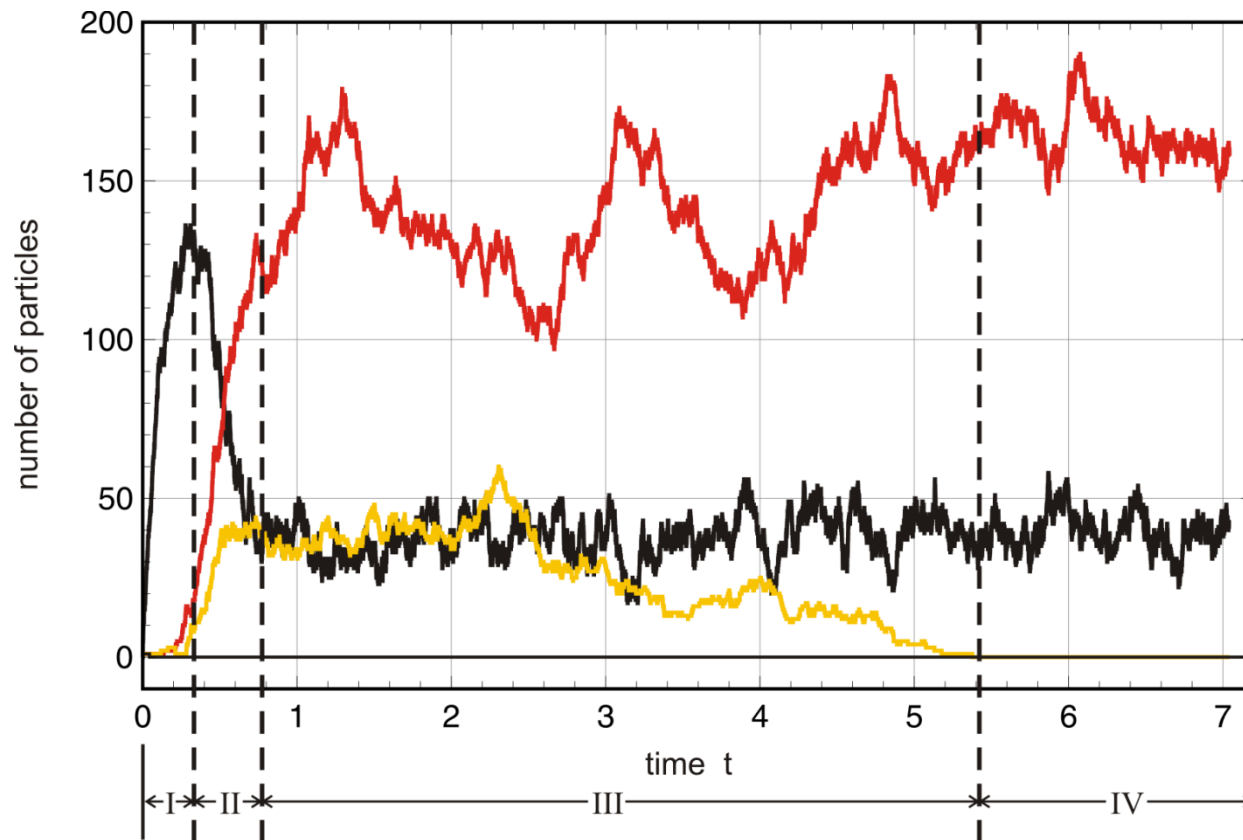
assorted sample of trajectories

$\Delta f / f$	t_e	Population size N = 100				Population size N = 200			
		A(t_e)	$X_1(t_e)$	$X_2(t_e)$	$X_3(t_e)$	A(t_e)	$X_1(t_e)$	$X_2(t_e)$	$X_3(t_e)$
0.0	600	1.5 ± 1.3	30.5 ± 3.9	34.2 ± 4.6	33.4 ± 4.1	0.5 ± 0.9	30.6 ± 4.6	30.9 ± 5.0	32.0 ± 4.7
0.02	600	1.8 ± 1.4	41.8 ± 4.8	32.9 ± 3.8	23.4 ± 4.0	0.6 ± 0.8	50.4 ± 5.7	27.7 ± 4.9	17.3 ± 2.6
0.04	400	2.4 ± 2.1	45.4 ± 5.0	31.3 ± 4.5	19.9 ± 2.5	0.7 ± 0.8	58.3 ± 4.6	25.6 ± 4.5	11.0 ± 2.9
0.1	400	2.1 ± 1.7	59.8 ± 5.5	28.0 ± 4.1	10.0 ± 2.9	0.4 ± 0.5	73.9 ± 4.1	20.6 ± 3.5	4.8 ± 1.9
0.2	400	1.9 ± 1.1	68.3 ± 4.5	23.1 ± 3.7	6.7 ± 2.8	0.5 ± 0.7	76.6 ± 4.1	19.3 ± 2.8	3.6 ± 1.7
0.4	400	2.3 ± 1.8	71.7 ± 6.0	20.8 ± 5.2	5.2 ± 2.4	0.9 ± 0.6	82.0 ± 4.2	13.8 ± 3.8	3.3 ± 1.7
1.0	200	2.7 ± 2.4	78.4 ± 4.7	15.8 ± 3.3	3.1 ± 1.5	0.9 ± 0.9	83.6 ± 4.0	12.6 ± 3.2	2.9 ± 1.5
1.8	200	4.3 ± 1.1	80.8 ± 2.9	13.6 ± 3.1	1.3 ± 1.2	1.5 ± 1.3	83.8 ± 3.3	12.7 ± 2.5	2.0 ± 1.7

$n = 3$: $X_1, f_1 = f + \Delta f / 2f$; $X_2, f_2 = f$; $X_3, f_3 = f - \Delta f / 2f$; $f = 0.1$

initial particle numbers: $X_1(0) = X_2(0) = X_3(0) = 1$

probability of selection



phase I: raise of $[A]$;

phase II: random choice of convergence to a quasi-stationary state;

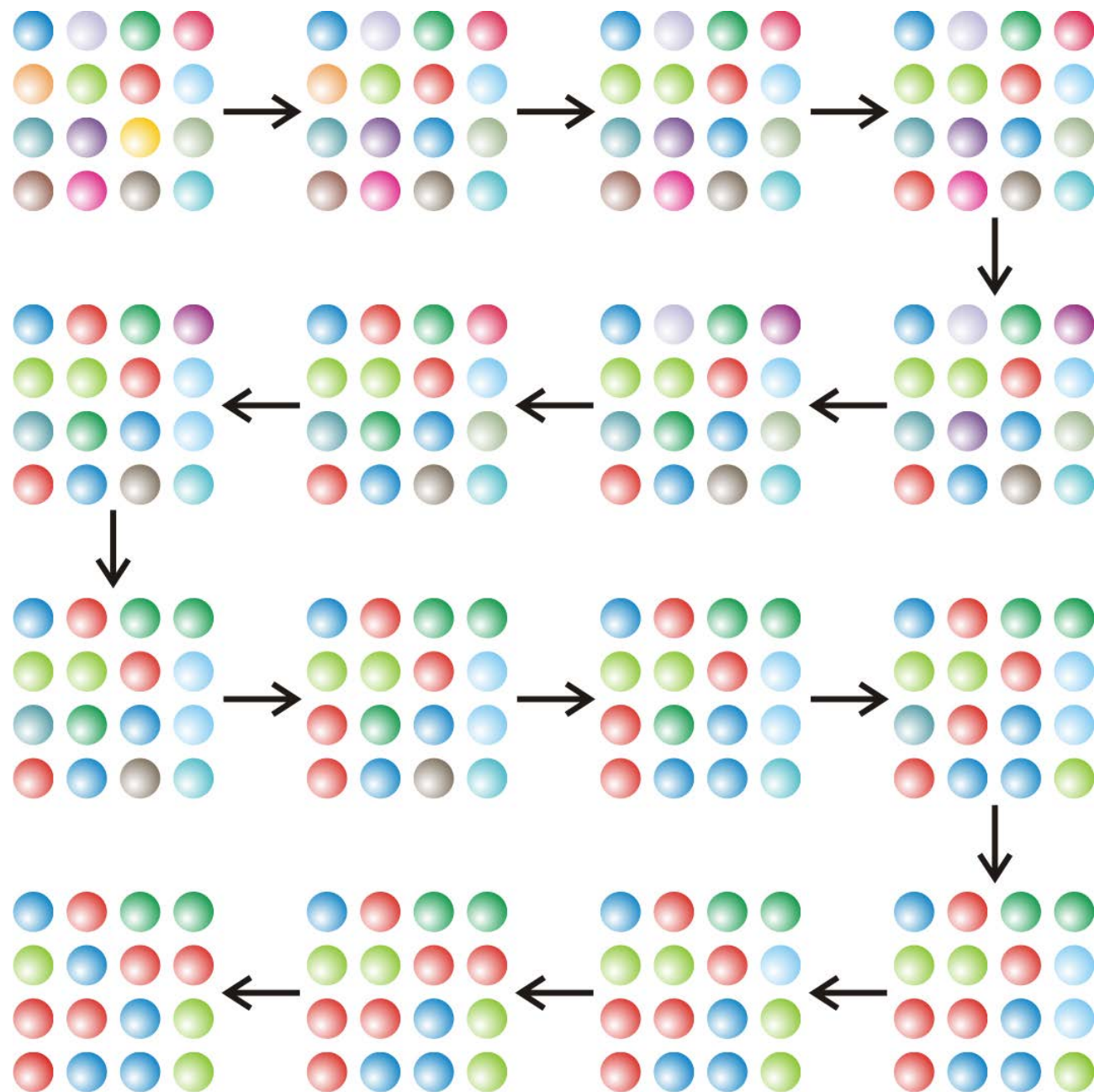
phase III: convergence to the quasi-stationary state;

phase IV: fluctuations around the values of the quasi-stationary state

color code:

A , X_1 , X_2 , X_3

phases of the approach towards steady states by individual trajectories

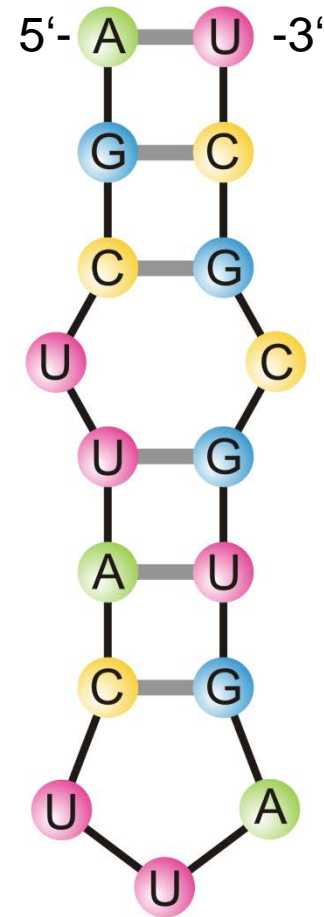


neutral evolution in
the Moran model

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7. Natural selection and evolution

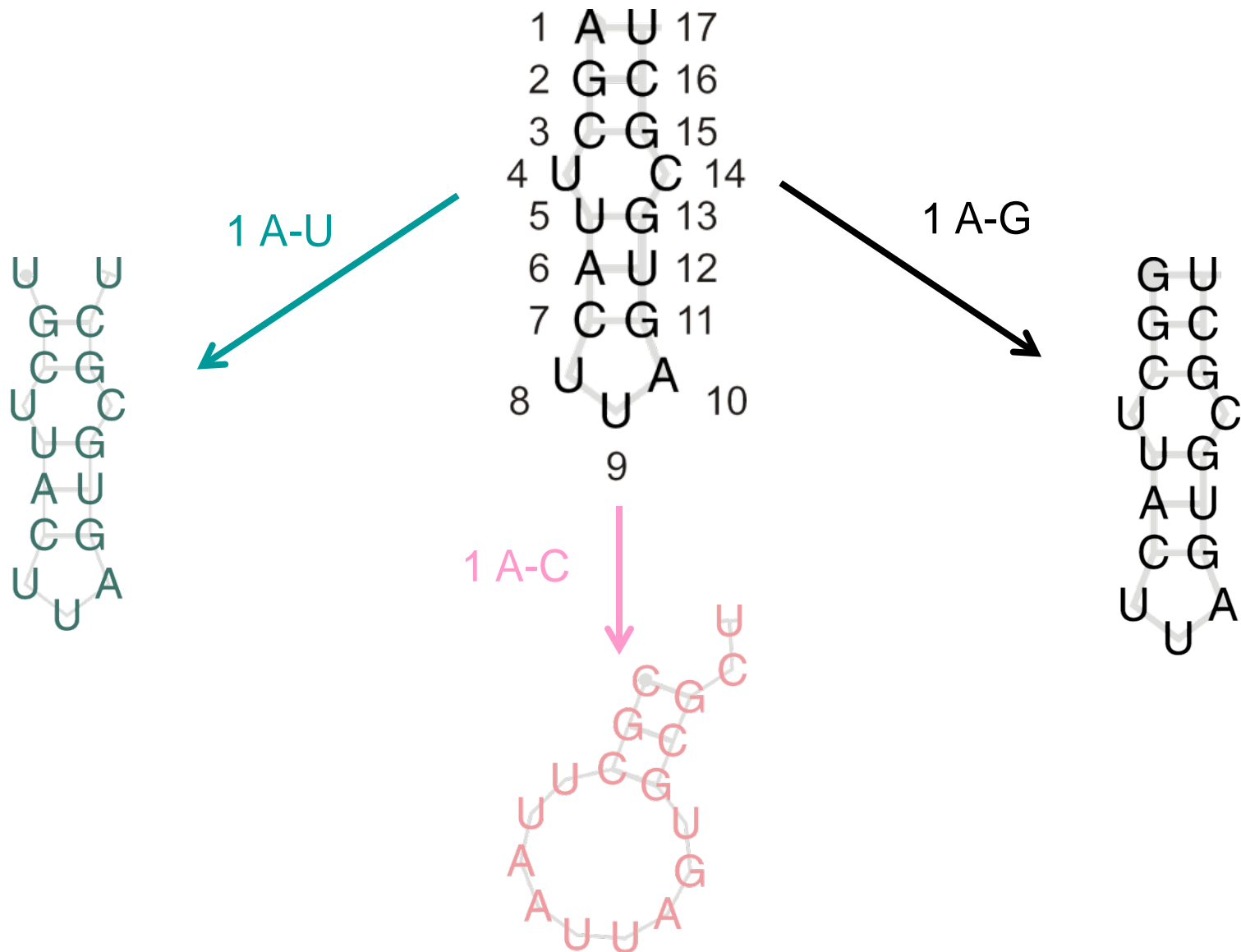
5'- AGCUUACUUAGUGCGCU-3'

5'-(((• (((• • •))) •))) -3'



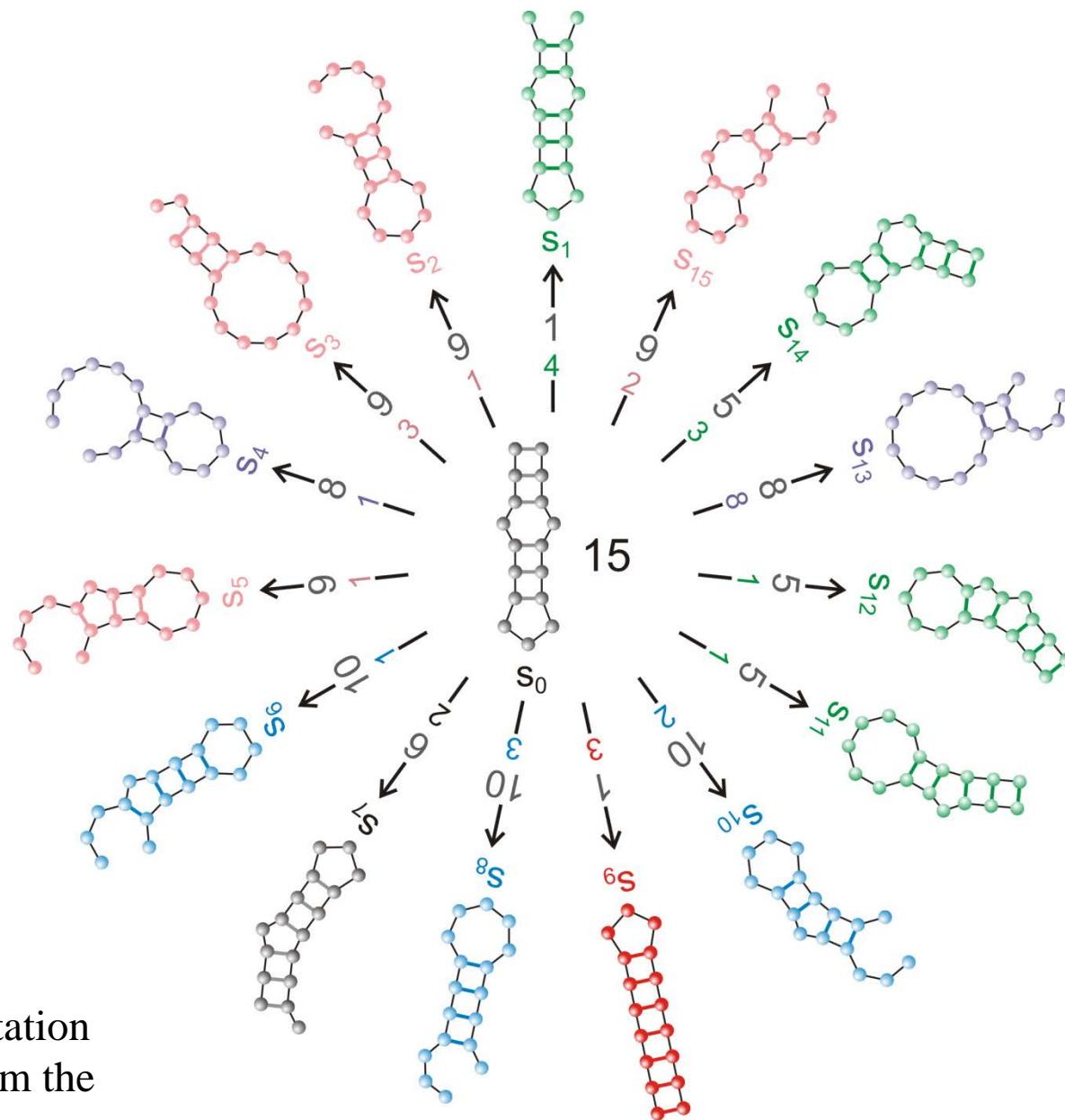
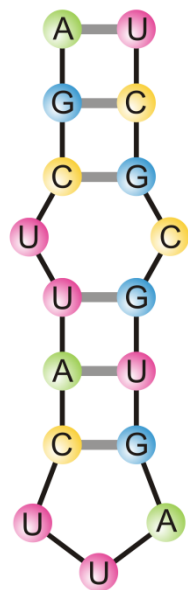
the minimum free energy
structure of a small RNA
molecule

AGCUUAACUUAGUCGCU



AGCUUACUUAGUGCGCU

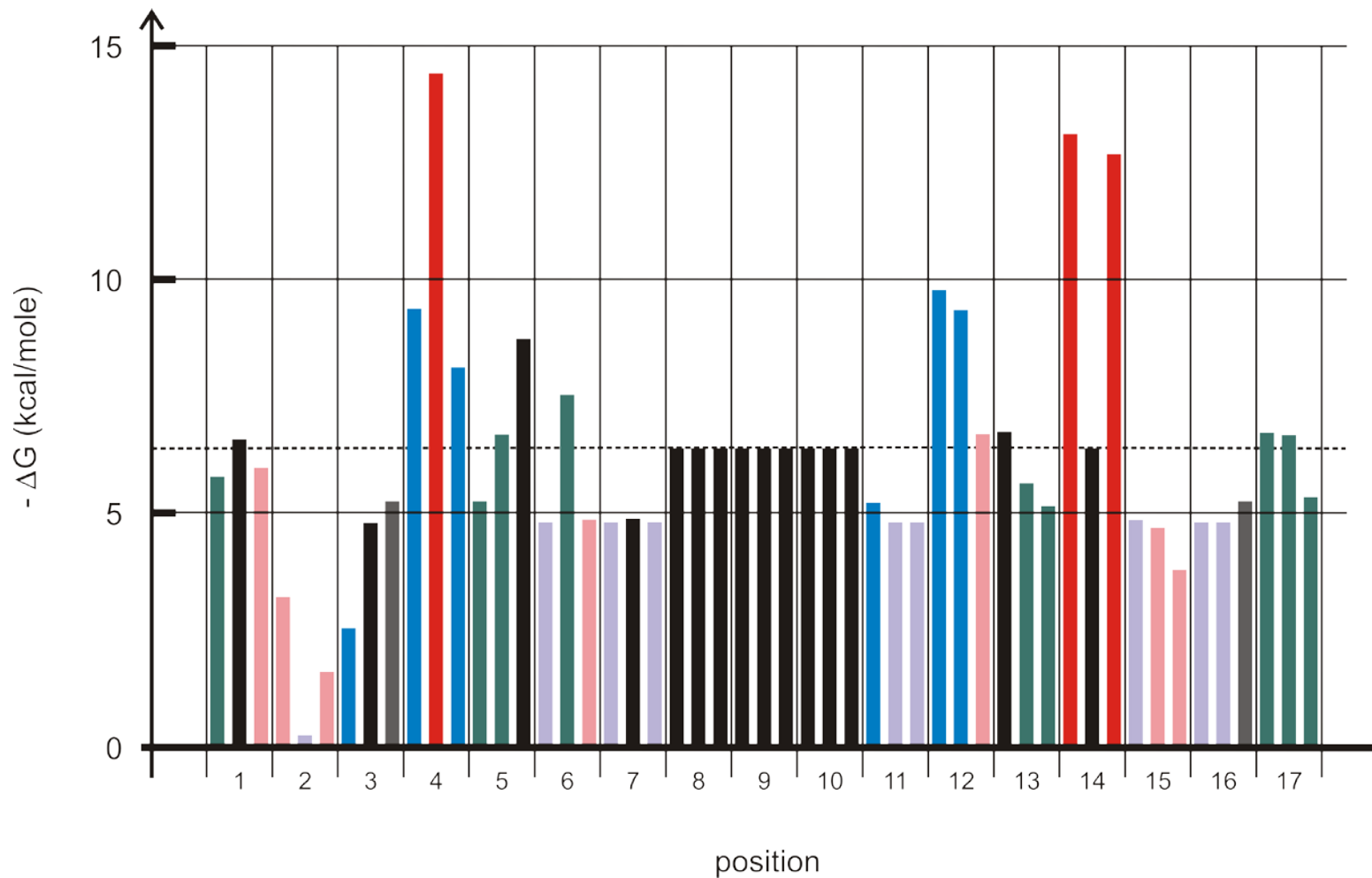
((((·(((·...)))·)))



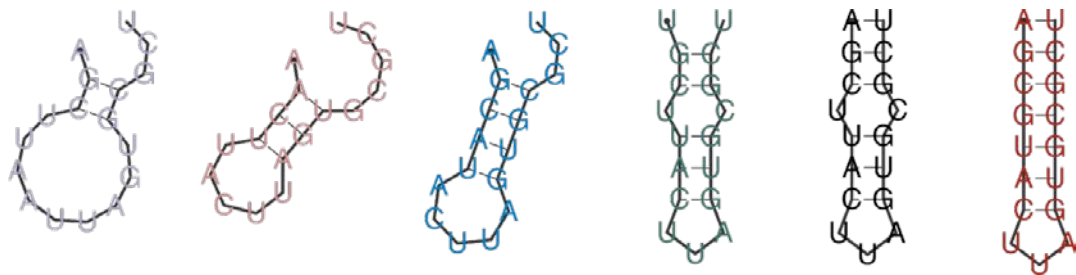
frequencies of 51 point mutation
structures and distances from the
reference structure

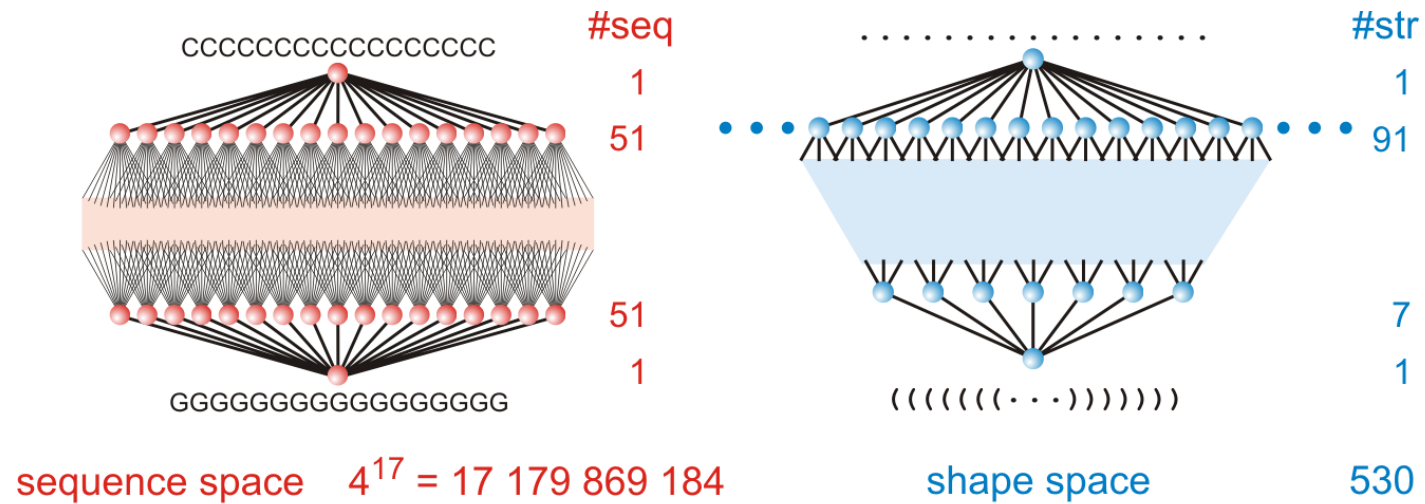
1 A U 17
 2 G C 16
 3 C G 15
 4 U C 14
 5 U G 13
 6 A U 12
 7 C G 11
 8 U U A 10
 9

reference



free energy of formation
 (ΔG_0) of 51 point mutants
 Of the reference sequence





\mathcal{Q}

\mathcal{S}

\mathbf{X}

$$\Phi: (\mathcal{Q}, d_H) \Rightarrow (\mathcal{S}, d_S)$$

$$\mathbf{S} = \Phi(\mathbf{X})$$

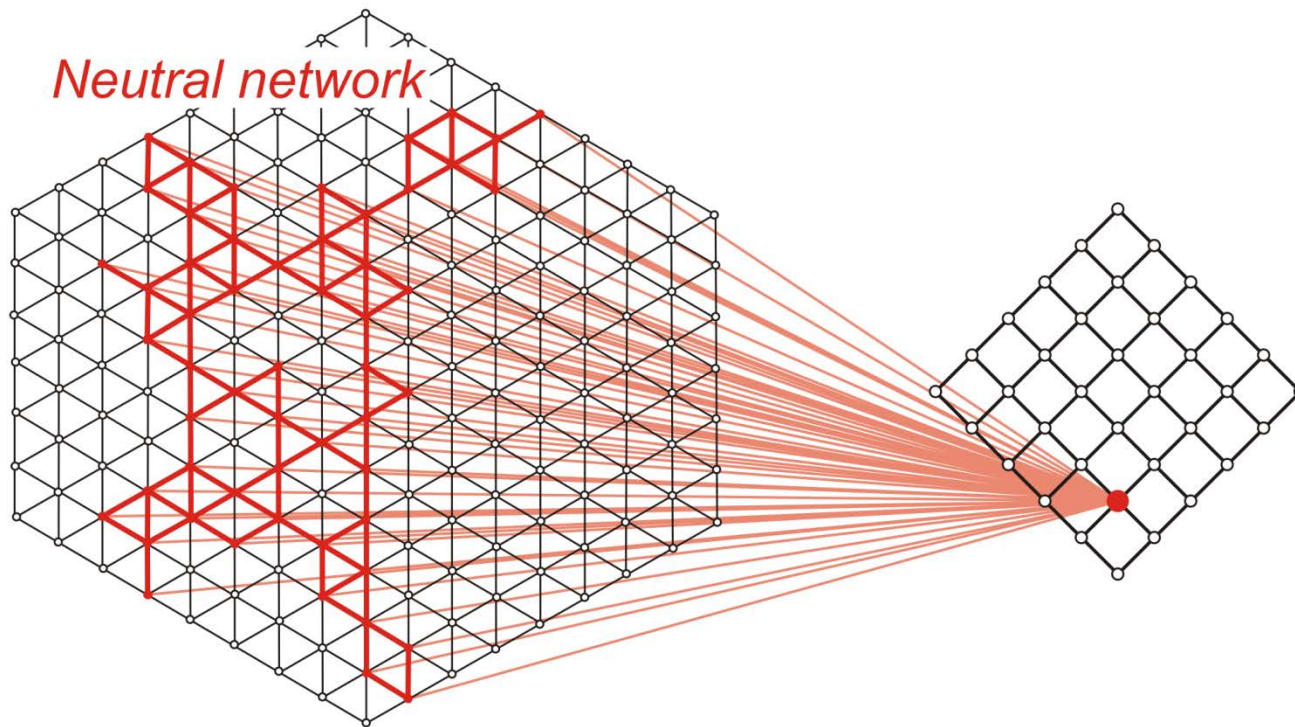
sequence

structure

genotype

phenotype

formation of RNA secondary structures as genotype-phenotype mapping



Sequence space

Structure space

many genotypes

\Rightarrow

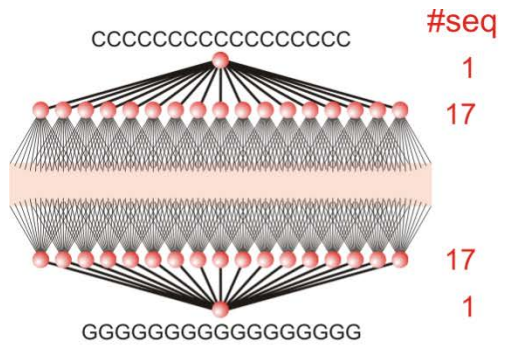
one phenotype

RNA sequence - structure mappings

1. ruggedness and neutrality
2. existence of extended neutral networks
3. shape space covering

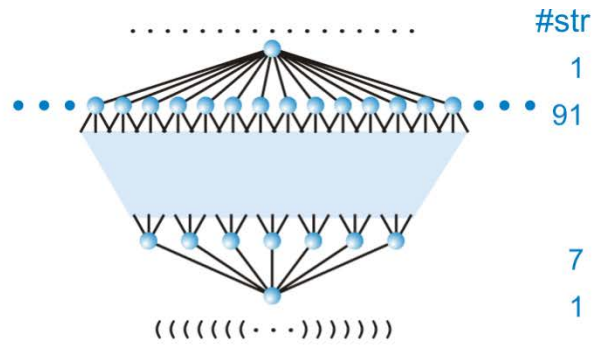
The results 1. and 2. are certainly true also for other biopolymers, for example for proteins.

Evidence for ruggedness, neutrality and the existence of neutral networks was obtained also from virus evolution and *in vitro* experiments with bacteria.



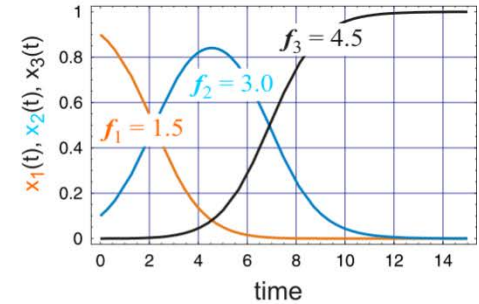
sequence space $2^{17} = 131\,072$

\mathcal{Q}



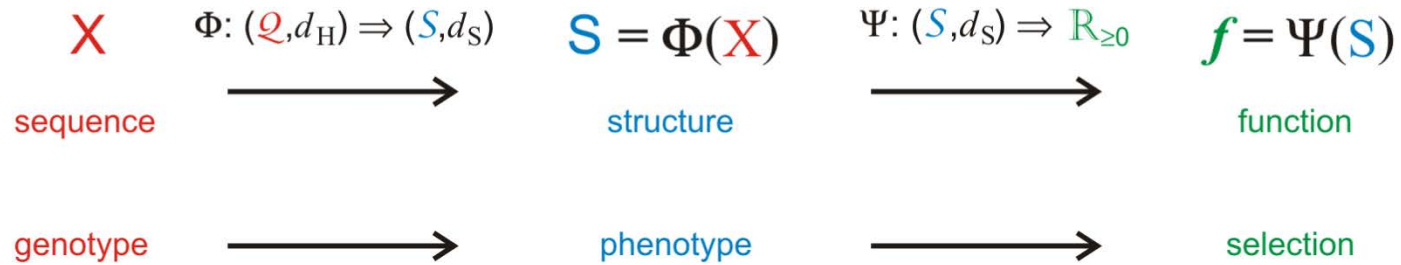
shape space 530

\mathcal{S}



parameter space

$\mathbb{R}_{\geq 0}$

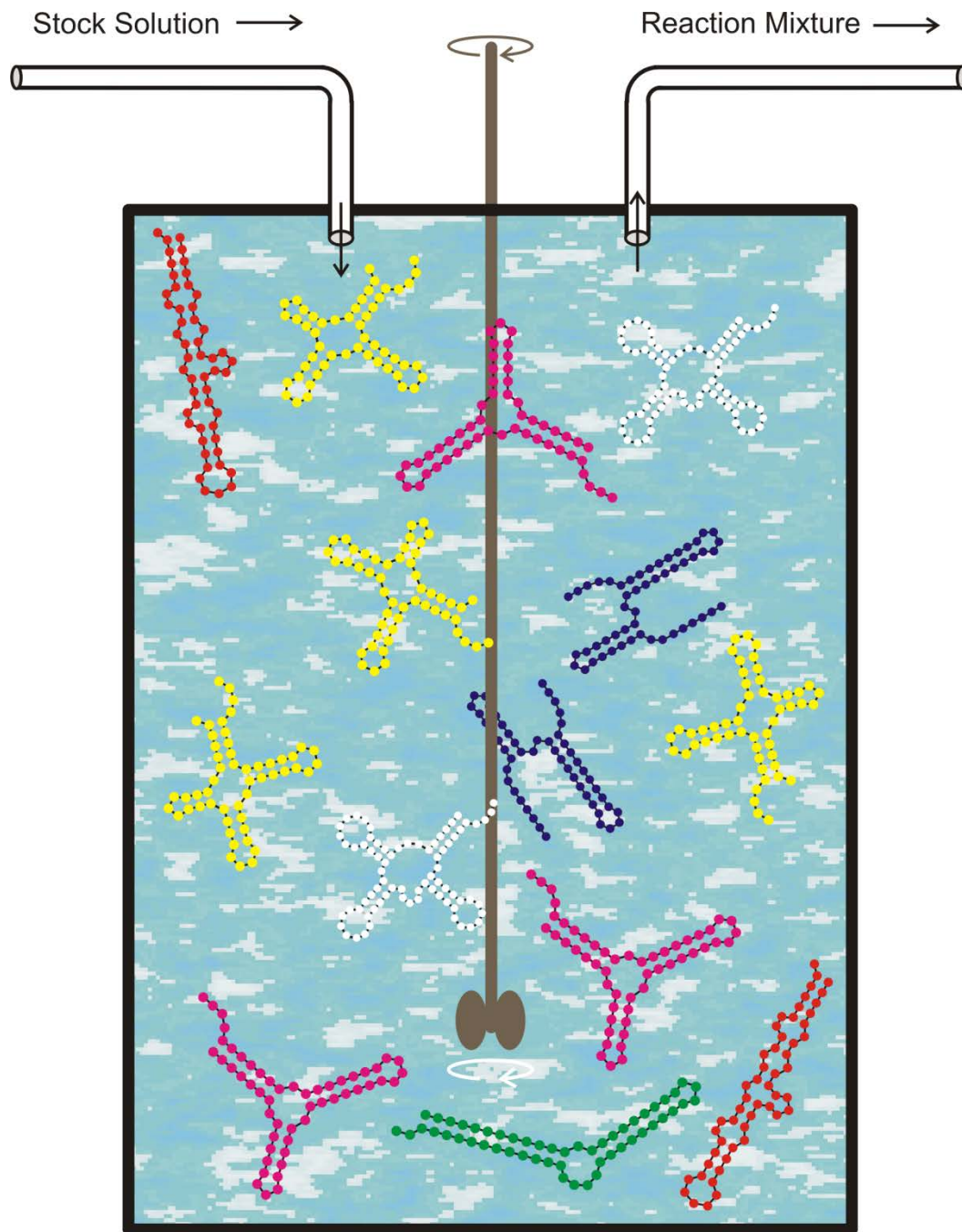


fitness of RNA secondary structures through evaluation of phenotypes

1. Is evolution possible ?
2. "Non-probabilities" ?
3. Protein folding - a(n almost) solved example
4. Evolution - The survival of the fittest?
5. Genotype-phenotype mapping and evolution
- 6. The interplay of adaptation and random drift**
7. Natural selection and evolution

Evolution under controlled and
analyzable conditions:

- (i) evolution *in silico*,
- (ii) evolution *in vitro*,
- (iii) virus evolution, and
- (iv) bacterial evolution.



replication rate constant or fitness:

$$f_k = \gamma / [\alpha + \Delta d_S^{(k)}] ; \Delta d_S^{(k)} = d_H(S_k, S_\tau)$$

selection pressure:

The population size, $N = \# \text{ RNA}$, molecules, is determined by the flow:

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

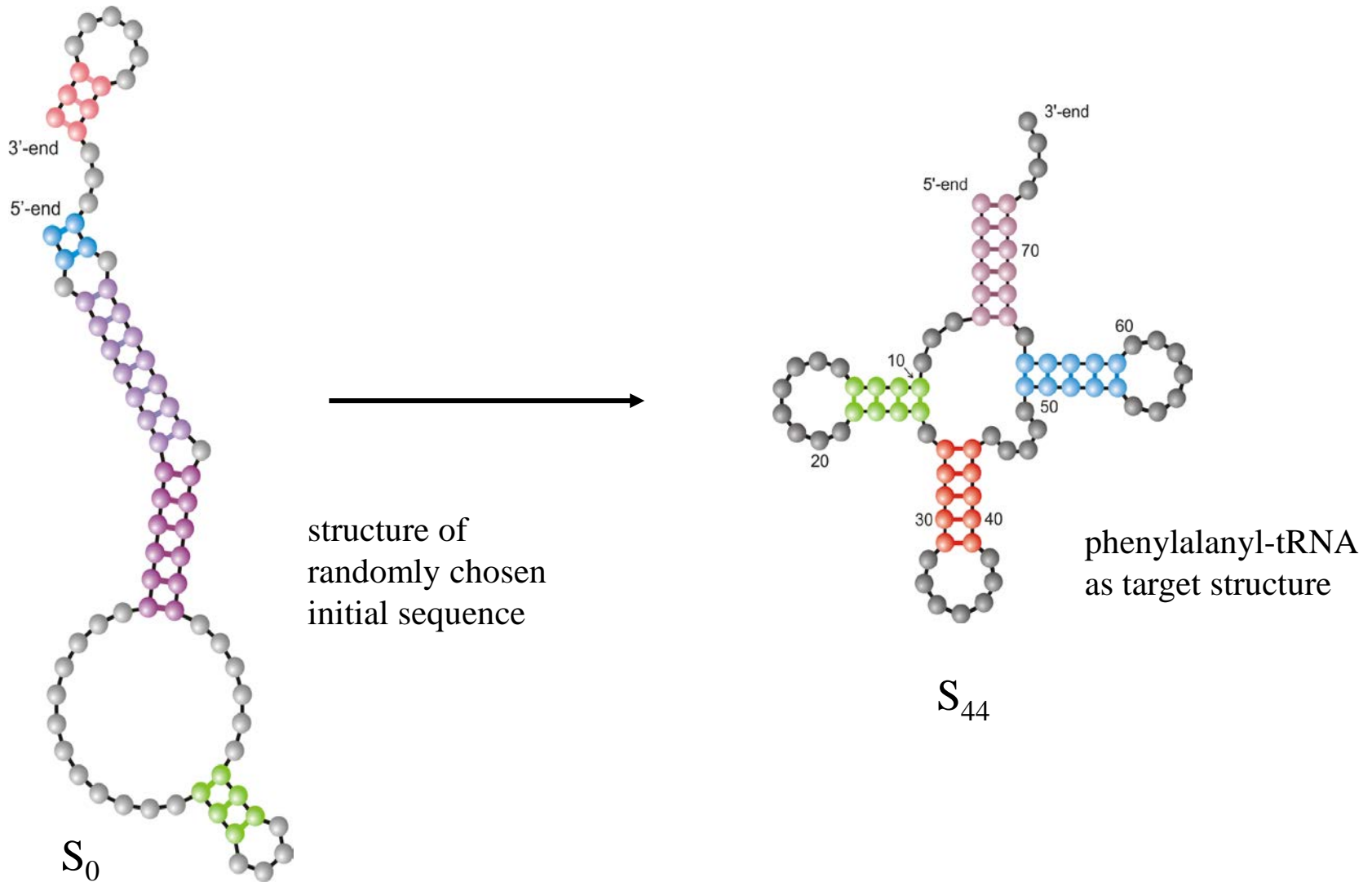
mutation rate:

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

the flow reactor as a device for studying the evolution of molecules *in vitro* and *in silico*.

evolution *in silico*

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



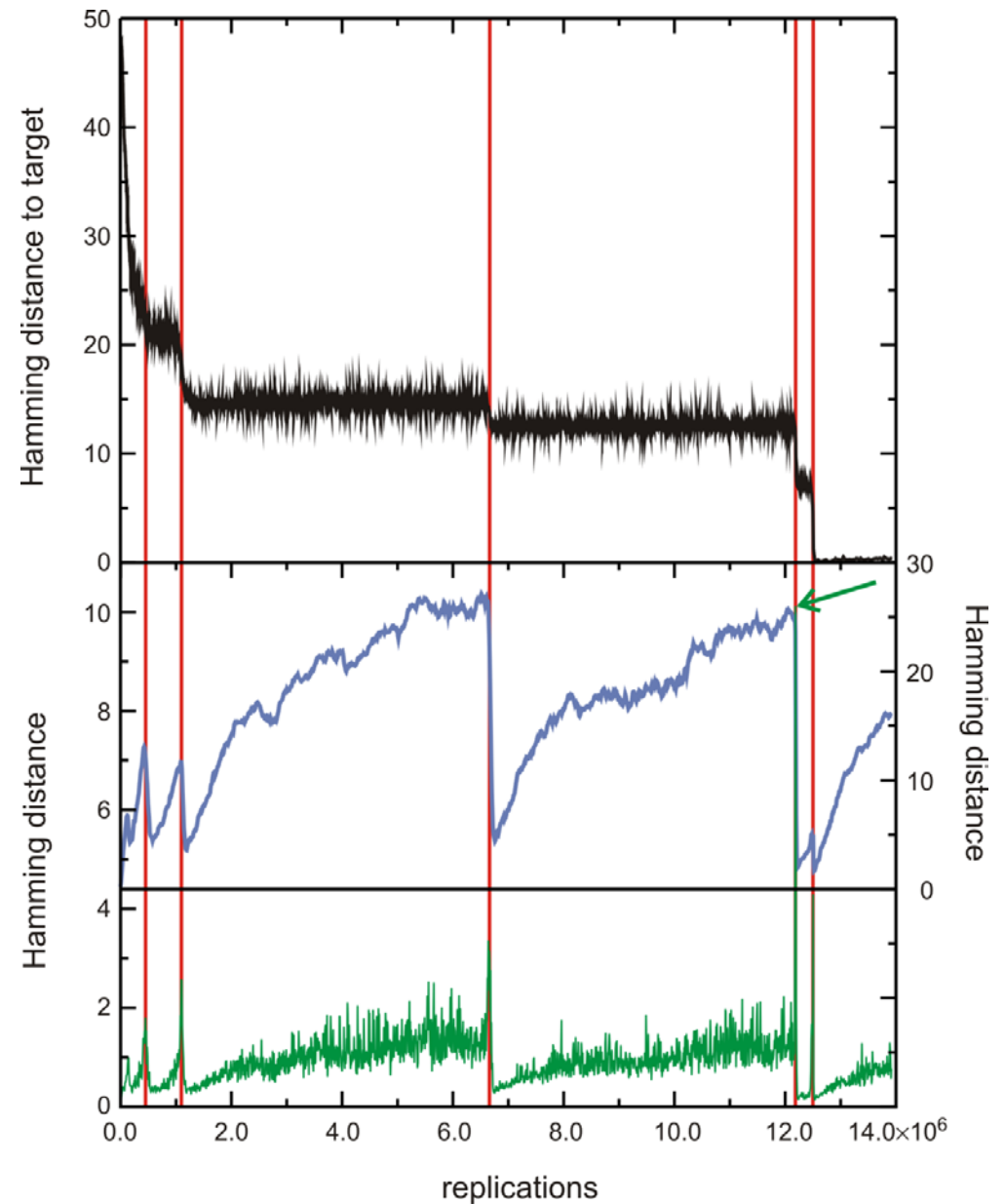
evolution *in silico*.

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

evolutionary trajectory

spreading of the population
on neutral networks

drift of the population center
in sequence space

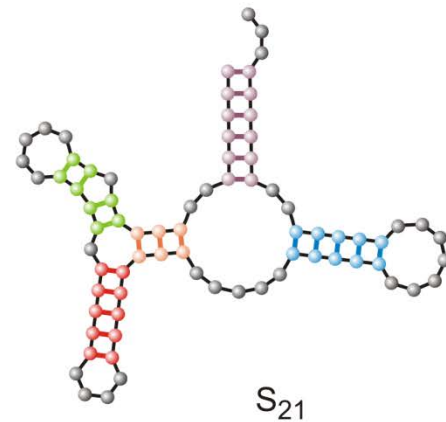
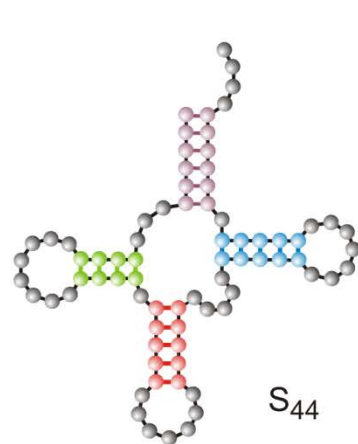
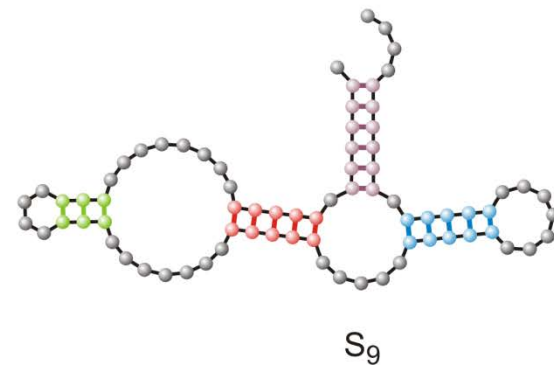
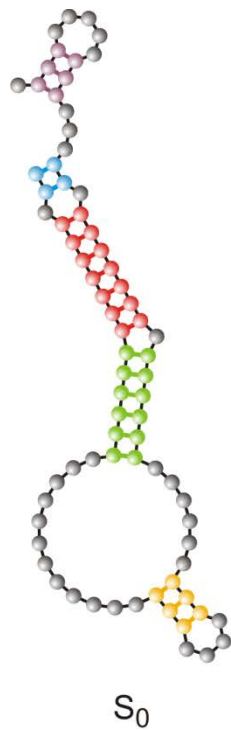


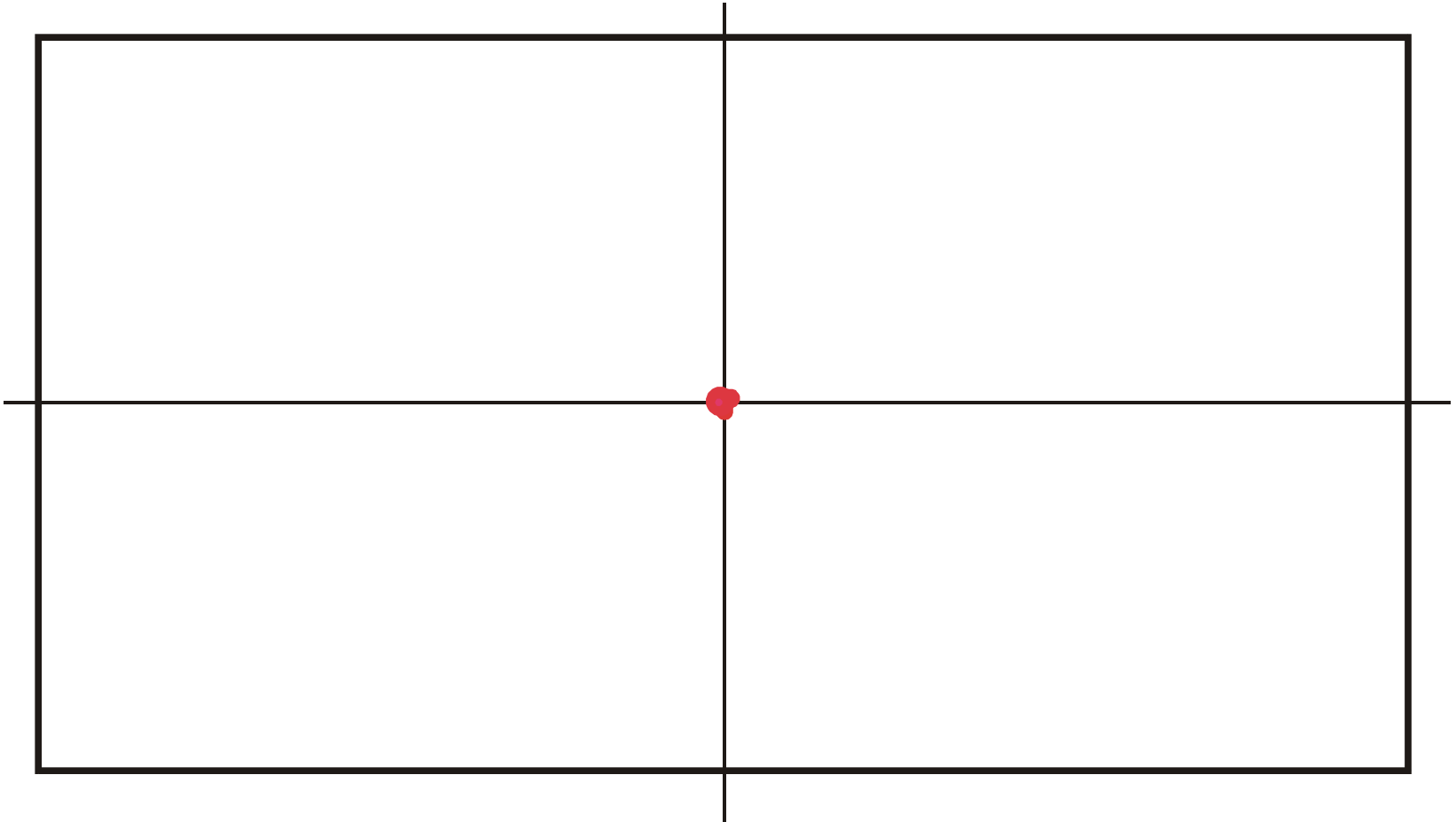
a targeted random walk to a predefined target structure

characteristic features:

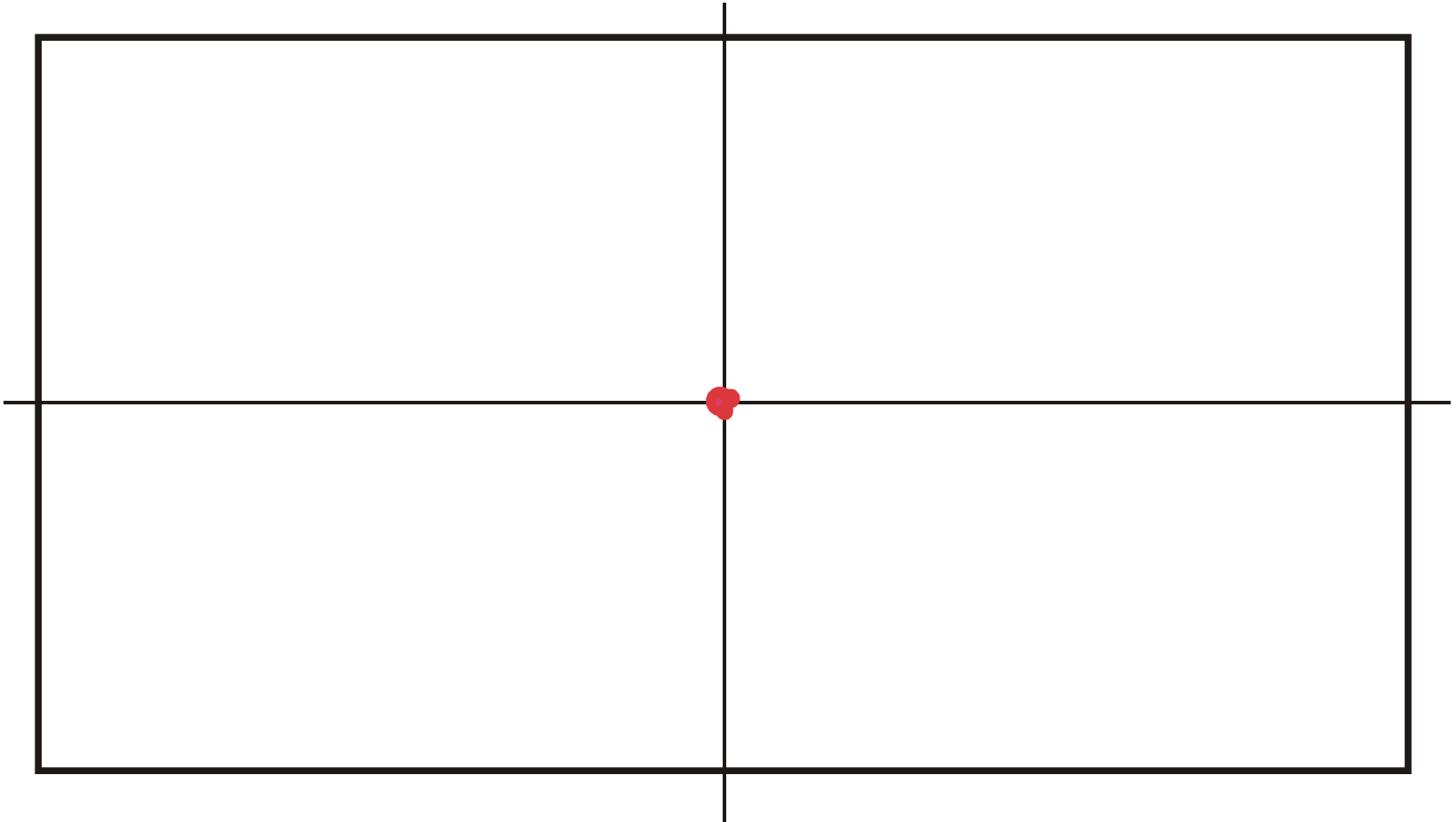
interior loops with two,
three, and four arms

key structures in the
approach towards the
optimal structure

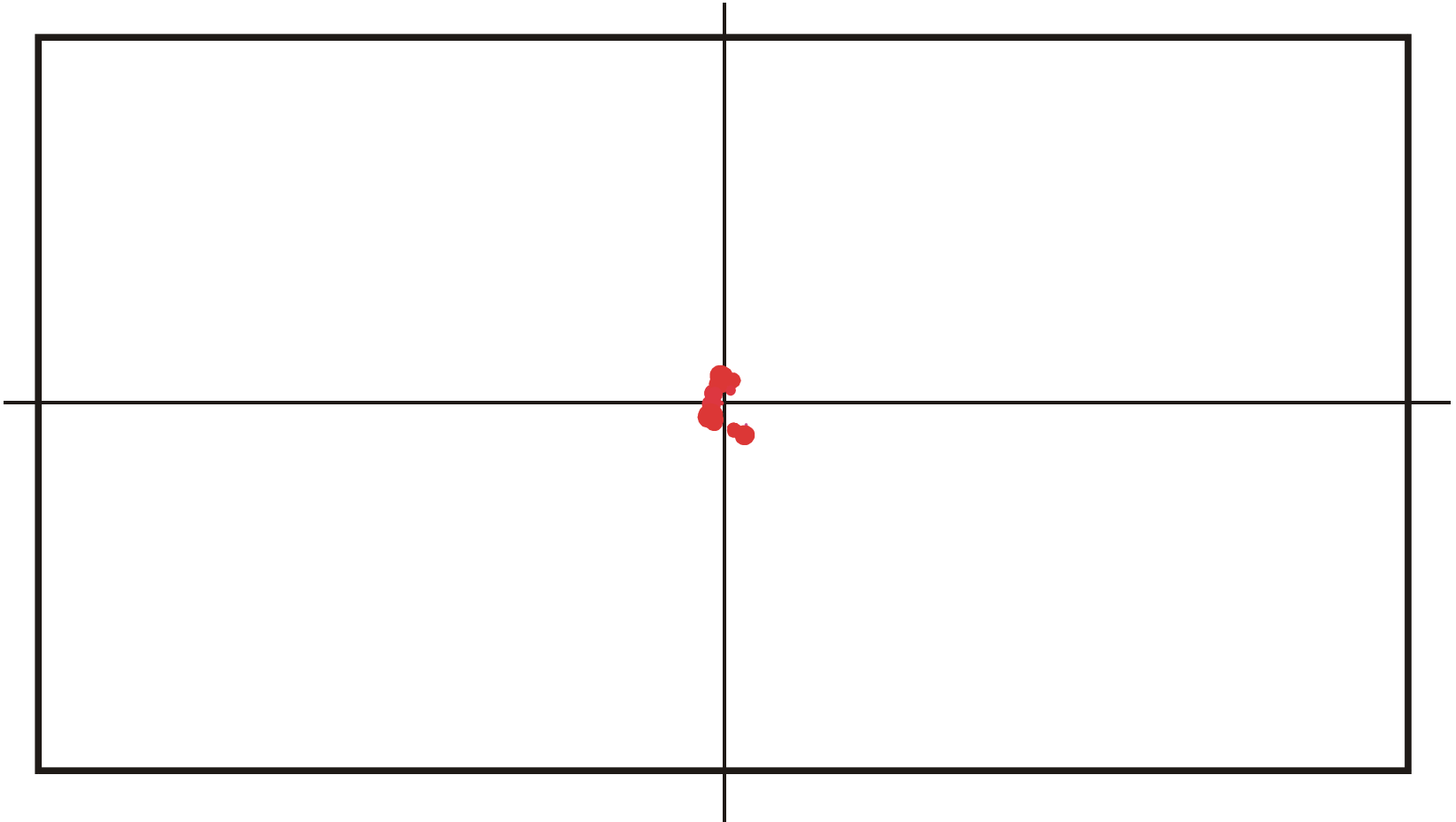




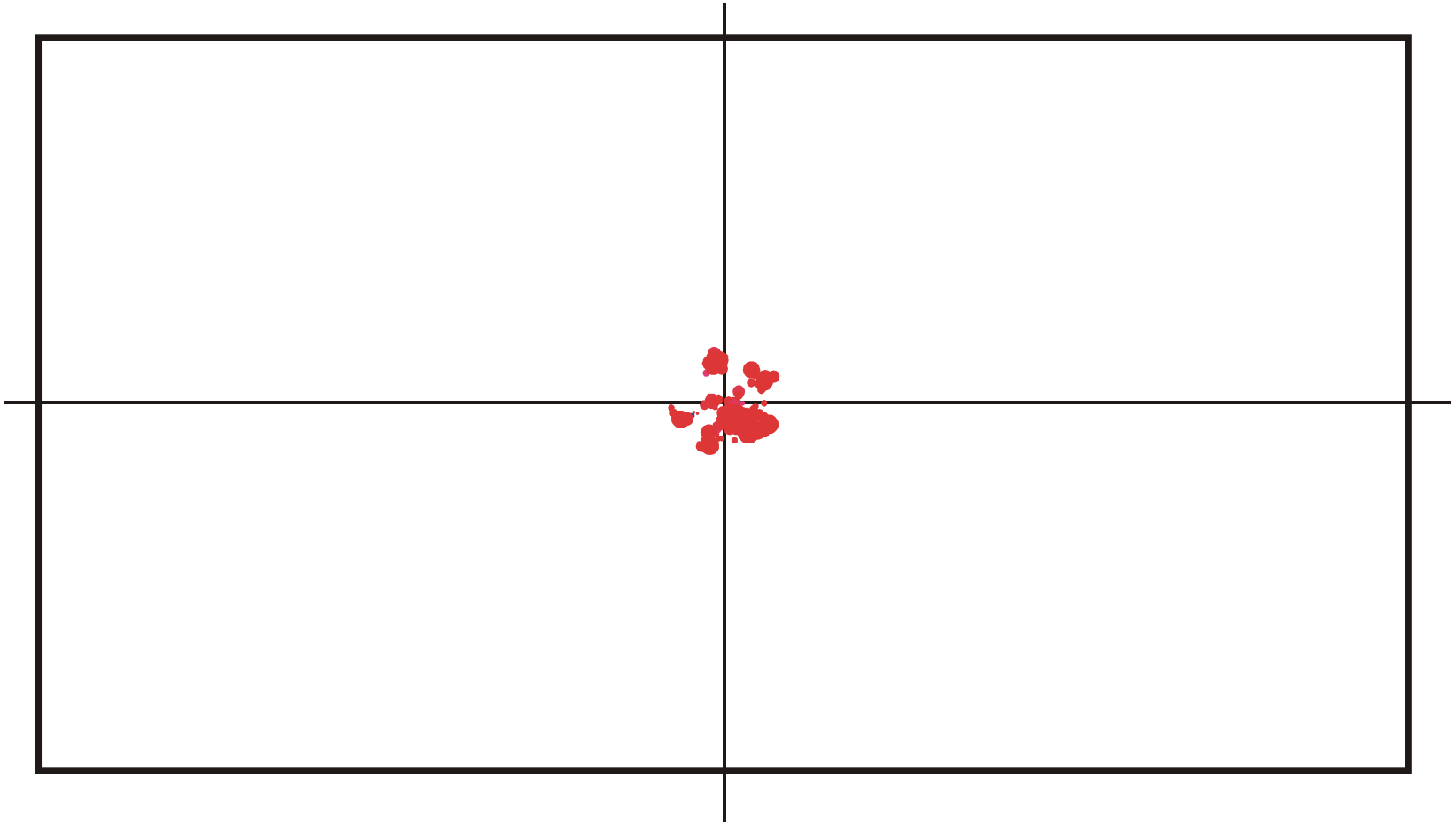
spreading and evolution of a population on a neutral network: $t = 150$



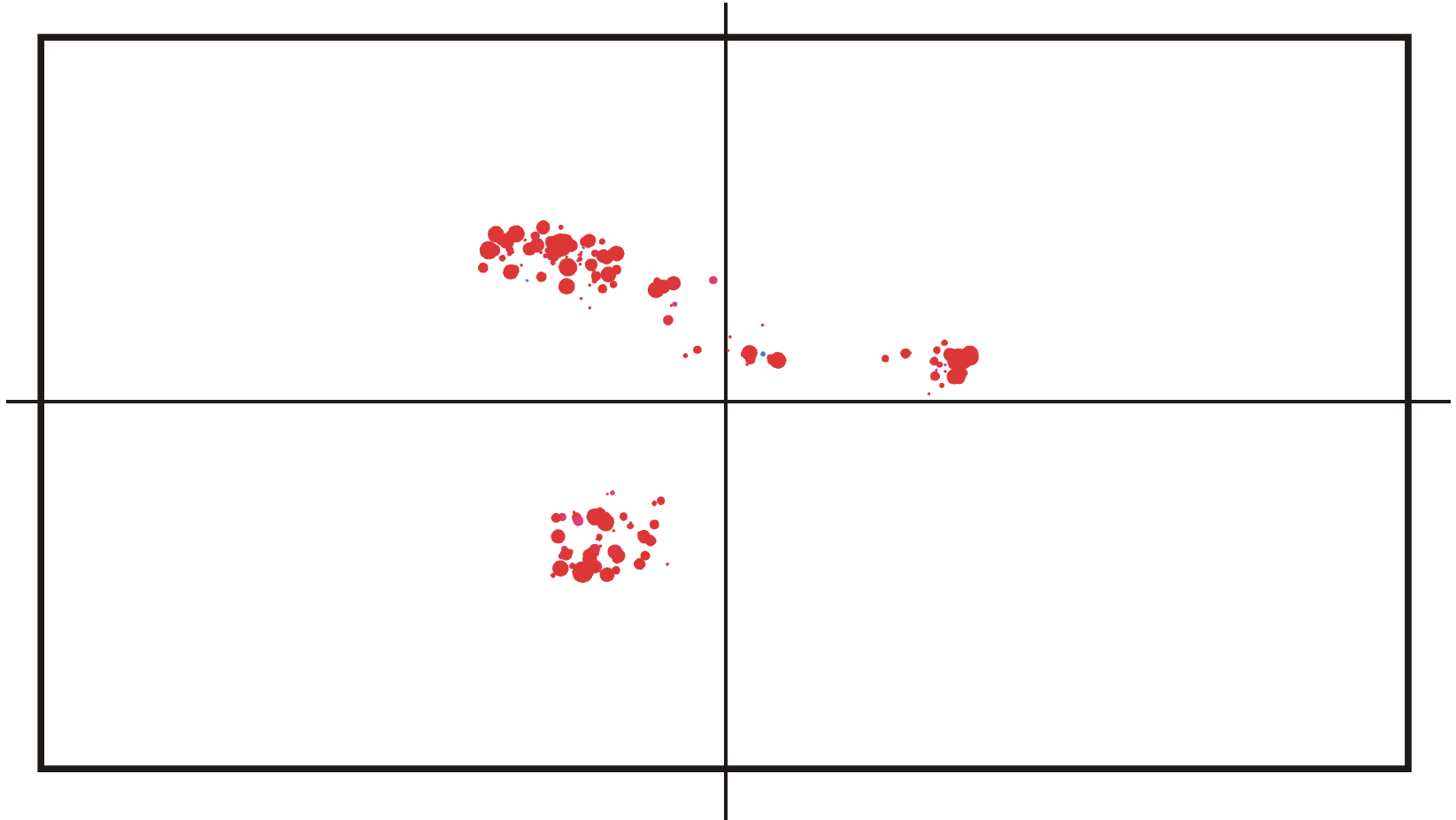
Spreading and evolution of a population on a neutral network: $t = 150$



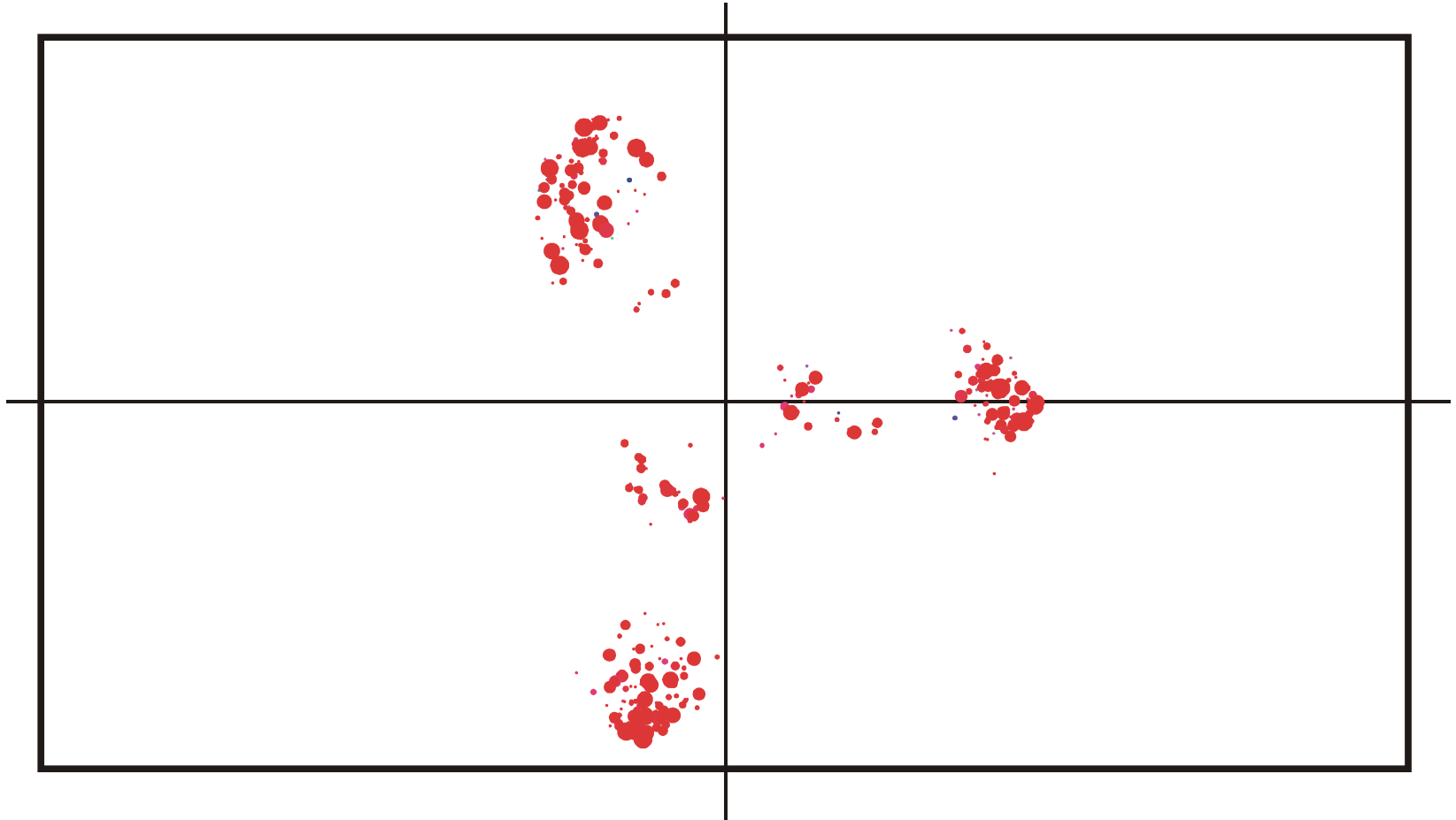
Spreading and evolution of a population on a neutral network: $t = 170$



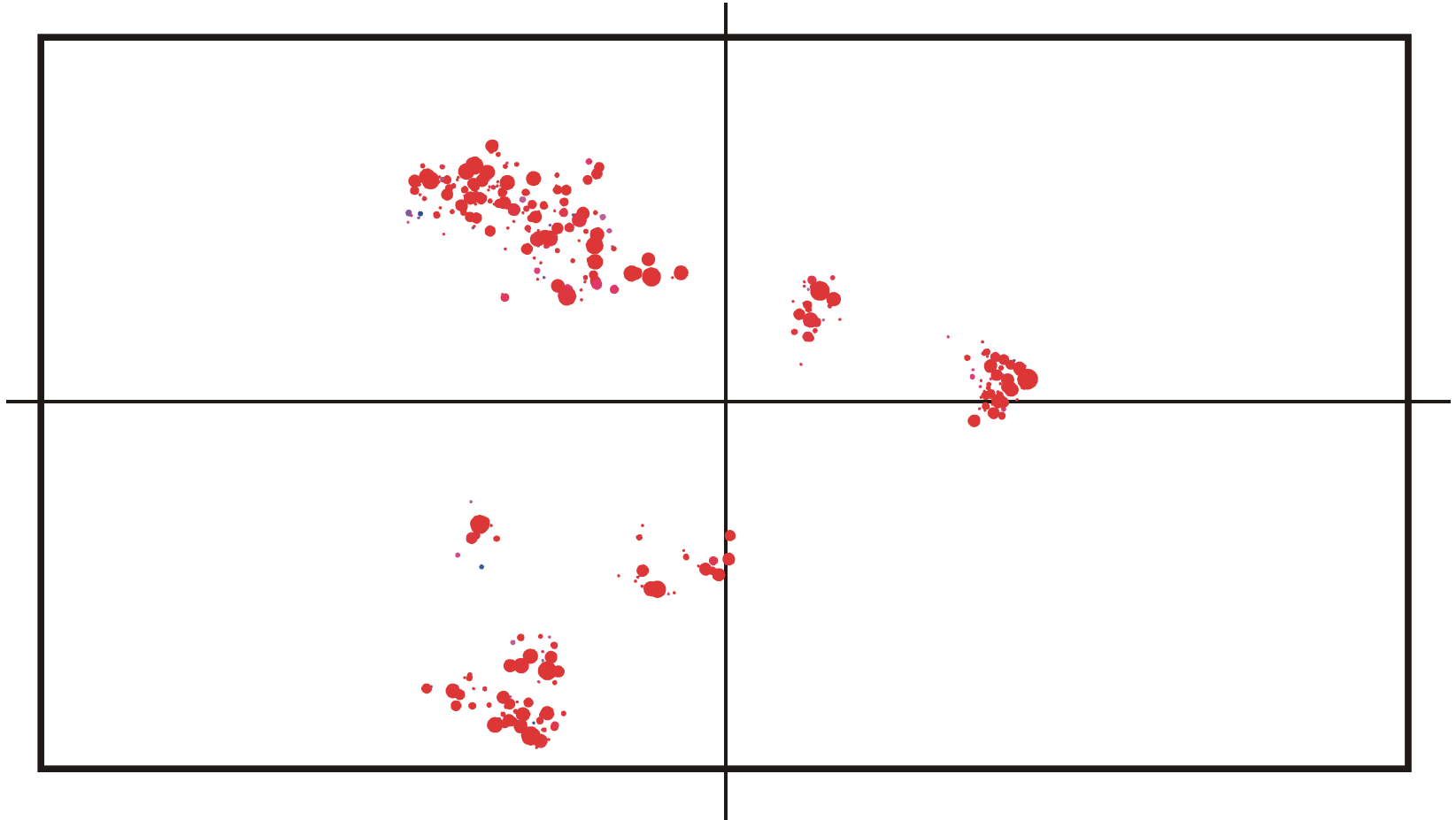
Spreading and evolution of a population on a neutral network: $t = 200$



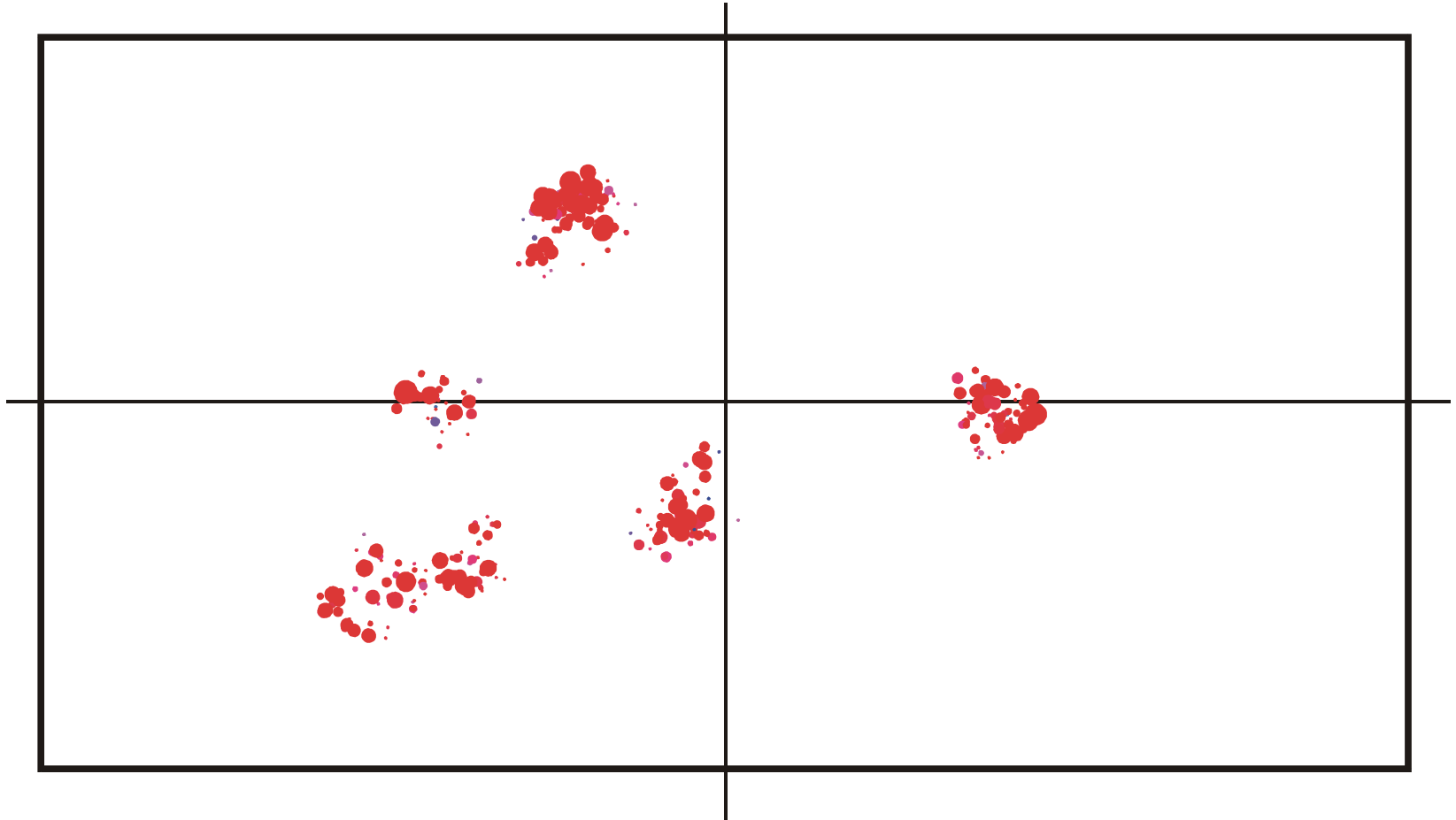
Spreading and evolution of a population on a neutral network: $t = 350$



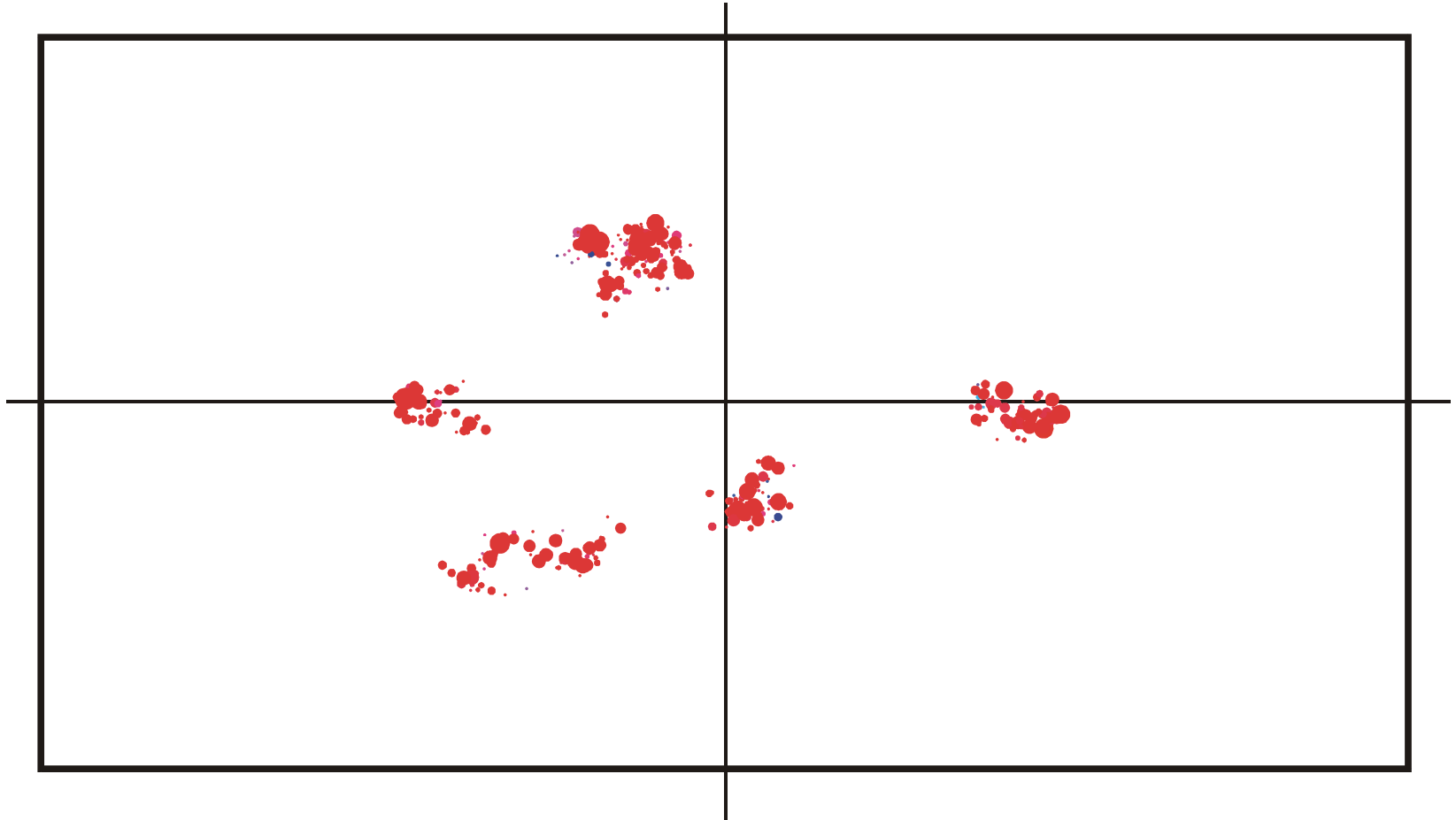
Spreading and evolution of a population on a neutral network: $t = 500$



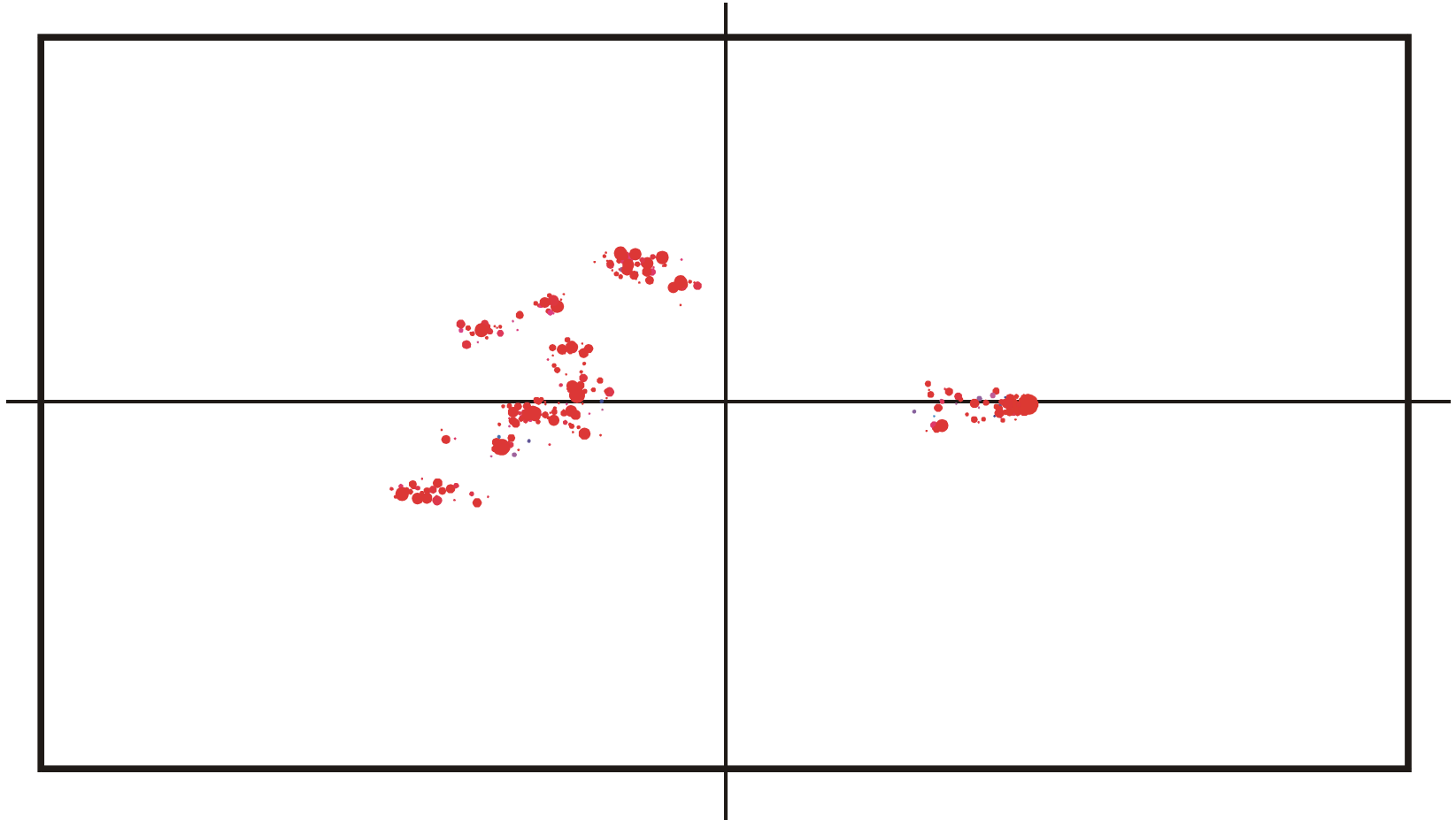
Spreading and evolution of a population on a neutral network: $t = 650$



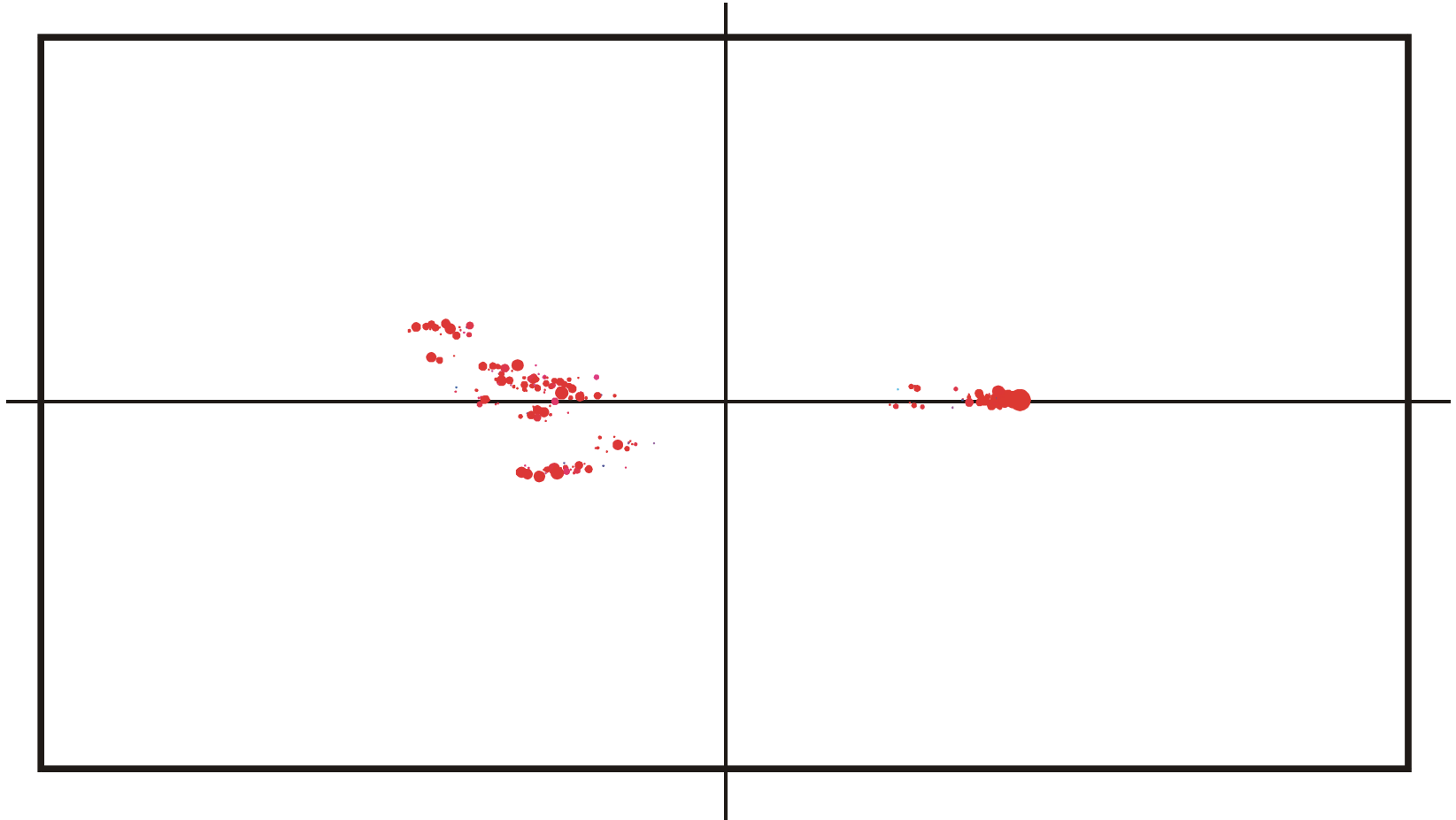
Spreading and evolution of a population on a neutral network: $t = 820$



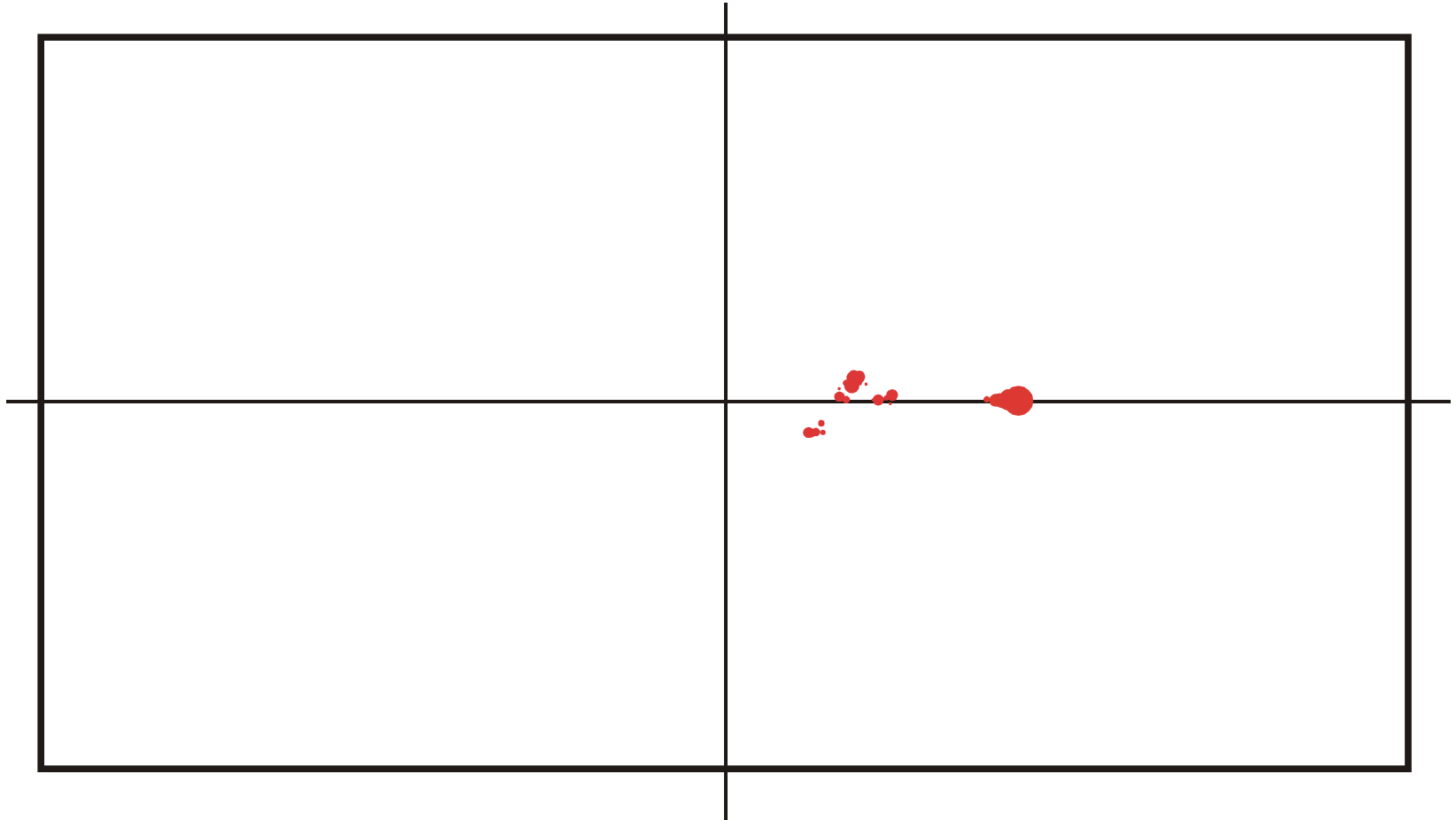
Spreading and evolution of a population on a neutral network: $t = 825$



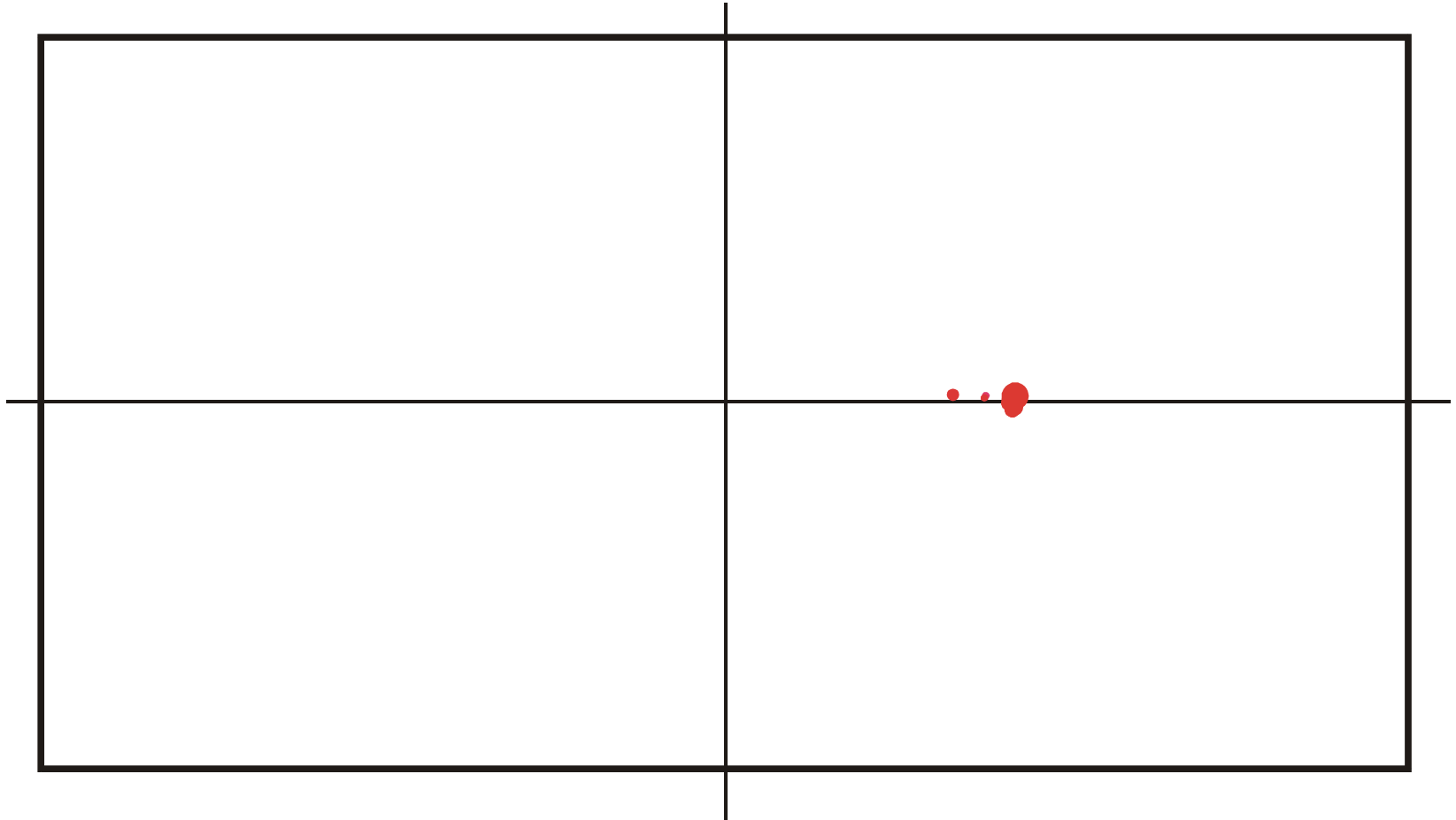
Spreading and evolution of a population on a neutral network: $t = 830$



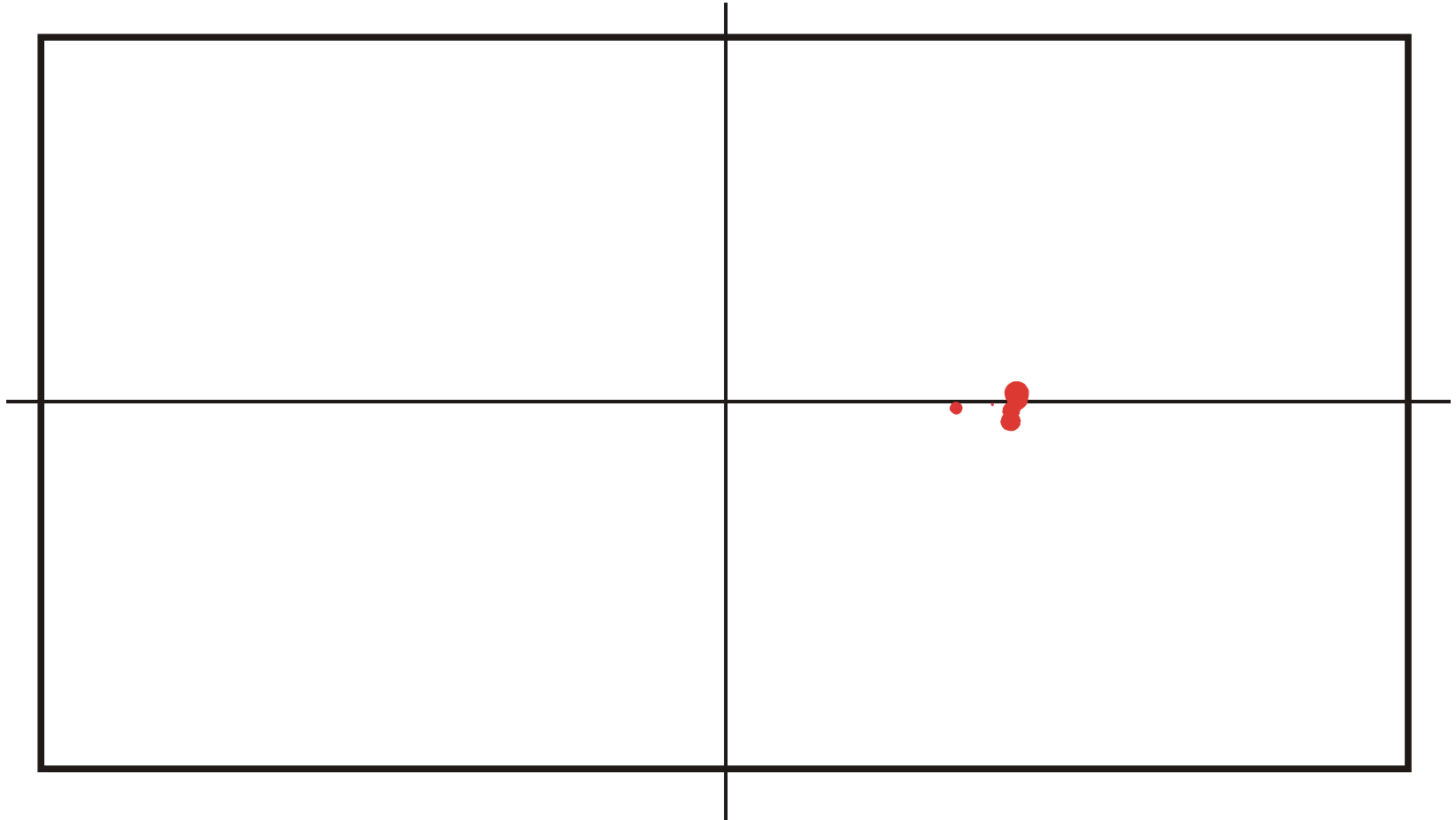
Spreading and evolution of a population on a neutral network: $t = 835$



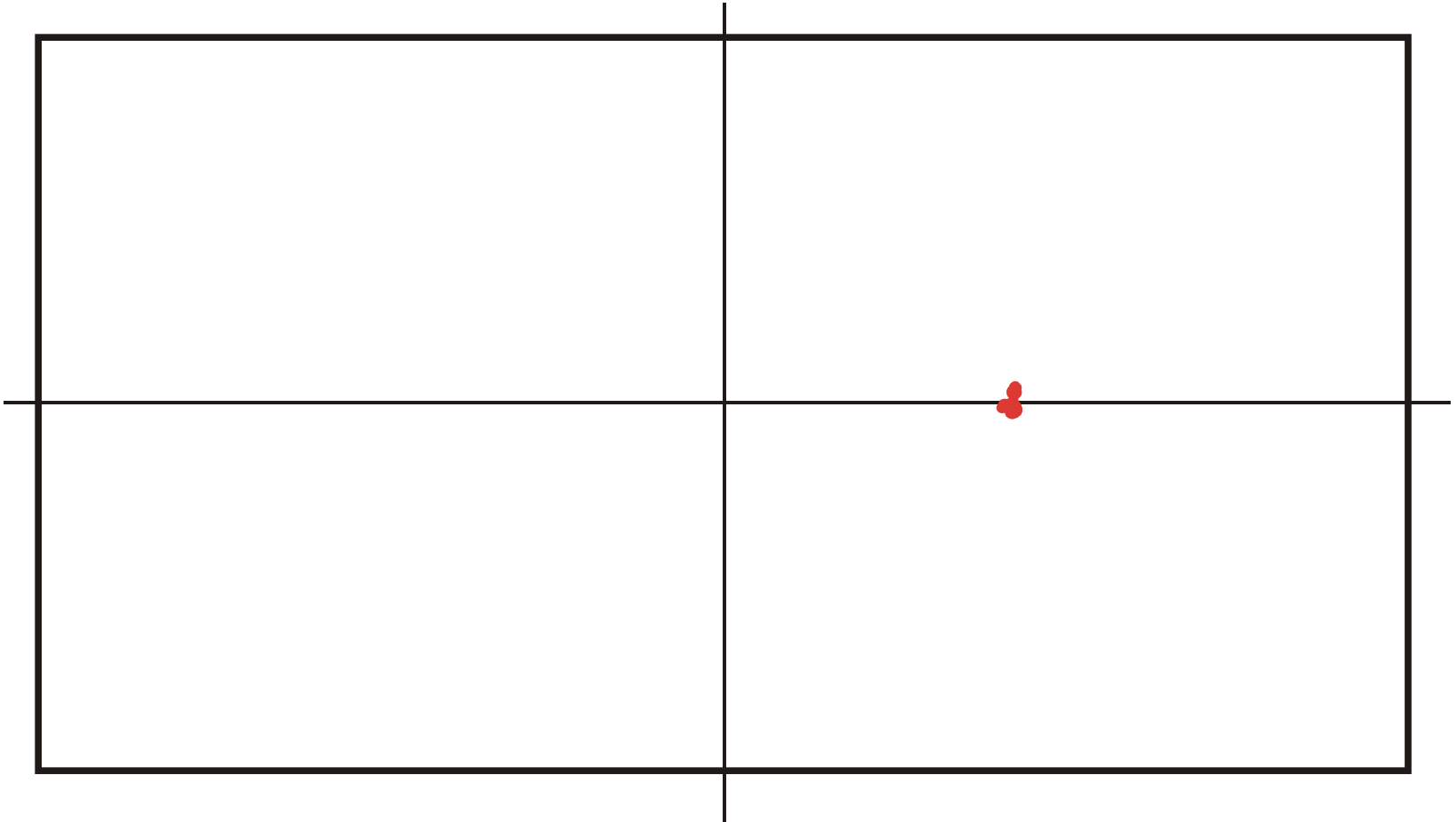
Spreading and evolution of a population on a neutral network: $t = 840$



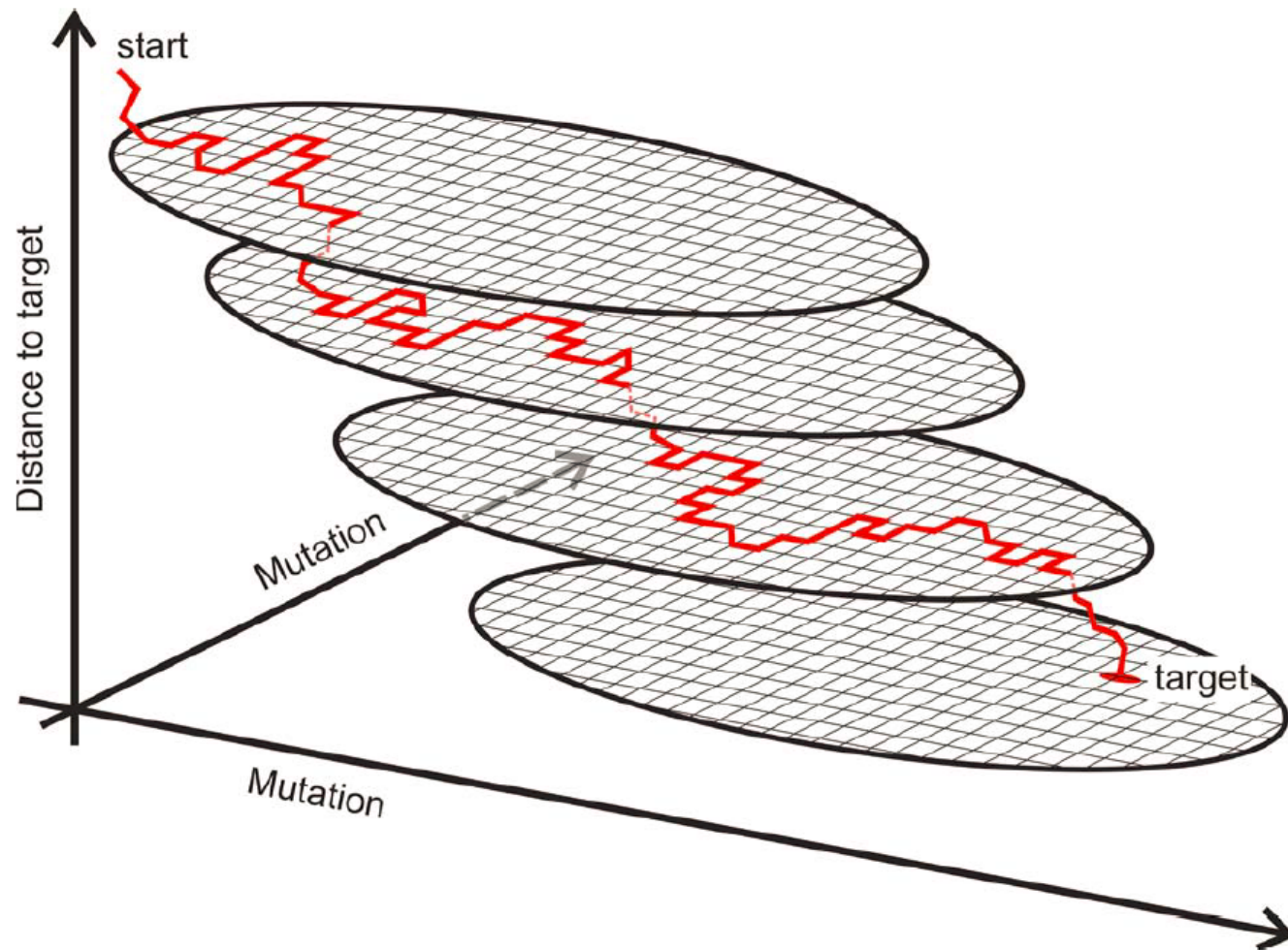
Spreading and evolution of a population on a neutral network: $t = 845$



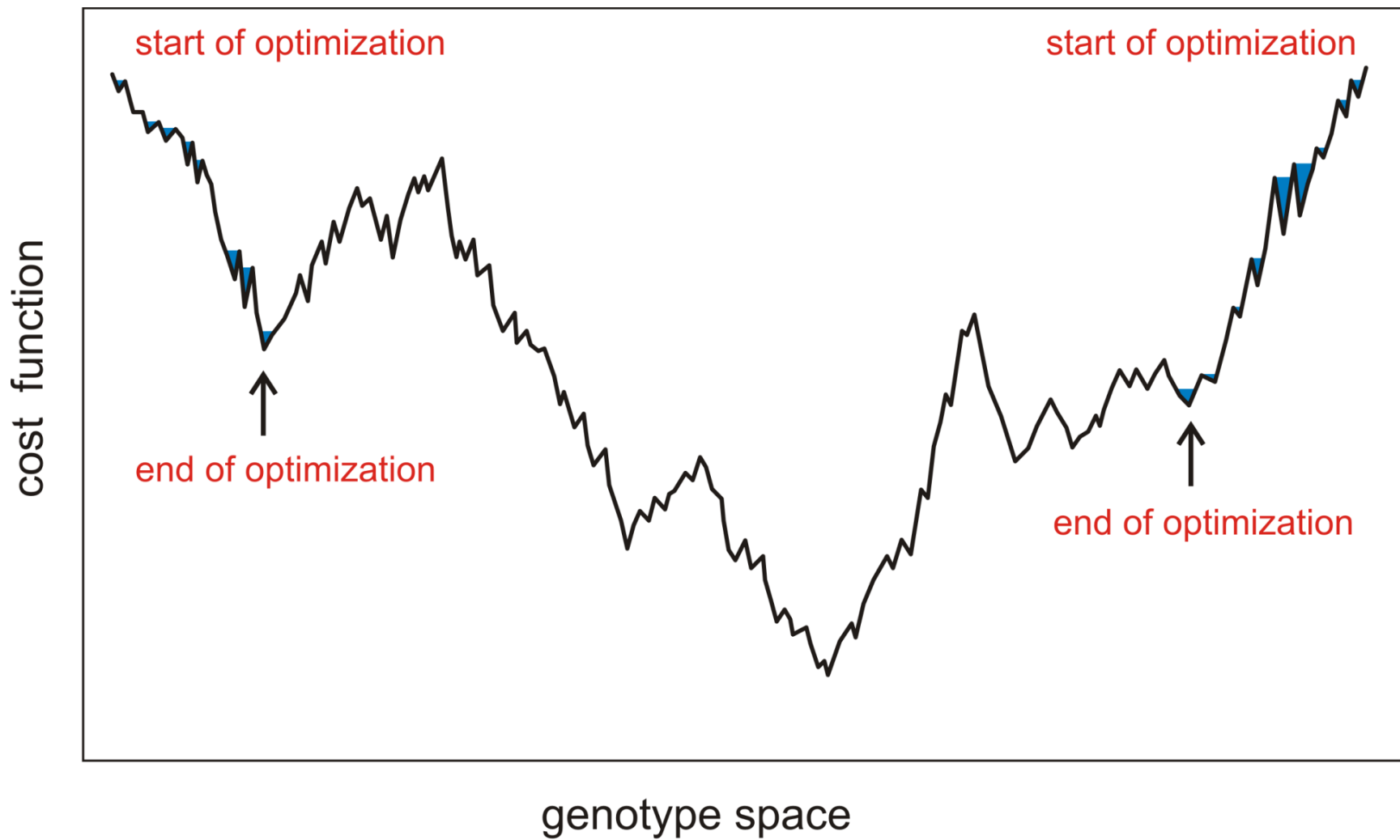
Spreading and evolution of a population on a neutral network: $t = 850$

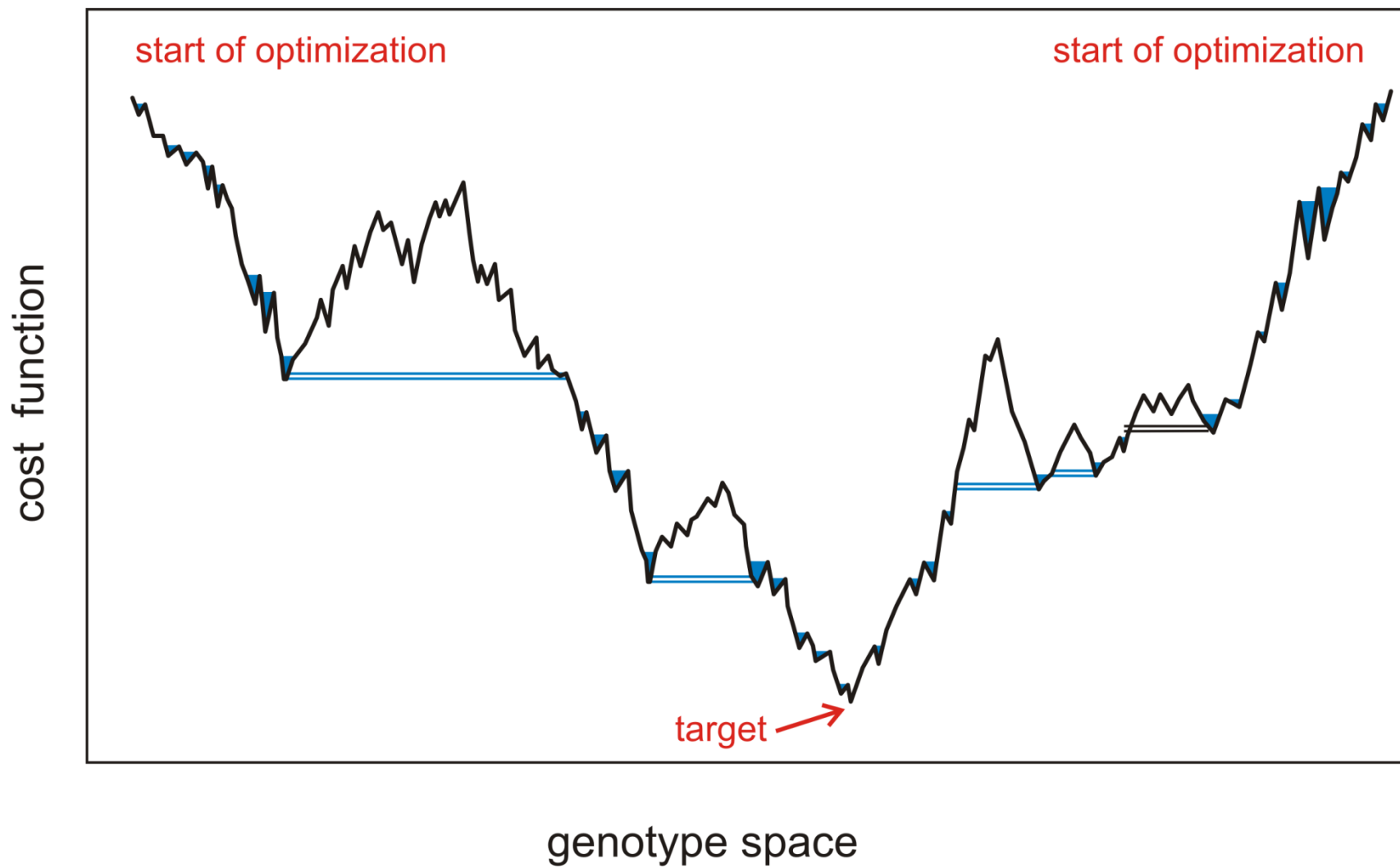


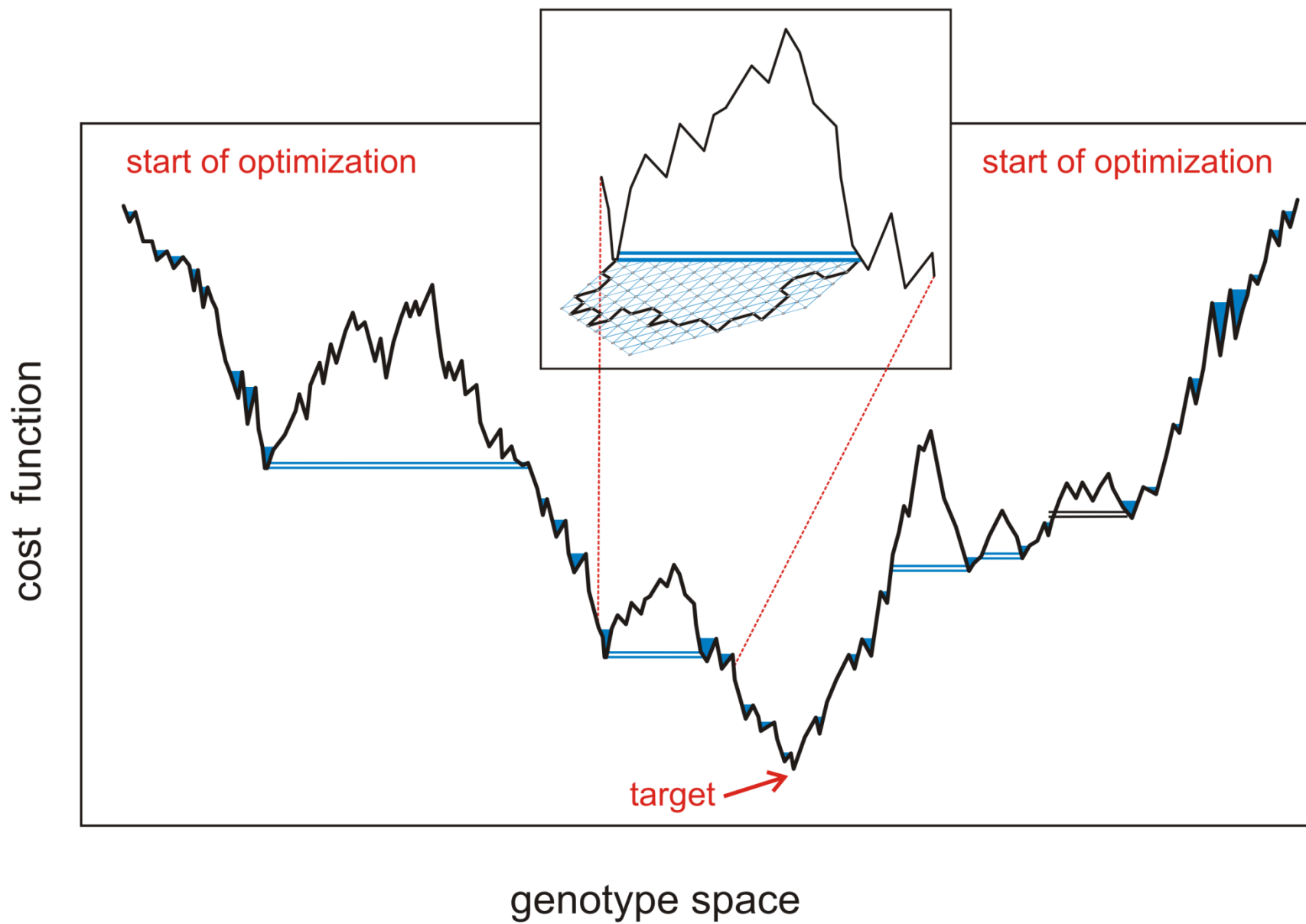
Spreading and evolution of a population on a neutral network: $t = 855$



a sketch of optimization on neutral networks







1. Is evolution possible ?
2. "Non-probabilities" ?
3. Protein folding - a(n almost) solved example
4. Evolution - The survival of the fittest?
5. Genotype-phenotype mapping and evolution
6. **Natural selection and evolution**

Reproduction leads to selection. In case of no effective fitness differences the selected variant is chosen at random.

Efficient evolution on natural fitness requires both adaptive periods of fitness increasing change and periods of phenotypic stasis with random drift in genotype space.

Thank you for your attention!

Web-Page for further information:

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

