Evolution I: Darwin 1859 und heute

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Fallstudien zur naturwissenschaftlichen Erkenntnis

Wien, 16.12.2013

Web-Page für weitere Informationen:

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

Programm

Vortrag:

1. Prolog
2. Darwinsche Selektion 1859 und heute
3. Darwinsche Selektion so einfach wie möglich
4. Replikation und Mutation
5. Von der Theorie zur Anwendung
6. Evolution zu höherer Komplexität
7. Viroide, Virusspezies und Bakterien
8. Epilog

Diskussion und Übungen:

1. Was ist Leben?
2. Wie ist irdisches Leben entstanden?
3. Genetik und Epigenetik
4. Gentechnik und Gentherapie
5. Evolution und Gesellschaft

Prolog

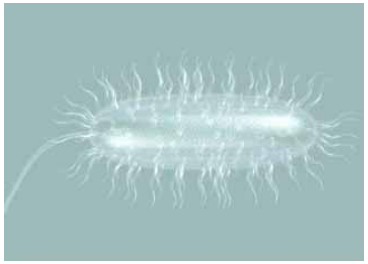
Nothing in biology makes sense except in the light of evolution.

Theodosius Dobzhansky,
1900 – 1975

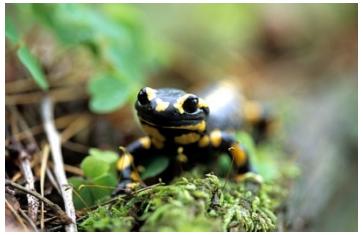
Darwinsche Selektion 1859 und heute

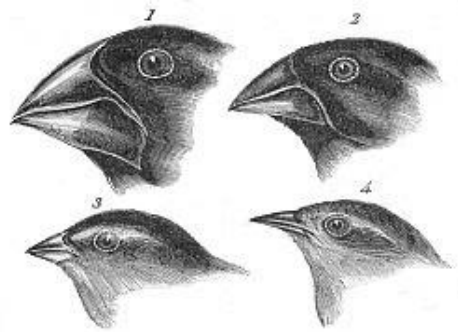
Charles Darwin, 1809 - 1882

Voyage on HMS Beagle, 1831 - 1836



Phänotypen





1. Geospiza magnirostris
2. Geospiza fortis
3. Geospiza parvula
4. Certhidea olivacea

Finches from Galapagos Archipelago

ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

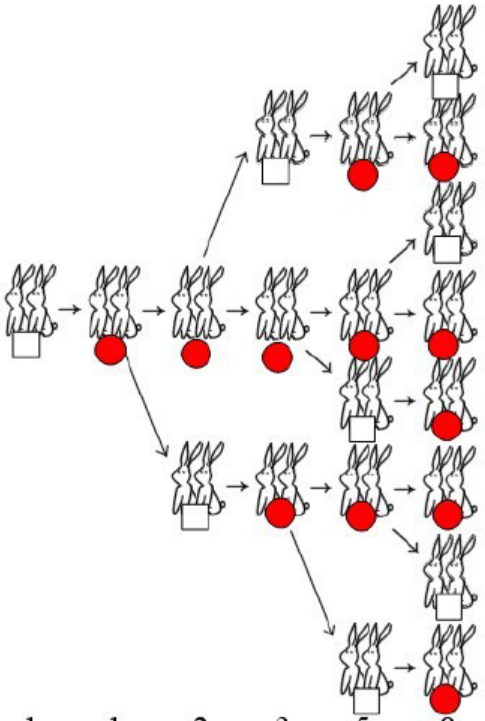
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

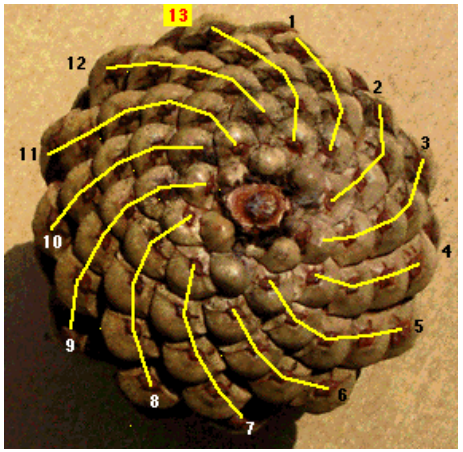
FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

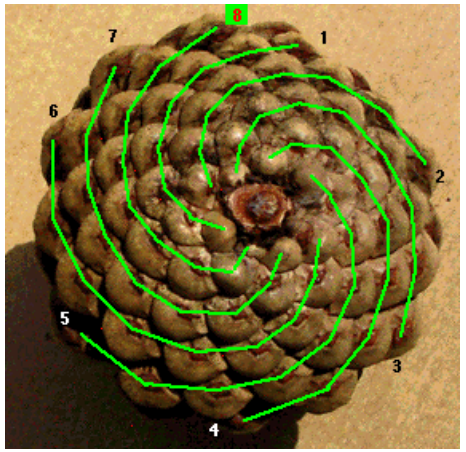
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

$$F_{n+1} = F_n + F_{n-1};\ F_0 = 0,\ F_1 = 1$$



Leonardo da Pisa
„Fibonacci“
~1180 – ~1240





Thomas Robert Malthus

1766 – 1834

Wachstum tierisch-menschlicher Populationen
führt auf eine geometrische Reihe:

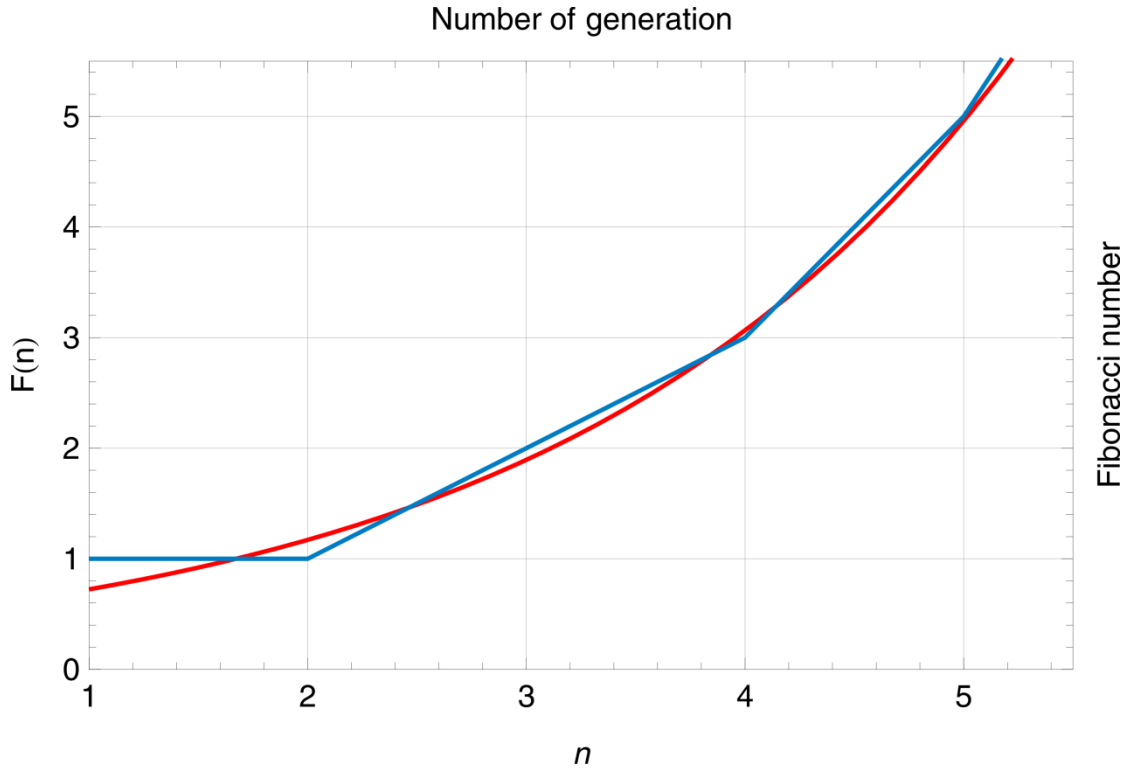
$2 \rightarrow 4 \rightarrow 8 \rightarrow 16 \rightarrow 32 \rightarrow 64 \rightarrow 128 \rightarrow 256 \rightarrow$

$$\frac{dN}{dt} = r\,N(t)\,, \quad N(t) = N_0\,\exp(r\,t)$$

Exponentialfunktion

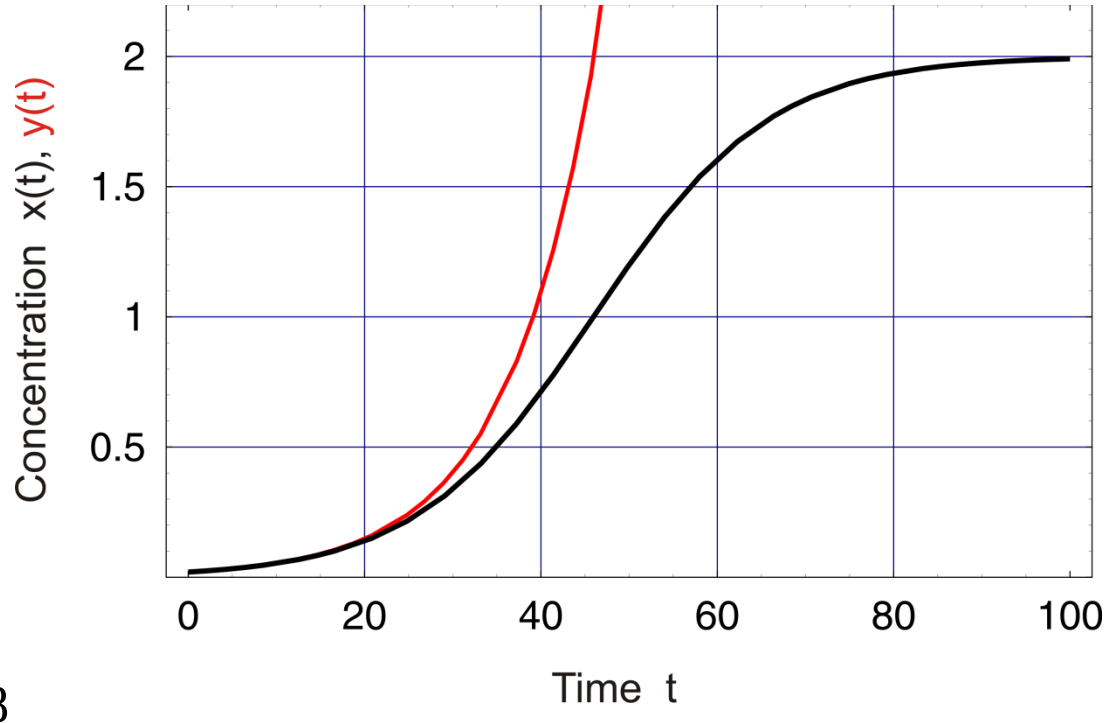
Leonhard Euler

1707 – 1783



Pierre-François Verhulst,
1804-1849

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



The logistic equation, 1828

Drei notwendige Bedingungen für Darwinsche Evolution sind:

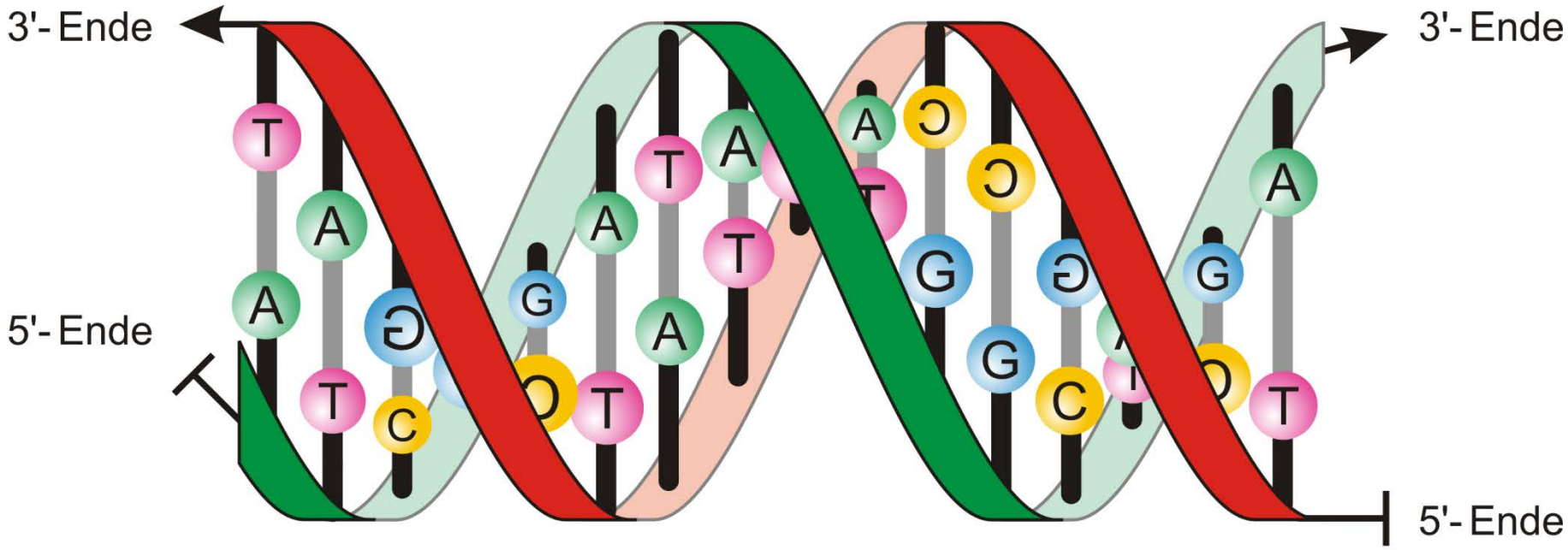
1. **Vermehrung** (und Vererbung),
2. **Variation**, und
3. **Selektion**.

Vermehrung führt zu exponentiellem Wachstum, das eine *conditio sine qua non* für Selektion darstellt.

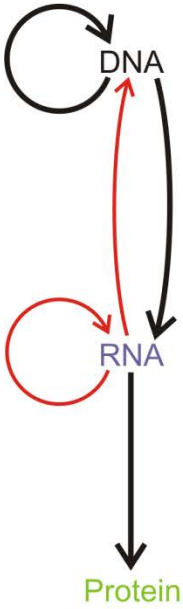
Variation ist ein Nebeneffekt des molekularen Mechanismus der Reproduktion.

Selektion ist eine Konsequenz der endlichen Ressourcen.

Da im Sinne der Optimierung von Fitness durch die Darwinsche Evolution nur Nachkommen gezählt werden, ist sie fast universell gültig.



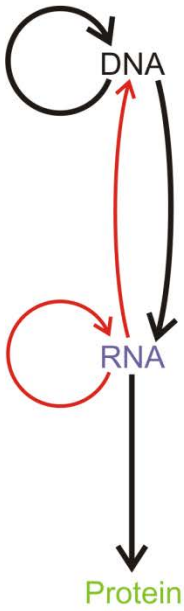
DNA-Doppelhelix

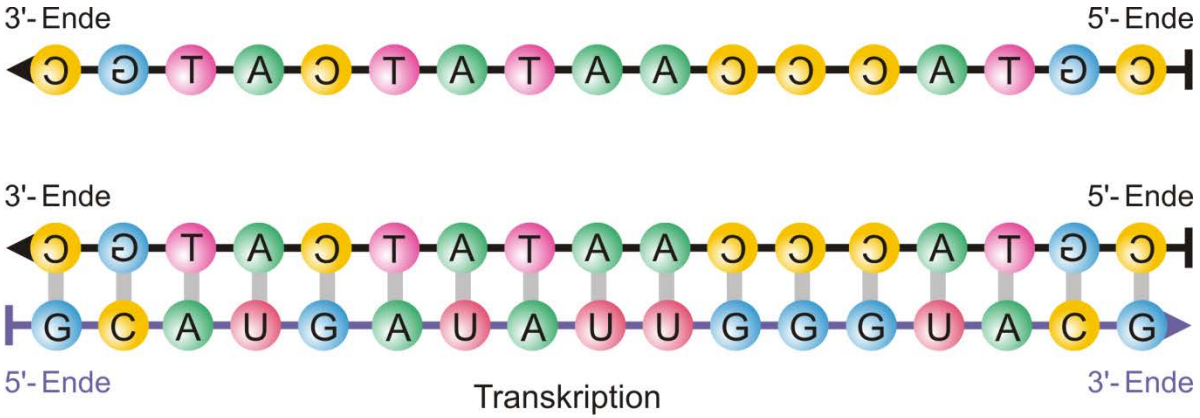


Adenin A Thymin T Uracil U

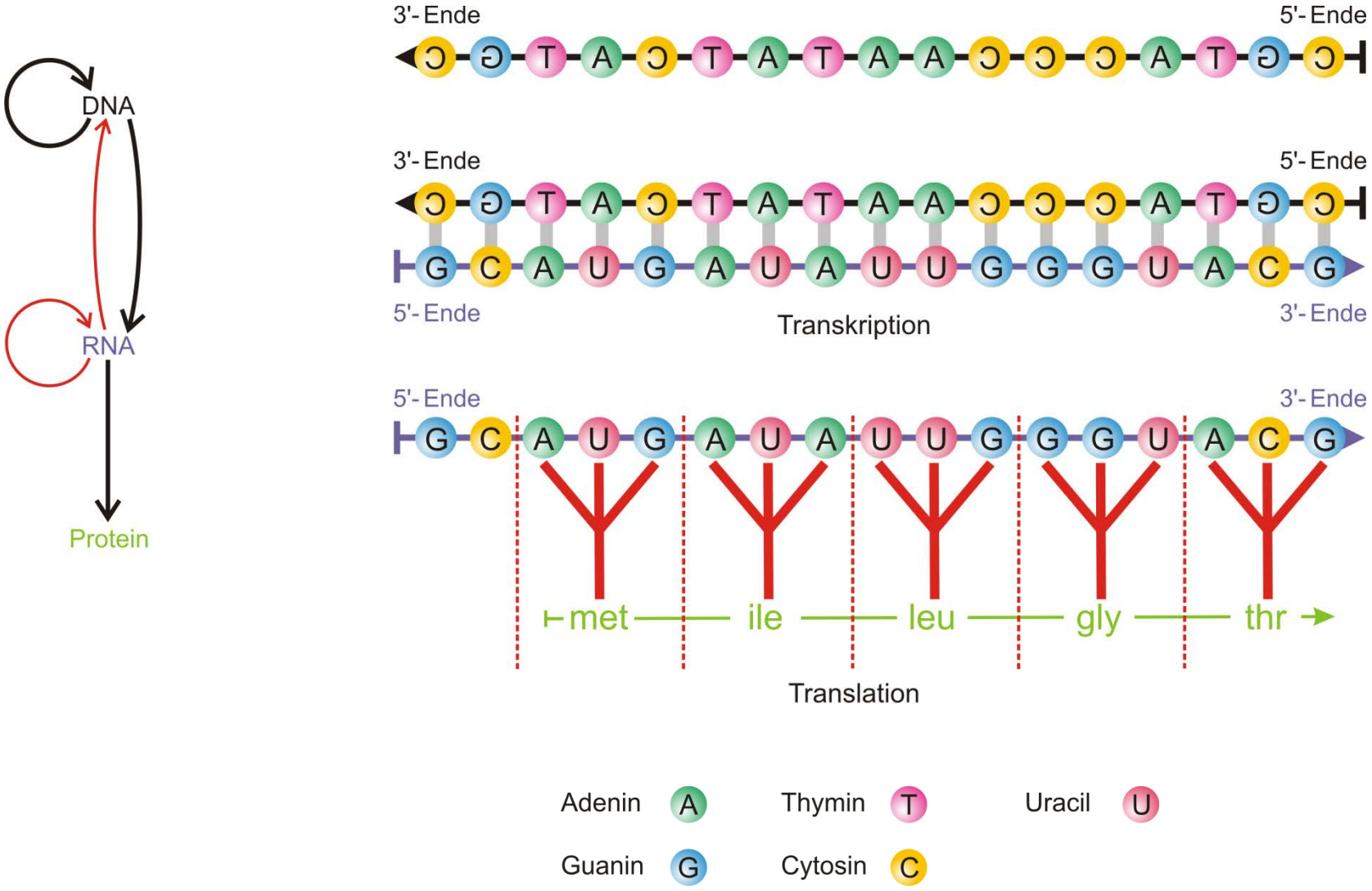
Guanin G Cytosin C

The ‚central dogma' of molecular biology





The ‚central dogma' of molecular biology



The ‚central dogma' of molecular biology

Darwins principle is still valid but **nothing** he said about **inheritance**, multiplication and **variation** is correct.

Darwinsche Selektion so einfach wie möglich

Charles Darwin, 1809-1882

Three necessary conditions for Darwinian evolution are:

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

All three conditions are fulfilled not only by cellular organisms but also by **nucleic acid molecules** – **DNA** or **RNA** – **in** suitable **cell-free experimental assays**:

Darwinian evolution in the test tube

autocatalysis

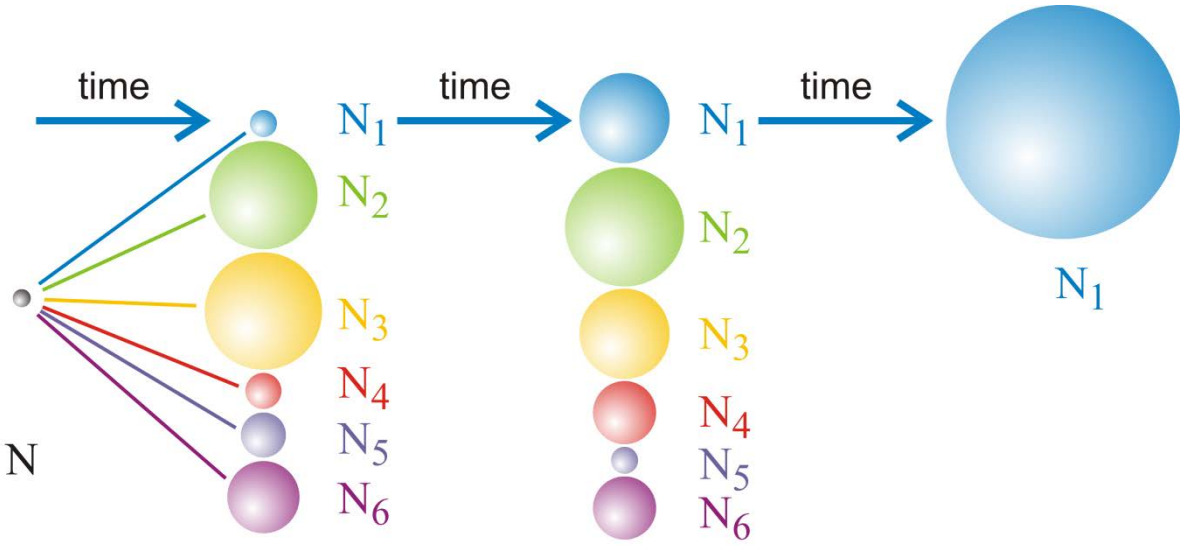
$$\frac{dx}{dt} = f\ x \quad \Rightarrow \quad x(t) = x(0)\exp(f\,t)$$

competition

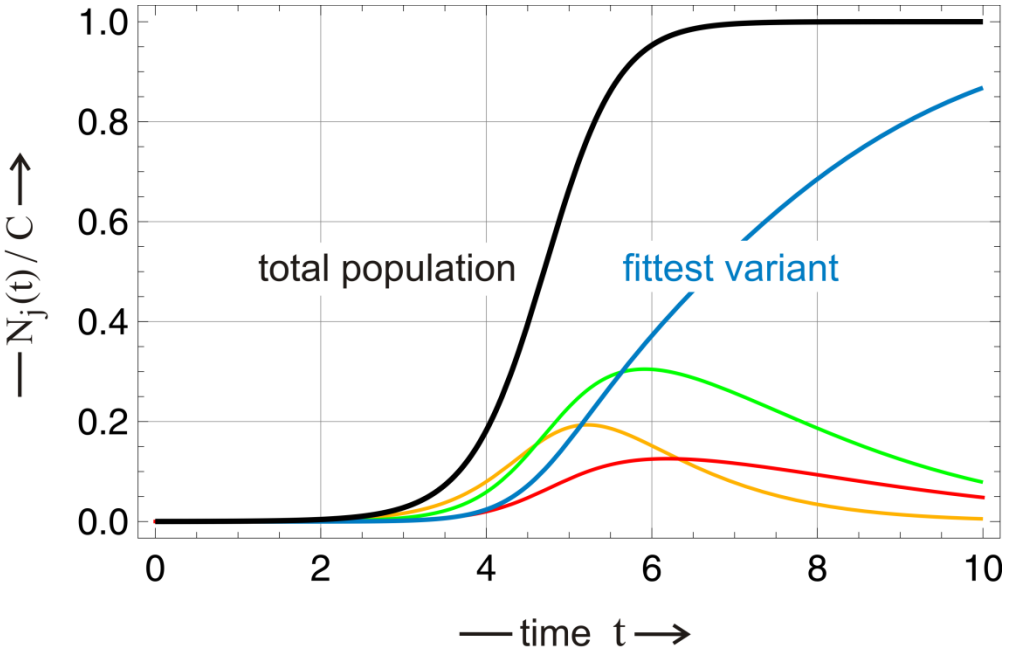
$$\frac{dx_k}{dt} = f_k\ x_k\ ; k = 1,2,\ldots,n$$

$$x_k(t) = x_k(0)\ \exp(f_k\,t)$$

The chemistry and the mathematics of reproduction



$$N = N_1 + N_2 + N_3 + N_4 + N_5 + N_6$$



fitness values:

$f_1 = 2.80$, $f_2 = 2.35$, $f_3 = 2.25$, and $f_4 = 1.75$

Sol Spiegelman,
1914 - 1983

Evolution im Reagenzglas:

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

DOI: 10.1002/anie.200701369

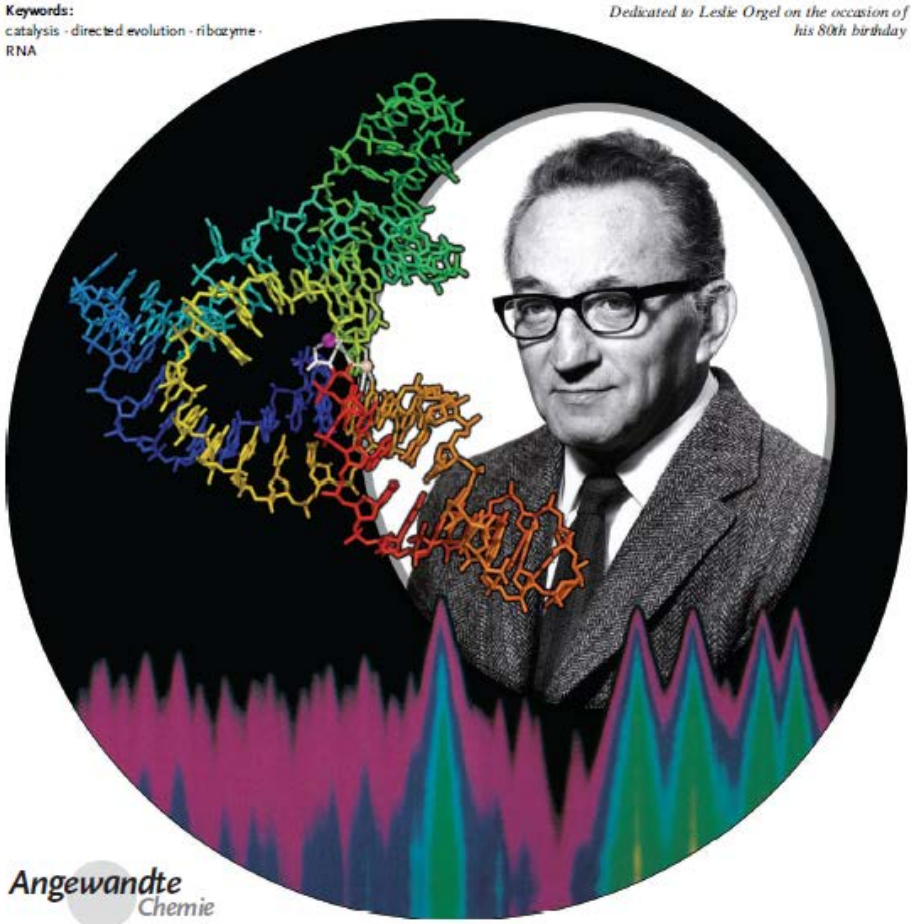
Molecular Evolution

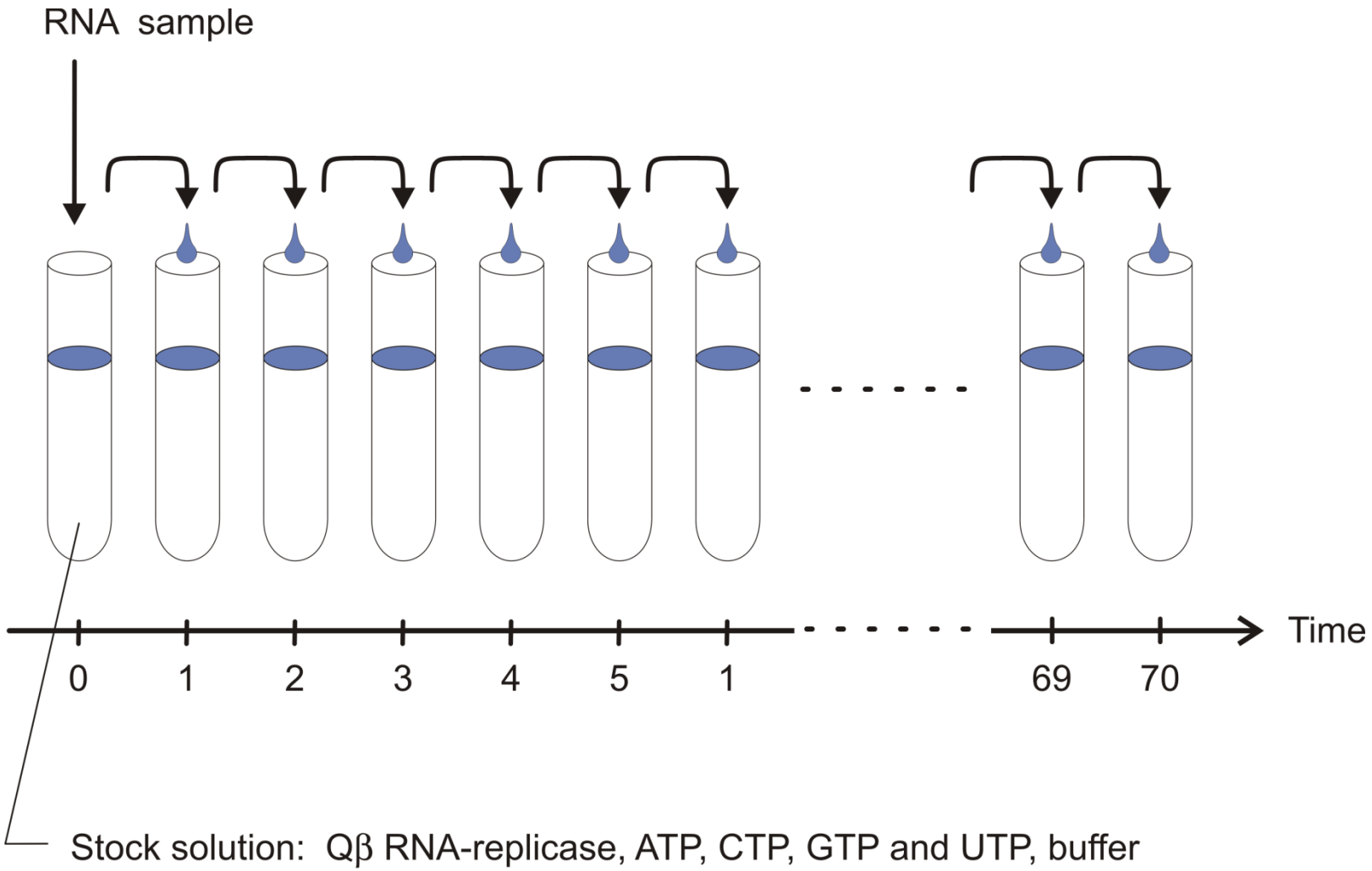
Forty Years of In Vitro Evolution**

*Gerald F. Joyce**

Keywords:
catalysis · directed evolution · ribozyme · RNA

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





Anwendung der Technik des seriellen Transfers zur Evolution von RNA im Reagenzglas

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

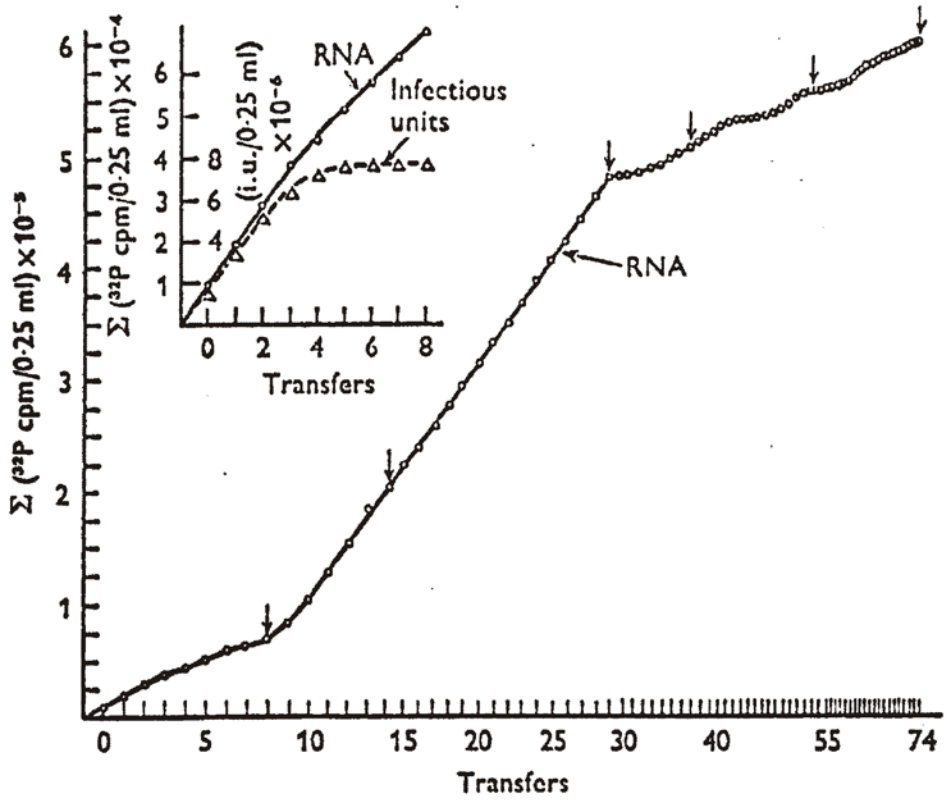
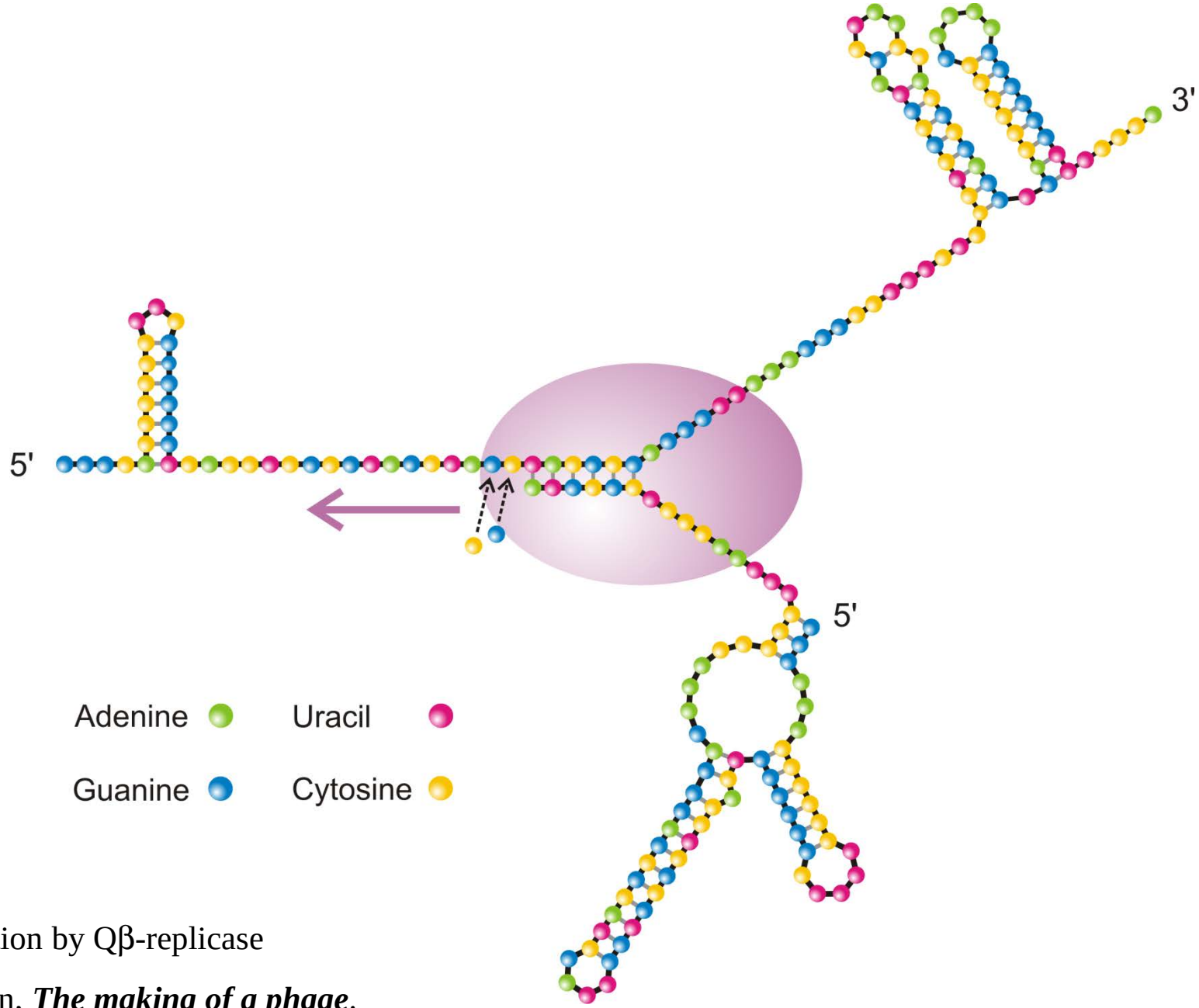


Fig. 9. Serial transfer experiment. Each 0·25 ml standard reaction mixture contained 40 μg of Qβ replicase and ^{32}P-UTP. The first reaction (0 transfer) was initiated by the addition of 0·2 μg ts-1 (temperature-sensitive RNA) and incubated at 35 °C for 20 min, whereupon 0·02 ml was drawn for counting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

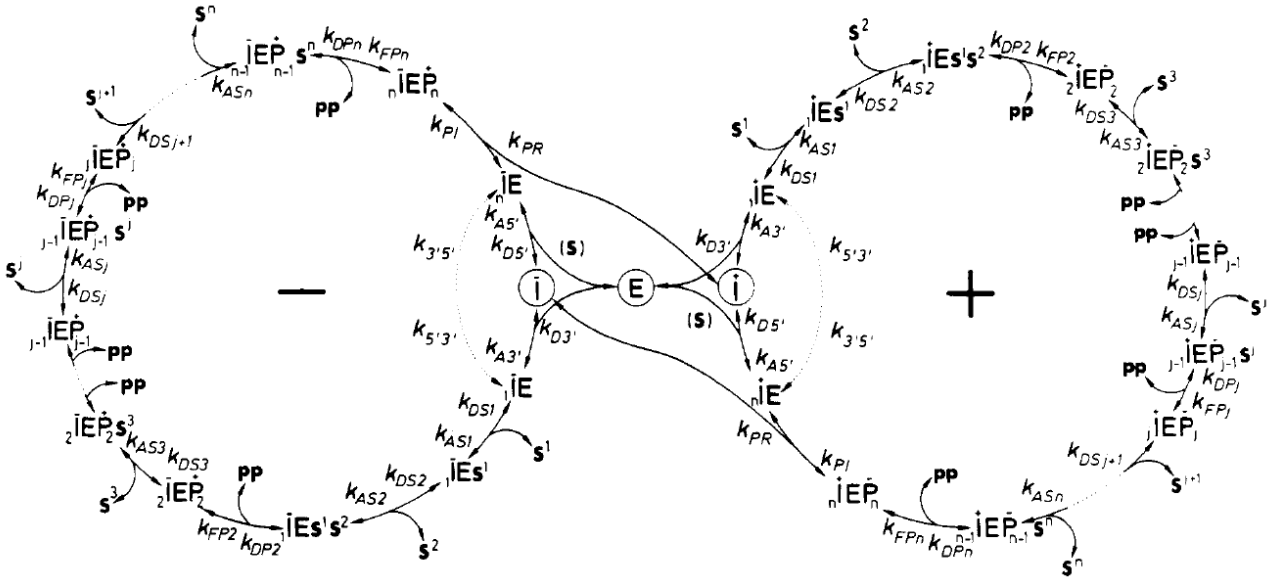
D.R.Mills, R,L,Peterson, S.Spiegelman, *An extracellular Darwinian experiment with a self-duplicating nucleic acid molecule*. Proc.Natl.Acad.Sci.USA **58** (1967), 217-224



RNA replication by Qβ-replicase

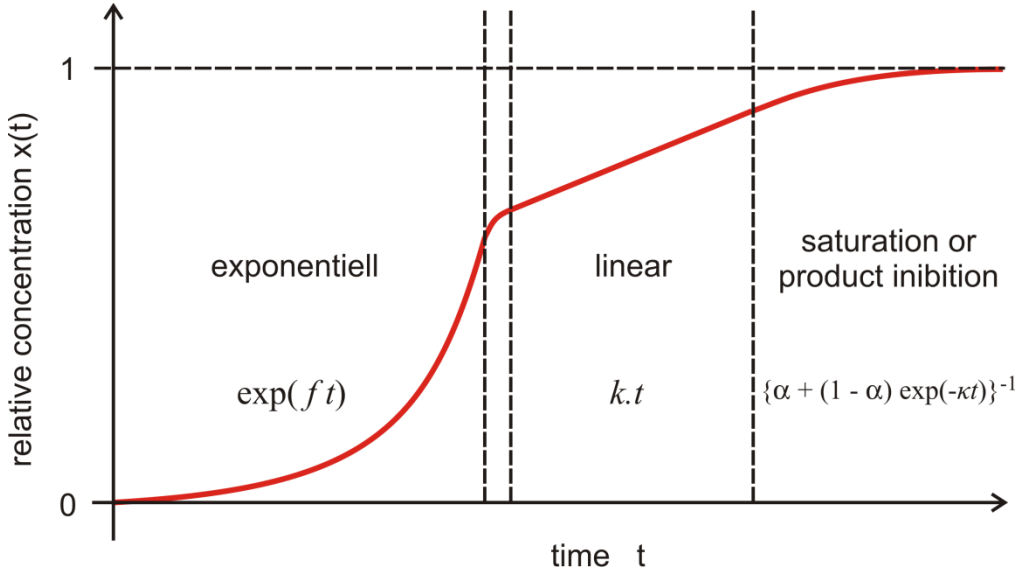
C. Weissmann, ***The making of a phage***.
FEBS Letters **40** (1974), S10-S18

Christof K. Biebricher,
1941-2009

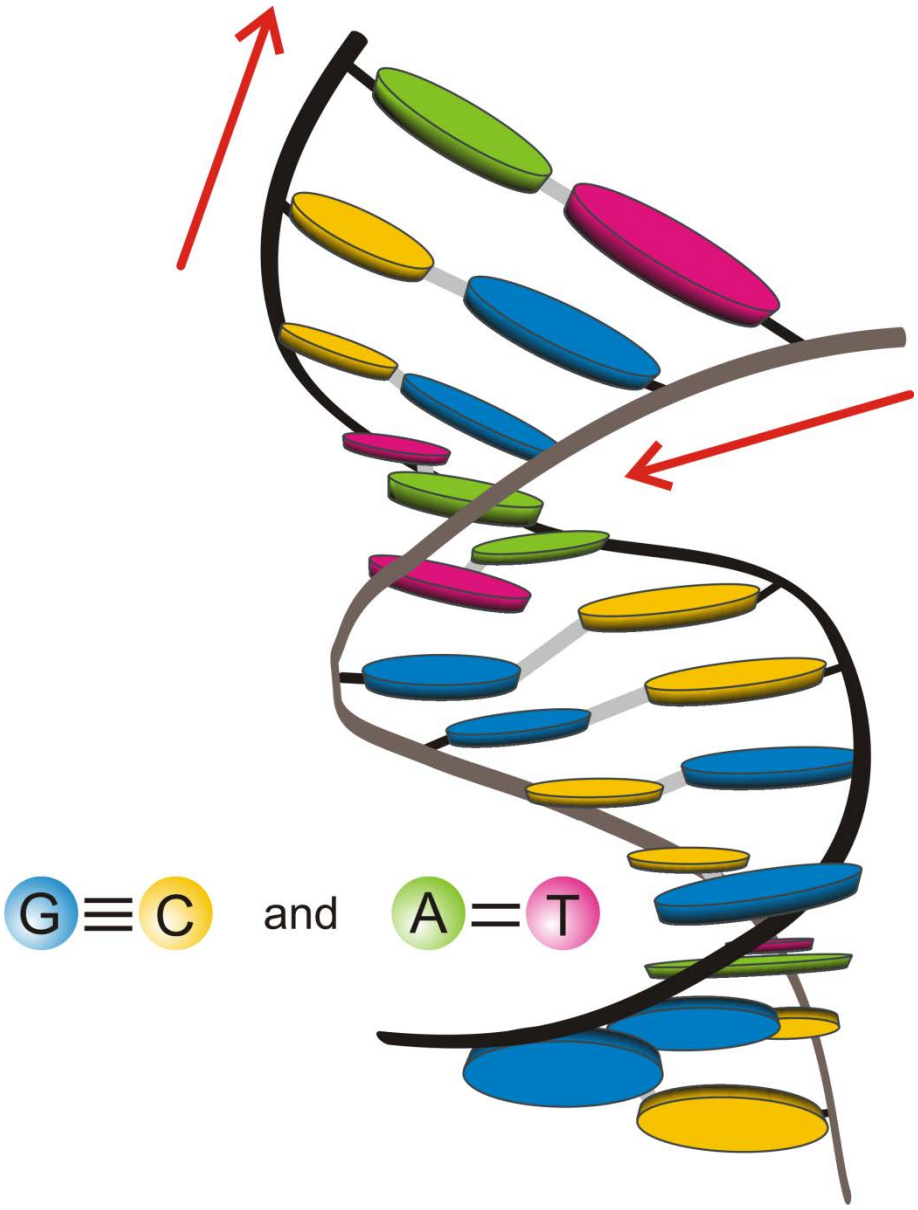


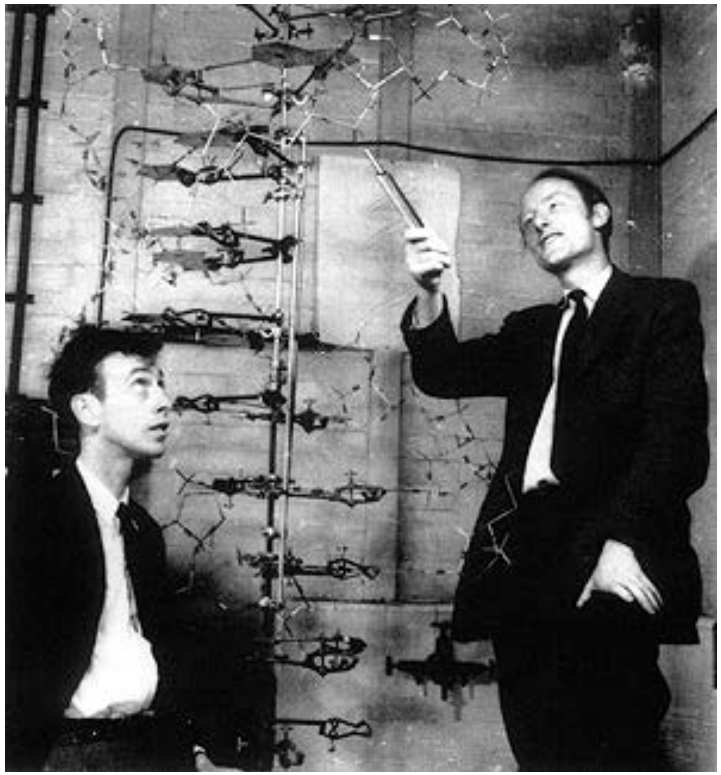
Kinetik der RNA Replikation

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



Replikation und Mutation

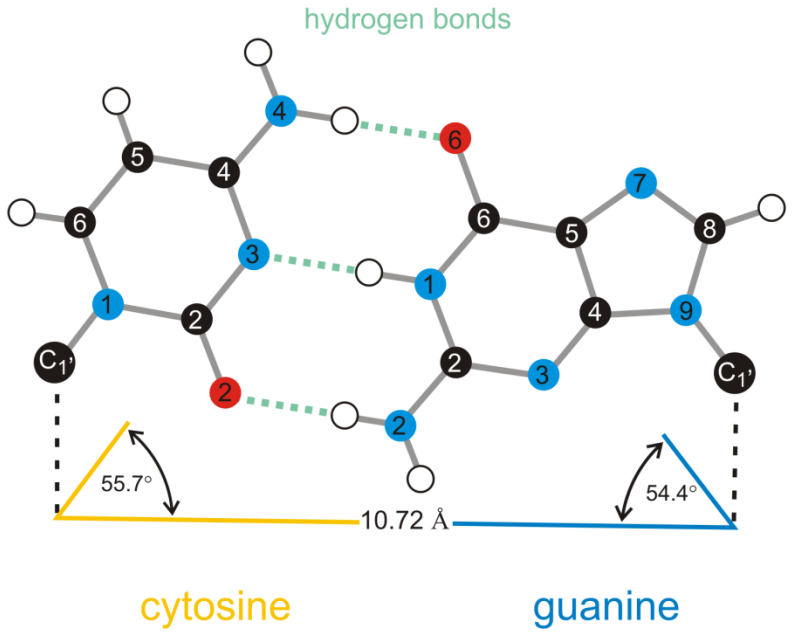




James D. Watson, 1928- , and Francis Crick, 1916-2004,
Nobel Preis 1962

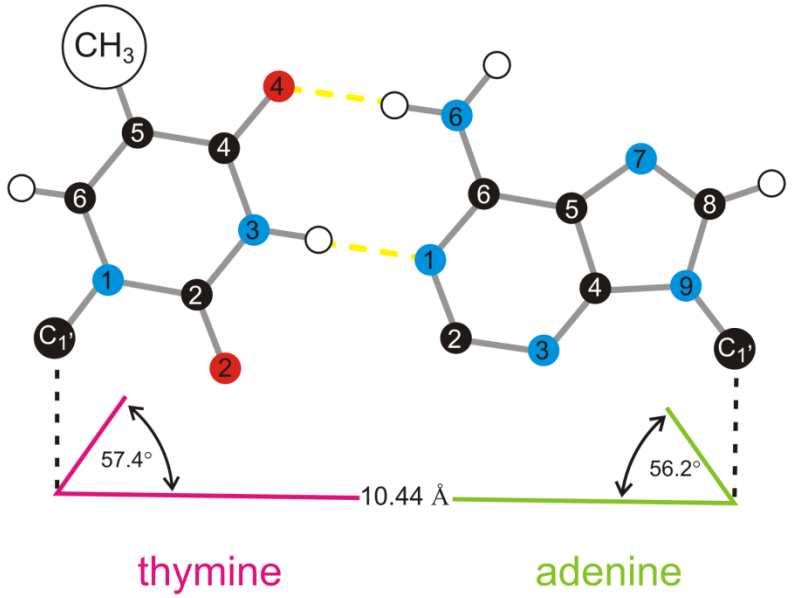
Die dreidimensionale Struktur eines kleinen Stückes der B-DNA

C ≡ G

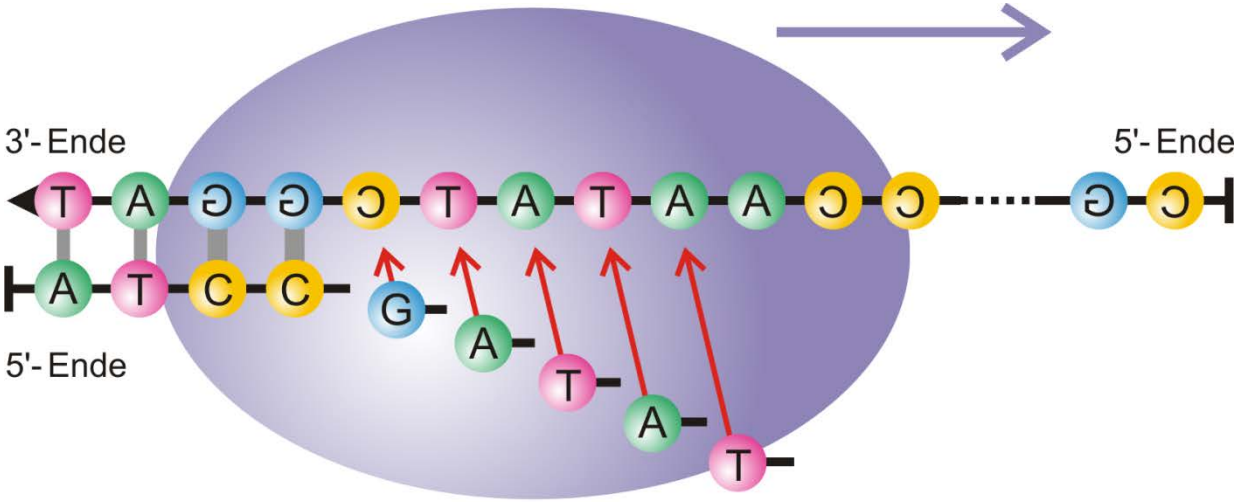


Obwohl die Wechselwirkungen mit G viel stärker sind als alle anderen Wechselwirkungen zwischen Nukleotidbasen, bilden A=T und G≡C gleichberechtigte Basenpaare.

T = A



Digitalisierung der Chemie:
The unique assigment of nucleotides in base pairs.



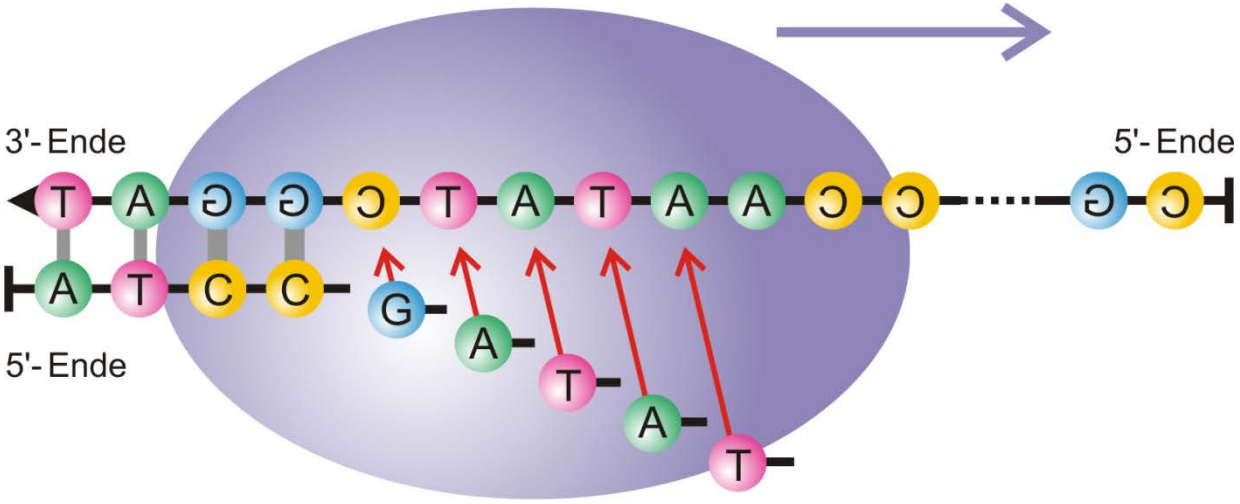
Adenin A Thymin T

Guanin G Cytosin C

korrekte Replikation

Die Logik der DNA (oder RNA) Replikation

Die Logik der DNA (oder RNA) Replikation



korrekte Replikation

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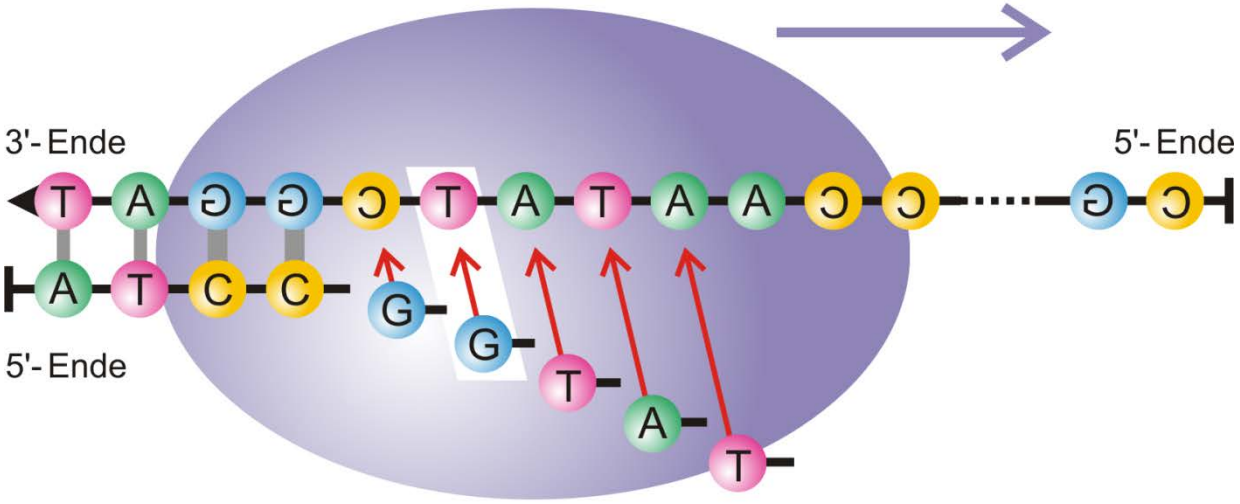
Guanin G Cytosin C

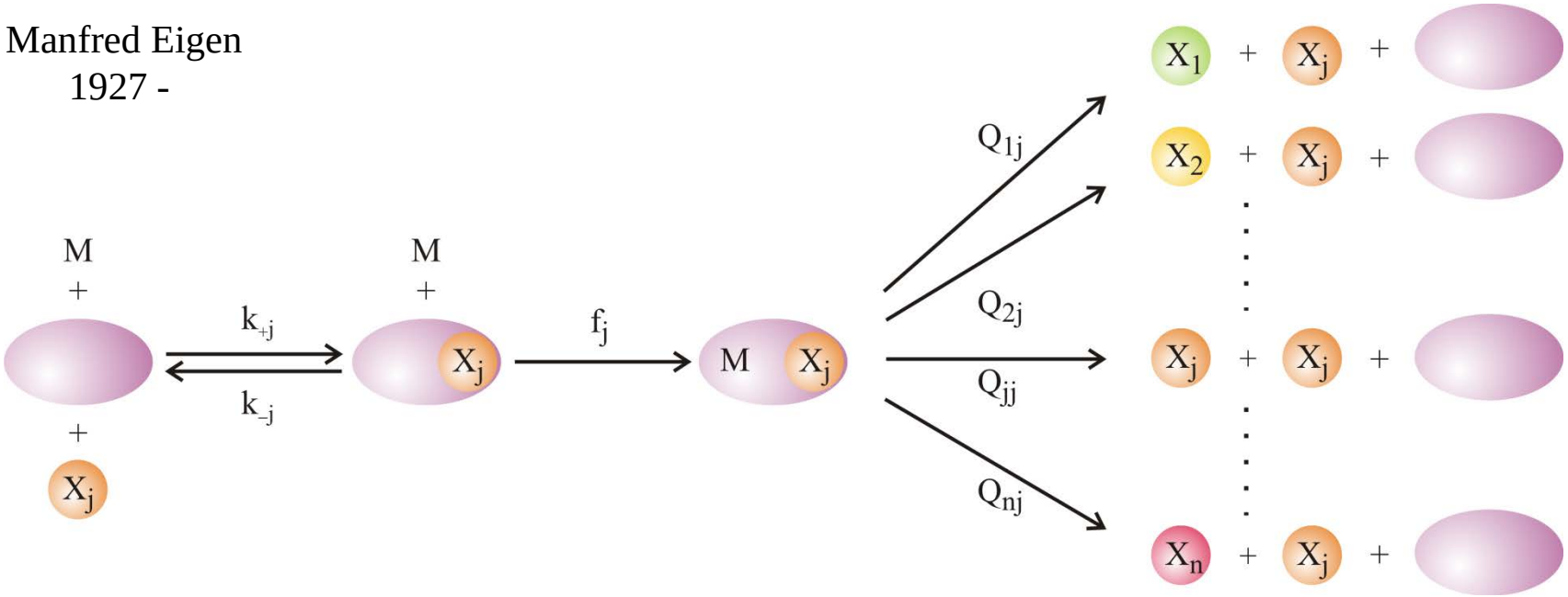


Mutation

Manfred Eigen
1927 -

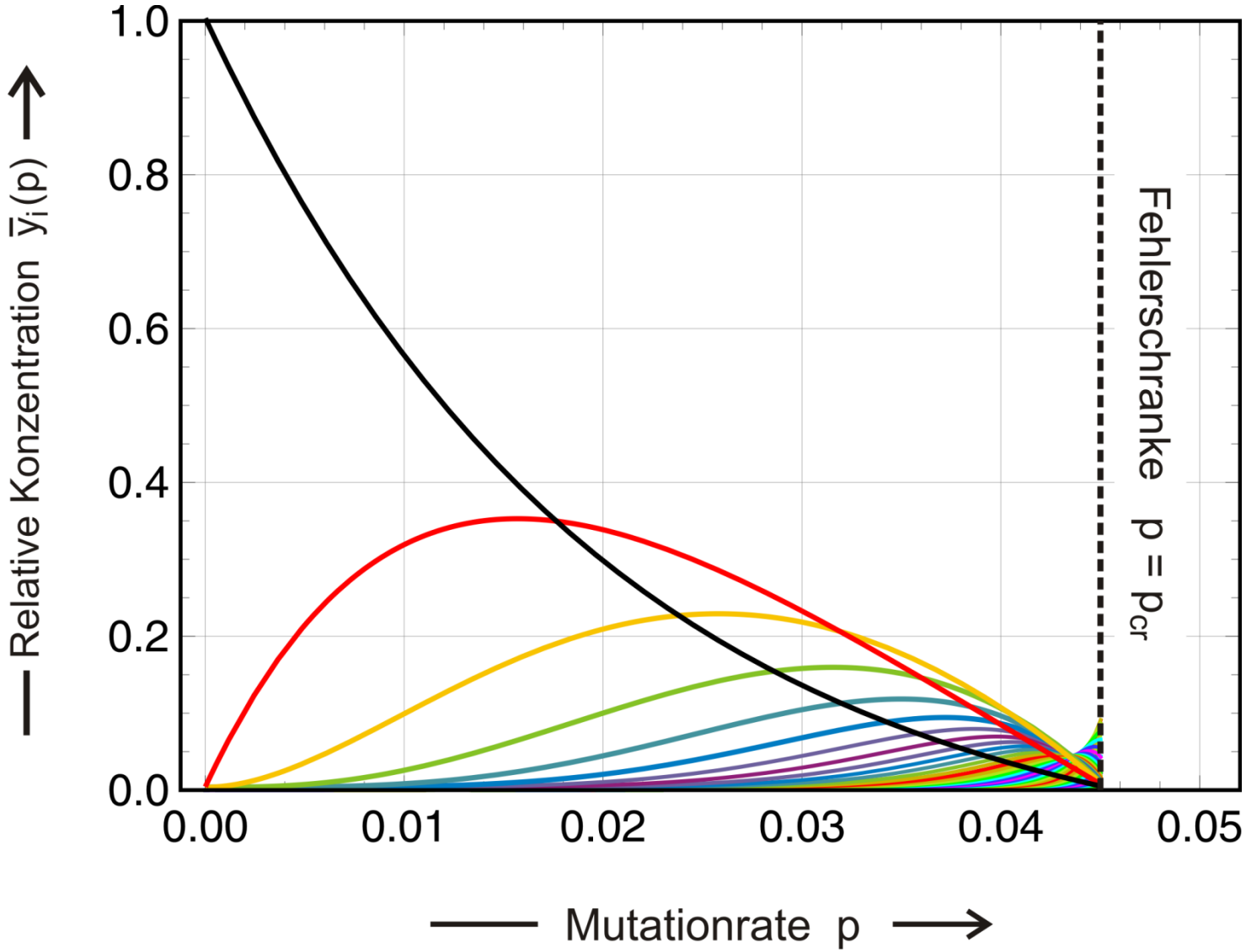
$$\frac{dx_i}{dt} = \sum_{j=1}^{n} Q_{ij} f_j x_j - x_i \Phi ; \; i = 1, 2, \ldots, n$$

$$\Phi = \sum_{j=1}^{n} f_j x_j ; \sum_{j=1}^{n} x_j = 1$$

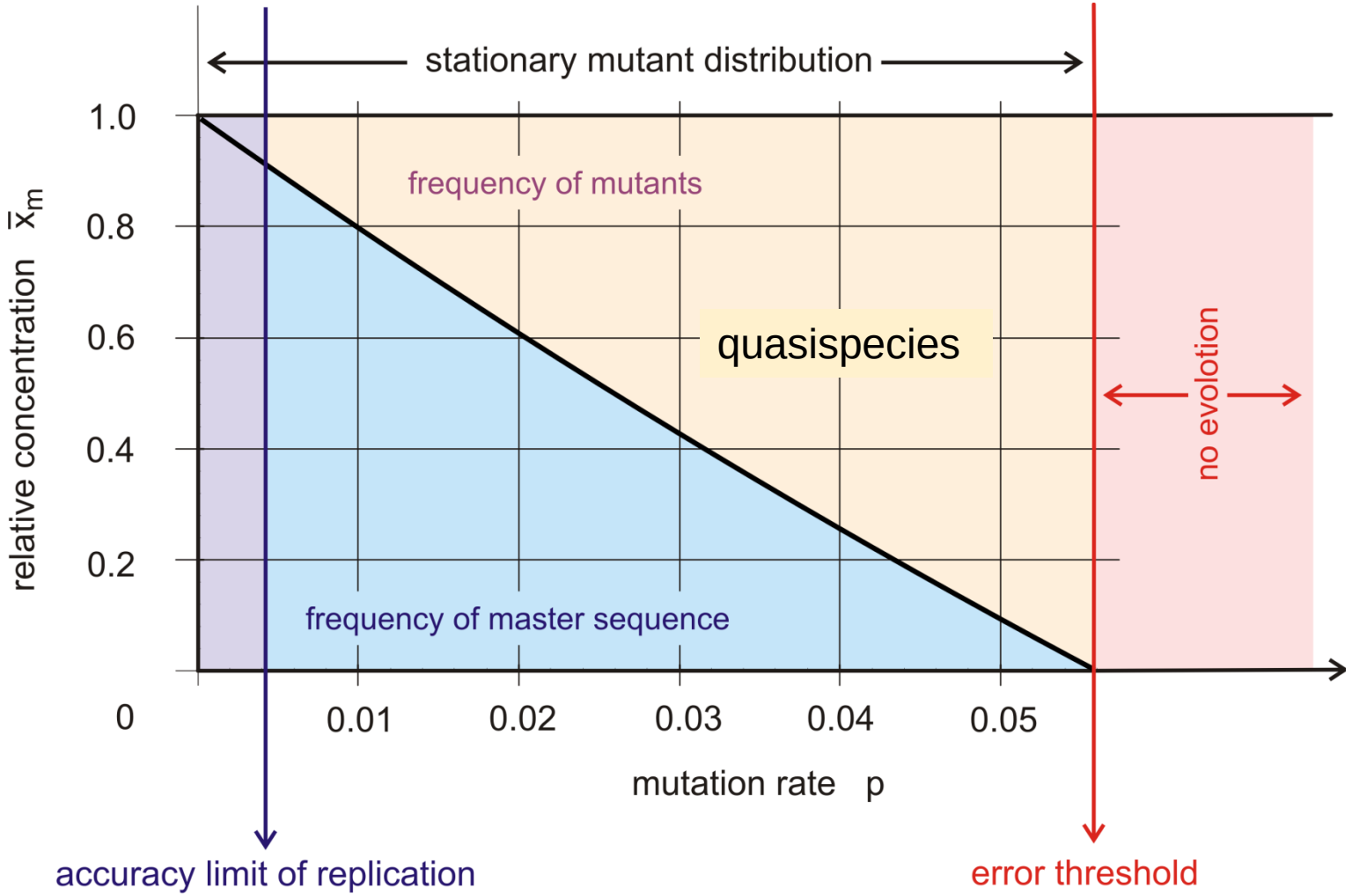


Mutation and (correct) replication as parallel chemical reactions

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



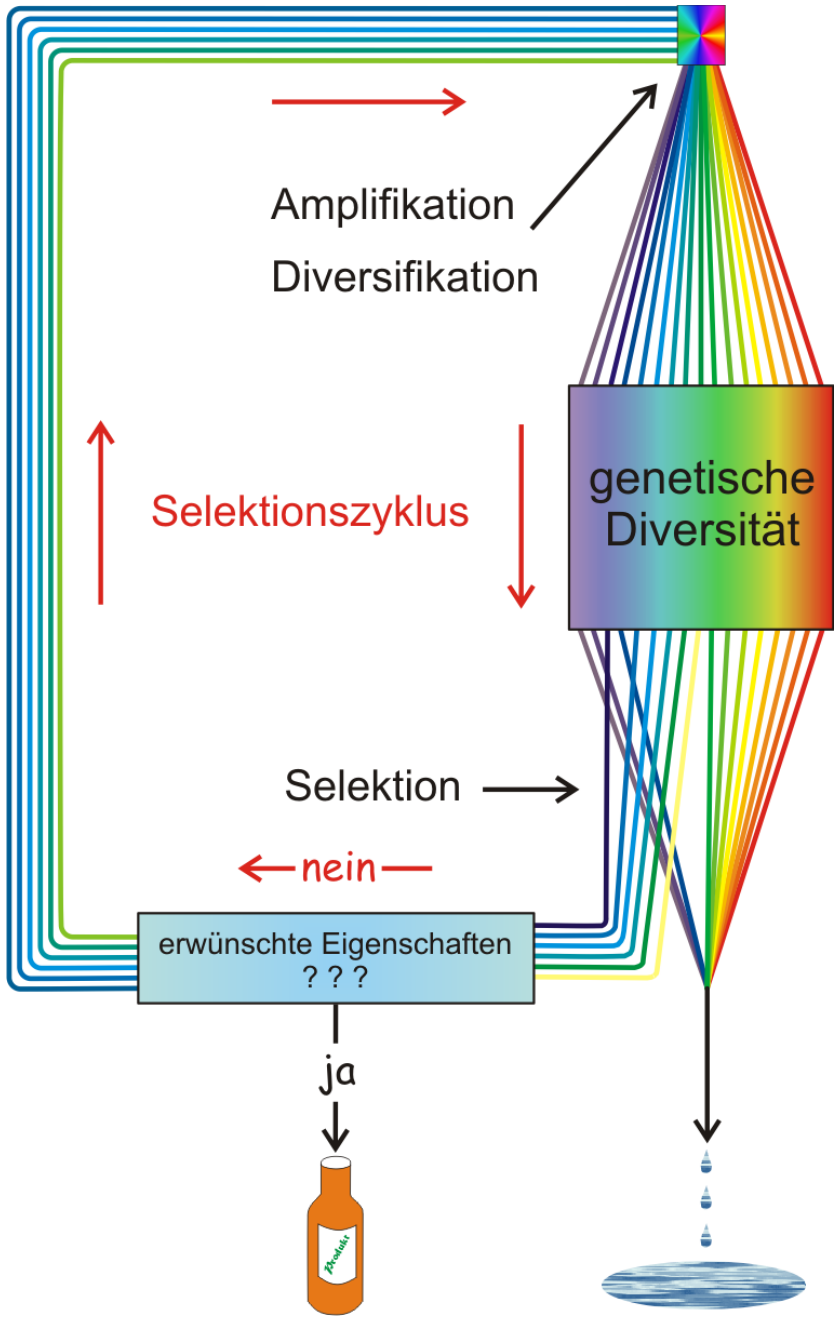
Die stationäre Mutatntenverteilung als Funktion der Mutationsrate p

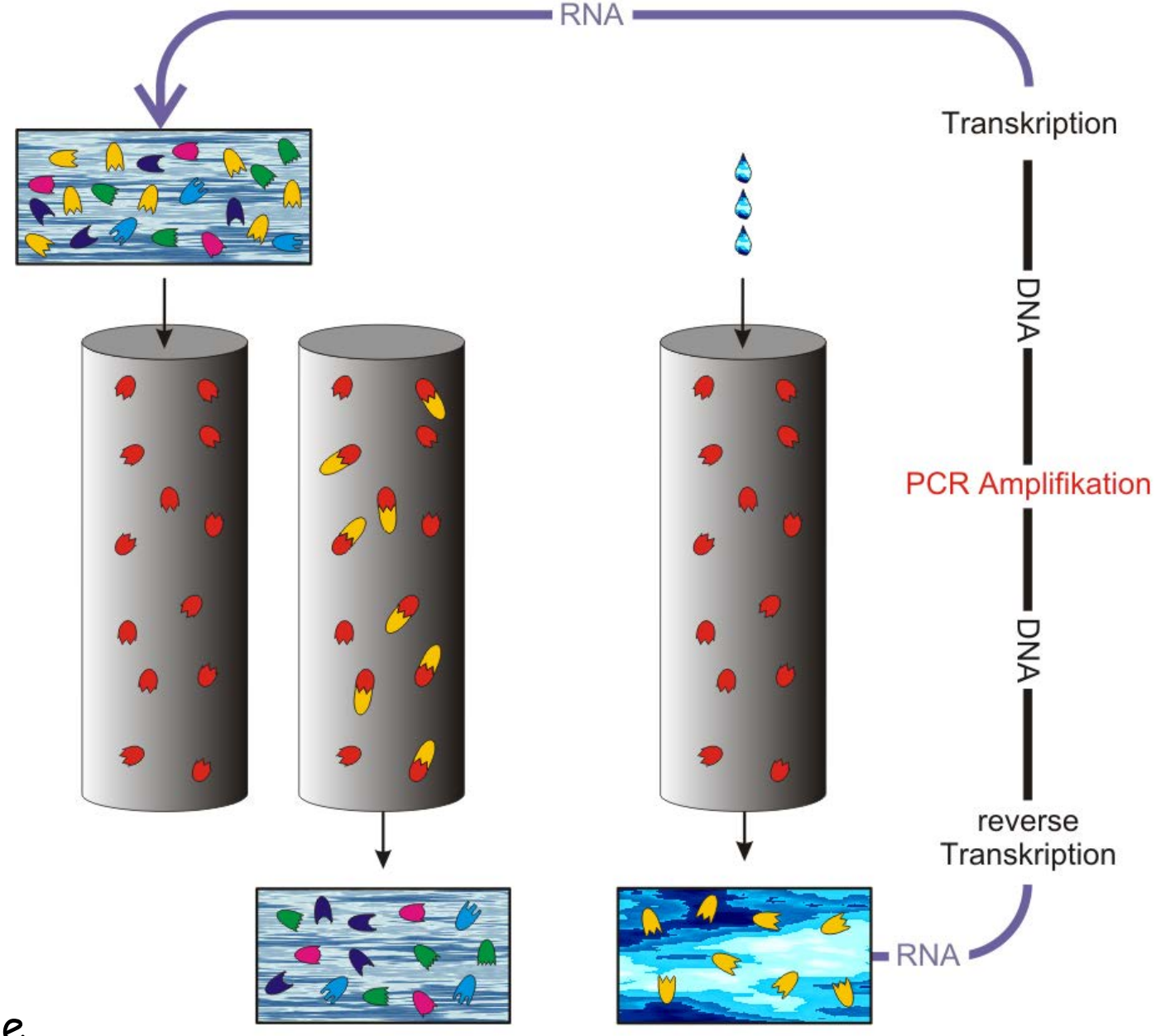


The error threshold in replication

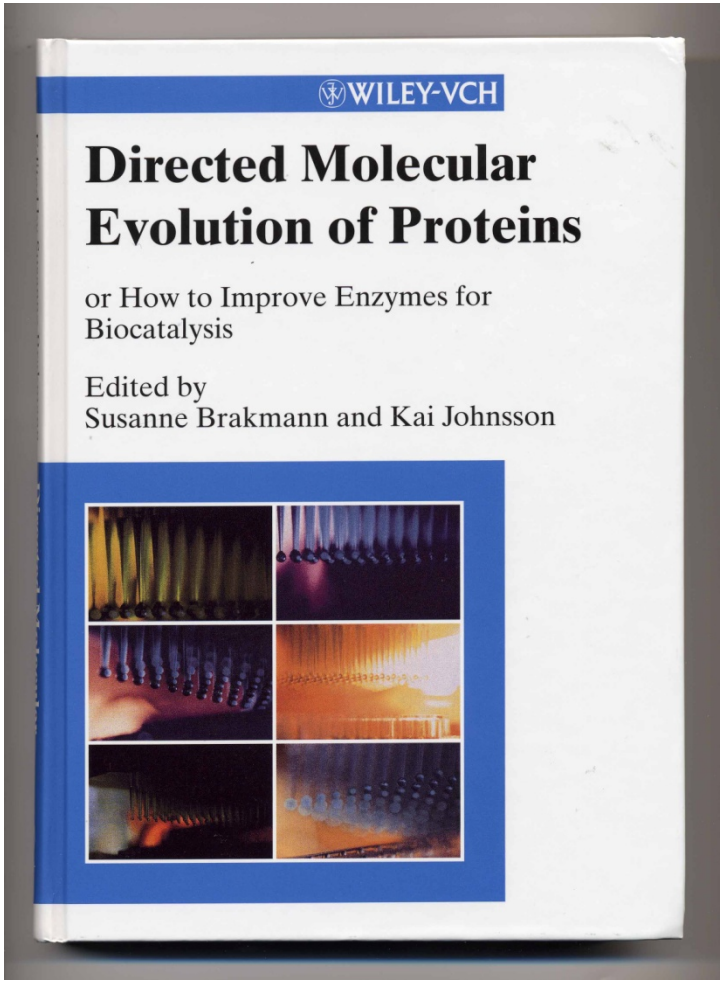
Von der Theorie zur Anwendung

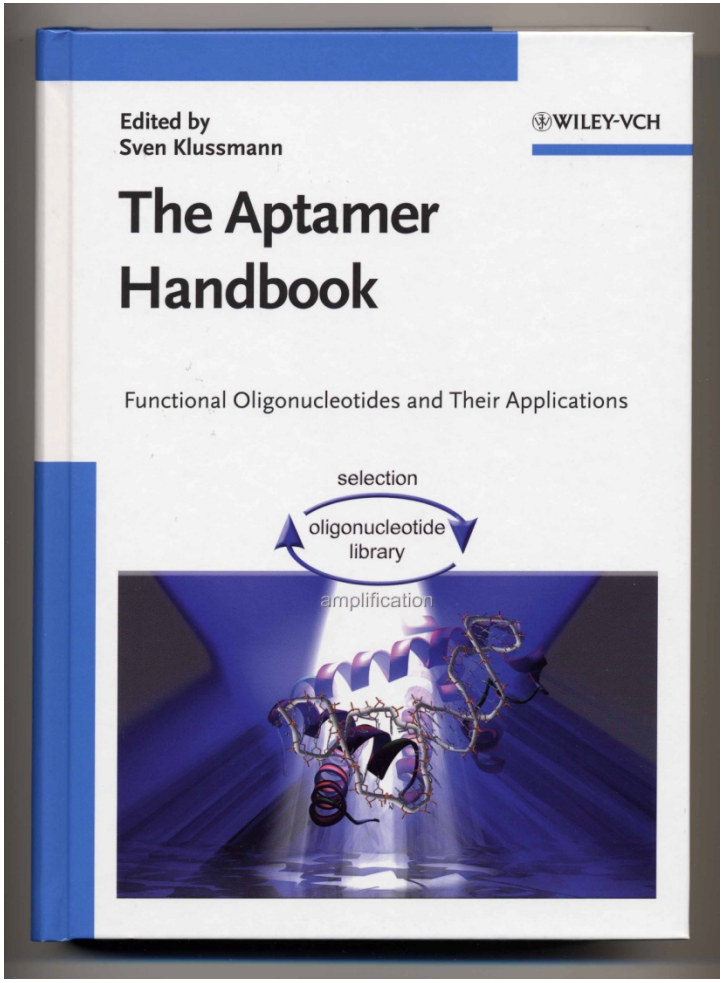
Das Prinzip der evolutionären Biotechnologie



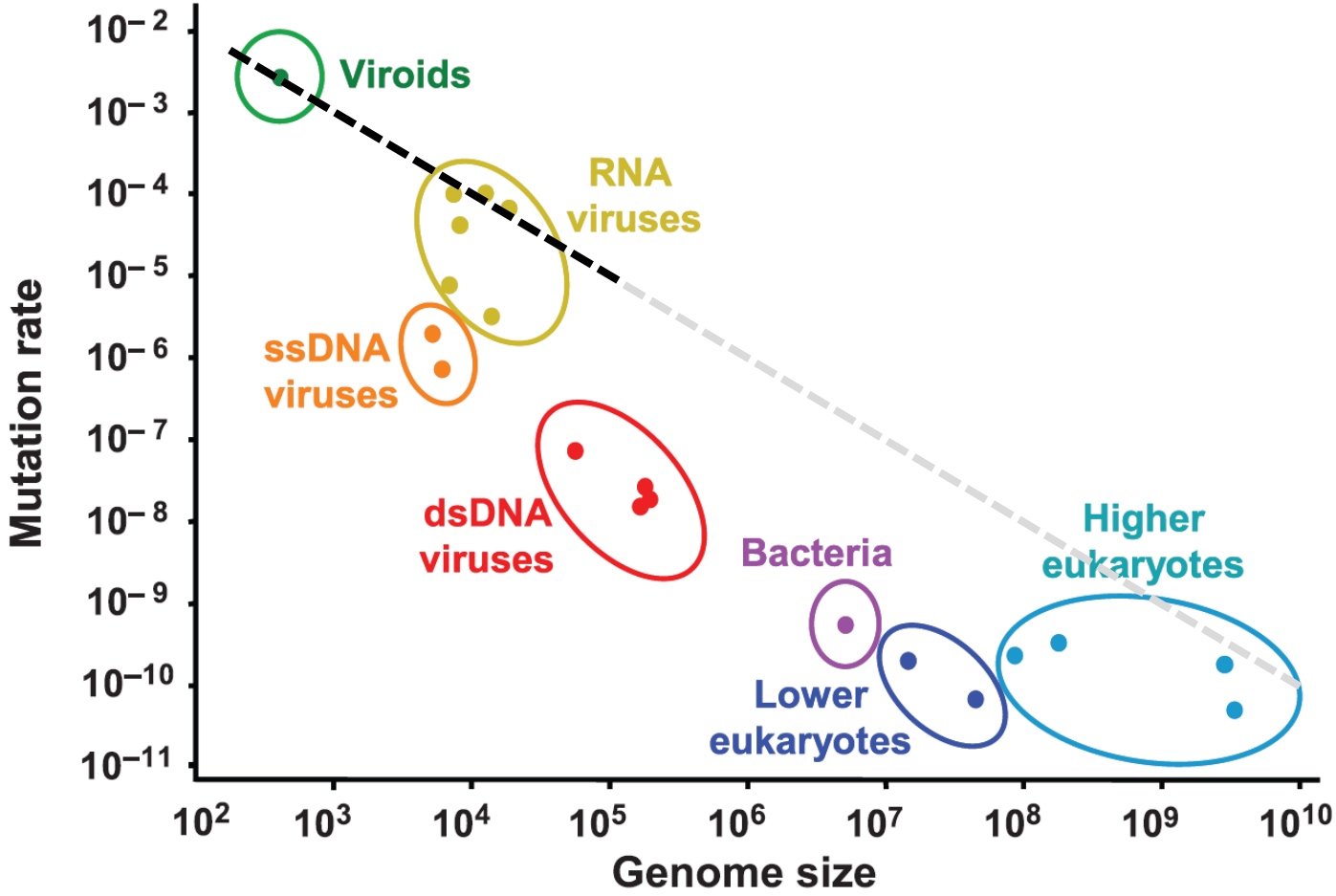


The PCR technique
as a selection tool



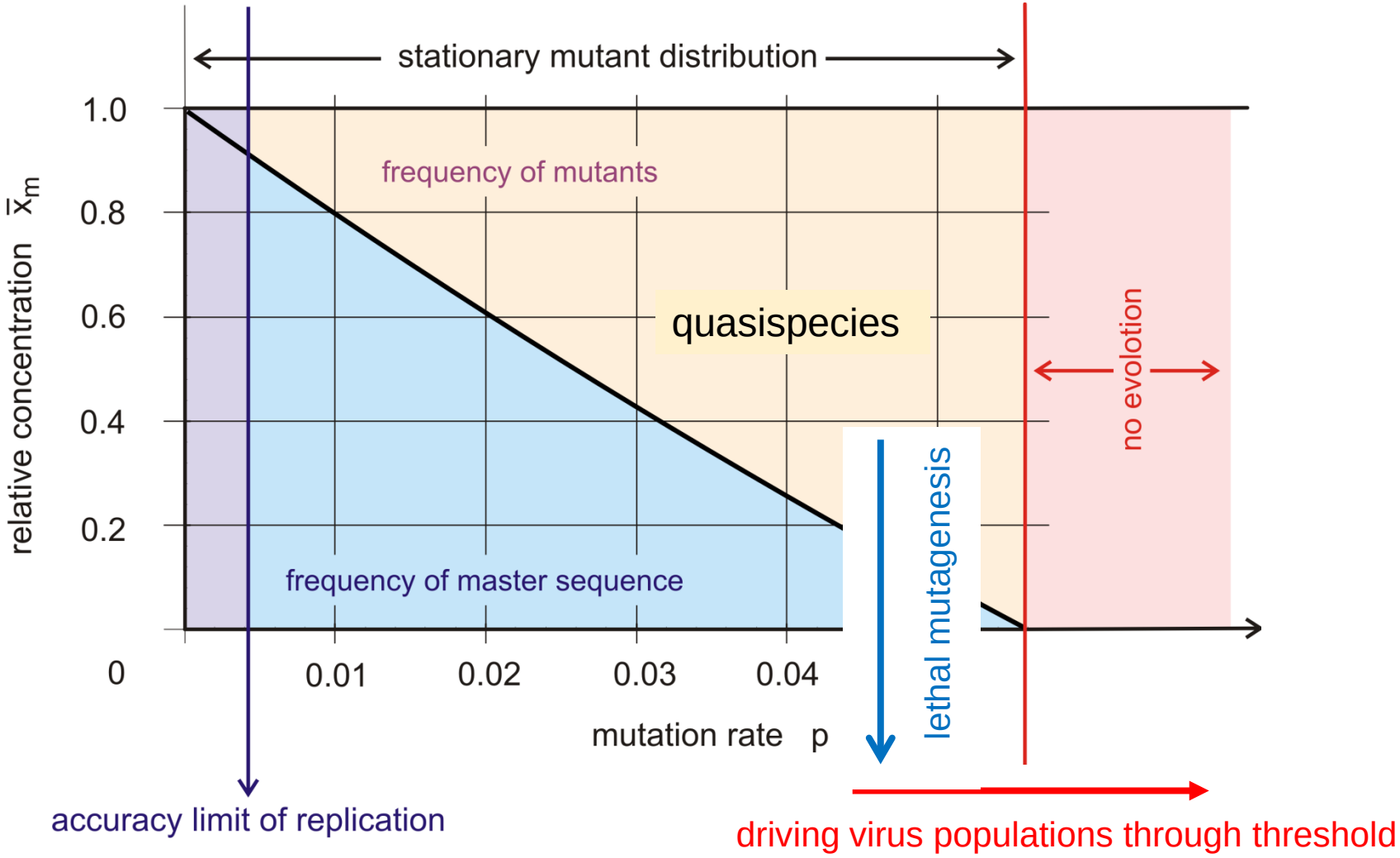


Application of molecular evolution to problems in biotechnology



Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. 2009, Extremely high mutation rate of a hammerhead viroid. Science 323:1308.

Mutation rate and genome size



The error threshold in replication

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Virus Research 107 (2005) 115–116
Virus Research
www.elsevier.com/locate/virusres

Preface

Antiviral strategy on the horizon

Error catastrophe had its conceptual origins in the middle of the XXth century, when the consequences of mutations on enzymes involved in protein synthesis, as a theory of aging. In those times biological processes were generally perceived differently from today. Infectious diseases were regarded as a fleeting nuisance which would be eliminated through the use of antibiotics and antiviral agents. Microbial variation, although known in some cases, was not thought to be a significant problem for disease control. Variation in differentiated organisms was seen as resulting essentially from exchanges of genetic material associated with sexual reproduction. The problem was to unveil the mechanisms of inheritance, expression of genetic information and metabolism. Few saw that genetic change is occurring at present in all organisms, and still fewer recognized Darwinian principles as essential to the biology of pathogenic viruses and cells. Population geneticists rarely used bacteria or viruses as experimental systems to define concepts in biological evolution. The extent of genetic polymorphism among individuals of the same biological species came as a surprise when the first results on comparison of electrophoretic mobility of enzymes were obtained. With the advent of in vitro DNA recombination, and rapid nucleic acid sequencing techniques, molecular analyses of genomes reinforced the conclusion of extreme inter-individual genetic variation within the same species. Now, due largely to spectacular progress in comparative genomics, we see cellular DNAs, both prokaryotic and eukaryotic, as highly dynamic. Most cellular processes, including such essential information-bearing and transferring events as genome replication, transcription and translation, are increasingly perceived as inherently inaccurate. Viruses, and in particular RNA viruses, are among the most extreme examples of exploitation of replication inaccuracy for survival.

Error catastrophe, or the loss of meaningful genetic information through excess genetic variation, was formulated in quantitative terms as a consequence of quasispecies theory, which was first developed to explain self-organization and adaptability of primitive replicons in early stages of life. Recently, a conceptual extension of error catastrophe that could be defined as "induced genetic deterioration" has emerged as a possible antiviral strategy. This is the topic of the current special issue of *Virus Research*.

Few would nowadays doubt that one of the major obstacles for the control of viral disease is short-term adaptability of viral pathogens. Adaptability of viruses follows the same Darwinian principles that have shaped biological evolution over eons, that is, repeated rounds of reproduction with genetic variation, competition and selection, often perturbed by random events such as statistical fluctuations in population size. However, with viruses the consequences of the operation of these very same Darwinian principles are felt within very short times. Short-term evolution (within hours and days) can be also observed with some cellular pathogens, with subsets of normal cells, and cancer cells. The nature of RNA viral pathogens begs for alternative antiviral strategies, and forcing the virus to cross the critical error threshold for maintenance of genetic information is one of them.

The contributions to this volume have been chosen to reflect different lines of evidence (both theoretical and experimental) on which antiviral designs based on genetic deterioration inflicted upon viruses are being constructed. Theoretical studies have explored the copying fidelity conditions that must be fulfilled by any information-bearing replication system for the essential genetic information to be transmitted to progeny. Closely related to the theoretical developments have been numerous experimental studies on quasispecies dynamics and their multiple biological manifestations. The latter can be summarized by saying that RNA viruses, by virtue of existing as mutant spectra rather than defined genetic entities, remarkably expand their potential to overcome selective pressures intended to limit their replication. Indeed, the use of antiviral inhibitors in clinical practice and the design of vaccines for a number of major RNA virus-associated diseases, are currently presided by a sense of uncertainty. Another line of growing research is the enzymology of copying fidelity by viral replicases, aimed at understanding the molecular basis of mutagenic activities. Error catastrophe as a potential new antiviral strategy received an important impulse by the observation that ribavirin (a licensed antiviral nucleoside analogue) may be exerting, in some systems, its antiviral activity through enhanced mutagenesis. This has encouraged investigations on new mutagenic base analogues, some of them used in anticancer chemotherapy. Some chapters summarize these important biochemical studies on cell entry pathways and metabolism of mutagenic agents, that may find new applications as antiviral agents.

This volume intends to be basically a progress report, an introduction to a new avenue of research, and a realistic appraisal of the many issues that remain to be investigated. In this respect, I can envisage (not without many uncertainties) at least three lines of needed research: (i) One on further understanding of quasispecies dynamics in infected individuals to learn more on how to apply combinations of virus-specific mutagens and inhibitors in an effective way, finding synergistic combinations and avoiding antagonistic ones as well as severe clinical side effects. (ii) Another on a deeper understanding of the metabolism of mutagenic agents, in particular base and nucleoside analogues. This includes identification of the transporters that carry them into cells, an understanding of their metabolic processing, intracellular stability and alterations of nucleotide pools, among other issues. (iii) Still another line of needed research is the development of new mutagenic agents specific for viruses, showing no (or limited) toxicity for cells. Some advances may come from links with anticancer research, but others should result from the designs of new molecules, based on the structures of viral polymerases. I really hope that the reader finds this issue not only to be an interesting and useful review of the current situation in the field, but also a stimulating exposure to the major problems to be faced.

The idea to prepare this special issue came as a kind invitation of Ulrich Desselberger, former Editor of *Virus Research*, and then taken enthusiastically by Luis Enjuanes, recently appointed as Editor of *Virus Research*. I take this opportunity to thank Ulrich, Luis and the Editor-in-Chief of *Virus Research*, Brian Mahy, for their continued interest and support to the research on virus evolution over the years.

My thanks go also to the 19 authors who despite their busy schedules have taken time to prepare excellent manuscripts, to Elsevier staff for their prompt responses to my requests, and, last but not least, to Ms. Lucía Horrillo from Centro de Biología Molecular "Severo Ochoa" for her patient dealing with the correspondence with authors and the final organization of the issue.

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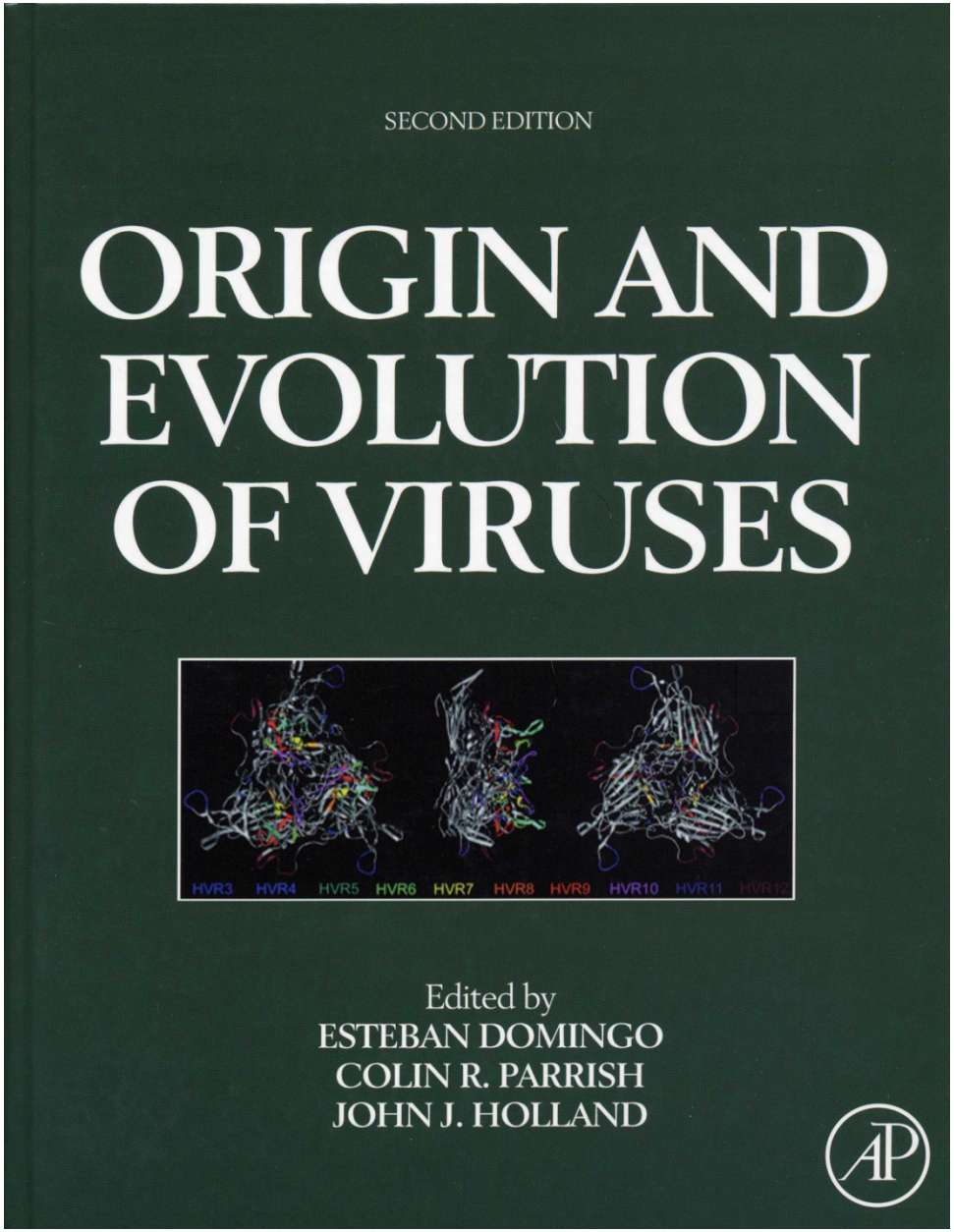
Available online 8 December 2004

doi:10.1016/j.virusres.2004.11.001

Esteban Domingo
1943 -

Application of quasispecies theory to the fight against viruses

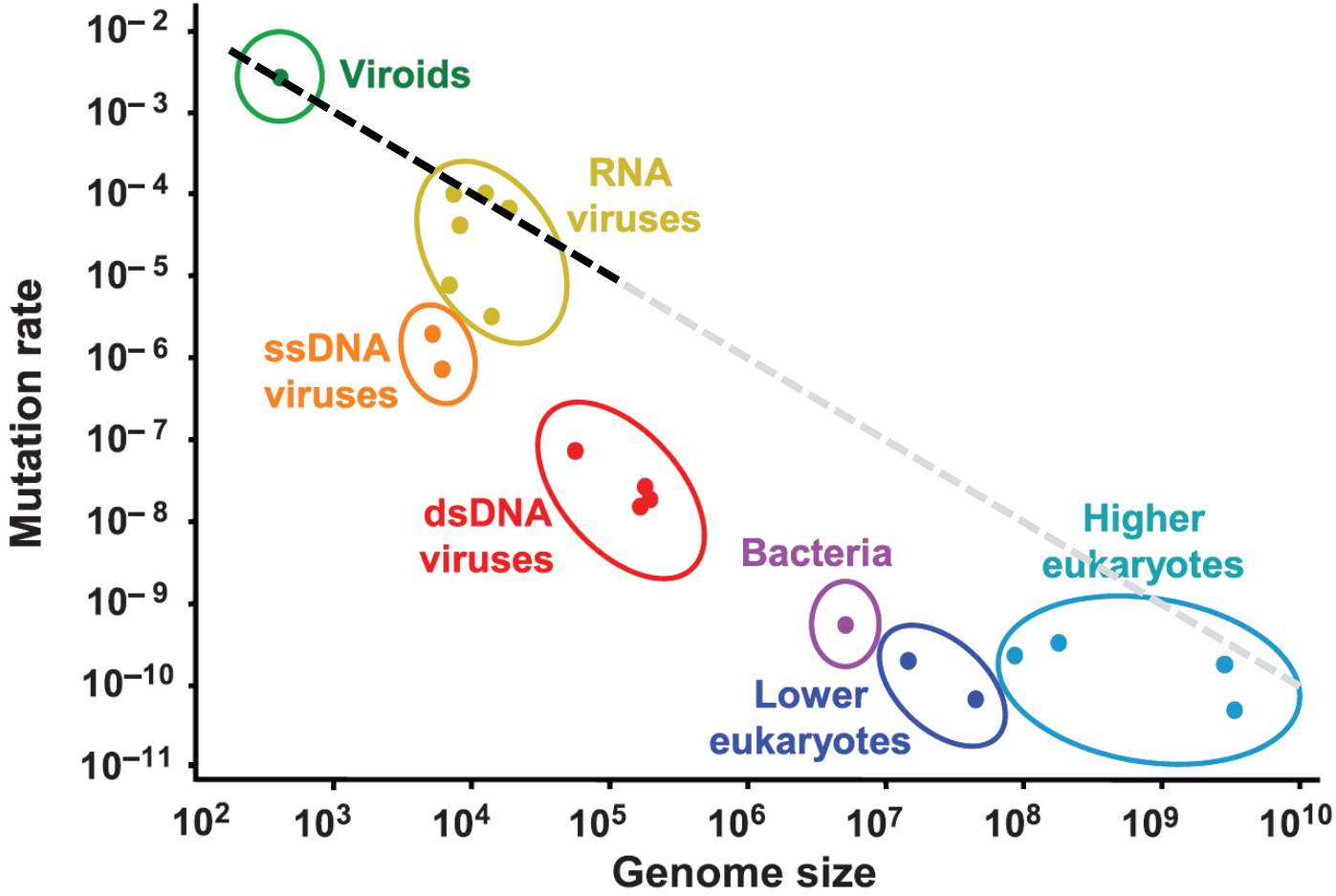
Molecular evolution of viruses



Evolution zu höherer Komplexität

Replizierende Moleküle		⇒	Moleküle in Kompartments
	Membranen, organisierte Teilung		
Unabhängige Replikatoren		⇒	Chromosomen
	Molekülverkettung, gemeinsame Replikation		
RNA als Gen und Enzyme		⇒	DNA und Protein
	Genetischer Code, Ribosom		
Prokaryoten		⇒	Eukaryoten
	Zusammenschluß durch Endosymbiose		
Asexuell vermehrende Klone		⇒	Sexuell vermehrende Populationen
	Ursprung der sexuellen Vermehrung		
Protisten		⇒	Pflanzen, Pilze und Tiere
	Zelldifferenzierung und Entwicklung		
Einzeln lebende Individuen		⇒	Tierkolonien
	Entstehung nicht-reproduktiver Kasten		
Primatengesellschaften		⇒	menschliche Gesellschaften
	Sprache, Schrift, Kultur, ...		

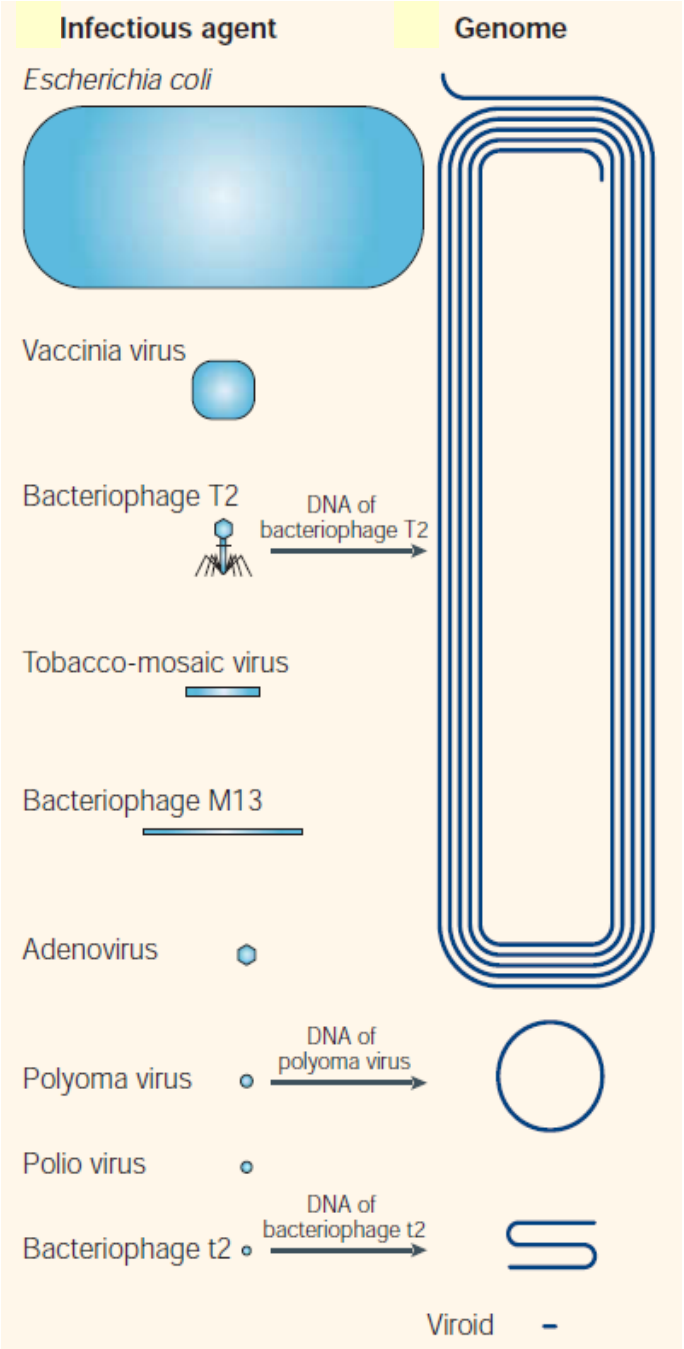
Viroide



Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. 2009, Extremely high mutation rate of a hammerhead viroid. Science 323:1308.

Mutation rate and genome size

Viroids: circular RNAs 246 - 401 nt long
infect inclusively plants

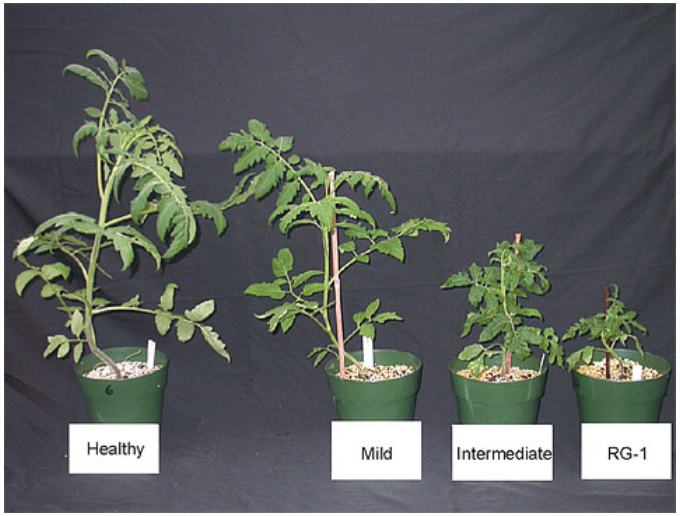


Theodor O. Diener. 2003. Discovering viroids –
A personal perspective.
Nat.Rev.Microbiology 1:75-80.

José-Antonio Daròs, Santiago F. Elena, Ricardo Flores.
2006. Viroids: An Ariadne‘s thread thorugh the
RNA labyrinth. EMBO Reports 7:593-598.

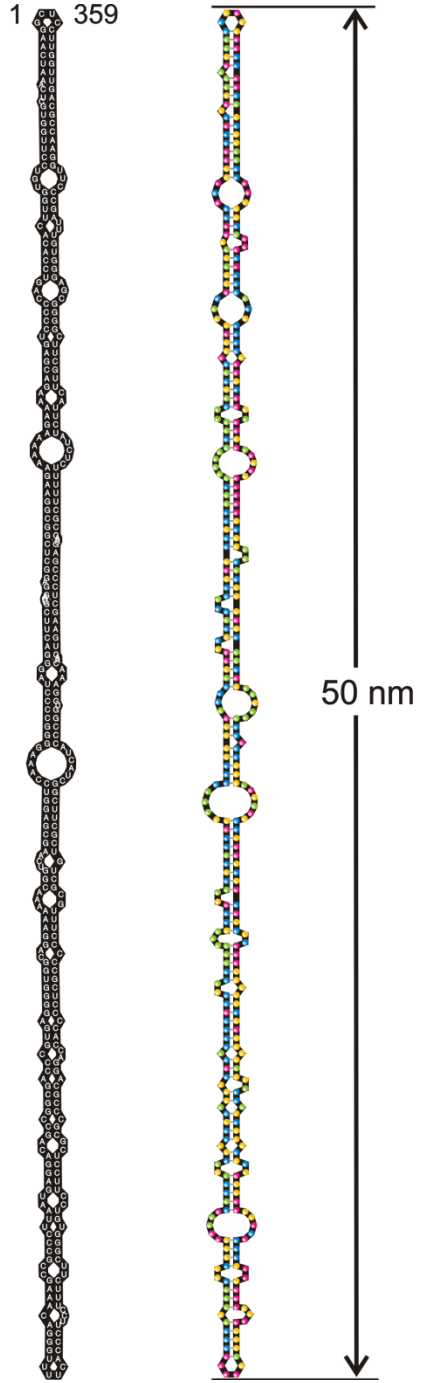
Ricardo Flores *et al*. 2009. Viroid replication: Rolling
circles, enzymes and ribozymes.
Viruses 2009:317-334.

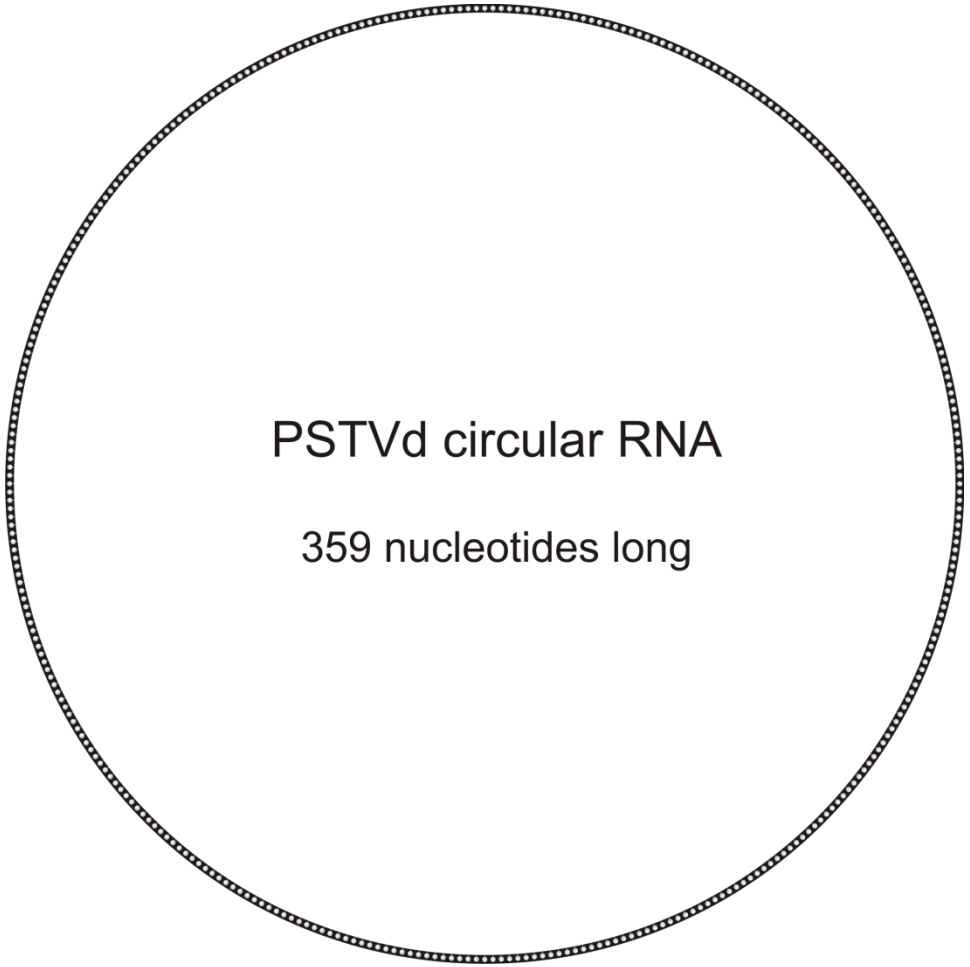
J. Demez. European and mediterranean plant protection organization archive. France



R.W. Hammond, R.A. Owens. Molecular Plant Pathology Laboratory, US Department of Agriculture

Plant damage by viroids





Adenine

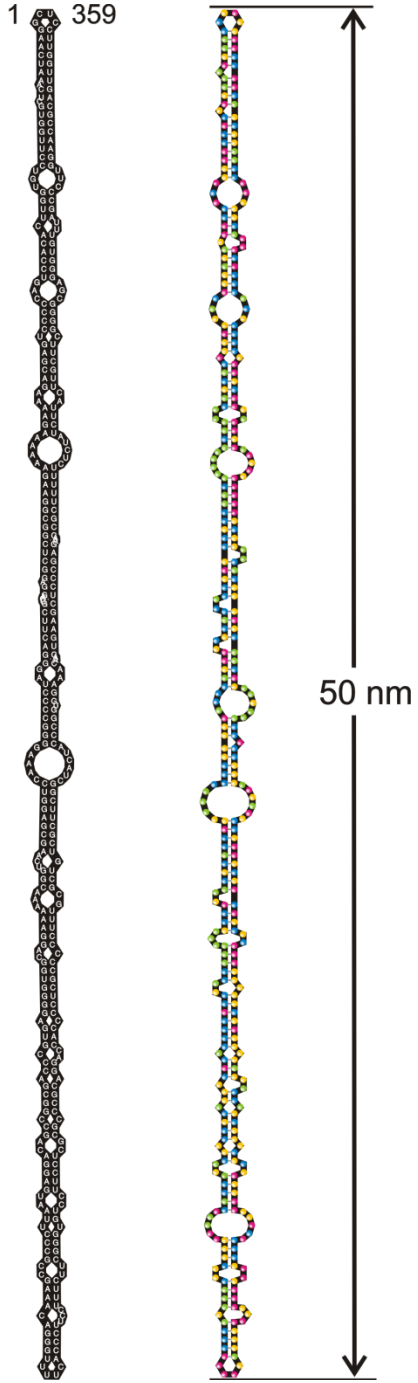
Uracil

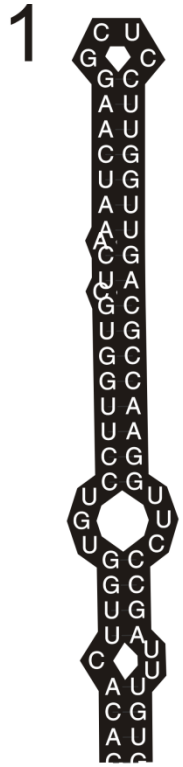
Guanine

Cytosine

Nucleotide sequence and secondary structure of the potato spindle tuber viroid RNA

H.J.Gross, H. Domdey, C. Lossow, P Jank, M. Raba, H. Alberty, and H.L. Sänger. *Nature* **273**:203-208 (1978)





Vienna RNA Package 1.8.2

Biochemically supported structure

Adenine

Uracil

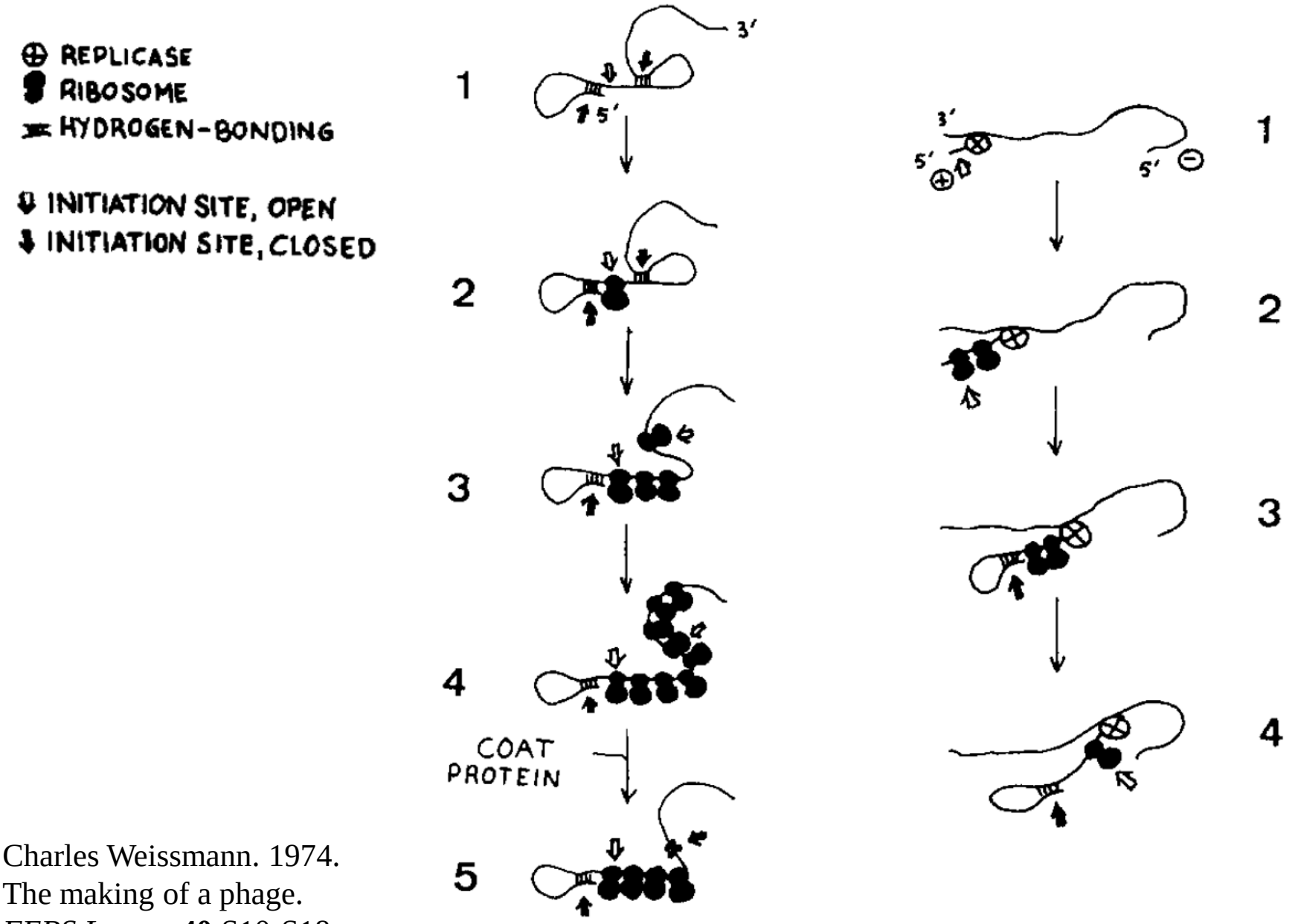
Guanine

Cytosine

Nucleotide sequence and secondary structure of the potato spindle tuber viroid RNA

H.J.Gross, H. Domdey, C. Lossow, P Jank, M. Raba, H. Alberty, and H.L. Sänger. *Nature* **273**:203-208 (1978)

Virusspezies



Charles Weissmann. 1974.
The making of a phage.
FEBS Letters **40**:S10-S18.

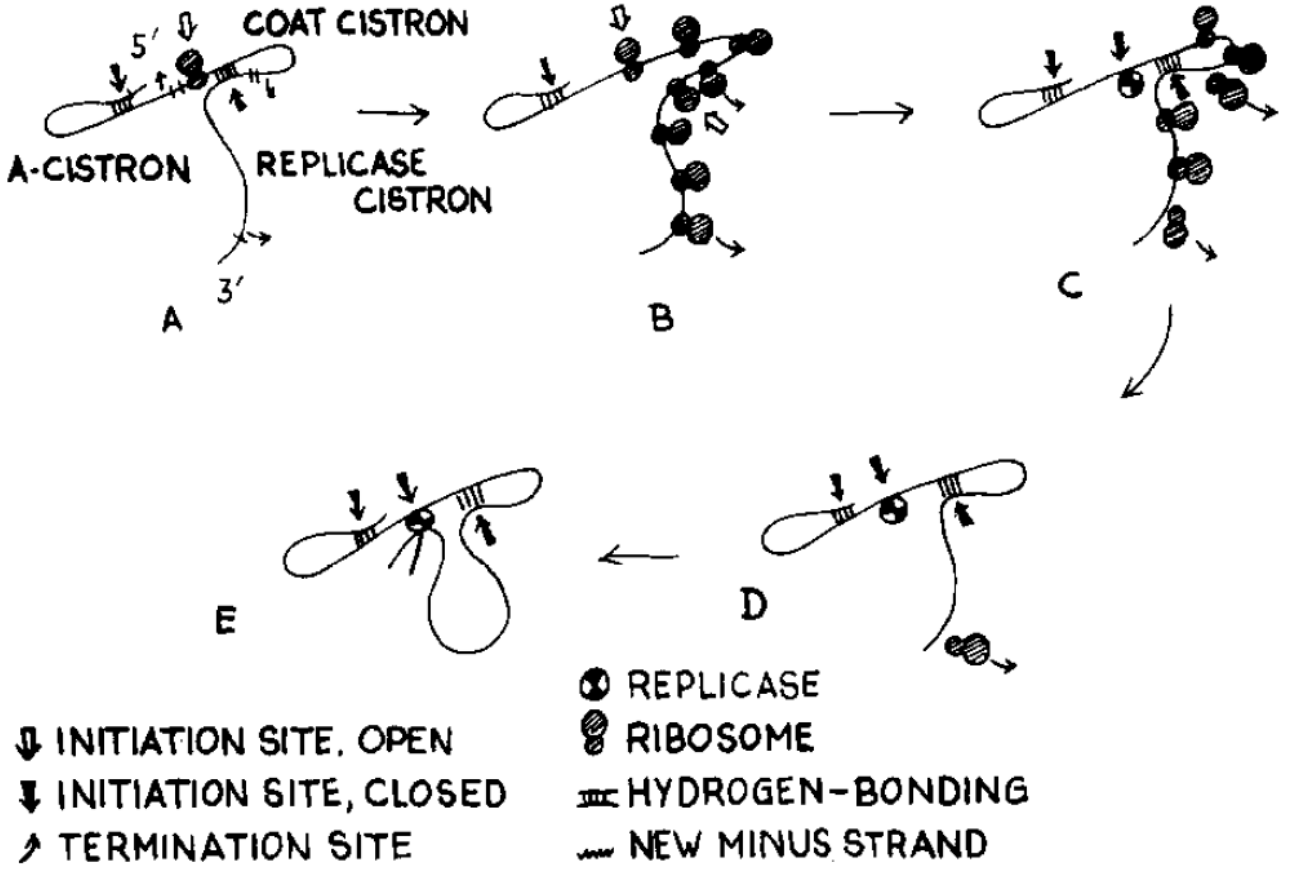
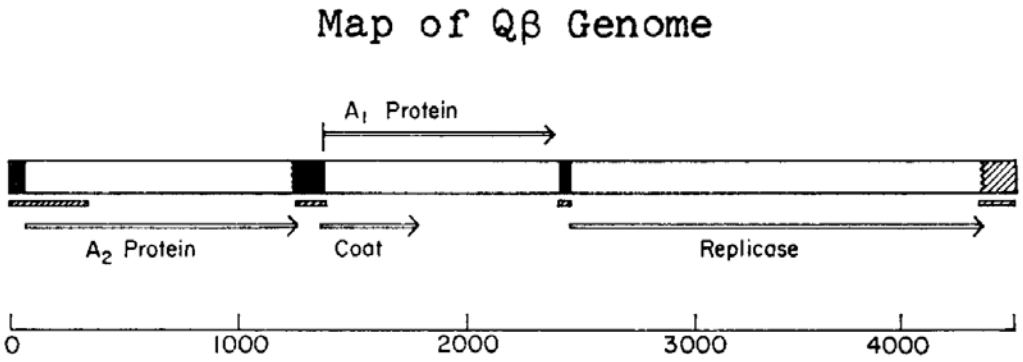
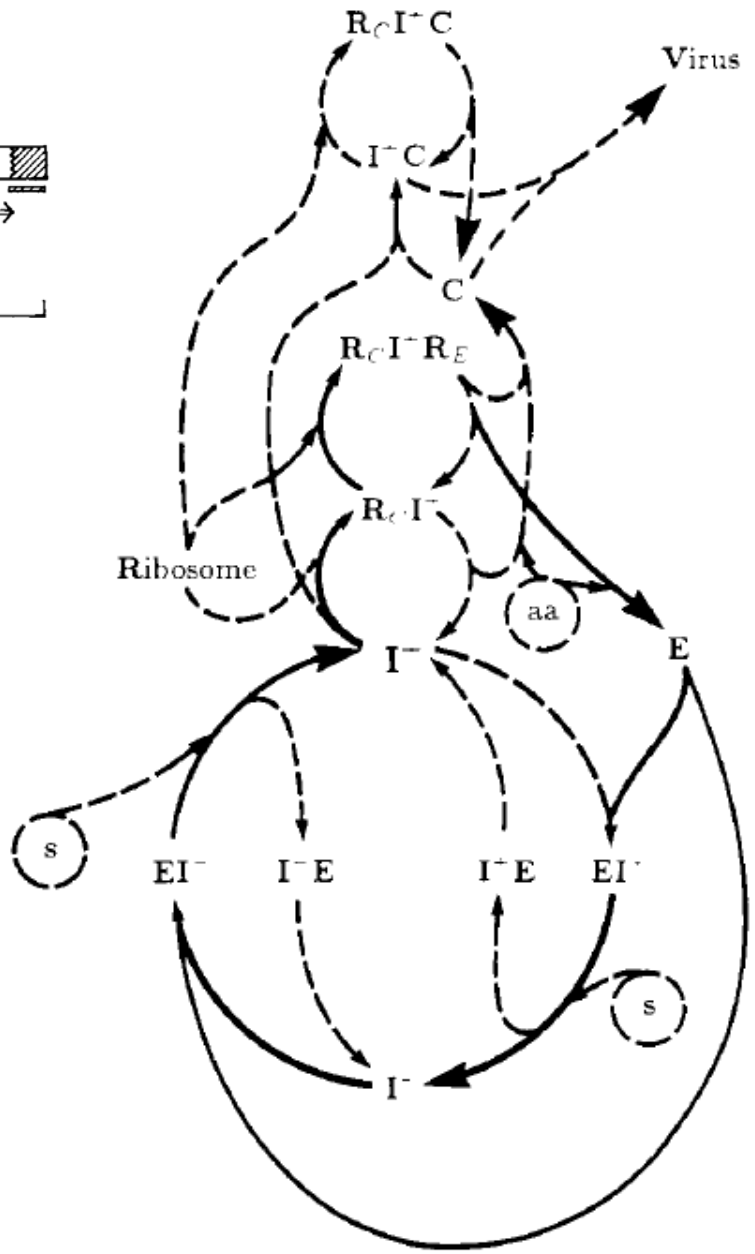


Fig. 3. Transition of phage RNA from polysome to replicating complex – repressor function of Qβ viral replicase.
(A) Ribosomes attach to the RNA at the coat initiation site. The initiation site of the replicase cistron is unavailable because of the secondary structure of the RNA. (B) Translation of the coat cistron ensues and the initiation site of the replicase cistron is exposed. The replicase cistron is translated. (C) When replicase becomes available, it attaches to the initiation site of the coat protein and blocks attachment of ribosomes in this position. The RNA refolds, preventing initiation at the replicase cistron. (D) The RNA is cleared of ribosomes. (E) Replicase can now attach to the 3′ terminus and initiate synthesis of the minus strand. The A cistron initiation site is at all times unaccessible to ribosomes because of the secondary structure of the mature RNA (cf. fig. 2) (from ref. [64]).

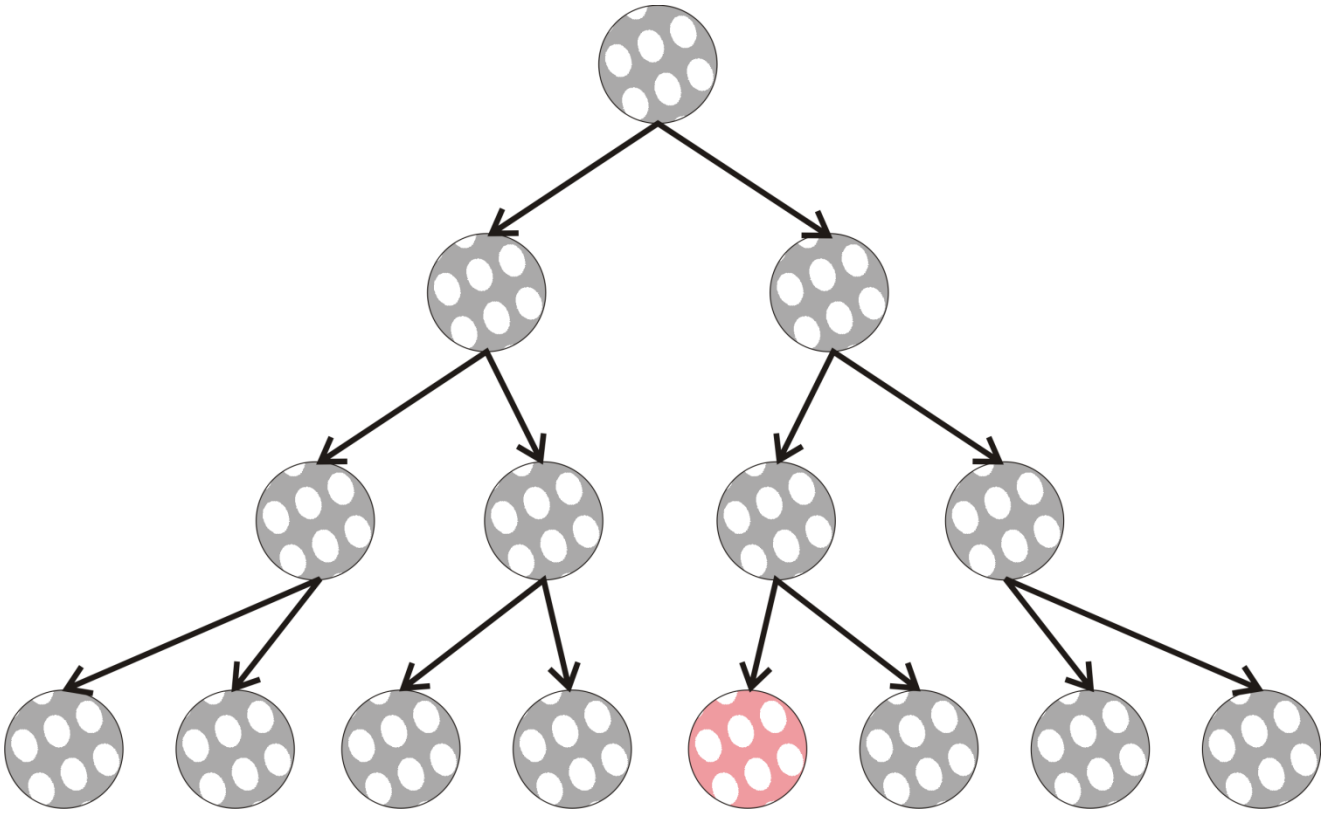




M. Eigen, C.K. Biebricher, M. Gebinoga, W.C. Gardiner. 1991. The hypercycle. Coupling of RNA and protein biosynthesis in the infection of an RNA bacteriophage. *Biochemistry* **30**:11005-11018.

Qβ phage infection of *Escherichia coli* cells.

Bakterien



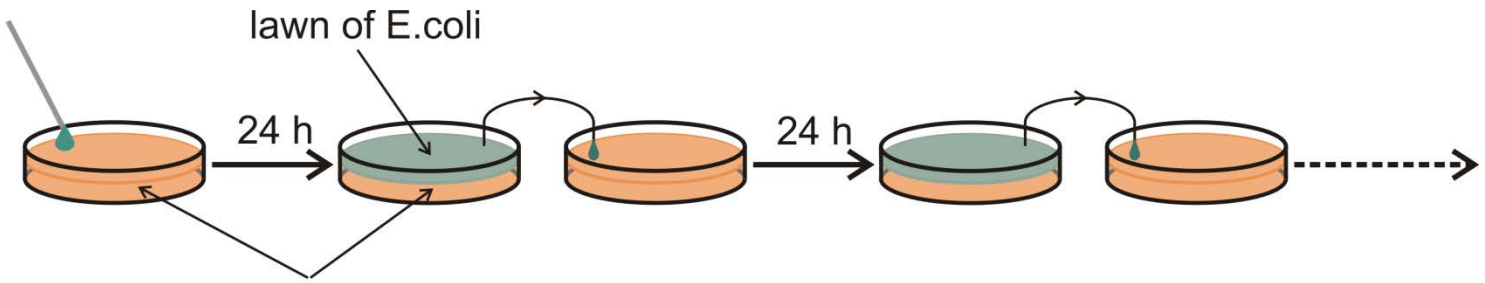
Complex replication dynamics, metabolism, and regulation efficiency are cast into fitness values

Bacterial evolution in cell-lines

Richard Lenski, 1956 -

Bacterial evolution under controlled conditions: A twenty years experiment.

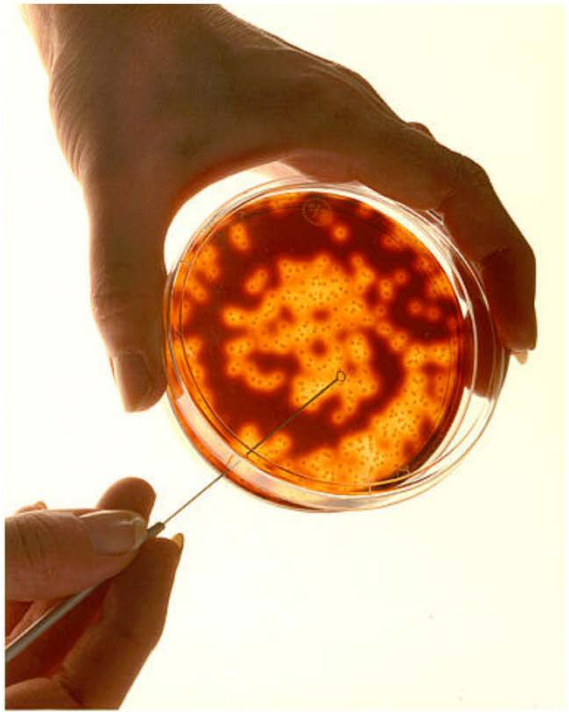
Richard Lenski, University of Michigan, East Lansing



medium supports $\approx 5 \times 10^8$ bacteria

1 day	≈	6.67 generations
1 month	≈	200 generations
1 year	≈	**2400 generations**

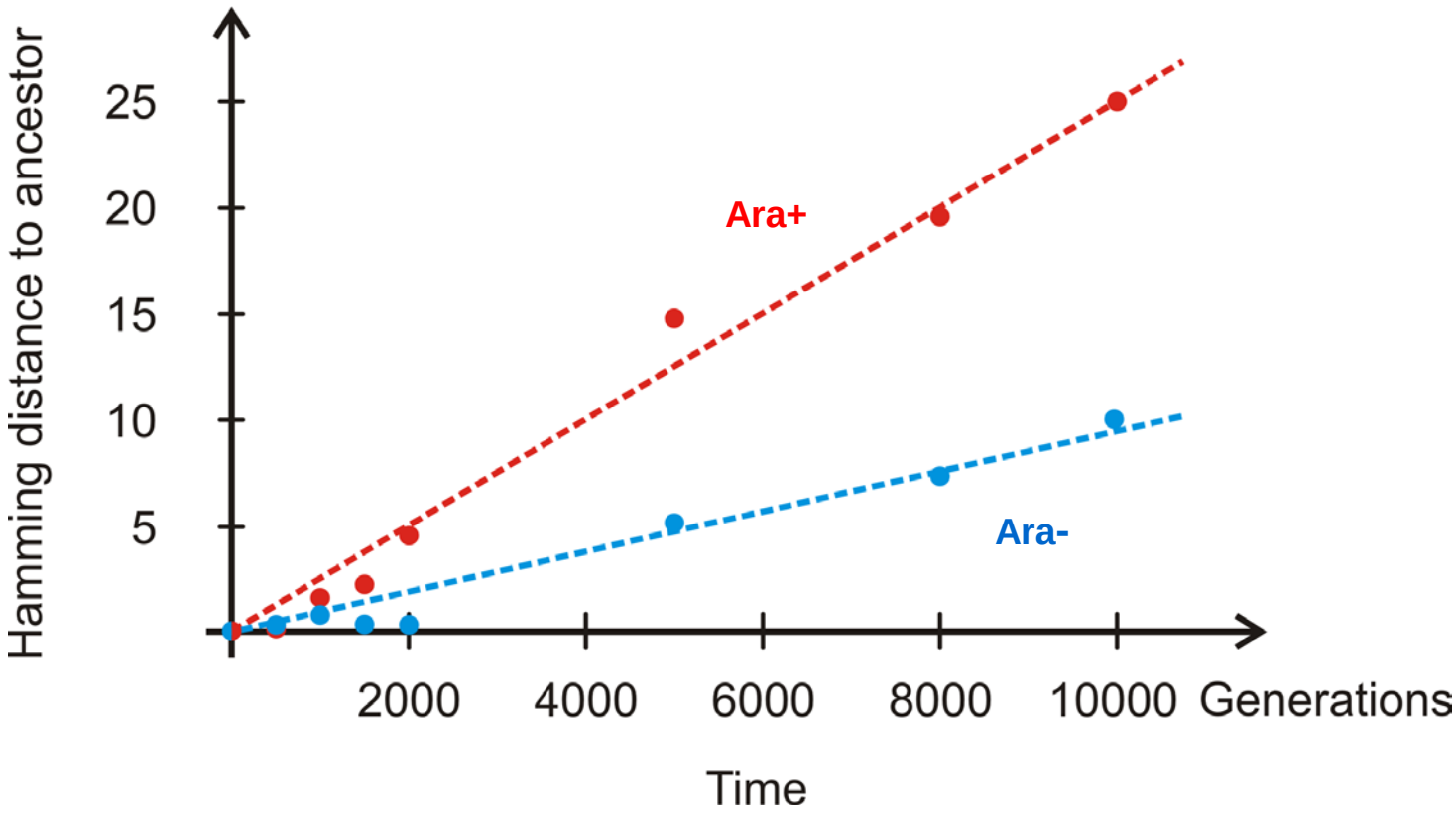
Serial transfer of bacterial cultures in Petri dishes



Bacterial evolution under controlled conditions: A twenty years experiment.

Richard Lenski, University of Michigan, East Lansing

The twelve populations of Richard Lenski‘s long time evolution experiment



Variation of genotypes in a bacterial serial transfer experiment

D. Papadopoulos, D. Schneider, J. Meier-Eiss, W. Arber, R. E. Lenski, M. Blot. *Genomic evolution during a 10,000-generation experiment with bacteria*. Proc.Natl.Acad.Sci.USA **96** (1999), 3807-3812

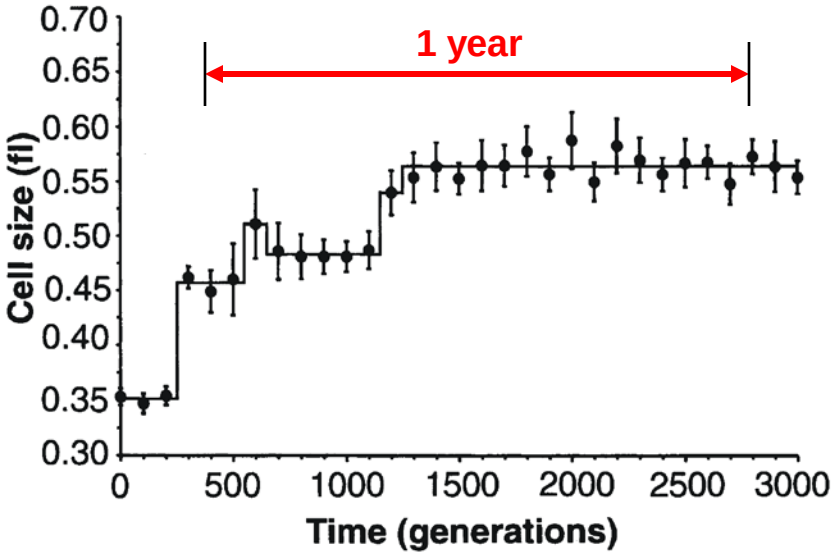
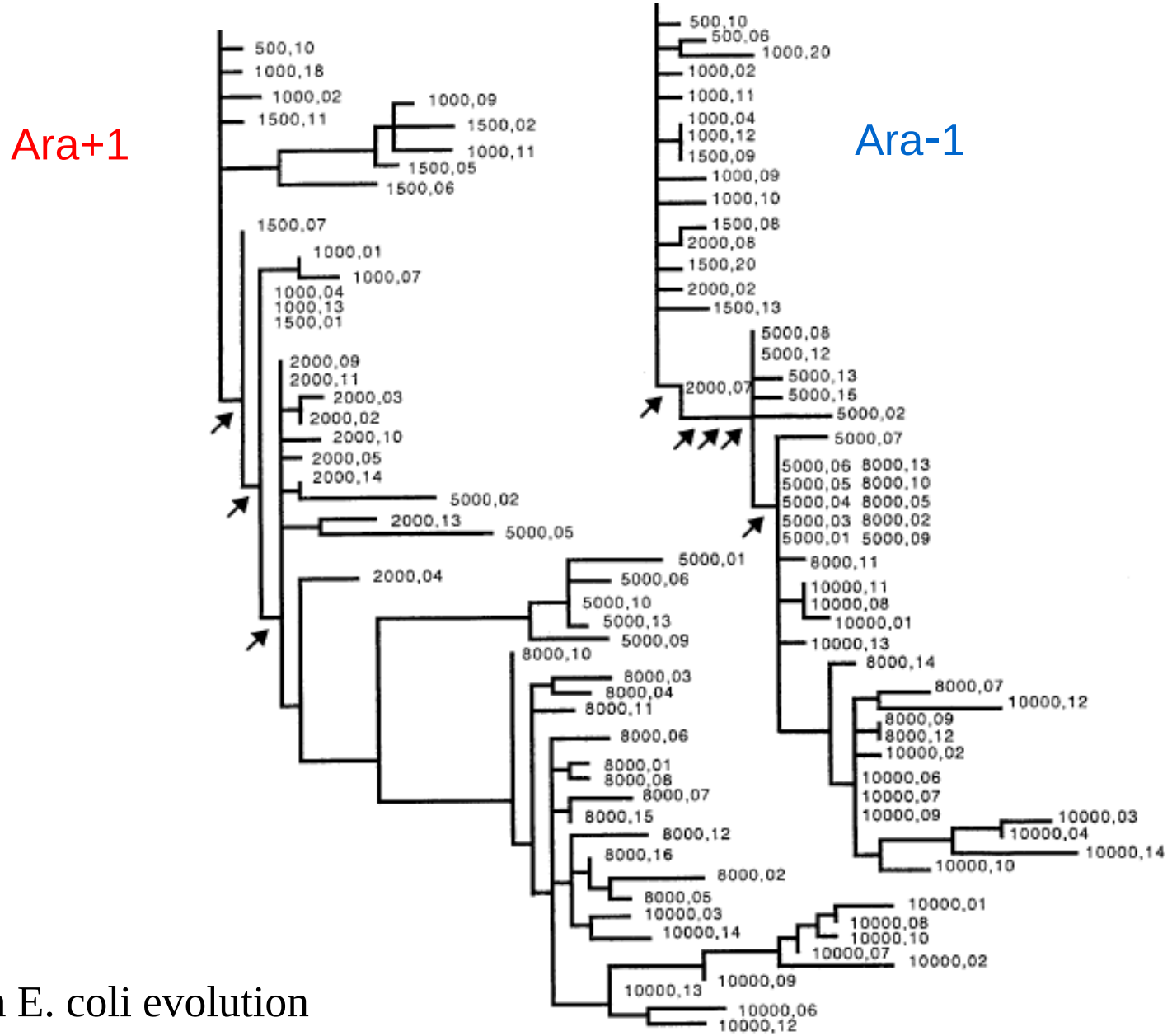


Fig. 1. Change in average cell size (1 fl = 10^{-15} L) in a population of *E. coli* during 3000 generations of experimental evolution. Each point is the mean of 10 replicate assays (*22*). Error bars indicate 95% confidence intervals. The solid line shows the best fit of a step-function model to these data (Table 1).

Epochal evolution of bacteria in serial transfer experiments under constant conditions

S. F. Elena, V. S. Cooper, R. E. Lenski. *Punctuated evolution caused by selection of rare beneficial mutants*. Science **272** (1996), 1802-1804



Phylogeny in E. coli evolution

The twelve populations of Richard Lenski‘s long time evolution experiment
Enhanced turbidity in population A-3

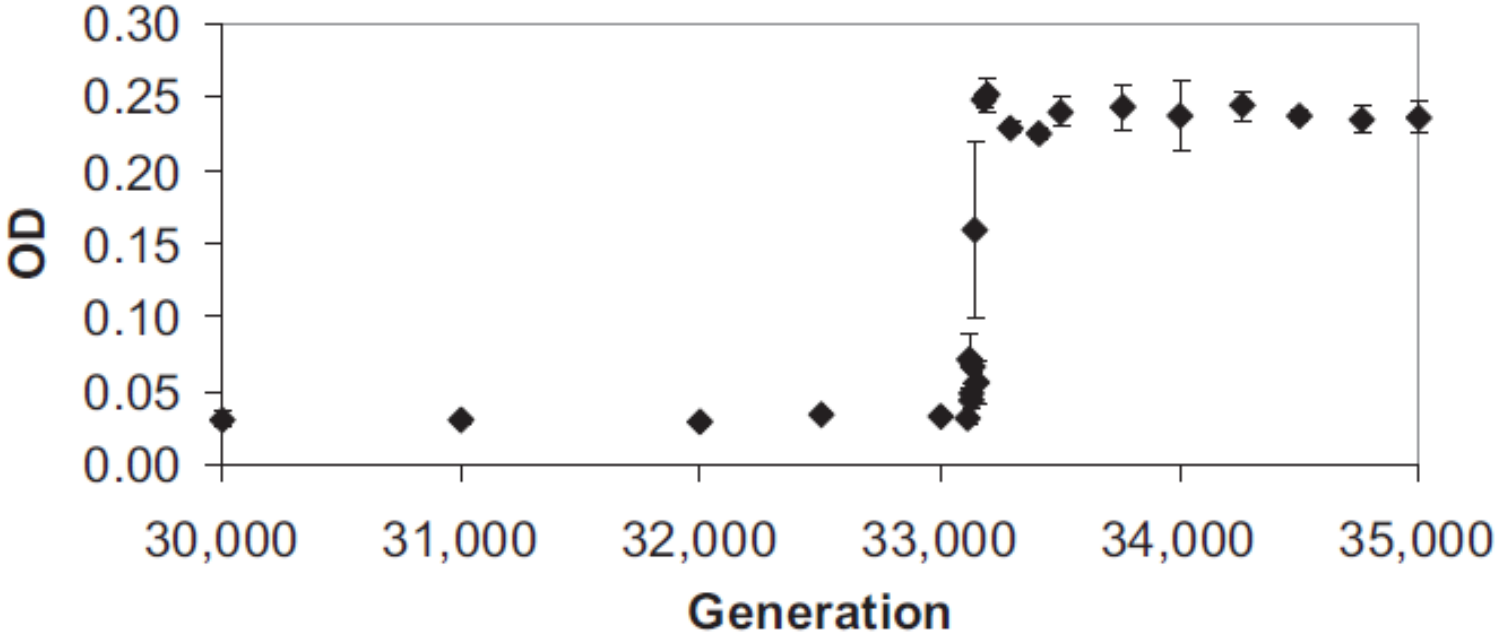


Fig. 1. Population expansion during evolution of the Cit$^+$ phenotype. Samples frozen at various times in the history of population Ara-3 were revived, and three DM25 cultures were established for each generation. Optical density (OD) at 420 nm was measured for each culture at 24 h. Error bars show the range of three values measured for each generation.

Innovation by mutation in long time evolution of Escherichia coli in constant environment

Z.D. Blount, C.Z. Borland, R.E. Lenski. 2008. Proc.Natl.Acad.Sci.USA 105:7899-7906

Table 1. Summary of replay experiments

	First experiment		Second experiment		Third experiment	
Generation	Replicates	Independent Cit$^+$ mutants	Replicates	Independent Cit$^+$ mutants	Replicates	Independent Cit$^+$ mutants
Ancestor	6	0	10	0	200	0
5,000	—	—	—	—	200	0
10,000	6	0	30	0	200	0
15,000	—	—	—	—	200	0
20,000	6	0	30	0	200	2
25,000	6	0	30	0	200	0
27,000	—	—	—	—	200	2
27,500	6	0	30	0	—	—
28,000	—	—	—	—	200	0
29,000	6	0	30	0	200	0
30,000	6	0	30	0	200	0
30,500	6	1	30	0	—	—
31,000	6	0	30	0	200	1
31,500	6	1	30	0	200	1
32,000	6	0	30	4	200	2
32,500	6	2	30	1	200	0
Totals	72	4	340	5	2,800	8

Contingency of E. coli evolution experiments

Epilog

Evolution im Licht der gegenwärtigen Molekulargenetik

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

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

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

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

Mycoplasma pneumoniae:	Genomelänge	820 000 bp
	# Gene:	733
	# Proteine (ORF):	689
	# tRNAs	37
	# rRNAs	3
	# andere RNAs	4

S. Kühner, V. van Noort, M. J. Betts, A. Leo-Macias, C. Batisse, M. Rode, T. Yamada, T. Maier, S. Bader, P. Beltran-Alvarez, D. Castaño-Diez, W.-H. Chen, D. Devos, M. Güell, T. Norambuena, I. Racke, V. Rybin, A. Schmidt, E. Yus, R. Aebersold, R. Herrmann, B. Böttcher, A. S. Frangakis, R. B. Russell, L. Serrano, P. Bork, and A.-C. Gavin. 2009.
Proteome organization in a genome-reduced bacterium. Science **326**:1235–1240.

E. Yus, T. Maier, K. Michalodimitrakis, V. van Noort, T. Yamada, W.-H. Chen, J. A. Wodke, M. Güell, S. Martínez, R. Bourgeois, S. Kühner, E. Raineri, I. Letunic, O. V. Kalinina, M. Rode, R. Herrmann, R. Gutiérez-Gallego, R. B. Russell, A.-C. Gavin, P. Bork, and L. Serrano. 2009.
Impact of genome reduction on bacterial metabolism and its regulation. Science **326**:1263–1268.

M. Güell, V. van Noort, E. Yus, W.-H. Chen, J. Leigh-Bell, K. Michalodimitrakis, T. Yamada, M. Arumugam, T. Doerks, S. Kühner, M. Rode, M. Suyama, S. Schmidt, A.-C. Gavin, P. Bork, and L. Serrano. 2009.
Transcriptome complexity in a genome-reduced bacterium. Science **326**:1268–1271.

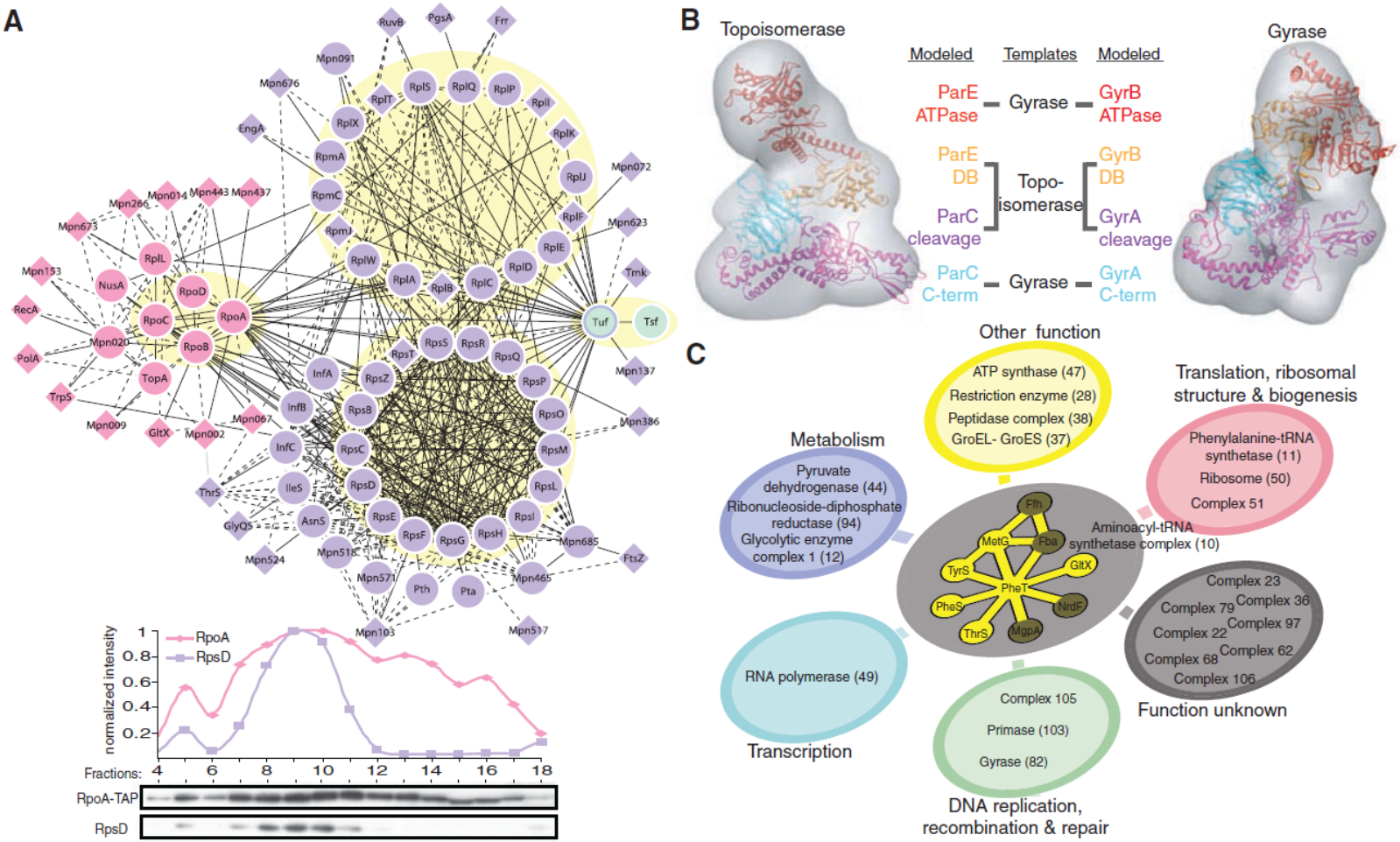


Fig. 3. Higher level of proteome organization. (**A**) The RNA polymerase–ribosome assembly. Core components are represented by circles, attachments by diamonds. The line attribute corresponds to socio-affinity indices: dashed lines, 0.5 to 0.86; plain lines, >0.86. Color code and shaded yellow circles around groups of proteins refer to individual complexes: RNA polymerase (pink), ribosome (purple), and translation elongation factor (green). The bottom graph shows that the ribosomal protein RpsD (23 kD) and the α subunit of the RNA polymerase, RpoA-TAP (57 kD), co-elute in high molecular weight fractions (MD range) during gel filtration chromatography. (**B**) DNA topoisomerase (diameter ~ 12 nm) is a heterodimer in bacteria: ParE (ATPase and DNA binding domains) and ParC (cleavage and C-terminal domains). The interaction between ParE-DNA–binding and ParC–cleavage domains was modeled by using yeast topoisomerase II as a template [Protein Data Bank (PDB) code 2rgr], and ParE-ATPase and ParC–C-terminal domains were modeled separately on structures of gyrase homologs (PDB 1kij and 1suu). All four domains were fitted into the electron microscopy density. Gyrase (~12 nm) is similarly split in bacteria into GyrA/GyrB, which are paralogs of ParE/ParC, and was modeled and fitted by using PDB 1bjt as a template for the GyrB-DNA–binding and GyrA-cleavage domains interaction. (**C**) Protein multifunctionality in *M. pneumoniae* illustrated with the AARS complexes.

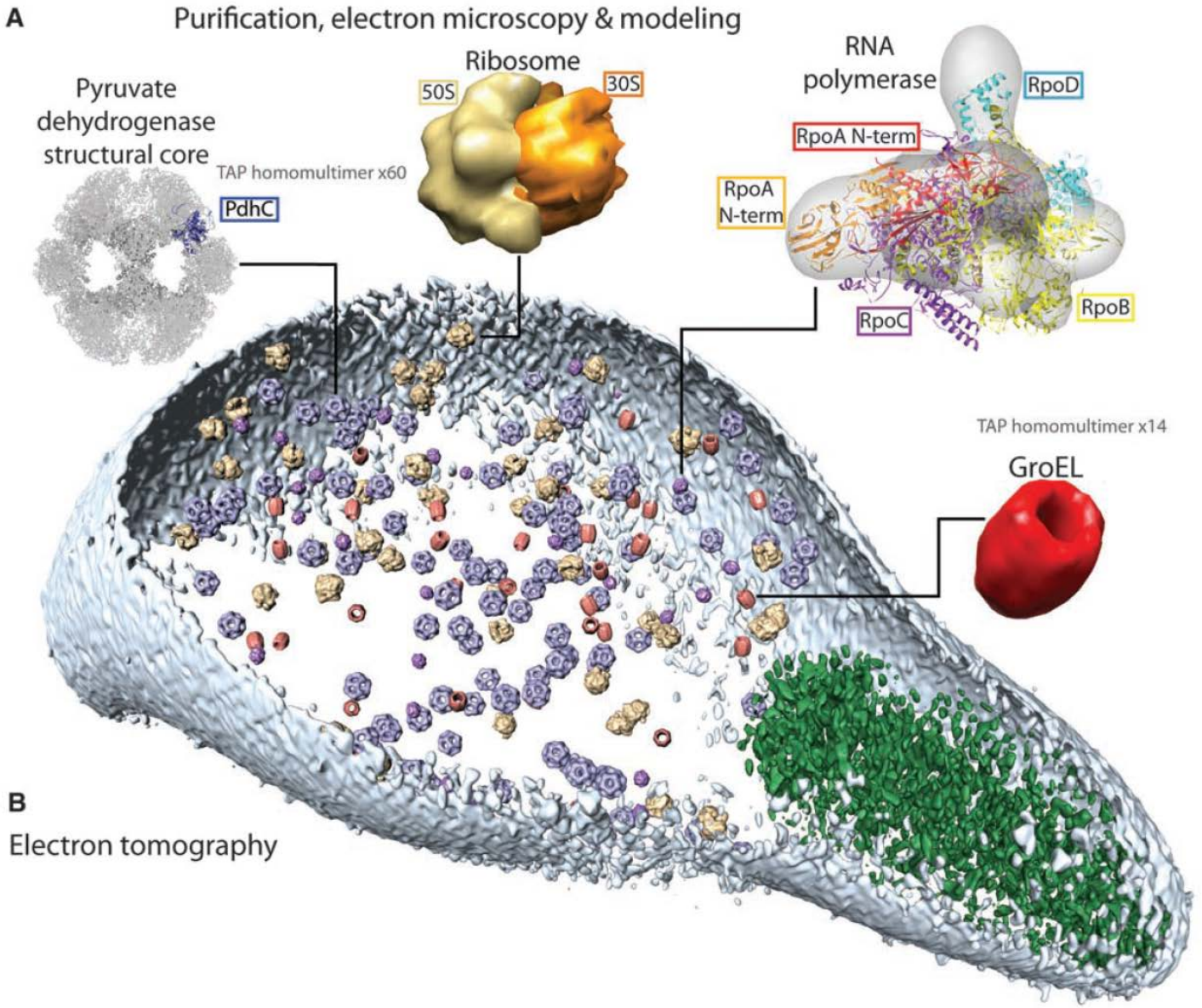
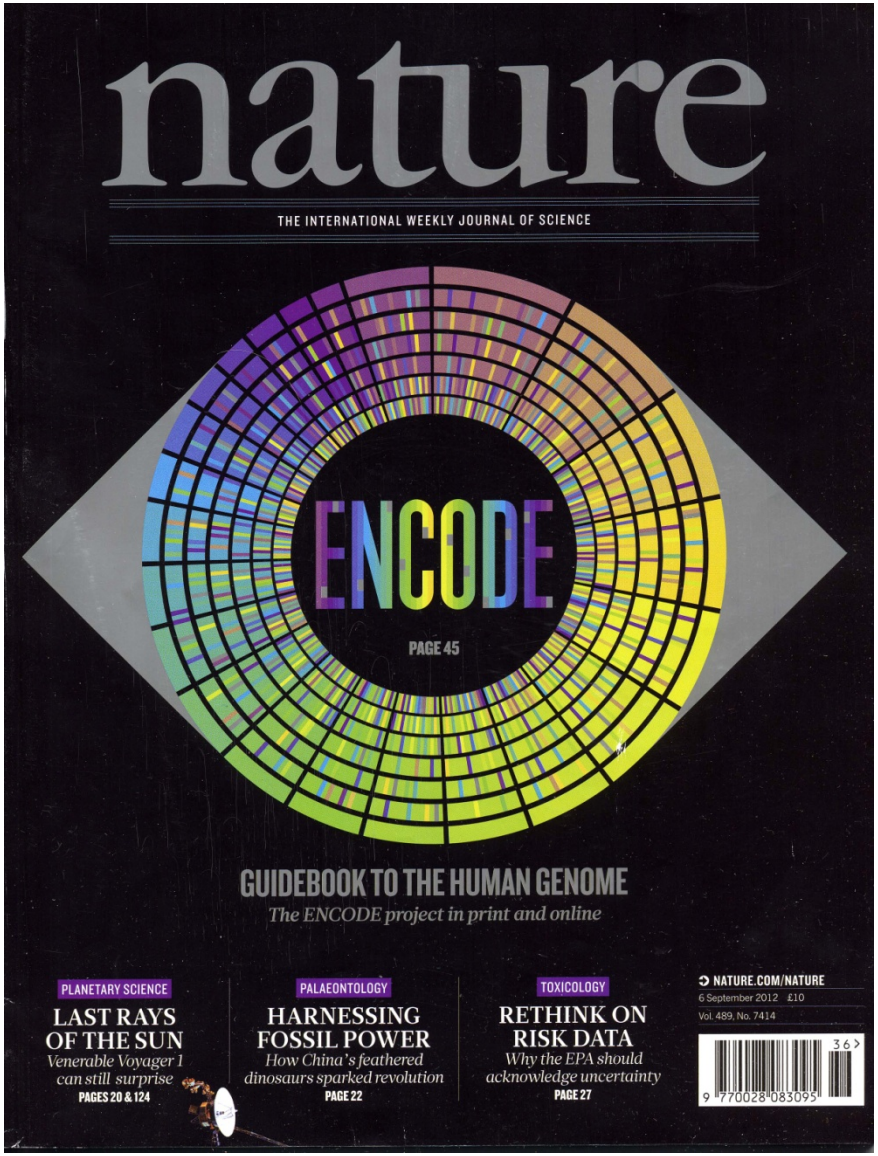


Fig. 4. From proteomics to the cell. By a combination of pattern recognition and classification algorithms, the following TAP-identified complexes from *M. pneumoniae*, matching to existing electron microscopy and x-ray and tomogram structures (**A**), were placed in a whole-cell tomogram (**B**): the structural core of pyruvate dehydrogenase in blue (~23 nm), the ribosome in yellow (~26 nm), RNA polymerase in purple (~17 nm), and GroEL homomultimer in red (~20 nm). Cell dimensions are ~300 nm by 700 nm. The cell membrane is shown in light blue. The rod, a prominent structure filling the space of the tip region, is depicted in green. Its major structural elements are HMW2 (Mpn310) in the core and HMW3 (Mpn452) in the periphery, stabilizing the rod (*42*).The individual complexes (A) are not to scale, but they are shown to scale within the bacterial cell (B).



2007 2012

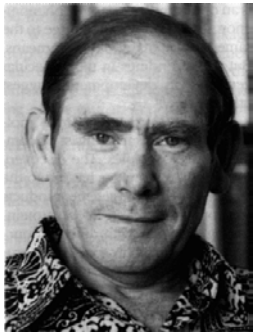
ENCyclopedia **O**f **D**NA **E**lements

Vorteile der molekularen Erforschung des Lebens

1. Komplexe Reproduktionsmechanismen sind erklärbar.

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

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



Sydney Brenner, 1927 -

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

Danke für die Aufmerksamkeit!

Web-Page für weitere Informationen:

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

Diskussion und Übungen

Kriterien des Lebens

(i) **Vermehrung** und **Vererbung**

(ii) **Mutation** infolge fehlerhafter Reproduktion und Rekombination

(iii) **Stoffwechsel** zur Erzeugung der molekularen Bausteine des Lebens

(iv) **Individualisierung** durch Einschließen in Kompartimente

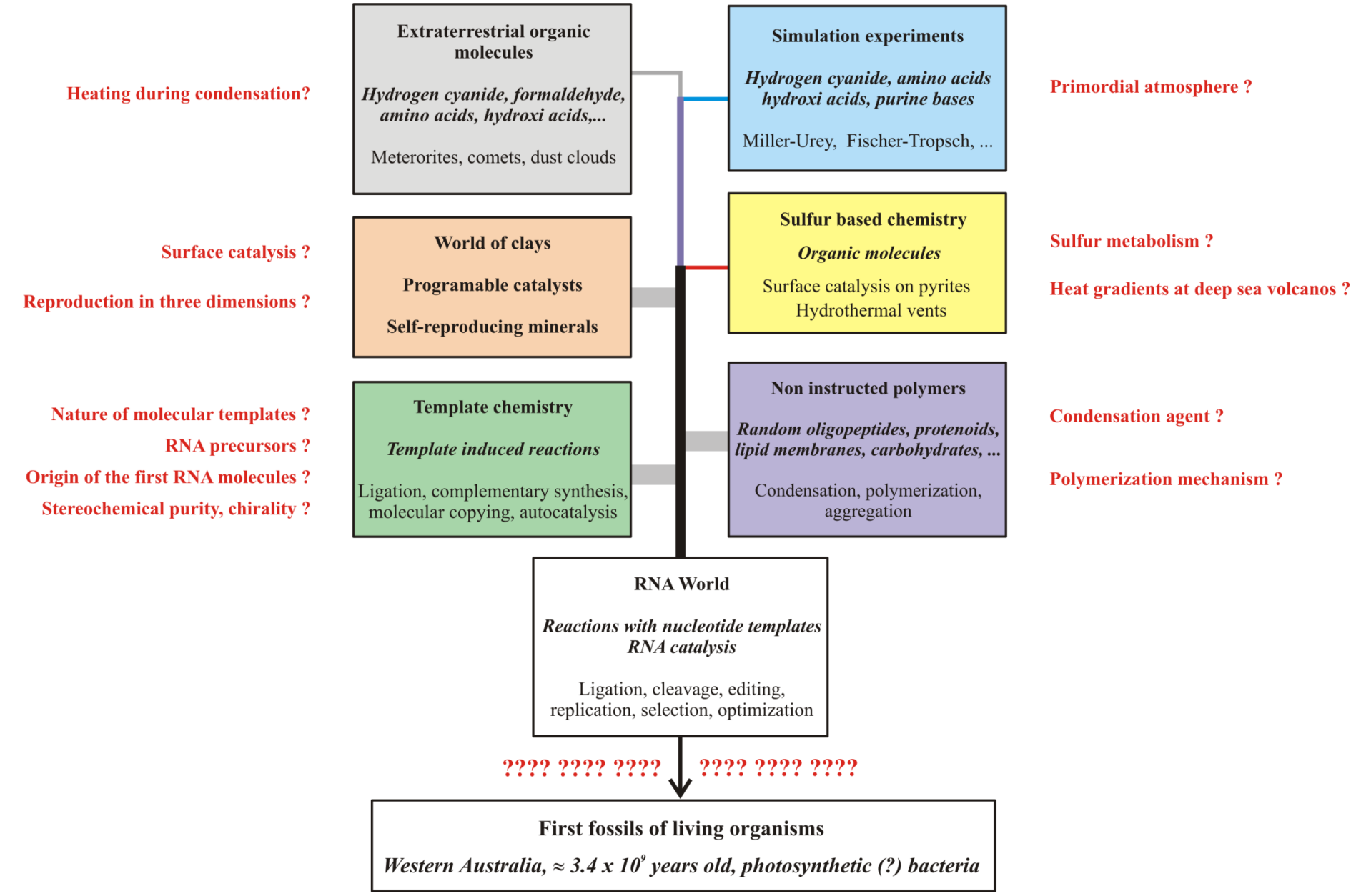
(v) **Autopoiese** und **Homöostase**

(vi) Organisierte Zellteilung – **Mitose**

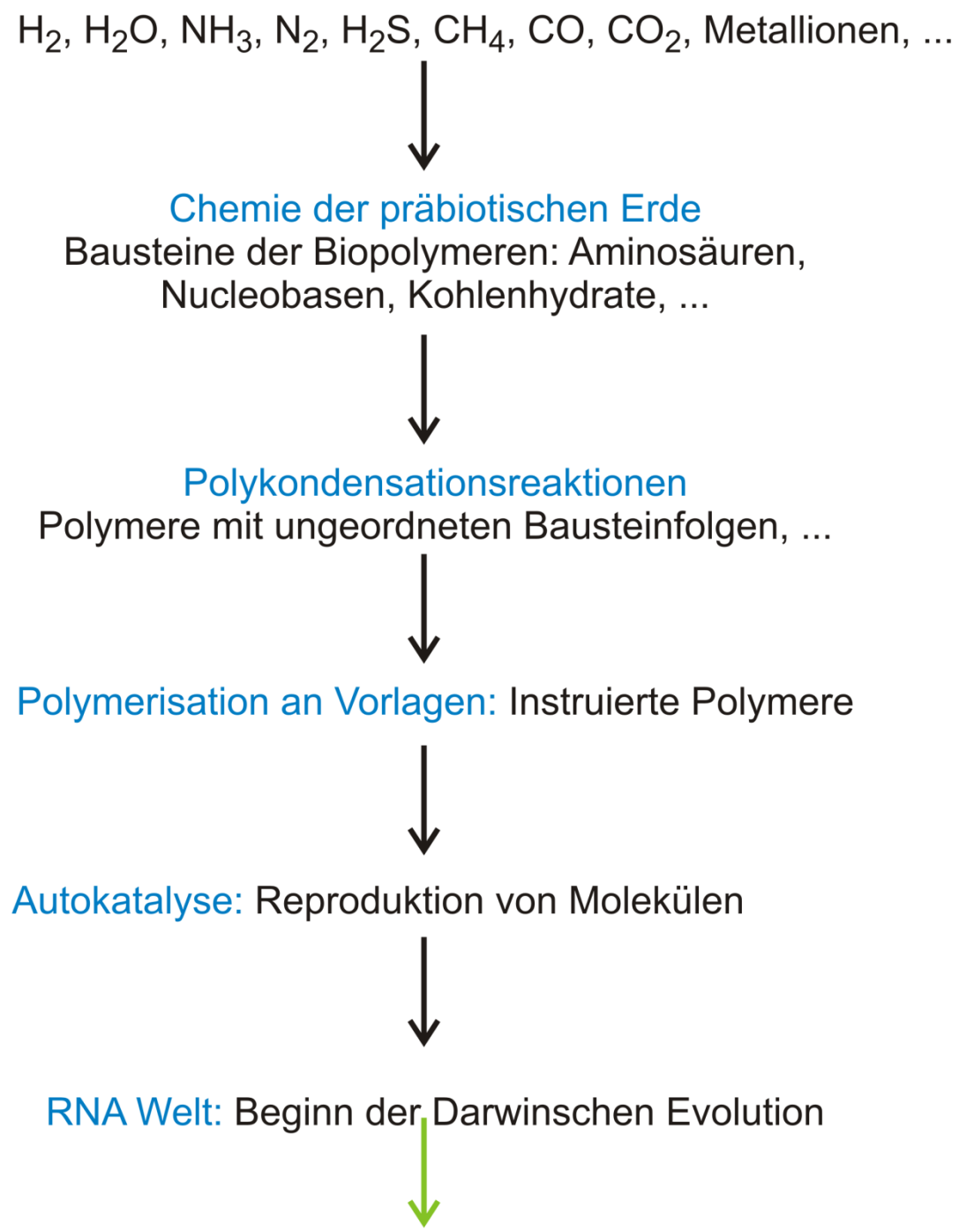
(vii) Sexuelle Reproduktion und Reduktions-Zellteilung – **Meiose**

(viii) **Zelldifferenzierung** in Zellen der Keimbahn und somatische Zellen

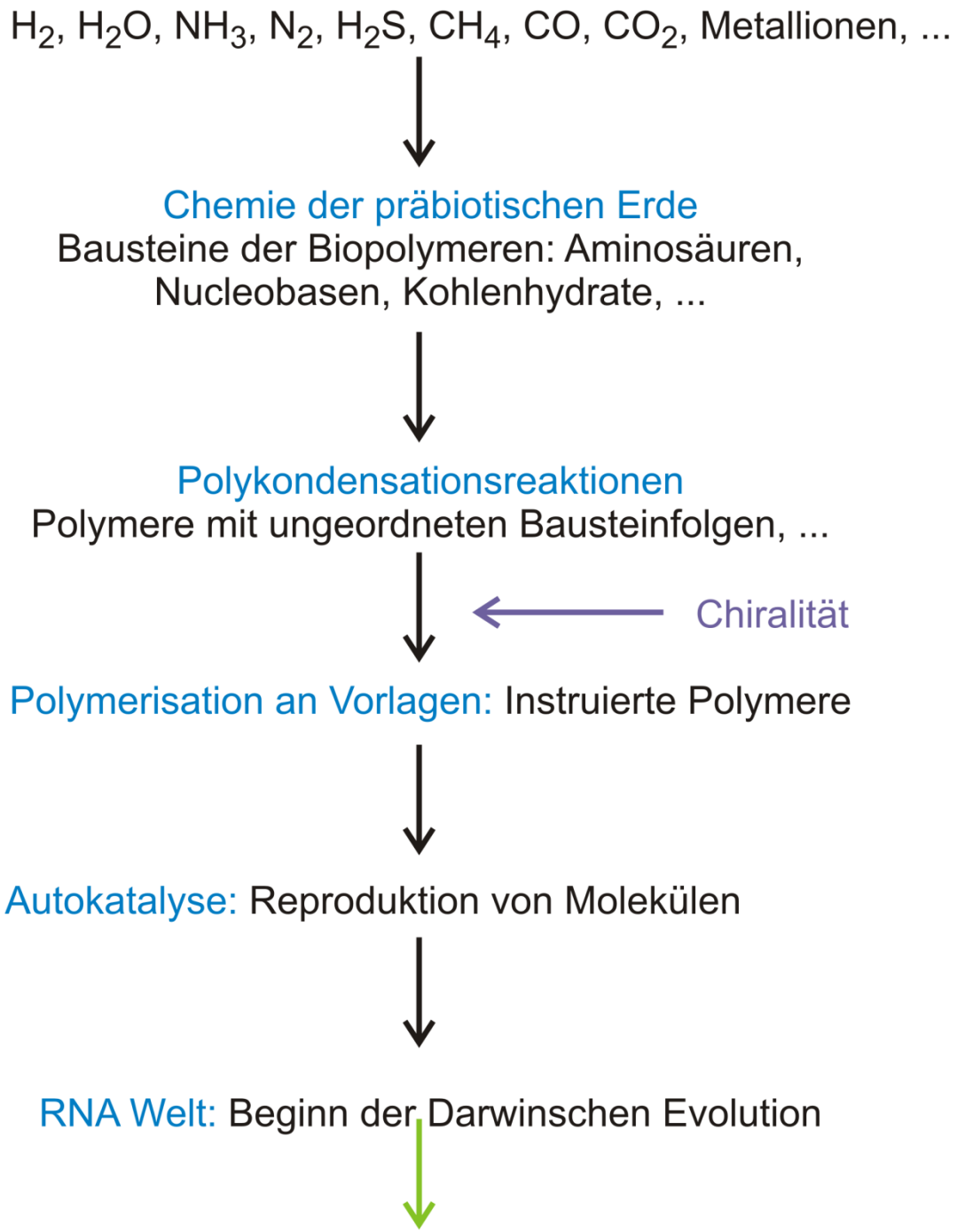
Chemische Evolution


Extraterrestrial organic molecules
Hydrogen cyanide, formaldehyde, amino acids, hydroxi acids,...
Meterorites, comets, dust clouds
Heating during condensation?
Simulation experiments
Hydrogen cyanide, amino acids hydroxi acids, purine bases
Miller-Urey, Fischer-Tropsch, ...
Primordial atmosphere ?
World of clays
Programable catalysts
Self-reproducing minerals
Surface catalysis ?
Reproduction in three dimensions ?
Sulfur based chemistry
Organic molecules
Surface catalysis on pyrites
Hydrothermal vents
Sulfur metabolism ?
Heat gradients at deep sea volcanos ?
Template chemistry
Template induced reactions
Ligation, complementary synthesis, molecular copying, autocatalysis
Nature of molecular templates ?
RNA precursors ?
Origin of the first RNA molecules ?
Stereochemical purity, chirality ?
Non instructed polymers
Random oligopeptides, protenoids, lipid membranes, carbohydrates, ...
Condensation, polymerization, aggregation
Condensation agent ?
Polymerization mechanism ?
RNA World
Reactions with nucleotide templates
RNA catalysis
Ligation, cleavage, editing, replication, selection, optimization
???? ???? ????
???? ???? ????
First fossils of living organisms
Western Australia, ≈ 3.4 x 10⁹ years old, photosynthetic (?) bacteria

‚Horsehead‘ nebula in orion contains a huge dark cloud



Präbiotische Chemie:
Von kleinen Molekülen zu molekularen Replikatoren



Präbiotische Chemie:
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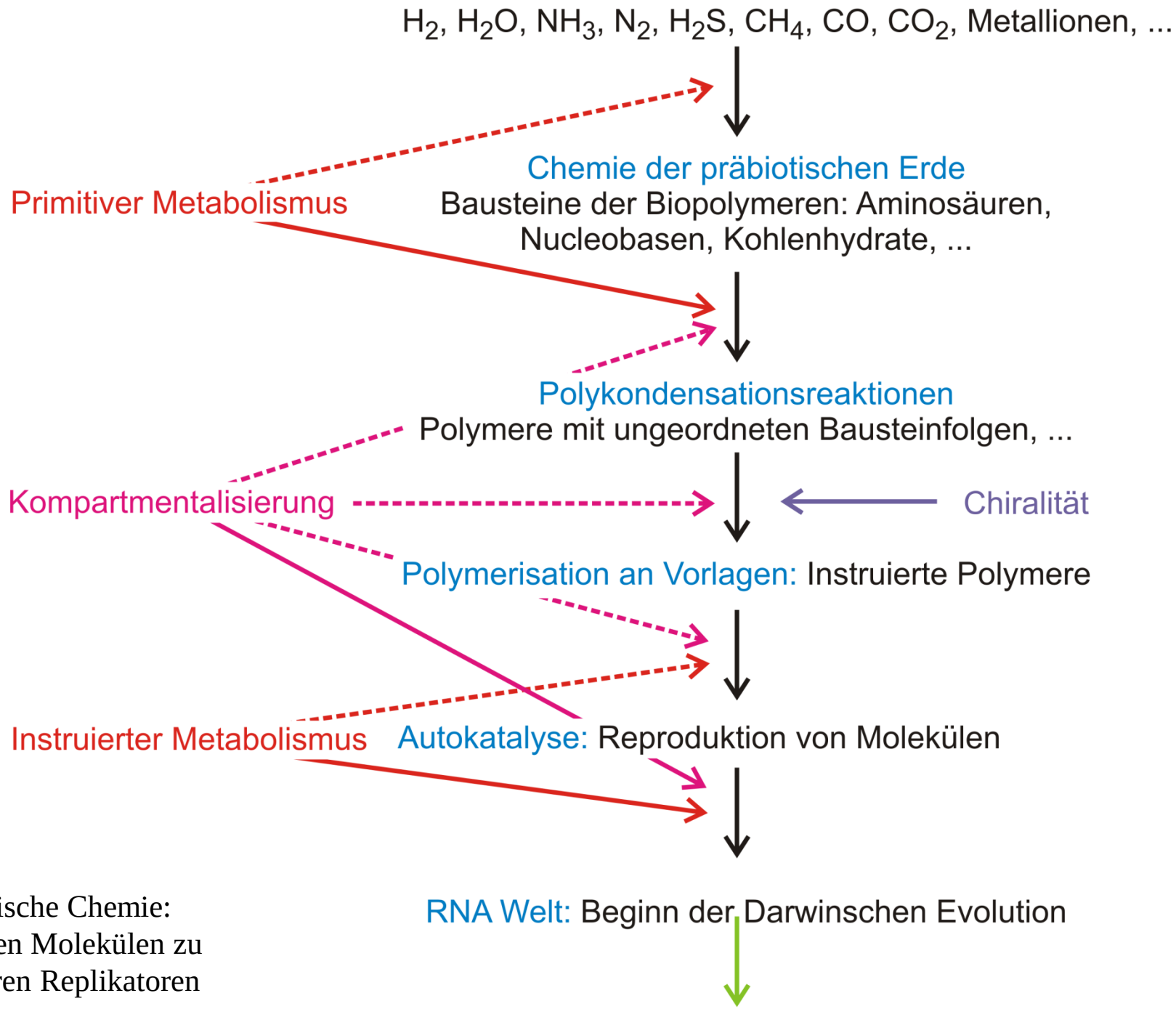


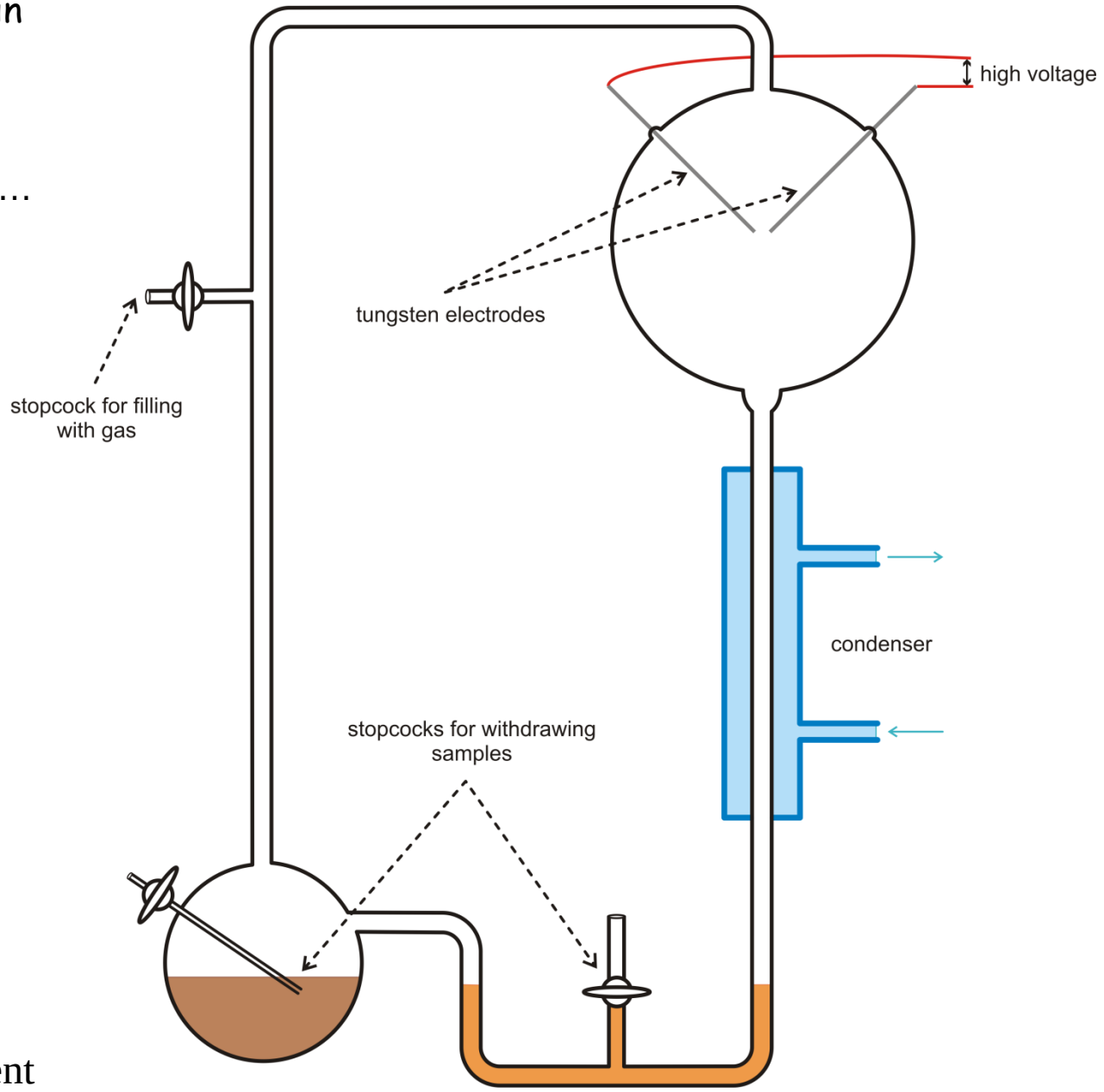
Präbiotische Chemie:
Von kleinen Molekülen zu molekularen Replikatoren

Von kleinen Molekülen zu molekularen Replikatoren

1. Woher kommen die Bausteine des Lebens?
2. Der Ursprung der Chiralität
3. Einfache Metabolismen

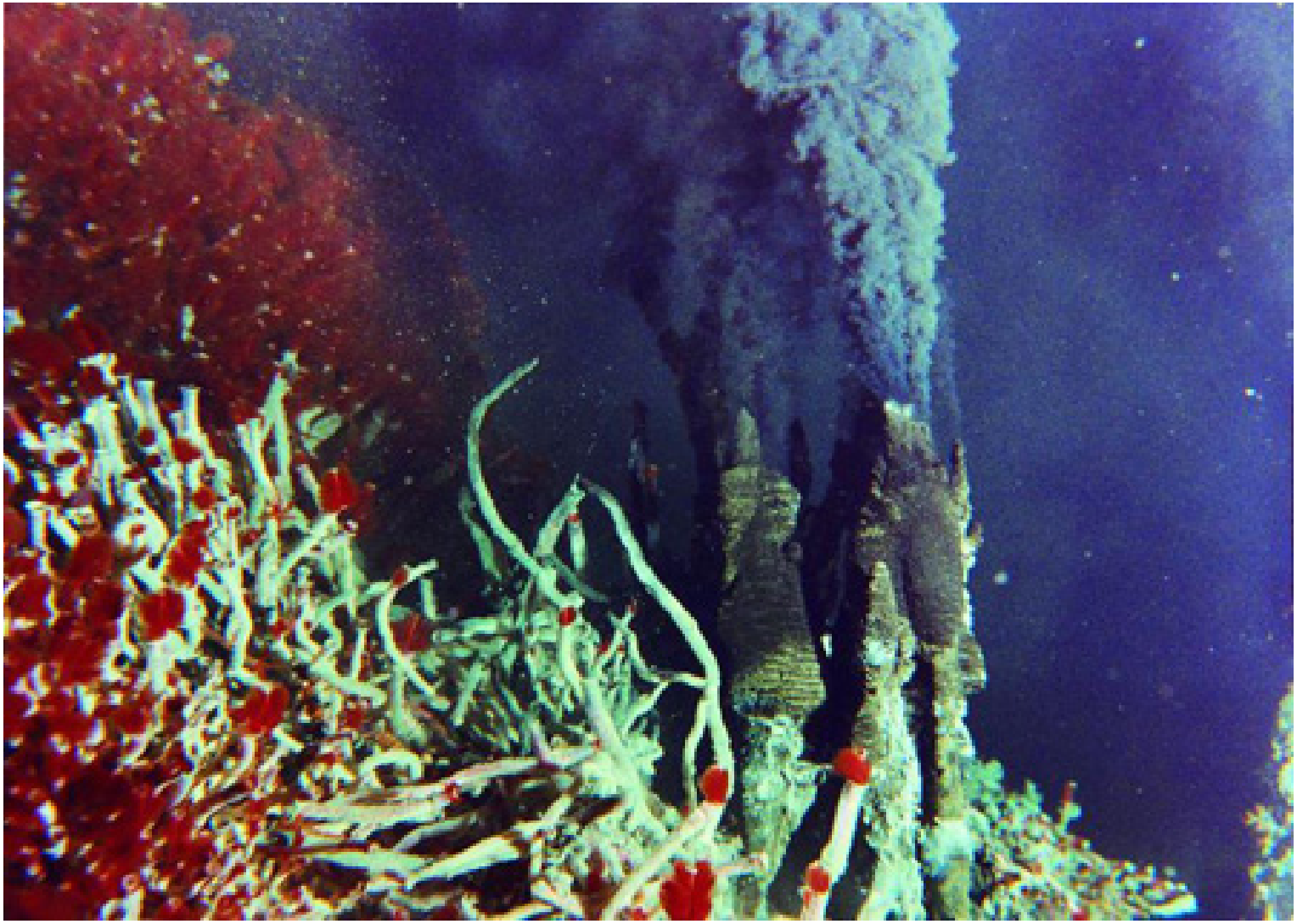
Elektrische Entladung in einer reduzierenden Atmosphäre:

CH_4, CO, NH_3, H_2O, H_2, …

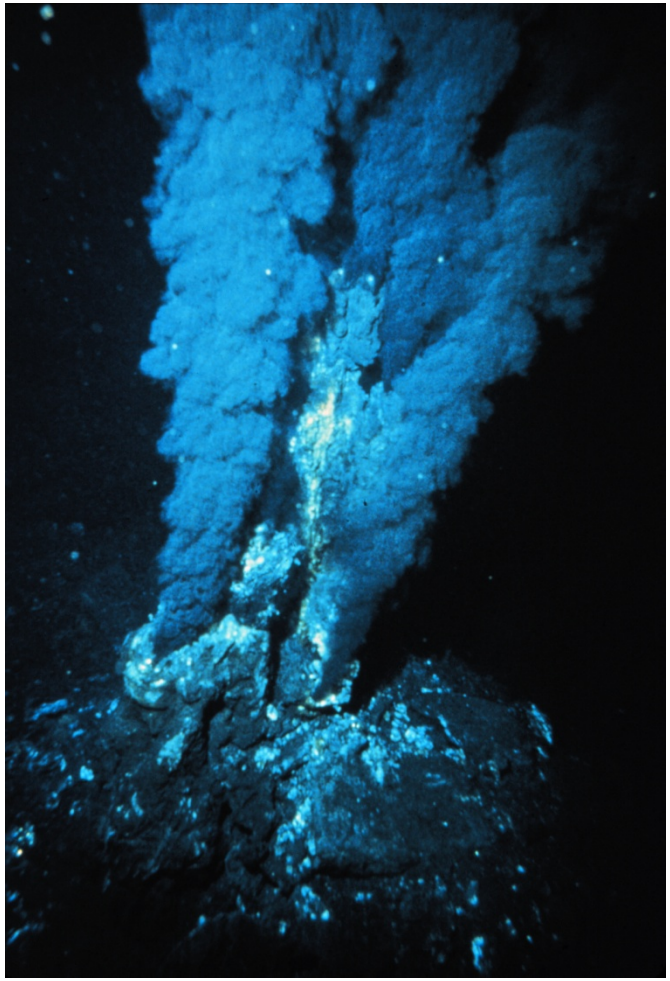


S.L.Miller. 1953. A production of amino acids under possible primitive earth conditions. *Science* **117**:528-529

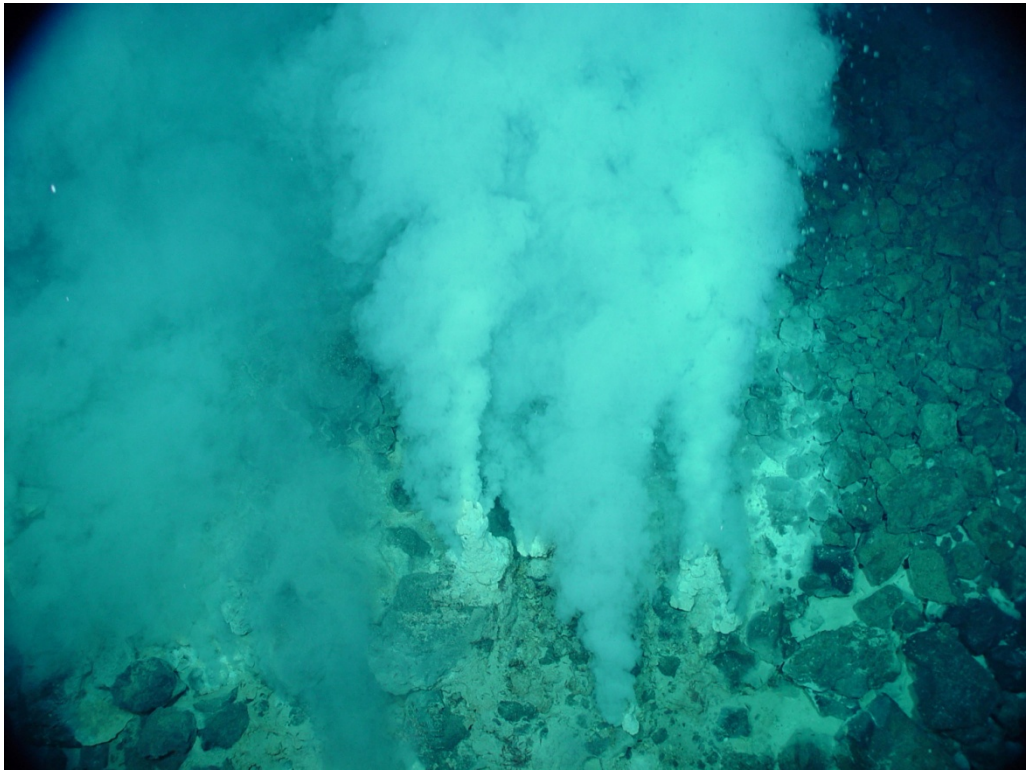
Das Miller-Urey Experiment



A hydrothermal vent



black smoker

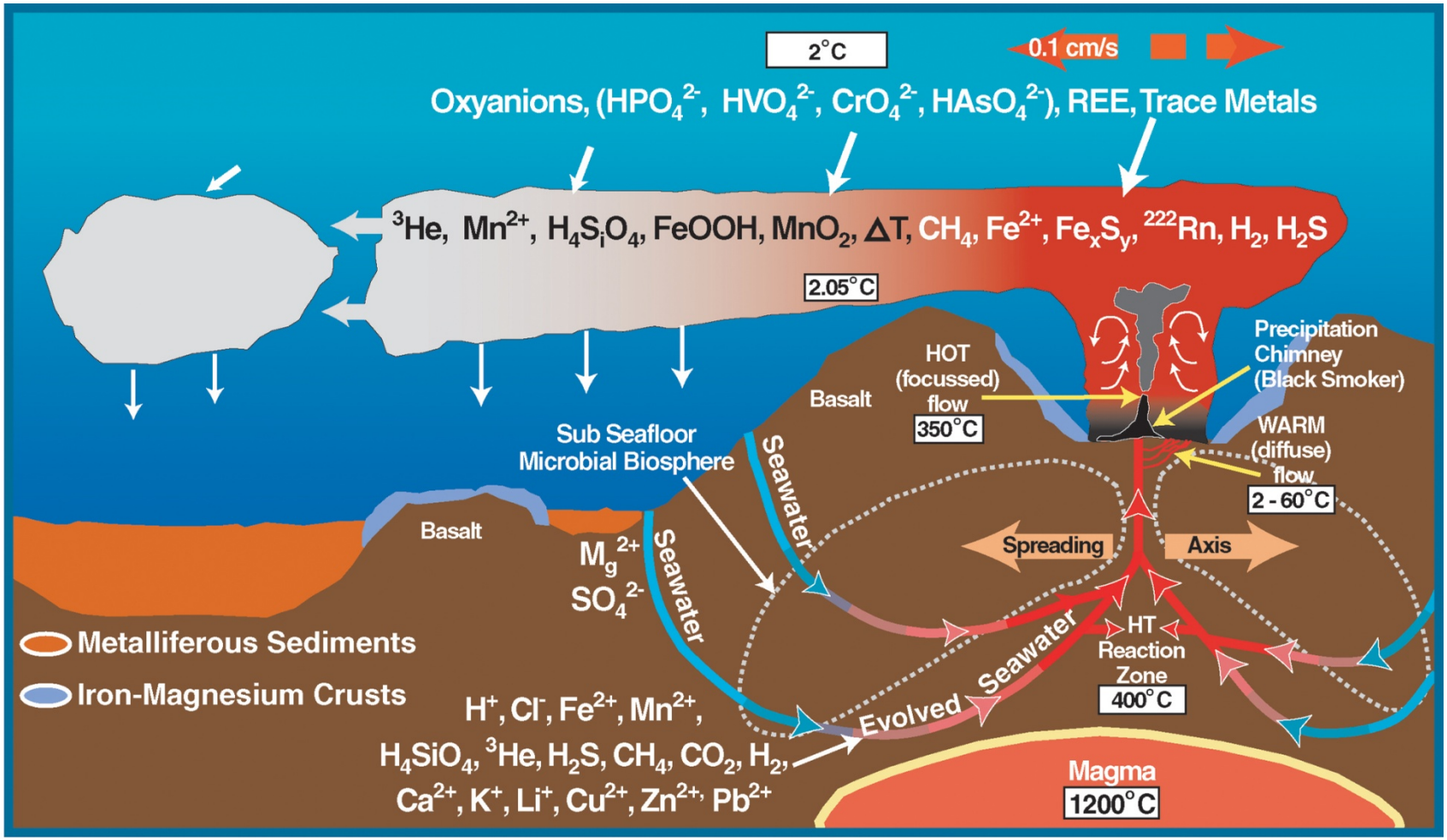


white smoker

Hydrothermale Quellen in der Tiefsee

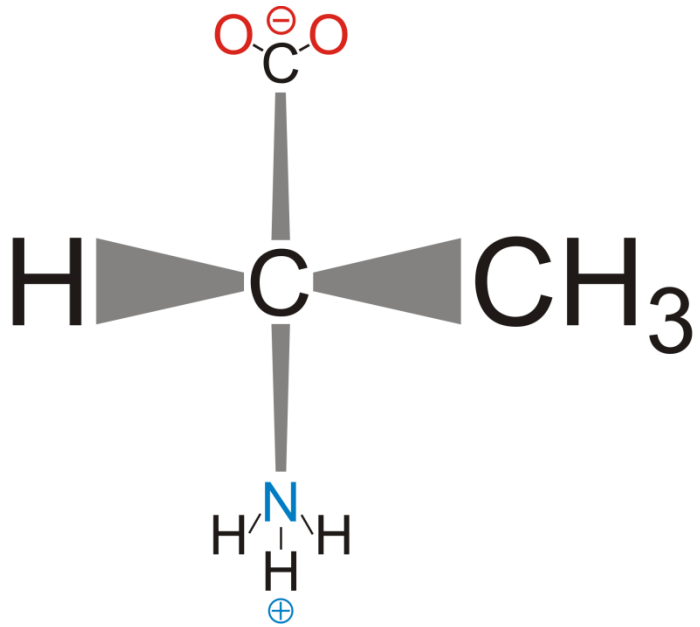
Vorkommen: mid-atlantic ridge, east pacific rise, …
in etwa 3000 m Tiefe

Source: Wikipedia: *Hydrothermal vent*, Nov. 15,2011

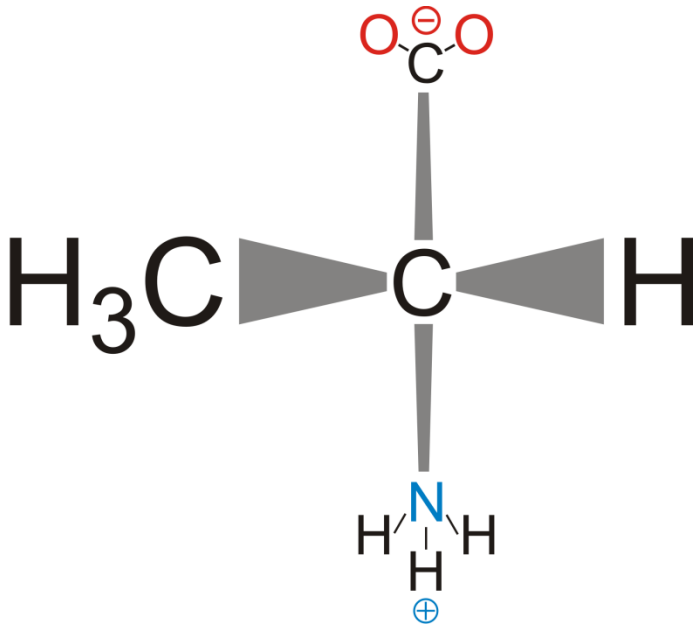


Bedingungen und Materialien in und um hydrothermale Quellen

Source: Wikipedia: *Hydrothermal vent*, Nov. 15,2011



L- (S-) *Alanin*



D- (R-) *Alanin*

Die zwei chiralen Formen von *Alanin*

ON SPONTANEOUS ASYMMETRIC SYNTHESIS

by

F. C. FRANK

The H. H. Wills Physical Laboratory, University of Bristol (England)

I am informed by my colleague Professor W. MOORE that there is still widely believed to be a problem of explaining the original "asymmetric synthesis" giving rise to the general optical activity of the chemical substances of living matter. I have long supposed that this was no problem on the basis of a supposition that the initial production of life is a rare event. We may take as the defining property of a living entity the ability to reproduce its own kind. Omitting such simple entities as flames, which are included by such a definition, and confining attention to chemical molecules, the complexity of any having this essential property of life is likely to be great enough to make it highly improbable that it has a centre of symmetry. It is likely, in fact, to contain α-amino acids which are necessarily asymmetric. Then, if the production of living molecules is an infrequent process, compared with the rate of multiplication of living molecules, the whole earth is likely to be extensively populated with the progeny of the first before another appears. In fact they may have so modified the environment by then that no other has a chance of generation. There are, of course, variants of this hypothesis: *e.g.* that a second living molecule is produced before the progeny of the first has colonised the whole earth, and competes successfully with it for nutrient material, "starving", or even "poisoning" the other out of existence. This leads to the same result, and depends essentially on the same initial hypothesis, that spontaneous germination of life is a rare event.

Die theoretische Vorhersage der Erzeugung von Chiralität durch autokatalytische asymmetrische Synthese im Jahre **1953** durch Frederick Charles **Frank**

Kenso Soai 1995

Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule

Kenso Soai, Takanori Shibata, Hiroshi Morioka & Kaori Choji

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

THE homochirality of natural amino acids and sugars remains a puzzle for theories of the chemical origin of life[1–18]. In 1953 Frank[7] proposed a reaction scheme by which a combination of autocatalysis and inhibition in a system of replicating chiral molecules can allow small random fluctuations in an initially racemic mixture to tip the balance to yield almost exclusively one enantiomer. Here we show experimentally that autocatalysis in a chemical reaction can indeed enhance a small initial enantiomeric excess of a chiral molecule. When a 5-pyrimidyl alkanol with a small (2%) enantiomeric excess is treated with diisopropylzinc and pyrimidine-5-carboxaldehyde, it undergoes an autocatalytic reaction to generate more of the alkanol. Because the reaction involves a chiral catalyst generated from the initial alkanol, and because the catalytic step is enantioselective, the enantiomeric excess of the product is enhanced. This process provides a mechanism by which a small initial imbalance in chirality can become overwhelming.

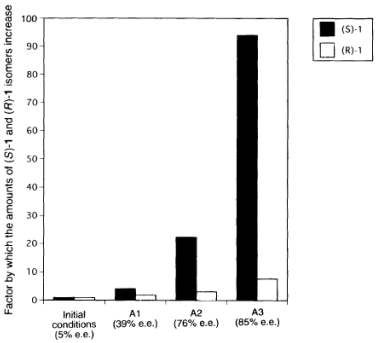


FIG 1. Asymmetric autocatalysis of chiral pyrimidyl alkanol (**1**). Runs A1–3 correspond to Table 1. The enantiomeric excess of (S)-**1** increases from 5 to 89% e.e. without the use of additional chiral auxiliaries. During the reactions (runs A1–3), the (*S*)-**1** increases by a factor of 94 times, while (*R*)-**1** increases by a factor of only eight times.

employed as asymmetric autocatalyst, the e.e. of the mixture of catalyst and the product was also 88% (run B5). Thus in series A and B, the low e.e. of (*S*)-**1** was autocatalytically amplified to 88–89%, and the amount of (*S*)-**1** was increased by a factor

WILEY InterScience® DISCOVER SOMETHING GREAT CHIRALITY 19:816–825 (2007)

Michael Mauksch and
Svetlana Tsogoeva 2007

Demonstration of Spontaneous Chiral Symmetry Breaking in Asymmetric Mannich and Aldol Reactions

MICHAEL MAUKSCH,* SVETLANA B. TSOGOEVA,*† SHENGWEI WEI, AND IRINA M. MARTYNOVA

Institute of Organic Chemistry I, University of Erlangen-Nuremberg, Henkestrasse 42, 91052 Erlangen, Germany

ABSTRACT Spontaneous symmetry breaking in reactive systems, known as a rare physical phenomenon and for the Soai autocatalytic irreversible reaction, might in principle also occur in other, more common asymmetric reactions when the chiral product is capable to promote its formation and an element of "nonlinearity" is involved in the reaction scheme. Such phenomena are long sought after in chemistry as a possible explanation for the biological homochirality of biomolecules. We have investigated homogeneous organic stereoselective Mannich and Aldol reactions, in which the product is capable to form H-bridged complexes with the prochiral educt, and found by applying NMR spectroscopy, HPLC analysis, and optical rotation measurements 0.3–50.8% of random product enantiomeric excess under essentially achiral reaction conditions. These findings imply a hitherto overlooked mechanism for spontaneous symmetry breaking and, hence, a novel approach to the problem of absolute asymmetric synthesis and could have also potential significance for the conundrum of homochirality. *Chirality 19:816–825, 2007.*

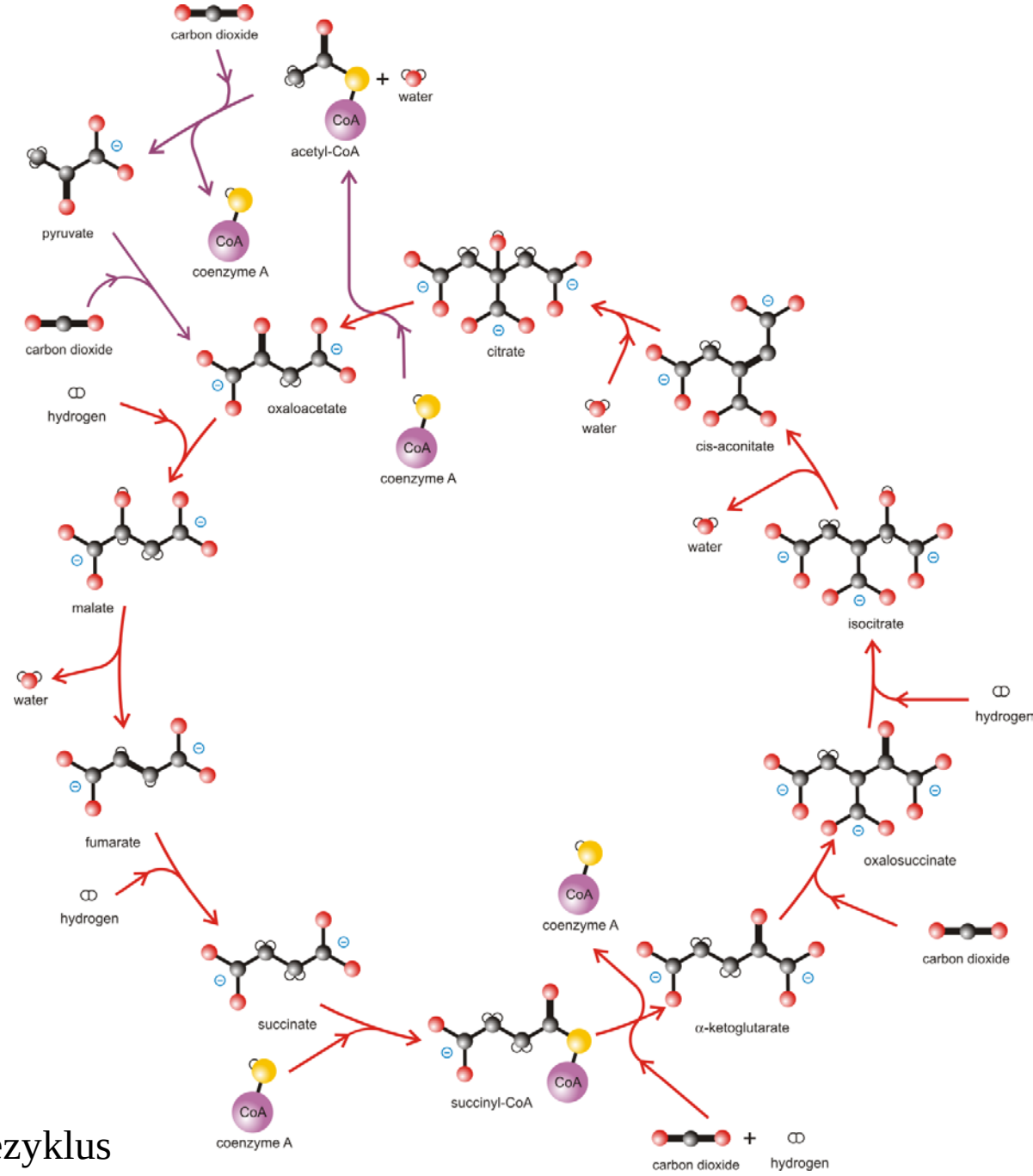
KEY WORDS: organocatalysis; spontaneous symmetry breaking; asymmetric autocatalysis; Mannich reaction; Aldol reaction; homochirality

Reaktionen mit einem etwas erweiterten Frank Mechanismus

Primitiver Metabolismus??

$2\ CO_2 + 4\ H_2 \rightleftharpoons CH_3COOH + 2\ H_2O$

zwölf Teilschritte



G. Wächtershäuser. Before enzymes and templates: Theory of surface metabolism. 1988. *Microbiol. Rev.* **52**:452-484.

Die Umkehrung des Zitronensäurezyklus