Evolution 1859 und heute

Was die molekulare Einsicht in die Genetik gebracht hat.

Peter Schuster

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

Dawin Day 2014

Oberösterreichisches Landesmuseum, Linz, 12.02.2014

Web-Page für weitere Informationen:

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

Peter Schuster. Evolution der Moleküle. Von der Evolution im Reagenzglas zur Erzeugung maßgeschneiderter Moleküle.

In: Martin Neukamm, Ed. Evolutionäres Denken. Evolution als Leitbild in den modernen Wissenschaften.
Wissenschaftliche Buchgesellschaft. WBG. Darmstadt, 2014.

1. Prolog – Darwin und Mathematik
2. Von Darwin zur Populationsgenetik
3. Frühe Molekularbiologie
4. Evolution in Reagenzglas
5. Molekularbiologie heute
6. Biologische Komplexität vor Augen

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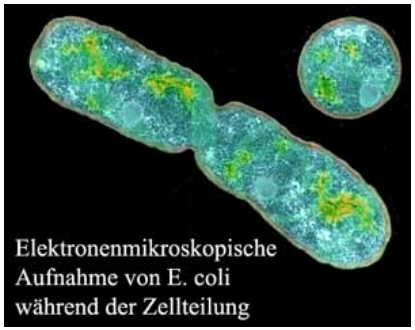
$A + X \rightarrow 2X$ …… asexuelle Vermehrung

Viren, Bakterien, einige höhere Organismen (Eukaryoten)



Quelle: www.tierklinik.de

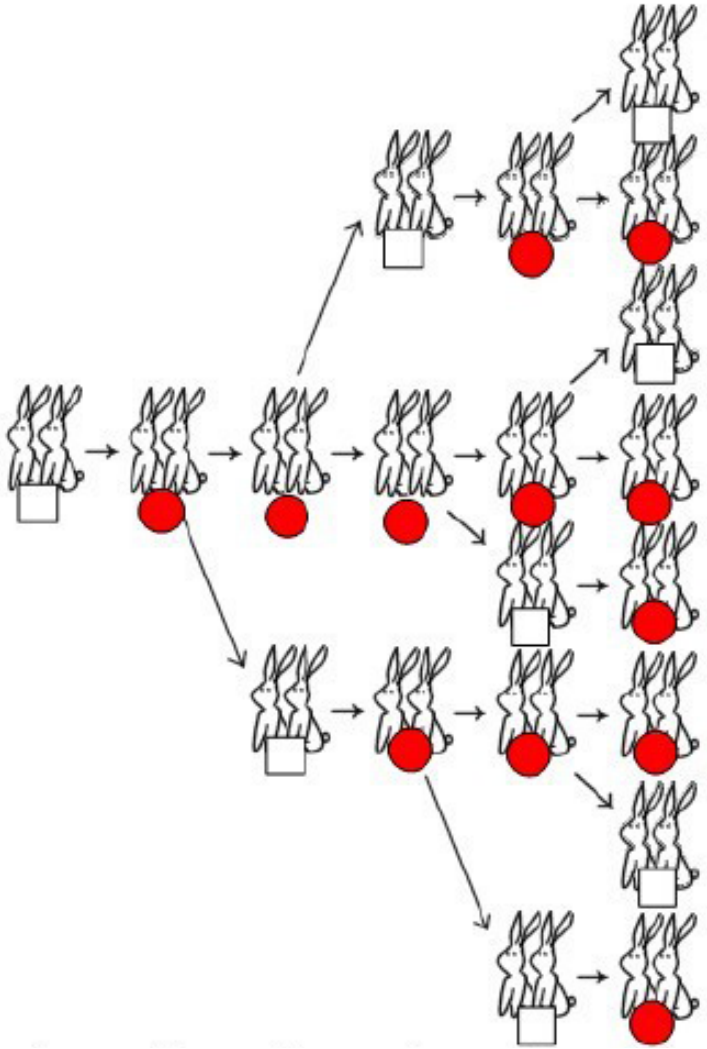
$A + X + Y \rightarrow X + Y + n\,Z$ …… sexuelle Vermehrung

die meisten höheren Organismen

obligatorisch bei Säugetieren

Quelle: Thomas Brodmann
animals-digital.de

Zwei Wege der Reproduktion in der Biologie



Leonardo da Pisa
„Fibonacci“

~1180 – ~1240

Paare 1 1 2 3 5 8 13 21 34 55 89 …..

Die Ursprünge des Gedankens vom exponentiellen Wachstums

Thomas Robert Malthus
1766 – 1834

Leonhard Euler, 1717 - 1783

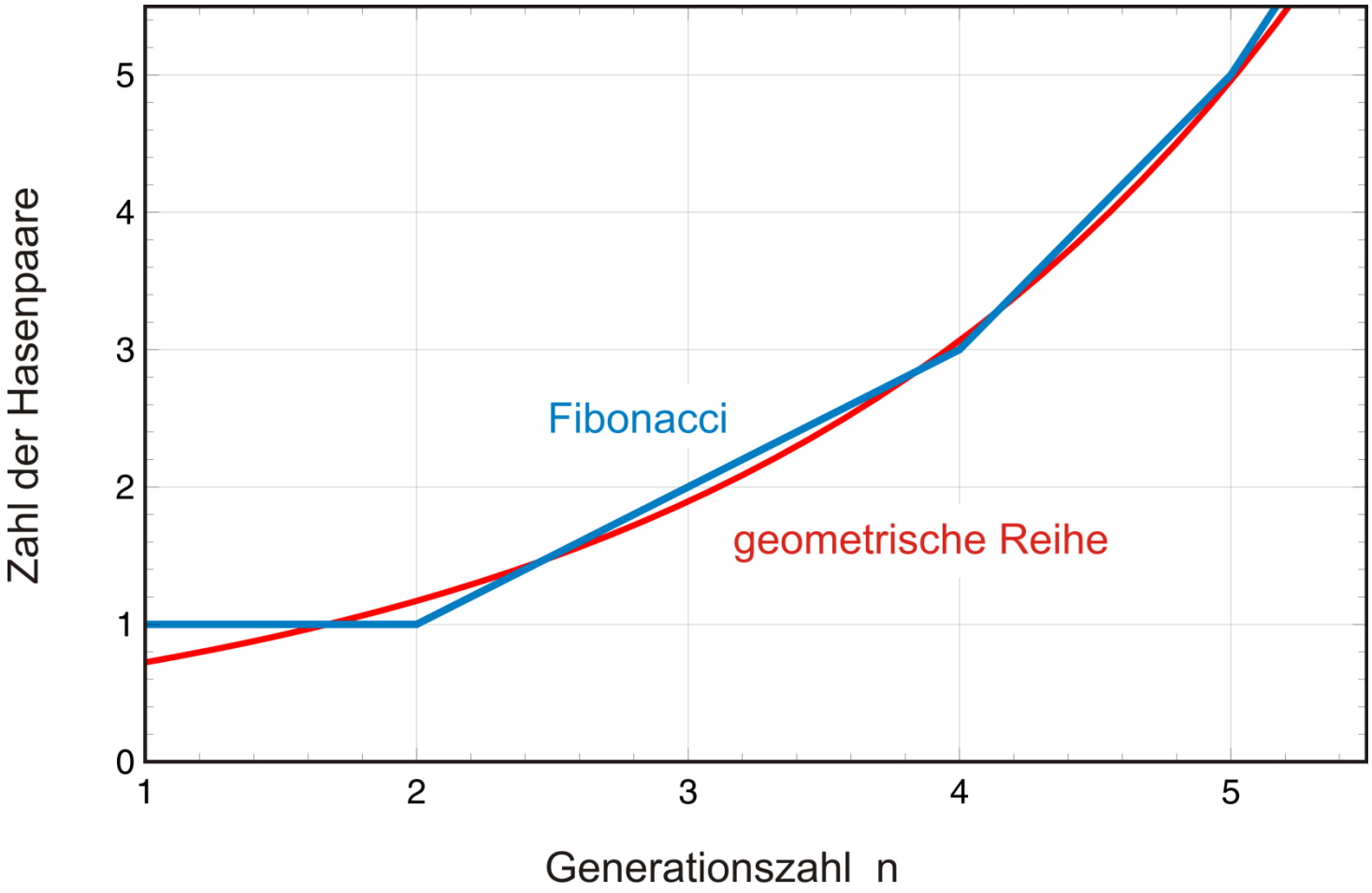
1, 2 , 4 , 8 ,16 , 32 , 64, 128 , ...

geometrische Reihe

$$\exp(x) \equiv \lim_{n\to\infty} (1+\frac{x}{n})^n$$

Exponentialfunktion

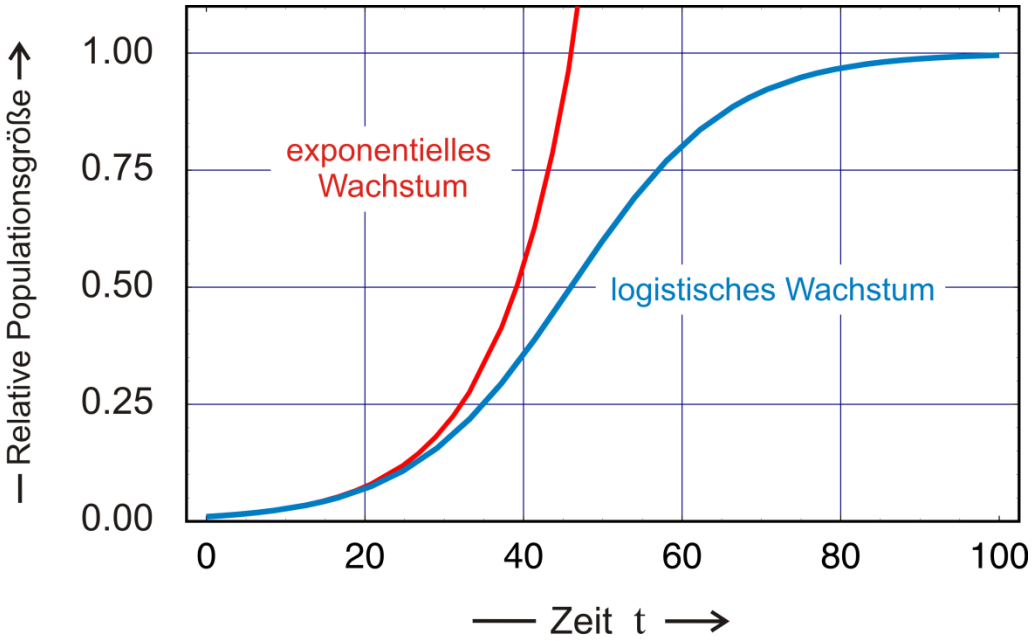
Die Ursprünge des Gedankens vom exponentiellen Wachstums



Die Ursprünge des Gedankens vom exponentiellen Wachstums

Pierre-François Verhulst,
1804-1849

Beschränkung des Wachstums durch begrenzte Ressourcen in der Umwelt

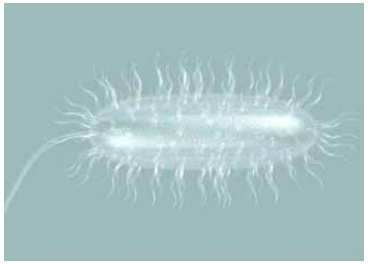


War schon 30 Jahre vor dem Erscheinen von Charles Darwins 'Origin of Species' bekannt

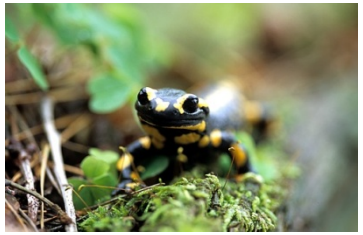
Die logistische Wachstumsfunktion, 1828

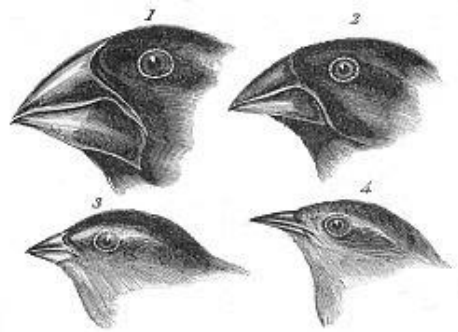
Charles Darwin, 1809 - 1882

Voyage on HMS Beagle, 1831 - 1836



Phänotypen





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

Finches from Galapagos Archipelago

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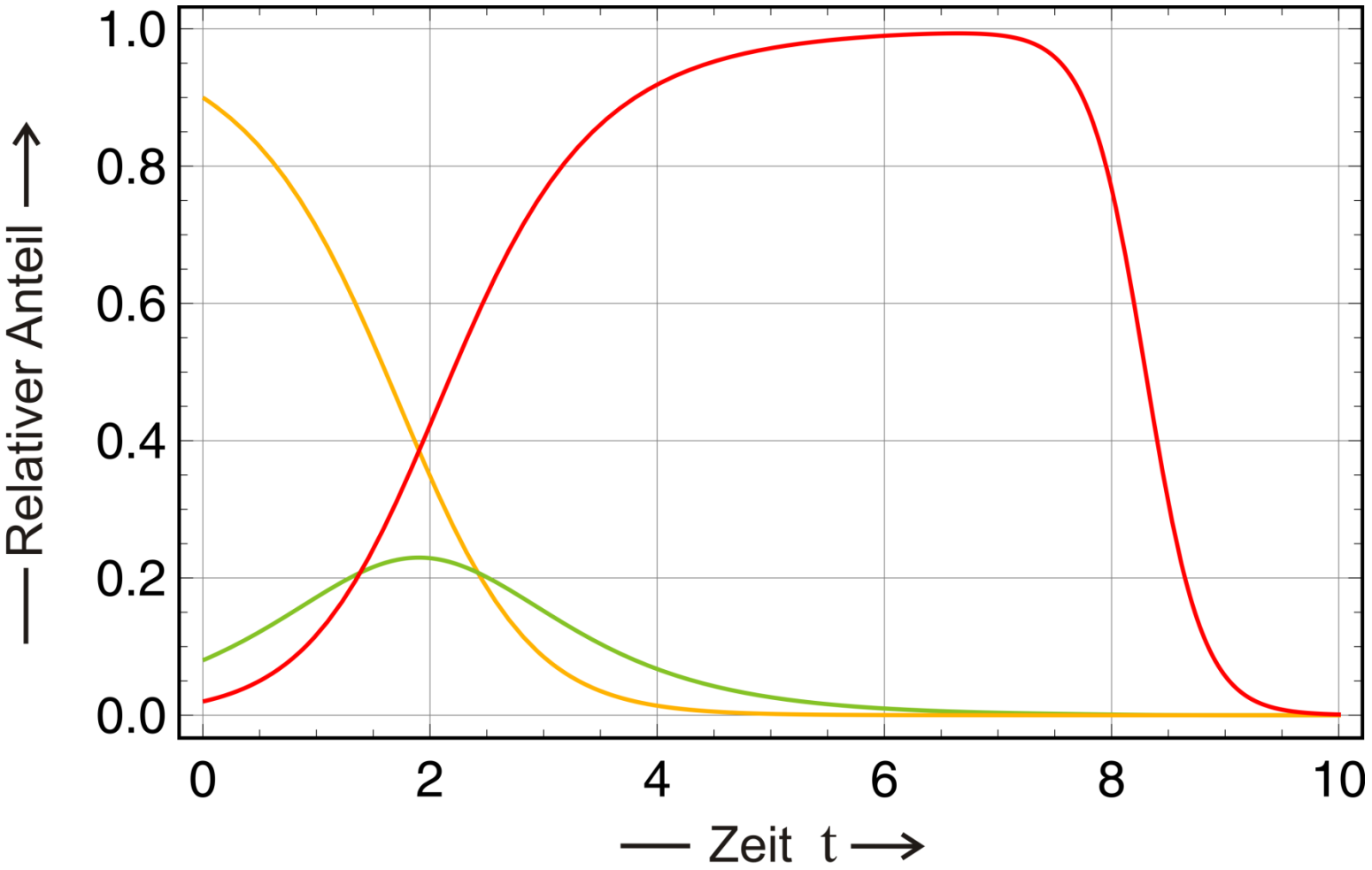
Die drei notwendigen Voraussetzungen für Darwinsche Evolution sind:

1. **Vermehrung,**
2. **Variation**, und
3. **Selektion**.

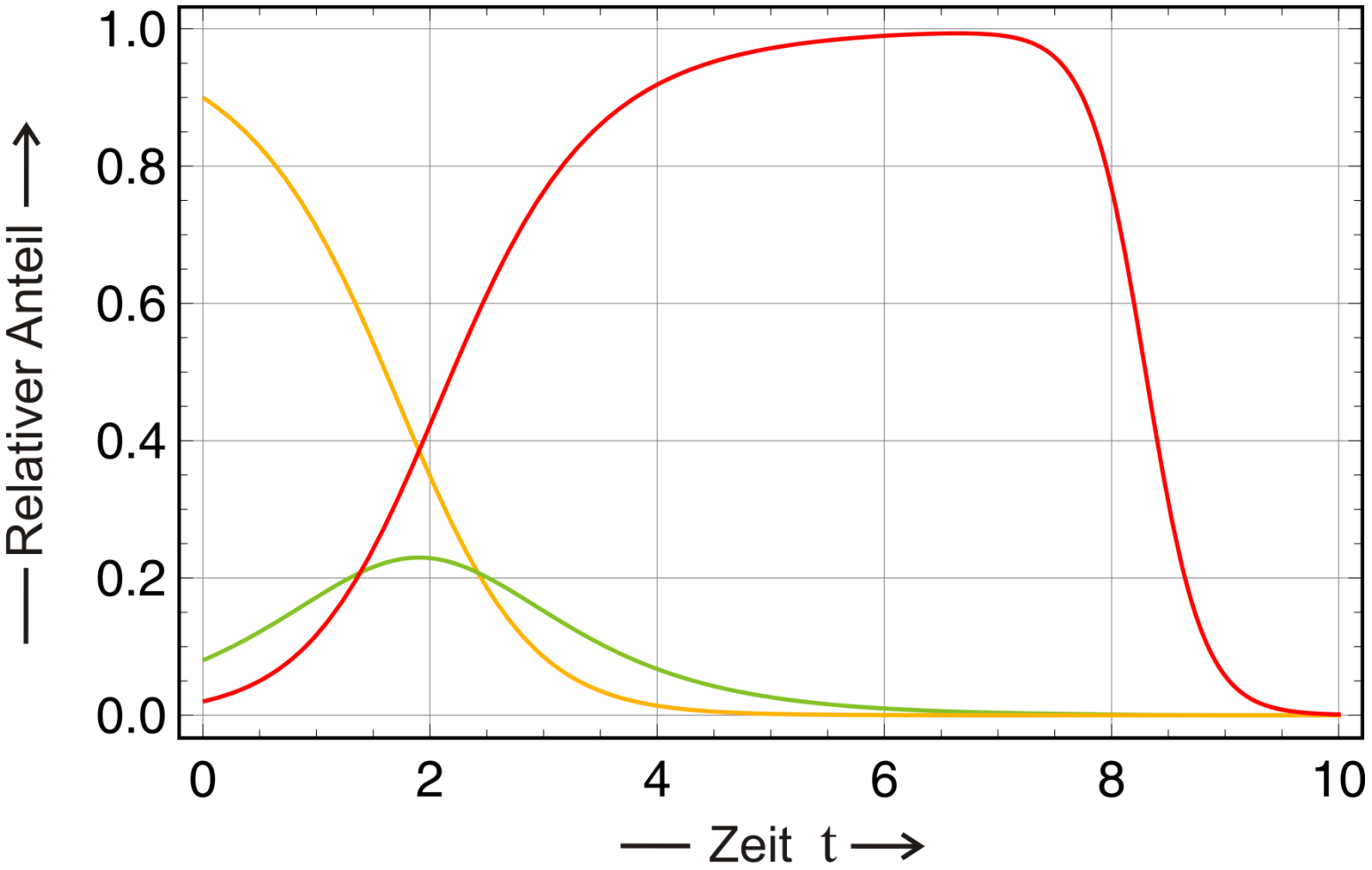
Darwin entdeckte das Prinzip der **natürlichen Auslese** durch empirische Beobachtungen in der Natur.

Darwin unternahm keinen Versuch, sein Prinzip mathematisch zu formulieren, obwohl alle Voraussetzungen dafür zu seiner Zeit gegeben waren.



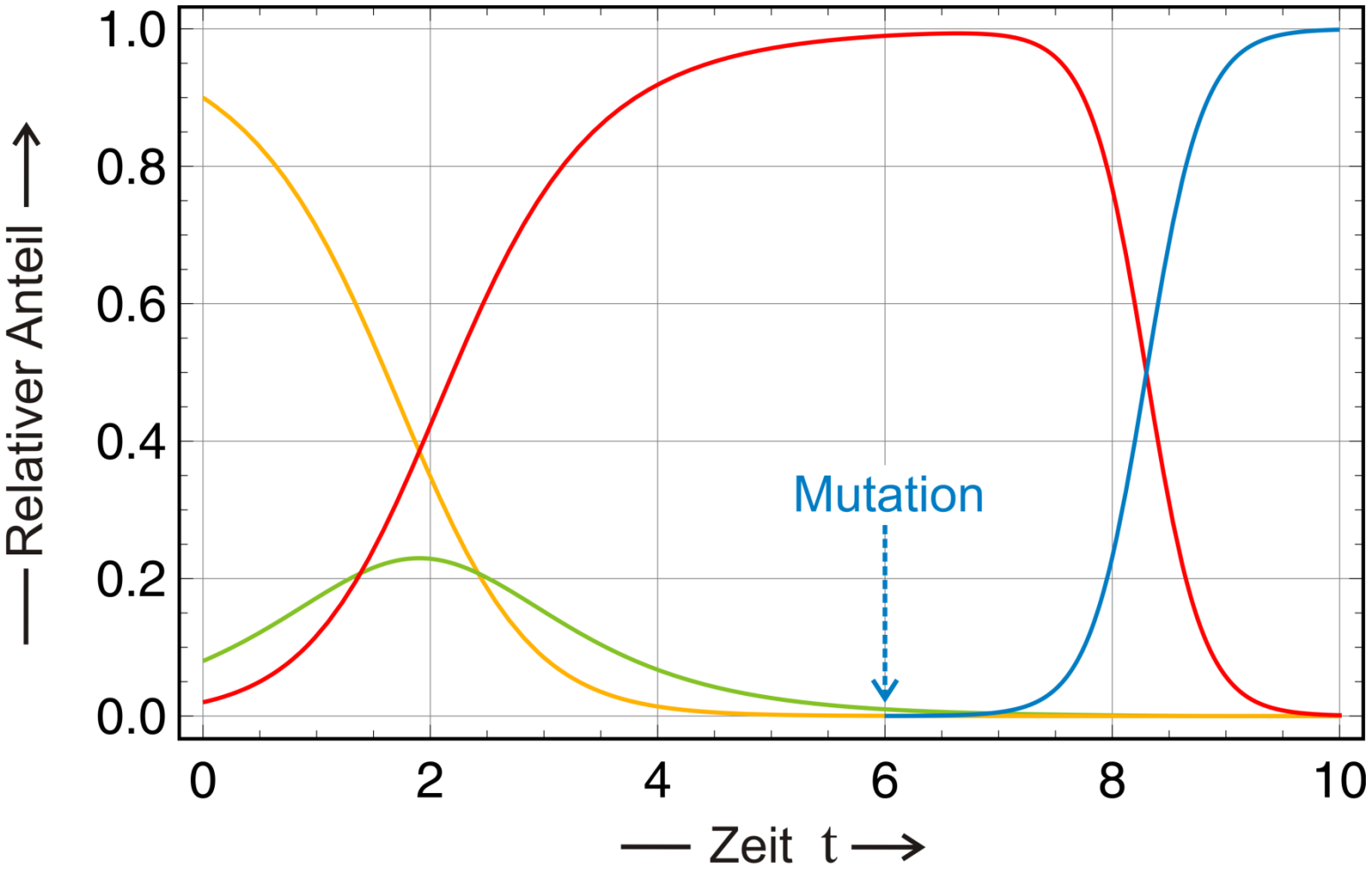
$f_1 = 1, f_2 = 2, f_3 = 3$

Darwins natürliche Selektion in einer Population mit konstanten Ressourcen



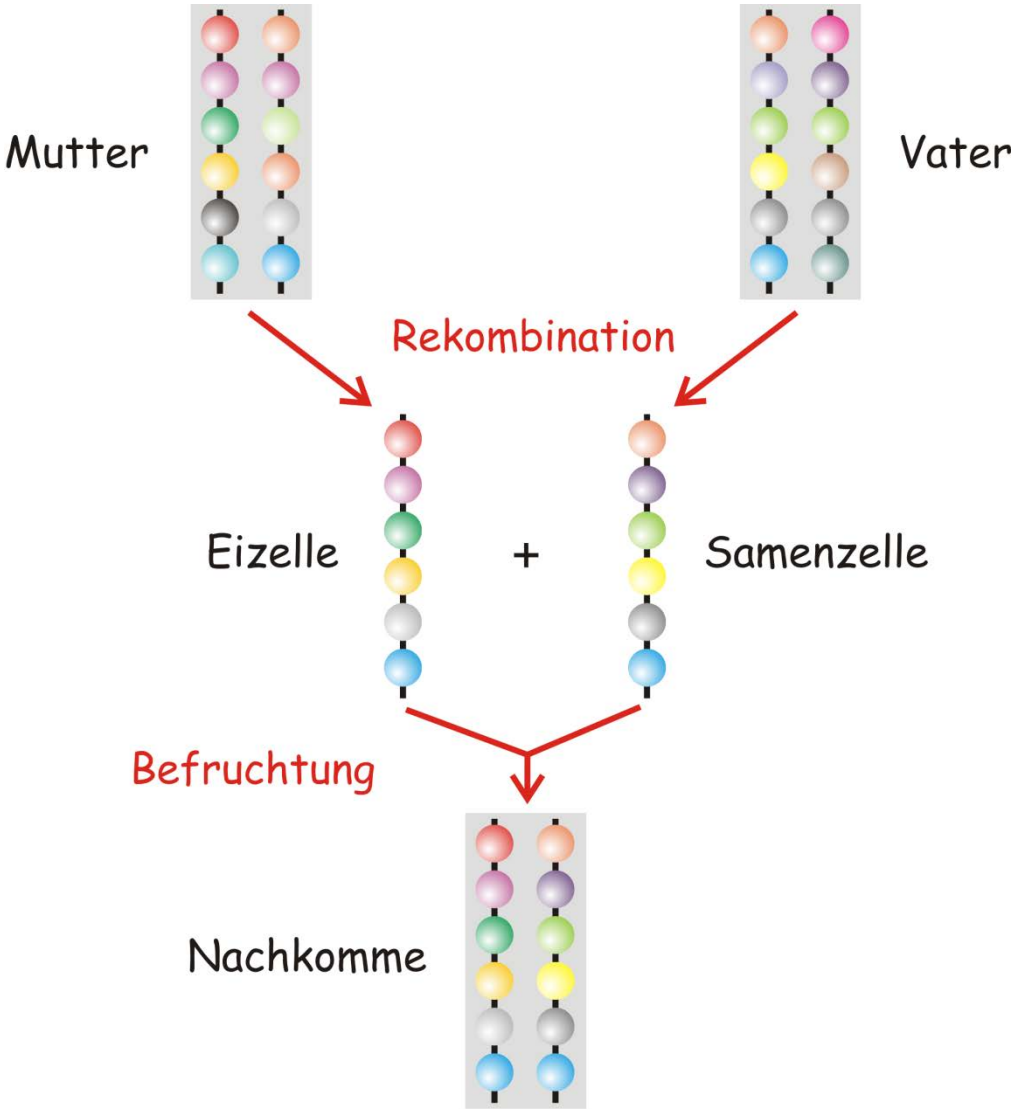
$f_1 = 1, f_2 = 2, f_3 = 3$

Vor der Entwicklung der Molekularbiologie wurde Mutation als ein "Deus ex Machina" behandelt



$f_1 = 1, f_2 = 2, f_3 = 3, f_4 = 7$

Vor der Entwicklung der Molekularbiologie wurde Mutation als ein "Deus ex Machina" behandelt

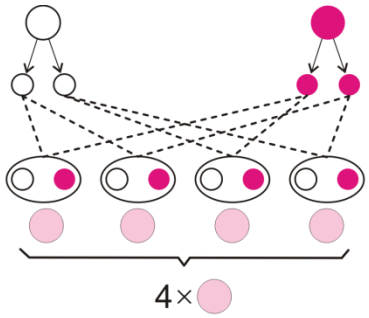


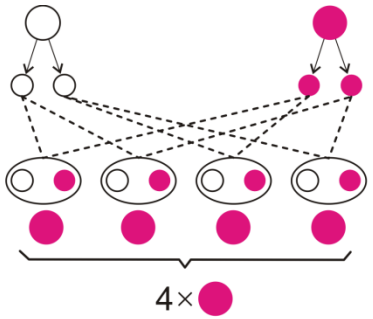
Gregor Mendel
1822 - 1884

Rekombination in Mendels Genetik

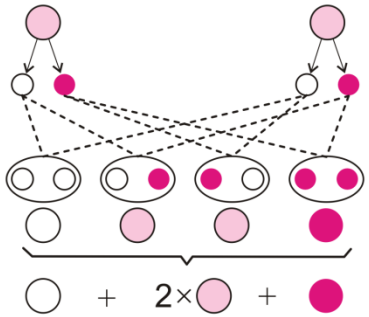
Mendels Genetik

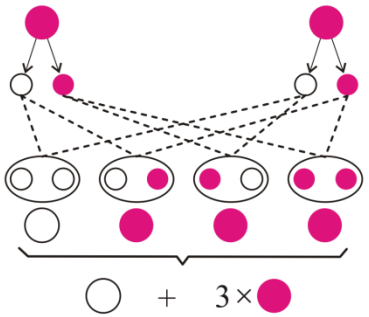
Die 3:1 Regel



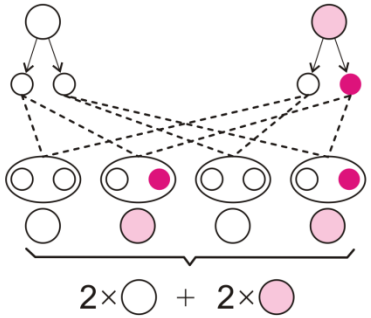


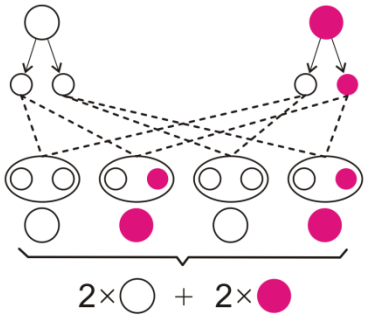
F1





F2





F1 × F2

Intermediäres Allelpaar

Dominant / rezessives Allelpaar

Ronald Fisher (1890-1962)

J. B. S. Haldane (1892-1964)

Sewall Wright (1889-1988)

Die drei Begründer der Populationsgenetik

Ronald Fisher (1890-1962)

Allele: $A_1, A_2, \ldots, A_n$

Häufigkeiten: $x_i = [A_i]$; Genotypen: $A_i \cdot A_j$

Fitnesswerte: $a_{ij} = f(A_i \cdot A_j),\ a_{ij} = a_{ji}$

Mendel

Darwin

$$\frac{dx_j}{dt} = \sum_{i=1}^{n} a_{ji}\, x_i\, x_j - \Phi\, x_j = x_j \left(\sum_{i=1}^{n} a_{ji}\, x_i - \Phi \right), \quad j = 1, 2, \ldots, n$$

$$\text{mit} \quad \Phi(t) = \sum_{j=1}^{n} \sum_{i=1}^{n} a_{ji}\, x_i\, x_j \quad \text{und} \quad \sum_{j=1}^{n} x_j = 1$$

$$\frac{d\Phi}{dt} = 2\left(< \bar{a}^2 > - < \bar{a} >^2 \right) = 2\, \mathrm{var}\{\bar{a}\} \geq 0$$

Ronald Fishers Selektionsgleichung: The genetical theory of natural selection. Oxford, UK, Clarendon Press, 1930.

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.

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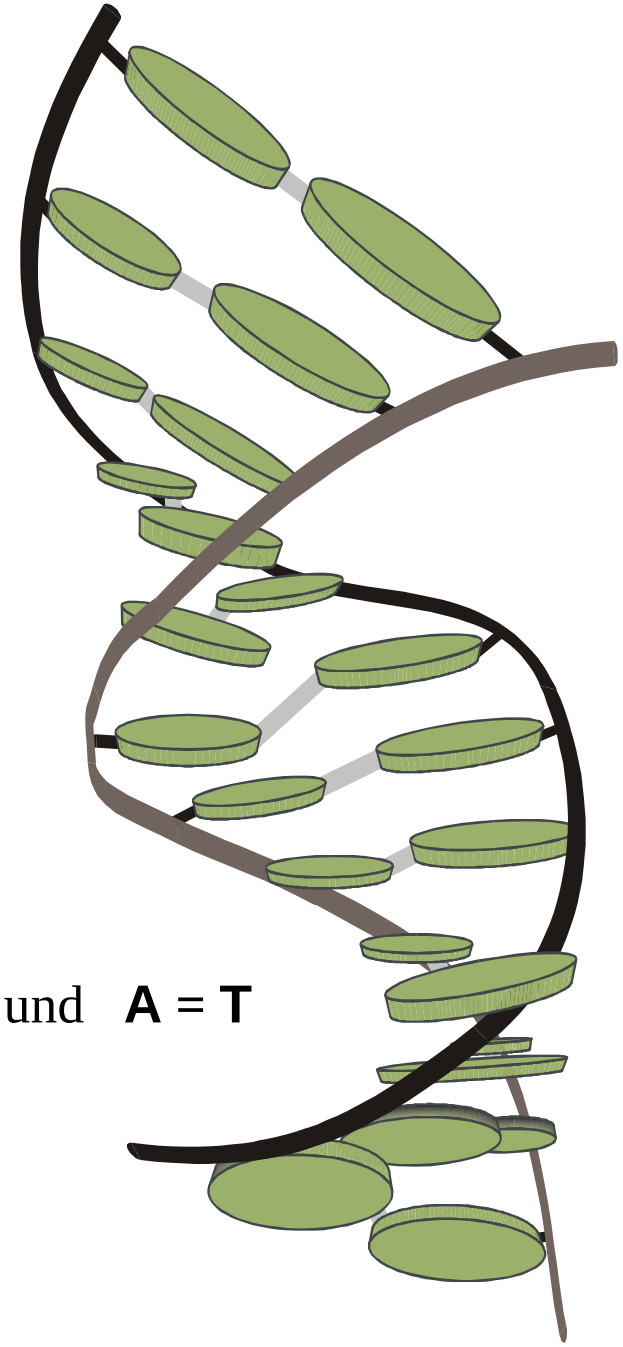
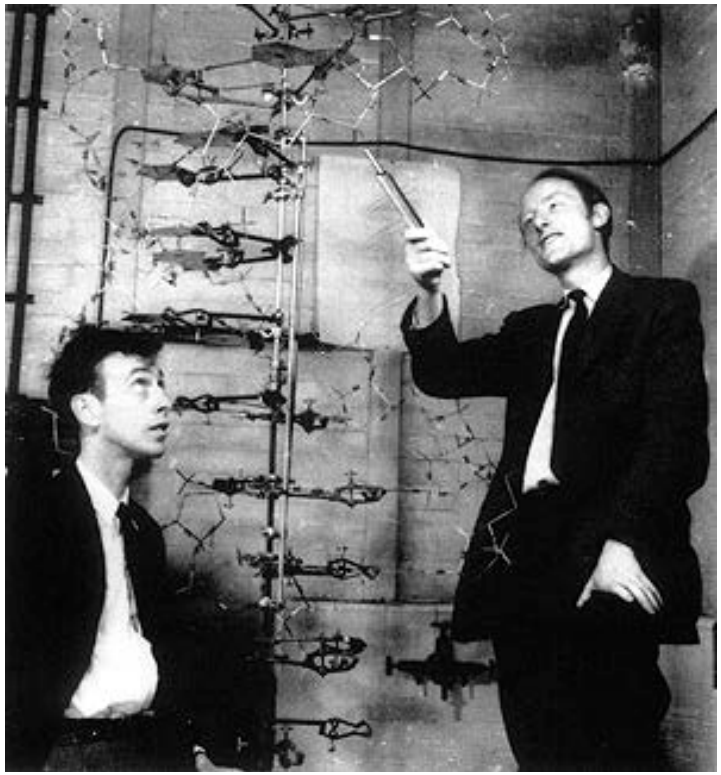
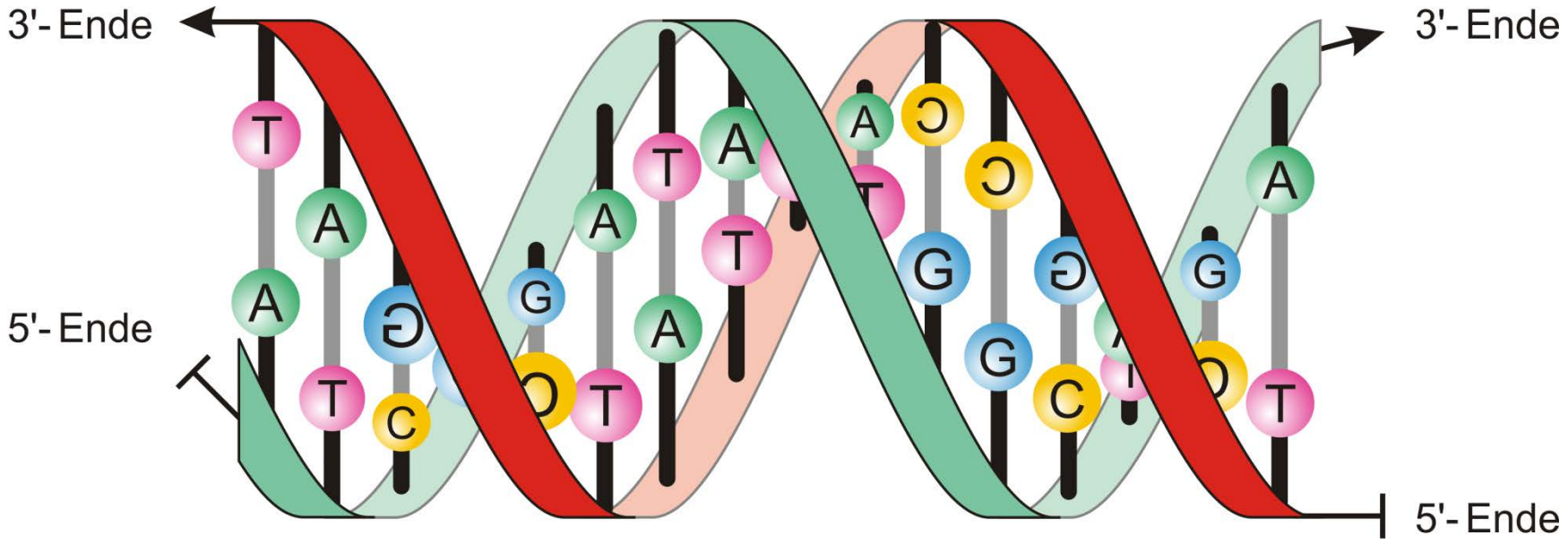


G ≡ C und **A = T**



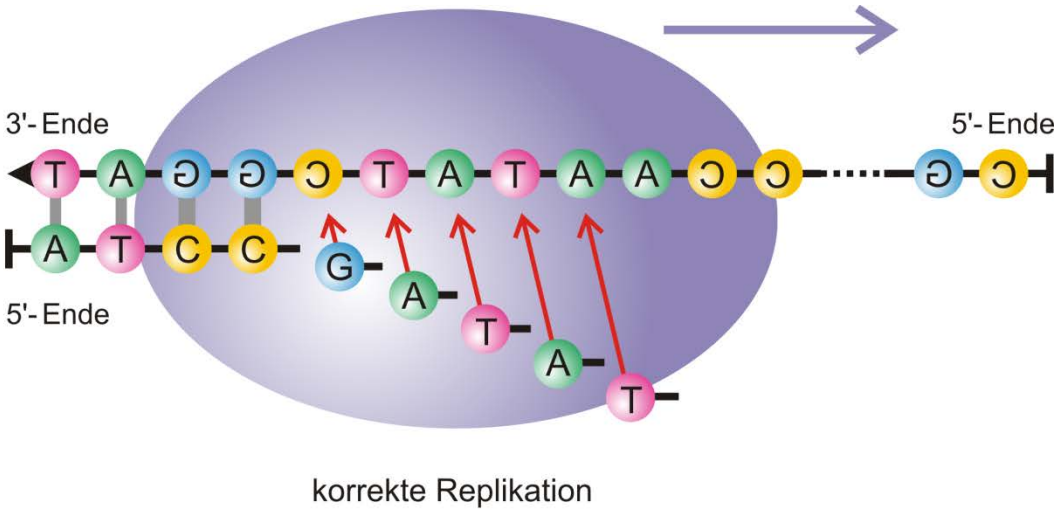
James D. Watson, 1928- , and Francis Crick, 1916-2004,
Nobel Preis 1962

Die dreidimensionale Struktur eines kleinen Stückes der B-DNA



Die B-Form der DNA-Doppelhelix

Taq-Polymerase



korrekte Replikation

Adenin A

Thymin T

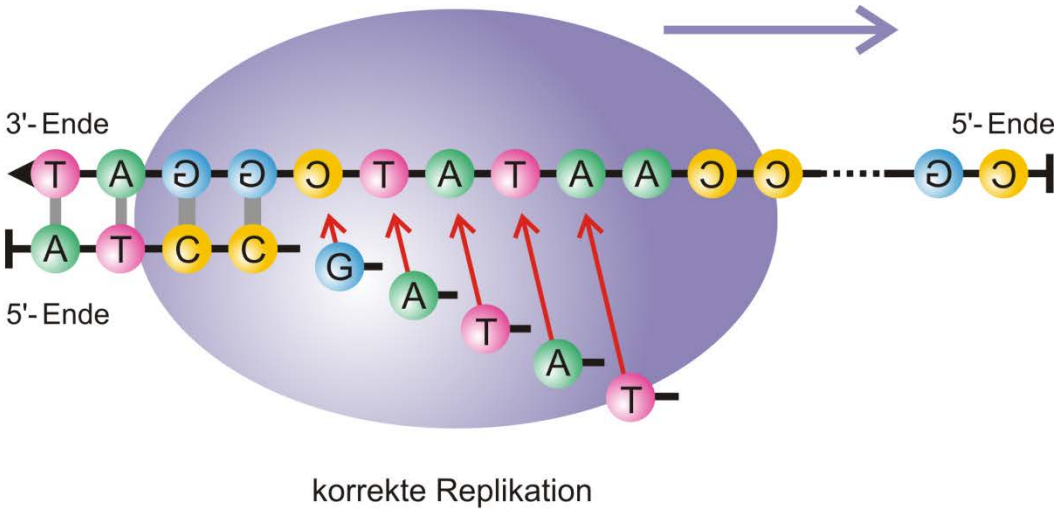
Uracil U

Guanin G

Cytosin C

Korrekte Replikation und Punktmutation

Taq-Polymerase



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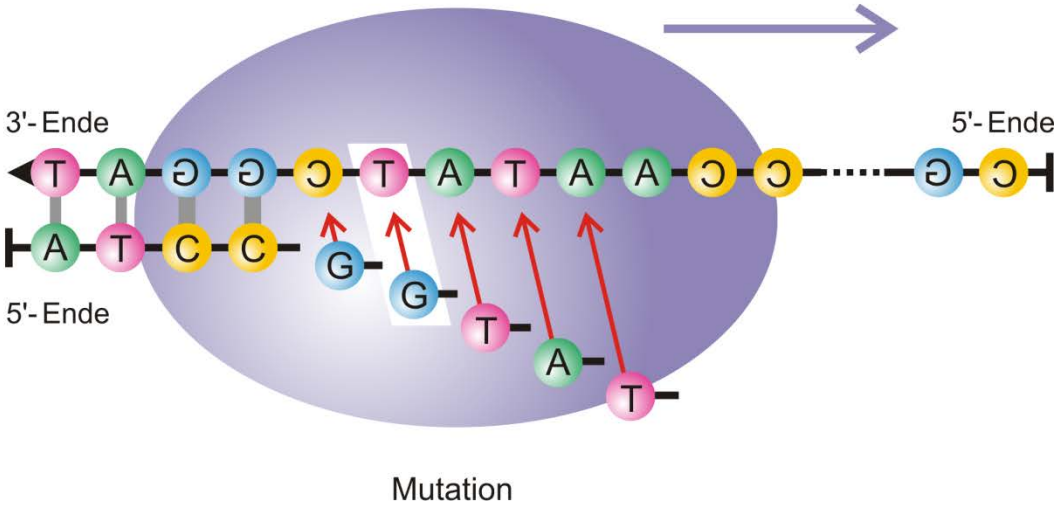
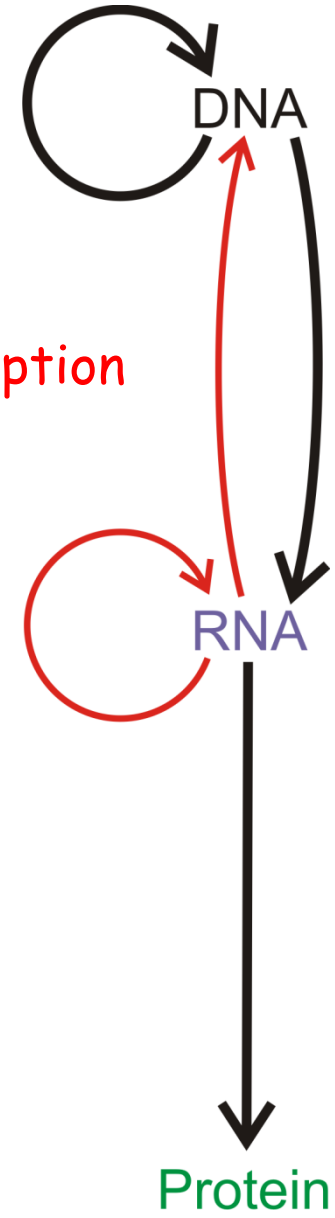


Korrekte Replikation und Punktmutation

Die codierte genetische Information in der Biologie fließt von Nukleinsäure zu Nukleinsäure und von Nukleinsäure zu Protein.

Die ein Gen ⇒ ein Protein Hypothese



Replikation

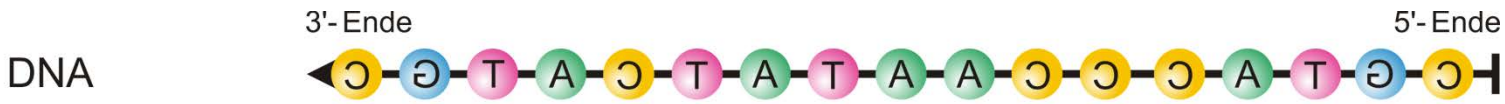
Transkription

Reverse Transkription

Replikation

Translation

Das zentrale „Dogma“ der Molekularbiologie

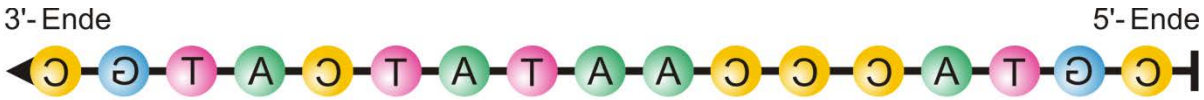


DNA ⇒ RNA

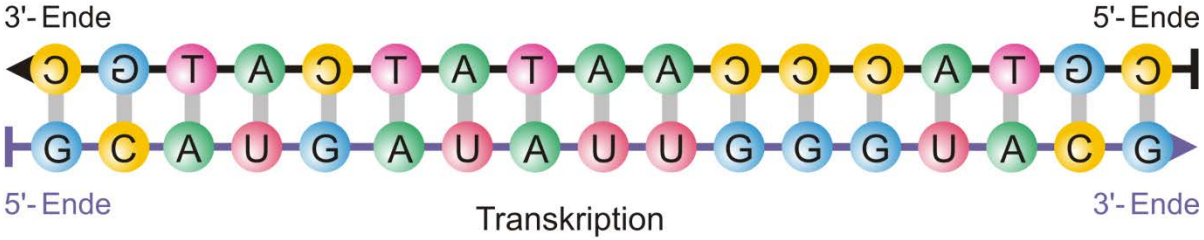
RNA ⇒ Protein

Transkription und Translation

DNA

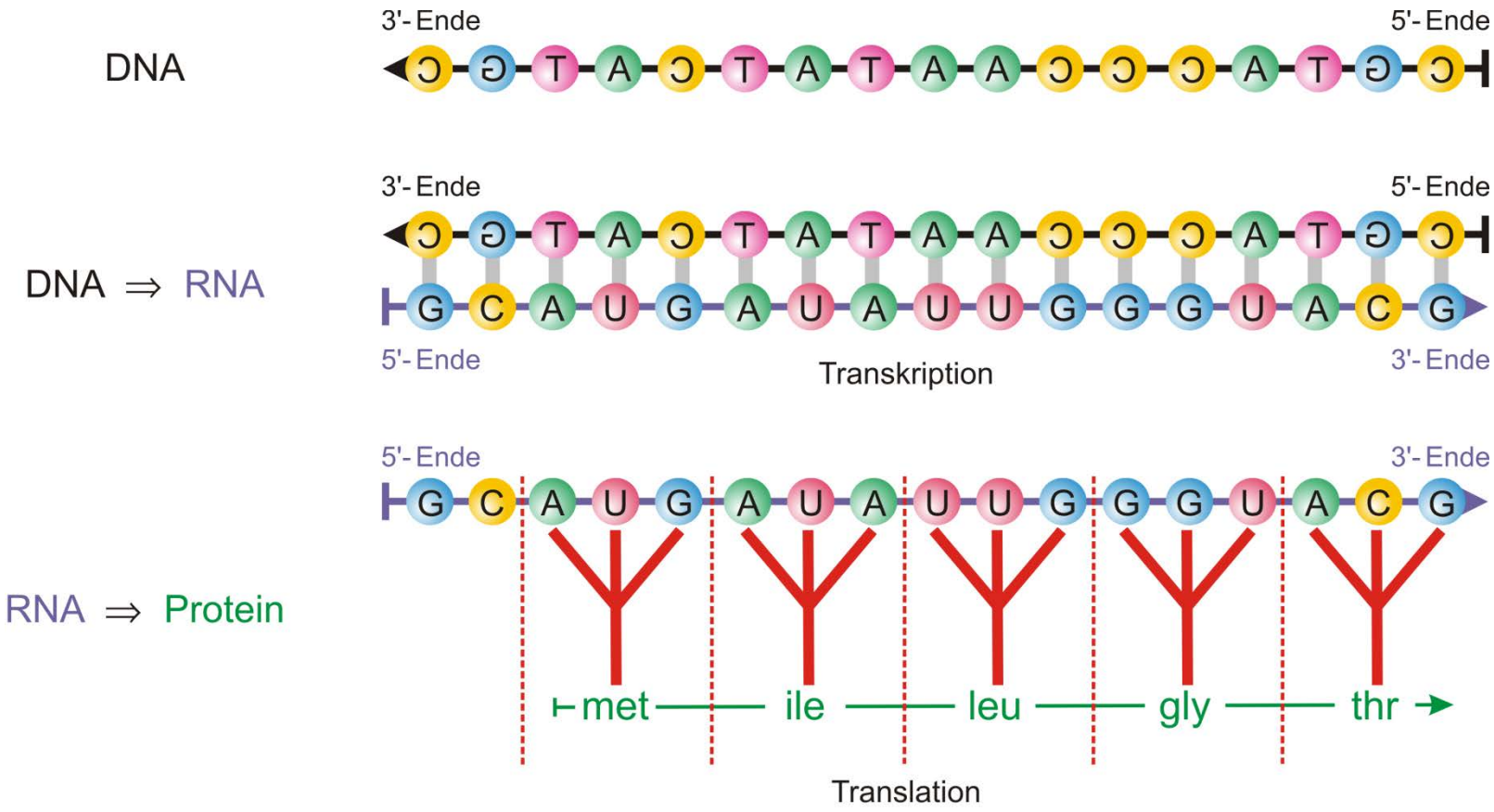


DNA ⇒ RNA

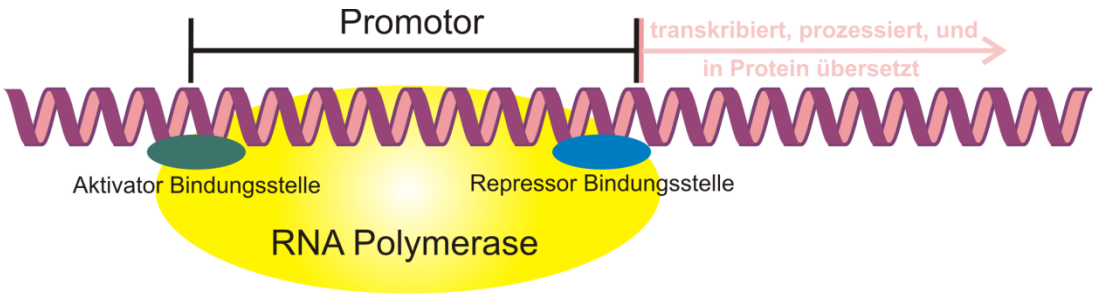


RNA ⇒ Protein

Transkription und Translation

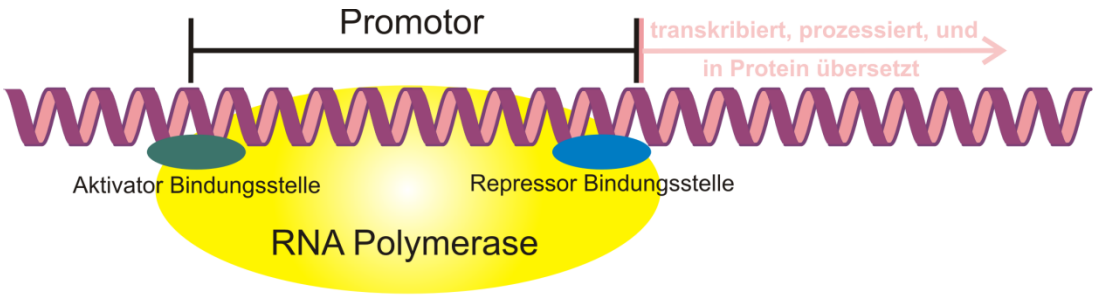


Transkription und Translation



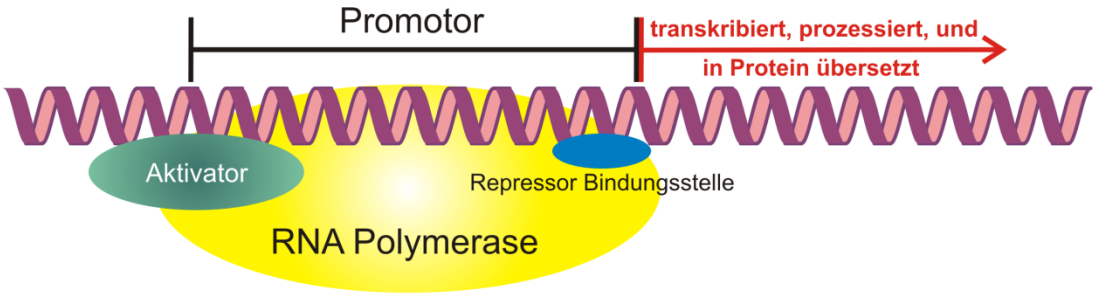
Zustand I:

Grundzustand



Zustand I:

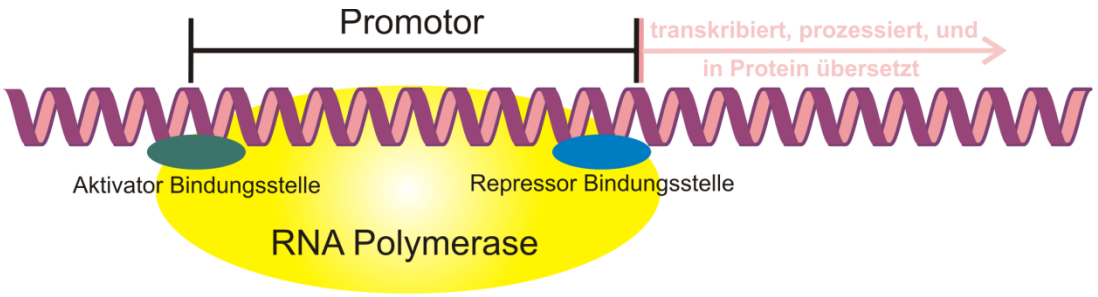
Grundzustand



Zustand II:

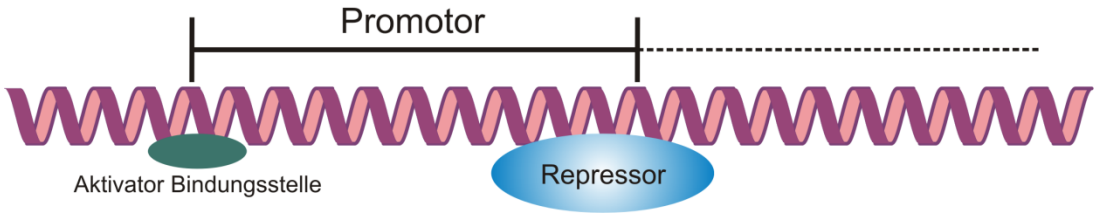
aktiver Zustand

Regulation der Genexpression



Zustand I:

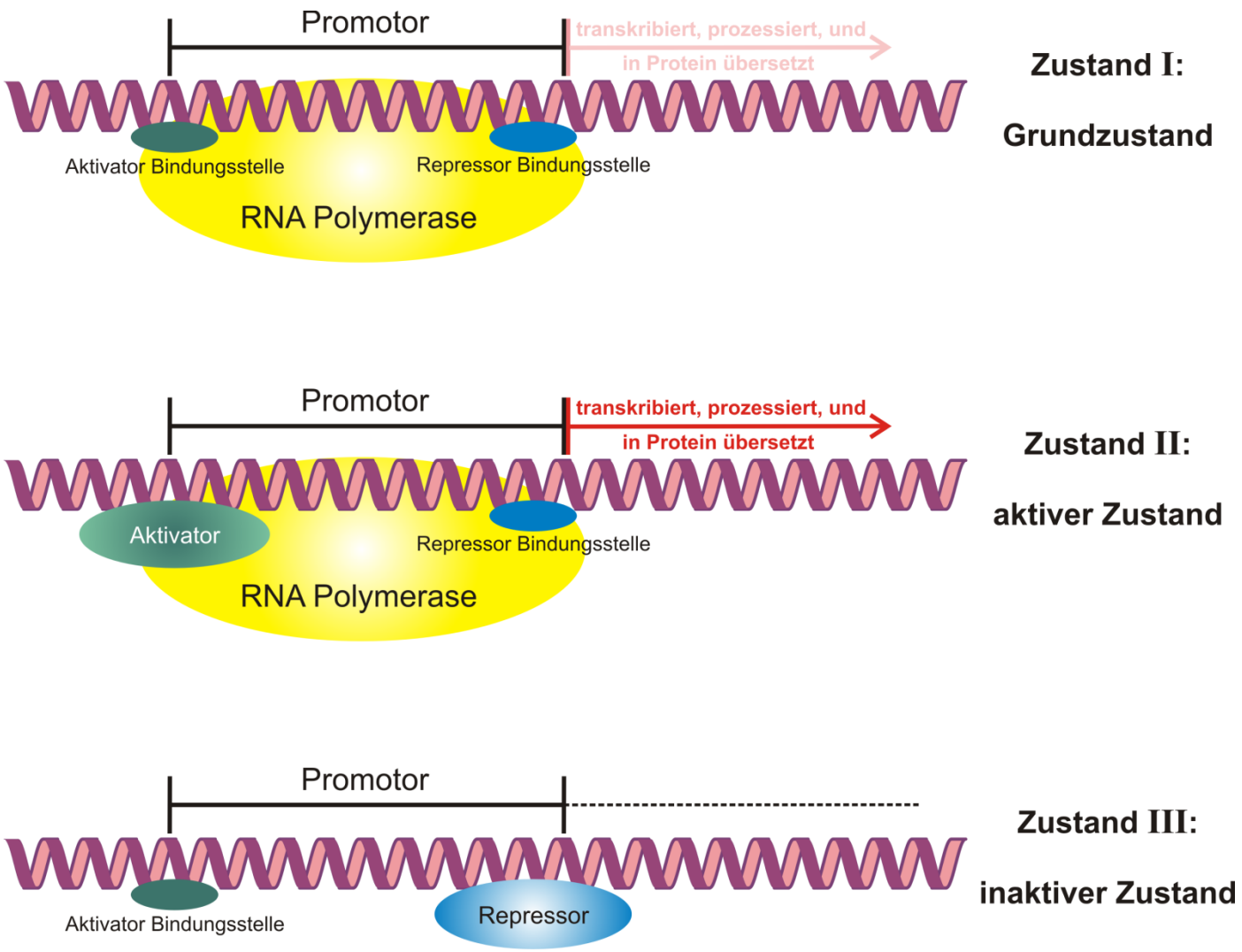
Grundzustand



Zustand III:

inaktiver Zustand

Regulation der Genexpression



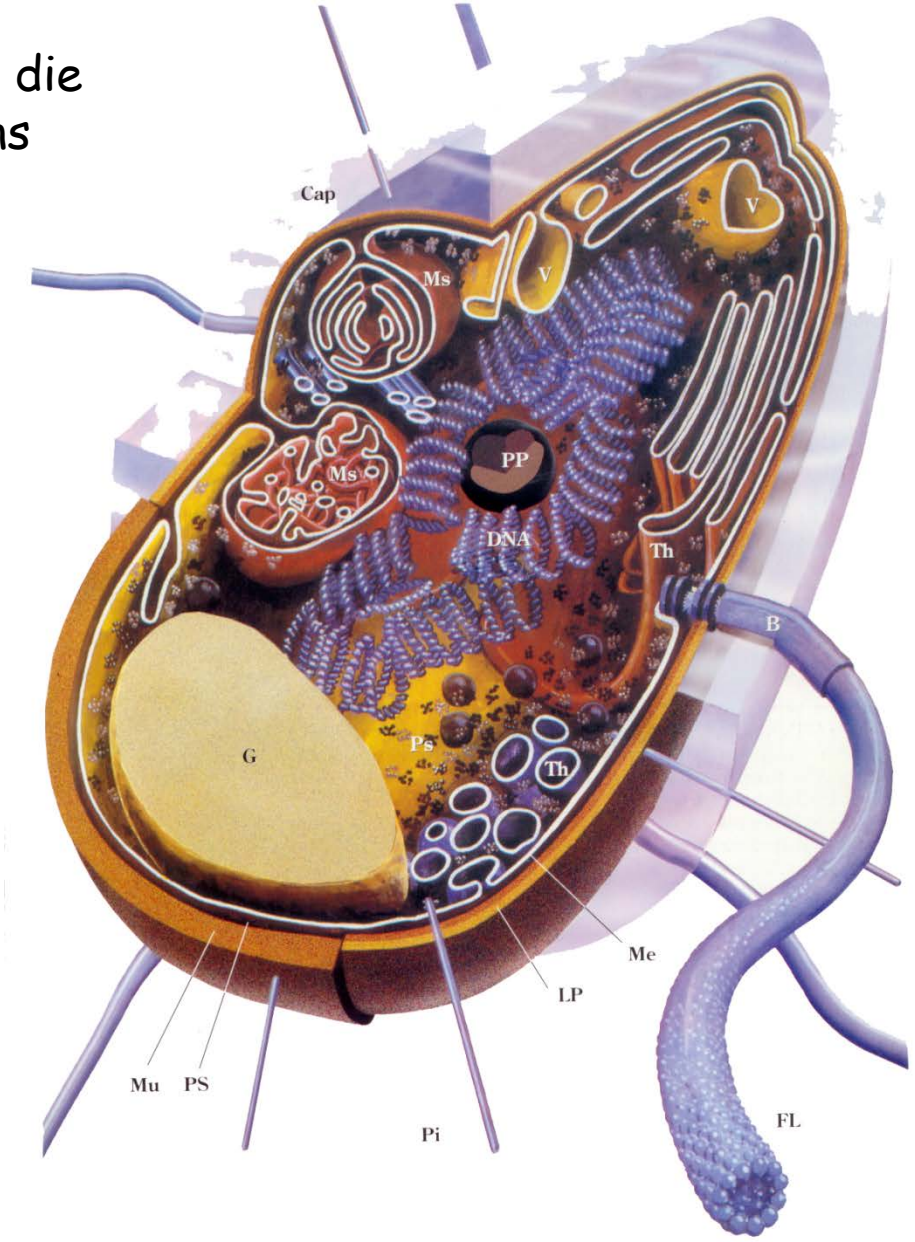
Regulation der Genexpression

Die Bakterienzelle als Beispiel für die einfachste Form autonomen Lebens

Das Escherichia coli Genom:

4 Millionen Nukleotide

4460 Gene



Die räumliche Struktur des Bakteriums *Escherichia coli*

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Die drei notwendigen Voraussetzungen für Darwinsche Evolution sind:

1. **Vermehrung,**
2. **Variation**, und
3. **Selektion**.

Alle drei Vorausetzungen werden nicht nur von zellulären Organismen erfüllt sondern auch von **Nukleinsäuremolekülen** – **DNA** oder **RNA** – **in** geeigneten **zellfreien Experimentalanordnungen**:

Darwinsche Evolution im Reagenzglas

Sol Spiegelman,
1914 - 1983

Evolution im Reagenzglas:

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

DOI: 10.1002/anie.200701369

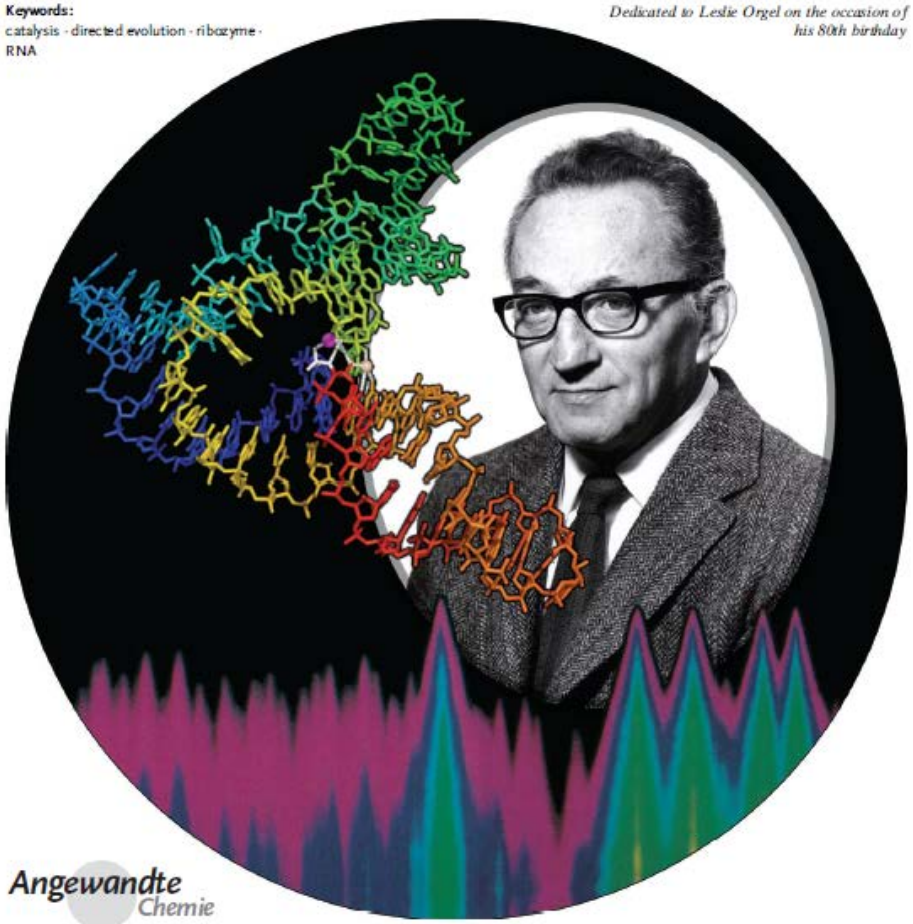
Molecular Evolution

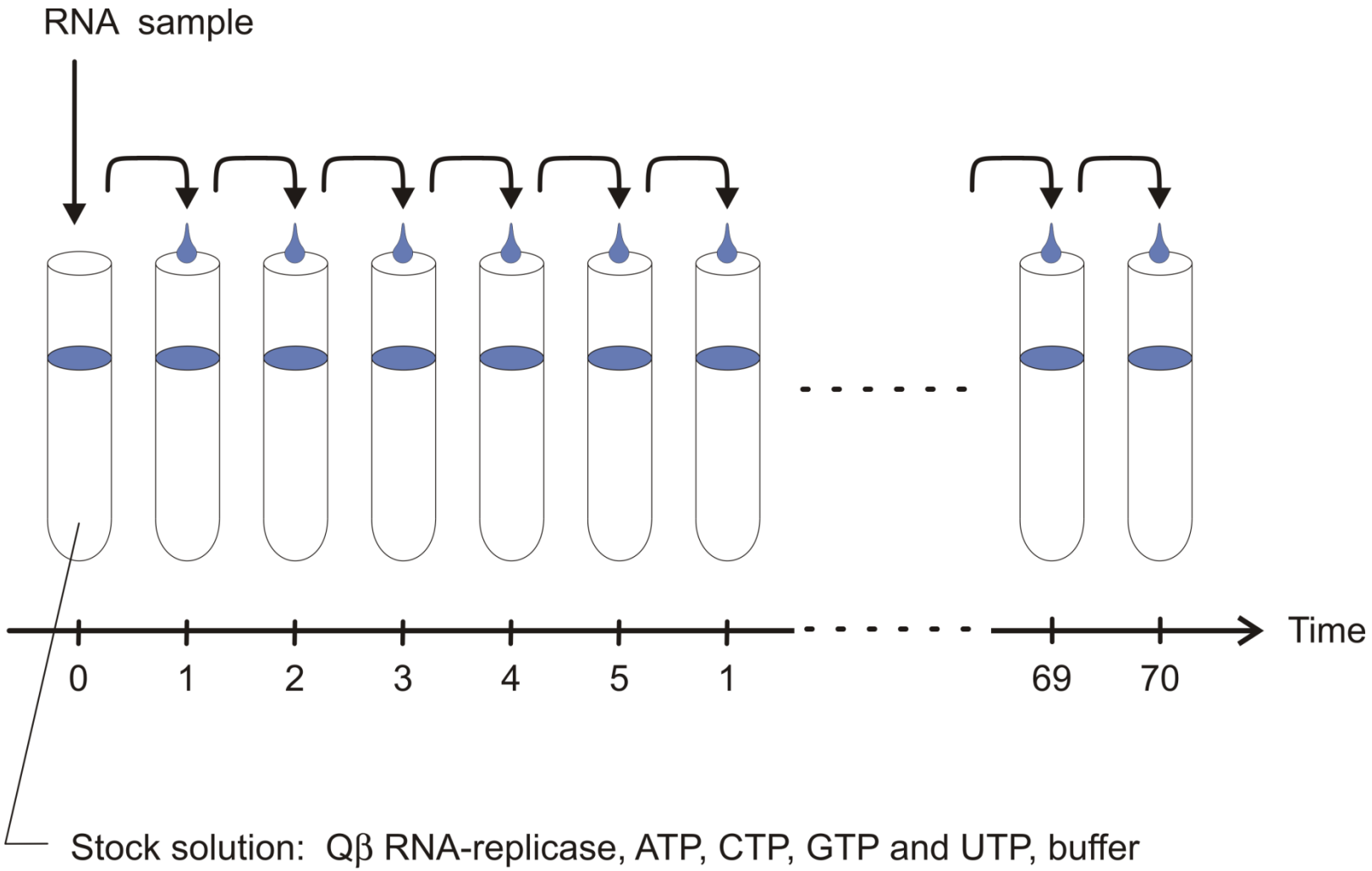
Forty Years of In Vitro Evolution**

*Gerald F. Joyce**

Keywords:
catalysis · directed evolution · ribozyme · RNA

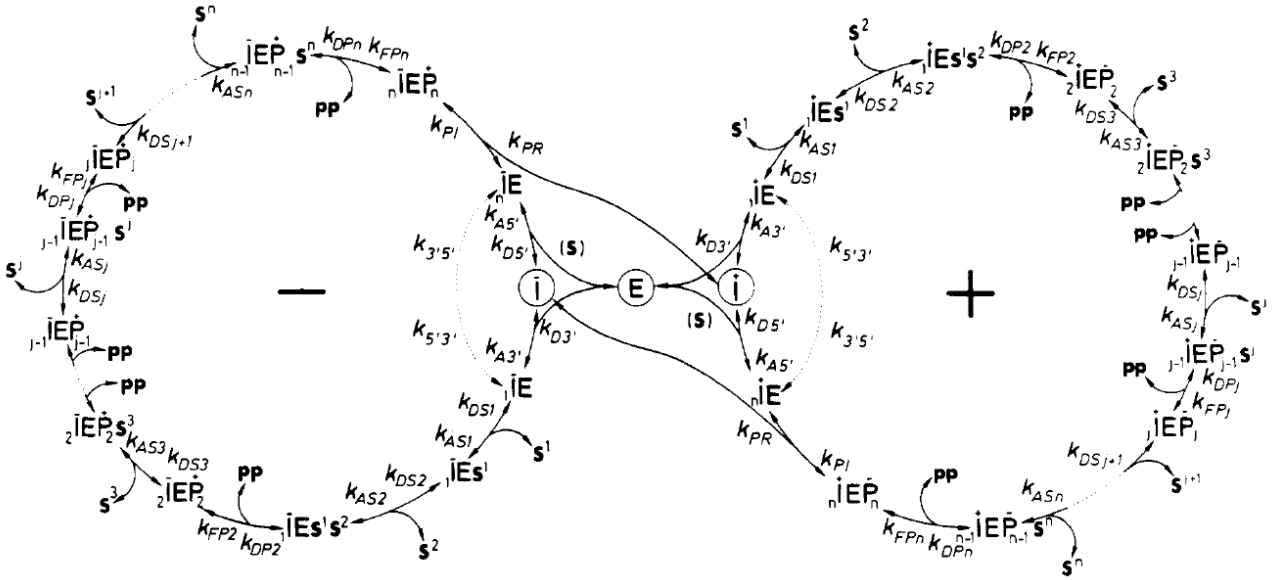
Dedicated to Leslie Orgel on the occasion of his 80th birthday





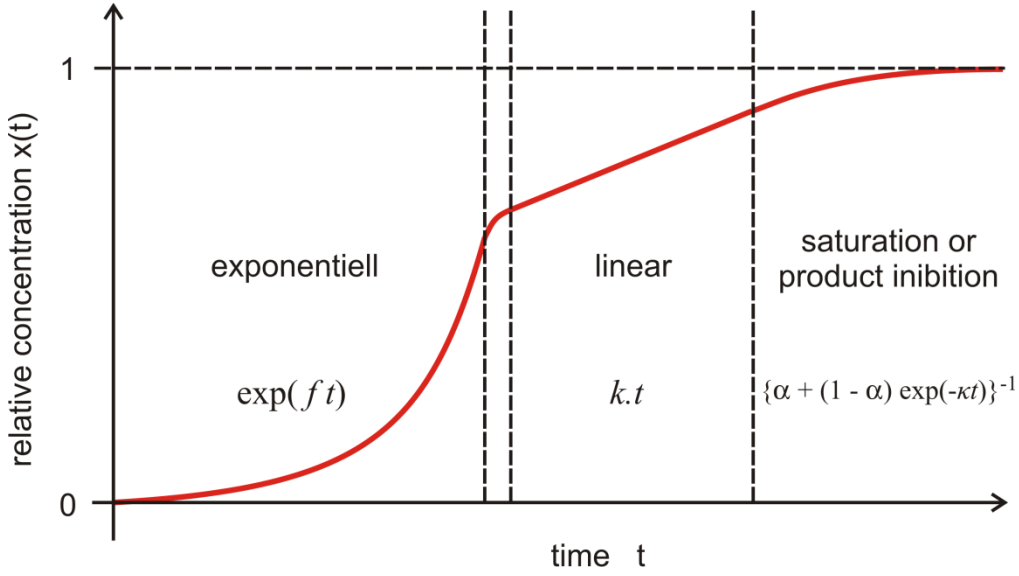
Anwendung der Technik des seriellen Transfers zur Evolution von RNA im Reagenzglas

Christof K. Biebricher,
1941-2009



Kinetik der RNA Replikation

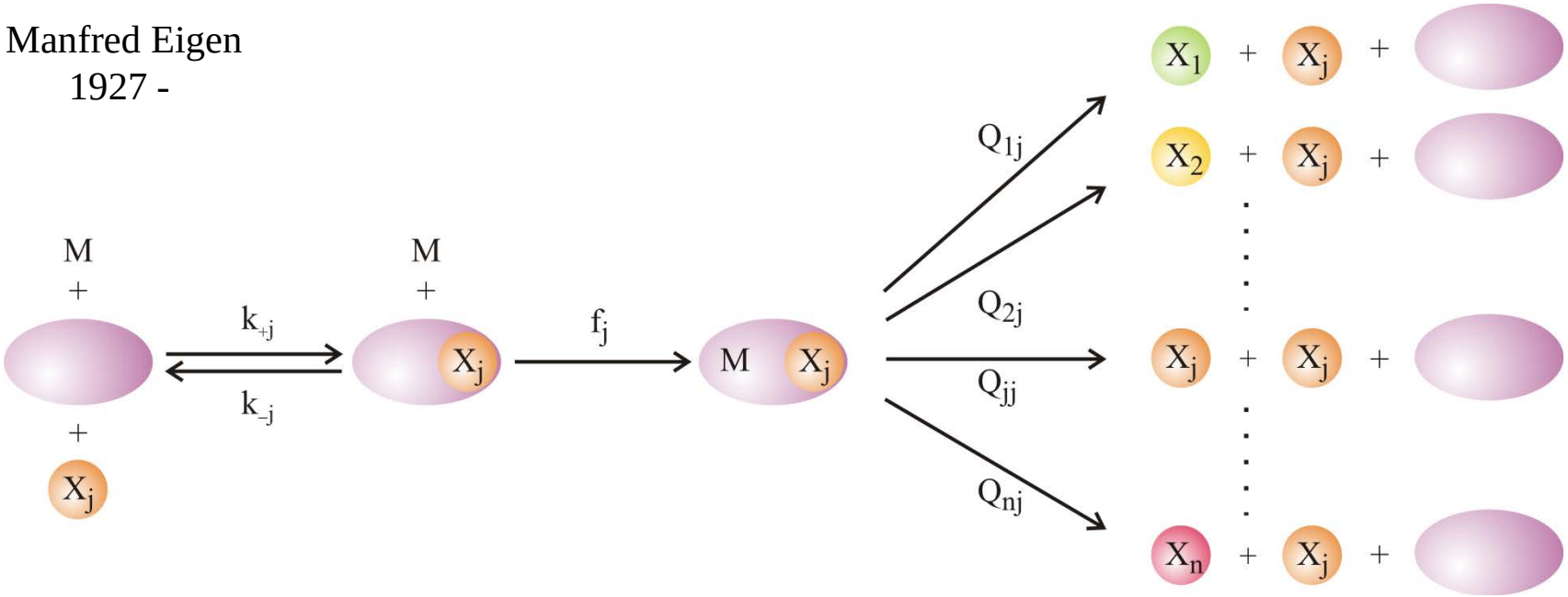
C.K. Biebricher, M. Eigen, W.C. Gardiner, Jr.
Biochemistry **22**:2544-2559, 1983



Manfred Eigen
1927 -

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

$$\Phi = \sum_{i=1}^{n} f_i\, x_i \Big/ \sum_{i=1}^{n} x_i$$



Mutation und (korrekte) Replikation als parallele chemische Reaktionen

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

Ergebnisse der Quasispezies-Theorie:

1. Die Selektion führt zu uneinheitlichen Populationen, die aus einer Anzahl molekularer Varianten bestehen.

2. Die stationäre Population bildet das genetische Reservoir einer sich asexuell vermehrenden Spezies und wird deshalb als Quasispezies bezeichnet.

3. Eine Quasispezies enthält eine fitteste Variante, die sogenannte Mastersequenz und ihre nahe verwandten Mutanten.

4. Jedem Replikationsmechanismus entspricht eine maximale Mutationsrate, die Fehlerschranke, welche nicht überschritten werden kann, ohne dass die Vererbung zusammenbricht.

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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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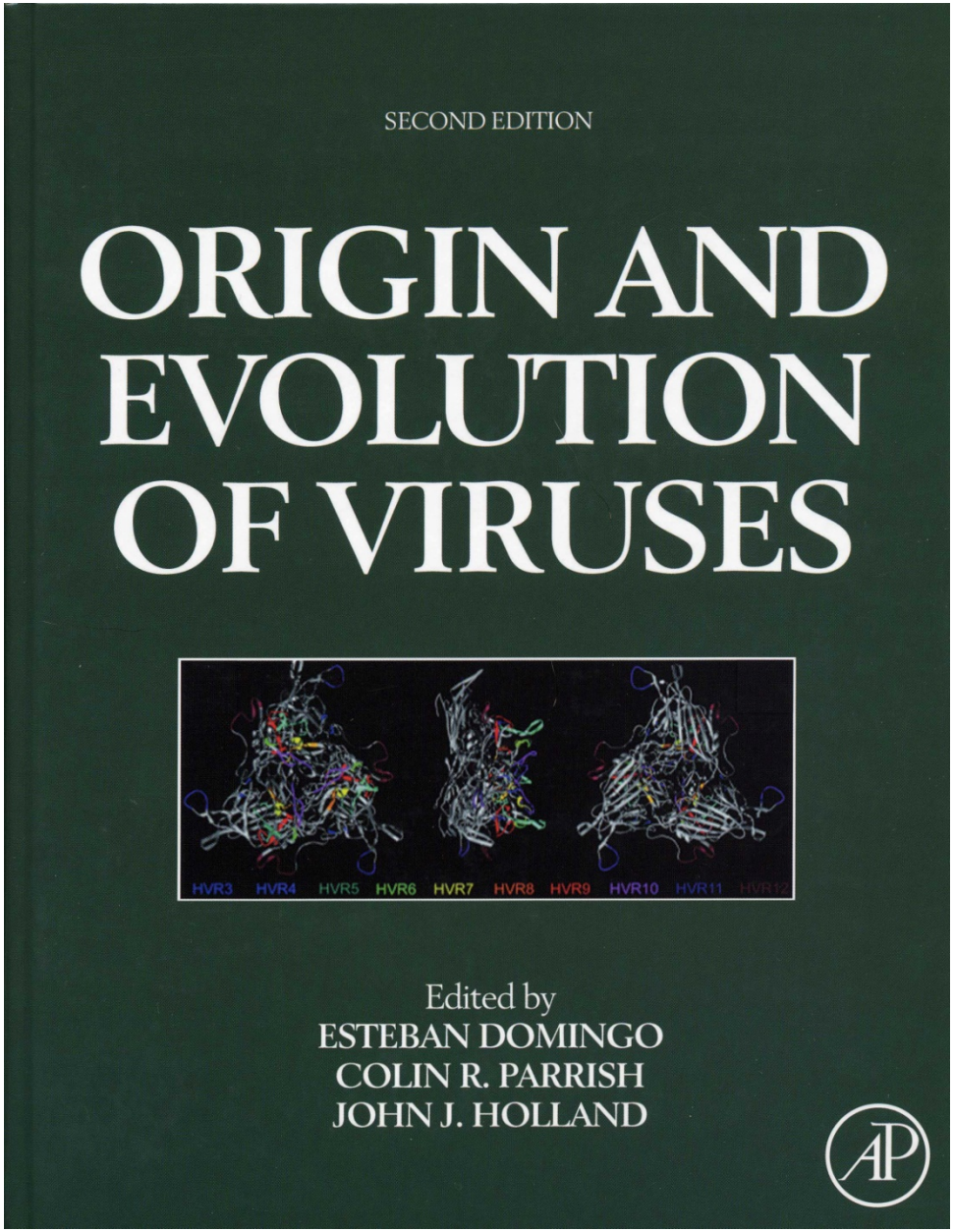
Available online 8 December 2004

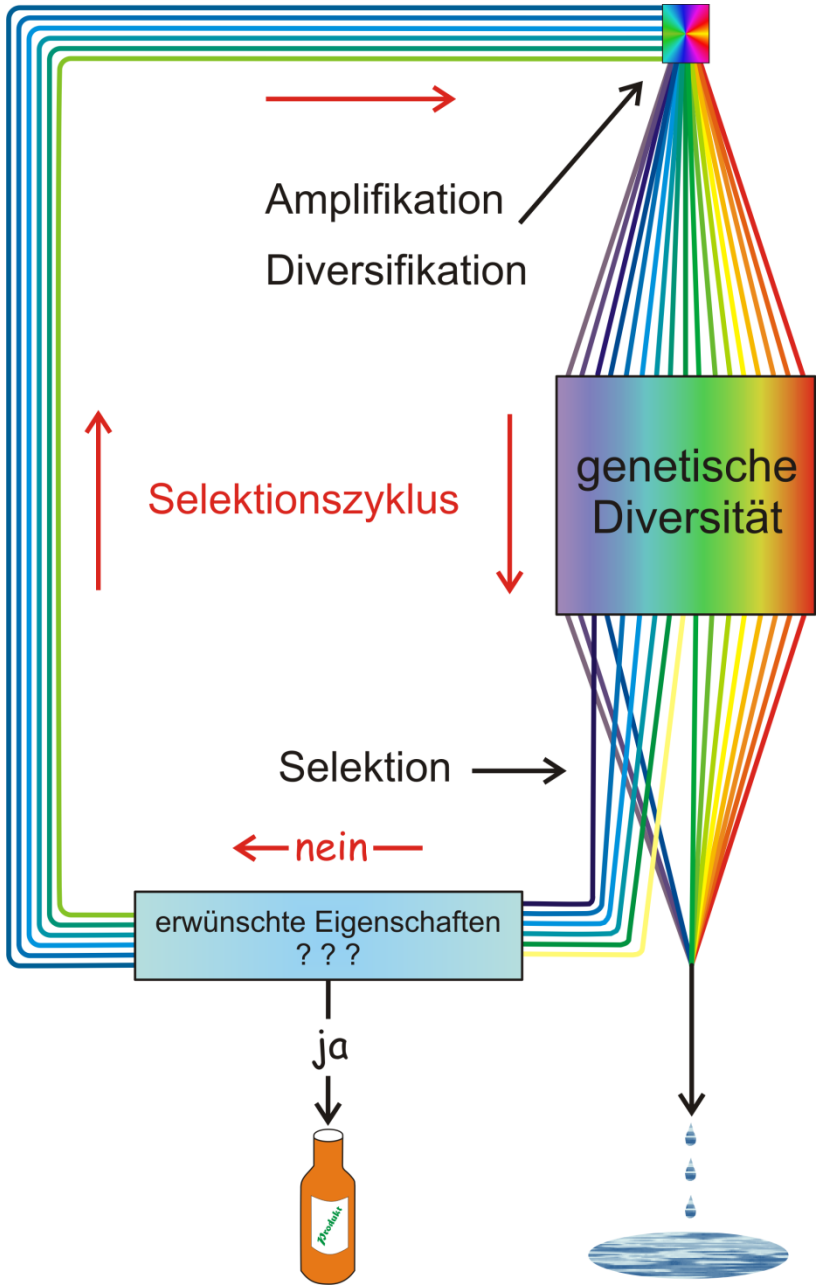
doi:10.1016/j.virusres.2004.11.001

Esteban Domingo
1943 -

Anwendung der Quasispezies-Theorie im Kampf gegen Viren

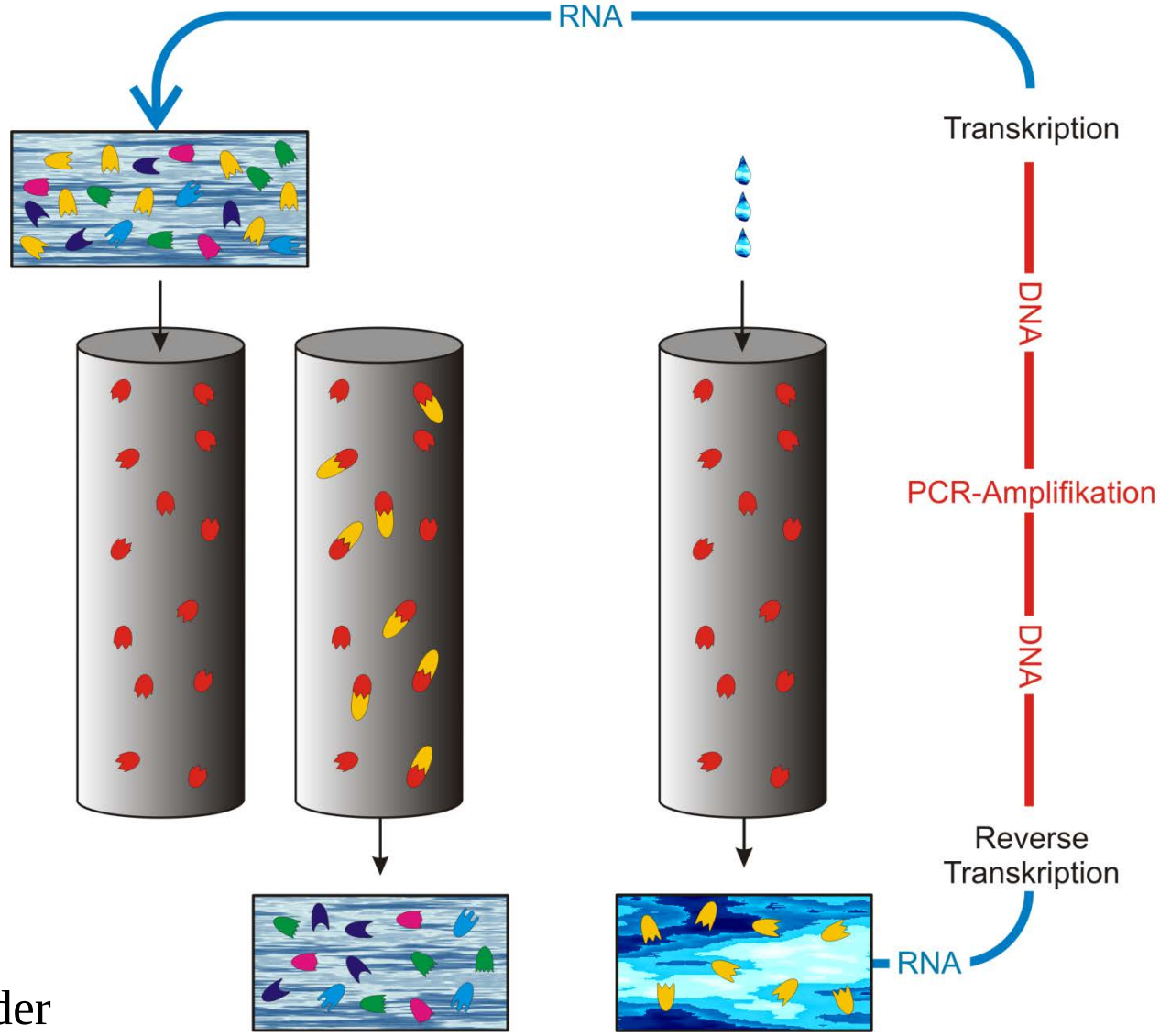


Molekulare Evolution der Viren

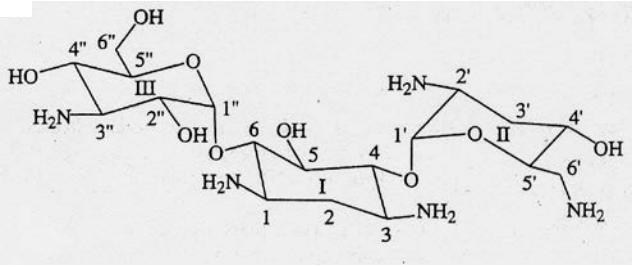


Das Grundprinzip der molekularen Biotechnologie

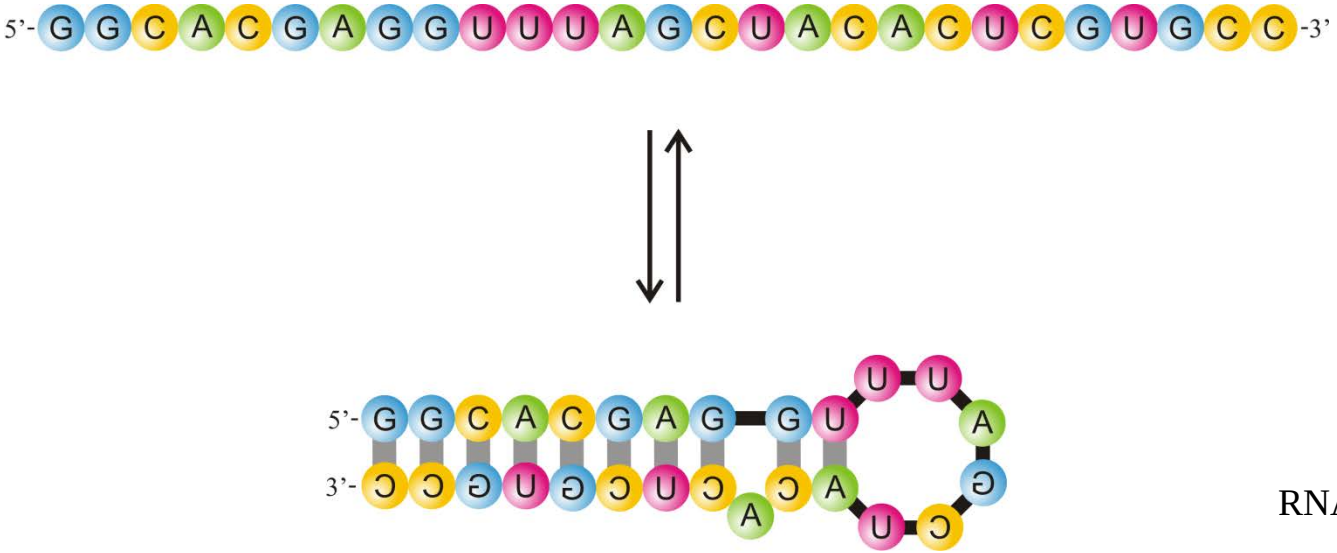
Selection by Exponential Enrichment



Die SELEX-Methode in der Evolutionären Biotechnologie



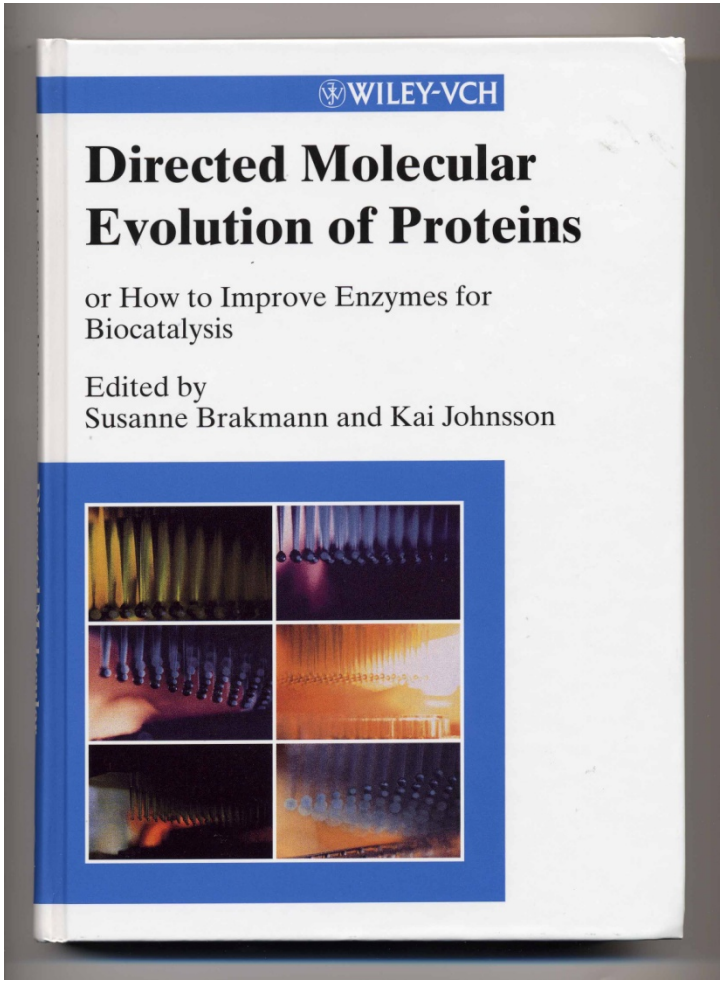
Tobramyzin

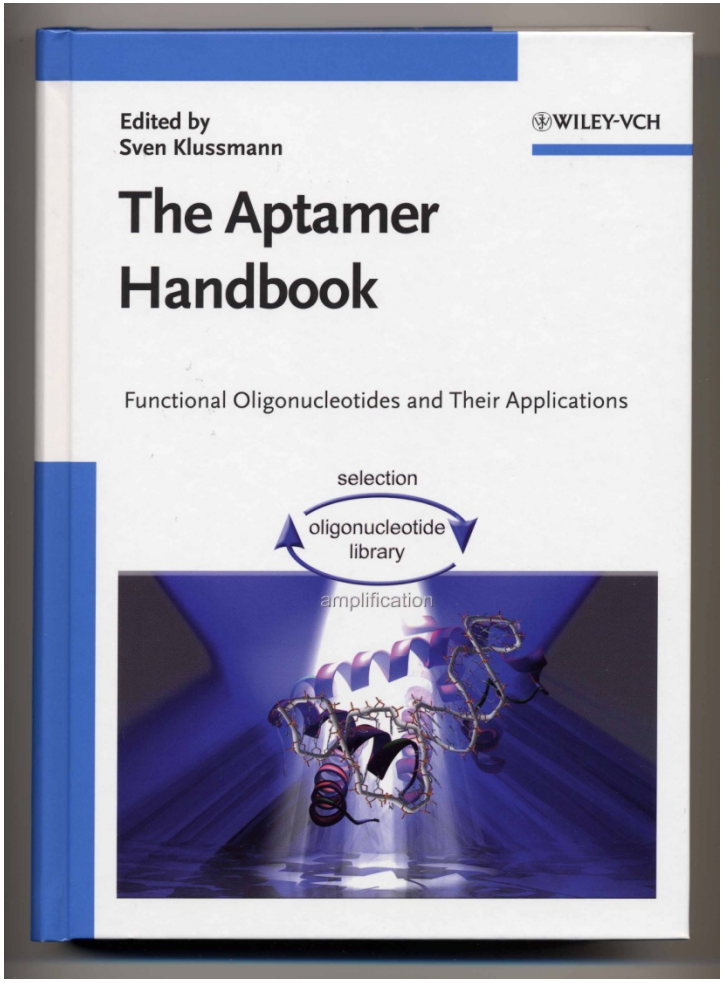


RNA aptamer

Die Struktur eines RNA –Aptameren, das Tobramyzin sehr fest bindet: K_D = 9 nM

L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, ***Saccharide-RNA recognition in an aminoglycoside antibiotic-RNA aptamer complex.*** Chemistry & Biology **4**:35-50 (1997)





Anwendung der molekularen Evolution auf Probleme der Biotechnologie

1. Prolog – Darwin und Mathematik
2. Von Darwin zur Populationsgenetik
3. Frühe Molekularbiologie
4. Evolution in Reagenzglas
5. **Molekularbiologie heute**
6. Biologische Komplexität vor Augen

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.

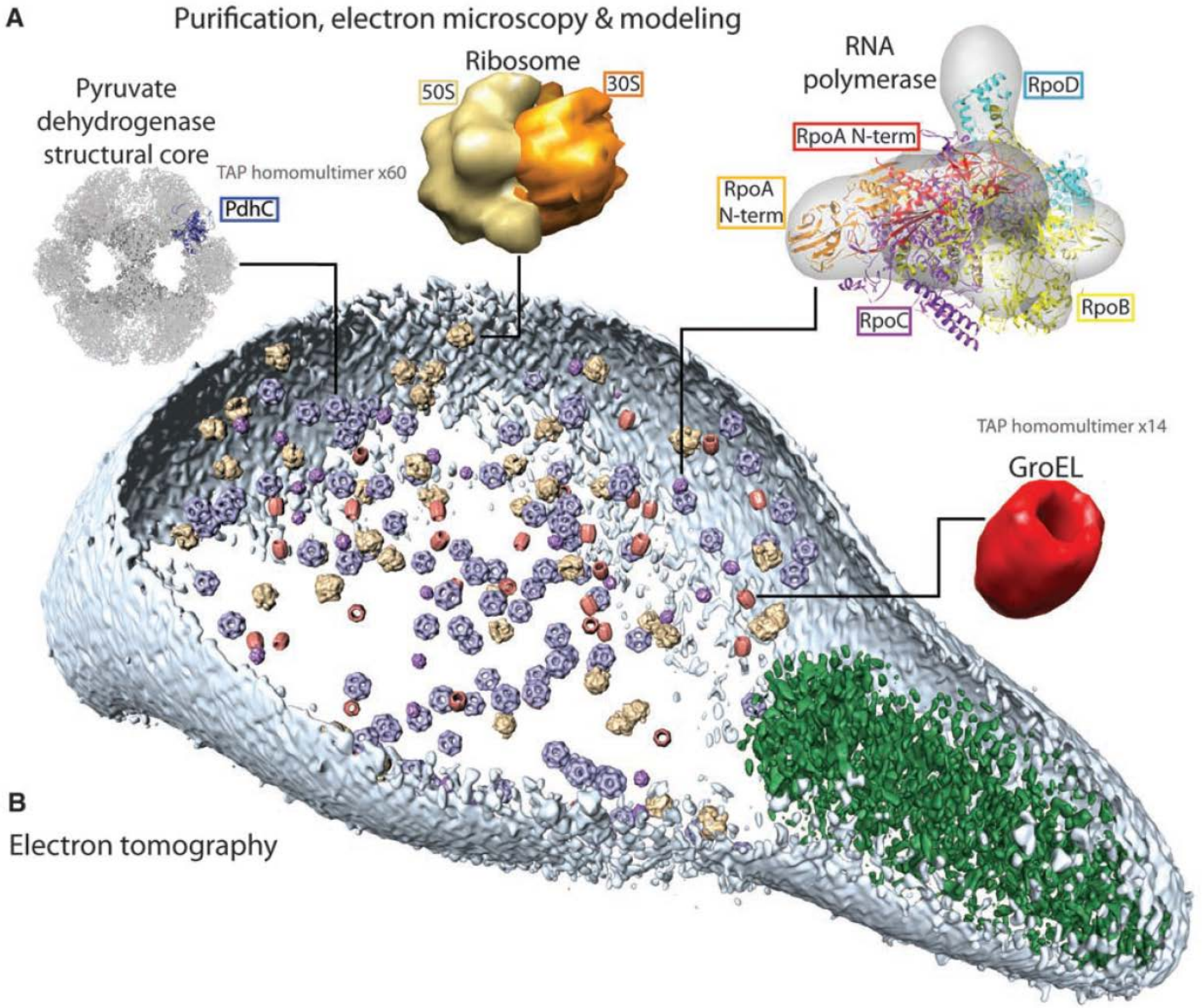
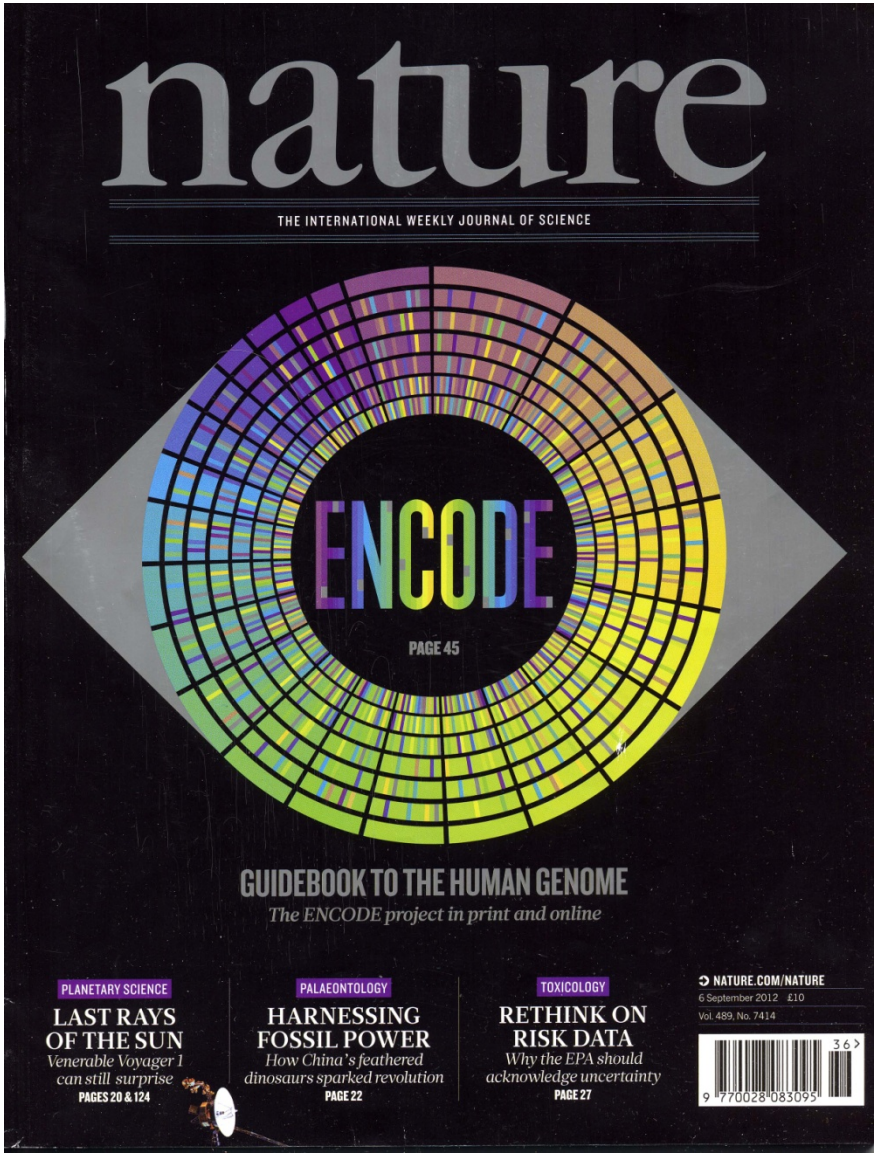


Fig. 4. From proteomics to the cell. By a combination of pattern recognition and classification algorithms, the following TAP-identified complexes from *M. pneumoniae*, matching to existing electron microscopy and x-ray and tomogram structures (**A**), were placed in a whole-cell tomogram (**B**): the 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

Evolution im Licht der gegenwärtigen Molekulargenetik

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

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

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

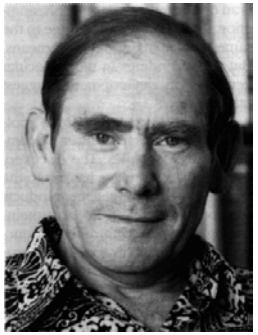
4. Komplexität, Robustheit und Plastizität der Organismen wird erst im Zusammenspiel von Genetik und Epigenetik verstehbar.

Vorteile der molekularen Erforschung des Lebens

1. Komplexe Reproduktionsmechanismen sind erklärbar.

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

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



Sydney Brenner, 1927 -

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

1. Prolog – Darwin und Mathematik
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4. Evolution in Reagenzglas
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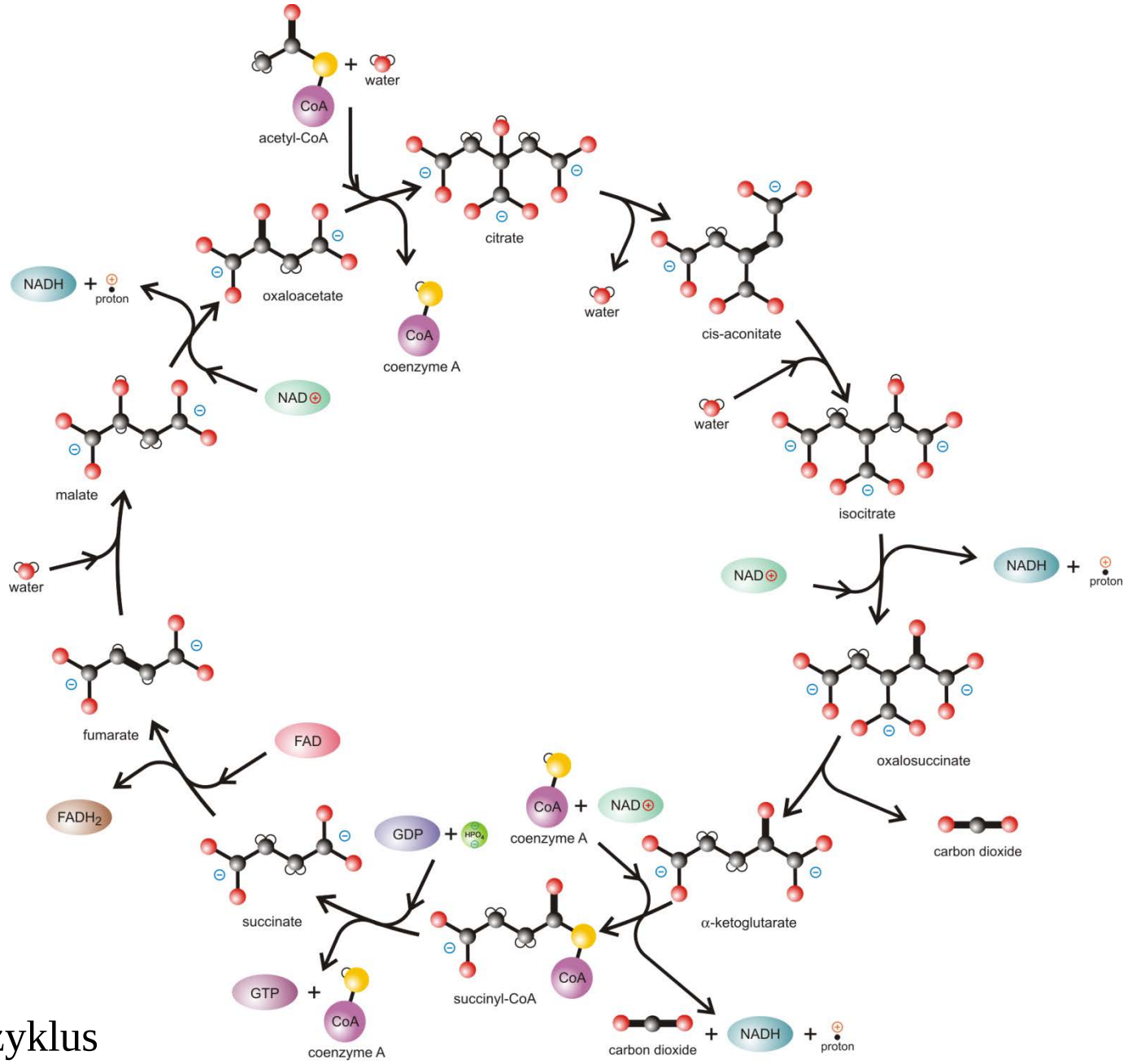
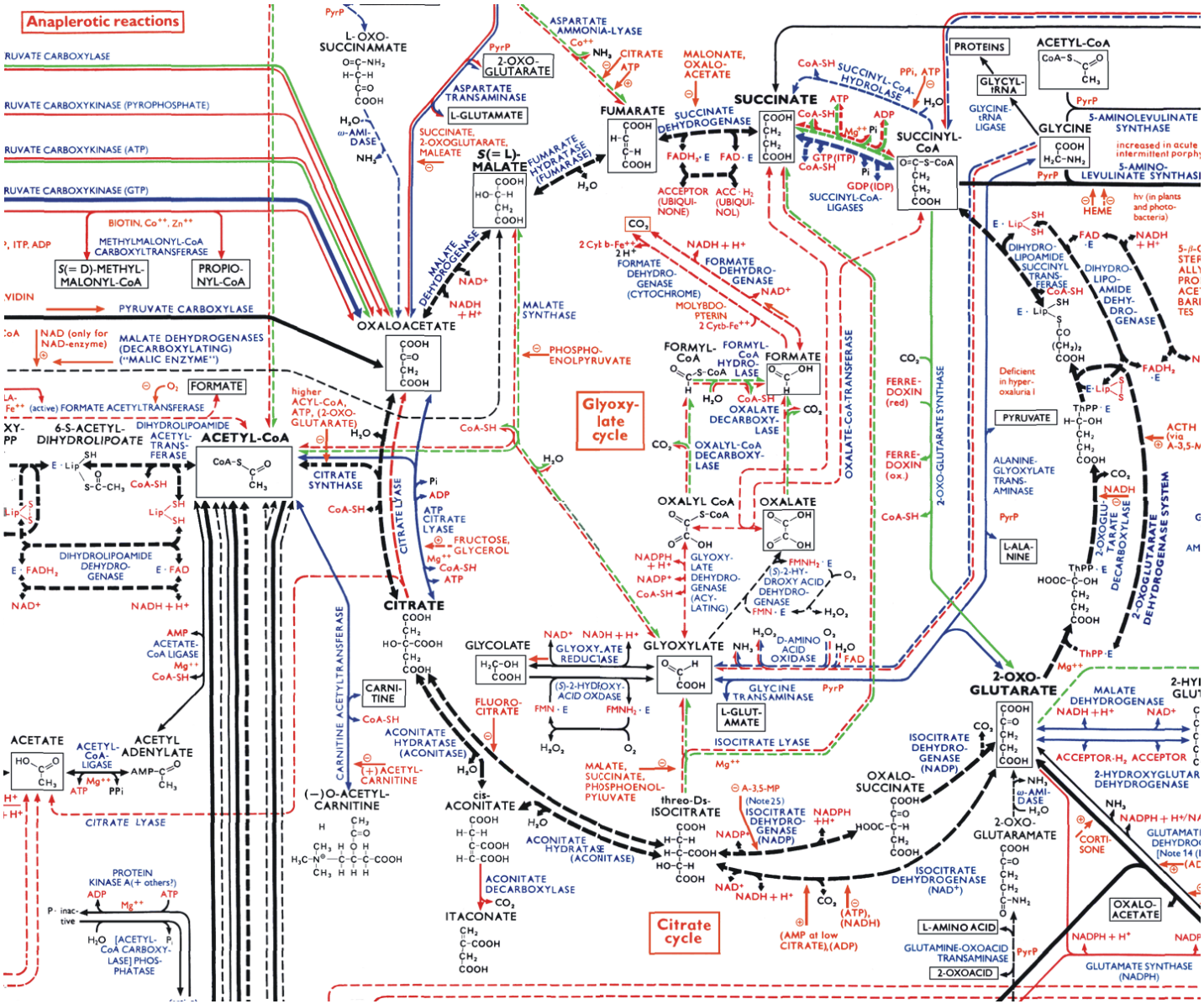
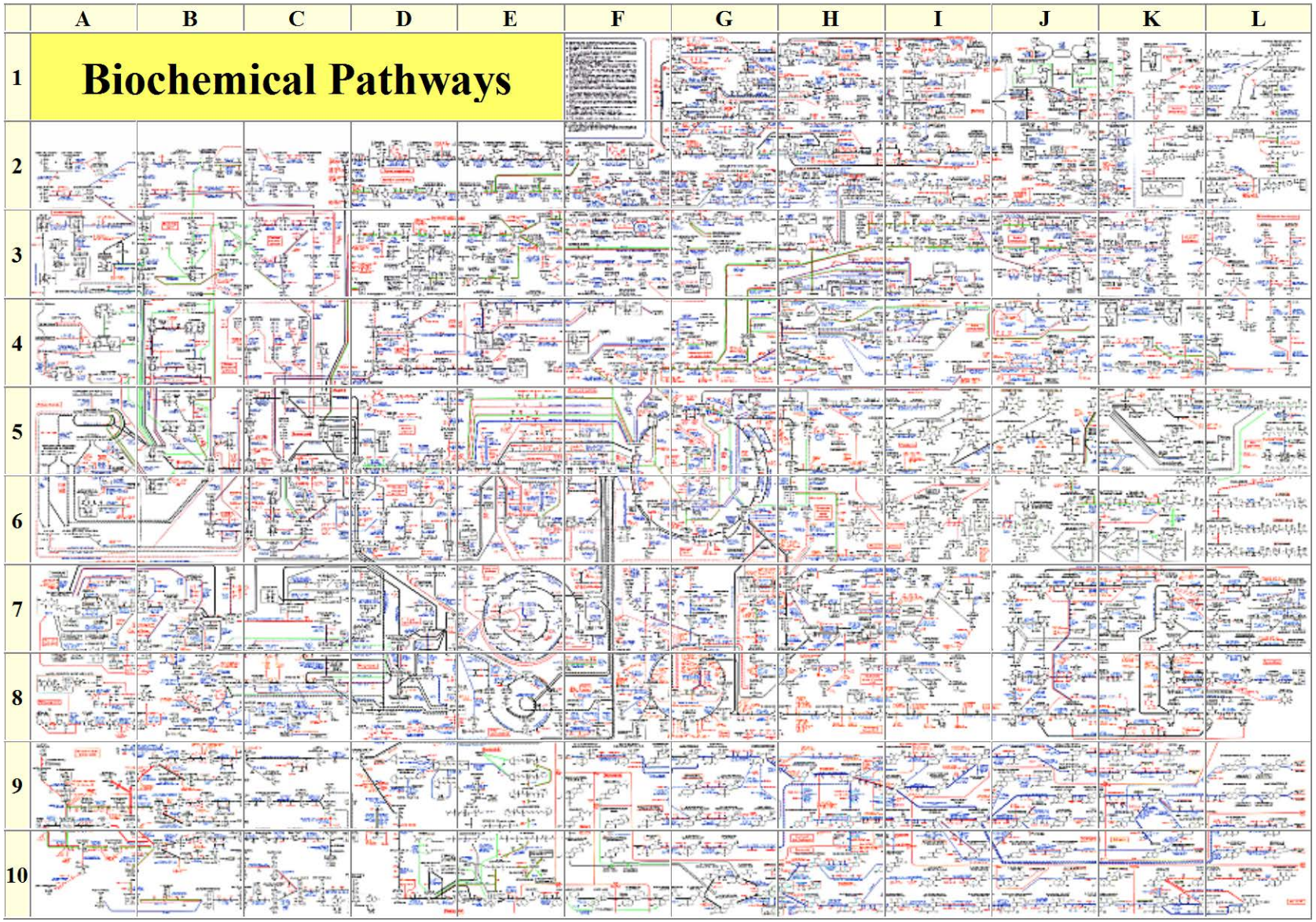
6. **Biologische Komplexität vor Augen**



Der Zitronensäurezyklus

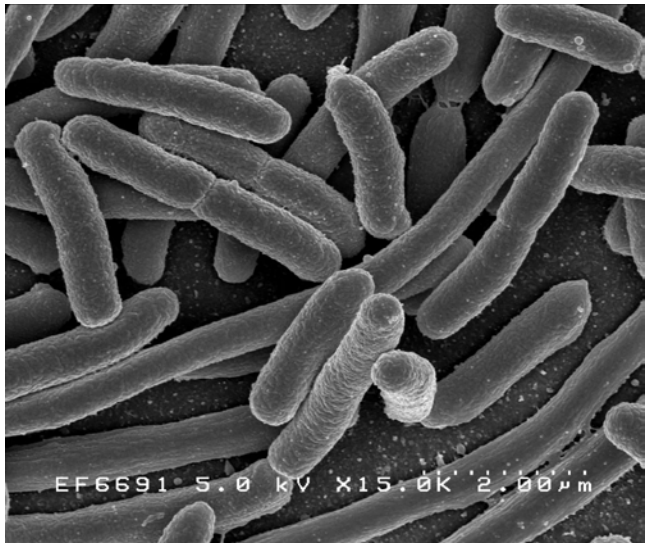

Anaplerotic reactions
PYRUVATE CARBOXYLASE
PYRUVATE CARBOXYKINASE (PYROPHOSPHATE)
PYRUVATE CARBOXYKINASE (ATP)
PYRUVATE CARBOXYKINASE (GTP)
BIOTIN, Co++, Zn++
METHYLMALONYL-CoA CARBOXYLTRANSFERASE
S(= D)-METHYL-MALONYL-CoA
PROPIO-NYL-CoA
PYRUVATE CARBOXYLASE
NAD (only for NAD-enzyme)
MALATE DEHYDROGENASES (DECARBOXYLATING) ("MALIC ENZYME")
FORMATE
(active) FORMATE ACETYLTRANSFERASE
6-S-ACETYL-DIHYDROLIPOATE
ACETYL-TRANS-FERASE
ACETYL-CoA
DIHYDROLIPOAMIDE DEHYDRO-GENASE
L-OXO-SUCCINAMATE
ω-AMI-DASE
2-OXO-GLUTARATE
ASPARTATE TRANSAMINASE
L-GLUTAMATE
ASPARTATE AMMONIA-LYASE
Co++
SUCCINATE, 2-OXOGLUTARATE, MALEATE
S(= L)-MALATE
FUMARATE HYDRATASE (FUMARASE)
FUMARATE
SUCCINATE DEHYDROGENASE
FADH2 · E
FAD · E
ACCEPTOR (UBIQUI-NONE)
ACC · H2 (UBIQUI-NOL)
SUCCINATE
SUCCINYL-CoA-HYDROLASE
SUCCINYL-CoA
GTP(ITP)
GDP(IDP)
SUCCINYL-CoA-LIGASES
MALONATE, OXALO-ACETATE
MALATE DEHYDROGENASE
NAD+
NADH + H+
OXALOACETATE
MALATE SYNTHASE
CO2
2 Cyt b-Fe++ 2 H+
FORMATE DEHYDRO-GENASE (CYTOCHROME)
MOLYBDO-PTERIN 2 Cyt-Fe++
FORMATE DEHYDRO-GENASE
PHOSPHO-ENOLPYRUVATE
FORMYL-CoA
FORMYL-CoA HYDRO-LASE
FORMATE
OXALATE DECARBOXY-LASE
OXALYL-CoA DECARBOXY-LASE
Glyoxy-late cycle
OXALATE-CoA-TRANSFERASE
2-OXOGLUTARATE SYNTHASE
FERRE-DOXIN (red)
FERRE-DOXIN (ox.)
PROTEINS
GLYCYL-tRNA
GLYCINE-tRNA LIGASE
GLYCINE
ACETYL-CoA
5-AMINOLEVULINATE SYNTHASE
5-AMINO-LEVULINATE SYNTHASE
increased in acute intermittent porphy
HEME
hν (in plants and photo-bacteria)
DIHYDRO-LIPOAMIDE SUCCINYL TRANS-FERASE
DIHYDRO-LIPO-AMIDE DEHY-DRO-GENASE
Deficient in hyper-oxaluria I
PYRUVATE
ALANINE-GLYOXYLATE TRANS-AMINASE
L-ALA-NINE
ACTH (via A-3,5-N
2-OXOGLU-TARATE DECARBOXYLASE
2-OXOGLUTARATE DEHYDROGENASE SYSTEM
higher ACYL-CoA, ATP, (2-OXO-GLUTARATE)
CITRATE SYNTHASE
CITRATE LYASE
ATP CITRATE LYASE
FRUCTOSE, GLYCEROL
CITRATE
OXALYL CoA
OXALATE
GLYOXY-LATE DEHYDRO-GENASE (ACY-LATING)
(S)-2-HY-DROXY ACID DEHYDRO-GENASE
GLYCOLATE
GLYOXY-ATE REDUCTASE
GLYOXYLATE
D-AMINO ACID OXIDASE
GLYCINE TRANSAMINASE
L-GLUT-AMATE
2-OXO-GLUTARATE
MALATE DEHYDROGENASE
2-HYDROXYGLUTAR DEHYDROGENASE
ACCEPTOR-H2 ACCEPTOR
ISOCITRATE DEHYDRO-GENASE (NADP)
ISOCITRATE LYASE
FLUORO-CITRATE
CARNI-TINE
CARNITINE ACETYLTRANSFERASE
(+)ACETYL-CARNITINE
(−)O-ACETYL-CARNITINE
ACONITATE HYDRATASE (ACONITASE)
cis-ACONITATE
threo-Ds-ISOCITRATE
MALATE, SUCCINATE, PHOSPHOENOL-PYLUVATE
A-3,5-MP
(Note 25)
ISOCITRATE DEHYDRO-GENASE (NADP)
OXALO-SUCCINATE
2-OXO-GLUTARAMATE
ISOCITRATE DEHYDROGENASE (NAD+)
(AMP at low CITRATE), (ADP)
(ATP), (NADH)
Citrate cycle
L-AMINO ACID
GLUTAMINE-OXOACID TRANSAMINASE
2-OXOACID
OXALO-ACETATE
GLUTAMATE SYNTHASE (NADPH)
ACETATE
ACETYL-CoA-LIGASE
ACETYL ADENYLATE
AMP-ACETATE-CoA LIGASE
CITRATE LYASE
PROTEIN KINASE A(+ others?)
P-inac-tive
[ACETYL-CoA CARBOXY-LASE] PHOS-PHATASE
ITACONATE
ACONITATE DECARBOXYLASE
CORTI-SONE



Das Reaktionsnetzwerk des zellulären Stoffwechsels nach Boehringer-Mannheim

E. coli:	Genomlänge	4×10^6 Nukleotide
	Zahl der Zelltypen	1
	Zahl der Gene	4 460

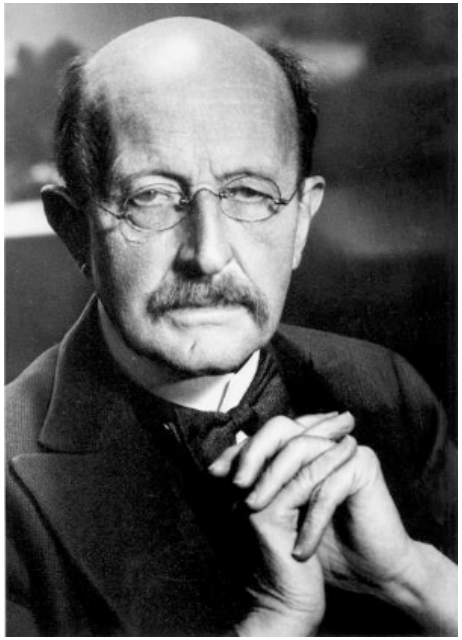
Vier Bücher zu je 300 Seiten



Man:	Genomlänge	3×10^9 nucleotides
	Zahl der Zelltypen	200
	Zahl der Gene	≈ 20 000

Eine Bibliothek mit 3000 Bänden zu je 300 Seiten

Die Komplexität der Biologie



Max Planck, 1859 - 1947

„Anwendung ohne Wissen ist gefährlich."

Coworkers

Universität Wien

Peter Stadler, **Bärbel M. Stadler**, Universität Leipzig, GE

Jord Nagel, **Kees Pleij**, Universiteit Leiden, NL

Walter Fontana, Harvard Medical School, MA

Martin Nowak, Harvard University, MA

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Kurt Grünberger, Michael Kospach , **Andreas Wernitznig**, **Stefanie Widder,**
Stefan Wuchty, **Jan Cupal**, **Stefan Bernhart**, **Ulrike Langhammer**,
Ulrike Mückstein, Universität Wien, AT

Danke für die Aufmerksamkeit!

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