From Schrödinger‘s „What is Life?“ to „All Life is Chemistry“

Peter Schuster

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

75 Years „What is Life?

Erwin Schrödinger Institute, 18.11.2019

Web-Page for further information:

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

1. Schrödinger's "What is Life?" and its reception
2. Structures of biological macromolecules
3. What is different in chemistry and biology?
4. Bridging from chemistry to biology

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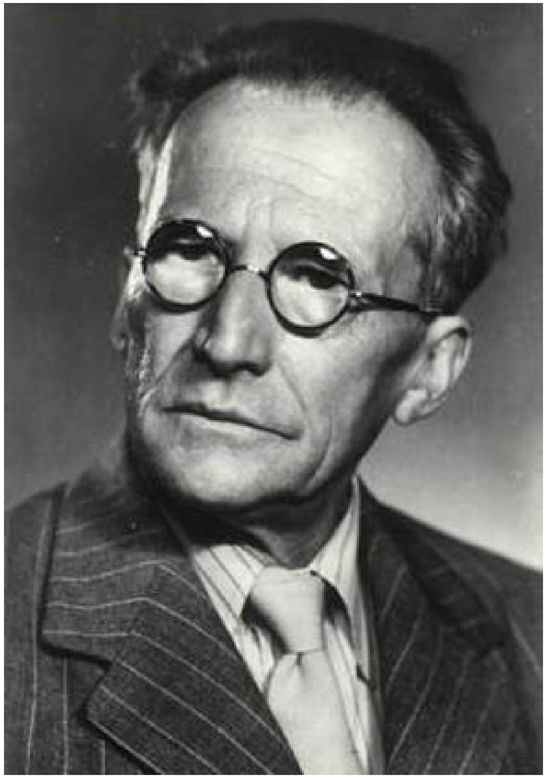
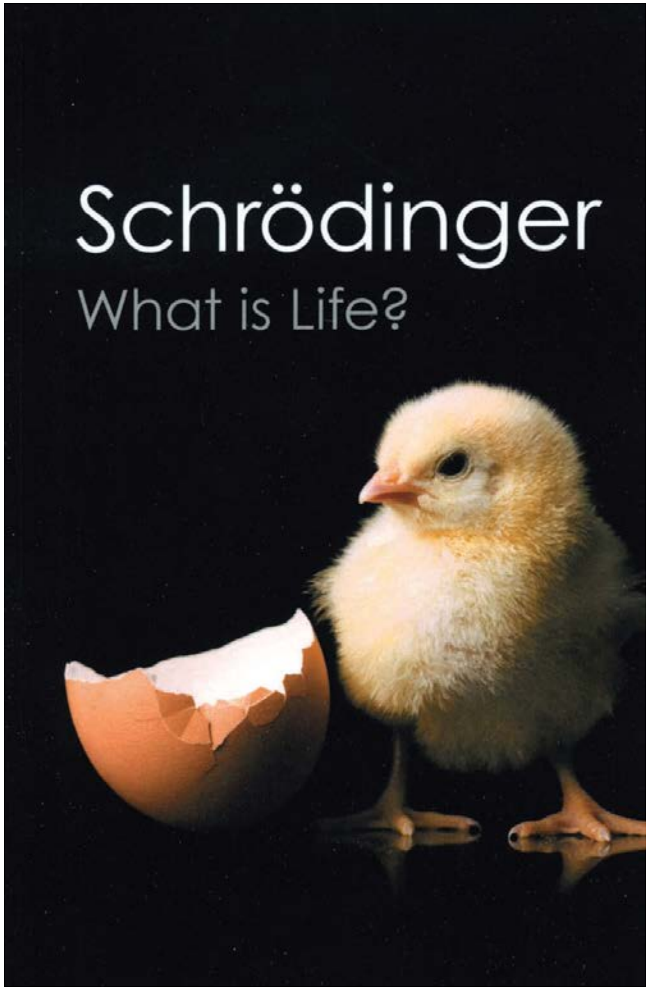


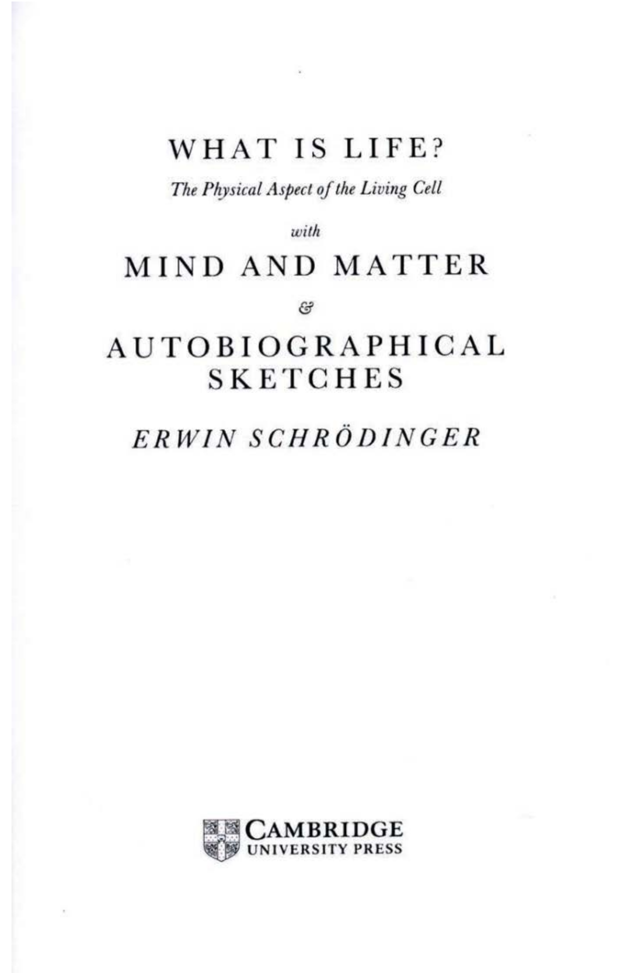
Erwin Schrödinger, 1887 – 1961

What is Life? The Physical Aspect of the Living Cell.

Erwin Schrödinger. Cambridge University Press, Cambridge, UK 1944

Based on lectures delivered under the auspiciis of the *Dublin Institute for Advanced Studies* at *Trinity College*, Dublin in February 1943.




WHAT IS LIFE?

The Physical Aspect of the Living Cell

with

MIND AND MATTER

&

AUTOBIOGRAPHICAL SKETCHES

ERWIN SCHRÖDINGER

CAMBRIDGE UNIVERSITY PRESS

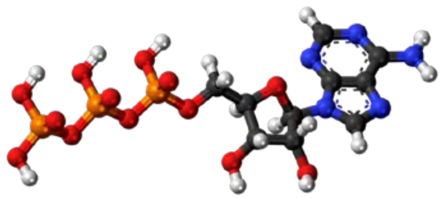
First printed 1992, 23rd printing 2018.

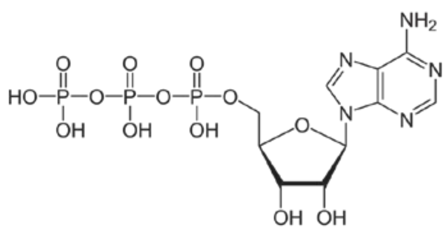
First published 1944, reprinted 1945, 1948, 1951, 1955, 1962.

… The development of molecular biology has resulted almost entirely from the introduction of the new ideas into chemistry that were stimulated by quantum mechanics. … Schrödinger, by formulating his wave equation, is basicly responsible for modern biology.

To what extent, aside from the discovery of the Schrödinger equation, did Schrödinger contribute to modern biology, to our understanding of the nature of life? It is my opinion that he did not make any contribution whatever, or that perhaps, by his discussion of „**negative entropy**" in relation to life, he made a negative contribution.

Linus Pauling. *Schrödinger's contribution to chemistry and biology*.
In: C.W. Kilmister. *Schrödinger. Centenary celebration of a polymath*. Cambridge University Press, New York 1987, pp.228 – 229.





adenosine triphosphate (ATP)

$$ATP + H_2O \leftrightarrow ADP + P_i$$

equilibrium concentrations: ΔG^0 = - 40 to -30 kJ/mol

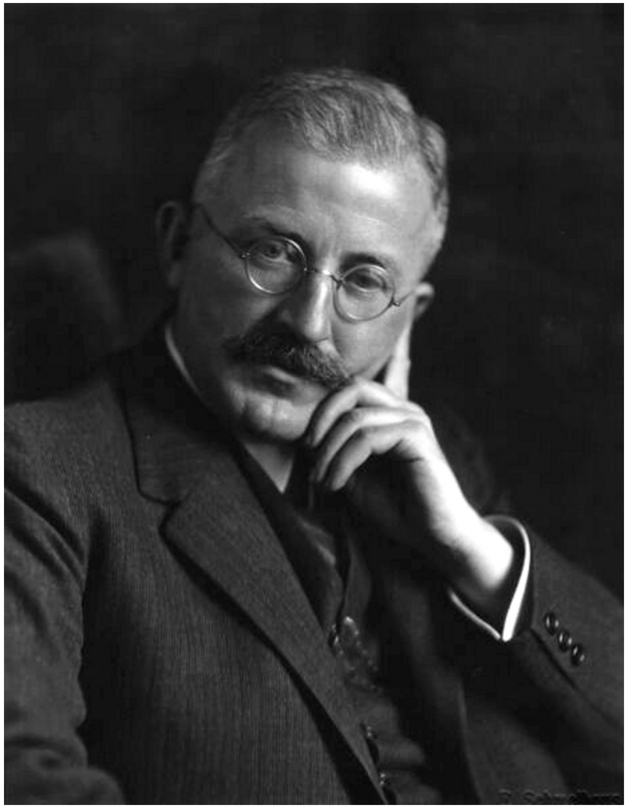
physiological conc.: $\Delta G = \Delta G^0 + RT \ln Q$ = -70 to -50 kJ/mol

R. Milo, R.Phillips. Cell biology by the numbers. Garland Science, Taylor & Francis. New York 2016.

conditions: T = 20°C, pH = 8.0, pMg = 2.5, I = 0.08 M

ΔG^0 = **-31.3** kJ/mol, ΔH^0 = **-28.1** kJ/mol, $-T\Delta S^0$ = **-3.2** kJ/mol or ΔS^0 = 11 J/(K·mol)

O. Pänke, B. Rumberg. Energy and entropy balance of ATP synthesis. BBA 1322: 183-194, 1997.



Hermann Staudinger, 1881 – 1865

H. Staudinger, J. Fritschi. Über Isopren und Kautschuk, 5.Mitt. Über die Hydrierung des Kautschuks und über seine Konstitution.
Helvetica Chimica Acta 5(5): 785-806, **1922**

Kautschuk = rubber
Rubber is polyisopren, a polymeric macromolecule

Nobel Prize for Chemistry 1953

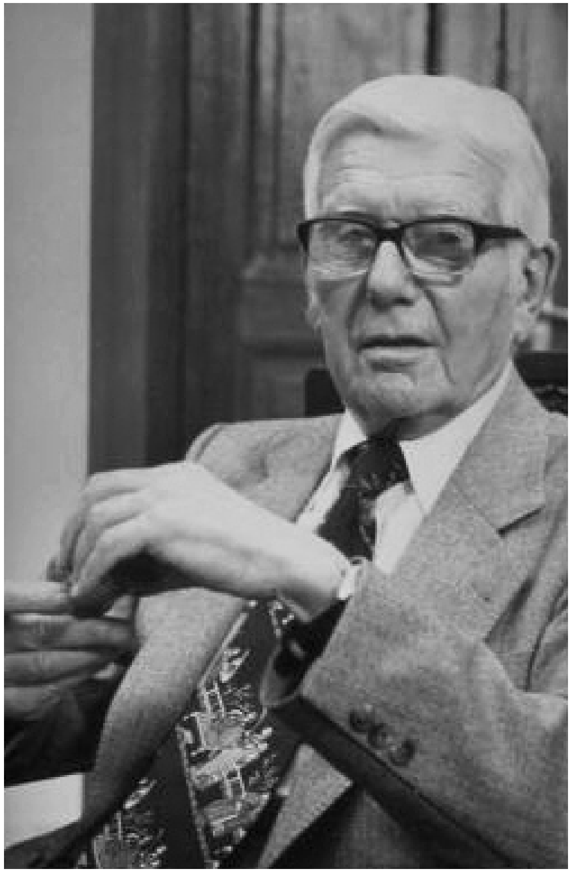
Hermann Mark was one of the founders of polymer science.
He was professor of phsical chemistry at the University of Vienna 1933 – 1938.
He founded 1944 the Institute of Polymer Research at the Polytechnic Institute of New York in Brooklyn.

Hermann Mark has never lost relations to Austria. Immediately after World War II he reactivated his contacts and contributed substantially to the build-up of companies in the Austrian chemical industry.

He presented the very popular ten partsTV-production

„All Life is Chemistry“

written 1978 by the Austrian author and historian Hellmut Andics and produced by Austrian television.



Hermann Franz Mark, 1895 – 1992

… I have come to call this „Schrödinger's fundamental error":

> „The chromosome structures are at the same time instrumental in bringing about the development they foreshadow. They are code law and executive power, or to use another simile, they are the architect and the builder's craft in one." Schrödinger, p.20.

… And that is wrong ! The chromosomes contain the information to specify the future organism and a description of the means to implement this, but not the means themselves.

In other words: The chromosomes carry the **instructions** to build the cellular machinery with ribosomes, metabolic enzymes, cell membranes, etc., but not the ribosomes, metabolic enzymes, cell mebranes, etc., themselves.

Sydney Brenner. *My Life in Science*. BioMed Central Ltd., New York 2001, pp. 33-34.

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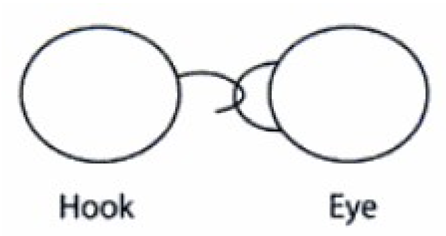
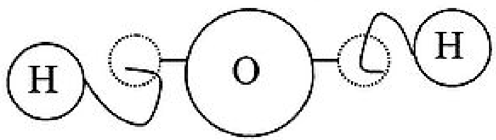
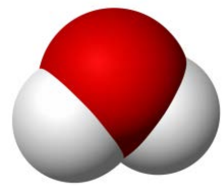
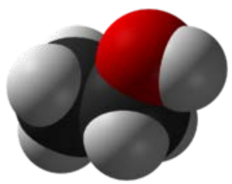
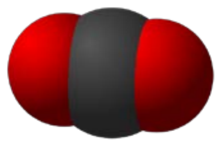
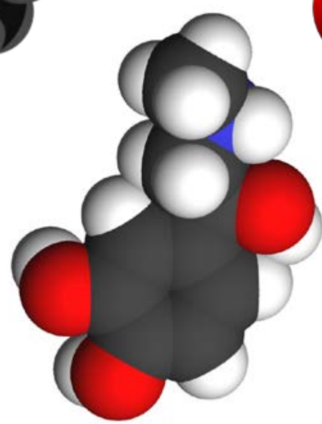


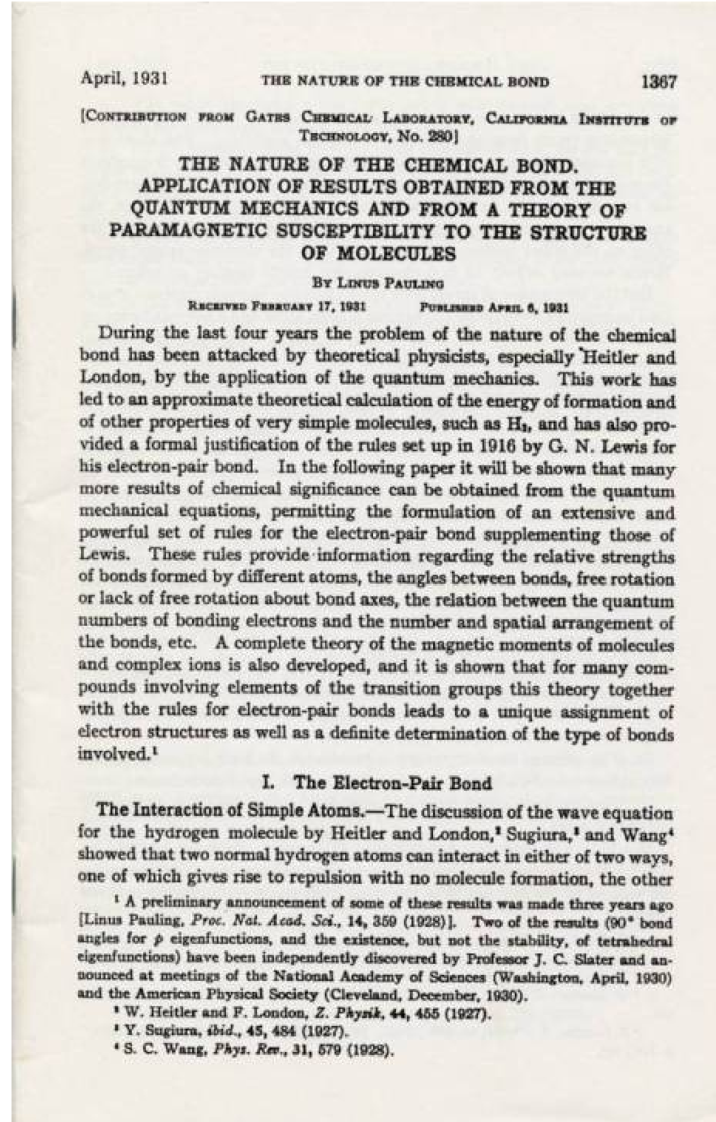












[CONTRIBUTION FROM GATES CHEMICAL LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 280]

THE NATURE OF THE CHEMICAL BOND. APPLICATION OF RESULTS OBTAINED FROM THE QUANTUM MECHANICS AND FROM A THEORY OF PARAMAGNETIC SUSCEPTIBILITY TO THE STRUCTURE OF MOLECULES

BY LINUS PAULING

RECEIVED FEBRUARY 17, 1931 PUBLISHED APRIL 6, 1931

During the last four years the problem of the nature of the chemical bond has been attacked by theoretical physicists, especially Heitler and London, by the application of the quantum mechanics. This work has led to an approximate theoretical calculation of the energy of formation and of other properties of very simple molecules, such as H_2, and has also provided a formal justification of the rules set up in 1916 by G. N. Lewis for his electron-pair bond. In the following paper it will be shown that many more results of chemical significance can be obtained from the quantum mechanical equations, permitting the formulation of an extensive and powerful set of rules for the electron-pair bond supplementing those of Lewis. These rules provide information regarding the relative strengths of bonds formed by different atoms, the angles between bonds, free rotation or lack of free rotation about bond axes, the relation between the quantum numbers of bonding electrons and the number and spatial arrangement of the bonds, etc. A complete theory of the magnetic moments of molecules and complex ions is also developed, and it is shown that for many compounds involving elements of the transition groups this theory together with the rules for electron-pair bonds leads to a unique assignment of electron structures as well as a definite determination of the type of bonds involved.[1]

I. The Electron-Pair Bond

The Interaction of Simple Atoms.—The discussion of the wave equation for the hydrogen molecule by Heitler and London,[2] Sugiura,[3] and Wang[4] showed that two normal hydrogen atoms can interact in either of two ways, one of which gives rise to repulsion with no molecule formation, the other

[1] A preliminary announcement of some of these results was made three years ago [Linus Pauling, *Proc. Nat. Acad. Sci.*, 14, 359 (1928)]. Two of the results (90° bond angles for *p* eigenfunctions, and the existence, but not the stability, of tetrahedral eigenfunctions) have been independently discovered by Professor J. C. Slater and announced at meetings of the National Academy of Sciences (Washington, April, 1930) and the American Physical Society (Cleveland, December, 1930).

[2] W. Heitler and F. London, *Z. Physik*, 44, 455 (1927).

[3] Y. Sugiura, *ibid.*, 45, 484 (1927).

[4] S. C. Wang, *Phys. Rev.*, 31, 579 (1928).

L. Pauling. The nature of the chemical bond. J.Am.Chem.Soc. 53:1367-1400, 1931

The fundamental laws necessary for the mathematical treatment of **a large part of physics and the whole of chemistry** are thus completely known, and the difficulty lies only in the fact that application of these laws leads to equations that are too complex to be solved.

Paul A.M. Dirac. *Quantum mechanics of many-electron systems*. Proceedings of the Royal Society A 123, 714-733 (1929)

There is no doubt that the Schrödinger equation provides the theoretical basis of chemistry.

Linus Pauling. *Schrödinger's contribution to chemistry and biology*. In: C.W. Kilmister. *Schrödinger. Centenary celebration of a polymath*. Cambridge University Press, New York 1987, pp.228 – 229.

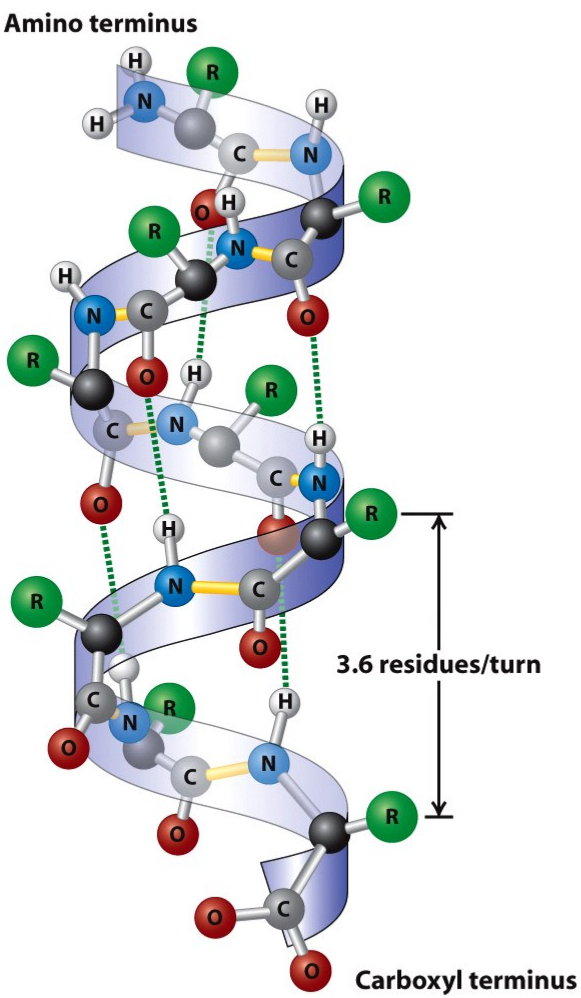


Figure 3-4
Molecular Cell Biology, Sixth Edition

α-helix

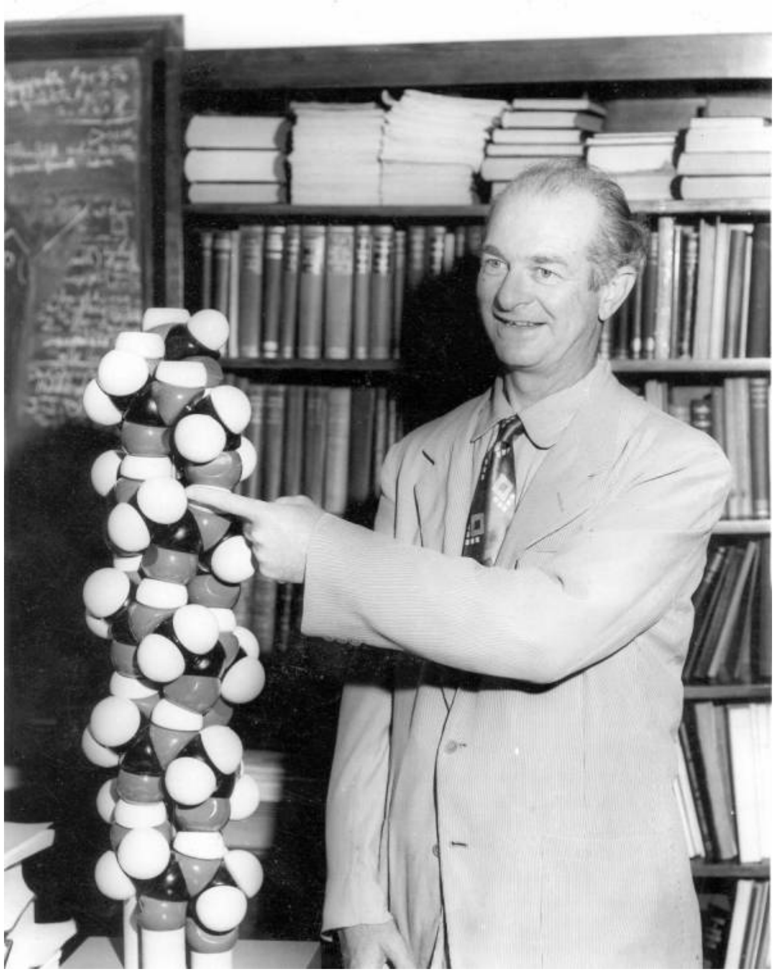
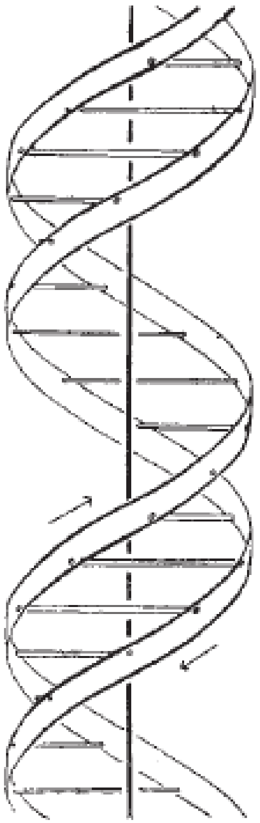


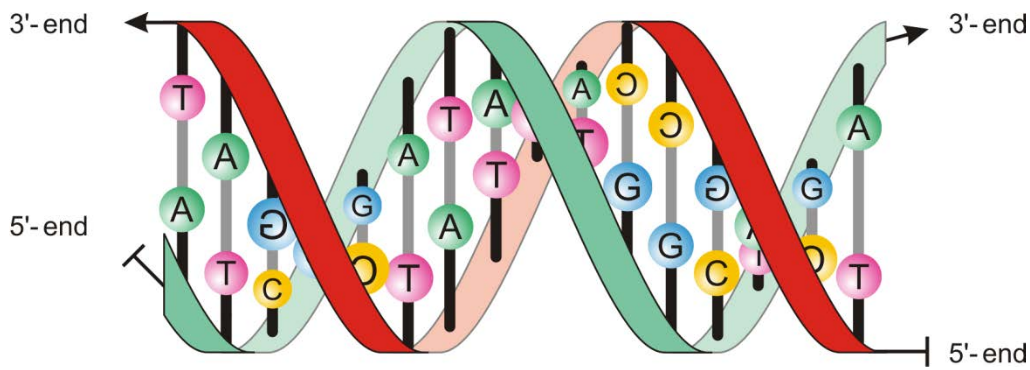
Photo by CalTech News Bureau

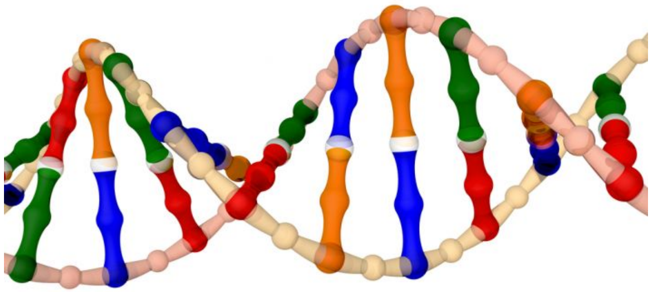
Linus Pauling, 1901-1994

L. Pauling, R.B. Corey, H.R. Branson. The structure of proteins: Two hydrogen-bonded helical configurations of the polypeptide chain. Proc.Natl.Acad.Sci.USA 37(4):205-2011. 1951.



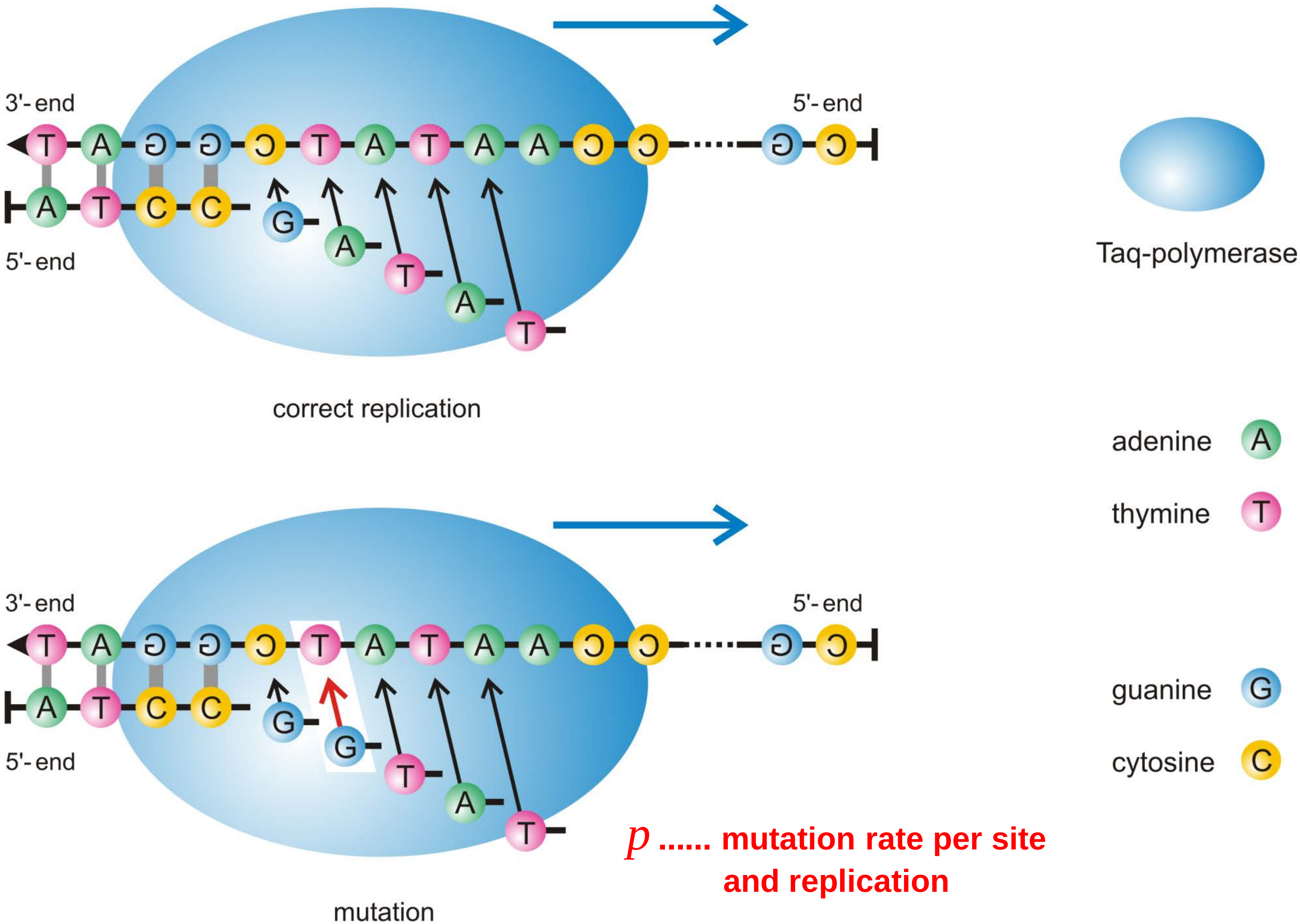
This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis



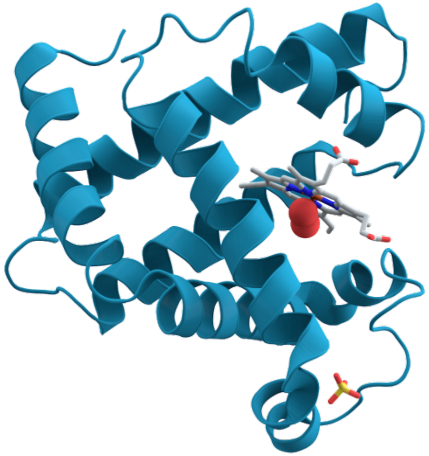


"It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible **copying mechanism for the genetic material**."

J.D. Watson, F. H.C. Crick. A structure for deoxyribose nucleic acid. Nature 171(4356):737-738, 1953.

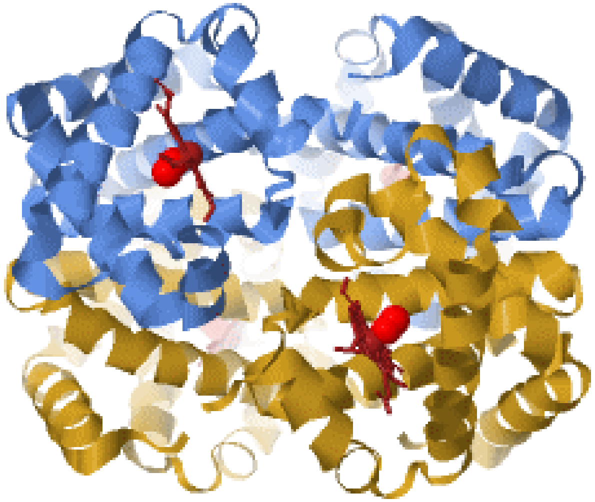


DNA replication and mutation

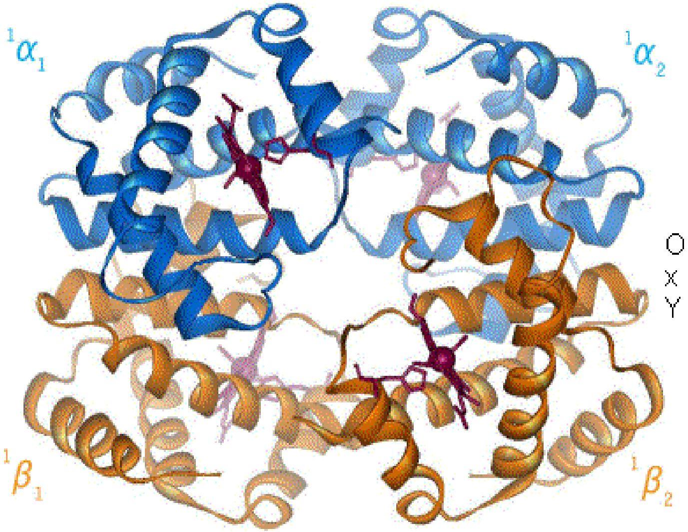


myoglobin structure

J.C. Kendrew et al. Nature 181:662-666, 1958



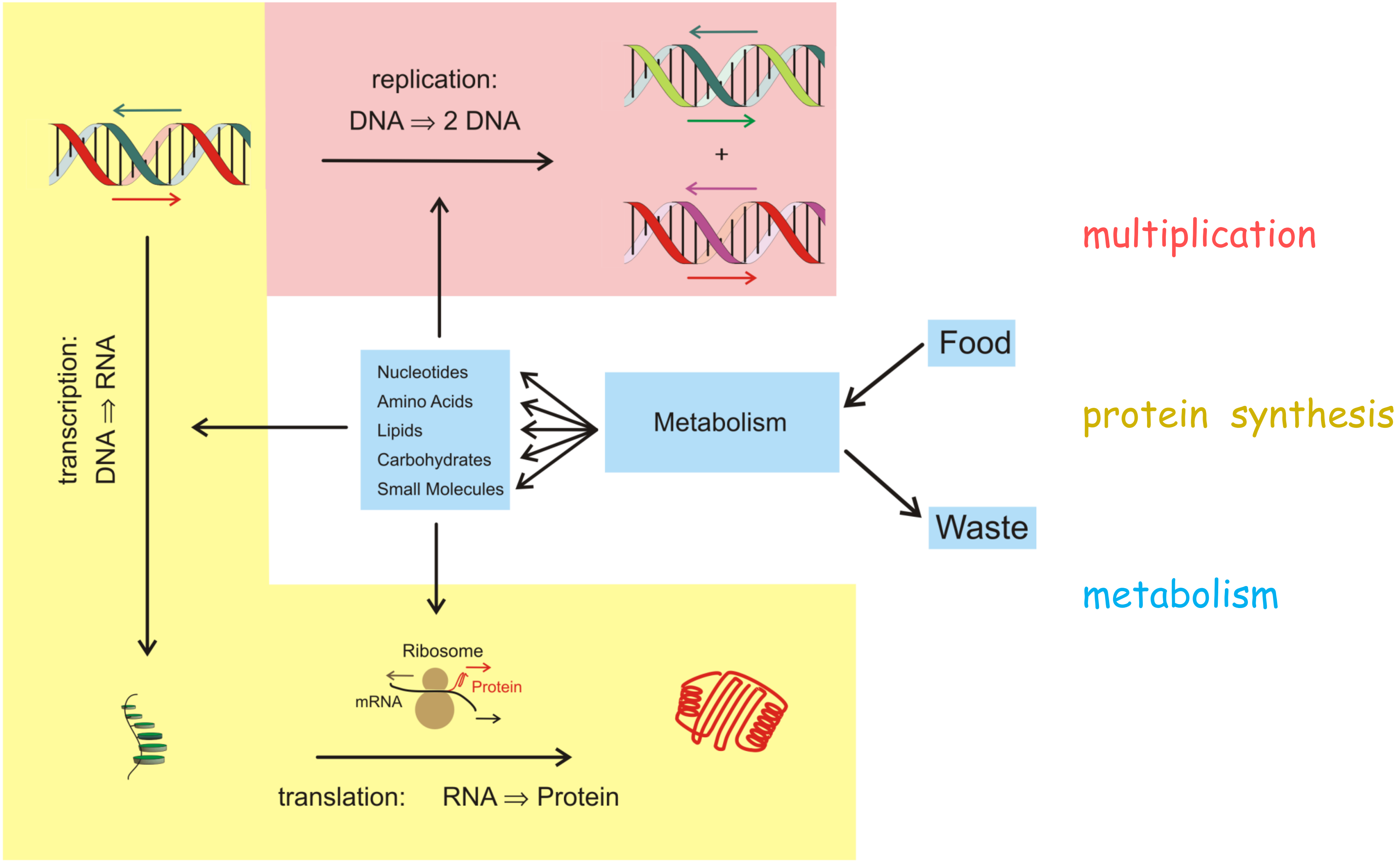
hemoglobin structure



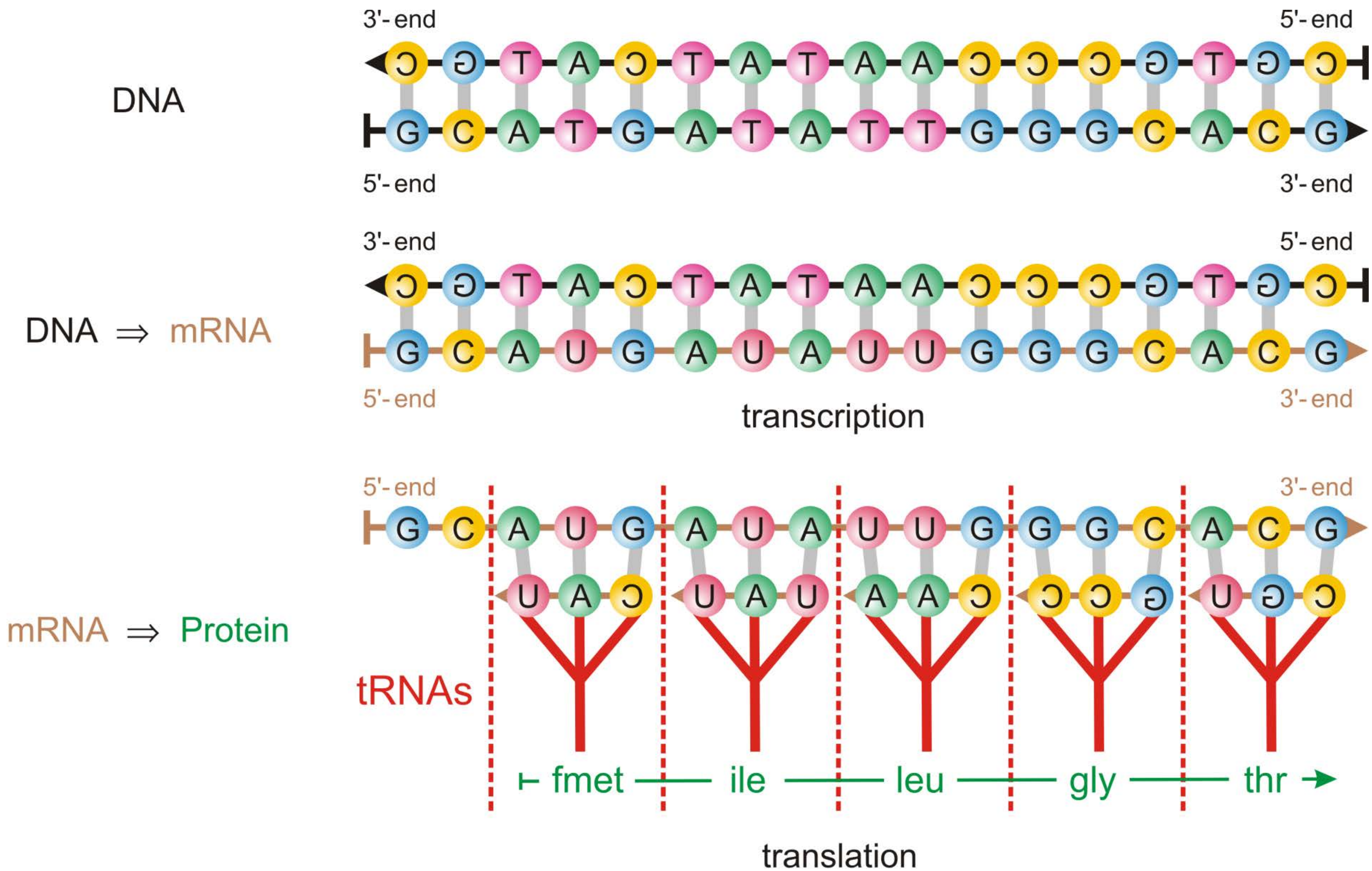
conformational change R ↔ T

M.F. Perutz et al. Nature 185:416-422, 1960

Theislikerice at http://proteopedia.org/wiki/index.php/Hemoglobin



sketch of the cellular metabolism after deciphering the genetic code



transcription and translation

1. Schrödinger's "What is Life?" and its reception
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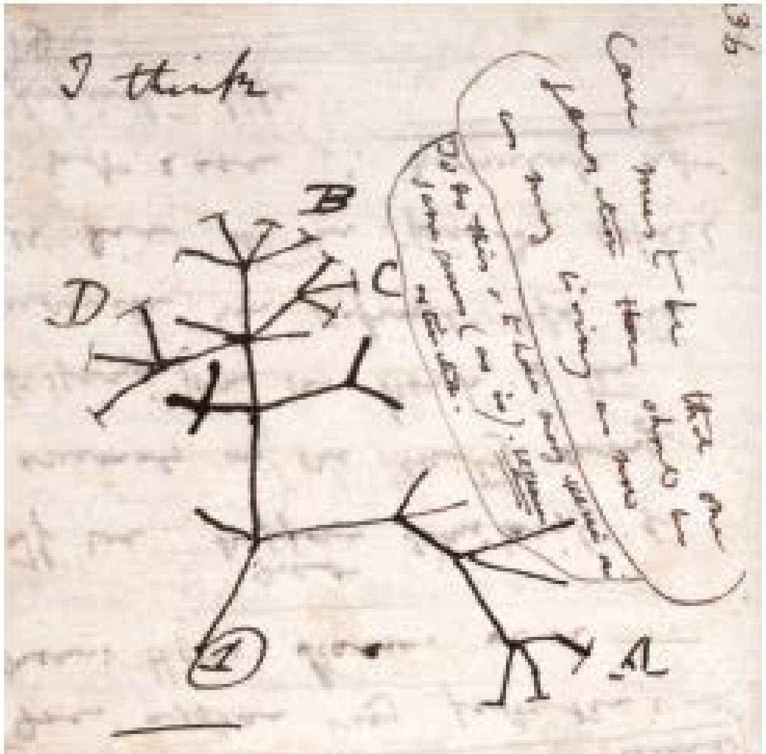
4. Bridging from chemistry to biology

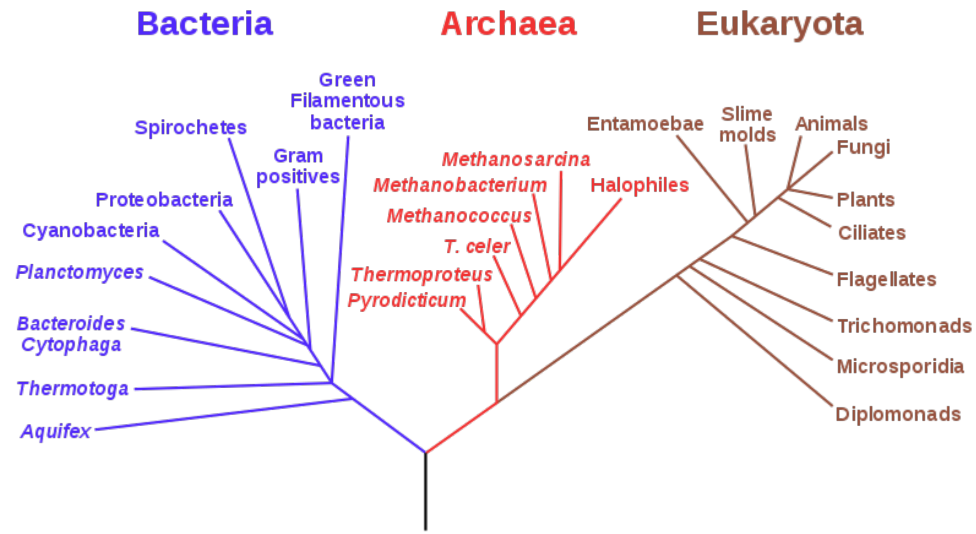
„Nothing in biology makes sense except in the light of evolution, …"

Theodosius Dobzhansky, 1900 - 1975

T. Dobzhansky. *Nothing in biology makes sense except in the light of evolution.* American Biology Teacher **35**(3):125-129, 1973 and

Biology, molecular and organismic. American Zoologist **4**:443-452, 1974.

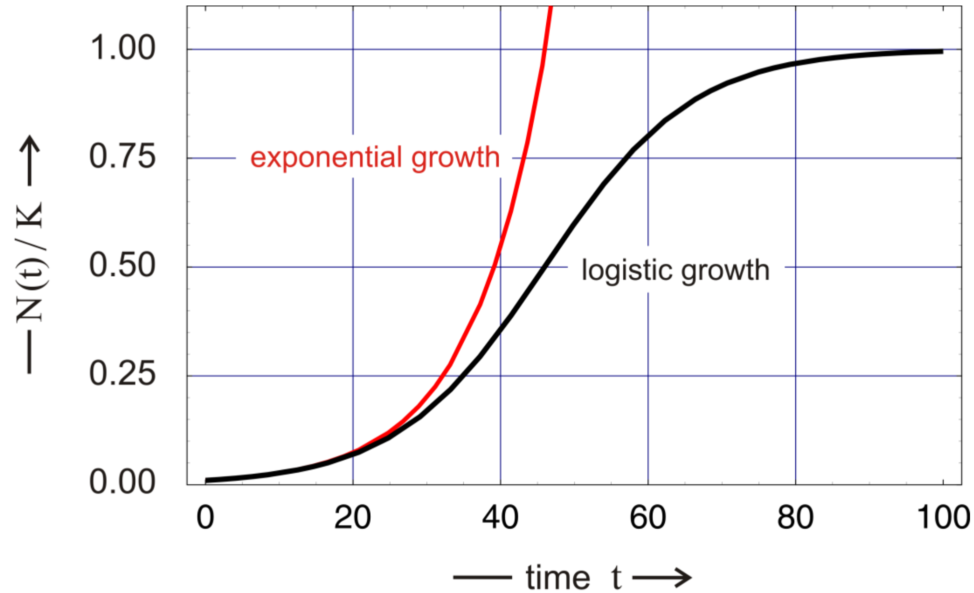




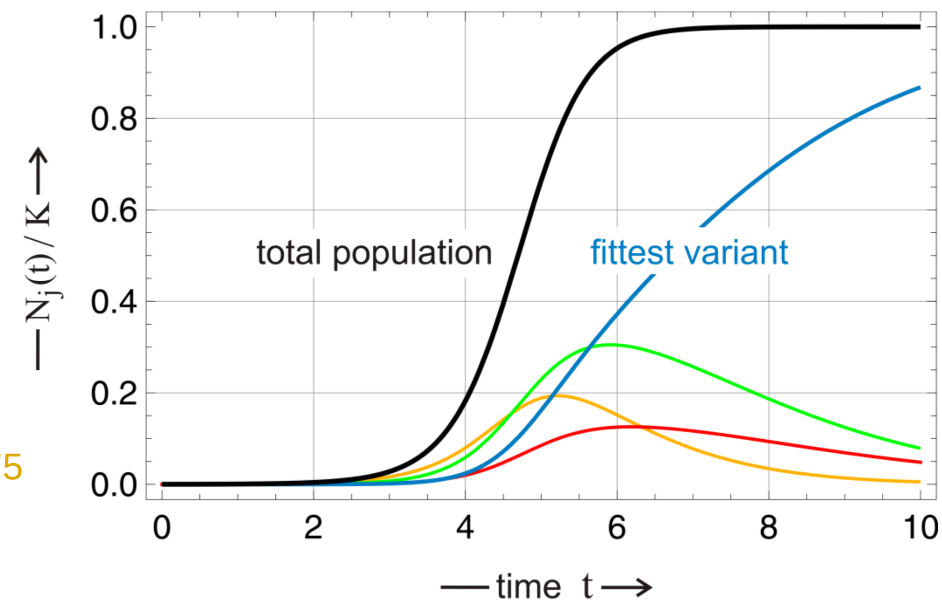
Modern phylogenetic tree with common ancestor. Source: Wikipedia, „Phylogenetic _tree", retrieved 07.11.2019

An evolutionary tree by Charles Darwin. The ancestral species is at position `1'. Extant species are denoted by endpoint and letters, and the remaining pendant edges represent extinctions. On the margin of his sketch of a tree Darwin had written, `I think', before expanding his idea in *The Origin of Species*: `The affinities of all the beings of the same class have sometimes been represented by a great tree. I believe this simile largely speaks the truth. The green and budding twigs may represent existing species; and those produced during each former year may represent the long succession of extinct species...'
First Notebook on Transmutation of Species, 1837, courtesy of Cambridge University Library.

Pierre-François Verhulst,
1804-1849



the consequence of finite resources



fitness values:

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

The logistic equation, 1828

P. Schuster. Theory Biosciences 130:71-89, 2011

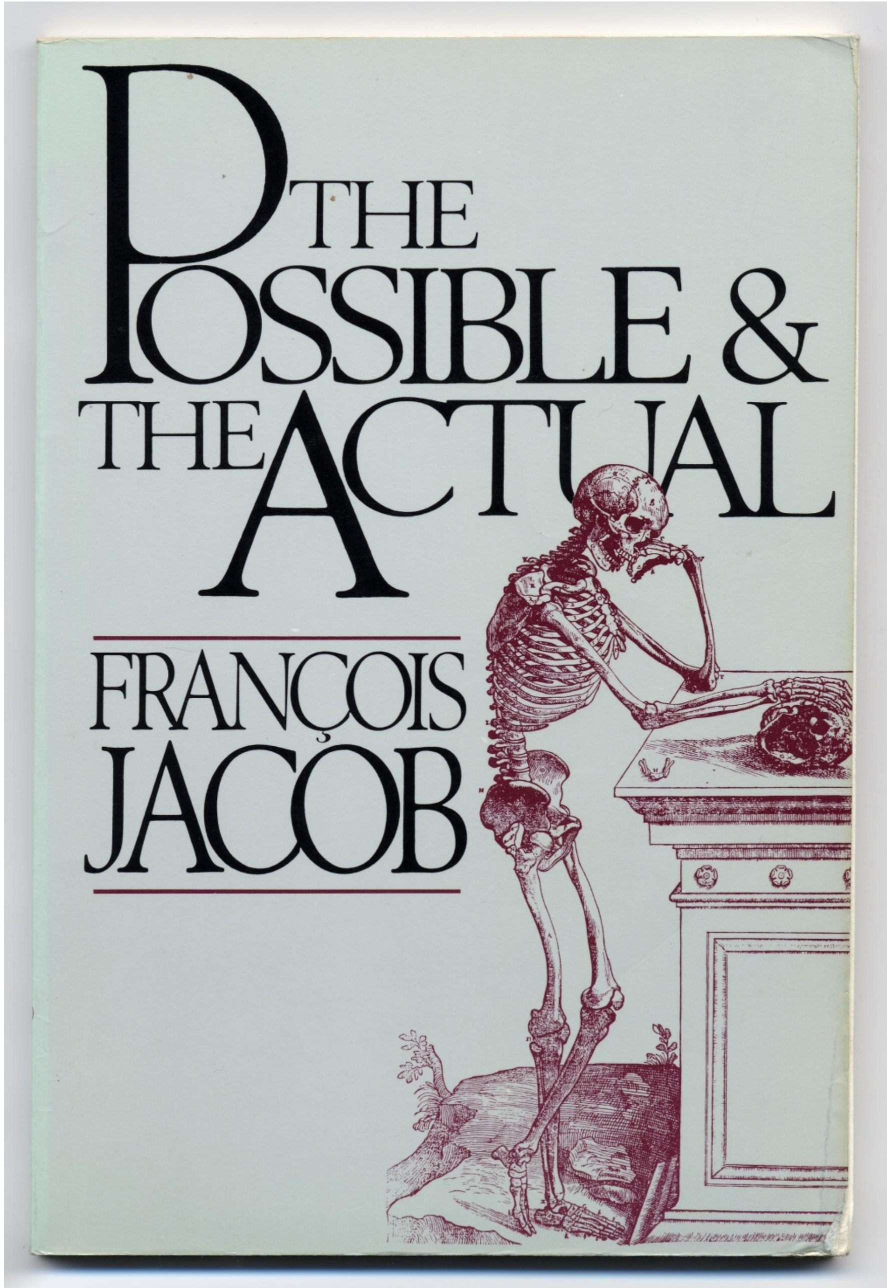
$$\frac{dX}{dt} = f\ X\left(1 - \frac{X}{C}\right) \quad \Rightarrow \quad X(t) = \frac{C\ X_0}{X_0 + (C - X_0)\ \exp(-f\,t)};\ X_0 = X(0)$$

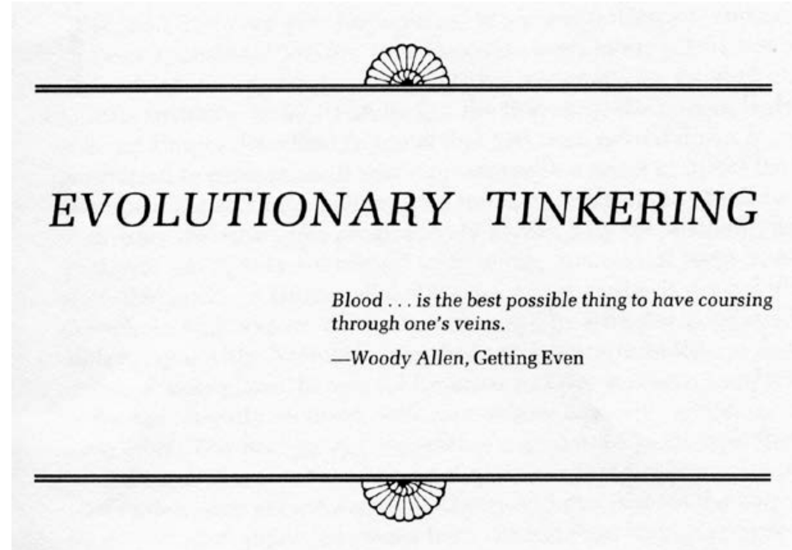
$$\frac{d\xi_j}{dt} = \xi_j\,(f_j - \Phi);\ \Phi = \sum_{i=1}^{n} f_i\ \xi_i \quad \Rightarrow \quad \xi_i(t) = \frac{\xi_j(0)\exp(f_j t)}{\sum_{i=1}^{n} \xi_i(0)\exp(f_i t)}$$

$$\xi_i(t) = \frac{X_i}{\sum_{i=1}^{n} X_i};\ \sum_{i=1}^{n} \xi_i = 1$$

$$\Pi = \left\{\mathrm{X}_m\right\} \quad \text{or} \quad \lim_{t \to \infty} \xi_m(t) = 1 \ \text{ and } \ \lim_{t \to \infty} \xi_{i \neq m}(t) = 0$$

the mathematics of selection





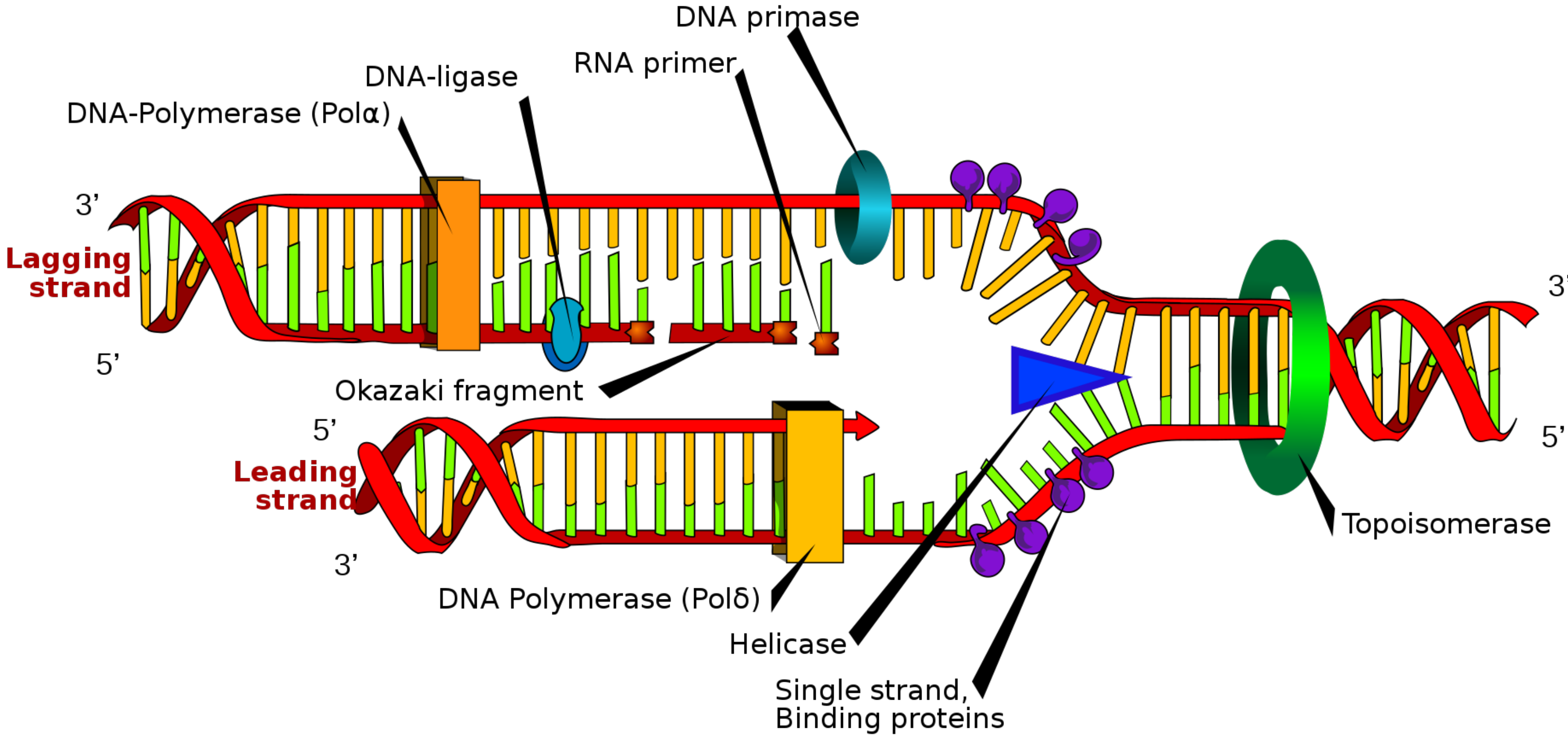
EVOLUTIONARY TINKERING

Blood . . . is the best possible thing to have coursing through one's veins.

—*Woody Allen,* Getting Even

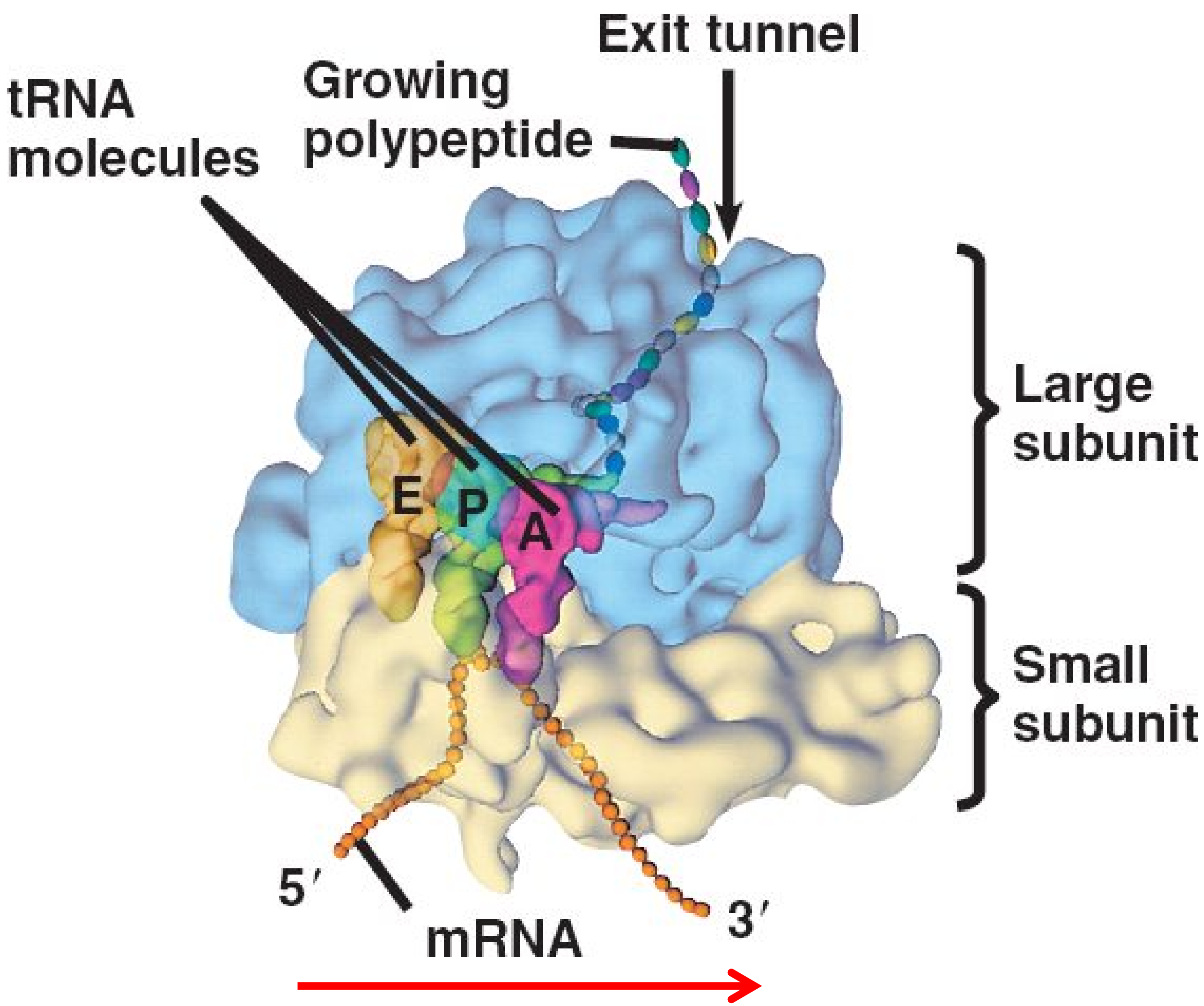
Evolution does not design with the eyes of an engineer, evolution works like a tinkerer.

Francois Jacob, Pantheon Books, New York 1982



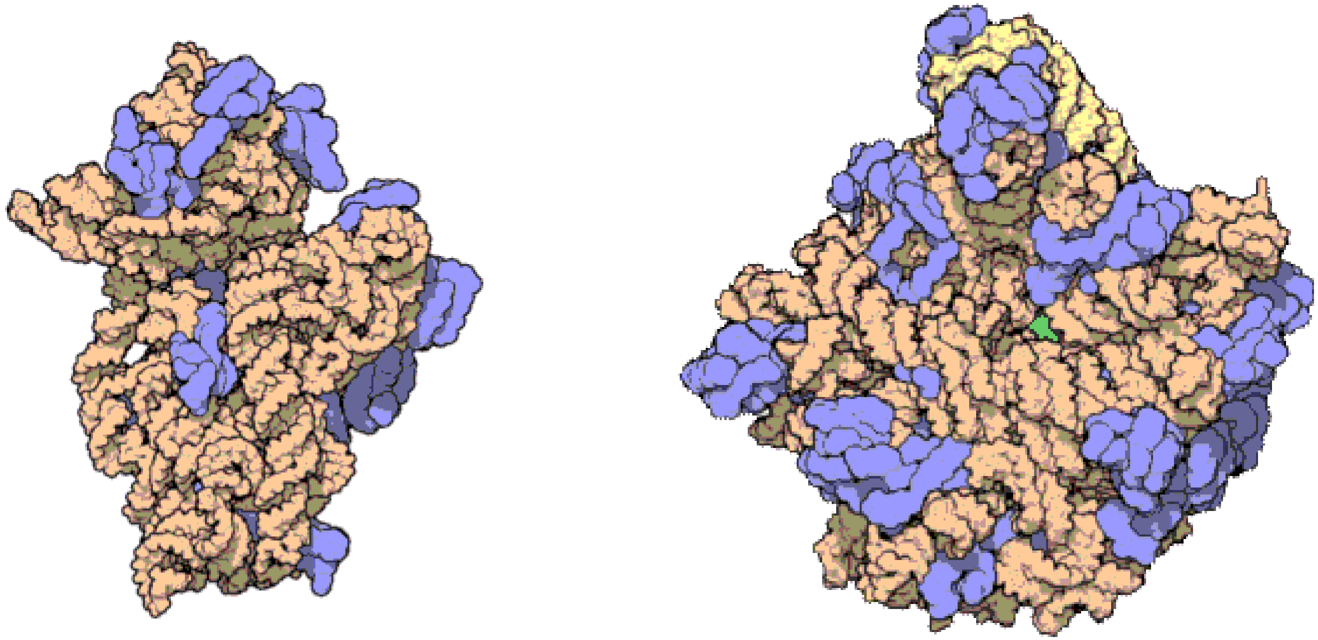
DNA replication machinery

source: Wikipedia, „DNA_replication“, retrieved 07.11.2019



polypeptide synthesis at the ribosome

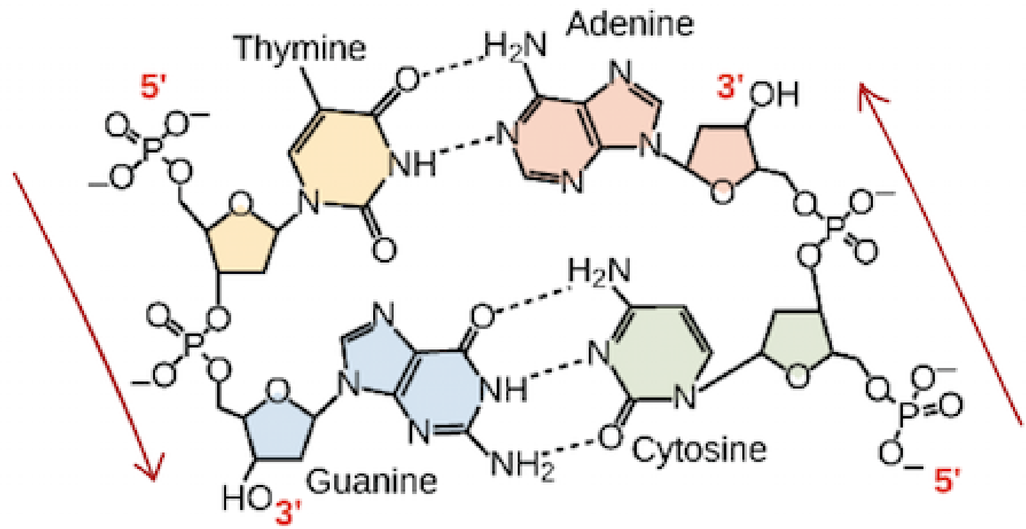
source: http://bio1151.nicerweb.com/Locked/media/ch17/ribosome.html , retrieved 10.11.2019



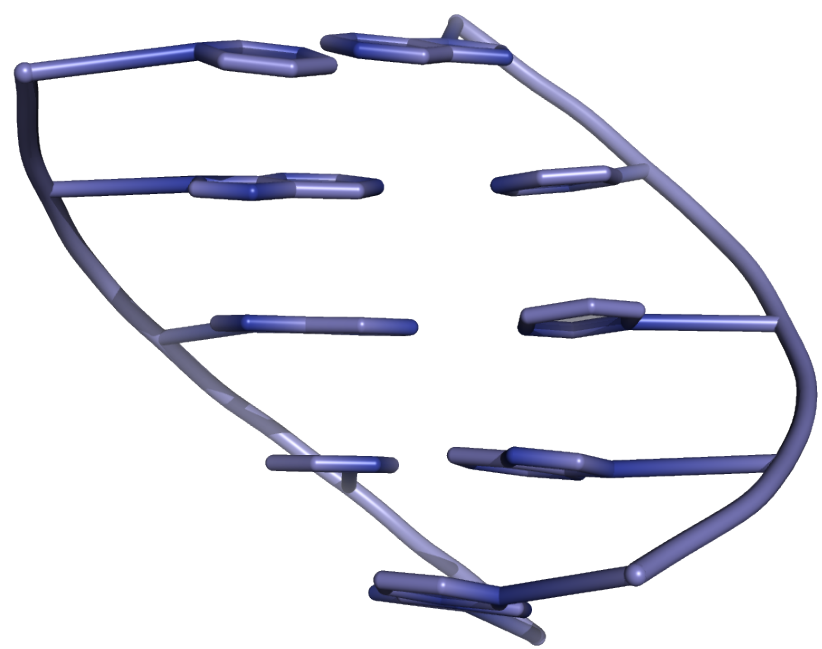
small and large subunit of the ribosome from Thermus thermophilus

Animation by David S. Goodsell, RCSB Protein Data Bank - Molecule of the Month at the RCSB Protein Data Bank, Public Domain, https://commons.wikimedia.org/w/index.php?curid=2839678

DNA base pairing



DNA base stacking



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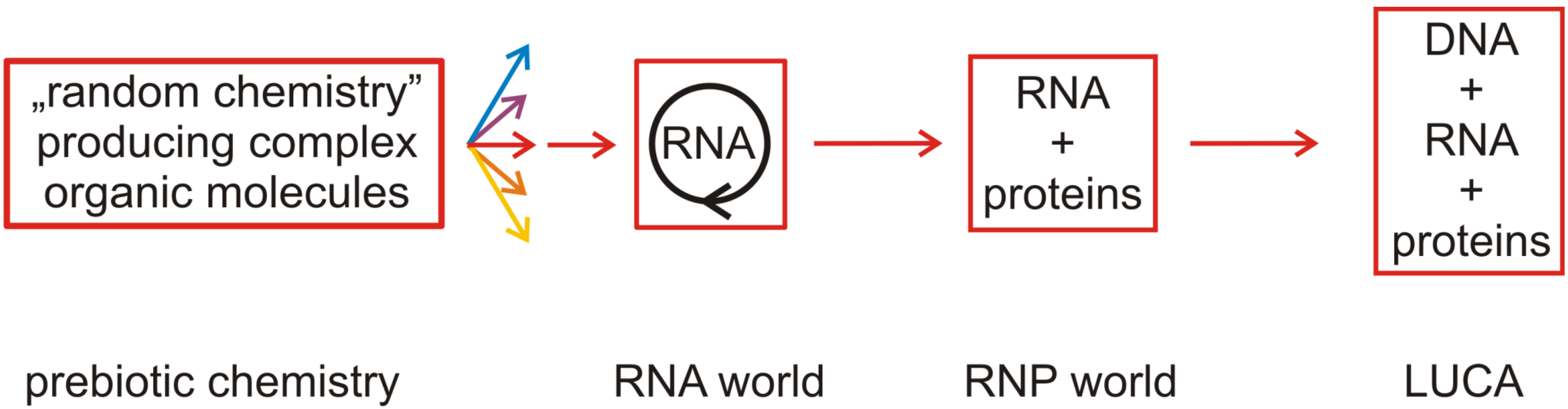
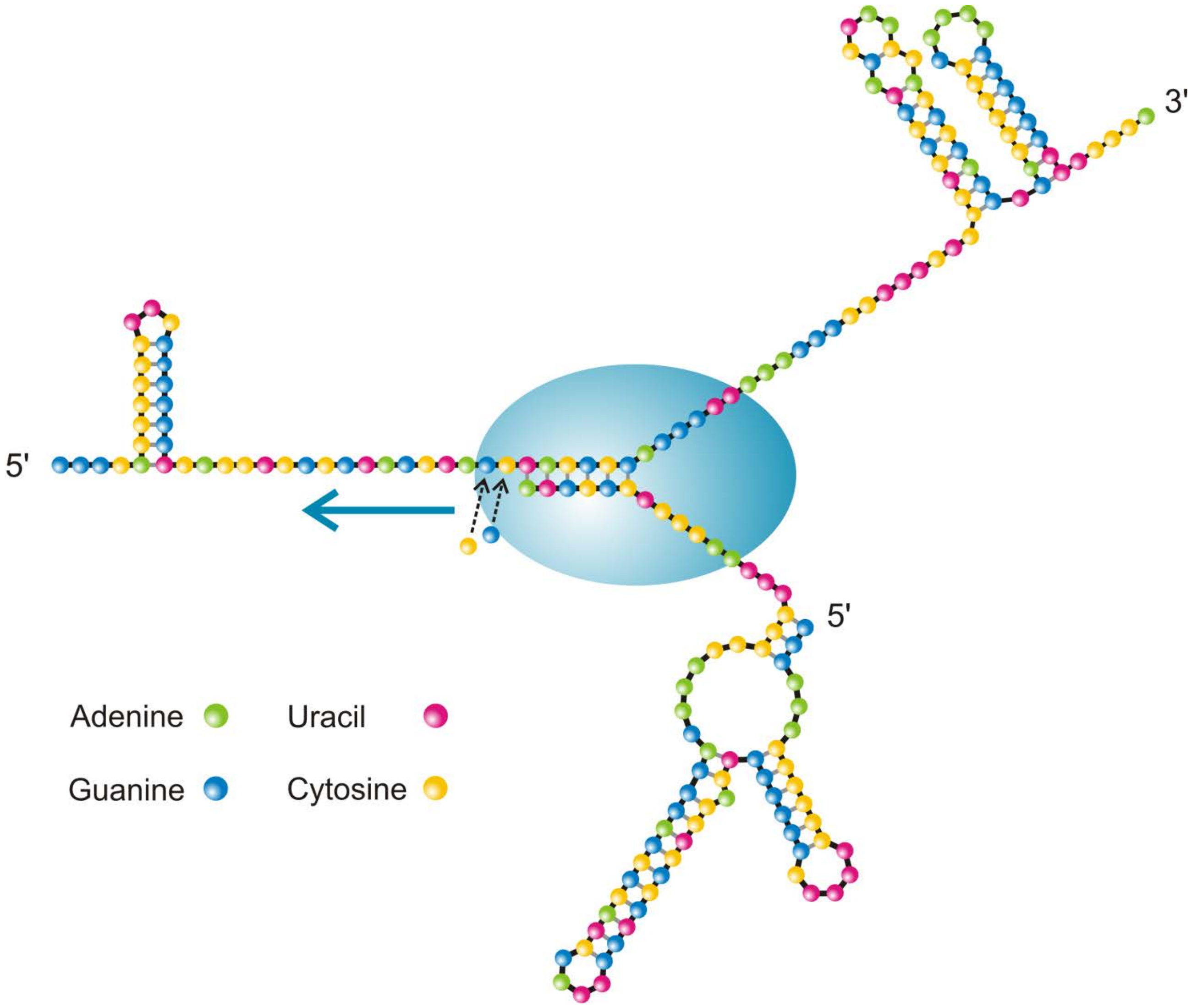
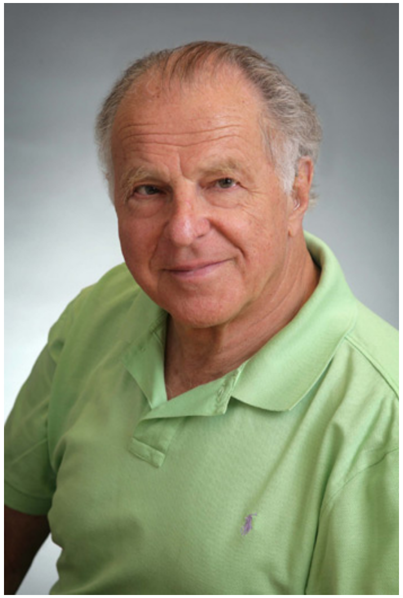


RNP = RNA + protein catalysts
LUCA = last universal common ancestor
„random chemistry" = noninstructed reactions

model of successive appearance of RNA, protein and DNA during the origin of life

T.R. Cech, The RNA worlds in context. Cold Spring Harb.Prospect.Biol. 4:a006742, 2012



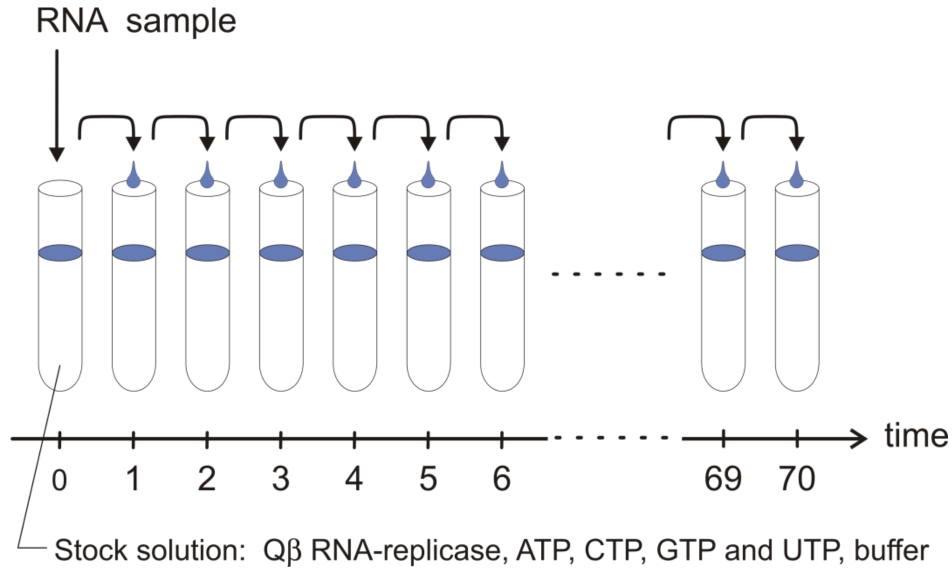


Charles Weissmann
1931-

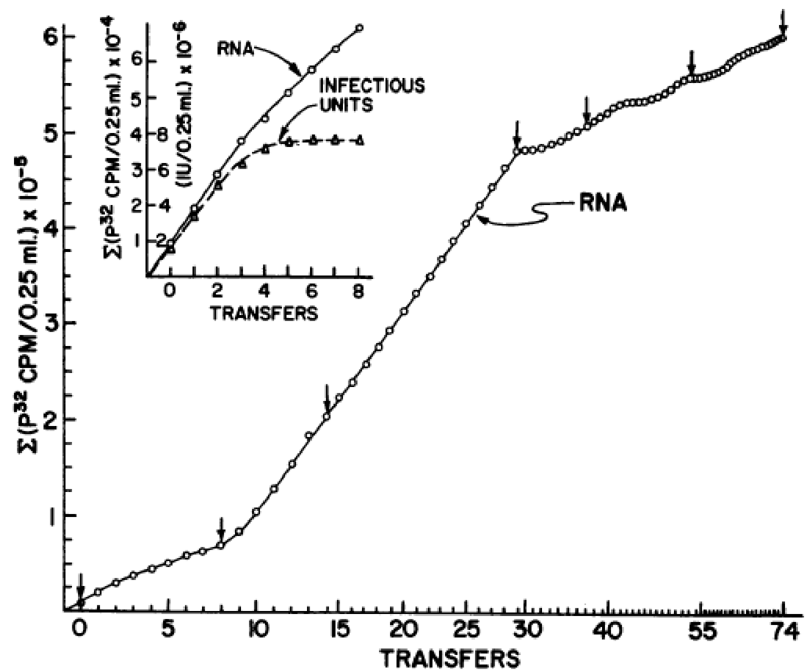
RNA replication by Qβ-replicase

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

Sol Spiegelman,
1914 - 1983

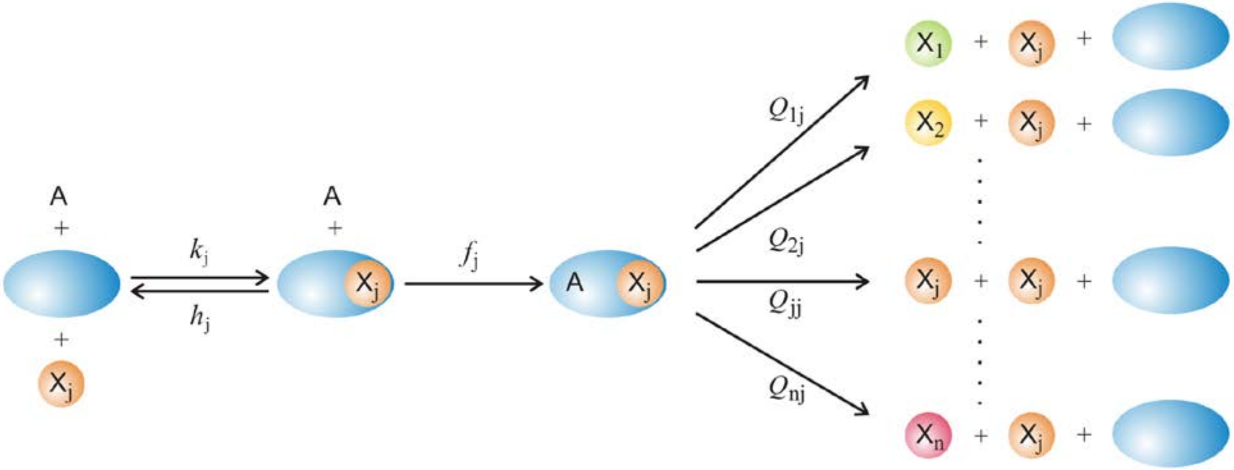


D.R. Mills, R.L. Peterson, S. Spiegelman.
An extracelllular Darwinian experiment with a self-duplicating nucleic acid molecule.
Proc.Natl.Acad.Sci.USA 58(1):217-224, 1967



Evolution in the test tube

Manfred Eigen,
1927 – 2019



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

$$W_{ji} = Q_{ji} \cdot f_i\,, \quad \sum_{i=1}^{n} x_i = 1, \quad \Phi = \sum_{i=1}^{n} f_i\, x_i$$

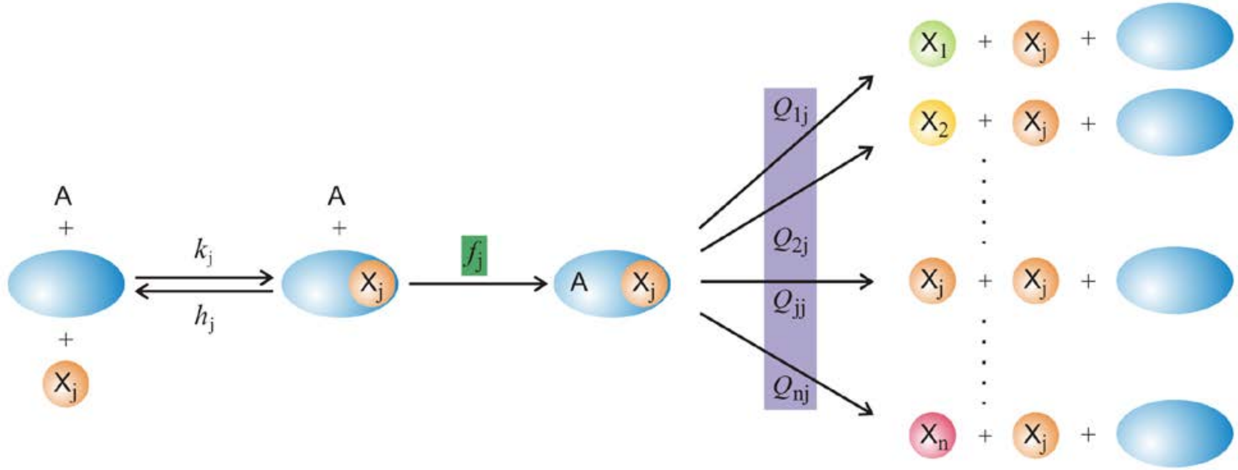
fitness landscape

mutation matrix

Mutation and replication as
parallel chemical reactions

M. Eigen. 1971. *Naturwissenschaften* 58:465,
M. Eigen & P. Schuster.1977-78. *Naturwissenschaften* 64:541, 65:7 und 65:341

Manfred Eigen,
1927 – 2019



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

$$W_{ji} = Q_{ji} \cdot f_i\,, \quad \sum_{i=1}^{n} x_i = 1, \quad \Phi = \sum_{i=1}^{n} f_i\, x_i$$

fitness landscape

mutation matrix

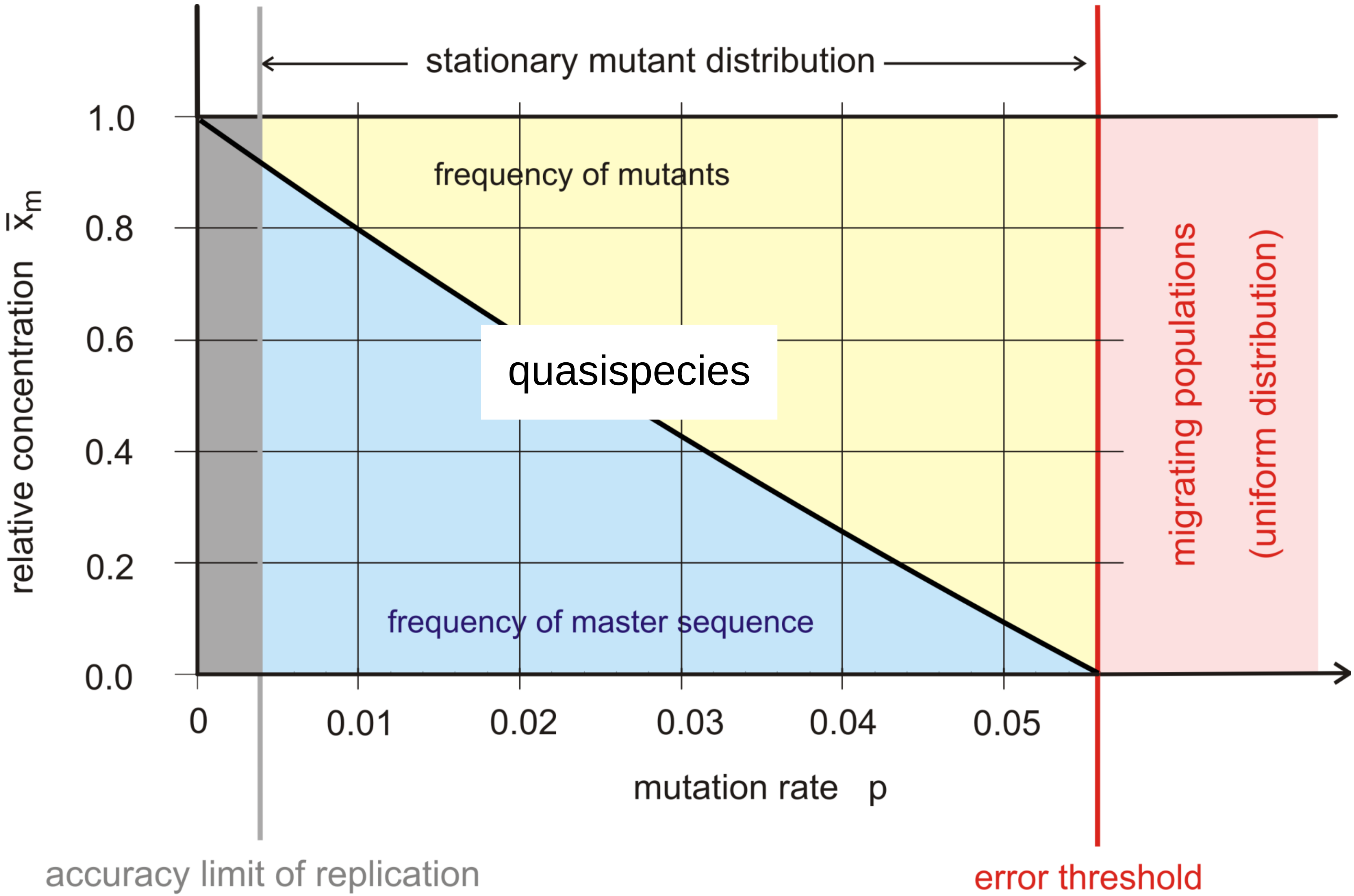
Mutation and replication as parallel chemical reactions

M. Eigen. 1971. *Naturwissenschaften* 58:465,
M. Eigen & P. Schuster.1977-78. *Naturwissenschaften* 64:541, 65:7 und 65:341

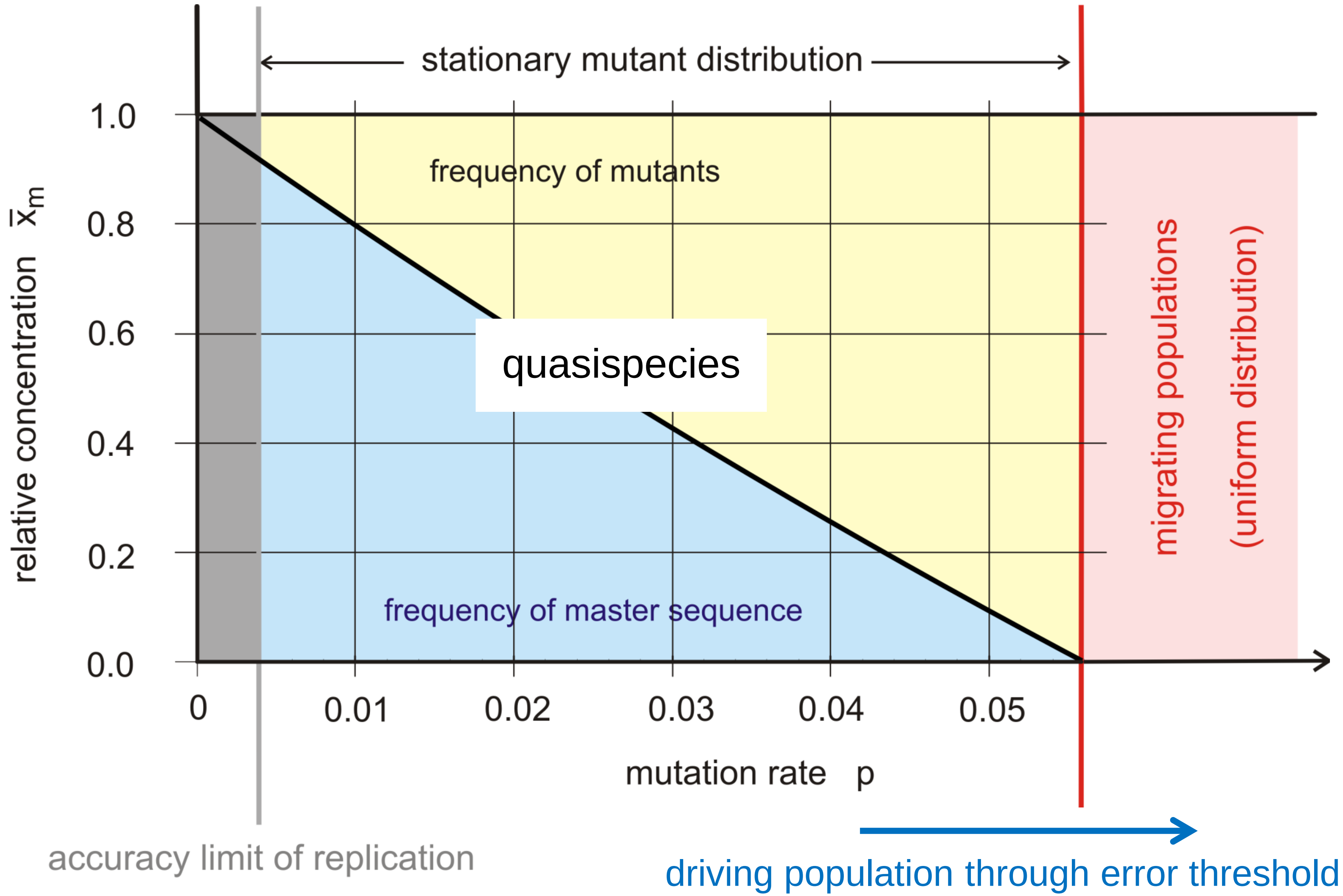
$$p_{\max} \approx \frac{\ln \sigma_m}{\ell} \quad \text{with} \quad \sigma_m = \frac{(1-\bar{\xi}_m)\, f_m}{\sum_{j\neq m} \bar{\xi}_j \; f_j} \quad \text{and} \quad \sum_{i=1}^{n} \bar{\xi}_i = 1$$

the chain length of RNA molecules, ℓ , is constant:
in vitro evolution, virus populations, …

error threshold defines a maximal mutation rate $p_{\max}$



the error threshold in the development of antiviral drugs

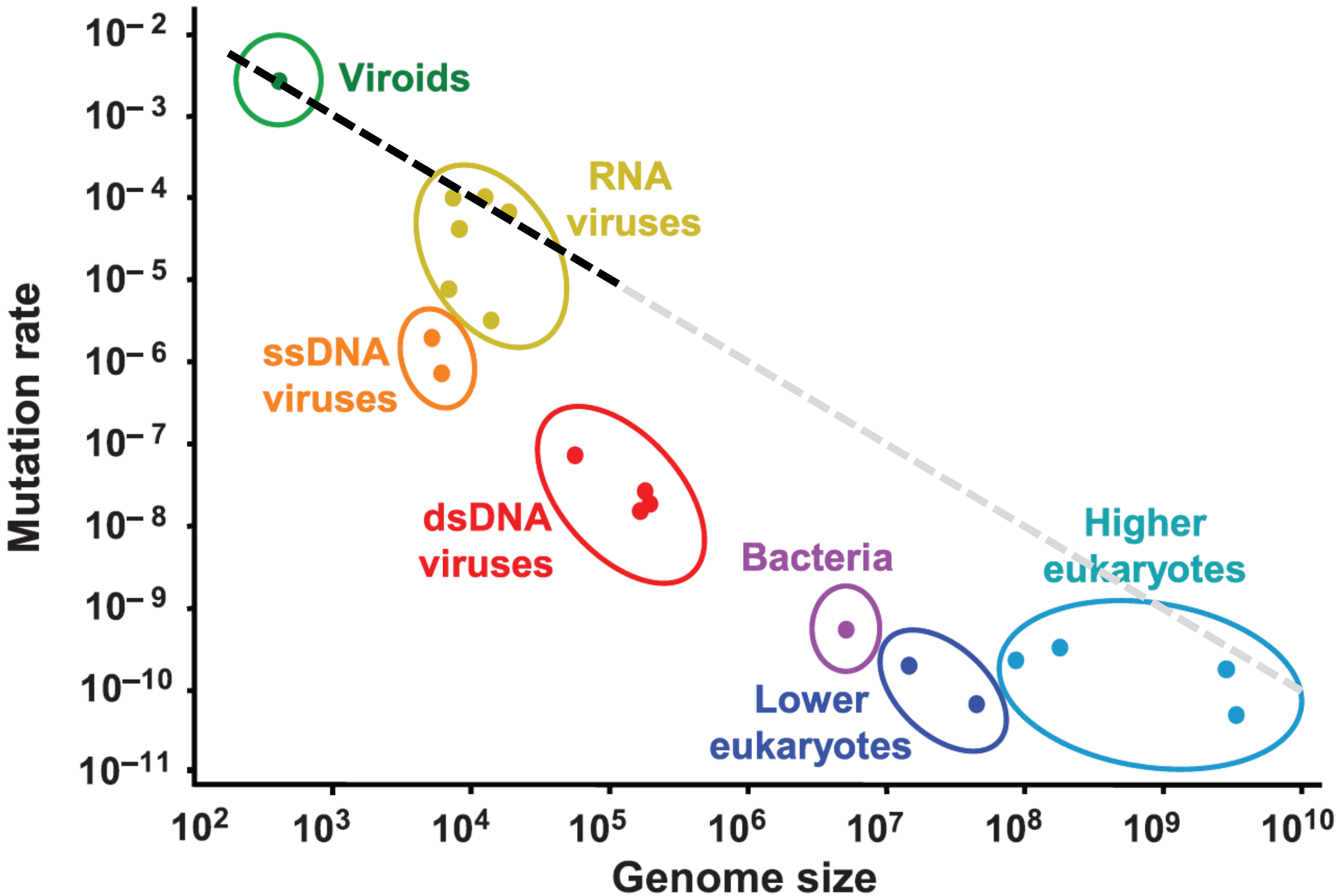


the error threshold in the development of antiviral drugs

$$\ell_{\max} \approx \frac{\ln \sigma_m}{p} \quad \text{with} \quad \sigma_m = \frac{(1-\bar{\xi}_m)\, f_m}{\sum_{j \neq m} \bar{\xi}_j\, f_j} \quad \text{and} \quad \sum_{i=1}^{n} \bar{\xi}_i = 1$$

the mutation rate of polynucleotide replication, *p*, is constant:
all kinds of organisms from viroids to higher eukaryotes

error threshold defines a maximal chain length $\ell_{\max}$



Selma Gago, Santiago F. Elena, Ricardo Flores, Rafael Sanjuán. Extremely high mutation rate of a hammerhead viroid. Science 323(5919):1308, 2009.

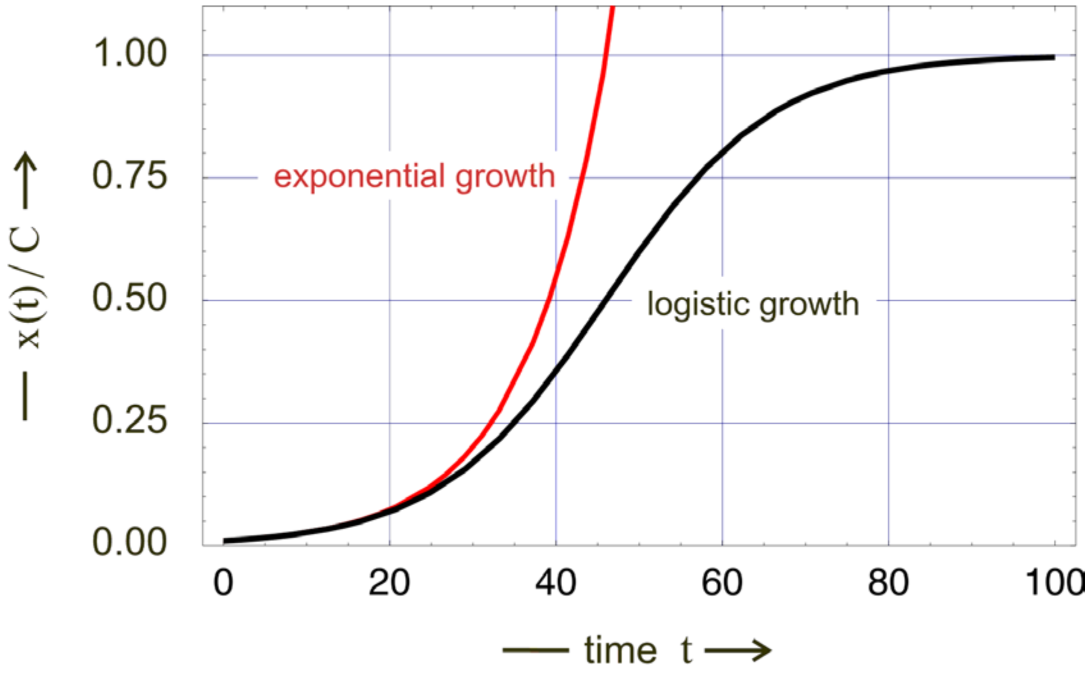
mutation rate and genome size

Thank you for your attention!

Web-Page for further information:

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

Pierre-François Verhulst, 1804-1849



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

the consequence of finite resources

$$\frac{dX}{dt} = f\,X\left(1 - \frac{X}{C}\right) \Rightarrow X(t) = \frac{C\,X_0}{X_0 + (C - X_0)\exp(-f\,t)};\; X_0 = X(0)$$

the logistic equation: Verhulst 1838

$$\frac{\mathrm{d}X}{\mathrm{dt}} = f\,X\left(1 - \frac{X}{C}\right) \quad \Rightarrow \quad \frac{\mathrm{d}X}{\mathrm{dt}} = f\,X - \frac{X}{C}\,f\,X$$

$$f\,X \equiv \Phi(\mathrm{t}),\, C = 1: \quad \frac{\mathrm{d}X}{\mathrm{dt}} = X\left(f - \Phi\right)$$

$$\Pi = \{\mathrm{X}_1, \mathrm{X}_2, \ldots, \mathrm{X}_n\}: \quad [\mathrm{X}_i] = X_i\,; \quad \sum_{i=1}^{n} X_i = C = 1$$

$$\frac{\mathrm{d}X_j}{\mathrm{dt}} = X_j\left(f_j - \sum_{i=1}^{n} f_i\,X_i\right) = X_j\left(f_j - \Phi\right)\,; \quad \Phi = \sum_{i=1}^{n} f_i\,X_i$$

Darwin

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

generalization of the logistic equation to *n* variables yields selection

$$\Pi = \{X_1, X_2, \ldots, X_n\}$$

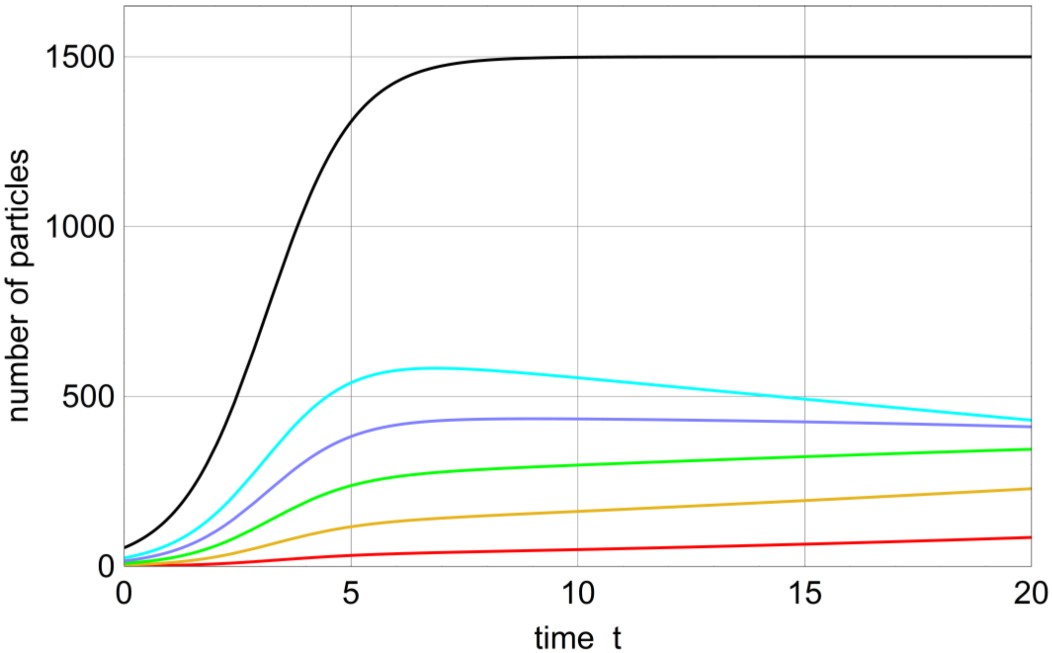
$$\mathbf{X}(t) = \big(X_1(t), X_2(t), \ldots, X_n(t)\big);\ N(t) = \sum_{i=1}^{n} X_i(t)$$

$$N(t) = \frac{N(0)\,C}{N(0) + \big(C - N(0)\big)\exp\big(-\Phi(t)\big)} \quad ; \quad \Phi(t) = \int_{\tau=0}^{t} \frac{\sum_{i=1}^{n} f_i\, X_i(t)}{N(t)}\, d\tau$$

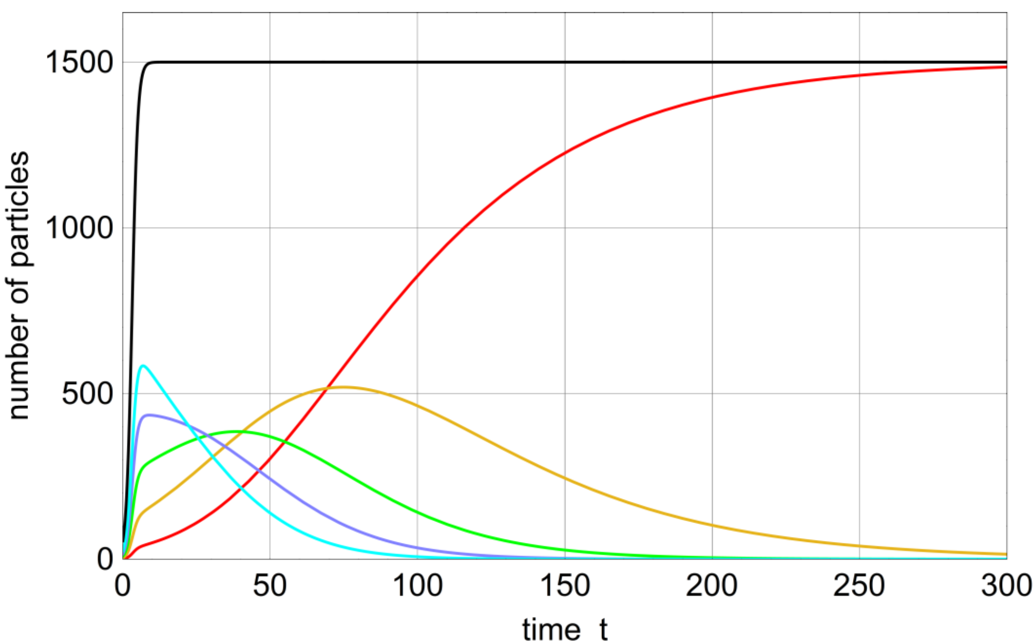
$\Phi(t)$ … time integral of mean fitness

$$\xi_j(t) = \frac{X_j(t)}{N(t)} = \frac{\xi_j(0)\exp(f_j\, t)}{\sum_{i=1}^{n} \xi_i(0)\exp(f_i\, t)}$$

solution of the logistic equation in *n* variables



$$\xi_j(t) = \frac{X_j(t)}{N(t)} = \frac{\xi_j(0)\exp(f_j\,t)}{\sum_{i=1}^{n}\xi_i(0)\exp(f_i\,t)}$$



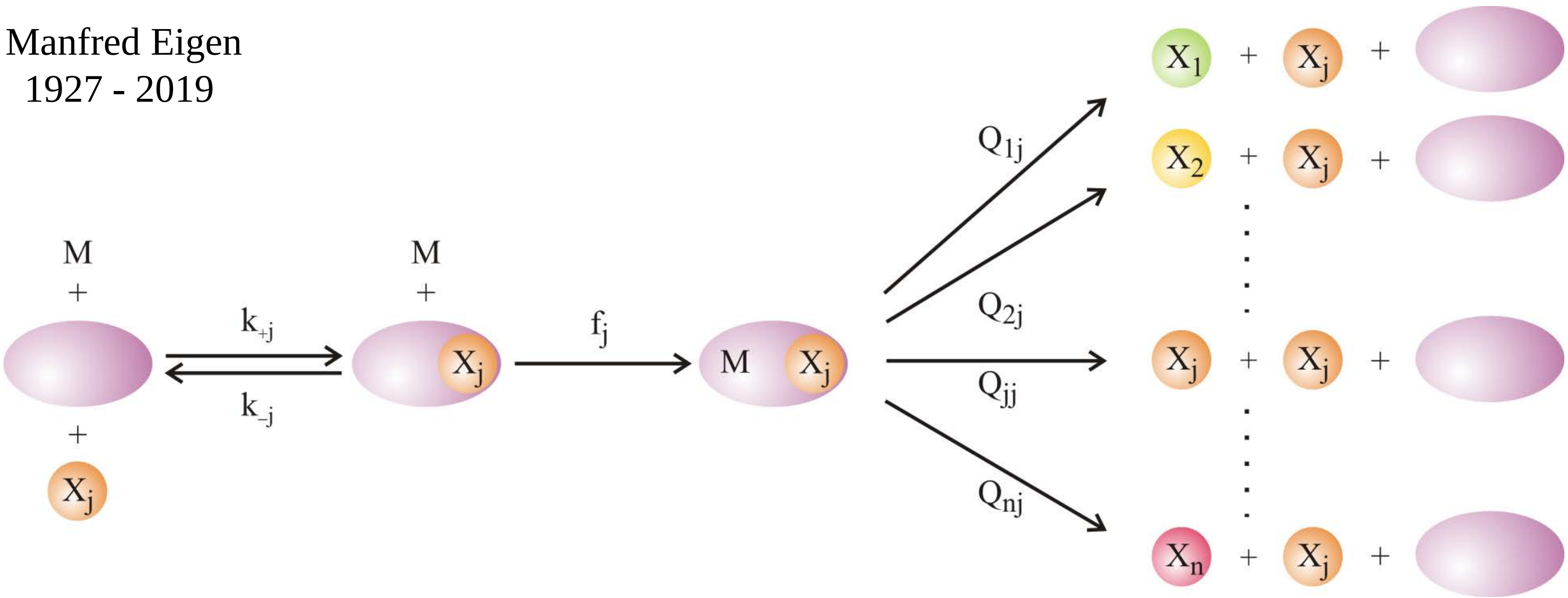
$\mathbf{X}(0) = (1,4,9,16,25)$

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

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

Manfred Eigen
1927 - 2019

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



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

$$\frac{\mathrm{d}x_j}{\mathrm{d}t} = \sum_{i=1}^{n} W_{ji}\, x_i - x_j\, \Phi = \sum_{i=1}^{n} Q_{ji}\, f_i\, x_i - x_j\, \Phi\,; \quad j = 1, 2, \ldots, n$$

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

Decomposition of matrix W

$$\mathrm{W} = \begin{pmatrix} w_{11} & w_{12} & \ldots & w_{1n} \\ w_{21} & w_{22} & \ldots & w_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ w_{n1} & w_{n2} & \ldots & w_{nn} \end{pmatrix} = \mathrm{Q} \cdot \mathrm{F} \quad \text{with}$$

$$\mathrm{Q} = \begin{pmatrix} Q_{11} & Q_{12} & \ldots & Q_{1n} \\ Q_{21} & Q_{22} & \ldots & Q_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ Q_{n1} & Q_{n2} & \ldots & Q_{nn} \end{pmatrix} \quad \text{and} \quad \mathrm{F} = \begin{pmatrix} f_1 & 0 & \ldots & 0 \\ 0 & f_2 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & f_n \end{pmatrix}$$

factorization of the value matrix W separates mutation and fitness effects.

mutation-selection equation: $[\mathrm{I}_i] = x_i \geq 0,\ f_i \geq 0,\ Q_{ij} \geq 0$

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

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

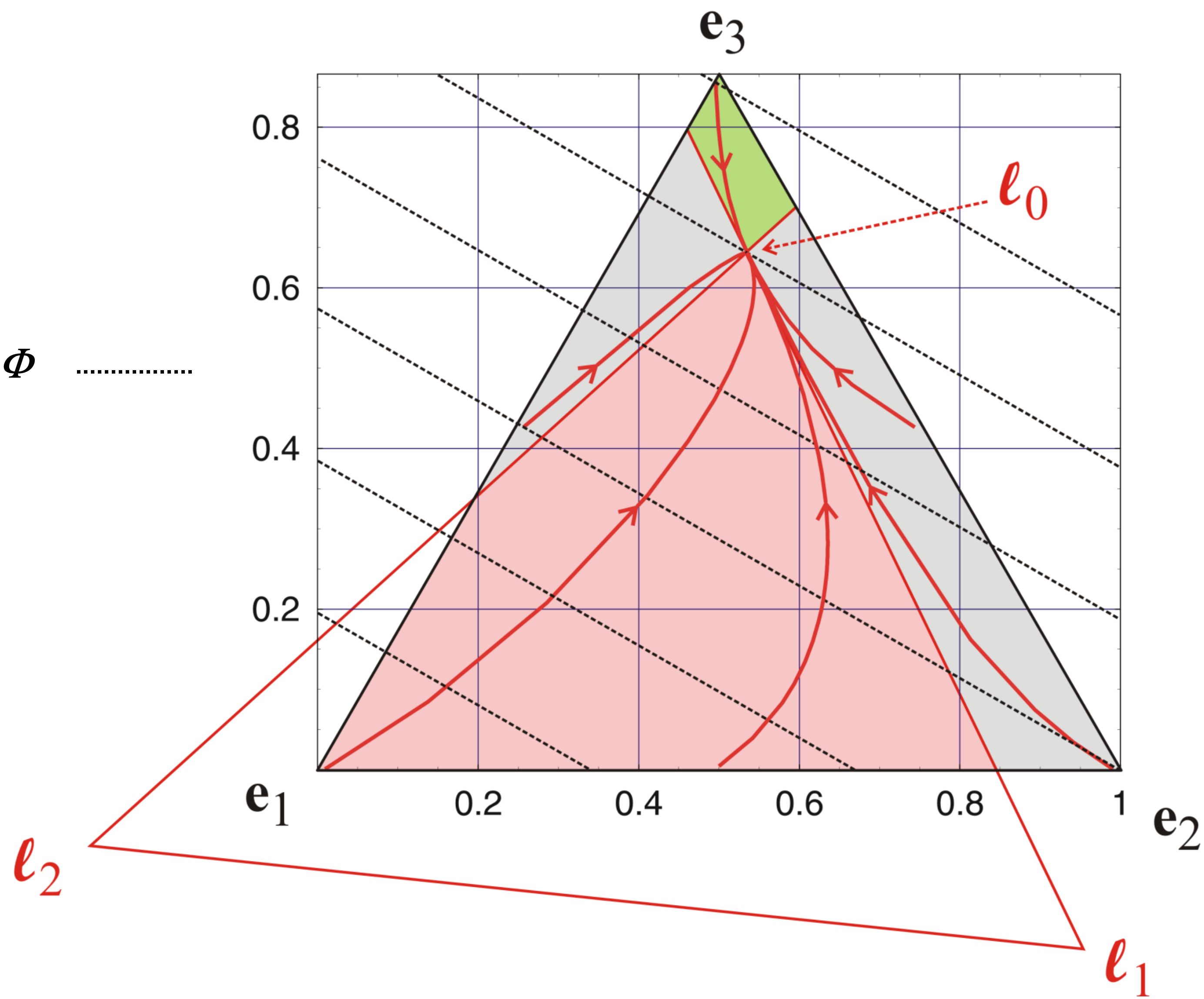
$$x_i(t) = \frac{\sum_{k=0}^{n-1} \ell_{ik} \cdot c_k(0) \cdot \exp(\lambda_k t)}{\sum_{j=1}^{n} \sum_{k=0}^{n-1} \ell_{jk} \cdot c_k(0) \cdot \exp(\lambda_k t)}; \quad i=1,2,\cdots,n; \quad c_k(0) = \sum_{i=1}^{n} h_{ki}\ x_i(0)$$

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

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

the quasispecies is the dominant eigenvector ℓ_0 of Λ

constant level sets of Φ ....



selection of quasispecies with $f_1 = 1.9$, $f_2 = 2.0$, $f_3 = 2.1$, and $p = 0.01$, parametric plot on S_3

Chain length and error threshold

$$Q \cdot \sigma_m \quad = \quad (1-p)^{\ell} \cdot \sigma_m \quad \geq \quad 1 \quad \Rightarrow \quad n \cdot \ln(1-p) \geq -\ln\sigma_m$$

$$p \;\ldots\; \text{constant}: \quad \ell_{\max} \approx \frac{\ln\sigma_m}{p}$$

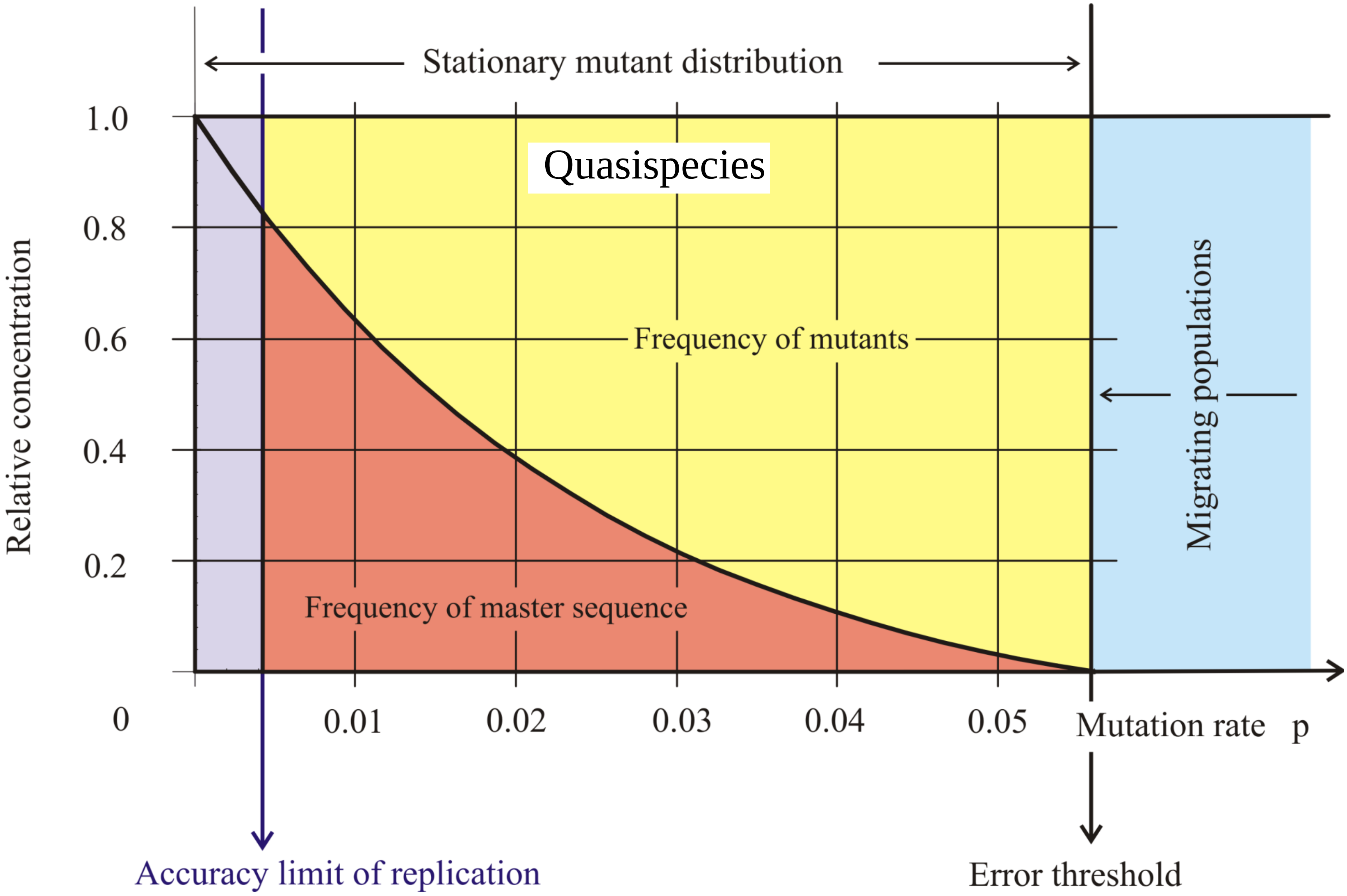
$$\ell \;\ldots\; \text{constant}: \quad p_{\max} \approx \frac{\ln\sigma_m}{\ell}$$

$Q = (1-p)^{\ell}$ ... replication accuracy

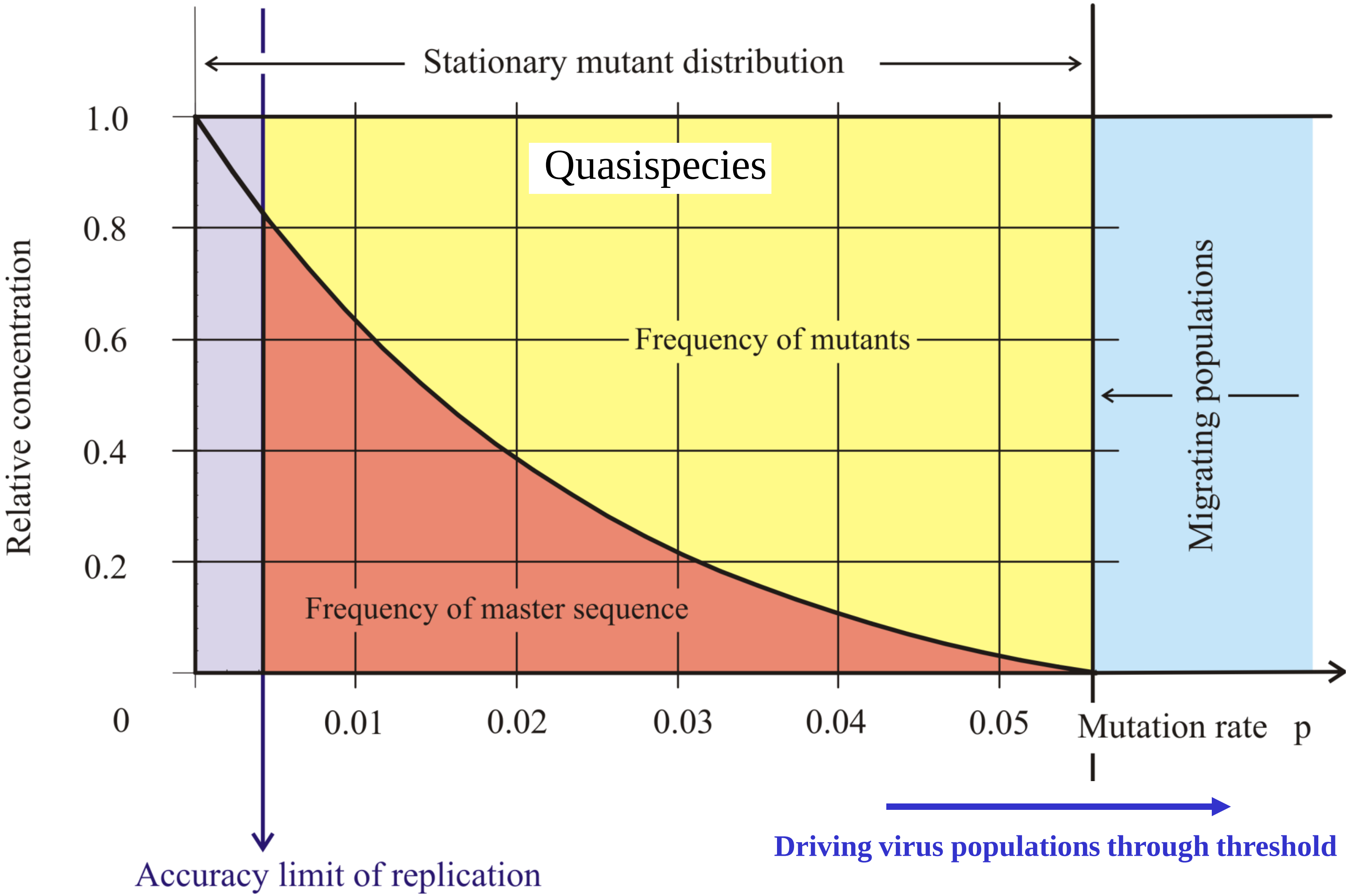
p ... error rate

ℓ ... chain length

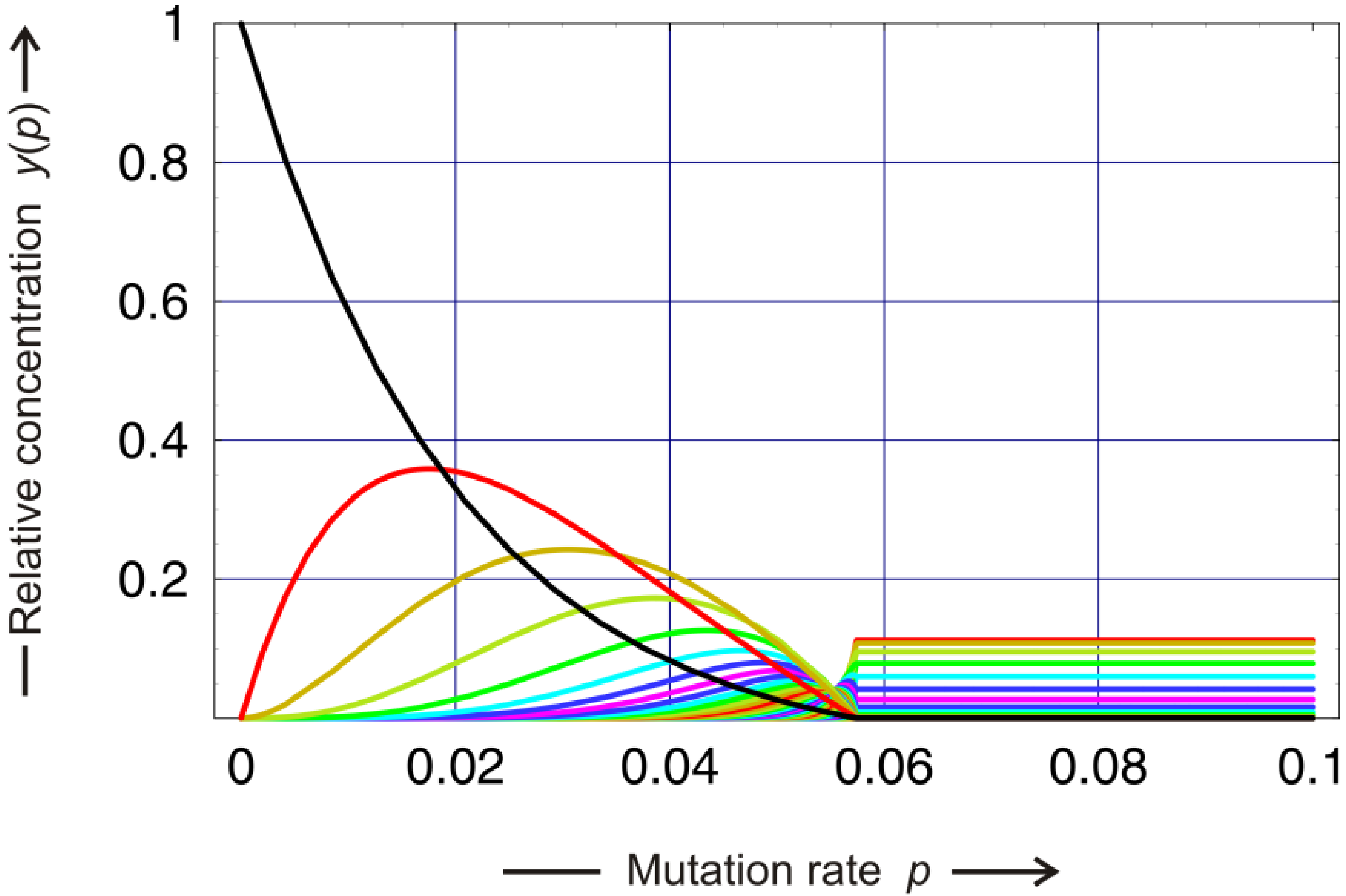
$$\sigma_m = \frac{(1-\bar{\xi}_m)\, f_m}{\sum_{j \neq m} \bar{\xi}_j \, f_j} \quad \ldots \quad \text{superiority of master sequence}, \sum_{i=1}^{n} \bar{\xi}_i = 1$$



The error threshold in replication: No mutational backflow approximation



The error threshold in replication: No mutational backflow approximation



single peak landscape: $\ell = 100,\ f_m = 10,\ f_0 = f_{\neq m} = 1$