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

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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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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.

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.

adenosine triphosphate (ATP)

\[
\text{ATP} + \text{H}_2\text{O} \leftrightarrow \text{ADP} + \text{P}_i
\]

equilibrium concentrations: \( \Delta G^0 = -40 \text{ to } -30 \text{ kJ/mol} \)

physiological conc.: \( \Delta G = \Delta G^0 + RT \ln Q = -70 \text{ to } -50 \text{ kJ/mol} \)


conditions: \( T = 20^\circ \text{C}, \text{pH} = 8.0, \text{pMg} = 2.5, I = 0.08 \text{ M} \)
\[
\Delta G^0 = -31.3 \text{ kJ/mol}, \quad \Delta H^0 = -28.1 \text{ kJ/mol}, \quad -T\Delta S^0 = -3.2 \text{ kJ/mol} \quad \text{or} \quad \Delta S^0 = 11 \text{ J/(K\cdotmol)}
\]

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 physical 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 parts TV-production „All Life is Chemistry“ written 1978 by the Austrian author and historian Hellmut Andics and produced by Austrian television.
... 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 membranes, etc., themselves.

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
April, 1931

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 H2, 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. The Electron-Pair Bond

The Interaction of Simple Atoms.—The discussion of the wave equation for the hydrogen molecule by Heitler and London, Sugiura, and Wang 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) 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).

1 Y. Sugiura, ibid., 45, 486 (1927).

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.


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

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

DNA replication and mutation

$p \ldots \text{mutation rate per site and replication}$
myoglobin structure


hemoglobin structure


conformational change $R \leftrightarrow T$

Theislierice at http://proteopedia.org/wiki/index.php/Hemoglobin
sketch of the cellular metabolism after deciphering the genetic code
transcription and translation
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"Nothing in biology makes sense except in the light of evolution, ..."

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.

Modern phylogenetic tree with common ancestor.
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

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

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

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

\[
\Pi = \{X_m\} \quad \text{or} \quad \lim_{t \to \infty} \xi_m(t) = 1 \quad \text{and} \quad \lim_{t \to \infty} \xi_{i \neq m}(t) = 0
\]

the mathematics of selection
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

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
DNA base pairing

DNA base stacking
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"random chemistry" producing complex organic molecules → RNA world → RNA + proteins → DNA + RNA + proteins

prebiotic chemistry RNA world RNP world LUCA

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

RNA replication by Qβ-replicase


Evolution in the test tube
Mutation and replication as parallel chemical reactions

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

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

*Mutation matrix*

*fitness landscape*

M. Eigen. 1971. *Naturwissenschaften* 58:465,
Mutation and replication as parallel chemical reactions

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

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

fitness landscape

mutation matrix

M. Eigen. 1971. *Naturwissenschaften* 58:465,
\[ p_{\text{max}} \approx \frac{\ln \sigma_m}{\ell} \quad \text{with} \quad \sigma_m = \frac{(1 - \bar{\xi}_m) f_m}{\sum_{j \neq m} \bar{\xi}_j f_j} \quad \text{and} \quad \sum_{i=1}^{n} \bar{\xi}_i = 1 \]

the chain length of RNA molecules, \( \ell \), is constant: 

\text{\textit{in vitro} evolution, virus populations, …}

error threshold defines a maximal mutation rate \( p_{\text{max}} \)
quasispecies

the error threshold in the development of antiviral drugs

stationary mutant distribution

frequency of mutants

quasispecies

frequency of master sequence

migrating populations
(uniform distribution)

accuracy limit of replication

mutation rate $p$

error threshold
quasispecies driving population through error threshold

the error threshold in the development of antiviral drugs
\[ \ell_{\text{max}} \approx \frac{\ln \sigma_m}{p} \quad \text{with} \quad \sigma_m = \frac{(1 - \bar{\xi}_m) f_m}{\sum_{j \neq m} \bar{\xi}_j f_j} \quad \text{and} \quad \sum_{i=1}^{n} \bar{\xi}_i = 1 \]

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 \( \ell_{\text{max}} \)

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

The logistic equation: Verhulst 1838

The consequence of finite resources

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

The logistic equation: Verhulst 1838

Population: \( \Pi = \{X\} \)
\[
\frac{dX}{dt} = f X \left(1 - \frac{X}{C}\right) \quad \Rightarrow \quad \frac{dX}{dt} = f X - \frac{X}{C} f X
\]

\[
f X \equiv \Phi(t), \quad C = 1: \quad \frac{dX}{dt} = X \left(f - \Phi\right)
\]

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

\[
\frac{dX_j}{dt} = X_j \left(f_j - \sum_{i=1}^n f_i X_i\right) = X_j \left(f_j - \Phi\right); \quad \Phi = \sum_{i=1}^n f_i X_i
\]

**Darwin**

\[
\frac{d\Phi}{dt} = 2 \left(\langle f^2 \rangle - \langle \bar{f} \rangle^2\right) = 2 \text{ var}\{f\} \geq 0
\]

generalization of the logistic equation to \(n\) variables yields selection
\[ \Pi = \{X_1, X_2, \ldots, X_n\} \]

\[ X(t) = (X_1(t), X_2(t), \ldots, X_n(t)); \quad N(t) = \sum_{i=1}^{n} X_i(t) \]

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

\[ \Phi(t) \ldots \text{ time integral of mean fitness} \]

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

solution of the logistic equation in \( n \) variables
\[ \xi_j(t) = \frac{X_j(t)}{N(t)} = \frac{\xi_j(0)\exp(f_j t)}{\sum_{i=1}^{n} \xi_i(0)\exp(f_i t)} \]

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

\[ \mathbf{f} = (1.10, 1.08, 1.06, 1.04, 1.02) \]
\[
\frac{dx_j}{dt} = \sum_{i=1}^{n} W_{ji} x_i - x_j \Phi; \quad j = 1, 2, \ldots, n
\]

\[
\Phi = \sum_{i=1}^{n} f_i x_i / \sum_{i=1}^{n} x_i
\]

Mutation and (correct) replication as parallel chemical reactions

M. Eigen. 1971. *Naturwissenschaften* 58:465,
\[
\frac{dx_j}{dt} = \sum_{i=1}^{n} W_{ji} \, x_i - x_j \, \Phi = \sum_{i=1}^{n} Q_{ji} \, f_i \, x_i - x_j \, \Phi; \quad j = 1, 2, \ldots, n
\]

\[
\Phi = \frac{\sum_{i=1}^{n} f_i \, x_i}{\sum_{i=1}^{n} x_i}
\]

Decomposition of matrix \( W \)

\[
W = \begin{pmatrix}
    w_{11} & w_{12} & \cdots & w_{1n} \\
    w_{21} & w_{22} & \cdots & w_{2n} \\
    \vdots & \vdots & \ddots & \vdots \\
    w_{n1} & w_{n2} & \cdots & w_{nn}
\end{pmatrix} = Q \cdot F \text{ with}
\]

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

factorization of the value matrix \( W \) separates mutation and fitness effects.
mutation-selection equation: $[I_i] = x_i \geq 0, f_i \geq 0, Q_{ij} \geq 0$

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

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

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

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

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

the quasispecies is the dominant eigenvector $\ell_0$ of $\Lambda$
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

\[ Q \cdot \sigma_m = (1 - p)^\ell \cdot \sigma_m \geq 1 \Rightarrow n \cdot \ln(1-p) \geq -\ln\sigma_m \]

\[ p \text{ ... constant: } \quad \ell_{\text{max}} \approx \frac{\ln\sigma_m}{p} \]

\[ \ell \text{ ... constant: } \quad p_{\text{max}} \approx \frac{\ln\sigma_m}{\ell} \]

\[ Q = (1 - p)^\ell \text{ ... replication accuracy} \]

\[ p \text{ ... error rate} \]

\[ \ell \text{ ... chain length} \]

\[ \sigma_m = \frac{(1 - \bar{\xi}_m) f_m}{\sum_{j \neq m} \bar{\xi}_j f_j} \text{ ... superiority of master sequence, } \sum_{i=1}^{n} \bar{\xi}_i = 1 \]
The error threshold in replication: No mutational backflow approximation
The error threshold in replication: No mutational backflow approximation
single peak landscape: $\ell = 100, f_m = 10, f_0 = f_{\neq m} = 1$