Vom Modell zur Steuerung

Sind wir überfordert von der Komplexität der Welt?

Peter Schuster

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

Leopoldina Workshop: Modeling Nature and Society

Can We Control the World?

Weimar, 30.06.– 02.07.2016

From Modeling to Control

Are We Unable to Cope with the Complexity of the World?

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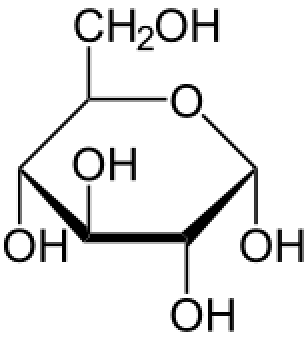
Web-Page for further information:

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

What means complexity and where does it come from?



$+ \quad 2\,[NAD]^+ + 2\,ADP + 2\,[H_2PO_4]^- \rightarrow$

$\rightarrow \quad 2\,[CH_3COCOO]^- + 2\,NADH + 2\,H^+ + 2\,ATP + 2\,H_20$

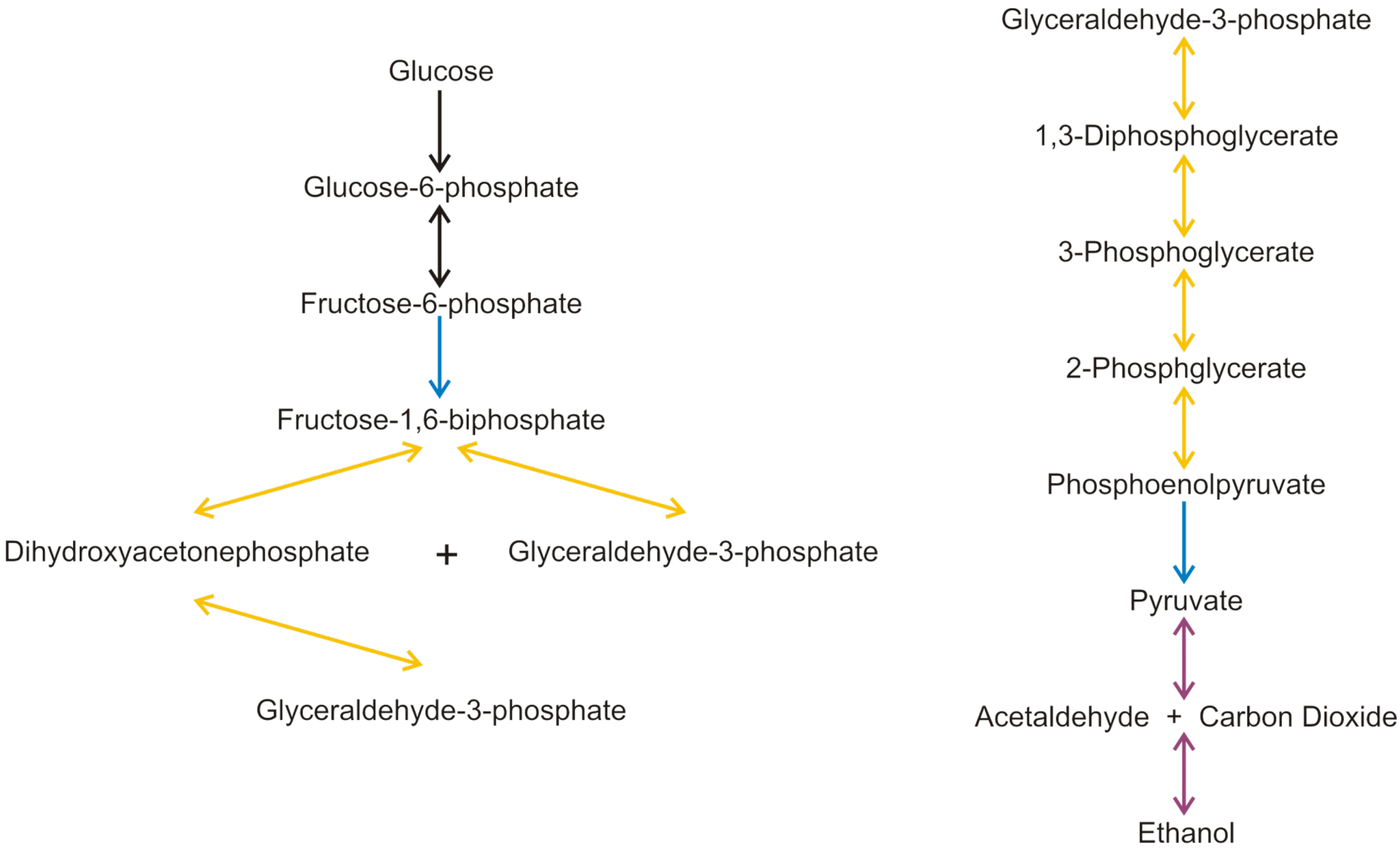
glucose → 2 pyruvate + 2 reduction equivalents + energy

$[CH_3COCOO]^- + NADH + 2\,H^+ \rightarrow C_2H_5OH + CO_2 + [NAD]^+$

pyruvate + reduction equivalent → ethanol + carbon dioxide

Reaction equation of **glycolysis** and **ethanol** fermentation

$C6 \Rightarrow 2 \times C3$ $C3 \Rightarrow C2 + C1$



Glucose

Glucose-6-phosphate

Fructose-6-phosphate

Fructose-1,6-biphosphate

Dihydroxyacetonephosphate + Glyceraldehyde-3-phosphate

Glyceraldehyde-3-phosphate

Glyceraldehyde-3-phosphate

1,3-Diphosphoglycerate

3-Phosphoglycerate

2-Phosphglycerate

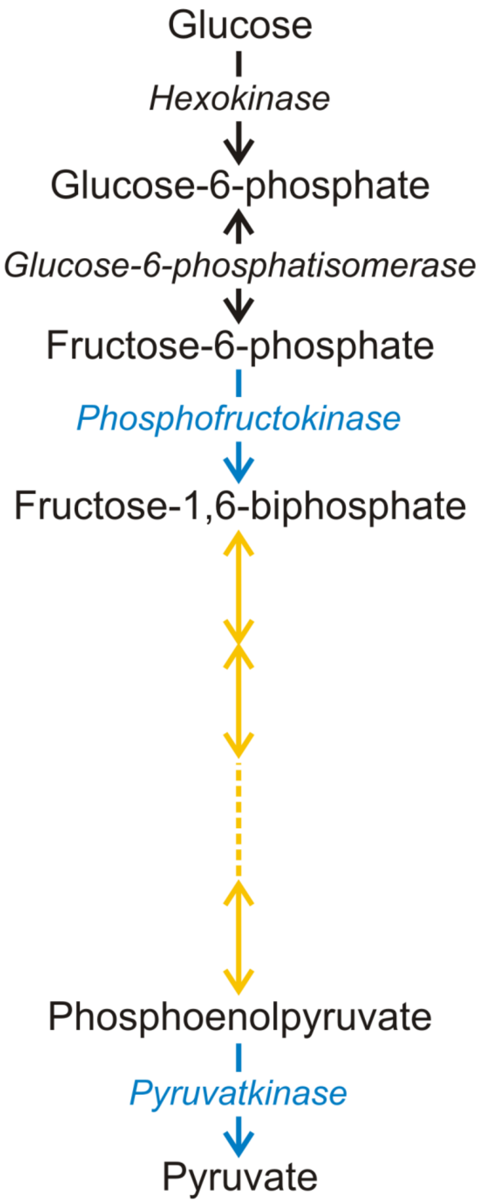
Phosphoenolpyruvate

Pyruvate

Acetaldehyde + Carbon Dioxide

Ethanol

Reaction chain of glycolysis and ethanol fermentation: 12 steps



Glucose

Hexokinase

Glucose-6-phosphate

Glucose-6-phosphatisomerase

Fructose-6-phosphate

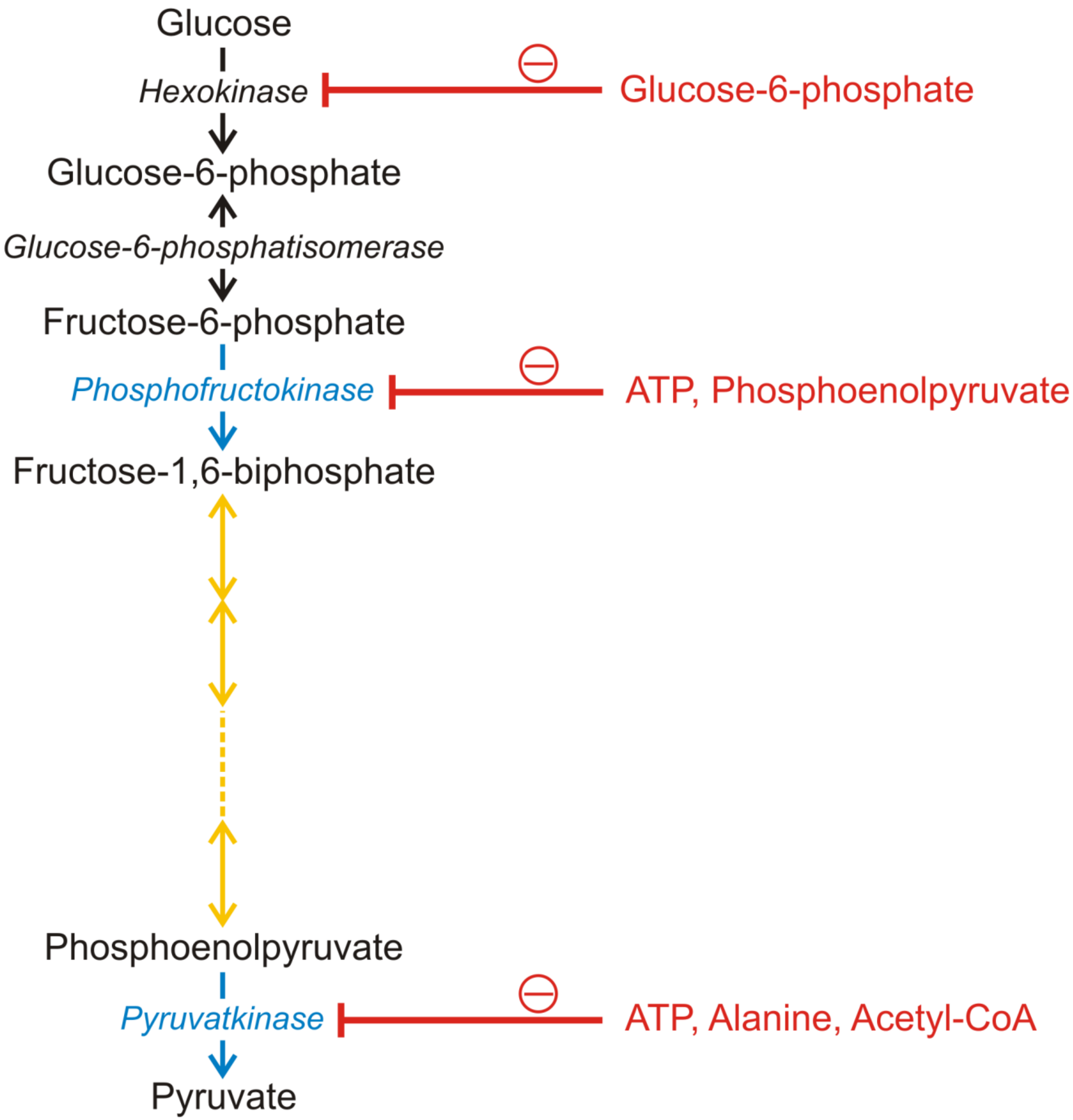
Phosphofructokinase

Fructose-1,6-biphosphate

Phosphoenolpyruvate

Pyruvatkinase

Pyruvate



Glucose

Hexokinase

Glucose-6-phosphate

Glucose-6-phosphate

Glucose-6-phosphatisomerase

Fructose-6-phosphate

Phosphofructokinase

ATP, Phosphoenolpyruvate

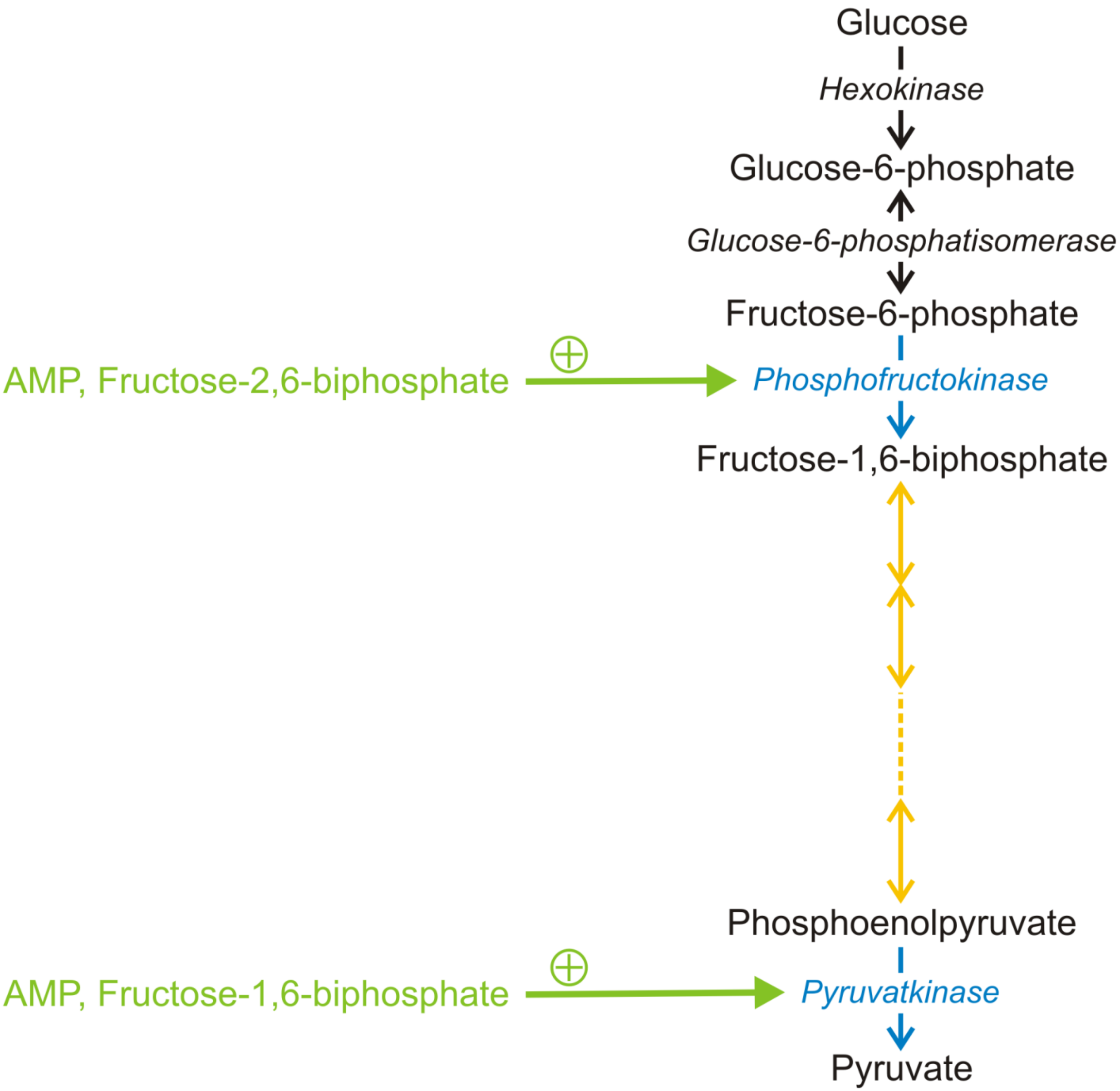
Fructose-1,6-biphosphate

Phosphoenolpyruvate

Pyruvatkinase

ATP, Alanine, Acetyl-CoA

Pyruvate



Glucose

Hexokinase

Glucose-6-phosphate

Glucose-6-phosphatisomerase

Fructose-6-phosphate

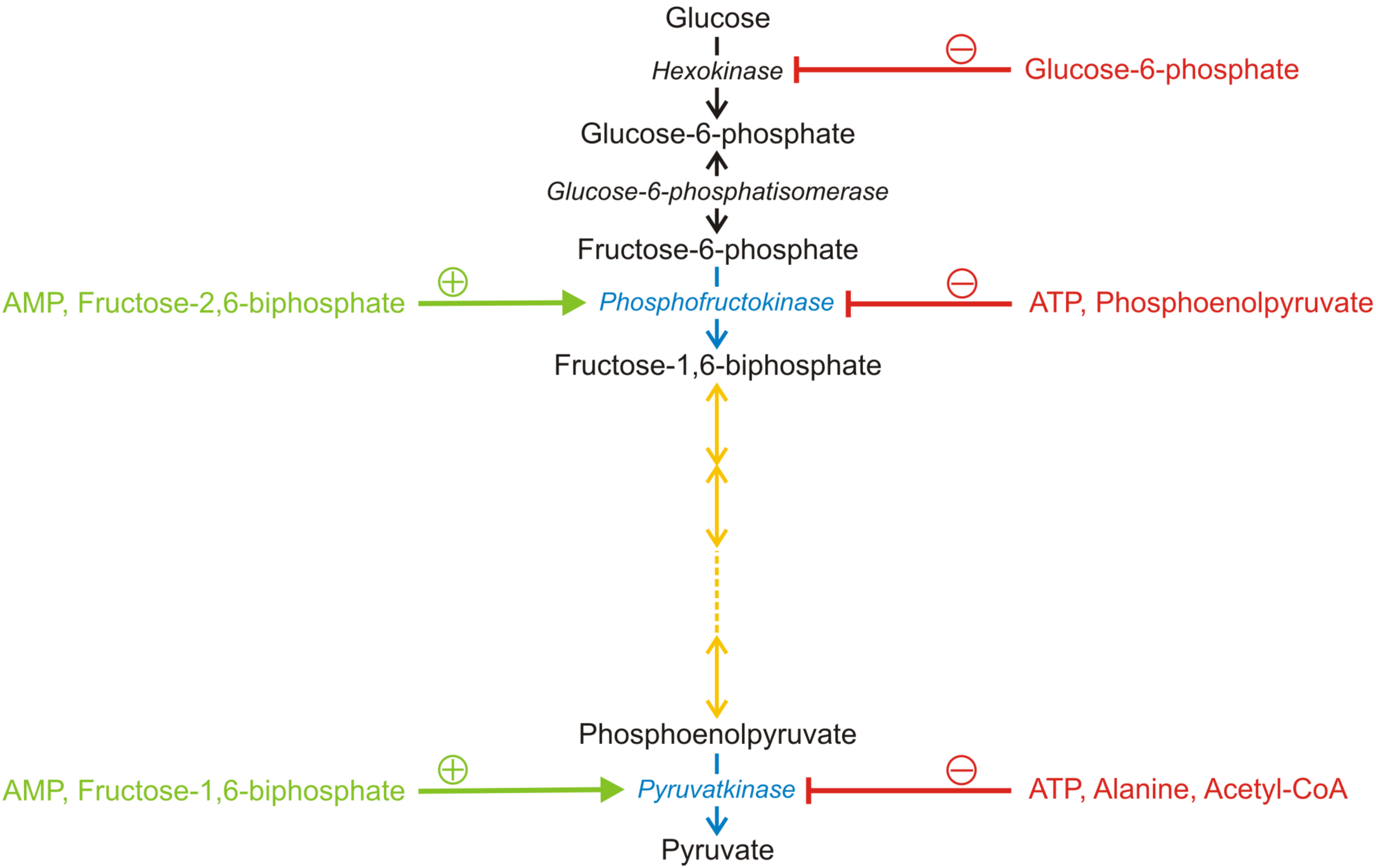
AMP, Fructose-2,6-biphosphate ⊕ *Phosphofructokinase*

Fructose-1,6-biphosphate

Phosphoenolpyruvate

AMP, Fructose-1,6-biphosphate ⊕ *Pyruvatkinase*

Pyruvate



Glucose

Hexokinase

⊖ Glucose-6-phosphate

Glucose-6-phosphate

Glucose-6-phosphatisomerase

Fructose-6-phosphate

AMP, Fructose-2,6-biphosphate ⊕

Phosphofructokinase

⊖ ATP, Phosphoenolpyruvate

Fructose-1,6-biphosphate

Phosphoenolpyruvate

AMP, Fructose-1,6-biphosphate ⊕

Pyruvatkinase

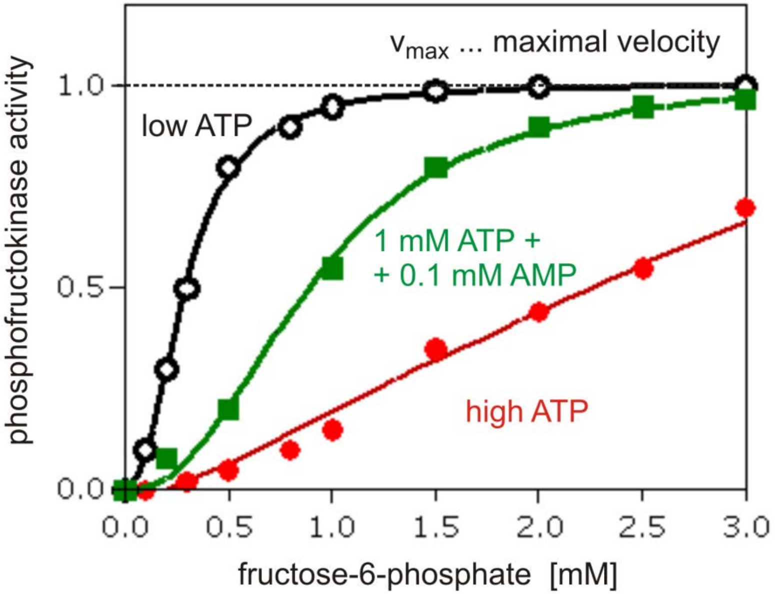
⊖ ATP, Alanine, Acetyl-CoA

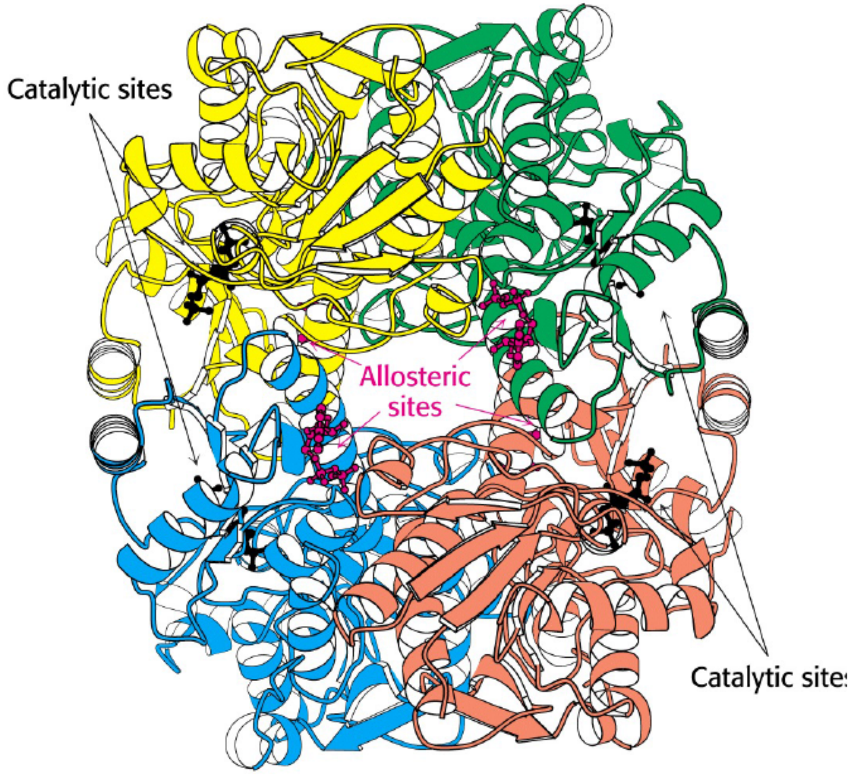
Pyruvate

$$v(s) = \frac{s^n}{K + s^n}$$

$n = 1$: linear response

$n > 1$: cooperativity





[fructose-6-phosphate] = 1 mM

0.1 mM ATP: $0.96\ v_{max}$

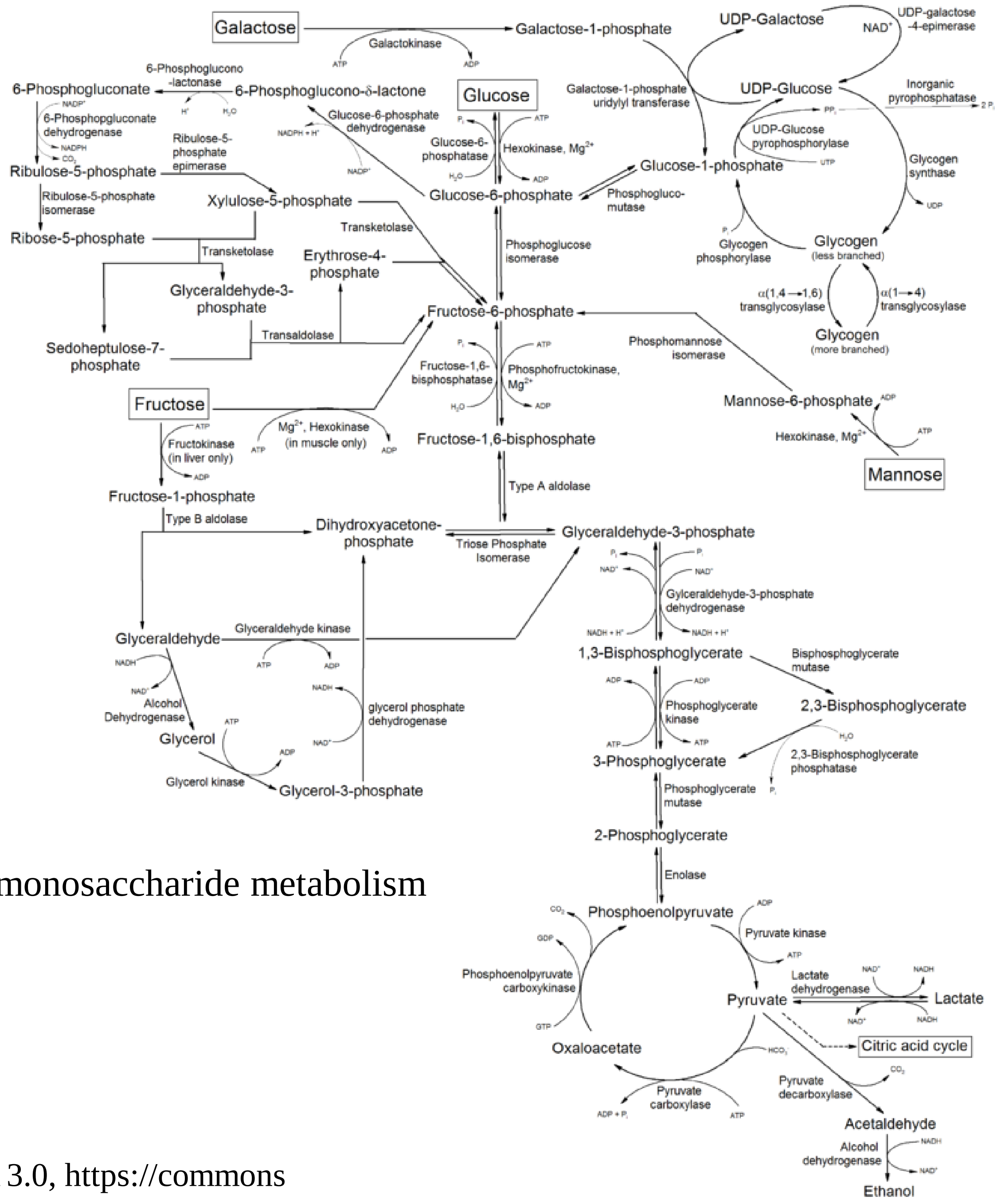
1 mM ATP + 0.1 mM AMP: $0.54\ v_{max}$

1 mM ATP: $0.15\ v_{max}$

Regulation of phosphofructokinase (PFK-1)

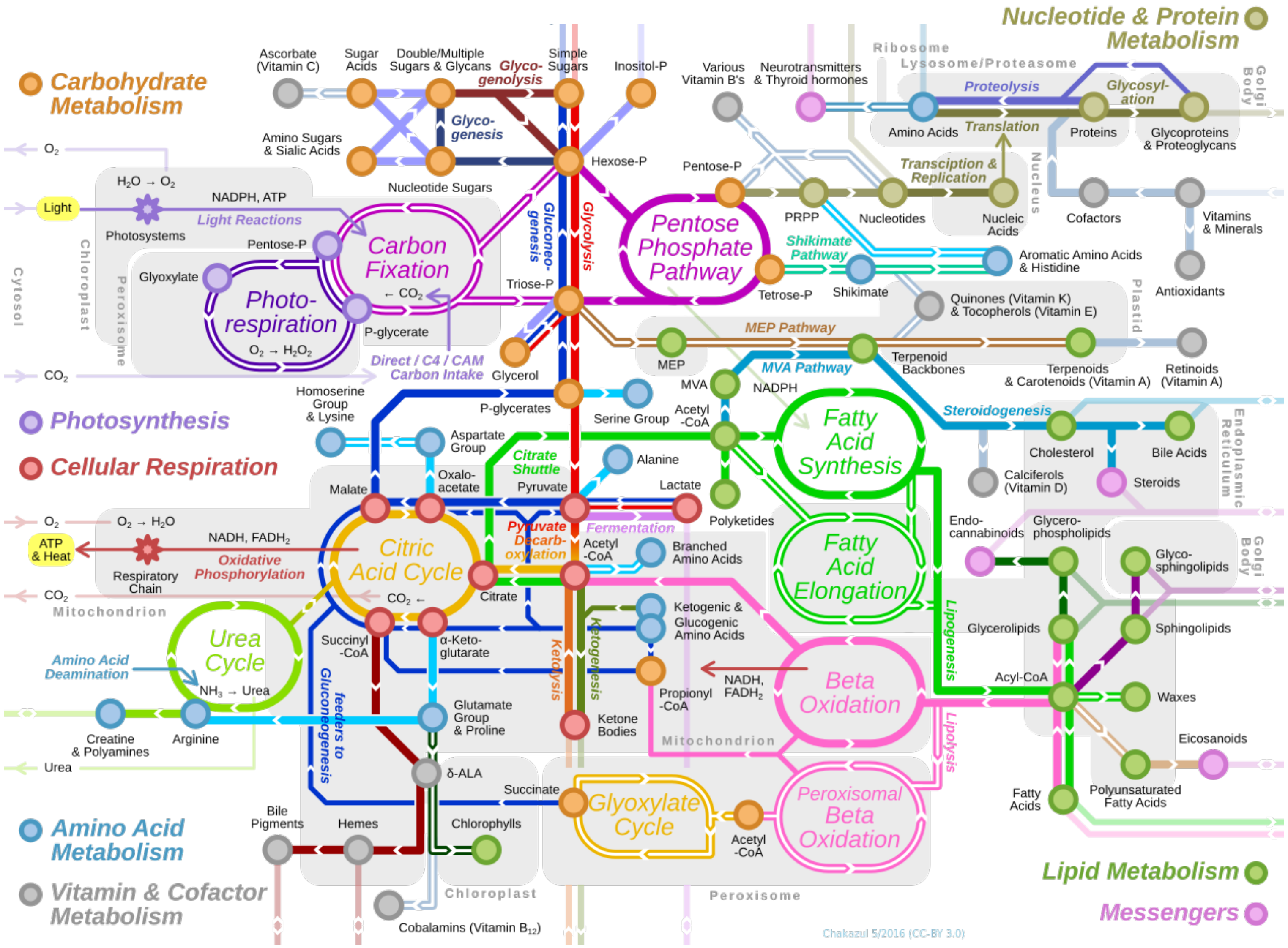
J.M.Berg, J.L.Tymoczko, L.Stryer. Biochemistry. 5th ed., p.444 (2002)

Complexity may result from embedding in complex environment



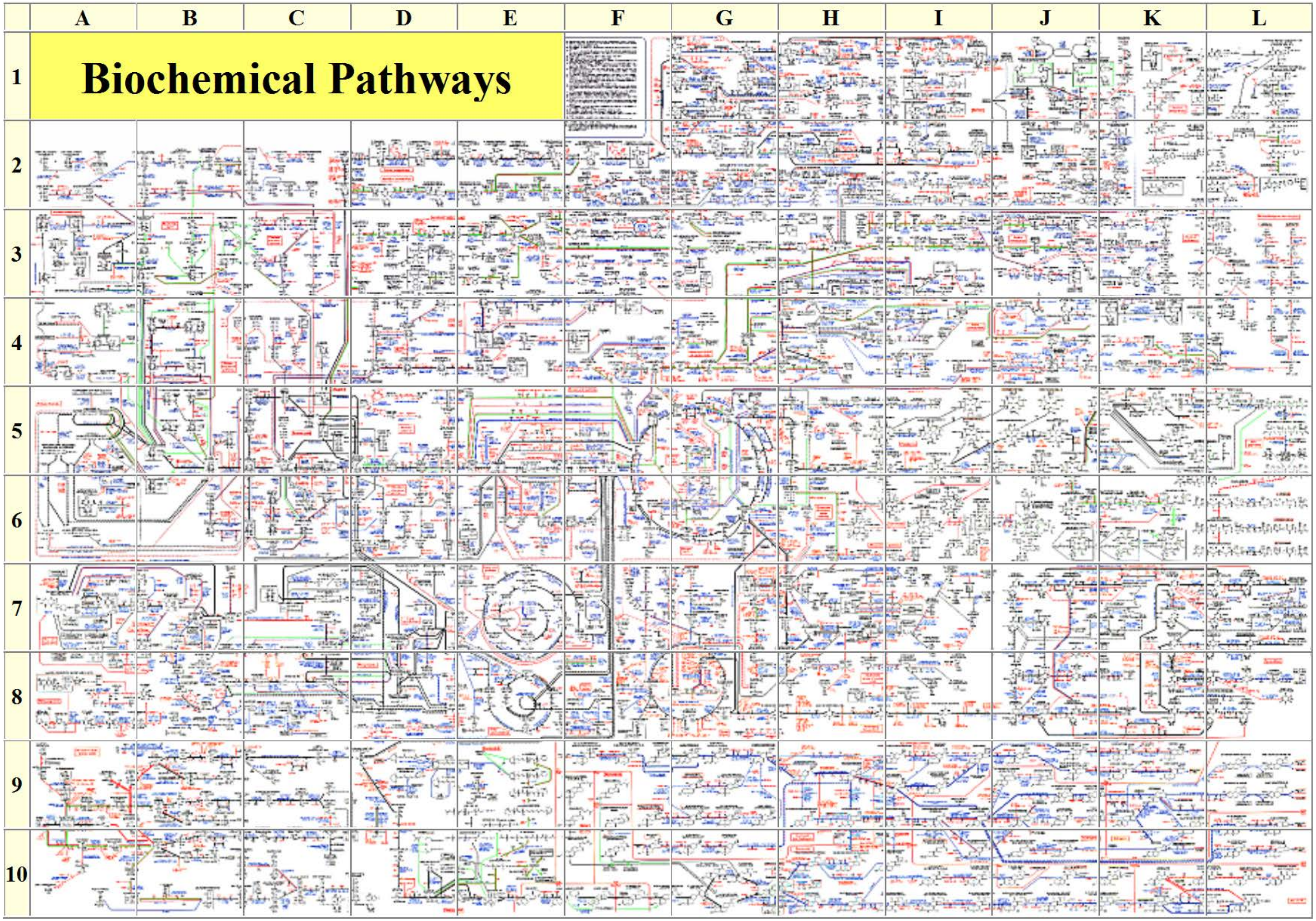
Embedding of glycolysis in the monosaccharide metabolism

By LHcheM-own work, CC BY-SA 3.0, https://commons



Bert Chan, Hong Kong: Metro map of metabolism

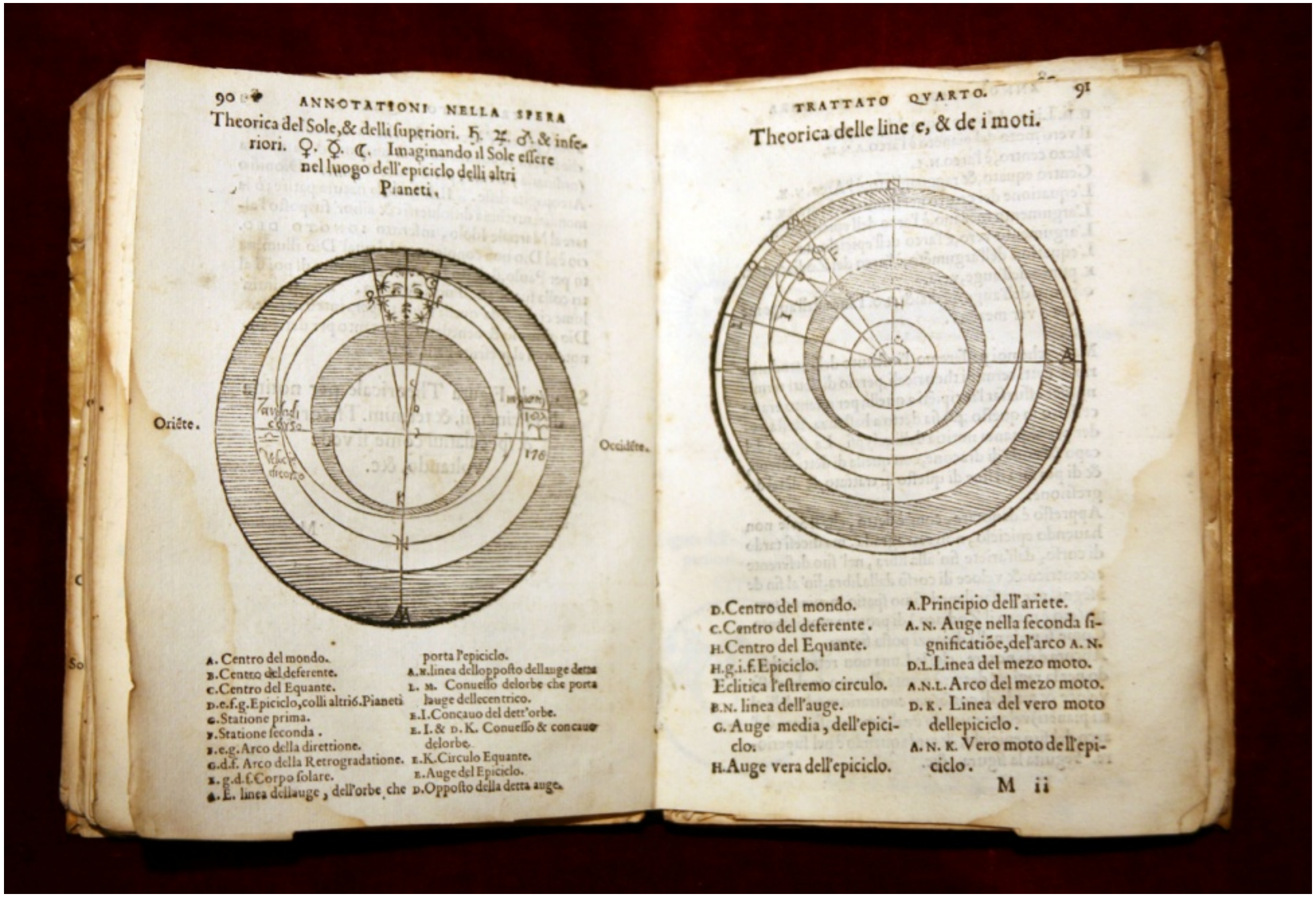
Glycolysis embedded in the cellular metabolism



The reaction network of cellular metabolism published by Boehringer-Mannheim.

Complexity may result from lack of insight

Sacrobosco's Tractatus de Sphaere, 1230



90 ANNOTATIONI NELLA SPERA

Theorica del Sole,& delli ſuperiori. ♄. ♃. ♂. & inferiori. ♀. ☿. ☾. Imaginando il Sole eſſere nel luogo dell'epiciclo delli altri Pianeti.

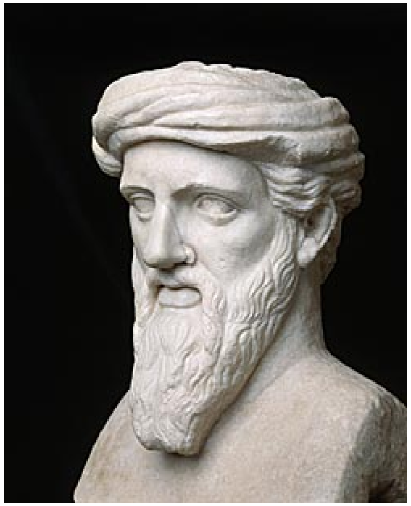
A. Centro del mondo.
B. Centro del deferente.
C. Centro del Equante.
D.e.f.g. Epiciclo, colli altri 6. Pianeti
G. Statione prima.
F. Statione ſeconda.
B.e.g. Arco della direttione.
G.d.f. Arco della Retrogradatione.
B.g.d.f. Corpo ſolare.
A.E. linea dellauge, dell'orbe che porta l'epiciclo.
A.H. linea delloppoſto dellauge detta
L. M. Conueſſo delorbe che porta lauge dellecentrico.
E.I. Concauo del dett'orbe.
E.I. & D.K. Conueſſo & concauo delorbe.
E.K. Circulo Equante.
E. Auge del Epiciclo.
D. Oppoſto della detta auge.

TRATTATO QVARTO. 91

Theorica delle line e, & de i moti.

D. Centro del mondo.
C. Centro del deferente.
H. Centro del Equante.
H.g.i.f. Epiciclo.
Eclitica l'eſtremo circulo.
B.N. linea dell'auge.
G. Auge media, dell'epiciclo.
H. Auge vera dell'epiciclo.
A. Principio dell'ariete.
A. N. Auge nella ſeconda ſignificatiõe, del'arco A. N.
D.L. Linea del mezo moto.
A.N.L. Arco del mezo moto.
D. K. Linea del vero moto dellepiciclo.
A. N. K. Vero moto dell'epiciclo.

M ii



Pythagoras, 575 – 495 BC

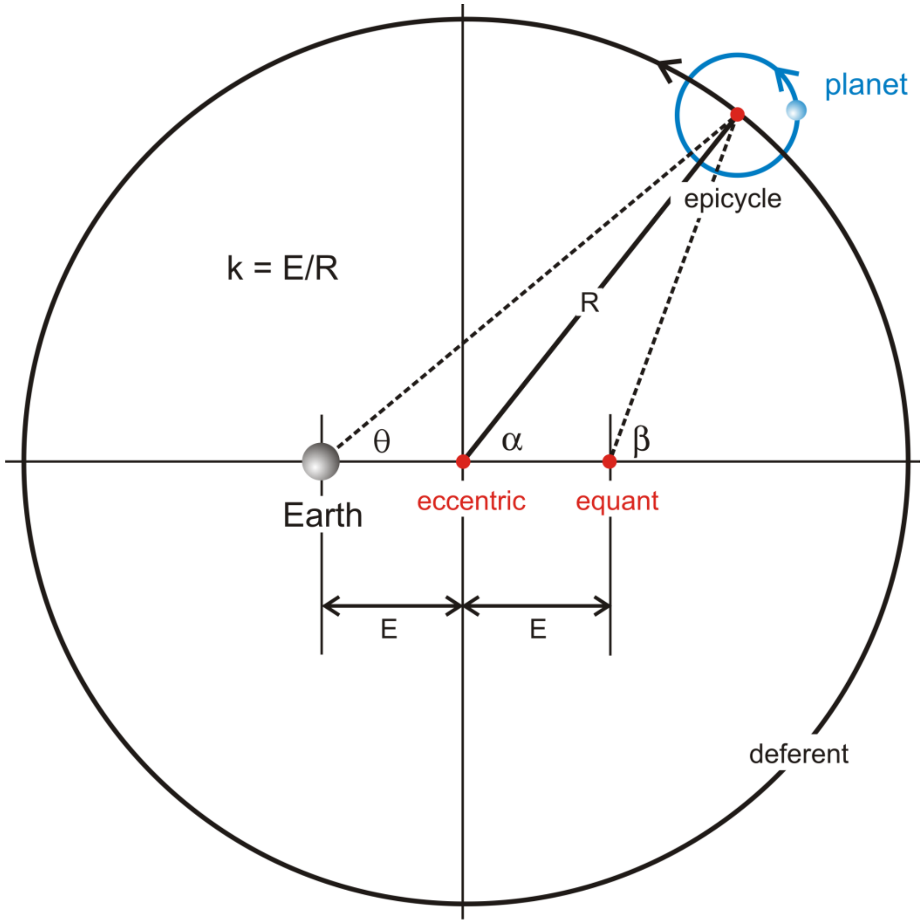
Celestial spheres and epicycles

$$\theta(t) = \arctan\left(\frac{\tan(\Omega t)}{1 - \dfrac{2k}{k\cos(\Omega t) - \sqrt{1 - k^2 \sin(\Omega t)^2}}} \right)$$

Ptolemy’s planetary motion

James Evans. On the function and the
probable origin of Ptolemy’s equant.
Am.J.Phys.52:1080-1089 (1984)

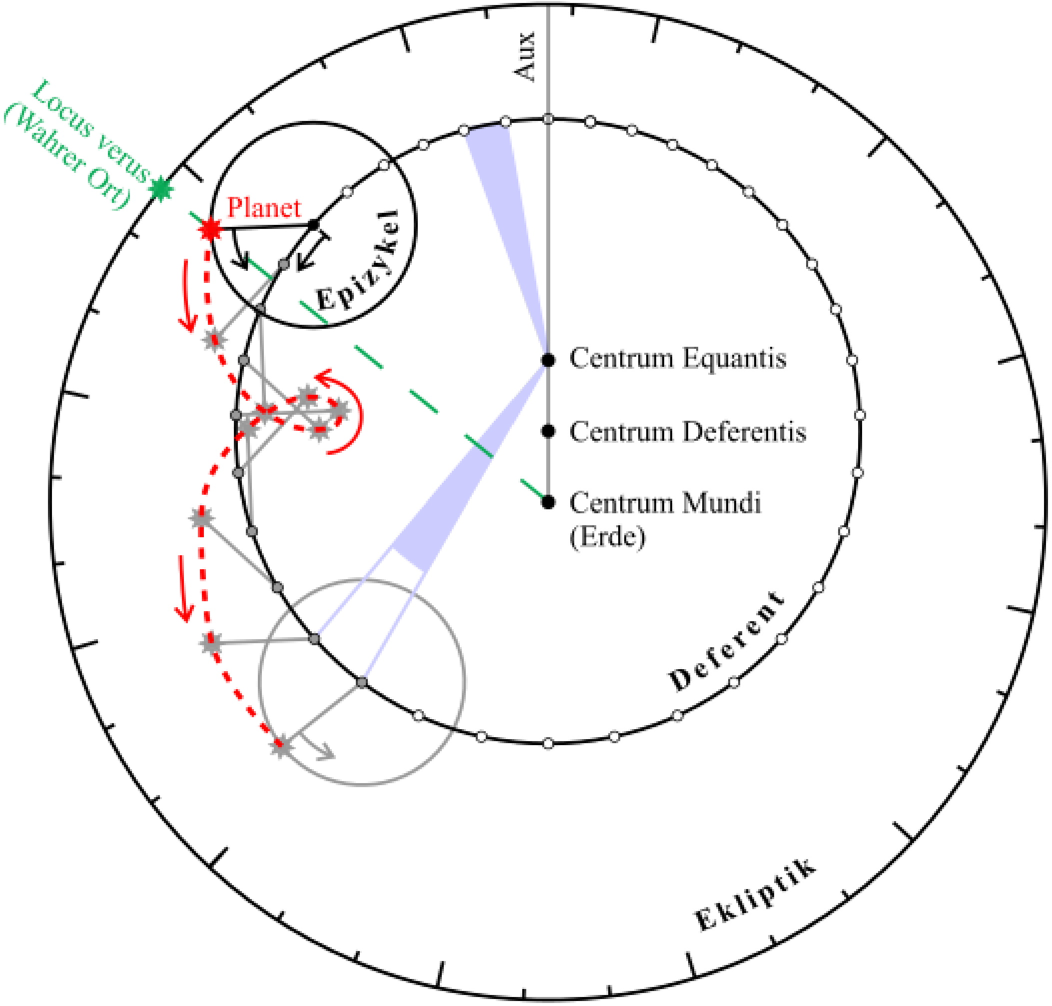
www.mathpages.com/home/kmath639/kmath639.htm



The geocentric system in Ptolemy’s astronomy

$$\theta(t) = \arctan\left(\frac{\tan(\Omega t)}{1 - \frac{2k}{k\cos(\Omega t) - \sqrt{1 - k^2 \sin(\Omega t)^2}}} \right)$$

Ptolemy’s planetary motion



Jorg-ks – eigenes Werk, CC-BY-SA 4.0

https://commons.wikimedia.org/w/index.php?curid=37885518

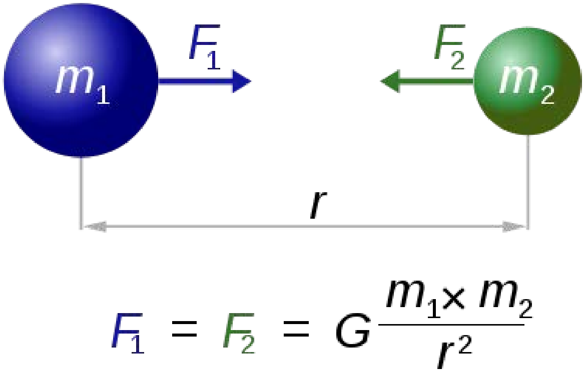
The geocentric system in Ptolemy’s astronomy

Johannes Kepler, 1571 - 1630

1. The orbit of a planet is an ellipse with the Sun at one of the two foci.
2. A line segment joining a planet and the Sun sweeps out equal areas during equal intervals of time.
3. The square of the orbital period of a planet is proportional to the cube of the semi-major axis of its orbit.

Kepler’s laws of planetary motion

Isaac Newton, 1643 - 1727



$$F_1 = F_2 = G\frac{m_1 \times m_2}{r^2}$$

law of universal gravity

Johannes Kepler, 1571 - 1630

1. The orbit of a planet is an ellipse with the Sun at one of the two foci.
2. A line segment joining a planet and the Sun sweeps out equal areas during equal intervals of time.
3. The square of the orbital period of a planet is proportional to the cube of the semi-major axis of its orbit.

Kepler’s laws of planetary motion

Isaac Newton, 1643 - 1727

1. straight and uniform motion,
2. $F = m \times a$, and
3. actio equals reactio

laws of motion

Complexity may result from lack of methods

Henri Poincaré,
1854 -1912

In 1889 the Swedish King Oscar II donated a prize for a proof that the Solar system is stable.

Poincaré (1899) was able to show that three-body motion – Earth-Sun-Planet – need not be stable and can be very sensitive to parameters and initial conditions.

The proof is rather complex and the result is not easy to illustrate.

Sensitivity to parameters and initial conditions

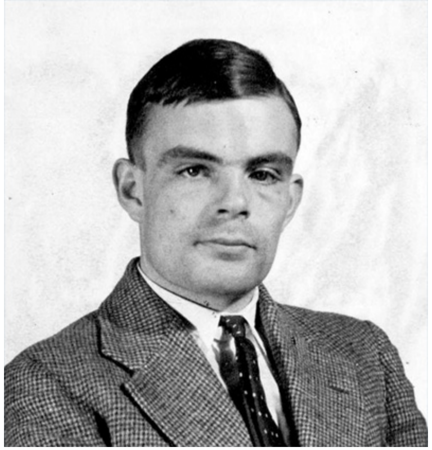
Henri Poincaré,
1854 -1912

“If we knew exactly the laws of nature and the situation of the universe at the initial moment, we could predict exactly the situation of that same universe at a succeeding moment. but even if it were the case that the natural laws had no longer any secret for us, we could still only know the initial situation approximately. If that enabled us to predict the succeeding situation with the same approximation, that is all we require, and we should say that the phenomenon had been predicted, that it is governed by laws.
But it is not always so; it may happen that **small differences** in the initial conditions produce very **great ones in the final phenomena**. A small error in the former will produce an enormous error in the latter. **Prediction becomes impossible**, and we have the fortuitous phenomenon.

Poincaré in a 1903 essay on "Science and Method“.

The visionary of deterministisches chaos

Sensitivity to parameters and initial conditions



Alan Turing, 1912 - 1954

mathematics of chemical
pattern formation 1952

1899 – 1900 oscillating
chemical reactions

Wilhelm Ostwald,1853-1932

Combination of rigorous mathematical analysis and computer simulation in the analysis of complex systems since 1980

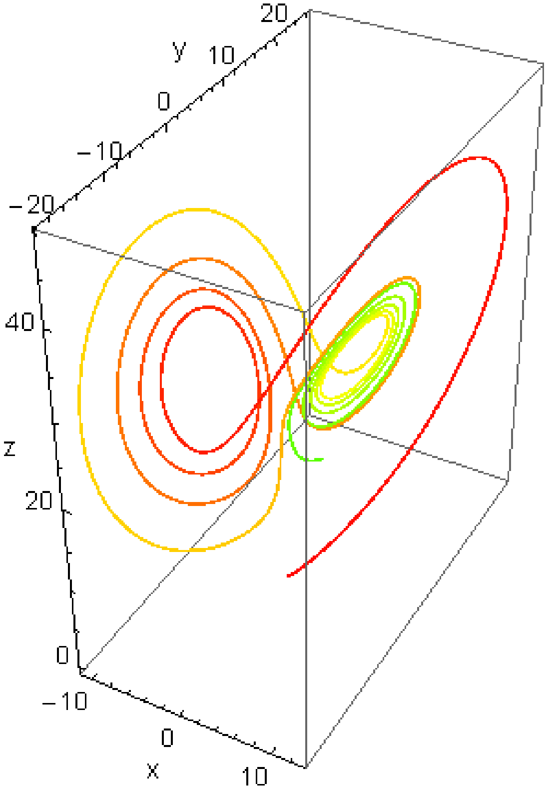
Pioneers in spatio-temporal chemical pattern formation

Edward N. Lorenz,
1917-2008

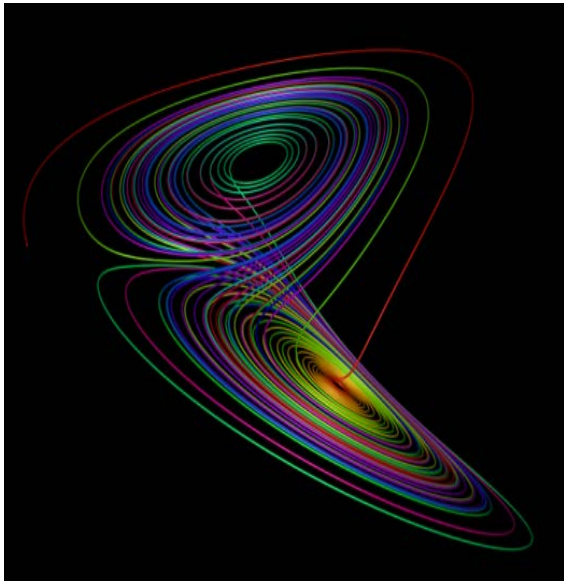
$$\frac{dx}{dt} = a\,(y - x)$$

$$\frac{dy}{dt} = x\,(b - z) - y$$

$$\frac{dz}{dt} = x\,y - c\,z$$

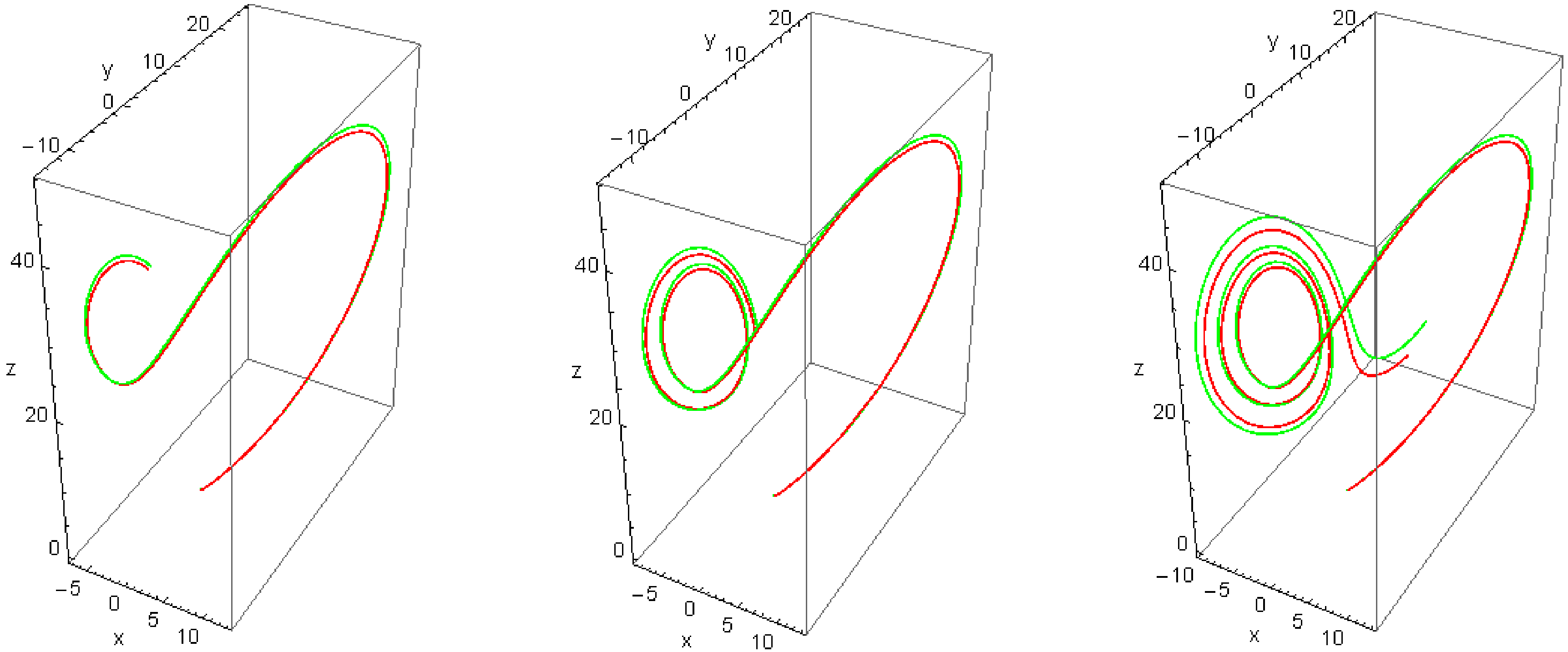


$a = 3$, $b = 28$, $c = 1$



Edward N. Lorenz.
Deterministic Nonperiodic Flow.
J. of the Atmospheric Sciences
20:130-141, 1963.

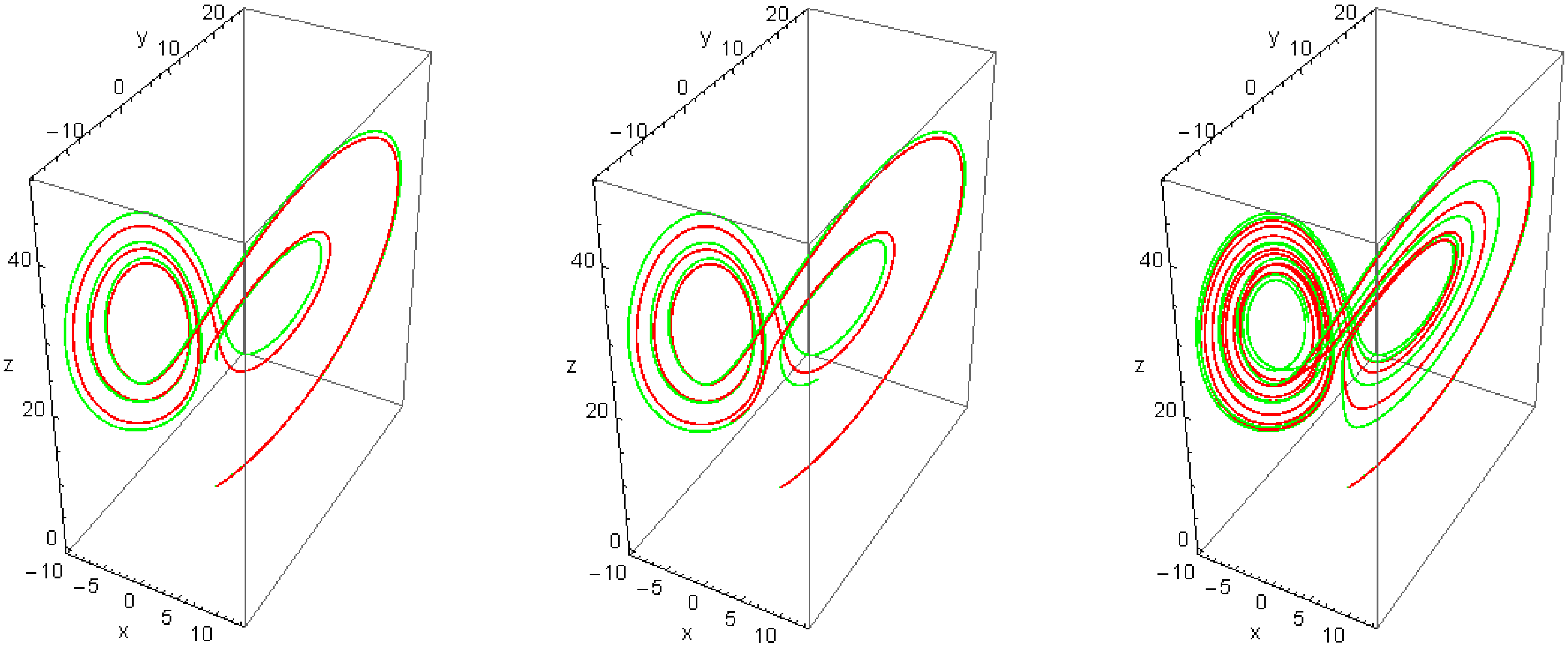
Deterministic chaos



t = 1.5 *t* = 3.0 *t* = 5.0

$a = 3$, $b = 27.8$, $b = 28.2$, $c = 1$

Sensitivity to parameters in deterministic chaos

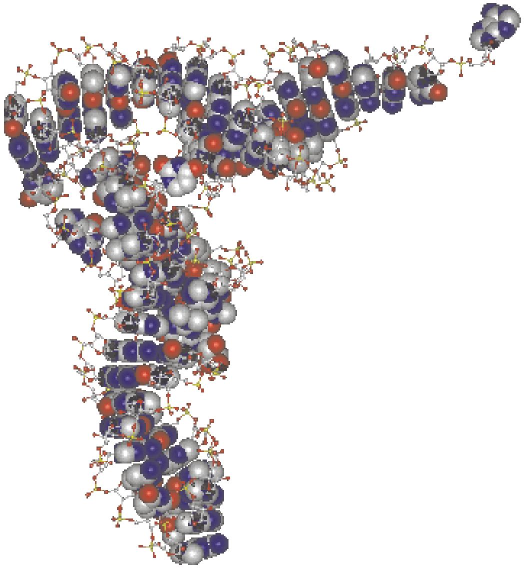


$t = 5.8$ $t = 6.3$ $t = 15.0$

$a = 3$, $b = 27.8$, $b = 28.2$, $c = 1$

Sensitivity to parameters in deterministic chaos

Complexity created by intrinsic diversity



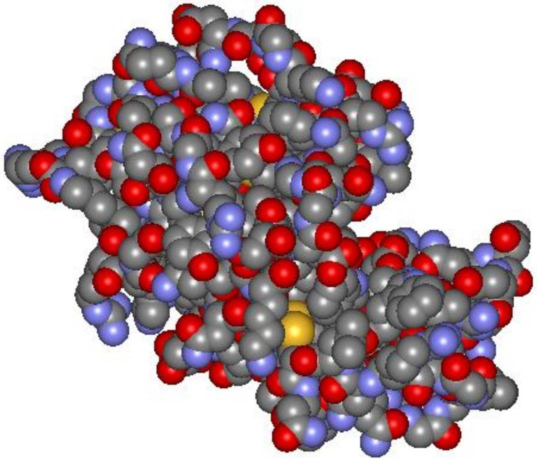
phenylalanyl-transfer-RNA – a small RNA with a sequence of **76** nucleotide residues

How many different RNA sequences of chain length **76** are possible ?

$$4^{76} = 5.7 \times 10^{45}$$

A relatively large sample of small RNA molecules contains about 10^{15} molecules

Diversity in biology – sequence space of RNA molecules



lysozyme – a small protein with a sequence of **129** amino acid residues

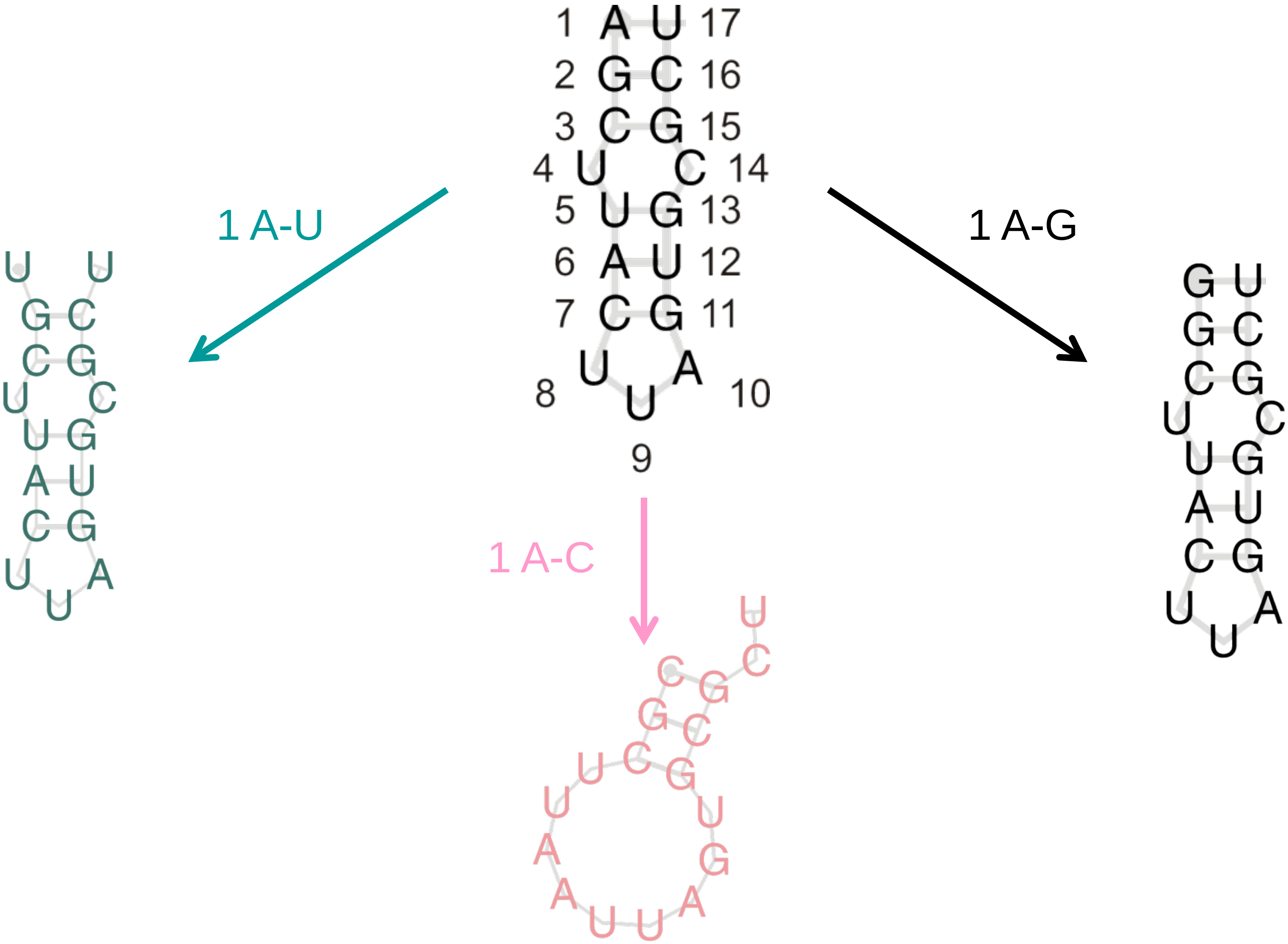
How many different protein sequences of chain length **129** are possible ?

$$20^{129} = 6.8 \times 10^{167}$$

The distribution of suitable structures and the mutation determined move sets in sequence space decide about the success of searches

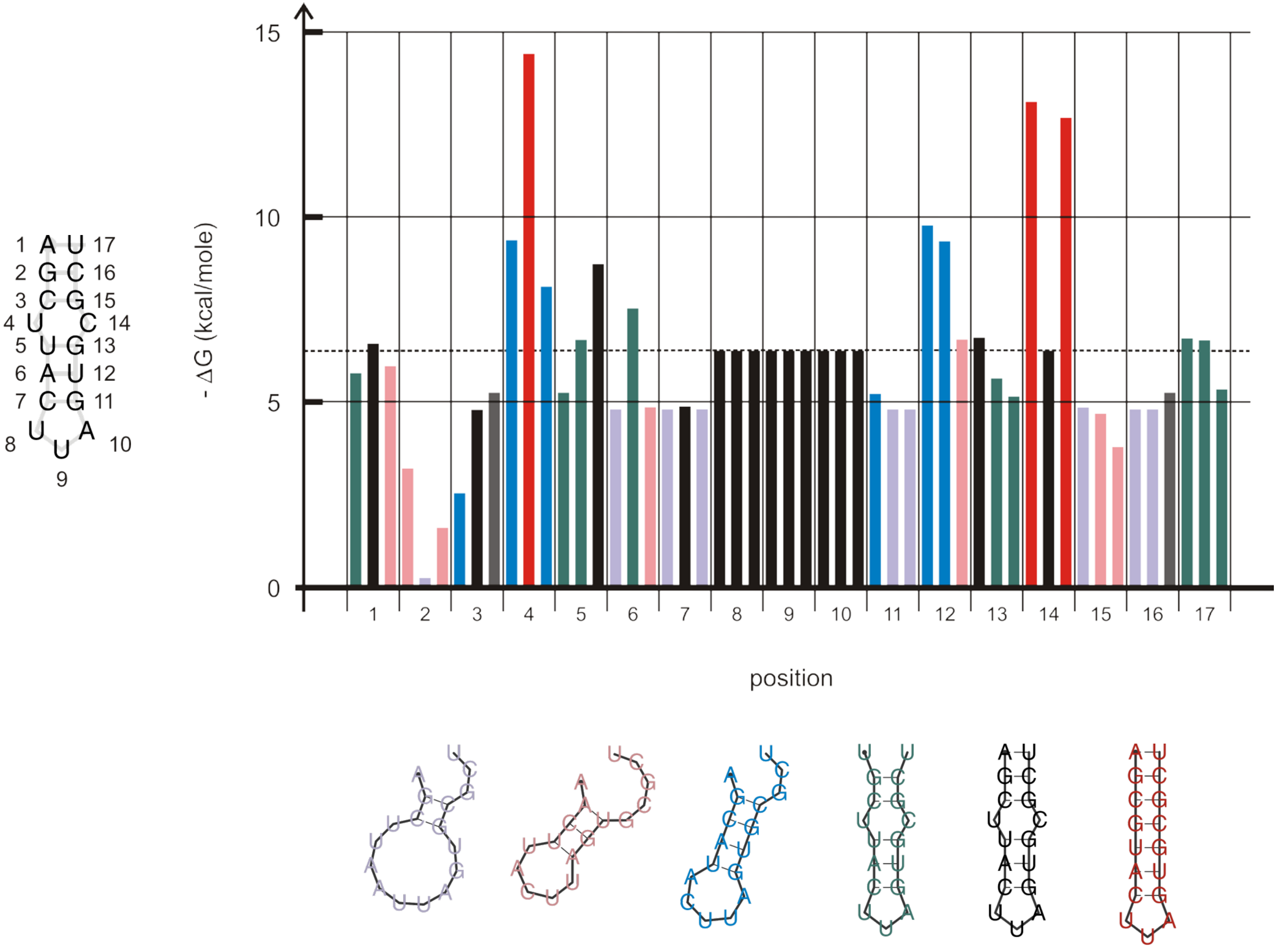
Diversity in biology – sequence space of proteins

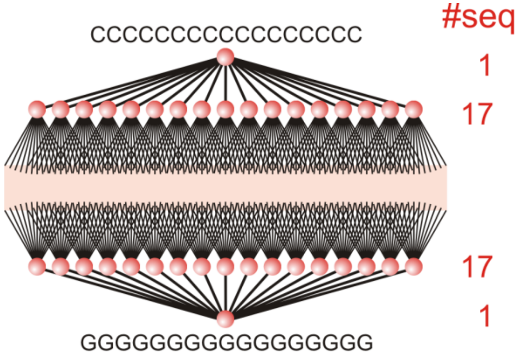
AGCUUAACUUAGUCGCU


1 A-U

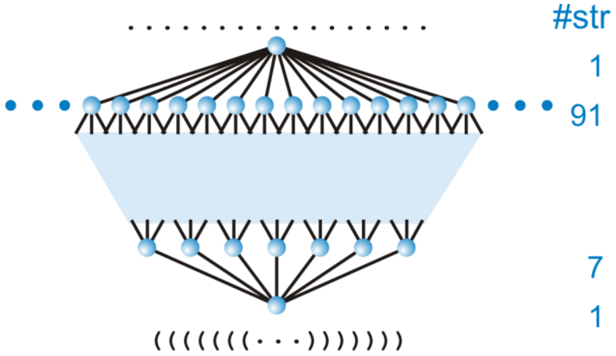
1 A-G

1 A-C

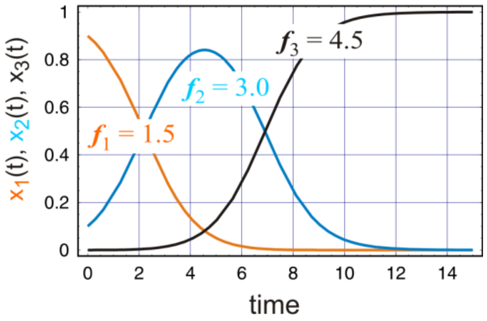

1 A U 17
2 G C 16
3 C G 15
4 U C 14
5 U G 13
6 A U 12
7 C G 11
8 U U A 10
9
- ΔG (kcal/mole)
15
10
5
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
position



sequence space 1.7×10^{10}



shape space 731



parameter space

$$X \longrightarrow S = \Phi(X) \longrightarrow f = \Psi(S)$$

sequence structure fitness

genotype → phenotype → selection

Evolutionary searches in sequence space

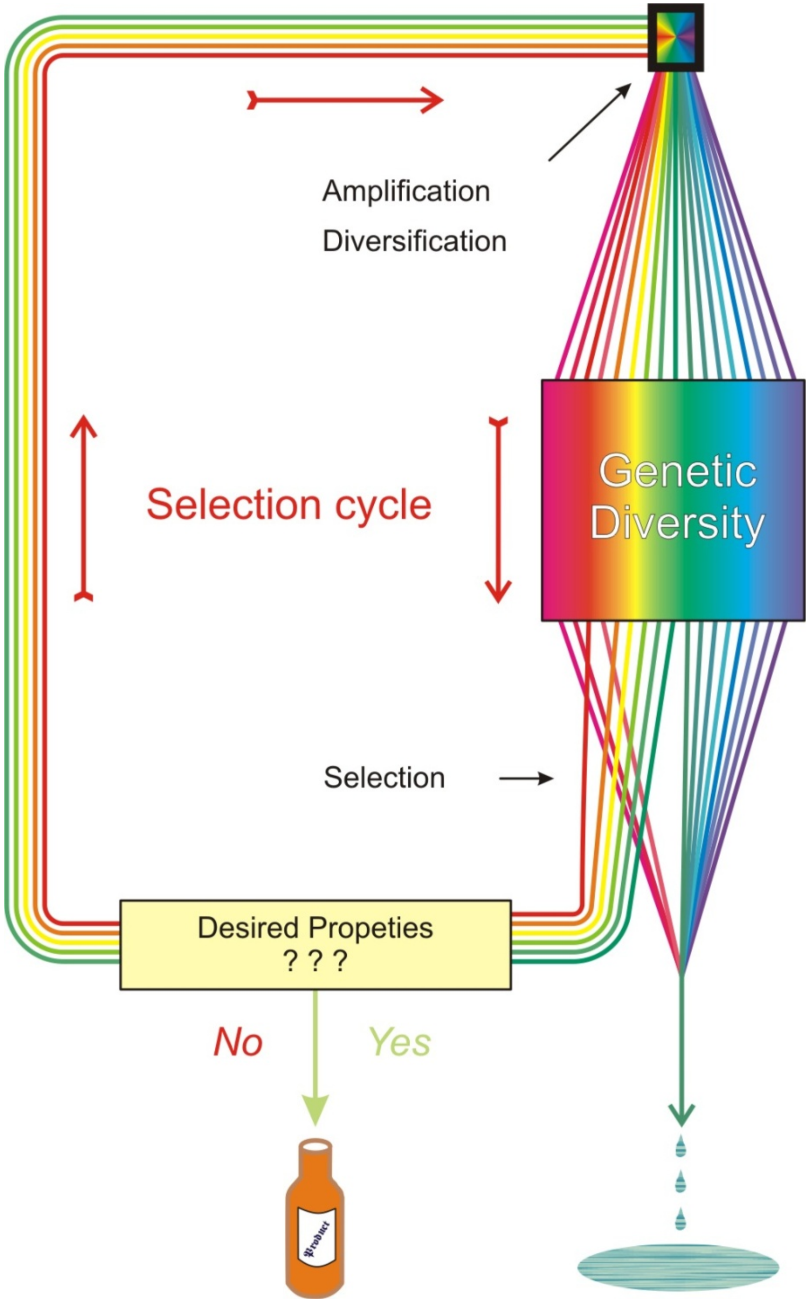
Control by evolution replaces control by knowledge

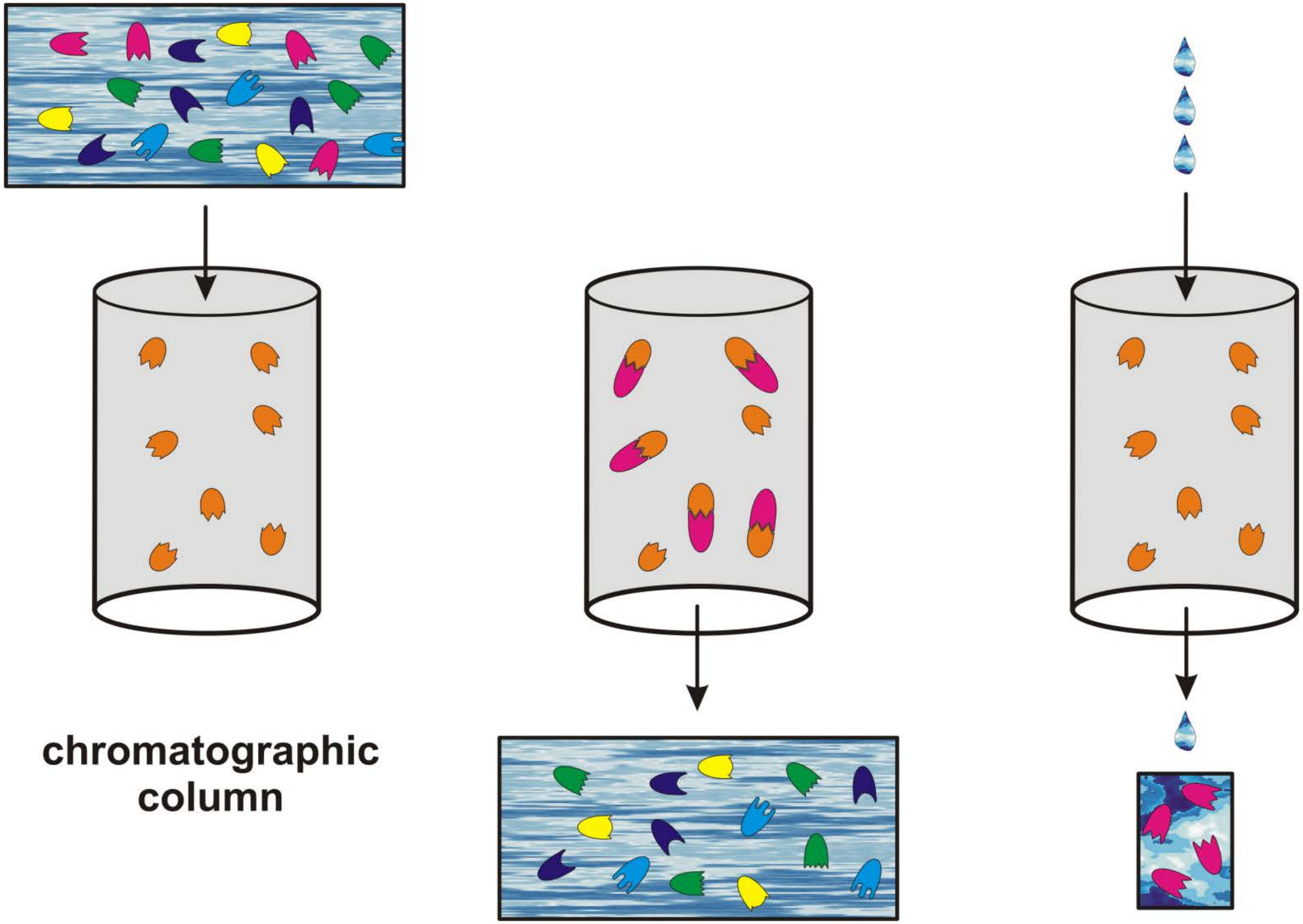
SELEX-method

C. Tuerk, L.Gold, Science **249**,
505-510, 1990

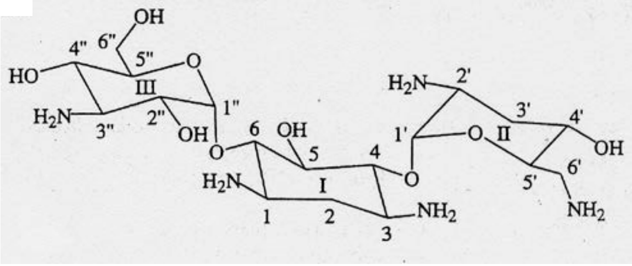
D. P. Bartel, J. W. Szostak, Nature **346** ,
818-822 1990

An example of ‘artificial selection’
with RNA molecules also called
‘breeding’ of biomolecules



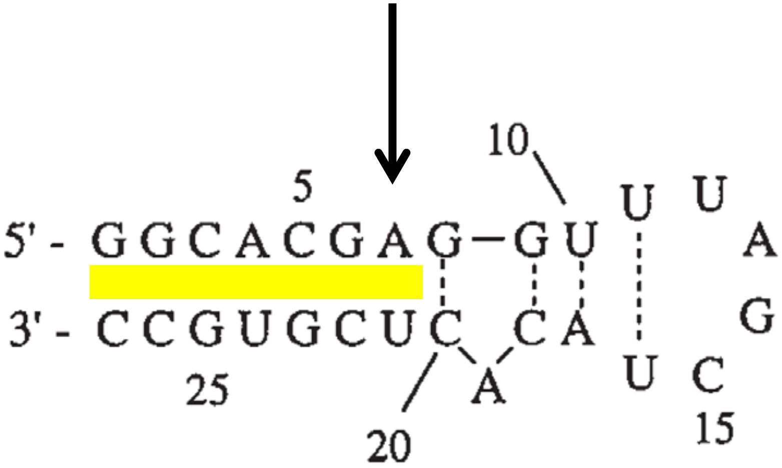


The SELEX-technique for evolutionary design of strongly binding molecules called aptamers



tobramycin

GGCACGAGGUUUAGCUACACUCGUGCC



$27^4 = 1.8 \times 10^{16}$

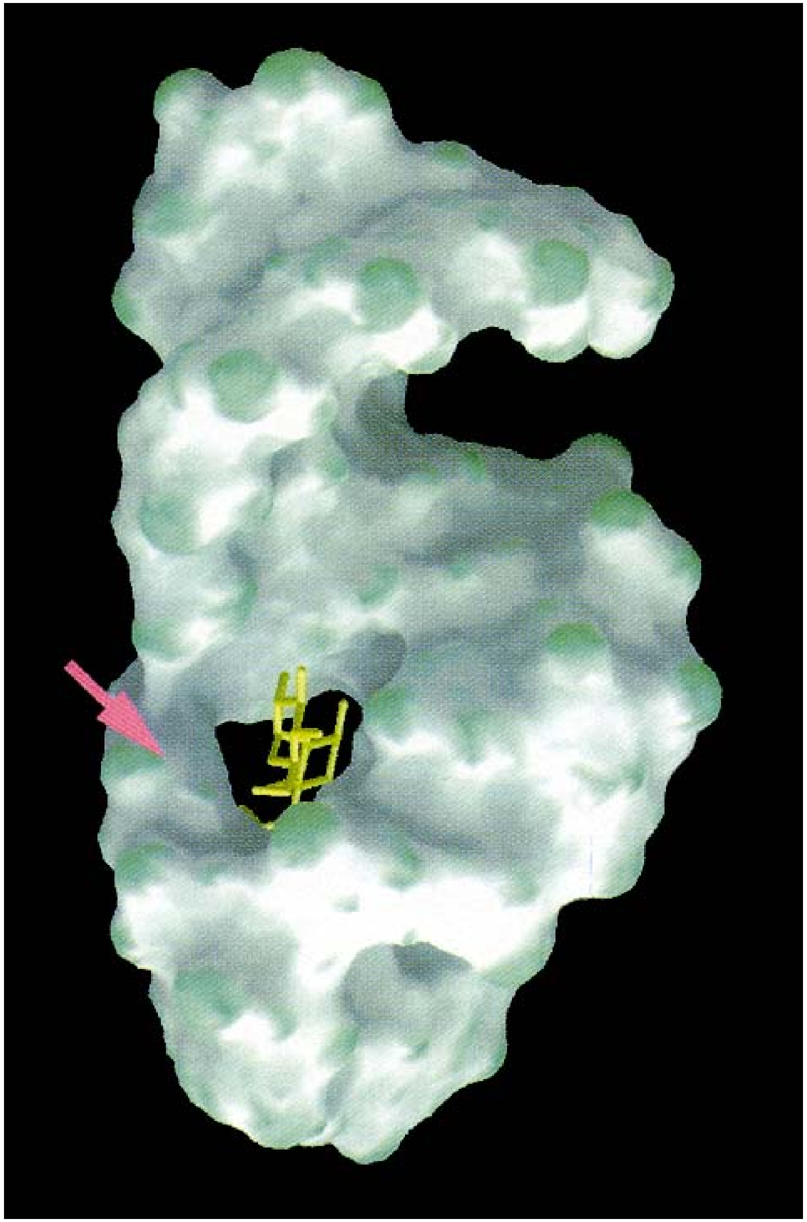
different RNA sequences

RNA aptamer, n = 27

Formation of secondary structure of the tobramycin binding RNA aptamer with **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)

L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, ***Solution structure of the tobramycin-RNA aptamer complex.*** Nature Structural Biology **5**:769-774 (1998)

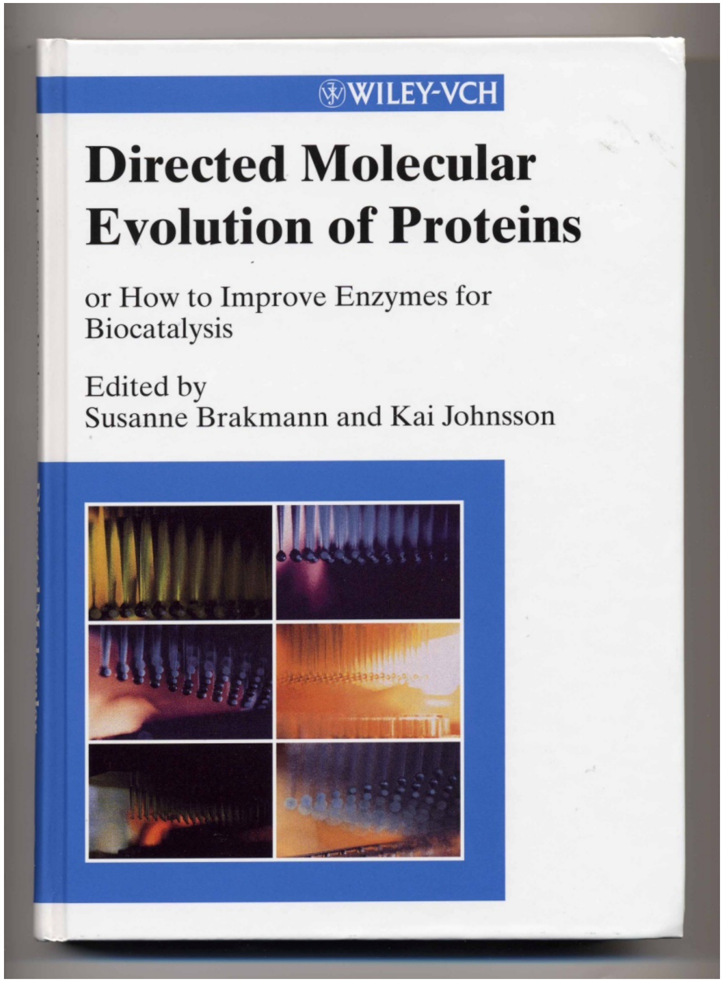


The three-dimensional structure of the tobramycin aptamer complex

L. Jiang, A. K. Suri, R. Fiala, D. J. Patel, Chemistry & Biology **4**:35-50 (1997)

Solution structure of the tobramycin-RNA aptamer complex

L. Jiang, D. J. Patel, Nature Structural Biology **5**:769-774 (1998)

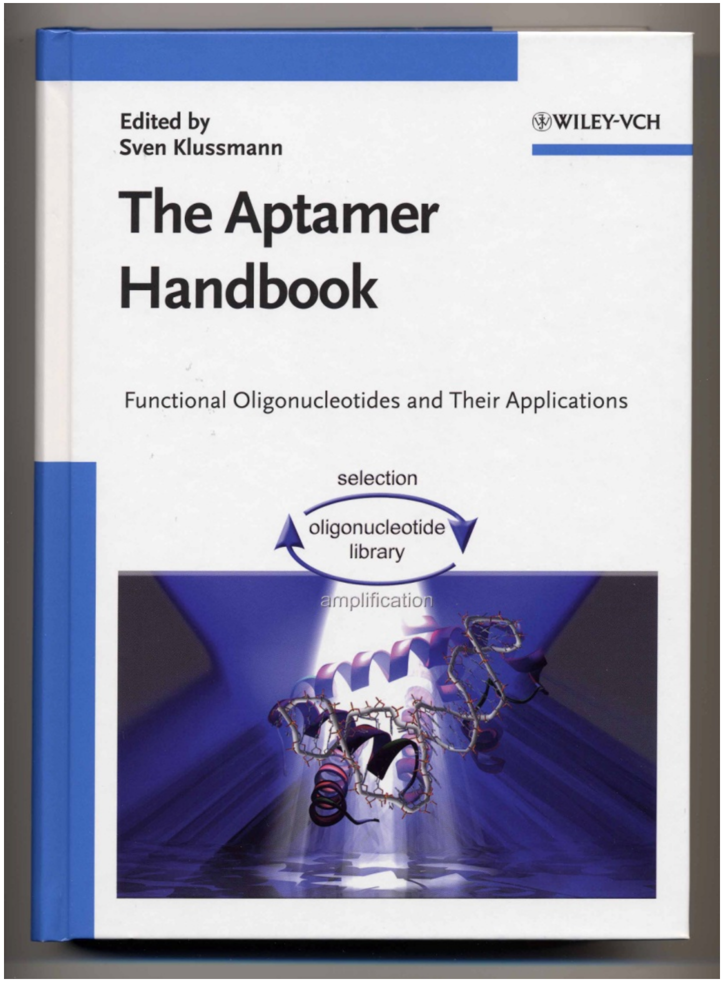


WILEY-VCH

Directed Molecular Evolution of Proteins

or How to Improve Enzymes for Biocatalysis

Edited by
Susanne Brakmann and Kai Johnsson



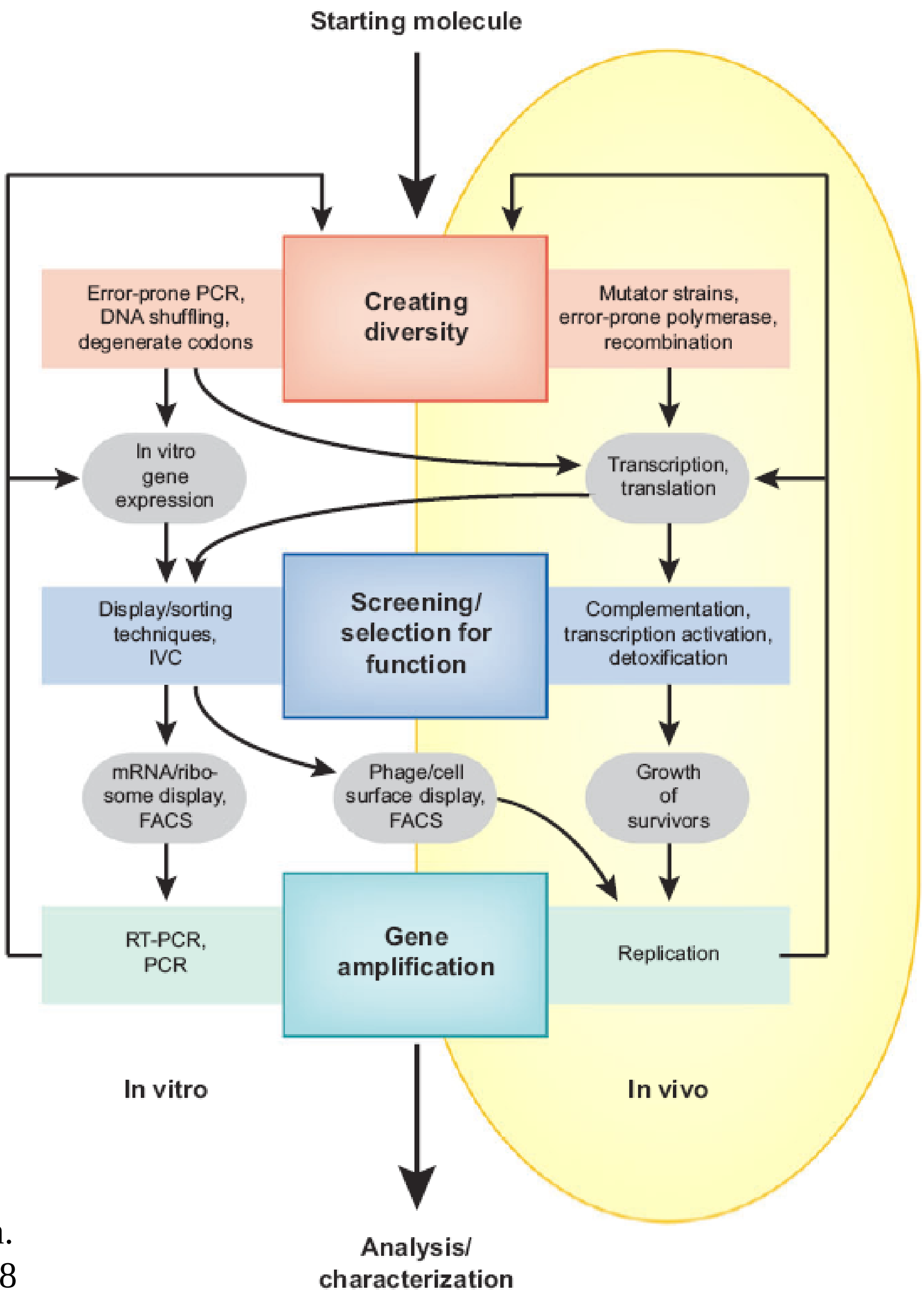
Edited by
Sven Klussmann

WILEY-VCH

The Aptamer Handbook

Functional Oligonucleotides and Their Applications

Application of molecular evolution based on replication, mutation and selection to problems in biotechnology



Starting molecule

Creating diversity

Error-prone PCR, DNA shuffling, degenerate codons

Mutator strains, error-prone polymerase, recombination

In vitro gene expression

Transcription, translation

Screening/ selection for function

Display/sorting techniques, IVC

Complementation, transcription activation, detoxification

mRNA/ribosome display, FACS

Phage/cell surface display, FACS

Growth of survivors

Gene amplification

RT-PCR, PCR

Replication

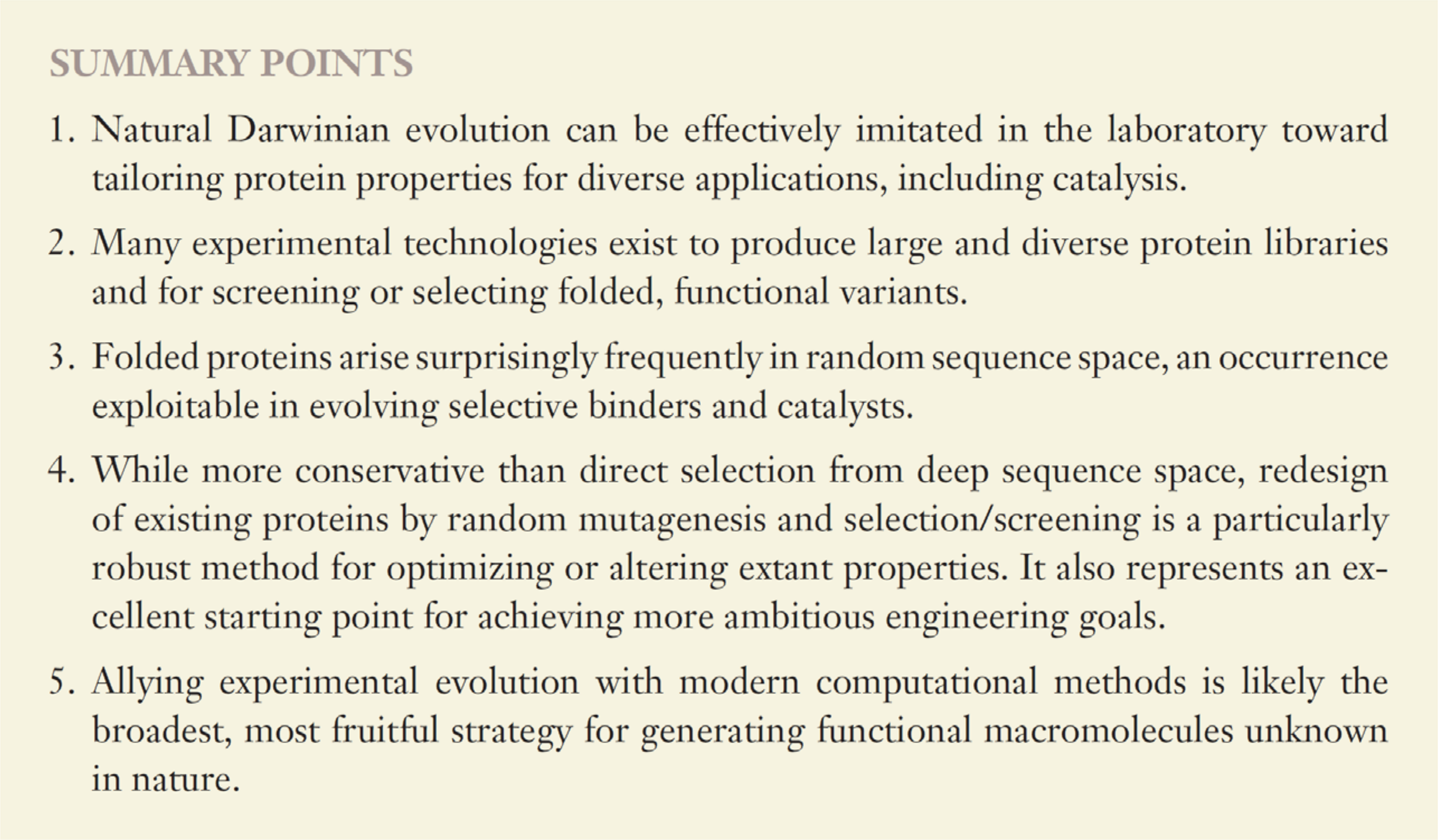
In vitro

In vivo

Analysis/ characterization

Schematic overview of the principal processes, strategies, and techniques of directed evolution. Today, numerous experimental methods are available to perform the fundamental processes of true Darwinian evolution (*central boxes*) in the laboratory, either in vivo within microorganisms or entirely in vitro in the test tube. Arrows indicate possible routes for connecting individual evolutionary steps. Abbreviations: PCR, polymerase chain reaction; RT-PCR, reverse transcription PCR; IVC, in vitro compartmentalization; FACS, fluorescence-activated cell sorting.

Christian Jäckel, Peter Kast, and Donald Hilvert.
Protein design by directed evolution.
Annu.Rev.Biophys. **37**:153-173, 2008

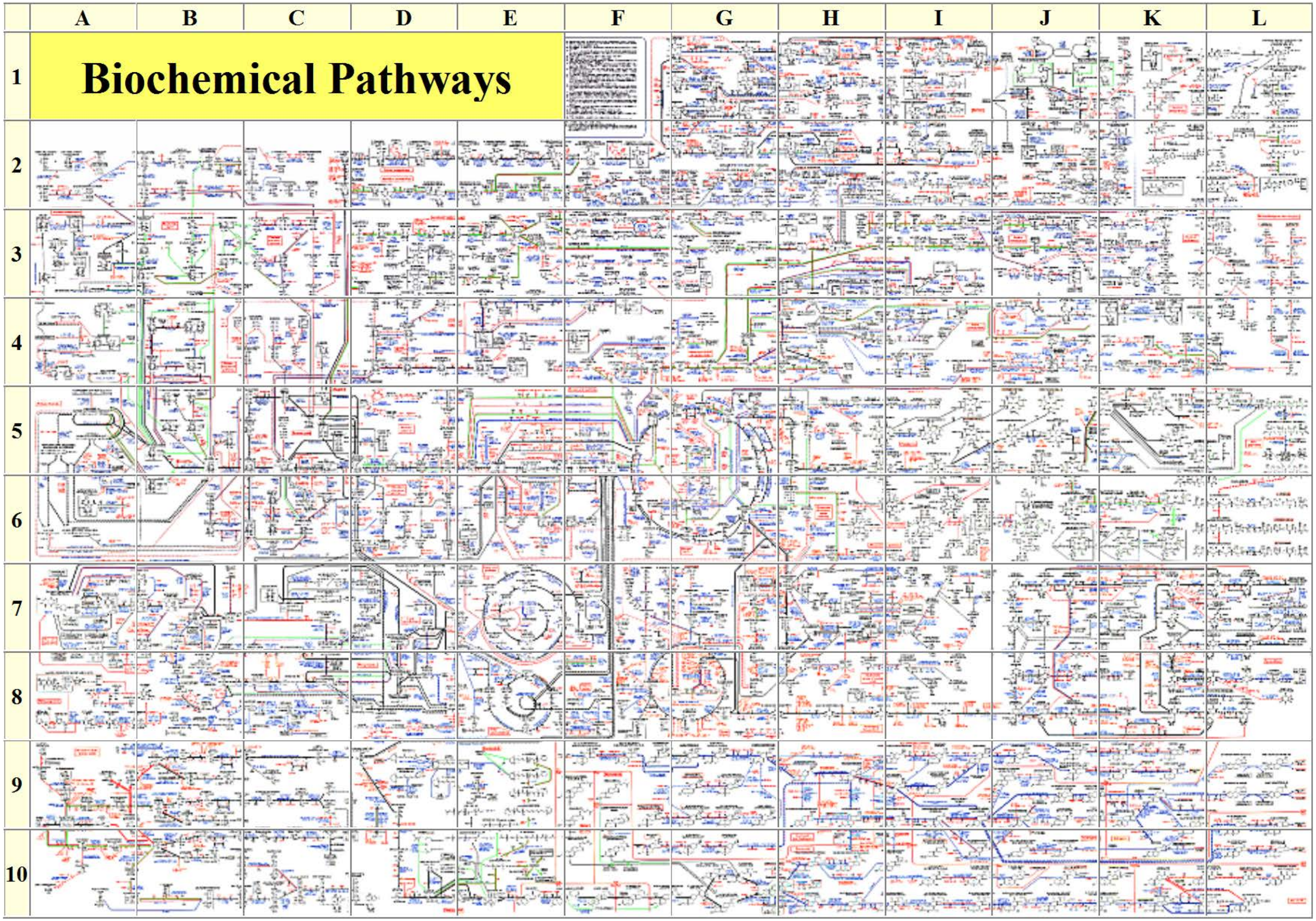


SUMMARY POINTS

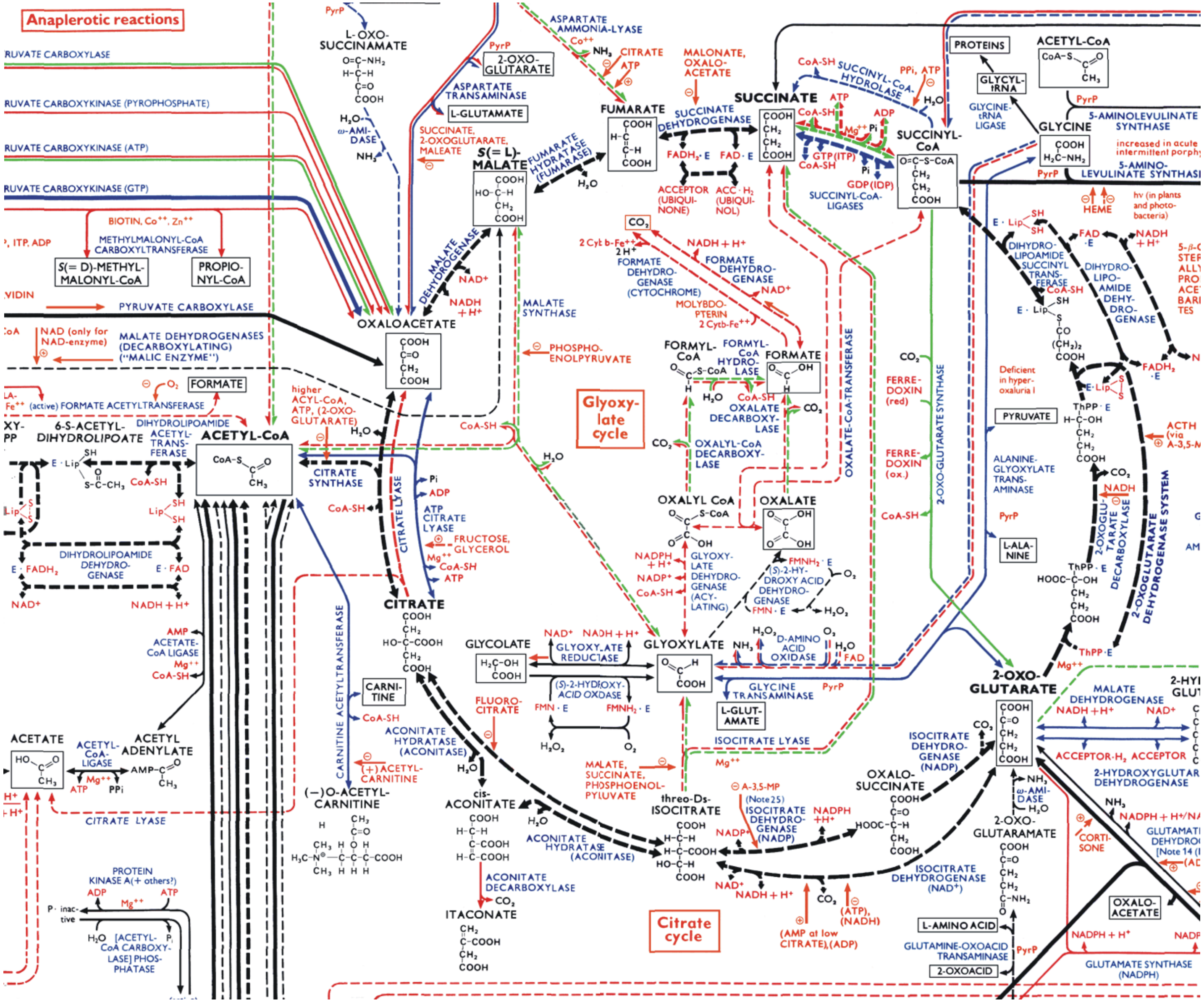
1. Natural Darwinian evolution can be effectively imitated in the laboratory toward tailoring protein properties for diverse applications, including catalysis.
2. Many experimental technologies exist to produce large and diverse protein libraries and for screening or selecting folded, functional variants.
3. Folded proteins arise surprisingly frequently in random sequence space, an occurrence exploitable in evolving selective binders and catalysts.
4. While more conservative than direct selection from deep sequence space, redesign of existing proteins by random mutagenesis and selection/screening is a particularly robust method for optimizing or altering extant properties. It also represents an excellent starting point for achieving more ambitious engineering goals.
5. Allying experimental evolution with modern computational methods is likely the broadest, most fruitful strategy for generating functional macromolecules unknown in nature.

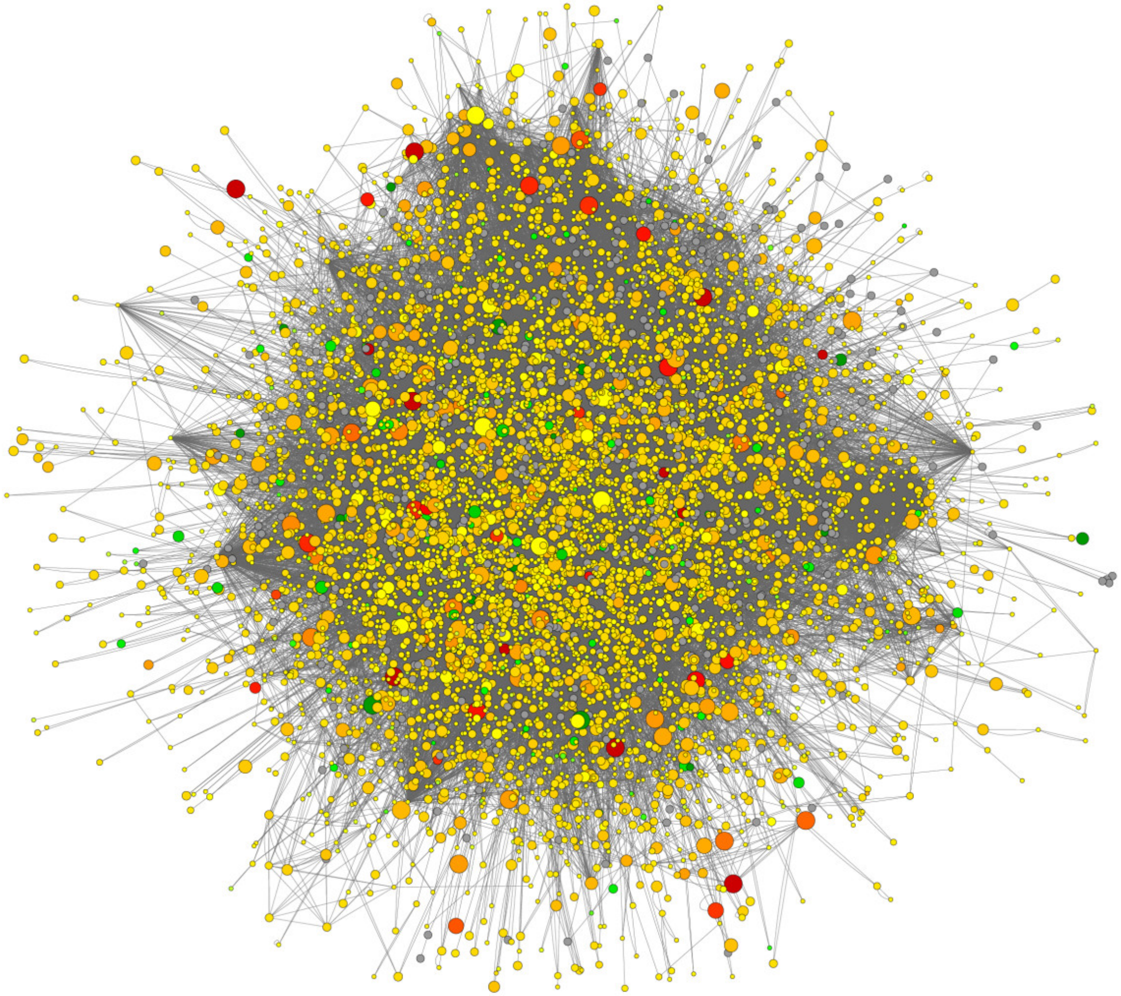
Christian Jäckel, Peter Kast, and Donald Hilvert.
Protein design by directed evolution. *Annu.Rev.Biophys*. **37**:153-173, 2008

Reduction of inherent complexity



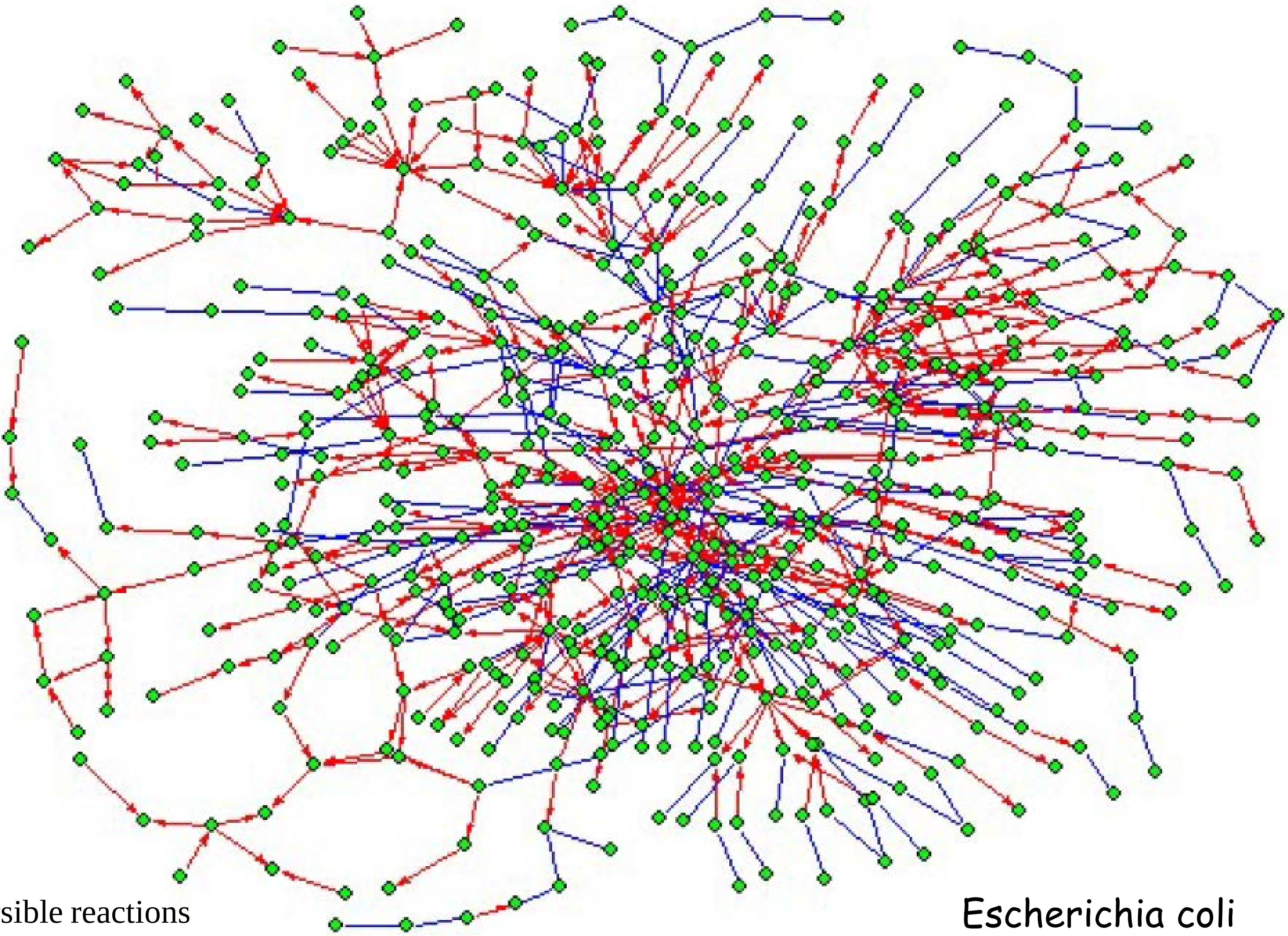
The reaction network of cellular metabolism published by Boehringer-Mannheim.


Anaplerotic reactions
RUVATE CARBOXYLASE
RUVATE CARBOXYKINASE (PYROPHOSPHATE)
RUVATE CARBOXYKINASE (ATP)
RUVATE CARBOXYKINASE (GTP)
BIOTIN, Co⁺⁺, Zn⁺⁺
METHYLMALONYL-CoA CARBOXYLTRANSFERASE
, ITP, ADP
S(= D)-METHYL-MALONYL-CoA
PROPIO-NYL-CoA
VIDIN
PYRUVATE CARBOXYLASE
NAD (only for NAD-enzyme)
MALATE DEHYDROGENASES (DECARBOXYLATING) ("MALIC ENZYME")
FORMATE
Fe⁺⁺ (active) FORMATE ACETYLTRANSFERASE
6-S-ACETYL-DIHYDROLIPOATE
DIHYDROLIPOAMIDE ACETYL-TRANSFERASE
ACETYL-CoA
CoA-SH
DIHYDROLIPOAMIDE DEHYDROGENASE
E · FADH₂
E · FAD
NAD⁺
NADH + H⁺
AMP
ACETATE-CoA LIGASE
Mg⁺⁺
ACETATE
ACETYL-CoA LIGASE
ACETYL ADENYLATE
ATP
PPi
CITRATE LYASE
PROTEIN KINASE A(+ others?)
ADP
P · inactive
[ACETYL-CoA CARBOXYLASE] PHOSPHATASE
PyrP
L-OXO-SUCCINAMATE
ω-AMIDASE
NH₃
2-OXO-GLUTARATE
ASPARTATE TRANSAMINASE
L-GLUTAMATE
SUCCINATE, 2-OXOGLUTARATE, MALEATE
S(= L)-MALATE
MALATE DEHYDROGENASE
NAD⁺
NADH + H⁺
OXALOACETATE
higher ACYL-CoA, ATP, (2-OXO-GLUTARATE)
CITRATE SYNTHASE
CITRATE LYASE
Pi
ADP
ATP CITRATE LYASE
FRUCTOSE, GLYCEROL
CITRATE
CARNITINE ACETYLTRANSFERASE
CARNITINE
(+) ACETYL-CARNITINE
(−)O-ACETYL-CARNITINE
ACONITATE HYDRATASE (ACONITASE)
FLUORO-CITRATE
cis-ACONITATE
ACONITATE DECARBOXYLASE
ITACONATE
ASPARTATE AMMONIA-LYASE
CITRATE
MALONATE, OXALOACETATE
FUMARATE
FUMARATE HYDRATASE (FUMARASE)
MALATE SYNTHASE
PHOSPHOENOLPYRUVATE
SUCCINATE DEHYDROGENASE
FADH₂ · E
FAD · E
ACCEPTOR (UBIQUINONE)
ACC · H₂ (UBIQUINOL)
SUCCINATE
SUCCINYL-CoA HYDROLASE
PPi, ATP
GTP(ITP)
GDP(IDP)
SUCCINYL-CoA LIGASES
SUCCINYL-CoA
CO₂
2 Cyt b-Fe⁺⁺⁺
FORMATE DEHYDROGENASE (CYTOCHROME)
MOLYBDOPTERIN
FORMATE DEHYDROGENASE
FORMYL-CoA
FORMYL-CoA HYDROLASE
FORMATE
OXALATE DECARBOXYLASE
OXALYL-CoA DECARBOXYLASE
OXALATE-CoA-TRANSFERASE
Glyoxylate cycle
OXALYL CoA
OXALATE
GLYOXYLATE DEHYDROGENASE (ACYLATING)
(S)-2-HYDROXY ACID DEHYDROGENASE
GLYCOLATE
GLYOXYLATE REDUCTASE
(S)-2-HYDROXY-ACID OXIDASE
GLYOXYLATE
D-AMINO ACID OXIDASE
GLYCINE TRANSAMINASE
L-GLUTAMATE
ISOCITRATE LYASE
MALATE, SUCCINATE, PHOSPHOENOLPYRUVATE
threo-Ds-ISOCITRATE
ISOCITRATE DEHYDROGENASE (NADP)
A-3,5-MP (Note 25)
OXALOSUCCINATE
ISOCITRATE DEHYDROGENASE (NAD⁺)
(ATP), (NADH)
(AMP at low CITRATE), (ADP)
Citrate cycle
PROTEINS
GLYCYL-tRNA
GLYCINE-tRNA LIGASE
ACETYL-CoA
GLYCINE
5-AMINOLEVULINATE SYNTHASE
increased in acute intermittent porphy
HEME
hv (in plants and photo-bacteria)
DIHYDROLIPOAMIDE SUCCINYLTRANSFERASE
DIHYDROLIPOAMIDE DEHYDROGENASE
FERREDOXIN (red)
FERREDOXIN (ox.)
2-OXOGLUTARATE SYNTHASE
Deficient in hyperoxaluria I
PYRUVATE
ALANINE-GLYOXYLATE TRANSAMINASE
L-ALANINE
ACTH (via A-3,5-MP)
2-OXOGLUTARATE DECARBOXYLASE
2-OXOGLUTARATE DEHYDROGENASE SYSTEM
ThPP · E
2-OXO-GLUTARATE
MALATE DEHYDROGENASE
ACCEPTOR-H₂ ACCEPTOR
2-HYDROXYGLUTARATE DEHYDROGENASE
ω-AMIDASE
2-OXO-GLUTARAMATE
L-AMINO ACID
GLUTAMINE-OXOACID TRANSAMINASE
2-OXOACID
CORTISONE
GLUTAMATE DEHYDROGENASE [Note 14]
OXALOACETATE
GLUTAMATE SYNTHASE (NADPH)



Christopher R. Bauer, Andrew M. Epstein, Sarah J. Sweeney, Daniela C. Zarnescu, and Giovanni Bosco.
BMC Systems Biology **2**:e101 (2008).

Genetic regulation networks of metabolism in drosophila

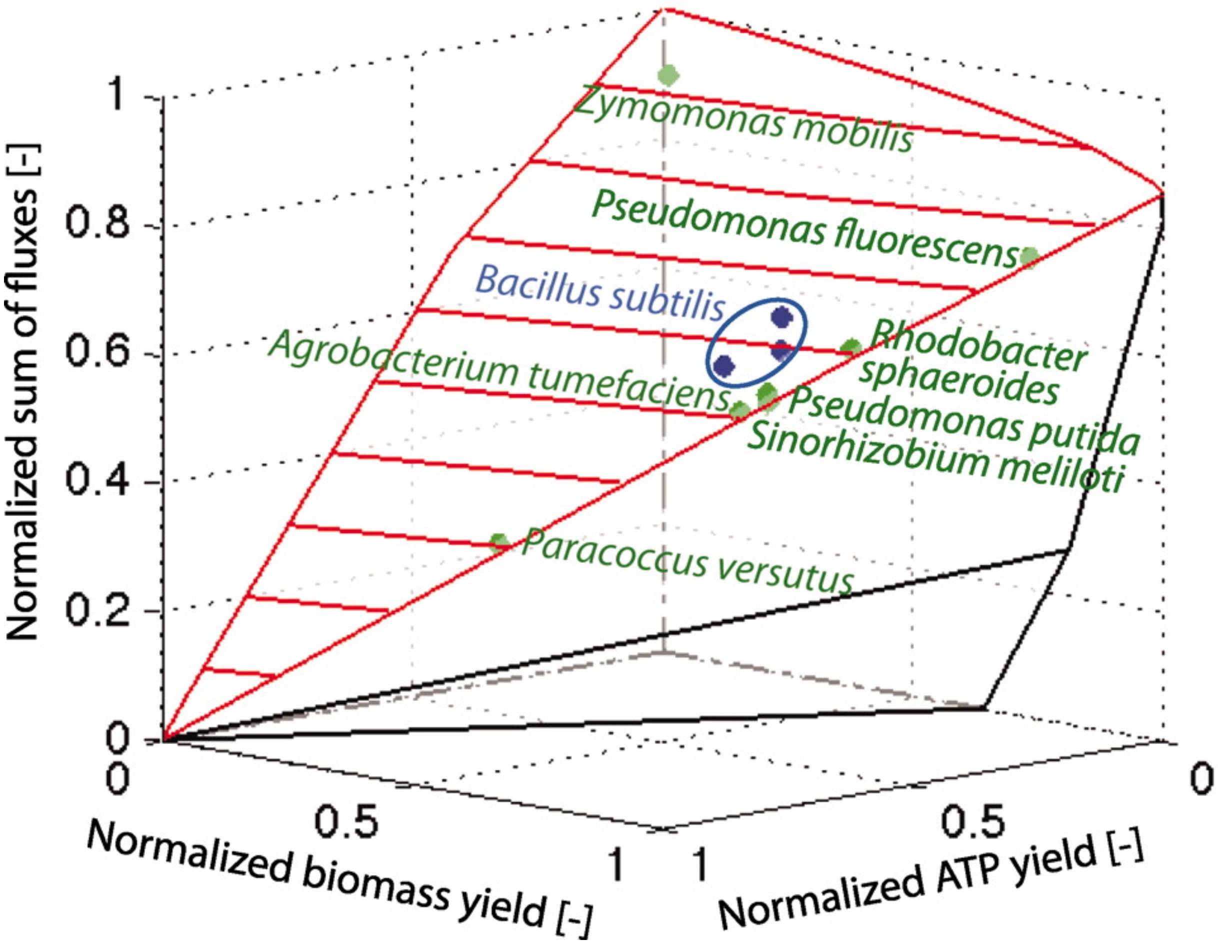


— reversible reactions

→ irreversible reactions

Escherichia coli

Hongwu Ma, An-Ping Zeng. Reconstruction of metabolic networks from genome data and analysis of their global structure for various organisms. *Bioinformatics* **18**:270-277 (2003).



Robert Schuetz, Nicola Zamboni, Mattia Zampieri, Matthias Heinemann, Uwe Sauer. Multidimensional optimality of microbial metabolism. *Science* **336**:601-604 (2012)

The open ended increase in complexity

1. Complexity of interacting biopolymers
2. Complexity of cellular metabolism
3. Complexity and diversity of individuals
4. Complexity of multicellular organisms
5. Complexity of development
6. Complexity in ecosystems
7. Complexity of interactions in populations
8. Complexity of interactions in societies
9. Complexity of human societies

The complexity of life

Complexity will be manageable in the future only
by the right combination of **rigorous mathematical analysis**,
„big data", and **computer simulation**

Thank you for your attention!

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