

Lecture 1: Introduction to Mathematical Molecular Bioscience and Biophysics

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NSF-CBMS Conference on Mathematical Molecular Bioscience and Biophysics

University of Alabama

Tuscaloosa, May, 13-17, 2019

Grant support: NSF, NIH, MSU, BMS, and Pfizer



Summary

Lecture 1: Introduction to Mathematical Molecular Bioscience and Biophysics

Lecture 2: Differential Geometry Based Biomolecular Surface Modeling

Lecture 3: Differential Geometry Based Models for Electrostatics and Solvation

Lecture 4: Variational Approaches to Membrane Transport

Lecture 5: Numerical Methods for Biomolecular Simulations

Lecture 6: Graph Theory Based Modeling and Analysis

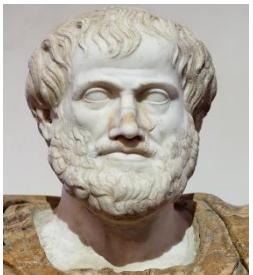
Lecture 7: Topology Based Modeling and Analysis

Lecture 8: de Rham-Hodge Theory Based Modeling and Analysis

Lecture 9: Mathematics for Biomolecular Data

Lecture 10: Mathematics for Drug Discovery

A Brief History of Biological Science



Aristotle (384-322 B.C.) First to classify living things. Divided the plants into herbs, shrubs and trees and animals into land dwellers, water dwellers and air dwellers.



Claudius Galen (A.D. 131-200) Anatomy of the human body based on dissections of apes and pigs.



Andreas Vesalius (1514-1564) Made the first studies on human anatomy by dissecting corpses *“De Humani Corporis Fabrica”*.



William Harvey (1578-1657) Pointed out that the heart pumps the blood and the blood circulates.

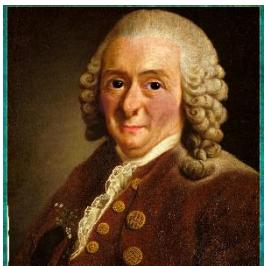
A Brief History of Biological Science



Marcello Malpighi (1628-1694) The anatomy of liver, brain, kidneys, spleen, bone, layer of the skin, and red blood corpuscles.



Anton van Leeuwenhoek (1632-1694) Discovery of microorganisms (including bacteria), sperm **cells** and single-celled organisms called protozoans.

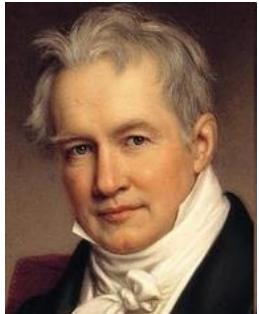


Carl Linnaeus (1707-1778) Developed binomial nomenclature to classify and organize plants and animals.



Antoine Lavoisier (1742-1794) Connected the animate and inanimate worlds through physics and chemistry.

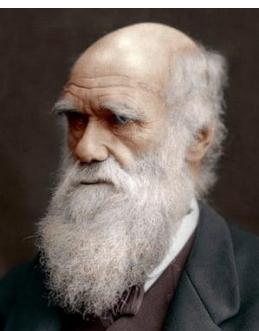
A Brief History of Biological Science



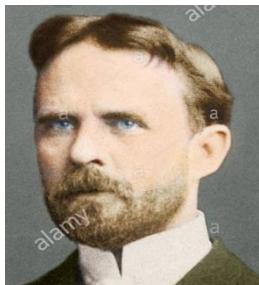
Alexander von Humboldt (1769 – 1859) Investigated the interaction between organisms and their environment, and founded biogeography, ecology and ethology.



Gregor Mendel (1822-1884) Developed the principle of heredity by studying the variation and heredity of seven pairs of inherited traits in pea plants.



Charles Darwin (1809-1882) A great biologist. In his “*Origin of Species*” (1859), he presented the theory of evolution by natural selection, which provided a unifying, organizing framework for the field of biology.

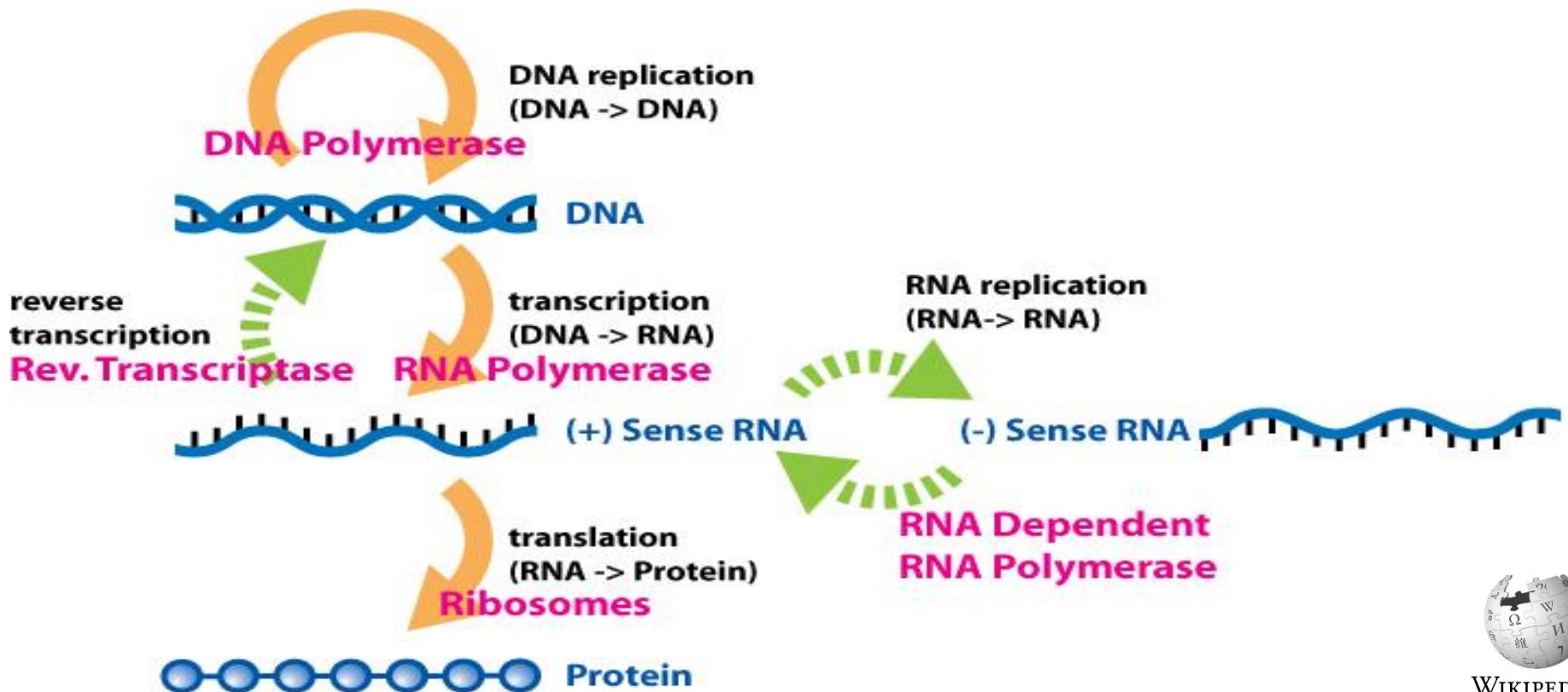


Thomas Morgan (1866 -1945) Nobel Prize in Physiology or Medicine in 1933 for discoveries elucidating the role that the chromosome plays in heredity.

A Brief History of Biological Science

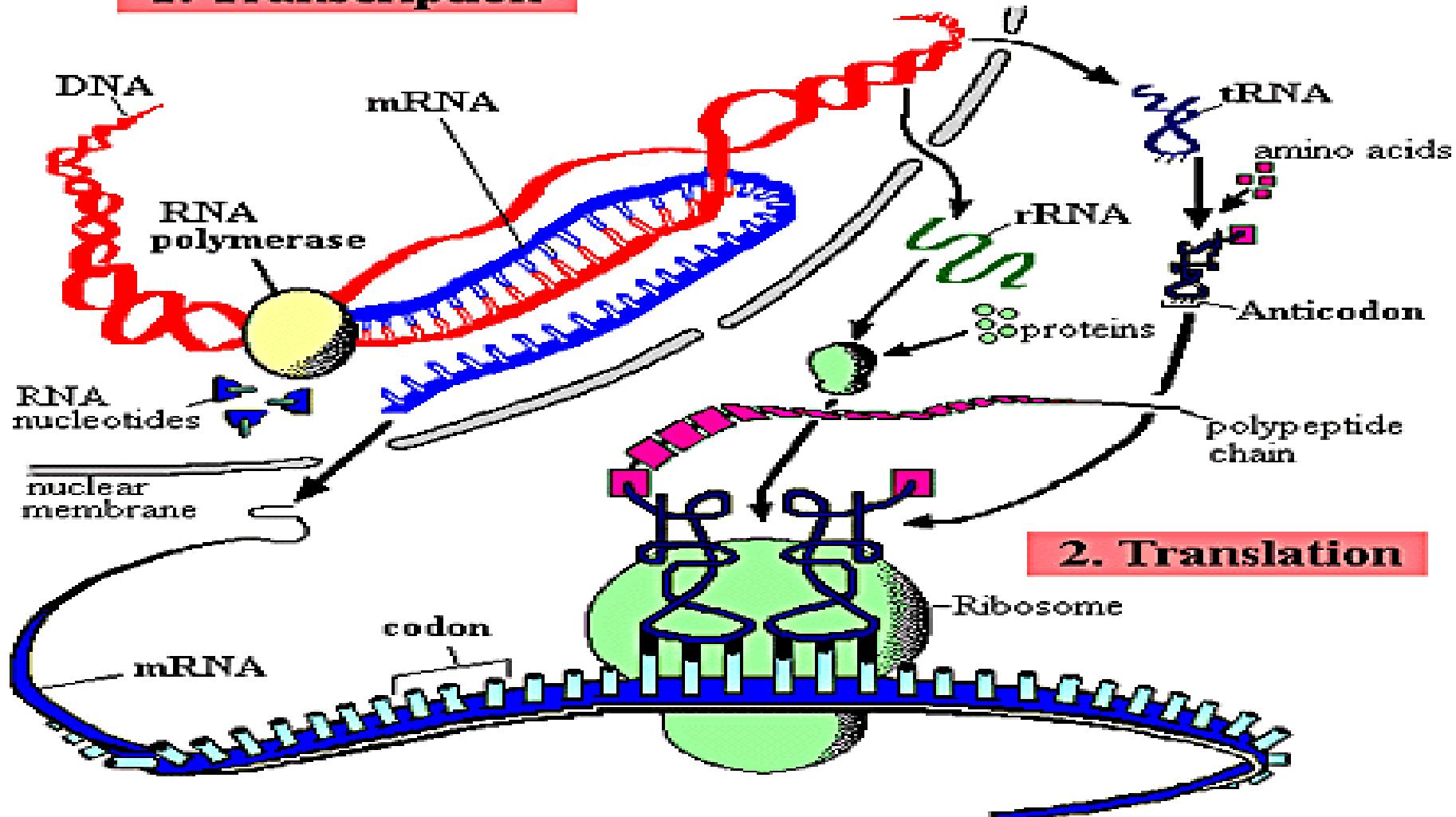


Francis Crick (1916 - 2004) and James Watson (1928 –) Nobel Prize in Physiology or Medicine in 1962 "for discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material", i.e., the **Central Dogma** of molecular biology:



Central dogma of biology

1. Transcription



Protein synthesis

<https://sites.google.com/site/pizzagranolahrim/protein-synthesis> (may not be original)

A Brief History of Biological Science - Genetic Code



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Theory: George Gamow (1953). Experiment: Crick, Brenner, Barnett and Watts-Tobin (1961). Completion: Marshall Nirenberg and Heinrich J. Matthaei (1961).

1st base	2nd base								3rd base
	U		C		A		G		
U	UUU	(Phe/F) <u>Phenylalanine</u>	UCU	(Ser/S) <u>Serine</u>	UAU	(Tyr/Y) <u>Tyrosine</u>	UGU	(Cys/C) <u>Cysteine</u>	U
	UUC		UCC		UAC		UGC		C
	UUA		UCA		UAA	Stop (Ochre) [B]	UGA	Stop (Opal) [B]	A
	UUG		UCG		UAG	Stop (Amber) [B]	UGG	(Trp/W) <u>Tryptophan</u>	G
C	CUU	(Leu/L) <u>Leucine</u>	CCU	(Pro/P) <u>Proline</u>	CAU	(His/H) <u>Histidine</u>	CGU	(Arg/R) <u>Arginine</u>	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	(Gln/Q) <u>Glutamine</u>	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	(Ile/I) <u>Isoleucine</u>	ACU	(Thr/T) <u>Threonine</u>	AAU	(Asn/N) <u>Asparagine</u>	AGU	(Ser/S) <u>Serine</u>	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	(Lys/K) <u>Lysine</u>	AGA	(Arg/R) <u>Arginine</u>	A
	AUG ^[A]		ACG		AAG		AGG		G
G	GUU	(Val/V) <u>Valine</u>	GCU	(Ala/A) <u>Alanine</u>	GAU	(Asp/D) <u>Aspartic acid</u>	GGU	(Gly/G) <u>Glycine</u>	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	(Glu/E) <u>Glutamic acid</u>	GGA		A
	GUG		GCG		GAG		GGG		G

Amino acid properties

nonpolar

polar

basic

acidic

Termination:
stop codon

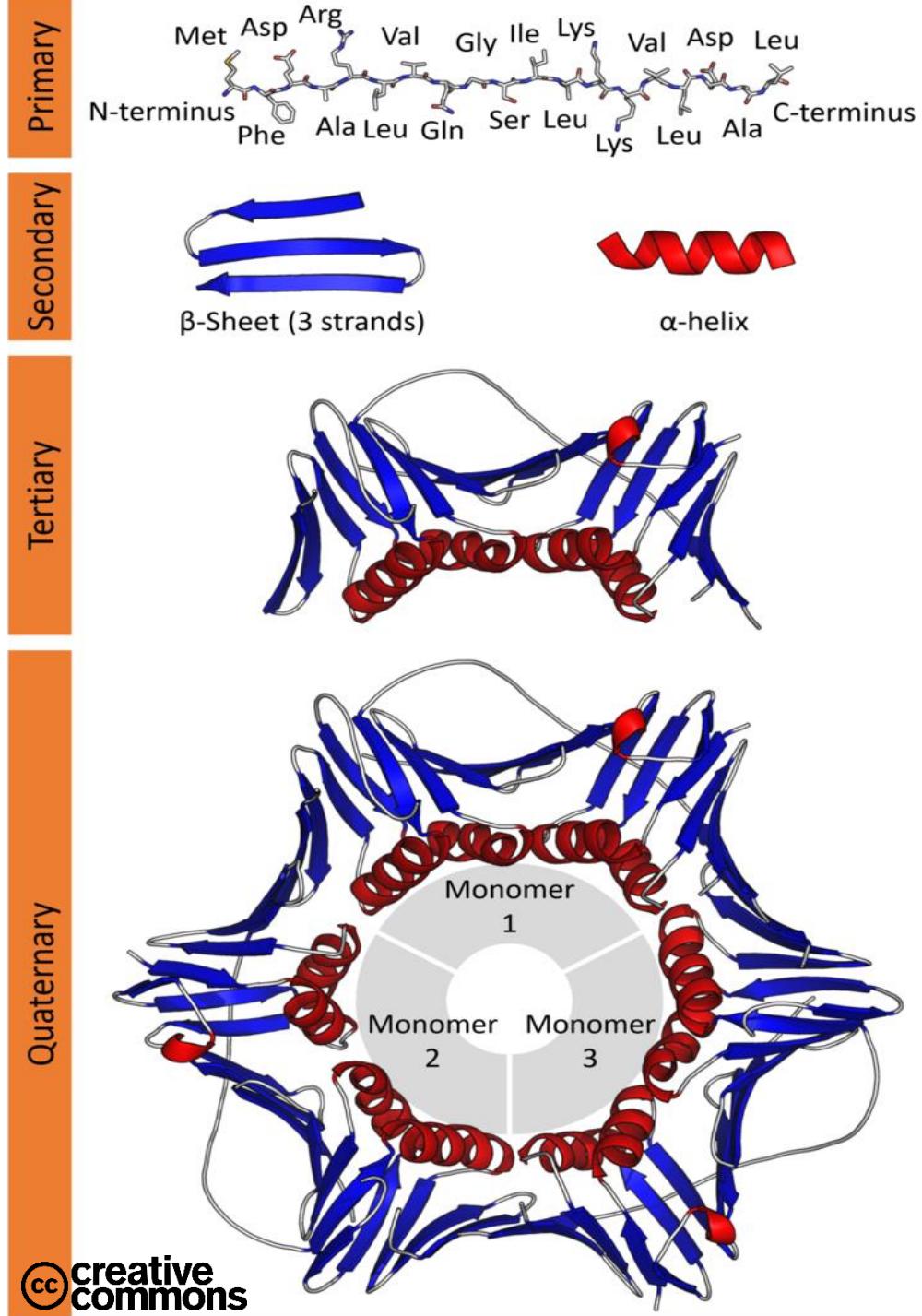
A Brief Summary of Modern Biological Science

1960	2000	2019
Organismal biology (i.e., nonliving organisms, living organisms, developmental biology, morphology, anatomy, physiology, and medicine)		Molecular organismal biology, organomics, connectomics, foodomics, physiomics, pharmacogenomics, ...
Ecology		Molecular ecology
Evolution (i.e., life, and evolutionary biology)		Molecular evolution
Molecular and cellular biology (i.e., cell biology, biochemistry, molecular biology, and genetics)		Omics (e.g., genomics, proteomics, metabolomics, metagenomics, lipidomics, glycomics, transcriptomics, epigenomics, ...)
Macroscopic	Mesoscopic	Microscopic

Protein Structure

Polypeptides formed from sequences of 20 amino acids.

Primary structure
Secondary structure
Tertiary structure
Quaternary structure



Nuclei Acid Structure

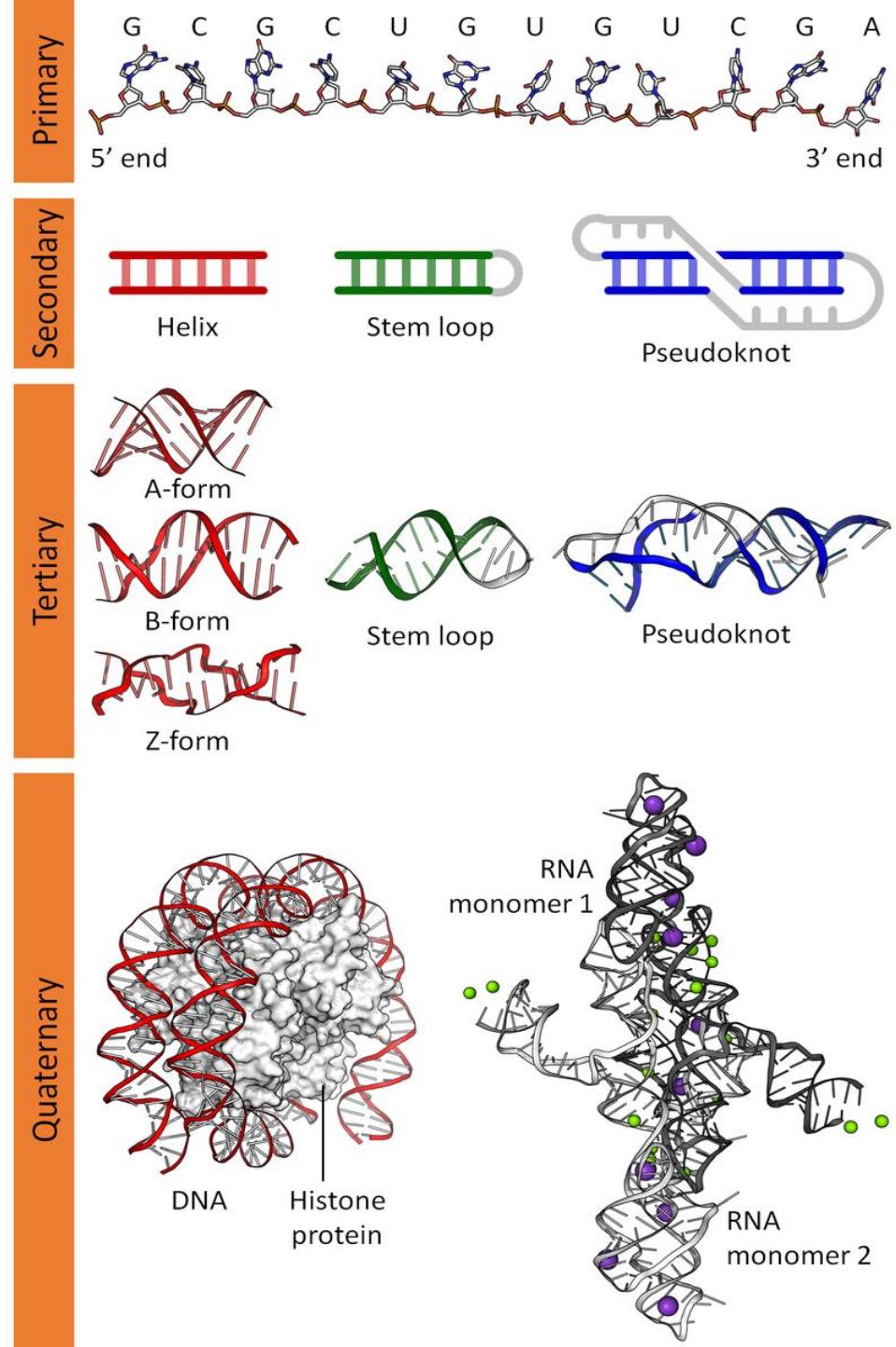
Nitrogenous base (Adenine, Guanine, Cytosine, Thymine (in DNA), Uracil (in RNA))

5-carbon sugar called deoxyribose (found in DNA) and ribose (found in RNA).

One or more phosphate groups.

Primary structure
Secondary structure
Tertiary structure
Quaternary structure

[Image credit: Thomas Shafee](#)



Biomolecular structure determination (By 05/11/2019)

X-ray crystallography (Structures: 135,596; Nobel Prizes:12)

Nuclear magnetic resonance spectroscopy (12,610; 6)

Electron microscopy (3130; 1)

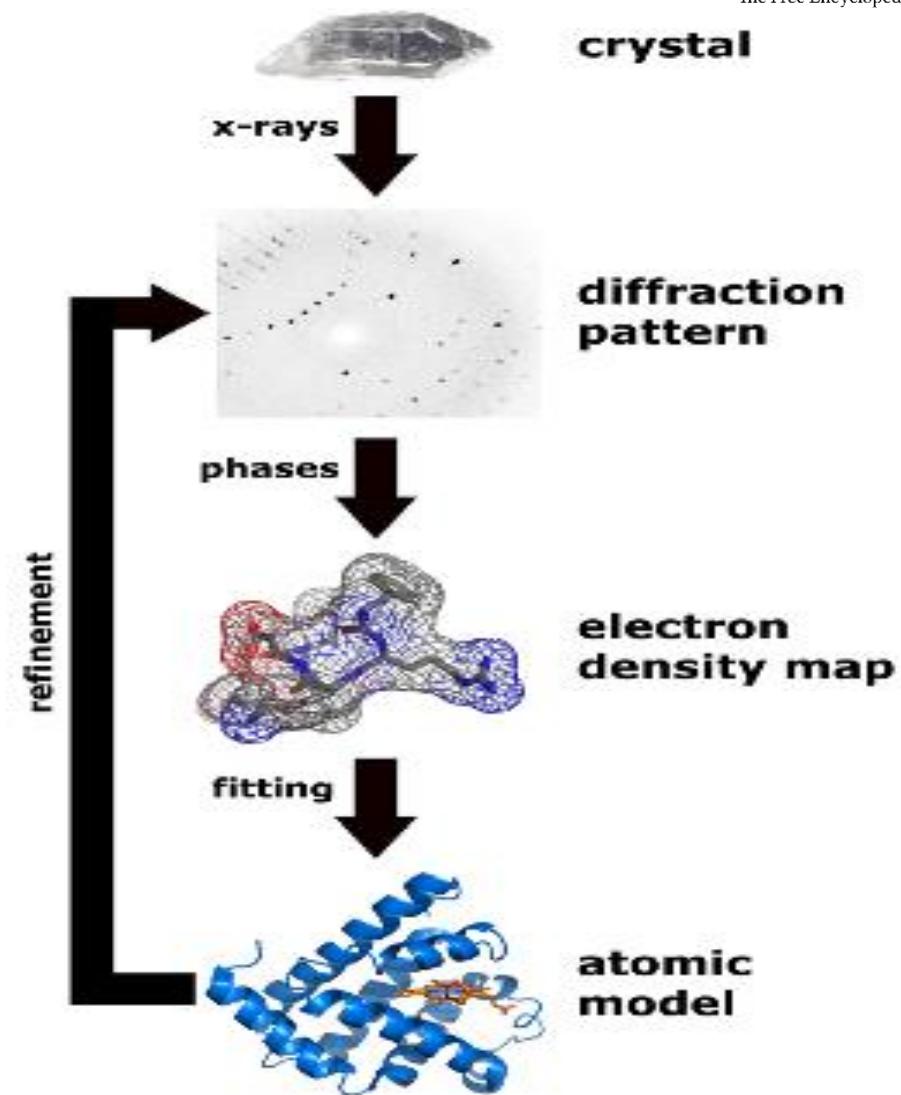
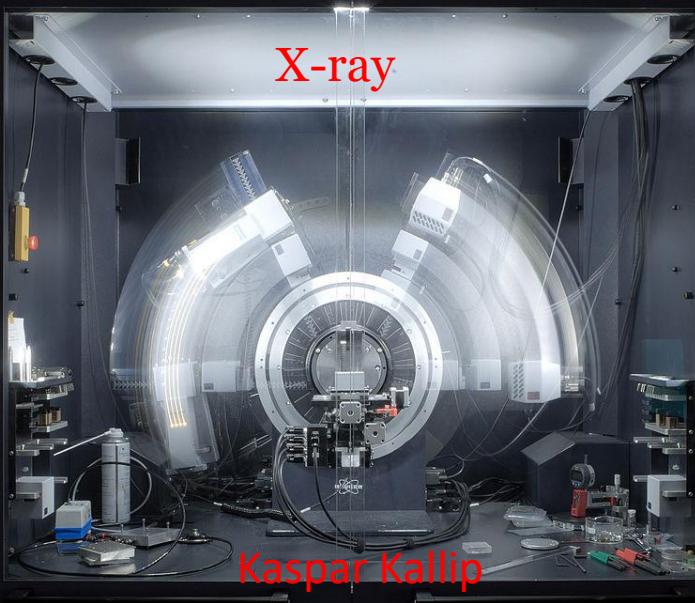
Other (279)

Multi methods (139)

Total: 151754



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Problems: Crystallization;
Membrane protein; RNA

Nuclear Magnetic Resonance Spectroscopy (NMR)



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Correlation spectroscopy (COSY)

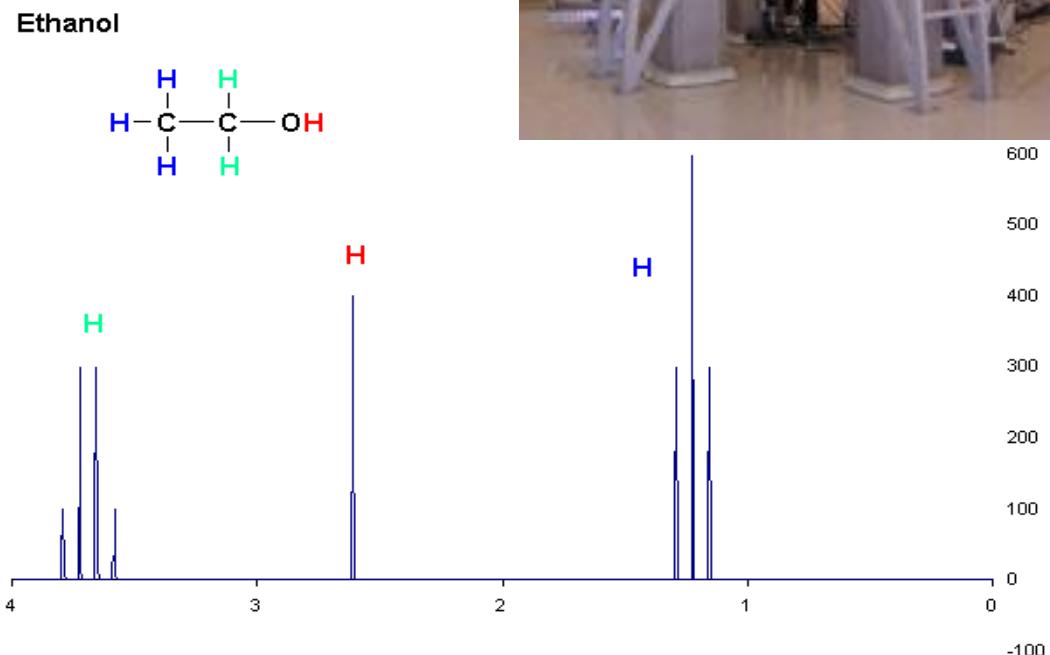
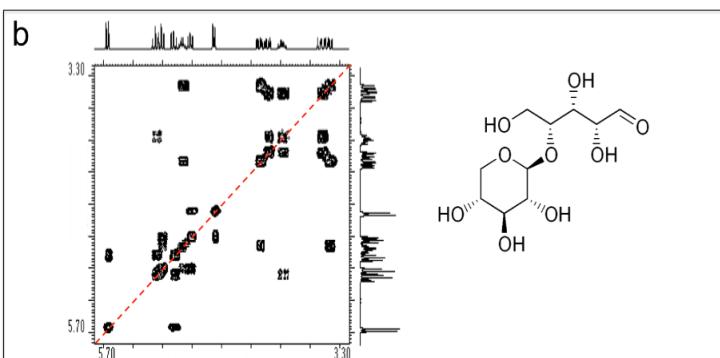
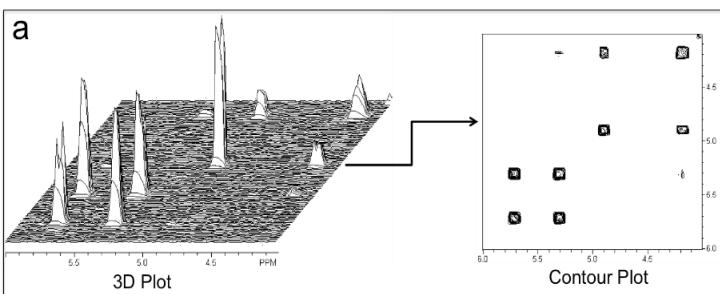
J-spectroscopy, exchange spectroscopy (EXSY)

Nuclear Overhauser effect spectroscopy
(NOESY)

Total correlation spectroscopy (TOCSY)

Heteronuclear correlation experiments
(e.g., HSQC, HMQC, and HMBC).

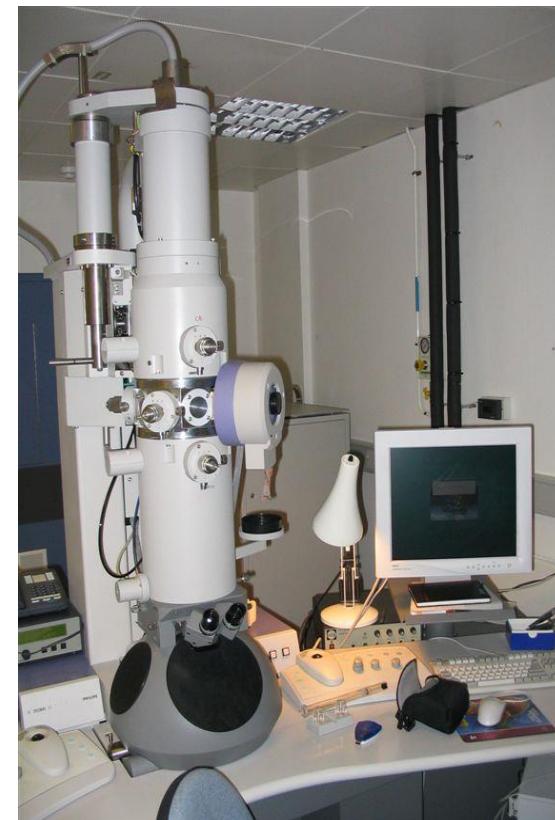
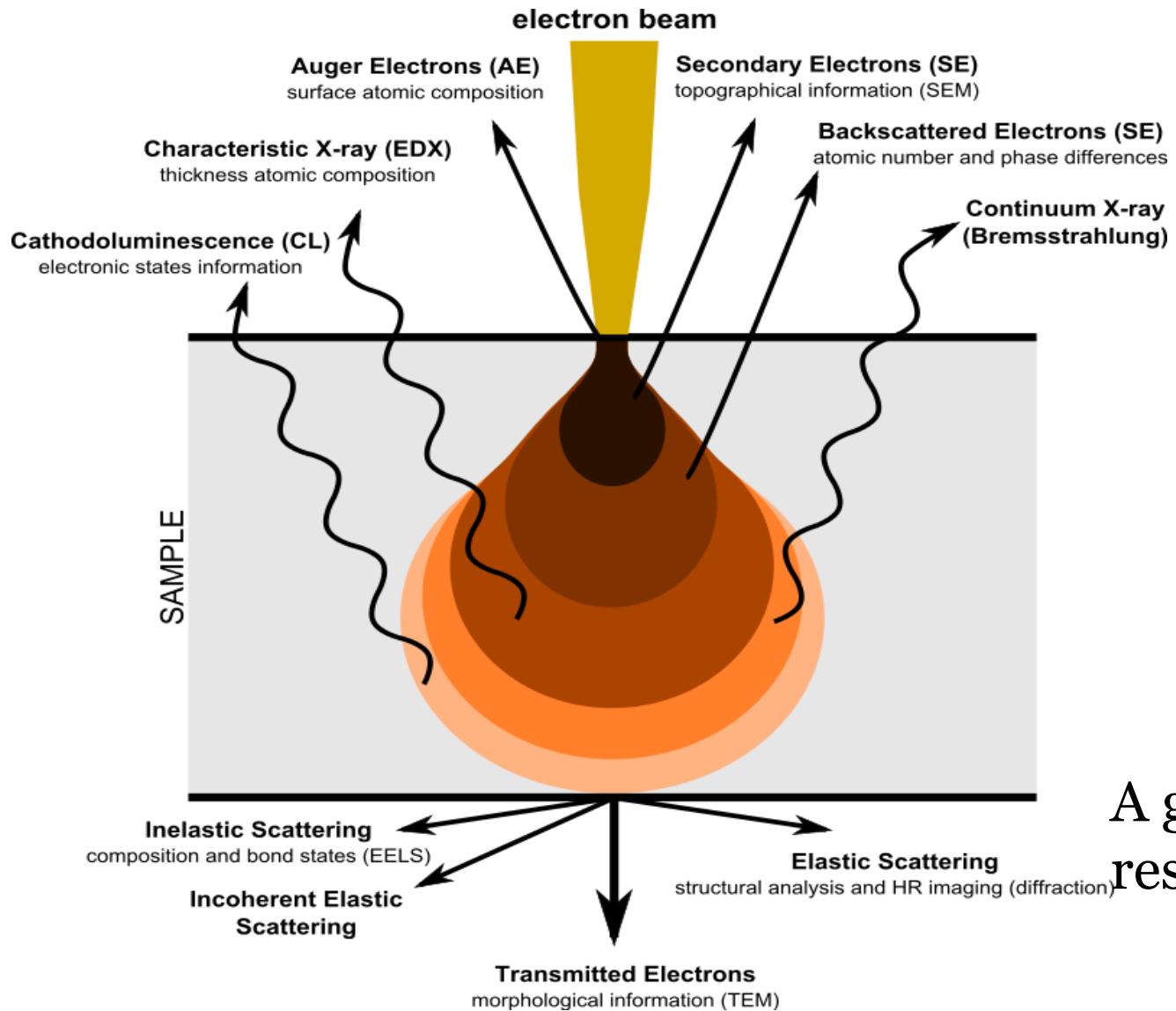
Limitation: ~less than 120 residues



Cryogenic Electron Microscopy (cryo-EM)

Advantages: Large systems, non-crystal

Limitation: Relatively low resolution



A good mathematical research topics



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DNA sequencing

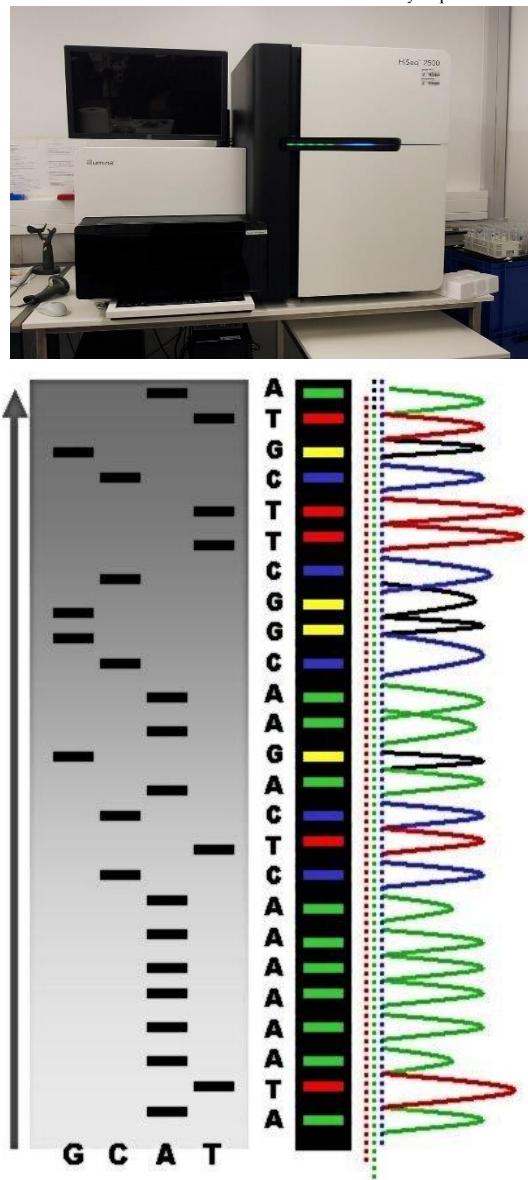
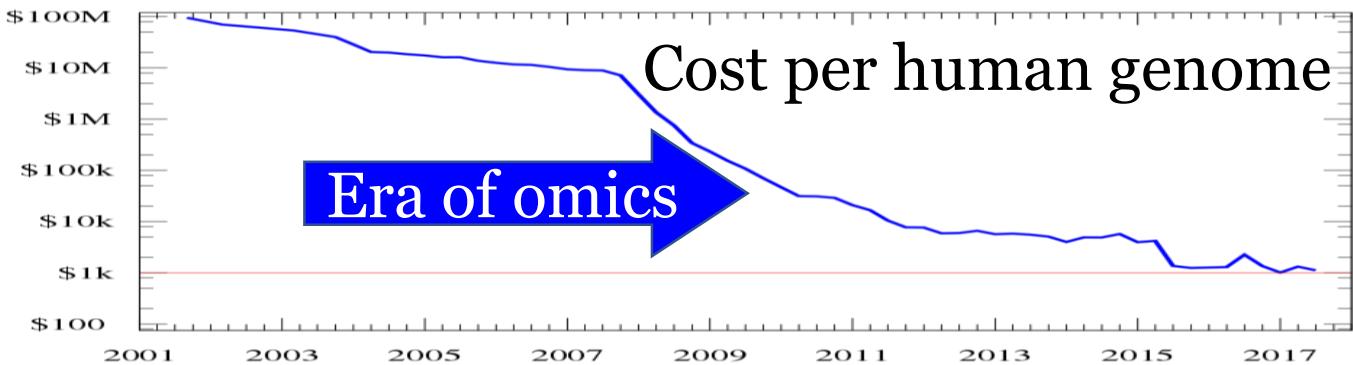
The process of determining the order of nucleotides, adenine (A), guanine(G), cytosine (C), and thymine (T).

Basic methods (Maxam-Gilbert (1976), chain-termination (1977))

Advanced methods and *de novo* sequencing
(Shotgun (1979), bridge PCR)

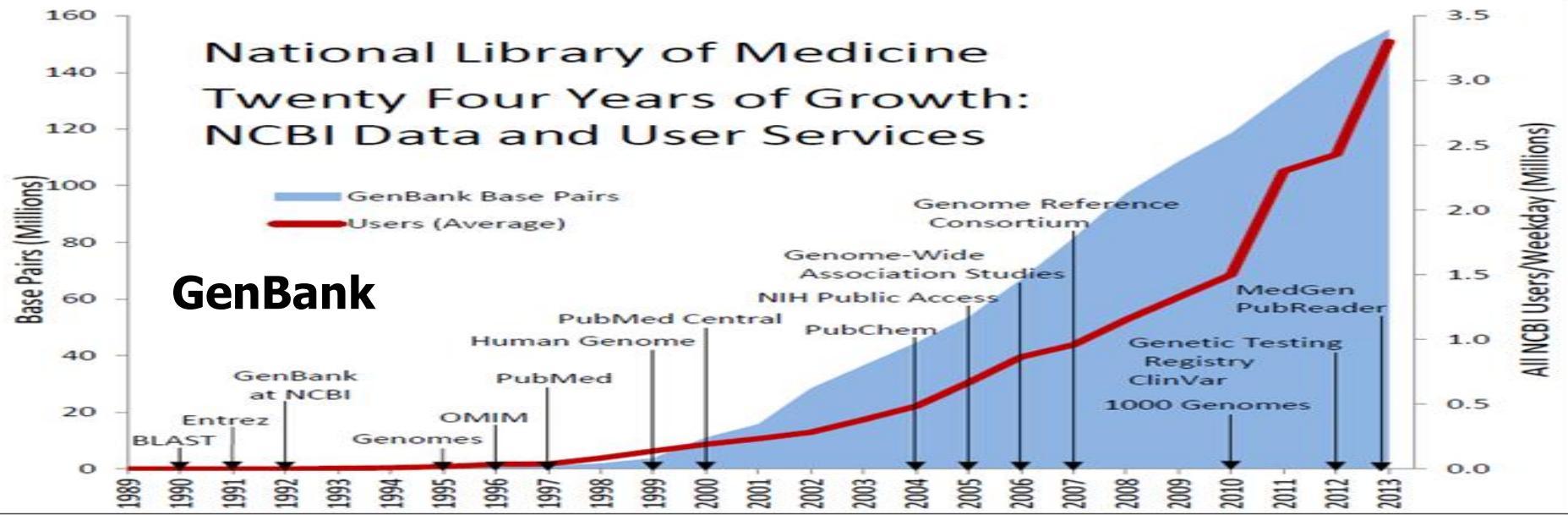
High-throughput methods (massively parallel signature, Polony etc.)

Methods in development (tunnelling currents, mass spectrometry, microfluidics, microscopy-based techniques, etc.)

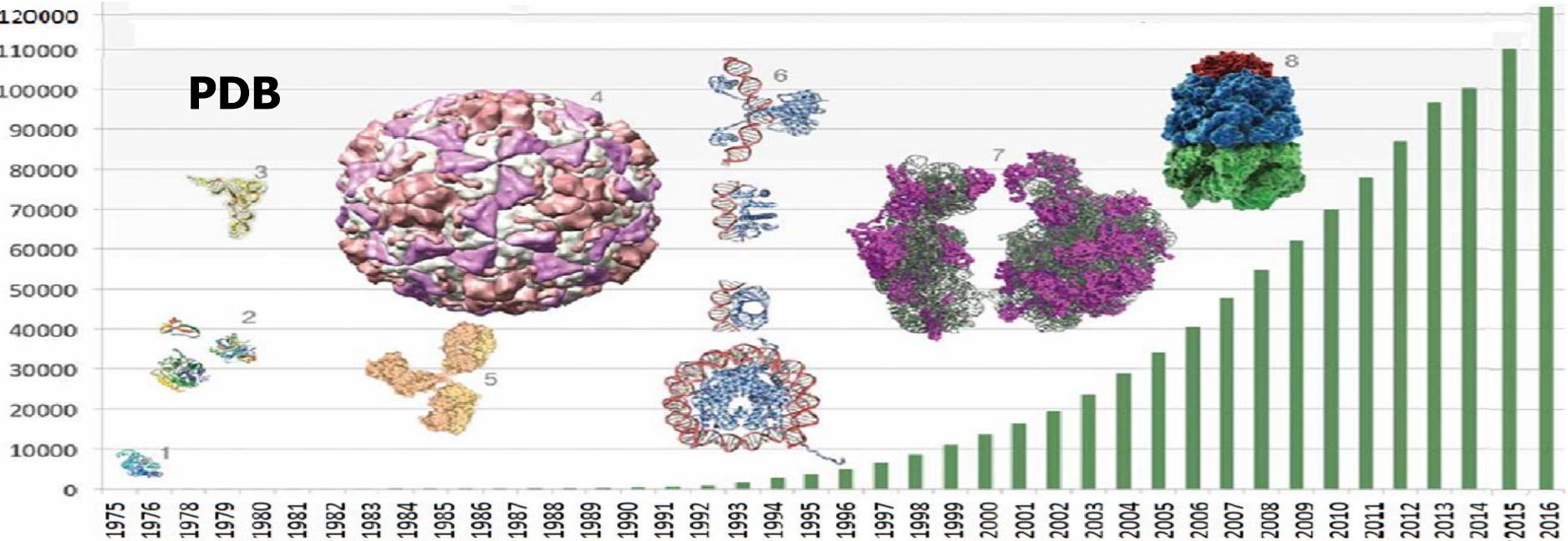


Biological data

National Library of Medicine Twenty Four Years of Growth: NCBI Data and User Services



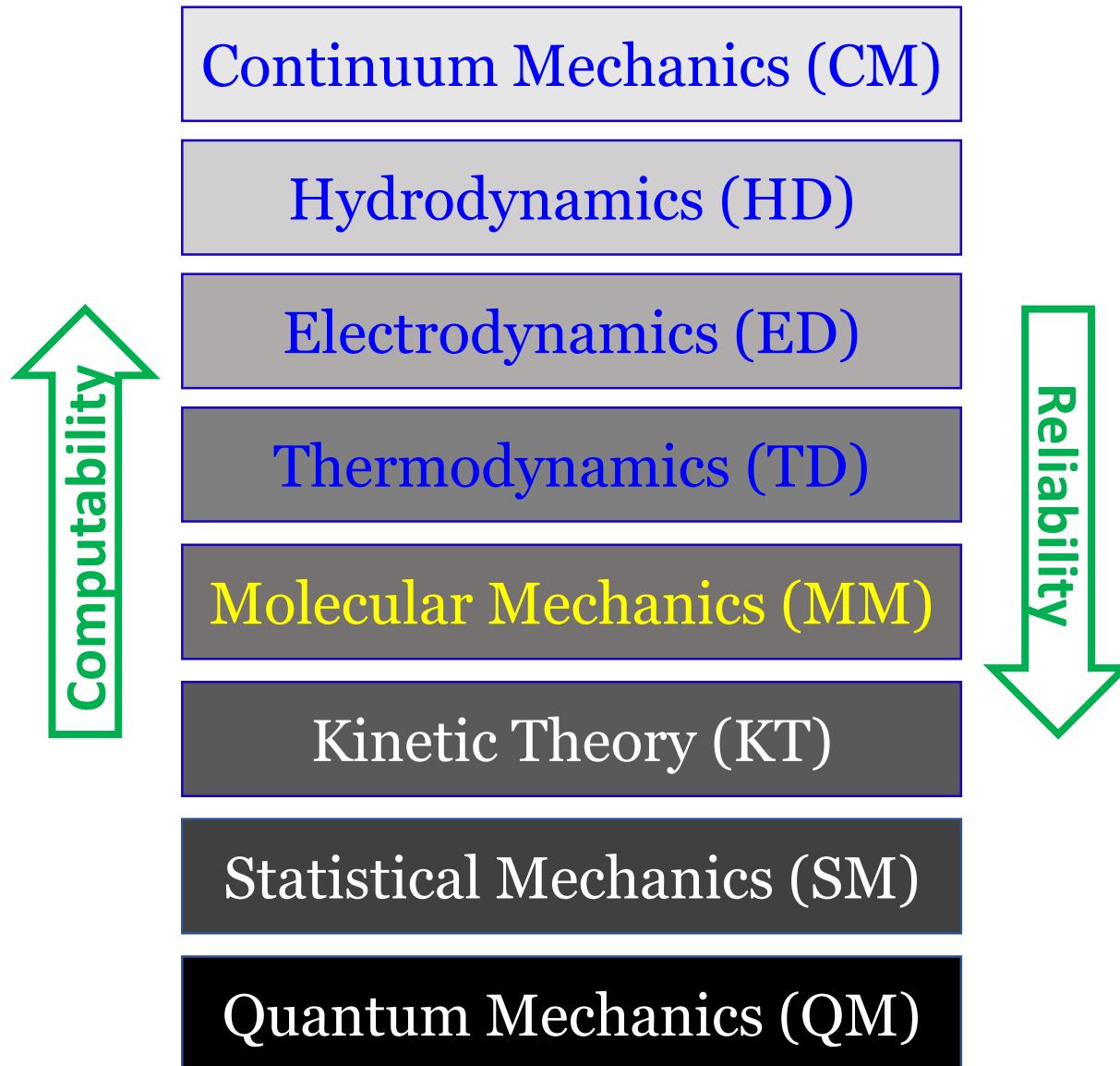
PDB



Biophysics

- 1) Biophysics is an interdisciplinary science that applies approaches and methods traditionally used in physics to study biological phenomena.
- 2) Biophysics covers all scales of biological organization, from molecular to organismic and populations
- 3) Molecular biophysics applies physical approach to model biomolecular systems and understand their interactions and structure-function relationship.
- 4) Unlike data-driven bioinformatics and knowledge-based systems biology, biophysics is mechanistic.

Foundations of Biophysics



Quantum Mechanics (QM)



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The Schrödinger equation:

Time dependent:

$$i\hbar \frac{\partial}{\partial t} |\psi(\mathbf{r}, t)\rangle = \hat{H} |\psi(\mathbf{r}, t)\rangle$$

Time independent:

$$\hat{H} |\psi_n(\mathbf{r})\rangle = E_n |\psi_n(\mathbf{r})\rangle$$

where

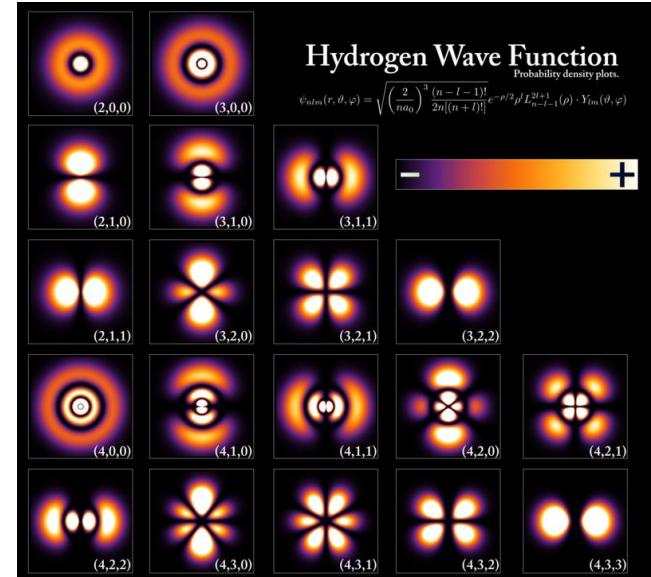
$$|\psi(\mathbf{r}, t)\rangle \in \mathcal{H}(\mathbb{R}^{3(N_e+N_n)+1})$$

$$|\psi_n(\mathbf{r})\rangle \in \mathcal{H}(\mathbb{R}^{3(N_e+N_n)})$$

$$\hat{H} = - \sum_{i=1}^{N_e} \frac{\hbar^2}{2m_i} \nabla_i^2 - \sum_{j=1}^{N_n} \frac{\hbar^2}{2M_j} \nabla_j^2 + V(\mathbf{r}_1, \dots, r_{N_e}, \mathbf{R}_1, \dots, R_{N_n}, t)$$

Feasibility: The full-scale quantum mechanics is feasible for very small systems and intractable for biomolecules.

Biological relevance: Chemical bonds, chemical reaction (enzymes), electrotransfer, photoreceptor, photosynthesis, mutations, proton activity, MM force fields, etc.



Approximation Methods

- Born-Oppenheimer approximation (Decoupling of atomic nuclei and electrons)
- Semi-empirical methods (e.g., Hückel method)
- Valence bond methods
- Density functional theory (one-electron density)
- Molecular orbital theory (Linear combination of atomic orbitals)
- Hartree-Fock method (neglecting instantaneous Coulombic electron-electron repulsion)
- Post-Hartree-Fock methods (e.g., Møller–Plesset perturbation theory)



Thermodynamics/Statistical Mechanics

- o) Bridges microscopic states with macroscopic measurements.
- 1) First law: Energy is conserved: $dE = dQ - dW$
- 2) Second law: It is impossible to transfer all heat into work.
- 3) Third law: It is impossible to reach the absolute zero of temperature by any finite number of processes.
- 4) State variables (P, V) , (T, S) and (n_i, μ_i) .
- 5) Thermodynamic potentials:

Internal energy:
$$dE = TdS - PdV + \sum_i \mu_i dn_i$$

Helmholtz free energy:
$$dA = -SdT - PdV + \sum_i \mu_i dn_i$$

Gibbs free energy:
$$dG = -SdT + VdP + \sum_i \mu_i dn_i$$

Enthalpy:
$$dH = TdS + VdP + \sum_i \mu_i dn_i$$

Thermodynamics/Statistical Mechanics

6) Microcanonical ensemble (N, V, E):

Partition function: $\Omega(N, V, E) = e^{S/k_\beta}$

Probability: $p_E = \begin{cases} e^{-S/k_\beta}, & E - \frac{\delta E}{2} \leq E \leq E + \frac{\delta E}{2} \\ 0, & \text{otherwise} \end{cases}$

Thermodynamic potential: $dE = TdS - PdV$

7) Canonical ensemble (N, V, T):

Partition function: $Q(N, V, T) = \sum_i e^{-\beta E_i} = e^{-\beta A}, \quad \beta := \frac{1}{k_\beta T}$

Probability: $p_i = \frac{1}{Q} e^{-\beta E_i}$

Thermodynamic potential: $dA = -SdT - PdV$

8) Grand Canonical ensemble (V, T, μ):

Partition function: $\Xi(V, T, \mu) = \sum_{N=0}^{\infty} Q(N, V, T) e^{\beta \mu N} = e^{\beta PV}$

Probability: $p_i(N) = \frac{1}{\Xi} e^{-\beta E_i(N)} e^{\beta \mu N}$

Thermodynamic potential: $d(PV) = SdT + PdV + Nd\mu$

9) Non-equilibrium thermodynamics and kinetic theory

Molecular Mechanics (MM)

Using classical particle assumption.

Newton's second law: $m_i \frac{d^2}{dt^2} \mathbf{r}_i = \mathbf{F} = -\nabla U(\mathbf{r}_1(t), \mathbf{r}_2(t), \dots, \mathbf{r}_n(t))$

Aproximation:
$$U = \sum_{\text{bonds}} K_d (d - d_0)^2 + \sum_{\text{angle}} K_\theta (\theta - \theta_0)^2$$
$$+ \sum_{\text{dihedrals}} K_\chi (1 + \cos(n\chi - \delta))$$
$$+ \sum_{\text{nonbond}} \left\{ \epsilon_{ij} \left[\left(\frac{R_{ij}^{\min}}{\mathbf{r}_{ij}} \right)^{12} - \left(\frac{R_{ij}^{\min}}{\mathbf{r}_{ij}} \right)^6 \right] + \frac{q_i q_j}{\epsilon \mathbf{r}_{ij}} \right\}$$

Langevin equation: $m \ddot{\mathbf{r}} = -\nabla V(\mathbf{r}) - \gamma \dot{\mathbf{r}} + \sqrt{2\gamma k_B T} R(t)$,
where, $\langle \mathbf{R}(t) \rangle = 0$, $\langle \mathbf{R}(t)\mathbf{R}(t') \rangle = \delta(t - t')$

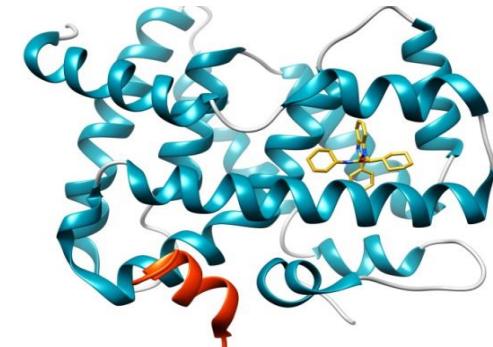
Explicit solvent/Implicit solvent/Coarse Grained

MM Software: AMBER/CHARMM/NAMD/TINKER/GROMOS

Research issues: high-order force fields, coarse grained methods, implicit MD, etc.

Protein Structure Prediction

SVYDAAAQLTADVKKDLRDSW
KVIGSDKKGNGVALMTTLFAD
NQETIGYFKRLGNVSQGMAND
KLRGHSITLMYALQNFIDQLD
NPDSLDLVCS



- 1) Understand protein structure-function relationship
- 2) Design protein with desired function
- 3) Drug development
- 4) Methods (knowledge-based):

Template-based modeling (homology modeling) is used when there is one or more similar known structures in PDB.

Ab initio structure prediction (e.g., Rosetta) is used when one cannot find any similar structure.

Deep learning (e.g., AlphaFold, CNN, RNN)

- 5) Evaluation:

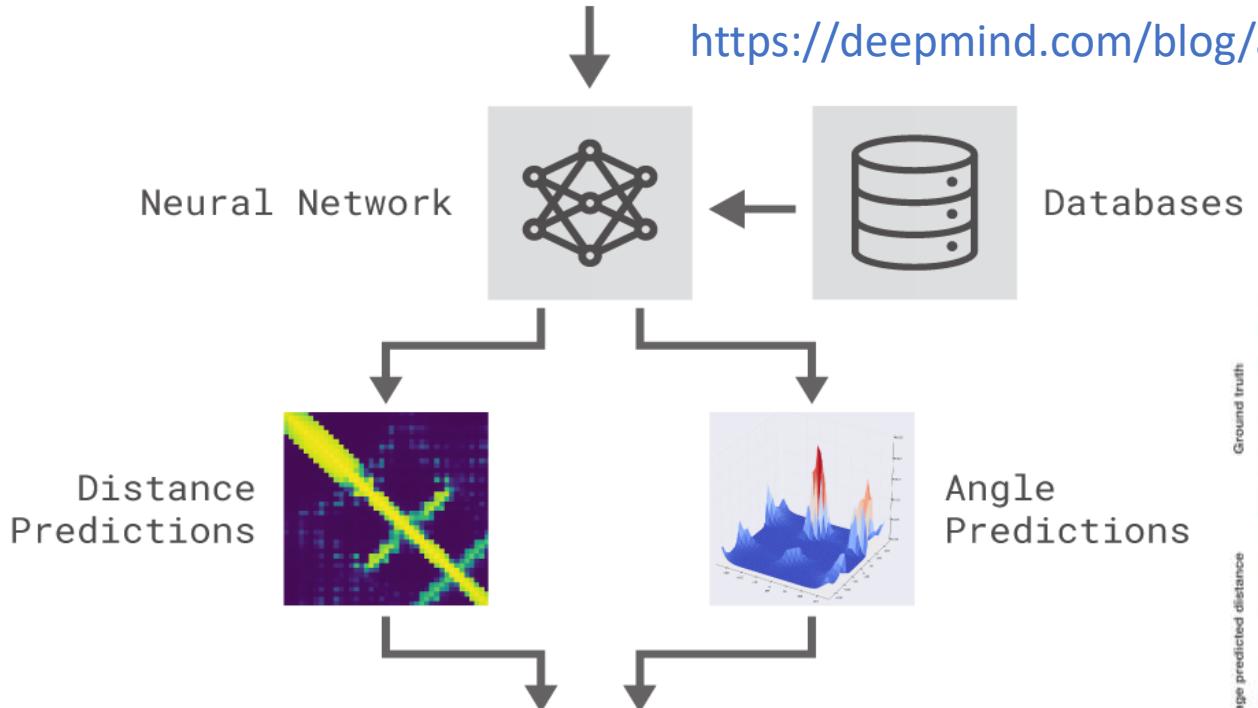
Critical Assessment of protein Structure Prediction (CASP)
Knowledge-based methods win; QM/MM do not work well.

ALPHA FOLD

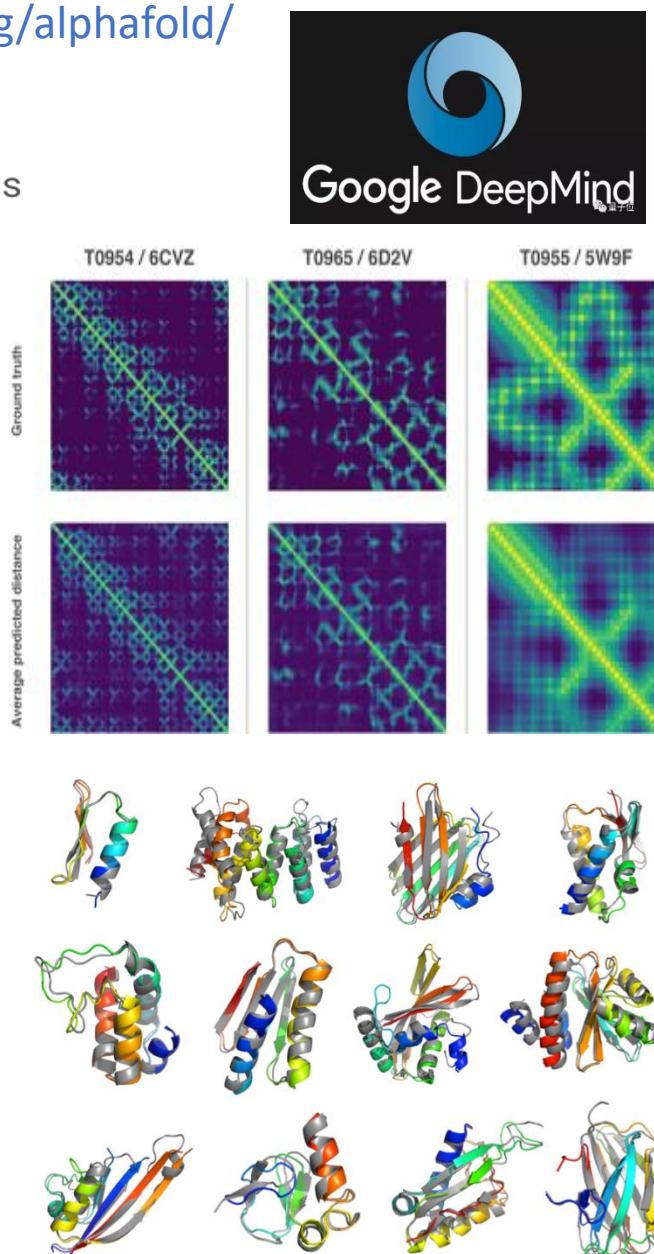
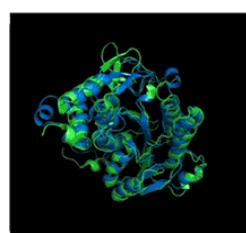
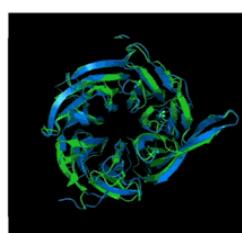
Protein Sequence

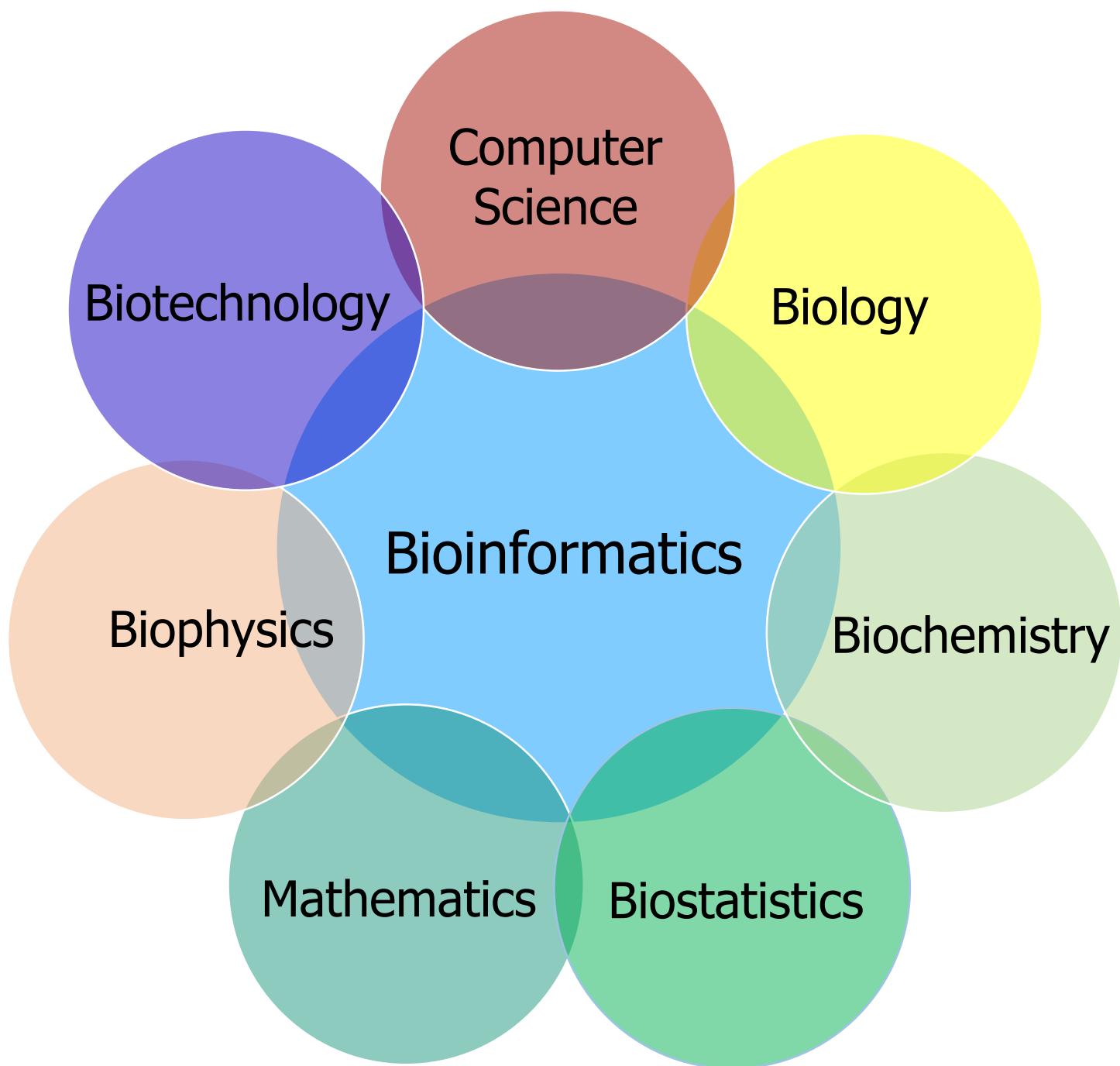
SQETRKKCTEMKKKFKNCEVRCDESNCHEVRCSDTKYTLC

<https://deepmind.com/blog/alphafold/>



Structures:
Ground truth (green)
Predicted (blue)





Bioinformatics

- 1) **Sequence analysis** (DNA sequencing, sequence assembly, genome annotation, comparative genomics, pan genomics, computational evolution, genetics, cancer mutation, etc.).
- 2) **Gene and protein expression** (Gene expression analysis, protein expression analysis, gene regulation, genotype–phenotype map, etc.).
- 3) **Systems biology** (Pan networks, integrated systems analysis).
- 4) **Cellular organization** (Microscopy and image analysis, protein localization, membrane mechanics, chromatin analysis, etc.).
- 5) **Structural bioinformatics** (Biomolecular structure and interaction, structure-function relationship, protein folding, protein design, etc..)
- 6) **Database and software.**
- 7) Unlike biophysics, bioinformatics is data-driven.

Systems Biology

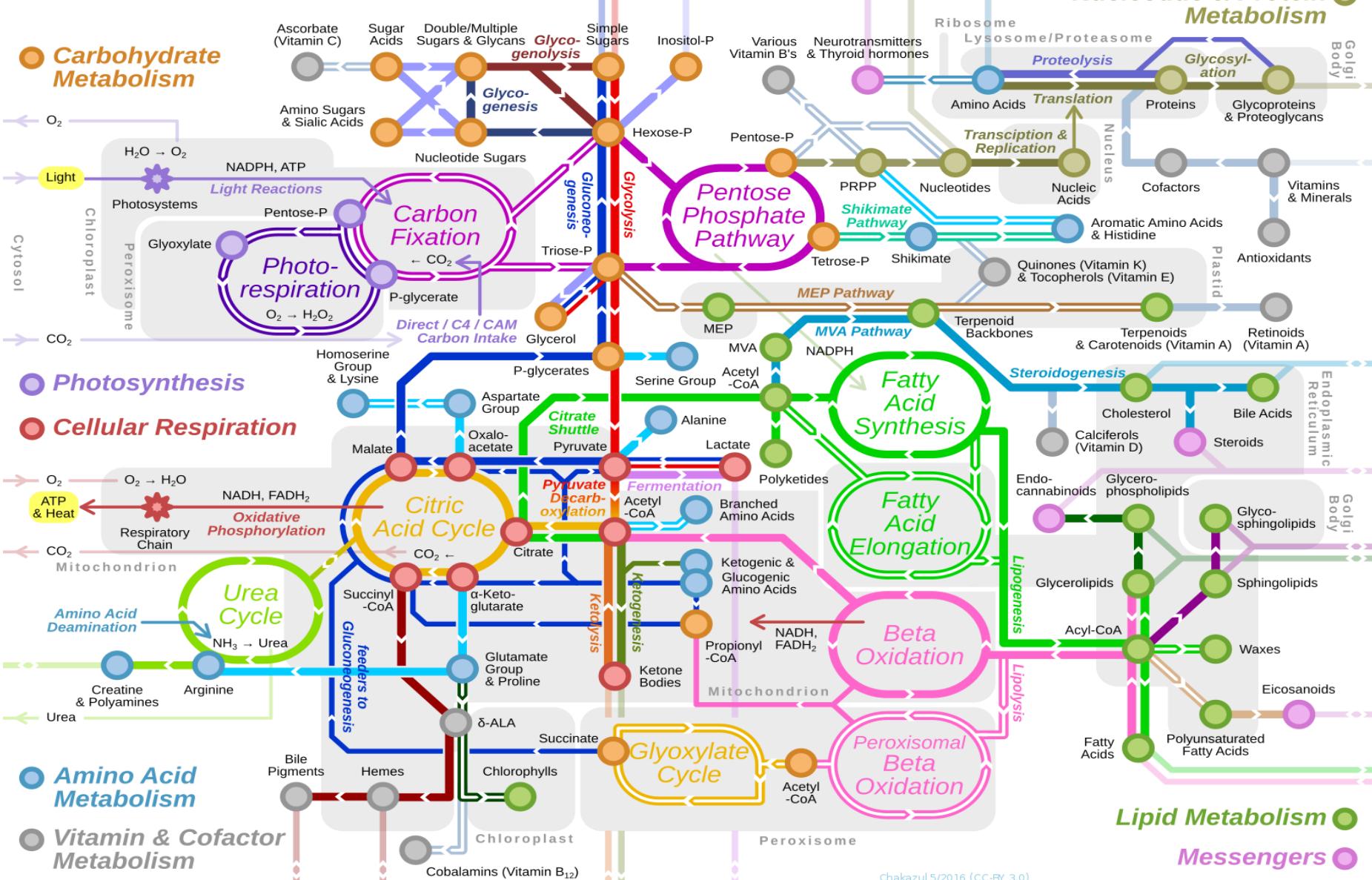
- 1) It concerns computational and mathematical modeling of complex biological systems.
- 2) It treats cells, tissues and organisms as interactive and integrated systems.
- 3) It deals with metabolic networks, cell signaling pathways, transcriptomics, metabolomics, proteomics, etc.
- 4) Unlike bioinformatics, system biology emphasizes dynamics.
- 5) Unlike biophysics, systems biology is knowledge-based.
- 6) Systems biology overreaches to quantitative systems physiology.
- 7) Systems biology relates to quantitative systems pharmacology.

Systems Biology



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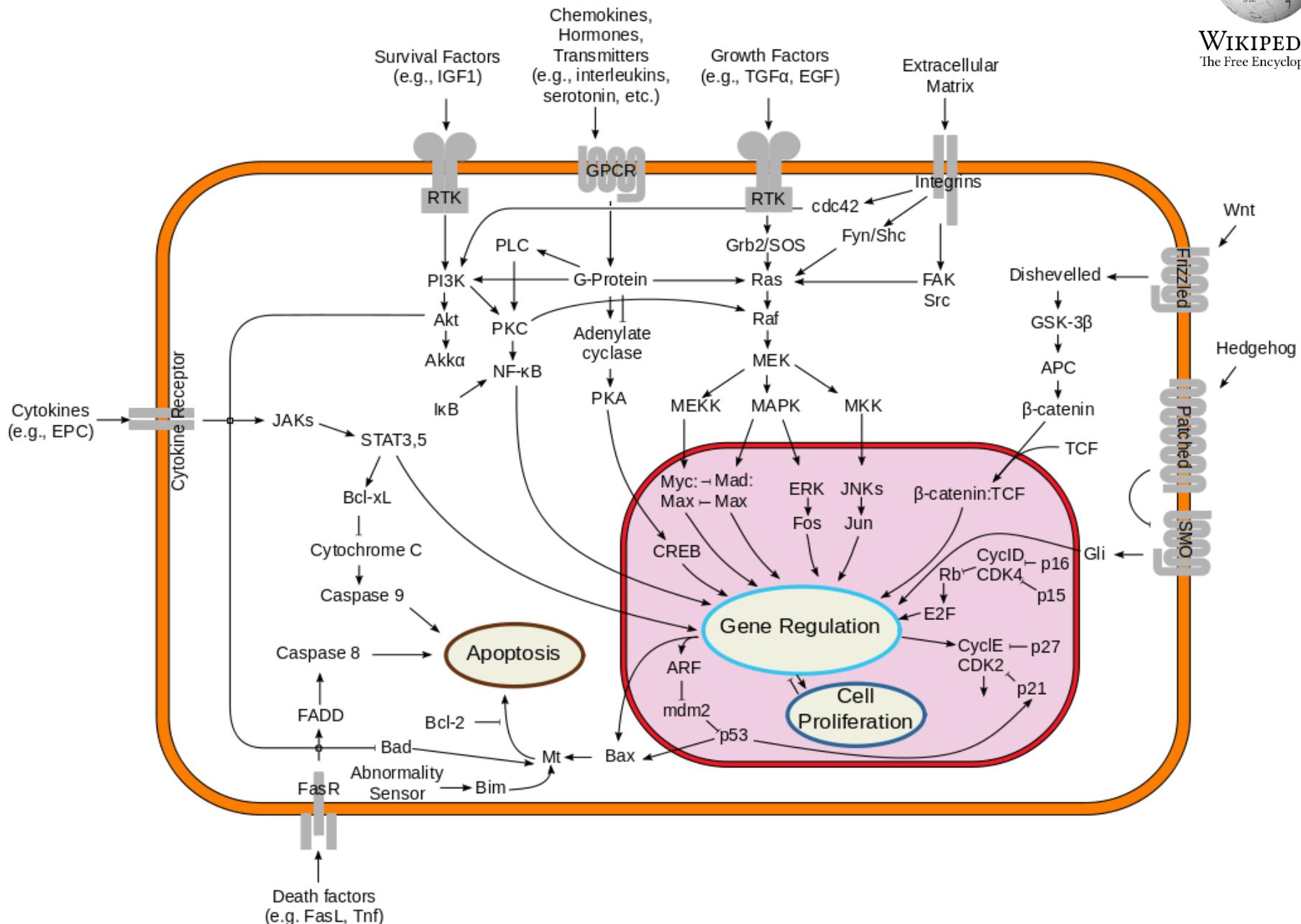
Metabolic Metro Map



Systems Biology



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New Trends in Biological Science

- 1) New bioscience is based on molecules and/or omics.
- 2) Integrative biology (from molecules, organism to environment).
- 3) Integration of biophysics, systems biology, and bioinformatics.
- 4) Integration of mathematics, data science, theoretical biology and experimental biology.
- 5) Mathematical molecular bioscience and biophysics.
- 6) Quantitative systems pharmacology (from systems biology, biomechanics, systems physiology to systems pharmacology).
- 7) Personalized medicine (precision medicine).

Mathematics Commonly Used in Molecular Bioscience

Geometry

D.W. Sumners, Isabel .K. Darcy , Mariel Vazquez, Dorothy Buck,
Tamar Schlick, Erica Flapan, Christian Reidys, Yusu Wang,
Peter Rogen, Jack Quine,

Algebra

Christine Heitsch, David Murrugarra, Reidun Twarock
Natasha Jonoska, R Brijder, HJ Hoogeboom,
Julie Mitchell

Group theory

Combinatorics

Analysis

M Karplus, M Levitt, A Warshel, B Honig, E Alxov, A Onufriev,...
B.S. Eisenberg, Chun Liu, Weishi Liu, Yun Kyong Hyon, TC Lin,

Calculus/Variation

JL Liu, TL Horng, YN Young, HX Huang, Lei Zhang, Tom Chou
J.A. McCammon, Michael Holst, Jingfang Huang, Benzhuo Lu,
Nathan Baker, Bo Li, LT Cheng, MX Chen, Shenggao Zhou,

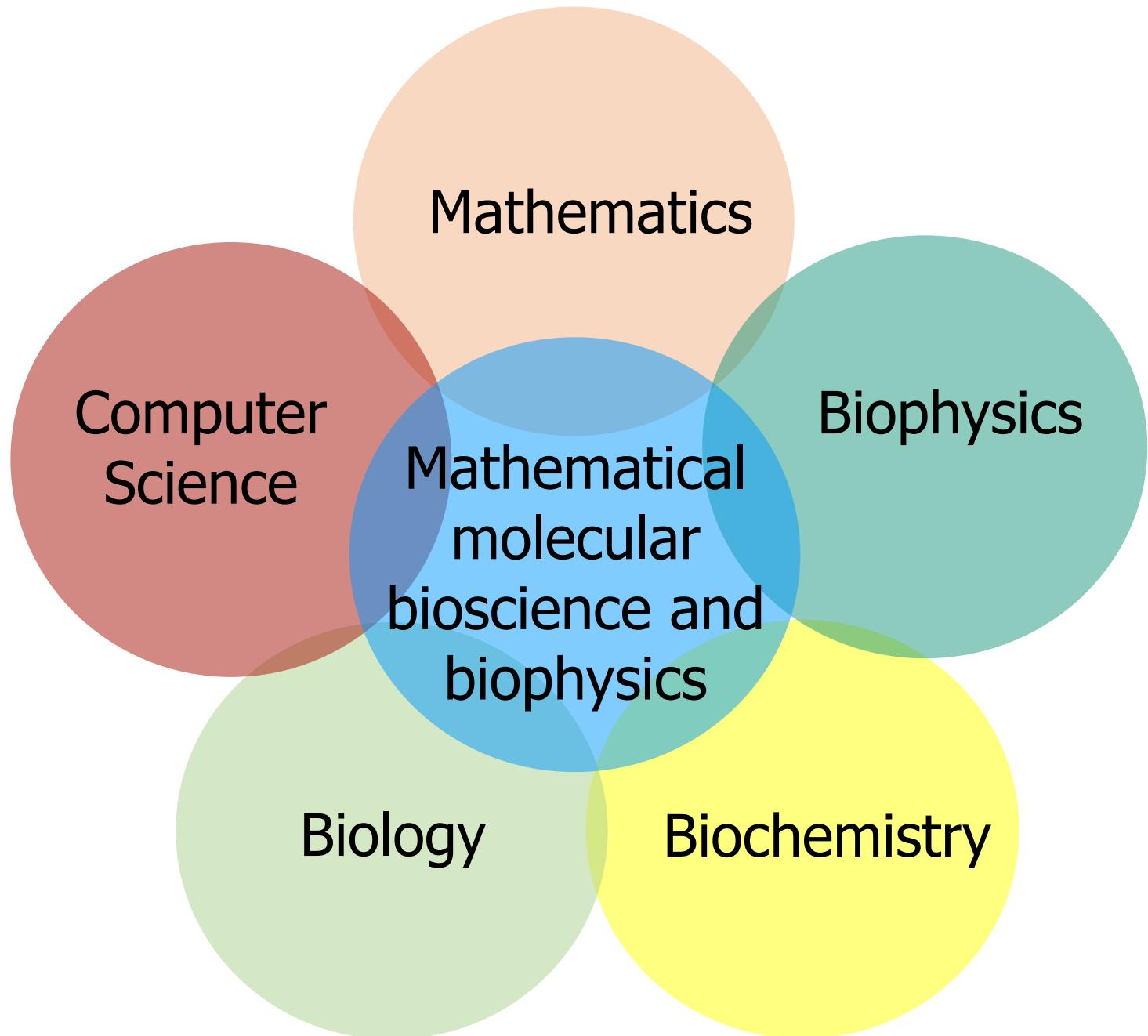
ODE and PDE

Numerical analysis

Keith Promislow, Shabin Dai, Nir Gavish, Robert Krasny, DX Xie,
LR Scott, Wei Cai, ZL Xu, Amit Singer, D. Kozakov, R Rizzo, D.
Green, R Ryham, LJ Cowen, ...

My collaborators: [Shan Zhao](#), [Yongcheng Zhou](#), [Weihua Geng](#), [Duan Chen](#), [Zhan Chen](#),
[Kelin Xia](#), [Lin Mu](#), [Duc Nguyen](#), [Bao Wang](#), [Zixuan Cang](#), [Jin Kyoung Park](#), [Dave Bramer](#),
[Jiahui Chen](#), ..., [Sining Yu](#), [Yuhui Sun](#), [Langhua Hu](#), [Kris Opron](#), [Yin Cao](#), [Kedi Wu](#),...
[Yiying Tong](#), [Xin Feng](#), [Beieai Liu](#), [Rundong Zhao](#),...

Mathematical Molecular Bioscience and Biophysics



Mathematical Molecular Bioscience and Biophysics

- 1) It concerns the mathematical foundation of biological science.
- 2) It is based on molecular bioscience and omics in contrast to macroscopic biosciences.
- 3) It overlaps with molecular biophysics, systems biology and bioinformatics but is distinguished from any mathematical biology that is macroscopic and phenomenological.
- 4) It exploits existing mathematics for describing biological observations and dynamics.
- 5) It makes use of computational algorithms and methods from mathematics, machine learning and statistics.
- 6) It has applications to a wide range of biological problems, including protein design, drug discovery, precision medicine, to mention only a few.
- 7) It generates new mathematics from biological challenges.



D3R Grand Challenge 2 (2016-2017)

Given: Farnesoid X receptor (FXR) and 102 ligands

Tasks: Dock 102 ligands to FXR, and predict their poses, binding free energies and energy ranking

Stage 1

[Pose Predictions \(partials\)](#)

[Scoring \(partials\)](#)

[Free Energy Set 1 \(partials\)](#)

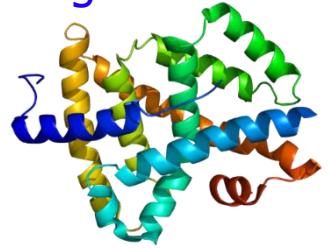
[Free Energy Set 2 \(partials\)](#)

Stage 2

[Scoring \(partials\)](#)

[Free Energy Set 1 \(partials\)](#)

[Free Energy Set 2 \(partials\)](#)

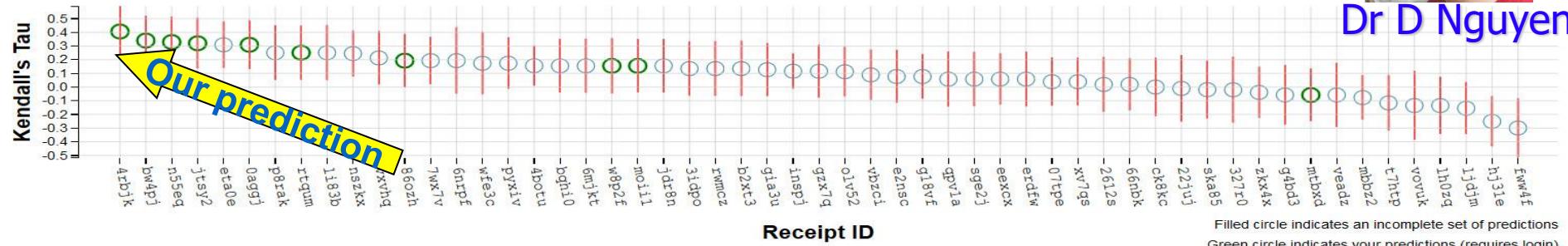


Dr D Nguyen

(Nguyen et al, JCAMD, 2018)

Grand Challenge 2

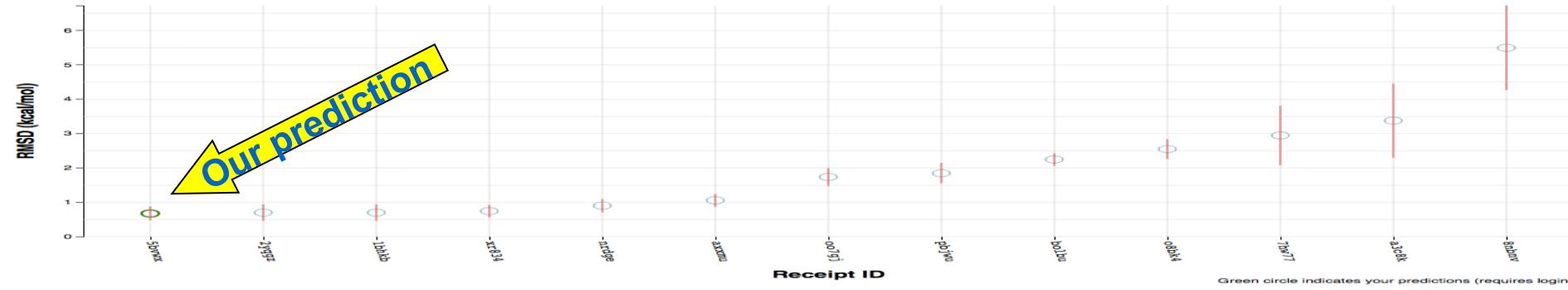
Free Energy Set 1 (Stage 2) - Kendall's Tau



Filled circle indicates an incomplete set of predictions
Green circle indicates your predictions (requires login)

Grand Challenge 2

Free Energy Set 1 (Stage 1) - RMSD



Green circle indicates your predictions (requires login)

D3R Grand Challenge 3 (2017-2018)

(Nguyen et al, JCAMD, 2018)



Pose Prediction

Cathepsin Stage 1A

[Pose Predictions \(partials\)](#)

Affinity Rankings excluding Kds > 10 μM

Cathepsin Stage 1

[Scoring \(partials\)](#)

[Free Energy Set](#)

VEGFR2

[Scoring \(partials\)](#)

JAK2 SC3

[Scoring](#)

[Free Energy Set](#)



Active / Inactive Classification

VEGFR2

[Scoring \(partials\)](#)

JAK2 SC3

[Scoring](#)

[Free Energy Set](#)



Affinity Rankings for Cocrystallized Ligands

Cathepsin Stage 1

[Scoring \(partials\)](#)

[Free Energy Set](#)



Cathepsin Stage 1B

[Pose Prediction](#)

Cathepsin Stage 2

[Scoring \(partials\)](#)

[Free Energy Set](#)

JAK2 SC2

[Scoring \(partials\)](#)

TIE2

[Scoring](#)



[Free Energy Set 2](#)



JAK2 SC2

[Scoring \(partials\)](#)

TIE2

[Scoring \(partials\)](#)



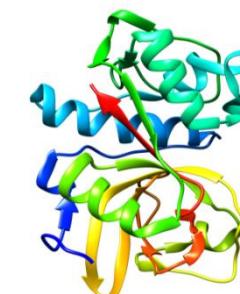
[Free Energy Set 1](#)



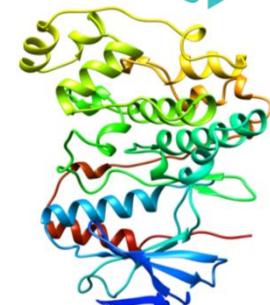
Cathepsin Stage 2

[Scoring \(partials\)](#)

[Free Energy Set](#)



Cathepsin S



Kinase: p38- α

p38- α

[Scoring](#)

ABL1

[Scoring \(partials\)](#)



p38- α

[Scoring \(partials\)](#)

ABL1

[Scoring \(partials\)](#)



Zixuan Cang



Dr D Nguyen

D3R Grand Challenge 4 (2018-2019)



Pose Predictions

BACE Stage 1A

Pose Predictions (Partials)



BACE Stage 1B

Pose Prediction (Partials)



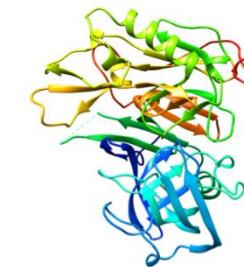
Affinity Predictions

Cathepsin Stage 1

Combined Ligand and Structure Based Scoring



Dr. Kaifu Gao Dr. D Nguyen



Structure Based Scoring



Free Energy Set



BACE Stage 1

Combined Ligand and Structure (No participation)

Ligand Based Scoring (Partials) (No participation)

Structure Based Scoring (Partials) (No participation)

Free Energy Set (No participation)

BACE Stage 2

Combined Ligand and Structure

Ligand Based Scoring (No participation)

Structure Based Scoring (Partials)



Free Energy Set

**Differential
equation**

**Algebraic
topology**

**Differential
topology**

**Geometric
topology**

**Algebraic
graph**

**Geometric
graph**

**Topological
graph**

**Linear
algebra**

Biology became microscopic (i.e., molecular) in 1960s and added an omics dimension around the dawn of the millennium.

Driving by mathematics, biology is transforming from qualitative, phenomenological and descriptive to quantitative, predictive and analytical.

The last frontier of science is biology, while the last frontier of biology is mathematics.

**Number
theory**

**Algebraic
geometry**

**Differential
geometry**

**Euclidean
geometry**

Lie algebra

**Complex
analysis**

**Real
analysis**

**Stochastic
analysis**



Baker Bates Bazil Burton Dickson Dong Hong Hu Lee Munch Tong Ye
PNNL MSU UKLR



Shan Zhao Alabama Y Zhou CSU W Geng SMU Duan Chen UNCC Zhan Che GSU Lin Mu UGA S Yang CU KH S.N. Yu NY Y.H. Sun Denver L. H. Hu Chicago J. Park Indiana



2019



thank you