

Computational Methods in Bioinformatics

2019-2020

Lecture 11

Indicators of impact

- Prizes and awards
- Highly cited publications
- Commercial applications

Sequences

- "for his work on the structure of proteins, especially that of insulin."
- <https://www.nobelprize.org/prizes/chemistry/1958/sanger/facts/>
- "for their contributions concerning the determination of base sequences in nucleic acids."
- <https://www.nobelprize.org/prizes/chemistry/1980/sanger/facts/>

Frederick Sanger

- "1958 Prize: Proteins, which are molecules made up of chains of amino acids, play a pivotal role in life processes in our cells. One important protein is insulin, a hormone that regulates sugar content in blood. Beginning in the 1940s, Frederick Sanger studied the composition of the insulin molecule. He used acids to break the molecule into smaller parts, which were separated from one another with the help of electrophoresis and chromatography. Further analyses determined the amino acid sequences in the molecule's two chains, and in 1955 Frederick Sanger identified how the chains are linked together."

<https://www.nobelprize.org/prizes/chemistry/1980/sanger/facts/>

Frederick Sanger

- "1980 Prize: An organism's genome is stored in the form of long rows of building blocks, known as nucleotides, which form DNA molecules. An organism's genome can be mapped by establishing the order of the nucleotides within the DNA molecule. In 1977, Frederick Sanger developed a method based on using small amounts of what are known as dideoxynucleotides. These can be inserted into the DNA chain, but at a certain nucleotide they stop growth of the chain so that fragments of different lengths are created. After undergoing what is known as electrophoresis, the nucleotide sequences in a DNA sample can be identified."

<https://www.nobelprize.org/prizes/chemistry/1980/sanger/facts/>

Linus Pauling

The Nobel Prize in Chemistry 1954 "for his research into the nature of the chemical bond and its application to the elucidation of the structure of complex substances"

- "During the 1930s Linus Pauling was among the pioneers who used quantum mechanics to understand and describe chemical bonding - that is, the way atoms join together to form molecules. Linus Pauling worked in a broad range of areas within chemistry. For example, he worked on the structures of biologically important chemical compounds. In 1951 he published the structure of the alpha helix, which is an important basic component of many proteins."

<https://www.nobelprize.org/prizes/chemistry/1954/pauling/facts/>

Structural Biology related Nobel Prizes

The Recipient(s)		
2009: Chemistry	Venkatraman Ramakrishnan, Thomas A. Steitz, Ada E. Yonath	Studies of the structure and function of the ribosome
2006: Chemistry	Roger D. Kornberg	Studies of the molecular basis of eukaryotic transcription
2003: Chemistry(1/2)	Roderick MacKinnon	Structural and mechanistic studies of ion channels
2002: Chemistry(1/2)	Kurt Wüthrich	Development of nuclear magnetic resonance spectroscopy for determining the three-dimensional structure of biological macromolecules in solution [Wüthrich].
1997: Chemistry(1/4)	John E. Walker	Elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP).
1991: Chemistry	Richard R. Ernst	Contributions to the development of the methodology of high resolution nuclear magnetic resonance (NMR) spectroscopy.
1988: Chemistry	Johann Deisenhofer, Robert Huber, Hartmut Michel	Determination of the three-dimensional structure of a photosynthetic reaction centre
1982: Chemistry	Aaron Klug	Development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes
1972: Chemistry(1/2)	Christian B. Anfinsen	Work on ribonuclease, especially concerning the connection between the amino acid sequence and the biologically active conformation
1964: Chemistry	Dorothy Crowfoot Hodgkin	Determinations by X-ray techniques of the structures of important biochemical substances
1962: Medicine	Francis Harry Compton Crick, James Dewey Watson, Maurice Hugh Frederick Wilkins	Discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material
1962: Chemistry	Max Ferdinand Perutz, John Cowdery Kendrew	Studies of the structures of globular proteins
1946: Chemistry(1/2)	James Batcheller Sumner	Discovery that enzymes can be crystallized

Some more recent Nobel Prizes in Chemistry

2012

- Robert J. Lefkowitz and Brian K. Kobilka “for studies of G-protein-coupled receptors”

2013

- Martin Karplus, Michael Levitt and Arieh Warshel “**for the development of multiscale models for complex chemical systems**”

2017

- Jacques Dubochet, Joachim Frank and Richard Henderson “for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution”

Channels

- Computational detection and analysis of channels ion proteins

Nobel Prize in Chemistry for 2003 “for discoveries concerning channels in cell membranes”

- “for the discovery of water channels”
(isolation of aquaporin)
- “for structural and mechanistic studies of ion channels”
(crystallographic structure of a potassium channel)

The Immune System

Nobel prizes and the immune system, 1901-2010 (or 1901-1996?)

<https://www.nobelprize.org/prizes/uncategorized/nobel-prizes-and-the-immune-system/>

More recently (2018)

- Phage display for the directed evolution of antibodies

<https://www.nobelprize.org/prizes/chemistry/2018/press-release/>

- discovery of cancer therapy by inhibition of negative immune regulation

<https://www.nobelprize.org/prizes/medicine/2018/press-release/>

The Immune System

Antibodies

- Comparative modelling to get insights
- Docking of antibodies with with antigens

Major Histocompatibility Complex (MHC)

- Side-chain modelling of binding grooves and peptides
- “Threading”-like approach to predict peptide-MHC interactions
- Deimmunization of therapeutic proteins

Commercially relevant

- Computational drug design
- Guest lecture on 11 December 2019
- GPCRs
- Therapeutic proteins

GPCRs

Hauser, A. S., Attwood, M. M., Rask-Andersen, M., Schiöth, H. B., & Gloriam, D. E. (2017). Trends in GPCR drug discovery: new agents, targets and indications. *Nature Reviews Drug Discovery*, 16(12), 829.

- "There are currently 475 drugs (~34% of all drugs approved by the FDA) that act on 108 unique GPCR targets."
- "Approximately 321 agents are currently in clinical trials, of which ~20% target 66 potentially novel GPCR targets that do not currently have an approved drug."

Therapeutic proteins

Lagassé, H. D., Alexaki, A., Simhadri, V. L., Katagiri, N. H., Jankowski, W., Sauna, Z. E., & Kimchi-Sarfaty, C. (2017). Recent advances in (therapeutic protein) drug development. *F1000Research*, 6.

- "Since 2011, the U.S. Food and Drug Administration Center for Drug Evaluation and Review (CDER) and the Center for Biologics Evaluation and Review (CBER) combined have **approved 62 recombinant therapeutic proteins**"
- "Of these 62 therapeutic proteins, **almost half (48%) were monoclonal antibodies** (for this analysis, we included antibody-drug conjugates and antibody fragment antigen binding in this group)."

Therapeutic antibodies

Ecker, D. M., Jones, S. D., & Levine, H. L. (2015, January). The therapeutic monoclonal antibody market. In *MAbs* (Vol. 7, No. 1, pp. 9-14). Taylor & Francis.

- “Since the commercialization of the first therapeutic monoclonal antibody product in 1986, this class of biopharmaceutical products has grown significantly so that, **as of November 10, 2014, forty-seven monoclonal antibody products have been approved** in the US or Europe for the treatment of a variety of diseases, and many of these products have also been approved for other global markets. At the current approval rate of ~ four new products per year, **~70 monoclonal antibody products will be on the market by 2020, and combined world-wide sales will be nearly \$125 billion.**”

Some highly cited papers (Google Scholar, 2019-12-08)

Citations	Description	Year
81189	Basic local alignment search tool (BLAST), Altschul et al.	1990
71893	Gapped BLAST AND PSI-BLAST, Altschul et al.	1997
63312	CLUSTAL W (multiple sequence alignment), Thompson, Higgins, Gibson	1994
45865	Optimization by simulated annealing, Kirkpatrick et al.	1983
40880	Equation of state calculations by fast computing machines, Metropolis et al.	1953
30711	Protein Data Bank, Berman et al.	2003
22486	PHYMLIP (Phylogeny Inference Package), Felsenstein	1993
22229	PROCHECK, Laskowski et al.	1993
21126	Fast and accurate short read alignment with BWT, Li and Durbin	2009
21009	UCSF Chimera, Pettersen et al.	2004

Some highly cited papers (Google Scholar, 2019-12-08)

Citations	Description	Year
18360	Cluster analysis and display of genome-wide expression patterns, Eisen et al.	1998
13738	FASTA, Pearson and Lipman	1988
13662	DSSP, Kabsch and Sander	1983
13053	Global pairwise sequence alignment, Needleman and Wunsch	1970
11555	Comparative modelling, Sali and Blundell	1993
11530	Identification of common molecular subsequences, Smith and Waterman	1981
9525	AutoDock Vina, Trott and Olson	2010
7649	SCOP: Structural classification of proteins	1995
6432	Solvent accessible surface, Lee and Richards	1971
4425	Protein structure alignment, DALI, Holm and Sander	1993