Nucleic Acids

Learning Outcomes

1. Know the difference between a nucleoside and a nucleotide.

2. Explain why a nitrogenous base is basic.

3. Explain base pairing according to hydrogen bonding.

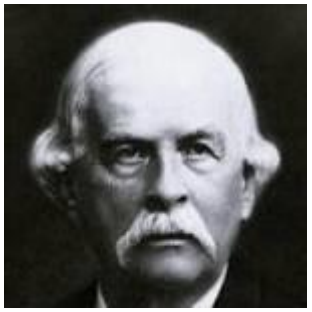
4. Describe the secondary and tertiary structure of DNA.

History of DNA

1869: Friedrich Miescher isolates “nuclein” from white blood cells. Nuclein was selected as the name since the substance was isolated from the cell’s nuclei.

History of DNA

1889: Nuclein found to have acidic properties by Richard Altmann, hence the name ***nucleic acid***.

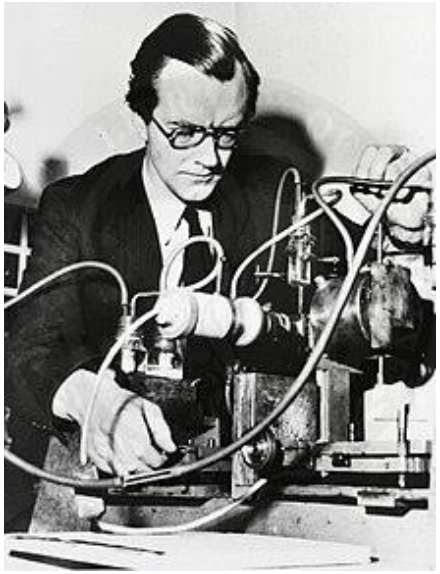


1938: First X-ray diffraction pattern of DNA by William Astbury and Florence Bell.

XRD pattern from Florence Bell's graduate thesis that provided key, atomic-distance information.

History of DNA

1953: Rosalind Franklin, Raymond Gosling, and Maurice Wilkins reported X-ray diffraction studies, which showed the helical structure of DNA.



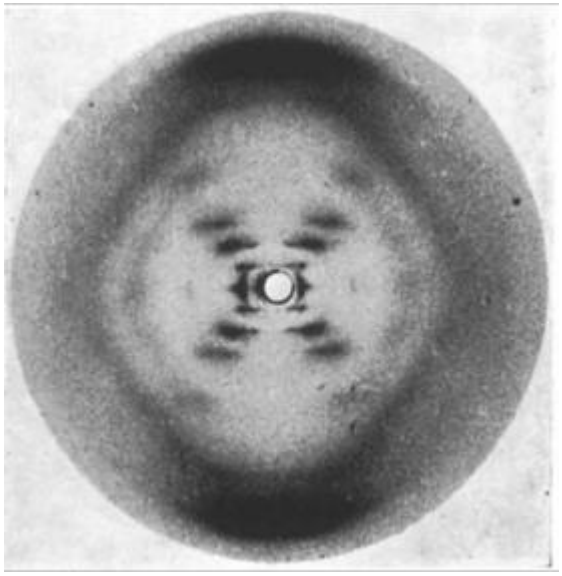


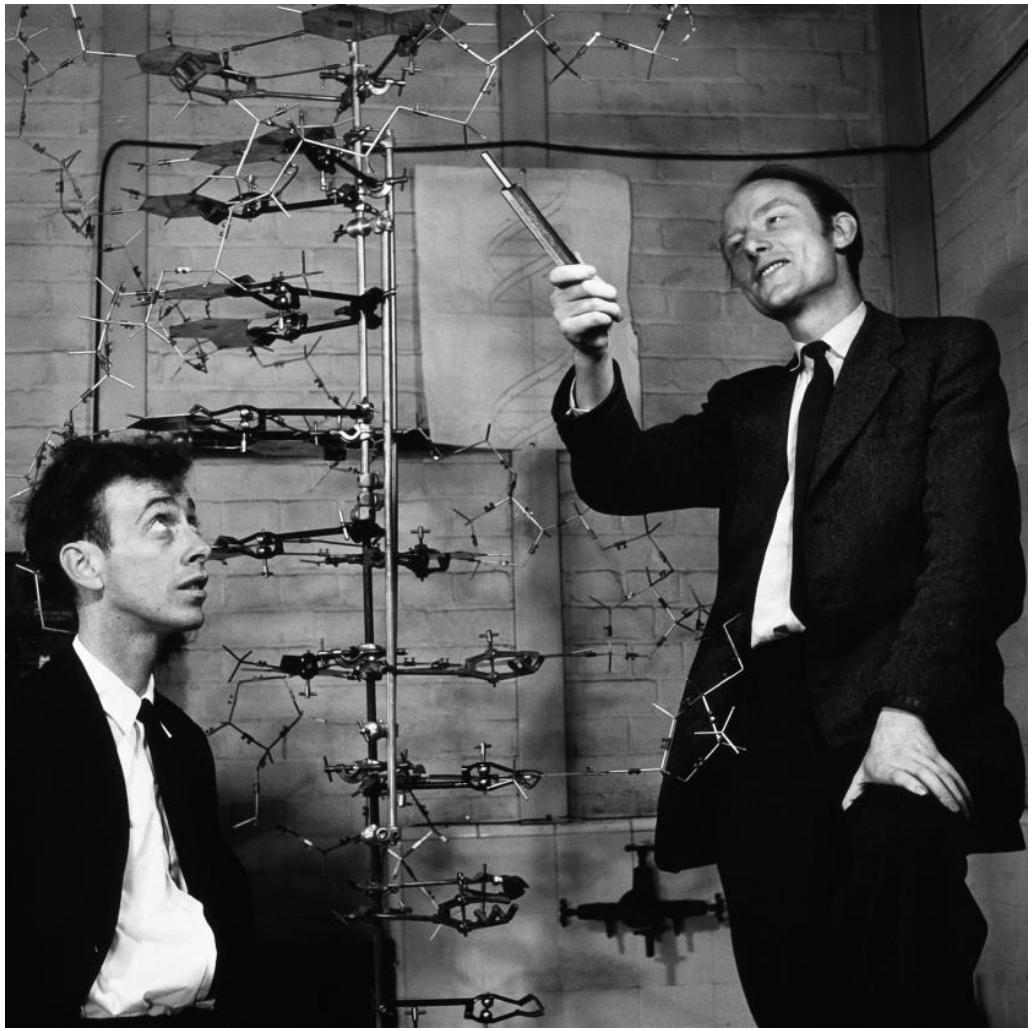
Photo 51

History of DNA

1953: Then, also in 1953, James Watson and Francis Crick combined

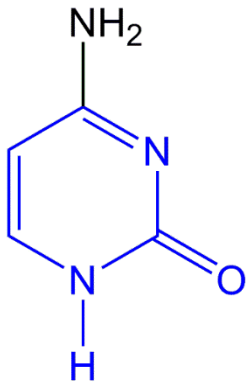
1) Franklin's X-ray data,

2) Chargaff's rules, and
3) examination of molecular models to determine that DNA is a base-paired double helix to arrive at the secondary structure of DNA.

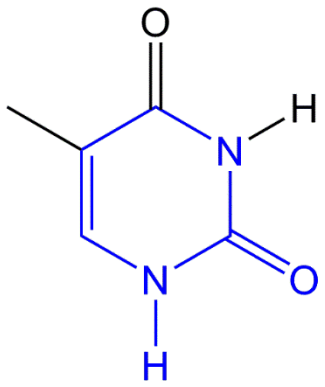


Nucleobases (Nitrogenous Bases)

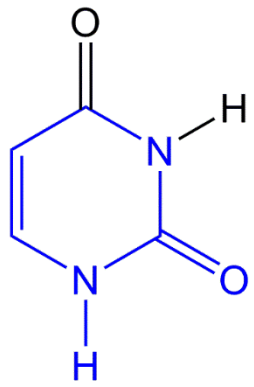
Pyrimidines



Cytosine (C)

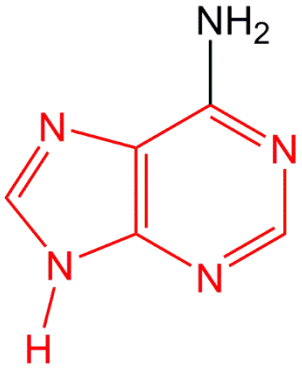


Tymine (T)

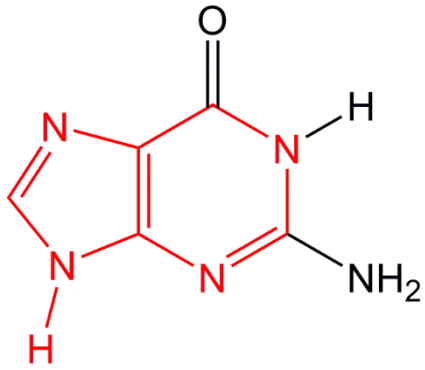


Uracil (U)
RNA

Purines



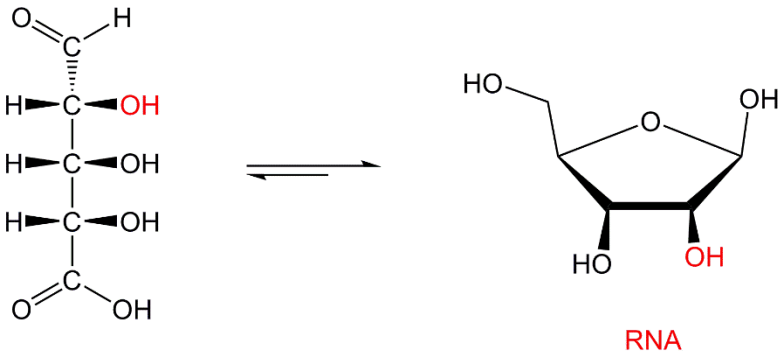
Adenine (A)



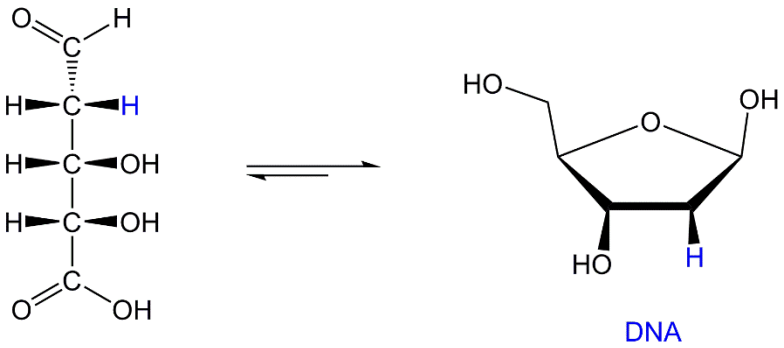
Guanine (G)

Ribofuranoses

Similar how a six-membered cyclic saccharide is a ***glycopyranose***, a five-membered cyclic saccharide is a ***ribofuranose***.



β -D-ribofuranose
(Ribonucleic acid)

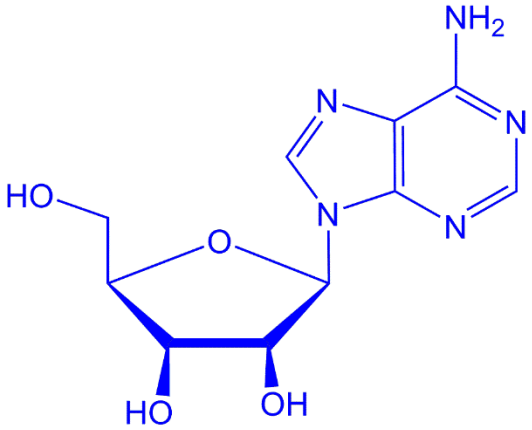


β -D-2-deoxyribofuranose
(Deoxyribonucleic acid)

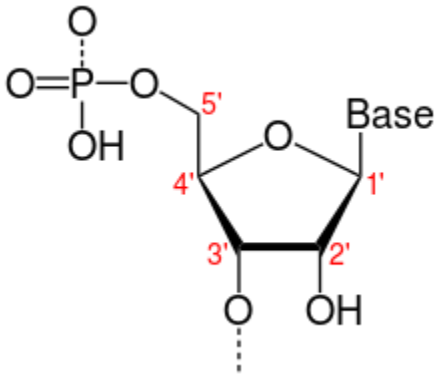
Nucleosides and Nucleotides

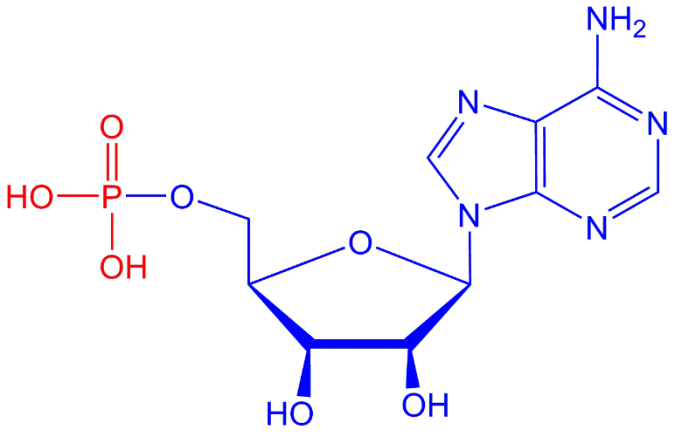
When a nucleobase is bonded to a ribofuranose anomeric carbon, the corresponding structure is a ***nucleoside***.

When a nucleoside forms a bond with phosphoric acid, a ***nucleotide*** is formed. Specifically, a nucleotide is a nucleoside with a phosphate on the 3 ′ or 5 ′ carbon.



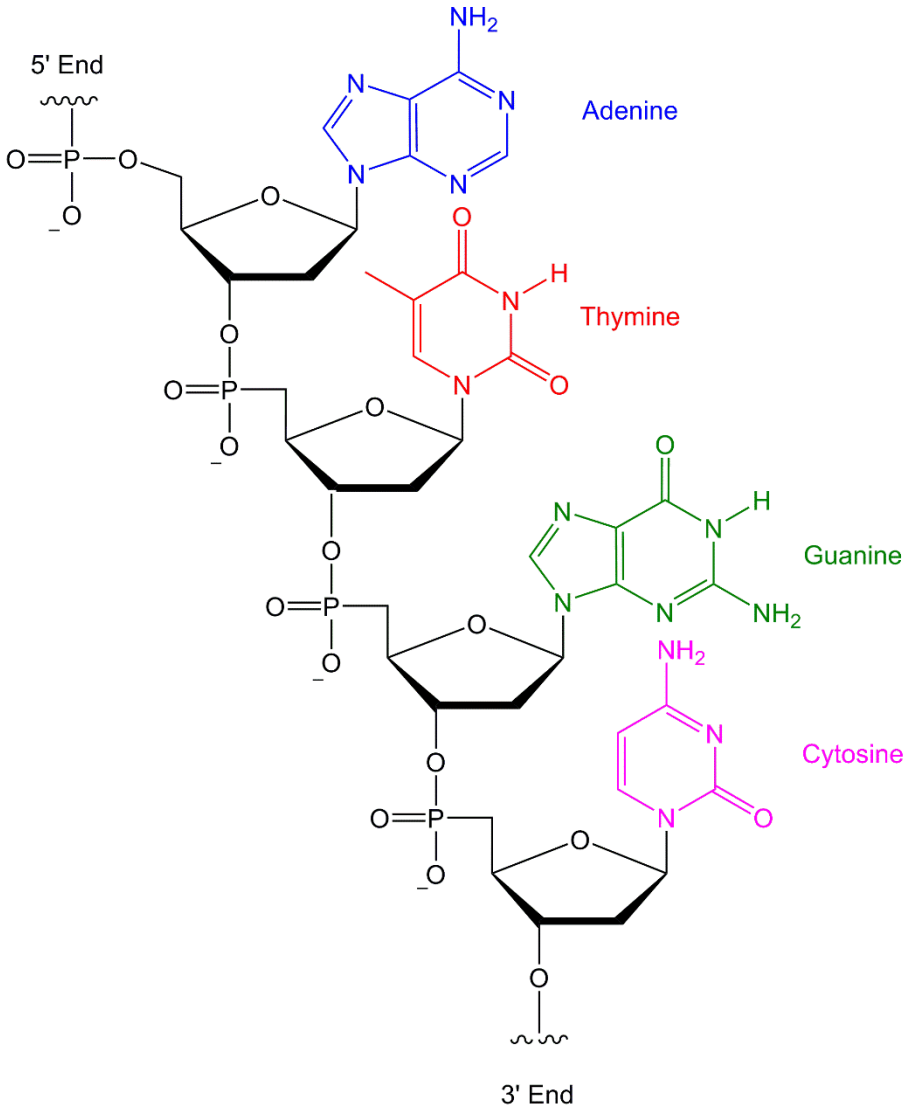
Adenosine
(A Nucleoside)





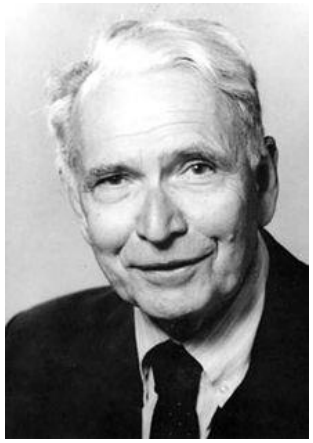
Adenylic Acid
(A Nucleotide)

DNA Is A Polymer!



Chargaff's Rules

Erwin Chargaff



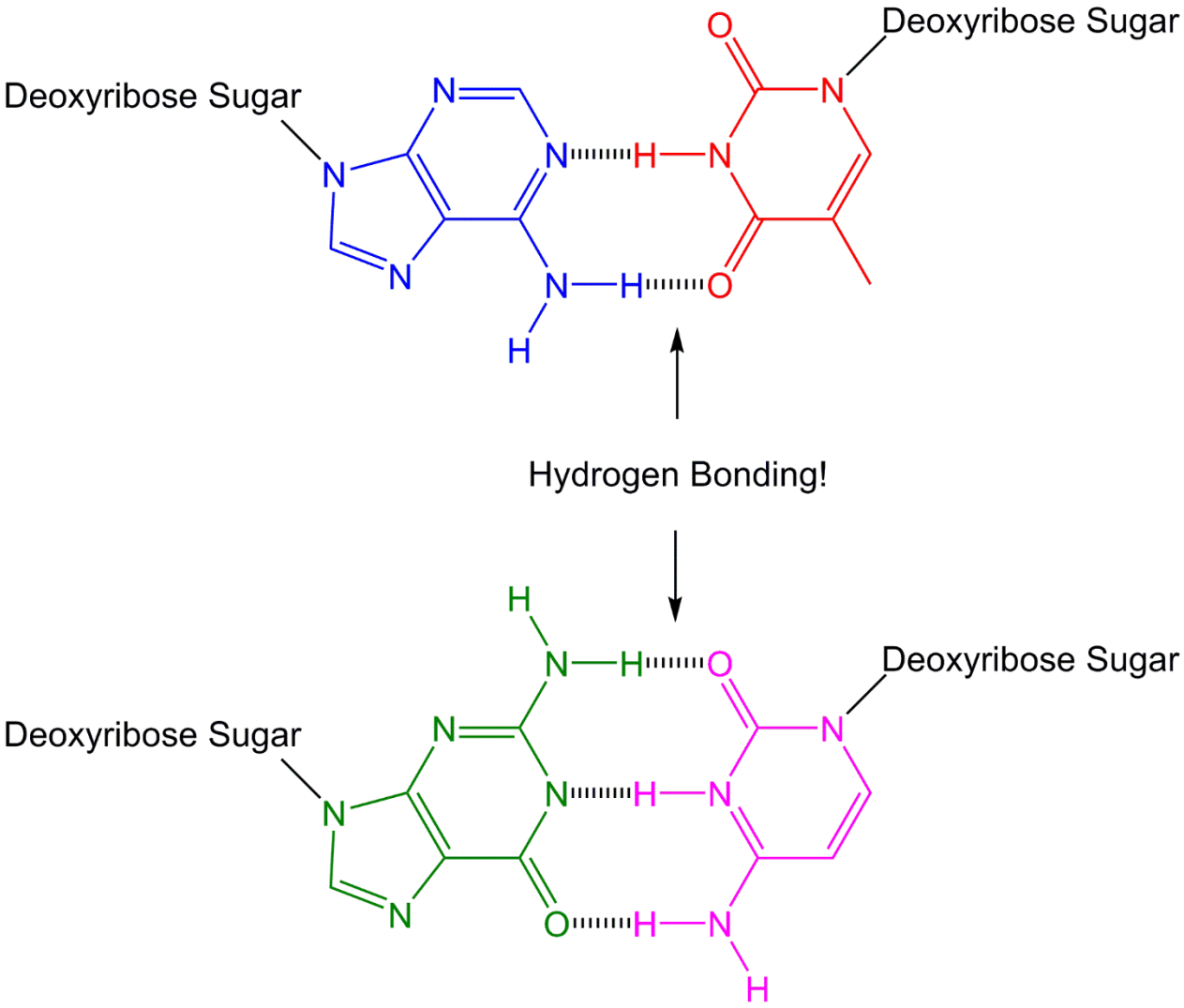
Species	% G	% A	% C	% T
S. aureus	21.0	30.8	19.0	29.2
E. coli	24.9	26.0	25.2	23.9
Wheat Germ	22.7	27.3	22.8	27.1
Bovine Thymus	21.5	28.2	22.5	27.8
Human Thymus	19.9	30.9	19.8	29.4
Human Liver	19.5	30.3	19.9	30.3

Chargaff's Rules: Math and Three Main Rules

Species	$\frac{G+A}{C+T}$	$\frac{A}{T}$	$\frac{G}{C}$
S. aureus	1.11	1.05	1.11
E. coli	1.08	1.09	0.99
Wheat Germ	1.00	1.01	1.00
Bovine Thymus	0.96	1.01	0.96
Human Thymus	1.01	1.05	1.01
Human Liver	0.98	1.00	0.98

1. $\frac{G+A}{C+T} = \frac{\text{Purines}}{\text{Pyrimidines}} = \frac{1}{1}$
2. $\frac{A}{T} = \frac{1}{1}$
3. $\frac{G}{C} = \frac{1}{1}$

Watson-Crick Base Pairs

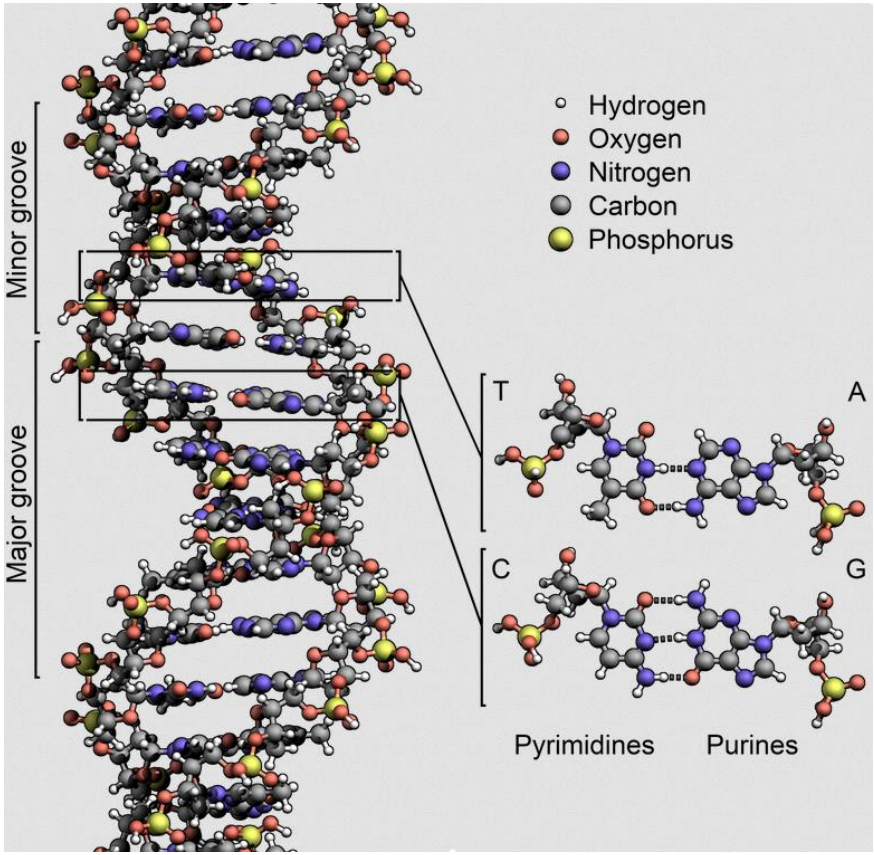


Structure Determination of DNA!

In 1953, the collective scientific knowledge on DNA consisted of Franklin's X-ray data and Chargaff's rules.

With this information in hand, James Watson and Francis Crick built and examined molecular models (follow their example in using molecular models!!) to determine that DNA is a base-paired ***double helix***.

This double-helix structure is the secondary structure for DNA.

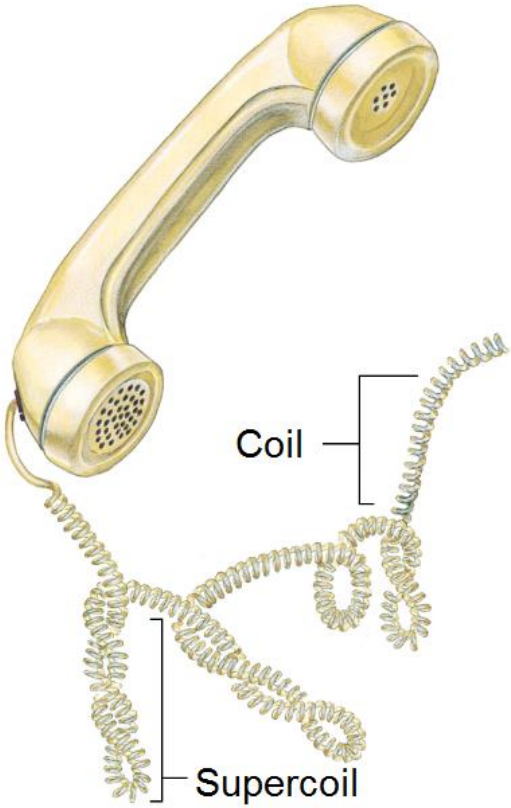


DNA 1962 Nobel Prize

The 1962 Nobel Prize in Physiology or Medicine was awarded “for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material” to Crick, Watson, and Wilkins.

Spatial Arrangement of DNA

The human genome consists of 3×10^9 base pairs (bp). As a result it is very long. The solution to this is for DNA to form a ***supercoil*** as its tertiary structure. An example of a supercoil is shown for a corded phone.



Spatial Arrangement of DNA

Similar to how a coil of a phone cord can be wrapped around to form a supercoil, the same applies for DNA!

DNA Tertiary Structure!!!

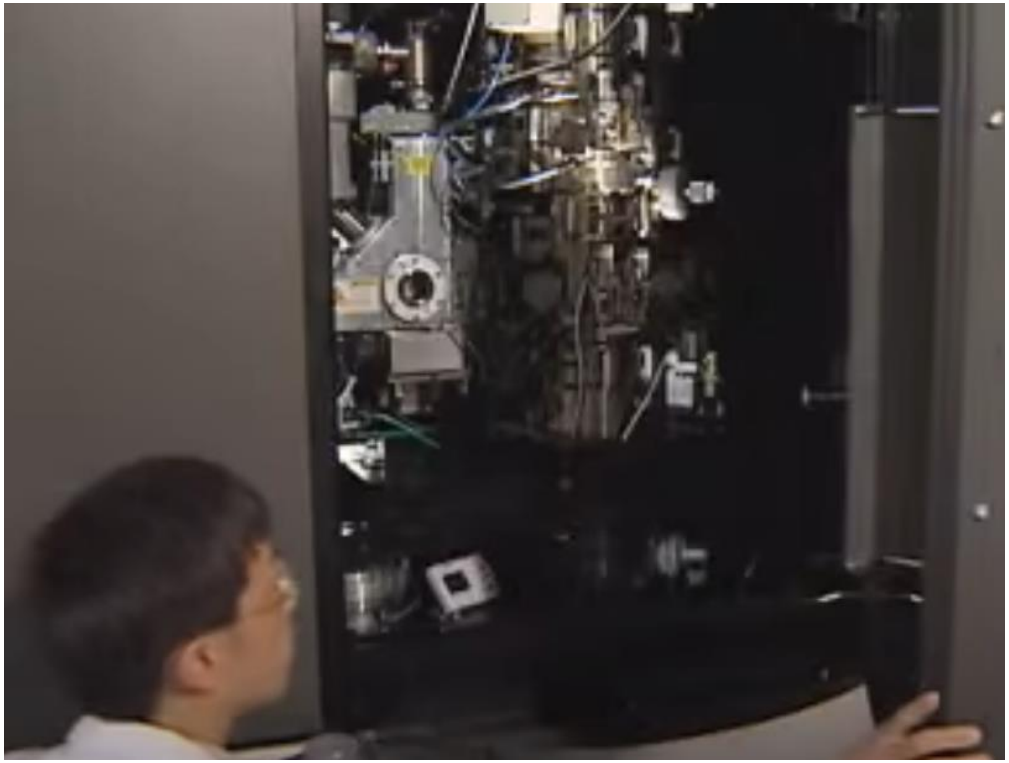
Electron cryo-tomography (cryoEM) data

"Structural Diversity of Supercoiled DNA," *Nature Communications*, **6**, 8440 (2015).

Electron Cryo-Tomography

https://www.youtube.com/watch?v=MkjtSo52XYM

5 minutes and 45 seconds



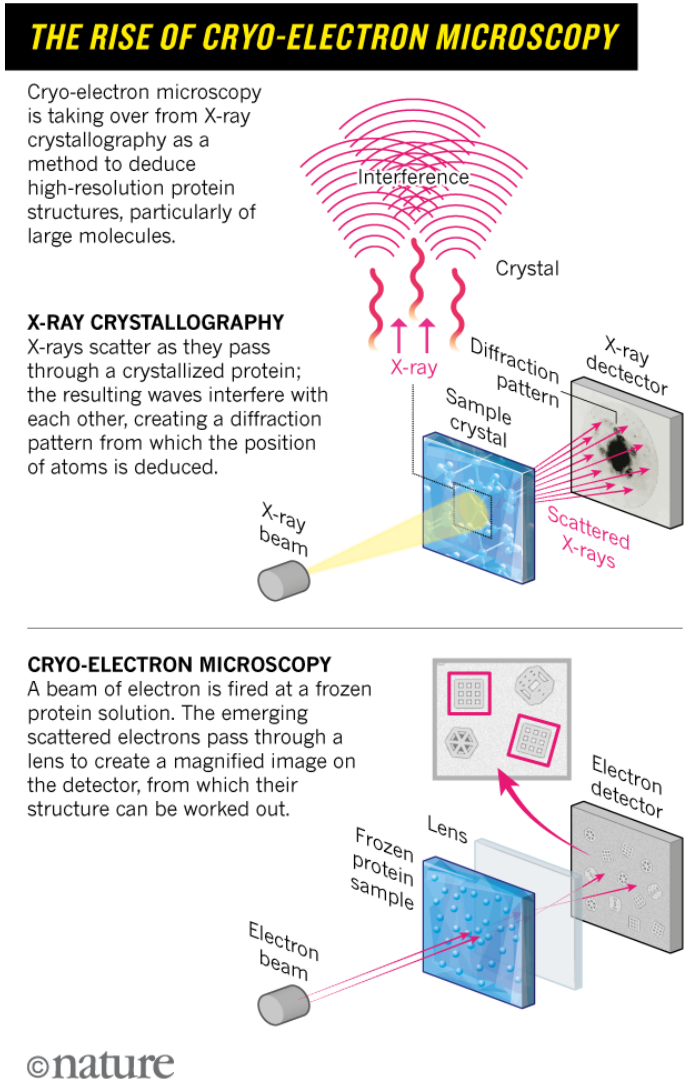
How Much Money Does It Take To Do State-Of-The-Art Science?

3.2 M (2006) or 4.1 M (2020; inflation adjusted)

The long-term goal of the California NanoSystems Institute (CNSI) at the University of California at Los Angeles (UCLA) is to create an enabling and cross-disciplinary environment for cutting-edge nanobiology and biomedical research. As an integral part of this goal, the Electron Imaging Center for Nanomachines (EICN) is established to meet the pressing need of advanced imaging techniques for visualizing macromolecular machineries at the nanometer scale and for the understanding of their mechanisms of action. This high-end shared instrumentation proposal seeks 50% of the funds ($1.6M) needed for the purchase of a SOOkV field emission gun electron microscope for EICN to augment our on-going three- dimensional (3D) structural studies of a broad range of nanomachineries, organelles, viruses and bacterial cells by electron cryomicroscopy (cryoEM) and tomography (ET). The critical need for a user-friendly, high-resolution, tomography-capable electron cryomicroscopy instrument is justified at multiple levels: The high-resolution electron microscope will provide essential instrumentation for over a dozen major users with NIH-funded research projects that require structure determinations either at subnanometer resolution by cryoEM or at molecular resolution by cryoET. Currently, there is no working cryoEM instrument on the UCLA campus. The cryoET-capable electron cryomicroscope in the neighboring Pasadena area at Caltech is not accessible to UCLA faculty members due to already full-capacity operation by local users there. Therefore, UCLA-based research would be greatly enhanced by the acquisition of the high-end electron cryomicroscope described in the application. High-resolution electron imaging will become an integral part of the very strong structural biology research community already established at UCLA. The new high-end EM instrumentation, together with the well-established X-ray crystallography, high-resolution NMR spectrometry, and the molecular modeling expertise will provide a valuable resource for faculty members who are eager to expand the scope of their current biomedical and nanobiology research projects to include cryoEM and cryoET. The new instrument will also meet a critical requirement of high-resolution data for pushing the envelope of cryoEM reconstruction to near atomic resolution. The diverse biological structures with their highly varied architectures offer a fertile source of data for developing and refining the methodology of high-resolution cryoEM, which will not only benefit our efforts but also the general electron imaging community at large. The identification often secondary/minor users with active federal funding shows that there is major interest across multiple departments/institutes among the colleges of natural sciences and engineering, as well as the UCLA medical school that may greatly benefit from the acquisition of the high-end instrument.

2017 Nobel Prized Awarded in CryoEM

Nobel Prize awarded "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution."



How CryoEM Works