CSI5180. Machine Learning for Bioinformatics Applications

Essential **Cellular Biology**

by

Marcel Turcotte

Version **November 6, 2019**

Preamble

Summary

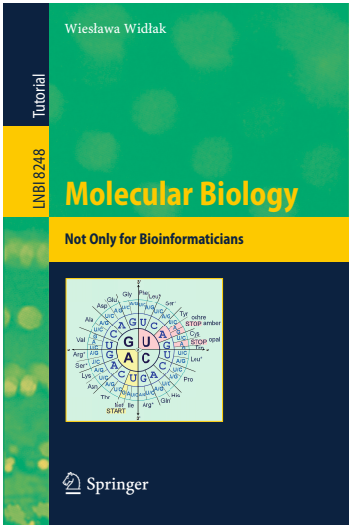
This lecture presents the **cell**, the **kinds of cells**, their **organization** and **composition**. Concepts from **molecular evolution** are briefly introduced. The lecture presents the **macromolecules** of the cell, with their basic organization. Throughout the presentation, we will highlight the importance of the concepts for machine learning and bioinformatics.

General objective

- **Describe** the organization of the cell and the macromolecules

Reading

- Lawrence Hunter, Life and its molecules: A brief introduction, *AI Magazine* **25** (2004), no. 1, 922.
- Wiesława Widłak, *Molecular Biology: Not Only for Bioinformaticians* (Vol. 8248). (2013), Springer. Chapters 1, 2, and 3.



link.springer.com/book/10.1007/978-3-642-45361-8

Personalized (and precision) medicine

- Therapeutic approaches based the **genetic** make-up of an individual and **metabolic** information offer many advantages:
  - **Best response** and **fewer side effects**;
  - Economically, the possibly to **repurposed drugs** having adverse effects for one subgroup, but not the other.
- **Unsupervised learning** to identify subgroups;
- **Dimensionality reduction** and **supervised learning** to identify **bio-markers**.
- 250,000 results on Google for the query: ``**personalized medicine**''" and (``**machine learning**'' or ``**artificial intelligence**'')

Personalized (and precision) medicine

- **"Cracking the code of personalized medicine"**: South Korea is at the vanguard of a revolution in AI AND BIG DATA HEALTHCARE.
  - https://www.nature.com/articles/d42473-019-00101-y
- **"FinnGen Research Project is an Expedition to the Frontier of Genomics and Medicine"**
  - Combining **genotype** and **health records** for 500,000 individuals by 2023.
  - https://www.finngen.fi/en
- **Dimensionality**
  - Genome = 3.2 Gbp, # protein coding genes = 20 K, # RNA coding genes = ?, size of the epigenome = ?.

Symbiosis

- **Symbiotic interactions** can be mutually beneficial (**mutualism**) or one organism, the parasite, causes harm to the other (**paratism**):
  - **Promote** favourable interactions;
  - **Prevent** negative interactions.
- **Microbiome host trait prediction**
- Applications in **medicine**, **agriculture**, and beyond.

Yi-Hui Zhou and Paul Gallins, *A review and tutorial of machine learning methods for microbiome host trait prediction*, Front Genet **10** (2019), 579.

BIOSECURITY

The fight to keep dangerous DNA out of terrorists' hands

Machine learning could help firms avoid making dangerous organisms on demand.

BY SARA REARDON

Biologists the world over routinely pay companies to synthesize snippets of DNA for use in the laboratory or clinic. But intelligence experts and scientists alike have worried for years that bioterrorists could hijack such services to build dangerous viruses and toxins — perhaps by making small changes in a genetic sequence to evade security screening.

Now, the US government is backing efforts that use machine learning to detect whether a DNA sequence encodes part of a dangerous pathogen. Researchers designing such artificial-intelligence-based screening tools are beginning to make progress, and several groups presented early results on 31 January at the American Society for Microbiology (ASM) Biothreats meeting in Arlington, Virginia.

Their findings could lead to a better understanding of how pathogens harm the body, as

ANNA SCHROLL/FOTOGLORIA/UIG VIA GETTY

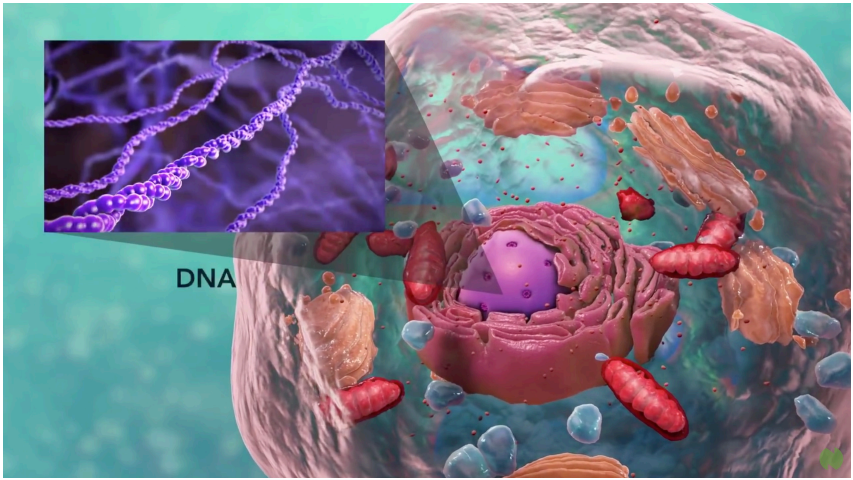
Dangerous pathogens are kept in high-security labs.

What movie is this?

https://youtu.be/qUaFYzFFbBU

The Cell

Cell Structure



https://www.youtube.com/watch?v=URUJD5NEXC8

Cells: building blocks of living organisms

Two **kinds** of cells (with and without nucleus)

Prokaryote (procaryote, prokaryotic cell, procaryotic organism): Cell or organism **lacking** a membrane-bound, structurally **discrete nucleus** and other sub-cellular compartments. Bacteria are prokaryotes.

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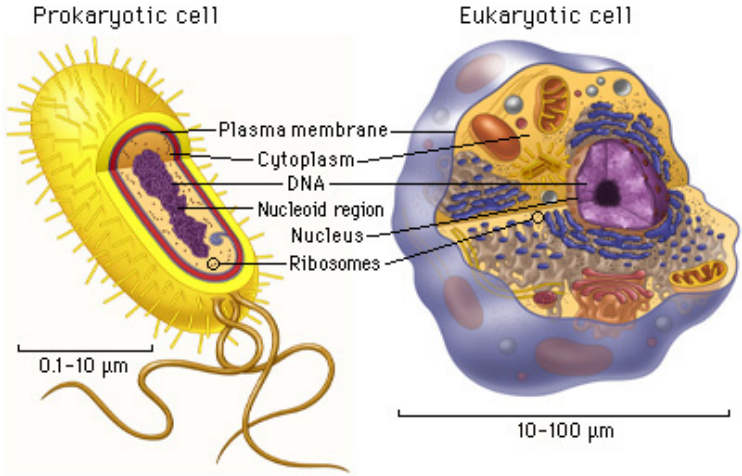
Eukaryote (eucaryote, eukaryotic cell, eucaryotic cell): Cell or organism **with** a membrane-bound, structurally **discrete nucleus** and other well-developed sub-cellular compartments. Eukaryotes include all organisms except viruses, bacteria, and cyanobacteria (blue-green algae).

Cells: building blocks of living organisms

- Eukaryotic cells are generally larger than prokaryotic cells.
- The packaging of the genetic information (DNA) is much more **structured** and compact in **Eukaryotes** compared to **Prokaryotes**.

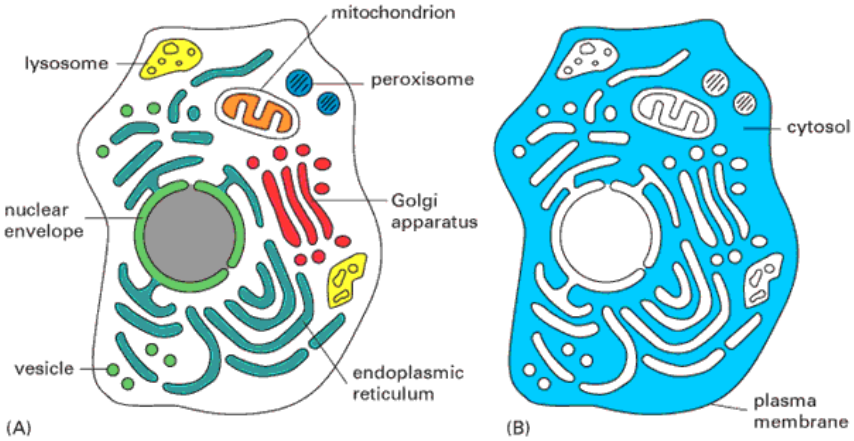
Cell theory: 1939 by Matthias Schleiden and Theodor Schwann.

Prokaryotic vs eukaryotic cell



www.phschool.com/science/biology_place/biocoach/cells/common.html

Organisation of an eukaryotic cell



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- Several organelles are believed to be engulfed prokaryotes (**endosymbiotic theory** made popular by Lynn Margulis)
- Mitochondrial genes are **inherited from the mother only**.

Bioinformaticist's point of view

- The **organization of genes** (genome structure) is quite different between the two kinds of cell.

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- Consequently the **gene-finding algorithms must be adapted**.
- Eukaryotic cells being more complex provide a richer set of problems: e.g. **protein sub-cellular localisation problem**.
- During the sequence assembly, one has to consider the possibility of contamination, mtDNA/nuclear DNA, bacterial DNA.

Resources

- Texas Education Agency
  Advanced Biotechnology Collection on iTunes U
  - https://itunes.apple.com/ca/itunes-u/tea-advanced-biotechnology/id876525204?mt=10
  - Specifically the **Cell Structure and Function** segment
- Help Me Understand **Genetics**
  - https://ghr.nlm.nih.gov/primer
- **BBC** The Cell The Hidden Kingdom
  - https://www.youtube.com/watch?v=aDuwkdQzb2g
- http://learn.genetics.utah.edu

kingdoms of life

(3) kingdoms of life

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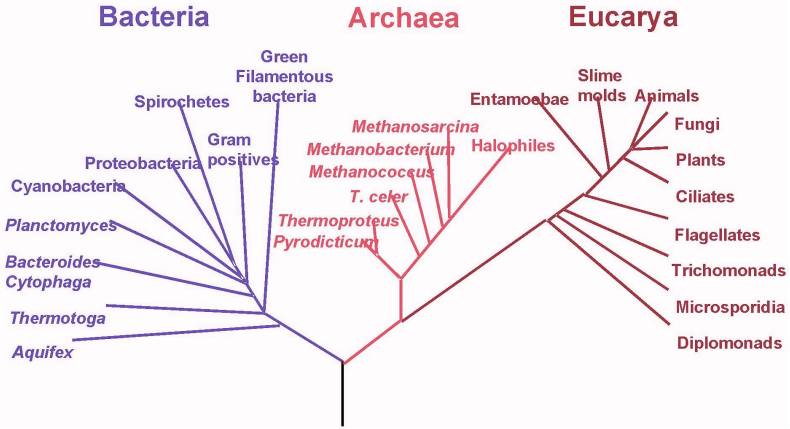
Archaea: (archaebacteria) like the prokaryotes **they lack the nuclear membrane** but have **transcription** and **translation mechanisms close to those of the eukaryotes**.

(3) kingdoms of life: Archaea

Methanococcus jannaschii is an **methane producing archaebacterium** which had its complete genome sequenced in 1996. This organism was discovered in 1982 in white smoker of a hot spot at the bottom of the Pacific ocean: depth **2600 meters**, **temperature 48-94° C (thermophilic)**, optimum at 85° C, 1.66 Mega bases, 1738 genes. 56% of its genes are unlike any known eukaryote or prokaryote, one kind of DNA polymerase (other genomes have several).

Phylogenetic Tree of Life



Phylogenetic tree

- "The objectives of phylogenetic studies are (1) to reconstruct the correct **genealogical ties between organisms** and (2) to estimate the **time of divergence** between organisms since they last shared a common ancestor."

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- "The **branch length** usually represents the **number of changes** that have occurred in that branch." (or some amount of time)

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Bioinformaticist's point of view

- **Bench-marking** (cross-validation) and **molecular evolution**
- **Molecular sequence alignment** : are the sequences evolutionary related?
- **Large phylogeny problem**: Reconstructing phylogenetic trees from molecular sequence data
- **Small phylogeny problem**: Reconstructing ancestral molecular sequences

Nothing in Biology Makes Sense Except in the Light of Evolution

Theodosius Dobzhansky

What about virus?

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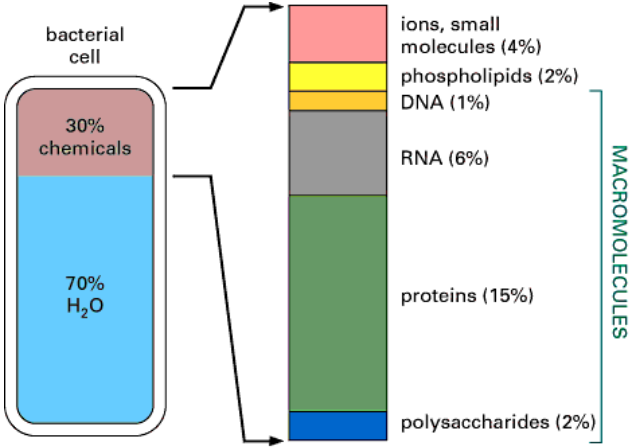
- Virus that infect bacteria are called phages or bacteriophages.
- Viroids don't even have a capsid – consists of a single-stranded RNA.

Composition of the Cell



⇒ **DNA**, **RNA** and **proteins** will be the main focus of the course.

Macromolecules: DNA, RNA and Protein

Bioinformatics is mainly concerned with three classes of molecules:

- **DNA** (deoxyribonucleic acid), **RNA** (ribonucleic acid) and **proteins** — collectively called **macromolecules** or **biomolecules**.

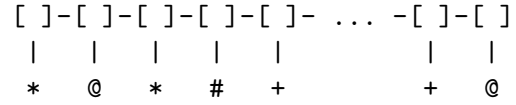
Macromolecules

Macromolecules: DNA, RNA and Protein

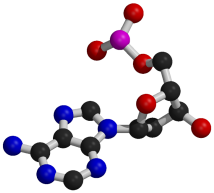
All three classes of macromolecules are **polymers**, that is they are composed of smaller units (molecules), called **monomers**, that are **linked sequentially** one to another forming **unbranched linear structures**.

Macromolecules: DNA, RNA and Protein

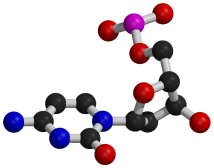
Generally speaking, the units (monomers) consits of two distinct parts, one that is **common** to all the monomers and defines the **backbone** of the molecule, and another part that confers the **identity** of the unit, and therefore its **properties**.



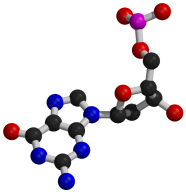
DNA's building blocks: ACGT



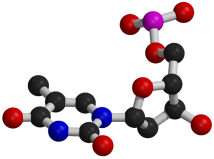
Adenine (A)



Cytosine (C)

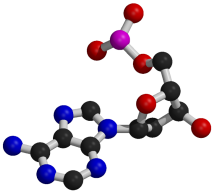


Guanine (G)

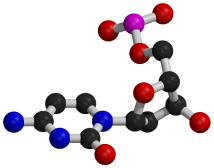


Thymine (T)

DNA's building blocks: ACGT



Adenine (A)



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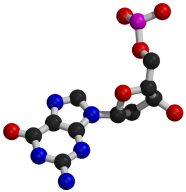

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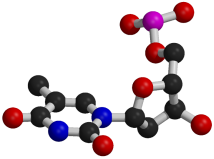
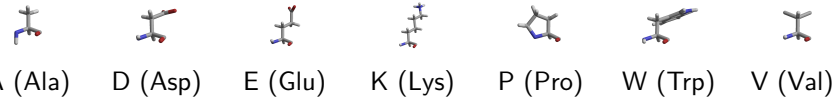


Thymine (T)

⇒ **Identify** the common and unique parts of each monomer.

(20) Amino Acids (Naturally Occuring)



A (Ala) D (Asp) E (Glu) K (Lys) P (Pro) W (Trp) V (Val)

R (Arg) C (Cys) G (Gly) I (Ile) M (Met) S (Ser) Y (Tyr)

N (Asn) Q (Gln) H (His) L (Leu) F (Phe) T (Thr)

$\Rightarrow$ Stick (licorice) representation.

Add a slide about proteins

From PDB, the depository of 3D structures:
https://youtu.be/wvTv8TqWC48

Structure

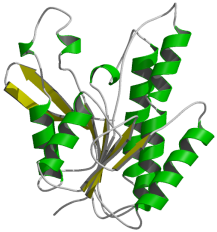
It's useful to distinguish between four **levels of abstraction** or **structure**: **primary**, **secondary**, **tertiary** and **quaternary** structure.

1, 2, 3, . . .

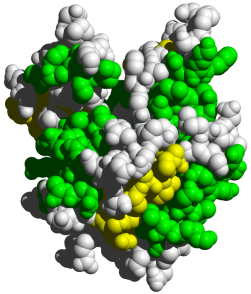
EARRVLVYGGRGALGSRCVQNW . . . (236) . . .

(a) primary structure

(b) secondary structure



(c) tertiary structure - ribbon



(d) tertiary structure - all atoms

Bioinformaticist's point of view

- A large number of computational problems are related to the **primary sequence**: sequence assembly, sequence alignment, phylogenetic tree inference, gene-finding, sequence motif discovery, etc.
- Predicting the **secondary, tertiary, and quaternary (docking) structure** are problems, on its own.
- These **abstractions** are allowing us to formulate efficient algorithms - understanding the implications is paramount.

Macromolecules: DNA, RNA and Protein

The primary structure or **sequence** is an ordered list of characters, from a given alphabet, written contiguously from left to right.
DNA (deoxyribonucleic acid): 4 letters alphabet,
$\Sigma = \{A, C, G, T\}$
RNA (ribonucleic acid): 4 letters alphabet,
$\Sigma = \{A, C, G, U\}$
Proteins : 20 letters alphabet,
$\Sigma = \{A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, Y\}$

Examples

In the case of **nucleic acids** (DNA and RNA), the building blocks are called **nucleotides**, whilst in the case of **proteins** they are called **amino acids**.

Examples of DNA, RNA and protein sequences.

```
> Chimpanzee Chromosome 1; A DNA sequence (size = 245,522,847 nt)
TAACCCTAACCCTAACCCTAACCCTAACC ... TCTCATGACAGTGAGTGAGTTCTCATGATC
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```
> A01592; An RNA sequence (coding Beta Globin gene) (size = 441 nt)
AUGGUGCACCUGACUCCUGAGGAGAAGUCUGC ... GCAAGGUGAACGUGGAUGAAGUUGGUGGUG
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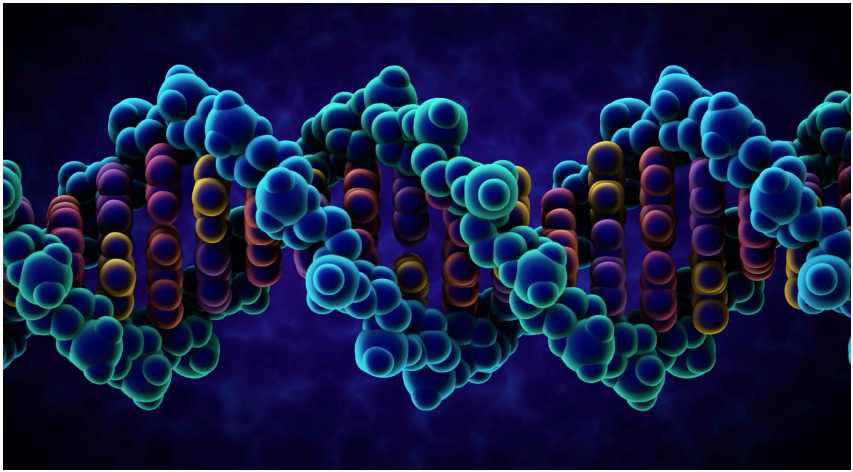
```

```
> Beta Globin; A protein sequence (size = 147 aa)
MVHLTPEEKSAVTALWGKVNVDEVGGEAL ... FFESFGDLSTPDAVMGNPKVKAHGKKVLGA
```

Bioinformaticist's point of view

- **Exact string** (sequence) comparison, **approximate matching** ($k-$mismatches), comparison under the **edit-distance**, **significance** of match, **multi-way** sequence comparison
- Finding **repeats**, **approximate repeats**, finding interesting **patterns**
- Secondary, tertiary and quaternary structure inference

DNA



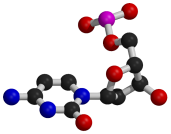
https://www.youtube.com/watch?v=o_-6JXLYS-k

Deoxyribonucleic acids (DNA)

- **DNA** was discovered by **Johann Friedrich Miescher** in **1869**. Who discarded the possibility that DNA might be related to heredity!
- The **double-helical structure** of DNA was proposed in **1953** by James Watson and Francis Crick (who died on July 28, 2004).
- This discovery is often referred to as the **most important breakthrough in biology of the 20th century**.
- The proposed model finally explained Chargaff's rule (same amount of adenine and thymine, same amount of guanine and cytosine).
- More importantly, the model finally explains **how DNA and heredity are linked!** (replication)

DNA's building blocks: ACGT

Adenine[a] (A)



Cytosine (C)

Guanine (G)

Thymine (T)

[a] Adenine refers to the nucleobase only. Here, the base is attached to a sugar and a phosphate group. The term for the whole unit is Adenosine. However, it is common to simply use the name of the nucleobase.

DNA/RNA's building blocks

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- In the case of **RNA**, the bases are Adenine (**A**), Cytosine (**C**), Guanine (**G**) and Uracil (**U**).

DNA/RNA's building blocks

- The length of a DNA/RNA molecule is often expressed in **bases**, e.g. a 10 **mega base** long region.
- Or, since nucleic acids molecules **hybridize** (bind together) to form a duplex (double helical) structure, the length of a molecule is often expression is base pairs to avoid confusion, e.g. a 10 **mega base** pairs region.

DNA/RNA's building blocks

- **DNA** stands for deoxyribonucleic acid, and **deoxy** comes from the fact that the **C2' carbon of the sugar has no oxygen**; while RNA has one. **RNA**'s O2' oxygen is key to its **functional versatility**!
- The other difference is the use of **T** (thymine) in the case of **DNA** vs **U** (uracil) in the case of **RNA**.
- Nucleotides are **always attached one to another in the same way** (well, almost always): the **C3' atom** of the nucleotide i is covalently linked to the **phosphate group** of the nucleotide $i + 1$.

DNA/RNA's building blocks

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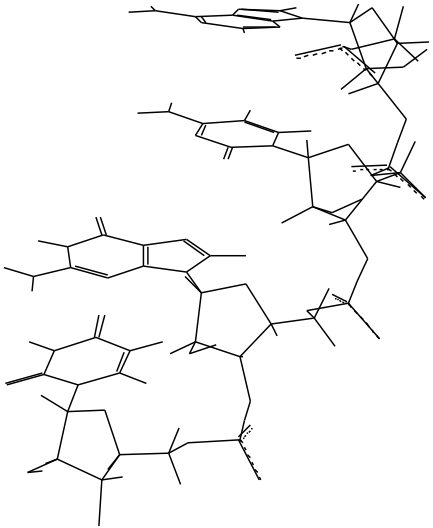
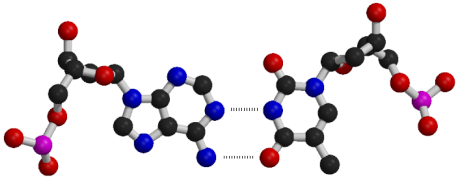
- The convention is to enumerate the string from its **5' end**; this correspond to the order into which information is process for certain key steps, to be described later. The features that are occurring **before the 5'** are said to be **upstream** while those occurring after the **3'** end are **downstream**, upstream and downstream signals.

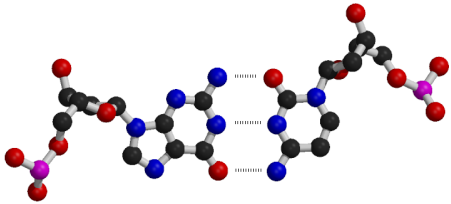
DNA strand



Watson-Crick (Canonical) base pairs



(Adenosine) A : T (Thymine)



(Guanine) G : C (Cytosine)

$\Rightarrow$ One of the two base pairs is stronger that the other, which one?

Watson-Crick (Canonical) base pairs

In the case of **DNA**, bases interact, i.e. form hydrogen bonds, primarily through the following set of rules:

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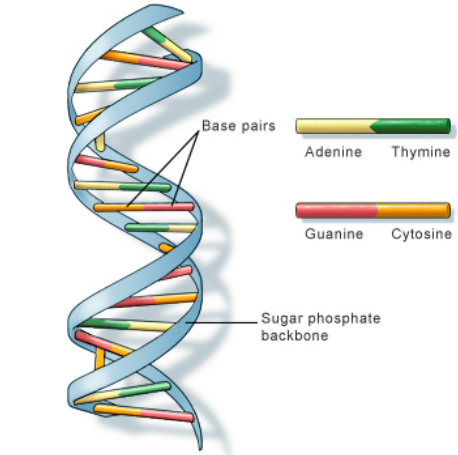
Those rules are the consequence of the fact that A:T and G:C pairs position the backbone atoms roughly at the same three-dimensional location and therefore both produces the same double helical structure; isosteric base pairs.

- **DNA** molecules generally form **right-hand** side helices in **B form**, while **RNA** are **A form**, also right-hand side. A left-hand side helix exists that is called **Z DNA**.
- **DNA** molecules **cannot exist as a single strand**, they are degraded, i.e. cut into pieces.
- A **DNA** molecule is made of **two complementary strands running in opposite directions**.



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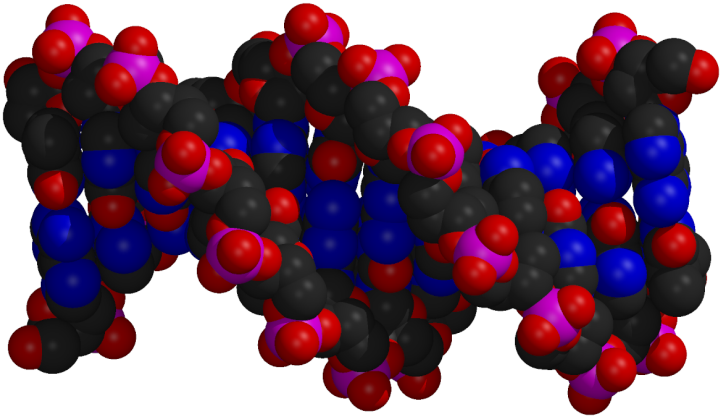
CPK representation of a fragment of a DNA

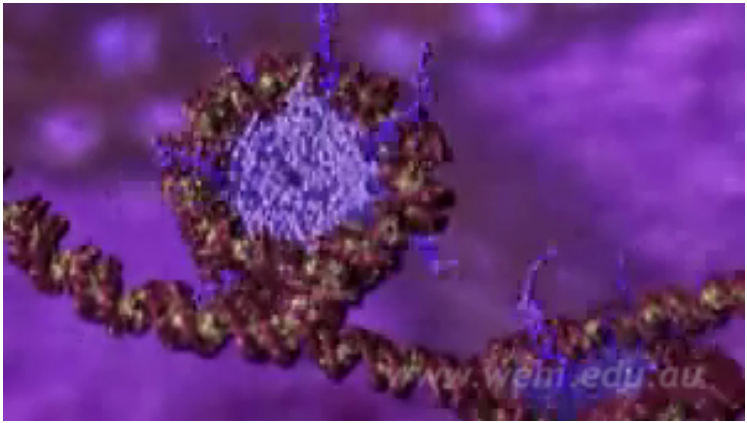


```
TAAGTTATTA                          AAAAAAATAC
|||||||||| ... (580,074 bp) ... ||||||||||
ATTCAATAAT                          TTTTTTTATG
```

About CPK

CPK stands for **Corey-Pauling-Koltun** representation. **Every atom** is represented as a sphere, with **radius proportional to its van der Walls radius**. The usual color scheme is to represent carbon atoms in black, nitrogen in blue, oxygen in red and phosphorus atoms in pink.

Chromosome



https://youtu.be/OjPcT1uUZiE?list=PLD0444BD542B4D7D9

About the animation

- **Histone proteins** attach to the **DNA**.
- **Histones interact one with another** to form a complex called **nucleosome**, but also forcing the DNA to wrap around it.
- The histone, nucleosome and DNA models were derived from their PDB (http://www.rcsb.org/pdb/) structures and other published data.

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- **Histone proteins** attach to the **DNA**.
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- The histone, nucleosome and DNA models were derived from their PDB (http://www.rcsb.org/pdb/) structures and other published data.
- Macromolecular structures cannot be directly oberserved. A molecular bond is between 1 and 2 Å (angstrom – 10^{-10} m) long, wave length in the visible spectrum are 400 to 700 nm (10^{-9} m).

Bioinformaticist's point of view

- Given DNA sequence information alone, **predict the locations where the histones will be binding**.
- Knowing the location of the histones might help predicting the **location of genes** as well as the **location of regulatory elements**.
- The **three-dimensional organization of the genome** is a hot topic.

Summary

- Two kinds of cells: **prokaryotic** and **eukaryotic**.
- **Eukaryotic cells have organelles**, and some organelles, such as the mitochondria, contain DNA.
- Three Kingdom of life: **Prokarya**, **Eukarya**, and **Archea**
- A **phylogeny** specifies the relationships between organisms and time of divergence.
- Three kinds of macromolecules: **DNA**, **RNA**, and **proteins**.
- **Macromolecules are linear (unbranched) polymers**, such that all the monomers have a common and a specific part (remember the analogy with the linked nodes).

References

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Springer, Berlin, 2013.

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