Lecture 1.1

Introduction:
Strings that encode Life

Life

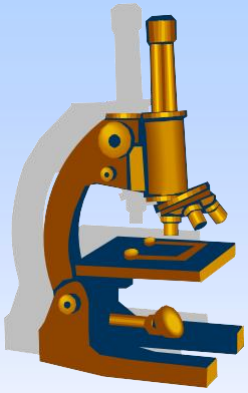
- A living organism is *an open, self-regulating and self-replicating system built from* ***bio-molecules***

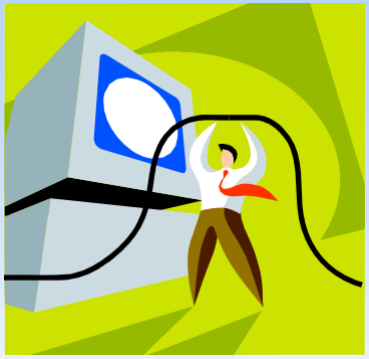
https://en.wikipedia.org/wiki/Life

Historical Perspective

►… – 1900 **Pre-Mendelian period**

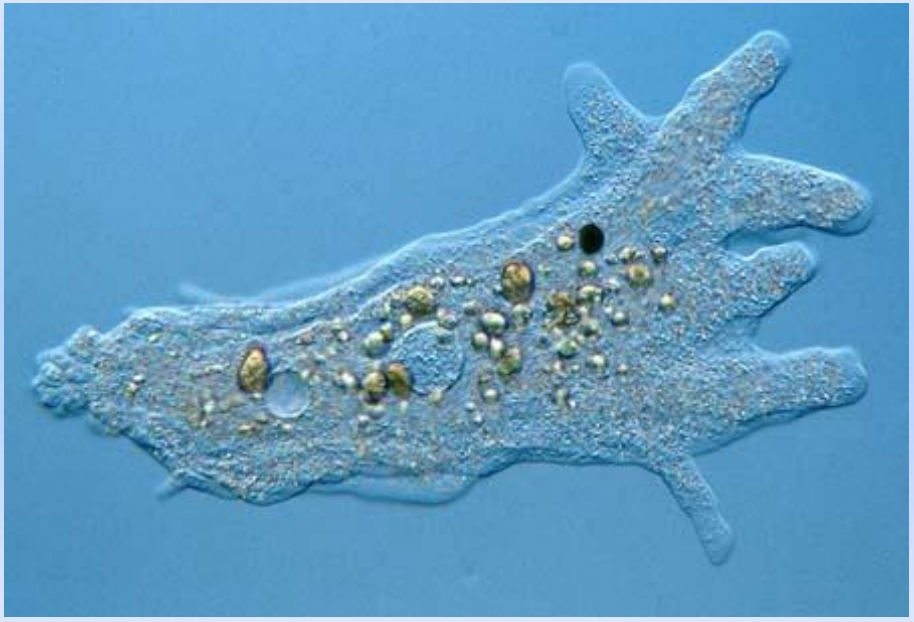
- 1900 – 1940 Pre-DNA period
- 1940 – 1990 DNA period
- 1990 – 2003 Genomic period
- 2003 – … Post-genomic era





The Pre-Mendelian Period

- Vital force
- Cells



1670s -Unicellular - amoeba

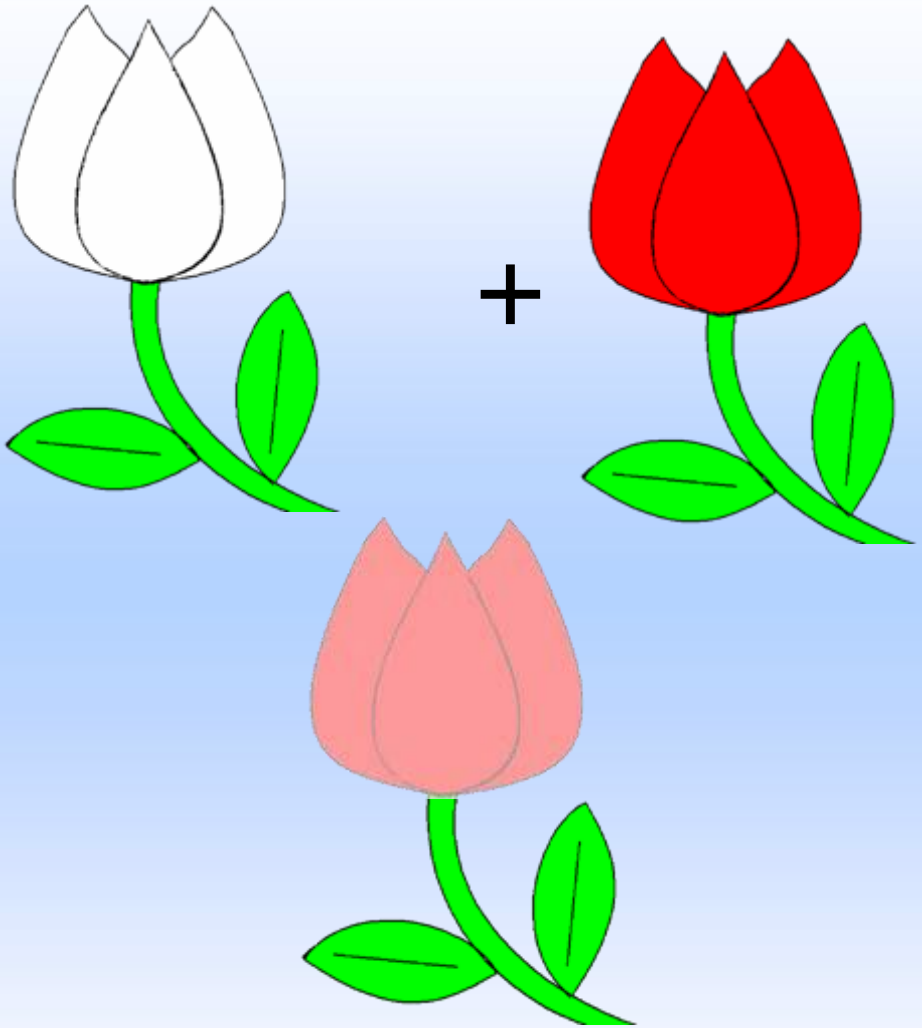
The Pre-Mendelian Period

- Vital force
- Cells
  - Male heredity

Anton van Leeuwenhoek

The Pre-Mendelian Period

- Vital force
- Male heredity
- Blending theory



The Pre-Mendelian Period - Summary

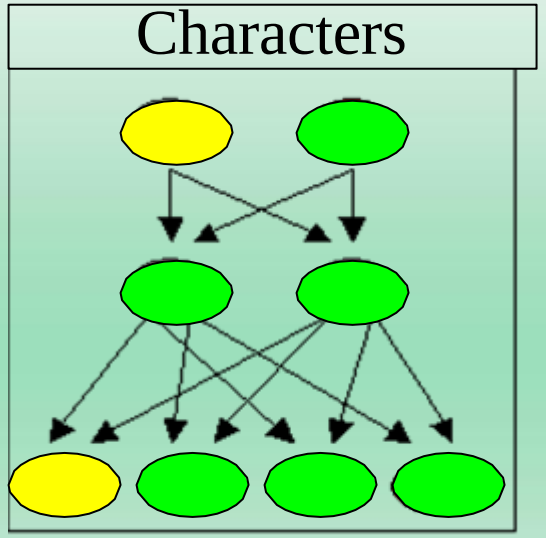
- Middle 19-th century - *Cell Theory*:
  - All living organisms consist of cells
  - Cells of different organisms have similar structure
  - Each new cell is obtained from the parent cell
- Gametes – sexual cells – participate in reproduction, and gametes of both sexes are somehow important.

Historical Perspective

- … – 1900 Pre-Mendelian period
- ►1900 – 1940 **Pre-DNA period**
- 1940 – 1990 DNA period
- 1990 – 2003 Genomic period
- 2003 – … Post-genomic era

The Pre – DNA Period

- 1865 - Gregor Mendel : discrete heredity



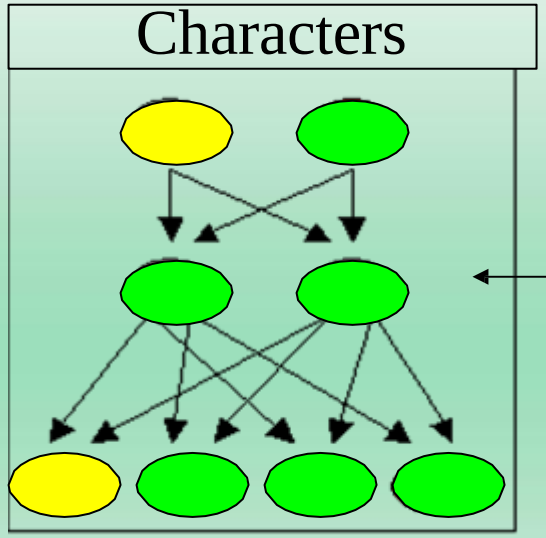
Pure lines

Inbreeding

Appeared again in proportion 3:1

The Pre – DNA Period

- 1865 - Gregor Mendel : discrete heredity – *elementum - gene*

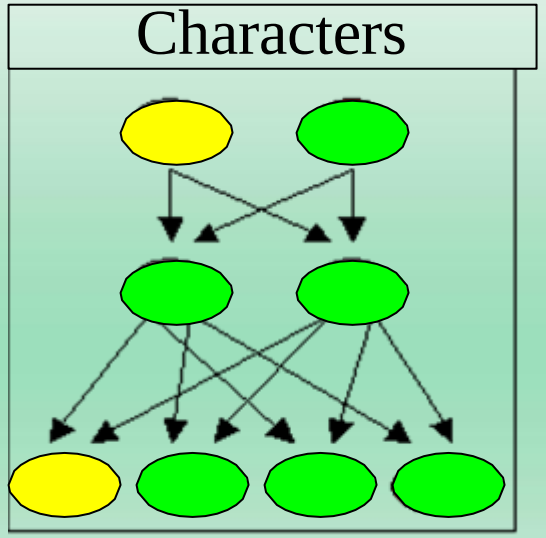


All are *Gy* - green

Gametes		*GG*-green	
		G	*G*
yy-yellow	y	*Gy*	*Gy*
	y	*Gy*	*Gy*

The Pre – DNA Period

- 1865 - Gregor Mendel : discrete heredity – *elementum - gene*



Gametes		*Gy*-green	
		G	*y*
Gy-green	G	*GG*	*Gy*
	y	*Gy*	*yy*

1/3 is *yy* - yellow

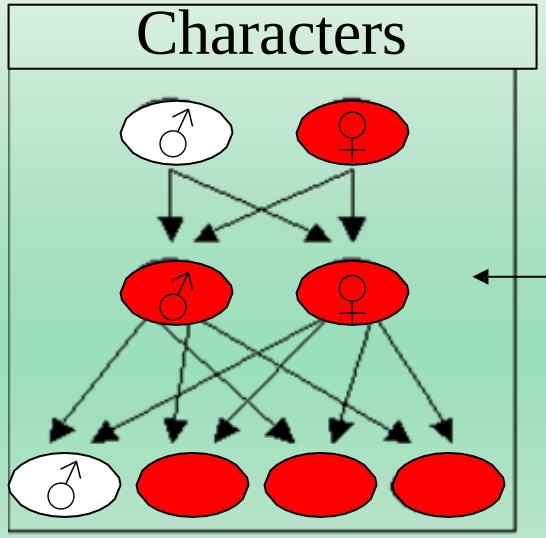
Accepted only in ~1900

Nucleus and Chromosomes

- Each species contains a specific, and always even, number of chromosomes
- Gametes contain half number of chromosomes.
- The cells of males differ from females by the shape of 1 chromosome. Specifically female carries XX chromosomes, while male carries XY.
- Chromosomes are distributed between two daughter cells in cell division

The Pre – DNA Period

- 1908 - Thomas Morgan – genes reside on chromosomes



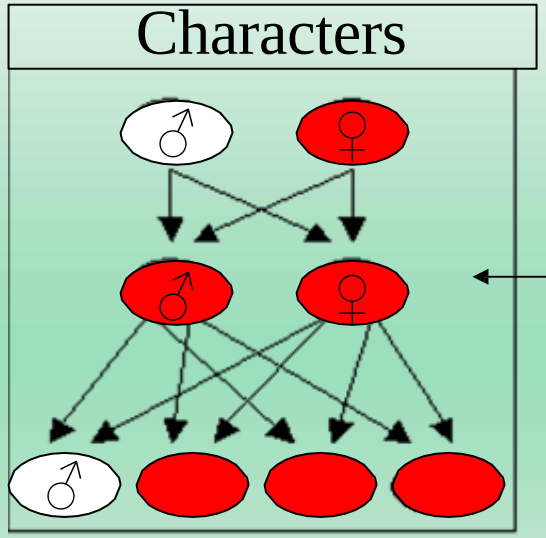
♀: X^+X^+ ♂: X^-Y^-

All have red eyes

Gametes		X^+X^+-red	
		X^+	X^+
X^-Y^-- white	X^-	X^+X^-	X^+X^- ♀
	Y^-	X^+Y^-	X^+Y^- ♂

The Pre – DNA Period

- 1908 - Thomas Morgan – genes reside on chromosomes



♀: X^+X^+ ♂: X^-Y^-

cross males with females

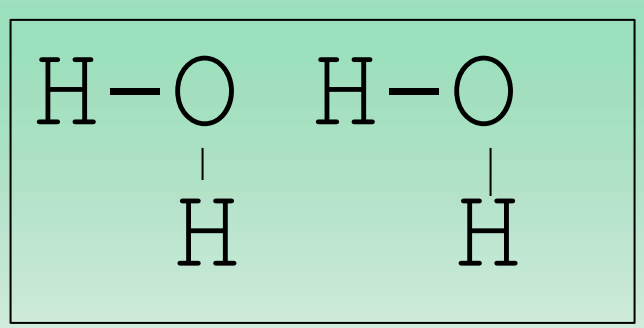
Gametes		X^+X^--red	
		X^+	X^-
X^+Y^-- red	X^+	X^+X^+	X^+X^- ♀
	Y^-	X^+Y^-	X^-Y^- ♂

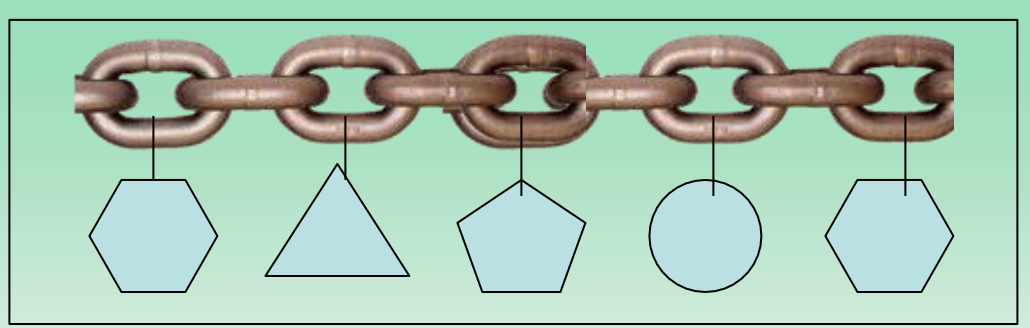
The Pre – DNA Period

The geneticist himself is helpless to analyze these properties further. Here the physicist, as well as the chemist, must step in. Who will volunteer to do so? (Muller 1936, 214)

The chemical nature of genetic material?

- Water?
- Nucleic acid?
- Protein?



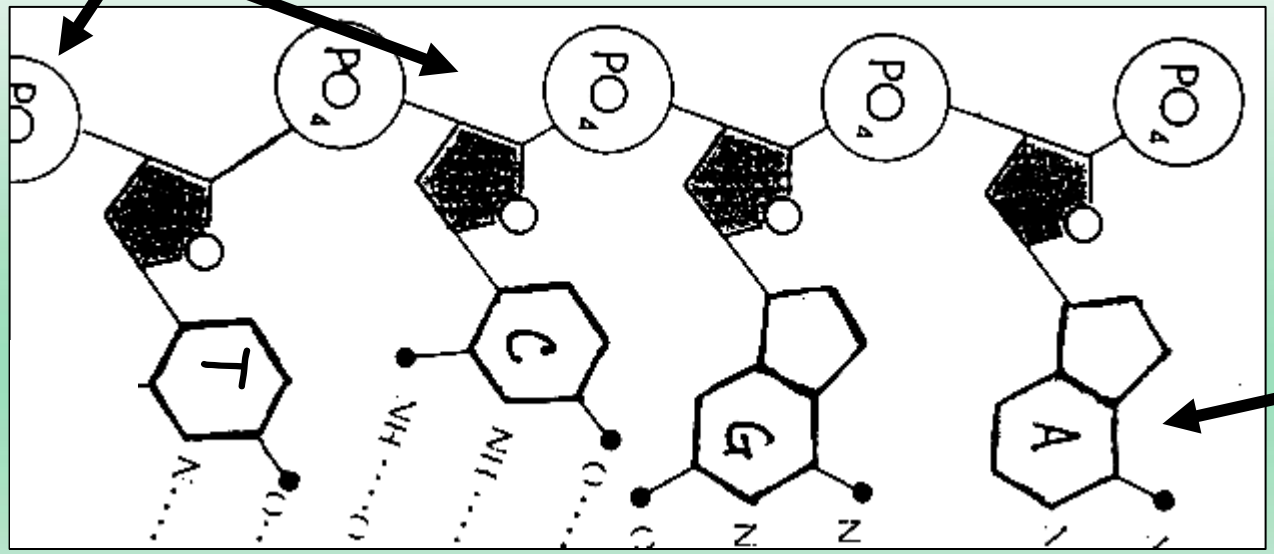


Polymer

The chemical nature of genetic material?

1868 - Friedrich Miescher – *nuclein* - **D**eoxyribo**N**ucleic **A**cid

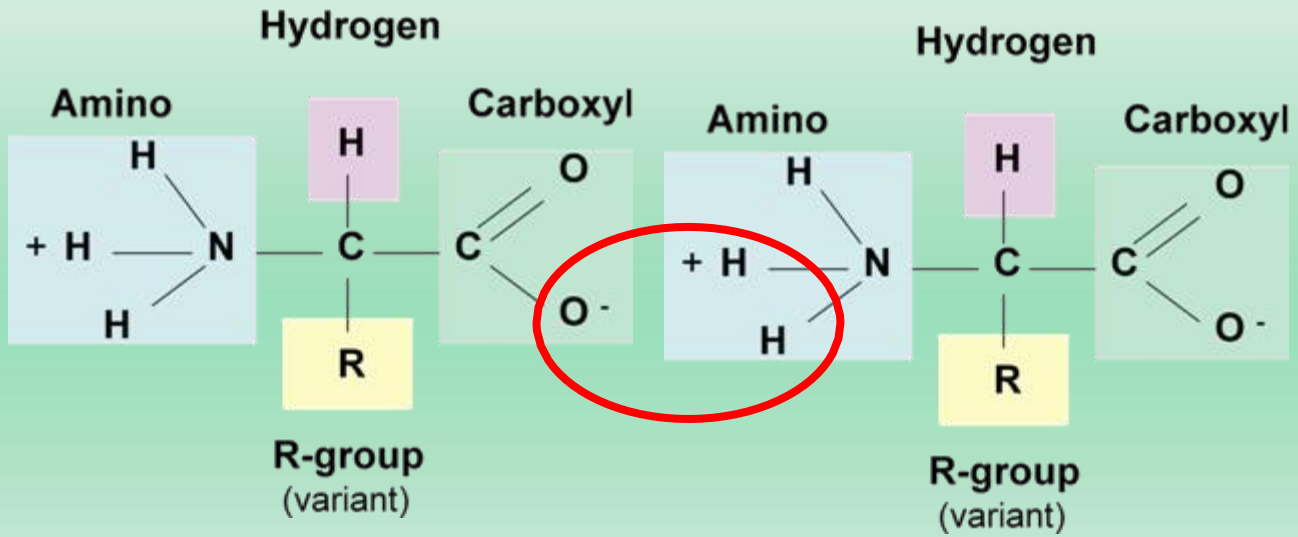
Sugar-phosphate backbone

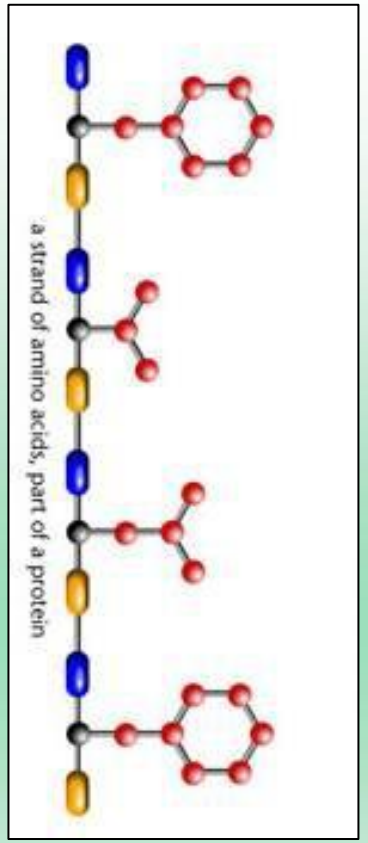


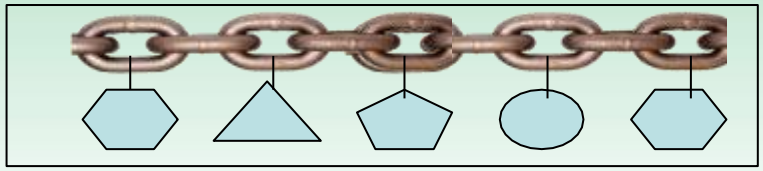
Regular polymer over just 4 bases
– cannot carry useful information?

The chemical nature of genetic material?

Protein – polymer of 20 aminoacids



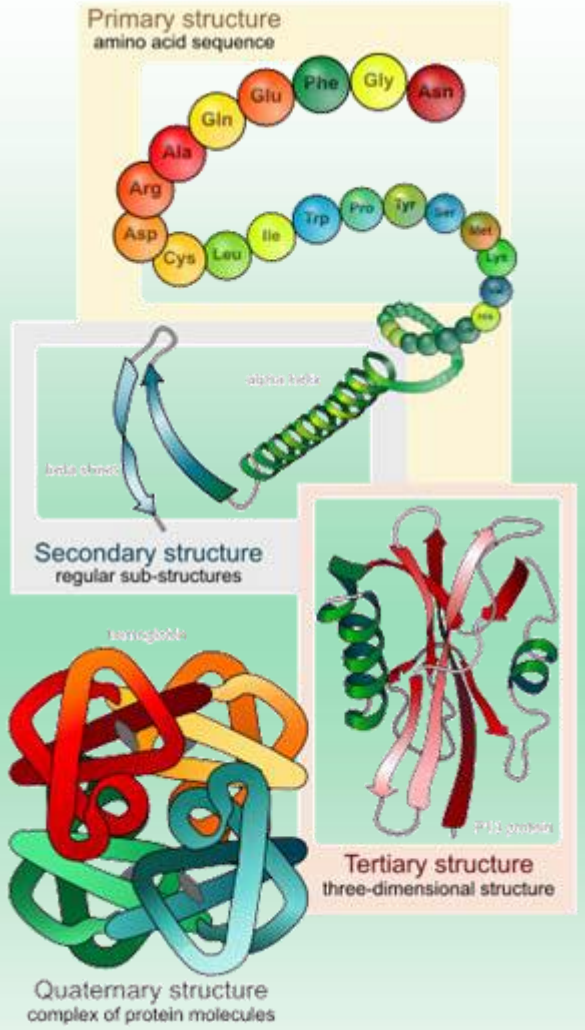




The chemical nature of genetic material?

Proteins come in a variety of functions and shapes (enzymes and structural proteins)

More likely, proteins carry the genetic information!



The Pre – DNA Period

- 1850s – Charles Darwin – *the theory of evolution*
  - Common ancestry
  - Descent with modification

The mechanism of passing traits from generation to generation

The Pre – DNA Period - Summary

- Genes are discrete units of heredity
- Genes generate enzymes that control structural and metabolic functions
- Genes reside on chromosomes
- Two candidates for gene encoding: DNA and protein

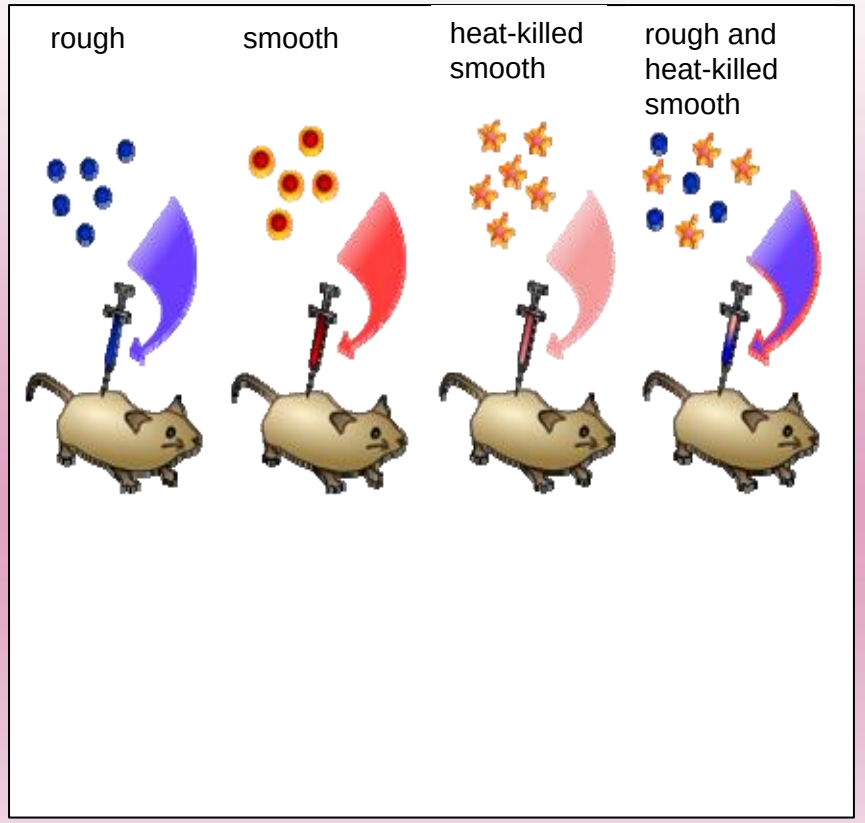
An Historical Perspective

- … – 1900 Pre-Mendelian period
- 1900 – 1940 Pre-DNA period
- ►1940 – 1990 **DNA period**
- 1990 – 2003 Genomic period
- 2003 – … Post-genomic era

The DNA Period

- 1936 – Oswald Avery – experiments with Pneumonia - causing bacteria:
  - rough – harmless
  - smooth – pathogenic

- Explanation: the DNA from the dead pathogenic bacteria used the live non-pathogenic bacteria to synthesize the pneumonia toxins
- The genetic material does not seem to be a protein, since the protein is destroyed by heat



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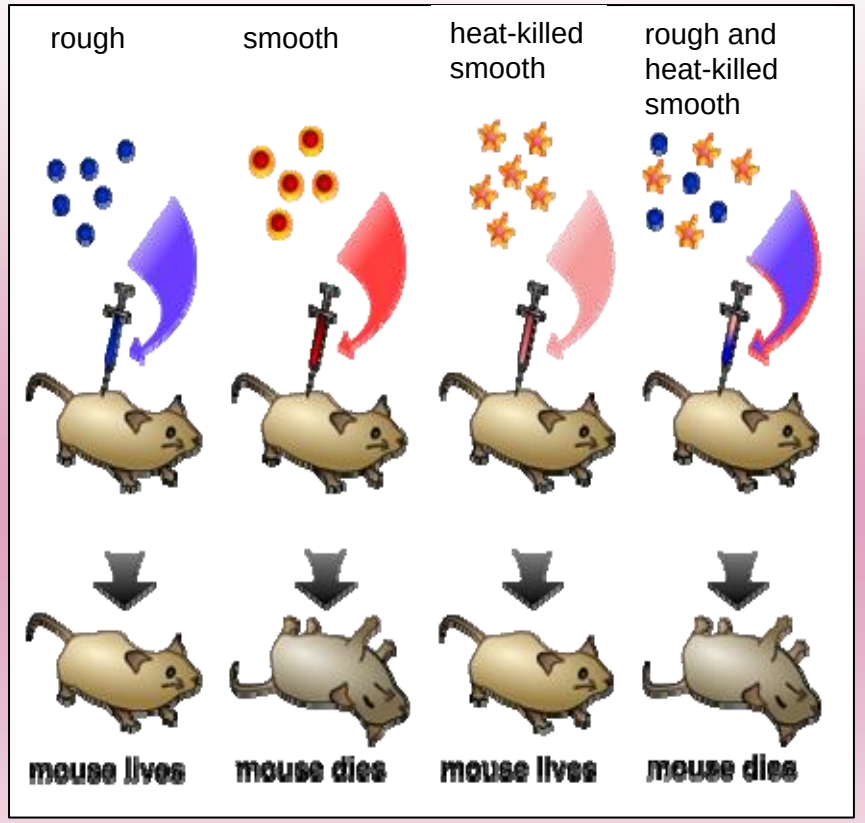
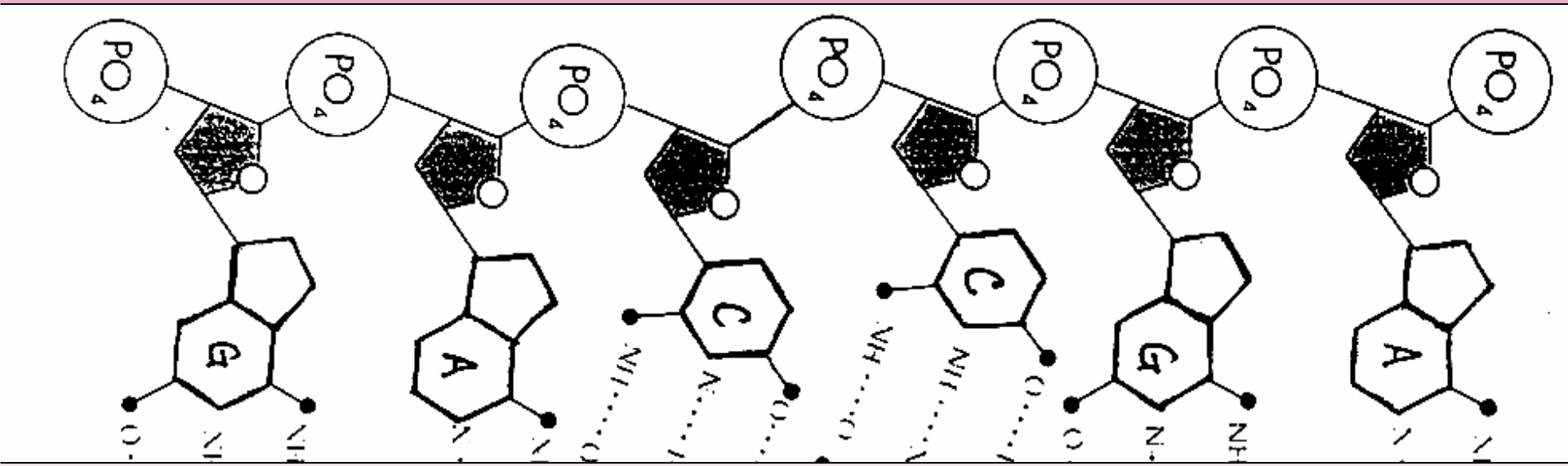


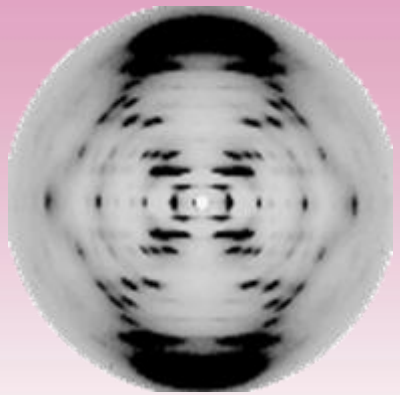
The DNA Period

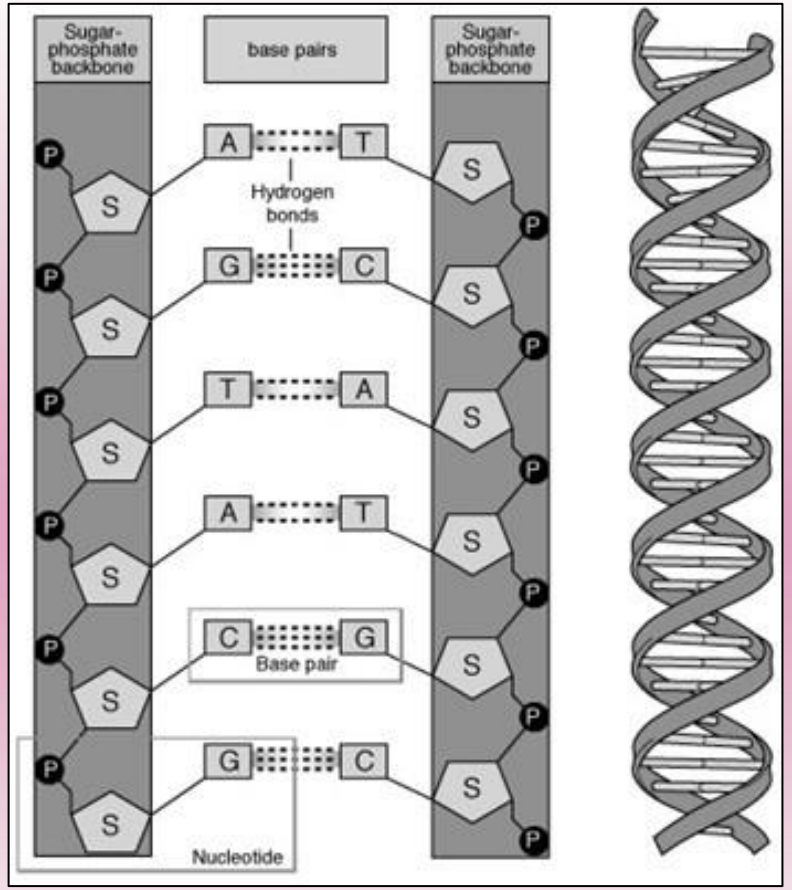
- The amount of A = T, C = G
- DNA is an ***irregular*** polymer
- Each species contains the specific amount of DNA
- Viruses – carriers of DNA



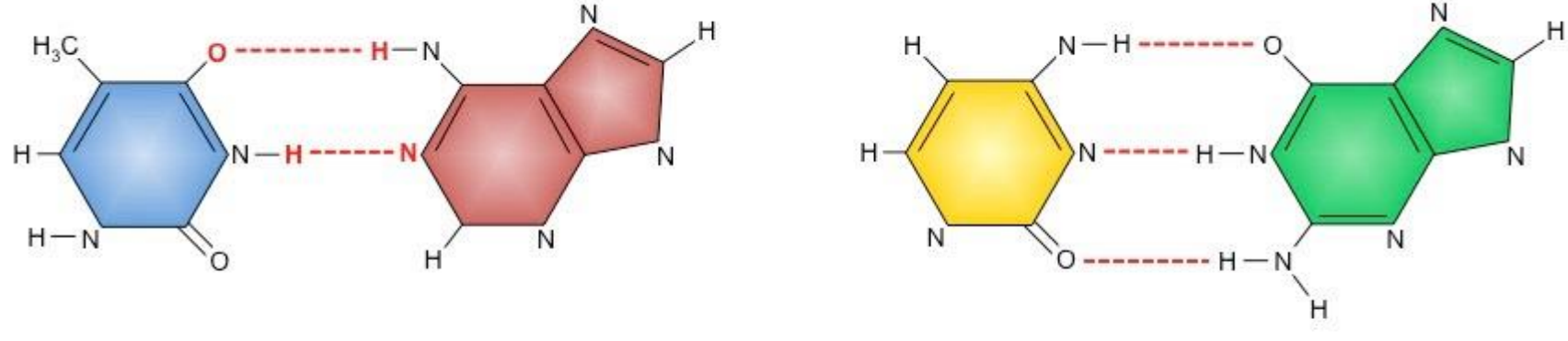
The DNA Period

- 1953 - James Watson and Francis Crick - double-helix model
- “The structure is good for replication”





Replication: complementary bases

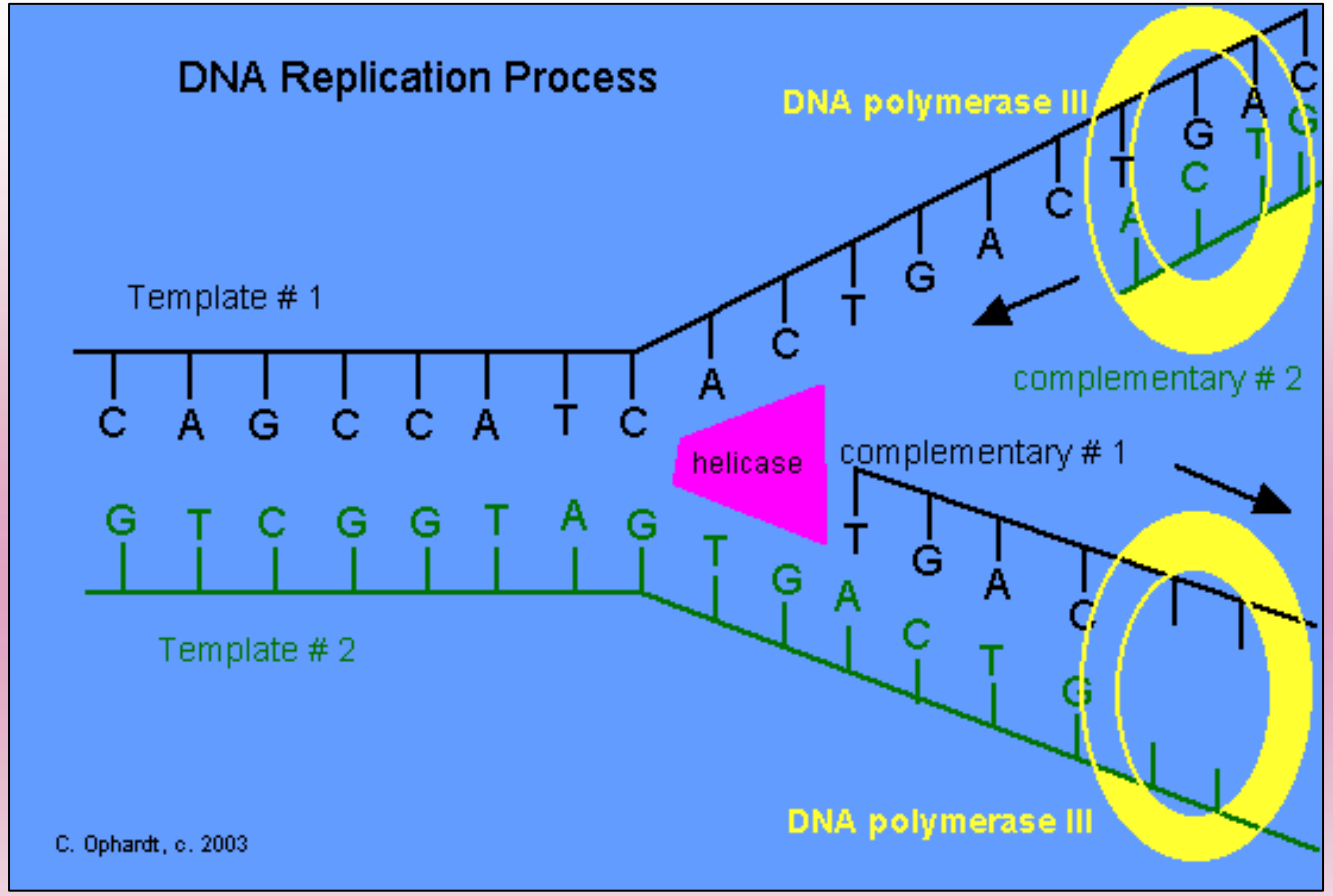


Thymine / Uracil pairs with Adenine
(2 hydrogen bonds)

Cytosine pairs with Guanine
(3 hydrogen bonds)

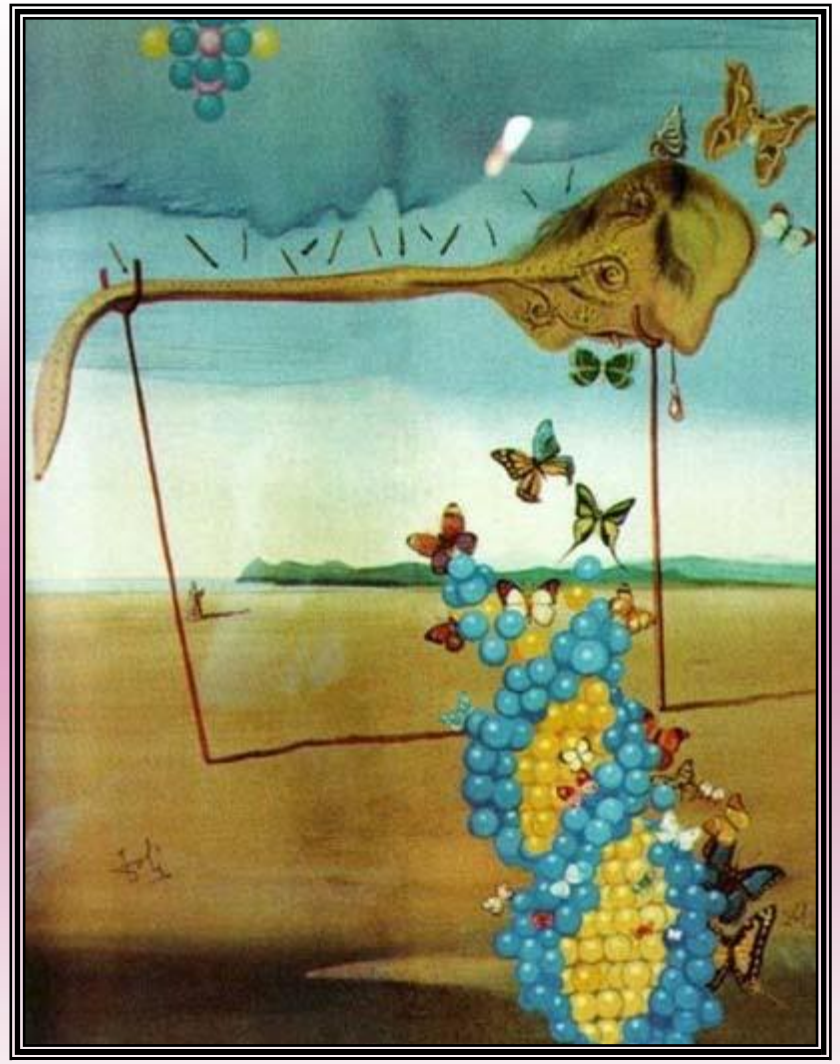
The shape determines complementarity

Replication



Video

DNA – a secular icon of modern society

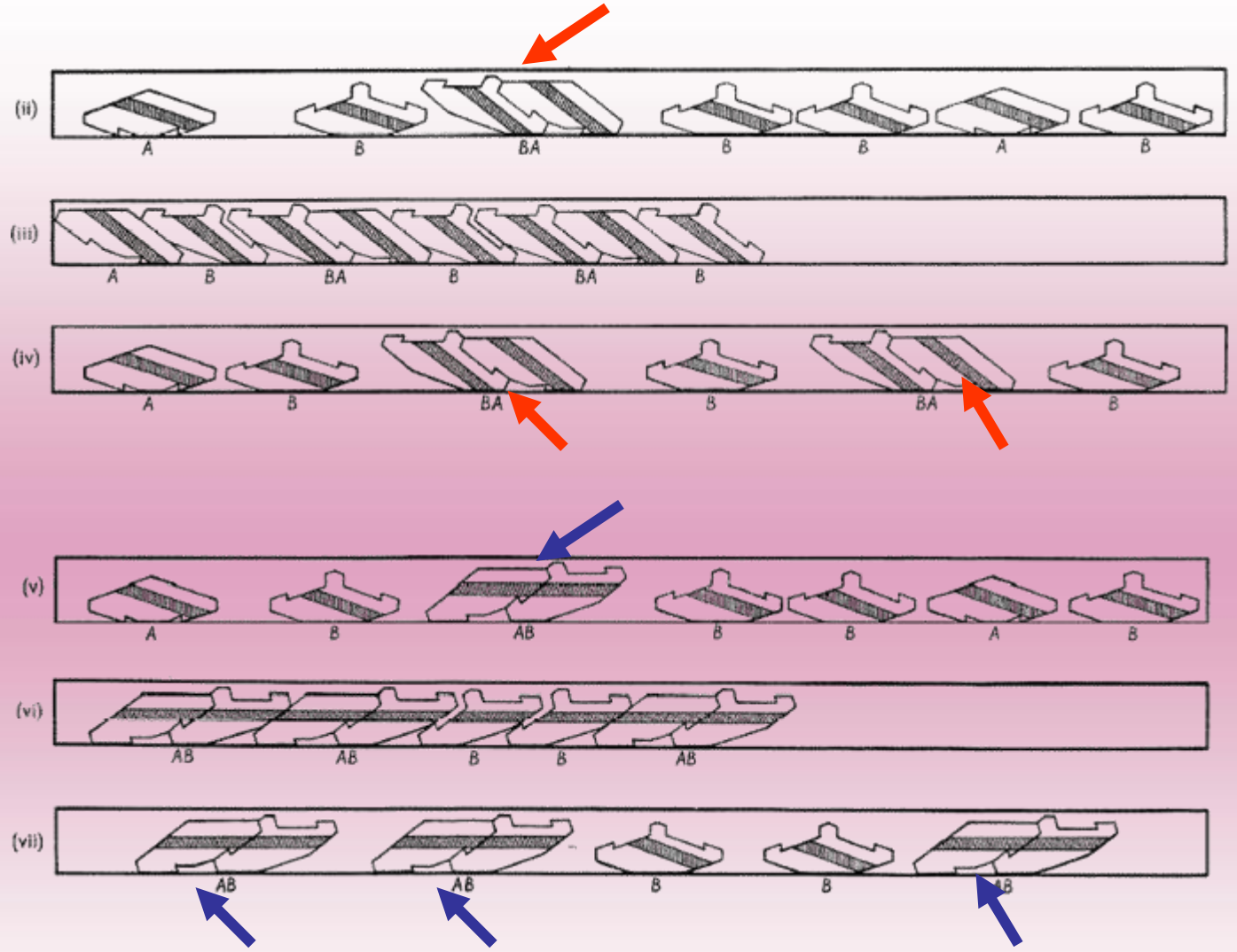


Salvatore Dali

Butterfly Landscape

created only a few years after Watson and Crick's announcement of the double- helix

Mechanical Self-Replicating Systems



Mechanical Self-Replicating Systems

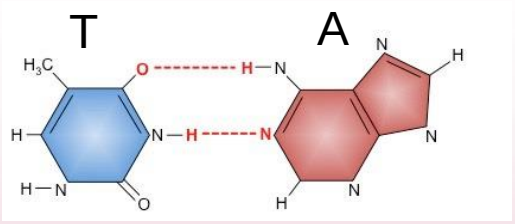
It might have been thought that, to achieve mechanical self-replication, some form of magnetic or electrical forces could have been conveniently used. This was a point carefully considered and it seemed in fact much simpler to use gravity, friction and collision as the forces determining the hooking and activating mechanisms which were evolved.

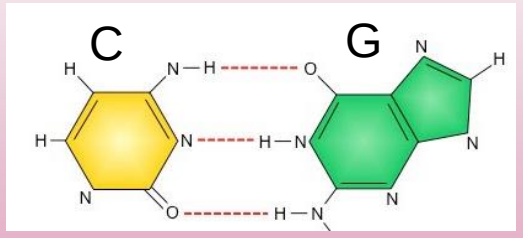
L.S. Penrose. Mechanisms of self-reproduction. 1958

Link

DNA replication

- Semi-conservative
- Errors-prone: substitutions





	A	**T**	**C**	**G**
A	0	5	5	1
T	5	0	1	5
C	5	1	0	5
G	1	5	5	0

A, G – 2-ring bases

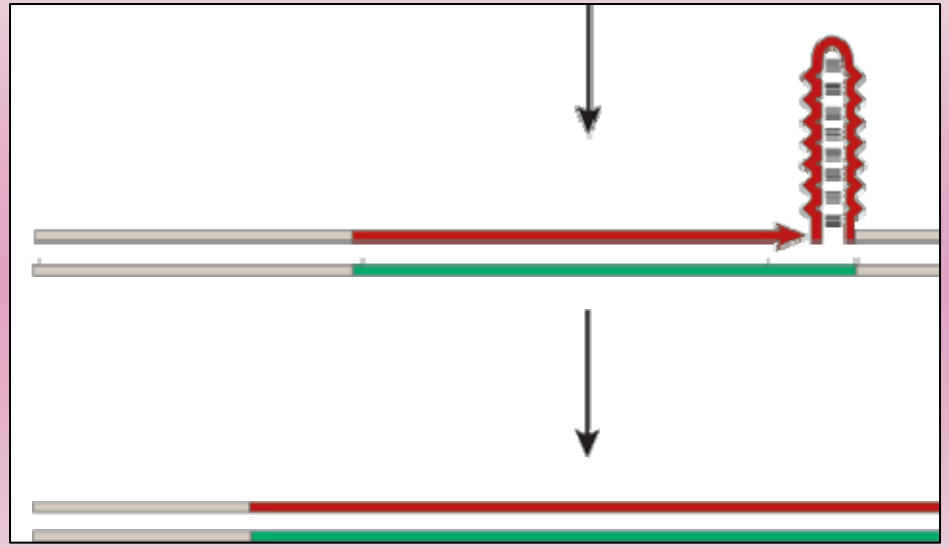
T, C – 1-ring bases

Mutation which preserves rings number is much more likely than changing the rings number.

If the penalty score of A → G is (1)
- than the score of A → T is (5)
5 times less likely

DNA replication

- Semi-conservative
- Errors-prone: deletions



Hairpin loop

DNA replication

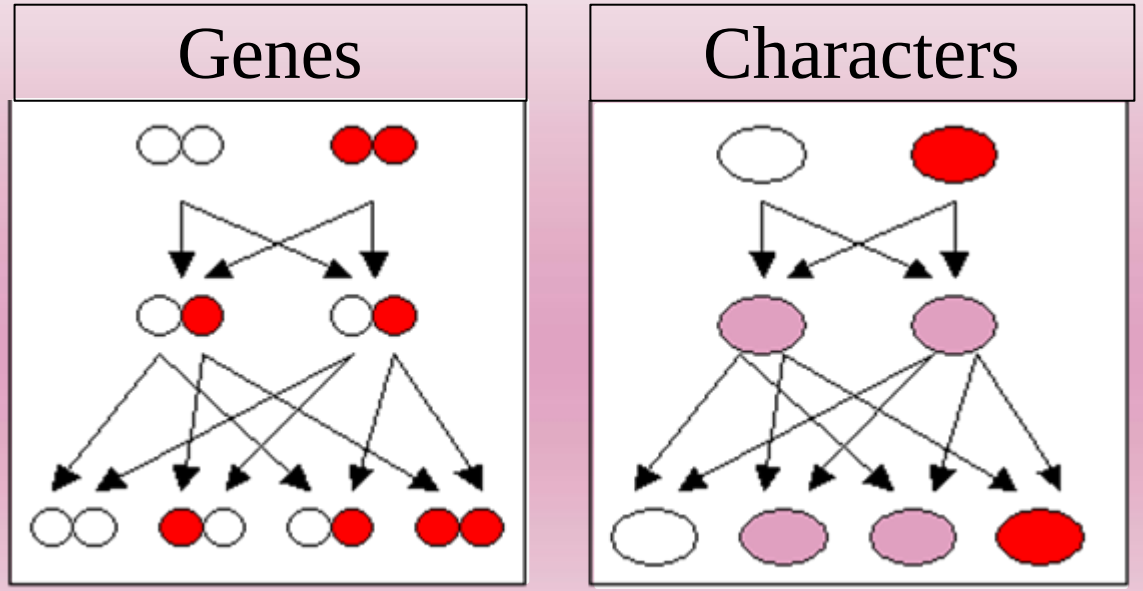
- Semi-conservative
- Errors-prone: point mutations, deletions, breaks
- DNA repair mechanisms

- This leads to the relative
  - *stability* of the DNA molecule over generations
  - and the ability to *change*

the basic mechanisms of evolution

From gene to protein

- *Phenotype* – an outward expression of discrete genetic characteristics. Proteins are responsible for phenotype



How information from the sequence of nucleotides is converted into a sequence of aminoacids ?

Protein Synthesis: Transcription

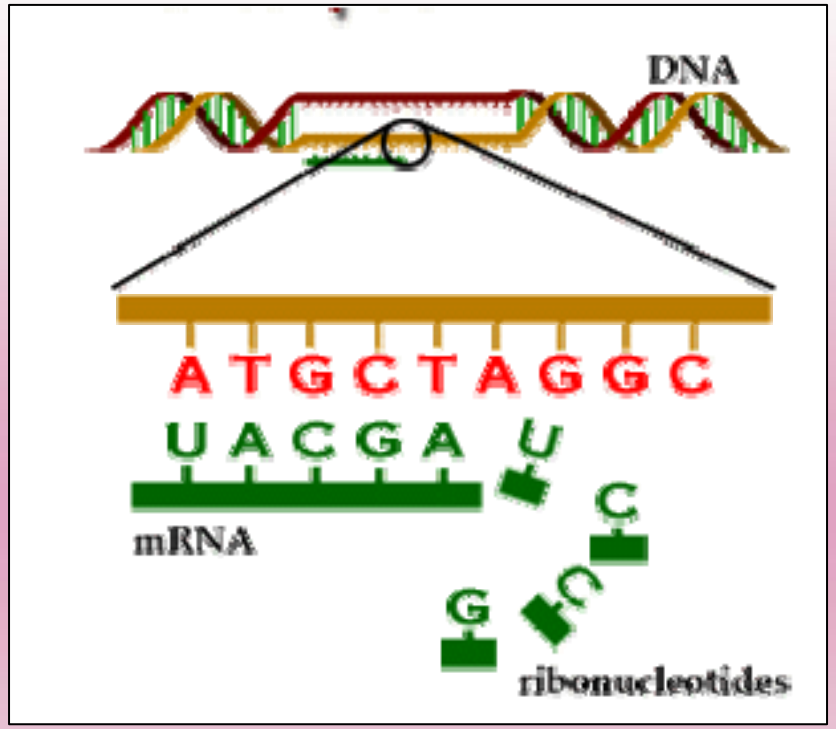
- RNA – **R**ibo**N**ucleic **A**cid -

  a short and unstable polymer of the same nucleotides as DNA:

  Adenine, **C**ytosine, **G**uanine, **U**racil (instead of **T**hymine)

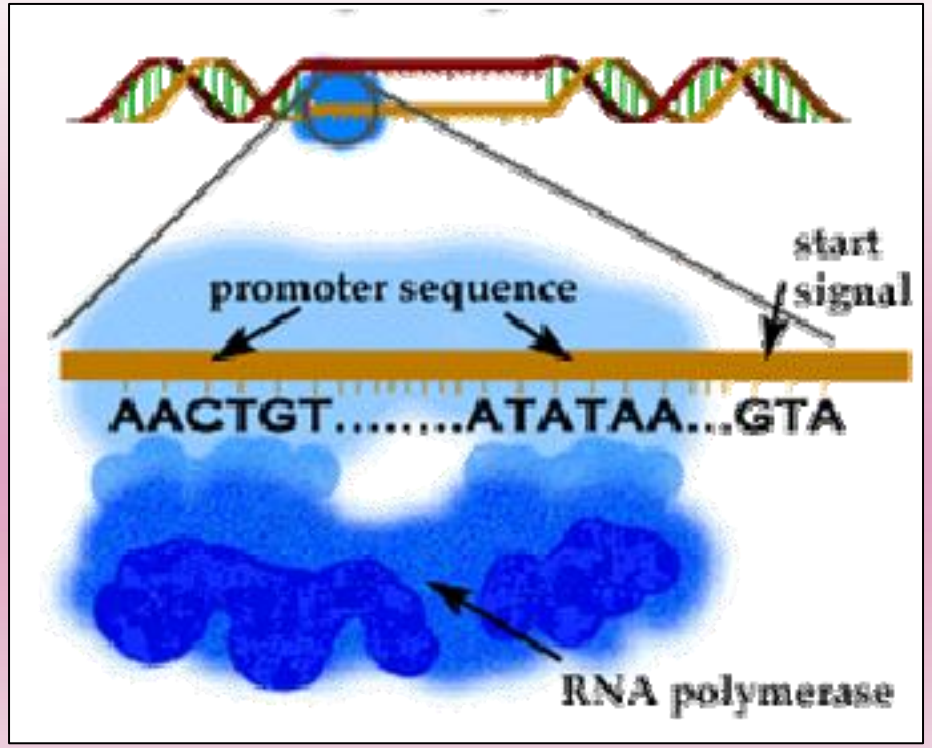
Messenger-RNA, **m-RNA**

- Copy of the template strand of DNA is made in the cell nucleus
- The copy moves into cytoplasm



Protein Synthesis: Transcription

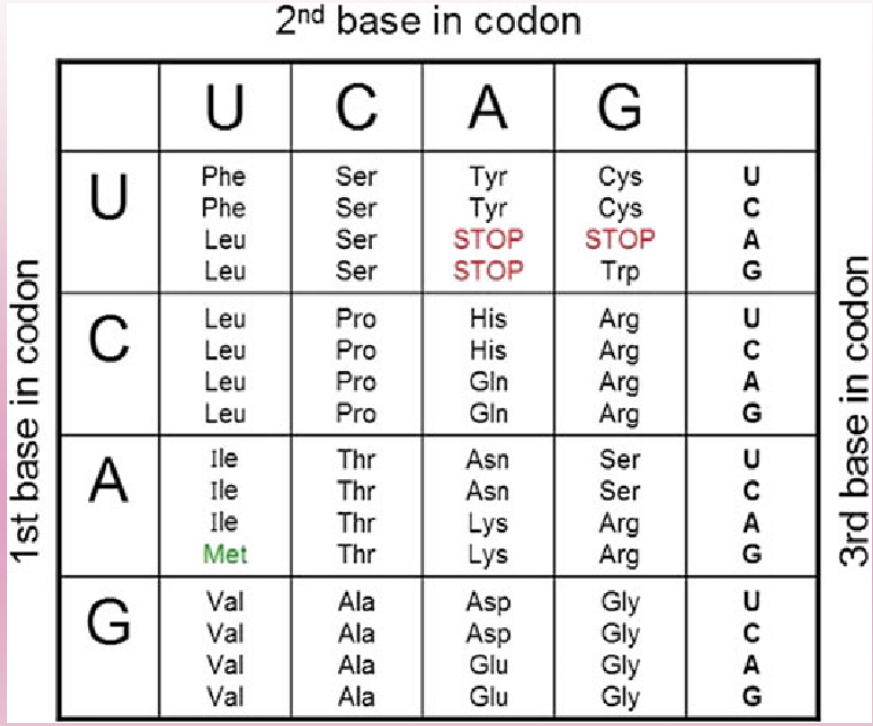
- Initiation with binding of the RNA polymerase to the ***promoter*** site (comparatively conserved sequences).
- The synthesis starts at ***start codon*** GTA (which then become bases CAU on the RNA molecule).



Video

Genetic Code

- There are 4^3=64 possible triplets – *codons*, but only 20 aminoacids and 3 stop codons.
- The code is ***degenerative***: different triplets code for the same aminoacid
- Important in keeping the proteins functional

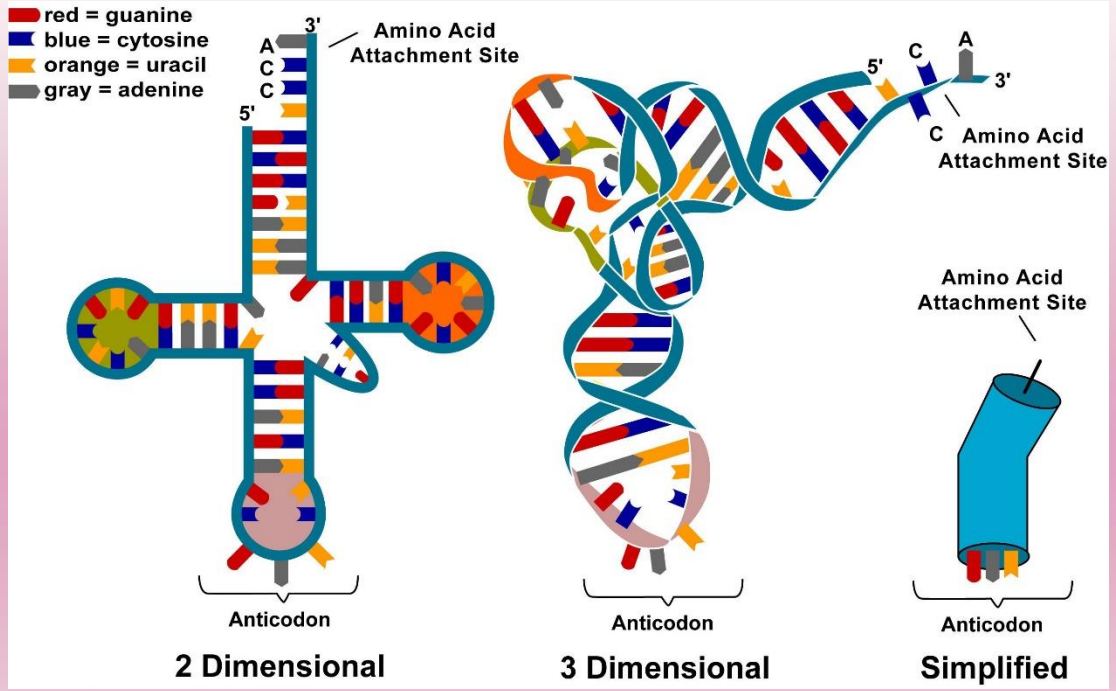


2nd base in codon

1st base in codon	U	C	A	G	3rd base in codon
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

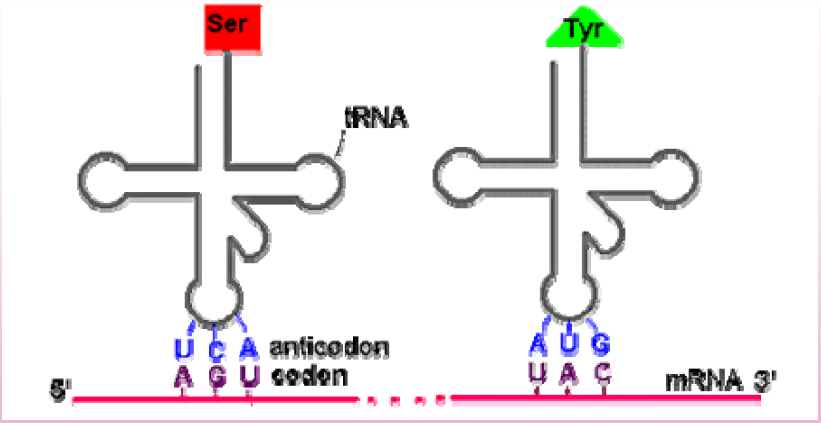
Protein Synthesis: Transport RNA

- **t-RNAs** are short
- Fold into a cloverleaf secondary structure
- Hydrogen bonds hold into an L-shaped tertiary structure



Protein Synthesis: Transport RNA

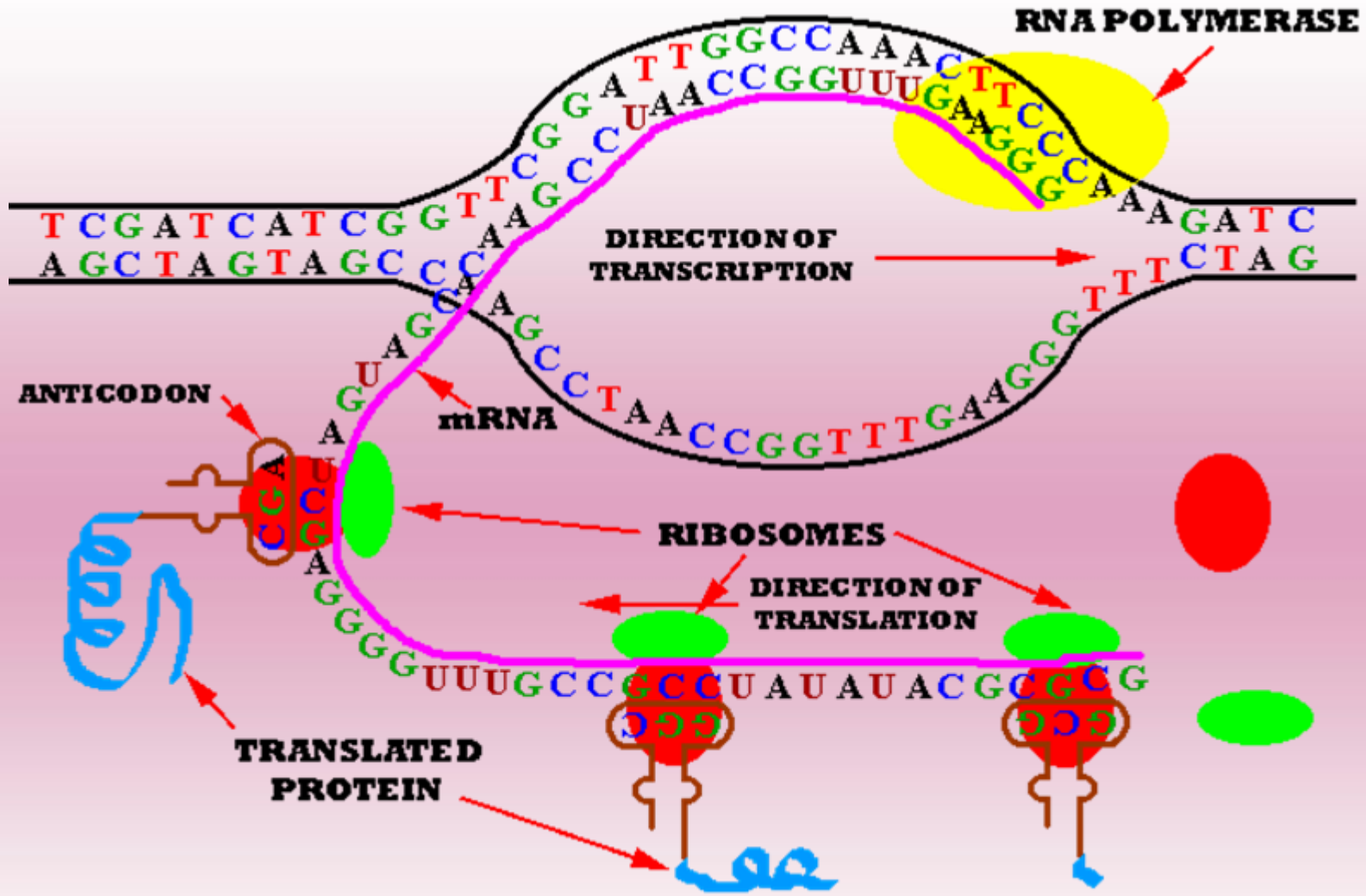
The anticodon is complementary to the triplet encoding the attached aminoacid, **according to the genetic code**



2nd base in codon

1st base in codon	U	C	A	G	3rd base in codon
U	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr STOP STOP	Cys Cys STOP Trp	U C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U C A G

Protein Synthesis



Central dogma of Molecular Biology

- DNA contains complete genetic information that defines the structure and function of an organism.
- Proteins are formed using genetic code stored in the DNA.
- Three different processes are responsible for the inheritance of genetic information and for its conversion from one form to another:

1. Replication
2. Transcription
3. Translation

Central dogma of molecular biology

Usual	**Special**	**Unknown**
DNA → DNA	RNA → DNA	protein → DNA
DNA → RNA	RNA → RNA	protein → RNA
RNA → protein	DNA → protein	protein → protein

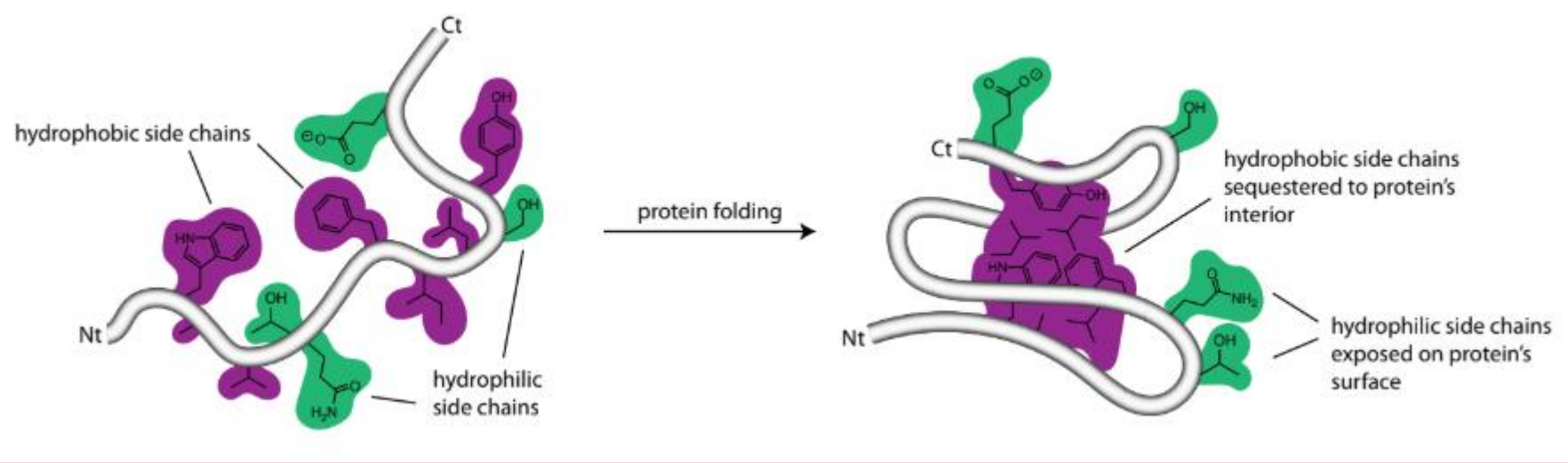
The direction of the information flow:

DNA → RNA → Protein,

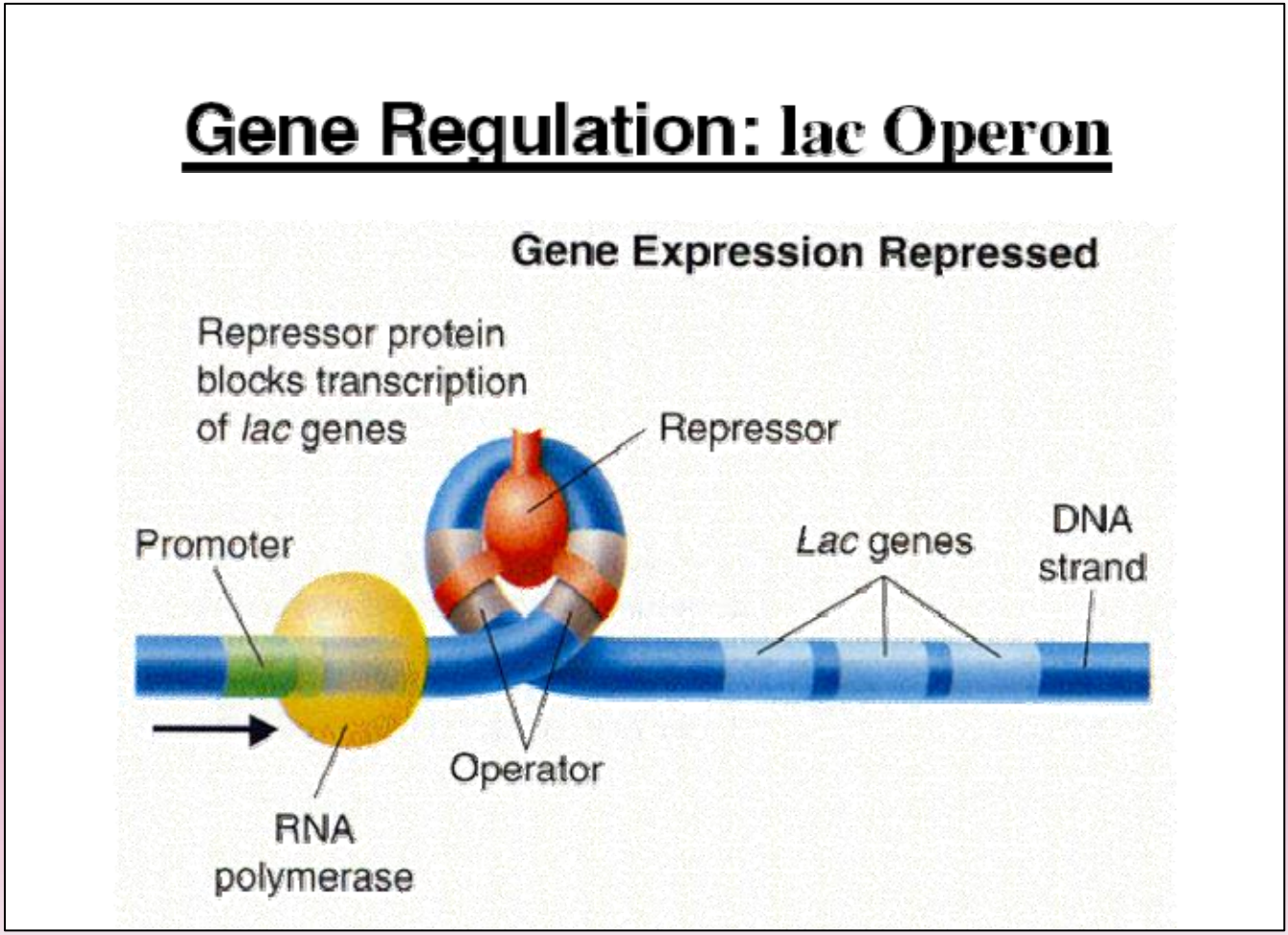
never Protein → DNA

Protein Folding

- The property of folding is spontaneous and is determined by the sequence of aminoacids
- The folding is mostly caused by hydrophobic-hydrophilic properties of aminoacid residues, which determine the orientation of these residues in a water environment, plus additional weak bonds



Regulation of gene expression



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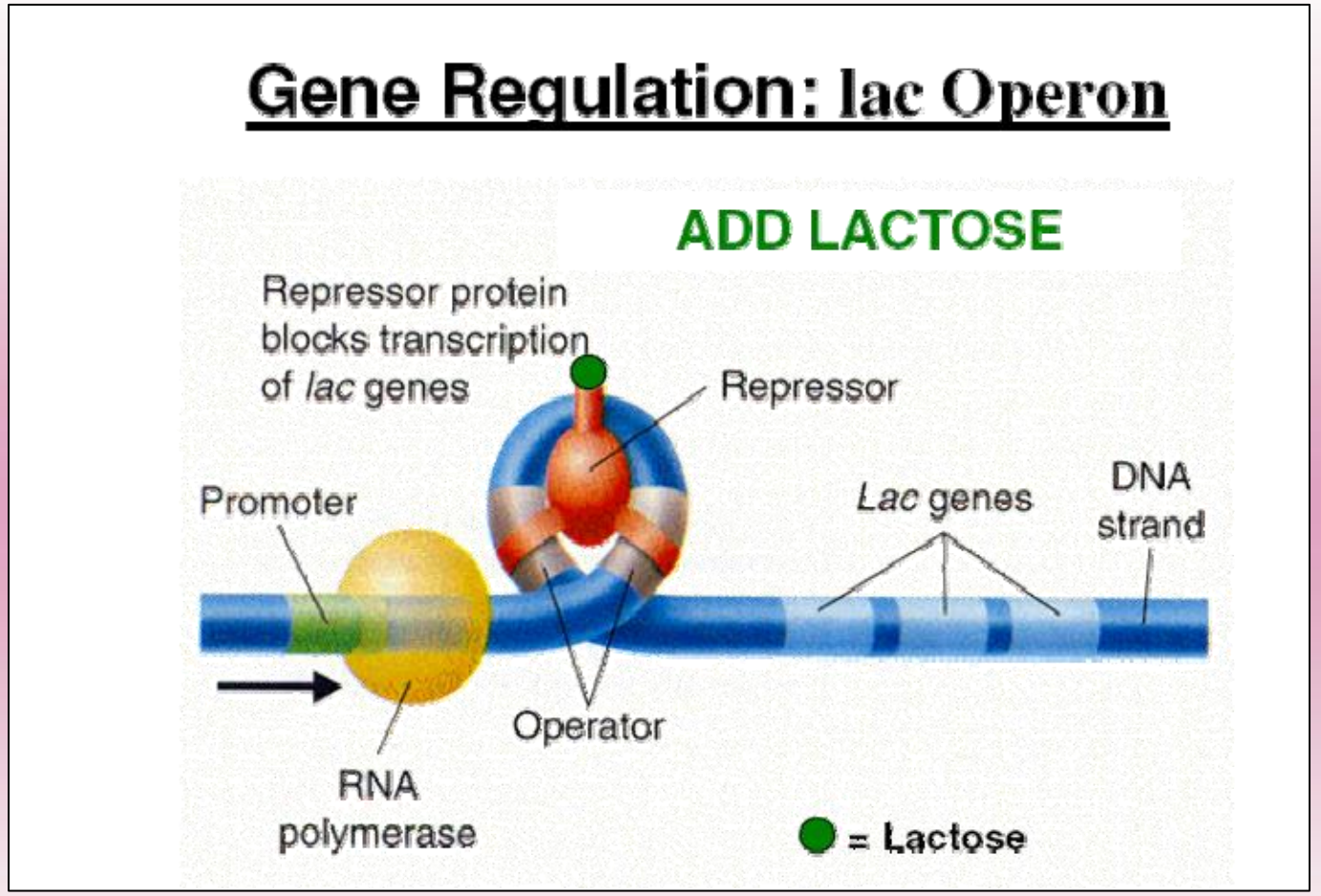
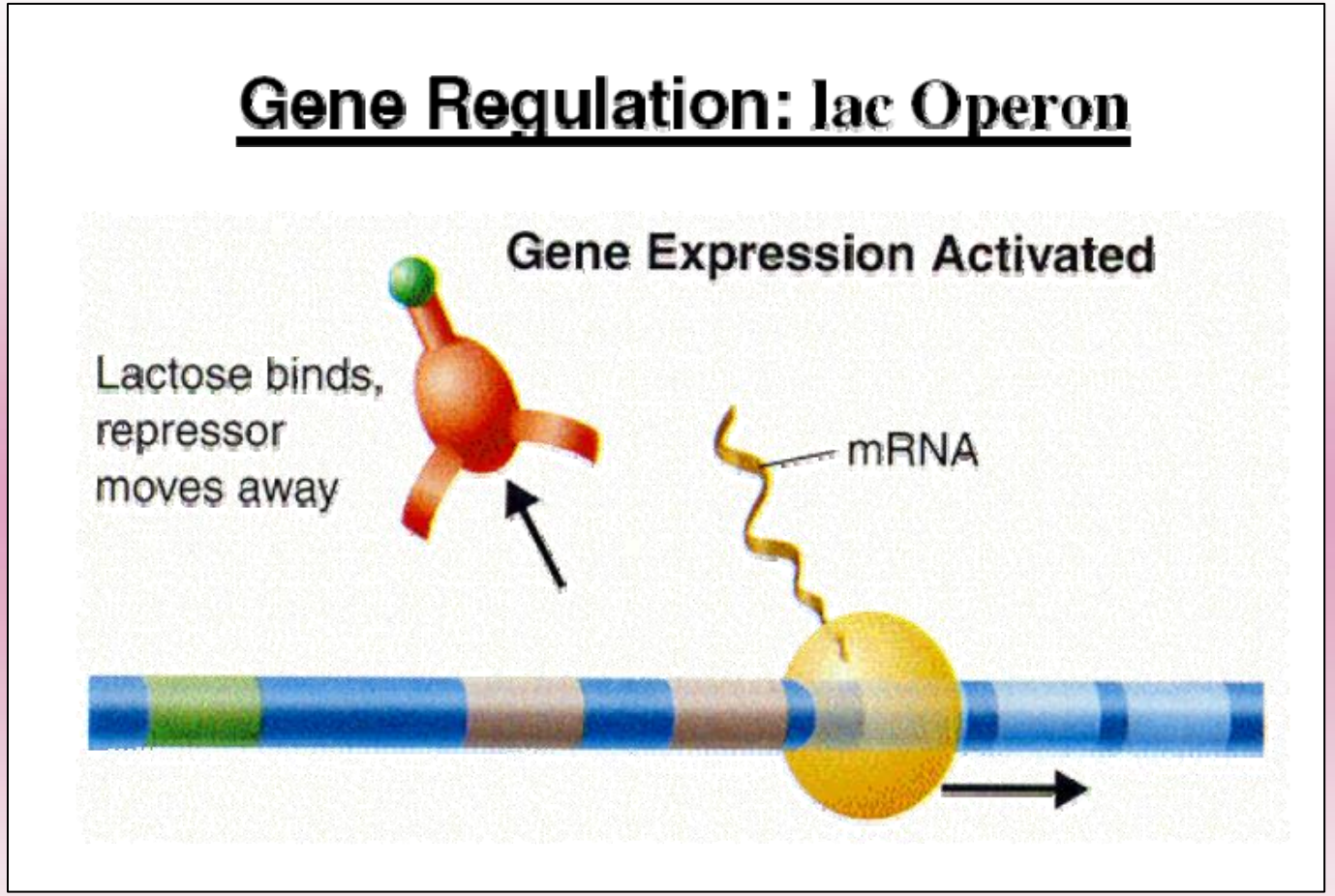
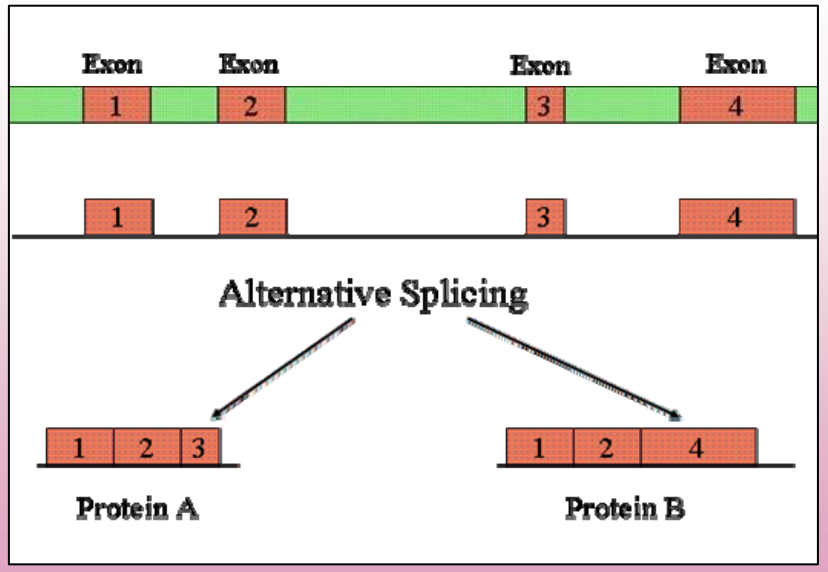


Regulation of gene expression



Gene to Protein: Complications



Original raw m-RNA transcript

Coding m-RNA to be used for protein synthesis

- Collinearity between the linear order of nucleotides and the linear order of aminoacids – did not persist after the 70-s:
  - Overlapping genes – different proteins from the same overlapping sequence of DNA
  - Interleaving *exons* (coding) and *introns* (non-coding) regions
  - **Alternative splicing** of exons

Concepts: summary

- DNA replication – semi-conservative, mutations, repair, stability and change
- Transcription from DNA to m-RNA – volatile RNA from stable DNA
- Splicing of m-RNA transcript into protein-coding sequence
- Translation – t-RNA, genetic code, degenerative code, stop-codons, promoters
- The central dogma of molecular biology – direction of the information flow

The DNA Period - Summary

- DNA – a polymer consisting of 4 types of nucleotides – carries all the information needed for life
- This information is expressed through synthesis of proteins. The aminoacid sequence of each protein determines its shape, which determines the function of the protein
- In bio-molecules **the information is conveyed through the order** of building blocks