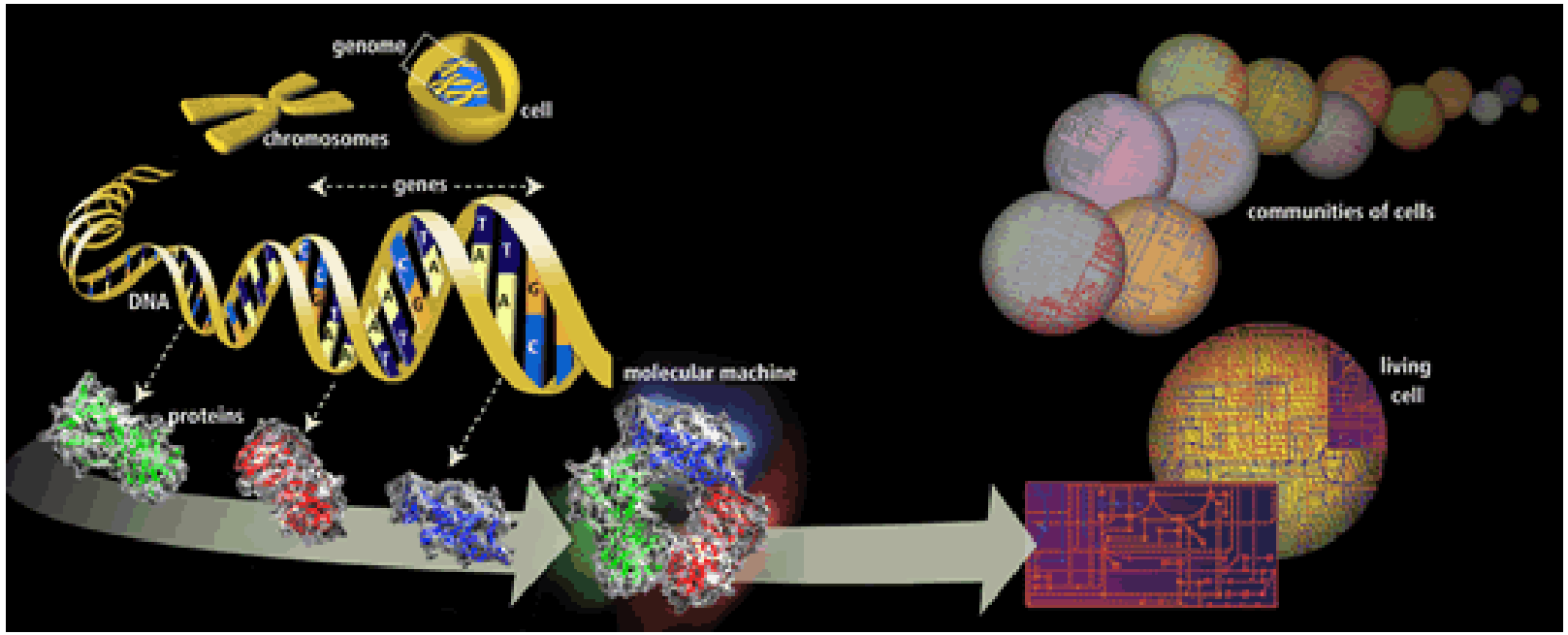
EECS730: Introduction to Bioinformatics

Lecture 1: Molecular Biology Primer



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Slides adapted from Dr. Shaojie Zhang (University of Central Florida)

- KUMC visit

EECS 730 Introduction to Bioinformatics

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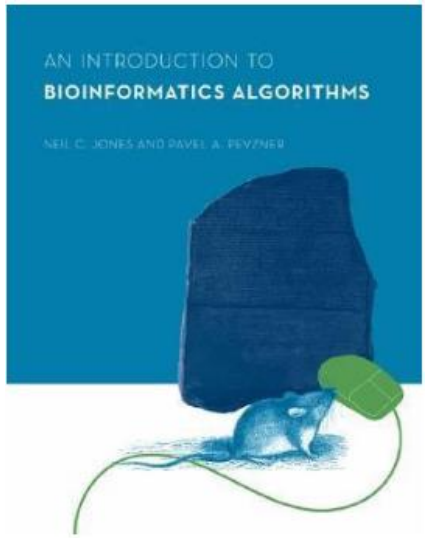
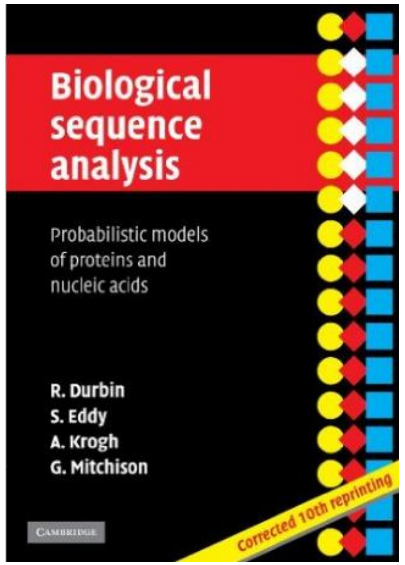
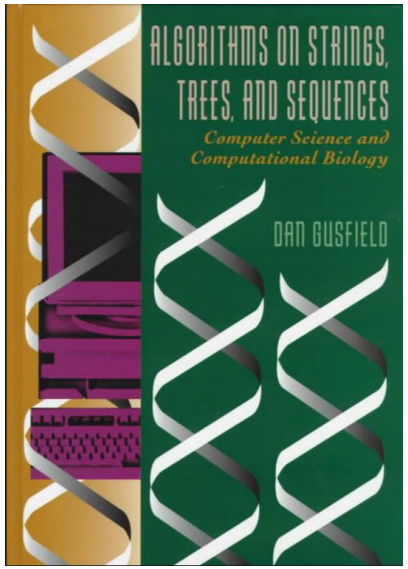
- Books



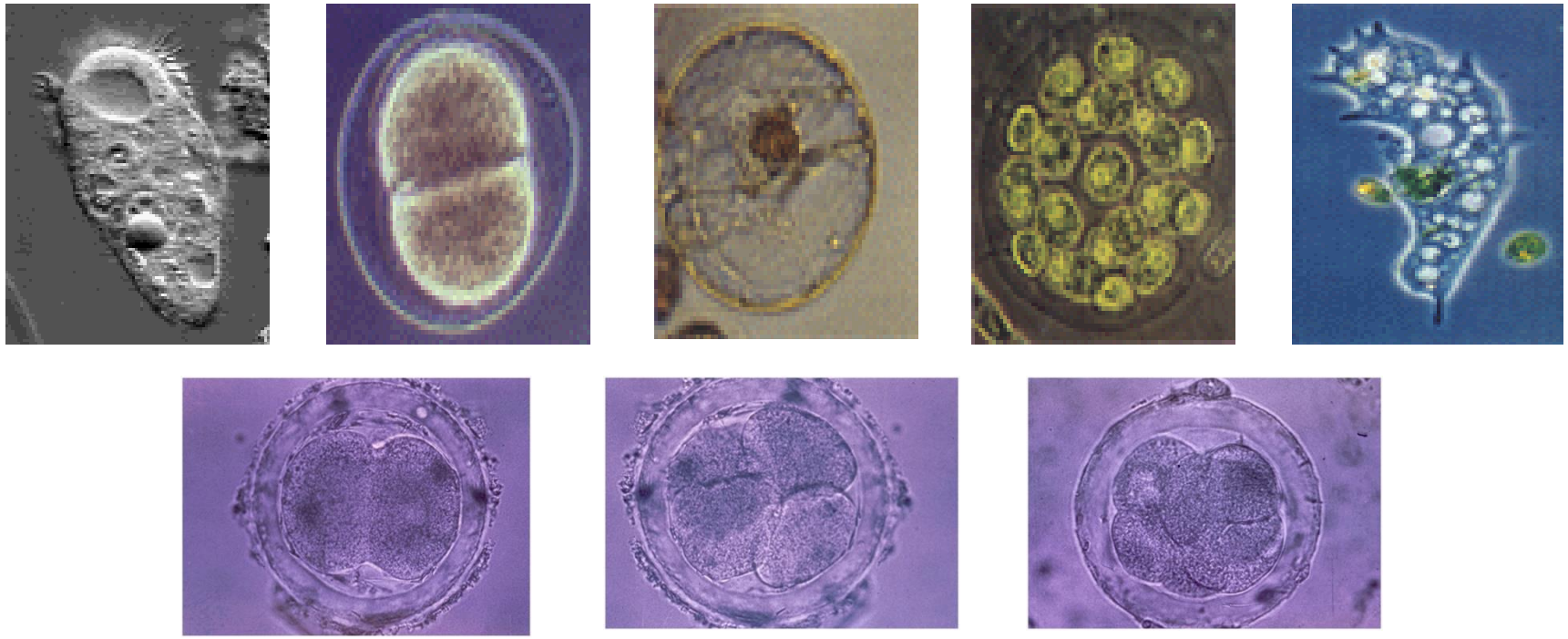




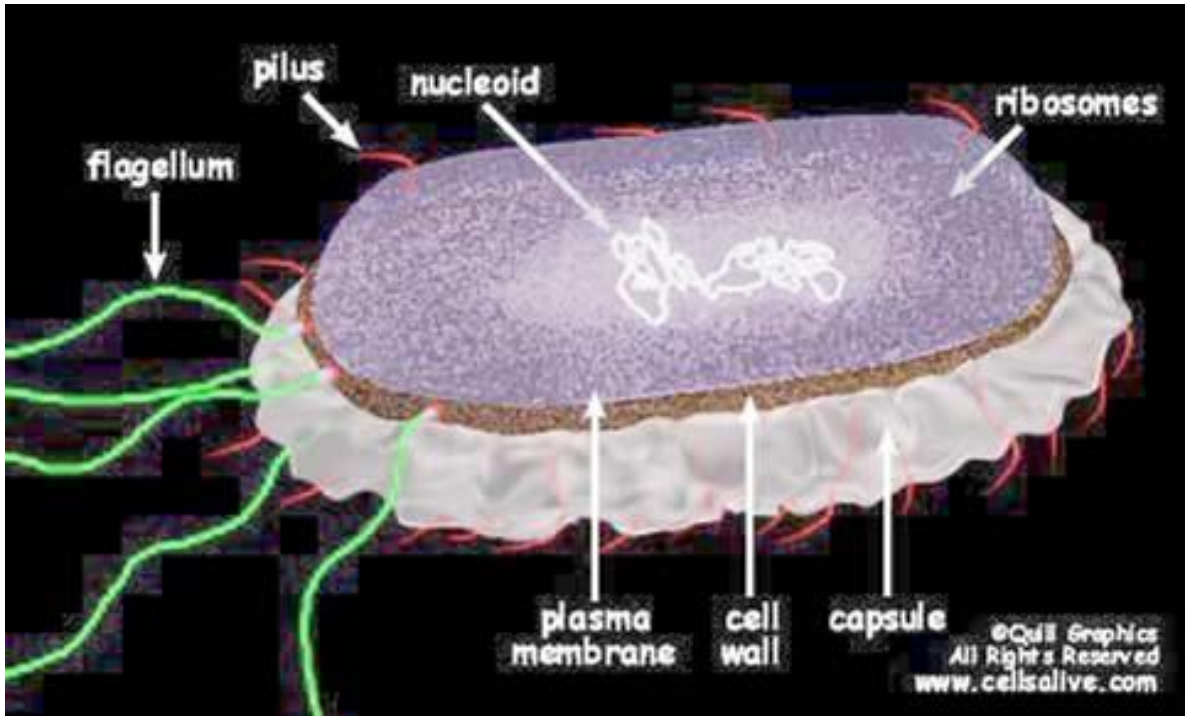
Outline

- Cells
- DNAs
- Transcription and RNAs
- Translation and proteins
- Comparative genomics

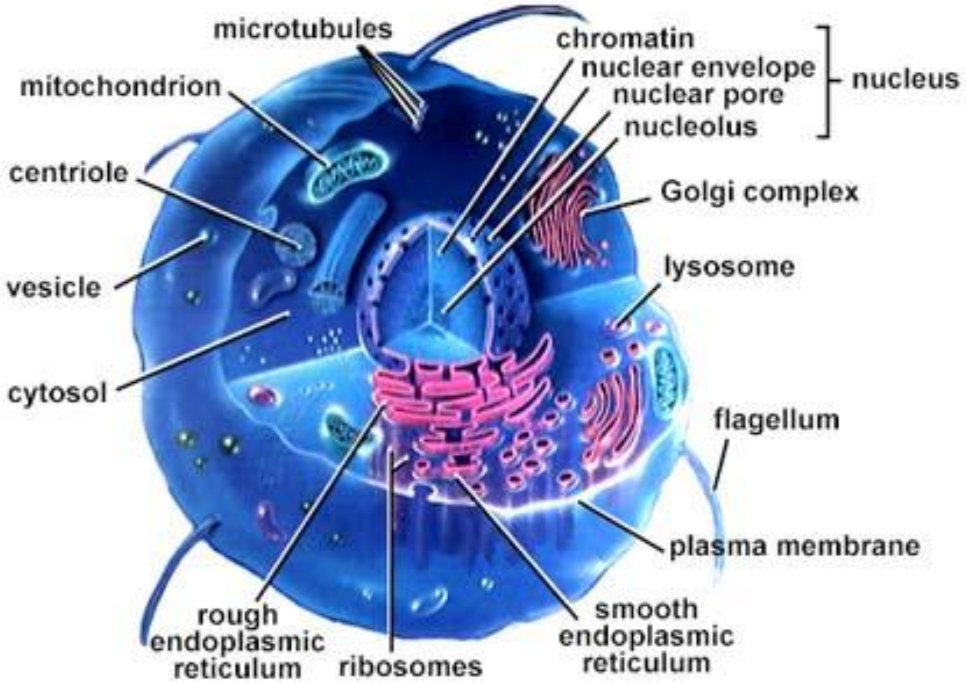
What is life made of?



Prokaryotes and Eukaryotes



Prokaryotic cell



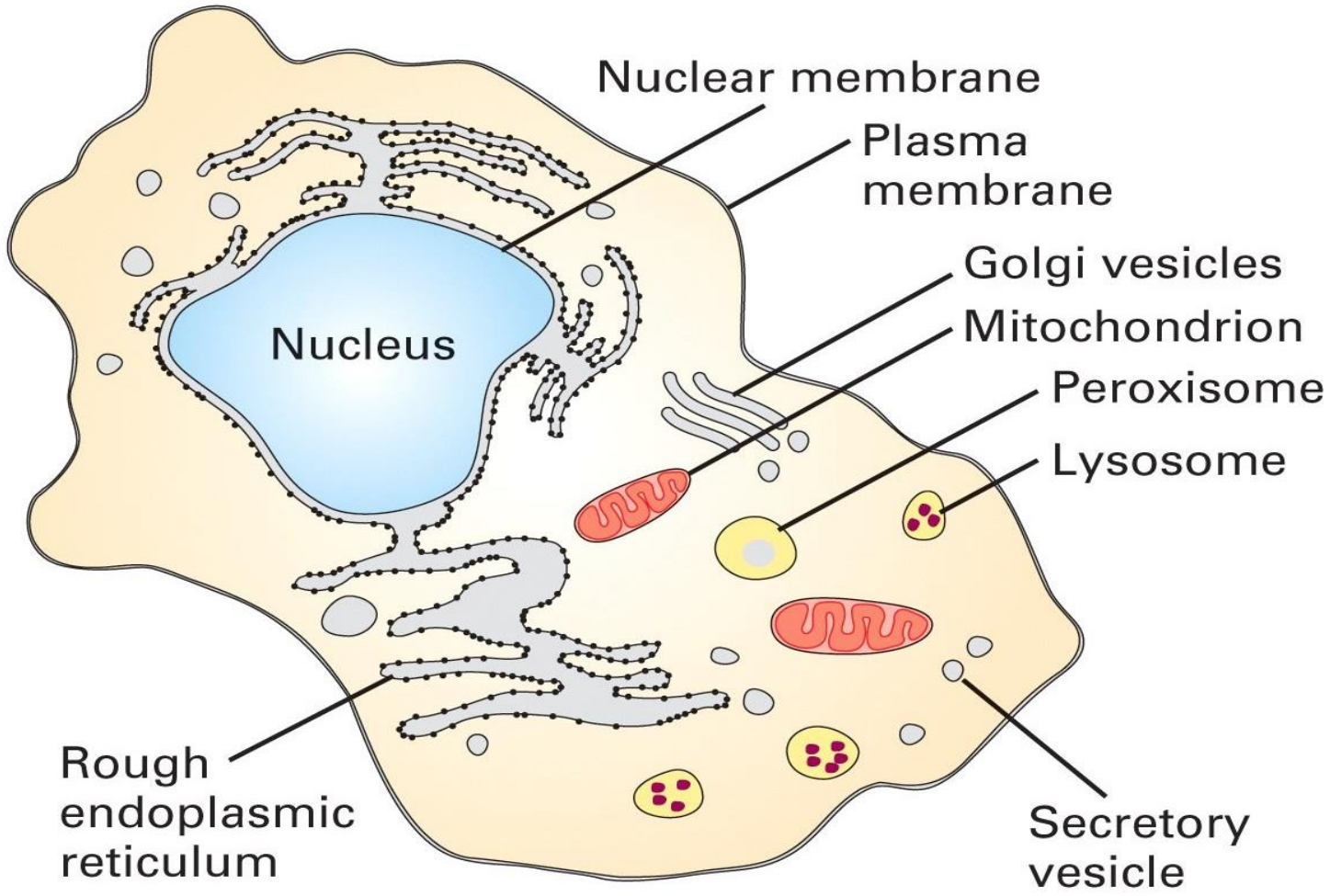
Eukaryotic cell

Prokaryotes and Eukaryotes cont.

Prokaryotes	**Eukaryotes**
Single cell	Single or multi cell
No nucleus	Nucleus
No organelles	Organelles
One piece of circular DNA	Chromosomes
No mRNA post transcriptional modification	Exons/Introns splicing

- A cell is a smallest structural unit of an organism that is capable of independent functioning
- All cells have some common features
- They Born, eat, replicate, and die

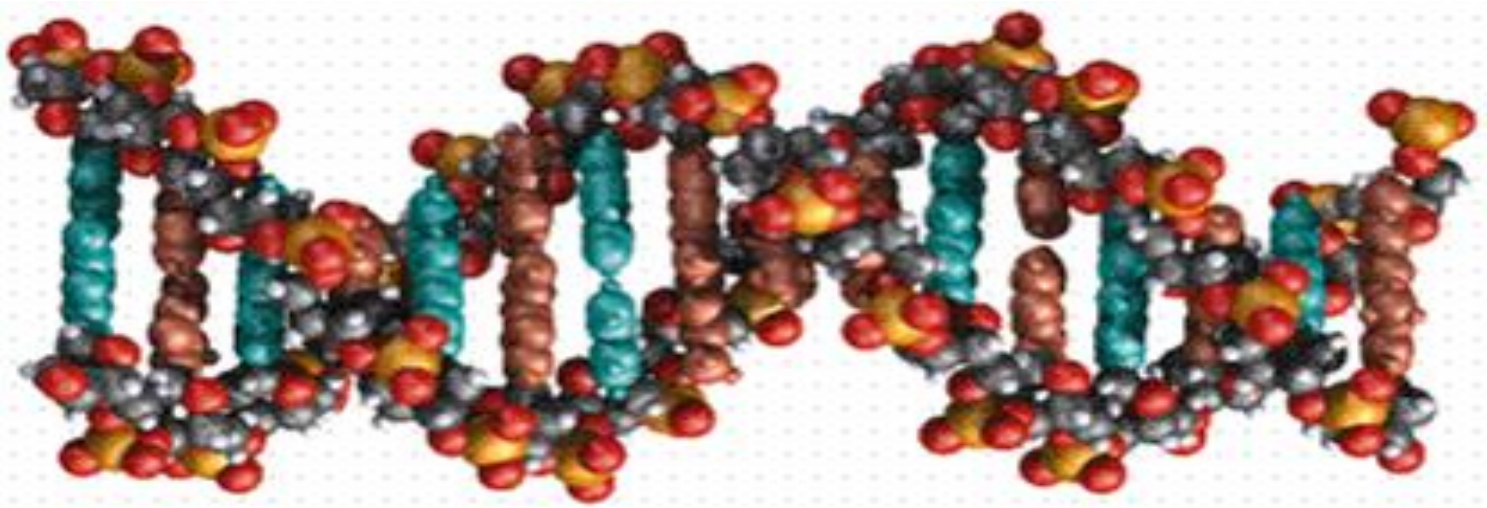
An eukaryotic cell



ORGANELLE	LOCATION	DESCRIPTION	FUNCTION
cell wall	plant, not animal	*outer layer *rigid, strong, stiff *made of cellulose	*support (grow tall) *protection *allows H2O, O2, CO2 to pass into and out of cell
cell membrane	both plant/animal	*plant - inside cell wall *animal - outer layer; cholesterol *selectively permeable	*support *protection *controls movement of materials in/out of cell *barrier between cell and its environment *maintains homeostasis
nucleus	both plant/animal	*large, oval	*controls cell activities
nuclear membrane	both plant/animal	*surrounds nucleus *selectively permeable	*Controls movement of materials in/out of nucleus
cytoplasm	both plant/animal	*clear, thick, jellylike material and organelles found inside cell membrane	*supports /protects cell organelles
endoplasmic reticulum (E.R.)	both plant/animal	*network of tubes or membranes	*carries materials through cell
ribosome	both plant/animal	*small bodies free or attached to E.R.	*produces proteins
mitochondrion	both plant/animal	*bean-shaped with inner membranes	*breaks down sugar molecules into energy
vacuole	plant - few/large animal - small	*fluid-filled sacs	*store food, water, waste (plants need to store large amounts of food)
lysosome	plant - uncommon animal - common	*small, round, with a membrane	*breaks down larger food molecules into smaller molecules *digests old cell parts

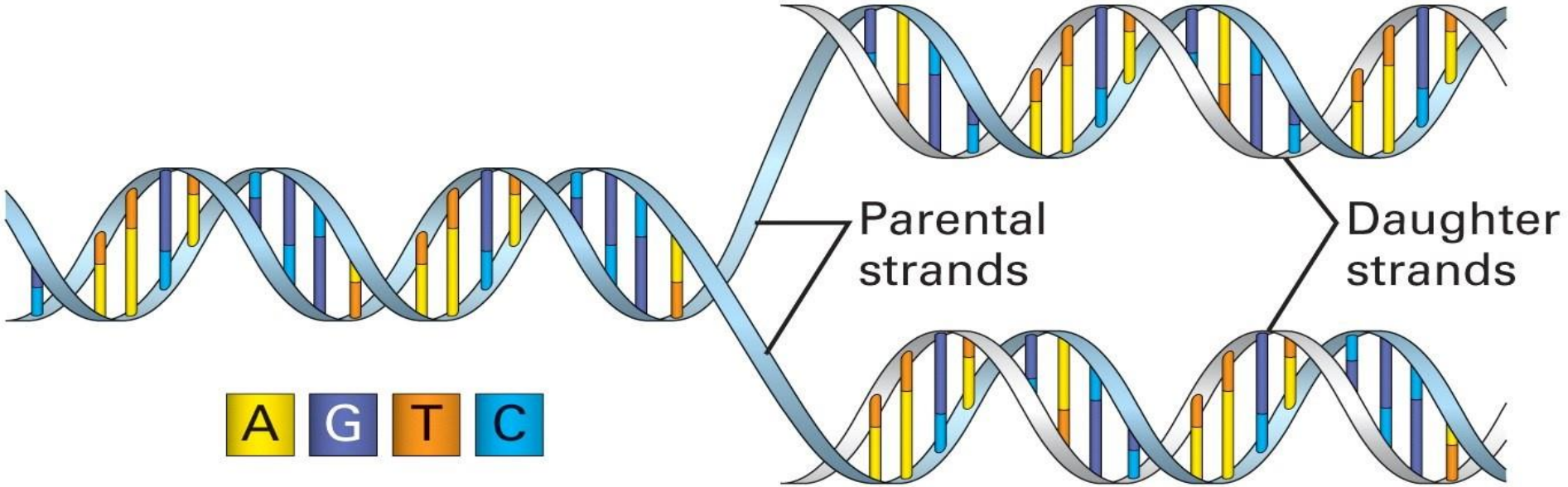
http://utahscience.oremjr.alpine.k12.ut.us/sciber00/7th/cells/sciber/orgtable.htm

Genetic material of life



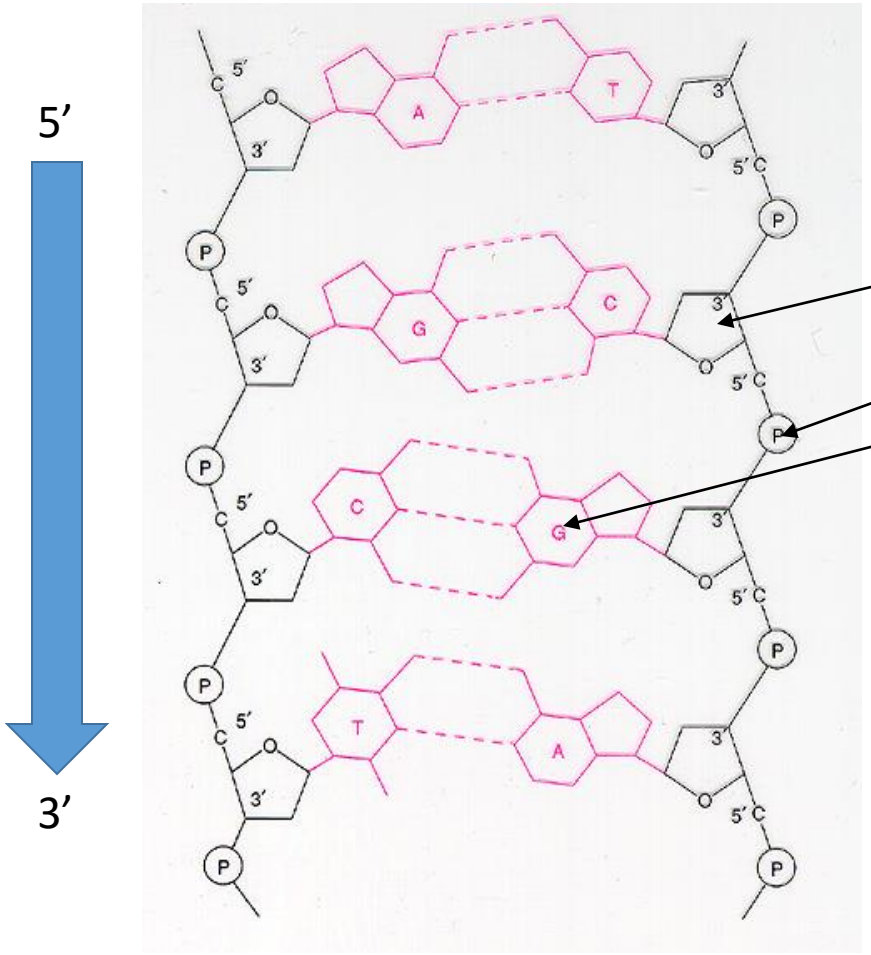
- What we inherit from our parents and what we pass down to our children (why we look like our parents?)
- The “blueprint” of life; easier to pass compared to the whole “building”

DNA: the code of life



- The structure and the four genomic letters code for all living organisms
- Adenine (A), Guanine (G), Thymine (T), and Cytosine (C) which pair A-T and C-G on complimentary strands.

DNA cont.

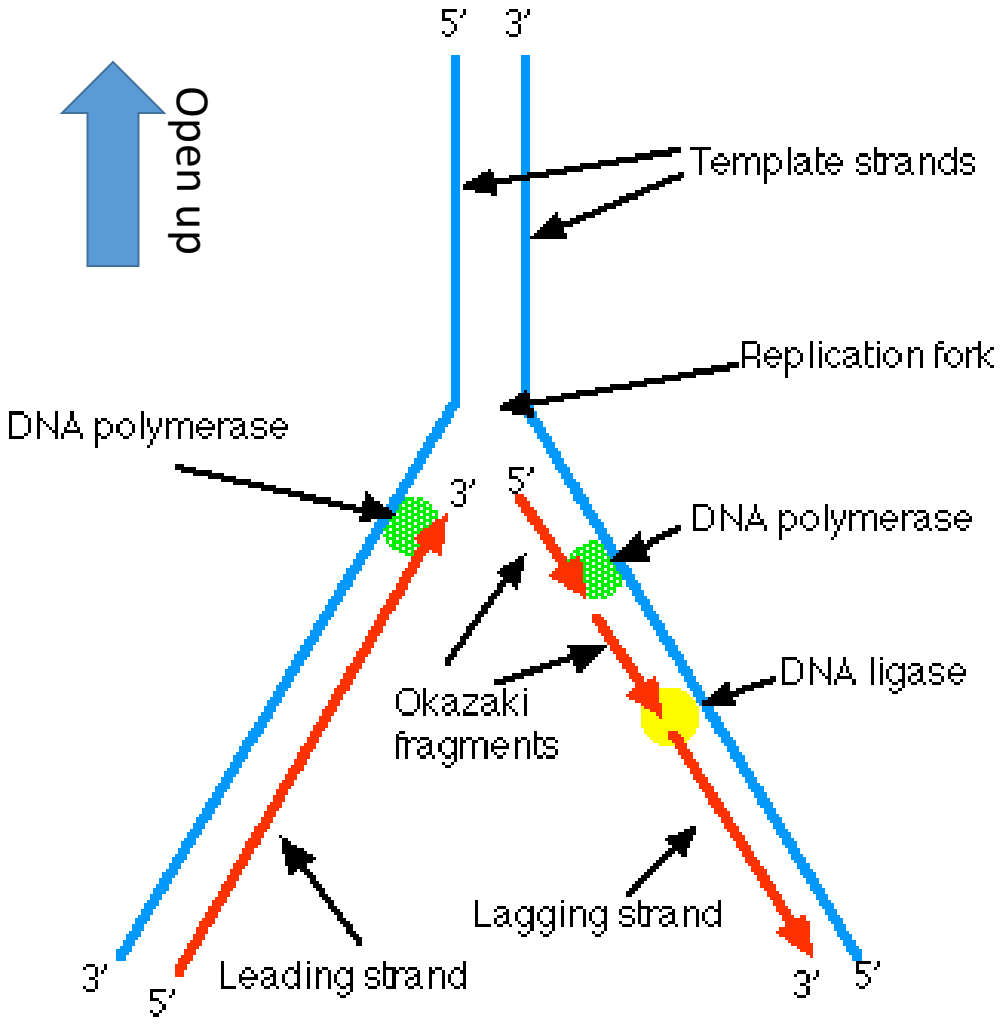


- DNA has a double helix structure which composed of
  - sugar molecule
  - phosphate group
  - and a base (A,C,G,T)

- DNA always reads from 5’ end to 3’ end for transcription replication
  - 5’ ATTTAGGCC 3’
  - 3’ TAAATCCGG 5’

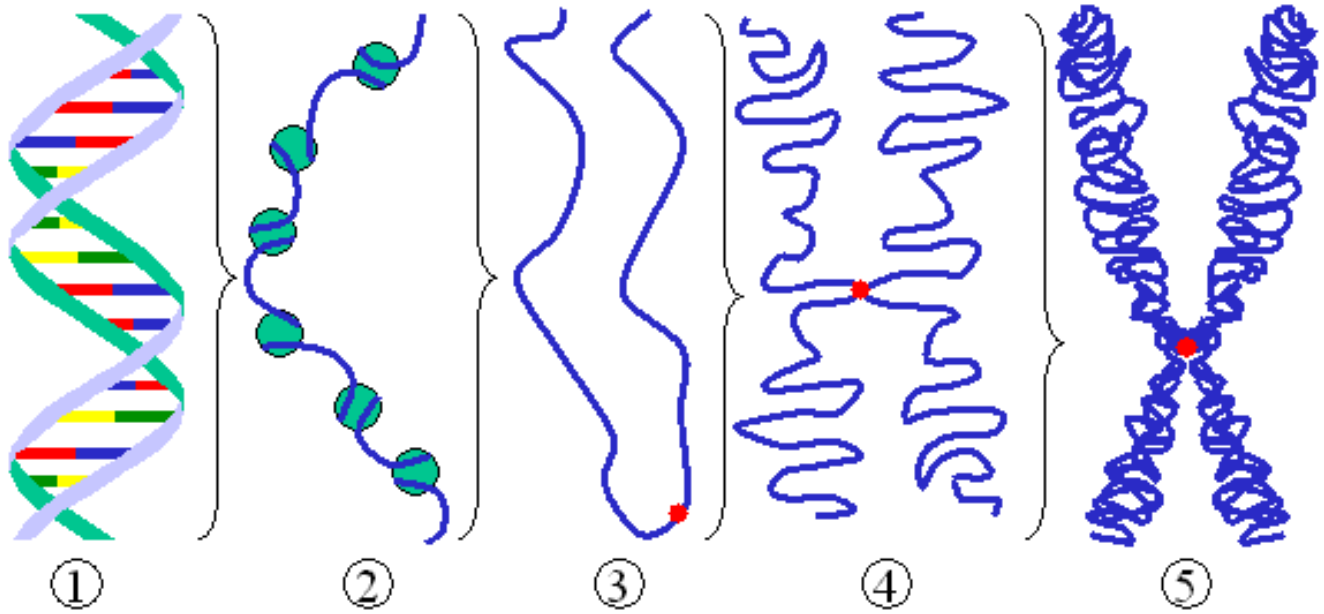
DNA replication

- DNA can replicate by splitting, and rebuilding each strand.
- Note that the rebuilding of each strand uses slightly different mechanisms due to the 5’ 3’ asymmetry, but each daughter strand is an exact replica of the original strand.

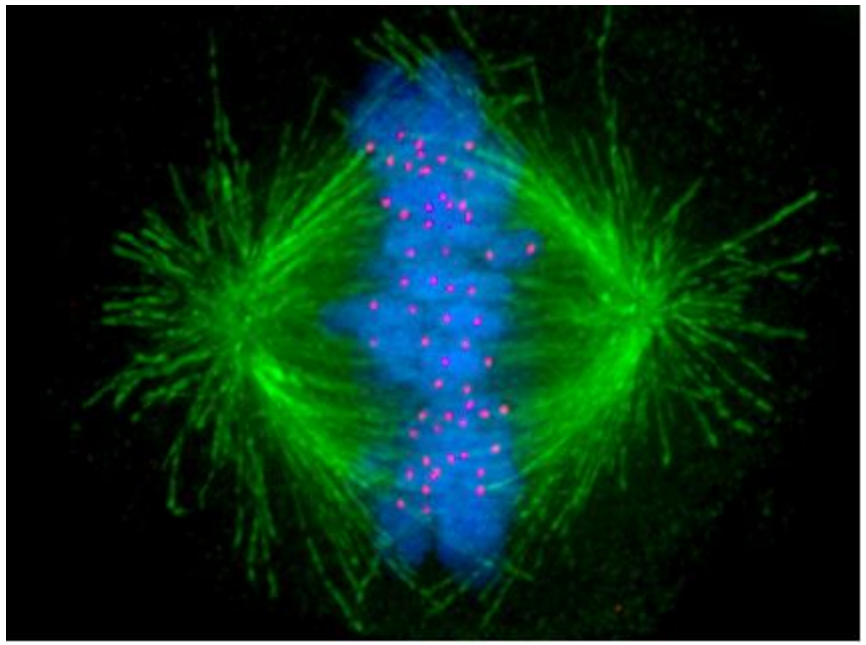


http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/D/DNAReplication.html

Packed DNA: Chromosomes



- (1) Double helix DNA strand.
- (2) Chromatin strand (DNA with histones)
- (3) Condensed chromatin during interphase with centromere.
- (4) Condensed chromatin during prophase
- (5) Chromosome during metaphase



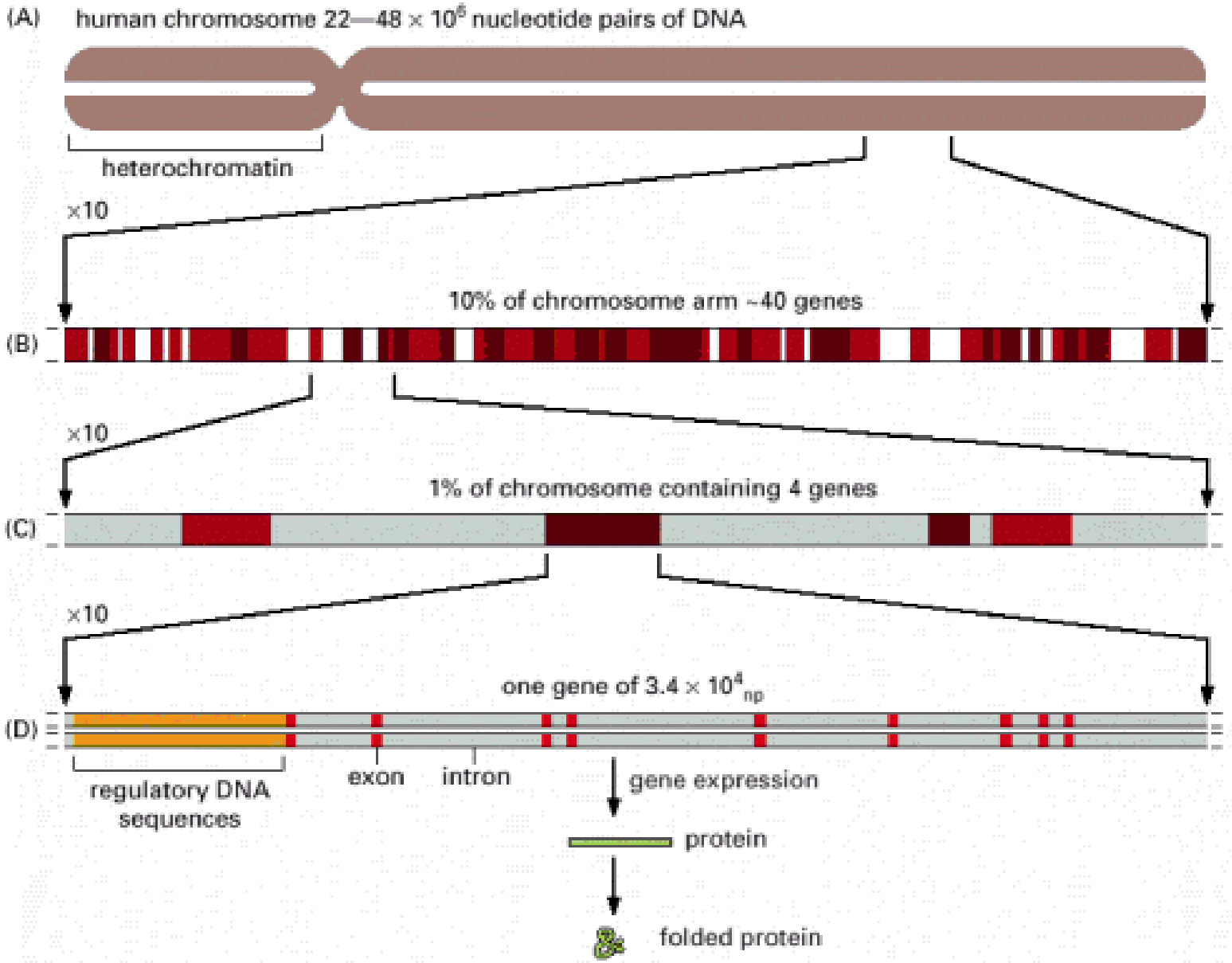
spindle fibers attach to the centromere via the kinetochore during mitosis

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

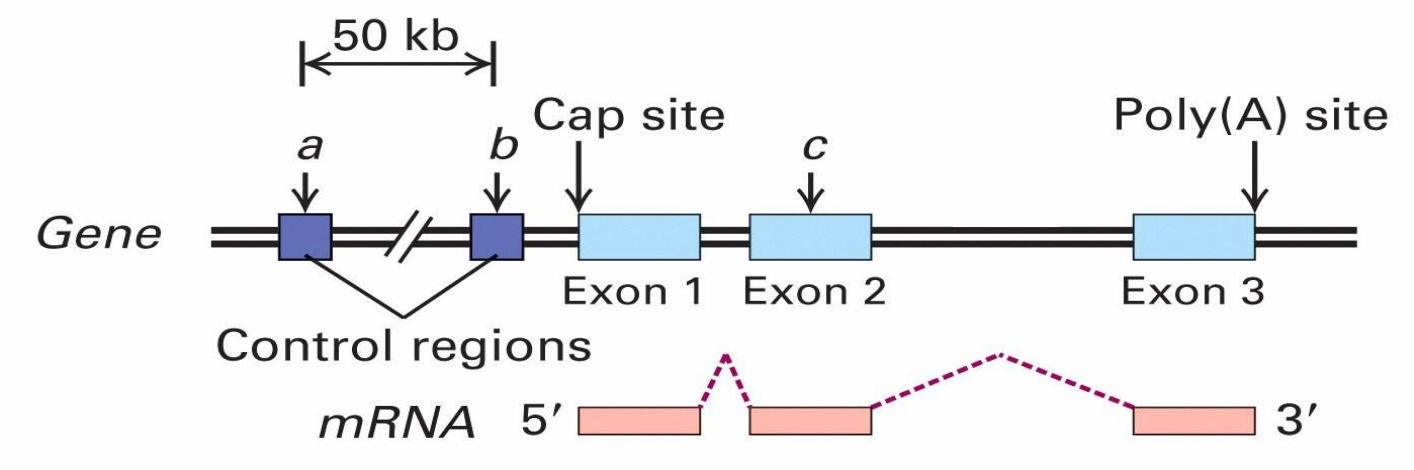
Chromosome

Organism	Number of base pair	number of Chromosomes
Prokayotic		
Escherichia coli (bacterium)	**$4x10^6$**	**1**
Eukaryotic		
Saccharomyces cerevisiae(yeast)	**$1.35x10^7$**	**17**
Drosophila melanogaster(insect)	**$1.65x10^8$**	**4**
Homo sapiens(human)	**$2.9x10^9$**	**23**
Zea mays(corn)	**$5.0x10^9$**	**10**

The organization of genes on a human chromosome

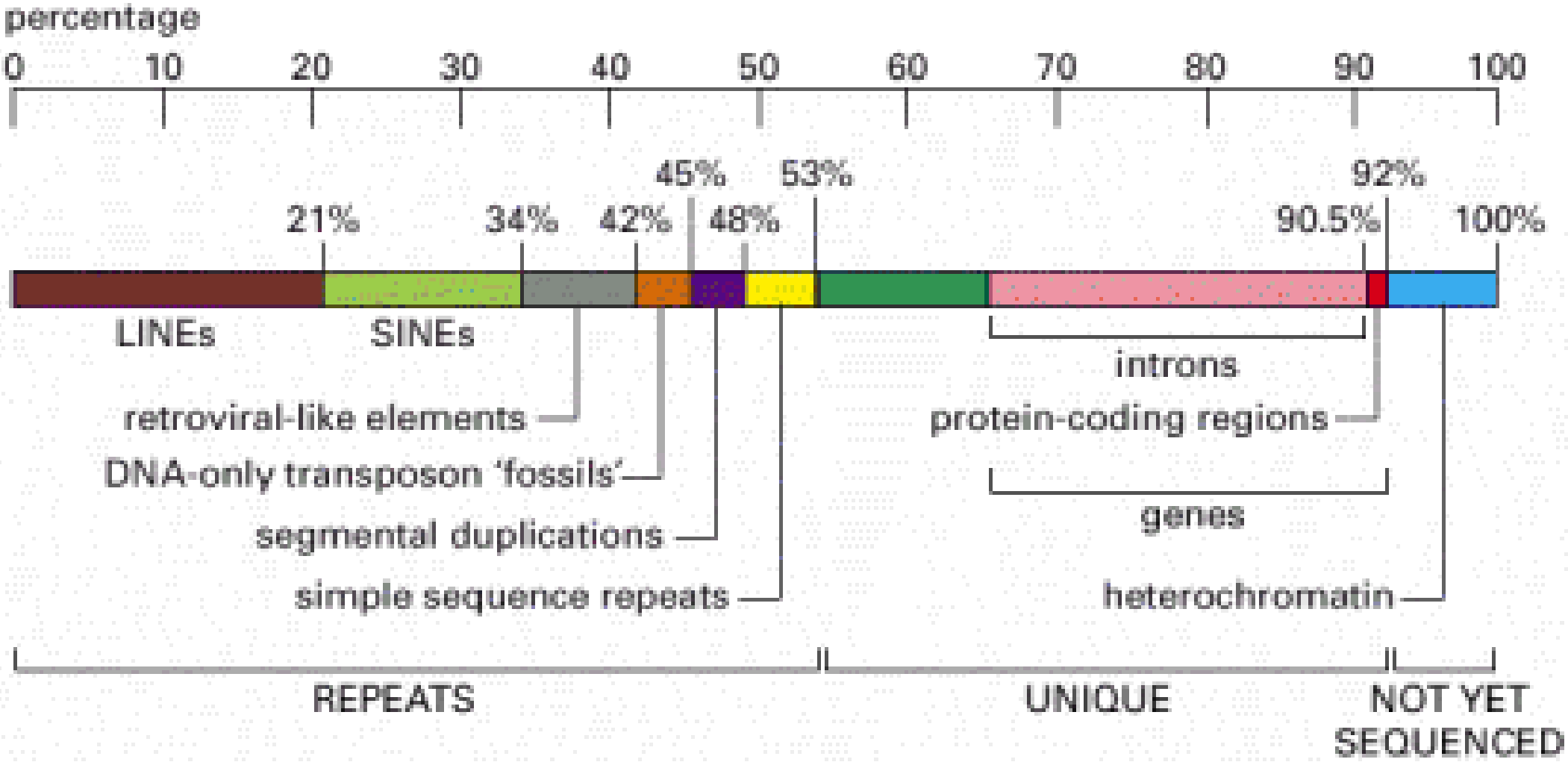


A closer look at the eukaryotic gene structure

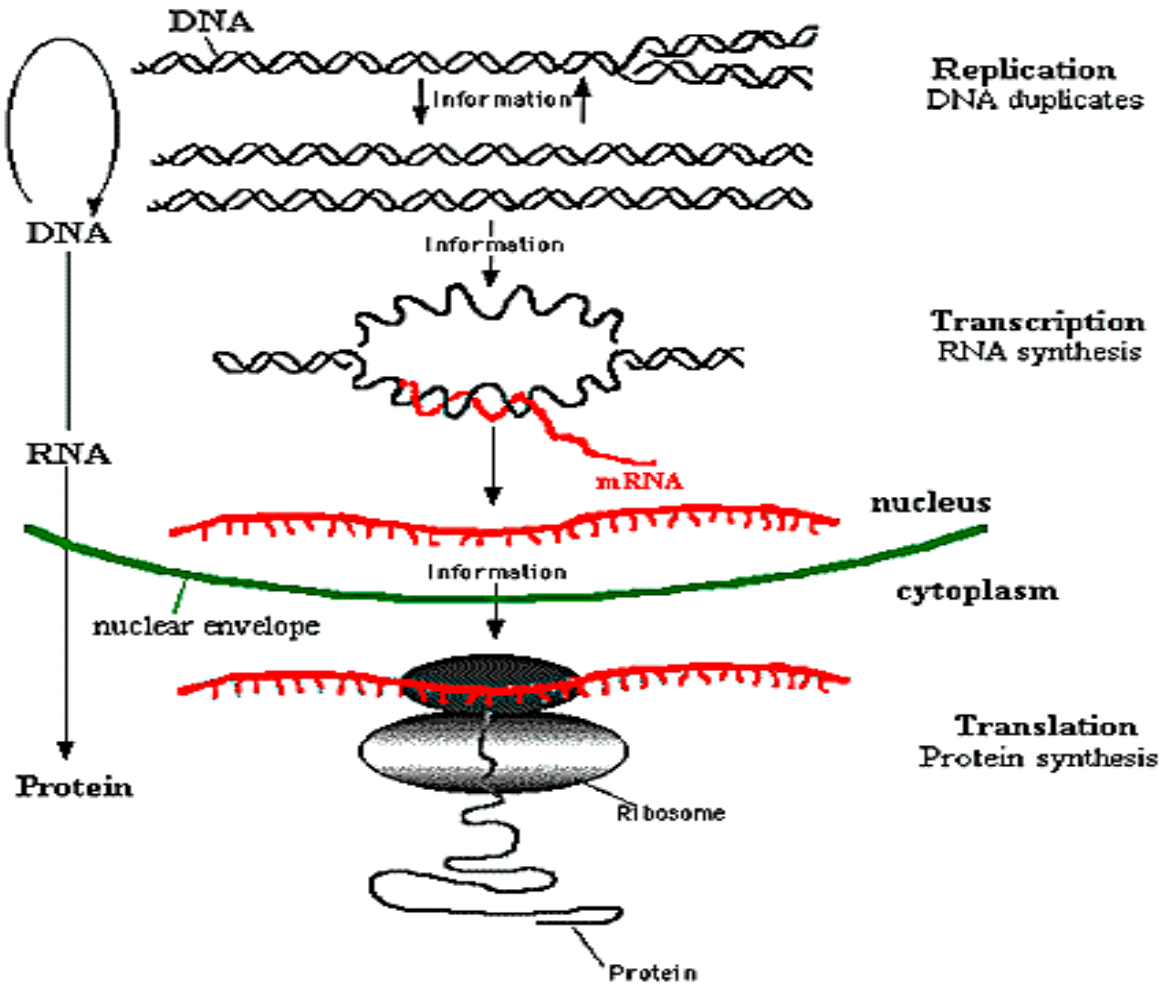


- **Regulatory regions: up to 50 kb upstream of +1 site**
- **Exons: protein coding and untranslated regions (UTR)**
  1 to 178 exons per gene (mean 8.8)
  8 bp to 17 kb per exon (mean 145 bp)
- **Introns: splice acceptor and donor sites, junk DNA?**
  average 1 kb – 50 kb per intron
- **Gene size: Largest – 2.4 Mb (Dystrophin). Mean – 27 kb.**

The human genome



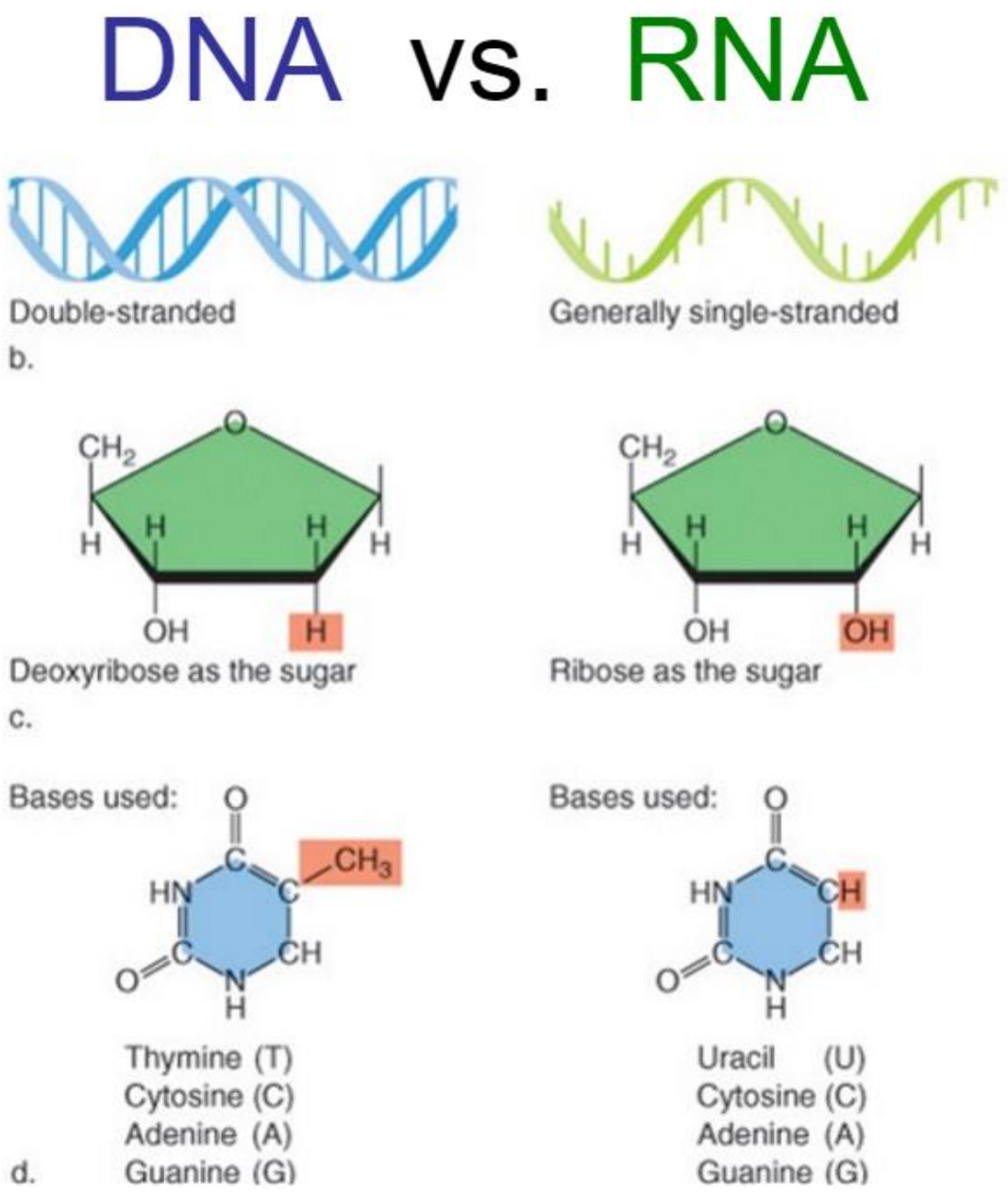
Central dogma



The Central Dogma of Molecular Biology

DNA → RNA: Transcription

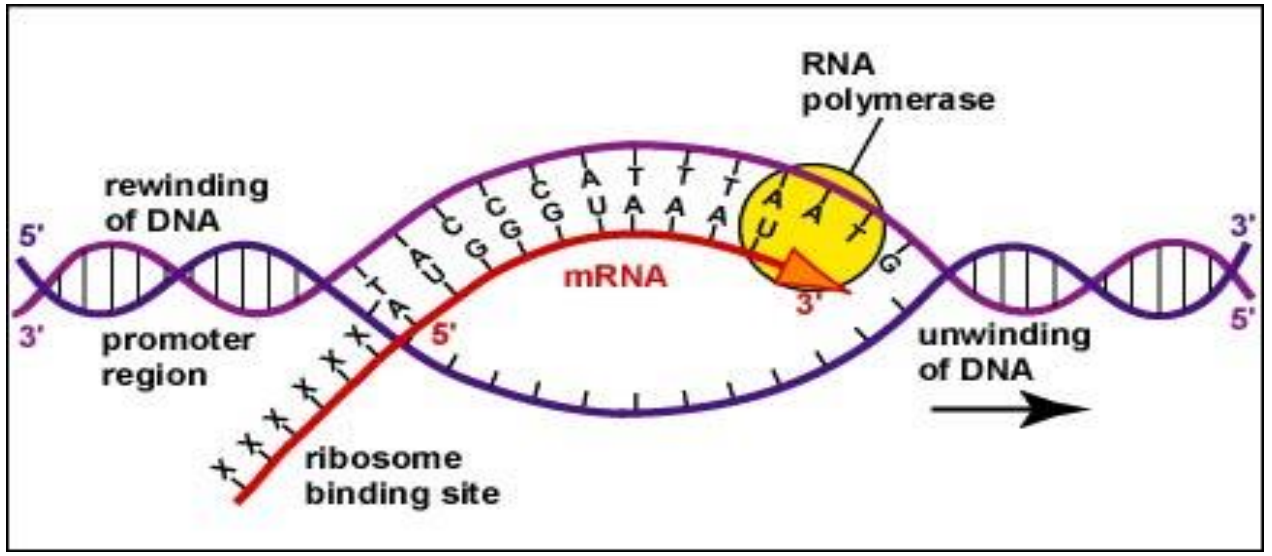
- DNA gets transcribed by a protein known as *RNA-polymerase*
- This process builds a chain of bases that will become mRNA (message RNA)
- RNA and DNA are similar, except that RNA is single stranded and thus less stable than DNA
  - Also, in RNA, the base uracil (U) is used instead of thymine (T), the DNA counterpart



http://slideplayer.com/slide/5670311/

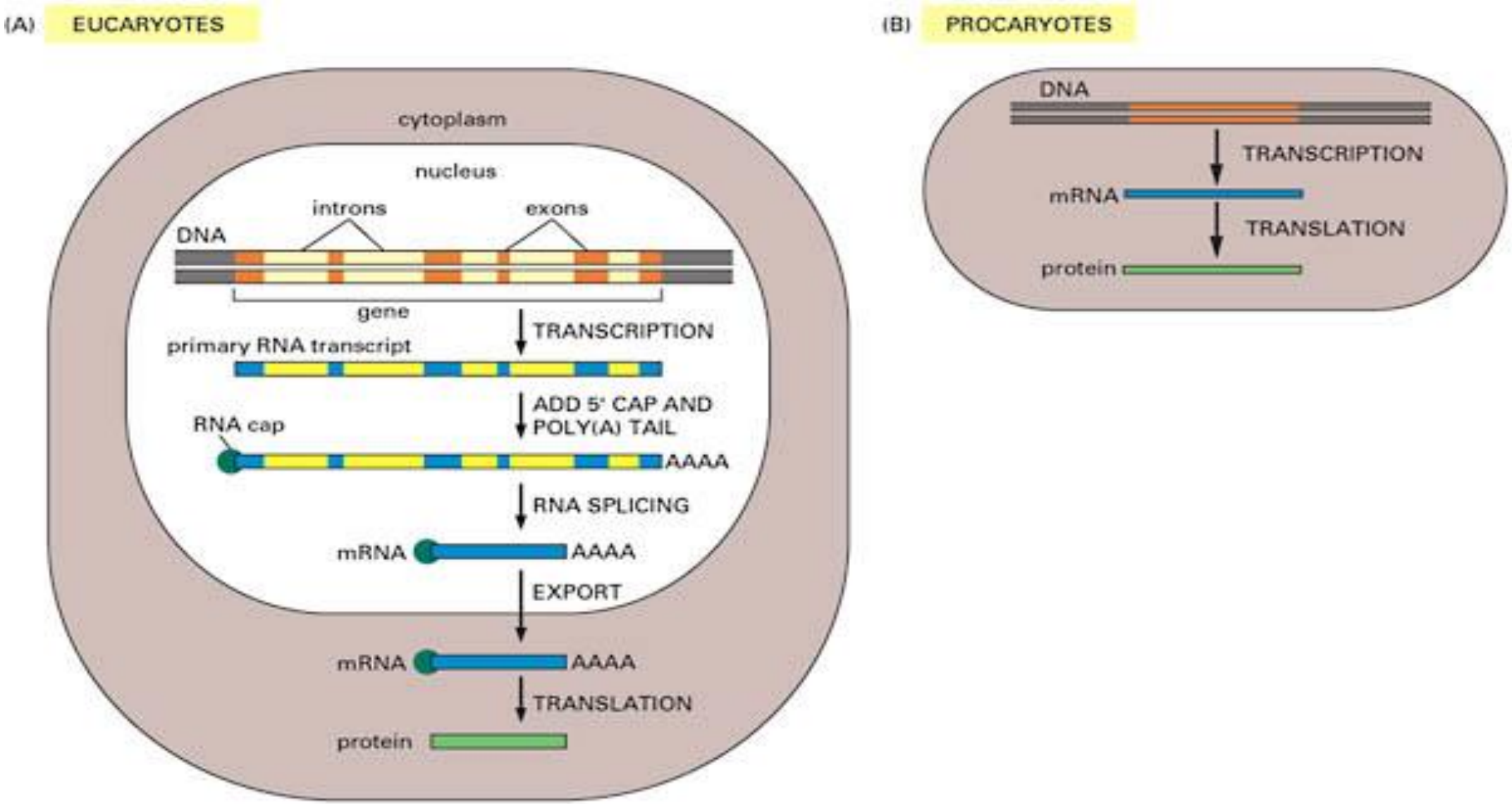
Transcription: DNA to pre-mRNA

- Transcription occurs in the nucleus.
- σ factor from RNA polymerase reads the promoter sequence and opens a small portion of the double helix exposing the DNA bases.

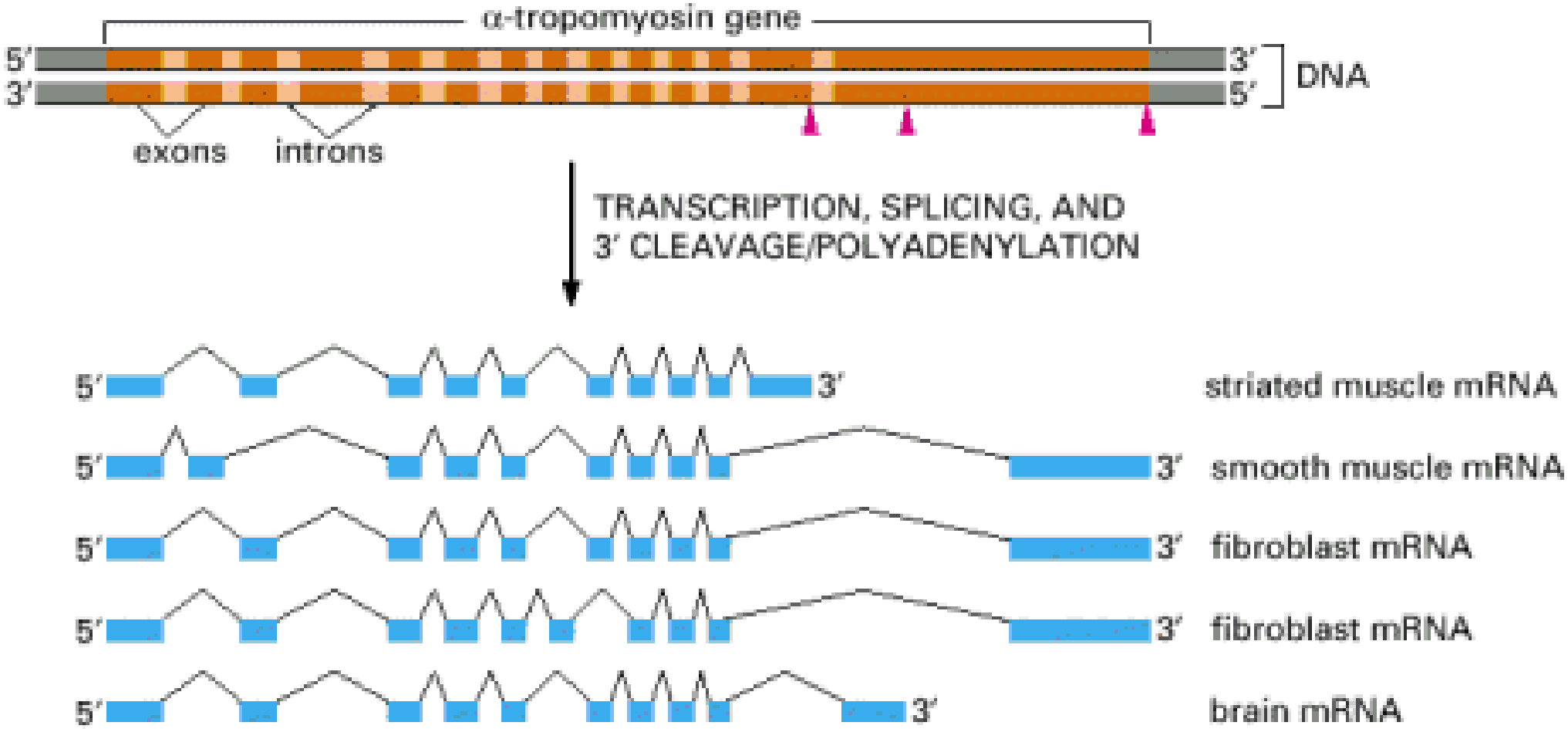


- RNA polymerase II catalyzes the formation of phosphodiester bond that link nucleotides together to form a linear chain from 5’ to 3’ by unwinding the helix just ahead of the active site for polymerization of complementary base pairs.
- The hydrolysis of high energy bonds of the substrates (nucleoside triphosphates ATP, CTP, GTP, and UTP) provides energy to drive the reaction.
- During transcription, the DNA helix reforms as RNA forms.
- When the terminator sequence is met, polymerase halts and releases both the DNA template and the RNA.

pre-mRNA to mature mRNA

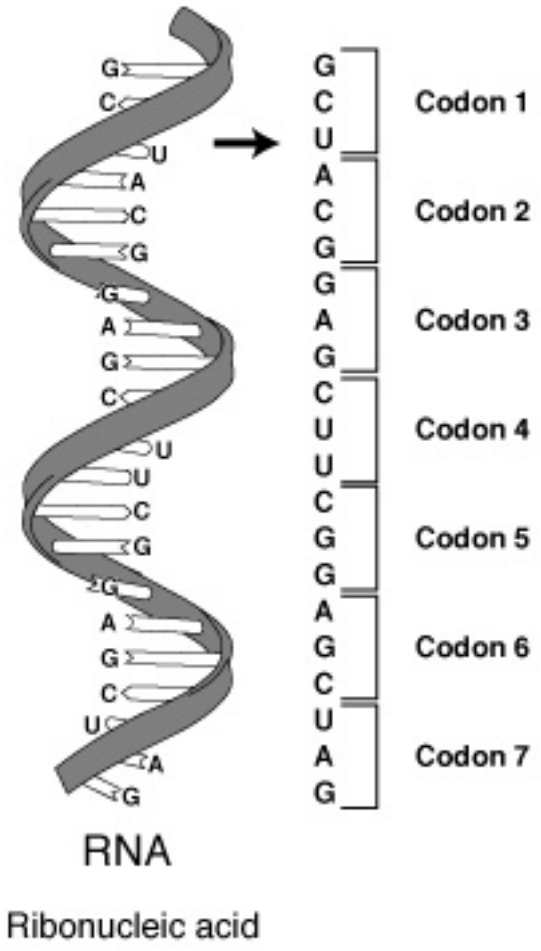


Alternative splicing



translation

- Happened in ribosome
- The process of going from RNA to polypeptide.
- Three base pairs of RNA (called a codon) correspond to one amino acid based on a fixed table.
- Always starts with Methionine and ends with a stop codon

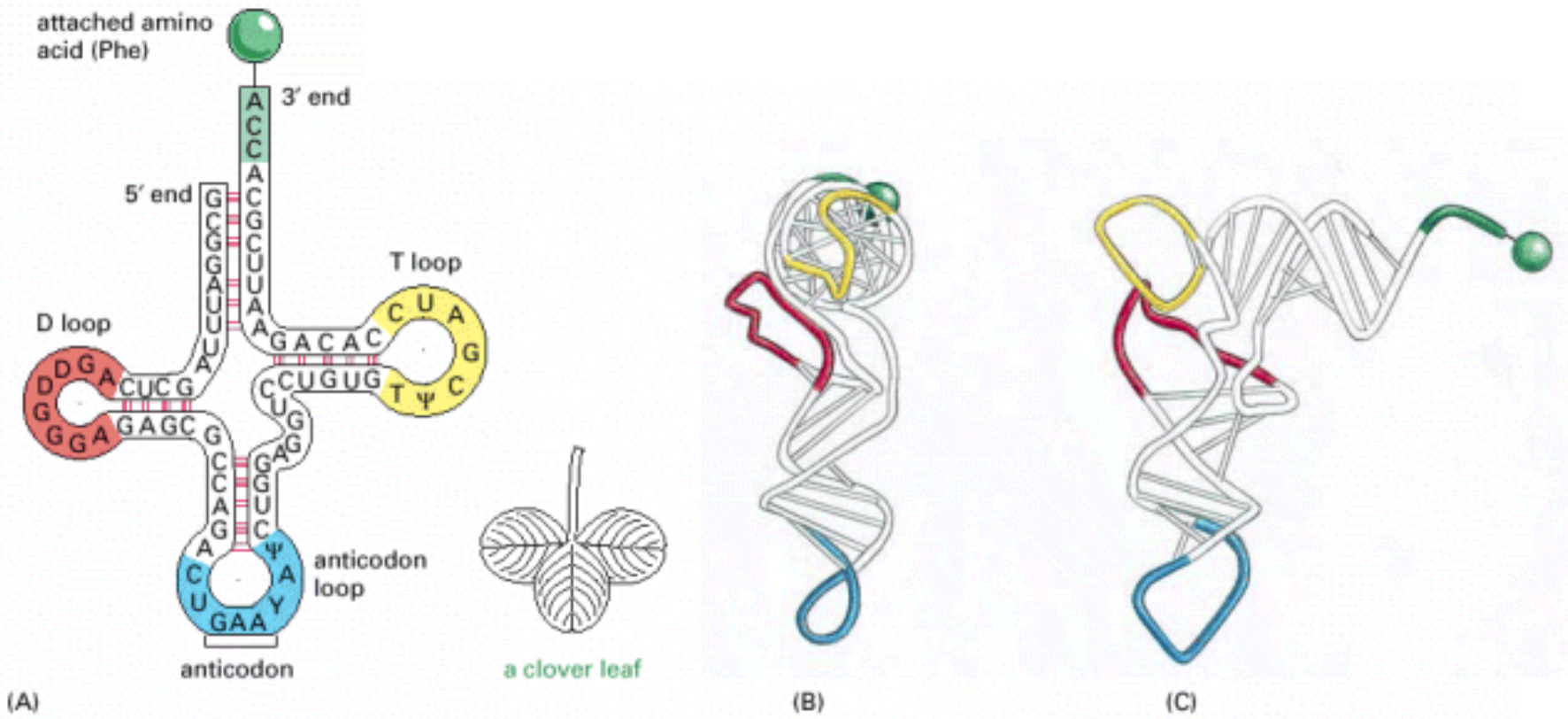


SECOND POSITION

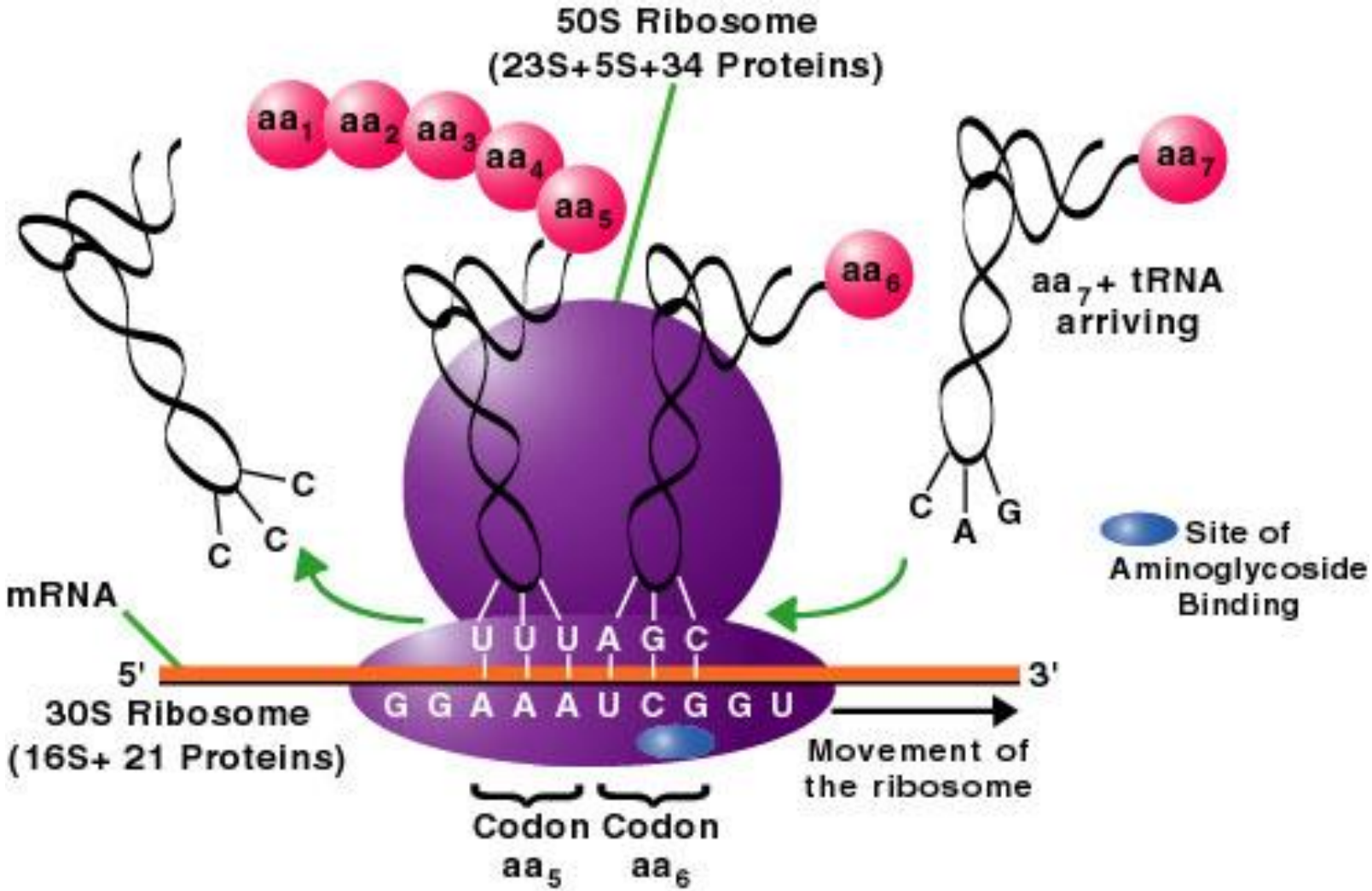
FIRST POSITION	U	C	A	G	THIRD POSITION
U	phenyl-alanine	serine	tyrosine	cysteine	U
					C
	leucine		stop	stop	A
			stop	tryptophan	G
C	leucine	proline	histidine	arginine	U
					C
			glutamine		A
					G
A	isoleucine	threonine	asparagine	serine	U
					C
			lysine	arginine	A
	* methionine				G
G	valine	alanine	aspartic acid	glycine	U
					C
			glutamic acid		A
					G

* and start

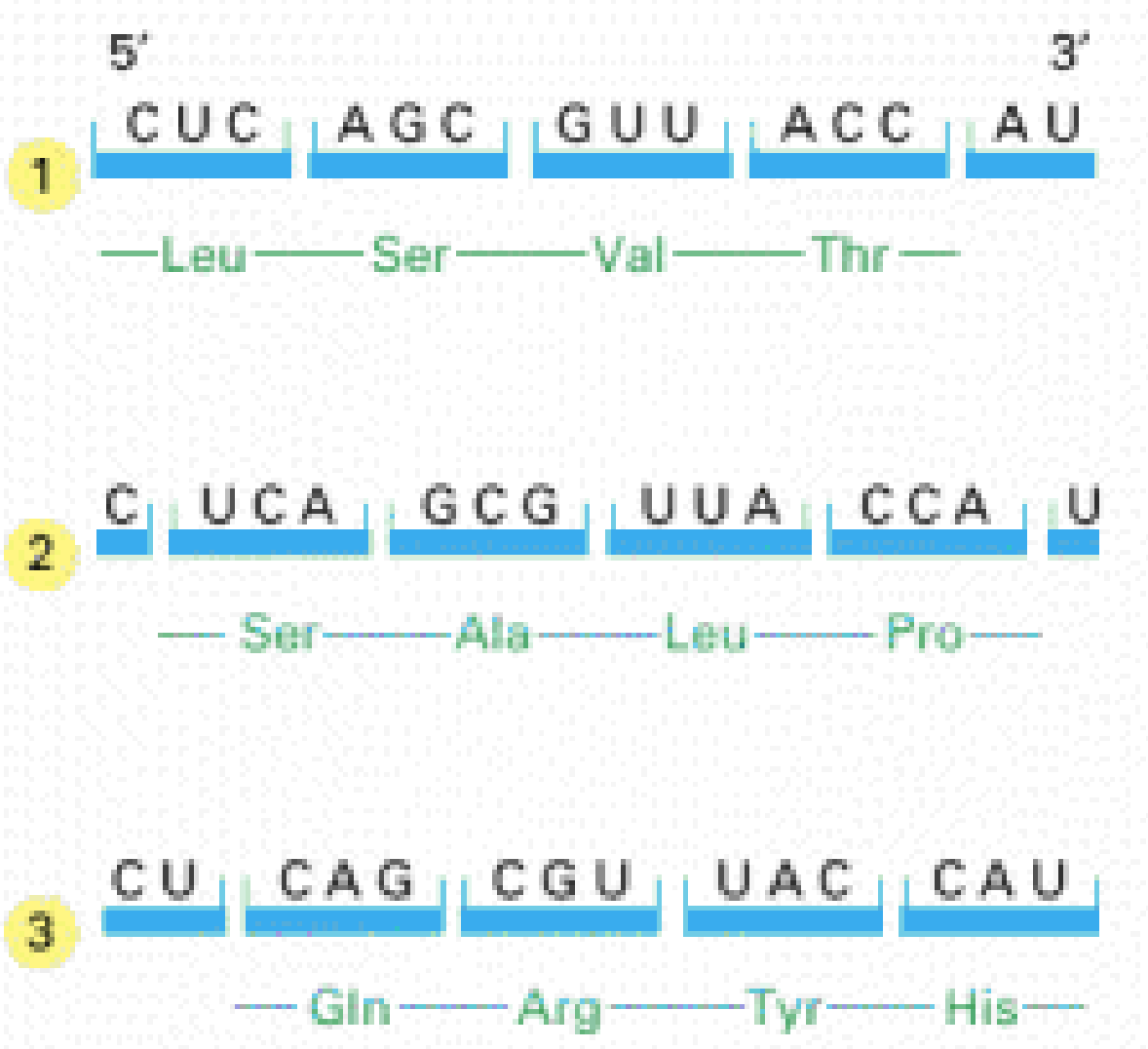
transfer RNA (tRNA)



Ribosome: the protein factory



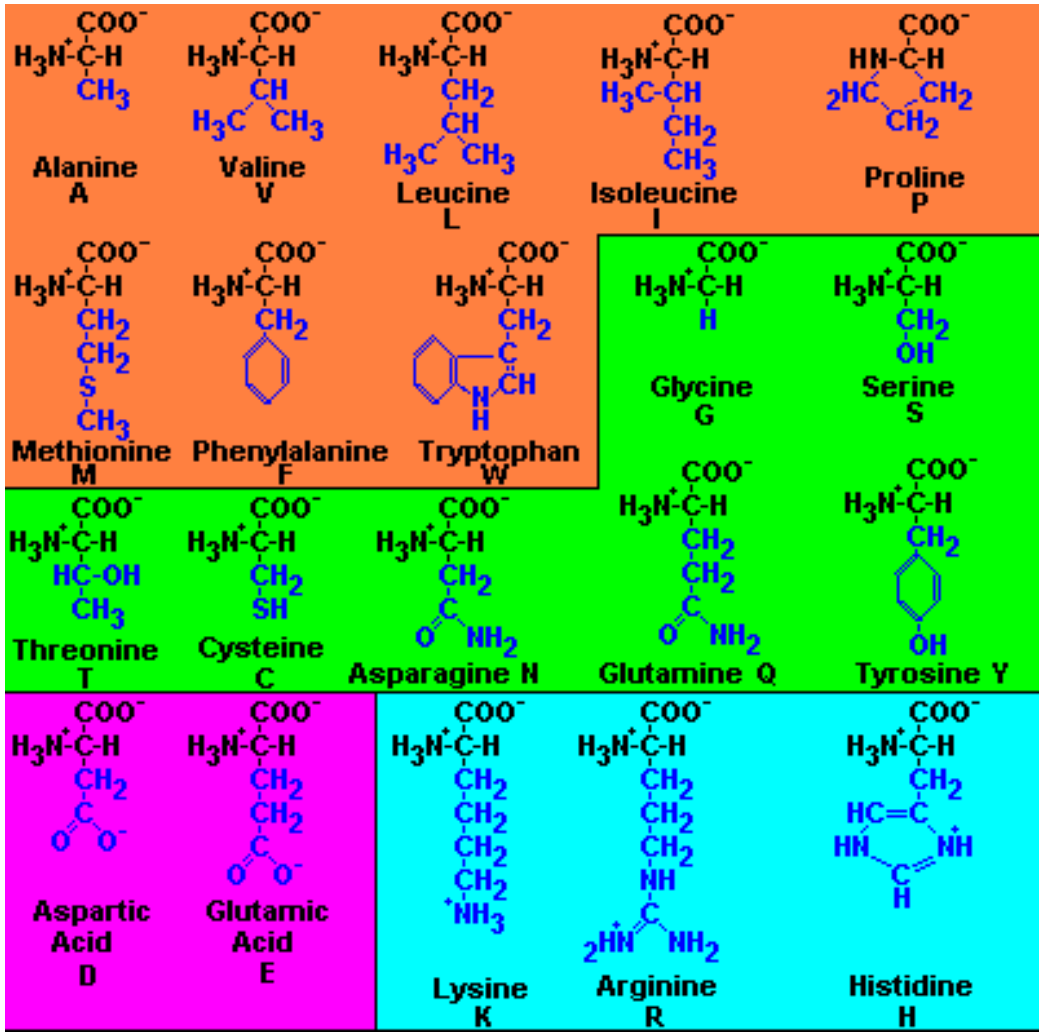
Open Reading frames (ORFs)

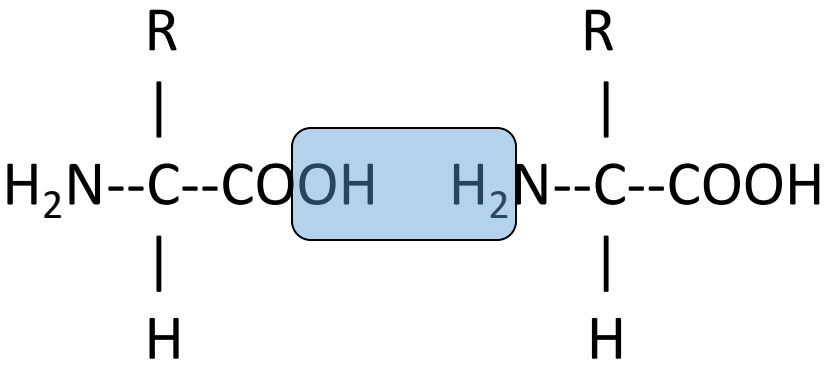


In fact we have 6 open reading frames!

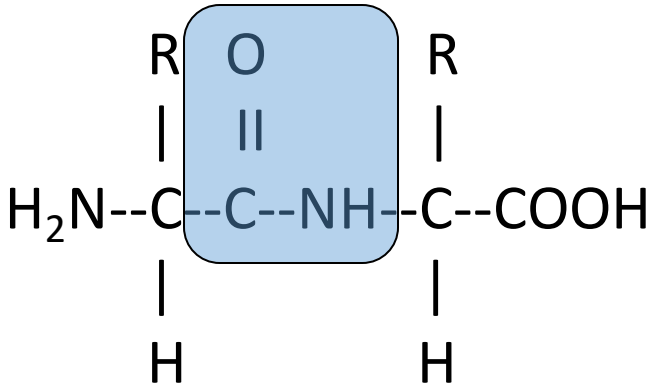
Remember the reverse complement!

Protein molecules



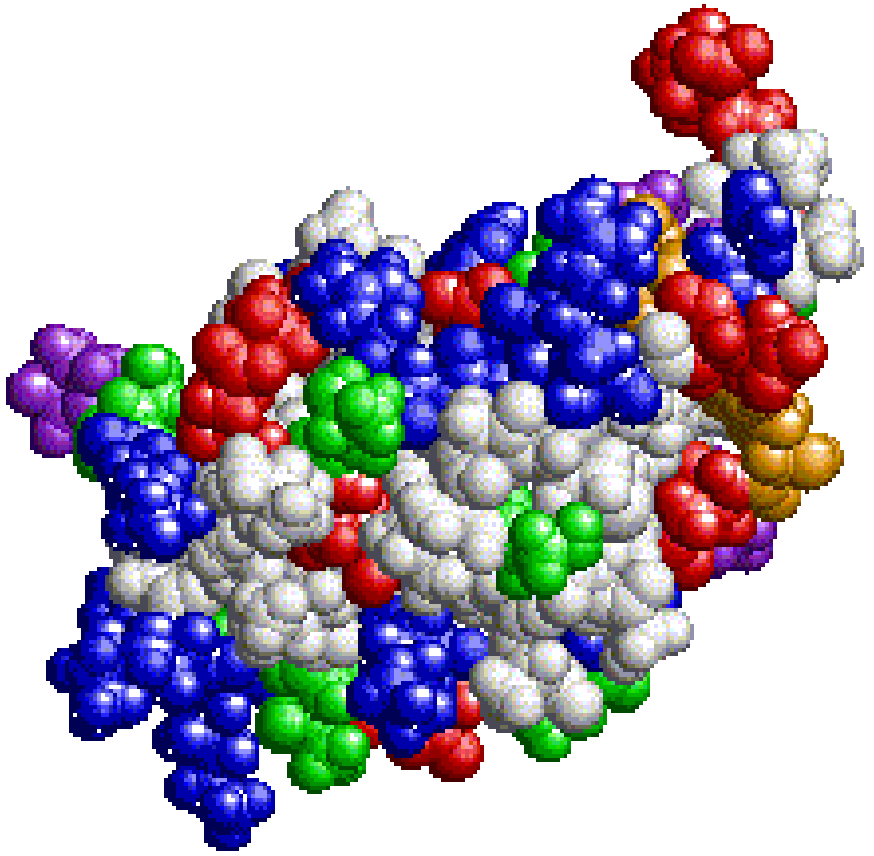


Peptide bond

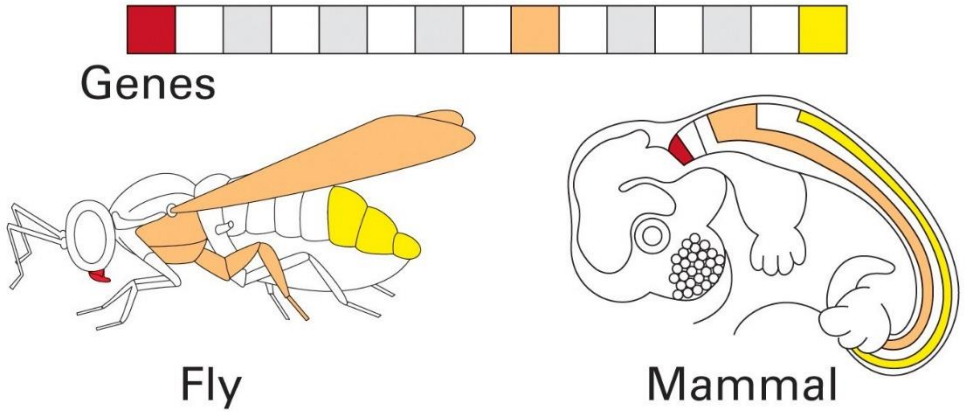


Protein structure-function relationship

- Linear sequence of amino acids folds to form a complex 3-D structure.
- The structure of a protein is intimately connected to its function.



DNA the Genetics Makeup



- Genes are inherited and are expressed
  - **genotype** (genetic makeup)
  - **phenotype** (physical expression)

- On the left, is the eye's phenotypes of green and black eye genes.

Comparative genomics (mammal vs mammal)

- Beta globin chains of closely related species are highly similar:
- Observe simple alignments below:

Human β chain: MVHLT**PE**EK**S**AV**TA**LWGKV N**V**D**E**VGGEALGRLL

Mouse β chain: MVHLT**DA**EK**A**AV**NG**LWGKVN**P**D**D**VGGEALGRLL

Human β chain: VVYPWTQR**F**F**E**SFGDLS**TPD**A**V**MGNPKVKAHGKKV**LG**

Mouse β chain: VVYPWTQR**Y**F**D**SFGDLS**SAS**A**I**MGNPKVKAHGKK V**IN**

Human β chain: AF**S**DGL**A**HLDNLKGTFA**T**LSELHCDKLHVDPENFRLLGN

Mouse β chain: AF**N**DGL**K**HLDNLKGTFA**H**LSELHCDKLHVDPENFRLLGN

Human β chain: **VL**V**C**VL**A**HH**F**GKEFTP**PV**QAA**Y**QKVVAGVA**N**ALAHKYH

Mouse β chain: **MI** V**I** VL**G**HH**L**GKEFTP**CA**QAA**F**QKVVAGVA**S**ALAHKYH

There are a total of 27 mismatches, or (147 – 27) / 147 = 81.7 % identical

Comparative genomics cont. (mammal vs aves)

Human β chain: MVH L TPEEKSAVTALWGKVNVDEVGGEALGRLL

Chicken β chain: MVHWTAEEKQL I TGLWGKVNVAECGAEALARLL

Human β chain: VVYPWTQRFFESFGDLSTPDAVMGNPKVKAHGKKVLG

Chicken β chain: IVYPWTQRFF ASFGNLSSPTA I LGNPMVRAHGKKVLT

Human β chain: AFSDGLAHLDNLKGTFATLSELHCDKLHVDPENFRLLGN

Chicken β chain: SFGDAVKNLDNIK NTFSQLSELHCDKLHVDPENFRLLGD

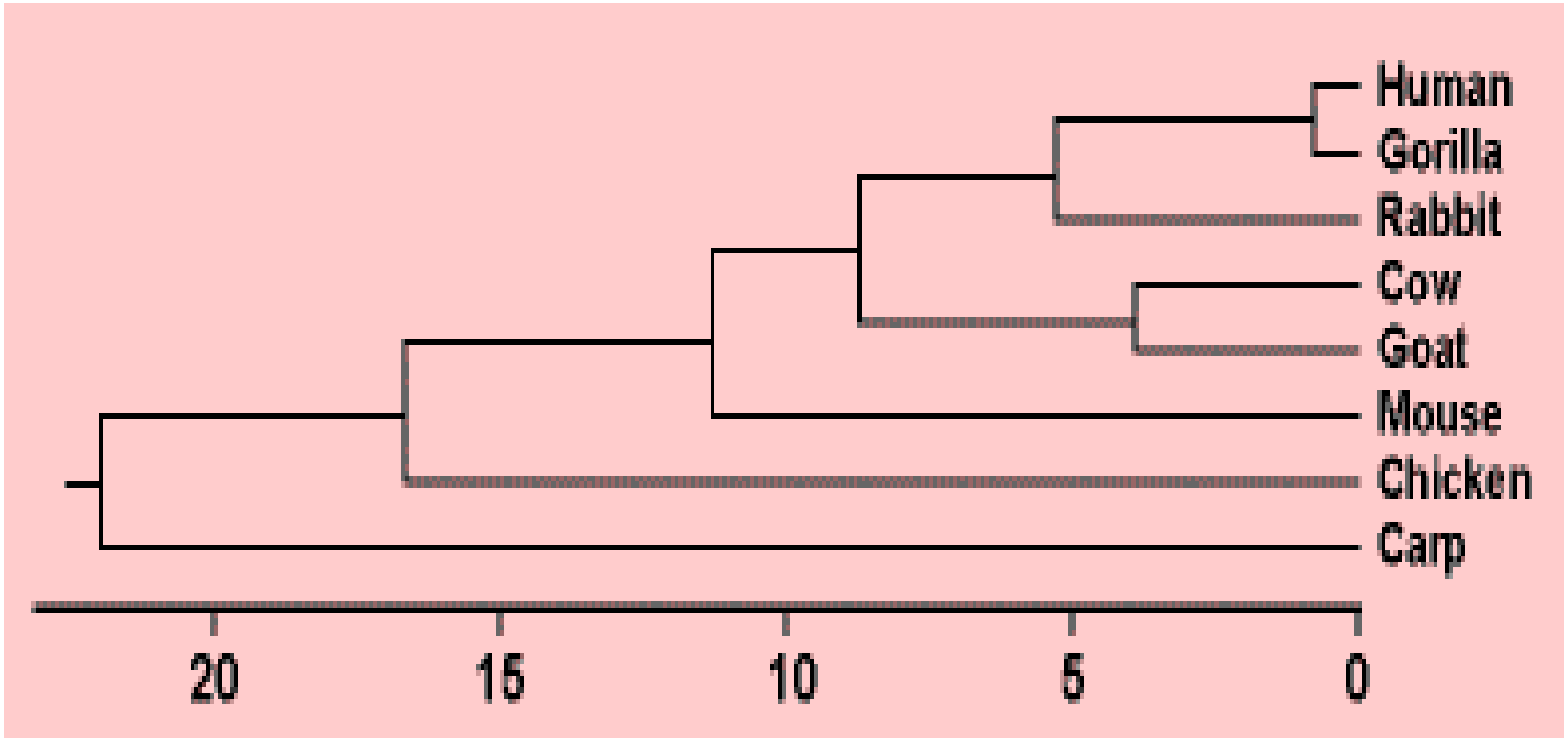
Human β chain: VLVCVLAHHFGKEFTPPVQAAY QKVVAGVANALAHKYH

Chicken β chain: I L I I VLAAHFSKDFTPECQAAWQKLVRVVAHALARKYH

-There are a total of 44 mismatches, or (147 – 44) / 147 = 70.1 % identical

- As expected, mouse β chain is *'closer'* to that of human than chicken's.

Molecular evolution



Phylogenetic tree of Beta globin (Aligned using Clustal, PAM250)

Comparative genomics

- **Which part of the gene/genome has been changed?**
- **How do we tie that to phenotypic change?**

- **Can we compare human and chimp genomes to find what gives us intelligence? Yes!!!**
- **Can we compare healthy human and diseased human to find what genomic changes lead to the disease? Yes!!!**

- **Well, we have to know how to compare sequences first!!!**