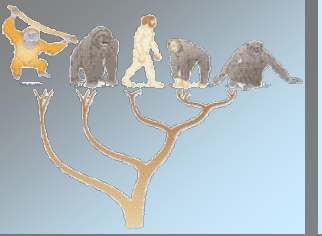
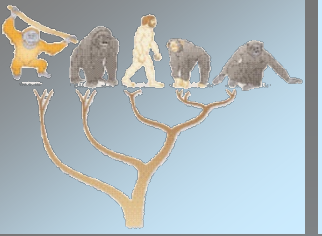


Sequence Analysis and Phylogenetics

Part 1

Sepp Hochreiter



Course no.: 365.060

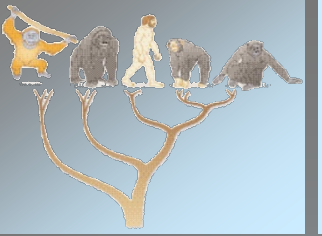
Time/locations: Mon 15:30-17:00, room S2 048

Mode: VL, 2h, weekly

Master Bioinformatics: complementary subject

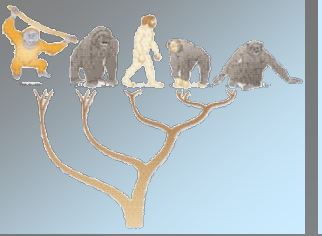
Bachelor Bioinformatics: mandatory subject

➥3 credits (plus 3 credits for exercises)



Biological Chemistry

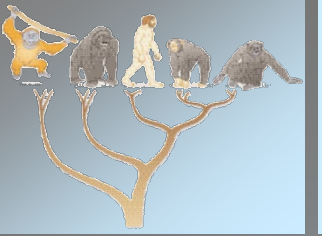
➥3 credits (plus 3 credits for exercises)



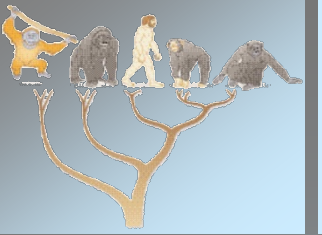
EXERCISE: Sequence Analysis and Phylogenetics

Course no.:	365.062
Lecturer:	Gundula Povysil
Mode:	2 hours, weekly
Time/location:	Fri, 10:15-11:45, room S3 058
Start:	Fri, Oct 6, 2017

3 credits

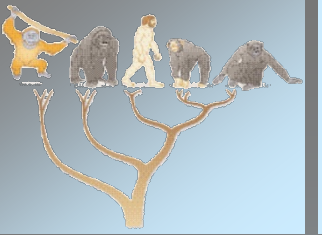


- Examination 4 times during the semester
- Course manuscript: http://www.bioinf.jku.at/teaching/current/ws_sapvl/
- Also videos



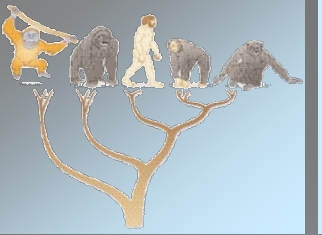
Schedule Bachelor Bioinf 2017 3. Sem.

	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
8:30-9:15		320.102 Topics in Genetics & Evolution, 2KV		347.310 English for Chemistry 1, 2KV	
9:15-10:00					
10:15-11:00			347.311 English for Chemistry 1, 2KV		**365.062 Sequence Analysis and Phylogenetics, 2UE**
11:00-11:45					
12:00-12:45	326.015 Information systems, 2KV / 344.014 Artificial Intelligence, 2VO				
12:45-13:30					
13:45-14:30	344.021 Artificial Intelligence, 1UE	344.023 Artificial Intelligence, 1UE	347.334 Chemie für Physiker II, 2VO		
14:30-15:15	344.022 Artificial Intelligence, 1UE				
15:30-16:15	**365.060 Sequence Analysis and Phylogenetics, 2VL**				
16:15-17:00					
17:15-18:00	347325 English for Chem. 1, 2KV	320.011 Bioanalytics I, 2VO			
18:00-18:45				347308 English for Chemistry 1, 2KV	
19:00-19:45					



Schedule Master Bioinf. 1. Semester

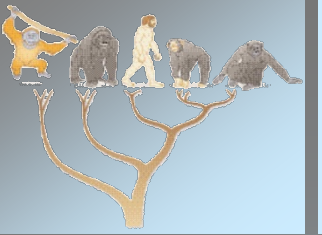
	MONDAY		TUESDAY		WEDNESDAY			THURSDAY		FRIDAY
8:30-9:15			ComplS 342.208 Logic, 2VL		ComplS 365.064 Num. & Symb. Methods 2, 2KV		ComplS 353.005 engl Systemnahe Programmierung, 2PR	ComplS 326.011 Algorithmen und Datenstrukturen,, 2KV		
9:15-10:00										
10:15-11:00			ComplS 366.554 Statistik 2, 2KV	ComplS 342.209 Logic, 1UE	ComplS 376.022 Basics in Chemistry Bioinf., 1KV	ComplS 376.022 Basics in Chemistry Bioinf., 1KV	ComplS 343.324 Software Engineering, 2VO	365.076 Machine Learning: Supervised Techniques, 1UE		ComplS 365.062 Seq. Analysis & Phylogenetics, 2UE
11:00-11:45										
12:00-12:45	ComplS 344.014 Artificial Intell., 2VL	ComplS 326.015 InSysteme, 2KV						ComplS 353.068 Comp. Forensics and IT Law, 2VL		
12:45-13:30										
13:45-14:30	ComplS 340.023 Algorithmen u. Datens. 2, 2VL	ComplS 351.001 InSysteme 1, 2VL			ComplS 347.334 Chemie für Physiker II, 2VL	ComplS 364.028 Visual Analytics, 2VL	ComplS 343.302 Software Engineering, 1UE	ComplS 351.003 or 351.004 Info-systeme 1, 2UE		
14:30-15:15										
15:30-16:15	ComplS 365.060 Sequence Analysis and Phylogenetics, 2VL				365.075 Machine Learning: Supervised Techniques, 2VL		ComplS 343.303 Software Engineering, 1UE	ComplS 351.002 & 351.005 Info-ssysteme 1, 2UE	365.074 Basic Methods of Data Analysis, 2KV	
16:15-17:00										
17:15-18:00	ComplS 320.007 Molekulare Bio. I, 2VL						ComplS 343.309 Software Eng., 1UE			
18:00-18:45										



Schedule Bachelor Bioinf 2016 3. Sem.

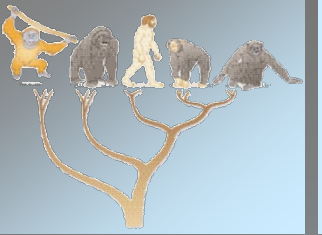
➥Bioanalytics I (1UE, 470WEBIBA1U14):

The course will be given on the first two days of February 2018

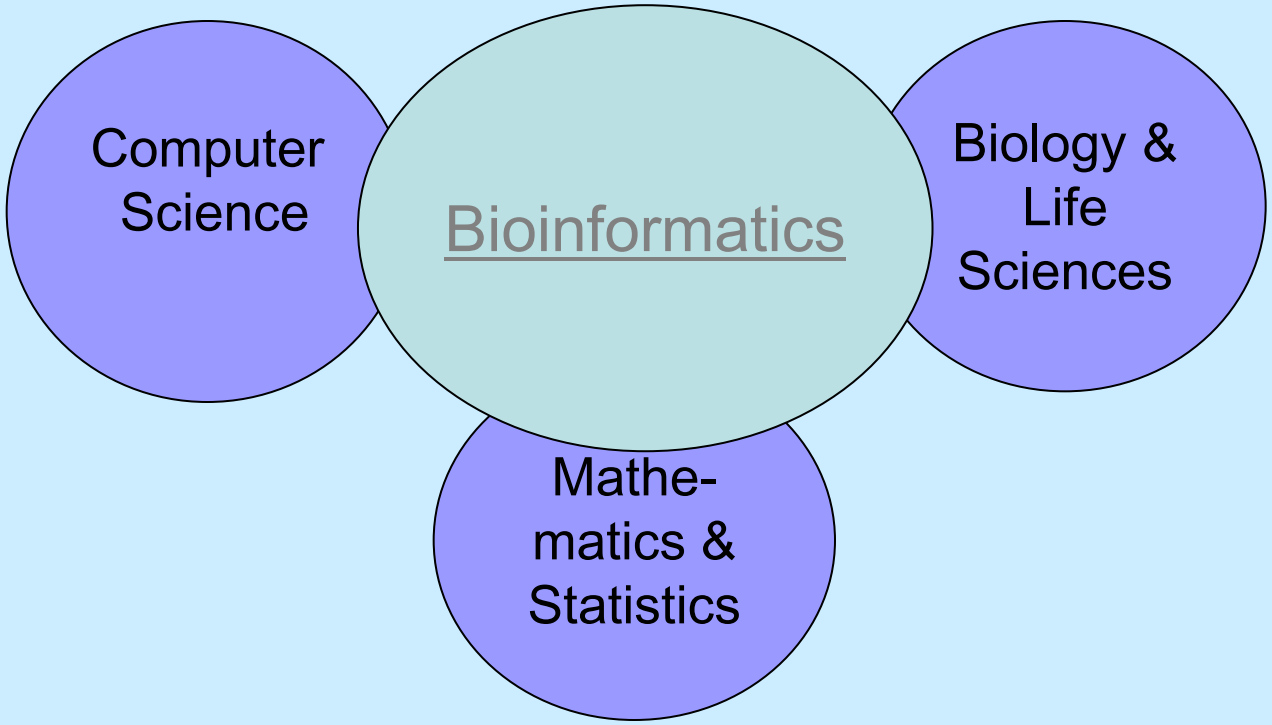


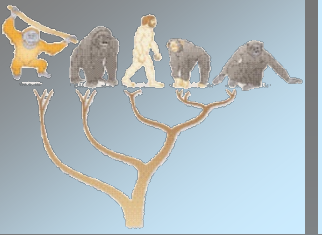
What is Bioinformatics?

- Interface of biology and computers
- Analysis of proteins, genes and genomes using computer algorithms and computer databases
- Analysis and storage of the billions of DNA base pairs that are sequenced by genomics projects



What is Bioinformatics?

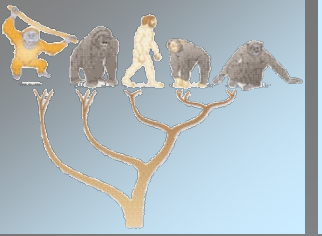




What is Bioinformatics?

- "Bioinformatics is a new subject of genetic data collection, analysis and dissemination to the research community." *Hwa A. Lim (1987)*

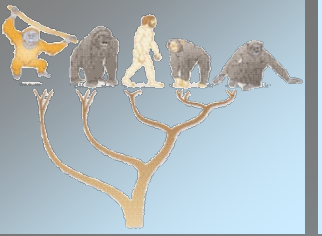
- *"Bioinformatics:* Research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral or health data, including those to acquire, store, organize, archive, analyze, or visualize such data." *NIH working definition (2000)*



What is Bioinformatics?

http://en.wikipedia.org/wiki/Bioinformatics (2010)

- creation and advancement of databases, algorithms, computational and statistical techniques, and theory to solve formal and practical problems arising from the management and analysis of biological data.
- mapping and analyzing DNA and protein sequences, aligning different DNA and protein sequences to compare them and creating and viewing 3-D models of protein structures.
- focus on developing and applying computationally intensive techniques (e.g., pattern recognition, data mining, machine learning algorithms, and visualization)
- Major research efforts in the field include sequence alignment, gene finding, genome assembly, protein structure alignment, protein structure prediction, prediction of gene expression and protein-protein interactions, genome-wide association studies and the modeling of evolution.



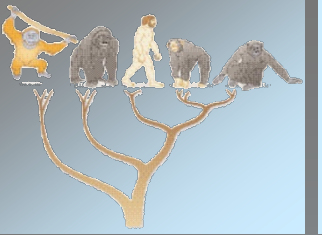
What is Bioinformatics?

http://en.wikipedia.org/wiki/Bioinformatics (2014)

Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data. As an interdisciplinary field of science, bioinformatics combines computer science, statistics, mathematics and engineering to study and process biological data.

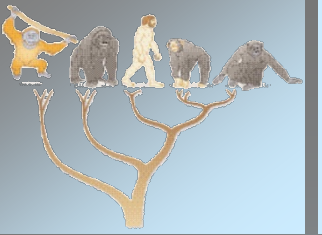
http://en.wikipedia.org/wiki/Bioinformatics (2016)

Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data. As an interdisciplinary field of science, bioinformatics combines computer science, statistics, mathematics, and engineering to analyze and interpret biological data.



Questions Answerd by Bioinformatics

- From where came the first human?
- Is Anna Anderson the tsar‘s daughter Anastasia?
- Are the neanderthals the ancestors of the humans?
- What are the evolutionary relationships between species?



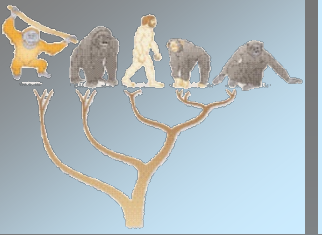
homo erectus

homo sapiens

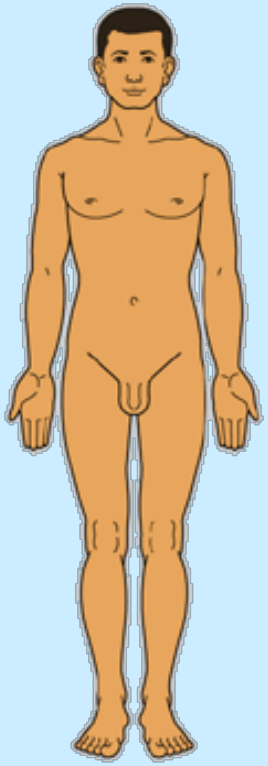
Is Anna Anderson the tsar‘s daughter Anastasia Romanov?

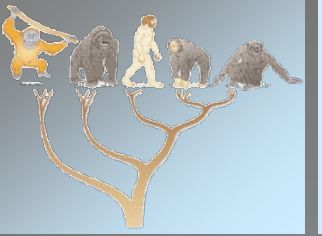
Anastasia (1909)
and
Anna Anderson (1959)

The kids of
the tsar



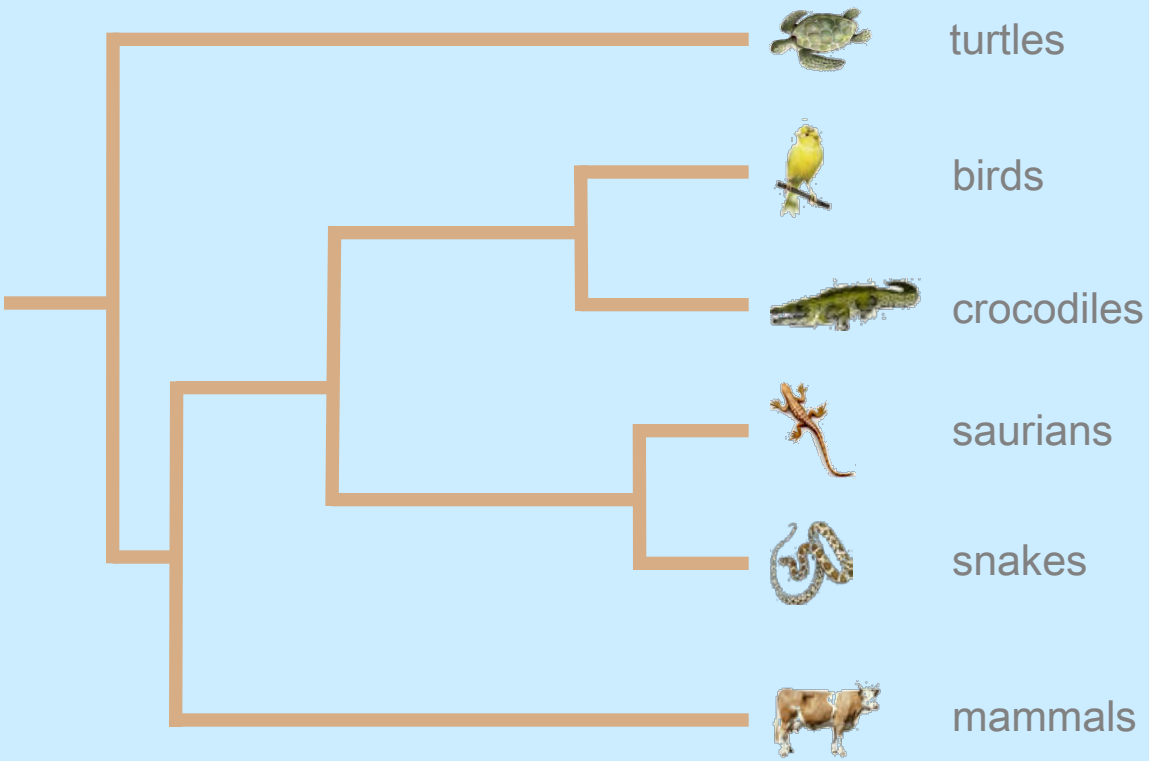
Are the neanderthals / homo erectus the human ancestors or a different species?

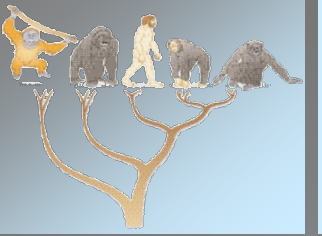




Phylogeny: history of species

Phylogenetic knowledge: evolutionary trees

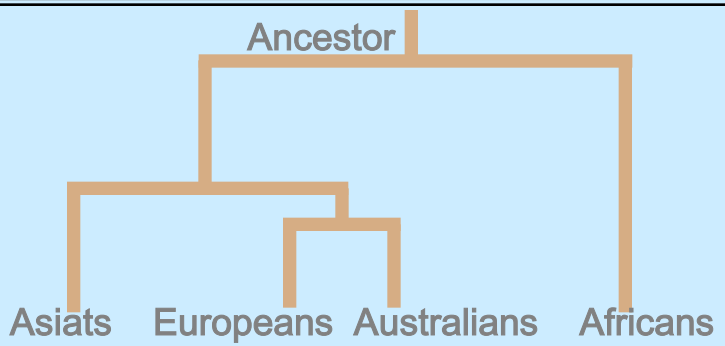




Three Anwers

➥From where came the first human?

Africa!



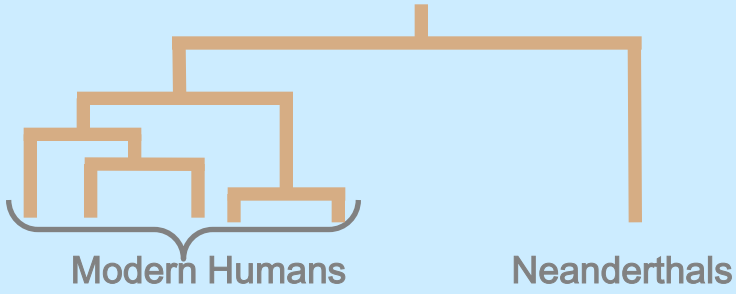
➥Is Anna Anderson the tsar‘s daughter Anastasia?

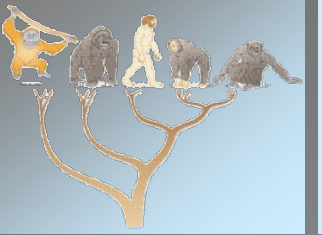
No!

	91 106	324 337
Anna Anderson	CCACCATGAATATTGC	TAGTCAAATCCCTT
Carl Maucher (Grand nephew F. Schanzkowska)	CCACCATGAATATTGC	TAGTCAAATCCCTT
Prince Philip (Grand nephew zar)	TCACCATGAATATTGT	CAGTCAAATCCCTC

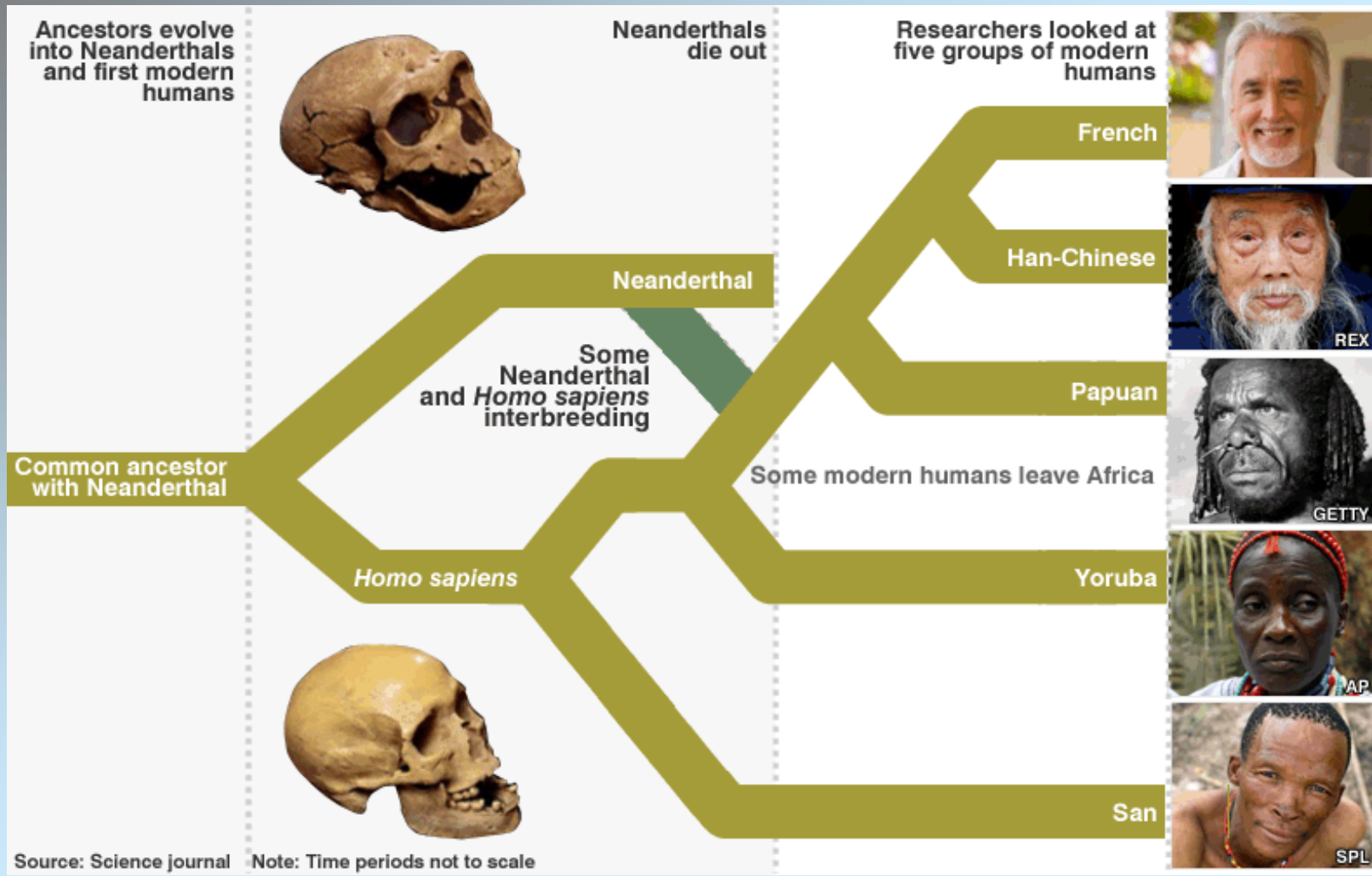
➥Are the neanderthals the ancestors of the humans?

No! Separate Species

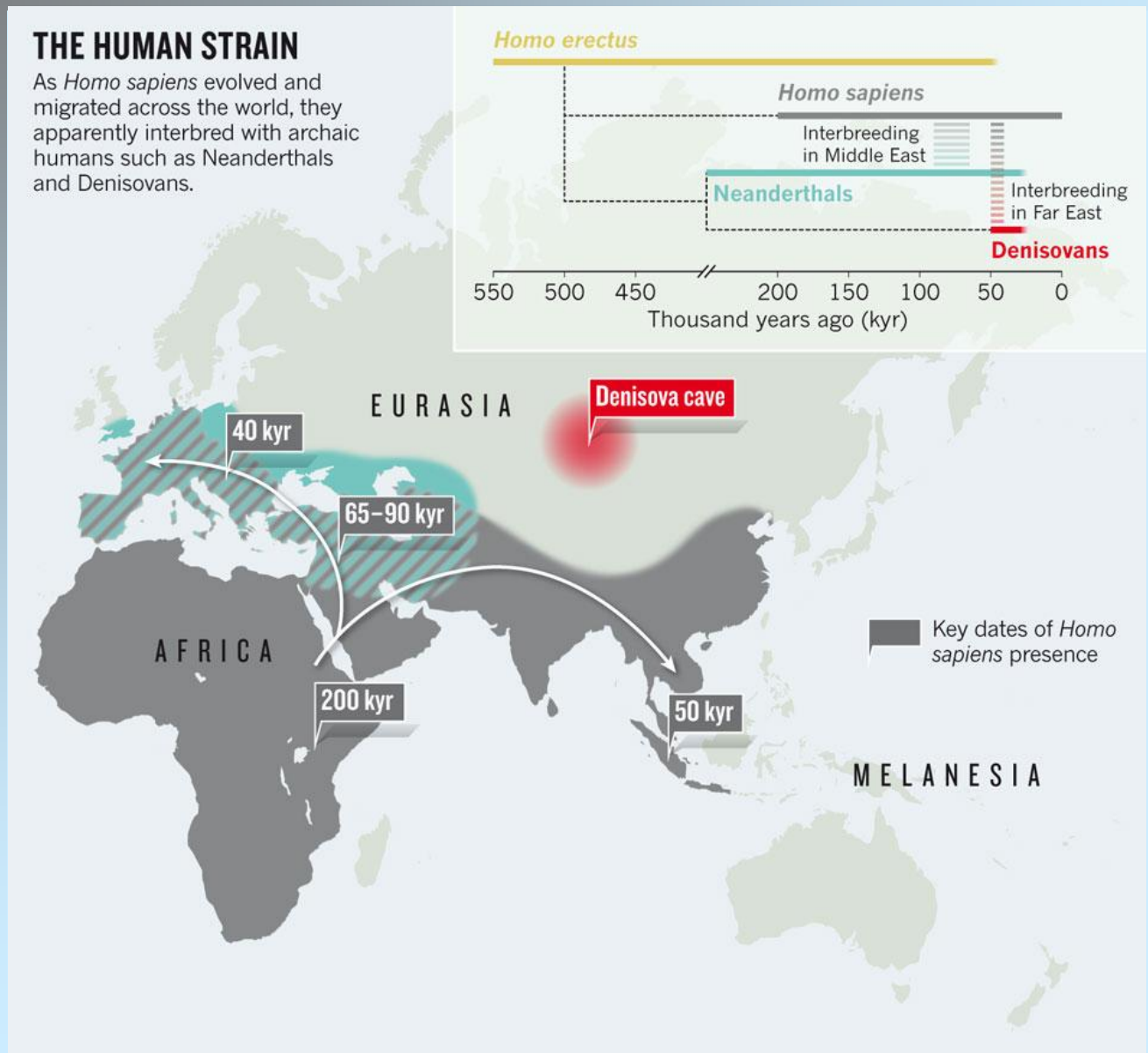


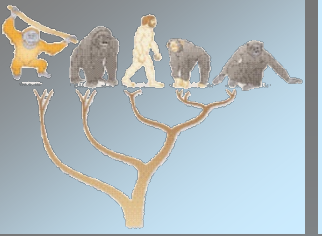


Actual Research



Actual Research





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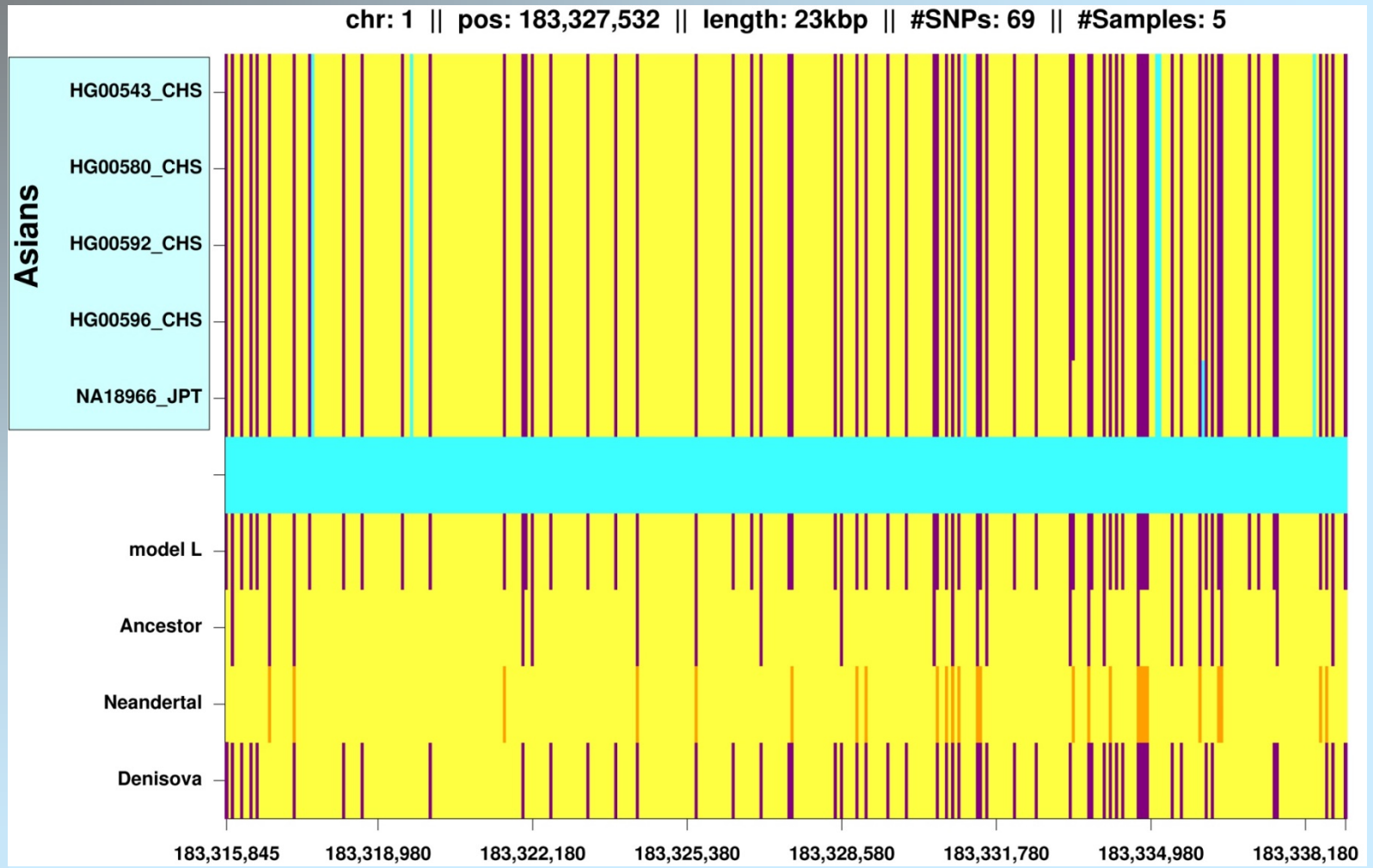

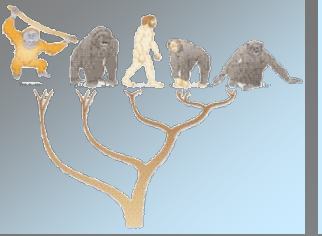

Literature

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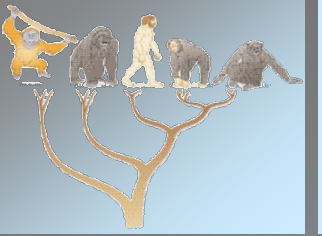
- Blast: http://www.ncbi.nlm.nih.gov/BLAST/tutuotial/Altschul-1.html



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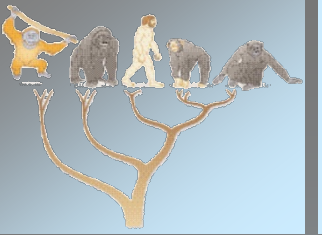

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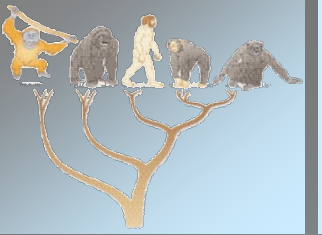

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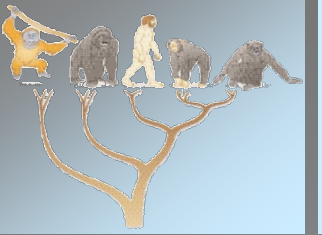
3.3.3 Fast Approximations: FASTA, BLAST and BLAT
3.4 Alignment Significance
3.4.1 Significance of HSPs
3.4.2 Significance of Perfect Matches



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4.3.3 Other Multiple Alignment Algorithms
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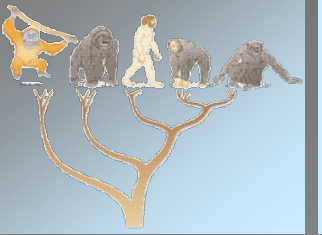

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5.3.2 Least Squares
5.3.3 Minimum Evolution
5.3.4 Neighbor Joining
5.3.5 Distance Measures
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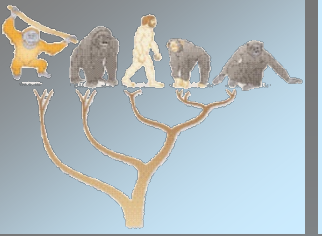

Biological Basics

1 Biological Basics
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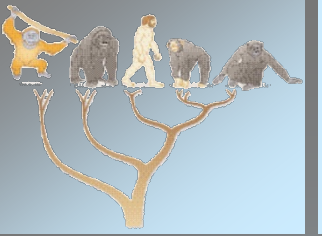
1.9 Translation
1.9.1 Initiation
1.9.2 Elongation
1.9.3 Termination
1.10 Folding

Bioinformatics processes data from molecular biology

Molecular biology attempts at discovering the principles of the cell which is the largest unit all lifeforms have in common



The Cell

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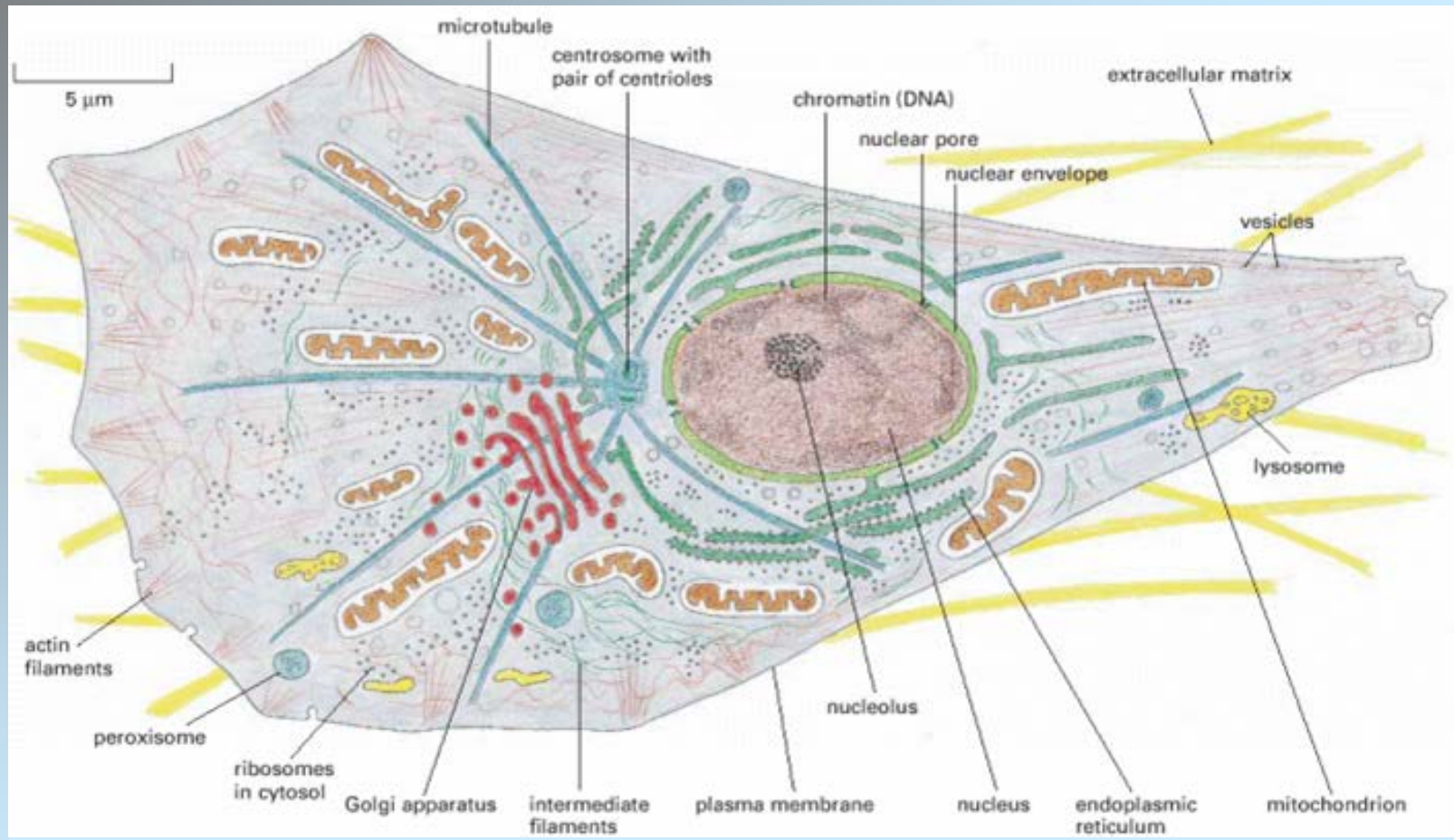

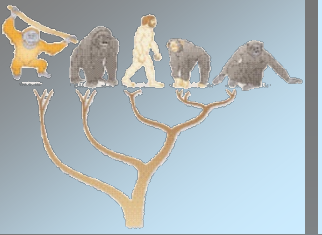

Organelles

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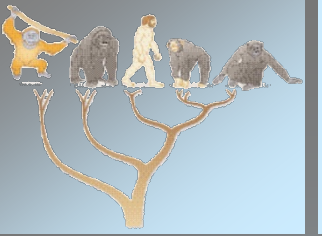
- **nucleus**: eukaryotes - a cell's information center →chromosomes, DNA
- **nucleolus**: ribosome subunits assembly
- **mitochondria** and **chloroplast**s: the power generators (oxidative phosphorylation, photosynthesis); own genome from mother
- **endoplasmic reticulum** (ER): eukaryotes - transport network for certain modifications and specific destinations; rough ER has ribosomes on its surface and secretes proteins into the cytoplasm
- **golgi apparatus:** eukaryotes - process & pack macromolecules; vesicles
- **ribosomes**: RNA/protein complex that synthesizes proteins from mRNA
- **lysosomes**: enzymes (acid hydrolases) that digest old organelles, food particles, and engulfed viruses or bacteria
- **peroxisomes**: rid the cell of toxic peroxides
- **centrosome**: cytoskeleton, microtubules for directing the transport through ER and golgi apparatus
- **vacuoles**: store food and waste



The Cell

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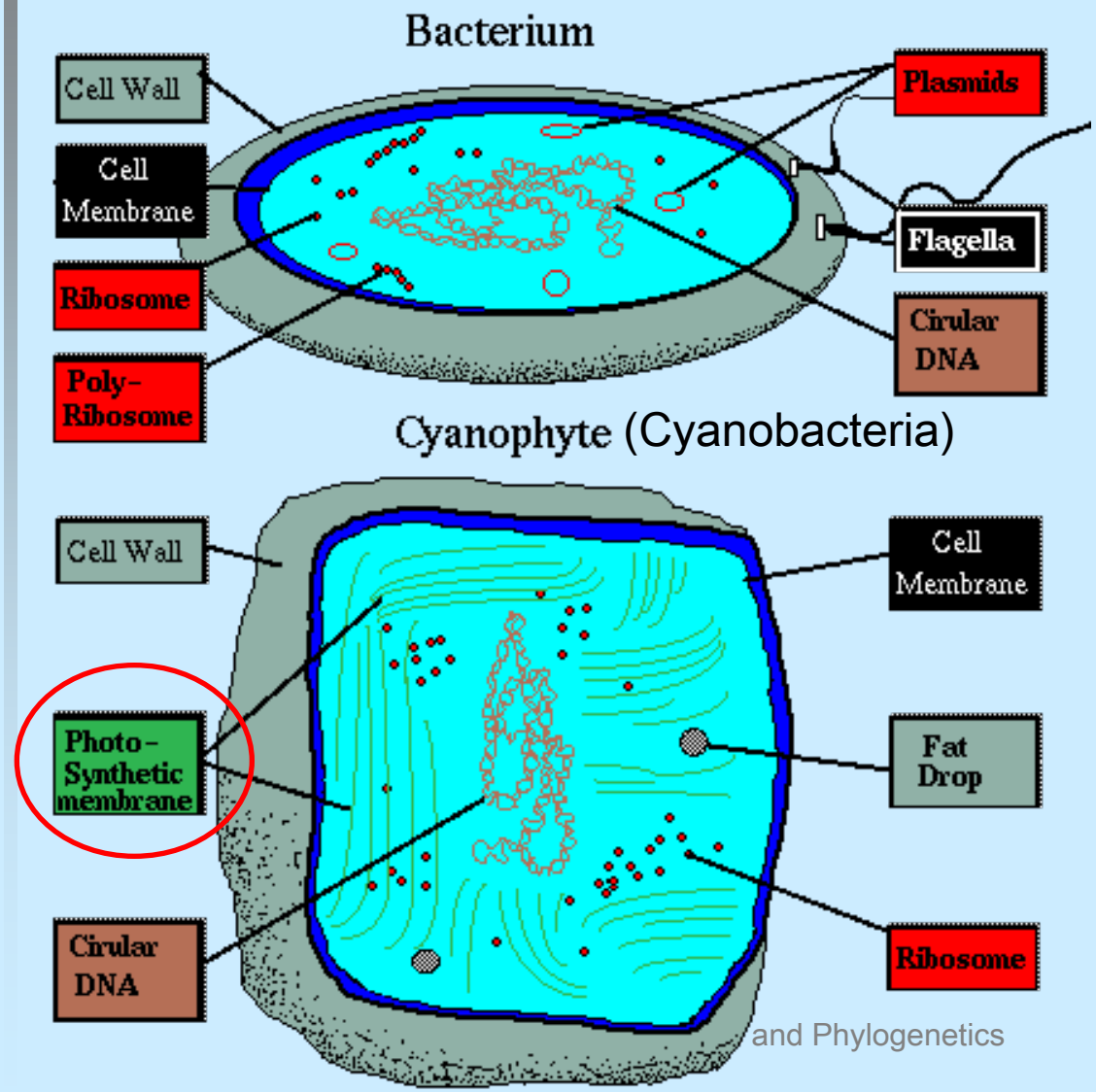
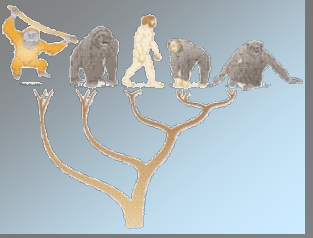


Eukaryotic cells possess a nucleus (plants, vertebrates)

Prokaryotic cells do not possess a nucleus (bacteria, archaea)



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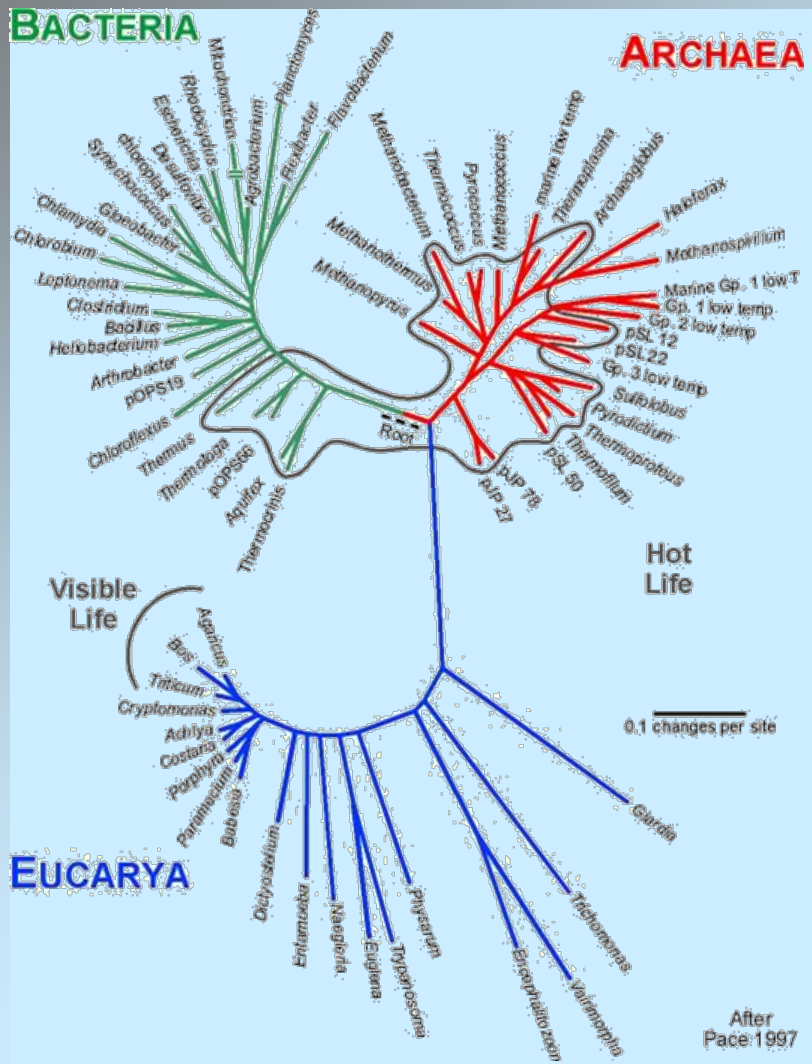

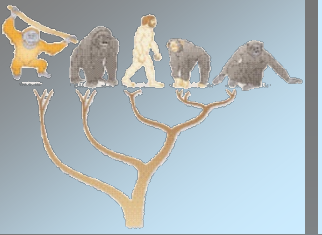

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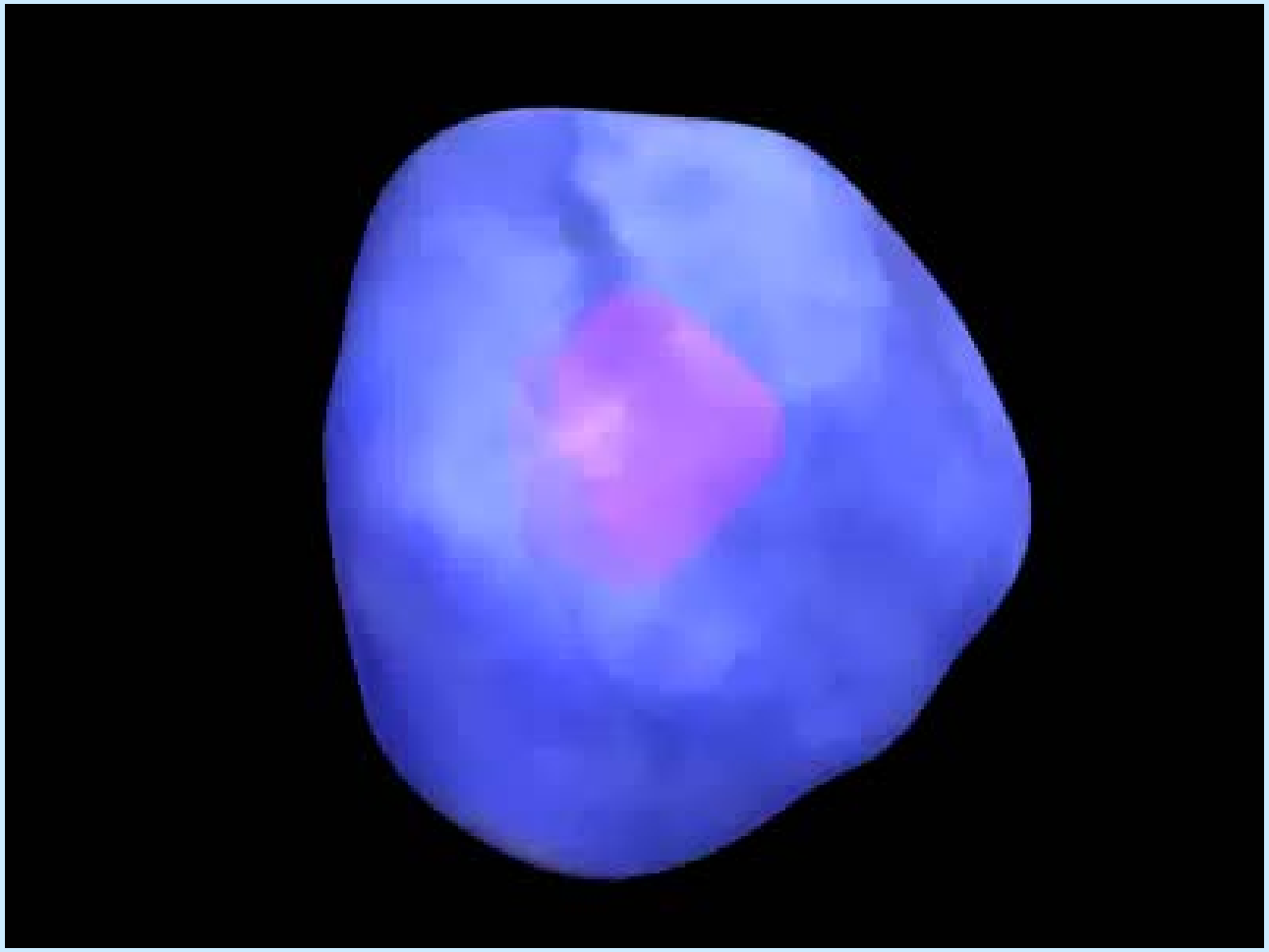
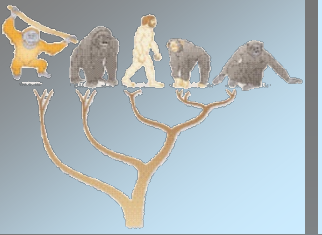


Cell surface



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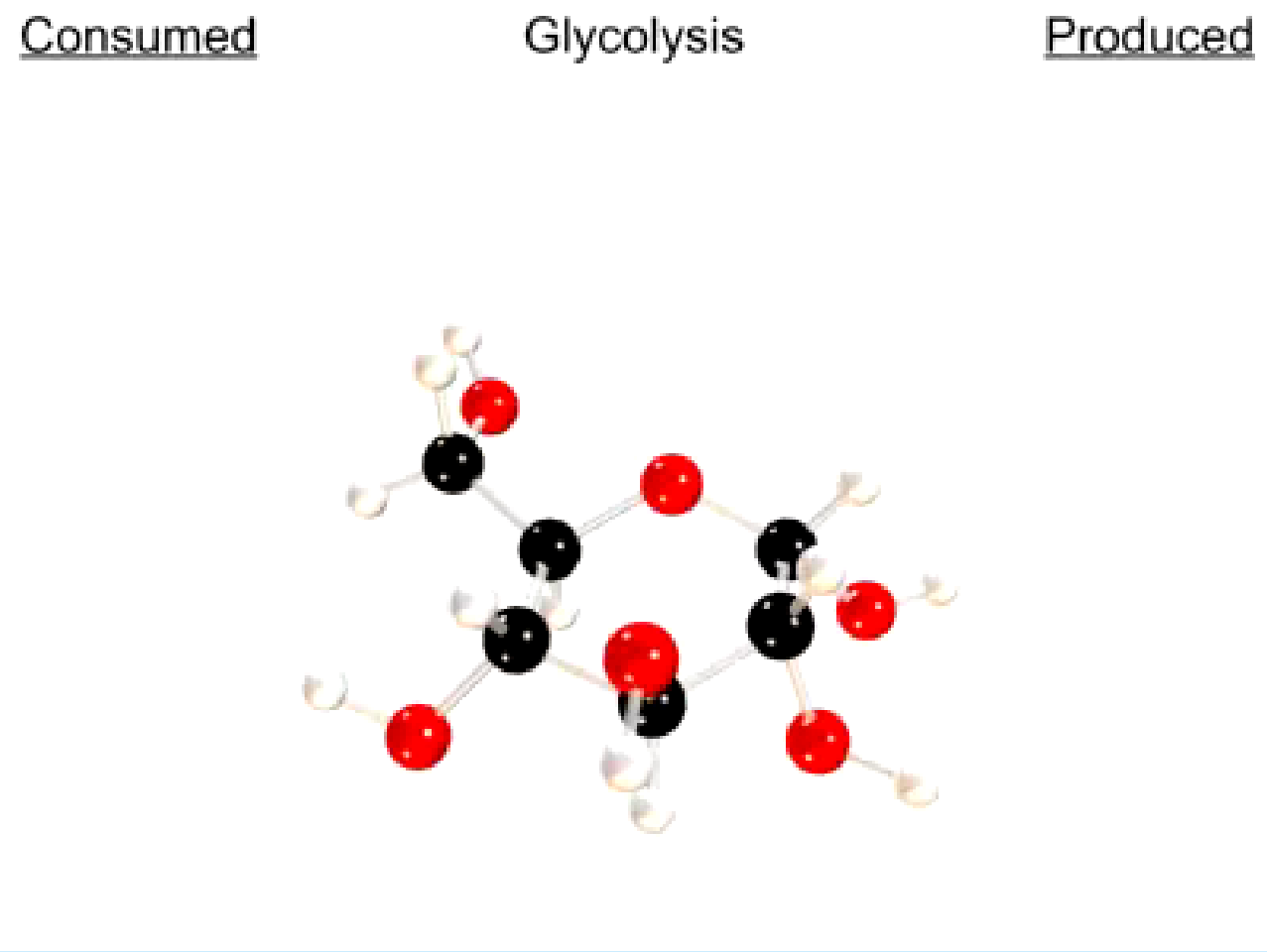
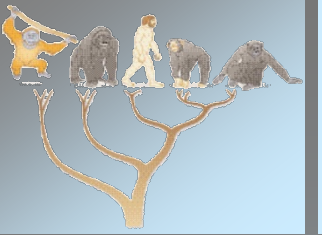


Glycolisis



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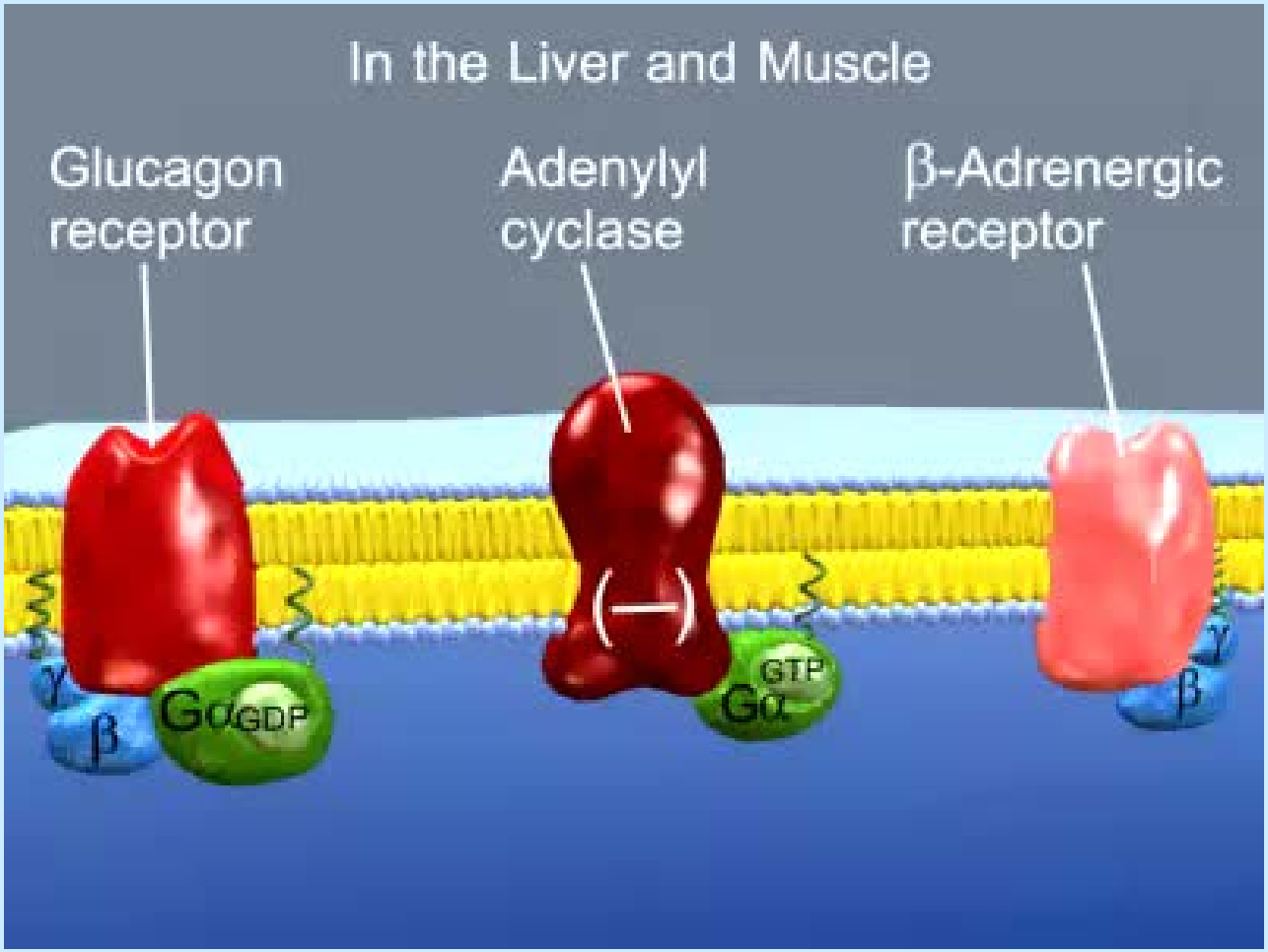
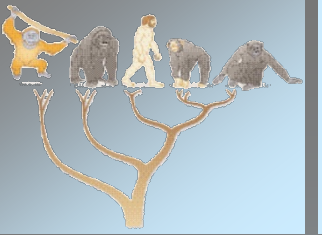


Pathway glycogen



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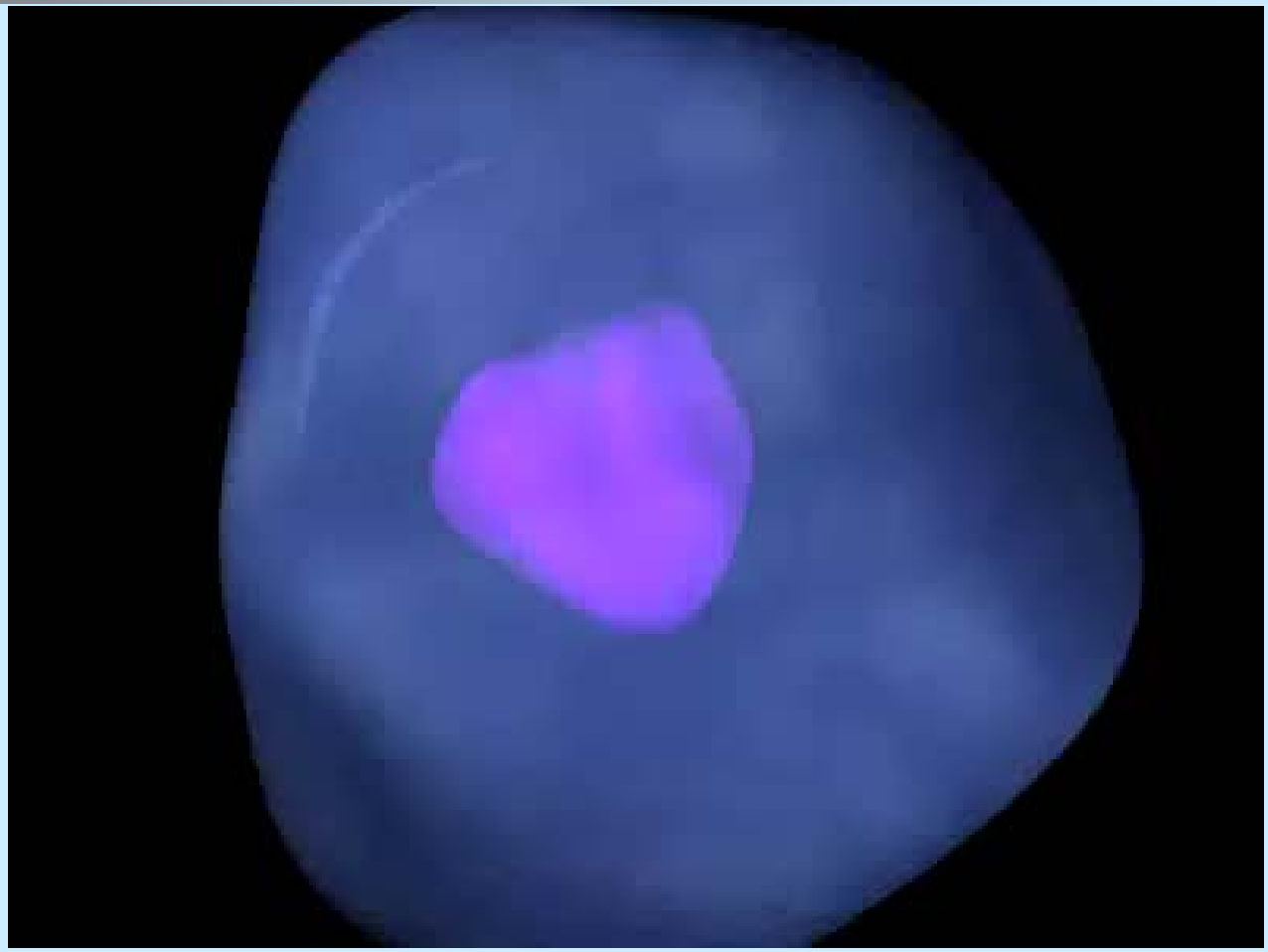
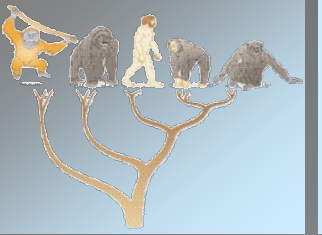


Pathway hormone



Central Dogma

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How are the nano-machines in the cell constructed?

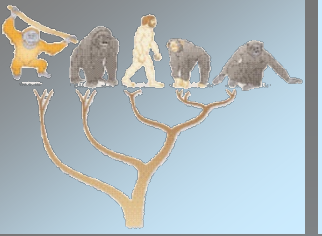
↪These machines are proteins or protein-RNA complexes

Where is the information about these machines stored?

↪Everything is stored in the DNA

How is the information in the DNA used to build proteins?

↪Central dogma: DNA ➔ RNA ➔ Proteins



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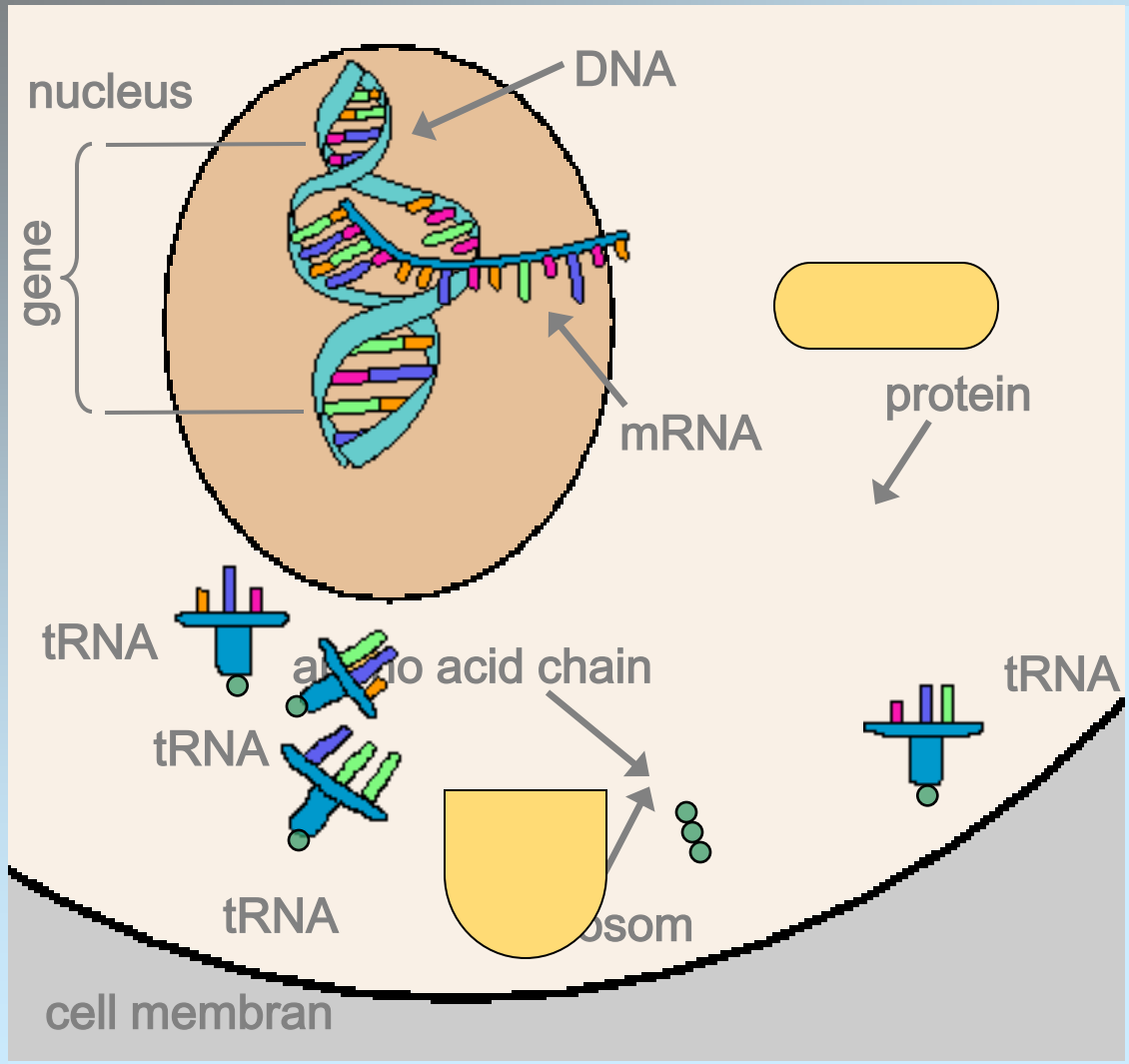
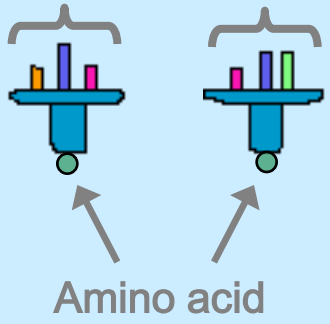
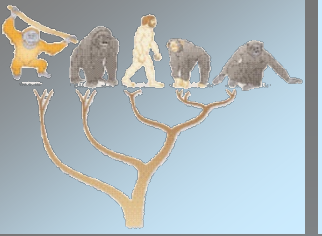


1. **transcription** (mRNA)
2. transport
3. **translation** (ribosom, tRNA)
4. folding (protein)

codons/basetriplets





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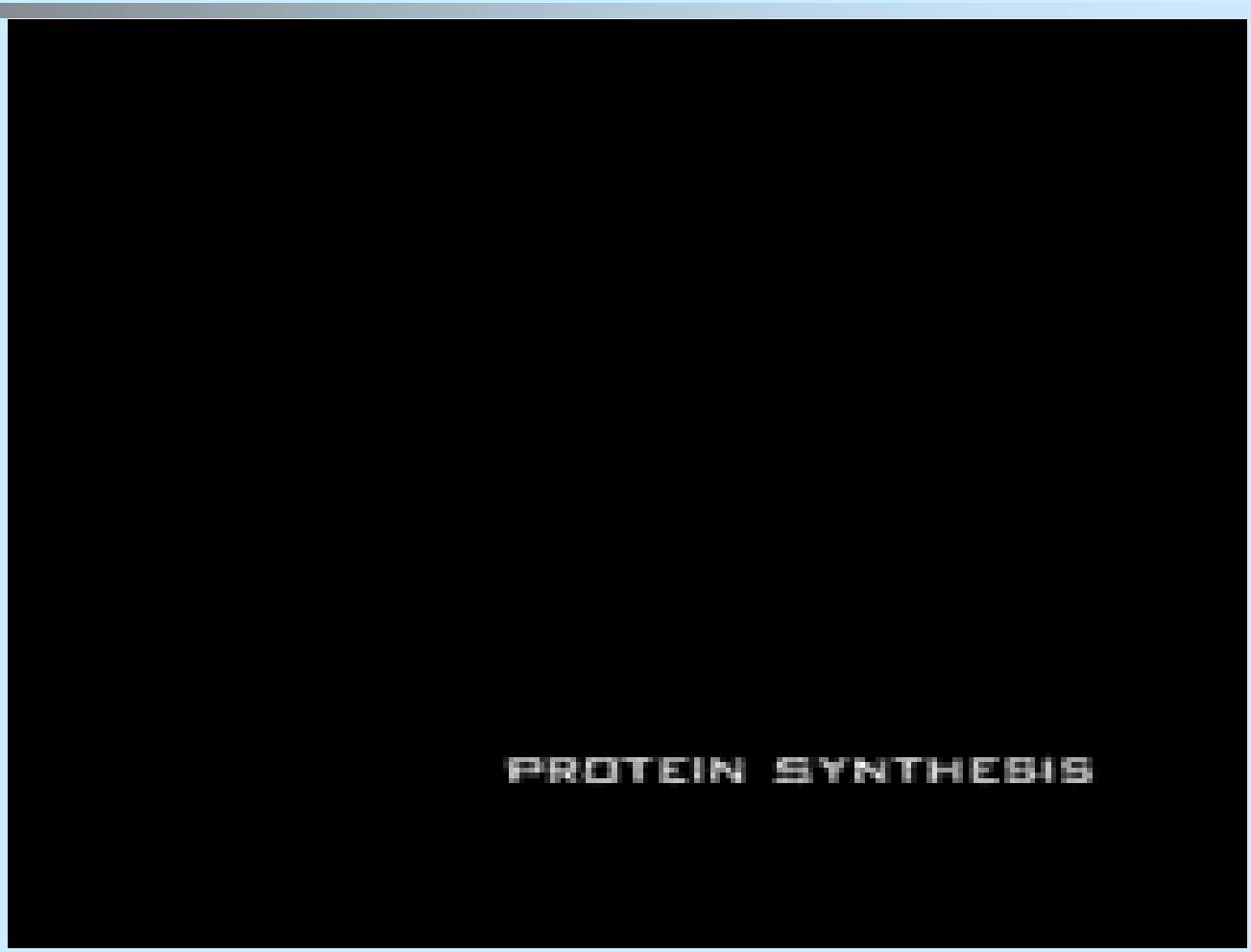
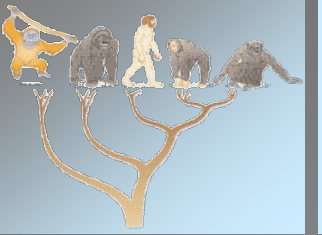


Dogma



DNA

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Deoxyribonucleic acid (DNA) codes all information of life

➥double helix as sequence of nucleotides with a deoxyribose

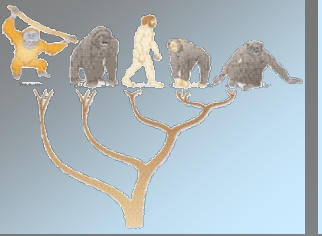
➥ends are called 5' and 3‘; DNA is written from 5' to 3‘

➥upstream is towards the 5' end downstream towards the 3'

➥5 nucleotides (nucleobases, bases): adenine (A), thymine (T), cytosine (C), guanine (G), and uracil (U)

➥first 4 in DNA whereas uracil in RNA instead of thymine

➥two classes: purines (A, G) / pyrimidines (C, U, T)



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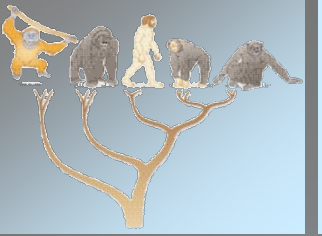
- hydrogen bonds between purines and pyrimidines
- base pairs: A—T and C—G
- each helix of the DNA is complementary to the other



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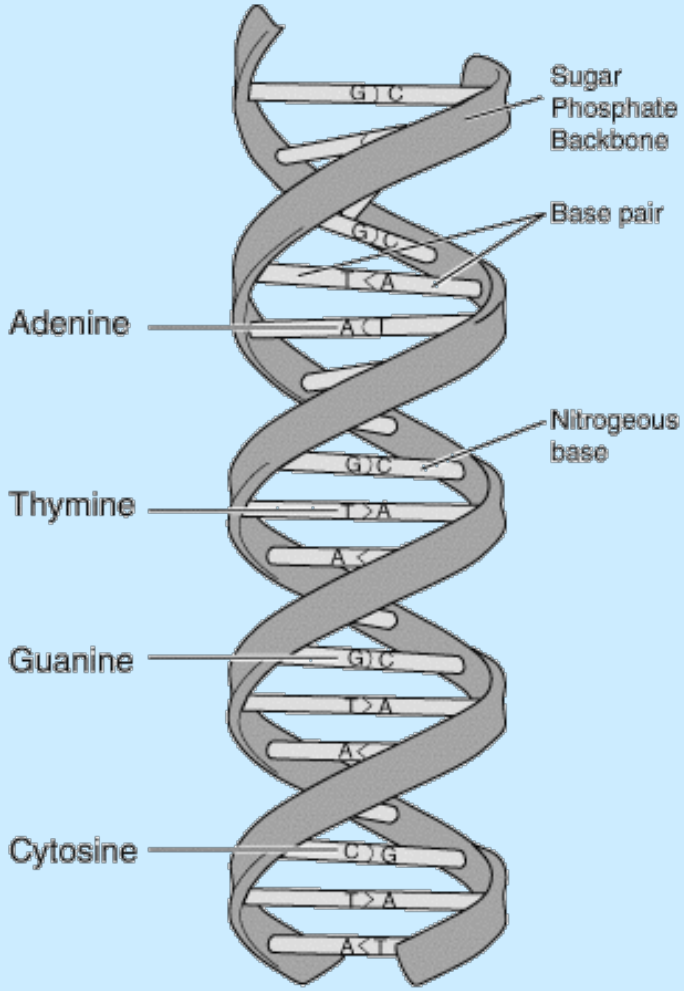

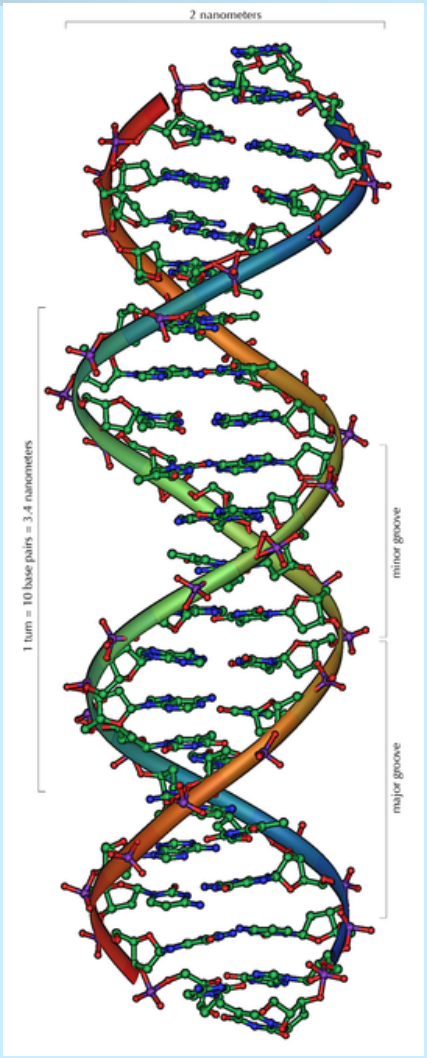

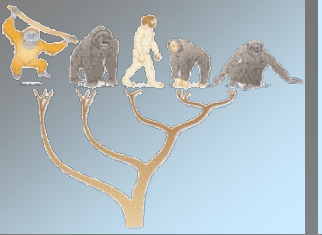

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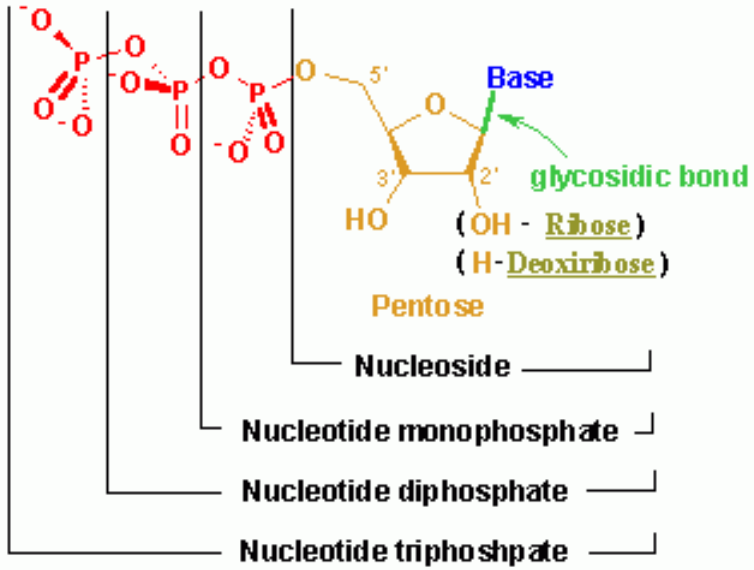

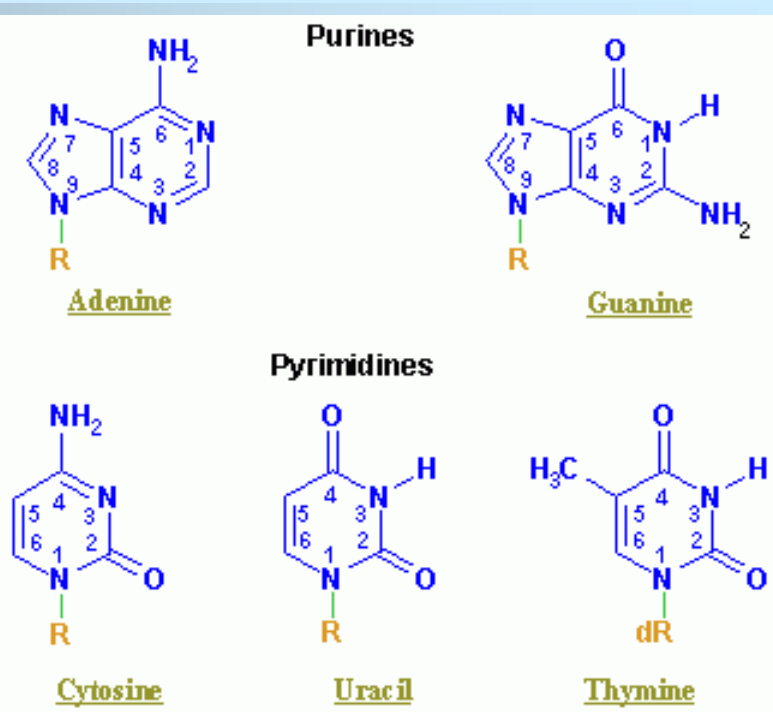

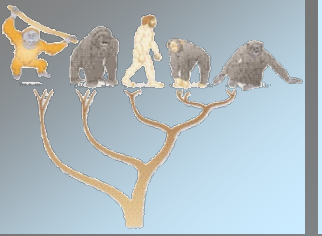

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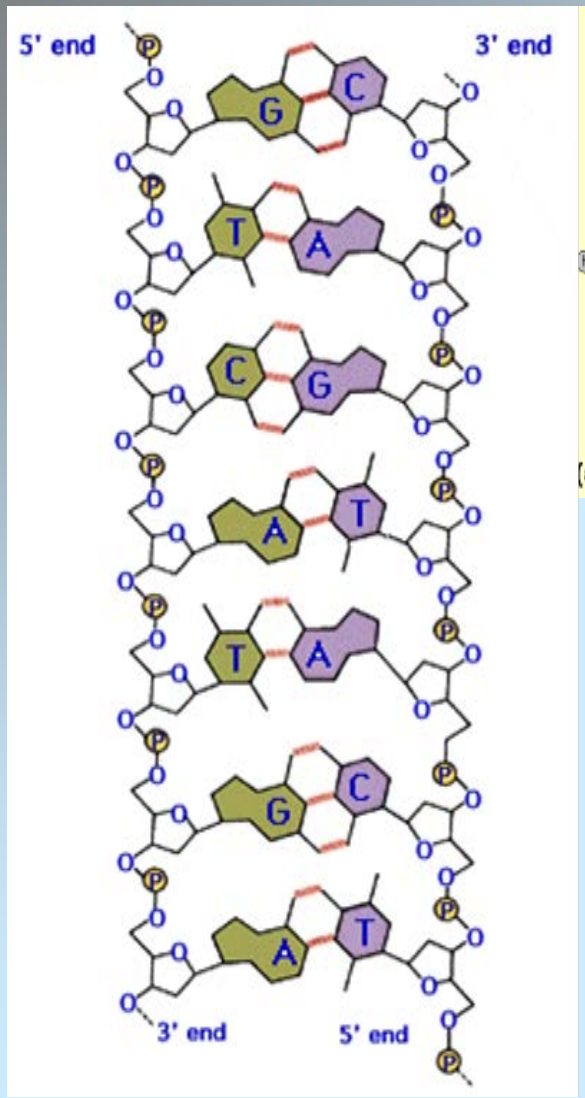

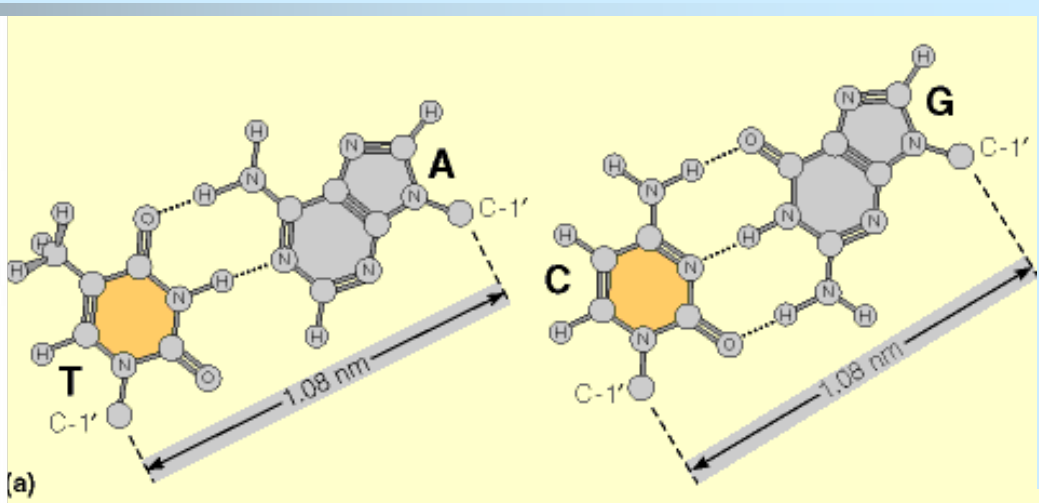

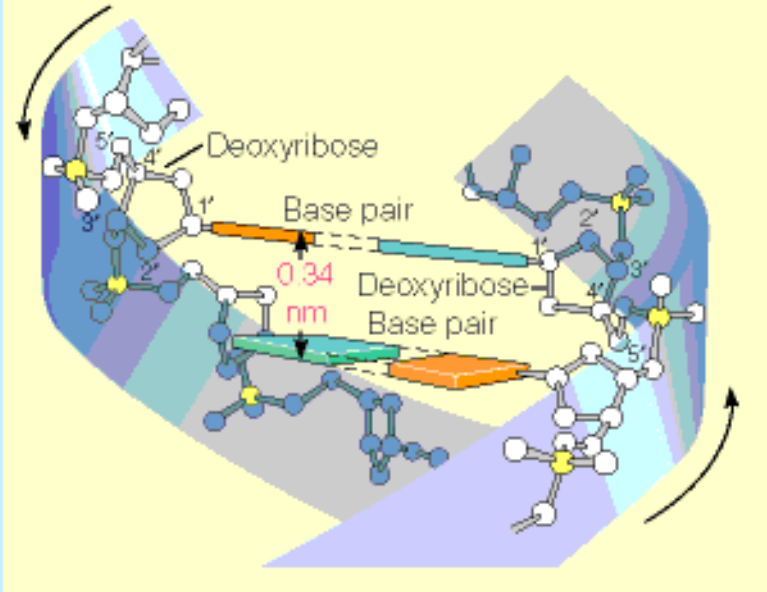

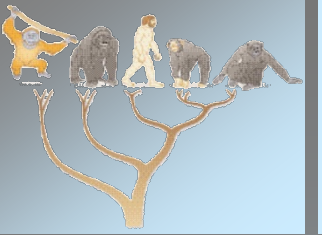

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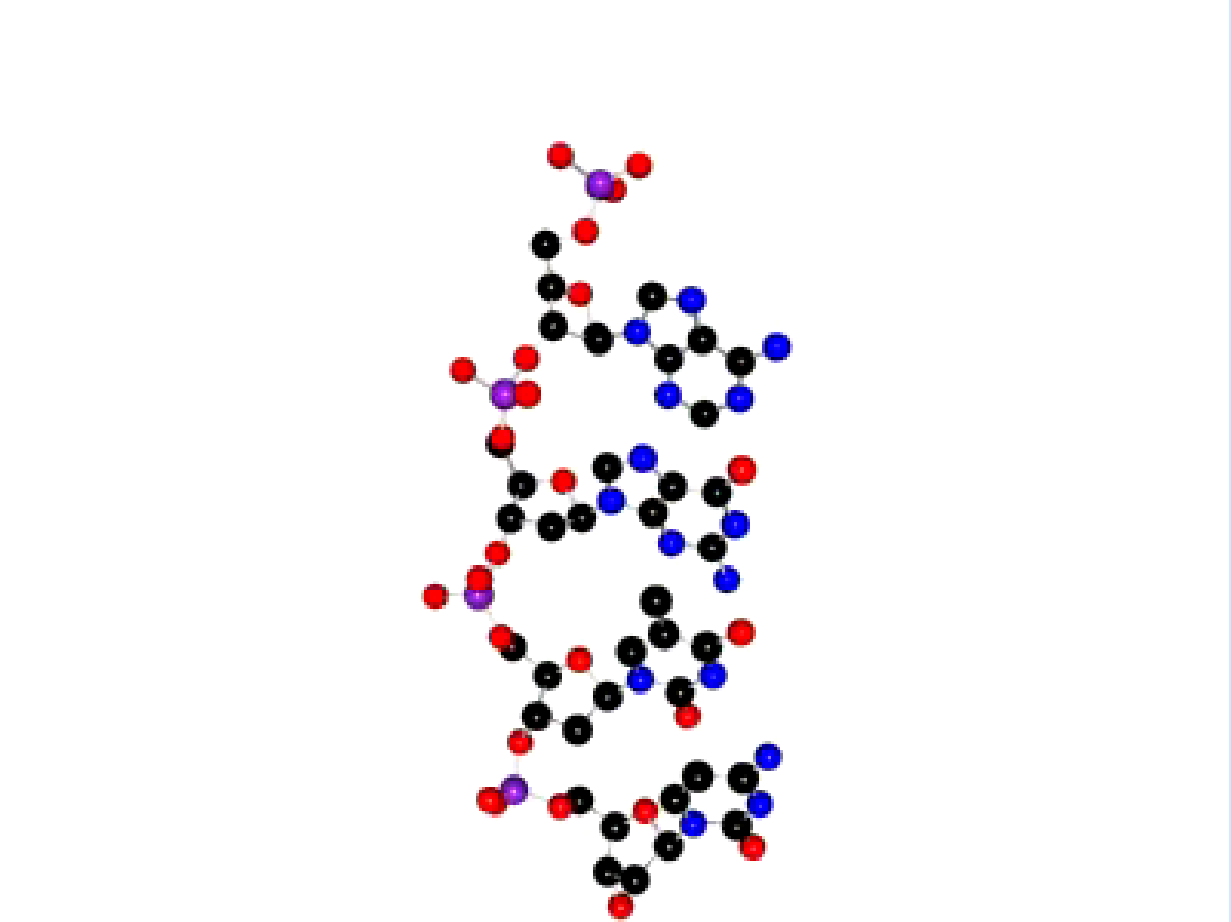
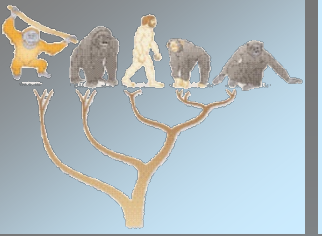


DNA



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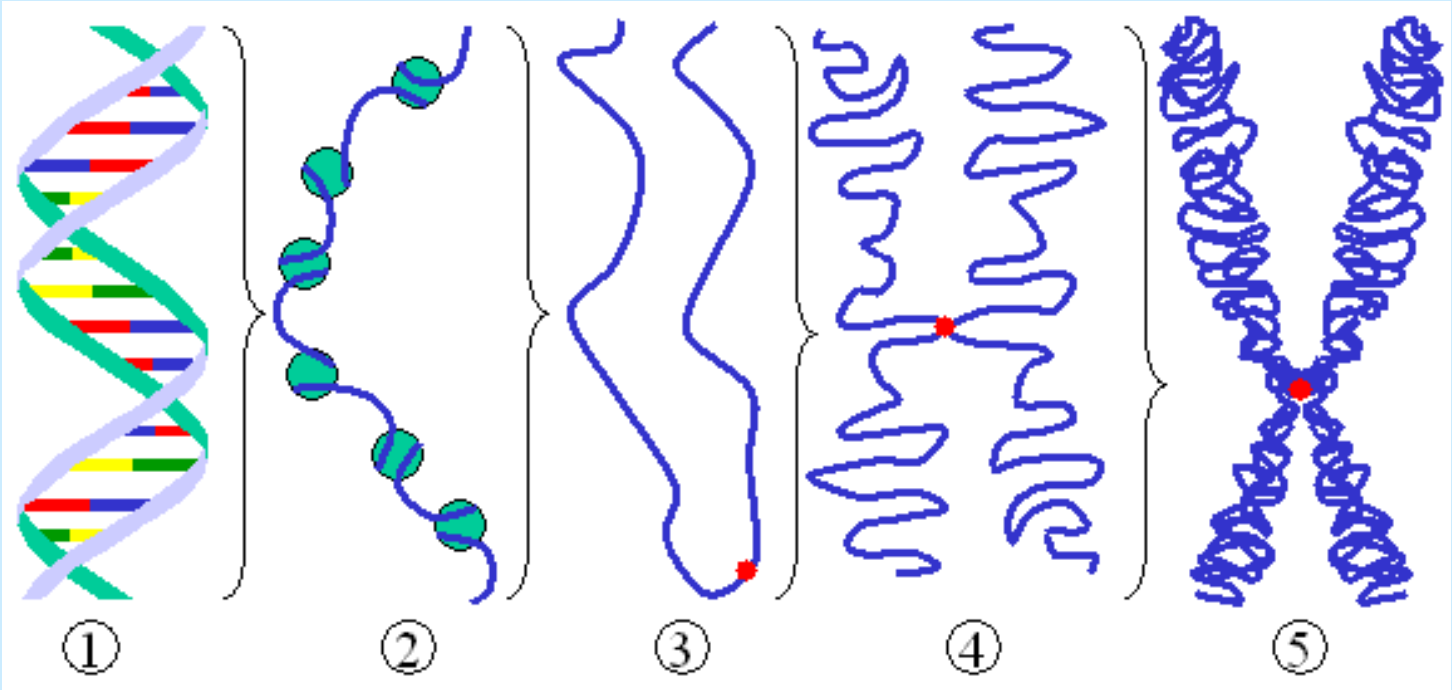
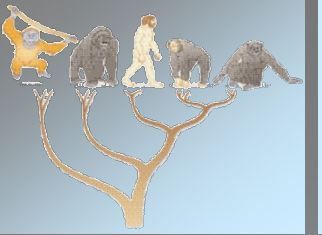
- The DNA is condensed in the nucleus in the chromosomes
- DNA wraps around histones resulting in chromatin
- Two chromatins linked at the centromere are a chromosome





DNA

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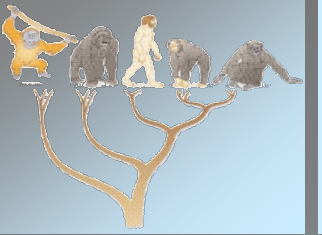
- Single DNA nucleotides differ at each human
- Small differences are inherited from both parents (except maternal mitochondrial DNA)
- Variation in the DNA at the same position in at least 1% of the population: **single nucleotide polymorphism** (SNP - pronounced snip)
- SNPs occur all 100 to 300 base pairs
- Current research relate diseases to SNPs (schizophrenia or alcohol dependence).



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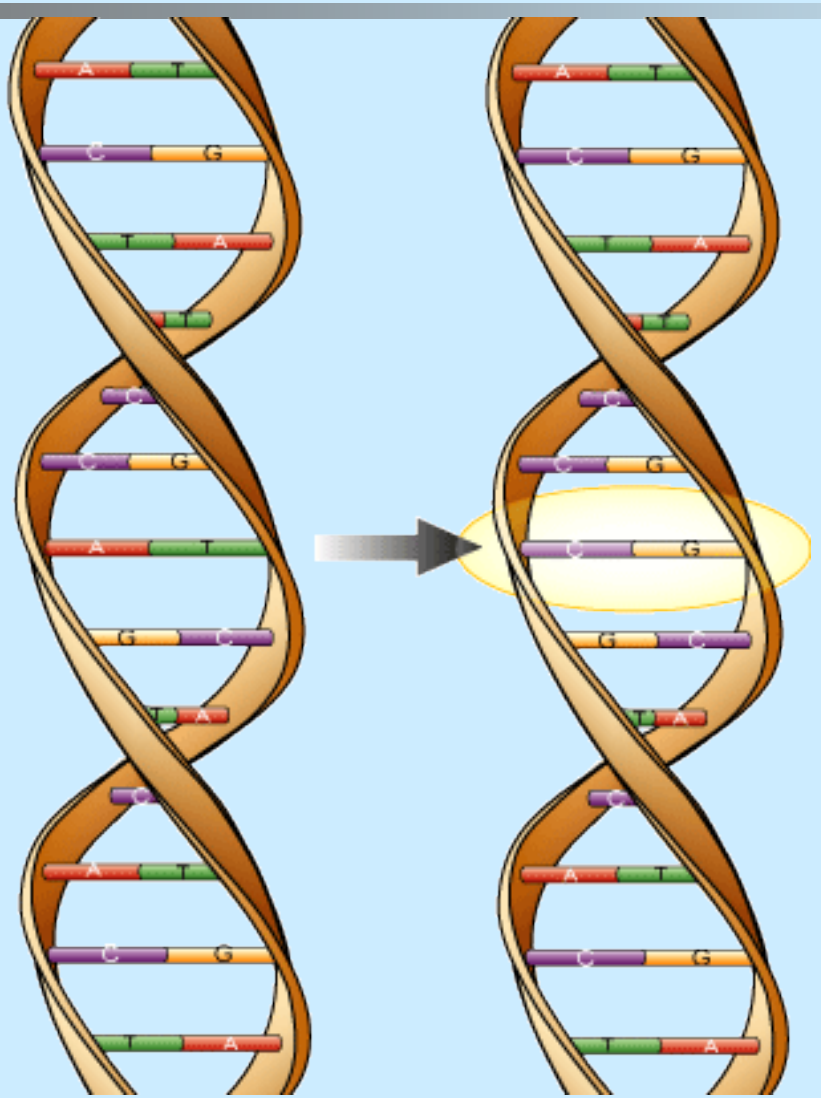

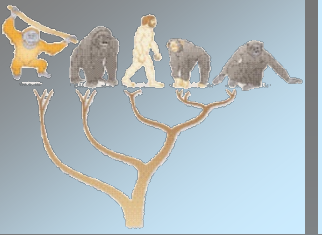

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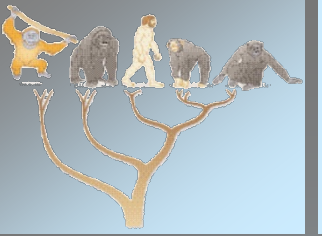
- Ribonucleic acid (RNA): sequence of nucleotides
- Contrast to DNA: ribose rings instead of deoxyribose; uracil instead of thymine
- transcribed from DNA through RNA polymerases
- kind of RNA:

mRNA (messenger),		tRNA (codon coding),
dsRNA (double stranded),		miRNA (micro),
RNAi (interference),		siRNA (small interfering),
ncRNA (non-coding)	like	rRNA (ribosomal)



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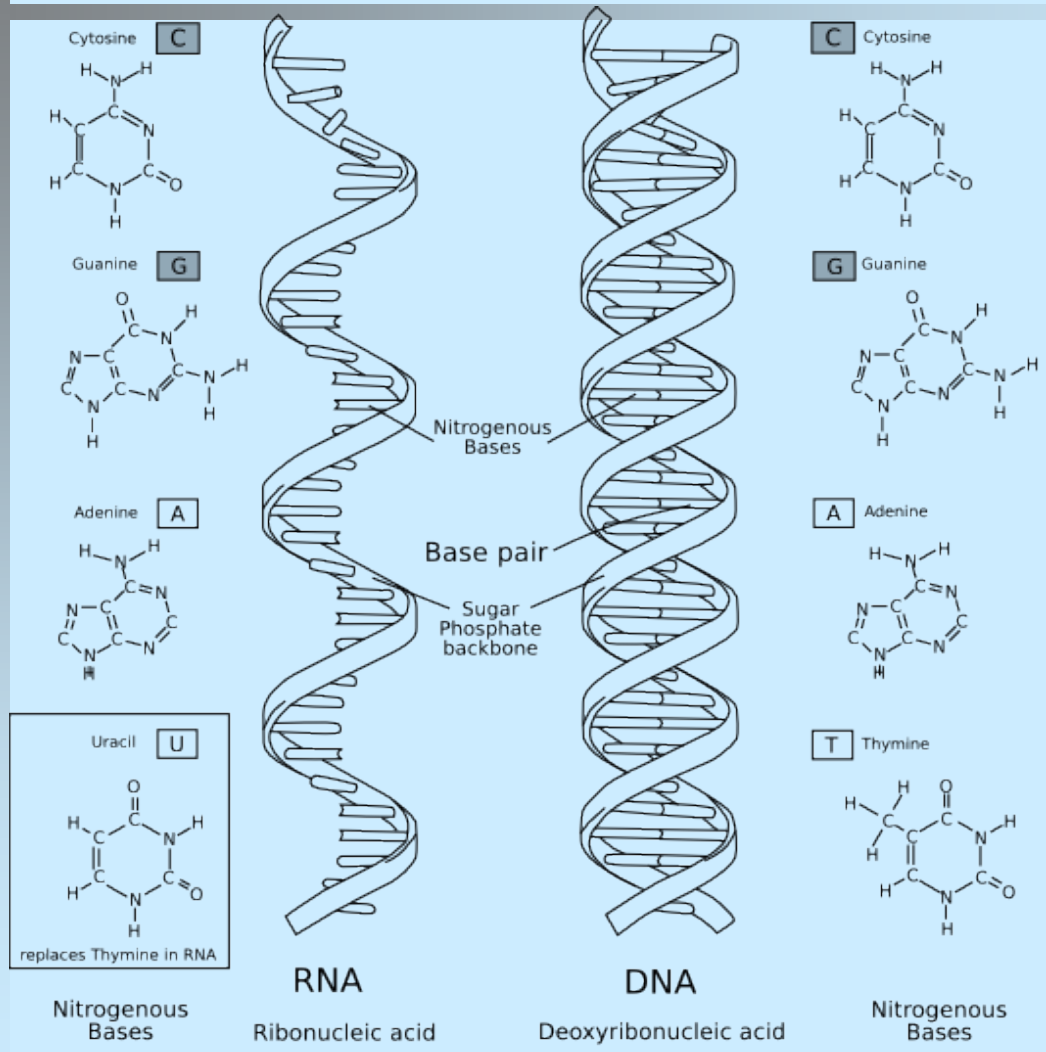

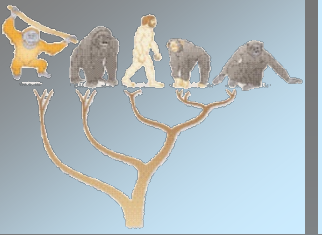

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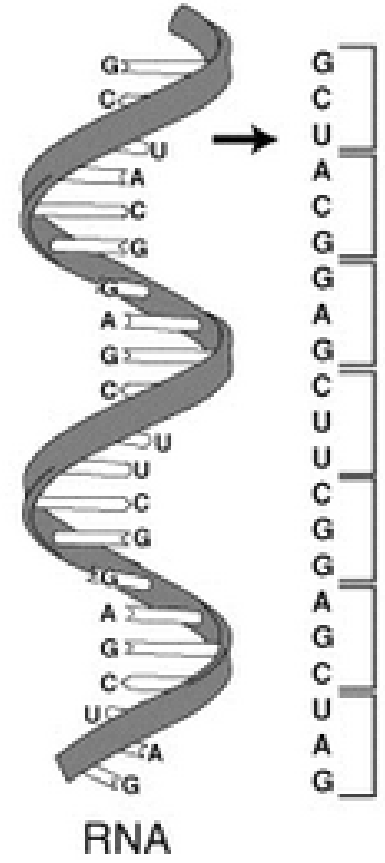

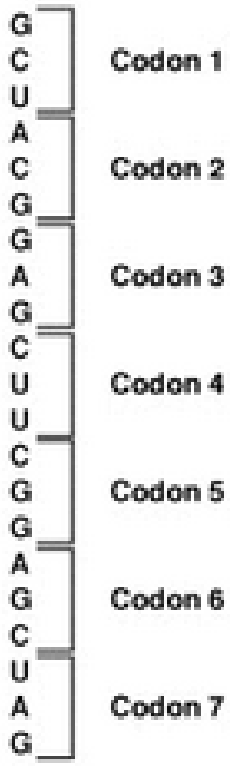

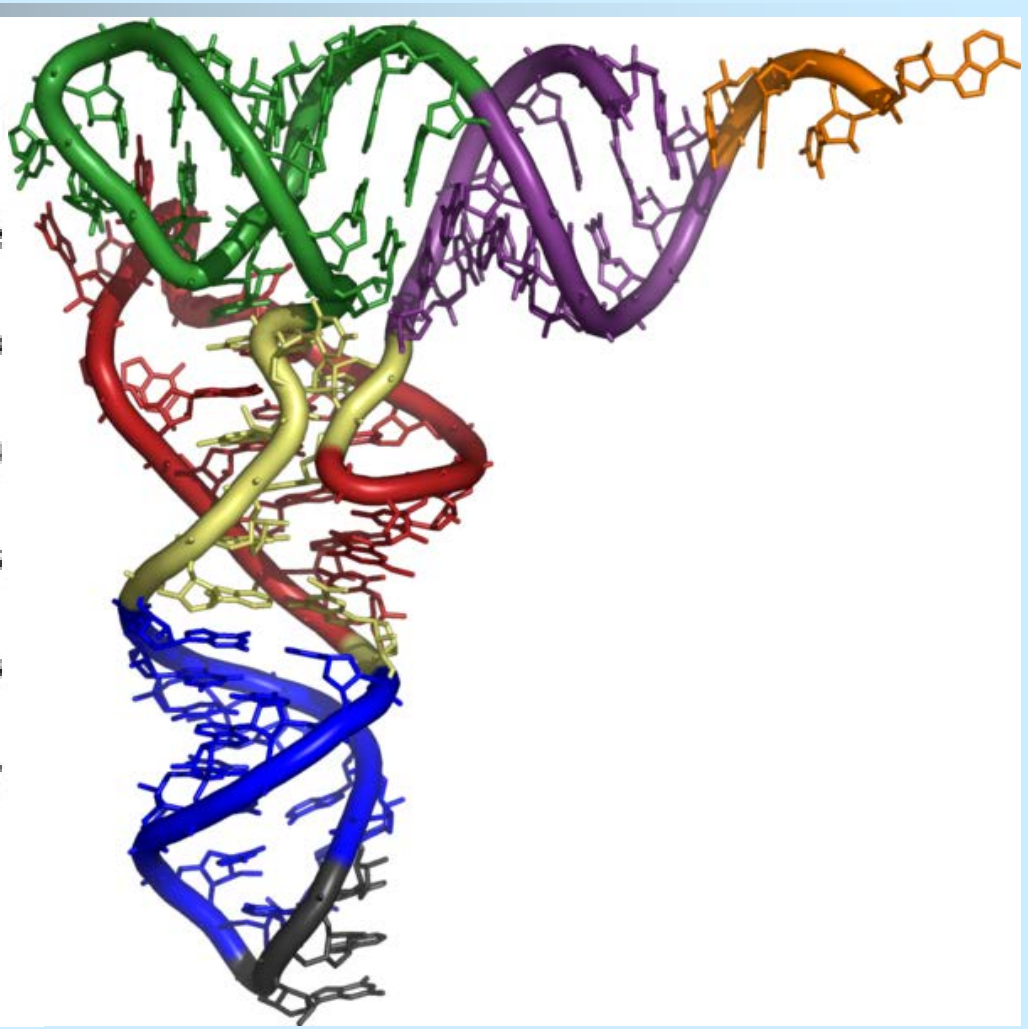

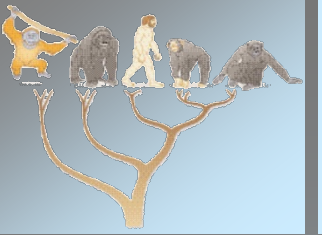

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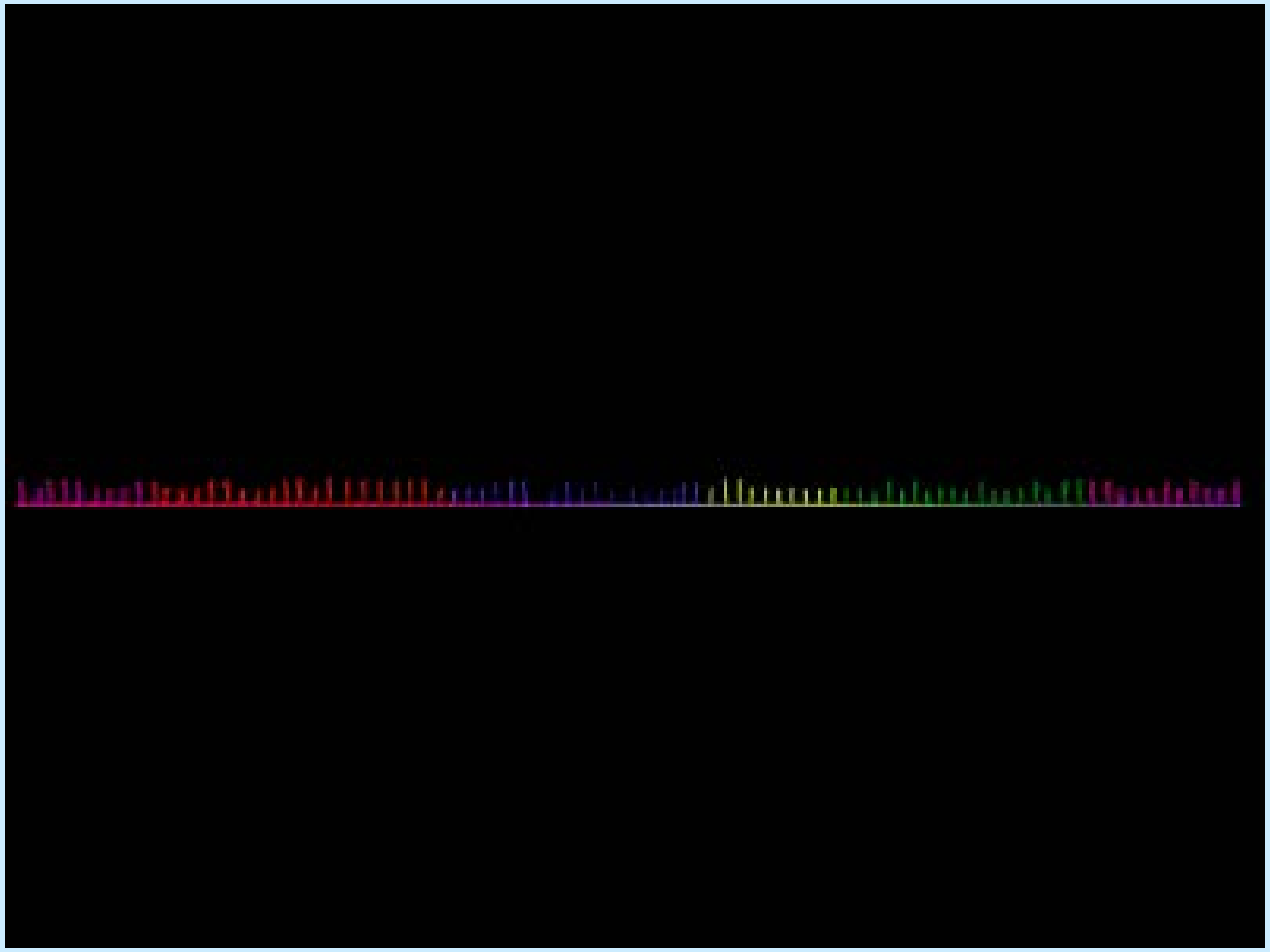
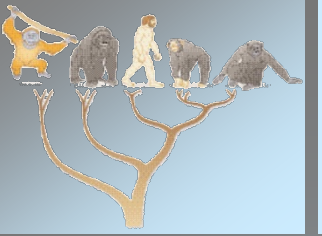


tRNA



Transcription

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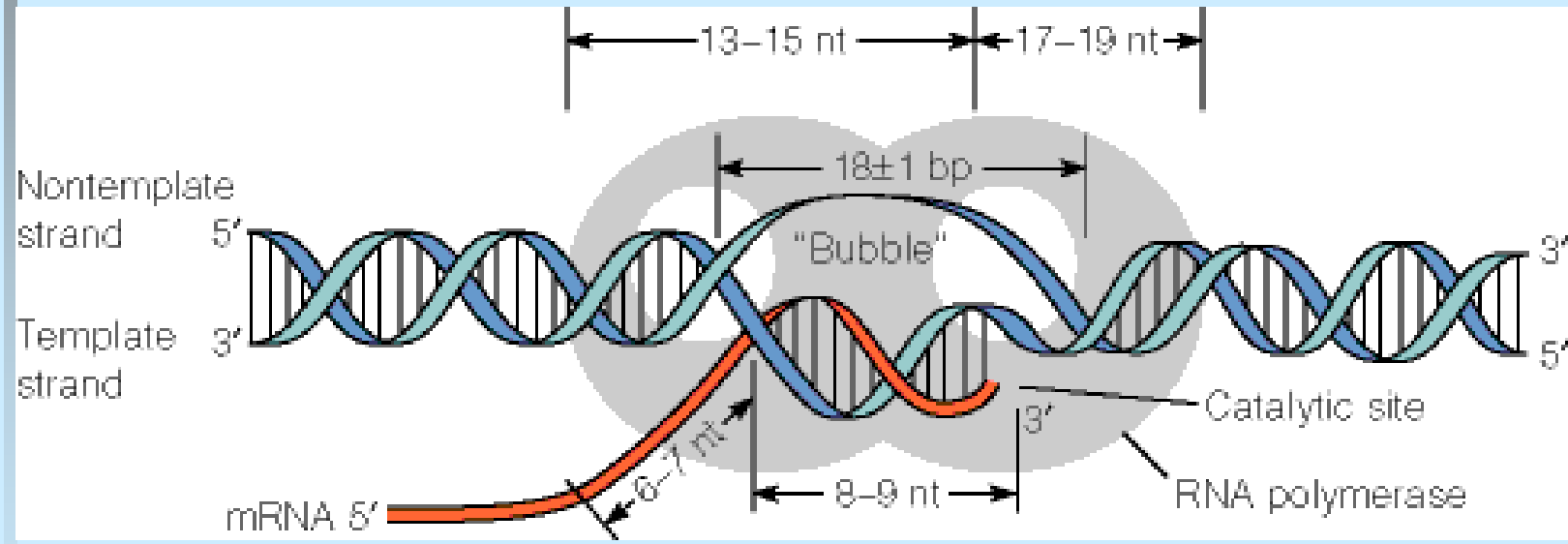
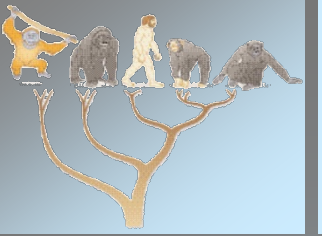
Transcription is the process of reading out a RNA (mRNA) from the DNA





Transcription Initiation

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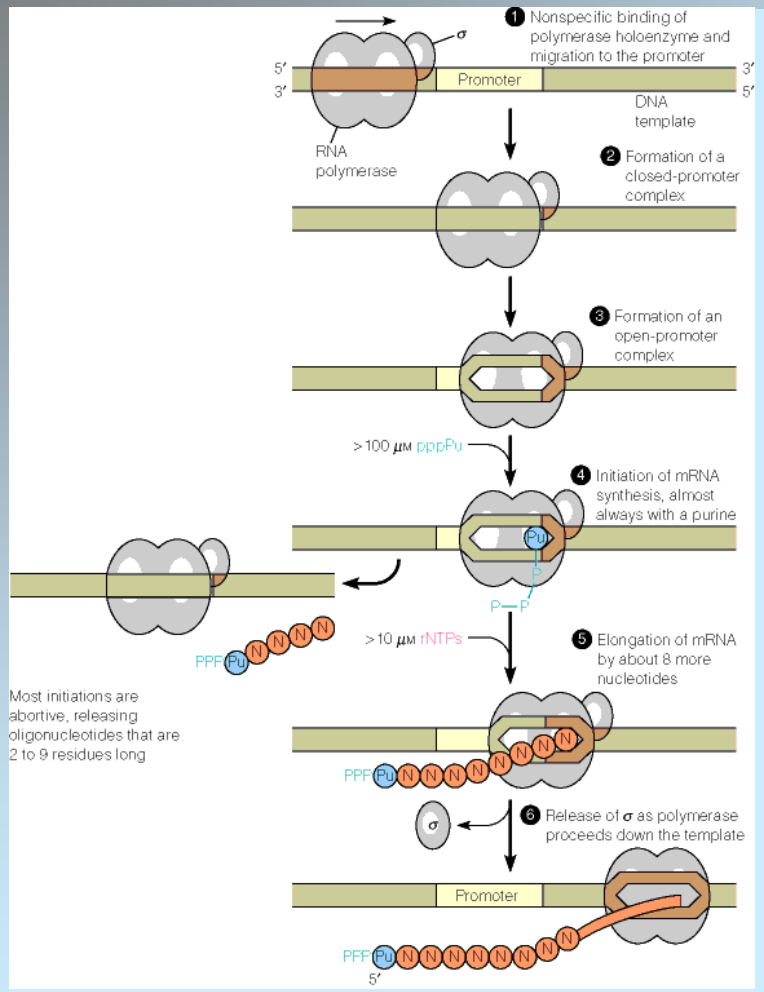

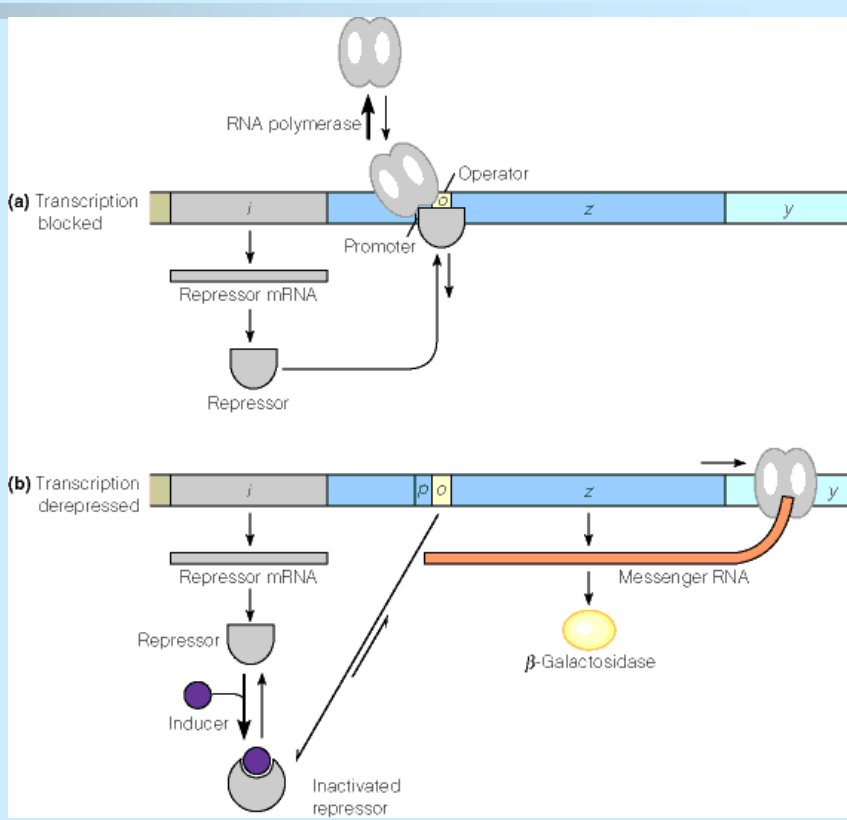

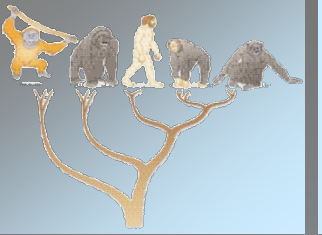

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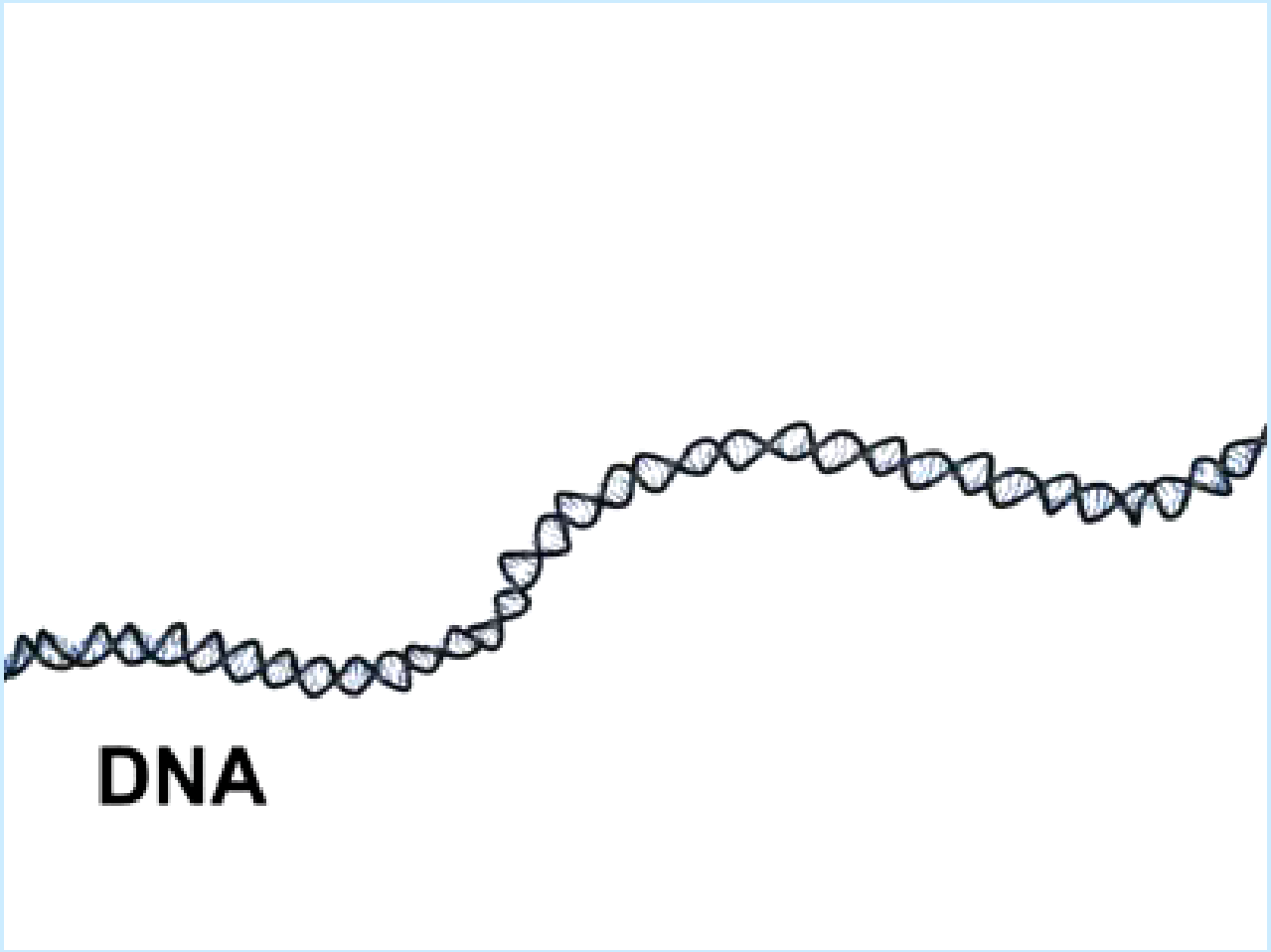
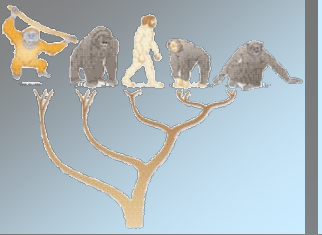


Transcription



Transcription Inhibition

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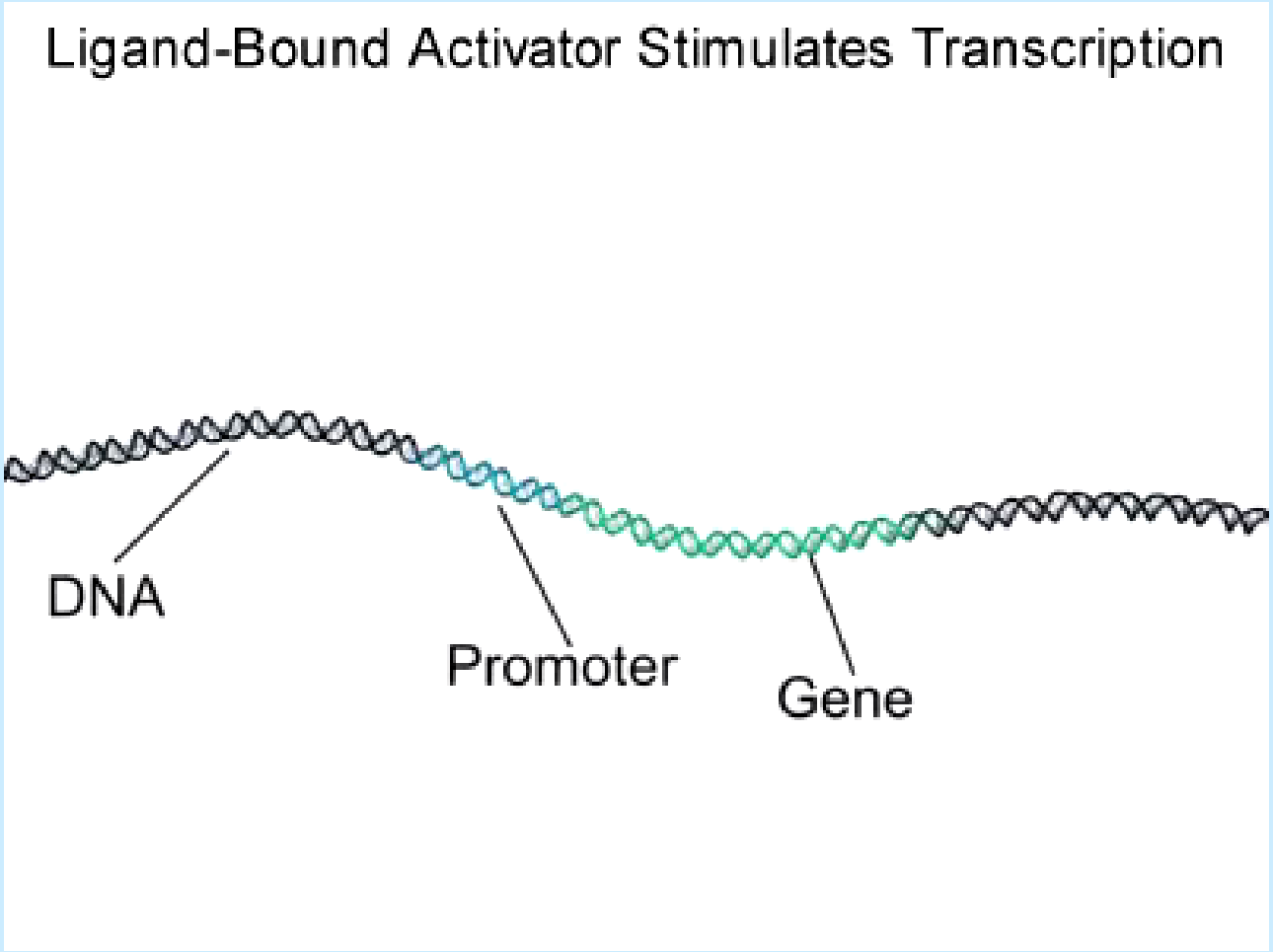
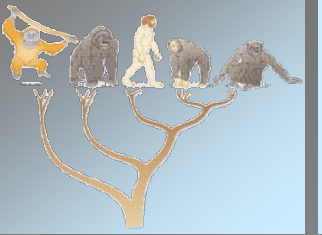


Transcription inhibition



Transcription Elongation

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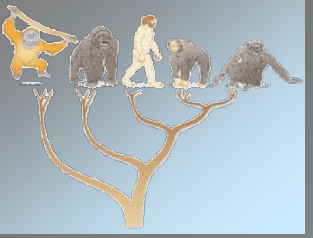
- After 8 nucleotides the sigma-subunit is dissociated from polymerase
- For elongation there exist promoters



Transcription Termination

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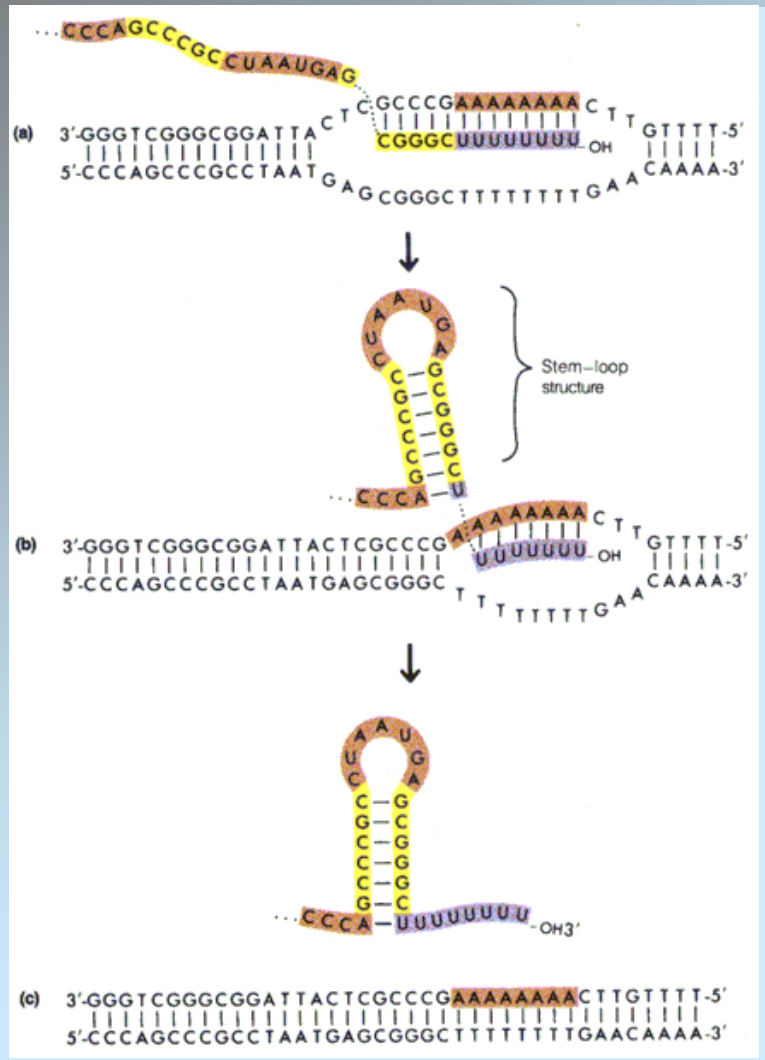

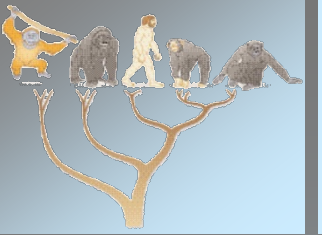

Splicing, Exons and Introns

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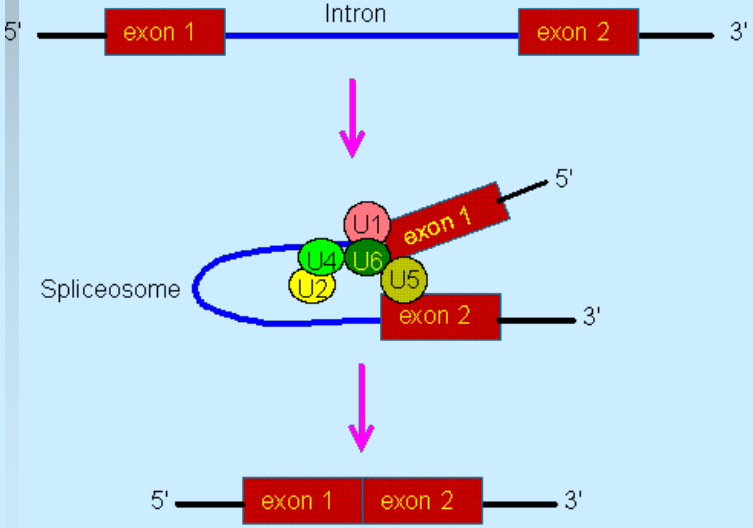
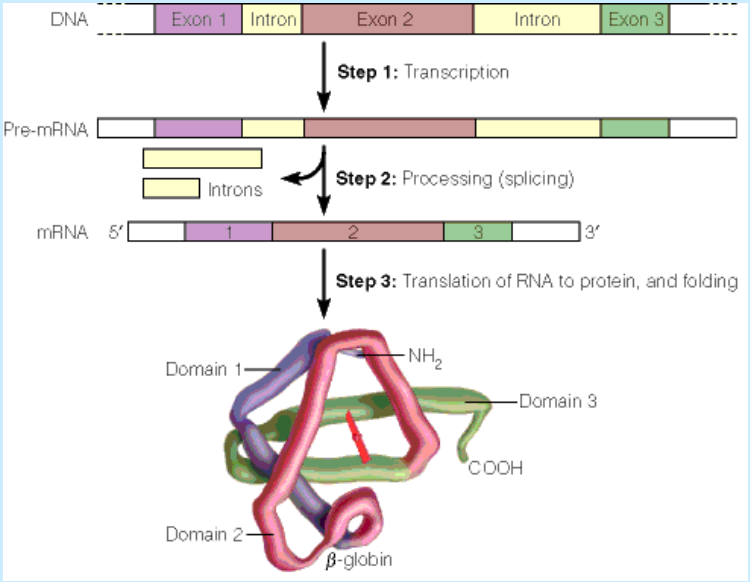
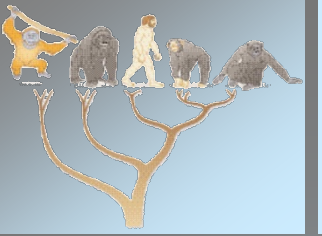
- Splicing modifies pre-mRNA released after transcription
- Non-coding sequences: introns (intragenic regions)
- coding sequences: exons are glued together
- A snRNA complex, the spliceosome, performs the splicing but some RNA sequences can perform autonomous splicing







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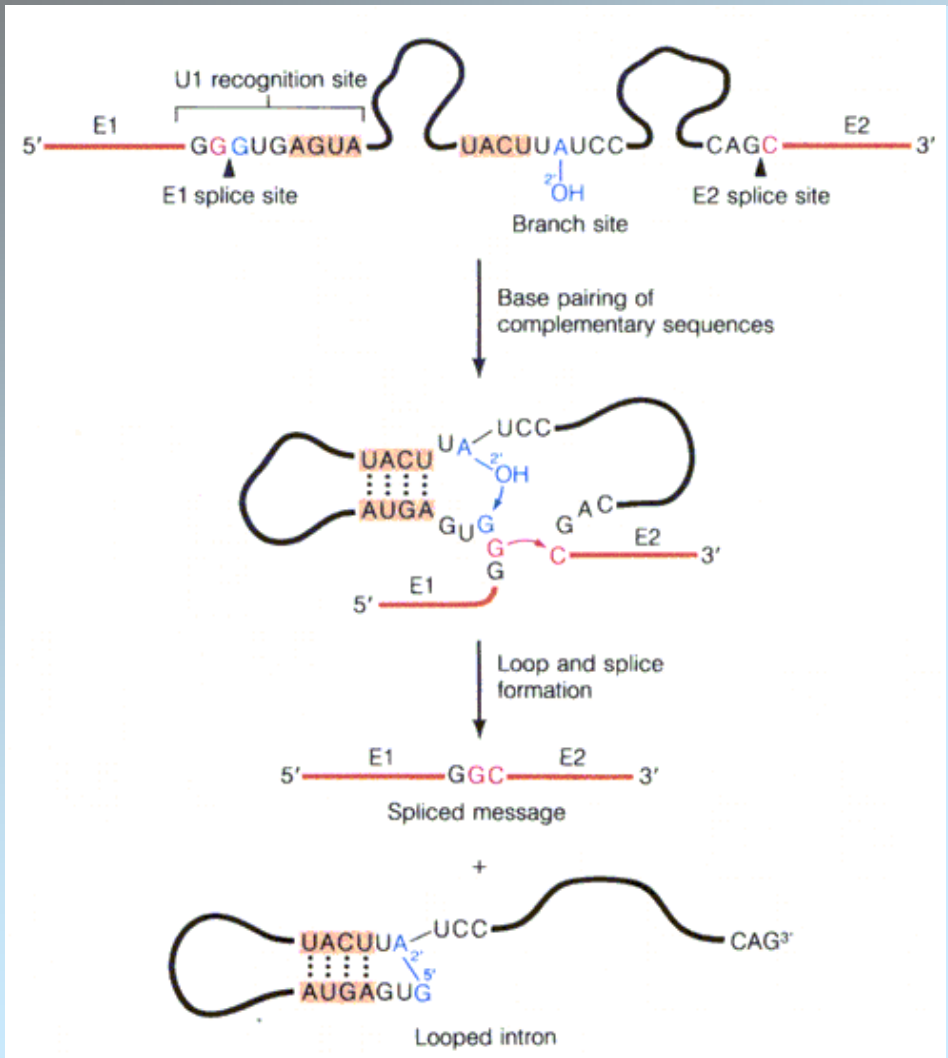
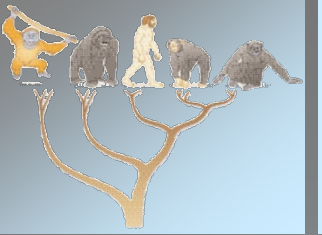


Self-splicing



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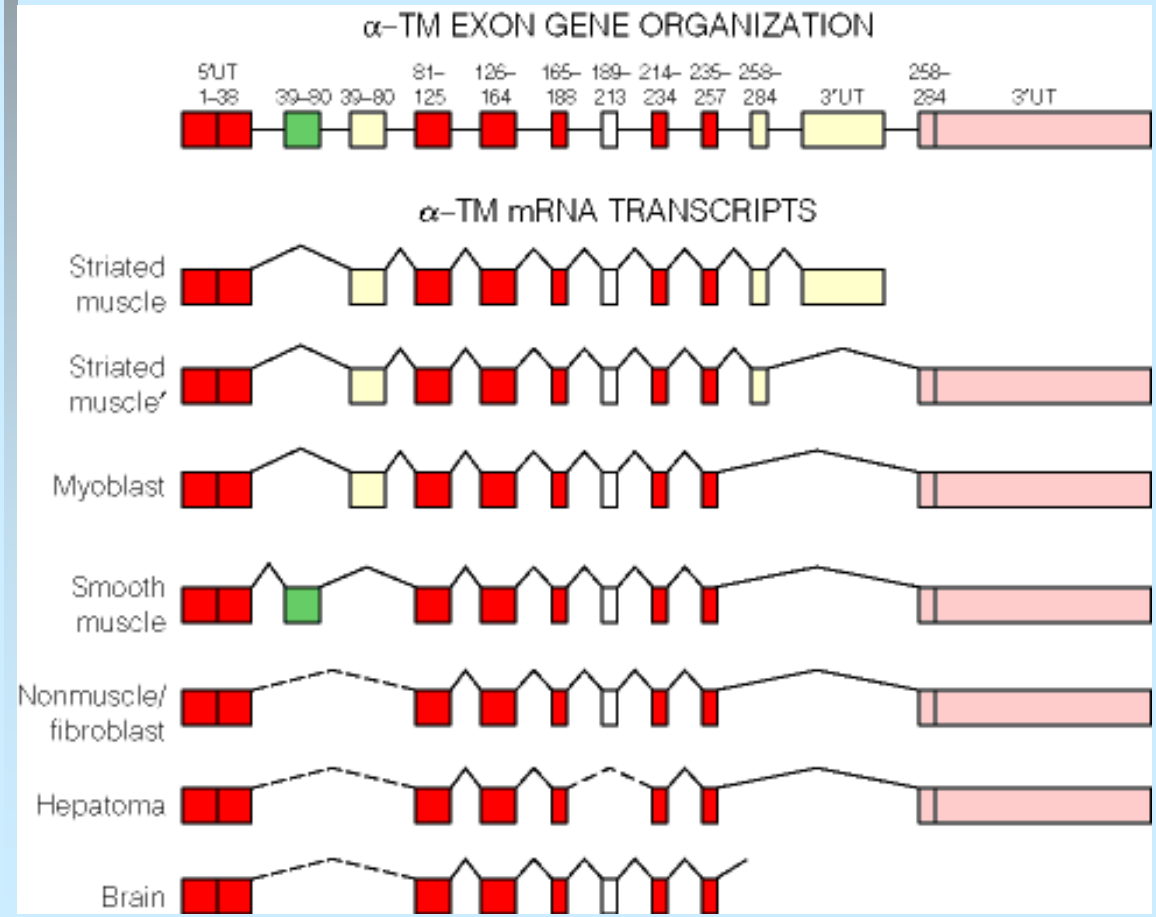
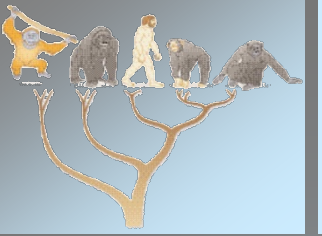
- pre-mRNA can be spliced in different ways: alternative splicing, therefore a gene can code different proteins
- Alternative splicing is controlled by signalling molecules



Alpha-tropomyosin

two-stranded alpha-helical coiled coil protein found in cell cytoskeletons



Amino Acids

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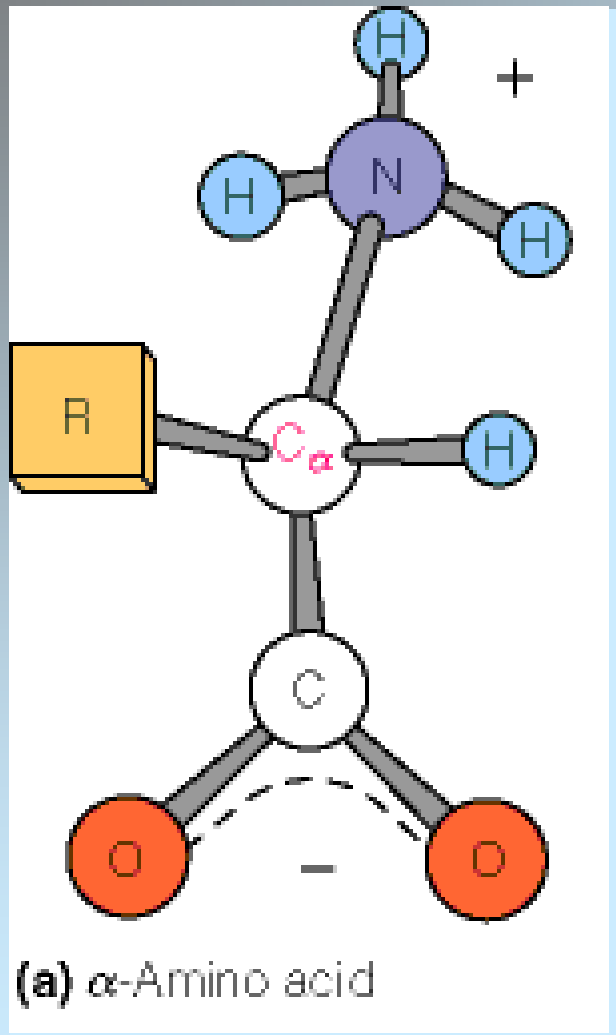
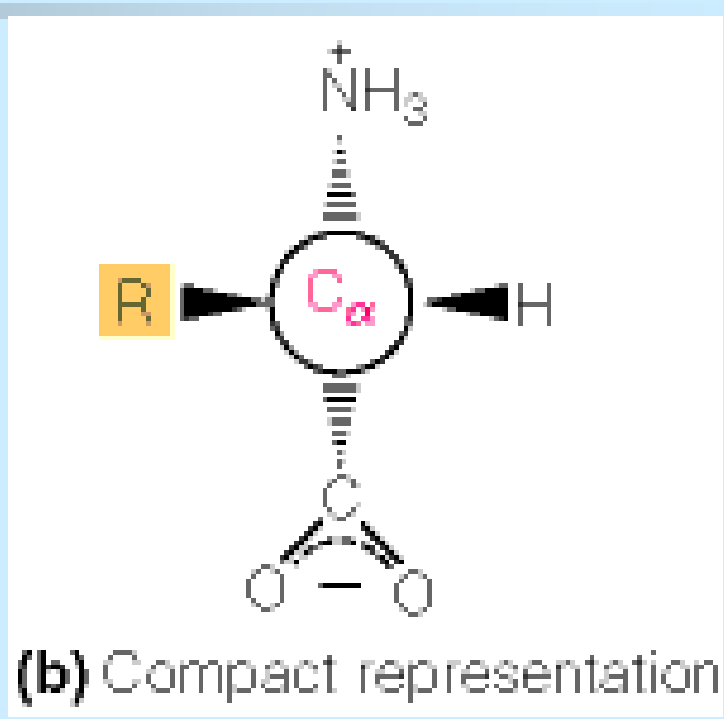
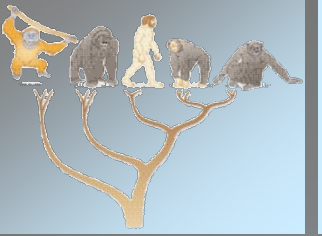


(a) α-Amino acid



(b) Compact representation



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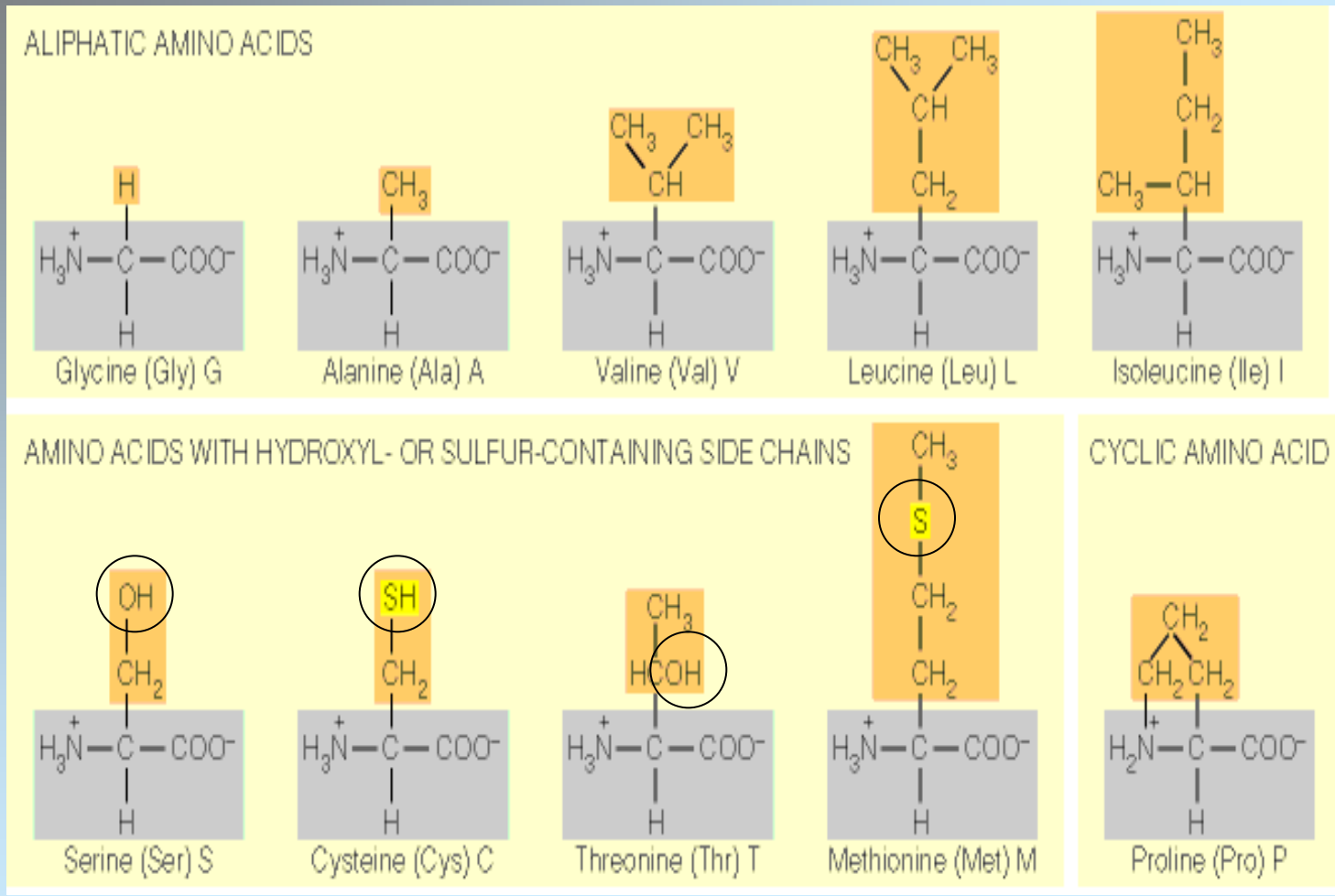

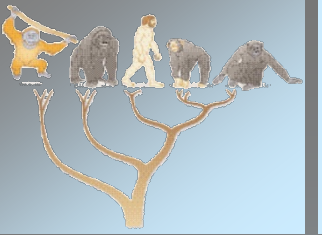

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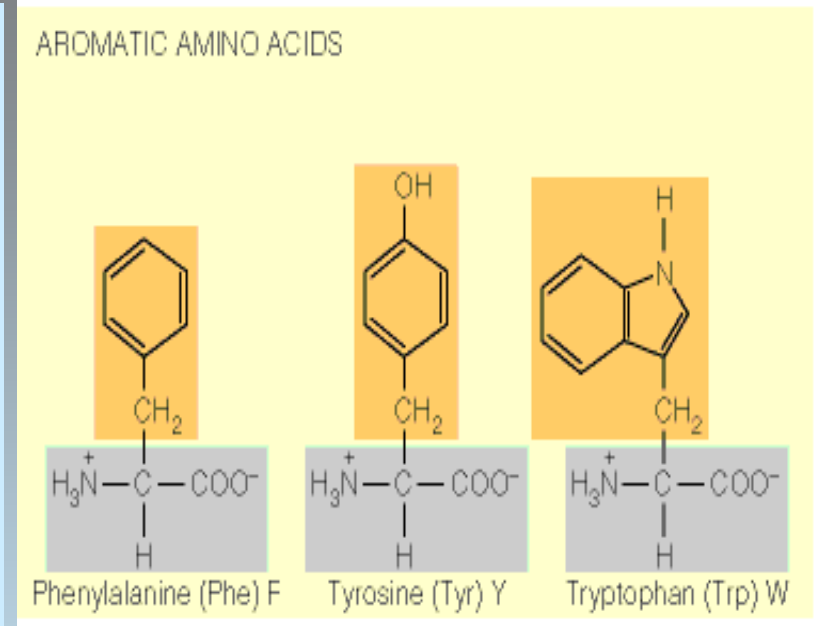

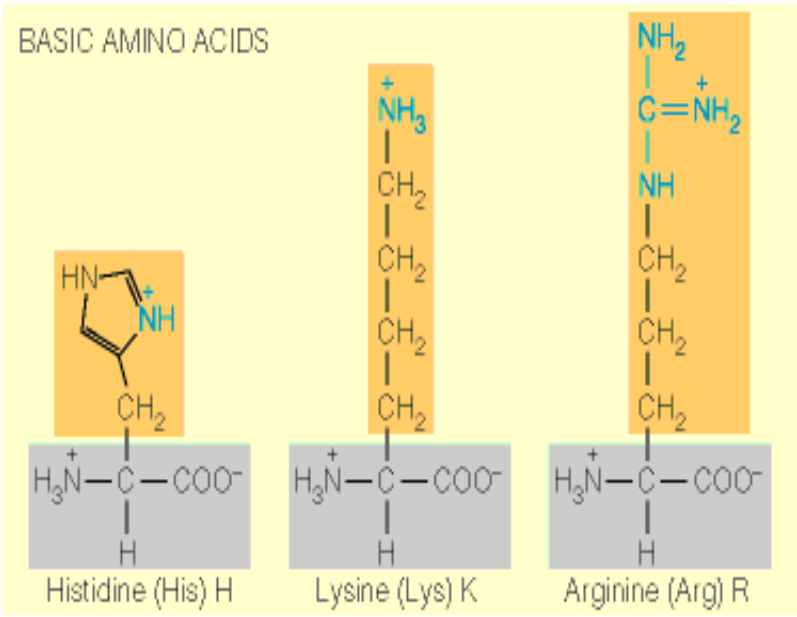

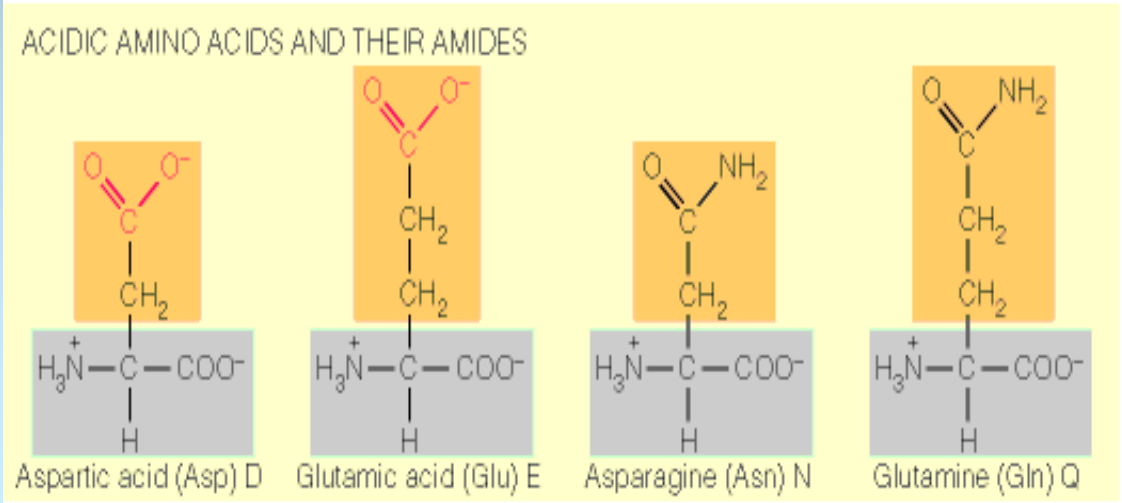

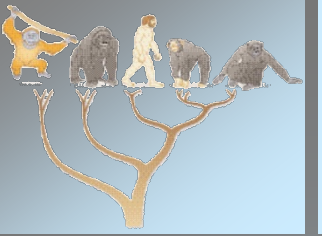

Amino Acids

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Hydrophobic (nonpolar):

glycine	Gly	G	methionine	Met	M
alanine	Ala	A	phenylalanine	Phe	F
valine	Val	V	tryptophan	Trp	W
leucine	Leu	L	proline	Pro	P
isoleucine	Ile	I			

Hydrophilic (polar)

serine	Ser	S	tyrosine	Tyr	Y
threonine	Thr	T	asparagine	Asn	N
cysteine	Cys	C	glutamine	Gln	Q

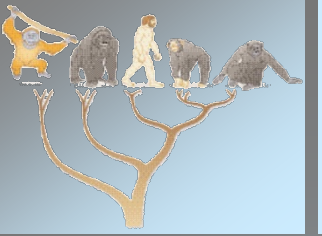
acidic (-,hydrophilic)

aspartic acid	Asp	D	glutamic acid	Glu	E

basic (+,hydrophilic)

lysine	Lys	K	arginine	Arg	R
histidine	His	H			

Cysteine and methionine: disulfide bonds



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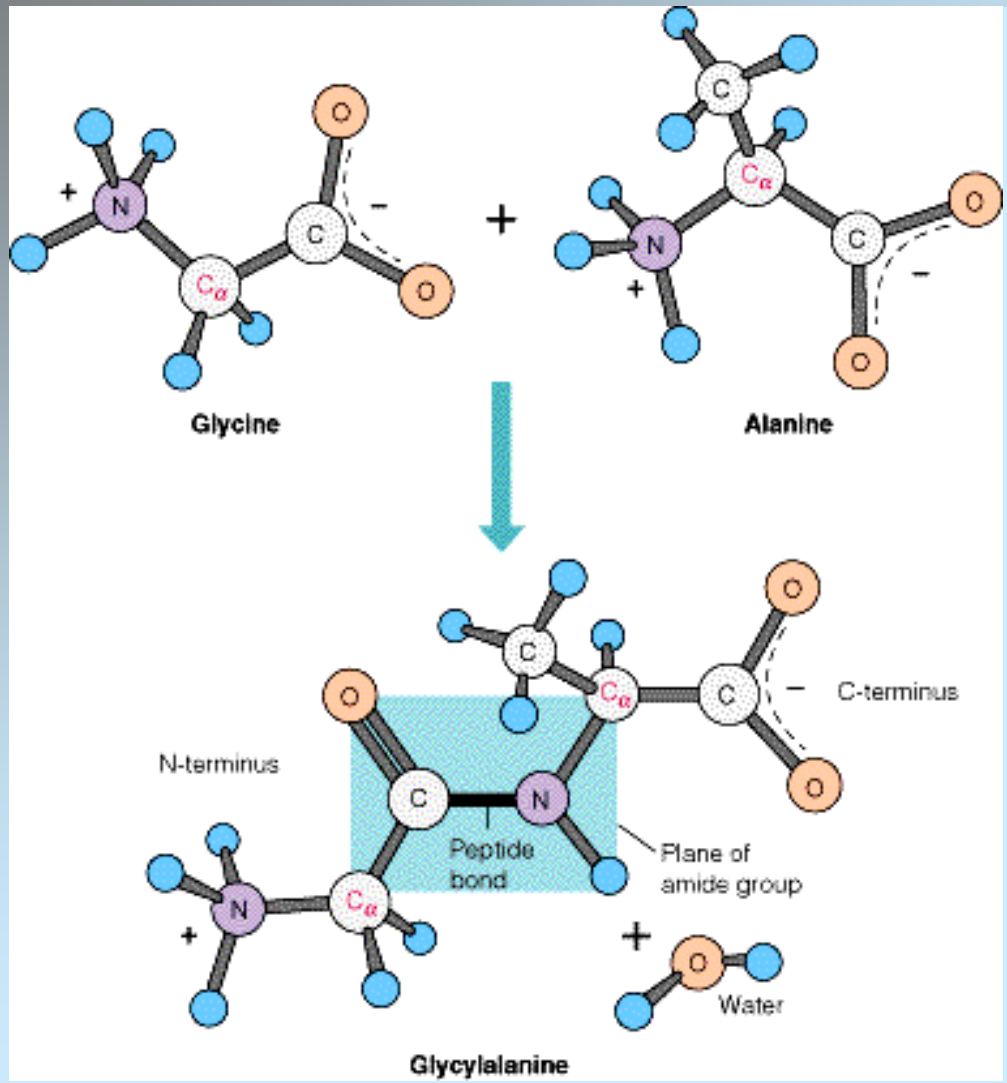

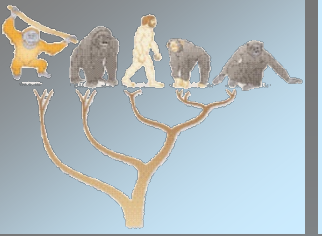

Genetic Code

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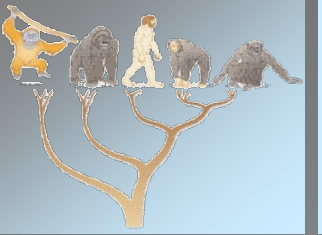
- all proteins consist of these 20 amino acids
- 3D interactions of the amino acids results in nano-machines
- genetic code: instructions for producing proteins from DNA
- protein in coded through a gene which is transcribed into mRNA and then translated into an amino acid sequence which automatically configures into a protein
- genetic code gives the rules for translation
- rules are simple: 3 nucleotides (codon) = one amino acid
  AUG and CUG: start codon



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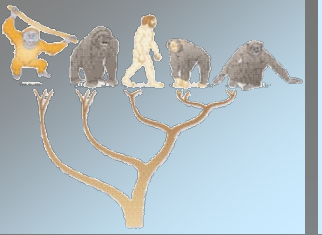
	U	C	A	G	
U	UUU phe UUC UUA leu UUG	UCU UCC UCA UCG ser	UAU tyr UAC UAA stop UAG	UGU cys UGC UGA stop UGG trp	U C A G
C	CUU CUC CUA CUG leu	CCU CCC CCA CCG pro	CAU his CAC CAA gln CAG	CGU CGC CGA CGG arg	U C A G
A	AUU AUC AUA ile AUG met	ACU ACC ACA ACG thr	AAU asn AAC AAA lys AAG	AGU ser AGC AGA arg AGG	U C A G
G	GUU GUC GUA GUG val	GCU GCC GCA GCG ala	GAU asp GAC GAA glu GAG	GGU GGC GGA GGG gly	U C A G

C = Cytosin, U = Uracil, A = Adenin, G = Guanin
Base pairs DNA: A-T and C-G (T = Thymin)



Translation

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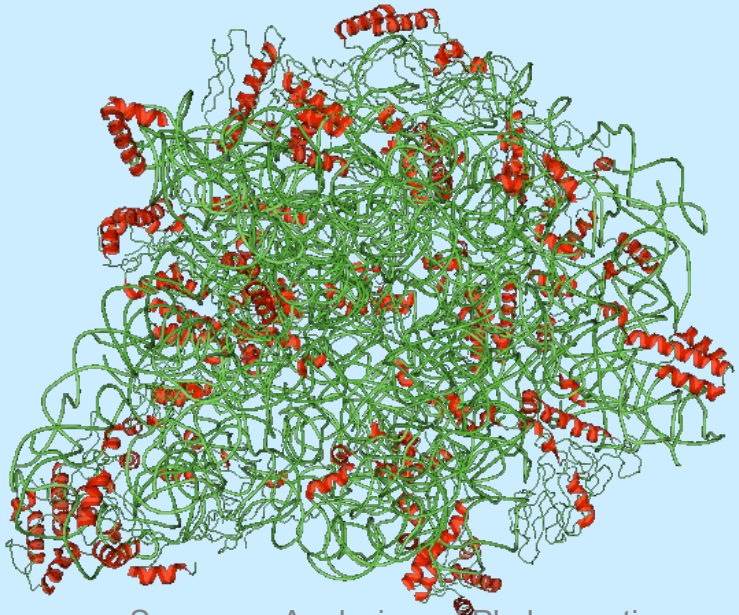
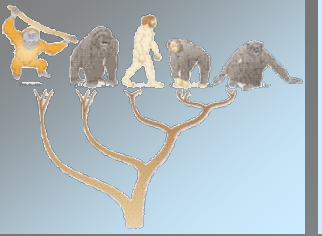
After transcription the pre-mRNA is spliced, edited, transported out of the nucelus into the cytosol (eukaryotes)

➥The ribosome (protein production machinery) assembles the amina acid sequences out of the mRNA

➥Ribosome consists of two subunits 60S and 40S in eukaryotes and 50S and 30S in bacteria





Translation Initiation

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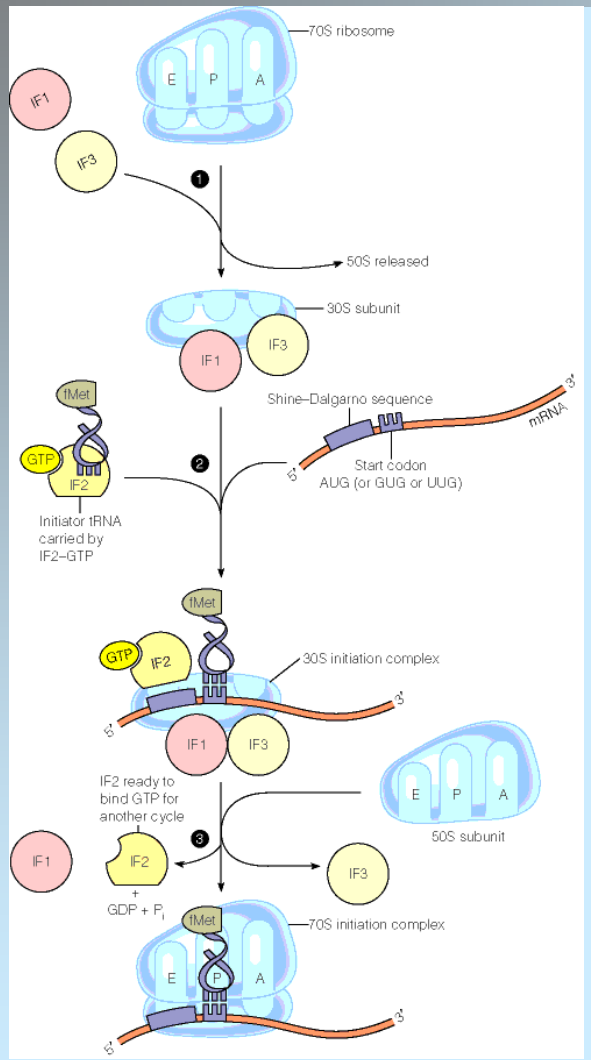
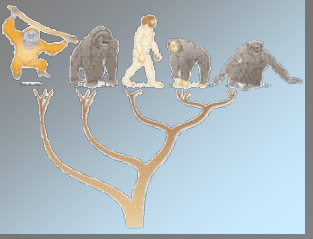


- Inactive ribosomes have dissociated subunits
- Ribosome binds to site at mRNA marked by AGGAGGU (Shine-Dalgarno)
- At this site the initiation factors IF1, IF2, IF3 and 30S ribosomal subunit bind
- The initiator tRNA binds to the start codon
- Then the 50S subunit binds to the complex and translation can start



Translation Elongation

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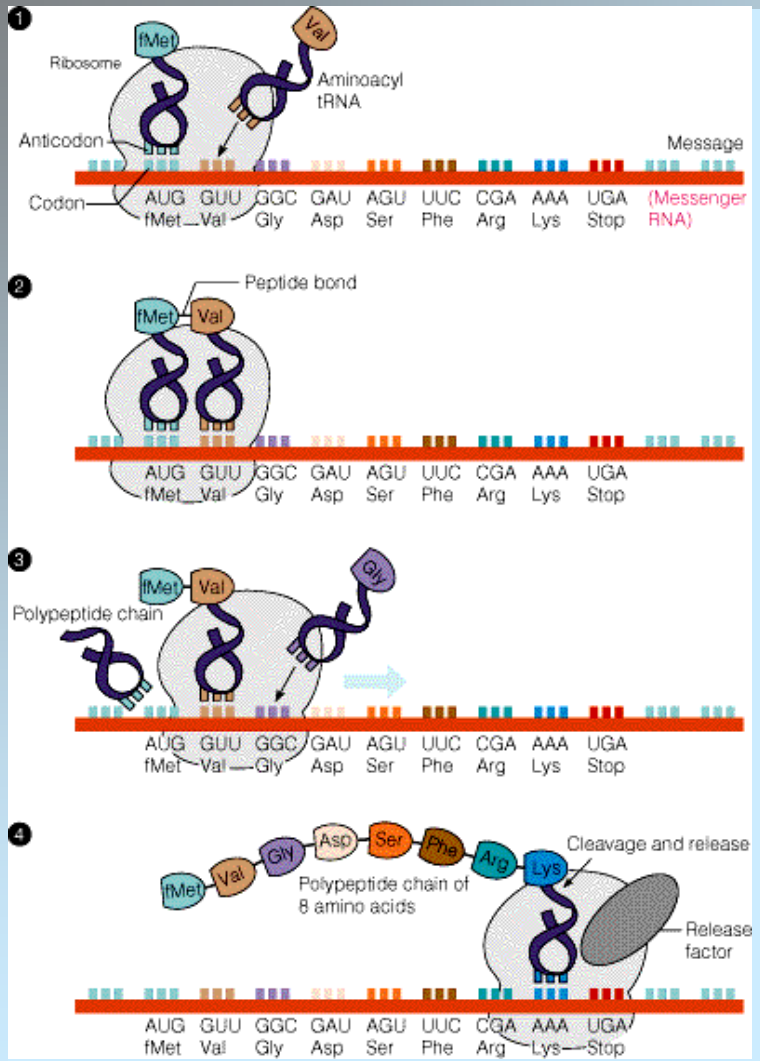

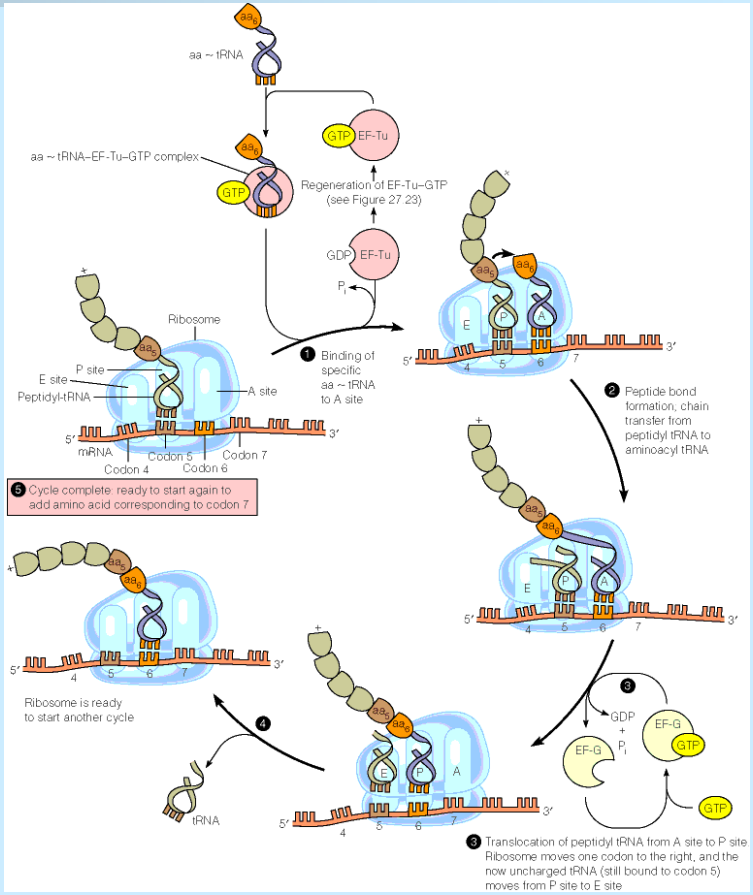

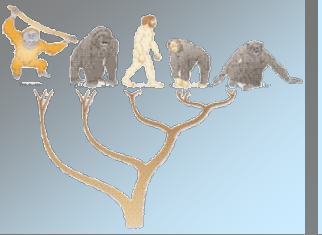

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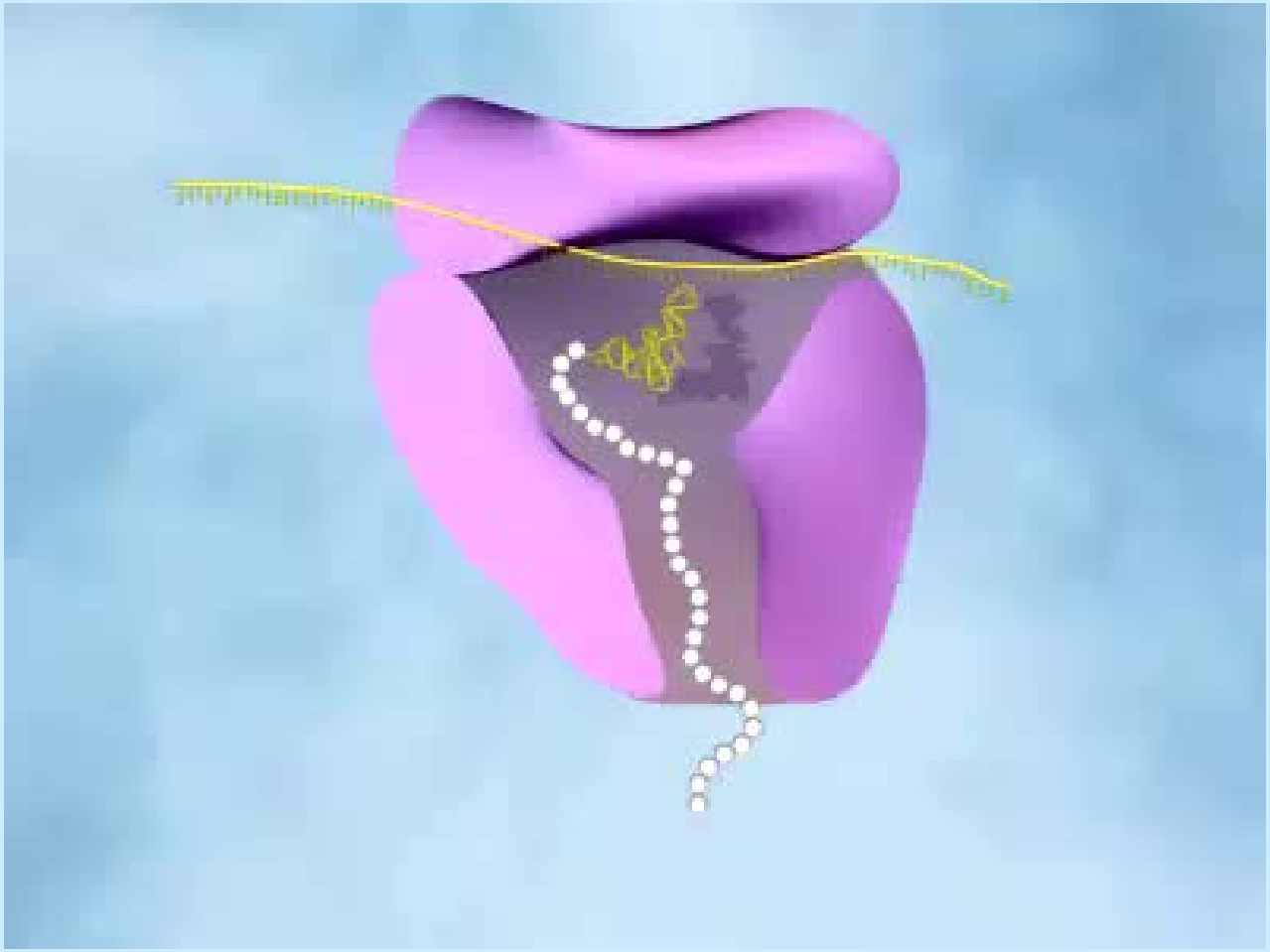
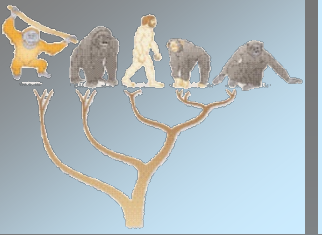


Ribosome



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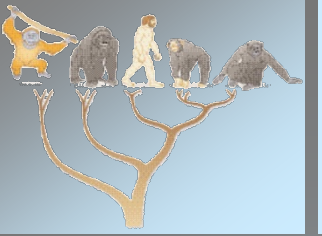
- Termination by a stop codon (UAA, UAG, UGA) which enters the A-site
- tRNAs cannot bind, however release factors bind at or near
- amino acid chain is released and the 70S ribosome dissociates
- 30S subunit remains attached to the mRNA and searching for the next Shine-Dalgarno pattern



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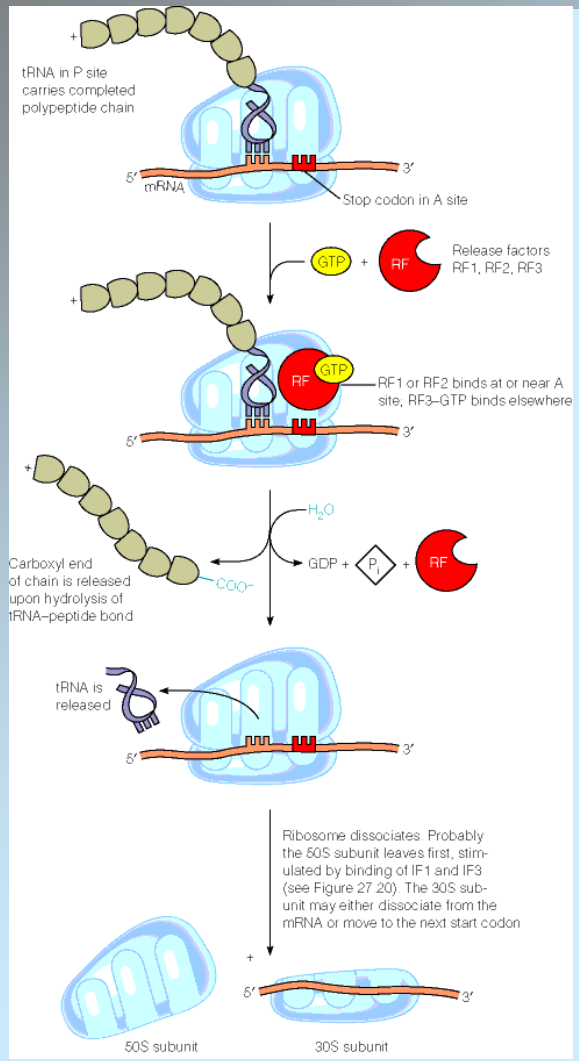

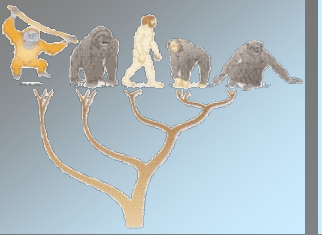

Folding of the Protein

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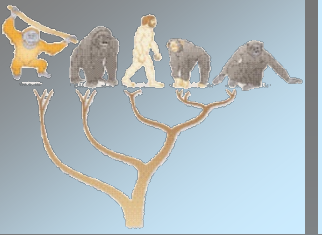
- Only the correct folded protein functions correctly (cf Creutzfeld-Jacob, Altzheimer, BSE, Parkinson)
- proteins always fold into their specific 3D structure
- complicated procedure with lots of interactions
- folding pathways are not unique and have intermediate states
- folding is assisted by special chaperones (hide the hydrophobic regions or act as containers)
- Folding time: milliseconds up to minutes or hours
- major tasks in bioinformatics is the prediction of the 3D structure to guess the function or to design new proteins



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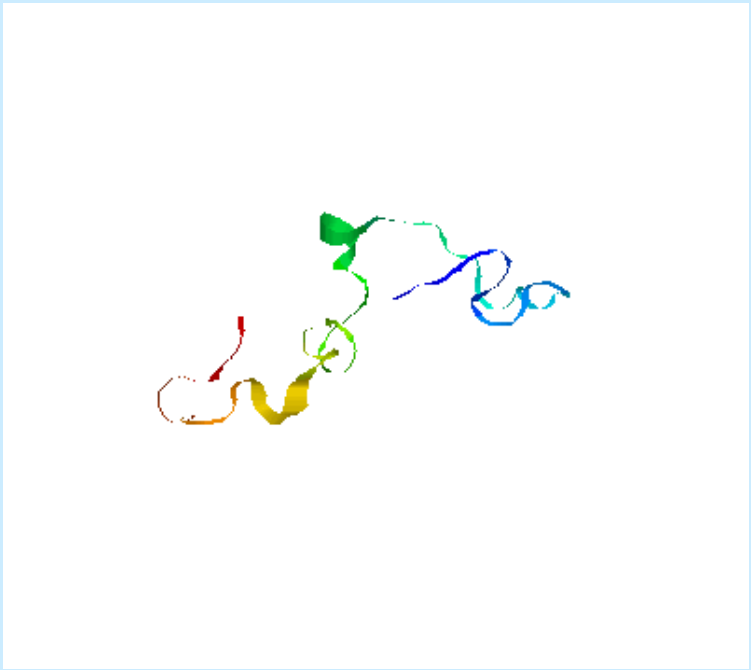

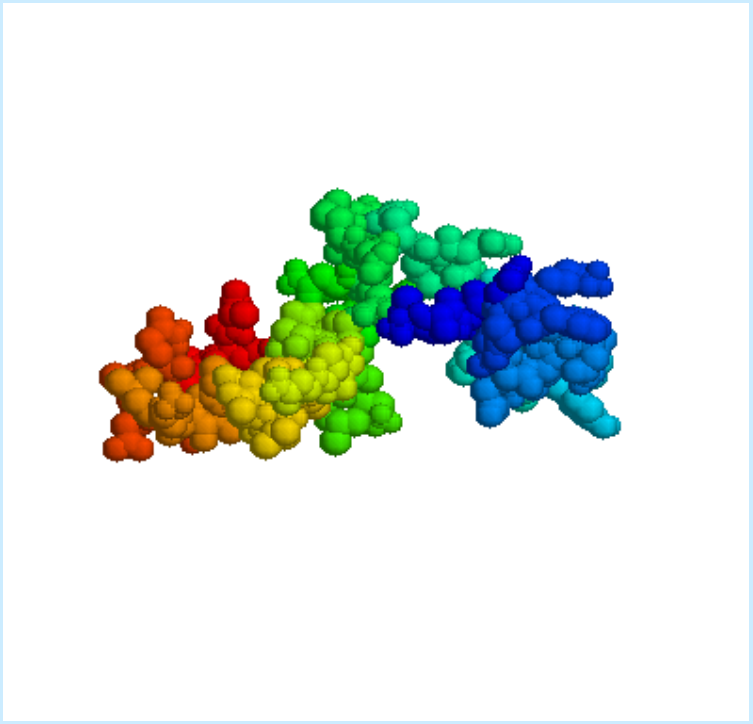

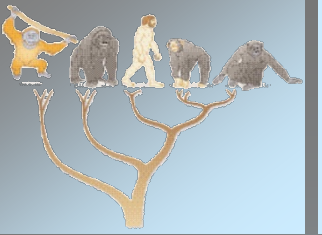

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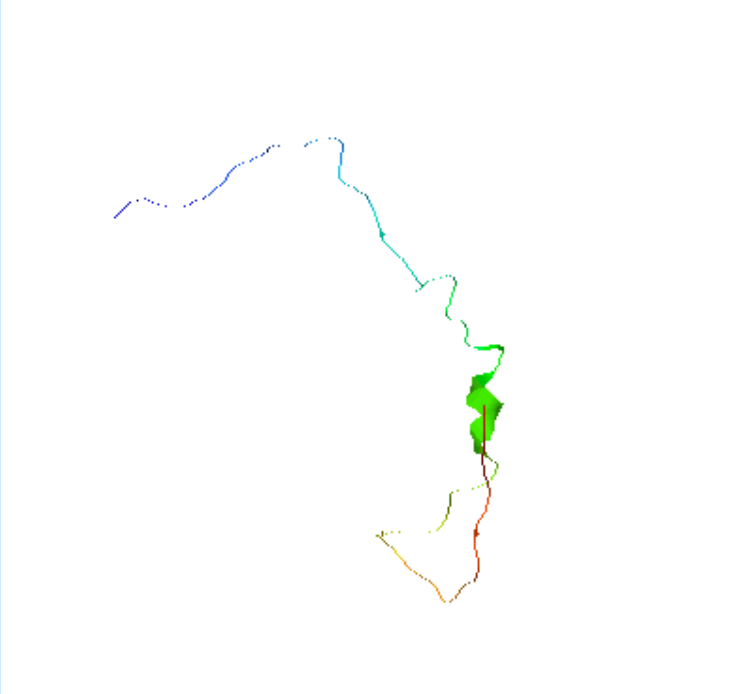

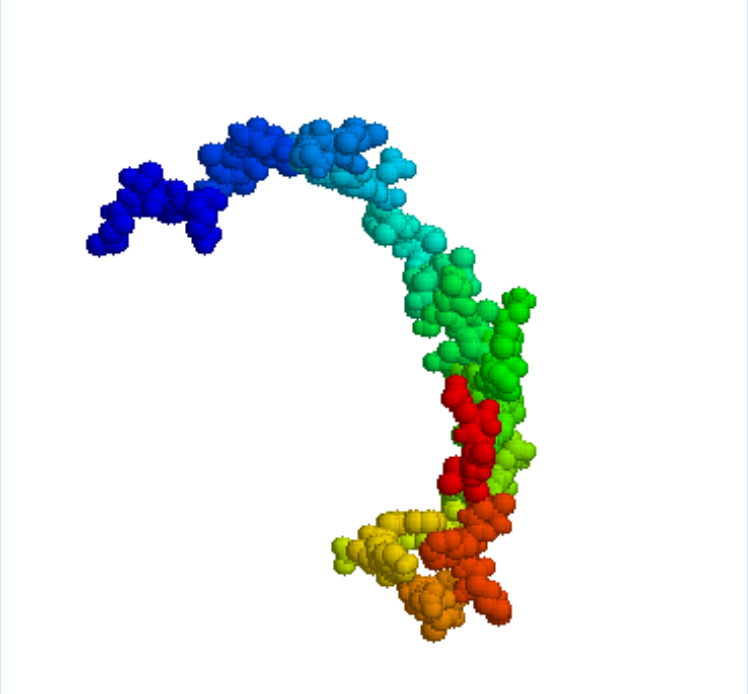

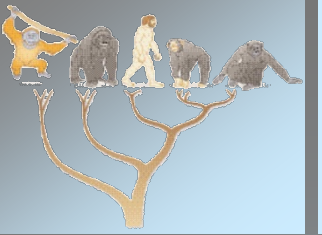

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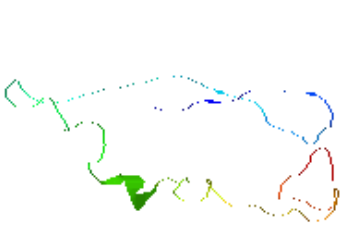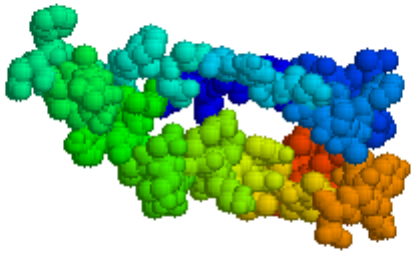
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