CAP 5510: Introduction to Bioinformatics
CGS 5166: Bioinformatics Tools

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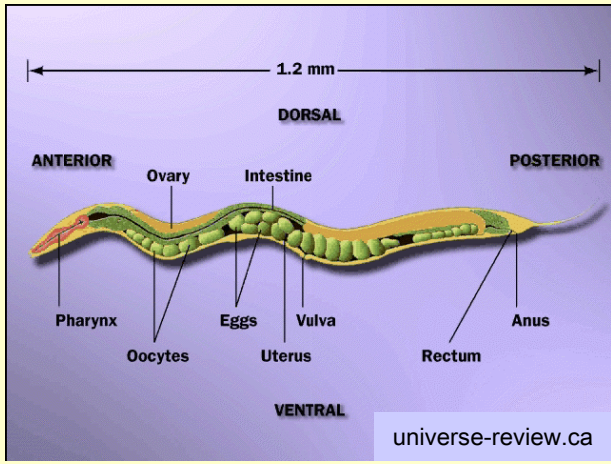
Genome Sizes

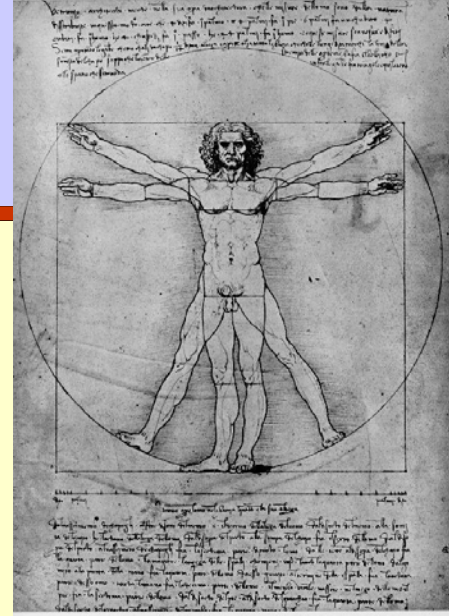
Organism	Size	Date	Est. # genes
HIV type 1	9.2 Kb	1997	9
H. influenzae	1.8 Mb	1995	1,740
M. genitalium	0.58 Mb	1998	525
E. coli	4.7 Mb	1997	4,000
S. cerevisiae	12.1 Mb	1996	6,034
C. elegans	97 Mb	1998	19,099
A. thaliana	100 Mb	2000	25,000
D. melanogaster	180 Mb	2000	13,061
M. musculus	3 Gb	2002	~30,000
H. sapiens	3 Gb	2001	32,000+

Caenorhabditis Elegans



- Entire genome – 1998; 8 year effort
- 1st animal; 2nd eukaryote (after yeast)
- Nematode (phylum)
- Easy to experiment with; Easily observable
- 97 million bases; 20,000 genes;
  12,000 with known function;
  6 Chromosomes; GC content 36%
- 959 cells; 302-cell nervous system
- 36% of proteins common with human
- 15 Kb mitochondrial genome
- Results in ACeDB
- 25% of genes in operons
- Important for HGP: technology, software, scale/efficiency
- 182 genes with alternative splice variants

Homo sapiens



- Sequenced – 2001; 15 year effort
- 3 billion bases, 500 gaps
- Variable density of Genes, SNPs, CpG islands

- ~ 1.1 % of the genome codes for proteins; 99%?
- ~ 40-48 % of the genome consists of repeat sequences
- ~ 10 % of the genome consists of repeats called ALUs
- ~ 5 % of the genome consists of long repeats (>1 Kb)
- 223 genes common with bacteria that are missing from worm, fly or yeast.
- Completed in April 2003

http://www.ibiblio.org/wm/paint/auth/vinci/sketch/vitruvian.jpg

The Suffix Tree Data Structure

- *Borrelia burgdorferi*
  - 1 million bases
  - Shotgun Sequencing:
    - 4612 fragments
    - 2 million bases long totally
    - Using suffix trees - 15 min for Fragment Assembly
    - Using Dynamic Programming - 10 days

Sequence Alignment – Why?

>gi|12643549|sp|O18381|PAX6_DROME Paired box protein Pax-6 (Eyeless protein)
MRNLPCLGTAGGSGLGGIAGKPSPTMEAVEASTASHRHSTSSYFATTYYHLTDDECHSGVNQLGGVFVGG
RPLPDSTRQKIVELAHSGARPCDISRILQVSNGCVSKILGRYYETGSIRPRAIGGSKPRVATAEVVSKIS
QYKRECPSIFAWEIRDRLLQENVCTNDNIPSVSSINRVLRNLAAQKEQQSTGSGSSSTSAGNSISAKVSV
SIGGNVSNVASGSRGTLSSSTDLMQTATPLNSSESGGASNSGEGSEQEAIYEKLRLLNTQHAAGPGPLEP
ARAAPLVGQSPNHLGTRSSHPQLVHGNHQALQQHQQQSWPPRHYSGSWYPTSLSEIPISSAPNIASVTAY
ASGPSLAHSLSPPNDIESLASIGHQRNCPVATEDIHLKKELDGHQSDETGSGEGENSNGGASNIGNTEDD
QARLILKRKLQRNRTSFTNDQIDSLEKEFERTHYPDVFARERLAGKIGLPEARIQVWFSNRRAKWRREEK
LRNQRRTPNSTGASATSSSTSATASLTDSPNSLSACSSLLSGSAGGPSVSTINGLSSPSTLSTNVNAPTL
GAGIDSSESPTPIPHIRPSCTSDNDNGRQSEDCRRVCSPCPLGVGGHQNTHHIQSNGHAQGHALVPAISP
RLNFNSGSFGAMYSNMHHTALSMSDSYGAVTPIPSFNHSAVGPLAPPSPIPQQGDLTPSSLYPCHMTLRP
PPMAPAHHHIVPGDGGRPAGVGLGSGQSANLGASCSGSGYEVLSAYALPPPPMASSSAADSSFSAASSAS
ANVTPHHTIAQESCPSPCSSASHFGVAHSSGFSSDPISPAVSSYAHMSYNYASSANTMTPSSASGTSAHV
APGKQQFFASCFYSPWV

>gi|6174889|PAX6_HUMAN Paired box protein (Oculorhombin) (Aniridia, type II protein)
MQNSHSGVNQLGGVFVNGRPLPDSTRQKIVELAHSGARPCDISRILQVSNGCVSKILGRYYETGSIRPRA
IGGSKPRVATPEVVSKIAQYKRECPSIFAWEIRDRLLSEGVCTNDNIPSVSSINRVLRNLASEKQQMGAD
GMYDKLRMLNGQTGSWGTRPGWYPGTSVPGQPTQDGCQQQEGGGENTNSISSNGEDSDEAQMRLQLKRKL
QRNRTSFTQEQIEALEKEFERTHYPDVFARERLAAKIDLPEARIQVWFSNRRAKWRREEKLRNQRRQASN
TPSHIPISSSFSTSVYQPIPQPTTPVSSFTSGSMLGRTDTALTNTYSALPPMPSFTMANNLPMQPPVPSQ
TSSYSCMLPTSPSVNGRSYDTYTPPHMQTHMNSQPMGTSGTTSTGLISPGVSVPVQVPGSEPDMSQYWPR
LQ

Drosophila Eyeless vs. Human Aniridia

```
Query: 57   HSGVNQLGGVFVGGRPLPDSTRQKIVELAHSGARPCDISRILQVSNGCVSKILGRYYETG 116
            HSGVNQLGGVFV GRPLPDSTRQKIVELAHSGARPCDISRILQVSNGCVSKILGRYYETG
Sbjct: 5    HSGVNQLGGVFVNGRPLPDSTRQKIVELAHSGARPCDISRILQVSNGCVSKILGRYYETG 64

Query: 117 SIRPRAIGGSKPRVATAEVVSKISQYKRECPSIFAWEIRDRLLQENVCTNDNIPSVSSIN 176
            SIRPRAIGGSKPRVAT EVVSKI+QYKRECPSIFAWEIRDRLL E VCTNDNIPSVSSIN
Sbjct: 65   SIRPRAIGGSKPRVATPEVVSKIAQYKRECPSIFAWEIRDRLLSEGVCTNDNIPSVSSIN 124

Query: 177 RVLRNLAAQKEQ 188
            RVLRNLA++K+Q
Sbjct: 125 RVLRNLASEKQQ 136
```

```
Query: 417 TEDDQARLILKRKLQRNRTSFTNDQIDSLEKEFERTHYPDVFARERLAGKIGLPEARIQV 476
           +++ Q RL LKRKLQRNRTSFT +QI++LEKEFERTHYPDVFARERLA KI LPEARIQV
Sbjct: 197 SDEAQMRLQLKRKLQRNRTSFTQEQIEALEKEFERTHYPDVFARERLAAKIDLPEARIQV 256

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           WFSNRRAKWRREEKLRNQRR
Sbjct: 257 WFSNRRAKWRREEKLRNQRR 276
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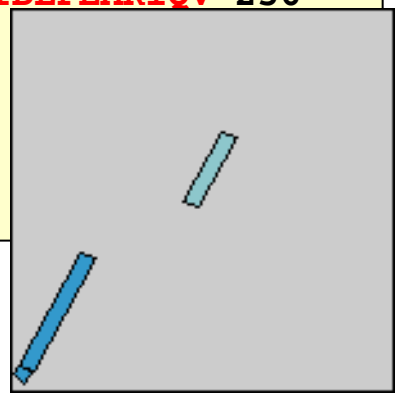


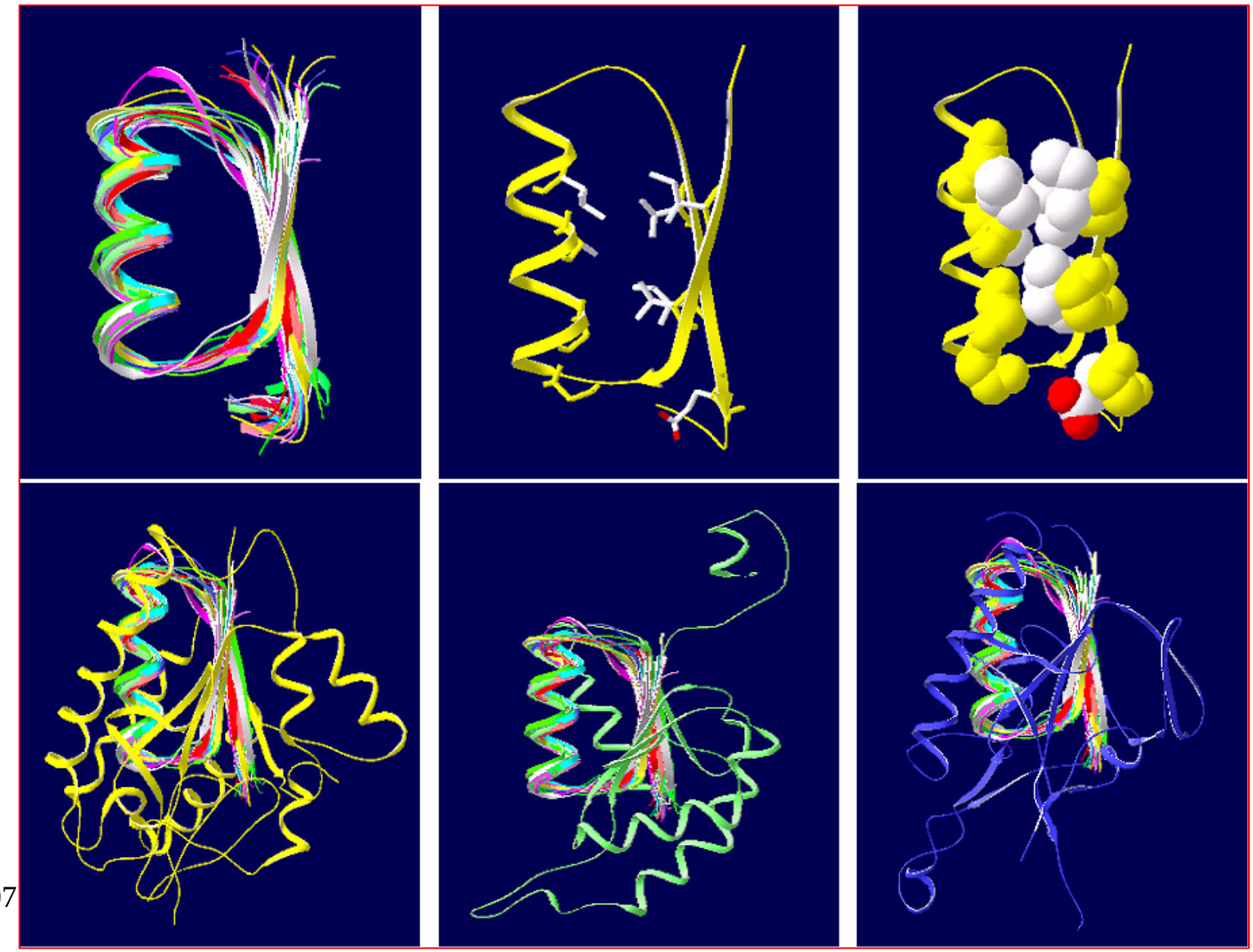
E-Value = 2e-31

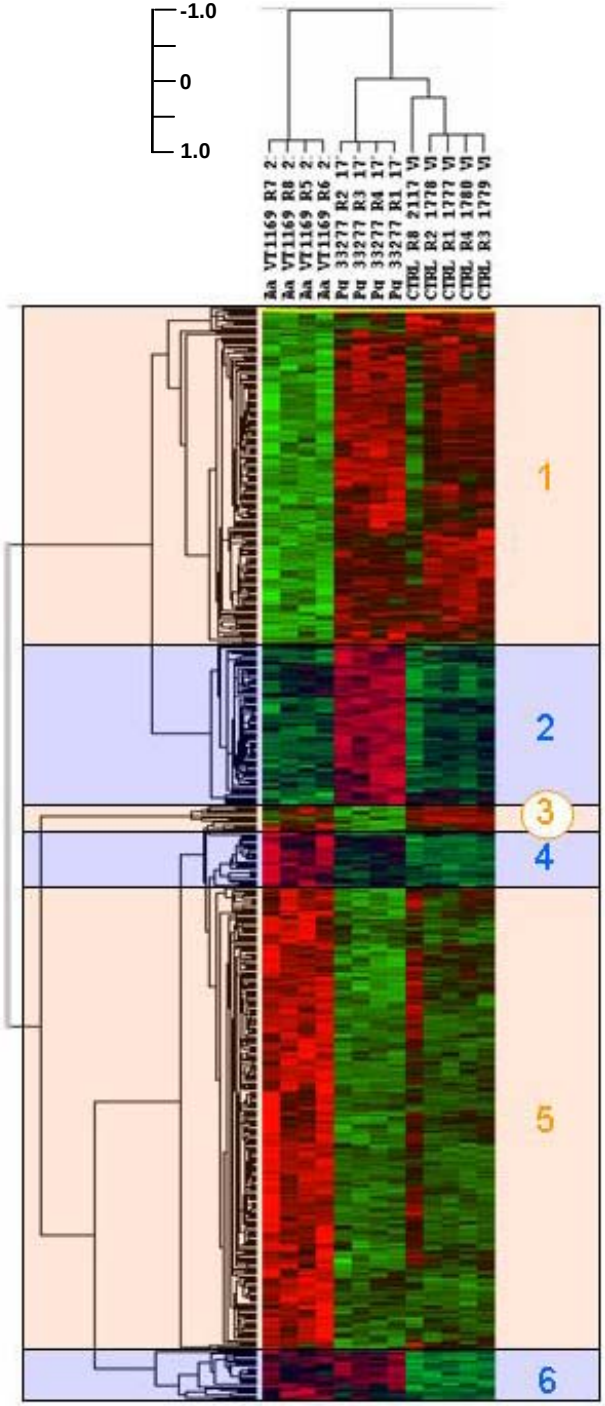
Motif Detection in Protein Sequences

- MTDKMQSLALAPVGNLDSYIRAANAWPMLSADEERALAEKLHYHGDLEAA
  KTLILSHLRFVVHIARNYAGYGLPQADLIQEGNIGLMKAVRRFNPEVGVR
  LVSFAVHWIKAEIHEYVLRNWRIVKVATTKAQRKLFFNLRKTKQRLGWFN
  QDEVEMVARELGVTSKDVREMESRMAAQDMTFDLSSDDDSDSQPMAPVLY
  LQDKSSNFADGIEDDNWEEQAANRLTDAMQGLDERSQDIIRARWLDEDNK
  STLQELADRYGVSAERVRQLEKNAMKKLRAAIEA

- MTDKMQSLALAPVGNLDSYIRAANAWPMLSADEERALAEKLHYHGDLEAA
  KTLILSHLRFVVHIARNYAGYGLPQADLIQEGNIGLMKAVRRFNPEVGVR
  LVSFAVHWIKAEIHEYVLRNWRIVKVATTKAQRKLFFNLRKTKQRLGWFN
  QDEVEMVARELGVTSKDVREMESRMAAQDMTFDLSSDDDSDSQPMAPVLY
  LQDKSSNFADGIEDDNWEEQAANRLTDAMQGLDERSQDIIRARWLDEDNK
  STLQELADRYGVSAERVRQLEKNAMKKLRAAIEA

Patterns in Protein Structures

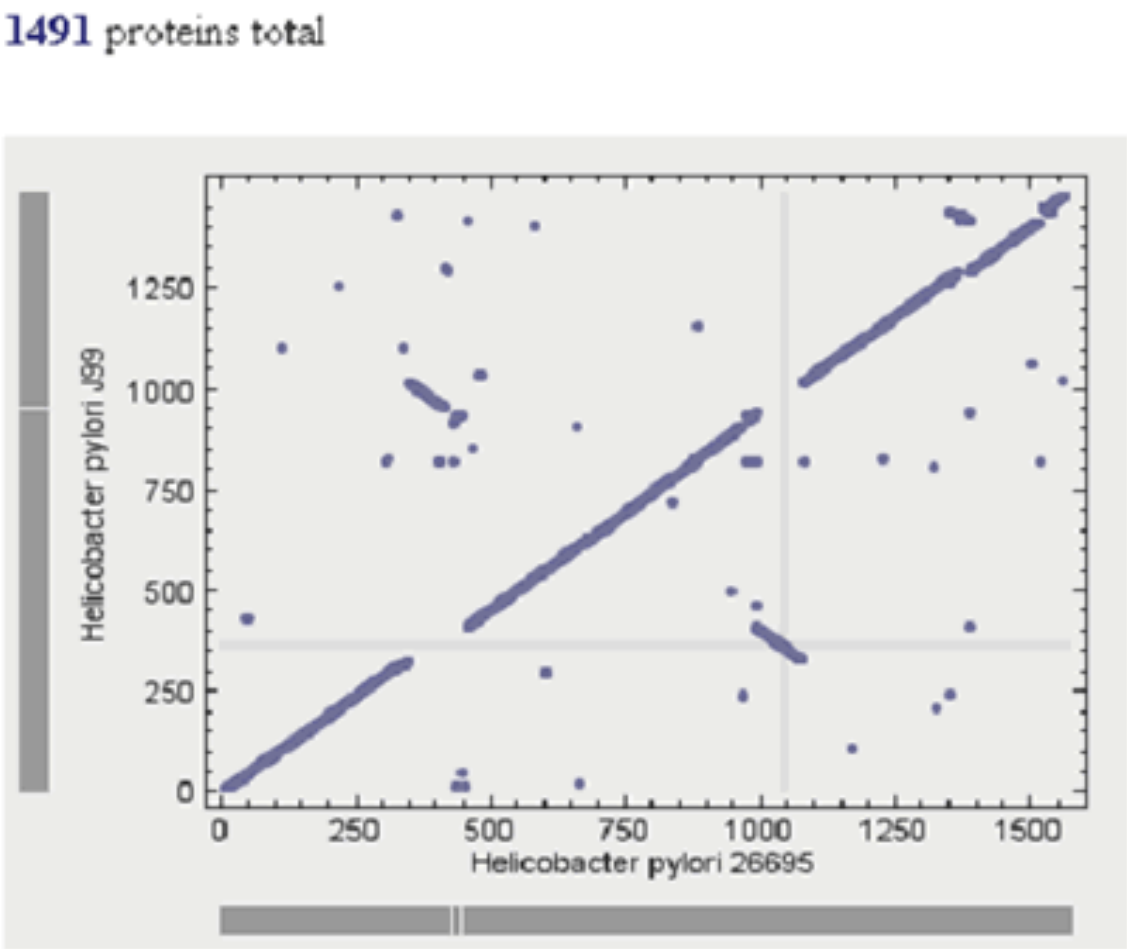




Microarray Analysis

Different patterns of gene expression of oral epithelial IHGK cells upon co-culture with A. actinomycetemcomitans or P. gingivalis.

Tools: GenePlot



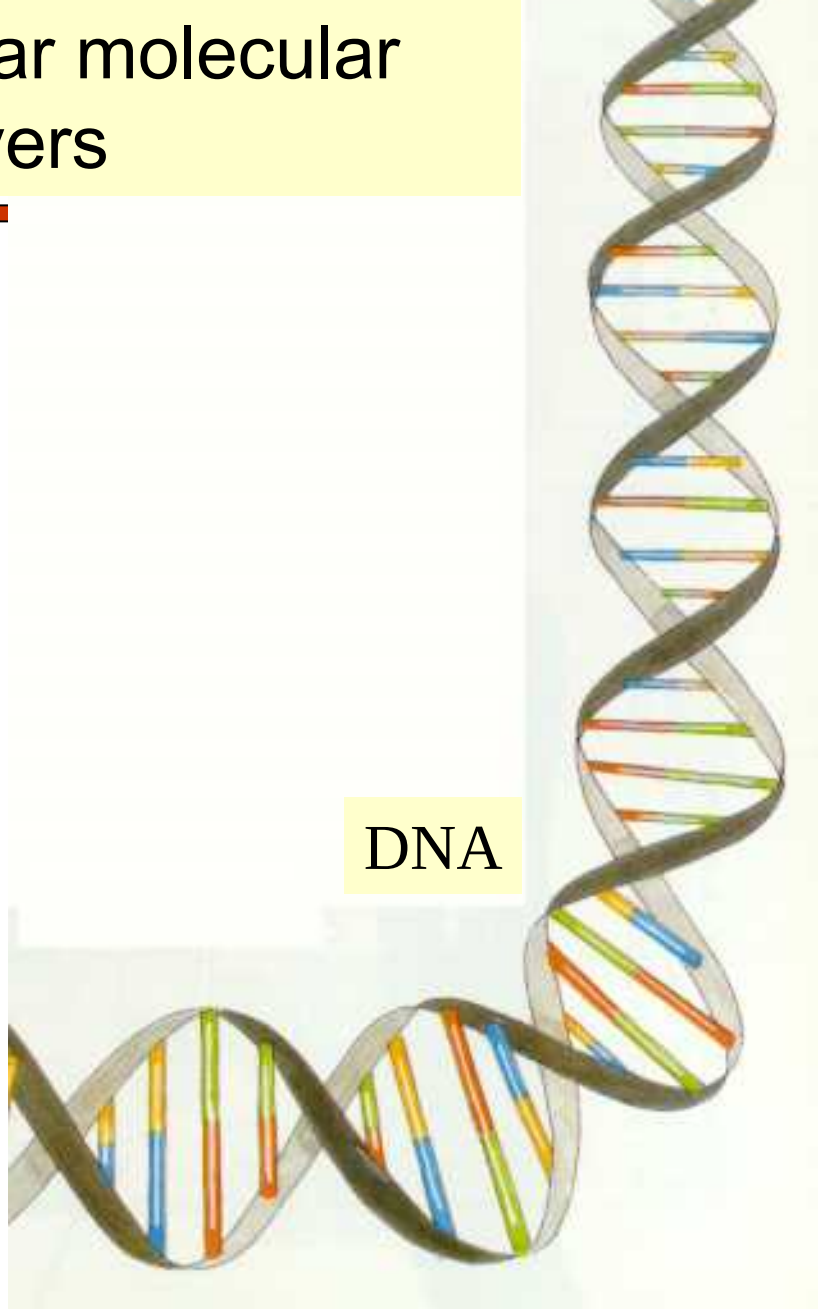
Comparison of proteins from two strains of Helicobacter Pylori, 26695 and J99. Each point represents a pair of proteins from the two organisms showing a symmetrical best BLAST score; the coordinates of each point correspond to the position of the protein genes in the 2 genomes. Note the juxtaposition and inversion of two segments of the genome between the two strains.

SIDS

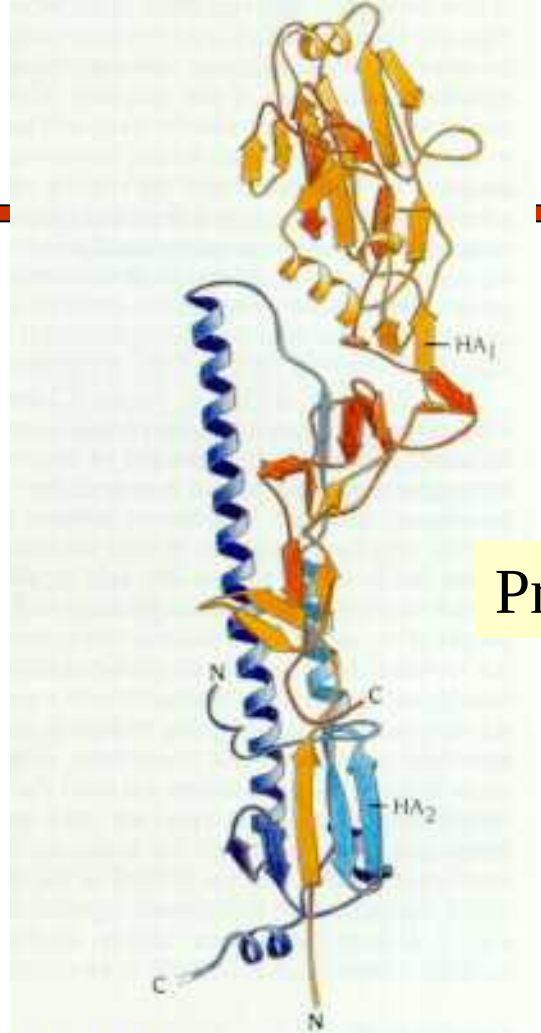
- 18000 Amish people in Pennsylvania
- Mostly intermarried due to religious doctrine
- rare recessive diseases occurred with high frequencies.
- SIDS: 3000 deaths/year (US); 21 deaths (Amish community)
- Many research centers failed to identify cause
- Collaboration between Affymetrix, TGEN & Clinic for special children solved the problem in 2 months
- Studied 10000 SNPs using microarray technology
- Their experiments showed that all the sick infants had two mutant copies of a specific gene, and their parents were carriers of the mutant gene.
- Conclusion: Disease caused by 2 abnormal copies of TSPYL gene
- Identified genes expressed in key organs (brainstem,testes)
- http://www.affymetrix.com/community/wayahead/modern_miracle.affx

Molecular Biology Background

2 star molecular players



DNA



Protein

Figure 5.21 Schematic diagram of the subunit structure of hemagglutinin from influenza virus. The structure comprises about 550 amino acids arranged in two chains HA_1 (red) and HA_2 (blue). The first half of each chain has a lighter color in the diagram. The subunit is very elongated with a long stemlike region built up by residues from both chains and includes one of the longest α helices known in a globular structure, about 75 Å long. The globular head is formed by residues only from HA_1. (Courtesy of Don Wiley, Harvard University.)

The Players

DNA

String with alphabet {A, C, G, T}

Nucleotides/Bases

RNA

String with alphabet {A, C, G, U} **Bases**

Protein

String with 20-letter alphabet

Amino acids/Residues

Typical DNA Sequence

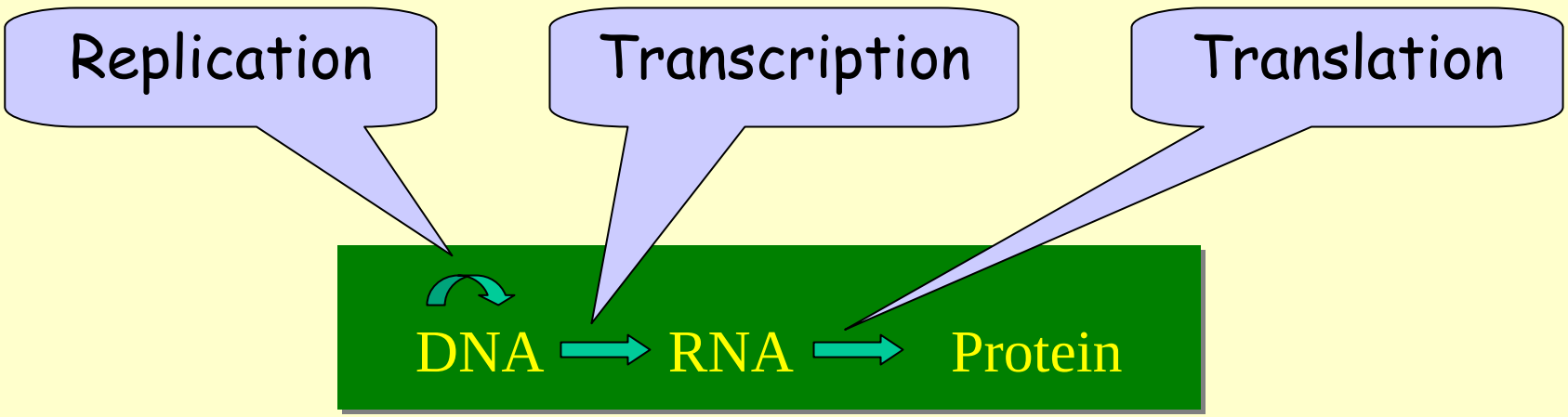
```
   1 gggagaacac ccggagaagg aggaggaggc gaagaaaagc aacagaagcc cagttgctgc
  61 tccaggtccc tcggacagag ctttttccat gtggagactc tctcaatgga cgtgccccct
 121 agtgcttctt agacggactg cggtctccta aaggtcgacc atggtggccg ggacccgctg
 181 tcttctagtg ttgctgcttc cccaggtcct cctgggcggc gcggccggcc tcattccaga
 241 gctgggccgc aagaagttcg ccgcggcatc cagccgaccc ttgtcccggc cttcggaaga
 301 cgtcctcagc gaatttgagt tgaggctgct cagcatgttt ggcctgaagc agagacccac
 361 ccccagcaag gacgtcgtgg tgcccccta tatgctagat ctgtaccgca ggcactcagg
 421 ccagccagga gcgcccgccc cagaccaccg gctggagagg gcagccagcc gcgccaacac
 481 cgtgcgcagc ttccatcacg aagaagccgt ggaggaactt ccagagatga gtgggaaaac
 541 ggcccggcgc ttcttcttca atttaagttc tgtccccagt gacgagtttc tcacatctgc
 601 agaactccag atcttccggg aacagataca ggaagctttg ggaaacagta gtttccagca
 661 ccgaattaat atttatgaaa ttataaagcc tgcagcagcc aacttgaaat ttcctgtgac
 721 cagactattg gacaccaggt tagtgaatca gaacacaagt cagtgggaga gcttcgacgt
 781 caccccagct gtgatgcggt ggaccacaca gggacacacc aaccatgggt ttgtggtgga
 841 agtggcccat ttagaggaga acccaggtgt ctccaagaga catgtgagga ttagcaggtc
 901 tttgcaccaa gatgaacaca gctggtcaca gataaggcca ttgctagtga cttttggaca
 961 tgatggaaaa ggacatccgc tccacaaacg agaaaagcgt caagccaaac acaaacagcg
```

Typical protein sequence

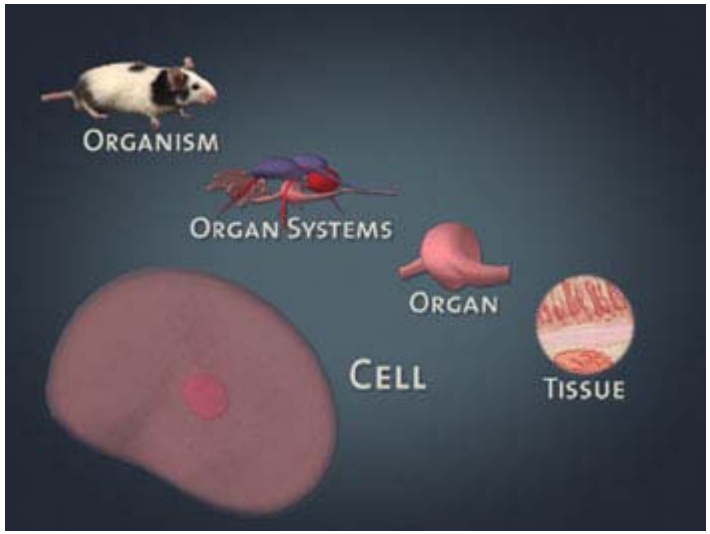
/translation="MVAGTRCLLVLLLPQVLLGGAAGLIPELGRKKFAAASSRPLSRP
SEDVLSEFELRLLSMFGLKQRPTPSKDVVVPPYMLDLYRRHSGQPGAPAPDHRLERAA
SRANTVRSFHHEEAVEELPEMSGKTARRFFFNLSSVPSDEFLTSAELQIFREQIQEAL
GNSSFQHRINIYEIIKPAAANLKFPVTRLLDTRLVNQNTSQWESFDVTPAVMRWTTQG
HTNHGFVVEVAHLEENPGVSKRHVRISRSLHQDEHSWSQIRPLLVTFGHDGKGHPLHK
REKRQAKHKQRKRLKSSCKRHPLYVDFSDVGWNDWIVAPPGYHAFYCHGECPFPLADH
LNSTNHAIVQTLVNSVNSKIPKACCVPTELSAISMLYLDENEKVVLKNYQDMVVEGCG
CR"

Central Dogma

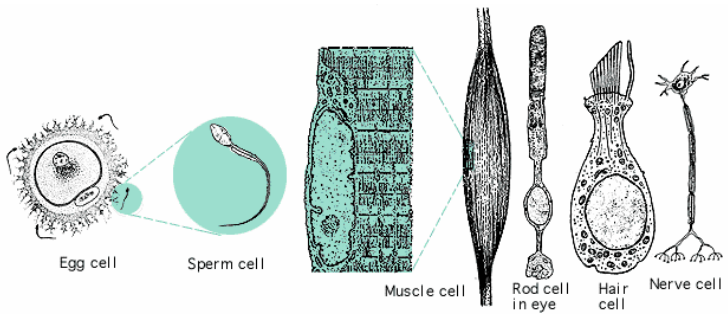
- DNA acts as a template to replicate itself.
- DNA is transcribed into RNA.
- RNA is translated into **Protein**.



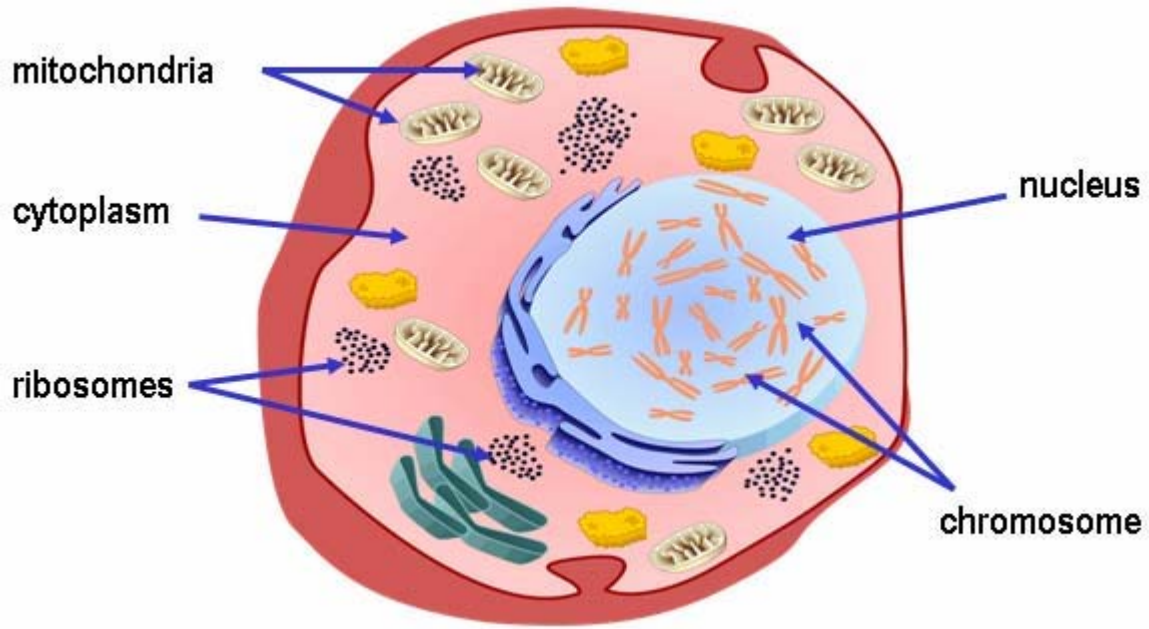
Cell



http://www.learner.org/channel/courses/essential/life/session1/closer1.html

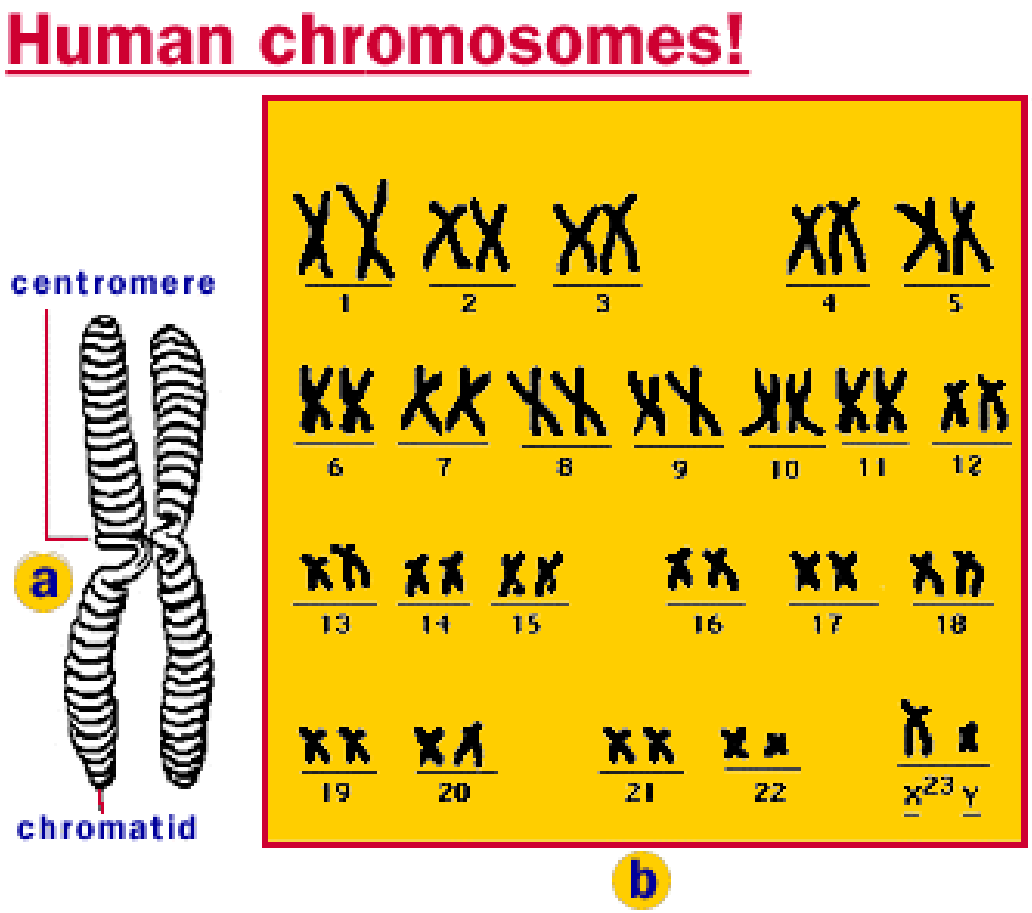


http://www.biology.eku.edu/RITCHISO/301notes1.htm

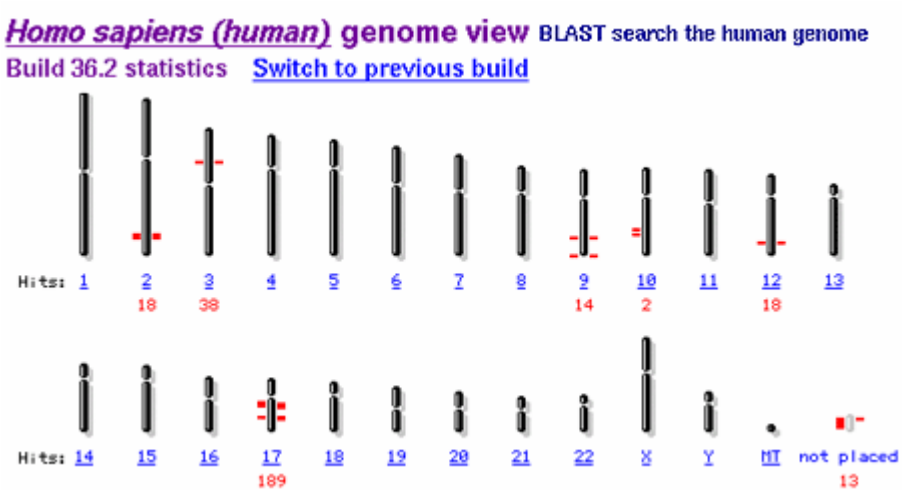


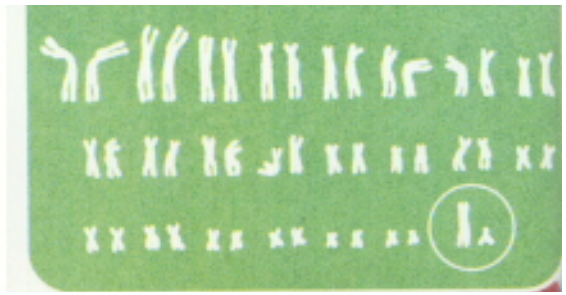
http://www.biotechnologyonline.gov.au/popups/img_cellwithlabels.cfm

Chromosomes

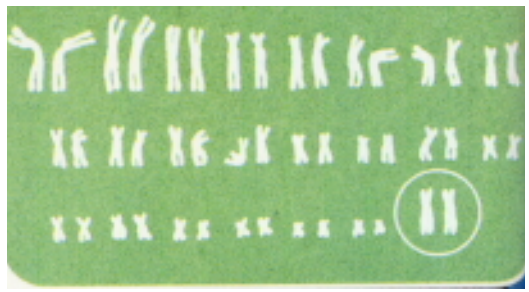


Chromosomes

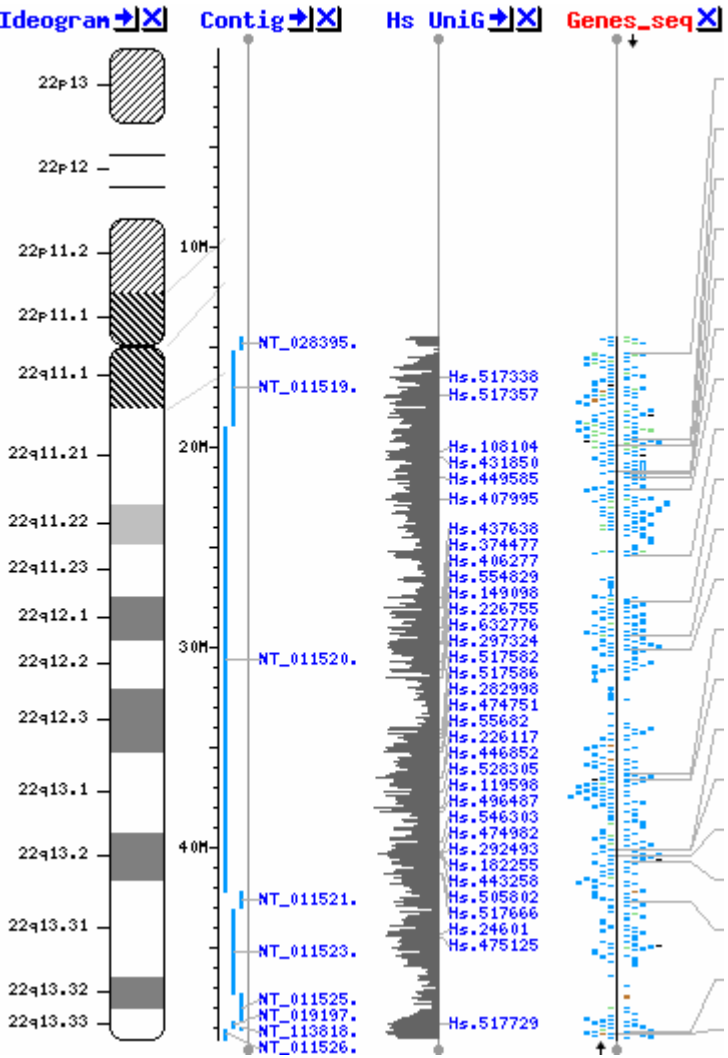




The chromosomal locations of several genes believed to be associated with the human BRCA1 gene implicated in breast cancer are highlighted.



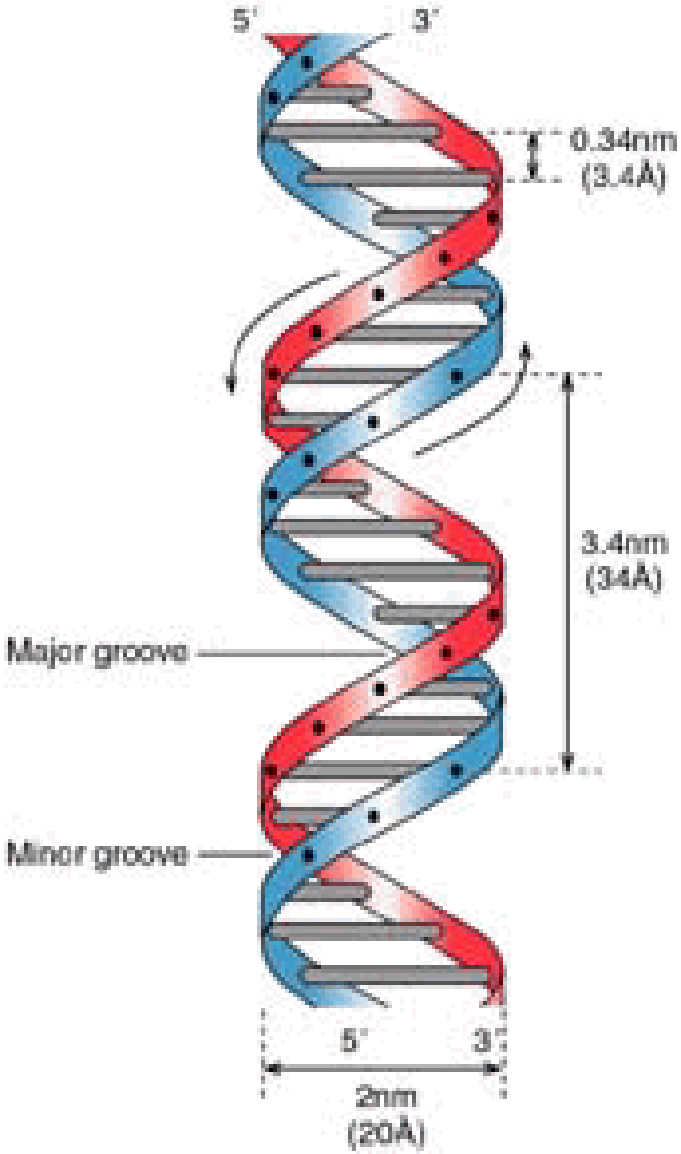
Human Chr 22



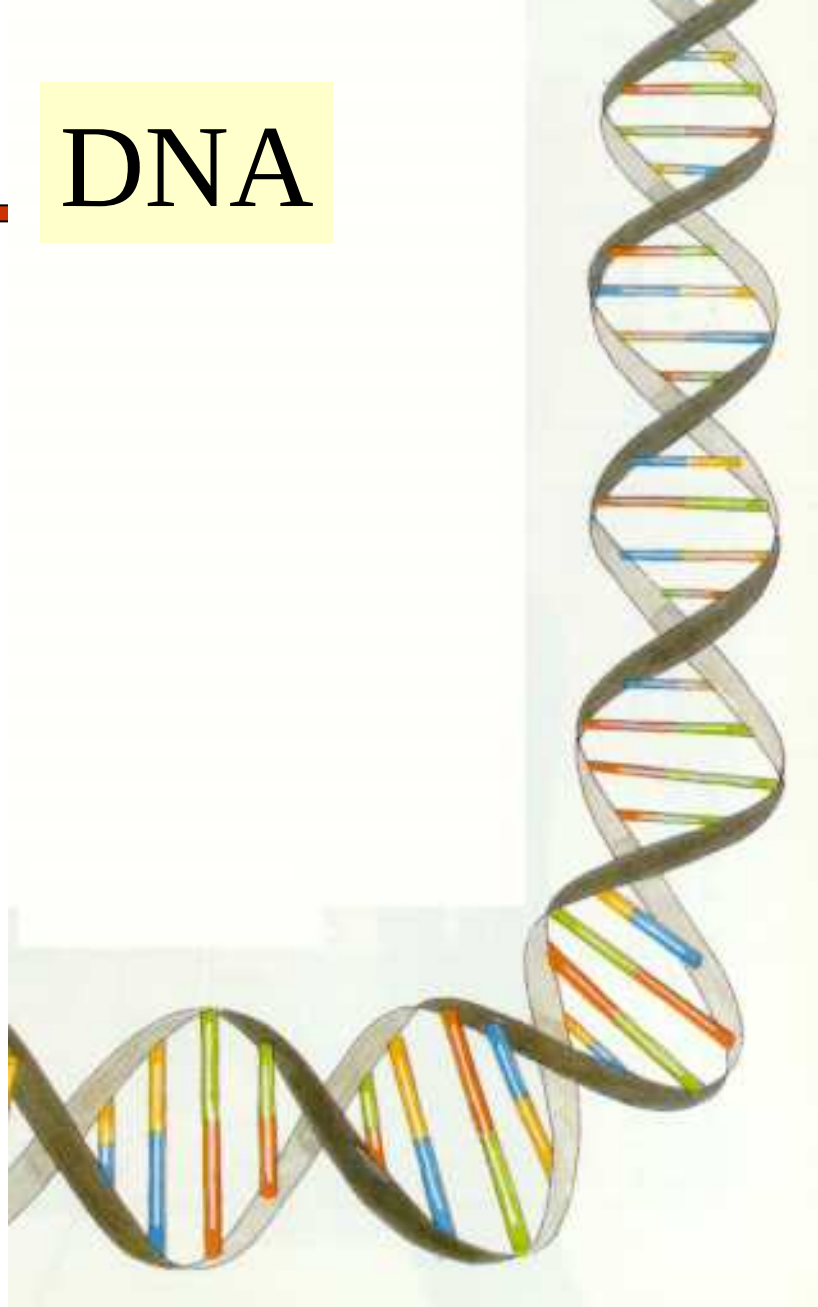
Symbol	Position	Description
ABCD1P4	22q11	ATP-binding cassette, sub-family D (ALD)
SNAP29	22q11.21	synaptosomal-associated protein

-
-
-

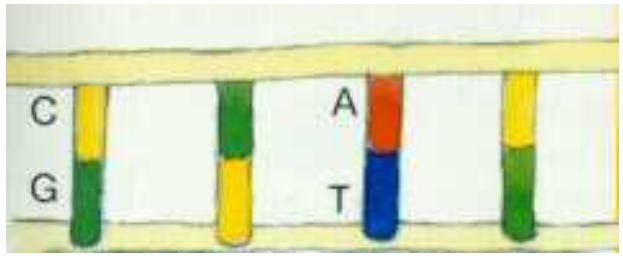
DNA Molecule



DNA



Complementary Bases



Proteins – Amino acids

amino acid	3 letter code	1 letter code
alanine	Ala	A
arginine	Arg	R
aspartic acid	Asp	D
asparginine	Asn	N
cysteine	Cys	C
glutamic acid	Glu	E
glutamine	Gln	Q
glycine	Gly	G
histine	His	H
isoleucine	Ile	I
leucine	Leu	L
lysine	Lys	K
methionine	Met	M
phenylalanine	Phe	F
proline	Pro	P
serine	Ser	S
threonine	Thr	T
tryptophan	Trp	W
tyrosine	Tyr	Y
valine	Val	V

Table 1.1: *Amino acid abbreviations*

RNA

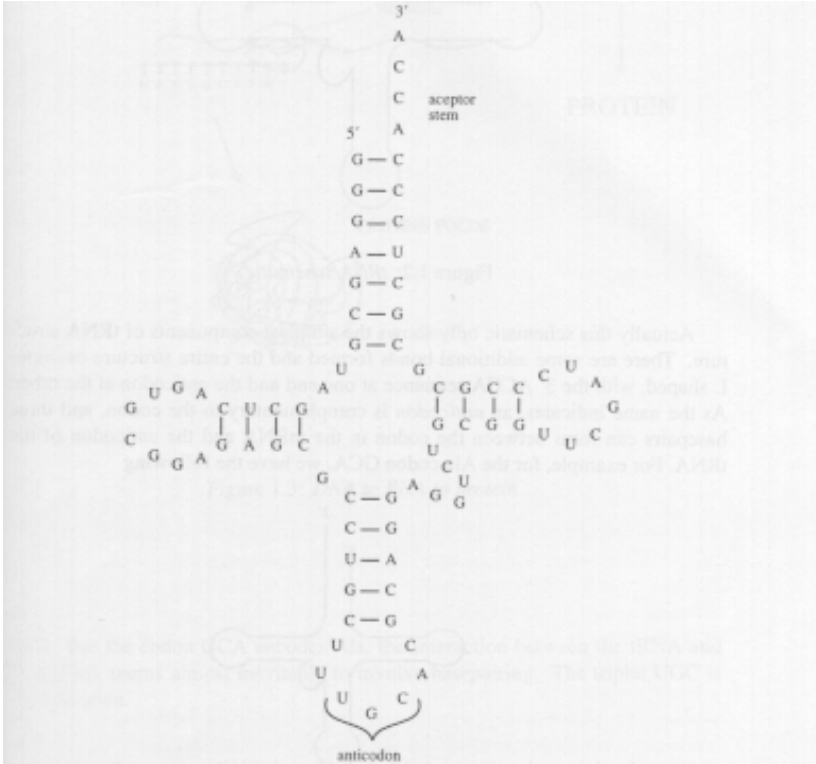
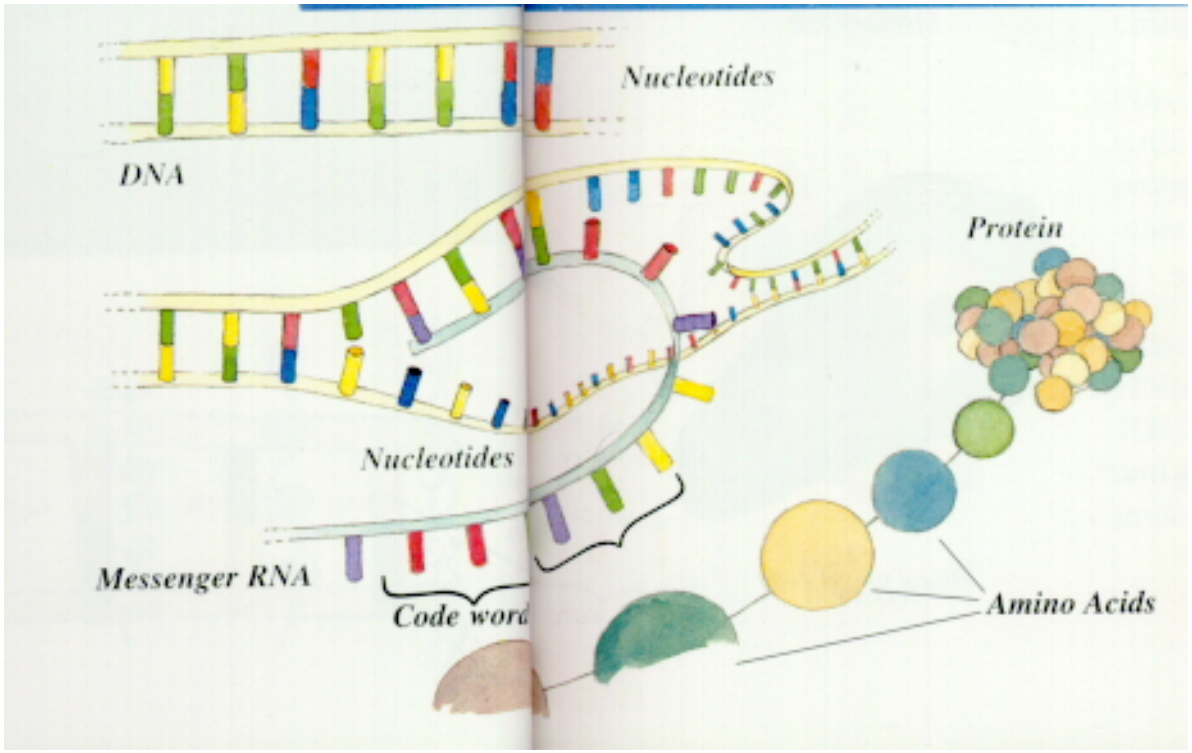


Figure 1.1: E. coli *Ala tRNA*

Genes

DNA → RNA → Protein



Basic Genetic Processes

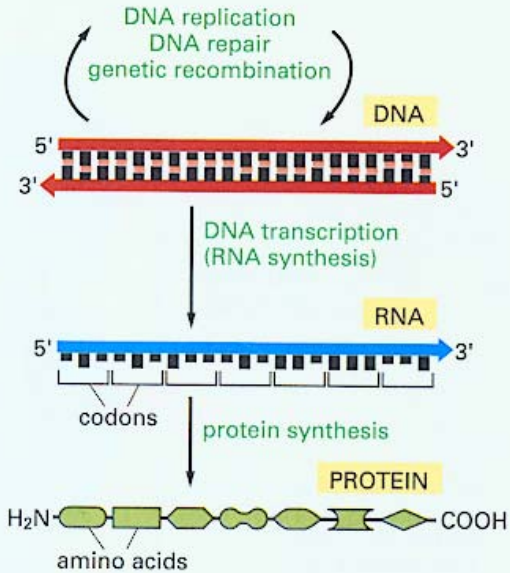
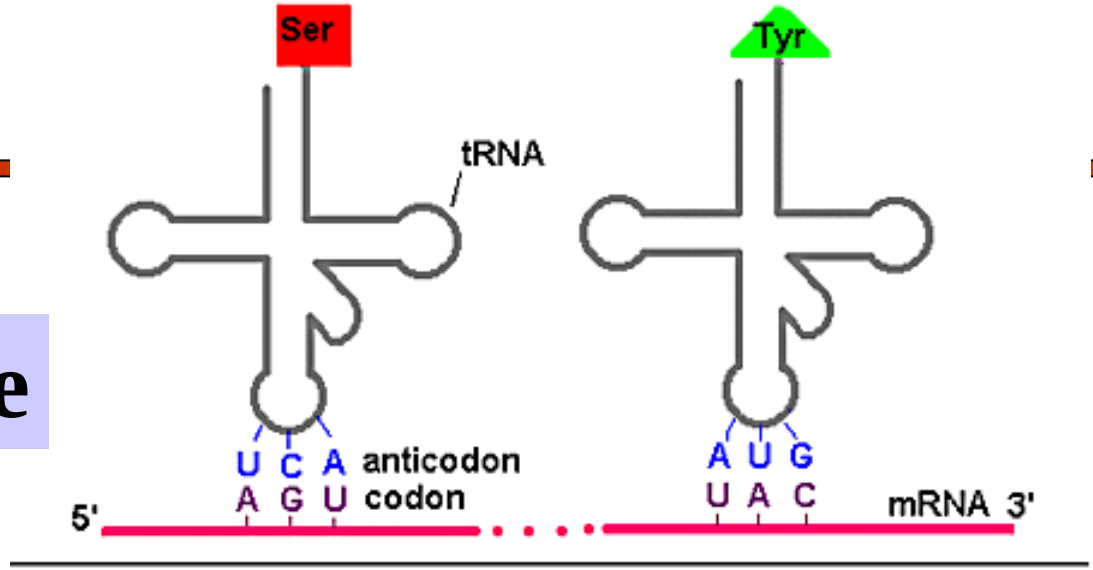


Figure 6–1 The basic genetic processes. The processes shown here are thought to occur in all present-day cells. Very early in the evolution of life, however, much simpler cells probably existed that lacked both DNA and proteins (see Figure 1–11). Note that a sequence of three nucleotides (a codon) in an RNA molecule codes for a specific amino acid in a protein.

The Genetic Code



2nd base in codon

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

The Genetic Code

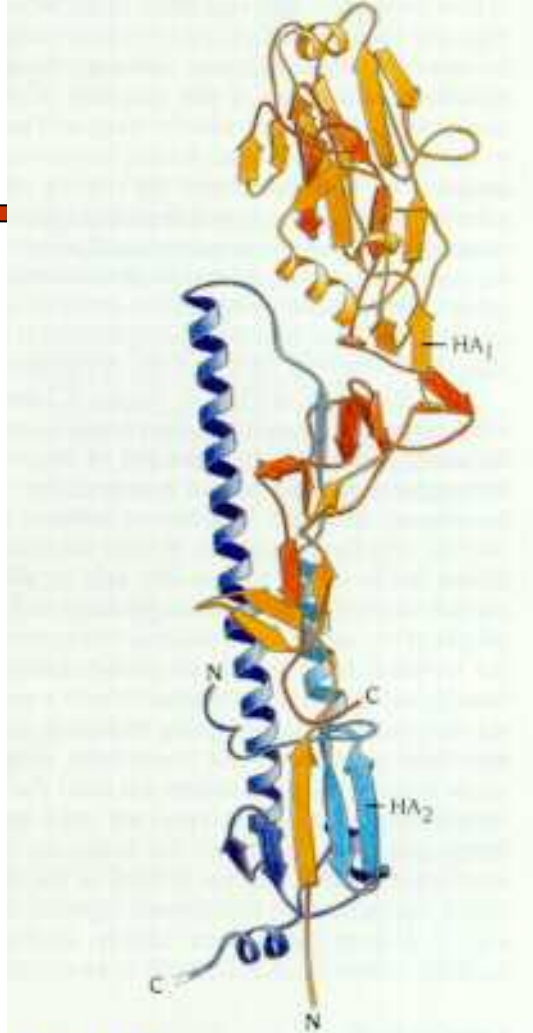
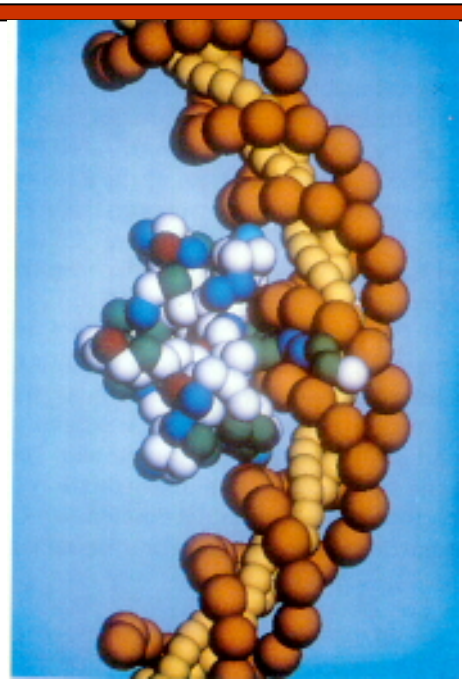
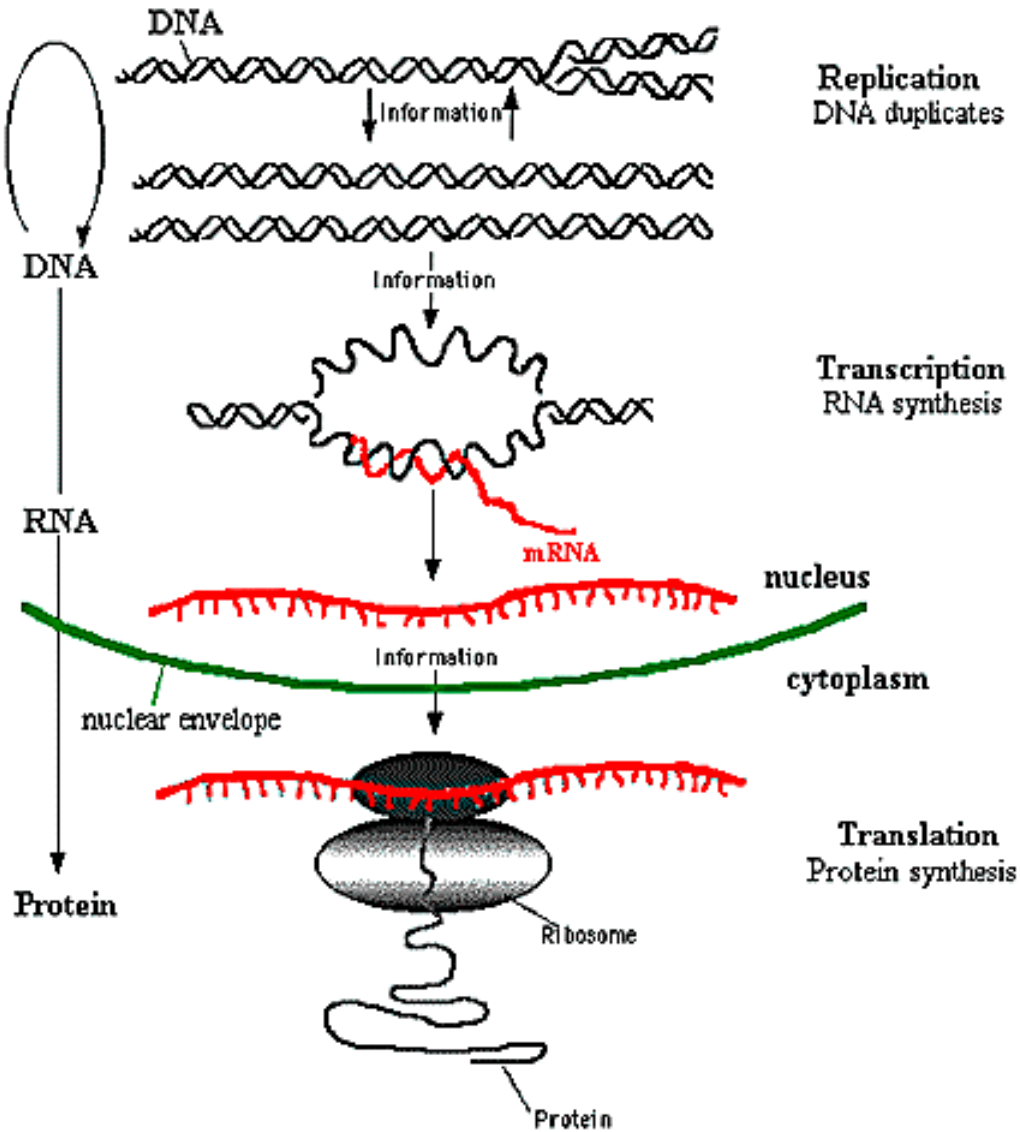
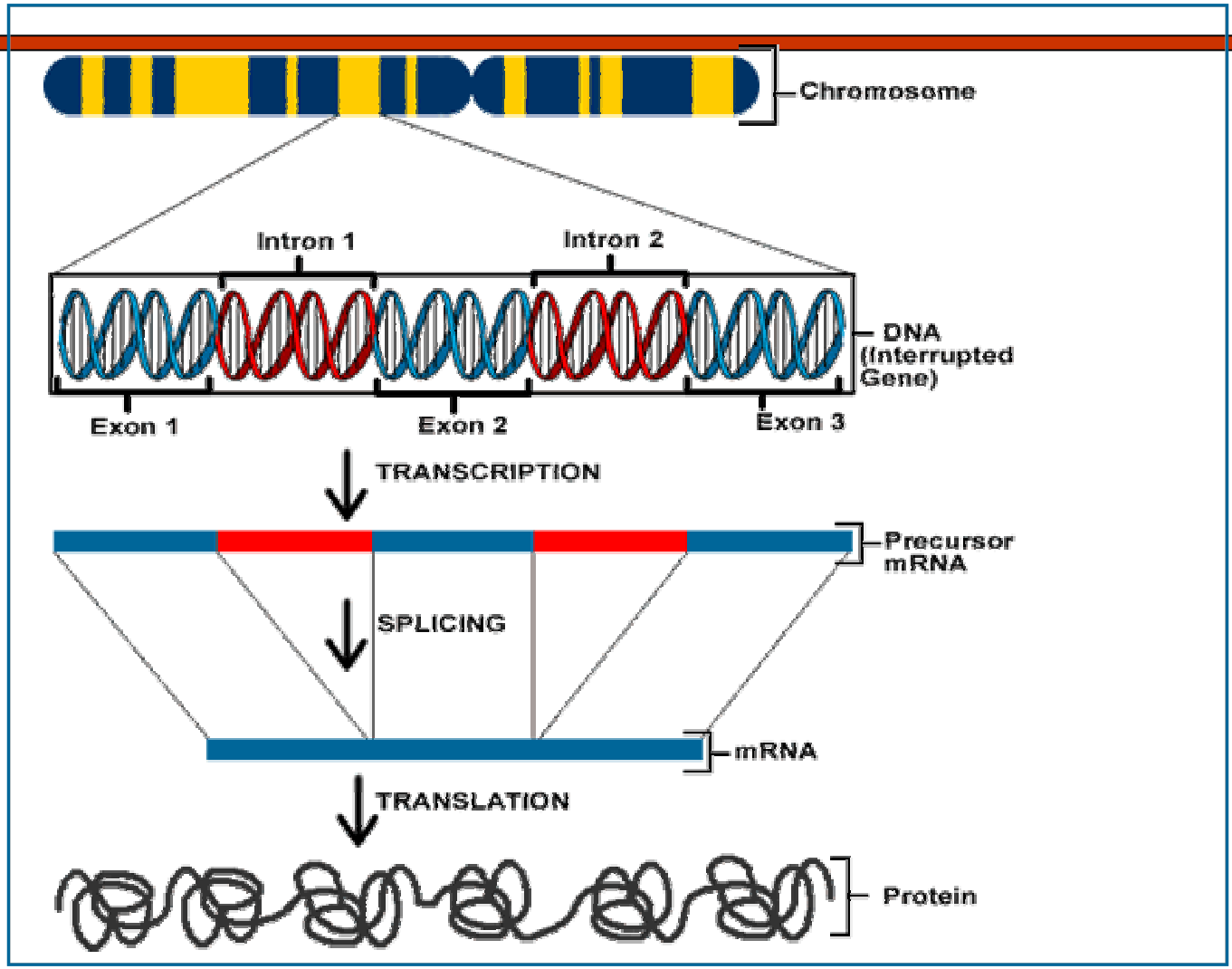


Figure 8.21 Schematic diagram of the subunit structure of hemagglutinin from influenza virus. The structure comprises about 550 amino acids arranged in two chains HA_1 (red) and HA_2 (blue). The first half of each chain has a lighter color in the diagram. The subunit is very elongated with a long stemlike region built up by residues from both chains and includes one of the longest α helices known in a globular structure, about 75 Å long. The globular head is formed by residues only from HA_1. (Courtesy of Don Wiley, Harvard University.)

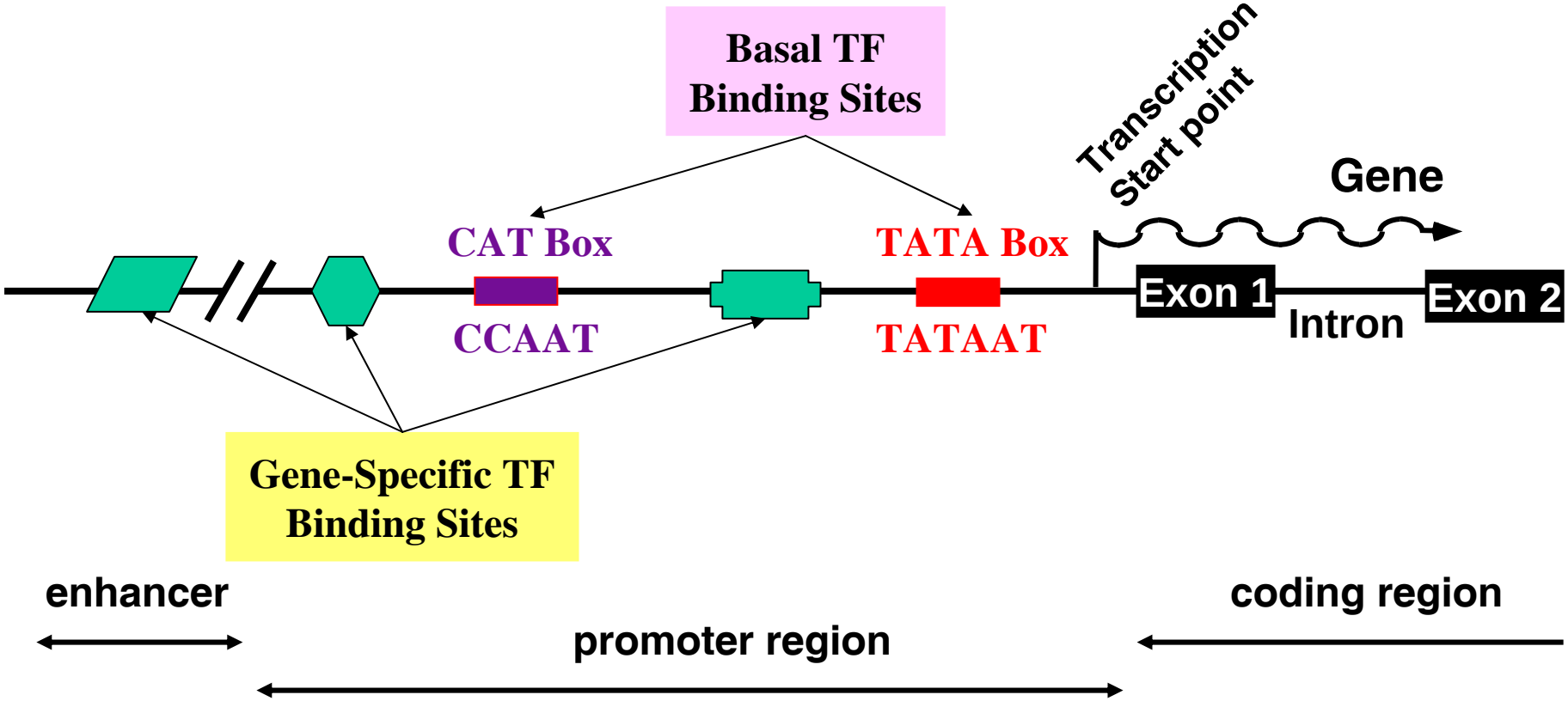




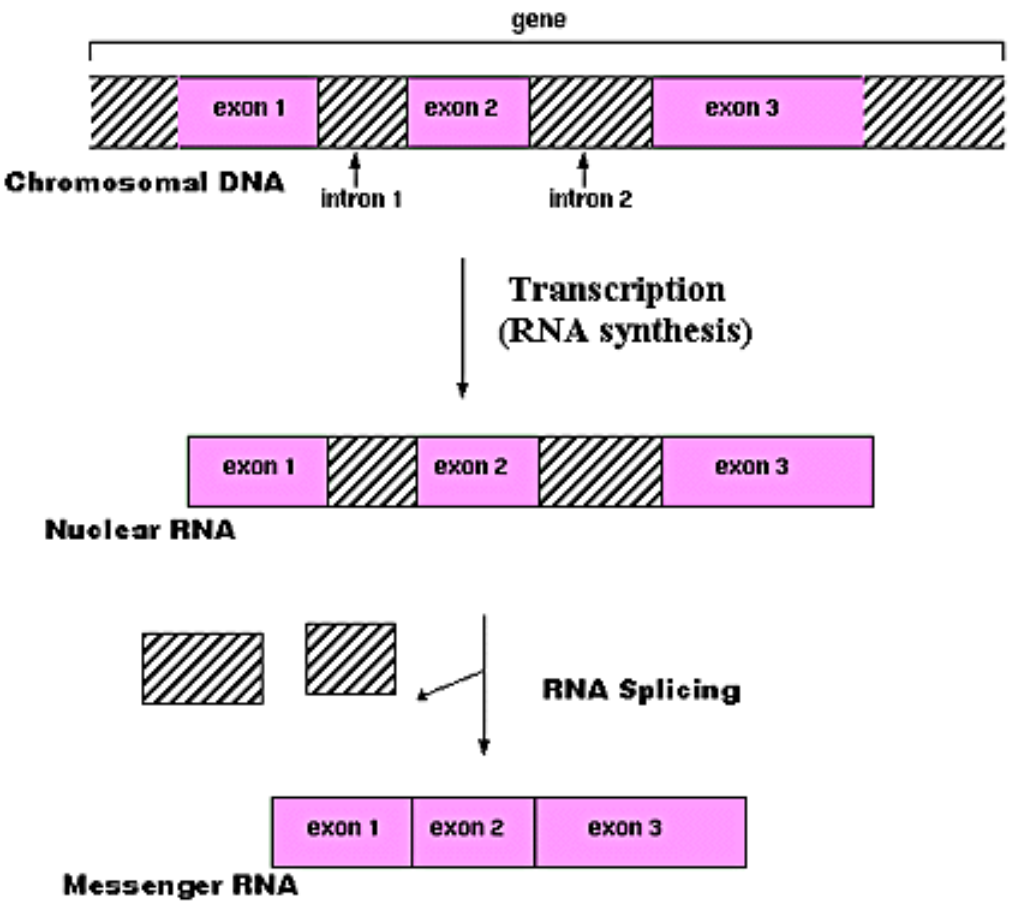
The Central Dogma of Molecular Biology


Chromosome
Intron 1
Intron 2
DNA
(Interrupted
Gene)
Exon 1
Exon 2
Exon 3
TRANSCRIPTION
Precursor
mRNA
SPLICING
mRNA
TRANSLATION
Protein

Transcription Regulation

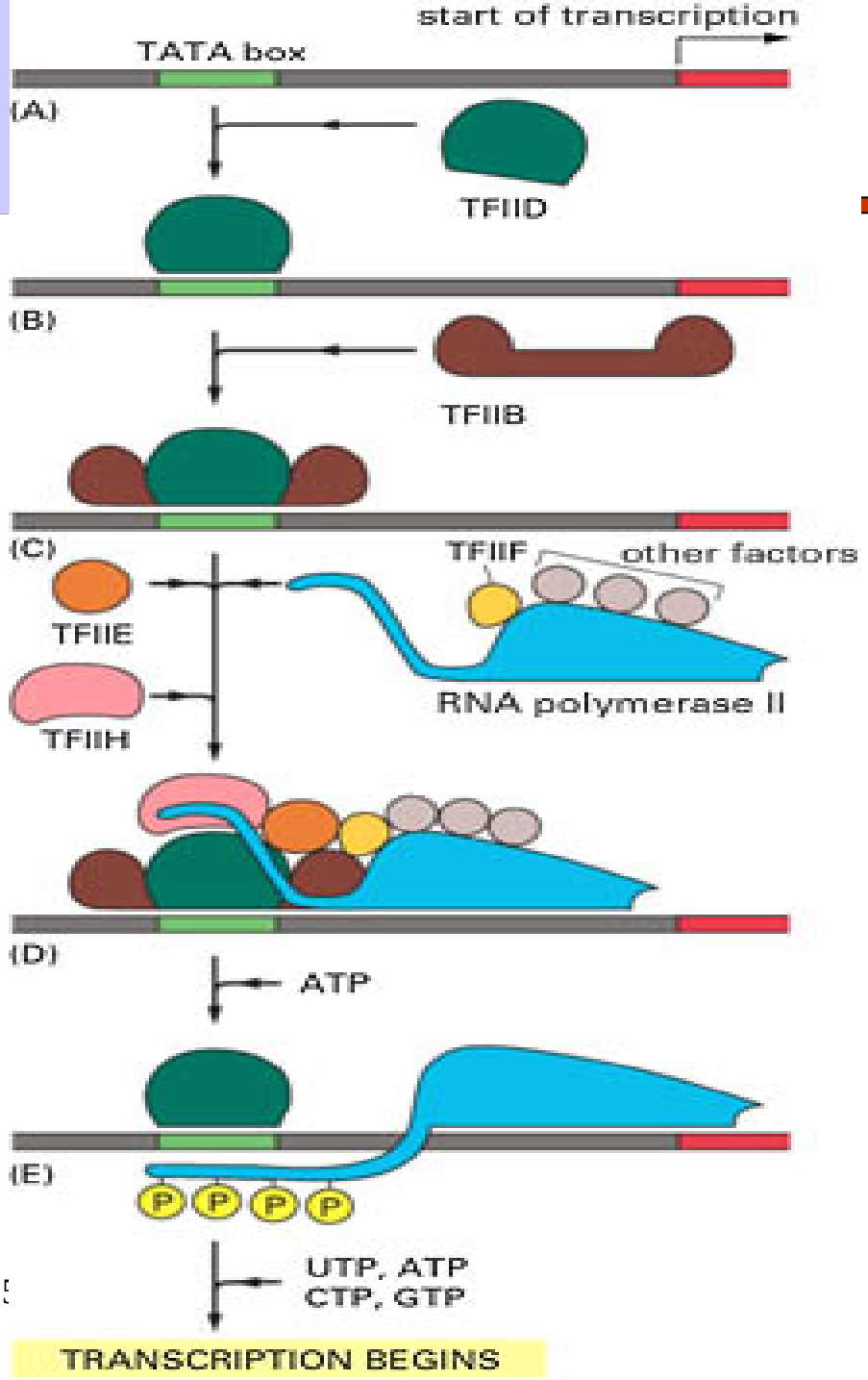


DNA Transcription



RNA synthesis and processing

Transcription Initiation



Transcription

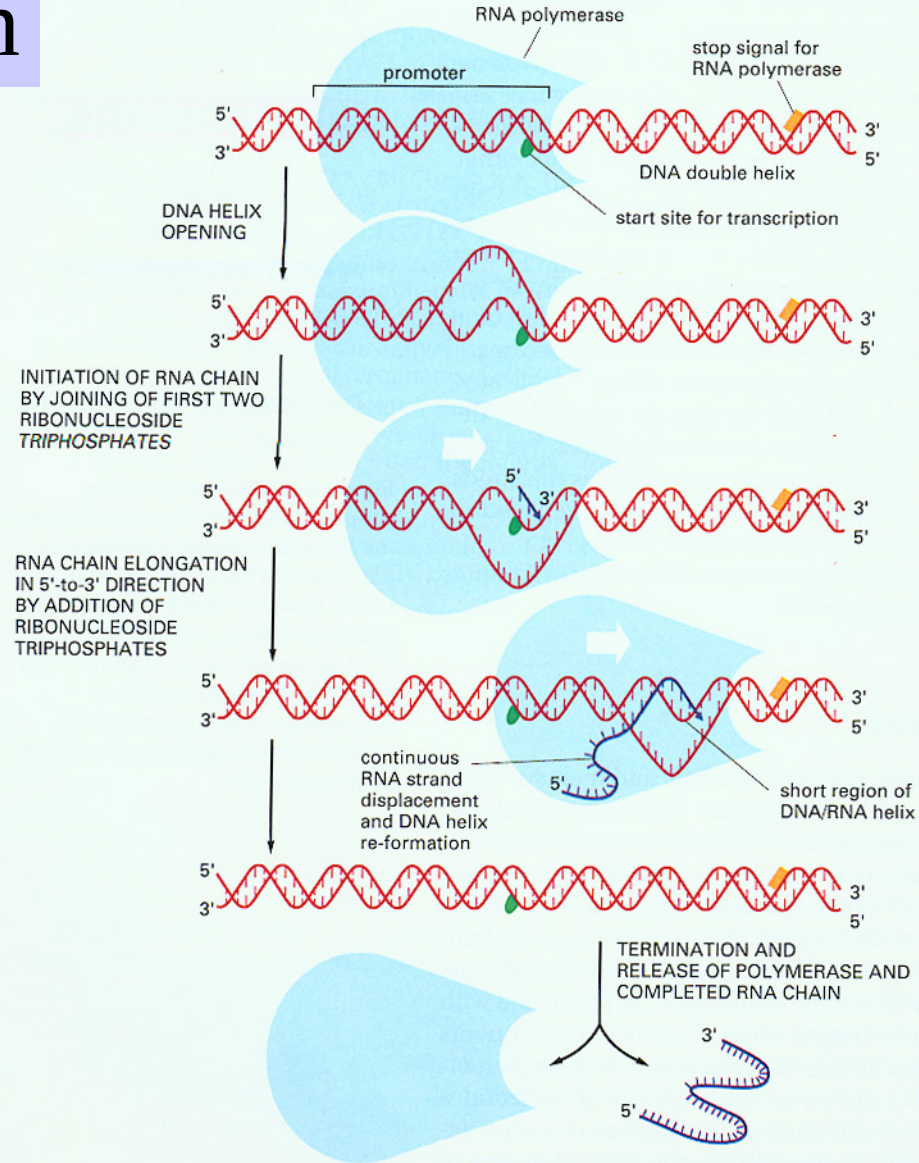


Figure 6–2 The synthesis of an RNA molecule by RNA polymerase. The enzyme binds to the promoter sequence on the DNA and begins its synthesis at a start site within the promoter. It completes its synthesis at a stop (termination) signal, whereupon both the polymerase and its completed RNA chain are released. During RNA chain elongation, polymerization rates average about 30 nucleotides per second at 37°C. Therefore, an RNA chain of 5000 nucleotides takes about 3 minutes to complete.

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Transcription Steps

RNA polymerase needs many transcription factors (TFIIA,TFIIB, etc.)

(A) The promoter sequence (TATA box) is located 25 nucleotides away from transcription initiation site.

(B) The TATA box is recognized and bound by transcription factor TFIID, which then enables the adjacent binding of TFIIB. DNA is somewhat distorted in the process.

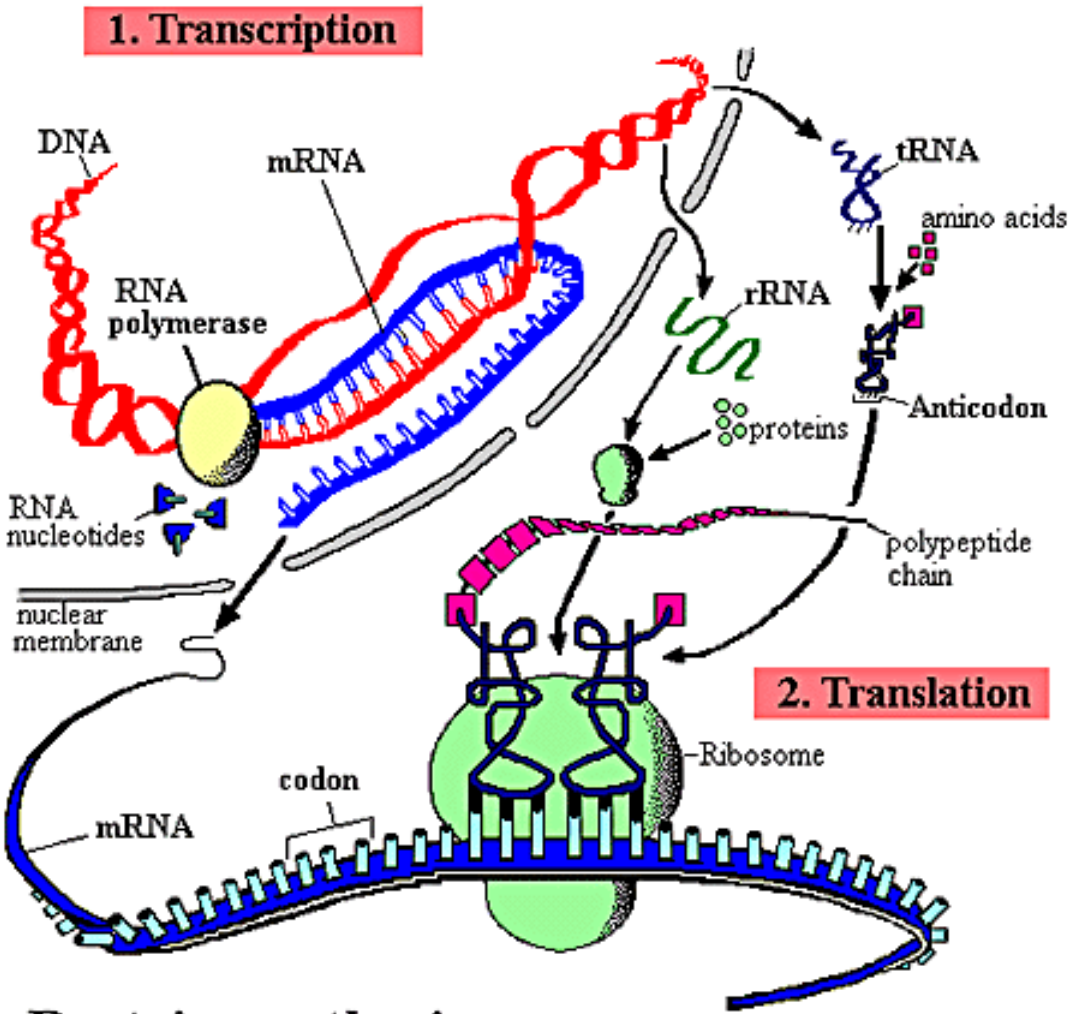
(D) The rest of the general transcription factors as well as the RNA polymerase itself assemble at the promoter. What order?

(E) TFIIH then uses ATP to phosphorylate RNA polymerase II, changing its conformation so that the polymerase is released from the complex and is able to start transcribing. As shown, the site of phosphorylation is a long polypeptide tail that extends from the polymerase molecule.

Transcription Factors

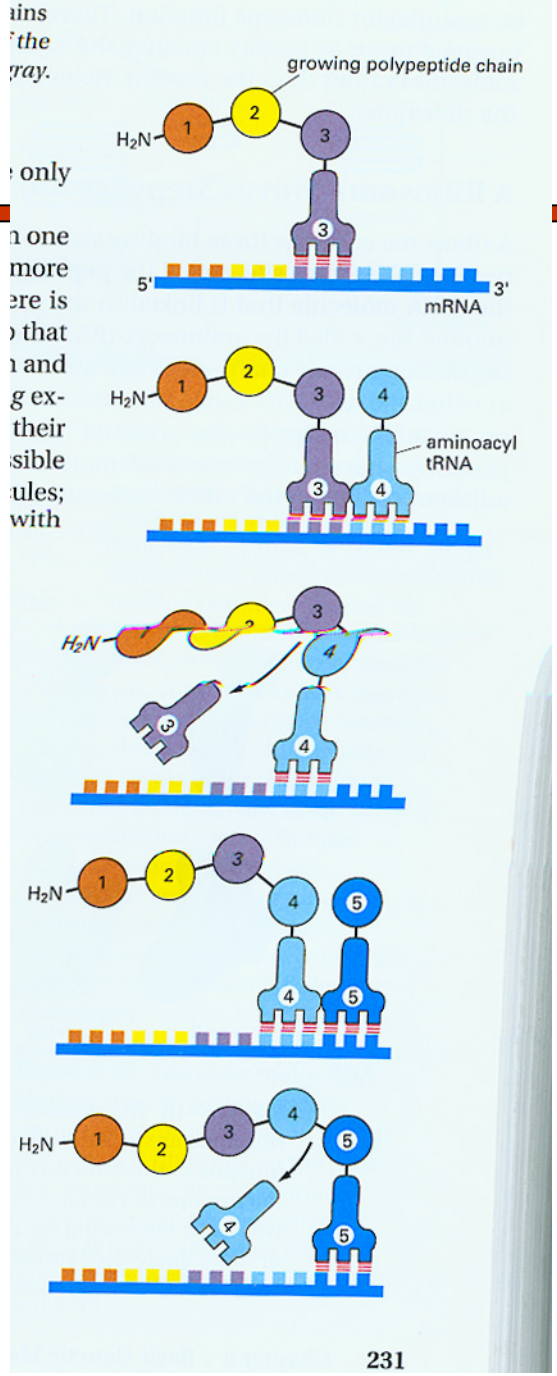
- The general transcription factors have been highly conserved in evolution; some of those from human cells can be replaced in biochemical experiments by the corresponding factors from simple yeasts.

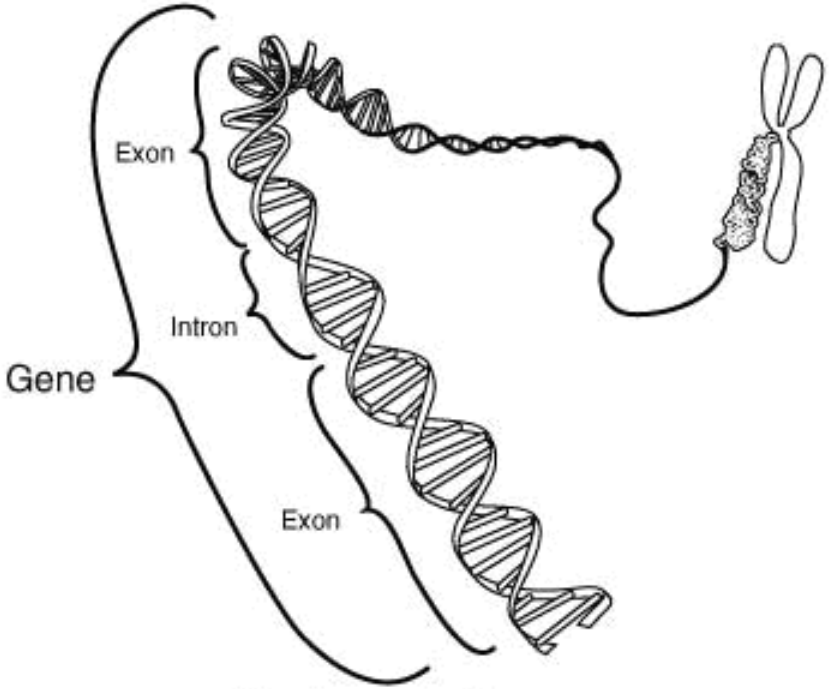
Protein Synthesis

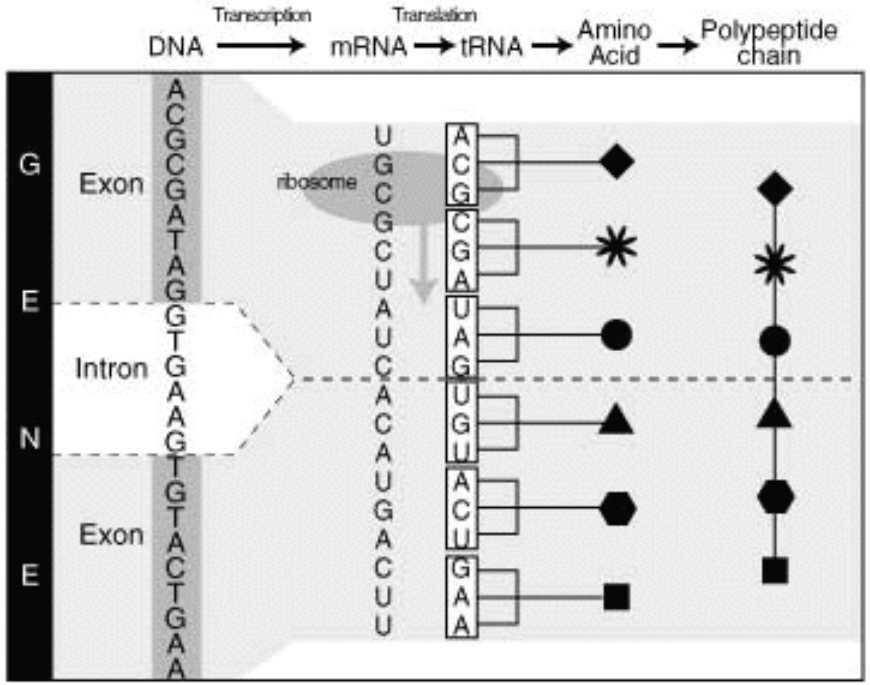


Protein Synthesis:

Incorporation of amino acid into protein




Exon
Intron
Gene
Exon


Transcription
Translation
DNA
mRNA
tRNA
Amino Acid
Polypeptide chain
G
E
N
E
Exon
Intron
Exon
ACGCGATAGGTGAAGTGTACTGAA
ribosome
UGCGCUAUCACAUGACUU
ACG
CGA
UAG
UGU
ACU
GAA