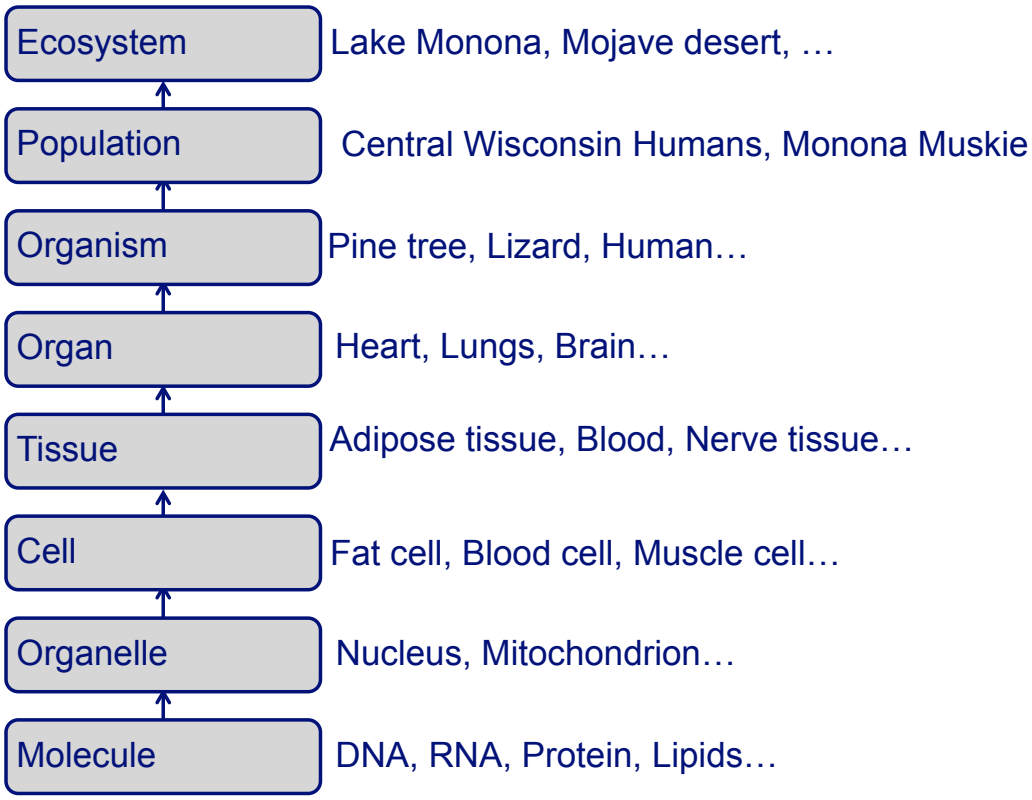
Introduction to Molecular Biology

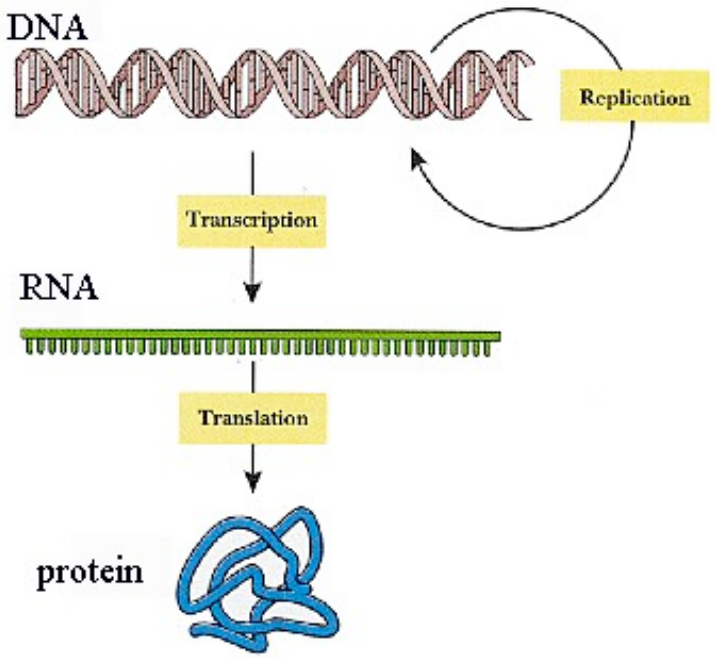
BMI/CS 576
www.biostat.wisc.edu/bmi576/
Mark Craven
craven@biostat.wisc.edu
Fall 2011

Levels of the biological hierarchy



The Central Dogma

Our discussion is going to be focused on the Central Dogma



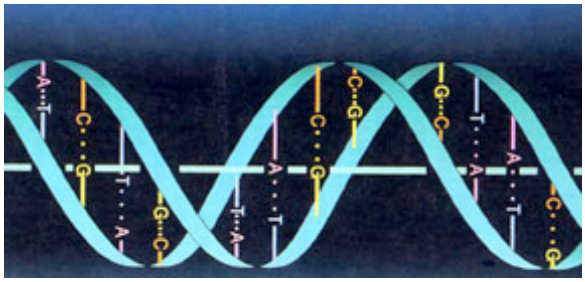
DNA

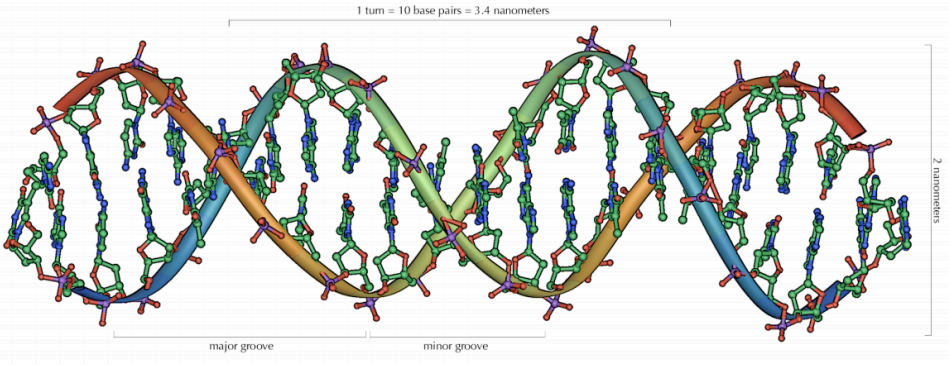
- can be thought of as the “blueprint” for an organism
- composed of small molecules called *nucleotides*
  - four different nucleotides distinguished by the four *bases*: adenine (A), cytosine (C), guanine (G) and thymine (T)
- is a *polymer* : large molecule consisting of similar units (nucleotides in this case)
- a single strand of DNA can be thought of as a string composed of the four letters: A, C, G, T

  `ctgctggaccgggtgctaggaccctgactgcccgggg`
  `ccgggggtgcggggcccgctgag`...

The double helix

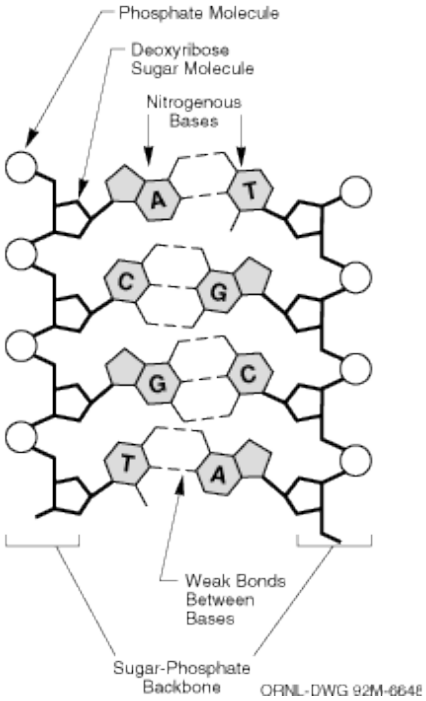
- DNA molecules usually consist of two strands arranged in the famous double helix





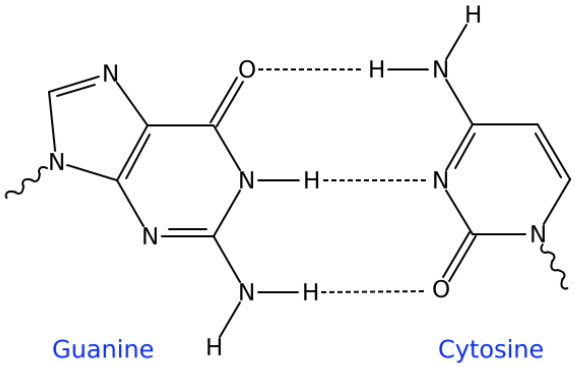
Watson-Crick base pairs

- in double-stranded DNA
  - A always bonds to T
  - C always bonds to G



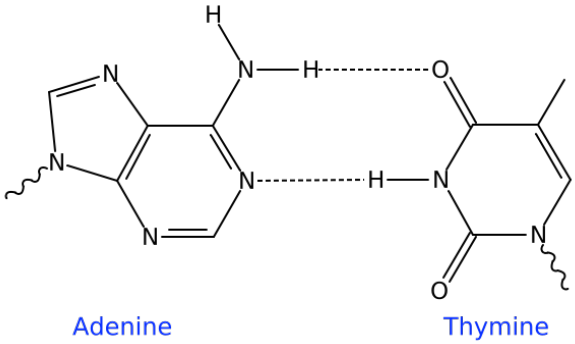
The alphabet of DNA: 4 bases

G



C

A



T

The double helix

- each strand of DNA has a “direction”
  - at one end, the terminal carbon atom in the backbone is the 5’ carbon atom of the terminal sugar
  - at the other end, the terminal carbon atom is the 3’ carbon atom of the terminal sugar
- therefore we can talk about the *5’* and the *3’* ends of a DNA strand
- in a double helix, the strands are *antiparallel* (arrows drawn from the 5’ end to the 3’ end go in opposite directions)

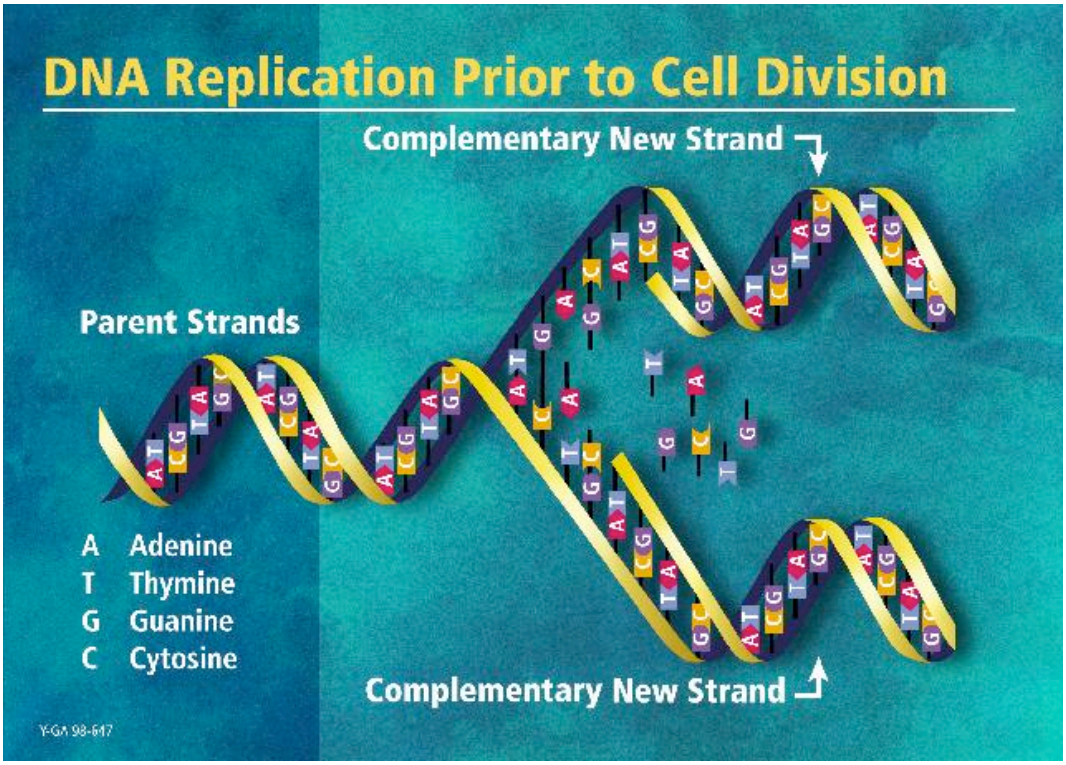


image from the DOE Human Genome Program
http://www.ornl.gov/hgmis

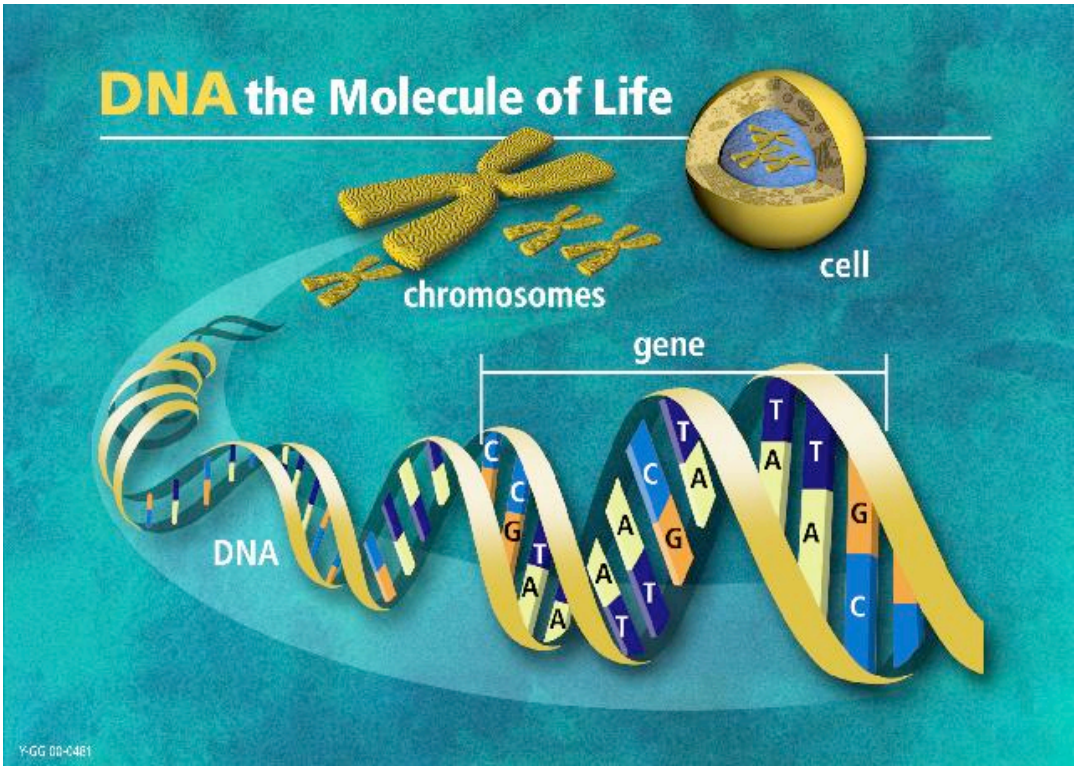
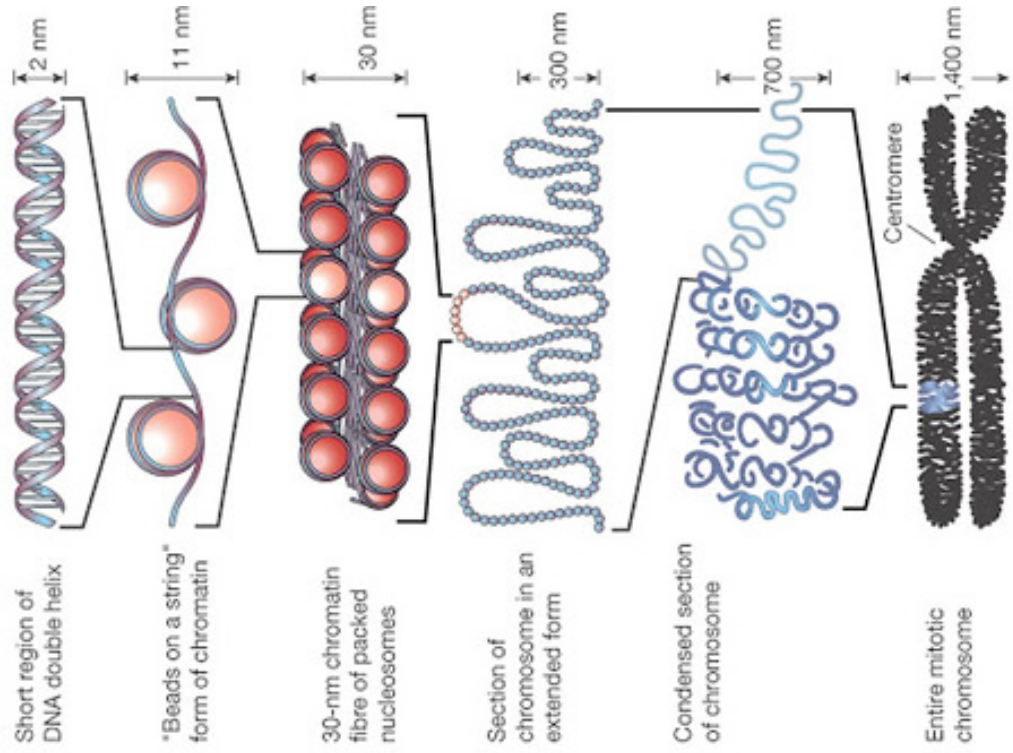


image from the DOE Human Genome Program
http://www.ornl.gov/hgmis

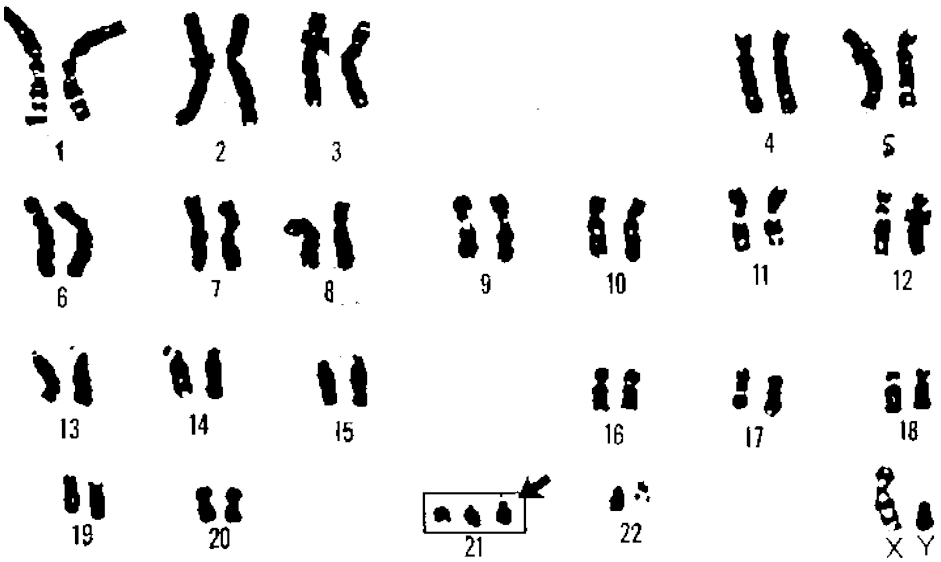
Chromosomes

- DNA is packaged into individual *chromosomes* (along with proteins)
- *prokaryotes* (single-celled organisms lacking nuclei) typically have a single circular chromosome
- *eukaryotes* (organisms with nuclei) have a species-specific number of linear chromosomes

DNA packing in eukaryotes



Human Chromosomes



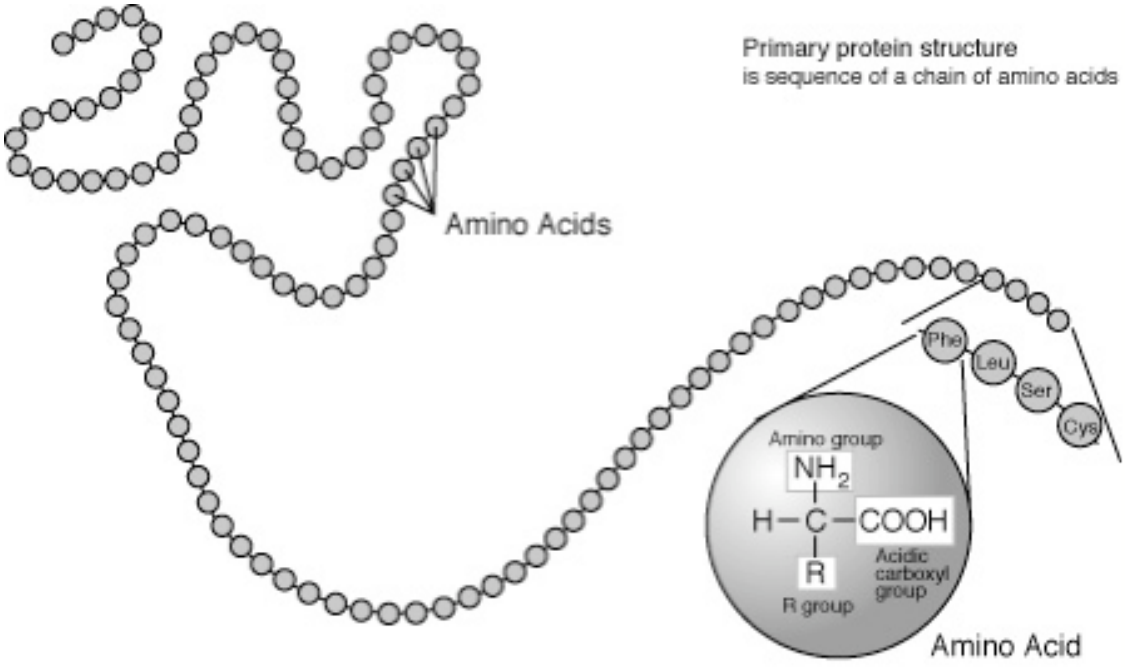
Genomes

- the term *genome* refers to the complete complement of DNA for a given species
- the human genome consists of 46 chromosomes
- every cell (except sex cells and mature red blood cells) contains the complete genome of an organism

Proteins

- proteins are molecules composed of one or more *polypeptides*
- a polypeptide is a polymer composed of *amino acids*
- cells build their proteins from 20 different amino acids
- a polypeptide can be thought of as a string composed from a 20-character alphabet

Protein: polymer of amino acids



Protein functions

- structural support
- storage of amino acids
- transport of other substances
- coordination of an organism's activities
- response of cell to chemical stimuli
- movement
- protection against disease
- selective acceleration of chemical reactions

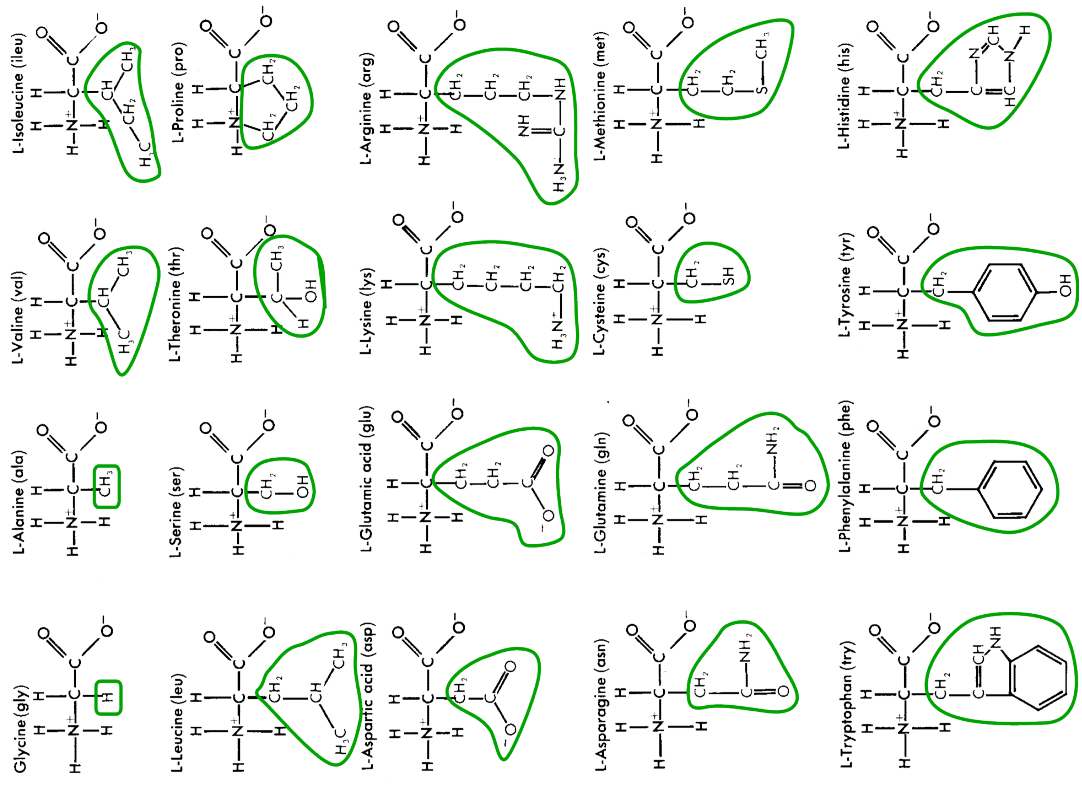
Examples of proteins

Protein	Role
alpha-keratin	component of hair
beta-keratin	component of scales
insulin	regulates blood glucose level
actin & myosin	muscle contraction
DNA polymerase	synthesis of DNA
ATP synthase	makes ATP
hemoglobin	transport of oxygen
endonuclease	cuts DNA (restriction enzyme)

The alphabet of proteins: 20 amino acids

Alanine	**Ala**	**A**
Arginine	**Arg**	**R**
Aspartic Acid	**Asp**	**D**
Asparagine	**Asn**	**N**
Cysteine	**Cys**	**C**
Glutamic Acid	**Glu**	**E**
Glutamine	**Gln**	**Q**
Glycine	**Gly**	**G**
Histidine	**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**

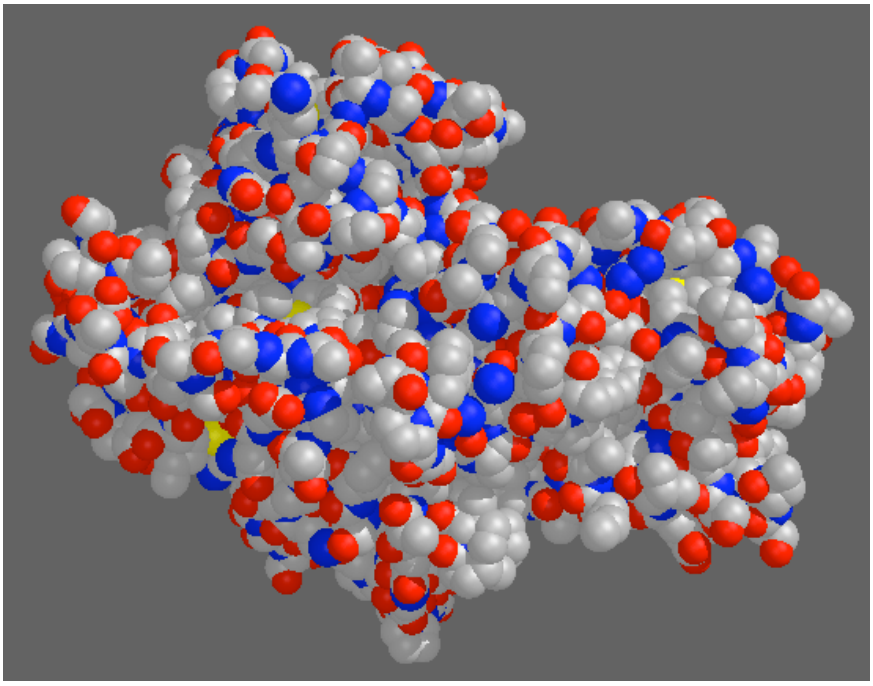
The alphabet of proteins: 20 amino acids



Amino acid sequence of hexokinase

```
          5         10        15        20        25        30
  1 A A S X D X S L V E V H X X V F I V P P X I L Q A V V S I A
 31 T T R X D D X D S A A A S I P M V P G W V L K Q V X G S Q A
 61 G S F L A I V M G G G D L E V I L I X L A G Y Q E S S I X A
 91 S R S L A A S M X T T A I P S D L W G N X A X S N A A F S S
121 X E F S S X A G S V P L G F T F X E A G A K E X V I K G Q I
151 T X Q A X A F S L A X L X K L I S A M X N A X F P A G D X X
181 X X V A D I X D S H G I L X X V N Y T D A X I K M G I I F G
211 S G V N A A Y W C D S T X I A D A A D A G X X G G A G X M X
241 V C C X Q D S F R K A F P S L P Q I X Y X X T L N X X S P X
271 A X K T F E K N S X A K N X G Q S L R D V L M X Y K X X G Q
301 X H X X X A X D F X A A N V E N S S Y P A K I Q K L P H F D
331 L R X X X D L F X G D Q G I A X K T X M K X V V R R X L F L
361 I A A Y A F R L V V C X I X A I C Q K K G Y S S G H I A A X
391 G S X R D Y S G F S X N S A T X N X N I Y G W P Q S A X X S
421 K P I X I T P A I D G E G A A X X V I X S I A S S Q X X X A
451 X X S A X X A
```

Space-filling model of hexokinase



Genes

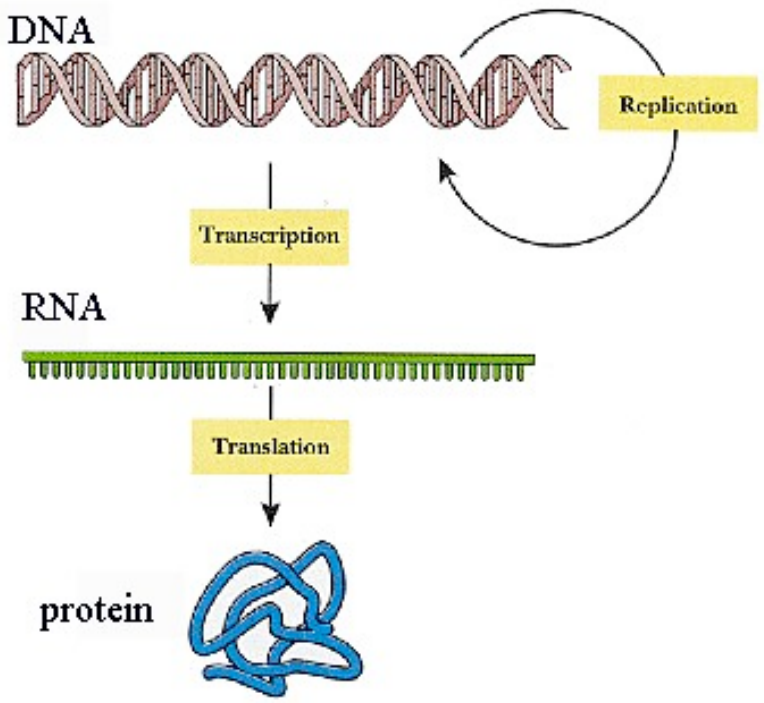
- genes are the basic units of heredity
- a gene is a sequence of DNA bases that carries the information required for constructing a particular protein (polypeptide)
- such a gene is said to *encode* a protein
- the human genome comprises ~ 25,000 protein-coding genes

Gene density

not all of the DNA in a genome encodes protein:

bacteria	~90% coding gene/kb
human	~1.5% coding gene/35kb

The Central Dogma

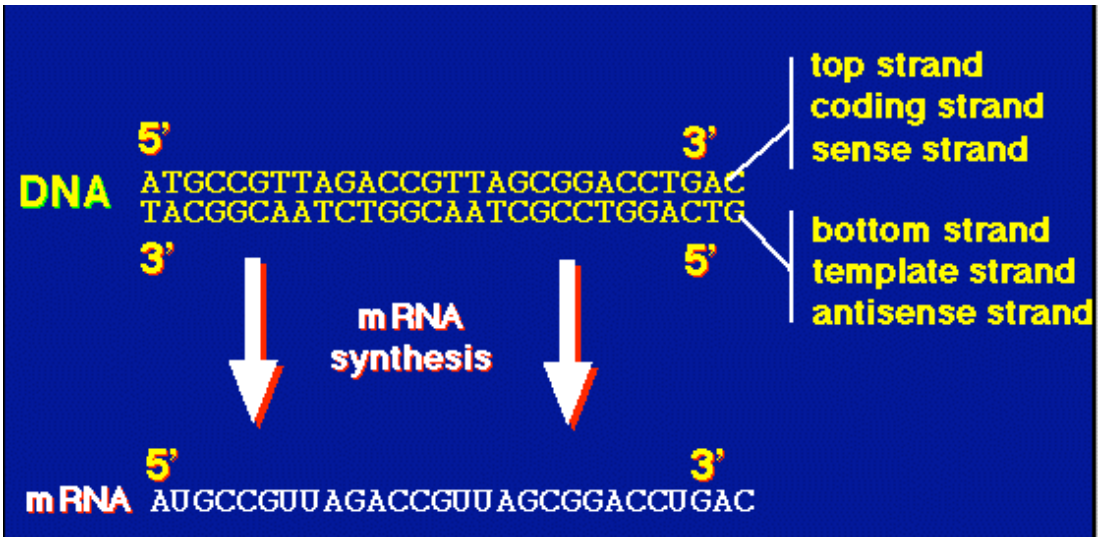


RNA

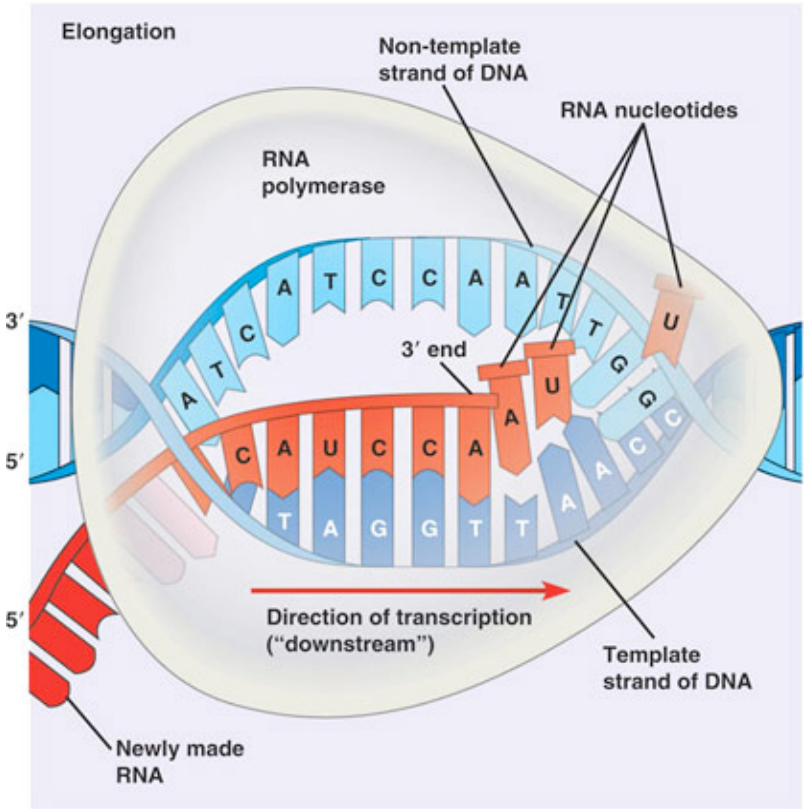
- RNA is like DNA except:
  - backbone is a little different
  - often single stranded
  - the base uracil (U) is used in place of thymine (T)
- a strand of RNA can be thought of as a string composed of the four letters: A, C, G, U

Transcription

Transcription is the process of creating a complementary RNA copy of a DNA subsequence



Transcription



Transcription

- *RNA polymerase* is the enzyme that builds an RNA strand from a gene
- RNA that is transcribed from a gene is called *messenger RNA* (mRNA)

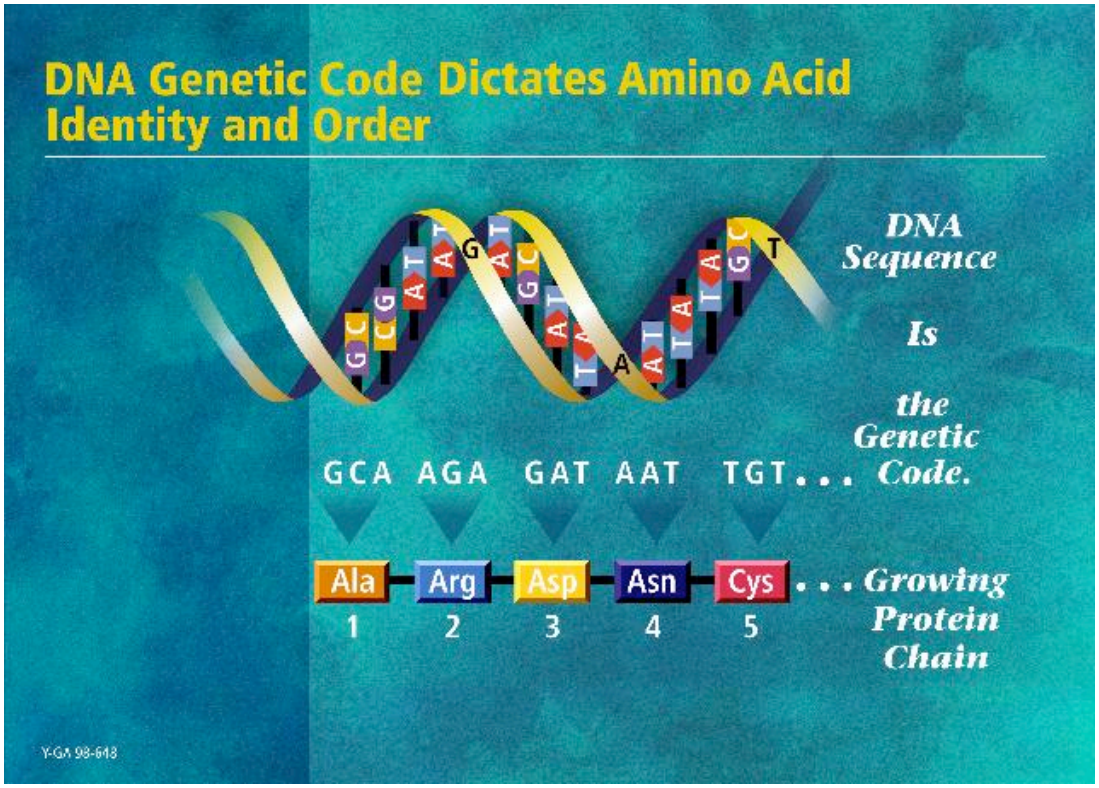
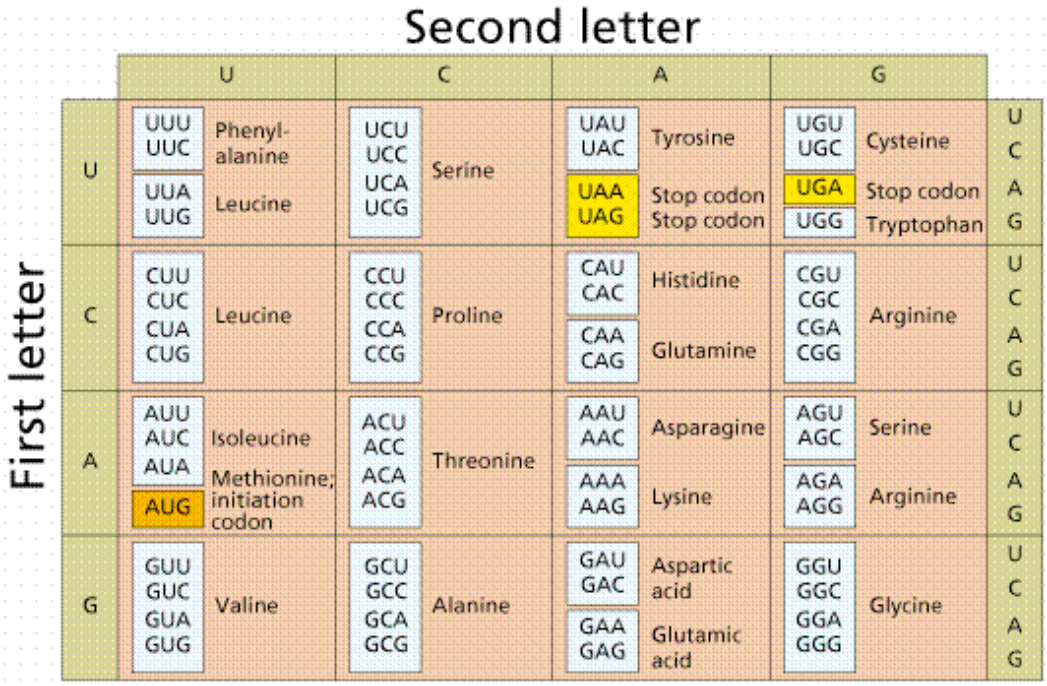


image from the DOE Human Genome Program
http://www.ornl.gov/hgmis

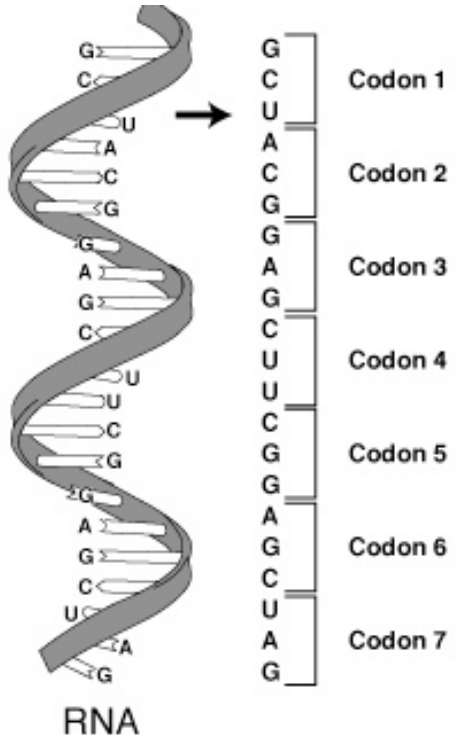
The genetic code



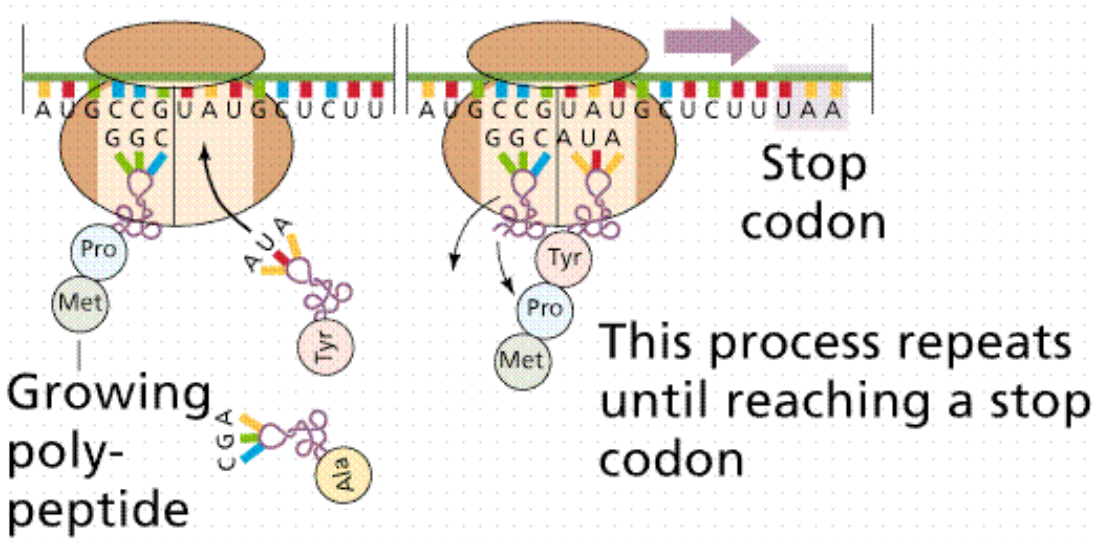
Translation

- *ribosomes* are the machines that synthesize proteins from mRNA
- triplets of bases encoding amino acids are called *codons*
- the grouping of codons is called the *reading frame*
- translation begins with the *start codon*
- translation ends with the *stop codon*

Codons and reading frames



Translation



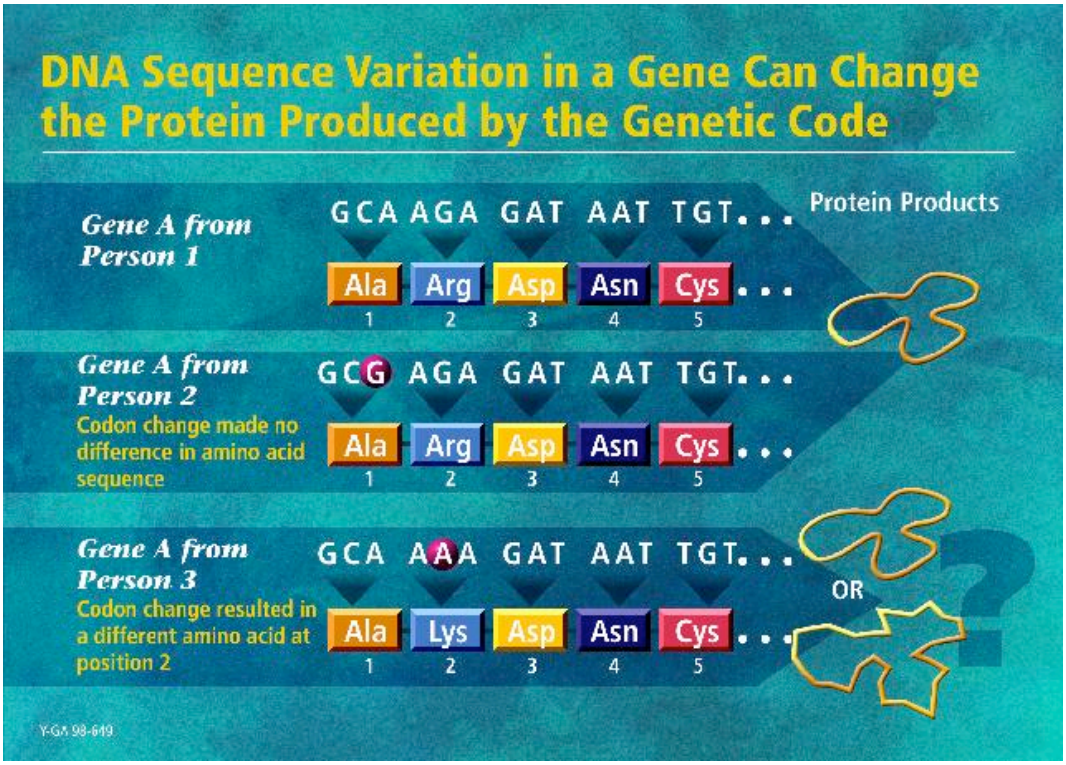
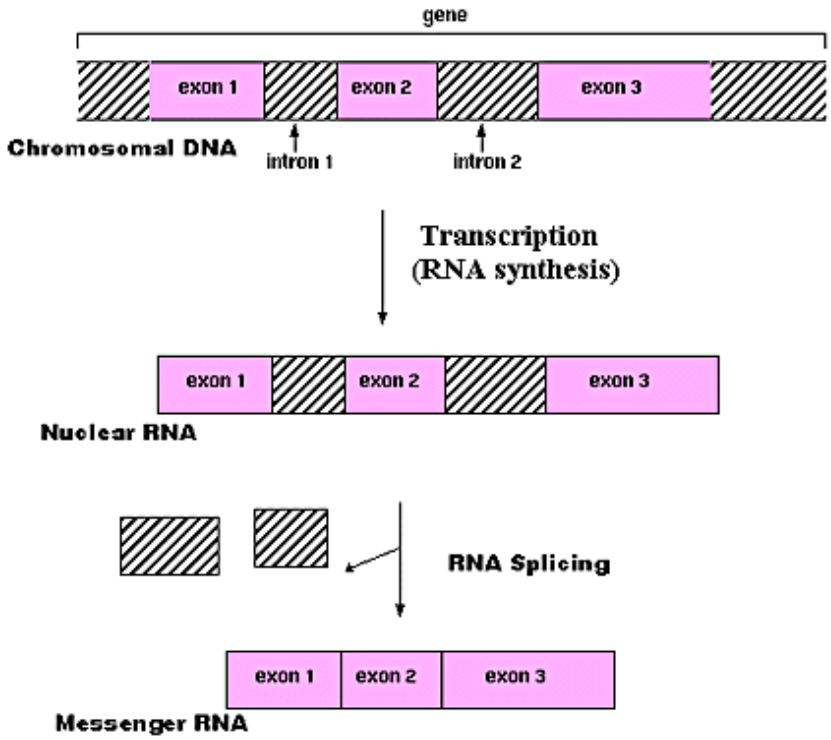


image from the DOE Human Genome Program
http://www.ornl.gov/hgmis

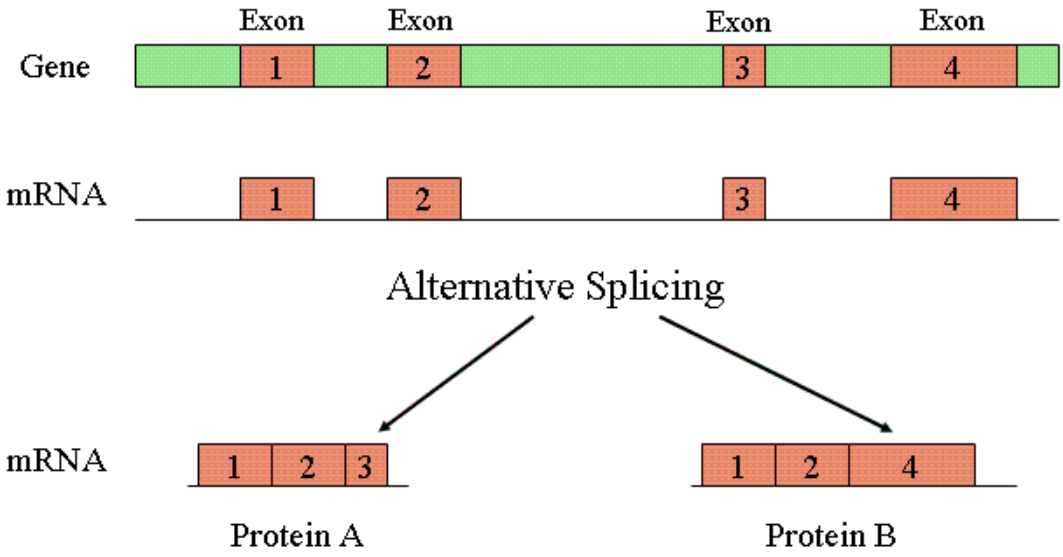
RNA processing in eukaryotes

- *eukaryotes* are organisms that have enclosed nuclei in their cells
- in many eukaryotes, genes/mRNAs consist of alternating *exon/intron* segments
- exons are the coding parts
- introns are spliced out before translation

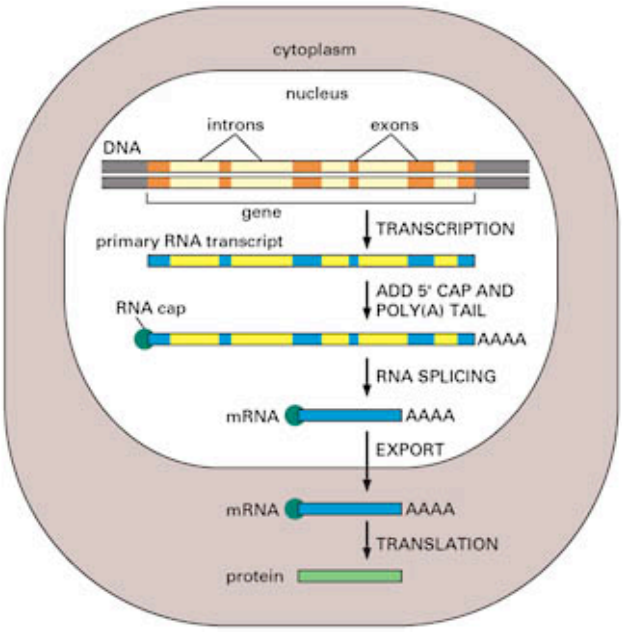
RNA splicing

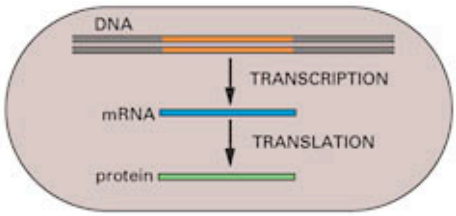


Alternative splicing



Protein synthesis in eukaryotes vs. prokaryotes





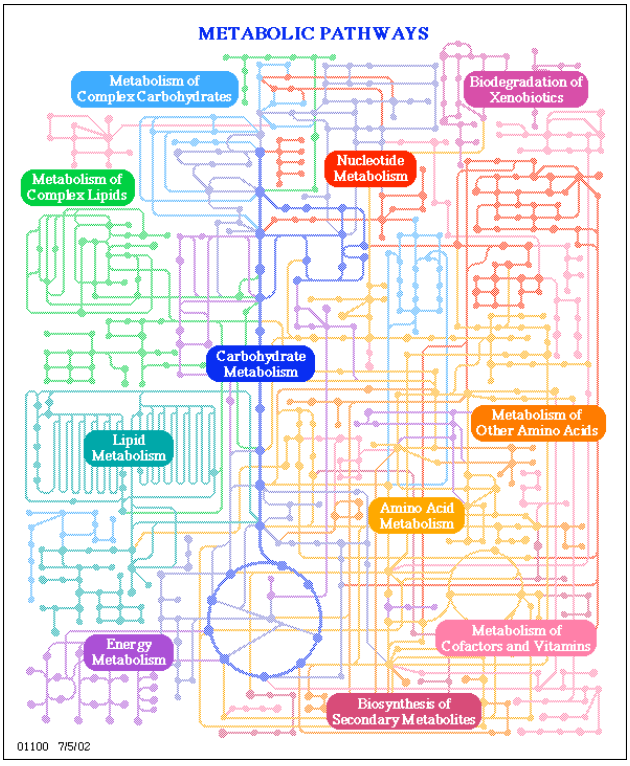
RNA genes

- not all genes encode proteins
- for some genes the end product is RNA
  - *ribosomal RNA* (rRNA), which includes major constituents of ribosomes
  - *transfer RNAs* (tRNAs), which carry amino acids to ribosomes
  - *micro RNAs* (miRNAs), which play an important regulatory role in various plants and animals
  - etc.

The dynamics of cells

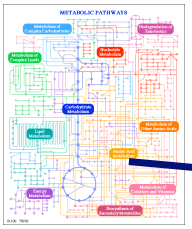
- all cells in an organism have the same genomic data, but the genes expressed in each vary according to cell type, time, and environmental factors
- there are networks of interactions among various biochemical entities in a cell (DNA, RNA, protein, small molecules) that carry out processes such as
  - metabolism
  - intra-cellular and inter-cellular signaling
  - regulation of gene expression

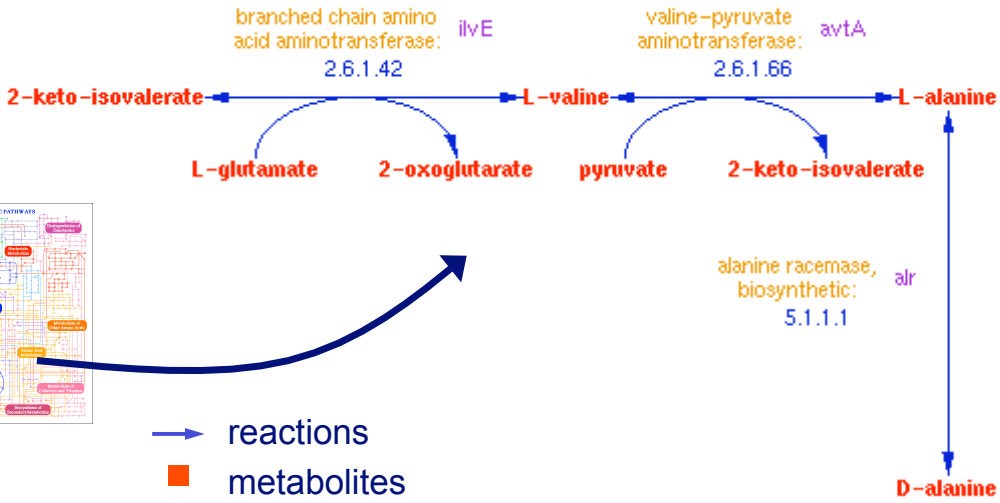
Overview of the E. coli metabolic pathway map



- circles represent metabolites (small molecules)
- lines represent reactions

The metabolic pathway for synthesizing the amino acid alanine

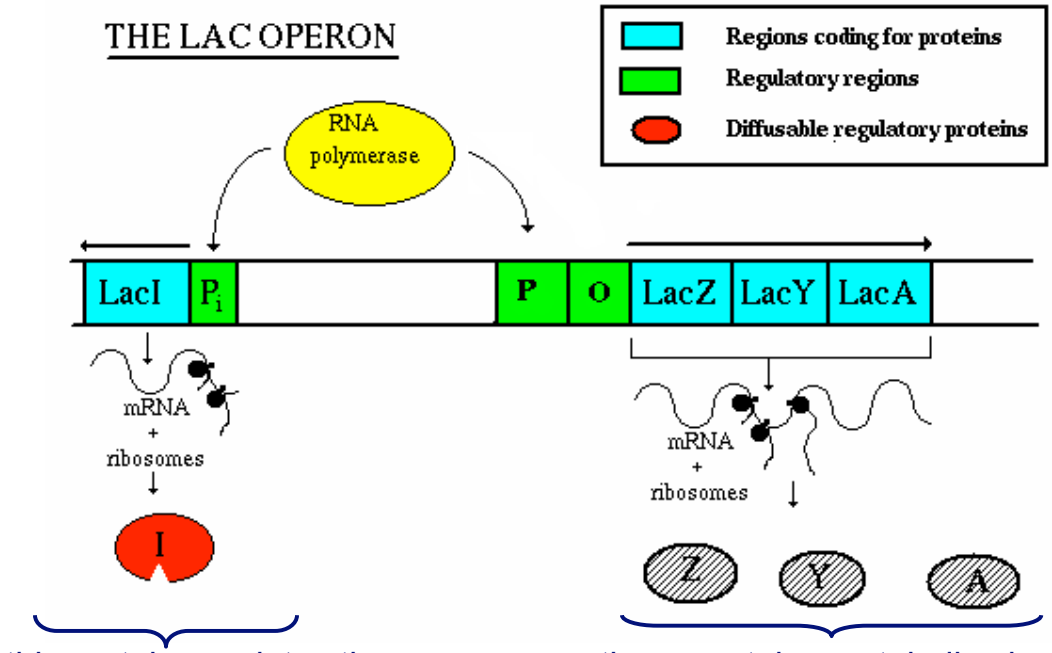




- reactions
- metabolites
- enzymes (proteins that catalyze reactions)
- genes encoding the enzymes

image from the Ecocyc database
www.biocyc.org

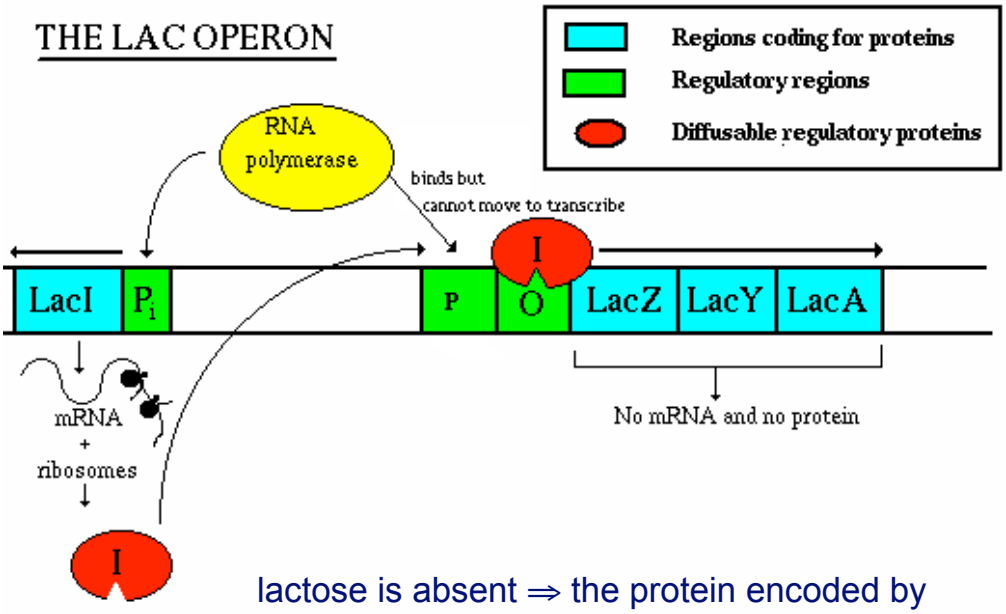
Gene regulation example: the lac operon



this protein regulates the transcription of LacZ, LacY, LacA

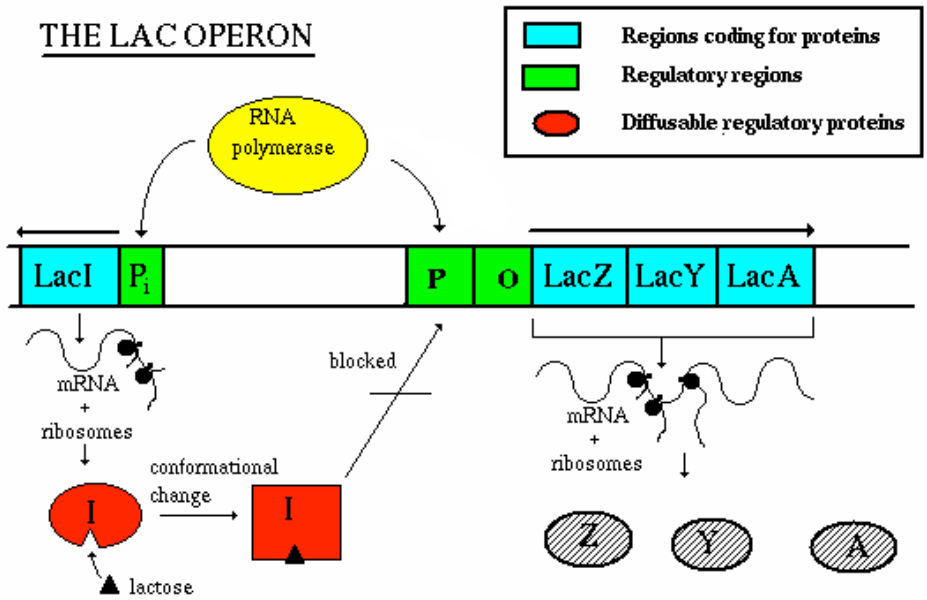
these proteins metabolize lactose

Gene regulation example: the lac operon



lactose is absent ⇒ the protein encoded by lacI represses transcription of the lac operon

Gene regulation example: the lac operon



lactose is present ⇒ it binds to the protein encoded by lacI changing its shape; in this state, the protein doesn't bind upstream ofthe lac operon; therefore the lac operon can be transcribed

Gene regulation example: the lac operon

- this example provides a simple illustration of how a cell can regulate (turn on/off) certain genes in response to the state of its environment
  - an *operon* is a sequence of genes transcribed as a unit
  - the lac operon is involved in metabolizing lactose
    - it is “turned on” when lactose is present in the cell
    - the lac operon is regulated at the transcription level

- the depiction here is incomplete; for example, the level of glucose in the cell also influences transcription of the lac operon