PROTEINS - perform most cellular functions:

- building blocks for cellular structures;
- enzymes that catalyze all of the cell's chemical reactions;
- regulate gene expression;
- enable cells to move

& to communicate with each other.

How is DNA organized in the nucleus?

Is the nucleus simply a bag of chromosomes?

TOPICS – next 4 courses:

- the structure of DNA;
- basic genetic mechanisms, how the genetic information of the cell is:
  - maintained
  - replicated
  - expressed
  - occasionally improved.

Course structure

I. DNA and CHROMOSOMES:

- **I.A.** The Structure and Function of DNA
- **I.B.** Chromosomal DNA and Its Packaging in the Chromatin Fiber
- **I.C.** The Global Structure of Chromosomes

I.A. The Structure and Function of DNA

CHROMOSOME&DNA HISTORY

- **Charles Robert Darwin (12 February 1809 – 19 April 1882)** - evolutionary theory

- **Gregor Johann Mendel (20 July 1822 – 6 January 1884)** - founder of the modern science of genetics:
  - Law of Segregation
  - Law of Independent Assortment,

The chromosome theory of inheritance

"Sutton-Boveri Theory“

(E.B. Wilson, 1902)

CHROMOSOMES:

- vectors of heredity (Boveri, mid-1880s);
- each chromosome carries a different genetic load (Wilhelm Roux);

1866 Mendel's paper is published: units of inheritance in pairs; dominance and recessiveness; equal segregation; independent assortment. These ideas are not recognized for 34 years.

1869 DNA (first called "nuclein") is identified by Friedrich Miescher as an acidic substance found in cell nuclei. The significance of DNA is not appreciated for over 70 years.

1900 Mendel's experiments from 1866 are "rediscovered" and confirmed by three separate researchers (one Dutch, one German, one Austrian). A British man (William Bateson) soon translates Mendel's paper into English and champions the study of heredity in England.

1902 A human disease is first attributed to genetic causes ("inborn errors of metabolism"). (Sir Archibald Garrod, alkaptonuria)

1902 The chromosome theory of heredity is proposed by Sutton. Boveri recognizes that individual chromosomes are different from one another, but he doesn't make a connection to Mendelian principles. Nevertheless, Boveri is given co-credit by friend E.B. Wilson (Sutton's supervisor) for proposing the chromosome theory of inheritance.

1905 The word "genetics" is coined by William Bateson.

1905 Some genes are linked and do not show independent assortment, as seen by Bateson and Punnett.

1903-9 First experiments on quantitative traits in broad beans by Wilhelm Johanssen and in wheat by Herman Nilsson-Ehle.

1910-11 The chromosome theory of heredity is confirmed in studies of fly eye color inheritance by T.H. Morgan and colleagues.

1913 First ever linkage map created by Columbia undergraduate Alfred Sturtevant (working with T.H. Morgan).

1910's-30's The eugenics movement is popular, fueling racist sentiment and leading to involuntary sterilization laws.

1925-27 H. Muller shows that X-rays induce mutations in a dose-dependent fashion.

1928 Some component of heat-killed virulent bacteria can "transform" a non-virulent strain to become virulent, as shown by Fred Griffith. This sets the stage for work done in 1944.

1931 Genetic recombination is caused by a physical exchange of chromosomal pieces, as shown in corn by Harriet Creighton and Barbara McClintock.

1941 One gene encodes one protein, as described by Beadle and Tatum.

1944 DNA is the molecule that mediates heredity, as shown in Pneumococcus transformation experiments by Avery, MacLeod, and McCarty. Most people were skeptical of these findings until 1952.

1946 Genetic material can be transferred laterally between bacterial cells, as shown by Lederberg and Tatum.

1950 In DNA, there are equal amounts of A and T, and equal amounts of C and G, as shown by Erwin Chargaff. However, the A+T to C+G ratio can differ between organisms.

1952 DNA is the molecule that mediates heredity, as shown in bacteriophage labeling experiments by Alfred Hershey and Martha Chase. This confirmation of the 1944 results really convinced everyone.

1953 DNA is in the shape of a double helix with antiparallel nucleotide chains and specific base pairing. This was deduced by Watson and Crick, who used Rosalind Franklin's data provided by Maurice Wilkins.

1958 DNA replication is semi-conservative, as shown by Meselson and Stahl using equilibrium density gradient centrifugation.

1959 Messenger RNA is the intermediate between DNA and protein.

1966 The genetic code is cracked by a number of researchers (including Nirenberg, Matthaei, Leder, and Khorana) using RNA homopolymer and heteropolymer experiments as well as tRNA labeling experiments.

1970 The first restriction enzyme is purified by Hamilton Smith.

1972-73 Recombinant DNA is first constructed by Cohen and Boyer.

1977 DNA sequencing technology is developed by Fred Sanger.

1986 PCR is developed by Kary Mullis.

1990's Genome projects are begun. The yeast genome is complete in 1996, and the C. elegans genome is done in 1998.

1990's DNA microarrays are invented by Pat Brown and colleagues.

1990's DNA fingerprinting, gene therapy, and genetically modified foods come onto the scene.

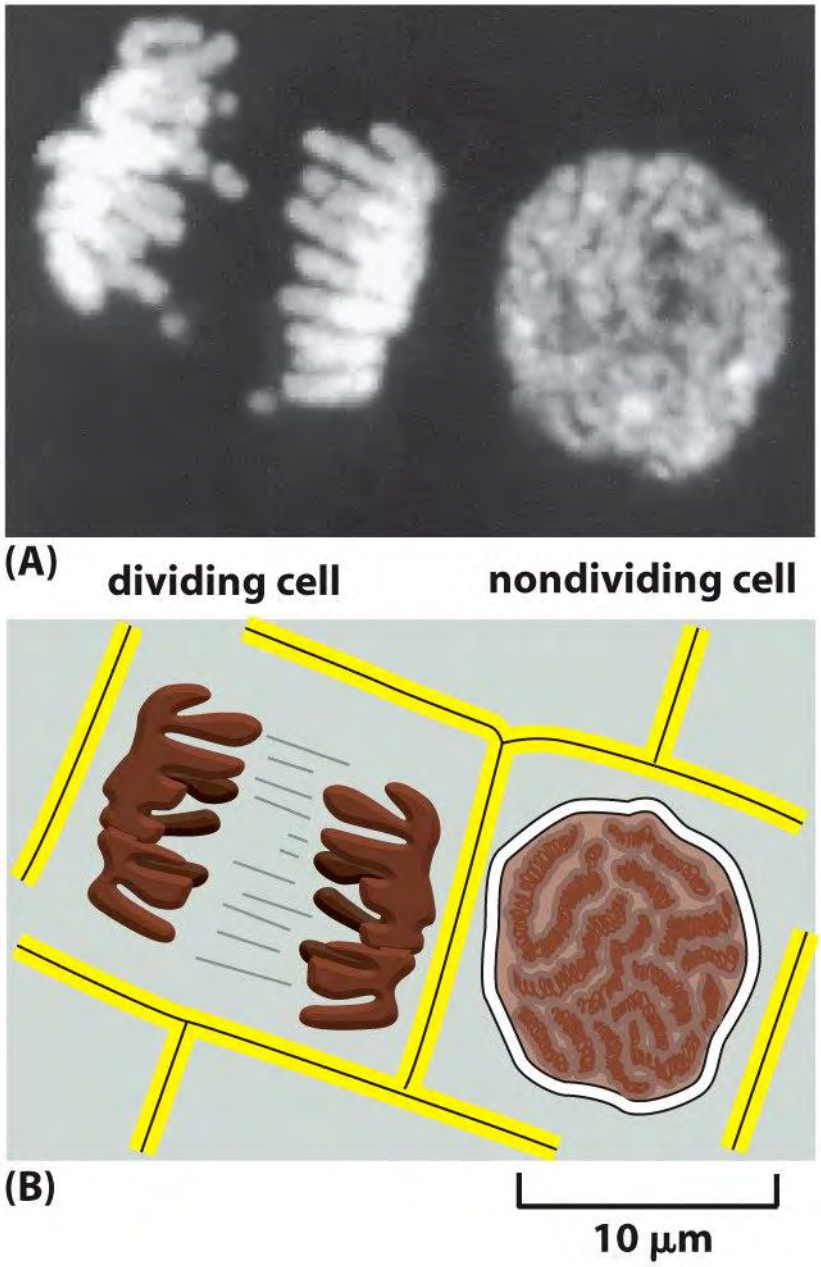
1995 Automated sequencing technology allows genome projects to accelerate.

1996-7 The first cloning of a mammal (Dolly the sheep) is performed by Ian Wilmut and colleagues, from the Roslin institute in Scotland.

2000 The Drosophila genome is completed. The Arabidopsis genome is completed. The human genome is reported to be completed.

2001 The sequence of the human genome is released, and the "post-genomic era" officially begins.

2009 Controversies continue over human and animal cloning, research on stem cells, and genetic modification of crops.



Plant cells photographed through a light microscope:

- **The DNA is present in chromosomes - visible only when they become compact structures in preparation for cell division.**
- **The cell on the right (not dividing) contains identical chromosomes, not distinguished - a more extended conformation.**

Figure 4-1 *Molecular Biology of the Cell* (© Garland Science 2008)

In the 1940s:

- deoxyribonucleic acid (DNA) - the likely carrier of genetic information;

- GENETIC INFORMATION consists primarily of instructions for making proteins.

Griffith's experiment, reported in **1928** by Frederick **Griffith**, was the first **experiment** suggesting that bacteria are capable of transferring genetic information through a process known as transformation.

Avery–MacLeod–McCarty experiment was an experimental demonstration, reported in 1944 that DNA is the substance that causes bacterial transformation

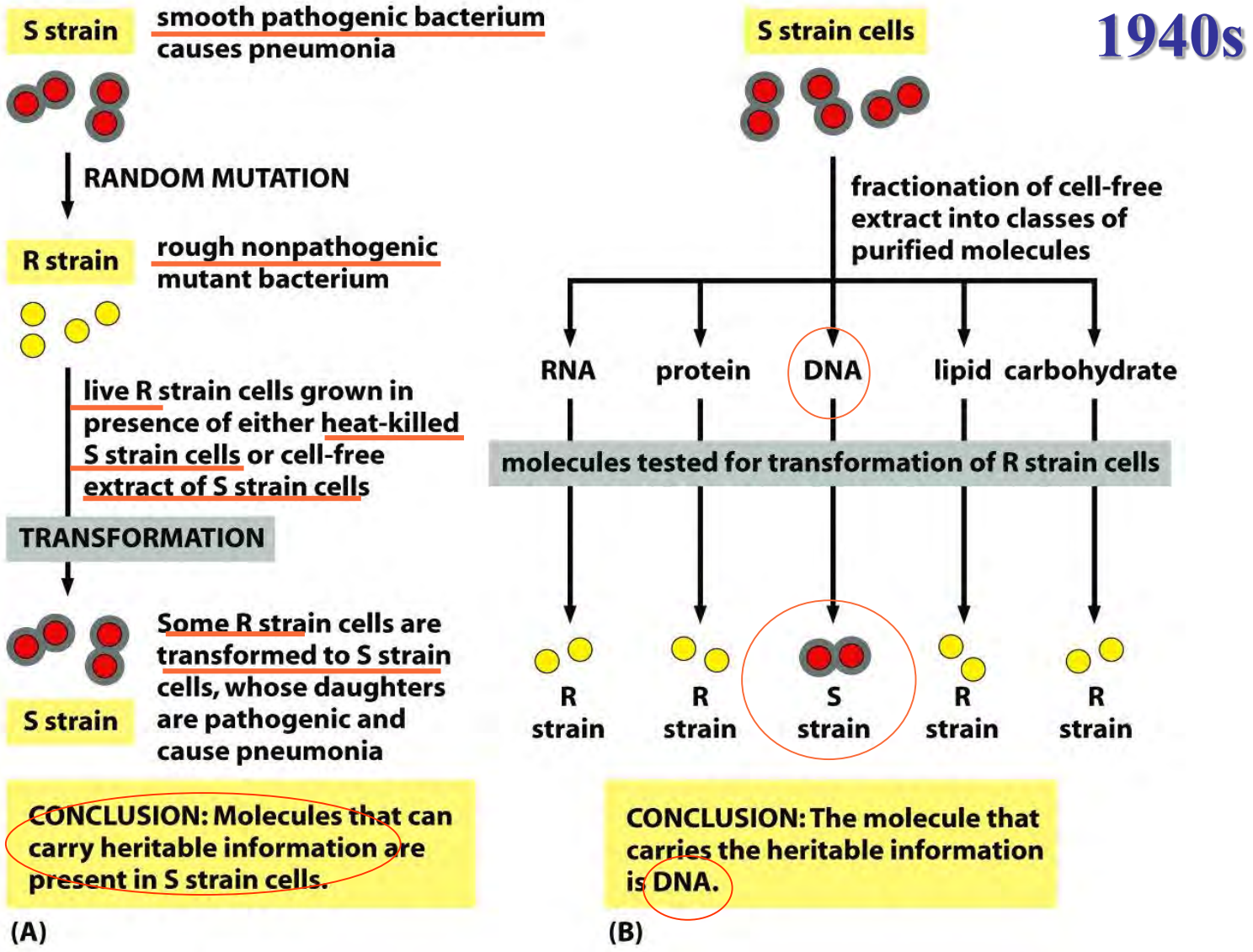


Figure 4-2 *Molecular Biology of the Cell* (© Garland Science 2008)

http://www.dnaftb.org/17/animation.html

History

DNA structure and function?

⇒ how a molecule of DNA might encode the instructions for making proteins *(how can the information for specifying an organism be carried in chemical form)*?

⇒ how the information might be copied, or replicated?

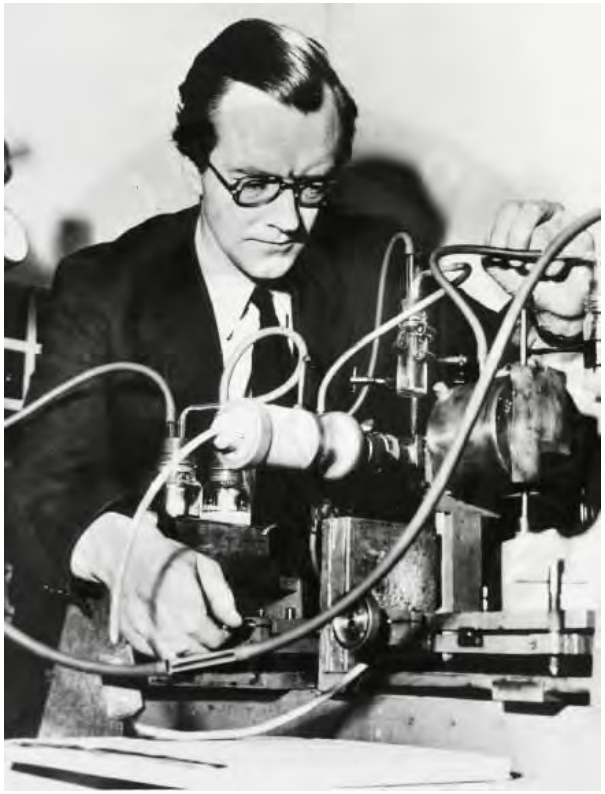
James Watson and Francis Crick & Maurice WILKINS

jointly awarded the 1962 Nobel Prize for Physiology or Medicine

"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"

1962 Nobel Prize for Physiology or Medicine

James WATSON & Francis CRICK



Maurice WILKINS

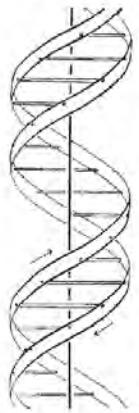
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

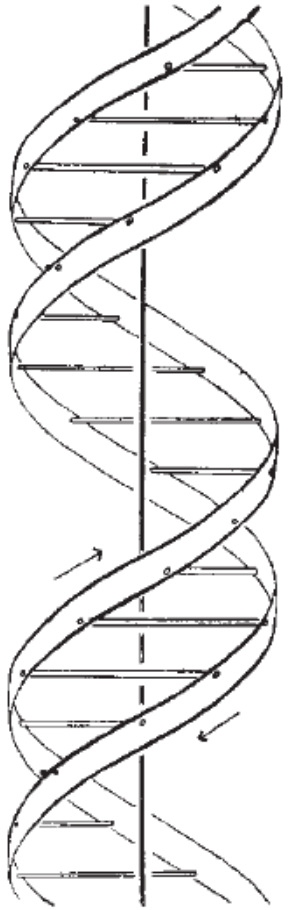
We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis



DNA structure and function?

- DNA - long polymer composed of only four types of subunits;
- the amount of guanine is equal to cytosine and the amount of adenine is equal to thymine (Chargaff's rules)
- x-ray diffraction analysis - two strands of the polymer wound into a helix (WILKINS);

A DNA molecule consists of two complementary chains/strands of nucleotides

Simple –> complex:

- 4 types of nucleotide subunits:
  - five-carbon sugar;
  - phosphate group;
  - nitrogen-containing base (A, G, C, T).

- 1 long polynucleotide chain (strand)

- 2 long polynucleotide chains => DNA

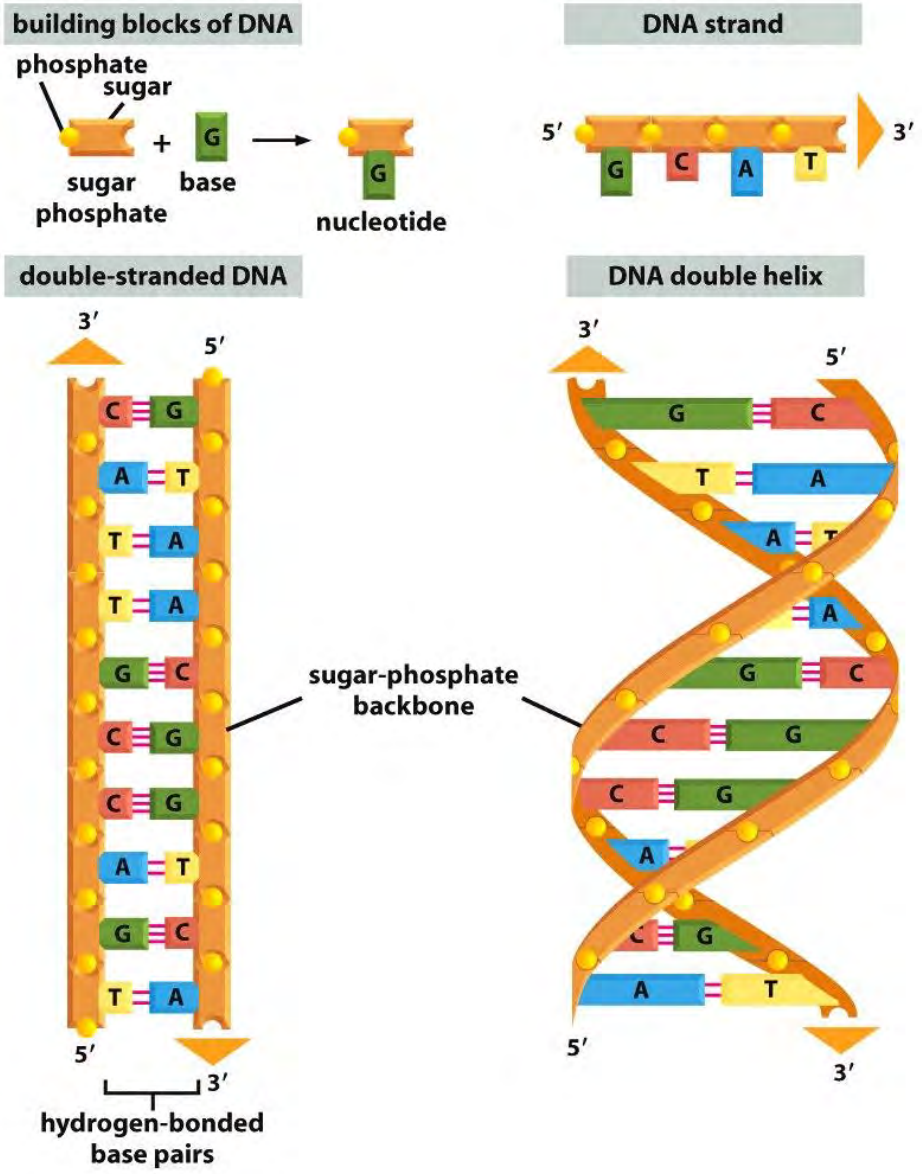


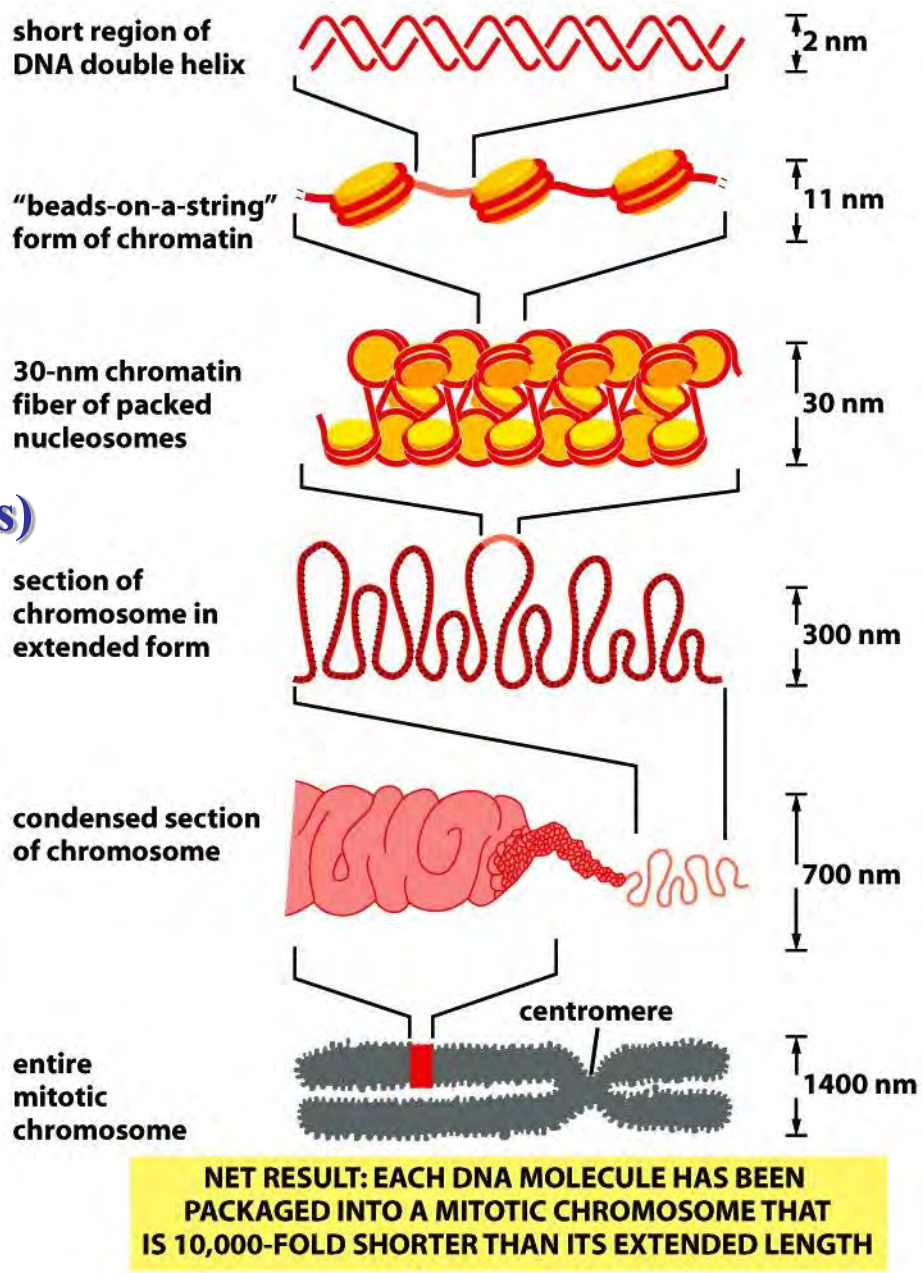
Figure 4-3 *Molecular Biology of the Cell* (© Garland Science 2008)

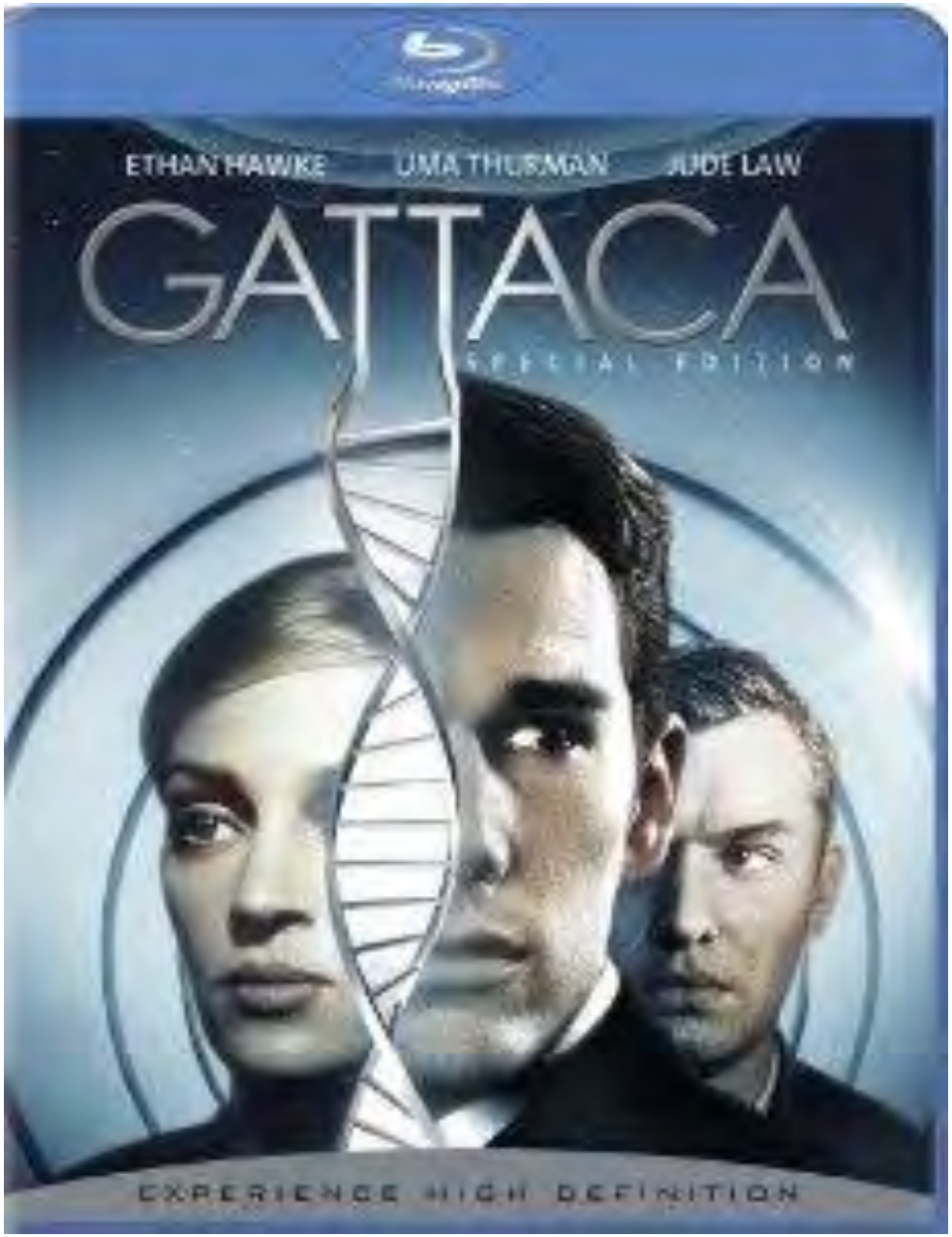
Simple –> complex:

- 1 chromatin fiber <=DNA+Proteins

- 1 chromosome (1 chromatid)

- 1 mitotic chromosome (2 sister chromatids)




ETHAN HAWKE
UMA THURMAN
JUDE LAW
GATTACA
SPECIAL EDITION
EXPERIENCE HIGH DEFINITION

One DNA molecule <=> BOOK.

Hard-cover - of alternating sugar-phosphate-sugar-phosphate.

The stories between covers:

- Each book has two versions (eg: M-chr1 and P-Chr.1).

- Each version is written twice in two different ways (positive&negative strands)

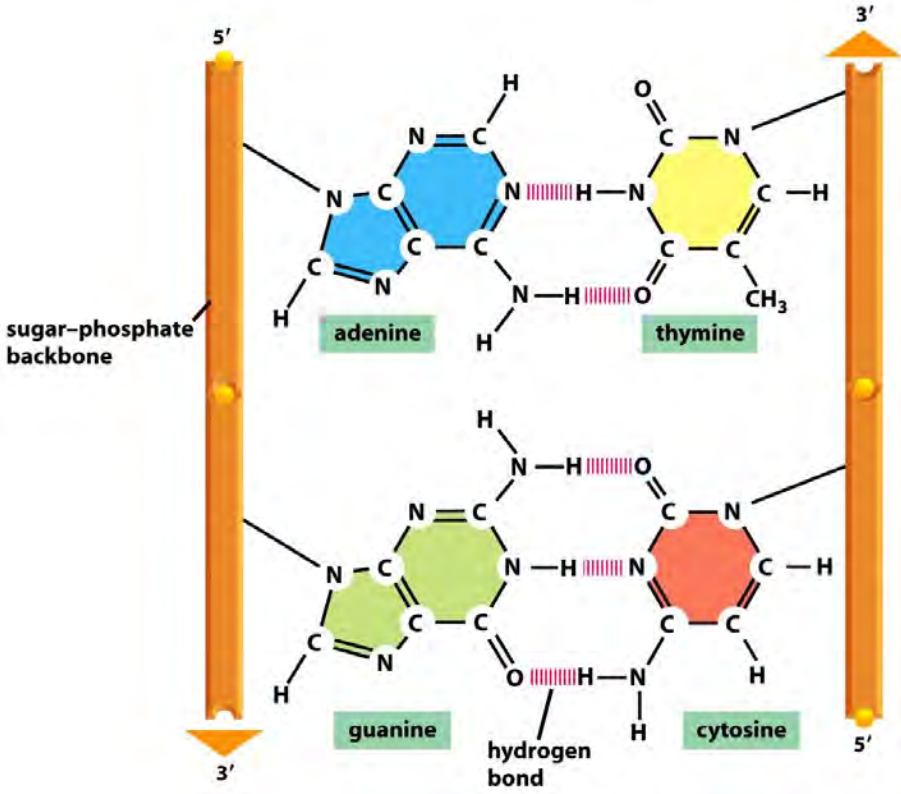
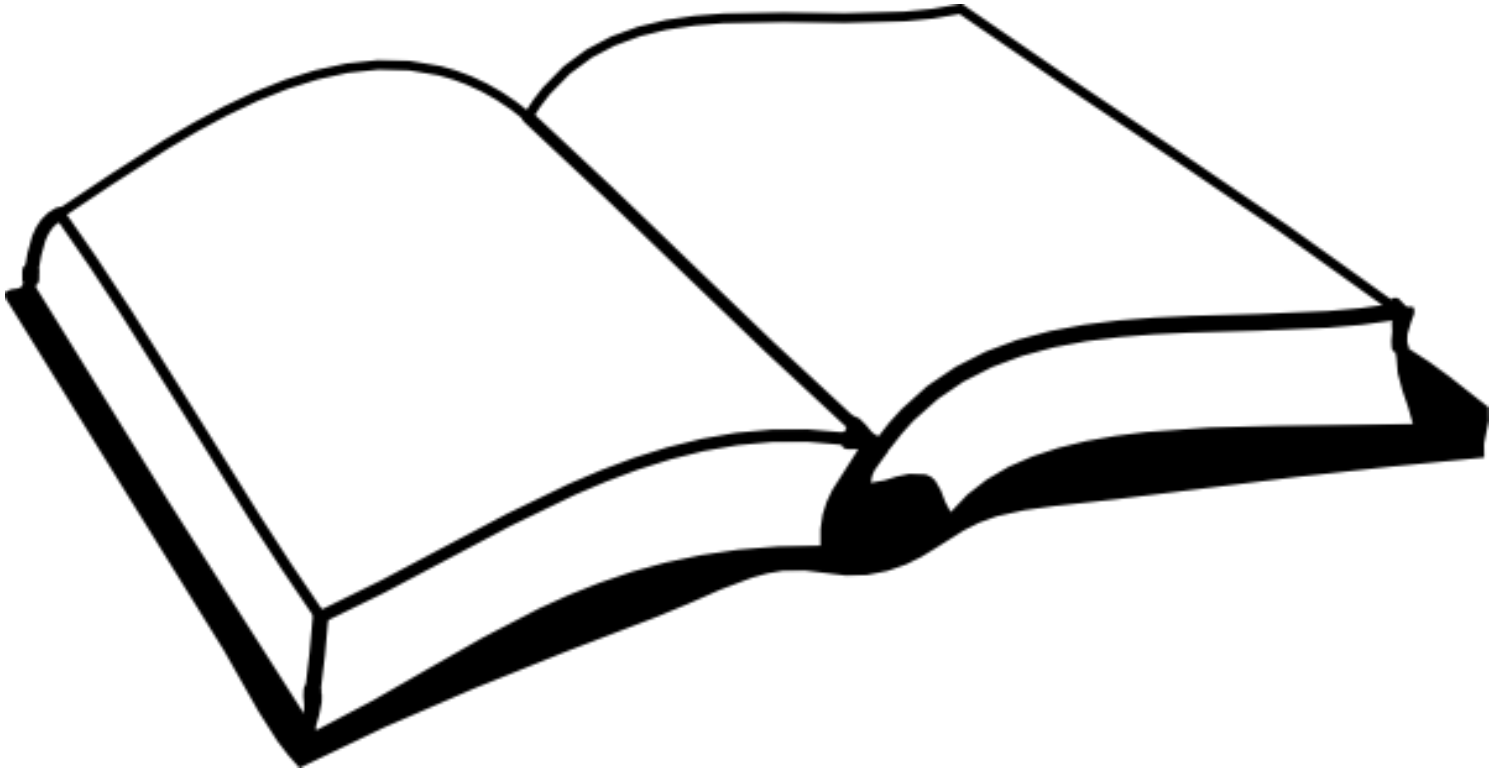


Figure 4-3 *Molecular Biology of the Cell* (© Garland Science 2008)

In order to read or copy the BOOK

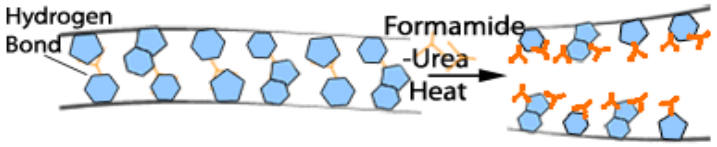
One must....

OPEN it!



DNA

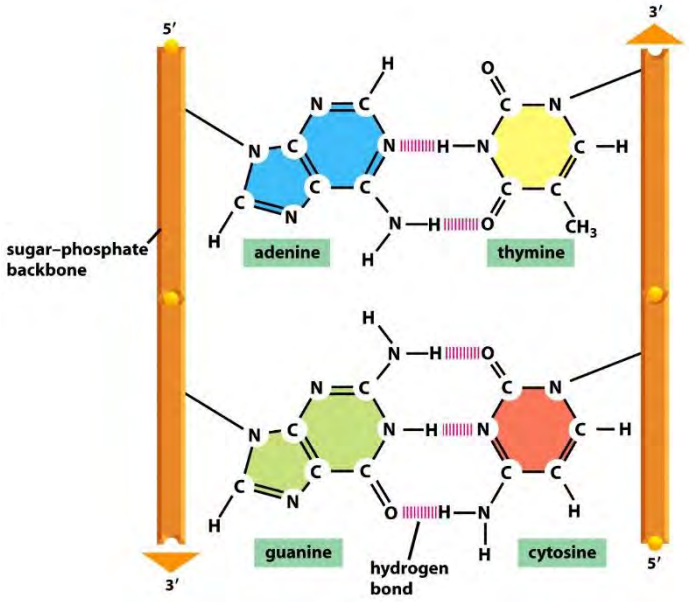
DENATURATION - the hydrogen bonds between the strands are broken;

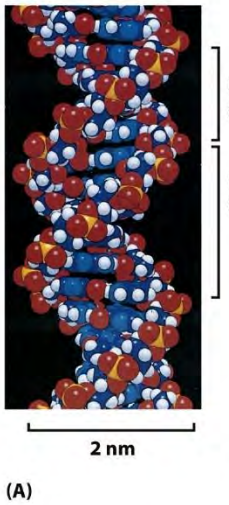


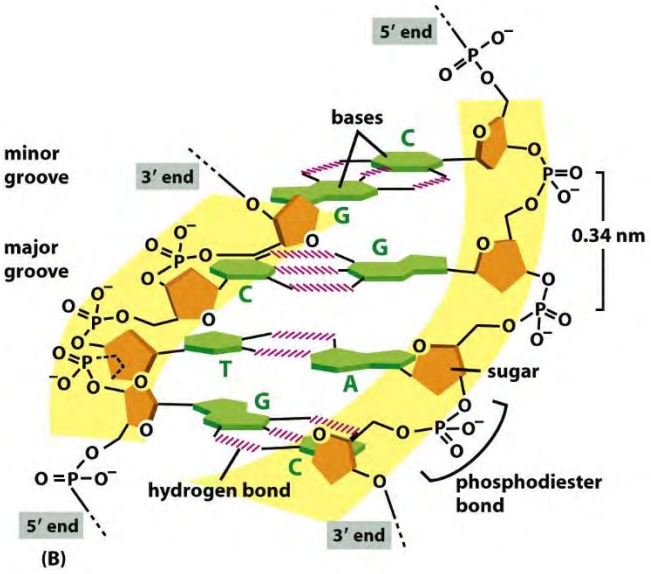
FRAGMENTATION - breaking of DNA strands into pieces, cleavage of phosphodiester bonds

The DNA molecule - 2 strands:

- chemical polarity: 5′ phosphate (end) - 3′ hydroxyl (end);
- three-dimensional structure - the double helix:
  - complementary base pairs in the DNA double helix;
  - maximized efficiency of base-pair packing - one complete turn every ten base pairs;
  - the two strands are antiparallel - the polarity of one strand is oriented opposite to that of the other strand.



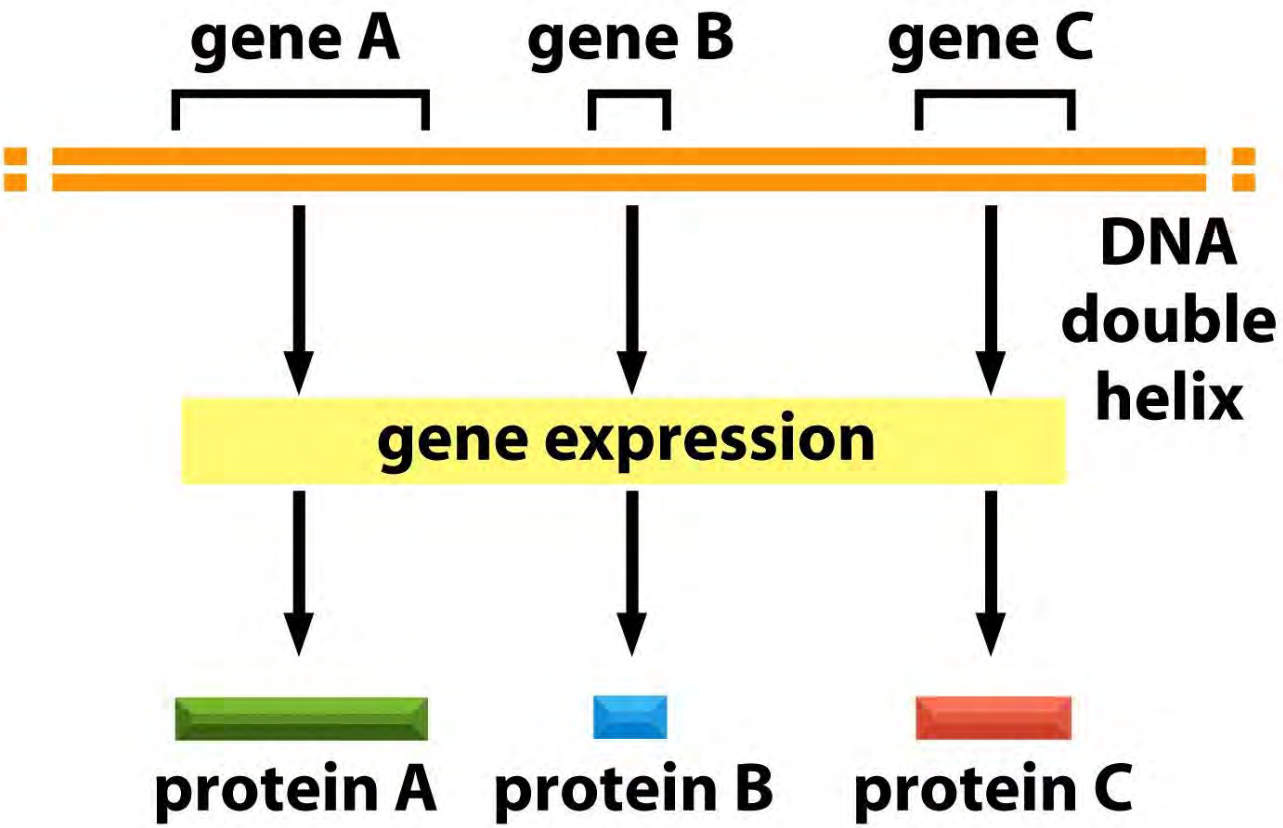




How can the information for specifying an organism be carried in chemical form?

DNA encodes information (messages) through the order, or sequence, of the nucleotides along each strand.

The linear sequence of nucleotides in a GENE "spell out" the linear sequence of amino acids in a protein.



The GENOME:

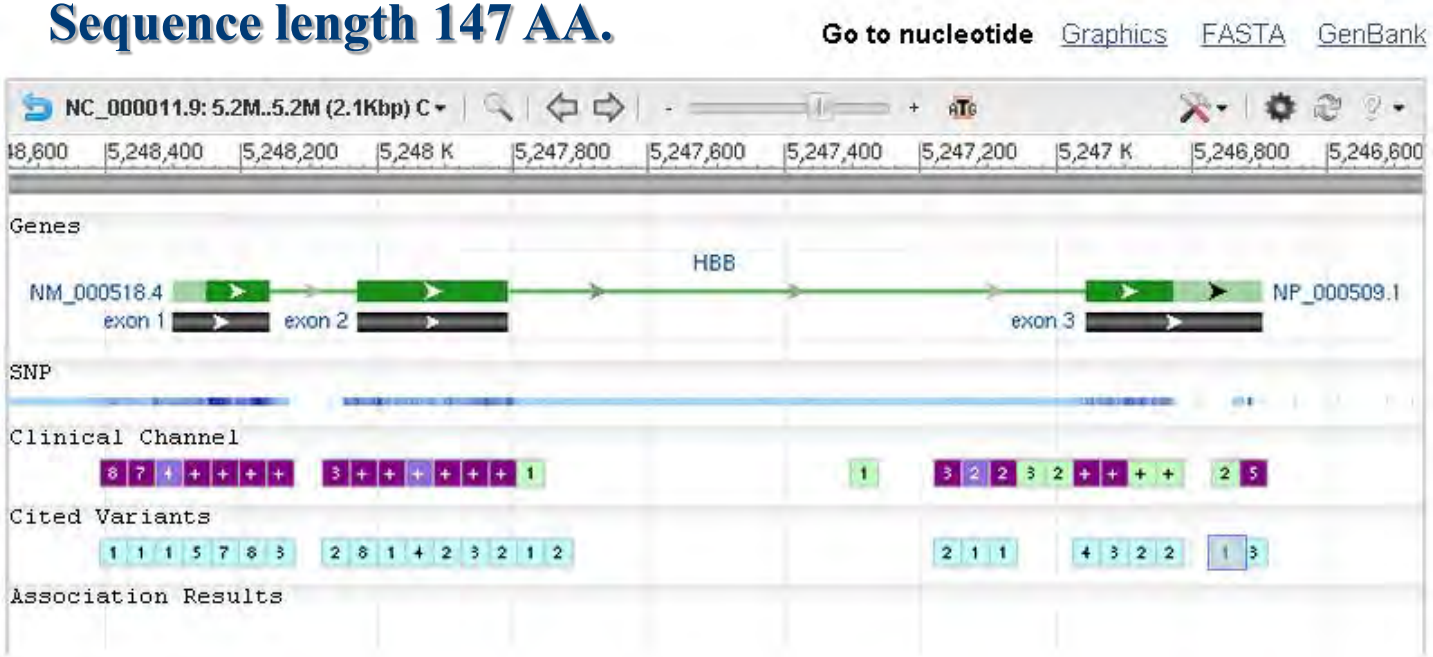
- **the complete set of information in an organism's DNA** ***(for all the proteins the organism will ever synthesize);***
- **the instructions for about 30,000 distinct proteins;**
- **2 meters of DNA** ***(a typical human cell)*****.**

β-globin gene - the human nucleotide sequence

Official Symbol: HBB

Location : 11p15.5

Sequence length 147 AA.



- The normal adult hemoglobin tetramer consists of two alpha chains and two beta chains.

- Mutant beta globin causes sickle cell anemia.

- Absence of beta chain causes beta-zero-thalassemia.

CCCTGTGGAGCCACACCCTAGGGTTGGCCA
ATCTACTCCCAGGAGCAGGGAGGGCAGGAG
CCAGGGCTGGGCATAAAAGTCAGGGCAGAG
CCATCTATTGCTTACATTTGCTTCTGACAC
AACTGTGTTCACTAGCAACTCAAACAGACA
CCATGGTGCACCTGACTCCTGAGGAGAAGT
CTGCCGTTACTGCCCTGTGGGGCAAGGTGA
ACGTGGATGAAGTTGGTGGTGAGGCCCTGG
GCAGGTTGGTATCAAGGTTACAAGACAGGT
TTAAGGAGACCAATAGAAACTGGGCATGTG
GAGACAGAGAAGACTCTTGGGTTTCTGATA
GGCACTGACTCTCTCTGCCTATTGGTCTAT
TTTCCCACCCTTAGGCTGCTGGTGGTCTAC
CCTTGGACCCAGAGGTTCTTTGAGTCCTTT
GGGGATCTGTCCACTCCTGATGCTGTTATG
GGCAACCCTAAGGTGAAGGCTCATGGCAAG
AAAGTGCTCGGTGCCTTTAGTGATGGCCTG
GCTCACCTGGACAACCTCAAGGGCACCTTT
GCCACACTGAGTGAGCTGCACTGTGACAAG
CTGCACGTGGATCCTGAGAACTTCAGGGTG
AGTCTATGGGACCCTTGATGTTTTCTTTCC
CCTTCTTTTCTATGGTTAAGTTCATGTCAT
AGGAAGGGGAGAAGTAACAGGGTACAGTTT
AGAATGGGAAACAGACGAATGATTGCATCA
GTGTGGAAGTCTCAGGATCGTTTTAGTTTC
TTTTATTTGCTGTTCATAACAATTGTTTTC
TTTTGTTTAATTCTTGCTTTCTTTTTTTTT
CTTCTCCGCAATTTTTACTATTATACTTAA
TGCCTTAACATTGTGTATAACAAAAGGAAA
TATCTCTGAGATACATTAAGTAACTTAAAA
AAAAACTTTACACAGTCTGCCTAGTACATT
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TATGTGTACACATATTGACCAAATCAGGGT
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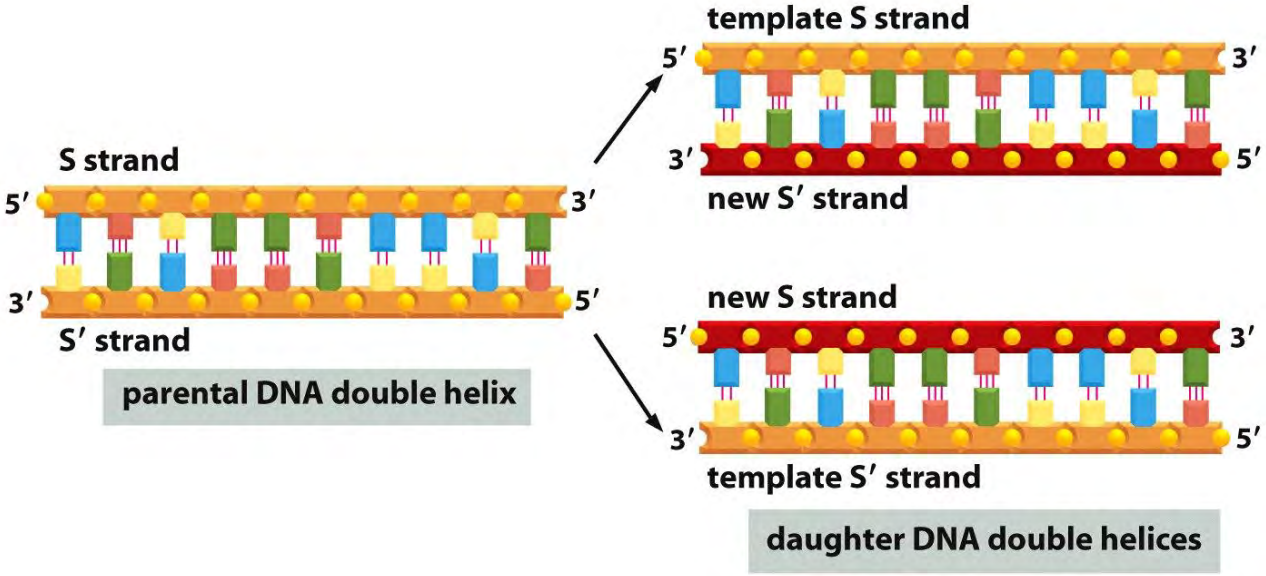
TTATTTCTAATACTTTCCCTAATCTCTTTC
TTTCAGGGCAATAATGATACAATGTATCAT
GCCTCTTTGCACCATTCTAAAGAATAACAG
TGATAATTTCTGGGTTAAGGCAATAGCAAT
ATTTCTGCATATAAATATTTCTGCATATAA
ATTGTAACTGATGTAAGAGGTTTCATATTG
CTAATAGCAGCTACAATCCAGCTACCATTC
TGCTTTTATTTATGGTTGGGATAAGGCTG
GATTATTCTGAGTCCAAGCTAGGCCCTTTT
GCTAATCATGTTCATACCTCTTATCTTCCT
CCCACAGCTCCTGGGCAACGTGCTGGTCTG
TGTGCTGGCCCATCACTTTGGCAAAGAATT
CACCCCACCAGTGCAGGCTGCCTATCAGAA
AGTGGTGGCTGGTGTGGCTAATGCCCTGGC
CCACAAGTATCACTAAGCTCGCTTTCTTGC
TGTCCAATTTCTATTAAAGGTTCCTTTGTT
CCCTAAGTCCAACTACTAAACTGGGGGATA
TTATGAAGGGCCTTGAGCATCTGGATTCTG
CCTAATAAAAAACATTTATTTTCATTGCAA
TGATGTATTTAAATTATTTCTGAATATTTT
ACTAAAAAGGGAATGTGGGAGGTCAGTGCA
TTTAAAACATAAAGAAATGATGAGCTGTTC
AAACCTTGGGAAAATACACTATATCTTAAA
CTCCATGAAAGAAGGTGAGGCTGCAACCAG
CTAATGCACATTGGCAACAGCCCCTGATGC
CTATGCCTTATTCATCCCTCAGAAAAGGAT
TCTTGTAGAGGCTTGATTTGCAGGTTAAAG
TTTTGCTATGCTGTATTTTACATTACTTAT
TGTTTTAGCTGTCCTCATGAATGTCTTTTC

How is the information accurately copied?

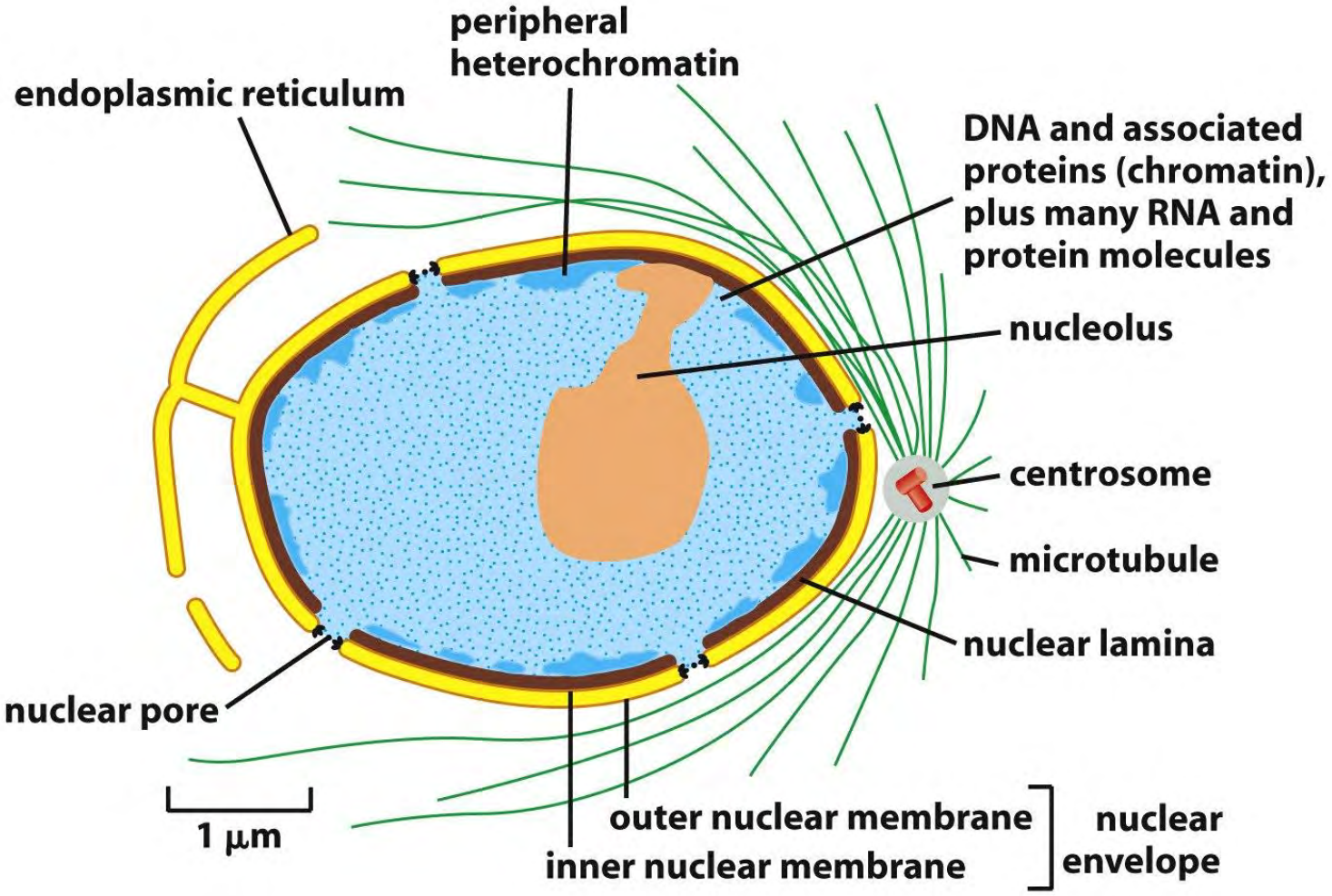
Copying the GENOME…

each strand of DNA contains a sequence of nucleotides that is exactly complementary to the nucleotide sequence of its partner strand

=> each strand can act as a template, or mold, for the synthesis of a new complementary strand



In Eucaryotes, DNA Is Enclosed in a Cell Nucleus



I.B. Chromosomal DNA and Its Packaging in the Chromatin Fiber

Facts:

- human cell - 2 meters of DNA if stretched end-to-end;
- the nucleus of a human cell - 6 μm in diameter.

Packaging DNA:

- specialized proteins that bind to and fold the DNA => coils and loops => increasingly higher levels of organization
- DNA available to the many enzymes in the cell that replicate it, repair it, and use its genes to produce proteins.

Eucaryotic DNA Is Packaged into a Set of Chromosomes

- human genome – approx. 3.2 billion nucleotides - distributed over 24 different chromosomes;

- the complex of DNA and proteins (pack&fold) = CHROMATIN

- CHROMOSOMES – associated with many other proteins (gene expression, DNA replication and DNA repair);

- each human cell (with few exceptions) - two copies of each chromosome, one inherited from the mother and one from the father;

Eucaryotic DNA Is Packaged into a Set of Chromosomes

- one pair = homologous chromosomes (homologs);

- in males - sex chromosomes - nonhomologous (X and Y).

- each human cell contains a total of 46 chromosomes - 22 pairs common to both males and females, plus two so-called sex chromosomes (X and Y in males, two Xs in females)

KARYOTYPE - arrangement of the full chromosome set

- painted chromosomes -

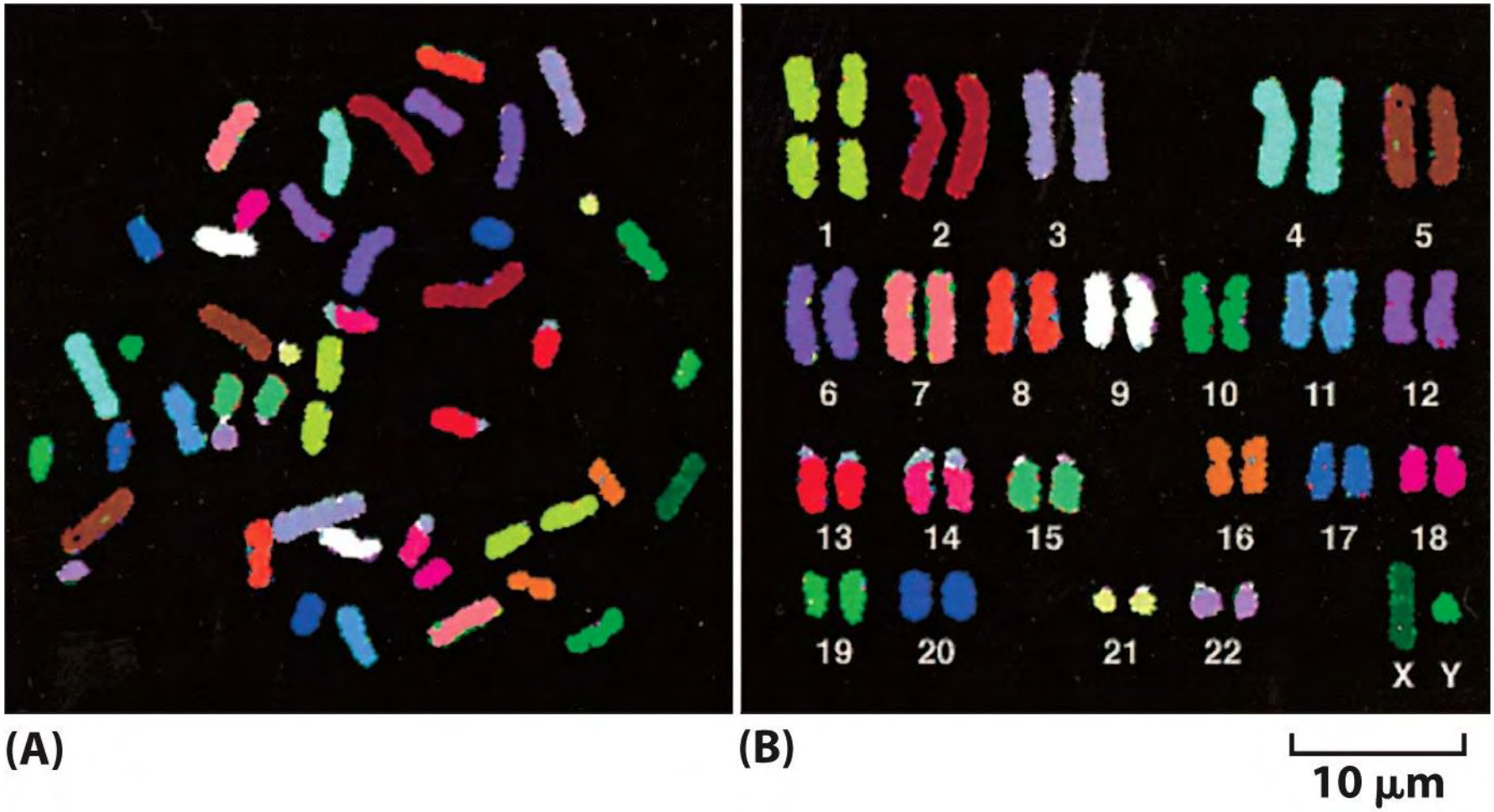


Figure 4-10 *Molecular Biology of the Cell* (© Garland Science 2008)

KARYOTYPE - arrangement of the full chromosome set

- Giemsa stained chromosomes -

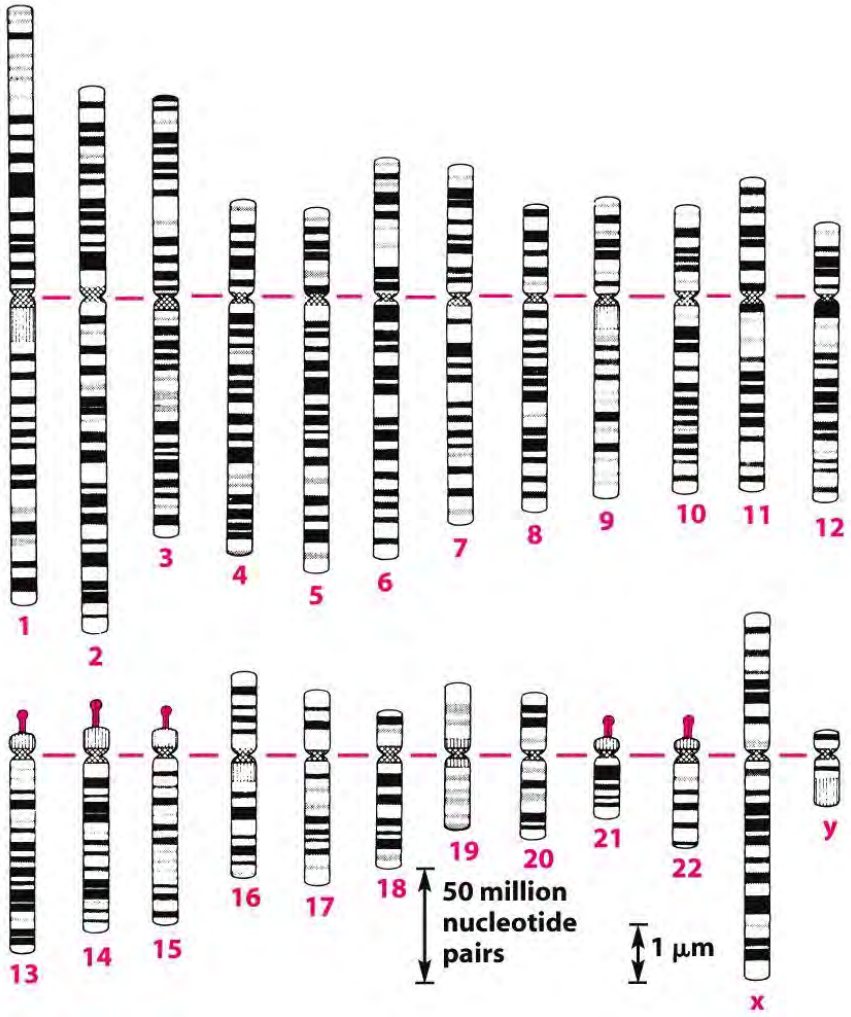


Figure 4-11 *Molecular Biology of the Cell* (© Garland Science 2008)

Chromosomes Contain Long Strings of Genes

CHROMOSOMES:

- carry genes - the functional units of heredity;
- interspersed DNA (junk DNA?) that does not seem to carry critical information.

** GENE - segment of DNA that contains the instructions - particular protein (or a set of closely related proteins) and RNA (eg: rRNA, tRNA, siRNA).*

Interesting facts:

HUMAN GENOME:

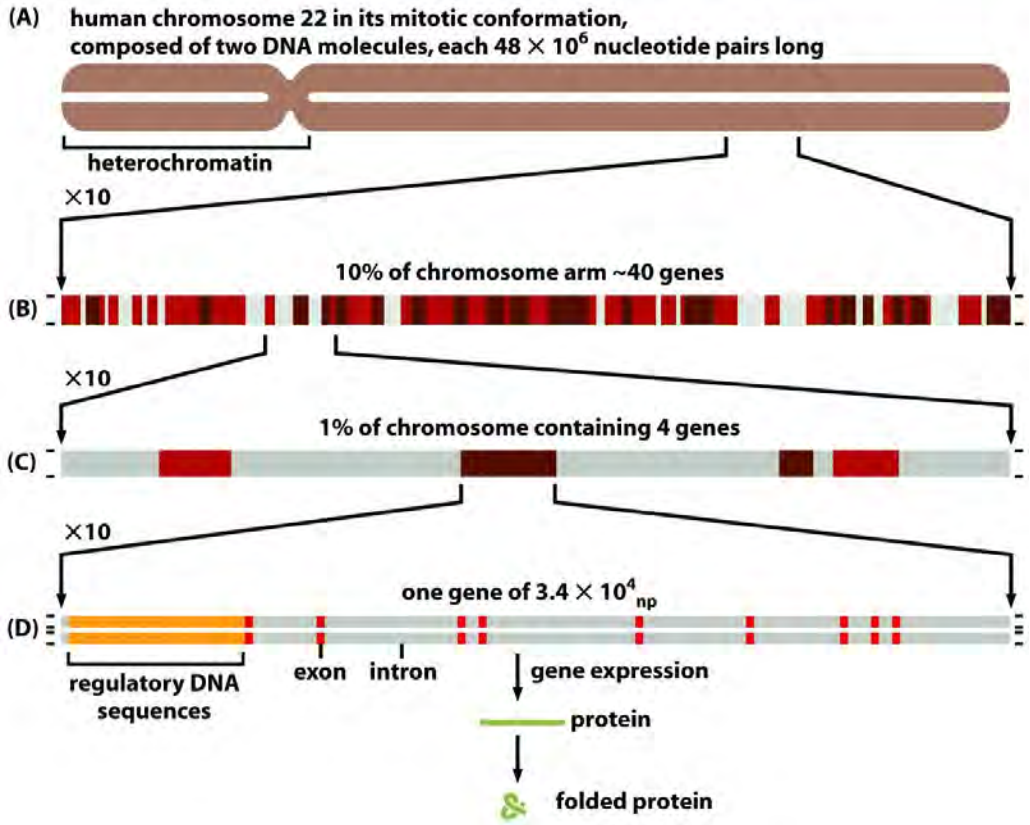
- 200 times larger than that of the yeast S. cerevisiae;
- 30 times smaller than that of some plants and amphibians;
- 200 times smaller than a species of amoeba.

- human - 46 chromosomes

vs over 100 – a species of carp

The Nucleotide Sequence of the Human Genome Shows How Genes Are Arranged in Humans:

- 1999 - the DNA sequence of human chromosome 22
- one of the smallest human chromosomes - approx. 1.5% of the entire HG



The Nucleotide Sequence of the Human Genome Shows How Genes Are Arranged in Humans:

- 2001- the "first draft" of the entire human genome
- only a few percent of Human genome codes for proteins or structural and catalytic RNAs

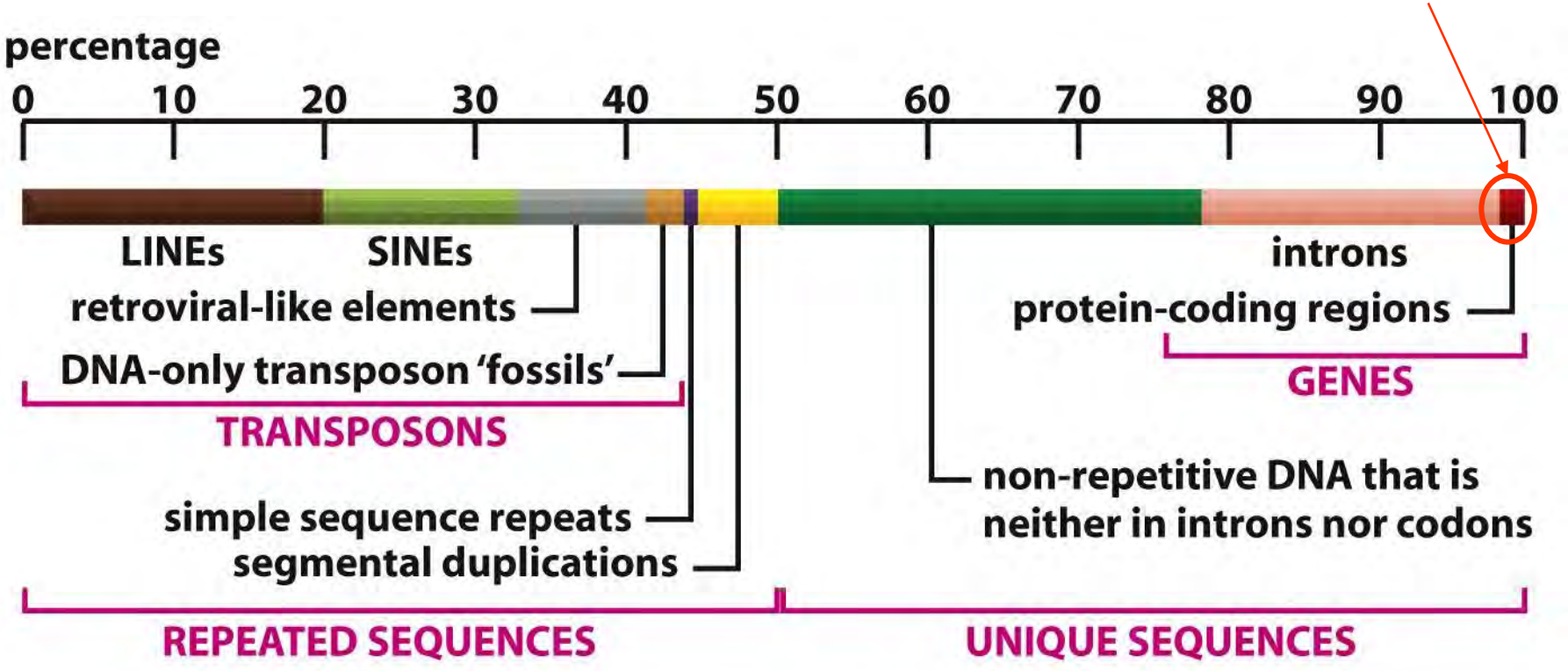


Table 4–1 Some Vital Statistics for the Human Genome

	HUMAN GENOME
DNA length	3.2×10^9 nucleotide pairs*
Number of genes	approximately 25,000
Largest gene	2.4×10^6 nucleotide pairs
Mean gene size	27,000 nucleotide pairs
Smallest number of exons per gene	1
Largest number of exons per gene	178
Mean number of exons per gene	10.4
Largest exon size	17,106 nucleotide pairs
Mean exon size	145 nucleotide pairs
Number of pseudogenes**	more than 20,000
Percentage of DNA sequence in exons (protein coding sequences)	1.5%
Percentage of DNA in other highly conserved sequences***	3.5%
Percentage of DNA in high-copy repetitive elements	approximately 50%

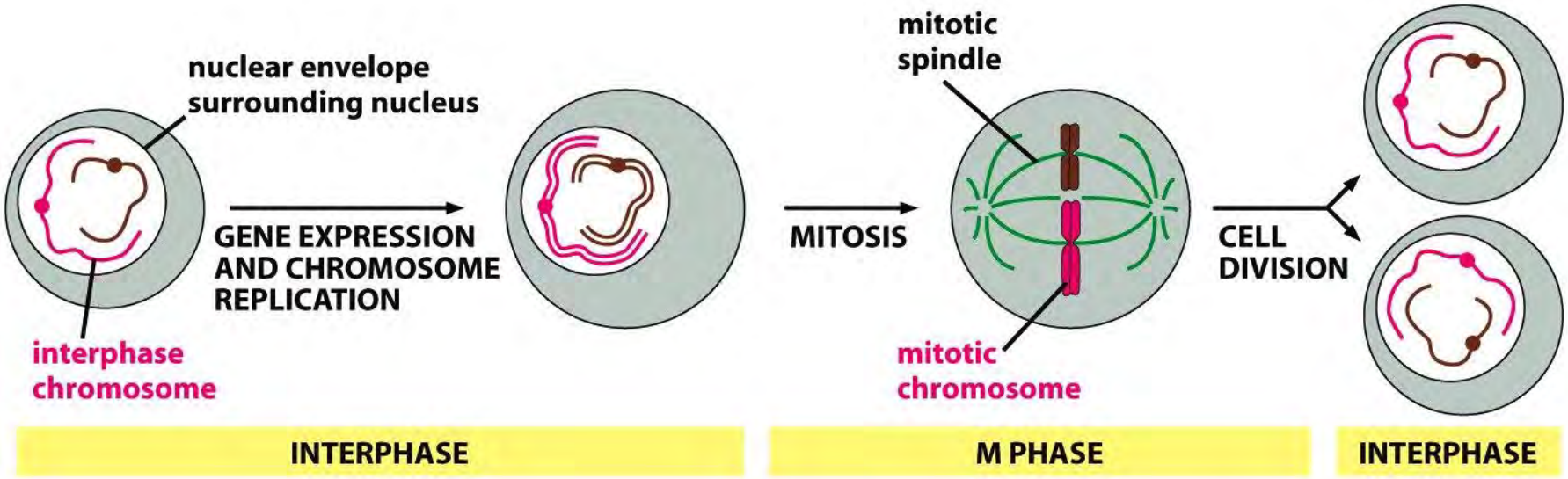
* The sequence of 2.85 billion nucleotides is known precisely (error rate of only about one in 100,000 nucleotides). The remaining DNA primarily consists of short highly repeated sequences that are tandemly repeated, with repeat numbers differing from one individual to the next.

** A pseudogene is a nucleotide sequence of DNA closely resembling that of a functional gene, but containing numerous mutations that prevent its proper expression. Most pseudogenes arise from the duplication of a functional gene followed by the accumulation of damaging mutations in one copy.

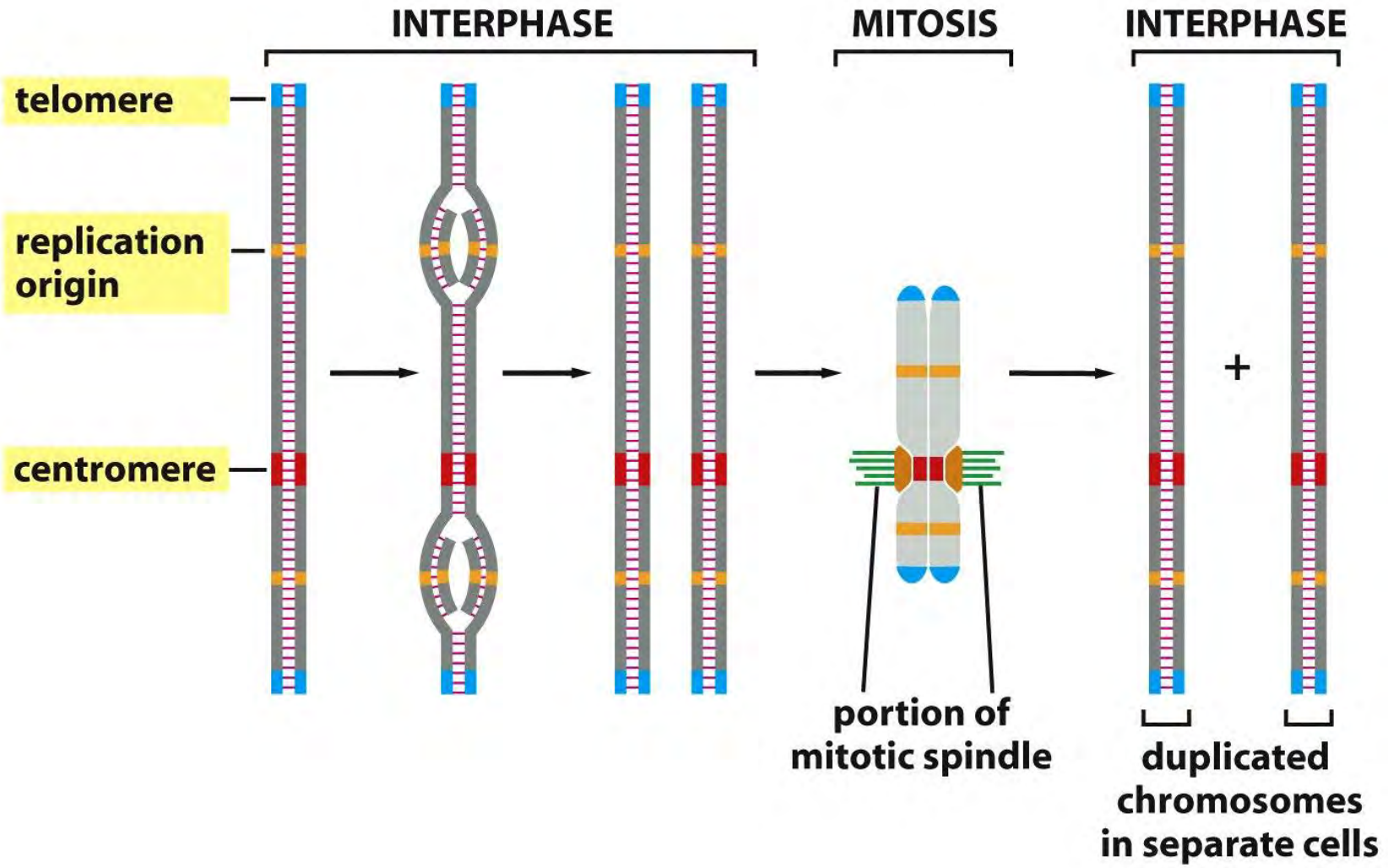
*** Preserved functional regions; these include DNA encoding 5′ and 3′ UTRs (untranslated regions), structural and functional RNAs, and conserved protein-binding sites on the DNA.

Chromosomes Exist in Different States Throughout the Life of a Cell

DNA molecules: carry genes, replicate and the replicated copies must be separated and reliably partitioned into daughter cells at each cell division.



Each DNA Molecule That Forms a Linear Chromosome Must Contain a Centromere, Two Telomeres, and Replication Origins



- DNA Molecules Are Highly Condensed in Chromosomes

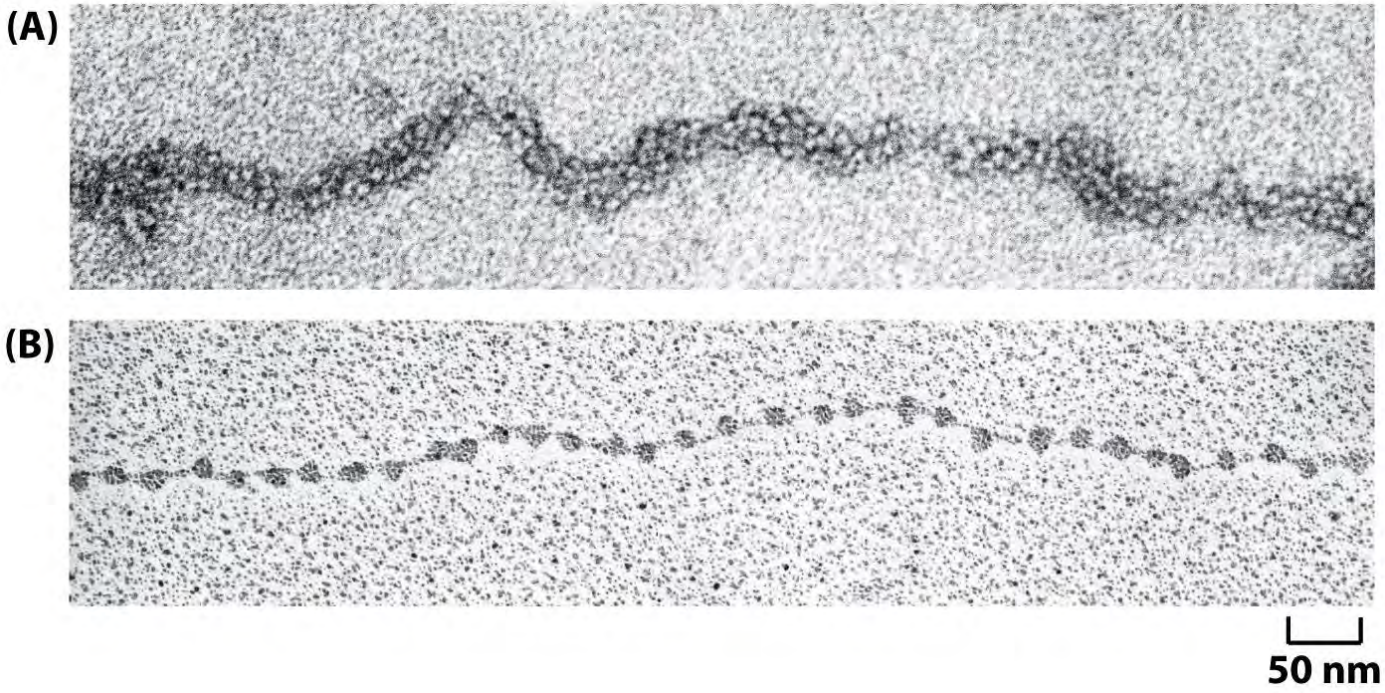
  - chromosome 22 DNA stretched out end to end - 1.5 cm;
  - mitotic 22 chromosome - 2 μm in length;
  - end-to-end compaction ratio of -10,000-fold;
  - interphase chromosomes - overall compaction ratio - 1000-fold

- Chromosome structure is dynamic

  - regions of the interphase chromosomes condense and decondense: gene expression, DNA repair, and replication.

CHROMATIN fiber

- The complex of the chromosomal proteins (histones and the nonhistone) with the nuclear DNA of eucaryotic cells;
- Histones - 60 million molecules of each type per human cell;
- The beads on a string represent the first level of chromosomal DNA packing.



NUCLEOSOME

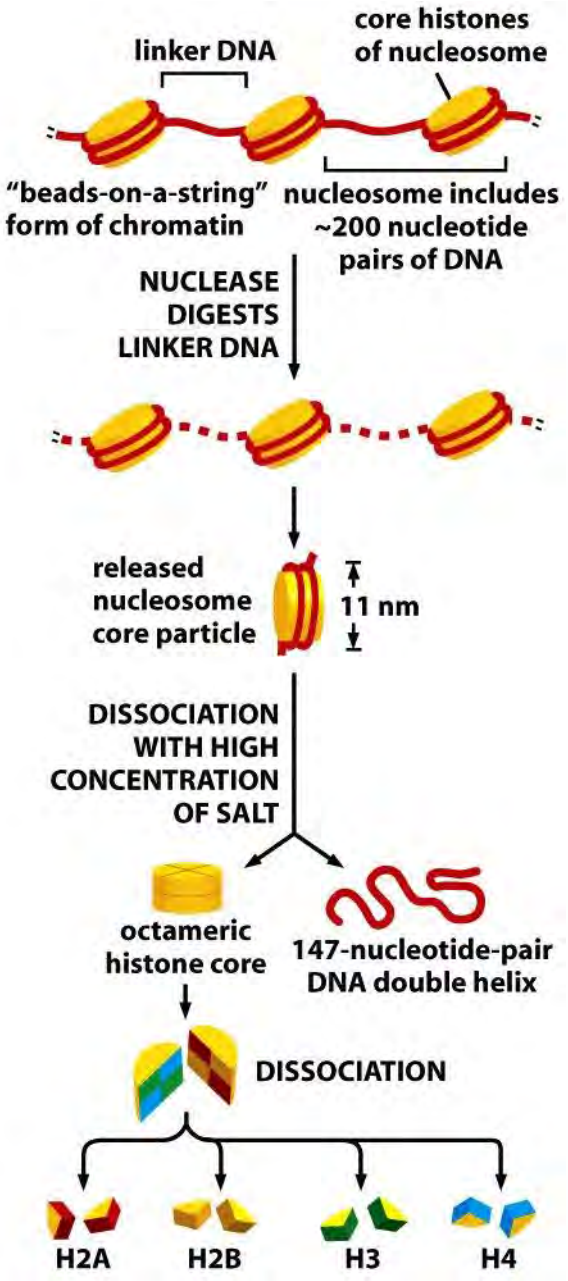
- the first and most basic level of chromosome organization

- the core particle - eight histone proteins - two molecules each of histones H2A, H2B, H3, and H4 + double-stranded DNA (146 nps).

- 2 nucleosomes - separated by linker DNA (up to 80nps).

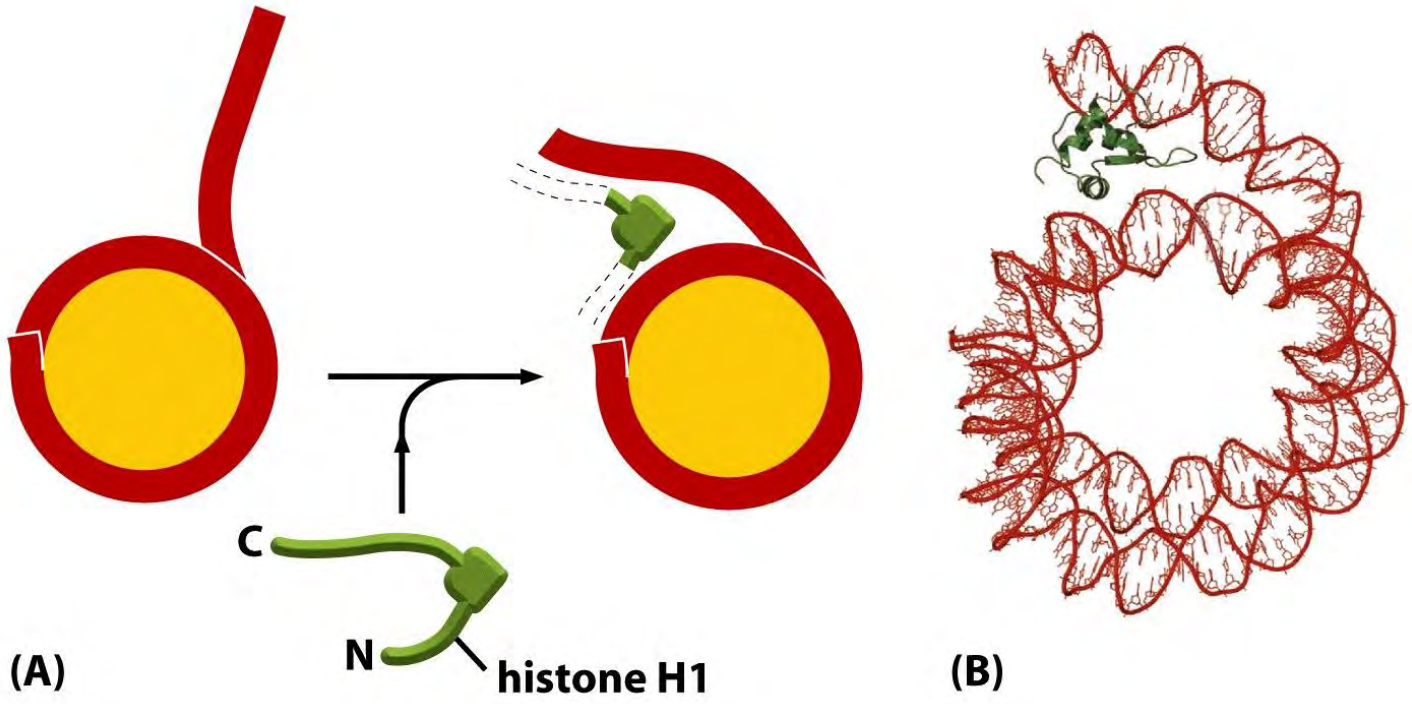
- the histones are among the most highly conserved eucaryotic proteins.

- covalent modification of the histone tails can profoundly affect chromatin (acetylation of lysines, methylation of lysines, and phosphorylation of serines)



Nucleosomes - packed compact chromatin fiber

- the nucleosomes are packed on top of one another => regular arrays in which the DNA is even more highly condensed;
- histone H1 molecule binds to each nucleosome, contacting both and protein, and changing the path of the DNA as it exits from the nucleosome.



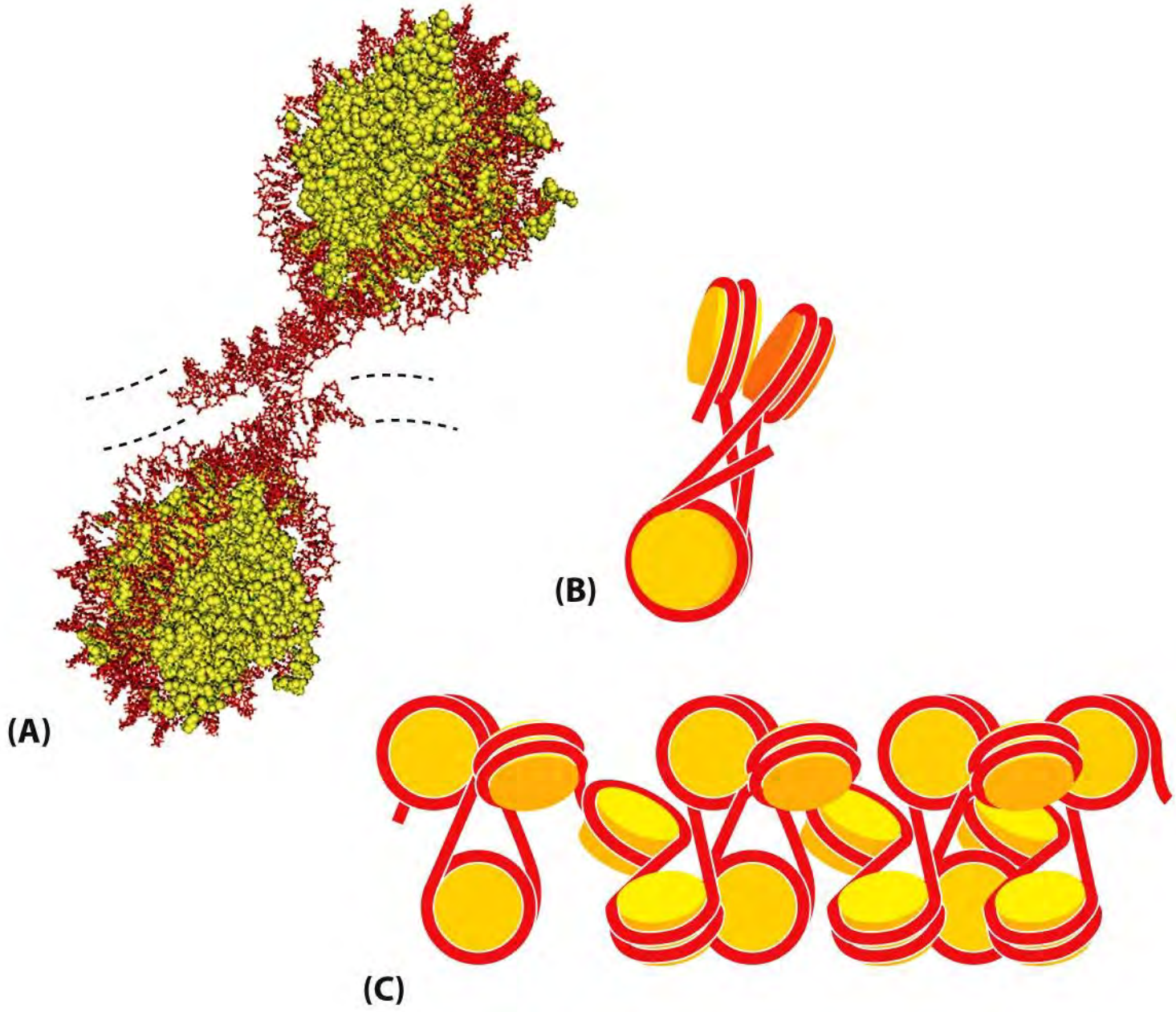
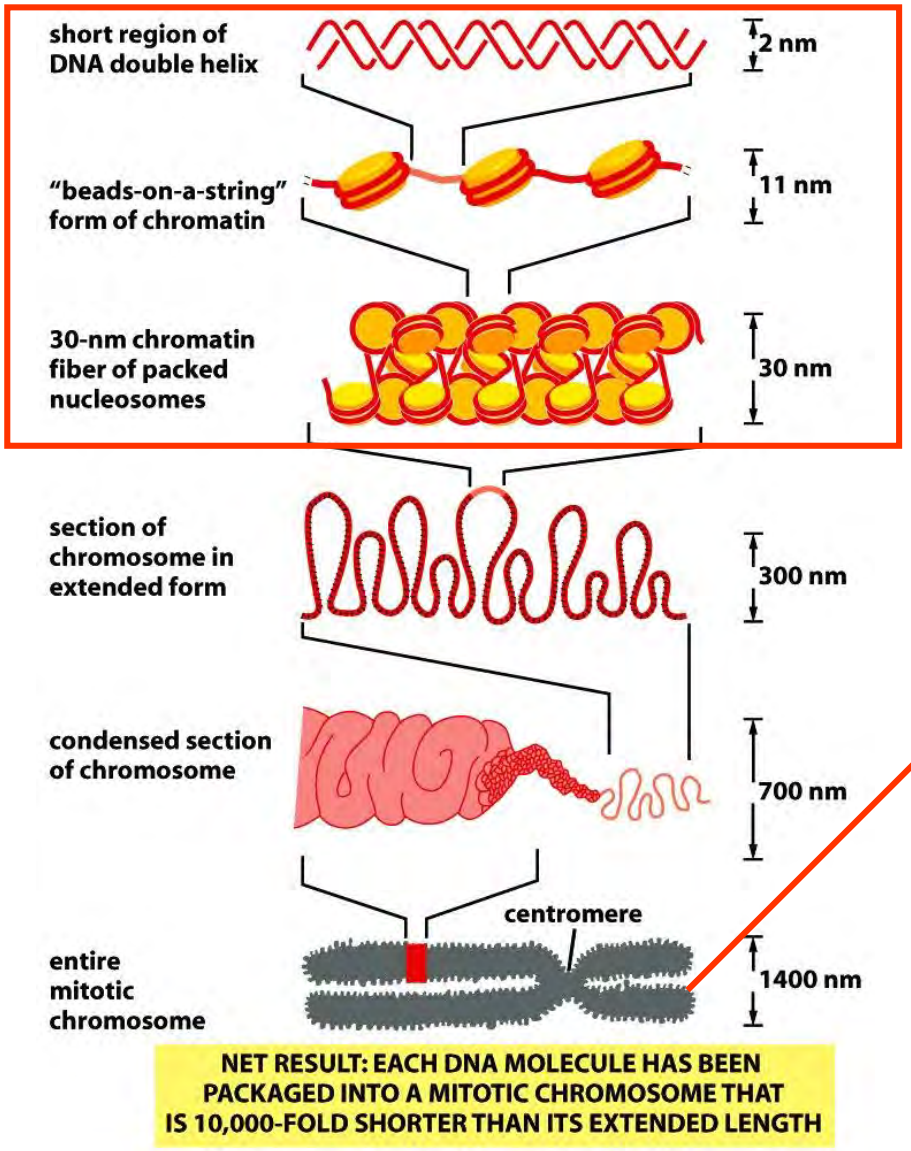
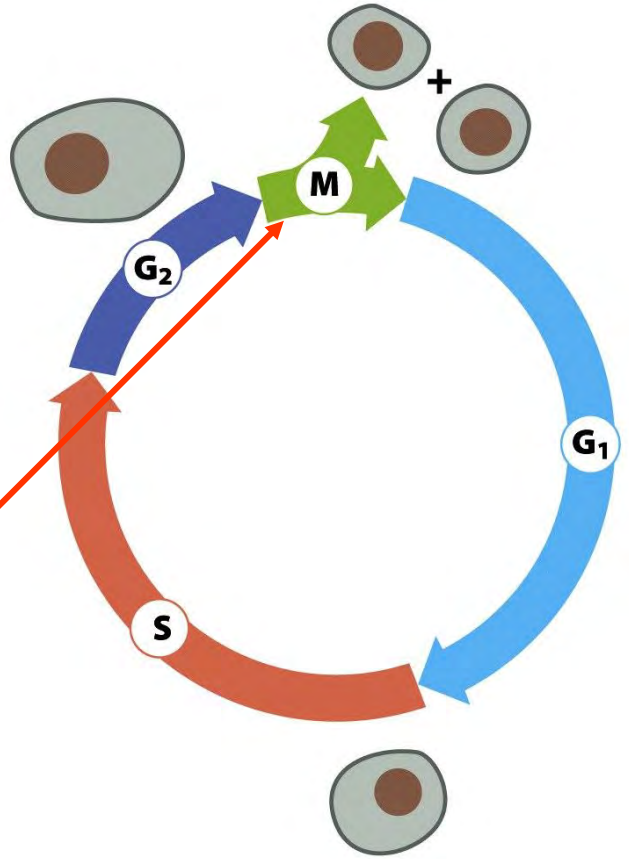


Figure 4-31 *Molecular Biology of the Cell* (© Garland Science 2008)

I.C. The Global Structure of Chromosomes





NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 10,000-FOLD SHORTER THAN ITS EXTENDED LENGTH

I.C. The Global Structure of Chromosomes

- As a 30-nm fiber, the typical human chromosome - 0.1 cm <=>100x nucleus.

=> higher level of folding (even in interphase chromosomes).

HETEROCHROMATIN

- highly condensed form of chromatin, a more compact levels of organization (more proteins)
- concentrated in specific regions, including the centromeres and telomeres.
- (most of HC) does not contain genes

EUCHROMATIN

- less condensed, contains genes

HETEROCHROMATIN

- histone tail modifications - allow nucleosomes to pack together into tighter arrays

- HC at the ends of chromosomes - advantages:
  - protection;
  - help to regulate telomere length;
  - assist in the accurate pairing and segregation of chromosomes during mitosis.

- HC at the Centromeres - *centric heterochromatin*:
  - persists throughout interphase

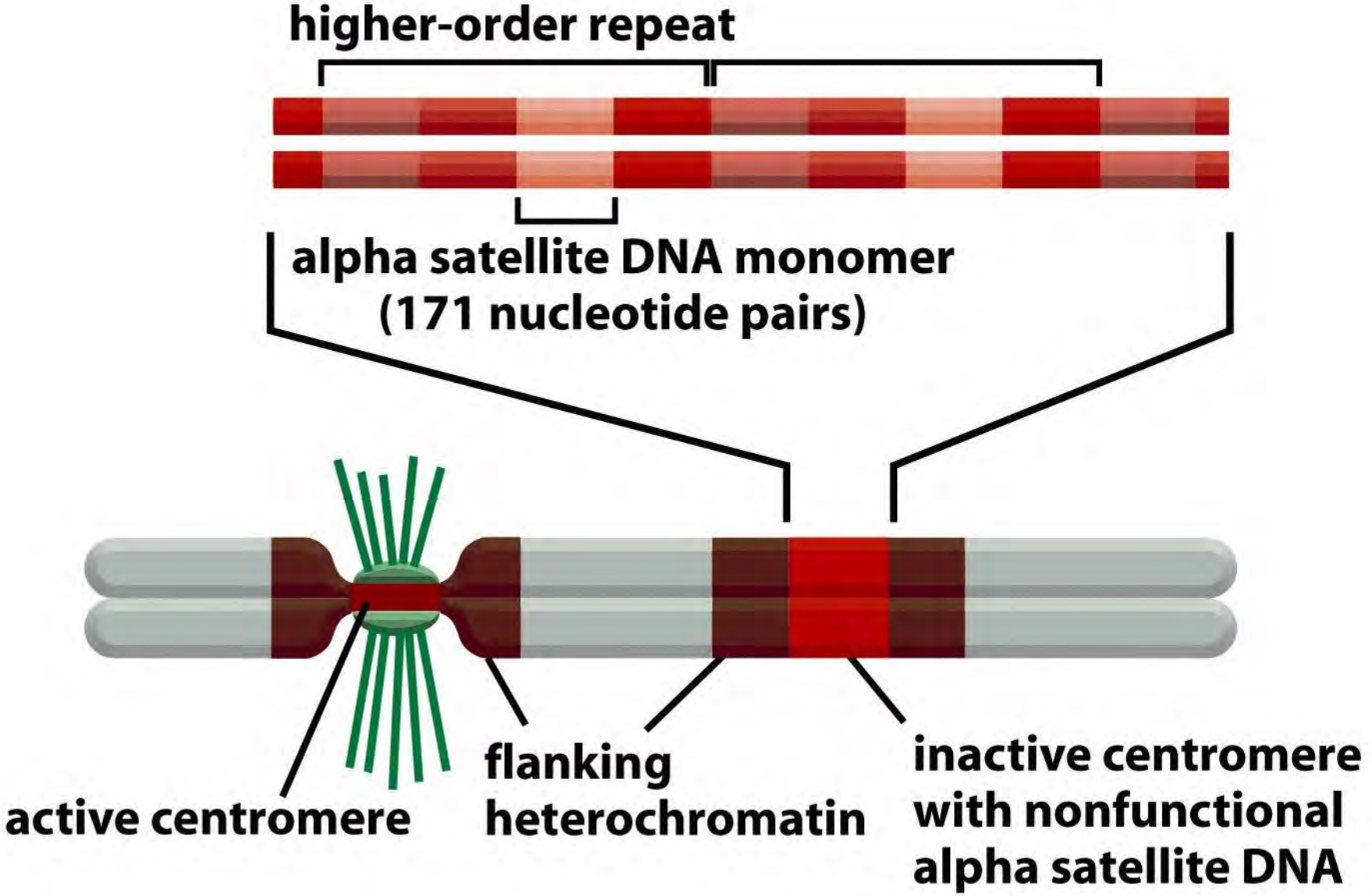


Figure 4-49a *Molecular Biology of the Cell* (© Garland Science 2008)

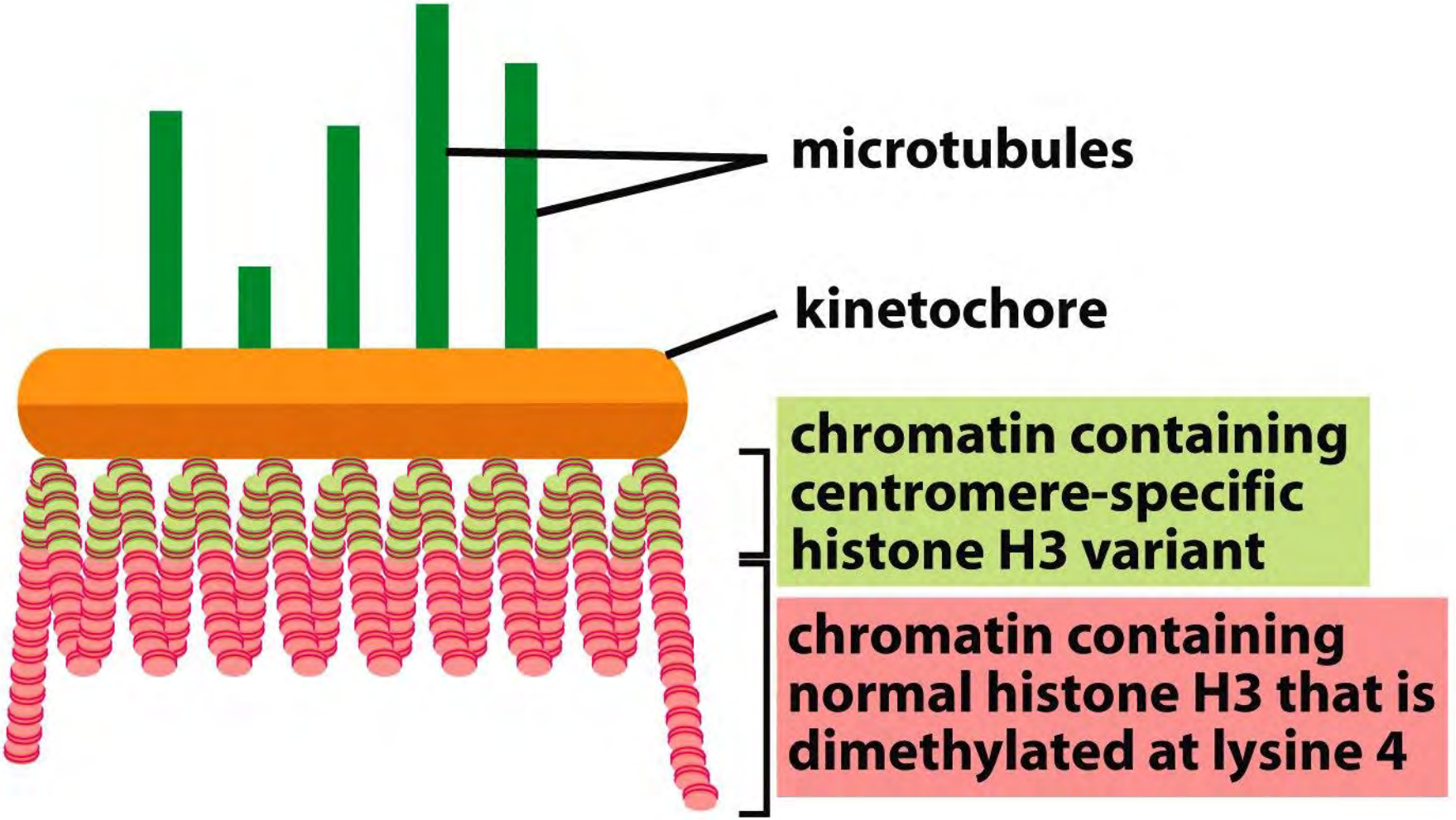


Figure 4-50b *Molecular Biology of the Cell* (© Garland Science 2008)

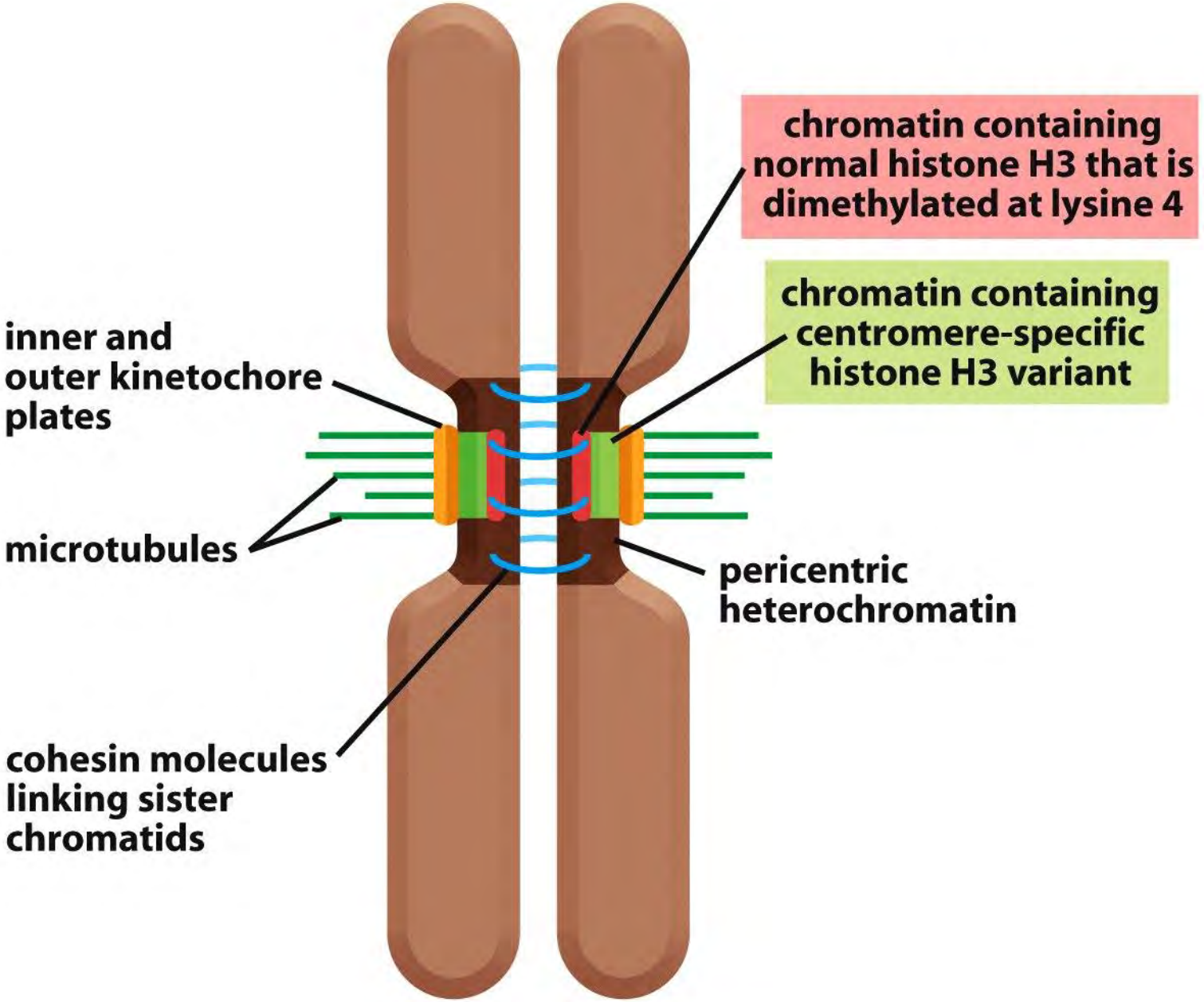


Figure 4-50c *Molecular Biology of the Cell* (© Garland Science 2008)

HETEROCHROMATIN - function

- may provide a defense mechanism against mobile DNA elements:

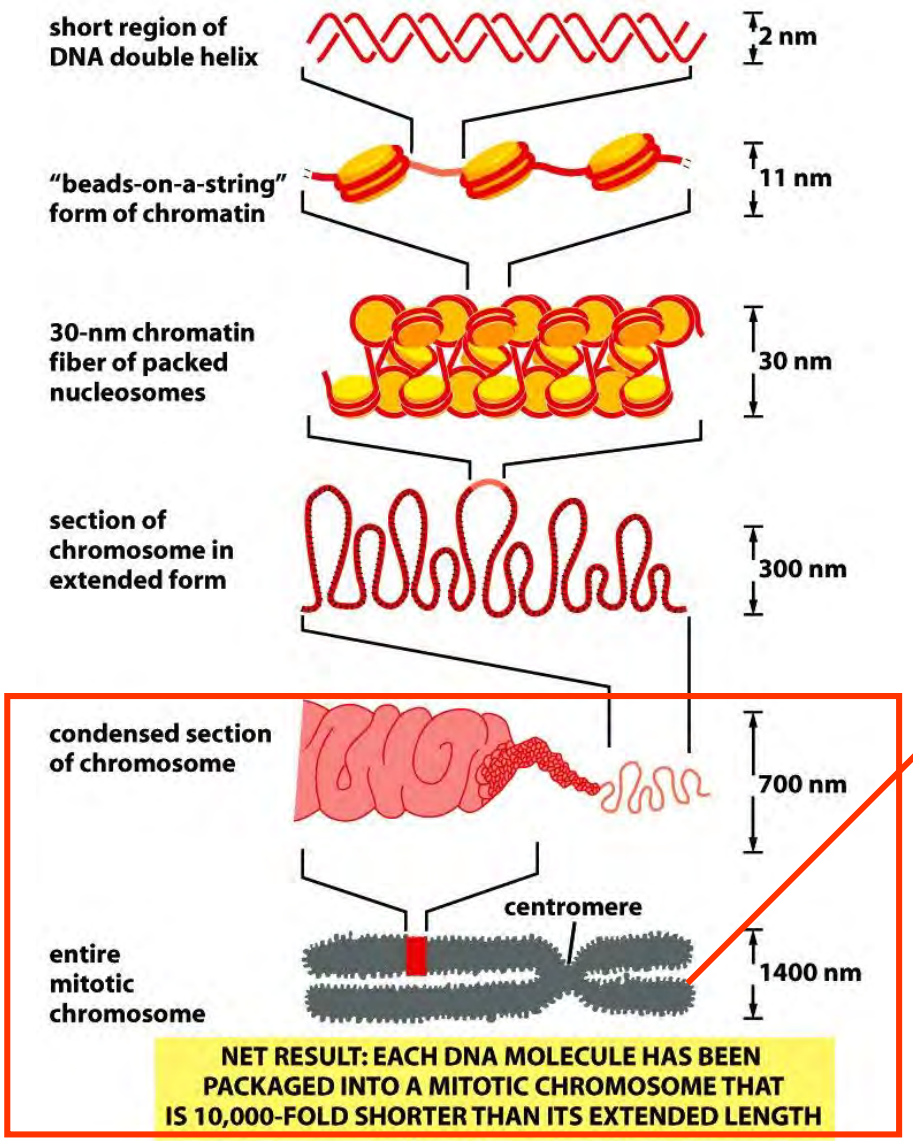
  - often consists of large tandem arrays of short, repeated sequences;
  - some types of repeated DNA may be a signal for heterochromatin formation.

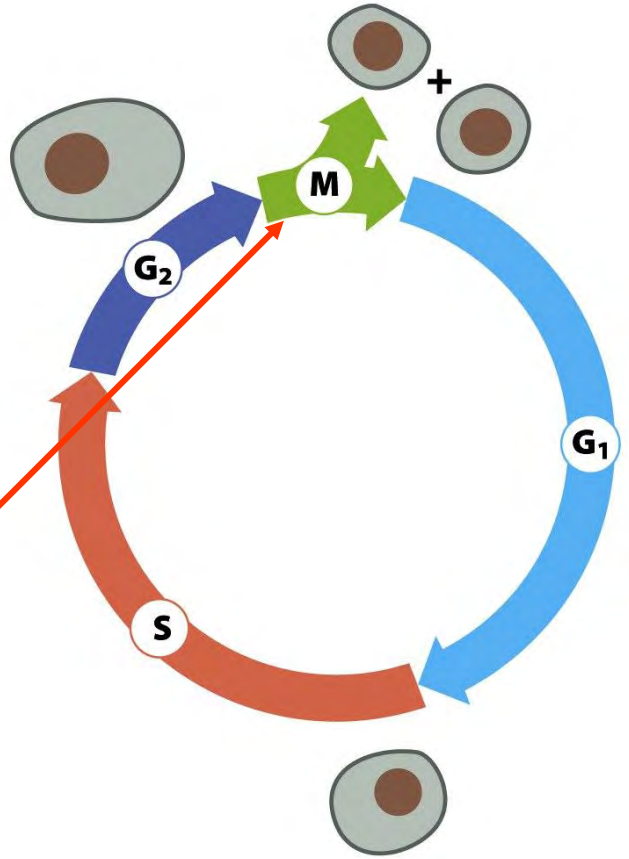
EXPERIMENTS - GENES artificially introduced into cells:

- in heterochromatin (repeated DNA) => silenced/have formed regions of HC
- in euchromatin – expressed

REPEAT-INDUCED GENE SILENCING - protects genomes from being overtaken by mobile genetic elements.

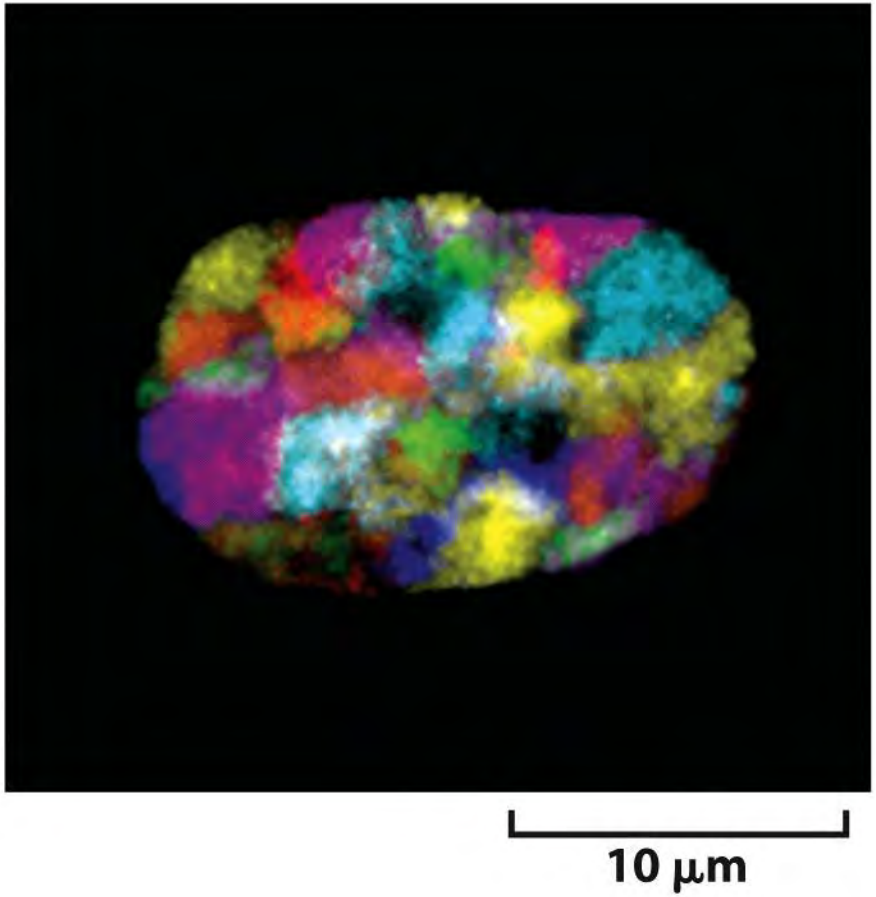
Mitotic Chromosomes = chromatin in its most condensed state

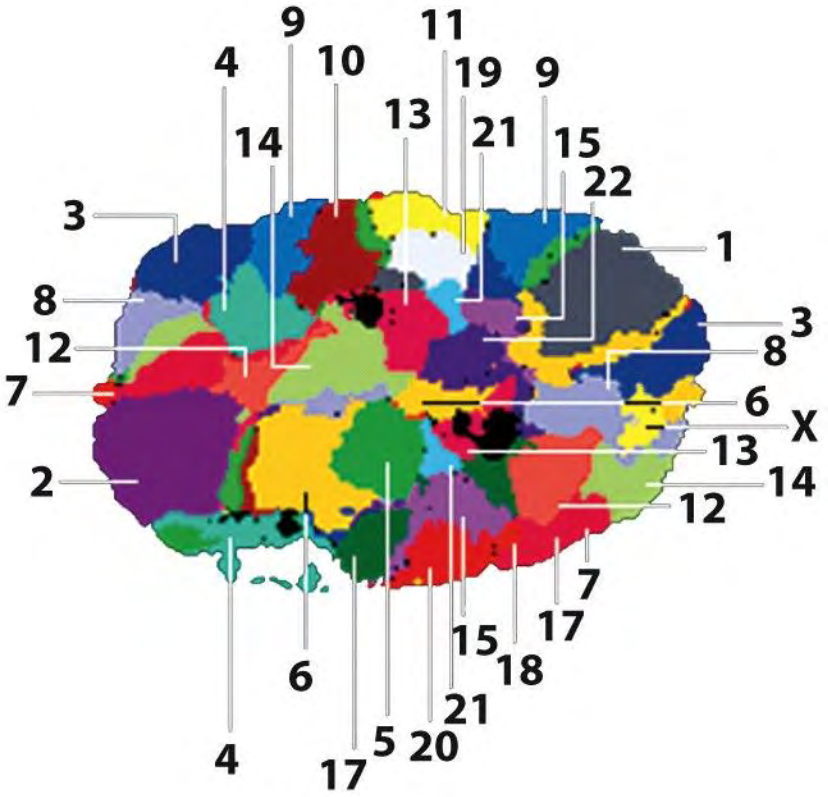




Is the nucleus simply a bag of chromosomes?

Individual Chromosomes Occupy Discrete Territories in an Interphase Nucleus





MULȚUMESC!