Central Dogma of Biology

Nucleic Acids

1.Quiz next Wednesday on Intro Stryer reading
2. By next Wed., should have ECB textbook.
(No class next Mon.—MLK celebration.)

Grading

(may be modified slightly if changes to course)

Grading

25%: Homework (about 9 total; drop lowest 1):

(You CANNOT drop the last homework!)

Work together, but turn in separately.

Hand in at start of class– in class! (Do not be late.)

25%: Written Project & Oral Project– Same topic

-- 12.5% on written report: 10 pg report.

-- 12.5% on oral report: 8-12 min plus 4 min for questions.

15% on midterm exam

15% on final exam

10% Quizzes (1% on each)

--5 min quizzes making sure that you've read readings

10% on classroom participation /class evaluation

Course Schedule

DNA & Proteins

1) Jan. 14th : Intro; King Kong; Temp. of Earth; DNA and Proteins; Evolution
2) Jan 16th : Nucleic Acids & Boltzmann Constant
3) Jan 23rd : Nucleic Acids & PCR, Amino Acids, Proteins
4) Jan 28th : DNA Fidelity, RNA Catalysis, & Gene Chips
5) Jan 30th : Gene Chips; Beginning of Enzymes

Imaging & Microscopy –seeing small things.

6) Feb 4th : Diffraction limit, different kinds of microscopy (EM, X-ray).
7) Feb 6th : Fluorescence: very useful form of microscopy. Can see single molecule!
8) Feb 11th : ATPase Operates at near 100% Efficiency
9) Feb 13th : FIONA; 1 nm accuracy (not resolution). Applied to Molecular Motors
10) Feb 18th : SHREC, PALM, STORM—20 nm resolution.
11) Feb 20st : STED, FRET
12) Feb 25th : FRET and DNA helicase—TJ's Science magazine article.

Magnetic Sensing: which way is home?

13) Feb 27th : **Klaus**—Magnetic sensing.

Mid-term Exam.

14) March 3rd : Review + tour of my lab
15) March 5th: **Mid-term Exam**

Optical Traps allow you to see Angstrom & Nanometer distance.

16) March 10th : **Yann Chemla**
17) March 12th : **Yann Chemla** + tour of his lab

March Vacation

Diffusion

18) March 24th : Freely jointed vs. Worm-like Chain of DNA: Magnetic Traps
19) March 26th : Diffusion: Inertia doesn't mean anything
20) March 31st : Diffusion and Bacteria Moving
21) April 2nd : **Student Presentation**
22) April 7th : **Students Presentation**

Vision & Ion Channels

23) April 9th : Ion Channels
23) April 14th : Ion Channels
24) April 16th : Vision

Most Genes are few in Number—some surprising results

25) April 21st : Studying Gene Activity in Individual Cells.
26) April 23rd : Studying Gene Activity in Individual Cells

Photosynthesis

27) April 28th : Photosynthesis.
28) April 30th : Instruction Ends
29) May 2nd -9th: Final Exam

Plagiarism

Not allowed! You will flunk the course.

In written project…

Something has always been written…
(unless you have truly come up with something new.)

Usually what's written will be clearer than you can write it.

But you want to independently understand it.
And show me that you independently understand it.

So…

Read book/article, then close it,
Then write your own version. This way you know you understand it, and can explain it in your own words.

Also, when you "steal" a picture from somewhere, write in your paper where you got it from. A picture is worth a thousand words, but give credit where due.

Physics and Biology

Physics says which of possible tricks evolution might use (are possible)

Physics places constraints
Tell what's possible and not possible

Biology must follow laws of physics

But within laws of physics many bio worlds are possible.

(e.g. we have DNA made up of 4 bases,
but why these 4 bases– have shown there are alternative bases)

Which world actually exists?
Many possible...
Often many ways of doing this
Our life form is just one.

Therefore, do:
Biology Experiments

Our existence predicated on
Central Dogma of Biology

DNA→ RNA→ Proteins
Central Dogma of Biology

DNA: series of 4 nucleotides (bases): A,T,G,C

↓ Transcription [DNA & RNA similar]

RNA: series of 4 nucleotides (bases): A,U,G,C

↓ Translation [RNA & Proteins different]

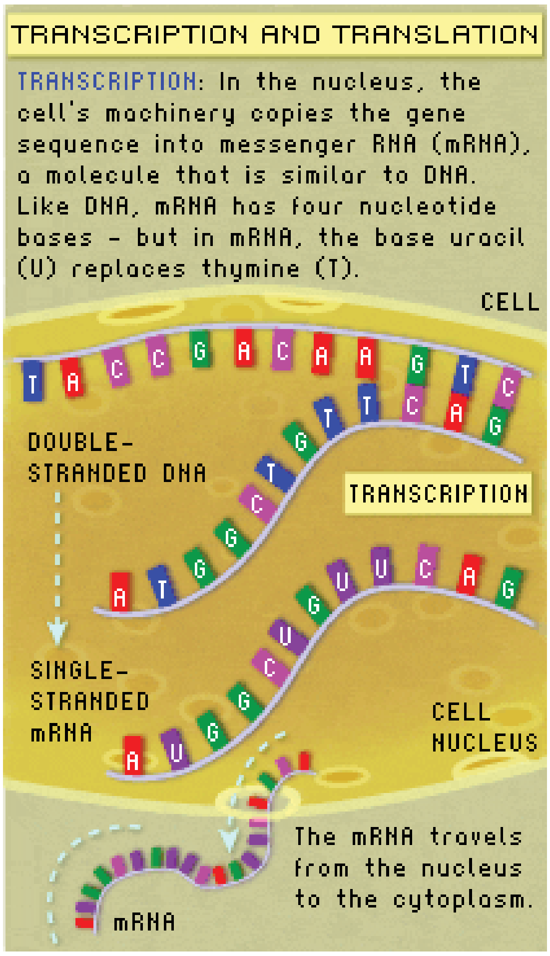
Proteins: series of 20 amino acids: Met-Ala-Val-…

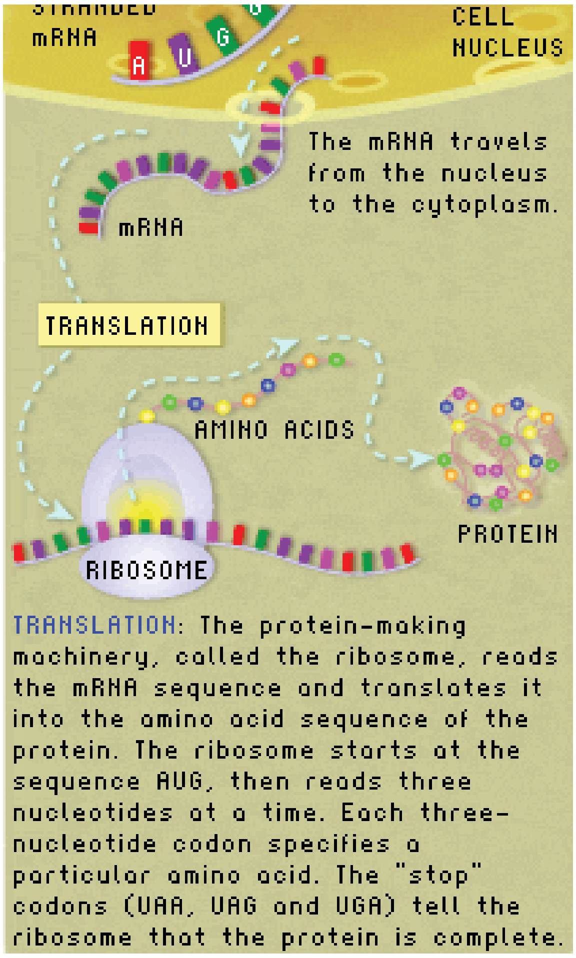
each coded by 3 bases → amino acid

AUG→ Methionine; GCU → Alanine; GUU→ Valine

Proteins are 3-D strings of linear amino acids

Do everything: structure, enzymes…





http://learn.genetics.utah.edu/units/basics/transcribe/

We are all related

Cauliflower, Whales, Chimps, Humans...

Genes: Whale and Humans have similar DNA sequence for Maleness.

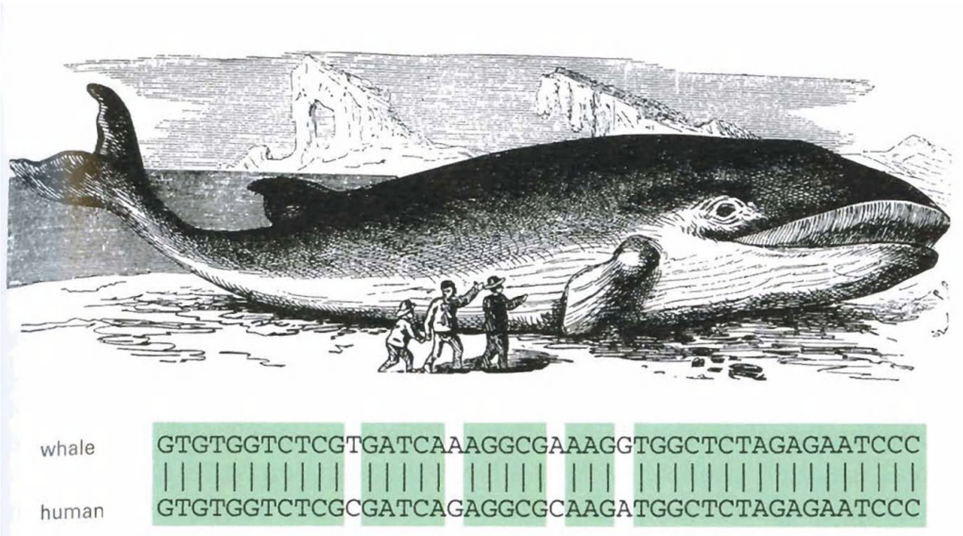


Figure 6-27 The sex-determination genes from humans and whales are unmistakably similar. Although their body plans are strikingly different, humans and whales are built from the same proteins. Despite the length of time since humans and whales diverged, the nucleotide sequences of many of their genes are still closely similar. The sequences of a part of the gene encoding the protein that determines maleness in humans and in whales are shown one above the other, and the positions where the two are identical are *shaded.*

ECB, p. 215

Molecular Evolution can be determined by DNA Sequences… or protein sequences... or protein structures.

[Nice chapter in Berg, Tymoczko, Stryer, 5th ed.]

Yes, we are related to a cauliflower!

You and parent same in DNA by >>99.9%
You and me (unrelated humans) same: 99.4%

You and chimp: 99% same.

Look at DNA of parent/relative to determine how closely related, can do same between species!

Protein structures most closely related to function… best. Sometimes can see similarities in structure where a.a. or DNA sequence so different hard to tell.

DNA sequence info most available.

Example: Myoglobin
Oxygen-carrying protein in muscle.

Amino acid sequence

GLSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETLEKFDKFKHLKSEDEMKASEDLKKHGATVLTALGGIL-
GLSDGEWQLVLNVWGKVEADIPGHGQEVLIRLFKGHPETLEKFDKFKHLKSEDEMKASEDLKKHGATVLTALGGIL-

KKKGHHEAEIKPLAQSHATKHKIPVKYLEFISECIIQVLHSKHPGDFGADAQGAMNKALELFRKDMASNYKELGFQG
KKKGHHEAEIKPLAQSHATKHKIPVKYLEFISECIIQVLQSKHPGDFGADAQGAMNKALELFRKDMASNYKELGFQG

Humans & Chimps myoglobin differ by 1 a.a. out of 153.

What's the probability that two peptide sequences are identical based on random chance?

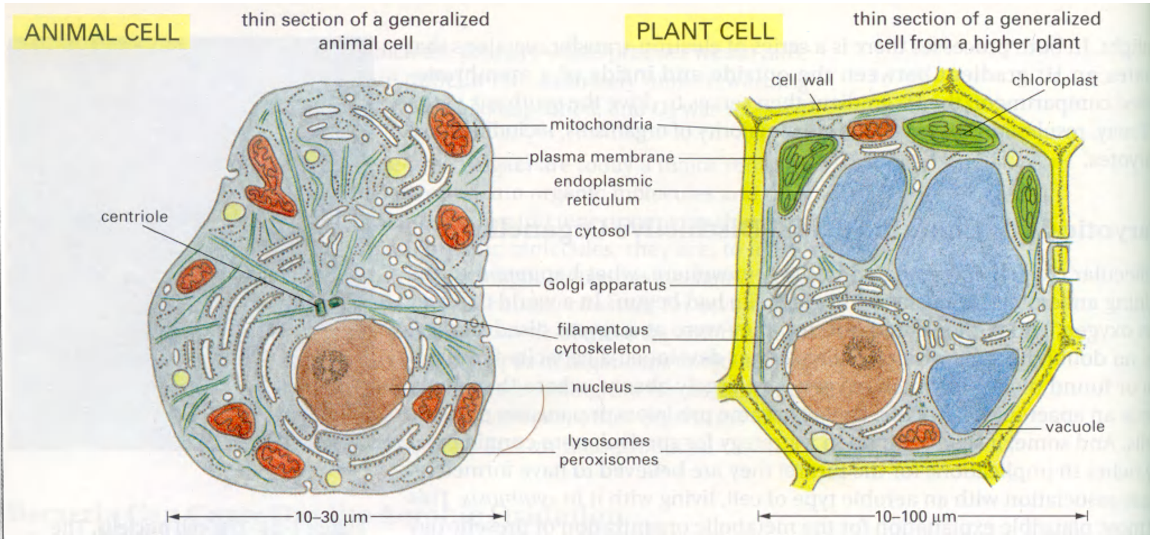
$$(1/20)^{153} \sim 0$$

Just as you and parent look alike cause you came from parent, you and monkey…you and cauliflower have a common "parent".

Cell Size

Bacteria - 1 µm

Eukaryotic cell – 10-100µm



←1 µm→

←10-30 µm→

←10-100 µm→

(Nucleus 3-10 µm)

How much DNA inside of every single cell?

1 meter

So a meter of DNA must pack 3-10 µm!

What does this tell about bendability of DNA?

We'll see how this is measured using magnetic tweezers

Interesting factoids:

1. ≈ 10^{14} cells in body…

…more stars than in Milky Way Galaxy.

2. ≈ 200 different types of cells in body.

Need to know Chemical Bonding

4 types: what are they?

1. Covalent – 100kT. Sharing of electrons. C-H

   Is light enough to break covalent bond?

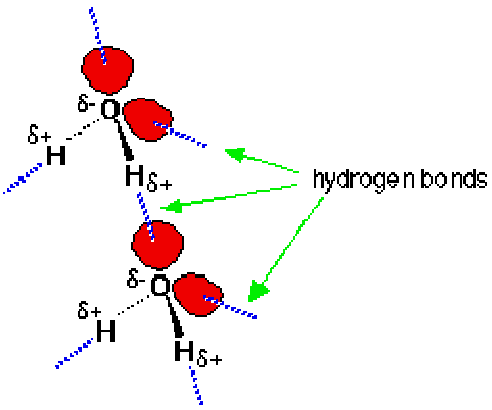
   1um=1eV; kT=1/20eV. 1um= 20kT: close (yup)

2. Ionic – varies tremendously, 100kT to few kT.

   + and – attract, but depends on solvent.

   $Na^+ Cl^-$ = few kT (break up easily)

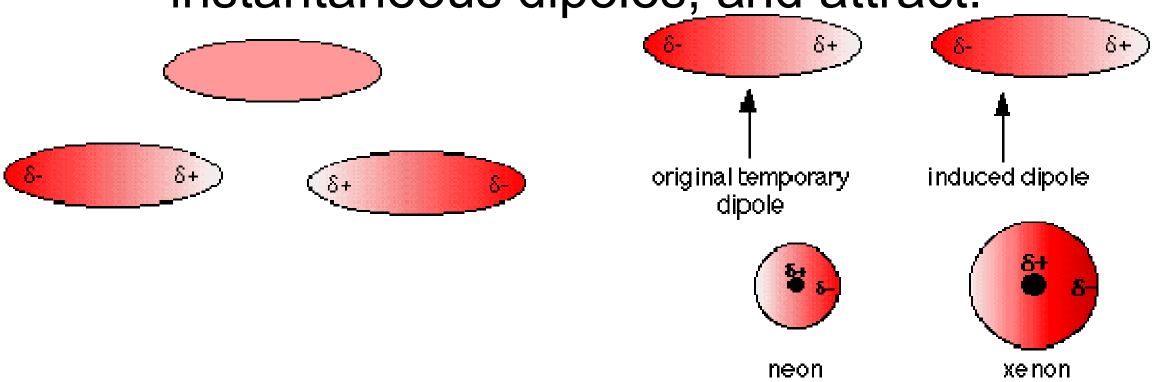
3. Hydrogen – few kT, up to 5kT



1. Hydrogen attached to a very electro-negative elements, (O, N) causing the hydrogen to acquire a significant amount of positive charge.
2. Lone pair– electrons in relatively small space, very negative.

Result is H is (+) and O is (-). Will bind to other molecules

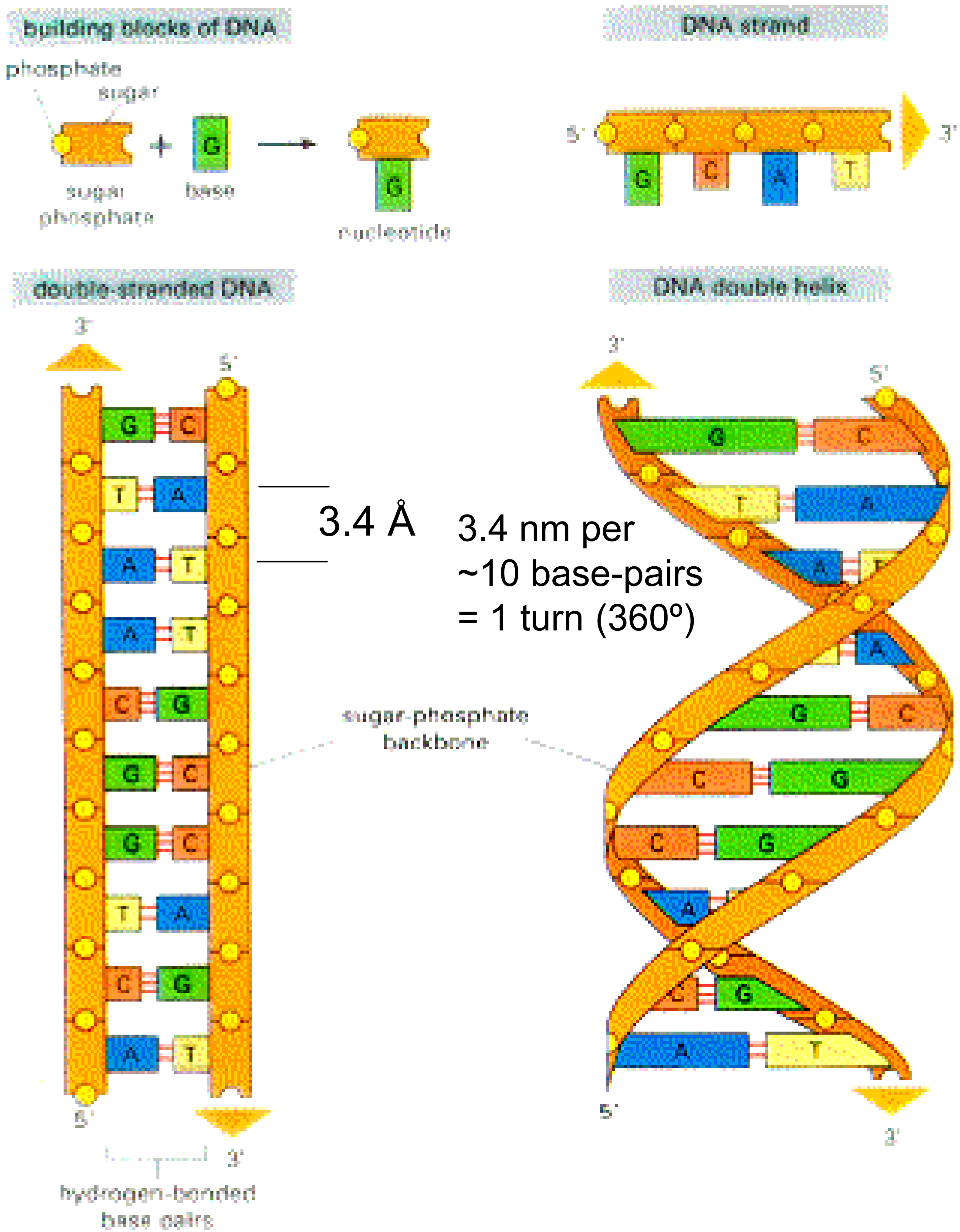
4. Van der Waals–kT (weakest, but many of them together--significant). Two neutral atoms have instantaneous dipoles, and attract.



Neon: -246°C; Xenon: -108°C

www.chemguide.co.uk/atoms/bonding/hbond.html#top

DNA is a double helix of anti-parallel strands



Must come apart for bases to be read.

Minimal knowledge about Nucleotides

- 4 nucleotides: A,T,G,C
- A=T ≈ 2kT two hydrogen bonds
  G≡C ≈ 4kT three hydrogen bonds
- Many weak bonds…very strong overall structure. DNA is stable.

Covalent bonds holding bases together —very strong

DNA is twisted & antiparallel for base pairing

Thymine

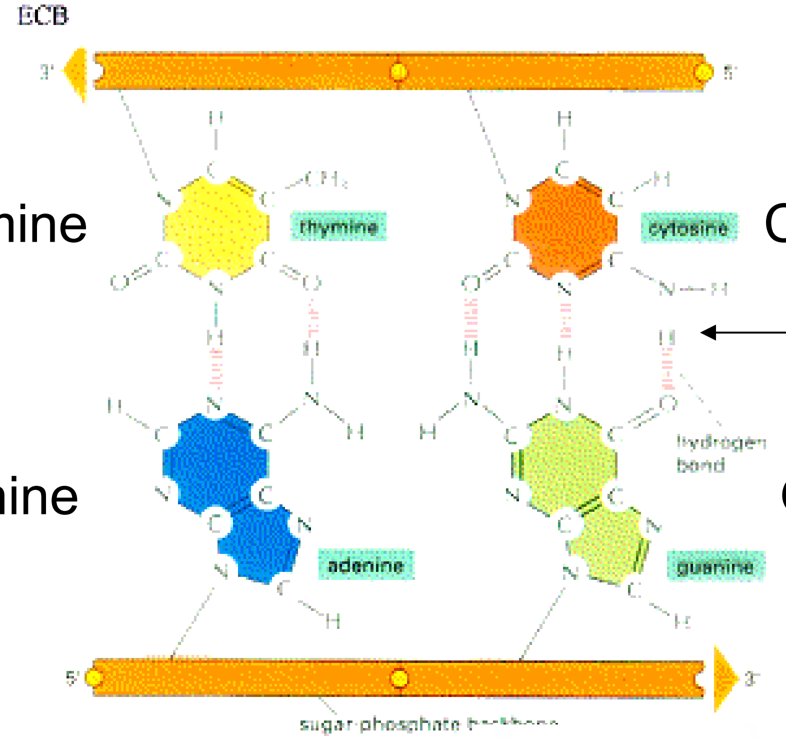
Cytosine

Hydrogen Bonds

(2kT)

Adenine

Guanine

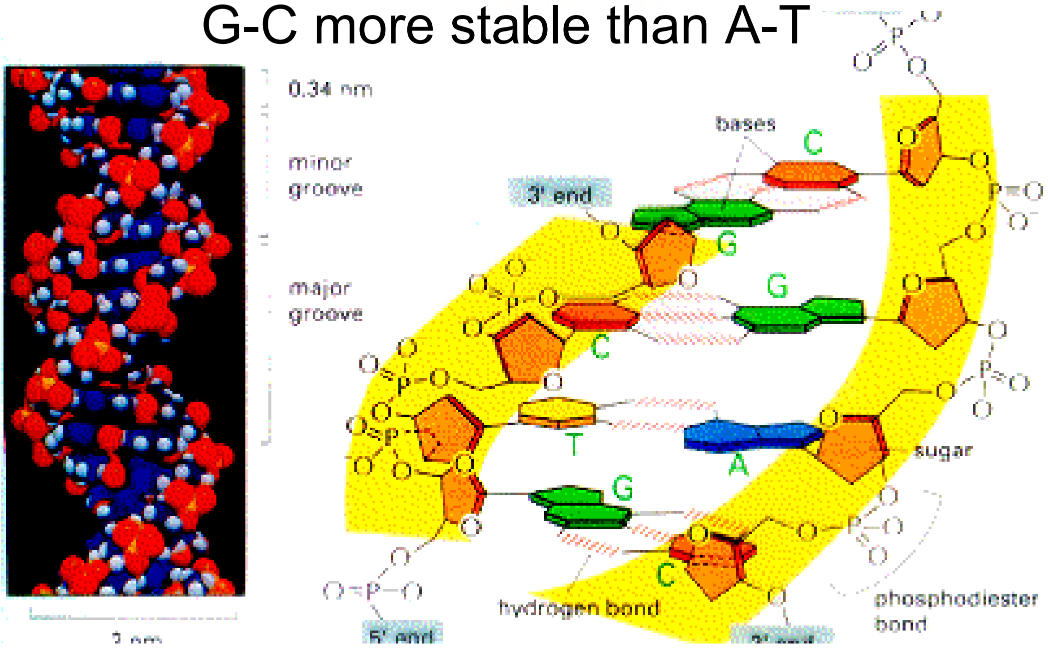


A = T (2 H bonds) G ≡ C (3 H bonds)

G-C more stable than A-T

Minor grove

Major grove



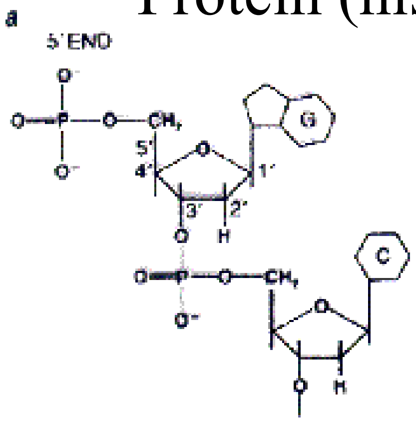
$\pi - \pi$ stacking keeps it together (Grease);

Phosphate negative charge makes it water soluble

(Sort of like soap)

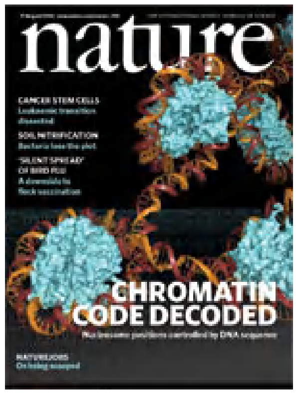
Size Scales of DNA (+ Protein)

Chromatin = Complex of DNA + Protein (histones + non-histones)



Nucleotides

[4 Diff. types, A,T,C,G]



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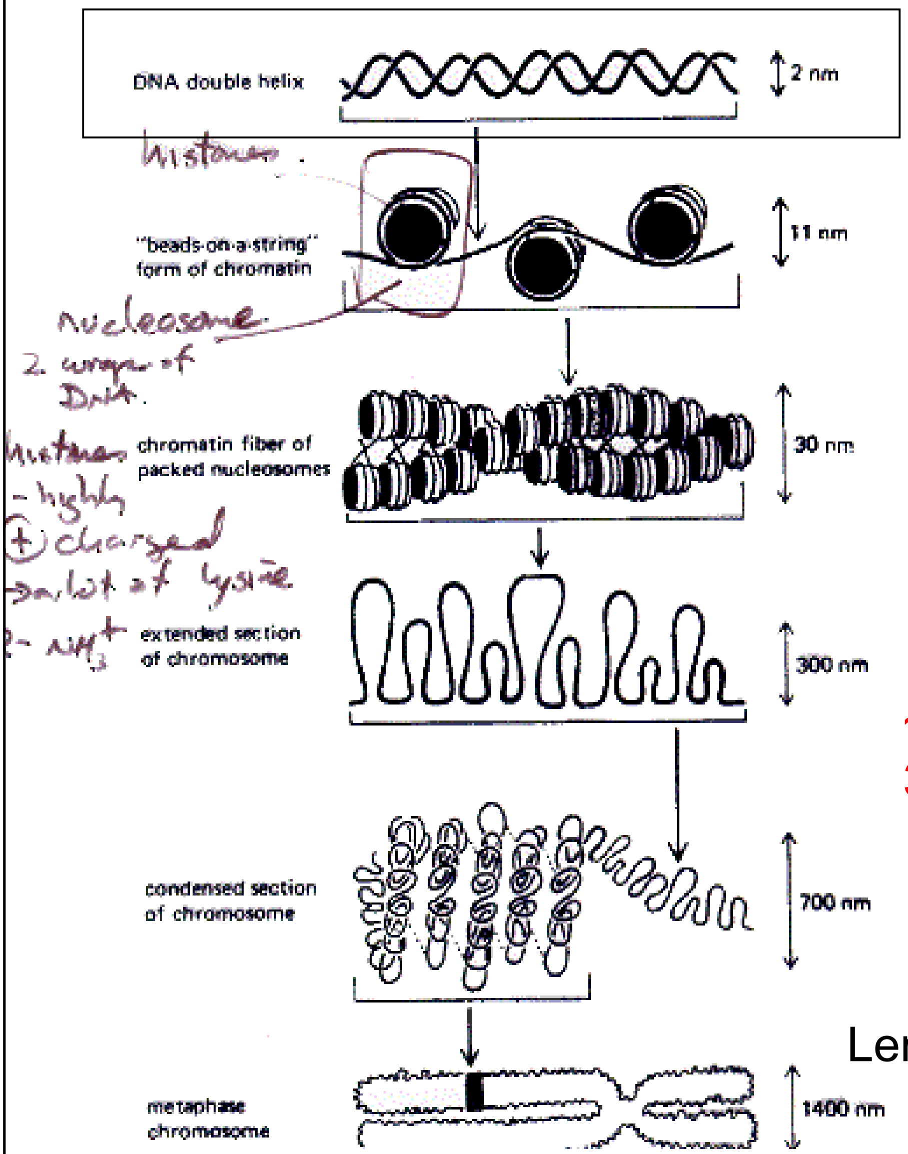


How many base pairs in human cell?

3×10^9 = 3 billion

How much length of DNA in a cell?

~ 1 meter

Flexibility of DNA?

~ 1 meter packed in 3-10 μm (size of nucleus)

chromosomes?

46 (ca. 50)

Length/chromosomes?

~ 1/50 meter = 2 cm!

Boltzman factor + Partition function

(review of basic Stat. Mech. – see Kittel, Thermal Physics

E_1 Temp, T

E_0

If T = 0 ºK, what proportion of particles will be in E_1, E_o?

Answer: E_o= 1 E_1 = 0

If T > 0 ºK, what proportion of particles will be in E_1, E_o?

$$P(E_i) = (\text{const.})\, e^{-E_i/kT}$$

$$\frac{P(E_1)}{P(E_0)} = e^{-(E_1 - E_0)kT}$$

Boltzman factor

$$\sum P(E_i) = 1$$

$$\text{const.} = \frac{1}{\sum_{j=0}^{N} e^{-E_j/kT}} = 1/Z$$

J= represents j^{th} state

$$Z = \text{partition function} = \sum_{j=0}^{N} e^{-E_j/kT}$$

$$P(E_i) = \frac{1}{z} e^{-E_i|kT}$$

Partition Function for 2-state system

$- |1\rangle \; E_1$

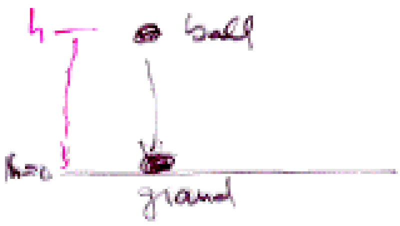
$- |o\rangle \; E_o$

$$P(E_1) = \frac{e^{-E_1/kT}}{e^{-E_o/kT} + e^{-E_1/kT}}$$

Simple case: Ball in gravitational field.

Thermal fluctuations, finite probability of being at height, h.

E = ??



$$E = mgh$$

$$E_o \; h = 0$$

$$E_1 \; h = (mg)(h \text{ meter})$$

$$\frac{P(h)}{P(0)} = e^{-mgh/kT}$$

As ball gets smaller, probability gets smaller / larger ?

"Ball" the size of O_2? Why can you breathe standing up?

What is 1/e height for O_2?

For O_2, 1/e height is ~10 km ~height of Mt. Everest.
(10 kM is "death zone")
Probability of dying if you go over 20,000 ft is 10% for every trip!!

Two states

A – B bonded: E ~ -5 kT (a few H-bonds)

A , B not bonded: E = 0

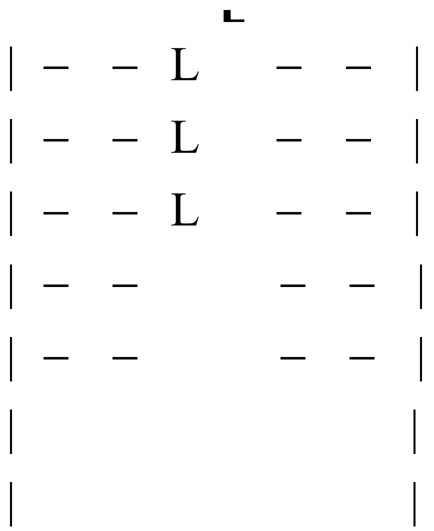
$$A + B \rightleftarrows A - B$$

149 molecules
148 will be A - B
1 will be A, B

DNA double helix: Many weak (H-bonds), makes for very stable structure.

If you have many weak bonds (e.g. each bond only few kT) you can get a biomolecule that will not fall apart.

H bonded ~ 2 kT



Zipped vs. unzipped

What if just one bond? Bond/unbound? $e^{-2} \sim 1/8$

What if 10 weak bonds? e^{-20}

Many base pairs, essentially completely stable.
Still have end-fraying, but probability that whole thing comes apart– essentially zero.

Class evaluation

1. What was the most interesting thing you learned in class today?

2. What are you confused about?

3. Related to today's subject, what would you like to know more about?

4. Any helpful comments.

Answer, and turn in at the end of class.