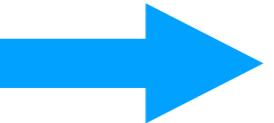


BBL342: Physical and Chemical Properties of Biomolecules

Evaluation policy

- 
1. Minor I - 20 marks
 2. Minor II - 20 marks
 3. Major – 40 marks
 4. Quiz 1-2 – 10 marks
 5. Tutorials - 10 marks (collected on weekly basis)

Grade	% marks
A	80
D	30
E	20

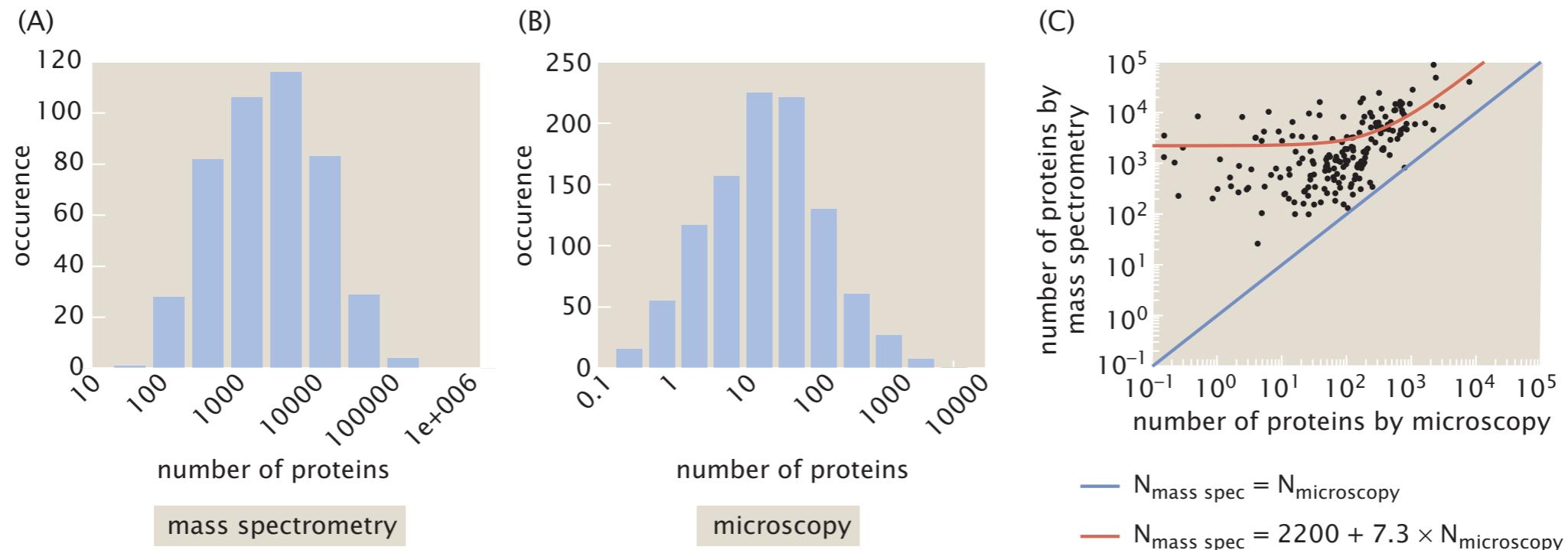
Audit pass policy: 75% attendance with D grade

Attendance policy:

I will keep regular attendance but won't enforce a grade loss,
if < 75% it is up to the academic section to decide.

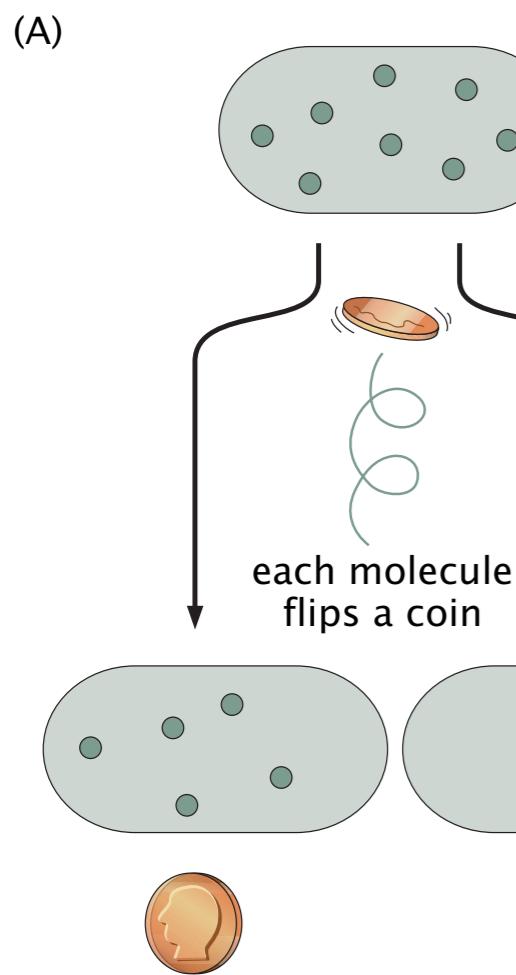
Why should we care biomolecular census of the cell?

- Quantitative understanding of the molecules involved and the physical space where they function — needed for building a realistic model
- Quantification of the effect of ‘molecular crowding’
- To design ‘realistic’ *in vitro* experiments
- To estimate the rates of synthesis of biomolecules during the cell cycle
- Quantification of cell-to-cell variability



- Understanding the ‘baseline’ for comparative biological experiments

Cell to cell variability can emerge simply from choices



Probability of having n_1 molecules out of N in daughter cell 1 is

$$p(n_1, N) = \frac{N!}{n_1!(N - n_1)!} p^{n_1} q^{N-n_1}$$

Binomial distribution

Binomial coefficients

Where p = probability of going to daughter 1

$q = 1 - p$ = probability of going to daughter 2

$p = q = 0.5$ if there is no active segregation mechanism

Let's do a case study for $N = 3$, $n_1 = 2$

What would be the average number of molecules in daughter 1?

First moment of binomial distribution or expectation value

$$\langle n_1 \rangle = Np$$

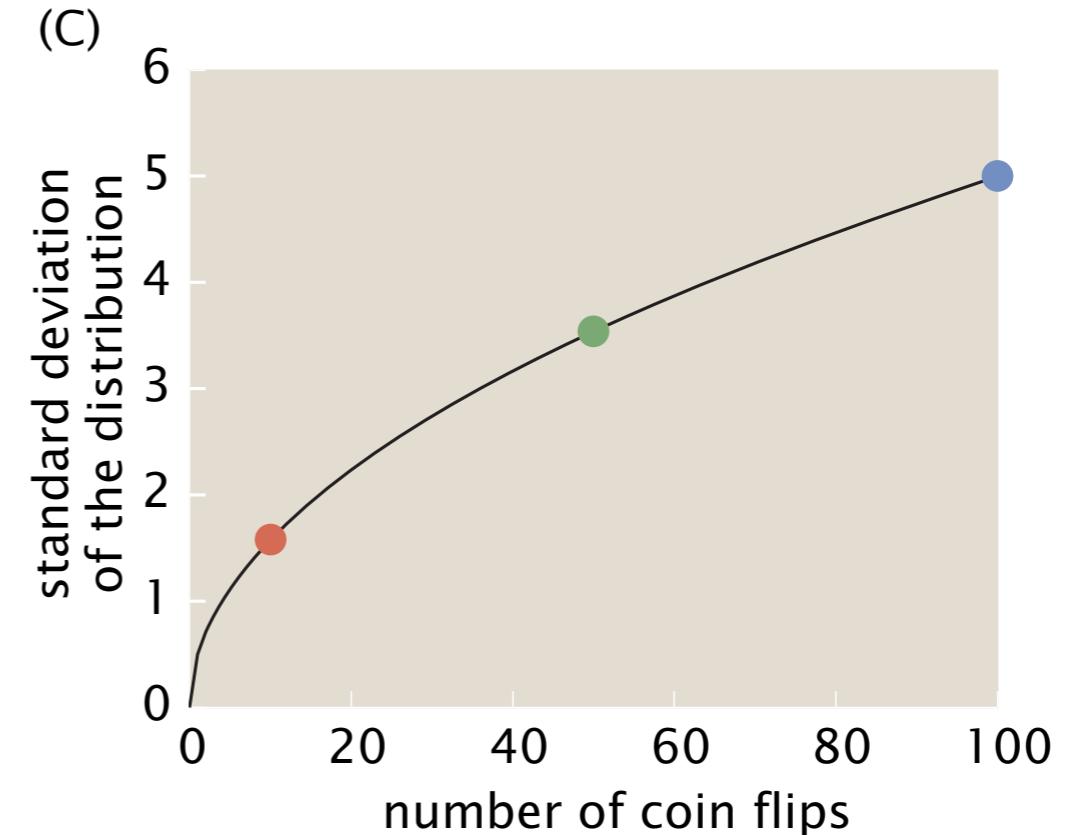
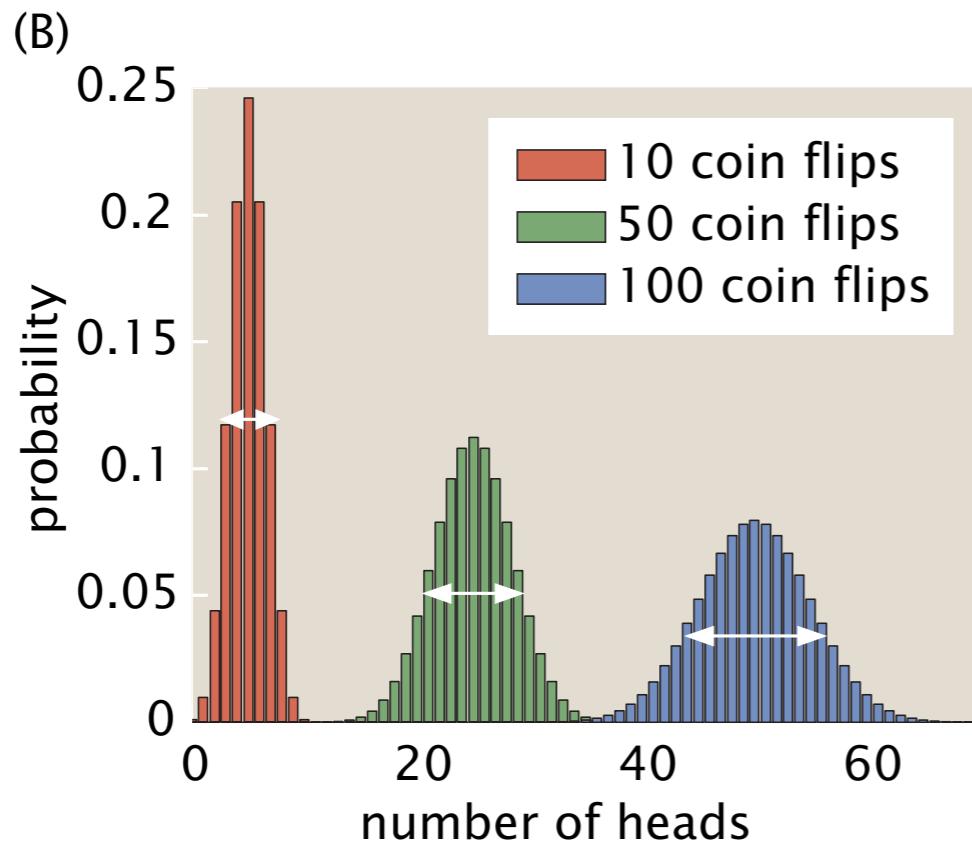
What would be the variance of molecules in daughter 1?

Second moment of binomial distribution
or square of standard deviation

$$\langle n_1^2 \rangle - \langle n_1 \rangle^2 = Npq$$

Width of the distribution of number of molecules

Cell to cell variability can emerge simply from choices...contd



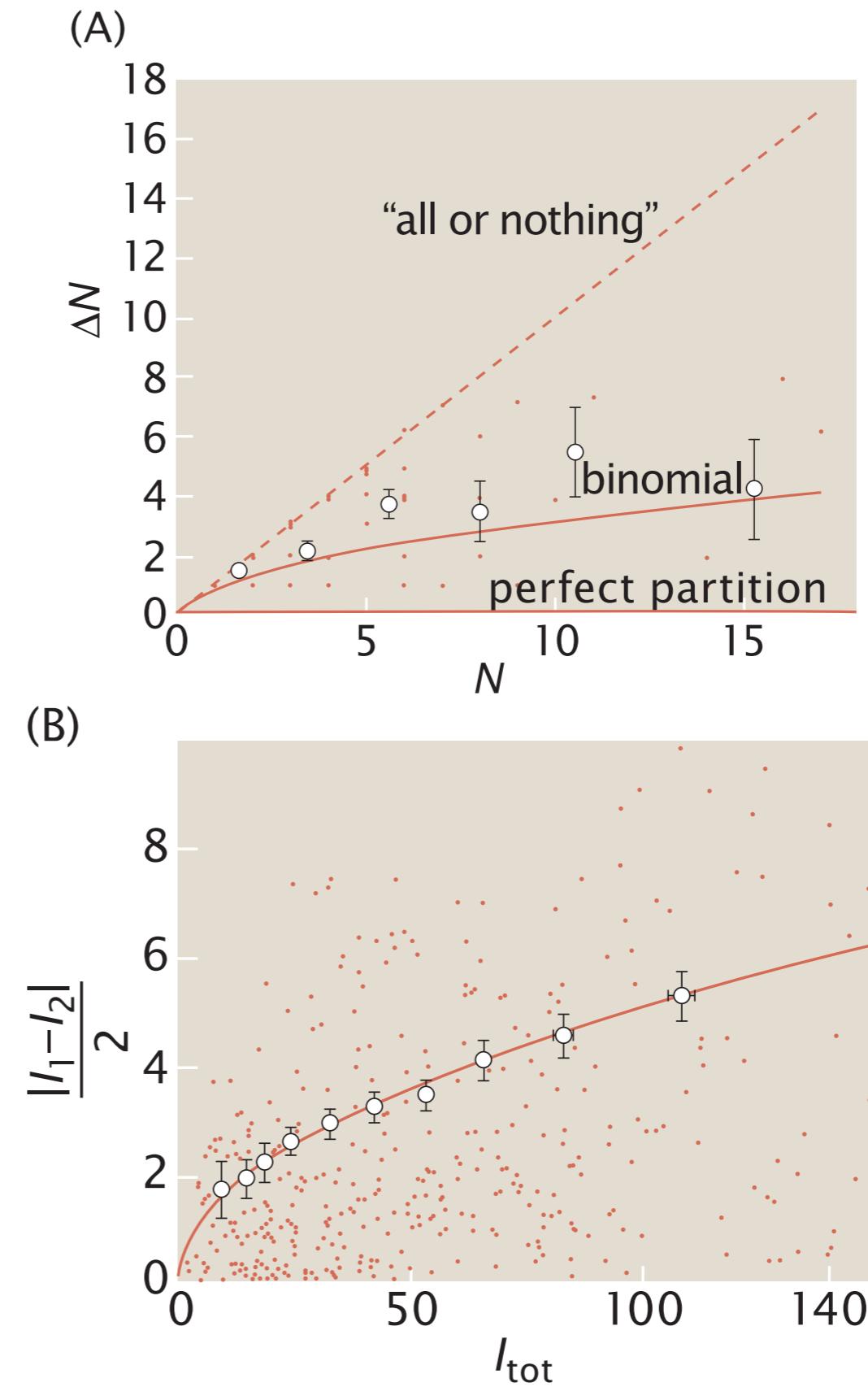
How to estimate the fluctuation that arise during partitioning?

$$\frac{\sqrt{\langle n_1^2 \rangle - \langle n_1 \rangle^2}}{\langle n_1 \rangle} = \frac{1}{\sqrt{N}}$$

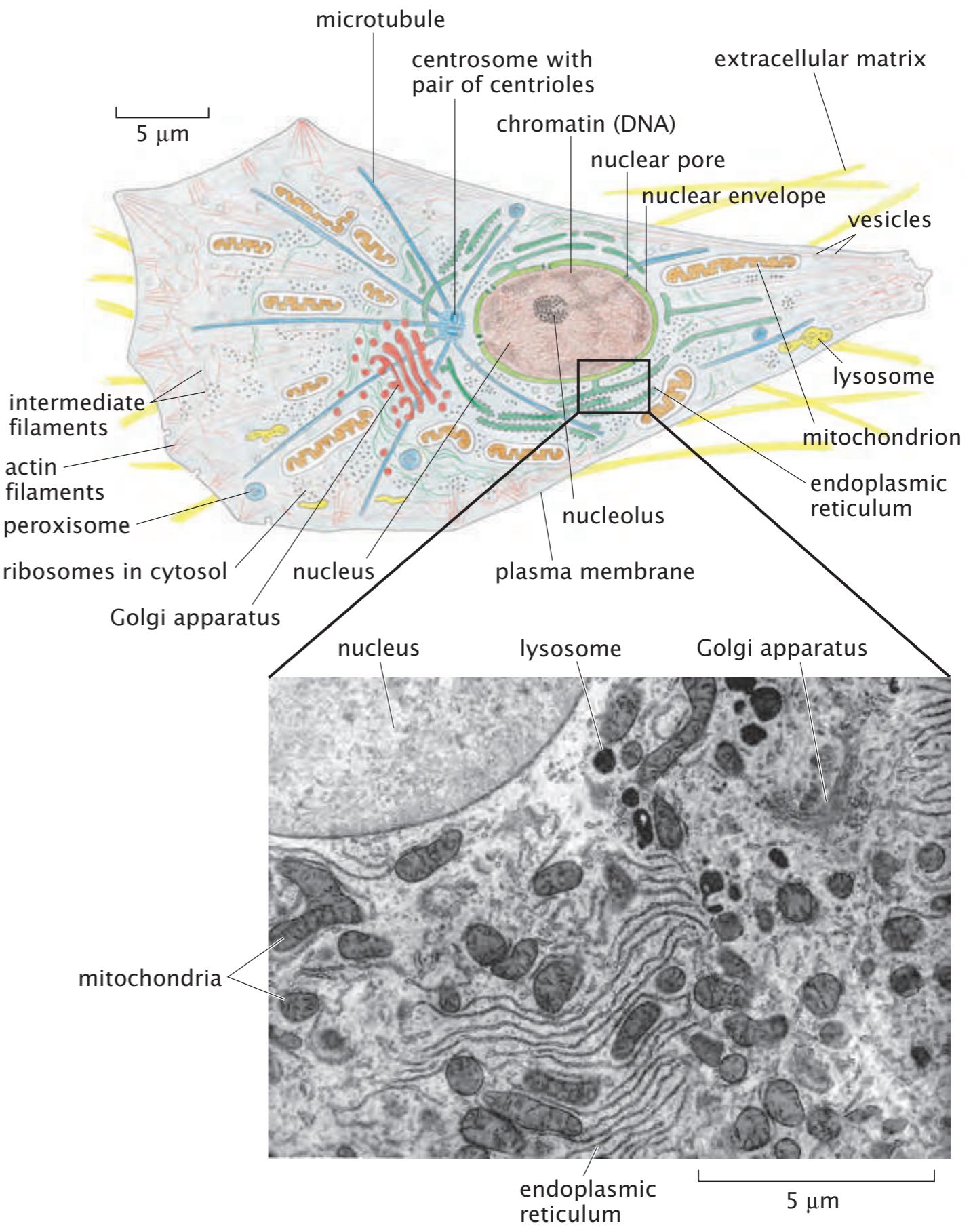
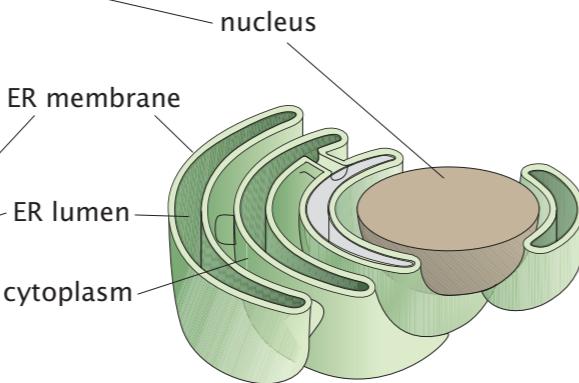
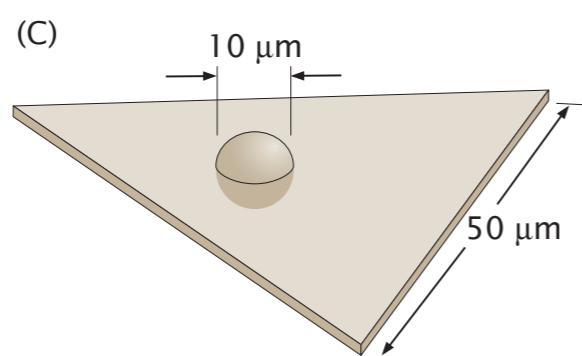
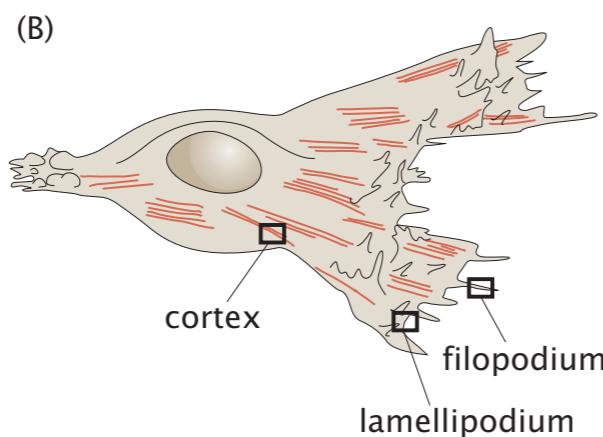
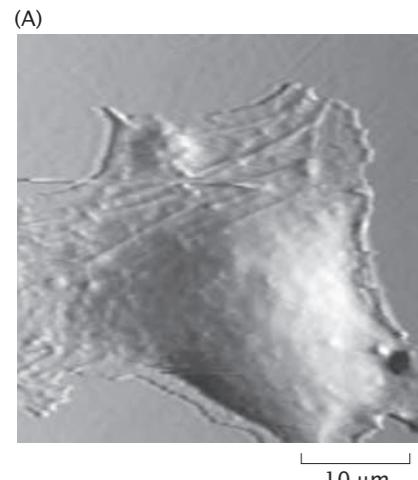
For small N , the fluctuation becomes a significant fraction of N

Applications of the binomial partition model for real data

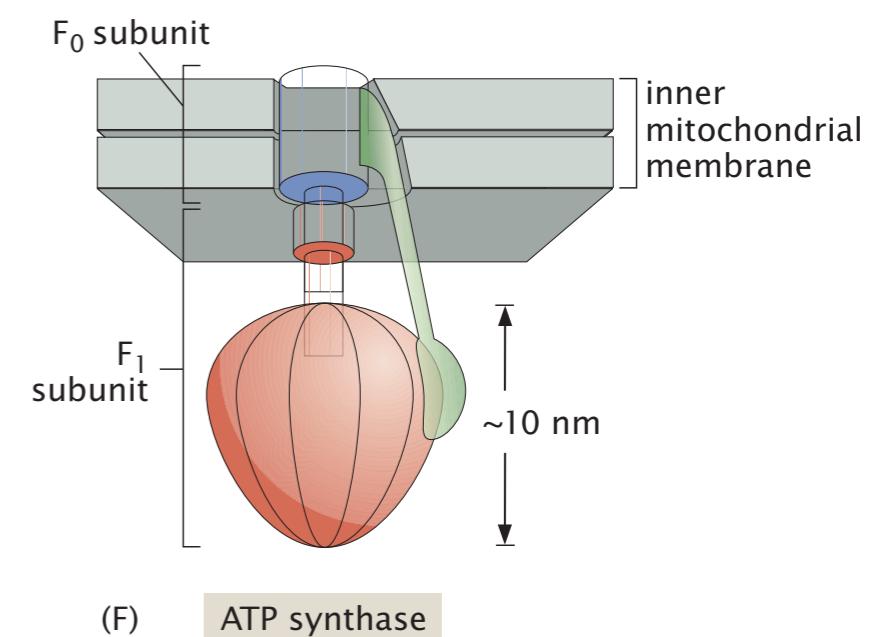
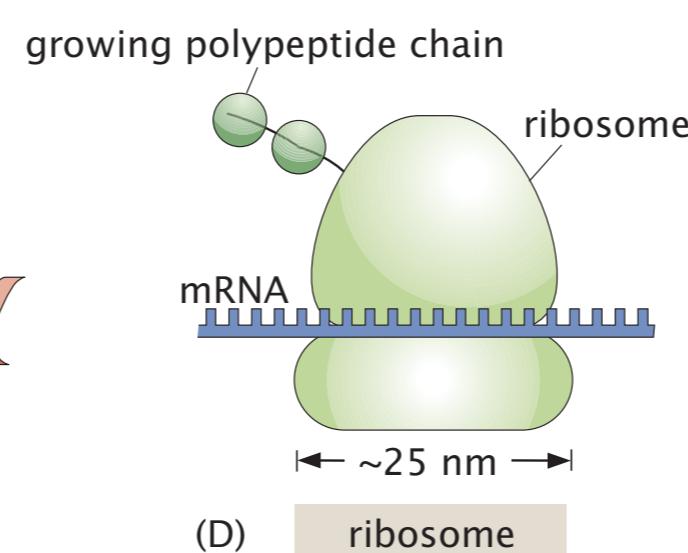
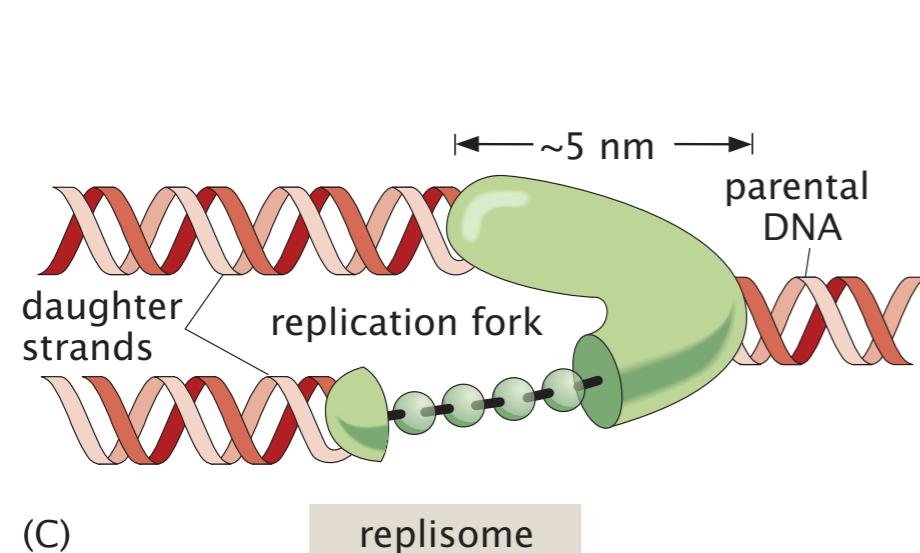
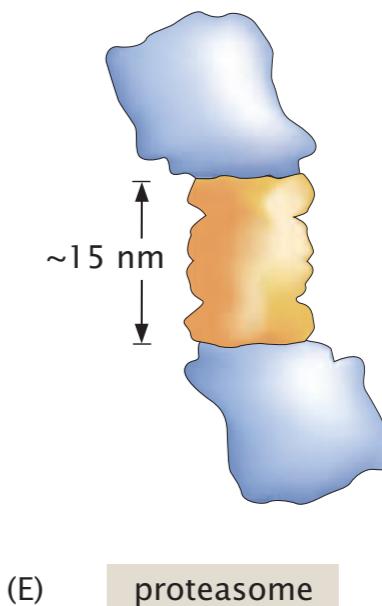
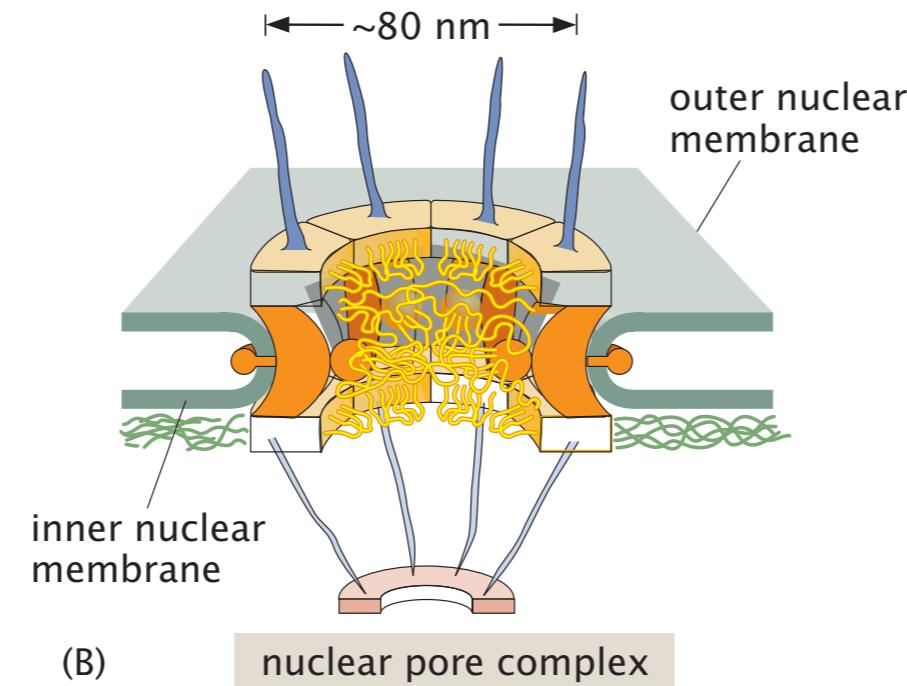
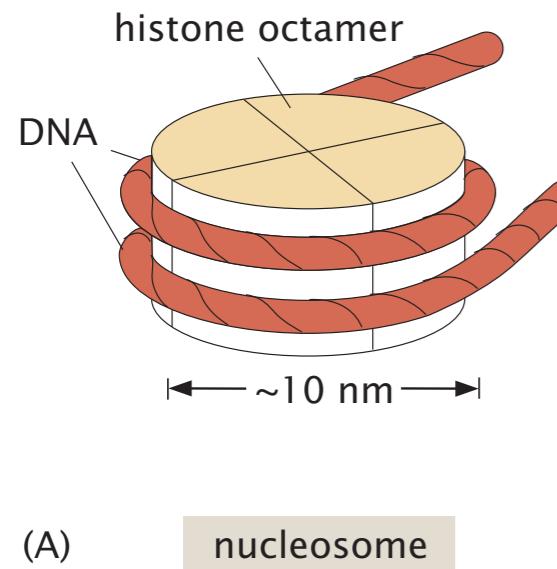
Figure 2.9: Binomial partitioning of mRNA and proteins in *E. coli* during cell division. (A) Difference ΔN in the number of mRNAs between the two daughters given that the mother has N mRNAs. The curves show three possible partitioning mechanisms involving “all or nothing” in which one daughter takes all of the mRNAs, binomial partitioning, and “perfect partitioning” in which each daughter gets exactly half of the proteins from the mother cell. (B) Difference in the fluorescence intensity of the two daughter cells for a fluorescent fusion to a repressor protein as a function of the fluorescence intensity of the mother cell. The line corresponds to binomial partitioning model. (A, adapted from I. Golding et al., *Cell* 123:1025, 2005; B, adapted from N. Rosenfeld et al., *Science* 307:1962, 2005.)



Eukaryotic cells and the structures within them



Biomolecular assemblies inside the cell



The whole is greater than the sum of its parts

Helical motifs are seen repeatedly in biomolecular assemblies

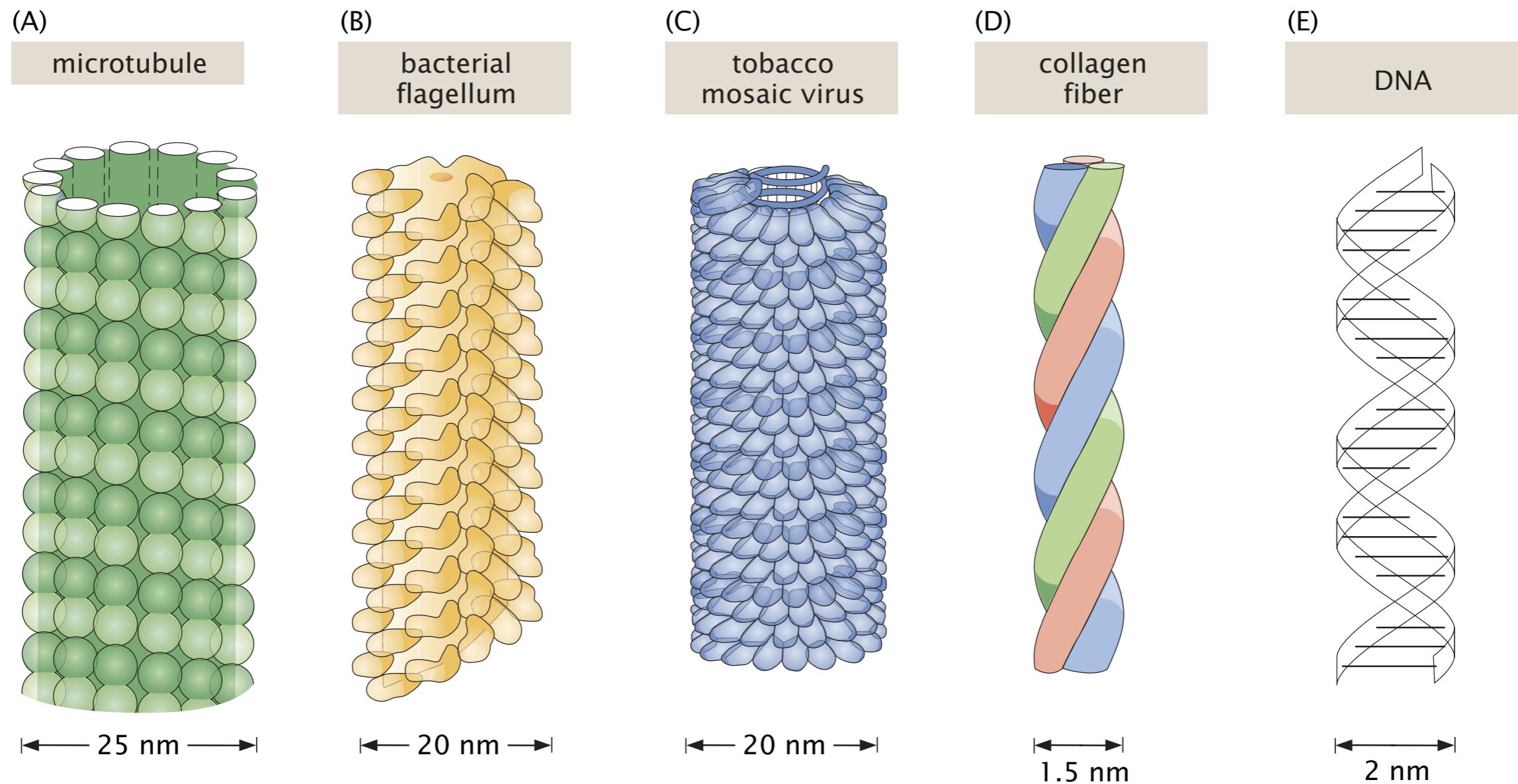
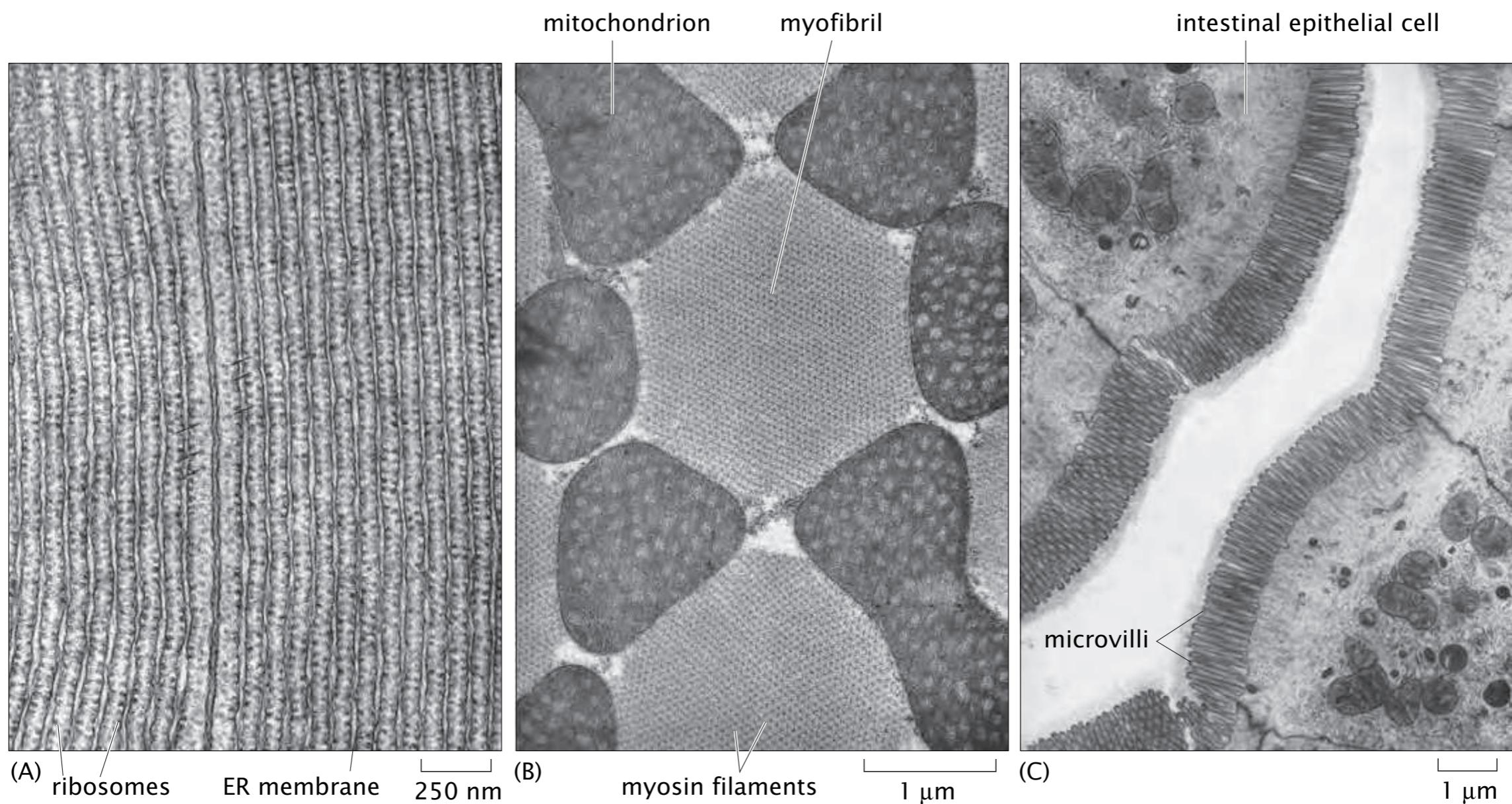
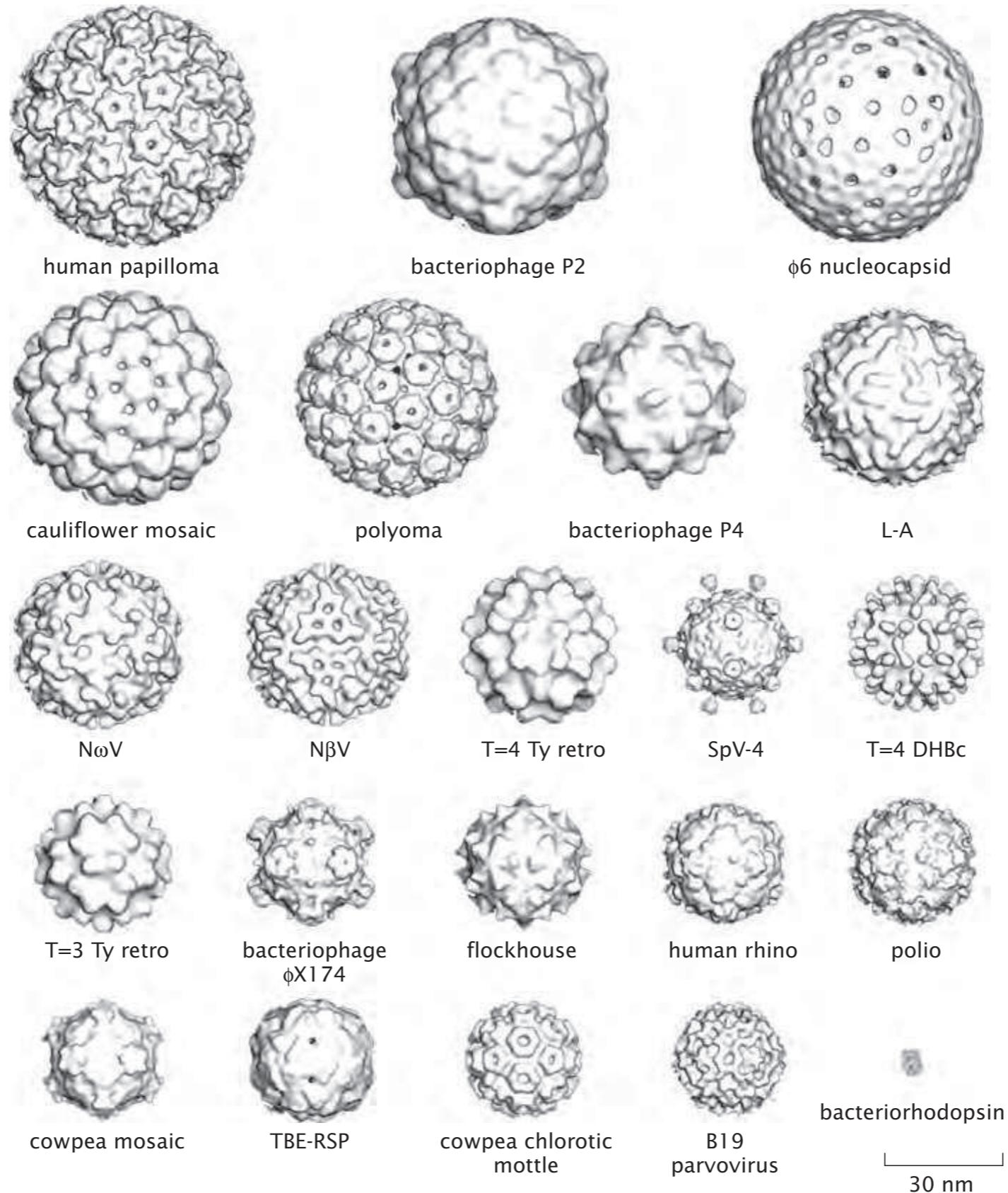


Figure 2.28: Ordered macromolecular assemblies. Collage of examples of macromolecules organized into superstructures. (A) Ribosomes on the endoplasmic reticulum (“rough ER”), (B) myofibrils in the flight muscle, and (C) microvilli at the epithelial surface. (A–C, adapted from D. W. Fawcett, *The Cell, Its Organelles and Inclusions: An Atlas of Fine Structure*. W. B. Saunders, 1966.)

Biomolecular assemblies are organized as superstructures

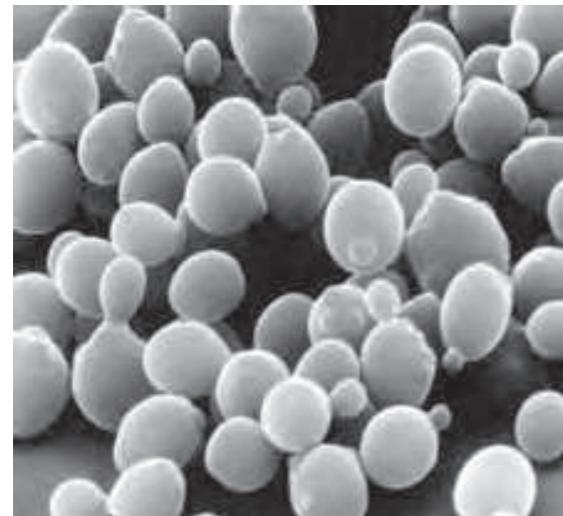


Viruses are biomolecular assemblies!

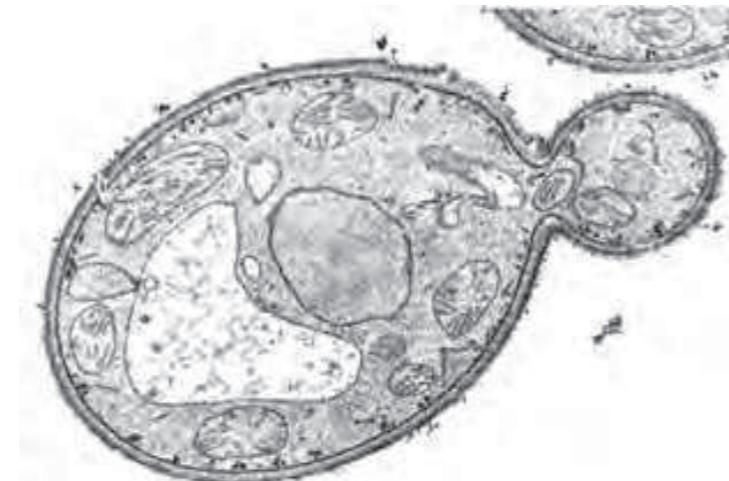


Taking a biomolecular census of an eukaryotic cell

Subject: Budding Yeast



(A)



(B)

Dimensions of yeast cell

yeast cell is a sphere of diameter $\sim 5 \mu\text{m}$

volume of yeast cell $\approx 60 \times V_{E.\text{coli}}$

Surface area of yeast cell $\approx 80 \mu\text{m}^2$

Decent result!

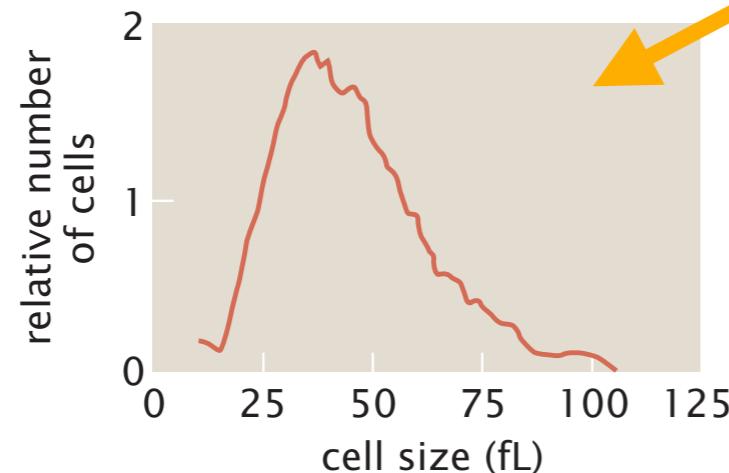


Figure 2.19: Yeast cell size distribution. Distribution of cell volumes measured for wild-type yeast cells. (Adapted from P. Jorgensen et al., *Science* 297:395, 2002.)

How packed is the yeast nucleus? Quantifying crowding

Useful info

- Yeast genome size is $1.2 \times 10^7 \text{ bp}$ (12 Mb)
- There are about 150 bp wrapped in each nucleosome and a 50 bp spacer between two

$$\text{Number of nucleosomes} = \frac{1.2 \times 10^7}{200} = 60000$$

This genome is packed inside a nucleus of approx diameter $2 \mu\text{m}$ and volume $\approx 4 \mu\text{m}^3$

If each bp has a volume of $\approx 1 \text{ nm}^3$, volume fraction of the genome is

$$= \frac{1.2 \times 10^7 \times 10^{-27}}{4 \times 10^{-18}} = 3 \times 10^{-3}$$

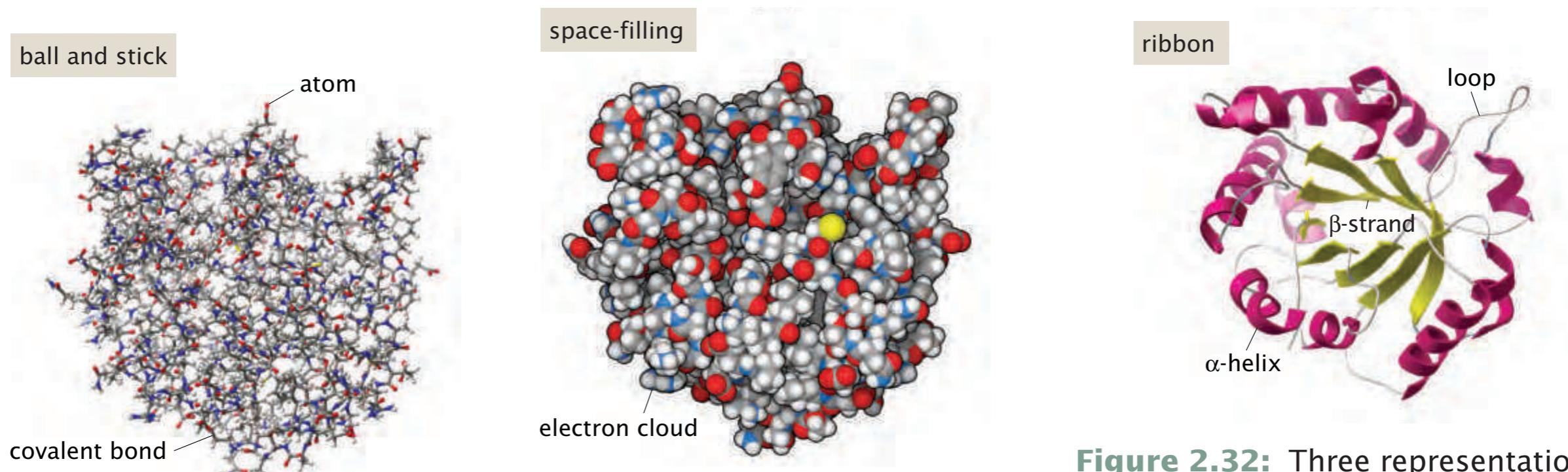
Now genome is packed by histones. Each histone is a spherocylinder of height $\sim 6 \text{ nm}$ and radius $\sim 3.5 \text{ nm}$, so volume $\approx 230 \text{ nm}^3$

$$\text{So, volume fraction of the histones is } = \frac{60000 \times 230 \times 10^{-27}}{4 \times 10^{-18}} \approx 3.5 \times 10^{-3}$$

These estimates highlight the robustness of genome organization in the nucleus

Molecular architecture of the cell

Macromolecular Structure Is Characterized Fundamentally by Atomic Coordinates

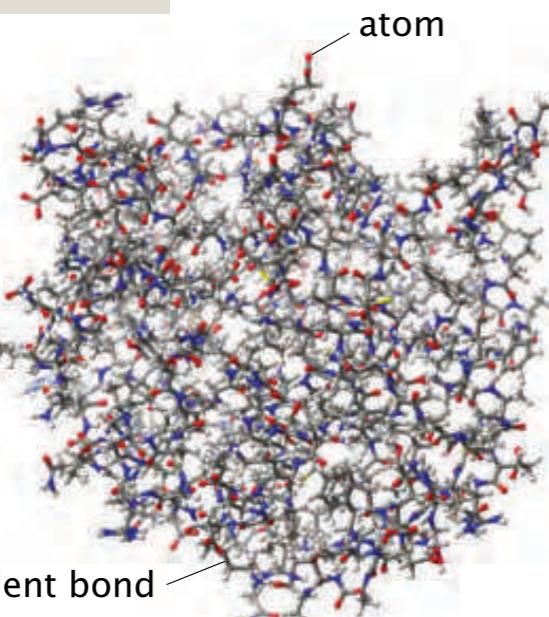


covalent bond

space-filling

ribbon

electron cloud



atomic coordinates measured as $\mathbf{r}_i = x_i\mathbf{i} + y_i\mathbf{j} + z_i\mathbf{k}$,

In reality, atomic coordinates time dept $\mathbf{r}_i(t) = x_i(t)\mathbf{i} + y_i(t)\mathbf{j} + z_i(t)\mathbf{k}$,

Experiments measure the time average $\langle \mathbf{r}_i(t) \rangle_{\text{time}}$

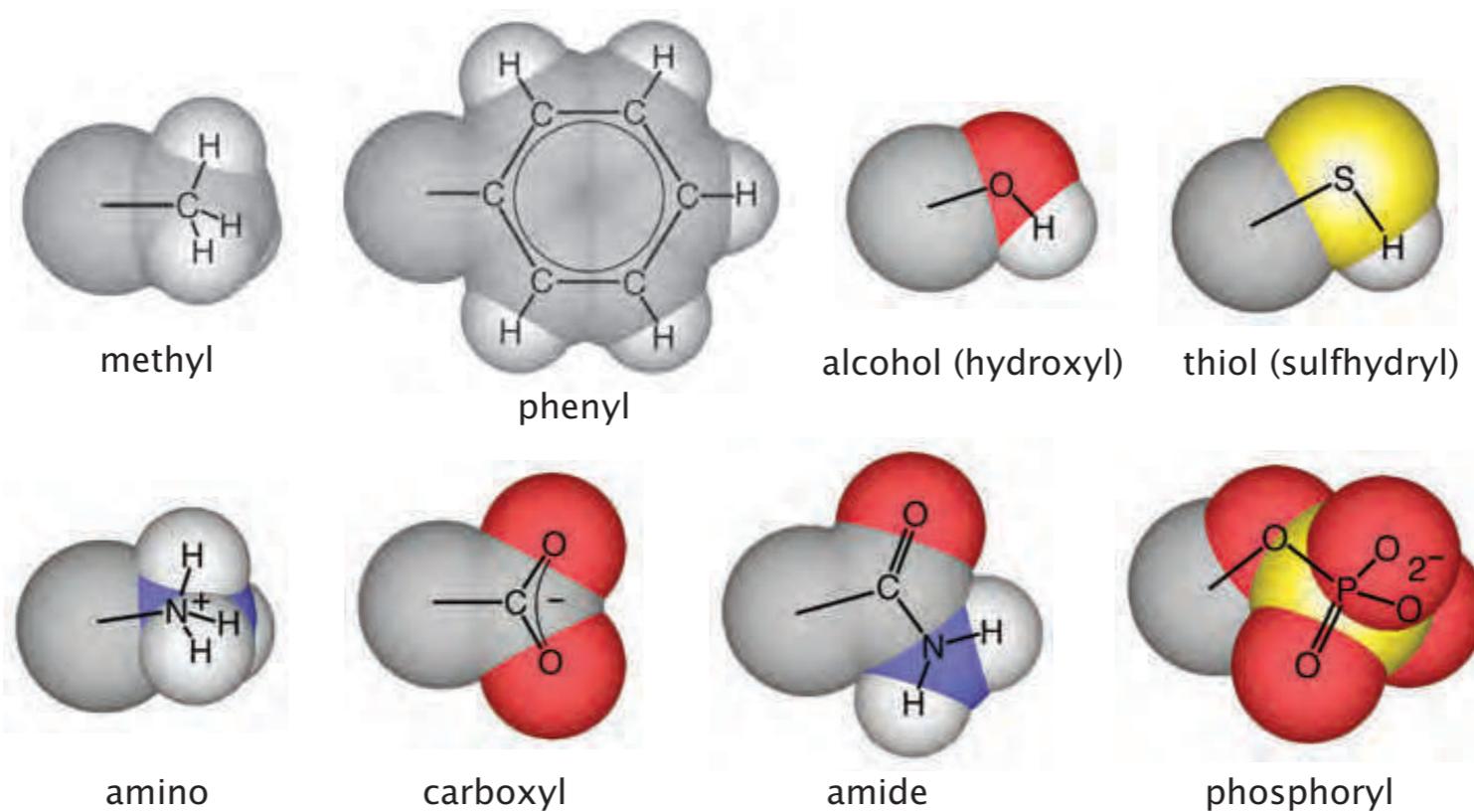
Figure 2.32: Three representations of triose phosphate isomerase. This enzyme is one of the enzymes in the glycolysis pathway (PDB 3tim). (Courtesy of D. Goodsell.)

Example protein structure file from PDB

ATOM	1	N	TRP	A	10	132.950	1.306	163.085	1.00	39.28		N
ATOM	2	CA	TRP	A	10	134.398	1.011	163.291	1.00	39.15		C
ATOM	3	C	TRP	A	10	134.619	0.021	164.431	1.00	38.81		C

Molecular architecture of the cell

Chemical Groups characterize the Structure of Macromolecules

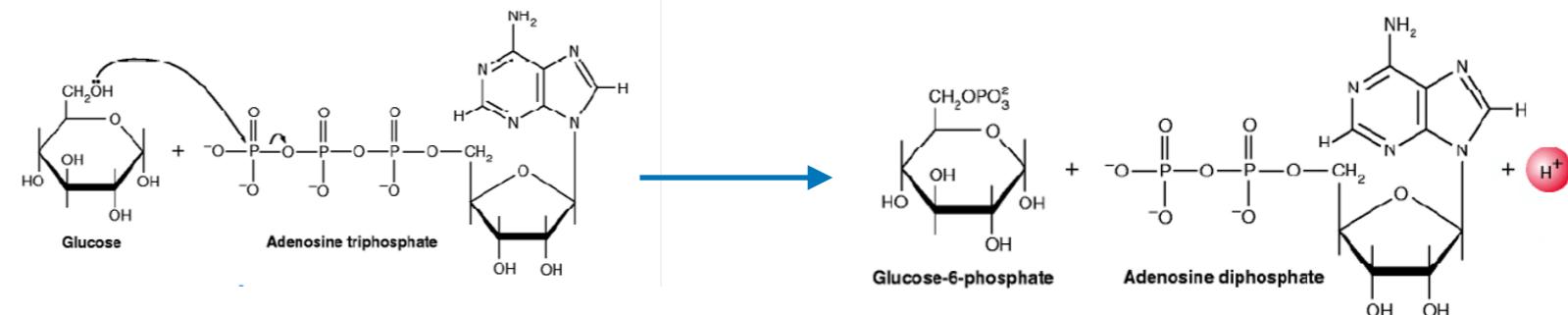


Combination of these groups dictate the *native* structure of the biomolecules (globular, sheet-like, pores and so on)

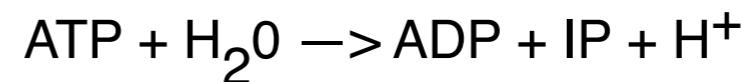
Cell is a vessel run by chemical reactions

metabolic functions of the cell are driven by diverse set of chemical reactions

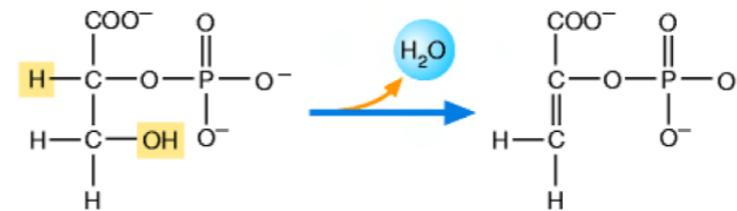
- Nucleophilic substitution



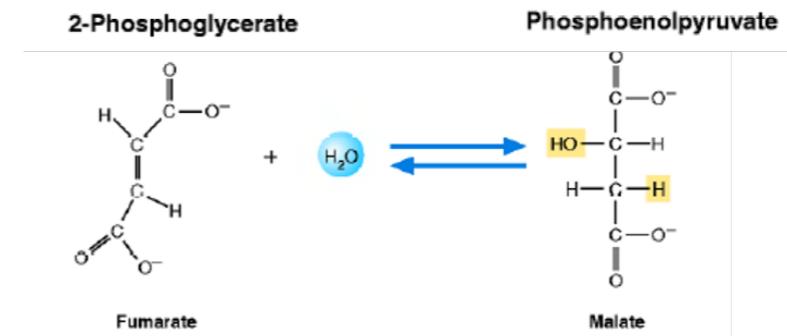
- Hydrolysis



- Elimination reactions



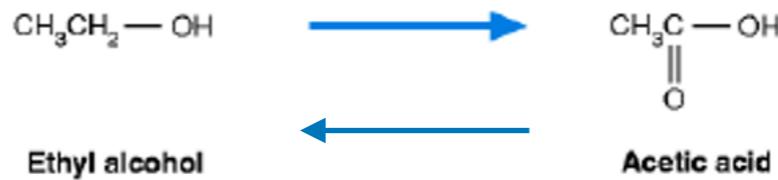
- Addition reactions



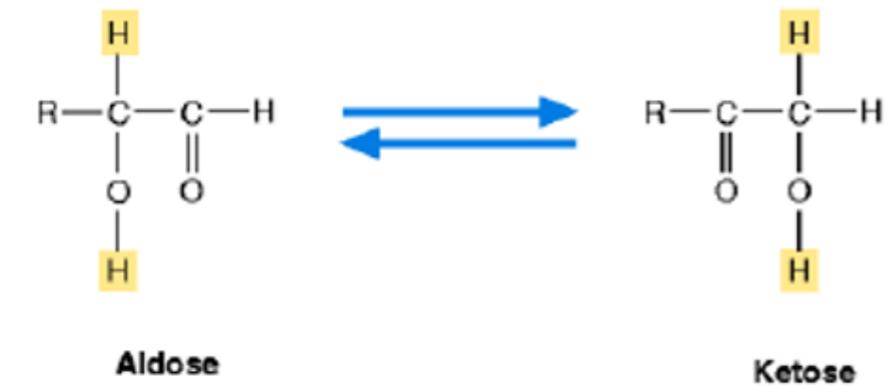
- Isomerization reactions



- Oxidation-reduction reactions



Cellular functions require energy flow



- Majority of chemical reactions are reversible
 - The direction of the reaction is determined by the availability of energy
 - Energy flow happens in the direction that increases the entropy of the universe
 - Cell requires a constant flow of energy for a certain reaction to occur
 - Life is determined by energy - entropy competition given by free energy, $G = U - TS + pV$
 - At cell death, the energy flow ceases and entropy takes over and everything disintegrates, free energy reaches minimum value and that is equilibrium

Life is maintained away from equilibrium

Next class:

Molecular forces in Biology