Biophysics

Lecture at National Center for Theoretical Sciences
2007/4/27

What do people study in this discipline?

Virtual Journal of Biological Physics Research   http://www.vjbio.org/bio/

- quantum mechanical dynamics
- physics of water and hydrogen-bonded solvents
- membrane biophysics
- fundamental polymer statics/dynamics
- protein conformational dynamics/folding
- DNA conformational dynamics
- single molecule dynamics
- intermolecular interactions
- physical studies of cell mechanics
- information transfer in biological systems
- multicellular phenomena
- biological networks
- quantitative genomics
- statistical and nonlinear physics
- instrumentation development
- miscellaneous

Outline

1. Physics in a cell
2. Self-assembling (protein folding)
3. Mechanics (membrane & filaments)
4. Energy transduction (biological motors)
5. Electrostatics (neuron cells & networks)
6. Thermodynamics (non-equilibrium biosystems)

1. Physics in a Cell
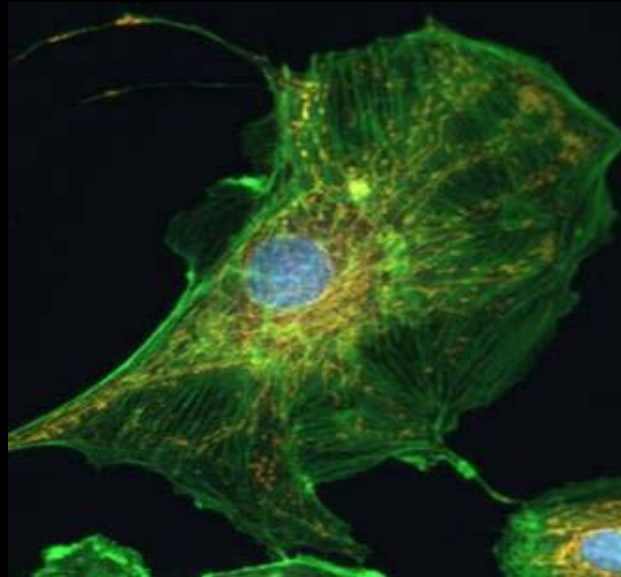
Size of different ingredients in a cell

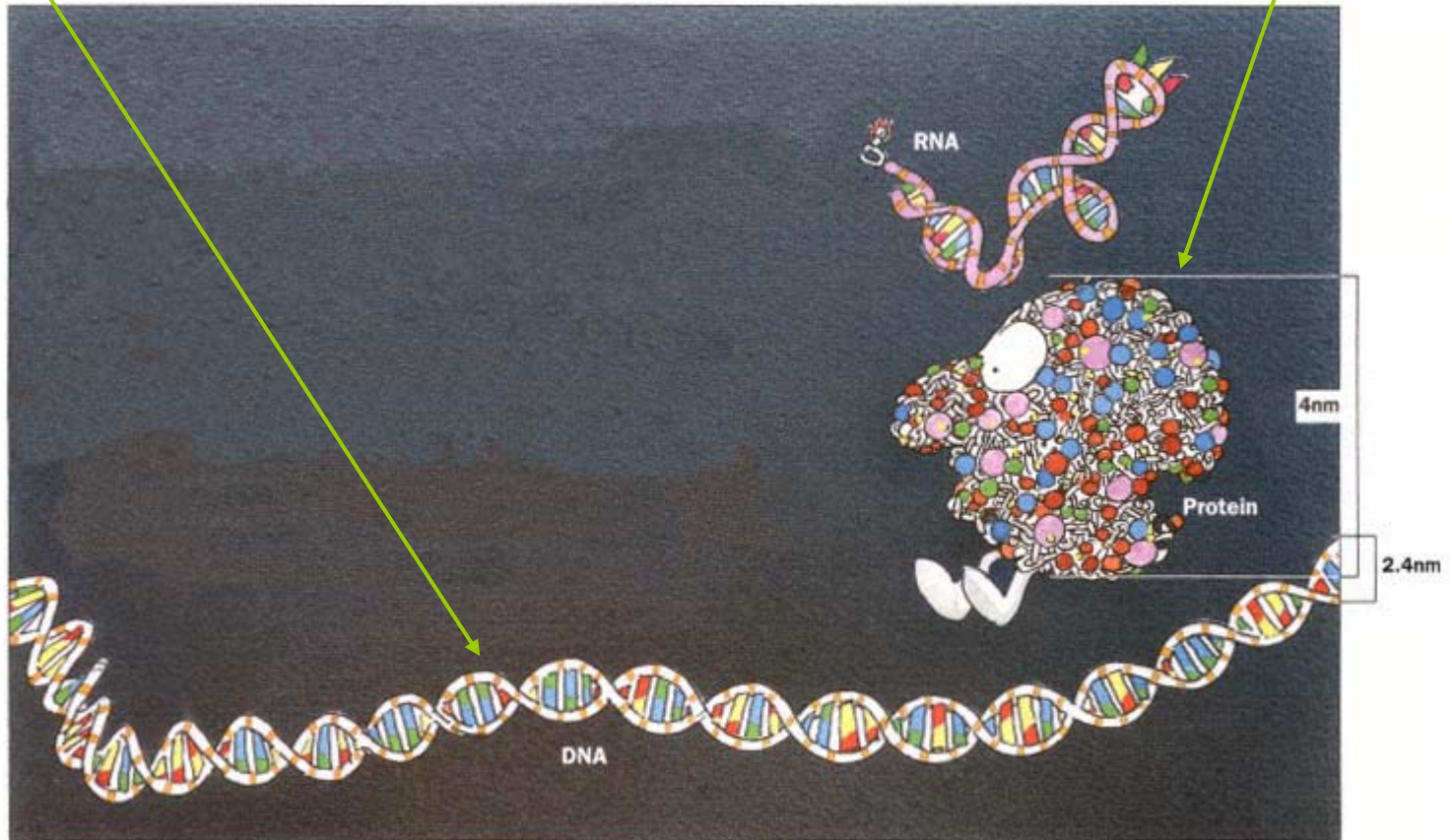Basic chemical elements in life: H, C, N, O, P, S
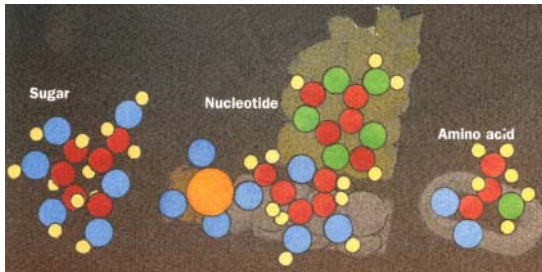
Small molecules (2-50 atoms)
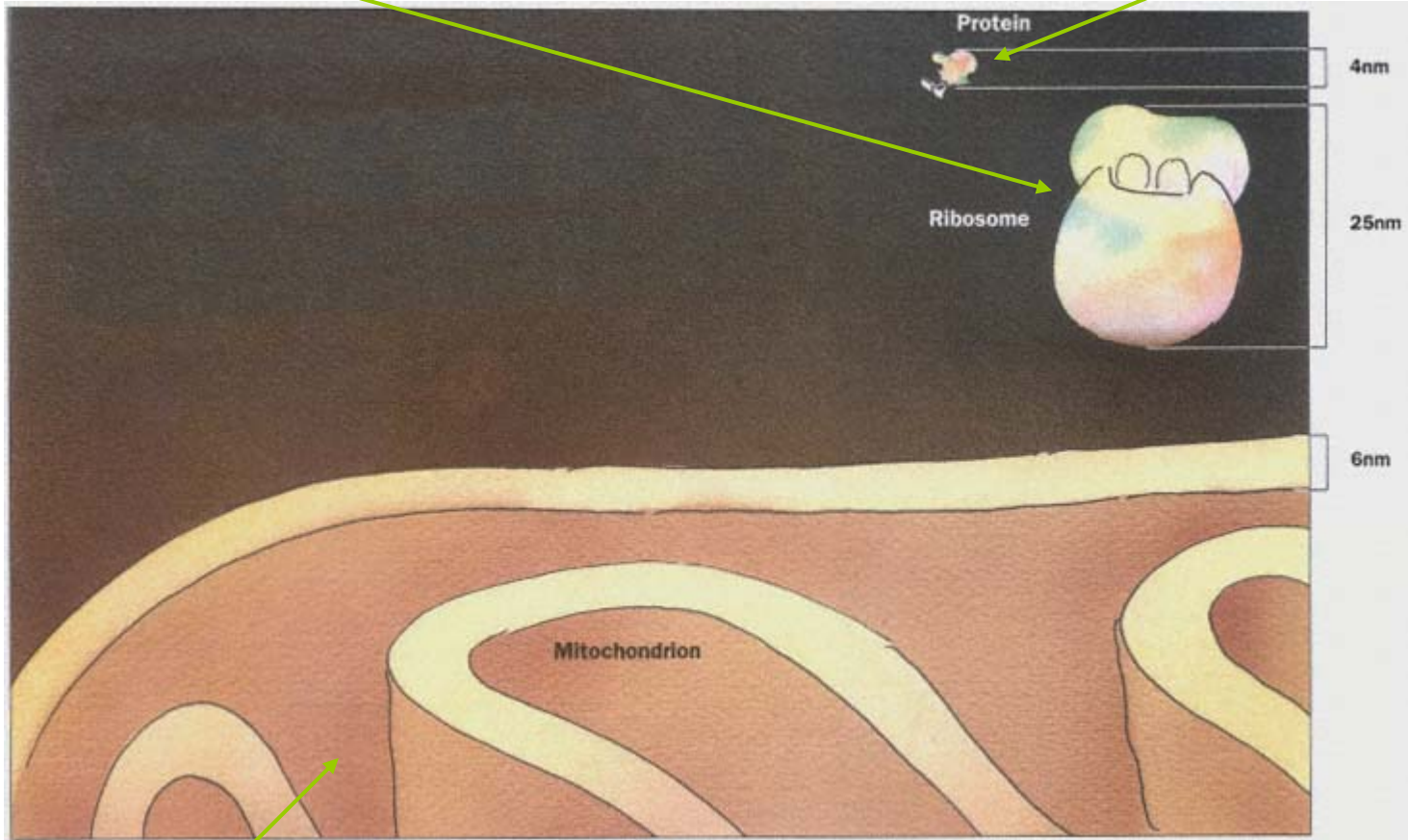
Big molecules (300-400 atoms?)

Size of different ingredients in a cell

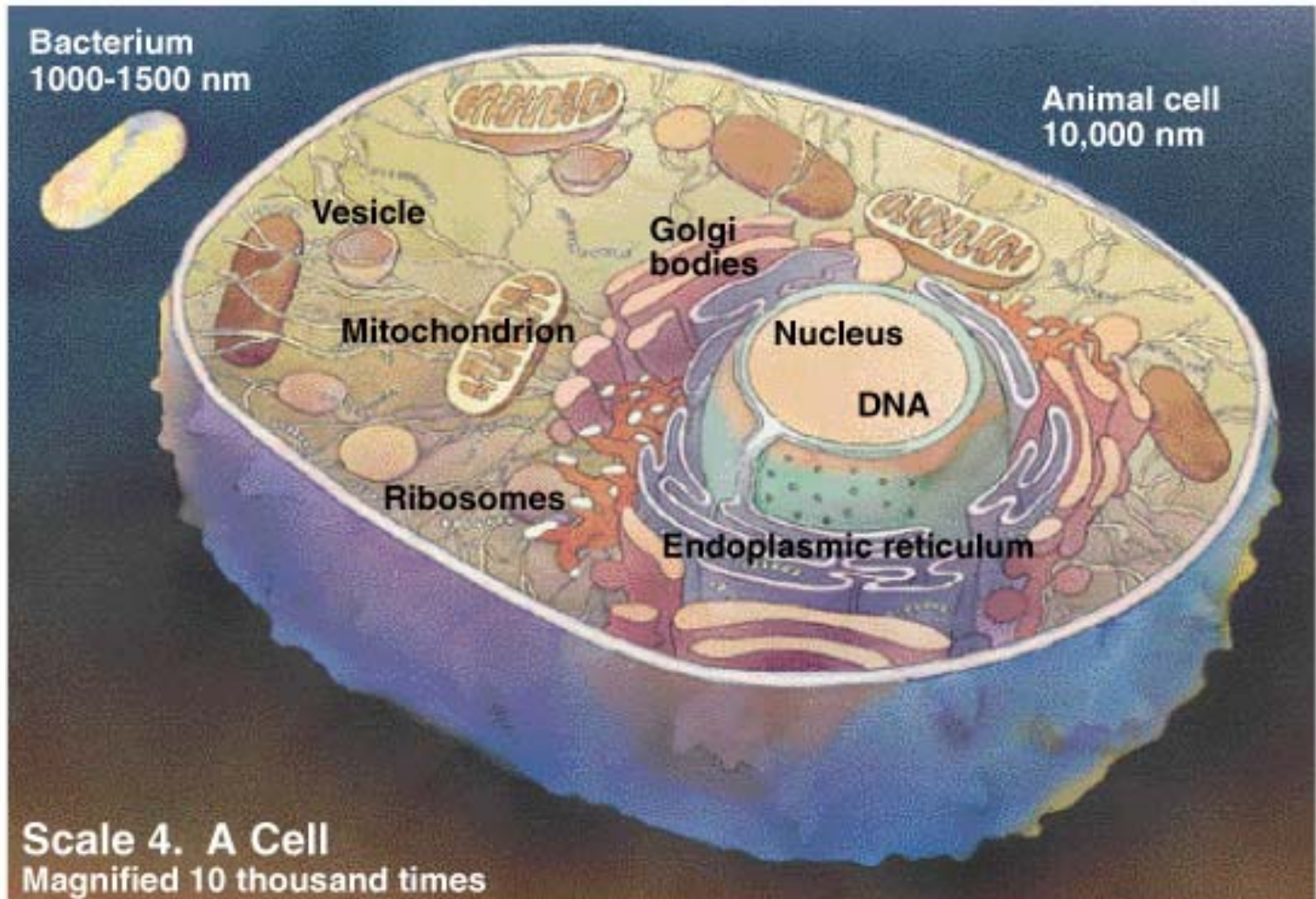DNA is a book describing how to produce proteins.

Size of different ingredients in a cell

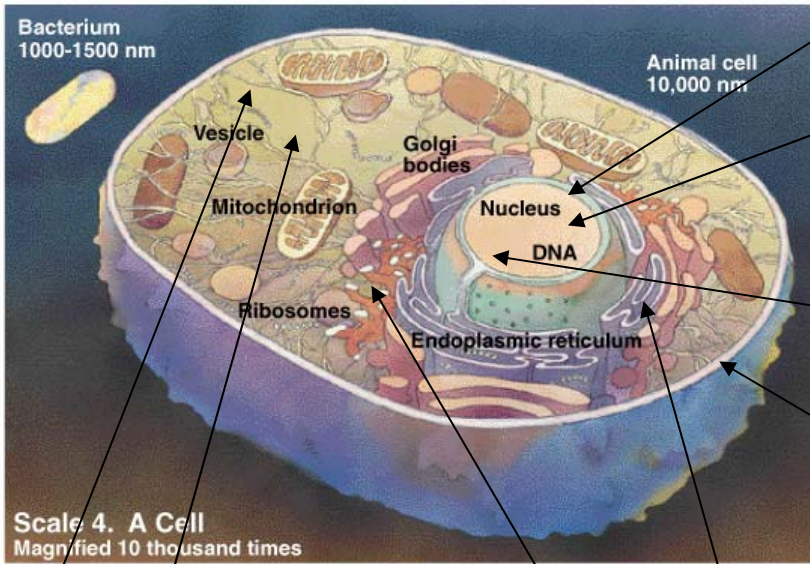Ribosome: an machine to produce proteins.

Protein

4nm

Ribosome

25nm

6nm

Mitochondrion

Mitochondrion: an factory to produce energy.

Size of different ingredients in a cell

Bacterium
1000-1500 nm

Animal cell
10,000 nm

Vesicle

Golgi
bodies

Mitochondrion

Nucleus

DNA

Ribosomes

Endoplasmic reticulum

Scale 4. A Cell
Magnified 10 thousand times

Components in an animal cell

Nucleus(細胞核): the repository of a cell's genetic information.

Nucleolus(核仁): large, spherical structure in the nucleus; the site of ribosomal assembly.

Chromosome(染色體): the protein-complexed DNA molecules that become observable during cell divisions.
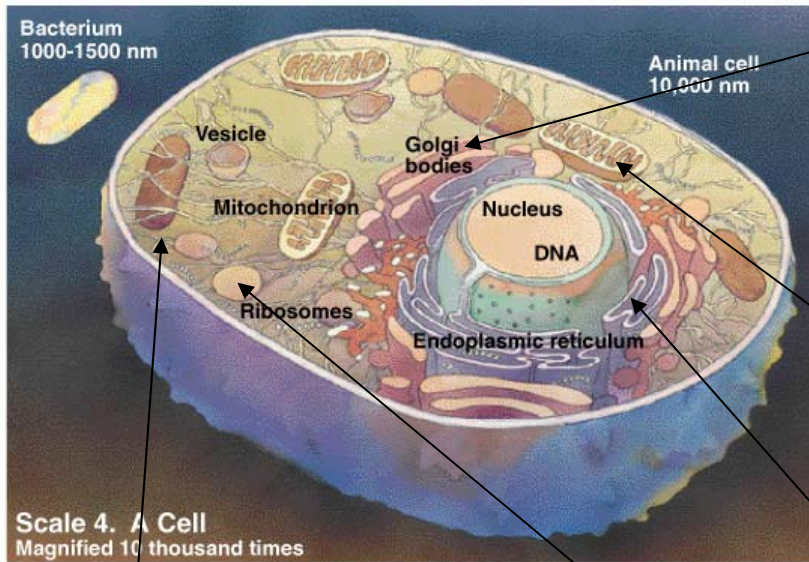
Membrane(細胞膜)

Cytosol(細胞液): the semifluid substance in which the organelles of the cytoplasm are suspended.

Cytoplasm(細胞質): the portion of interior of a cell that is not occupied by the nucleus.

Endoplasmic reticulum (ER) (內質網): network of interconnected membranes distributed throughout the cytoplasm.

Rough ER: ER studded with ribosomes on its side; involved in protein synthesis.

Smooth ER: ER that has no attached ribosomes; involved in packaging of secretory proteins and synthesis of lipids.
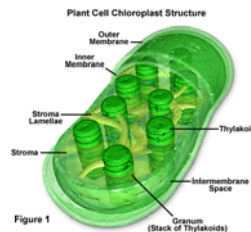
Golgi apparatus(高基氏體**)**: stacks of flattened, disk-shaped membrane cisternae; involved in the processing & packaging of secretory proteins and in the synthesis of complex polysaccharides.

Mitochondrion(粒線體**)**: double membrane-enclosed cytoplasmic organelle; the site of aerobic respiration.

**Ribosome(**核糖體**)**: molecular machinery for protein synthesis.

Lysosome（溶酶體）: membrane-bounded organelle containing digestive enzymes capable of degrading all the major classes of biological macromolecules; formed by budding from the Golgi apparatus.

Cytoskeleton(骨架**)**: 3-dim network of filaments (microtubules, microfilaments, and intermediate filaments) that provides structure to the cytoplasm.

Chloroplast(葉綠體**)**: double membrane-enclosed organelle of plants & algae that contains chlorophyll（葉綠素）and the enzymes necessary to carry out photosynthesis.

(a) Mitochondrion
(b) Rough ER
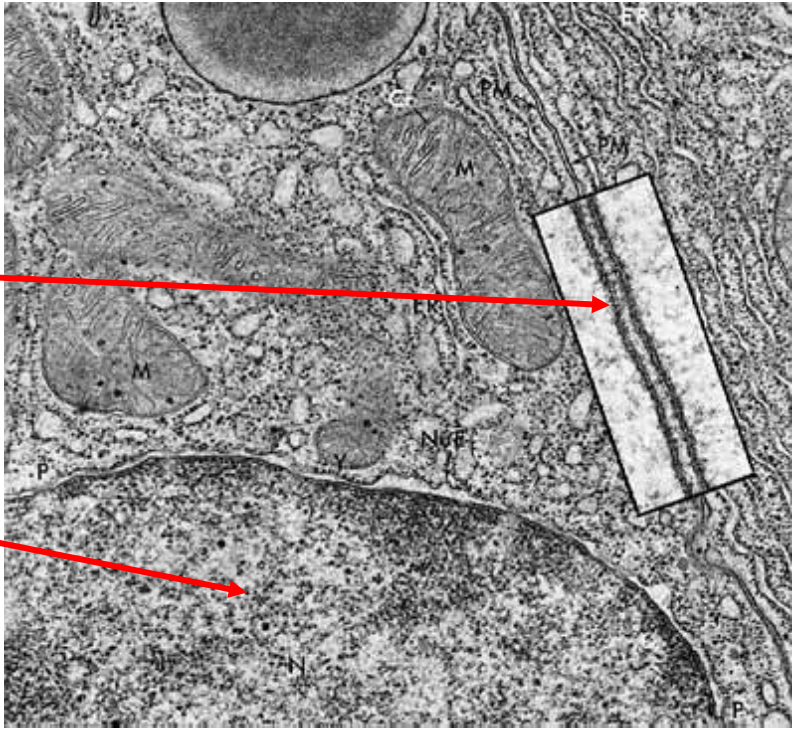(c) Nucleolus
(d) Cell membrane
(e) Nucleus

(a)

(b) black points
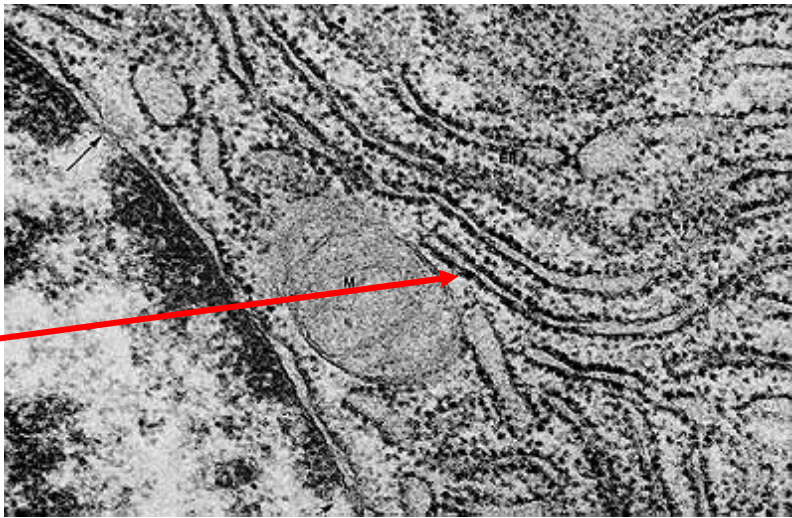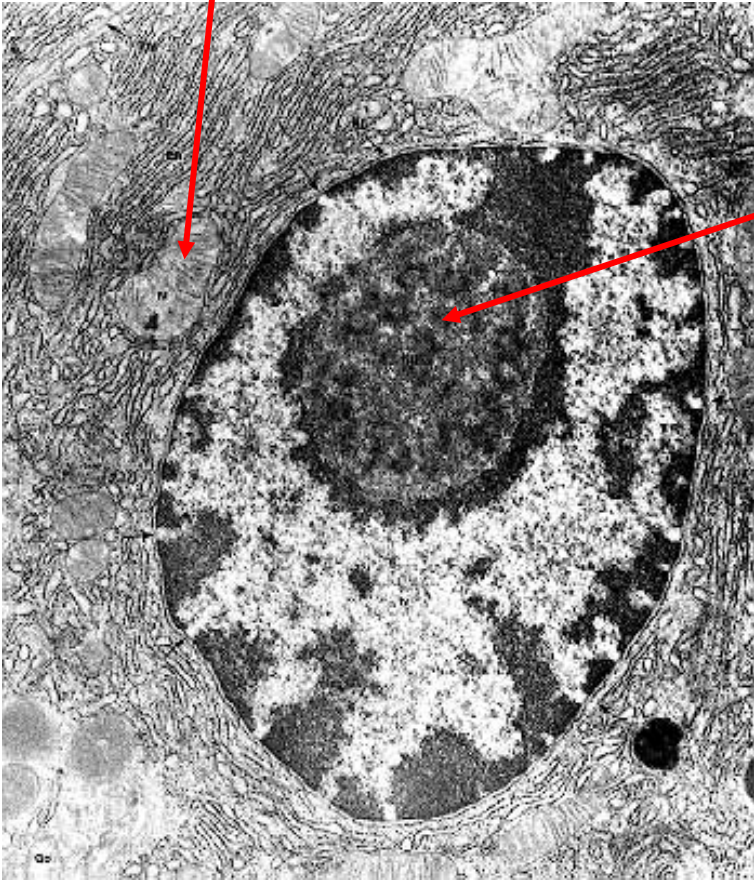
(c)

(d)

(e)

Physical problems inside a cell
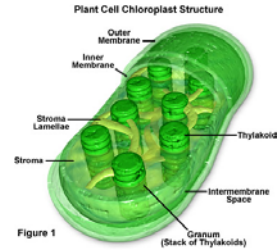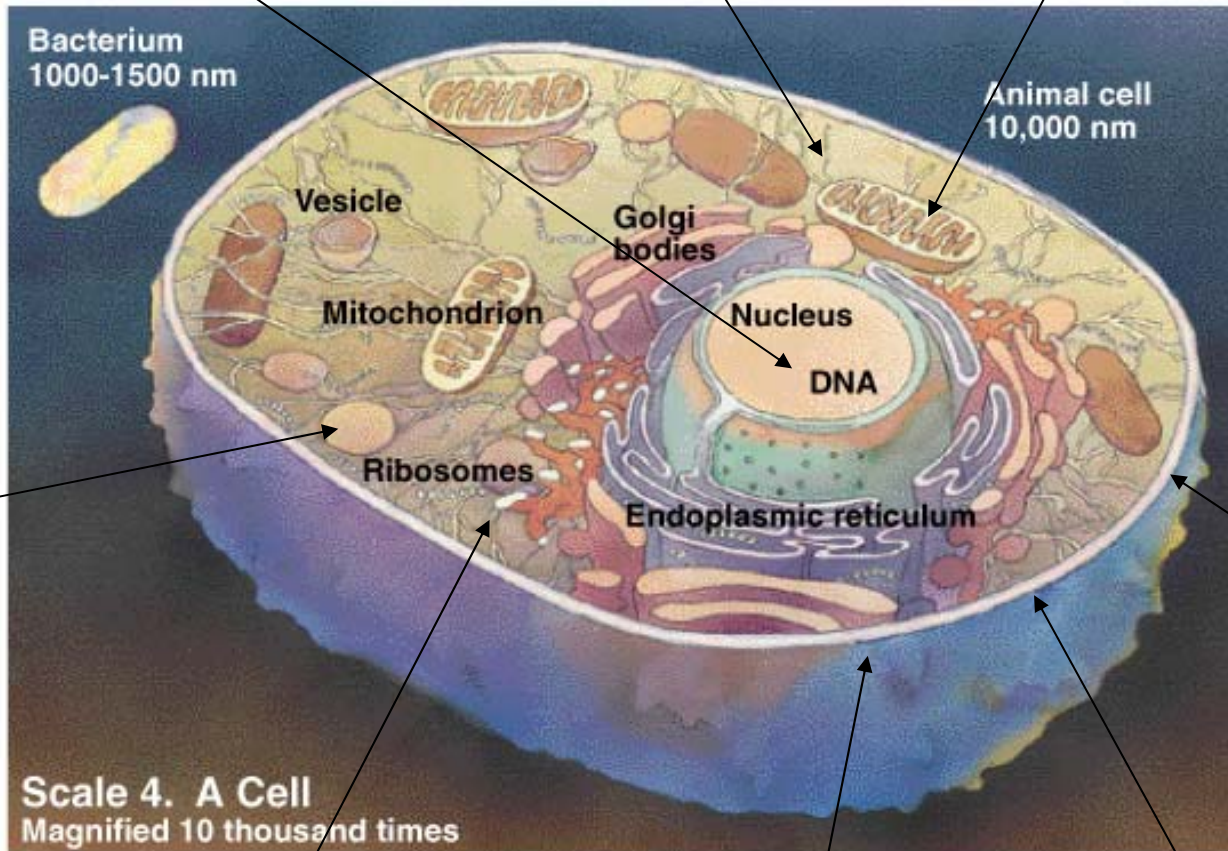
Polymer: DNA   Transport: filaments   Energy: ATP, Chloroplast

Bacterium
1000-1500 nm

Animal cell
10,000 nm

Vesicle

Golgi bodies

Mitochondrion

Nucleus

Structure: protein

DNA

Ribosomes

Endoplasmic reticulum

Plant Cell Chloroplast Structure

Outer Membrane

Inner Membrane

Stroma Lamellae

Stroma

Thylakoid

Intermembrane Space

Granum (Stack of Thylakoids)
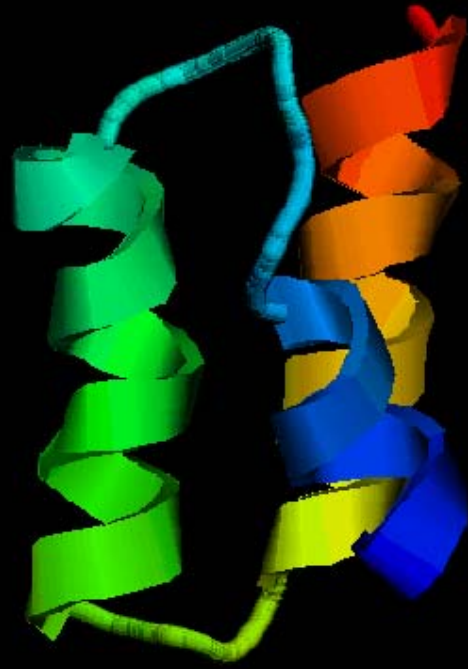
Figure 1

Ion channel

Scale 4. A Cell
Magnified 10 thousand times

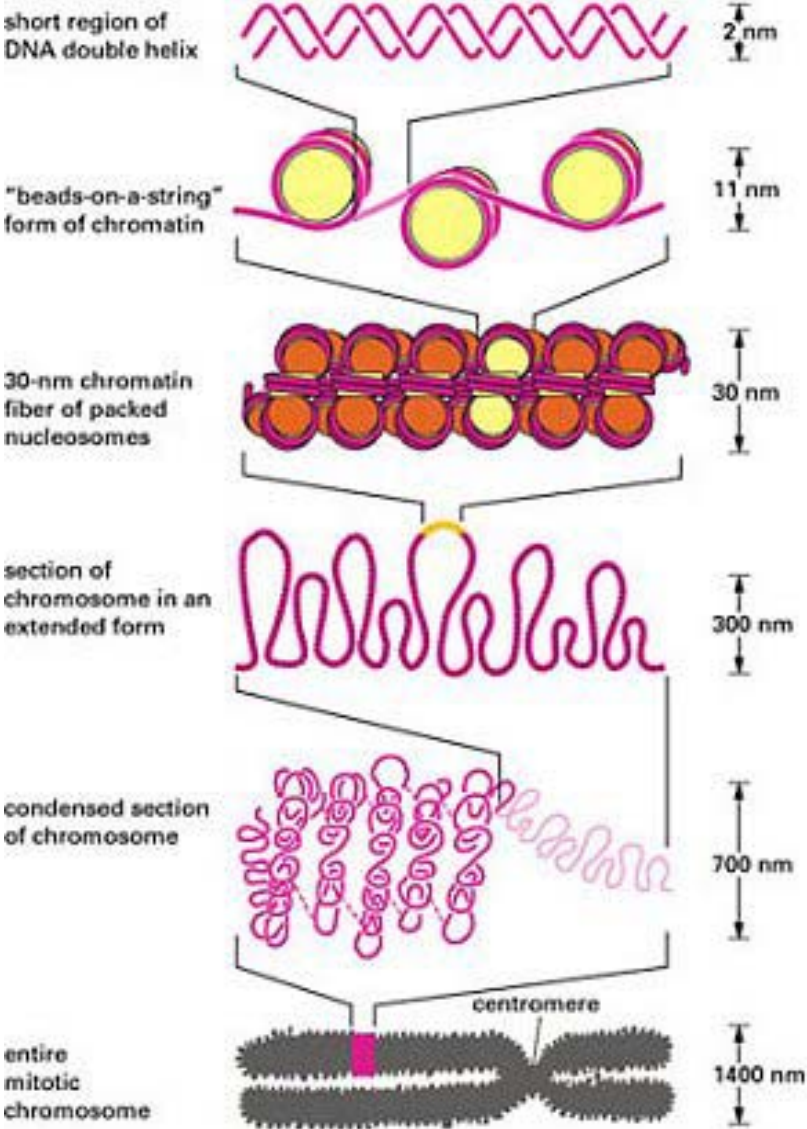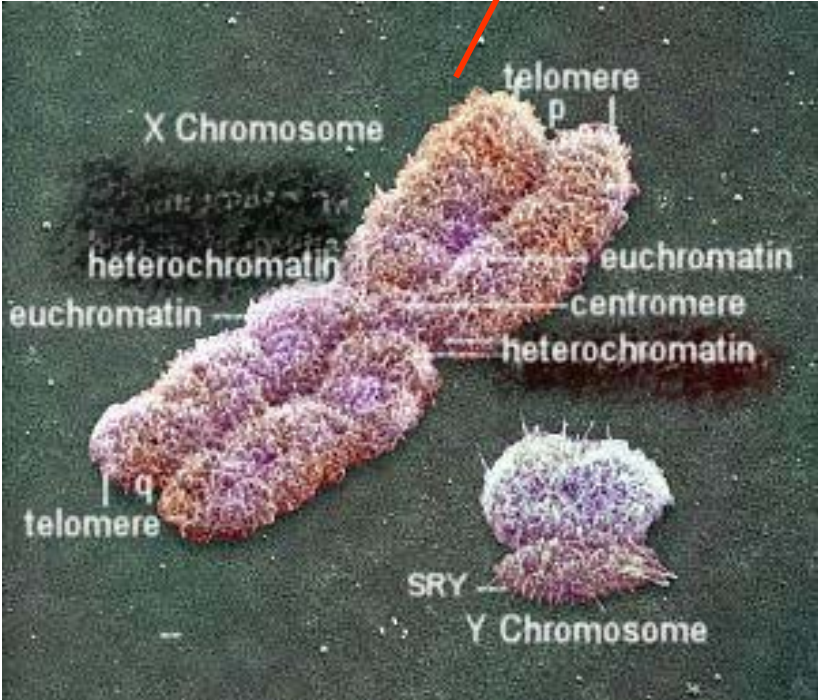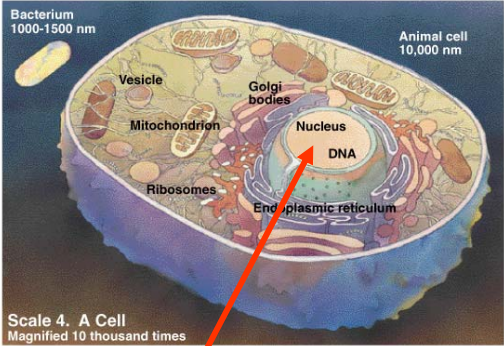Colloid: cytoplasm   Membrane: bilayer   Motors: ion pump
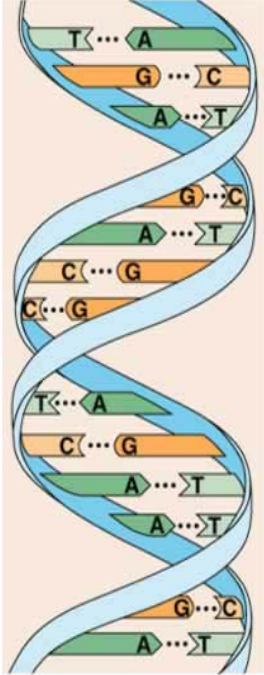
2. Self-assembly (protein folding)

Chromosome and DNA

http://universe-review.ca/F11-monocell.htm

short region of DNA double helix — 2 nm

"beads-on-a-string" form of chromatin — 11 nm

30-nm chromatin fiber of packed nucleosomes — 30 nm

section of chromosome in an extended form — 300 nm

condensed section of chromosome — 700 nm
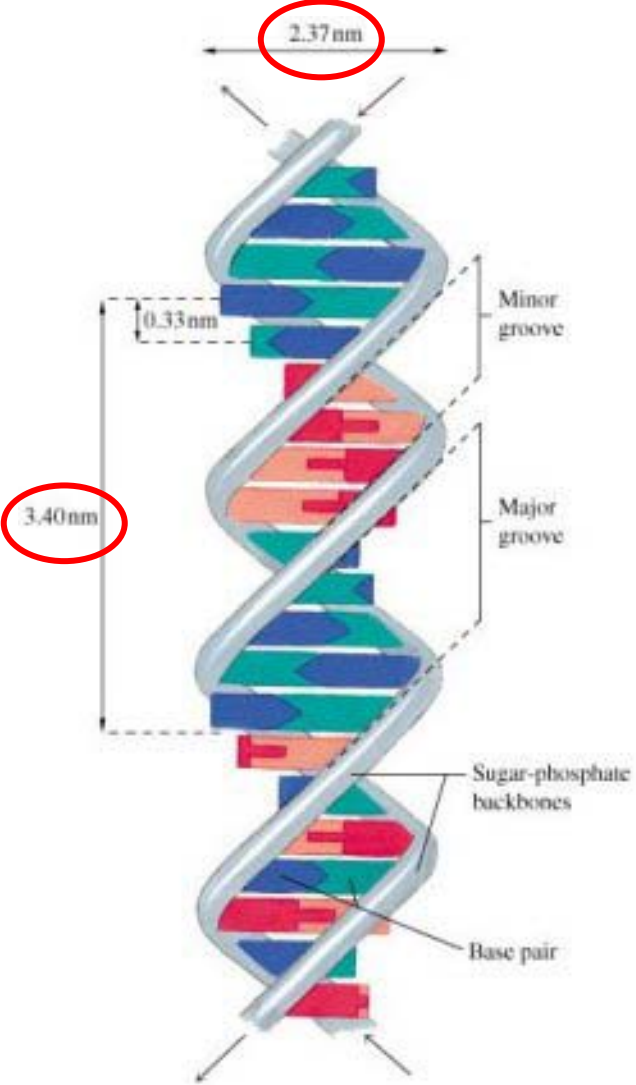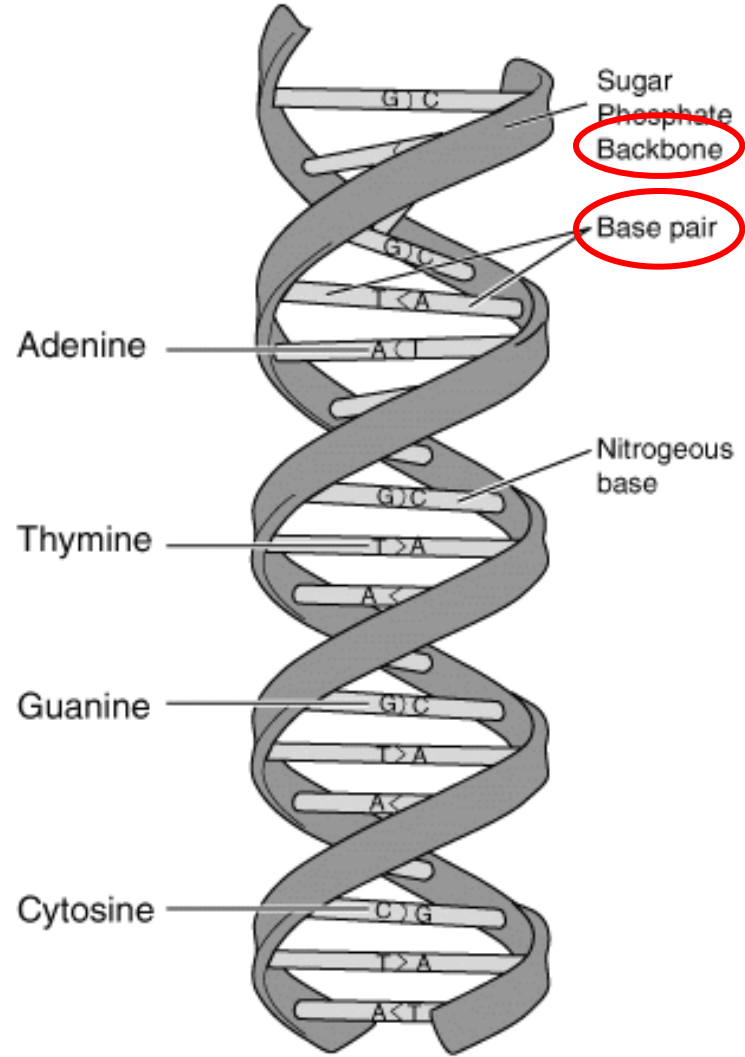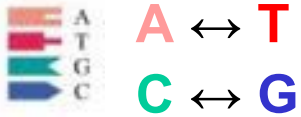
entire mitotic chromosome — 1400 nm

NET RESULT: EACH DNA MOLECULE HAS BEEN PACKAGED INTO A MITOTIC CHROMOSOME THAT IS 50,000x SHORTER THAN ITS EXTENDED LENGTH

DNA double helix

2.37 nm

0.33 nm

3.40 nm

Minor groove

Major groove

Sugar-phosphate backbones

Base pair

©Addison Wesley Longman, Inc.

Sugar Phosphate Backbone

Base pair

Adenine

Thymine

Guanine

Cytosine

Nitrogeous base

A ↔ T
C ↔ G

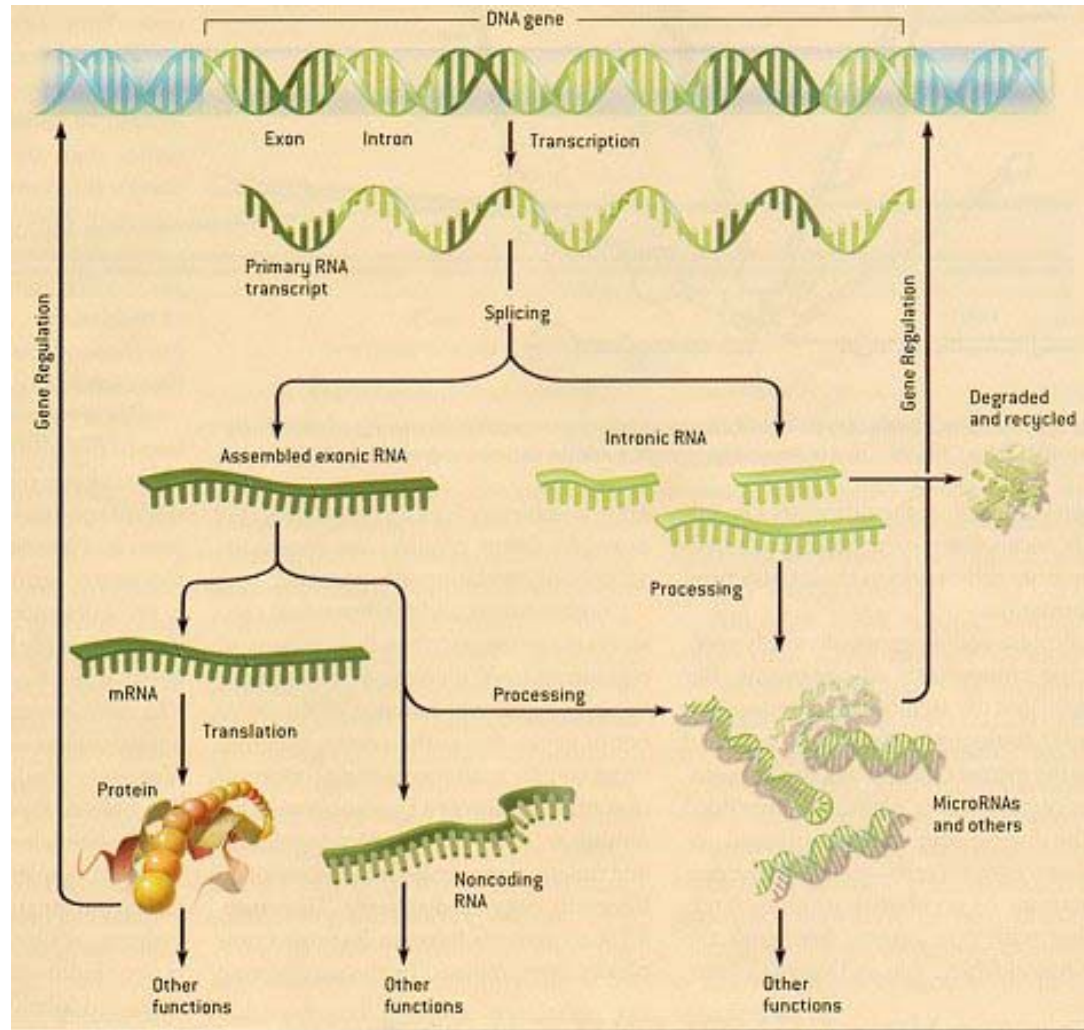4 nucleotides (核甘酸)

Gene

DNA =
(i) genes & (ii) junk DNA

(i) contains protein information
(ii) non-coding DNA with
   repeated sequences
   inserted within a region
   of coding gene.

The purpose of the noncoding
DNA, if any, is not understood.
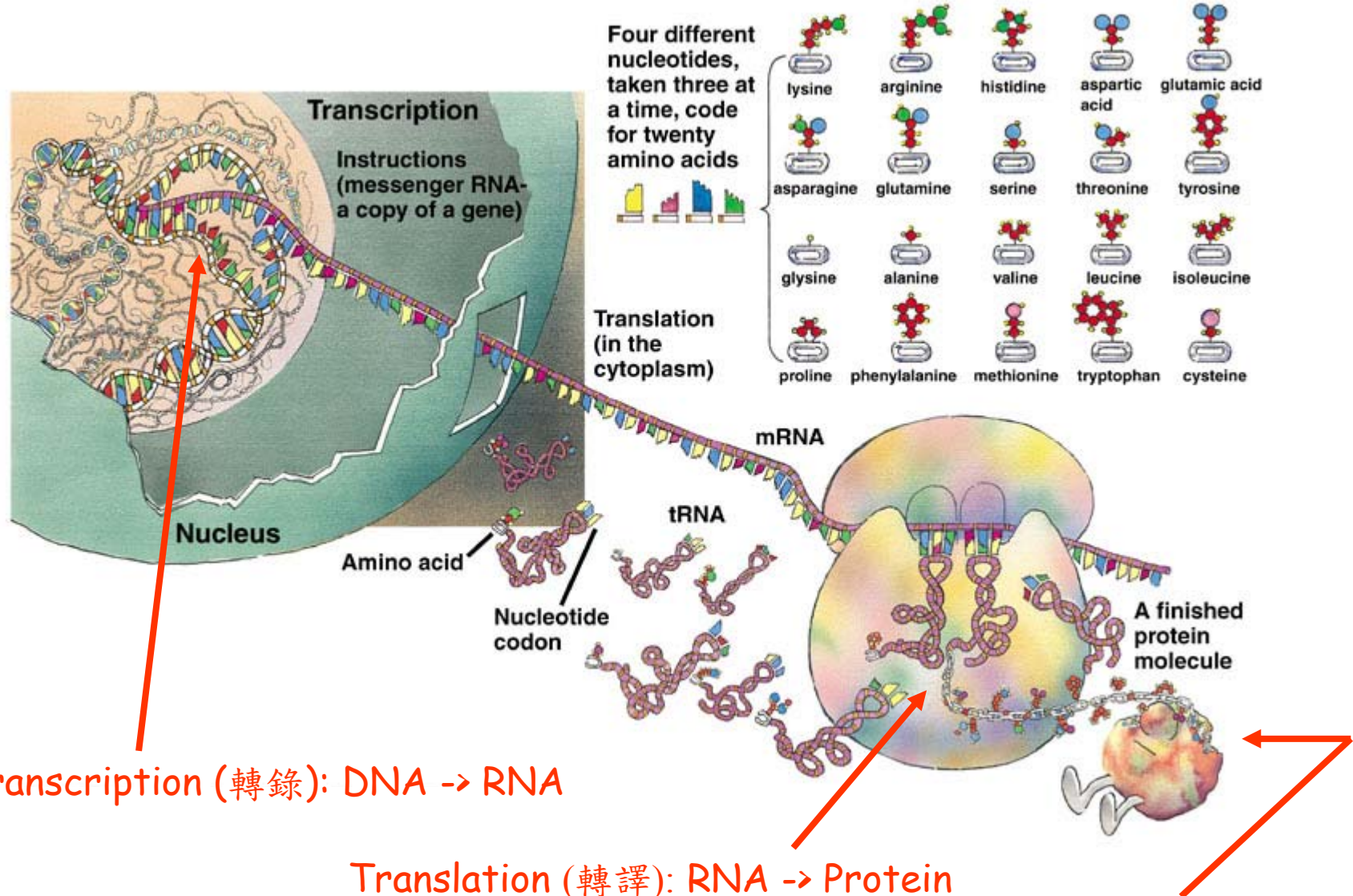As much as 97% of human
DNA is noncoding.

Some researches show that
they might be used as testing
site for genetic mutation.

Genome

the sum of all genes that make
up the genetic code of an individual.

Gene expression: DNA -> RNA -> Protein

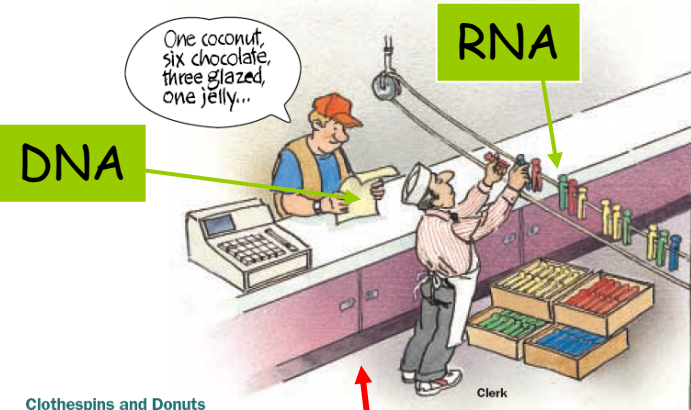Transcription (轉錄): DNA -> RNA

Translation (轉譯): RNA -> Protein

Protein folding

Transcription (轉錄): DNA -> RNA
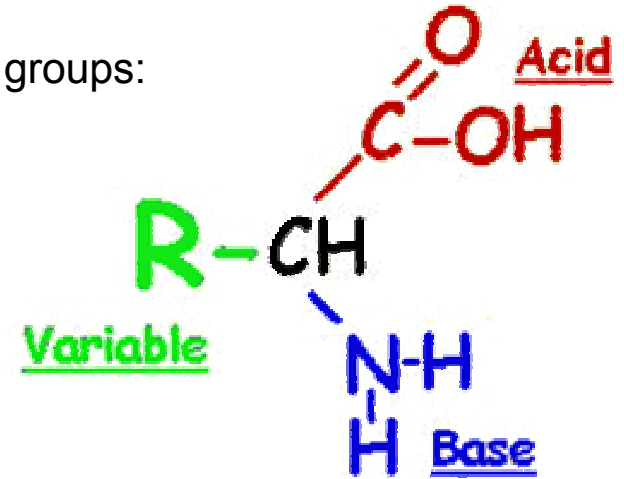
Nucleotides

Amino acids

RNA

DNA
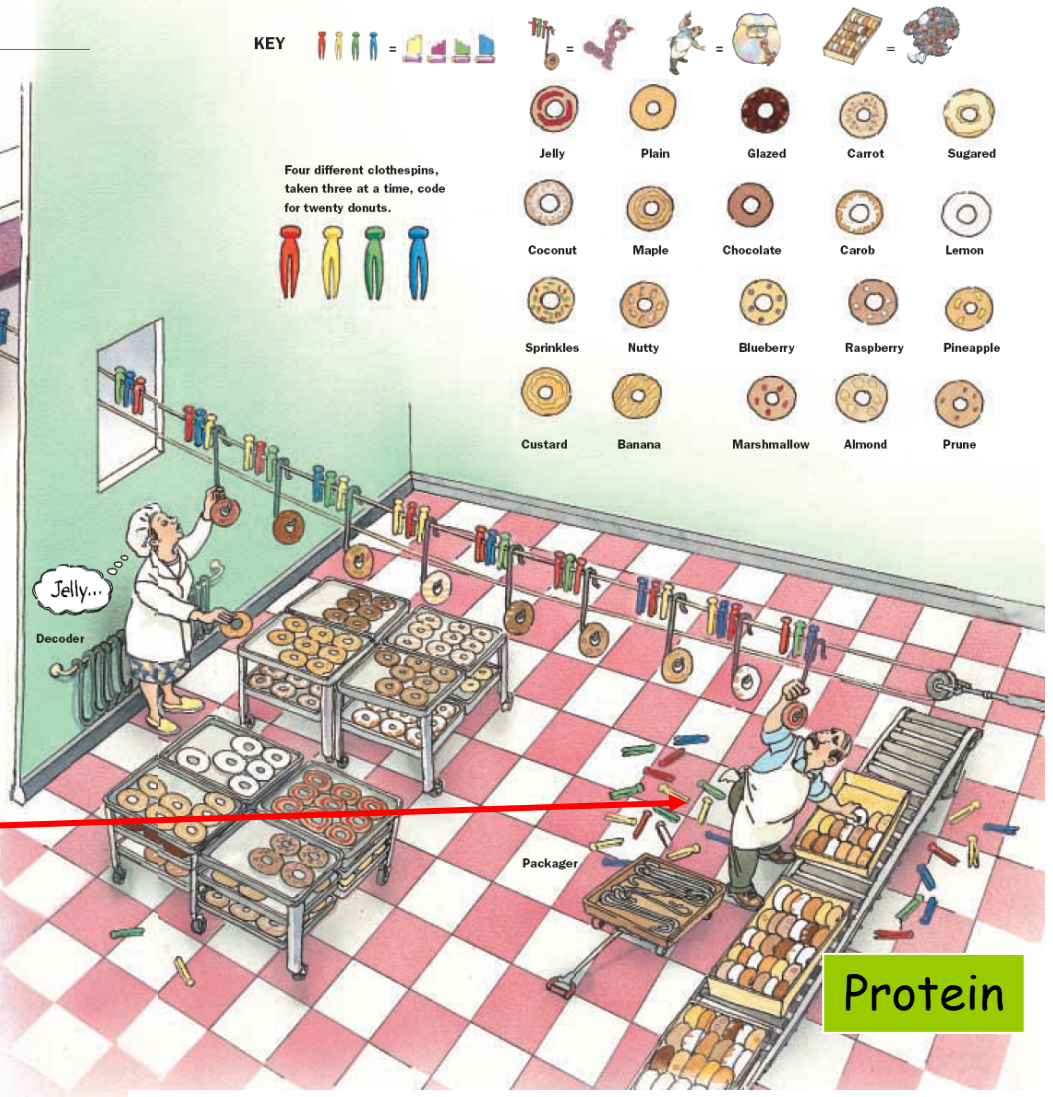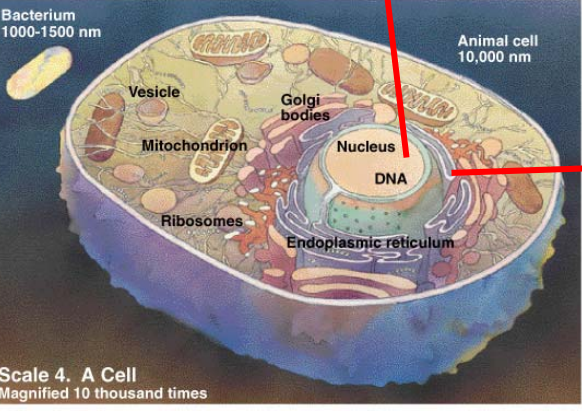
Protein

Translation (轉譯): RNA -> Protein

Amino acid (胺基酸)

Proteins are necklaces of **amino acids**

A **amino acids** consists of a central carbon C_α linked by 4 groups:

- carboxyl group **COOH** (acidic). （羧基）→ COO^-
- aminio group **NH₂** (basic).   （胺基）→ NH_3^+
- hydrogen **H**.
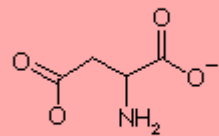- residue **R**.

A theoretical amino acid

All 20 different amino acids have this same structure.

But their **side chain R** may vary in size, shape, charge, hydrophobicity, and reactivity.
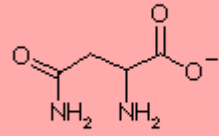
Different combinations of **R** give different proteins.

http://www.rothamsted.ac.uk/notebook/courses/guide/aa.htm
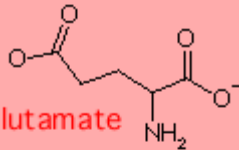
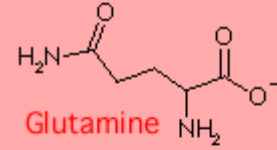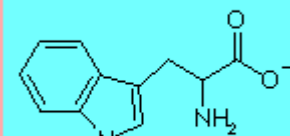**The side chains of 20 amino acids:**

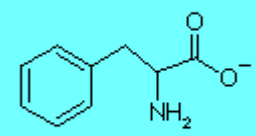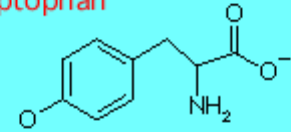Acidic and amide side chains
Aspartate
Asparingine
Glutamate
Glutamine

Aromatic side chains
Tryptophan
Phenylalanine
Tyrosine
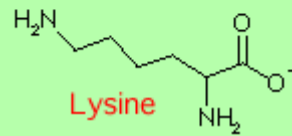
Basic side chains
Lysine
Histidine
Arginine
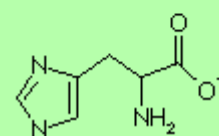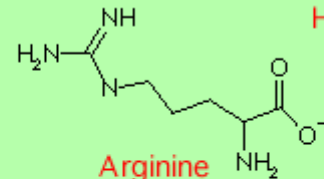
Aliphatic side chains
Valine
Isoleucine
Glycine
Alanine
Leucine
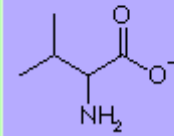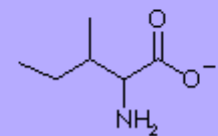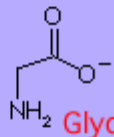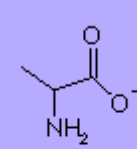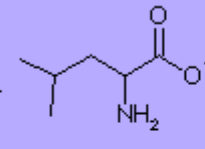
Hydroxyl or sulfur-containing side chains
Serine
Methionine
Threonine
Cysteine
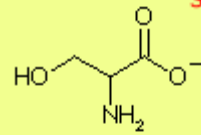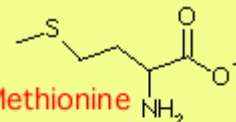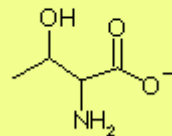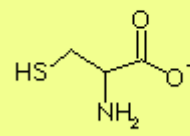
Cyclic side chain
Proline
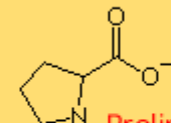
胺基酸地下鐵道圖

BASIC
AROMATIC
中山線
南港線
AMIDE
ACIDIC
ALIPHATIC
HYDROXYL SULFUR
IMINO, CIRCULAR

Polar — One-letter code
Non-polar — One-letter code

西北線
中央線
雙和線
環狀線

Arg R   R = C-C-C-N-C-N with N$^+$
Lys K   R = C-C-C-C-NH$_3^+$
His H   R = C with N—N$^+$ ring
Gly G   R = H
Ala A   R = CH$_3$
Trp W   R = C with indole ring
Tyr Y   R = C—◯—OH
Phe F   R = C—◯
Asn N   R = C-CONH$_2$
Gln Q   R = C-C-CONH$_2$
Asp D   R = C-COO$^-$
Glu E   R = C-C-COO$^-$
Val V   R = C with C, C branch
Ile I   R = C-C-C
Leu L   R = C-C-C
Ser S   R = C with OH
Thr T   R = C-C with OH
Cys C   R = C-SH
Met M   R = C-C-S-C
Pro P   R = (cyclic) HN—C-COOH, α

http://juang.bst.ntu.edu.tw/BCbasics/Amino1.htm#F2
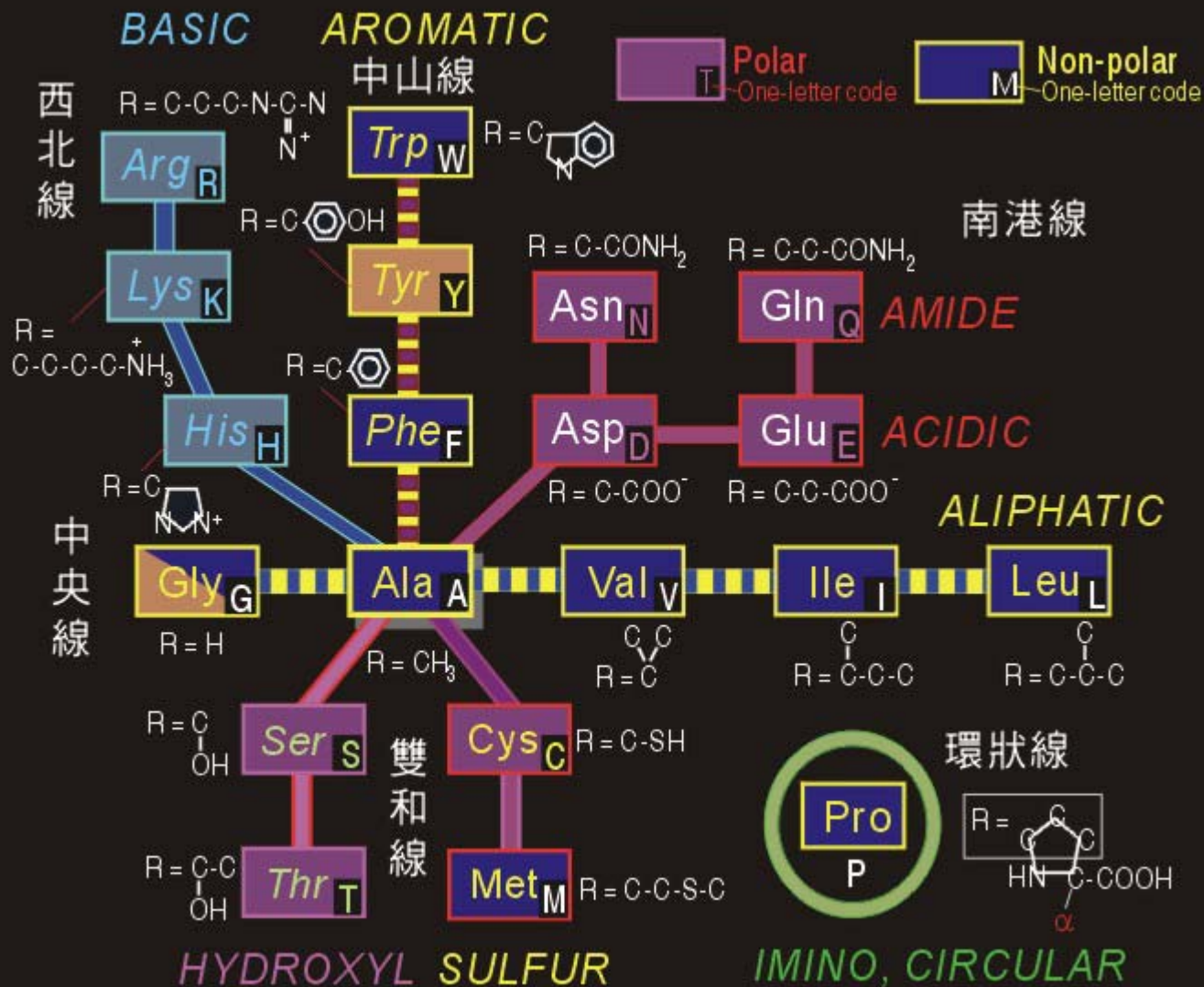
Peptide (胜肽，縮氨酸)

Two amino acids can react together and create a dipeptide (basic reaction involved in the synthesis of proteins).

A molecule of water is released in the process.

Peptides = {dipeptide, tripeptide, …}.
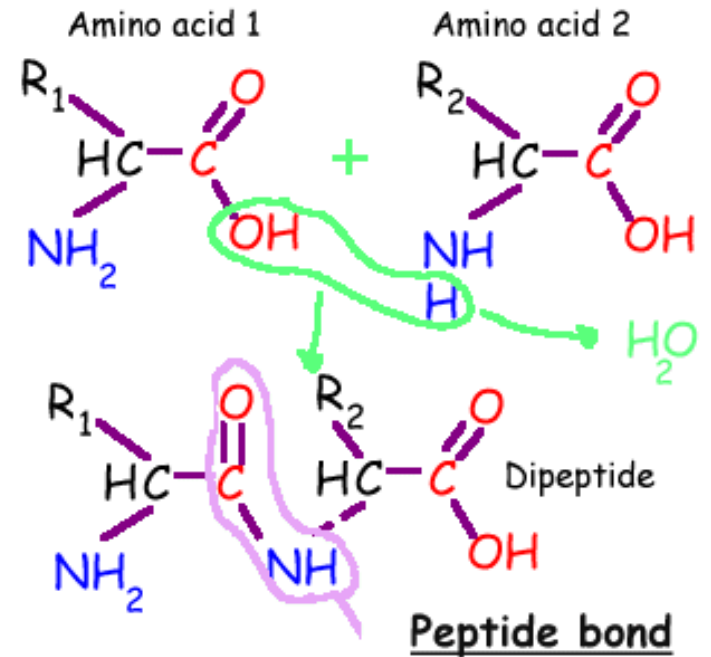
Polypeptide

A series of applications of the peptide bond give rise to the **polypeptide** chain.

backbond

http://cnx.org/content/m11624/latest/
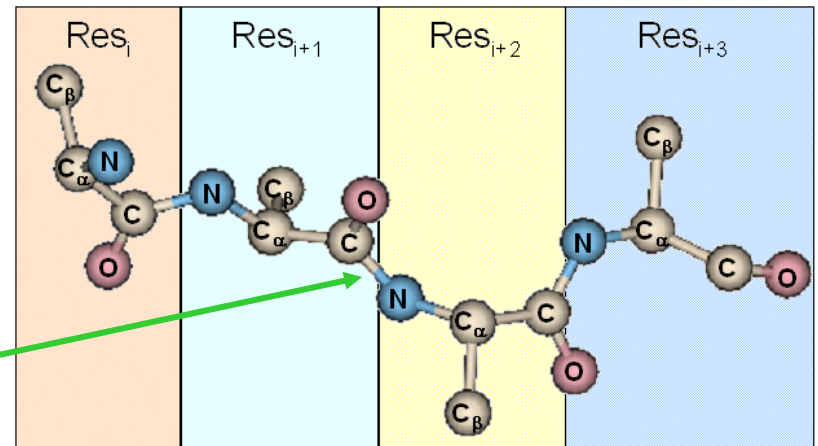
Protein folding:

Put a polypeptide chain into water. Which structure would it form?

random coil   native state
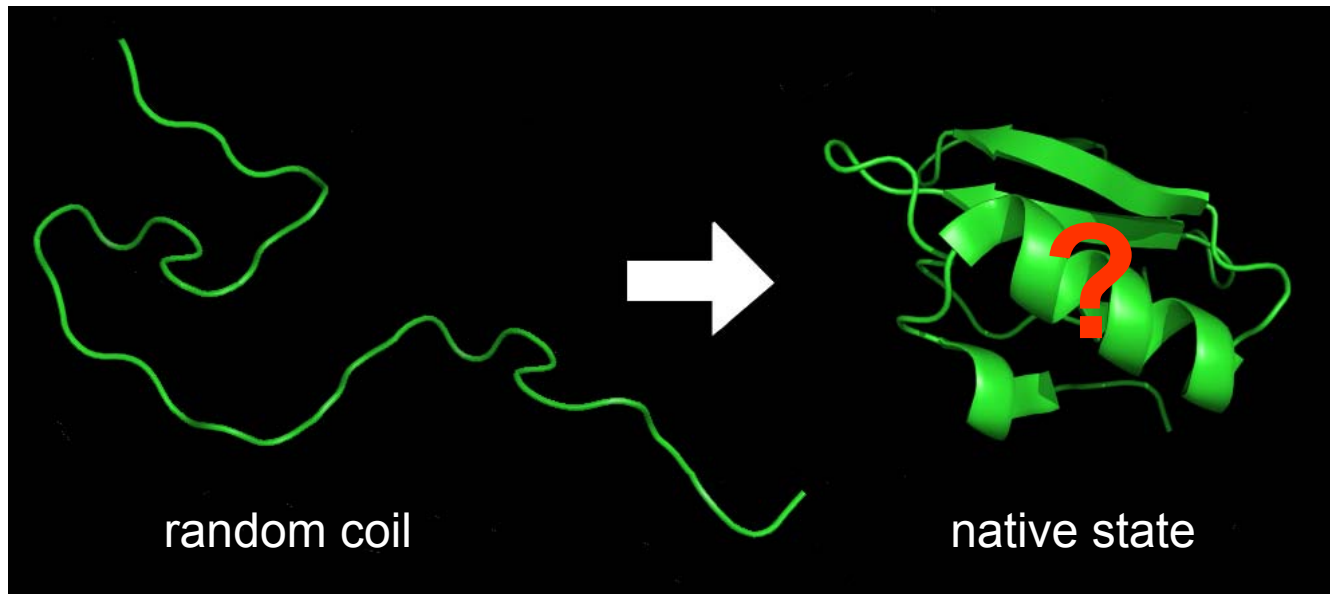
Anfinsen's dogma:

The native structure corresponds to the state with the lowest free energy of the protein-solvent system.

Funnel theory
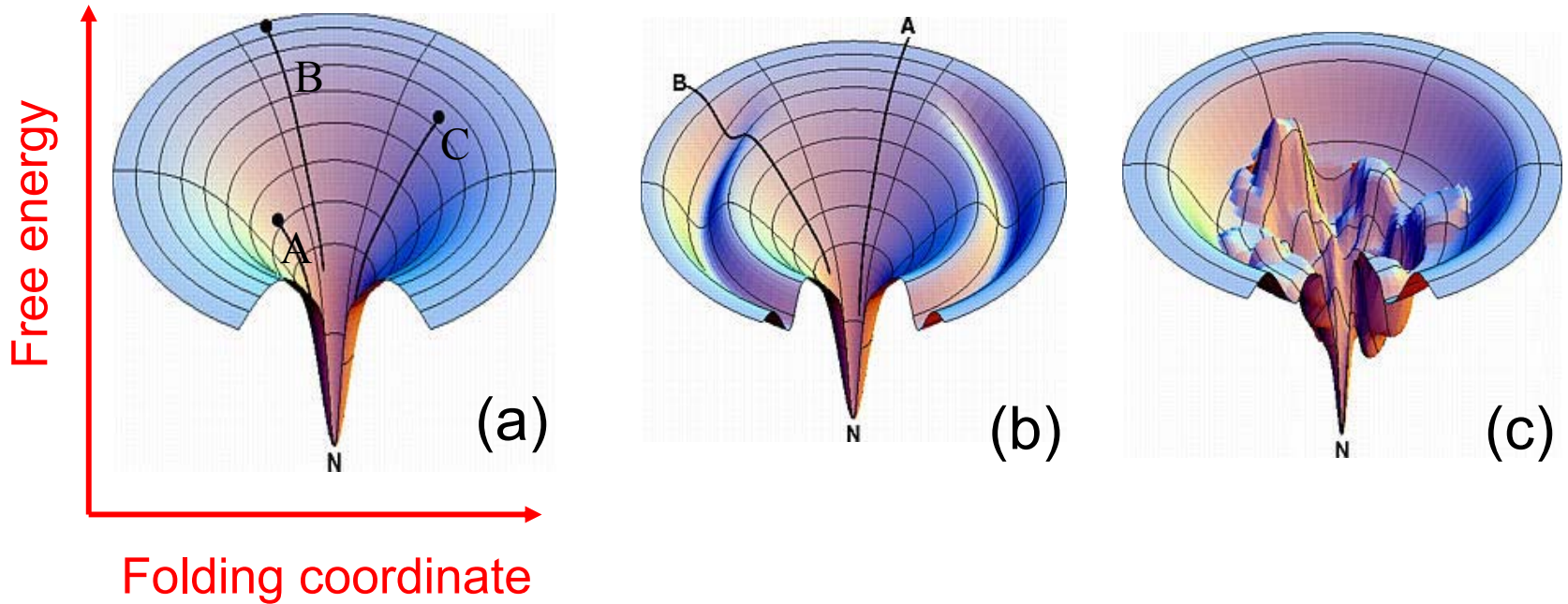
For a multidimensional smooth landscape like (a), to find its minimum is simple.

A real landscape is much more complex, with multiple local minima (folding traps) like (c).

Ken Dill's at UCSF

Funnel theory

Gain of binding energy pulls peptide down.
Reduction of entropy keeps peptide up.

（高能/無序）

（低能/有序）

Entropy

ΔE

Collapsed
States

Energy

δE_s

Q

Transition state region

Glass Transition

Free energy

Discrete Folding
Intermediates

E_{nat}

1.0

Folded State
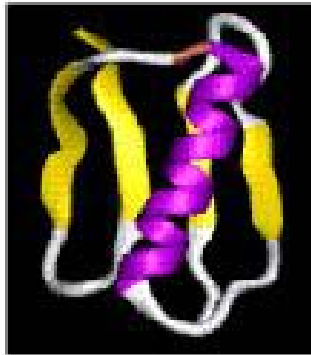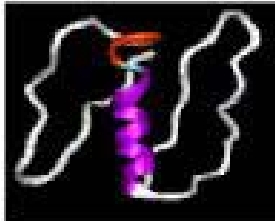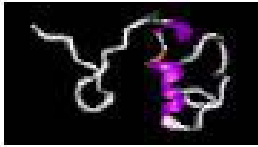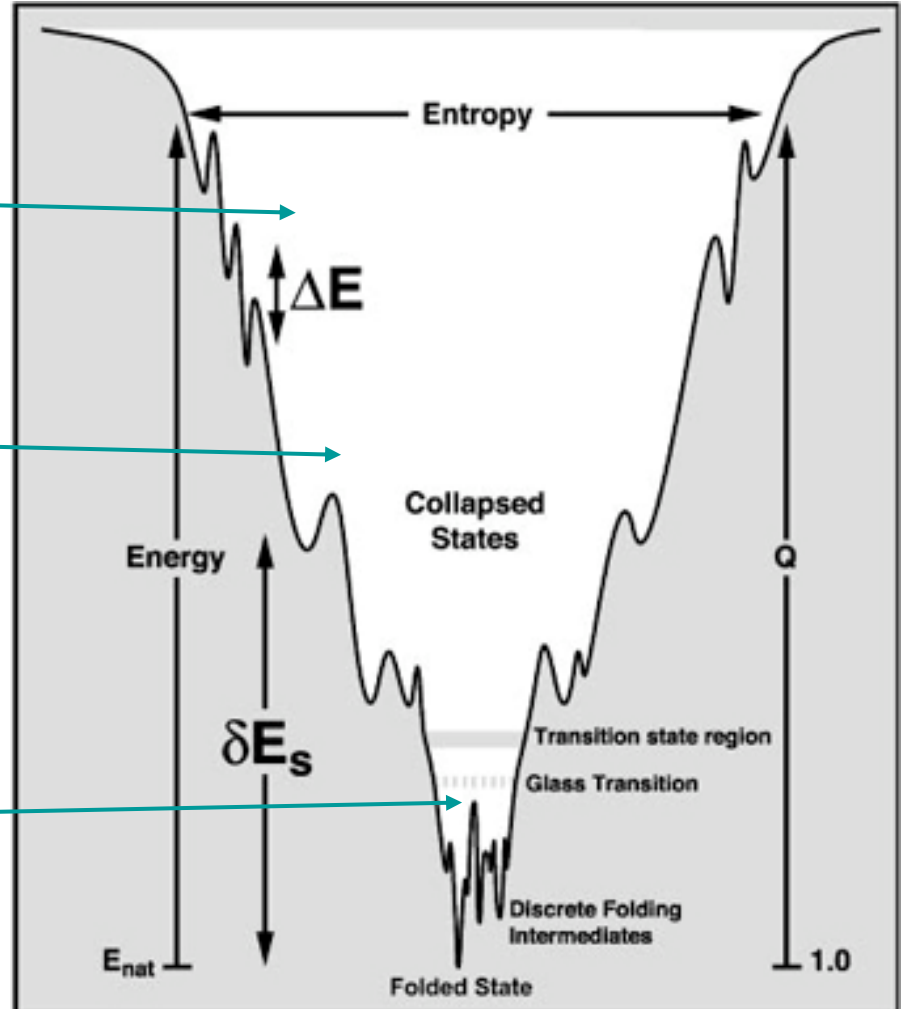
Levinthal Paradox:

Suppose

  (i) each amino acid has 3 conformations.

  (ii) a protein consists of 100 amino acid residues
     with a total conformation number $3^{100} \approx 5 \times 10^{47}$.

  (iii) 100 psec (10^{-10} sec) are required for a conformational change.
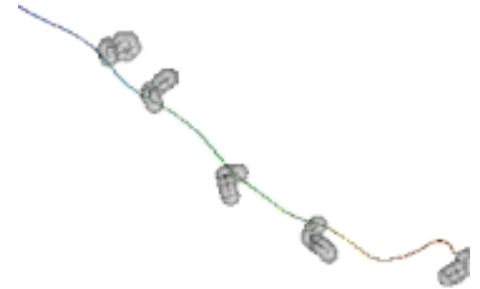
Then a random search of all conformations would require around 10^{30} years.

Nevertheless, folding of a real protein takes place in msec to sec order.

Protein folding cannot be via a random search.

Dynamics of Protein Structures

Electron transport:	$10^{-15} - 10^{-10}$ s
Bond vibration:	$10^{-14} - 10^{-12}$ s
Bond rotation:	$10^{-13} - 10^{-11}$ s
Rotation aromatic ring:	$10^{-9} - 10^{-3}$ s
Hinge movement:	$10^{-12} - 10^{-4}$ s
Folding/unfolding:	$\boxed{10^{-3} - 10^{0}\ s}$ $(10^{-9} - 10^{4}$ s) *
Rotational relaxation time	
of water:	10^{-11} s
of Mb:	10^{-8} s
Rotation of γ unit of F_1:	$10^{1} - 10^{0}$ s
Exchange of labile H:	$10^{-5} - 10^{5}$ s
Backbone motion during enzyme	
Catalysis (NMR):	$10^{-1}\ 10^{1}$ s
Myosin movement:	10^{-8} m s^{-1}
Diffusion 1 nm particle:	25×10^{-6} ms^{-1}
Diffusion CO in Mb:	$10^{-9} - 10^{2}$ s

Force and energy in proteins

Degrees of freedom in a protein

Bond stretching

Angle Bending

Bond rotation (torsion)

Non-bonded interactions (electrostatic)

Non-bonded interactions (van der Waals)

http://folding.stanford.edu/education/molmodel.html
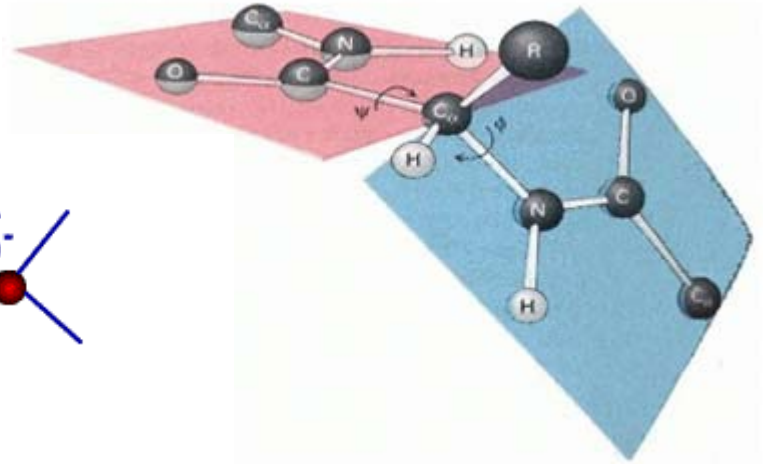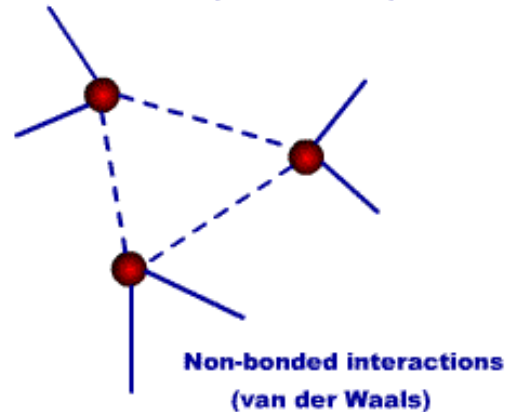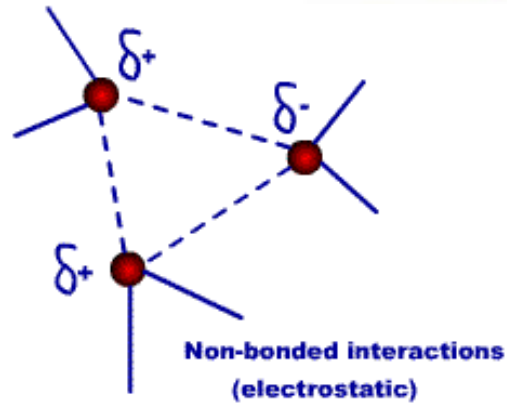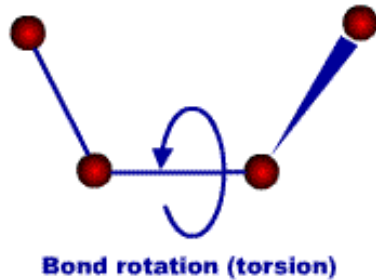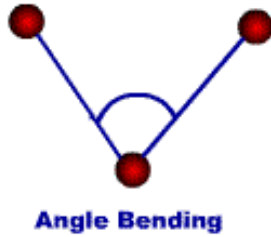
Most flexible degrees of freedom:

torsion Φ between N-C_α
torsion Ψ between C-C_α
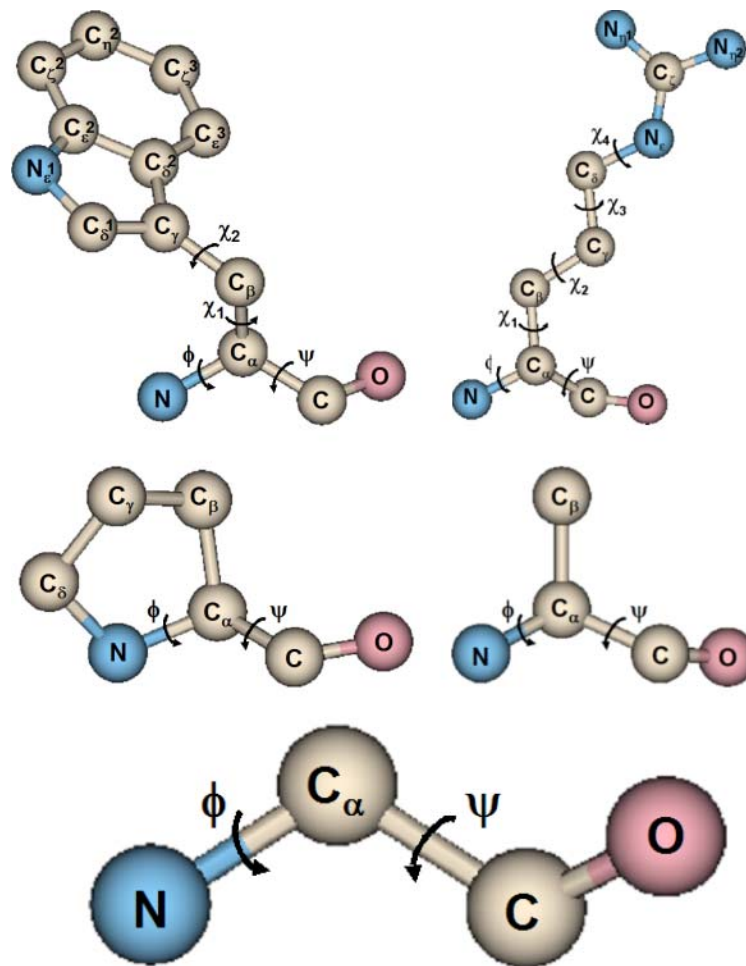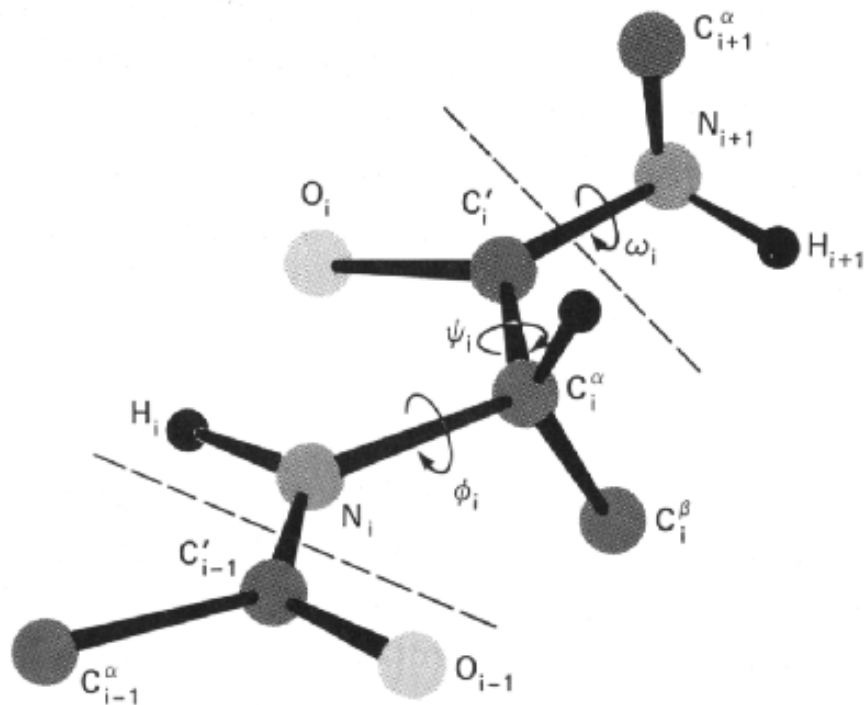
Forces acting on Proteins
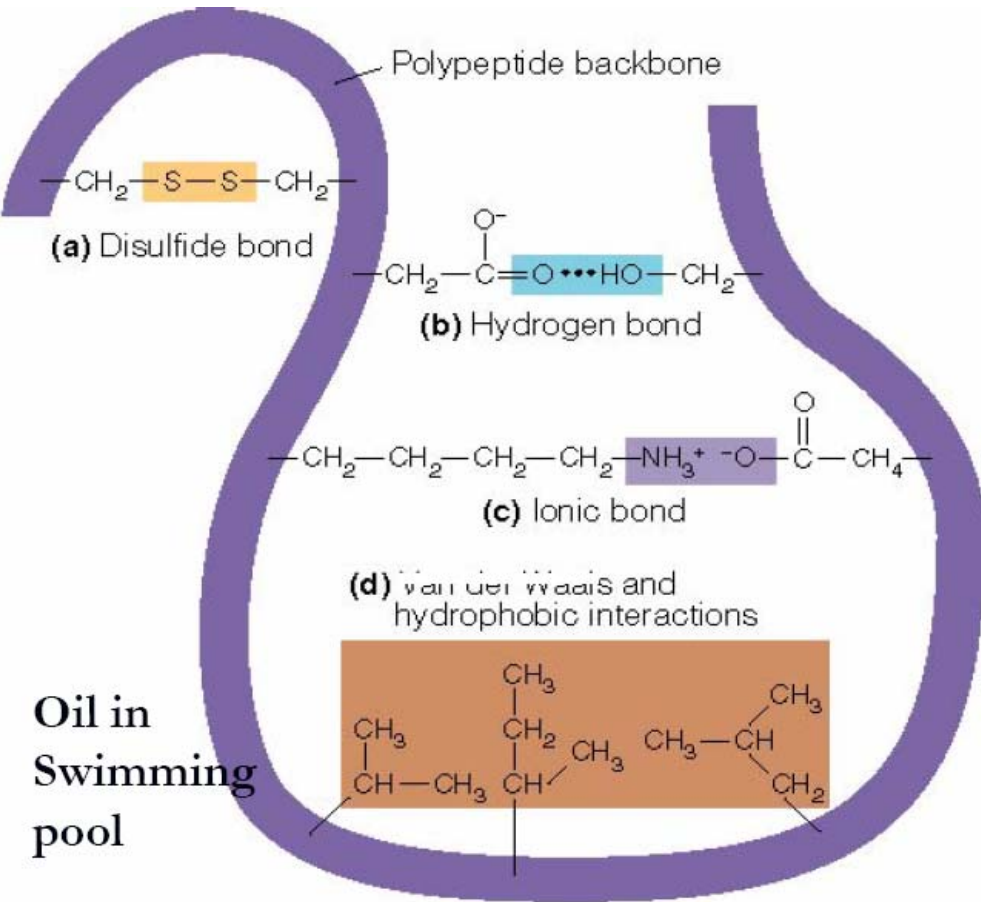
(a) Disulfide bond
(b) Hydrogen bond
(c) Electrostatic interaction
(d) van der Waals interaction
(e) Hydrophobic interaction
(f) Intrinsic properties
    (conformational preference)

Hydrophobicity:

the dominant force in protein folding (Dill, 1990).
The presence of water is important for this interaction.

Force scales

室溫   ATP 水解   共價鍵   葡萄糖氧化

0.1   1   10   100

二級鍵
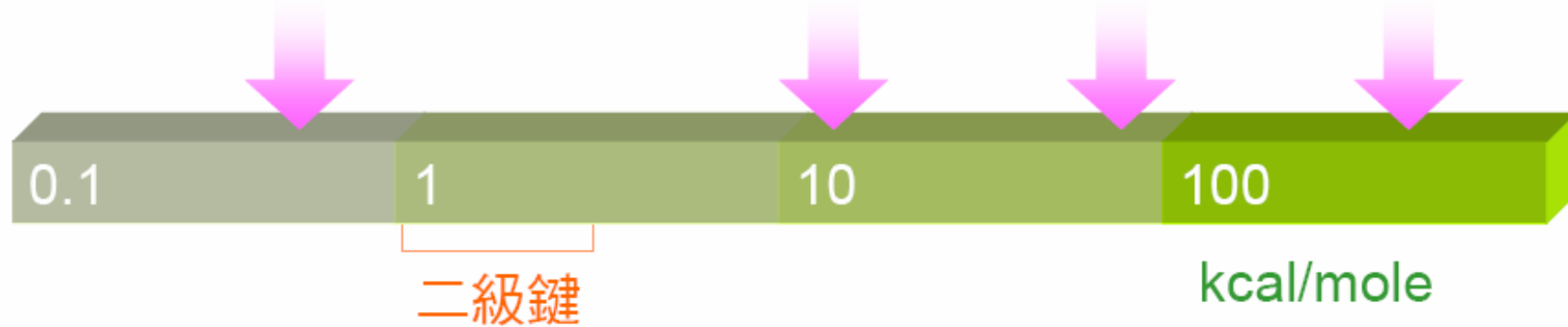
kcal/mole

凡得瓦爾力   0.1 kcal/mole

疏水鍵   1 kcal/mole

氫 鍵   1 kcal/mole

離子鍵   3 kcal/mole

共價鍵   90 kcal/mole

For room temperature 300K:
1kT =1.38 x 10^{-23} J/K· 300 K
    ≈ 4.1 x 10^{-21} J
    ≈ 2.5 x 10^{-19} eV
    ≈ 0.6 kcal / mole
    ≈ 2.5 kJ / mole

Models and Methods

Hierarchy of protein structure

Primary

D — V — E — G — E — A — L
T — N — V — V — L — T — A
M — R — G — I — V — K — V
G — P — A — K — V — A — A

Hydrophobic amino acids — Polar amino acids

Charged amino acids — Glycine

@Banana

Secondary

β sheets   α helix

Tertiary

Quaternary

Hierarchy of protein structure

(a) Primary structure

List of
Amino acids
From N terminus
To C terminus
Covalent bond
Connects amino
acids

(b) Secondary structure

Small loops: Helix or
B pleated Sheet
(only H bonding)

(c) Tertiary structure

Big loops

Disulfide bridge, all
Weak bonds stabilize
3 and 4th deg structure

subunits

(d) Quaternary structure

Model for protein folding:

(i) **Framework model** describes a step-wise mechanism to greatly narrow the conformational search. This involves a hierarchical assembly whereby local elements of secondary structure are formed according to the primary sequence, but independent from tertiary structure. These elements then diffuse until they collide, whereupon they coalesce to form the tertiary structure.

(ii) **Nucleation model** suggests that tertiary structure forms as an immediate consequence of the formation of secondary structure. Nucleation occurs through the formation of native secondary structure by only a few residues (e.g. a beta-turn, or the first turn of an alpha-helix), and structure propagates out from this nucleus.

(iii) **Hydrophobic collapse model** hypothesises that the native protein conformation forms by rearrangement of a compact collapsed structure. Hydrophobic collapse to form a molten globule therefore constitutes an early step in the folding pathway.

(iv) **Nucleation-condensation model** suggests that a diffuse folding nucleus is formed in (ii) and consolidated through the transition state, concomitant with tertiary structure formation.

(i), (ii), and (iv) suggest the formation of kinetic intermediates,
whereas (iii) does not. (A. R. Fersht. *Curr. Opin. Struc. Biol.*, 1997, **7**, 1, 3-9.)

Models for protein folding:

(a) Framework model
(b) Hydrophobic collapse model
(c) Nucleation–condensation mechanism

(a) Formation of elements of secondary structure → Assembly of secondary structure

(b) Hydrophobic collapse → Growth of secondary structure

(c) Nucleation–condensation → Hierarchical assembly

Folding nucleus

Folded conformation

Unfolded state

Proteins (2000) 41, 288-298
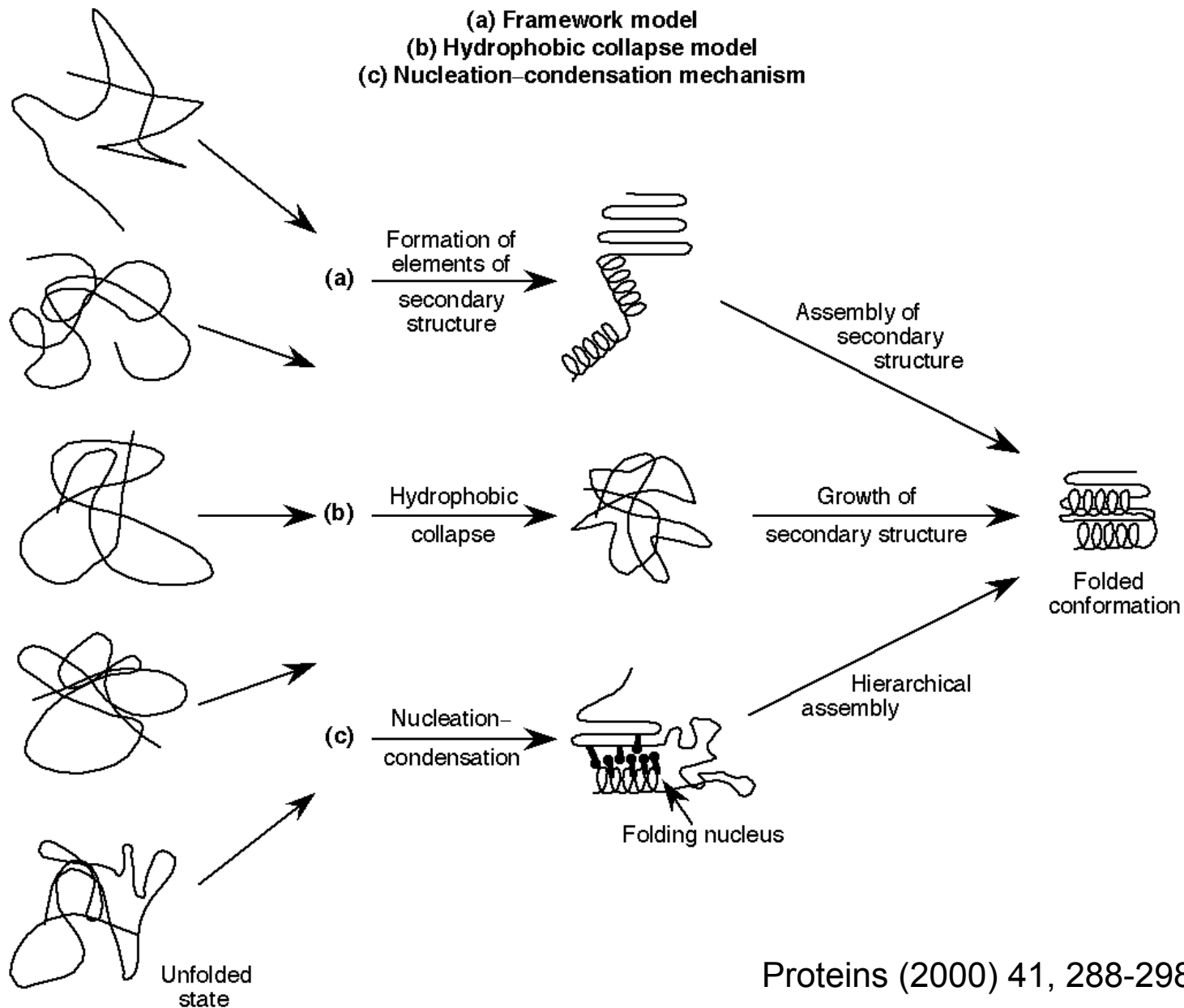
HP Lattice Models

• Put each residue in the polypeptide to a site of a 2D (or 3D) lattice.
A protein structure is represented as a path through lattice points.
Empty lattice cells represent water.

• The dominant interaction in protein folding is residue with water:
hydrophobic (厭水) and hydrophilic (親水), represented by H and P.
In the native conformation of a protein, hydrophobic residues tend to be
buried, hydrophilic residues tend to be exposed to water.

• Dividing residues into H and P groups, a polypeptide becomes a binary
sequence.
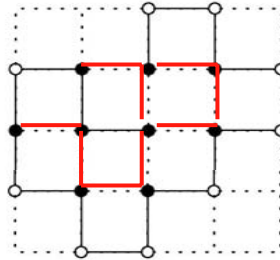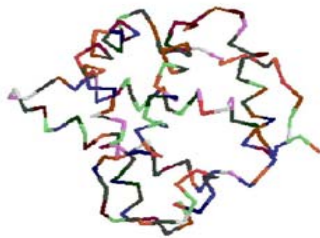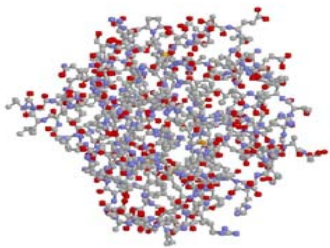
● hydrophobic amino acid

○ hydrophilic amino acid

— Covalent bond

— H-H contact

Goal: maximize the number of H-H contacts

Molecular Dynamics (MD)

Newton's equation of N atoms of mass m_i at r_i under force $F_i(t)$:

$$m_i \frac{\mathrm{d}^2 \mathbf{r}_i(t)}{\mathrm{d}t^2} = \mathbf{F}_i(t), \quad (i = 1, 2, \cdots, N).$$

$$\mathbf{r}_i(t + \Delta t) = 2\mathbf{r}_i(t) - \mathbf{r}_i(t - \Delta t) + \frac{1}{m_i}\mathbf{F}_i(t)\Delta t^2 + O(\Delta t^4) \qquad \text{(finite difference method)}$$

$$\mathbf{F}_i = -\nabla_i V(\mathbf{r}_1, \mathbf{r}_2, \cdots, \mathbf{r}_N),$$

Δt should be approximately 1/10 the time of the fastest motion in the system. The fastest motion in a protein is the stretching of light atoms, e.g., O-H, C-H, with periods around 10^{-14} sec. Thus Δt is usually taken as 1 fsec.

Huge number of water molecules are considered in MD simulations. Their non-bonded interactions (van der Waals, electrostatic interactions) increases in order of N^2 (N is the number of atoms).

Usually only a few tens of nanoseconds simulation is performed.

Energy function in Molecular Dynamics
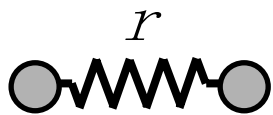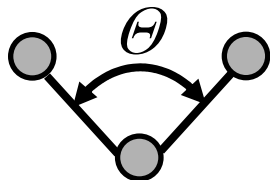
stretching term   **bending term**   **Dihedral term**
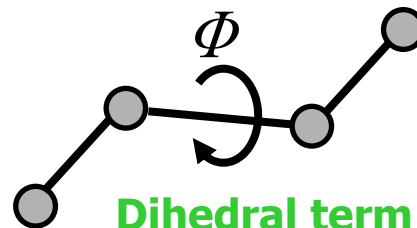
$$V_{\text{total}} = \sum_{\text{bonds}} K_b (r - r_0)^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} K_\phi [1 + \cos(n\phi - \gamma)]$$

$$+ \sum_{\substack{\text{Hbonds}}} \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}} \right) + \sum_{\substack{\text{van der Waals} \\ i,j \text{ pairs}}} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} \right) + \sum_{\substack{\text{electrostatic} \\ i,j \text{ pairs}}} \frac{q_i q_j}{\varepsilon r_{ij}}$$

The most time demanding part.

H-bonding term   **Van der Waals term**   **Electrostatic term**
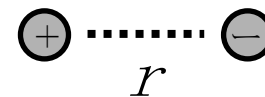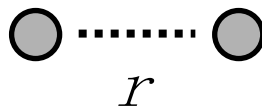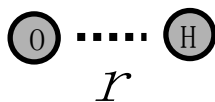
Time scales of MD and protein motions

Permeation of an ion through an ion channel & Elastic vibrations of proteins

α -Helix folding

β -Hairpin folding

Bond stretching

Protein folding

| 10⁻¹⁵ | 10⁻¹² | 10⁻⁹ | 10⁻⁶ | 10⁻³ | 10⁰ |

10^{-15} (fs)　　10^{-12} (ps)　　10^{-9} (ns)　　10^{-6} (μ s)　　10^{-3} (ms)　　10^{0} (s)

MD

Time
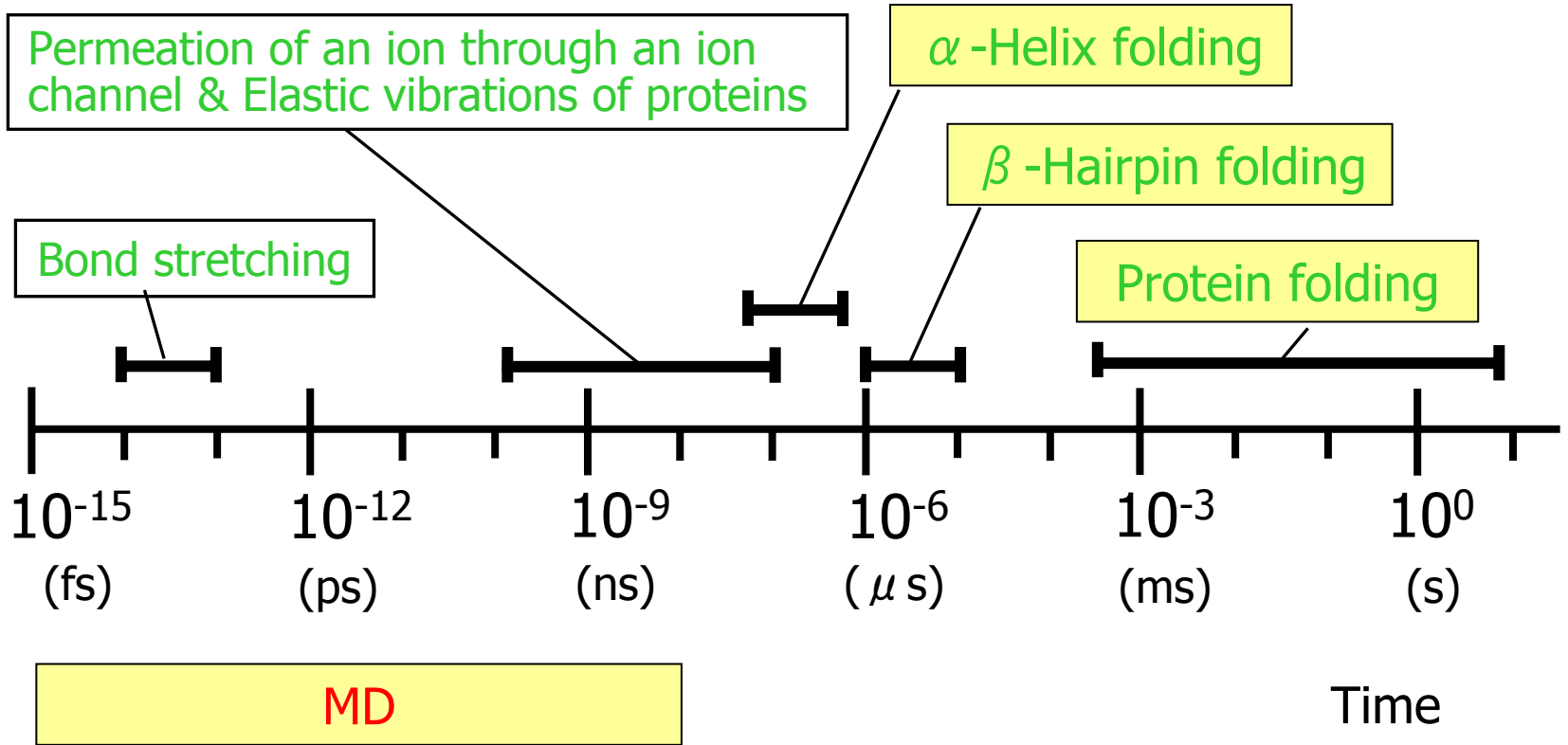
MD is hard to simulate a whole process of a protein folding.

Brownian Dynamics (BD)

The dynamic contributions of the solvent are incorporated as a dissipative random force.

Thus, water molecules are not treated explicitly.

MD
304 protein atoms
+ 7377 water atoms

With water molecules

BD
304 protein atoms

Without water molecules
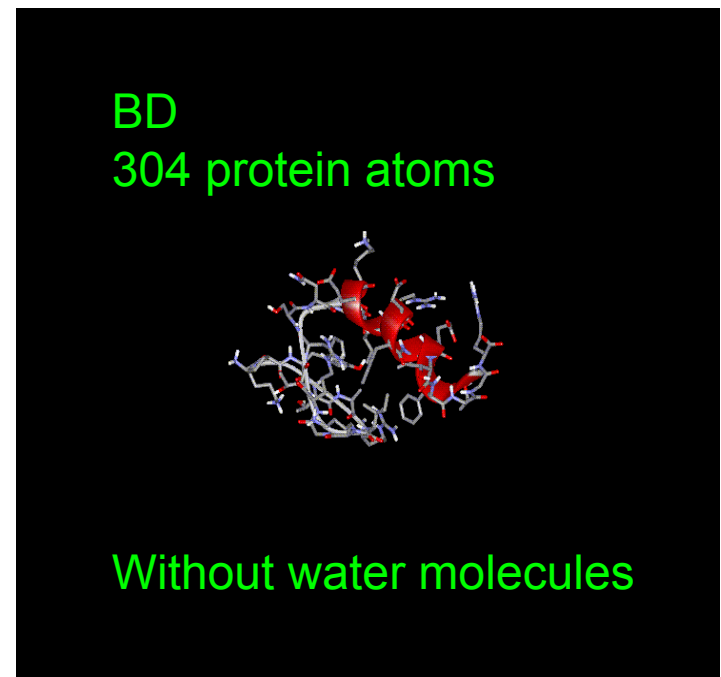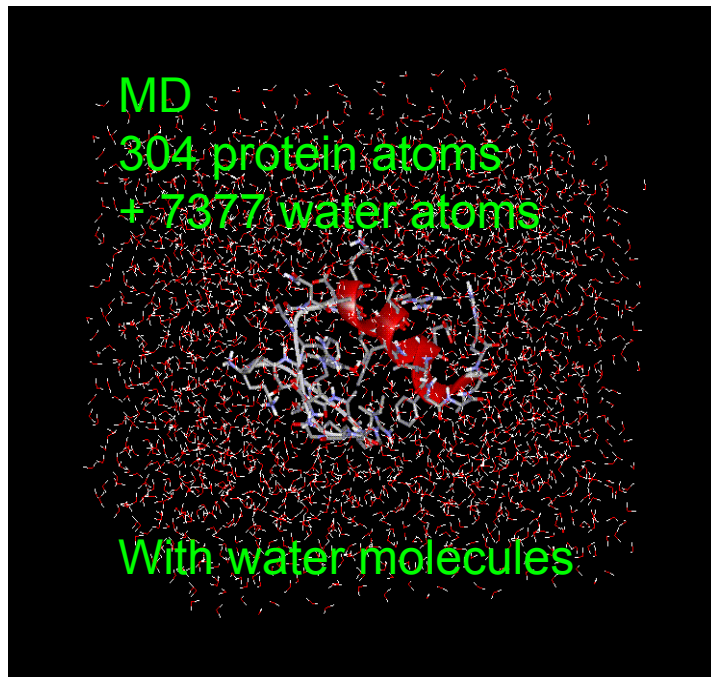
Brownian Dynamics

The Langevin equation can be expressed as

$$m_i \frac{d^2 \mathbf{r}_i}{dt^2} = -\zeta_i \frac{d\mathbf{r}_i}{dt} + \mathbf{F}_i + \mathbf{R}_i$$

with the viscosity η of water, the frictional coeff. $\zeta_i = 6\pi a_i \eta$ (determined by Stokes' law), a Stokes radius a_i of atom i, the systematic force F_i on atom i, a random force R_i on atom i with zero mean $<R_i(t)> = 0$ and a variance $<R_i(t)R_j(t)> = 6\zeta_i kT \delta_{ij}\delta(t)$ which accounts for the solvent effects.

In the overdamped limit, we have

$$\zeta_i \frac{d\mathbf{r}_i}{dt} = \mathbf{F}_i + \mathbf{R}_i$$

Integrating this equation yields the Brownian Dynamics:

$$\mathbf{r}_i(t + \Delta t) = \mathbf{r}_i(t) + \frac{\mathbf{F}_i(t)}{\zeta_i}\Delta t + \sqrt{\frac{2k_B T}{\zeta_i}\Delta t}\,\boldsymbol{\omega}_i$$

with a random noise vector ω_i obtained from Gaussian distribution.

Difficulties in Protein folding

- Very time-consuming
- Not clear if the energy function V used is precise enough.

General problems in biophysics:

Physics is an art of reduction which reduces systems of high degree of freedom to (effective) models with low degree of freedom, via symmetry or constrains.

However, symmetry and constrains are weak in biosystems.

Hard to truncate or reduce problems to effective simple models.

Example: potential V used in protein folding.

3. Mechanics
(membrane & filaments)
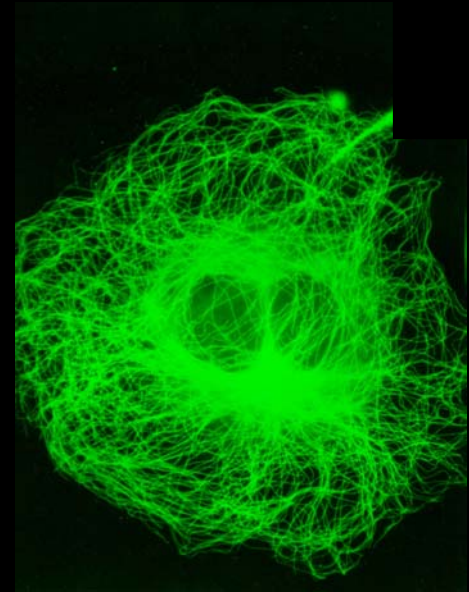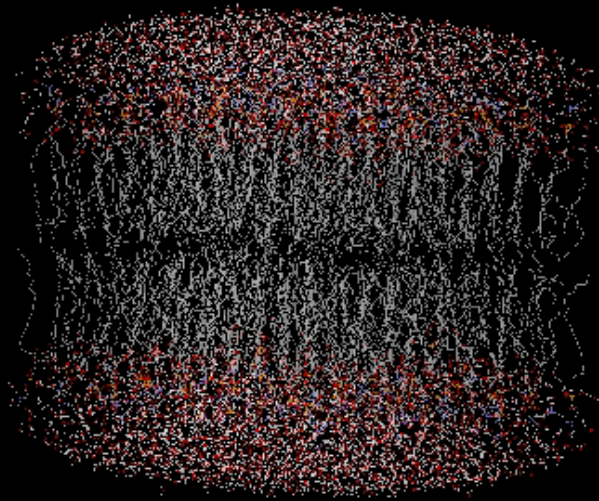
Cell membranes

Structure of a biological membrane

Bacterium
1000-1500 nm

Animal cell
10,000 nm

Vesicle

Golgi bodies

Mitochondrion

Nucleus

DNA

Ribosomes

Endoplasmic reticulum

Scale 4. A Cell
Magnified 10 thousand times
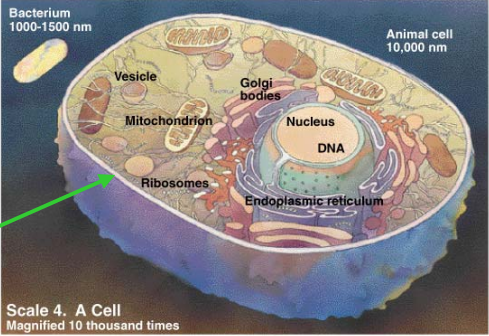
Inclusion
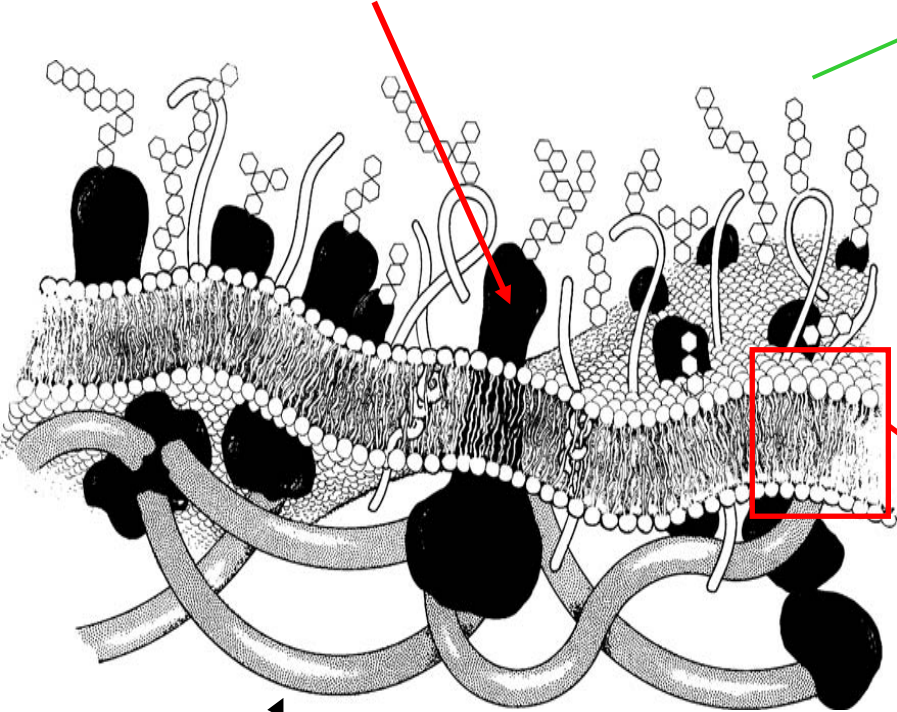
Filament (骨架)

Primary building blocks
- Lipid (脂質), or fat
- Protein (蛋白質)

lipid bilayers

~ 4nm
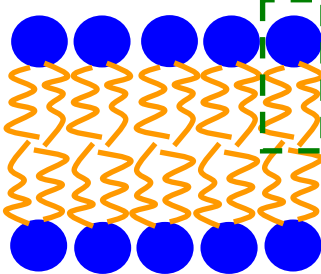
Lipids are in liquid crystalline (2D liquid) phase

Structure of an artificial membrane

Biological Membrane

Artificial Membrane
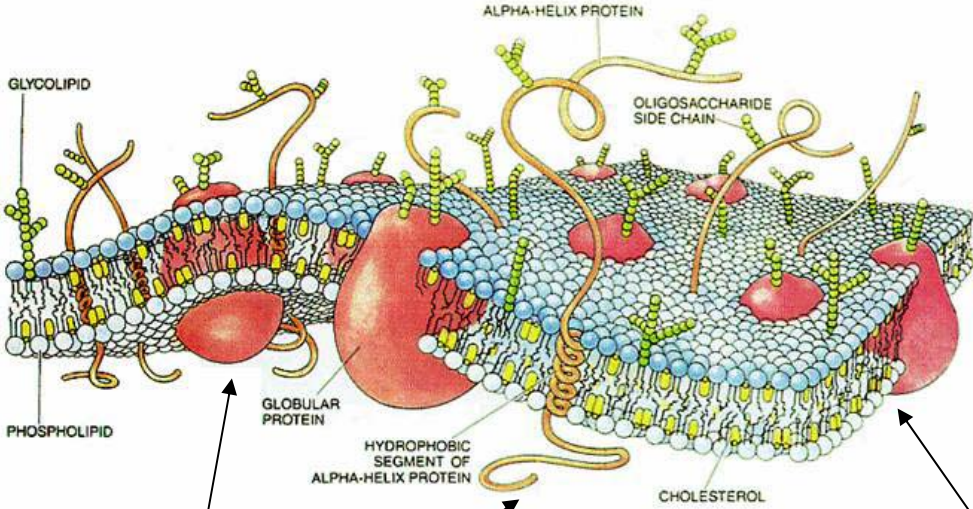
Inclusion

Lipid bilayer
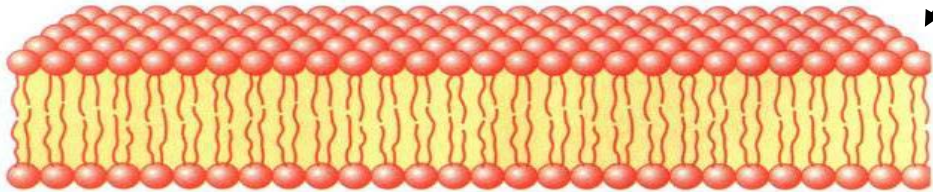
Lipid is an amphipathic molecules
(molecules containing both polar
and nonpolar parts).

水

Headgroup:
polar
hydrophilic 親水
(water-loving)

Tail (or acyl chain):
non-polar
Hydrophobic 厭水
(water-fearing)

$O-CH_2-CH_2-N(CH_3)_3$

$O-P=O$

CH_2

H_2C-C-C

$O=C$ CH_2 H_2C CH_2

H_2C CH_2 H_2C

H_2C CH_2 H_2C C_2H

H_2C CH_2 H_2C CH

H_2C CH_2 H_2C

H_2C CH_2 CH

H_2C CH_2 H_2C CH

H_2C CH_2 H_2C CH

H_2C CH_2 H_2C CH

H_2C CH

H_2C CH
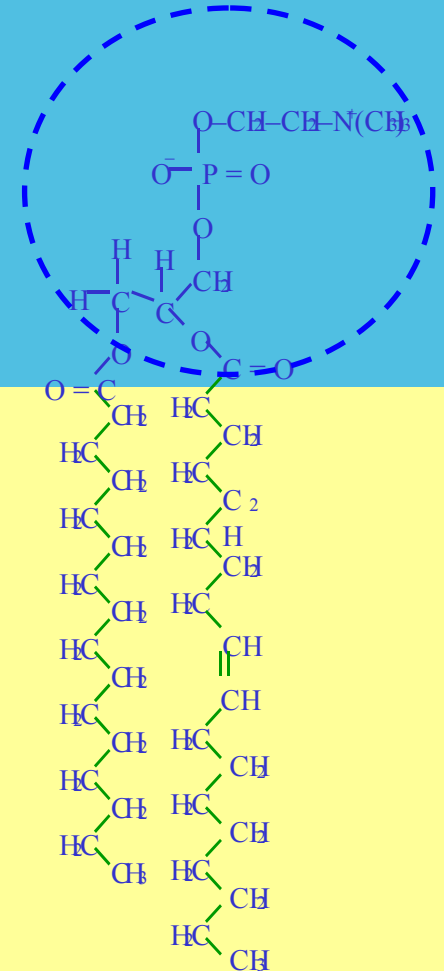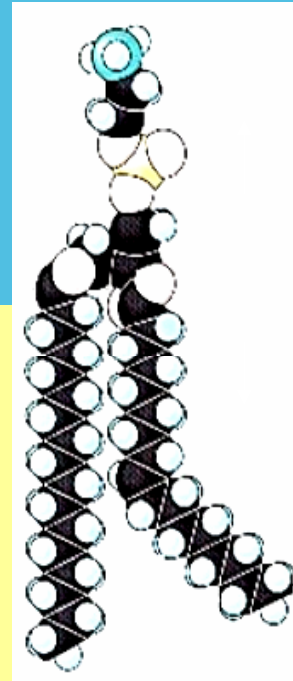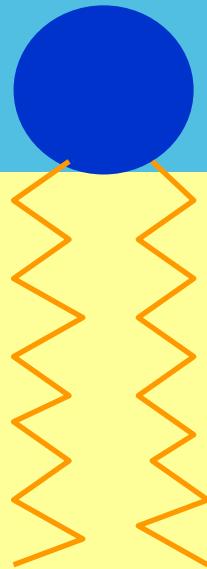
Different (microscopic) phases

(These microscopic 'phases' are differently defined from the assembly 'phases' in the previous page)

CRYSTAL
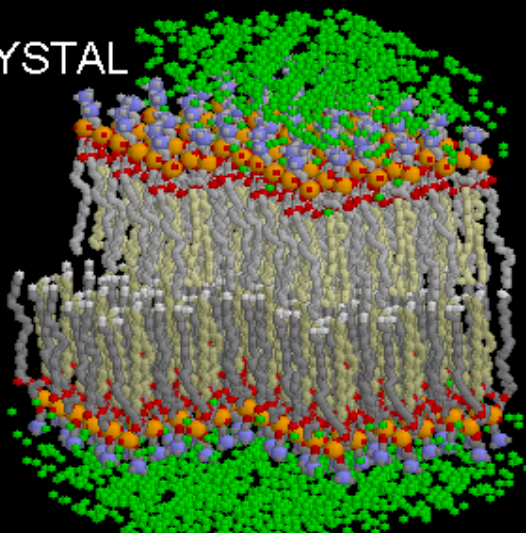
GEL
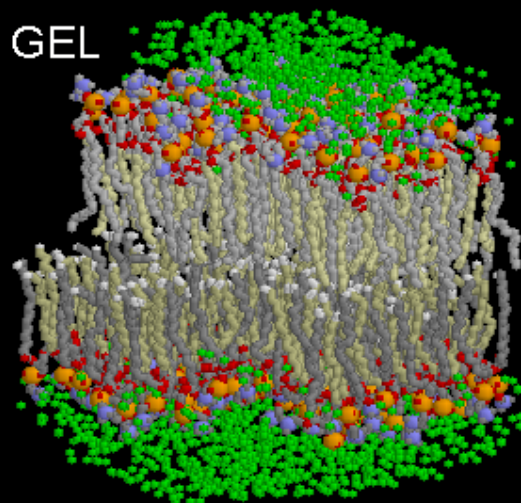
FLUID
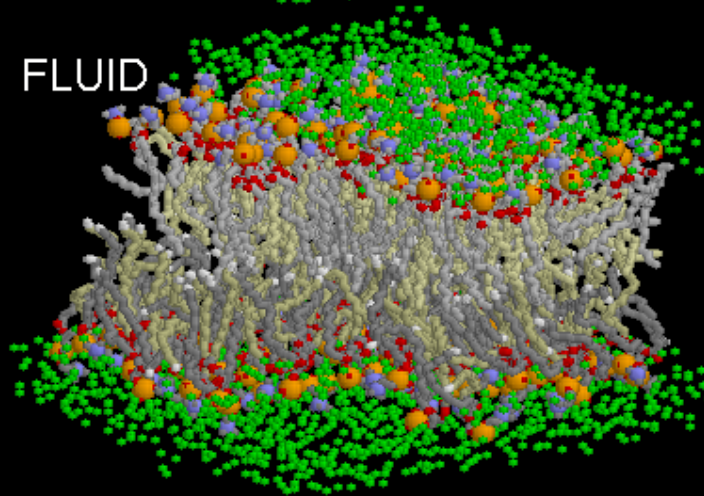
of Phosphatidyl Choline Bilayer

Carbon/Palmitic   Oleic
Nitrogen   Oxygen   Phosphorus
Water Oxygens

H Heller, M Schaefer, K Schulten,
J Phys Chem 97:8343, 1993.
RasMol Image by E Martz

Phase transition

gel → liquid crystal transition
lattice melting & chain melting

Crystal

Gel

Fluid

Eric Martz with
RasMol
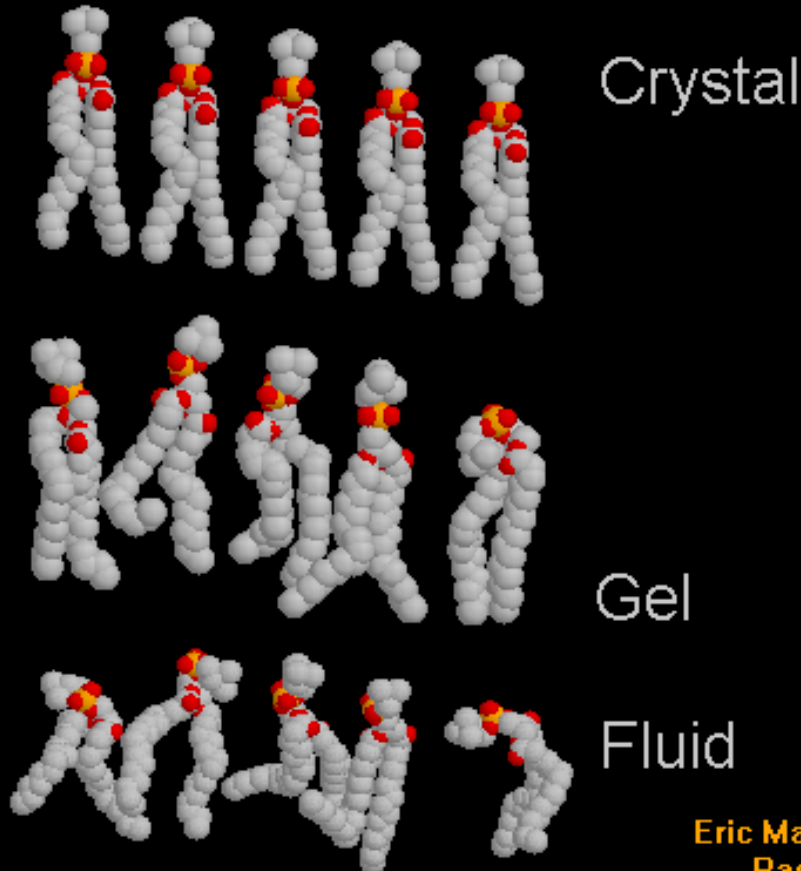
Gel phase
- solid-ordered (so) phase
- not important to cell function
- ordered (all-trans) chains
  arranged on a crystalline lattice

Liquid crystalline phase
liquid-disorder (ld) phase
- important to cell function
- disordered (many gauches)
  chains with random lateral
  arrangement.
- Lateral diffusion constant:
  $D \sim 10^{-12}$ m^2/sec

!!

Lipid rafts (浮冰)

AFM image

Liquid-ordered (lo) phase (like 冰山):
- Enriched in Cholesterol and sphingolipids
- Cholesterol(膽固醇)-associated phase
- lateral motion: slower than ld (half of ld's)
- highly ordered chain (only a few gauches)
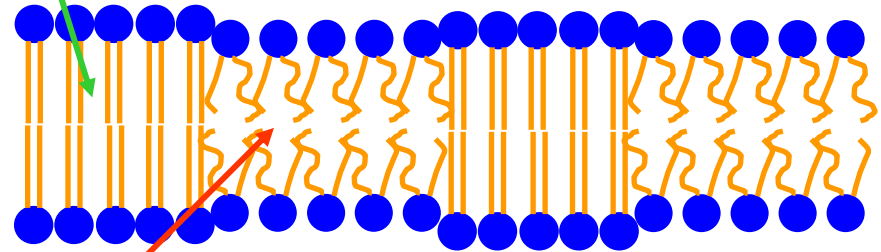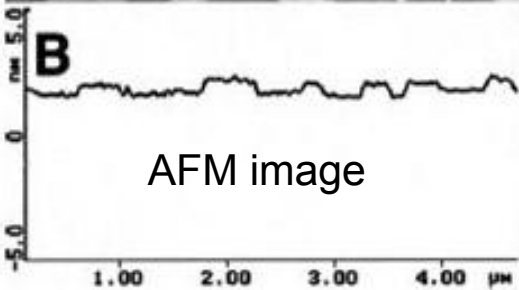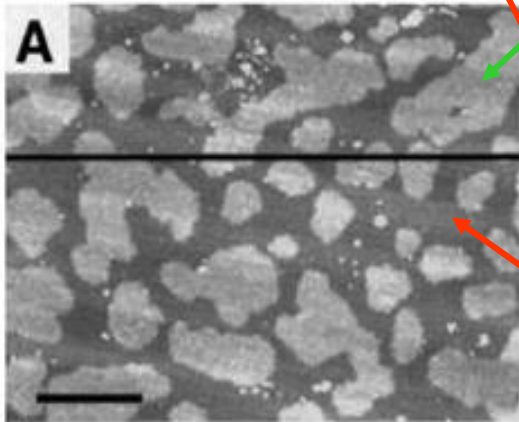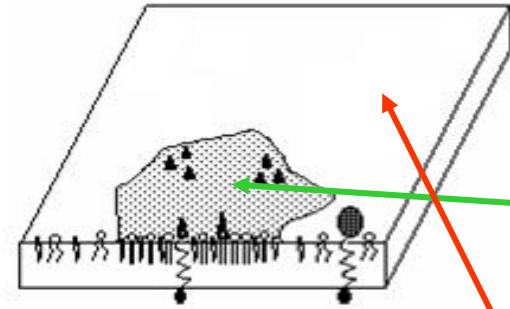
Liquid-disorder (ld) phase (like 海洋):
- disordered with many gauches chains
- with random lateral arrangement

Intrinsic curvature

Elastic free energy density

$$H_{el} = \int dA \left(\gamma + \frac{\kappa}{2} [c - c_0]^2 \right)$$

γ: surface energy ~ kT/(nm)²

κ: curvature elastic modulus ~ 10 kT

c : curvature of the membrane

c_0 : intrinsic curvature

Curvature-induced interaction

lipid

inclusion
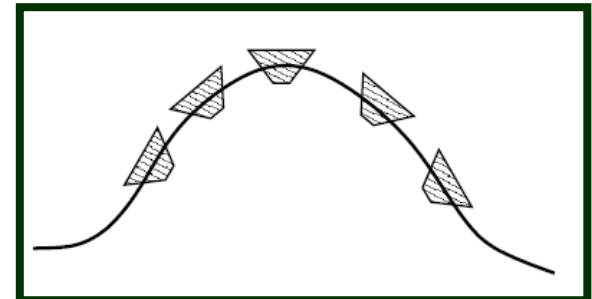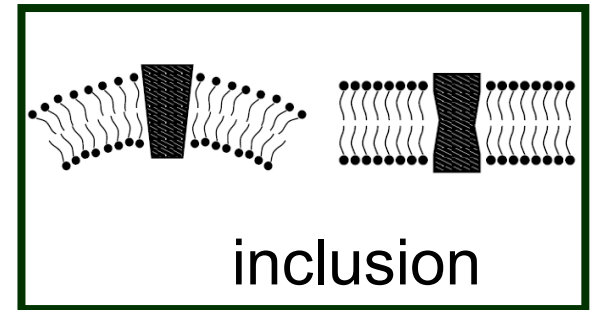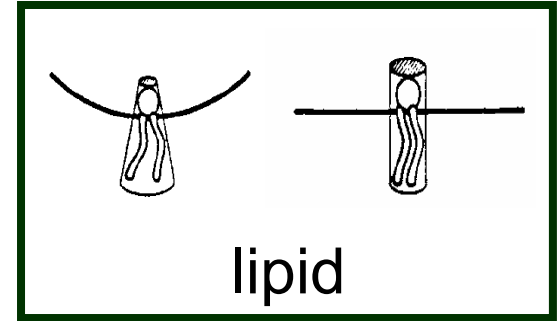
Different (macroscopic) phases

Micelle
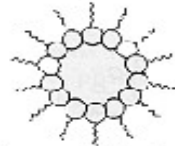
Inverse Micelle
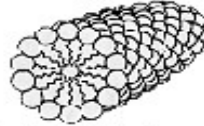
Prolate Micelle
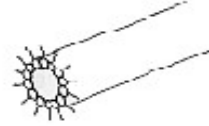
Inverse Prolae Micelle

Hexagonal phase
Normal

Hexagonal phase
Inverse

Lamellar vesicle
(multi- or uni-layer)
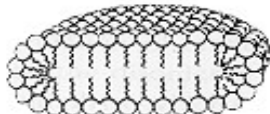
Oblate Micelle,
bilayered fragments
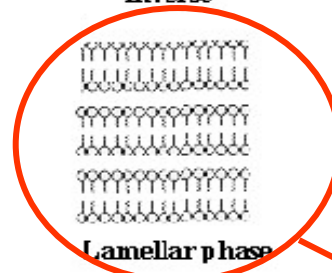
Lamellar phase
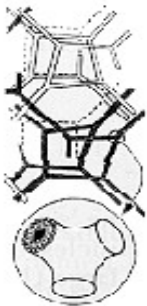
Cubic phases

Lamellar phase
important for
cell membranes.

The stalk-pore model for cell fusion (Example: viruses with cells37)
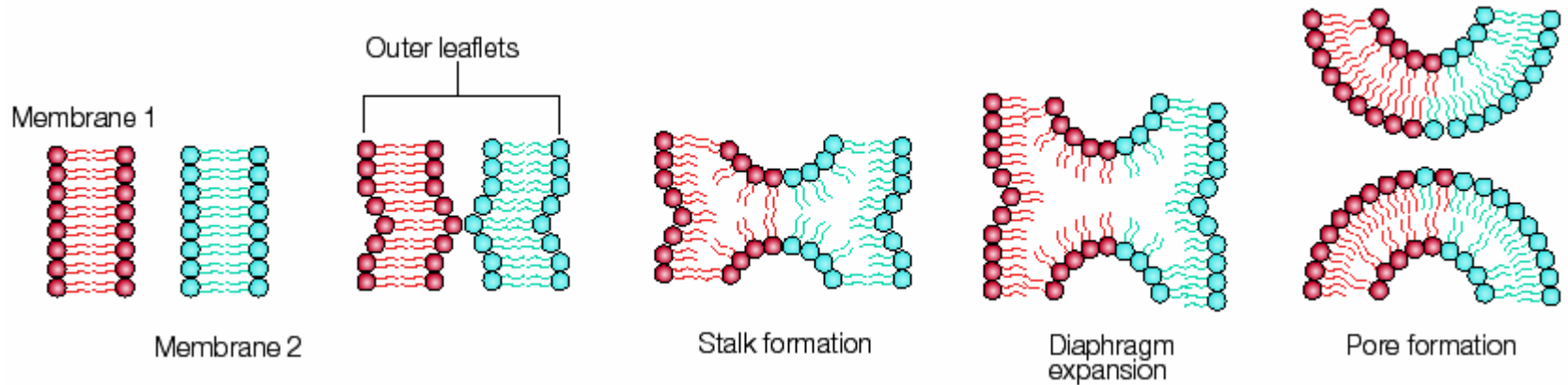
The polar heads of phospholipids in the outer leaflets of plasma membranes of two cells approach one another.

The energy required for this approach of negatively charged leaflets might be facilitated by receptor–ligand interactions (not shown).

The outer leaflets fuse to form a stalk-like structure, which expands to create a diaphragm.

Forces generated from the extension of the diaphragm promote fusion of the inner leaflets and the creation of a fusion pore.

Functions of filaments

The three polymer systems of a fibroblast cytoskeleton

A, the actin cytoskeleton
B, the microtubule cytoskeleton
C, the intermediate filament cytoskeleton
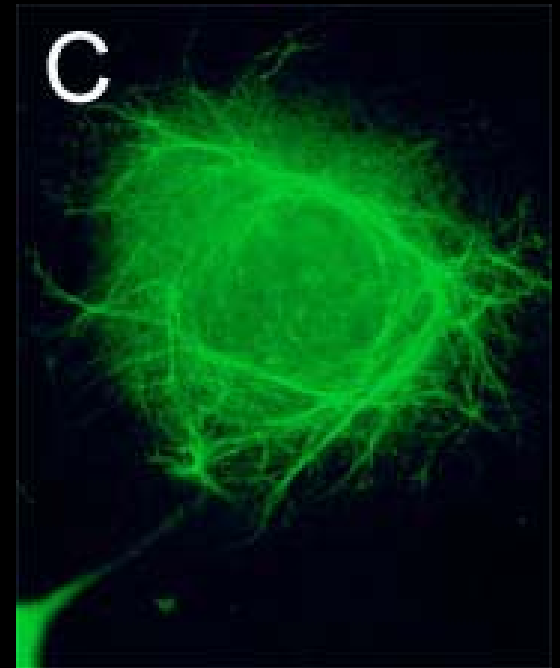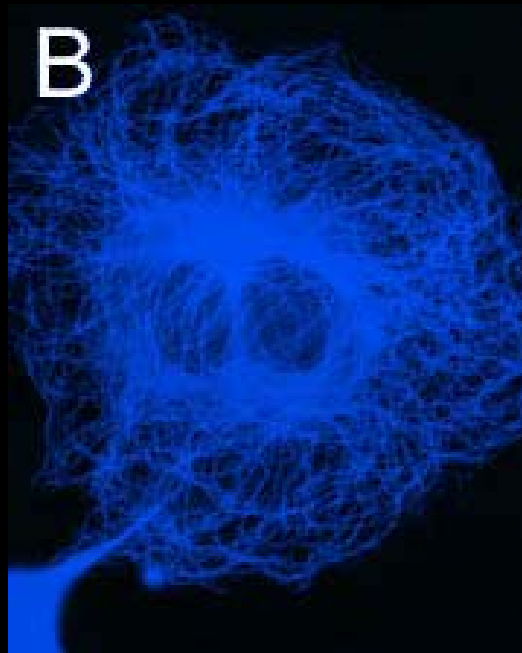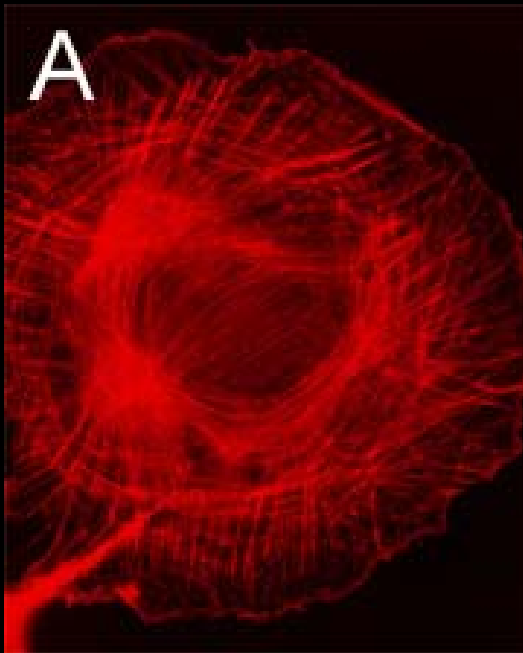
Different kinds of filaments

(1) Structure and Support (2) Intracellular Transport (3) Contractility and Motility (4) Spatial Organization

Actin filaments

Intermediate filaments

Microtubule

Motor protein

(a) Epithelial cell

Motor protein Intermediate filament Microtubule

(1) (2) (3)

Nerve cell (b)

Motor protein Actin filaments

Microtubule

(c) Dividing cell

○ = G-actin monomer

actin filament

8 nm

48 nm

10 nm

8 nm

α β

25 nm
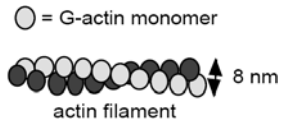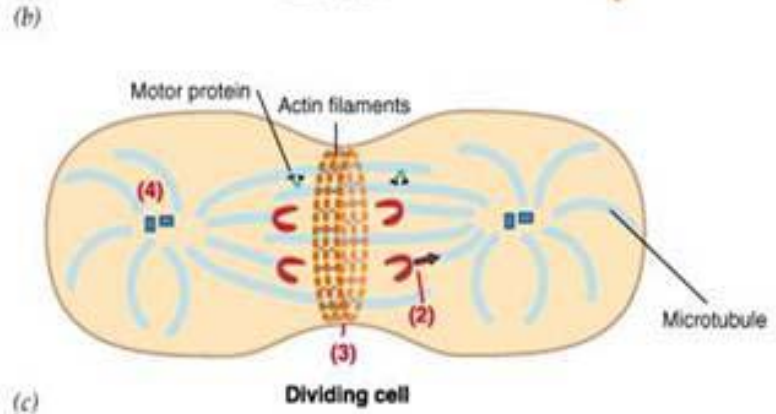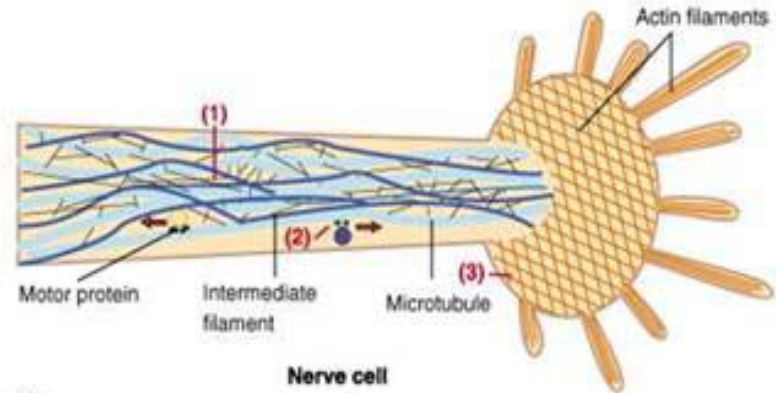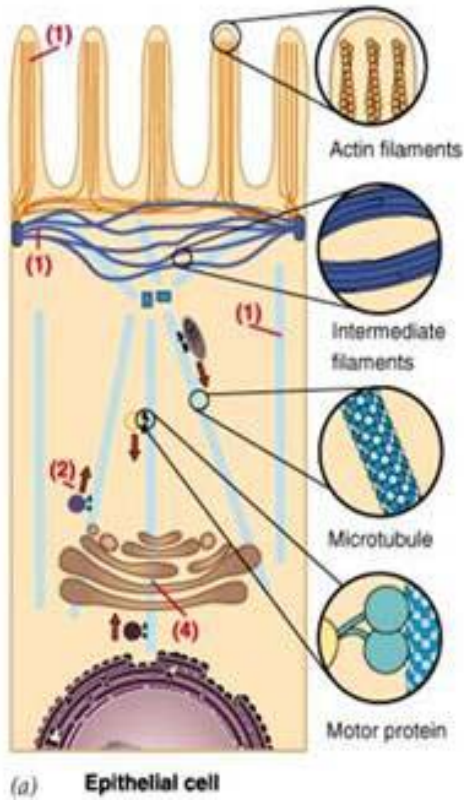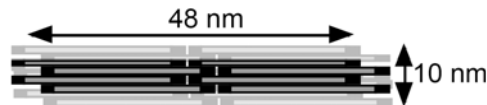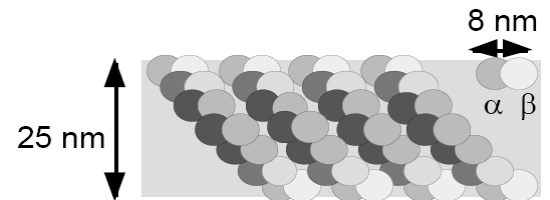
Actin   Actin   Microtubules

Actin – cell movement

- Fibroblasts（纖維母細胞）move along a substrate, adhering by the sheet-like lamellipodium（片足）direction of cell motion.

- The leading edge is actin-rich, with plus ends at the cell boundary.

EGFP-p20 ArpC4

cell body

thin lamellipodium

actin filaments

direction of cell motion

http://cellix.imolbio.oeaw.ac.at/Videotour/video_tour_5.html
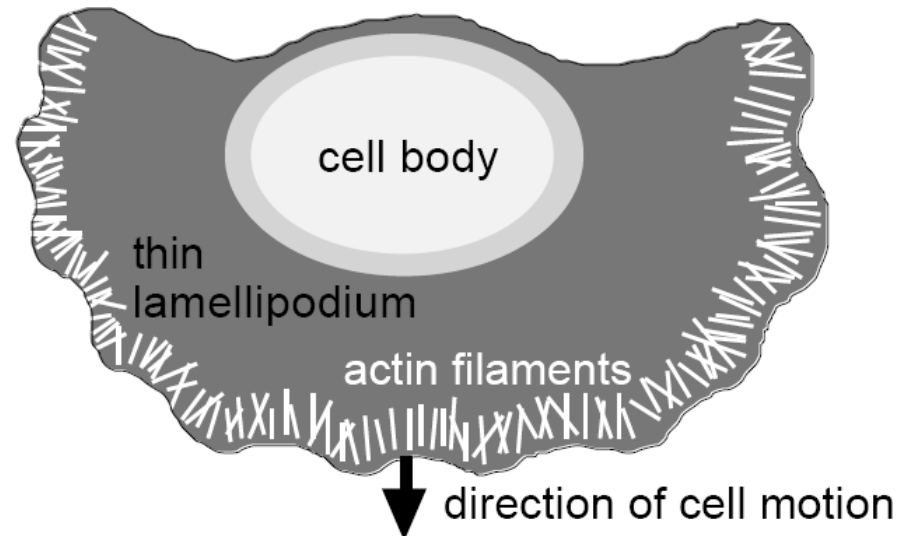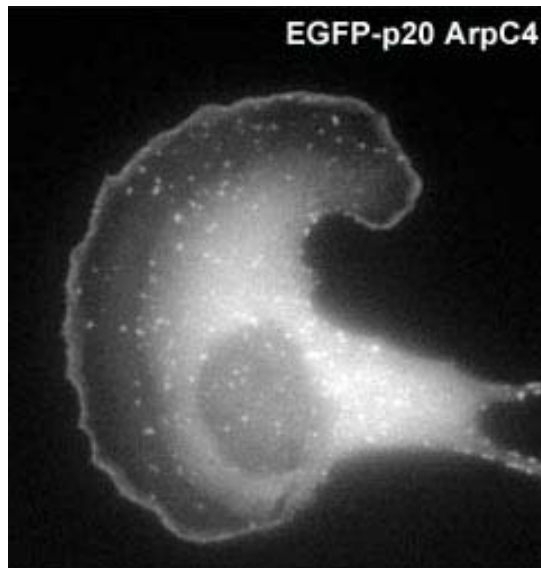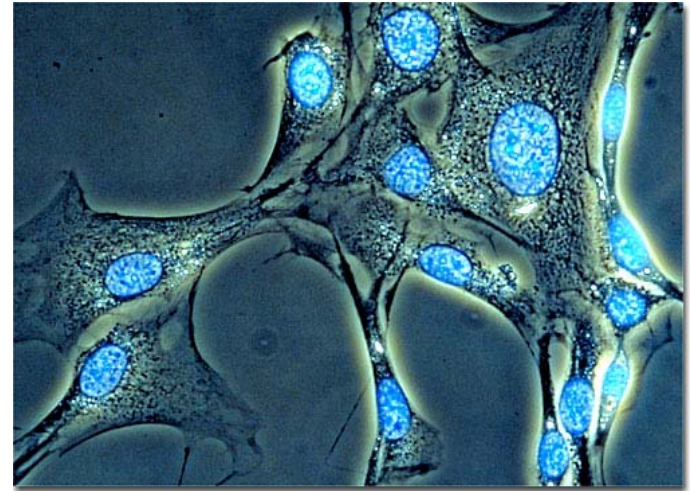
Actin – cell movement

In keratocytes (角膜細胞), actin filaments move back through the cell body at roughly the speed of the cell, such that a given position on a filament remains roughly stationary with respect to the substrate (Theriot et al, 1991).

Compression of an actin-myosin network into a bundle at the lamellipodial of a fish keratocyte is coupled to forward translocation.
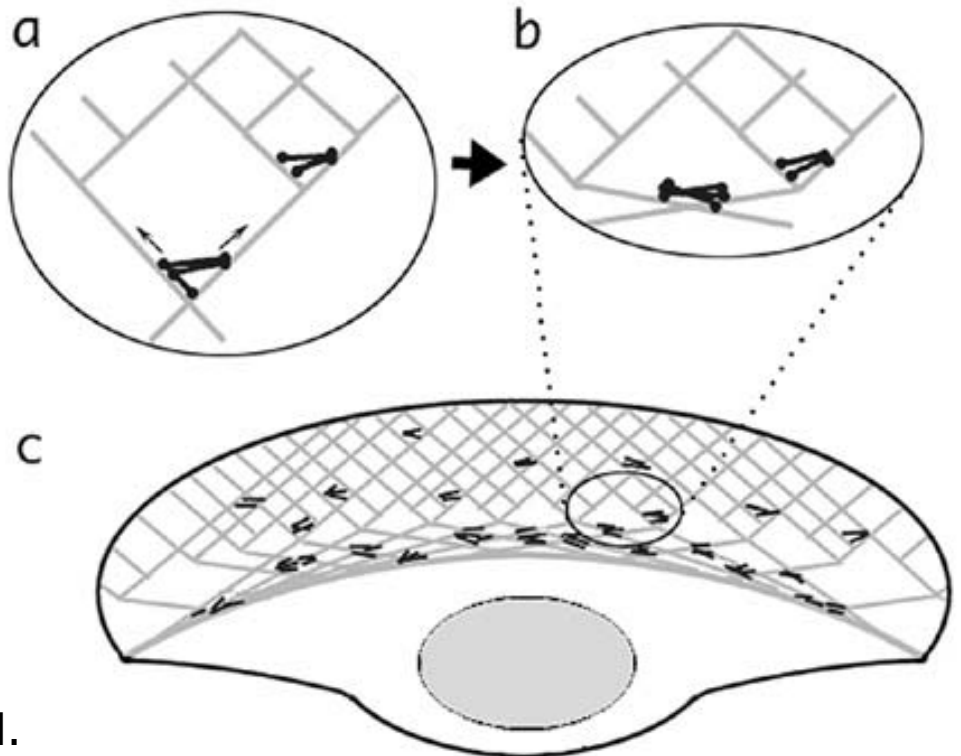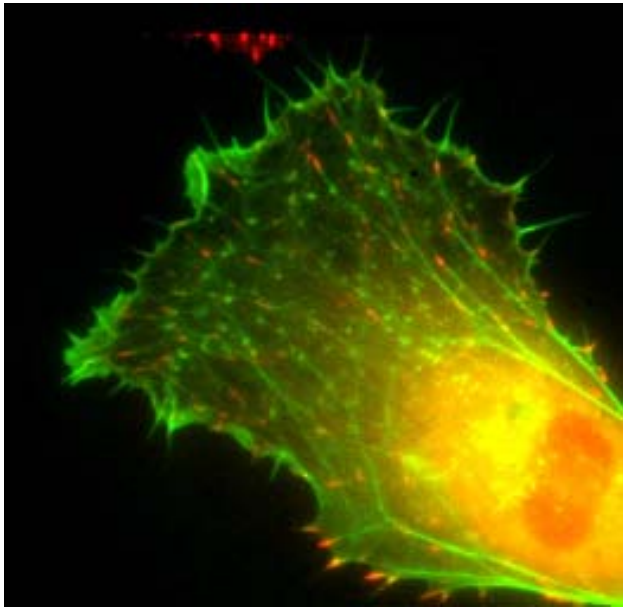
Adhesion points are colored red.

Actin - track of motor protein

Myosins move on actin (to plus end)

- Actin and myosin may be organized into highly cooperative structures in our muscles.

- Thick filaments are bundles of more than 100 myosins.

- Walking towards the plus end of the actin, mysosin pulls the minus ends of the filament towards one another, contracting the muscle along the horizontal direction.
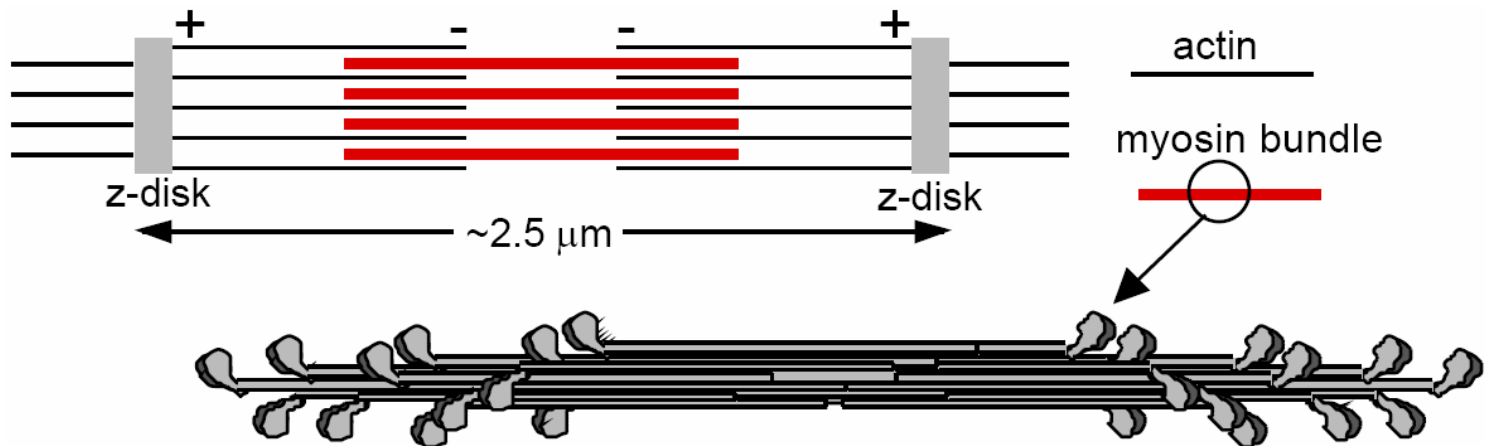
Microtubules – highways in cells

Cells need a mechanism for directed transport of materials from production to consumption site.

NOT diffusion via $<x^2> = 2Dt$ with $D = k_BT / 6\pi\eta R$.

For 10 nm proteins, $D = 10^{-10}$ m²/s in water and 10^{-14} m²/s in lipids.

Taking $D = 10^{-12}$ m²/s,

if $<x^2> = 1$ μm²
    → t ~ 1 second (ok for local transport)

if $<x^2> = 1$ m²
    → t ~ 10^{12} secs = 30,000 years
    (hopeless for long transport along neurons)

At speeds up to 2-5 μm/s, a chemical cargo can be transported in 2-6 days from a production site in the brain to the end of a neuron a meter away.

Such cargo is transported on microtubules in a cell.

Motors on microtubules

- Hundreds of microtubules radiate from the centrosome of most animal cells.

- By probing the cell surface, the microtubules can push the nucleation region towards the center of the cell.

- Because they are relatively stiff, microtubules provide highways for transport in the cell.

dynein
+ → −

kinesin
− → +
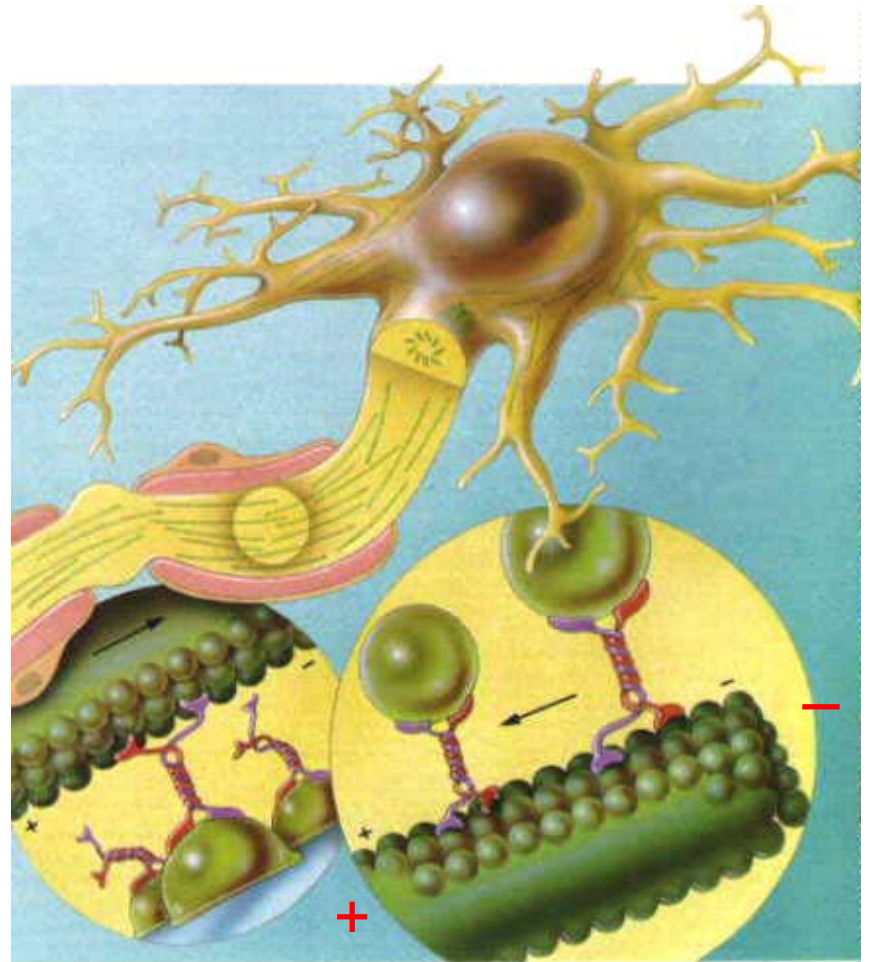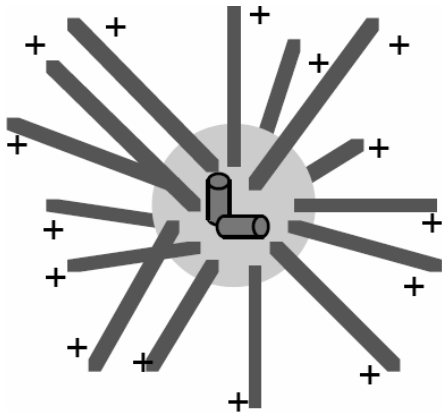
http://cellbio.utmb.edu/cellbio/microtubule_structure.htm#Formation

Microtubules in mitosis

Different microtubules are involved in separating chromosomes during cell division, including

(i) Polar microtubules,
(ii) Chromosomal microtubules,
(iii) astral microtubules.
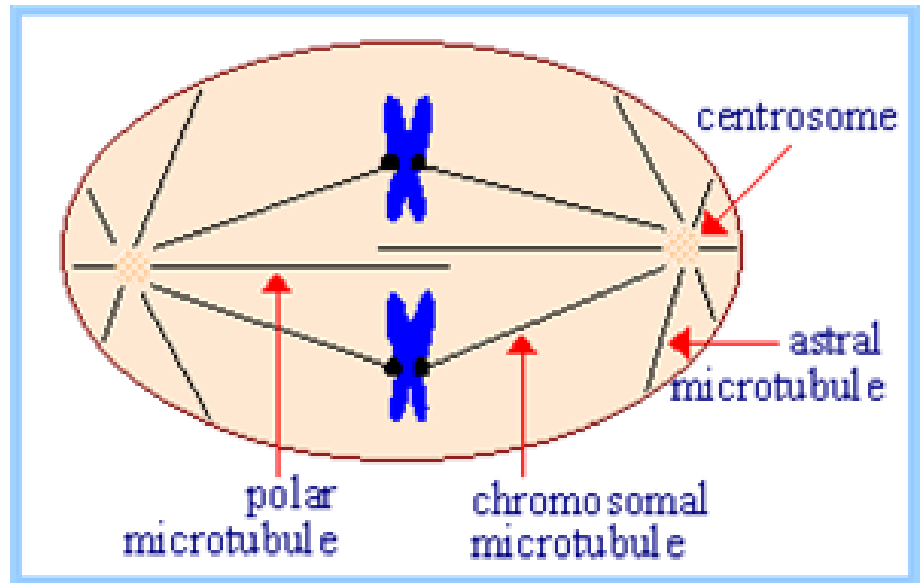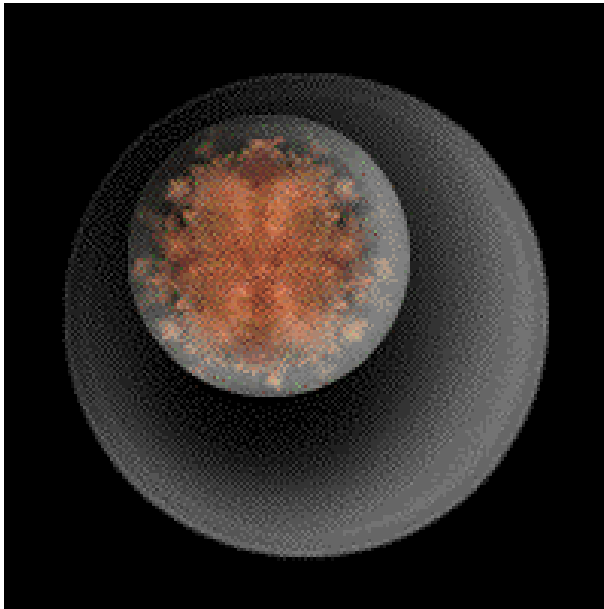
Animation: http://www.virtualscience.com/gallery_animations.htm

1D filament formation/mechanics

Structure of microtubules

Basic unit: α, β-tubulin (球形分子) heterodimer.

Each tubulin is a G-actin (globular actin).

A chain of these tubulins is called a F-actin (fibrous actin).

The heterodimer does not come apart, once formed.
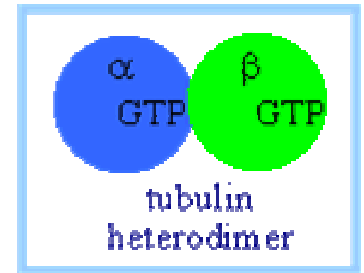
α-tubulin has a bound molecule of GTP,
  that does not hydrolyze.

β-tubulin may have bound GTP or GDP.
  Under certain conditions β-tubulin
  can hydrolyze its bound GTP to
  GDP plus Pi, release the Pi, and
  exchange the GDP for GTP.
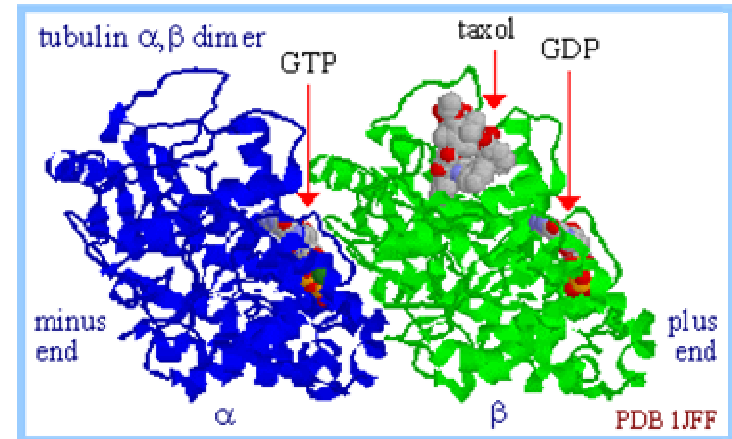
Microtubules

Protofilaments are formed by joining the α and β tubulins alternately.

A microtubule is a hollow cylinder about 25 nm in diameter, which is formed by putting 13 protofilaments to a helical cylinder wall.

GTP must be bound to both α and β subunits for a tubulin heterodimer to associate with other heterodimers to form a protofilament or microtubule.
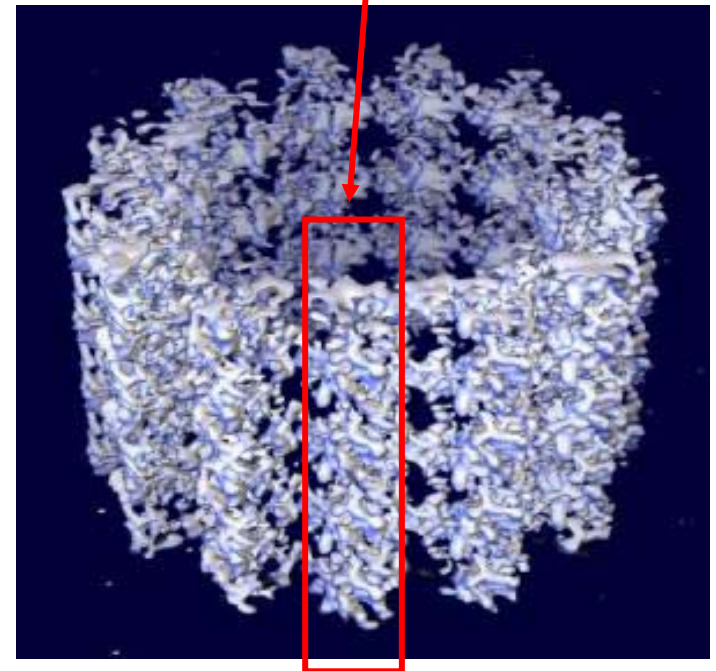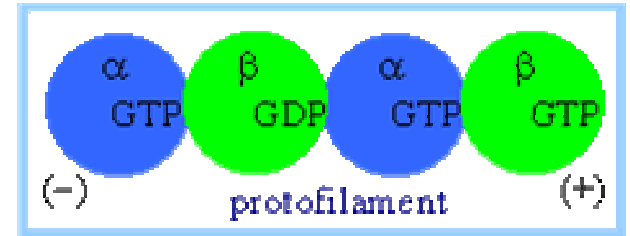
Polymerization of microtubules

Subunit addition brings β-tubulin that was exposed at the plus end into contact with α-tubulin.

This promotes hydrolysis of GTP bound to the now interior β-tubulin.

Pi dissociates, but β-tubulin within a microtubule cannot exchange its bound GDP for GTP.

The GTP on α-tubulin does not hydrolyze.

tubulin heterodimer

minus end - slow addition

+

−

plus end - rapid addition

α-tubulin subunit faces towards the plus end of the filament (Oakley; 1994)
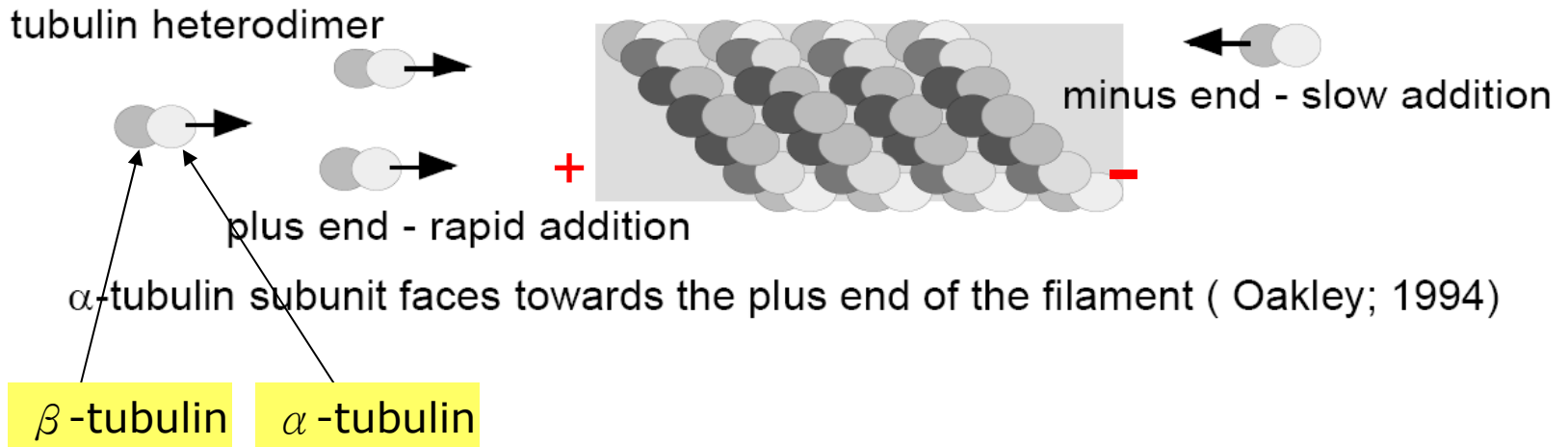
β-tubulin α-tubulin

Polymerization of actin and tubulin

(I) Equivalent filament ends:

    n = number of monomers in a single filament;
    t = time;
    [M] = concentration of free monomer in solution.
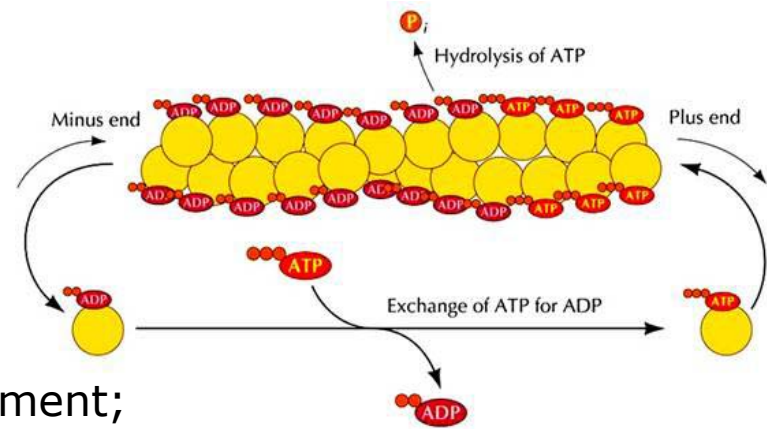
Capture rate of monomers by a single filament is proportional to the number of monomers available for capture

$$dn/dt = +k_{on} [M] \qquad \text{(capture)} \qquad\qquad (1)$$

k_{on} = capture rate constant, with units of [concentration $\cdot$ time]$^{-1}$

Release rate does not depend on [M]

$$dn/dt = -k_{off} \qquad\qquad \text{(release)} \qquad\qquad (2)$$

k_{off} has units of [time]$^{-1}$

The net change of filament size is

$$dn/dt = +k_{on} [M] - k_{off} \qquad\qquad (3)$$

Obtain k_{on} and k_{off} from a plot of dn /dt against [M]

dn /dt < 0 → filament is shrinking

Minimum concentration for filament growth (often called the critical concentration) occurs at dn /dt = 0, where

$$[M]_c = k_{off} / k_{on.}$$
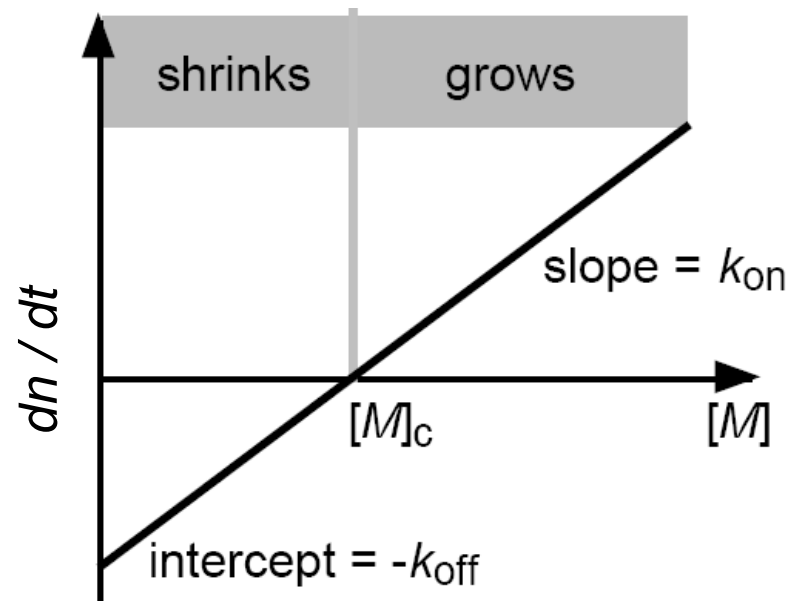
(II) Chemically inequivalent filament ends with different rate constants:

Treadmilling (Wegner, 1976)

Example: 2 x 2 inequivalent rate constants (+/− refer to the filament end):

$$dn^+/dt = k_{on}^+ [M] - k_{off}^+ \qquad (5a)$$
$$dn^-/dt = k_{on}^- [M] - k_{off}^- \qquad (5b)$$

Take [M] to be the concentration of free triphosphate proteins.

Probably different critical concentration at each end

$$[M]_c^+ = k_{off}^+ / k_{on}^+$$
$$[M]_c^- = k_{off}^- / k_{on}^- \qquad (6)$$

Using data above for actin:

$$[M]_{ss} = 0.17 \ \mu M \quad \text{and } dn^+/dt = 0.6$$

Direct measure of $[M]_{ss}$ under not
dissimilar solution conditions yields
0.16 μM (Wegner, 1982).
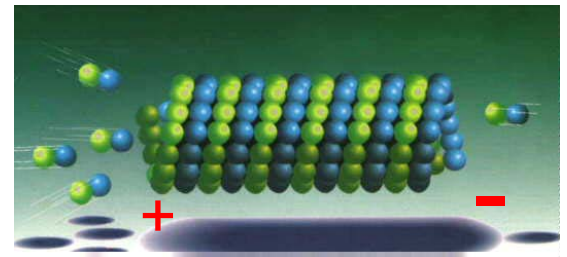
The filament doesn't change length,

(I) if

$$[M]_c^+ = [M]_c^- \text{ (as in tubulin):}$$

both ends grow or both ends shrink simultaneously.

(II) if

$$dn^+ /dt = - dn^- /dt :$$

one end of the filament grows at the same rate as the other shrinks.

This occurs at steady state value $[M]_{ss}$

$$[M]_{ss} = (k_{off}^+ + k_{off}^-) / (k_{on}^+ + k_{on}^-)$$
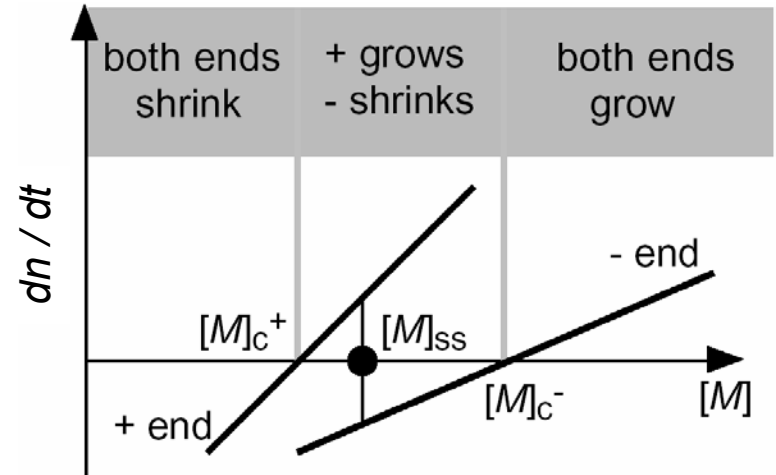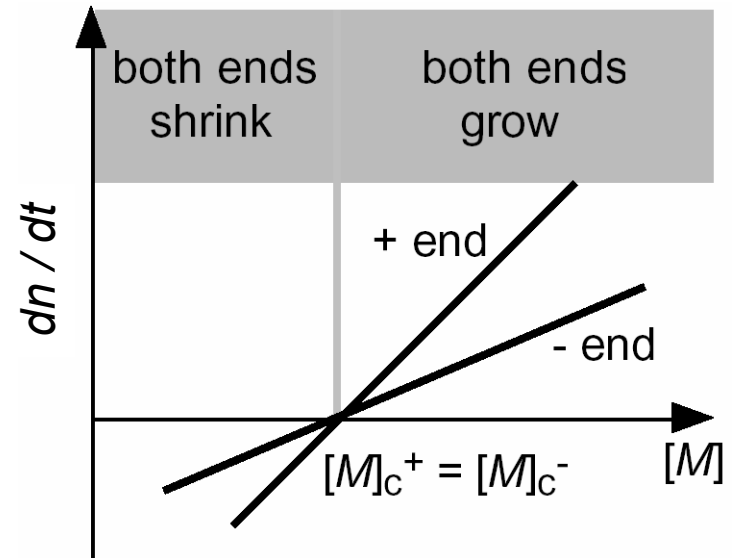
Bending energy of a thin polymer rod   (Kratky-Porod model)

A straight rod of length L_c with uniform density and cross section, bent into an arc. The total energy becomes

$$E_{bend} = (k_f/2) \int_0^{Lc} (\partial \mathbf{t}/\partial s)^2 \, ds,$$

where k_f = flexural rigidity; units of [energy] · [length]

$\mathbf{t}(s)$ = unit tangent vector at point $\mathbf{r}(s)$

s = arc length

$\mathbf{r}(s)$ = position of point on curve

$\mathbf{t}(s)$ θ

Δr_x

θ Δr_y

Δs
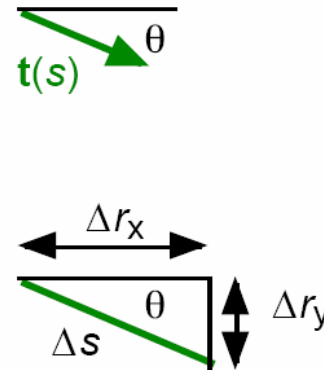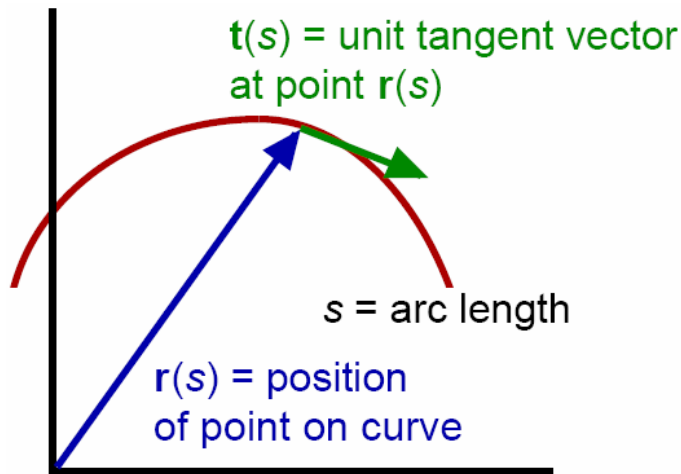
Thermal fluctuations and persistence length

At T > 0, shape of a filament can fluctuate:

The entropic force is the main driving in such a small filament.

increasing energy ⟶

Arc s of a circle with radius R_c: $\theta = s / R_c$ has an energy:

$$E_{arc} = k_f\, s/2R_c^2 = k_f\, \theta^2 / 2s$$
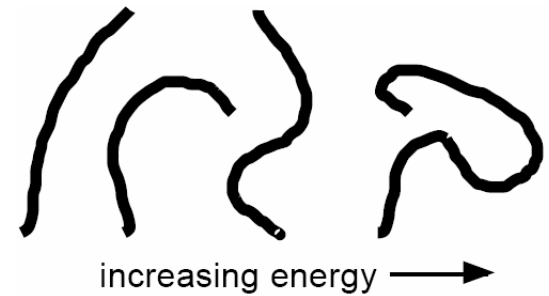
Persistence length ξ_p decreases with increasing temperature

2 dim: $<E_{arc}> = k_B T /2$
$<\theta^2> = s / \beta k_f.$
$\xi_p = 2 \beta k_f.$

3 dim $<E_{arc}> = k_B T$
$<\theta^2> = 2s / \beta k_f.$
$\xi_p = \beta k_f.$
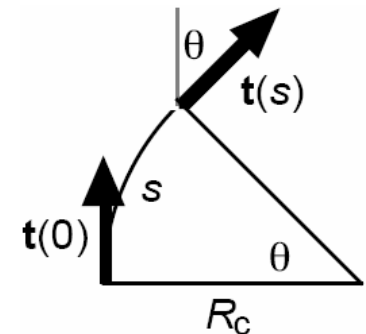
Sizes of flexible polymer chains

Radius of gyration of N particles is $R_g = \Sigma^N_{k=1} (r_k - r_m)^2/N$, where r_k is position of the k-th particle and r_m is the mean position of the particles.

Summary of scaling exponents for $<R_g^2>^{1/2} \sim N^\nu$

Configuration	d = 2	d = 3	d = 4
Ideal chains	1/2	1/2	1/2
Self-avoiding chains	3/4	0.59	1/2
Branched polymers	0.64	1/2	
Collapsed chains	1/2	1/3	1/4
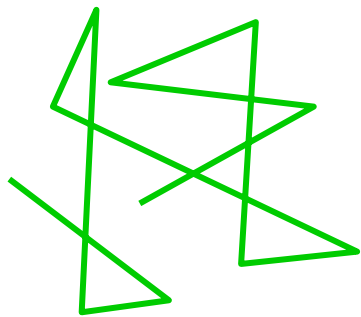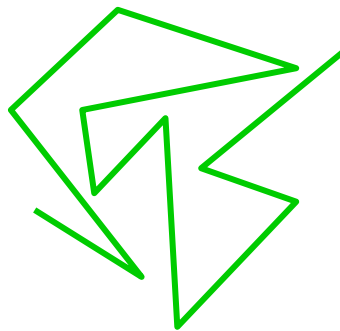
Ideal (random)   Self-avoiding   Branched   Callapsed
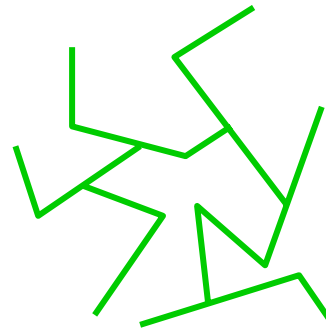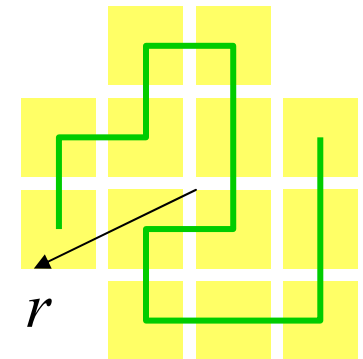
2D filament network

The explosion pressure on cells

(a) In a hot air balloon, a thin membrane confines the gas within the balloon, and an external network provides mechanical attachment points and may aid in maintaining the balloon's shape.
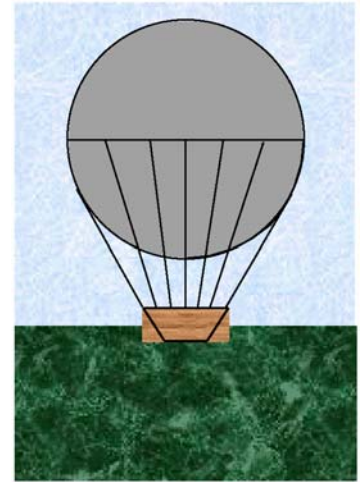
(b) A two-dimensional network of spectrin is attached to the red blood cell membrane to provide shear resistance (Liu, Derick and Palek, 1987).

The interior pressure of some cells, such as many varieties of bacteria, may be much higher than their surroundings. Thus, the engineering problem facing a bacterium is one of explosion like balloon rather than collapse.
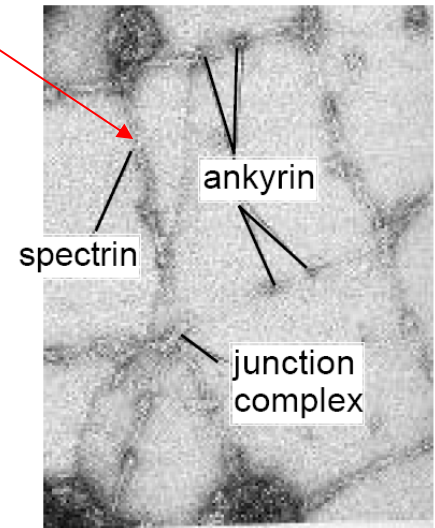
(from Byers and Branton, 1985)

Deformation energy in 2D network

The strain tensor u_{ij}, related to the rate of change of **u** with position **x** by

$$u_{ij} = 1/2[\ \partial u_i / \partial x_j + \partial u_j / \partial x_i + \sum_k (\partial u_k / \partial x_i)(\partial u_k / \partial x_j)],$$

$$\approx 1/2\ [\partial u_i / \partial x_j + \partial u_j / \partial x_i].\qquad \text{(small deformations)}$$

where i,j,k are Cartesian indices.

Just as the potential energy of a Hooke's law spring is quadratic in the square of the displacement, the change in the free energy density ΔF of a continuous object under deformation is quadratic in the strain tensor u_{ij}:

$$\Delta F = 1/2\ \sum_{i,j,k,l} C_{ijkl}\ u_{ij} u_{kl}.$$

with the elastic stiffness constants or elastic moduli C_{ijkl}.

Network size at non-zero temperature

The network has a negative coefficient of thermal expansion at low temperatures (Lammert and Discher, 1998).

At higher temperatures, the area increases linearly with temperature with a slope close to 1/2.
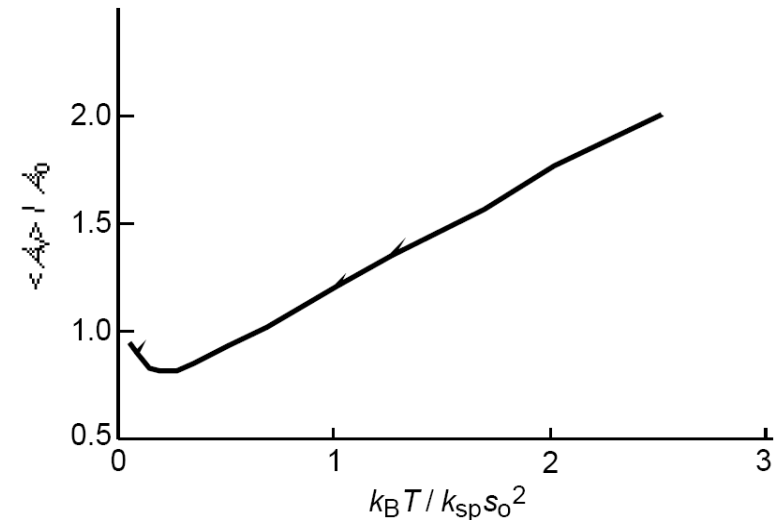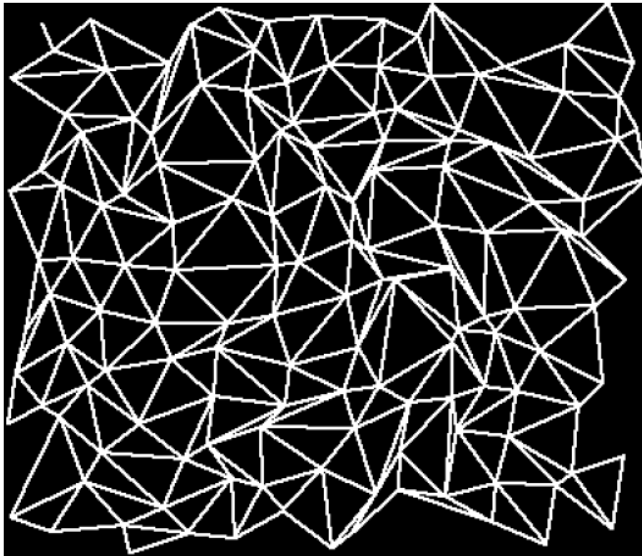
Snapshot of a triangular network of springs at of $k_B T = k_{sp} s_o^2 / 4$.

4. Energy transduction (biological motors)

FoF₁-ATPase

Biological motor I

DNA packing motor in phage = bacteriophage (噬菌體)

head

free phage   neck

tail

tail fibre   baseplate
bacterial cell wall

one tail
fibre bound

tail fibre
consolidation

baseplate
binding

tail sheath
contraction
(ATP -> ADP)

DNA
expelled
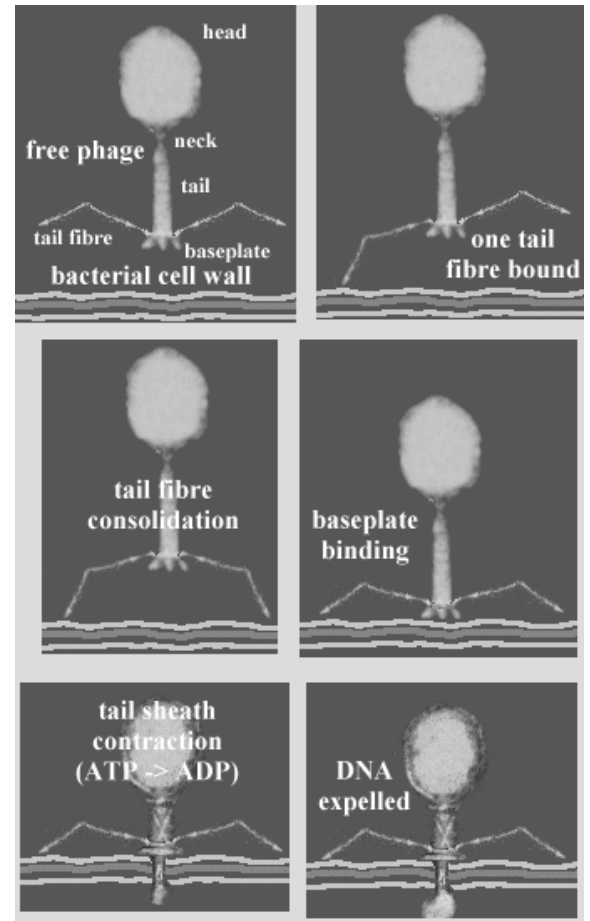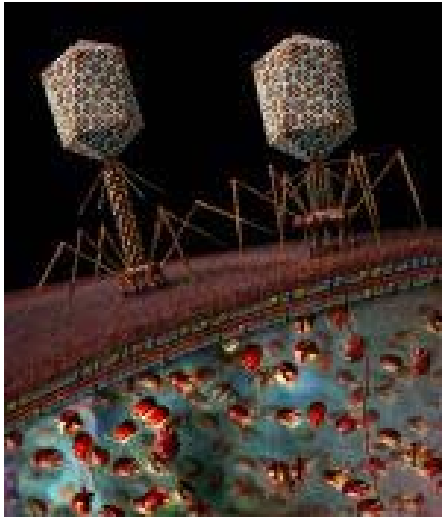
Phage T4 - Enterobacteria phage T4, genus "T4-like Viruses", family *Myoviridae*, or viruses with 34-170 kbp dsDNA genomes, isometric heads and contractile tails - infects the gram-negative bacterium *E coli.*

http://www.mcb.uct.ac.za/tutorial/virusentbacteria.htm

Packing motor

Morphogenesis of Bacteriophage φ29

New Virus made from Viral DNA

Viral DNA Replication

DNA Packaging Motor

New Viral DNA loaded into new virus

Infected Bacteria

φ29

18 October 2001

nature

International weekly journal of science

$10.00   www.nature.com

Viral DNA packing unravelled

Polymerized C$_{60}$ A room-temperature ferromagnet
RNA splicing Catalysis by spliceosomal snRNAs
Herbig-Haro objects The X-ray perspective

new journals

Fluorescent Label

dsDNA

Polystyrene Bead

φ29

Laser Trap

Bacteriophage phi29 (DNA packaging motor 60 pN**)**
packages a DNA about 130 times longer than the viral shell
in just 3 minutes (60 atmosphere inside the viral shell).

Biological motor II

Myosin: Muscle contraction (5pN)

Cytology of a skeletal muscle

Myofibrils

http://www.gdn.edu/Faculty/pjen/Anatomy%20and%20
physiology%202211K%20-%20lecture%201%20notes.htm

Animation: http://entochem.tamu.edu/MuscleStrucContractswf/index.html

Myosin head

http://www.sci.sdsu.edu/movies/actin_myosin_gif.html
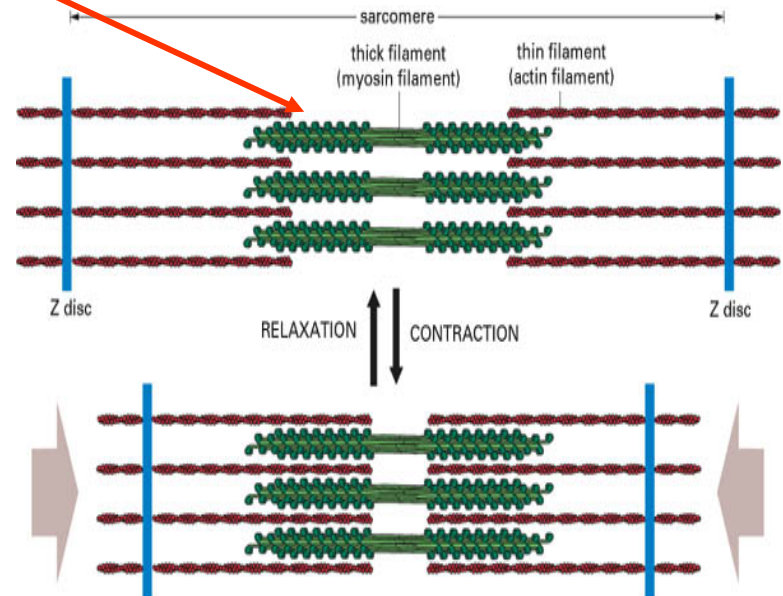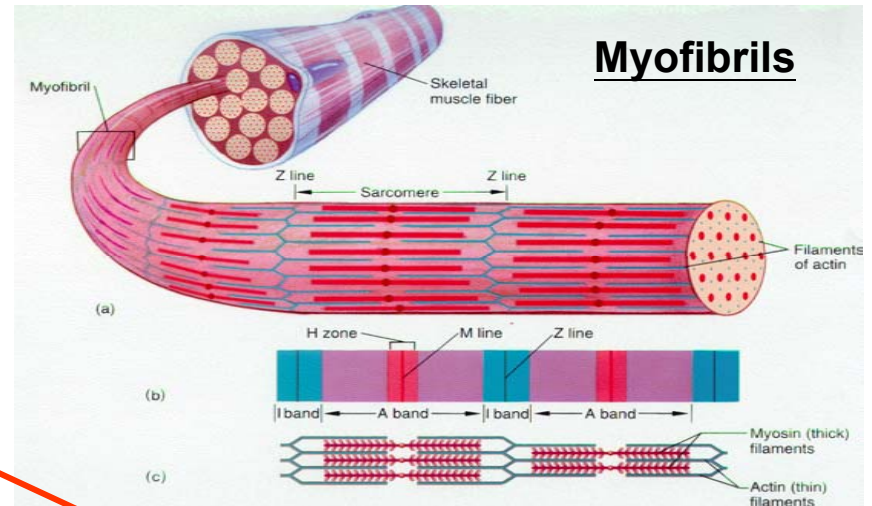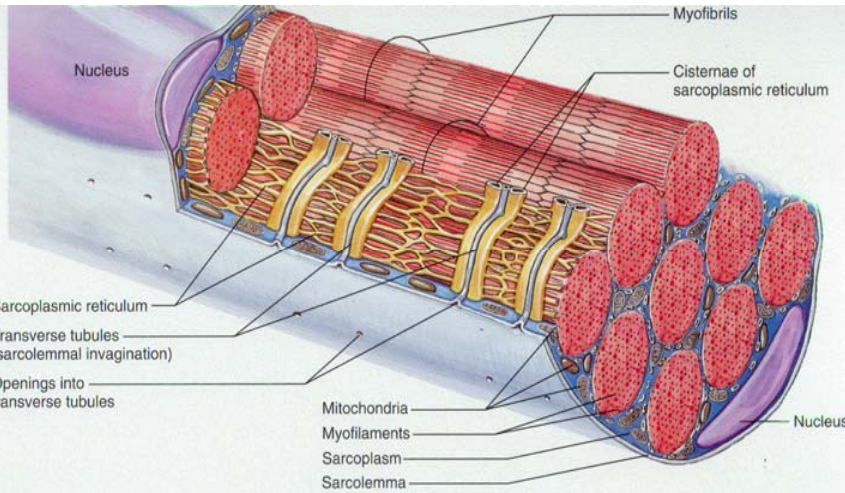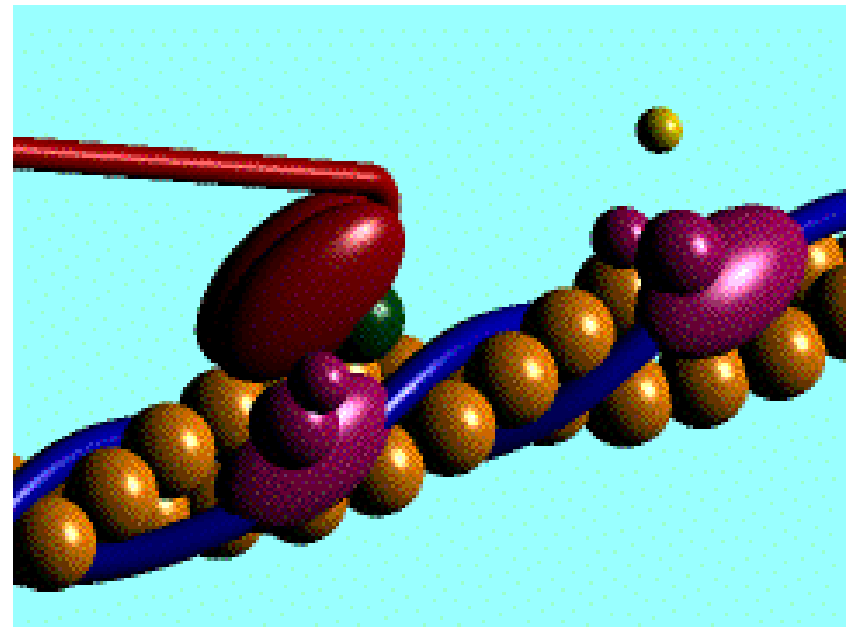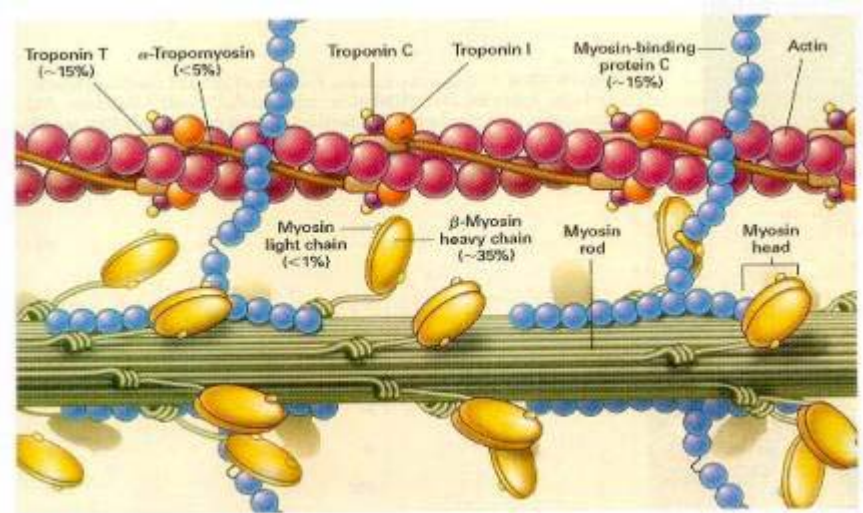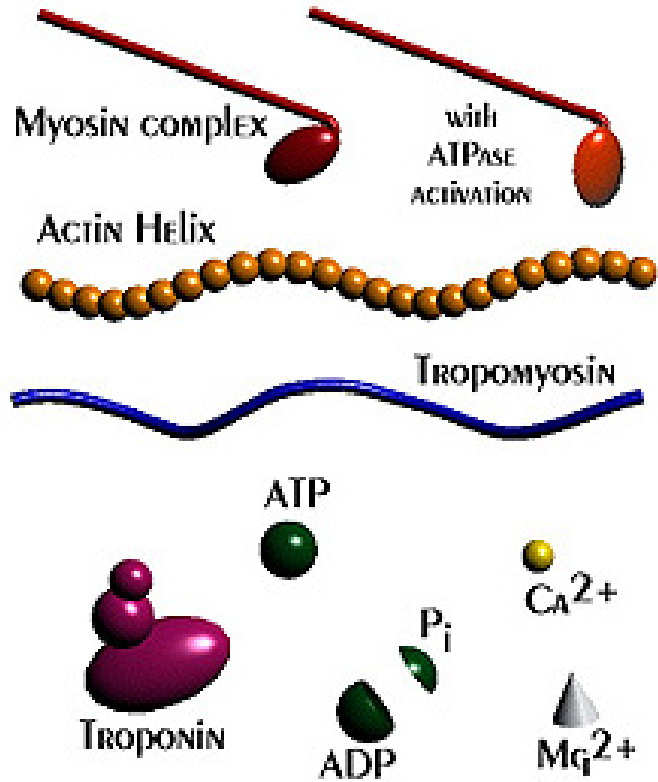
Biological motor III

F_0F_1 ATPase: a machine to produce ATP
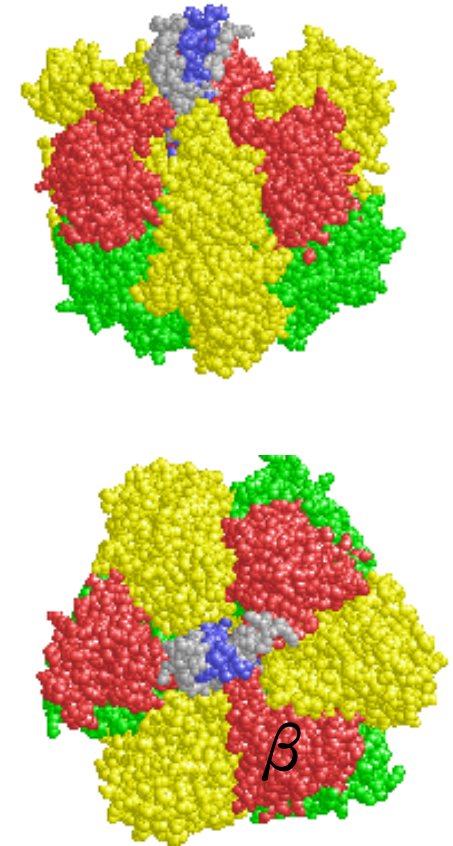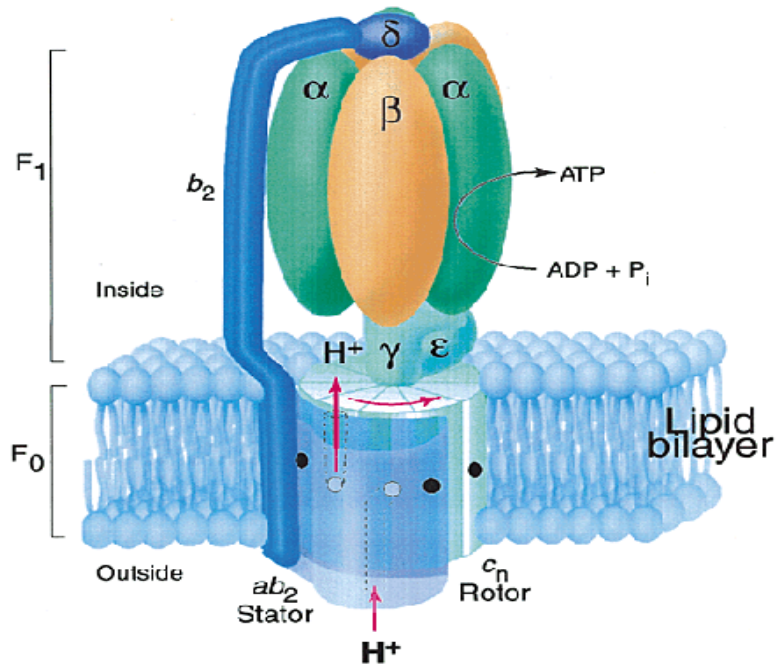
generates energy ATP (synthesis) ADP + Pi → ATP
consumes energy ATP (hydrolysis)   ATP → ADP + Pi

Animation: http://plantcell.lu.se/ltm/06/3ATP.html
http://vcell.ndsu.nodak.edu/animations/atpgradient/movie.htm

Rotation Experiments
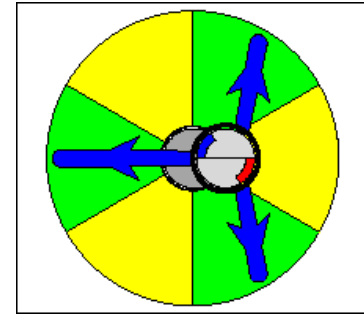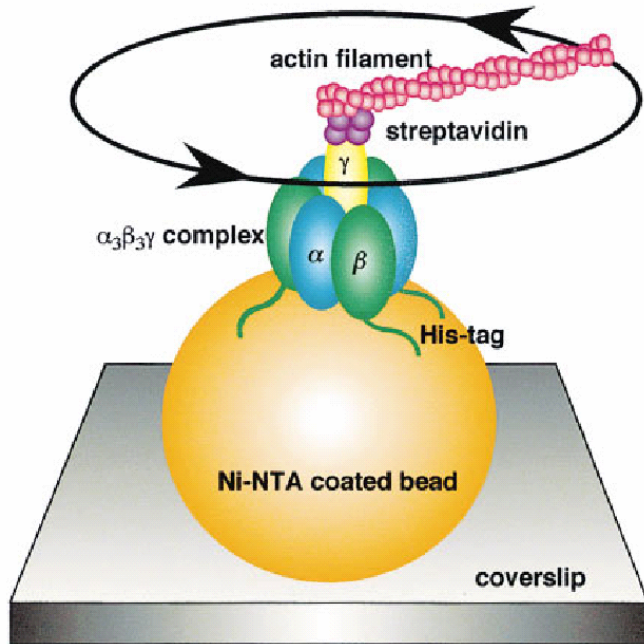
Figure 1. Experimental System (Not to Scale)

consume ATP
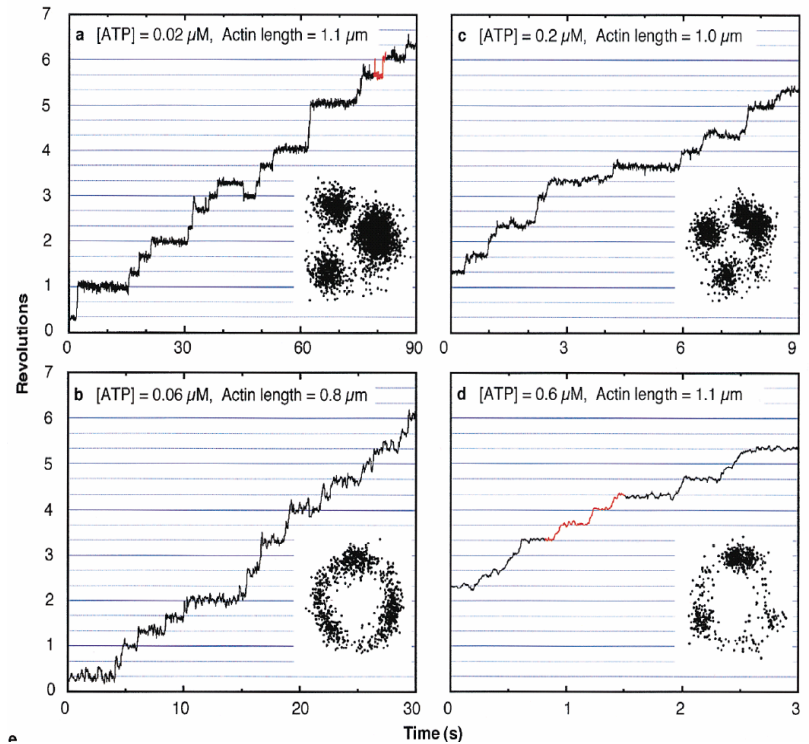
Biological motor IV

Ion pump

(Na,K-ATPase,

Ca-ATPase)
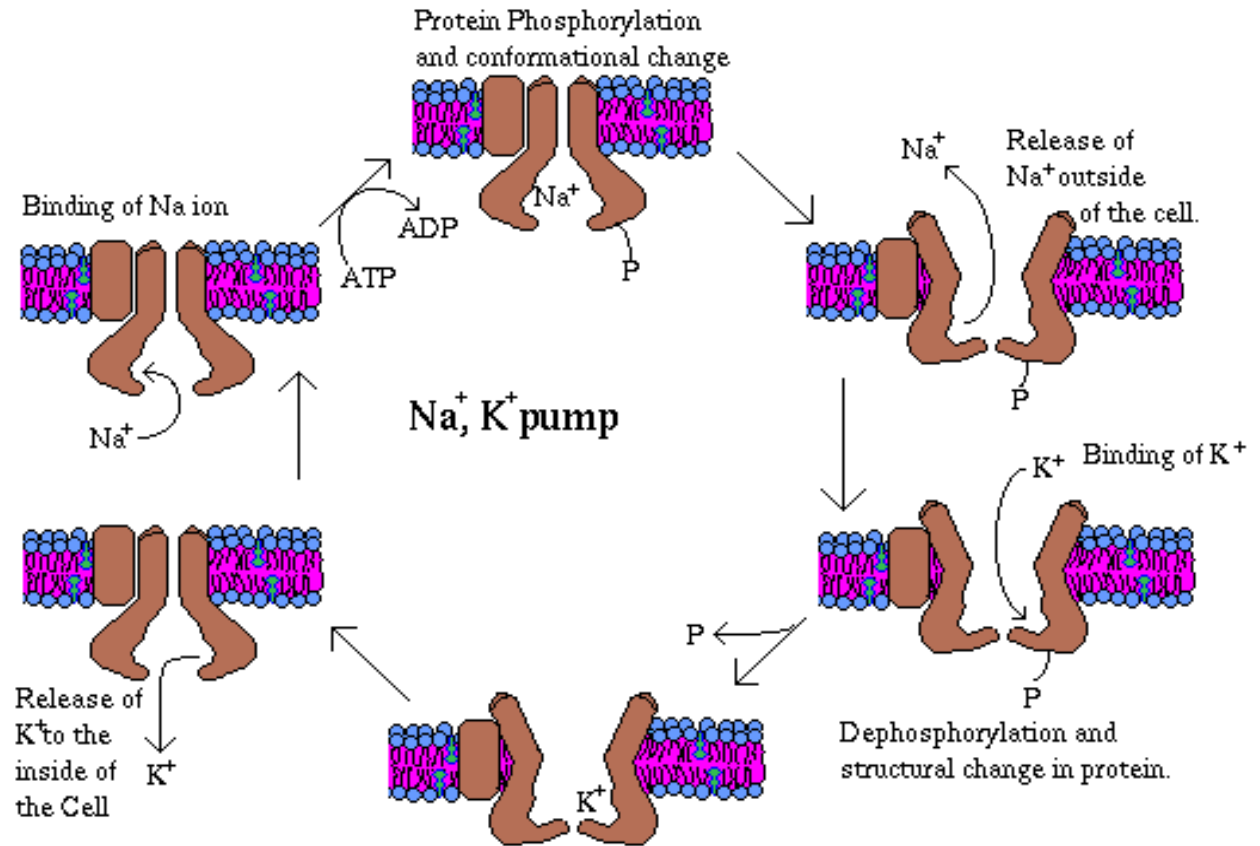
Animation:
http://www.cm.utexas.edu/academic/courses/Spring1999/CH339K/Caras/Web339K/Animations/IonPump.html

Biological motor V

Flagellar motor in E. coli
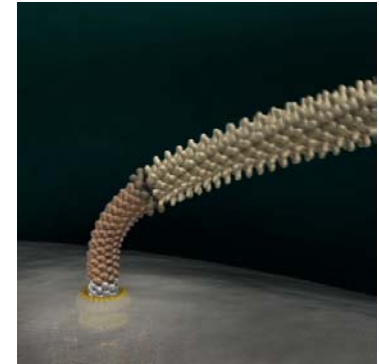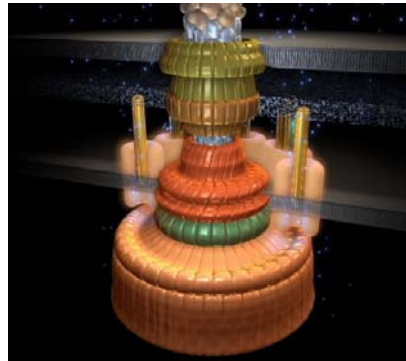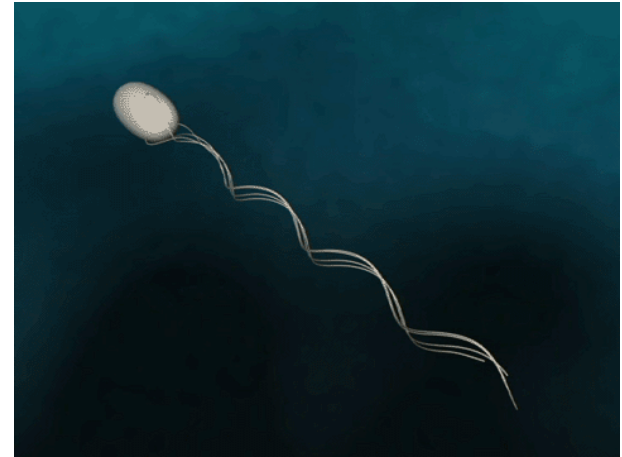
Biological motors

Category	Motion	Function	Force (pico N)	Weight (kDa)
Myosin	Muscle Filament	Muscle contraction Cell divetion	5-6	460-500
Kinesin	Microtuble	Chromoson deviation Cell unit transport	~ 6	400
Dynein	Microtuble	Fragellan	Unclear	1000
RNA Polymerase	DNA	Synthesis	25-30	490
DNA Polymerase	DNA	Synthesis	34	94
Helicase	DNA	DNA rewinding	Unclear	100
ATP synthase	None	ATP synthesis & hydrolysis	80	500000
Flagellar motor	None	Swimming	200	Rather large

Transcription, Translation
http://vcell.ndsu.nodak.edu/animations

$1Da = 1\ u \approx 1.66 \times 10^{-27}$ kg,   C atom has 12 Da.

Working principle of biological motors:

cyclic conformational change

Two states

ATP

Forward/backward different rates

Multi-states

ATP
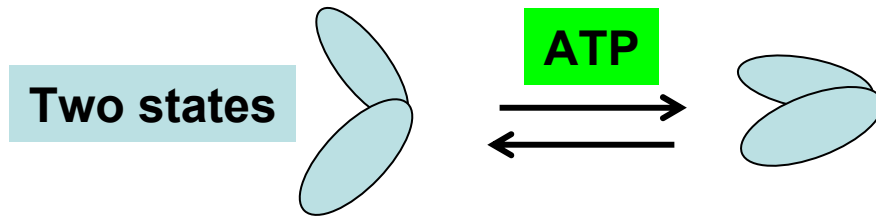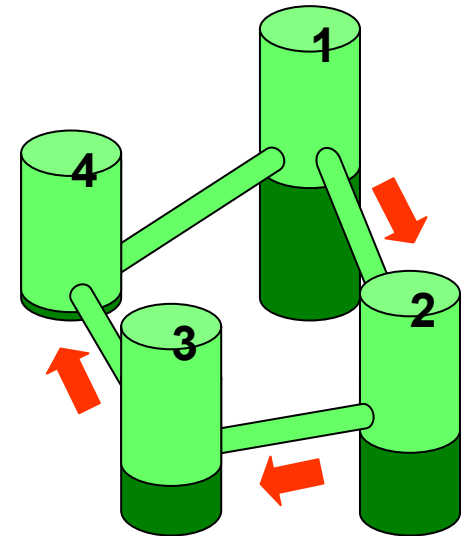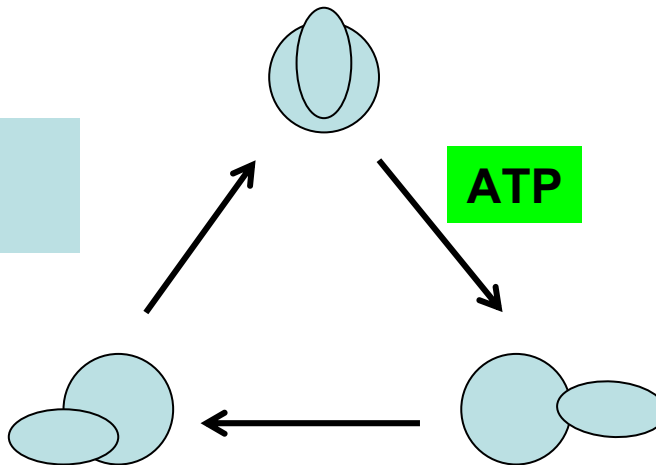
Free energy 1>2>3>4

Example: Myosin three-state model
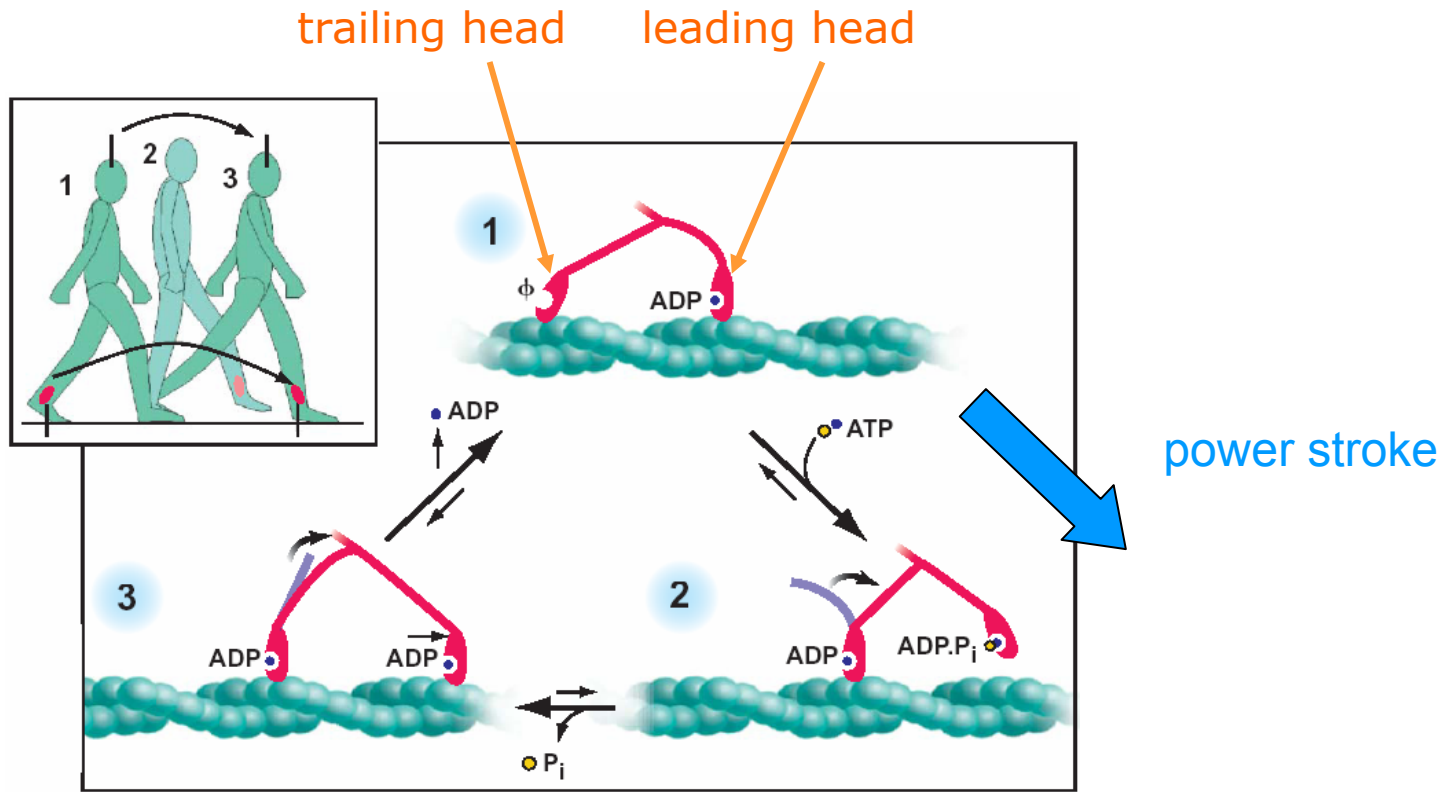
ATP = ADP (●) + inorganic phosphate (○).

The molecule dwells in state 1 at low ATP concentrations (because the empty site, φ, requires ATP to bind before it can be released from actin)

Justin E. Molloy and Claudia Veigel, Science 300, 2046 (2003)

Force and speed of motors on a filament

Stokes' Law

For spherical objects of radius R at low speeds moving through a fluid of viscosity η, the drag force it encounters is

$$F_{drag} = c_1 v \quad \text{with } c_1 = 6\pi\eta R.$$

If an object has an initial speed v_o, it will come to rest in a distance $x = mv_o / c_1$ with a linear dependence of F_{drag} on v.

Example:
A vesicle of radius 50 nm is carried along a filament at speed 0.5 μm/s in a cell with viscosity 10^{-1} kg / m · s which is 100 times more viscous than water. Thus

$$c_1 = 6\pi\eta R = 6\pi \cdot 10^{-1} \cdot 5 \times 10^{-8} = 30\pi \cdot 10^{-9} = 9.4 \times 10^{-8} \text{ kg/s.}$$
$$F_{drag} = c_1 v = 9.4 \times 10^{-8} \cdot 5 \times 10^{-7} = 5 \times 10^{-14} \text{ N} = 0.05 \text{ pN.}$$

A typical molecular motor can generate 2-4 pN of force, easily enough to drive the vesicle.

Typical speed and viscosity

Observed speed of movement

motion	typical speed (μm/s)	example
actin filament growth	10^{-2} - 1	0.3 μm/s at $[M]$ = 10 μM
actin-based cell crawling	10^{-2} - 1	fibroblasts move at ~10^{-2} μm/s
myosin on actin	10^{-2} - 1	0.1 - 0.5 μm/s common in muscles
microtubule growth	up to 0.3	0.03 μm/s at $[M]$ = 10 μM
microtubule shrinkage	0.4 - 0.6	0.5 μm/s
fast axonal transport	1-4	
slow axonal transport	10^{-3} - 10^{-1}	

$[M]$ = monomer concentration. Fast axonal transport involves kinesin or dynein moving along microtubules.

Viscosity of different fluids

Fluid	η (kg/m•sec at 20 ℃)
Water	1.0×10^{-3}
Olive oil	0.084
Glycerine	1.34
Glucose	10^{13}

Force scale at the molecular level

Langevin force is the force bacteria encountered under Brownian motion, which is about

10^{-14} N.

Biological motor perform a force of the order:

10^{-11} N.

Cohesion force for (i) hydrophobic interactions and (ii) hydrogen bonding contributing to the stability of biomolecules is of order

10^{-10} N.

Covalent bond is the strongest force at the molecular level, which can denature a protein and is on the order of

10^{-9} N.

Energy currency ATP

Energy source of the motors

ATP (adenosine triphosphate) 三磷酸腺苷

ATP = $C_{10}H_{16}N_5O_{13}P_3$
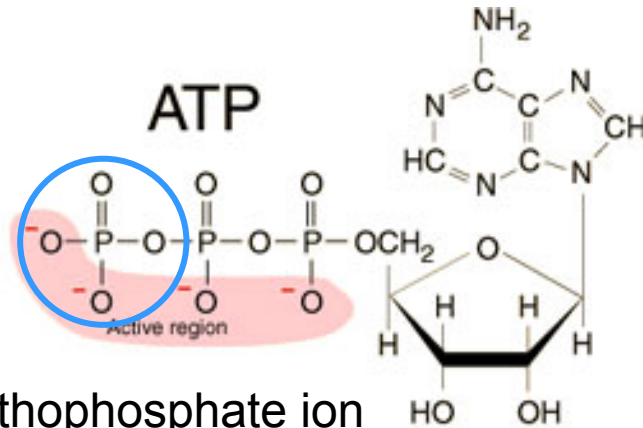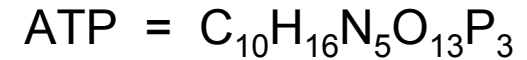
The orthophosphate ion HPO_4^{2-} written as P_i is the inorganic phosphate.
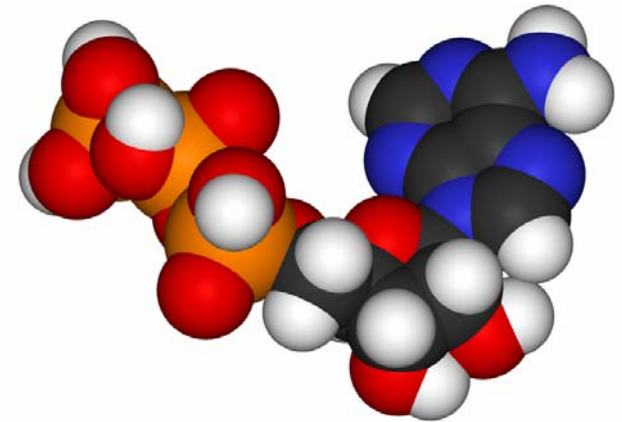
A ATP contains energy 5×10^{-20} J, corresponding to -31 kJ/mol.
A typical biological motor consumes 10^2-10^3 ATP/sec ($\approx 10^{-16}$-10^{-17}W).
Each cell contains 10^9 ATP.
The total human body contains about 50 grams ATP.
Our average daily ATP consumption is 180 kg.
(Kornberg, Arthur. 1989. *For the love of enzymes*. Harvard Uni. Press. P.65)

Energy released by hydrolysis of ATP

新觀念生物學（藝軒出版社）
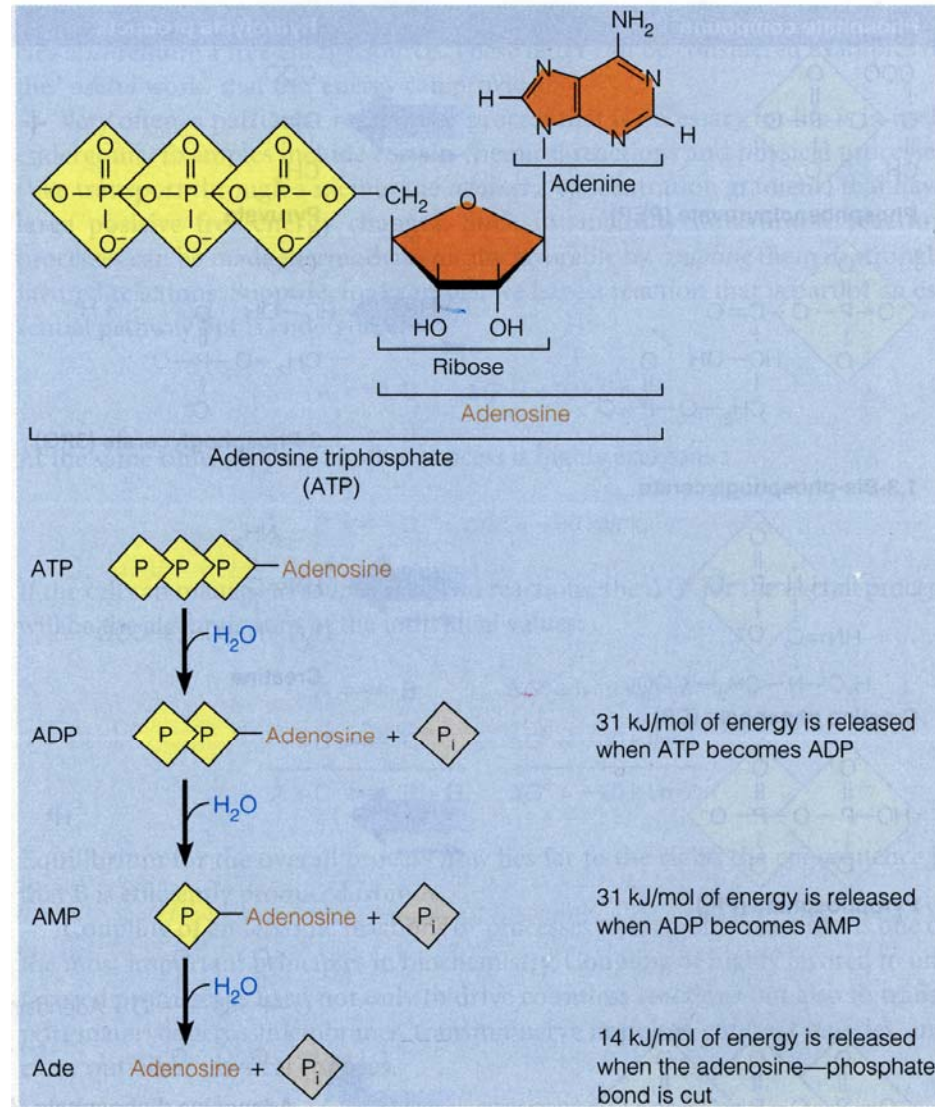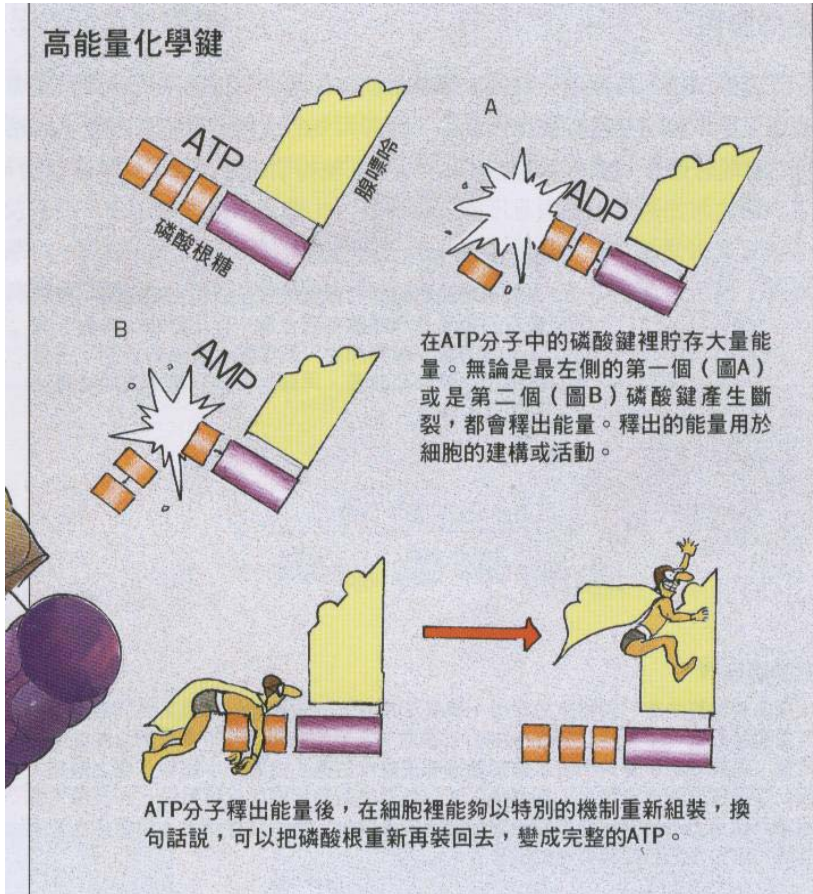
Physical picture of a high energy bond

1. 原子是由帶負電荷的電子，環繞著帶正電荷的原子核組成。

2. 當兩個原子碰撞時，通常會彼此彈開，因爲帶負電荷的電子彼此會「同性相斥」。

3. 如果撞在一起的力量夠大時，電子會重新排列並且共享原子核……

4. 共享的電子有時繞著一個原子核打轉，有時會繞另一個原子核打轉，這種共享的現象稱爲「共價鍵」。以這樣結合在一起的原子就形成一個分子。

共價鍵的另一個表現方式：兩個電子的軌道，或者說是「外殼」會結合在一起。
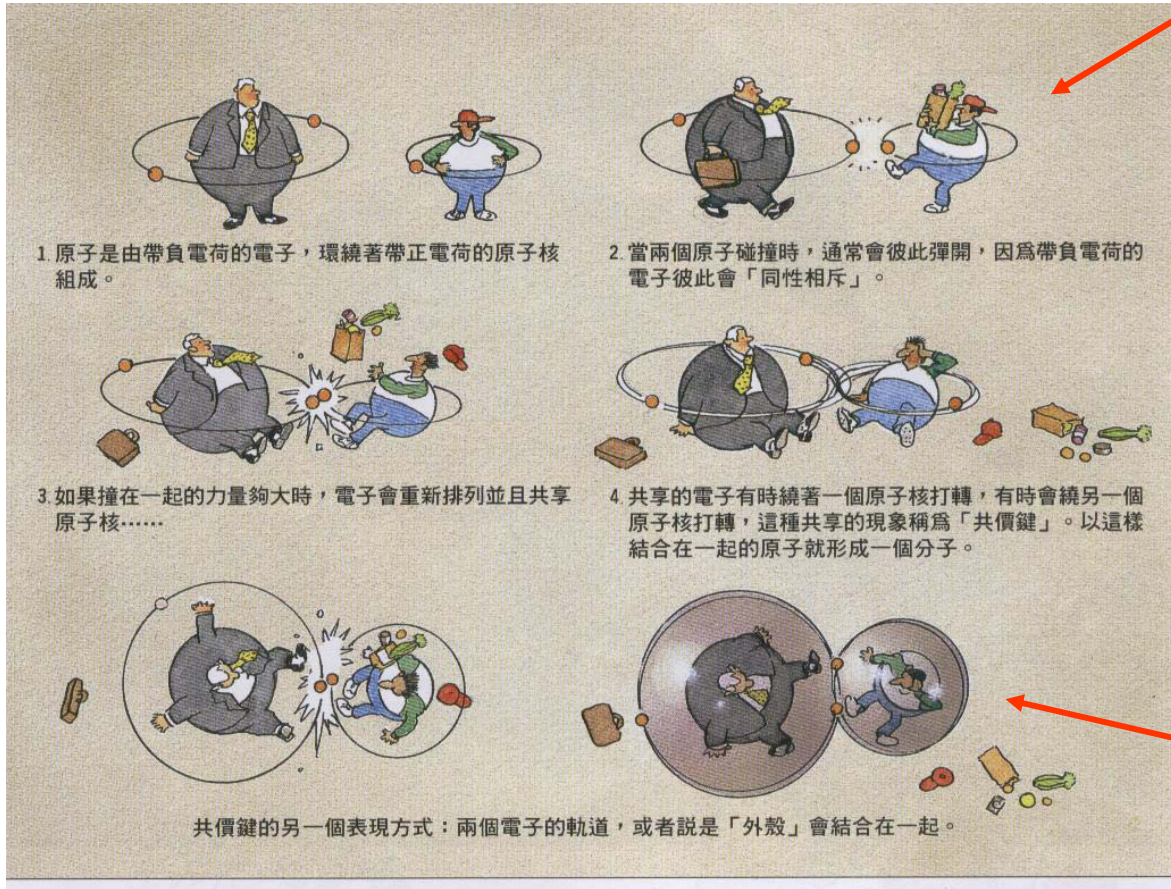
Steric repulsion (exchange repulsion, hard core repulsion) comes from the overlap of electron clouds of atoms. This repulsion is a quantum mechanical effect and empirically behaves like

$$U \propto \frac{1}{r^n}$$

where *n* is an integer between 9 and 16.

After the collision the kinetic energy is largely reduced.

A bond has high energy because high kinetic energy is converted and stored in potential energy.

Energy exchange

A proper collision may convert kinetic energy to potential energy (a) → (b).

(a)

(b)
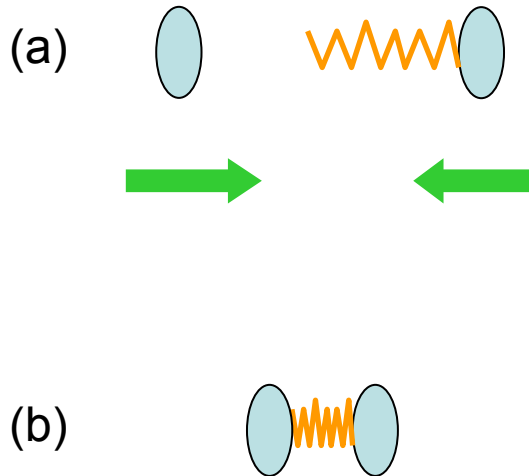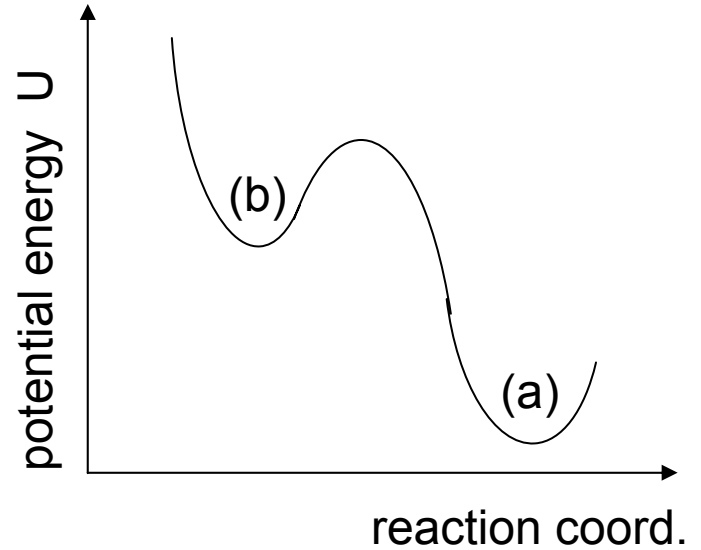
有些時候，用力的撞擊使原子結合成分子。

理論上，原子間成功的一連串撞擊應該能形成一串長鏈分子。

有時強力的撞擊會把鍵結打斷使原子分開。

能量以熱的形式釋放出來。

A proper collision also may release energy (b) → (a)

Energy exchange between molecules

能量能夠在一個鍵結到另一個鍵結間移轉

A

B

一個含高能量的分子將要和從右邊過來的分子相撞。

如果相撞的位置和角度都正確，那麼含高能量分子中的主要鍵結將會斷裂⋯⋯

⋯⋯斷裂的結果，把原來的能量傳遞到新的分子中，並拋掉含能量分子中被換掉的那一部分。
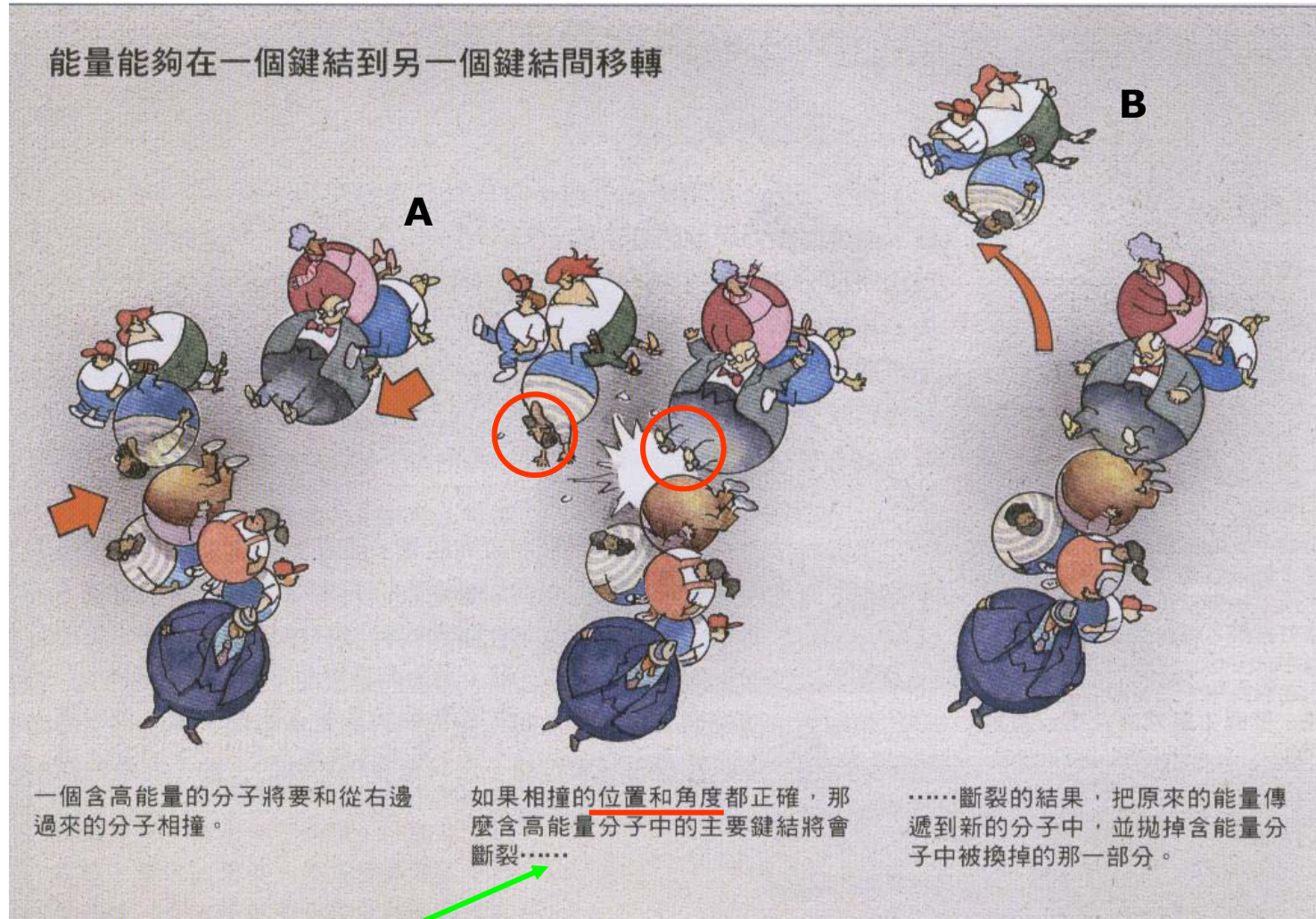
Even the kinetic energy of A is lower than B.

Energy exchange in a motor

ATP

Motor

ADP

Motor

In some cases ADP is attached to the motor instead of P_i.

Motor

P_i

ADP

conformational change
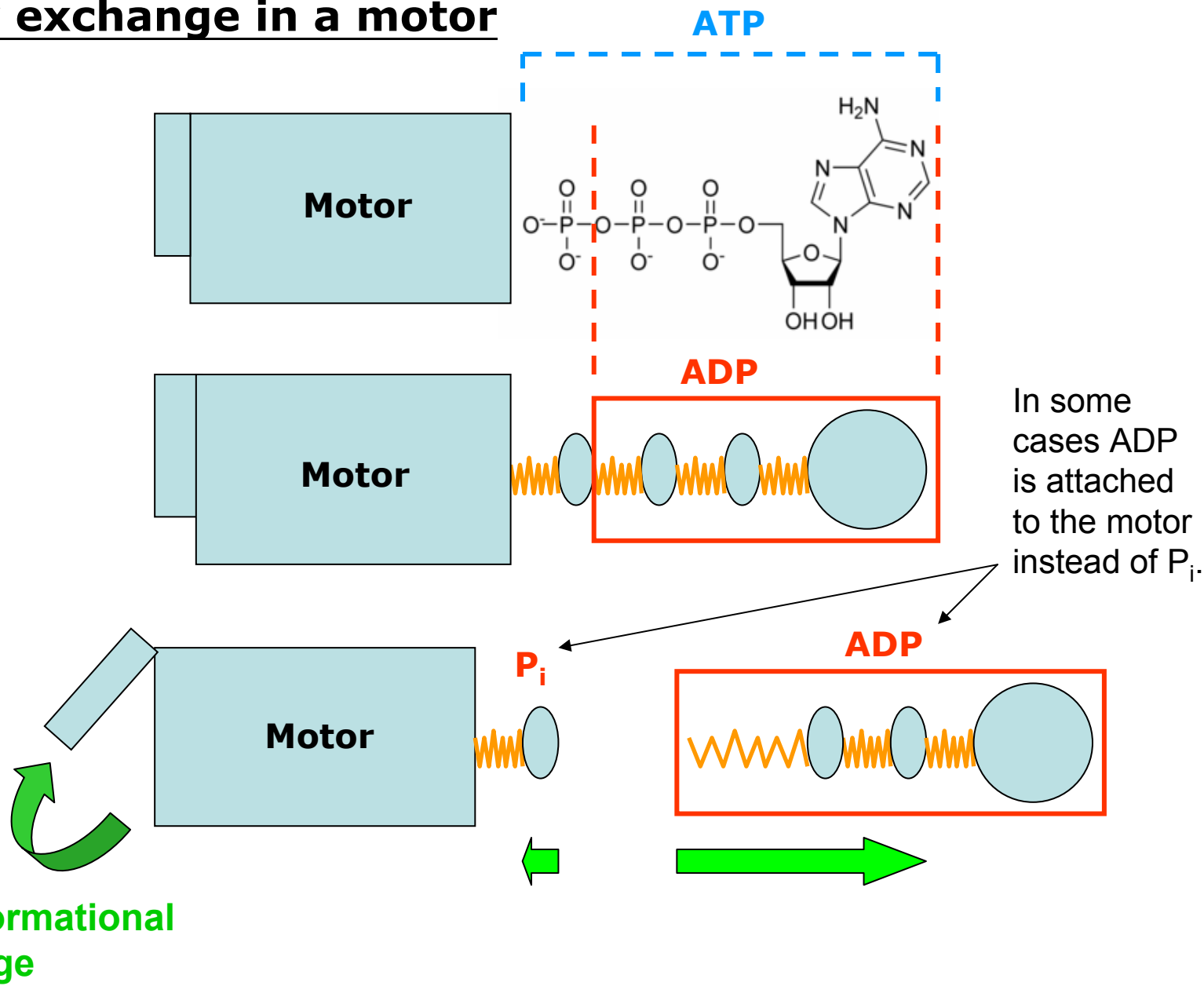
Ratchet (directed motion)

Ratchet effect
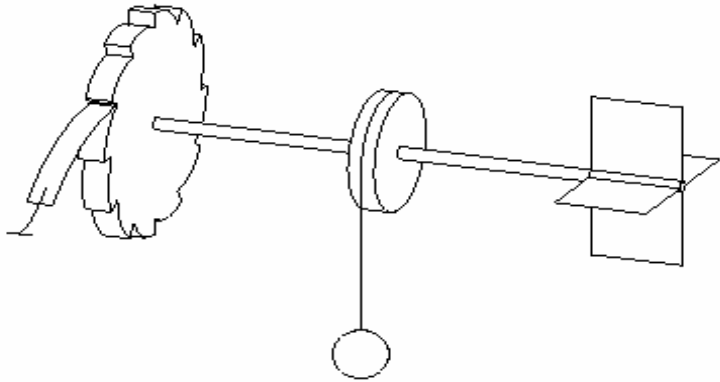
Thought experiment of a perpetuum mobile against the Second Law of Thermodynamics
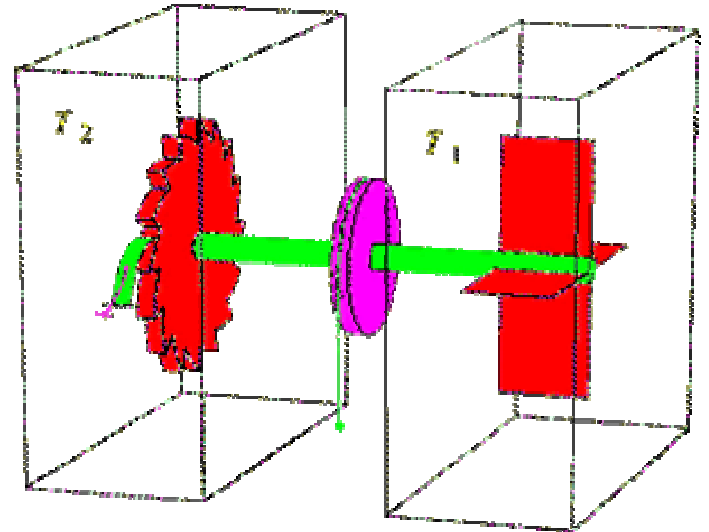
The Second Law of Thermodynamics is **not violated.**

Non-equilibrium + proper asymmetry = directed motion

A simple mathematical Ratchet Model

Ratchet ingredients:
- Brownian particle (mass *m*)
- periodic asymmetric potential *V(x,t)*
- driving forces *f(t)* of zero mean, i.e., $\langle f(t) \rangle = 0$

Ratchet model:
$$m\ddot{x} + \gamma\dot{x} + \frac{d\,V(x,t)}{d\,x} = f(t)$$
damping coefficient γ

Interesting behavior: $\langle \dot{x} \rangle \neq 0$ even when $\langle f(t) \rangle = 0$

Animation: http://monet.physik.unibas.ch/~elmer/bm/
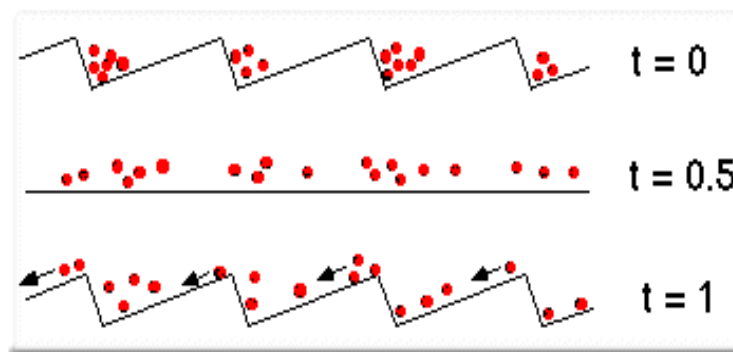
General classification of Ratchet Models

(1) A Langevin-based approach (Horsthemke 1994)

$$\xi \frac{dx}{dt} = -\partial_x W(x) + F(t) \qquad \langle F(t) \rangle = 0$$

(2) An approach with fluctuating potential (Astumian & Bier 1994)

$$\xi \frac{dx}{dt} = -\partial_x W(x,t) + f(t) \qquad \langle f(t) \rangle = 0, \quad \langle f(t)f(t') \rangle = 2\xi T \delta(t-t')$$

(3) A mode with several internal states of the particle described by the Langevin equation that depends on the state i = 1,2, …,N

$$\xi_i \frac{dx}{dt} = -\partial_x W_i(x) + f_i(t) \qquad \langle f_i(t) \rangle = 0, \quad \langle f_i(t)f_j(t') \rangle = 2\xi_i T \delta(t-t') \delta_{ij}$$

where W is the potential the particle experiences;
  F(t) is a fluctuating force of zero average (not white noise);
  f(t) is a Gaussian white noise.

Frank Jülicher, et al Modeling molecular motors, Rev. Mod. Phys. 69, 1269 (1997)

Related problems:
Focker-Planck equation, Dissipation fluctuation relation, Einstein relation, …

Flashing ratchet & Muscle contraction

Depending on whether ATP is on or away from the myosin head, the head is dissociated from or attached to the filament and experiences a flat respectively ratchet potential.
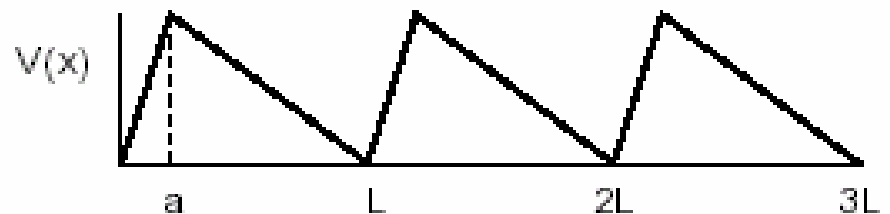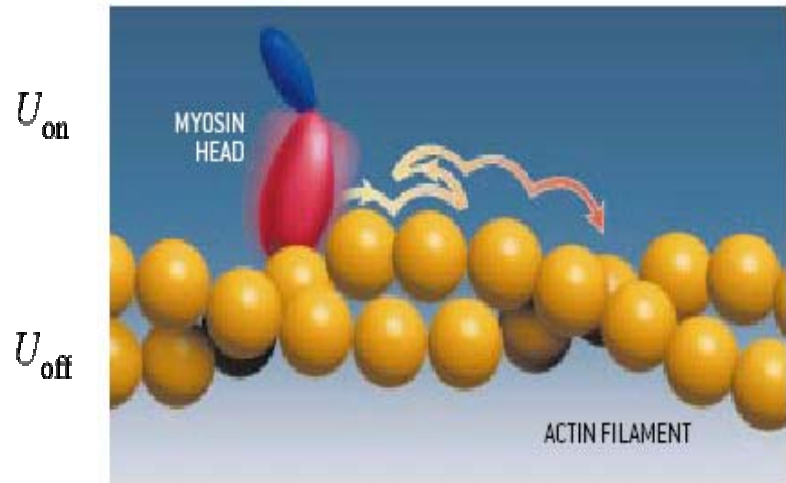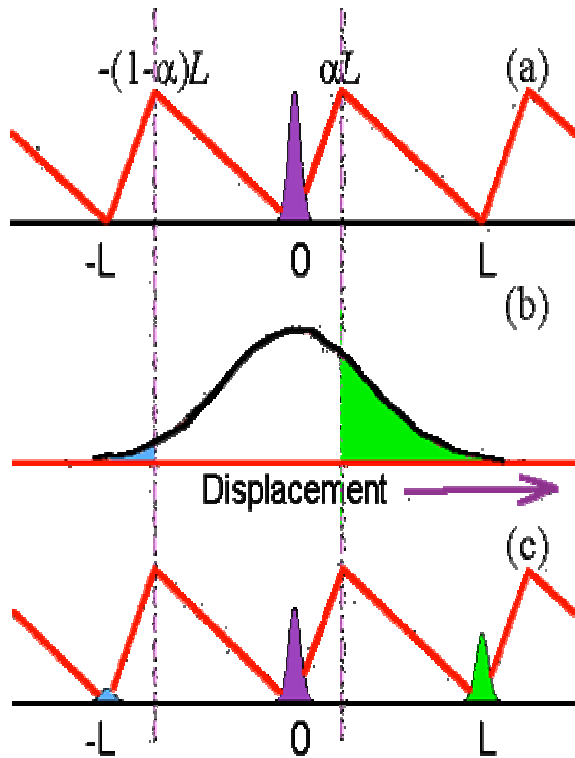
Note that without noise, the myosin head cannot move !!

Problem in energy transduction:

Chemical bond $\leftrightarrow$ mechanical work

From an energetic point of view, however, it seems unlikely that the protein is able to extract, in an efficient manner, the free energy released during ATP catalysis, since the latter is an ultrafast process taking place on a femtosecond time scale. This was recently corroborated by computer simulations (Dittrich *et al.*, 2003, 2004) which revealed that no net free energy is released during ATP catalysis itself. In their paper (Dittrich *et al.*, 2003, 2004), the authors showed that the catalysis reaction energy profile changed from strongly endothermic in the β_{TP} catalytic site to approximately equienergetic in β_{DP}. This leaves either reactant binding (ATP), product unbinding (ADP, Pi), or both as possible candidates for force generation.

(Markus Dittrich and Klaus Schulten
Journal of Bioenergetics and Biomembranes, Vol. 37, No. 6, 441, 2005)

5. Electrostatics (neuron cells & networks)

Perception of electrical stimulation
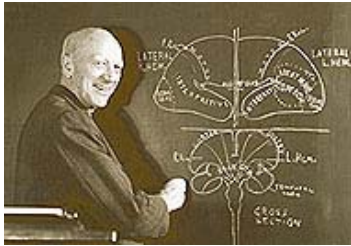
Dr. Wilder Penfield stimulated different areas of the primary somatosensory cortex of his patient and drew the map of the brain:

map of the brain
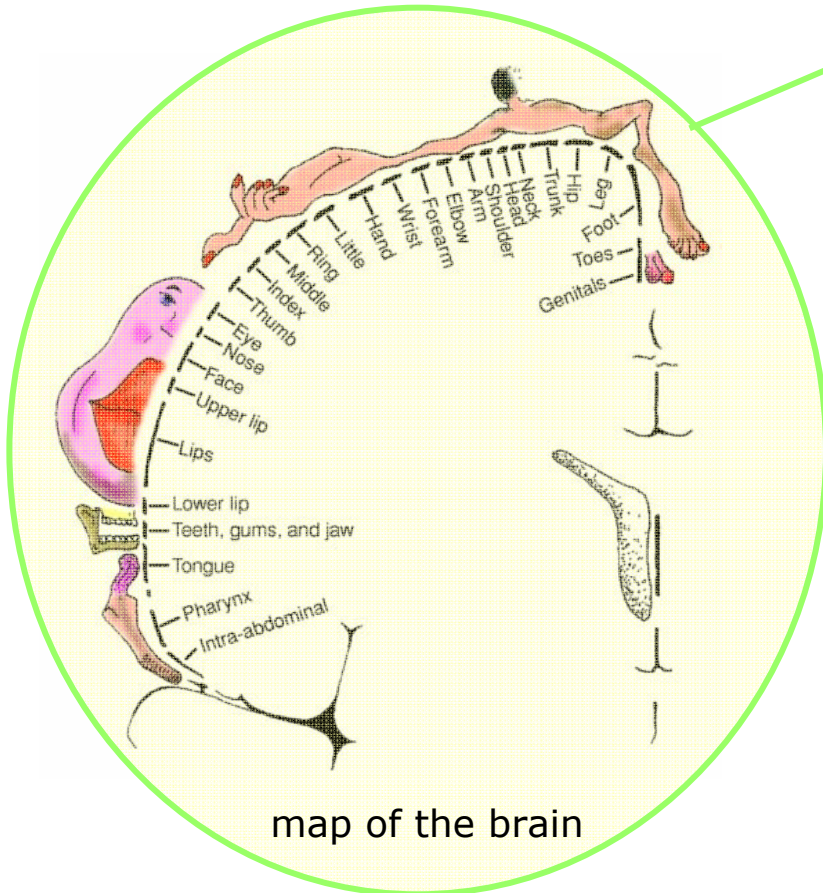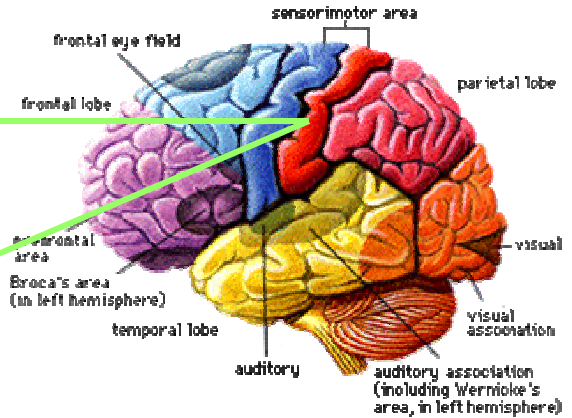
Homunculus (小矮人)

Neuron cell

Endoplasmic reticulum
Nucleus
Nucleolus
Synaptic endings
DNA
Golgi apparatus
Dendrite
Mitochondrion
Axon hillock
Schwann shell sheath around axon
Lipofuchsin
Axon
Myelin sheath
Node of Ranvier
Schwann cell nucleus
Muscle cell nucleus
Neuromuscular junction
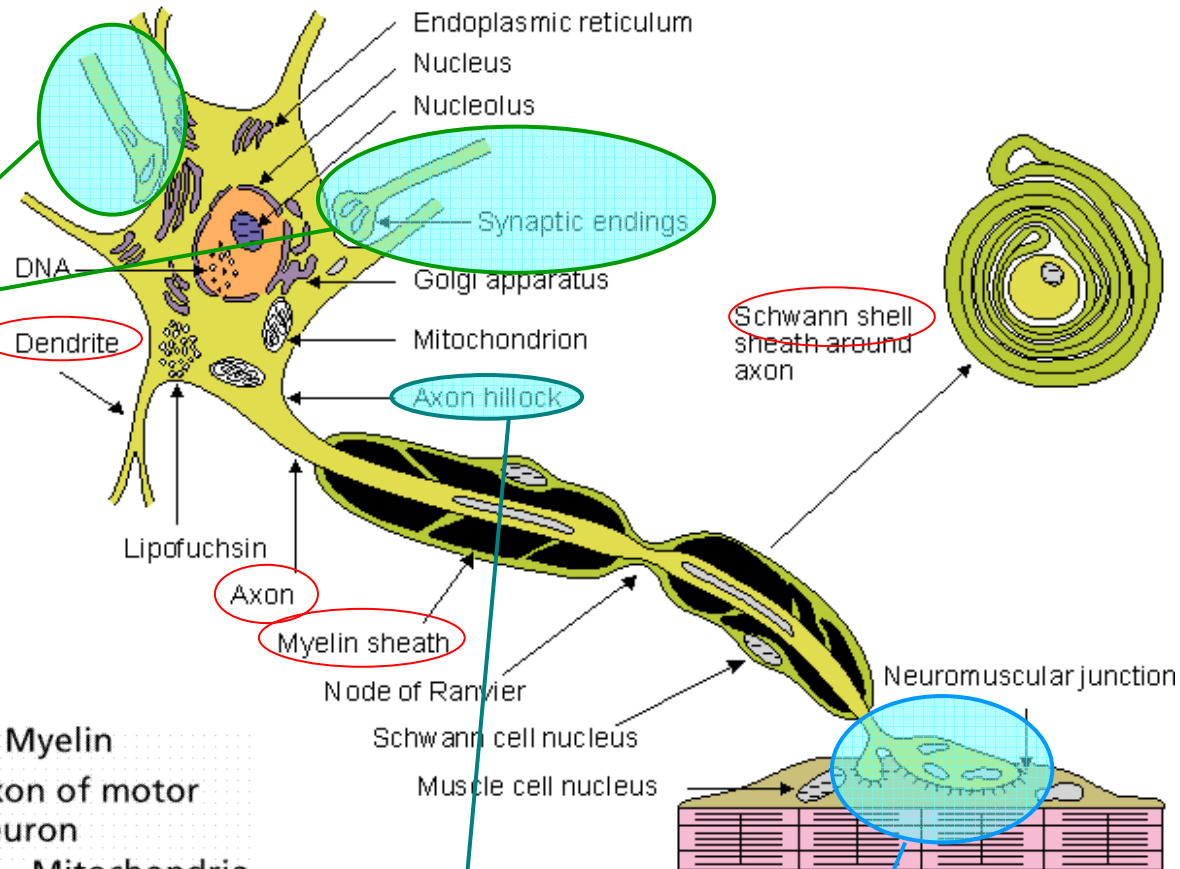
Signal input: Collect signals from the synapse of other cells.

Neurotransmitter vesicles
Myelin
Synaptic cleft
Axon of motor neuron
Mitochondria
Motor end plate
Skeletal muscle fiber
Neurotransmitter receptors
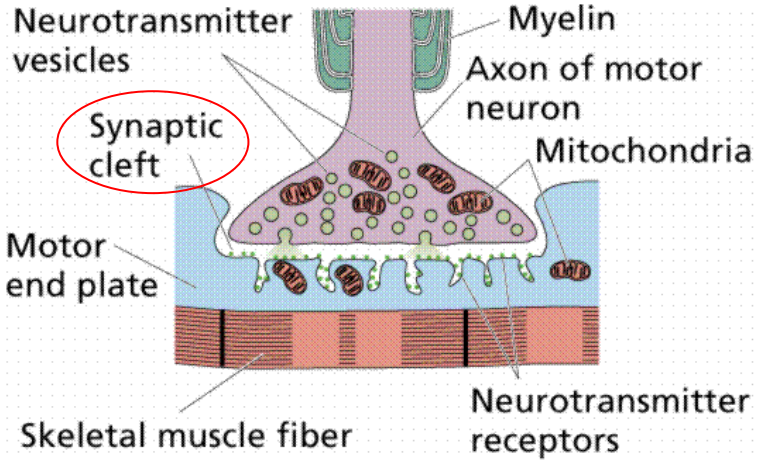
Signal control: Fire a signal, if the total strength of the signal exceeds a threshold.

Signal output: Release signal through its own synapse to other cells.

Measurement of action potentials

Action potentials are measured with the recording techniques. An oscilloscope recording the membrane potential from a single point on an axon shows each phase of the action potential as the wave passes.

These phases trace an arc that resembles a distorted sine wave.

Its amplitude depends on whether the action potential wave has reached that point or passed it and how long ago.

The speed and simplicity of action potentials vary between different types of cells. However, the amplitudes of the voltage swings tend to be roughly the same. Within any one cell, consecutive action potentials typically are indistinguishable.
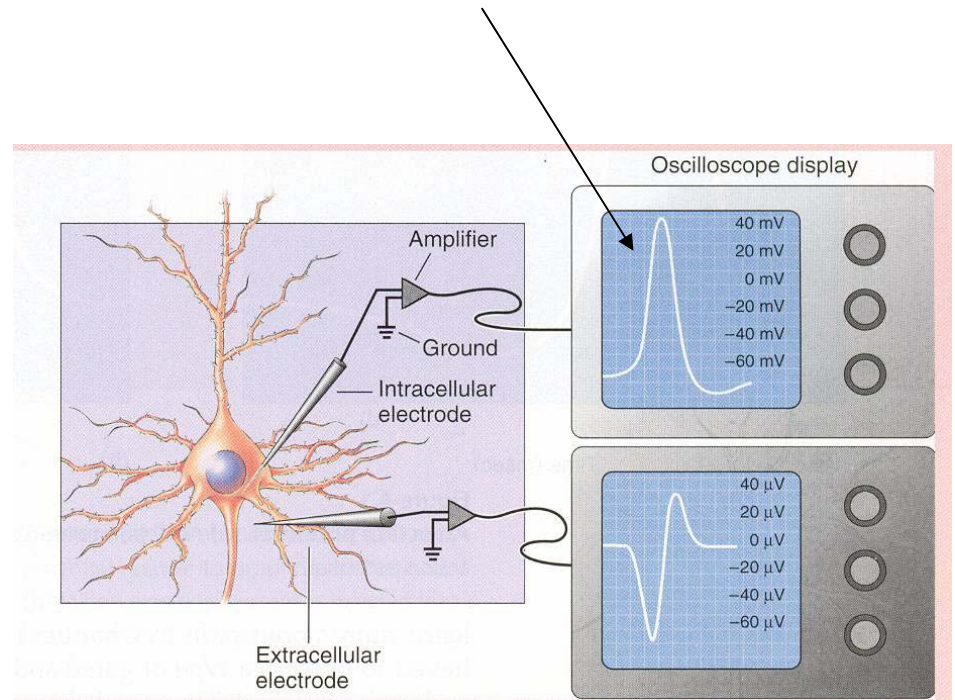
Internal neuron signal transmission (through axon)

axon

synapse

Basic Neural Processes
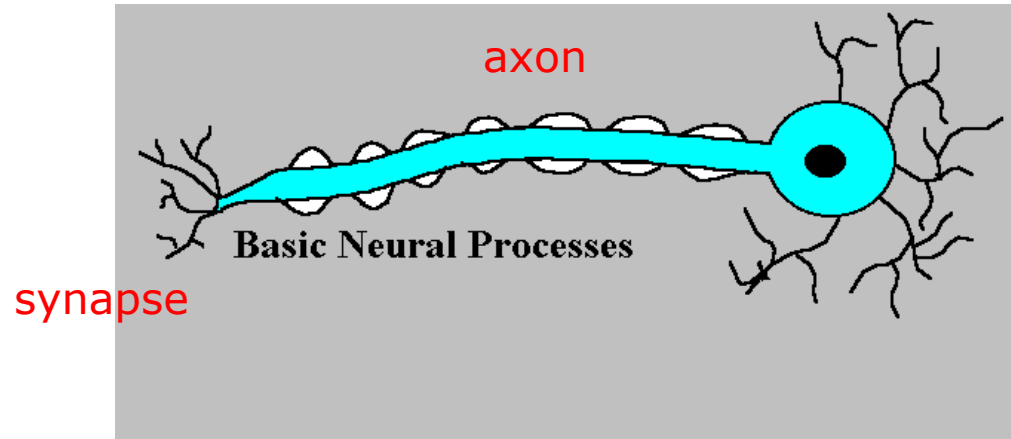
Action potential

- is a wave of electrical discharge that travels along the membrane of a cell.

- carries fast internal messages between tissues and can be created by many types of body cells.

- is an essential carrier of the neural signal. Its properties may enable centralized control and coordination of organs and tissues.

http://entochem.tamu.edu/neurobiology/index.html

External signal transmission (through synapse)
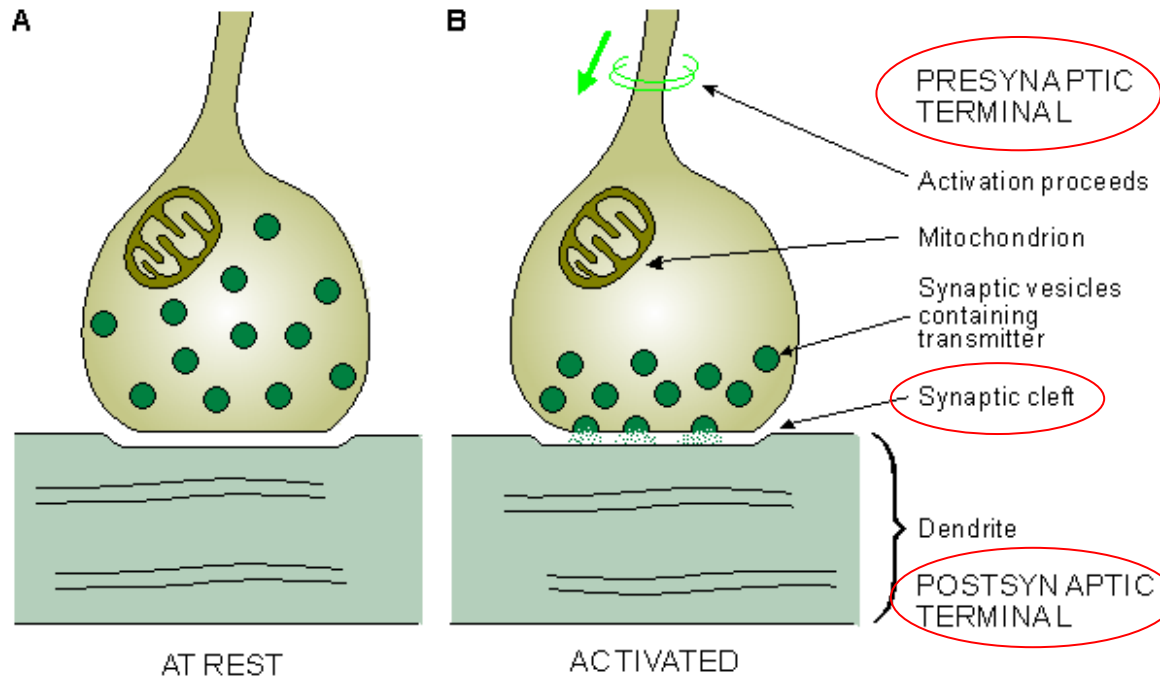
A The synaptic vesicles contain a chemical transmitter.

B When the activation reaches the presynaptic terminal the transmitter is released and it diffuses across the synaptic cleft to activate the postsynaptic membrane.

http://entochem.tamu.edu/neurobiology/index.html

The formation of the action potential

When the membrane potential of an excitable cell is depolarized beyond a threshold, the cell will undergo an action potential (fire a spike).

Four activities:

(1) The outside and inside of the membrane is at a resting potential.

(2) Sodium (Na^+) moves inside the cell causing an action potential, the influx of positive sodium ions makes the inside of the membrane more positive than the outside.

(3) Potassium (K^+) ions flow out of the cell, restoring the resting potential net charges.

(4) Na^+ are pumped out of the cell and K^+ are pumped into the cell, restoring the original distribution of ions.

Three phases:

These four activities will lead to four phases in a cycle:

(A) resting phase
(B) rising phase
(C) falling phase.

ion channel   ion pump

http: //cas.bellarmine.edu/tietjen/Laboratories/
Bio%20Pix%204%20U/Bio%20Pix.htm
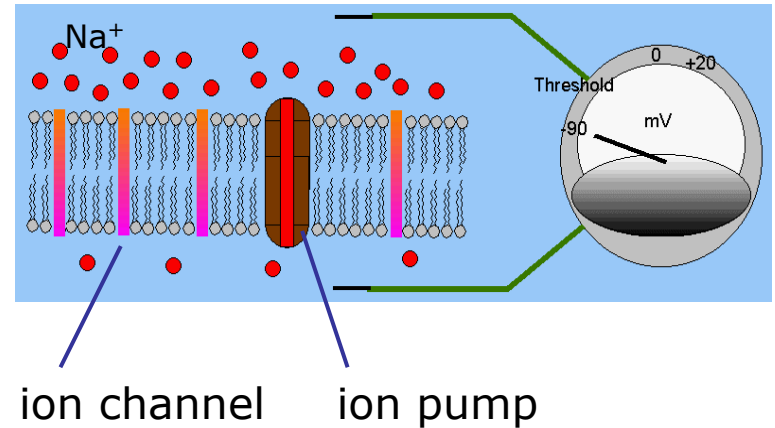
Propagating direction of the action potential

Usually action potentials travel unidirectionally along the axon.

Reason: where membrane has undergone an action potential, a refractory period follows. This period arises primarily because of the voltage-dependent inactivation of sodium channels (Hodgkin and Huxley in 1952).
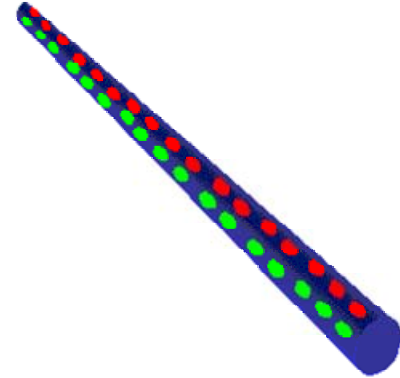
(i) Absolute refractory period: immediately after an action potential, virtually all sodium channels are inactivated and thus it is impossible to fire another action potential in that segment of membrane.

(ii) Relative refractory period: with time, sodium channels are reactivated in a stochastic manner and as they become available, it becomes possible to fire an action potential, though one with a much higher threshold.

These two refractory periods together last approximately 5×10^{-3} seconds.

Propagating velocity of the action potential

For a unmyelinated axon,

$$v = \sqrt{\frac{i_{Na\ max}}{r_i c_m^2 V_{th}}}$$

where

v = velocity of the nerve impulse [m/s]
$i_{Na\ max}$ = maximum sodium current per unit length [A/m]
V_{th} = threshold voltage [V]
r_i = axial resistance per unit length [W/m]
c_m = membrane capacitance per unit length [F/m]
Example: for unmyelinated sensory neurons is 5 - 25 m / s.

For a myelinated axon:

$$v = 6d$$

where

v = velocity of the nerve impulse [m/s]
d = axon diameter ~ 2-20 [µm]
Example: for mammalian motor neurons is 10 - 120 m / s.

Question: Can a baseball hitter hit a ball of 90 m/s?
The distance between the pitcher and the home base is 18.44 m.
The time before the ball arrives at the hitter is 18/90 = 0.2 s.
The propagating distance of the action potential is 10 x 0.2 = 2 m.

Hodgkin-Huxley model

Goal: understanding the propagation of action potentials
(originally on the giant axon of the squid).

The semipermeable cell membrane separates the interior of the cell from the extracellular liquid and acts as a capacitor.

If an input current is injected into the cell, it may add further charge on the capacitor, or leak through the channels in the cell membrane.

Because of active ion transport through the cell membrane, the ion concentration inside the cell is different from that in the extracellular liquid.

The Nernst potential generated by the difference in ion concentration is represented by a battery.
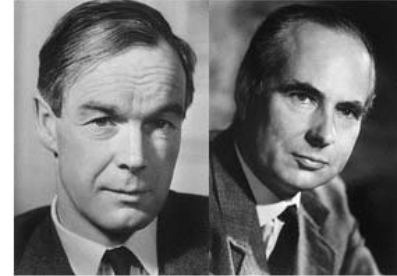
Hodgkins and Huxley
Nobel Prize, 1963

Mantle axons   Stellate ganglion   Water forced out for propulsion
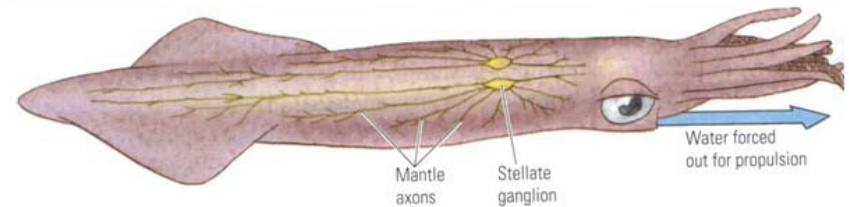
RC Circuit model

Membrane = insulator with capacitor and high fixed resistor
Voltage-gated channel = conductor with low various resistor
Leak channel = conductor with low fixed resistor
Voltage gradient of Na^+ and K^+ across the membrane = battery
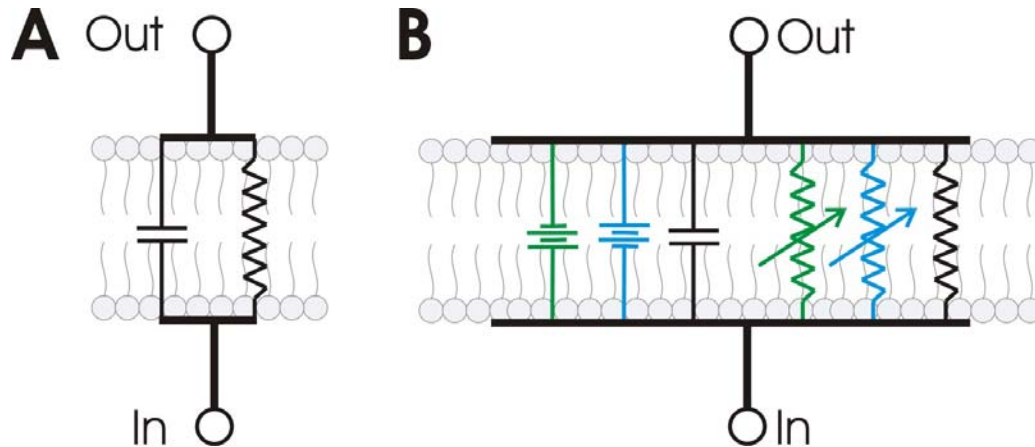
A. Membrane without ion channels without transmembrane ion gradient.
B. Membrane with Na^+ (blue) and K^+ (green) ion channels and gradient.

Propagating depolarization in the circuit model

(T1) A local depolarization opens local Na$^+$ channels at P$_1$.

(T2) Na$^+$ current spreads to the right adjacent membrane at P$_2$ and causes a new depolarization there.

(T4) This depolarization opens the Na$^+$ channels at P$_2$ and new Na$^+$ current to cause new depolarization spreading further down the membrane to P$_3$ and P$_4$.

Meanwhile, the delayed K$^+$ current flows in the membrane patch at P$_1$, causing the falling phase of the action potential.
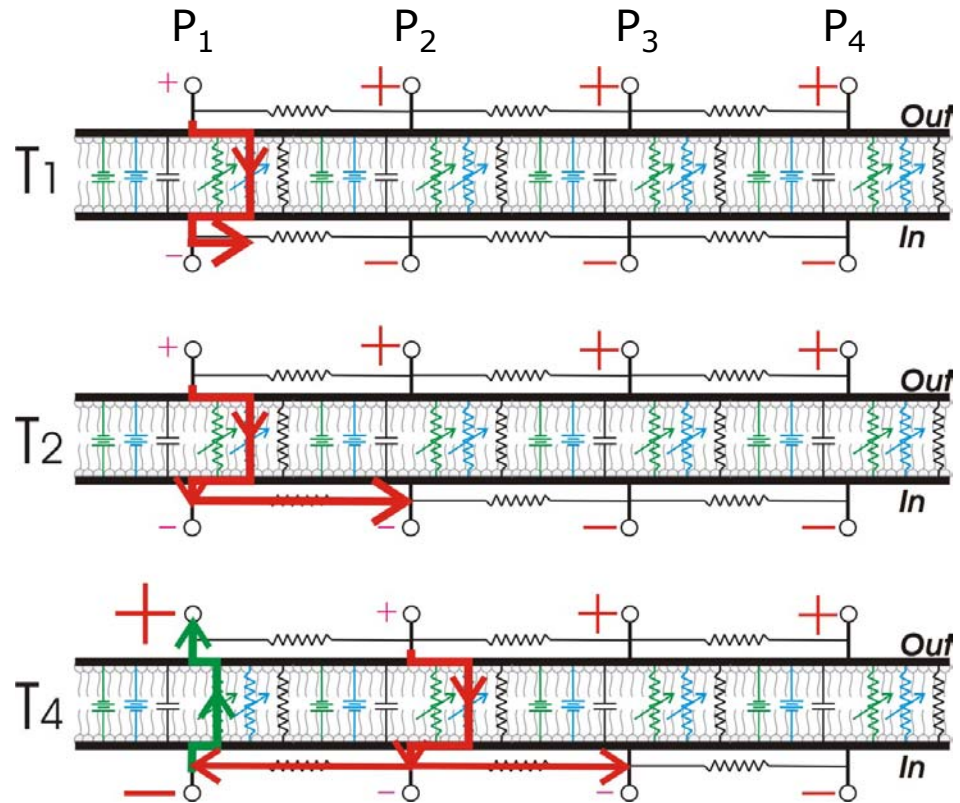
Note the size change of '+' and '-'.

Mathematical Model

An input current I(t) onto the membrane may be split in
a capacitive current I_C which charges the capacitor C and
further components I_k which pass through the ion channels.
Thus

$$I(t) = I_C(t) + \sum_k I_k(t),$$

where

• I_C = C du/dt with the membrane capacity C = Q/u = 1 F/cm², in which
  Q is a charge and u is the voltage across the capacitor (membrane).

• the sum of $I_k(t)$ runs over the following 3 ion channels:

  (i) an unspecific leakage channel
      with a constant resistance R and a constant conductance g_L=1/R,

  (ii) two voltage-gated channels (Na channel & K channel)
       with a time-dependent resistance and conductance,
       Suppose their maximum conductances are g_{Na} and g_K.
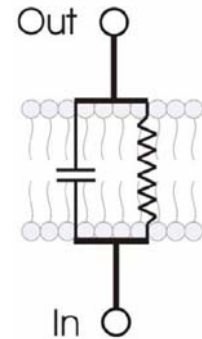
The time-dependent conductance is determined by the open probability m, n, and h of the channels with

$$dm/dt = \alpha_m(u)(1-m) - \beta_m(u)m \qquad \text{(fast Na}^+ \text{ gate)}$$
$$dn/dt = \alpha_n(u)(1-n) - \beta_n(u)n \qquad \text{(slow Na}^+ \text{ gate)} \qquad (1)$$
$$dh/dt = \alpha_h(u)(1-h) - \beta_h(u)h \qquad \text{(K}^+ \text{ gate)}$$

where α_i and β_i are some functions of the transmembrane voltage u.

Hodgkin and Huxley formulated the three current components as

$$\Sigma_k I_k = g_{Na}\, m^3 h\, (u - E_{Na}) + g_K\, n^4\, (u - E_K) + g_L\, (u - E_L),$$

with the reversal potentials E_{Na}, E_K, and E_L which together with g_{Na}, g_K, and g_L as well as α_i and β_i are empirical (Hodgkin and Huxley):

x	E_x	g_x	x	$\alpha_x(u/\mathrm{mV})$	$\beta_x(u/\mathrm{mV})$
Na	115 mV	120 mS/cm^2	n	$(0.1 - 0.01\,u)\,/\,[\exp(1 - 0.1\,u) - 1]$	$0.125\,\exp(-u/80)$
K	-12 mV	36 mS/cm^2	m	$(2.5 - 0.1\,u)\,/\,[\exp(2.5 - 0.1\,u) - 1]$	$4\,\exp(-u/18)$
L	10.6mV	0.3mS/cm^2	h	$0.07\,\exp(-u/20)$	$1\,/\,[\exp(3 - 0.1\,u) + 1]$

Dynamics

Using this parameters in the Hodgkin-Huxley equation:

$$C\, du/dt \;=\; -\,\Sigma_k\, I_k(t) + I(t).$$

many important features of action potential can be realized:

1. Spike generation

2. Mean firing rate

3. Stimulation by
   time-dependent input

http://diwww.epfl.ch/~gerstner/SPNM/node14.html#SECTION02121000000000000000

Models outside the neuron cell   Rate model

TABLE I. Summary of many frequently used neuronal models.

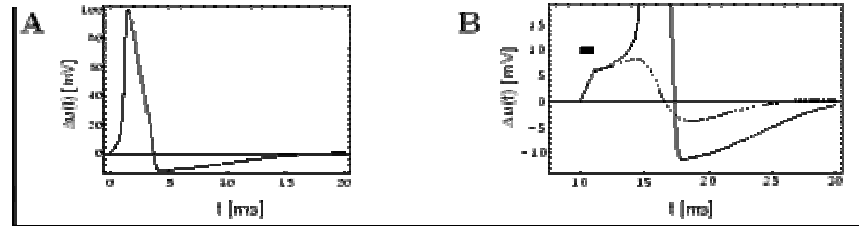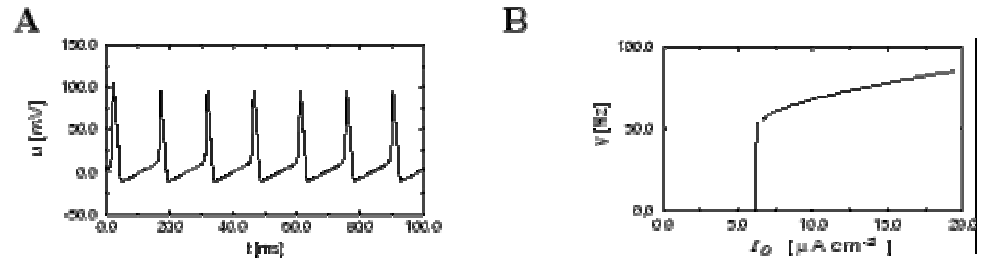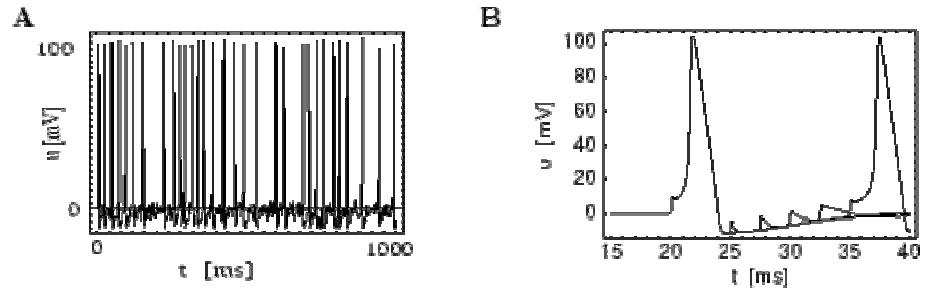| Model	Example	Variables	Remarks	References
Integrate-and-fire neurons	$\dfrac{dv(t)}{dt}$ $= \begin{cases} -\dfrac{v(t)}{\tau} + I_{ext} + I_{syn}, & 0 < v(t) < \theta \\ v(t_0^+) = 0, & v(t_0^-) = \theta \end{cases}$ $I_{syn}(t) = g \sum_{spikes} f(t - t_{spike})$ and $f(t) = A[\exp(-t/\tau_1) - \exp(-t/\tau_2)]$	$v(t)$ is the neuron membrane potential; θ is the threshold for spike generation. I_{ext} is an external stimulus current; I_{syn} is the sum of the synaptic currents; and τ_1 and τ_2 are time constants characterizing the synaptic currents.	A spike occurs when the neuron reaches the threshold θ in $v(t)$ after which the cell is reset to the resting state.	Lapicque, 1907
Rate models	$\dot{a}_i(t) = F_i(a_i(t))[G_i(a_i(t)) - \sum_j \rho_{ij} Q_j(a_j(t))]$	$a_i(t) > 0$ is the spiking rate of the ith neuron or cluster; ρ_{ij} is the connection matrix; and F, G, Q are polynomial functions.	This is a generalization of the Lotka-Volterra model [see Eq. (9)].	Fukai and Tanaka, 1997; Lotka, 1925; Volterra, 1931
McCulloch and Pitts	$x_i(n+1) = \Theta(\sum_j g_{ij} x_j(n) - \theta)$ $\Theta(x) = \begin{cases} 1, & x > 0 \\ 0, & x \le 0 \end{cases}$	θ is the firing threshold; $x_j(n)$ are synaptic inputs at the discrete "time" n; $x_i(n+1)$ is the output. Inputs and outputs are binary (one or zero); the synaptic connections g_{ij} are 1, -1, or 0.	The first computational model for an artificial neuron; it is also known as a linear threshold device model. This model neglects the relative timing of neural spikes.	McCulloch and Pitts, 1943
Hodgkin-Huxley	$C\dot{v}(t) = g_L[v_L - v(t)]$ $+ g N_a m(t)^3 h(t)[v N_a - v(t)]$ $+ g K n(t)^4 (v_K) - v(t) + I,$ $\dot{m}(t) = \dfrac{m_\infty(v(t)) - m(t)}{\tau_m(v(t))}$ $\dot{h}(t) = \dfrac{h_\infty(v(t)) - h(t)}{\tau_h(v(t))}$ $\dot{n}(t) = \dfrac{n_\infty(v(t)) - n(t)}{\tau_n(v(t))}$	$v(t)$ is the membrane potential, $m(t)$, and $h(t)$, and $n(t)$ represent empirical variables describing the activation and inactivation of the ionic conductances; I is an external current. The steady-state values of the conductance variables $m_\infty, h_\infty, n_\infty$ have a nonlinear voltage dependence, typically through sigmoidal or exponential functions.	These ODEs represent point neurons. There is a large list of models derived from this one, and it has become the principal tool in computational neuroscience. Other ionic currents can be added to the right-hand side of the voltage equation to better reproduce the dynamics and bifurcations observed in the experiments.	Hodgkin and Huxley, 1952
FitzHugh-Nagumo	$\dot{x} \mu x - cx^3 - y + I, \quad \dot{y} = x + by - a$	$x(t)$ is the membrane potential, and $y(t)$ describes the dynamics of fast currents; I is an external current. The parameter values a, b, and c are constants chosen to allow spiking.	A reduced model describing oscillatory spiking neural dynamics including bistability.	FitzHugh, 1961; Nagumo et al., 1962

TABLE I. (Continued.)

Model	Example	Variables	Remarks	References
Wilson-Cowan	$\mu \dfrac{\partial E(x,t)}{\partial t} = -E(x,t) + [1 - rE(x,t)]$ $\times \mathcal{L}_e[E(x,t) \otimes w_{ee}(x)$ $- I(x,t) \otimes w_{ei}(x) + I_e(x,t)]$ $\mu \dfrac{\partial I(x,t)}{\partial t} = -I(x,t) + [1 - rI(x,t)]$ $\times \mathcal{L}_i[E(x,t) \otimes w_{ie}(x)$ $- I(x,t) \otimes w_{ii}(x) + I_i(x,t)]$	$\{E(x,t), I(x,t)\}$ are the number density of active excitatory and inhibitory neurons at location x of the continuous neural media. $(w_{ee}(x), w_{ie}(x), w_{ei}(x), w_{ii}(x))$ are connectivity distributions among the populations of cells. $\{\mathcal{L}_e, \mathcal{L}_i\}$ are nonlinear responses reflecting different populations of thresholds. The operator $\otimes$ is a convolution involving the connectivity distributions.	The first "mean-field" model. It is an attempt to describe a cluster of neurons, to avoid the inherent noisy dynamical behavior of individual neurons; by averaging to a distribution noise is reduced.	Wilson and Cowan, 1973
Morris-Lecar	$\dot{v}(t) = g_L[v_L - v(t)] + n(t)g_n$ $\times [v_n - v(t)]$ $+ g_m m_\infty(v(t))[v_m - v(t)] + I,$ $\dot{n}(t) = \lambda(v(t))[n_\infty(v(t)) - n(t)]$ $m_\infty(v) = \dfrac{1}{2}\left(1 + \tanh\dfrac{v - v_m}{v_m^0}\right)$ $n_\infty(v) = \dfrac{1}{2}\left(1 + \tanh\dfrac{v - v_n}{v_n^0}\right)$ $\lambda(v) = \phi_n \cosh\dfrac{v - v_n}{2v_n^0}$	$v(t)$ is the membrane potential; $n(t)$ describes the recovery activity of a calcium current; I is an external current.	Simplified model that reduces the number of dynamical variables of the HH model. It displays action potential generation when changing I leads to a saddle-node bifurcation to a limit cycle.	Morris and Lecar, 1981
Hindmarsh-Rose	$\dot{x}(t) = y + ax(t)^2 - bx(t)^3 - z(t) + I$ $\dot{y}(t) = C - xx(t)^2 - y(t)$ $\dot{z}(t) = r\{s[x(t) - x_0] - z(t)\}$	$x(t)$ is the membrane potential; $y(t)$ describes fast currents; $z(t)$ describes slow currents; and I is an external current.	Simplified model that uses a polynomial approximation to the right-hand side of a Hodgkin-Huxley model. This model fails to describe the hyperpolarized periods after spiking of biological neurons.	Hindmarsh and Rose, 1984
Phase oscillator models	$\dfrac{d\theta_i(t)}{dt} = \omega + \sum_j H_{ij}(\theta_i(t) - \theta_j(t))$	$\theta(t)$ is the phase of the ith neuron with approximately periodic behavior; and H_{ij} is the connectivity function determining how neuron i and j interact.	First introduced for chemical oscillators; good for describing strongly dissipative oscillating systems in which the neurons are intrinsic periodic oscillators.	Cohen et al., 1982; Ermentrout and Kopell, 1984; Kuramoto, 1984
Map models	$x_{t+1}(i) = \dfrac{\alpha}{1 + x_t(i)^2} + y_t(i)$ $+ \dfrac{\epsilon}{N}\sum_j x_t(j)$ $y_{t+1}(i) = y_t(i) - \sigma x_t(i) - \beta$	x_t represents the spiking activity and y_t represents a slow variable. A discrete time map.	One of a class of simplephenomenological models for spiking, bursting neurons. This kind of model can be computationally very fast, but has little biophysical foundation.	Cazelles et al., 2001; Rulkov, 2002

Mikhail i. Rabinovich et al, Reviews of modern physics, vol 78, 2006

Neuron network

A Schematic Map of Olfactory Representations in the Adult Brain

For the 13 PNs analyzed, each PN sends dendrites to a single antennal glomerulus and an axon giving one to four major branches in the MB calyx. KC dendrites are segregated into 17 complementary domains defined by two orthogonal factors (four vertical K1–K4 clonal divisions by four horizontal sequential birth domains plus one 4-fold K5 domain).
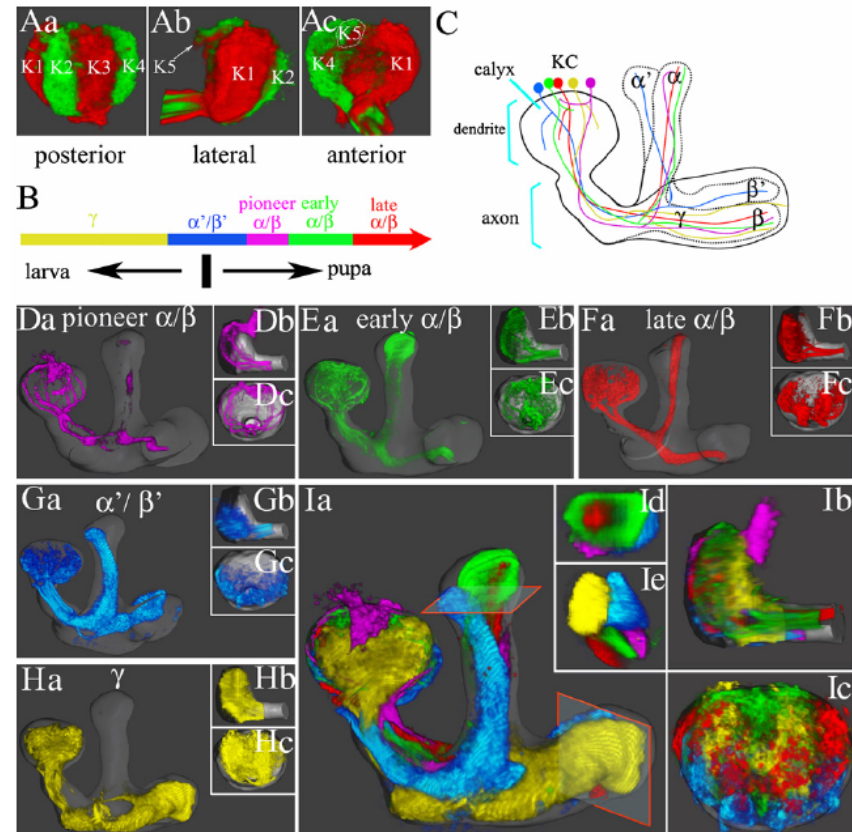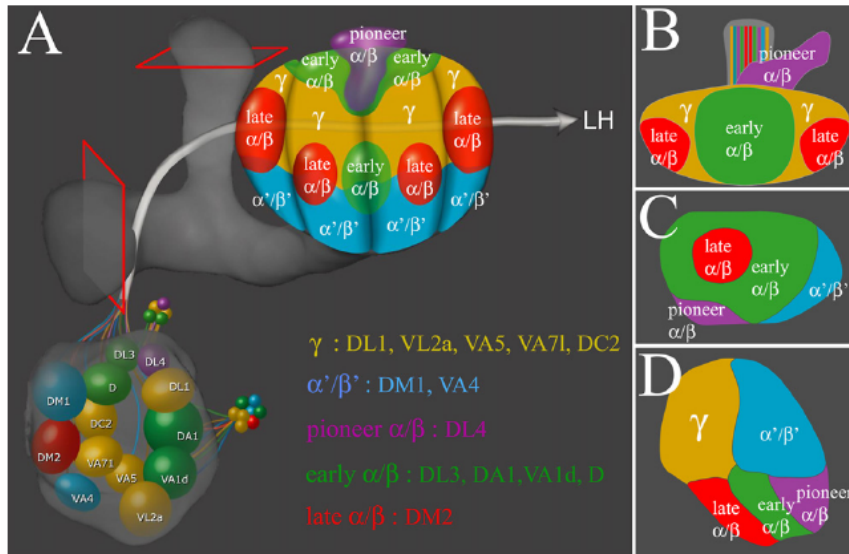
6. Thermodynamics (non-equilibrium biosystems)
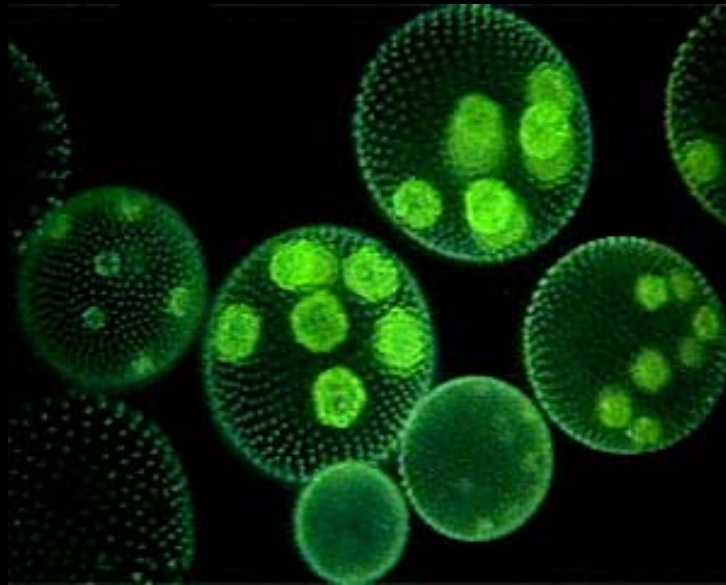
Useful work and free energy

The 2. law tells us

$$dS_O + dS \geq 0$$

Since

$$dS_O = -dQ/T$$

and

$$dU = dQ + dW$$

we have

$$dU - dW - T\,dS \leq 0.$$
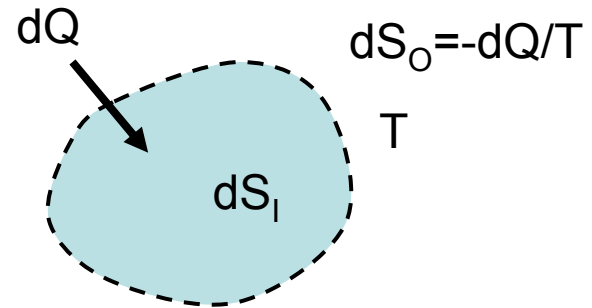
Since the work W includes the hydrostatic work $-PdV$ performed on the system and other non-hydrostatic work W', it yields

$$dU + P\,dV - d\,W' - T\,dS \leq 0.$$

At constant P and T,

$$dW' \geq d\,(U - TS + PV) = dG. \qquad \text{(Gibbs free energy)}$$

For system in which P and V are irrelevant, W = W' and

$$dW \geq d\,(U - TS) = dF. \qquad \text{(Helmholtz free energy)}$$

dQ

$dS_O = -dQ/T$

T

dS_I

That is in a thermodynamic process from a state (macro) to another state, the work performed on the system is larger than the difference of the free energies between these two states:

$$W \geq \Delta G, \qquad \text{(where W' has been simplified as W).}$$

The inequality is ascribed to the inequality in the 2. law:

$$\Delta S \geq 0.$$

These two relations become equalities when the process is reversible, for which the process has to be infinitely slow so that

$$\Delta S = \Delta Q/T = (\Delta U - W) / T = 0 \qquad \Rightarrow \qquad \Delta U = W.$$

That is the work from the environment can be perfectly transformed to and completely stored in the internal energy.

In such a reversible process,

$$\Delta G = W_{rev}.$$

Jarzynski's Equality

Therefore, the external work W performed on the system can be used to estimate the maximum possible value of the free energy difference:

$$\triangle G \leq <W>$$ (Gibbs free energy   G = U + PV − TS)

where the <> denotes an average over several experimental measurements under identical conditions.

- Since that work given to the system is bound to dissipate away partially, this inequality is quite understandable.

- Determining free energy difference from measuring the work done on the system will require infinitely slow processes and therefore is impossible in practice.

- Nevertheless, recently Jarzynski showed that the identity for any process:

$$\exp\left(-\frac{\Delta G}{k_{\mathrm{B}}T}\right) = \left\langle \exp\left(-\frac{W}{k_{\mathrm{B}}T}\right)\right\rangle$$

- This gives the important implication that the equilibrium quantity $\triangle F$ or $\triangle G$ can be extracted from non-equilibrium (real) measurements.

RNA Experiment on Jarzynski equality

A molecule of RNA is attached to two beads and subjected to reversible and irreversible cycles of folding and unfolding.

A piezoelectric actuator controls the position of the bottom bead.

An optical trap captures the top bead and determines the force exerted on the RNA.

The position difference of the two beads gives the end-to-end length of the molecule.

The diameter of the beads is around 3000 nm, much greater than the 20-nm length of the RNA.
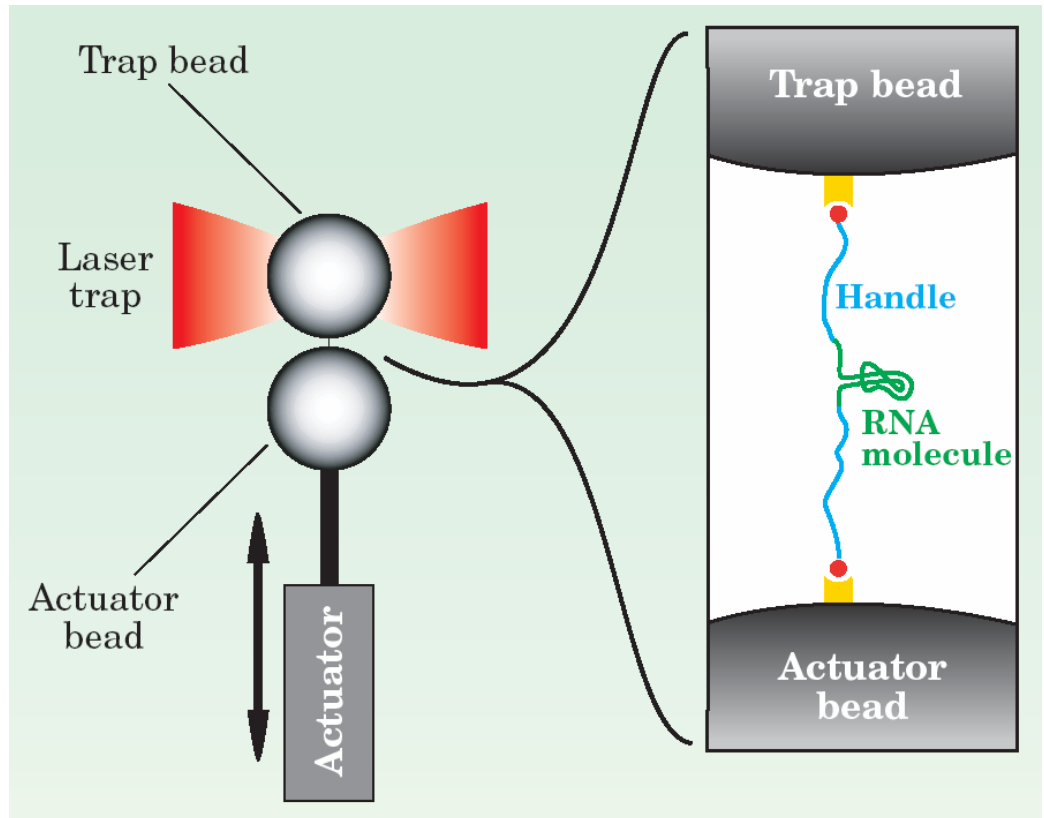
The work to stretch a polymer

a. The work required to stretch a short polymer is a fluctuating function,
As shown in the three different nonequilibrium trajectories obtained as the
control parameter X varies from 0 to X_f.
The continuous black line is the work averaged over all trajectories.

b. In the nonlinear regime, the work probability distribution P(W) has a
Gaussian component plus long non-Gaussian tails describing rare
processes.
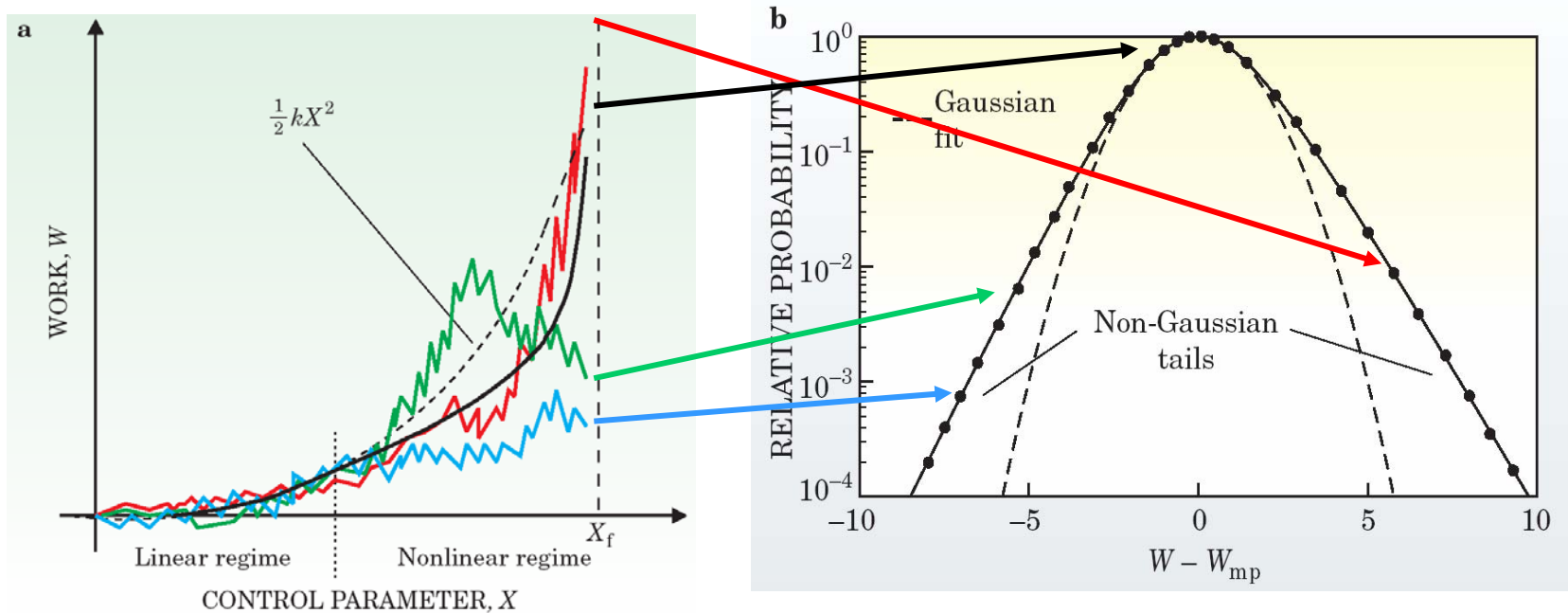
Crooks fluctuation theorem

Jarzynski's equality can be proved from the Crooks theorem.

Consider the forward (F) and reverse paths (R) with:

$$x_F(t) \quad \text{and} \quad x_R(t) = x_F(t_f - t).$$

At the beginning of the F and R paths the system is in equilibrium with the bath at temperature T.

Crooks fluctuation theorem:

$$\frac{P_F(W)}{P_R(-W)} = \exp\left(\frac{W - \Delta G}{k_B T}\right).$$

Rewriting this relation as

$$P_F(W) \exp(\Delta G/k_B T) = P_R(-W) \exp(W/k_B T),$$

and integrating both sides along paths, one gets the Jarzynski's equality after some steps of calculations.

Physical problems in Bio system

Molecular level: Quantum mechanics

Cell level: Mechanics, Electrodynamics, Thermodynamics

Tissue level: Nonlinear science, statistical mechanics