Grundlagen der Biologie
Zellbiologie IIA

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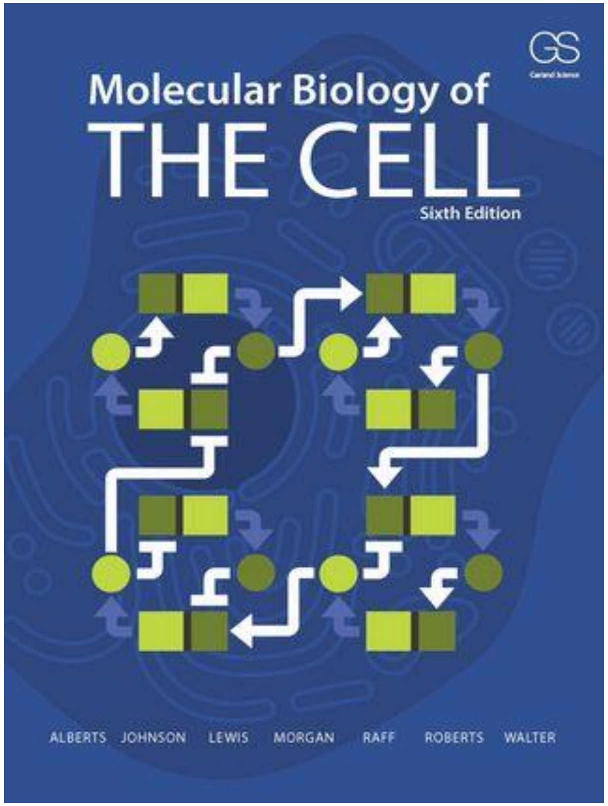
Questions about the course: Ernst Hafen

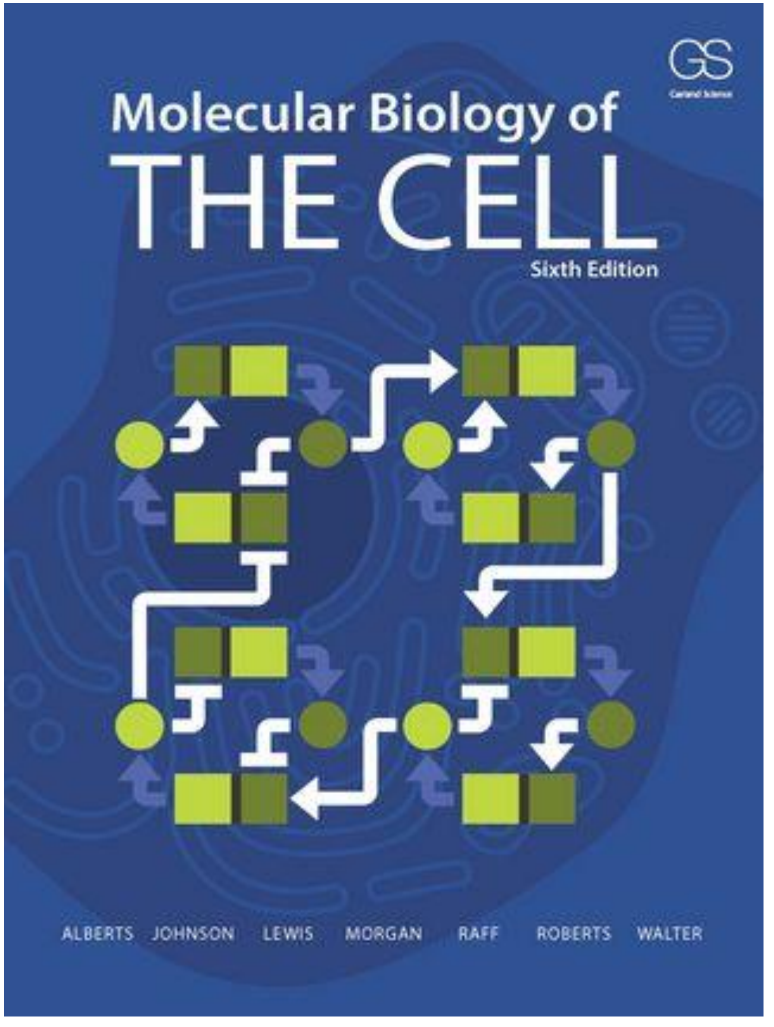
Questions about the exams: Ueli Suter



Paul Scherrer Institut

An der Aare gelegen
zwischen Baden / Brugg / Koblenz
unabhängiges Institut der ETH

Lecture 1: Introduction to cell biology



Overview

1. Introduction to Cell Biology

Tuesday, 19.9.2017

2. Membrane Lipids

Tuesday, 19.9.2017

Chapter 10 (565 - 576)

3. Membrane Proteins I

Thursday, 21.9.2017

Chapter 10 (576 - 596)

4. Membrane Proteins II

Monday, 25. 9. 2017

Chapter 10 (576 - 596)

5. Working with Membrane Proteins

Monday, 25. 9. 2017

Chapter 8 (439 - 462)

Topics of introductory lecture

- Atoms to organisms
- Cell as basic unit of life
- What is Cell Biology?
- Recurring themes
  - The structure/ function relationship
  - Short range interactions
  - Molecular machines
  - The fourth dimension: evolution
  - Domains; the ‘Lego principle’
  - The ever-present regulatory networks
  - Dynamics and motion
  - Biosynthesis-degradation / Assembly-disassembly
  - Quality control
  - Compartmentalization

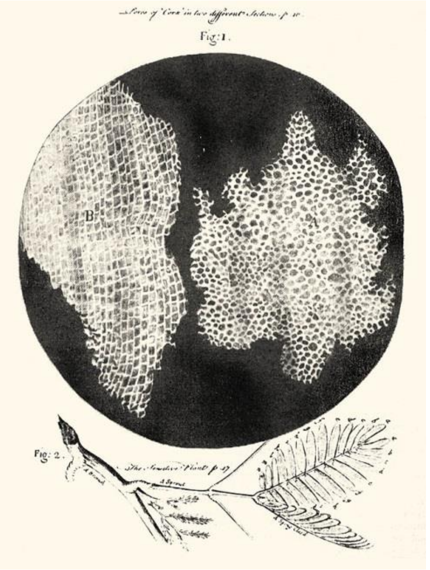
Time domains in biology

- Evolution: Million of years
- Human life cycle: 80 years
- Circadian day night rhythm: one day
- Cell division: hours
- Enzyme activation: milliseconds
- Protein motion: microseconds
- Formation of early photoproduct: picoseconds
- Retinal isomerzation: femtoseconds
- Photon capture orbital rearrangements: atoseconds

Hierarchy of life

- Atoms
- Molecules
- Macromolecules
- Macromolecular complexes
- Cellular organelles
- Cells
- Tissues
- Organs
- Organisms
- Social and environmental entities

Basic facts about cells - 1



Cells are the smallest units capable of independent life and reproduction

Identified by Robert Hooke in 1665

Antoni van Leeuwenhoek discovers bacteria and red blood cells (1670-1700)

Cells always derive from cells (Omnis cellula e cellula). Rudolf Virchow, 1855

Cells do not appear spontaneously. Louis Pasteur

Before: (generatio spontanea)

Basic facts about cells - 2

They have evolved from a common ancestor cell through natural selection.

Our body contains about 10^{13}-10^{14} cells. More then 200 different cell types, many of them highly specialized (may be many more unknown types!)

Each cell carries, as a rule, the full genomic blueprint of the organism in the form of DNA.

In the human genome there are about 20,000 genes encoding >100,000 different proteins and nucleic acid molecules.

Since membranes are always derived from membranes, the fertilized egg also provides the 'seed' membranes for all our membrane-bounded organelles.

What is Cell Biology?

- Atoms
- Molecules
- Macromolecules
- Macromolecular complexes
- Cellular organelles
- Cells
- Tissues
- Organs
- Organisms
- Social and environmental entities

Biochemistry

Cell Biology

Physiology

At each level, the functions and properties of each unit are determined by:

- Intrinsic properties
- The context

Example 1. An atom in a protein

-The properties of an atom in the amino acid side chain of a protein is primarily determined by its intrinsic properties (i.e. what type of atom it is: C,N,O,H..).

-However, in the case of a particular atom it also affected by neighboring atoms through local interactions.

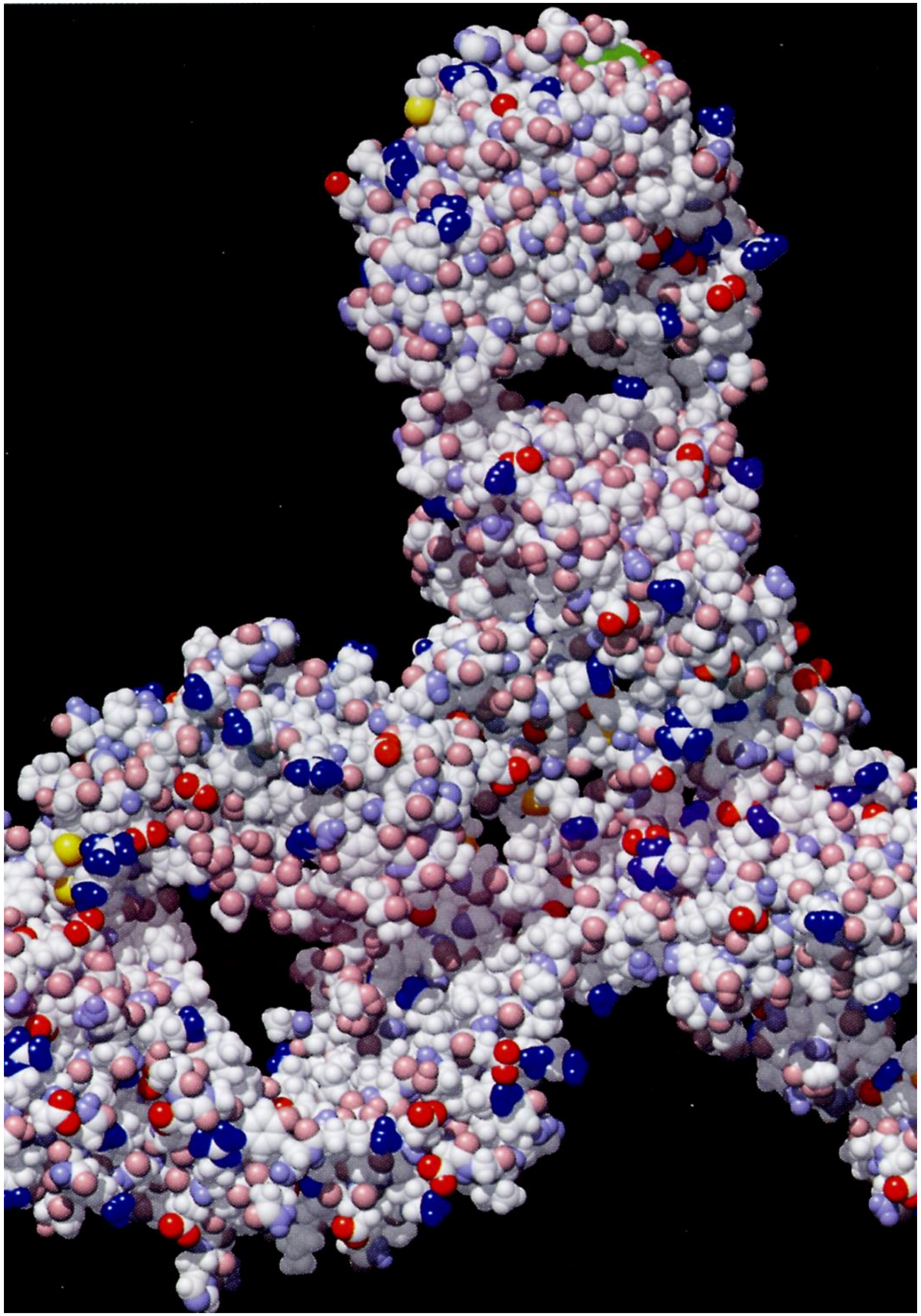
-The atom may, however, have been brought together with its local neighbors in the folded protein by distant folding features that determine the over-all three dimensional structure of the protein molecule.

The properties of the atom therefore depends on its: 1) intrinsic properties, and 2) the context (local and global).

for example nmr NMR NOE spin state of atoms that are close

Example 1: An atom in a protein

The crystal structure of an immunoglobulin molecule, IgG, with all atoms shown.

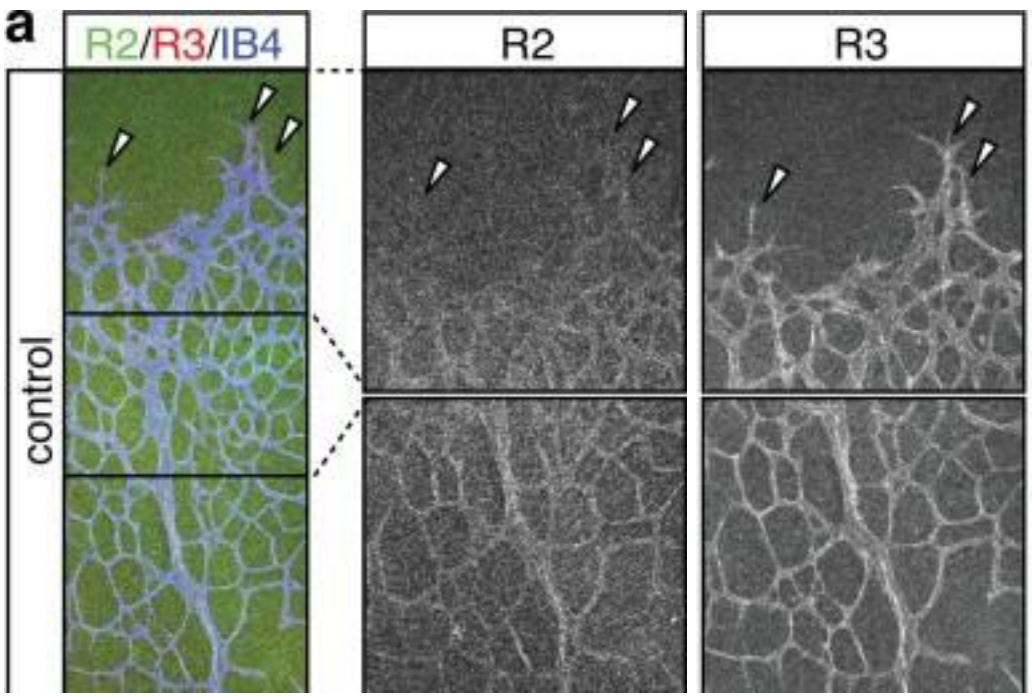


Example 2: Proteins in a cell

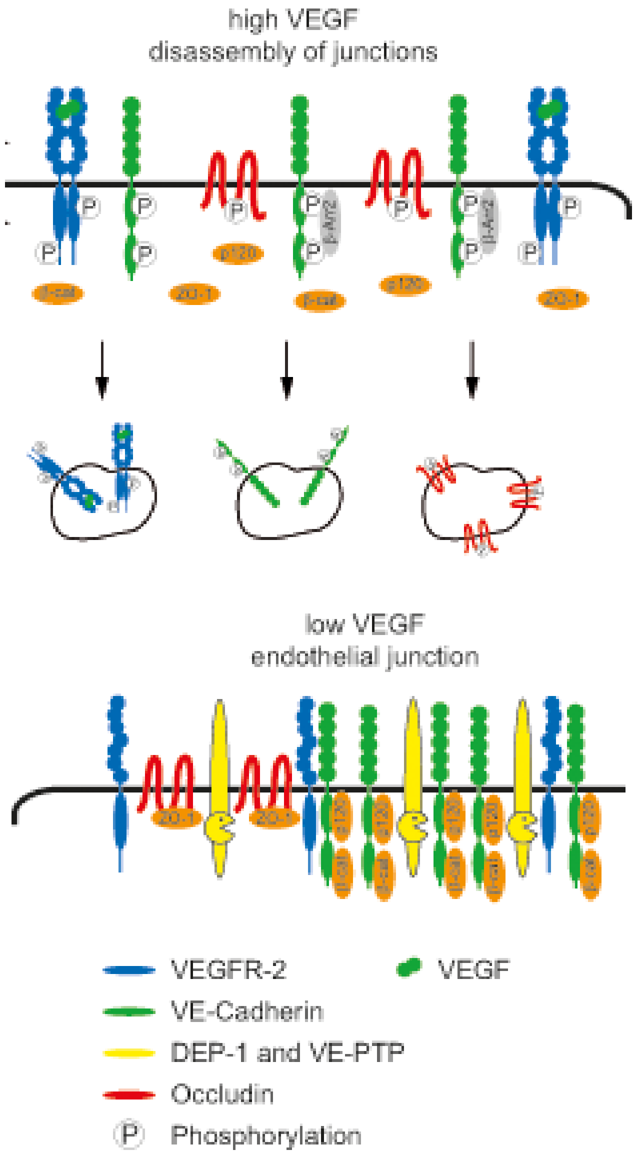
- The properties of a particular protein is determined by what type of protein it is.
- However, it is also influenced by interacting proteins, by post-translational modifications, by the concentrations of substrates and inhibitors, by its location, etc.
- It is not only regulated by molecules that interact with it directly and locally, and but also by molecules that interact with it indirectly, i.e. it is affected by distant molecules in the network.
- The protein's functions are determined by: 1) its intrinsic properties, and 2) by influences determined by the context (local and global).

Example 2: VEGFR in endothelial cells

VEGFR: Vascular endothelial growth factor
VE-Cadherin: part of adherens junctions



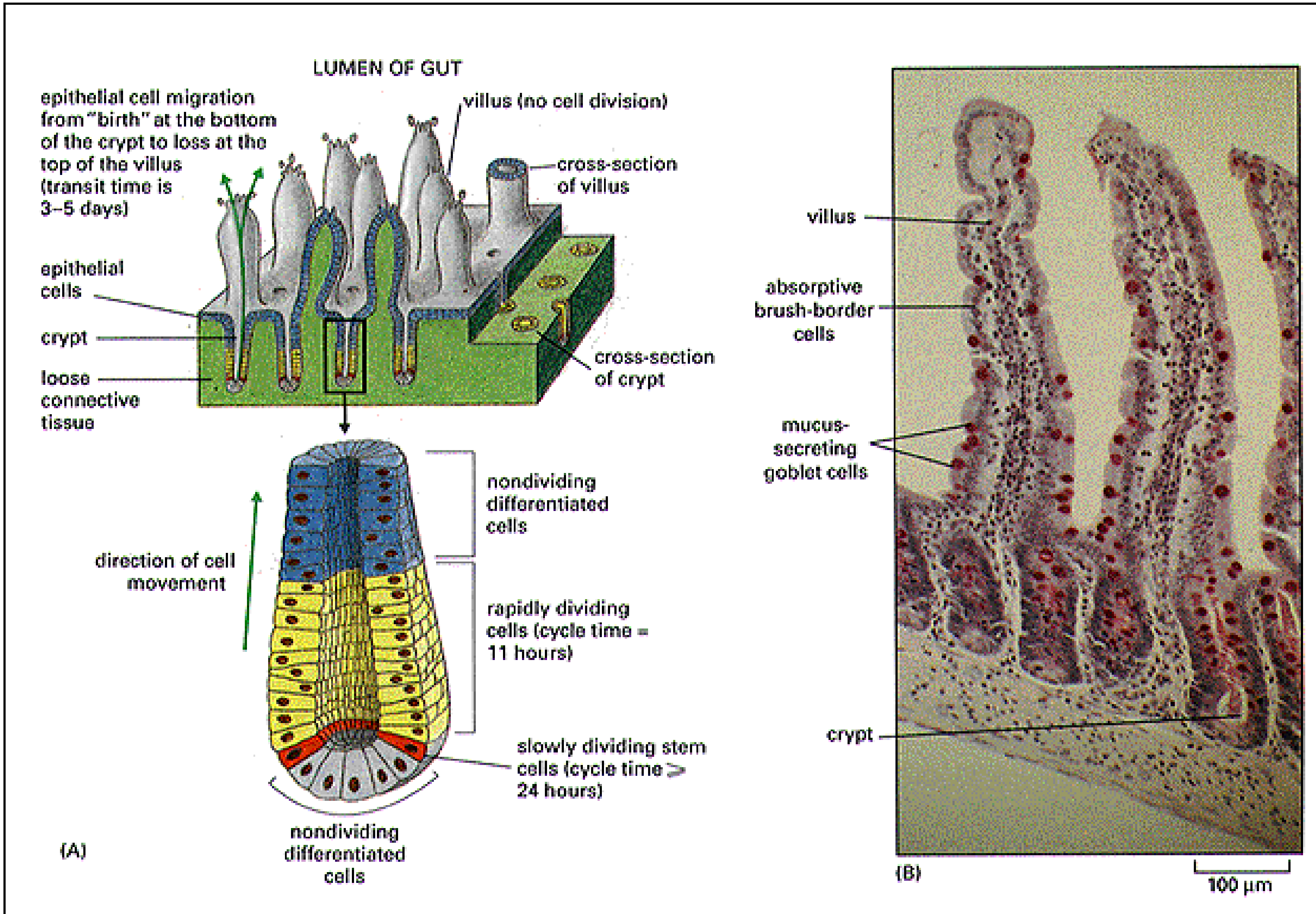
Nakayama et al., Nat Cell Biol., 2013



Example 3: Cells in a tissue

- In a multicellular organism, the properties of a particular cell is determined by what cell type it belongs to.
- However, it is also controlled by a multitude of messages and signals that it receives from neighboring cells and from distant cells via direct contacts, hormones, and other signaling molecules.
- The cell's functions, its state of differentiation, its fate, and behavior are thus determined by 1) its intrinsic properties, and 2) by influences determined by the context (local and global).

Example 3: Cells in a tissue communicate



10 Central Themes

There are many themes in Cell Biology.

During the course many of them will come up over and over:

Knowing them ahead of time may help you to understand the basic conceptual frame work of cell life.

Summary of the 10 themes

1. Structure-function relationship
2. Short range interactions
3. Molecular machines
4. The evolutionary perspective (homology)
5. Modularity in structure (the Lego principle)
6. Regulation and signaling networks
7. Everything is dynamic
8. Biosynthesis-degradation; assembly/disassembly
9. Quality control
10. Compartmentalization

Theme 1

The structure/function relationship

From the smallest molecule to the largest organism, structure always reflects function, and function determines structure. Therefore, a huge effort is spent in trying to determine the structure of proteins, organelles, cells, tissues, biological networks, etc.

"The aim of modern biology is to interpret the properties of the organism by the structure of its constituent molecules."

Francois Jacob 'The logic of life' 1973

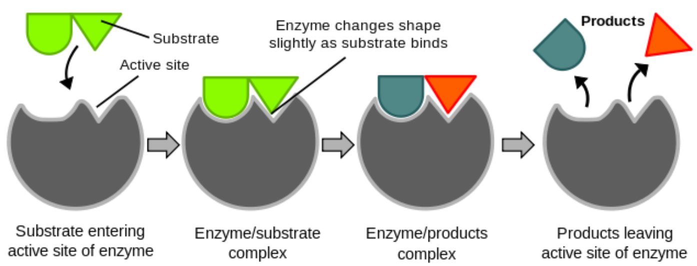
"If we are to understand how cells are constructed and how they function, we must use the language of chemistry"

Christian de Duve 'A guided tour of the living cells' 1984

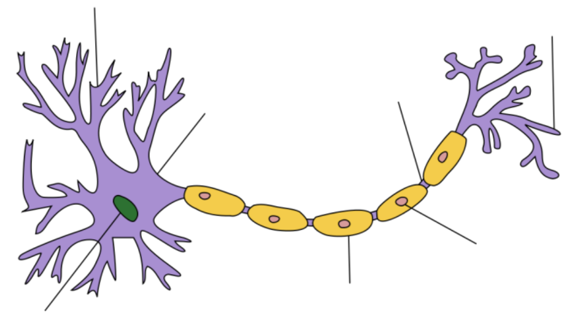
Theme 1 - Examples

The structure/function relationship

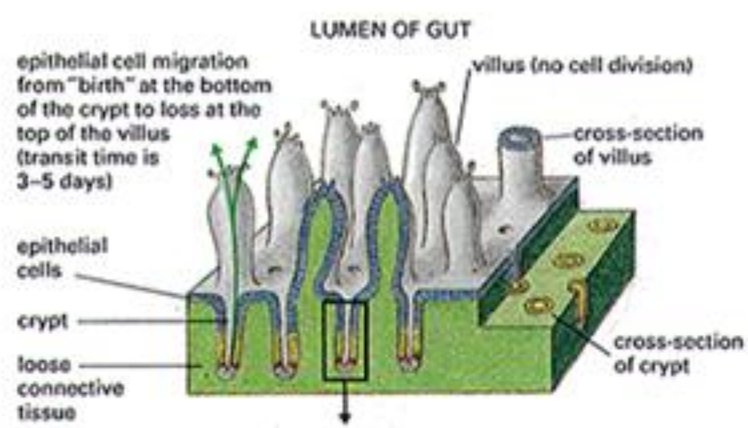
Molecular level – catalysis



Cellular level – signal transmission



Tissue level – food uptake



Social level – sports

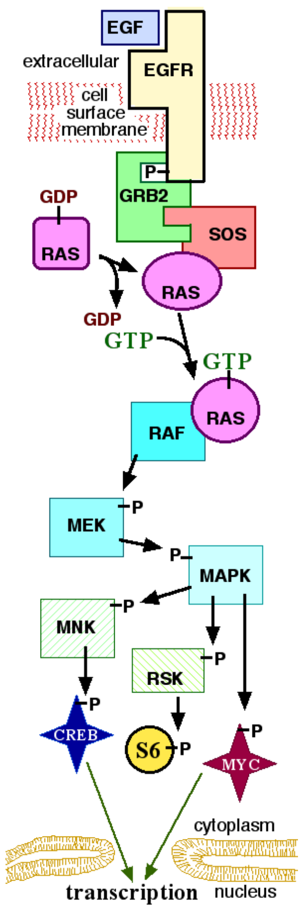
Theme 2. Short-range interactions

- Cellular functions depend on specific molecules and their mutual interactions.
- As a rule, cellular processes depend on direct, short-range interactions between molecules.
- Often, these involve contacts between complementary surfaces of macromolecules.

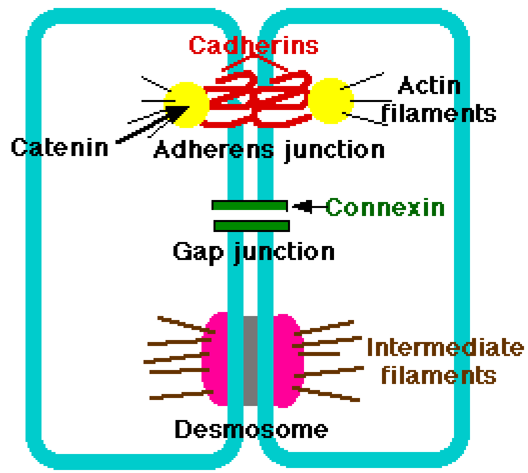
Theme 2 – Examples

Short-range interactions

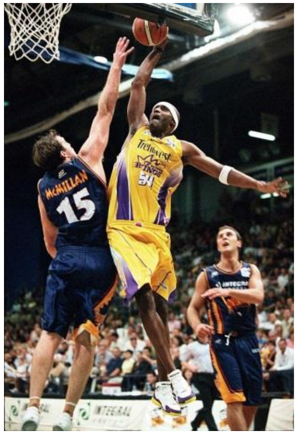
Molecular level



Cellular level



Social level



Theme 3. Molecular machines

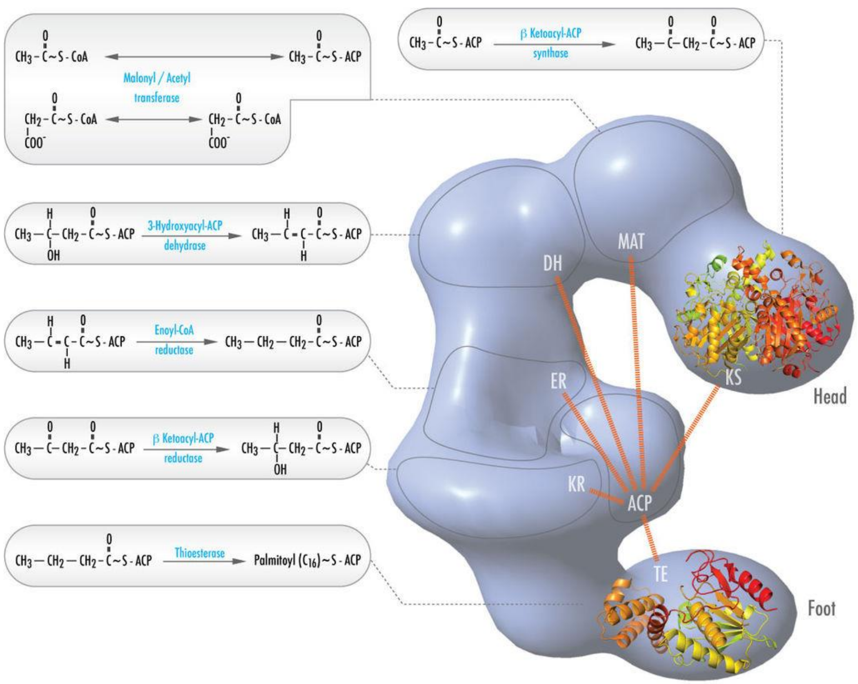
•Macromolecules and macromolecular assemblies constitute, as a rule, solid bodies. They interact with each other through surface contacts.

•Their functions can often be understood in ‘mechanical’ terms. To describe molecules and their functions, words such as ‘hinges’, ‘levers’, ’arms’, ’rotors’, ‘spacers’, ’adaptors’, ’coats’, ’tunnels’, ’motors’, ’scaffolds’, ‘fingers’ etc. are frequently used. These are words with a defined meaning in our macroscopic world. However, they can be applied surprisingly well to describe the microscopic processes in cells.

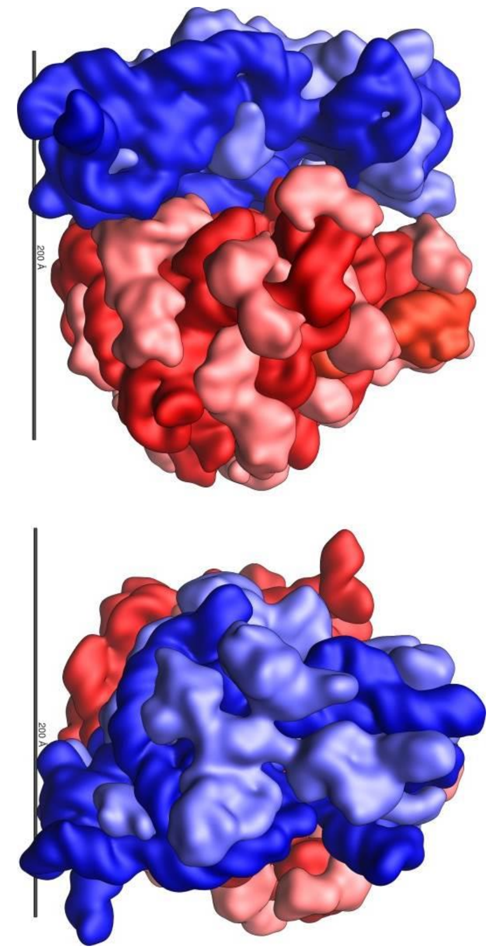
•Many macromolecules and macromolecular assemblies can, in fact, be viewed as ‘miniature machines’ designed to perform specific functions. They do their job accurately, efficiently, and consistently.

Theme 3 – Examples
Molecular machines

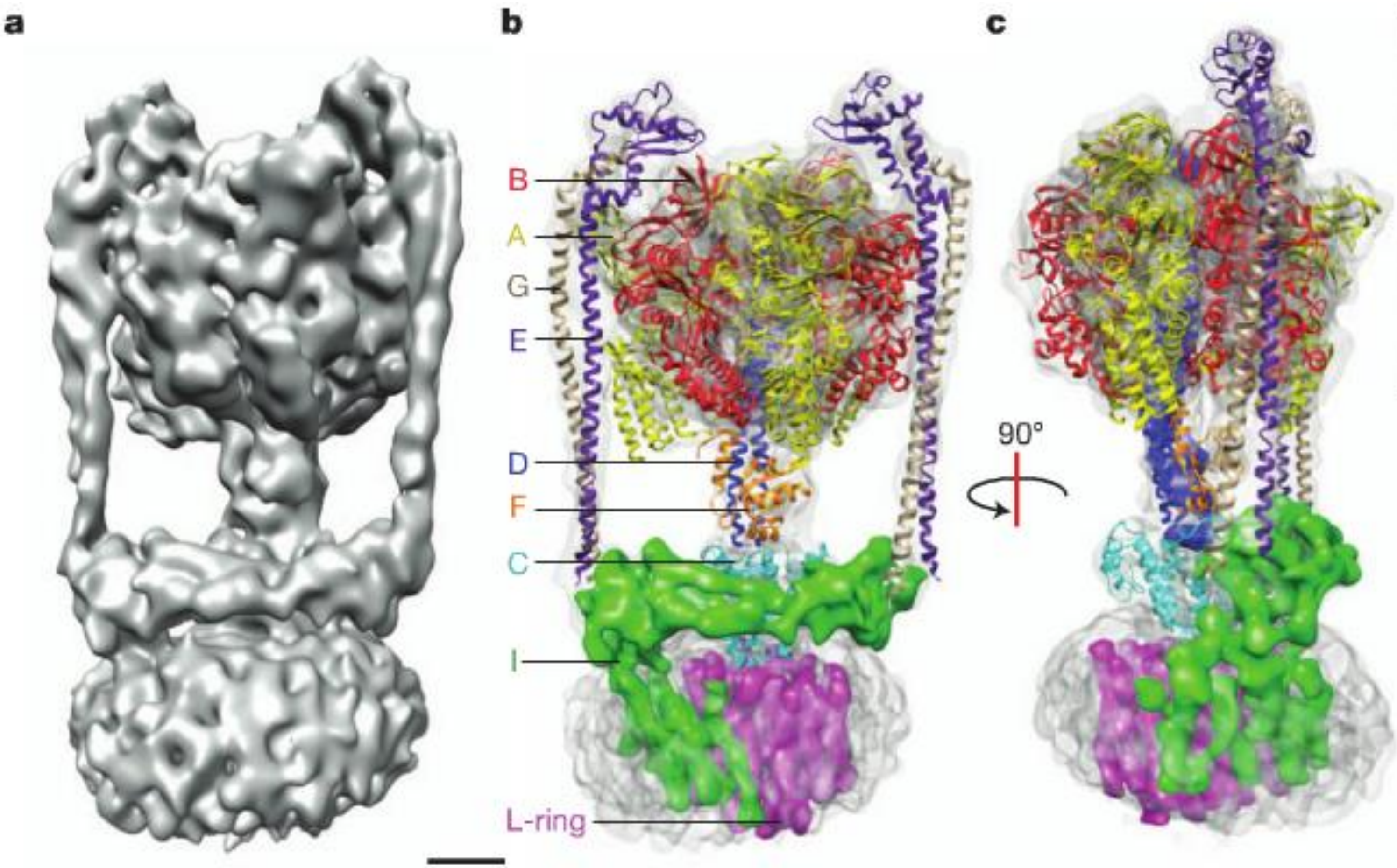
Fatty acid synthase



Ribosome



ATP Synthase



25Å

LETTER

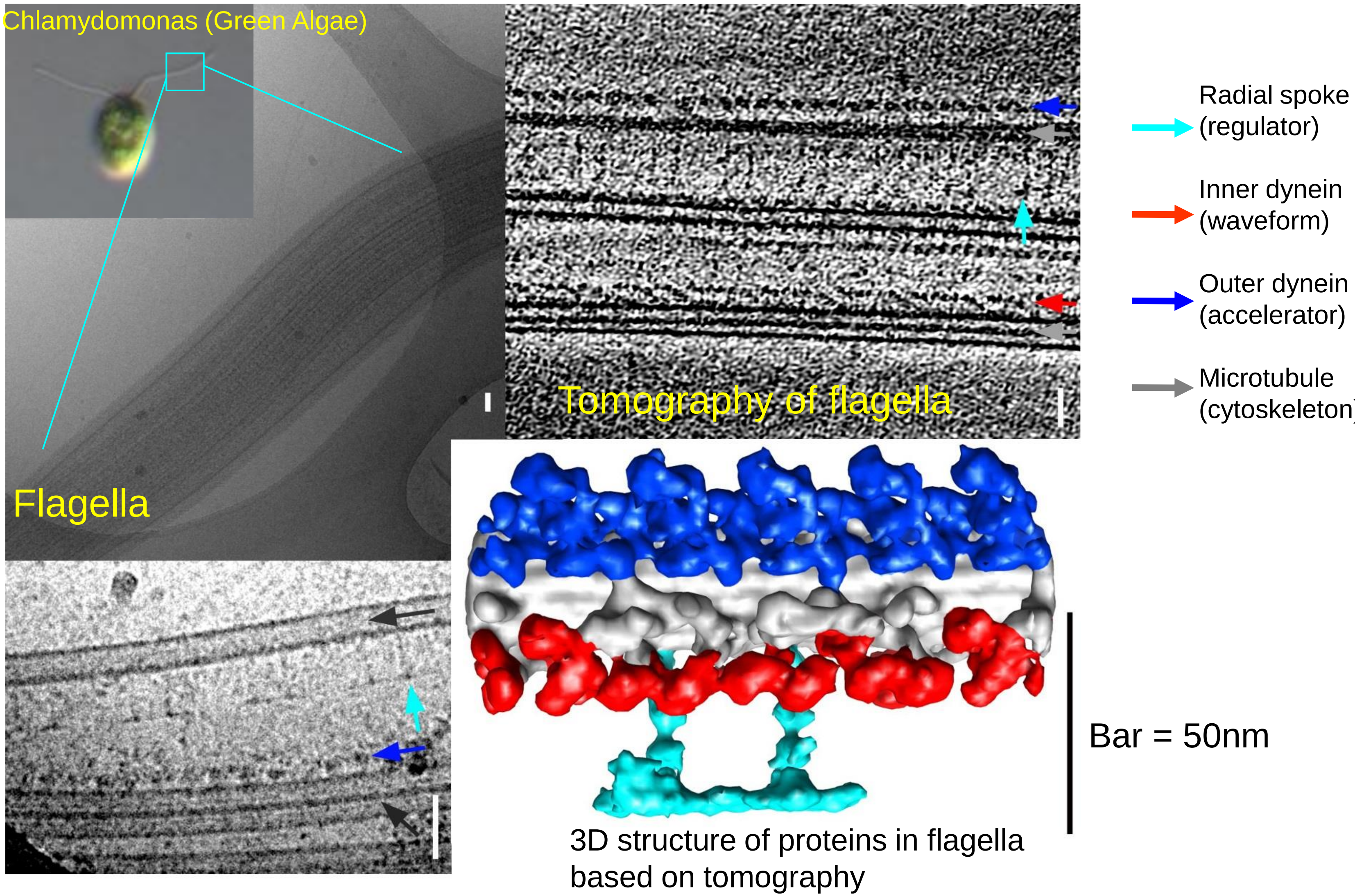
doi:10.1038/nature10699

Subnanometre-resolution structure of the intact *Thermus thermophilus* H$^+$-driven ATP synthase

Wilson C. Y. Lau[1,2] & John L. Rubinstein[1,2,3]

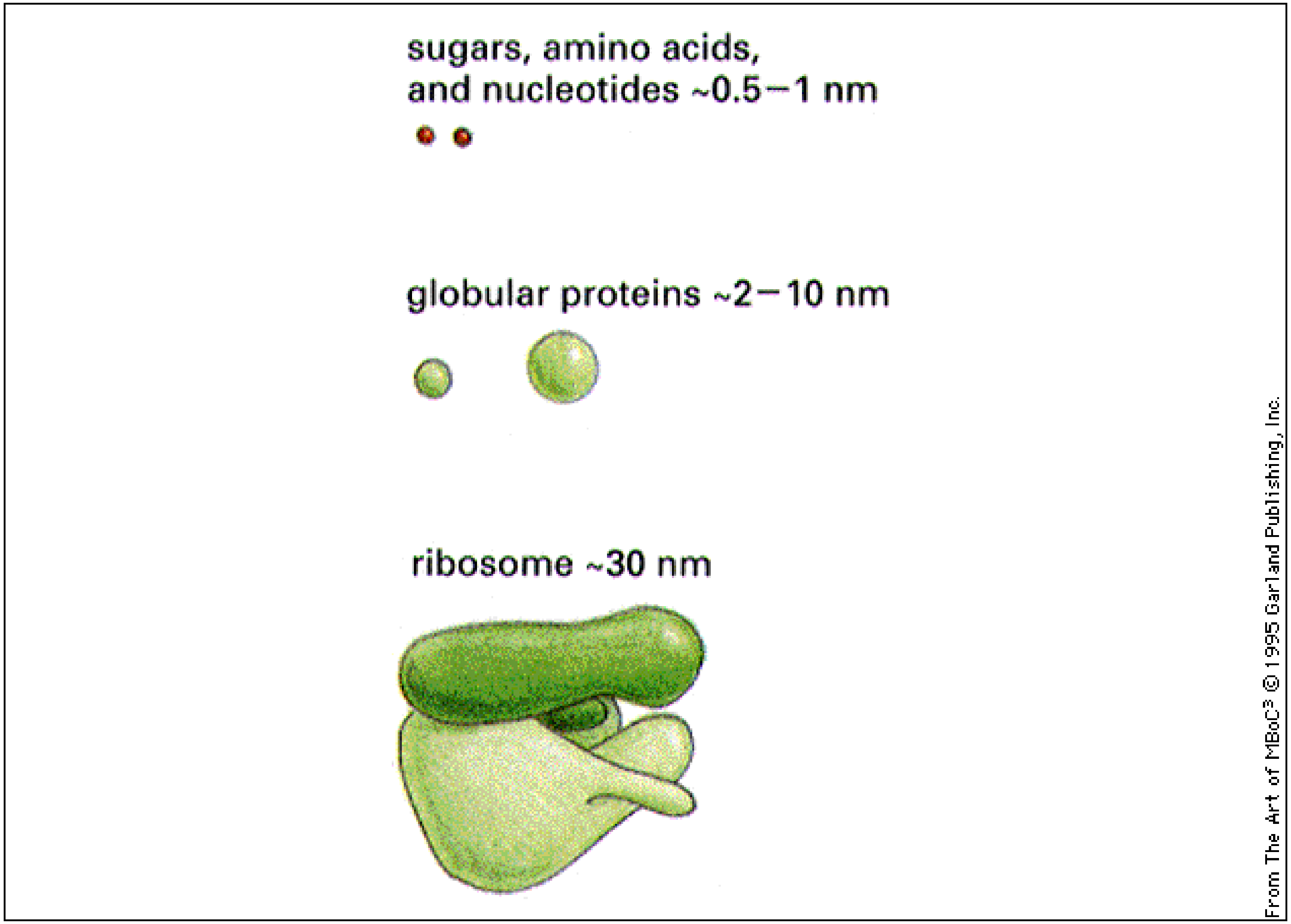
Single Particle Cryo-Electron Microscopy

Cryo-electron tomography of flagella and cilia

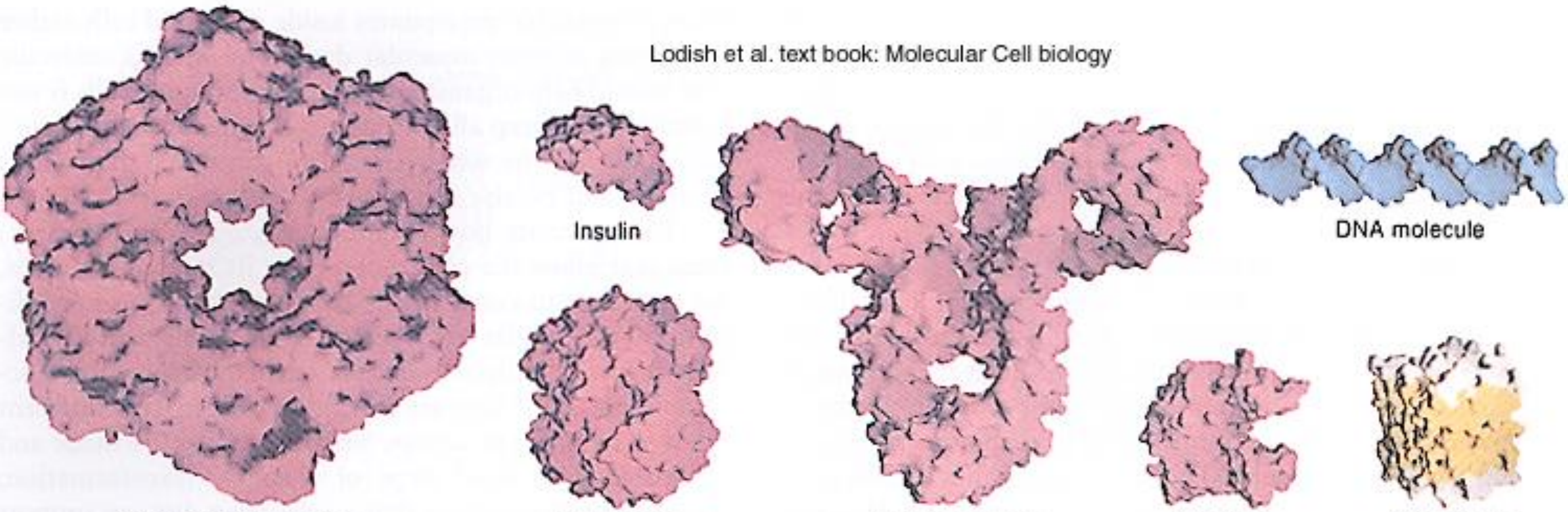


Modified from Bui et al. (2009) J. Cell Biol. 186, 437; Movassagh et al. (2010) Nat. Struct. Mol. Biol. 17, 761.

It is useful for you to develop a sense for the relative sizes of molecules and assemblies



A sense of scale and size relationships



▲ FIGURE 1-7 Shapes and sizes of proteins. Shown is a representative set of proteins, drawn to a common scale and compared with the sizes of a lipid bilayer sheet and a DNA molecule. Each protein has a defined three-dimensional shape held together by numerous chemical bonds. The illustrated proteins include enzymes (adenylate kinase and glutamine synthetase), a hormone (insulin), an antibody (immunoglobulin), and the blood's oxygen carrier (hemoglobin). [Courtesy of Gareth White. Lipid bilayer: adapted from Richard M. Venable, et al., 1993, *Science* **262**:223; Immunoglobulin G: J. Deisenhofer, 1981, *Biochemistry* **20**:2361, and H. D. Kratzin et al., (1989) Biol. Chem. Hoppe-Seyler **370**:263; glutamine synthetase: M. M. Yamashita, et al., 1989, Journal of Biological Chemistry **264**:17681; adenylate kinase: D. Dreusicke, et al., 1988, J. of Mol. Biol. **199**:359; insulin: E. N. Baker et al., 1988, *Philos. Trans. R. Soc. London* **319**:369; hemoglobin: B. Shaanan, 1983, J. Mol. Bio. **171**:31.]

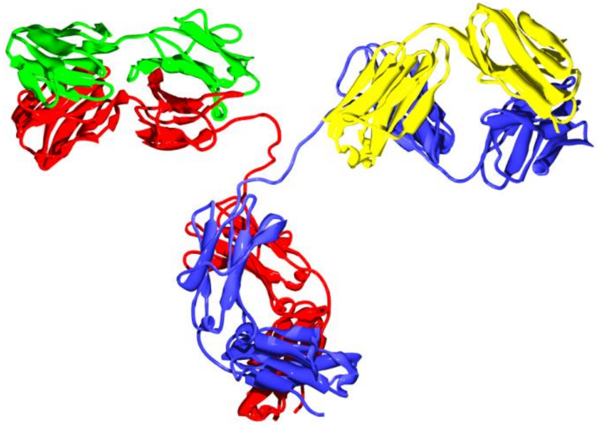
Theme 4: Evolution allows us to make sense of the bewildering variety in the living world

- All life forms have likely evolved from a single primordial cell
- Evolution works by modifying the already existing:
  - point mutations for fine tuning molecular properties.
  - genetic recombination for more major changes.
  - gene duplication to introduce variations of existing themes.
- The mechanism of change involves random modifications in the genome followed by selection for fitness
- Structures and functions therefore show similarity in all forms of life. There is fundamental homology across all species.
- It follows that all organisms are relevant as objects of analysis in molecular and cellular biology

Theme 5. 'The Lego principle'

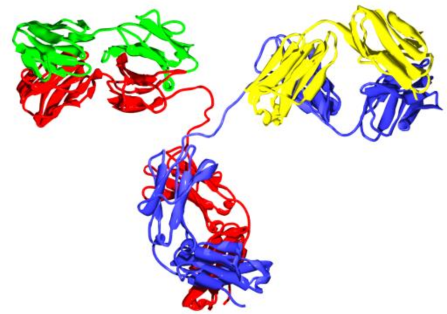
- Building blocks are modified and reused
  - 20 amino acids form many different proteins
  - protein domains are used in many proteins
  - cell types form an organism

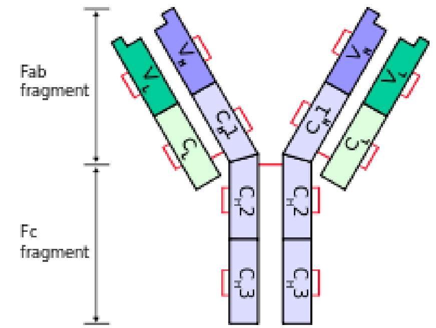
Immunoglobulin domain
90-110 amino acids



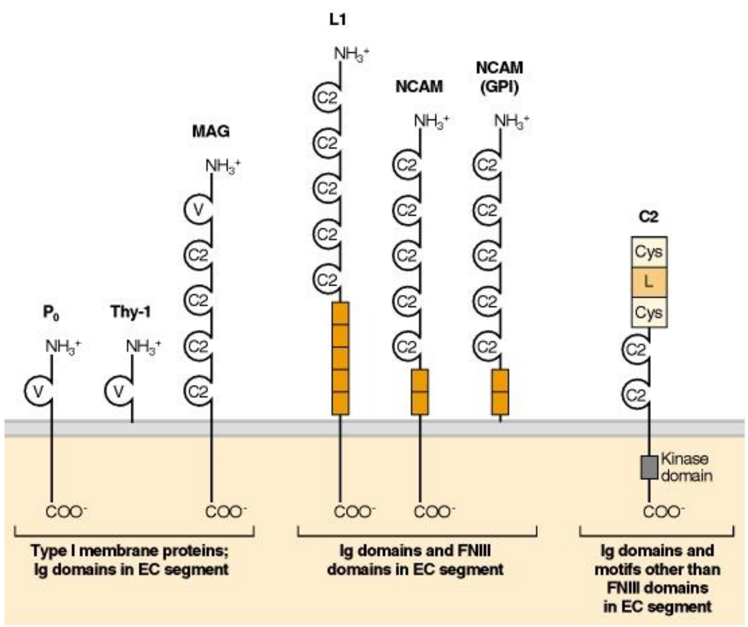
Example: Ig Domains

Immunoglobulin domain
90-110 amino acids





Initially identified
in Immunoglobulins



But this domain can be found in more than 250 proteins

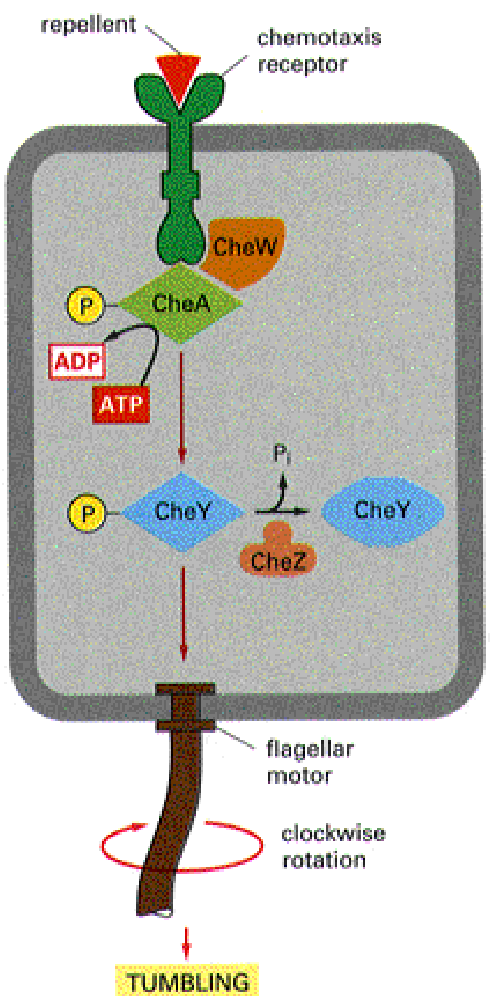
Often in combination with other domains

Theme 6: Regulatory networks

Every aspect of cell life is regulated

- by the cell's differentiation program
- by the immediate neighbours via contacts
- by hormones, growth factors, neurotransmitters, extra-cellular matrix components, supply of nutrients.
- by physical stimulation
- by internal regulatory networks
- by pathogens, etc.

Example of simple regulatory system:Chemotaxis receptors control the flagellar motor in E.coli.15-66



Example 2. Typical signaling pathway involving extracellular agent that induces activation of genes

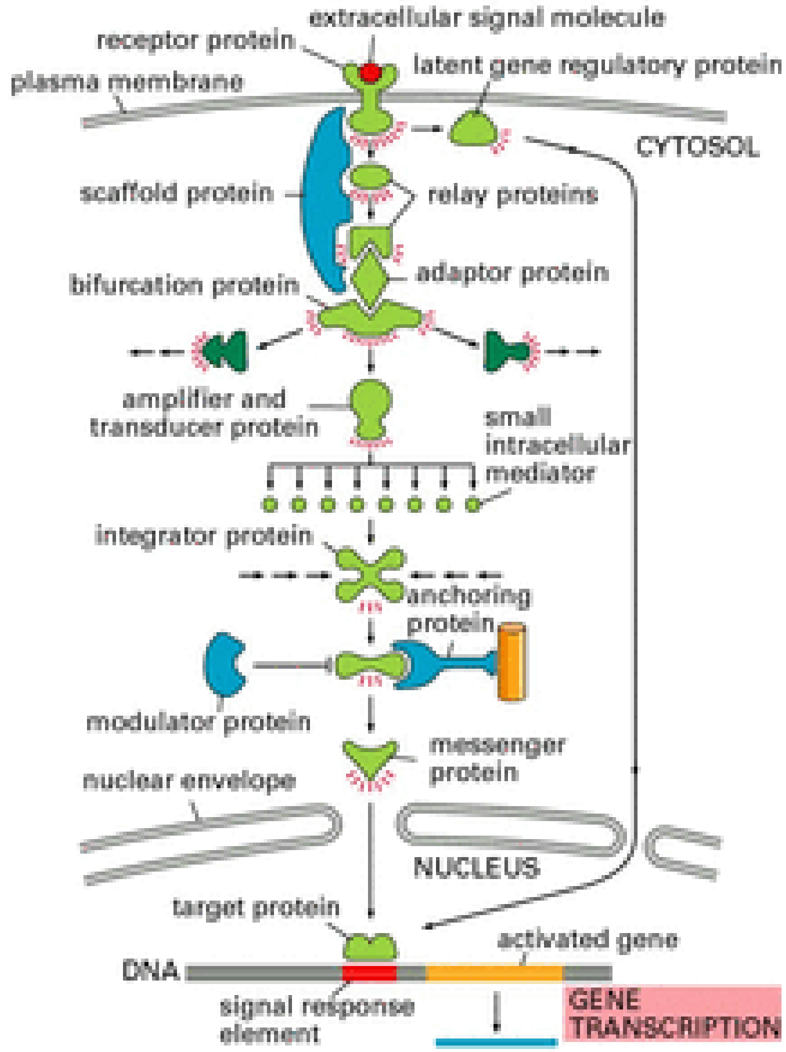
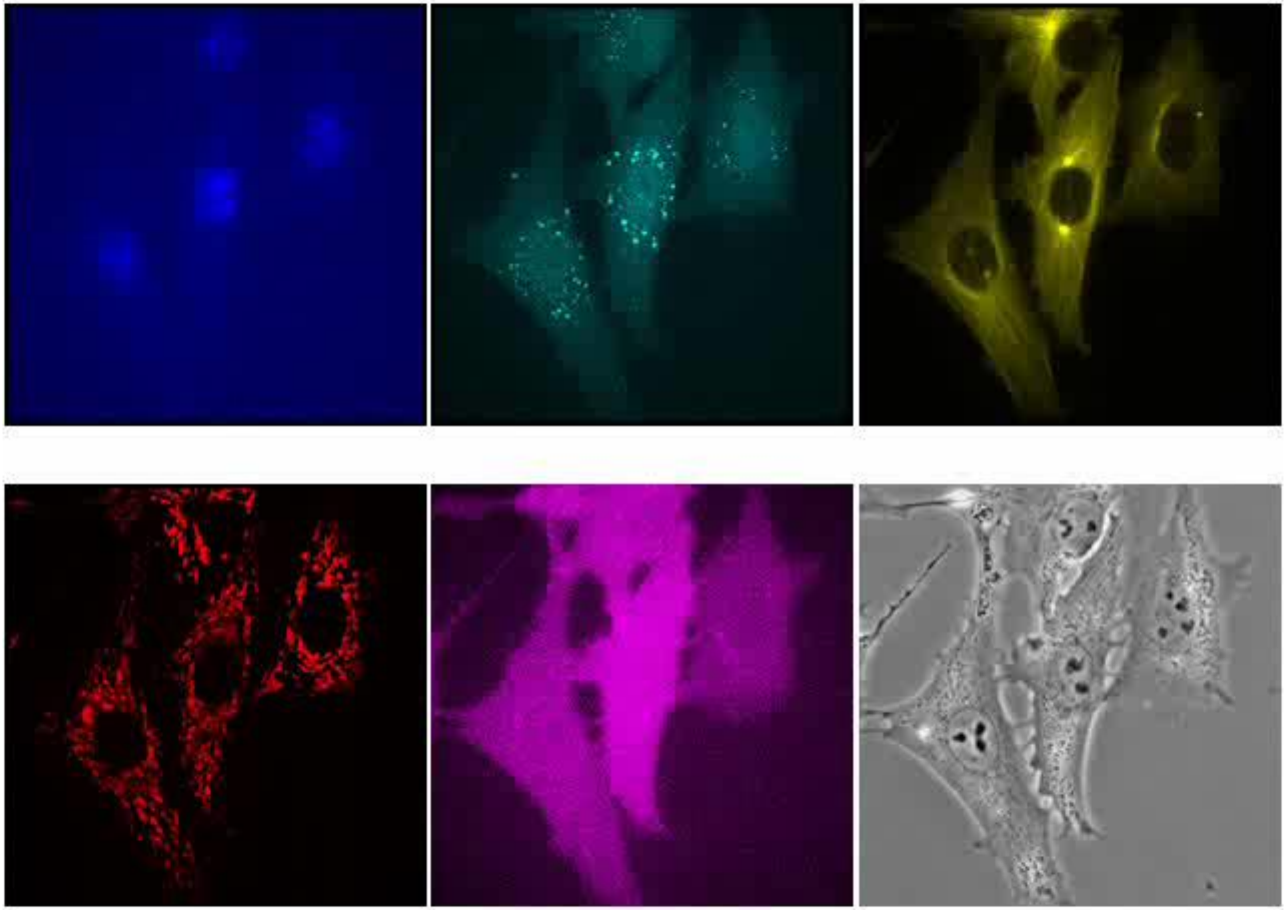


Figure 15-16. Molecular Biology of the Cell, 4th Edition.

Theme 7: Processes in the cell are dynamic



EBFP-Nuc

mTFP1-FYVE

EYFP-tubulin

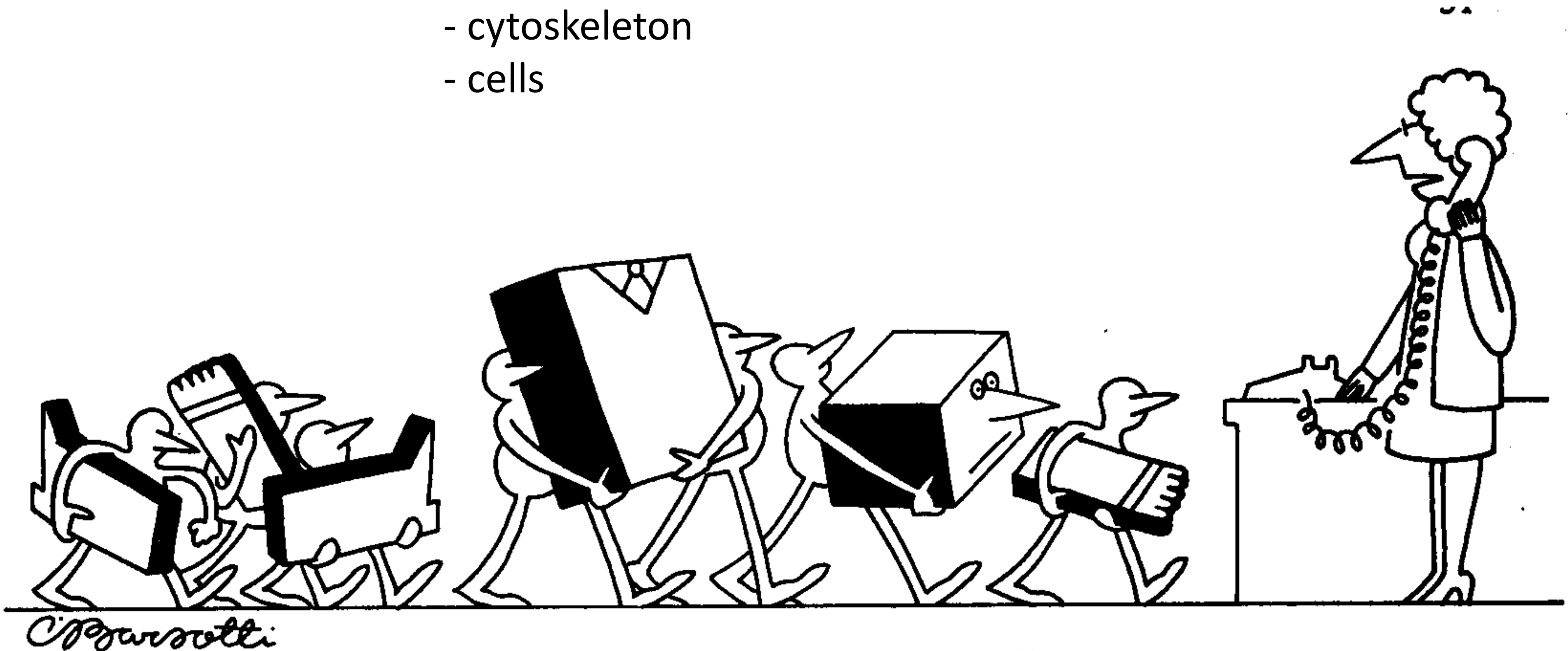
Mito-dsRed

Plum-PLCδ-PH

Movie_640_480

Theme 8: Structures are continuously assembled/disassembled, and synthesized/degraded.

Examples:
- proteins
- cytoskeleton
- cells



"Hang on, he's coming now."

Theme 9: Quality control

The fidelity of central processes is under continuous control:

- DNA proof reading
- Protein translation control
- Protein folding

etc.

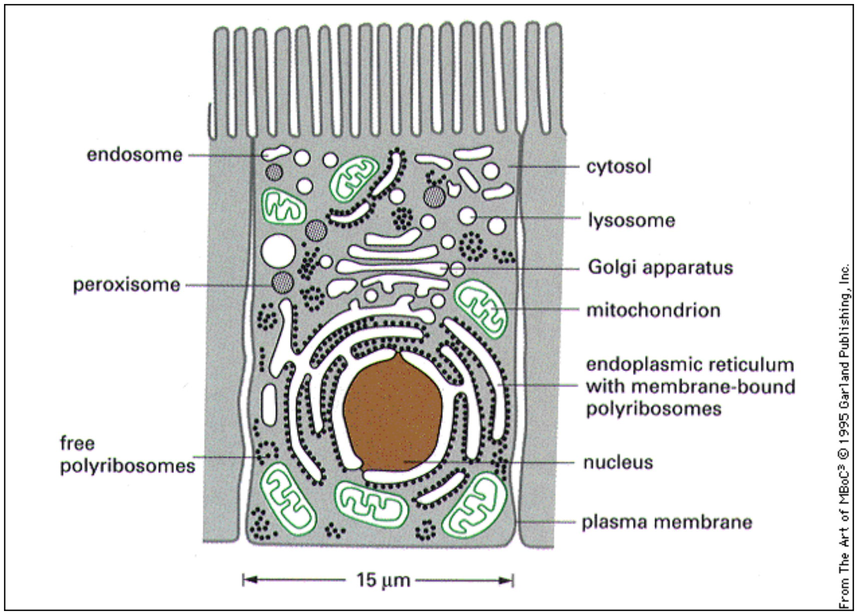
The functionality and structural intactness of cells and cellular components is also under continuous supervision:

DNA repair

Degradation of misfolded proteins

Apoptosis of infected or otherwise compromised cells etc.

Theme 10: Compartmentation allows functional differentiation



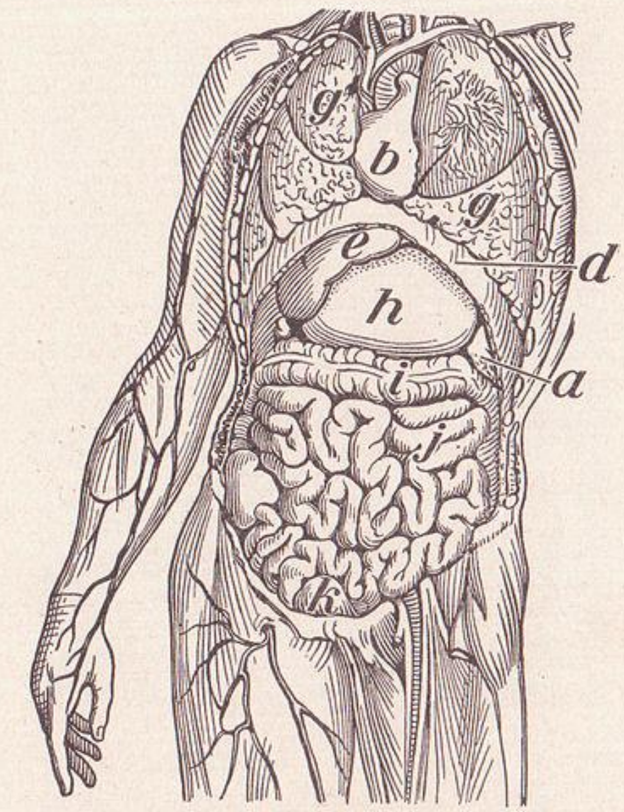


FIG. 52. — Front view of the viscera. *a*, spleen; *b*, heart; *d*, diaphragm; *e*, liver; *g*, lung; *h*, stomach; *i*, large intestine; *j* small intestine; *k*, bladder.

Summary of the 10 themes

- Structure-function relationship
- Short range interactions
- Molecular machines
- The evolutionary perspective (homology)
- Modularity in structure (the Lego principle)
- The ever-present regulation and signaling networks
- Everything is dynamic
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- Quality control
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Pause