The living cell

The earth is about 4.5×10^9 years old, and at about 4×10^9 years ago the earth had an environment that was not too harsh to be compatible with living systems.

From a statistical geometrical analysis of the sequences of t-RNA it has been estimated that the genetic code could be as old as 3.8×10^9 years (Eigen et al., 1989, Science 244, 673-9).

This estimate would mean that it did not last very long after the earth was cool enough to support some type of “modern” chemistry that the basis of life was available (this is also good evidence that life-molecules did not [have to] be imported to the earth from the outside).

The most ancient fossils found so far are bacteria from about 3.5×10^9 years ago. Therefore, it seems that the entire molecular biology that we know of probably originated in about 1 billion years.

After the bacteria were present, then the rest of “life-forms” developed as we know it in the next 3-3.5x10^9 years. This may seem surprising that the transition from a lifeless planet to a fully developed life form took such little time compared to the later evolution of the later forms of life which we know today.

Many experiments have been performed (even more than 50 years ago) which showed that if you bombard a mixture of HCN, NH_3, formaldehyde, and other chemical substances that would very probably be around in the early atmosphere, with an electric discharge (simulating lightening), that all the nucleic acid bases, as well as many of the amino acids will be formed. So it appears that a rich mixture of “building blocks” of molecules for the nucleic acids and proteins was not difficult to get.

<u>How did “life” get started?</u> The jump from a nonliving state to a living state probably involved molecules (polymers) with the property to replicate themselves (or synthesize specifically something else, which would eventually wind up synthesizing the original molecule again) and this probably requires that the “molecule” have a well-determined shape (to interact specifically), but they should not have to be too large (would be too complex in the beginning).

We guess that shape (secondary and/or tertiary structure) was important because we have seen in the whole course that the functions of all molecules (especially enzymes) require molecules with specific shapes, and the probability that the first “biomolecules” would be large is small.

Prebiotic evolution: What are good candidates for these first molecules with the property that they would have well defined shapes, and could also replicate (even with a rather large rate of error compared to today)?

We are not asking that the proposed original system have any complex machinery as today, where the synthesis of DNA/RNA/protein takes the cooperative action of more that 200 proteins. It was undoubtedly very simple compared to today, and probably did not involve a complex synergistic organization of many different molecules.

To answer this is an active area of research, and there are, as you would imagine, **no hard answers**.

We have seen earlier in the course that proteins must be usually fairly large in order to fold into some particular three dimensional form; this is because the interactions between the side groups on a protein (peptide) are not strong, and the final forms of the proteins are a balance between many relatively "small" intramolecular interactions and entropy.

Proteins are flexible, as well as specifically folded – a trait good for their action, but difficult to start with (Dyson disagrees).

On the other hand, the intramolecular interactions in nucleic acids have a high stability (base stacking), and they can form well defined two- and three-dimensional forms with only a small number of monomeric units (duplexes, hairpins, bulges, etc.).

For this reason it is usually considered that the first molecules with these properties were nucleic acids (it is of course possible that the original molecules are no longer around). For instance we have also seen earlier (at the beginning of the semester) that the t-RNA molecules have only 80 nucleotides, and yet fold into very specific structures, and are very stable.

In addition it is now known that RNA molecules can carry out catalytic reactions (*ribozymes*), and this adds great interest in these molecules as candidates for the original biomolecules, because they could carry out catalysis, as well as make structures.

Whatever the original molecules were, the self replicating molecules were probably polymers (we discussed this before) and by some type of "mutation scheme" they would tend to increase the speed and efficiency of this process of self-replication by "natural selection"

There were very probably more systems than one if it was possible (and probable) at all that such systems arose (and they did). It has been shown that such molecular systems with these properties (or at least systems very close to this) do exist in the laboratory, and they do function in this "*competitive*" way.

In the beginning probably the only “fitness” criterion for a “*replicator*” was the speed of replication – that which was faster became more. Shorter molecules will be replicated faster, but the molecules will have to have a certain length in order to have a specific shape and be recognized.

In addition, the molecular system needs to have a way to mutate (change the sequence), so that new structures can be explored, and compared (through synthesis and replication) to the older molecules. An example of what an experiment of this phenomenon would look like is in the following figure (Spiegelman – 1970):

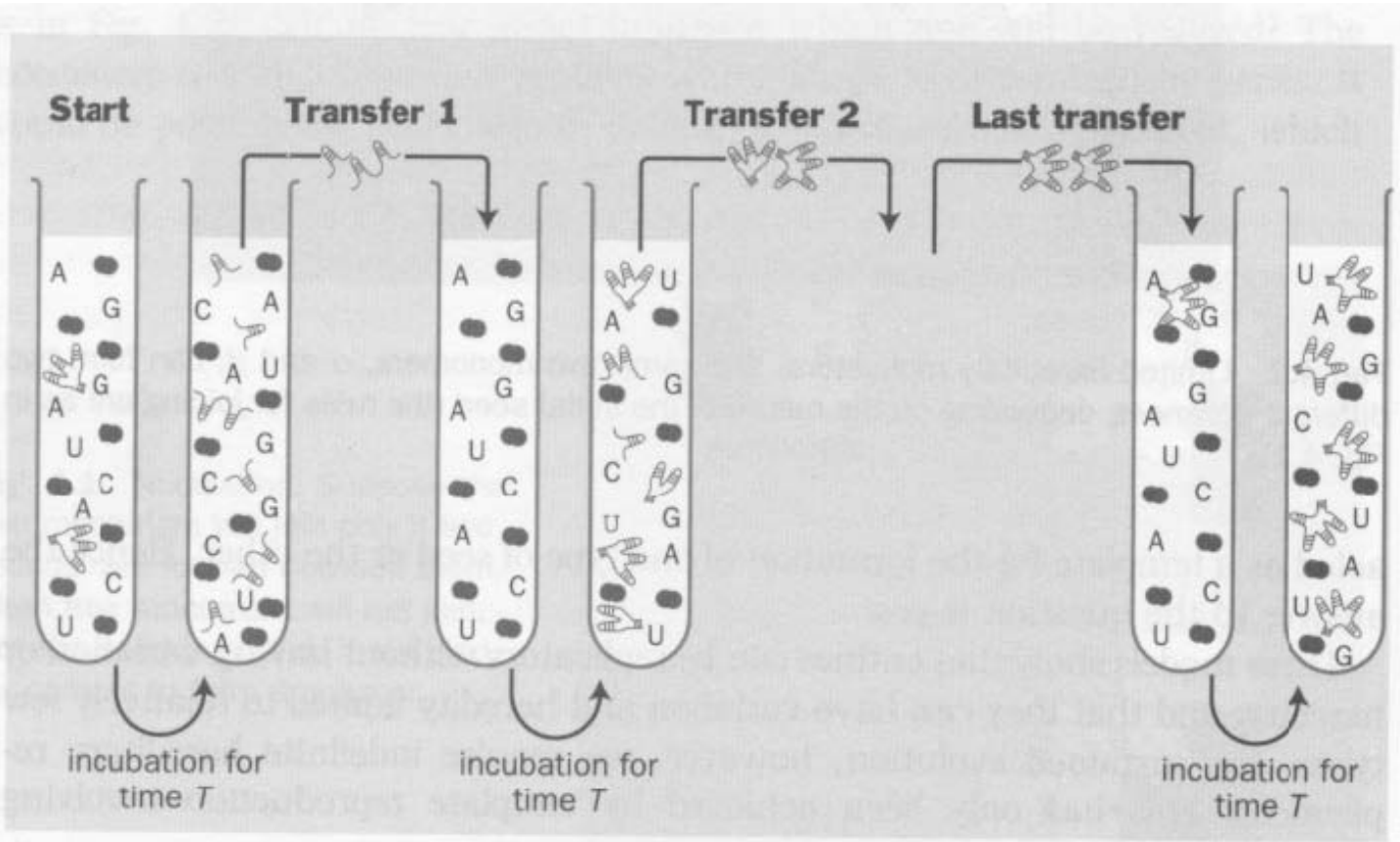

Fig. 4.3 Evolution *in vitro*. The initial tube contains the four nucleotides from which RNA is synthesized, the replicase enzyme from the Qβ phage and a 'primer' RNA molecule. This molecule is copied many times, with some errors. After incubation for time *T*, a drop of solution is transferred to a new tube containing nucleotides and replicase (but not, of course, any primer). The process of incubation and transfer can be repeated indefinitely, and evolutionary changes in the population of RNA molecules can be observed.

Let's look at the basic properties that such a system should have, and see if we can derive some restraints on the size of the polymer system, *and* the accuracy which should exist for the replication (that is, the *error rate*).

We will assume that we are dealing with the synthesis (replication) of a ribonucleic acid (RNA) – a single strand. We define the copying fidelity for one base as "q" (0<q<1). Then the error rate for one base is: (1-q).

Assume all bases have the same fidelity. For a polymer of N nucleotides the copying fidelity of the "template" is $Q=q^N$ (independent errors). So for large N the probability of replicating free of errors is very small.

There is a distribution of n different molecules, and assign each molecule (template) a number i=1 to n. The concentration of species "i" is x_i. The rate of change of x_i is:

$$\dot{x}_i = (A_i Q - E)x_i + \sum_{j=1}^{n} w_{ij} x_j$$

A_i is the total rate of copying sequence "i" irrespective of fidelity; w_{ij} is the mutation rate, which

gives the probability of producing “i” from a mutation (miscopying) in “j”; E is included to keep the total concentration the same (the molecules also *decompose*, and this variable imposes selection on the whole population).

In this equation we have assumed that all molecules have the same length and so Q is a constant. The sequence with the highest A_iQ value will displace all the others. Divide the population into two subpopulations. The fittest is the master sequence subpopulation (m) and the other subpopulation is all the mutants.

We replace all the sequences in the mutant category as an average sequence (call it “j”). Ignore the back mutations (the last term of the equation above) to the master, because this is highly unlikely to mutate to the master sequence subpopulation.

Then we can write the following rate equations:

$$\dot{x}_m = A_m Q x_m - x_m E$$

and

$$\dot{x}_j = A_j x_j + A_m (1 - Q) x_m - x_j E ;$$

with the constraint

$$x_j + x_m = 1$$

(normalized concentrations).

One sequence can only grow at the expense of the others. If there is to be a coexistence of the mutants and the master, we *set the time derivatives to zero*, and solve the equations.

For this see: Eigen, M. (1971) “Self-organization of matter and the evolution of biological macromolecules.” *Naturwissenschaften* 58; 465-523.

This turns out to give the following “equilibrium”, or steady state, solution:

$$Q > A_j / A_m = 1/s$$

where “s” is the selective superiority of the master subpopulation.

Because q must be close to 1, we know that :$Q = q^N \approx e^{-N(1-q)}$. Combining the two equations we have:

$$N < \ell n(s)/(1-q)$$

This **sets the limit of the amount of information (N) that can be copied with sufficient fidelity** so that a “master” subpopulation will survive. A figure representing the situation is:

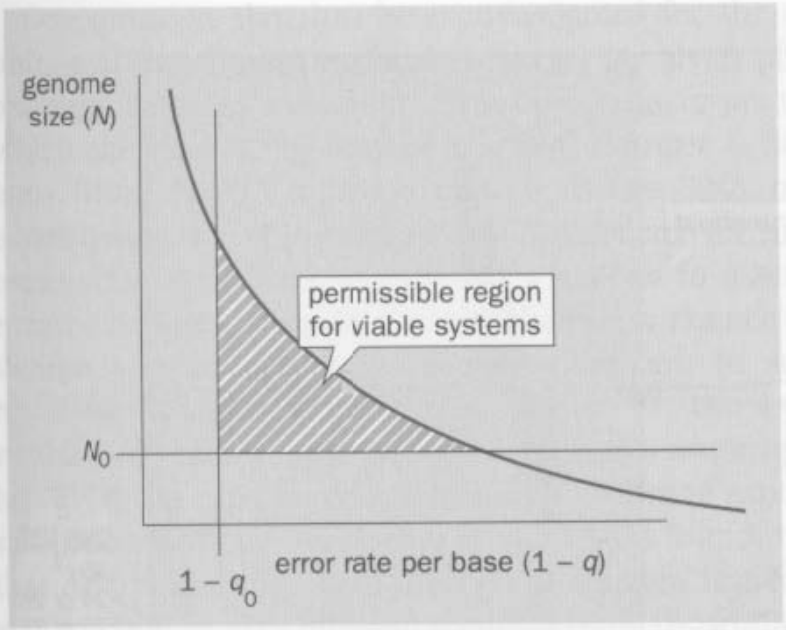

Fig. 4.4 Permissible genome size as a function of replication accuracy. N is the number of base pairs and q the probability that a single base is correctly replicated. The hyperbola is drawn for $\ln s = 1$, where s is the selective advantage of the 'master' copy over its mutants. Viable systems must lie below the hyperbola (text equation 4.6). There are other constraints. Genome size must exceed some threshold N_0, to encode sufficient information; the error rate cannot be reduced below some threshold $1 - q_0$ without excessive costs in replication time and energy. Hence, the permissible region is the hatched one.

The more accurate the *replication*, the longer the polymer that forms the stable master sequence subpopulation can be. If the error becomes too large for any sequence, including the master sequence, it will quickly deteriorate; provided that the master is below the error threshold, the population exists of a distribution of very close sequences, called a "quasi-species". *This quasi-species behaves as a species,* even though it consists of actual

different sequences which are related by the condition that they are stable. Note that there is not just one sequence, and this is important for the quasi-species to adjust to new environments rapidly.

Look at some numbers. For the system Qβ replicase, (1-q)=5x10-4, and the virus approaches it error threshold with N=4500 bases. This is not a system with only the nucleic acid; it has an added enzyme.

In general, it has been estimated from the magnitude of the physical interactions between RNA molecules (base pairing) that $q < 0.99$, so $N < 100$ for RNA molecules alone. This seems large enough to have enough information to start some type of replicative system.

In order to increase the length of the replicator molecules, other physical forces are required to increase the fidelity (as above for the Qβ replicase). That is we need a replicase molecule.

But there is a problem here - the **Prebiotic evolution paradox**.

If the replicase molecule is to be made from the replicator (which is limited to about 100 bases) we would need longer polymers, and we have just shown that this is impossible.

If there were different “genes”, and they were unlinked, they would compete, and all but one subpopulation (the master quasi-species) would disappear.

If they were directly linked, the polymer would get too long, and surpass the error threshold.

This is the Prebiotic evolution paradox. It can be solved by introducing the idea of hypercycles. There must be some other interaction between the molecules other than just the rate competition.

It is argued that some functional interaction between different RNA subpopulations is necessary, and this interaction can happen because RNA molecules have the ability to act as replicases themselves. It turns out that it is necessary to have not just one replicase, but several, and they successively support the replication of the next one in a closed sequence in the following hypercycle:

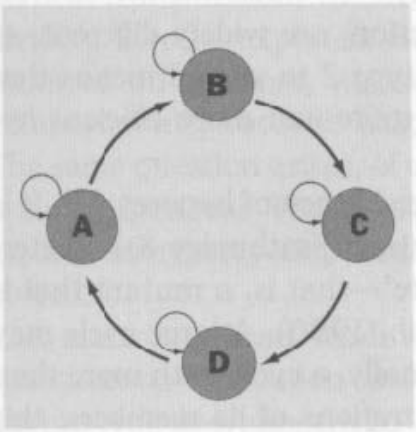

Fig. 4.6 The hypercycle. Each of the units A,B,C and D is a replicator. The rate of replication of each unit is an increasing function of the concentration unit immediately preceeding it. Thus the rate of replication of B is an increasing function of the concentration of A, and so on round the cycle.

Eventually other molecules (either of another nature or the same) besides the very first - probably inefficient systems - participated, and then the different systems worked synergistically - both “cycles” of replicative activity supporting each other (hypercycles – we may discuss these later) - and this would eventually increase the efficiency of the whole system. Throughout all such processes there would be competition between different processes that may be *using the same basic chemicals*.

For instance, perhaps self-replicating RNA molecules eventually aided in the *synthesis* of peptides (by aiding in the joining of the amino acids), and then in turn the newly formed

oligopeptides aided in the *synthesis* of the RNA molecules. If such a combined system was at advantage, it would naturally tend to “take over” a larger share of the resources. In this way, it is possible that the first “open” living systems were formed (crude, but nevertheless with the basic properties to be called living). Once such a system was there (or probably several or many) then the process would lead to more complexity.

It is easy to imagine that the RNA sequence would divide into different sections, some that were used to “synthesize” the proteins (or whatever), and others that were there primarily for self-replication. Maybe such a thing was the precursor to ribosomal RNA.

Apparently DNA was also synthesized, and had the advantage of being more stable (to preserve the “code”) than the RNA. Of course, things might have been very different. But this is certainly a possibility for an open, “cell free”, replicative and cooperative molecular system.

The system could not be at equilibrium, and there would have to be a constant influx of material and energy, but this seems to be no problem. There are of course many different proposals of the origin of life, but at this time, this looks most plausible, and the closest to experimental evidence to date.

We note that the hypercycle is not an individual (like a bacterium), but is a population of molecules which interact ecologically. They therefore cannot form a real unit of evolution.

The replicators are all acting altruistically for the good of the whole system. The hypercycles need a way to stabilize, and develop the possibility to spread, and experiment with mutations, and not get in the situation that parts of the hypercycle will take advantage of the conditions of the hypercycle, and break out, leaving the hypercycle and thereby destroying the hypercycle by being a better replicator for just itself.

This would decrease the possibility of increasing complexity – it would just lead to faster replicators – with no other characteristics that would lead to a more complex living system. A system has to develop a way to retain this altruistic synergy between the components of the hypercycle, and yet still allow freedom to “experiment” for new functions. One way to do this is to put the hypercycles into compartments – that is, enclose them in a membrane. This would allow the formation of new hypercycles and then the separate evolution of different hypercycles such that the different hypercycles would not interfere, and destroy, each other.

A picture of this idea is:

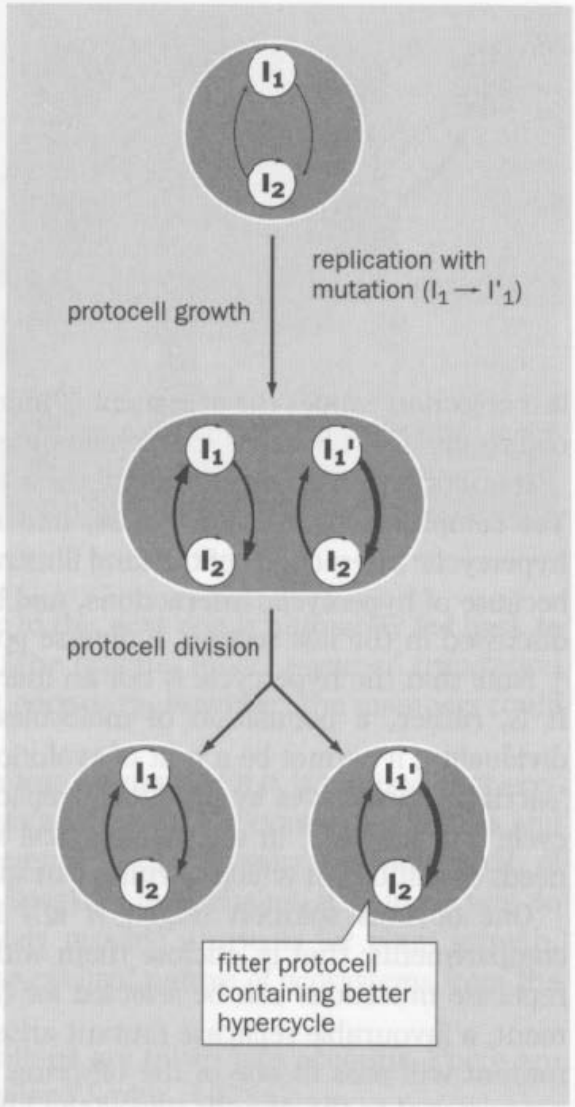

Fig. 4.9 Selecting improved replicase mutations by compartmentation of hypercycles. Molecule I′, arises by mutation from I, and is a better replicase.

Now when a compartment divides, the favorable replicase mutants can arise, and the different possibilities can coexist, without destroying each other by direct interactions until one of the “protocells” simply leaves more descendents that the one before. This will allow more evolutionary “*tinkering*”. **This is of course all speculation**; but it is at least to a great extent compatible with certain experiments.

If such a system were there, it is easy to see what an advantage it would have to develop “living compartments” (the beginnings of a “cell”). Polymers are made of monomers, and to synthesize polymers the monomers have to “*find*” each other (bimolecular reaction), and this is more difficult to do in a completely open three dimensional system, than in a system that is enclosed.

“Control mechanisms” would probably evolve to synchronize different processes. Especially as the self-replicating system grew in complexity, and encompassed more and more components, it would be necessary to simultaneously bring together more than two components, and this becomes increasingly difficult unless the room available for the “reacting” molecules is drastically limited. This is all aided by putting things into a compartment.

The basic structures of a bacterium cell and a eukaryotic cell are:

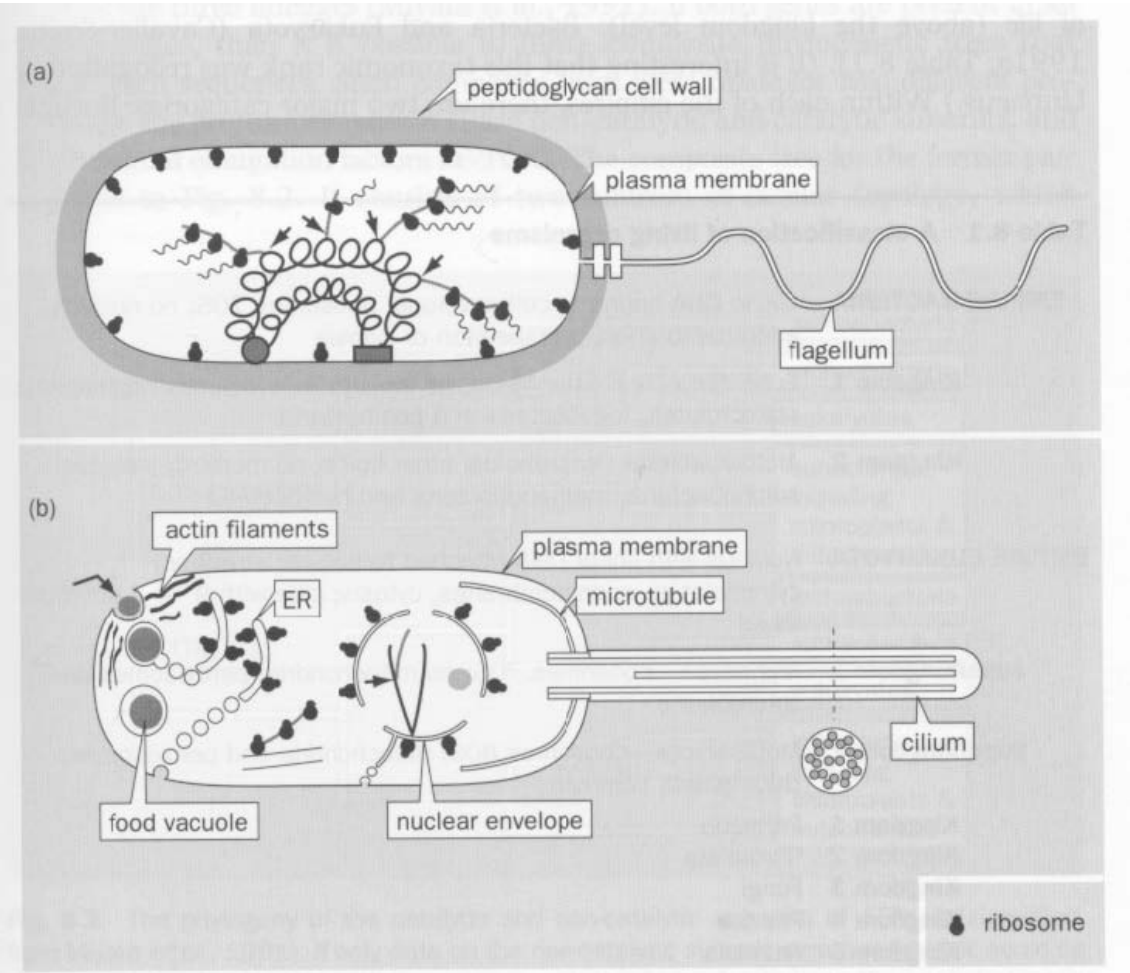

Fig. 8.1 The structure of (a) a prokaryotic and (b) a eukaryotic cell (after Cavalier-Smith, 1988). ER, endoplasmic reticulum; →, replicase.

Some of the major differences are:

1) The bacterial cell has a rigid outer wall – usually from peptidoglycan and murein. In eukaryotic cells the rigid wall is not universal, and the cell shape is primarily maintained by an internal cytoskeleton of filaments and microtubules.

2) Eukaryotic cells have a complex system of internal membranes, including a nuclear envelope, endoplasmic reticulum and lysosomes (and mitochondria or protoplasts – not shown in the figure).

3) Bacteria have a single circular chromosome, attached to the rigid outer wall. In eukaryotes, linear chromosomes are contained in a nuclear envelope, and this envelope separates transcription and translation; there is communication between the nucleus and the cytoplasm via pores in the nuclear envelope.

4) Eukaryotes have a complex cytoskeleton. The actomyosin system powers cell division, phagocytosis, amoeboid motion and the overall contractile characteristics and controls shape changes due to osmosis. Microtubules and the associated “motor proteins” (kinesin, dynein and dynamin) ensure the accurate segregation of the chromosomes in mitosis, control the ciliary motion and the movement of transport vesicles. The intermediate filaments help to anchor the nucleus in the cytoplasm, and also form the structural basis for the association of the endomembranes and the nuclear-pore complexes with the chromatin to form the nuclear membrane.

5) Mitochondria or chloroplasts are present in eukaryotes, and not in bacteria. There are indications that these intracellular organelles seem to have been taken up by the eukaryotic

cells later in their development.

In a bacterium (which is much smaller than a mammalian cell) this is not difficult; for instance only 10 molecules of *lac*-repressor (a control molecule) exist at one time in a bacterium. This “concentration” of molecules is high enough in such a small space so that molecules can diffuse throughout the whole space looking for binding partners within a reasonable time, and bind to them with the required affinity and speed to serve as a control mechanism in a cell.

The *lac* repressor is a negative control;

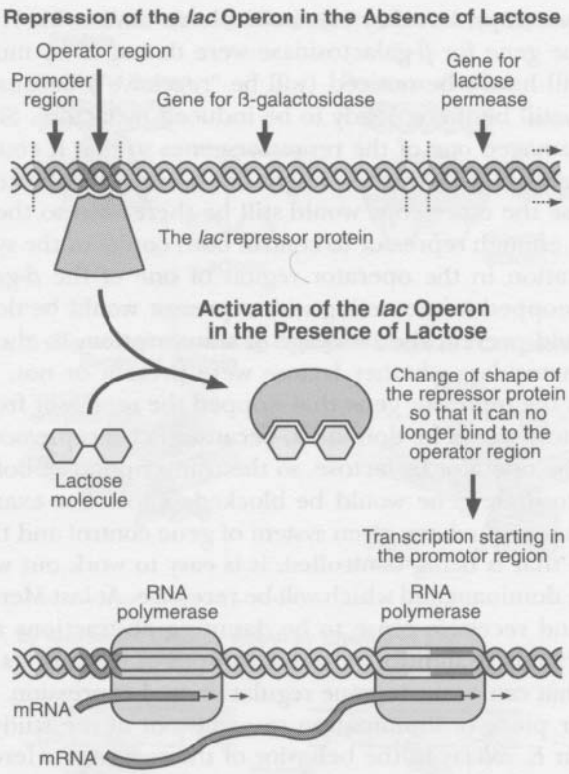

Figure 3.6. The regulation of expression of the genes of the *lac* operon (which is concerned with the use of the sugar lactose). When an RNA polymerase transcribes the genes coding for the proteins that handle lactose it starts at a special sequence ("the promoter region") just to the left of the genes, and it moves from there along the DNA transcribing one of the strands into messenger RNA. In the absence of lactose, it cannot attach to the promoter sequence because a regulatory protein (the *lac* repressor) is bound to a special sequence (the operator region) just to the right of the promoter region. But when lactose is present, it alters the shape of the *lac* repressor so that the protein is no longer able to attach itself to the operator region, and this then allows the RNA polymerase to attach to the promoter region and start transcription. So the control of transcription depends on an "allosteric" change in shape of the repressor brought about by lactose.

such simple negative controls do not exist in larger cells, probably because it is then too hard for the participating interacting molecules to find each other quickly, and bind with sufficient affinity.

In addition, in order to guarantee binding of a negative control molecule, the investment for a larger cell (for instance, a mammalian cell with a volume 10^4 times larger volume than a bacterium) to keep the number of controlling molecules per cell equal to the concentration of the *lac* repressor in the small bacterium would be enormous.

So, the cell would tend to evolve such that smaller multiple compartments would be formed; this would also make the organization of all the required reactions of a more complex system easier, and much more efficient. Having multiple different compartments in a cell would also avoid unwanted accidental interactions between molecular components which would otherwise interact in an open enclosure.

Cell types

There are about **200** types of **cellular phenotypes** in the human body. They all have the same genetic material (if they have a nucleus) and the type of cell they are depends on the signals that control which genes, or set of genes, are expressed.

Tissue comes from the Latin word *texere* which means **to weave**, and this was the name given by the French surgeon Bichat to describe the concept that the different parts of the body were made of material with different "textures".

There are only **four basic types of cells**:

1) epithelial
2) connective
3) muscle
4) nervous

1) Cells of the Epithelium

a) Exterior of body and internal surfaces.
b) Close cell-to-cell contact that forms strong, tight connections for the passage of fluids.
c) They are polarized: apical and basolateral surfaces
d) They can secrete fluids produced by the cells – lubrication or secretion into the blood stream

2) Cells of connective tissue

a) Support, connect and nourish cells in other tissues

b) Produce large amounts of extracellular matrix material (collagens, fibronectin, lamin, etc..

c) Produces the basement membrane on which epithelial cells are supported.

d) The “fibroblast” is a relatively undifferentiated connective tissue cell. It is a precursor cell to other types of connective tissue, such as fat cells (adipocytes), smooth muscle cells, and bone- and cartilage-producing cells (happens through the life of the organism).

e) Blood cells, including erythrocytes, monocytes, neutrophiles, basophils, eosinophils and platelets are derived from connective tissue cells (in the bone marrow).

3) Cells of muscle tissue

a) Specialized for contraction

b) Four categories of muscle cells:

i) Skeletal or striated muscle cells

(1) Elongated shape and are known as “muscle fibers”

(2) Contain many nuclei in a common cytoplasm (syncytium)

ii) Cardiac (heart) muscle cells

iii) Smooth muscle cells (derived from fibroblasts)

iv) Myoepithelial cells (derived from ectoderm).- regulate the response of certain

sensory cells, such as the iris, sweat, milk and other glands which respond to sensory information.

4) Cells of the nervous tissue

a) Capacity to conduct electrical pulses
b) Communications network of the body
c) Axons terminate at synapses
d) Electrical impulses are transmitted from one neuron to the next by the secretion of a chemical substance called a neurotransmitter at the synaptic junction.
e) **Neurons** are divided into three major groups (representing the number of processes that arise from the cell body)

i) Unipolar

(1) single primary process with many branches (usually in invertebrates.

ii) Bipolar

(1) dendric process to convey information from the periphery to the cell
(2) axon to convey information to other neurons
(3) Communicates signals to the central nervous system (CNS) through a neuron relay system.

iii) Multipolar

(1) Present in the CNS of vertebrates
(2) Have a single axon, but many dendrites (sometimes up to 150,000 – in the cerebellum)

f) Glial cells

i) 10 – 50 times more glial cells than neurons

ii) Three main types

(1) Oligodendroglial

(2) Schwann cells

(3) Astrocytes

iii) Perform several major functions

(1) Support for neurons – insulate neurons from each other

(2) Produce myelin – is an insulating material for certain neurons

(3) Scavenger cells to clear cellular debris

(4) Help form the blood-brain barrier – cellular barrier between the brain and the capillaries.

(5) Other functions for these cells are continually being discovered.

These four types of cells have been modified in a multitude of ways, and form phenotypes that with very different morphologies from the progenitor cells. A list of the cells of the human body are listed on the next two pages – just for reference, and to see the number of ways that these cells have been modified.

Table 1–1. Adult human cell types.[1]

Keratinizing epithelial cells
- Keratinocyte of epidermis (= differentiating epidermal cell)
- Basal cell of epidermis (stem cell)
- Keratinocyte of fingernails and toenails
- Basal cell of nail bed (stem cell)
- Hair shaft cells
  - Medullary
  - Cortical
  - Cuticular
- Hair-root sheath cells
  - Cuticular
  - Of Huxley's layer
  - Of Henle's layer
  - External
- Hair matrix cell (stem cell)

Cells of wet stratified barrier epithelia
- Surface epithelial cell of stratified squamous epithelium of cornea, tongue, oral cavity, esophagus, anal canal, distal urethra, vagina
- Basal cell of these epithelia (stem cell)
- Cell of urinary epithelium (lining bladder and urinary ducts)

Epithelial cells specialized for exocrine secretion
- Cells of salivary gland
  - Mucous cell (secretion rich in polysaccharide)
  - Serous cell (secretion rich in glycoprotein enzymes)
- Cell of von Ebner's gland in tongue (secretion to wash over taste buds)
- Cell of mammary gland, secreting milk
- Cell of lacrimal gland, secreting tears
- Cell of ceruminous gland of ear, secreting wax
- Cell of eccrine sweat gland, secreting glycoproteins (dark cell)
- Cell of eccrine sweat gland, secreting small molecules (clear cell)
- Cell of apocrine sweat gland (odoriferous secretion, sex-hormone sensitive)
- Cell of gland of Moll in eyelid (specialized sweat gland)
- Cell of sebaceous gland, secreting lipid-rich sebum
- Cell of Bowman's gland in nose (secretion to wash over olfactory epithelium)
- Cell of Brunner's gland in duodenum, secreting alkaline solution of mucus and enzymes
- Cell of endometrium of uterus, secreting mainly carbohydrates
- Isolated goblet cell of respiratory and digestive tracts, secreting mucus
- Mucous cell of lining of stomach
- Zymogenic cell of gastric gland, secreting pepsinogen
- Oxyntic cell of gastric gland, secreting HCl
- Acinar cell of pancreas, secreting digestive enzymes and bicarbonate
- Paneth cell of small intestine, secreting lysozyme
- Type II pneumocyte of lung, secreting surfactant
- Clara cell of lung (function unknown)

Cells specialized for secretion of hormones
- Cells of anterior pituitary, secreting
  - Growth hormone
  - Follicle-stimulating hormone
  - Luteinizing hormone
  - Prolactin
  - Adrenocorticotropic hormone
  - Thyroid-stimulating hormone
- Cell of intermediate pituitary, secreting
  - Melanocyte-stimulating hormone
- Cells of posterior pituitary, secreting
  - Oxytocin
  - Vasopressin
- Cells of gut and respiratory tract, secreting
  - Serotonin
  - Endorphin
  - Somatostatin
  - Gastrin
  - Secretin
  - Cholecystokinin
  - Insulin
  - Glucagon
  - Bombesin
- Cells of thyroid gland, secreting
  - Thyroid hormone
  - Calcitonin
- Cells of parathyroid gland, secreting
  - Parathyroid hormone
  - Oxyphil cell (function unknown)
- Cells of adrenal gland, secreting
  - Epinephrine
  - Norepinephrine
  - Steroid hormones
    - Mineralocorticoids
    - Glucocorticoids
- Cells of gonads, secreting
  - Testosterone (Leydig cell of testis)
  - Estrogen (theca interna cell of ovarian follicle)

Epithelial absorptive cells in gut, exocrine glands, and urogenital tract
- Brush border cell of intestine (with microvilli)
- Striated duct cell of exocrine glands
- Gall bladder epithelial cell
- Brush border cell of proximal tubule of kidney
- Distal tubule cell of kidney
- Nonciliated cell of ductulus efferens
- Epididymal principal cell
- Epididymal basal cell

Cells specialized for metabolism and storage
- Hepatocyte (liver cell)
- Fat cells
  - White fat
  - Brown fat
  - Lipocyte of liver

Epithelial cells serving primarily a barrier function, lining the lung, gut, exocrine glands, and urogenital tract
- Type I pneumocyte (lining air space of lung)
- Pancreatic duct cell (centroacinar cell)
- Nonstriated duct cell of sweat gland, salivary gland, mammary gland, etc (various)
- Parietal cell of kidney glomerulus
- Podocyte of kidney glomerulus
- Cell of thin segment of loop of Henle (in kidney)
- Collecting duct cell (in kidney)
- Duct cell of seminal vesicle, prostate gland, etc (various)

Epithelial cells lining closed internal body cavities
- Vascular endothelial cells of blood vessels and lymphatics
  - Fenestrated
  - Continuous
  - Splenic
- Synovial cell (lining joint cavities, secreting largely hyaluronic acid)
- Serosal cell (lining peritoneal, pleural, and pericardial cavities)
- Squamous cell (lining perilymphatic space of ear)
- Cells lining endolymphatic space of ear
  - Squamous cell
  - Columnar cells of endolymphatic sac
    - With microvilli
    - Without microvilli
  - "Dark" cell

Table 1–1 (cont'd). Adult human cell types.[1]

- **Ciliated cells with propulsive function**
  - Of respiratory tract
  - Of oviduct and of endometrium of uterus (in female)
  - Of rete testis and ductulus efferens (in male)
  - Of central nervous system (ependymal cell lining brain cavities)
- **Cell specialized for secretion of extracellular matrix**
  - Epithelial
    - Ameloblast (secreting enamel of tooth)
    - Planum semilunatum cell of vestibular apparatus of ear (secreting proteoglycan)
    - Interdental cell of organ of Corti (secreting tectorial "membrane" covering hair cells of organ of Corti)
  - Nonepithelial (connective tissue)
    - Fibroblasts (various—of loose connective tissue, of cornea, of tendon, of reticular tissue of bone marrow, etc)
    - Pericyte of blood capillary
    - Nucleus pulposus cell of intervertebral disc
    - Cementoblast/cementocyte (secreting bonelike cementum of root of tooth)
    - Odontoblast/odontocyte (secreting dentin of tooth)
    - Chondrocytes
      - Of hyaline cartilage
      - Of fibrocartilage
      - Of elastic cartilage
    - Osteoblast/osteocyte
    - Osteoprogenitor cell (stem cell of osteoblasts)
    - Hyalocyte of vitreous body of eye
    - Stellate cell of perilymphatic space of ear
- **Contractile cells**
  - Skeletal muscle cells
    - Red (slow)
    - White (fast)
    - Intermediate
    - Muscle spindle–nuclear bag
    - Muscle spindle–nuclear chain
    - Satellite cell (stem cell)
  - Heart muscle cells
    - Ordinary
    - Nodal
    - Purkinje fiber
  - Smooth muscle cells (various)
  - Myoepithelial cells
    - Of iris
    - Of exocrine glands
- **Cells of blood and immune system**
  - Red blood cell
  - Megakaryocyte
  - Macrophages and related cells
    - Monocyte
    - Connective-tissue macrophage (various)
    - Langerhans cell (in epidermis)
    - Osteoclast (in bone)
    - Dendritic cell (in lymphoid tissues)
    - Microglial cell (in central nervous system)
  - Neutrophil
  - Eosinophil
  - Basophil
  - Mast cell
  - T lymphocyte
    - Helper T cell
    - Suppressor T cell
    - Killer T cell
  - B lymphocyte
    - Immunoglobulin M
    - Immunoglobulin G
    - Immunoglobulin A
    - Immunoglobulin E
  - Killer cell
  - Stem cells and committed progenitors for the blood and immune system (various)
- **Sensory transducers**
  - Photoreceptors
    - Rod
    - Cones
      - Blue sensitive
      - Green sensitive
      - Red sensitive
  - Hearing
    - Inner hair cell of organ of Corti
    - Outer hair cell of organ of Corti
  - Acceleration and gravity
    - Type I hair cell of vestibular apparatus of ear
    - Type II hair cell of vestibular apparatus of ear
  - Taste
    - Type II taste bud cell
  - Smell
    - Olfactory neuron
    - Basal cell of olfactory epithelium (stem cell for olfactory neurons)
  - Blood pH
    - Carotid body cell
      - Type I
      - Type II
  - Touch
    - Merkel cell of epidermis
    - Primary sensory neurons specialized for touch (various)
  - Temperature
    - Primary sensory neurons specialized for temperature
    - Cold sensitive
    - Heat sensitive
  - Pain
    - Primary sensory neurons specialized for pain (various)
  - Configurations and forces in musculoskeletal system
    - Proprioceptive primary sensory neurons (various)
- **Autonomic neurons**
  - Cholinergic (various)
  - Adrenergic (various)
  - Peptidergic (various)
- **Supporting cells of sense organs and of peripheral neurons**
  - Supporting cells of organ of Corti
    - Inner pillar cell
    - Outer pillar cell
    - Inner phalangeal cell
    - Outer phalangeal cell
    - Border cell
    - Hensen cell
  - Supporting cell of vestibular apparatus
  - Supporting cell of taste bud (type I taste bud cell)
  - Supporting cell of olfactory epithelium
  - Schwann cell
  - Satellite cell (encapsulating peripheral nerve cell bodies)
  - Enteric glial cell
- **Neurons and glial cells of central nervous system**
  - Neurons (huge variety of types—still poorly classified)
  - Glial cells
    - Astrocyte (various)
    - Oligodendrocyte
- **Lens cells**
  - Anterior lens epithelial cell
  - Lens fiber (crystallin-containing cell)
- **Pigment cells**
  - Melanocyte
  - Retinal pigmented epithelial cell
- **Germ cells**
  - Oogonium/oocyte
  - Spermatocyte
  - Spermatogonium (stem cell for spermatocyte)
- **Nurse cells**
  - Ovarian follicle cell
  - Sertoli cell (in testis)
  - Thymus epithelial cell