Cell: The Unit of Life - Part 2

Objectives

After learning from this lesson, the learners will be able to:

- Enumerate different processes in a cell
- Distinguish different components in a cell
- Discuss the role of cell mechanics
- Elaborate upon

Content Outline

- Introduction
- Cell Components
- Cell Processes
- Cell Mechanics and Processes

Introduction

The cell is a basic unit for life forms. It offers an enabling sophisticated control of biochemical processes by providing compartments and regulating chemical fluxes between them. Cells also have structural integrity and can exert forces. In the case of multicellular organisms (animals and plants), each cell contributes some mechanical property to the tissue it forms together with other cells. Furthermore, many cells are eliminated during the life of a complex organism (e.g. skin layers in animals), which entails cell division and restructuring of the organisation with neighbours. There are different types and shapes of cell, wherein some types of cells are very motile, moving through tissues (e.g. various immune system cells and some cancer cells). This dynamic aspect is even more obvious during the development of multicellular organisms, when many stages of cell division and migration take place.

Cell Components

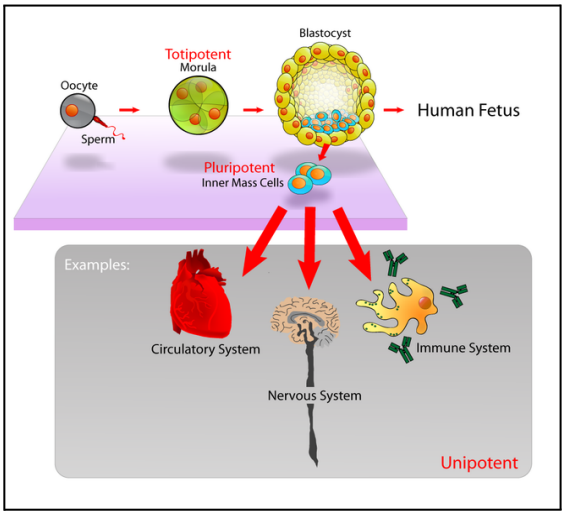
A first division of organisms is between those whose cells have within them a nucleus, the structure containing most of the genetic material in the form of DNA, and those whose cells don’t. The nucleated cells are called eukaryotic and are found in animals, plants, fungi, protozoa and algae. In contrast, bacteria (and the less common archaea) do not have a nucleus

and their DNA is spread throughout the cell. These cells are called **prokaryotic**. Eukaryotic organisms can be unicellular or multicellular while all prokaryotes are unicellular.

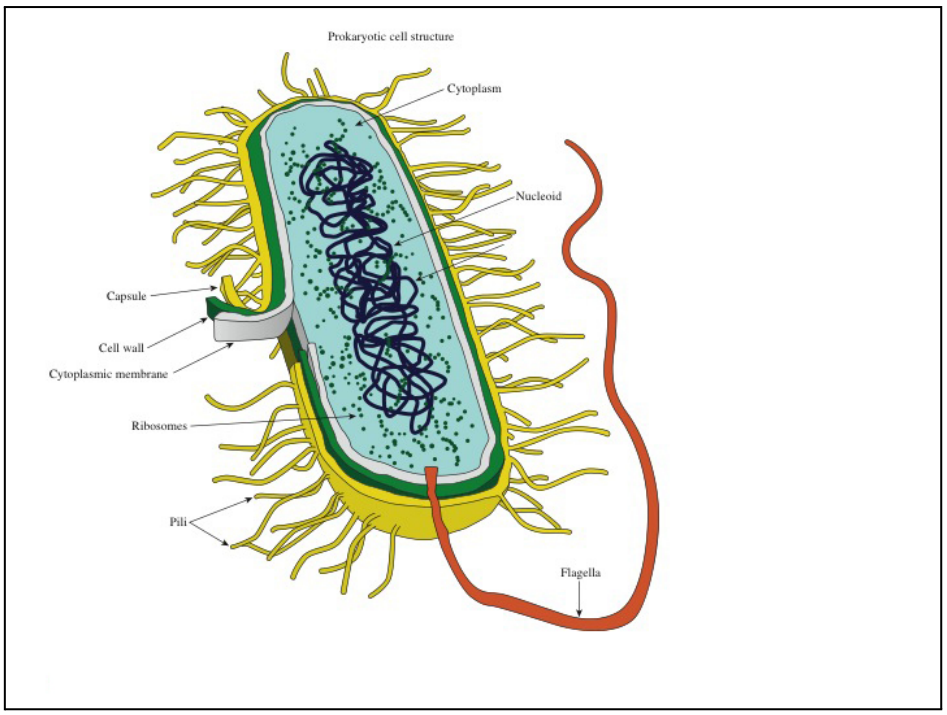
In a multicellular eukaryotic organism, all cell types arise from stem cells (Inner mass cells), which are pluripotent in nature and can give rise to different types of specialized cells.

Which structures are stiffest?

Lipid membranes are generally soft, meaning that they easily deform due to thermal fluctuations, although energies greater than the thermal $k_B T$ are needed to bend lipid bilayers. (Lipid bilayers and membranes are also discussed in lectures 5 and 6 of the Statistical Thermodynamics topic.) In contrast with lipid structures, we can identify protein structures, in particular the filaments called microtubules (made of the protein tubulin, polymerised together) and actin filaments (made of the protein actin). These form the cell's **cytoskeleton** and are quite stiff, in the sense that thermal energy is not sufficient to bend them significantly on the scale of a cell radius: they are straight rods.



Slide 1 shows a prokaryotic cell, which has a simpler architecture than a eukaryotic cell, but many common aspects in both structure and function. It compares and contrasts these two types of cell. Bacteria are probably the most important type of prokaryotic organism. Note in particular the absence of a nuclear membrane: – here the DNA is spread throughout the cell. All bacteria are single-cell organisms (although to understand their evolution, and how they survive, it only makes sense to consider their collective behaviour in a colony). Many bacteria, under appropriate nutrient conditions, can replicate extremely quickly (the bacterium *E. coli* can duplicate every 20 minutes, in contrast with fast eukaryotic division, which may only occur every 24 hours), giving rise to an exponential increase in cell number with time.



Source: Slide 1 The main structural elements of a prokaryotic cell

Cell Processes

Cells regulate their behaviour and their function by controlling the concentration (in some cases it may be small numbers) of different proteins. Some proteins perform a function themselves, whereas others serve to control protein production rates. (See the lectures on the topic "Regulatory Networks".) This "network" of interactions is analogous to a computing machine, and, indeed, cells can compute. However, the circuit is not hard set. It is not enough to know the genetic code since the cell behaviour will also depend most importantly on the concentration of all proteins, but also on other factors among which are the conformation of the DNA and the composition of lipids in the membranes. There is recent evidence that forces acting on a cell, and more generally the mechanical environment around a cell, can affect the process of gene regulation, maybe one day offering new opportunities to exploit stem cells for regenerative medicine. Before looking at how this might work, it is useful to review very briefly the essential processes that take place in a cell.

Cells contain DNA, which is a sequence of amino-acid bases. The cells in a human all have the same DNA but are clearly very different. About 200 different cell types are classified in a human (bone, skin, blood, muscle, etc.). The differences between cells (biologists would call this the **phenotype**) are due to each being in a different steady state of protein expression. Proteins are constantly being made (see below) and degraded in a cell. The rate of production

is finely controlled, involving a sophisticated interplay between binding constants determined by detailed protein structures, and statistical physics.

Despite much research in the medical and biological communities, and joined by increasing numbers of physicists and engineers, it is still not fully understood how this fine level of control of the steady state is achieved. (Also see the topic "Biological Molecules" Lecture 1 "The structure of DNA and RNA".) This is a key question, the importance of which is clear if we think of **stem cells**. These are cells, present in all multicellular organisms (at least during some stage of their development from single cell embryos), that are in a state from which they are able to differentiate into any other cell type. Clearly they have the same genetic material as any other cell, and yet they have the unique property of easily becoming "other" cell types. Understanding better how they maintain their special non-differentiated state, and also the cues (which may be chemical or mechanical) that control their differentiation fate, could allow breakthroughs in the treatment of various diseases.

The accepted view of this general way in which a cell works is often called the **central dogma** of molecular cell biology. This can be summarised as "DNA makes RNA makes proteins" and is discussed in more detail in "Biological Molecules" (Lecture 6 "An introduction to Molecular Biology and Evolution"). Short sequences of DNA containing the information sufficient to describe a protein sequence (a **gene**) are copied (by a protein machine called RNA polymerase) into RNA. This process is known as **transcription**.

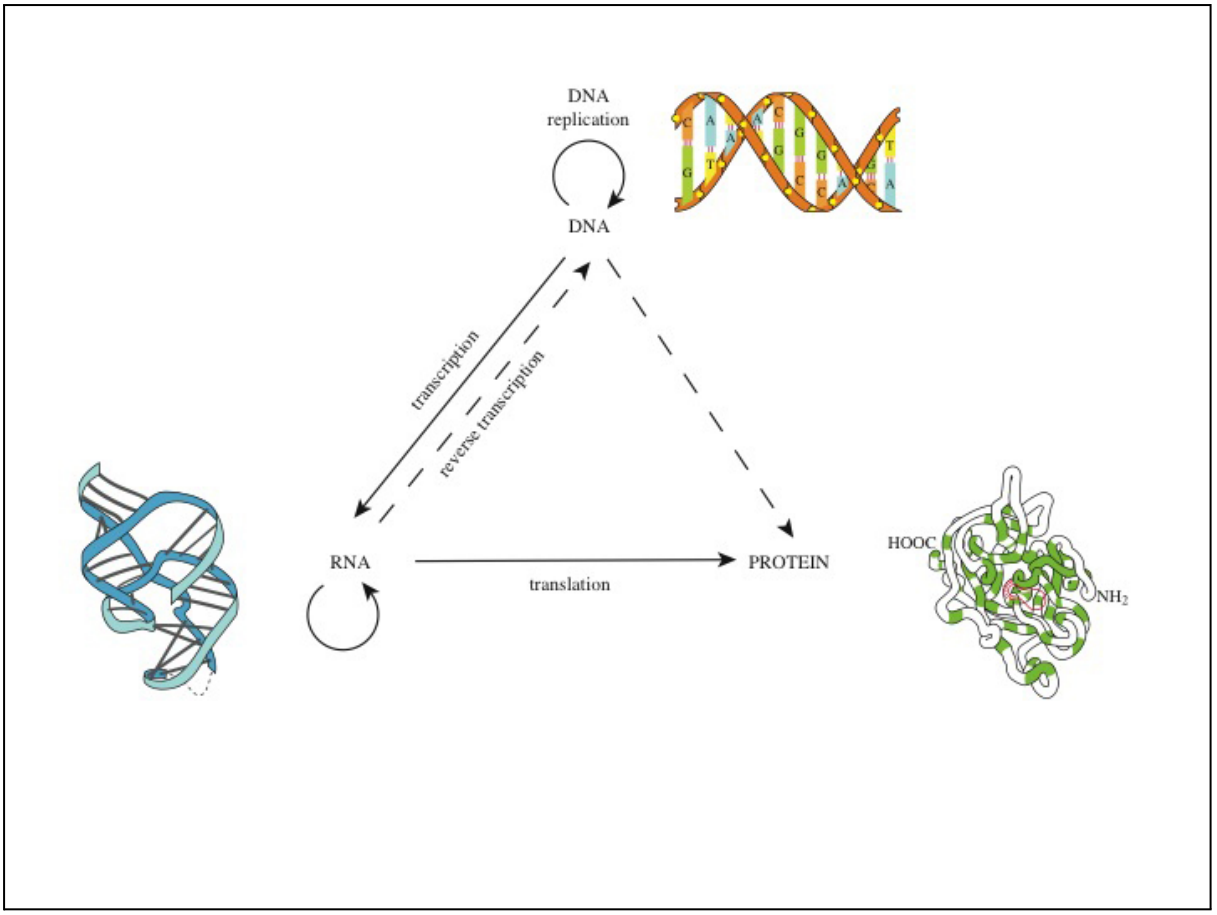
There are subtle different functions for the RNA, but the main one is for these RNA sequences (in this case called messenger-RNA: mRNA) to be made into proteins. This process, through which the RNA code is read, and "translated" into a sequence of residues to make a specific **protein**, is called translation and involves a protein machine called the **ribosome**.

Proteins are the main "workhorses" of a cell: they do things either in isolation or by assembling multiple units of each other, or of different proteins. The combinations are almost endless. (See Biological Molecules, Lecture 3 "Proteins".) As a general principle, cells need to have different proteins at different times, and also they need to use the energy and

materials at their disposal efficiently. For both reasons the production of each type of protein is regulated.

This regulation of gene expression happens most importantly at the transcription stage, since this is the first stage and hence it is most efficient to take regulating action there. The main process of regulation involves RNA polymerase binding to DNA in order to start transcription, and this binding affinity can be controlled by certain proteins known as "transcription regulation factors". So by making a few more regulation factor proteins, a cell can tune how many of various other proteins to make.

There is also regulation at the other stages, with subtle but important effects, for example, on the control of noise, and these are ideas still under investigation. (For more detail, see Regulatory Networks Lecture 3 "Biochemical Noise".) The general picture outlined here (the central dogma of molecular biology, Slide 2) is one of the most important ideas in cell biology because it is general and applies to all cells. It has been elucidated by the brilliant work of many people during the decades since the discovery of DNA structure (awarded a Nobel Prize in 1962). (See Biological Molecules, Lecture 1 "DNA and RNA" and Lecture 6 "Self-Organisation and Evolution")



Source: [Slide 2 The central dogma of molecular biology]

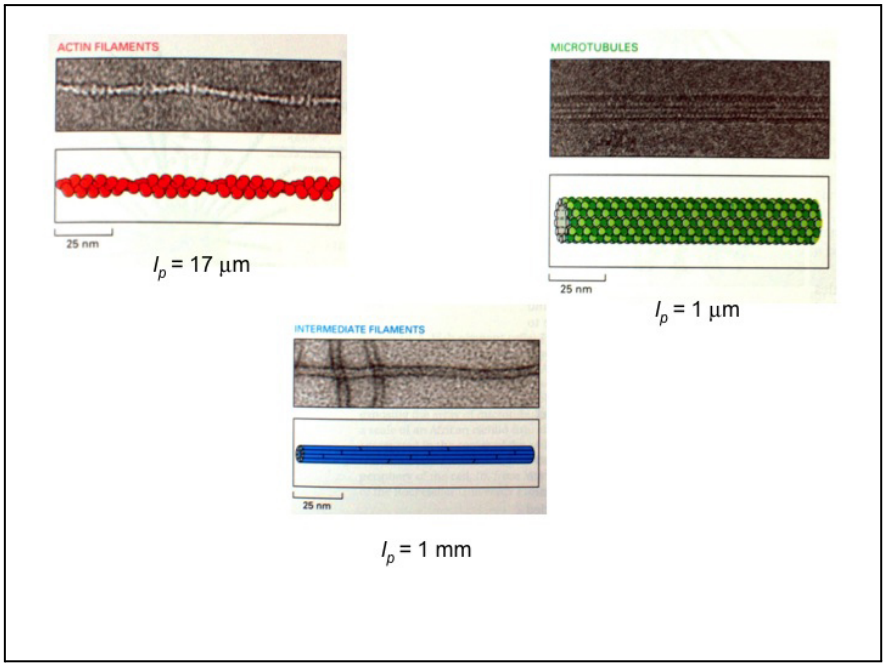
Cell Mechanics and Processes

Interplay of Forces and Structures

As noted above, there is evidence that forces acting on a cell, and its general mechanical environment, can affect protein formation and hence the process of gene regulation. How this takes place is still not known, but the most obvious issues to consider are whether the external force has an effect on the binding of some transcription factor, or on the production rate of some other important intermediate molecule.

Much better accepted is the idea that a cell has mechanical stability and can exert forces on the surroundings (Slide 3). Processes such as motility and adhesion to a substrate require dynamic control of the architecture. There are three main types of semiflexible filaments in eukaryotic cells, made from different proteins, and they differ substantially in their resistance to bending. The filaments have many roles in the cell: providing mechanical stability; facilitating directional intracellular transport (they are tracks for motors); and determining the

symmetric separation of the nucleus and cell during cell division, enabling cell motility. Slide 3 shows the three main types of filament that perform these functions. In Slide 3, l_p is the **persistence length** – that is, the distance along the rod over which the direction (statistically) changes. (Also see Biological Molecules Lecture 2 "Modelling DNA and RNA".)



Source: Slide 3 The three types of protein filaments present in many eukaryotic cells

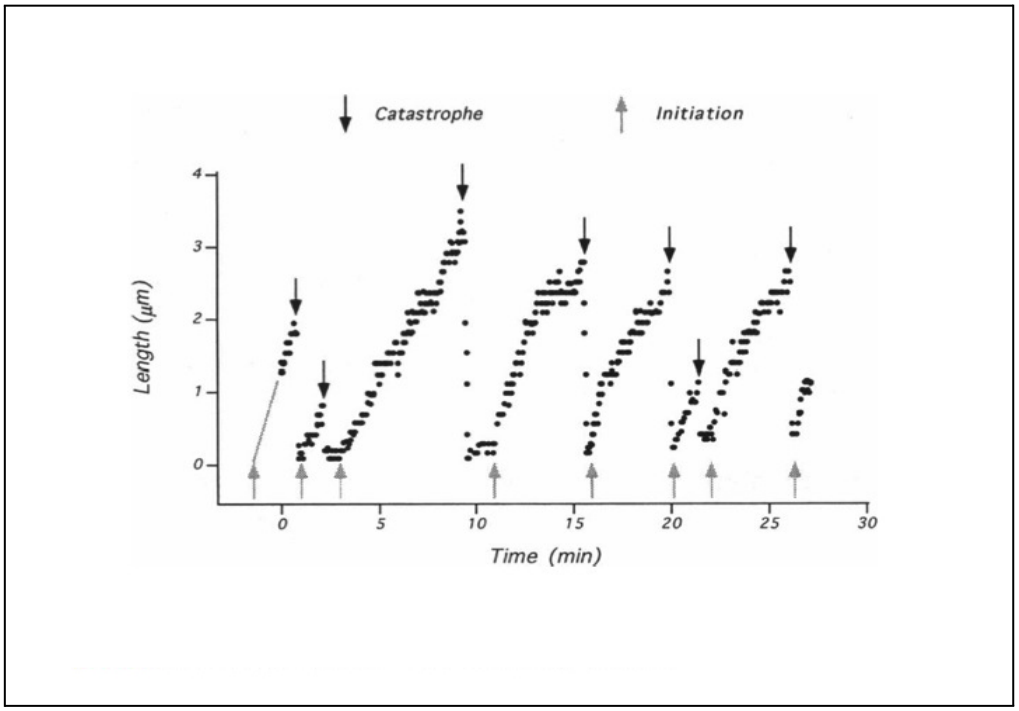
Timescales of adaptation to the environment

Making a protein is a process that takes around 60 minutes in an animal cell (roughly 30 minutes to transcribe a gene and 30 minutes to translate the protein [Alon, 2007]). In a bacterium the process is much faster, with transcription and translation taking just a few minutes each (significant time is "saved" by not having to cross the nuclear membrane). The proteins can remain functional for anything between a few seconds up to indefinitely (until they are used, or diluted when a cell divides). A cell might divide a few times per hour (typical of bacteria in a good growth environment), or every few days (cells in an embryo and some cancer cells) or never (various cells in a developed organism don't divide, such as neurons). Having an idea of these timescales is important because it shows that if a tissue needs to sustain some transient force (e.g. we press a finger on our skin), or if a bacteria colony needs to respond to a sudden change in temperature, this will take place with the proteins available at the time, in the cells (there is no time for gene expression). However,

given a few minutes, bacteria could have new “adequate” proteins in place, in response to the changed conditions.

However, the assembly and interaction of proteins with each other inside a cell can happen over shorter timescales than gene expression. Of particular importance to the structure and dynamic behaviour of eukaryotic cells is the assembly of tubulin and actin into their respective filaments, and the equilibrium between assembled and free (monomeric) protein. (This is a simplified view; there are also “cap” proteins that terminate the polymers, and some other molecules involved.)

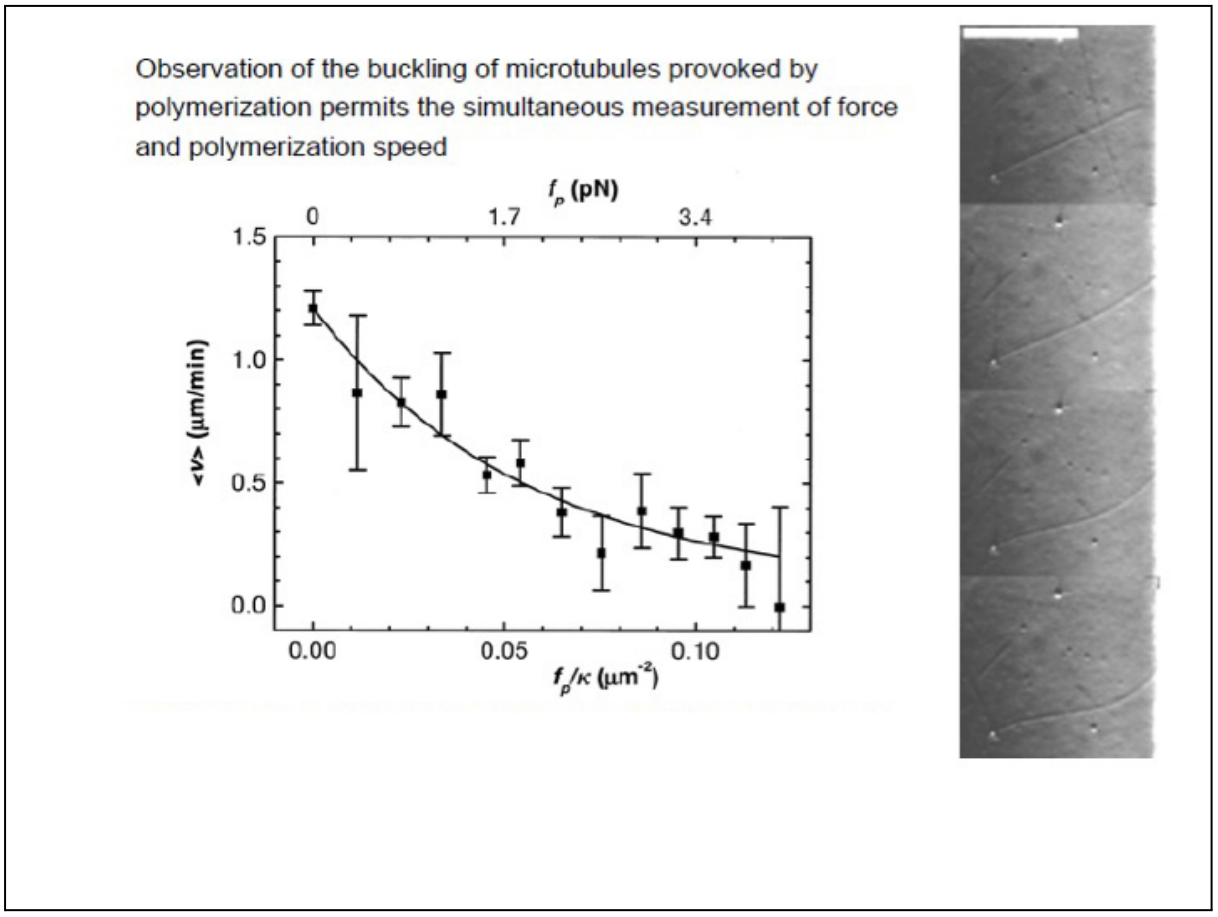
Many structures inside cells are typically in a dynamic steady state – that is, they are constantly being assembled/disassembled, rather than being permanent features. In Slide 1, the graph of the length of one microtubule over time shows alternating periods of growth, where tubulin monomers join a filament at one end, and fast depolymerisation. This equilibrium can easily and rapidly be unbalanced by physical forces, and, indeed, this is at the heart of how a cell can probe the environment, and “decide” in which direction to migrate, or in which direction it might “want” to exert a pulling force.



Source: Slide 4 Microtubules can alternately grow and shrink

Observation of the buckling of microtubules provoked by polymerisation permits simultaneous measurement of force (f_p) and mean polymerisation speed <v>. The right image

in Slide 5 shows a microtubule growing against a wall and buckling. The bead on the left of the tube is held in an optical trap, measuring the force on the tube. The chart on the left shows the force at buckling, for tubes growing at various speeds. Growth is affected by mechanical forces, and also growth determines tube strength.

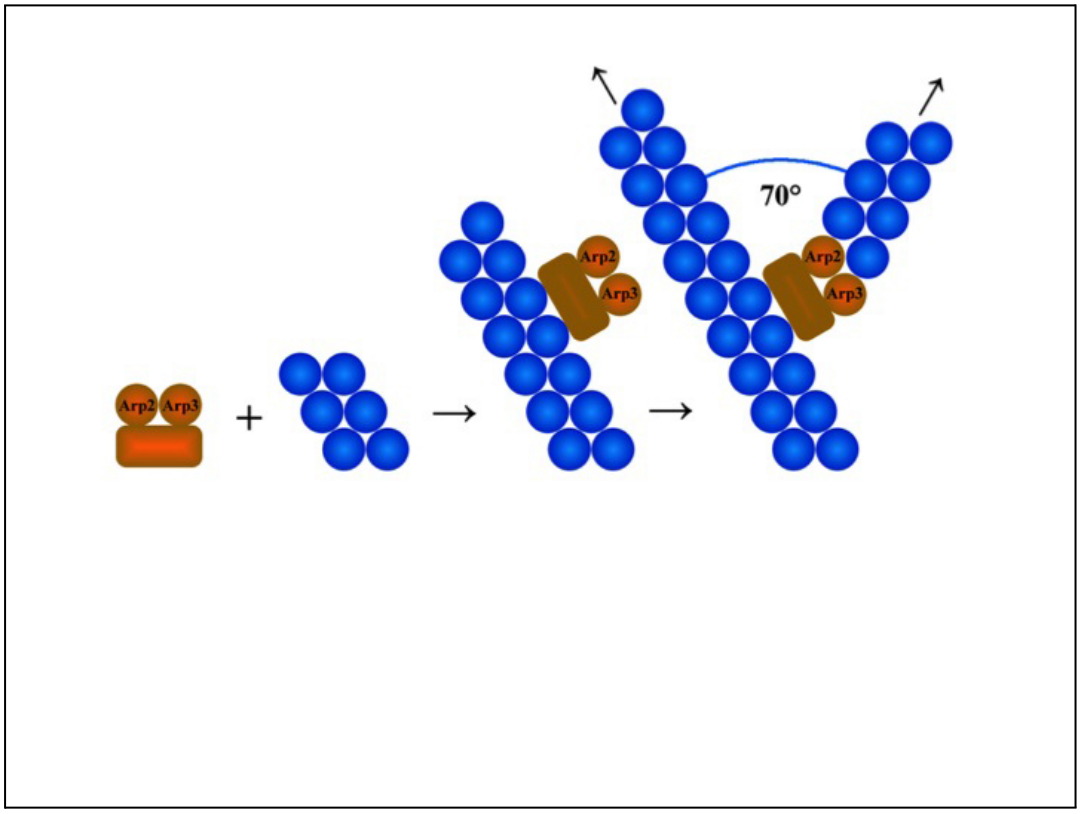


Source: [Slide 5 Measurements of force and polymerisation speed during the buckling of microtubules]

Cell Mechanics

The behaviour of a cell is determined by the concentrations and interactions of a set of proteins. It can be regarded essentially as a computation, the inputs for which are the levels of a set of proteins, and the finetuning of their interactions. In laboratory experiments on cells, it is very challenging to set or control these values; experimenters have to rely on observing the mean behaviour over many cells, and attempt to deduce the "algorithm" through which cells determine the outcome. A typical example is **chemotaxis** – that is, how a cell responds to a gradient of concentration of some chemical. Many cells will initiate migration towards the source of the chemical.

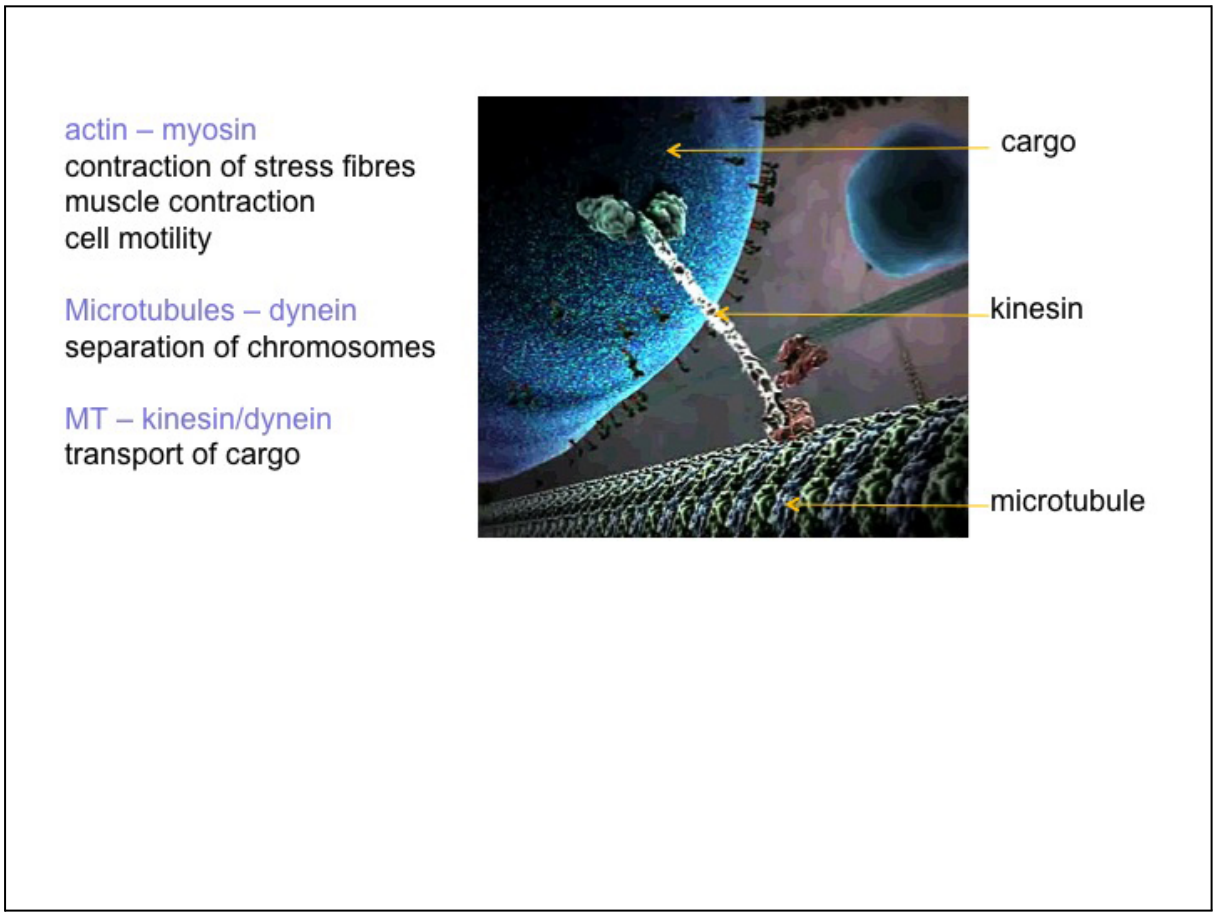
Microtubules, which are typically arranged radially in the cell, enable control over the transport of molecules in the cell. They are stiff enough to resist compression and they play a key role in moving the two copies of the genetic material to opposite sides of a cell when cell division takes place. Individual actin filaments are too soft to "push" effectively against other cellular structures), but they link with each other via other proteins that act as crosslinkers (Slide 3). The **network** formed in this way (it is a polymer gel in the language of soft matter physics) is strong enough to push out (or pull in) the external cell membrane, and indeed actin filament gels are the key element at work in cell motility. Myosin (Slide 4) is a molecular motor that is able to travel in one direction along an actin filament.



Source: [Slide 6 A network of actin filaments enables a cell to extend a leading edge (push) and to retract or exert traction (pull)]

Active forces are originated by particular protein assemblies, known as **molecular motors.** These are complex structures that can transform chemical energy (stored as ATP molecules in cells) into conformational changes – that is, mechanical energy. (Also see Biological Energy lectures 1 and 2.)

Some motors (myosin) can pull two actin filaments towards each other, which is how an actin gel can exert a tensile force. Other motors are used for directed (and non-random) transport of material through a cell: kinesin and dynein are molecular motor machines that are able to travel (in opposite directions, positive and negative, respectively) along microtubules, "carrying" cargo such as vesicles. (Also see Molecular Machines, lectures 1 to 3.)



Source: Slide 7 Functions of molecular motors in connection to cytoskeletal filaments

A cell crawling on a surface is an example of a biological process that calls for a number of physical considerations, such as mechanics of the cell interior (cytoskeleton) and membrane; forces of adhesion; and mechanisms for the extension of cell protrusions (lamellipodia) in the forward direction.

Further reading

Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, and Peter Walter, *Molecular Biology of the Cell 5th edn*, Garland Science 2008

Bruce Alberts, Dennis Bray, Karen Hopkin, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts, Peter Walter *Essential Cell Biology, 3rd edn*, Garland Science 2009.

Uri Alon, *An Introduction to Systems Biology: Design Principles of Biological Circuits*, Chapman & Hall 2007 Karen E Kasza, Amy C Rowat, Jiayu Liu, Thomas E Angelini, Clifford P Brangwynne, Gijsje H Koenderink and David A Weitz *The Cell as a Material* Current Opinion in Cell Biology (2007) 19: 101–107

Philip Nelson, *Biological Physics: Energy, Information, Life*, W H Freeman 2007

Rob Philips, Jane Kondev and Julie Theriot, *Physical Biology of the Cell*, Garland Science 2008.