

# Cell Motility

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## Introduction

Movement is a major characteristic of living organisms, and can take the form either of movements of cells or of movements within cells themselves. Lower prokaryotic cells, such as some bacteria, are able to swim within their environment with the aid of fine appendages, but the motile repertoire exhibited by higher eukaryotic cells is much greater. Higher cells may also have beating appendages in the form of numerous short cilia or fewer longer flagella, and in unicellular protozoa these function in a coordinated way, not only to propel the organism but also to assist feeding. Cilia are also present on cells of certain differentiated tissues of metazoans, where their beating serves to move the environment relative to the stationary cells. Not all protozoa move by means of cilia and flagella. Some, such as freshwater and soil amoebae, crawl over their substrates, and a variety of cells, such as leucocytes, in multicellular organisms show similar crawling movements.

Higher cells, as well as being much larger than bacteria, have separate nuclear and cytoplasmic compartments and often show considerable asymmetry. This has necessitated the development of mechanisms for moving components intracellularly, a property that is well illustrated by plant cells, many of which show different forms of exaggerated cytoplasmic streaming. Intracellular movement is also an important feature of animal cells in which organelles, vesicles and genetic messages are transported to and from specific sites within the cell. Replicated genetic material within chromosomes is also separated into two prospective daughter cells by similar mechanisms.

Many cells are capable of shape changes as a result of reversible or irreversible contraction. The most obvious examples of cellular contraction are seen in muscle tissue. Similar contractions, however, also occur in cells of other tissues, and the division of a cell's cytoplasm following the separation of its genetic material at mitosis is the result of a drawstring-like contraction.

A further type of movement is typified by fibroblasts, cells of mesodermal origin, which migrate individually through connective tissue and synthesize collagen in the extracellular matrix. Their movement differs from that of amoebae in that they do not show continual deformation during migration, but glide over their substrate as a result of extension, attachment and contraction of a broad, flattened, leading edge. Indeed, in a similar fashion the growth cone at the tip of axons of differentiating nerve cells

## Introductory article

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is thought to extend, interact with its substrate, and contract to extend the axon and thereby innervate tissues.

As well as moving independently, cells change shape and move as aggregates during development. This is seen most obviously and dramatically as early as gastrulation, following extensive cleavage of the fertilized egg, when interrelated movements of sheets of cells lay down the different cell layers of the embryo. The movement of aggregates of cells also occurs extensively at later stages of development in numerous well-documented examples of organogenesis.

The cytoskeleton forms the basis for most of the active movements exhibited by higher cells. In some instances motility is generated simply by its regulated assembly and disassembly. In others cases motility results from the activities of 'motor' proteins which interact with the different cytoskeletal elements, and both phenomena are discussed elsewhere.

## Swimming Cells: Bacteria, Ciliates and Flagellates, Sperm

Many bacteria can sense various aspects of their surroundings and respond by moving towards or away from stimuli, for example by migrating up and down chemical gradients of attractants and repellents. Some motile bacteria glide over surfaces. Other bacteria, such as *Escherichia coli*, swim by means of a number of fine helical filamentous flagella approximately 20 nm in diameter and several micrometres in length. These act as propellers, rotating rapidly at about 300 Hz, driven by a rotary motor at their base. The energy for driving the motor derives directly from the transmembrane proton gradient. The rotatory motors on any one cell are capable of turning in both directions, and their collective direction determines the swimming path. Observations have shown that when all the flagellar motors are rotating in the same direction the flagella form a bundle and the bacterium is propelled

smoothly and continuously. When, however, one or more rotates in the opposite direction the flagella are splayed, movement is more irregular and the cell is seen to 'tumble'. A cell normally alternates between these swimming patterns, performing what is known as a random walk. In response to a stimulus the emphasis on a particular direction of flagellar rotation changes, and the pattern of swimming is altered. Flagellar rotation is genetically complex, with around 50 genes required for flagellar assembly and functioning, so that it is unsurprising that the mechanism of torque production is not understood.

Certain higher cells throughout the plant and animal kingdoms also possess motile appendages on their cell surfaces and use these either for swimming or for moving fluid over their surfaces. Some protozoa, for example, are covered by numerous short cilia, whereas others possess fewer longer flagella, and these are used to propel the unicell through its environment. Considerable variation exists in the pattern of ciliary and flagellar movement. However, in general, a cilium beats via a rapid sideways bending – the effective stroke – and this is followed by a slower recovery stroke in which a wave passes from its base to the tip to return the cilium to its original position. The many cilia on the cell surface are arranged in rows and beat synchronously while being slightly out of phase with the adjacent row, to form coordinated metachronal waves of beating. Flagella, by contrast, are much longer and normally propagate bending waves of constant amplitude from their bases to their tips. The beating of flagella results in the forward propulsion of the cell, and may be accentuated or modified in some instances by the possession of fine flimmer hairs on their surfaces. Various other modifications to particular environments also occur, as illustrated by parasitic flagellates found in blood, where the flagellum is attached to the side of the cell by an undulating membrane. As well as propelling the protozoan, experiments have shown that ciliary and flagellar beating may be reversed or altered to change the direction of swimming and so allow the cell to avoid or be attracted to a range of external stimuli.

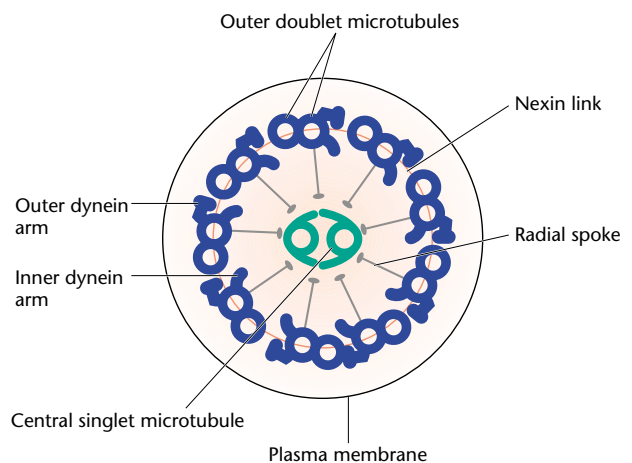
Motile male gametes of most animals are propelled by a flagellum similar to that of protozoa. During metamorphosis of spermatids into spermatozoa, in addition to the condensation and shaping of the nucleus to form the sperm head, organelles including mitochondria and the centrosome migrate to the posterior end of the nucleus. There they form the midpiece of the sperm, and part of the centrosome acts as a so-called 'basal body' from which a sperm tail grows. In animals with internal fertilization the flagellum is used by the sperm to swim through the fluids within the female genital tract, or through a range of other environments in those showing external fertilization. In many marine invertebrates enormous numbers of sperm are shed along with eggs into the sea and the swimming of the sperm ensures their confluence, while chemoattractants increase the probability of fertilization.

As well as propelling unicells, cilia propel multicellular organisms and embryos. Indeed, most organisms possess cilia or flagella at some stage in their life cycle. They also occur extensively on the epithelia of many organisms, where they serve to move fluid over the cell surfaces. The activities of ciliated epithelia serve a wide range of functions and in humans, for example, occur in the lungs and airways, the eustachian tubes, the middle ear, the pharynx, the lining of the brain, as well as in the female reproductive tract.

Cilia and flagella of higher organisms are structurally and functionally different from bacterial flagella. Both possess an internal axoneme comprised of a characteristic arrangement of nine peripheral doublet microtubules with a central pair of single microtubules (**Figure 1**), and the basis of their movement is the relative sliding of the outer doublets driven by a pair of projecting arms consisting of the motor protein, dynein. Sliding is then converted into bending by additional links and spokes comprised of the large numbers of polypeptides identified in the organelle.

## Crawling Cells: Amoebae, Leucocytes

A wide variety of cells move by means of crawling over substrates rather than swimming through their environment. Since microscopes began to be used to look at cells, observers have been fascinated by the movements of free-living protozoans, such as the freshwater *Amoeba proteus*. Observations of *A. proteus* have shown that it advances over its substrate by extending large processes known as pseudopodia and that their direction of extension from the



**Figure 1** Diagram of a transverse section of a cilium or a flagellum. The major elements of the internal axoneme are nine peripheral microtubule doublets surrounding a central pair of single microtubules. Pairs of dynein arms attached to one doublet interact with the adjacent doublet to produce relative sliding. This is then converted into ciliary or flagellar bending by other structures including nexin links and radial spokes.

cell surface may be in response to food. Within an extending pseudopodium, endoplasm (known as plasmasol) can be seen to flow forward through a more rigid outer layer of ectoplasm. When the forward-flowing plasmasol reaches the so-called hyaline cap at the pseudopod tip, it disperses in a fountain-like streaming pattern before being converted to stationary granular ectoplasmic plasmagel. At the tail or uroid of *A. proteus*, the converse occurs and plasmagel is recruited to plasmasol which flows forward rapidly to complete the cycle. Many different amoeboid cells living in freshwater, seawater and also the soil migrate in this fashion, the main difference being the size of the pseudopodial extensions which vary from broad lobopodia to much finer filopodia.

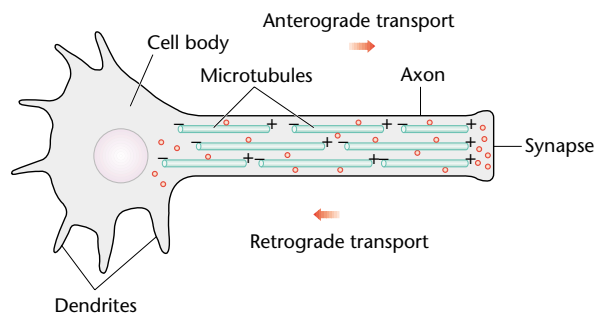
The basis of the pseudopodial crawling movement emerged from studies with a related amoeba, *Chaos chaos*. This is a much larger organism than *A. proteus*, from which it is possible to obtain isolated cytoplasmic extracts. These extracts contain both actin and myosin in filamentous form, and contract and relax on application of the same experimental conditions that bring about the contraction and relaxation of skeletal muscle. Such experiments provided evidence that cytoplasmic streaming in crawling amoebae is based on contractile events during the plasmasol–plasmagel interconversions, and provoked considerable experimentation and debate as to the site of contraction, which may in fact be throughout the whole length of the organism.

A similar movement to that of free-living amoebae is also exhibited by certain cells of metazoans, notably leucocytes, in mammalian blood. Cell migration is particularly important in the functioning of different leucocytes, and these cells show some of the fastest rates of movement. This is seen with lymphocytes during their role in the inflammatory response. Chemoattractants called chemokines direct the migration of lymphocytes out of the blood and lymph vessels into the extracellular matrix and lymphoid organs where they associate with antigen-presenting cells. As they migrate, they adopt a distinct polarity which is inherent to their crawling behaviour, forming a flat lamellipodium at the leading edge and a bulbous uropod at the tail. Crawling T lymphocytes show actin networks continuously forming at their leading edges and linked to surface receptors, while actin–myosin contractions pull the cell forwards. Their leading edges recognize and bind antigen-presenting cells and, once bound, cytoskeletal rearrangement results in cessation of migration. Following tissue injury or local infection, other leucocytes, including small neutrophils and larger macrophages, change shape, extending lamellipods while developing polarity, and migrate in a comparable way to lymphocytes out of the blood vessels into surrounding tissues where they are attracted by chemotactic factors to engulf infecting bacteria.

## Internal Movements: Cytoplasmic Streaming, Vesicle Transport

Plant cells are often large with substantial central vacuoles and there are numerous instances of cytoplasmic streaming associated with this. Patterns of streaming vary considerably, but certain examples are particularly spectacular and have been chosen for experimental investigation. One such is the staminal hairs of the flowers of *Tradescantia*. Staminal hairs are comprised of elongated cells joined end to end. Cytoplasmic strands traverse the central vacuole and not only does the deployment of the strands constantly change but streaming in individual strands shows a complex pattern at rates of the order of  $20 \mu\text{m s}^{-1}$ . A quite different type of streaming occurs in the exceptionally large internodal cells of the alga *Nitella*. In this case there is a circulatory rotational streaming of the endoplasmic layer inside a stationary layer of ectoplasm. Here streaming is unidirectional and at a rate of approximately  $100 \mu\text{m s}^{-1}$ . Both types of cytoplasmic streaming have been shown to be based on myosin-driven movements along actin filaments appropriately arranged in the plant cell cytoplasm.

Compared with cytoplasmic streaming, animal cells tend to show a slower translocation of organelles and vesicles along another cytoskeletal component: microtubules. In undifferentiated cells microtubules derive from a region close to the nucleus and extend towards the cell periphery. In differentiated cells they are invariably found parallel to axes of asymmetry, and indeed are responsible for maintaining asymmetrical cell shape. While occurring throughout all cells, vesicle translocation is often greatly emphasized in cell extensions or processes. One of the most extensively studied examples is the vertebrate neuron, which has short dendrites and a long axon extending from the cell body (**Figure 2**). Components synthesized in the cell body pass outwards in an anterograde direction along the axon to the synapse, and do so at a fast rate of approximately  $5 \mu\text{m s}^{-1}$ . This is superimposed on a slower,



**Figure 2** Diagram of a vertebrate nerve cell showing the extended axon and a number of short dendrites. The polarity of the axonal microtubules is shown, and the bidirectional anterograde (outward) and retrograde (backward) transport along the axon is indicated.

outward, axonal transport of structural proteins for maintaining and extending the axon. There is also the simultaneous translocation of vesicles in the retrograde direction back towards the cell body. The movement of pigment granules in pigment cells or chromatophores is another example that has received much attention and has been particularly valuable for studying the regulation of intracellular movement. In response to hormonal stimulation, the granules migrate outwards along extended cell processes or back towards the cell centre, and the dispersal or aggregation of the pigment granules is responsible for the observed colour changes of the organism.

While specific systems have provided amenable models for investigating microtubule-based translocation, the phenomenon is believed to occur in almost all higher cells and to involve the translocation of a wide range of membrane-bound organelles including nuclei, mitochondria, lysosomes and a wide range of vesicular traffic in secretory and endocytic pathways. Indirect evidence also exists, particularly but not exclusively from studies of eggs and embryos, that certain messenger ribonucleic acids are translocated along microtubules to different locations in cells in a comparable way.

It has also become increasingly clear that in many cells a dual system for intracellular transport exists, and in such cases it is envisaged that microtubules provide the tracks for long distance travel whereas actin filaments provide those for local movement. A large number of microtubule motor proteins (kinesins and dyneins) have been identified, and these are believed to transport a wide range of cellular cargoes in different directions along microtubule substrates to their cellular destinations, while different members of the myosin family which drive vesicles along actin filaments have been identified.

## Dividing Cells, Contracting Cells

Some of the most dramatic movements seen within cells and exhibited by cells occur at cell division. At the start of mitosis, which partitions the genetic material equally between the two prospective daughter cells, the nuclear envelope breaks down and the microtubule-based mitotic spindle forms in the vicinity of the centrioles which have previously migrated to opposite poles of the cell. The chromatin condenses to form chromosomes which are captured at their centromeres by the spindle microtubules. Having attached to the spindle, the chromosomes oscillate between the poles with decreasing amplitude until their centromeres reach the equator of the cell. After a short pause the two chromatids comprising a particular chromosome separate and then move along with other chromatids towards opposite poles of the cell. In some cells the poles themselves also move further apart, effectively to increase the distance between the two sets of chromatids. To an

extent, movements of the chromosomes and chromatids at mitosis may result from the polymerization and depolymerization of the spindle microtubules. More important, however, are the activities of a battery of microtubule motors which transport the genetic material along the spindle microtubules and also affect the movement of spindle microtubules relative to each other.

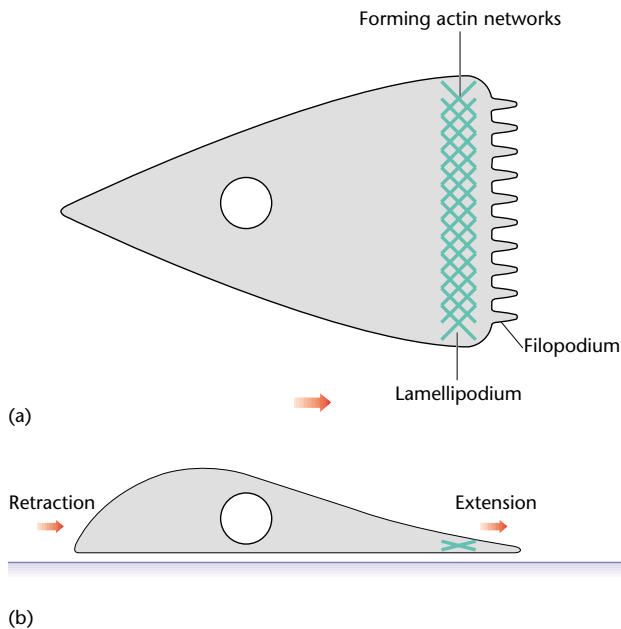
Once nuclear division has taken place, the cytoplasm divides by a process known as cytokinesis. This is brought about by the activities of a contractile ring comprised of actin filaments and myosin molecules which forms around the equator of the cell at right angles to the mitotic spindle. This gradually pinches the cytoplasm in a drawstring fashion, eventually resulting in separation of the two daughter cells. However, the fact that in some cases cytokinesis can occur in the absence of myosin has indicated that other actin-binding proteins are also important.

Similar contractile events based on actin and different members of the myosin family are the basis of the motility of many cells and cellular processes. The contractile microvilli on the surface of the intestinal epithelium of vertebrates, for example, contain a central parallel core of actin microfilaments. Many of the actin-associated proteins in this system are the same as those found in striated muscle, and a muscle-like myosin located at the bases of the villi is thought to interact with the actin filaments in the system.

## Movements in Tissues: Fibroblasts, Growth Cones, Cancer Cells

Cells from a wide variety of tissues are capable of movement. When released from tissue and placed in culture, such cells have been shown to flatten and then to migrate randomly over their substrate. Fibroblasts are typical of this and their movements have been studied extensively. A fibroblast migrates over a substrate by extending a broad, flat, leading edge or lamella in conjunction with finer filopodia. These attach to the substrate at specific attachment points, called focal adhesions. The cell then moves forward as a result of traction within the cytoplasm, and the cycle is completed by release and retraction of the tail of the cell.

The leading edge of a migrating fibroblast, which because of its behaviour and appearance is often known as a ruffled membrane, has a complex network of actin microfilaments (**Figure 3**). These are extremely dynamic, and the assembly of microfilaments nucleated at the membrane of the leading edge is believed to be responsible for the localized and exploratory extensions of the cell. Important in regulating the dynamic properties of both the actin and the microtubule cytoskeleton are the Rho family of small guanosine triphosphate-binding proteins. One



**Figure 3** Diagram showing the shape of a migrating fibroblast, (a) from above and (b) in profile. The leading edge of the cell is thought to extend as a result of the formation of actin filaments in the broad flattened lamellipodium and numerous fine filopodia.

member, Rac, regulates a signal transduction pathway leading to the formation of lamellipodia and membrane ruffles, and another, Cdc42, controls finer filopodia formation. Anterior attachment of the cell is integral to its movement and the cell-surface glycoproteins responsible for this are linked to the microfilaments via transmembrane proteins called integrins. Integrins, which are complexed with other proteins in focal adhesions, transmit signals bidirectionally across the cell membrane, and in conjunction with the Rho family function to coordinate the organization of the cytoskeleton. Rho itself leads to the assembly of focal adhesions and actin-based stress fibres which run backwards from the leading edge into the cytoplasm and are thought to interact with myosin motor proteins to produce the contractions that result in the cell moving forwards.

Random movements of fibroblasts have been shown to be influenced by a range of external stimuli. Important amongst these are the topography of the substrate over which they are migrating. For example, in tissue culture, fibroblast movement is seen to be focused along grooves in the substrate. It has also long been known that migrating fibroblasts are influenced by one another, displaying contact inhibition. When one cell touches another, their leading edges cease to show ruffling. New ruffled membranes then form at different regions of the cells, leading to their separation.

The growing tip of a nerve axon possesses a growth cone, which behaves in many ways like the leading edge of a

migrating fibroblast. During development, or regeneration of the nervous system after injury, axonal processes grow and extend sometimes considerable distances from the cell body to establish the appropriate synaptic contacts. Axons navigate by means of their distal growth cones, which extend and retract lamellipodia and filopodia as they sense attractive or repulsive signals in their surroundings. Having firmly attached to their substrate, contraction within the growth cone results in axonal extension, and myosin has been shown to be appropriately localized to bring this about.

The invasion of cancer cells has been linked to enhanced cell motility and directional migration and, while a number of factors influence this, the organization of the cytoskeleton is a major factor. Cancer cells show altered integrin-mediated responses. Adhesion molecules in the cell membrane, such as the integrins, may link with the cytoskeleton to maintain stable adhesive contacts, but alternatively may interact with the actin cytoskeleton to develop lamellae and so enhance invasive migration, and metastasis.

## Cell Movements in Development

Some of the most dramatic cell movements occur in embryos during early development. After fertilization, successive cell divisions and a variety of patterns of embryonic cleavage result in a multicellular blastula, which in some instances possesses an internal cavity, the blastocoel. Blastula formation is followed by gastrulation, which is the period when cells and tissues start to move in a coordinated way, becoming extensively rearranged and so forming new relationships with neighbouring cells. These cell movements serve to establish the body plan and, in particular, the three germ layers of the organism. Gastrulation takes a variety of forms in different organisms, and the movements involved are very varied; they include the spreading and infolding of cohesive sheets of cells, the inward migration of cell aggregates as well as the contraction within individual cells. All involve cooperation of adhesive systems between the cells and their actin cytoskeletons to generate the forces involved. Gastrulation has been studied extensively in a number of organisms but is at its simplest and most easily observed in marine invertebrates. Many of the different cell movements that occur in early development can be seen in sea urchins. Here, at the onset of gastrulation, cells at the vegetal pole move into the blastocoel while forming fine filopodia. Once in the blastocoel these primary mesenchyme cells migrate along defined paths in response to a number of identified positional messages to form a ring at the edges of the vegetal region of the blastocoel. Shape changes occur in the vegetal layer of cells, resulting in the beginning of its invagination to form the archenteron. In the meantime the

filopodia extended from the mesenchyme cells reach and adhere to the internal animal surface of the blastocoel, and their contraction then completes the invagination. Moreover, a similar repertoire of collective and individual cell movements is involved in the different forms of gastrulation in other organisms and also in later stages of development, starting with the formation of the central nervous system at neurulation.

## Further Reading

- Baggiolini M (1998) Chemokines and leukocyte traffic. *Nature* **392**: 565–568.
- Blair DF (1995) How bacteria sense and swim. *Annual Review of Microbiology* **49**: 489–552.
- Goodson HV, Valetti C and Kreis T (1997) Motors and membrane traffic. *Current Opinion in Cell Biology* **9**: 18–28.
- Hynes RO (1992) Integrins: versatility, modulation and signalling in cell adhesion. *Cell* **69**: 11–25.
- Keely P, Parise L and Juliano R (1998) Integrins and GTPases in turnover and cell growth. *Trends in Cell Biology* **8**: 101–106.
- Lane J and Allan V (1998) Microtubule-based membrane movement. *Biochimica et Biophysica Acta* **1376**: 27–55.
- Langford GM (1995) Actin- and microtubule-dependent organelle motors: interrelationships between the two motility systems. *Current Opinion in Cell Biology* **7**: 82–88.
- Mermall V, Post PL and Mooseker MS (1998) Unconventional myosins in cell movement. *Science* **279**: 527–533.
- Mitchison TJ and Cramer LP (1996) Actin-based cell motility and cell locomotion. *Cell* **84**: 371–379.
- Okabe S and Hirokawa N (1989) Axonal transport. *Current Opinion in Cell Biology* **1**: 91–97.
- Sanchez-Madrid F and del Pozo MA (1999) Leukocyte polarization in cell migration and the immune response. *EMBO Journal* **18**: 501–511.
- Sawin KE and Endow SA (1993) Meiosis, mitosis and microtubule motors. *Bioessays* **15**: 399–407.
- Stossel TP (1993) On the crawling of animal cells. *Science* **260**: 1086–1094.
- Whitman GB (1990) Introduction to cilia and flagella. In: Bloodgood RA (ed.) *Ciliary and Flagellar Membranes*, pp. 1–30. New York: Plenum.