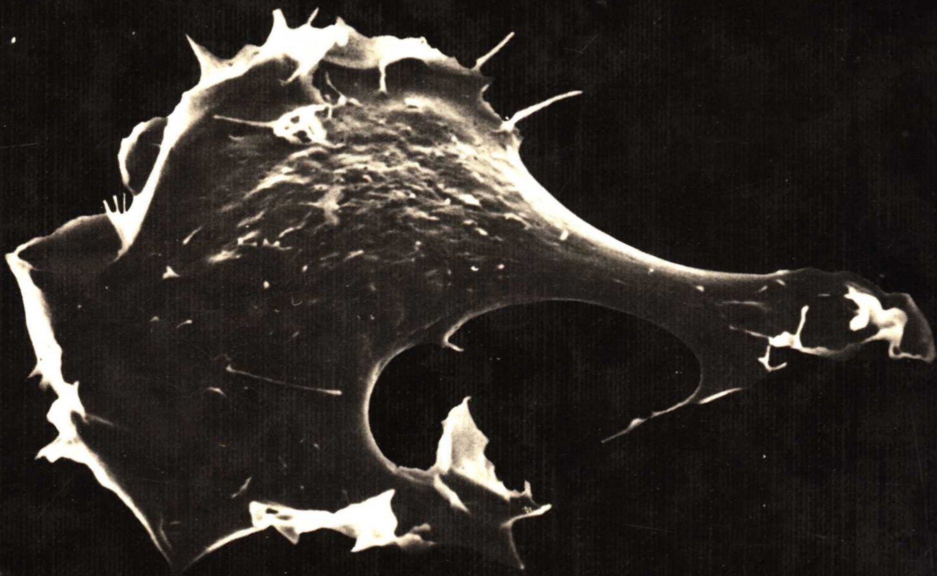
CELL MOVEMENT AND CELL BEHAVIOUR



J. M. Lackie

CELL MOVEMENT AND CELL BEHAVIOUR

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PREFACE

Some years ago a book reviewer, perhaps with Freudian honesty, remarked that the book in question 'filled a much needed gap in the literature'. That phrase has haunted the writing of this gap-filler and this preface may be considered an apologia.

For a number of years I have found myself teaching various groups of students about cell locomotion and cell behaviour; sometimes science students specializing in cell or molecular biology, sometimes immunologists or pathologists who only wanted a broad background introduction. Those students who were enthusiastic, or who wished to appear so, asked for a general background text (to explain my lectures perhaps), and that is what I hope this book will provide. With luck, other scientists who have only a peripheral interest in cell movement will also find this a useful overview. The more proximate origin of the book was a special 'option' subject which I taught for two years to our Senior Honours Cell Biology students in Glasgow, an option cunningly juxtaposed against a very non-cellular topic so that I had a reasonably sized group of test consumers. Since more students chose the option the second time round I felt slightly encouraged. If writing the book does nothing else, it will make it easier to teach the option!

Although I knew from the outset that cell movement was a very broad topic I soon came to realize how small an area I really knew well and how superficial my treatment of many topics was going to be. Inevitably I have relied on other people's reviews and books. The virtue of a monograph is that it is a single person's view of things and is in theory more integrated than a multi-author text; its weakness is that one head contains more ignorance than two, surprising though that might seem. My approach has been to try to extract those things which I myself have found interesting or illuminating and to concentrate more on those areas, sacrificing completeness in so doing. The bibliography is by no means exhaustive; the papers I have quoted are the ones which I have found useful and which are reasonably accessible (not just the ones I have reprints of!), but many excellent papers have been omitted. Too many references make the text unreadable and my intention was to put in only enough to lead the reader into the right part of the primary literature in a fairly direct manner, and I have not attempted to be comprehensive. At the end of each chapter I have listed a few reviews, with cryptic comments on their relevance. The main reference list is at the end of the book. Jargon is always a problem to the uninitiated which is why we use it (it keeps out those who might otherwise see things too clearly) so I have traitorously put in a glossary, which may demystify some terms.

One major problem in dealing with the topic of cell movement is in knowing where to start; should a description of the cellular phenomena precede the detailed discussion of the molecular machinery, or should we start with the motor system and come to the more complicated controls later? Although I have chosen to put the horse (the motor) before the cart, this is not necessarily the way in which the book has to be read. Those who know the general biological background will find the order of the chapters straightforward; others may prefer to read Chapters 5 and 6 first. There are three major sections to the book, Chapters 2–4 which deal with motors, Chapters 5 and 6 which deal with the mechanism of movement, and Chapters 7, 8, 9, and 10 which deal with factors controlling and directing movement. The sections are more-or-less independent, but I have referred back more than I have referred forward, for obvious reasons. In teaching I have invariably followed the sequence of the chapters.

Several of the discussions draw on an analogy between the behaviour of cells and the behaviour of traffic seen from a vantage point; the analogy is given in detail in Chapter 1, and it is deliberately far-fetched because so many students confuse the use of analogy and homology. The discerning reader may recognize the origin of some passages as verbal harangues aimed at students on sleepy afternoons; perhaps that is no bad thing, since it may also stir the somnolent reader. Not everybody cares for analogy of course, and there are traps in anthropomorphic thinking; in fairness to my colleagues I should point out that they did try hard to curb my excesses.

Although my fondness for analogy has not been cured, the comments of many colleagues have been very helpful, and I am grateful to all those who have listened, commented, argued or even remained indifferent – conspicuous boredom in the face of an argument is very instructive. I would like to record my gratitude to those who read drafts of chapters for me: John Edwards, John Freer, Bob Hard, Joan Heaysman, Ann Lackie, Doug Neil, Peter Sheterline, Mike Vicker and Peter Wilkinson. Their comments were a great help, and they cannot be blamed for the mistakes and the infelicities of style which are mine alone. Many people have helped by lending material for figures; they are acknowledged in the legends. The first draft of the book was written while visiting Oregon State University at Corvallis, and I am grateful to all those people who made the summer there such an enjoyable experience. Finally, I would like to thank my colleagues in the Cell Biology Department, who put up with my constant talk of writing; Unity Miller who helped transform manuscript to disc; the students who make it all necessary and last, but by no means least, my family who helped, encouraged, interrupted rarely, and constantly brought me back to reality.

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1
INTRODUCTION

1.1 Why is movement interesting?
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1.1 Why is the movement of cells interesting?

'It's alive – it's moving!'

All the movements of which living systems are capable derive from movement within cells or groups of cells, and the study of cellular movement forms a bridge between the disciplines of biochemistry and of whole-organism biology or physiology. A lot of cellular activities can be considered under the general heading of movement, and a range of different cellular systems must operate to bring about movement; this means that we need a multidisciplinary approach, and this is not an area solely for the narrow specialist. The phenomena of cell movement have an appeal at a primitive or childlike level. Movement catches the eye and begs the questions: 'how?, why?, what for?'. The apparent naivety of the questions does not mean that they will be answered easily.

1.2 What do we mean by movement?

One of the characteristics of living things is their ability to move. The movement may be conspicuous, as with animals, or slow and rather restricted, as with plants: we would expect to find movement even at the cellular level. Movement is, however, a very broad term and we must distinguish between movements which are brought about by the activities of the organism and movements imposed by external forces, as well as distinguishing the various categories of active movement which occur. An analytical approach to the question of what we mean by movement will assist us in subdividing the topic of cell movement and will form the basis of the subdivisions of the book.

We will not concern ourselves with the movements of small molecules, although the movement of ions across membranes is crucial to the normal function of most cells, and the movement of specific molecules from one compartment to another plays an important part in the internal economy of the cell. With the exception of active transport, these movements are imposed by external forces, the kinetic energy of the molecular species involved, and are regulated by the manipulation of permeability. Arbitrarily we will limit our discussion to the movement of very large molecules which are in multimolecular arrays, although in many cases the movement of sub-units will be important and the boundary between this level and that of small molecules is somewhat imprecise. The movement of organelles within the cell is a category of movement that we will need to consider, and it is clear that cells have had to tackle this problem as their size increased. Within a bacterium the diffusion of molecules suffices to keep things going, bringing substrates into contact with enzymes and permitting all of the cytoplasm to be maintained at an homogeneous level of ions, oxygen and so on. Once organelles become 'necessary' to increase the local concentrations of enzymes, substrates, or information, then inequality of production, inhomogeneity of the cytoplasm and the separation of nucleus from cytoplasm means that some distributive mechanism is needed. Once the cell becomes very large, as for example the giant amoeba *Chaos chaos*, the acellular slime mould *Physarum polycephalum*, or the internodal cells of characean algae such as *Nitella*, then the 'soup' must be stirred by active cytoplasmic streaming lest it 'burn onto the pan'. Such streaming probably occurs on a small scale in most cells but its conspicuous manifestations in these giant cells capture our attention and provide models with which to play.

No student of cell biology seriously thinks of cells as smooth spheres, although sometimes we pretend that they are, and appendages dangle from many cells, often with dimensions at around the limit of resolution of the light microscope. These appendages include those designed for specific purposes: for moving the cell around, for increasing the surface area of the cell, or serving as a reservoir of membrane to permit rapid expansion of the cell volume or to allow a marked change in geometry. In fact appendages for a variety of functions exist and we will need to consider them in some detail since they are not static projections but move, either in space or time. The cell, while remaining stationary, may gesture wildly with its appendages, reaching out to sample or manipulate the environment.

The cell may change its shape conspicuously: in cytokinesis where the change is irreversible, in phagocytosis when objects are engulfed within a pseudopodial cup, in contraction, as in a muscle cell, and during the movement of the whole cell. Less conspicuous shape changes may cause an epithelial sheet to curl up into a tube, cause a tube of cells such as a capillary blood vessel to change its internal diameter, or may cause a multicellular array to move, as with the shape changes of cells within the pulvinus which move the whole leaf.

Last, but by no means least, the cell may move position, moving from one location to another, either freely within its environment as in the case of unicellular organisms, or within a multicellular array as, for example, leucocytes during inflammation, tumour cells in malignant invasion, epithelial sheets in wound healing and embryonic cells in **morphogenesis**. The locomotory activity of cells is of particular interest because it is perhaps the most sophisticated level of cellular activity, certainly the most complex of cellular movements. Some of the movements mentioned previously will play a part in cell locomotion, but the activity is coordinated to achieve an overall movement which may be influenced in a variety of ways by the nature of the environment: the behaviour of a cell moving as a unit offers a variety of problems which will occupy much of the last part of this book.

We may, therefore, subdivide movement into the movement of:

(a) molecules,
(b) parts within the cell,
(c) appendages,
(d) the whole cell in one place,
(e) the whole cell from place to place.

We should then begin to ask another sort of question, 'what causes the various kinds of movement?'

1.3 What causes movement?

Having in the previous section subdivided 'movement' according to what is happening, we can go further and ask how the movement comes about, and this in turn will generate a lot of other questions. Within the general topic of cell movement we can recognize certain levels or areas that are of interest. The way in which the motor system is organized and controlled within the cell has an appeal, particularly to the more biochemically and ultrastructurally minded. Problems concerning the nature of the components, the way in which they interact to generate and control movement, to circulate the cytoplasm, to redistribute membrane proteins or to distribute the products of chromosomal division are among the other questions that come to mind. The contribution of the motor system to the mechanical properties of the cell as a whole, and the influence of the motor system on the shape of the whole cell are related questions.

The movement of appendages on a cell may influence the local environment: ciliary tracts on the gills of bivalve molluscs beat in a coordinated way to sort and to transport food particles; **microvilli** on intestinal epithelial cells may stir the local nutritive soup, facilitating absorption; coordinated shape changes in groups of cells may generate waves of peristalsis or, in the most dramatic of examples, drive whole animals by the operation of skeletal (and cardiac) musculature. Movements are involved in phagocytosis, and phagocytes within Metazoa are important elements of the body's defence system. Small free-living organisms are motile by means of the activity of cellular appendages that enable the organism to swim, or by the ability of the cell to crawl. In the examples above the motile activity is being considered in a more complex way, the activity of the motor is taken for granted, the question of interest is the use to which the motor is being put. Then we can ask questions about cell behaviour, much as animal behaviourists and plant physiologists have done with whole multicellular organisms. Why, for example, do cells accumulate in a particular place, how do they respond to directional cues, and what happens when they collide with one another?

A tertiary level of interest in cell movement is in the consequences of movement and the way in which cellular movements influence the spatial organization of tissues and of the embryo – the processes of **histogenesis** and morphogenesis. Pathologists also have an interest in movement: wound-healing involves movement of cells, as does **invasion** of tissues by neoplastic cells. The movements of leucocytes in inflammation and the coming together of cells cooperating in immune responses are motile phenomena, and their perturbation is of clinical significance.

Not only is movement complex but in all of the examples mentioned, even malignant invasiveness, the outcome of movement is a precise ordering of the population. This is particularly true in morphogenetic processes and we will be interested, particularly in the later chapters, in trying to determine the environmental factors that influence movement and the cessation of movement.

As indicated above, cell movement is a broad topic and it has a further interest for the cell biologist: it is one of the most complex of cellular activities and involves the cooperative interaction of many cellular processes. The ability of a cell to move depends on the normal functioning of a range of cellular systems associated with energy redistribution, contractile events and environmental sensing; the challenge of trying to understand this activity lies partly in its very complexity.

1.4 An analogy

The aim of this book is to cover the general topic of cell movement, a fairly ambitious task. It may be useful to develop an analogy to which we can refer and which will to some extent dictate the structure of the succeeding chapters.

Imagine that you stand or hover at some vantage point overlooking the streets of a busy town and its surrounding countryside. That the town is inhabited is clear from the movement of small objects – people, dogs, vehicles etc. The larger moving objects are motor vehicles, and as an enquiring person you wonder how they move . . . what sort of engine do they have, is it reciprocating or rotary, is it petrol, diesel or coal that provides the fuel? Is the engine mounted in front or behind? How does the engine make the car move? A wheeled vehicle may be front- or rear-wheel drive (or both), and the careful observer may notice that the vehicles driving on smooth city streets are less likely to have four-wheel drive than those on rough country roads. The tracked vehicles are either tanks or bulldozers, and stop for nothing. Cars and other vehicles, being larger, attracted our attention first but there are also people moving around clearly using a very different mechanism, and not everything is restricted to moving over the ground surface (moles, underground trains, birds, helicopters and aeroplanes!).

If we concentrate again on the cars: they do not, despite first impressions, move completely randomly, they are being steered and their speed can vary: some element of control exists. More complex rules also seem to govern movement, cars move only in one direction on one side of the road, stop when lights shine red or when waved at by the arms of policemen, and do not collide with one another very often (altering the frictional interaction with the road surface can dramatically alter collision frequency). Some vehicles are restricted to roads whilst others roam freely over marshy ground and up steep slopes. People and cars seem to move independently though collision may lead to cessation of movement. Some vehicles pick up passengers, others release them in larger numbers at particular sites.

Let us attempt an experiment from our vantage point: arrange that the surfaces of roads are covered by snow. What effect will it have on the movement and what does it tell us? Our questions fall into four major categories, concerning:

(a) engines,
(b) traction methods,
(c) steering and control devices,
(d) traffic rules.

These are the headings we will use in the following chapters.

1.5 Motor design – an abstract exercise

Can we design movement systems in abstract, can we play at inventing ways of causing the movements mentioned above? This sort of exercise, of trying to design systems, might help us to understand what is actually going on and provide a framework of hypothetical possibilities which can be explored in seeking to find the basis of movements we discover when we look at real cells. Having tackled the problem from a position of ignorance we can go on, in later chapters, to see how cells have adapted particular mechanisms to achieve a desired end, although Table 1.1 gives a sneak preview. In fact there seems to be a real example of almost all the possible solutions to the problem of generating movement. So, given a basic construction kit of molecules, how could we cause a movement to occur?

Consider first an 'open' system, an unbounded compartment in which our components are unrestrained. This is useless, although we can get the molecules themselves to change their shape (Fig. 1.1a) we cannot make use of these shape changes (unless we want to control the rate of a reaction through an allosteric change in an enzyme for example); we must put some constraints on the system. If we link molecules together we could achieve

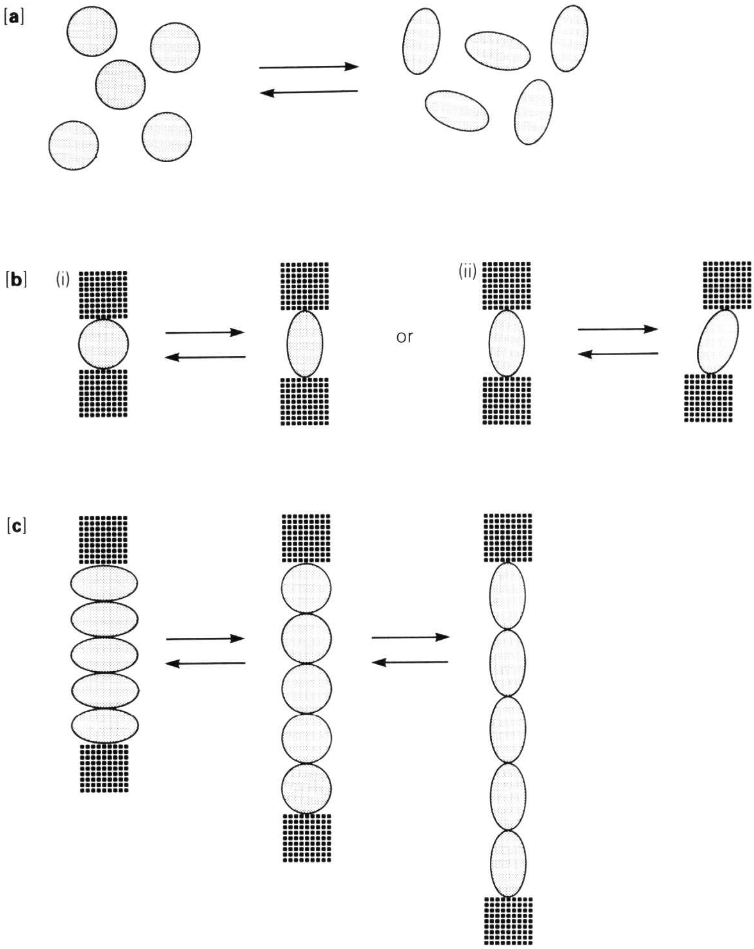
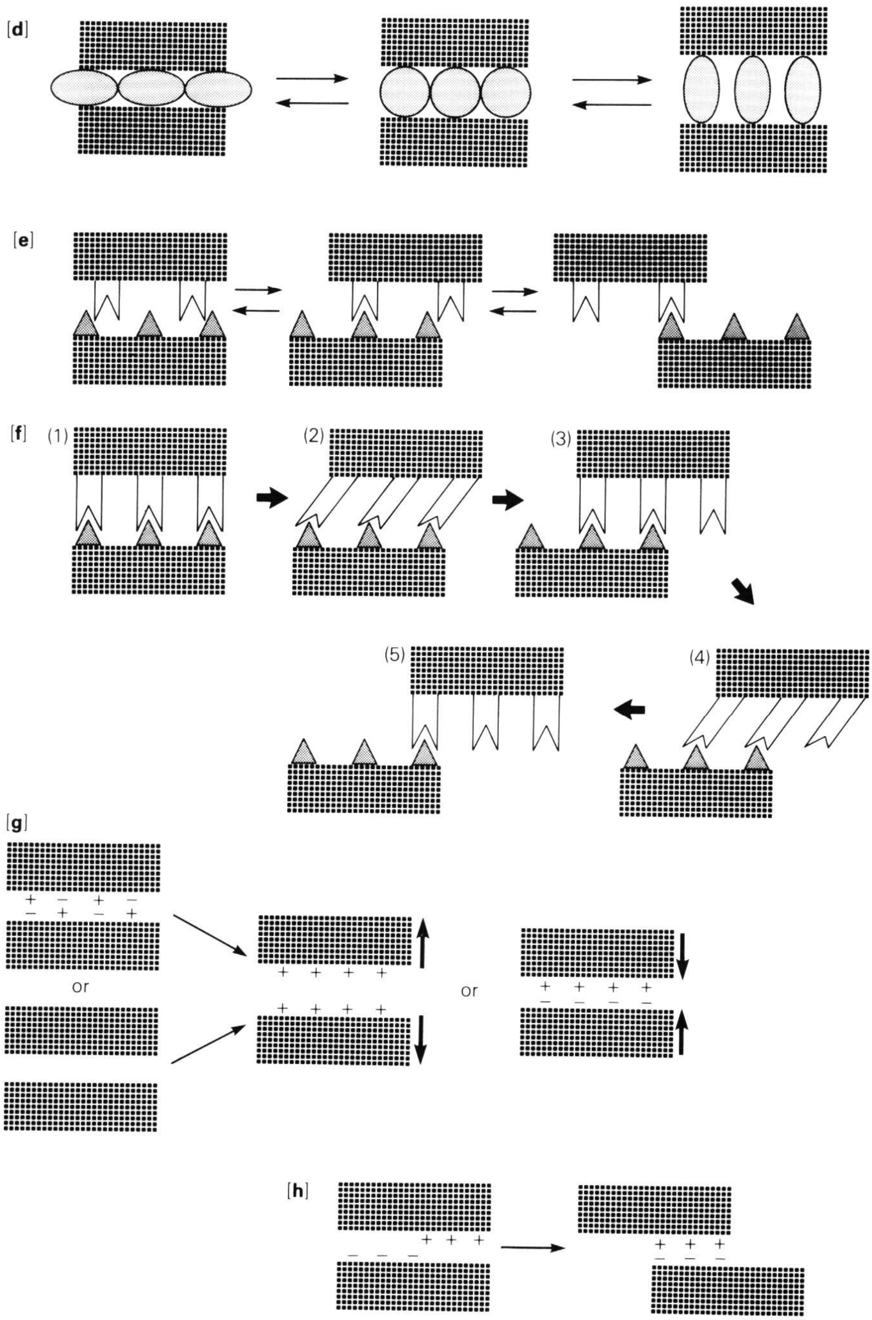


Figure 1.1 Methods of generating movement The molecular assembly kit consists of motor components which play an active rôle (circles), anchorage sites (squares or rectangles), and receptors – molecules that can bind to other molecules. In (a) molecules change shape in an open, unconstrained system, whereas in (b) they are attached to anchorages and in changing shape they cause a change in the relative positions of the anchorage points: a movement. By linking such molecules in series (c) or parallel (d) the movement or the force can be amplified. If to one anchorage we fasten receptors which can bind ligands on the other anchorage then exchanging receptor–ligand pairings may cause (random) movement (e); if the rule is to form new pairings only to the right of the previous ones then the two anchorages will slide (f). The relative movement of the anchorages might come about as a result of electrostatic repulsion or attraction if the charge on the components was varied (g), and this could be used in a manner analogous to that of (f), as shown in (h). Assembly of protomers as in (i) might push the terminal anchorages apart and disassembly might permit their closer approach. Linked assembly and disassembly, as in (j) might be used to push/pull with the cursor (▲) being sent hand-to-hand, or the whole complex might treadmill (see later chapters). The expansion of components, perhaps by altering the hydration, could also push things apart (k).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