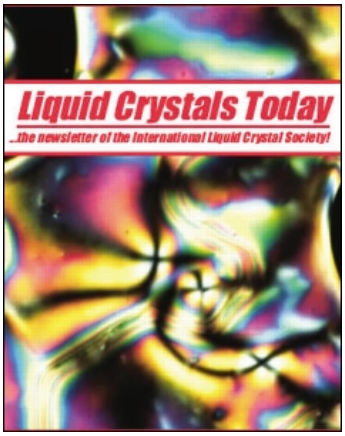

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Microtubules: Nature's smartest mesogens — a liquid crystal model for cell division

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Microtubules: Nature's smartest mesogens — a liquid crystal model for cell division

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It is proposed that the process of cell division by mitosis involves virtually the entire contents of the cell assuming a liquid crystalline state and that the mitotic spindle can be modelled in terms of the known properties of nematic phases. The key molecules involves in the process are tubulin units which self-assemble to produce mircotubules.

1. The dance of the chromosomes

When cells divide, remarkable things happen. When nineteenth century scientists first focussed their optical microscopes on dividing cells, they were amazed to see the carefully orchestrated process which, with some justification, they called 'the dance of the chromosomes'. We call it mitosis (from the Greek word for thread, 'mitos') because, in the early stages of the process, thread-like chromosomes appear. These coil and supercoil until they become condensed into **x**-shaped bodies. (We now know that the DNA strands compact themselves by a factor of 10,000 times during this process). These bodies move into position in a plane across the centre of the cell. At some signal, all the chromosomes break into two daughter chromatids, which then separate and move, as if they were being pulled by invisible strings fastened to their centres, towards 'poles' at opposite ends of a 'spindle'. Finally, when the two sets of chromatids are safely separated, the cell breaks into two daughter cells, the chromosome progressively unwind until the strands become so fine that they become indistinguishable again. One of the most impressive features of this process is the rate at which it happens. These events can be remarkably fast. In an extreme case for example, in the early stages of the development of the fruit fly early embryo, the whole complex process is completed in four minutes (figure 1) [1, 2].

Like so much in molecular biology, at first sight, mitosis appears to be an unnecessarily over-complicated process, but when the full scale of the task is appreciated, one is left with the feeling that there really is no other way to do it. Bearing in mind the enormous length of the fragile strands of genetic material (which are only two molecules wide) and the problem of separating the duplicated strands equally, gene for gene, between the daughter cells, one is forced to ask how else it could be done.

2. Similarity with liquid crystalline behaviour

When the same early microscopists turned their attention to the new 'liquid crystalline' materials discovered at the end of the nineteenth century, they were struck by the way in which the phases appeared to be alive. They watched in fascination as nematic phases were formed by cooling. They saw droplets of mesophase appearing as small 'germs', which grew, came into contact, writhed and coalesced with dramatic molecular rearrangement and intriguing interaction between disclinations. In the 1890's, Lehman recorded his observations in pages of beautiful hand-coloured drawings in his classic publications, and referred in colourful terminology to the 'copulation' of the germs (figure 2) [3].

3. Modelling mitosis in terms of the known properties of mesophases

There is certainly something very obviously liquid crystalline about the dividing cell; the way in which it is structured yet fluid, the spontaneous appearance of the poles, the way in which the chromosomes 'know' where to assemble. An earlier paper at this conference (The British Liquid Crystal Conference, Exeter, 2005) outlined the work of Dmitry Miroshnychenko, Nick Hill and Nigel Mottram in modelling the way in which the geometry of the dividing cell is created in terms of the known properties of nematic phases [4].

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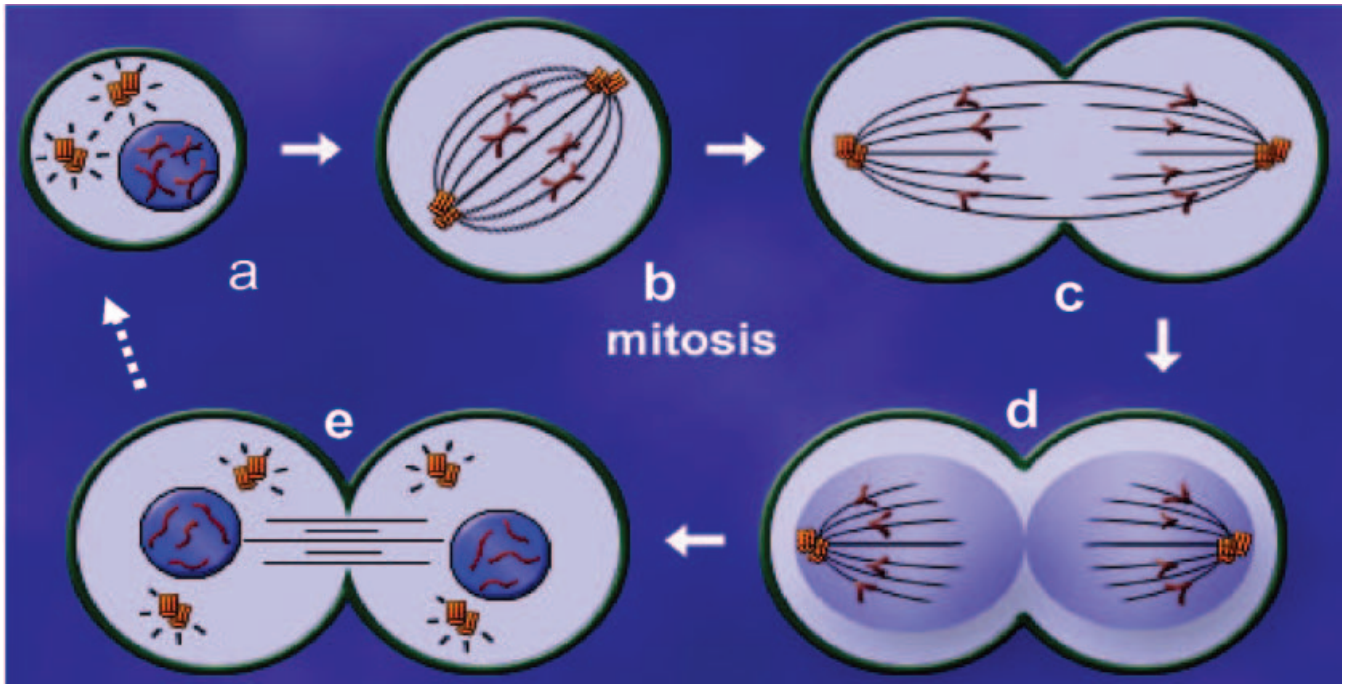

Figure 1. The stages of mitosis: This stylised representation shows the major events which take place during mitosis. (a) Shows the 'resting' cell with a distinct nucleus surrounded by a nuclear envelope. The chromosomes then become visible as supercoiled X-shaped structures and the asters appear and move into the polar positions. The nuclear envelope disappears and the chromosomes drift towards the equatorial plane, (b) shows the 'metaphase' with spindle formation completed and with the chromosomes aligned in the equatorial plane anchored to spindle microtubules. (d) and (e) show the daughter chromatids separating and moving towards the poles. The cell then begins to revert to the 'resting' state, the chromatids unwind, the nucleus reappears and the asters disintegrate. From http://www.swbic.org

This lecture attempts to take the picture a stage further. The mitotic cell is not just a *structure* it is a *machine* for separating the daughter chromatids. This machine aligns the chromosomes in the central plane and, when the daughter chromatids separate, it pulls them towards the poles where they become incorporated into the nuclei of the two daughter cells. It is suggested that the processes which place the parts of this machine in the correct places, involve the cytoplasm of the cell becoming liquid crystalline and the geometry of the whole process can be modelled in terms of known properties of liquid crystal director fields.

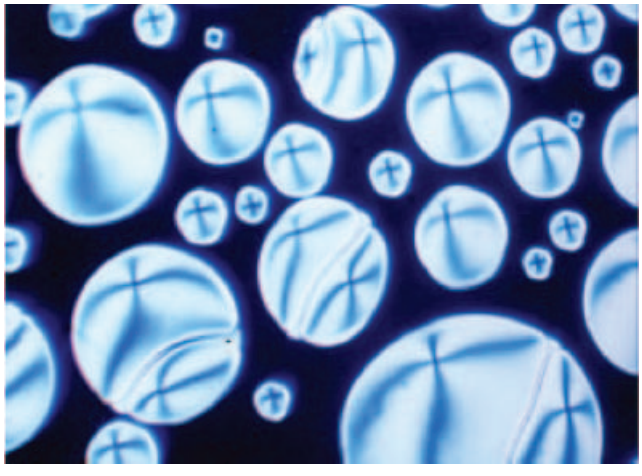

Figure 2. Coalescing germs: Optical micrograph showing nematic droplets ('germs') coalescing at the **I→N** transition. The almost living appearance of the dynamic interaction between disclinations during this process prompted Lehmann to describe this process as the 'copulation of the germs'. From Dr John Bunning, School of Materials Science, Hallam University, Sheffield, UK.

The key players in this process appear to be self-assembling mesogenic units, too small to be seen directly in the optical microscope, but visible in the electron microscope (and with the optical microscope when they are highlighted with fluorescent markers). These have most remarkable properties and are far smarter than anything we have yet been able to synthesise.

3.1 *Bernal's tactoid model*

One of the earliest liquid crystal models for the dividing cell was that of the great J. D. Bernal who compared the spindle to a nematic 'tactoid' (figures 3 and 4) [5, 6]. (This is the name given to the zeppelin-shaped droplets of nematic phases formed when the internal nematic

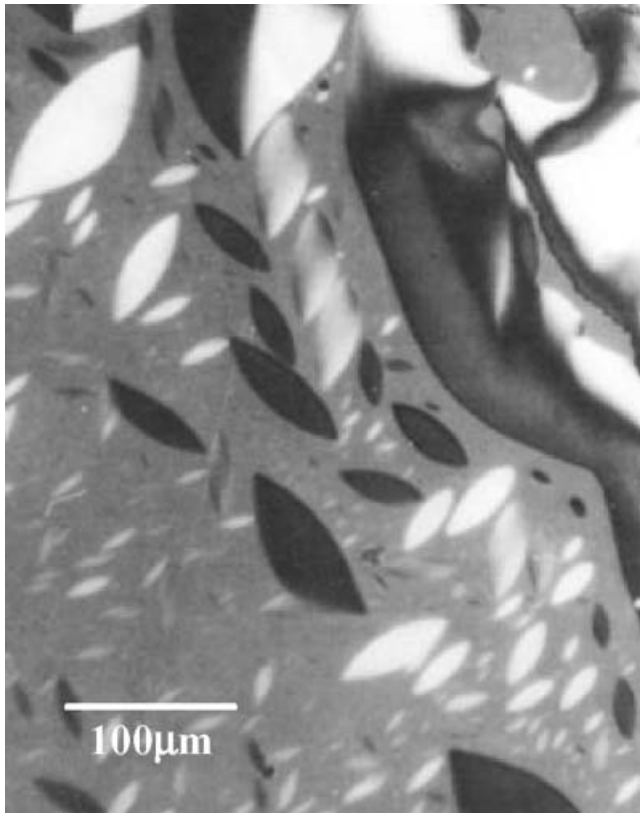

Figure 3. Tactoids: Optical micrograph of tactoids (of silk fibroin from the silk gland of the silk moth, *Bombxy mori*). Crossed polars. Droplets of a nematic phase dispersed in an isotropic host phase sometimes form characteristic zeppelin-shaped tactoids as a result of a compromise between the 'external' affect of the surface tension which attempts to make the droplets spherical and the 'internal' affect of the nematic ordering (viewed between crossed polars). Reproduced from the PhD thesis of W. R. Kenchington, Department of Biomolecular Structure, University of Leeds, 1965.

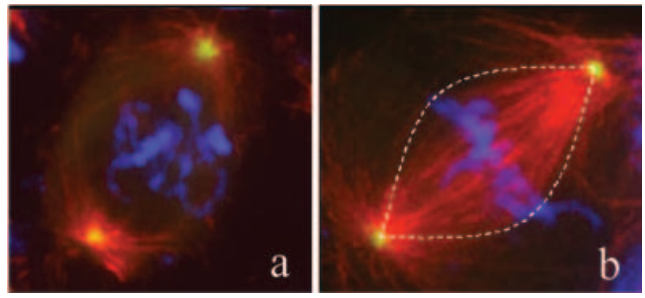

Figure 4. The part of a mitotic cell which resembles a tactoid. The left hand micrograph shows a cell in the preliminary stages of mitosis, when the chromosomes have condensed, but before they have assembled in the equatorial plane. The right hand figure shows the same cell at the subsequent metaphase stage of mitosis with the tactoid-like region outlined. This preparation has been fluorescently labelled to show the chromosomes (in pale blue) the microtubules (in red) and the microtubule organising regions at the spindle poles (in yellow). Note that when Bernal proposed that the spindle resembled a tactoid, half a century ago, fluorescent labelling had not been developed. The only features clearly visible would have been the chromosomes (stained red with haematoxylin).

alignment is strong enough to overcome the attempts of the surface tension to make the droplet spherical). Surprisingly however (in view of Bernal's awesome reputation as one of the greatest polymaths of his age) this view was never taken seriously. For reasons that look less than totally justified in hindsight, liquid crystal research was going out of fashion in the late 1940's and the bald statement that the spindle was not a tactoid seems to have been enough to kill the idea dead. No one (with any public voice) seems to have mentioned liquid crystals and dividing cells in the same sentence for the next half century.

(An analogy can be drawn with the way Wegener's idea of continental drift was treated at more or less the same time. The geological establishment felt that they could not take the idea seriously, not so much because there was insufficient evidence to make it credible — but because they could not see any possible mechanism by which it could occur. Sometimes you can be too close to a problem).

As this paper will try to convince you, we now know a great deal more about both liquid crystals and biochemistry — and we can put together a plausible model involving the temporary liquid crystalline state of the cell contents, in a way that will make sense and which can be convincingly modelled — and leave us with the opinion that Bernal's picture contained a key element of the truth.

This lecture is an attempt to argue that the *geometry* of the process can indeed be modelled in terms of known properties of mesophases and that the *mechanics* can be explained in terms of known biochemistry. Furthermore, it proposes that the key players in the whole process are microtubules (and suggests that these will prove to be the source of commercially exploitable properties in the future).

Those aspects of mitosis which might be termed 'descriptive' cell biology, cytology and biochemistry mentioned in this story are well-documented and can be found in a variety of secondary sources (for example [1, 2]) but what is not widely accepted (and my excuse for giving this talk at this meeting) is the idea that in setting up the mitotic machinery, the entire contents of the cell become liquid crystalline.

In addition to the paper of Miroshnychenko *et al.* [4], there are features of two other papers given yesterday that are very relevant to the model I will present. Let me refer back to them. The first was in the talk given by Ben Broughton [7]. He was talking about a device with a

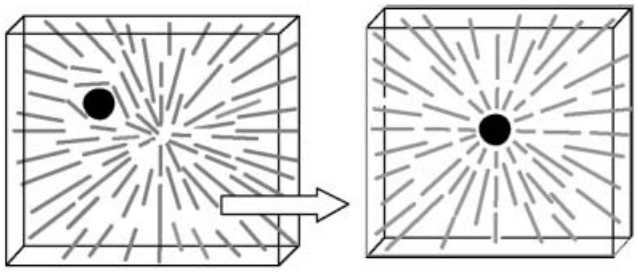

Figure 5. The tendency of polymeric material to accumulate in the disclinations in a host mesophase. (See [6].)

cell containing a mixture of liquid crystalline phase and some polymeric material. You will recall that he commented that bits of polymer tended to accumulate in the disclinations in the host mesophase (figure 5). This is an observation that has been made by many workers over the last half century (and because these regions are singularities in the director field, it is not altogether surprising) but there has not been any systematic study, as far as the author is aware.

The second point occurred in the talk by Ingo Dierking, concerning carbon nanotubules aligned by a small molecule nematic host phase (figure 6) [8]. Although he did not explicitly mention the point, it would seem to be a fair presumption that there is a synergism between the two components — with the host phase aligning the nanotubules and reciprocally, the nanotubules stiffening the mesophase. Amongst other things, we would expect the order parameter of the host nematic phase to be enhanced by the presence of the nanotubules and the N-I transition temperature to be raised.

In this model all the cytoplasm becomes a single domain of a lyotropic nematic phase. If we introduce two +1 disclinations into this, they will spontaneously move apart to equilibrium positions forming the bipolar spindle structure. In this director field pattern, there is a unique central plane lying half way between the poles. This is not just unique in terms of its geometrical position, it is unique in terms of the curvature of the phase and hence it is not difficult to postulate conditions under which alien bodies will drift towards it and settle there, in exactly the same way that polymer strands tend to accumulate at disclinations.

4. Variations on a theme

The scheme of spindle formation discussed here is the norm for higher animals and plants, but it is by no means the only pattern used by living systems. Many 'lower' organisms display a range of variations on the basic theme. Most have a two-pole spindle, but variants with only one, or even none at all, appear to function effectively. In most organisms the poles float apparently freely within the cytoplasm and move to their equilibrium positions — but in some organisms, one (or both) may be anchored on the inner surface of the cell membrane. Usually the nuclear envelope disappears completely — but in some systems it only becomes perforated and in many unicellular organisms such as yeasts, (with perhaps faint echoes of the 'RNA world' thought to have preceded the evolution of the genetic

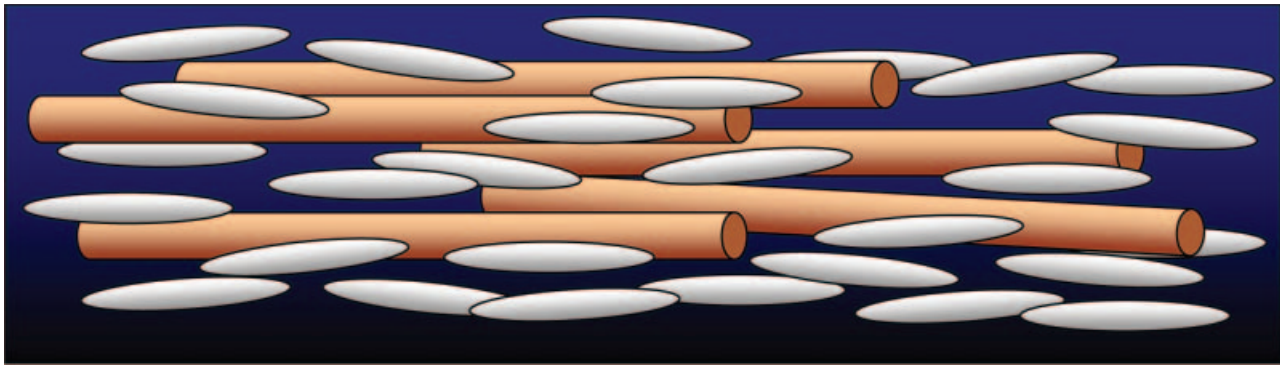

Figure 6. Carbon nanotubes in a nematic host phase. Stylised sketch of the synergic interaction between the two components in an oriented dispersion of carbon nanotubes in a host nematic phase. The small molecule nematic host aligns the nanotubes and conversely, the nanotubes stiffen the mesophase. We would expect this positive reinforcement to result in an improvement in order parameter and a raised N→I transition temperature. I suggest that, in the early stages of mitosis, the cell contents begin to form a nematic liquid crystalline phase of this type. The key structural elements creating this phase appear to be microtubules, which are formed by the self assembly of tubulin units, (but I suspect that other smaller molecules must be involved also) and the postulated mesophase involves molecules with a range of different sizes and resembles that of the dispersion of carbon nanotubes dispersed in a small-molecule mesophase host phase. It would seem likely that conformational changes occur in some of the proteins and nucleic acids present, making them more amenable to the formation of the complex mesophase. Optical microscopy of dividing cells viewed between crossed polars appears to verify this picture (or at least, is not incompatible with it).

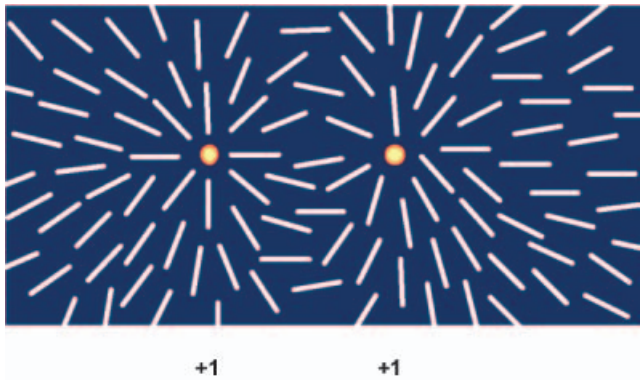

Figure 7. The director field pattern resulting from two +1 disclinations in a nematic liquid crystal phase: In this schematic 2-dimensional representation, the two yellow circles indicate the positions of the +1 'poles'. Because of the curvature energy in this pattern, the 'poles' will appear to repel each other. Boundary conditions caused by anchoring the mesophase at the walls of the container will also play a part in dictating the director field pattern and the poles will move apart until they reach equilibrium positions within the cell.

code) the whole process appears to take place within an intact nuclear envelope. Here, after the genetic material has separated, the nucleus itself breaks into two as the daughter cells are formed and there are no obvious changes occurring in the surrounding cytoplasm [9].

It is tempting to regard this overall picture as the biological system exploring all possible ways of carrying out the separation of the genetic material — and finally decided on an optimum. This viewpoint may be to some extent justified, but one must bear in mind that some of these 'unorthodox' systems have been successfully replicating for 4,000 million years. They can not be all that ineffective.

(One can draw many parallels with overviews of this kind in biology. An obvious one concerns the evolution of plants. In 'primitive' seaweeds such as the blue-greens and red algae for example, 'unorthodox' chlorophylls are present and a range of polysaccharides including polymers of mannose and xylose are used as the structural material of the cell walls. But, by the time plants began to colonise dry land, the combination of the familiar green chlorophyll coupled with a cellulose cell wall had become established as the 'standard' pattern).

There is not time here to discuss these unorthodox patterns of mitosis — but, as far as can be judged, none of them involve features that are inexplicable in terms of the liquid crystal model proposed (and in this sense, they would appear to strengthen the hypothesis).

There is one obvious, major variation in the pattern of mitotic spindle formation. This concerns a distinction between plant and animal cells. In animal cells the regions at the centres of the poles (also called 'microtubule organising centres' or the 'centrosomes') contain a pair of distinctive bodies (called centrioles). Each of these has a complex structure with nine sets of triplet microtubules forming a hollow ring (in a 9+0 pattern). For most plant cells however, the centrioles are absent and regions at the centre of the poles are tantalisingly diffuse. It may well be the case that the centrioles are a consequence rather than the cause of the polar array, but in any case, this presents no real problem for a liquid crystal model. It is the director field which is important and you can have a polar disclination in a director field without the presence of an actual polar body in this position.

5. Optical microscopy of mitosis

Although mitosis is universal in biology, there are certain favourite tissues which have been found to be convenient for demonstrating cell division. Onion root tip for example is widely used for teaching and research. Amongst the more esoteric animal tissues recommended is newt lung (figure 8).

Early optical microscopy of dividing cells showed only the chromosomes — but it was clear that they were being manipulated and positioned by changes in the ordering of the surrounding medium. Something was happening to the cytoplasm of the cell when the spindle assembly was formed. Molecular units too small to be resolved with the light microscope were becoming organised and aligned. (In the parlance of liquid crystals, a director field was being created). This view

Figure 8. Fluorescence microscope picture of mitotic cell.

appeared to be confirmed by subsequent studies using polarised light microscopy and later, by phase contrast microscopy. Over the last 10–15 years, techniques have been developed which combine confocal microscopy with highly specific staining using fluorescent dyes. With these we can highlight the distribution of specific biochemical species in the mitotic cell. Optical micrographs like those shown in figures 4, 9 and 16 indicate the distribution of microtubules in the mitotic spindle.

6. Microtubules

In the 1940s and 1950s, the electron microscope caused a revolution in biology. It revealed an unexpected wealth of sub-cellular detail and a new dimension was added to cytology. When dividing cells were first examined by electron microscopy, it was found that, within the mitotic spindle there are arrays of long rods about 24 nm in diameter, radiating outwards from the two poles of the spindle. Subsequently, studies at higher magnification showed that these 'microtubules' are hollow cylindrical structures. As shown in figure 10, they are built from strings of approximately spherical protein subunits of two slightly different kinds (termed alpha and beta tubulin) arranged in an alternating pattern. A cross-section of a microtubule shows thirteen tubulin units.

The aggregation of globular subunits to create elongated polymeric structures in this fashion, is a recurrent theme in biochemistry. The cytoskeleton of cells (the framework of protein fibres which controls the shape and movement of cells and organises many of the metabolic functions), consists of microtubules, intermediate filaments and actin microfilaments. All three of these are assembled from globular subunits in a similar fashion.

Microtubules are versatile. In addition to their role in the cell division, they are involved in intracellular motility, and cellular organisation. Optical microscopy of living cells (particularly of plant cells), shows organelles moving along invisible highways in journeys around the cell. At a molecular level, these highways appear to be microtubule rail tracks along which molecular locomotives can move, dragging organelles behind them. There are two families of these; the dyneins and kinesin-like motors. These are essentially mechanochemical enzymes which can use the energy derived from ATP hydrolysis to walk along microtubules. The dyneins are large multi-component proteins that move

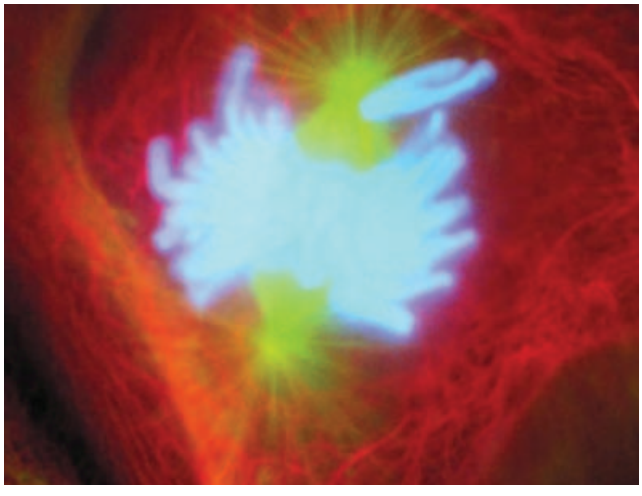

Figure 9. Fluorescence microscopy image of the dividing cell: Modern techniques of fluorescence microscopy can highlight the distribution of different biochemical components in the dividing cell with remarkable clarity. In this micrograph the microtubules are coloured yellow and the chromosomes appear pale blue. From http://www.emtl.de/groupOrProgrammeImage/66

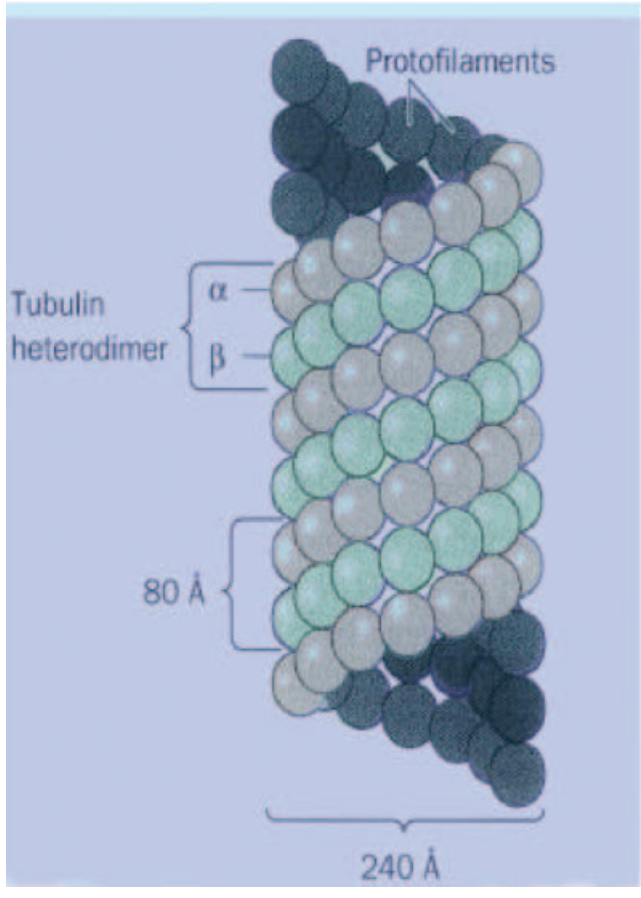

Figure 10. The structure of a microtubule: Electron microscopy shows that microtubules are hollow cylindrical structures about 24 nm in diameter built from 13 strings of approximately spherical, tubulin subunits. The subunits are single globular proteins about 40 Å in diameter and of mass 50 kDa. There are two slightly different kinds of tubulin (α and β) arranged in an alternating pattern.

only towards the −ve end. Kinesins are smaller dimeric units. Kinesin itself can only move towards the +ve end, but other members of the family move in the opposite direction (figure 11) (ref. [10], chapter 5).

The picture which has emerged is that the cell cytoplasm contains a pool of tubulin units, which can be assembled or dispersed and re-assembled in different patterns as the cell requires. One of the body tissues richest in microtubules is nerve axons (and animal brain is used as a source of tubulin for research purposes). In what must surely be the ultimate role for microtubules, Roger Penrose has proposed an imaginative and highly controversial model for that enigmatic phenomenon we call consciousness [11]. He suggests that consciousness involves quantum scale information processing and since (for unavoidable physical reasons) this can not take place within structures as large as neurons, it must occur within the cores of microtubules.

7. Microtubule organisation

When the globular 'tubulin' monomer units spontaneously stack together to form microtubules they all point in the same direction and produce an assembly which is 'polar' (in the sense of the word as used by crystallographers). As we shall see, this directionality is most important in the functioning of microtubules. The two ends of microtubules have been arbitrarily labelled + and −. (Note that this designation has nothing to do with electrostatic charge — or the strengths of disclinations). Because of this polarity, the growth rates at the two ends of a microtubule are very different and there is evidence that, even in a microtubule which is apparently maintaining a constant length, there is dynamic, rather than static equilibrium. Not only are individual microtubules polar but they are able to form polar arrays where they are all pointing in the same direction. This remarkable feat of self-organisation is achieved when the spindle is created.

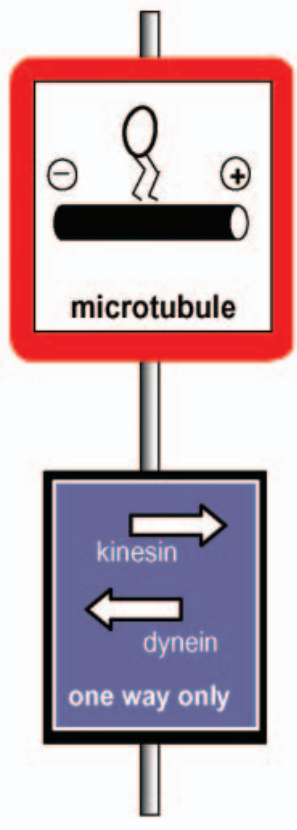

Figure 11. Dynamic instability of microtubules.

8. The formation of the spindle

The assembly of microtubules in the spindle appears to be nucleated by some kind by 'microtubule organising centres'. In a typical resting cell, there will be a single active microtubule-organising centre, usually lying close to the nuclear envelope. At the beginning of mitosis this separates into two and a radiating aster of microtubules develops around each. As the process proceeds, the asters settle at equilibrium positions in the cell, forming the familiar dipolar spindle. The minus ends are anchored in the centres of the asters and the plus ends grow outwards towards the periphery of the cell and the equatorial plane.

9. The dynamic nature of microtubules

The assembly of tubulin units to form a microtubule is not just a simple polymerisation process. It is complicated by the involvement of the 'high energy compound' guanosine triphosphate (GTP) which can bind to unpolymerised tubulin units. Only those units which have a molecule of GTP bonded to them are able to join onto the growing end of a microtubule. After a period of time the GTP tends to hydrolyse to the diphosphate GDP. For tubulin units within the body of a microtubule this does not matter much, because they are firmly held on both sides, but if this happens to the terminal unit, the attachment is appreciably weakened and it will fall off. This will start the 'fraying' process at the +ve end and the microtubule will rapidly shrink. When microtubules are growing, the plus ends are protected by the presence of the bound GTP — but once they stop growing they become vulnerable.

Microtubules therefore exist in a precarious dynamic state — continually assembling and disintegrating, growing and shrinking. It has been estimated that the average lifetime of an astral microtubule is only about five minutes. This fluctuating pattern of growth and

decay appears to be an important aspect of mitotic machine. It enables microtubules to make exploratory extensions to seek out the attachment points on the chromosomes. If a microtubule does not find an attachment site it will become unstable and disintegrate but if it chances on the crucial 'kinetochore' region it will become anchored. Its vulnerable plus end will be protected and it will survive.

Microtubules are 'living' systems in the sense that a polymer chemist would use the word. The polymeric

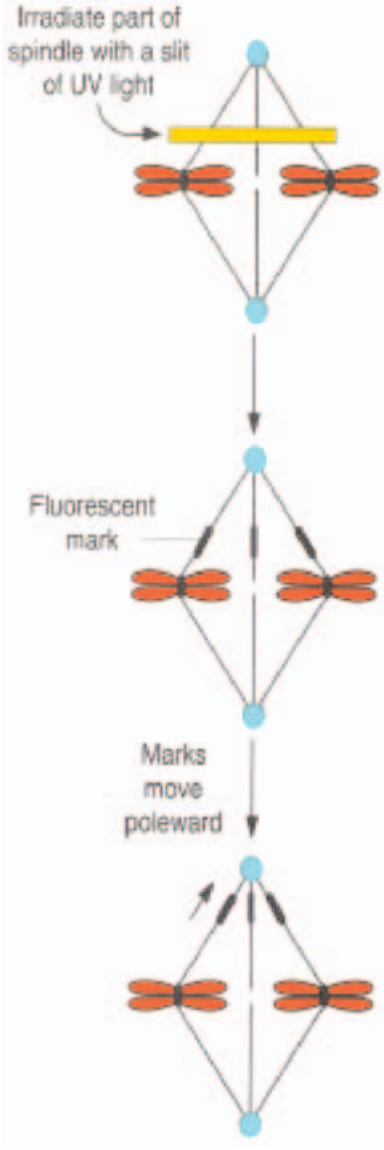

Figure 12. Demonstration of the dynamic state of a microtubule: The constant dynamic movement of tubulin units (towards the poles) within the apparently static spindle has been demonstrated in a most elegant way using fluorescent markers. The cell is injected with modified fluorescent labelled tubulin. Then a narrow band of UV light is shone across a strip of the spindle to create a band of fluorescing material. The lifetime of the fluorescence is sufficient for the movement of the highlighted region to be observed. Adapted from [10], figures 5–13.

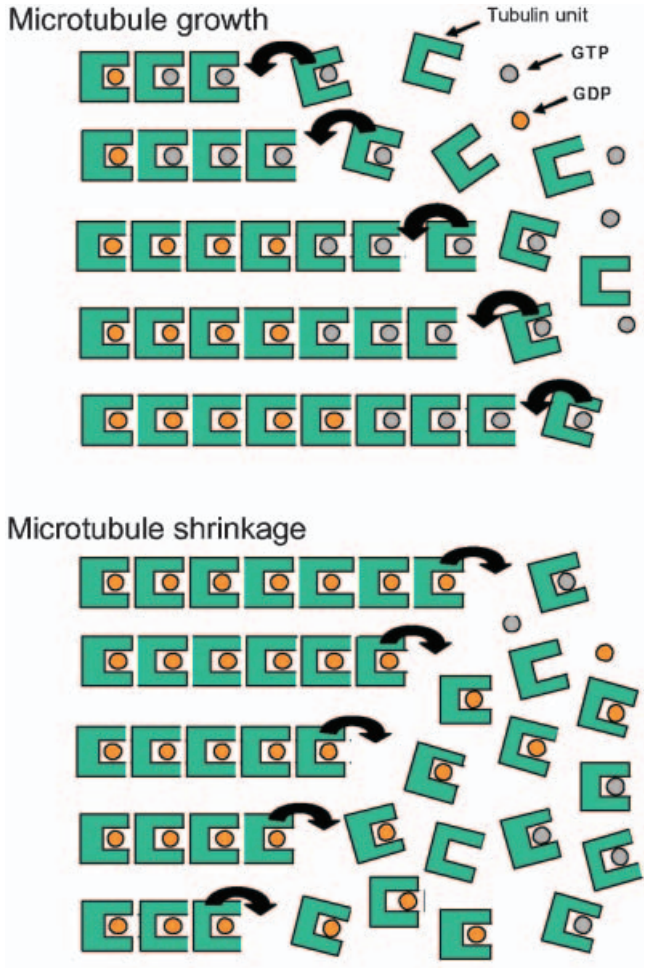

Figure 13. The dynamic instability of microtubules: Microtubules are inherently unstable and this instability is an important factor in the mitotic process. It is a consequence of the way in which 'high energy' molecules are trapped between the tubulin units during the assembly of a microtubule. Microtubules grow principally at their (+) ends, and tubulin units can only be attached to the growing end if they are bound to a molecule of guanosine triphosphate (GTP). Shortly after a tubulin/GTP unit is added to a microtubule, it is hydrolysed to guanosine diphosphate (GDP) releasing a considerable amount of energy. A GDP-bound tubulin unit in the middle of a microtubule is inaccessible and can not spontaneously disengage itself — but a GDP bound tubulin subunit at the plus end of a molecule is in an unstable situation and will fall off. This means that a rapidly-growing microtubule is given a short breathing space to elongate — but when it stops growing the hydrolysis of the GTP at the exposed+end is initiates a catastrophic depolymerisation process. The only hope for a microtubule is to find some way to stabilise is vulnerable+end. One of the ways it can do this is to find one of the attachment centres on a chromosome.

assemblies exist in a dynamic state, where slight differences in conditions can result in them growing or shrinking (figure 12). The mesophase they form is therefore subtle and transient and can be highly inhomogeneous. This 'paranematic' mesophase is not something which can easily be taken out of the cell and bottled (figure 13).

The manoeuvring of the chromosomes into the equatorial plane and their attachment to the spindle fibres is a remarkably dynamic process. When viewed in the optical microscope the chromosomes can be observed jostling and oscillating backwards and forwards until they are position correctly and each is safely attached to microtubules from both poles.

It appears that a chromosome is subjected to two contrasting forces. The chromosome arms are pushed away from the poles but once the spindle is established the linear motors on the attachment points (centromeres) reel in the separated daughter chromatids towards the poles. The presence of these two conflicting forces can be demonstrated by slicing off the chromosomes' arms as shown in figure 14.

10. The liquid crystal model for spindle formation

When setting up the mitotic apparatus, the cell builds the spindle from the pool of unpolymerised tubulin units in the cytoplasm and from those obtained by dismantling some of the cytoskeleton. As the microtubules increase in length and become more abundant, the cell contents become more liquid crystalline. The values of the elastic constants become more significant. The microtubule organising centres which are already present effectively act as liquid crystal poles. The increase in liquid crystallinity of the medium around them creates a director field which causes them to repel each other and move into equilibrium positions. The 'dipolar' director field of the spindle is created. Within this, the equatorial plane is unique, since it is the only region in the cell where the director field is parallel. Chromosomes drift towards this position and are sought out and 'hooked' by the +ve ends of the microtubules. The machinery for separating the daughter

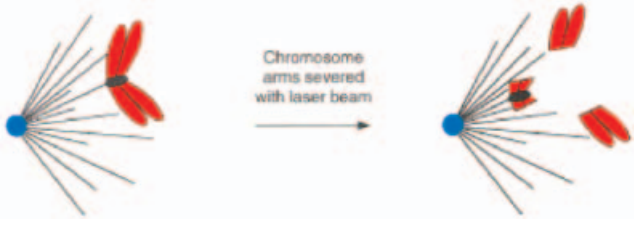

Figure 14. The result of severing the chromatid arms: If the arms of a chromatid are cut off (by a laser beam), the role of spindle microtubules in the movement of daughter chromatids becomes apparent. The central region where the chromatid is attached to the spindle microtubules is drawn towards the pole, but the chromatid fragments are carried away by the 'polar wind' and drift in the opposite direction. Adapted from [10], figures 5–15.

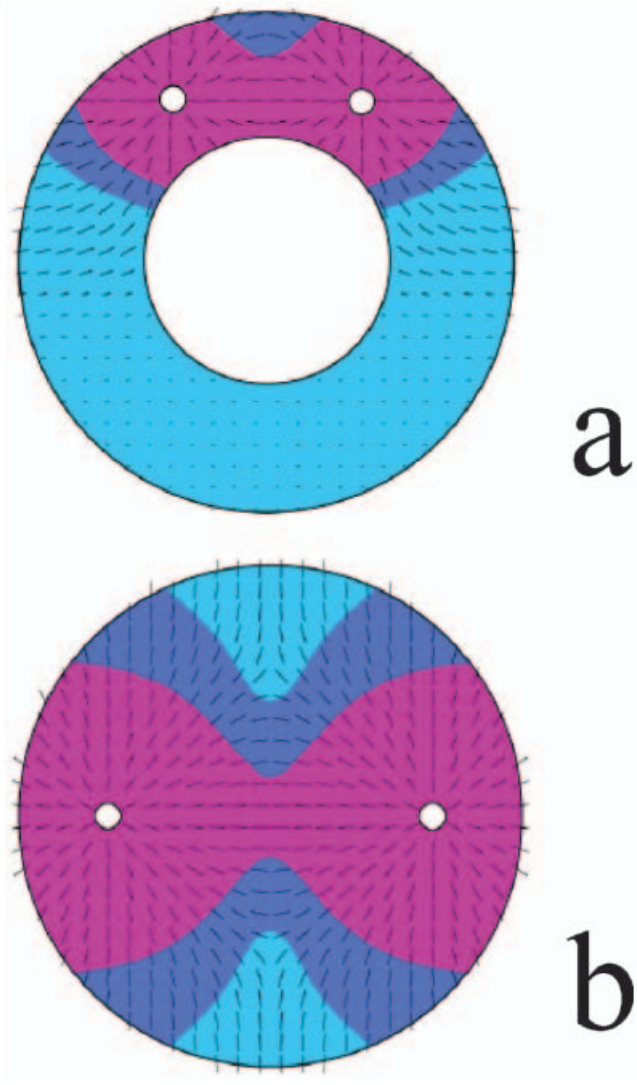

Figure 15. Computer modelling of the creation of the mitotic spindle: In this modelling, the cytoplasm of the cell is treated as a being in a weakly nematic state. The only parameters fed into the calculation are the shape of the cell, the epitaxial orientation at the surface and the elastic constants of the mesophase. These figures show a slice through a spherical cell, in the plane of the centromeres. The colour indicates the value of the order parameter (red>dark blue>light blue). (a) Shows the earliest stage of the process (prometaphase) where the centromeres are just beginning to act as liquid crystal poles and the nuclear membrane is still intact. (b) Shows the later stage (metaphase) where the full spindle has been formed; the nuclear envelope has disappeared and the centrometres have moved to their equilibrium positions.

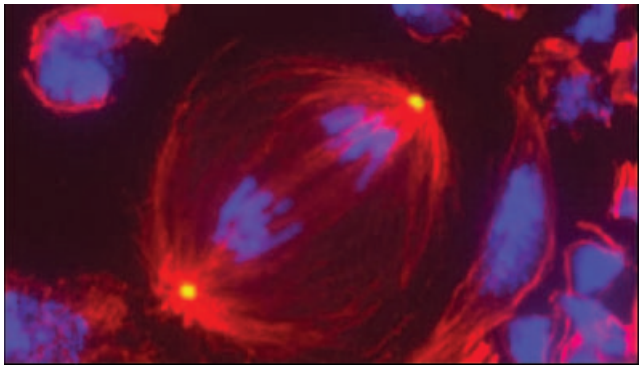

Figure 16. Endgame: The mitotic machine is beginning to operate the final stage of mitosis. Condensed chromosomes have separated into daughter chromatids and these are now being pulled towards the poles by microtubule motors. When the separation is complete, the chromosomes will unwind, the nuclear envelope will reform and the two daughter cells will return to the 'resting' state.

chromatids and reeling them in towards the opposite poles is now in place. The engine for separating the chromosomes has assembled itself (figures 15 and 16).

To invoke a liquid crystalline state in the creation of the mitotic spindle is more than a trivial piece of analogy. It brings into play a well-defined package deal of properties. The geometry of a director field is determined by a number of parameters in a way which can be modelled quantitatively. In addition to the intrinsic physical properties of the mesophase, the shape of the container and the epitaxial alignments at the surface are all factors that determine the resulting pattern. The sensitivity of mesophase systems to small changes in the composition of the phase offers a mechanism for signalling and coordination of events from one part of the cell to another.

It is suggested that this liquid crystal model will offer a general explanation for the widely differing patterns of mitosis in living systems and go some way into explaining how evolutionary precursors to such a complex system could have operated.

11. Postscript

The 'smart' properties of microtubules begin to look much more comprehensible and less mysterious when explained in terms of the dynamic nature of the spindle structure. The concept that knowledge is power, is nowhere truer than at the nanotechnology/molecular biology interface. I foresee, in the near future, the creation of a new generation of medical diagnostic tools based on specific antibodies coupled to microtubule motors. ''This is the stuff that dreams are made on''.

12. Endnote

In previous years, I have rounded off this lecture with a few lines of doggerel - so, with apologies to whoever did write the 24th sonnet and John O'Gaunt's speech in Richard II, I offer the following parody:-

Let me not to the microtubules of the mind admit impediment,
Life is not life without its consciousness.
Does the to be or not to be of our existence hang on molecules such as these?
These precious asters set in a director field,
These chromosomes: this GTP,
These centromeres - made by God against the dead hand of entropy,
These hollow tubes of dimers: these microtubules.

Acknowledgements

I pay tribute to the elegant computer modelling of Dmitri Miroshnychenko, Nigel Mottram and Nick Hill (of Strathclyde University) described in an earlier talk at this conference. I thank my colleague, Dr John Walker, in the Faculty of Biology at Leeds University, for his helpful comments.

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