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A model for chromosome movement during mitosis

Review article

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Summary. We present a new model for poleward chromosome movement during mitosis. The key points of the model are: (1) Kinetochore spindle fibres contain kinetochore microtubules linked to filaments; both the microtubules and the filaments are attached to the kinetochore. (2) Motor molecules which are fixed in a spindle matrix push poleward on the kinetochore microtubules in anaphase, and push on the associated filaments as well. (3) In addition to the kinetochore fibre pulling the kinetochore poleward, there are forces on the chromosomes themselves that push the chromosome arms poleward in anaphase; the forces on the chromosome arms are independent of the forces on the kinetochore spindle fibres and also may arise from motor molecules in the spindle matrix. (4) Kinetochore microtubules add subunits at the kinetochore and lose subunits from both the pole and the kinetochore; both polymerization and depolymerization are regulated by "compression" forces and by "stretching" forces on the microtubules themselves. Compression is caused by motor molecules pushing the kinetochore microtubules into the pole (during anaphase) or into the kinetochore (during prometaphase), and is caused by motor molecules pushing the chromosomes into the kinetochore fibres; stretching is caused by motor molecules pulling kinetochore microtubules out from the kinetochore.

We view our model as a new way of looking at mitotic processes, with most details yet to be worked out, rather than as a detailed description of mitosis.

Keywords: Chromosome movement; Spindle fibres; Mitosis; Motor molecules; Spindle matrix; Ultraviolet microbeam.

Introduction

Previous models

In this paper we present a new model for chromosome-to-pole motion during anaphase of mitosis. Before presenting our model we summarize briefly other models relevant to the discussion.

For many years the most popular models for explaining how chromosomes moved to the pole were "traction fibre" models (Cornman 1944), in which the chromosome is anchored to the kinetochore spindle fibre and is pulled poleward as the fibre shortens at the pole. (We use the term "kinetochore spindle fibre" as defined by Schrader (1953), to refer to that spindle fibre seen light microscopically to be attached to the chromosome at the kinetochore and to extend to the spindle pole.) At present, traction fibre models have been replaced in popularity by "PacMan" models (Cassimeris et al. 1987) in which the kinetochore "chews" its way to the spindle pole, producing its own force as it depolymerizes the kinetochore microtubules (see Nicklas 1989, Gorbsky 1992). PacMan models require (a) that during chromosome-to-pole movement the kinetochore fibre depolymerizes at the kinetochore, and (b) that the kinetochore is associated with "motor molecules" that translocate kinetochores along the kinetochore microtubules while (c) the same (or other) molecules at the kinetochore depolymerize the kinetochore microtubules and while (d) the same (or other) molecules maintain connection to the not-depolymerized portions of the kinetochore microtubules (e.g., Mitchison et al 1986, McIntosh et al. 1989, Vallee 1990).

Direct evidence that the kinetochore microtubules depolymerize at the kinetochore comes from experiments in which fluorescent tubulin incorporated into spindles is photobleached in a local region: the bleached region remains stationary during metaphase (e.g., Wadsworth

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and Salmon 1986) and at anaphase the chromosomes move poleward through and past the bleached region (Gorbsky et al. 1987, 1988; Gorbsky and Borisy 1989). Several lines of evidence indicate that the kinetochore contains microtubule motor proteins: (1) Prometaphase kinetochores slide along microtubules in vivo (Rieder and Alexander 1990). (2) Motor molecules are identified in situ at kinetochores using immunofluorescence (e.g., Pfarr et al. 1990, Steuer et al. 1990) and using electron microscopy (e.g., Wordeman et al. 1991). (3) Kinetochores slide along microtubules in vitro, in either direction, depending on conditions (Hyman and Mitchison 1991).

All these lines of evidence are consistent with PacMan models in which chromosomes with motor molecules at their kinetochores chew their way poleward in anaphase. Data that we discuss below, however, point out intricacies in mitosis that are not yet understood. Considerations of these intricacies have led us to view chromosome movement in a different way than PacMan models; we now describe our model.

Our model

In our model for chromosome-to-pole movement the force for chromosome motion is *not* produced by the fibre itself but is transmitted to the fibre from outside elements, essentially a variation of the "wind and sails" model (Östergren et al. 1960) in which the spindle fibres are like "sails" that are propelled poleward by "winds" produced by the spindle. Our model incorporates the following assumptions.

(1) The kinetochore fibre contains microtubules and filaments, both of which are attached to the kinetochore. Filaments associated with kinetochore microtubules have been described previously (e.g., Pickett-Heaps et al. 1982, Pickett-Heaps 1986, Rieder and Alexander 1990). In previous models the kinetochore filaments were thought to slide against the kinetochore microtubules; in our model, however, *in anaphase* the filaments are attached to the kinetochore by means of "rigor" bonds, without sliding (though sliding may have occurred in earlier stages). Thus, because of the "rigor" bonds, a poleward force either on microtubules or on filaments also results in a force on the other component.

(2) Motor molecules that are embedded in (or attached to) a "spindle matrix" (e.g., Pickett-Heaps et al. 1984) interact with the kinetochore fibre to produce forces that push the kinetochore fibre polewards in anaphase. (The forces perhaps are in both directions in earlier stages.) We assume that the motor molecules are more-or-less stationary in the matrix, similar to kinesin or other motor molecules stuck to glass slides which cause microtubules or actin filaments to move over the surface of the slides (e.g., Walker et al. 1990, Vale et al. 1992). We also assume that motor molecules push separately on both the kinetochore microtubules and the kinetochore filaments, and that there may be several kinds of motor molecules involved. In this way the matrix acts as the "wind" that pushes on the kinetochore fibre "sail". Sawin et al. (1992 b) argued that poleward flux along kinetochore microtubules might be driven by a plus-end directed motor protein tethered to the pole; we have extended their argument to assume that there is a variety of motor proteins embedded throughout the spindle matrix.

(3) The chromosome arms are pushed poleward in anaphase by forces independent of the forces that push the kinetochore fibre poleward; the forces on the chromosome arms also may arise from motor molecules associated with the spindle matrix.

(4) We assume that addition of tubulin subunits to

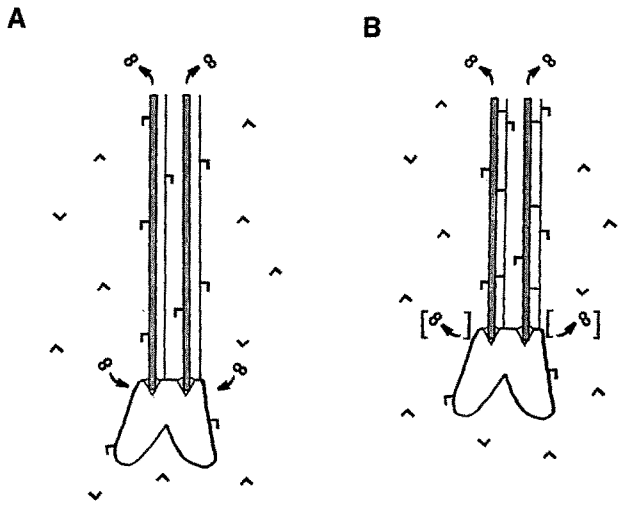


Fig. 1. Cartoons illustrating salient points of our model in metaphase (**A**) and in anaphase (**B**). In both diagrams the chromosomes are at the bottom of the diagram and the attached kinetochore microtubules are the grey regions inside double lines, with tubulin subunits (∞) depolymerizing at the pole ends (**A** and **B**) and polymerizing at the kinetochore ends (**A**), as indicated by arrows. (The arrows and subunits at the kinetochore in **B** are in brackets to indicate that depolymerization may or may not occur, as discussed in the text.) Single lines attached to the kinetochore represent kinetochore filaments, which, in anaphase, are attached to kinetochore microtubules by "rigor" bonds (horizontal lines in **B**). Motor molecules in the spindle matrix are represented as V-shaped units; motor molecules that produce force are represented by having one of the arms attached horizontally to the component they produce force against (kinetochore microtubules, kinetochore filaments, or chromosomes)

kinetochore microtubules occurs at the kinetochore, removal of tubulin subunits from kinetochore microtubules occurs at the pole and at the kinetochore, and that both polymerization and depolymerization of kinetochore microtubules are regulated (at least in part) by "compression" forces and "stretching" forces on the kinetochore microtubules. "Compression" of kinetochore microtubules arises when motor molecules push the kinetochore fibre into the kinetochore or pole, and arises when motor molecules push the chromosome into the kinetochore fibre. "Stretching" arises when motor molecules pull the kinetochore fibre out of the kinetochore.

Salient features of our model are illustrated in Fig. 1. We now use our model to explain various experiments on mitosis.

Explanations of experimental results using our model

Fluorescent tubulin in vivo

When fluorescence was activated on "caged" tubulin in anaphase newt cells, the marked regions on kinetochore fibres moved poleward (Mitchison and Salmon 1992). In early anaphase this poleward "flux" of kinetochore microtubules accounted for about 25% of the poleward chromosome movement while depolymerization at the kinetochore accounted for 75% of the poleward chromosome movement; in some late anaphase cells the poleward "flux" of the kinetochore microtubules accounted for nearly all of the poleward chromosome movement. Since poleward "flux" of kinetochore microtubules is accompanied by depolymerization at the pole, one concludes that early anaphase in newt cells involves simultaneous PacMan and traction mechanisms, and that later anaphase may involve traction alone. On the other hand, in LLC-PK cells poleward chromosome movement during anaphase (as determined using locally uncaged tubulin fluorescence) is a mixture of 84% PacMan and 16% traction (Zhai et al. 1993). Yet again, in crane fly spermatocytes initial anaphase separation (as determined from the distribution of acetylated tubulin along the kinetochore fibre during metaphase and anaphase; see Wilson and Forer 1989 b) most likely is only PacMan whereas the rest of anaphase is almost all traction (Wilson and Forer 1993 and in prep.). Our model explains these otherwise puzzling differences in results, as follows.

Motor molecules push the kinetochore fibres poleward, producing "compression" forces on the kinetochore microtubules at the pole. Forces on chromosome arms push the chromosomes into the kinetochore fibre, producing compression at the kinetochore and, because the fibre in turn is pushed into the pole, producing compression at the pole. The amount of anaphase "flux" (depolymerization at the pole) compared with PacMan (depolymerization at the kinetochore) will depend on how active the pole and kinetochore are in depolymerizing the kinetochore fibre microtubules in response to compression forces. Thus, one could imagine that in some cells or circumstances depolymerization at the pole is much slower than at the kinetochore, resulting in chromosome movement due to almost 100% PacMan. In other cells or circumstances depolymerization at the pole might be much faster than at the kinetochore, resulting in chromosome movement due to almost 100% traction. In yet other cells or circumstances one might obtain a mixture of the two.

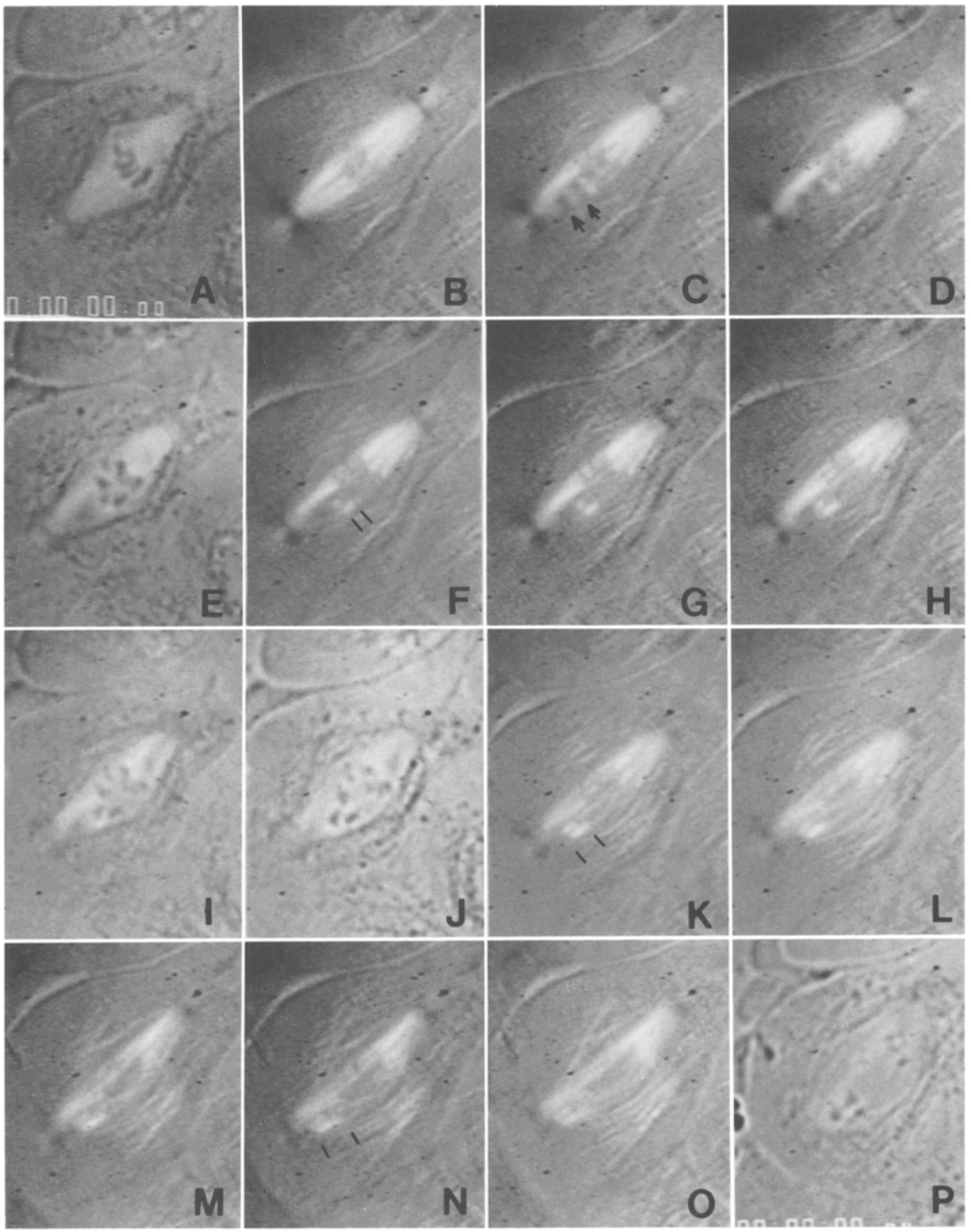
In addition to explaining how relative amounts of PacMan and traction mechanisms might arise, our model also explains results of ultraviolet (UV) microbeam irradiations that otherwise seem to us to be very difficult to understand.

UV microbeam irradiations of crane-fly spermatocytes

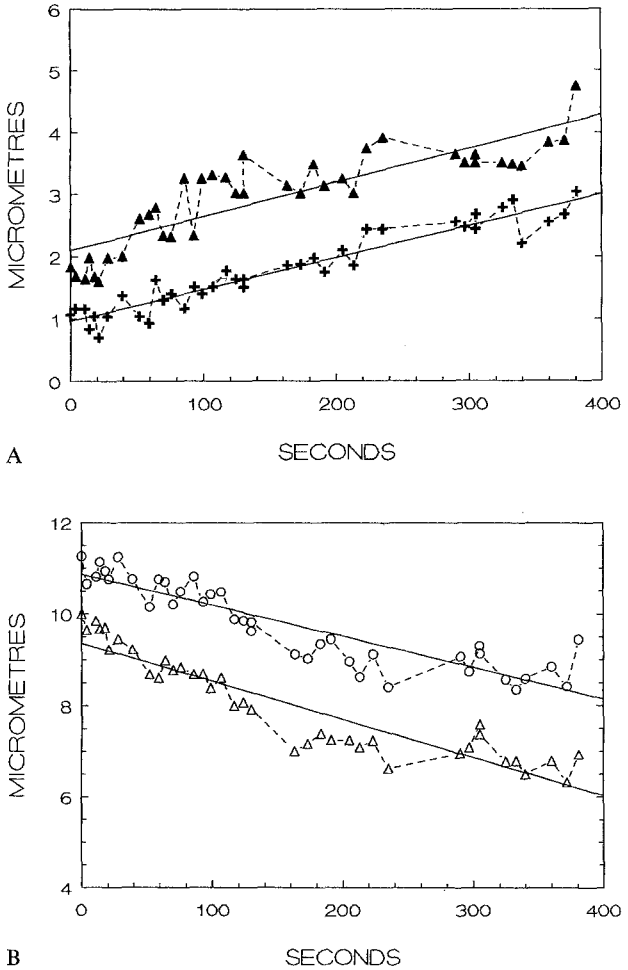
(1) UV microbeam irradiations of crane-fly spermatocyte kinetochore fibres can produce areas of reduced birefringence (ARBs), regions in which the kinetochore microtubules have been depolymerized (Wilson and Forer 1988, Snyder et al. 1991). Chromosomes are able to move poleward with ARBs in their kinetochore fibres (Sillers and Forer 1983); when they do, the chromosome and ARB most often move poleward at the same speed (Forer 1966). Further, chromosomes can move poleward even when the ARB is adjacent to the kinetochore (Forer 1966).

It is difficult to understand these results with PacMan models, but our model can explain them: chromosome movement with an ARB adjacent to the kinetochore is caused by forces from the matrix-associated motor molecules acting on kinetochore filament(s) continuous across the ARB. Other explanations for chromosome movement with an ARB adjacent to the kinetochore are possible in terms of our model, but we tentatively have rejected them. For example, one could imagine that chromosome movement with an ARB adjacent to the kinetochore might be due to forces on the microtubules poleward from the ARB with force transmitted to the kinetochore via kinetochore filament(s) which remain continuous across the ARB. We tentatively re-

ject this explanation, however, because it does not explain how the chromosome continues to move after the poleward side of the ARB reaches the pole and kinetochore microtubules poleward from the ARB no longer exist. As another possibility, one might imagine that chromosome movement was due to the forces acting directly on the chromosome arms, pushing the chromosome poleward. This poleward force on the chromosome (and kinetochore) ordinarily is resisted by the kinetochore microtubules, but with an ARB adjacent to the kinetochore the adjacent kinetochore microtubules are absent; one therefore would expect the chro-



mosome to be pushed through the ARB until it reaches and encounters resistance from the non-depolymerized microtubules. This does not occur – the ARB does not fill in – so we tentatively reject this explanation also. Thus it seems to us that chromosome movement with an ARB adjacent to the kinetochore arises because motor molecules push on filament(s) present in the ARB.



ARB behaviour in anaphase is part of our rationale in assuming that in anaphase there are "rigor" bonds between the kinetochore filaments and the kinetochore microtubules. If the filaments slide with respect to the kinetochore microtubules, then the chromosome would move through an adjacent ARB until it reaches the non-depolymerized kinetochore microtubules, which it does not do. Further, if the kinetochore filaments slide with respect to the kinetochore microtubules, when an ARB is in the middle of a kinetochore fibre the two sides of the ARB would move towards each other, to fill in the ARB, which they do not do. Thus in explaining these results we argue that in anaphase, at least, the filaments are in "rigor" with respect to the kinetochore microtubules, and that motor molecules push polewards on filaments in the ARB region of the kinetochore fibre (as well as on microtubules and filaments along the length of the remaining kinetochore fibre).

(2) UV microbeam irradiations along the length of the kinetochore fibre can block chromosome movement without producing an ARB (Forer 1966, Sillers and Forer 1983), i.e., without depolymerizing the kinetochore microtubules at the irradiation site. How does

Fig. 3. Elongation of spindle fibres in anaphase (**A**) and chromosome motion to the bottom pole (**B**) for the irradiation illustrated in Fig. 2. For both graphs time = 0 is 1 s after the illustration in Fig. 2 D. **A** The lengths of the spindle fibres attached to the kinetochores (ordinate) versus time (abscissa). ▲ Lengths of the lower spindle fibre, + lengths of the central spindle fibre. 'Least-mean-squares' analysis lines have been drawn; the upper and lower lines have slopes of 0.30 μm/min and 0.28 μm/min, respectively, both with R values > 0.90. **B** Kinetochore-to-pole distances (ordinate) versus time (abscissa). ○ Distances for the lower chromosome, △ distances for the central chromosome. 'Least-mean-squares' analysis lines have been drawn; the upper and lower lines have slopes of 0.41 μm/min and 0.50 μm/min, respectively, both with R values > 0.89

Fig. 2 A–P. Spindle fibre elongation during anaphase (in a crane-fly spermatocyte) while the associated chromosomes move poleward normally. Individual illustrations are from videotaped images using polarized light microscopy except for **A, E, I, J,** and **P**, which used "pseudophase-contrast" microscopy (Wilson and Forer 1988); experimental and microscopical conditions are as in Wilson and Forer (1989 a). Times are with respect to the end of the irradiation. **A** −65 s; the three bivalents are at the equator, in metaphase. **B** −28 s; the chromosomal spindle fibres (seen as bright against a dark background) extend from the chromosomes to the poles. **C** +3 s; the two irradiated regions (indicated by arrows) each have lost birefringence. **D** +9 s; the birefringence is disappearing between the two irradiation regions (Wilson and Forer 1989 a). **E** +54 s; shortly after the start of anaphase. The anaphase chromosomes are seen in 'pseudophase contrast'. **F** +1 min and 13 s. The birefringence between the two irradiated spots has disappeared. The remaining fibres (attached to the lower and central chromosomes moving to the lower pole) extend from the chromosomes by about 2 μm and 1 μm respectively; the lower fibre is marked with lines. **G** +1 min and 41 s. **H** +2 min and 13 s; the irradiated spindle fibres have increased in length. **I** +2 min and 42 s; 'pseudophase', showing that the chromosomes associated with the irradiated spindle fibres continue to move poleward. **J** +4 min and 43 s; 'pseudophase'. The chromosomes associated with the irradiated spindle fibres continue to move poleward. **K** +5 min and 4 s; the irradiated fibres (indicated by the lines) have continued to elongate; at this time they extend from the lower and central half-bivalents by about 3.5 μm and 2 μm, respectively. **L** +5 min and 52 s. **M** +8 min and 26 s. **N** +9 min and 31 s; the irradiated fibres (the lower fibre is indicated by the lines) have continued to elongate. **O** +11 min and 8 s. **P** +15 min and 17 s; 'pseudophase'; the chromosomes have nearly reached the bottom pole. × 1200

an irradiation several micrometres from the kinetochore block chromosome movement, with no visible change in the kinetochore microtubules, if the motor is at the kinetochore? In our model, chromosome movement is blocked in these experiments because the irradiation depolymerizes the filament(s) in the kinetochore fibre.

(3) After irradiations produce ARBs in anaphase cranefly spermatocytes, the kinetochore microtubules that remain attached to the kinetochore can *elongate* as the associated chromosome moves poleward (e.g., Forer 1966, Wilson and Forer 1989 a). This result, which seems to us to be very difficult to understand with the PacMan model, is illustrated in Figs. 2 and 3: spindle fibres were irradiated doubly in metaphase, the kinetochore microtubules between the two ARBs rapidly depolymerized (Wilson and Forer 1989 a) and anaphase began with two autosomes having kinetochore microtubules extending about 1 μm from each kinetochore (Fig. 2 D). By the end of anaphase the kinetochore microtubules extended by at least an additional 2 μm (Figs. 2 N and 3). We find it difficult to understand how the anaphase force could arise from a PacMan model in which the kinetochore chews its way along kinetochore microtubules, since the kinetochore microtubules elongate during anaphase, but we can explain this result with our model. We assume that the poleward forces on the kinetochore fibre are not resisted by attachment to the pole, since the kinetochore microtubules are severed at the ARB. With no resistance, the poleward push on the kinetochore fibre produces "stretching" forces on the microtubules attached to the kinetochore, tending to pull them out from the kinetochore; the "stretching" in turn causes polymerization at the kinetochore, which occurs while the chromosome is pulled poleward.

This explanation points to a *third* mode by which anaphase movements can take place; that is, in addition to depolymerization at the pole (traction fibre) and depolymerization at the kinetochore (PacMan), there can be incorporation of subunits at the kinetochore (polymerization of microtubules) as the chromosome moves poleward. This does not seem to us to create conceptual difficulties, though, because the additional mechanism required is similar to (though the reverse of) that assumed to take place in the PacMan model, namely a mechanism in which the chromosome is able to hold onto the traction fibre that pulls it while at the same time allowing subunits to be added to microtubules at the kinetochore. The following experiment points to the same conclusion.

(4) Some UV microbeam irradiations during anaphase produce ARBs and also stop chromosome motion; the ARBs nonetheless move poleward, even though the chromosomes do not (Forer 1966, Sillers and Forer 1983). Since we assume that poleward motion of the ARB is due to motor molecules pushing the kinetochore fibre poleward, we conclude that the poleward force on the kinetochore fibre need not necessarily be transmitted to the kinetochore – that is, the kinetochore can be attached to kinetochore microtubules in such a way that when tubulin subunits are added at the kinetochore the kinetochore is not necessarily pulled polewards by the poleward movement of the kinetochore fibre.

We now discuss evidences for various aspects of the model.

Evidences in support of the assumptions of our model

Kinetochore fibre filaments

Kinetochore fibre filaments have been described by Pickett-Heaps et al. (1982), Pickett-Heaps (1986), and Rieder and Alexander (1990). Various kinetochore fibre components have been identified that have the distribution required of our putative kinetochore filaments, including tektin (Steffen and Linck 1992), "spoke" (Paddy and Chelsky 1991), MSA-35 (Rattner et al. 1992), and actin (Czaban and Forer 1992); we do not know the composition of the putative filaments in our model but, nonetheless, it is worth noting that actin filaments, in addition to being distributed properly (Czaban and Forer 1992), have several properties expected of the putative kinetochore filaments. For one, UV microbeam irradiations depolymerize kinetochore actin filaments separately from kinetochore microtubules (Czaban and Forer 1994). For another, some motor molecules and microtubule-binding proteins can interact with actin as well as with microtubules (Cross et al. 1993). Further, recent evidence that there is a close link between actin and the microtubule elements of the cytoskeleton (Staiger and Cande 1991, Czaban and Forer 1992, Goldstein and Vale 1992, Lees-Miller et al. 1992, Cross et al. 1993, Kuznetsov et al. 1992) supports the view that actin and kinetochore microtubules might act together in kinetochore fibres as a substrate for single motor molecules.

Motor molecules associated with a spindle matrix

We assumed that motor molecules are associated with a spindle matrix. With respect to the spindle matrix,

the concept has been discussed (in relation to chromosome movement) by Pickett-Heaps et al. (1982, 1984); additional evidence for such a matrix comes both from early studies of isolated spindles (e.g., Goldman and Rebhun 1969, Forer et al. 1976) and from more recent work (Leslie et al. 1987, Steffen and Linck 1992). With respect to motor molecules associated with the matrix, there is ample evidence that motor molecules such as kinesin and dynein are localized in the spindle, generally throughout the spindle as opposed to just at the kinetochore (Mohri et al. 1976, Pratt et al. 1980, Hirokawa et al. 1985, Scholey et al. 1985, Hisanaga et al. 1987, Leslie et al. 1987, Neighbours et al. 1988, Pfarr et al. 1990, Steuer et al. 1990, Yoshida et al. 1990, Hoyt et al. 1992, Saunders and Hoyt 1992, Sawin et al. 1992 a). The only experimental test we know of for involvement with spindle matrix indicates that at least one motor molecule is tightly bound to a non-microtubule spindle matrix (Leslie et al. 1987).

Genetic evidences for the involvement of motor molecules in mitosis are compatible with our model, for they indicate that those motor molecules studied are not involved with movement to the pole per se but rather with spindle organization and integrity (Hoyt et al. 1992, Saunders and Hoyt 1992), and with the control of normal segregation both in oocytes (Carpenter 1991, Therkauf and Hawley 1992) and, perhaps, in early mitotic divisions in the zygotes (Hatsumi and Endow 1992). Furthermore, our model suggests considerable redundancy in that motor molecules push on kinetochore filaments, on kinetochore microtubules, and on the chromosomes themselves; genetic evidences indicate that there is indeed functional redundancy in spindle motor molecules (Goldstein 1993).

Microtubule polymerization and depolymerization

Our model supposes that microtubule polymerization and depolymerization are regulated by forces on the microtubules. The theoretical basis for this suggestion and the implications to models of mitosis have been discussed previously (Pickett-Heaps 1986, Pickett-Heaps et al. 1986). In addition to the arguments in those articles, there is experimental evidence that stretching produces polymerization in vivo, because spindles elongate when cells are flattened (Inoué 1952). Further, stretching forces stimulate microtubule assembly in neurites (Zheng et al. 1993).

Forces on chromosome arms

Our model supposes that there are forces on chromosome arms that are separate from the pulling force at the kinetochore. Several lines of evidence indicate that these forces exist.

(1) Chromosome arms often move poleward in anaphase, ahead of the kinetochores, after UV microbeam irradiation of crane-fly spermatocyte kinetochore spindle fibres in anaphase (Fig. 4) (Forer 1966: figs. 17, 19, and 23; Marzec 1993) or in metaphase (Fig. 5). Appropriate calculations and observations show that this movement is not due to momentum and that the arms actively move poleward (Marzec 1993).

(2) Chromosome arms move poleward after inversion bridges are maximally stretched and the kinetochores

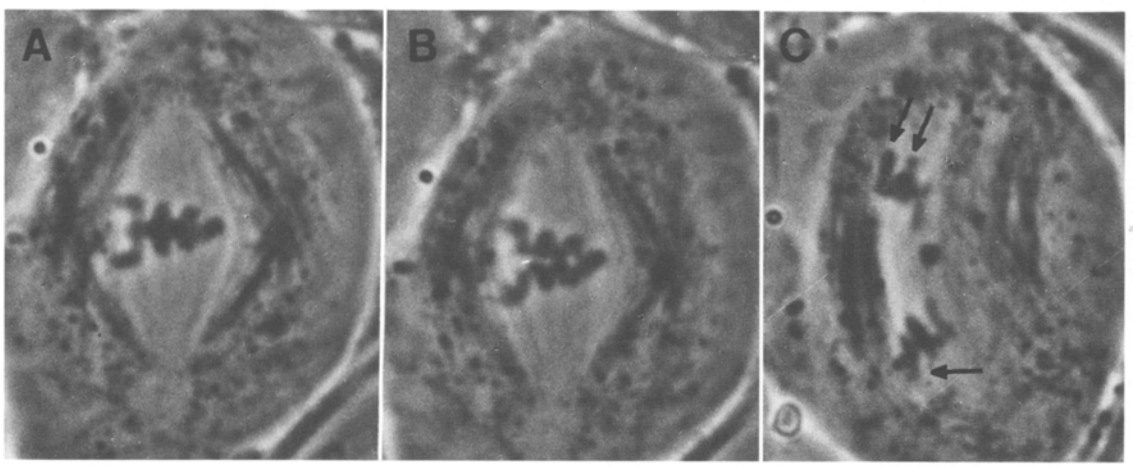


Fig. 4. Chromosome arms moved poleward ahead of the kinetochores after UV microbeam irradiation of anaphase spindle fibres. (Cells were irradiated as in Forer 1966.) **A** Metaphase, 8.5 min before UV microbeam irradiation. **B** Start of anaphase, 6.5 min before UV microbeam irradiation. **C** 13 min after UV microbeam irradiation. The arms indicated with arrows are closer to the poles than are the kinetochores of the same chromosomes. × 1500

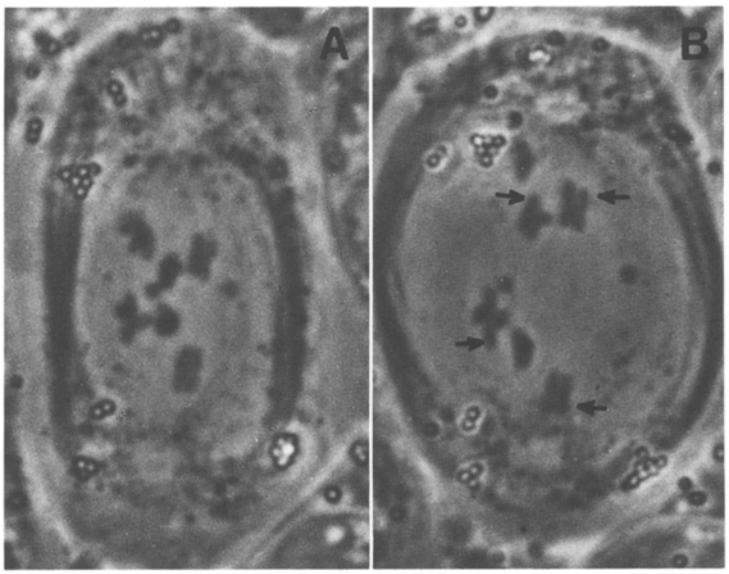


Fig. 5

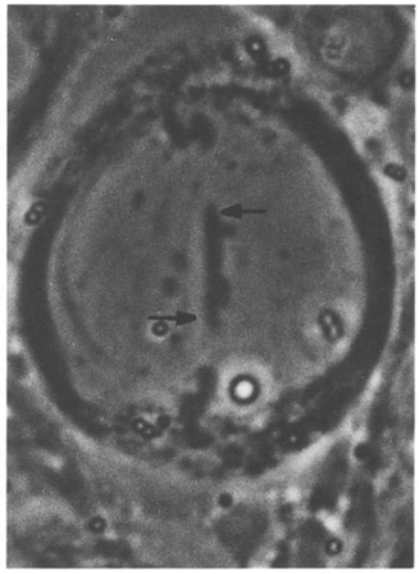


Fig. 6

Fig. 5. Chromosome arms moved poleward in anaphase, ahead of the kinetochores, after UV microbeam irradiation of metaphase spindle fibres. (Cells were irradiated as in Forer 1966.) **A** 8 min after the start of anaphase. **B** 31 min after the start of anaphase. Most autosomal half-bivalents moved poleward with arms ahead of the associated kinetochores; in **B**, the arrows from the left indicate single arms ahead of the kinetochores, and the arrows from the right indicate two arms ahead of the kinetochores. × 1500

Fig. 6. Bridged half-bivalents (in late anaphase) with arms poleward from the kinetochores (indicated by arrows). × 1500

no longer are able to move poleward (Fig. 6) (Dietz 1972: fig. 4; Bajer and Östergren 1963: fig. 9; McClintock 1931: fig. 36, and 1933: figs. 28 and 29).

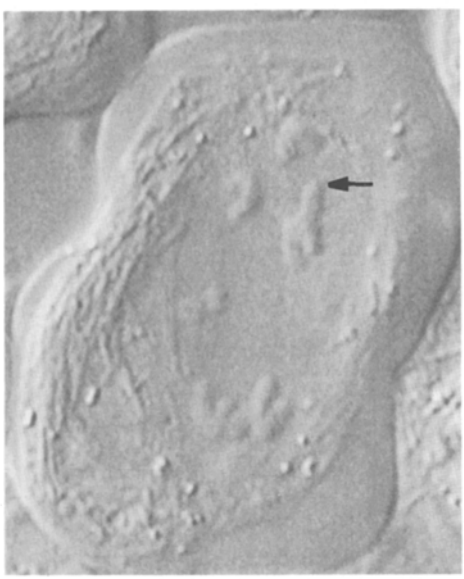


Fig. 7. A non-irradiated (control) crane-fly spermatocyte, in anaphase. In one chromosome the kinetochore is preceded to the pole by a chromosome arm (indicated by the arrow). Photograph from DIC microscope images recorded on optical disk by Dr. J. Pickett-Heaps. × 2200

(3) Chromosome arms sometimes move ahead of the kinetochore in anaphase in normal cells (Fig. 7) (Forer 1980: fig. 6.3; Bajer and Molè-Bajer 1956: fig. 16; A. Bajer pers. comm., concerning *Haemanthus* endosperm cells).

(4) Chromosome arms move poleward (behind the chromosomes) after being severed from anaphase chromosomes (Liang et al. 1993).

These observations confirm our assumption that there are forces on chromosome arms independent of those from the kinetochore fibre because they show that chromosome arms can actively move poleward independent of forces on the kinetochore.

We now digress from our consideration of evidences in support of the assumptions of our model to point out that our model offers explanation of why chromosome arms sometimes move ahead of the kinetochores. In our model, the forces on the chromosome arms push the chromosome and the associated kinetochore fibre poleward and thereby results in "compression" on the kinetochore fibre at both pole and kinetochore. Forces on the chromosome arms are resisted by kinetochore fibres; as long as the kinetochore fibres depolymerize reasonably rapidly, as occurs in normal anaphase, the arms do not move poleward, because in order to move poleward they need to over-

come resistance due to viscosity and resistance due to "polar ejection forces" (Rieder et al. 1986). The forces on the arms *will* cause the arms to move poleward if the resistance of the kinetochore fibre to compression is too high; this will occur when the depolymerization of the kinetochore fibre is blocked, as in the inversion bridges. The forces on the arms also will cause the chromosomes to move poleward if the resistance from the "polar ejection forces" is reduced; this would occur in the ultraviolet microbeam experiments because those irradiations greatly reduce (or even eliminate) the non-kinetochore microtubules (Wilson and Forer 1988, and Forer unpubl. obs.) which are thought to give rise to the polar ejection forces (Rieder et al. 1986). Arms only occasionally will move poleward ahead of the kinetochore in normal cells because only occasionally will the forces on the arms be stronger than the counter forces.

Implications to other stages of mitosis

In presenting our model we have concentrated on chromosome movement to the pole during anaphase. The same general ideas can be applied to earlier stages of mitosis as well. They can be used, for example, to explain shortening and elongating of prometaphase spindle fibres; independent poleward and away-from-the pole movements of oppositely directed kinetochores (e.g., Fuge 1987, 1989; Skibbens et al. 1993); how interactions between motor molecules and kinetochore filaments and microtubules might be important in setting up the metaphase spindle; and the forces on chromosomes in metaphase being proportional both to lengths of kinetochore fibres (Hays et al. 1982) and to numbers of kinetochore microtubules (Hays and Salmon 1990).

Conclusion

We have presented an outline of a model that helps us understand mitosis. In particular, we think that motor molecules in the spindle matrix produce force on kinetochore microtubules, kinetochore filaments, and chromosome arms; that in anaphase kinetochore filaments and kinetochore microtubules do not slide, but are attached in "rigor"; that compression and stretching forces influence kinetochore microtubule depolymerization and polymerization, respectively; and that as a consequence of these forces and variable polymerization/depolymerization rates at kinetochores and poles, one obtains different relative amounts of PacMan versus traction during anaphase chromosome movements. We consider our model more a way of looking at mitotic processes than as a set of hard and fast details of how spindles work. Various predictions can be made from the model, and can be used to test various aspects of the model.

Note added in proof: K. E. Sawin and T. J. Mitchison [Mol Biol Cell 5: 217–226 (1994)] also have suggested, as one possible model to explain some of their results, that motor molecules embedded in a spindle matrix might push (or pull) spindle microtubules to the spindle pole.

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