Modelling chromosome dynamics in mitosis: a historical perspective on models of metaphase and anaphase in eukaryotic cells

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Mitosis is the process by which the genome is segregated to form two identical daughter cells during cell division. The process of cell division is essential to the maintenance of every form of life. However, a detailed quantitative understanding of mitosis has been difficult owing to the complexity of the process. Indeed, it has been long recognized that, because of the complexity of the molecules involved, their dynamics and their properties, the mitotic events that mediate the segregation of the genome into daughter nuclei cannot be fully understood without the contribution of mathematical/quantitative modelling. Here, we provide an overview of mitosis and describe the dynamic and mechanical properties of the mitotic apparatus. We then discuss several quantitative models that emerged in the past decades and made an impact on our understanding of specific aspects of mitosis, including the motility of the chromosomes within the mitotic spindle during metaphase and anaphase, the maintenance of spindle length during metaphase and the switch to spindle elongation that occurs during anaphase.

1. Introduction

Mitotic cell division is an absolute requirement for survival of both uni- and multi-cellular organisms. Indeed, cell division errors are typically associated with lethality in unicellular organisms; and development of multi-cellular organisms requires a number of tightly regulated and highly ordered cell divisions. Moreover, cell division is essential for morphogenesis and tissue homeostasis. Cell division is the final stage of a cell life cycle (the cell cycle) and is the stage during which the genetic material is partitioned equally between two daughter cells. In preparation for mitosis, the DNA is replicated during a previous stage (S-phase) of the cell cycle, but the two DNA molecules produced during replication of each chromosome are held together by specialized chromosome-associated proteins that form the cohesin complexes. Thus, each mitotic chromosome consists of two paired sister chromatids. Segregation of sister chromatids into two daughter cells relies on dynamic interactions between the microtubules of the mitotic spindle and the chromosomes. These interactions and the forces produced lead to a series of highly coordinated and dynamic events that have fascinated scientists for centuries [1]. Mitosis has also been a subject of interest to scientists outside of the life sciences, including physicists, who have long been interested in the mechanical properties of the mitotic apparatus components and the forces they produce, and mathematicians, who have long been interested in developing mathematical models of mitosis. Here, we first provide an overview of the mitotic process, and then we describe some of the key models of mitosis that have been developed over the years. These models will be described in chronological order to provide a historical perspective of how, thanks to the increased knowledge of mitosis at the cellular and molecular level, these mathematical models have become more and more complex and comprehensive.
2. An overview of mitosis

The ultimate goal of mitosis is the equal partitioning of the replicated genome into two daughter cells (figure 1). In eukaryotic cells, mitosis is typically divided into five distinct stages: prophase, prometaphase, metaphase, anaphase and telophase (figure 1). Cytokinesis, which follows mitosis and partly overlaps with it, leads to partitioning of the cytoplasm, thus completing cell division [2]. This review, however, will exclusively focus on mitosis, or nuclear division.

In mitotic prophase, the chromatin condenses, so that individual chromosomes become discernible. Prophase is also marked by a change in microtubule dynamics, which leads to the disassembly of interphase microtubules (long and not very dynamic), and the assembly of mitotic microtubules (short and highly dynamic). The centrosomes, which are replicated during S-phase and serve as microtubule-organizing centres in most animal cells, move apart during prophase and an aster starts forming around each duplicated centrosome [3] with microtubule plus ends extending outwards. This process initiates the assembly of a dynamic macromolecular machine: the mitotic spindle.

The breakdown of the nuclear envelope marks the onset of prometaphase, and a bipolar spindle forms when microtubule plus ends extending from opposite asters overlap and form bundles enabled by the concerted action of multiple microtubule-based motors and microtubule-associated proteins (MAPs). During this phase, the dynamic microtubule plus ends switch between polymerization and depolymerization phases within the nuclear region, where they may encounter a kinetochore, a specialized protein structure that mediates chromosome–microtubule attachment. Kinetochore can initially establish lateral interactions with microtubules [4,5], but these attachments are subsequently converted into end-on attachments, and this is believed to increase microtubule stability [6]. In most model organisms, individual kinetochores bind multiple microtubules, which will form a microtubule bundle, also referred to as a kinetochore–microtubule bundle (sister kinetochore attached and one unattached). These monotelic chromosomes can either become amphitely attached to microtubules from opposite poles and then move to the spindle equator, thanks to lateral kinetochore–microtubule interactions, and then become amphitely attached [4,5]. During prometaphase, chromosomes progressively become amphitely attached and aligned at the spindle equator in a process called chromosome congression.

After all chromosomes have aligned at the spindle equator, the cell is said to be in metaphase, and the chromosomes lined up at the spindle equator are said to form the metaphase plate. In many cell types, chromosomes at the metaphase plate exhibit continuous oscillations back and forth about the spindle equator [7].

Anaphase onset is marked by the abrupt and synchronous separation of the sister chromatids, which is due to the sudden degradation of the cohesin complexes between the sister chromatids [8]. During anaphase, the two sister chromatids, now daughter chromosomes, move opposite poles of the mitotic spindle as their respective k-fibres shorten. This process is also referred to as anaphase A, to distinguish it from anaphase B, in which the spindle elongates, thus moving the two groups of segregating chromosomes further apart. In most organisms, there is temporal overlap between anaphase A and B.

By telophase, the chromosomes have reached the spindle pole regions, and start to decondense. Meanwhile, the nuclear envelope starts to reassemble around the decondensing chromosomes to form two daughter interphase nuclei. Cytokinesis normally starts during the later stages of mitosis.
3. The mechanics and dynamics of mitotic spindle, microtubules and chromosomes during mitosis

Forces generated in the mitotic spindle are required for proper positioning of the sister chromatids within the spindle, for mitotic progression and for accurate segregation of the genome during mitosis (reviewed in [9]). Moreover, forces generated in the mitotic spindle control spindle organization and length (reviewed in [10]). Microtubules in the spindle can generate polymerization ratcheting forces that push the chromosome arms and/or the spindle poles, and depolymerization of microtubules at their plus or minus ends can pull the kinetochores poleward with or without the help of microtubule depolymerases. In addition, multiple minus- and plus-end-directed microtubule-based motor proteins exert forces on the kinetochores, chromosome arms or the centromeres by moving towards the plus or minus end of their microtubule tracks within the spindle. Although the microtubule-based mitotic spindle maintains an overall stable structure and organization, the microtubules that form the spindle scaffold display rapid dynamics, as assayed by fluorescence recovery after photobleaching [11]. The rapid fluorescence recovery, with a half-life ranging from a few seconds to a few minutes depending on the organism, is attributed mainly to dynamic instability of microtubule plus ends, and to a lesser extent to poleward transport of the microtubule lattice and depolymerization of centromere-associated microtubule minus ends in a process called microtubule poleward flux [12].

Following its assembly at the onset of prometaphase, the mitotic spindle goes through multiple phases of elongation and steady-state length maintenance until its disassembly during telophase. The elongation rate and the steady-state length of the spindle during these phases are determined through a balance of forces generated by the antagonistic and/or complementary action of microtubule dynamics at plus ends, depolymerization at minus ends, and microtubule-based motor proteins associated with spindle microtubules, chromosomes, kinetochores and spindle poles (the mechanical and dynamic control of spindle length is reviewed in [10]).

The k-fibres of amphitelically attached sister chromatids pull the sister kinetochores in opposite directions and thereby exert tension and stretch the cohesin bonds between the sisters. These forces mediate the congression of the sister chromatids to the spindle equator during prometaphase [13] in a process often accompanied by the oscillation of the sister chromatids along the pole–pole axis. The oscillations of the sister chromatids between the spindle poles persist throughout metaphase in many vertebrate culture cells, and is termed chromosome directional instability [7]. The tension between the sisters may also play a role in cell cycle progression by silencing the mitotic checkpoint, as suggested by micromanipulation studies in which mechanical stretch of monotelically attached chromosomes resulted in precocious anaphase (reviewed in [9]). In addition, classic laser microsurgery experiments showed that disrupting kinetochore–microtubule attachment on one sister chromatid of an amphitelic chromosome resulted in the rapid movement of both sister chromatids (whole chromosome) towards the pole associated with the intact k-fibre [14], indicating that the balance of forces between the k-fibres of amphitelically attached sister chromatids determines their position and their motility rate within the spindle.

The maximum force that the spindle components can exert on a chromosome during anaphase was measured and found to be approximately 700 pN in classic micromanipulation experiments [15], corresponding to a 10–15 pN force (typical stall force of a few motor proteins) per individual microtubule in a k-fibre [16]. Other mechanical properties of the mitotic spindle, including the elastic modulus of chromosomes, the viscosity of the cytoplasm and the magnitude of polar ejection forces (forces directed away from the spindle poles and acting on the chromosome arms [17]), were also estimated based on the analysis of the three-dimensional motion of chromosome arms over time [18]. More recently, the distribution of polar ejection forces within the spindle was also determined by analysing the changes in velocity and range of motion of chromosomes subsequent to arm-severing by ultrafast laser microsurgery [19].

In an attempt to identify the magnitude of tension exerted on pairs of sister kinetochores oscillating between the spindle poles, where one sister moves poleward (leading) and the other moves away from its pole (trailing), recent studies used probes to mark the pole-proximal and the centromeric ends of pairs of sister kinetochores undergoing directional instability in metaphase spindles of cultured vertebrate cells [20]. The authors found that the poleward-moving sister kinetochore is compressed, whereas its trailing sister is stretched, and attributed this finding to the presence of an elevated friction at the site of active force generation (i.e. at the poleward-moving sister kinetochore).

Finally, studies using metaphase spindles formed in Xenopus laevis egg extracts tested the possible contribution of an elastic matrix to forces generated within the spindle by using microneedles to skew the spindle during metaphase [21]. The findings of such studies suggested that a spindle matrix does not contribute significantly to the motility of the spindle parts, but instead intrinsic forces dominate movements.

4. The chronology of mathematical modelling of mitosis

As the structure, organization and dynamics of the protein machine called the mitotic apparatus was being visualized and the inventory of the molecules involved was being gathered, scholars of mitosis set out to gain a quantitative understanding of the dynamic events that lead to chromosome segregation, in terms of the interacting molecular parts and physical and chemical principles. Significant efforts have been
placed in developing mathematical models of various mitotic subprocesses, including spindle assembly, metaphase chromosome oscillations and anaphase chromosome segregation. Here, we do not discuss models of mitotic spindle assembly and establishment of kinetochore attachment [22–24]. Instead, we primarily focus on the quantitative models of metaphase chromosome dynamics and briefly review the models of metaphase spindle length control and anaphase spindle elongation.

4.1. Kinetochore–microtubule attachments and chromosome motility

Among many puzzling phenomena, one that remains to be solved is how kinetochores are able to maintain attachment to shortening microtubule tips during metaphase and anaphase. Indeed, one of the earliest theoretical models (the Hill sleeve model; figure 2a) of a mitotic event concerned this process [25]. In this classic study, based on thermodynamic and kinetic arguments, the author quantitatively shows how a shortening microtubule tip can remain attached to and maintain a steady insertion depth inside a kinetochore region referred to as the ‘sleeve’. It is assumed that the tubulin subunits in the microtubule lattice interact with a finite number of sites along the length of this sleeve with moderate affinity. However, because the translocation of the microtubule inside the sleeve requires detachment of existing bonds, driven by the thermal fluctuations of the binding sites inside the sleeve, as well as re-binding, the potential barrier/resistance increases for increased number of interactions between the sleeve and the lattice. This effectively slows down the relative movement of the microtubule inside the sleeve and a steady-state penetration length of the lattice inside the sleeve is maintained, even for a microtubule depolymerizing at approximately 1 μm min⁻¹.

The Hill sleeve idea was developed further in a force-balance approach [26] (figure 3a), where the authors accounted for the metaphase oscillations (directional instability) of sister kinetochores capable of forming attachments with multiple microtubules through Hill sleeves arranged in parallel at each kinetochore, and anchored to the kinetochore via Hookean springs. In this study, tension forces between the sister kinetochores arising from the stretched cohesin bonds and the polar ejection forces were taken into account. However, poleward flux of the microtubules was not accounted for. As in reference [25], here too the poleward movement of a sleeve with respect to its microtubule requires the detachment and re-binding of all bonds, setting a large energy barrier for the movement at high sleeve insertion depths. This mechanism effectively prevents the poleward movement of a sleeve (and hence its kinetochore) when the microtubule is in the polymerization state, which naturally leads to deeper insertion of the microtubule into the sleeve, while favouring the poleward movement of a sleeve (and hence its kinetochore) when the microtubule is in the depolymerization state, which reduces the insertion depth. Thus, in this force-balance Hill sleeve model, the primary factor driving the poleward or anti-poleward movement of the metaphase kinetochore is microtubule dynamics [26].

An alternative to the Hill sleeve model for microtubule–kinetochore interactions was put forward based on the presence and requirement of microtubule-based motors at the kinetochore for chromosome motility in many organisms. Theoretical investigation of this model in a force-balance approach [27] (figure 3a) was based on the presence of two antagonistic kinetochore motors, dynein and CENP-E, and the two members of the kinesin-13 family microtubule depolymerases located at the kinetochore and at the spindle poles, incorporating the poleward flux of kinetochore–microtubules (figure 2b). This model successfully accounted for metaphase and anaphase chromosome behaviour in a wide range of organisms through adjustments in model parameters. Notably, this model reproduced qualitatively different metaphase chromosome dynamics, such as directional instability and steady positioning, and a wide range of anaphase chromosome-to-pole velocities. It also quantitatively showed that the transition from metaphase positioning to anaphase poleward motility can be achieved merely through the degradation of the cohesin bonds between the sister chromatids and the removal of the polar ejection forces [27]. This model formed the basis of several other models that were proposed later [28–30].

Two models, derived from the Civelekoglu-Scholey et al. [27] force-balance model, were developed by the Tournier group to investigate chromosome behaviour in fission yeast [28,29]. Their first force-balance model addressed the...
correction of merotelic attachments during anaphase in fission yeast and did not account for amphitelic kinetochore pairs [28]. This model was derived from the Civelekoglu-Scholey et al. and Brust-Mascher et al. models [27,31] with additional simplifying assumptions. A second quantitative model developed by the Tournier group accounted for the dynamics of amphitelic kinetochore pairs [29]. Similar to their previous study [28], this second study by the Tournier group also relied upon a macroscopic approach [29]. Indeed, all kinetochore components are represented by a homogeneous viscoelastic ‘unit’ that can attach/detach from microtubule plus ends, assumed to be homogeneously distributed within the spindle [29]. However, because the positions and dynamic states of microtubule plus ends are not accounted for, neither the effect of kinetochore tension on microtubule plus-end dynamics nor the effect of microtubule plus-end dynamics on the attachment/detachment from the kinetochore are considered [29]. In particular, the kinetochore–microtubule binding and detachment in this model occur at fixed, average rates (implemented stochastically), implying that a kinetochore is equally likely to encounter a ‘free’ microtubule plus end from prometaphase through anaphase (‘free’ microtubule plus ends are assumed to be as abundant in all phases), and does so regardless of the

\[ F_{\text{drag}}^{\text{chr}} = \text{sum of all forces exerted on the chromosome} \]
\[ F_{\text{drag}}^{\text{chr}} = \mu v_{\text{chr}} \]
\[ F_{\text{drag}}^{\text{chr}} = \sum \left( F_{\text{KT}}^{\text{kin}} + F_{\text{cohesin}}^{\text{kin}} + F_{\text{PE}}^{\text{kin}} + F_{\text{poly}}^{\text{kin}} \right) \]

\[ F_{\text{cohesin}} \]
\[ F_{\text{poly}} \]

\[ F_{\text{KT}} \]

\[ F_{\text{drag}} \]

\[ F_{\text{drag}}^{\text{chr}} \]

Figure 3. The force-balance approach and models for spindle length control. (a) Force-balance models assume the sum of the forces generated by various spindle parts to be balanced by the viscous drag forces on the moving module (e.g. the chromosome). Viscous drag forces are proportional to the rate of movement and the friction coefficient of the module. Forces exerted on the module are determined based on simple diagrams through consideration of various spindle parts interacting with the module. (b) Two competing models for spindle length changes from steady state (metaphase) to elongation (anaphase B). Top panel: the sliding and switch from minus-end depolymerization to spindle elongation model. In this model, the sliding of antiparallel overlapping microtubules by bipolar kinesin-5 motors (in red) is balanced by depolymerization of microtubule minus ends near the poles during metaphase and the cessation of microtubule minus-end depolymerization engages the sliding motors to push the poles apart and to elongate the spindle in anaphase. Bottom panel: the slide and cluster model. In this model, microtubule dynamics is restricted to plus ends, microtubules are nucleated near the spindle equator, and their sliding rate (resulting from the combined action of dynein and kinesin-5 motors) and the half-life of the microtubules determine the steady-state spindle length. Slowing down of microtubule plus-end dynamics (e.g. slower turnover by reduced catastrophe at microtubule plus ends) can lead to spindle elongation. In this model, microtubule minus ends do not depolymerize. (Online version in colour.)
kinetochore position within the spindle (‘free’ microtubule plus ends are uniformly distributed along the pole–pole axis of the spindle) [29]. Furthermore, because individual microtubules are not accounted for, a microtubule is assumed to instantly switch to polymerization or depolymerization and follow the direction of the kinetochore upon attachment [29]. Thus, some key questions, such as (i) how are the growth/shrinkage state and rate of different microtubules attached to each kinetochore coordinated and (ii) how are the sister kinetochores coordinated to give rise to the observed sister kinetochore movements, are not and cannot be addressed in this simplified framework.

Another force-balance model [32], developed independently of the model by Civelekoglu-Scholey et al. [27], used a simplified approach to describe and account for movements and oscillations of monotelic chromosomes. In this model, the chromokinesin motors anchored on the chromosome arms generated anti-poleward forces by walking towards the plus ends of the spindle microtubules they encounter, whereas the opposing poleward force, dependent on kinetochore attachment to microtubules, was assumed to be constant. Neither the dynamic instability of microtubule plus ends nor the poleward flux of microtubules was accounted for in this model. Nevertheless, the authors showed that the heterogeneity of the microtubule plus-end distribution within the spindle, together with a force-sensitive dissociation property of the chromokinesin motors are sufficient to account for the oscillatory behaviour of monotelic chromosomes.

The original Civelekoglu-Scholey force-balance model [27] was more recently adapted and extended to understand the dichotomy of chromosome behaviour seen in metaphase PtK1 cells [30], where peripheral sister kinetochores remain steady at the metaphase plate, whereas sister kinetochores in the middle of the metaphase plate oscillate back and forth between the poles [30,33–35]. In this recent model, non-motor proteins, modelled as elastic bonds, provide the link between the kinetochore and the microtubules (figure 2c). This was based on recent studies that identified the KMN network of proteins, specifically the Ndc80 complex, as the ‘coupler’ between the kinetochore and the microtubule (reviewed in references [36–40]). As for the kinetochore-bound motors in the original Civelekoglu-Scholey model [27], but in contrast with the Hill sleeve bonds proposed by Joglekar & Hunt [26], these elastic bonds bind to and detach from the microtubule lattice independently from one another (non-synchronously) [30]. While the primary factor driving the poleward kinetochore movement is poleward flux by pulling on and stretching the microtubule-bound protein complexes at the kinetochore, the depolymerization rate of kinetochore–microtubule plus ends is governed by the dynamics of these bonds, which in turn is regulated by tension forces [30,41]. Like the original Civelekoglu-Scholey model [26], the elastic bonds have a high association constant for the microtubule, but, in this new model, the detachment rates for these bonds are assumed to be force sensitive and to display different kinetics depending on whether the microtubule tips are polymerizing or depolymerizing [30]. Specifically, it is assumed that bonds detach easily under low and high tension, but the bond life is increased under moderate tension from a depolymerizing microtubule tip, a ‘catch bond’ interaction, and the detachment rate from a polymerizing microtubule tip increases linearly with increasing tension, a ‘slip bond’ interaction [30,42,43]. Consequently, in contrast with the Joglekar and Hunt model [26], in this new model, bonds with a polymerizing microtubule are generally ‘weak’, and those with a depolymerizing microtubule are generally ‘strong’, in agreement with recent in vitro biophysical studies [37].

Following the identification of ring-like protein complexes at the kinetochore–microtubule interface in budding yeast [44,45], and the slender fibrils connecting the kinetochore to the flaring out tips of depolymerizing microtubules in vertebrate cells [46], new quantitative models addressed the ability of these ‘couplers’ to mediate stable attachment of the kinetochores to dynamic microtubule tips [46,47]. By investigating the biomechanical properties of the coupling interaction between a ring-like structure and a microtubule tip in a theoretical framework, Efremov et al. [47] found that the optimal coupling occurs when the ring is bound to the microtubule via flexible linkers that bind strongly. They further showed that by such a coupling mechanism the kinetochore ring can faithfully follow a depolymerizing microtubule tip by harnessing the energy released from the power stroke as the protofilaments in the lattice curl outwards, and maintain attachment with straight (polymerizing) microtubule tips under load [47]. Finally, the authors showed that the slender fibrils observed in electron tomographic images in vertebrate cell kinetochores [46] can form efficient couplers between the kinetochore and the microtubules and can sustain load, even in the absence of rings around the microtubule tips, if the binding is strong [47]. In fact, this study showed that direct kinetochore–microtubule coupling via fibrils, modelled as elastic elements, works more efficiently than kinetochore–microtubule coupling via rings and elastic links along depolymerizing microtubules, because the microtubule depolymerization rate becomes limited by the ring’s sliding rate in the latter case. These theoretical models of kinetochore–microtubule couplers, however, have not yet been extended to account for the binding of a kinetochore to multiple microtubules, or to account for sister kinetochore dynamics in metaphase or anaphase spindles, in the presence of polar ejection forces, cohesin spring tension and with microtubules undergoing poleward flux.

Another notable theoretical approach in understanding kinetochore motility emerged from studies aimed at understanding the behaviour of chromosomes in the budding yeast Saccharomyces cerevisiae [48–50]. In the budding yeast, where spindle microtubules do not undergo poleward flux, and only a single microtubule binds to each kinetochore, the maintenance of each kinetochore’s attachment to the spindle pole relies upon the dynamic instability of a single microtubule plus end. The computational models in these studies addressed both the mechanical (e.g. tension dependent) and the molecular (e.g. kinesin-5) regulation of the plus-end dynamics of a kinetochore-bound microtubule, and successfully accounted for the behaviour of yeast kinetochores in metaphase and made valuable experimentally testable predictions [49,50].

Several other theoretical models in the literature proposed to account for the metaphase and anaphase behaviour of chromosomes, but used speculative approaches with unidentified interactions and/or feedback loops, or made gross simplifying assumptions with the aim of providing a simple physical description of these events. Unfortunately, these strategies compromised the purpose of theoretical modelling, which is to provide a quantitative understanding of the behaviour resulting from interacting molecules, based on the principles of physics and chemistry. Some of the mathematical and computational models of kinetochore attachment to
microtubules and/or metaphase and anaphase kinetochore/chromosome behaviour discussed here, and some others not considered here, have been previously reviewed [51–53].

4.2. Metaphase spindle length and anaphase spindle elongation

During metaphase, which lasts for tens of seconds to hours depending on the organism, the spindle poles are maintained at constant spacing, giving rise to a steady spindle length. During this period, however, the microtubules that make up the spindle scaffold undergo two types of highly dynamic processes: dynamic instability of microtubule plus ends and microtubule poleward flux resulting from the microtubules’ poleward translocation by the combined action of multiple motor proteins, coupled to their depolymerization at their minus ends. Quantitative understanding of how such dynamic microtubules can maintain the spindle at a constant length, for extended periods of time in some species, has been a popular subject of theoretical investigation.

In particular, how multiple motors with opposite polarity working on the same or different overlapping microtubules and which combination of motors, with which type of properties, can achieve this goal has been addressed in an important computational model in which details of microtubule plus-end dynamics, motor kinetics and force generation, elastic properties of the microtubules and viscosity of the spindle environment were all accounted for [54]. The authors in this work surprisingly concluded that only motors referred to as ‘hetero-complexes’, i.e. bipolar motors with a minus-end- and a plus-end-directed head at opposite ends, were able to maintain a stable centrosome separation [54]. This early computational model was later developed further and has been successfully modified, extended and applied to account for spindle length maintenance or spindle bipolarity in many organisms [55–59].

Steady spindle length maintenance during metaphase and the subsequent linear spindle elongation was later addressed in a force-balance framework where the plus-end dynamics of microtubules was accounted for [31] (figure 3b, top panel). The underlying qualitative model based on experimental observations suggested that, during metaphase, plus-end-directed bipolar motors on anti-parallel microtubule overlaps slide them apart, whereas the minus ends that are dynamic? (ii) How do kinetochores maintain faithful attachments with dynamic microtubule plus ends for accurate segregation, while allowing the correction of misattachments? and (iii) How can a spindle constituted of highly dynamic microtubules maintain a constant length? Realistically, the answers to these questions must take into account the chemical and physical properties of the molecular components of the mitotic apparatus and its environment, as well as the interactions between such components, and therefore inevitably require mathematical/computational modelling.

Models that in the past made an impact on our understanding of mitotic events were often based on cartoon depictions providing snap shots of a dynamic process, and quantitatively forms during late anaphase is determined by the sliding of anti-parallel overlapping interchromosomal microtubules, whose length and position depend on depolymerization at their minus end by Kif2a, which in turn is controlled by an Aurora B gradient [62].

An alternative to the model ‘switch from poleward flux to spindle elongation’ was later proposed to account for the steady spindle length observed in metaphase spindles formed in *Xenopus laevis* egg extracts, and it was referred to as the ‘slide and cluster’ model [63] (figure 3b, bottom panel). In this force-balance model, microtubules are nucleated near the spindle equator, where they are organized to form anti-parallel overlaps. Initially, plus-end-directed bipolar motors (sliding motors) slide these newly nucleated microtubules apart polewards, and minus-end-directed motors (clustering motors) anchored at the microtubules’ minus ends also pull them polewards along other microtubules, helping the bipolar motors [63]. As the microtubules move poleward, first, the minus-end-directed motors on newly nucleated anti-parallel overlapping microtubules near the equator start pulling them inwards, antagonizing the bipolar motors, then the microtubule plus-end dynamics parameters favour full depolymerization of the microtubules over time, effectively setting a maximal microtubule length and life time. Thus, in the ‘slide and cluster’ model [63], microtubules near the equator slide outwards towards the poles, but their minus ends do not depolymerize when they reach the poles. In addition, microtubules near the poles are pulled towards the equator by the minus-end-directed motors on overlapping microtubules whose minus ends are closer to the equator. Within the framework of this model, a steady spindle length can be achieved and maintained, and it simply depends on the sliding rate and the relative ratio of the sliding to clustering motors and the plus-end dynamics of the microtubules [63]. Finally, this model posits that a change in the plus-end dynamics of the microtubules (e.g. a reduction in the catastrophe frequency of microtubule plus ends) can tip the balance and, in principle, lead to the elongation of the spindle to a different steady-state length. However, these possibilities have not yet been tested.

5. Concluding remarks

Despite the discovery of the key components that drive chromosome segregation in the mitotic spindle, and the characterization of their chemical and biophysical properties, many questions, particularly related to the bewildering dynamic of the mitotic apparatus, remain to be answered. For instance, (i) how does a kinetochore bind to multiple microtubule plus ends that are dynamic? (ii) How do kinetochores maintain faithful attachments with dynamic microtubule plus ends for accurate segregation, while allowing the correction of misattachments? and (iii) How can a spindle constituted of highly dynamic microtubules maintain a constant length? Realistically, the answers to these questions must take into account the chemical and physical properties of the molecular components of the mitotic apparatus and its environment, as well as the interactions between such components, and therefore inevitably require mathematical/computational modelling.
tested the validity of such cartoons/static models. However, in the past couple of decades, mathematical modelling of mitosis has been used with a different purpose, as models began to make testable predictions, challenging the underlying mechanism, and significantly speeding up the process of achieving a full understanding of mitotic events. In addition, the increased use of computational tools in mathematical modelling allowed the recent models to account for an increasing number of molecules, interactions and details of the events, rendering the models more comprehensive and realistic. An increasing number of studies have combined experimental and computational approaches, which allowed fine-tuning of the model parameters and experimental testing of the model predictions. Commitment to pursue such interdisciplinary studies that integrate experimental and computational approaches will be essential for the achievement of a full, comprehensive quantitative understanding of mitosis, a key process for the perpetuation of life.

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