

# Computer simulations predict that chromosome movements and rotations accelerate mitotic spindle assembly without compromising accuracy

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The mitotic spindle self-assembles in prometaphase by a combination of centrosomal pathway, in which dynamically unstable microtubules search in space until chromosomes are captured, and a chromosomal pathway, in which microtubules grow from chromosomes and focus to the spindle poles. Quantitative mechanistic understanding of how spindle assembly can be both fast and accurate is lacking. Specifically, it is unclear how, if at all, chromosome movements and combining the centrosomal and chromosomal pathways affect the assembly speed and accuracy. We used computer simulations and high-resolution microscopy to test plausible pathways of spindle assembly in realistic geometry. Our results suggest that an optimal combination of centrosomal and chromosomal pathways, spatially biased microtubule growth, and chromosome movements and rotations is needed to complete prometaphase in 10–20 min while keeping erroneous merotelic attachments down to a few percent. The simulations also provide kinetic constraints for alternative error correction mechanisms, shed light on the dual role of chromosome arm volume, and compare well with experimental data for bipolar and multipolar HT-29 colorectal cancer cells.

assembly speed and accuracy | merotelic attachments | microtubules | search and capture

The mitotic spindle is a complex molecular machine segregating chromosomes (1, 2). Molecular inventory and general principles of the spindle dynamics are becoming clear (3), but quantitative understanding of spindle mechanics in general and its self-assembly in particular is lacking. The first hypothesis of how the spindle assembles, elegantly called “search and capture” (Fig. 1A), was put forward in ref. 4 after the discovery of the dynamic instability phenomenon: Microtubules (MTs) grow and shorten rapidly and repeatedly from the centrosomes in random directions “searching” for the kinetochores (KTs), specialized chromosome structures that function as an interface between the chromosomes and the mitotic spindle. Whenever a growing MT plus end runs into a KT, this MT is stabilized; the assembly is complete when all KT are thus captured transforming two MT asters into a typical bipolar spindle. Capture of a single astral MT by a KT has been visualized directly in newt lung cell cultures (5).

How can hundreds of MTs turning over in tens of seconds capture tens of chromosomes within 10–20 min (6) is one of the fundamental questions of mitosis. Mathematical modeling has been instrumental in attempts to answer this question, because it is very hard to experimentally resolve individual MTs, follow their formation, and perturb their dynamics (7). First applications of modeling were the analyses (8, 9) suggesting that the dynamic instability parameters have to be optimized to ensure fast assembly, so that a MT switches from growth to shortening when it is as long as the distance between the centrosome and the chromosome. This analysis was extended (10) to simulate hundreds of MTs searching for tens of KT in realistic geometry. The simulations demonstrated that even optimally fine-tuned dynamic instability cannot explain the typical observed prometaphase duration of 10–20 min. How-

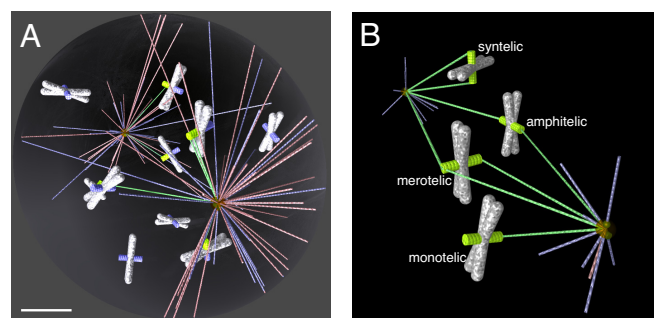


Fig. 1. Computer model of spindle assembly. (A) MTs (growing in blue, shortening in red, captured in green) searching from two foci (centrosomes) for KT (captured in green, not captured in blue) on the chromosomes (white/gray). (Scale bar, 2  $\mu$ m.) (B) Four possible types of chromosome attachments. Amphitelic attachment: The two sister KT are bound to MTs coming from opposite poles. Monotelic attachment: One sister KT is bound to MTs, whereas the other is unattached. Syntelic attachment: Both sister KT are bound to MTs from the same spindle pole. Merotelic attachment: One KT is bound to MTs from opposite spindle poles.

ever, a spatially biased search and capture process, in which the MTs grow without catastrophes within the nuclear sphere (i.e., volume through which chromosomes are distributed upon nuclear envelope breakdown) and catastrophe very fast away from it is predicted to be fast enough (10). The likely mechanisms for such spatial bias are the RanGTP gradient around the chromosomes (11, 12) and motor-dependent mechanisms (13, 14) locally regulating MT dynamics.

Three factors limit predictive power of our previous model (10). First, for technical reasons, the chromosome arms were “transparent” to the searching MTs, which led to overly optimistic predictions: MTs were able to search the whole nuclear space, although in reality, most of it is blocked by the chromosome arms. Second, the search-and-capture cannot explain mitosis in cells lacking centrosomes. In such cells, MTs are nucleated near the chromosomes, and then sorted into arrays with their minus ends extending outward, and finally focused at the minus ends as a result of complex activities of mitotic motors (15) establishing the spindle poles (16). It was thought that the centrosome-, and chromosome-directed pathways operate in different cells, but previously undiscovered data have demonstrated that centrosome-independent pathway occurs in cells that possess centrosomes (7) and that cells adopted

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both pathways for spindle self-assembly (17). Namely, the astral, centrosome-nucleated MTs capture the bundles of the KT-nucleated MTs, rather than KTs themselves, and then integrate the centrosomal–chromosomal bundles into a spindle-like structure (7). Third, in our previous study (10), we were concerned only with the speed of spindle self-assembly, but the assembly also has to be accurate: Ideally, all chromosomal connections have to be correct amphitelic attachments, in which the two sister KTs on each chromosome are captured from the opposite spindle poles, but monotelic, syntelic, or merotelic attachments are also possible (Fig. 1*B*). Erroneous attachments exist in early mitosis (18, 19), but later, most of them are corrected (19–22). The questions about how many erroneous attachments would result from the search-and-capture process, what kind of correction mechanisms have to be deployed, and what are the kinetic constraints on such mechanisms were raised qualitatively (23, 24), but never examined quantitatively.

In this study, we explore computationally the simplest “stochastic/geometric” hypothesis of erroneous attachment formation (19, 23): Merotelic and syntelic attachments are established as errors inherent to the stochastic nature of the search-and-capture mechanism when one KT is “visible” from both spindle poles, so the MTs from the respective poles reach this KT almost simultaneously (merotely) or when sister KTs are visible from the same pole and, again, are captured from this pole at once (syntely). We estimated the number of such attachments and found it to be tremendous, exceeding by far the numbers observed experimentally. We therefore tested a number of potential error-correction mechanisms including MT turnover and chromosome turning after the first capture, and found stringent constraints on kinetics of these error-correction mechanisms. The simulations revealed that chromosomes also have to move rapidly to ensure timely spindle assembly. The model suggests that the finite chromosome volume plays a dual role, on the one hand hindering the assembly by shielding KTs at the center of the nucleus, but on the other hand accelerating MT cycles by promoting MT catastrophes. The simulations further illustrate that in the hybrid assembly pathway, the longer the chromosomal MT bundles are, the faster, but also less accurate, the assembly is, hinting that the cell has to optimize the MT dynamics to achieve the conflicting goals of efficiency (rapid assembly) and accuracy (minimizing number of erroneous attachments). We calibrated the model by quantifying prometaphase dynamics, timing, and spindle geometry in HT-29 colorectal cancer cells.

## Model

We simulated vertebrate cells’ spindle assembly in realistic 3D geometry (Fig. 1*A*). In the model, the chromosomes, KTs, and MTs are dynamic objects behaving according to computational rules inferred from cell biological hypotheses. The model rules and assumptions are: Each of two centrosomes placed at the opposite poles of the nuclear sphere’s diameter anchor minus ends of 250 astral MTs. Each MT is a rod of zero thickness undergoing dynamic instability; its plus end grows steadily until a catastrophe occurs with a constant rate, upon which the MT shortens with a constant speed. While growing, the MT does not turn, and the new cycle starts with growth in a random direction. There are no MT rescues: We undertook exhaustive simulations that showed that the fastest capture occurs at zero rescue frequency, because when a MT grows with no KT on the growth path, rescues prolong such futile searches. We simulated both unbiased and biased searches. In the former, the constant catastrophe frequency is equal approximately to the MT growth rate divided by 85% of the nuclear sphere’s diameter: At this frequency, a MT on average reaches the length optimal to reach the majority of KTs (10), yet does not waste time on longer cycles. In the latter, MTs are stable in the chromosomes’ proximity and do not undergo any catastrophe events inside the nuclear sphere. Once a MT plus end goes beyond the volume of the nuclear sphere, it undergoes a catastrophe event and shrinks all the way back to the centrosome. In both scenarios, MTs start shortening immediately

upon a collision with a chromosome arm [see discussion in [supporting information \(SI\) Text](#)]. A MT plus end is instantly stabilized upon encountering a KT, and this KT is said to be captured. Upon such capture, a new dynamic MT replaces the stabilized one at the same pole.

Chromosomes are modeled as solid 3D cylinders that are uniformly randomly distributed within the nuclear sphere and oriented in random directions. In the static regime ([Movie S1](#)), the chromosomes stay put, whereas in the dynamic one ([Movie S2](#)), they move and rotate randomly. KTs are modeled as cylindrical objects and are placed in pairs on opposite sides of the cylindrical surface of the chromosomes, midway along their length (Fig. 1). To simulate the chromosomal MTs, we assume that they are bundled into cylindrical objects extending from the KTs outward, so that the bundle’s radius is equal to that of the KT. Therefore, when we model the hybrid centrosomal–chromosomal pathway, we simply consider longer targets placed exactly like the KTs on the chromosomal surface. When a centrosomal MT reaches the chromosomal bundle, we assume that the capture takes place, upon which, respective MTs get cross-linked by motors and ultimately establish a K-fiber. Chromosomes continue to move when one or both KTs are captured. Each KT (or extended target) has 10 binding sites on it; as soon as 10 MTs attach to a KT, any next MT that encounters such KT undergoes a catastrophe. Below, we describe additional optional model mechanisms of the error correction. The parameters and technical implementation of the computer simulations are described in *Materials and Methods* and *SI Text*.

## Results

**Chromosome Arms Both Hinder the Search by Shielding KTs and Accelerate the Search by Shortening Unproductive MT Cycles.** The first problem one encounters when tens of chromosomes of realistic size are uniformly and randomly distributed within the volume of the nuclear sphere is that the chromosome arms crowd the space to the extent that the chromosomes at the periphery completely shield the KTs in the interior from the MTs protruding from the spindle poles (Fig. 2*A*). We generated thousands of random chromosome configurations and gathered statistics of the number of the visible KTs (such that a projectile from the pole can reach these KTs without encountering a chromosome arm on the way) (Fig. 2*A*) and observed that <10% of the KTs can be captured at all if their number is >30. Thus, there has to be a special mechanism that makes all tens of KTs available for the centrosome-guided search.

Next, we tested the assembly process for “smartly” arranged chromosomes: In many configurations, chromosomes were randomly distributed within the nuclear sphere but only special configurations were chosen for testing, so that all KTs were either partially or completely visible from at least one of the centrosomes. Then, the assembly was simulated many times for each such configuration. The resulting average spindle assembly time is presented in Fig. 2*B* as a function of the KT number and compared with the results of our previous model with transparent chromosome arms (10). For >6 chromosomes, the average assembly time with finite chromosome volume is significantly greater compared with the transparent chromosome model. Moreover, this time increases almost linearly with the number of KTs, much faster than the logarithmic increase predicted by the simplified model (10). The simple explanation for this is that more chromosomes shield a greater fraction of the KT area, so the effective target area decreases with the KT number. This rapidly lengthens the assembly time because more MT cycles are necessary before MT growth in the right direction leads to a capture event.

We noticed, however, that when the chromosome number is small, then the average search time, counterintuitively, decreases when the chromosome arms work as a shield (Fig. 2*B Inset*). The explanation that we gleaned from following the time-lapse movies of the *in silico* dynamics is that many MTs growing in the wrong







of the increased size of the effective search targets. This finding predicts that MT ends growing from the KT should be incorporated within the forming mitotic spindle. Indeed, there is increasing evidence that such a pathway contributes to spindle assembly in a number of cell types (7, 29).

However, although the combined centrosomal and chromosomal pathway can speed up the process, it leads to a high number of erroneous attachments, which is in disagreement with observed frequencies of such misattachments in experimental models (19, 30). We also found that securing amphitelic attachments does not fix the problem. We tested, further, whether the widely discussed schematic mechanism of detecting and dissolving the syntelic (and partially merotelic) attachments works and saw that although such mechanism, indeed, “proofreads” the spindle very effectively, it leads to delays of the assembly, so in this case, accuracy comes at the price of speed. Finally, we found that the spindle assembly can be accurate without compromising its speed if, within  $\approx 10$ – $20$  sec after the first capture, chromosomes are rotated so that the captured KT faces the pole from which it was captured, and the sister KT becomes shielded from this pole by the chromosome arms. We further discuss the correction and rotation mechanisms and molecular pathways in the *SI Text*.

These conclusions provide quantitative constraints and hypotheses for future studies of mitotic spindle assembly. We calibrated the model using observations of bi- and multipolar colorectal cancer (HT-29) cells. The predictive power of the model is confirmed by the correct predictions of the numbers of the merotelic attachments in bipolar and multipolar HT-29 cells. The model is also in qualitative agreement with recent observations (38) that doubling the chromosome number adds  $\approx 10$  min to a  $\approx 20$ -min cell division. Additional suggestions for future experiments to test the model predictions can be found in *SI Text*.

For clarity, we kept the computational model simple and did not include possible elaborate mechanisms, some reported and other

hypothetical, which could significantly accelerate the assembly without compromising the accuracy. For example, we did not consider cooperative chromosome behavior (39, 40). We did not test the possibility of a temporal coordination of the hybrid chromosomal-centrosomal assembly pathway, in which the chromosomal MT bundles growth is delayed relative to the astral MT search (29). More hypothetical mechanisms include clustering of chromosomes or nucleation/branching of nascent MTs off the sides of the K-fibers (41). We discuss relevant issues further in *SI Text*. In the future, when quantitative data on MT and KT dynamics in prometaphase become available, it will not be hard to add and test an impact of these additional mechanisms on the speed and accuracy of the spindle self-assembly.

## Materials and Methods

**Model Simulations.** To simulate the spindle assembly model, we implemented the time-dependent, explicit agent-based simulations (42). In the beginning of each simulation, three classes of objects—chromosomes, KTs (or combined KT-chromosomal bundles), and MTs—were constructed, and then their positions and orientations were changed in the 3D space according to the computational rules described in *Model*, above. Technical details of the simulations and model parameters are described in *SI Text*.

**Experimental Observations.** The model was calibrated and tested by using colorectal cancer HT-29 cells and by using a number of approaches, including high-resolution confocal microscopy and 3D analysis, phase-contrast time-lapse microscopy, and combined phase-contrast/fluorescence live-cell imaging. The detailed methods are described in *SI Text*.

For additional information, see Figs. S1–S5 and Table S1.

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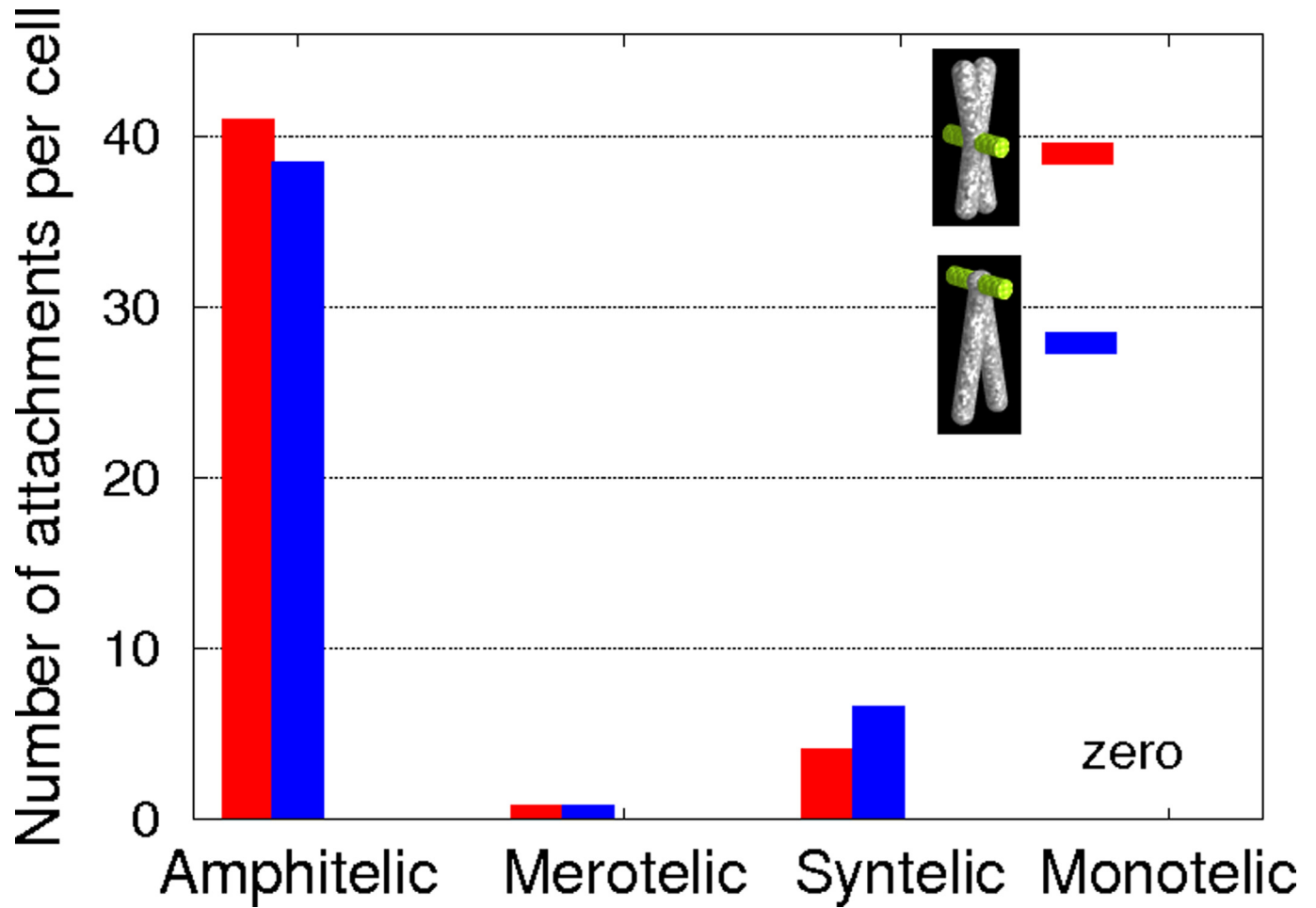
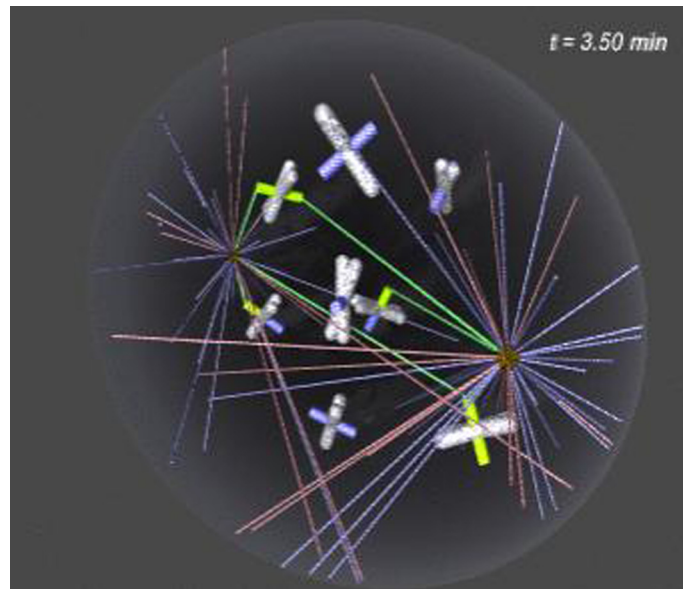


Fig. 55. Numbers of four distinct attachments in cells with metacentric and telocentric chromosomes. The results are obtained from simulations with chromosome number, volume, and other model parameters being the same for both types of chromosomes.

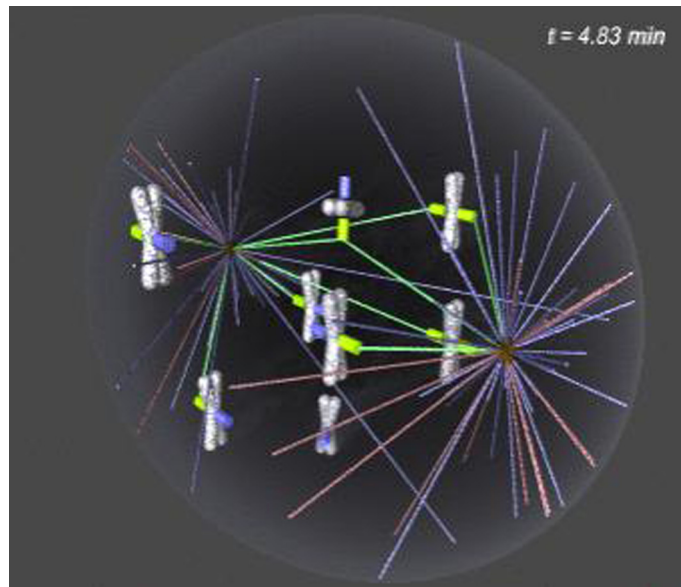
**Table S1. Model parameters**

Symbol	Description	Value
$N_{CH}$	Chromosome number in the simulations	1–50
$N_{KT}$	KT number in the simulations	2–100
$N_{MT}$	Number of dynamic MTs at each pole	250
$R_{CH}$	Chromosome radius	1 $\mu\text{m}$
$R_{KT}$	KT radius	0.44 $\mu\text{m}$
$l_{CH}$	Chromosome length	2 $\mu\text{m}$
$l_{KT}$	Target (KT or K-fiber) length	0.1–1.5 $\mu\text{m}$
$R_{nuc}$	Radius of the nuclear sphere	7 $\mu\text{m}$
$\nu_g$	MT growth rate	0.35 $\mu\text{m}/\text{sec}$
$\nu_s$	MT shortening rate	1 $\mu\text{m}/\text{sec}$
$F_{cat}$	Catastrophe frequency in the unbiased search	$3\nu_g/4R_{nuc} \approx 0.04/\text{sec}$
$f_{res}$	Rescue frequency	0
$\tau$	Chromosome rotation time after the capture	1–200 sec
$f$	Frequency of chromosomal movements across the nuclear sphere	0.001–0.1/sec



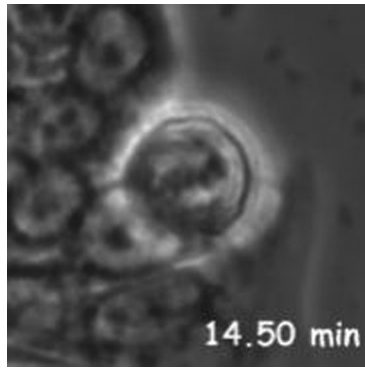
**Movie 1.** Time-lapse time movies of the computer search and capture simulation with static chromosomes. Growing MTs are blue, shortening MTs are red, captured MTs are green; captured KT's are green, not captured KT's are blue.

[Movie S1 \(WMV\)](#)



**Movie S2.** Time-lapse time movies of the computer search and capture simulation with dynamic chromosomes. Growing MTs are blue, shortening MTs are red, captured MTs are green; captured KTs are green, not captured KTs are blue.

[Movie S2 \(WMV\)](#)



**Movie S3.** Time-lapse movie of HT-29 cell entering mitosis and aligning its chromosomes at the metaphase plate. The cell is in interphase when the movie starts, but it rounds up and enters mitosis at 7 min. The movie ends when the cell completes chromosome alignment at the metaphase plate (20:50). Elapsed time shown in min:sec.

[Movie S3 \(AVI\)](#)