Supplemental Materials for
“Cell Shape and Intercellular Adhesion Regulate Mitotic Spindle Orientation”
J Li, L Cheng and H Jiang*

1 Supplementary Details of the Simulations

1.1 Bundling of microtubules

Besides the nucleation and dynamics of microtubules as given in the main text, bundling behavior of microtubules is essential to many cellular functions, for instance the kinetochore-microtubule interactions [21]. It has been reported that the mechanism of microtubule bundle formation is the minus-end-directed molecular motor kinesin-14 cooperates with the plus-end tracker EB1 to guide the growing plus end along existing microtubules (Inset 2 of Figure S1) [21]. In the model, we add an extra nucleation rate of $k_l k_0$ to grow along the direction of the existing kinetochore microtubules. Here $k_l$ is far less than 1 so that it only brings a little influence on the total nucleation. In this way, the microtubules in the kinetochore-fibers can be supplied enough to ensure the tension on the sister kinetochores. It should be noted that this nucleation for bundling exists only if there have been existing kinetochore microtubules.

Therefore, the total nucleation rate from a centrosome is $k^*_0 = k_0 + k_n k_0 \theta/(2 \pi) + N k_l k_0$. Here, $\theta$ is the total angle range in which growing microtubules can reach chromosomes, and $N$ is the number of pairs of the centrosome and kinetochores, between which there have been kinetochore microtubules. When we use $k_n=2$ and $k_l=0.015$, the self-assembly of a bipolar spindle and the density of microtubules from one pole are shown in Figure S2. Polar microtubules have a higher density than astral microtubules. In the meanwhile, the peaks appear at the kinetochores due to the formation of microtubule bundling.

1.2 Microtubules interact with chromosomes

Since the diameter of chromosome arms is around $1\mu m$ [20], only a fraction of microtubules can be blocked by the chromosomes, and most of microtubules can bypass the chromosomes. Microtubules blocked by the chromosome or close to the chromosome can be bound by the chromokinesin on arms [4, 26] or the kinetochore. Considering these factors, we assume all microtubules cannot be blocked by the chromosomes in our 2D model, but the microtubules across the chromosome can be bound by the chromokinesin at a rate of $k_{b,c}$ or the kinetochore at a rate of $k_{b,k}$ (Inset 4 of Figure S1).

The force generated by the chromokinesin on the microtubule is also velocity-dependent [4] as $f_{b,c}^+ = f_0^+ (1 - v^+/v_0^+)$, where $f_0^+$ and $v_0^+$ are the stall force and the unloaded velocity of kinesin; $v^+$ is the walking velocity of the motor, i.e., the component in the microtubule direction of the relative velocity between the centrosome and the chromosome. It should be also noted that the velocity is positive when the microtubule is elongating, while it is negative when the microtubule is shortening. In addition, since the microtubules bound by the chromokinesin are also applied a pushing force, the microtubules can also be buckled when the force is larger than the Euler buckling force. Therefore, the pushing force generated by the chromokinesin is given as

$$f_e^+ = \min \left[ f_0^+ \left( 1 - \frac{v^+}{v_0^+} \right), \pi^2 \kappa / L^2 \right].$$

Here $L$ is not the total length of the microtubule, but the length between the centrosome and the binding site.

The binding chromokinesin can unbind from the microtubule as well. The unbinding rate is also load-dependent [4] as

$$k_{u,c}^+ = k_0^+ e^{f_u^+/f_0^+},$$

where $f_u^+$ is a characteristic force representing the sensitivity of the unbinding rate to the load, and $k_0^+$ is the unloaded unbinding rate of kinesin.
Figure S1: The computational model for the mitotic spindle. Microtubules can be nucleated either from the centrosome, or near the chromosomes, or from existing microtubules as branches in the spindle region. Considering the microtubules nucleated near the chromosomes are converged to the spindle pole by minus end-directed motor proteins [10], and the branching microtubules have the same polarity as their mother microtubules [24], we assume all microtubules are nucleated from the centrosomes for simplicity (Inset 1). Microtubules can form bundles at the kinetochore through the mechanism that the minus-end-directed molecular motor kinesin-14 cooperates with the plus-end tracker EB1 to guide the growing plus end along existing microtubules [21] (Inset 2). Through polymerization or depolymerization of microtubules or various molecular motors, the cell cortex (Inset 3), chromosomes (Inset 4), antiparallel microtubules (Inset 5), or cytoplasm (Inset 6) can generate pushing forces or pulling forces on microtubules. Black arrows indicate the directions of forces on the microtubule. These forces can drive the movements of centrosomes and chromosomes.

We define the central region of the chromosome (~0.2 of the chromosome length) as the kinetochore region. The microtubules encountering the kinetochores can attach to the kinetochores, and generate pulling forces due to the depolymerization of microtubules [1] (Inset 4 of Figure S1). The pulling force is both microtubule length-dependent [11] and velocity-dependent [5]. Therefore, we assume the pulling force is

\[ f_k^- = l f_{k,0} \left( 1 - \frac{v^-}{v_0} \right), \]  

where \( l \) is the length of the microtubule; \( f_{k,0} \) is the force per length of the microtubule; and \( v^- \) equals the component in the microtubule direction of the relative velocity between the centrosome and the chromosome. The velocity is negative when...
the microtubule is elongating, while it is positive when the microtubule is shortening. Similarly, the binding of kinetochore can also unbind at a rate of \( k_{u,k} \), which is load-dependent [4, 14, 18] as Eq. 4. After unbinding, the microtubule become depolymerization state.

### 1.3 Molecular motors cross-link antiparallel microtubules

Some molecular motors, such as kinesin-5, Ncd and dynein, can serve as cross-linkers to link a pair of antiparallel microtubules, and generate interactional forces on the microtubules (Inset 5 in Figure S1) [17, 18, 25]. We consider both dynein and kinesin here, and they can generate pulling force and pushing force, respectively. The two crossing microtubules from different centrosomes can be bound by dynein or kinesin at the rates of \( k_{b,r} \) and \( k_{b,l} \), respectively. The forces generated by motors are also velocity-dependent as Eqs. 3 and S1. Therefore, we need to get the velocity of the motor bound on the \( p^{th} \) microtubule from \( j^{th} \) centrosome and the \( q^{th} \) microtubule from \( j^{th} \) centrosome. Based on the theorem of velocity composition of a particle, the absolute velocity of the motor is

\[
\mathbf{V}_i + \phi_p L_p r_p^* + v_p r_p = \mathbf{V}_j + \phi_q L_q r_q^* + v_q r_q. \tag{S4}
\]

Here, the left and right are the absolute velocity of the motor computed by \( p^{th} \) and \( q^{th} \) microtubule, respectively. The first two items represent the transport velocity of the motor; \( \mathbf{V}_i \) and \( \mathbf{V}_j \) are the velocity vectors of the centrosomes; \( \phi_p \) and \( \phi_q \) are the angular velocities of the microtubules; \( L_p \) and \( L_q \) are the lengths of the microtubules from the centrosome to the linked point; and \( r_p^* \) and \( r_q^* \) are the unit normal vectors of the microtubules (rotating 90 degrees counterclockwise from the microtubule growing direction). In the third item, \( v_p \) and \( v_q \) are the relative velocity between the motor and the microtubules; and \( r_p \) and \( r_q \) are the unit vectors of the microtubule growing directions. The force on the motor can be decomposed into the microtubule direction and its normal direction as

\[
\mathbf{F}_{mo} = (f^+_p)_p \mathbf{r}_p + F_p r_p^* = (f^+_q)_q \mathbf{r}_q + F_q r_q^*, \tag{S5}
\]

Here, \( (f^±)_p = f^±_l \left(1 \pm v_p / v^0_p \right) \) and \( (f^±)_q = f^±_l \left(1 \pm v_q / v^0_q \right) \) are the forces generated by the motor walking along the microtubules, where the plus sign represents kinesin and minus sign represents dynein. \( F_p \) and \( F_q \) are the forces in the normal direction, which can drive the rotary movement of the microtubules. Thus, they equal the drag force, \( F_p = \phi_p \xi l_p L_p \) and \( F_q = \phi_q \xi l_q L_q \), where \( \phi_p \) and \( \phi_q \) are the angular velocities of the microtubules; \( \xi \) is the rotary resistance coefficient of the microtubule with unit length; \( l_p \) and \( l_q \) are the total lengths of the microtubules; \( L_p \) or \( L_q \) are the microtubule lengths between the force-application point and the centrosomes.

Therefore, we can solve the four equations (Eqs. S4 and S5 can be decomposed into \( x \)- and \( y \)-directions) to obtain four unknowns, \( \phi_p, \phi_q, v_p \) and \( v_q \). The motor forces along the microtubules can be obtained based on the motor velocity \( v_p \) and \( v_q \). The cross-linked microtubules can change their direction at the angular velocity \( \phi_p \). It also should be noted that if the pushing force generated by kinesin is larger than the Euler buckling force, the microtubule is also buckled and the force equals the buckling force. The length used in the Euler buckling formula is the length of the microtubule from the centrosome to the linked point (\( L_p \) or \( L_q \)). In addition, the cross-linker can also unbind from the microtubules at the load-dependent rates (Eqs. 4 and S2).
1.4 Anti-overlapping force

The centrosomes and chromosomes cannot overlap with each other, and also cannot penetrate the cell cortex. To avoid the overlap or penetration, we define the short-range repulsive force between any two objects (centrosomes, chromosomes or the cell cortex) as

\[ F_v = \begin{cases} 200/d - 200, & d \leq 1\mu m, \\ 0, & d > 1\mu m. \end{cases} \quad (S6) \]

Here \( d \) is the least distance between the two objects, including the centrosomes, chromosomes and the cell cortex.

Besides, since the microtubules are very thin, they can provide axial forces, but transverse forces are negligible. The number of microtubules is large, and thus the complexity of computation will be largely increased if the deformation of microtubules is considered. Therefore, we ignore the colliding between microtubules, and the elastic deformation of microtubules except the bulking. We only consider the state, direction and length of each microtubule, instead of the detailed shape.

1.5 Motions of centrosomes and chromosomes

Now we have various forces on the microtubules (Figure S1). All of microtubules can transfer their axial forces to the centrosome. Therefore, we can give the force balance equation of one centrosome as

\[ \sum f^\pm + \sum f^+_c + \sum f^-_k + \sum f^+_r + \sum F_v + \zeta_p V = 0. \quad (S7) \]

Here, the first four items represent the forces generated by microtubules nucleated from this centrosome; the fifth item represents the anti-overlapping forces generated by all other centrosomes, all chromosomes and the cortex; the sixth item represents the viscous drag on the centrosome generated by the cytoplasm, where \( \zeta_p \) is the viscous drag coefficient and \( V \) is the velocity of the centrosome. It should be noted that we have neglected the inertial forces due to the low Reynolds number of this system.

We assume a chromosome is a rigid rod, and its central region is the kinetochore (Figure S1). Microtubules attaching the chromosomes can apply forces on the chromosomes. Similarly, the force balance equations of one chromosome are given as

\[ \sum f^+_c + \sum f^-_c + \sum F_v + \zeta_c V_c = 0, \quad (S8) \]

\[ \sum f^+_c \times r_b + \sum f^-_c \times r_b + \zeta_c \dot{\Theta} = 0. \quad (S9) \]

Here \( r_b \) is the vector pointing from the chromosome center to the binding site; \( V_c \) is the centroid velocity of the chromosome; and \( \Theta \) is the direction angle of the chromosome. For simplicity, we define the circumcircle of chromosome as its boundary here to compute the minimal distance of the anti-overlapping force, thus the anti-overlapping forces have no torque applied on the chromosome.

1.6 The cell shape polarity and the tricellular junction polarity

The polarity direction and anisotropy of the cell shape and tricellular junctions are obtained based on the same method in Ref. [2]. Specifically, the inertia matrix of the cell shape is constructed as

\[ S_{sh} = \frac{1}{n_{sh}} \sum_{i=1}^{n_{sh}} r_i \otimes r_i. \quad (S10) \]

Here, the cell outline is discretized by pixels, \( n_{sh} \) is the number of the pixels, and \( r_i \) is the vector pointing from the barycentre of the cell to each pixel. The anisotropy of the cell shape can be defined as

\[ \eta_{sh} = 1 - \lambda_1 / \lambda_2, \quad (S11) \]

where \( \lambda_1 \) and \( \lambda_2 \) are the eigenvalues of \( S_{sh} \) (\( 0 < \lambda_1 < \lambda_2 \)). The eigenvector corresponding to the eigenvalue \( \lambda_2 \) is the direction of the cell shape polarity, and then the direction angle \( \theta_{shape} \) can be obtained. Similarly, the direction and anisotropy of tricellular junctions can also be obtained by their inertia matrix

\[ S_{tcj} = \frac{1}{n_{tcj}} \sum_{j=1}^{n_{tcj}} u_j \otimes u_j. \quad (S12) \]
**Figure S3:** The simulation method and the state switching of microtubules. (A) The program flow chart of the simulation. (B) The microtubule states considered in the simulation. (C) The switches of microtubule states in the simulation.

Here, $n_{tCj}$ is the number of the tricellular junctions, and $u_j$ is the unit vectors pointing from the barycentre of the cell to each tricellular junction. The anisotropy of the tricellular junctions can also be defined by the eigenvalues of $S_{tCj}$ as

$$\eta_{tCj} = 1 - \frac{\lambda_1^{tCj}}{\lambda_2^{tCj}},$$

where $0 < \lambda_1^{tCj} < \lambda_2^{tCj}$. The polarity direction ($\theta_{T,C,j}$) of the tricellular junctions can also be obtained from the eigenvector corresponding to $\lambda_2^{tCj}$.

### 1.7 Simulation step and method

Monte Carlo simulation is performed in MATLAB to simulate the motion and formation of mitotic spindles (Figure S3A). Initially, the positions of centrosomes and chromosomes are randomly given in the cell. The initial number of the microtubules on each centrosome is 50, and these microtubules are evenly distributed in all directions. During each step, a certain number of new microtubules are generated according to the nucleation rate in a step ($k_0^t / \Delta t$). If the nucleation rate in a step is not an integer, a random number in $(0, 1)$ uniformly is generated, and compared with its decimal part. If the random number is less than the decimal part, the nucleation number equals the nucleation rate rounded up, otherwise, the nucleation number equals the nucleation rate rounded down. For each microtubule, we record its state (as shown in Fig S3B), length and direction. We change all microtubule states based on given method (Figure S3C), subsequently change the lengths and directions of all microtubules, delete the completely shrinking microtubules, and compute the resultant force and instantaneous velocity of each centrosome and chromosome (Eqs. S7~S9). Finally, we change the positions of all centrosomes and chromosomes according to their velocities by $p_{t+\Delta t} = p_t + v \Delta t$. The system is iteratively solved.

All microtubule states in the simulations are shown in Figure S3B, and their switches are shown in Figure S3C. A new microtubule is growing freely (1-1), its length increases at the growing speed $v_1$, and its direction keeps unchanged. The freely growing microtubule (1-1) can reach the cortex (3-1), or switch to freely shrinking state (2-1) through catastrophe...
(\(k_2\)). The freely shrinking microtubule (2-1) decreases its length at the shrinking speed \(v_2\), and also keeps its direction. The freely shrinking microtubule (2-1) can also switch to freely growing state (1-1) through rescue (\(k_1\)), or completely depolymerize (delete). The microtubule blocked by the cortex does not change its length and direction, and can switch to freely shrinking state (2-1) through catastrophe (\(k_2^*\)). All free microtubules (1-1,2-1,3-1) can be bound by chromokinesin (\(k_{b,a}\)) or kinetochore (\(k_{b,k}\)) if they cross with one of chromosomes, or be bound by the cross-linker (\(k_{b,r}\)) if they cross with other microtubules nucleated from the other centrosome. Accordingly, when the microtubule is bound by the chromosome or cross-linker [(1,2,3)-(3,4,5)], it changes their length as growing or shrinking as usual, but adapts its direction to keep the binding site fixed. When the microtubule is bound by cortical dynein or kinetochore [4-(2,6)], it adapts its length and direction to keep the end fixed. Microtubules can recover free if the motor unbinds (\(k_{u,a}\), \(k_{u,k}\), \(k_{u,r}\), or \(k_{-u}\)) or the microtubule shrinks its length to leave the crossing site. It should be noted that we assume each microtubule can only be bound by one molecular motor for simplicity, because the force will be very complex if the microtubule is simultaneously bound by more than one of chromokinesins, kinetochores, cross-linkers and cortical dyneins. Four switches, including catastrophe, rescue, binding and unbinding, are random events (colorful arrows in Figure S3C), while the reaching is a deterministic event (black arrows in Figure S3C). Each random event has its rate (collectively denoted as \(k\) for the moment). To determine if the random event occurs in the time step, a random \(\delta\) in (0, 1) uniformly is generated for each event. If \(\delta \leq 1 - e^{-k\Delta t}\), the event occurs in the step, otherwise, it does not occur [18]. The parameters used in the simulations are summarized in Table S1 unless otherwise indicated.
### Table S1: Parameters used in the simulations.

| Parameter | Description |
|-----------|-------------|
| **Geometric parameters** |  |
| $R_{cell} = 20\mu m$ | Diameter of the cell. |
| $\lambda = 1 \sim 2$ | The aspect ratio of the cell. It is defined as the ratio of the long axis to the short axis. |
| $L_{ch} = 2.5\mu m$ | Length of the chromosome. |
| $L_{kin} = 0.5\mu m$ | Size of the kinetochore. |
| **Microtubule dynamics** |  |
| $v_i = 0.12\mu m/s$ | Free polymerization rate (growing velocity) of microtubules [9, 10, 13, 27, 31]. |
| $v_o = 0.2\mu m/s$ | Free depolymerization rate (shrinking velocity) of microtubules [9, 10, 13, 27, 31]. |
| $k_1 = 0.04s^{-1}$ | Rescue rate of microtubules (from shrinking to growing) [9, 10, 27, 31]. |
| $k_2 = 0.02s^{-1}$ | Catastrophe rate of microtubules (from growing to shrinking) [9, 10, 27, 31]. |
| $k_3 = 0.03s^{-1}$ | Catastrophe rate of microtubules stopped by the cell cortex [14]. |
| $k_4 = 3s^{-1}$ | Nucleation rate of microtubules from one centrosome [15, 16, 23, 31]. |
| $k_5 = 2$ | Additional nucleation rate coefficient of microtubules from one centrosome to all chromosomes [18]. |
| $k_6 = 0.015$ | Additional nucleation rate of bundle microtubules. Estimation. |
| $\kappa = 53.12pN\mu m^2$ | Bending rigidity of microtubules [8]. |
| $f_{stall} = 10pN$ | Stall force of microtubule polymerization [6, 23]. |
| $f_{k,0} = 1pN/\mu m$ | Depolymerization force of unit length microtubule at the kinetochore [1, 5, 11]. |
| $\xi = 100pN/\mu m^2$ | Friction coefficient of microtubule rotation [16, 23]. |
| **Molecular motor dynamics** |  |
| $k_{b,c} = 0.005s^{-1}$ | Binding rate of cortical dyneins [3, 16, 31]. |
| $k_{b,c} = 0.05s^{-1}$ | Binding rate of chromokinesins [4, 5, 29]. |
| $k_{b,k} = 0.08s^{-1}$ | Binding rate of kinesins [4, 5, 29]. |
| $k_{b,r} = 0.05s^{-1}$ | Binding rate of kinesins as cross-linkers [19, 22]. |
| $k_n = 0.01s^{-1}$ | Binding rate of dyneins as cross-linkers [19, 22]. |
| $k_{b,a} = 0.08s^{-1}$ | Binding rate of dyneins at tricellular junctions [2]. |
| $f_{c} = 5pN$ | Stall force of kinesins [7, 28]. |
| $f_{d} = 5pN$ | Stall force of dyneins [10, 28]. |
| $v_{c} = 0.2\mu m/s$ | Unloaded velocity of kinesins [7, 28]. |
| $v_{d} = 0.2\mu m/s$ | Unloaded velocity of dyneins [10, 28]. |
| $f_{b,c} = 0.01s^{-1}$ | Unloaded unbinding rate of kinesins [4, 5, 29]. |
| $f_{b,k} = 0.02s^{-1}$ | Unloaded unbinding rate of dyneins [3, 16, 31]. |
| $f_{b,a} = 0.005s^{-1}$ | Unloaded unbinding rate of kinetochore [1, 5]. |
| $f_{c} = 20pN$ | Characteristic force represents the sensitivity of the unbinding rate of kinesins to the load [4, 19]. |
| $f_{d} = 20pN$ | Characteristic force represents the sensitivity of the unbinding rate of dyneins or kinetochores to the load [16, 19]. |
| $\mu = 0.01pN/\mu m$ | Cytoplasmic pulling force per unit microtubule length. Estimated in Ref. [18]. |
| **Centrosome and chromosome dynamics** |  |
| $\xi_c = 10pN/\mu m$ | Viscous drag coefficient of centrosome. Estimated in Ref. [18]. |
| $\xi = 30pN/\mu m$ | Translational viscous drag coefficient of chromosome. Estimated in Ref. [18]. |
| $\zeta_c = 1255.5pN/\mu m$ | Rotational viscous drag coefficient of chromosome. Estimated in Ref. [18]. |

## 2 Supplemental Results and Discussion

In the main text, we investigated the competition between cell shape and intercellular adhesion (bilateral and unilateral) determines spindle orientation in the side view. We also mentioned another cell shape, ellipse, observed when the tissue was stretched [30]. Although the elliptical shape seems impossible to appear in the two cases above, we also perform simulations in the elliptical cells as a discussion on the influence of cell shape. Firstly, we assume the elliptical cell adheres to neighbouring cells in the tissue as Figure 3 (i.e., bilateral adhesion), and find the results are totally similar to the stadium shape (Figure S10). However, under the same condition, the critical aspect ratio in elliptical cells is larger (Figure S13), which indicates the ellipse shape can ensure more planar division than the stadium shape. This is probably because the two poles of the elliptical short axis are curving outward, and thus have a smaller repulsion on the spindle than the straight lines of the stadium shape.

Secondly, we also assume the elliptical cell has the unilateral adhesion, i.e., adheres to the E-cadherin-coated matrix as Figures 4 and 5. The results are also totally similar to the stadium shape, but the phenomenon of double platforms cannot be observed apparently (Figures S11 and S12). The reason may be that the larger curvature at two poles of the elliptical long axis can limit the spindle orientation more strongly. Therefore, the spindle is little slanted in the same cases. Taken together, the elliptical shape has a greater influence on the spindle orientation than the stadium shape, and the influence of unilateral adhesion is total weaker than the bilateral adhesion in all cases (Figure S13).
In addition, in the case of unilateral adhesion, the adhesive length was considered increasing with the compression. We also consider this in the case of bilateral adhesion, and find the results are similar to the fixed adhesive length in both cell shapes (Figure S11). Compared to the cases of fixed adhesive length of 12µm, the critical aspect ratio is larger in the stadium cell with varying adhesive length, but is smaller in the elliptical cell with varying adhesive length (Figure S13). This is obviously because the stadium cell has a larger contact length with the substrate than the elliptical cell under the current assumption of the adhesion condition.

Supporting References

1. Banigan EJ, Chiou KK, Ballister ER, Mayo AM, Lampson MA, Liu AJ (2015). Minimal model for collective kinetochore–microtubule dynamics. Proceedings of the National Academy of Sciences 112(41), 12699–12704.
2. Bosveld F, Markova O, Guirao B, Martin C, Wang Z, Pierre A, Balakireva M, Gaugue I, Ainslie A, Christophorou N, et al. (2016). Epithelial tricellular junctions act as interphase cell shape sensors to orient mitosis. Nature 530(7591), 495–498.
3. Burakov A, Nadezhina E, Slepenko B, Rodionov V (2003). Centrosome positioning in interphase cells. The Journal of cell biology 162(6), 963–969.
4. Campas O, Sens P (2006). Chromosome oscillations in mitosis. Physical review letters 97(12), 128102.
5. Civelekoglu-Scholey G, Sharp D, Mogilner A, Scholey J (2006). Model of chromosome motility in drosophila embryos: adaptation of a general mechanism for rapid mitosis. Biophysical journal 90(11), 3966–3982.
6. Dogterom M, Yurke B (1997). Measurement of the force-velocity relation for growing microtubules. Science 278(5339), 856–860.
7. Gao T, Blackwell R, Glaser MA, Betterton M, Shelley MJ (2015). Multiscale polar theory of microtubule and motor-protein assemblies. Physical review letters 114(4), 048101.
8. Gittes F, Mickey B, Nettleton J, Howard J (1993). Flexural rigidity of microtubules and actin filaments measured from thermal fluctuations in shape. Journal of cell biology 120, 923–923.
9. Gombos L, Neuner A, Berynskyy M, Fava LL, Wade RC, Sachse C, Schiebel E (2013). Gip regulates the microtubule nucleation activity of γ-tubulin. Nature cell biology 15(11), 1317–1327.
10. Goshima G, Nédélec F, Vale RD (2005). Mechanisms for focusing mitotic spindle poles by minus end–directed motor proteins. J Cell Biol 171(2), 229–240.
11. Hays TS, Wise D, Salmon E (1982). Traction force on a kinetochore at metaphase acts as a linear function of kinetochore fiber length. The Journal of Cell Biology 93(2), 374–382.
12. Howard J, Garzon-Coral C (2017). Physical limits on the precision of mitotic spindle positioning by microtubule pushing forces: mechanics of mitotic spindle positioning. BioEssays 39(11), 1700122.
13. Inoué S, Salmon ED (1995). Force generation by microtubule assembly/disassembly in mitosis and related movements. Molecular Biology of the Cell 6(12), 1619–1640.
14. Jiang H (2015). Cell size modulates oscillation, positioning and length of mitotic spindles. Scientific reports 5.
15. Kozlowski C, Srayko M, Nedelec F (2007). Cortical microtubule contacts position the spindle in c. elegans embryos. Cell 129(3), 499–510.
16. Laan L, Pavin N, Husson J, Romet-Lemonne G, Van Duijn M, López MP, Vale RD, Jülicher F, Reck-Peterson SL, Dogterom M (2012). Cortical dynein controls microtubule dynamics to generate pulling forces that position microtubule asters. Cell 148(3), 502–514.
17. Lancaster OM, Le Berre M, Dimitracopoulos A, Bonazzi D, Zlotek-Zlotkiewicz E, Picone R, Duke T, Piel M, Baum B (2013). Mitotic rounding alters cell geometry to ensure efficient bipolar spindle formation. Developmental cell 25(3), 270–283.
18. Li J, Jiang H (2017). Geometric asymmetry induces upper limit of mitotic spindle size. Biophysical journal 112(7), 1503–1516.
19. Loughlin R, Heald R, Nédélec F (2010). A computational model predicts xenopus meiotic spindle organization. The Journal of cell biology 191(7), 1239–1249.
20. Maciejowski J, Li Y, Bosco N, Campbell PJ, de Lange T (2015). Chromothripsis and kataegis induced by telomere crisis. Cell 163(7), 1641–1654.
21. Molodtsov MI, Mieck C, Dobbellaere J, Dammermann A, Westermann S, Vaziri A (2016). A force-induced directional switch of a molecular motor enables parallel microtubule bundle formation. Cell 167(2), 539–552.
22. Nédélec F (2002). Computer simulations reveal motor properties generating stable antiparallel microtubule interactions. The Journal of cell biology 158(6), 1005–1015.
23. Pavin N, Laan L, Ma R, Dogterom M, Jülicher F (2012). Positioning of microtubule organizer centers by cortical pushing and pulling forces. New Journal of Physics 14(10), 105025.
24. Quintyne NJ, Reing JE, Hoffelder DR, Gollin SM, Saunders WS (2005). Spindle multipolarity is prevented by centrosomal clustering. Science 307(5706), 127–129.
25. Tokai-Nishizumi N, Ohsumi Y, Suzuki E, Yamamoto T (2005). The chromokinesin kid is required for maintenance of proper metaphase spindle size. Molecular biology of the cell 16(11), 5455–5463.
26. Verde F, Dogterom M, Stelzer E, Karsenti E, Leibler S (1992). Control of microtubule dynamics and length by cyclin a-and cyclin
b-dependent kinases in Xenopus egg extracts. The Journal of Cell Biology 118(5), 1097–1108.

28. Wang Z, Khan S, Sheetz MP (1995). Single cytoplasmic dynein molecule movements: characterization and comparison with kinesin. Biophysical Journal 69(5), 2011–2023.

29. Wollman R, Cytrynbaum E, Jones J, Meyer T, Scholey JM, Mogilner A (2005). Efficient chromosome capture requires a bias in the search-and-capture process during mitotic-spindle assembly. Current Biology 15(9), 828–832.

30. Wyatt TP, Harris AR, Lam M, Cheng Q, Bellis J, Dimitracopoulos A, Kabla AJ, Charras GT, Baum B (2015). Emergence of homeostatic epithelial packing and stress dissipation through divisions oriented along the long cell axis. Proceedings of the National Academy of Sciences 112(18), 5726–5731.

31. Zhu J, Burakov A, Rodionov V, Mogilner A (2010). Finding the cell center by a balance of dynein and myosin pulling and microtubule pushing: a computational study. Molecular biology of the cell 21(24), 4418–4427.
Figure S4: Self-assembly, positioning, and orientation of the mitotic spindle with three chromosomes and two centrosomes in the round cell. (A) Screenshots of the simulation (see also Movie S1). The diameter of the cell is 20 µm. Initially, the centrosomes and chromosomes are randomly located inside the cell. Scale bar: 5 µm. (B) The schematic diagram illustrates the indicators of the spindle position $d_s$, spindle orientation $\alpha_s$, spindle length $L_s$. 10 simulations with different initial conditions show the time evolution of the (C) spindle position, (D) spindle length, and (E) spindle orientation.
Figure S5: Self-assembly, positioning, and orientation of the mitotic spindle with three chromosomes and two centrosomes in the stadium cell. (A) Screenshots of the simulation (see also Movie S2). The cell area is the same as the round cell with the diameter of 20µm, but the aspect ratio is λ=1.5. Initially, the centrosomes and chromosomes are randomly located inside the cell. Scale bar: 5µm. 10 simulations with different initial conditions show the time evolution of the (B) spindle position, (C) spindle length, (D) spindle orientation, (E) x-coordinate of the chromosomes, and (F) Chromosome orientation.
Figure S6: Self-assembly, positioning, and orientation of the mitotic spindle with three chromosomes and two centrosomes in the elliptical cell. (A) Screenshots of the simulation (see also Movie S2). The cell area is the same as the round cell with the diameter of 20µm, but the aspect ratio is λ=1.5. Initially, the centrosomes and chromosomes are randomly located inside the cell. Scale bar: 5µm. 10 simulations with different initial conditions show the time evolution of the (B) spindle position, (C) spindle length, (D) spindle orientation, (E) x-coordinate of the chromosomes, and (F) Chromosome orientation.
Figure S7: Self-assembly, positioning, and orientation of the mitotic spindle with three chromosomes and two centrosomes in the adhesive round cell. (A) Screenshots of the simulation. The cell diameter is 20 μm. The red region indicates the intercellular adhesion. The adhesive length is $L = 12 \mu m$, and the binding rate of cortical dynein at the adhesive region is $k = 11$ times higher than the other region. Initially, the centrosomes and chromosomes are randomly located inside the cell. Scale bar: 5 μm. 10 simulations with different initial conditions show the time evolution of the (B) spindle position, (C) spindle length, (D) spindle orientation, (E) y-coordinate of the chromosomes, and (F) Chromosome orientation.

Figure S8: Influences of (A) unbinding rate of cortical dynein and (B) spindle length (binding rate of cross-linking kinesin) on spindle orientation.
Figure S9: Asymmetric intercellular adhesion versus cell shape regulates the spindle orientation. (A) schematic shows the adhesive region is asymmetric to the short axis of the cell. (B) The spindle orientation is plotted against the aspect ratio of the cell shape with different adhesive strengths ($L=12\mu m$). (C) The spindle orientation is plotted against the aspect ratio of the cell shape with different adhesive lengths ($k=11$).

Figure S10: Regulating the spindle orientation via the elliptical cell shape and the bilateral intercellular adhesion. (A) The schematic shows the cell shape and intercellular adhesion of a dividing epithelial cell in the 2D simulation. The cell is regarded as the elliptical shape, and the red segments represent the intercellular adhesion. (B) The snapshots of simulated spindles in the cells with different aspect ratios but the same adhesive length and strength ($L=12\mu m, k=11$). Scale bar: $5\mu m$. (C) The spindle orientation is plotted against the aspect ratio of the cell shape with different adhesive strengths. (D) The spindle orientation is plotted against the aspect ratio of the cell shape with different adhesive lengths. (E) The critical aspect ratios $\lambda_T$ obtained by fitting are the functions of the adhesive strength and length.
Figure S11: Role of the adhesive strength in governing the spindle orientation in elliptical or stadium cell with unilateral or bilateral adhesion. The spindle orientations are plotted against the aspect ratio of cell shape with different adhesive strengths. Besides those cases which have been shown in Figures 3-5, we show all the other cases here, including (A) the stadium cell with bilateral adhesion of varying adhesive length, (B) the elliptical cell with bilateral adhesion of varying adhesive length, (C) the stadium cell with unilateral adhesion of fixed adhesive length 12µm, and (D) the elliptical cell with unilateral adhesion of varying adhesive length.
Figure S12: Regulating the spindle orientation via cell compression versus unilateral intercellular adhesion in elliptical cells with fixed adhesive length. (A) The schematic shows the cell shape after compression and the substrate coated by E-cadherin with given length. Scale bar: 5 µm. (B) The snapshots of the simulated spindles in the cells with different aspect ratios and adhesive lengths, but the same adhesive strength ($k=11$). (C) The spindle orientation is plotted as the function of the aspect ratio of the cell shape with different adhesive strengths. (D) The spindle orientation is plotted as the function of the aspect ratio of the cell shape with different adhesive lengths. (E) The curves of spindle orientation versus cell aspect ratio can also be fitted by using Eq. 1, and then the critical aspect ratios $\lambda_T$ can be obtained, and are the functions of adhesive length and strength. When the adhesion length is large, the spindle always parallels to the substrate independent of the cell shape (indicated by white).

Figure S13: Regulating the spindle orientation via various cell shapes and adhesion geometries. The cells of stadium shape (S) or elliptical shape (E) adhere to neighboring cells in the tissue (bilateral adhesion, B) or to E-cadherin-coated matrix under compression (unilateral adhesion, U). The adhesive length is fixed (F), or varying with the elongation of the cell (V). In each case, the spindle orientation is plotted against the cell aspect ratio. To compare them, we give the adhesive strength in all cases as $k=11$ and the adhesive length in the fixed cases as $L=12\mu m$. 
Figure S14: Regulating the spindle orientation via cell shape and tricellular junctions in stadium cells. (A) The schematic shows the metaphase cell shape and the tricellular junctions similar to Figure 7A in the main text, but the cell shape is assumed as the stadium shape. (B) The snapshots of the simulated spindles in the cells with different aspect ratios ($f=5\,\text{pN}$, $\theta=15^\circ$). Scale bar: 5$\mu$m. (C) The spindle orientation is plotted against the aspect ratio of the cell shape with different anisotropy of the tricellular junctions. (D) The spindle orientation is plotted against the aspect ratio of the cell shape with different forces generated at the tricellular junctions. The pulling force is changed with the stall force $f$ of the dynein at the tricellular junctions. (E) The critical aspect ratios $\lambda_T$ obtained by fitting (Eq. 1) are the functions of the anisotropy and the pulling force at the tricellular junctions.