# Modeling the assembly and stability of the mitotic spindle using a modified XY model

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The mitotic spindle consists of thousands of microtubules that attach themselves to the chromosomes in a specific configuration that allows them to separate the chromosomes into daughter cells during mitosis. Assembly of the spindle involves the dynamic action of many cellular components. However, the molecular details of these processes are difficult to model due to their number, complexity and potential specificity. For this reason, we would like a toy model to explore what coarse-grained "ingredients" are necessary for self-assembly of spindle-like structures. Here, we describe the results of a simulation describing basic spindle self-assembly in a two-dimensional system using a modified XY model. We find that using certain parameters, spindle-like configurations become stable using this model, though disordered initial configurations may not stabilize to these spindle-like configurations on physical timescales using random perturbations alone. We conclude that considering specific molecular mechanisms as effective energy "potentials" can give insight into what forces are necessary for obtaining and maintaining a spindle configuration, though these considerations may not alone be adequate for modeling the dynamics of how the spindle assembles.

## 1. INTRODUCTION

The mitotic spindle is a structure that forms during the early stages of cell division, and is primarily responsible for the even distribution of genetic material into daughter cells during mitosis. It consists of short, thin structural elements, microtubules, which align and extend as fibers through the cell. These microtubules bond to chromosomes at the center of the cell along its midplane. When all of the chromosomes are bound to microbutules, structures at the poles of the cells pull the microtubule fibers inward, splitting the paired chromosomes.

Current knowledge about the assembly of the mitotic spindle indicates that its mechanism involves complex interactions among signaling proteins, microtubules, chromosomes, molecular motors, and, usually, *centrosomes*, regions at the poles that guide microtubule production ([1], [2], [3]). Moreover, dynamic instability of microtubules is thought to play a role in the spindle assembly ([4], [5]). Given the inherent complexity and degrees of freedom in a model involving all of the signaling proteins and molecular motors, we ask, what general "ingredients" and interactions are necessary in order to create and maintain a stable spindle-like structure? Answering such a question can help to categorize the various specific molecular mechanisms that are necessary for spindle assembly, and to understand their relative importances.

To this end, we do not consider specific molecular mechanisms, but instead probe the interactions that are necessary for a spindle-like structure by modeling the overall effect of interactions as energy terms that tend to align microtubules in a specific way and in specific locations. Since there are many microtubules in a given cell, and they are acting through interactions with each other and external energy terms, an XY model from statistical mechanics seems an appropriate place to start. We consider a highly simplified two-dimensional model, studying the conditions under which spindle-like structures are stable, and determining if they arise from suitably time-evolving random configurations.

The paper is organized as follows. We begin by describing the XY model and the simulation techniques used in Section 2, Methods. We then detail the results obtained from the simulation in Section 3, Data. Finally, we observe general patterns and insights in Section 4, Conclusions. In that section, we also suggest expansions and future work along these lines.

## 2. METHODS

The XY model is traditionally used to study weakly interacting spins distributed spatially in an external field. We write the Hamiltonian of each spin as

$$\epsilon_i = E_{\text{ext}} - \sum_{\text{neighbors } j \text{ of } i} w \cdot \cos\left(\theta_i - \theta_j\right), \qquad (1)$$

where $w$ is a weight for the pair terms, $\theta_i$ is the angle of the given spin, and external effects are lumped as $E_{\text{ext}}$. Considering microtubules as spins that tend to align suggests a natural extension of the XY model to a spindle-assembly system.

We model a two-dimensional system of microtubules and study the stability of ordered "spindle-like" ordered states, where "spindle-like states" have microtubules that align along the vertical axis and decrease in density with distance from the midplane $x = 0$. In this system, alignment is modeled as a nearest-neighbor interaction, while position-dependent energies are modeled as external energies. We take the external energy to impose a density decay with distance from the midplane.

The simulations were carried out on a $10x10$ grid containing 50 microtubules, each of which occupies one lattice point and is associated with a unit vector describing

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its angle. The allowable angles were $0, \pi/6, \ldots, 11\pi/6$. A Monte-Carlo simulation was employed, with samples generated using a Metropolis-Hastings algorithm ([6]) with symmetric proposal density. In particular, if the current state has energy $E_1$, a proposed state with energy $E_2$ was accepted if $E_2 < E_1$ or if

$$\alpha < e^{-\beta(E_2 - E_1)},$$

where $\alpha$ is a random variable uniformly distributed over $[0, 1]$ and $\beta = 1/(k_B T)$, with $k_B$ being Boltzmann's constant. At each timestep, a new proposed state was generated by randomly selecting one microtubule and changing its position and angle. At most one microtubule was allowed at each location.

Two initial states were studied: an ordered spindle-like state, and a randomly generated state. The first was used to test the stability of the spindle state, and the second was used to determine if the system thermalizes to a spindle state in a given number of steps. Each simulation was run with a burn-in of 1000 timesteps, and simulations were run for $10^4$ timesteps following the burn-in; however, as discussed later, it is not clear that this was sufficient to thermalize the systems of interest, though we can still make conclusions about the stability of the ordered states over this timescale. Energy units were chosen arbitrarily so that the pairing weight $w = 1$ and the strength of other interactions was determined by their weights and dependence on location; appropriate values of $\beta$ were thus chosen to examine a variety of temperature limits relative to the energies computed.

## 3. RESULTS

The Hamiltonian modeled here was as in equation 1, with

$$E_{\text{ext}} = w_2 \cdot |(y_i - y_m)|^k, \tag{2}$$

where $y_i$ is the $y$-coordinate of the microtubule in question, $y_m$ is the $y$-coordinate of the midplane, and different values of $w_2$ and $k$ were tested.

We first checked that a highly ordered spindle-like configuration remained essentially stable for a variety of temperatures and exponents $k$ after $10^4$ timesteps and a 1000-timestep burn-in period. We note that at low temperatures, the spindle-like configuration is essentially stable, with microtubules pointing along the $y$-axis and density falling off from the midplane. However, as expected, at high temperatures the stability breaks down, and, also as expected, the stability depends strongly on the value of $k$ (higher values of $k$ lead to more stable spindle-like structures for higher temperatures).

We then started with random configurations to see if they would approach spindle-like configurations over the timescale studied. However, it seemed that although spindle-like configurations were stable with this energy scale, even under very extreme values of $w_1$ and $w_2$, the system did not assume a spindle-like configuration from a random configuration over this timescale. A typical result is shown in figure 6 where $w_1 = w_2 = 1000$, $k = 10$ and $k_B T = 1$, all extreme values, but the end configuration is not spindle-like or particularly ordered.

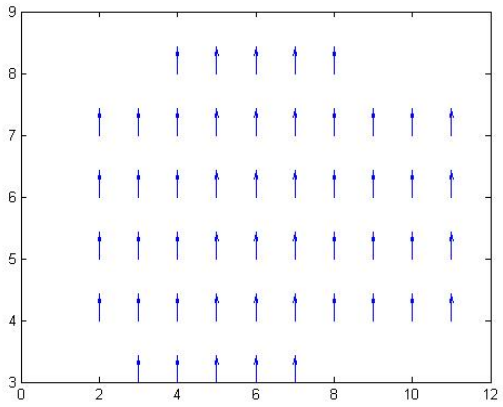

FIG. 1: Initial spindle-like configuration

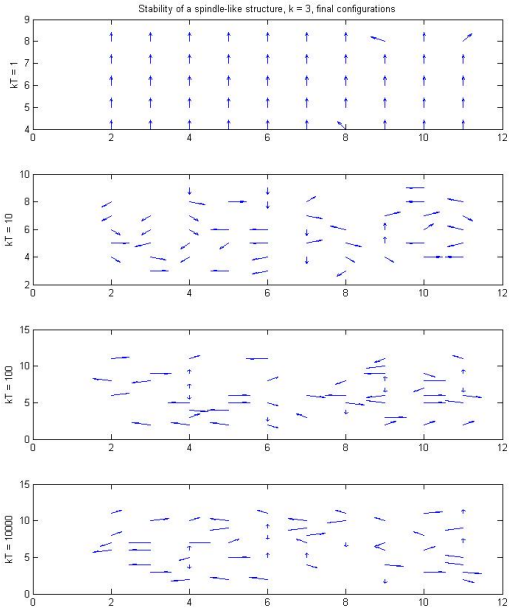


FIG. 2: End configurations for various temperatures after starting from a spindle-like configuration, $k = 3$

## 4. CONCLUSIONS

We conclude that in an XY model for spindle assembly taking into account nearest-neighbor interactions and density fall-off as one gets further from the mid-

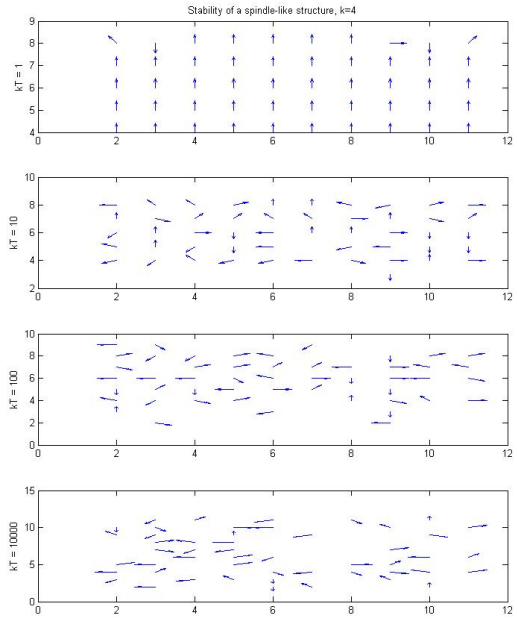


FIG. 3: End configurations for various temperatures after starting from a spindle-like configuration, $k = 4$

plane, simulations that began with spindle configurations tended to stay in spindle-like configurations for the timescale of interest for temperatures low enough, where the temperature at which spindle-like configurations break down depended strongly on the exponent that determined the density fall-off. However, random states did not tend to thermalize to spindle-like configurations, even under very strict initial parameters. These results indicate that the given XY model is not sufficient to adequately model assembly of the spindle, though it does capture its stability once the system has reached a spindle-like state. This result could indicate that in order to model the assembly of the spindle-like state, a different method of sampling may be needed; it would be interesting if a similar model with a method of sampling that more closely mimicked active cellular processes that are known to participate in the assembly of the spindle could produce spindle-like configurations from random configurations. There are many possible refinements to the simple model presented here. The most obvious one is to consider a model that includes centrosomes. It would be interesting to add spatially-dependent attractive points at either end of the cell, such that these points tend to cluster microtubules at either end to the center $x$-value. Moreover, such centrosomes could tend to align the microtubules along the $y$-axis in a spatially-dependent way. A model including centrosomes like this could give rise to more intricate spindle-like structures, and could give better insight into the process of spindle assembly. Would a model including centrosomes have the property that

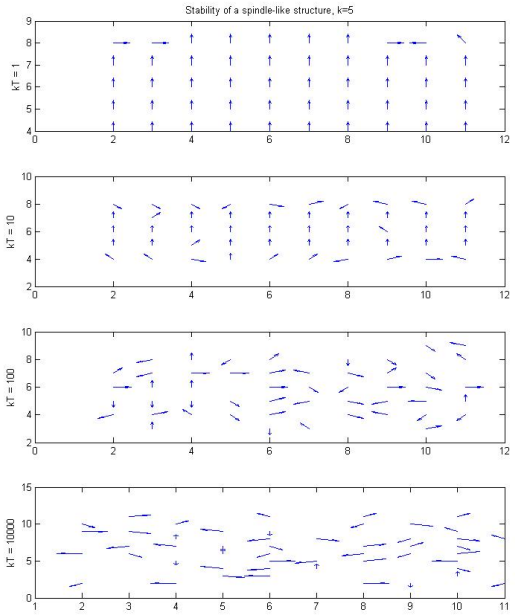


FIG. 4: End configurations for various temperatures after starting from a spindle-like configuration, $k = 5$

random initial conditions lead to spindle-like configurations on timescales like those considered here? There are many interesting questions to consider here, and the results of this simulation indicate that similar simulations along with this one could provide further insight into what kinds of interactions are necessary in order to obtain stability and self-assembly of microtubules into a spindle-like structure.

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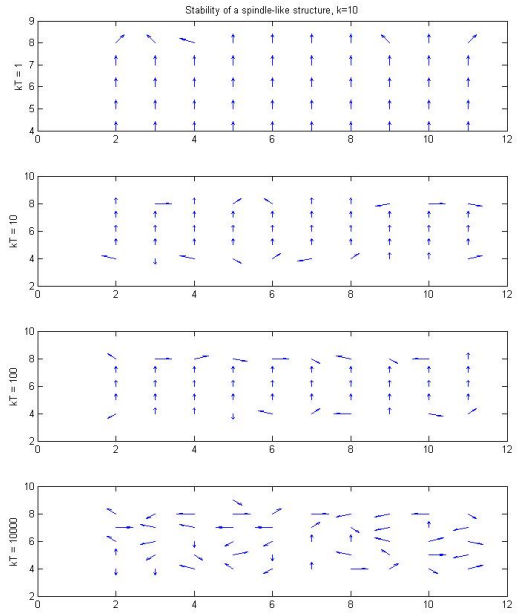


FIG. 5: End configurations for various temperatures after starting from a spindle-like configuration, $k = 10$

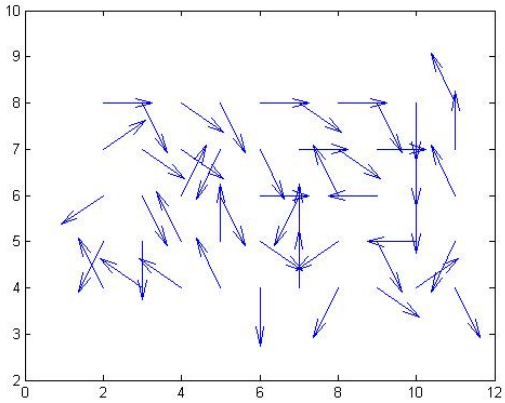

FIG. 6: An end configuration after beginning with a random state