A computational study of pattern formation in the mitotic spindle using the XY model

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Abstract

We describe here a computational study of pattern formation in the mitotic spindle using a minimalist approach. Our model is an adaptation of the well-known XY model in statistical physics, which we simulate using Langevin dynamics. The microtubule filaments are modeled as spins on a 2-D lattice such that nearest neighbors prefer to align mutually. A symmetry breaking field is introduced in the center of a cell to model the chromatin. The computational setup is validated in the limiting condition of a zero field XY model and its behavior under the presence of the field are described.

The spindle is an intricate molecular machine composed principally of short microtubules, which are polymers of the protein tubulin. The spindle self-organizes during cell division and is responsible for partitioning the chromosomes into daughter cells[1]. The self-organization is a highly non-equilibrium process, which is driven by the consumption of energy in the form of ATP. It combines the processes of growth of microtubule filaments and the transport of tubulin and motor proteins like dynein and myosin[2]. A host of other proteins and small molecules act as activators and inhibitors (e.g. taxol) of this process, and these in turn are regulated by signaling networks.

Over the years, a number of *in vitro*[3] and more recently, experiments employing Xenopus laevis egg extracts[4] have shed insight into the dynamics of spindle formation. A particular focus of these studies has been the spatial patterns of microtubules that are formed in the process of self-organization. Recent experimental studies of spindle organization by the Needleman group at Harvard have suggested that the spindle consists of thousands of short microtubules (cf. Fig 1). Neighboring microtubules tend to align with each other and chromosomes at the center of the cell favor orthogonal alignment of the microtubules. Inspired by these observations, this paper explores a computational study of the self-organization process using the simplest physical ingredients. In particular, we simulate an adaptation of the XY model, which has been extensively explored by statistical physicists[5]. Here, the microtubules are modeled as two component spins on a 2-D lattice. Neighboring spins are coupled ferromagnetically such that mutual alignment is favored.

While the tendency of neighboring microtubules to align is likely due to the action of motor proteins[7], we do not model this explicitly. Likewise, we also do not explicitly consider the growth of individual microtubules[2] and hence model them as unit length spins that can orient in any direction $\theta \in [0, 2\pi)$ on the 2-D plane. Such a system is said to have continuous symmetry. To adapt such a model to describe the self-organization of the mitotic spindle, we break this symmetry in certain local regions by preferential alignment of the microtubules caused by an external magnetic field, which mimics the induced polarization of microtubules that are proximal to the daughter chromatin strands.

Starting from random initial orientations of the spins (henceforth used interchangeably with "microtubules"), we simulate the non-equlibirum dynamics of this system using Langevin equations and explore its behavior as a function of different parameters - thermal noise (temperature T) and strength of the chromatin field (h) relative to the coupling

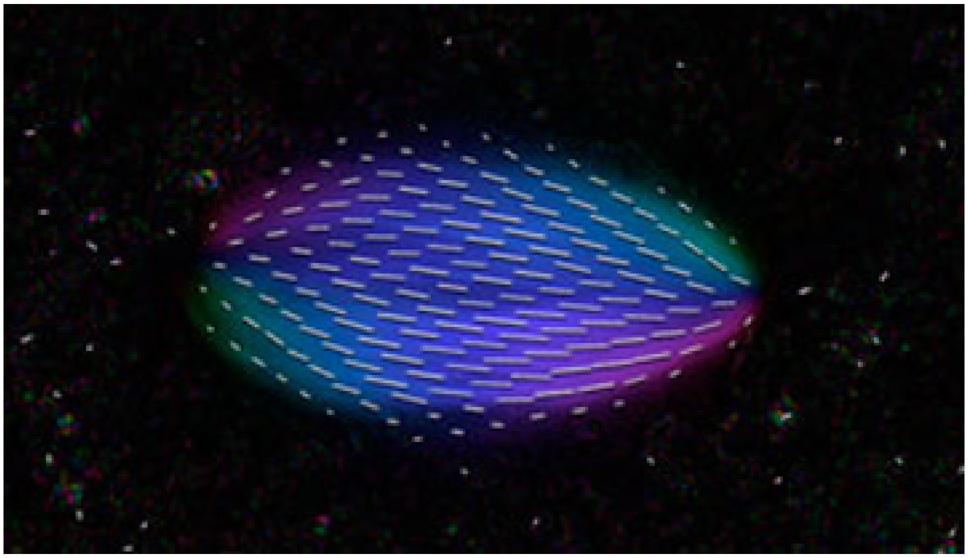


FIG. 1: Organization of microtubule filaments in the metaphase spindle suggests a likeness to an XY system of spins (Optical microscopy image downloaded from the Needleman Lab website[6])

strength between neighboring spins, and different boundary conditions.

I. MODEL

The system of spins has the Hamiltonian,

$$\mathcal{H} = -J \sum_{\langle ij \rangle} \cos\left(\theta_i - \theta_j\right) - \sum_i \left(k_x^i \cos\theta_i + k_y^i \sin\theta_i\right) \tag{1}$$

where J is the interaction strength favoring alignment among nearest neighbor microtubules. Here $\vec{k^i} = (k_x^i,\, k_y^i)$ is the local magnetic field at lattice site i. The Langevin equations[8,9] for the time evolution of this system are,

$$\begin{aligned} \frac{d\theta_i}{dt} &= -\frac{\partial \mathcal{H}}{\partial \theta_i} + \eta_i(t) \\ &= -\sum_{\langle j \rangle} \sin\left(\theta_i - \theta_j\right) - \left(h_x^i \sin\theta_i - h_y^i \cos\theta_i\right) + \eta_i(t) \end{aligned} \tag{2}$$

where, we measure units of time such that the coupling constant between neighboring spins is normalized to 1. $\vec{h^i} = (h_x^i, h_y^i)$ is the corresponding normalized field which we write as, $\vec{h^i} = h^i \cos\phi_i\, \hat{x} + h^i \sin\phi_i\, \hat{y}$. $\eta_i(t)$ is the thermal noise at site i and satisfies the fluctuation-dissipation relation $\langle \eta_i(t)\eta_j(t')\rangle = 2T\delta_{ij}\delta(t-t')$ where T is the temperature of the system.

II. SIMULATION

We solve this system of equations using the Forward Euler scheme[8,9],

$$\theta_i(t+\Delta t) = \theta_i(t) - \Delta t \left(\sum_{\langle j\rangle} \sin(\theta_i - \theta_j) + h^i \sin(\theta_i - \phi_i) \right) + (2T\Delta t)^{1/2}\, r_i \tag{3}$$

Here, r_i are independent Gaussian variables with mean 0 and standard deviation 1. For time steps, we have used $\Delta t = 0.05$. For a few cases, we have checked that employing $\Delta t = 0.005$ does not change our results. All our simulations are conducted on a $L \times L$ lattice for $L = 100$. Our results are consistent for $L = 80$ and 200. A spin at location $(k,\, m)$ on the lattice has the index $i = (m-1)L+k$, where $k \in [1,\, L]$ is the row index and $m \in [1,\, L]$ is the column index. The fields are such that spins along column $m = L/2 - d$ experience a field with magnitude h and direction $\phi = 0$, while spins along column $m = L/2+d$ experience a field with magnitude h and direction $\phi = \pi$. The location of the columns correspond to the locations of the two daughter chromatin strands. In our simulations, d is typically small (= 2-4). The fields at all other spin locations, $\vec{h^i} = 0$.

The bottom and top rows of spins ($k = 1$ and $k = L$) are connected through periodic boundary conditions. On the other hand, we employ either reflective[2] or free boundary conditions at the left-most ($m = 1$) and right-most ($m = L$) columns of spins.

III. VALIDATION

In the absence of any externally imposed field, the XY model is known to exhibit a remarkable phase transition characterized by a divergence of magnetic susceptibility but in the absence of any symmetry breaking. The zero field XY model has zero magnetization at finite T according to the Mermin-Wagner theorem[10], thus ruling out a conventional (symmetry-breaking) phase transition at finite temperatures. The evidence for such a phase transition was suggested first by Stanley and Kaplan[11], but its mechanism was ultimately articulated in a seminal work by Kosterlitz and Thouless[12]. Vortices are elementary topological defects that can occur in a 2-D system of continuous spins. At low temperatures, vortices and antivortices exist as tightly-bound pairs. Increasing the temperature of the system results in a phase transition arising from the unbinding of vortices leading to macroscopic separations between vortex and antivortex pairs.

In order to validate our code, we decided to simulate the zero-field XY model and recover known properties. To that end, we simulated an $L = 100$ system for $\vec{h} = 0$, and with periodic boundary conditions everywhere. Random orientations of spins were chosen for the initial conditions. Following, McCarthy[8], we define our susceptibility per spin as,

$$\frac{\chi}{N} = \frac{1}{N^2}\langle S_{tot}^2\rangle \tag{4}$$

where $S_{tot}^2 = \left(\sum_i \cos\theta_i\right)^2 + \left(\sum_i \sin\theta_i\right)^2$ and $N = L^2$. We simulated the Langevin equations for 150,000 time steps of $\Delta t = 0.05$ each and computed the time average of this quantity after neglecting the first 20,000 steps for equilibriation. We can see that the susceptibility curve (cf. Fig. 2) matches Fig. 4 in McCarthy[8].

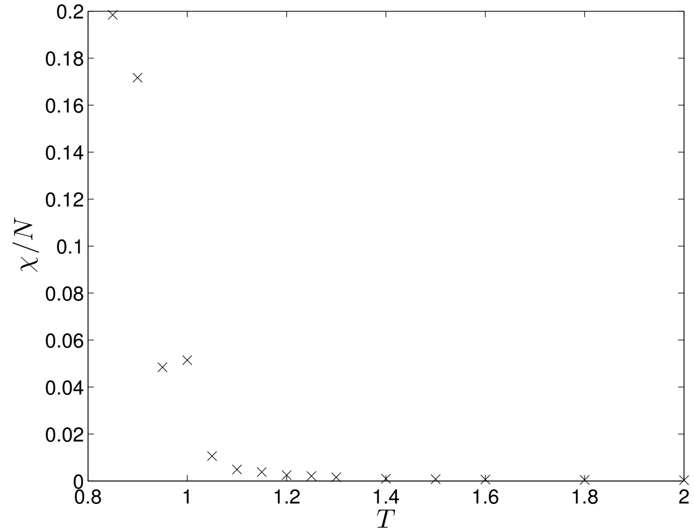


FIG. 2: Susceptibility per spin of the zero-field XY model as a function of temperature

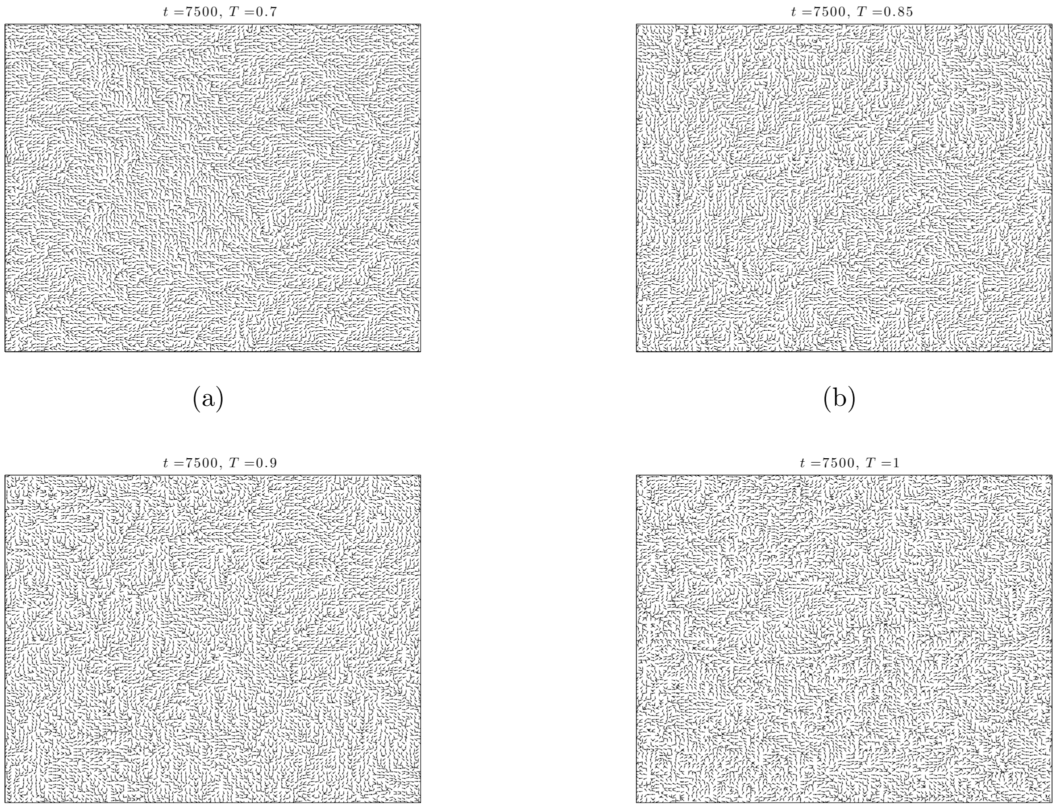
According to exact spin-wave results at low temperatures[12,13],

$$\langle |M| \rangle \approx 1 - \frac{T}{8\pi}\left(\ln 2N\right) \tag{5}$$

$$\frac{1}{N}\chi = \frac{1}{N^2}\langle S_{tot}^2\rangle \approx N^{-T/4\pi} \tag{6}$$

At $T = 0.1$, these results predict $\langle |M| \rangle = 0.96$ and $\frac{1}{N}\chi = 0.93$ for $L = 100$. From our simulations, we calculated $\langle |M| \rangle = 0.9587$ and $\frac{1}{N}\chi = 0.929$, thus indicating close agreement. For $T = 0.3$, the analytical predictions were $\langle |M| \rangle = 0.88$ and $\frac{1}{N}\chi = 0.802$. The corresponding numerical results were $\langle |M| \rangle = 0.86$ and $\frac{1}{N}\chi = 0.783$.

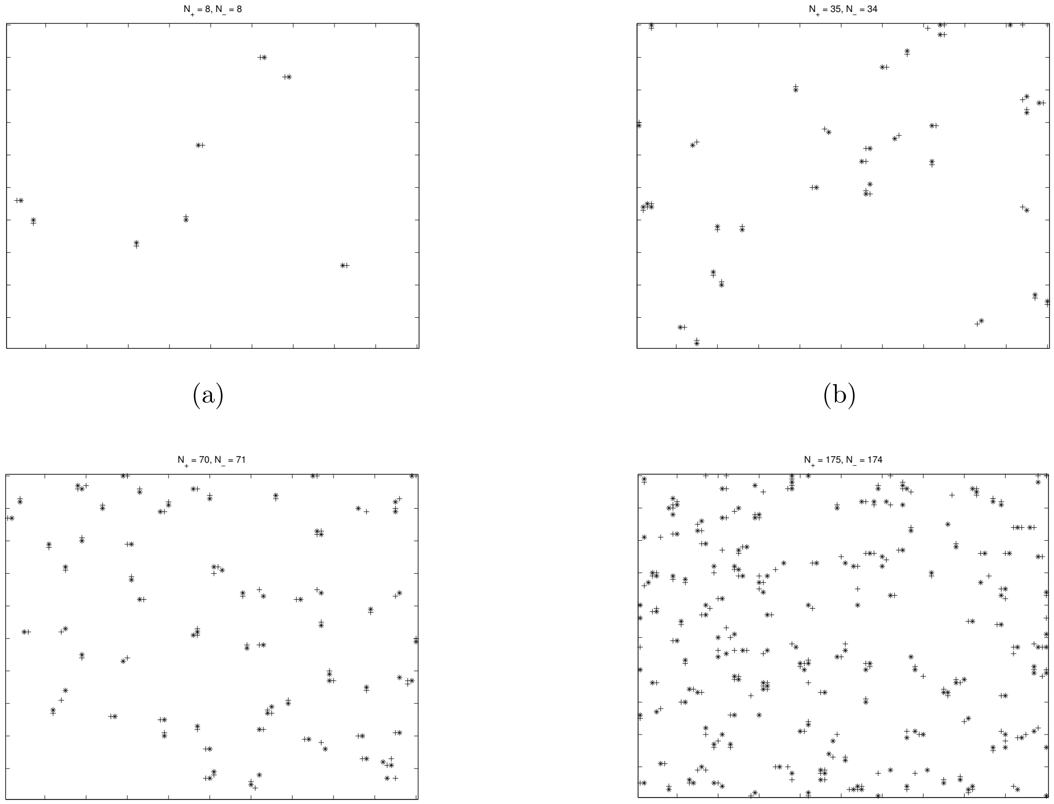
Fig. 3 shows snapshots of equilibriated spin configurations at $T = 0.7, 0.85, 0.9$ and 1.0. Fig. 4 shows the locations of the corresponding vortices and anti-vortices at these temperatures. As can be readily discerned, vortices and anti-vortices remain tightly bound at $T = 0.7$. At $T = 0.85$, we see a single vortex-antivortex pair with separation equal to the lattice spacing. At higher temperatures $T = 1.0$, we vividly see that the vortices are unbound. These results are consistent with a critical temperature $T_c = 0.9$ from Kosterlitz-Thouless theory.



(a) (b)

(c) (d)

FIG. 3: Long time snapshots of the zero-field XY model at different temperatures - (a) $T = 0.7$, (b) $T = 0.85$, (c) $T = 0.9$, (d) $T = 1.0$



(a)

(b)

(c)

(d)

FIG. 4: Locations of vortices (+) and antivortices ($*$) in the snapshots depicted in Fig. 3. It can be seen that vortices and antivortices in the low temperature phase (panel a) are tightly bound. Vortices and anti-vortices can be seen to separate until the lattice spacing in panel b ($T = 0.85$). Macroscopically separated vortex pairs can be seen at $T = 0.9$ (panel 3) and $T = 1$ (panel 4).

IV. RESULTS

We now introduce fields at $m = L/2 - d$ and $m = L/2 + d$ and simulate equation 2 for various values of $h (> 0)$ and T. As indicated earlier, in these simulations the boundary conditions are periodic along each column, while they are either free or reflective at the ends of each row. In the range of parameters we have explored, the reflective and free boundary conditions yield similar results.

The presence of the fields breaks the symmetry of the XY model and therefore, at low enough temperatures, there is ordering consistent with the direction of the fields. We quantify this ordering using the order parameter $\langle\cos\theta\rangle_{left}$ and $\langle\cos\theta\rangle_{right}$ where "left" and "right" refer to the two halves of our "cell". These order parameters reflect the extent of ordering produced by the chromosomal fields. In the absence of any fields, $\langle\cos\theta\rangle_{right} = \langle\cos\theta\rangle_{left} = 0$ at all temperatures as a consequence of the Mermin Wagner theorem. On the other hand at small temperatures, one would expect $\langle\cos\theta\rangle_{right} > 0$ and $\langle\cos\theta\rangle_{left} < 0$ as aligning to the fields would be energetically favorable.

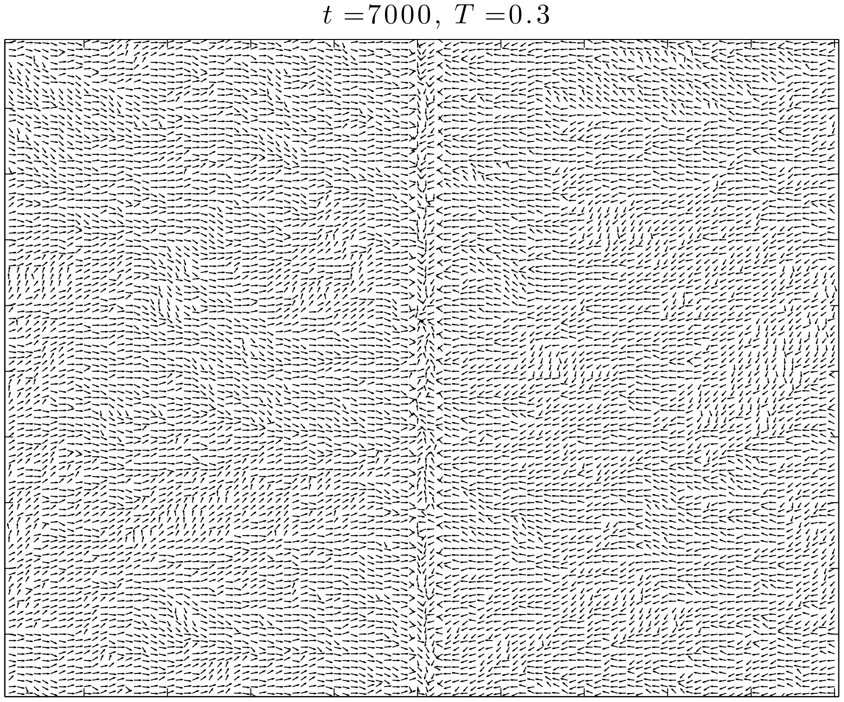


FIG. 5: Snapshot of spins at $T = 0.3$, $h = 10$.

Indeed we find that for $h = 10$ and $T = 0.6$, we find that $\langle\cos\theta\rangle_{left} = -0.86$ and $\langle\cos\theta\rangle_{left} = 0.858$. On the other hand, for the same value of h, at $T = 1.2$, $\langle\cos\theta\rangle_{left} = -0.06$ and $\langle\cos\theta\rangle_{left} = -0.01$, indicating that lower temperatures are important for the system for correlations to persist. The connection between the model temperature and the physiological temperature is unclear at present, so we simply stick to the thermodynamic interpretation of T as a parameter that determines the strength of fluctuations.

Next we tried to compute the behavior of the system at a fixed T (which is conducive to long range order) while the strength of the magnetic field h is varied. Curiously, we find that at intermediate temperature there is a switching of the sign of the order parameter, which is not transient. That is, this seems to be the steady state behavior of the system

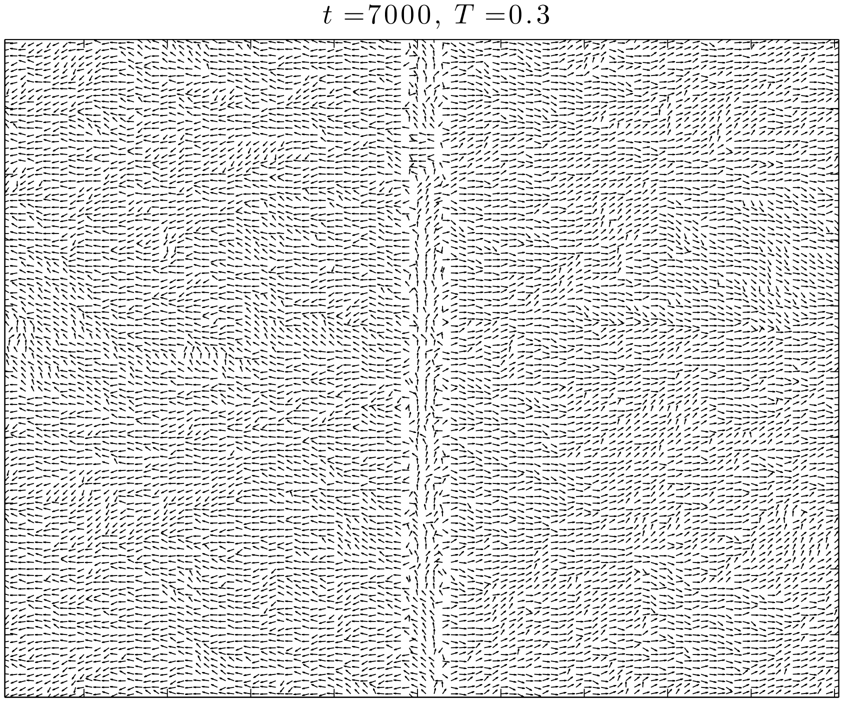


FIG. 6: Snapshot of spins at $T = 0.3$, $h = 80$.

at least within the time-scale of our simulation (200,000 steps). This is conveyed in Fig. 6, where we plot the value of the order parameter as a function of the field strength. This switching behavior is also reproduced at a higher and lower temperatures as long as there is ordering, although the value of the order parameter is different. For instance, at higher temperatures (cf. Fig. 7), it is considerably smaller as we would expect because fluctuations are important.

V. CONCLUSIONS

This paper is an exploratory study of adapting the well known XY model to understand pattern formation in the mitotic spindle. Naturally, we do not expect such a simple model to reproduce the full spectrum of observed patterns in nature, which require the explicit modeling of growth and transport processes and also involve the interplay of other entities like motors and signaling molecules. Our barebone analysis clearly suggests that some of these phenomena need to be incorporated in the model. On the other hand, despite its apparent simplicity of description, the XY model is known to exhibit rich phenomena like a vortex-unbinding transition and coarsening of spins during a quench. Even in our case,

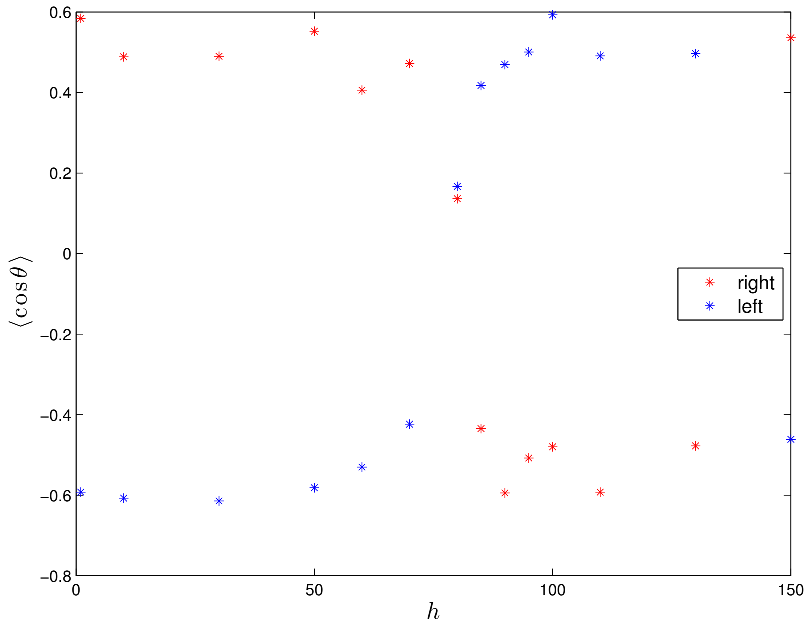


FIG. 7: Order parameter as a function of field strength at $T = 0.8$

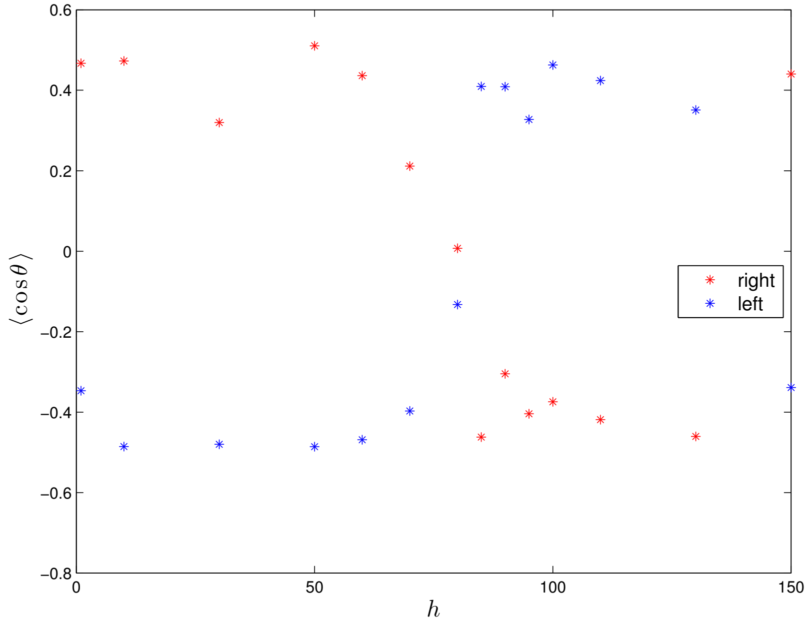


FIG. 8: Order parameter as a function of field strength at $T = 0.9$

we find that while some results are as expected, the adaptation of the XY model that we consider produces a strange behavior as the strength of the chromosomal field is increased. More work is clearly need in understanding this behavior and we have barely scratched the surface.

VI. ACKNOWLEDGMENTS

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