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Tug-of-war between opposing molecular motors explains chromosomal oscillation during mitosis

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HIGHLIGHTS

- We model the oscillation of a chromosome observed during mitosis.
- The model probes the role of various molecular motors and dynamics of microtubules.
- A tug-of-war like mechanism between opposite motor species stalls chromosome.
- Duration of a stalled state depends upon the number of kinetochore microtubule.
- Exit from the stall is achieved by stochastically binding the favorable motor species.

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ABSTRACT

Chromosomes move towards and away from the centrosomes during the mitosis. This oscillation is observed when the kinetochore, a specific protein structure on the chromosome is captured by centrosome-nucleated polymer called microtubules. We present a computational model, incorporating activities of various molecular motors and microtubule dynamics, to demonstrate the observed oscillation. The model is robust and is not restricted to any particular cell type. Quantifying the average velocity, amplitude and periodicity of the chromosomal oscillation, we compare numerical results with the available experimental data. Our analysis supports a tug-of-war like mechanism between opposing motors that changes the course of chromosomal oscillation. It turns out that, various modes of oscillation can be fully understood by assembling the dynamics of molecular motors. Near the stall regime, when opposing motors are engaged in a tug-of-war, sufficiently large kinetochore–microtubule generated force may prolong the stall durations.

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1. Introduction

During prometaphase of mitotic cell division, centrosomal microtubules (MTs) search for a specific chromosomal protein complex, called the kinetochore (KT), to establish primary MT–KT attachment (Maiato et al., 2004; Mitchison and Salmon, 2001). In most of the vertebrate cells, while the sister KT waits to be captured, mono-oriented chromosomes exhibit a series of poleward (P) and away from pole (AP) motion (Skibbens et al., 1993; Bajer, 1982; Levesque and Compton, 2001; Rieder et al., 1986; Ke et al., 2009). Once the sister KT is captured and chromosome biorients, oscillation continues with a variable time-period and relatively smaller amplitude. The abrupt switching between P and AP motion is often termed as “directional instability” (Skibbens et al., 1993; Rieder et al., 1986; Gardner et al., 2008). Although

there is incomplete understanding why such a to-and-fro motion of the chromosome would be necessary, recent advancement in microscopy and application of sophisticated techniques at the molecular level reveal that synergistic movement of chromosomes may be required to maintain the accuracy of chromosomal segregation during mitosis (Magidson et al., 2011). Both experimental and theoretical studies (Skibbens et al., 1993; Bajer, 1982; Ke et al., 2009; Campàs and Sens, 2006; Onuchic et al., 2007) have supported the crucial role of microtubule dynamics and multiple molecular motors in orchestrating the chromosomal oscillation. Skibbens et al. showed the trajectory of a chromosome as it is captured by MTs from one pole and subsequently from the spindle pole (pole refers to the spindle-pole). It is observed that after the initial capture, the chromosome is rapidly pulled towards the pole, where it pauses instantaneously. Immediately after this pause, the chromosome swiftly moves back towards the spindle equator and from there, again it swings towards the pole and so on. This uninterrupted cyclic motion of the chromosome continues until another MT from the opposite pole captures the virgin sister KT,

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resulting equatorial congression of the chromosome followed by a small amplitude irregular oscillation. RNA interference, reducing the activity of selected motor proteins, has shown that both chromokinesin and dynein play significant roles for a sustained chromosomal oscillation (Levesque and Compton, 2001; Sharp et al., 2000; Pfarr et al., 1990).

In general, mechanistic oscillations follow from the resultant of two opposing forces that vary with position and time. This idea has been implemented in prior theoretical studies in developing purely mechanical (Campàs and Sens, 2006) and mechanobiochemical (Onuchic et al., 2007) models. Such models consist of microtubules pushing on the chromosome arm in the AP direction against a poleward tension originated at the MT–KT junction. In the mechanical model, AP force is assumed to be the polar ejection force (Skibbens et al., 1993; Levesque and Compton, 2001; Inoue and Salmon, 1995; Joglekar and Hunt, 2002), arising from the interaction between MTs and the chromosome arms mediated by chromokinesin motors (Levesque and Compton, 2001). Polar ejection force assumed to be responsible for pushing the chromosome away from the pole in a distance dependent manner. It has been suggested that the AP force decays as square of the distance from the pole, whereas, the P force is of constant (Campàs and Sens, 2006) magnitude irrespective of the position of the chromosome. More recently, Civelekoglu-Scholey et al. (2006) presented another model focusing on the metaphase oscillation of a chromosome after bi-orientation. The underlying mechanism of their approach is the balance of several deterministic forces. Interestingly, stochastic binding/unbinding and characteristic asymmetry between forward and backward motion of molecular motors has been ignored in the latter model. Besides, the primary driving force in this model comes from the interaction between a KT and the MTs embedded within the KT (KMT). Finally, in the mechanobiochemical model (Onuchic et al., 2007) plus end dynamics of KMTs are considered as the key ingredient for the chromosomal motion. This approach couples mechanics of the chromosomal motion with the biochemical reactions occurring within the KT. The underlying feedback mechanism does not explicitly consider the dynamics of molecular motors. A large body of evidence suggests that far away from the switching regime, chromosome moves roughly at a constant speed (Rieder et al., 1986; Skibbens et al., 1993). However, close the pole, slowing down of chromosome facilitates more MTs to bind with the KT, ensuring a stable end-on attachment (Rieder and Salmon, 1998; Cleveland et al., 2003; Akiyoshi et al., 2010). It is interesting to notice that, to maintain an MT driven sustained chromosomal oscillation, a large number of KMTs most likely have to grow and shrink in a coherent manner, so that a sufficiently large net force is applied on the chromosome. To our knowledge, no physical mechanism has been identified yet that can explain the coherent dynamics of all the KMTs during mitosis. Therefore, respecting the widely believed hypothesis that catastrophe (f_c) and rescue frequencies (f_r) of different MTs as uncorrelated events, it can be argued that the dynamic instability parameters play merely a passive role in the present context. Thus, recent data (Maiato et al., 2004; Ke et al., 2009; Rieder and Salmon, 1998; Li et al., 2007) and various facts we have discussed here support the hypothesis that chromosomal oscillation may have a dominant contribution from the molecular motors.

Here we propose a computational model incorporating stochastic and spatio-temporal coordination of various motor activities (Chowdhury, 2013a,b). We aim to focus on a number of important characteristic features that are frequently present in the experimental data, but did not receive any prior attention from the theoretical perspective. In this study, we try to include all possible ingredients that are known to generate mechanical forces during mitosis and most likely contribute to the chromosomal oscillation. The current model is based on a variable P force arising from the

activity of dynein at the MT–KT junction (Maiato et al., 2004; Sharp et al., 2000; Rieder and Salmon, 1998). AP force is assumed to be originated from the interaction between the chromosome arm and the impinging MTs (Levesque and Compton, 2001; Brouhard and Hunt, 2005; Ault et al., 1991; Yajima et al., 2003) mediated by chromokinesins. In addition to pure motor forces, pushing force on the chromosome arm due to the polymerization of MTs has also been taken into account. Movements of the KMT tip and the chromosome are considered to be coherent and effect of the external mechanical perturbation on the KMT dynamics (Civelekoglu-Scholey et al., 2006; Gardner et al., 2005; Fernandez et al., 2009; Cheeseman et al., 2006) is incorporated in the model.

Using extensive Monte-Carlo simulation, we have been able to quantify and interpret the characteristic chromosomal oscillation observed during prometaphase and metaphase of mitotic cell division. Our results suggest that a tug-of-war mechanism (Skibbens et al., 1993; Ault et al., 1991; Soppina et al., 2009) between chromokinesin and dynein is most likely responsible for switching the direction of oscillation. Although bidirectional transport of a vesicle, arising due to the proposed stochastic tug-of-war, may not be observed for a small number of motors (Kunwar et al., 2011), a similar scenario turns out to be irrelevant in the context of chromosomal oscillation. It is believed that an assembly of large number of motors drives the chromosomal cargo and therefore a mean field based approach (where the engaged motors equally share the applied load) is applicable. Data for the chromosomal oscillation predicted by our model are found to be compatible with the available experimental results (Skibbens et al., 1993; Bajer, 1982; Levesque and Compton, 2001; Rieder et al., 1986; Ke et al., 2009; Khodjakov and Rieder, 1996).

2. Model

Motivated by earlier attempts devoted to understand motor mediated bidirectional cargo transport and chromosomal oscillation (Campàs and Sens, 2006; Onuchic et al., 2007; Joglekar and Hunt, 2002; Civelekoglu-Scholey et al., 2006), we propose a comprehensive model consisting of a pair of centrosomes (poles), a single chromosome with two unattached sister kinetochores, molecular motors and dynamic MTs. Instantaneous configuration of the model system is shown in Fig. 1. In this composite system, the motion of the chromosomal cargo is achieved by molecular motors and dynamics of MTs. Motors attach to and detach from the MT filament while they remain firmly adhered to the chromosomal cargo. Before we discuss the specific model for the chromosomal oscillation, it is important to talk about the general framework for a motor mediated cargo transport based on which our numerical model is developed. The fundamental equation governing the probability distribution P_n of n attached motors of a single motor-species is given by a well known master equation (Klumpp and Lipowsky, 2005):

$$\frac{\partial P_n}{\partial t} = K_{n+1}^{\text{off}} P_{n+1} + K_{n-1}^{\text{on}} P_{n-1} - (K_n^{\text{off}} + K_n^{\text{on}}) P_n. \quad (1)$$

Here K_n^{on} and K_n^{off} represent the attachment and detachment rates of a motor when there are already n motors attached to the filament. The stationary solution of Eq. (1) is identified by

$$K_{n+1}^{\text{off}} P_{n+1} = K_n^{\text{on}} P_n. \quad (2)$$

Once the P_n and P_0 are known, the average number of attached motors and the velocity of the cargo can be estimated. In the absence of any external load and for mutually noninteracting motors, K_n^{on} , K_n^{off} can be simplified as: $K_n^{\text{on}} = (n_{\text{max}} - n)K^{\text{on}}$ and $K_n^{\text{off}} = nK^{\text{off}}$, where, K^{on} , K^{off} are the attachment rate, detachment rate of a single motor, respectively and n_{max} is the maximum number of motors available for the cargo transportation. The velocity $v(F)$ of a single motor

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