

An Integrated Mechano-Biochemical Model of Chromosome Congression and Segregation during Mitosis

Jian Liu¹, Arshad Desai², Jose' N. Onuchic¹, Terence Hwa¹

Center for Theoretical Biological Physics¹; Ludwig Institute for Cancer Research/Cellular & Molecular Medicine², University of California at San Diego, La Jolla, California, USA

During mitosis, chromosome pairs line up along the cell equator before being pulled apart and divided precisely into the two daughter cells. How the chromosomes find the cell equator has remained as one of the outstanding mysteries of cell biology. For vertebrate cells, it is long known that the chromosomes undergo a series of spectacular oscillatory movements right before congressing at the cell equator. This oscillation is commonly attributed to be the result of a mechanical “tug-of-war” between opposing forces that attempt to pull the chromosome to the two sides. However, the pure “tug-of-war” scenario cannot explain how chromosomes congress to the equator, as (i) the balance of two opposing mechanical forces is difficult to achieve without careful coordination, and (ii) the force balance itself is independent of the location of the chromosome along the spindle.

We recently pointed out that mechanical force balance is only one of several key ingredients controlling chromosome motility [1]. Specifically, as each chromosome is end-on attached to the kinetochore microtubule (KMT) plus-ends during its oscillation, its poleward (anti-poleward) movement must involve the shrinkage (growth) of the underlying

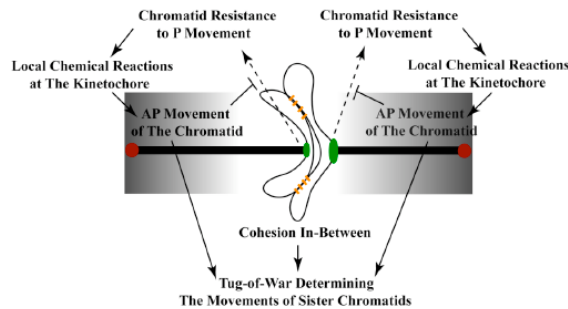


Figure 1. Schematics of the mechano-biochemical feedback model of chromosome motility. Filled red circles indicate the two poles (P) from which microtubule spindles emanate. Filled green ellipses indicate the kinetochore to which the microtubules are end-on attached. Orange stitches indicate the linkage between the sister chromosomes. Shrinkage of the kinetochore microtubules (thick solid lines) which are controlled ultimately by the state of the regulatory proteins localized to the kinetochore, pulls the chromosome towards its respective pole. However, as the chromosomes move to either side of the equator, they experience increasing “AP ejection force”, which are forces exerted by motors on the microtubule spindles to the bulk of the chromosomes to keep them away from the poles. The spatial force gradient is indicated in grey. The imbalance between the AP ejection force and the pulling force on the kinetochore leads to a tension on the chromosome (as indicated by the distorted shape); this tension is modifies sensor proteins which deactivates the regulatory proteins at the kinetochore. Reduced level of the active regulatory proteins leads to the growth of KMT hence the movement of chromosomes away from a pole.

KMTs. It then follows that chromosome oscillation needs to be at least coordinated with, if not limited by, the local chemical reactions that regulate the KMT plus-end dynamics. By further taking into account of the fact that the local chemical reactions at the kinetochore is affected by the mechanical forces exerted on the chromosome through tension-sensing regulatory proteins, we developed a mechano-biochemical feedback model of chromosome motility [2]; see Fig. 1.

We find computationally that the proposed feedback mechanism generates robust chromosome oscillation in the physiological parameter range. Upon enhancement in the turnover of these sensor proteins, the model exhibits rapid damping of the oscillation, ending up with chromosome pairs settling down at the cell equator (Fig. 2). Further separation

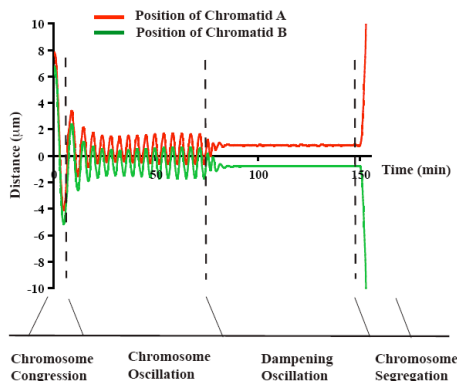


Figure 2. Time course of the chromosome motion from prometaphase onto anaphase.

The positions of the two kinetochores are indicated by the green and red curves respectively. After capturing by microtubules at time $t=0$, the system oscillates stably around the cell equator (zero of the vertical axis), until a time (indicated by the 2nd vertical dashed line) when the turnover of sensor protein increased. As a result, the oscillation quickly dampens and the chromosome settles down equi-distance from the cell equator. At the metaphase/anaphase transition indicated by the 3rd vertical dashed line (modeled by the brokage of spring connecting the two chromosomes together with an increased degradation of the regulatory proteins at the kinetochores, the two chromosomes move rapidly to the two poles.

of the chromosome pairs follows in our model, provided that the linkage between the two chromosomes are broken *and* the regulatory proteins that promote KMT plus-end growth are rapidly degraded (Fig. 2). It appears likely that the two

conditions in fact occur simultaneously at the metaphase/anaphase transition. For example, the degradation of regulatory proteins Cdk/cyclin B kinase by APC/C at metaphase/anaphase transition results in the loss of protection of the cohesins linking the chromosome pair. Our model thus explains, for the first time, all the essential features of chromosome motilities from prometaphase to anaphase in a coherent manner. Moreover, the analysis of our model shed light on possible physiological functions of chromosome oscillation as well as the roles of the different regulatory proteins, in mitosis and in cell cycle progression. Many predictions of our model are unique to the proposed mechano-biochemical feedback mechanism and may be directly tested experimentally.

1. J. Liu, A. Desai, J. N. Onuchic, T. Hwa. A Mechano-biochemical mechanism for Mono-oriented Chromosome Oscillation in Mitosis. *PNAS* **104**: 16104-9 (2007).

2. J. Liu, A. Desai, J. N. Onuchic, T. Hwa. An Integrated Mechano-Biochemical Feedback Mechanism Describes Chromosome Motility from Prometaphase to Anaphase in Mitosis. (in submission, 2008).