Influence of mass chromosome distribution in equatorial plane on oscillatory energy of mitotic spindle trough biomechanical oscillatory model of mitotic spindle

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Abstract: Distribution of chromosomes in equatorial plane of mitotic spindle, chromosome territories (CT) and dynamics of chromosome movements towards centrosomes could carry additional epigenetic information. CT within cell nucleus manifest spacious, temporal and cell specificity. The aim of this work is to study haw different mass distribution of chromosomes in equatorial plane influence distribution of potential and kinetic energy in the system dynamics of mitotic spindle. For this purposes an oscillatory model of mitotic spindle is developed. Mitotic spindle was considered as a system of coupled oscillators where one oscillatory pair consists of centrosome, microtubule and related chromosome that are interconnected with its homolog pair. In biomechanical oscillatory model of mitotic spindle centrosomes are presented as mass particles that represent two rheonomic centres of oscillations. Microtubules are presented with standard light visco-elastic element. Homologue chromosomes are represented as mass particles that are interconnected with standard light massless elastic spring. Analytical expression for potential and kinetic energy as well as for total mechanical energy of oscillating pair of homologues chromosomes is given. Influence of mass chromosome distribution in equatorial plane on oscillatory energy of mitotic spindle is discussed. Different distribution of energy in the system of mitotic spindle could represent additional level of codding information that is transferred into the next cell generation and could be of interests in process of cell differentiation.

1. Introduction

During the cell division process, chromosomes –the carriers of genetic material move within the cell on a specific way, not just in interphase but also in metaphase stage of cell division cycle showing functional character in spatial, temporal and cell type specific organization [1,2]. One of the models that explain organization of chromosomes during mitosis predicts central location of gene rich chromosomes within cell nucleus and gene-poor chromosomes located in a zone close to the nuclear edge [1,3]. Distribution of chromosomes in equatorial plane of mitotic spindle, chromosome territories (CT) [4] and dynamics of chromosome movements towards centrosomes could carry additional epigenetic information.

The aim of this work was to study haw different mass distribution of chromosomes in equatorial plane influence distribution of potential and kinetic energy in the system dynamics of mitotic spindle. For this purposes an oscillatory model of mitotic spindle is developed and disused different total mechanical energy oscillatory regimes.

1.1. Biomechanical oscillatory model of mitotic spindle

Detail description of the biomechanical model of mitotic spindle is given in [5,6]. Schematic representation of the basic concept of biomechanical model of mitotic spindle is given in Fig.1: Mitotic spindle is considered as a system of coupled oscillators. The coupling is realized through centrosome. Centrosomes are presented as mass particles on the cell poles and represent two rheonomic centers of oscillations. Microtubules could be presented with standard light massless elastic or visco-elastic or fractional order type element depending of the age of the specific cell. In this paper, for the simplicity of the model, microtubules are considered elastic. Homologue chromosomes are represented as mass particles that are interconnected with standard light massless linear elastic spring. Homologue chromosomes have equal masses and different chromosomes have different masses. System is, in static equilibrium no forced state, symmetrical in relation to horizontal plane like an image in the mirror. Homologue chromosomes are arranged in two symmetric and parallel planes to equatorial plane. Centrosomes - microtubule organizing centers generate oscillations and governed movements of microtubules and attached chromosomes in mitotic spindle [7].

Assumptions of the model: rheonomic centers of oscillation with masses M_1 and M_2 generate oscillations and oscillate along vertical axis. Oscillations are transfer trough standard light elastic or visco-elastic element to homolog chromosome – mass particle and its homologue pair. During anaphase A homologues chromosomes are disconnected (elastic spring that interconnects mass particles breaks) and homologues are moving in oscillatory manner to the corresponding centrosomes-spindle rheonomic oscillatory centers. For the simplicity of the model we consider that system is conservative without energy dissipation; kinematical excitation of rheonomic centers of oscillations is each with a single frequency and only in vertical axis, movement of centrosomes in other axis is neglected. Frequency of excitation of rheonomic centers of oscillations in this paper is considered equal. We assume that eigen oscillations of the subsystem are negligible, and is not considered.

To study haw different mass distribution of chromosomes in equatorial plane influence distribution of potential and kinetic energy in the system of mitotic spindle for the case of forced oscillations we considered two cases: 1. when homologue chromosomes with heavier masses are located in the central zone of metaphase equatorial plane, and 2. when homologue chromosomes with heavier masses are located in the peripheral zone of metaphase equatorial plane. Fig 2.

Expression of kinetic $\mathbf{E}_{K,ik}$ and potential energy $E_{p,ik}$, as well as for total mechanical energy of oscillating pair of homologues chromosomes is given.

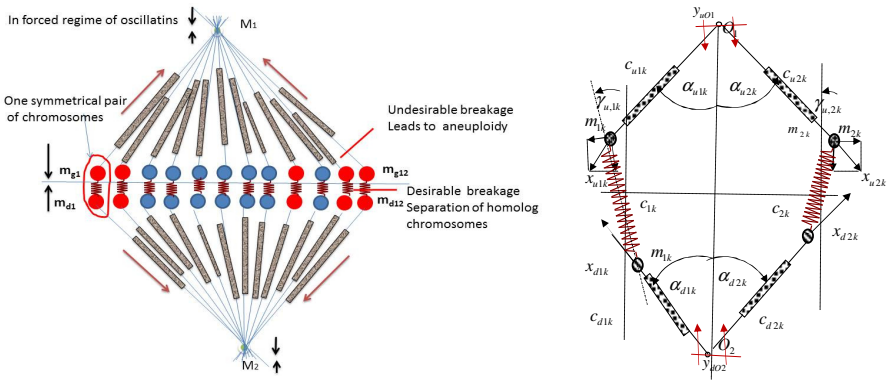


Figure 1.A. Biomechanical model of mitotic spindle in forced regime of oscillations with different distribution of chromosomes with different masses. Rectangles denote visco-elastic elements that represent microtubules. Elastic springs denote connection between pair of homologues chromosomes-kinetochore complexes. B. General oscillatory model of mitotic spindle with inertia elements on the poles of the cell that represents centrosomes. Only two pairs of homologues chromosomes are presented.

1.2. The potential and kinetic energy in the system of mitotic spindle in the pure elastic model

Total kinetic energy $\mathbf{E}_{K,ik}$ of ik -pair of homologues chromosomes/material particles including kinetic energies of centrosomes caused by rheonomic excitation coupled with standard light elastic element under angle $\alpha_{uik} = \alpha_{dik} = \alpha_{ik}$ with direction of kinematic excitation (see Fig.1.B and Refs [8-10]) are:

$$\mathbf{E}_{K,uik} = \frac{1}{2} m_{uik} v_{gik}^2 = \frac{1}{2} m_{uik} \left[\left(\dot{x}_{uik} + \dot{y}_{uO1} \cos \alpha_{uik} \right)^2 + \left(\dot{y}_{uO1} \sin \alpha_{uik} \right)^2 \right] \tag{1}$$

$$\mathbf{E}_{K,dik} = \frac{1}{2} m_{dik} v_{lik}^2 = \frac{1}{2} m_{dik} \left[\left(\dot{x}_{dik} + \dot{y}_{dO2} \cos \alpha_{dik} \right)^2 + \left(\dot{y}_{dO2} \sin \alpha_{dik} \right)^2 \right] \tag{2}$$

$$\begin{aligned} \mathbf{E}_{K,ik} = {} & \frac{1}{2} m_{uik} \left[\left(\dot{x}_{uik} + \dot{y}_{uO1} \cos \alpha_{uik} \right)^2 + \left(\dot{y}_{uO1} \sin \alpha_{uik} \right)^2 \right] + \frac{1}{2} M_u \left(\dot{y}_{uO1} \right)^2 + \\ & + \frac{1}{2} m_{dik} \left[\left(\dot{x}_{dik} + \dot{y}_{dO2} \cos \alpha_{dik} \right)^2 + \left(\dot{y}_{dO2} \sin \alpha_{dik} \right)^2 \right] + \frac{1}{2} M_d \left(\dot{y}_{dO2} \right)^2 \end{aligned} \quad ;i = 1,2...20 \tag{3}$$

with assumption that rheonomic centers of excitations are equal.

Where m_u and m_d are masses of homologue chromosomes (upper and down respectively), $\dot{x}_u$ and $\dot{x}_d$ are relative velocity for upper and down homologue chromosomes in direction of standard light elastic element, $\dot{y}_{uO1}\cos\alpha_{uik}$ and $\dot{y}_{dO1}\cos\alpha_{dik}$ are components of transfer velocity in collinear and $\dot{y}_{uO1}\sin\alpha_{uik}$ and $\dot{y}_{dO1}\sin\alpha_{dik}$ in orthogonal direction of standard light elastic element for upper and down homologue chromosomes. M_u and M_d are masses and $\dot{y}_{uO1}$ and $\dot{y}_{dO2}$ are velocities of rheonomic centers of oscillations. See ref [6].

Expression of potential energy $E_{p,ik}$ of two standard elastic and one standard light elastic element in each sub-system of a pair of coupled homologue chromosomes and rheonomic center is:

$$E_p = \frac{1}{2}c_{uik}x^2_{uik} + \frac{1}{2}c_{dik}x^2_{dik} + \frac{1}{2}c_{ik}[(y_{uO1} + y_{dO1}) + (x_{uik}\sin\alpha_{uik} + x_{dik}\sin\alpha_{dik})]^2 \; i = 1, 2..20 \qquad (4)$$

where x_{uik} and x_{dik} are independent generalized coordinates, y_{uO1} and y_{dO2} are rheonomic coordinates –kinematical mobility of rheonomic centers, c_{uik}, c_{dik} are rigidities of standard light elastic element- that correspond to rigidity of microtubules, c_{ik} is rigidity of elastic elements – coupling between pair of mass particles-homologue chromosomes that corresponds to rigidity of metaphase chromosomes (see denotation on Fig.1. and Refs.[8, 9]). Total mechanical energy for each pair of homologue chromosomes subsystem is calculated by expressions (3) and (4) from formula:

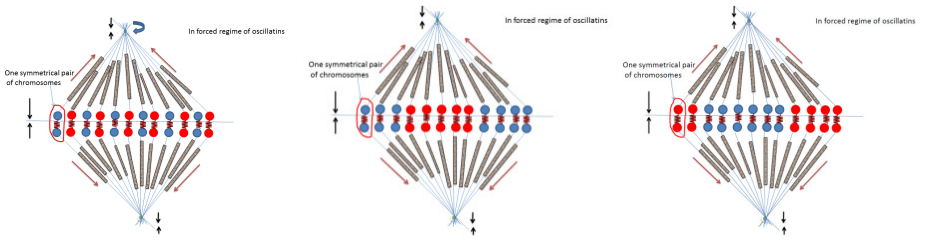
$$E_{T,ik} = E_{k,ik} + E_{p,ip} \; i = 1, 2...20 \qquad (5)$$

2. Distribution of mechanical energies in mitotic spindle regarding mass distribution

Regarding the distribution of chromosomes in equatorial plane of mitotic spindle and its impact on mitotic spindle dynamics, especially oscillatory movements of homologue chromosomes towards corresponding centrosome, we analyze, in this paper, how different distribution of homologue chromosome masses in equatorial plane during metaphase influence distribution of kinetic and potential energy in the system of mitotic spindle. For numerical analysis we considered two cases: 1. when homologue chromosomes with heavier masses are located in the central zone of metaphase equatorial plane, and 2. when homologue chromosomes with heavier masses are located in the peripheral zone of metaphase plane. See Fig 2. In Fig. 2 are presented a basic model where microtubules are represented with standard light visco-elastic elements, but for numerical analysis we consider microtubules elastic and represent them with standard light elastic element. Numerical analyses were done for mouse chromosome masses. Mouse has 20 pair of chromosomes.

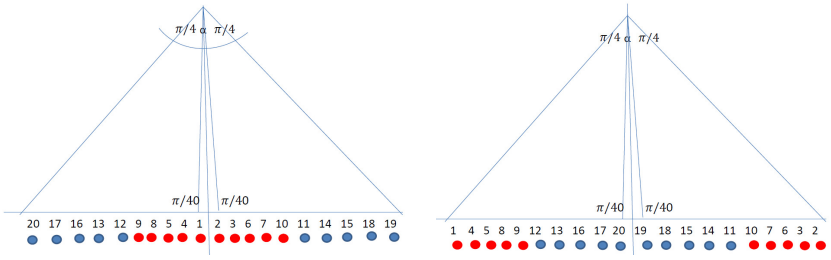
Angle of mitotic spindle-an angle between rheomnomic centers and the chromosomes on the very periphery of the mitotic spindle was taken as π/2. Regarding the vertical axis that interconnect two

opposite rheonomic centers- centrosomes, homologue chromosome are equally distributed. See Fig.3. Angle of mitotic spindle was taken as π/2, angles between centrosome-rheonomic center of oscillations and direction of microtubules - elastic element are assumed to equally enlarged from central to peripheral zone of mitotic spindle (for π/40). Distribution of chromosome masses are assumed to be relatively symmetrically distributed regarding symmetry line that interconnects two rheonomic centers (intercentromeres' distance). Model has relatively balanced distribution of chromosomal masses in vertical axis of symmetry, and identical distribution of masses in horizontal plane- homolog chromosomes. See Fig. 3.



A B C

Figure 2.A. Biomechanical model of mitotic spindle in forced regime of oscillations with different distribution of chromosomes with different masses-symmetrical distribution of chromosomes mass in the mitotic spindle. B. Heavy chromosomes are in central position. C. Heavy chromosomes are in peripheral position. Rectangles denote visco-elastic elements that represent microtubules. Elastic springs denote connection between pair of homologues chromosomes.



A B

Figure 3. Schematic representation of potential distribution of mouse mitotic chromosomes in equatorial plane in metaphase used for numerical modeling with biomechanical model of mitotic spindle-half section. A. Case when chromosomes with heavier masses are in the central zone of mitotic spindle. B. Case when chromosomes with heavier masses are in the peripheral zone of mitotic spindle.

Data for chromosomal mass for mouse chromosomes were taken from ref [11]. As data in the ref [11] denotes masses for 4 chromatids data from the table from ref [11] were divided with 2 and expressed in kg. Data for rigidity of eukaryote metaphase chromosomes c_c was calculated from the formula $c_c = \frac{E_c r^2 \pi}{l_c}$ where E_c is Young's modulus of eukaryote metaphase chromosome, r is diameter and l_c is length of eukaryote metaphase chromosome taken from [12] ($E_c = 10^3 Pa$, $r = 3\mu m$, $l_c = 20\mu m$, $c_c = 1.413 \times 10^{-3} N/m$). Rigidity for microtubules at 37° C c_m were calculated according to the formula $c_m = \frac{E_m (R_o^2 - R_i^2)\pi}{l_m}$ where E_m is Young's modulus of microtubules at 37°C, R_O and R_i are outer and inner diameter of microtubules respectively, l_m is length of microtubules taken from ref [13] ($E_m = 1.9 \times 10^8 Pa$, $R_O = 30nm$, $R_i = 18nm$, $c_m = 3.44 \times 10^{-6} N/m$). Data for rheonomic centers of oscillation was calculated according to the data for angular frequency oscillation for centrosome were taken from [14] (2π/T, T=20s). Centrosome mass was calculated from centrosome volume (1,5μm^3) from http://www.proteinatlas.org/humancell/centrosome and density - (density was taken approximatively as data for density for cell organelle- mitochondria 1,05g/ml) – (1.575x10^{-15}kg) [15]. Data for centrosome amplitude oscillations was taken from [16] (2.1μm=2.1x10^{-6}m).

3. Results

Total mechanical energy for each pair of homologue chromosomes subsystem for the case when heavy chromosomes take central position in mitotic spindle are presented in Fig 4. From the graph it is evident that amplitudes of total energy for each pair of homologue chromosomes subsystem have lower values in the central zone of mitotic spindle compare to the amplitudes of total mechanical energy for each pair of homologue chromosomes positioned at the periphery of the mitotic spindle.

Distribution of total mechanical energy of each chromosome pair for the case when chromosomes with heavier masses are positioned in the peripheral part of equatorial plane are presented on Fig. 5. In this case amplitudes of total mechanical energy for each pair of homologue chromosomes have also lower values in the central zone of mitotic spindle compare to the amplitudes of total mechanical energy for each pair of homologue chromosomes positioned at the periphery of the mitotic spindle but values of amplitudes are higher compare to the first case when chromosomes with heavier masses are positioned in central part of mitotic spindle. Kinetic and potential energy for each pair of homologue chromosomes follow the same pattern (data not shown). If this biomechanical system follow the minimum energy principle for its stability, than the system of mitotic spindle will be more stable in

the case when chromosomes with heavier masses are positioned in the central zone of the metaphase plate.

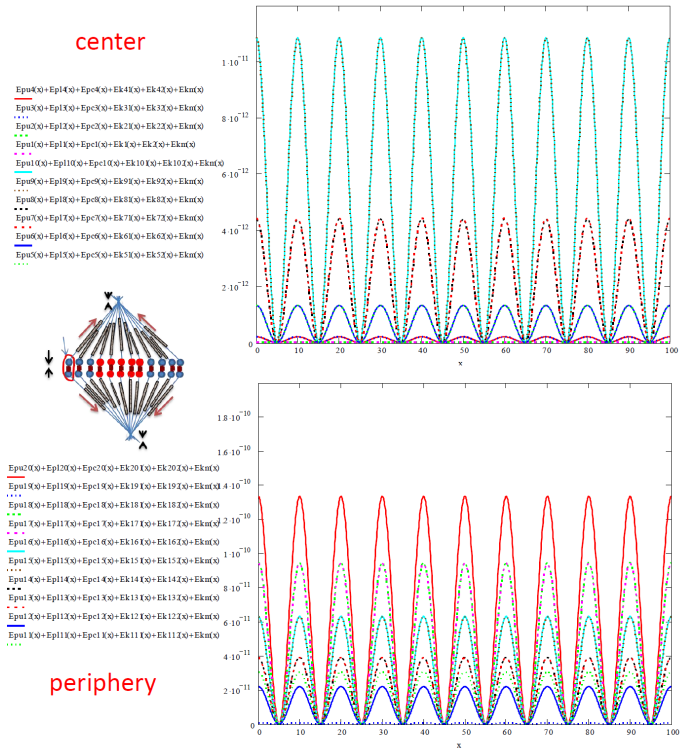


Figure 4. Distribution of total energy of each chromosome pair for the case when chromosomes with higher masses are positioned in the central part of equatorial plane. Lower values of energy of each pair of homolog chromosomes are arranged in central part of biomechanical model of mitotic spindle (upper diagram). On vertical axis is energy (in J). On horizontal axis (x) is time in seconds (s).

4. Conclusions

In this paper we analyzed how different mass distribution of chromosomes in equatorial plane in static equilibrium position, in dynamical oscillatory state and forced regimes influence distribution of potential, kinetic and total mechanical energy for each pair of homologue chromosomes subsystems in the system of mitotic spindle for the case of forced oscillations trough biomechanical oscillatory model of mitotic spindle. Regardless the distribution of chromosome masses (central or peripheral position of chromosomes with heavier masses) kinetic, potential and total mechanical energy for each particular pair of homologue chromosomes are lower in the central zone of mitotic spindle, but

amplitudes of kinetic, potential and total mechanical energy for each pair of homologue chromosomes subsystems are lower when chromosomes with heavier masses are positioned in central zone of mitotic spindle compare to the case when they have peripheral positions in mitotic spindle.

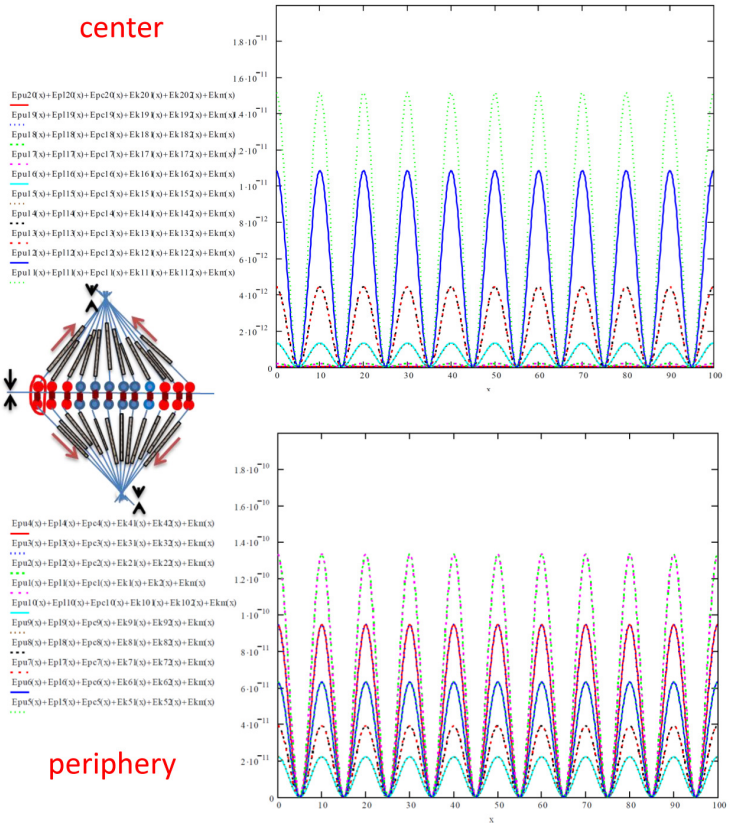


Figure 5. Distribution of total energy of each chromosome pair for the case when chromosomes with higher masses are positioned in the peripheral part of equatorial plane. Lower values of energy of each pair of homolog chromosomes are arranged in central part of biomechanical model of mitotic spindle (upper diagram). On vertical axis is energy (in J). On horizontal axis (x) is time in seconds (s).

The results we obtain by numerical analysis could be explained by non-linear dependence of the angle between microtubule (elastic element) and centrosome-rheonomic center. This difference in energy distribution could be of importance for the stability of the system of mitotic spindle and its energy balance. Also this difference in energy distribution during metaphase may carry additional epigenetic information and could be important for process of differentiation.

At the end, we must point out, that all numerical analysis are conducted for the conservative model without energy dissipation and for forced oscillatory regime when rheonomic centers are excited by single frequency. In considered case we assume that eigen vibrations of the subsystem are negligible, and are not taken into calculations. Our model is possible to analyze as visco-elastic system with linear dissipation of energy of the system, and also as fractional order type system with fractional order dissipation energy. But these results will be subject of next investigation. The obtained results for linear and conservative system of mitotic spindle dynamic are basis for next complex investigation.

Future research: narrow and long mitotic spindle as well as wide and short are indicative for some mitotic spindle disorders typical for old or cancer cells. It will be of interest to study influence of width of mitotic spindle on energy distribution in the system of mitotic spindle using this biomechanical oscillatory model. Also centrosomes –rheonomic centers in real biological system could have different frequency as well different amplitudes of oscillations which will have influence on amplitudes of energy of oscillations for each pair.

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