Analysis of oscillatory motions of chromosomes during anaphase using biomechanical oscillatory model of mitotic spindle

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Summary. Biomechanical oscillatory model of mitotic spindle is proposed. System is like object and its mirror image and has two planes of symmetry: pairs of homologues chromosomes are presented as material particles with different masses interconnected with standard light linear elastic element. Microtubules are represented with standard light fractional order element (SLFE) that has visco-elastic properties. Centrosomes represent sources of oscillations. Oscillatory motions of chromosomes are describe by fractional order differential equations. Influence of chromosomal arrangement and mechanical properties of SLFE on oscillatory behavior of mitotic spindle are discussed. A generalized function of the fractional order dissipation of energy of the system is defined. Model is suitable for describing motion of chromosomes in mitotic spindle in young and aged cells.

Biomechanical oscillatory model of mitotic spindle

Mitotic spindle is a complex structure necessary for equal division of chromosomes in two new cells during cell division [1, 2]. During metaphase homologues chromosomes are connected by kinetochore and arranged in equatorial plane. During anaphase homologues chromosomes are "disconnected" and moving towards polls of the cell driven by microtubules and specific oscillations of centrosomes [1]. Orientation of mitotic spindle and position of the centrosome affects polarity and function of new cells [3, 4, 5]. Polarity of the cells plays a great role in cell differentiation. There are biomechanical models that describe dynamics of microtubules in mitotic spindle [6]. These models are oriented on microtubules micro-dynamics and involved modelling of motions of specific proteins that form microtubules. Recently we proposed biomechanical oscillatory model of mitotic spindle [7]. Biomechanical oscillatory model is more general model of mitotic spindle; it does not take into account different molecules and complexity of microtubules and chromosomes. The main assumptions of the biomechanical oscillatory model of mitotic spindle [7] are: chromosomes are presented as material particles with different masses; pairs of homologues chromosomes are interconnected with standard light linear elastic element while arranged in equatorial plane; microtubules that interconnect each homologues chromosome with centrosome are represented with standard light fractional order element that has visco-elastic properties; mechanical properties of standard light fractional order element is consider equal; centrosomes, on the pole of the cell represent autonomous sources of oscillations; each of standard light fractional order element forms different angle with direction of source of oscillations; angles remain constant during oscillatory motions of chromosomes. System is like object and its mirror image and has two planes of symmetry, see Fig.1a. Non-linearity of oscillatory motion of chromosomes during anaphase is mainly determined by standard light fractional order element and forced oscillations originated from centrosomes-autonomous sources of kinematical oscillatory excitations. Proposed biomechanical fractional order oscillatory model Figure 1. a, b and c represents nonlinear rheonomic system.

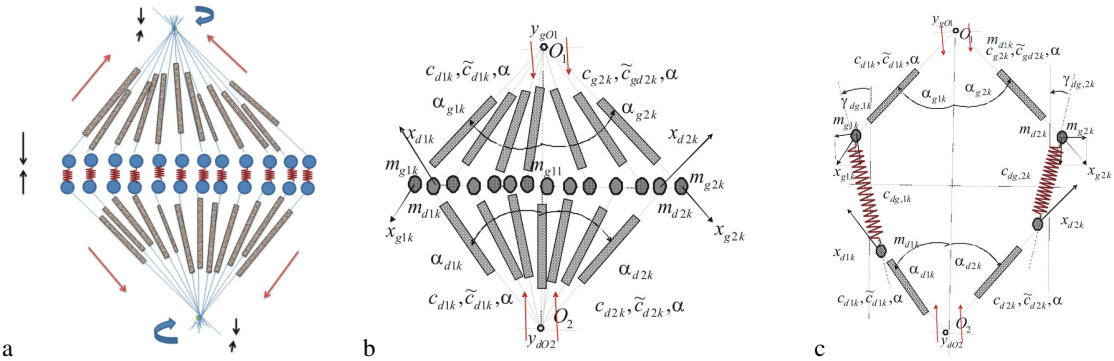

Figure 1. Biomechanical oscillatory model of the mitotic spindle. 1a. case when chromosomes are arranged in equatorial plane. 1b. case when homologues chromosomes are disconnected and start moving towards cell poles in forced oscillatory regime. 1c. part of the model with only two chromosomes. Beads represent chromosomes with certain mass m, rectangles represent standard light fractional order element (SLFE) that has visco-elastic properties and denotes microtubules. O_1 and O_2 are autonomous oscillatory centers. $\alpha_{d,ik}$ or $\alpha_{d,ik}$ is an angle between direction of SLFE and source of oscillations, c_{gik}, $\tilde{c}_{gik}$ or c_{dik}, $\tilde{c}_{dik}$ are linear rigidity and fractional order coefficients for SLFE. x_{gik} or x_{dik} -coordinates of relative displacements of chromosomes, $y_{gO1}(t)$ or y_{dO2} –rheonomic coordinates of displacements of oscillatory center O_1 and O_2, kinematically excited. Arrow denotes directions of motions.

Oscillatory motions of chromosomes/material particles

Oscillatory motions of chromosomes/material particles are describe by fractional order differential equations. Component velocities of chromosomes/material particles are: relative velocity for upper $\dot{x}_{gik}$ and lower $\dot{x}_{dik}$ homologues chromosomes in direction of SLFE and components of transfer velocity: in collinear $\dot{y}_{gO1}\cos\alpha_{gik}$ and $\dot{y}_{gO1}\sin\alpha_{gik}$ and in orthogonal $\dot{y}_{dO1}\cos\alpha_{dik}$ and $\dot{y}_{gO1}\sin\alpha_{gik}$ directions of SLFE. Square of absolute velocity of one chromosome/ k -th material particle in each subset –are:

$$v_{gik}^2=\left(\dot{x}_{gik}+\dot{y}_{gO1^2}\cos\alpha_{gik}\right)^2+\left(\dot{y}_{gO1}\sin\alpha_{gik}\right)^2,\ v_{dik}^2=\left(\dot{x}_{dik}+\dot{y}_{dO1^2}\cos\alpha_{dik}\right)^2+\left(\dot{y}_{dO1}\sin\alpha_{dik}\right)^2\ i=1,2,\ \ k=1,2,3,4,...,N \quad (1)$$

Approximate value of elongation of standard light linear elastic element that interconnect pairs of homologues chromosomes are:

$$\Delta\ell_{ik}\approx-\left[\left(y_{gO1}+y_{dO1}\right)+\left(x_{gik}\sin\alpha_{gik}+x_{dik}\sin\alpha_{dik}\right)\right],\ i=1,2,\quad k=1,2,3,4,...,N \quad (2)$$

Different arrangement of chromosomes with different masses in mitotic equatorial plane as well as in mitotic spindle will affect oscillatory motions of the whole system if we assume that the forced regimes of oscillations generated by kinematical excitations of oscillatory centres are permanent. In a case that arrangement of chromosomes with different masses remains permanent and that forced regime of oscillations of oscillatory centres vary over time we will also have different oscillatory behaviour of the whole system.

Mechanical energies and generalized function of fractional order dissipation of energy of biomechanical model of mitotic spindle

Expression of the total kinetic energy of the proposed biomechanical system, presented in Fig. 1c. is:

$$\mathbf{E}_K=\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}m_{gik}\left[\left(\dot{x}_{gik}+\dot{y}_{gO1^2}\cos\alpha_{gik}\right)^2+\left(\dot{y}_{gO1}\sin\alpha_{gik}\right)^2\right]+\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}mn_{dik}\left[\left(\dot{x}_{dik}+\dot{y}_{dO1^2}\cos\alpha_{dik}\right)^2+\left(\dot{y}_{dO1}\sin\alpha_{dik}\right)^2\right] \quad (3)$$

where expressions under square denote square of absolute velocity of one chromosome/ k -th material particle.

Expression of potential energy of the chromosome displacements along axial deformation of the SLFE is:

$$\mathbf{E}_P=\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\mathbf{E}_{P,gik}+\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\mathbf{E}_{P,dik}=\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}c_{gik}x_{gik}^2+\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}c_{dik}x_{dik}^2 \quad (4)$$

Expression of potential energy of the standard light linear elastic element that interconnects two mass particles/homologues chromosomes, taking into account expression (2) is in the following form:

$$\mathbf{E}_{PE}\approx\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}c_{ik}\left\langle\left[\left(y_{gO1}+y_{dO1}\right)+\left(x_{gik}\sin\alpha_{gik}+x_{dik}\sin\alpha_{dik}\right)\right]\right\rangle^2 \quad (5)$$

Expression of generalized function of fractional order dissipation of energy for the proposed model is:

$$\mathbf{P}_W=\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\mathbf{P}_{W,gik}+\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\mathbf{P}_{W,dik}=\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\tilde{c}_{gik}\left(\mathsf{D}_t^{\alpha}\left[x_{gik}\right]\right)^2+\frac{1}{2}\sum_{k=1}^{k=N}\sum_{i=1}^{i=2}\tilde{c}_{dik}\left(\mathsf{D}_t^{\alpha}\left[x_{dik}\right]\right)^2 \quad (6)$$

where D is fractional order α differential operator Liouville type.

Conclusions

To analyze oscillatory motions of chromosomes during anaphase biomechanical oscillatory model of mitotic spindle is proposed. The main advantage of this biomechanical model is that model could describe how different arrangement of chromosomes with different masses affects oscillatory behavior of chromosomes in mitotic spindle, spatially in a case when at least one standard light fractional order element-microtubule changes its mechanical properties. The model is suitable for explaining mitotic spindle disorders in context of numerical chromosomal aberrations and oscillatory behavior of chromosomes in mitotic spindle in young and aged cells.

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References

[1] Winey M., Bloom K. (2012) Mitotic Spindle Form and Function. *Genetics,* 190:1197–1224.
[2] Weise et al. (2016) Chromosomes in a genome-wise order: evidence for metaphase architecture. *Molecular Cytogenetics* 9:36.
[3] Ibrahim B., Diekmann, S., Schmitt, E., Dittrich, P., (2008), In-Silico Modeling of the Mitotic Spindle Assembly Checkpoint, PLoS ONE 3(2): e1555.
[4] Maly V.I., (2011) 'Systems biomechanics of centrosome positioning A conserved complexity". *Communicative & Integrative Biology* 49 2):230-235.
[5] Jüschke C., Xie Y., Postiglione P.M., Knoblich A.J., (2014) Analysis and modeling of mitotic spindle orientations in three dimensions. *PNAS,* 111, 3, pp 1014–1019. |
[6] Civelekoglu-Scholey G., Cimini D., (2014) Modelling chromosome dynamics in mitosis: a historical perspective on models of metaphase and anaphase in eukaryotic cells, *Interface Focus* 4: 20130073.
[7] Hedrih A., (Stevanovic) Hedrih K. (2016) Biomechanical oscillatory model of mitotic spindle in *Booklet of abstracts of mini-symposium Biomechanics and modeling of biological systems*. December 7, 2016, Belgrade, Serbia. ISBN 978-86-7746-630-5 (MISANU).