RAD Conference Proceedings, vol. 3, pp. 225–230, 2018
ISSN 2466-4626 (online) | DOI: 10.21175/RadProc.2018.47
www.rad-proceedings.org

KINETIC ENERGY OF DYADS OF SISTER CHROMATIDS IN A BIOMECHANICAL OSCILLATORY MODEL OF THE MITOTIC SPINDLE

Andjelka Hedrih[1*], Katica (Stevanović) Hedrih[1,2]

[1]Mathematical Institute of the SASA, Belgrade, Serbia
[2]Faculty of Mechanical Engineering University of Niš, Niš, Serbia

Abstract. *The aim of this work is to study how different oscillatory behavior of centrosomes and their mass arrangement affect the kinetic energy of pairs of dyads of sister chromatids in the system of a mitotic spindle during metaphase. The analyses are done through a biomechanical oscillatory model of the mitotic spindle. Analytical expressions for the kinetic energy of the oscillating dyads of sister chromatids are given for the case when the biomechanical system of the mitotic spindle is conservative, linear, and when it oscillates under external single frequency oscillation. Numerical analyses with some approximation for mouse chromosomes are done. Our numerical experiment reveals that the kinetic energy of the oscillating dyads of sister chromatids has an oscillatory character and is affected by the chromosomes' mass distribution and the frequency of centrosome excitation. The difference in energy distribution regarding different centrosome oscillatory frequencies in the same cell and the mass chromosome distribution may carry additional epigenetic information and could be important for the process of cell differentiation.*

Key words: *Biomechanical model, centrosome, chromosomes, kinetic energy, mitotic spindle, oscillations*

1. INTRODUCTION

The pattern of chromosome movements during the cell division process is specific in each phase of the cell division cycle, showing spatial, temporal, and cell-type-specific organization [1], [2]. At the spindle equator, chromosomes have different patterns of oscillations [3]. Inspired by this different pattern of chromosome movement behavior, a mechanical oscillatory model of the mitotic spindle is created [4] to explain the chromosome movement dynamics in the metaphase and anaphase of the cell division cycle.

The centrosome, a cell organelle that functions as a microtubule organizing center, governs the movements of chromosomes during metaphase and anaphase. As the cell has one centrosome, the centrosome has to divide and move to the opposite poles of the cell to form a mitotic spindle. As a result of that centrosome division and movements, the poles of the mitotic spindle contain one old and one young centrosome. The positioning of the centrosome influences the directionality of cell division [5]. In an asymmetric division of stem cells, the age of centrosomes affects the stability of the microtubule-kinetochore complex. Kinetochore-microtubules associated to old centrosomes are more stable than those associated to young centrosomes [6]. The repositioning of a centrosome in cells with pseudopods stabilizes a chosen direction of movement [7]. Whether a neuroblast divides symmetrically or asymmetrically often depends on the orientation of the mitotic spindle, and this is dictated by centrosomes. The centrosomal protein centrobin is responsible for asymmetric centrosome behavior [8].

The aim of this work is to study how a different oscillatory behavior of centrosomes and their mass arrangement affect the kinetic energy of pairs dyads of sister chromatids in the system of the mitotic spindle during metaphase. The analyses are done through a biomechanical oscillatory model of the mitotic spindle.

2. METHODS

The analyses of the kinetic energy of dyads of sister chromatidsin the mitotic system are done through the biomechanical oscillatory model of the mitotic spindle. The numerical analyses were based on our previous studies [9], [10]. The biomechanical oscillatory model of the mitotic spindle is presented as a system of coupled oscillators where coupling is made over two rheonomic centers – centrosomes. One oscillatory pair consists of a centrosome, a microtubule, and a related chromosome and these are interconnected with their homologous pair. Each element in the model has its mechanical counterpart. See Fig 1B and ref [4], [9], [10].

The analytical expressions for the kinetic energy of the oscillating dyads of sister chromatids are given for the case when the biomechanical system of the mitotic

handjelka@turing.mi.sanu.ac.rs

spindle is conservative, linear, and when it oscillates under external single-frequency oscillation. These are the assumptions of the model. Although the environment (cytoplasm) where chromosomes are oscillating in metaphase and anaphase can be considered as a fluid with low Reynold number for the simplicity of mathematical formulations we do not take into account turbulent damping and viscose drag.

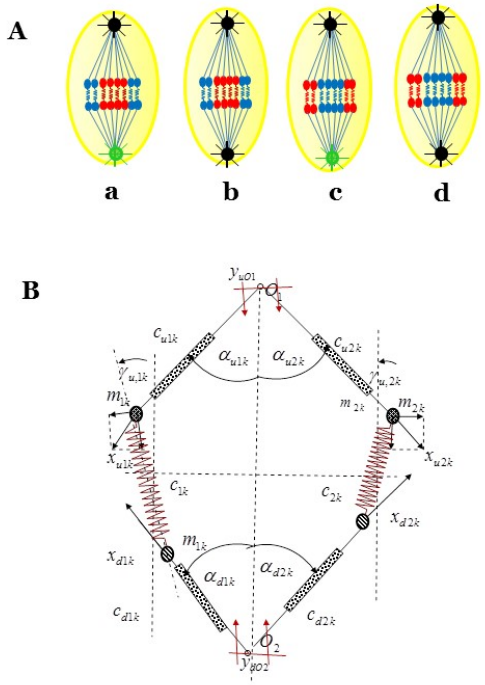

Figure 1. **A**. The schematic representation of the centrosome oscillatory frequencies and different positions of chromosomes in the metaphase equatorial plane. Chromosomes with heavier masses are marked red. The same color of the centrosome denotes that centrosomes oscillate with the same oscillatory frequency. **B**. The general proposed oscillatory model of the mitotic spindle with inertia elements on the poles of the cell that represent centrosomes. Only two coupled pairs of homologue chromosomes are presented.

Numerical analyses with some approximation for mouse chromosomes were done for the cases when centrosomes oscillate with the same and with different single frequencies. The arrangement of chromosomes with different masses was varied for both cases. See Fig. 1A.

The assumptions of the model: the rheonomic centers of oscillation with masses M1 and M2 generate oscillations and oscillate along a vertical axis. Oscillations are transferred trough a standard light elastic element to the homologous chromosome – mass particle and its homologue pair. During anaphase, dyads of sister chromatids are disconnected (the elastic spring that interconnects mass particles breaks) and the dyads move in an oscillatory manner to the corresponding centrosome-spindle rheonomic oscillatory centers. For the sake of the simplicity of the model, we consider that the system is conservative without any energy dissipation; the kinematical excitation of the rheonomic centers of oscillation is each with a single frequency and only in the vertical axis while the movement of the centrosomes in the other axis is neglected. We assume that the eigen oscillations of the subsystem are negligible so they are not considered.

This model utilized the principle of dynamical equilibrium. On basis of this principle we create system of differential equations that describes sum of active, reactive and fictive forces that are present in system of mitotic spindle. Using the particular solutions of the system of differential equations we determined the kinetic energy of dyads of sister chromatids corresponded to forced vibrations.

2.1. The kinetic energy in the system of the mitotic spindle in the pure elastic model

The total kinetic energy $\mathbf{E}_{K,ik}$ of the $_{ik}$ - dyads of sister chromatidsincluding the kinetic energies of centrosomes caused by rheonomic excitation coupled with a standard light elastic element under the $\alpha_{uik} = \alpha_{dik} = \alpha_{ik}$ angle with the direction of kinematic excitation (see Fig. 1B and Refs [11]-[13]) is:

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

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

$$\mathbf{E}_{K,ik} = \frac{1}{2} m_{uik} \left[\left(\dot{x}_{uik} + \dot{y}_{uO1} \cos\alpha_{uik} \right)^2 + \left(\dot{y}_{uO1} \sin\alpha_{uik} \right)^2 \right] + \frac{1}{2} M_u \left(\dot{y}_{uO1} \right)^2 + \\ + \frac{1}{2} m_{dik} \left[\left(\dot{x}_{dik} + \dot{y}_{dO2} \cos\alpha_{dik} \right)^2 + \left(\dot{y}_{dO2} \sin\alpha_{dik} \right)^2 \right] + \frac{1}{2} M_d \left(\dot{y}_{dO2} \right)^2$$

$$i = 1, 2 \ldots 20 \tag{3}$$

with the assumption that the rheonomic centers of excitation are equal;

where m_u and m_d are masses of the homologue chromosomes (upper and lower, respectively), $\dot{x}_u$ and $\dot{x}_d$ are the relative velocities for the upper and lower dyads of sister chromatidsin the direction of the standard light elastic element, and $\dot{y}_{uO1} \cos\alpha_{uik}$ and $\dot{y}_{dO1} \cos\alpha_{dik}$ and $\dot{y}_{uO1} \sin\alpha_{uik}$ and $\dot{y}_{dO1} \sin\alpha_{dik}$ are, respectively, the components of the transfer velocity in the collinear and orthogonal direction of the standard light elastic element for upper and lower dyads of sister chromatids. M_u and M_d are the masses and $\dot{y}_{uO1}$ and $\dot{y}_{dO2}$ are the velocities of the rheonomic centers of oscillations. See ref [4]. x_{u1k}, x_{u2k}, x_{d1k}, and x_{d2k} are independent generalized coordinates for upper and lower dyads of sister chromatids, y_{gO1} and y_{gO2} are the rheonomic coordinates, i.e., the kinematical mobility of the rheonomic centers, and c_{u1k}, c_{u2k}, c_{d1k}, and c_{d2k} are the rigidities of standard light elastic elements that represent microtubules. In this paper, the rigidities of all microtubules are considered equal. c_{1k} and c_{2k} are rigidities of coupling between a pair of homologue chromosomes and correspond to the rigidity of

chromatin. In this paper, the rigidities of coupling between a pair of homologue chromosomes are considered equal. α_{u1k}, α_{u2k}, α_{d1k}, and α_{d2k} are angles between the microtubules and the direction of kinematic excitation, which is in this case considered equal. See Fig 1B.

A mouse has 20 pairs of chromosomes. The angle of mitotic spindle – an angle between the rheonomic centers and the chromosomes on the very periphery of the mitotic spindle – was taken to be $\pi/2$. Regarding the vertical axis that interconnects the two opposite rheonomic centers – centrosomes, we assume that the dyads of sister chromatidsare equally distributed. The distribution of chromosome masses is assumed to be relatively symmetrical regarding the symmetry of the line that interconnects two rheonomic centers (intercentromeric distance). The model has a relatively balanced distribution of chromosome masses in the vertical axis of symmetry and an identical distribution of masses in the horizontal plane – dyads of sister chromatids. See ref [10].

The data on the chromosome mass for mouse chromosomes were taken from ref [14]. As data in ref [14] denote masses for 4 chromatids, data from the table from ref [14] were divided by 2 and expressed in kg. The numerical analysis thus corresponds to the first meiotic division. The data on the rigidity of the eukaryote metaphase chromosomes c_c was calculated from the equation $c_c = \frac{E_c r^2 \pi}{l_c}$ where E_c is Young's modulus of the eukaryote metaphase chromosome, r is the diameter and l_c is the length of the eukaryote metaphase chromosome taken from [15] ($E_c = 10^3 Pa$, $r = 3\mu m$, $l_c = 20\mu m$, $c_c = 1.413\times10^{-3} N/m$). The rigidity for the microtubules at 37°C c_m was calculated according to the equation $c_m = \frac{E_m(R_o^2 - R_i^2)\pi}{l_m}$ where E_m is Young's modulus of microtubules at 37°C, R_O and R_i are the outer and inner diameter of microtubules respectively, l_m is the length of the microtubules taken from ref [16] ($E_m = 1.9\times10^8 Pa$, $R_O = 30nm$, $R_i = 18nm$, $c_m = 3.44\times10^{-6} N/m$). The data for the rheonomic centers of oscillation were calculated according to the data for angular frequency oscillation for centrosome taken from [17] ($2\pi/T$, for T_1=20 s and T_2=15 s, $\Omega_1 = 0.314/s$, $\Omega_2 = 0.419/s$. For the case when centrosomes are considered to oscillate with the same frequency, T1 was used for numerical calculations. The centrosome mass was calculated from the centrosome volume (1.5 μm³) from http://www.proteinatlas.org/humancell/centrosome and density (taken approximately as the data for the density for the cell organelle – mitochondria 1.05 g/ml) – ($1.575\text{x}10^{-15}$ kg) [18]. The data for centrosome amplitude oscillations were taken from [19] (2.1 μm=$2.1\text{x}10^{-6}$ m).

What was determined was the distribution of kinetical energies of dyads of sister chromatidsin the mechanical oscillatory model of the mitotic spindle regarding the different/same frequency of centrosome excitation when:

A. chromosomes with heavier masses have the central position – Fig. 1A and Fig. 1B;
B. chromosomes with heavier masses have a peripheral position – Fig. 1C and Fig. 1D.

3. Results and Discussion

3.1. Distribution of kinetic energies in the mitotic spindle regarding mass distribution and centrosome excitation

If centrosomes oscillate with different frequencies, the energy of dyads of sister chromatids has a non-linear oscillatory character. The maximum values of the amplitudes of the kinetic energy of the same dyad are equal in the case of equal frequencies of forced centrosome excitation.

The kinetic energies of a dyads of sister chromatids (mouse chromosome 1 to chromosome 10) when chromosomes with heavier masses are positioned in the central part of the equatorial plane of the mitotic spindle are presented in Fig. 2 for the case with different (Fig. 2A) and same (Fig. 2B) oscillatory frequencies.

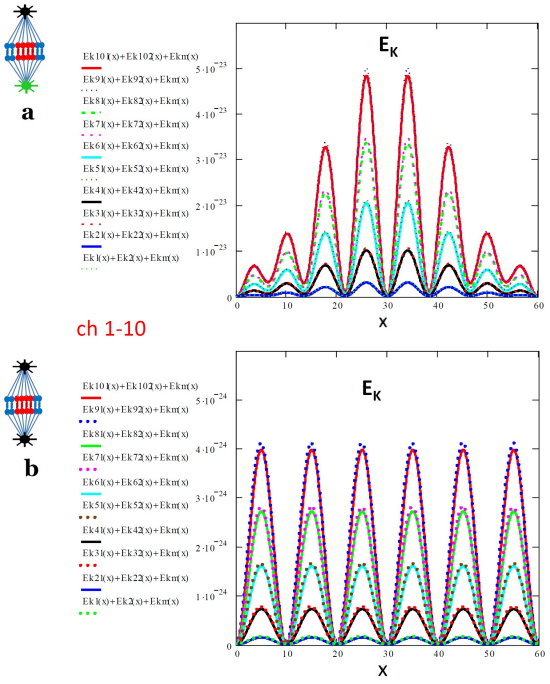

Figure 2. **A**. The kinetic energy for the first 10 pairs of mouse chromosomes when they occupied the central part of the mitotic spindle and when centrosomes oscillate with different single frequencies. **B**. The kinetic energy for the first 10 pairs of mouse chromosomes when they occupied the central part of the mitotic spindle and when centrosomes oscillate with the same single frequency.

When the same 10 pairs of dyads of sister chromatids are positioned at the peripheral part of the mitotic spindle, the kinetic energies of a dyads of sister chromatids are approximately higher for one order of magnitude regardless of the fact whether the centrosome oscillates with the same or different single frequency. See Fig. 3.

Regardless of the distribution of chromosome masses (central or peripheral position of chromosomes with heavier masses), the kinetic energy for each particular dyads of sister chromatids is lower in the central zone of the mitotic spindle, but the amplitudes of the kinetic energy for each dyad of sister chromatids subsystems are lower when chromosomes with heavier masses are positioned in the central zone of mitotic spindle compared to the case when they have peripheral positions in the mitotic spindle.

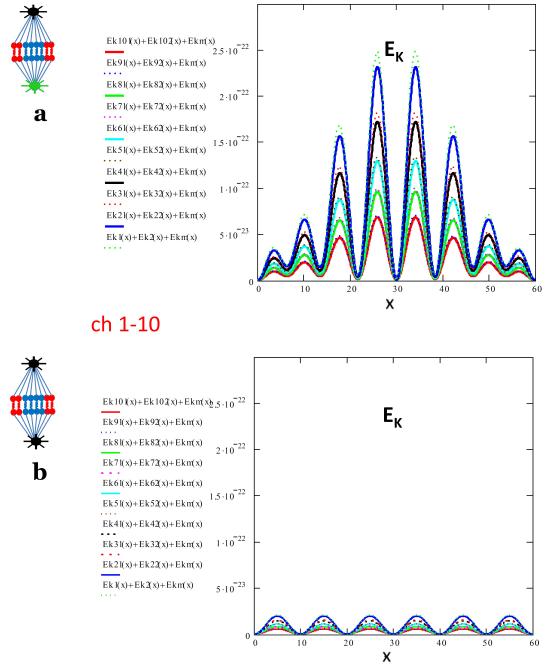

Figure 3. **A**. The kinetic energy for the first 10 pairs of mouse chromosomes when they occupied a peripheral part of the mitotic spindle and when centrosomes oscillate with different single frequencies. **B**. The kinetic energy for the first 10 pairs of mouse chromosomes when they occupied a peripheral part of the mitotic spindle and when centrosomes oscillate with the same single frequency.

The oscillatory model of the mitotic spindle shows that the kinetic energy of oscillating dyads of sister chromatids has not only a temporal but also a special oscillatory character, indicating that kinetic energy is not constant during the metaphase and not constant in each part of the mitotic spindle. We are free to suggest that this difference in energy distribution regarding different centrosome oscillatory frequencies in the same cell and mass chromosome distribution may carry additional epigenetic information and could be important for the process of cell differentiation. The repositioning of the centrosome in the cells with pseudopods stabilizes a chosen direction of movement [7].

In ref [20], the authors show that spindle oscillations in anaphase are species-specific and that the maximum amplitude of spindle oscillations is determined by the time spent in the oscillating phase. “Spindle shape asymmetry is a highly conserved mechanism that also operates in the mouse developing mammalian cerebral cortex where it plays a major role in the tight spatiotemporal control of self-renewal and differentiation during corticogenesis” [21]. In that context, the numerical analysis which uses an oscillatory model of the mitotic spindle indicates that different centrosome excitation could be an important factor in the process of cell differentiation. The cell differentiation process is governed by the activation of certain genes that is time-specific. The cell microenvironment contributes to the process of gene activation. Centrosome behavior is also governed by specific genes. Differences in the kinetic energy pattern of moving chromosomes when centrosomes are oscillating with the same and with different frequencies could not only be just the manifestation of different centrosome behavior that is governed by specific genes, but it could also carry additional epigenetic information within the cell that could influence the process of cell differentiation. The position of chromosomes in the mitotic spindle also affects the kinetic energy not only because of the different angle that microtubules forms with the direction of the kinematic excitation but also because of the different distribution of chromosome masses within the system of the mitotic spindle. Civelekoglu-Scholey and Cimini [22] review the quantitative models of metaphase chromosome dynamics, the models of metaphase spindle length control and anaphase spindle elongation: force-balance models, spindle elongation model and the slide and cluster model. These models are mostly focus on dynamics at the kinetochors, or sliding between MTs. Force-balance models assume the sum of the forces generated by various spindle parts to be balanced by the viscous drag forces on the moving chromosome. “Viscous drag forces are proportional to the rate of movement and the friction coefficient of the module.” [22] A new and very interesting model of mitotic spindle as a whole was recently proposed by Iakovliev et al [23]. They create a finite element parameterised model of interpolar microtubules (MTs), astral MTs and MT connectors varying the number of MT filaments and the arrangement of their interconnections to study the stability of equilibrium of a mitotic spindle as a whole. In their model, MTs and connectors are modeled on a basis on linearly elastic isotropic Bernoulli-Euler beam, all parts of the spindle are elastically coupled; any post-buckling is ignored. They perform modal buckling analysis and obtain critical buckling loads and associated modes. In our model we do not take into account turbulent damping and viscose drag for the simplicity of mathematical formulations. We did the assumption that the system of mitotic spindle is conservative. Behavior of chromosome movements in viscous environment can be partially explained by modeling microtubules as a viscoelastic element, but that will be considered in our future investigations. Our model is an oscillatory model

which uses a different approach from the force-balance models. Considering centrosomes as rheonomic centers of oscillation is a new concept in modeling dynamics of mitotic spindle.

4. Conclusion

We study how different oscillatory behavior of centrosomes and mass chromosome distribution in the equatorial plane during metaphase affect the kinetic energy of dyads of sister chromatids in the system of the mitotic spindle.

The analyses are done through the biomechanical oscillatory model of the mitotic spindle. Thenumerical experiment reveals that the kinetic energy of an oscillating dyads of sister chromatids has an oscillatory character and is affected by the mass chromosome distribution and the frequency of centrosome excitation. Phenomenologically, this indicates that position of chromosome and oscillatory pattern of centrosomes are very important for the distribution of energy inside the cytoplasm, postulating existence of energy compartments inside the cell during the cell division.

We are free to propose that cytoplasm energy compartments due to different centrosome oscillatory frequencies and different arrangements of chromosomes may carry additional epigenetic information and could be important for the process of cell differentiation. If we can create an energy map of dividing cell and learn how to interpret it, we can develop a new experimental set up for detection of cell differentiations and cancerogenesis. It is possible that each cell line has its energy map in healthy and pathological states. If we can learn how to read it, we can improve the diagnostics and develop new therapeutic approaches.

There some limitations of the model: system is considered conservative, although real cell is non-conservative system, turbulent dumping and viscous drag are not included into the model. The effects of viscous drag may be covered by modeling the microtubules as viscoelastic elements. We will try to overcome these limitations of the model in our future investigations.

Acknowledgements: *Parts of this research were supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia through the Mathematical Institute of the SASA, Belgrade Project ON174001 "Dynamics of hybrid systems with complex structures. Mechanics of materials".*

References

1. A. Weise et al., "Chromosomes in a genome-wise order: evidence for metaphase architecture," *Mol. Cytogenet.*, vol. 9, no. 36, pp. 1 – 11, Apr. 2016.
   DOI: 10.1186/s13039-016-0243-y
   PMid: 27123045
2. E. A. Franklin, W. Z. Cande, "Nuclear Organization and Chromosome Segregation," *Plant Cell*, vol. 11, no. 4, pp. 523 – 534, Apr. 1999.
   DOI: 10.1105/tpc.11.4.523
   PMid: 10213775
3. V. Magidson et al., "The Spatial Arrangement of Chromosomes during Prometaphase Facilitates Spindle Assembly," *Cell*, vol. 146, no. 4, pp. 555 – 567, Aug. 2011.
   DOI 10.1016/j.cell.2011.07.012
   PMid: 21854981
   PMCid: PMC3291198
4. A. N. Hedrih, K. Hedrih, "Resonance as potential mechanism for homolog chromosomes separation trough biomechanical oscillatory model of mitotic spindle," in *Proc. 6th Int. Congress of Serbian Society of Mechanics*, Mountain Tara, Serbia, 2017. pp. 1 – 10.
   Retrieved from: https://www.researchgate.net/publication/318113047_Resonance_as_potential_mechanism_for_homologue_chromosomes_separation_trough_biomechanical_oscillatory_model_of_mitotic_spindle;
   Retrieved on: Jun. 3, 2018
5. I. V. Maly, "Systems biomechanics of centrosome positioning A conserved complexity," *Commun. Integr. Biol.*, vol. 4, no. 2, pp. 230 – 235, Mar. 2011.
   DOI: 10.4161/cib.4.2.14548
   PMid: 21655449
   PMCid: PMC3104588
6. I. Gasic, P. Nerurkar, P. Meraldi, "Centrosome age regulates kinetochore–microtubule stability and biases chromosome mis-segregation," *Elife*, vol. 4, pp. 1 – 15, Aug. 2015.
   DOI: 10.7554/eLife.07909
   PMid: 26287477
   PMCid: PMC4579388
7. M. Ueda, R. Graf, H. K. Macwilliams, M. Schliwa, U. Euteneuer, "Centrosome positioning and directionality of cell movements," *PNAS*, vol. 94, no. 18, pp. 9674 – 9678, Sep. 1997.
   DOI: 10.1073/pnas.94.18.9674
   PMid: 9275182
8. P. T. Conduit, "The dominant force of Centrobin in centrosome asymmetry," *Nat. Cell. Biol.*, vol. 15, no. 3, pp. 235 – 237, Mar. 2013.
   DOI: 10.1038/ncb2704
   PMid: 23449145
9. A. Hedrih, "Relation between centrosome excitation and oscillatory energy of mitotic spindle in metaphase trough biomechanical oscillatory model of mitotic spindle" in *Book of Abstr. 4th Int. Seminar "Nonlinear Phenomenology Advances",* Saint Petersburg, Russia, 2017.
   A. Hedrih, K. Hedrih. "Influence of mass chromosome distribution in equatorial plane on oscillatory energy of mitotic spindle trough biomechanical oscillatory model of mitotic spindle," in *14th Int. Conf. Dynamical Systems – Theory and Applications (DSTA 2017)*, Lodz, Poland, 2017.
   Retrieved from: https://www.dys-ta.com/abs_view?pkey=agxzfmR5cy10YS10cmRyEgsSBVBhcGVyGICAgKC-q4kJDA;
   Retrieved on: Jun. 3, 2018
10. Д. Рашковић, *Теорија осцилација*, 3. изд, Београд, Србија: Грађевинска књига, 1974. (D. Rašković, *Theory of oscillations*, 3rd ed., Belgrade, Serbia: Građevinska knjiga, 1974.)
    Retrieved from: https://www.scribd.com/document/165759261/Teorija-Oscilacija-D-Raskovic;
    Retrieved on: Jun. 3, 2018
11. А. А. Андронов, А. А. Витт, С. Э. Хайкин, *Теория колебаний*, Москва, Россия: Наука, 1981. (A. A. Andronov, A. A. Witt, S. E. Khaikin, *Theory of oscillations*, Moscow, Russia: Nauka, 1981.)
12. K. Hedrih, "Dynamics of coupled systems," *Nonlinear Analysis: Hybrid Systems*, vol. 2, no. 2, pp. 310 – 334, Jun. 2008.

DOI: 10.1016/j.nahs.2006.06.003
13. G. L. Ortega, A. Stoholski, R. C. Mellors, J. Hlinka, "Chromosomal mass in germinal cells and in cancer cells of the mouse," *Exp. Cell. Res.*, vol. 12, no. 3, pp. 560 – 567, Jun. 1957.
DOI: 10.1016/0014-4827(57)90171-4
14. B. Houchmandzadeh, J. F. Marko, D. Chatenay, A. Libchaber, "Elasticity and structure of eukaryote chromosomes studied by micromanipulation and micropipette aspiration," *J. Cell. Biol.*, vol. 139, no. 1, pp. 1 – 12, Oct. 1997.
DOI: 10.1083/jcb.139.1.1
PMid: 9314524
PMCid: PMC2139812
15. A. Kis, S. Kasas, A. J. Kulik, S. Catsicas, L. Forró, "Temperature-dependent elasticity of microtubules," *Langmuir*, vol. 24, no. 12, pp. 6176 – 6181, Jun. 2008.
DOI: 10.1021/la800438q
PMid: 18494514
16. I. V. Maly, *Systems Biomechanics of the Cell*, New York (NY), USA: Springer, 2013.
DOI: 10.1007/978-1-4614-6883-7
17. R. Milo, R. Phillips, "Concentrations and absolute numbers," in *Cell Biology by the Numbers*, New York (NY), USA: Taylor & Francis Group, 2016. ch 2. sec. 2, pp. 87 – 128.
18. R. J. Kuhn, M. Poenie, "Dynamic polarization of the microtubule cytoskeleton during CTL-mediated killing," *Immunity*, vol. 16, no. 1, pp. 111 – 121, Jan. 2002.
DOI: 10.1016/S1074-7613(02)00262-5
19. S. Riche et al., "Evolutionary comparisons reveal a positional switch for spindle pole oscillations in Caenorhabditis embryos," *J. Cell. Biol.*, vol. 201, no. 5, pp. 653 – 662, May 2013.
DOI: 10.1083/jcb.201210110
PMid: 23690175
20. D. Delaunay, V. Cortay, D. Patti, K. Knoblauch, C. Dehay, "Mitotic spindle asymmetry: aWnt/PCP-regulated mechanism generating asymmetrical division I ncortical precursors," *Cell Rep.*, vol. 6, no. 2, pp. 400 – 414, Jan. 2014.
DOI: 10.1016/j.celrep.2013.12.026
PMid: 24412369
21. G. Civelekoglu-Scholey, D. Cimini, "Modelling chromosome dynamics in mitosis: a historical perspective on models of metaphase and anaphase in eukaryotic cells," *Interface Focus*, vol. 4, no. 3, 20130073, Jun. 2014.
DOI: 10.1098/rsfs.2013.0073
PMid: 24904736
PMCid: PMC3996585
22. A. Iakovliev, S. Dasmahapatra, A. Bhaskar, "Stability of mitotic spindle using computational mechanics," unpublished.