RESONANCE AS POTENTIAL MECHANISM FOR HOMOLOG CHROMOSOMES SEPARATION TROUGH BIOMECHANICAL OSCILLATORY MODEL OF MITOTIC SPINDLE

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Abstract

During uniform distribution of chromosomes throughout cell division process an important role plays complex machinery called mitotic spindle. Biomechanics of mitotic spindle is very complex involving specific forces generated in the- and outside the spindle. Elongation speed of mitotic spindle, as well as elongation length of mitotic spindle during anaphase B mainly depends on cell type and conditions in which cell division take place. There are several theoretical models of anaphase B: slide and flux or elongate model, slide and cluster model, and cell size dependent spindle elongation model. The aim of this work was to consider a mitotic spindle as a system of coupled oscillators and to analyze the conditions for sister chromatid separation in anaphase trough the biomechanical oscillatory model of mitotic spindle. The basic concept of biomechanical model of mitotic spindle is given: centrosomes are presented as mass particles that represent two rheonomic centers of oscillations. Microtubules are presented with standard light visco-elastic element. Sister chromatids are represented as mass particles that are interconnected with standard light massless elastic spring. Homologue chromosomes have equal masses and different chromosomes have different masses. In the case of excitation of reonomic centers of oscillations each with a single frequency, two differential equations of motion for each pair of homologue chromosomes are given. An expression for total mechanical energy of oscillating pair of homologues chromosomes is also given. We assume that resonance could be a condition for disconnection of homologue chromosomes that is desirable event in anaphase, but also resonance could also be the condition (form the mechanical point of view) for disconnection between kinetochore and microtubule which, when occurs, leads to aneuploida-non equal distribution of genetic material between cells. Conditions for resonance occurrence are analyzed.

Key words: chromosomes, mitotic spindle, oscillations, resonance, biomechanical model

1. Introduction

Mechanism of chromosomes movements within cell during cell division requires precise functioning of a complex structure named mitotic spindle. Biomechanics of mitotic spindle is very complex involving specific forces generated in the- and outside the spindle [1]. The way chromosomes move within the cell is called functional genomic architecture and include chromosomal territories (CTs). Weise et al [2] postulate that functional genomic architecture is not only present in interphase but also in metaphase stage of cell division cycle. These nuclear CTs show a functional character in spatial, temporal and cell type specific organization [2]. Several models exist to explain this organization. One of the models predicts central location of gene rich chromosomes within cell nucleus and gene-poor chromosomes located in a zone close to the nuclear edge [1, 2]. Different chromosomes have different chromatid separation times: some chromosomes begin anaphase movements toward the spindle poles before others (e.i. the chromosomes with the largest blocks of pericentric heterochromatin are the last to separate) [3]. This specific spatial organization of mitotic spindle observed in many cell types [4] still need an exact explanation. **"**The separation of sister chromatids during anaphase consists of two distinct processes: Anaphase A, the movement of chromosomes toward spindle poles via shortening of the connecting fibers, and anaphase B, separation of the two poles from one another via spindle elongation" [5]. Elongation speed of mitotic spindle as well as elongation length of mitotic spindle during anaphase B mainly depend on cell type and conditions in which cell division take place [6]. There are several theoretical models of anaphase B: the slide and flux-or-elongate, the slide-and-cluster model and the cell-size dependent spindle elongation model [6]. Anaphase B spindle design is different in different organisms [6].

Poleward movement during anaphase A is mostly but not entirely unidirectional-it exhibits non-linear oscillatory behavior.-generally it the time/distance curve of kinetochore directional instability during anaphase A has declining shape with local min and maximum [5]. Many protein structures are involve in regulation of mitotic spindle proper functioning: Usp16 (ubiquitin specific peptidase) regulates the kinetochore localization of Plk1 to promote proper alignment and timely separation of chromosomes. "Plk1 is an important mitotic regulator that play a critical role in regulating chromosome alignment. Cdk1 phosphorylates Usp16 and enhances its binding to Plk1" [7].

There are some age related changes in proper functioning of mitotic spindle: "Inter-kinetochore distance in bivalents during metaphase I increase with maternal age"[5]. "In human eggs, aneuploidy increases with age and can result in infertility and genetic diseases. Studies in mouse oocytes suggest that reduced centromere cohesion and spindle assembly checkpoint (SAC) activity could be at the origin of chromosome missegregation. Little is known about these two features in humans" [8]. Castro et al [8] showed that inter-kinetochore distances of bivalent chromosomes in human eggs, strongly increase with age. According to their results BUB1 and BUBR1 proteins localize at the kinetochore with a similar temporal timing than in mitotic cells and in a MPS1-dependent manner. Their results suggest that mitotic spindle checkpoint is inactivated when centromere cohesion is lost in MI (meiosis I) and consequently cannot inhibit premature sister chromatide separation. The kinetochore localization of BUB1 and BUBR1 proteins decreases with the age of the oocyte donors. This could contribute to oocyte aneuploidy" [8].

"The Spindle assembly check point–SAC is a safeguard mechanism to avoid premature chromosome segregation before correct kinetochore binding to the spindle. In human mitotic cells, SAC activity delays anaphase onset until all chromosomes are correctly attached to the spindle. Without SAC, mitosis is accelerated and chromosome missegregation occurs" [8].

The aim of this work was to give the basic description of the oscillatory model of mitotic spindle, to analyze and discuss conditions for obtaining resonance as potential mechanism for homolog chromosomes separation trough this model. To find the conditions for resonance to occur as a potential mechanism for homolog chromosome separation we use biomechanical oscillatory model

2

of mitotic spindle [9]. Model is developed for animal cells. Proposed oscillatory model represents different approach from existed anaphase models of mitotic spindle. The purpose of the oscillatory model of mitotic spindle is to explain behavior and movements of chromosomes during anaphase of the cell division process from the biomechanical point of view on a simplified way. Complex molecular structures like microtubules, kinetochores, centrosome are represent with simple mechanical structures in order to explain their oscillatory movements.

As aging causes a loss of meiotic chromosome cohesion [8], the proposed model could be suitable for explaining age related aberrations in mitotic spindle functioning.

2. Basic concept of the biomechanical oscillatory model of mitotic spindle

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 are presented with standard light visco-elastic fractional order element. Homologues chromosomes are represented as mass particles that are interconnected with standard light linear elastic element. Homologue chromosomes have equal masses but masses of different chromosomes could be different. Elastic spring that interconnects mass particles represents centromere structure. See Fig. 1. 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 visco-elastic element to homolog chromosome – mass particle and its homologue pair. Structure of oscillatory model of mitotic spindle is horizontally symmetric like mirror image. 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 - rheonomic oscillatory centers. Breakage of elastic springs are desirable breakage thus this ensure equal distribution of genetic material in sister cells. If the breakage occurs in visco-elastic element (microtubule) aneuploidia occurs - the whole chromosome moves to the opposite pole of the cell and that cell will has one chromosome more and the other cell will has one chromosome less and all gens that are coded on that chromosome will lack in one cell and will be duplicated in another cell with corresponding consequences in both cells.

Component velocities of homologue chromosomes/material particles are: relative velocity for upper $\dot{x}_{gik}$ and lower $\dot{x}_{dik}$ homologues chromosomes in direction of standard light visco-elastic element and components of transfer velocity: in collinear $\dot{y}_{gO1}\cos\alpha_{gik}$ and $\dot{y}_{dO1}\cos\alpha_{dik}$ and in orthogonal $\dot{y}_{gO1}\sin\alpha_{gik}$ and $\dot{y}_{dO1}\sin\alpha_{dik}$ directions of standard light visco-elastic element, see Fig 2. We assume that angles between direction of microtubule-standard light visco-elastic element and vertical axis that interconnect opposite rheonomic centres α_{gik} and α_{dik} are relatively constant.

Square of absolute velocity of one homologue chromosome/ k -th material particle in each subset – are (see Refs.[10, 11, 12]):

$$v_{gik}^2 = \left(\dot{x}_{gik}+\dot{y}_{gO1^2}\cos\alpha_{gik}\right)^2 + \left(\dot{y}_{gO1}\sin\alpha_{gik}\right)^2, \quad v_{dik}^2 = \left(\dot{x}_{dik}+\dot{y}_{dO2}\cos\alpha_{dik}\right)^2 + \left(\dot{y}_{dO2}\sin\alpha_{dik}\right)^2 \tag{1}$$

$i = 1,2,..,N$

In human cells $N = 24$.

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

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

with assumption that inclination of the standard light linear elastic element could be neglected.

3

In the case of kinematical excitation of rheonomic centers of oscillations (centrosomes) each with single frequency, differential equations of motion for each pair of homologue chromosomes are derived.
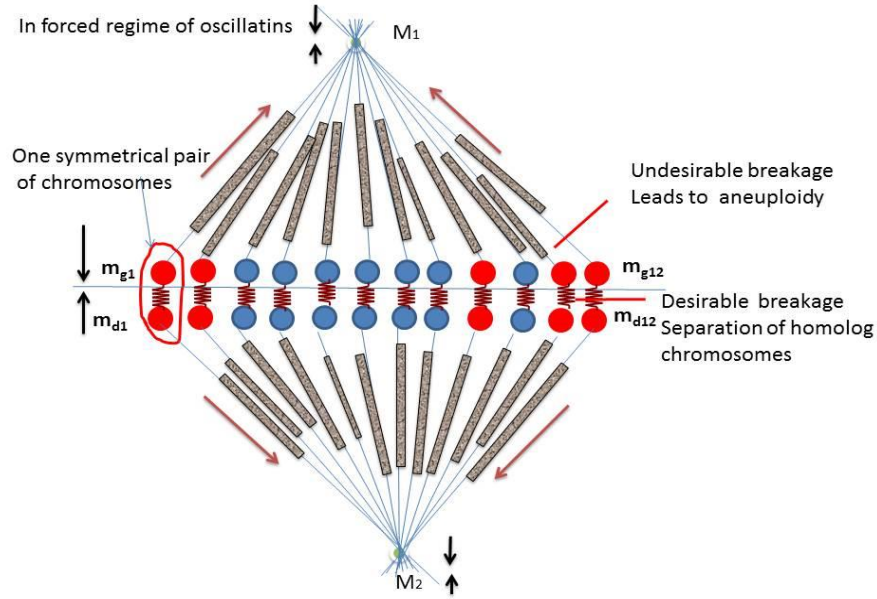

Fig. 1. Biomechanical model of mitotic spindle in forced regime of oscillations with different distribution of chromosomes with different masses. Rectangles denote visco-elastic elements that represent microtubules. Elastic springs denote connection between pair of homologues chromosomes-kinetochore complexes.
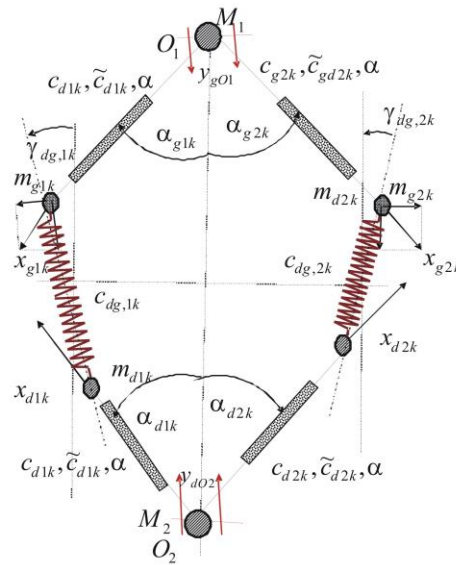

Fig. 2. General oscillatory model of mitotic spindle with inertia elements on the poles of the cell, that represent centrosomes. Only two pairs of homologues chromosomes are presented. Kinematical excitation of mitotic spindle occur in the rheonomic centers in vertical axis with synchronous or asynchronous kinematic excitation.

4

When kinematic excitation of rheonomic centers with masses M_1 and M_2 occurs, their velocities are: $v_{O1} = \dot{y}_{gO1}, v_{O2} = \dot{y}_{gO2}$.

Total kinetic energy $\mathbf{E}_{K,ik}$ of ik-pair of homologues chromosomes/material particles including kinetic energies of centrosome caused by rheonomic excitation coupled with standard light visco-elastic element under angle $\alpha_{gik} = \alpha_{dik} = \alpha_{ik}$ with direction of kinematic excitation is (see Refs, [10-13]):

$$\mathbf{E}_{K,ik} = \frac{1}{2}m_{gik}\left[\left(\dot{x}_{gik} + \dot{y}_{gO1}\cos\alpha_{gik}\right)^2 + \left(\dot{y}_{gO1}\sin\alpha_{gik}\right)^2\right] + \frac{1}{2}m_{dik}\left[\left(\dot{x}_{dik} + \dot{y}_{dO2}\cos\alpha_{dik}\right)^2 + \left(\dot{y}_{dO2}\sin\alpha_{dik}\right)^2\right] + \frac{1}{2}M_1\dot{y}_{gO1}^2 + \frac{1}{2}M_2\dot{y}_{gO2}^2 \tag{3}$$

with assumption that rheonomic centers of excitations are equal.

Expression of potential energy $\mathbf{E}_P$ of two standard visco-elastic and one standard light elastic elements containing in each of the sub-system with one pair of coupled two mass particles and rheonomic center is:

$$\mathbf{E}_P = \mathbf{E}_{P,gik} + \mathbf{E}_{P,dik} + \mathbf{E}_{PE,ik}$$

$$\mathbf{E}_P = \frac{1}{2}c_{gik}x_{gik}^2 + \frac{1}{2}c_{dik}x_{dik}^2 + \frac{1}{2}c_{ik}\left[\left(y_{gO1} + y_{dO2}\right) + \left(x_{gik}\sin\alpha_{gik} + x_{dik}\sin\alpha_{dik}\right)\right]^2 \tag{4}$$

x_{gik} and x_{dik} are independent generalized coordinates, y_{gO1} and y_{gO2} are rheonomic coordinates –kinematical mobility of rheonomic centers, c_{gik}, c_{dik} and c_{ik} are rigidities of standard light visco-elastic and elastic elements – coupling between pair of mass particles (see denotation on Fig.2. and Refs. [11, 12]).

Standard light fractional order creep element for which the constitutive stress-strain relation for the restitution force as the function of element elongation is given by fractional order derivatives in the form (see Refs [14, 15]):

$$P(t) = -\left\{c_0 x(t) + c_\alpha \mathfrak{D}_t^\alpha[x(t)]\right\} \tag{5}$$

where $\mathfrak{D}_t^\alpha[\bullet]$ is operator of the αth derivative with respect to time t in the following form:

$$\mathfrak{D}_t^\alpha[x(t)] = \frac{d^\alpha x(t)}{dt^\alpha} = x^{(\alpha)}(t) = \frac{1}{\Gamma(1-\alpha)}\frac{d}{dt}\int_0^t \frac{x(\tau)}{(t-\tau)^\alpha}d\tau \tag{6}$$

where c_0, c_α are rigidity coefficients – momentary and prolonged one, and α a rational number between 0 and 1, $0 < \alpha < 1$.

Generalized function of fractional order dissipation of energy is in the form (see Refs [14, 15]):

$$\mathbf{P}_{W,ik} = \mathbf{P}_{W,gik} + \mathbf{P}_{W,dik} = \frac{1}{2}\tilde{c}_{gik}\left(\mathfrak{D}_t^\alpha[x_{gik}]\right)^2 + \frac{1}{2}\tilde{c}_{dik}\left(\mathfrak{D}_t^\alpha[x_{dik}]\right)^2 \tag{7}$$

Considering the coupling of homologues chromosomes in the proposed mechanical oscillatory model of mitotic spindle, in general case, we will have system of N coupled subsystems of ordinary fractional order differential equations that describes motions of the material particles in the system in forced oscillatory regime. If we expressed properties of visco-elastic elements with constitutive relation in fractional order derivatives by generalized function of fractional order dissipation of subsystem energy by (7), we will have system of fractional order differential

equation, obtained by extended Lagrange's differential equations in the following form (see Refs, [14, 15]):

$$\frac{d}{dt}\left(\frac{\partial \mathbf{E}_K}{\partial \dot{x}_{gik}}\right) - \frac{\partial \mathbf{E}_K}{\partial x_{gik}} + \frac{\partial(\mathbf{E}_P + \mathbf{E}_{PE})}{\partial x_{gik}} + \frac{\partial \mathbf{P}_W}{\partial(\mathfrak{D}_t^\alpha[x_{gik}])} = X_{gik},\tag{8}$$

$$\frac{d}{dt}\left(\frac{\partial \mathbf{E}_K}{\partial \dot{x}_{dik}}\right) - \frac{\partial \mathbf{E}_K}{\partial x_{dik}} + \frac{\partial(\mathbf{E}_P + \mathbf{E}_{PE})}{\partial x_{dik}} + \frac{\partial \mathbf{P}_W}{\partial(\mathfrak{D}_t^\alpha[x_{dik}])} = X_{dik}, \; i = 1,2, \; k = 1,2,3,4,...,N\tag{9}$$

For human cells $N = 24$. By use previous extended Lagrange's differential equations in the following matrix form (8) and (9) for generalized coordinates x_{gik} and x_{dik}, we will obtain system with 24 sub-systems, each with one pair of the ordinary fractional order differential equations in the following form:

$$\frac{d}{dt}\left[m_{gik}\left(\dot{x}_{gik} + \dot{y}_{gO1}\cos\alpha_{gik}\right)\right] + c_{gik}x_{gik} + c_{ik}\left[\left(y_{gO1} + y_{dO1}\right) + \left(x_{gik}\sin\alpha_{gik} + x_{dik}\sin\alpha_{dik}\right)\right]\sin\alpha_{gik} + \tilde{c}_{gik}\left(\mathfrak{D}_t^\alpha[x_{gik}]\right) = 0\tag{10}$$

$$\frac{d}{dt}\left[m_{dik}\left(\dot{x}_{dik} + \dot{y}_{dO2}\cos\alpha_{dik}\right)\right] + c_{dik}x_{dik} - c_{ik}\left[\left(y_{gO1} + y_{dO1}\right) + \left(x_{gik}\sin\alpha_{gik} + x_{dik}\sin\alpha_{dik}\right)\right]\sin\alpha_{dik} + \tilde{c}_{dik}\left(\mathfrak{D}_t^\alpha[x_{dik}]\right) = 0\tag{11}$$

$$i = 1,2, \quad k = 1,2,3,4,...,N\tag{11}$$

For human cells $N = 24$. $\tilde{c}_{gik}$ and $\tilde{c}_{dik}$ are rigidities from fractional properties of energy dissipation, $\mathfrak{D}_t^\alpha[x_{gik}]$ and $\mathfrak{D}_t^\alpha[x_{dik}]$ are fractional derivatives for upper and lower visco-elastic element that interconnects homologue chromosomes with rheonomic center of oscillations.

3. Condition for resonance as potential mechanism for homolog chromosomes separation

Pairs of coupled fractional order differential equations could be solved independently from other coupled pairs of the mitotic spindle oscillatory system. Expressions for equations (10) and (11) could be rewritten in the form:

$$\ddot{x}_{gik} + \left(\omega_{gik}^2 + \hat{\omega}_{gik}^2\sin^2\alpha_{gik}\right)x_{gik} + \left(\hat{\omega}_{gik}^2\sin\alpha_{dik}\sin\alpha_{gik}\right)x_{dik} + \tilde{\omega}_{gik}^2\left(\mathfrak{D}_t^\alpha[x_{gik}]\right) =$$
$$= \left(\Omega_g^2 h_{0,gik} - \hat{\omega}_{gik}^2\tilde{h}_{0,gik}\right)\cos\Omega_g t - \hat{\omega}_{gik}^2\tilde{\tilde{h}}_{0,gik}\cos\Omega_d t\tag{12}$$

$$\ddot{x}_{dik} + \left(\omega_{dik}^2 + \hat{\omega}_{dik}^2\sin^2\alpha_{dik}\right)x_{dik} + \tilde{\omega}_{dik}^2\left(\mathfrak{D}_t^\alpha[x_{gik}]\right) - \left(\hat{\omega}_{dik}^2\sin\alpha_{gik}\sin\alpha_{dik}\right)x_{gik} =$$
$$= \left(\Omega_d^2 h_{0,dik} + \hat{\omega}_{dik}^2\tilde{h}_{0,dik}\right)\cos\Omega_d t + \hat{\omega}_{dik}^2\tilde{\tilde{h}}_{0,dik}\cos\Omega_g t\tag{13}$$

where the following notations are introduced:

$$\omega_{gik}^2 = \frac{c_{gik}}{m_{gik}}, \quad \tilde{\omega}_{gik}^2 = \frac{\tilde{c}_{gik}}{m_{gik}}, \quad h_{0,gik} = y_{go}\cos\alpha_{gik}$$

$$\omega_{dik}^2 = \frac{c_{dik}}{m_{dik}}, \quad \tilde{\omega}_{dik}^2 = \frac{\tilde{c}_{dik}}{m_{dik}}, \quad h_{0,dik} = y_{do}\cos\alpha_{dik}$$

$$\widehat{\omega}_{gik}^2 = \frac{c_{ik}}{m_{gik}}, \qquad \widehat{\omega}_{dik}^2 = \frac{c_{ik}}{m_{dik}},$$

$$\widetilde{h}_{0,gik} = y_{g0}\sin\alpha_{gik}, \qquad \widetilde{\widetilde{h}}_{0,gik} = y_{d0}\sin\alpha_{gik}$$

$$\widetilde{h}_{0,dik} = y_{d0}\sin\alpha_{dik}, \qquad \widetilde{\widetilde{h}}_{0,dik} = y_{g0}\sin\alpha_{dik} \tag{14}$$

where Ω_g and Ω_d, are frequencies of forced oscillations of kinematic excitations of centrosomes with masses M_1 and M_2 amplitudes y_{g0} and y_{d0}. Rheonomic coordinates of kinematic excitation are in the form: $y_{gO1}(t) = y_{g0}\cos\Omega_g t$ and $y_{dO1}(t) = y_{d0}\cos\Omega_g t$.

From pairs of coupled differential equations (12) and (13) in which are not visible explicate, but we can conclude that M_1 and M_2 do not have direct influence on dynamics of coupled homologues chromosomes. Influence is indirectly via generalized forces Q_{g2} and Q_{d2} that are obligated for kinematic excitation of the centers. These generalized force for rheonomic coordinates $y_{gO1}(t)$ and $y_{dO1}(t)$, we can determine by following Lagrange's equations:

$$Q_{gO1} = \frac{d}{dt}\left(\frac{\partial\mathbf{E}_K}{\partial\dot{y}_{gO1}}\right) - \frac{\partial\mathbf{E}_K}{\partial y_{gO1}} + \frac{\partial(\mathbf{E}_P + \mathbf{E}_{PE})}{\partial y_{gO1}} + \frac{\partial\mathbf{P}_W}{\partial\left(\mathfrak{D}_t^\alpha\left[y_{gO1}\right]\right)} \tag{15}$$

$$Q_{d2} = \frac{d}{dt}\left(\frac{\partial\mathbf{E}_K}{\partial\dot{y}_{dO2}}\right) - \frac{\partial\mathbf{E}_K}{\partial y_{dO2}} + \frac{\partial(\mathbf{E}_P + \mathbf{E}_{PE})}{\partial y_{dO2}} + \frac{\partial\mathbf{P}_W}{\partial\left(\mathfrak{D}_t^\alpha\left[y_{dO1}\right]\right)} \tag{16}$$

For the case when microtubules are approximated with standard light ideally elastic elements, fractional derivatives in expressions (12) and (13) are omitted. In this paper, we consider linearized case when in system of differential equation (12) and (13), we take that $\widetilde{\omega}_{gik}^2 = 0$ and $\widetilde{\omega}_{dik}^2 = 0$ -we take into consideration these differential equations without terms $\widetilde{\omega}_{gik}^2\left(\mathfrak{D}_t^\alpha\left[x_{gik}\right]\right)$ and $\widetilde{\omega}_{dik}^2\left(\mathfrak{D}_t^\alpha\left[x_{gik}\right]\right)$. Than particular solutions of modified ordinary differential equations (12) and (13) for the case of single frequency forced kinematical excitations of each centre of centrosomes with masses M_1 and M_2, are in the two-frequency form:

$$x_{Pgik} = D_{gik}\cos\Omega_g t + \widetilde{D}_{gik}\cos\Omega_d t \tag{17}$$

$$x_{Pdik} = D_{dik}\cos\Omega_g t + \widetilde{D}_{dik}\cos\Omega_d t \tag{18}$$

Introducing proposed particular solutions (17) and (18) and their second derivatives into differential equations (12) and (13) we got system of differential equations that could be transform in the system of coupled non-homogeneous algebraic equations with unknown amplitudes of proposed particular solutions in the following forms:

$$\left[\left(\omega_{gik}^2 + \widehat{\omega}_{gik}^2\sin^2\alpha_{gik}\right) - \Omega_g^2\right]D_{gik} + \left(\widehat{\omega}_{gik}^2\sin\alpha_{dik}\sin\alpha_{gik}\right)D_{dik} = \left(\Omega_g^2 h_{0,gik} - \widehat{\omega}_{gik}^2\widetilde{h}_{0,gik}\right)$$

$$\left[\left(\omega_{gik}^2 + \widehat{\omega}_{gik}^2\sin^2\alpha_{gik}\right) - \Omega_d^2\right]\widetilde{D}_{gik} + \left(\widehat{\omega}_{gik}^2\sin\alpha_{dik}\sin\alpha_{gik}\right)\widetilde{D}_{dik} = -\widehat{\omega}_{gik}^2\widetilde{\widetilde{h}}_{0,gik} \tag{19}$$

$$\left[\left(\omega_{dik}^2 + \widehat{\omega}_{dik}^2\sin^2\alpha_{dik}\right) - \Omega_g^2\right]D_{dik} + \left(\widehat{\omega}_{dik}^2\sin\alpha_{gik}\sin\alpha_{dik}\right)D_{gik} = \widehat{\omega}_{dik}^2\widetilde{h}_{0,dik}$$

$$\left[\left(\omega_{dik}^2 + \widehat{\omega}_{dik}^2\sin^2\alpha_{dik}\right) - \Omega_d^2\right]\widetilde{D}_{dik} + \left(\widehat{\omega}_{dik}^2\sin\alpha_{gik}\sin\alpha_{dik}\right)\widetilde{D}_{gik} = \left(\Omega_d^2 h_{0,dik} + \widehat{\omega}_{dik}^2\widetilde{\widetilde{h}}_{0,dik}\right) \tag{20}$$

this coupled system could be further decupled into to independent subsystems (19) and (20).

Determinant of the sub-system (19) is in the form:

$$\Delta_{ik} = \begin{vmatrix} \left[\left(\omega_{gik}^2 + \widehat{\omega}_{gik}^2 \sin^2 \alpha_{gik} \right) - \Omega_g^2 \right] & \left(\widehat{\omega}_{gik}^2 \sin \alpha_{dik} \sin \alpha_{gik} \right) \\ \left(\widehat{\omega}_{dik}^2 \sin \alpha_{gik} \sin \alpha_{dik} \right) & \left[\left(\omega_{dik}^2 + \widehat{\omega}_{dik}^2 \sin^2 \alpha_{dik} \right) - \Omega_g^2 \right] \end{vmatrix} \neq 0 \qquad (21)$$

and have to be different than zero, for obtaining finite value of amplitudes and proposed particular solutions (17).

For application of Cramer's rule for solving non homogeneous algebra equations (17), we compose two determinants by substitution into determinant of the system (21), successively, first and second column by column composed by terms in right hand side of the algebra equations of the system (19), and we obtain the following determinants:

$$\Delta_{1,ik} = \begin{vmatrix} \left(\Omega_g^2 h_{0,gik} - \widehat{\omega}_{gik}^2 \widetilde{h}_{0,gik} \right) & \left(\widehat{\omega}_{gik}^2 \sin \alpha_{dik} \sin \alpha_{gik} \right) \\ \widehat{\omega}_{dik}^2 \widetilde{h}_{0,dik} & \left[\left(\omega_{dik}^2 + \widehat{\omega}_{dik}^2 \sin^2 \alpha_{dik} \right) - \Omega_g^2 \right] \end{vmatrix} \qquad (22)$$

$$\Delta_{2,ik} = \begin{vmatrix} \left[\left(\omega_{gik}^2 + \widehat{\omega}_{gik}^2 \sin^2 \alpha_{gik} \right) - \Omega_g^2 \right] & \left(\Omega_g^2 h_{0,gik} - \widehat{\omega}_{gik}^2 \widetilde{h}_{0,gik} \right) \\ \left(\widehat{\omega}_{dik}^2 \sin \alpha_{gik} \sin \alpha_{dik} \right) & \widehat{\omega}_{dik}^2 \widetilde{h}_{0,dik} \end{vmatrix} \qquad (23)$$

Unknown amplitudes of proposed particular solution (17) are now determined:

$$D_{gik} = \frac{\Delta_{1,ik}}{\Delta_{ik}}, \qquad D_{dik} = \frac{\Delta_{2,ik}}{\Delta_{ik}} \qquad (24)$$

The analog could be obtained for the second pair of the unknown amplitudes of proposed particular solution (18) are now determined:

$$\widetilde{D}_{gik} = \frac{\widetilde{\Delta}_{1,ik}}{\widetilde{\Delta}_{ik}}, \qquad \widetilde{D}_{dik} = \frac{\widetilde{\Delta}_{2,ik}}{\widetilde{\Delta}_{ik}} \qquad (25)$$

Particular solutions of linearized ordinary differential equations (12) and (13) in proposed form (17) and (18) are in the form:

$$x_{Pgik} = D_{gik} \cos \Omega_g t + \widetilde{D}_{gik} \cos \Omega_d t = \frac{\Delta_{1,ik}}{\Delta_{ik}} \cos \Omega_g t + \frac{\widetilde{\Delta}_{1,ik}}{\widetilde{\Delta}_{ik}} \cos \Omega_d t \qquad (26)$$

$$x_{Pdik} = D_{dik} \cos \Omega_g t + \widetilde{D}_{dik} \cos \Omega_d t = \frac{\Delta_{2,ik}}{\Delta_{ik}} \cos \Omega_g t + \frac{\widetilde{\Delta}_{2,ik}}{\widetilde{\Delta}_{ik}} \cos \Omega_d t \qquad (27)$$

3. Discussion

Now, we can discuss different conditions for different combinations of dynamical absorption and resonance. When determinant of one system is $\Delta_{ik} = 0$ or $\widetilde{\Delta}_{ik} = 0$, we can obtain resonant frequencies of kinematic excitation of rheonomic centers with masses M_1 or M_2. When one of the amplitudes $D_{gik} = \dfrac{\Delta_{1,ik}}{\Delta_{ik}} = 0$ or $D_{dik} = \dfrac{\Delta_{2,ik}}{\Delta_{ik}} = 0$ or $\widetilde{D}_{gik} = \dfrac{\widetilde{\Delta}_{1,ik}}{\widetilde{\Delta}_{ik}} = 0$ or $\widetilde{D}_{dik} = \dfrac{\widetilde{\Delta}_{2,ik}}{\widetilde{\Delta}_{ik}} = 0$ is equal to zero, or determinants $\Delta_{1,ik} = 0$ and $\Delta_{2,ik} = 0$ or/and $\widetilde{\Delta}_{1,ik} = 0$, $\widetilde{\Delta}_{2,ik} = 0$, appear dynamical absorption of corresponding amplitude and corresponding forced mode with

corresponding force frequency, and corresponding material particle-homologue chromosome occurs. This could be explanation, from theory of oscillations, for the mechanism way movements of some pairs of homologues chromosomes are postponed while other pairs of homologues are not in the right position in equatorial plain.

Comparing determinant of the system for free oscillations with determinant for the sub-system for obtaining amplitudes of particular solutions for forced oscillations (determinant for the system of free oscillations should be equal to zero and determinant for sub-system for forced oscillations should be different from zero) we can conclude that for each of two frequencies of kinematic excitation of kinematic centers with masses M_1 and M_2 of mitotic spindle there are two resonant frequencies and resonance occur when external kinematic excitation frequency is equal to eigen circular frequency, expressed in the form:

$$\Omega_g^2 = \omega_{i,s}^2, \ \Omega_d^2 = \omega_{i,s}^2, \ s = 1,2 \tag{28}$$

According to the (2), dilatation of standard light linear elastic element that interconnects homologue chromosomes and particular solutions (26) and (27) are important for analysis of elastic and microtubule elements breakage.

When resonance occurs expressions (2), (26) and (27) tends to infinity in resonance time period than one of the circular frequency of kinematic excitation is equal to the one of eigen circular frequency of the coupled homologues chromosomes in the simplified system of two pairs of coupled homologues chromosomes.

If dilatation $\left(\Delta\ell_{ik}\right)_{critical}$ according to the (2) reaches, in resonant state, critical value for disconnection of pair of homologues chromosomes-material particles before the critical value of breakage of opposite microtubules-both dilatations $\left(x_{Pgik}\right)_{critical}$ and $\left(x_{Pdik}\right)_{critical}$ ((26) and (27)) is reached, homologues chromosomes are separated and move to the corresponding centrosome. In the case when one of the dilatations $\left(x_{Pdik}\right)_{critical}$ or $\left(x_{Pdik}\right)_{critical}$ reaches the critical value of breakage, in resonate state, before $\left(\Delta\ell_{ik}\right)_{critical}$ is reached, occurred aneuploidia and aberrant spindle assembly-an undesirable and unfavorable state for equal distribution of genetic material in sister cells.

Which of this scenario will occur depends on resonant frequencies of excitation of rheonomic centers, angles between microtubules (standard light visco-elastic element) and centrosome (rheonomic center of excitation) as well as of rigidities and chromosomal masses in oscillatory system of mitotic spindle.

For specific conclusion, multi-parametric analysis for conditions for resonant states for one of these scenarios, multi-parametric numerical experiment is needed.

As aging causes a loss of meiotic chromosome cohesion, which can explain premature disjunction of sister chromatids [8], the proposed model could be suitable for explaining age related aberrations in mitotic spindle.

4. Conclusions

Oscillatory model of mitotic spindle is presented. Conditions for resonance as a mechanism for homolog chromosomes separation in anaphase is analyzed and discussed. Compare to the complicated and complex molecular models, that describes metaphase and anaphase separately, oscillatory model of mitotic spindle offers different biomechanical approach replacing complex molecular structures with biomechanical elements. Mechanism of different chromatid separation

times in different chromosomes as well as age related aberration in mitotic spindle functioning could be explain with proposed oscillatory model of mitotic spindle.

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