Chromosome segregation model - detailed description

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Introduction

This is a more detailed version of the kinetochore segregation model to be published in the JCB article, which should be referred to for all the experimental, biological and non-technical aspects of this work.

1 Definitions

1.1 State vector

The mitotic spindle is described by the speeds and position along the x axis of two spindle pole bodies, N chromosomes with two centromeres and M_k attachment sites per centromere.

Positions are noted as follow:

- The left and right spindle pole bodies (SPBs), x_s^L and x_s^R
- The N centromeres, x_n^A, $x_n^B, n \in \{1, \cdots, N\}$
- The M_k attachment sites of each centromere, x_{nm}^A, $x_{nm}^B, n \in \{1, \cdots, N\}, m \in \{1, \cdots, M_k\}$

The speeds are noted with a dot: $dx/dt = \dot{x}$.

As all the interactions are assumed to be parallel to the spindle axis, only the positions along this axis are considered, in a coordinate system with its origin at the center of the spindle, which means that $x_s^L(t) = -x_s^R(t) \, \forall t$.

1.2 Random variables for the attachment

We define ρ_{nm}^A and λ_{nm}^A, two random variables that govern the attachment state of the site x_{nm}^A, such that:

$$\lambda_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the left SPB} \\ 0 & \text{otherwise} \end{cases} \tag{1}$$

$$\rho_{nm}^A = \begin{cases} 1 & \text{if the site is attached to the right SPB} \\ 0 & \text{otherwise} \end{cases} \tag{2}$$

Note that ρ_{nm}^A and λ_{nm}^A are not independent, as an attachment site can't be attached to both poles. To take this into account, we can define the variable $\pi_{nm}^A = \rho_{nm}^A - \lambda_{nm}^A$ such that:

$$\pi_{nm}^A = \begin{cases} -1 & \text{if the site is attached to the left SPB} \\ 0 & \text{if the site is not attached} \\ 1 & \text{if the site is attached to the right SPB} \end{cases} \tag{3}$$

We have:

$$\lambda_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} - 1\right)/2 \tag{4}$$
$$\rho_{nm}^{A} = \pi_{nm}^{A}\left(\pi_{nm}^{A} + 1\right)/2 \tag{5}$$

We also define N_n^{AL} and N_n^{AR} as the number of ktMTs of centromere A attached to the left and right SPBs, respectively:

$$N_n^{AL} = \sum_{m=1}^{M_k} \lambda_{nm}^{A} \text{ and } N_n^{AR} = \sum_{m=1}^{M_k} \rho_{nm}^{A} \tag{6}$$

Note that $N_n^{AL} + N_n^{AR} \leqslant M_k \,\forall\, \pi_{nm}$ The same definitions apply for the centromere B and left SPB.

2 Mechanical system

2.1 Forces

The following force balances are considered:

2.1.1 Forces at the right SPB

- Friction forces (viscous drag): $F_s^f = -\mu_s \dot{x_s}^R$
- Midzone force generators (applied at the right SPB):

$$F_{mid} = F_z\left(1 - (\dot{x}_s^R - \dot{x}_s^L)/V_z\right) = F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} & - \rho_{nm}^{A} F_k\left(1 - (\dot{x}_{nm}^{A} - \dot{x}_s^R)/V_k\right) \\ & + \lambda_{nm}^{A} F_k\left(1 - (\dot{x}_{nm}^{A} + \dot{x}_s^R)/V_k\right) \\ & - \rho_{nm}^{B} F_k\left(1 - (\dot{x}_{nm}^{B} - \dot{x}_s^R)/V_k\right) \\ & + \lambda_{nm}^{A} F_k\left(1 - (\dot{x}_{nm}^{B} + \dot{x}_s^R)/V_k\right) \end{aligned}$$

2.1.2 Forces at the left SPB :

Because of the reference frame definition, $\dot{x_s}^R = -\dot{x_s}^L \,\forall t$. Here we substituted x_s^L with $-x_s^R$

- Friction forces (viscous drag): $F_f^L = \mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid}^{L} = -F_z\left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^{T} = \sum_{n=1}^{N}\sum_{m=1}^{M_k} & - \lambda_{nm}^{A} F_k\left(1 + (\dot{x}_{nm}^{A} + \dot{x}_s^R)/V_k\right) \\ & - \lambda_{nm}^{B} F_k\left(1 + (\dot{x}_{nm}^{B} + \dot{x}_s^R)/V_k\right) \end{aligned}$$

2.1.3 Forces at the right SPB

- Friction forces (viscous drag): $F_f^R = -\mu_s \dot{x_s}^R$
- Midzone force generators:

$$F_{mid} = F_z \left(1 - (\dot{x}_s^R - \dot{x}_s^L)/V_z\right) = F_z \left(1 - 2\dot{x}_s^R/V_z\right)$$

- Total kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^T = \sum_{n=1}^{N} \sum_{m=1}^{M_k} & - \rho_{nm}^A F_k \left(1 - (\dot{x}_{nm}^A - \dot{x}_s^R)/V_k\right) \\ & - \rho_{nm}^B F_k \left(1 - (\dot{x}_{nm}^B - \dot{x}_s^R)/V_k\right) \end{aligned}$$

2.1.4 Forces at centromere An

- Drag: $F_c^f = -\mu_c \dot{x_n}^A$
- Cohesin bond (Hook spring) restoring force exerted by centromere[1]:

$$F_{BA} = \begin{cases} \kappa_c(x_n^B - x_n^A - d_0) & \text{if} \quad x_n^A \leqslant x_n^B \\ \kappa_c(x_n^B - x_n^A + d_0) & \text{if} \quad x_n^A > x_n^B \end{cases} \tag{7}$$

  With $F_{AB} = -F_{BA}$.

- Total visco-elastic bond between the centromere A and the attachment sites:

$$F_v^T = \sum_{m=1}^{M_k} -\kappa_k(x_n^A - x_{nm}^A) - \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

2.1.5 Forces at attachment site Anm

- Visco-elastic bond between the centromere A and the attachment sites:

$$F_v = \kappa_k(x_n^A - x_{nm}^A) + \mu_k(\dot{x}_n^A - \dot{x}_{nm}^A)$$

- Kinetochore microtubules force generators:

$$\begin{aligned} F_{kMT}^A &= F_{kMT}^{RA} + F_{kMT}^{LA} \\ F_{kMT}^{RA} &= \rho_{nm}^A F_k \left(1 - \frac{\dot{x}_{nm}^A - \dot{x}_s^R}{V_k}\right) \\ F_{kMT}^{LA} &= \lambda_{nm}^A F_k \left(-1 - \frac{\dot{x}_{nm}^A - \dot{x}_s^L}{V_k}\right) \end{aligned} \tag{8}$$

  With $F_k = 1$ and $V_k = 1$ (for now on, we are taking F_k as unit force and V_k as unit speed), this gives:

$$F_{kMT}^A = \rho_{nm}^A \left(\dot{x}_s^R - \dot{x}_{nm}^A + 1\right) - \lambda_{nm}^A \left(\dot{x}_s^R + \dot{x}_{nm}^A + 1\right) \tag{9}$$

  Eventually, substituting $\lambda_{nm}^A - \rho_{nm}^A$ with π_{nm}^A and $\lambda_{nm}^A + \rho_{nm}^A$ with $|\pi_{nm}^A|$:

$$F_{kMT}^A = \pi_{nm}^A(\dot{x}_s^R + 1) - |\pi_{nm}^A|\dot{x}_{nm}^A \tag{10}$$

[1] We want the centromeres to be able to cross each over. In one dimension, this introduces a discontinuity. In the previous version, the 'swap' mechanism was solving this directly (as x_A and x_B are exchanged). This is not possible any more, as the 'swap' mechanism is now irrelevant, as there is no prefered side for a given centromere.

2.2 Set of coupled first order differential equations

In the viscous nucleoplasm, inertia is negligible. Newton first principle thus reduces to: $\sum F = 0$. This force balance equation can be written for each elements of the spindle. To simplify further, the equations for the right and left SPBs can be combined:

$$\begin{aligned} -\mu_s \dot{x}_s^R + F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} -\rho_{nm}^A \left(\dot{x}_s^R - \dot{x}_{nm}^A + 1\right) = 0 \text{ for the right SPB} \\ \mu_s \dot{x}_s^R - F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} \lambda_{nm}^A \left(\dot{x}_s^R + \dot{x}_{nm}^A + 1\right) = 0 \text{ for the left SPB} \end{aligned} \tag{11}$$

The difference of those two expressions gives, with the same substitutions as before:

$$-2\mu_s \dot{x}_s^R + 2F_z\left(1 - 2\dot{x}_s^R/V_z\right) + \sum_{n,m} -(|\pi_{nm}^A| + |\pi_{nm}^B|)(\dot{x}_s^R + 1) + \pi_{nm}^A \dot{x}_{nm}^A + \pi_{nm}^B \dot{x}_{nm}^B = 0 \tag{12}$$

All the equations are gathered together in the system of equations:

$$\mathbf{A}\dot{X} + \mathbf{B}X + C = 0$$

The vector X has $1 + 2N(M_k + 1)$ elements and is defined as follow[2]:

$$X = \{x_s^R, \{x_n^A, \{x_{nm}^A\}, x_n^B, \{x_{nm}^B\}\}\} \text{ with } n \in 1 \cdots N \text{ and } m \in 1 \cdots M_k$$

In matrix form, we have:

$$X = \begin{pmatrix} x_s^R \\ x_n^A \\ x_{nm}^A \\ x_n^B \\ x_{nm}^B \end{pmatrix} = \begin{pmatrix} \text{right SPB} \\ \text{centromere } A, n \\ \text{attachment site } A, n, m \\ \text{centromere } B, n \\ \text{attachment site } B, n, m \end{pmatrix}$$

$$A = \begin{pmatrix} -2\mu_s - 4F_z/V_z - \sum(|\pi_{nm}^A| + |\pi_{nm}^B|) & \cdots & \pi_{nm}^A & \cdots & \pi_{nm}^B \\ \cdots & -\mu_c - M_k\mu_k & \mu_k & \cdots & \\ \pi_{nm}^A & \mu_k & -\mu_k - |\pi_{nm}^A| & \cdots & \\ \cdots & \cdots & \cdots & -\mu_c - M_k\mu_k & \mu_k \\ \pi_{nm}^B & \cdots & \cdots & \mu_k & -\mu_k - |\pi_{nm}^B| \end{pmatrix},$$

$$B = \begin{pmatrix} 0 & \cdots & \cdots & \cdots & \cdots \\ \cdots & -\kappa_c - M_k\kappa_k & \kappa_k & \kappa_c & \cdots \\ \cdots & \kappa_k & -\kappa_k & \cdots & \\ \cdots & \kappa_c & \cdots & -\kappa_c - M_k\kappa_k & \kappa_k \\ \cdots & \cdots & \kappa_k & -\kappa_k & \end{pmatrix}$$

$$C = \begin{pmatrix} 2Fz - \sum_{n,m}(|\pi_{nm}^A| + |\pi_{nm}^B|) \\ -\delta_n\kappa_c d_0 \\ \pi_{nm}^A \\ \delta_n\kappa_c d_0 \\ \pi_{nm}^B \end{pmatrix} \text{ with } \delta_n = \begin{cases} 1 & \text{if} \quad x_n^A < x_n^B \\ -1 & \text{if} \quad x_n^A > x_n^B \end{cases} \tag{13}$$

As is actually done in the python implementation, A can be decomposed into a time invariant part A_0 and a variable part A_t with:

[2]Note that the left SPB is omitted in X.

$$A_0 = \begin{pmatrix} -2\mu_s - 4F_z/V_z & \dots & \dots & \dots \\ \dots & -\mu_c - M_k\mu_k & \mu_k & \dots \\ \dots & \mu_k & -\mu_k & \dots \\ \dots & \dots & -\mu_c - M_k\mu_k & \mu_k \\ \dots & \dots & \mu_k & -\mu_k \end{pmatrix}$$

$$A_t = \begin{pmatrix} -\sum(|\pi^A_{nm}| + |\pi^B_{nm}|) & \dots & \pi^A_{nm} & \dots & \pi^B_{nm} \\ \dots & \dots & \dots & \dots & \dots \\ \pi^A_{nm} & \dots & -|\pi^A_{nm}| & \dots & \dots \\ \dots & \dots & \dots & \dots & \dots \\ \pi^B_{nm} & \dots & \dots & \dots & -|\pi^B_{nm}| \end{pmatrix} \tag{14}$$

For the sake of clarity, B can be decomposed in a kinetochore and a cohesin part, $B = B_c + B_k$:

$$B = \kappa_k \begin{pmatrix} 0 & \dots & \dots & \dots \\ \dots & -M_k & 1 & \dots \\ \dots & 1 & -1 & \dots \\ \dots & \dots & -M_k & 1 \\ \dots & \dots & 1 & -1 \end{pmatrix} + \kappa_c \begin{pmatrix} 0 & \dots & \dots & \dots & \dots \\ \dots & -1 & \dots & 1 & \dots \\ \dots & \dots & \dots & \dots & \dots \\ \dots & 1 & \dots & -1 & \dots \\ \dots & \dots & \dots & \dots & \dots \end{pmatrix} \tag{15}$$

3 Continuous time Markov chain description of the attachment – detachment process

3.1 Attachment and detachment rates

The attachment sites attach or detach stochastically with rates $k_a^{R/L}$ and k_d, i.e:

$$\begin{aligned} p^A_{nm} = 1 &\xrightarrow{k_d} p^A_{nm} = 0 \xrightarrow{k_a^R} p^A_{nm} = 1 \\ p^A_{nm} = -1 &\xrightarrow{k_d} p^A_{nm} = 0 \xrightarrow{k_a^L} p^A_{nm} = -1 \end{aligned} \tag{16}$$

The detachment rate depends on the position of the attached site with respect to the chromosome center:

$$k_d = k_a d_\alpha / d, \text{with } d = \left| x^A_{nm} - \left(x^A_n + x^B_n\right)/2 \right| \tag{17}$$

The attachment rate depends on the state of the other attachment sites:

$$k_a^R = k_a \left(1/2 + \beta \frac{N_n^{AR} - N_n^{AL}}{2\left(N_n^{AR} + N_n^{AL}\right)}\right) \tag{18}$$

In the discrete time step model, the rates are calculated at each time step for each attachment site.

3.2 Discrete state-space approximation of the stochastic process

3.2.1 Definitions

The coupling of k_d with the mechanical aspects of the global model prevents a straightforward description of the model as a continuous time Markov chain. This section presents a discrete approximation, as a first attempt.

We now consider only one chromosome with two centromeres and M_k attachment sites. The state of this model is then completely specified by the four random variables $N^{AL}, N^{AR}, N^{BL}, N^{BR}$ as defined in equation 6.

We define the variables P^A (and similarly P^B):

$$\Pi^A = N^{AR} - N^{AL} = \sum_{M_k} \pi_m^A \tag{19}$$

With π_m^A as defined in equation 3. Π^A can be viewed as the force balance at the centromere A. Each of those variables can change of one unit at a time, reflecting the attachment or detachment of one attachment site with a microtubule.

3.2.2 Correct and erroneous attachment

In the above definitions, the role of centromere A and B are completely symmetrical with respect to the left and right pole. Yet, the whole point is to segregate centromere A to one pole and centromere B to the other. We define the correct and erroneous attachments N^{AC} and N^{AE} to take this into account.

For example, in the case of A being linked mainly toward the left SPB and B toward the right SPB, correct attachments are given by $N^{AC} = N^{AL}$ and $N^{BC} = N^{BR}$. More generaly, the correct directions are the one exerting the maximal traction force:

$$\begin{aligned}
\text{if } N^{AL} + N^{BR} \geqslant N^{AR} + N^{BL} : N^{AC} &= N^{AL}, \\
N^{BC} &= N^{BR}, \\
N^{AE} &= N^{AR}, \\
N^{BE} &= N^{BL} \\
\text{if } N^{AL} + N^{BR} < N^{AR} + N^{BL} : N^{AC} &= N^{AR}, \\
N^{BC} &= N^{BL}, \\
N^{AE} &= N^{AL}, \\
N^{BE} &= N^{BR}
\end{aligned} \tag{20}$$

For commodity, we define the factor σ such that:

$$\sigma = \begin{cases} 1 & \text{if } N^{AL} + N^{BR} \geqslant N^{AR} + N^{BL} \\ -1 & \text{if } N^{AL} + N^{BR} < N^{AR} + N^{BL} \end{cases} \tag{21}$$

And the state vector $\Phi = \left(N^{AC}, N^{AE}, N^{BE}, N^{BC}\right)$.

3.2.3 Detachment process

Considering for example the detachment for N^{AL}:

$$N^{AL} \xrightarrow{N^{AL} k_d} N^{AL} - 1 \tag{22}$$

In the mechanical model, the detachment rate k_d depends on the distance between the centromeres. Here, we consider that at equilibrium, this distance d_{eq} varies linearly with the net force applied to the chromosome by the attached microtubules. If centromere B goes to the right and centromere A goes to the left ($\sigma = 1$):

$$d_{eq} = d_0 + F_k(P^B - P^A)/\kappa_c$$

In vivo, the distance between the centromeres never exceeds several times the rest length d_0. A typical value for d_{max} (around 1.2μm) is four times d_0 (0.3μm). Taking d_0 as unit length and F_k as unit force, and substituting $P^A + P^B$ by $2M_k$ in the above equation, we have:

$$d_{max} = 1 + 2M_k/\kappa_c \simeq 4 \Rightarrow \kappa_c \simeq 3/2 * M_k$$

And thus:

$$d_{eq} = 1 + 3\sigma \left(P^B - P^A\right)/2M_k \tag{23}$$

We thus calculate the detachment rate k_d with:

$$k_d = k_a \frac{d_\alpha}{1 + 3\sigma \left(P^B - P^A\right)/2M_k} \tag{24}$$

3.2.4 Attachment process

The total number of attached ktMTs at centromere A can augment of one unit, with a rate proportional to the number of unattached sites, $M_k - N^{AL} - N^{AR}$:

$$N^{AL} + N^{AR} \xrightarrow{\left(M_k - N^{AL} - N^{AR}\right)k_a} N^{AL} + N^{AR} + 1 \tag{25}$$

To decide whether N^{AL} or N^{AR} augment, we state that the probability that it is N^{AL} is given by

$$P_L^A = 1/2 + \beta \left(N^{AL} - N^{AR}\right)/2(N^{AL} + N^{AR})$$

if $N^{AL} + N^{AR} \neq 0$ and $P_L^A = 1/2$ if $N^{AL} + N^{AR} = 0$. Consequently:

$$\begin{aligned} N^{AL} &\xrightarrow{P_L^A\left(M_k - N^{AL} - N^{AR}\right)k_a} N^{AL} + 1 \\ N^{AR} &\xrightarrow{\left(1 - P_L^A\right)\left(M_k - N^{AL} - N^{AR}\right)k_a} N^{AR} + 1 \end{aligned} \tag{26}$$

3.2.5 Markov chain generator

The matrix Q is the generator of the Markov chain. Let $\Psi_i = (N^{AL}, N^{AR}, N^{BL}, N^{BR})$ and $\Psi_j = (N^{AL\prime}, N^{AR\prime}, N^{BL\prime}, N^{BR\prime})$, then the transition rate between Ψ_i and Ψ_j is given by q_{ij} if $i \neq j$, the diagonal terms q_{ii} are given by $q_{ii} = -\sum_{j \neq i} q_{ij}$.

We used the above rules for the transition rates to write the matrix Q for all the acceptable vectors Ψ. The invariant measure of the process is then given by the normalized vector μ such that: $\mu^T Q = 0$.

4 Classification of the defects and analysis

We base the analysis of the invariant measure on the classification between correct and erroneous attachment described above (equation 20).

We follow the biological classification of the mitotic defects. With $\Phi = (N^{AC}, N^{AE}, N^{BE}, N^{BC})$, the chromosome can be either (modulo a permutation between A and B):

- Unattached if $\Phi = (0, 0, 0, 0)$,
- Monotelic if $\Phi \in \{(0, 0, 0, N^{BC}), \text{with } N^{BC} > 0\}$,
- Syntelic if $\Phi \in \{(N^{AC}, 0, N^{BE}, 0), N^{AC} > 0, \text{with } N^{AE} > 0\}$ or
- Merotelic if $\Phi \in \{(N^{AC}, N^{AE}, N^{BC}, N^{BE}), \text{with } N^{AC} > 0, N^{AE} > 0, \forall N^{BC}, N^{BE}\}$