Tension-clock control of human mitotic chromosome oscillations

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During cell division paired (sister) chromosomes are observed to perform approximate saw-tooth oscillations across the cell mid-plane. Experimental data suggests that these oscillations are regulated through intersister tension. We propose a time dependent tension threshold model that exhibits three stable periodic solutions and the phase diagram can be generated semi-analytically. Incorporation of diffusive noise reproduces realistic oscillations, with realistic periods, amplitudes and reproducing the observation that either sister of the pair can switch direction first.

High fidelity cell division in mammals relies on retaining duplicated chromosomes (called chromatids) together in a holding pattern near the cell equator until all paired chromatids are correctly attached to the spindle. In particular, sisters needs to be attached by microtubules to separate spindle poles [1, 2]. Whilst in this holding pat-
ttern, chromatid pairs are observed to oscillate parallel to the spindle axis in the majority of animal cells, including humans [3–5]. Oscillations are pseudo-periodic with sections of near constant speed separated by a directional switching event whereby both of the sisters switch direction, Fig. 1A. Oscillations are predictive of segregation errors, [6] and are attenuated in cancer cells [7].

A number of mathematical models of chromosome oscillations have been proposed incorporating various mechanisms, reviewed in [8][9], oscillations typically arising from mechanical processes [10][14] or chemical feedbacks [15][14]. Microtubules are intrinsically dynamic, exhibiting dynamic instability [20] which provides a natural driver for oscillations. Collective modelling of microtubule binding with force dependent catastrophe/rescue respectively depolymerising (TIDS) and associating (LIDS), respectively depolymerising (TIDS) microtubules, Fig. 1B, [21]. This raises the question of how control of chromatid direction through the spring tension can give rise to oscillations where both of these states can occur with seemingly little impact on the global oscillation characteristics, including the oscillation period and amplitude. We propose a new mathematical model, formulating the tension clock hypothesis of [23]. It is a force dependent control model, where a dynamic tension threshold controls the time of directional switching of the attached microtubules.

We model the movement of the kinetochores, multiprotein machines that assemble near the middle of each sister chromatid. Kinetochores facilitate the mechanical attachment of the chromosome to a bundle of microtubules, called the K-fiber, that connect the chromatid to one of the spindle poles. K-fiber dynamics is substantially slower than single microtubules, [23][20]. There are 4 principle forces: a drag force (drag coefficient $\gamma$) and an antipoleward polar ejection force (strength $\alpha$) acting on the chromosomes, a centromeric spring (spring constant $k$, natural length $L$) connecting the sister kineto-
chores, and a pushing/pulling force $f_\pm$ from a polymerising (+), depolymerising (−) attached K-fiber, Fig. 1C. Force balance then give the dynamics, (intersister distance $\Delta = x_1 - x_2$), [21]

$$\frac{dx_1}{dt} = -\frac{f_{x_1}(t)}{\gamma} - \frac{k}{\gamma}(\Delta - L) - \frac{\alpha}{\gamma}x_1 + \sqrt{2D}\xi_1,$$

$$\frac{dx_2}{dt} = \frac{f_{x_2}(t)}{\gamma} + \frac{k}{\gamma}(\Delta - L) - \frac{\alpha}{\gamma}x_2 + \sqrt{2D}\xi_2,$$  \hspace{1cm} (1)

where $x_1, x_2$ are the positions of the two sister kineto-
chores (normal to the spindle equatorial plane). Sisters are orientated such that $x_1 > x_2$ on average, i.e. sister 1 is attached to the spindle pole to the right, sister 2 to the left. $\xi_k$ are standard white noise modelling thermal and active noise components acting on the kineto-
chore, parametrised by an effective diffusion coefficient
These forces have been inferred from kinetochore tracking data \[21\,23\], demonstrating that the spring is in low tension throughout the oscillation compared to the dominant force generated by depolymerising microtubules. Sister direction is labelled by \(\sigma^k(t) \in \{-, +\}\) for sister \(k = 1, 2\). The saw-tooth like oscillations then correspond to a sequence of coherent sections where the sisters move in the same direction, one attached to polymerising (\(\sigma^k = +\)), the other depolymerising (\(\sigma^k = -\)) microtubules, separated by a fast double switching event where both sisters switch direction (in either order), i.e. after the first sister switches there is an incoherent section when both sisters are either attached to polymerising (LIDS) or depolymerising (TIDS) microtubules.

The tension-clock hypothesis, \[28\], provides a mechanism to control directional switching. Analysis of (inferred) force profiles in HeLa cells, \[21\,23\], and RPE1 cells \[27\] provides evidence of sister direction arising from ageing/degradation of the K-fibre from the time since the last switch. Specifically, polymerising K-fibres are proposed to require increasing pulling forces to remain polymerising, while depolymerising K-fibres have a decreasing load threshold triggering rescue events, Fig. 1C, analogous to observations of yeast kinetochore interactions with single microtubules \[28\].

We implement the tension-clock dependence as a (linearly) time-varying threshold for each K-fibre, a sister switching direction when the spring tension hits its threshold, Fig. 1C. At a switching event we assume a K-fibre is restored to a ‘prime’ state with tension thresholds \(T^0_{\text{pol}}, T^0_{\text{depol}}\), for polymerising, respectively depolymerising K-fibre, these thresholds then evolve linearly over time (age) \(T_{\text{pol}}(t) = T^0_{\text{pol}} + a_+(t - t^*)\), \(T_{\text{depol}}(t) = T^0_{\text{depol}} - a_-(t - t^*)\), where \(t^*\) is the time that the sister last switched with rates \(a_+, a_- \geq 0\). Thus, a coherent state survives provided \(T_{\text{pol}}(t) < T(t) < T_{\text{depol}}(t)\), with (rescaled) spring tension \(T = \kappa(\Delta - L)/\gamma\), and ends when one of these thresholds is reached, thereby switching the associated sister, Fig. 1C. For incoherent states, the sister that previously switched earlier (the older sister) will reach its threshold first. This is a piecewise-smooth dynamical system \[29\,30\], with reset maps on the threshold switching condition manifolds. Newton’s cradle is a familiar exemplar of such a system.

We initially analyse the deterministic version of Eqn. \[1\] with \(D = 0\). We solve Eqns. \[1\] during sections of constant polymerisation or depolymerisation. The intersister distance \(\Delta = x_1 - x_2\) decouples,

\[
\frac{d\Delta}{dt} = -\left(\frac{f_{\sigma_1} + f_{\sigma_2}}{\gamma} + \frac{2\kappa L}{\gamma}\right) + \frac{2(\kappa + \alpha)\Delta}{\gamma}. \tag{2}
\]

Between switching events we have the analytical solution \(\Delta(t) = \Delta_{\sigma_1,\sigma_2}(1 - e^{-(2\kappa + \alpha)(t - t^*)/\gamma}) + \Delta_+ e^{-(2\kappa + \alpha)(t - t^*)/\gamma}\), where \(\Delta_+\) is the separation at previous switching time \(t^*\). Here \(\Delta_{\sigma_1,\sigma_2} = (2\kappa L(f_{\sigma_1} + f_{\sigma_2}))/((2\kappa + \alpha))\), corresponding to the steady states for the fixed directional states \(\sigma = \{+, +, -, -\}\). Since the spring force is a function of \(\Delta\) only, switching dynamics is only a function of the \(\Delta\) dynamics.

Periodic solutions can be constructed by suitably combining sections of these solutions through a sequence of states \(\sigma\), giving oscillatory solutions in the \((\Delta, T^1, T^2)\) space, where \(T^k(t)\) is the threshold for sister \(k\). Oscillatory solutions are defined by their switching choreography, and the times \(t_i, i = 1..n\), of the \(n\) sections. There are at least 5 periodic solutions ( subscript denoting number of sections), Fig. 2A-C:

1. **LIDS\(_2\) (TIDS\(_2\)) oscillation**: an oscillation with LIDS (TIDS) choreography throughout.

2. **BKT\(_4\) oscillation**: Biased kinetochore oscillation where one of the sisters always switches first (alternate LIDS, TIDS events).

3. **Asymmetric LIDS\(_1\) oscillation**: LIDS choreography throughout with asymmetric sections.

4. **Breather**, with anti-correlated sisters.

We performed a stability analysis and bifurcation analysis of these solutions in the \(a_+, a_-\) phase plane. These oscillatory solutions occur only in particular regions of the \(a_+, a_-\) phase plane, Fig. 2D. TIDS and BKT oscillations are always stable, LIDS\(_4\) unstable and LIDS\(_2\) can be either stable or unstable. The system exhibits standard bifurcations and border collision bifurcations, additional bifurcations of smooth piecewise dynamical systems \[29\,30\], where the fixed point collides with the switching manifold. Specifically we have the following collision surfaces:

- **Σ\(_{LIDS}\)**. On this surface LIDS\(_2\) and LIDS\(_4\) solutions collide, i.e. there are continuations in parameter space for both solutions. This is a standard bifurcation; there is a change in stability of LIDS\(_2\) in a period doubling bifurcation (the period of \(\Delta\) doubles between LIDS\(_2\) and LIDS\(_4\)).

- **Σ\(_{\Delta+}\)**. On this surface LIDS\(_2\), TIDS\(_2\) and BKT solutions meet when an incoherent section time \(\rightarrow 0\) (a joint switch) and the kinetochores are stationary, \(x_{1,2} = \pm \Delta_{\alpha}/2\) whilst only \(T_k(t)\) oscillates. This is a border collision bifurcation where a fixed point collides with the switching manifold \[30\]; on this surface the threshold conditions change, the sister who switches sows over, eg LIDS\(_2\) \(\sigma = \{+, +, +, +\}\) to TIDS\(_2\) \(\sigma = \{+, -, -, +\}\). There is no change in stability.

- **Σ\(_{LIDS:BKT}\)**. On these surfaces a BKT (either sister) and a LIDS\(_4\) solution meet as an incoherent section time \(\rightarrow 0\). This is a border collision bifurcation.
A (schematic) bifurcation diagram in a...
Figure Legends

Figure 1. The tension-clock model of chromosome oscillations. A. Typical oscillatory dynamics of a pair of human kinetochores annotated for LIDS and TIDS, see [23] for methods. B. Inferred spring force through a LIDS (magenta, 1614 events) or TIDS (black, 449 events) event, showing relaxation, respectively overstretched of the spring force after the switching event. C. Schematic of the tension-clock mechanical model. Chromosome movement is dependent on forces generated by microtubules, [12]. Here a pair of sister kinetochores have microtubule attachments to respective spindle poles. Microtubules, bundled in K-fibres, are assumed to have an evolving threshold, and switch direction if that threshold is met, upper panel. A, B reproduced from [21] with permission.

Figure 2. Dynamic behaviour of the deterministic tension-clock model. Simulations of the tension-clock model showing A. Breather state (coincident switching of sisters), B. LIDS oscillation, C. Biased KT oscillation (BKT, sister 1 always switching). Directional switching events are shown, first sister switching marked with cyan for LIDS, magenta for TIDS. D. Trajectories in $x_1 - x_2$ plane. D. Phase plot showing existence of LIDS, TIDS and BKT oscillations in the $a_+, a_-$ phase plane. E. Bifurcation diagram for $a_-$ constant cross section of D, with schematic of trajectory phase plane (in $x_1 - x_2$). Bifurcations: pitchfork bifurcations, red, purple, border collision bifurcation blue. The solutions continue (dashed) beyond the border surface as unphysical solutions, i.e. there is a solution with the same switching choreography but the second sister switches upon the second meeting of the threshold condition (from the wrong direction). F Period of oscillatory solutions with $a_-$ ($a_+ = 5 \times 10^{-4}$; stable oscillations shown with solid lines). Mechanical parameters are set to $f_+ = 15$ nm/s, $f_- = -5$ nm/s, $\kappa/\gamma = 0.025$ s$^{-1}$, $\alpha/\gamma = 0.01$ s$^{-1}$, typical for oscillatory trajectories, [21]. Thresholds are initialised to $T^0_{\text{pol}} = -0.1$ nm/s, $T^0_{\text{depol}} = 12$ nm/s. $a_\pm$ in $\mu$m$^2$/s.

Figure 3. The stochastic tension-clock model. A/C. Fraction of time that sisters are coherent as a function of the threshold gradients $a_\pm$ for A. low noise $D = 10^{-6}$ $\mu$m$^2$/s, C. high noise $D = 1.25 \times 10^{-4}$ $\mu$m$^2$/s. B/D. Fraction of switching events that are LIDS for cases A/C. E/F/G. Typical trajectories in the BKT oscillation region of Fig 2D ($a_+ = 3 \times 10^{-4}$, $a_- = 2 \times 10^{-5}$) with increasing diffusive noise: E. low diffusive noise $D = 10^{-6}$, F. medium diffusive noise $D = 10^{-5}$, G. high diffusive noise $D = 10^{-4}$. H Stochastic tension-clock model with a reset period of 15 s and other parameters as G. In E-H LIDS events are shown in cyan, TIDS in magenta. Other parameters as Fig. 2. $a_\pm$ in $\mu$m$^2$/s.
FIG. 1.
