Where history matters: inference for a tension clock model of chromosome oscillation dynamics

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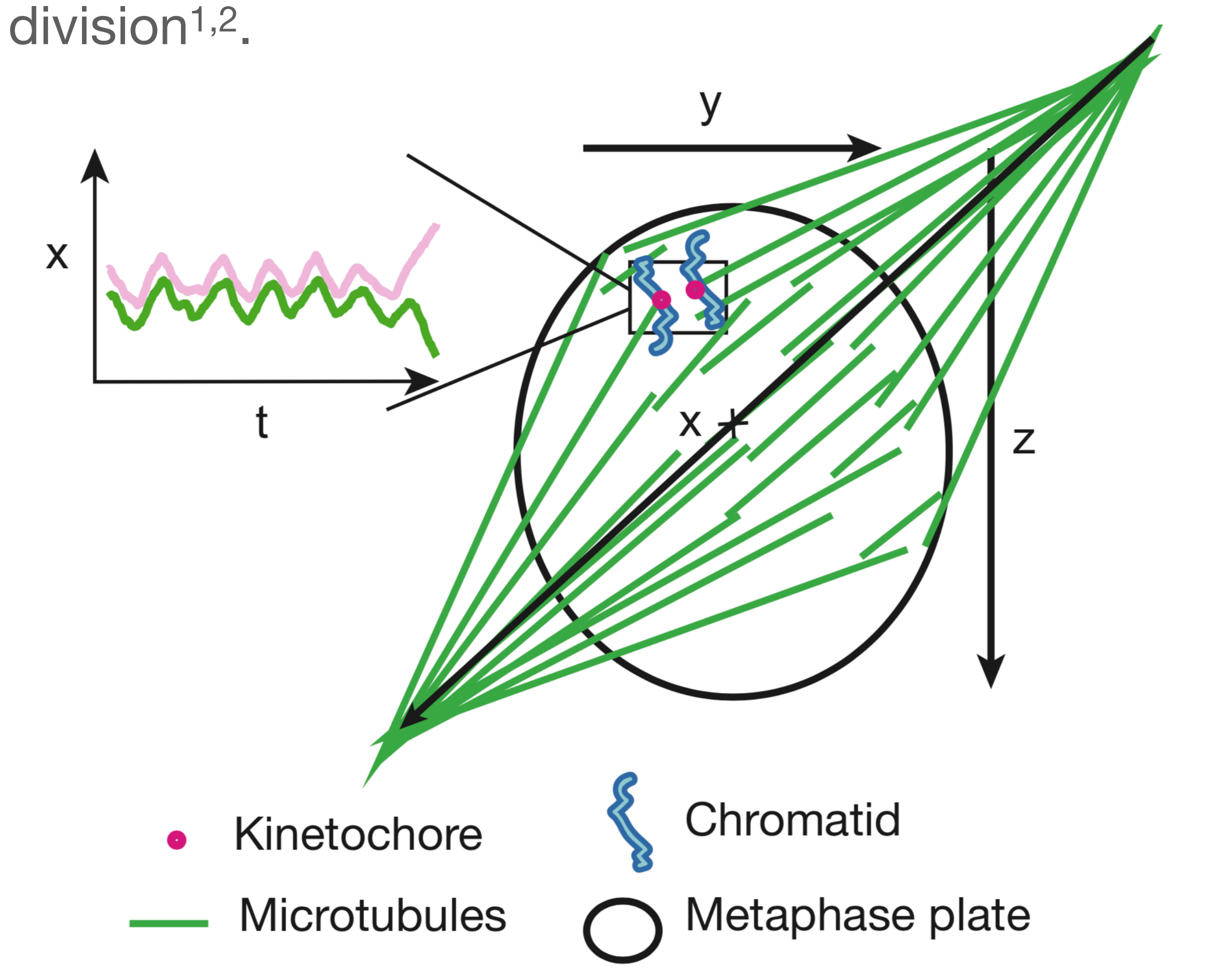
Mitotic cell division

Every time a cell divides, it must ensure that each daughter cell receives a complete copy of the genome. Modelling chromosome dynamics offers insight into how cells avoid errors during division[1,2].



Chromosome oscillation model

$$dX_t^1 = \left(-v_{\sigma_t^1} - \kappa(X_t^1 - X_t^2 - L) - \alpha X_t^1\right) dt + s\, dW_t^1$$

$$dX_t^2 = \left(v_{\sigma_t^2} - \kappa(X_t^2 - X_t^1 + L) - \alpha X_t^2\right) dt + s\, dW_t^2$$

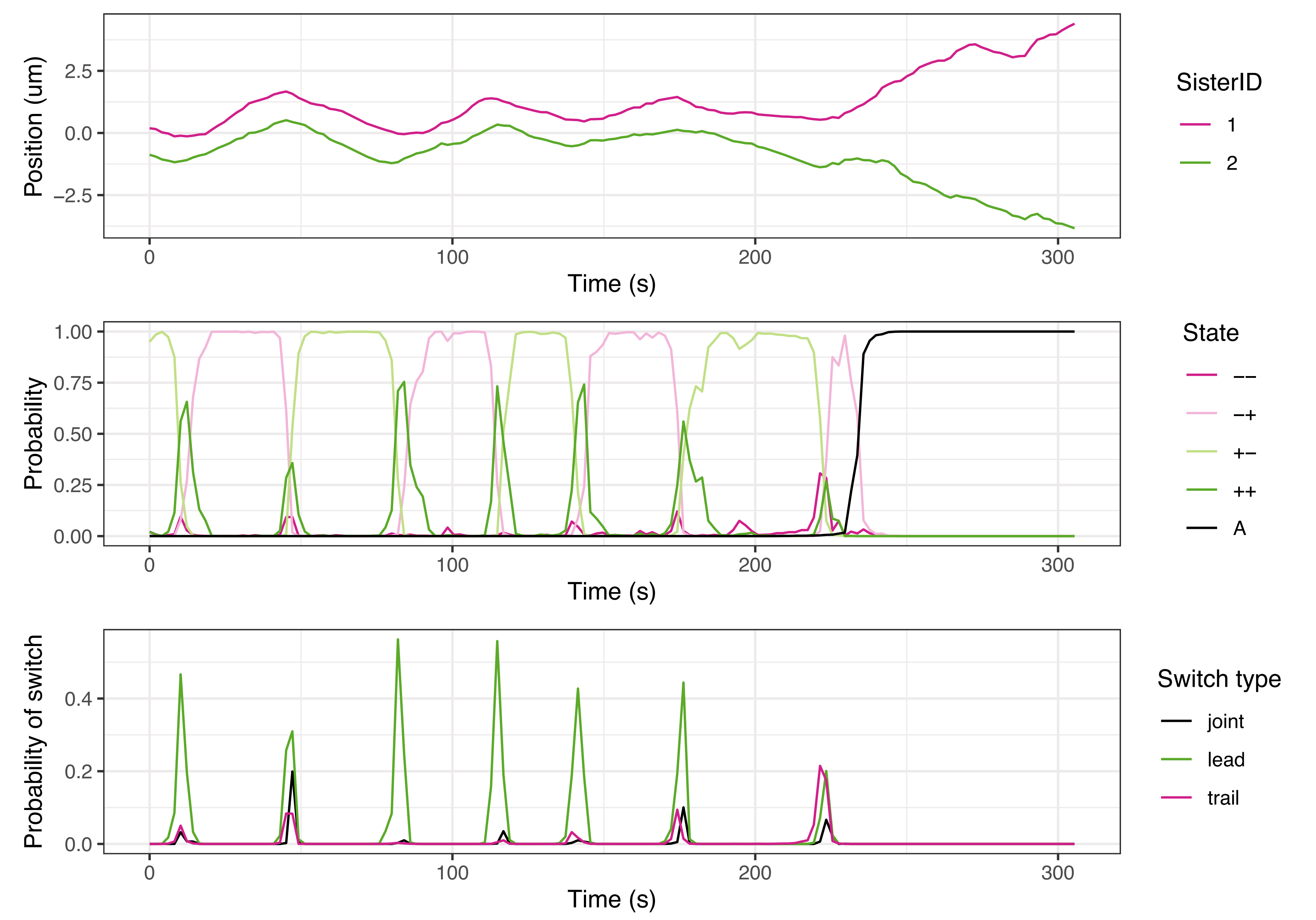
Hidden states for microtubule polymerisation/ depolymerisation governed by a Markov process

$$p(\sigma_{t+1}^j = \sigma_t^j \,|\, \sigma_t^1 \neq \sigma_t^2) = p_c$$

$$p(\sigma_{t+1}^j = \sigma_t^j \,|\, \sigma_t^1 = \sigma_t^2) = p_{ic}$$

$$\sigma_t^j \in \{(++), (+-), (-+), (--)\} \quad j = 1,2$$

Losing the Markov property makes inference for state space models much **harder**. With a small number of states and the Markov property, we can **marginalise out states** and get **fast** inference.



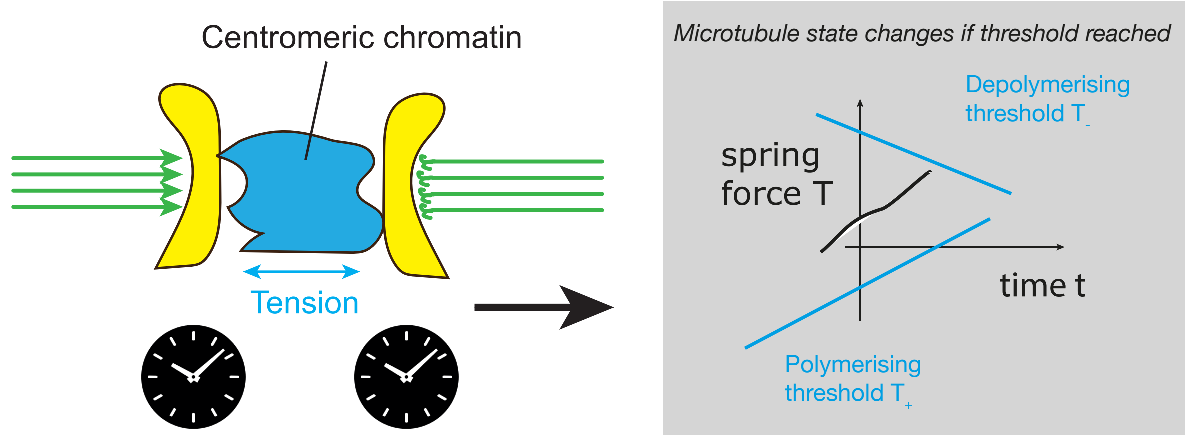
Tension clock model

To capture regular switching seen in experimental data, we must get rid of the Markov assumption and introduce dependence on history via age-dependent tension thresholds!

$$T_+(t) = T_+^0 + a_+(t - t^*)$$

$$T_-(t) = T_-^0 - a_-(t - t^*)$$

where t^* is the time since the last directional switch (transition to different state).



Marginalise out discrete variables when computing the likelihood for efficient inference

$$\log L\left(x_{1:T} \,|\, \theta\right) = \sum_{t=1}^{T} \log\left(P(x_t \,|\, x_{1:t-1}; \theta)\right),$$

$$P(x_t \,|\, x_{1:t-1}; \theta) = \sum_{\sigma_{t-1}} \sum_{\sigma_t} P(\sigma_t \,|\, \sigma_{t-1}; \theta)\, \xi_{\sigma_{t-1}, t-1}\, \eta_{\sigma_t, t},$$

$$\xi_{\sigma_t, t} = \frac{\sum_{\sigma_{t-1}} P(\sigma_t \,|\, \sigma_{t-1}; \theta)\, \xi_{\sigma_{t-1}, t}\, \eta_{\sigma_t, t}}{P(x_t \,|\, x_{1:t-1}; \theta)}.$$

where $\xi_{\sigma_t, t} = P(\sigma_t \,|\, x_{1:t}; \theta)$ and $\eta_{\sigma_t, t} = P(x_t \,|\, \sigma_t, x_{1:t-1}; \theta)$

But with history dependence there are TOO MANY STATES eg. For 4 states and 100 time points, 4^{100} possible states which has 61 digits. Other approaches needed such as approximating *(t-t*)* via its expectation.

[1] Harrison, Sen et al. 2021 *bioRxiv* https://doi.org/10.1101/2021.12.16.472953

[2] Sen, Harrison et al 2021 *Dev. Cell* https://doi.org/10.1016/j.devcel.2021.10.007

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