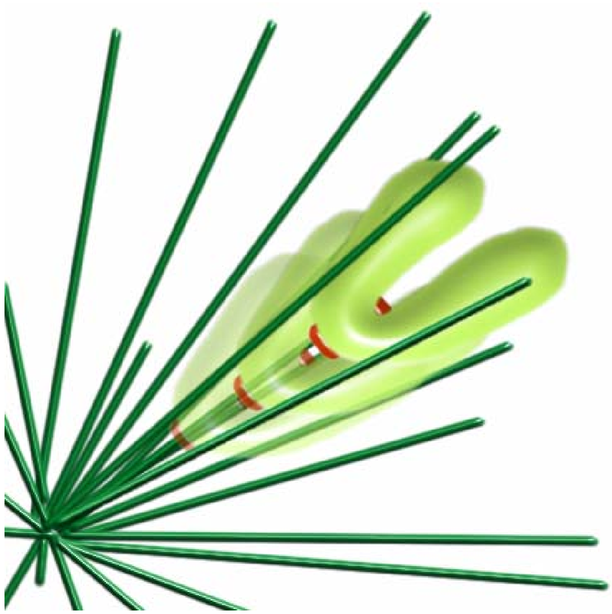
Chromosome Oscillations in Mitosis



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[2] Dept. Estructura i Constituents de la Matèria, Universitat de Barcelona

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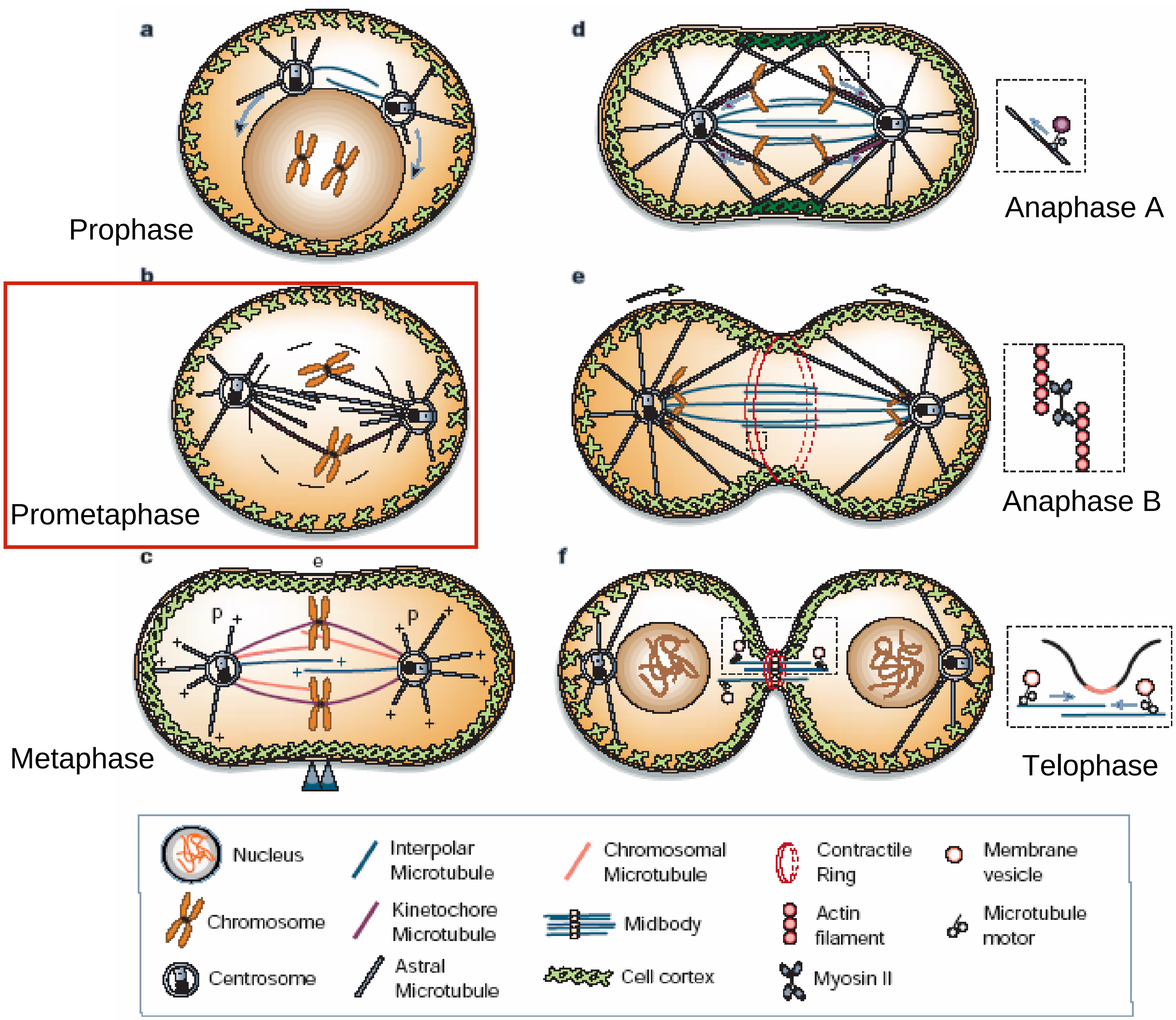
Phases of cell division



Scholey et al., Nature 422, 746 (2003)

Chromosome mouvement in mitosis

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décompresseur Sorenson Video 3
sont requis pour visionner cette image.

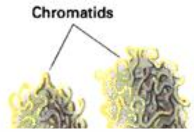
QuickTime™ et un
décompresseur TIFF (non compressé)
sont requis pour visionner cette image.

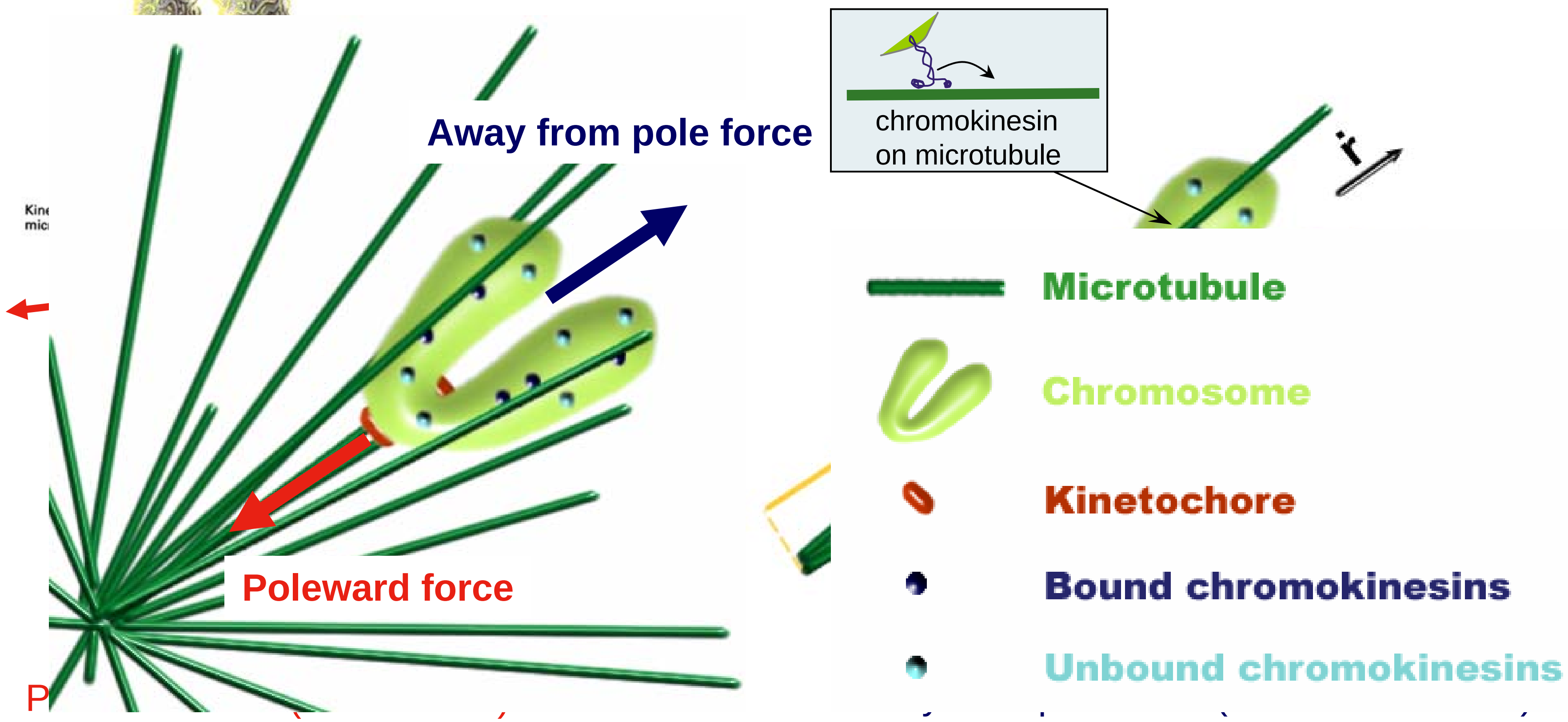
Rieder et al., Science 300, 91 (2003)

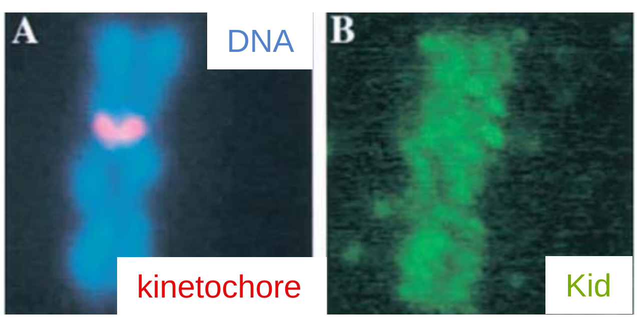
Schematic representation of "typical" chromosome motions. M - monooriented, characterized by oscillatory motion; C - congression, characterized by movement away from the attached spindle pole by the trailing kinetochore and movement toward the attached spindle pole by the leading kinetochore; B - bioriented and congressed, characterized by oscillatory motion; A - anaphase, characterized by poleward movement of all kinetochores. G refers to a short rapid poleward glide that often occurs during initial monooriented attachment.

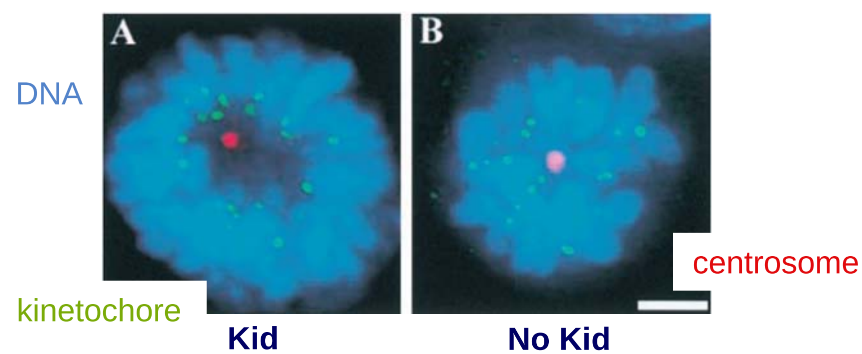
R. V. Skibbens, Victoria P. Skeen, and E. D. Salmon
J. Cell Biol., **122** (1993) 859-875

Balance of forces on the chromosome









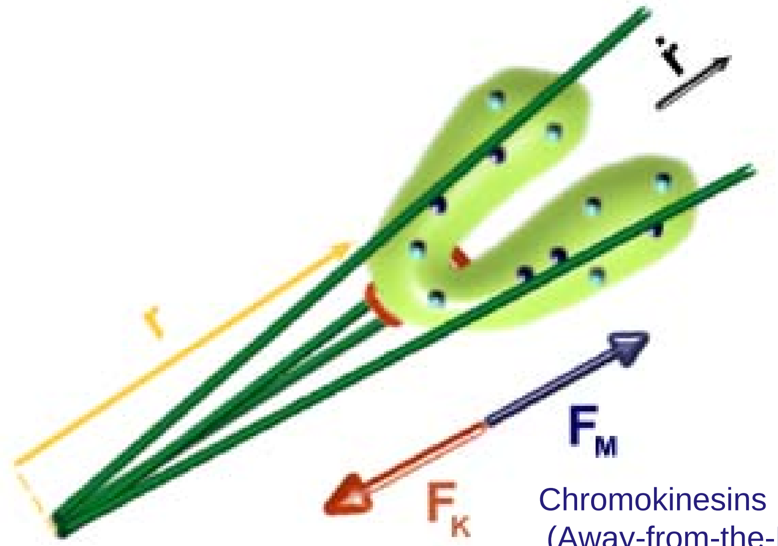
Levesque & Compton, J. Cell Biol. 154, 1135 (2001)

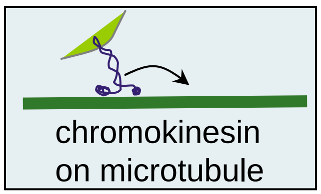
Balance of forces on the chromosome

Equation for chromosome motion

$$\boxed{\xi_\infty \dot{r} = F_m - F_k}$$

Phenomenological friction



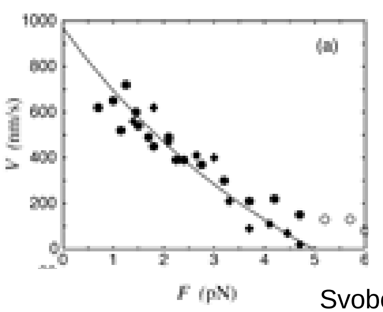


Force - Velocity

$$V \simeq V_0 \left(1 - \frac{f}{f_s}\right)$$

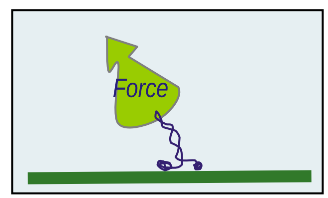
Maximal velocity
(at zero force)

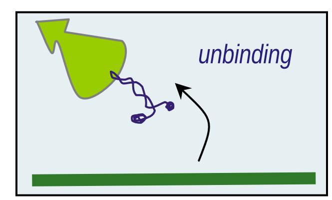
Stall force



Svoboda & block

Force - Unbinding



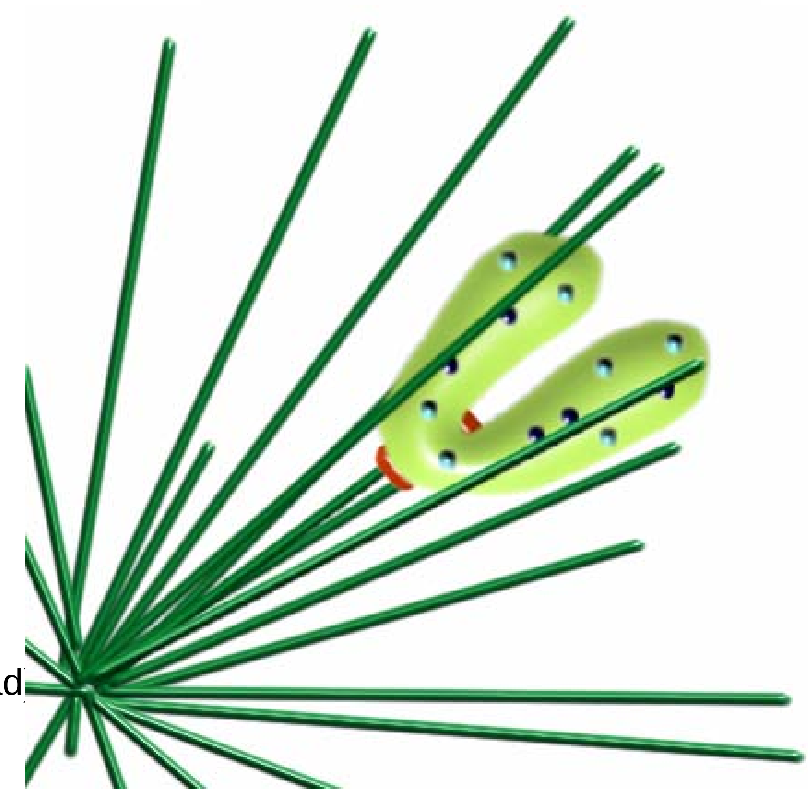


$$k_u = k_u^{(0)} e^{f a / k_B T}$$

Unbinding rate

Microscopic length

Chromokinesin Kinetics



Equation for the number of bound motors

(that can exert a force on the chromosome)

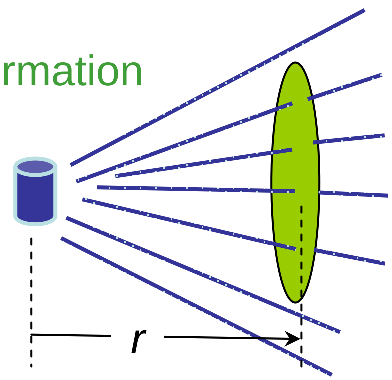
Available motors

$$\boxed{\frac{dn}{dt} = k_b(N - n) - k_u n}$$

Binding rate
(depends on MT concentration)

Unbinding rate
(depends on motor load)

Spatial information



$$k_b(r) \quad \left(\sim \frac{1}{r^2}\right)$$

for an isotropic aster

Collective effects

$$k_u = k_u^{(0)} \exp\left(\frac{1}{\boxed{n}} \frac{F_m a}{k_B T}\right)$$

$$V = V_0 \left(1 - \frac{F_m}{\boxed{n} f_s}\right)$$

The total force is equally shared by all motors

Dynamical equations

chromosome motion & motor binding

$$\boxed{\dot{r} = V}$$

Motor speed = chromosome velocity

$$\boxed{\begin{aligned} \dot{n} &= k_b(r)(N-n) - k_u^{(0)} \exp\left(f\frac{n_s+n_\xi}{n+n_\xi}\right) n \\ \dot{r} &= V_0 \frac{n-n_s}{n+n_\xi} \end{aligned}}$$

Main control parameters

where $\boxed{n_s \equiv F_k/f_s}$, $\boxed{n_\xi \equiv \xi_\infty V_0/f_s}$, and $\boxed{f \equiv f_s a/(k_B T)}$.

Stall number
(number of motors needed
to balance the kinetochore force)

Friction number
(kinetochore friction compared to
Effective chromokinesin friction f_s/V_0)

Detachment force
(influence of applied force
on detachment rate)

$k_u^{(0)} \simeq 5\ \mathrm{s}^{-1}$ $\quad$ $f_s \sim 6pN$ and $f = 2-3$ $\quad$ $V_0 \simeq 160\ \mathrm{nm/s}$

Linear Dynamics

Stability of the fixed point

$$\begin{aligned} n_s &\equiv F_k/f_s \\ n_\xi &\equiv \xi_\infty V_0/f_s \\ f &\equiv f_s a/(k_B T) \end{aligned}$$

$$\begin{aligned} \dot{n} &= k_b(r)(\bar{n}-n) - k_u^{(0)} \exp\left(f\frac{n_s+n_\xi}{n+n_\xi}\right) n \\ \dot{r} &= V_0\frac{n-n_s}{n+n_\xi} \end{aligned}$$

Dynamical system

fixed point

$$\dot{r} = 0 \ \& \ \dot{n} = 0$$

$$n_f = n_s \quad , \qquad k_b(r_f) = k_u^{(0)} e^f \frac{n_s}{n-n_s}$$

gives r_f

Stability of the fixed point

Linear stability analysis

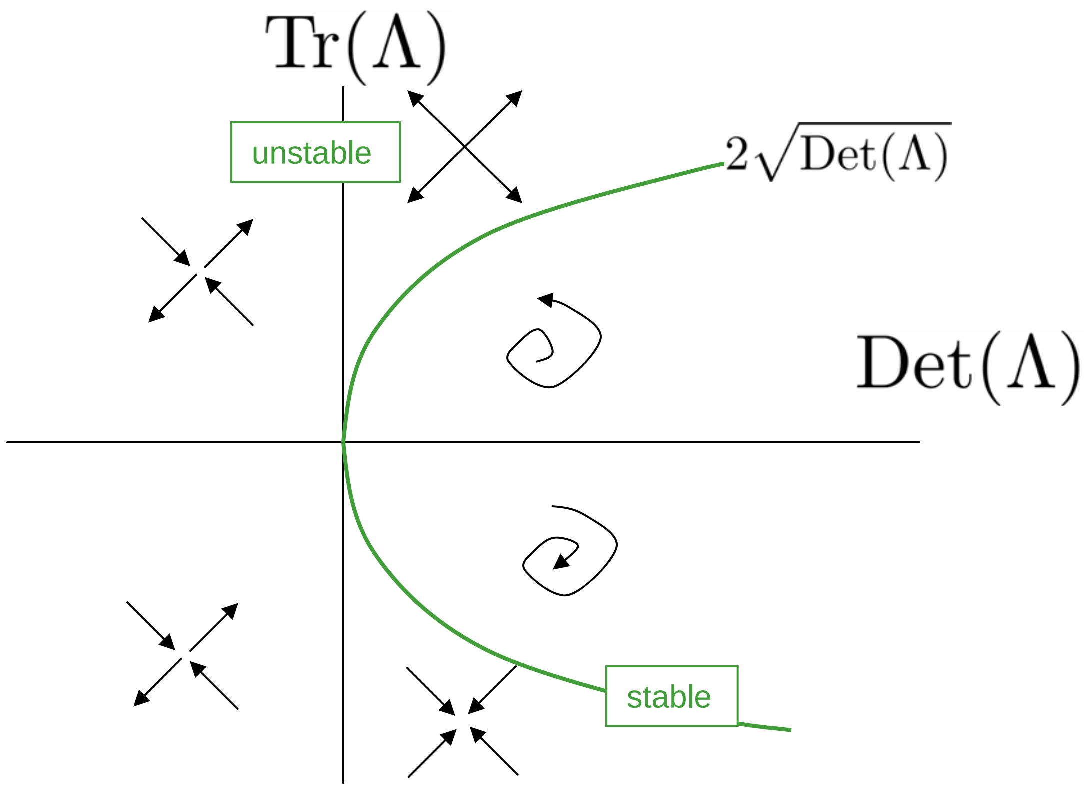
$$\frac{d}{dt}\begin{pmatrix} \delta n \\ \delta r \end{pmatrix} = \underbrace{\begin{pmatrix} k_u^0 e^f \left[f\frac{n_s}{n_s+n_\xi} - \frac{\bar{n}}{\bar{n}-n_s}\right] & \frac{\partial k_b(r_f)}{\partial r}(\bar{n}-n_s) \\ \frac{V_0}{n_s+n_\xi} & 0 \end{pmatrix}}_{\Lambda} \begin{pmatrix} \delta n \\ \delta r \end{pmatrix}$$

Eigenvalues

$$\lambda_\pm = \frac{1}{2}\left(\mathrm{Tr}(\Lambda) \pm \sqrt{\mathrm{Tr}(\Lambda)^2 - 4\mathrm{Det}(\Lambda)}\right)$$

Dynamical behavior

$$\boxed{\lambda_{\pm} = \frac{1}{2}\left(\mathrm{Tr}(\Lambda) \pm \sqrt{\mathrm{Tr}(\Lambda)^2 - 4\mathrm{Det}(\Lambda)}\right)}$$



$$\mathrm{Det}(\Lambda) = -V_0 \frac{\partial k_b(r_f)}{\partial r} \frac{\bar{n} - n_s}{n_s + n_\xi}$$

$$\boxed{> 0}$$

$$\mathrm{Tr}(\Lambda) < 0, \quad \frac{n_\xi}{\bar{n}} > f\frac{n_s}{\bar{n}}\left(1 - \frac{n_s}{\bar{n}}\right) - \frac{n_s}{\bar{n}}$$

Independent of

$\bar{n}$

Linear Dynamics

Stability of the fixed point

$n_\xi > n_\xi^C$ Stable fixed point t

$n_\xi < n_\xi^C$ Unstable fixed point t

$$\boxed{\frac{n_\xi^C}{N} \equiv f\,\frac{n_S}{N}\left(1-\frac{n_S}{N}\right)-\frac{n_S}{N}}$$

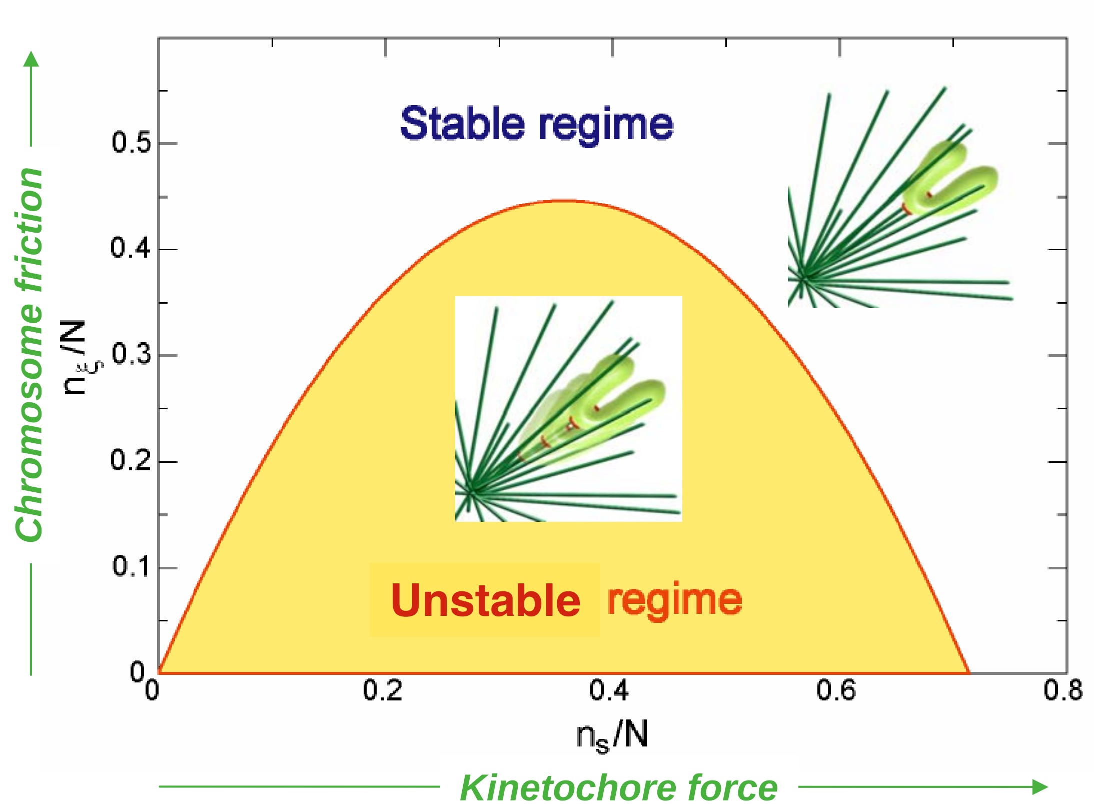
Unbinding rate

$$k_u = k_u^{(0)} \exp\left(\frac{1}{n}\frac{F_m a}{k_B T}\right)$$

$$\frac{F_m a}{n k_B T} = f\,\frac{n_s + n_\xi}{n + n_\xi}$$

High friction $F_m/n = f_s$
each motor feels its stall force (small velocity)
and is independent from the other ones

Low friction, $F_m/n = F_k/n$
the motors share the kinetochore force (no friction force)
Very cooperative:the unbinding rate depends strongly on 'n'



Unstable at low friction

Non-Linear Dynamics

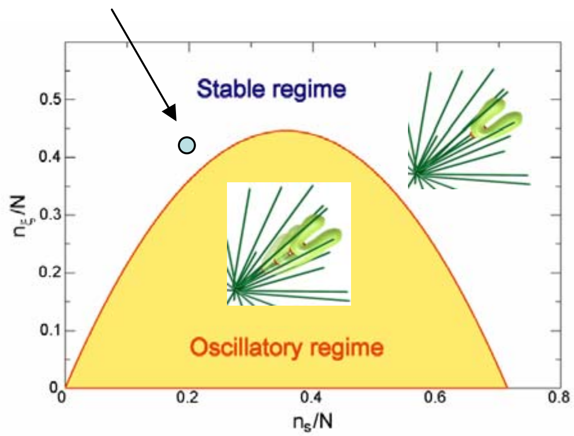
Nullclines and Phase flows

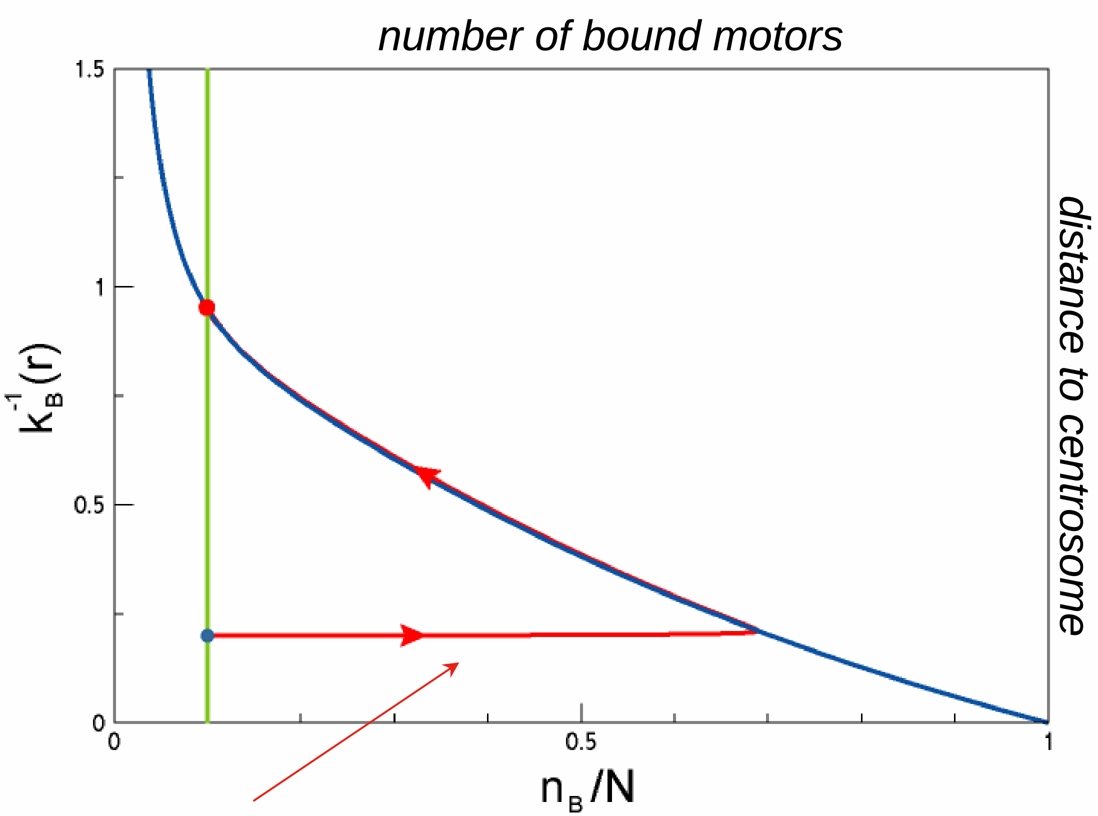
NullCline

$$\dot{r} = 0 \qquad n = n_s$$

$$\dot{n} = 0 \qquad k_b(r) = k_u^{(0)} \frac{n}{\bar{n} - n} \exp f \frac{n_s + n_\xi}{n + n_\xi}$$

Stable fixed point





The motor kinetics is much faster than the motion of the chromosome

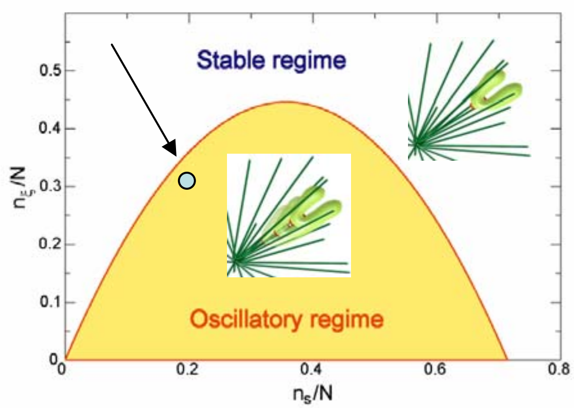
Non-Linear Dynamics
Nullclines and Phase flows

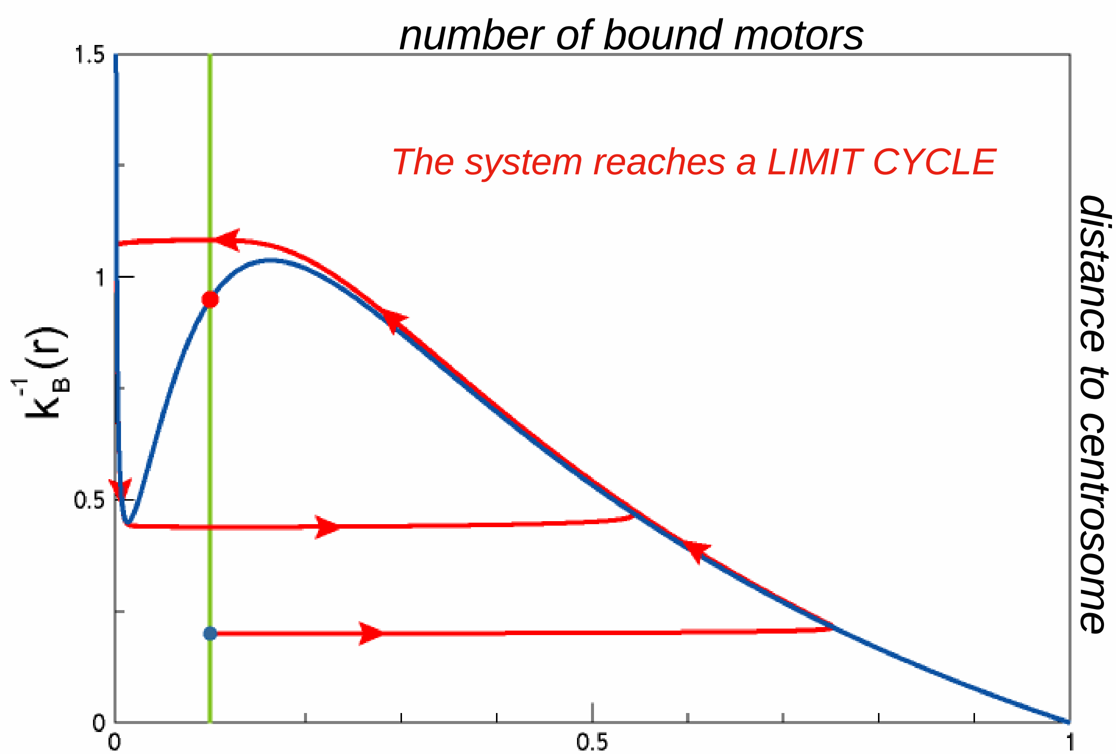
NullCline

$$\dot{r} = 0 \qquad n = n_s$$

$$\dot{n} = 0 \qquad k_b(r) = k_u^{(0)} \frac{n}{\bar{n} - n} \exp f \frac{n_s + n_\xi}{n + n_\xi}$$

Unstable fixed point



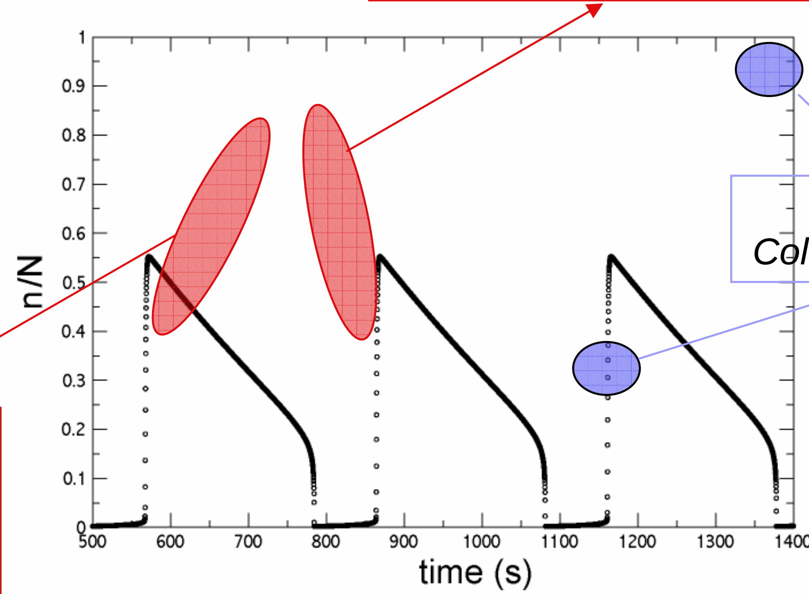


The n-Nullcline is non-monotonous

Numerical Integration and comparizon with experiments

(slow) linear motion at constant speed
No of bound CK
motion at natural Kinetochore speed

$$V_P \simeq F_K/\xi$$



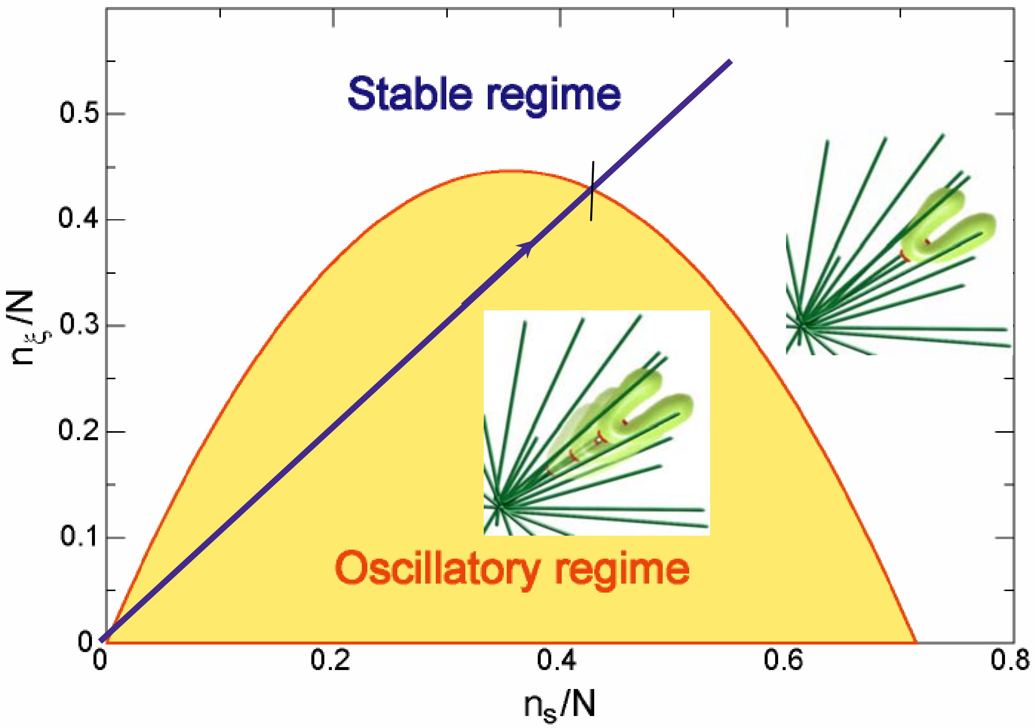
Sharp change of direction
Collective CK binding or unbinding

(slow) linear motion
at constant speed
Lot of bound CK
motion at maximum CK speed

$$V_{AP} \simeq V_0$$

Asymmetry of the oscillations: $$\frac{V_{AP}}{V_P} = \frac{n_\xi}{n_s}$$

Experimental predictions



$$\boxed{\begin{aligned} n_s &\equiv F_k/f_s \\ n_\xi &\equiv \xi_\infty V_0/f_s \\ f &\equiv f_s a/(k_B T) \end{aligned}}$$

Easiest parameter to modify: Total number of motors: N

There is a critical number of motors below which oscillations stop

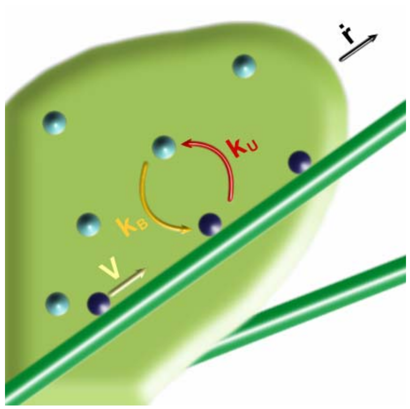
$$N_c = \frac{f n_s}{f - (1 + n_\xi/n_s)}$$

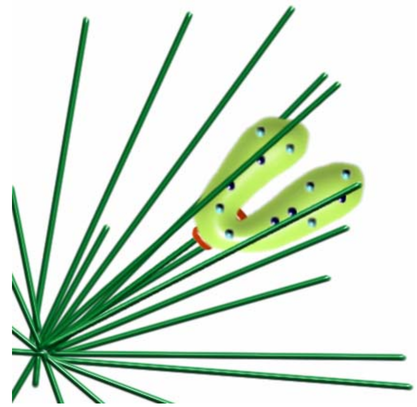
Main outcome of the model

Chromosome instability occurs because of collective motor dynamics

-

Chromosome oscillations occur because the astral MTs provide a ‘position-dependent’ substrate for CK binding





Refinement: Force-sensitive kinetochore

‘Concept: ‘smart kinetochore’
Can sense both position and force

Our model so far: ‘very dumb kinetochore’
Constant force and constant firction

The kinetochore is treated like one big (infinitely processive) motor

$$V = \boxed{\frac{F_K}{\xi}}\left(1 - \frac{F_M}{\boxed{F_K}}\right)$$

Maximum velocity *Stall force*

Conclusions

• Oscillations arise from the interplay between the cooperative dynamics of chromokinesins and the morphological properties of the MT aster.

• Highly non-linear oscillations, similar to those observed *in-vivo*, appear in a considerable region of the parameter space.

•Sawtooth shaped oscillations come from different kinetics of chromosome motion and motor binding dynamics

•Testable prediction - critical number of CK for oscillations