Mechanical stability of bipolar spindle assembly

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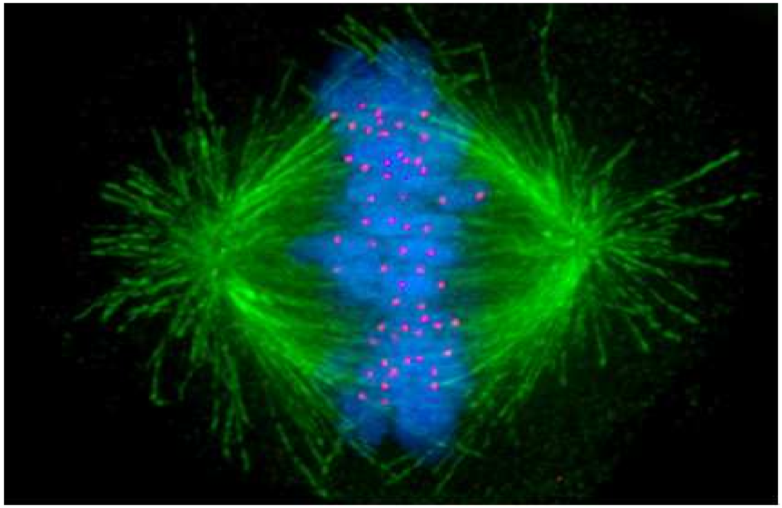
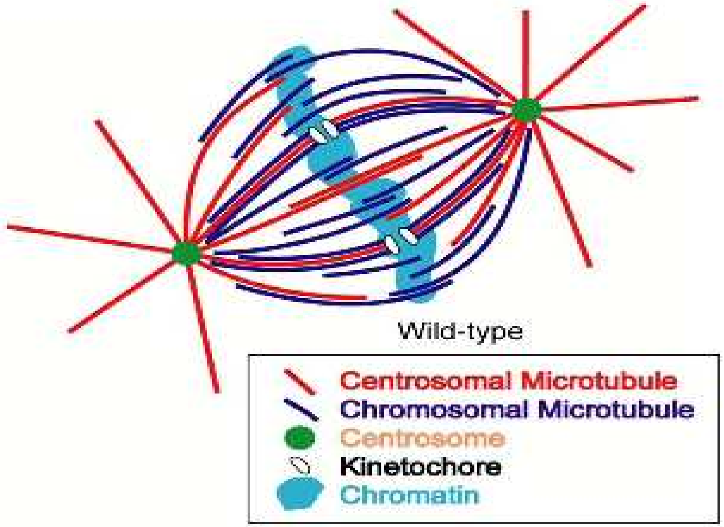
Mitotic spindle





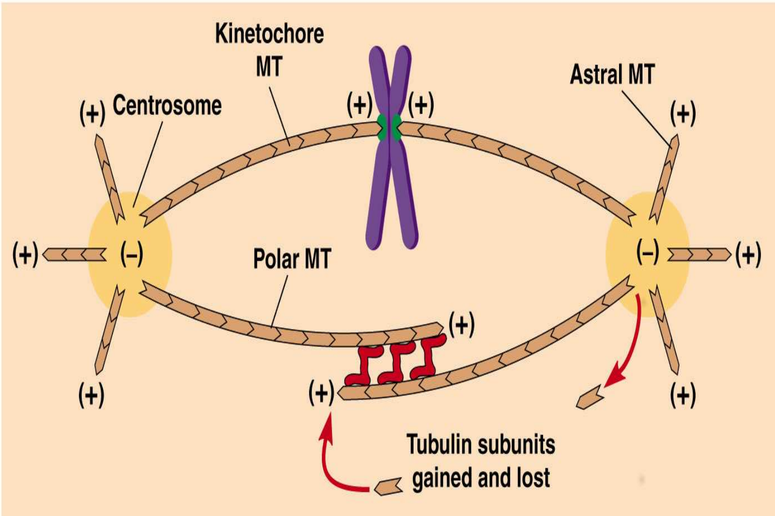
Mitotic Cell Division

- Replication of genomes and segregation of copies in daughter cells
- Process mediated with formation of Spindle
- Microtubules(MTs) from centrosomes overlap
- Chromosomes are arranged in the midzone during metaphase
- MTs interact with chromosomes,motors and kinetochores

What determines the stability of spindle structure ?

Model of Spindle Assembly

Schematic of centrosomes separated by distance 2x



Forces between the centrosomes:

(a) MTs interacting with chromosome arms

(b) Motors sliding overlapping MTs

(c) MTs getting joined by kinetochore

(d) Astral MTs interacting with cell cortex

Net Force - Single Chromosome

MTs nucleating from centrosomes interacting with single chromosome

- MTs nucleating from centrosome have length distribution: $N(l) \propto e^{-l/L}$

(a) Force due to MTs interacting with chromosome arm:$F_a \propto e^{-x/L}$

(b)Force due to motors sliding MTs: $F_b \propto 2xe^{-2x/L}$

(c)Force due MT-kinetochore interaction is constant

(d) Astral MT- cell cortex interaction: $\propto e^{-R_c/L}$, where R_c is the cell radius

$$F(x) = Ae^{-x/L} + 2Bxe^{-2x/L} - C + De^{-R_c/L}$$

Ferenz et.al Curr.Biol 19,1833 (2009)
Sutradhar et.al PRE 92, 042714 (2015)

Model for spindle formation

•Force between centrosomes when N chromosomes:

$$F_x = 2Bxe^{-2x/L} + \sum_{i=1}^{N} \frac{x}{R_i} \left(Ae^{-R_i/L} - C \right)$$

• Short range repulsion between chromosomes linear in separation

• Equations of motions for centrosomes and N chromosomes in overdamped limit

Results

• Relative strength of the different interactions regulate spindlelength

• Final spindle configuration is seen to be sensitive to initial conditions

•Chromosomes are distributed on a disc or a ring configuration

Sutradhar et.al PRE 92, 042714 (2015)

Chromosomes distributed over disc

For homogenous distribution of chromosomes lying on disc,

$$F = 2Bxe^{-2x/L} + \frac{Nx}{\pi R_d^2} \int_0^{R_d} \int_0^{2\pi} \frac{r dr d\theta}{\sqrt{x^2 + r^2}} \left(Ae^{-\sqrt{x^2+r^2}/L} - C \right)$$

Estimate R_d:

Each chromosome occupies a surface area πr_{ch}^2 within the disc, where r_{ch} is the radius of a single chromosome with $R_d \sim r_{ch}\sqrt{N}$.

Scaling variables

$x_o = x/L$, $F_o = \frac{FR_d^2}{2NAL^2}$, $R_o = R_d/L$, $C_o = C/A$, $B_o = \frac{BR_d^2}{NAL}$.

Force in terms of Scaling variables

$$F_o(x_o) = x_o \left[B_o e^{-2x_o} + e^{-x_o} - e^{-\sqrt{x_o^2+R_o^2}} - C_o \left(\sqrt{x_o^2 + R_o^2} - x_o \right) \right]$$

Condition for Mechanical Stability

Effective potential energy (V_o)

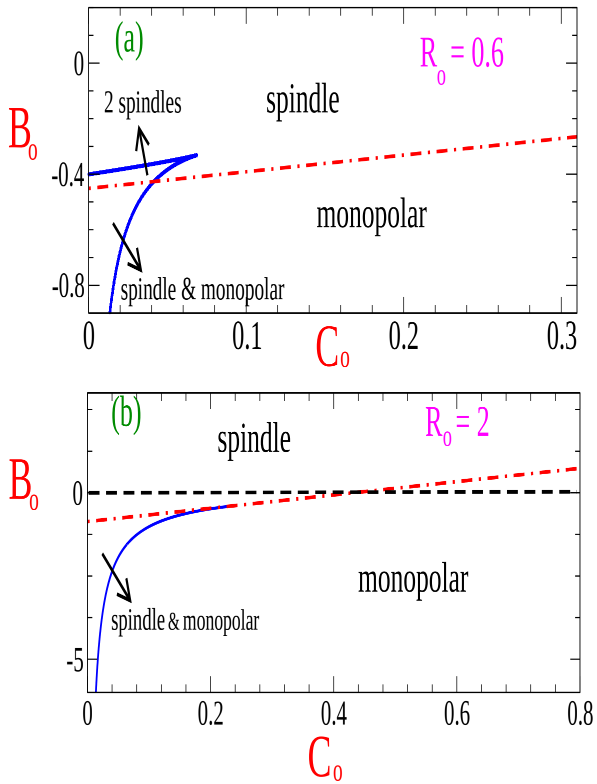
$$V_o = \frac{C_o}{3}\left[\left(\sqrt{x_o^2+R_o^2}-x_o\right)^{\frac{3}{2}}-x_o^3\right]-e^{-x_o}(x_o+1)$$
$$- \quad e^{-\sqrt{x_o^2+R_o^2}}\left(\sqrt{x_o^2+R_o^2}+1\right)-\frac{B_o}{4}e^{-2x_o}(2x_o+1)$$

Condition for mechanical stability:

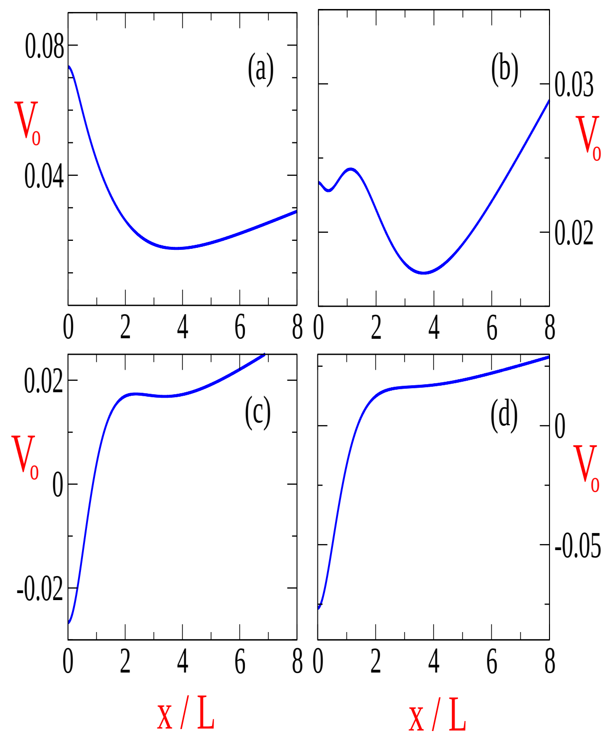
$F(x_e)=0$, $(\frac{dF}{dx})_{(x=x_p)}<0$

This determines the stability diagram in terms of B_o and C_o

Stability Diagram: Chromosomes on disc



$C_o = 0.02, R_o = 0.6$



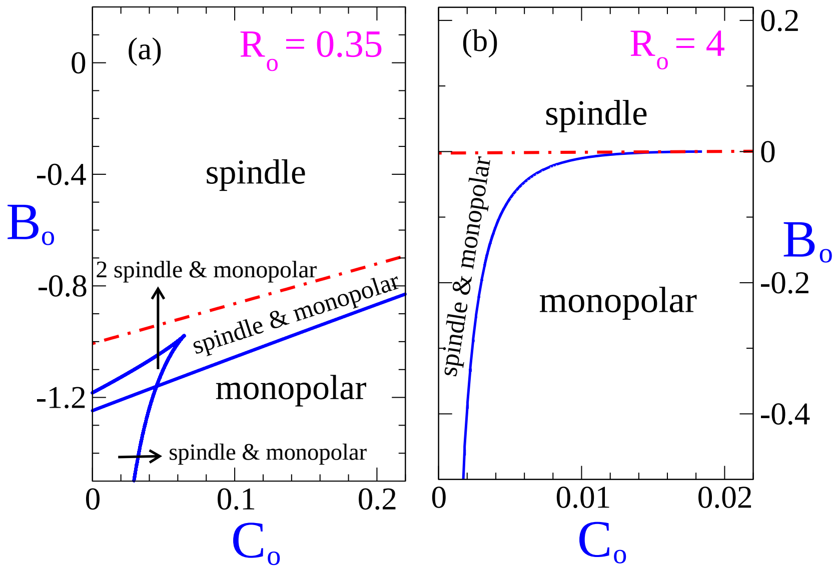
(a) $B_o = -0.2$, only bipolar spindle stable

(b) $B_o = -0.4$, 1 stable bipolar spindle + monopolar stable.

(b) $B_o = -0.6$: 2 stable bipolar spindles + monopolar stable

(d) $B_o = -0.8$, only monopolar solution stable

Stability Diagram: Chromosomes on ring



Here $R_r = 4$, obtained by estimating for $N = 46$ and $L = 4$

For ring geometry, even for relatively low value of C, the bipolar spindle can be unstable, consistent with results of computational model

As R_o is increased, stability of the bipolar spindle decreases

Comparison with Computational model

Parameter values: $L = 4\,\mu m$, $N = 46$, $C = 10\,pN$, $A = 125\,pN$

Computational Model results: (Sutradhar et.al PRE 92, 042714 (2015))

For B= 0 and $C_o > 0.08$ bipolar spindle was unstable

Predictions from our stability diagram

Bipolar spindle configuration is unstable for $B = 0$ only for $C_o > 0.4$.

However for lower values of B i.e; $(B = -25\,pN/\mu m)$, bipolar spindle is unstable

Summary and Conclusions

• Analyzed stability of spindle structure using a minimal model which incorporates the interactions between MTs with Chromosomes and kinetochore, and sliding forces on MT due to motors

• if there is a net outward sliding forces by motors $(B > 0)$ then bipolar spindle is stable, whereas fo $(B < 0)$, monopolar configuration is stable.

• For $B < 0$, below a threshold value of C, there are regimes of bistability.

• Bistable behavior can be associated with multiple minima in the potential energy function

Paolo Malgaretti and SM, EPL 28001 (2016)

THANKS