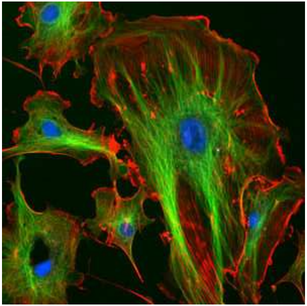
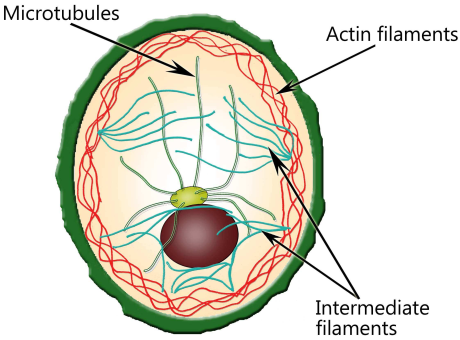
Causes and Consequences of aging in microtubule catastrophe

Jemseena V

International Centre for Theoretical Sciences

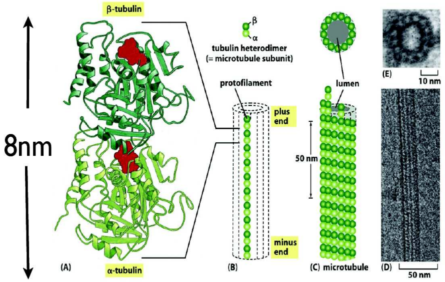
Cytoskeleton: Skeleton of the cell

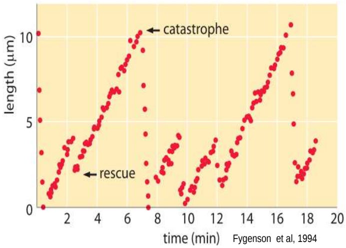




Cytoskeleton of a eukaryotic cell consists of three types of filaments: Actin filaments, microtubules and intermediate filaments

Microtubule structure and dynamics

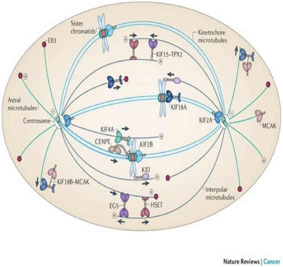




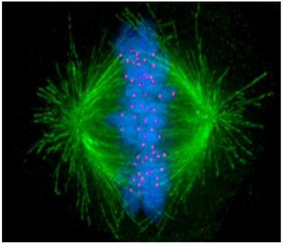
- Length typically of the order of a few microns and diameter of 25 nm
- 12-14 protofilaments
- Made up of globular proteins called α-β tubulins with β-tubulin carrying a rapidly hydrolyzable GTP

'GTP' powered microtubules stay out of equilibrium

Functions



Tracks for cargo transport



As force generators

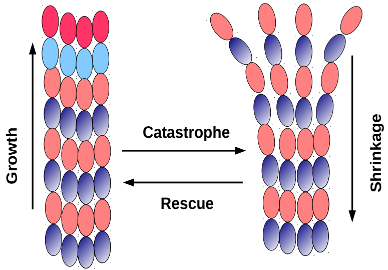
- Function as tracks for molecular motors
- Search for targets such as chromosomes during mitosis
- Segregation of chromosomes, positioning of nucleus etc.

Modeling attempts...

1. **Microtubule catastrophe from protofilament dynamics; age-dependent catastrophe**

2. **Dynamic instability with age-dependent catastrophe**

More about catastrophe transition...

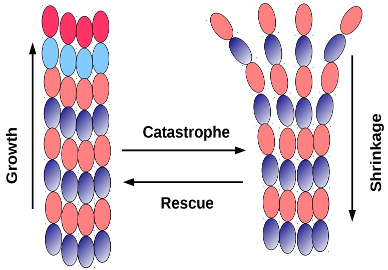


“Dynamic instability”

‘GTP cap’ theory :

As long there exits a GTP-rich region at the tip of microtubule, it continues to grow. Once the GTP cap is lost by hydrolysis, the filament starts to shrink (Mitchison et al, 1984).

More about catastrophe transition...



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Does the catastrophe transition require uncapping of all the 13 protofilaments or less?

Multi-step model for catastrophe

Catastrophe: a first passage event

$n^* - 1$ protofilaments have already undergone local catastrophe by time t, the n^*th one undergoes between t and $t + dt$, defines a catastrophe transition for the entire filament.

1. Quantitative study of dynamics of individual protofilaments, mainly local catastrophes
2. Derive MT catastrophe based on protofilament dynamics

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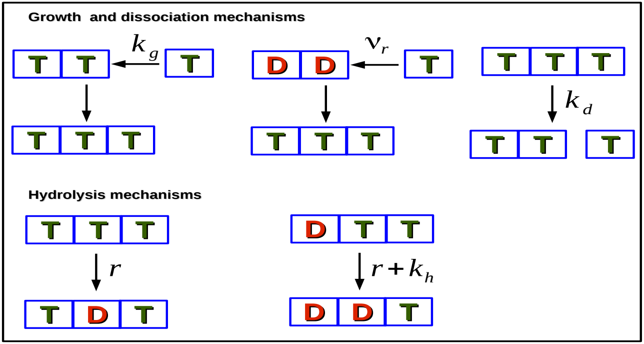
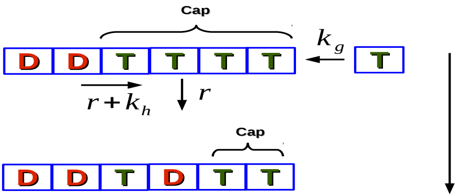
MT "lattice model"

Protofilament dynamics





A single protofilament at two time instants

T_{mers} at the tip constitute 'protofilament cap'

Protofilament cap dynamics

$$\frac{dP_n(t)}{dt} = k_h[P_{n+1}(t) - P_n(t)] + k_g[P_{n-1}(t) - P_n(t)] - rnP_n(t) + r\sum_{m=n+1}^{\infty} P_m(t)$$

Protofilament (local) catastrophe

$$\nu_c'(t) = \frac{(r+k_h)P_1(t)}{1-P_0(t)} \leq r + k_h,$$

ν_c'	$k_g = 0$	$k_g > k_h$	$k_g \gg k_h$
$\nu_r' > 0$	$r + k_h$	$\frac{rk_h(2k_g - k_h)}{(k_g - k_h)^2} + \mathcal{O}(r^2)$	$\sim \frac{2rk_h}{k_g}$
$\nu_r' = 0$	$r + k_h$	$\frac{rk_h}{(k_g - k_h)} + \mathcal{O}(r^2)$	$\sim \frac{rk_h}{k_g}$

Microtubule dynamics

$$\frac{dQ_n}{dt} = k_-^{n+1} Q_{n+1} + k_+^{n-1} Q_{n-1} - (k_+^n + k_-^n) Q_n,$$

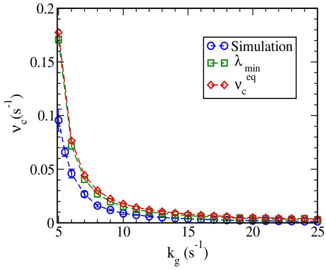
$$k_+^n = (13 - n)\nu_c'' \quad ; \quad k_-^n = n\nu_r'$$

$$\nu_c''(t) \equiv \nu_c'(t) \frac{1 - P_0(t)}{1 - P_0'(t)}$$

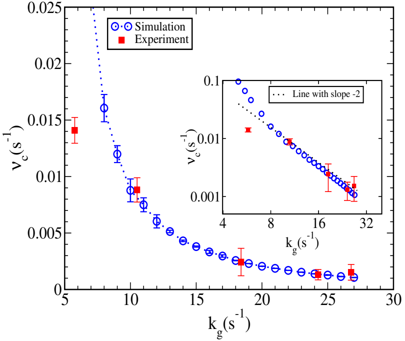
Analytical results *vs* simulations

Microtubule catastrophe

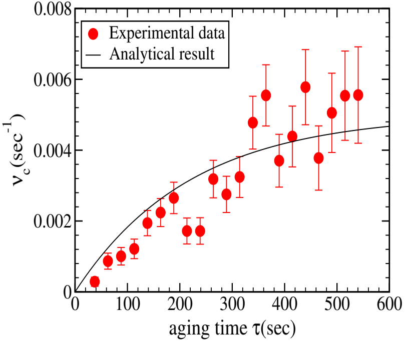
$$\nu_c(t) = \frac{(14 - n^*)\nu_c''(t) Q_{n^*-1}(t)}{\sum_0^{n^*-1} Q_j(t)}$$



Microtubule catastrophe: steady-state and kinetics



catastrophe *vs* growth rate



kinetics of catastrophe

- Out of 13 protofilaments in a microtubule, GTP cap loss in 2-3 protofilaments may be sufficient to trigger catastrophe.
- Gives insights to age-dependent catastrophe

Jemseena. V and Manoj. G., PRE(2013)

Dynamic instability with aging present: A two-state model

Growing state

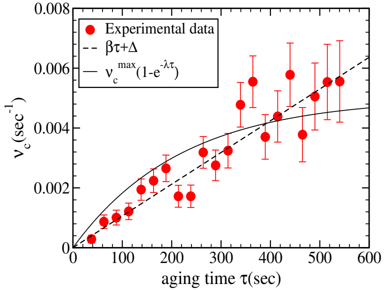
$$\frac{\partial G'_{1j}(x,\tau,t|x_0,0)}{\partial t} = -v_g \frac{\partial G'_{1j}(x,\tau,t|x_0,0)}{\partial x} - \frac{\partial G'_{1j}(x,\tau,t|x_0,0)}{\partial \tau}$$
$$-\nu_c(\tau) G'_{1j}(x,\tau,t|x_0,0) + \nu_r G_{0j}(x,t|x_0)\delta(\tau)$$

Shrinking state

$$\frac{\partial G_{0j}(x,t|x_0)}{\partial t} = v_s \frac{\partial G_{0j}(x,t|x_0)}{\partial x} + \int_0^\infty d\tau \ \nu_c(\tau) G'_{1j}(x,\tau,t|x_0,0)$$
$$-\nu_r G_{0j}(x,t|x_0)$$

$$\frac{dx}{dt} = v_g; \qquad \frac{d\tau}{dt} = 1 \qquad \text{(Growing state)}$$
$$\frac{dx}{dt} = -v_s; \qquad \tau = 0 \qquad \text{(Shrinking state)}$$

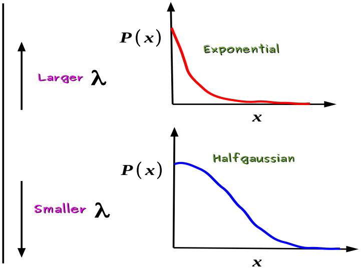
- MT is assumed to be one dimensional
- MT nucleates at a rate ν
- Elongates with velocity v_g
- Shrinks with velocity v_s
- Growth $\underset{\nu_r}{\overset{\nu_c(\tau)}{\rightleftharpoons}}$ Shrinkage



1. Exponential aging $\nu_c(\tau) = \nu_c^{\max}(1 - e^{-\lambda\tau})$
2. linear aging $\nu_c(\tau) = \beta\tau$

Results

1)Length distribution

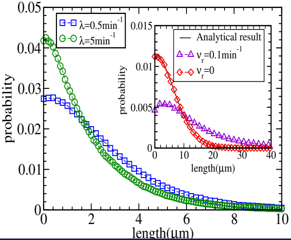


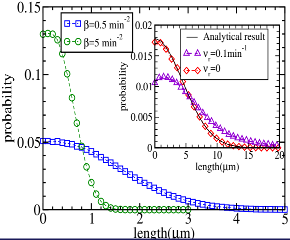
$$P(x) \propto \exp(-\frac{\nu_c^{max} x}{v_g})$$

$$P(x) \propto \exp(-\frac{\nu_c^{max}}{v_g}x - \frac{\nu_c^{max} e^{-\frac{\lambda}{v_g}x}}{\lambda})$$

$$P(x) \propto \exp(-\frac{\alpha x^2}{v_g^2})$$

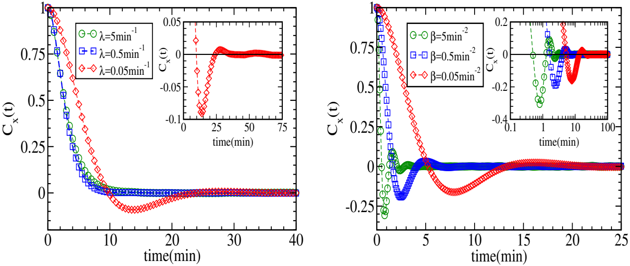
Numerical simulations



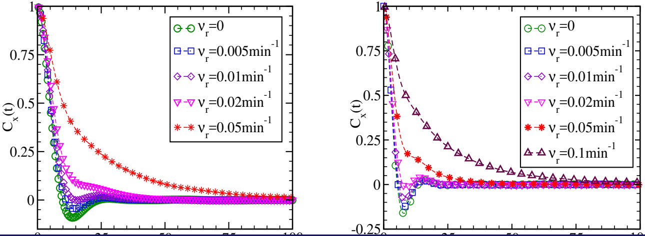


2)Length autocorrelation function

Rescue absent



Rescue present



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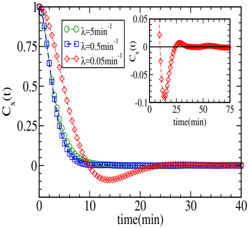

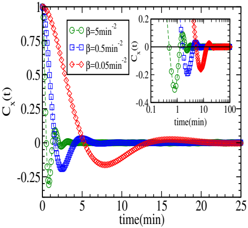

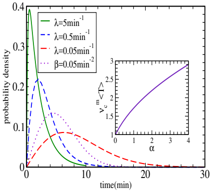

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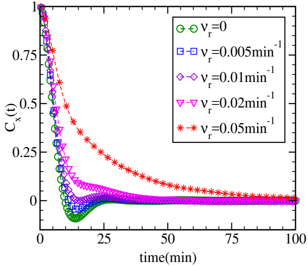
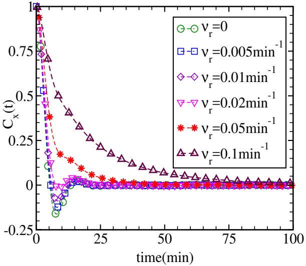
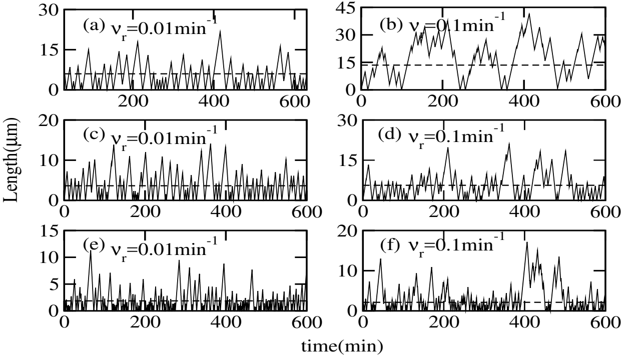




Microtubule trajectories



- Aging significantly affects the statistical properties of a microtubule population.
- The bidirectional motion of the microtubule tip can be revamped into oscillatory motion, for sufficiently small aging rate and rescue frequency.

Jemseena. V and Manoj. G., PRE(2015)