Dynamics of Microtubule Growth & Catastrophe

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U Mass Amherst, March 15, 2007

Basic question:

Why do microtubules fluctuate wildly under steady conditions?

Main result:

These large fluctuations & rich dynamics are captured by a simple, soluble model.

Outline:

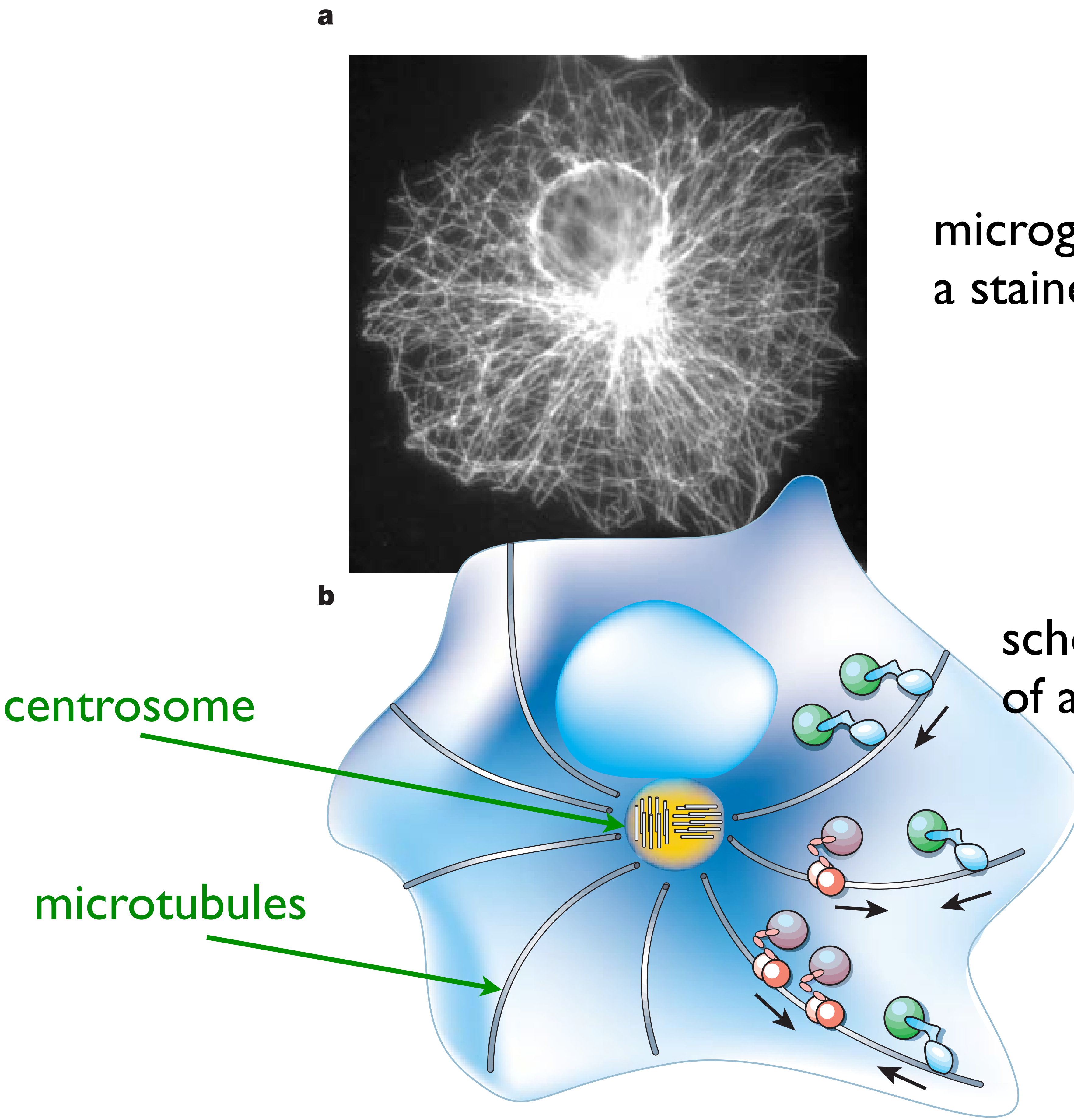
What is a microtubule? What does it do?

Microscopic modeling.

Master equation & probabilistic results.

What is a Microtubule?

Howard & Hyman, Nature 2003

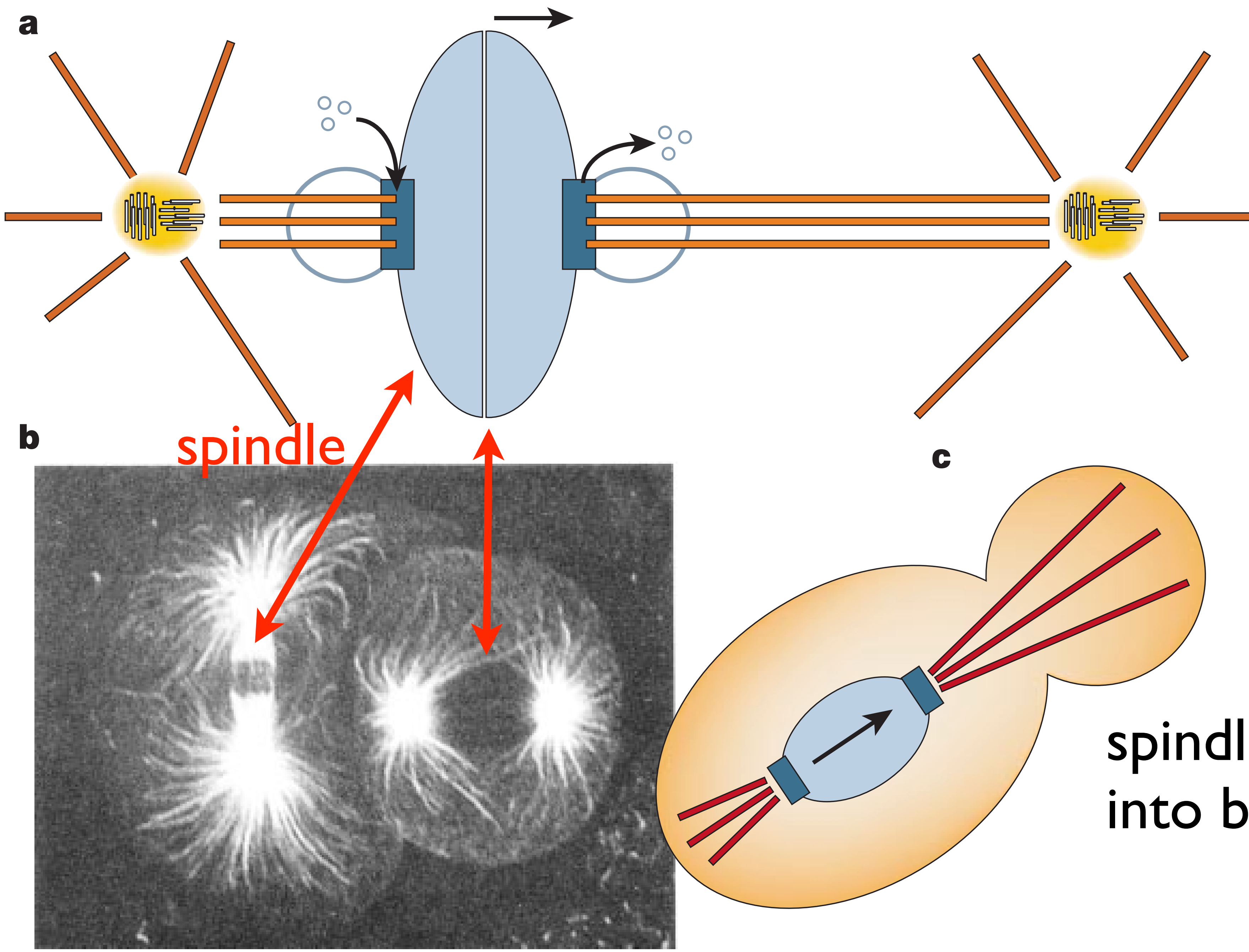


micrograph of a stained cell

schematic picture of a cell

What Do Microtubules Do?

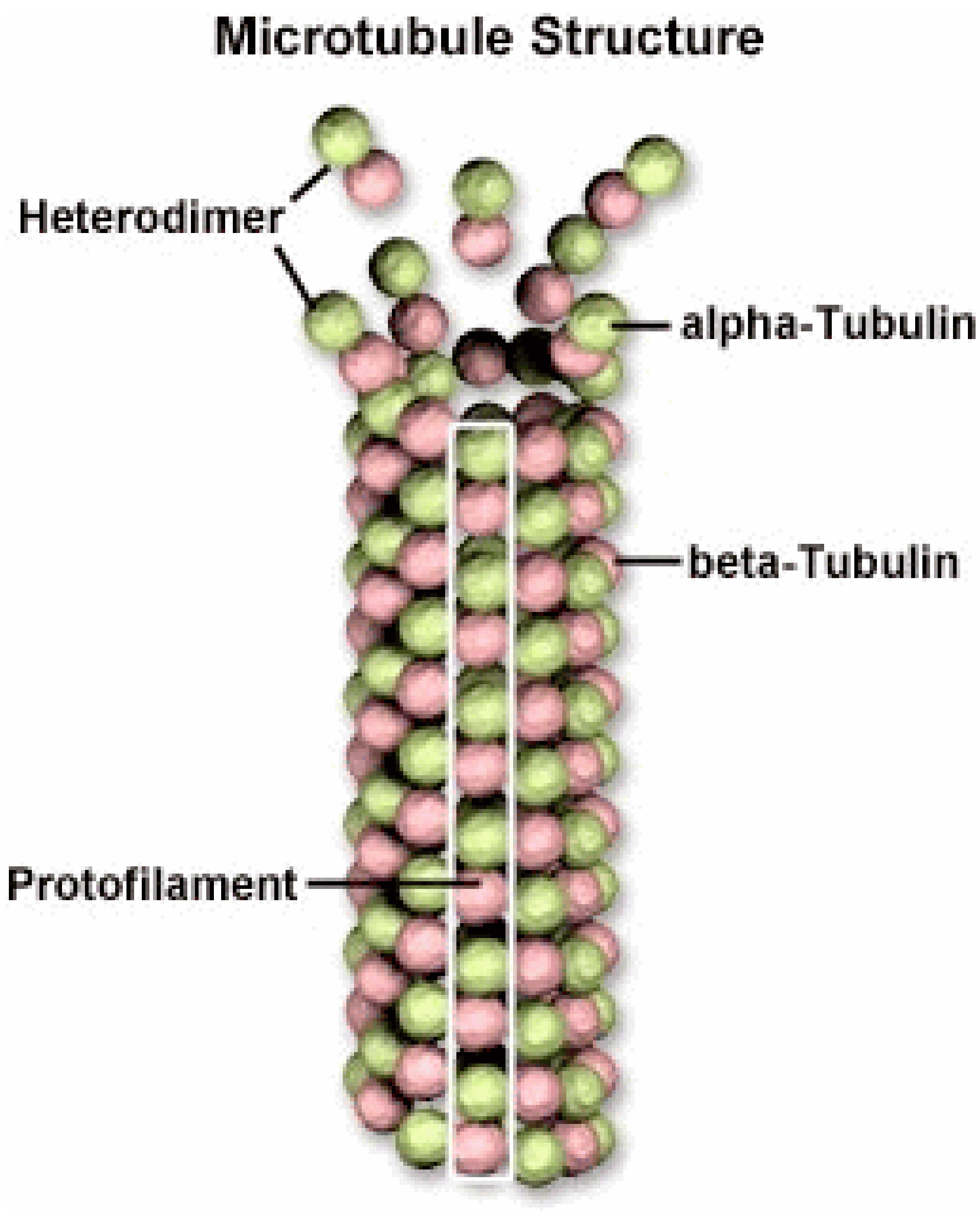
chromosome transport
during mitosis metaphase

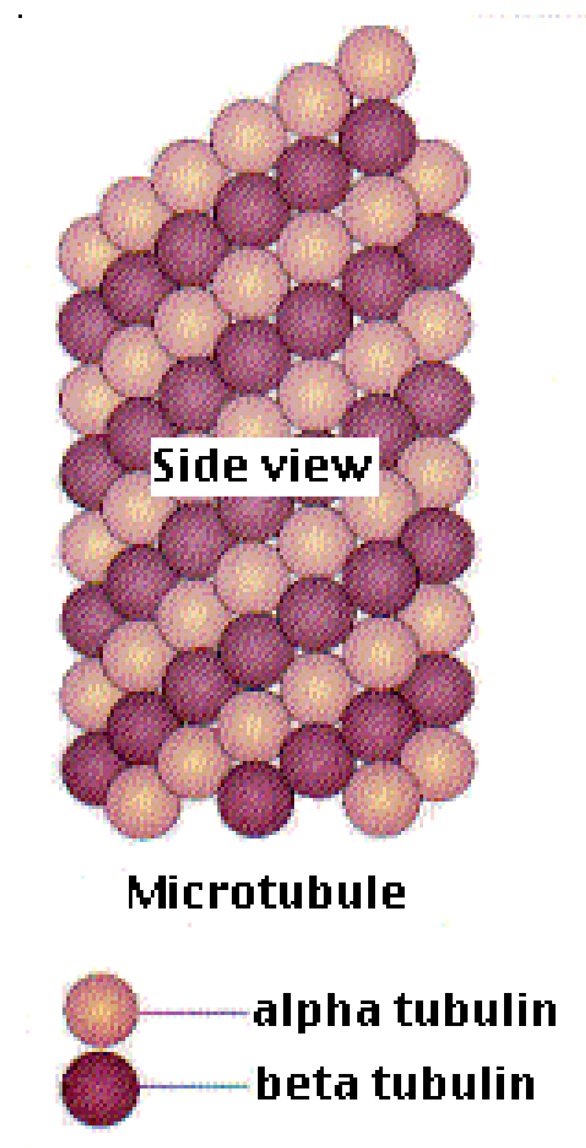


spindle transport
into bud

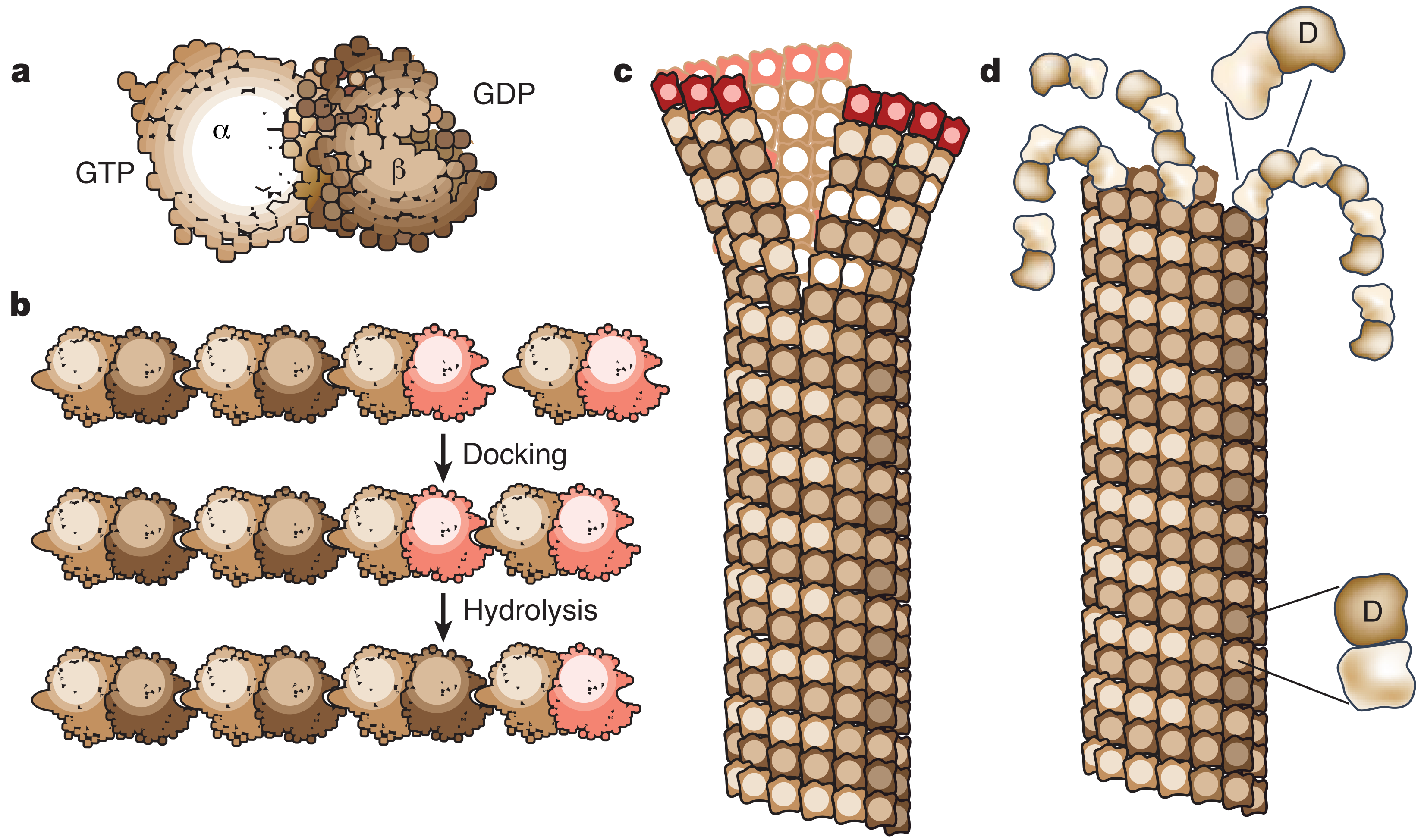
What is a Microtubule Made Of?

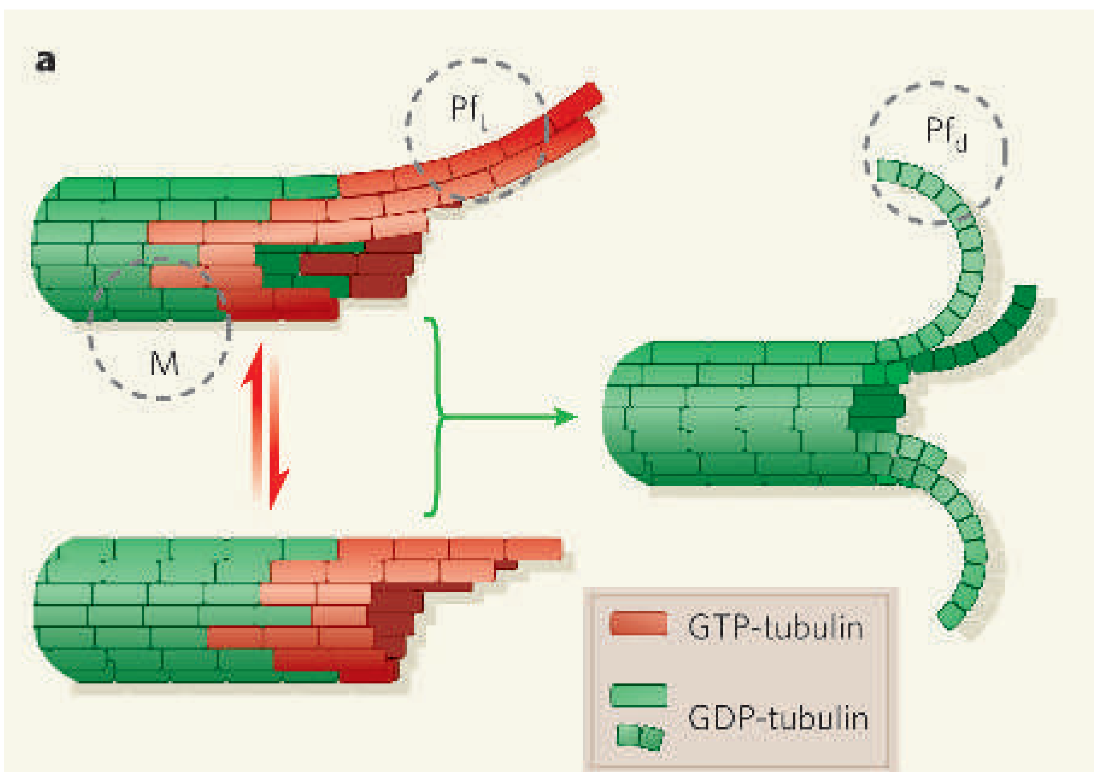
from wikipedia





How Do Microtubules Grow and Shrink?

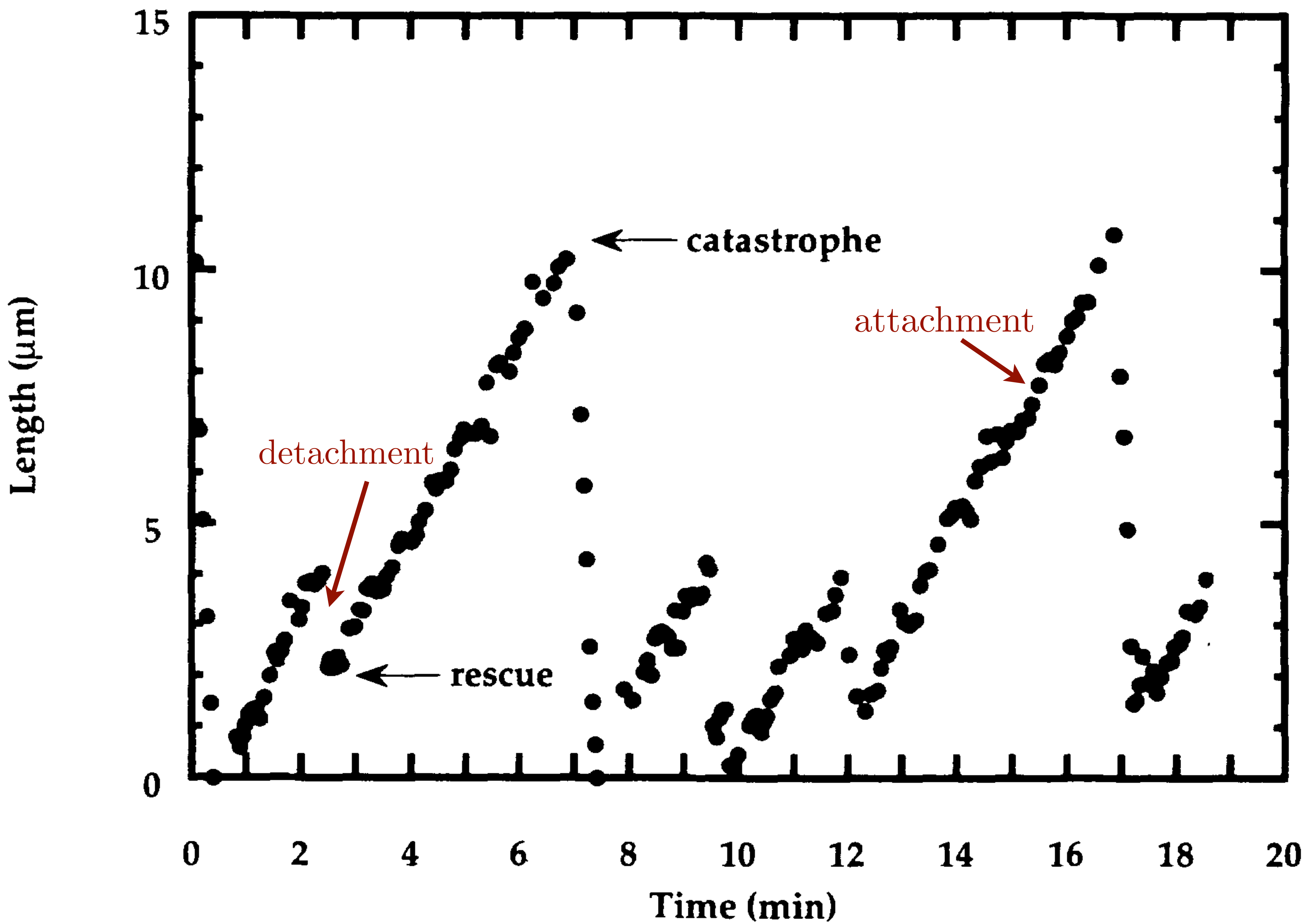




Mahadevan & Mitchison, Nature 2005

Microtubule Evolution

Fygenson et al., PRE (1994)



Microscopic Model

1. **Growth:** attachment of a GTP^+ monomer.

$$|\cdots +\rangle \Longrightarrow |\cdots + +\rangle \qquad \text{rate } \lambda$$

$$|\cdots -\rangle \Longrightarrow |\cdots - +\rangle \qquad \text{rate } p\lambda$$

2. **Conversion:** GTP^+ hydrolysis to a GDP^- monomer.

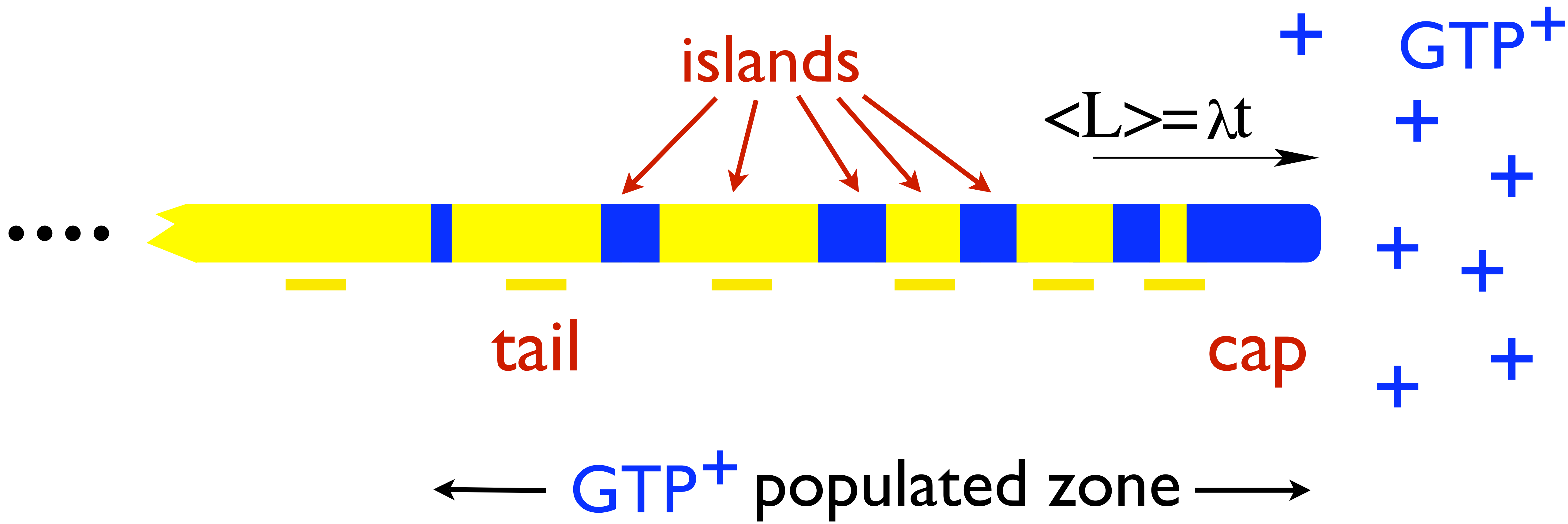
$$|\cdots + \cdots\rangle \Longrightarrow |\cdots - \cdots\rangle \qquad \text{rate } 1$$

3. **Shrinking:** detachment of a GDP^- *from the microtubule end.*

$$|\cdots -\rangle \Longrightarrow |\cdots\rangle \qquad \text{rate } \mu$$

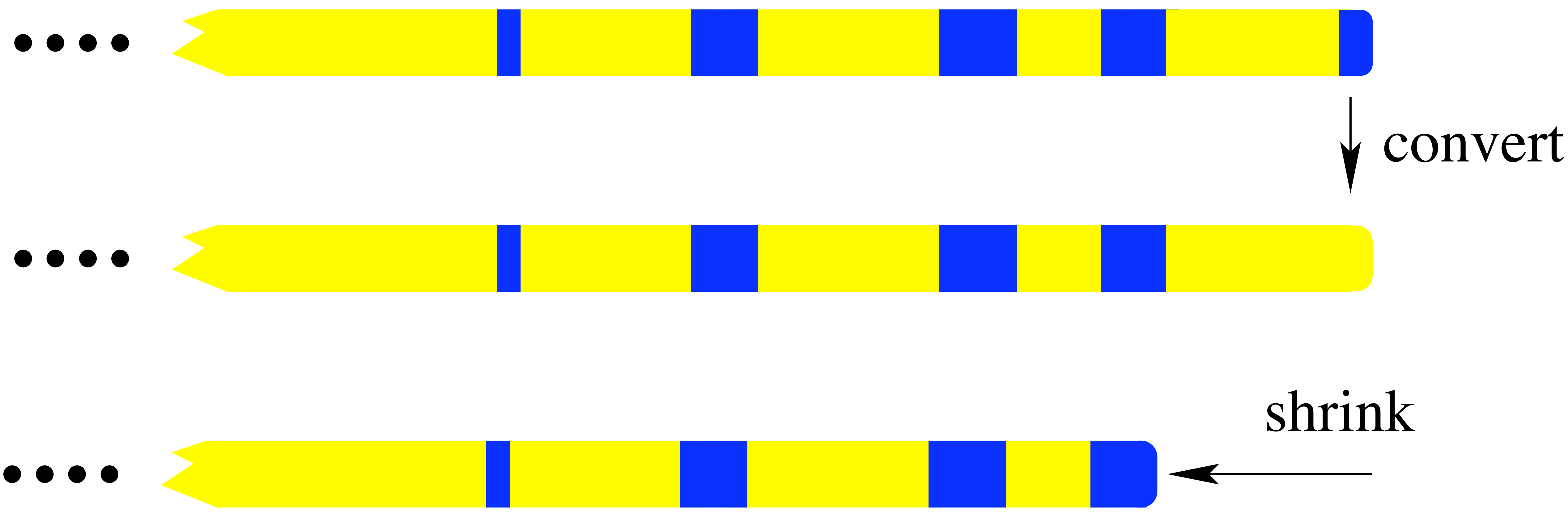
Cartoon of Growing Microtubule

no detachment, $\mu = 0$



Cartoon of Shrinking Microtubule

$$\lambda < \mu$$



Dynamics of Unrestricted Growth

no detachment: $\mu = 0$

color-blind attachment: $p = 1$

$N \equiv$ number of GTP$^+$

Rate equation: $$\frac{d}{dt}\langle N\rangle = \lambda - \langle N\rangle \qquad \rightarrow \langle N\rangle = \lambda$$

$\Pi_N \equiv$ prob. that tubule contains N GTP$^+$

conversion: N→N-1 *attachment: N→N+1* *attachment: N-1→N* *conversion: N+1→N*

Master equation: $$\frac{d\Pi_N}{dt} = -(N+\lambda)\Pi_N + \lambda\Pi_{N-1} + (N+1)\Pi_{N+1}$$

Solution: $$\Pi_N(t) = \frac{[\lambda(1-e^{-t})]^N}{N!}\, e^{-\lambda(1-e^{-t})}$$

Generating Function Solution

generating function: $\Pi(z) \equiv \sum_{N=0}^{\infty} \Pi_N z^N$

$$\frac{d\Pi_N}{dt} = -(N+\lambda)\Pi_N + \lambda\Pi_{N-1} + (N+1)\Pi_{N+1}$$

$$\to \frac{\partial \Pi}{\partial t} = (1-z)\left(\frac{\partial \Pi}{\partial z} - \lambda \Pi\right).$$

define $Q = \Pi e^{-\lambda z}$, $y = \log(1-z)$,

$$\to \frac{\partial Q}{\partial t} + \frac{\partial Q}{\partial y} = 0,$$

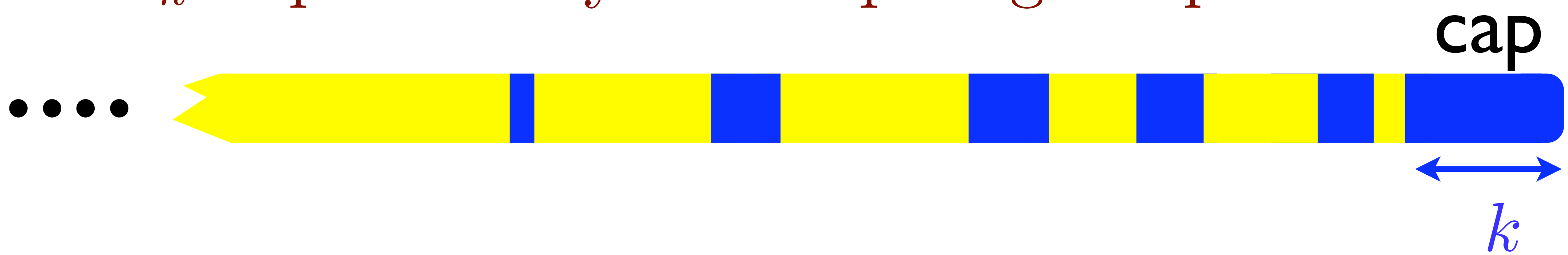
formal solution: $Q = F(t-y) = F(e^{-t}(1-z))$

for initial condition $\Pi_N(t=0) = \delta_{N,0}$

$$\to \Pi(z,t) = e^{-\lambda(1-z)(1-e^{-t})}$$

Cap Length Distribution

$n_k \equiv$ probability that cap length equals k



attach to (k-1)-cap | *attach to k-cap* | *convert k-cap* | *convert >k-cap*

Master equation: $$\dot{n}_k = \lambda(n_{k-1} - n_k) - k n_k + \sum_{s \geq k+1} n_s$$

Steady state: $$N_k = \frac{\lambda}{k+\lambda} N_{k-1} \qquad N_k = \sum_{s \geq k} n_s$$

Solution: $$N_k = \frac{\lambda^k \, \Gamma(1+\lambda)}{\Gamma(k+1+\lambda)}$$

$$\rightarrow \langle k \rangle = \sum_{k \geq 0} k n_k \sim \sqrt{\frac{\pi\lambda}{2}} \qquad \lambda \rightarrow \infty$$

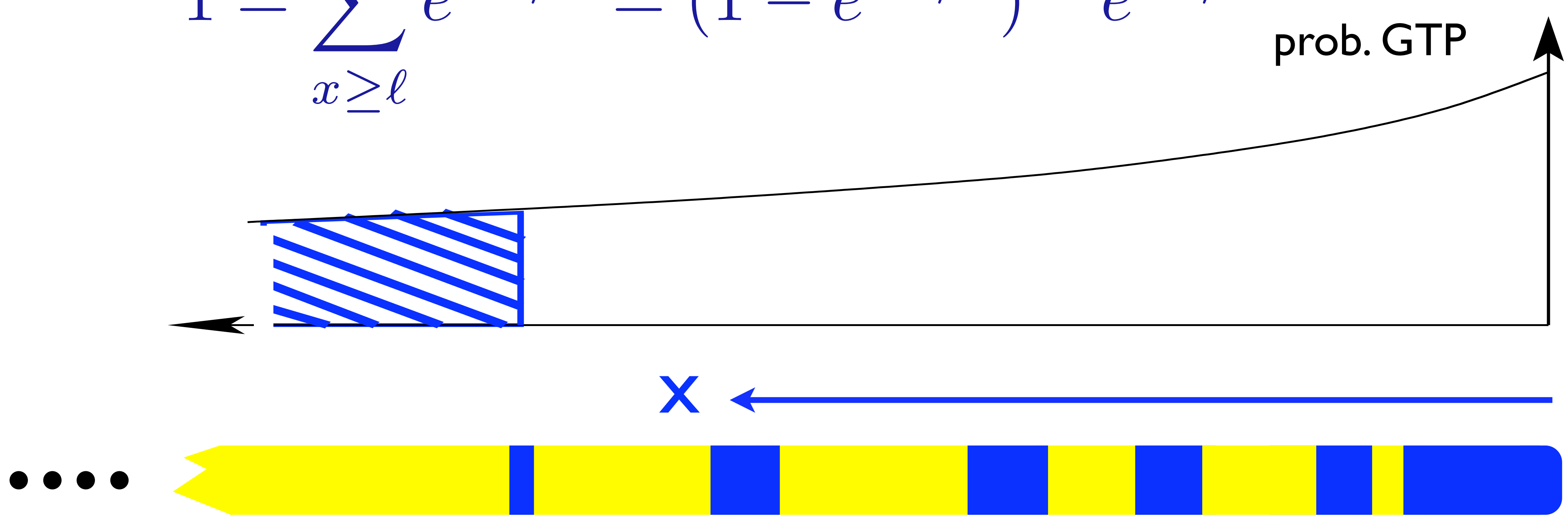
Island Distributions: Continuum Limit

$\lambda \to \infty$

prob. GTP^+ distance x from tip does not convert: $e^{-\tau} = e^{-x/\lambda}$

extreme criterion: 1 GTP^+ beyond ℓ

$$1 = \sum_{x \geq \ell} e^{-x/\lambda} = (1 - e^{-1/\lambda})^{-1} e^{-\ell/\lambda}$$



The GTP^+ populated zone:

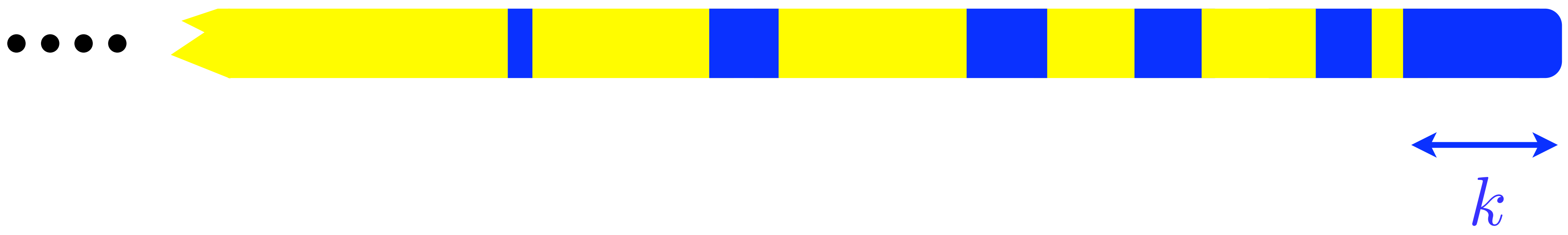
$$\longleftarrow \quad \ell = \lambda \ln \lambda \quad \longrightarrow$$

Cap Length Distribution (*continuum*)

prob. that cap has length k: $$\left(1 - e^{-(k+1)/\lambda}\right) \prod_{j=1}^{k} e^{-j/\lambda}$$

monomer k+1 converts

all monomers within k of the tip do not convert



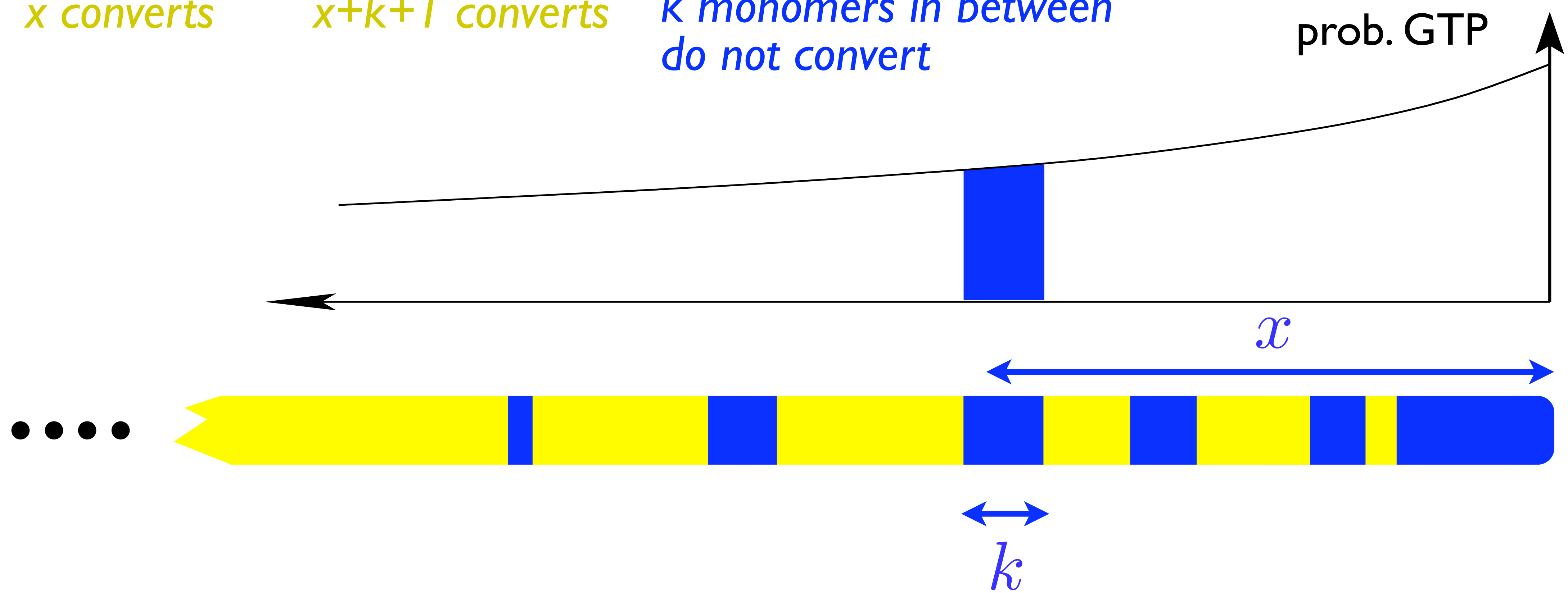
$$n_k \sim \frac{k+1}{\lambda}\, e^{-k(k+1)/2\lambda} \quad \rightarrow \langle k \rangle \propto \sqrt{\lambda}$$

Island Length Distributions

prob. positive island at x has length k:

$$(1-e^{-x/\lambda})(1-e^{-(x+k+1)/\lambda})\prod_{j=1}^{k} e^{-(x+j)/\lambda} \;\rightarrow\; (1-e^{-x/\lambda})^2\, e^{-kx/\lambda}$$

monomer at x converts — *monomer at x+k+1 converts* — *k monomers in between do not convert*



$$I_k \equiv \text{density of islands of length k}$$

$$= \int_0^\infty dx\,(1-e^{-x/\lambda})^2 e^{-kx/\lambda} = \frac{2\lambda}{k(k+1)(k+2)}$$

prob. negative island at x has length k:

$$e^{-2x/\lambda}(1 - e^{-x/\lambda})^k$$

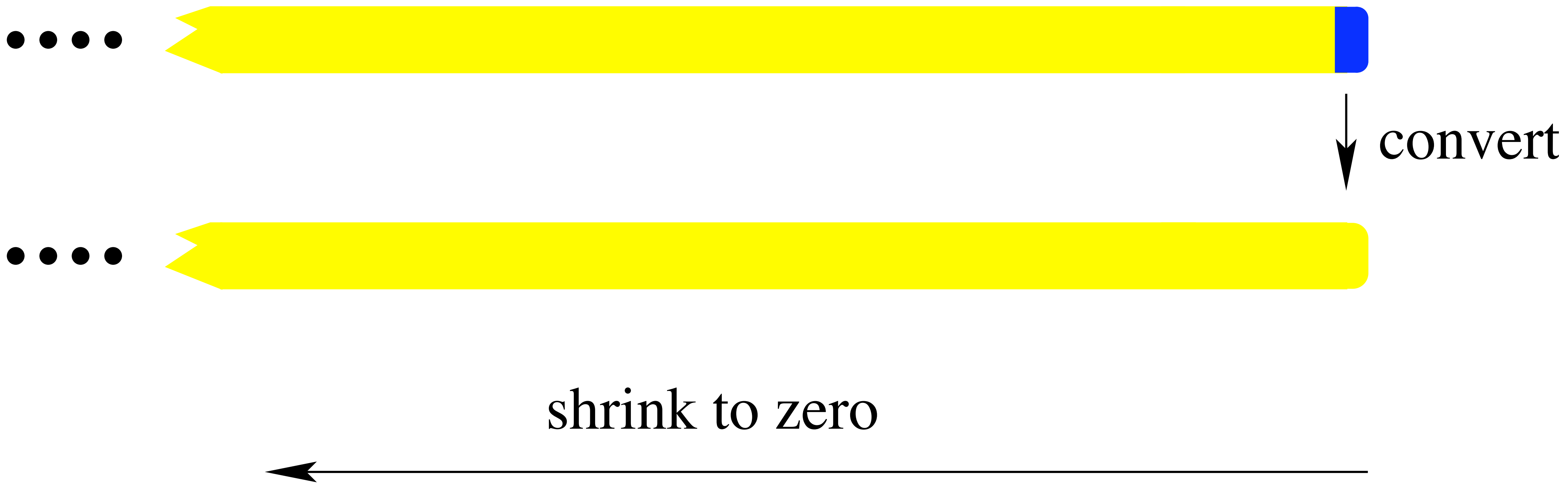
end monomers do not convert

k monomers in between convert

$$J_k = \int_0^\infty dx\, e^{-2x/\lambda}(1 - e^{-x/\lambda})^k = \frac{\lambda}{(k+1)(k+2)}$$

away from tip:
- shorter GTP^+ islands: k^{-3} distribution
- longer GDP^- islands: k^{-2} distribution

Catastrophes



catastrophe probability: $$\mathcal{C}(\lambda) = \frac{1}{1+\lambda} \prod_{n=1}^{\infty} (1 - e^{-n/\lambda})$$

prob. last monomer converts before new attachment

prob. rest of tubule has converted

Dedekind η function: $$\eta(z) = e^{i\pi z/12} \prod_{n=1}^{\infty} (1 - e^{2\pi i n z})$$

$$\eta(-1/z) = \sqrt{-iz}\,\eta(z)$$

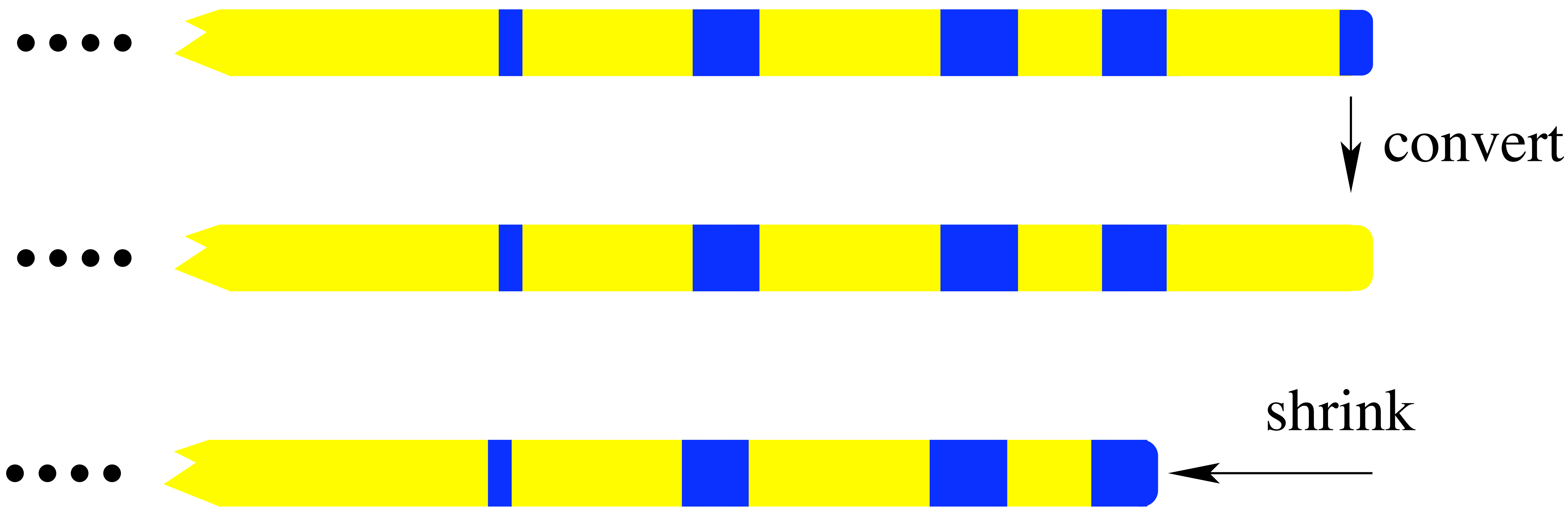
$$\prod_{n=1}^{\infty} (1 - e^{-2an}) = \sqrt{\frac{\pi}{a}}\, e^{(a-b)/12} \prod_{n=1}^{\infty} (1 - e^{-2bn})$$

$$b = \frac{\pi^2}{a}$$

$$\mathcal{C}(\lambda) = \frac{\sqrt{2\pi\lambda}}{1+\lambda}\, e^{-\pi^2\lambda/6}\, e^{1/24\lambda} \prod_{n\geq 1} (1 - e^{-4\pi^2\lambda n})$$

$$\sim \sqrt{\frac{2\pi}{\lambda}}\, e^{-\pi^2\lambda/6}$$

Avalanches



avalanche probability:

$$A_k = \frac{1}{1+\lambda} \prod_{n=1}^{k-1} (1 - e^{-n/\lambda})$$

prob. last monomer converts before new attachment

prob. k monomers of tubule have converted

expand exponential to 2nd order:

$$A_k = \lambda^{-k} \Gamma(k) \prod_{n=1}^{k-1} \left(1 - \frac{n}{2\lambda}\right) \sim \lambda^{-k} \Gamma(k)\, e^{-k^2/4\lambda}$$

Microtubule Phase Diagram

$\lambda, \mu \ll 1$

fast conversion $\to$ end is GDP^{-}

attach (grow) with rate $p\lambda$ $\quad v = p\lambda - \mu \;\to\; \mu^* = p\lambda$

detach (shrink) with rate μ

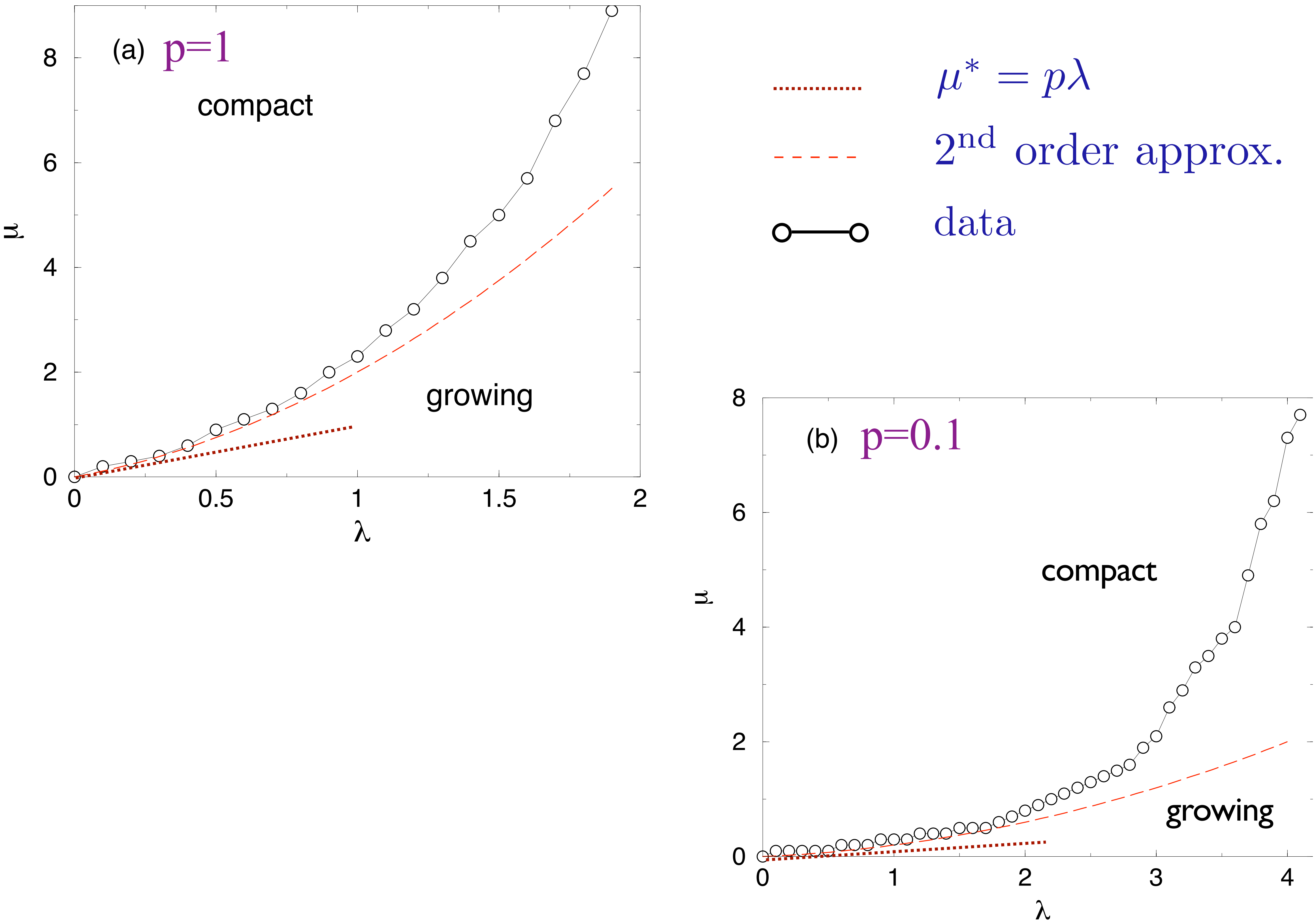
$\lambda, \mu \gg 1$

during growth: $L = vt \approx e^{\pi^2 \lambda/6}$

ignore power-law terms in λ compared to exponential terms

rescue occurs if: $t_{\text{shrink}} = \frac{L}{\mu} > \frac{1}{p\lambda} \;\to\; \mu^* \approx p\, e^{\pi^2 \lambda/6}$

Microtubule Phase Diagram



Summary & Outlook

microtubules have rich dynamical behavior

dynamics solvable by probabilistic approaches

reality checks

comparison with real data

validation of model parameters