LECTURE 7

BB 101: MODULE II

PHYSICAL BIOLOGY

Review of Lecture 6

- Thermal energy can bend the filaments. However filament would appears straight if their length is less than persistence length

- Externally applied forces can buckle filaments and critical buckling force

- Examples of force generation by microtubule and actin filaments

- Measurement of forces exerted by microtubule and actin network

Microtubule Dynamics

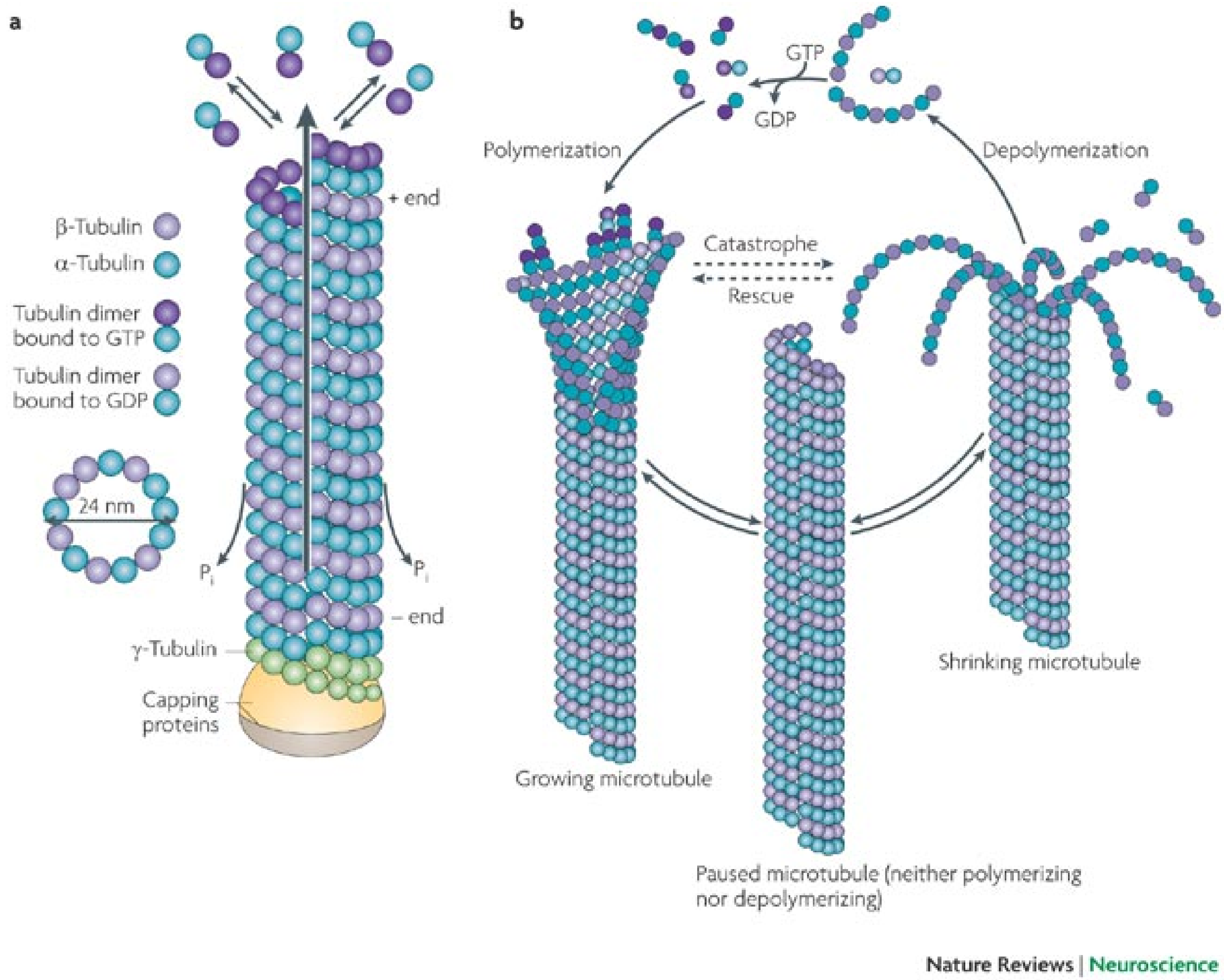
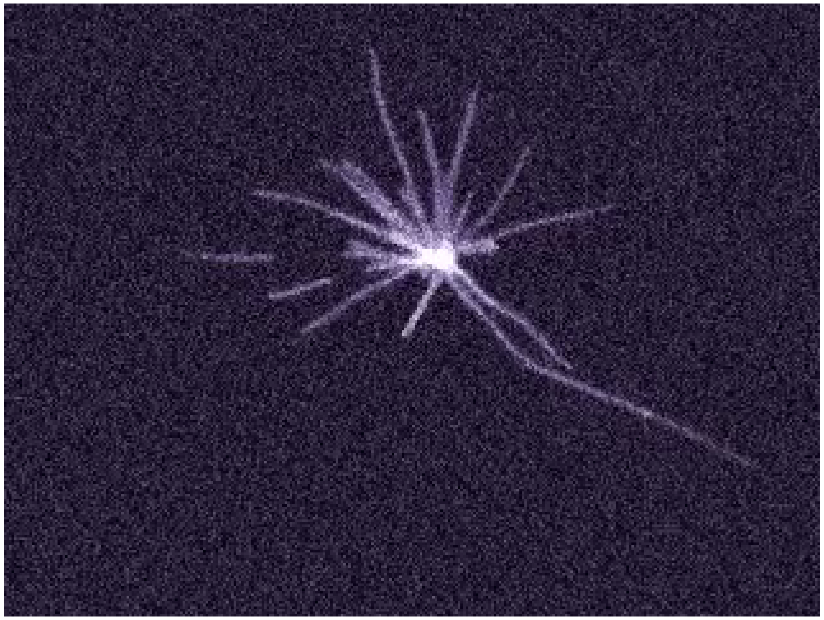


Figure Source: http://www.nature.com/scitable/topicpage/microtubules-and-filaments-14052932

Dynamic instability



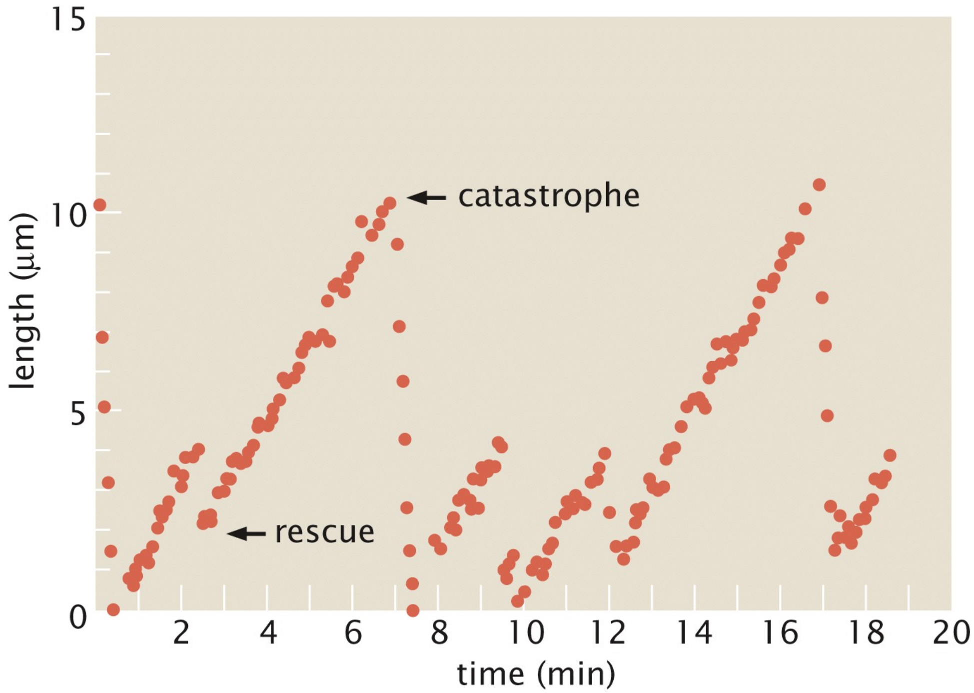


Figure 15.34 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

Watch Microtubule Dynamics Instability video on following link:
https://www.youtube.com/watch?v=tJKXNarWpqE

Microtubule Treadmilling

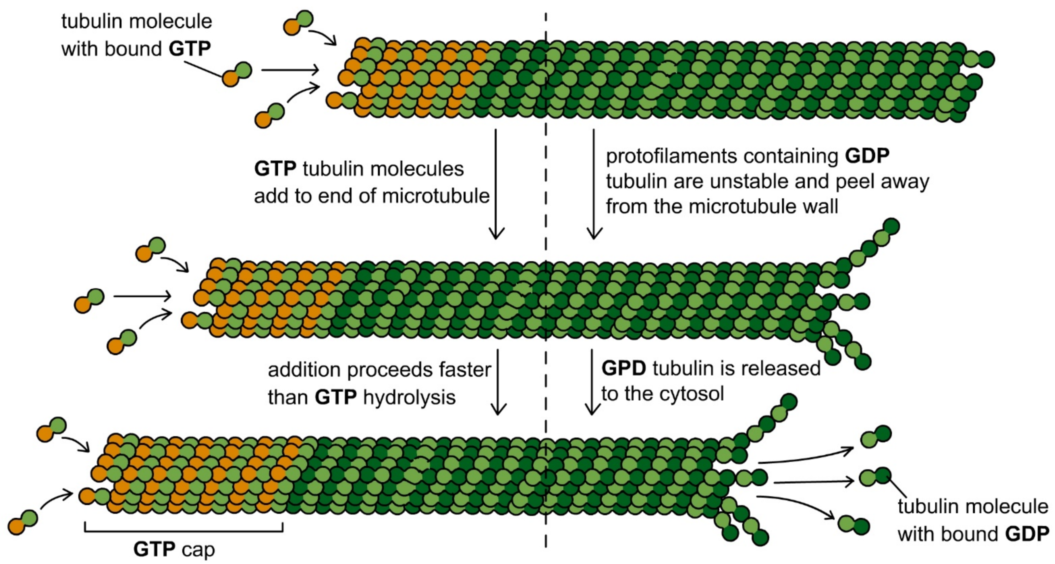


Figure Source: http://cc.scu.edu.cn/G2S/Template/View.aspx?courseType=1&courseId=17&topMenuId=113305&menuType=1&action=view&type=&name=&linkpageID=113700

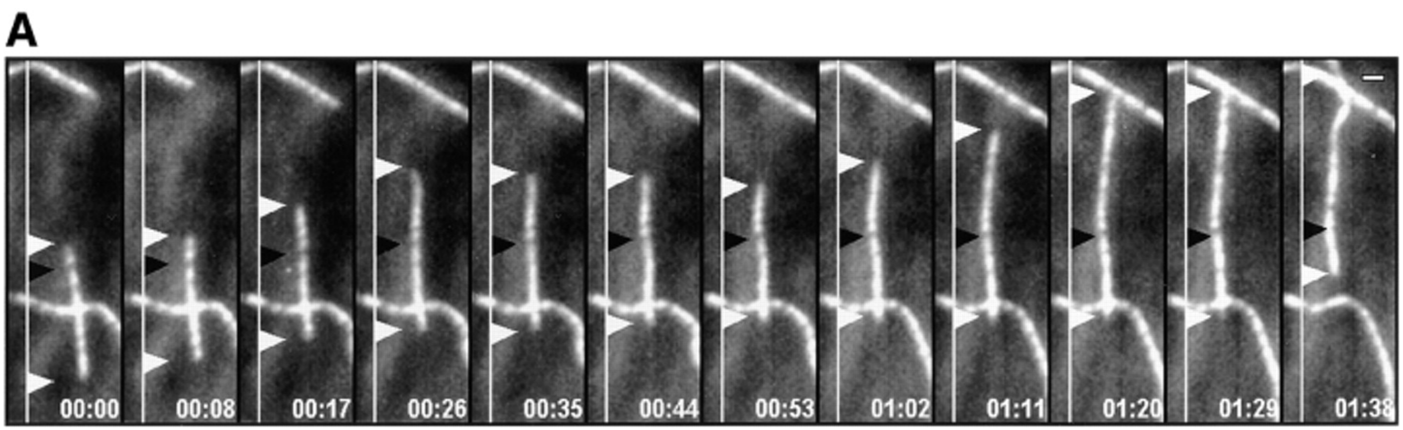


Figure Source: Clare M. Waterman-Storer, and E.D. Salmon J Cell Biol 1997;139:417-434

Actin Dynamics

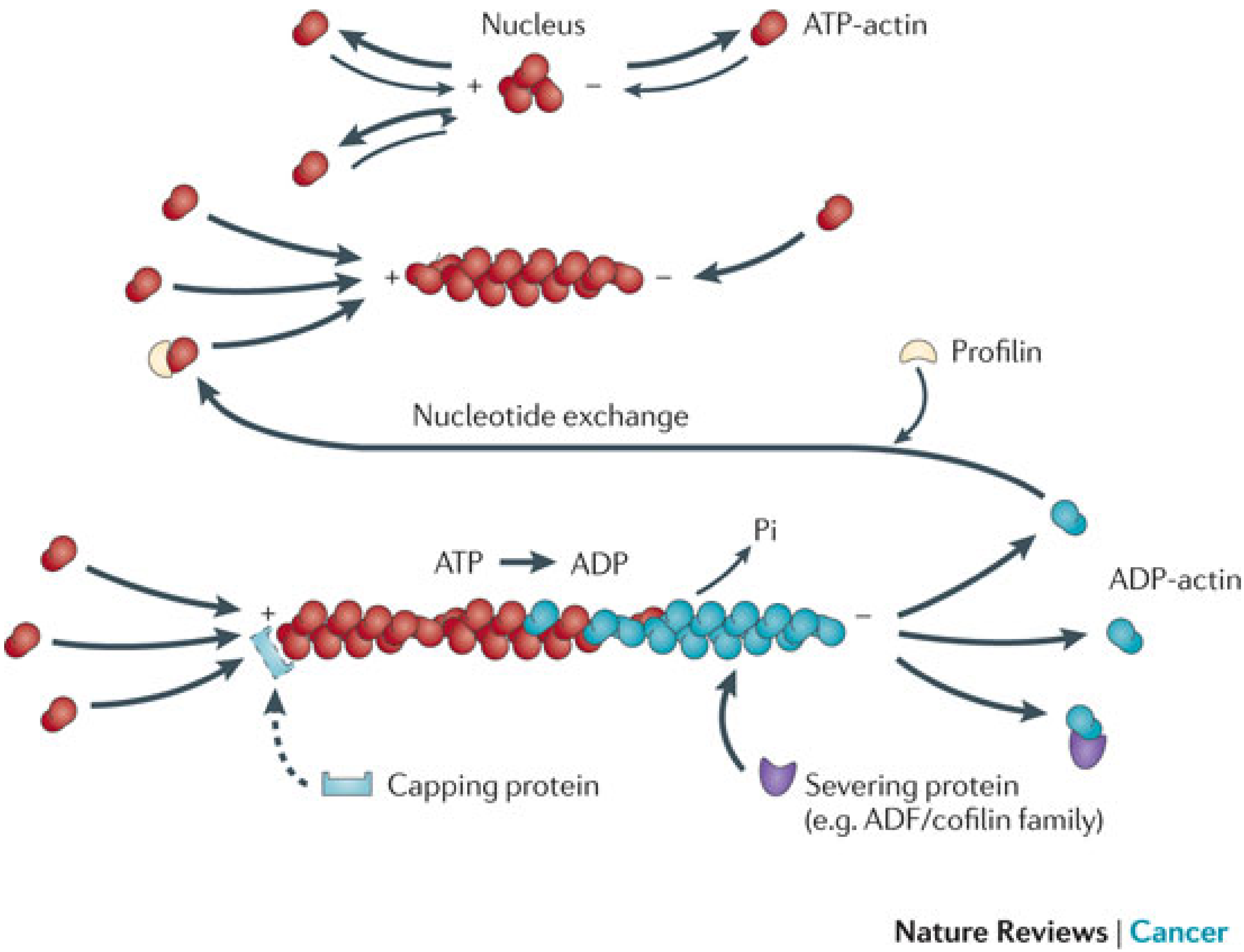
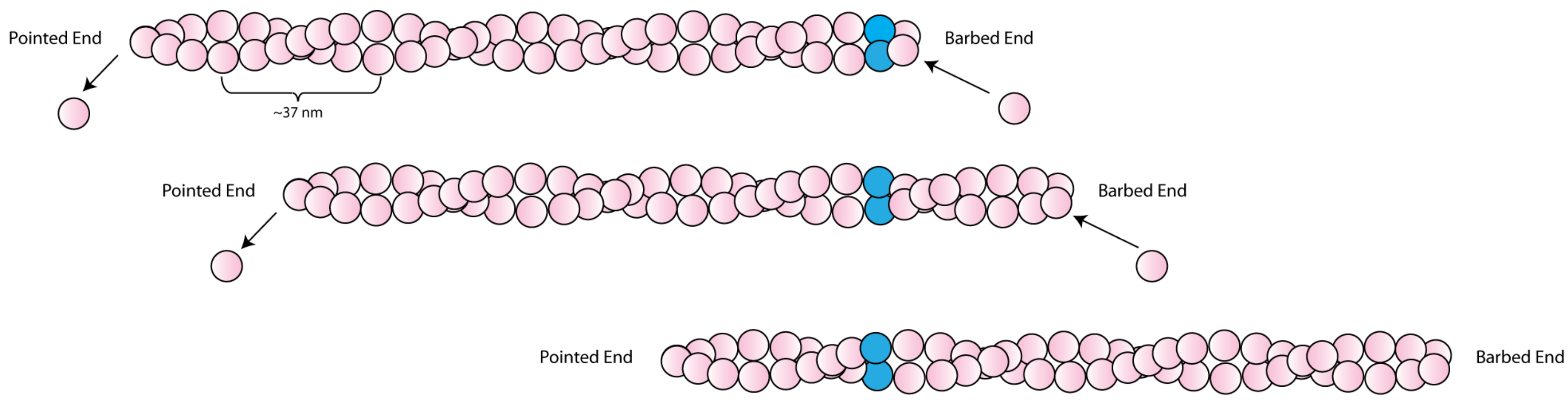


Figure Source: Alexander Nürnberg, Thomas Kitzing & Robert Grosse, Nature Reviews Cancer, Vol. 11, 177-187 (2011)

Actin Treadmilling



Watch Actin Treadmilling Video on following link:
https://www.youtube.com/watch?v=VVgXDW_8O4U

Models of Cytoskeletal Filament Polymerization

(A) Polymerization with equal rates on both ends

(B) Polymerization with unequal rate a two ends due to structural asymmetry

(C) Polymerization with unequal rates and vectorial hydrolysis

(D) Polymerization with hydrolysis that can take place on any monomer of the filament

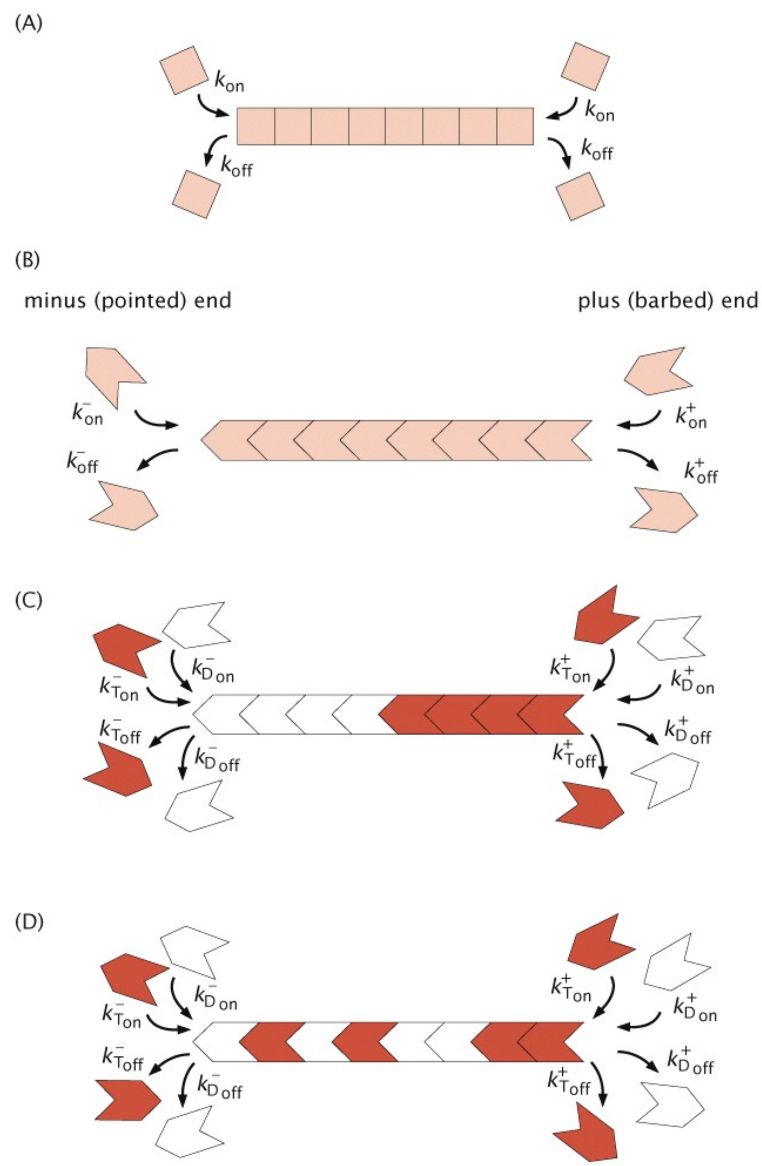


Figure 15.21 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

A Simple Model for Cytoskeletal Filament Polymerization

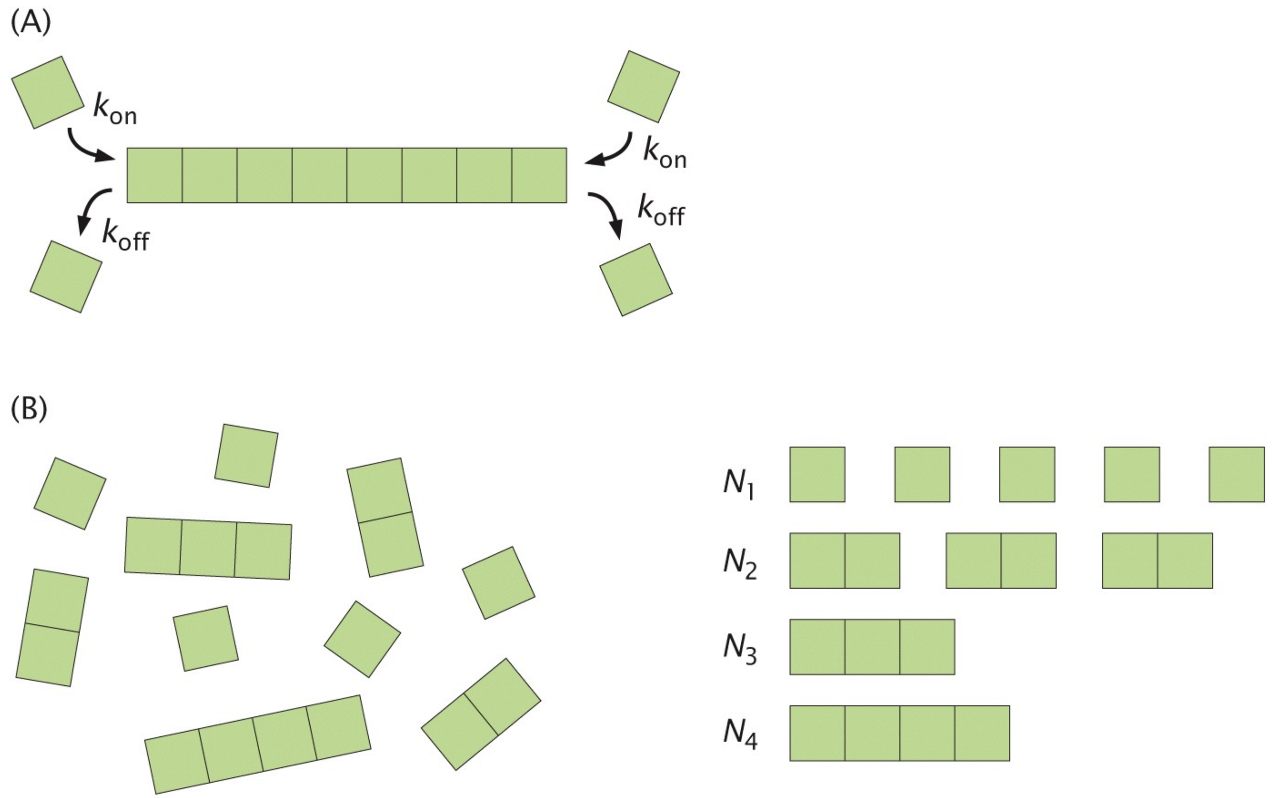


Figure 15.28 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Monomers each of length b are being added to the filament with rate k_{on} and they are being removed with rate k_{off}
- Can we calculate average length of the filament in the steady?

A Simple Model for Cytoskeletal Filament Polymerization

- What is average length?

$$\langle L \rangle = \sum_{n=1}^{\infty} L_n P_n = \sum_{n=1}^{\infty} nbP_n$$

Where P_n is the probability of finding a filament with n monomers

$$P_{n-1} + P_1 \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} P_n$$

$$P_n + P_1 \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} P_{n+1}$$

A Simple Model for Cytoskeletal Filament Polymerization

Master equation

$$\frac{dP_n}{dt} = \underbrace{k_{on}P_{n-1}P_1}_{Addition\ to\ P_{n-1}} + \underbrace{k_{off}P_{n+1}}_{removal\ from\ P_{n+1}} - \underbrace{k_{on}P_nP_1}_{Addition\ to\ P_n} - \underbrace{k_{off}P_n}_{removal\ from\ P_n}$$

$$\frac{d\langle L\rangle}{dt} = \sum_{n=1}^{\infty} nb\,\frac{dP_n}{dt}$$

$$\frac{d\langle L\rangle}{dt} = \sum_{n=1}^{\infty} nb\left(k_{on}P_{n-1}P_1 + k_{off}P_{n+1} - k_{on}P_nP_1 - k_{off}P_n\right)$$

$$\frac{d\langle L\rangle}{dt} = \sum_{n=1}^{\infty} nbk_{on}P_1(P_{n-1} - P_n) + \sum_{n=1}^{\infty} nbk_{off}(P_{n+1} - P_n)$$

A Simple Model for Cytoskeletal Filament Polymerization

Let's use following identities

$$\sum_{n=1}^{\infty} nP_{n-1} = 2P_1 + 3P_2 + \cdots = \sum_{n=1}^{\infty} (n+1)P_n$$

$$\sum_{n=1}^{\infty} nP_{n+1} = \sum_{n=1}^{\infty} (n-1)P_n$$

$$bk_{on}P_1 \sum_{n=1}^{\infty} n(P_{n-1} - P_n) = bk_{on}P_1 \sum_{n=1}^{\infty} [(n+1) - n]P_n$$

$$= bk_{on}P_1 \sum_{n=1}^{\infty} P_n$$

A Simple Model for Cytoskeletal Filament Polymerization

$$\frac{d\langle L\rangle}{dt} = (k_{on}P_1 - k_{off})b$$

$$\frac{d\langle L\rangle}{dt} = 0 \text{ when } P_1 = c_* = \frac{k_{off}}{k_{on}}$$

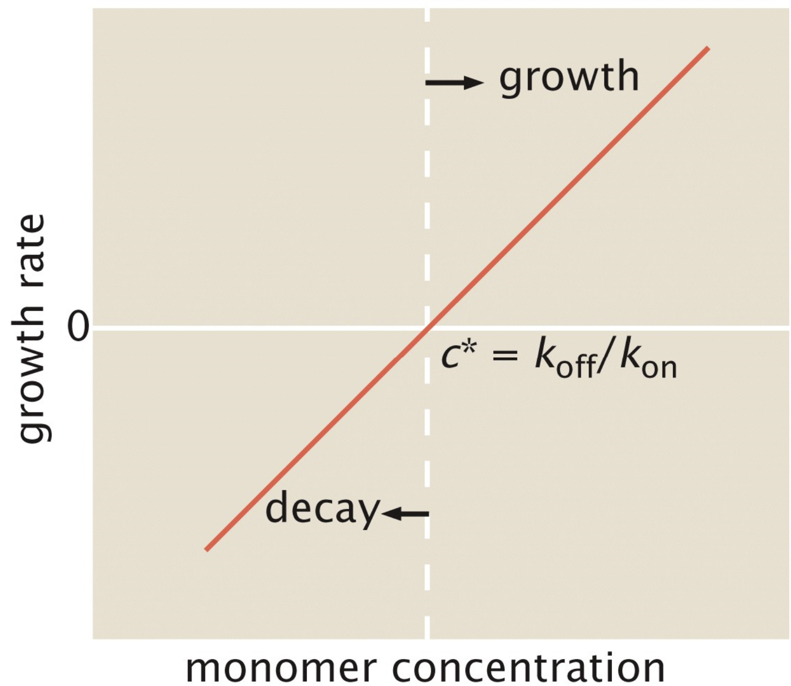
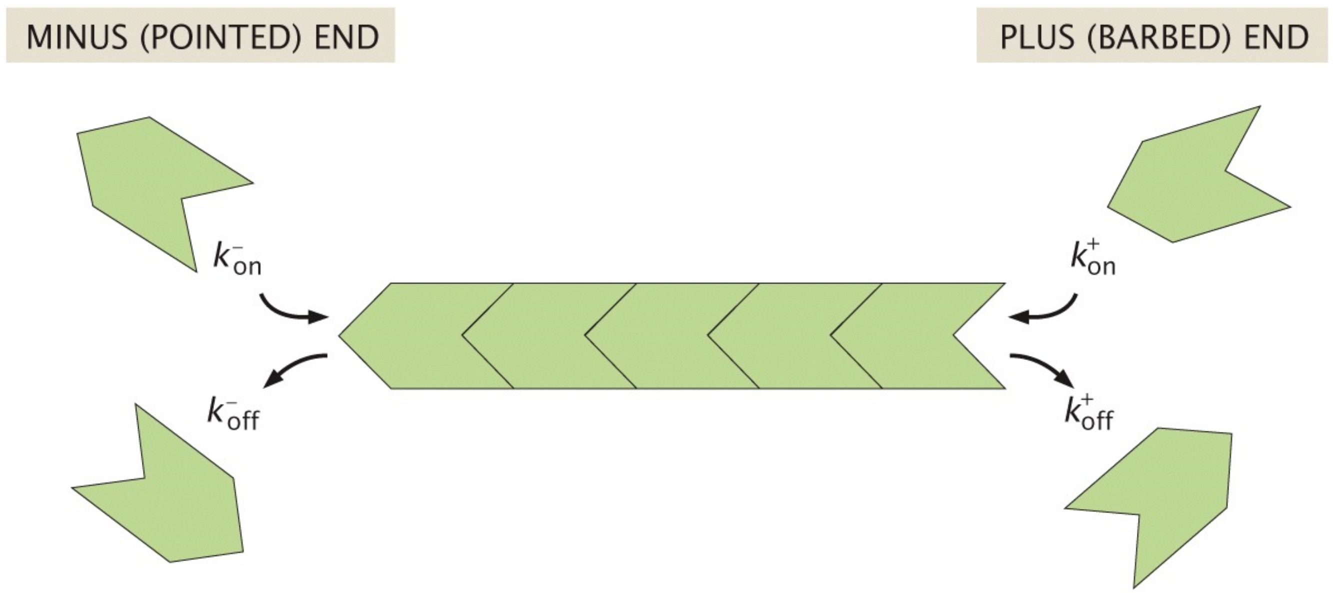


Figure 15.29 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

A Simple Model for Treadmilling



- Treadmilling: Addition from one end and removal from other
- Filament would grow if concentration greater than c* otherwise they would shrink

$$\frac{dn}{dt} = k_{on}c - k_{off}$$

A Simple Model for Treadmilling

$$\frac{dn_+}{dt} = k_{on}^+ c - k_{off}^+$$

$$\frac{dn_-}{dt} = k_{on}^- c - k_{off}^-$$

Condition for treadmilling

$$\frac{dn_+}{dt} = -\frac{dn_-}{dt}$$

$$\boxed{c_{TM} = \frac{k_{off}^+ + k_{off}^-}{k_{on}^+ + k_{on}^-}}$$

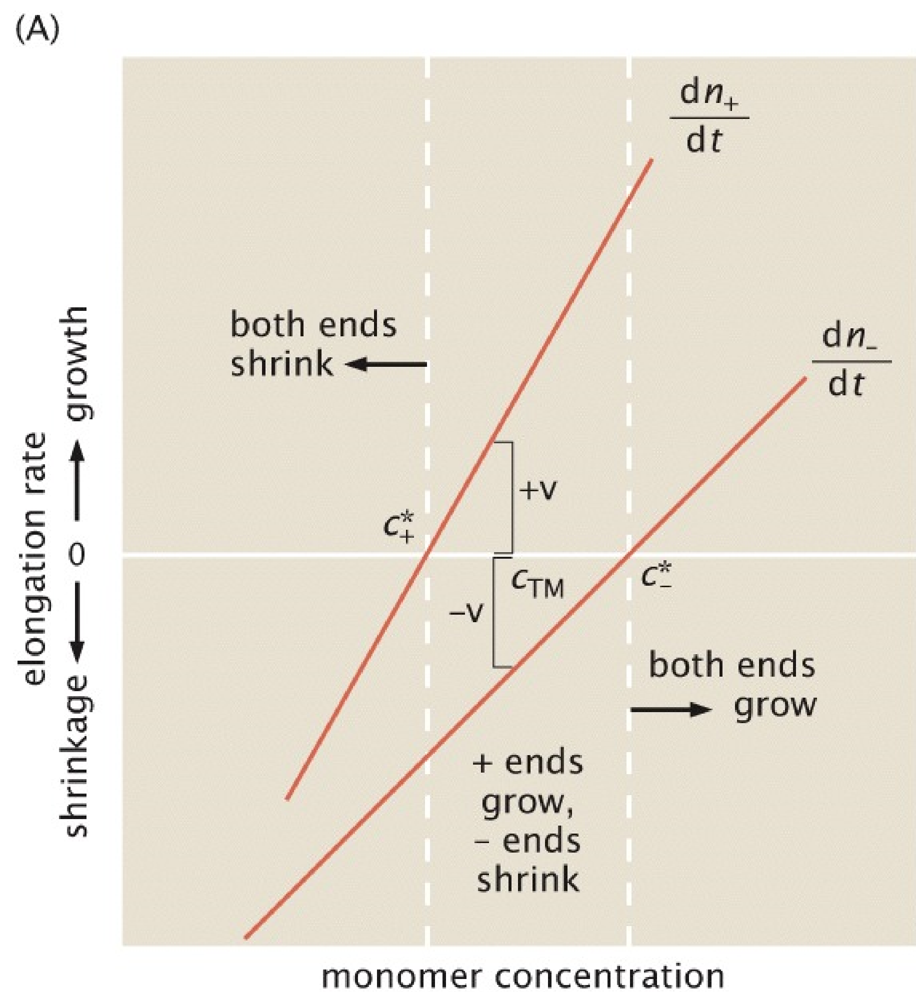


Figure 15.32 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

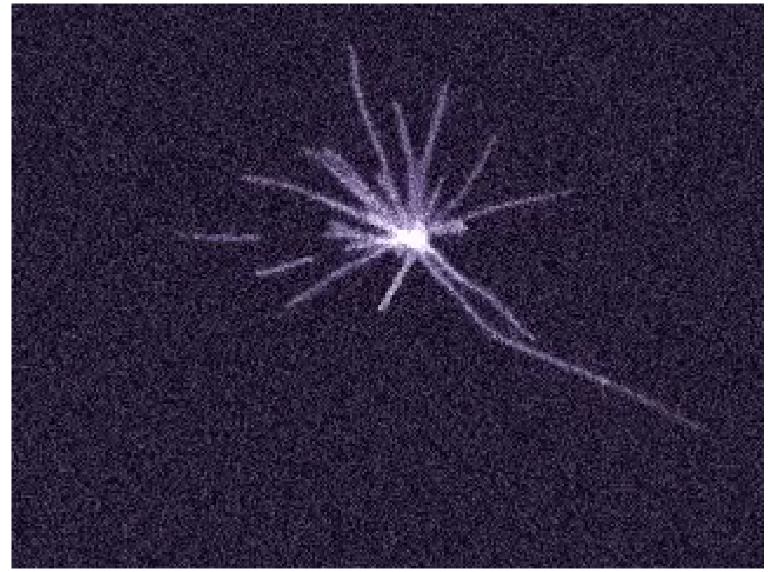
A Simple Model for Dynamics Instability

- A microtubule can be either in growing phase (+) or shrinking phase (-)

- When in growing phase it grows with rate v_+ and shrinking phase it shrinks with velocity v_+

- A microtubule in growing phase can stochastically switch to shrinking phase with rate f_{+-}

- A microtubule in shrinking phase can stochastically switch to growing phase with rate f_{-+}



https://www.youtube.com/watch?v=tJKXNarWpqE

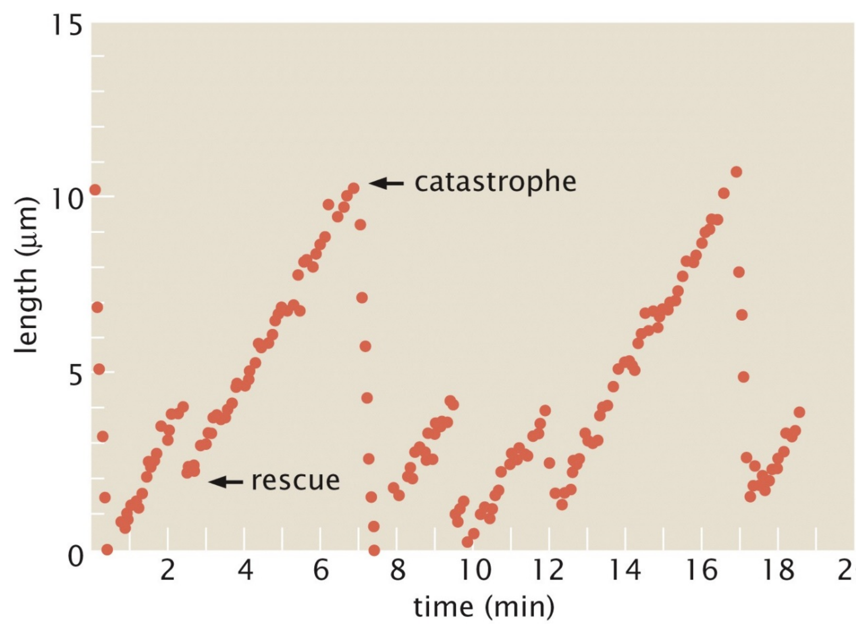


Figure 15.34 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

A Simple Model for Dynamics Instability

$$\frac{\partial p_+(n,t)}{\partial t} = v_+ p_+(n-1,t) - v_+ p_+(n,t) + f_{-+} p_-(n,t) - f_{+-} p_+(n,t)$$

In above equation four terms capture following:

1) Filament with length $n-1$ can grow with rate v_+ to become of length n

2) Filament with length n can also grow with rate v_+ to become of length $n+1$

3) Filament with length n in shrinking phase can switch to growing phase with rate f_{-+}

4) Filament with length n in growing phase can switch to shrinking phase with rate f_{-+}

A Simple Model for Dynamics Instability

$$\frac{\partial p_-(n,t)}{\partial t} = v_- p_-(n+1,t) - v_- p_-(n,t) + f_{+-} p_+(n,t) - f_{-+} p_-(n,t)$$

Using Taylor expansion for factors like $\boldsymbol{P_+(n-1,t) - P_+(n,t)}$and $\boldsymbol{P_+(n+1,t) - P_+(n,t)}$

$$\frac{\partial p_+(n,t)}{\partial t} = -v_+ \frac{\partial p_+(n,t)}{\partial n} + f_{-+} p_-(n,t) - f_{+-} p_+(n,t)$$

$$\frac{\partial p_-(n,t)}{\partial t} = v_- \frac{\partial p_-(n,t)}{\partial n} + f_{+-} p_+(n,t) - f_{-+} p_-(n,t)$$

In steady state

$$\frac{\partial p_\pm(n,t)}{\partial t} = 0$$

A Simple Model for Dynamics Instability

HOMEWORK

$$p_+(n) = \frac{P_+}{n_0} e^{\left(-\frac{n}{n_0}\right)}$$

$$p_-(n) = \frac{P_-}{n_0} e^{\left(-\frac{n}{n_0}\right)}$$

$$p(n) \equiv p_+(n) + p_-(n) = \frac{1}{n_0} e^{\left(-\frac{n}{n_0}\right)}$$

$$n_0 = \frac{v_+ v_-}{v_- f_{+-} - v_+ f_{-+}}$$ (for $v_- f_{+-} > v_+ f_{-+}$)

$$P_+ \equiv \int_{n=0}^{\infty} p_+(n) dn = \frac{v_-}{v_- - v_+} = 1 - P_-$$

A Simple Model for Dynamics Instability

$$p(n) = \frac{1}{n_0} e^{\left(-\frac{n}{n_0}\right)}$$

$$n_0 = \frac{v_+ \, v_-}{v_- \, f_{+-} - v_+ \, f_{-+}}$$

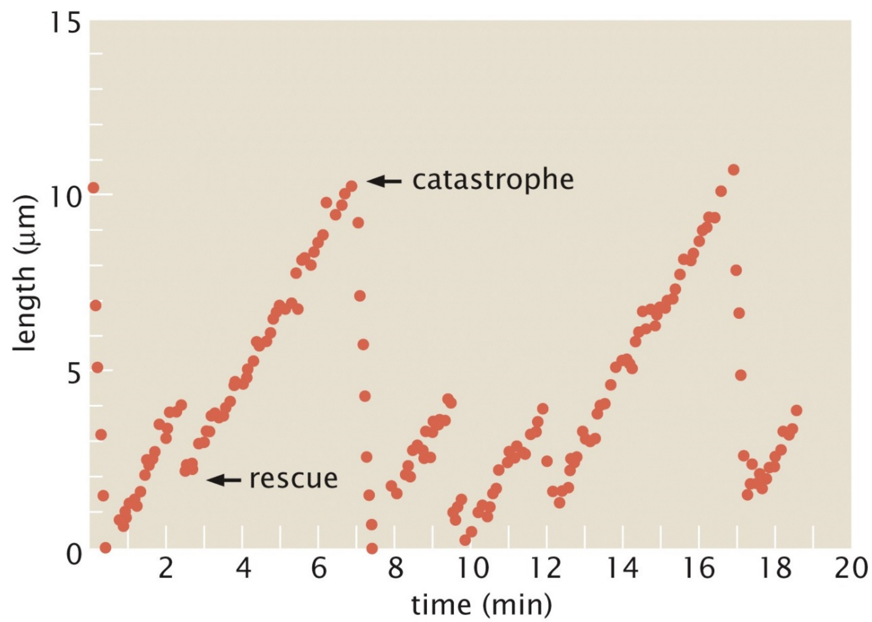


Figure 15.34 Physical Biology of the Cell, 2ed. (© Garland Science 2013)

- Average length of the microtubule can be calculated. How?

- v_+ , v_-, f_{+-} and f_{-+} can be determined directly from the experimental data

Summary

- Dynamics of Microtubule and Actin Filaments
- Treadmilling of microtubule and actin filament
- A simple model for cytoskeletal filament polymerization
- A simple model for treadmilling of cytoskeletal filaments
- A simple model for Dynamics instability