Chem 452 - Lecture 11
Molecular Motors
Part 1

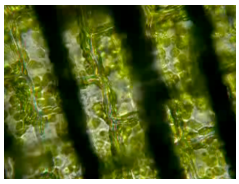
Question of the Day: How is the movement of vesicles around the cell like a stroll in the park?

Introduction

- Motion is of critical importance to biological systems,
  - For obtaining food
  - And avoiding danger
- Motion occurs at all levels
  - Whole organisms move about their environment
  - There is also considerable motion within a living cell.

Introduction

- Motion is of critical importance to biological systems.
- Motion occurs at all levels
  - Whole organisms move
  - Intracellular movement



Philly at night

Introduction

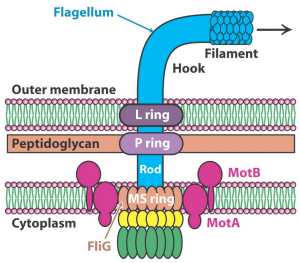
- Free energy is required for this movement.
- Like membrane pumps,
  - Motion can be directly coupled to the hydrolysis of ATP (NTP).
  - Or it can be coupled to concentration gradients across membranes.

Introduction

- Often the movement is directed along protein tracks.
  - Actin filaments
    - Muscles (myosin)
  - Microtubules
    - Cellular trafficking (kinesin)
    - Eukaryotic flagella (dynein)

Introduction

- We will also look at the bacterial flagellum, which operates remarkably like a nanoscale electrical motor.



Movement Along Tracks

- This movement is coupled to the direct hydrolysis of ATP.
- Hydrolysis involves P-loop NTPases.
  - Similar to G-proteins
  - Similar to the Slime mold myosin II that we considered with catalytic strategies.
- The P-loop NTP ATPases that move along tracks include,
  - Heavy chain of myosin
  - Kinesin
  - Dynein

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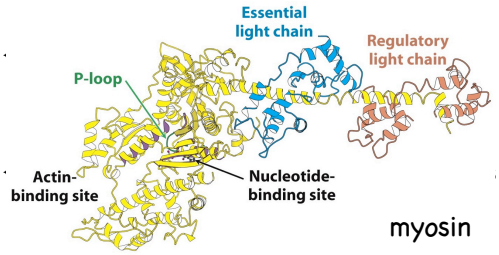

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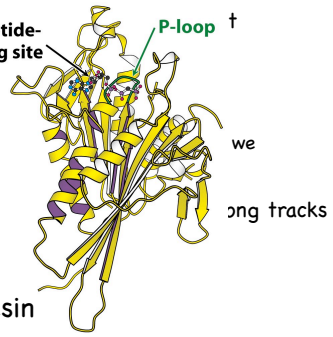

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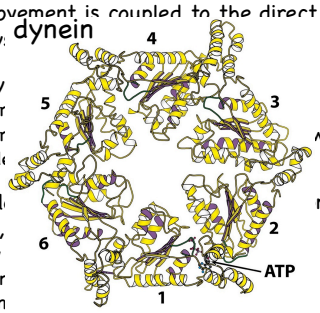

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Movement Along Tracks

- The hydrolysis of ATP is coupled to the a conformational change, which results in movement.

Movement Along Tracks

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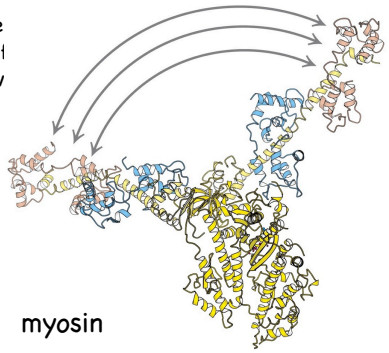

myosin

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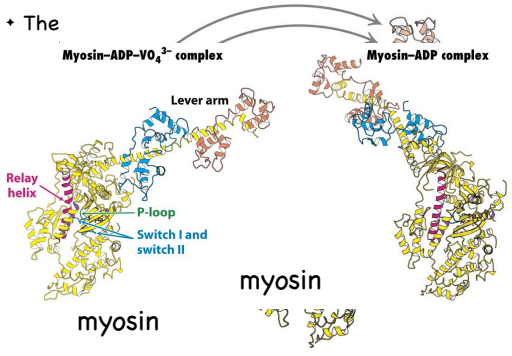

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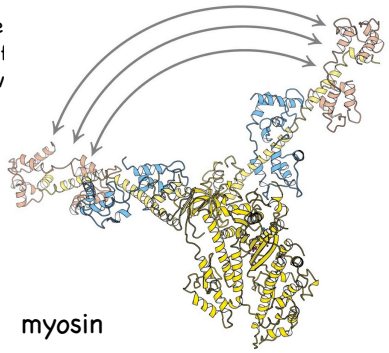

myosin

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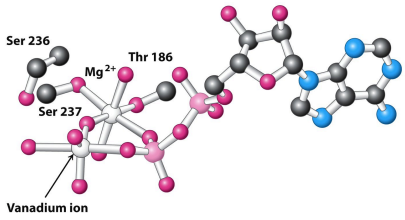
Myosin ATPase

- An X-ray crystal structure of myosin II ATPase with a transition state analogue for ATP revealed a mechanism
  - VO_4^{3-} + ADP was substituted for ATP.



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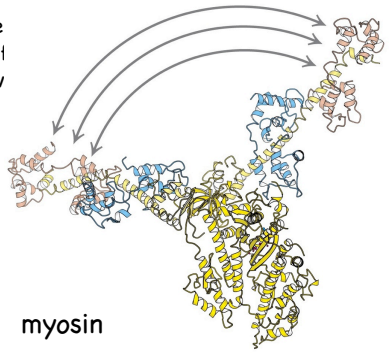

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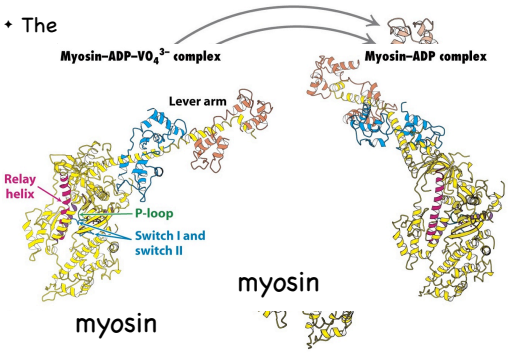

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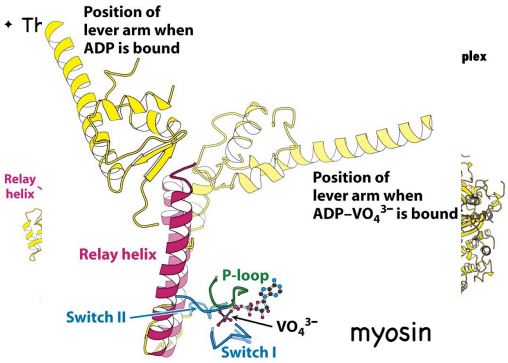

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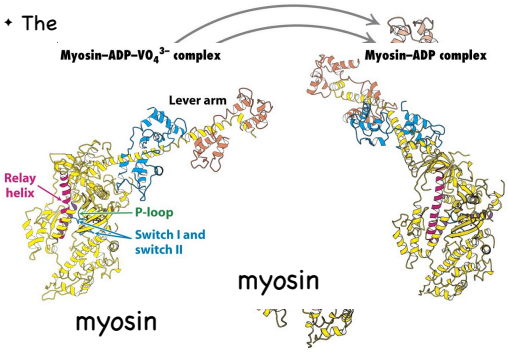

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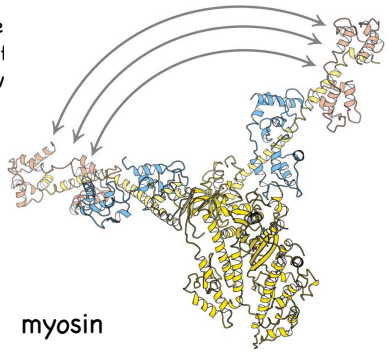

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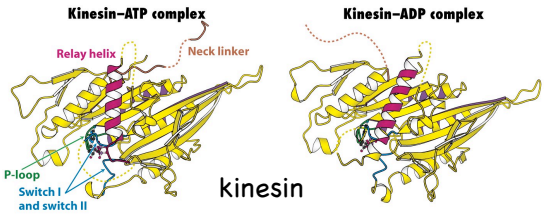
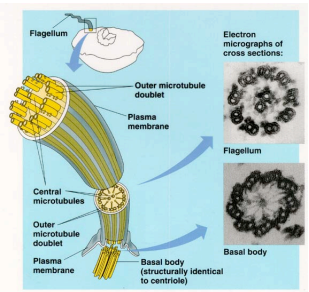


kinesin

Movement Along Tracks

- Dynein also moves along microtubules.



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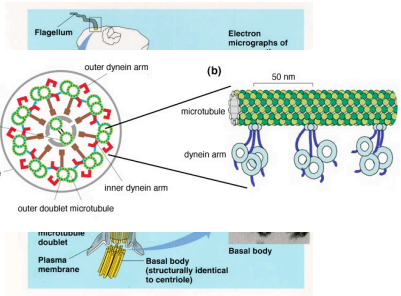

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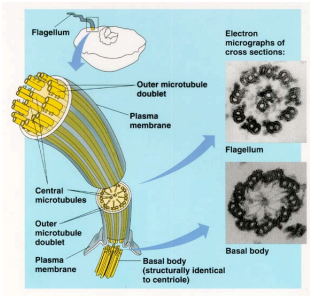
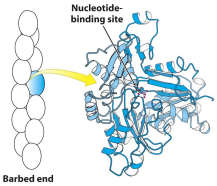


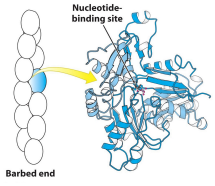
Actin

- Actin is a 42 kd protein
  - ≈ 10%, it is one of the most abundant proteins in eukaryotic cells.
- Actin filaments help create the cytoskeleton and are continuously formed and degraded.



Actin

- Actin has a P-loop nucleotide binding site, which.
- ATP binding and hydrolysis influence the polymerization of actin monomers (G-actin) into actin filaments (F-actin).



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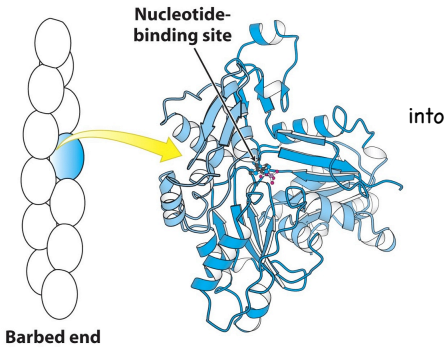

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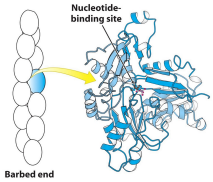
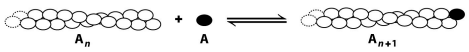


Actin

- Actin filaments can self-assemble in a process called polymerization
  - The nucleation of assembly is the most unfavorable step in the polymerization process.
    - Protein complexes, such as Arp2/3, help the nucleation.
  - Nucleation is followed by elongation.

$$K_d = \frac{[A_n]\,[A]}{[A_{n+1}]}$$



Actin

- K_d as a **dissociation** constant for elongation of F-actin
  - $K_d \approx [A]$ is still valid.
  - K_d defines the monomer concentration at which the polymerization process takes place.
    - If $[A] > K_d$ polymerization takes place
    - If $[A] < K_d$ depolymerization takes place
    - K_d is referred to as the **critical concentration**.

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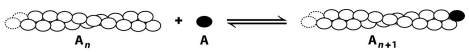

Actin

- The K_d for ATP-actin is 20 times lower than that for ADP-actin.

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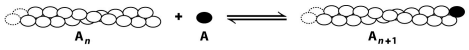

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Consequently, does ATP ⇔ ADP exchange favor polymerization?

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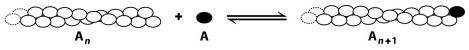

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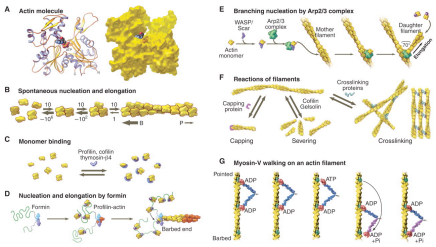
This Week in Science

- Pollard and Cooper, "Actin, a Central Player in Cell Shape and Movement", Science **2009,** 326 1208-1212.



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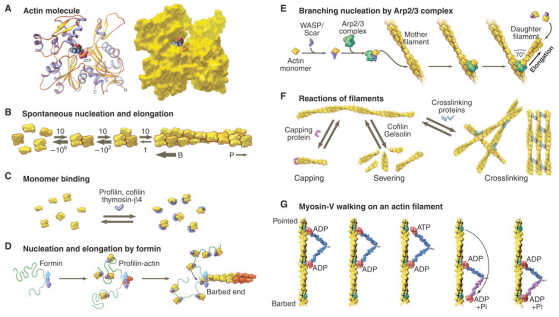

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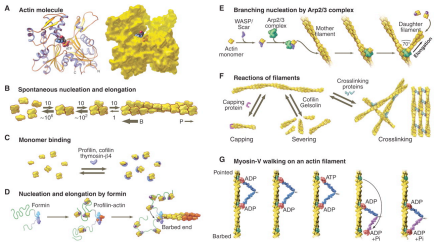
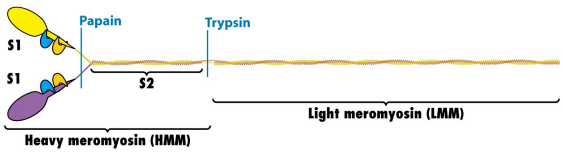


Myosin

- Myosin and actin work together in muscle contractions.



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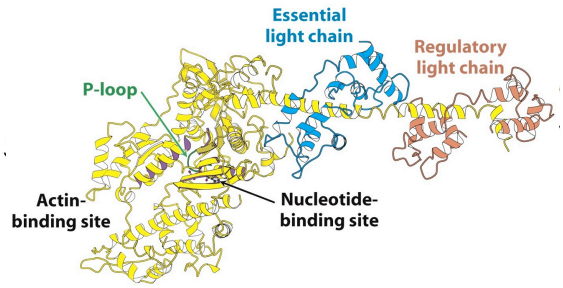

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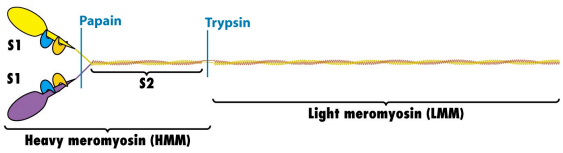

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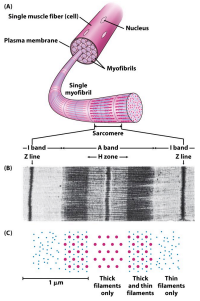

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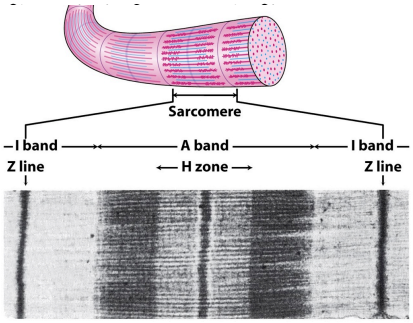

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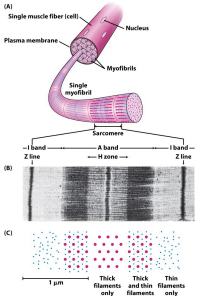

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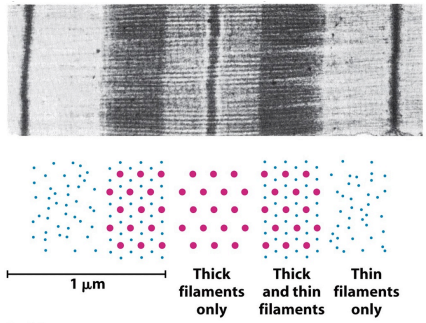

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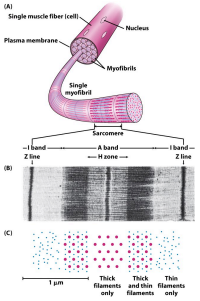

Myosin

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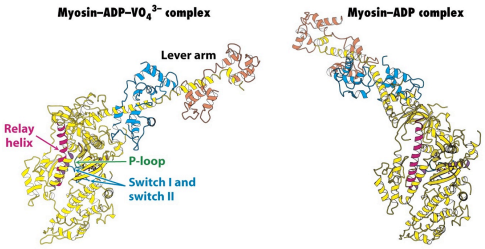

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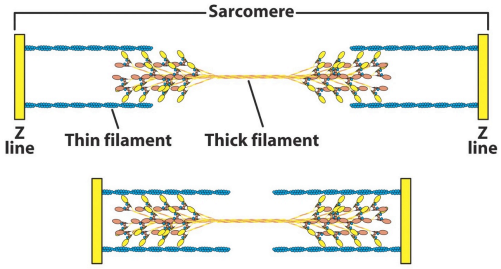

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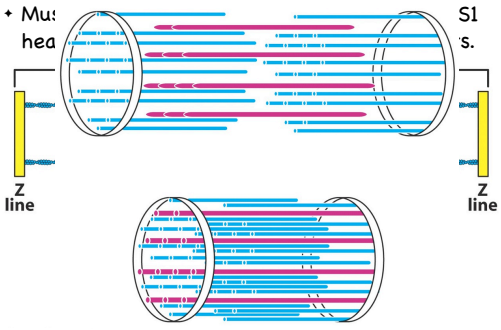

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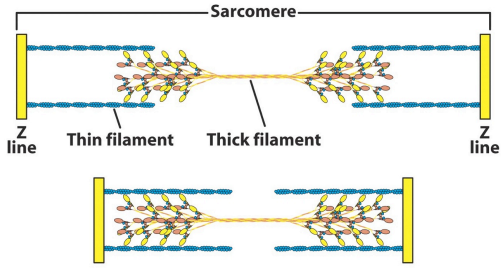

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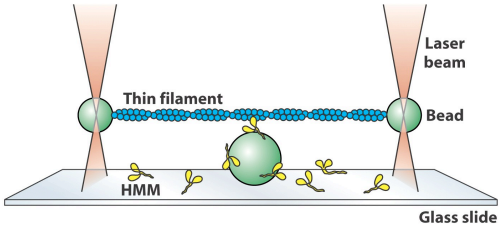

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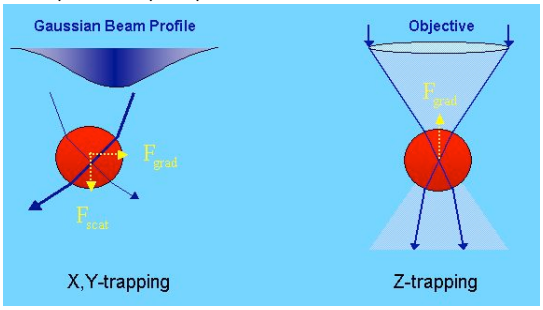

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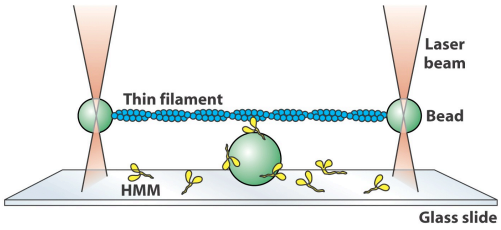

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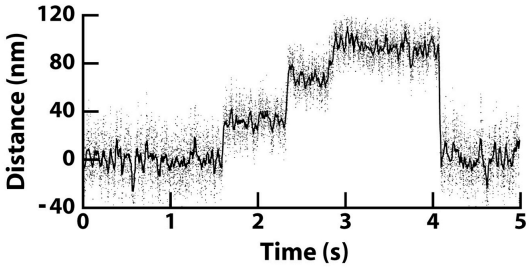

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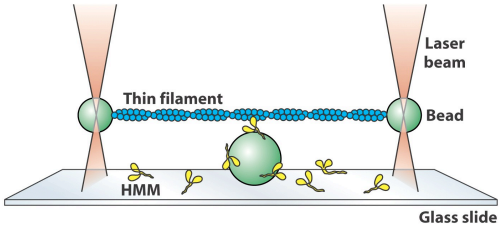
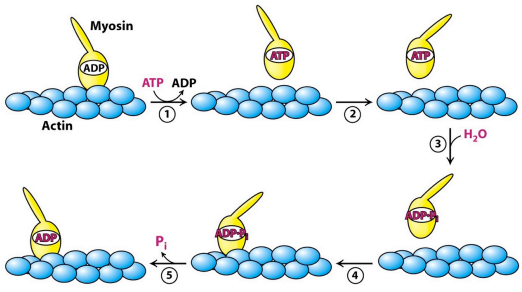


Myosin

- The cycle:
  - The exchange of ADP for ATP by myosin causes it to dissociate from the actin filament.
  - A conformation change causes the myosin S1 head to move relative to the actin filament ≈ 110 Å.
  - ATP is hydrolyzed
    - The ADP-myosin attaches to the actin filament.
    - The P_i is released.
  - P_i release leads to a second conformational change and triggers the power stroke.
  - The cycle begins again.

Myosin

- The cycle:



Myosin

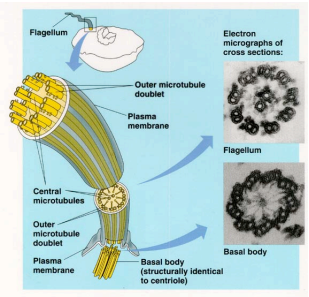
- Muscle contraction occurs when the myosin S1 head groups walk along the actin filaments.

Microtubles

- Like actin, microtubules are filamentous assemblies of protein, which are used as tracks.
  - They serve as tracks for kinesins and dyneins.
- Dyneins are used in eukaryotic flagella and cilia to move one microtubule relative to another
- Kinesins are like porters, that carry organelles and other cargo about the cell.

Movement Along Tracks

- Dynein also moves along microtubules.



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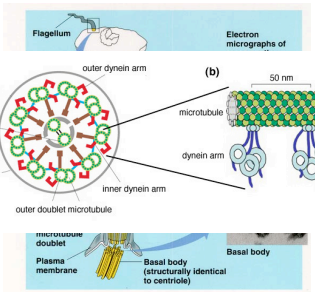

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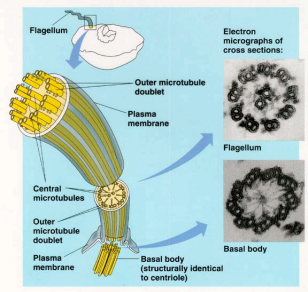
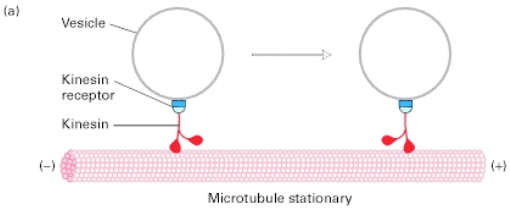


Movement Along Tracks

- Kinesisn also moves along microtubules, and carry cargo along the way..



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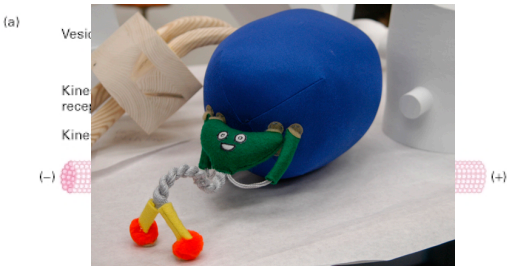

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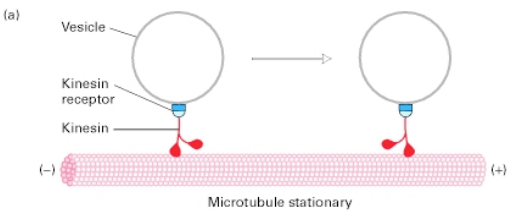
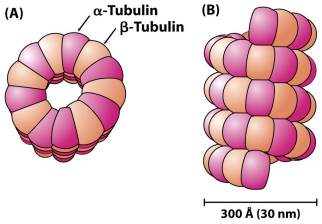
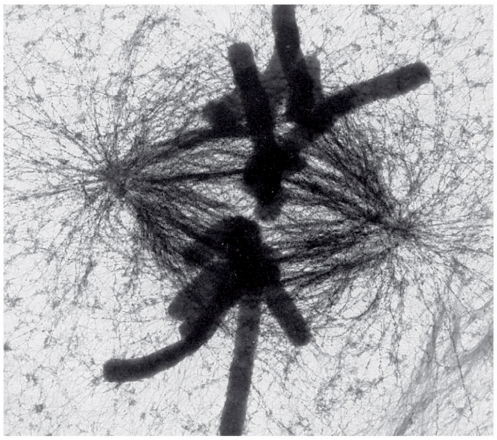


Microtubles

- Microtubles are built from two 50 kd proteins, α-tubulin and β-tubulin.
  - They are important to determining cell shape and in separating chromosomes during mitosis and myosis.





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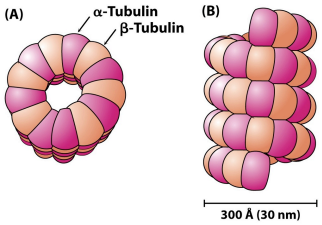
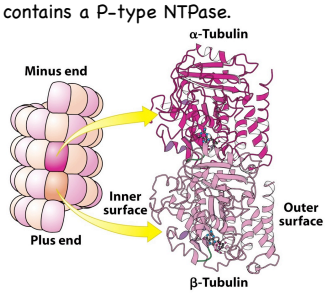


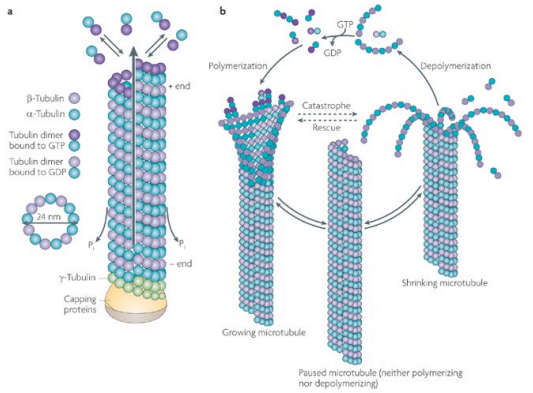
Microtubles

- α-tubulin and β-tubulin are 40% homologous.
  - Each contains a P-type NTPase.



Microtubles

- Like actin, microtubules are dynamic structures that constantly polymerize and depolymerize.
- Like actin, the binding and hydrolysis of nucleotides influences their assembly and disassembly
  - Unlike actin, they use GTP/GDP instead of ATP/ADP
- The critical concentration for polymerization is lower for GTP-bound tubulin.



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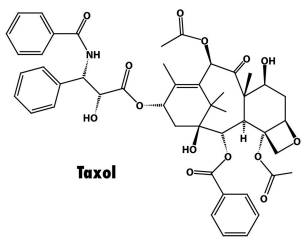
Microtubles

- Some anticancer drugs, such as taxol (paclitaxel), target microtubles.
  - Taxol binds to and stabilizes the polymerized form of microtubles.



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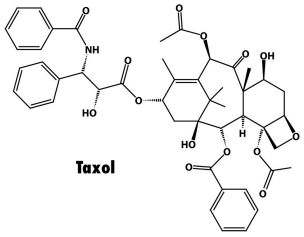
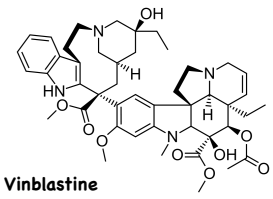


Taxol

Microtubles

- Another anticancer drug that targets microtubules is vinblastine.
  - It inhibits M-phase microtuble formation and is used to halt cell division at interphase.



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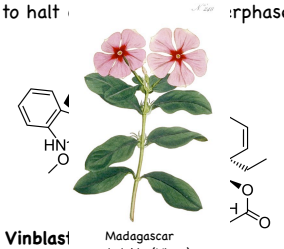

Vinblast

Madagascar periwinkle (Vinca)

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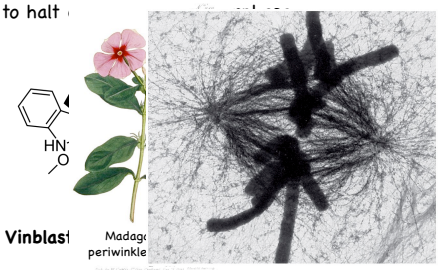

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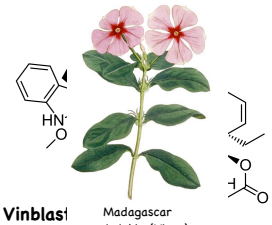

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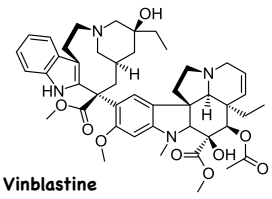
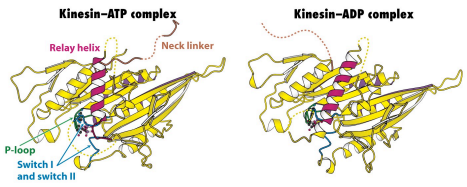


Vinblastine

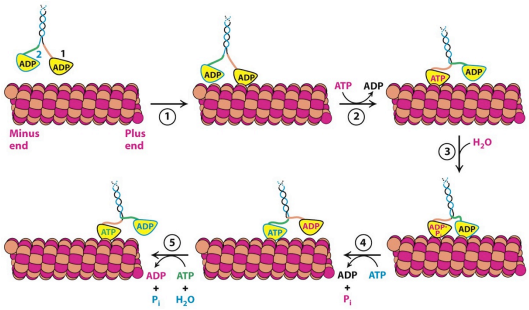
Kinesins

- Like myosin, the movement is correlated to the hydrolysis of ATP.
  - Unlike myosin, it is the ATP-bound form of kinesis that has the higher affinity for binding to the microtubule.



Kinesins

- The cycle:



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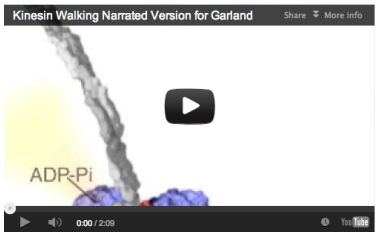
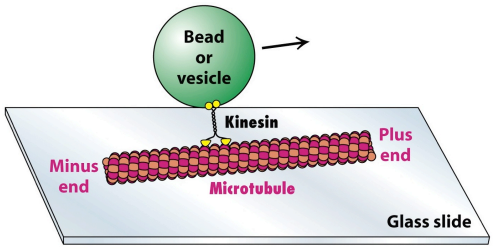


Kinesins

- The cycle:

Kinesins

- Kinesins "walk" along the microtubules.



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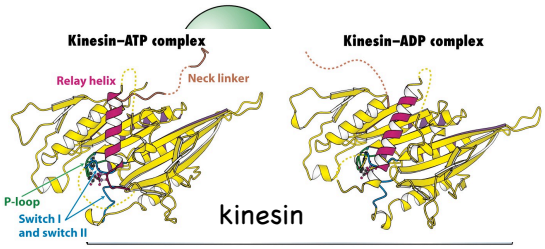

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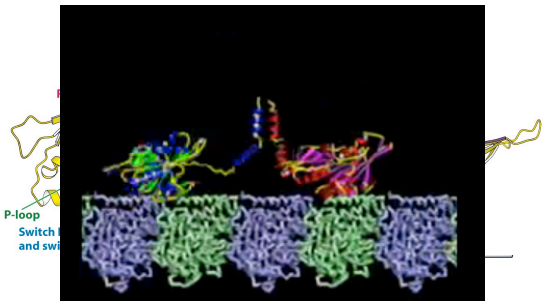

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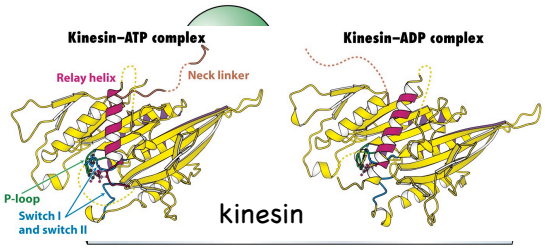

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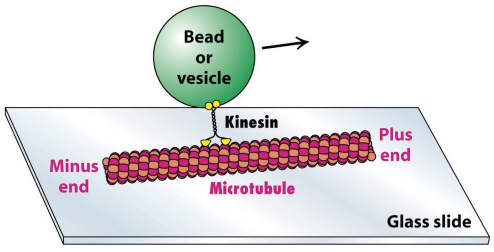

Next up

- Lecture 11, Molecular Motors (con'd). (Chapter 35)
  - Bacterial flagella