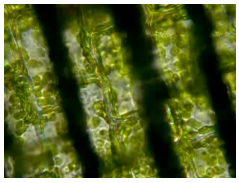
Chem 452 - Lecture 11
Molecular Motors
111205

For living cells, location means everything. In multicellular organisms location determines what a cell does and how it interacts with its neighbors. Many organisms, both multicellular and unicellular, must also be able to move in order to locate foods sources and to avoid dangerous situations. Location is also important at the intracellular level, where the cellular components must be able to locate themselves where they are needed for the cell to function properly. In this section we will examine the molecular motors that are used to move the components within a cell as well as whole organisms. There are many common themes for these molecular motors, such as movement along tracks, including actin filaments and microtubules, and the use of nucleotide triphosphates to both influence the polymerization of these tracks and to fuel the movement along them. We will also look at the bacterial flagella, which looks and functions remarkably like an electrical motor, but which derives its free energy not from the hydrolysis of nucleotides, but from and ion gradient across the cell membrane.

Introduction

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



Philly at night

Introduction

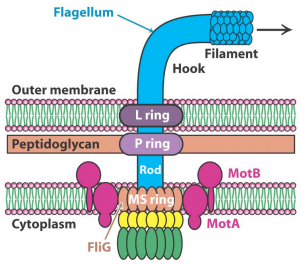
- Free energy is required for this movement.
- Like membrane pumps,
  - Directly coupled to the hydrolysis of ATP (NTP).
  - Coupled to concentration gradients across membranes.

Introduction

- Often the movement is 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 an electrical motor.



Movement Along Tracks

- 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.
- These include
  - Heavy chain of myosin
  - Kinesin
  - Dynein

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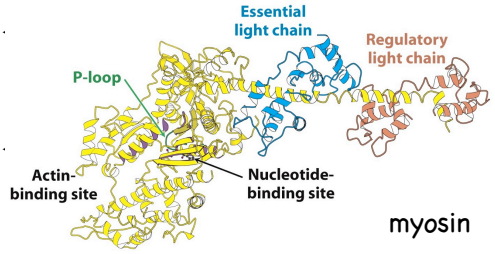

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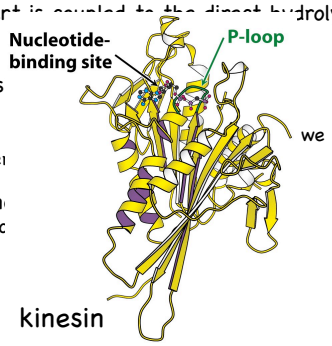

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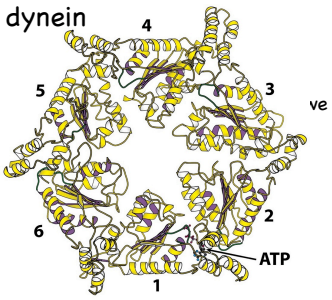

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Movement Along Tracks

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

Movement Along Tracks

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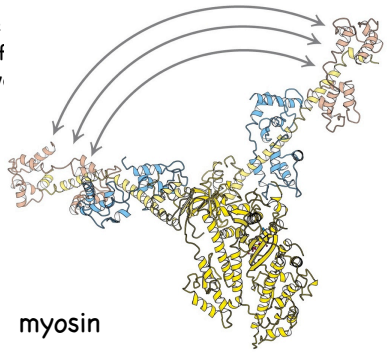

myosin

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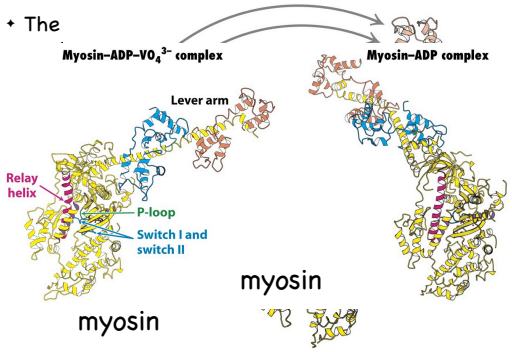

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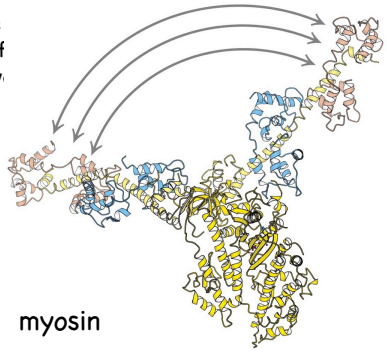

myosin

Movement Along Tracks

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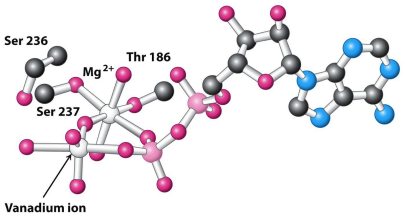
Myosin ATPase

- 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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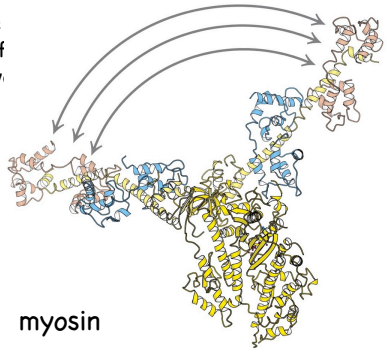

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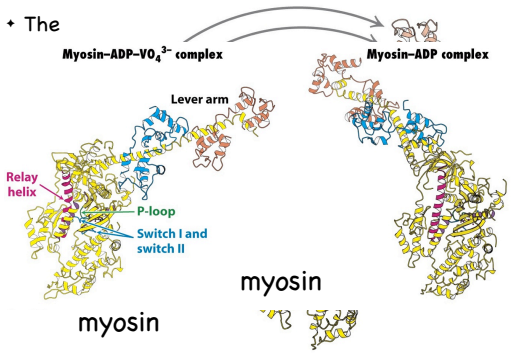

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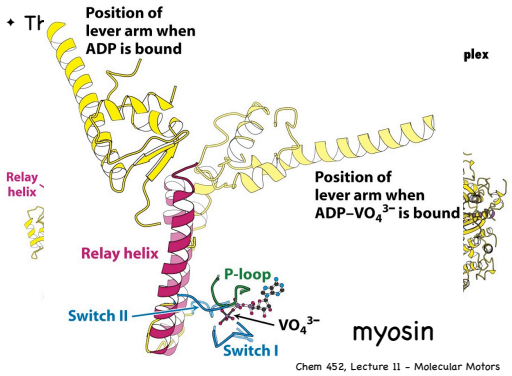

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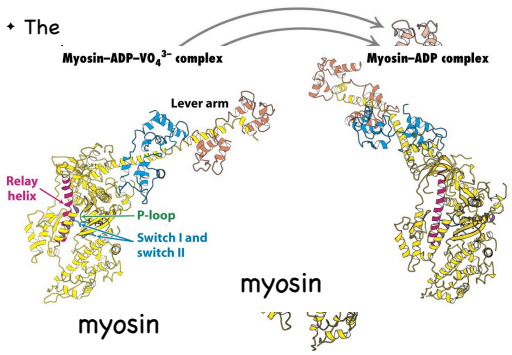

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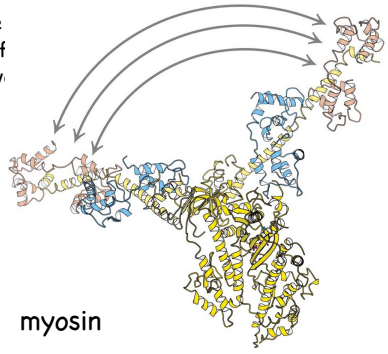

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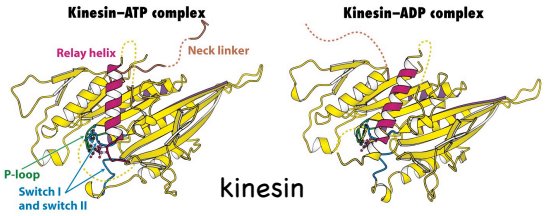
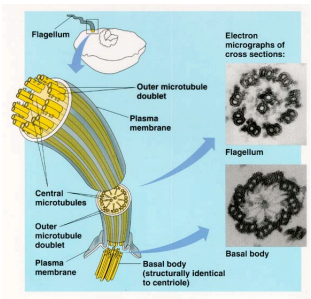


Movement Along Tracks

- Dynein also moves along microtubules.



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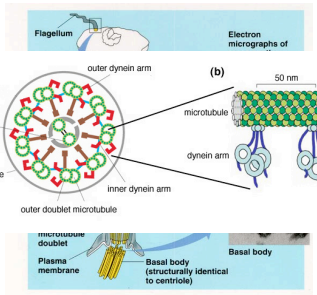

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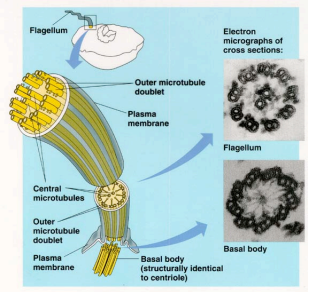
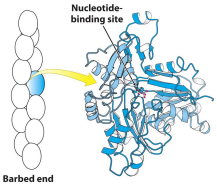


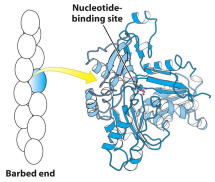
Actin

- 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-type 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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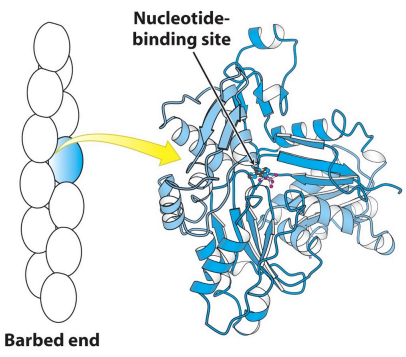

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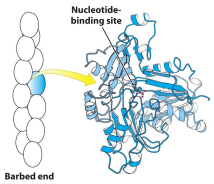
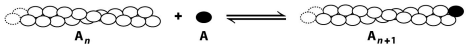


Actin

- 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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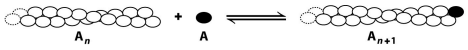

Actin

- The K_d for ATP-actin is 20 times lower than that for ADP-actin.
- Does ATP ⇔ ADP exchange favor polymerization?

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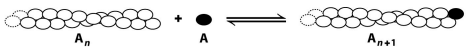
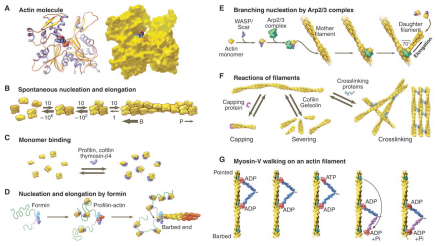


This Week in Science

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



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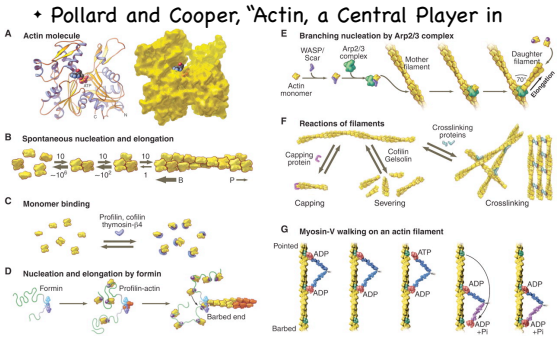

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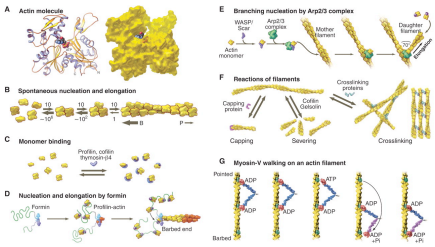

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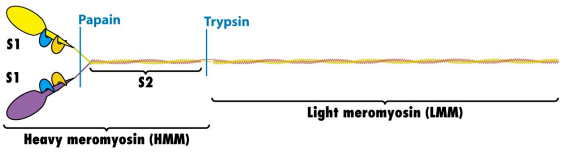
Myosin

- Myosin and actin work together in muscle contractions.



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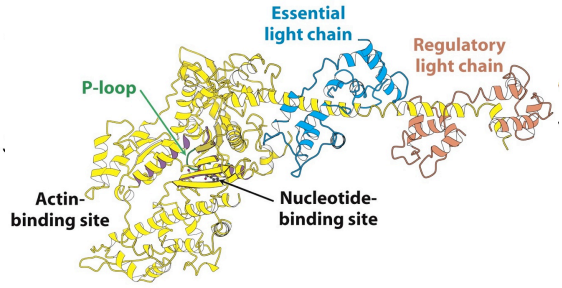

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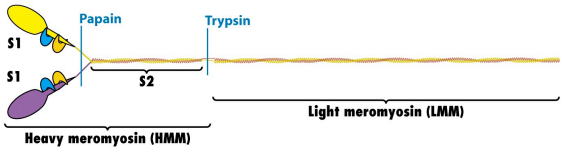

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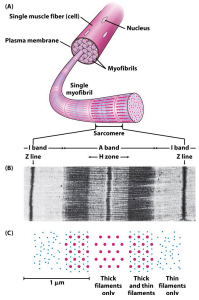

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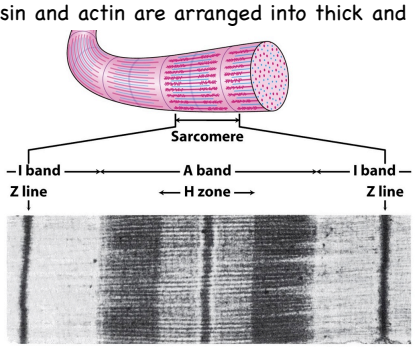

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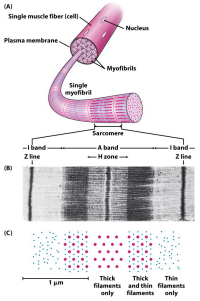

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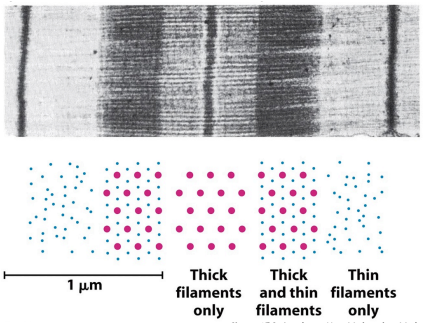

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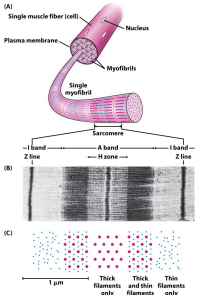

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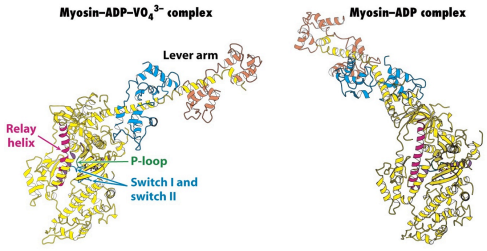
- Muscle contraction occurs when the myosin S1 head groups walk along the actin filaments.



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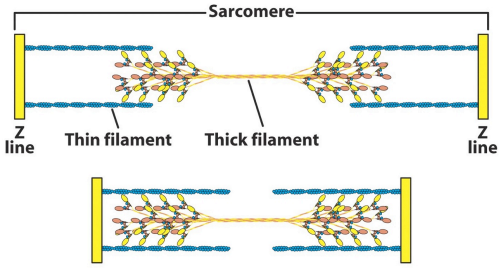

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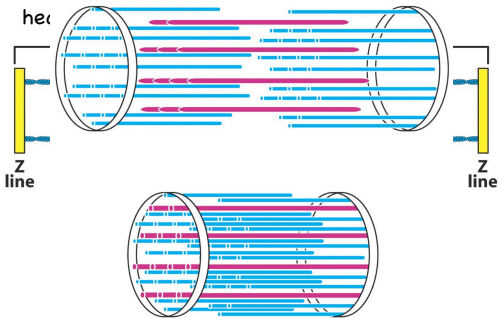

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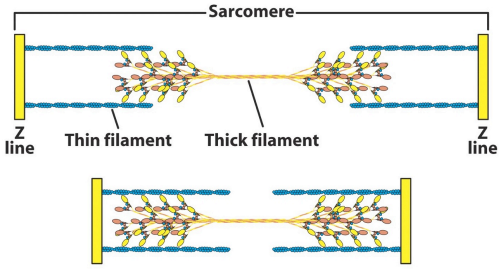
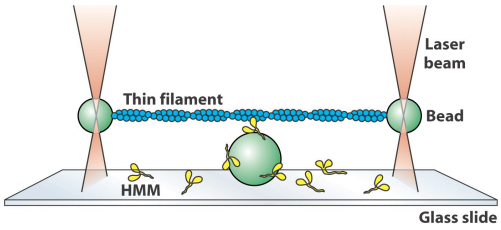


Myosin

- Optical traps (optical tweezers) have been used to monitor the movement of mysin along an actin filament.



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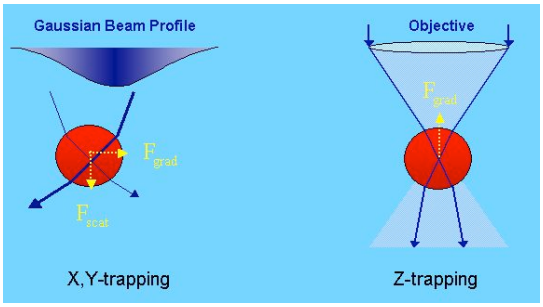

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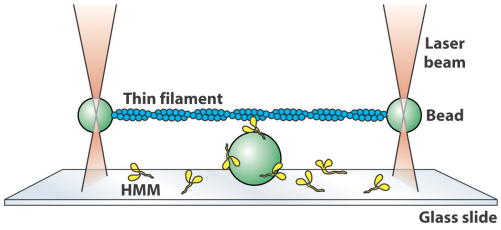

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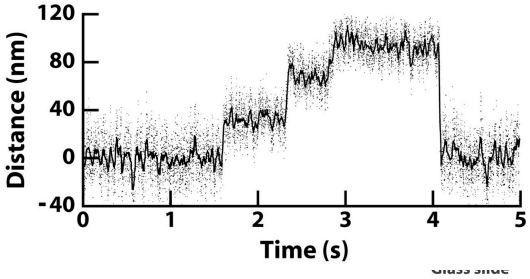

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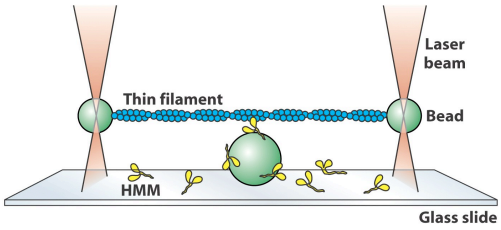
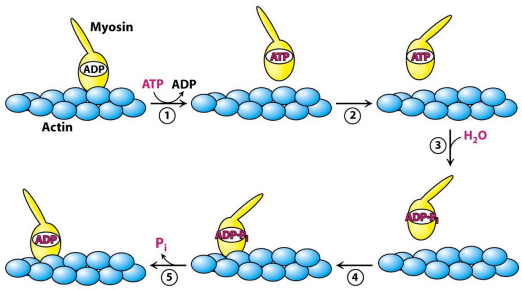


Myosin

- 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.

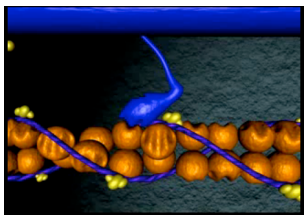
Myosin

- The cycle:



Myosin

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

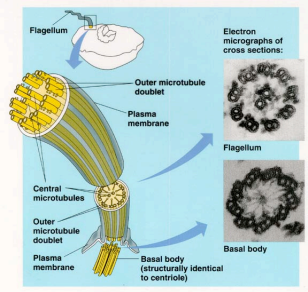


Microtubles

- 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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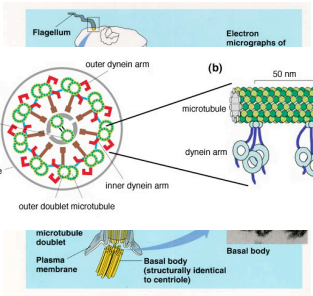

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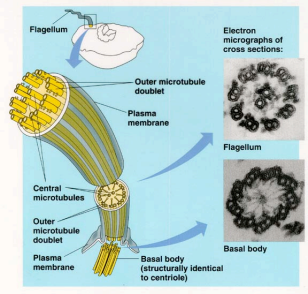
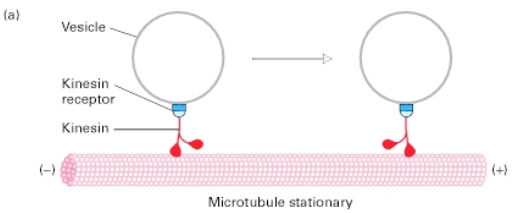


Movement Along Tracks

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



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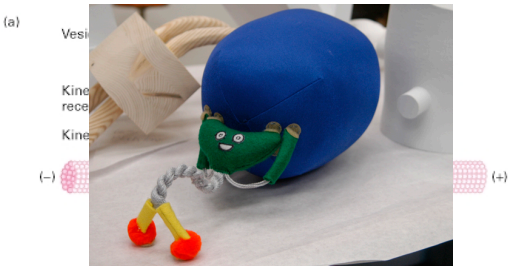

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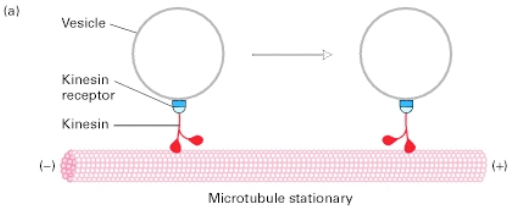
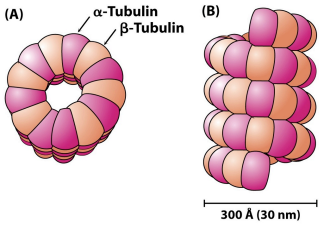
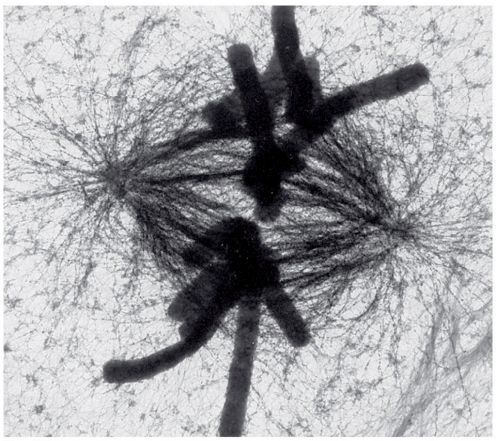


Microtubles

- 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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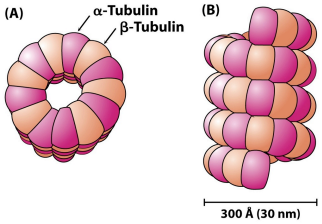
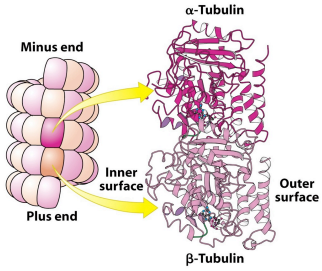


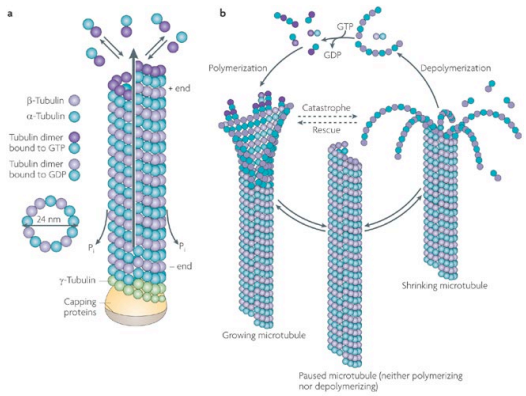
Microtubles

- 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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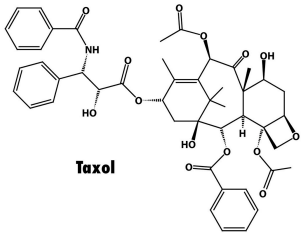
Microtubles

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



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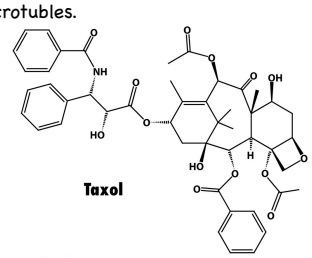
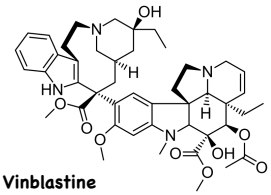


Taxol

Microtubles

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



Vinblastine

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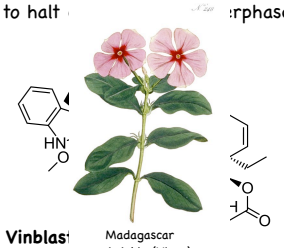

Vinblas

Madagascar periwinkle (Vinca)

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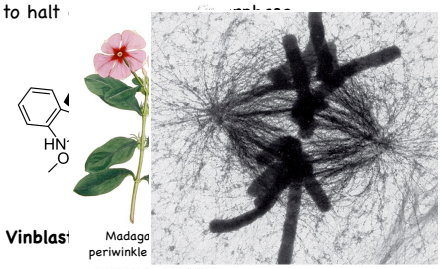

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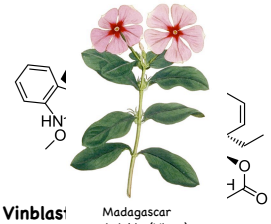

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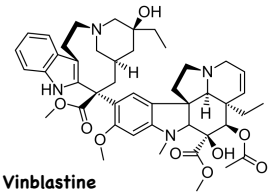
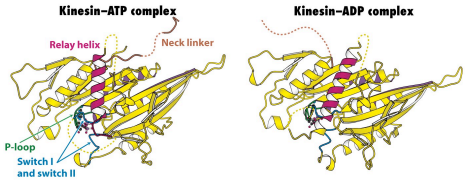


Vinblastine

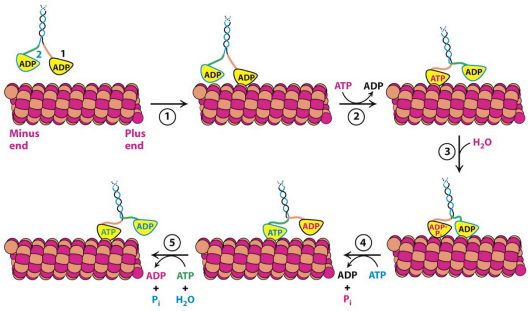
Kinesins

- 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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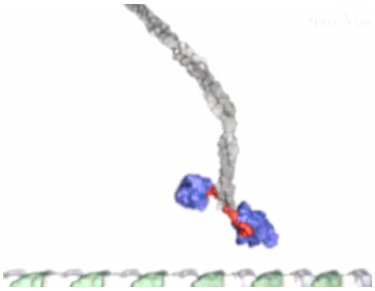
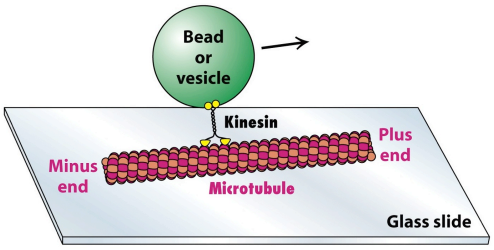


Kinesins

- The cycle:

Kinesins

- Kinesins walk along the microtubules.



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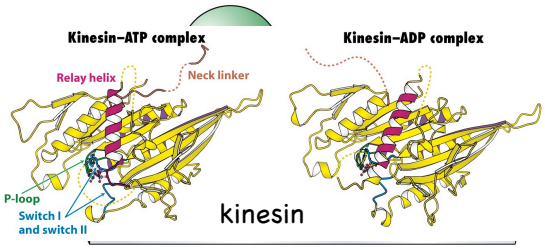

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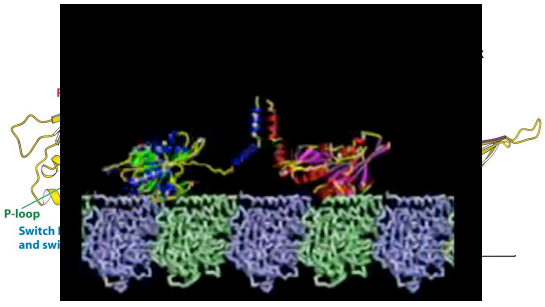

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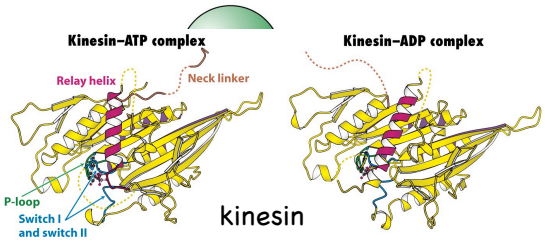

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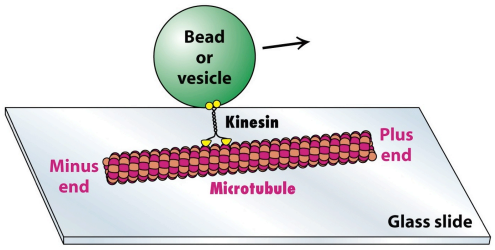

Next up

- Lecture 11, Molecular Motors (con'd). (Chapter 35)
  - Kinesin and movement along microtubules
  - Bacterial flagella