Physical Principles in Biology
Biology 3550
Spring 2025

Lecture 38

Myosin, Kinesin and Dynein

Wednesday, 16 April 2025

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Announcements

- Problem Set 6:
  - Due Monday, 28 April at 11:59 PM
  - Submit pdf file on Gradescope
- Final Exam:
  - Friday, 25 April, 8:00 -10:00 AM
  - HEB 2002

The Sliding Filament Model

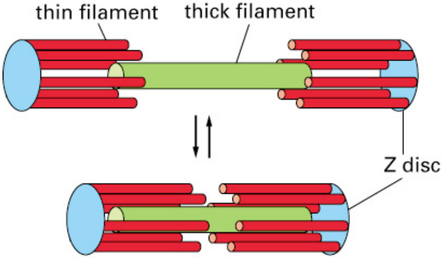
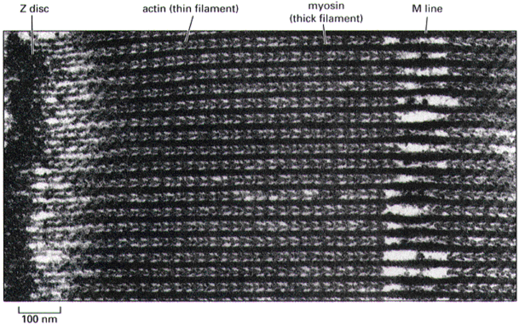


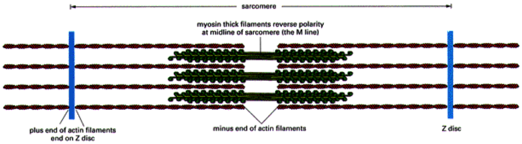
Figure 16–71. Molecular Biology of the Cell, 4th Edition.

- What causes the filaments to slide past each other?

Clarke, M. (2004). Muscle: The sliding filament at 50. *Nature*, 429, 145.
http://dx.doi.org/10.1038/429145a

Cross-Bridges Between Thick and Thin Filaments



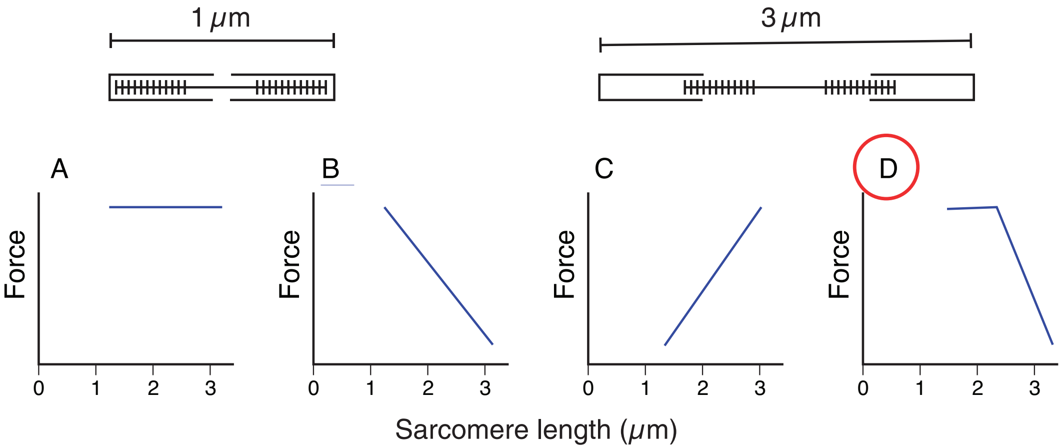


- Cross-bridges observed by H. Huxley in 1957, by electron microscopy of very thin slices of muscle tissue.
- Huxley proposed that cross-bridges were location of ATPase activity and force generation.

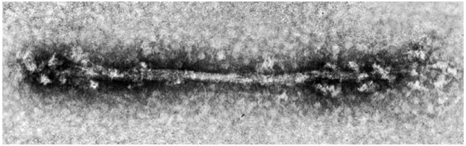
Figure from Molecular Biology of the Cell, Alberts et. al., 2nd Edition.

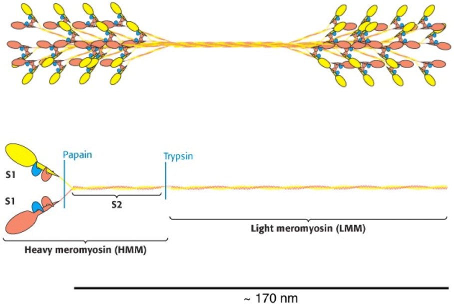
Clicker Question #1

How does the cross-bridge model predict that force will depend on sarcomere length during contraction and relaxation?



Thick Filament Structure

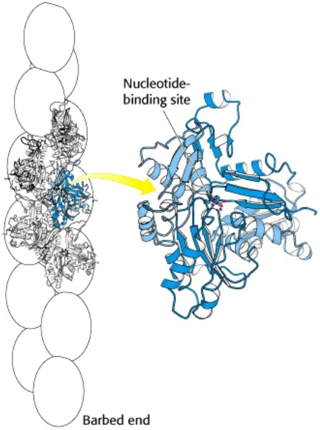




- Long "tails" are α-helices.
- Two myosin molecules dimerize by forming "coiled-coils".
- Multiple myosin dimers form thick filament.
- ATPase activity is in S1 "heads".

Figure from Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th edition. New York: W H Freeman; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK22418/

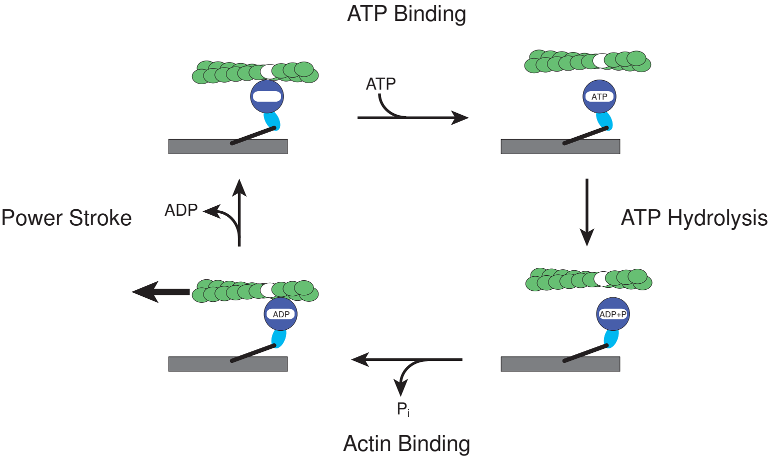
Thin Filament Structure



- Globular actin subunits assemble to form thin filament.
- Nucleotide (ATP or ADP) binding regulates assembly, but not muscle contraction.
- Fibers have polarity.
- Actin filaments are found in all eukaryotic cell types, where they control shape.

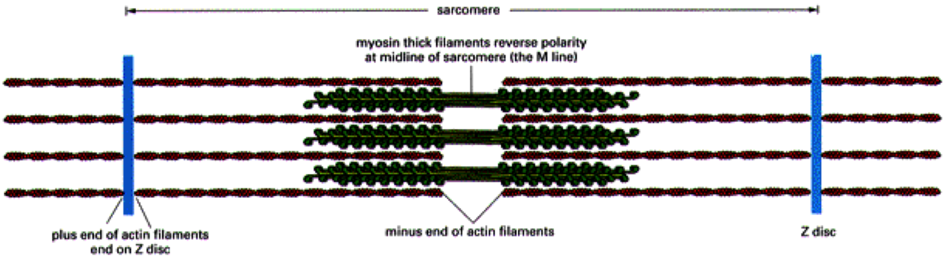
Figure from Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th edition. New York: W H Freeman; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK22418/

ATPase - Crossbridge Cycle



Lymn, R. & Taylor, E. (1971). Mechanism of adenosine triphosphate hydrolysis by actomyosin. *Biochemistry*, 10, 4617–4624. http://dx.doi.org/10.1021/bi00801a004

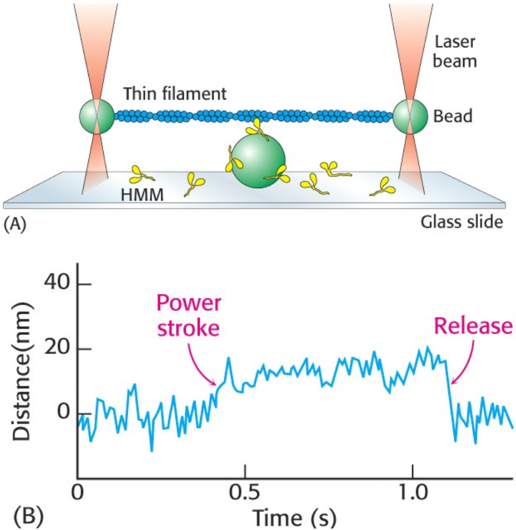
Individual Myosin Heads Act Independently



- At any instant, many heads are bound to an actin filament.
- Filaments have intrinsic elasticity to accommodate individual crossbridge cycles.
- After each step, myosin heads are likely to bind further along the actin filament.
- Biased Brownian motion leads to overall motion.
- No inertia!

Figure from Molecular Biology of the Cell, Alberts et. al., 2nd Edition.

Single Molecule Measurements of Myosin Force Generation



- Optical traps hold actin filament.
- Myosin heads are held to surface.
- Optical traps measure displacement and force.
- $\approx$ 10 nm displacement per step
- 3-4 pN force

Figure from Berg *et al.* Biochemistry. 5th edition. New York: W H Freeman; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK22418/

Adapted from Finer, J., Simmons, R. & Spudich, J. (1994). *Nature*, 368, 113–119.
http://dx.doi.org/10.1038/368113a0

Clicker Question #4

How much work is generated in a single myosin cycle?

A) 3×10^{-20} J

B) 3×10^{-17} J

C) 3×10^{-14} J

D) 3×10^{-11} J

E) 3×10^{-8} J

Work from a Single Myosin Cycle

- $w = \int F\,dx = F_{\text{avg}} \times \text{distance}$

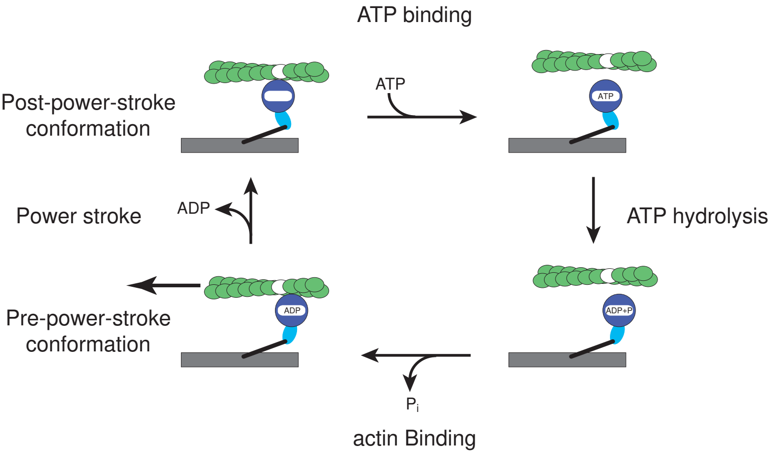
$$\begin{aligned} w &= 10\,\text{nm} \times 3\,\text{pN} \\ &= 10^{-8}\,\text{m} \times 3 \times 10^{-12}\,\text{N} = 3 \times 10^{-20}\,\text{N} \cdot \text{m} \\ &= 3 \times 10^{-20}\,\text{J} \end{aligned}$$

- Free energy change for hydrolysis of one molecule of ATP, under standard state conditions:

$$\begin{aligned} \Delta G^\circ &= -30 \times 10^{3}\,\text{J/mole} \div 6.02 \times 10^{23}\,\text{molecules/mole} \\ &= -5 \times 10^{-20}\,\text{J} \end{aligned}$$

- Does this seem reasonable?
- During strenuous exercise, about 1 mole of ATP is hydrolyzed per minute by a human.

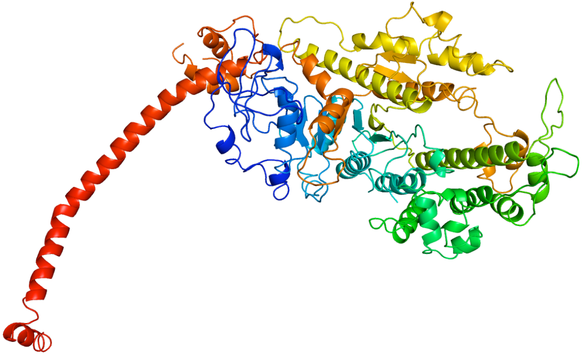
ATPase - Crossbridge Cycle



What do the conformational changes really look like?

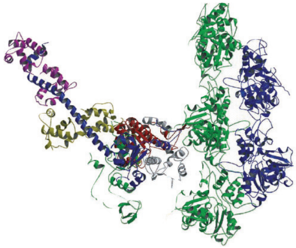
Lymn, R. & Taylor, E. (1971). Mechanism of adenosine triphosphate hydrolysis by actomyosin. *Biochemistry*, 10, 4617–4624.
http://dx.doi.org/10.1021/bi00801a004

Atomic-Resolution Structure of the Myosin Head

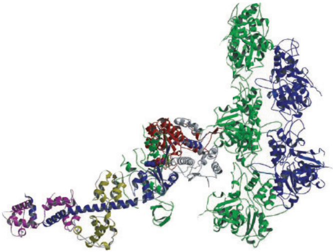


Rayment, I., Rypniewski, W., Schmidt-Base, K., Smith, R., Tomchick, D., Benning, M., Winkelmann, D., Wesenberg, G. & Holden, H. (1993). Three-dimensional structure of myosin subfragment-1: a molecular motor. *Science*, 261, 50–58.
http://dx.doi.org/10.1126/science.8316857

The Actin-Myosin Power Stroke



Pre-power-stroke
(ADP bound)

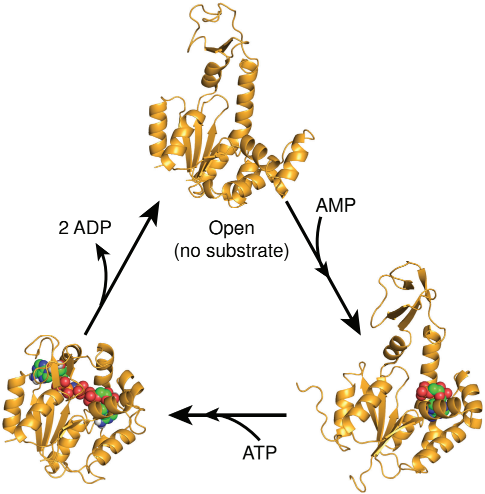


Post-power-stroke
(empty binding site)

- These are *models* based on electron microscopy and crystal structures of the individual components under different conditions!
- Animation from Vale lab at UCSF: https://vimeo.com/157524452
  https://valelab.ucsf.edu

Geeves, M. & Holmes, K. (1999). Structural mechanism of muscle contraction. *Ann. Rev. Biochem.*, 68, 687–728.
http://dx.doi.org/10.1146/annurev.biochem.68.1.687

An Enzyme that Moves: Adenylate Kinase

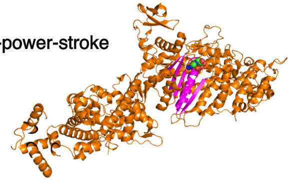


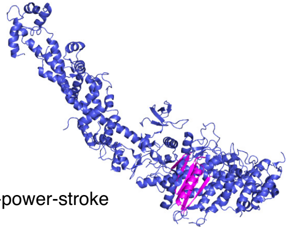
- Substrate binding induces structure to change, enclosing substrates.
- Closed structure protects ATP from being hydrolyzed and releasing phosphate.
- After conversion of ATP + AMP to two ADP molecules, structure reopens to release ADP.

Molecular Motion in Two Enzymes

Myosin

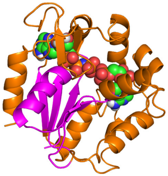
Pre-power-stroke

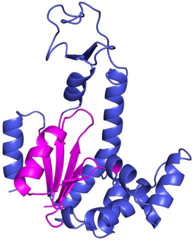




Post-power-stroke

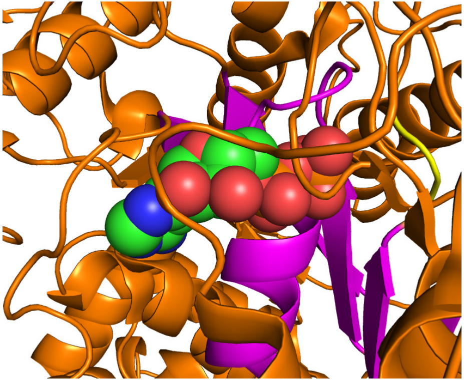
Adenylate kinase



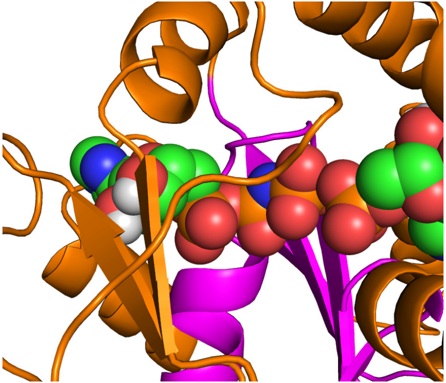


Nucleotide Binding Sites

Myosin



Adenylate Kinase



Different Classes of Myosins

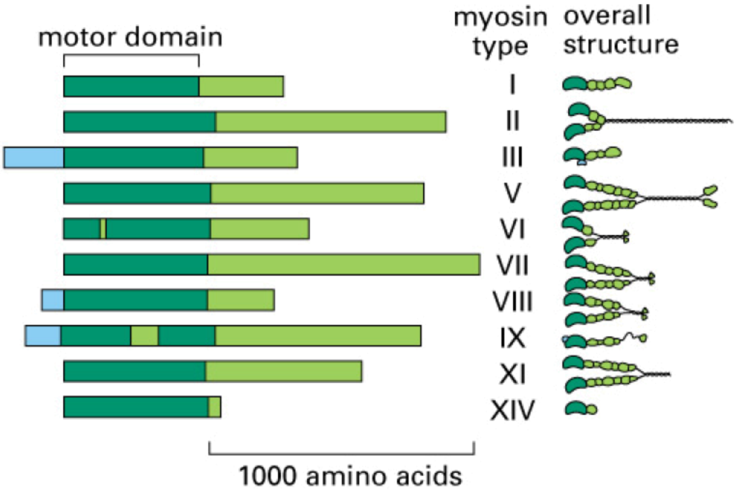
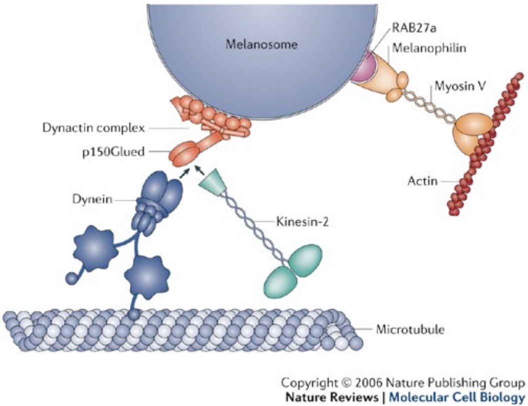


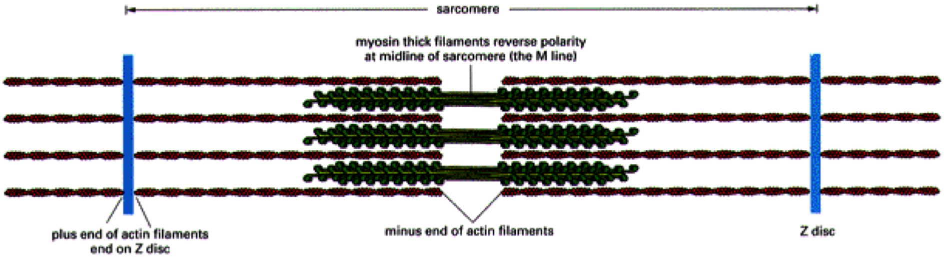
Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26888/#A3050

Vesicle Transport: One Function of Non-muscle Myosins (and other motor proteins)



Soldati, T. & Schliwa, M. (2006). Powering membrane traffic in endocytosis and recycling. *Nature Rev. Mol. Cell. Biol.*, 7, 897–908. http://dx.doi.org/10.1038/nrm2060

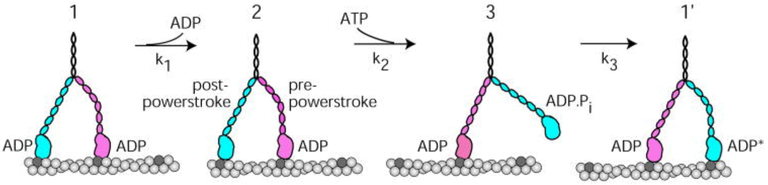
Special Requirements for Myosin in Muscle



- Individual myosin heads act independently.
- At any instant, many heads are bound to an actin filament.
- Once completing power stroke, heads release quickly.
- Low duty ratio: Each head is bound to actin about 5% of the time.

Figure from Molecular Biology of the Cell, Alberts et. al., 2nd Edition.

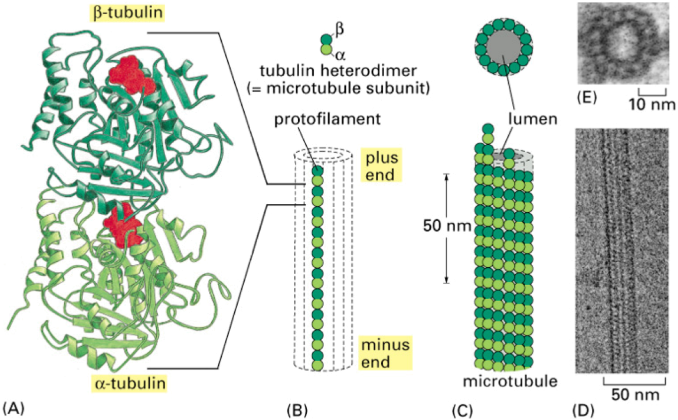
Another Kind of Myosin: Myosin V



- Transports vesicles and other structures along actin fibers in cytoplasm.
- Long lever arms allow 36-nm steps, compared to 10 nm for muscle myosin.
- Processive motion: One head is always bound to actin fiber to keep myosin and cargo from falling off. "Hand-over-hand" motion.
- High duty ratio: Each head is bound to actin about 70% of the time.
- Catalytic cycles of the two heads are coupled (poorly understood).

Trybus, K. M. (2008). Myosin V from head to tail. *Cell. Mol. Life Sci.*, 65, 1378–1389.
https://dx.doi.org/10.1007%2Fs00018-008-7507-6

Microtubules



- Larger diameter and more rigid than actin filaments.
- Help define shapes of cells.
- Move chromosomes during cell division.
- Serve as “tracks” upon which lipid vesicles are moved within cells.
- Many functions require motors to move along the microtubule.

Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26862/

Microtubule Motors

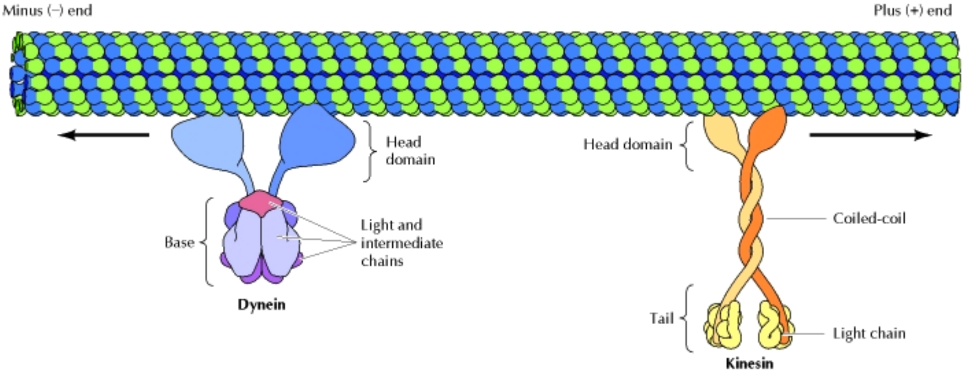
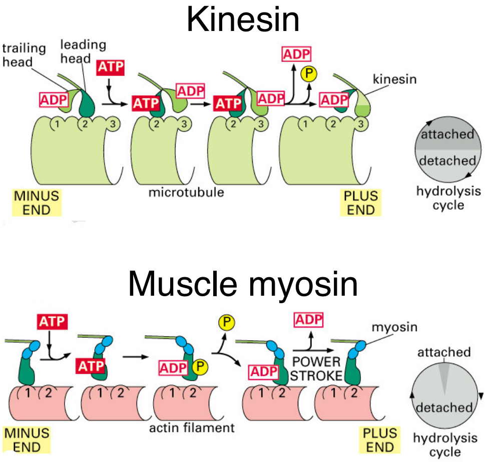


Figure from Cooper GM. The Cell: A Molecular Approach. 2nd edition. Sunderland (MA): Sinauer Associates; 2000. Microtubule Motors and //www.ncbi.nlm.nih.gov/books/NBK9833/

A Microtubule Motor, Kinesin, Compared to Myosin



- Kinesins have high duty ratios, like myosin V, to allow walking along microtubules.
- The kinesin heads are coupled kinetically, like myosin V.
- Animation from Vale lab at UCSF
  https://vimeo.com/157524451
  https://valelab.ucsf.edu

Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26888/#A3050

Structural Similarity Between Myosin and Kinesin

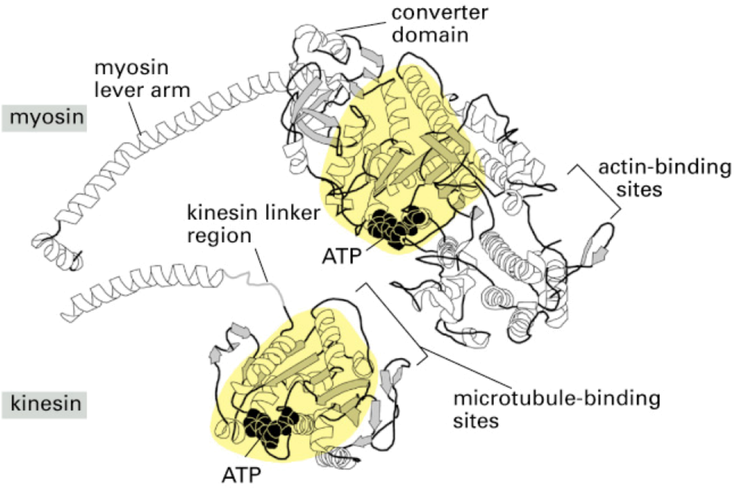
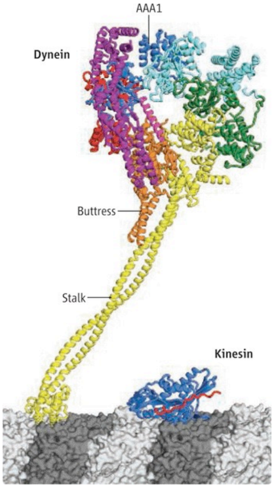


Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26888/#A3050

A Very Different Microtubule Motor: Dynein



- Motor domain is ring of six AAA domains. (ATPases Associated with diverse cellular Activities)
- Motions within AAA ring are transmitted to microtubule-binding domain via coiled-coils.
- Animation from Vale lab at UCSF
  https://vimeo.com/157524450
  https://valelab.ucsf.edu

Carter, A. P., Cho, C., Jin, L. & Vale, R. D. (2011). Crystal structure of the dynein motor domain. *Science*, 331, 1159–1165.
http://dx.doi.org/10.1126/science.1202393
Spudich, J. A. (2011). Molecular motors, beauty in complexity. *Science*, 331, 1143–1144.