Physical Principles in Biology
Biology 3550
Spring 2025

Lecture 37

Introduction to Molecular Motors and Muscle Structure

Monday, 14 April 2025

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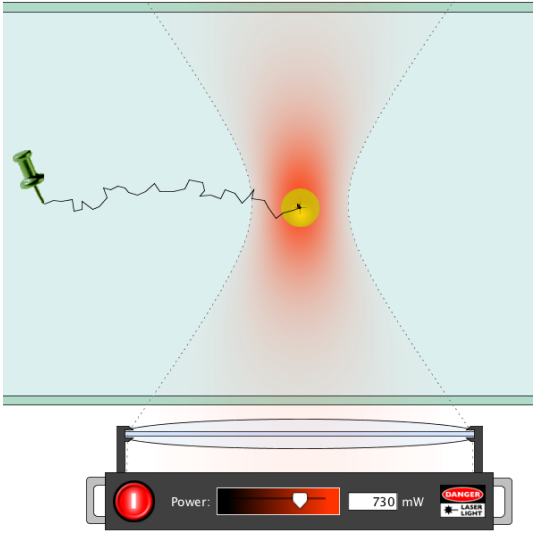
Announcements

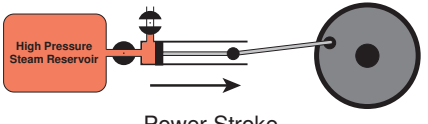
- Problem Set 6:
  - Due Monday, 28 April at 11:59 PM
  - Submit pdf file on Gradescope
- Final Exam:
  - Friday, 25 April, 8:00 -10:00 AM
  - HEB 2002

Stretching DNA with Optical Tweezers

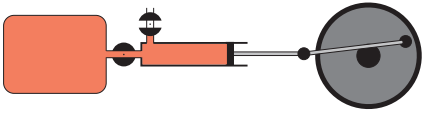


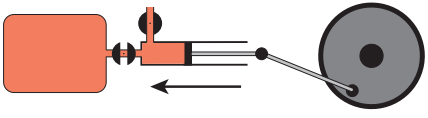
- Force is entropic in nature: There are more possible conformations with the ends closer together.
- Thermal motion is required in order for the DNA to sample conformations.
- Force increases as DNA ends are moved further apart.
- Could a force like this be used as a molecular motor?

A Simple Steam Engine



Power Stroke

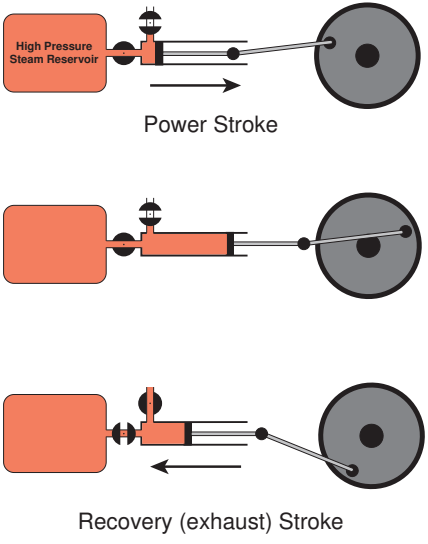




Recovery (exhaust) Stroke

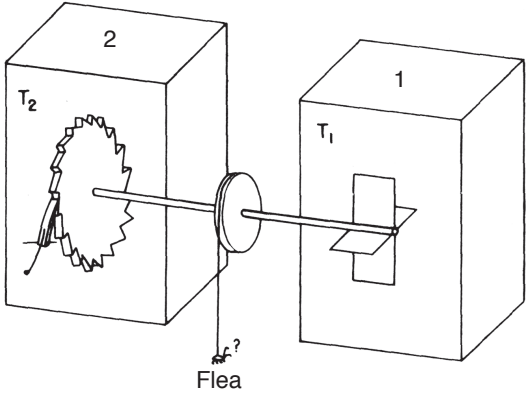
- Energy source is a pressure difference, created by a temperature difference.
- Free energy of steam is lost as it expands.
- Expansion of steam is coupled to movement of piston and flywheel, capturing some of the energy.
- Momentum of the flywheel returns engine to starting state.
- Valves control flow of steam and must be synchronized to piston movement.
- If expansion of steam is unlinked from motion of piston or wheel, free energy is lost.

A Simple Steam Engine



- Similar requirements for a molecular motor:
  - Loss of free energy (*e.g.,* ATP hydrolysis) must be coupled to mechanical work.
  - Motor must operate cyclically.
  - Individual steps in cycle must be regulated.
- Important differences for a molecular motor:
  - No temperature differences at the molecular scale.
  - No momentum at the molecular scale.

A “Brownian Ratchet”

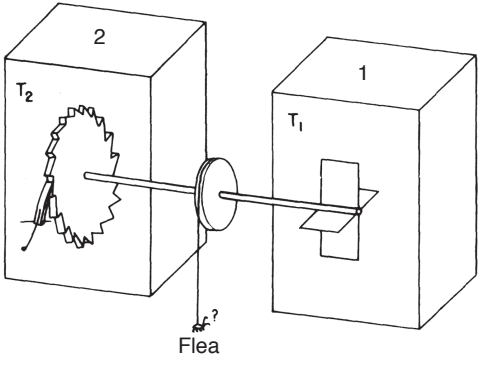


- Thermal motions of gas molecules in compartment 1 make paddle wheel jiggle back and forth.
- Ratchet mechanism in compartment 2 allows motion in only one direction.
- String is wound onto the pulley and the flea is slowly lifted.
- Will this work?

Feynman, R. P., Leighton, R. B. & Sands, M. (2013). *The Feynman Lectures on Physics*, volume I, chapter 46. Basic Books
http://www.feynmanlectures.caltech.edu/I_46.html

Clicker Question #1

Will the Brownian ratchet lift the flea?



A) Yes

B) Only if the temperature of compartment 1 is greater than that of 2.

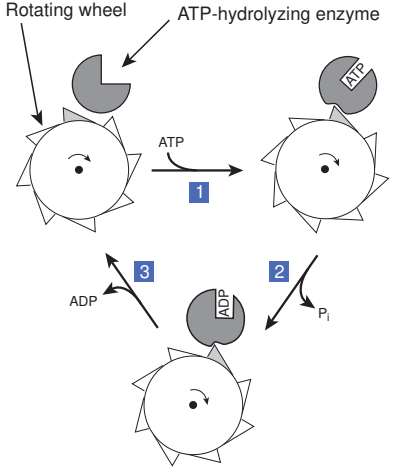
C) Only if the temperature of compartment 2 is greater than that of 1.

D) No way!

All answers count for now.

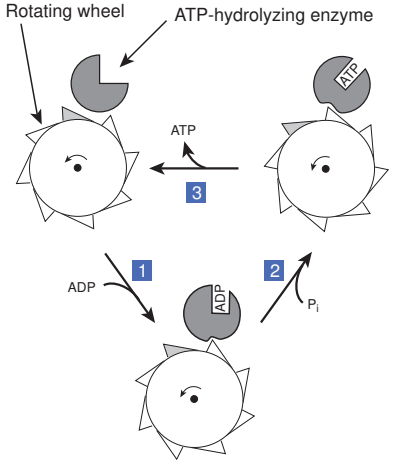
In the absence of a temperature difference (or other source of free energy), thermal motion can generate a force and directional motion, but cannot drive a cyclic motor.

A Hypothetical ATPase Ratchet



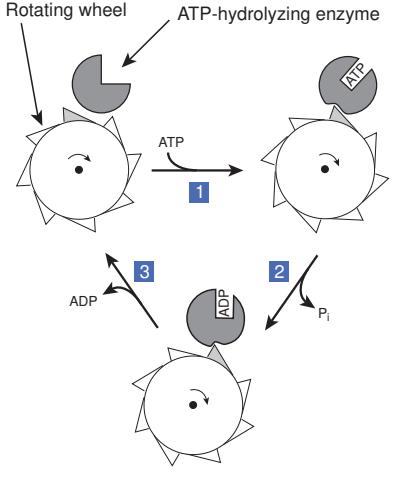
- Enzyme changes conformation during catalytic cycle.
- Changes in enzyme conformation control motion of the wheel.
- Steps in the cycle
  1. Enzyme binds ATP and changes conformation.
     Wheel rotates clockwise.
  2. ATP is hydrolyzed, phosphate ion is released and enzyme changes conformation.
     Wheel rotates clockwise.
  3. ADP is released and enzyme returns to its original conformation.
     Wheel rotates clockwise.

A Hypothetical ATPase Ratchet in Reverse



- When ATP, ADP and P_i concentrations favor ATP synthesis.
- Steps in the cycle
  1. Enzyme binds ADP and changes conformation.
     Wheel rotates counter-clockwise.
  2. Phosphate is bound, enzyme condenses ADP and P_i, and changes conformation.
     Wheel rotates counter-clockwise.
  3. ATP is released and enzyme returns to its original conformation.
     Wheel rotates counter-clockwise.
- Enzyme conformations and binding states are identical to those in forward cycle.

A Hypothetical ATPase Ratchet



- Direction of the wheel rotation is linked to direction of catalyzed reaction:

  $ATP \rightleftharpoons ADP + P_i$
- If ATP, ADP and P_i are at equilibrium concentrations:

  $\Delta G = 0$, and wheel moves randomly in both directions.
- If ATP, ADP and P_i concentrations make $\Delta G < 0$:

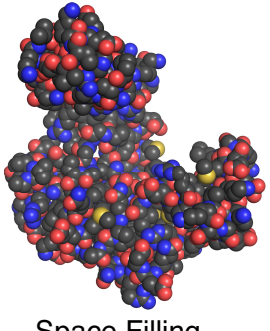
  Hydrolysis reaction is favored, and wheel moves preferentially in clockwise direction.
- If ATP, ADP and P_i concentrations make $\Delta G > 0$:

  Synthesis reaction is favored, and wheel moves preferentially in counter-clockwise direction.
- What if the wheel is turned by an outside force?

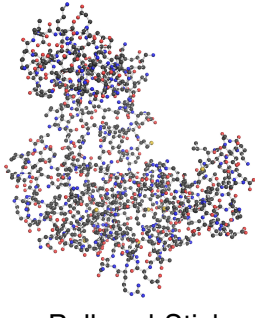
An Enzyme that Moves: Adenylate Kinase

$$\mathrm{ATP} + \mathrm{AMP} \rightleftharpoons \mathrm{ADP} + \mathrm{ADP}$$

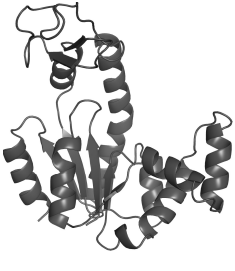
- Functions to recover ATP from ADP, when ATP reserves are low.
- Three representations of adenylate kinase structure:



Space Filling

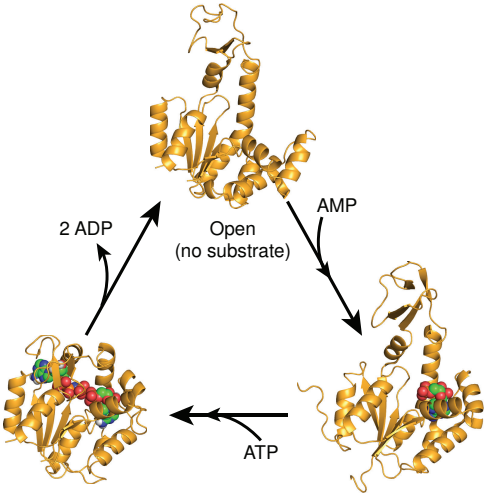


Ball-and-Stick



Ribbon

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.
- Could this motion be used to do work?

Clicker Question #2

For the reaction: $\mathrm{ATP} + \mathrm{AMP} \rightleftharpoons \mathrm{ADP} + \mathrm{ADP}$,

what is the standard free energy change, ΔG°?

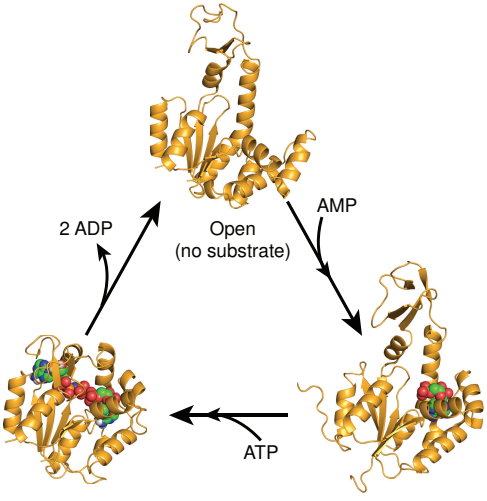
A) Less than zero

B) About zero

C) Greater than zero

All answers count for now.

An Enzyme that Moves: Adenylate Kinase



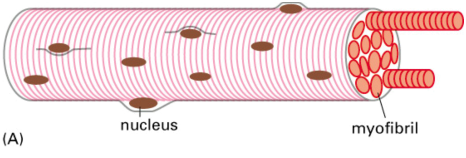
- Suppose that ATP, AMP and ADP are at equilibrium concentrations, and $\Delta G = 0$.
- Will the protein stop moving?
- Could the motions be used to do work?

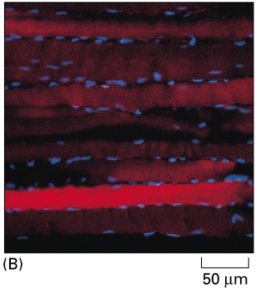
Warning!

Direction Change

Muscle, Myosin and Actin

Muscle Cells





- Single cells formed from fusion of many precursor cells.
- Up to several cm long (full length of a muscle).
- $\approx$ 50 μm in diameter.
  1 cm diameter muscle contains $\approx$ 400,000 cells.

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/#A3065

Structure of Myofibrils

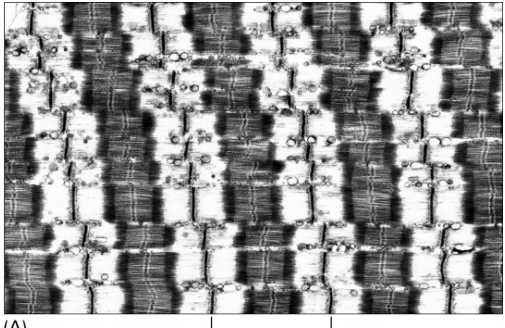


Figure 16–69 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

- Low magnification electron micrograph.
- Dark regions indicate presence of protein.
- Parallel myofibrils.
- Repeating units, sarcomeres, seen as alternating regions of high and low protein density.

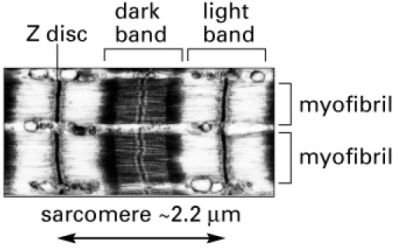
Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26888/#A3065

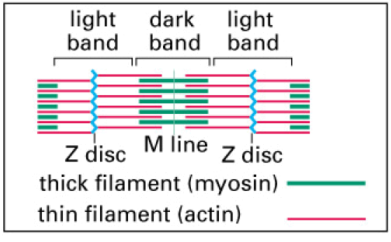
Protein Composition of Muscle Fibers

First characterized by Albert Szent-Györgyi and colleagues at University of Szeged, Hungary, in 1930s and 40s.

- Actin
  - 42,000 Da molecular weight
  - Assembles into long, thin fibers
- Myosin
  - $\approx$ 500,000 Da molecular weight
  - Forms thick filaments
  - ATP hydrolyzing activity, especially in presence of actin

Locations of Actin and Myosin in Myofibrils





Deduced in Early 1950s:

- Myosin: Dark bands
- Actin: Light bands

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/#A3065

Cross Section of Insect Flight Muscle

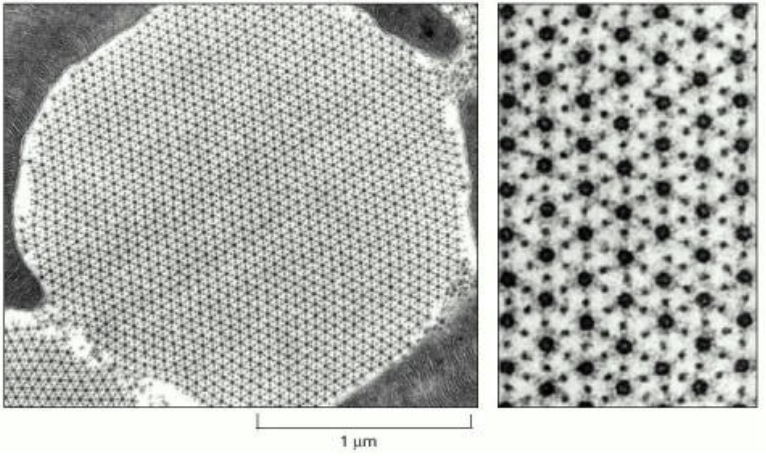
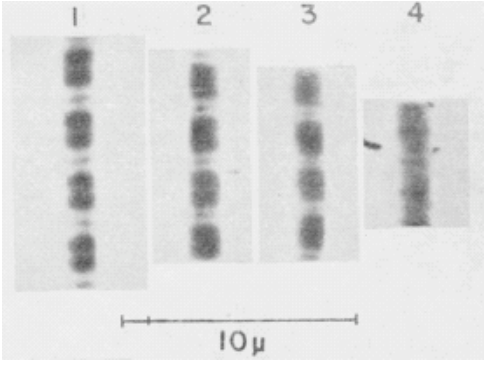


Figure from Alberts B, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.
https://www.ncbi.nlm.nih.gov/books/NBK26888/#A3065
(From J. Auber, J. de Microsc. 8:197232, 1969.)

The Great Discovery: 1954



During contraction:

- Length of dark bands remains constant.
- Light bands shorten.
- Overall length of the myofibril decreases.
- Diameter of myofibril remains constant.

Huxley, A. & Niedergerke, R. (1954). Structural changes in muscle during contraction: Interference microscopy of living muscle fibres. *Nature*, 173, 971–973. http://dx.doi.org/10.1038/173971a0

Huxley, H. & Hanson, J. (1954). Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation. *Nature*, 173, 973–976. http://dx.doi.org/10.1038/173973a0

The Sliding Filament Model

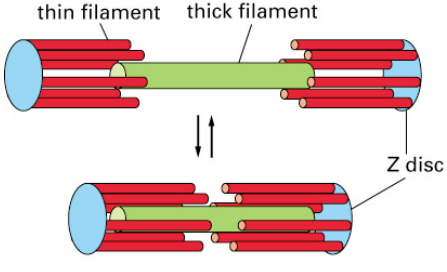


Figure 16–71. Molecular Biology of the Cell, 4th Edition.

- 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