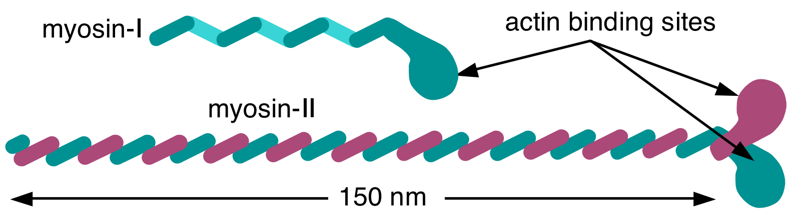
PHYS 4xx Molecular motors

Motor proteins

<u>myosins</u>

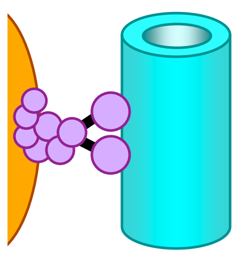


- myosin-I is a monomer, myosin-II is a dimer
- heads have size ~ 15-20 nm
- walk in plus direction

<u>kinesin</u>

- dimer; same general shape as myosin-II
- the tail region is shorter: 60-70 nm; heads are smaller: 10-15 nm
- each strand of the tail terminates in several intermediate length chains
- both heads attach to a single microtubule and slide parallel to a protofilament
- tail is perpendicular to the axis of the microtubule
- walks towards plus end of MT

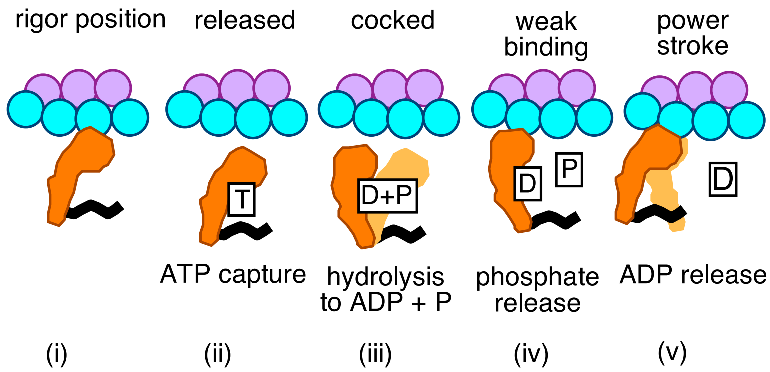
<u>cytoplasmic dynein</u>



- two spherical heads of diameter 9-12 nm
- links MT to a vesicle (if cytoplasmic) or other MT (if ciliary)
- walks towards minus end
- note: ciliary dynein is variable, with between 1 and 3 heads

Mechanism of motion

- energy source is ATP
- proposed mechanism for the structural changes of <u>myosin</u>, based on x-ray study of its head geometry (Rayment *et al.*)

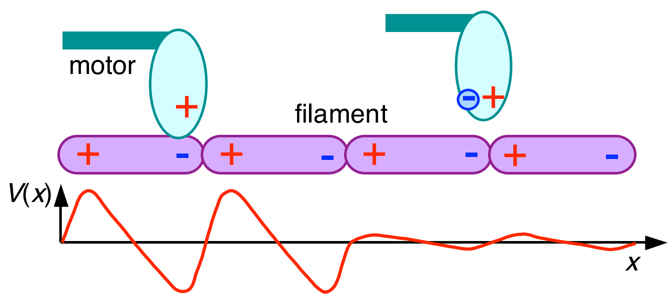


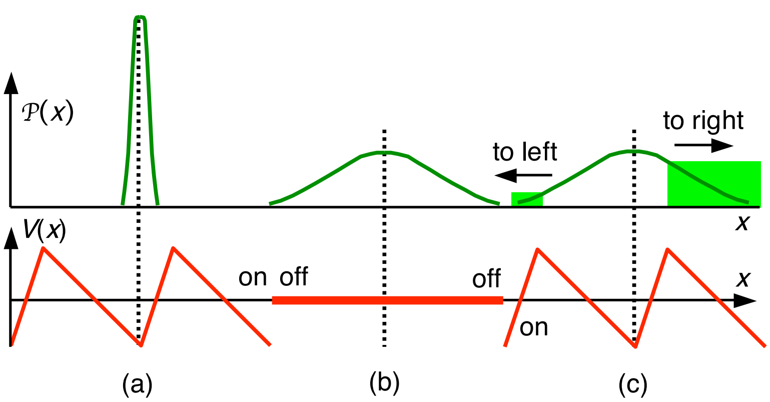
(ATP, ADP and phosphate are indicated by the symbols T, D and P, respectively)

- typical displacement of the head is 5 nm, occurring with a repetition rate exceeding a cycle per second

Thermal ratchets

- model may apply to cells because of charge of ATP (Astumian and Bier; Prost *et al.*)



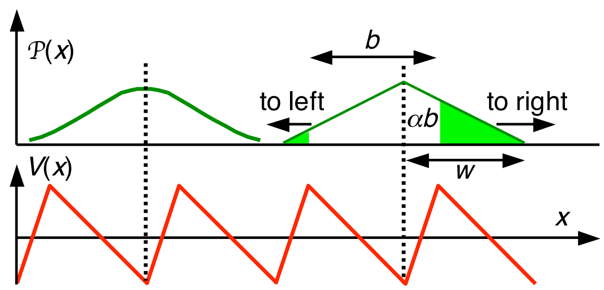


- non-symmetric, oscillating potential $V(x)$, lower part of diagram
- when potential is "on", the particle at the left sits near the bottom of the potential well, with a sharp probability distribution $\boldsymbol{P}(x)$
- the particle diffuses when the potential is "off" (middle frame)

- once the potential is restored, the particle may hop into neighboring minima with differing probability (right frame)
- other potentials can be used, with more or less efficiency

simple analytical model

•spatial period of potential is b and shortest peak to trough distance is αb



- replace Gaussian probability distribution $P(x) = (2\pi\sigma^2)^{-1/2} \exp(-x^2/2\sigma^2)$ by a triangular form of base $2w$ and height $P(0) = 1/w$, such that $\int P(x)\,dx = 1$:

  $P(x) = (1 - |x|/w) / w$
- find dispersion $\langle x^2 \rangle$:

  $\langle x^2 \rangle = \int x^2 (1 - |x|/w)/w\,dx \;/\; 1/2 = (2/w) \int (x^2 - x^3/w)\,dx = (2/w) \cdot (w^3/12) = w^2/6$
- equating the dispersions $\langle x^2 \rangle = \sigma^2$ and $\langle x^2 \rangle = w^2/6$ gives

  $w = \sqrt{6}\,\sigma \cong 2.5\,\sigma,$ (1)

- in this approximation:

  probability of moving to the right = P_R

  = 1/2 • [*area of shaded triangle*] / [*area of large triangle to right of apex*]

  $= 1/2 \cdot [(w - \alpha b)/w]^2 = (1 - \alpha b/w)^2/2$ for $w > \alpha b$

  probability of moving to the left = P_L

  = 1/2 • [*area of shaded triangle*] / [*area of large triangle to left of apex*]

  $= 1/2 \cdot [(w - b + \alpha b)/w]^2 = (1 - b/w + \alpha b/w)^2/2$ for $w > (1-\alpha)b$.

  •net probability of motion $P_{net} = P_R - P_L$

	$= 0$	$0 < w < \alpha b$	(2a)
P_{net}	$= (1 - \alpha b/w)^2/2$	$\alpha b < w < (1-\alpha)b$	(2b)
	$= (b/w) \cdot (1 - b/(2w)) \cdot (1 - 2\alpha)$	$(1-\alpha)b < w.$	(2c)

- algebra for Eq. (2c):

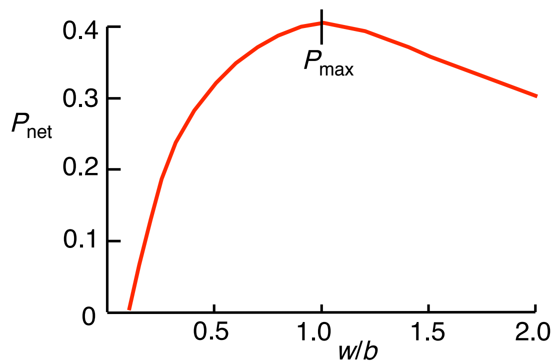
$$
\begin{aligned}
P_{net} &= (1 - \alpha b/w)^2/2 - (1 - b/w + \alpha b/w)^2/2 \\
&= 1/2\,\{1 - 2\alpha b/w + (\alpha b/w)^2 - [1 - 2b/w + 2\alpha b/w - 2(b/w \cdot \alpha b/w) + (b/w)^2 + (\alpha b/w)^2]\,\} \\
&= 1/2\,\{-2\alpha b/w + (\alpha b/w)^2 + 2b/w - 2\alpha b/w + 2(b/w \cdot \alpha b/w) - (b/w)^2 - (\alpha b/w)^2\} \\
&= 1/2\,\{-2\alpha b/w + 2b/w - 2\alpha b/w + 2(b/w \cdot \alpha b/w) - (b/w)^2\} \\
&= b/w \cdot 1/2 \cdot \{-2\alpha + 2 - 2\alpha + 2\alpha b/w - b/w\}
\end{aligned}
$$

$= b/w \cdot \{-\alpha + 1 - \alpha + \alpha b/w - b/2w\}$
$= b/w \cdot \{1 - 2\alpha - (b/2w) \cdot (1 - 2\alpha)\}$
$= b/w \cdot (1 - b/2w) \cdot (1 - 2\alpha)$ (2c)

- properties of $\boldsymbol{P}_{net}$:
  - $\boldsymbol{P}_{net} = 0$ if potential is symmetric [at $\alpha = 1/2$: (2a & 2c) = 0, (2b) has no domain]
  - $\boldsymbol{P}_{net} \leq 1/2$ if potential is vertical [$\alpha = 0$: (2a) has no domain, (2b) = 1/2, (2c) $\leq$ 1/2]
  - $\boldsymbol{P}_{net}$ has a maximum at $\boldsymbol{P}_{max}$ for intermediate values of α
    - imposing $d\boldsymbol{P}_{net}/dw = 0$ on Eq. (2c) gives
    - $0 = d/dw\,[b/w \cdot (1 - b/2w)]$
      - $= b\,[-w^{-2}(1 - b/2w) + w^{-1}\,(-b/2)\,(-w^{-2})\,]$
      - $= (b/w^2) \cdot [-(1 - b/2w) + b/2w\,]$
      - $= (b/w^2) \cdot (b/w - 1)$
    - satisfied by $b/w = 1$ (3)

    - substituting Eq. (3) back into (2c) gives
    - $\boldsymbol{P}_{max} = (1 - 2\alpha)/2$ (4)

- numerical example for $\alpha = 0.1$; $\boldsymbol{P}_{max} = 0.4$ at $w/b = 1$



<u>caveats</u>
- physical potential is likely to appear bumpy because of the charge distribution
- the time for switching the potential on and off is not instantaneous
- these effects permit more diffusion, and reduce the net flux
- Astumian and Bier and Prost *et al.*, find that $\boldsymbol{P}_{max}$ may be 0.25 or less

<u>expectations for flux</u>
- a diffusing particle obeys a Gaussian distribution with $\sigma^2 = 2Dt$, where D is the diffusion constant and t is the time
- hence, $w = \sqrt{6}\,\sigma = (12Dt)^{1/2}$
- using $D \sim 10^{-12}$ to 10^{-14} m^2•s, then $t = 5 \times 10^{-6}$ to 5×10^{-4} s at $\boldsymbol{P}_{max}$: $w = b = 8$ nm
- very small time scale: 1000 to 10^5 steps per second (period = $2t$)!
- time scale for hydrolysis of ATP or GTP in actin filaments or microtubules is ~ $k_{on}[M]$ at modest monomer concentrations $[M]$, say 10^2 per second

- at 10^3 steps per second, 8 nm per step, and $\boldsymbol{P}_{net}$ = 0.1 (say), motor speed is 800 nm/s; however, time is needed for ATP to replenish
- (note, if $t \sim 10^{-2}$ sec and $D = 10^{-12}$ $m^2 \cdot s$, motor has diffused too far unless held by another head: $(6Dt)^{1/2} = (6 \cdot 10^{-12} \cdot 10^{-2})^{1/2}$ = 245 nm!!)
- experimental range ~0.5 μm/s for kinesin motors (Svoboda *et al.*)
- BUT, experimentally measured efficiency is at least 1/2 Svoboda *et al.* from the fluctuations as a function of time in the position of a kinesin motor sliding on a MT