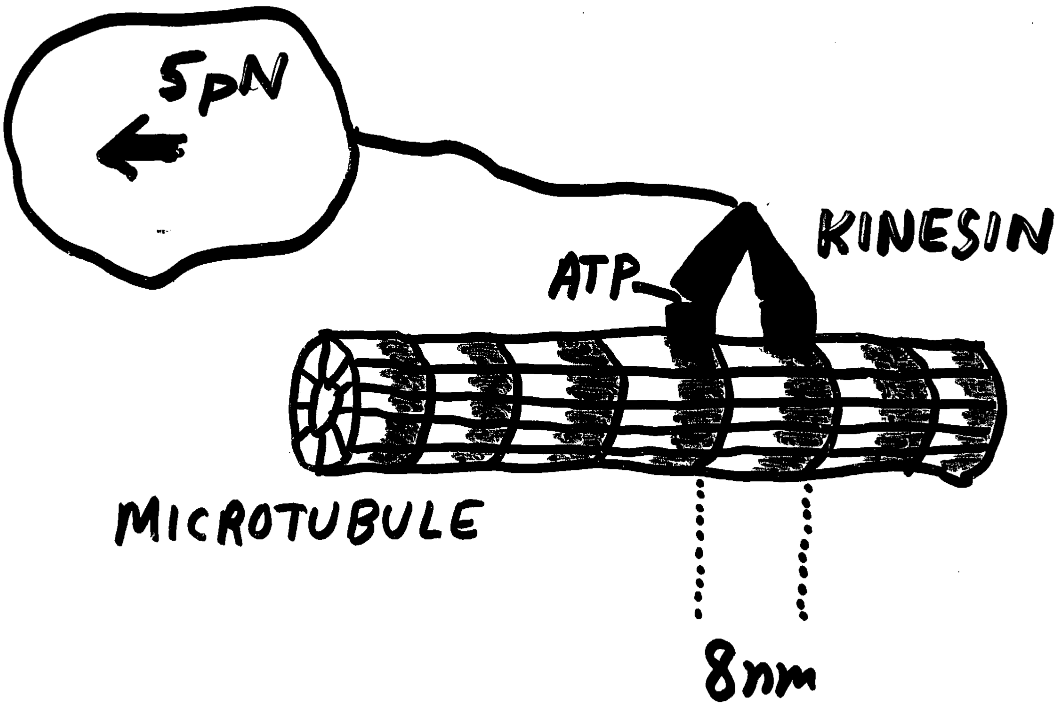
A TWO-FOOTED MOLECULAR WALKER*

Oster / Peskin

* Peskin CS and Oster GF: Coordinated hydrolysis explains the mechanical behavior of kinesin. Biophysical Journal 68: S202-S211, 1995



$k_B T \approx 4\ pN \cdot nm$

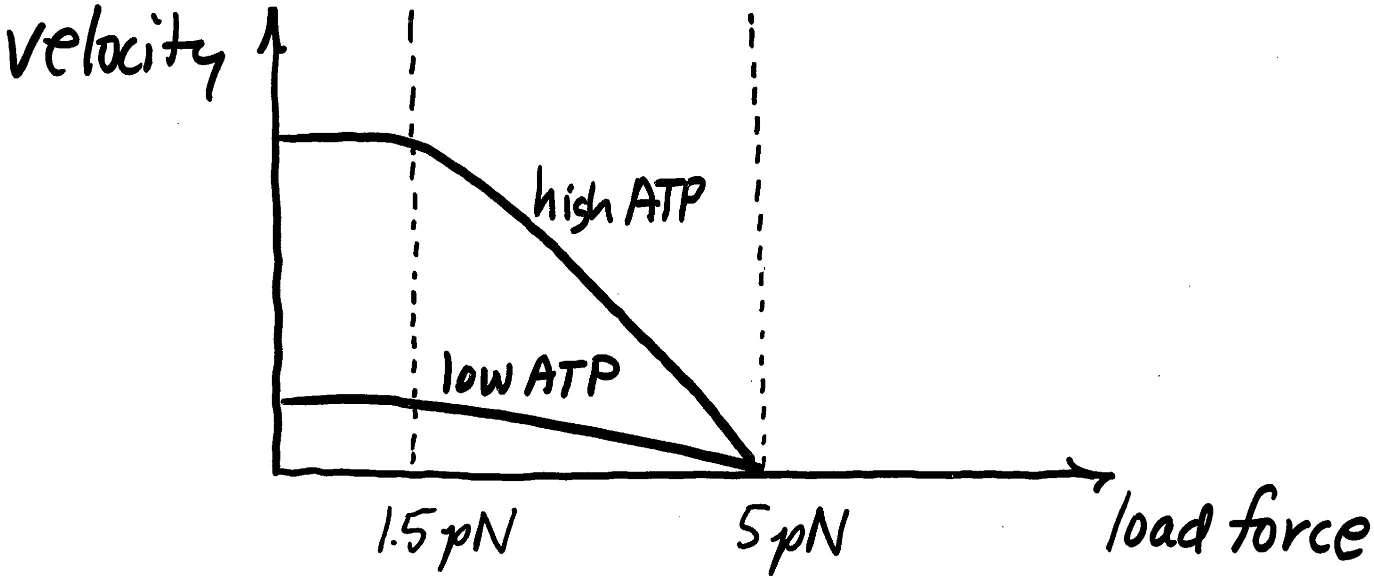
Summary of Experimental Data

Svoboda / Block *

1) Analysis of trajectories reveals 8 nm steps at random times.

2) Stepping times are <u>not</u> Poisson.

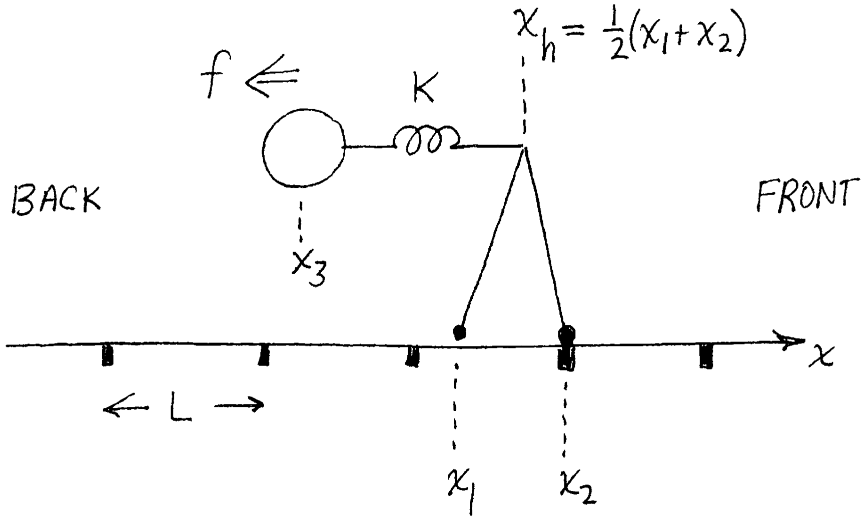
3) Force-velocity curves:



* Nature 365 : 721-727, 1993

C. Peskin 4/22/94

A TWO-FOOT MOLECULAR WALKER



A two-foot walker moves along a molecular track. The track has equally spaced sites, separated by a distance L, where the feet may be bound. At most one foot may be bound to any given site at any given time. The feet may freely pass each other. Let distance along the track be denoted by x, and let x_1 and x_2 be the coordinates of the feet. There is a hinge connecting the two legs of the walker. Let the x coordinate of the hinge be

$$x_h = \frac{1}{2}(x_1 + x_2)$$

We assume that the hinge swings freely within its range of motion, but that it imposes the restriction

$$|x_1 - x_2| \le L$$

The walker is asymmetrical. We may distinguish the <u>front</u> from the <u>back</u>. We assume that the front of the walker faces to the right, in the direction of increasing x.

The walker tows a large bead, the x coordinate of which is denoted x_3. The bead is connected to the hinge of the walker by a linear spring of stiffness K.
A load force f directed to the left (towards the back of the walker) is applied to the bead.
Let D_3 denote the diffusion coefficient of the bead.

Let each foot of the walker have two possible states, denoted 0 and 1, with transition rate constants as follows:

$$0 \underset{\beta(x_h - x)}{\overset{\alpha}{\rightleftarrows}} 1$$

In state 0, the foot in question glides freely along the track and does not interact at all with the binding sites. In state 1, the foot binds to the first empty binding site that it encounters, and we assume that the process of finding an empty site is essentially instantaneous (see below). Once the foot in state 1 becomes bound, it remains bound at the same fixed site until the transition $1 \to 0$ occurs.

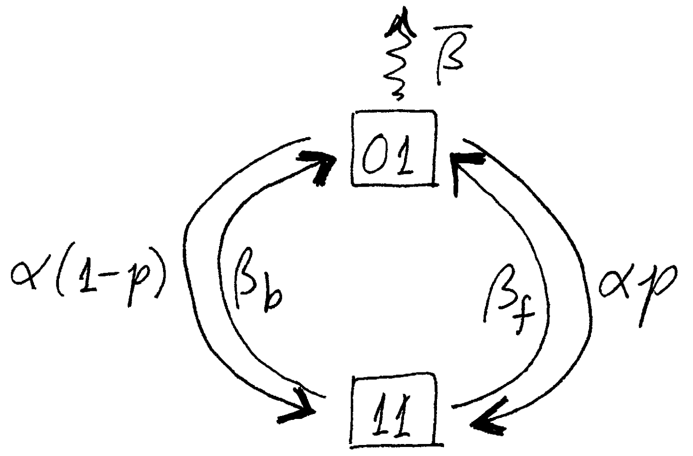
The rate constant for the transition $1 \to 0$ is assumed to depend on the angle that the bound leg makes with the track, this angle being determined by the relative position of the hinge and the foot. Note that

$$\beta_1 = \beta(x_h - x_1) = \beta\left(\frac{x_1 + x_2}{2} - x_1\right) = \beta\left(\frac{x_2 - x_1}{2}\right)$$

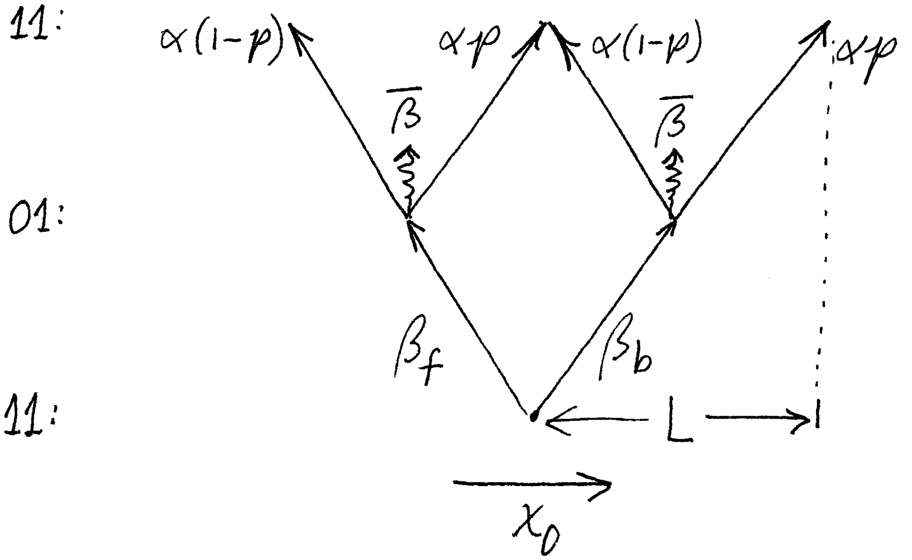
$$\beta_2 = \beta(x_h - x_2) = \beta\left(\frac{x_1 + x_2}{2} - x_2\right) = \beta\left(\frac{x_1 - x_2}{2}\right)$$

This provides a mechanism of interaction between the two feet. Suppose, for example, that β is an increasing function. Then $x_1 < x_2 \Rightarrow \beta_1 > \beta_2$. This means that the back foot is more likely to be picked up than the front foot. It is this asymmetry that drives the walker.

If we ignore the labels "1" and "2" of the feet, the walker as a whole now has just three distinguishable states: 11, $01 \equiv 10$, and 00. In state 00, however, both feet are free, and the walker dissociates from the track, terminating the walk. Therefore, we need only consider states 11 and 01. The possible transitions and the progress of the walker may be depicted as follows:



STATES AND TRANSITIONS



NET PROGRESS

(see next page)

In the diagram on the previous page, the β's are the rate constants for picking up a bound foot. When both feet are bound, β_b is the rate constant for picking up the back foot and β_f is the rate constant for picking up the front foot. When only one foot is bound, $\bar{\beta}$ is the rate constant for picking it up (and terminating the walk). When only one foot is bound, α is the rate constant for binding the free foot and p is the probability that it binds in <u>front</u> of the bound foot (so that $1-p$ is the probability that it binds <u>behind</u> the front foot).

In the lower diagram, which shows the progress of the walker, X_0 represents the position of the <u>hinge</u> when both feet are bound (state 11) and the position of the <u>bound foot</u> when only one foot is bound (state 01). Thus X_0 changes in increments of $\pm L/2$ during the transitions. Over a full cycle $11 \rightarrow 11$, however, the change in X_0 is 0 or $\pm L$.

In the upper diagram, the arrows with clockwise curvature represent forward progress of the walker, and those with counterclockwise curvature represent backwards progress. The net progress of any cycle is depicted, roughly speaking, by the net area enclosed in a clockwise sense.

We now give a more detailed analysis of states 11 and 01. Such analysis is needed to determine the motion of the bead in each case and to find specific expressions for the rate constants of the transitions, some of which are dependent on the position of the bead.

State 11: Both feet bound

In this state the walker is rigid; its feet occupy adjacent sites on the track and the hinge is halfway in between the feet. Let X_0 be the position of the hinge. Then the front foot is at $X_0 + L/2$ and the back foot is at $X_0 - L/2$.

In this situation the bead diffuses in the potential

$$\phi_{11}(X_3, X_0) = f(X_3 - X_0) + \frac{1}{2} K (X_3 - X_0)^2$$

with diffusion coefficient D_3.

The rate constants for leaving state 11 are as follows:

$$\beta_b = \beta\left(X_0 - \left(X_0 - \tfrac{L}{2}\right)\right) = \beta\left(\tfrac{L}{2}\right) = \text{rate constant for picking up } \underline{\text{back}} \text{ foot}$$

$$\beta_f = \beta\left(X_0 - \left(X_0 + \tfrac{L}{2}\right)\right) = \beta\left(-\tfrac{L}{2}\right) = \text{rate constant for picking up } \underline{\text{front}} \text{ foot}$$

STATE 01 ≡ 10 : One foot bound, one foot free.

In this state, let

X_0 = coordinate of bound foot
X = coordinate of free foot

Recall that in state 11, X_0 was the coordinate of the hinge. Thus X_0 jumps $\pm L/2$ during any transition between state 01 and state 11 (in either direction). Between transitions, X_0 is constant.

As long as state 01 persists, we have a coupled diffusion problem to consider involving the free foot (x) and the bead (X_3), with $X_0 - L \le X \le X_0 + L$ and $-\infty < X_3 < \infty$.

The potential energy of this coupled diffusion is as follows

$$\Phi_{01}(X, X_3, X_0) = f(X_3 - X_0) + \frac{1}{2}K\left(\frac{X+X_0}{2} - X_3\right)^2 + W\left(\frac{X+X_0}{2} - X_0\right)$$

$$= f(X_3 - X_0) + \frac{1}{2}K\left(\frac{X-X_0}{2} - (X_3 - X_0)\right)^2 + W\left(\frac{X-X_0}{2}\right)$$

where W gives the potential energy of interaction between the bound leg and the track. This is assumed to depend on the angle of the leg, which is determined by the relative position of the hinge and the bound foot. The second form of Φ_{01} written above emphasizes the fact that $\Phi_{01}(x, x_3, x_0)$ actually depends only on the two variables $x - x_0$ and $x_3 - x_0$.

Instead of studying this coupled diffusion problem in detail, we consider the situation in which the diffusion coefficient D of the free foot is much greater than the diffusion coefficient D_3 of the bead. In fact, we shall let $D \to \infty$. In that limit, the free foot equilibrates instantaneously forming a probability cloud over the interval $[x_0 - L, x_0 + L]$ according to the probability density function

$$\rho(x \mid x_3, x_0) = \frac{\exp\left(-\frac{\Phi_{01}(x, x_3, x_0)}{k_B T}\right)}{\displaystyle\int_{x_0-L}^{x_0+L} \exp\left(-\frac{\Phi_{01}(x', x_3, x_0)}{k_B T}\right) dx'}$$

The notation $\rho(x \mid x_3, x_0)$ indicates that this is a conditional probability density function, given x_3 and x_0. As x_3 changes because of the diffusion of the bead (see below) the probability cloud shifts.

*see Appendix on Free Energy

Under these circumstances ($D \to \infty$), it can be shown* that the bead diffuses as though it were in the effective potential (free energy) given by

$$\Phi_{01}(x_3, x_0) = -k_B T \log \int_{x_0-L}^{x_0+L} \exp\left(-\frac{\Phi_{01}(x, x_3, x_0)}{k_B T}\right) dx$$

with diffusion coefficient D_3. This determines (in a statistical sense) the motion of the bead throughout the duration of the state 01.

We may now consider the processes that terminate the state 01.

First, the bound foot may become free, terminating the entire walk. The rate constant for this process depends on the instantaneous position of the bead, and is obtained by averaging over the various angles assumed by the bound leg during the rapid diffusion of the free leg:

$$\bar{\beta}(x_3, x_0) = \int_{x_0-L}^{x_0+L} \beta\left(\frac{x+x_0}{2} - x_0\right) \rho(x \mid x_3, x_0)\, dx$$

$$= \int_{x_0-L}^{x_0+L} \beta\left(\frac{x-x_0}{2}\right) \rho(x \mid x_3, x_0)\, dx$$

The second possibility is that the free foot becomes bound, taking the system back to the state 11. The rate constant for this process is simply the given parameter α, but does the free foot bind at (X_0+L) or at (X_0-L) ?

let

$$p(x_3,X_0) = \text{probability that the free foot binds at } X_0+L$$

$$1-p(x_3,X_0) = \text{probability that the free foot binds at } X_0-L$$

where X_3 is the position of the bead and X_0 is the position of the bound foot at the instant when the reaction occurs that makes it possible for the free foot to bind to the track.

We can determine $p(x_3,X_0)$ from the following considerations. As soon as the free foot becomes "sticky", it diffuses rapidly until it encounters an empty site on the track, to which it sticks. The two sites available to it are at the ends of its diffusion interval $X_0 \pm L$. On the time scale of the walk as a whole, this process of finding a site is essentially instantaneous $(D\to\infty)$, but we may analyze it on a <u>fast</u> time scale in the following way.

Let τ denote the fast-scale time since the instant that the free foot becomes sticky, and let

$$c(x,\tau \mid x_3, x_0) \qquad J(x,\tau \mid x_3, x_0)$$

be the probability density and flux of the free foot for $\tau > 0$.

On the fast scale of τ, x_3 is a constant. It is the position of the bead at the instant of the transition. Note that x_0 is also constant. It is the position of the bound foot before and during the search of the free foot for an empty site to which it can bind.

For c and J, we have the following equations:

$$\frac{\partial c}{\partial \tau} + \frac{\partial J}{\partial x} = 0$$

$$J = -D\left(\frac{\partial c}{\partial x} + \frac{1}{k_B T} c \frac{\partial \phi_{01}}{\partial x}\right)$$

$$c(x, 0 \mid x_3, x_0) = \rho(x \mid x_3, x_0)$$

$$c(x_0 - L, \tau \mid x_3, x_0) = c(x_0 + L, \tau \mid x_3, x_0) = 0$$

The quantity that we seek to determine is

$$p(x_3, x_0) = \int_0^\infty J(x_0+L, \tau \,|\, x_3, x_0)\, d\tau$$

This suggests that we integrate the diffusion equation with respect to τ over $(0,\infty)$ and introduce the quantity

$$F(x \,|\, x_3, x_0) = \int_0^\infty J(x, \tau \,|\, x_3, x_0)\, d\tau$$

Because of the absorbing boundary conditions, $c \to 0$ as $\tau \to \infty$, and we have

$$0 - \rho(x \,|\, x_3, x_0) + \frac{\partial F}{\partial x}(x \,|\, x_3, x_0) = 0$$

from which it follows that

$$F(x \,|\, x_3, x_0) = F(x_0+L \,|\, x_3, x_0) - \int_x^{x_0+L} \rho(x' \,|\, x_3, x_0)\, dx'$$

$$= p(x_3, x_0) - \int_x^{x_0+L} \rho(x' \,|\, x_3, x_0)\, dx'$$

From the equation for J, we have

$$J \exp \frac{\phi_{01}}{k_B T} = -D \frac{\partial}{\partial x}\left(c \exp \frac{\phi_{01}}{k_B T}\right)$$

$$\int_{x_0-L}^{x_0+L} J \exp\left(\frac{\phi_{01}}{k_B T}\right) dx = 0$$

$$\int_{x_0-L}^{x_0+L} F \exp\left(\frac{\phi_{01}}{k_B T}\right) dx = 0$$

which may also be written

$$\int_{x_0-L}^{x_0+L} F(x|x_3,x_0)\,\sigma(x|x_3,x_0)\,dx = 0$$

where

$$\sigma(x|x_3,x_0) = \frac{\exp\left(\dfrac{\phi_{01}(x,x_3,x_0)}{k_B T}\right)}{\displaystyle\int_{x_0-L}^{x_0+L} \exp\left(\frac{\phi_{01}(x',x_3,x_0)}{k_B T}\right) dx'}$$

Substituting the formula for F at the bottom of p.12 into this integral relation that F must satisfy, we get

$$p(x_3, x_0) = \int_{x_0-L}^{x_0+L} \sigma(x|x_3, x_0) \int_{x}^{x_0+L} \rho(x'|x_3, x_0)\, dx'\, dx$$

It can be checked that $p(x_3, x_0)$ actually depends only on the single variable $x_3 - x_0$.

This formula expresses the influence of the bead on the placement of the free foot as it becomes bound.

```
while (state >= 0 )
  if(state)
      % Both feet bound (11)
      x3 = x3 + dtmu * f11 (x3-xm) + deltax * randn
      r = rand
      if ( r < betab * dt )
           xm = xm + L/2
           state = 0
      elseif ( r < (betab + betaf) * dt )
           xm = xm - L/2
           state = 0
      end
  else
      % One foot bound; one free (01 )
      x3 = x3 + dtmu * f01 (x3-xm) + deltax * randn
      r = rand
      if ( r < alpha * dt )
           state = 1
           if ( rand < p(x3-xm))
                xm = xm + L/2
           else
                xm = xm - L/2
           end
      elseif ( r < alpha * dt + betabar(x3-xm) * dt )
           state = -1   % Walk ends here !
      end
  end
end
```

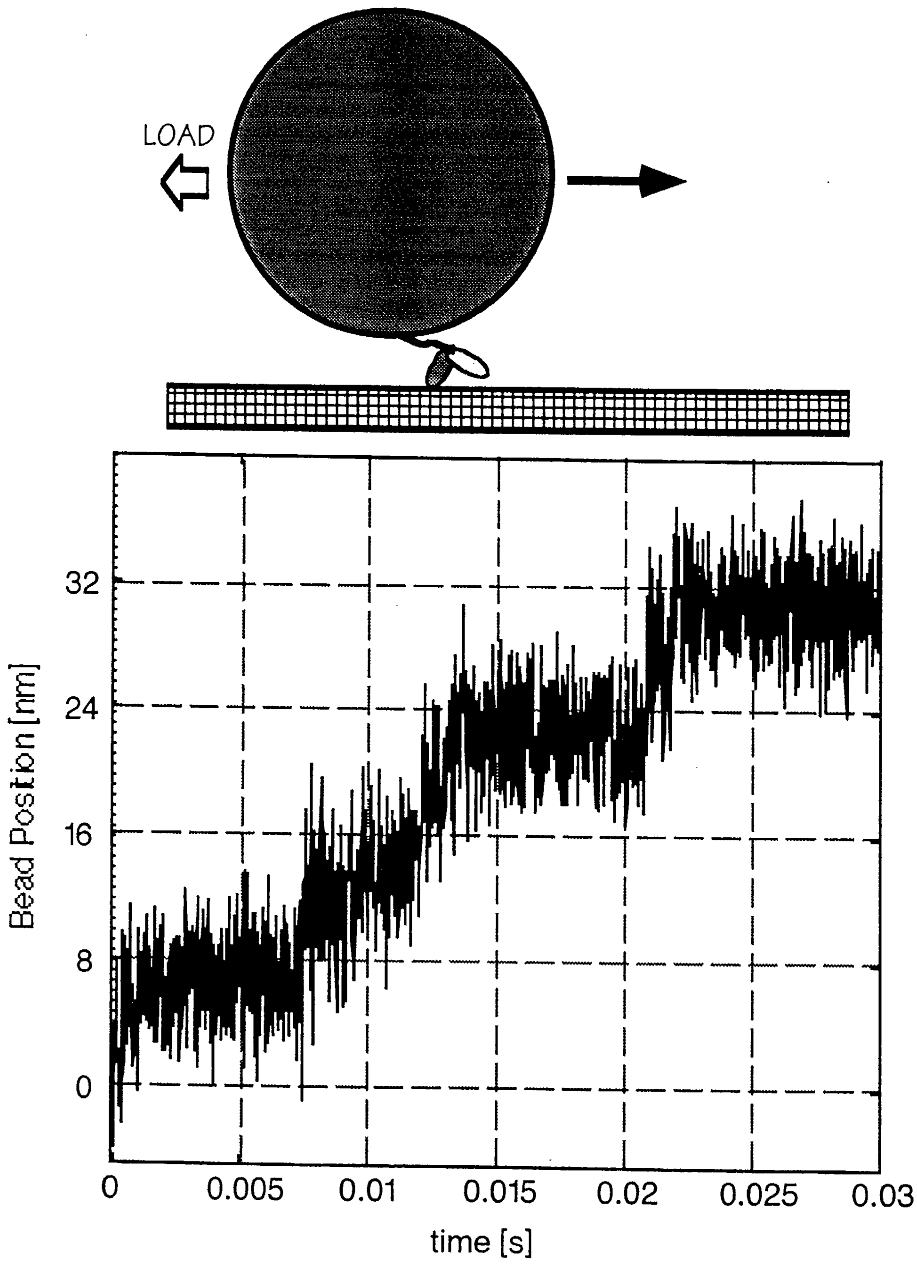
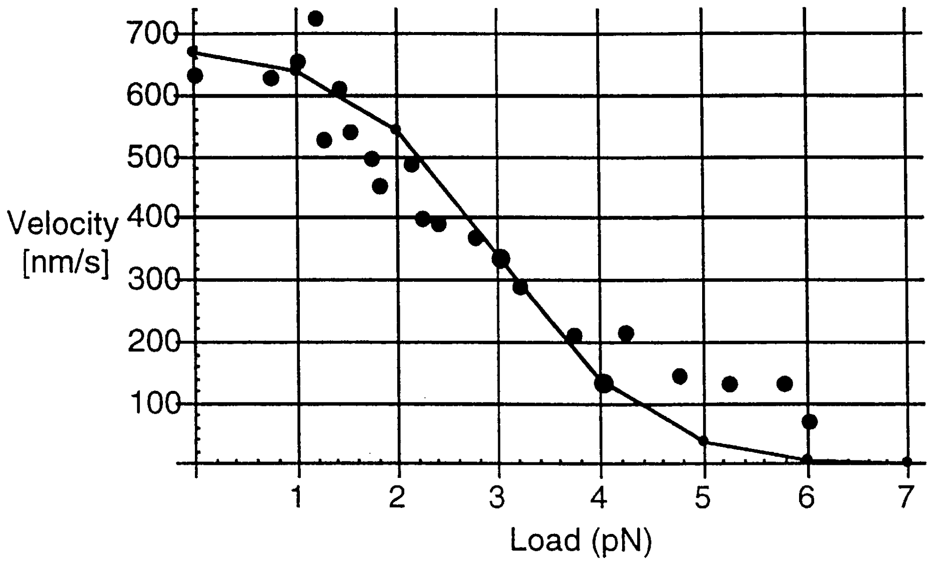
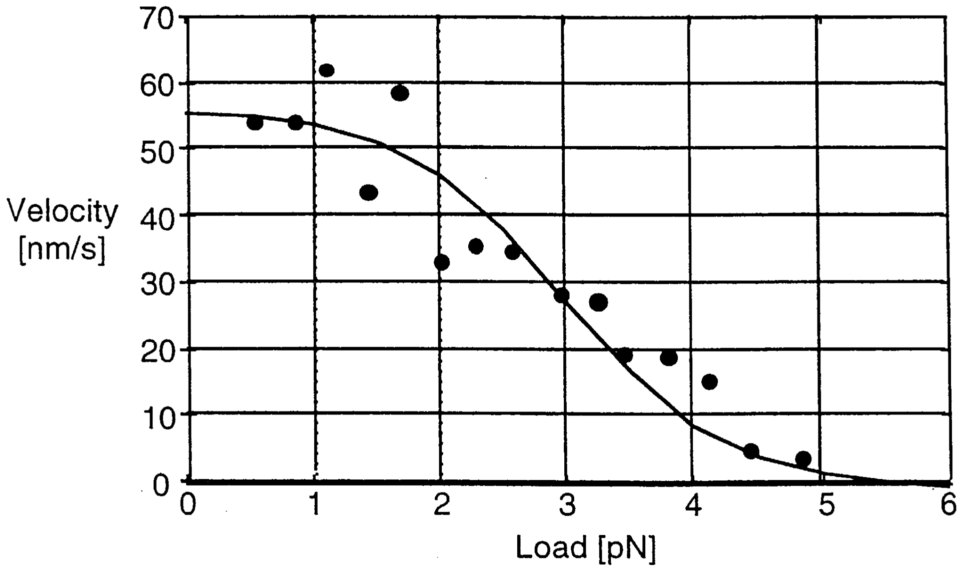

LOAD
32
24
16
8
0
Bead Position [nm]
0
0.005
0.01
0.015
0.02
0.025
0.03
time [s]

Fig. 3


700
600
500
400
300
200
100
Velocity
[nm/s]
1
2
3
4
5
6
7
Load (pN)

(a)


70
60
50
40
30
20
10
0
Velocity
[nm/s]
0
1
2
3
4
5
6
Load [pN]

(b)

Fig. 4

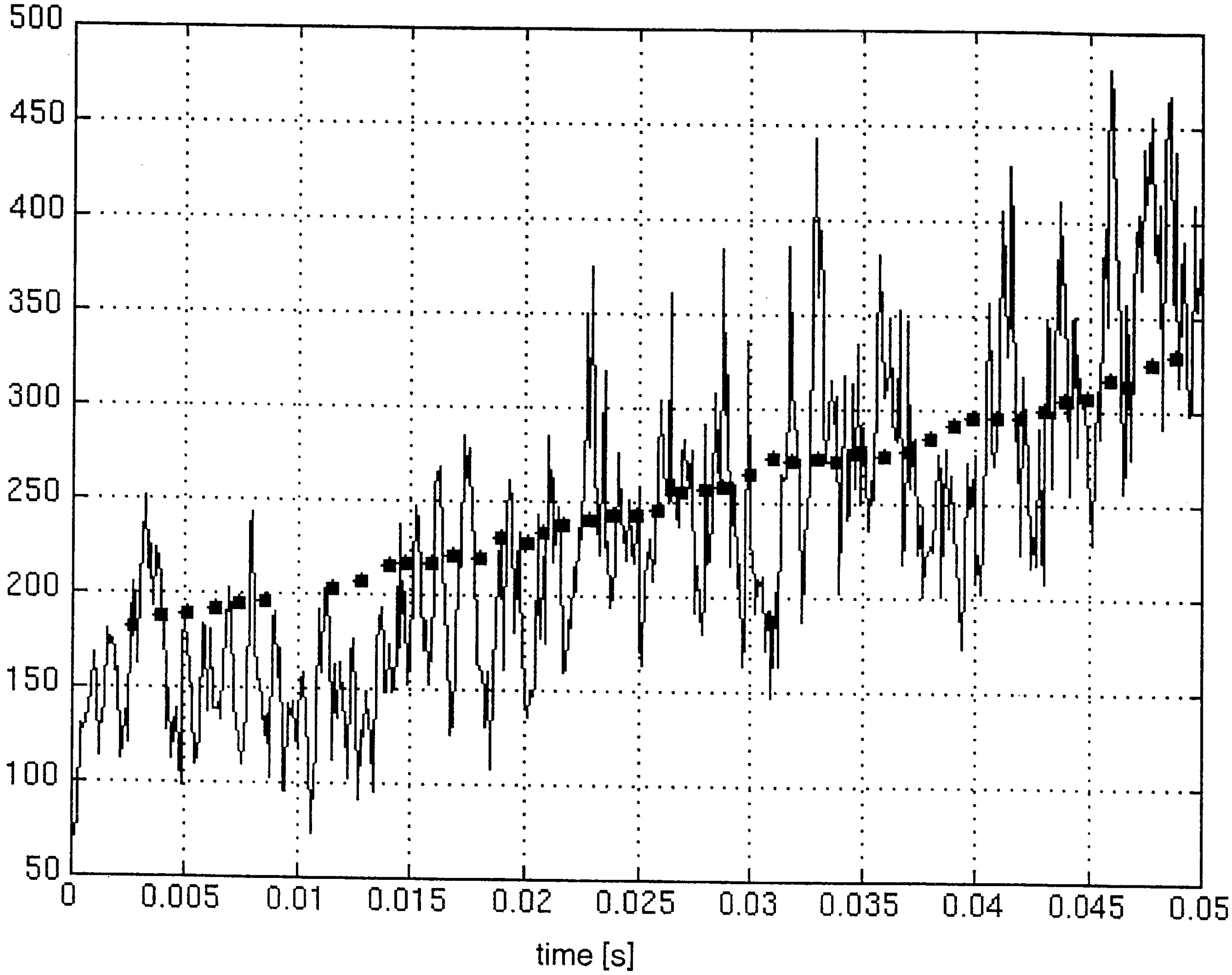

500
450
400
350
300
250
200
150
100
50
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045
0.05
time [s]

Fig. 5

15*

C. Peskin 8/15/94

THE LIMIT OF FAST BEAD DIFFUSION (SLOW REACTION KINETICS)

Suppose

$$\frac{2D_3}{L^2} \gg \alpha$$

and

$$\frac{2D_3}{L^2} \gg \beta(y), \qquad -\frac{L}{2} \le y \le \frac{L}{2}$$

Then we may assume that the bead equilibrates rapidly with the effective potential that it feels in any given state. Accordingly, we may average over all possible positions of the bead.

This has no influence on State 11, in which both feet are bound, since in that state the bead itself has no influence on the behavior of the walker.

In State 01, however, with one foot bound and one foot free, the position of the bead influences

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*Continuation of "A TWO-FOOT MOLECULAR WALKER" (4/22/94) both the rate constant for picking up the bound foot (thereby terminating the walk) and also the probability that the free foot (if it reattaches at all) will reattach in front of the bound foot. These functions of X_3 are given, respectively, by

$$\bar{\beta}(x_3, x_0) = \int_{x_0-L}^{x_0+L} \beta\left(\frac{x-x_0}{2}\right) \rho(x|x_3,x_0)\,dx$$

$$p(x_3,x_0) = \int_{x_0-L}^{x_0+L} \sigma(x|x_3,x_0) \int_{x}^{x_0+L} \rho(x'|x_3,x_0)\,dx'\,dx$$

In both cases, these are actually functions of $x_3 - x_0$, and not of x_3 and x_0 separately. Now the effective potential for x_3, in the state 01 is

$$\Phi_{01}(x_3, x_0) = -k_B T \log \int_{x_0-L}^{x_0+L} \exp\left(-\frac{\phi_{01}(x,x_3,x_0)}{k_B T}\right) dx$$

which is also a function of $x_3 - x_0$. The equilibrium probability density function for the bead in this potential is given by

$$r_{01}(x_3|x_0) = \left[\frac{\exp\left(-\dfrac{\Phi_{01}(x_3,x_0)}{k_B T}\right)}{\displaystyle\int_{-\infty}^{\infty} \exp\left(-\dfrac{\Phi_{01}(x_3',x_0)}{k_B T}\right) dx_3'} \right]$$

$$= \frac{\displaystyle\int_{x_0-L}^{x_0+L} \exp\left(-\dfrac{\phi_{01}(x,x_3,x_0)}{k_B T}\right) dx}{\displaystyle\int_{-\infty}^{\infty}\int_{x_0-L}^{x_0+L} \exp\left(-\dfrac{\phi_{01}(x,x_3',x_0)}{k_B T}\right) dx\, dx_3'}$$

which is actually a function of $x_3 - x_0$. The density $r_{01}(x_3|x_0)$ can be used to compute appropriate weighted averages of $\beta(x_3, x_0)$ and $p(x_3, x_0)$. These are

$$B = \int_{-\infty}^{\infty} r_{01}(x_3|x_0)\,\overline{\beta}(x_3, x_0)\,dx_3$$

$$P = \int_{-\infty}^{\infty} r_{01}(x_3|x_0)\,p(x_3, x_0)\,dx_3$$

Since r_{01}, $\overline{\beta}$, and p are functions only of $x_3 - x_0$, B and P are independent of x_0.

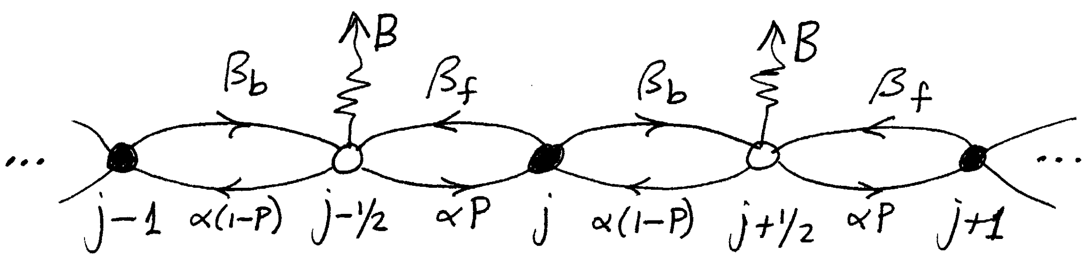
In the State 01, and in the limit under consideration here:

B is the rate constant for the bound foot to become free, terminating the walk.

If the free foot binds, P is the probability that it binds in front of the bound foot, whereas $1-P$ is the probability that it binds in back of the bound foot.

Both B and P are functions of the applied load f.

Now $X_0(t)$ is a sample path of a Markov process with the following state diagram, in which state j denotes $X_0(t) = jL$



Let $C_j(t)$ be the probability of finding the system in state j at time t. For integer values of j, we have the following equations

$$\frac{dC_j}{dt} = \alpha P C_{j-1/2} + \alpha(1-P) C_{j+1/2} - (\beta_b + \beta_f) C_j$$

$$\frac{dC_{j+1/2}}{dt} = \beta_b C_j + \beta_f C_{j+1} - (\alpha + B) C_{j+1/2}$$

Moment equations:

Let

$$M_k = \sum_j j^k c_j$$

$$N_k = \sum_j (j+1/2)^k c_{j+1/2}$$

(sums over integer values of j)
$k = 0, 1, 2, \dots$

We can derive differential equations for $M_k(t)$, $N_k(t)$ as follows. First, consider $k=0$:

$$\frac{d}{dt} M_0 = \alpha P N_0 + \alpha(1-P)N_0 - (\beta_b+\beta_f)M_0$$

$$= \alpha N_0 - (\beta_b+\beta_f)M_0$$

$$\frac{d}{dt} N_0 = (\beta_b+\beta_f)M_0 - (\alpha+B)N_0$$

i.e.

$$\frac{d}{dt}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -(\alpha+B) \end{pmatrix} \begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

Next, consider M_1 and N_1

We have

$$\frac{d}{dt}\left(j C_j\right) = \alpha P\left(j-\tfrac{1}{2}+\tfrac{1}{2}\right) C_{j-1/2}$$

$$+ \alpha(1-P)\left(j+\tfrac{1}{2}-\tfrac{1}{2}\right) C_{j+1/2}$$

$$-(\beta_b+\beta_f)\, j C_j$$

$$= \alpha P\left(j-\tfrac{1}{2}\right) C_{j-1/2} + \alpha(1-P)\left(j+\tfrac{1}{2}\right) C_{j+1/2}$$

$$+ \tfrac{1}{2}\alpha P\, C_{j-1/2} - \tfrac{1}{2}\alpha(1-P)\, C_{j+1/2}$$

$$-(\beta_b+\beta_f)(j C_j)$$

So

$$\frac{d}{dt} M_1 = \alpha N_1 - (\beta_b+\beta_f) M_1 + \alpha\left(P-\tfrac{1}{2}\right) N_0$$

and similarly

$$\frac{d}{dt}\left(\left(j+\tfrac{1}{2}\right)c_{j+1/2}\right) = \beta_b\left(j+1/2\right)c_j$$

$$+\beta_f\left(j+1-\tfrac{1}{2}\right)c_{j+1}$$

$$-(\alpha+B)(j+1/2)\;c_{j+1/2}$$

$$= \beta_b\left(j c_j\right) + \beta_f\,(j+1)\;c_{j+1}$$

$$-(\alpha+B)\,(j+1/2)\,c_{j+1/2}$$

$$+\tfrac{1}{2}\beta_b c_j - \tfrac{1}{2}\beta_f\,c_{j+1}$$

so

$$\frac{d}{dt}N_1 = (\beta_b+\beta_f)M_1 - (\alpha+B)N_1$$

$$+\tfrac{1}{2}(\beta_b-\beta_f)M_0$$

In summary

$$\frac{d}{dt}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -(\alpha+B) \end{pmatrix}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix}$$

$$+\begin{pmatrix} 0 & \alpha(P-\frac{1}{2}) \\ \frac{1}{2}(\beta_b-\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

Finally, consider M_2 and N_2:

$$\frac{d}{dt}\left(j^2 c_j\right) = \alpha P\left(j-\tfrac{1}{2}+\tfrac{1}{2}\right)^2 c_{j-1/2}$$

$$+\alpha(1-P)\left(j+\tfrac{1}{2}-\tfrac{1}{2}\right)^2 c_{j+1/2} - (\beta_b+\beta_f)\, j^2 c_j$$

$$= \alpha P\left(j-\tfrac{1}{2}\right)^2 c_{j-1/2} + \alpha P\left(j-\tfrac{1}{2}\right) c_{j-1/2} + \alpha P \tfrac{1}{4} c_{j-1/2}$$

$$+\alpha(1-P)\left(j+\tfrac{1}{2}\right)^2 c_{j+1/2} - \alpha(1-P)\left(j+\tfrac{1}{2}\right) c_{j+1/2} + \alpha(1-P)\tfrac{1}{4} c_{j+\frac{1}{2}}$$

$$-(\beta_b+\beta_f)\, j^2 c_j$$

which implies

$$\frac{d}{dt} M_2 = \alpha N_2 - (\beta_b + \beta_f) M_2 + 2\alpha\left(P - \frac{1}{2}\right) N_1 + \frac{1}{4}\alpha N_0$$

Similarly:

$$\frac{d}{dt}\left(\left(j+\frac{1}{2}\right)^2 C_{j+1/2}\right) = \beta_b\left(j+\frac{1}{2}\right)^2 C_j + \beta_f\left(j+1-\frac{1}{2}\right)^2 C_{j+1} - (\alpha+B)\left(j+\frac{1}{2}\right)^2 C_{j+1/2}$$

$$= \beta_b j^2 C_j + \beta_b j C_j + \beta_b \frac{1}{4} C_j$$

$$+ \beta_f (j+1)^2 C_{j+1} + \beta_f (j+1) C_{j+1} + \beta_f \frac{1}{4} C_{j+1}$$

$$- (\alpha + B)\left(j+\frac{1}{2}\right)^2 C_{j+1/2}$$

which implies

$$\frac{d}{dt} N_2 = (\beta_b + \beta_f) M_2 - (\alpha + B) N_2 + (\beta_b - \beta_f) M_1$$

$$+ \frac{1}{4}(\beta_b + \beta_f) M_0$$

In summary, the equations for M_2, N_2 are

$$\frac{d}{dt}\begin{pmatrix} M_2 \\ N_2 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -(\alpha+B) \end{pmatrix}\begin{pmatrix} M_2 \\ N_2 \end{pmatrix}$$

$$+\begin{pmatrix} 0 & 2\alpha\left(P-\frac{1}{2}\right) \\ (\beta_b-\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix}$$

$$+\begin{pmatrix} 0 & \frac{1}{4}\alpha \\ \frac{1}{4}(\beta_b+\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

Suppose $B=0.$* Then

$$\frac{d}{dt}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -\alpha \end{pmatrix}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

$$\frac{d}{dt}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -\alpha \end{pmatrix}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix}$$

$$+\begin{pmatrix} 0 & \alpha(P-\frac{1}{2}) \\ \frac{1}{2}(\beta_b-\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

$$\frac{d}{dt}\begin{pmatrix} M_2 \\ N_2 \end{pmatrix} = \begin{pmatrix} -(\beta_b+\beta_f) & \alpha \\ (\beta_b+\beta_f) & -\alpha \end{pmatrix}\begin{pmatrix} M_2 \\ N_2 \end{pmatrix}$$

$$+2\begin{pmatrix} 0 & \alpha(P-\frac{1}{2}) \\ \frac{1}{2}(\beta_b-\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_1 \\ N_1 \end{pmatrix}$$

$$+\frac{1}{4}\begin{pmatrix} 0 & \alpha \\ (\beta_b+\beta_f) & 0 \end{pmatrix}\begin{pmatrix} M_0 \\ N_0 \end{pmatrix}$$

*From here on, we neglect the probability that the walker dissociates from the track.

The equations for (M_0, N_0) have a steady solution, which we normalize to $M_0 + N_0 = 1$:

$$M_0 = \frac{\alpha}{\alpha + \beta_b + \beta_f}$$

$$N_0 = \frac{\beta_b + \beta_f}{\alpha + \beta_b + \beta_f}$$

Adding the equations for (M_1, N_1) we find the mean velocity of the system

$$v = L \frac{d}{dt}(M_1 + N_1)$$

$$= L\left[\frac{1}{2}(\beta_b - \beta_f)\frac{\alpha}{\alpha + \beta_b + \beta_f} + \alpha\left(P - \frac{1}{2}\right)\frac{\beta_b + \beta_f}{\alpha + \beta_b + \beta_f}\right]$$

$$= L\frac{\alpha}{\alpha + \beta_b + \beta_f}\left[\frac{1}{2}(\beta_b - \beta_f) + \left(P - \frac{1}{2}\right)(\beta_b + \beta_f)\right]$$

For example, suppose

$$\beta_b = \beta_b^0 \frac{[ATP]}{K_{ATP}}$$

$$\beta_f = \beta_f^0 \frac{[ATP]}{K_{ATP}}$$

$$v = L \frac{\alpha \frac{[ATP]}{K_{ATP}}}{\alpha + (\beta_b^0 + \beta_f^0)\frac{[ATP]}{K_{ATP}}} \left[\frac{1}{2}(\beta_b^0 - \beta_f^0) + (P - \tfrac{1}{2})(\beta_b^0 + \beta_f^0) \right]$$

where $P = P(f)$

Note that the equation for the stall force is

$$\frac{1}{2}(\beta_b^0 - \beta_f^0) + (P - \tfrac{1}{2})(\beta_b^0 + \beta_f^0) = 0$$

or

$$P = \frac{\frac{1}{2}(\beta_b^0 + \beta_f^0) - \frac{1}{2}(\beta_b^0 - \beta_f^0)}{\beta_b^0 + \beta_f^0} = \frac{\beta_f^0}{\beta_b^0 + \beta_f^0}$$

i.e. kinesin stalls when the probability of binding in front equals the probability of picking up the front foot.

We also need some information about M_1 and N_1 separately

$$\frac{dM_1}{dt} = -(\beta_b+\beta_f)M_1 + \alpha N_1 + \alpha\left(P-\tfrac{1}{2}\right) N_0$$

$$\frac{dN_1}{dt} = (\beta_b+\beta_f)M_1 - \alpha N_1 + \tfrac{1}{2}(\beta_b-\beta_f) M_0$$

$$\frac{d}{dt}\left(\frac{M_1}{M_0}\right) = -(\beta_b+\beta_f)\frac{M_1}{M_0} + \alpha \frac{N_1}{N_0}\,\frac{N_0}{M_0} + \alpha\left(P-\tfrac{1}{2}\right)\frac{N_0}{M_0}$$

$$\frac{d}{dt}\left(\frac{N_1}{N_0}\right) = (\beta_b+\beta_f)\frac{M_1}{M_0}\,\frac{M_0}{N_0} - \alpha \frac{N_1}{N_0} + \tfrac{1}{2}(\beta_b-\beta_f)\frac{M_0}{N_0}$$

$$\frac{d}{dt}\left(\frac{M_1}{M_0}\right) = -(\beta_b+\beta_f)\left(\frac{M_1}{M_0}\right) + (\beta_b+\beta_f)\left(\frac{N_1}{N_0}\right) + \left(P-\tfrac{1}{2}\right)(\beta_b+\beta_f)$$

$$\frac{d}{dt}\left(\frac{N_1}{N_0}\right) = \alpha\left(\frac{M_1}{M_0}\right) - \alpha\left(\frac{N_1}{N_0}\right) + \tfrac{1}{2}(\beta_b-\beta_f)\frac{\alpha}{\beta_b+\beta_f}$$

Subtracting these equations, we find:

$$\frac{d}{dt}\left(\frac{M_1}{M_0}-\frac{N_1}{N_0}\right) = -(\alpha+\beta_b+\beta_f)\left(\frac{M_1}{M_0}-\frac{N_1}{N_0}\right)$$

$$+\left(P-\frac{1}{2}\right)(\beta_b+\beta_f) - \frac{1}{2}(\beta_b-\beta_f)\frac{\alpha}{\beta_b+\beta_f}$$

Therefore, as $t \to \infty$

$$\left(\frac{M_1}{M_0}-\frac{N_1}{N_0}\right) \to \frac{\left(P-\frac{1}{2}\right)(\beta_b+\beta_f) - \frac{1}{2}\left(\frac{\beta_b-\beta_f}{\beta_b+\beta_f}\right)\alpha}{\alpha+\beta_b+\beta_f}$$

We can now analyze the variance:

$$\text{Variance} = L^2\left[(M_2+N_2)-(M_1+N_1)^2\right]$$

$$\frac{d}{dt}\text{Variance} = L^2\left[\frac{d}{dt}(M_2+N_2) - 2(M_1+N_1)\frac{d}{dt}(M_1+N_1)\right]$$

$$\frac{d}{dt}(M_2+N_2) = 2\left[\tfrac{1}{2}(\beta_b-\beta_f)M_1 + \alpha\left(P-\tfrac{1}{2}\right)N_1\right] + \frac{1}{2}\,\frac{\alpha(\beta_b+\beta_f)}{\alpha+\beta_b+\beta_f}$$

$$\frac{d}{dt}(M_1+N_1) = \frac{1}{2}(\beta_b-\beta_f)\frac{\alpha}{\alpha+\beta_b+\beta_f} + \alpha\left(P-\frac{1}{2}\right)\frac{\beta_b+\beta_f}{\alpha+\beta_b+\beta_f}$$

$$= \left[\tfrac{1}{2}(\beta_b-\beta_f)M_0 + \alpha\left(P-\tfrac{1}{2}\right)N_0\right]$$

$$2(M_1+N_1)\frac{d}{dt}(M_1+N_1) = 2\left[\tfrac{1}{2}(\beta_b-\beta_f)M_0(M_1+N_1) + \alpha\left(P-\tfrac{1}{2}\right)N_0(M_1+N_1)\right]$$

$$\frac{d}{dt}(M_2+N_2)-2(M_1+N_1)\frac{d}{dt}(M_1+N_1)$$

$$= \frac{1}{2}\,\frac{\alpha(\beta_b+\beta_f)}{\alpha+\beta_b+\beta_f}$$

$$+2\Big[\tfrac{1}{2}(\beta_b-\beta_f)\{(1-M_0)M_1-M_0N_1\}$$

$$+\alpha\left(P-\tfrac{1}{2}\right)\{(1-N_0)N_1-N_0M_1\}\Big]$$

$$= \frac{1}{2}\,\frac{\alpha(\beta_b+\beta_f)}{\alpha+\beta_b+\beta_f}$$

$$+2\left[\tfrac{1}{2}(\beta_b-\beta_f)(N_0M_1-M_0N_1)+\alpha\left(P-\tfrac{1}{2}\right)(M_0N_1-N_0M_1)\right]$$

$$= \frac{1}{2}\,\frac{\alpha(\beta_b+\beta_f)}{\alpha+\beta_b+\beta_f}+2M_0N_0\left[\tfrac{1}{2}(\beta_b-\beta_f)-\alpha\left(P-\tfrac{1}{2}\right)\right]\left[\frac{M_1}{M_0}-\frac{N_1}{N_0}\right]$$

Let $\boxed{\begin{aligned}\gamma &= \beta_b + \beta_f \\ \delta &= \beta_b - \beta_f\end{aligned}}$

We have

$$M_0 = \frac{\alpha}{\alpha+\gamma} \quad , \quad N_0 = \frac{\gamma}{\alpha+\gamma}$$

and, according to our previous result for large t,

$$\left(\frac{M_1}{M_0} - \frac{N_1}{N_0}\right) = \frac{\left(P-\frac{1}{2}\right)\gamma - \frac{\alpha}{\gamma}\frac{\delta}{2}}{\alpha+\gamma}$$

Therefore

$$\frac{d}{dt}(\text{Variance}) = L^2\left[\frac{1}{2}\frac{\alpha\gamma}{\alpha+\gamma} - 2\frac{\alpha\gamma}{(\alpha+\gamma)^3}\left(\alpha\left(P-\tfrac{1}{2}\right)-\frac{\delta}{2}\right)\left(\gamma\left(P-\tfrac{1}{2}\right)-\frac{\alpha}{\gamma}\frac{\delta}{2}\right)\right]$$

$$= \frac{1}{2}L^2\frac{\alpha\gamma}{\alpha+\gamma}\left(1 - \frac{4\left(\alpha\left(P-\frac{1}{2}\right)-\frac{\delta}{2}\right)\left(\gamma\left(P-\frac{1}{2}\right)-\frac{\alpha}{\gamma}\frac{\delta}{2}\right)}{(\alpha+\gamma)^2}\right)$$

As a check, prove that $\frac{d}{dt}(\text{Variance}) \geq 0$:

Since $\delta = \beta_b - \beta_f$ and $\gamma = \beta_b + \beta_f$,

we have $|\delta| \leq \gamma$. Also, since $0 \leq P \leq 1$,

$|P - \frac{1}{2}| \leq \frac{1}{2}$

Therefore

$$\left| 4\left(\alpha\left(P-\tfrac{1}{2}\right) - \frac{\delta}{2}\right)\left(\gamma\left(P-\tfrac{1}{2}\right) - \frac{\alpha}{\gamma}\frac{\delta}{2}\right)\right|$$

$$= \left| 4\alpha\gamma\left(P-\tfrac{1}{2}\right)^2 + \frac{\alpha\delta^2}{\gamma} - 2\delta\left(P-\tfrac{1}{2}\right)\left(\gamma + \frac{\alpha^2}{\gamma}\right)\right|$$

$$\leq \alpha\gamma + \alpha\gamma + \gamma\left(\gamma + \frac{\alpha^2}{\gamma}\right)$$

$$= 2\alpha\gamma + \gamma^2 + \alpha^2 = (\alpha+\gamma)^2$$

As another check, consider the changes

$$P \to (1-P)$$

$$\beta_b \to \beta_f$$

$$\beta_f \to \beta_b$$

This interchanges the front and back feet. It changes the sign of δ and of $P-\frac{1}{2}$, so it leaves the variance unchanged.

Instructive Special Case: $P = 1$ and $\beta_f = 0$

Then $\gamma = \delta = \beta_b$, and

$$\frac{d}{dt}(\text{Variance}) = \frac{1}{2} L^2 \frac{\alpha\beta_b}{\alpha+\beta_b}\left(1 - \frac{(\alpha-\beta_b)(\beta_b-\alpha)}{(\alpha+\beta_b)^2}\right)$$

$$= \frac{1}{2} L^2 \frac{\alpha\beta_b}{\alpha+\beta_b}\left(1 + \frac{(\alpha-\beta_b)^2}{(\alpha+\beta_b)^2}\right)$$

Recall that the mean velocity in this case is

$$v = L\frac{\alpha\beta_b}{\alpha+\beta_b}$$

Thus

$$\boxed{\frac{1}{2} L v \le \frac{d}{dt}(\text{Variance}) \le L v}$$

The minimum is achieved by setting $\alpha = \beta_b$, and the maximum by making α and β_b very different.

Peskin 9/24/96

Appendix:

Free Energy

Consider a coupled diffusion

$$\frac{\partial c}{\partial t} + \frac{\partial J_x}{\partial x} + \frac{\partial J_y}{\partial y} = 0$$

$$J_x = -D_x \left(\frac{\partial c}{\partial x} + \frac{c}{k_B T} \frac{\partial \phi}{\partial x} \right)$$

$$J_y = -D_y \left(\frac{\partial c}{\partial y} + \frac{c}{k_B T} \frac{\partial \phi}{\partial y} \right)$$

where $\phi(x,y)$ is some given potential.

Let $D_x \to \infty$. Then J_x remains finite only if

$$\frac{\partial c}{\partial x} + \frac{c}{k_B T} \frac{\partial \phi}{\partial x} = 0$$

so

$$c(x,y,t) = \bar{c}(y,t) \frac{\exp\left(-\frac{\phi(x,y)}{k_B T}\right)}{\int_{-\infty}^{\infty} \exp\left(-\frac{\phi(x',y)}{k_B T}\right) dx'}$$

F2

Note that

$$\overline{C}(y,t) = \int_{-\infty}^{\infty} C(x,y,t)\, dx$$

and define

$$\overline{J_y}(y,t) = \int_{-\infty}^{\infty} J_y(x,y,t)\, dx$$

Then

$$\frac{\partial \overline{C}}{\partial t} + \frac{\partial \overline{J_y}}{\partial y} = 0$$

Since $\displaystyle\int_{-\infty}^{\infty} \frac{\partial J_x}{\partial x}\, dx = 0$

(no flux at ∞)

Also

$$\overline{J_y}(y,t) = -D_y\left(\frac{\partial \overline{C}}{\partial y} + \frac{1}{k_B T}\int_{-\infty}^{\infty} C(x,y,t)\,\frac{\partial \phi}{\partial y}(x,y)\, dx\right)$$

F3

But

$$\int_{-\infty}^{\infty} C(x,y,t)\, \frac{\partial \phi}{\partial y}(x,y)\, dx$$

$$= \bar{C}(y,t)\, \frac{\int_{-\infty}^{\infty} \exp\left(-\frac{\phi(x,y)}{k_B T}\right) \frac{\partial \phi}{\partial y}(x,y)\, dx}{\int_{-\infty}^{\infty} \exp\left(-\frac{\phi(x,y)}{k_B T}\right) dx}$$

$$= \bar{C}(y,t)\, \frac{\partial}{\partial y}\, \Phi(y)$$

where $\Phi(y) = -k_B T \log \int_{-\infty}^{\infty} \exp\left(-\frac{\phi(x,y)}{k_B T}\right) dx$

Φ is the "free energy" or "effective potential" since

$$\overline{J_y}\,(y,t) = -D_y \left(\frac{\partial \bar{C}}{\partial y} + \frac{1}{k_B T}\, \bar{C}\, \frac{\partial \Phi}{\partial y} \right)$$