Supplementary material S2: Deriving the unbinding rate

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March 9, 2009

We now introduce a simple mechanical model from which we will derive the unbinding rate $k_a^-(x)$ and the binding rate $k_a(x)$ using the two dimensional form of Kramers' theory:

$$k_a^- = \frac{1}{2\pi\gamma}\sqrt{\frac{|\lambda_1^\ddagger|\lambda_1^a\lambda_2^a}{\lambda_2^\ddagger}}\exp\left(\frac{-V^\ddagger + V_b^0}{k_{\mathrm{B}}T}\right) \tag{1}$$

Where $\lambda_1^\ddagger$ is the negative eigenvalue of the Hessian of the potential energy surface at the transition state, λ_i^a are the eigenvalues of the Hessian at the bound state. Note that a similar expression exists for k_a, the binding rate, but in this expression we evaluate the Hessian at the unbound state. Equation 1 is the Kramers' theory expression for a two dimensional potential energy surface.

Consider myosin interacting with actin. We might expect, for small displacements, that the mechanics of this system are well-modeled by a point mass moving in 2D attached to a linear, zero-length spring. At any given time, the position of the actin binding site on myosin is $\boldsymbol{\varepsilon} = \varepsilon_1\boldsymbol{i} + \varepsilon_2\boldsymbol{j}$. We may assume that the spring is fixed in space, attached at a point we arbitrarily call $0\boldsymbol{i} + 0\boldsymbol{j}$. Some distance $\boldsymbol{\varepsilon}_0 = x\boldsymbol{i} + L\boldsymbol{j}$ away, there is a binding site (see Fig. 1). The spring creates a potential that may be described as:

$$V_s = \frac{k}{2}(\varepsilon_1^2 + \varepsilon_2^2)$$

the binding site creates a potential well $V_b(\boldsymbol{\varepsilon})$ that, for simplicity, we assume to be deep and narrow.

In this simple mechanical model, there are two states. The system can be bound (i.e. in the basin of attraction of the binding site) or the system can be unbound (i.e. in the basin of attraction of the spring's potential well). Using Kramers' theory (Eq. 1), we can write an expression for the rate constant for binding, $k_a(x)$, where x is the distance between the center of the binding site and the attachment point of the spring.

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First, however, we need expressions for $V_u(x)$ and $V^\ddagger(x)$. Assuming that the binding site is narrow, its position will have a negligible effect on $V_u(x)$, and so we may write $V_u(x) = V_j^0 = 0$. We expect that the exact shape of the binding site will have a minor effect on the rate constant, so here we posit a rather unphysical potential to ease the mathematics. Later, we show that our result is independent of this assumption. Thus, we define:

$$V_b(\varepsilon) = -E_b \exp\left(-\frac{(\varepsilon - \varepsilon_0)^2}{2\sigma^2}\right)$$

So that

$$V(\varepsilon) = \frac{k}{2}\varepsilon^2 - E_b \exp\left(-\frac{(\varepsilon - \varepsilon_0)^2}{2\sigma^2}\right)$$

Note that $\varepsilon_0 = x\mathbf{i} + L\mathbf{j}$ and $\varepsilon = \varepsilon_1\mathbf{i} + \varepsilon_2\mathbf{j}$. Thus,

$$\frac{\partial V(\varepsilon)}{\partial \varepsilon_1} = k\varepsilon_1 + \frac{E_b(\varepsilon_1 - x)}{\sigma^2}\exp\left(-\frac{(\varepsilon - \varepsilon_0)^2}{2\sigma^2}\right)$$

and

$$\frac{\partial V(\varepsilon)}{\partial \varepsilon_2} = k\varepsilon_2 + \frac{E_b(\varepsilon_2 - L)}{\sigma^2}\exp\left(-\frac{(\varepsilon - \varepsilon_0)^2}{2\sigma^2}\right)$$

If the binding site is narrow and deep, then $\varepsilon \approx \mathbf{0}$ will cause both partial derivatives to disappear and will therefore be the critical point associated with the unbound state. Neglecting terms of order $\sigma^2 k/(\sigma^2 k + E_b)$, $\varepsilon \approx \varepsilon_0$ will cause both partial derivatives to disappear and will therefore be the critical point associated with the bound state.

For a circular potential well, the three critical points (the bound, unbound and transition states) must lie on a straight line by symmetry arguments. If this potential well is relatively deep and narrow, we might expect that the distance from the bound state to the transition state, w, is approximately constant with x. Then, from geometry, we may derive the following expressions for $\varepsilon_1^\ddagger(x)$ and $\varepsilon_2^\ddagger(x)$ as shown in Fig. 1c and d:

$$\varepsilon_1^\ddagger(x) = x - \frac{wx}{\sqrt{x^2 + L^2}}$$

and

$$\varepsilon_2^\ddagger(x) = L - \frac{wL}{\sqrt{x^2 + L^2}}$$

Note that these results are independent of the exact form of the binding well, provided that it is approximately circular. These expressions do an adequate job of predicting the exact position of the transition state (see Fig. 1b); though, since w is not exactly a constant we may use slightly different values for w to best-fit different sections of the x-dependence of the transition state.

Therefore, we may write $V^\ddagger$

$$V^\ddagger \approx V_0^\ddagger - \frac{k}{2}(L - w)^2 + \frac{k}{2}\left(\left(x - \frac{wx}{\sqrt{L^2 + x^2}}\right)^2 + \left(L - \frac{wL}{\sqrt{L^2 + x^2}}\right)^2\right)$$
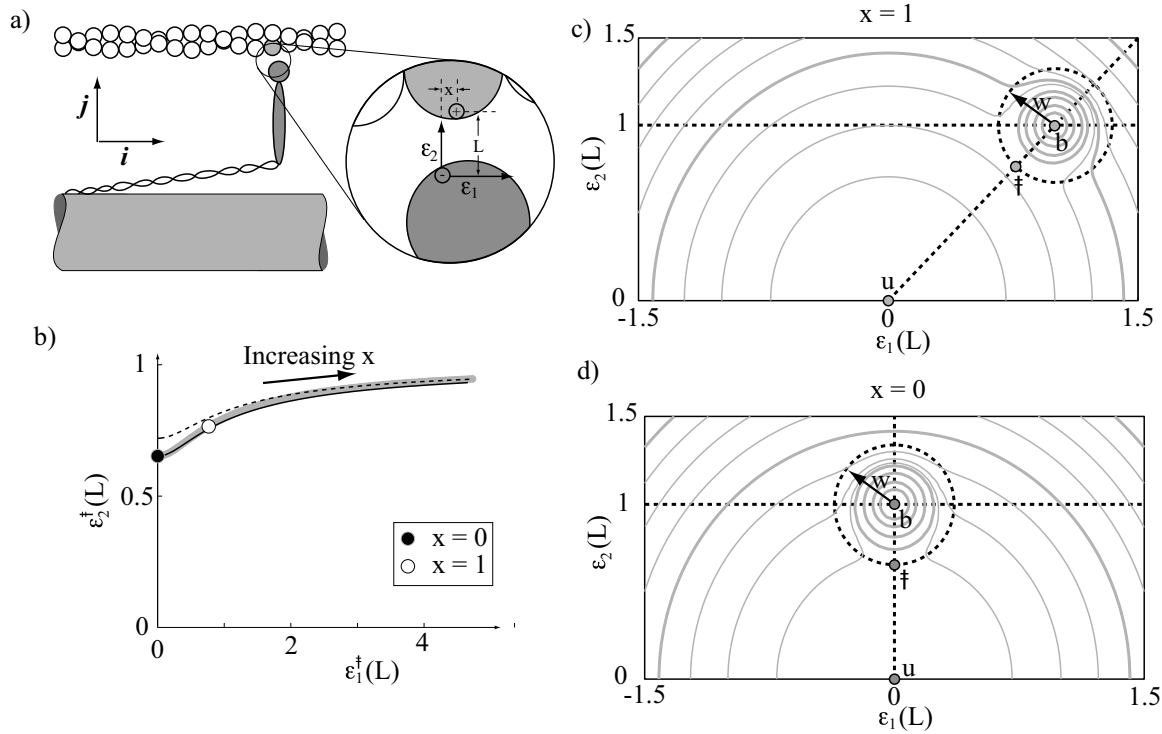
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Figure 1: The potential energy surface for the mechanical model and estimates of the position of the transition state. a) schematic of the mechanical model. A binding site (denoted with the "+" sign) interacts with the actin binding domain of myosin (denoted with the "-" sign). Note that we use these signs for simplicity, we do not mean to imply that the binding interaction is electrostatic in nature. The position of the binding site relative to the equilibrium position of the actin binding site of myosin is denoted $x\boldsymbol{i} + L\boldsymbol{j}$. The position of the actin binding domain is $\varepsilon_1\boldsymbol{i} + \varepsilon_2\boldsymbol{j}$. b) a plot of transition state position as a function of x. Gray dots are numerical simulations. Both solid curves are analytic estimates that assume the width of the binding well w is constant as described in the text. Since w is not exactly constant, different estimates of w fit different parts of the data better. The solid black curve uses an estimate of w that fits the first part (low x) of the curve, and dashed curve uses an estimate of w that fits the large x region. Right, contour plots of potential energy (units of $k_\mathrm{B}T$) as a function of the two spatial dimensions ε_1 and ε_2. The bound (b), unbound (u) and transition (‡) state are shown as gray dots. Two different values of x are shown: c) is $x = 1$ and d) is $x = 0$.

Thus, since the potential energy of the unbound state is 0 for any value of x:

$$k_a(x) = \frac{k}{2\pi\gamma}\sqrt{\frac{\lambda_1^\ddagger}{\lambda_2^\ddagger}}\exp\left(\frac{-V_0^\ddagger}{k_\mathrm{B}T}\right)\exp\left(\frac{k(L-w)^2}{2k_\mathrm{B}T}\right)\exp\left(-\frac{k(x^2+L^2)(1-w/\sqrt{L^2+x^2})^2}{2k_\mathrm{B}T}\right)$$

Where $V_0^\ddagger$ is the potential energy of the transition state when $x = 0$. While, in general $\lambda_i^\ddagger$ could be a function of x, if the binding well is very steep then this will be a very weak function, so we assume it to be a constant. We can define the variable k_a^0 to be the reaction rate when $x = 0$

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– i.e. the maximum reaction rate. Then, we may write:

$$k_a(x) = k_a^0 \exp\left(-\frac{kx^2 - 2kw(\sqrt{L^2 + x^2} - L)}{2k_\mathrm{B}T}\right) \tag{2}$$

Neglecting terms of order $\sigma^2 k/(\sigma^2 k + E_b)$, the bound state has a potential energy minimum at $\boldsymbol{\varepsilon} = x\boldsymbol{i} + L\boldsymbol{j}$ – e.g. $V_j \approx k/2(x^2 + L^2) - E_b$. Similarly, we may write and simplify an expression for the unbinding rate constant k_a^-.

$$k_a^-(x) = k^0 \exp\left(\frac{kw(\sqrt{L^2 + x^2} - L)}{k_\mathrm{B}T}\right) \tag{3}$$

We may simplify these equations if we take the limit as $k \to \infty$ – i.e. the molecular spring becomes very stiff. However, in order to have the chemical reactions occur at a non-negligible rate, we must also adjust w and L, letting them become very small. Recall, w is the effective radius of the binding well, which depends on some combination of σ and E_b. Therefore, we may pick w and L to scale as $1/k$, $w = c_w k_\mathrm{B}T/(\ell k)$ and $L = c_L k_\mathrm{B}T/(\ell k)$, where c_w and c_L are non-dimensional constants and ℓ is the spacing between binding sites. Then, plugging into Eq. 2 we find:

$$k_a(x) = \lim_{k \to \infty} k_a^0 \exp\left(-\frac{kx^2}{2k_\mathrm{B}T} + \frac{c_w}{\ell}\left(\sqrt{\left(\frac{c_L k_\mathrm{B}T}{\ell k}\right)^2 + x^2} - \frac{c_L k_\mathrm{B}T}{\ell k}\right)\right) \approx k_a^0 \exp\left(-\frac{kx^2}{2k_\mathrm{B}T}\right) \tag{4}$$

And plugging into Eq. 3:

$$k_a^-(x) = \lim_{k \to \infty} k^0 \exp\left(\frac{c_w}{\ell}\left(\sqrt{\left(\frac{c_L k_\mathrm{B}T}{\ell k}\right)^2 + x^2} - \frac{c_L k_\mathrm{B}T}{\ell k}\right)\right) \approx k^0 \exp(a|x|) \tag{5}$$

Where $a = c_w/\ell$ is a constant.

Comment 1: Note that Eq.'s 4 and 5 might seem to violate the law of detailed balance (i.e. that $k_a/k_a^- = \exp(-\Delta G/k_\mathrm{B}T) = \exp(-kx^2/2k_\mathrm{B}T)$. However, note that for the exact expressions, Eq.'s 2 and 3, detailed balance is satisfied. The stiff spring approximation allows us to neglect the region of space where detailed balance would be violated.

Comment 2: The form of Eq 5 means that at large strain, cross-bridges may be ripped from their binding sites. Intuitively, this results makes sense. However, for small a, there is little functional difference at reasonable loads between assuming constant k_a^- and using Eq 5.