Exit Time Problems for Protein Folding

Pak-Wing Fok

UniDel/GEMS Seminar
UniDel Advisee: Daniel Brumley

July 15, 2019

Inference in single-molecule biophysics

Goal: Inference of mechanical strength/functional characteristics/energies of chemical bonds from atomic force spectroscopy or optical tweezers experiments.

Modes of operation:

- Force ramp mode: $v > 0$
- Force clamp mode: $v = 0$

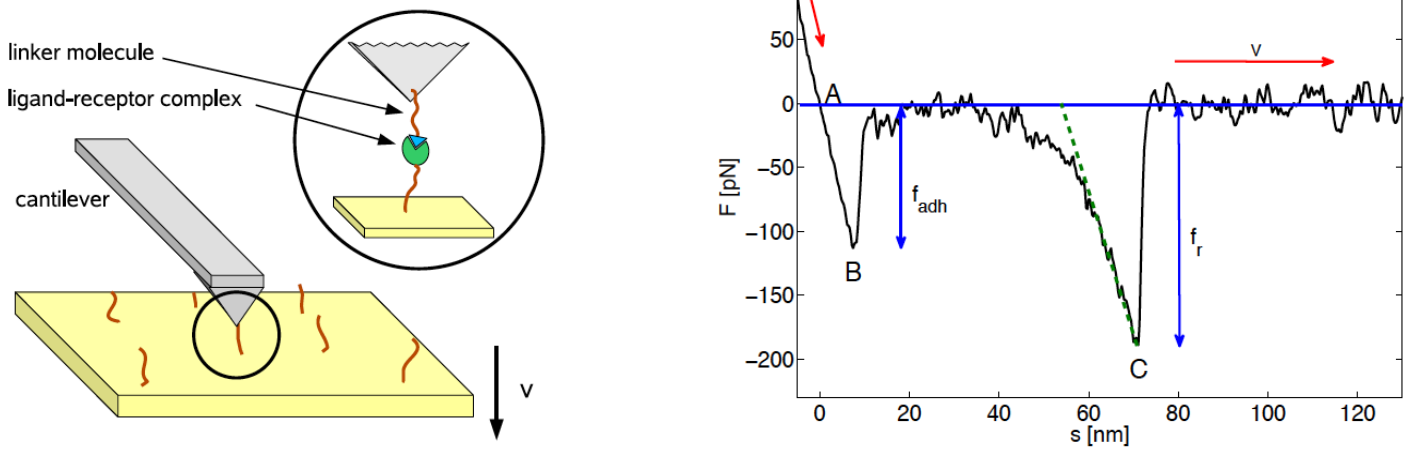


Figure: Left: Atomic force microscopy applied to ligand-receptor complex. Right: Possible force-extension curve generated by AFM when $v > 0$.

Single-Molecule Experiments

Over the past two decades, these experiments have given us new insights into physics and biology at single-molecule lengthscales.

The data from these experiments can take many forms:

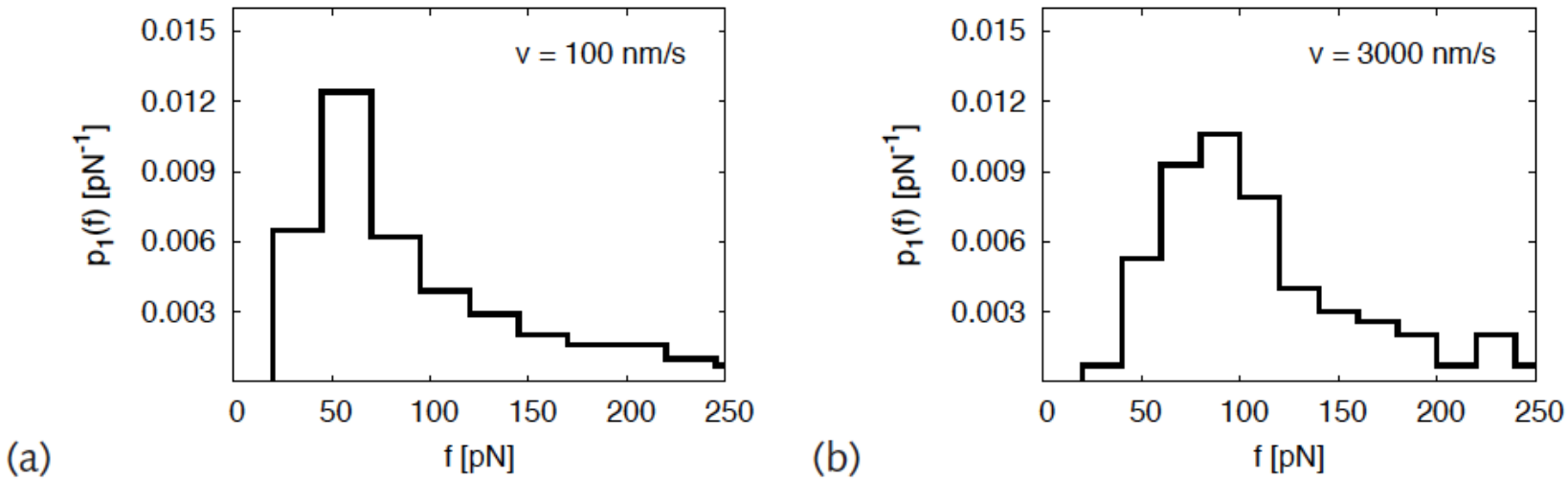
- Rupture force distributions (Dudko, Hummer, Szabo, 2008)
- Rupture time distributions (Evans et al., 2001)
- Dwell time distributions (Woodside and Block, 2014)

Big-picture question: How do we interpret these data sets to inform our understanding of chemical bond breaking, protein folding, DNA zipping/unzipping etc.?

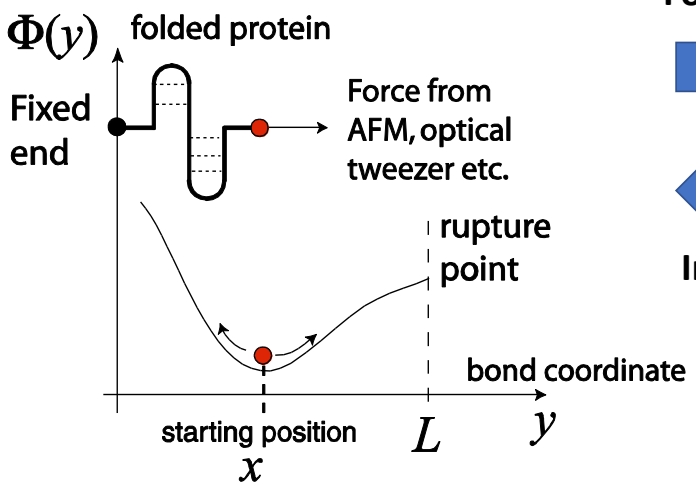
Physical model: Microscopic, stochastic evolution of a reaction coordinate on 1D energy landscape (Freund, 2009; Evans and Ritchie, 1997)

Force ramp mode and a stochastic model

- For fixed v, rupture does not always occur at the same force $\Rightarrow$ rupture force *distribution*
- When v is larger, the rupture distribution shifts to higher values
- Bond rupture could be modeled by *thermally-activated escape* (stochastic model).

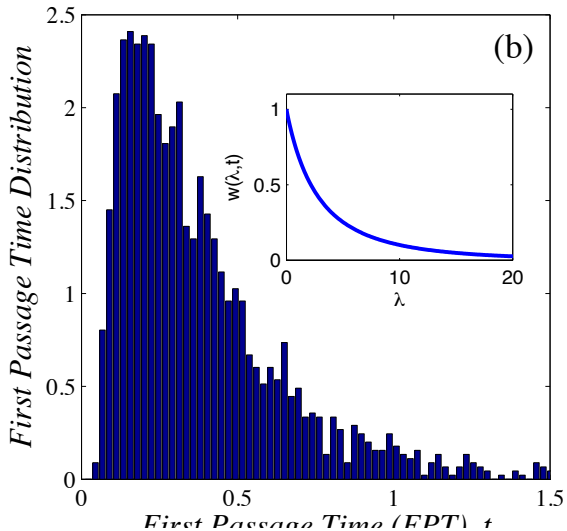


Exit Time or First Passage Time Problem



Forward Problem

Inverse Problem



- Given $\Phi(y)$, find distribution of FPT $w(t)$ (forward problem)
- Given $w(t)$, find $\Phi(y)$ (inverse problem)
- Smoluchowski dynamics. Underlying stochastic model is diffusive in position: $dX = -\frac{D\Phi'(X)}{k_B T}dt + \sqrt{2D}dW$ (Fok & Chou, Proc. Royal Soc. 2010)

Analysis

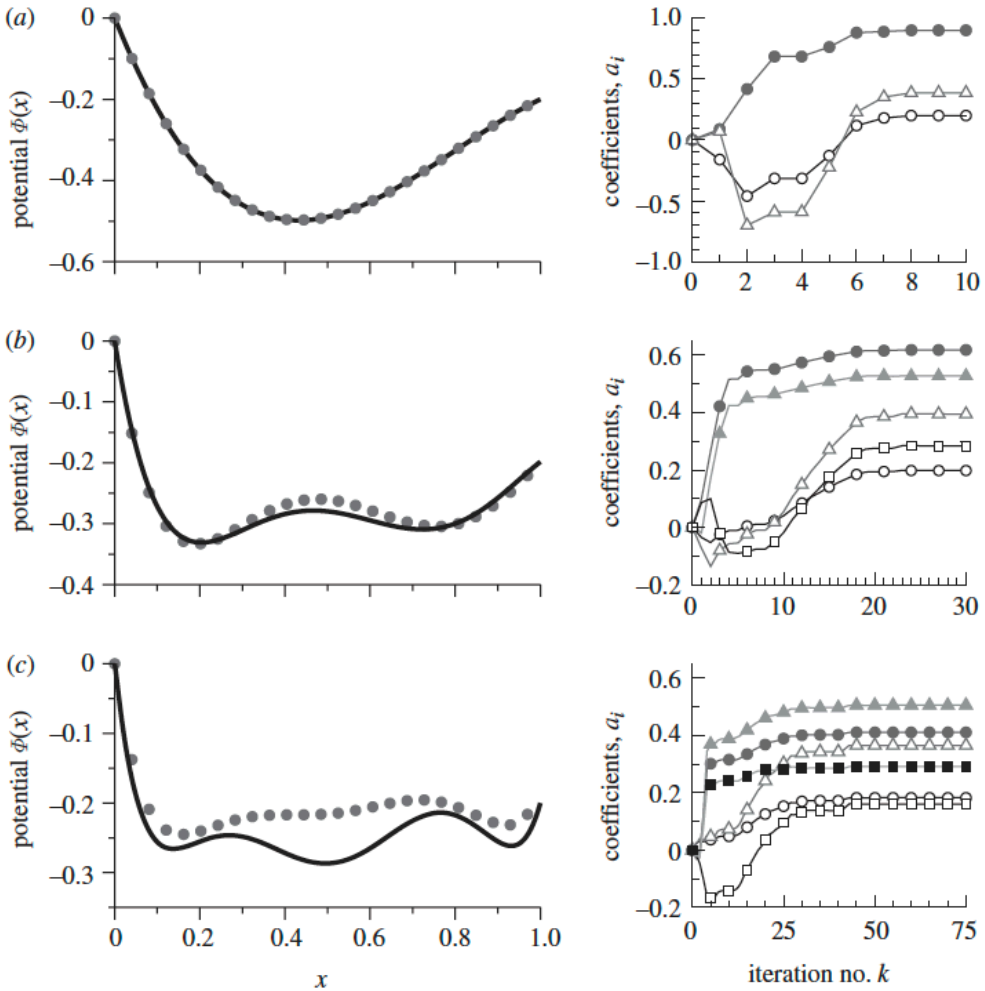
Let $w(x_0, t)$ be the exit time distribution given that $X(t = 0) = x_0$. Then $w(x_0, t)$ satisfies the *backward* Smoluchowski equation

$$\frac{\partial w}{\partial t} + \underbrace{\frac{D}{k_B T}\frac{d\Phi}{dx_0}}_{-U(x_0)}\frac{\partial w}{\partial x_0} = D\frac{\partial^2 w}{\partial {x_0}^2}$$

subject to initial and boundary conditions

$$\begin{aligned} w(x_0, 0) &= 0, \\ \left.\frac{\partial w}{\partial x_0}\right|_{x_0=0} &= 0, \\ w(L, t) &= \delta(t). \end{aligned}$$

Potential Reconstruction



Outline of algorithm

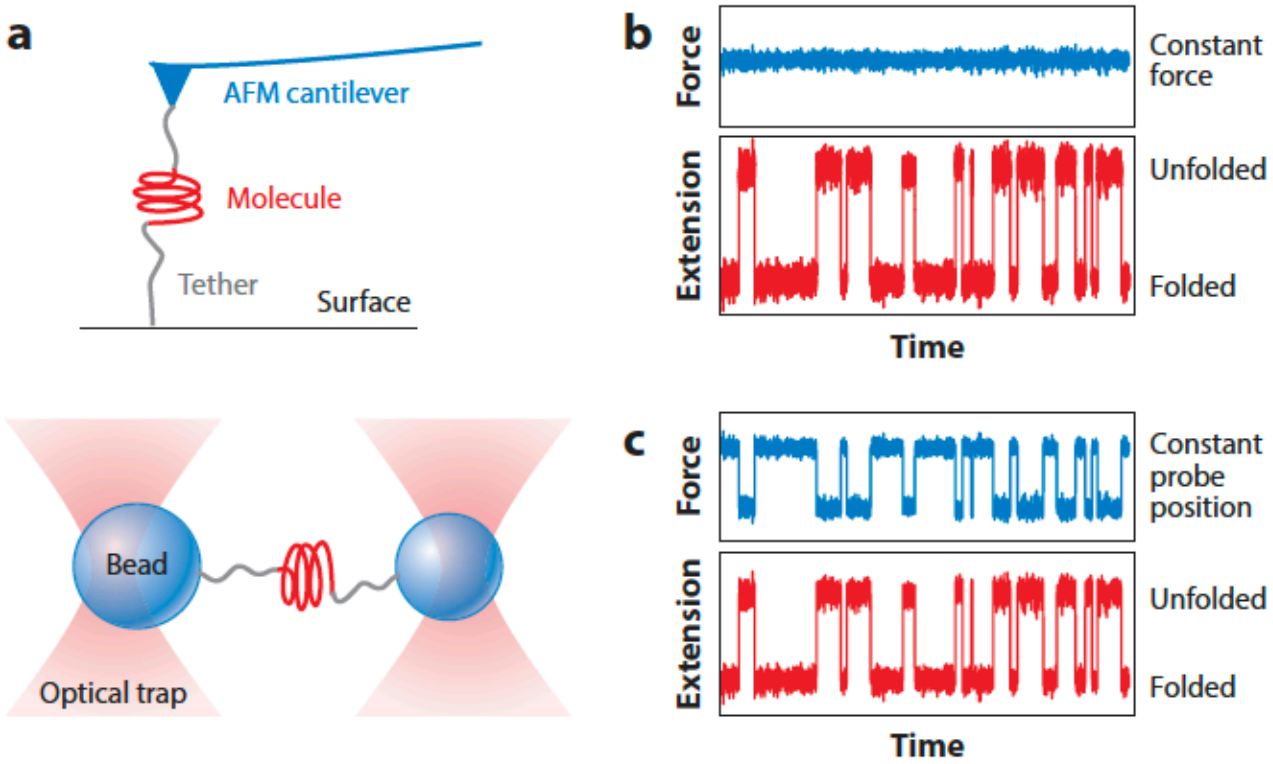
- Represent $U = \sum_{k=1}^{N} a_k \varphi_k(x)$
- Forward problem: $w = w(x_0, t; a_1, \ldots, a_N)$
- Find **a** so that

$$||w_{\text{data}}(t) - w(x_0, t; \mathbf{a})||^2$$

is minimized

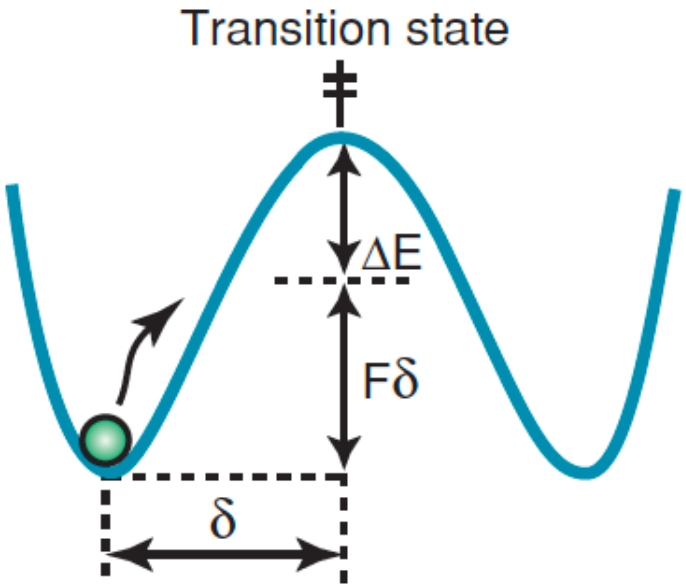
Force clamp AFM

- No bond breaking/rupture; dwell times only
- Two-state stochastic model



(From Woodside and Block, Annual Reviews of Biophysics 2014).

Possible model for 2-state protein

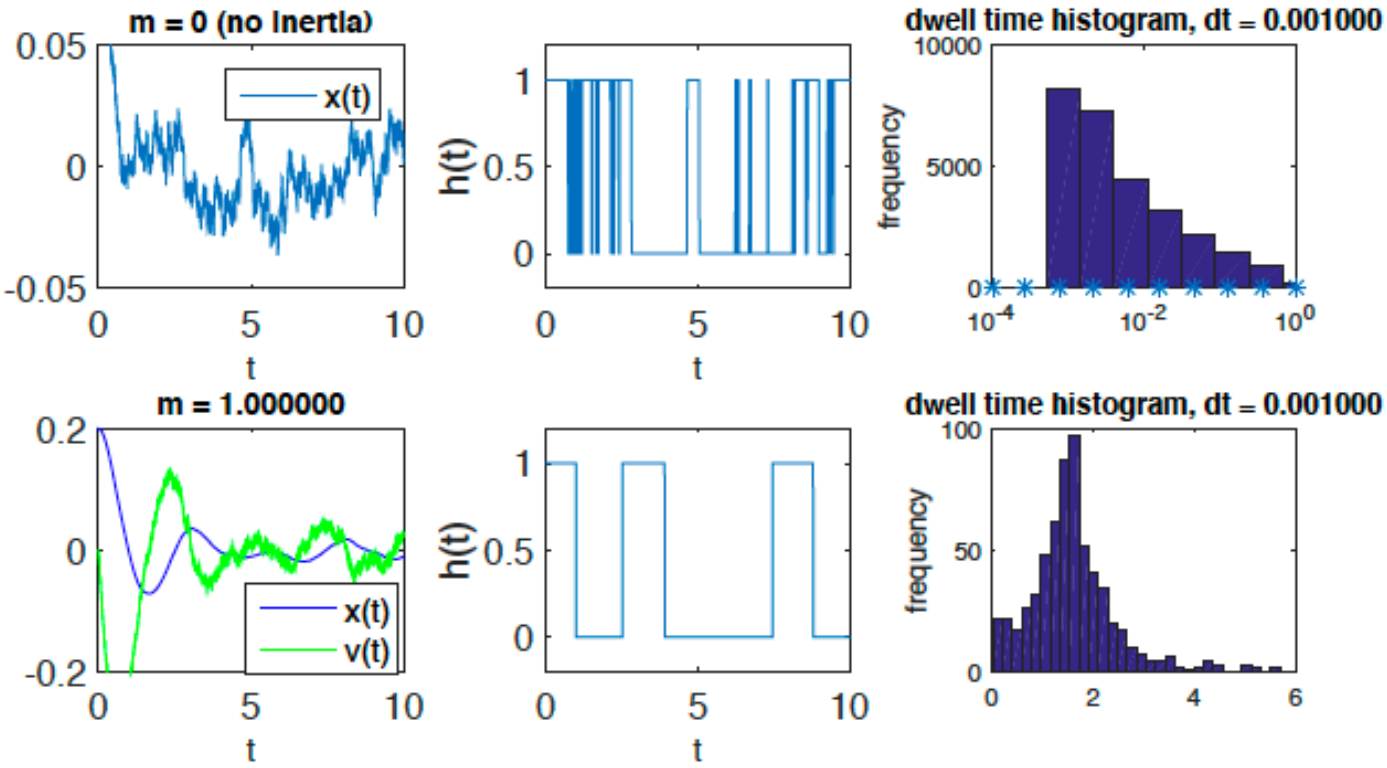


- Left of maximum $\Leftrightarrow$ State 0
- Right of maximum $\Leftrightarrow$ State 1
- Stochastic transitions between two states
- Kramers escape problem
- Multiple crossings and importance of inertia (next slide)

Preliminary Results from Simulation

Coupled stochastic differential equation:

$$\begin{aligned} dx &= v dt \\ m dv &= -\left[\frac{d\Phi}{dx} + \gamma v\right] dt + \sqrt{2\gamma k_B T}\, dW \end{aligned}$$



Kramers Partial Differential Equation

Fokker-Planck (Kramers) equation for $P(x, v, t)$:

$$\frac{\partial P}{\partial t} + v\frac{\partial P}{\partial x} = \frac{1}{m}\frac{\partial}{\partial v}\left(\left[\frac{d\Phi}{dx} + \gamma v\right]P\right) + \frac{\gamma k_B T}{m^2}\frac{\partial^2 P}{\partial v^2}$$

- In principal, given appropriate boundary conditions, the dwell times can be computed from this PDE
- Goal: infer the potential Φ from the dwell time distribution

Tools:

- Backward Equation
- Survival Probability
- Conservation laws

Main issues

- No notion of initial position/velocity; random walk is sampling from a stationary distribution
- How to incorporate multiple crossings into the backward equation?
- Need to derive the backward Kramers equation
- Need value of drag coefficient γ