Analyzing Cell Adhesion Experiment Using Hidden Markov Model

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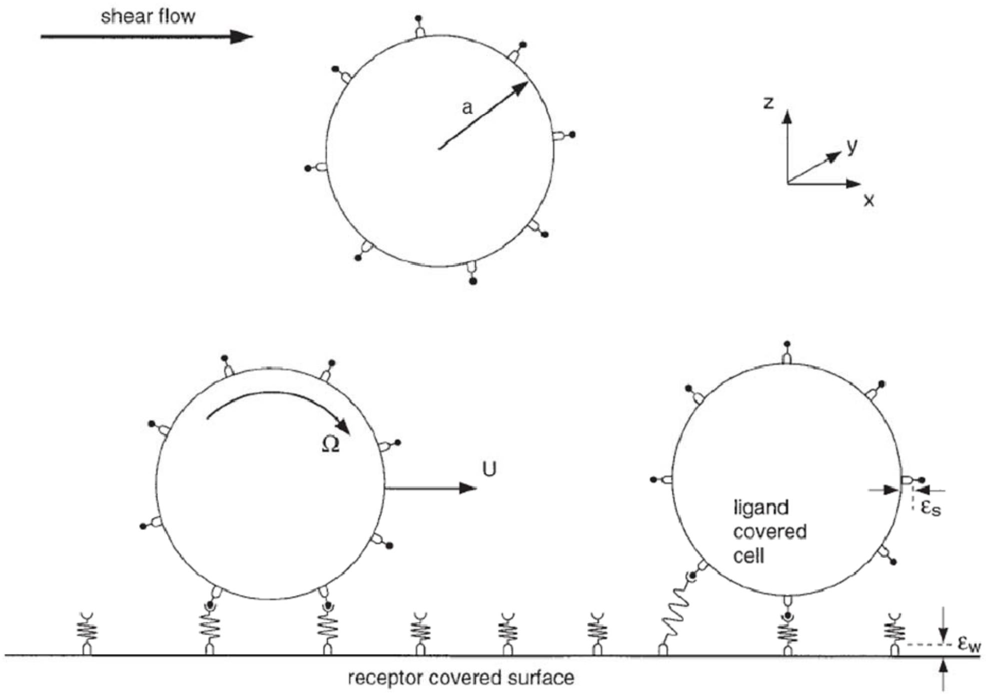
Cell Adhesion Experiment

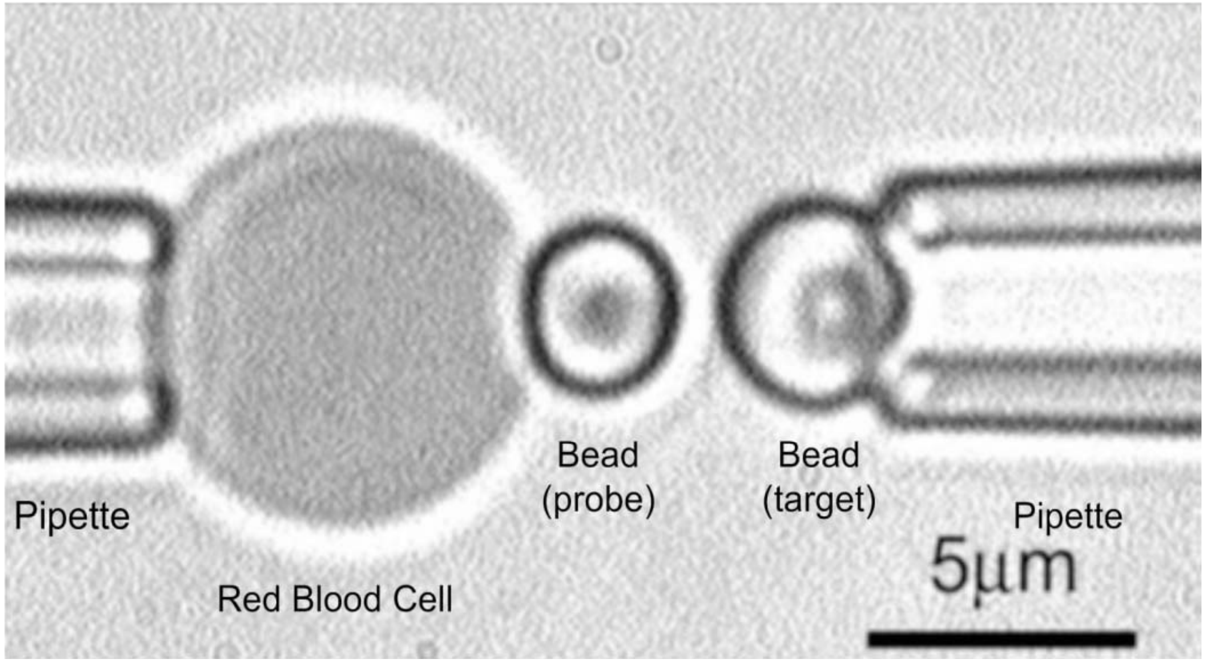
- Cell adhesion is interactions between receptors and ligands.
- It is important in many physiological and pathological processes.
- Thermal fluctuation experiment uses the reduced thermal fluctuations to indicate the presence of receptor-ligand bonds.
- Objective: Identify association and dissociation points of receptor-ligand bonds.

Cell Adhesion Experiment



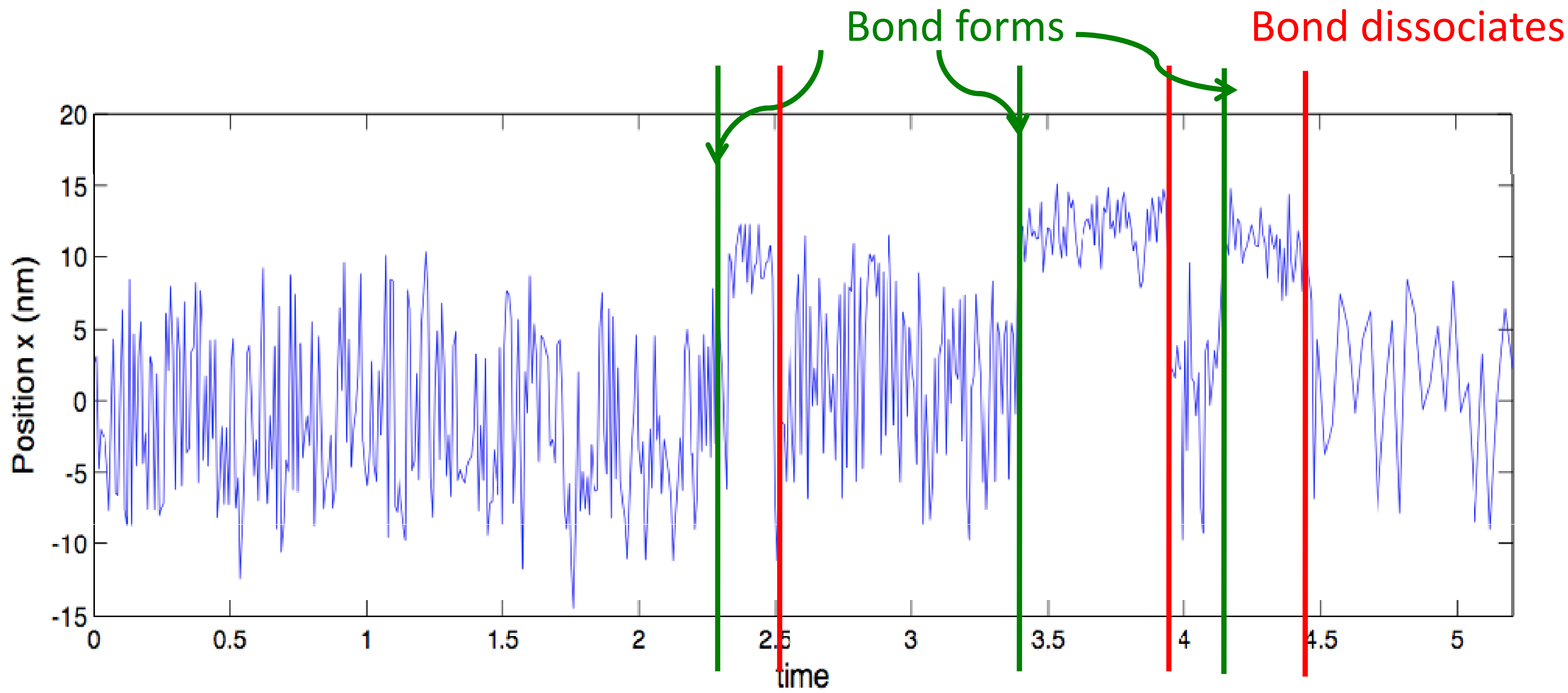
Experimental Setting

- The experiment consists of approach-push-retract-hold-return cycle.
- The left pipette was held stationary to allow the probe and the target to contact.



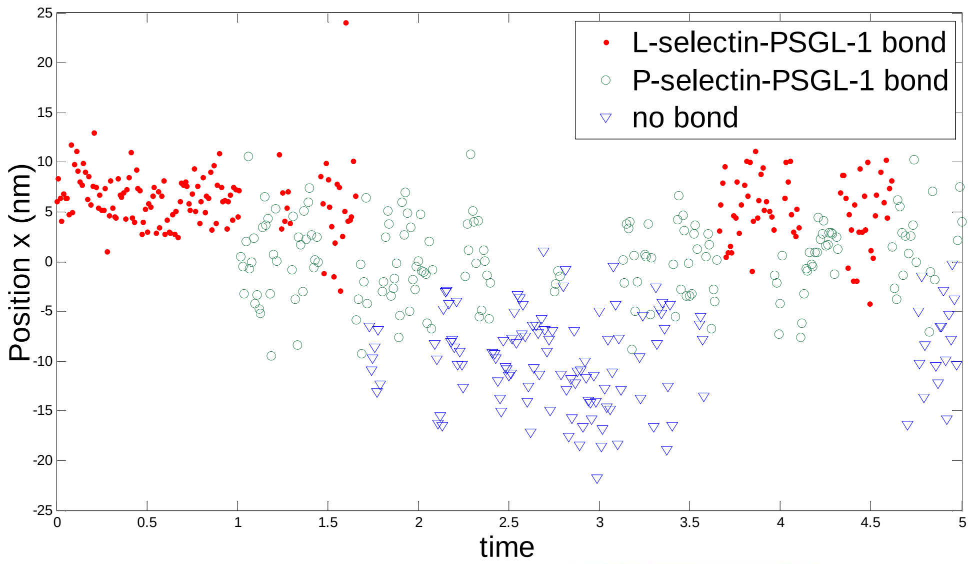
Data Collection

- The position of the probe was tracked by image analysis software to produce the data.
- The fluctuation decreases when a receptor-ligand bond forms and resumes when the bond dissociates.



Challenges

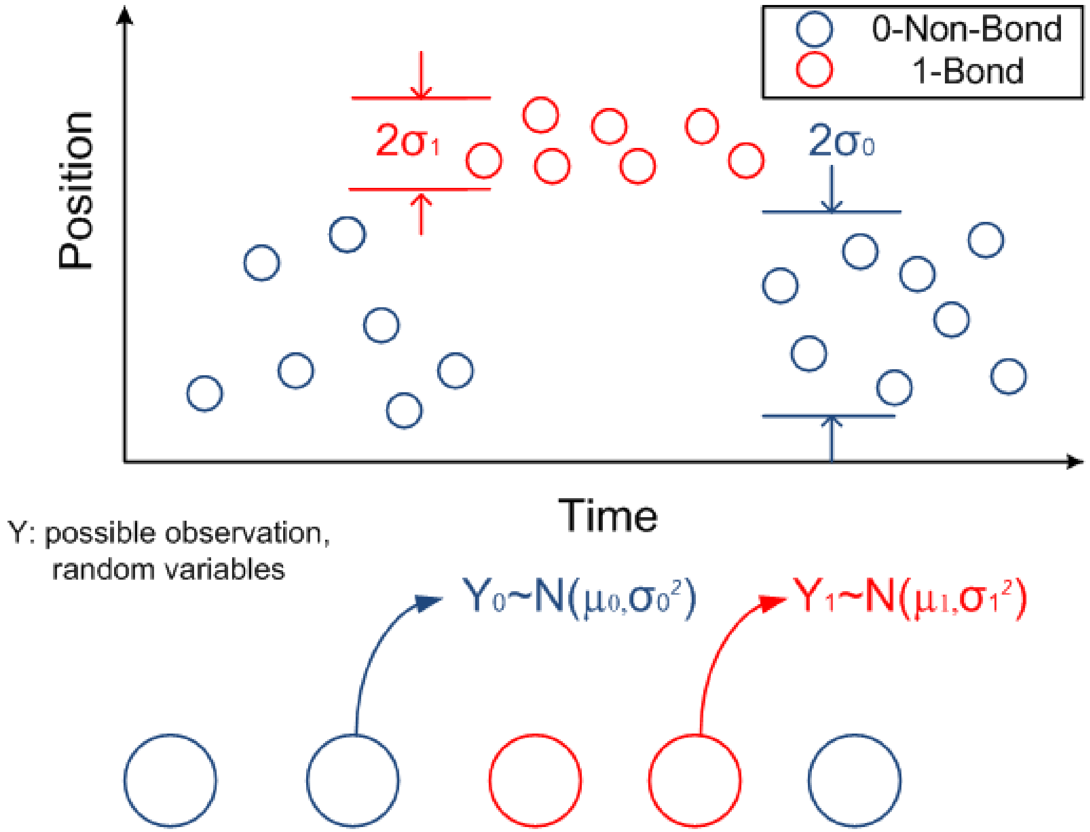
- Association/dissociation points are not directly observable. Can only be detected by variance changes.
- Observations are dependent. Binding probability increases if there is a binding in the immediate past. (memory effect)
- Data contains an unknown number of bond types. Each bond associated with different fluctuation decrease.



Hidden Markov Models

- Assume the probe fluctuates with different variances that correspond to different underlying binding states.
- These states are unobservable but can be captured by a Markov chain.
- Such Markov chain process can be used to capture the cell memory effect.

Hidden Markov Model with two states



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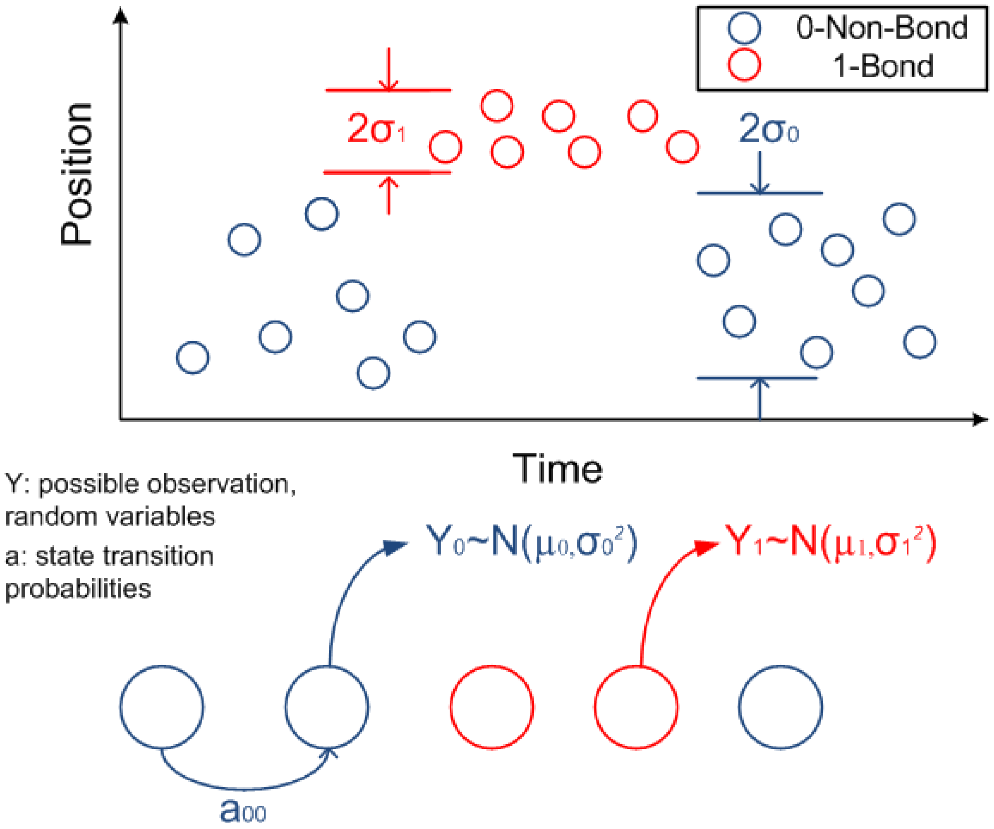
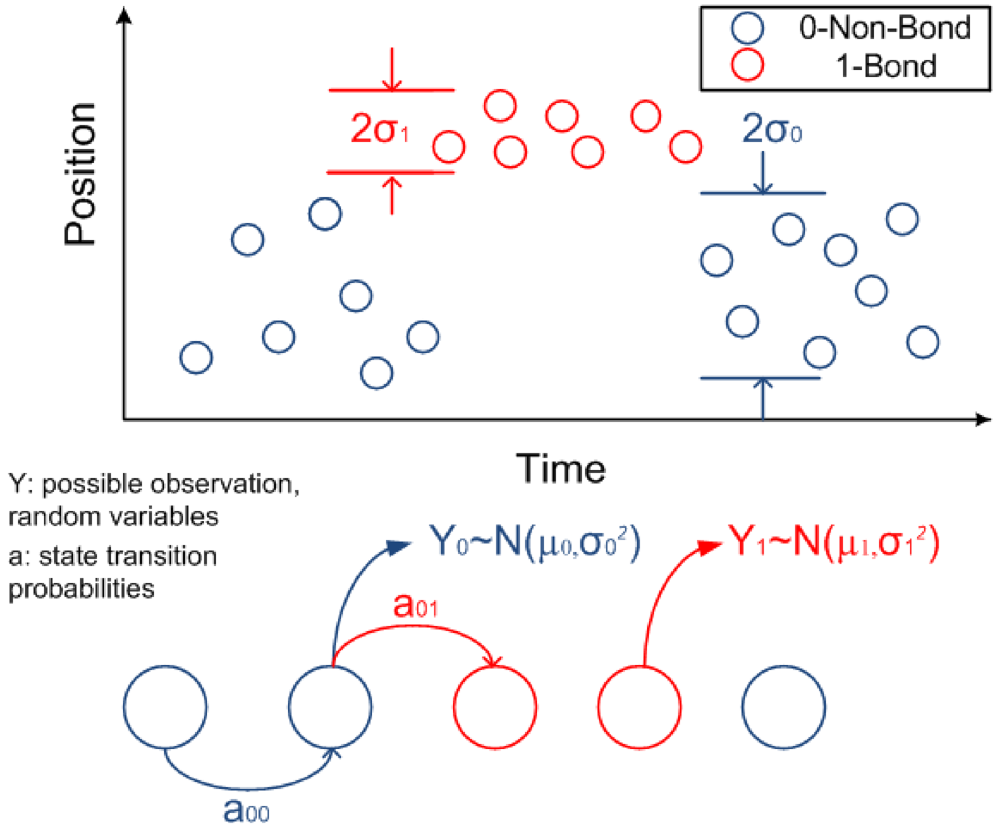
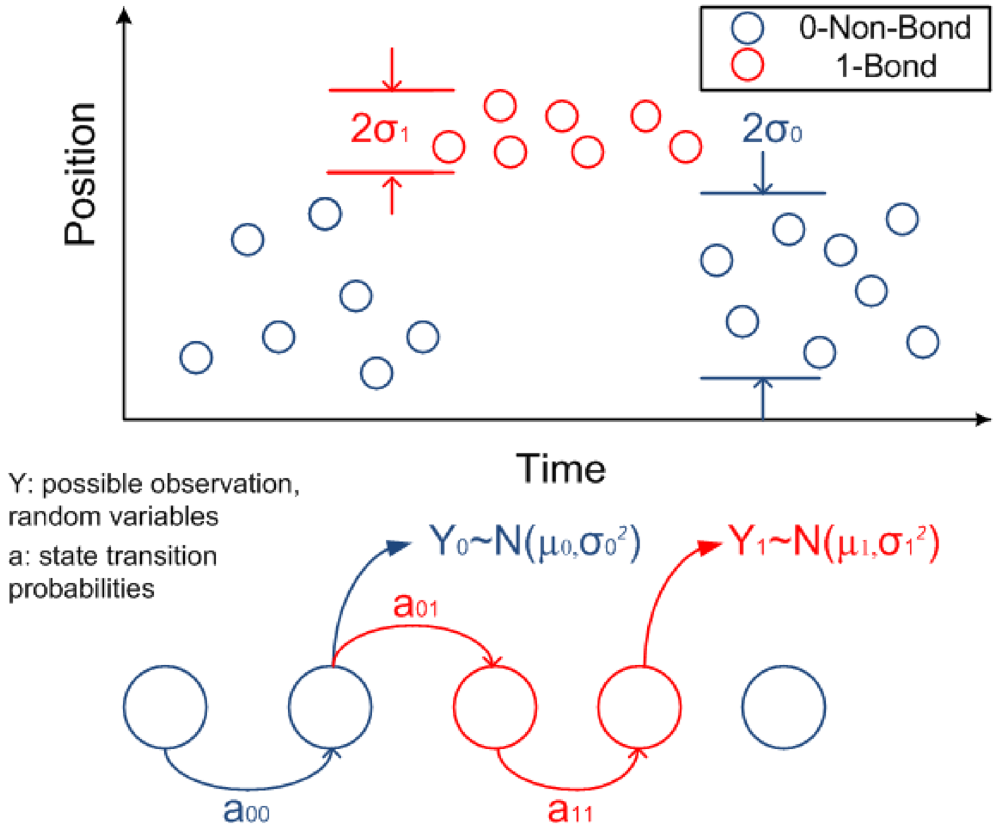
Hidden Markov Model with two states



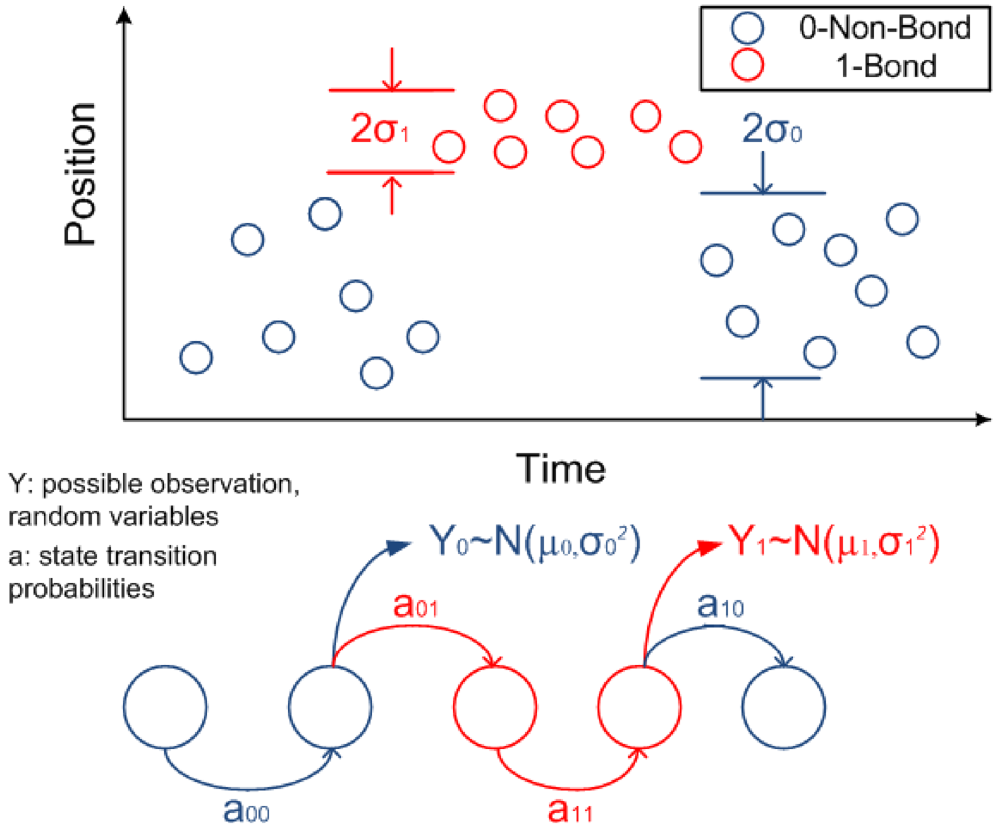
Hidden Markov Model with two states



Hidden Markov Model with two states



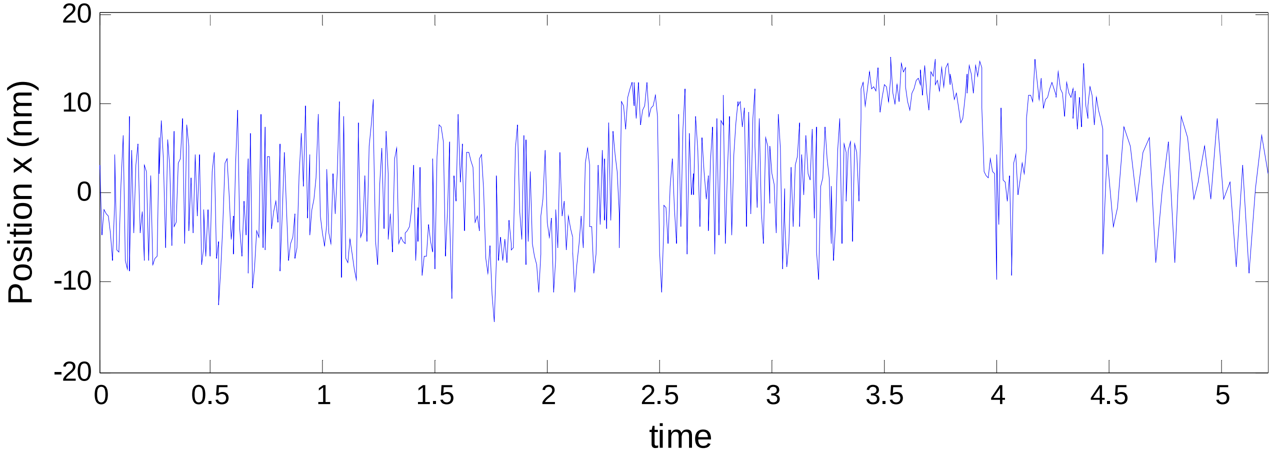
Hidden Markov Model with two states

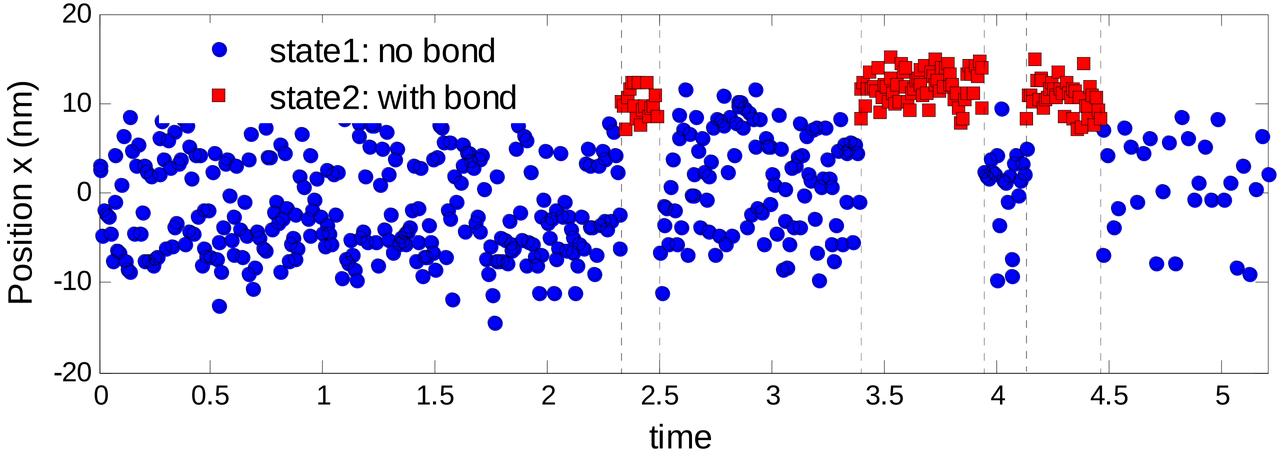


Test of Memory Effect

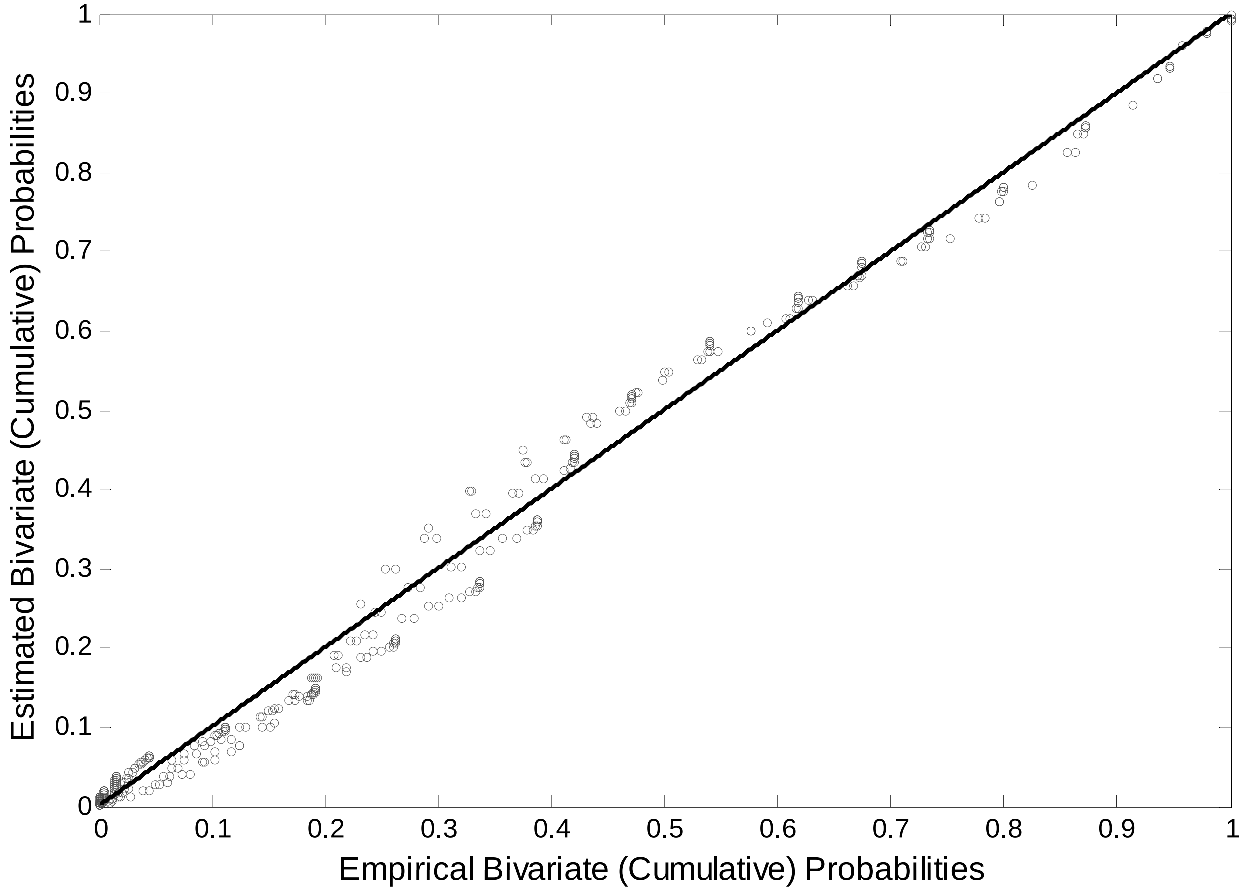
- a_{ij} denotes the probability of going from state i to state j.
- $H_0: a_{10} \geq a_{11}$ vs $H_1: a_{10} < a_{11}$.
- Using likelihood-ratio test, we evaluate the maximum log-likelihood under H_0 and under H_1.
- Comparing to the χ^2 distribution with one df leads to a p-value close to 0. This confirms memory effect.

Results


20
10
0
-10
-20
Position x (nm)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
time


state1: no bond
state2: with bond
20
10
0
-10
-20
Position x (nm)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
time

Goodness of Fit



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Some Asymptotic Results

- Model: HMM with q, the unknown # of states.
- To avoid overfitting q, use double penalized likelihood for estimate.
- Asymptotic properties:

$$\hat{q} \to q \qquad \text{w.p. } 1$$

$$\hat{\mu} \to \mu \qquad \text{w.p. } 1$$

$$\hat{\sigma} \to \sigma \qquad \text{w.p. } 1$$

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