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

Y: possible observation, random variables

\[ Y_0 \sim N(\mu_0, \sigma_0^2) \quad Y_1 \sim N(\mu_1, \sigma_1^2) \]
Hidden Markov Model with two states
Hidden Markov Model with two states

- \( Y \): possible observation, random variables
- \( a \): state transition probabilities
- \( Y_0 \sim N(\mu_0, \sigma_0^2) \)
- \( Y_1 \sim N(\mu_1, \sigma_1^2) \)
Hidden Markov Model with two states

\[ Y \sim N(\mu_0, \sigma_0^2) \]

\[ Y_i \sim N(\mu_1, \sigma_1^2) \]

\[ a_{00}, a_{01}, a_{10}, a_{11} \]

0-Non-Bond
1-Bond
Hidden Markov Model with two states

$Y$: possible observation, random variables
$a$: state transition probabilities

$Y_0 \sim N(\mu_0, \sigma_0^2)$
$Y_1 \sim N(\mu_1, \sigma_1^2)$

0-Non-Bond
1-Bond
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 $\chi^2$ distribution with one df leads to a p-value close to 0. This confirms memory effect.
Results

![Graph showing position x (nm) vs. time for two states: state 1: no bond and state 2: with bond.]

- State 1: no bond
- State 2: with bond

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Goodness of Fit

![Graph showing goodness of fit with estimated bivariate cumulative probabilities vs. empirical bivariate cumulative probabilities. The graph includes a scatter plot with a diagonal line indicating a perfect fit.]
Some Asymptotic Results

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

\[
\hat{q} \rightarrow q \quad \text{w.p. 1}
\]
\[
\hat{\mu} \rightarrow \mu \quad \text{w.p. 1}
\]
\[
\hat{\sigma} \rightarrow \sigma \quad \text{w.p. 1}
\]