Bayesian model selection: Mechanistic models of Erk MAP kinase phosphorylation dynamics

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Motivation

- Post-translational modification important process
- 30% of all proteins in any eukaryotic cell phosphorylated at any time \(^2\)
- 500 different protein kinases in human genome \(^1\)

\(^1\) (Manning et al., Science, 2002)

\(^2\) (Mann et al., Trends Biotechnology, 2002)
Outline

1. Data

2. Phosphorylation models

3. Model selection
   - Existing approaches
   - ABC SMC Bayesian model selection algorithm

4. Results
High throughput \textit{in vivo} data of Erk signaling pathway

(Sasagawa et al., Nature Cell Biology, 2005)
High throughput *in vivo* data of Erk signaling pathway

1. Individual cell ppMek vs ppErk data

2. Averaged time course data

- ppMek = active MAPKK
- ppErk = Mpp

How can we use these data to study the phosphorylation mechanisms of Erk by ppMek?
Dual phosphorylation mechanisms

Figure 1: Distributive phosphorylation.

Figure 2: Processive phosphorylation.
Dual phosphorylation mechanisms

**Distributive (disassociation)**

\[
M + \text{MAPKK} \xrightarrow{k_1} \text{M} \cdot \text{MAPKK} \xrightarrow{k_2} \text{Mp} + \text{MAPKK}
\]

\[
\text{Mp} + \text{MAPKK} \xrightarrow{k_3} \text{Mp} \cdot \text{MAPKK} \xrightarrow{k_4} \text{Mpp} + \text{MAPKK}
\]

**Processive (bind and slide)**

\[
M + \text{MAPKK} \xrightarrow{k_1} \text{M} \cdot \text{MAPKK} \xrightarrow{k_2} \text{Mp} \cdot \text{MAPKK} \xrightarrow{k_4} \text{Mpp} + \text{MAPKK}
\]
Question

- *In vitro* phosphorylation MAPK is distributive (*Burack 1997, Ferrel 1997*).
- *In vitro* de-phosphorylation MAPK is distributive (*Zhao 2001*).
- Is it the same *in vivo*? Cannot study phosphorylation and dephosphorylation separately.
Question

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<table>
<thead>
<tr>
<th>Phosphorylation</th>
<th>Dephosphorylation</th>
<th>num. parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-D</td>
<td>distributive</td>
<td>distributive</td>
</tr>
<tr>
<td>P-D</td>
<td>processive</td>
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Individual cell data plots

What does the slope of the fitted Hill curve tell us about phosphorylation?
In vitro:
slope = 1: processive
slope = 2: distributive
What does the slope of the fitted Hill curve tell us about phosphorylation?  
In vitro:  
slope = 1: processive  
slope = 2: distributive  

Our guess:  
slope = 1: P-P, P-D  
slope = 2: D-P, D-D  

Result:  
slope = 1: P-P, P-D, D-P  
slope = 2: D-D
Steady state invariants, Gunawardena

A) D-D
B) D-P
C) P-D
D) P-P

(Gunawardena, Biophysical Journal, 2008)
Steady state invariants, Gunawardena

(A) D-D
(B) D-P
(C) P-D
(D) P-P

Need:
steady state measurements of M, Mp, Mpp

(Gunawardena, Biophysical Journal, 2008)
Bayesian model selection

![Diagram showing candidate models: M1, M2, M3, M4, M5, M6.]

Bayes factor

\[
BF_{i,j} = \frac{P(D|M_i)}{P(D|M_j)} = \frac{P(M_i|D)P(M_j)}{P(M_j|D)P(M_i)}
\]

\[
P(M_i|D) \propto \int_{\theta_i} P(M_i, \theta_i|D)P(M_i)P(\theta_i)d\theta_i
\]
Bayesian model selection

Bayes factor

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ABC framework for estimation of $P(\theta|D)$

R1 Sample $\theta^c$ from $P(\theta)$.
R2 Simulate a data set $D^c$ from the model with $\theta^c$.
R3 If $\text{dist}(D, D^c) \leq \epsilon$, accept $\theta^c$, otherwise reject.
R4 Return to R1.
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Prior
$P(\theta)$

Posterior
$P(\theta|D)$

time
ABC framework for estimation of $P(\theta|D)$

1. Sample $\theta^c$ from $P(\theta)$.
2. Simulate a data set $D^c$ from the model with $\theta^c$.
3. If $\text{dist}(D, D^c) \leq \epsilon$, accept $\theta^c$, otherwise reject.
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Prior $P(\theta)$

Posterior $P(\theta|D)$
ABC SMC for estimation of $P(\theta | D)$

(Toni et al., 2008, Journal of Royal Society Interface)
Bayesian model selection with ABC SMC

We know

\[ \text{ABC SMC \ obtain} \quad P(\theta|D) \]

ABC Model Selection

- Include model \( \mathcal{M} \) as an extra parameter: \((\mathcal{M}, \theta_1, \ldots, \theta_M)\).
- Do ABC SMC to get posterior \( P(\mathcal{M}, \theta_1, \ldots, \theta_M|D) \).
- Marginalize to obtain \( P(\mathcal{M}|D) \).
- Calculate Bayes factor

\[
BF_{i,j} = \frac{P(M_i|D)P(M_j)}{P(M_j|D)P(M_i)}
\]
Gaussian Process regression and fitting

MAPKK data: input to models

Mpp data: for fitting
Model selection results

Marginal posterior distribution $P(M|D)$

D-D  P-P  D-P  P-D
Future work

Averaged data
- Study dependence on Gaussian Process regression, priors.

Population data
- Extra information contained in population vs. averaged data.
- Adaptation of ABC SMC algorithm for population data.
- Main source of variability.
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