Inference of Key Transcriptional Regulators in Endothelial Cell Apoptosis using Bayesian State Space Models

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joint work with

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Outline

Challenge

- Response of HUVEC to serum withdrawal, triggering apoptosis
- Timecourse with only a few measurements
- Challenge is to identify candidate regulators

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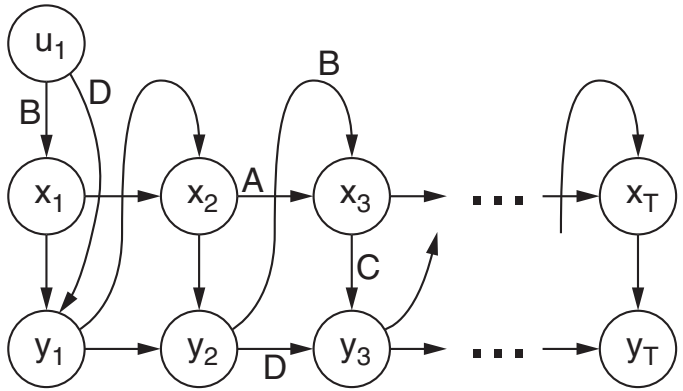
A Gaussian State-Space Model with Feedback



Output equation: $\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{y}_{t-1} + \mathbf{v}_t$

State dynamics equation: $\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{y}_{t-1} + \mathbf{w}_t$

Key Concept: $\mathbf{y}_t$ represents the measured gene expression level at time step t and $\mathbf{x}_t$ models the many unmeasured (hidden) factors such as

- genes that have not be included in the microarray,
- levels of regulatory proteins,
- the effects of mRNA and protein degradation, etc.

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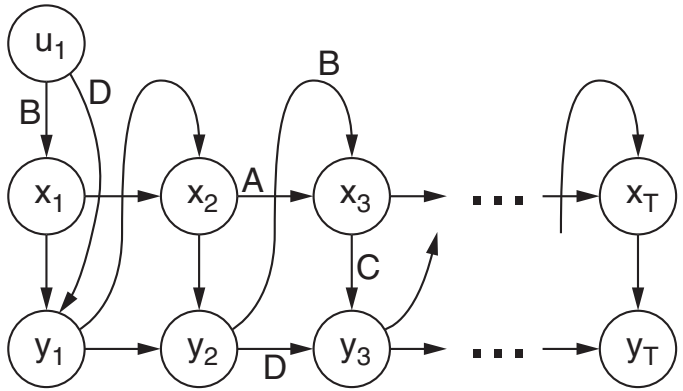

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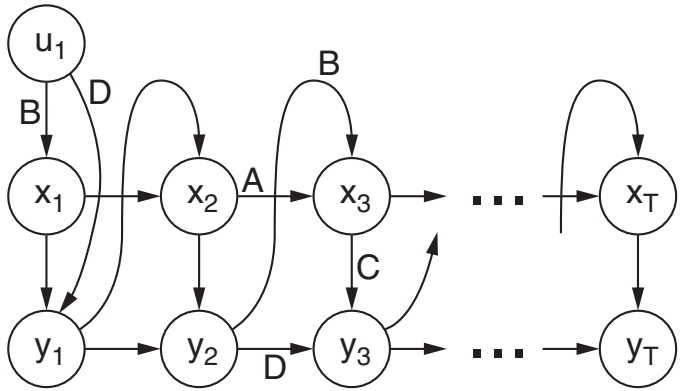

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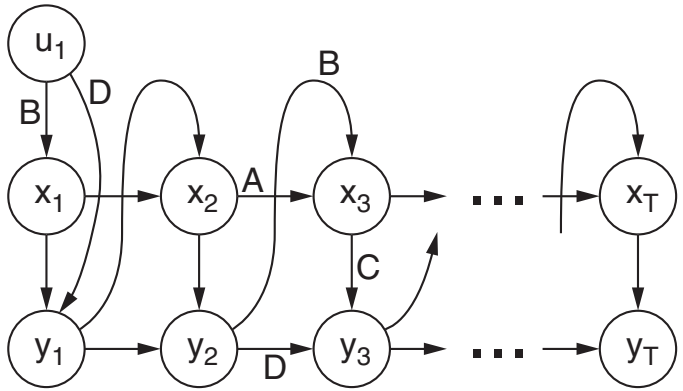

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Our Approach

- Let $\theta = \{A, B, C, D, R\}$ be the parameters of the model (R models noise covariance).
- Elements of matrix $[CB + D]$ represent all gene-gene interactions
- Exact Bayesian inference would give us $p(\theta|\mathcal{D})$, which tells us confidence in each parameter and can be used to infer model structure.
- Unfortunately, exact inference is computationally intractable.
- We can use variational approximations to approximate Bayesian inference in state-space models (Beal et al., 2005).

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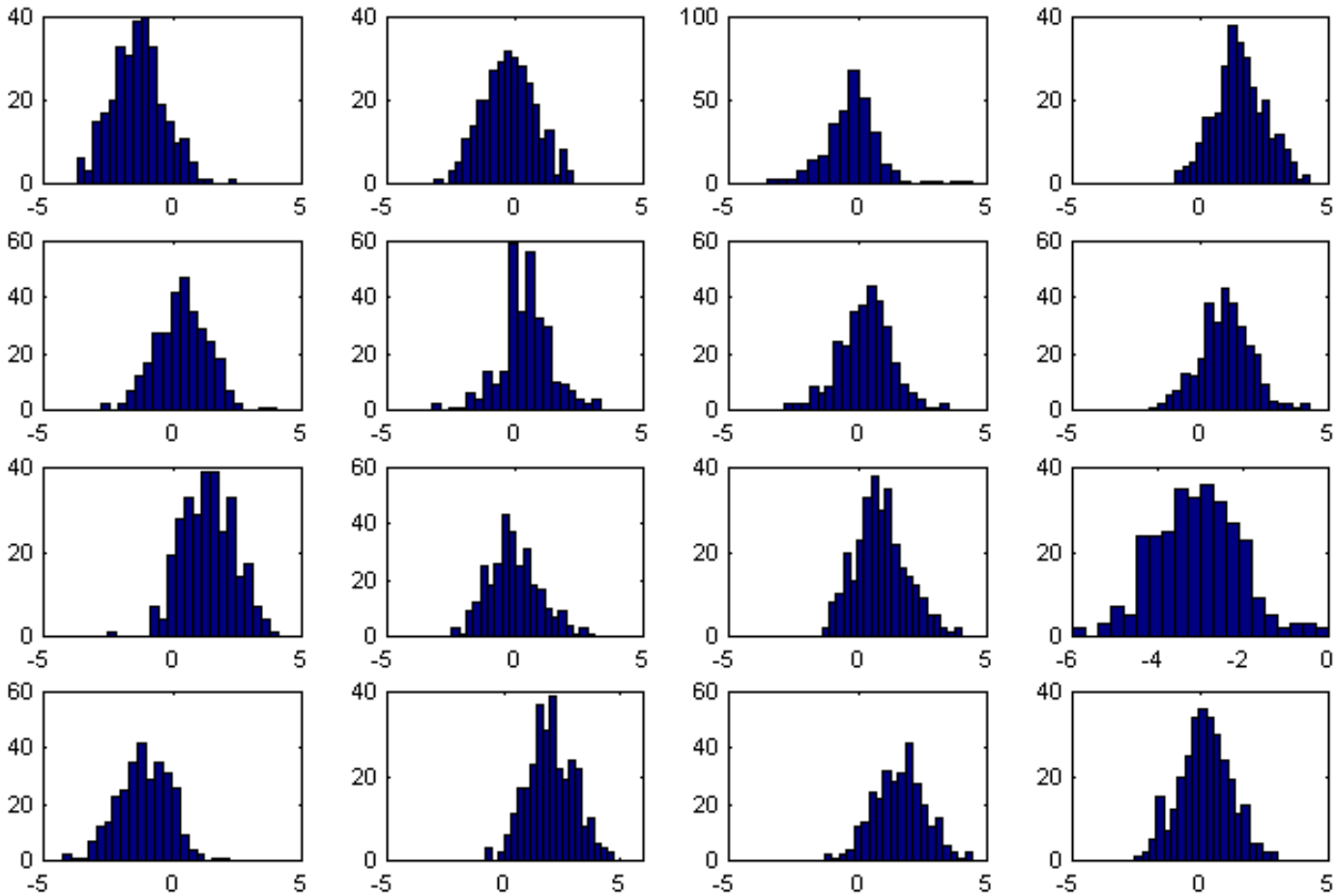
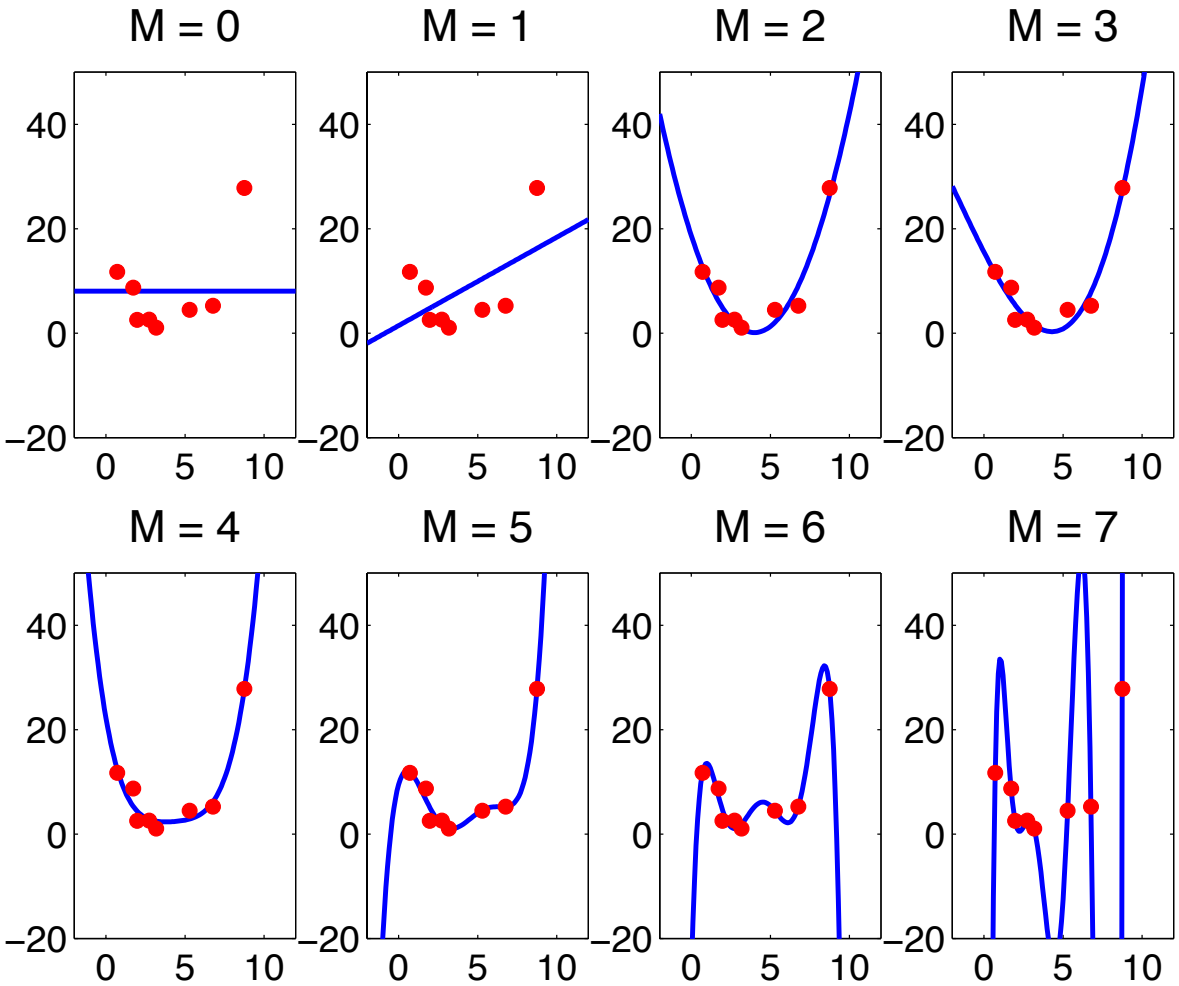
Parameter Distributions



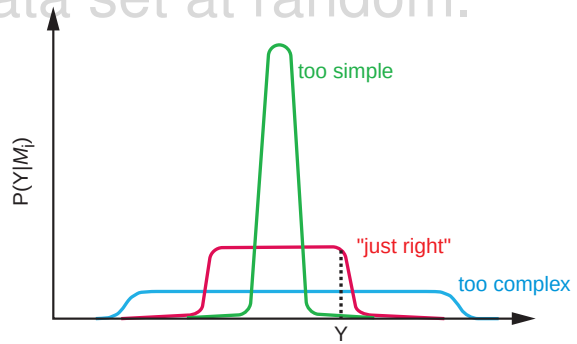
Model structure and overfitting: a simple example



Using Bayesian Occam's Razor to Learn Model Structure

Select the model class m_i with the highest probability given the data by computing the Marginal Likelihood ("evidence"):
Interpretation: The probability that *randomly selected* parameters from the prior would generate the data set.

- Model classes that are too simple are unlikely to generate the data set.
- Model classes that are too complex can generate many possible data sets, so again, they are unlikely to generate that particular data set at random.



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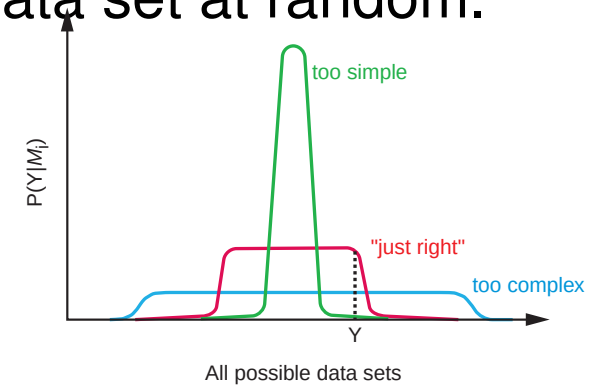
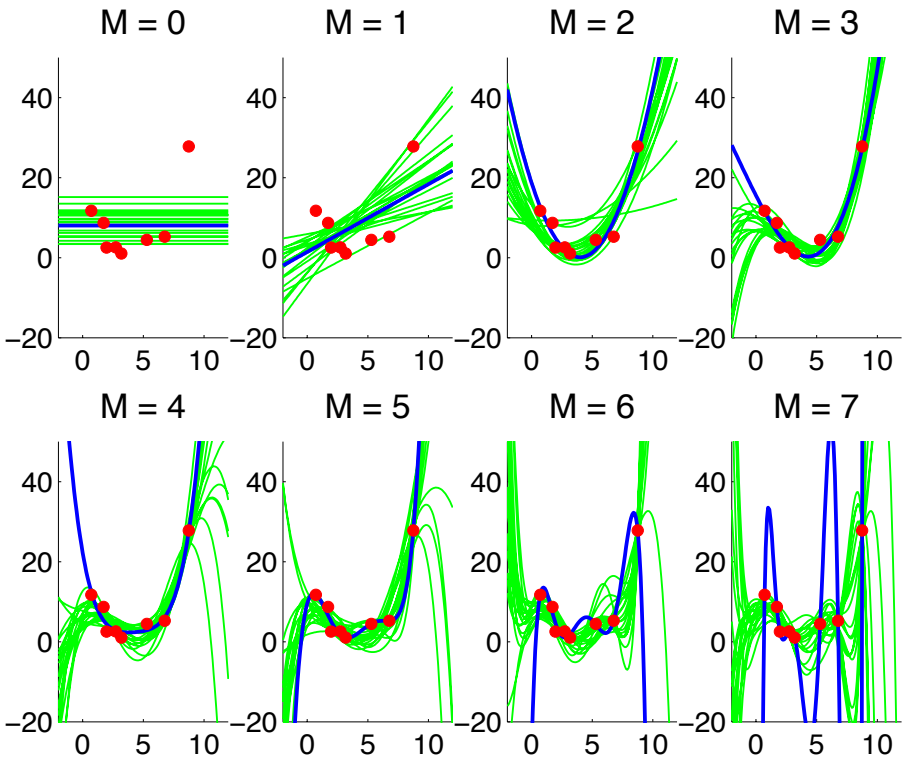
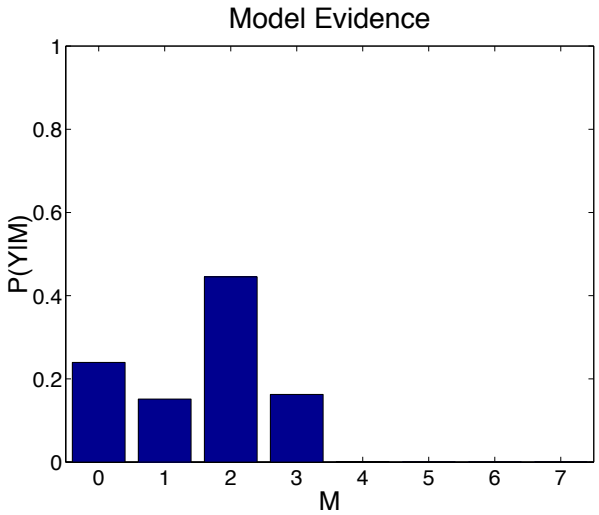


Bayesian Model Selection: Occam's Razor at Work

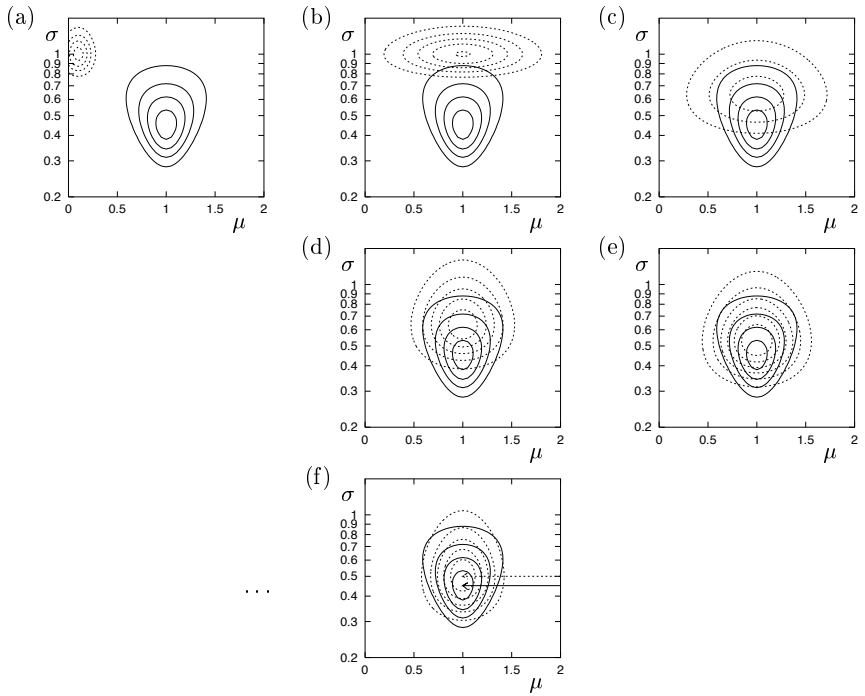




e.g. for quadratic (M=2): $y = a_0 + a_1 x + a_2 x^2 + \epsilon$, where $\epsilon \sim \mathcal{N}(0, \tau)$ and $\theta_2 = [a_0\ a_1\ a_2\ \tau]$

Variational Bayesian Approach

Variational free energy minimization is a method of approximating a complex distribution $p(\mathbf{x})$ by a simpler distribution $q(\mathbf{x};\theta)$. We adust the parameters θ so as to get q to best approximate p in some sense.



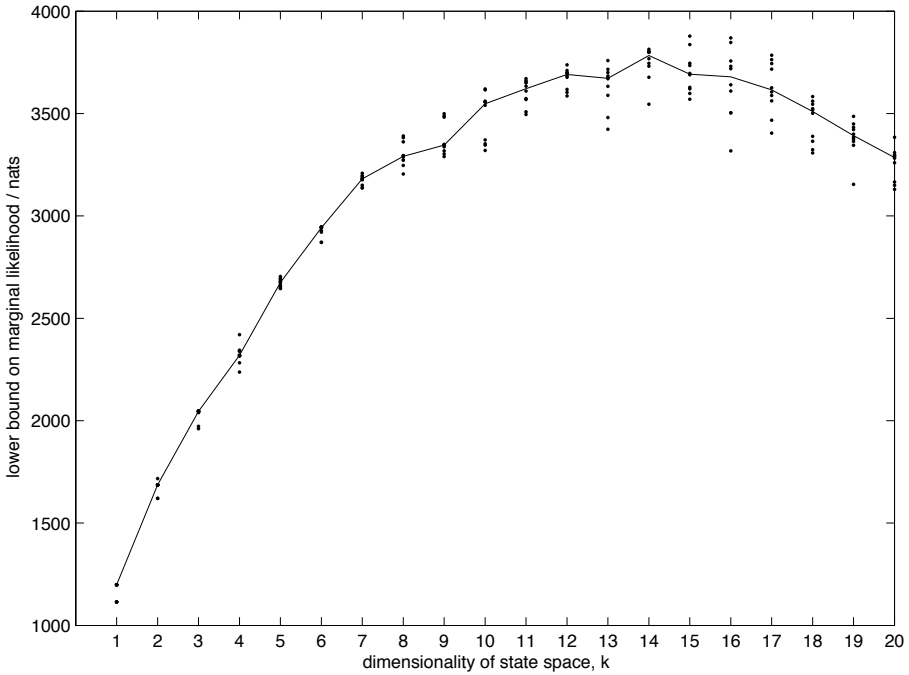
From David J.C. MacKay “Information Theory, Inference and Learning Algorithms”

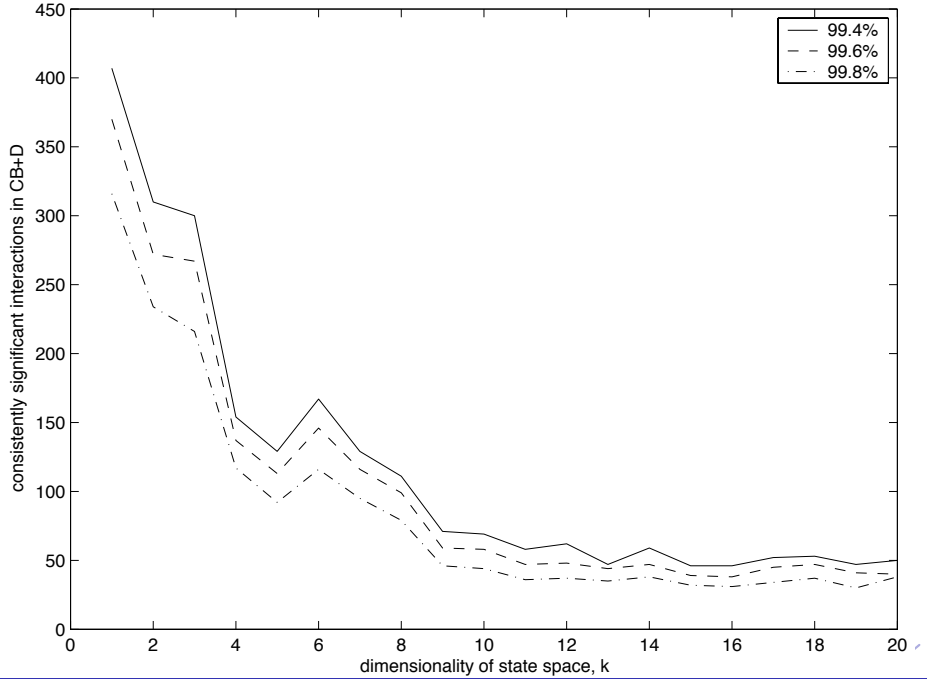
Lower Bounding the Marginal Likelihood

We can also lower bound the marginal likelihood:
Using a simpler, factorised approximation to
$q(\mathbf{x}, \theta) \approx q_{\mathbf{x}}(\mathbf{x}) q_{\theta}(\theta)$:

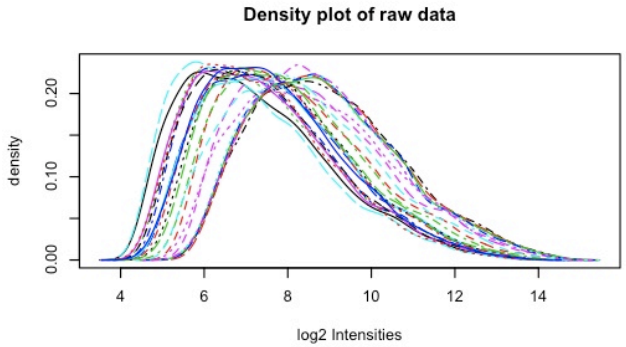
$$\ln p(\mathbf{y}|m) \quad = \quad \mathcal{F}_m(q_{\mathbf{x}}(\mathbf{x}), q_{\theta}(\theta), \mathbf{y}).$$

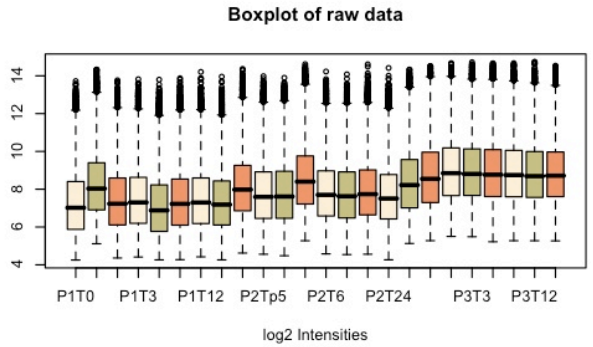
Maximizing this lower bound, $\mathcal{F}_m$, leads to **EM-like** iterative updates. $-\mathcal{F}_m$ is a variational free energy

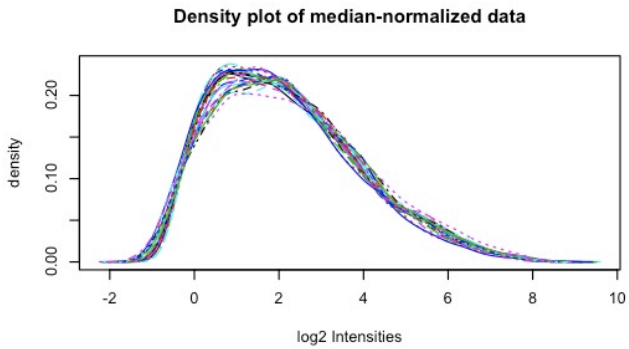


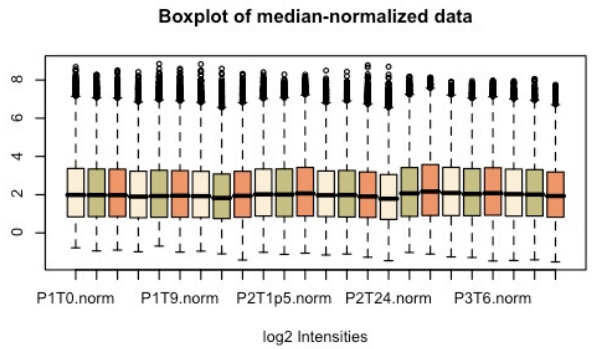


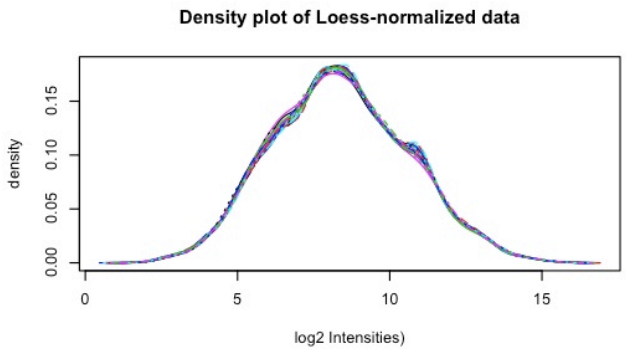
Data Normalization

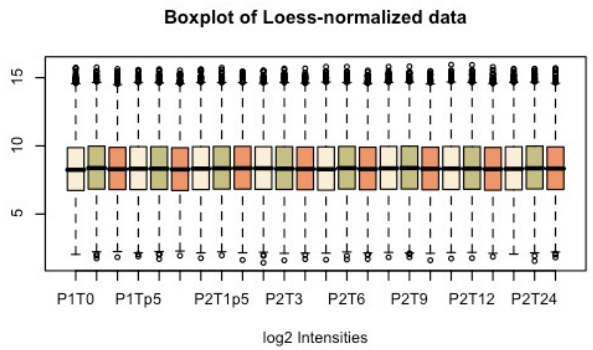




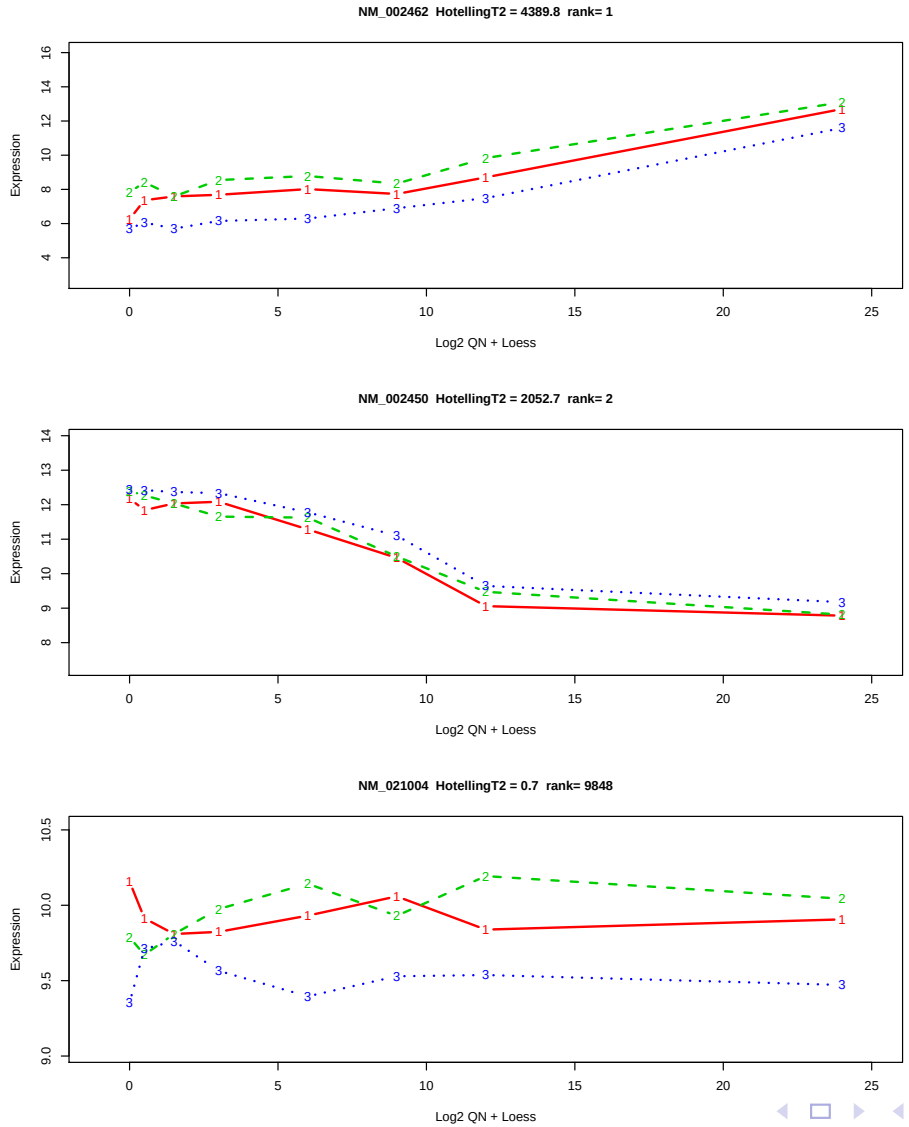




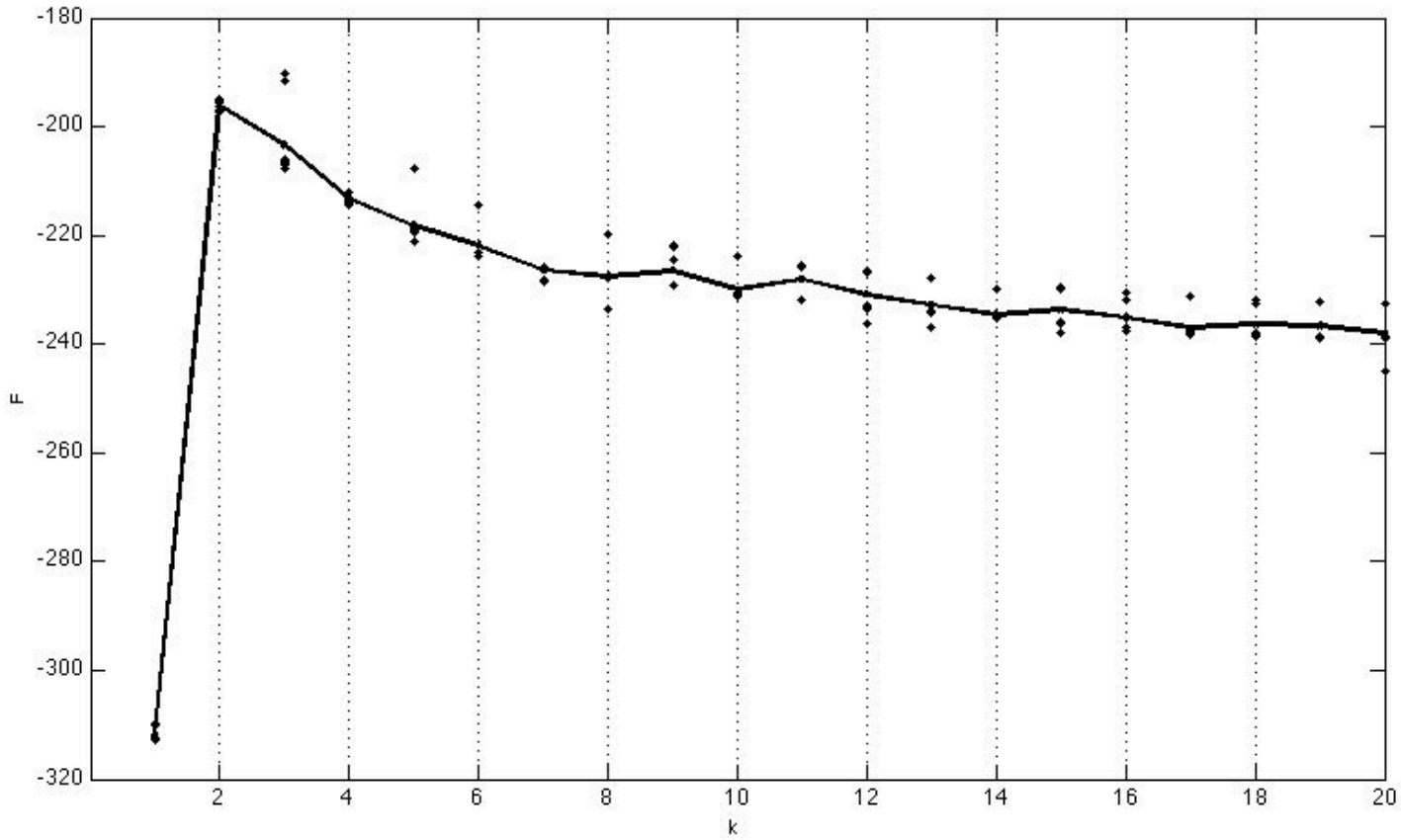




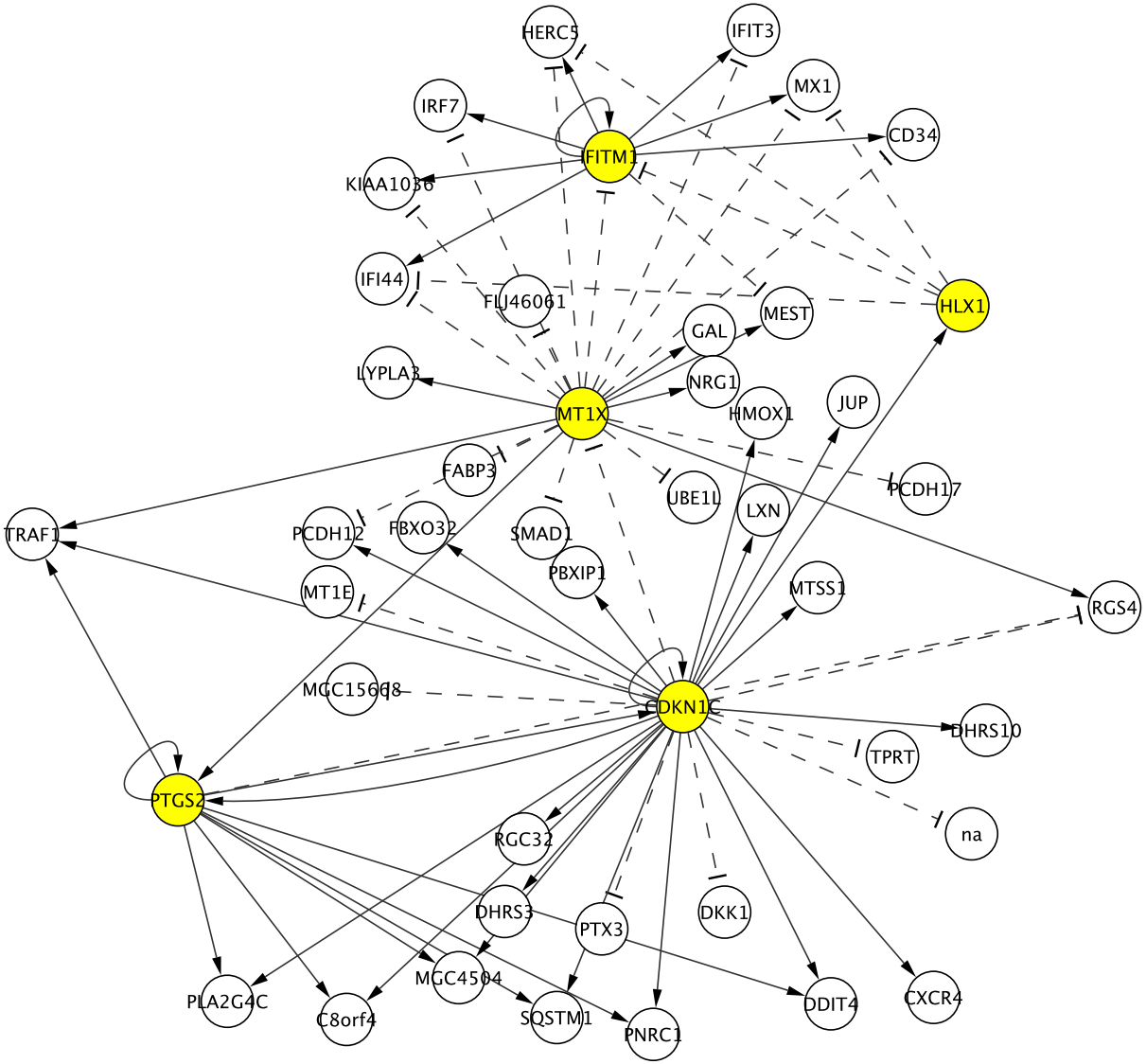
Gene Selection - Method of Tai and Speed



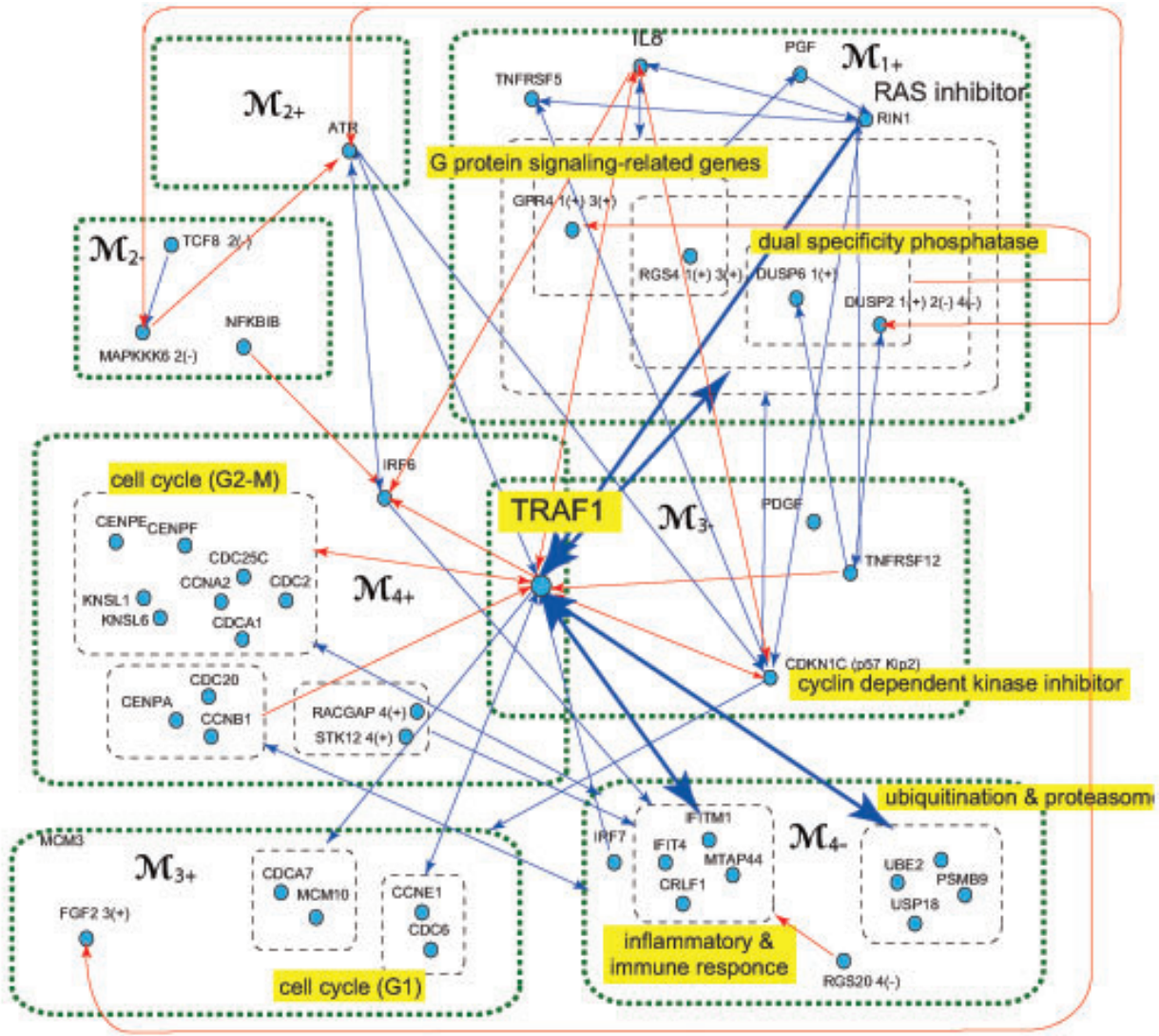
Model Selection



Inferred Network - Top 50 Ranked Genes



Inferred Network from Hirose et al. (2008)



Conclusions

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- *Candidate regulators* predicted as major hubs in inferred network
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