A Bayesian approach to reconstructing genetic regulatory networks with hidden factors [Beal et al., 2004]

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Modeling, Simulation and Inference
of Complex Biological Systems

Outline

Introduction
- Biological Background
- Experiment
- Properties of the experimental data

Methods
- The linear dynamical system model
- The Bayesian Approach to SSMs
- Variational-Bayes model fitting

Results

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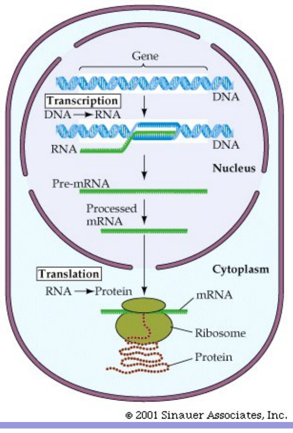
The *Central Dogma* of molecular biology



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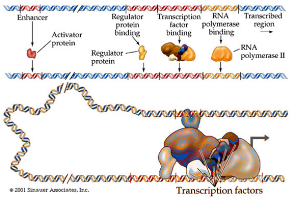
- DNA : where the genetic information lies
- RNA : an intermediate product of gene expression
- Proteins : active molecules of life

Gene regulation : the big picture



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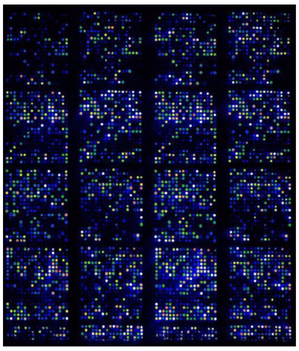
- coding region : where the gene is
- promoter region : determines gene activation conditions
- RNA polymerase : DNA to RNA transcription enzyme
- Transcription factors complex, repressors
- Regulators, enhancers, and the dynamics

Microarray experiment



For a given gene, what do we call *expression level* ?

- non-proportional
- noise
- reproducibility

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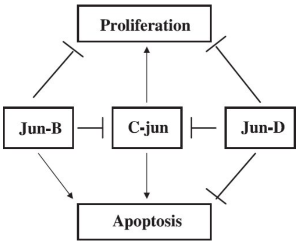
Goal of the study



Proliferation
Jun-B
C-jun
Jun-D
Apoptosis

- genetic regulation cascade occuring during T-cell activation
- what genes are activated / shut down ?

Can statistical modeling help us to better understand T-cell activation ?

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Microarray experiment description

- T-cell activation under PMA and iomicin
- time-series : 10 time points
- 58 genes being monitored

What does our model has to take into account ?

- multivariate data (experimental design)
- time-series (experimental design)
- noisy measurements (microarrays)
- missing data (biology is complex)
- causal inference (goal)

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Linear State-Space models

aka: Linear Dynamical Systems, Kalman filter models

Assumptions

- hidden state variables
- noisy continuous measurements
- Markovian dynamics

Variables and topology

- observed data : $(\mathbf{y}_1, \dots, \mathbf{y}_T), \mathbf{y}_i \in \mathbb{R}^p$
- $\mathbf{y}_t$ generated from hidden $\mathbf{x}_t$, with $\mathbf{x}_t \in \mathbb{R}^k$
- $\mathbf{x}$ follows 1^{st}-order Markov process

Therefore :

$$p(\mathbf{x}_{1:T}, \mathbf{y}_{1:T}) = p(\mathbf{x}_1)p(\mathbf{y}_1|\mathbf{x}_1)\prod_{t=2}^{T} p(\mathbf{x}_t|\mathbf{x}_{t-1})p(\mathbf{y}_t|\mathbf{x}_t)$$

Variables and topology (2)

Assuming

- linear dynamics of hidden variables $p(\mathbf{x}_t|\mathbf{x}_{t-1})$,
- linear dynamics of output function $p(\mathbf{y}_t|\mathbf{x}_t)$,
- model stationarity,
- and state evolution and observation have Gaussian noise

we obtain the linear-Gaussian state-space model (SSM) :

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \tag{1}$$

$$\mathbf{y}_t = C\mathbf{x}_t + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \tag{2}$$

where A is the *kxk* state dynamics matrix (HMM: transition) and C the *pxk* observation matrix (HMM: emission)

Variables and topology (3)

Straighforward extension of our model

Let $\mathbf{u}_{1:T}$ be a time-serie of d-dimensional driving inputs. Then,

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{u}_t + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \tag{3}$$

$$\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{u}_t + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \tag{4}$$

where B is the *dxk* input-to-state matrix and D the *dxp* input-to-observation matrix.
What happens if :

- we provide driving input a constant bias ?
- we want to do control ?
- we define $\mathbf{u}_t := \mathbf{y}_{t-1}$?

Variables and topology (4)

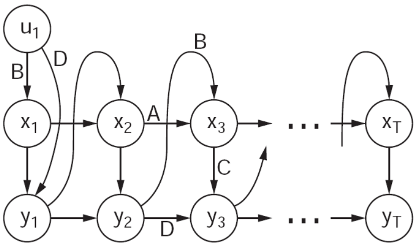
Let $\mathbf{u}_t := \mathbf{y}_{t-1}$. Then,

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{y}_{t-1} + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \qquad (5)$$
$$\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{y}_{t-1} + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \qquad (6)$$

Consequence

Hidden states can now concentrate on modeling hidden factors while Markovian dependencies between successive outputs are now modeled by output-input feedbacks.

Graphical Model



$$\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{y}_{t-1} + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \qquad (7)$$
$$\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{y}_{t-1} + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \qquad (8)$$

Genetic network parameters

Which are the parameters of interest for the genetic regulation network inference problem ?
We have :

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{y}_{t-1} + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \qquad (9)$$
$$\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{y}_{t-1} + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \qquad (10)$$

Plugging in the definition of $\mathbf{x}_t$, $\mathbf{y}_t$ can be written

$$\mathbf{y}_t = (CB + D)\mathbf{y}_{t-1} + \mathbf{r}_t$$

where

$$\mathbf{r}_t = \mathbf{v}_t + C\mathbf{w}_t + CA\mathbf{x}_{t-1}$$

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Bayesian ?! Why ?

Bayesian methodology applied to Kalman filtering

- Assessing parameters $(CB + D)$ significativity : a posteriori distribution instead of bootstrap
- Model fitting : ML estimation in low sampling conditions

Model comparison

- Why ? Determine hidden state space dimension
- Cross-validation and the low-sampling issue
- Evidence framework

The Evidence framework

Let's say we want to compare n models $m_1, m_2, \ldots, m_n$ given observed data $\mathbf{y}$.

$$p(m_k|\mathbf{y}) = \frac{p(\mathbf{y}|m_k)p(m_k)}{p(\mathbf{y})} = \frac{\text{likelihood} * \text{prior}}{\text{normalizing-constant}}$$

Assuming θ is the set of all the parameters, the likelihood $p(\mathbf{y}|m)$ can be written

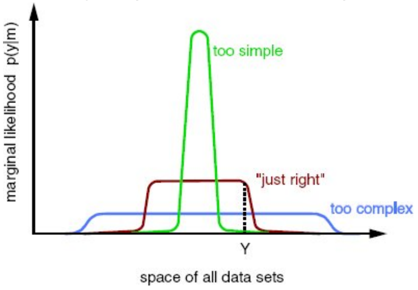
$$p(\mathbf{y}|m) = \int p(\mathbf{y}|\theta, m)p(\theta|m)d\theta$$

Key idea

In the absence of a prior, evidence alone drives model selection [Mackay, 1991].

Occam's razor and the evidence

Parsimony : why does computing the evidence result in choosing simple models over complex ones ?



(picture from [Beal, 2003])

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Simplifying assumptions

Remember our model :

$$\mathbf{x}_t = A\mathbf{x}_{t-1} + B\mathbf{y}_{t-1} + \mathbf{w}_t, \qquad \mathbf{w}_t \sim N(\mathbf{0}, Q) \tag{11}$$

$$\mathbf{y}_t = C\mathbf{x}_t + D\mathbf{y}_{t-1} + \mathbf{v}_t, \qquad \mathbf{v}_t \sim N(\mathbf{0}, R) \tag{12}$$

We make simplying assumptions on the noise covariance matrices :

- $Q :=$ Id (no loss of generality, A will adjust)
- $R :=$ diag(σ) (white noise, with sigma one-dimensional σ)

and define the vector of parameters

$$\theta := (A, B, C, D, R)$$

Simplifying assumptions

To fit the model, we want to maximize the log-likelihood (or log-evidence). But this is computationally intractable (too many variables).

$$\begin{aligned}
\ln p(\mathbf{y}|m) &= \ln \int p(\mathbf{y}, \mathbf{x}, \theta|m) d\mathbf{x} d\theta && (13)\\
&= \ln \int q_1(\mathbf{x}) q_2(\theta) \frac{p(\mathbf{y}, \mathbf{x}, \theta|m)}{q_1(\mathbf{x}) q_2(\theta)} d\mathbf{x} d\theta && (14)\\
&\geq \int q_1(\mathbf{x}) q_2(\theta) \ln \left(\frac{p(\mathbf{y}, \mathbf{x}, \theta|m)}{q_1(\mathbf{x}) q_2(\theta)} \right) d\mathbf{x} d\theta && (15)\\
&= \mathcal{F}(q_1(\mathbf{x}), q_2(\theta), \mathbf{y}) && (16)
\end{aligned}$$

where the step with the inequality follows from appealing to Jensen's inequality.

Goal

- Maximize $\mathcal{F}$ with respect to the free distributions $q_1(\mathbf{x})$ and $q_2(\theta)$
- Joint maximization of $q_1(\mathbf{x})$ (hidden process distribution likelihood) and $q_2(\theta)$ (parameter distribution likelihood)

The Variational-Bayes EM Algorithm

At iteration l,

VB-E step

Find $q_1^{(l+1)}(\mathbf{x})$ that maximzes

$$E\{\mathcal{F}(q_1(\mathbf{x}), q_2^{(l)}(\theta), \mathbf{y})\}$$

VB-M step

Find $q_2^{(l+1)}(\theta)$ that maximzes

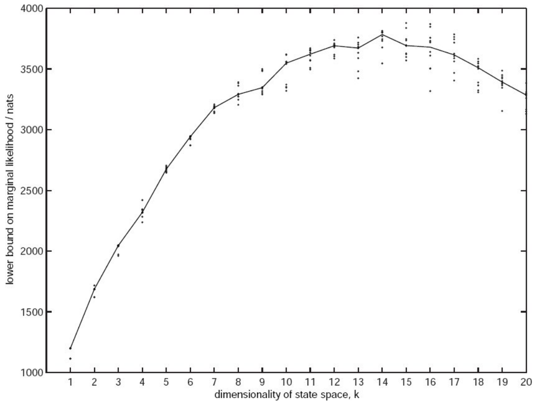
$$E\{\mathcal{F}(q_1^{(l+1)}(\mathbf{x}), q_2(\theta), \mathbf{y})\}$$

and iterate until convergence.

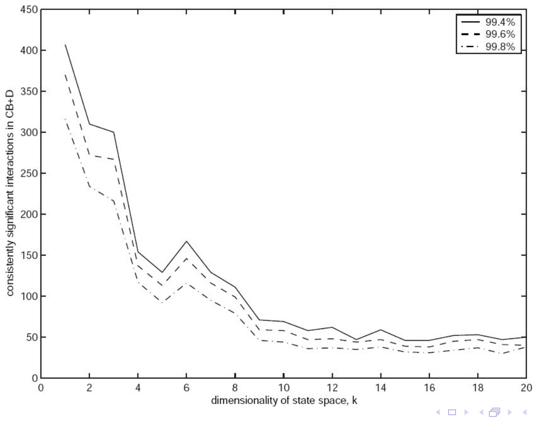
Consequence

- Update hyperparameters and prior parameters to maximize the lower bound on the marginal likelihood
- By applying the VB-EM algorithm, we actually minimize the KL divergence between the approximation $q_1(\mathbf{x})q_2(\theta)$ and the true posterior $p(\mathbf{x}, \theta|\mathbf{y}, m)$ [Beal, 2003]

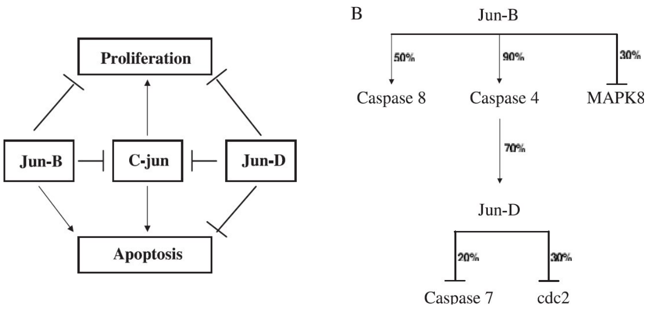
Model comparison



Significant interactions



Biological consequences for the JunB - JunD pathway



Summary

- Kalman filtering : model causal dependencies in auto-correlated, multivariate, noisy data while allowing hidden states
- Bayesian methodology & Kalman filtering : assessing parameter significance, avoiding overfitting when selecting a model (Occam's razor)
- Model fitting with Variational Bayes EM algorithm

- Outlook
  - Test new model biologicaly and investigate what the hidden states account for.
  - Allow for non-linear interactions (expression saturation effects, multiplicative effects).

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