PRIB Tutorial: Gaussian Processes and Gene Regulation

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Motivation

Probabilistic Model for $f(t)$

Cascade Differential Equations

Discussion
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Probabilistic Model for $f(t)$

Cascade Differential Equations

Discussion
“It is difficult to find a black cat in a dark room, especially if there is no cat.”

- Biological systems are immensely complicated.
- Lazebnik argues the need for models that are quantitative.
  - Such models should be predictive of biological behaviour.
  - Such models need to be combined with biological data.
- Systems biology:
  - Build mechanistic models (based on biochemical knowledge) of the system.
  - Identify modules, submodules, and parameterize the models.
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Gene Expression to Transcriptional Regulation.

A “data exploration” problem (computational biology/bioinformatics):

- Use gene expression data to speculate on coregulated genes.
- Traditionally use clustering of gene expression profiles.

Contrast with (computational) systems biology approach:

- Detailed mechanistic model of the system is created.
- Fit parameters of the model to data.
- Problematic for large data (genome wide).
- Need to deal with unobserved biochemical species (TFs).
General Approach

Broadly Speaking: Two approaches to modeling

- **data modeling**
- **mechanistic modeling**
General Approach
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*data modeling*
let the data “speak”

*mechanistic modeling*

General Approach
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**data modeling**
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impose physical laws
General Approach
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- **data modeling**: let the data “speak”
- computational models

- **mechanistic modeling**: impose physical laws

Figure: Computational biology vs systems biology.
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- differential equations
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- PCA, clustering

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- **data modeling**
  - let the data “speak”
  - computational models
  - adaptive models
  - PCA, clustering

- **mechanistic modeling**
  - impose physical laws
  - systems models
  - differential equations
  - SDE, ODE models

Figure: Computational biology vs systems biology.
A Hybrid Approach
Introduce aspects of systems biology to computational models

- We advocate an approach *between* systems and computational biology.
- Introduce aspects of systems biology to the computational approach.
  - There is a computational penalty, but it may be worth paying.
  - Ideally there should be a smooth transition from pure computational (PCA, clustering, SVM classification) to systems (non-linear (stochastic) differential equations).
- This work is one part of that transition.
Radiation can damages molecules including DNA.
Most DNA damage is quickly repaired—single strand breaks, backbone break.
Double strand breaks are more serious—a complete disconnect along the chromosome.

Cell cycle stages:
- **G$_1$**: Cell is not dividing.
- **G$_2$**: Cell is preparing for meitosis, chromosomes have divided.
- **S**: Cell is undergoing meitosis (DNA synthesis).

Main problem is in G$_1$. In G$_2$ there are two copies of the chromosome. In G$_1$ only one copy.
p53 “Guardian of the Cell”

- Responsible for Repairing DNA damage
- Activates DNA Repair proteins
- Pauses the Cell Cycle (prevents replication of damage DNA)
- Initiates apoptosis (cell death) in the case where damage can’t be repaired.
- Large scale feedback loop with NF-κB.
**Figure:** p53. *Left* unbound, *Right* bound to DNA. Images by David S. Goodsell from [http://www.rcsb.org/](http://www.rcsb.org/) (see the “Molecule of the Month” feature).
Figure: Repair of DNA damage by p53. Image from Goodsell (1999).
**Some p53 Targets**

**DDB2** DNA Damage Specific DNA Binding Protein 2. (also governed by C/EBP-beta, E2F1, E2F3,...).

**p21** Cycline-dependent kinase inhibitor 1A (CDKN1A). A regulator of cell cycle progression. (also governed by SREBP-1a, Sp1, Sp3,...).

**hPA26/SESN1** sestrin 1 Cell Cycle arrest.

**BIK** BCL2-interacting killer. Induces cell death (apoptosis)

**TNFRSF10b** tumor necrosis factor receptor superfamily, member 10b. A transducer of apoptosis signals.
Assume p53 affects targets as a single input module network motif (SIM).

Figure: p53 SIM network motif as modelled by Barenco et al. 2006.
Assume that coregulated genes will cluster in the same groups.
Perform clustering, and look for clusters containing target genes.
These are candidates, look for confirmation in the literature etc.
Differential equation model of system.

\[ \frac{d x_j(t)}{dt} = b_j + s_j f(t) - d_j x_j(t) \]

- Rate of mRNA transcription, baseline transcription rate, transcription factor activity, mRNA decay
- We have observations of \( x_j(t) \) from gene expression.
Differential equation model of system.

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d_jx_j(t) + \frac{dx_j(t)}{dt} = b_j + s_jf(t)
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Reorder differential equation.
Mathematical Model

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- Reorder differential equation.
- An estimate of \( \frac{dx_j(t)}{dt} \) is obtained through fitting polynomials.
- Jointly estimate \( f(t) \) at observations of time points along with \( \{b_j, d_j, s_j\}_{j=1}^g \).
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- Fit parameters by maximum likelihood or MCMC sampling.
Clustering model is equivalent to assuming $d_j$, $b_j$, and $s_j$ are very large.

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We have observations of $x_j(t)$ from gene expression.

Reorder differential equation and ignore gradient term.
Mathematical Model

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- We have observations of $x_j(t)$ from gene expression.
- Reorder differential equation and ignore gradient term.
- This suggests genes are scaled and offset versions of the TF.
- By normalizing data and clustering we hope to find those TFs.
Method

Ranked prediction of p53 targets using hidden variable dynamic modeling

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Figure: Results from Barenco et al. (2006). Top is parameter estimates. Bottom is inferred profile.
Figure: Results from Barenco et al. (2006). Activity profile of p53 was measured by Western blot to determine the levels of ser-15 phosphorylated p53 ($\text{ser15P-p53}$).
Outline

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Discussion
Zero mean Gaussian distribution

A multi-variate Gaussian distribution is defined by a mean and a covariance matrix.

\[
\mathcal{N}(\mathbf{f}|\mu, \mathbf{K}) = \frac{1}{(2\pi)^{n/2} |\mathbf{K}|^{1/2}} \exp \left( - (\mathbf{f} - \mu)^\top \mathbf{K}^{-1} (\mathbf{f} - \mu) \right).
\]

We will consider the special case where the mean is zero,

\[
\mathcal{N}(\mathbf{f}|0, \mathbf{K}) = \frac{1}{(2\pi)^{n/2} |\mathbf{K}|^{1/2}} \exp \left( - \frac{\mathbf{f}^\top \mathbf{K}^{-1} \mathbf{f}}{2} \right).
\]
Multi-variate Gaussians

- We will consider a Gaussian with a particular structure of covariance matrix.
- Generate a single sample from this 25 dimensional Gaussian distribution, \( \mathbf{f} = [f_1, f_2 \ldots f_{25}] \).
- We will plot these points against their index.
Figure: A sample from a 25 dimensional Gaussian distribution.
Covariance Function

The covariance matrix

- Covariance matrix shows correlation between points $f_i$ and $f_j$ if $i$ is near to $j$.
- Less correlation if $i$ is distant from $j$.
- Our ordering of points means that the function appears smooth.
- Let’s focus on the joint distribution of two points from the 25.
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Prediction of $f_2$ from $f_1$

demGpCov2D([1 2])

**Figure:** Covariance for $\begin{bmatrix} f_1 \\ f_2 \end{bmatrix}$ is $K_{12} = \begin{bmatrix} 1 & 0.966 \\ 0.966 & 1 \end{bmatrix}$. 
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Prediction of $f_5$ from $f_1$

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Figure: Covariance for $\begin{bmatrix} f_1 \\ f_5 \end{bmatrix}$ is $K_{15} = \begin{bmatrix} 1 & 0.574 \\ 0.574 & 1 \end{bmatrix}$.
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Covariance Functions

Where did this covariance matrix come from?

**Exponentiated Quadratic Kernel Function (RBF, Squared Exponential, Gaussian)**

\[ k(t, t') = \alpha \exp \left( -\frac{||t - t'||^2}{2\ell^2} \right) \]

- Covariance matrix is built using the *inputs* to the function \( t \).
- For the example above it was based on Euclidean distance.
- The covariance function is also known as a kernel.
Covariance Samples

demCovFuncSample

Figure: Exponentiated quadratic kernel with $\ell = 0.3$, $\alpha = 1$
Covariance Samples

demCovFuncSample

Figure: Exponentiated quadratic kernel with $\ell = 1, \alpha = 1$
Figure: Exponentiated quadratic kernel with $\ell = 0.3$, $\alpha = 4$
Figure: Linear covariance function, $\alpha = 16$. 

demCovFuncSample
Figure: MLP covariance function, $\sigma^2_w = 100$, $\sigma^2_b = 100$, $\alpha = 8$. 
Figure: MLP covariance function, $\sigma_w^2 = 100$, $\sigma_b^2 = 0$, $\alpha = 8$.
Figure: Bias term, $\alpha = 4$
Figure: Exponentiated quadratic $\ell = 0.3$, $\alpha = 1$ plus bias term with $\alpha = 1$ plus white noise with $\alpha = 0.01$. 
Figure: Ornstein-Uhlenbeck (stationary Gauss-Markov) covariance function $\ell = 1, \alpha = 4$. 
Figure: Real example: BACCO (see e.g. (Oakley and O’Hagan, 2002)). Interpolation through outputs from slow computer simulations (e.g. atmospheric carbon levels).
Gaussian Process Interpolation

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Graph of a GP

- Relates input variables, \( t \), to vector, \( x \), through \( f \) given kernel parameters \( \theta \).
- Plate notation indicates independence of \( x_i|f_i \).
- Noise model, \( p(x_i|f_i) \) can take several forms.
- Simplest is Gaussian noise.

Figure: The Gaussian process depicted graphically.
Gaussian noise model,

\[ p(x_i|f_i) = \mathcal{N}(x_i|f_i, \sigma^2) \]

where \( \sigma^2 \) is the variance of the noise.

Equivalent to a covariance function of the form

\[ k(t_i, t_j) = \delta_{i,j} \sigma^2 \]

where \( \delta_{i,j} \) is the Kronecker delta function.

Additive nature of Gaussians means we can simply add this term to existing covariance matrices.
Figure: Examples include WiFi localization, C14 calibration curve.
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Learning Kernel Parameters
Can we determine length scales and noise levels from the data?

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\log \mathcal{N} (x|0, K) = -\frac{n}{2} \log 2\pi - \frac{1}{2} \log |K| - \frac{x^\top K^{-1} x}{2}
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Example: Transcriptional Regulation

First Order Differential Equation

\[
\frac{dx_j(t)}{dt} = b_j + s_jf(t) - d_jx_j(t)
\]

It turns out that our Gaussian process assumption for \( f(t) \), implies \( x(t) \) is also a Gaussian process.

The new Gaussian process is over \( f(t) \) and all its targets: \( x_1(t), x_2(t), \ldots \) etc.

Our new covariance matrix gives correlations between all these functions.

This gives us a *probabilistic* model for transcriptional regulation.
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RBF covariance function for $f(t)$

\[ x_i(t) = \frac{b_i}{d_i} + s_i \exp(-d_i t) \int_0^t f(u) \exp(d_i u) \, du. \]

▶ Joint distribution for $x_1(t)$, $x_2(t)$, $x_3(t)$, and $f(t)$.

▶ Here:

<table>
<thead>
<tr>
<th>$d_1$</th>
<th>$s_1$</th>
<th>$d_2$</th>
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<td>5</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
RBF covariance function for $f(t)$

$$x = b/d + \sum_i e_i^\top f \quad f \sim \mathcal{N}(0, \Sigma_i) \rightarrow x \sim \mathcal{N}\left(b/d, \sum_i e_i^\top \Sigma_i e_i\right)$$

- Joint distribution for $x_1(t), x_2(t), x_3(t),$ and $f(t)$.
- Here:

<table>
<thead>
<tr>
<th>$d_1$</th>
<th>$s_1$</th>
<th>$d_2$</th>
<th>$s_2$</th>
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RBF covariance function for $f(t)$

$$x_i(t) = \frac{b_i}{d_i} + s_i \exp(-d_i t) \int_0^t f(u) \exp(d_i u) \, du.$$
Joint Sampling of $f(t)$ and $x(t)$

Figure: Joint samples from the ODE covariance, *black*: $f(t)$, *red*: $x_1(t)$ (high decay/sensitivity), *green*: $x_2(t)$ (medium decay/sensitivity) and *blue*: $x_3(t)$ (low decay/sensitivity).
Joint Sampling of $f(t)$ and $x(t)$

- **simSample**

**Figure:** Joint samples from the ODE covariance, **black:** $f(t)$, **red:** $x_1(t)$ (high decay/sensitivity), **green:** $x_2(t)$ (medium decay/sensitivity) and **blue:** $x_3(t)$ (low decay/sensitivity).
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Artificial Example: Inferring $f(t)$

Inferring TF activity from artificially sampled genes.

True “gene profiles” and noisy observations.

Inferred transcription factor activity.
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Inferred transcription factor activity.
Gaussian process modelling of latent chemical species: applications to inferring transcription factor activities

Pei Gao\(^1\), Antti Honkela\(^2\), Magnus Rattray\(^1\) and Neil D. Lawrence\(^1,\ast\)

\(^1\)School of Computer Science, University of Manchester, Kilburn Building, Oxford Road, Manchester, M13 9PL and 
\(^2\)Adaptive Informatics Research Centre, Helsinki University of Technology, PO Box 5400, FI-02015 TKK, Finland

ABSTRACT

Motivation: Inference of latent chemical species in biochemical interaction networks is a key problem in estimation of the structure

A challenging problem for parameter estimation in ODE models occurs where one or more chemical species influencing the dynamics are controlled outside of the sub-system being modelled. For
p53 Results with GP

(Gao et al., 2008)
Ranking with ERK Signalling

- Target Ranking for Elk-1.
- Elk-1 is phosphorylated by ERK from the EGF signalling pathway.
- Predict concentration of Elk-1 from known targets.
- Rank other targets of Elk-1.
Elk-1 target selection

Fitted model used to rank potential targets of Elk-1
Outline

Motivation

Probabilistic Model for $f(t)$

Cascade Differential Equations

Discussion
Model-based method for transcription factor target identification with limited data

Antti Honkela\textsuperscript{a,1}, Charles Girardot\textsuperscript{b}, E. Hilary Gustafson\textsuperscript{b}, Ya-Hsin Liu\textsuperscript{b}, Eileen E. M. Furlong\textsuperscript{b}, Neil D. Lawrence\textsuperscript{c,1}, and Magnus Rattray\textsuperscript{c,1}

\textsuperscript{a}Department of Information and Computer Science, Aalto University School of Science and Technology, Helsinki, Finland; \textsuperscript{b}Genome Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany; and \textsuperscript{c}School of Computer Science, University of Manchester, Manchester, United Kingdom

Edited by David Baker, University of Washington, Seattle, WA, and approved March 3, 2010 (received for review December 10, 2009)

We present a computational method for identifying potential targets of a transcription factor (TF) using wild-type gene expression time series data. For each putative target gene we fit a simple differential equation model of transcriptional regulation, and the model likelihood serves as a score to rank targets. The expression of a gene is controlled by the transcription factor that regulates it, and we take the former approach. We use Bayesian inference to score putative targets. This results in a parsimonious model with respect to the number of TFs that are necessary to explain the data, and we integrate out these functional degrees of freedom. This greatly reduces the number of parameters required to model the data, which is required to apply our method is wild-type time series collected over a period where TF activity is changing. Our approach allows for complementary evidence from expression data and for genes that are differentially expressed in loss-of-function mutants. Targets of Twist display diverse expression profiles, and in this case a model-based approach performs significantly better than scoring based on correlation with TF expression. Our approach is integrated with ChIP binding data for a specific TF without carrying out TF perturbations.
Transcription factor protein also has governing mRNA. This mRNA can be measured. In signalling systems this measurement can be misleading because it is activated (phosphorylated) transcription factor that counts. In development phosphorylation plays less of a role.
Collaboration with Furlong Lab in EMBL Heidelberg.

- Mesoderm development in Drosophila melanogaster (fruit fly).
- Mesoderm forms in triploblastic animals (along with ectoderm and endoderm). Mesoderm develops into muscles, and circulatory system.
- The transcription factor Twist initiates Drosophila mesoderm development, resulting in the formation of heart, somatic muscle, and other cell types.
- Wildtype microarray experiments publicly available.
- Can we use the cascade model to predict viable targets of Twist?
We take the production rate of active transcription factor to be given by

\[
\frac{df(t)}{dt} = \sigma y(t) - \delta f(t)
\]

\[
\frac{dx_j(t)}{dt} = b_j + s_j f(t) - d_j x_j(t)
\]

The solution for \( f(t) \), setting transient terms to zero, is

\[
f(t) = \sigma \exp(-\delta t) \int_0^t y(u) \exp(\delta u) \, du.
\]
RBF covariance function for $y(t)$

$$f(t) = \sigma \exp(-\delta t) \int_0^t y(u) \exp(\delta u) \, du$$

$$x_i(t) = \frac{b_i}{d_i} + s_i \exp(-d_i t) \int_0^t f(u) \exp(d_i u) \, du.$$
Joint Sampling of $y(t)$, $f(t)$, and $x(t)$

- disimSample

Figure: Joint samples from the ODE covariance, *blue*: $y(t)$ (mRNA of TF), *black*: $f(t)$ (TF concentration), *red*: $x_1(t)$ (high decay target) and *green*: $x_2(t)$ (low decay target)
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**Figure**: Joint samples from the ODE covariance, blue: $y(t)$ (mRNA of TF), black: $f(t)$ (TF concentration), red: $x_1(t)$ (high decay target) and green: $x_2(t)$ (low decay target).
Use mRNA of Twist as driving input.

For each gene build a cascade model that forces Twist to be the only TF.

Compare fit of this model to a baseline (e.g. similar model but sensitivity zero).

Rank according to the likelihood above the baseline.

Compare with correlation, knockouts and time series network identification (TSNI) (Della Gatta et al., 2008).
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0002526.
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0003486.
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0011206.
Results for Twi using the Cascade model

**Figure:** Model for flybase gene identity FBgn00309055.
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0031907.
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0035257.
Results for Twi using the Cascade model

Figure: Model for flybase gene identity FBgn0039286.
Evaluation methods

- Evaluate the ranking methods by taking a number of top-ranked targets and record the number of “positives” (Zinzen et al., 2009):
  - targets with ChIP-chip binding sites within 2 kb of gene
  - (targets differentially expressed in TF knock-outs)
- Compare against
  - Ranking by correlation of expression profiles
  - Ranking by $q$-value of differential expression in knock-outs
- Optionally focus on genes with annotated expression in tissues of interest
Results

**Global ChIP: twi**

- Top N to consider: 20, 100, 250
- Relative enrichment (%)

**Global ChIP: mef2**

- Top N to consider: 20, 100, 250
- Relative enrichment (%)

**Focused ChIP: twi**

- Top N to consider: 20, 100, 250
- Relative enrichment (%)

**Focused ChIP: mef2**

- Top N to consider: 20, 100, 250
- Relative enrichment (%)

- Single−target GP
- Multiple−target GP
- Knock−outs
- Correlation
- Filtered
- Random

'***': $p < 0.001$, '**': $p < 0.01$, '*': $p < 0.05$
Cascade models allow genomewide analysis of potential targets given only expression data.

Once a set of potential candidate targets have been identified, they can be modelled in a more complex manner.

We don’t have ground truth, but evidence indicates that the approach can perform as well as knockouts.
Outline

Motivation

Probabilistic Model for $f(t)$

Cascade Differential Equations

Discussion
Discussion and Future Work

- Integration of probabilistic inference with mechanistic models.
- Applications in modeling gene expression.
- Cascade model introduces model of translation.
- Challenges:
  - Non linear response and non linear differential equations.
  - Scaling up to larger systems.
  - Stochastic differential equations.
Acknowledgements

- Investigators: Neil Lawrence and Magnus Rattray
- Researchers: Pei Gao, Antti Honkela, Guido Sanguinetti, and Jennifer Withers
- Martino Barenco and Mike Hubank at the Institute of Child Health in UCL (p53 pathway).
- Charles Girardot and Eileen Furlong of EMBL in Heidelberg (mesoderm development in *D. Melanogaster*).

Funded by the BBSRC award “Improved Processing of microarray data using probabilistic models” and EPSRC award “Gaussian Processes for Systems Identification with applications in Systems Biology”


Experimental Structure of Arrays

Nonlinear Response
Molecular biology time series

Antti Honkela

- Biological systems are dynamic, observing their time evolution very helpful
- Time series measurements of gene expression, protein activity, protein binding, ...
- Problem: most of these assays are highly disruptive to the sample
- Therefore: time series = series of independent experiments run for different lengths of time
- This has implications for modelling...
Simulated molecular biology time series

Simulated Mef2 protein

Simulated FBgn0030955 mRNA
Simulated molecular biology time series

Simulated Mef2 protein

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Simulated FBgn0030955 mRNA
Real gene expression time series
Example model: Linear ODE model of transcription

▶ Linear Activation Model (Barenco et al., 2006, Genome Biology)

\[ \frac{dx_j(t)}{dt} = b_j + s_j f(t) - d_j x_j(t) \]

▶ \(x_j(t)\) – concentration of gene \(j\)'s mRNA
▶ \(f(t)\) – concentration of active transcription factor
▶ Model parameters: baseline \(b_j\), sensitivity \(s_j\) and decay \(d_j\)
▶ Placing a Gaussian process (GP) prior on \(f(t)\) leads to a joint GP over all concentration profiles (Gao et al., 2008, Bioinformatics)
How to connect the model to data?

1. Assume independent profiles for each complete (biological) repeat
   - Loses statistical power for extra independence assumptions
   - Is it meaningful to order the repeats?

2. Assume one shared underlying profile with independent observations
   - Potentially sensitive to outliers
Exchangeability analysis

Assume $x_{j}^{k}(t_{i})$ observation of $k$th repeat of $j$th gene at $i$th time

$$
\begin{align*}
    x_{j}^{k}(t_{i}) & \leftrightarrow x_{j}^{k'}(t_{i}) \\
    x_{j}^{k}(t_{i}) & \leftrightarrow x_{j'}^{k}(t_{i})
\end{align*}
$$

“swap arrays”

“swap single gene”

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<td>2. Shared profile</td>
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Solution: hierarchical GP model

- Assume the underlying $f(t)$ is composed of a shared and an experiment-specific part $f_{ik}(t)$

\[
\frac{dx_j(t)}{dt} = b_j + s_j[f_{\text{shared}}(t) + f_{ik}(t)] - d_jx_j(t)
\]

- Covariance is of the same form as usual
- Introduces additional covariance terms for measurements from the same experiment
- Alternative parametrisations of variance of $f_{ik}(t)$
  - Shared across all experiments
  - Sampled independently for each experiment
Assume $x_j^k(t_i)$ observation of $k$th repeat of $j$th gene at $i$th time

$x_j^k(t_i) \leftrightarrow x_j^{k'}(t_i)$ \hspace{1cm} \text{“swap arrays”}

$x_j^k(t_i) \leftrightarrow x_j^{k'}(t_i)$ \hspace{1cm} \text{“swap single gene”}

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Assume TF is transcriptionally regulated with related mRNA $y(t)$

This yields a system of ODEs (Gao et al., 2008)

\[
\frac{df(t)}{dt} = \sigma y(t) - \delta f(t)
\]

\[
\frac{dx_j(t)}{dt} = b_j + s_j f(t) - d_j x_j(t)
\]

The corresponding GP model can be derived analogously to the previous case
Independent profiles

FBgn0011656 mRNA (input)

Inferred TF Protein Concentration

FBgn0010434 mRNA

FBgn0010434 mRNA
Hierarchical model

FBgn0011656 mRNA (input)

Inferred TF Protein Concentration

FBgn0010434 mRNA
Outline

Experimental Structure of Arrays

Nonlinear Response
Consider the model of transcription,

\[ \frac{dx_j(t)}{dt} = b_j + s_j g(f(t)) - d_j x_j(t), \]

where \( g(\cdot) \) is a non-linear function. The differential equation can still be solved,

\[ x_j(t) = \frac{b_j}{d_j} + s_j \int_0^t e^{-d_j(t-u)} g_j(f(u)) \, du \]
Laplace’s method: approximate posterior mode as Gaussian

\[ p(f \mid x) = \mathcal{N}(\hat{f}, A^{-1}) \propto \exp \left( -\frac{1}{2} (f - \hat{f})^\top A (f - \hat{f}) \right) \]

where \( \hat{f} = \arg\max p(f \mid x) \) and \( A = -\nabla\nabla \log p(f \mid x) \mid_{f=\hat{f}} \) is the Hessian of the negative posterior at that point. To obtain \( \hat{f} \) and \( A \), we define the following function \( \psi(f) \) as:

\[ \log p(f \mid x) \propto \psi(f) = \log p(x \mid f) + \log p(f) \]
Assigning a GP prior distribution to $f(t)$, it then follows that

$$\log p(f) = -\frac{1}{2} f^\top K^{-1} f - \frac{1}{2} \log |K| - \frac{n}{2} \log 2\pi$$

where $K$ is the covariance matrix of $f(t)$. Hence,

$$\nabla \psi(f) = \nabla \log p(x|f) - K^{-1} f$$

$$\nabla \nabla \psi(f) = \nabla \nabla \log p(x|f) - K^{-1} = -W - K^{-1}$$
Estimation of $\psi(f)$

Newton’s method is applied to find the maximum of $\psi(f)$ as

$$f^{\text{new}} = f - (\nabla\nabla \psi(f))^{-1} \nabla \psi(f)$$

$$= (W + K^{-1})^{-1} (Wf - \nabla \log p(x|f))$$

In addition, $A = -\nabla\nabla \psi(\hat{f}) = W + K^{-1}$ where $W$ is the negative Hessian matrix. Hence, the Laplace approximation to the posterior is a Gaussian with mean $\hat{f}$ and covariance matrix $A^{-1}$ as

$$p(f \mid x) \approx N(\hat{f}, A^{-1}) = N(\hat{f}, (W + K^{-1})^{-1})$$
The marginal likelihood is useful for estimating the model parameters $\theta$ and covariance parameters $\ell$

$$p(x|\theta, \phi) = \int p(x|f, \theta) p(f|\phi) \, df = \int \exp(\psi(f)) \, df$$

Using Taylor expansion of $\psi(f)$,

$$\log p(x|\theta, \phi) = \log p(x|\hat{f}, \theta, \phi) - \frac{1}{2} f^\top K^{-1} f - \frac{1}{2} \log |I + KW|$$

The parameters $\eta = \{\theta, \phi\}$ can be then estimated by using

$$\frac{\partial \log p(x|\eta)}{\partial \eta} = \left. \frac{\partial \log p(x|\eta)}{\partial \eta} \right|_{\text{explicit}} + \frac{\partial \log p(x|\eta)}{\partial \hat{f}} \frac{\partial \hat{f}}{\partial \eta}$$
The Michaelis-Menten activation model uses the following non-linearity

\[ g_j(f(t)) = \frac{e^{f(t)}}{\gamma_j + e^{f(t)}}, \]

where we are using a GP \( f(t) \) to model the log of the TF activity.
Figure: Laplace approximation error bars along with samples from the true posterior distribution.
DNA damage in bacteria may occur as a result of activity of antibiotics.

LexA is bound to the genome preventing transcription of the SOS genes.

RecA protein is stimulated by single stranded DNA, inactivates the LexA repressor.

This allows several of the LexA targets to transcribe.

The SOS pathway may be essential in antibiotic resistance Cirz et al. (2005).

Aim is to target these proteins to produce drugs to increase efficacy of antibiotics Lee et al. (2005).
Data from Courcelle et al. (2001)

UV irradiation of *E. coli*. in both wild-type cells and lexA1 mutants, which are unable to induce genes under LexA control.

Response measured with two color hybridization to cDNA arrays.
Given measurements of gene expression at N time points \((t_0, t_1, \ldots, t_{N-1})\), the temporal profile of a gene \(i\), \(x_i(t)\), that solves the ODE in Eq. 1 can be approximated by

\[
    x_i(t) = x_i^0 e^{-d_i t} + \frac{b_i}{d_i} + s_i e^{-d_i t} \int_0^t g(f(u)) e^{d_i u} \, du.
\]

\[
    x_i(t) = x_i^0 e^{-d_i t} + \frac{b_i}{d_i} + s_i e^{-d_i t} \frac{1}{t_{j+1} - t_j} \sum_{j=0}^{N-2} g(\bar{f}_j) (e^{d_i t_{j+1}} - e^{d_i t_j})
\]

where \(\bar{f}_j = \frac{(f(t_j) + f(t_{j+1}))}{2}\) on each subinterval \((t_j, t_{j+1})\), \(j = 0, \ldots, N - 2\). This is under the simplifying assumption that \(f(t)\) is a piece-wise constant function on each subinterval \((t_j, t_{j+1})\). Repression model: \(g(f(t)) = \frac{1}{\gamma + e^{f(t)}}\).
Figure: Fig. 2 from Khanin et al. (2006): Reconstructed activity level of master repressor LexA, following a UV dose of 40 J/m².
**Figure:** Fig. 3 from Khanin et al. (2006): Reconstructed profiles for four genes in the LexA SIM.
We can use the same model of repression,

\[
g_j(f(t)) = \frac{1}{\gamma_j + e^{f(t)}}
\]

In the case of repression we have to include the transient term,

\[
x_j(t) = \alpha_j e^{-d_j t} + \frac{b_j}{d_j} + s_j \int_0^t e^{-d_j(t-u)} g_j(f(u)) du
\]
Pei Gao

Figure: Our results using an MLP kernel. From Gao et al. (2008).
Sample in Gaussian processes

\[ p(f|x) \propto p(x|f)p(f) \]

Likelihood relates GP to data through

\[ x_j(t) = \alpha_j e^{-d_j t} + \frac{b_j}{d_j} + s_j \int_0^t e^{-d_j (t-u)} g_j(f(u)) du \]

We use control points for fast sampling.
The Metropolis-Hastings algorithm

- Initialize $f^{(0)}$
- Form a Markov chain. Use a proposal distribution $Q(f^{(t+1)}|f^{(t)})$ and accept with the M-H step

$$
\min \left( 1, \frac{p(x|f^{(t+1)})p(f^{(t+1)})}{p(x|f^{(t)})p(f^{(t)})} \frac{Q(f^{(t)}|f^{(t+1)})}{Q(f^{(t+1)}|f^{(t)})} \right)
$$

- $f$ can be very high dimensional (hundreds of points)
- How do we choose the proposal $Q(f^{(t+1)}|f^{(t)})$?
  - Can we use the GP prior $p(f)$ as the proposal?
Sampling using control points

- Separate the points in $\mathbf{f}$ into two groups:
  - few control points $\mathbf{f}_c$
  - and the large majority of the remaining points $\mathbf{f}_\rho = \mathbf{f} \setminus \mathbf{f}_c$

- Sample the control points $\mathbf{f}_c$ using a proposal $q\left(\mathbf{f}_c^{(t+1)}|\mathbf{f}_c^{(t)}\right)$

- Sample the remaining points $\mathbf{f}_\rho$ using the conditional GP prior $p\left(\mathbf{f}_\rho^{(t+1)}|\mathbf{f}_c^{(t+1)}\right)$

- The whole proposal is

$$Q\left(\mathbf{f}^{(t+1)}|\mathbf{f}^{(t)}\right) = p\left(\mathbf{f}_\rho^{(t+1)}|\mathbf{f}_c^{(t+1)}\right) q\left(\mathbf{f}_c^{(t+1)}|\mathbf{f}_c^{(t)}\right)$$

- It's like sampling from the prior $p(\mathbf{f})$ but imposing random walk behaviour through the control points
Sample 121 points using 10 control points
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points
Sample 121 points using 10 control points
Sample 121 points using 10 control points
Sample 121 points using 10 control points
Sample 121 points using 10 control points
Sampling using control points

Few samples drawn during MCMC
Again consider the Michaelis-Menten kinetic equation
\[
\frac{dx_j(t)}{dt} = b_j + s_j \frac{1}{\exp(f(t)) + \gamma_j} - d_j x_j(t)
\]

- We have 14 genes (5 kinetic parameters each)
- Gene expressions are available for \( T = 6 \) time slots
- TF \((f)\) is discretized using 121 points
- MCMC details:
  - 6 control points are used (placed in a equally spaced grid)
  - Running time was 5 hours for 2 million sampling iterations plus burn in
  - Acceptance rate for \( f \) after burn in was between 15\% - 25\%
Results in E.coli data: Predicted gene expressions

- **dinF Gene**
- **dinI Gene**
- **lexA Gene**
- **recA Gene**
- **recN Gene**
- **ruvA Gene**
Results in E.coli data: Predicted gene expressions
Results in E.coli data: Predicted gene expressions
Results in E.coli data: Protein concentration
Results in E.coli data: Kinetic parameters

- Basal rates
- Decay rates
- Sensitivities
- Gamma parameters
Results in E.coli data: Genes with low sensitivity value

Sensitivities

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<tr>
<th>Gene</th>
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<tr>
<td>yjiW</td>
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</tr>
</tbody>
</table>
Results in E.coli data: Confidence intervals for the kinetic parameters

Basal rates

Decay rates

Sensitivities

Gamma parameters
One transcription factor (p53) that acts as an activator. We consider the Michaelis-Menten kinetic equation

\[
\frac{dx_j(t)}{dt} = b_j + s_j \frac{\exp(f(t))}{\exp(f(t)) + \gamma_j} - d_j x_j(t)
\]

We have 5 genes

Gene expressions are available for \( T = 7 \) times and there are 3 replicas of the time series data

TF \((f)\) is discretized using 121 points

MCMC details:

- 7 control points are used (placed in a equally spaced grid)
- Running time 4/5 hours for 2 million sampling iterations plus burn in
- Acceptance rate for \( f \) after burn in was between 15\% – 25\%
Data used by Barenco et al. (2006): Predicted gene expressions for the 1st replica
Data used by Barenco et al. (2006): Protein concentrations

Linear model (Barenco et al. predictions are shown as crosses)

Nonlinear (Michaelis-Menten kinetic equation)
Our results (grey) compared with Barenco et al. (2006) (black). Note that Barenco et al. use a linear model.