

Model Based Target Identification from Expression Data

Neil D. Lawrence

work with Magnus Rattray (co-PI)

Post-docs: Pei Gao, Guido Sanguinetti

Visitor: Antti Honkela

University of Sheffield
Gene Profiling Workshop at Liverpool

12th October 2011

Outline

Motivation

Probabilistic Model for $p(t)$

Cascade Differential Equations

Discussion and Future Work

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Probabilistic Model for $p(t)$

Cascade Differential Equations

Discussion and Future Work

Can a Biologist Fix a Radio? Lazebnik (2002)

The Case for Systems Biology

"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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Coregulation of Gene Expression

The Case for Computational Biology

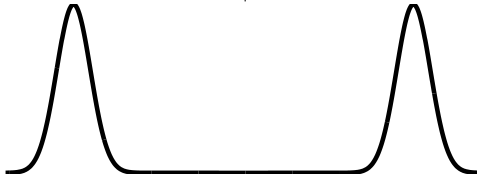
- ▶ Gene Expression to Transcriptional Regulation.
- ▶ A “data exploration” problem (computational biology/bioinformatics):
 - ▶ Use gene expression data to speculate on coregulated genes.
 - ▶ Traditionally use clustering of gene expression profiles.
- ▶ Contrast with (computational) systems biology 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).

Computational Biology vs Computational Systems Biology

Broadly Speaking: Two approaches to modeling

data-modeling

mechanistic-modeling



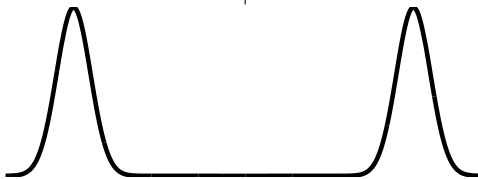
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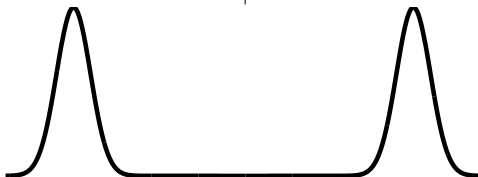
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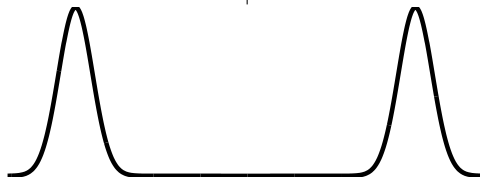
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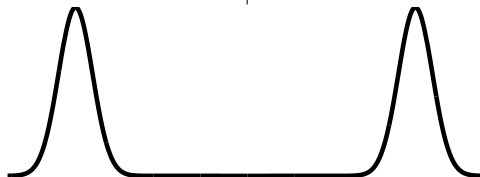
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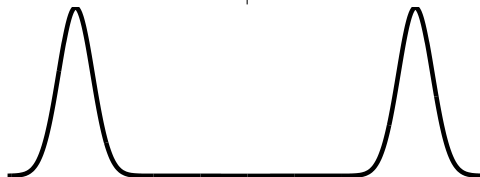
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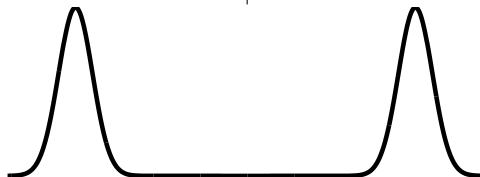
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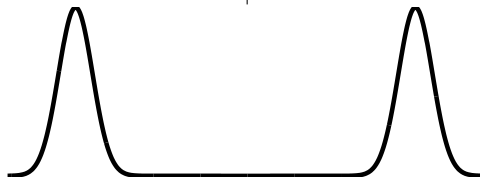
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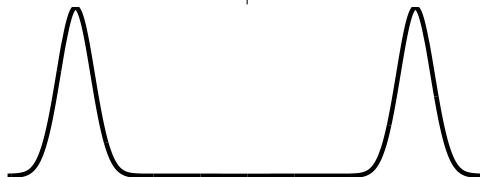
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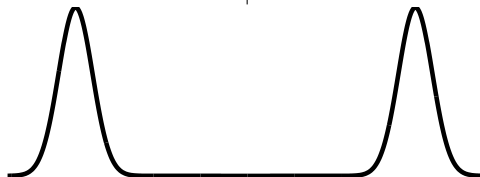
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Weakly Mechanistic

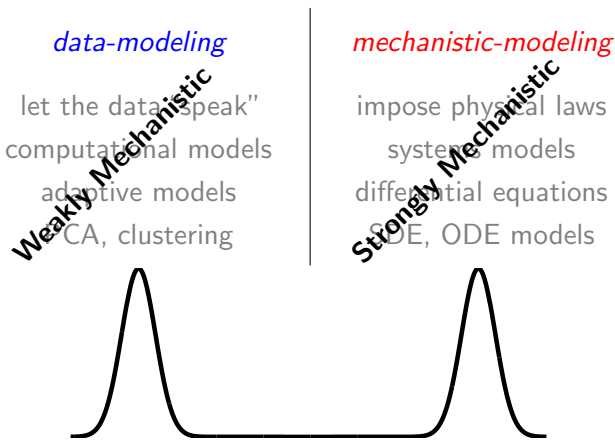
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Computational Biology vs Computational Systems Biology

Broadly Speaking: Two approaches to modeling



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 Damage in the Cell

- ▶ Radiation can damage 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 meiosis, chromosomes have divided.
 - ▶ S: Cell is undergoing meiosis (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- κ B.

p53 DNA Damage Repair

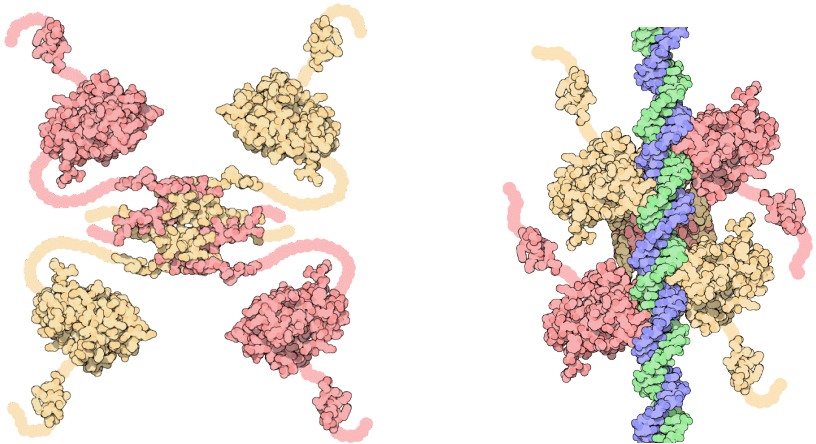


Figure: p53. *Left* unbound, *Right* bound to DNA. Images by David S. Goodsell from <http://www.rcsb.org/> (see the "Molecule of the Month" feature).

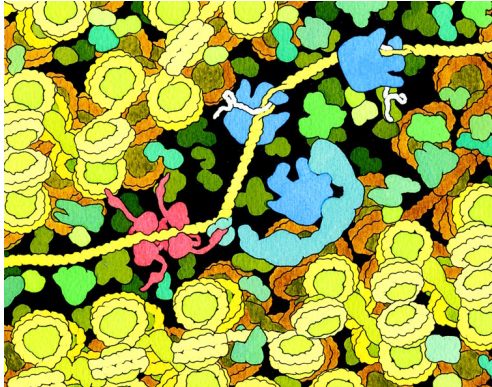


Figure: Repair of DNA damage by p53. Image from Goodsell (1999).

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.

Modelling Assumption

- ▶ Assume p53 affects targets as a single input module network motif (SIM).

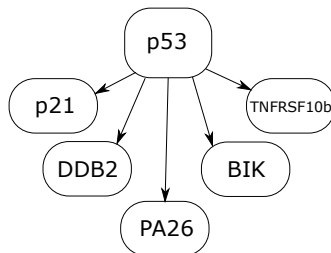


Figure: p53 SIM network motif as modelled by Barenco et al. 2006.

Standard Approach

Clustering of Gene Expression Profiles

- ▶ 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.

Method

Open Access

Ranked prediction of p53 targets using hidden variable dynamic modeling

Martino Barenco^{*†}, Daniela Tomescu^{*}, Daniel Brewer^{*†}, Robin Callard^{*†}, Jaroslav Stark^{†‡} and Michael Hubank^{*†}

Addresses: ^{*}Institute of Child Health, University College London, Guilford Street, London WC1N 1EH, UK. [†]CoMPLEX (Centre for Mathematics and Physics in the Life Sciences and Experimental Biology), University College London, Stephenson Way, London, NW1 2HE, UK. [‡]Department of Mathematics, Imperial College London, London SW7 2AZ, UK.

Correspondence: Michael Hubank. Email: m.hubank@ich.ucl.ac.uk

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Mathematical Model

- Differential equation model of system.

$$\frac{dm_j(t)}{dt} = b_j + s_j p(t) - d_j m_j(t)$$

rate of mRNA transcription, baseline transcription rate,
transcription factor activity, mRNA decay

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

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$$\frac{dm_j(t)}{dt} = b_j + s_j p(t) - d_j m_j(t)$$
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- ▶ We have observations of $m_j(t)$ from gene expression.
- ▶ Reorder differential equation.

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- Jointly estimate $p(t)$ at observations of time points along with $\{b_j, d_j, s_j\}_{j=1}^g$.

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- ▶ Jointly estimate $p(t)$ at observations of time points along with $\{b_j, d_j, s_j\}_{j=1}^g$.
- ▶ Fit parameters by maximum likelihood or MCMC sampling.

Mathematical Model

- ▶ Clustering model is equivalent to assuming d_j , b_j , and s_j are v. large.

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- ▶ We have observations of $m_j(t)$ from gene expression.
- ▶ Reorder differential equation and ignore gradient term.

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- ▶ We have observations of $m_j(t)$ 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.

Response of p53

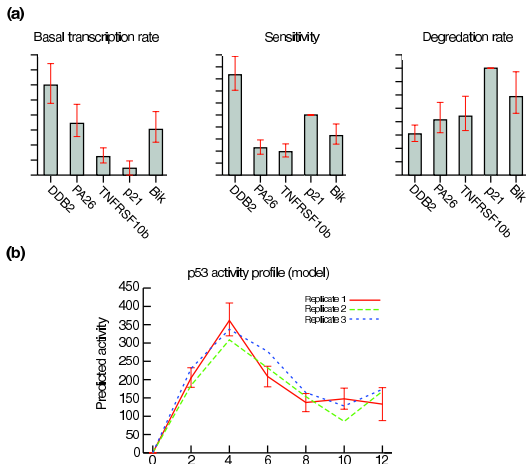


Figure: Results from Barenco et al. (2006). Top is parameter estimates. Bottom is inferred profile.

Response to p53 ...

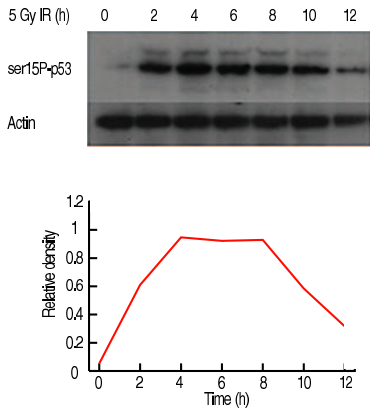


Figure: Results from Barenco et al. (2006). Activity profile of p53 was measured by Western blot to determine the levels of ser-15 phosphorylated p53 (ser15P-p53).

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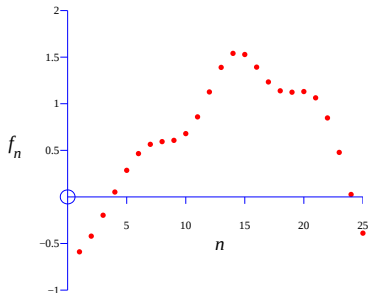
Probabilistic Model for $p(t)$

- ▶ We introduce a probabilistic model for $p(t)$.
- ▶ It is known as a Gaussian process, but we can think of it as a multivariate Gaussian (also known as a multivariate normal) distribution.
- ▶ The distribution has a mean vector, $\mathbf{m}$ and a covariance matrix, $\mathbf{K}$.
- ▶ We will consider the mean to be zero: $\mathbf{m} = 0$.
- ▶ The covariance matrix will be structured to give correlation between samples.
- ▶ We will sample 25 points from the Gaussian distribution.
- ▶ Samples are governed by a 25×25 correlation matrix.

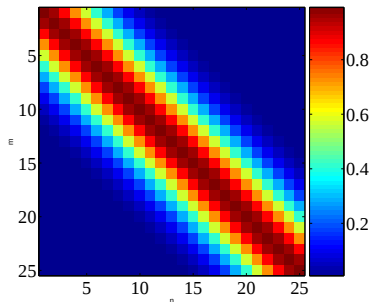
Multi-variate Gaussians

- ▶ We will consider a Gaussian with a particular structure of covariance matrix.
- ▶ Generate a single sample from this 25 dimensional Gaussian distribution, $\mathbf{f} = [f_1, f_2 \dots f_{25}]$.
- ▶ We will plot these points against their index.

Gaussian Distribution Sample



(a) A 25 dimensional correlated random variable (values plotted against index)



(b) colormap showing correlations between dimensions

Figure: A sample from a 25 dimensional Gaussian distribution.

The covariance matrix

- ▶ Covariance matrix shows correlation between points p_m and p_n if n is near to m .
- ▶ Less correlation if n is distant from m .
- ▶ Our ordering of points means that the *function appears smooth*.
- ▶ In practice covariance matrix is computed as a function of time—index is equivalent to time.
- ▶ Different covariance functions give different characteristics.
- ▶ Because the models are *probabilistic* we can sample different characteristics.

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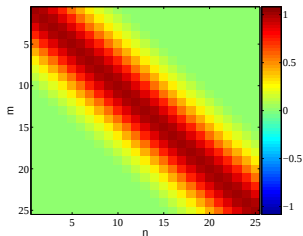
Covariance Functions

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

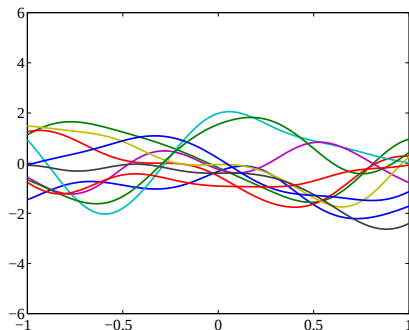


Figure: Exponentiated quadratic kernel with $\ell = 0.3$, $\alpha = 1$

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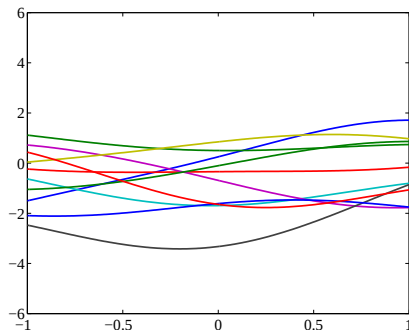


Figure: Exponentiated quadratic kernel with $\ell = 1$, $\alpha = 1$

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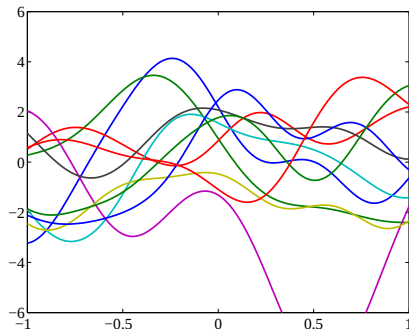


Figure: Exponentiated quadratic kernel with $\ell = 0.3$, $\alpha = 4$

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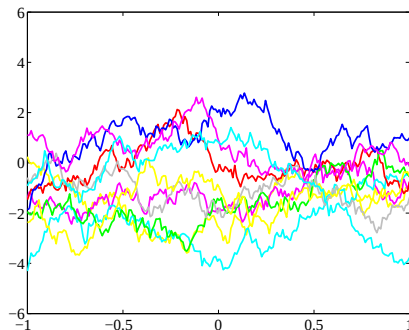


Figure: Ornstein-Uhlenbeck (stationary Gauss-Markov) covariance function $\ell = 1$, $\alpha = 4$

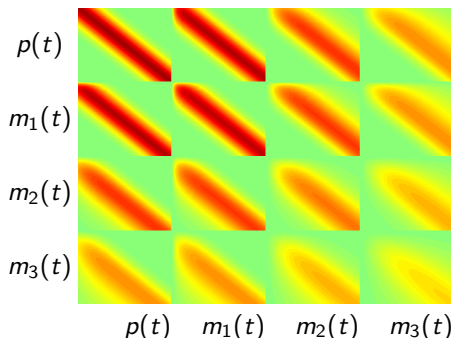
Covariance for Transcription Model

RBF covariance function for $p(t)$

$$m_i(t) = \frac{b_i}{d_i} + s_i \exp(-d_i t) \int_0^t p(u) \exp(d_i u) du.$$

- ▶ Joint distribution for $m_1(t)$, $m_2(t)$, $m_3(t)$, and $p(t)$.
- ▶ Here:

d_1	s_1	d_2	s_2	d_3	s_3
5	5	1	1	0.5	0.5



Covariance for Transcription Model

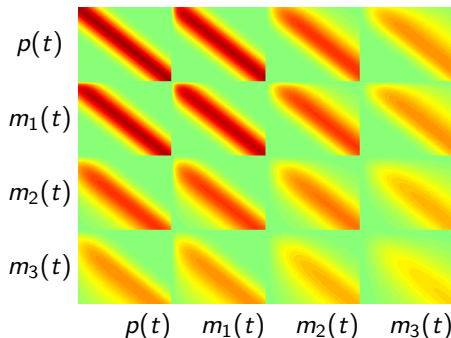
RBF covariance function for $p(t)$

$$m = b/d + \sum_i \mathbf{e}_i^\top \mathbf{p} \quad \mathbf{p} \sim \mathcal{N}(\mathbf{0}, \Sigma_i) \rightarrow m \sim \mathcal{N}\left(b/d, \sum_i \mathbf{e}_i^\top \Sigma_i \mathbf{e}_i\right)$$

- ▶ Joint distribution for $m_1(t)$, $m_2(t)$, $m_3(t)$, and $p(t)$.

- ▶ Here:

d_1	s_1	d_2	s_2	d_3	s_3
5	5	1	1	0.5	0.5



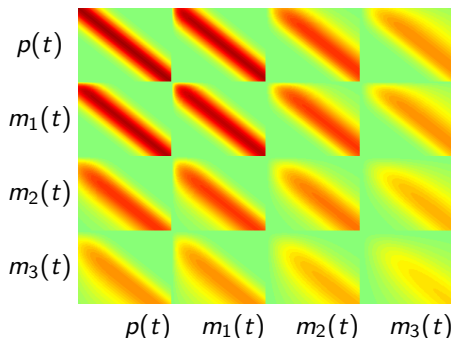
Covariance for Transcription Model

RBF covariance function for $p(t)$

$$m_i(t) = \frac{b_i}{d_i} + s_i \exp(-d_i t) \int_0^t p(u) \exp(d_i u) du.$$

- ▶ Joint distribution for $m_1(t)$, $m_2(t)$, $m_3(t)$, and $p(t)$.
- ▶ Here:

d_1	s_1	d_2	s_2	d_3	s_3
5	5	1	1	0.5	0.5



Joint Sampling of $f(t)$ and $x(t)$

► `simSample`

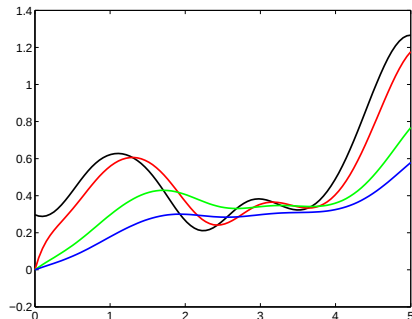


Figure: Joint samples from the ODE covariance, *black*: $p(t)$, *red*: $m_1(t)$ (high decay/sensitivity), *green*: $m_2(t)$ (medium decay/sensitivity) and *blue*: $m_3(t)$ (low decay/sensitivity).

Joint Sampling of $f(t)$ and $x(t)$

► `simSample`

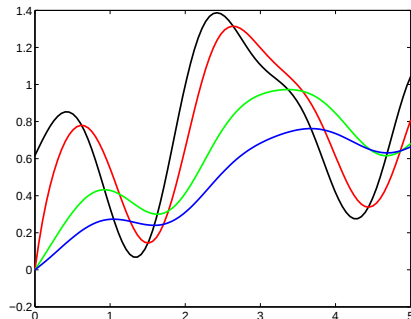


Figure: Joint samples from the ODE covariance, *black*: $p(t)$, *red*: $m_1(t)$ (high decay/sensitivity), *green*: $m_2(t)$ (medium decay/sensitivity) and *blue*: $m_3(t)$ (low decay/sensitivity).

Joint Sampling of $f(t)$ and $x(t)$

► `simSample`

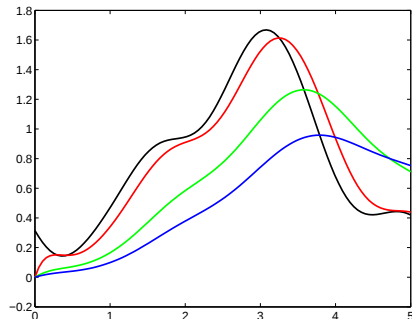


Figure: Joint samples from the ODE covariance, *black*: $p(t)$, *red*: $m_1(t)$ (high decay/sensitivity), *green*: $m_2(t)$ (medium decay/sensitivity) and *blue*: $m_3(t)$ (low decay/sensitivity).

Joint Sampling of $f(t)$ and $x(t)$

► `simSample`

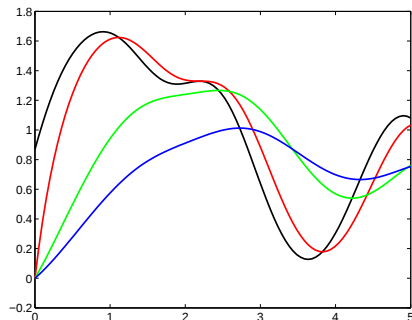
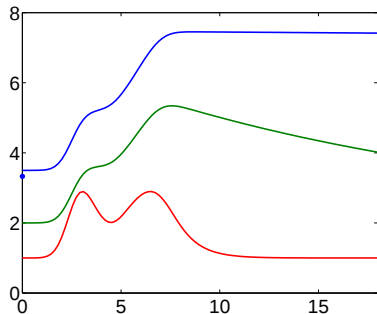


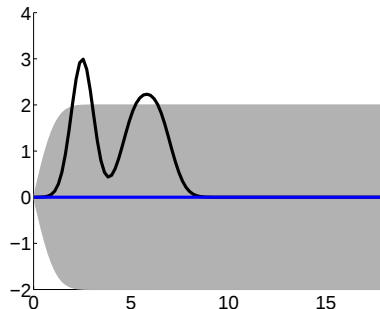
Figure: Joint samples from the ODE covariance, *black*: $p(t)$, *red*: $m_1(t)$ (high decay/sensitivity), *green*: $m_2(t)$ (medium decay/sensitivity) and *blue*: $m_3(t)$ (low decay/sensitivity).

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



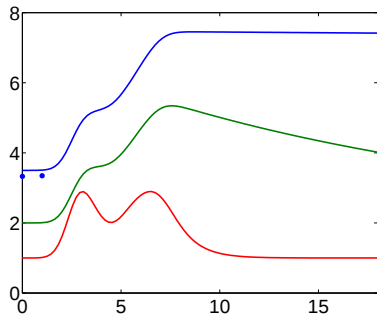
True “gene profiles” and noisy observations.



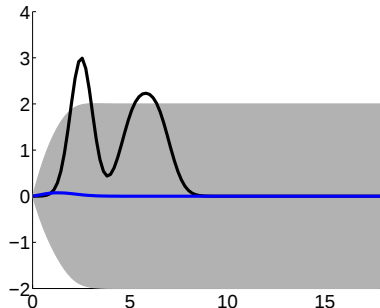
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



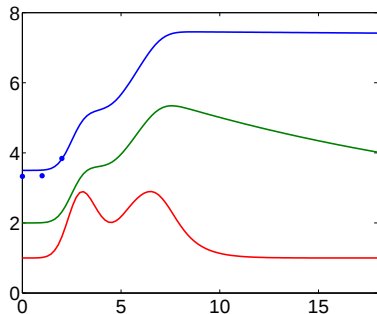
True “gene profiles” and noisy observations.



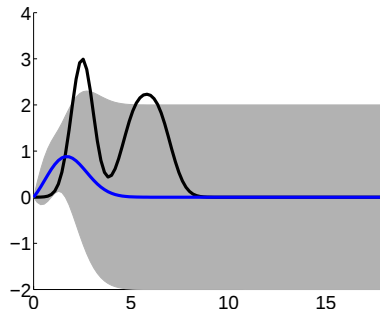
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



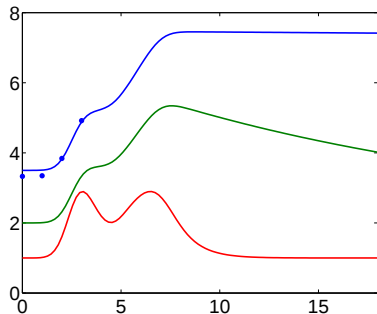
True “gene profiles” and noisy observations.



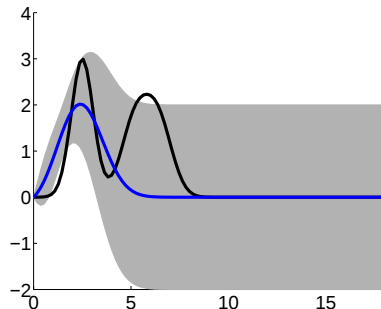
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

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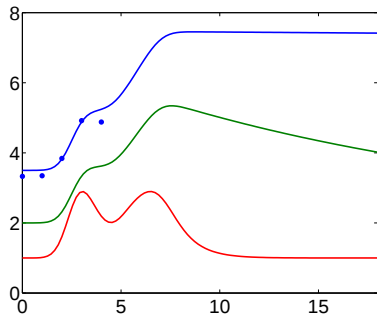
True “gene profiles” and noisy observations.



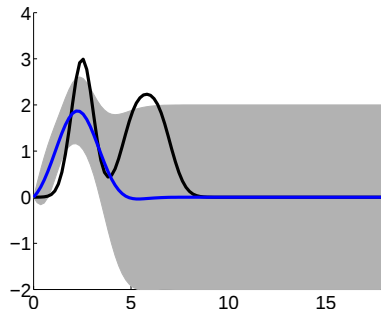
Inferred transcription factor activity.

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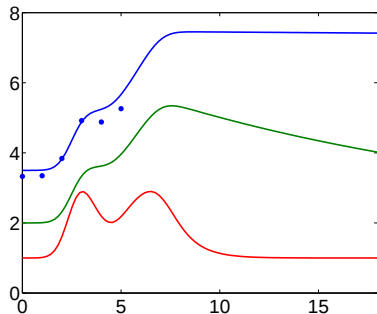
True “gene profiles” and noisy observations.



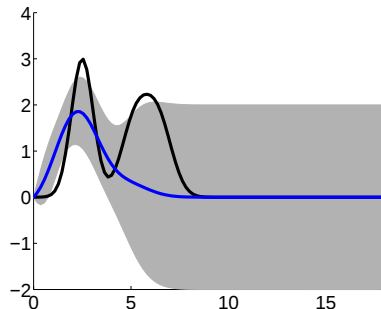
Inferred transcription factor activity.

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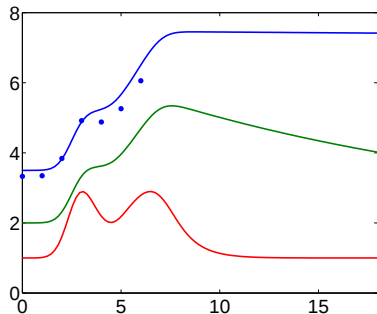
True “gene profiles” and noisy observations.



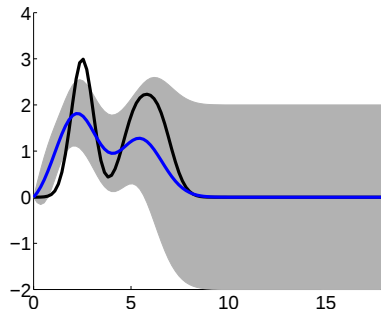
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



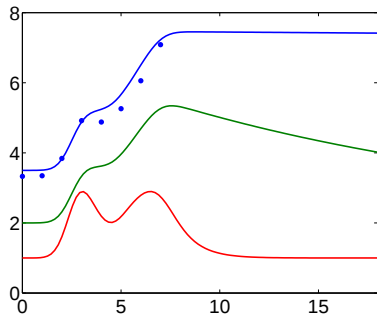
True “gene profiles” and noisy observations.



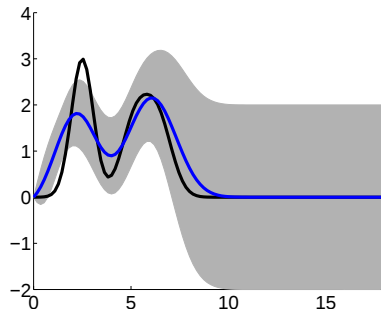
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



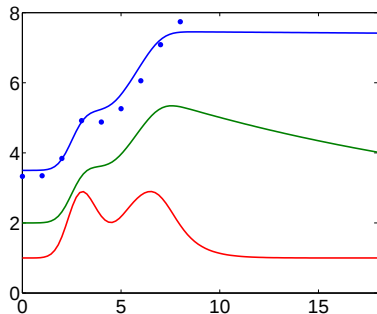
True “gene profiles” and noisy observations.



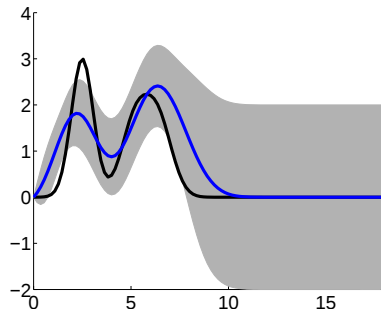
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



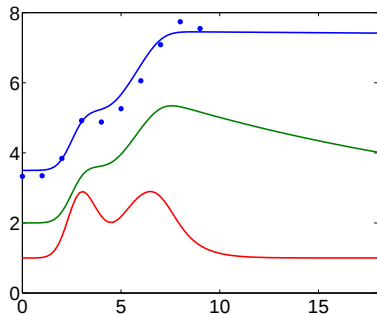
True “gene profiles” and noisy observations.



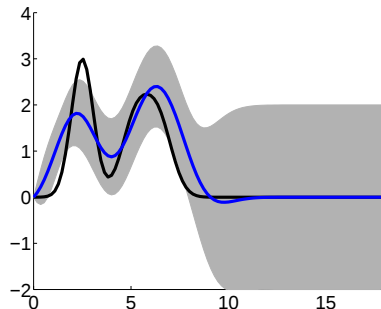
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



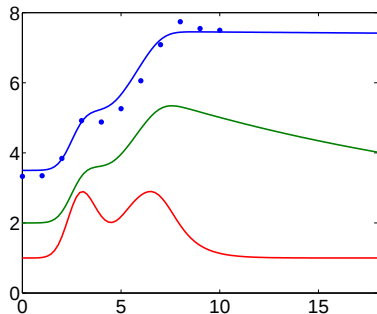
True “gene profiles” and noisy observations.



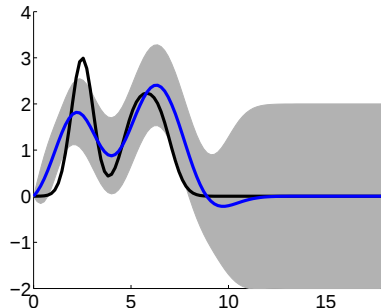
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



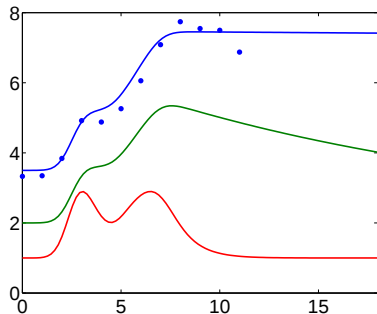
True “gene profiles” and noisy observations.



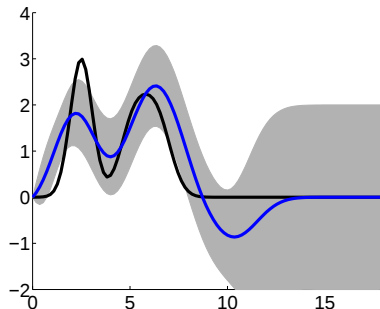
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



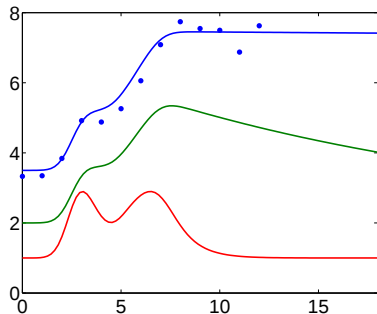
True “gene profiles” and noisy observations.



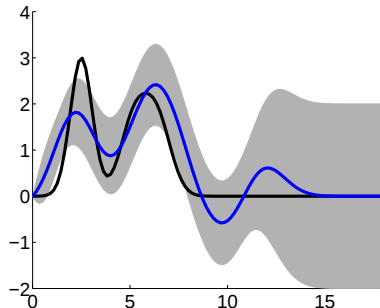
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



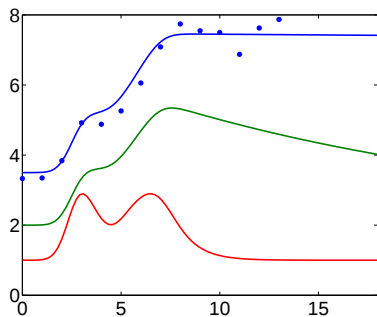
True “gene profiles” and noisy observations.



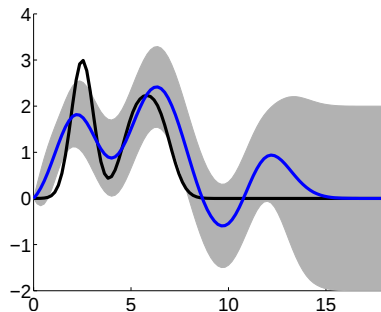
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



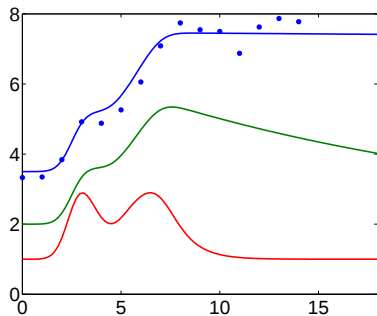
True “gene profiles” and noisy observations.



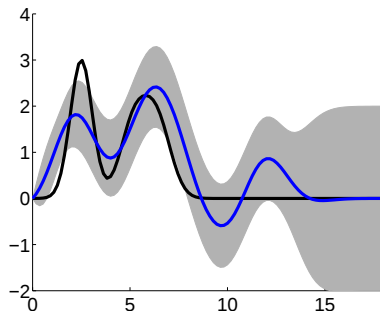
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



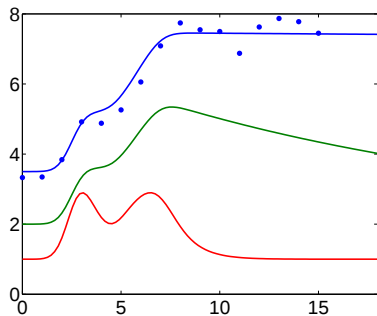
True “gene profiles” and noisy observations.



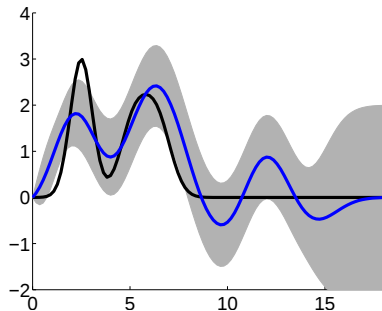
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



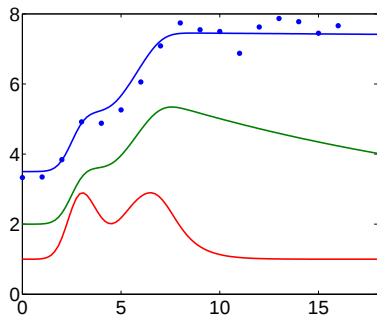
True “gene profiles” and noisy observations.



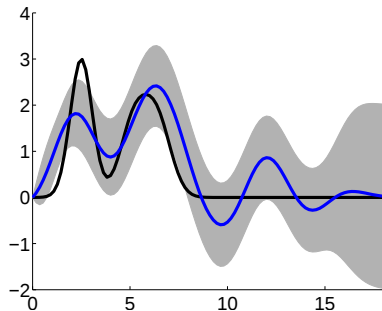
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



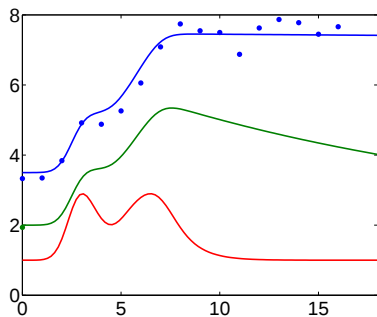
True “gene profiles” and noisy observations.



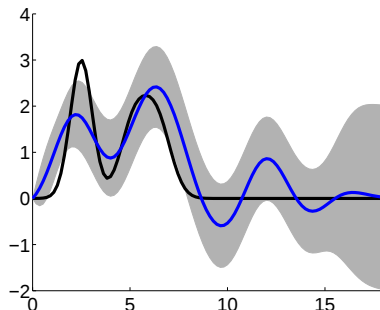
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



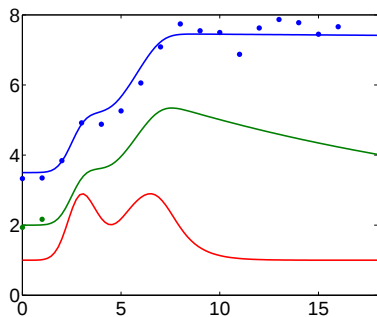
True “gene profiles” and noisy observations.



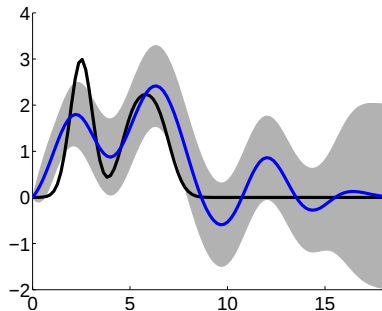
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

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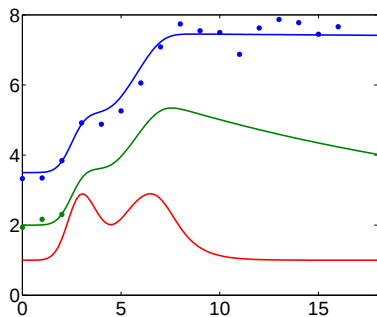
True “gene profiles” and noisy observations.



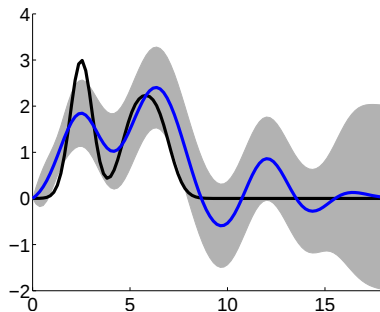
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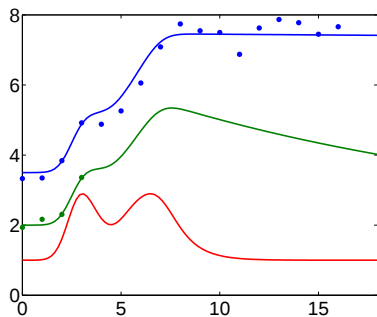
True “gene profiles” and noisy observations.



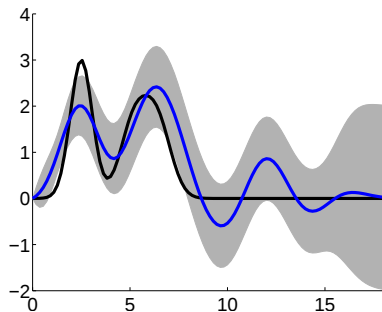
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



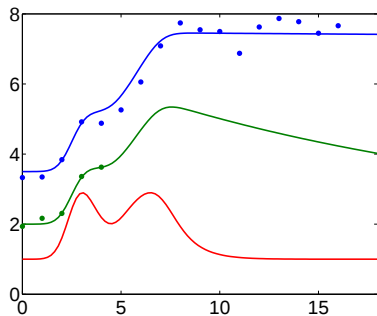
True “gene profiles” and noisy observations.



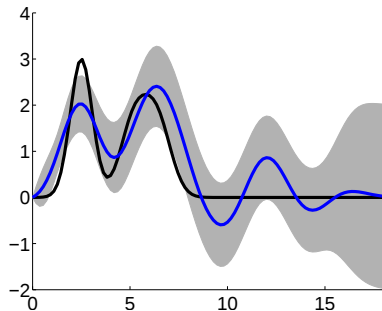
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



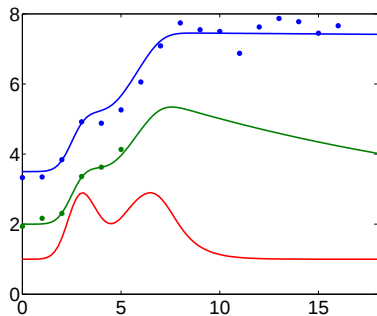
True “gene profiles” and noisy observations.



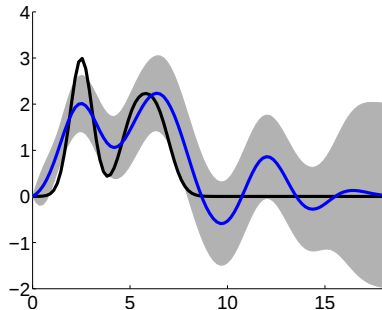
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



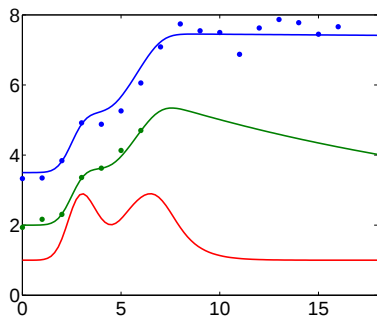
True “gene profiles” and noisy observations.



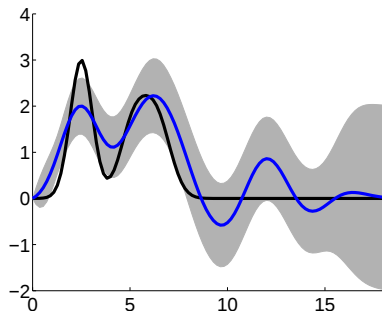
Inferred transcription factor activity.

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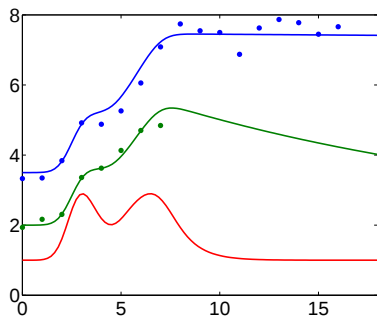
True “gene profiles” and noisy observations.



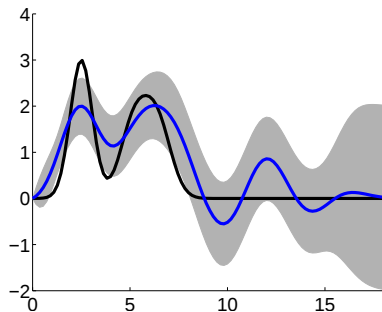
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



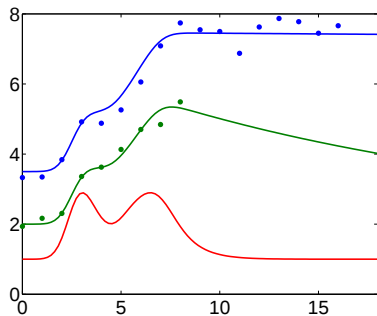
True “gene profiles” and noisy observations.



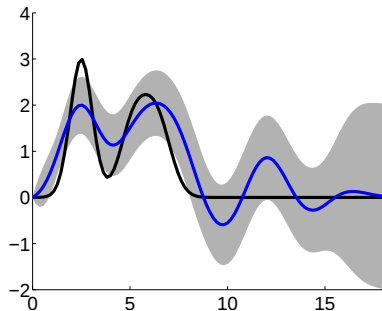
Inferred transcription factor activity.

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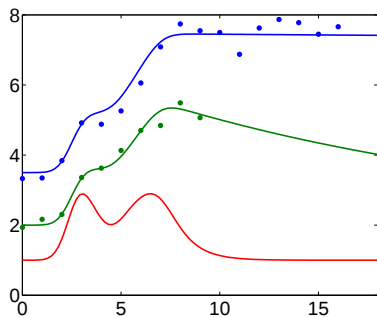
True “gene profiles” and noisy observations.



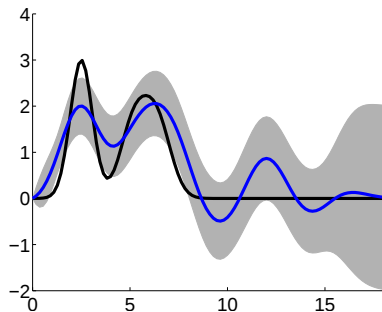
Inferred transcription factor activity.

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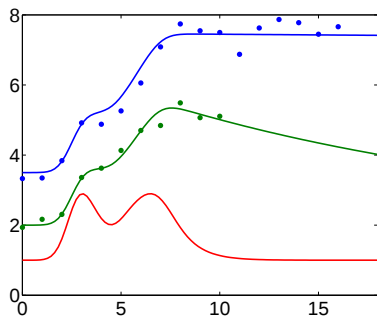
True “gene profiles” and noisy observations.



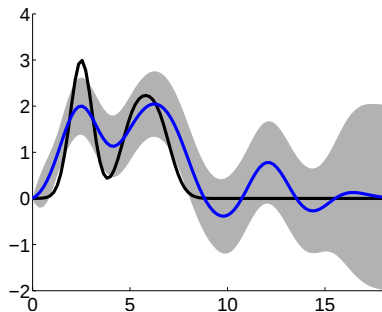
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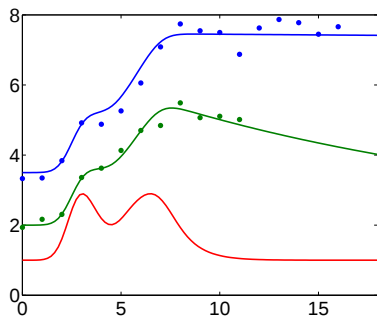
True “gene profiles” and noisy observations.



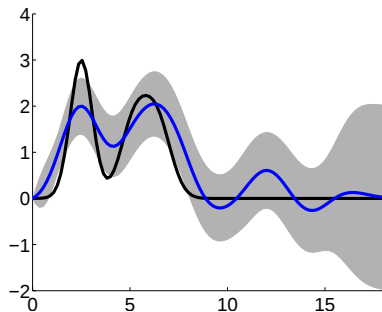
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



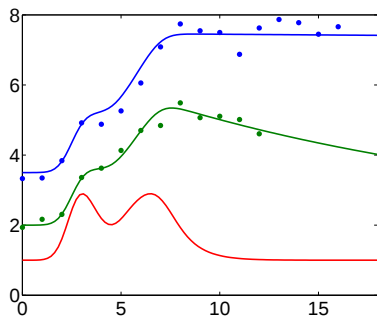
True “gene profiles” and noisy observations.



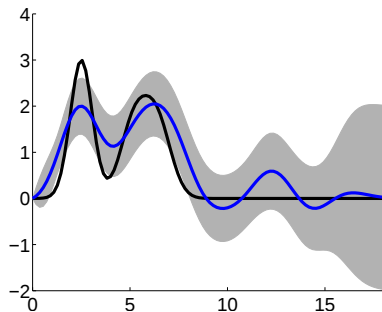
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



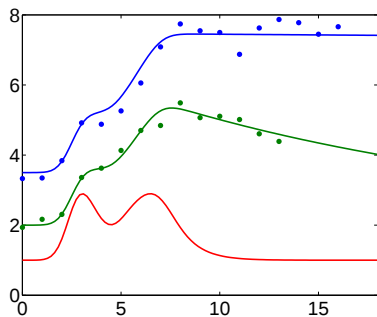
True “gene profiles” and noisy observations.



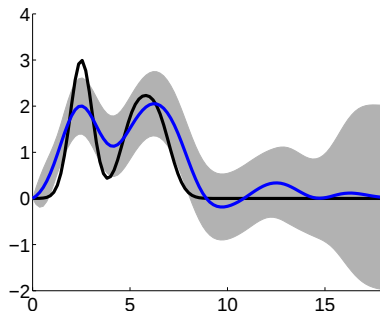
Inferred transcription factor activity.

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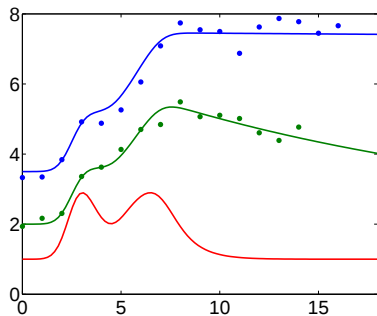
True “gene profiles” and noisy observations.



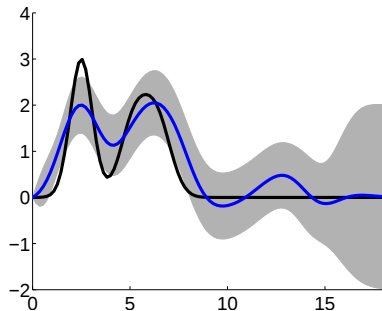
Inferred transcription factor activity.

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Inferring TF activity from artificially sampled genes.



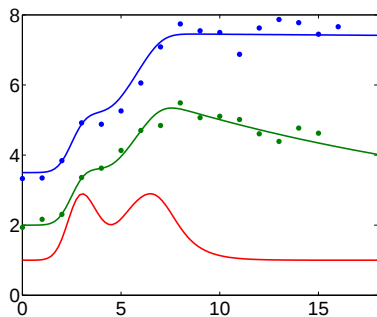
True “gene profiles” and noisy observations.



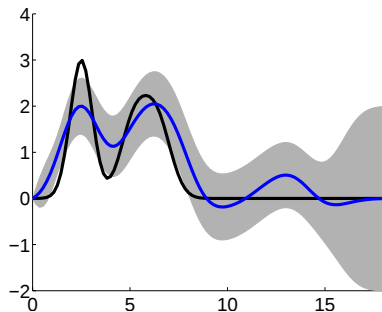
Inferred transcription factor activity.

Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



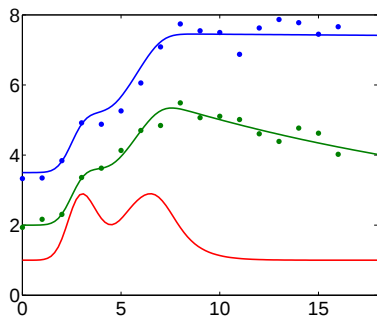
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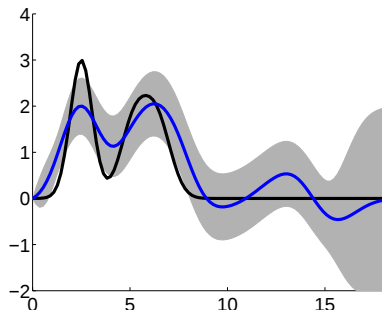
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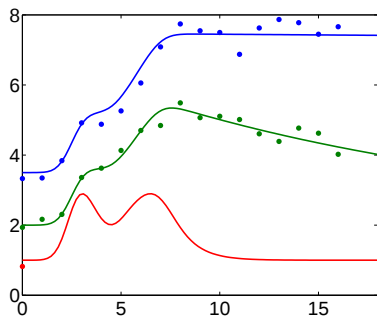
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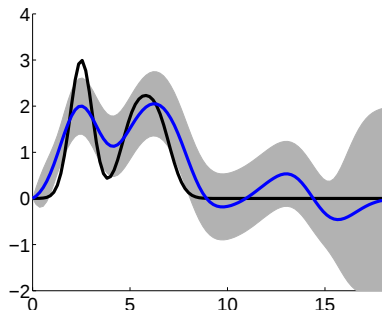
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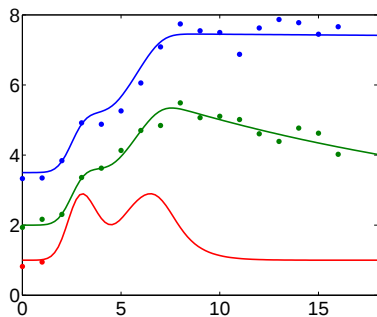
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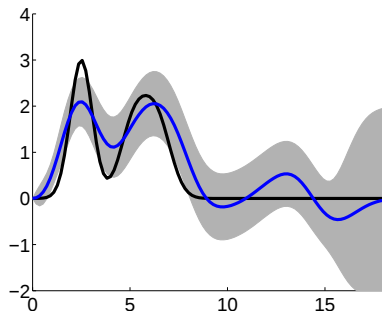
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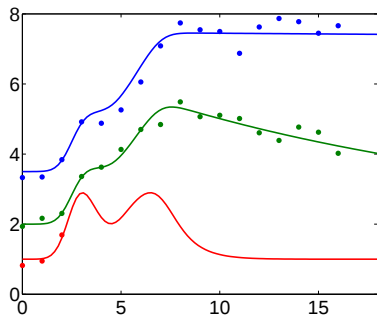
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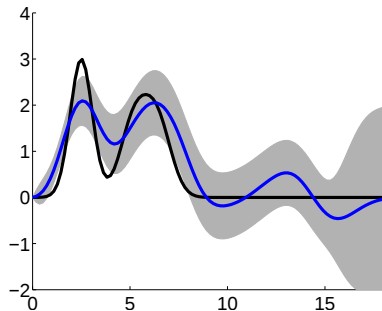
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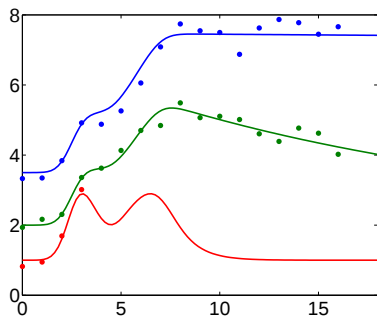
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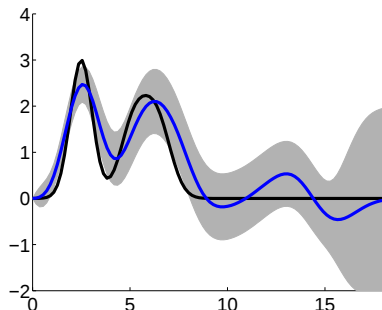
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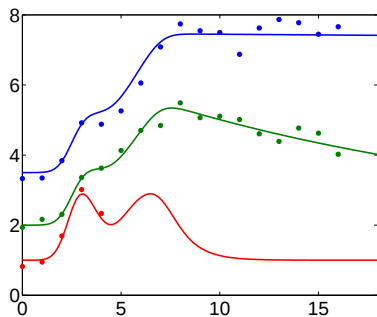
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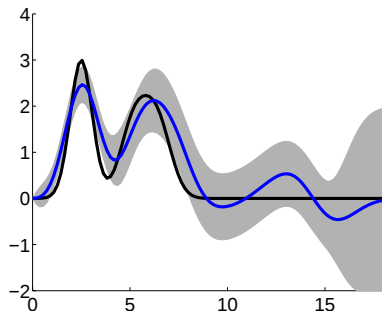
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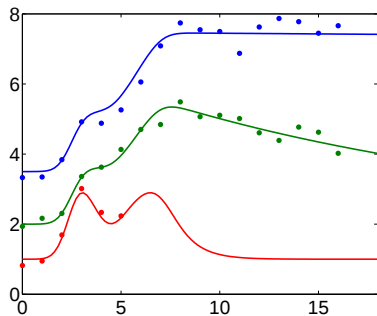
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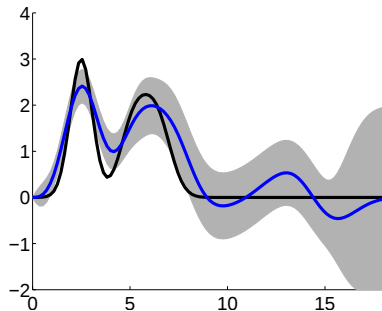
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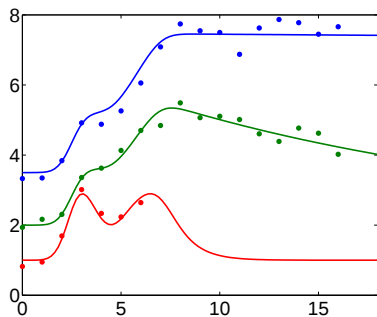
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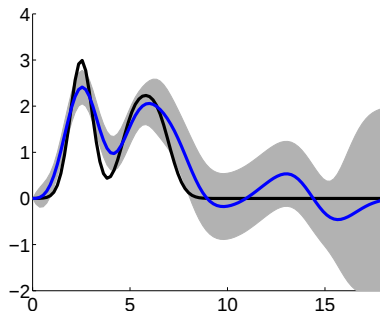
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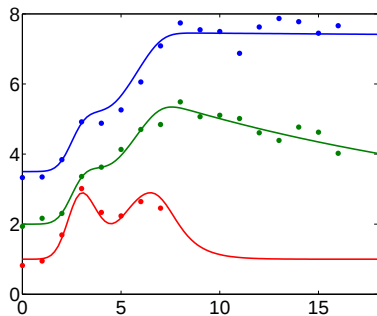
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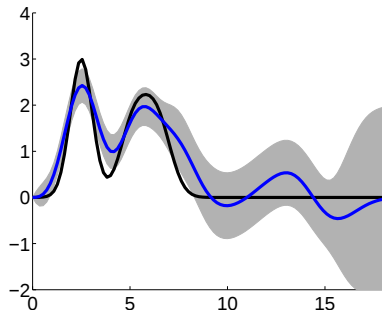
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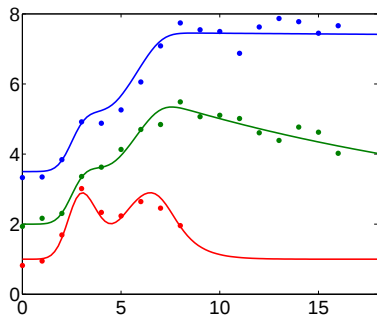
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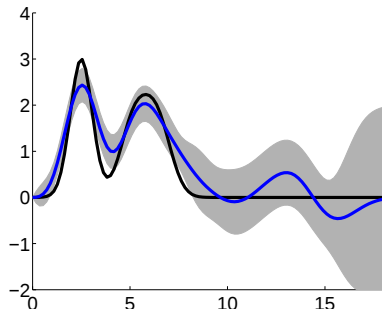
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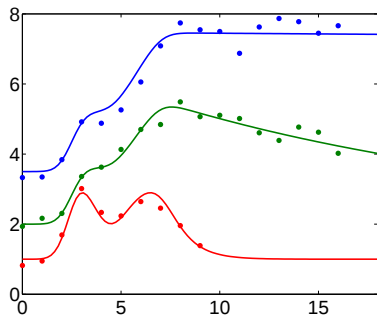
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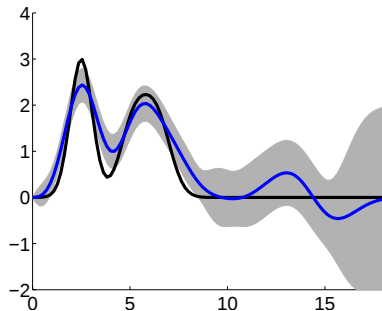
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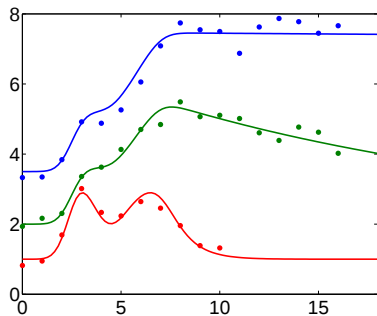
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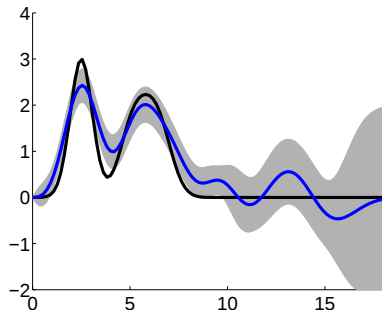
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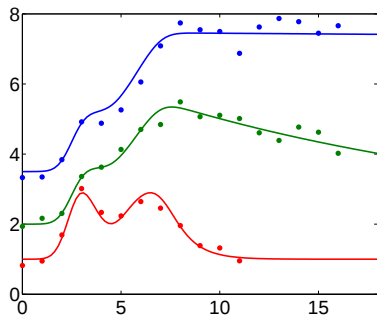
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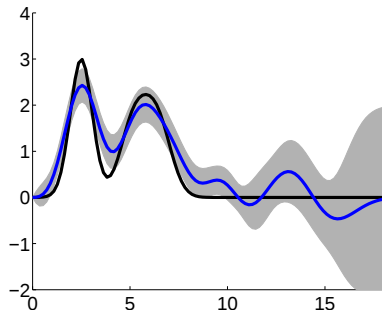
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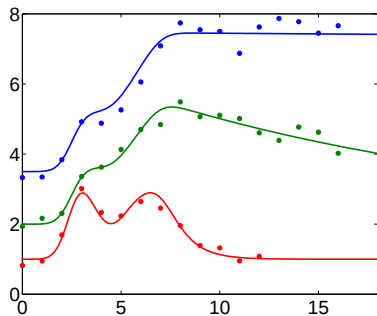
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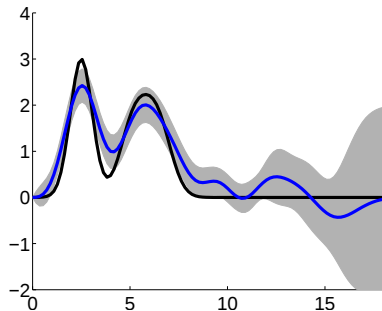
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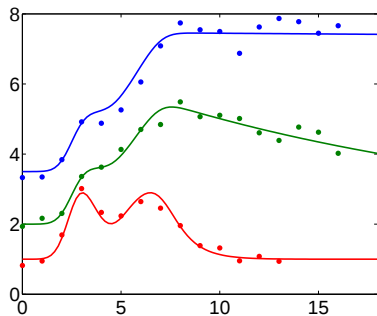
True “gene profiles” and noisy observations.



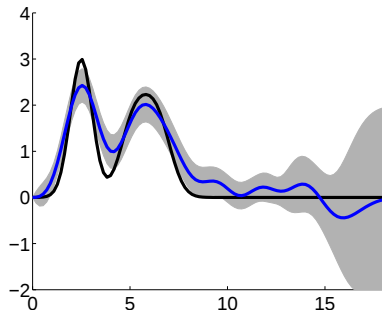
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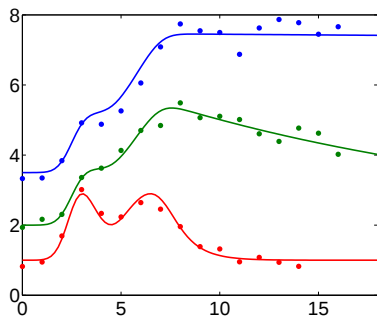
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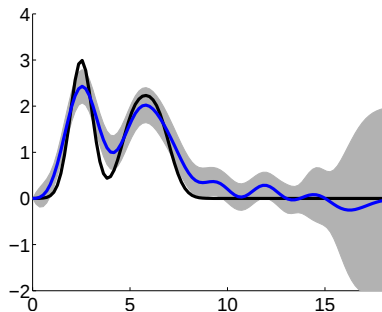
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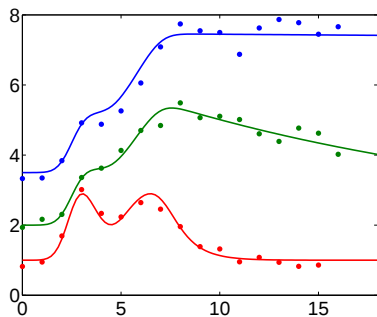
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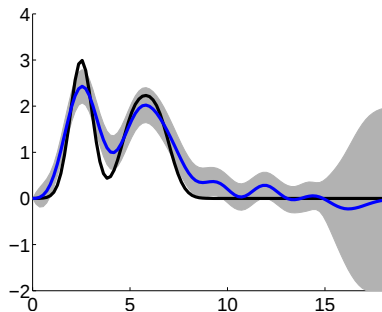
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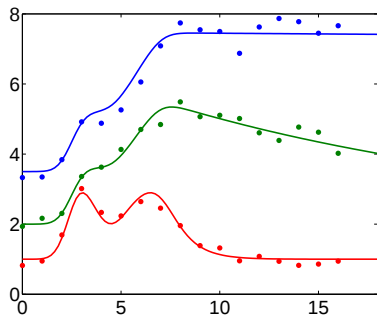
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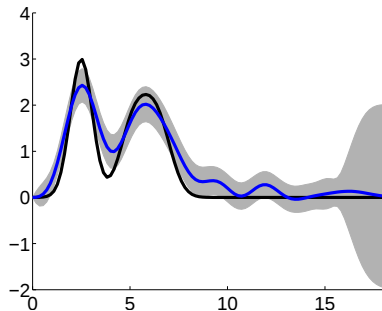
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Artificial Example: Inferring $p(t)$

Inferring TF activity from artificially sampled genes.



True “gene profiles” and noisy observations.



Inferred transcription factor activity.

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

Pei Gao¹, Antti Honkela², Magnus Rattray¹ and Neil D. Lawrence^{1,*}

¹School of Computer Science, University of Manchester, Kilburn Building, Oxford Road, Manchester, M13 9PL and

²Adaptive Informatics Research Centre, Helsinki University of Technology, PO Box 5400, FI-02015 TKK, Finland

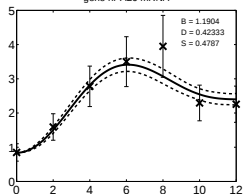
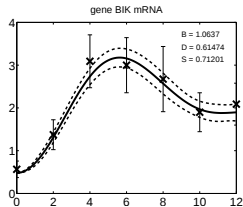
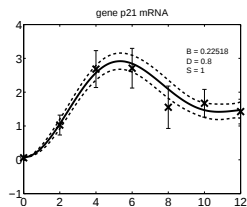
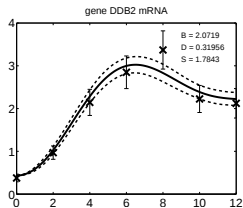
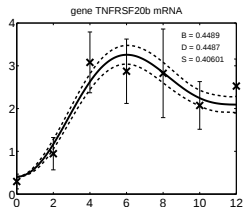
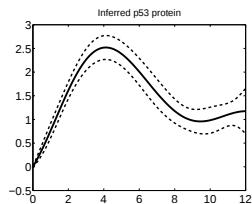
ABSTRACT

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)

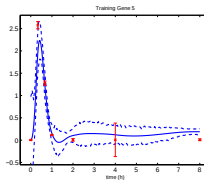
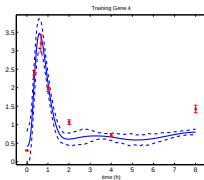
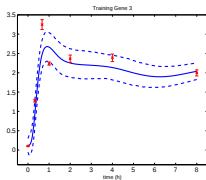
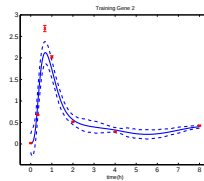
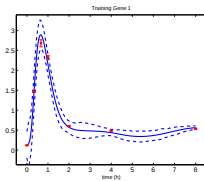
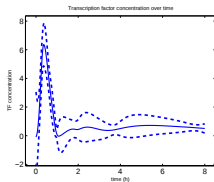


Ranking with ERK Signalling

- ▶ 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.

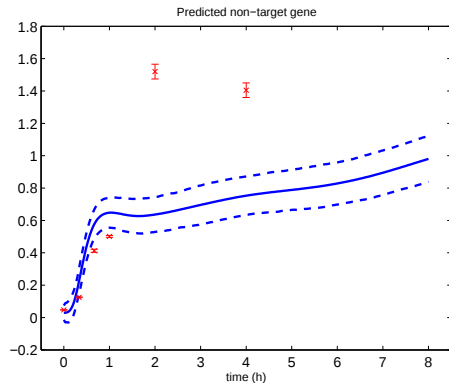
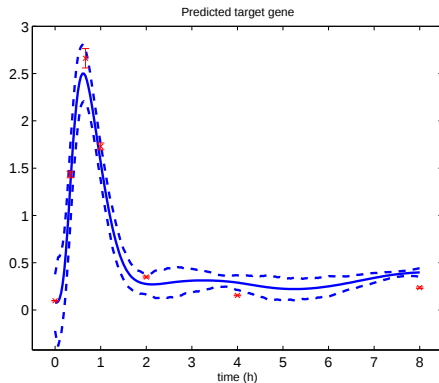
Elk-1 (MLP covariance)

Jennifer Withers



Elk-1 target selection

Fitted model used to rank potential targets of Elk-1



Outline

Motivation

Probabilistic Model for $p(t)$

Cascade Differential Equations

Discussion and Future Work

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

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

^aDepartment of Information and Computer Science, Aalto University School of Science and Technology, Helsinki, Finland; ^bGenome Biology U European Molecular Biology Laboratory, Heidelberg, Germany; and ^cSchool 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

used for genome-wide scoring of putative target genes. The only data required to apply our method is wild-type time series data collected over a period where TF activity is changing. Our method allows for complementary evidence from expression

(Honkela et al., 2010)

- ▶ 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.

Twist Results

- ▶ 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

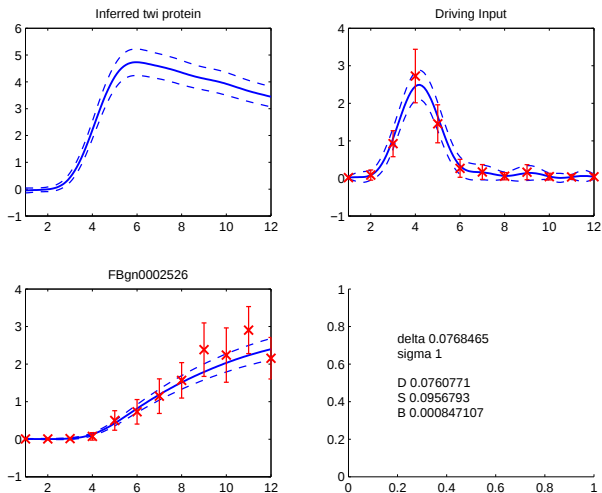


Figure: Model for flybase gene identity FBgn0002526.

Results for Twi using the Cascade model

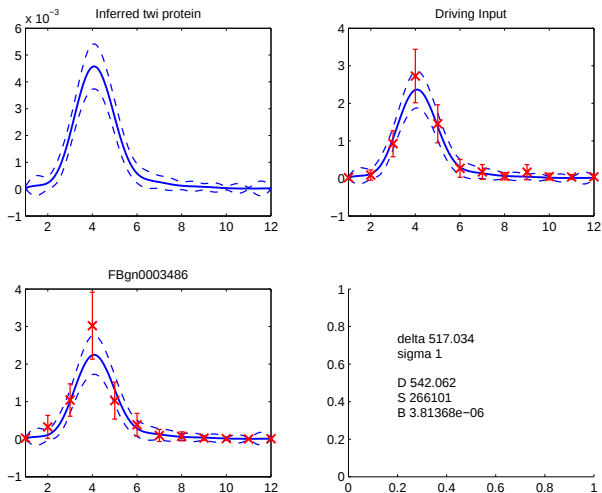


Figure: Model for flybase gene identity FBgn0003486.

Results for Twi using the Cascade model

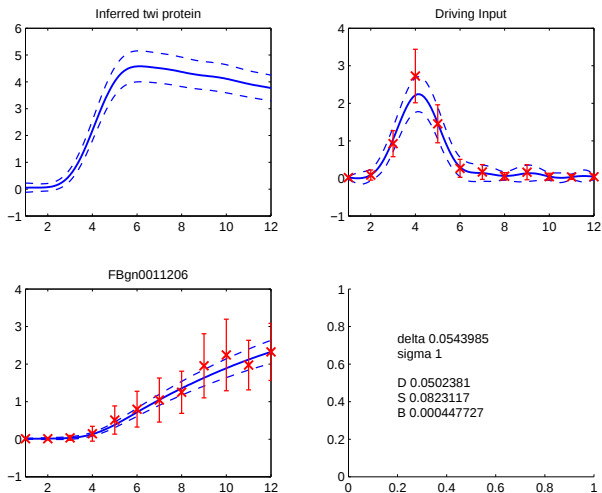


Figure: Model for flybase gene identity FBgn0011206.

Results for Twi using the Cascade model

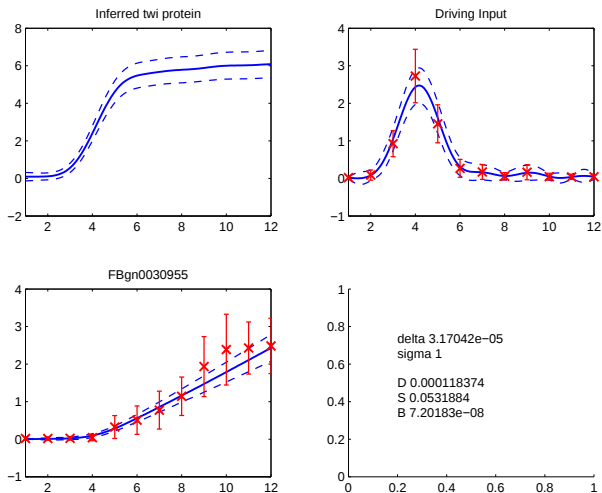


Figure: Model for flybase gene identity FBgn00309055.

Results for Twi using the Cascade model

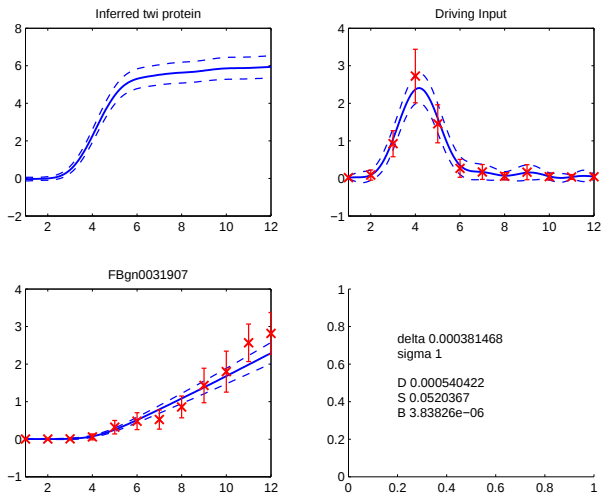


Figure: Model for flybase gene identity FBgn0031907.

Results for Twi using the Cascade model

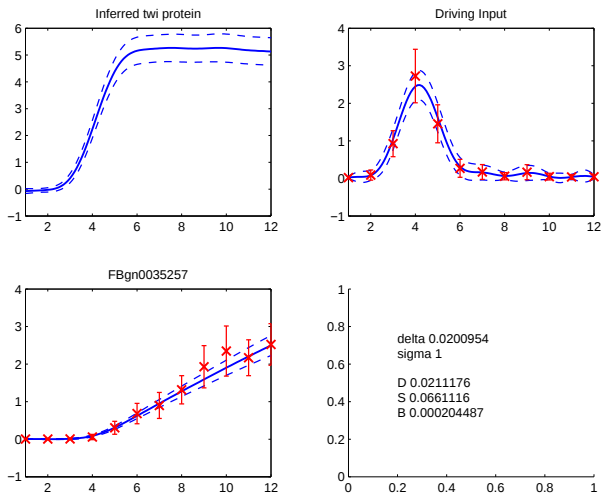


Figure: Model for flybase gene identity FBgn0035257.

Results for Twi using the Cascade model

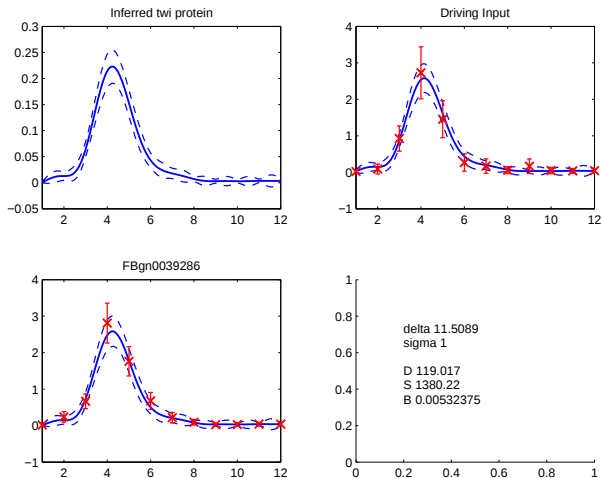
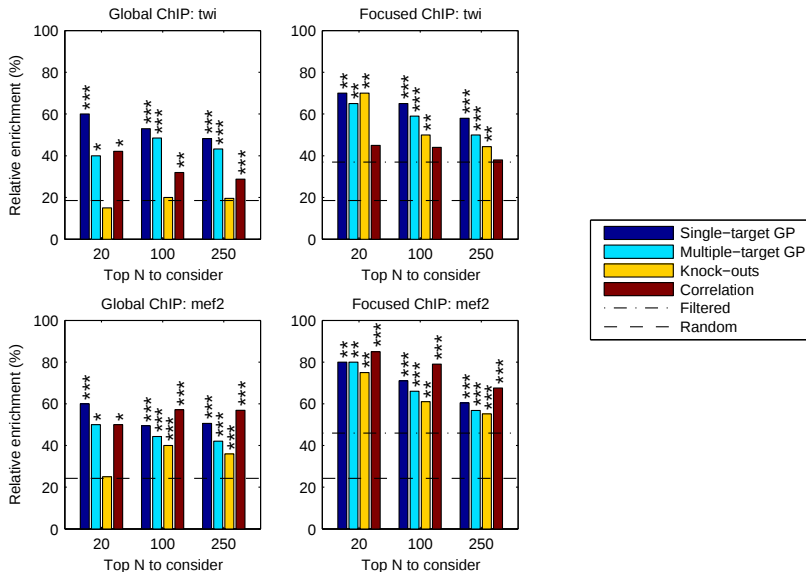


Figure: Model for flybase gene identity FBgn0039286.

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



****: $p < 0.001$, ***: $p < 0.01$, **: $p < 0.05$

Summary

- ▶ 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 $p(t)$

Cascade Differential Equations

Discussion and Future Work

Discussion and Future Work

- ▶ Integration of probabilistic inference with mechanistic models.
- ▶ Software available through bioconductor (TIGRE Package)
<http://bioconductor.org/packages/2.6/bioc/html/tigre.html>.
- ▶ Applications in modeling gene expression.
- ▶ Ongoing/other work:
 - ▶ Non linear response and non linear differential equations.
 - ▶ Improving computational complexity.
 - ▶ Stochastic differential equations.
 - ▶ Cascade model introduces model of translation.

Acknowledgements

- ▶ Investigators: Neil Lawrence and Magnus Rattray
- ▶ Researchers: Pei Gao, Antti Honkela, Guido Sanguinetti, Michalis Titsias.
- ▶ 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*).

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