Model Based Target Identification from Gene Expression with Gaussian Processes

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19th October 2009

Outline

Motivation

Probabilistic Model for $f(t)$

Cascade Differential Equations

Discussion and Future Work

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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).

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 the DNA.
- Most of this 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 G1. In G2 there are two copies of the chromosome. In G1 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 feeback loop with NF-κB.

p53 DNA Damage Repair

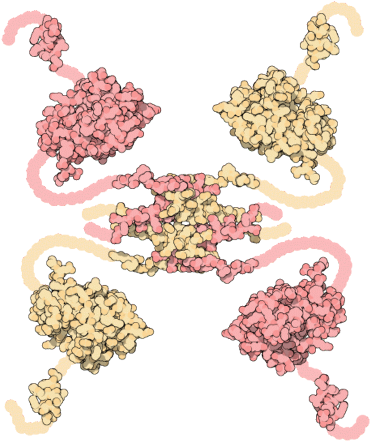

Figure: p53. *Left* unbound, *Right* bound to DNA. Images by David S. Goodsell from `http://www.rcsb.org/` (see the“Molecule of the Month” feature).

p53

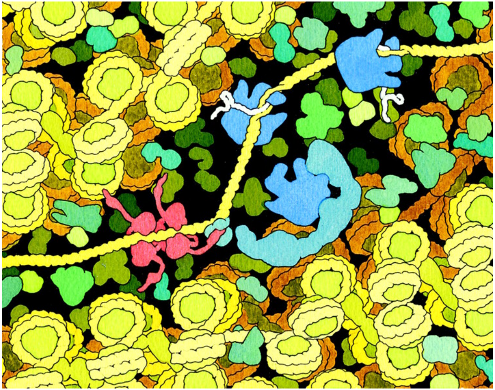

Figure: Repair of DNA damage by p53. Image from Goodsell (1999).

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 goverened 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).

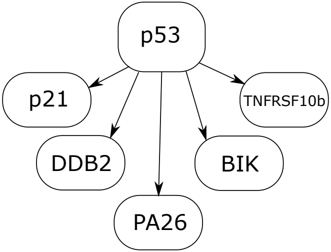

Figure: p53 SIM network motif as modelled by Barenco et al. 2006.

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.

Mathematical Model

- Differential equation model of system.

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j f(t) - D_j x_j(t)$$

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

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

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- Jointly estimate $f(t)$ 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 $x_j(t)$ 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.

Response of p53

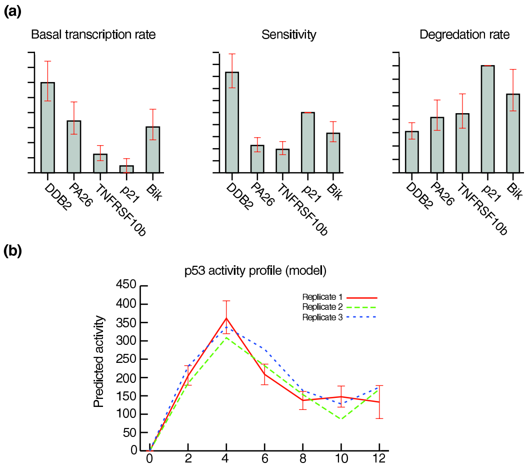

Figure: Results from Barenco et al. (2006). Top is parameter estimates. Bottom is inferred profile.

Respose to p53 ...

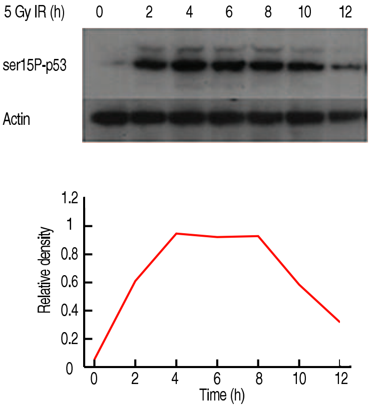

Figure: Results from Barenco et al. (2006). Activity profile of p53 was measured by Western blot to determine the levels of ser-15 phosphorylated p53 (ser15P-p53).

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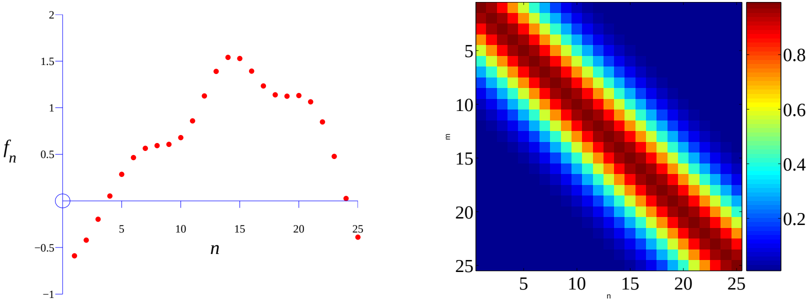
Probabilistic Model for $f(t)$

- We introduce a probabilistic model for $f(t)$.
- 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.

Gaussian Distribution Sample



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

(b) colormap showing correlations between dimensions

Figure: A sample from a 25 dimensional Gaussian distribution.

Covariance Function

The covariance matrix

- Covariance matrix shows correlation between points f_m and f_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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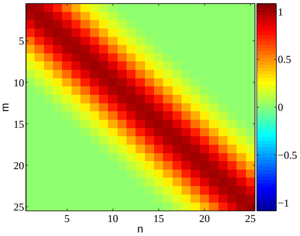
Covariance Functions

Where did this covariance matrix come from?

RBF Kernel Function

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

- 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 know as a kernel.



Covariance Samples

`demCovFuncSample`

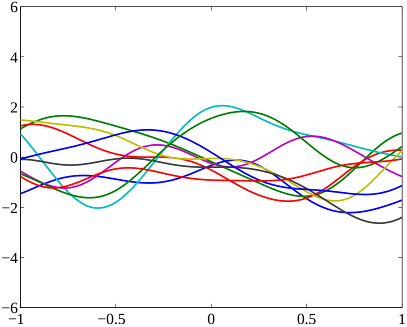


Figure: RBF kernel with $\ell = 10^{-\frac{1}{2}}$, $\alpha = 1$

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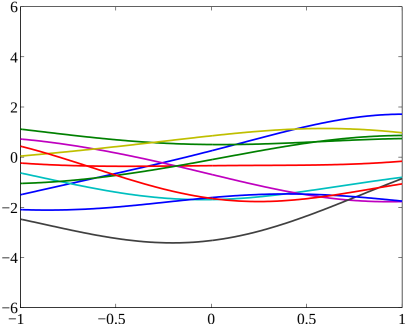

Figure: RBF kernel with $\ell = 1$, $\alpha = 1$

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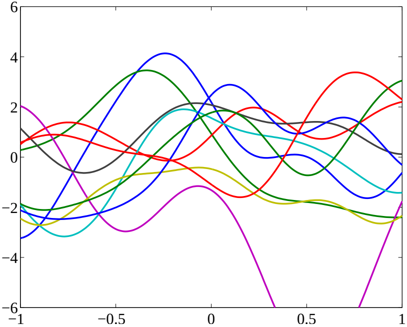

Figure: RBF kernel with $\ell = 0.3$, $\alpha = 4$

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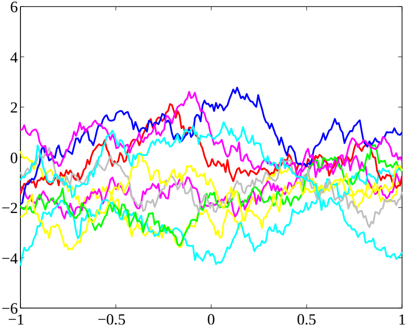

Figure: Ornstein-Uhlenbeck (stationary Gauss-Markov) covariance function $\ell = 1$, $\alpha = 4$

Example: Transcriptional Regulation

- First Order Differential Equation

$$\frac{\mathrm{d}x_j\left(t\right)}{\mathrm{d}t} = B_j + S_j f\left(t\right) - D_j x_j\left(t\right)$$

- 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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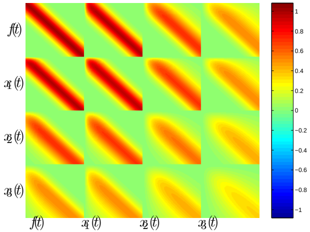
Covariance for Transcription Model

RBF covariance function for $f(t)$

$$x_i(t) = \frac{B_i}{D_i} + S_i \exp(-D_i t) \int_0^t f(u) \exp(D_i u)\, \mathrm{d}u.$$

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

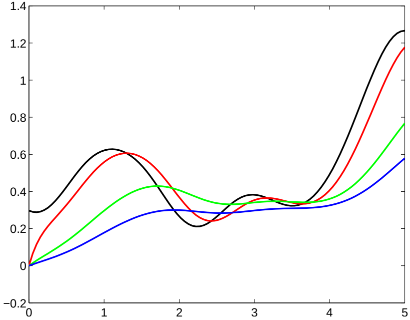


Figure: Joint samples from the ODE covariance, *black*: $f(t)$, *red*: $x_1(t)$(high decay/sensitivity) and *green*: $x_2(t)$ (medium decay/sensitivity). and *blue*: $x_3(t)$ (low decay/sensitivity).

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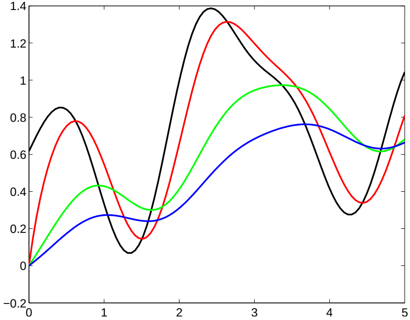

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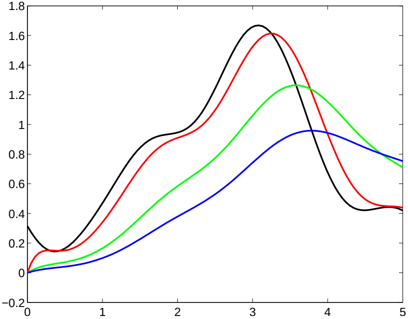

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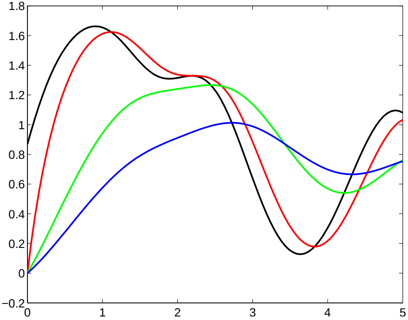

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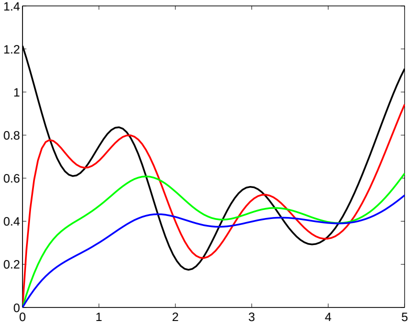

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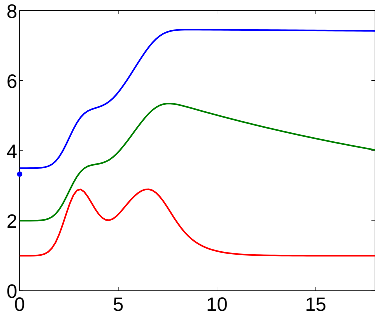
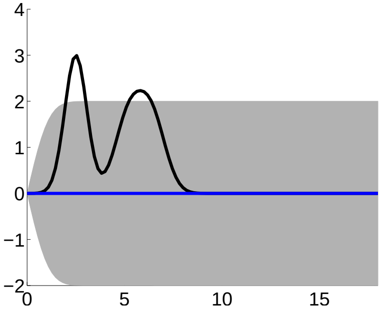
Artificial Example: Inferring $f(t)$

Inferring TF activity from artificially sampled genes.



True "gene profiles" and noisy observations.



Inferred transcription factor activity.

Artificial Example: Inferring $f(t)$

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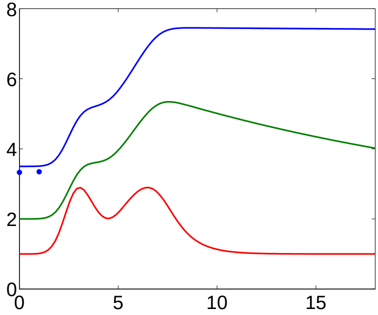

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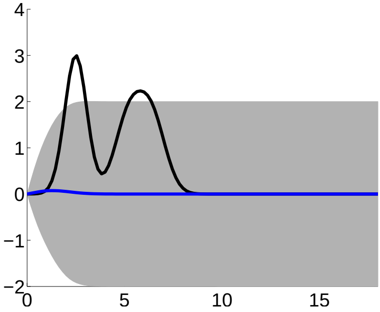

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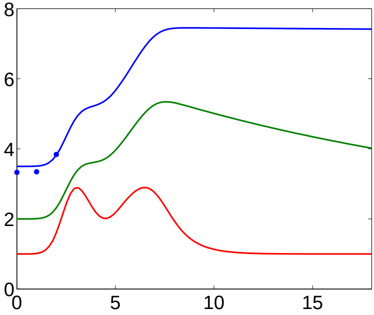

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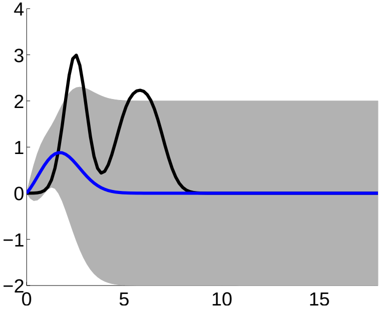

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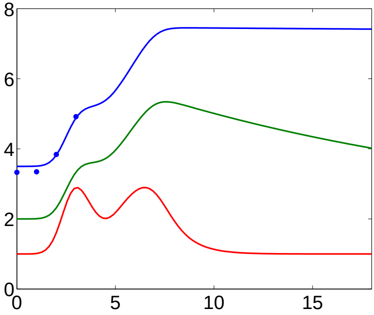

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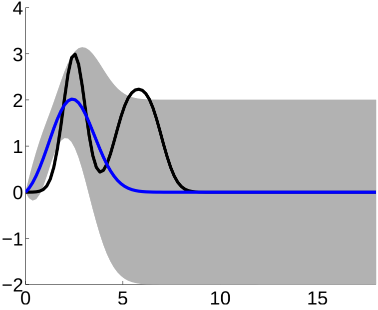

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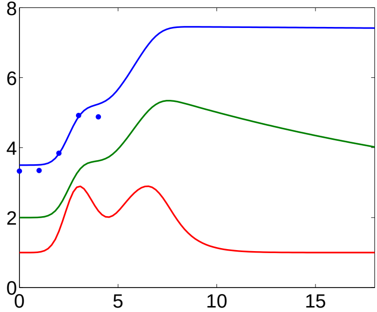

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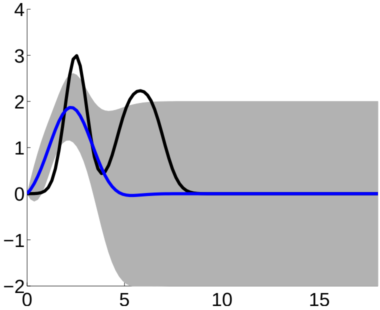

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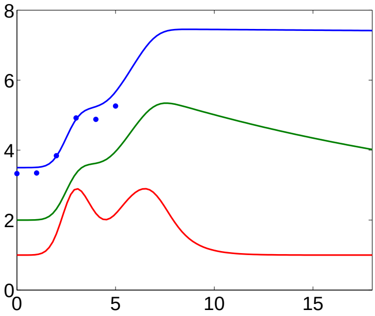

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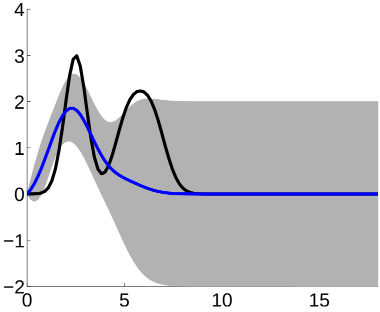

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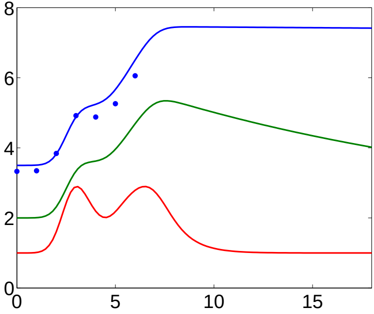

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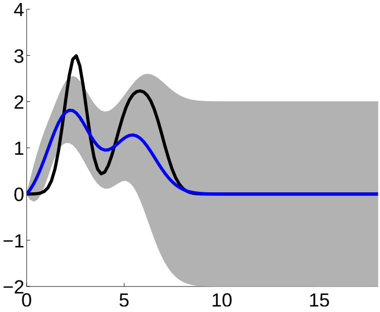

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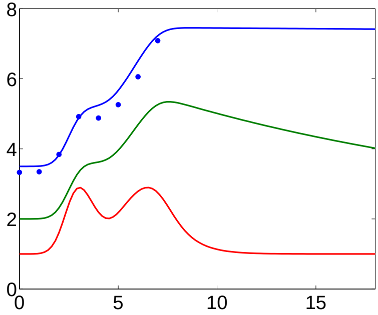

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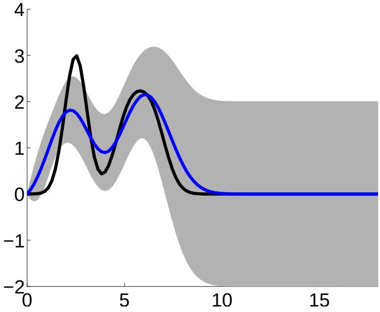

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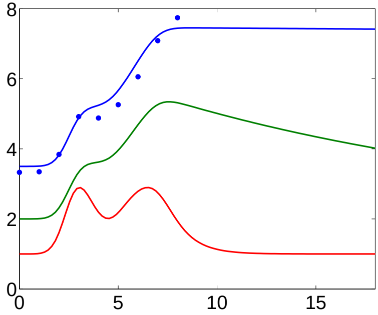

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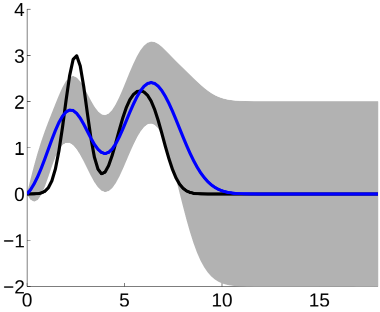

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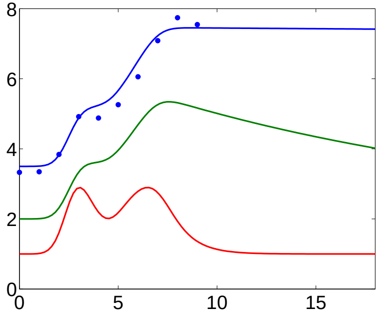

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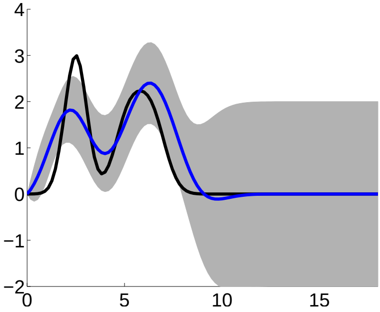

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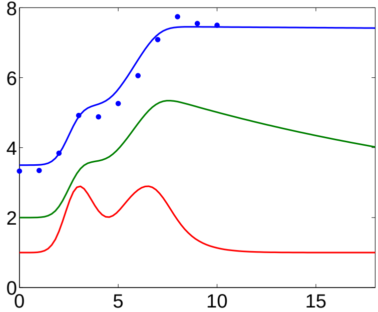

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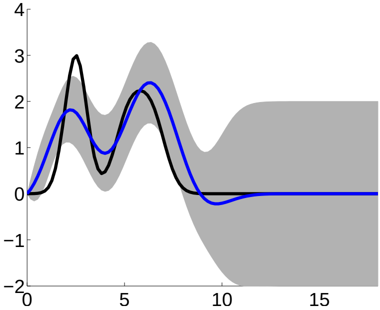

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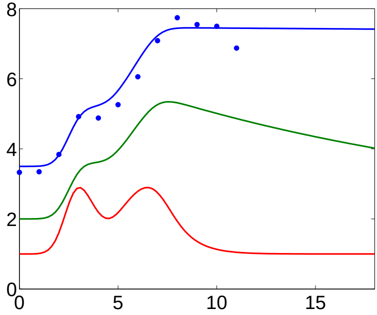

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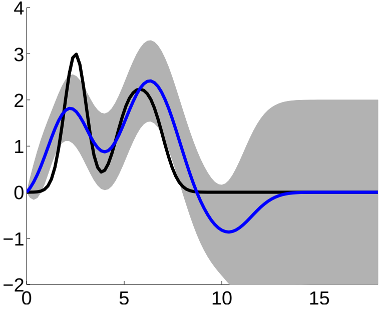

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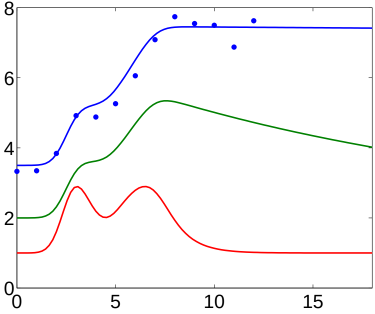

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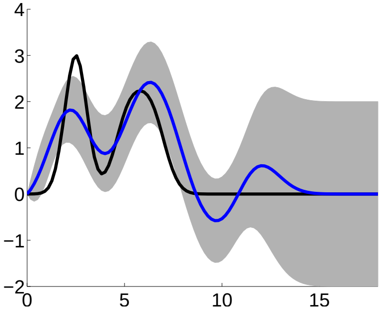

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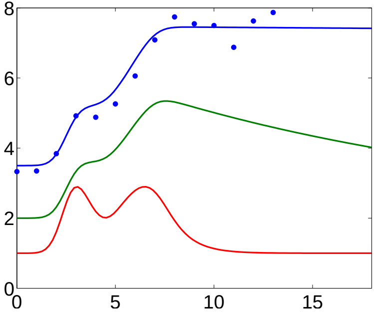

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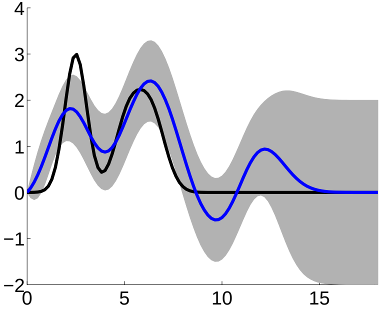

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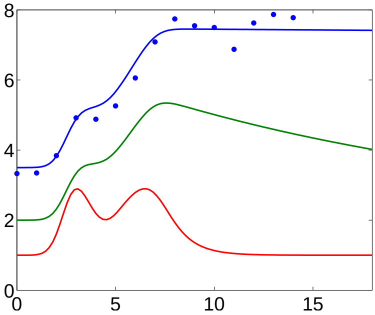

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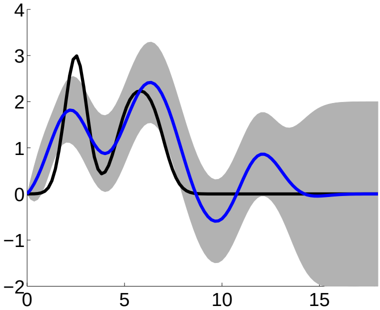

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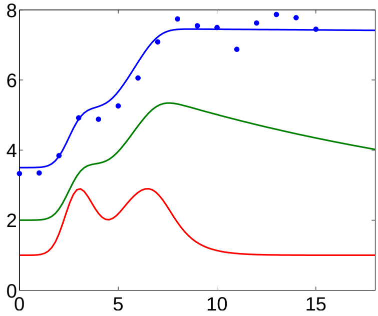

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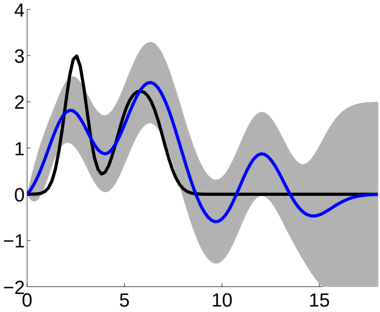

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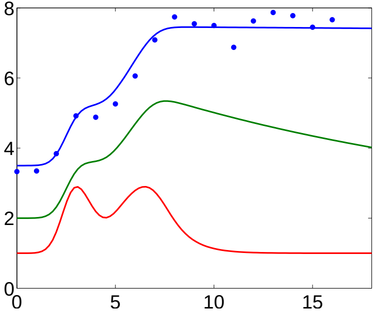

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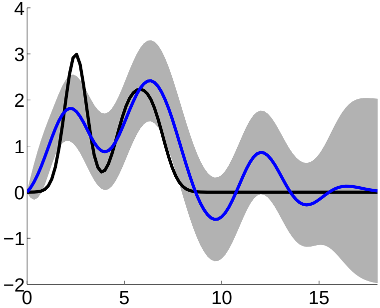

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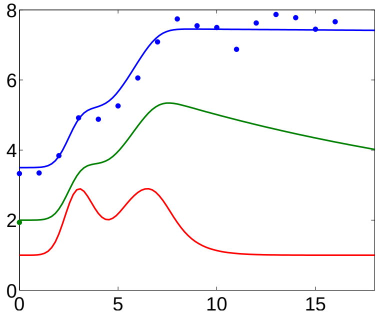

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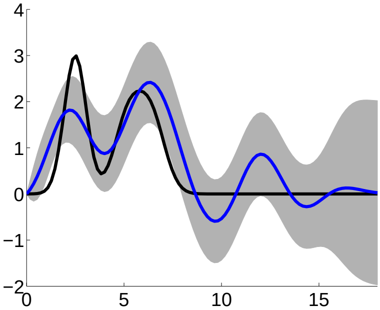

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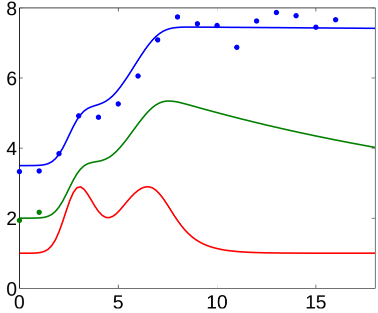

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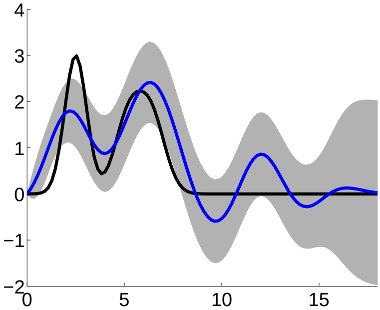

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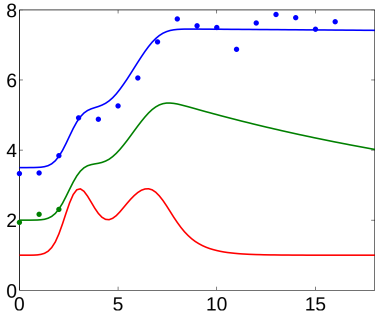

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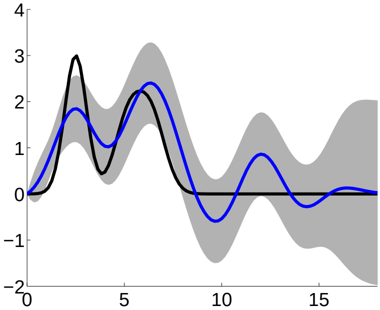

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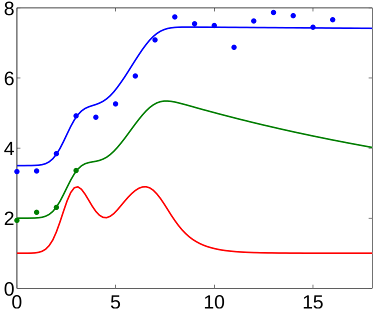

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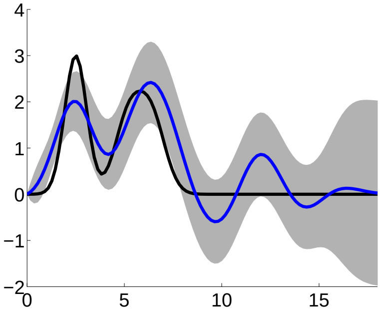

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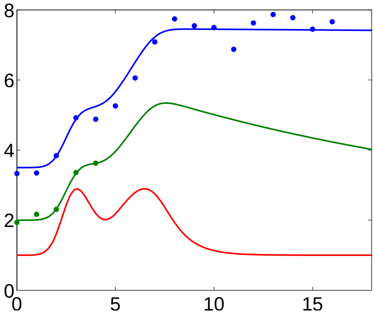

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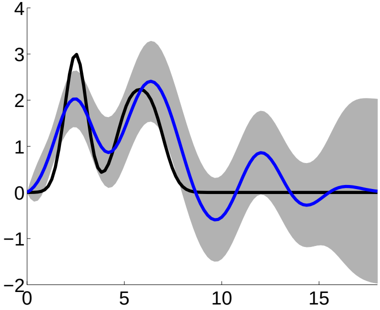

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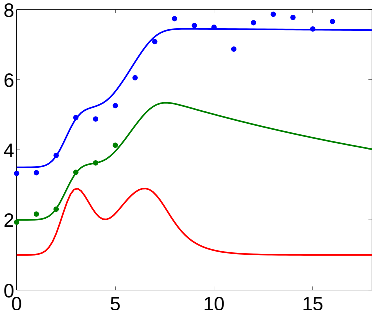

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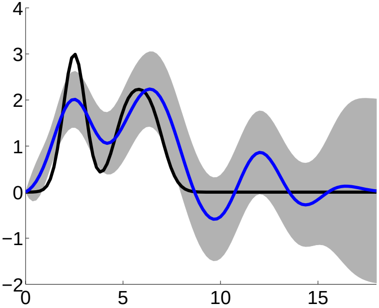

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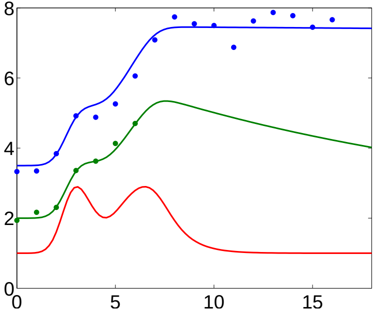

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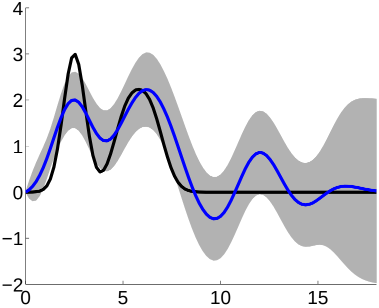

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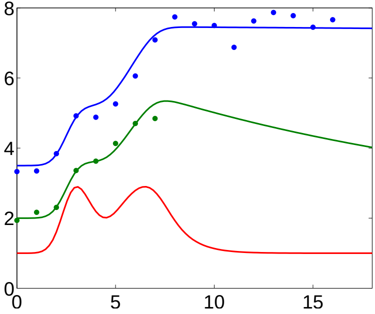

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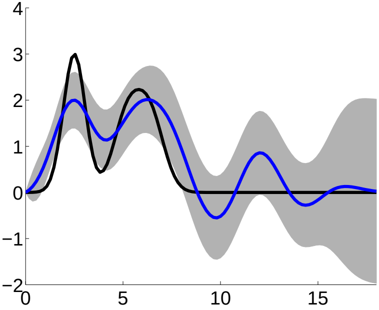

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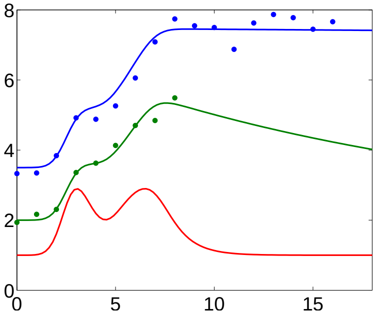

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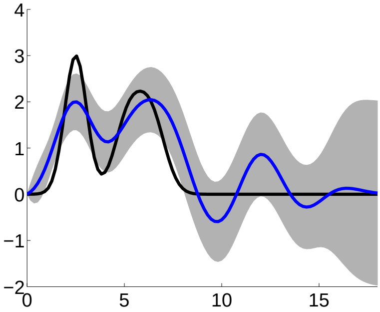

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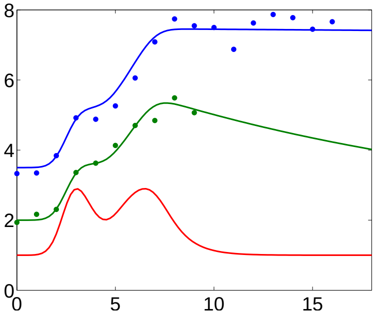

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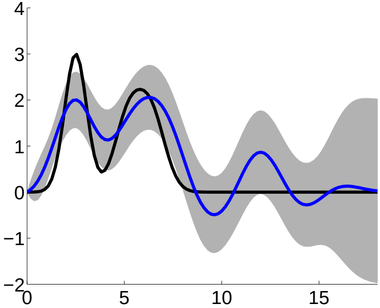

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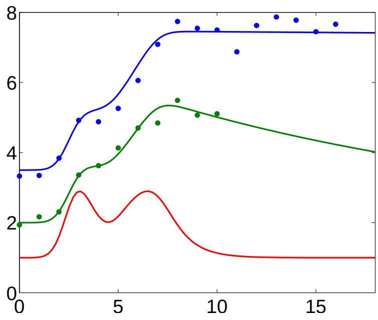

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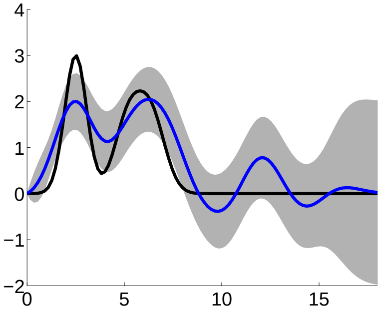

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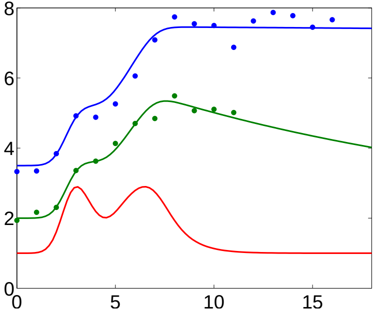

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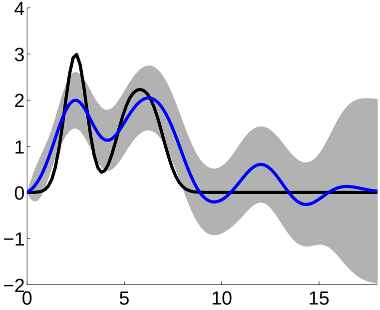

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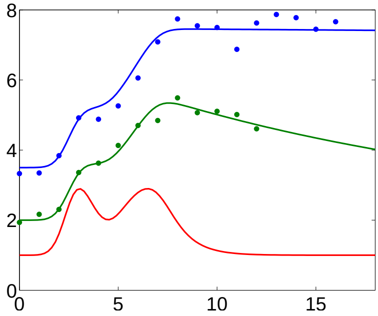

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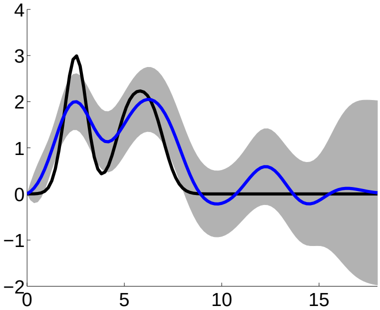

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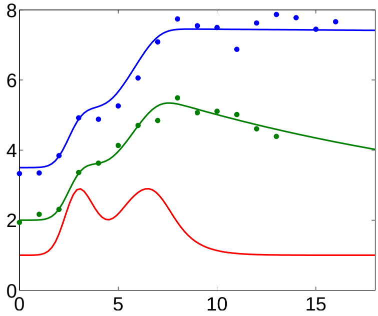

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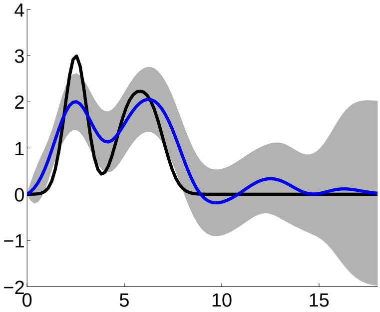

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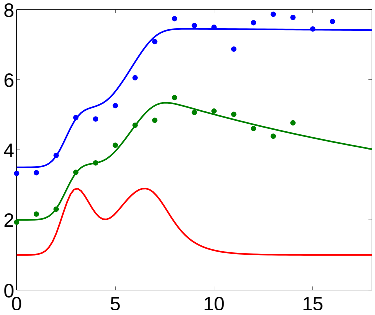

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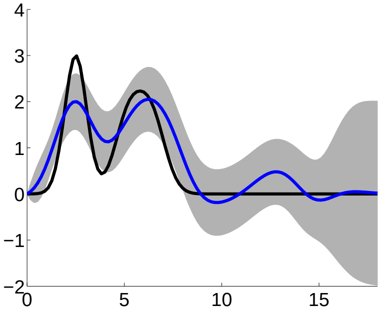
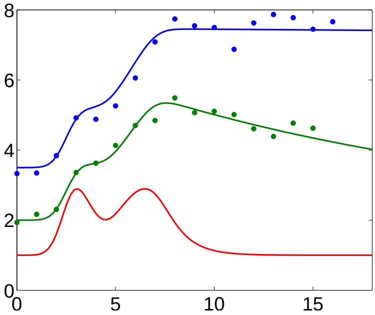


Inferred transcription factor activity.

Artificial Example: Inferring $f(t)$

Inferring TF activity from artificially sampled genes.



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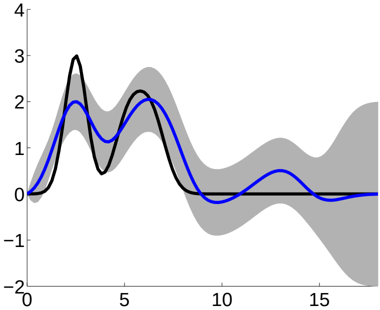

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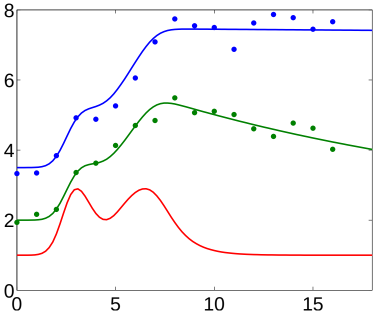

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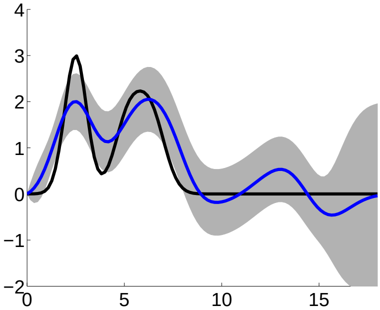

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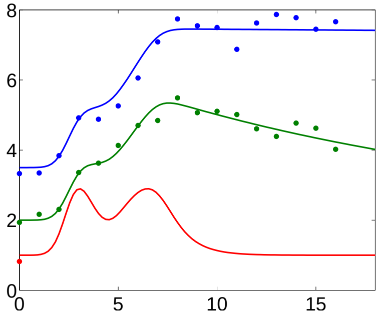

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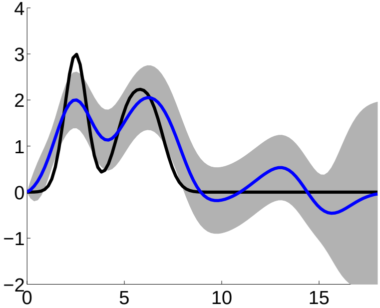

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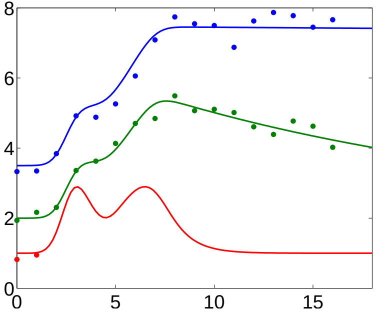

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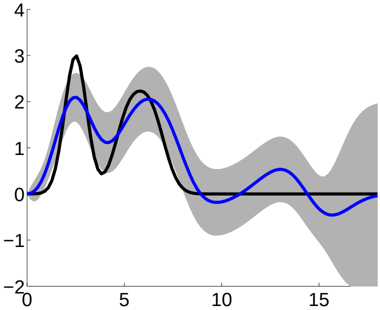

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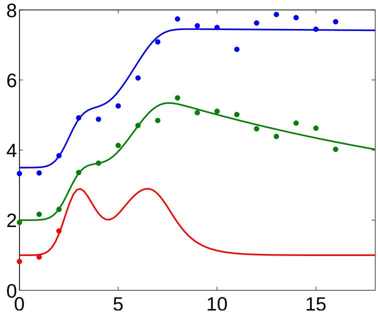

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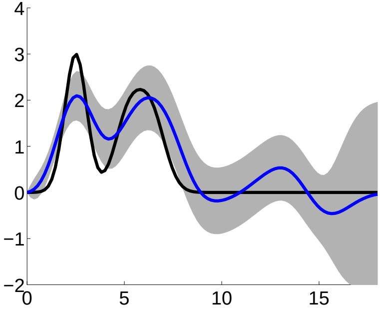

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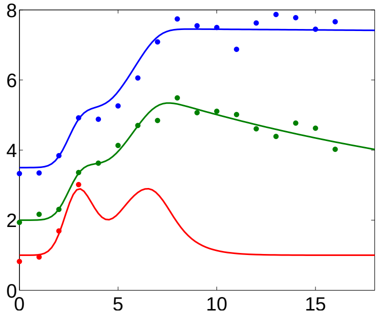

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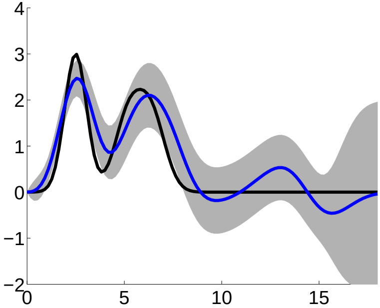

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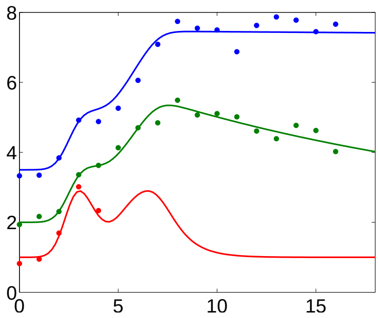

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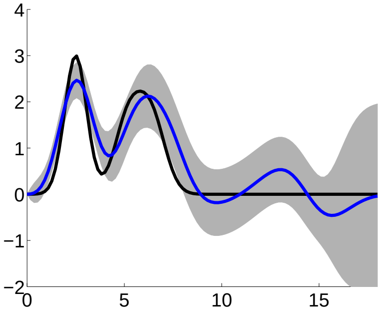

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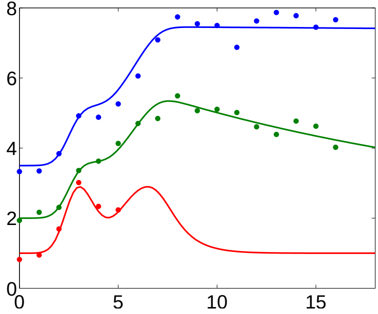

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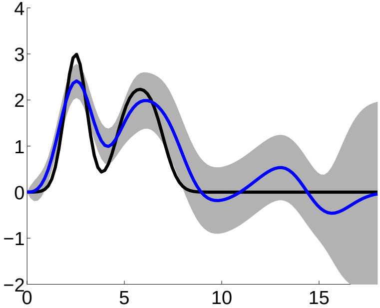

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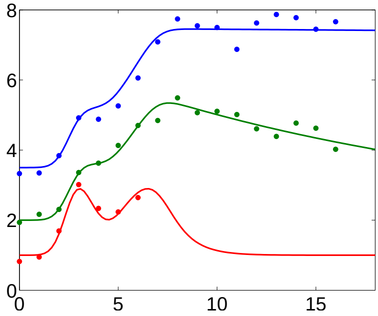

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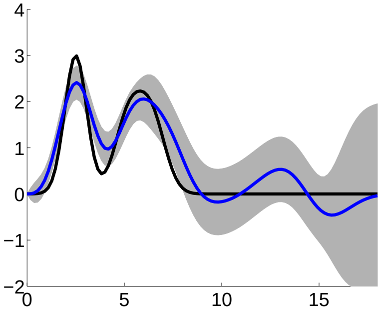

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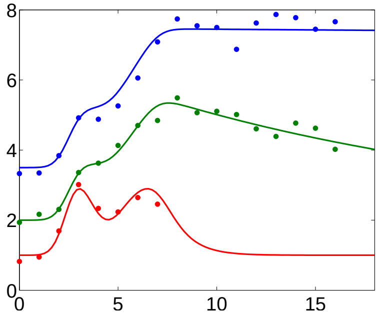

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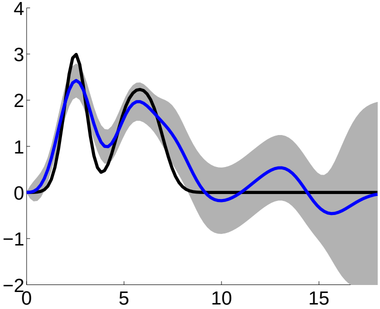

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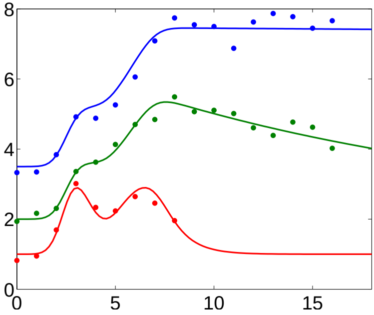

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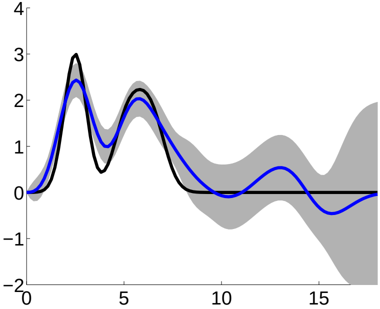

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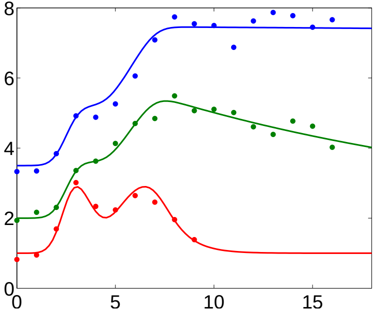

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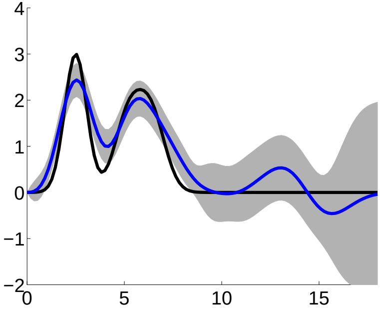

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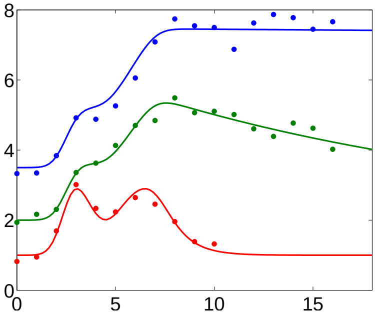

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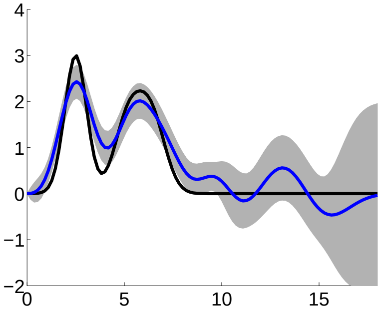

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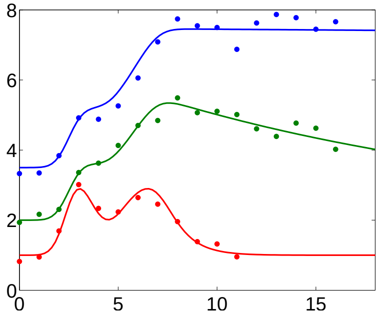

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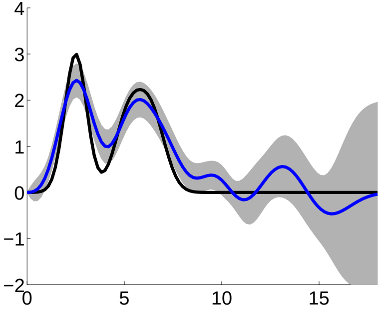

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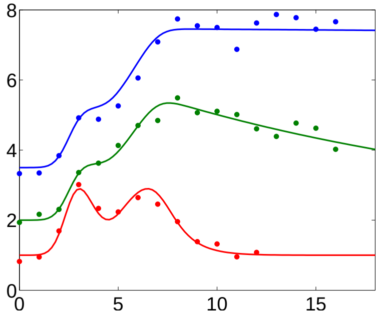

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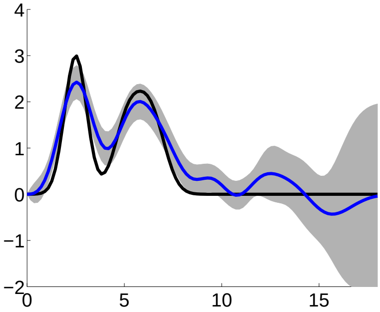

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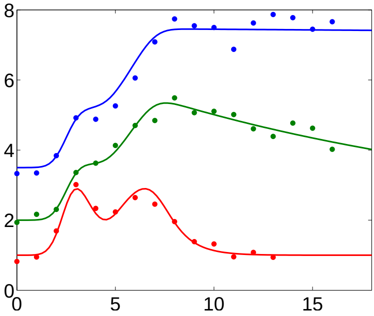

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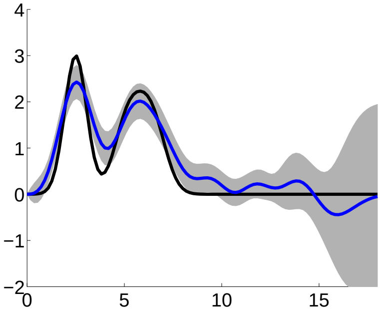

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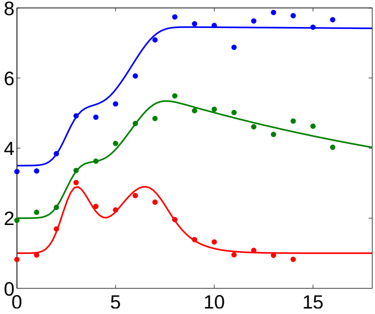

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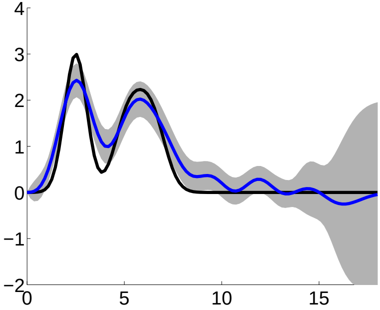

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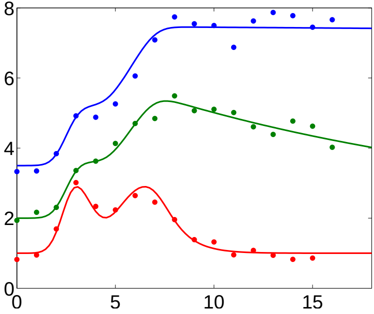

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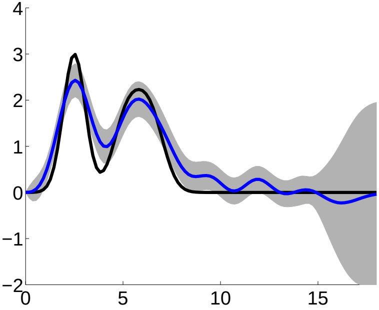

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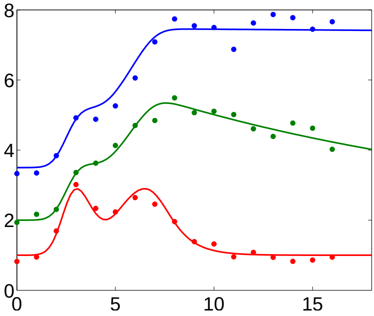

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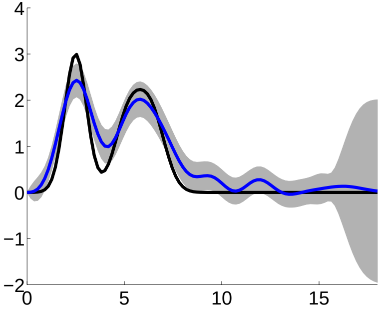
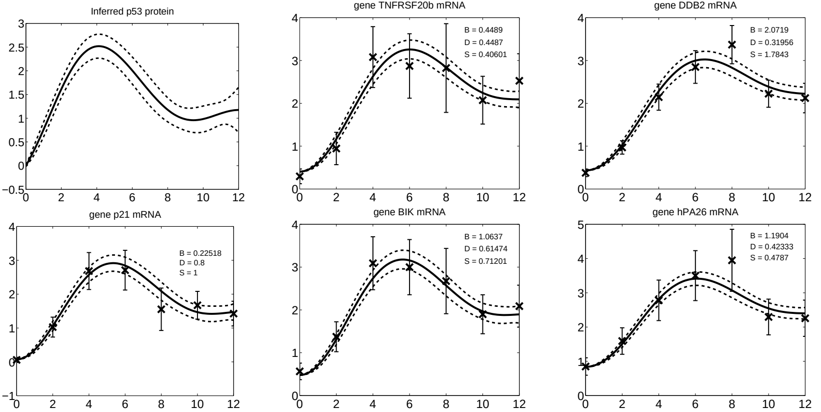


Inferred transcription factor activity.

p53 Results with GP

Pei Gao

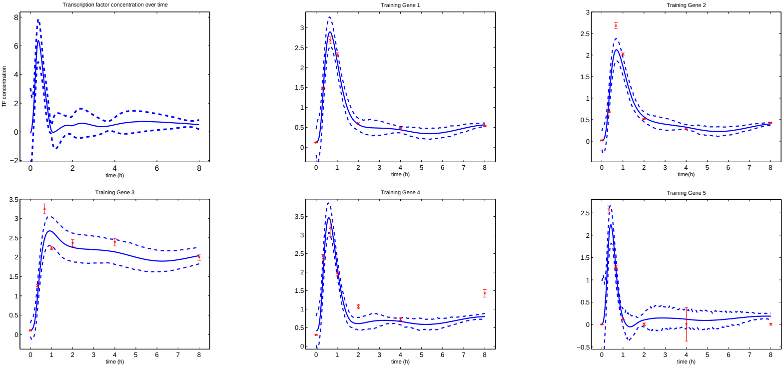


Ranking with ERK Signalling

- 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.

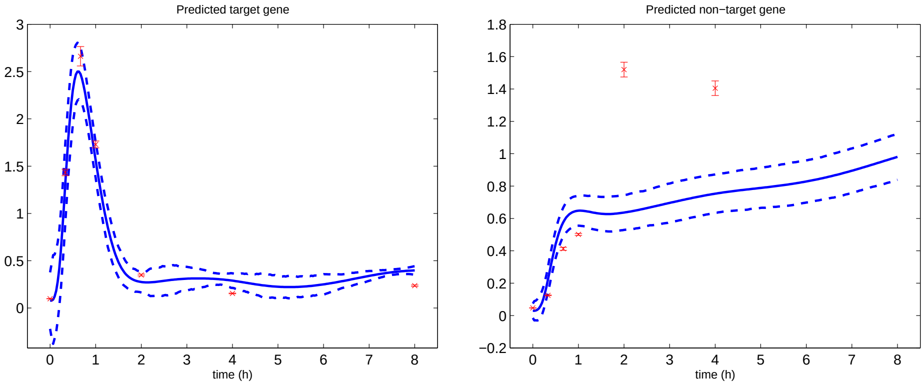
Elk-1 (MLP covariance)

Jennifer Withers



Elk-1 target selection

Fitted model used to rank potential targets of Elk-1



Outline

Cascaded Differential Equations

Antti Honkela

- 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.

Drosophila *Mesoderm* Development

Collaboration with Furlong Lab in EMBL Heidelberg.

- Mesoderm development in Drosophila melanogaster (fruit fly).
- Mesoderm forms in triplobastic 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?

Cascaded Differential Equations

Antti Honkela

We take the production rate of active transcription factor to be given by

$$\begin{aligned}\frac{\mathrm{d}f\left(t\right)}{\mathrm{d}t} &= \sigma y\left(t\right)-\delta f\left(t\right)\\ \frac{\mathrm{d}x_j\left(t\right)}{\mathrm{d}t} &= B_j+S_jf\left(t\right)-D_jx_j\left(t\right)\end{aligned}$$

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

$$f(t)=\sigma\exp\left(-\delta t\right)\int_0^t y(u)\exp\left(\delta u\right)\mathrm{d}u\ .$$

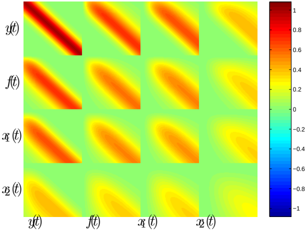
Covariance for Translation/Transcription Model

RBF covariance function for $y(t)$

$$
\begin{aligned}
f(t) &= \sigma \exp(-\delta t) \int_0^t y(u) \exp(\delta u) \, \mathrm{d}u \\
x_i(t) &= \frac{B_i}{D_i} + S_i \exp(-D_i t) \int_0^t f(u) \exp(D_i u) \, \mathrm{d}u.
\end{aligned}
$$

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

δ	D_1	S_1	D_2	S_2
1	5	5	0.5	0.5



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

- `disimSample`

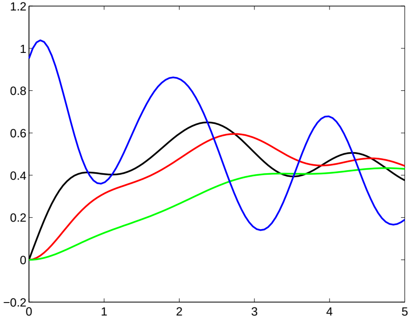


Figure: Joint samples from the ODE covariance, *blue*: $y(t)$ (mRNA of TF), *black*: $f(t)$ (TF concentration), *red*: $x_1(t)$(high decay target) and *green*: $x_2(t)$ (low decay target)

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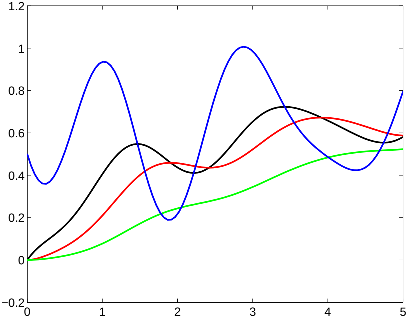

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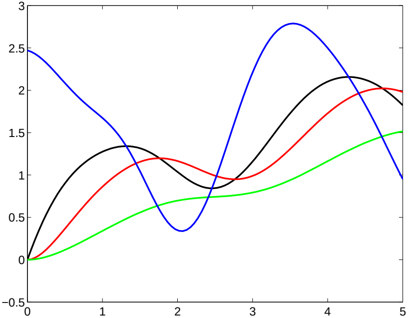

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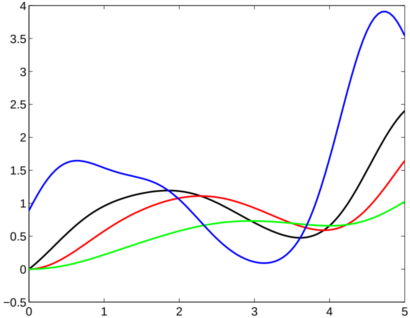

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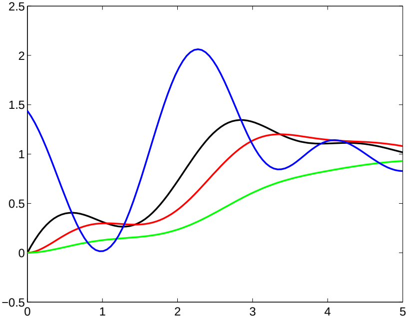

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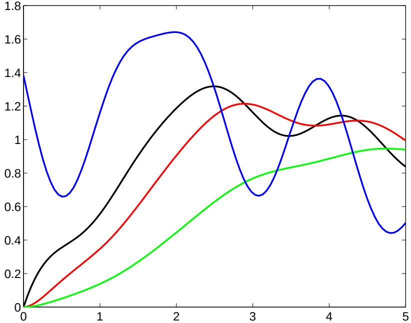

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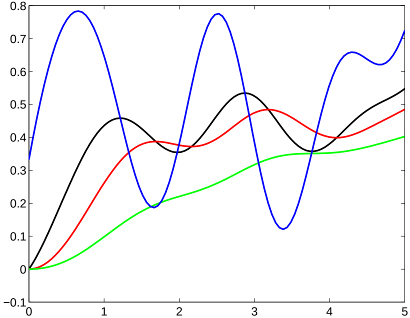

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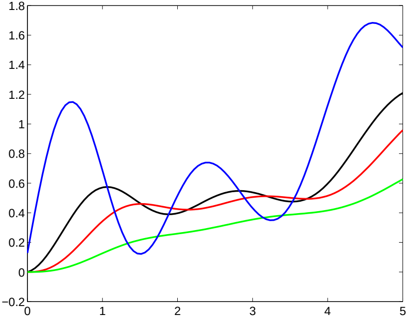

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Twist Results

- 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.

Results for Twi using the Cascade model

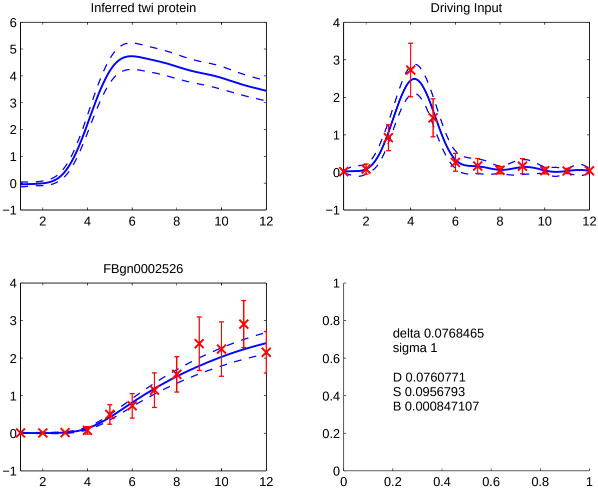

Figure: Model for flybase gene identity FBgn0002526.

Results for Twi using the Cascade model

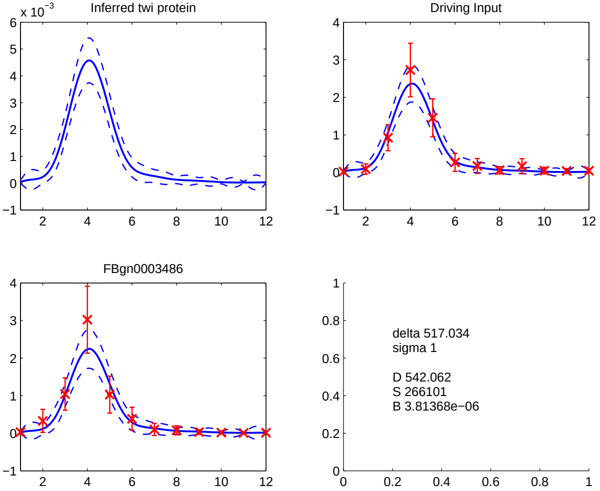

Figure: Model for flybase gene identity FBgn0003486.

Results for Twi using the Cascade model

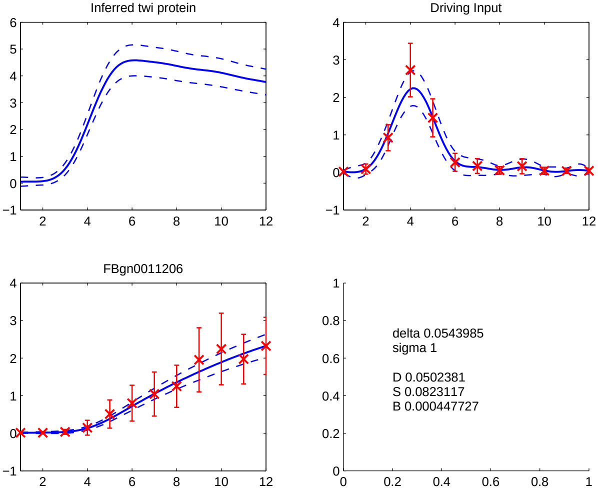

Figure: Model for flybase gene identity FBgn0011206.

Results for Twi using the Cascade model

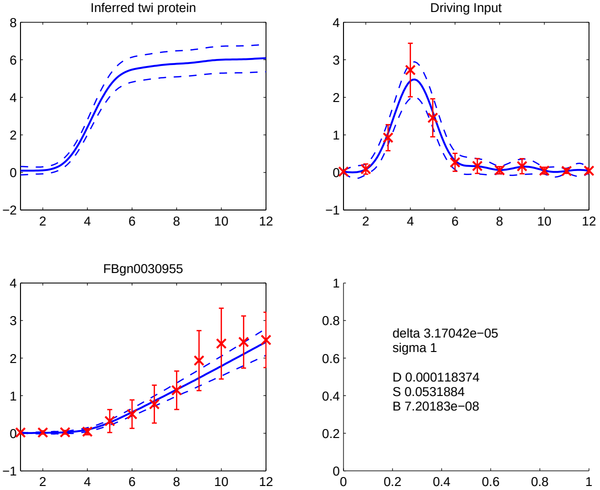

Figure: Model for flybase gene identity FBgn00309055.

Results for Twi using the Cascade model

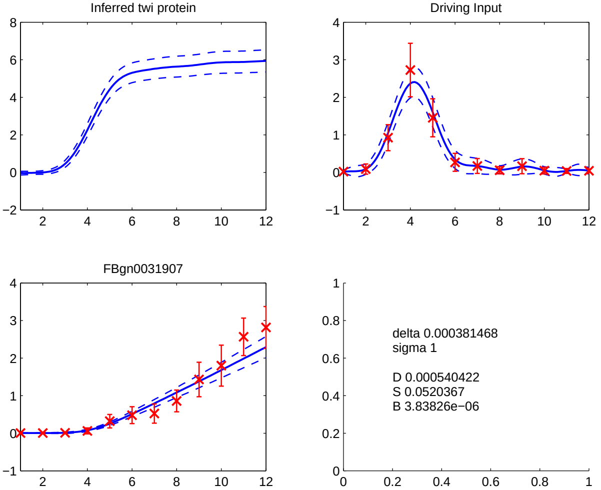

Figure: Model for flybase gene identity FBgn0031907.

Results for Twi using the Cascade model

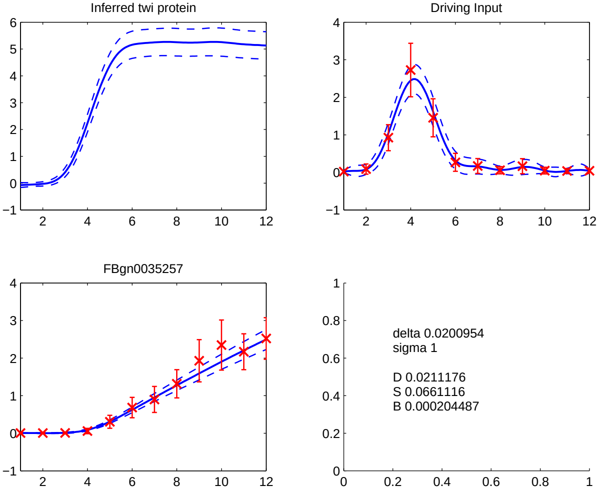

Figure: Model for flybase gene identity FBgn0035257.

Results for Twi using the Cascade model

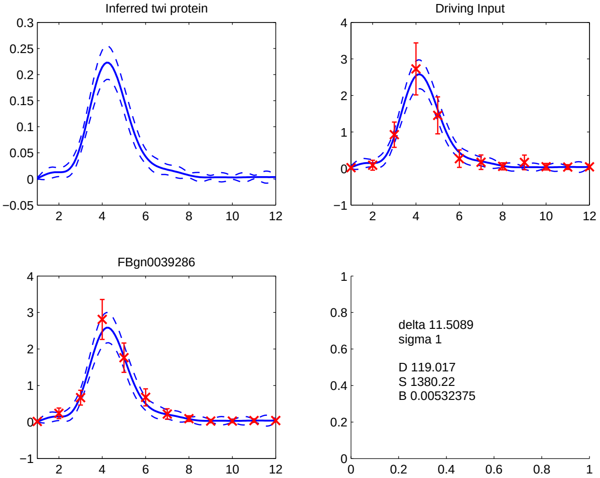

Figure: Model for flybase gene identity FBgn0039286.

Results of Ranking

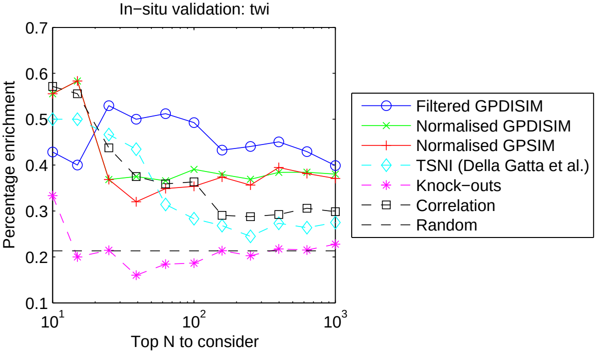

Figure: Percentage enrichment for top N targets for relevant terms in *Drosophila* in situs.

Results of Ranking

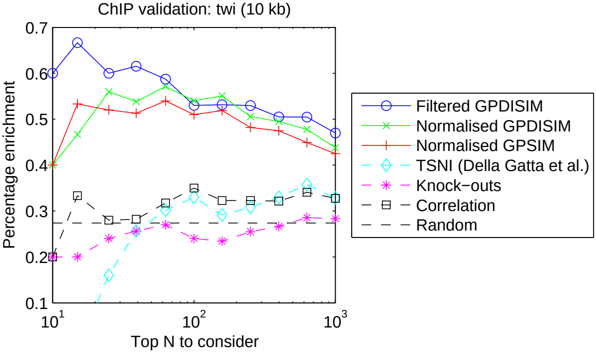

Figure: Percentage enrichment for top N targets for ChIP-chip confirmed targets.

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 $f(t)$

Cascade Differential Equations

Discussion and Future Work

Discussion and Future Work

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

Acknowledgements

- Investigators: Neil Lawrence and Magnus Rattray
- Researchers: Peo Gao, Antti Honkela, Michalis Titsias, 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"

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Outline

Nonlinear Response

Nonlinear Response Models

Consider the following modification to the model,

$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j g(f(t)) - D_j x_j(t),$$

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

$$x_j(t) = \frac{B_j}{D_j} + S_j \int_0^t e^{-D_j(t-u)} g_j(f(u))\,\mathrm{d}u$$

MAP-Laplace Approximation

Based on Laplace's method,

$$p\left(\mathbf{f} \mid \mathbf{x}\right) = N\left(\hat{\mathbf{f}}, \mathbf{A}^{-1}\right) \propto \exp\left(-\frac{1}{2}\left(\mathbf{f} - \hat{\mathbf{f}}\right)^{T} \mathbf{A}\left(\mathbf{f} - \hat{\mathbf{f}}\right)\right)$$

where $\hat{\mathbf{f}} = \mathrm{argmax} p(\mathbf{f} \mid \mathbf{x})$ and $\mathbf{A} = -\nabla\nabla \log p\left(\mathbf{f} \mid \mathbf{y}\right)|_{\mathbf{f}=\hat{\mathbf{f}}}$ is the Hessian of the negative posterior at that point. To obtain $\hat{\mathbf{f}}$ and $\mathbf{A}$,

we define the following function $\psi\left(\mathbf{f}\right)$ as:

$$\log p(\mathbf{f}|\mathbf{x}) \propto \psi(\mathbf{f}) = \log p\left(\mathbf{x} \mid \mathbf{f}\right) + \log p\left(\mathbf{f}\right)$$

MAP-Laplace Approximation

Assigning a GP prior distribution to $f(t)$, it then follows that

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

where $\mathbf{K}$ is the covariance matrix of $f(t)$. Hence,

$$\begin{aligned} \nabla\psi(\mathbf{f}) &= \nabla \log p(\mathbf{x}|\mathbf{f}) - \mathbf{K}^{-1}\mathbf{f} \\ \nabla\nabla\psi(\mathbf{f}) &= \nabla\nabla \log p(\mathbf{x}|\mathbf{f}) - \mathbf{K}^{-1} = -\mathbf{W} - \mathbf{K}^{-1} \end{aligned}$$

Estimation of $\psi(\mathbf{f})$

Newton's method is applied to find the maximum of $\psi(\mathbf{f})$ as

$$\begin{aligned}\mathbf{f}^{new} &= \mathbf{f} - (\nabla\nabla\psi(\mathbf{f}))^{-1}\nabla\psi(\mathbf{f}) \\ &= (\mathbf{W} + \mathbf{K}^{-1})^{-1}(\mathbf{W}\mathbf{f} - \nabla \log p(\mathbf{x}|\mathbf{f}))\end{aligned}$$

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

$$p(\mathbf{f} \mid \mathbf{x}) \simeq N(\hat{\mathbf{f}}, \mathbf{A}^{-1}) = N(\hat{\mathbf{f}}, (\mathbf{W} + \mathbf{K}^{-1})^{-1})$$

Model Parameter Estimation

The marginal likelihood is useful for estimating the model parameters θ and covariance parameters l

$$p\left(\mathbf{x}|\boldsymbol{\theta},\phi\right)=\int p\left(\mathbf{x}|\mathbf{f},\boldsymbol{\theta}\right)p\left(\mathbf{f}|\phi\right)df=\int\exp\left(\psi\left(\mathbf{f}\right)\right)df$$

Using Taylor expansion of $\psi(\mathbf{f})$,

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

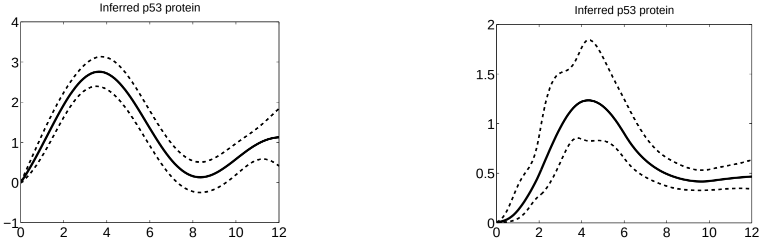
The parameters $\boldsymbol{\eta}=\{\boldsymbol{\theta},\boldsymbol{\phi}\}$ can be then estimated by using

$$\frac{\partial\log p\left(\mathbf{x}|\boldsymbol{\eta}\right)}{\partial\boldsymbol{\eta}}=\frac{\partial\log p\left(\mathbf{x}|\boldsymbol{\eta}\right)}{\partial\boldsymbol{\eta}}\ |_{\text{explicit}}+\frac{\partial\log p\left(\mathbf{x}|\boldsymbol{\eta}\right)}{\partial\hat{\mathbf{f}}}\frac{\partial\hat{\mathbf{f}}}{\partial\boldsymbol{\eta}}$$

Michaelis-Menten Kinetics

Pei Gao

- The Michaelis-Menten activation model uses the following non-linearity
$$g_j\left(f\left(t\right)\right)=\frac{e^{f(t)}}{\gamma_j+e^{f(t)}},$$
where we are using a GP $f\left(t\right)$ to model the log of the TF activity.



(a) (b)

Valdiation of Laplace Approximation

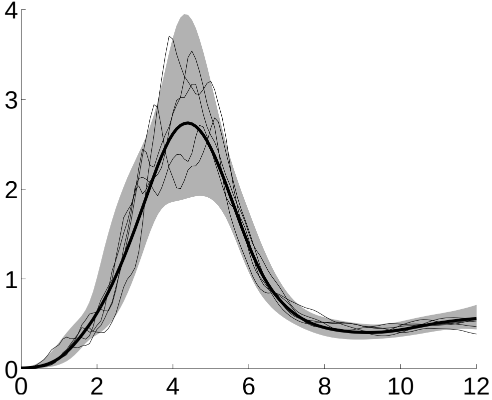


Figure: Laplace approximation error bars along with samples from the true posterior distribution.

SOS Response

- DNA damage 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 repessor.
- 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).

LexA Experimental Description

- 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.

Their Model

Given measurements of gene expression at N time points $(t_0, t_1, \ldots, t_{N-1})$, the temporal profile of a gene i, $x_i\left(t\right)$, that solves the ODE in Eq. 1 can be approximated by

$$x_i\left(t\right) = x_i^0 e^{-\delta_i t} + \frac{B_i}{D_i} + S_i e^{-\delta_i t} \frac{1}{D_i} \sum_{j=0}^{N-2} \left(e^{D_i t_j + 1} - e^{D_i t_j}\right) \frac{1}{\gamma_i + \bar{f}_j}$$

where $\bar{f}_j = \frac{\left(f\left(t_j\right) + f\left(t_j + 1\right)\right)}{2}$ on each subinterval $\left(t_j, t_j + 1\right), j = 0, \ldots, N-2$. This is under the simplifying assumption that $f\left(t\right)$ is a piece-wise constant function on each subinterval $\left(t_j, t_j + 1\right)$.

Khanin et al. (2006) Results Reminder

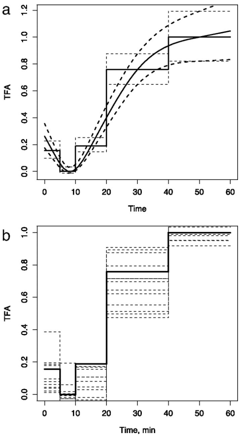


Figure: Fig. 2 from Khanin et al. (2006): Reconstructed activity level of master repressor LexA, following a UV dose of 40 J/m2.

Their Results

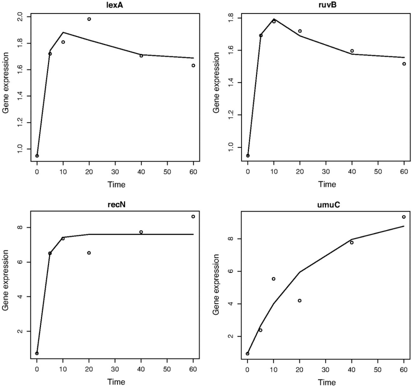


Figure: Fig. 3 from Khanin et al. (2006): Reconstructed profiles for four genes in the LexA SIM.

Repression Model

Pei Gao

- We can use the same model of repression,

$$g_j\left(f\left(t\right)\right) = \frac{1}{\gamma_j + e^{f(t)}}$$

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

$$x_j\left(t\right) = \alpha_j e^{-D_j t} + \frac{B_j}{D_j} + S_j \int_0^t e^{-D_j(t-u)} g_j(f\left(u\right))\mathrm{d}u$$

Results for the repressor LexA

Pei Gao

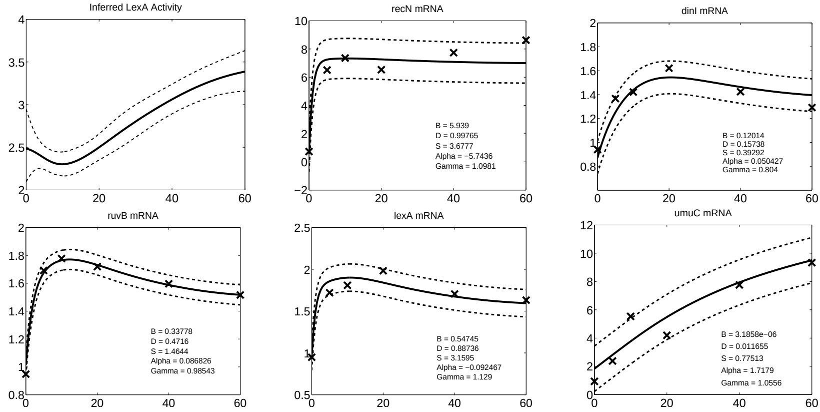


Figure: Our results using an MLP kernel. To apear at ECCB08 Gao et al. (2008).

Use Samples to Represent Posterior

Michalis Titsias

- Sample in Gaussian processes

$$p\left(\mathbf{f}|\mathbf{x}\right) \propto p\left(\mathbf{x}|\mathbf{f}\right) p\left(\mathbf{f}\right)$$

- Likelihood relates GP to data through

$$x_j\left(t\right) = \alpha_j e^{-D_j t} + \frac{B_j}{D_j} + S_j \int_0^t e^{-D_j(t-u)} g_j(f\left(u\right))\mathrm{d}u$$

- We use *control points* for fast sampling.

MCMC for Non Linear Response

The Metropolis-Hastings algorithm

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

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

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

Sampling using control points

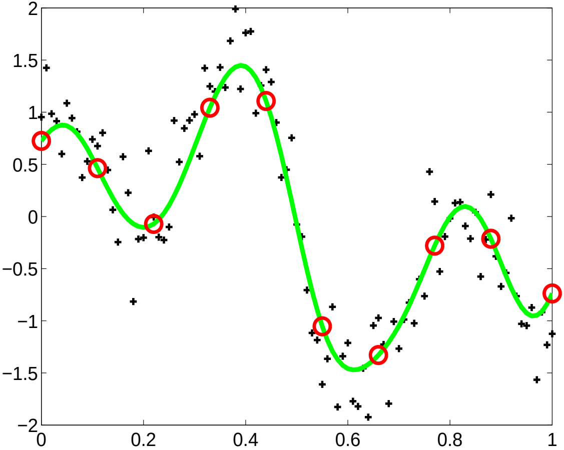
- Separate the points in $\mathbf{f}$ into two groups:
  - few control points $\mathbf{f}_c$
  - and the large majority of the remaining points $\mathbf{f}_\rho = \mathbf{f} \setminus \mathbf{f}_c$
- Sample the control points $\mathbf{f}_c$ using a proposal $q\left(\mathbf{f}_c^{(t+1)} | \mathbf{f}_c^{(t)}\right)$
- 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

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

- Its like sampling from the prior $p(\mathbf{f})$ but imposing random walk behaviour through the control points

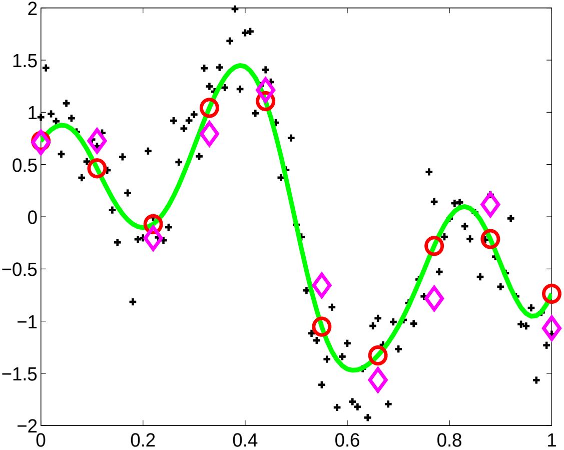
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



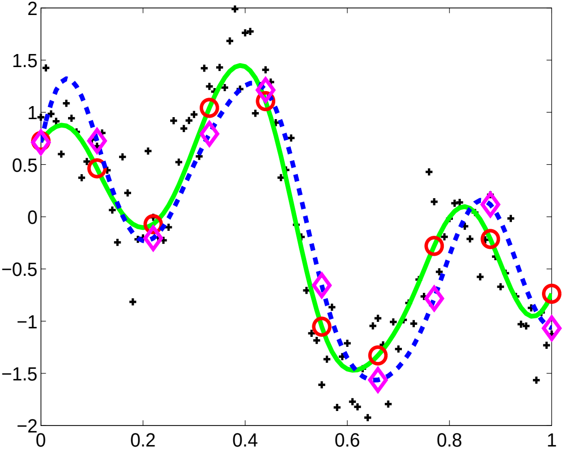
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



Sampling using control points: Regression-Examples

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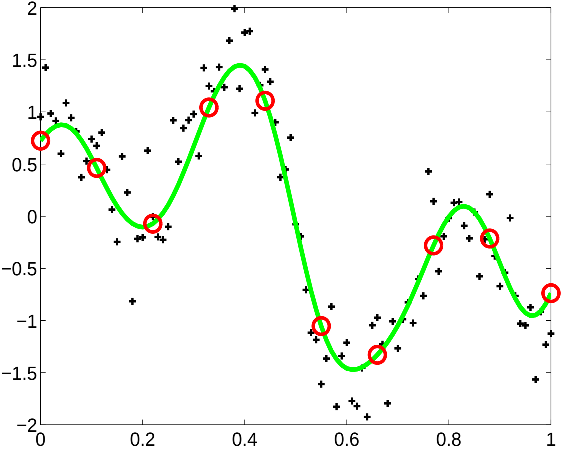
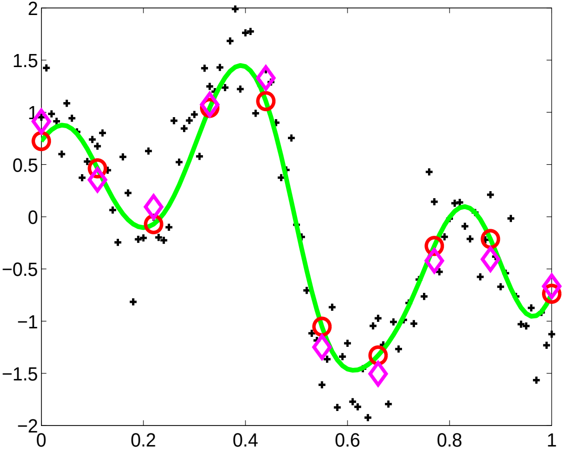


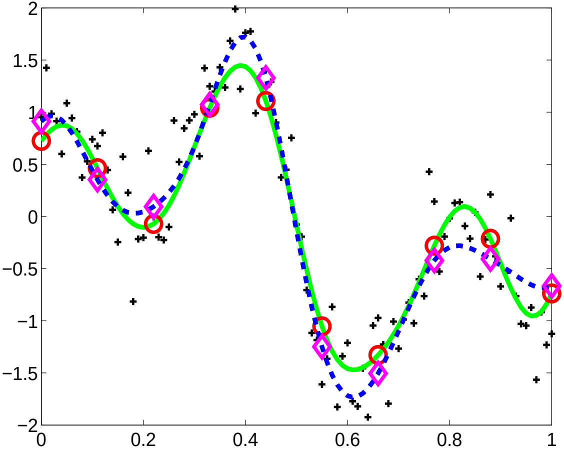
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



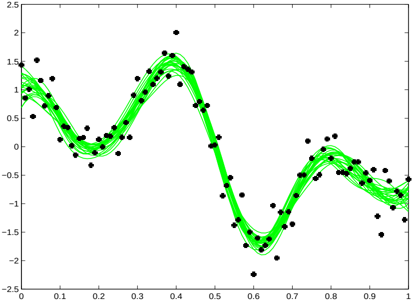
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



Sampling using control points

Few samples drawn during MCMC



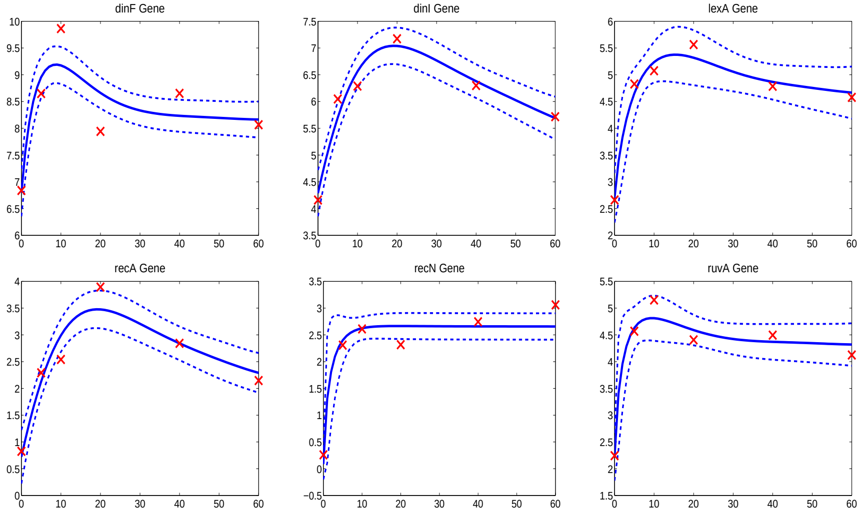
Results on SOS System

- Again consider the Michaelis-Menten kinetic equation

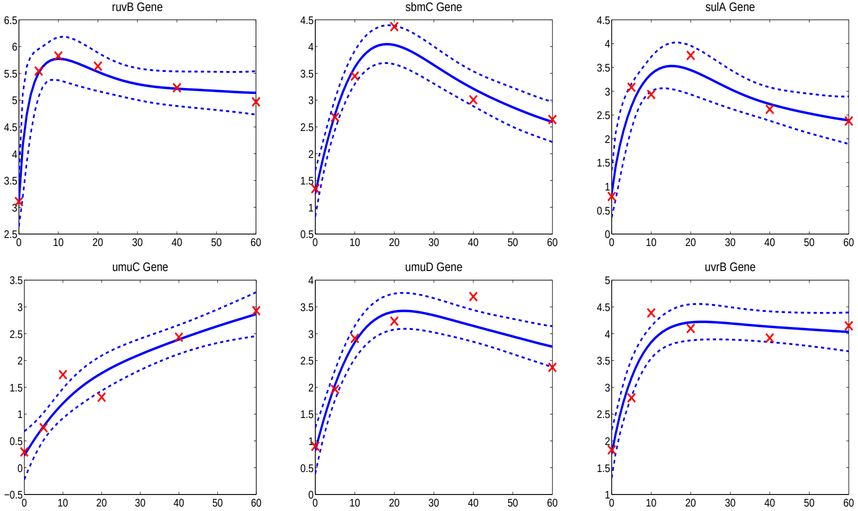
$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j \frac{1}{\exp(f(t)) + \gamma_j} - D_j x_j(t)$$

- 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 $15\% - 25\%$

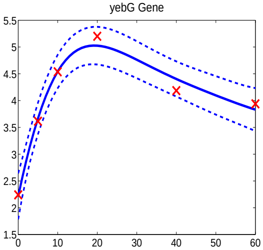
Results in E.coli data: Predicted gene expressions

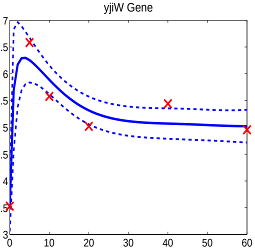


Results in E.coli data: Predicted gene expressions

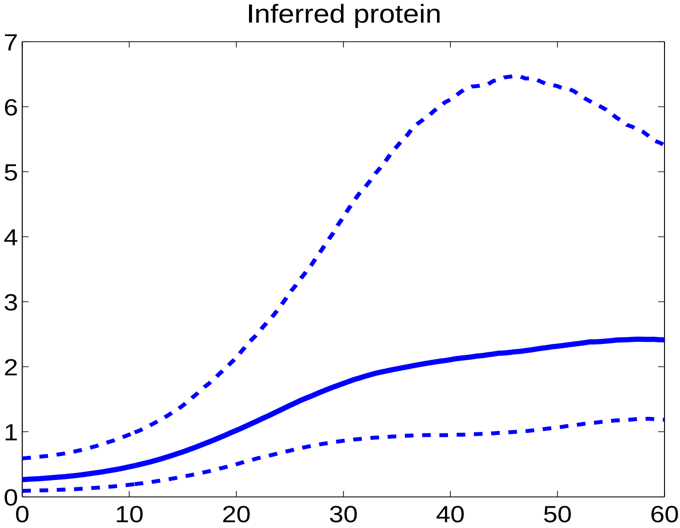


Results in E.coli data: Predicted gene expressions

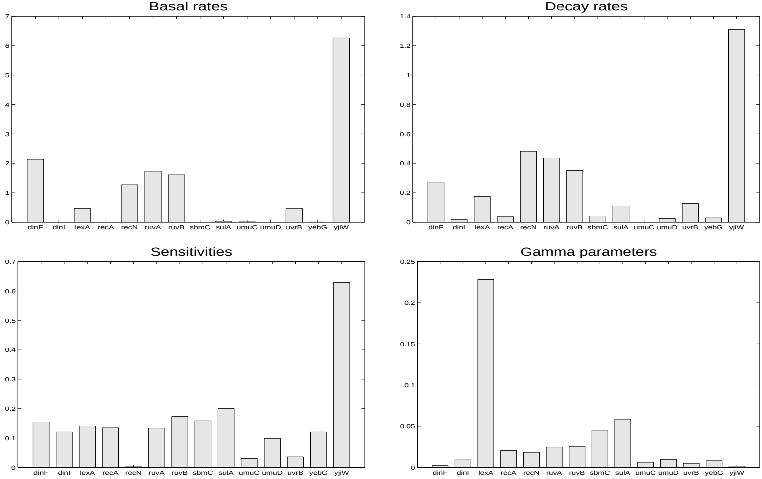




Results in E.coli data: Protein concentration



Results in E.coli data: Kinetic parameters



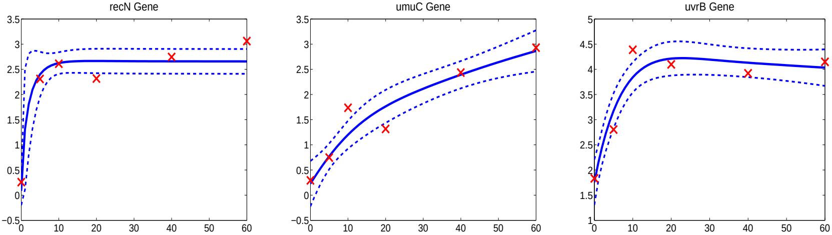
Basal rates

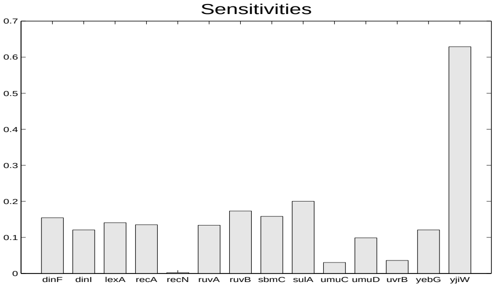
Decay rates

Sensitivities

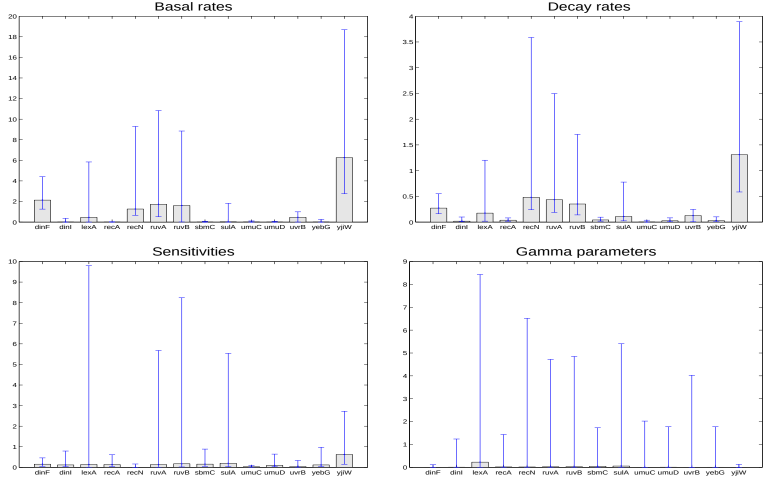
Gamma parameters

Results in E.coli data: Genes with low sensitivity value





Results in E.coli data: Confidence intervals for the kinetic parameters



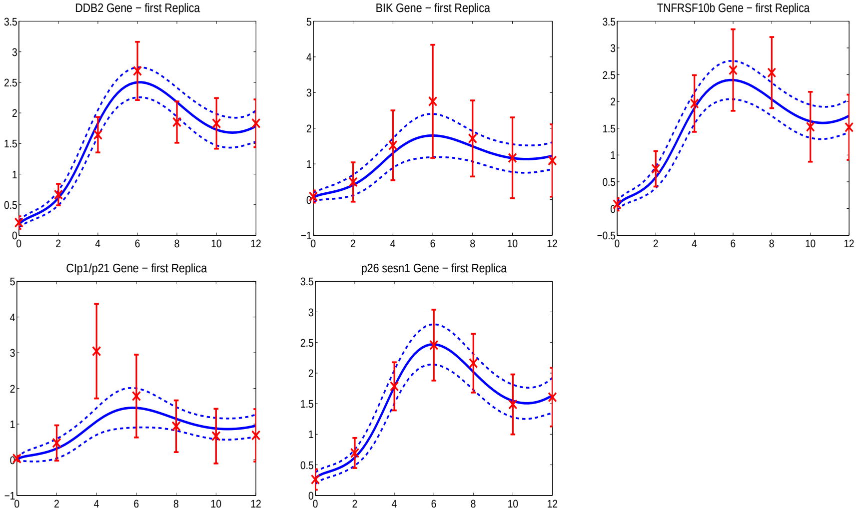
p53 System Again

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

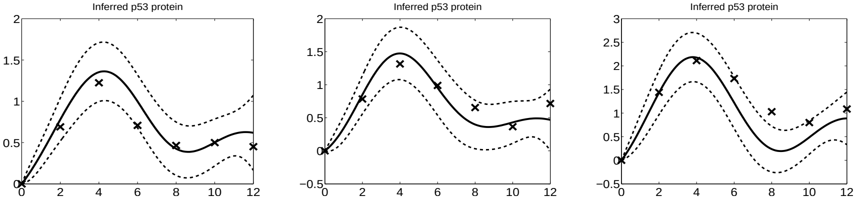
$$\frac{\mathrm{d}x_j(t)}{dt} = B_j + S_j \frac{\exp(f(t))}{\exp(f(t)) + \gamma_j} - D_j x_j(t)$$

- 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 $15\% - 25\%$

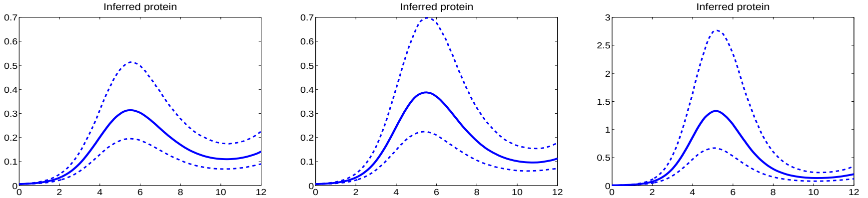
Data used by Barenco et al. (2006): Predicted gene expressions for the 1st replica



Data used by Barenco et al. (2006): Protein concentrations

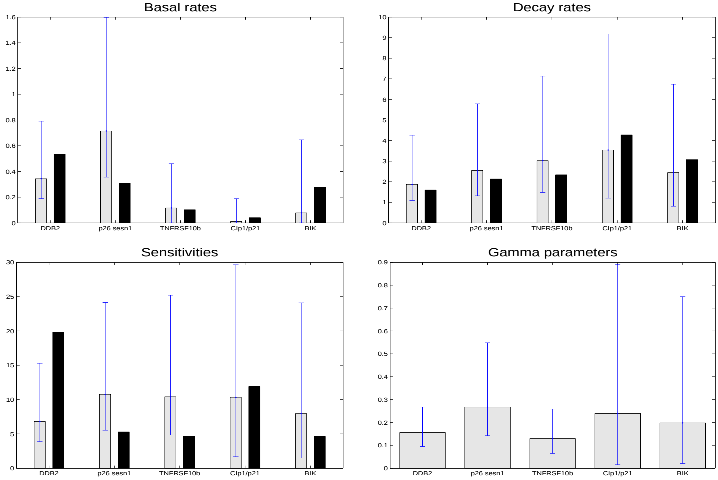


Linear model (Barenco et al. predictions are shown as crosses)



Nonlinear (Michaelis-Menten kinetic equation)

p53 Data Kinetic parameters



Our results (grey) compared with Barenco et al. (2006) (black).
Note that Barenco et al. use a linear model